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Non-Enzymatic Synthesis of Polysaccharides, Nucleosides and Nucleic Acids and the Origin of Self-Reproducing Systems

BY PROF. DR. G. SCHRAMM [*], DR. H. GRÖTSCH, AND DIPL.-CHEM. W. POLLMANN
MAX-PLANCK-INSTITUT FÜR VIRUSFORSCHUNG, TÜBINGEN

Compounds containing free amino, hydroxyl or carbonyl groups can be activated by reaction with polyphosphate ester. If the compounds contain a second functional group, polycondensations are possible; e.g. amino acids → polypeptides, carbohydrates → polysaccharides, nucleotides → polynucleotides. In the presence of polyadenylic acid, polymerization of uridylic acid is speeded up tenfold. This mutual effect of complementary nucleotide strands constitutes the experimental basis for a hypothesis concerning the terrestrial origin of systems capable of self-reproduction.

Schramm and *Wissmann* [1] have described a synthesis of polypeptides carried out with the help of polyphosphate esters in which the amino group of one component was made reactive by forming a phosphamide ester, reacting subsequently with the carboxyl group of the second component. This procedure is particularly well suited for the purpose of polymerization. Thus, it has been possible to prepare in this manner high-molecular weight peptides containing as many as 24 amino acids by starting with alanyl-glycyl-glycine [1]. Similarly, a polyarginine (mol. wt. 4000–5000) was prepared from arginine and high molecular weight peptides were obtained from various substituted and unsubstituted aminobenzoic acids.

These experiments will be described in greater detail elsewhere. The procedure has the advantage that condensation occurs under exceedingly mild conditions and without racemization. The polyphosphate ester can be readily produced by dissolving P_2O_5 in ether and other solvents containing alkoxyl groups. Its precise structure is not yet well known; it seems likely that it is a mixture of cyclic and straight-chain esters.

Activation of Hydroxyl-Containing Compounds

Experiments were carried out in order to discover whether or not polyphosphate ester can also be used to activate hydroxyl groups. We were prompted to undertake these studies by the fact that in the vast majority of cases, cellular biosynthetic processes are initiated by the transformation of hydroxy compounds into reactive phosphate esters by adenosine triphosphate or similar polyphosphates; these esters in turn react with either the nitrogen or oxygen of another compound while giving up their phosphate group. Examples of such reactions are listed in Table 1. In the case of reactions (1) to (4)

Table 1. Biochemical Syntheses

(1)	glucose-1-diphospho-uridine + fructose		saccharose + uridine diphosphate
(2)	glucose-1-phosphate	phosphorylase	starch + phosphate
(3)	ribose-1-phosphate + uracil	uridine phosphorylase	uridine + phosphate
(4)	5-phosphoribosyl-1-pyrophosphate + adenine	nucleotide pyrophosphorylase	adenylic acid + pyrophosphate
(5)	nucleoside diphosphate	polynucleotide phosphorylase	RNA + phosphate
(6)	deoxynucleoside triphosphate		DNA + pyrophosphate
(7)	amino acid + ATP + s-RNA		aminoacyl-s-RNA → protein

[*] Preliminary communication: *G. Schramm, H. Grötsch,* and *W. Pollmann,* Angew. Chem. *73,* 619 (1961).

[1] *G. Schramm* and *H. Wissmann,* Chem. Ber. *91,* 1073 (1958).

the activation involves an acetal hydroxyl; in the case of reactions (5) and (6) a secondary phosphate group is activated, whereas in reaction (7) a carboxyl group undergoes activation. Our first attempts were therefore directed towards the activation of acetal hydroxyl groups and phosphate esters by means of polyphosphate ester.

Preparation of O-Glycosides

We have found that when polyphosphate ester is allowed to react with aldoses and ketoses, the acetal hydroxyl group is attacked and the resulting reactive intermediate can readily undergo further reactions with other hydroxyl-containing compounds. If, for example, glucose dissolved in dimethylformamide is allowed to react with methyl glucose in the presence of polyphosphate ester, the splitting-off of the methyl group is accompanied by a good yield of a uniform disaccharide which upon chromatography can be clearly differentiated from maltose and gentiobiose, and can be identified as cellobiose (see Diagram 1). Thus, there arises in this case, a $\beta 1 \rightarrow 4$-glucosidic compound. The surprisingly sterically uniform course of the reaction has been confirmed in many other examples.

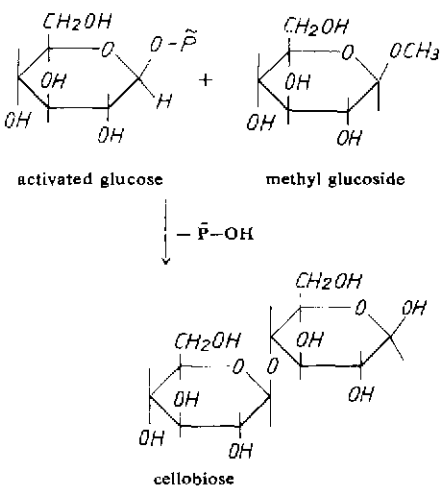


Diagram 1

So far it has not been possible to isolate in pure form the active intermediate (glucose-1-P) which is formed from glucose and polyphosphate ester. Undoubtedly, the first step in the reaction involves a phosphorylation of the acetal hydroxyl group. Within a few minutes following the addition of the polyphosphate ester in the cold, the aldehyde group of the glucose can no longer be titrated with iodine; moreover, when the mixture was analyzed, glucose-1-phosphate was found. However, the active intermediate is not identical with glucose-1-phosphate as the latter does not react to form glucosides under the conditions described. Possibly, the intermediate compound is an ethyl ester of glucose-1-phosphate or glucose-polyphosphate.

Preparation of Polysaccharides

Polymerization of sugars in acid solution has been observed repeatedly. *Micheel* and co-workers [2] were able to isolate polyglycosides in good yields when they treated glucose and other sugars in dimethyl sulfoxide with hydrochloric acid, provided the water formed in the course of the reaction was distilled off. However, the polysaccharides that were formed were highly branched.

If sugars that have a free carbonyl group are allowed to interact in an inert solvent in the presence of polyphosphate ester, high molecular weight polyglycosides result which are largely linear and unbranched. We obtained a polymer from glucose in dimethylformamide from which we were able to separate low molecular weight oligosaccharides by means of dialysis. With a yield of 30–50 %, there remained a polyglucoside with a mean molecular weight of 50000. Its specific viscosity, $[\eta] = 100$, corresponded to that of cellulose of equal molecular weight. This indicates that the vast majority of molecules formed are of the long-chain, unbranched type. Both optical rotation (+38 °), and the infrared spectral data, indicate the presence of β-glycosidic linkages. However, the polyglucoside still contained small amounts of phosphate, probably because a proportion of the non-acetal hydroxyl groups were also phosphorylated in the course of the reaction. These non-acetal phosphate esters do not seem to be sufficiently rich in energy to allow them to undergo further condensations. The phosphorylation can be prevented with the use of formamide solutions. Polyphosphate ester dehydrates acid amides to the corresponding nitriles. When the reaction is carried out in formamide, hydrocyanic acid results, and the acetamide is transformed quantitatively into acetonitrile. This reaction has also been described by others [3]. Formamide slows the phosphorylating action of the polyphosphate ester sufficiently for a mixture of both phosphate-free and phosphate-containing glycosides to form. These compounds can easily be separated from one another by means of a basic ion-exchanger. With an over-all yield of 10–20 %, a phosphate-free polyglucoside with a molecular weight of approximately 50000 and an optical rotation of +16 ° was obtained from glucose. The precise molecular composition of this glucoside is still being determined. Upon decomposition with periodate it uses up one mole of $NaIO_4$; this is to be expected if only $1 \rightarrow 4$-glycosidic linkages are present.

Ketoses, *e.g.* fructose and pentoses, will polymerize in an analogous fashion in the presence of polyphosphate ester (see Table 2). We have studied the polyriboside in more detail. As was found for glucose, a phosphate-free polyriboside, which on the basis of viscosity and sedimentation determinations had a molecular weight of 40000, was obtained. The optical rotation amounted

[2] *F. Micheel* and *A. Böckmann*, Angew. Chem. *72*, 209 (1960); *F. Micheel, A. Böckmann*, and *W. Meckstroth*, Makromolekulare Chem. *48*, 1 (1961).

[3] *T. Mukaiyama* and *T. Hata*, Bull. chem. Soc. Jap. *34*, 99 (1961); quoted from Angew. Chem. *73*, 414 (1961).

Table 2. Synthesis of Polysaccharides with Polyphosphate Ester

Monosaccharide	Polysaccharide	Molecular weight
Glucose	Polyglucoside (β1→4)	50000
Ribose	Polyriboside (α1→5)	40000
Fructose	Polyfructoside	40000

to +35 °. On the basis of its optical rotation, as well as its reaction with periodate, it appears to be a sterically uniform product with predominantly α1→5-glycosidic linkages. This polyriboside readily decomposes into ribose in dilute acid and is therefore comparable with other furanoside compounds.

Under mild conditions, sugars will react with polyphosphate ester to yield oligosaccharides with a low degree of polymerization. These can be readily separated by means of chromatography. In addition to yielding uniform products, this procedure has the advantage that even the more labile polyglycosides can be produced; furthermore, small amounts of water do not interfere with the reaction. Glucose, with the usual water of crystallization, can readily serve as starting material.

Example: Preparation of Polyphosphate Ester

Pure P_2O_5 (150 g.) is boiled under reflux in the presence of 150 ml. chloroform and 300 ml. ether until the solution is clear. This takes about 12 hours. The solvent is then evaporated and the viscous, colorless residue is used directly in the subsequent synthesis.

Example: Preparation of Phosphate-Free Polyglucosides

Glucose monohydrate (5 g.) and the polyphosphate ester (10 g.) are dissolved in 50 ml. formamide and heated with stirring to 50–60 °C. for 6 hrs. After the solution has cooled to room temperature, an equal volume of water is added and dialysis is carried out for 48 hrs. The residue inside the dialysis bag is then reduced to dryness in a rotary evaporator, triturated with methanol, and washed with ether. The powdery residue is taken up in a small volume of water and passed onto a basic ion-exchanger (Dowex 1 X 10) which has been pretreated with formic acid. After elution with water, a phosphate-free polyglucoside is obtained in a yield of about 15 %.

Preparation of Nucleosides

Sugars readily react in acid solution with primary or secondary amines to form the corresponding *N*-glycosides. These in turn are easily decomposed. It is more difficult to make sugars react with heterocyclic bases to form *N*-glycosides of the type that occur in nature as nucleosides. In order to synthesize the latter, Hg or Ag salts of the bases are prepared. Some of these are not readily available. In the case of adenine, for example, it is necessary to carry out a chlorination in order to loosen the proton at the *N*(9)-position sufficiently for salt formation to occur. Following glycoside formation, the halogen atoms must be removed by means of catalytic reduction. In the free form, sugars do not react with salts of the heavy metals, but must first be transformed into the 1-halogenides by means of acylation of all hydroxyl groups. However, these halogenides are frequently quite unstable. At the end of the reaction the protecting acyl groups must be removed. As a large number of steps is involved, the yields are frequently quite low [4].

Because of the selective action of polyphosphate ester on the aldehyde groups, free sugars can be reacted with purine and pyrimidine bases in one step. Thus, by allowing adenine to react with deoxyribose we obtained an approximately 30 % yield (on the basis of the quantity of sugar employed) of 2'-deoxyadenosine, which in all of its characteristics, *i.e.* UV. absorption and R_f values in various solvent systems, was identical with the natural product. As indicated in Diagram 2, adenosine was

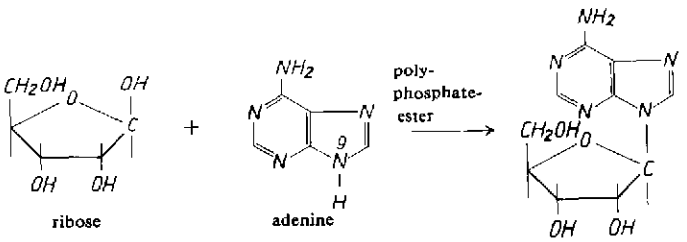


Diagram 2

prepared in good yield from ribose and adenine; on the basis of ultraviolet and infrared spectral data, and its behavior on chromatography, this compound was identical with the natural product. This means that substitution occurred only in the 9-position. It is interesting to note that the amino group in the 6-position was unaffected. If it reacted at all, it was undoubtedly reformed in the course of the purification. The only sideproduct was a small quantity of 5'-adenylic acid which also was identical with the natural product. The preparation of the corresponding nucleosides from adenine with fructose or acetylglucosamine proceeded in similar fashion (see Table 3). In order to prevent the sugars from polymerizing, the reaction was always carried out in the presence of an excess of base. Yields varied between 20 and 60 % relative to the quantity of sugar used. For the reaction, a certain amount of water in the solvent is advantageous, since otherwise the sugars decompose. The mode of formation corre-

Table 3. Synthesis of Nucleotides with Polyphosphate Ester

ribose + adenine ——— ——→ adenosine (+2',3'-adenosine phosphate)

deoxyribose + adenine —— ——→ deoxyadenosine

fructose + adenine ———— ——→ fructosyladenine

N-acetylglucosamine + adenine —→ *N*-acetylglycosaminyl adenine

[4] Review article: *A. M. Michelson*, Annu. Rev. Biochem. *30*, 133 (1961).

sponds in large measure to the biosynthesis of these nucleotides. This may be the reason why the isomers occurring in nature are formed preferentially.

Example: Preparation of Adenosine (9-[1'-β-ribosyl]-adenine)

Adenine (1 g.) is dissolved with magnetic stirring in 100 ml. dimethylformamide (water content ca. 0.2 %) with the addition of 0.5 ml. concentrated HCl. After the addition of polyphosphate ester (3–4 g.), 200 mg. D-ribose dissolved in 50 ml. dimethylformamide is added dropwise with stirring. The solution is kept in a glycerine bath at 50 °C. for 20 hours and then the dimethylformamide is distilled off *in vacuo*. The moist residue is dissolved in a little water and brought to pH 7. Part of the unreacted adenine usually precipitates after about 3 hours in the ice-box. The solution is filtered, adjusted to pH 10 with ammonia, and passed onto a Dowex-1 ion-exchange column (previously prepared in the formate form). Adenosine, adenine, and adenylic acid are eluted according to the method of *Cohn* [5].

Synthesis of Nucleic Acids from Apurinic Acids

It is well known that the *N*-glycosidic linkages between deoxyribose and either adenine or guanine can be broken in deoxyribonucleic acids (DNA) by cautious treatment with acid, without causing at the same time many of the phosphate bridges between the nucleotides to split. These purine-free nucleic acids have been studied in detail by *Chargaff* and collaborators who have termed them apurinic acids [6]. In order to develop a quantitative basis for the synthesis of apurinic acids, *Schramm* and *Pollmann* [7] have compared the rate of splitting of phosphate bridges between sugar residues with the rate of splitting of *N*-glycosidic linkages. A potentiometric method was developed in order to measure the rate at which phosphate di-esters are split to form secondary phosphates. The splitting-off of purine residues was determined chromatographically. It was found that the rate of hydrolysis of phosphate groups, as well of the glycosidic linkages, was proportional to the hydrogen ion concentration, but that the ratio of these rates to one another was independent of the pH. Table 4 lists the rates of hydrolysis of deoxyribonucleic acid and ribonucleic acid at pH 2.4. The table shows that the rate of phosphate hydrolysis is the same for both types of nucleic acids, but that the glycosidic linkages are broken 650 times faster in the deoxyribonucleic acid than they are in the ribonucleic acids. Thus the stabilizing effect of the 2'-hydroxyl group in the ribonucleic acids is surprisingly strong. Therefore in DNA, a large number of purine residues can be split off by acid hydrolysis without breaking the chain. In the case of RNA, on the other hand, the molecule undergoes rupture in six places before a purine residue is split off.

Table 4. Rate Constants for Hydrolysis at pH 2.4; T = 37 °C.

	$k_{pu} \cdot 10^6$ [min^{-1}]	$k_{phosphate} \cdot 10^6$ [min^{-1}]
RNA	1.2	6.4
DNA	780	6.6

In view of the genetic role played by DNA it seemed of interest to fill the gaps caused by the removal of adenine and guanine with other purines or pyrimidines. The free aldehyde groups in the apurinic acid were activated by means of polyphosphate ester and allowed to react with the corresponding bases. In the case of DNA from thymus gland, it proved possible to quantitatively fill with adenine the gaps which were caused by the removal of more than 90 % of the purine bases (Diagram 3).

$$\text{DNA} \xrightarrow{H^+} \text{apurinic acid} + \text{adenine} + \text{guanine}$$

$$\text{apurinic acid} \xrightarrow[\text{(adenine)}]{+\ \text{polyphosphate ester}} \text{DNA}_{\text{adenine}}$$

Diagram 3.

The newly synthesized nucleic acid, in contrast to the apurinic acid, no longer exhibited an aldehyde group; following hydrolysis it proved possible to demonstrate chromatographically the amounts of deoxyadenosine expected from theoretical considerations. A further argument in favor of the natural configuration of this synthetic product is the fact that it could be hydrolyzed both by deoxyribonuclease and by snake venom diesterase.

By activation with polyphosphate ester, it was possible to make the apurinic acids react with other bases. In order to measure the incorporation quantitatively we employed radioactive bases. A reaction in which the polyphosphate ester was replaced by an equivalent amount of phosphoric acid served as a control. The rates of incorporation are shown in Table 5, which

Table 5. Incorporation of ^{14}C-Bases into Apurinic Acid in the Presence of Polyphosphate Ester. Reaction in Dimethylformamide at 37 °C.

Base	Incorporation [%]	Time of reaction [hrs.]
adenine	96	24
guanine	40	24
orotic acid	40	24
thymine	5	48
uracil	8	48

indicates that pyrimidines are incorporated more slowly than are purines. The amounts incorporated can be increased by permitting the reactions to proceed for longer periods.

It is of interest that the incorporation of the bases proceeded not only in dimethylformamide but also in aqueous solution, although the yield was smaller in the latter instance. This raises the possibility of altering the DNA in a cell in a controlled manner and, thereby, to

[5] *W. E. Cohn*, J. Amer. chem. Soc. *72*, 1471 (1950).

[6] *Ch. Tamm, M. E. Hodes*, and *E. Chargaff*, J. biol. Chemistry *195*, 49 (1952).

[7] *W. Pollmann* and *G. Schramm*, Z. Naturforsch. *16b* 673, (1961).

study the effect of such alteration of the sequence of bases on the gene function. Some experiments are now in progress. In addition to acid hydrolysis, other methods are available for selectively removing certain bases from a DNA or RNA molecule. *Schuster* [8], working in our Institute, studied the removal of uracil from RNA by means of hydroxylamine. Activation of liberated aldehyde groups with polyphosphate ester and incorporation of either those bases which occur in nature, or others that do not, can lead to the production of a wide spectrum of different nucleic acids.

Synthesis of Nucleic Acids by Polymerization of Nucleotides

The procedure described above can be considered a partial synthesis of nucleic acids. We have also achieved total non-enzymatic synthesis of nucleic acids by starting from nucleotides. Many laboratories have worked on the general problem of polymerizing nucleotides to form nucleic acids.

Khorana and co-workers [9] allowed thymidylic acid to react with dicyclohexyl carbodiimide and they were able to make the activated phosphates polymerize to form oligonucleotides, achieving an average degree of polymerization of 3 to 4. *Michelson* [10] was able to transform nucleotides in dry dioxane into cyclic 2′,3′-phosphates by adding tri-n-butylamine and either tetraphenyl pyrophosphate or diphenyl phosphorochloridate. If additional tetraphenylpyrophosphate was allowed to act on the ammonium salts of these cyclic phosphates, oligonucleotides were formed with a maximum chain length of 12 nucleotides. *Cramer* [11] has described a method of polymerizing nucleotides which consists of sharply drying the latter and then causing them to react with the enol phosphate of malonic ester in absolute dimethylformamide and tributylamine. In this manner *Cramer* obtained an adenosine diethylpyrophosphate ester which could be polymerized to form polyadenylic acid. His yield was only 3 % of a polythymidylic acid with a maximum number of 5 nucleotide units.

All methods used so far have led to oligonucleotides with a small degree of polymerization. One of the principal difficulties is that these oligonucleotides were cyclized intramolecularly, a lengthening of the chain thereby being prevented. It can be readily understood, however, that high degrees of polymerization can only be achieved with highly concentrated nucleotide solutions. By reversing Ziegler's dilution principle, intermolecular condensation may take precedence over intramolecular cyclization. In order to achieve maximum concentration the nucleotides to be polymerized were mixed directly with the viscous polyphosphate ester and the resulting mass was allowed to rotate at 50–60 °C. The addition of pyridine proved particularly favorable; this compound is known to act as a catalyst in similar reactions because of its nucleophilic properties. Table 6 lists the properties of high molecular weight, non-dialyzable polynucleotides obtained from various nucleotides. We also prepared a number of mixed polymers from various nucleotides; the properties of these polymers resembled those of the uniform polynucleotides. It is interesting that this method makes possible the polycondensation of the unstable 2′-deoxynucleotides. With 2′-deoxythymidine-5′-phosphate as a starting material, the only free group is the 3′-hydroxyl. There can be no doubt, therefore, that in the polythymidylic acid (Poly-T) phosphate bridges are established between the 3′- and the 5′-hydroxyl groups, thus yielding the same configuration as exists in the natural DNA. Further support for this argument comes from the fact that deoxyribonuclease attacks the synthetic polydeoxythymidylic acid. The average molecular weight calculated on the basis of sedimentation and diffusion determinations is 15000 to 50000. It may be possible to increase this by modifying the procedure further. Polyribonucleotides may be prepared by making use of 2′-, 3′- or 5′-nucleoside monophosphates or cyclic 2′,3′-phosphates. The nature of the primary active intermediates has not yet been determined. In all likelihood the monophosphates are first transformed into cyclic phosphates which in turn react with the polyphosphate ester to form pyrophosphate esters. Inasmuch as two hydroxyl groups are available for reacting with the phosphate groups of the adjoining molecule, one cannot be sure of the steric uniformity of the synthetic polynucleotides. Various experiments suggest, however, that in the majority of cases, at least, the configuration corresponds to that of the natural nucleic acids. Thus synthetic polyribonucleotides that contain pyrimidine nucleotides can be hydrolyzed by pancreatic ribonuclease; this would be unlikely if the predominant linkage were the unnatural $2' \rightarrow 3'$- or $2' \rightarrow 5'$-linkage. Pancreatic ribonuclease acts specifically on the 3′-phosphate group of the pyrimidine nucleotides.

Table 6. Properties of the Synthetic Polynucleotides

	s_{20}	$[\eta]_v$	Molecular weight	Hyperchromia
Poly-A	2.5	25	21000	37 %
Poly-C	2.0	23	15000	16 %
Poly-G	2.9	28	28000	28 %
Poly-U	4.0	35	50000	20 %
Poly-T	2.3	24	18000	47 %

Examination of the synthetic polyadenylic acid by electron microscopy reveals long fibers very similar in appearance to those in natural, high molecular weight RNA (Figure 1). Branched chains seem, there-

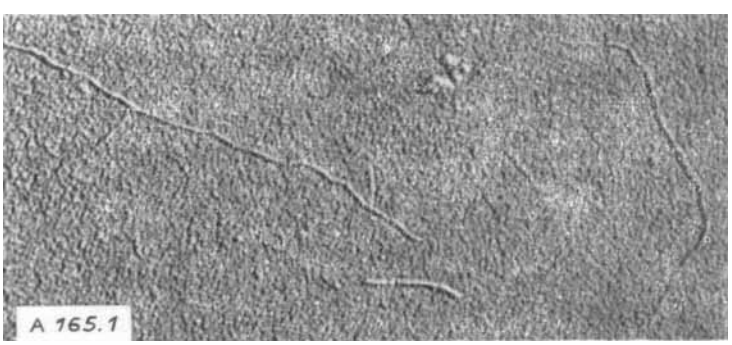


Fig. 1. Electron Micrograph (× 60000) of Synthetic Polyadenylic Acid

[8] *H. Schuster*, J. mol. Biology *3*, 447 (1961).

[9] *G. M. Tener, H. G. Khorana, R. Markham*, and *E. H. Pol*, J. Amer. chem. Soc. *80*, 6223 (1958).

[10] *A. M. Michelson*, J. chem. Soc. (London) 1371, 3655 (1959).

[11] *F. Cramer*, Angew. Chem. *73*, 49 (1961).

fore, to be infrequent. The length of these fibers indicates that quite high molecular weights appear to have been achieved at times. As with the natural materials, so the synthetic polynucleotides exhibit a high degree of hyperchromia. In high-molecular weight nucleic acids the ultraviolet extinction coefficient is diminished because of interaction between the heterocyclic bases. The extinction coefficients rise when the polymers are hydrolyzed to mononucleotides, the values being equal to those calculated by summing individual values for the nucleotides. *Michelson* [12] has shown that in various oligonucleotides, hyperchromia is a function of the molecular weight. The appreciable hyperchromic values listed in Table 6 are further indication of the high molecular weight of the synthetic products. Experiments by *Rich* [13] have shown that enzymatically produced polyadenylic acid will combine with its complementary polyuridylic acid to form a double helix; at the same time the extinction value will drop. We were able to observe a similar effect when we mixed synthetic polyadenylic acid with synthetic polyuridylic acid. This phenomenon is likely to occur only when both compounds have a helical structure similar to that of the natural nucleic acids.

It is also possible to prepare polynucleotides in one step directly from nucleosides by means of phosphorylation and subsequent condensation. However, the yield is lower than when starting from nucleotides. The direct one-step preparation is of interest in connection with our subsequent discussion of the possible origin of polynucleotides in the course of terrestrial evolution.

Example: Preparation of Polyadenylic Acid from 2'- and 3'-Monophosphates

Adenylic acid (350 mg.) was mixed with polyphosphate ester (8 g.) and heated for 18 hours in a rotating flask which was suhmerged in an oil bath of 55 °C. After cooling, the mixture was dissolved in water (50 ml.) and dialyzed against water containing $NaHCO_3$ for a period of four days in order to remove the orthophosphate and the low molecular weight oligonucleotides. Polyadenylic acid was obtained in the form of a white powder after freeze-drying the solution. Yield: approxymately 20 %.

The Origin of Systems Capable of Self-Reproduction

Taken together, our experiments have shown that the most important biological macromolecules can be prepared in simple fashion with the aid of polyphosphate ester. Protein-like polypeptides are obtained from amino acids, polysaccharides from sugars, nucleosides from sugars and heterocyclic bases; the nucleosides in turn can be converted to nucleotides and ultimately into nucleic acids by continued reaction with polyphosphate ester. The simple way in which these compounds are formed suggests the possibility that polyphosphate esters may have had a role in the formation of macromolecules in the course of terrestial evolution. This suggestion derives support from the fact that polyphosphate esters continue to be of fundamental significance in relation to the metabolism of organisms living today. A number of primitive micro-organisms contain large quantities of inorganic polyphosphates which can be incorporated into organic compounds as needed. At the beginning of this paper we alluded to the role played by ATP and similar polyphosphates in plant and animal metabolism. For this reason *Schramm* [14] suggested some time ago that polyphosphates or their derivatives may have played a role when living organisms or their precursors originated, and that their role continued to become more specific as life continued to evolve.

This hypothesis is in accord with geological fact. It is likely that in the sterile period, *i.e.* before the origin of life, the surface of the earth was rich in all kinds of organic materials which may have originated as a result of electrical discharges or ultraviolet irradiation [15, 16]. This organic material may have contained heterocyclic bases. *Bredereck* [17] has observed that adenine forms in surprisingly large quantities when certain simple nitriles are heated. *Oro* [18] has also noted that adenine is formed when aqueous solutions of ammonium cyanide are heated. At temperatures above 300 °C. phosphoric acid occurs only in the forms of polyphosphate; it can therefore be assumed that when the crust of the earth began to cool down a supply of polyphosphates, and reactive phosphorus oxides, was available which may have reacted with alkoxy compounds to form phosphate esters. The latter in turn may have reacted with amino acids, sugars and heterocyclic bases, causing them to polymerize. The model experiments have made it clear that the pyranose hexoses polymerize preferably to form stable polysaccharides, compounds which even in present-day organisms constitute important structural elements, as for example cellulose .The furanose pentoses form unstable polysaccharides, but react readily with heterocyclic bases to form nucleosides.

However, these polymerizations lead to only random arrangements of the monomers in the macromolecules, which consequently are incapable of specific functions. It is extremely unlikely that monomers arrange by chance to form even the most primitive organism imaginable. Such an event can hardly have occurred within the finite time that the earth has existed. It must be emphasized that the formation of randomly arranged proteins and nucleic acids can in no way be considered an explanation of the origin of life.

[12] *A. M. Michelson*, J. chem. Soc. (London) 1371 (1959).

[13] *G. Felsenfeld* and *A. Rich*, Biochim. biophysica Acta *26*, 457 (1957).

[14] *G. Schramm* in: Proceedings of the International Symposium on the Origin of Life on Earth, held in Moscow. Pergamon Press, London, New York 1960, p. 216.

[15] *L. Roka:* Vermutungen über die Entstehung des Lebens. Mosbacher Kolloquium über Vergleichend Biochemische Fragen. Springer-Verlag, Heidelberg 1956.

[16] *A. J. Oparin:* Die Entstehung des Lebens auf der Erde. Verlag Volk und Wissen, Berlin/Leipzig 1947.

[17] *H. Bredereck, F. Effenberger*, and *G. Rainer*, Angew. Chem. *73*, 63 (1961).

[18] *J. Oro*, Fed. Proc. *20*, 352 (1961).

The formation of biological macromolecules with a specific sequence of building units can be imagined if it is assumed that simple molecules underwent a stepwise development that gradually made them capable of increasingly complex performance. Biological development presupposes, however, the existence of mechanisms capable of self-duplication, *i.e.* systems that give rise to offspring. According to *Darwin*'s theory of evolution by mutation and selection, those molecular systems capable of self-duplication would predominate that can multiply most readily and most precisely. Small changes that the system undergoes in the course of multiplication could then lead to its continued improvement.

What are the minimum conditions for the development of a self-reproducing system? This question can be answered best by considering the molecular processes taking place in organisms living at the present time. Nucleic acids are known to play a commanding role. With the utmost simplification, the self-reproduction of organisms can be reduced to the following principle: Using chemical and steric arguments *Watson* and *Crick* [19] have shown that in molecules consisting of a chain of nucleotides, pairing can occur only if the nucleotide chain is complementary. Subsequent research has demonstrated that one strand of nucleotides serves as a matrix for a complementary strand, which in turn is the matrix for the formation of the original strand. In other words, matrix M catalyzes the formation of matrix M_C, which in turn catalyzes the formation of M (Diagram 4).

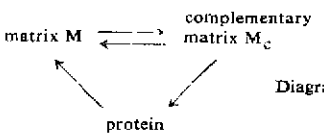


Diagram 4

However, these matrices undoubtedly also serve purposes other than self-duplication; indeed they determine in a quite complicated fashion which will not be discussed here, the structure of proteins, which in turn influence and control the self-duplication of the nucleotide chains by acting as enzymes.

We have found that we can demonstrate the existence of the principle of mutually and catalytically interacting matrices, even under the conditions of non-enzymatic synthesis of nucleic acids. We have studied the polymerization of uridylic acid in the presence, and absence, of its complementary polyadenylic acid. Figure 2 shows that the polymerization of uridylic acid was accelerated more than tenfold by polyadenylic acid, whereas polyuridylic acid had no such effect. This means that polymerization to polynucleotide chains is favored

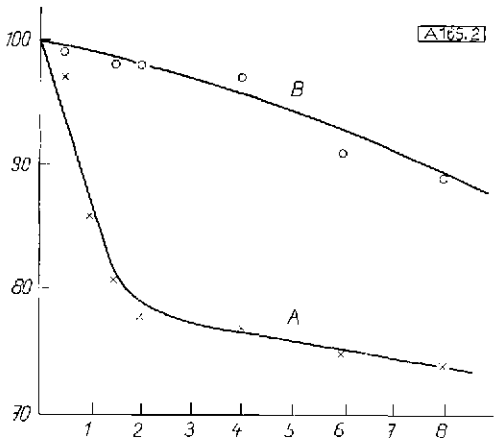


Fig. 2. Polymerization of Uridine Monophosphate in the Presence (A) and in the Absence (B), of Polyadenylic acid. (The decrease of free uridine monophosphate was measured chromatographically).
Abscissa: Time [hours]
Ordinate: % Free Uridine Monophosphate (referred to the amount of starting material)

by complementary strands. If, therefore, in the course of the evolution of the earth the formation of a nucleotide strand carried certain selective advantages, then these in turn favored the formation of the complementary strand, which again speeded up the formation of the original strand. This then indicates how such a system can reach increasing perfection. We have also observed that the addition of a synthetic polypeptide, *i.e.* of polyarginine, favors the formation of a polynucleotide chain. Further study is needed in order to determine whether nucleotide matrices can speed up the non-enzymatic synthesis of such polypeptides. If this is the case, the cycle of self-duplicating and mutually stimulating catalysts would be closed; this would then make it possible to postulate a cycle which would continue to improve as a result of small, chance alterations. The basic idea is, therefore, that small chance alterations in one catalyst determine the formation of a second, dependent catalyst which in turn affects the formation of the first, now improved catalyst. What path could lead from these molecular systems to the origin of life shall not be discussed here.

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[19] *J. D. Watson* and *F. C. C. Crick*, Nature (London) *171*, 737, 964 (1953).

Novel Methods of Preparative Organic Chemistry IV

The α-Addition of Immonium Ions and Anions to Isonitriles Accompanied by Secondary Reactions

BY DOZ. DR. IVAR UGI [1]

INSTITUT FÜR ORGANISCHE CHEMIE DER UNIVERSITÄT MÜNCHEN

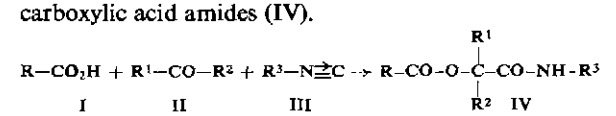
The α-addition of immonium ions and anions (OH^-, SeH^-, $S_2O_3^{2-}$, N_3^- NCO^-, NCS^-, $R-CO_2^-$, $RO-CO_2^-$) to isonitriles, accompanied by secondary reactions, provides a means for the one-stage synthesis of organic nitrogen compounds starting with two to five different components. Thus, by the condensations of amines (ammonia, primary, and secondary aliphatic and aromatic amines, hydrazines) and aldehydes or ketones with isonitriles and acids, a number of α-aminocarboxylic acid amides, thioamides, selenoamides, 1,5-disubstituted tetrazoles, hydantoin imides, thiohydantoin imides, α-acylamino carboxylic acid amides, oligopeptide derivatives, β-lactams, derivatives of penicillanic acid, urethanes, diacylimides, and various hydrazine derivatives, can be prepared. The reactions are easily carried out and take place under mild conditions. Yields of more than 90 % are frequently encountered.

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   1.2. Reactions of Isonitriles with Diphenylketene and Carboxylic Acids
   1.3. Formation of 1,5-Disubstituted Tetrazoles from Isonitriles, Carbonyl Compounds and Hydrazoic Acid
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1. α-Additions to Isonitriles Accompanied by Rearrangements

1.1. Passerini Reaction

Passerini [2] discovered in the reaction between carboxylic acids and carbonyl compounds with isonitriles, an elegant and generally applicable synthesis of α-acyloxycarboxylic acid amides (IV).



I II III IV

[1] The author advanced this synthetic principle in several lectures in the period from February 1960 to February 1961.

[2] *M. Passerini*, Gazz. chim. ital. *61*, 964 (1931) and preceeding communications.

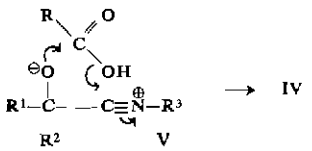
Had *Passerini* been conversant with present day views on reaction mechanisms while studying the reaction which now bears his name, he would probably have added ammonia or the primary amines, to his three starting materials and thereby discovered the α-amino alkylation of isonitriles and acids [3].

Passerini postulated that a half-acetal type compound from I+II is an intermediate in the formation of structure IV. About twenty years later, *Dewar* [4] reasoned that the reaction proceeds via the formation of a polar adduct from II+III, which then reacts with the acid through a multiple-

[3] This is a more convenient, though not completely accurate term for the "α-addition of immonium ions and anions to isonitriles accompanied by secondary reactions."

[4] *M. J. S. Dewar:* Electronic Theory of Organic Chemistry. Clarendon Press, Oxford 1949, p. 116.

center process (V) to yield IV. This conception was elaborated by *Baker* and *Stanonis* [5]. They concluded from the observed third-order kinetics that the addition II + III is a mobile equilibrium and that the step described by V is rate-determining.

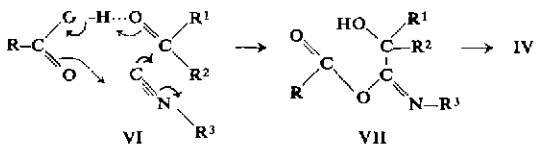


V

IV

However, the empirical data do not lend plausibility to such a mechanism. *Passerini*'s components react faster and result in better yields in aprotic, nonpolar solvents than in highly polar ones, which tend to compete for hydrogen bonds. This fact is difficult to explain by a reaction sequence in which an extremely polar intermediate plays a dominant role. It is also not clear why an intermediate nitrilium-alkoxide zwitterion should react slowly with acids according to V, instead of rapidly forming VII.

The α-addition (VI) of the hydrogen-bonded adduct of the carboxylic acid and the carbonyl compound to the isonitrile, accompanied by rearrangement of the α-adduct (VII, cf. XIVg) [6b] seems however to be a satisfactory mechanism. It accounts for all observations concerning the Passerini reaction and agrees with the well-established tendency of isonitriles to undergo α-additions [7].



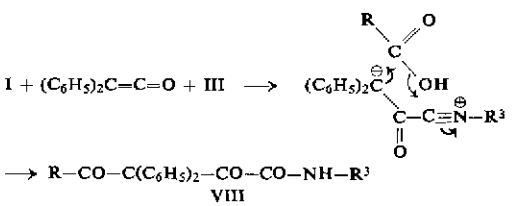
VI

VII

IV

1.2. Reactions of Isonitriles with Diphenylketene and Carboxylic Acids

The formation of α,γ-diketocarboxylic acid amides (VIII) [8a] from diphenyl ketene, carboxylic acids and isonitriles might be accounted for by a mechanism similar to V.

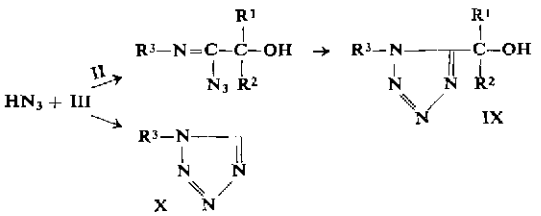


VIII

1.3. Formation of 1,5-Disubstituted Tetrazoles from Isonitriles, Carbonyl Compounds and Hydrazoic Acid

If the Passerini reaction is considered as an α-addition accompanied by rearrangement, it may be expected that other suitable acids would react in an analogous manner with isonitriles and carbonyl compounds. The only acids which can replace the carboxylic acid component in the Passerini reaction are those which react faster with the combination of an isonitrile and a carbonyl compound than with an isonitrile alone.

Hydrazoic acid fits the above condition. 1,5-Disubstituted tetrazoles IX (*e.g.* IXa and b from isobutyraldehyde or chloral respectively) result from the combination of reactive aldehydes or ketones and isonitriles with hydrazoic acid [6b]. With less reactive carbonyl compounds, the formation of 1-substituted tetrazoles (X) is a competing reaction [9]. This side-reaction does not take place, however, when aluminum azide is the acid component [6b].



IX

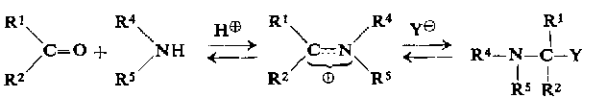
X

IXa: R^1 = H– R^2 = iso-C_3H_7– R^3 = cyclo-C_6H_{11}– (85 %)
b: H– CCl_3– *p*-$(C_2H_5)_2N$-C_6H_4– (95 %)

1.4. Immonium Ions and Anions as Partners in α-Additions to Isonitriles

1.41. Immonium Ions

Immonium ions (XII) [10], which are formed from carbonyl compounds and amines or their condensation products, in solutions of suitable acidity, are recognized as the reactive intermediates in α-amino alkylation reactions such as the Mannich reaction [11, 12], the Strecker synthesis [12], and the Asinger condensation [12, 13]. Together with some di- and tri-arylmethyl



II XI XII XIIa

cations, pyrylium ions and the tropylium ion, they are among the few reactive species with carbonium ion character which can exist at low acidity.

Immonium ions in combination with suitable anions are ideal reaction partners for the acid-sensitive isonitriles, which in most cases react by electrophilic α-additions [7].

1.42. Anions

Only anion components which react reversibly with immonium ions (XII ⇌ XIIa) are suitable. As α-amino alkylations take place in solutions of relatively low

[5] *R. H. Baker* and *D. Stanonis*, J. Amer. chem. Soc. *73*, 699 (1951) and preceeding communications.

[6] *I. Ugi* and *R. Meyr*, [a] Angew. Chem. *70*, 702 (1958); Chem. Ber. *93*, 239 (1960); [b] Chem. Ber. *94*, 2229 (1961).

[7] Review articles: *V. Migrdichian:* The Chemistry of Cyanogen Compounds. Reinhold Publ. Corp., New York 1947, p. 393; *P. Kurtz* in *Houben-Weyl:* Methoden der Organischen Chemie. Georg Thieme, Stuttgart 1952, Vol. 8, p. 351; *E. Jungermann* and *F. W. Smith*, J. Amer. Oil Chemists' Soc. *36*, 388 (1959); *I. Ugi* and *U. Fetzer*, Chem. Ber. *94*, 1116, 2239 (1961).

[8] *I. Ugi* and *K. Rosendahl*, [a] Chem. Ber. *94*, 2233 (1961); [b] unpublished results; [c] Angew. Chem. *73*, 656 (1961).

[9] *E. Oliveri-Mandala* and *B. Alagna*, Gazz. chim. ital. *40*, II, 441 (1910).

[10] With regard to their chemistry, one can also call immonium ions α-aminoalkyl ions. This would provide a rational basis for nomenclature. For example, the immonium ion which results from benzylmethylketone and benzylamine by adding a proton would be the called 1-phenyl-2-benzylamino-2-propyl cation.

[11] Review articles: *F. F. Blicke*, Org. Reactions *1*, 303 (1942); *E. R. Alexander* and *E. J. Underhill*, J. Amer. chem. Soc. *71*, 4014 (1949); Monograph: *B. Reichert:* Die Mannich-Reaktion. Springer, Berlin 1959; *T. F. Cummings* and *J. R. Skelton*, J. org. Chemistry *25*, 419 (1960).

[12] Monograph: *H. Hellmann* and *G. Opitz:* α-Aminoalkylierung. Verlag Chemie, Weinheim 1960.

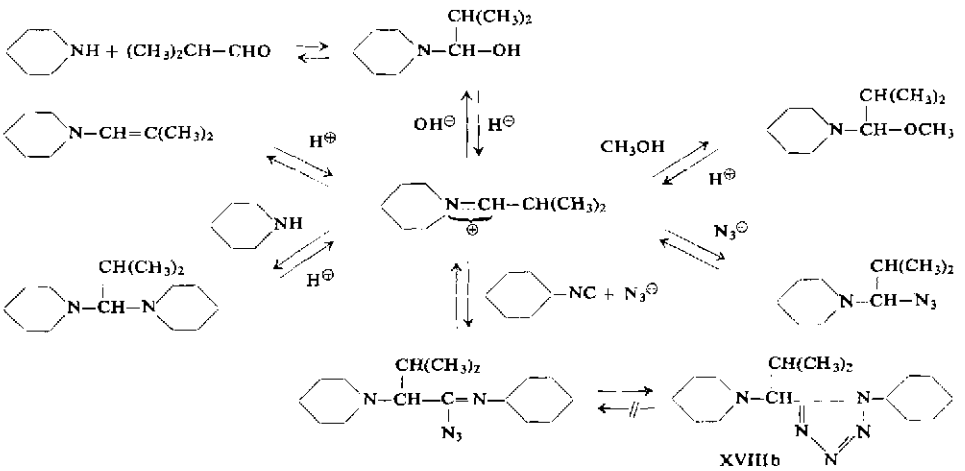
[13] Review article: *F. Asinger* and *M. Thiel*, Angew. Chem. *70*, 667 (1958).

acidity, the choice of anions is not limited by the affinity of the acid to the isonitrile component [6b]. OH^-, SeH^-, $S_2O_3^{2-}$, N_3^-, NCO^-, NCS^-, $R-CO_2^-$, and $RO-CO_2^-$ are anions which investigation has shown to fulfil the requirements specified. These anions can be divided into two classes on the basis of the observed secondary reactions of their α-adducts (see Sections 1.441 and 1.442). Further anions for which reactions of the same kind seem possible are TeH^-, NO_2^-, NO_3^-, $NCSe^-$, $RN-NO_2$, $RN-CN^-$, $R-COS^-$, $R-CS_2^-$, and $R-SO_2NH^-$, as well as the anions of diacyl imides, hydantoins, acylated sulfonamides and acids derived from various oxidation stages of sulfur and phosphorus.

Formulae XIVa–XXIIc and Section 1.41–1.42) the α-adduct rearranges into a stable α-aminocarboxylic acid derivative. In such a case the practically irreversible formation of the end-products supplies the driving force for the overall reaction and ensures a high yield of a single product.

A uniform product is obtained from the components II, III, XI, and HY if the secondary reaction of the α-adduct is the only, or by far the fastest, irreversible reaction in the system. Frequently this is the case only at high concentrations. At low concentrations the disparity in the rates of the main- and of the irreversible side-reactions is not as favorable.

The condensation of cyclohexyl isocyanide with isobutyraldehyde, piperidine and hydrazoic acid in benzene/methanol to

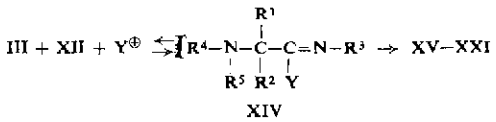


give compound XVIIIb (see also Sections 2.21 and 2.22) is mentioned here in order to show that the irreversible secondary reaction enforces the formation of a single end-product from a multiple component system of coupled equilibria [11, 12, 14a].

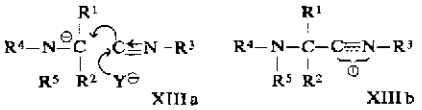
The irreversible secondary reactions make possible the use of even those combinations of amine and carbonyl components which, owing to the unfavorable position of the equilibria II + XI ⇌ XII ⇌ XIIa (see also the above formulae), react unsatisfactorily in other α-amino alkylations [12] (cf. XVIIIh–j; XIXb–l, XXa–e, XXIa–e, o–s, XXIXc–k, and XLVIIa–Lk).

1.43. The α-Addition Step

The immonium ion, the anion Y^- and the isonitrile combine to form the α-adduct XIV. This can take place either by a



direct union of the three reactants in a one-step three-center process (XIIIa) or by a two-step mechanism involving a nitrilium ion intermediate (XIIIb).



With attention to the preponderant influence of the anion component on both rate and yield (see Sections 2.11–3.3) the tendency is towards the one-step mechanism rather than the two-step alternative, in which the second step or the subsequent rearrangement (cf. XIVa–g) would determine the rate. A direct union of III, XII, and Y^- seems statistically improbable. However it must be noted hat the simultaneous collision of three reacting species is favored by the attraction of the opposite charges of XII and Y^-, which, indeed, are present as an ion-pair in equilibrium with XIIa. Furthermore, the high dipole moment of the isonitrile group (ca. 3.5 D [14]) is also a conducive factor.

1.44. The Secondary Reaction

The behavior of the α-adduct (XIV) is very dependent upon the character of the anion component Y^-. When the anion has certain structural characteristics (see

1.441. The Formation of Non-Acylated Derivatives of α-Amino Acids

The α-adducts (XIVa–d) from isonitriles, immonium ions and hydroxyl-, hydrogen selenide-, thiosulfate- or azide-ions stabilize themselves by secondary reactions in which the nitrogen atom derived from the amine component does not take part. Therefore combinations of primary or secondary amines with these anions lead to analogous reactions.

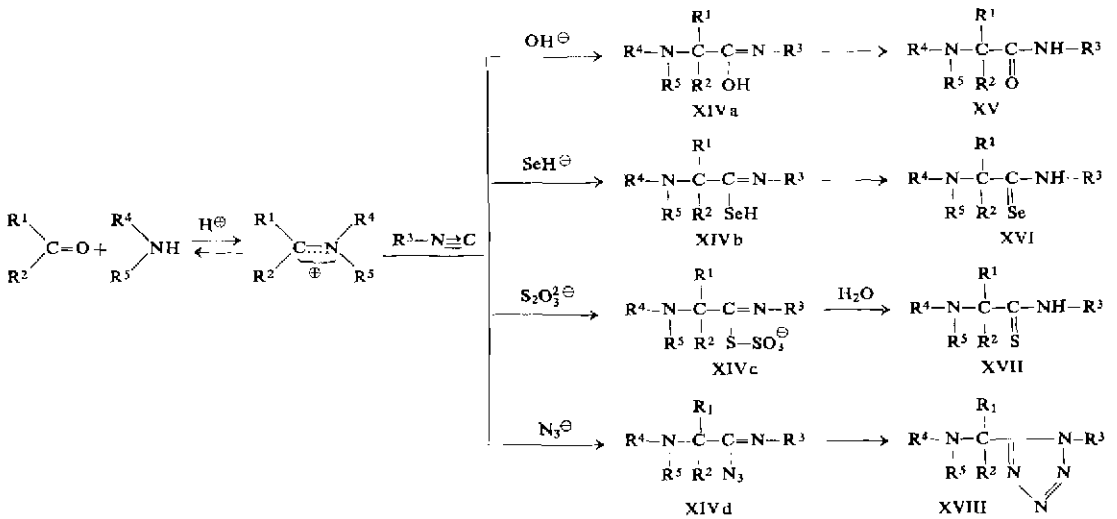
α-Adducts (XIVa and b), resulting from hydroxyl- or hydrogen selenide ions, are transformed by a proton shift into the stable end products (XV and XVI). Thiosulfate yields α-adducts (XIVc) which are stabilized in aqueous solutions by hydrolysis. 1,5-Disubstituted tetrazoles (XIVd) are produced by spontaneous cyclization of the α-adduct from the azide.

[14] Review article: *N. V. Sidgwick*, Chem. Rev. *9*, 77 (1931).

[14a] *G. Opitz* and *W. Merz* report on α-aminoalkyl azides, their reactions with isonitriles and on reactions analogous to those described here in Section 2.45 (Liebigs Ann. Chem. (1962), in press).

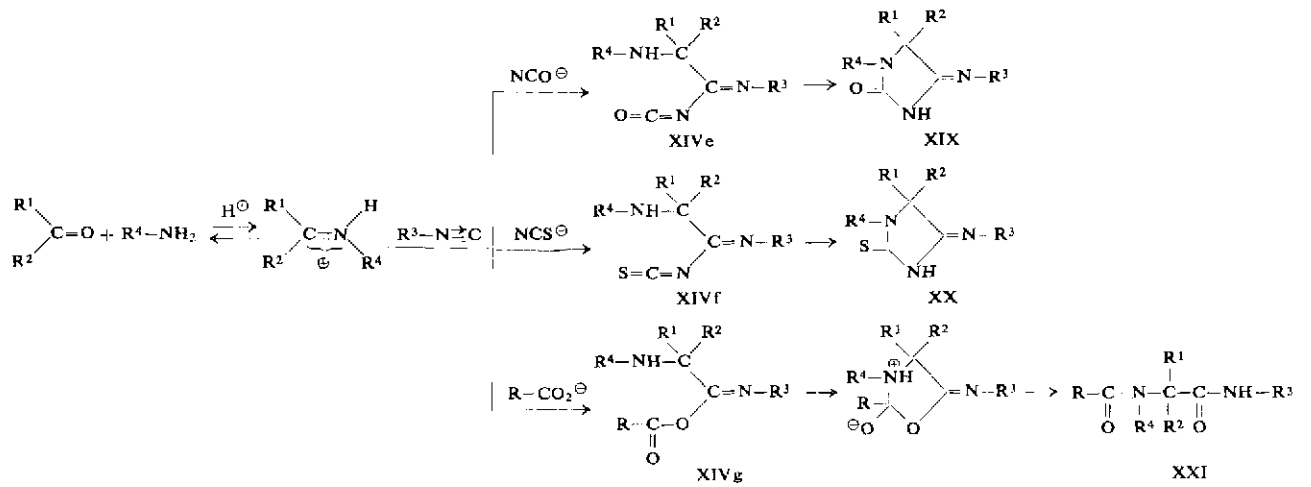
1.442. *Acylation Reactions*

Cyanate, thiocyanate, as well as the anions of carboxylic and methylcarbonic acids form intermediates (XIVe–g) which undergo intramolecular acylation. The nitrogen atom of the α-aminoalkyl group in the α-adduct is acylated by means of a cyclic mechanism provided that a N–H bond is available (see also Section 2.45).

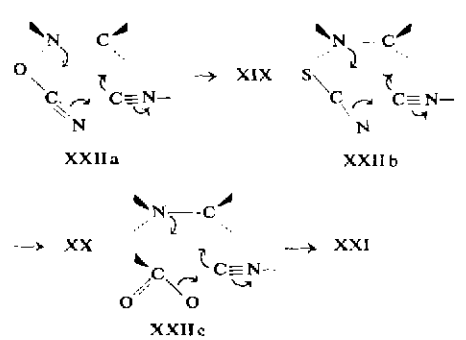


The hydantoin- and thiohydantoin-imides (XIX and XX) are formed in this manner.

The α-adducts (XIVg) of carboxylic acids are converted by intramolecular acyl migration to the α-acylamino carbonic acid amides (XXI). If acylating α-adducts were present during the course of the reaction in appreciable concentration, one would expect the α-adducts to



acylate the amine component, particularly when the latter is present in excess and the carbonyl component is a ketone. As this complication has never been observed, it may be concluded that the intramolecular secondary reaction takes place very quickly. It is possible that in some cases the formation of the end-product from the immonium ion, anion and isonitrile components proceeds by an overall one-step mechanism, such as XXIIa–c, which synchronizes with the addition step.



1.45. General Remarks

The mechanism outlined in sections 1.43 and 1.44 accounts satisfactorily for the experimental facts and can be assumed to approximate closely to the course of the reactions, although no conclusive proof is, as yet, at hand. A more specific discussion of the mechanism must be postponed until sufficient kinetic data are available.

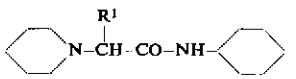
2. Syntheses of α-Amino Acid Derivatives

The α-additions of immonium ions and anions to isonitriles accompanied by secondary reactions are, in most cases, easy to conduct (see Sections 4.1–4.2): A concentrated solution of an amine, a carbonyl compound, an isonitrile and an acid is allowed to stand at 0–20 °C. The end of the reaction is indicated by the disappearance of the intense odor which characterizes isonitriles. The α-amino acid derivative formed either crystallizes out during the course of the reaction or is obtained by evaporation.

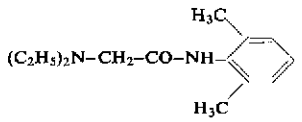
2.1. α-Amino Acid Amides, -Thioamides and -Selenoamides

2.11. Amides

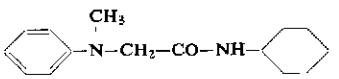
Isonitriles condense with aldehydes and primary or secondary amines in aqueous methanol to form α-amino acid amides (XV) [15a, b]. The water in the solvent supplies the anion component for the α-addition. The syntheses of XVa or b from piperidine, cyclohexyl isocyanide, and formaldehyde or isobutyraldehyde, of XVc from diethylamine, formaldehyde and 2,6-dimethylphenyl isocyanide, and of XVd from methylaniline, formaldehyde and cyclohexyl isocyanide serve as examples for the preparation of simple α-amino carboxylic acid amides (XV).



XVa: R^1 = H– (78 %)
b: iso-C_3H_7– (60 %)

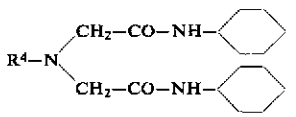


XVc (80 %)

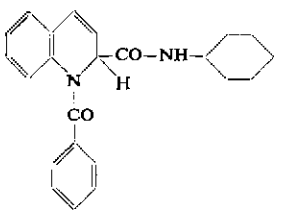


XVd (41 %)

Compounds XVe and f result from cyclohexyl isocyanide, formaldehyde and isopropyl- or n-butylamine. Sometimes primary amines react twice. This double reaction is most pronounced when the other components are in excess.



XVe: R^4 = iso-C_3H_7– (41 %)
f: n-C_4H_9– (52 %)

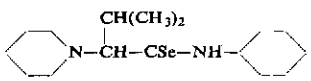


XVg (24 %)

The formation of XVg from benzoyl chloride, quinoline, cyclohexyl isocyanide, and water [16a], in which the benzoylquinolinium ion [16b, 17] is the electrophilic intermediate, also belongs to this class of reactions.

2.12. Selenoamides

The hydrogen selenide anion reacts as an α-addition partner in a manner analogous to the reaction of hydroxide ion. The reaction between piperidine hydrochloride, isobutyraldehyde, cyclohexyl isocyanide, and sodium selenide, serves to illustrate the route [15a] by which XVIa is obtained.



XVIa (51 %; cf. 4.2)

[15] *I. Ugi* and *C. Steinbrückner*, [a] Angew. Chem. *72*, 267 (1960); [b] Chem. Ber. *94*, 734 (1961); [c] Chem. Ber. *94*, 2802 (1961); [d] *C. Steinbrückner*, Ph. D.-Thesis, Univ. München, 1961.

[16] *I. Ugi* and *F. Beck*, [a] unpublished results, [b] Chem. Ber. *94*, 1839 (1961); *M. L. Bender*, Chem. Reviews *60*, 53 (1960).

[17] Cf. *A. Reissert*, Ber. dtsch. chem. Ges. *38*, 1603, 3415 [1905]; Review article *O. Bayer* in *Houben-Weyl*: Methoden der Organischen Chemie. G. Thieme, Stuttgart 1954, Vol. 7/1, p. 291.

2.13. Thioamides

Instead of hydrogen sulfide, which has a high tendency to react directly with immonium ions [12], thiosulfate must be used for the synthesis of α-aminocarboxylic acid thioamides. Thus the combination of dimethylamine hydrochloride, formaldehyde, sodium thiosulfate, and cyclohexyl or benzyl isocyanide in aqueous acetone yields compounds XVIIa and b [15a], respectively.

$(CH_3)_2N-CH_2-CS-NH-R^3$

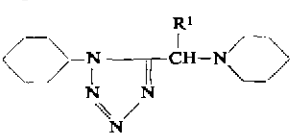
XVIIa: R^3 = cyclo-C_6H_{11}– (86 %; cf. 4.1)
b: $C_6H_5-CH_2$– (82 %)

2.2. 1,5-Disubstituted Tetrazoles [15b]

The formation of 1,5-disubstituted tetrazoles (XVIII) from immonium ions, isonitriles, and azide is reminiscent of the tetrazole synthesis of *Oliveri-Mandala* [9], in which the addition of a proton and an azide ion to an isonitrile is the primary step. Owing to the easy isolation and purification of 1,5-disubstituted tetrazoles and the ready availability of cyclohexyl isocyanide [6a], the formation of 1-cyclohexyl-5-aminoalkyltetrazoles XVIII a–n; see Tables 1 and 2) was studied in order to determine the influence on the rate and yield of both the constitution and origin (see Sections 2.21 and 2.22) of the immonium ions.

2.21. Immonium Ions Generated from Amines and Carbonyl Compounds

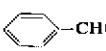
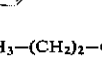
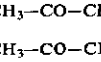
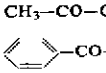
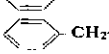
Highly reactive combinations of amine and carbonyl components, for example, piperidine in the presence of formaldehyde, isobutyraldehyde or benzaldehyde, react with cyclohexyl isocyanide and hydrazoic acid even in aqueous acetone, forming compounds XVIIIa–c.



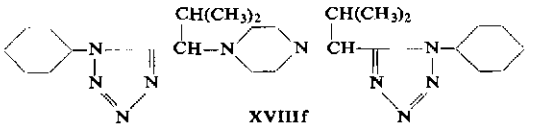
XVIIIa: R^1 = H– (92 %)
b: iso-C_3H_7– (71 %)
c: C_6H_5– (34 %)

Generally, however, the combination of amines, carbonyl compounds, isonitriles, and hydrazoic acid requires a non-aqueous solvent (see Table 1); this is probably attributable to a more favorable position of the equilibrium II + XI + H^+ ⇌ XII + H_2O in the absence of water (cf. Section 1.44).

Table 1. Preparation of 1-cyclohexyl-5-aminoalkyltetrazoles (XVIII b–j) from carbonyl compounds (II), amines (XI), cyclohexyl isocyanide and hydrazoic acid in benzene/methanol at 0–20 °C. [15b].

No.	R^1-CO-R^2 (II)	R^4-NH-R^5 (XI)	Yield [%]	Time [hrs.]
XVIIIb	$(CH_3)_2CH-CHO$		91	0.3
c			90	3
d	$CH_3-(CH_2)_2-CHO$		90	1
e	$(CH_3)_2CH-CHO$		64 (cf. 4.3)	2
f	$(CH_3)_2CH-CHO$		87	0.15
g	$CH_3-CO-CH_3$		93	120
h	$CH_3-CO-CH_3$		90 (cf. 4.5)	300
i			60	500
j			69	72

Owing to the bifunctionality of the amine component, the condensation of piperazine with isobutyraldehyde, cyclohexyl isocyanide, and hydrazoic acid produces compound XVIIIf.

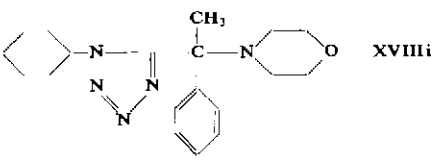


XVIIIf

2.22. Immonium Ions Generated from Schiff Bases, Enamines or Aminals [*]

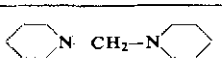
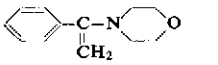
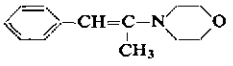
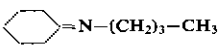
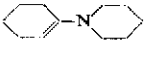
As the overall rate of the α-aminoalkylation of isonitriles and acids depends upon the rate of formation of immonium ions or their equilibrium concentration, it is frequently advantageous to replace the amine and carbonyl components, especially the more unreactive combinations, with condensation products such as Schiff bases, enamines or aminals. Thereby, the union of the amine and carbonyl components, which often is slow or impeded by an unfavorable position of the equilibria involved (see Table 2), is by-passed.

Whereas acetophenone, morpholine, cyclohexyl isocyanide, and hydrazoic acid (the concentration of all the components being approximately 1 mole/litre in benzene/methanol) combine at 20–25 °C. during the course of three weeks to form 68 % of crude product (XVIIIi). The same product results from α-morpholinostyrene, hydrazoic acid, and cyclohexyl isocyanide under similar reaction conditions, but at 0–10 °C. in 15 minutes and in 94 % yield.



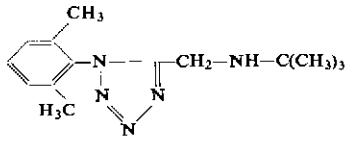
XVIIIi

Table 2. Preparation of 1-cyclohexyl-5-aminoalkyltetrazoles (XVIII) from cyclohexyl isocyanide, hydrazoic acid and Schiff bases, enamines or aminals in benzene/methanol at 0–20 °C. [15b].

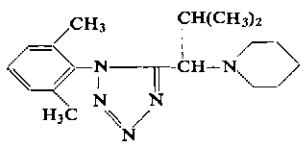
No.	Immonium ion from	Yield [%]	Time [min.]
XVIIIa		92	10
b	$(CH_3)_2C{=}CH{-}N$	93	15
i		86	15
j		87	120
k	$(CH_3)_2CH{-}CH{=}N{-}(CH_2)_2{-}CH_3$	73	30
l	$(CH_3)_2C{=}N{-}CH(CH_3)_2$	82	500
m		92	10
n		76	10

The aforementioned reactions of cyclohexyl isocyanide serve as a guide to syntheses involving other isonitriles. This also holds true (to a certain degree) for other conversions which do not involve azides, but some other anion component.

The structure of the isonitrile component has little influence on the course of the condensations. For example, 2,6-dimethylphenyl isocyanide, a comparatively inert isonitrile, condenses no less smoothly than cyclohexyl isocyanide with hydrazoic acid and formaldehyde-t.-butyl imide, and also with piperidine and isobutyraldehyde, forming compounds XVIIIo and p respectively.



XVIIIo (85 %)



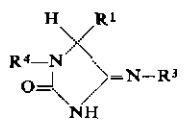
XVIIIp (95 %; cf. 4.4)

[*] Aminals are condensation products from two moles of an amine and one mole of a carbonyl compound (resembling acetals).

2.3. Hydantoin Derivatives

2.31. Hydantoin Imides

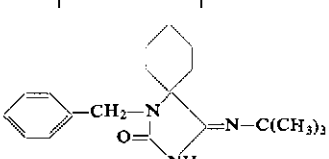
Hydantoin-4-imides, such as compounds XIX a–o, are easily obtained from an α-addition of cyanate and immonium ions to isonitriles. Upon the addition of ammonium chloride, or the hydrochloride of a primary amine, to a solution of potassium cyanate, a reactive carbonyl compound and an isonitrile in aqueous methanol, a crystalline precipitate of a hydantoin-4-imide is formed [18]. In this manner compounds XIXa–l (Table 3) are obtained from aldehydes; compound XIXm is the result of the condensation of t.-butyl isocyanide with cyclohexanone, benzylamine hydrochloride and potassium cyanate. Ethylenediamine hydrochloride reacts bifunctionally with isobutyraldehyde, t.-butyl isocyanide and potassium cyanate to form compound XIXn.



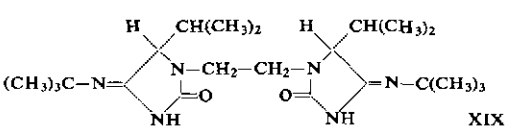
XIX a–l

Table 3. Preparation of hydantoin-4-imides (XIX) from aldehydes, isonitriles, potassium cyanate and ammonium chloride or the hydrochlorides of primary amines in aqueous methanol or glycol at 0–20 °C.

No.	R^1	R^2	R^3	Yield [%]
XIXa	H–	$C_6H_5{-}CH_2{-}$	$C_6H_5{-}CH_2{-}$	74
b	n-C_3H_7–	t.-C_4H_9–	CH_3–	68
c	iso-C_3H_7–	t.-C_4H_9–	H–	45
d	iso-C_3H_7–	t.-C_4H_9–	t.-C_4H_9–	87
e	iso-C_3H_7–	t.-C_4H_9–	C_6H_5–	83
f	iso-C_3H_7–	t.-C_4H_9–	2-$CH_3{-}C_6H_4$–	87 (cf. 4.6)
g	iso-C_3H_7–	t.-C_4H_9–	2,6-$(CH_3)_2C_6H_3$–	89
h	iso-C_3H_7–	cyclo-C_6H_{11}–	n-C_4H_9–	84 [15a]
i	iso-C_4H_9–	t.-C_4H_9–	iso-C_3H_7–	94
j	iso-C_4H_9–	$C_6H_5{-}CH_2$–	4-$NO_2{-}C_6H_4$–	33
k	C_6H_5–	cyclo-C_6H_{11}–	n-C_4H_9–	49
l	C_6H_5–	cyclo-C_6H_{11}–	C_6H_5–	86



XIXm (47 %)

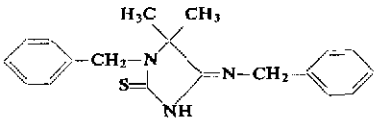


XIXn (71 %)

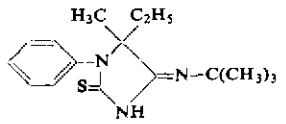
[18] *I. Ugi* and *K. Offermann*, unpublished results.

2.32. Thiohydantoin Imides

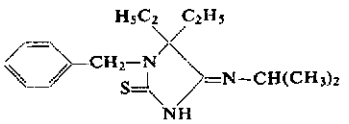
Primary amines, ketones, isonitriles, and thiocyanates can be converted to 2-thiohydantoin-4-imides, compounds XX a–e, in an analogous manner [8b].



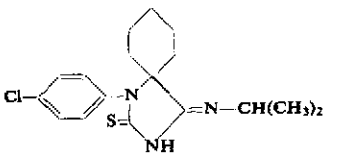
XXa (71 %)



XXb (79 %)

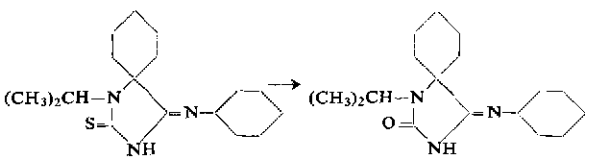


XXc (74 %)

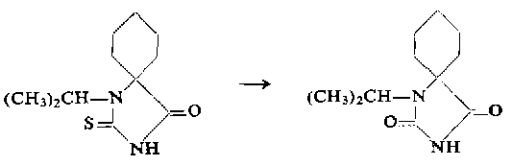


XXd (60 %)

Isopropylammonium thiocyanate condenses with cyclohexanone and cyclohexyl isocyanide to give compound XXe. This is oxidized by potassium permanganate in pyridine to compound XIXo, which can also be obtained according to Section 2.31. Potassium hydroxide in ethylene glycol at 170–180 °C. hydrolyzes compounds XXe and XIXo to XXIII and XXIV respectively. With Raney nickel in isopropanol, XXe can be desulfurized to 1-isopropyl-4-cyclohexylimino-5,5-pentamethylene-imidazoline. This can be hydrolyzed by hydrochloric acid to 1-isopropyl-5,5-pentamethylene-imidazolin-2-one and cyclohexylamine.

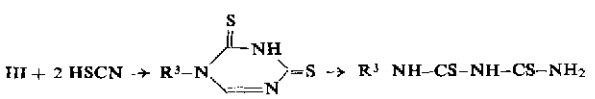


XXe (81 %; cf. 4.7) XIXo



XXIII XXIV

It is of parenthetical interest that isonitriles and thiocyanic acid also react. Triazine derivatives (XXVa) result [8c]; on alkaline hydrolysis these yield the dithiobiurets (XXVb).



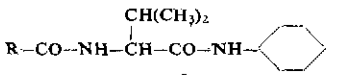
XXVa XXVb

2.4. Acylated α-Aminocarboxylic Acid Amides

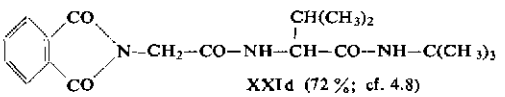
Carboxylic acids, carbonyl compounds and isonitriles, the components of the Passerini reaction, combine with ammonia or primary amines to form α-acylamino carboxylic acid amides (XXI). This reaction is closely related to the Passerini reaction both with respect to components and mechanism (see Section 1.1). With regard to the large number of reactive carboxylic acids and the variety of obtainable products, the α-addition of carboxylate and immonium ions to isonitriles accompanied by intramolecular acyl migration is the most important part of the condensation principle with which this article is concerned. The pronounced tendency of carboxylate ions to react with isonitriles and immonium ions is related ultimately to the energetic advantage of the formation of two amide groups.

2.41. Simple α-Acylaminocarboxylic Acid Amides

The use of ammonia as an amine component is successful only in combination with cyanate, thiocyanate, and carboxylate anions, since no definable products result with other anions. Carboxylate anions combine best with ammonia. For example, the α-acylaminocarboxylic acid amides (XXIa–d) are produced by the condensation of the ammonium salts of formic and acetic acids, or of acetyl- or phthalylglycine, with isobutyraldehyde and t.-butyl- or cyclohexyl isocyanide [15c].

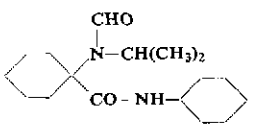


XXIa: R = H– (54 %)
b: CH_3– (52 %)
c: CH_3–CO–NH–CH_2– (40 %)



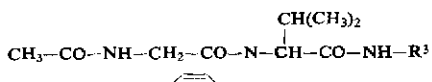
XXId (72 %; cf. 4.8)

When a primary amine is the amine component, the syntheses generally give excellent yields. Even α-acylaminocarboxylic acid amides which carry bulky groups, and therefore are synthesized only with difficulty by other methods, *e.g.* compound XXIe, are readily obtained [8b].



XXIe (87 %; cf. 4.9)

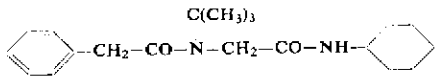
The yields arising from the combination of acetylglycine, benzylamine, isobutyraldehyde, and various isonitriles to give compounds XXIf–k [15c] emphasize the minor influence of the structure of the isonitrile component (see Section 2.22).



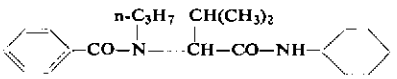
XXIf: R^3 = C_2H_5– (78 %)
g: iso-C_3H_7– (92 %)
h: n-C_4H_9– (85 %)
i: t.-C_4H_9– (94 %)
j: cyclo-C_6H_{11}– (88 %)
k: C_6H_5–CH_2– (95 %)

The synthesis of compounds XXI l–s from formaldehyde-t.-butylimine, isobutyraldehyde n-propylimine, benzaldehyde-cyclohexylimine, and cyclohexanone-n-

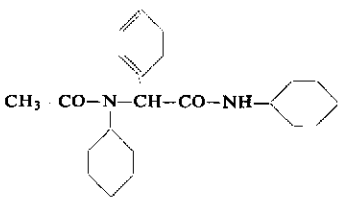
butylimine illustrate both the usefulness of aldimines and ketimines as condensation components, and the variety in structure of the carboxylate component.



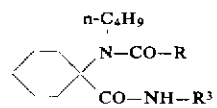
XXIl (72 %)



XXIm (80 %)



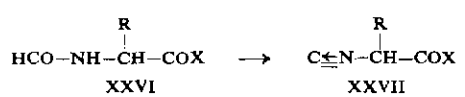
XXIn (78 %)



XXIo: R = $Cl-CH_2-$ R^3 = cyclo-$C_6H_{11}-$ (93 %)
p: CF_3- 2.6-$(CH_3)_2(C_6H_3)-$ (84 %)
q: $CHO-NH-CH_2-$ cyclo-$C_6H_{11}-$ (95 %)
r: $CHO-NH-CH_2-$ $(CH_3)_3C-$ (75 %)
s: $CH_3-CO-NH-CH(iso\text{-}C_3H_7)-$ cyclo-$C_6H_{11}-$ (91 %)

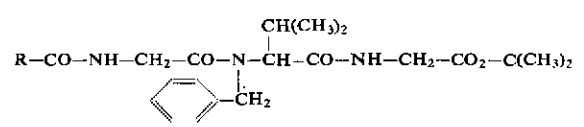
2.42. Peptide Derivatives

α-Formylaminocarboxylic acid derivatives, in which the –COX group in formula XXVI is an ester or substituted amide group, can be converted to isonitriles by means of phosgene in triethylamine [19].



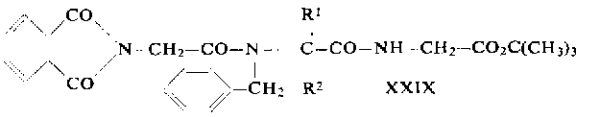
XXVI XXVII

The above-mentioned reaction makes possible simplified syntheses of oligopeptides. In contrast to established methods, it is now possible to form simultaneously two peptide links and one new amino acid unit by condensing an α-isocyanocarboxylic acid derivative with N-protected amino acids or peptides, carbonyl compounds and primary amines with a cleavable C–N bond. If the amine component is omitted depsipeptides result [20].



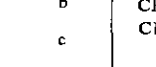
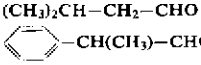
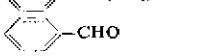
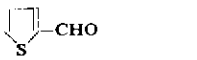
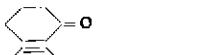
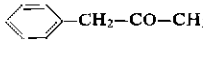
XXVIIIa: R = CH_3- (88 %)
b: CF_3- (87 %; cf. 4.10)

Compounds XXVIIIa and b are easily accessible from acetylglycine or trifluoroacetylglycine and benzylamine, isobutyraldehyde, and t.-butyl isocyanoacetate [15c]. The syntheses of compounds XXIXa–k from phthalylglycine, benzylamine, t.-butyl isocyanoacetate and aldehydes or ketones demonstrate the diversity of α-amino acids which can thus be employed as the "linkage units" in peptides (see Table 4).

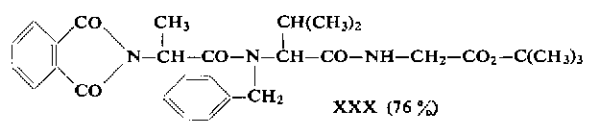


XXIX

Table 4. Preparation of substituted (*N*-Phthalylglycyl-*N*-benzyl)glycylglycine-t.-butyl ester (XXIX) from phthalylglycine, benzylamine, carbonyl compounds (II) and t.-butyl isocyano-acetate in methanol at approximately 20 °C. [15c].

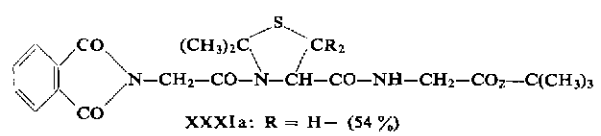
No.	R^1-CO-R^2 (II)	Yield [%]	Time [hrs.]
XXIXa	CH_2O	83 (cf. 4.11)	48
b	CH_3-CHO	73	5
c		67 (cf. 4.12)	3
d	$(CH_3)_2CH-CHO$	92	5
e	$CH_3-S-(CH_2)_2-CHO$	69	8
f	$(CH_3)_2CH-CH_2-CHO$	78	1.5
g		74	150
h		91	15
i		63	100
j		90	240
k [21]		91 (cf. 4.13)	70

In an analogous manner to the formation of compound XXIXd, compound XXX can be prepared from phthalyl-DL-alanine.



XXX (76 %)

The cysteine and penicillamine derivatives (XXXIa and b) [22] are readily available [18] from 2,2-dimethyl- or 2,2,5,5-tetramethyl-Δ^3-thiazolines [13], respectively.



XXXIa: R = H– (54 %)
b: CH_3- (74 %; cf. 4.14)

2.43. Asymmetrically Induced Syntheses

In the α-aminoalkylation of isonitriles and acids a new asymmetric center is formed from asymmetrically substituted carbonyl compounds (II, $R^1 \neq R^2$). Diastereoisomers are produced from optically active starting materials in a molar ratio of about 1:1. Racemic starting materials yield mixtures of more than two diastereoisomers. This makes difficult the synthesis of compounds with more than one asymmetric carbon atom, *e.g.* of optically active peptides.

In order to make possible the synthesis of optically active peptides (tripeptides as well as higher oligopeptides) two conditions must be fulfilled: it must be

[19] *I. Ugi, W. Betz, U. Fetzer*, and *K. Offermann*, Chem. Ber. *94*, 2814 (1961); see also [6a].

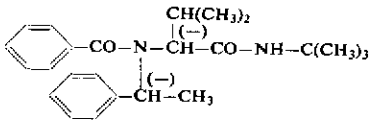
[20] *I. Ugi* and *U. Fetzer*, Angew. Chem. *73*, 621 (1961).

[21] As the reaction of benzyl methyl ketone, benzylamine and the two other components was not completed in four weeks, benzyl methyl ketone-benzylimine was used instead.

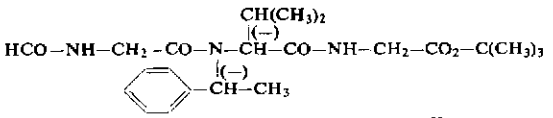
[22] *F. E. King, J. W. Clark-Lewis*, and *R. Wade*, J. chem. Soc. (London) *1957*, 880; *J. C. Sheehan* and *D. D. H. Yang*, J. Amer. chem. Soc. *80*, 1158 (1958).

possible to influence the steric course of the α-aminoalkylation of isonitriles and acids by asymmetric induction [23] and it must be possible to separate pairs of diastereoisomers.

The syntheses of compounds XXXIIa and b which under proper conditions experience remarkable asymmetric induction, represent the first successful experiments in this field [18]. These compounds are obtained by condensing (−)-α-phenylethylamine and isobutyraldehyde with benzoic acid and t.-butyl isocyanide, or with formylglycine and t.-butyl isocyanoacetate.

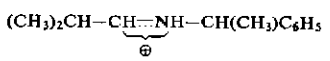


XXXIIa (85 %) [24]

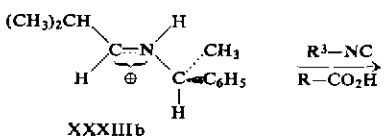


XXXIIb (94 %) [24]

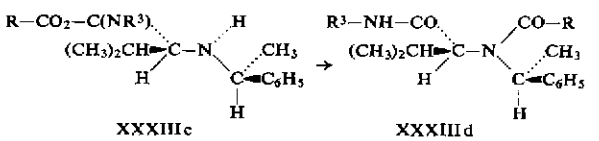
The recently advanced theories on asymmetrically induced syntheses [23b, c] inadequately account for the pronounced effect of temperature and solvent changes upon the diastereoisomer ratio. Another difficulty is the fact that the steric course of the condensation varies with the employment of isobutyraldehyde + (−)-α-phenylethylamine or the corresponding Schiff base. The experimental observations cannot satisfactorily be explained on the basis of the favored nucleophilic attack on the sterically less hindered sites of the conformers of the immonium ions XXXIIIa (see also Formulae XXXIIIb → d).



XXXIIIa



XXXIIIb



XXXIIIc XXXIIId

It is probable that equilibria encountered in the case of the ion (XXXIIIa) and the various conformers of isobutyraldehyde-(−)-α-phenylethylimine, the diastereoisomeric pairs of (−)-α-phenylethylamino-2-methyl-1-propanol (and its esters and ethers if alcohols are present) influence the steric course of the reactions. In addition, if the (+)(−)- and (−)(−)-diastereoisomers of the α-adduct XIVg (*e.g.* XXXIIIc) are sufficiently rapidly interconvertible, the differences in acyl migration rates of the (+)(−)- and (−)(−)-forms of the α-adducts will affect the diastereoisomer ratio of the end products.

One cannot exclude entirely a reaction mechanism according to XXIIc. In such a case, the stereochemical role of the starting materials is even more difficult to describe. The cyclic character of this mechanism leads to an increased possibility for asymmetric induction.

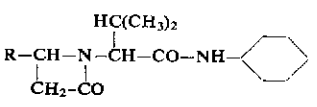
[23] [a] Review article *E. E. Turner* and *M. M. Harris*, Quart. Rev. *1*, 299 (1947); see also [b] *D. J. Cram* and *F. A. A. Elhafez*, J. Amer. chem. Soc. *74*, 5828 (1952); [c] *V. Prelog* and *H. Scherrer*, Helv. chim. Acta *42*, 2227 (1959) and preceeding communications.

[24] Contaminated by a slight amount of the (+)(−)-diastereoisomer.

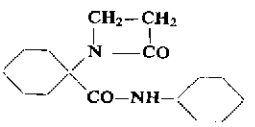
2.44. β-Lactams

2.441. β-Aminocarboxylic Acids as Condensation Components [15a, c]

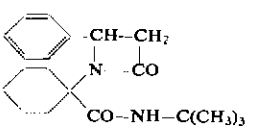
Another ramification of the general principle is the synthesis of β-lactams. The well-known difficulties involved in the syntheses of β-lactams by other methods [25] are not encountered. Thus, from β-alanine or β-phenyl-β-alanine, isobutyraldehyde and cyclohexyl isocyanide, compounds XXXIVa and b respectively are obtained in 80 and 84 % yields. Compound XXXIVc may be formed from β-alanine, cyclohexanone, and cyclohexyl isocyanide, while XXXIVd results from the union of β-phenyl-β-alanine, cyclohexanone, and t.-butyl isocyanide (see Section 4.15).



XXXIVa: R = H− (80 %)
b: C_6H_5− (84 %)

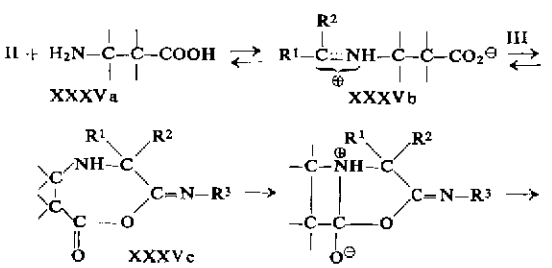


XXXIVc: (95 %)

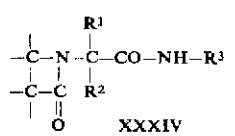


XXXIVd: (89 %; cf. 4.15)

In such conversions the β-amino acid (XXXVa) has simultaneously the functions of both the amine and carboxylic acid components.



XXXVa XXXVb XXXVc



XXXIV

The formation of the ring intermediate (XXXVc) via the immonium betaine is favored by the mutual attraction of the opposite charges at the reactive centers of the structure XXXVb. The β-lactam (XXXIV) results from a transannular acyl migration in the cyclic α-adduct (XXXVc). It is not yet known whether lactams of other ring sizes can be created by similar processes.

2.442. Penicillanic Acid Derivatives [26, 27]

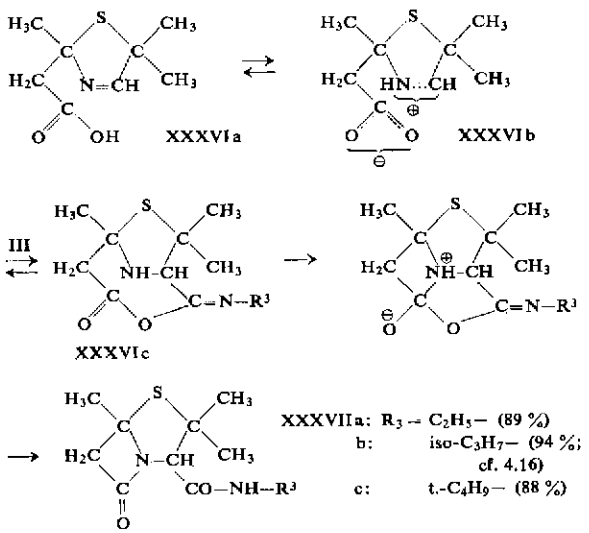
The syntheses of the 5- and 6-methylpenicillanic alkylamides, XXXVIIa–c and XXXIXa–c [27], are the most conspicuous examples of the versatility of the α-additions of ammonium ions and anions to isonitriles. Compound XXXVIa, which is easily produced by an

[25] Review article: *J. C. Sheehan* and *E. J. Corey*, Org. Reactions *9*, 388 (1957).

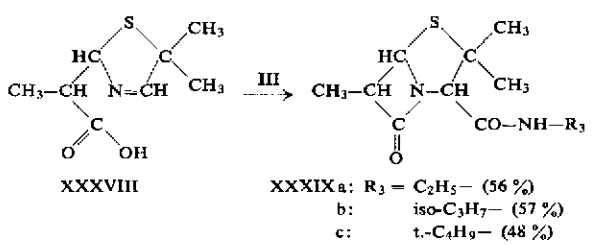
[26] The author is greatly indebted to Prof. *J. C. Sheehan* for his helpful advice on this subject.

[27] *I. Ugi* and *E. Wischhöfer*, Chem. Ber. *95* (1962), in press.

Asinger condensation [13] of ethyl acetoacetate, α-mercaptoisobutyraldehyde and ammonia with subsequent hydrolysis of the ester, reacts quickly and smoothly with isonitriles to form the 5-methylpenicillanic alkylamides (XXXVIIa–c).



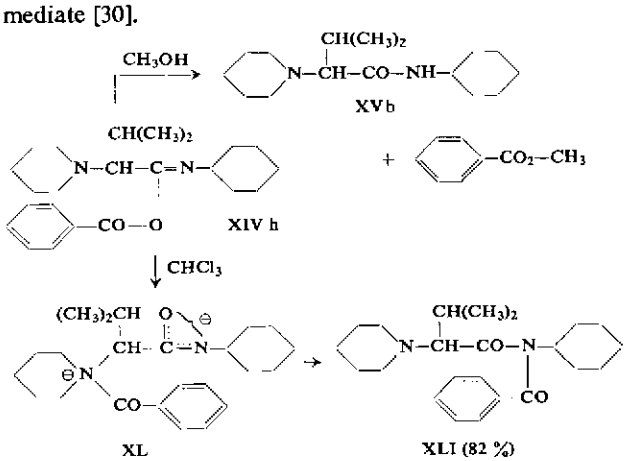
In polar solvents [28] compound XXXVIa is present in equilibrium with the immonium betaine XXXVIb. This betaine is capable of addition to the isonitrile, forming the cyclic adduct XXXVIc which then yields compound XXXVII by transannular acyl migration. Owing to the bicyclic nature of the intermediate (XXXVIc), the β-lactam ring and the amide group must exist in a *cis*-relationship. Thus the configuration of the newly-formed asymmetric center in compounds XXXVIIa–c is completely pre-determined by the constitution of the starting material.



In an analogous manner, the 6-methylpenicillanic acid amides (XXXIXa–c) may be obtained from compound XXXVIII. Incidentally, these syntheses lend support to the one-step, three-center α-addition mechanism (see Section 1.43).

2.45. Diacylimides

The formation of α-acylaminocarboxylic acid amides (XXI) is possible only when ammonia, or primary amines, are used as amine components (see Section 2.4). With a secondary amine, the reaction takes a completely different course. α-Piperidino-isovaleric acid cyclohexylamide (XVb) and methyl benzoate result from combining piperidine, isobutyraldehyde, cyclohexyl isocyanide and benzoic acid in methanol. In this reaction the primary adduct acylates the hydroxylic solvent; in chloroform solution it stabilizes itself by a Mumm rearrangement [29], giving rise to XLI [15c]. The acyl ammonium betaine XL [16b] is a possible intermediate [30].

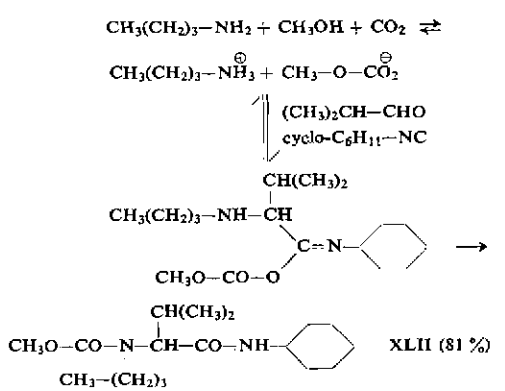


It is worth mentioning that compound XLI, in contrast to compound XIVh, is stable for a short time in boiling methanol, but is readily cleaved into the structure XVb and benzylbenzamide by cold benzylamine.

α-Morpholinostyrene, cyclohexyl isocyanide, and acetic acid react in an analogous manner, as do morpholinoisobutene, ethyl isocyanide and chloroacetic acid [31], except that in the latter combination secondary complications arise from the N-alkylating properties of the chloroacetyl-group.

2.46. Urethanes

Methyl hydrogen carbonate [32] behaves towards n-butylamine, isobutyraldehyde, and cyclohexyl isocyanide like a carboxylic acid. Specifically, the result of adding isobutyraldehyde and cyclohexyl isocyanide to a solution of n-butylamine in methanol saturated with carbon dioxide and allowing the mixture to stand for 20 hours at approximately 20 °C., is the formation of urethane XLII in 97 % crude yield [15c].



[28] The reaction leads to XXXVIIa–c and to XXXIXa–c only if water is present; in nonaqueous solvents the polycondensation of XXXVIa and XXXVIII with isonitriles prevails.

[29] *O. Mumm, H. Hesse,* and *H. Volquartz,* Ber. dtsch. chem. Ges. *48,* 379 (1915); *C. L. Stevens* and *M. E. Munk,* J. Amer. chem. Soc. *80,* 4065 (1958); *F. Cramer* and *K. Baer,* Chem. Ber. *93,* 1231 (1960); *R. B. Woodward* and *R. A. Olofson,* J. Amer. chem. Soc. *83,* 1007 (1961).

[30] The author is indebted to Prof. *D. H. R. Barton* and Prof. *C. L. Stevens* for helpful suggestions.

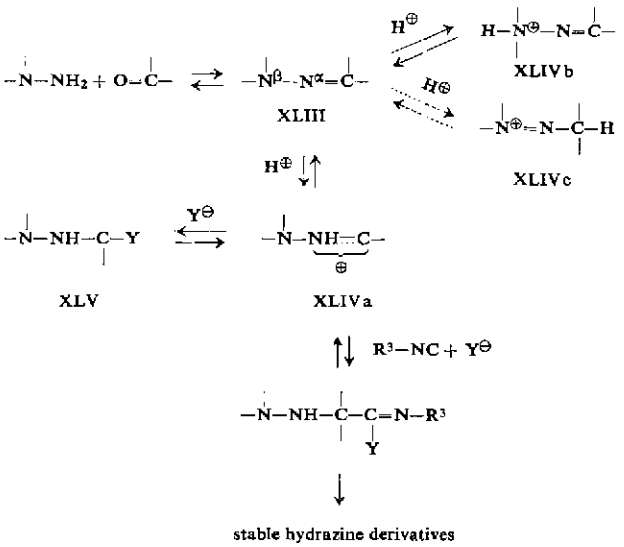
[31] Unpublished results with *E. Böttner.*

[32] Review article: *S. Petersen* and *H. M. Piepenbrink* in *Houben-Weyl:* Methoden der Organischen Chemie. G. Thieme, Stuttgart 1952, vol. 8, p. 105.

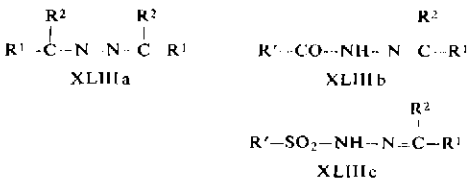
This reaction is unprecedented in that five different components combine almost quantitatively [15c] to give a product which includes all five molecules in its structure. The explanation for this lies in the fact that all side reactions are reversible, and indeed, the main reaction appears to be a chain of concerted equilibria terminated by the irreversible final rearrangement. In future investigations of the α-aminoalkylation of isonitriles and acids, further condensations between more than four different components can be expected. In fact, this should occur whenever an anion resulting from two, or an immonium ion stemming from more than two components, is involved.

3. Syntheses of Hydrazine Derivatives

The addition of hydrogen cyanide to hydrazones [33] can be interpreted as an α-aminoalkylation, in which a hydrazine plays the role of the amine component, according to equations XLIII ⇌ XLIVa ⇌ XLV (Y = CN). It is not yet known whether hydrazines and carbonyl compounds or hydrazones (XLIII), the easily formed condensation products, also react with other proton-acid components in an analogous manner [12].



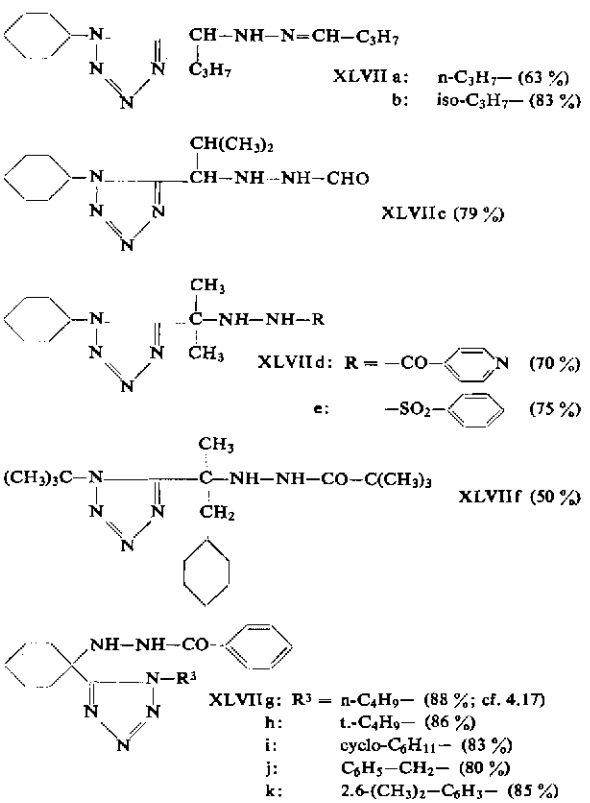
If the β-nitrogen atoms of the hydrazones (XLIII) do not bear electron-attracting substituents their proton-affinity (see Formula XLIVb) is comparable to that of hydrazine. The basicity of the α-nitrogen atom is much lower owing to the adjacent carbon-nitrogen double bond. This leads to a lower equilibrium concentration of XLIVa, the key intermediate of α-hydrazinoalkylation reactions. Therefore reversible additions of proton-acid components to hydrazones (XLIII + HY ⇌ XLV) are not expected to be frequently encountered. On the other hand, irreversible reactions of the cation XLIVa, such as combination with isonitriles and anions accompanied by secondary reactions, are less susceptible to the (thermodynamically disadvantageous) influence of the equilibria between compounds XLIII and XLV.



Thus azines, for example XLIIIa, in which the α- and β-nitrogen atoms are equivalent, and acyl-hydrazones (XLIIIb and c), in which the acyl group diminishes the basicity of the β-nitrogen atom, combine smoothly in many cases with isonitriles and suitable HY acids by means of α-addition of the electrophilic proton-adduct (XLIVa) of the hydrazone and the anion Y⊖. Compound XLVI rearranges to form stable hydrazine derivatives (see Section 1.44).

3.1. 1,5-Disubstituted Tetrazoles [34a]

By combining n- or iso-butyraldazine with cyclohexyl isocyanide and hydrazoic acid, the labile tetrazole derivatives XLVIIa and b are obtained. However compounds XLVIIc–k which are derived from acylated hydrazones, isonitriles, and hydrazoic acid, are stable.



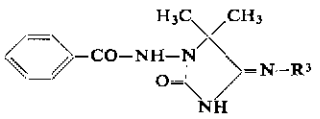
3.2. 1-Aminohydantoin-4-imides [34b]

Acylated hydrazones react with isonitriles and cyanic acid to form 1-acylamino-hydantoin-4-imides. The corresponding thio-compounds result from hydrogen thiocyanate. Compounds XLVIIIa and b were prepared from acetone benzoylhydrazone and hydrogen cyanate

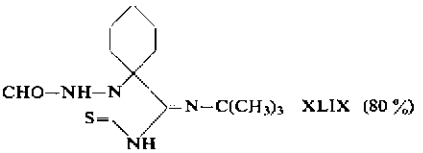
[33] For example: *W. v. Miller* and *J. Plöchl*, Ber. dtsch. chem. Ges. *25*, 2020 [1892]; *J. Thiele* and *K. Neuser*, Liebigs Ann. Chem. *90*, 1 (1896).

[34] *I. Ugi* and *F. Bodesheim*, [a] Chem. Ber. *94*, 2797 (1961); [b] unpublished results.

coupled with either t.-butyl or cyclohexyl isocyanide, respectively. In an analogous manner compound XLIX arises from condensation between cyclohexanone formylhydrazone, t.-butyl isocyanide and hydrogen thiocyanate.



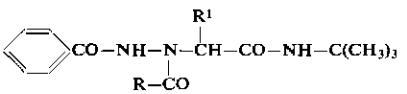
XLVIIIa: R^3 = t.-C_4H_9– (68 %; cf. 4.18)
b: cyclo-C_6H_{11}– (61 %)



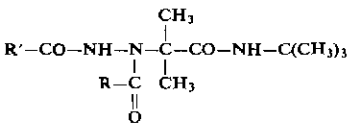
XLIX (80 %)

3.3. α-(N,N'-Diacylhydrazino)carboxylic Acid Amides

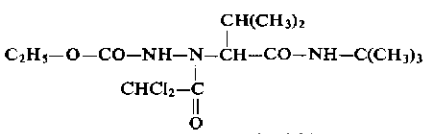
α-(N,N'-Diacylhydrazino)carboxylic acid amides are produced by the combination of acylated hydrazones or semicarbazones, isonitriles, and carboxylic acids [34b]. The syntheses of compounds from acylated hydrazones, t.-butyl isocyanide and carboxylic acids serve as examples.



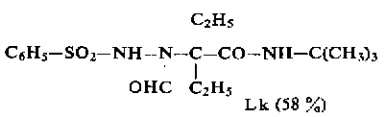
La: R^1 = iso-C_3H_7– R = H– (76 %; cf. 4.19)
b: iso-C_3H_7– $ClCH_2$– (79 %)
c: C_6H_5–CH_2– C_6H_5–CH_2– (31 %)



I.d: R = CH_3– R' = C_6H_5– (61 %)
e: $ClCH_2$– H– (65 %)
f: $ClCH_2$– C_6H_5– (71 %)
g: $ClCH_2$– NH_2– (80 %; cf. 4.20)
h t.-C_4H_9– C_6H_5– (33 %)
i: C_6H_5– C_6H_5– (56 %)



Lj (80 %)



Lk (58 %)

4. Experimental Procedures

1. *N*-[(*N*,*N*-Dimethyl)thioglycyl]benzylamine hydrochloride [15a] (XVIIb)

Dimethylamine hydrochloride (2.45 g.; 0.030 mole), aqueous 10 M formaldehyde solution (3 ml.; 0,030 mole) and 9.93 g. sodium thiosulfate pentahydrate (0.040 mole) are dissolved in a mixture of 40 ml. water and 35 ml. acetone. Benzyl isocyanide (2.93 g.; 0.025 mole) is added dropwise during the course of 15 minutes with stirring and ice-cooling. Stirring is continued for 3 hrs. at 20 °C. On saturating with potassium carbonate, two separable liquid phases are formed. The aqueous phase is extracted with three 15 ml. portions of acetone and the combined extracts are dried over K_2CO_3. After vacuum evaporation, 5.24 g. of a yellow oil remain. This is dissolved in 80 ml. benzene/petroleum ether (6:4) and the solution saturated with dry hydrogen chloride at 0 °C. The crude product, 5.59 g., m.p. 160–165 °C. (decomp.), is filtered off and crystallized from methanol. The colorless needles, 5.02 g. (82 %), melt at 170–171 °C.

2. *N*-[α-(Piperidino)selenoisovaleryl]cyclohexylamine [15a] (XVIa)

Sodium (1.84 g.; 0.080 mole) is dissolved in 100 ml. liquid ammonia contained in a 250 ml. three-necked flask fitted with a stirrer and gas inlet. Selenium (3.16 g.; 0.040 mole) is added in portions under vigorous stirring and in an atmosphere of nitrogen, whereupon the blue color of the sodium disappears [35]. After replacing the solvent ammonia by 20 ml. methanol, 2.73 g. cyclohexyl isocyanide, (0.025 mole), 2.39 g. piperidine (0.030 mole), 8 ml. 10 N hydrochloric acid (0.080 mole) and 2.16 g. isobutyraldehyde (0.030 mole) are added in 40 ml. 50 % methanol. After 20 hours at 20 °C. in the absence of oxygen, the filtered reaction mixture is evaporated *in vacuo* and the reddish-brown residue extracted with hot petroleum ether. On partial evaporation of the petroleum ether solution, a yellow crystalline mass appears. Yield: 4.41 g. (51 %), m.p. 154–157 °C. (decomp.). After recrystallization from aqueous methanol, the product melts at 155–157 °C. (decomp.).

3. 1-Cyclohexyl-5-(1-α-pyridylamino-2-methylprop-1-yl)-tetrazole [15d] (XVIIIe)

2-Aminopyridine (2.82 g.; 0.030 mole), 2.16 g. isobutyraldehyde (0.030 mole), 2.73 g. cyclohexyl isocyanide (0.025 mole), 19.5 ml. hydrazoic acid (5.5 % in benzene; 0.025 mole), and 10 ml. methanol are mixed together and allowed to stand for 2 hours at 20 °C. On concentration, a brown crystalline mass, m.p. 85–95 °C., is obtained. After recrystallizing from benzene/petroleum ether (1:10), the final yield is 4.80 g. (64 %), m.p. 166–168 °C.

4. 1-(2,6-Dimethylphenyl)-5-(1-piperidino-2-methylprop-1-yl)tetrazole [15b] (XVIIIp)

Piperidine (5.10 g.; 0.060 mole), 4.32 g. isobutyraldehyde (0.060 mole), 6.56 g. 2,6-dimethylphenyl isocyanide (0.050 mole), 30.6 ml. hydrazoic acid (7.3 % in benzene; 0.052 mole), and 30 ml. methanol are mixed together and left to stand for 5 hours at 20 °C. Colorless prisms, m.p. 123–126 °C. are obtained on evaporation; after recrystallization from benzene/petroleum ether (1:2), the yield is 14.86 g. (95 %), m.p. 126–127 °C.

5. 1-Cyclohexyl-5-(2-*p*-anisylaminoprop-2-yl)tetrazole [15b] (XVIIIh)

p-Anisidine, (3.69 g.; 0.030 mole) is mixed with 2.73 g. cyclohexyl isocyanide (0.025 mole), 30 ml. acetone, 10 ml. methanol, and 19.5 ml. hydrazoic acid (5.5 % in benzene; 0.025 mole). The mixture is allowed to stand at 20–25 °C. for 12 days and then evaporated. The residue (7.88 g.) melts between 124 and 128 °C.; after recrystallization from benzene/petroleum ether (2:1) the yield is 7.10 g. (90 %), m.p. 130 to 132 °C.

6. 1-*o*-Tolyl-5-isopropylhydantoin-4-t.-butylimine [18] (XIXf)

To a solution of 2.16 g. isobutyraldehyde (0.030 mole) and 2.49 g. t.-butyl isocyanide (0.025 mole) in 20 ml. methanol is added firstly 2.44 g. potassium cyanate (0.030 mole) in 10 ml. water and then 4.30 g. *o*-toluidine hydrochloride (0.030 mole). These operations are carried out with ice-cooling and stirring. The crystalline precipitate (7.12 g.; m.p. 224–230 °C.)

[35] Procedure according to *M. Schmidt*, Munich.

is filtered at the pump after 2 hours at 20 °C. Recrystallization is carried out from ethanol/water (1:1). Yield: 6.73 g. (87 %), m.p. 238–240 °C.

7. 1-Isopropyl-5,5-pentamethylene-2-thiohydantoin-4-cyclohexylimine [8b] (XXe)

Hot solutions of isopropylamine hydrochloride (3.18 g.; 0.033 mole) in methanol (5 ml.), and potassium thiocyanate (3.24 g.; 0.030 mole) in methanol (50 ml.), are mixed and the precipitated potassium chloride filtered off. The solution is evaporated *in vacuo* and the residue dissolved in 30 ml. chloroform. With ice-cooling, 2.95 g. cyclohexanone (0.030 mole) and 2.73 g. cyclohexyl isocyanide (0.025 mole) in 5 ml. chloroform is added drop-wise. After 120 hours at 20 °C. the reaction mixture is evaporated. Crude yield: 7.75 g. (quantitative), m.p. 210–220 °C. (decomp.). The product can be recrystallized from methanol. Final yield: 6.22 g. (81 %), m.p. 229–231 °C.

If the reaction is carried out in methanol, the crude yield is 78 %.

8. *N*-(Phthalylglycylvalyl)-t.-butylamine [15c] (XXId)

A solution of 1.08 g. isobutyraldehyde (0.015 mole) and 1.25 g. t.-butyl isocyanide (0.015 mole) in 20 ml. methanol is placed in a three-necked flask fitted with a condenser, stirrer, and dropping funnel, and within 30 minutes mixed with a suspension of ammonium phthalylglycinate (3.33 g.; 0.015 mole) in methanol (40 ml.) at a bath temperature of 80 °C. After 45 minutes a part of the methanol is distilled off, the solution cooled and the crystalline precipitate (4.41 g.; m.p. 283–287 °C.) removed by filtration. Yield (after recrystallization from ethanol): 3.91 g. (72 %); m.p. 286 to 288 °C.

9. 1-(*N*-Formyl-*N*-isopropylamino)cyclohexane-1-carboxylic acid cyclohexylamide [8b] (XXIe)

Isopropylamine (7,08 g.; 0.12 mole), 10.78 g. cyclohexanone (0.11 mole), 5.18 g. 98 % formic acid (0.11 mole) and 10.9 g. cyclohexyl isocyanide (0.10 mole) in 25 ml. isopropanol are heated together for 4 hours under reflux. On cooling to ca. 20 °C. the colorless crystalline mass is sucked off and washed with isopropanol. Yield: 23.5 g. (87 %), m.p. (crude) 187 to 191 °C. After recrystallization from isopropanol, m.p. 191 to 192 °C.

10. t.-Butyl *N*-(*N*-trifluoroacetylglycyl)-*N*-(*N*-benzylvalyl)-glycinate [15c] (XXVIIIb)

Trifluoroacetylglycine (2.56 g.; 0.015 mole) in 10 ml. methanol is added with shaking to an ice-cooled solution of benzylamine (1.61 g.; 0.015 mole), t.-butyl isocyanoacetate (2.12 g.; 0.015 mole) and isobutyraldehyde (1.08 g.; 0.015 mole) in methanol (5 ml.). After the solution has been allowed to stand for 2 hours at 20 °C. the resinous residue obtained by evaporation crystallizes in the presence of added petroleum ether and a few drops of ethyl acetate within 2 days. Crude yield: 7.16 g., m.p. (crude) 105–125 °C.; the crude product can be recrystallized from methanol/water (1:1). Yield: 6.15 g. (87 %), m.p. 128–132 °C.

11. t.-Butyl *N*-(*N*-Phthalylglycyl)-*N*-(*N*-benzylglycyl)-glycinate [15c] (XXIXa)

Benzylamine (1.61 g.; 0.015 mole), 1.5 ml. 10 M aqueous formaldehyde (0.015 mole) and 2.12 g. t.-butyl isocyanoacetate (0.015 mole) are dissolved in absol. methanol (20 ml.) and mixed with shaking and ice-cooling with a solution of *N*-phthalylglycine (3.08 g.; 0.015 mole) in methanol (20 ml.). After 2 days standing at 20 °C. the crystalline precipitate is sucked off and the filtrate evaporated *in vacuo* to yield a further small amount of reaction product. Crude yield: 6.45 g., m.p. (crude) 160–163 °C. Colorless prisms, 5.80 g. (83 %) are obtained by recrystallization from ethyl acetate; m.p. 163–164 °C.

12. t.-Butyl α-[*N*-(phthalylglycyl)-*N*-benzylamino]-β,γ-epoxybutyrylglycinate [15c] (XXIXc)

Benzylamine (3.21 g.; 0.030 mole), glycidaldehyde (2.88 g.; 0.040 mole), t.-butyl isocyanoacetate (4.23 g.; 0.030 mole) and 6.15 g. *N*-phthalylglycine (0.030 mole) are dissolved in methanol (80 ml.) with ice-cooling, and then allowed to stand for 2 hours at 20 °C. After distilling off a part of the methanol, colorless prisms, m.p. 143–145 °C. (10.63 g.) can be removed at the pump. A yield of 10.25 g. (67 %) product, melting at 147–148 °C., is obtained by recrystallization from ethanol.

13. t.-Butyl (*N*-phenylglycyl-*N*-benzyl-α-methylphenylalanyl) glycinate [15c] (XXXIXk)

To 80 ml. methanol are added 6.69 g. methyl benzyl ketone-benzylimine (0.030 mole), 4.23 g. t.-butyl isocyanoacetate (0.030 mole) and 6.15 g. (0.030 mole) *N*-phthalylglycine. After 3 days standing at 20 °C. the solvent is taken off and the amorphous residue crystallized in the presence of petroleum ether and a few drops of ethyl acetate. Yield: 17.08 g., m.p. (crude) 158–163 °C. By recrystallization from ethanol a 91 % yield (15.52 g.) of colorless prisms, m.p. 182–184 °C., is obtained.

14. 2,2,5,5-Tetramethyl-3-(phthalylglycyl)thiazolidine-4-carboxylic acid t.-butoxycarbonylmethylamide [18] (XXXIb)

N-Phthalylglycine (5.12 g.; 0.025 mole), 2,2,5,5-tetramethyl-Δ^3-thiazoline (3.58 g.; 0.025 mole) and t.-butyl isocyanoacetate (3.52 g.; 0.025 mole) are dissolved together in methanol (25 ml.) and allowed to stand for 3 weeks at 20 °C. The solution is cooled to 0 °C. and the crystalline product sucked off after 2 hours. Yield: 8.82 g. (74 %), m.p. 89–91 °C. The already pure material can be recrystallized in good yield from methanol.

15. 1-(2-Oxo-4-phenylazetidin-1-yl)cyclohexane-1-carboxylic acid t.-butylamide [15c] (XXXIVd)

A suspension of 4.95 g. finely powdered β-Amino-β-phenylpropionic acid (0.030 mole) in methanol (50 ml.) is added to 9.82 g. cyclohexanone (0.10 mole) and 2.49 g. t.-butyl isocyanide (0.030 mole), and then stirred for 72 hours at 20 °C. After concentration, the yellow resinous residue can be made crystalline by grinding in the presence of petroleum ether. Crude yield: 9.42 g., m.p. (crude) 84–89 °C. Purification by recrystallization from petroleum ether yields 8.78 g. (89 %) colorless crystals, m.p. 92–94 °C.

16. 5-Methylpenicillanic acid isopropylamide [27] (XXXVIIb)

A mixture of 0.5 g. finely powdered 2,5,5-trimethyl-Δ^3-thiazolin-2-ylacetic acid (0.00267 mole), 0.83 g. isopropyl cyanide (0.012 mole), 3 ml. petroleum ether (b.p. 40–80 °C.), and 10 ml. water is vigorously stirred at 20 °C. for 30 minutes. The organic phase is removed after addition of methylene chloride (10 ml.) and then concentrated *in vacuo* at 20 °C. The residue (0.68 g.; m.p. 57–62 °C.) is purified by high-vacuum sublimation (0.001 mm. Hg; bath temperature ca. 60 °C.). Yield: 0.64 g. (94 %), m.p. 64–66 °C.

17. 1-n-Butyl-5-[1-(β-benzoylhydrazino)cyclohex-1-yl]-tetrazole [34a] (XLVIIg)

To a solution containing 4.32 g. cyclohexanone-benzoylhydrazone (0.020 mole) and 1.66 g. n-butyl isocyanide (0.020 mole) in methanol (25 ml.) is added 1.95 g. sodium azide in water (8 ml.). 6 N Hydrochloric acid (4.5 ml.) is added drop-wise, with stirring and ice-cooling, and the mixture allowed to stand for 50 hours. After evaporation, the residue is purified by dissolving in methanol, filtering, concentrating, and recrystallizing from aqueous methanol. Yield: 6.02 g. (88 %), m.p. 114–116 °C.

18. 1-Benzoylamino-5,5-dimethylhydantoin-4-t.-butylimine [34b] (XLVIIIa)

t.-Butyl isocyanide (0.83 g.) is added to a mixture of 1.76 g. acetone-benzoylhydrazone (0.010 mole) in methanol (15 ml.)

and 1.64 g. potassium cyanate (0.020 mole) in water (3 ml.). 6 N Hydrochloric acid (2 ml.) is added drop-wise and with ice-cooling. After 1 hour, 4 N ammonia (10 ml.) is added and the product filtered off. Yield: 2.06 g. (68 %), m.p. 337 to 340 °C.

19. α-(α'-Formyl-β'-benzoylhydrazino)isovaleryl-t.-butylamine [34b] (La)

Isobutyraldehyde-benzoylhydrazone (1.90 g.; 0.010 mole), t.-butyl isocyanide (0.83 g.; 0.010 mole) and formic acid (0.47 g.; 0.010 mole) are dissolved in 2 ml. methylene chloride at 20 °C. After 30 minutes, the solution is concentrated *in vacuo* and the residue triturated with ethyl acetate. Crude yield: 2.96 g., m.p. (crude) 148–155 °C. Following recrystallization from ethyl acetate or aqueous methanol, the yield is 2.43 g. (76 %), m.p. 173–174 °C.

20. 1-Chloroacetyl-1-[2-(t.-butylaminocarbonyl)prop-2-yl] semicarbazide [34b] (Lg)

A methanol solution (15 ml.) containing 1.15 g. acetone-semicarbazone (0.010 mole), 0.83 g. t.-butyl isocyanide (0.010 mole) and 1.00 g. chloroacetic acid (0.0105 mole) is allowed to stand for 4 days at 20 °C. After concentration *in vacuo* there remains a resin which contains crystalline material. It may be purified by recrystallization from aqueous methanol. Yield: 2.43 g. (82 %), m.p. 231–233 °C. (decomp.).

The author wishes to express his cordial thanks to Mrs. T. Poland, Prof. J. F. Bunnett, Dr. J. A. Zoltevicz, and Mr. R. Srb for their kind help in translating this article into English.

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Enrichment of Heavy Water by High Pressure Exchange Between Hydrogen and an Aqueous Catalyst Suspension[*]

Part II: Construction and Operation of a Pilot Plant

BY DR. S. WALTER, DR. E. NITSCHKE, AND DR. C. BODE

FRIEDRICH UHDE GMBH., DORTMUND

AND PROF. DR. E. W. BECKER, DR. R. P. HÜBENER, DR. R. W. KESSLER, AND DR. U. SCHINDEWOLF

KERNFORSCHUNGSZENTRUM KARLSRUHE, INSTITUT FÜR KERNVERFAHRENSTECHNIK DER TECHNISCHEN HOCHSCHULE KARLSRUHE

The construction and operation of a pilot plant for the enrichment of heavy water by high pressure exchange between hydrogen and an aqueous catalyst suspension are described. A continous experiment carried out for a period of 86 days proved the technical feasibility of the process and the validity of the assumptions used in an earlier discussion of the economic aspects.

In the first paper of this description [1] it was shown that high pressure exchange between hydrogen and an aqueous suspension of platinum on activated charcoal powder can be used as the basis for an economical enrichment of heavy water. The estimate was based on measurements of the isotope exchange rate in a laboratory plant in which highly compressed hydrogen cycled through the catalyst suspended over a sieve plate. The optimum conditions were evaluated on the basis of a theoretical study by *K. Bier* [2].

The present work describes the construction and operation of a pilot plant which was developed by Friedrich Uhde GmbH., Dortmund, and which was erected on the grounds of Farbwerke Hoechst AG., Frankfurt/M.-Hoechst[**]. With this plant experimental enrichment could be carried out for the first time. Through these experiments the accuracy of the previous estimate has been verified, and basic observations concerning the behavior of the catalyst suspension in continuous operation have been obtained.

Principle of the Installation

For the enrichment of heavy water on the basis of the isotope exchange between hydrogen and an aqueous catalyst suspension, the procedures shown in Figures 1a and b are the most important ones.

a) Hot-Cold Operation [3]

In this case, deuterium enrichment is obtained by passing the two phases counter-currently through two columns

[*] The study was carried out in cooperation with Degussa, Frankfurt/M. We thank the director of the Physical Chemistry Laboratory of Degussa in Konstanz, Dr. *F. Endter*, as well as Dr. *E. Koberstein* for their valuable suggestions, and for carrying out a large portion of the analytical work. The catalyst was manufactured in the Hanau Plant of Degussa.

[**] We are greatly indebted to Dr. *Ertel*, Farbwerke Hoechst, for his valuable assistance with regard to the construction and operation of the plant.

[1] *E. W. Becker, R. P. Hübener*, and *R. W. Kessler*, Chemie-Ing.-Techn. *30*, 288 (1958). Designated as Part I in the following.

[2] *K. Bier*, Chemie-Ing.-Techn. *28*, 625 (1956); *31*, 22 (1959).

[3] *E. W. Becker*, Angew. Chem. *68*, 6 (1956); D.B.P. 1,003,698 of 8/14/1957, Appl. 9/8/1954.

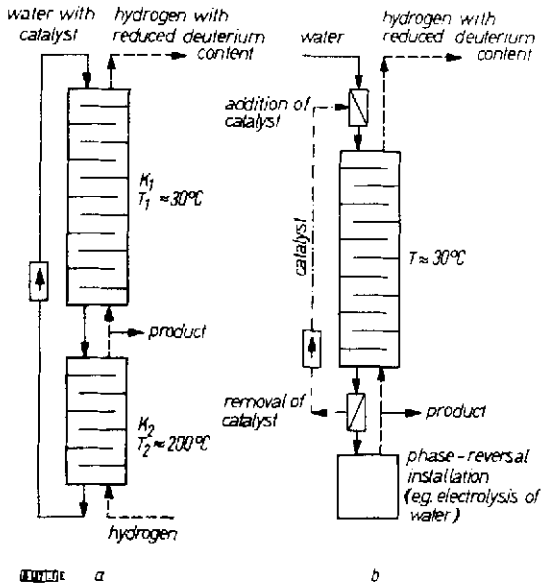


Figure 1. Multiplication of the elementary effect in high pressure exchange between hydrogen and an aqueous catalyst suspension; a) hot-cold operation, b) phase reversal operation.

which are kept at different temperatures. Hydrogen, or a hydrogen/nitrogen mixture, serves as feed material, while the catalyst suspension circulates through the two columns [4]. The product is withdrawn at a point between the columns and, if necessary, is further enriched in another pair of hot-cold columns or by a separate method. Suitable feed gases under the required high pressure are available in sufficient quantity in hydrogenation or ammonia synthesis plants.

b) Phase Reversal Operation [5]

In phase reversal operation, deuterium enrichment results from the passage of the two phases counter-currently through a cold column. The hydrogen is produced continuously from the enriched water leaving the column after having been freed from catalyst. The removed catalyst is returned to the water at the head of the column. The product is removed at the lower end of the column and, if necessary, is further enriched in other cold columns, pairs of hot-cold columns, or by other means. This method is particularly economical if the costs for the hydrogen production are borne by another commercial process, as in the case of hot-cold operation, and if the hydrogen generator operates without considerable deuterium losses and without significant intake of extraneous hydrogen-containing material. Particularly favorable conditions are offered by the electrolysis of water which is used for producing hydrogen for ammonia synthesis in localities where the cost of electricity is low.

The estimate in Part I [1] applies to hot-cold equipment operating according to Scheme 1 a. It was found that in this case, about the same specific investment costs can be expected as for the hydrogen sulfide process [6], while considerable savings can be counted on with respect to the specific energy consumption. In the earlier report it was already pointed out that both costs can be further reduced by using phase reversal according to Figure 1 b provided a suitable hydrogen production plant is available without additional cost. Phase reversal operation, being conducted at normal temperatures, also places less stringent requirements with regard to the stability of the catalyst and the construction materials. Thus it was the preferred process when we were attempting the first commercial realization of the high pressure exchange. The pilot plant, however, was constructed as a hot-cold system since experience with a hot-cold system were necessary anyhow for later applications.

Determining the Operating Conditions

The experiments described in Part I [1] were carried out with a single sieve plate without overflow pipe, and with the liquid at rest. The determination of the operating conditions and the pilot plant design required that the results obtained be applied and extended to countercurrent operation. Scrubbing and tray loading experiments with a counter-current liquid stream were carried out, also in Frankfurt/M.-Hoechst, in a column containing 5 trays with overflows. This apparatus was then used in addition to the pilot plant for studying various insert shapes. A perforated plate having holes in a hexagonal arrangement was chosen for constructing the trays in the pilot plant; on the basis of the preliminary experiments, mixing properties similar to those of the original plate with 276 holes of 1 mm. diameter could be expected. The height of the overflow was chosen in such a way that with the predicted operating conditions approximately the same amount of suspension was kept stationary on the plate as was used in the experiments for determining the pressure and temperature influence in Part I [1] ($\approx$ 300 cm³).

At a temperature of 30 °C. and a gas pressure of 200 atm., 600 m³ (at N.T.P.) of hydrogen per hour and 200 l. of suspension per hour were circulated counter-currently through the column with diaphragm pumps. The evaluation was carried out on the basis of the formulae given in Part I [1]. With a suspension of 25 g. of carbon/l. [7] and a weight ratio of platinum/carbon = 0.1, we obtained the exchange constant

$$k^* = 30 \text{ mol./h plate.}$$

For the plate 276/1.0

$$k^* = 28 \text{ mol./h plate}$$

had been determined for 30 °C. and 200 atm. by extrapolation. Since the two results agree within the limit of

[4] Hot-Cold Operation using water as a feed material is not considered here since it leads to considerably higher specific expenditures than the procedures shown in Figures 1 a and b. Compare also references [3] and [2].

[5] German Patent Application U 3962 IVa/12i of June 16, 1956 and U 4061 IVa/12i of August 9, 1956 by Friedrich Uhde GmbH.

[6] At present, by far the largest portion of heavy water in the world is produced with the hydrogen sulfide process. Compare for example *W. P. Bebbington* and *V. R. Thayer*, Chem. Engng. Progr. *55*, No. 9, 70 (1959).

[7] For technical reasons, the catalyst concentration was chosen 10 g./l. higher than in the experiments with the plate 276/1.0 used for the estimate.

error, it could be assumed that the other results of the earlier work could be transferred to the plate provided for the pilot plant with sufficient accuracy. Thus, on the basis of the optimum conditions described in Part I [1], the values shown in Table 1 were set as guiding values for the operating conditions of the plant.

Table 1. Operating Conditions of the Plant.

Gas pressure	200 atm.
Temperature of the hot column	200°C.
Temperature of the cold column [8]	30°C.
Gas throughput	600 m³/hr. (at N.T.P.)
Mol. flow ratio gas/liquid	2.5
Catalyst concentration [7]	25 g. carbon/l.
Weight ratio platinum/carbon	0.1

Construction and Starting of the Installation

In order to make the experimental operation independent of any special peculiarities of a hydrogen generating plant, the hydrogen as well as the catalyst suspension were circulated through the columns.

The schematic diagram of the installation is shown in Figure 2. It consists of Towers I to III arranged side by

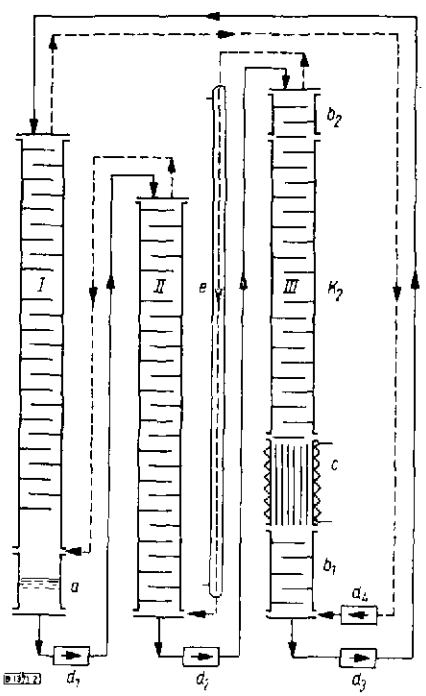


Figure 2. Schematic diagram of the pilot plant. I, II, III — towers; a — sump; b_1, b_2 — heat exchangers; c — heater; d_1 to d_4 — pumps; e — gas cooler.

side in a framework. Tower II and the upper section of Tower I, with an overall length of 28 m., together form the cold column K_1 (compare Figure 1a). An empty column section (a) of 2 m. length which operates as a sump is attached at the foot of Tower I. Tower III consists of the hot column K_2 with a length of 10 m., the lower direct heat exchanger b_1 with a length of 3 m., the upper direct heat exchanger b_2 with a length of 1.5 m. and the electrically operated heater c with a length of 3 m. Sieve trays were used as inserts for the columns.

The suspension is transported from sump (a) to the head of Tower II by means of an adjustable diaphragm pump d_1 [9]. At the foot of this tower, it is taken over by the oversized pump d_2 and transported to the head of Tower III. Pump d_3, which is also oversized, finally returns the suspension to the head of Tower I.

The hydrogen coming from the head of Tower I is forced into the foot of Tower III by means of a diaphragm compressor d_4. It passes upwards through this tower and reaches the foot of Tower II over the gas cooler e. From the head of this tower, it returns to the foot of Tower I, thus closing the cycle.

The flow of the gas is measured via an orifice by means of a Barton-cell and is regulated with a valve which bridges compressor d_4. The flow velocity of the liquid is adjusted with the proportioning pump d_1. The flow of the suspension can furthermore be observed through an inspection glass at the head of each tower. A further viewing window shows the level of the suspension in sump a. Gas samples, whose deuterium mol. fractions n_0 or n_1 are to be determined with a mass spectrometer, can be removed at the head of Tower I and at the foot of Tower II. At the foot of Tower I, there



Figure 3. View of the pilot plant.

[8] The temperature of the cold column was chosen 10 °C lower than the temperature determined in Part I [1] for the smallest column volume. The specific column volume is only insignificantly increased by this measure, while the possible deuterium yield increases considerably.

[9] The contents of the sump are continuously stirred by a small stream of hydrogen.

is also a valve for removing suspension samples. All parts of the equipment which come into contact with the suspension are made of, or are lined with, stainless steel. Figure 3 gives an overall view of the experimental plant.

To start the operation, the equipment is flushed with nitrogen and then with hydrogen coming from a compressor. Subsequently, the equipment is charged with hydrogen to about 20 atm. Now the catalyst suspension is pumped from a stirring vessel to the head of Tower II with the pump d_1. While the suspension flows in, the gas pressure in the plant is gradually increased and the cycling compressor d_4 is set in operation. As soon as the sump of Tower I has filled with suspension, the suction line of pump d_1 is switched to the sump and thereby the suspension cycle is closed. When 175 atm. gauge pressure have been reached and a stationary state in the cycle has been set up, the heater c is switched on.

The Experiments

According to the method of calculation [2] used in the earlier estimate, an expected enrichment factor

$$A = \frac{n_t(1-n_0)}{n_0(1-n_t)} = 1.28$$

is obtained with the k*-value determined by the scrubbing experiments in the column containing 5 trays, and the temperature dependence of the exchange rate determined in Part I [1].

The enrichment process was to be verified and the basis of the earlier estimate to be checked with these experiments. Furthermore, experiences with respect to the behavior of the catalyst suspension in continuous operation were to be gained. Since phase reversal operation was of prime interest for a first commercial realization of the process, and since in this process the catalyst suspension is exposed only to the temperature of the cold column (see above), three hot-cold periods of about 100 hours each and, interspersed, two cold periods of about 1000 hours each, were allowed for in the experiment.

In the hot-cold operation the temperature at the lower end of the hot column K_2 was maintained at about 205 °C. by automatic control of the heat output of the heater c and this resulted in a temperature of about 195 °C. at the upper end of column K_2. The temperature of the gas leaving at the head of heat exchanger b_2 was about 100 °C., while the suspension from the foot of heat exchanger b_1 still had a temperature of about 40 °C. The average operating temperature of the two cold columns was maintained at 30 °C. by regulating the flow of the cooling water in e. For cold operation, the temperature of the whole plant was adjusted to about 30 °C.

The behavior of the enrichment factor as a function of time is shown in Figure 4. Accordingly, the average value in the first hot-cold period is 1.32, in the second

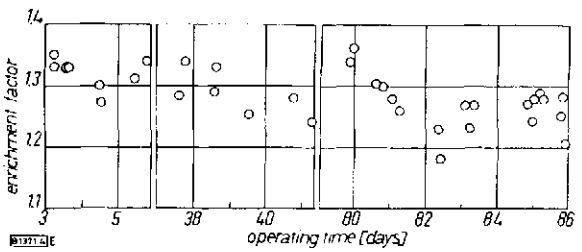


Figure 4. The enrichment factor as a function of time.

1.29 and in the third 1.27. The value A = 1.29 obtained by averaging over the whole experimental period, agrees within the experimental limits with that calculated on the basis of the scrubbing experiments (see above).

The slight decrease in the exchange capacity which might be deduced from the drop of the enrichment factor appears to have taken place essentially during the hot-cold period. The fact that during the cold operation periods of several weeks the exchange properties of the catalyst suspension remained apparently practically constant is of particular importance for the commercial realization of the phase reversal process.

The good agreement between the measured value of the enrichment factor and that calculated on the basis of the scrubbing experiments proves the validity of the theoretical formulae [2] used and thereby verifies the assumptions of the economic estimate indicated in Part I [1].

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Chemical Reactions in the Atmosphere [*]

BY PROF. DR. P. HARTECK AND DR. R. R. REEVES

CHEMISTRY DEPARTMENT, RENSSELAER POLYTECHNIC INSTITUTE, TROY, N.Y., USA.

Chemical reactions in the upper atmosphere may be investigated by sending rockets into the region of interest or by simulating conditions in the laboratory. Ultraviolet solar radiation dissociates and ionizes all types of particles present in the chemosphere. This results in recombination reactions of radicals, charge transfers, and chemical reactions of ions with neutral particles. In addition bimolecular reactions between neutral particles and reactions involving excited molecules take place.

Introduction

Ten years ago this journal published a paper by the senior author concerning the chemistry and photochemistry of the Earth's atmosphere [1]. At that time it was still possible to give a relatively short resumé of the field. In the meantime the research effort in this direction has grown probably faster than any other: Some special fields, such as the anomalous distribution of tritium in the atmosphere, now have research territories of their own. We must, therefore, limit ourselves to a discussion of the most important reactions in the "chemosphere".

There are two different approaches to the investigation of the behavior of the chemosphere. The more direct one is to send rockets with the necessary instrumentation into the region of interest and make the measurements directly on the spot. The other method is to stimulate conditions of the upper atmosphere in the laboratory. The direct approach (sending rockets into the region of interest) is obviously orders of magnitude more expensive, but cannot be avoided if we want to know what the real conditions are in the upper atmosphere; as for example, what type of positive and negative ions are present, or what type of radiation is emitted from the sun and is absorbed in the upper layers of the atmosphere.

Once we have learned from rocket experiments the different types of radiation in the near and far ultraviolet region which fall in the upper atmosphere and their original intensities, we obviously can simulate and investigate quite comfortably in the laboratory all the chemical reactions which will occur in the upper atmosphere.

When simulating these chemical reactions in the laboratory one important point should be kept in mind: the chemosphere starts at an altitude of 90 to about 100 km. and the region where most of the ion reactions occur is at still higher altitudes. But at 100 km. altitude the pressure is only about a micron and where most of the ion reactions occur the pressure is a few decades less. Since at one micron pressure the mean free path of the particles is about 6 cm., it becomes obvious that no simple experiments can be performed in the laboratory under conditions which resemble those of the upper atmosphere. The chemosphere behaves like a huge reaction vessel, whereas at a micron pressure or less the wall reactions become dominant in laboratory experiments conducted in vessels of feasible size. Therefore most experiments intended to simulate reactions in the upper atmosphere are performed at much higher pressures (about 1 mm). Under these conditions two-body collisions are about 1000 times as frequent as in the chemosphere, but fortunately many of these fast reactions are then easy to measure and the average lifetime of atoms that recombine due to three-body reactions, which in the chemosphere is in the order of days and weeks, is reduced to seconds and less at 1 mm. pressure so that these reactions also can be readily measured. Therefore, most of the chemical reactions of the chemosphere can be simulated by laboratory experiments and the results can be extrapolated to the lower pressures which prevail in the chemosphere.

There are, however, certain types of reactions in the upper atmosphere which cannot easily be duplicated in the laboratory. It is known for example, that molecules formed by three-body collisions will have initially a large amount of vibrational energy or they may be formed in an electronically excited state [2]. At very low pressures these molecules may radiate this excitation energy predominantly, whereas under laboratory conditions the emission of radiation may be overlooked because the energy is frequently dissipated by collisions.

In addition to the recombination processes of ions, two types of ion reactions occur which are supposed to have a high cross section in the upper atmosphere. One type (charge transfer) takes place when the positive ion of a molecule with higher ionization potential collides with a molecule with lower ionization potential. The other type is the reaction between an ion and a neutral particle. Sometimes, with the same reactants,

[*] This work has been sponsored by the Geophysics Research Directorate of the Air Force Cambridge Research Laboratories, Air Research Division. – The present paper is an extended version of a lecture given at the International Symposium on Chemical Reactions in the Lower and Upper Atmosphere, San Francisco, April 18–20, 1961. The Proceedings of this Symposium have been published by Interscience Publishers (New York and London).

[1] *P. Harteck*, Angew. Chem. *63*, 1 (1951).

[2] *E. Bauer* and *M. Salkoff*, J. chem. Physics *33*, 1202 (1960).

both types of reactions are possible. The absolute velocities of these reactions are not known at present and in some important cases not even the order of magnitude. The conditions for these reactions which occur in the upper atmosphere are not easy to simulate in the laboratory.

activation was determined from thermal ozone decomposition data [3]. More recent direct experiments with atomic oxygen indicate a value of about 3 kcal./mole [4]. This gives a higher rate of reaction, especially in the low temperature regions of the upper atmosphere, than was previously anticipated [*]. The ozone problem

Table I. Recombination Reactions in Three-Body Collision [2]

Reaction [*]	k[(cm³/particle)²sec⁻¹]	k[(cm³/mole)²sec⁻¹]	ΔHactivation [kcal]	Ref. [*]	Remarks [*]
(1) $O + O + M \rightarrow O_2 + M$	$2.7 \cdot 10^{-33}$	$1.0 \cdot 10^{15}$		[5]	300°K.
	$2.2 \cdot 10^{-33}$	$8 \cdot 10^{14}$		[6]	Shock tube studies, high temp.
	$1 \cdot 10^{-33}$	$4 \cdot 10^{14}$		[7]	
	$6 \cdot 10^{-34}$	$2 \cdot 10^{14}$		[8]	350°K.
	$8.8 \cdot 10^{-33}$	$3.2 \cdot 10^{15}$		[9]	300°K.
(2) $O + O_2 + M \rightarrow O_3 + M$	$4.5 \cdot 10^{-34}$	$1.6 \cdot 10^{14}$	−0.60	[3]	300°K., M=O_3
	$6 \cdot 10^{-34}$	$2.2 \cdot 10^{14}$		[10]	300°K., M=O_2
	$4.2 \cdot 10^{34}$	$1.5 \cdot 10^{14}$	+0.3	[11]	300°K., M=O_3
	$5.5 \cdot 10^{-34}$	$2.05 \cdot 10^{14}$		[12]	300°K., M=O_2
(3) $N + N + M \rightarrow N_2 + M$	$1.7 \cdot 10^{-32}$	$6.2 \cdot 10^{15}$		[13]	300°K.
	$1.7 \cdot 10^{-32}$	$6.0 \cdot 10^{15}$		[14]	300°K.
	$0.74 \cdot 10^{-32}$	$2.7 \cdot 10^{15}$		[15, 16]	(200–450°K.)
(4) $O + N + M \rightarrow NO + M$	$5 \cdot 10^{-33}$	$1.8 \cdot 10^{15}$		[17]	±50 % [**]
(5) $NO + O + M \rightarrow NO_2 + M$	$6 \cdot 10^{-32}$	$2.2 \cdot 10^{16}$		[18]	300°K.
	$7.6 \cdot 10^{-32}$	$2.8 \cdot 10^{16}$		[19]	300°K.
	$5.0 \cdot 10^{-32}$	$1.8 \cdot 10^{16}$		[20]	300°K.

[*] M = third body.

[**] We do not know of a more reliable value at this time.

[+] All references have not been given, because it is difficult to cover every work and also some results are not considered reliable.

Recombination Reactions

Ultraviolet solar radiation dissociates and ionizes all types of particles present in the chemosphere. The dissociation of oxygen molecules into atoms constitutes by far the most abundant photochemical process in the upper atmosphere. At altitudes above 100 km. most of the oxygen is present in atomic form. Therefore, the most abundant recombination process in the upper atmosphere is the recombination of O-atoms which are consumed by the three-body recombination reaction:

(1) $O + O + M \rightarrow O_2 + M$

At lower altitudes, below 90 km., where molecular oxygen becomes much more abundant than the O-atoms the reaction:

(2) $O + O_2 + M \rightarrow O_3 + M$

becomes dominant for the consumption of O-atoms. The O_3 formation may be followed by the reaction:

(13) $O_3 + O \rightarrow 2O_2$

although the reaction $O_3 + H \rightarrow OH^* + O_2$ may consume a larger share of the ozone, as seen from the emission of the OH bands (see page 29).

The rates of these reactions are now reasonably well known. The recombination reaction (1), according to our measurements, has a rate coefficient of $3 \cdot 10^{-33}$ (cm³/particles)²·sec⁻¹ which is substantially faster than the rate coefficient for the ozone formation (reaction 2). Until recently the heat of activation for reaction (13) was generally assumed to be 6 kcal./mole. This heat of

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[4] *F. Leighton, H. B. Urbach*, and *J. A. Wojtowicz*, 136th Meet. Amer. Chem. Soc., Atlantic City, 1959, Abstr. of Papers 46 S.

[*] The proper measurement of this reaction of $O_3 + O \rightarrow 2O_2$ is rather difficult because the system must be almost entirely free of H-atoms. The catalytic recombination occurs if the H-atoms are present via reactions (12) and (18) ($O_3 + H \rightarrow O_2 \rightarrow OH$; $OH + O \rightarrow O_2 + H$). The ratio of H-atoms to O-atoms should be less than 1/1000 which is difficult to obtain by simple experimental techniques.

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[11] *J. A. Zaslowsky, H. B. Urbach, F. Leighton, R. J. Wnuk*, and *J. Wojtowicz*, J. Amer. chem. Soc. *82*, 2682 (1960).

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[13] *P. Harteck, R. R. Reeves*, and *G. Mannella*, J. chem. Physics *29*, 608 (1958).

[14] *T. Wentink Jr., J. O. Sullivan*, and *K. L. Wray*, J. chem. Physics *29*, 231 (1958).

[15] *J. T. Herron, J. L. Franklin, P. Bradt*, and *V. H. Dibeler*, J. chem. Physics *30*, 879 (1959).

[16] *J. T. Herron, J. L. Franklin, P. Bradt*, and *V. H. Dibeler*, J. chem. Physics *29*, 230 (1958).

[17] *P. Harteck, R. R. Reeves Jr.*, and *G. G. Mannella*, AFCRC-TR 60–264 (1960).

[18] *F. Kaufman*, J. chem. Physics *28*, 352 (1958).

[19] *P. Harteck, R. R. Reeves*, and *G. G. Mannella*, J. chem. Physics *29*, 1333 (1958).

[20] *H. W. Ford* and *N. Endow*, J. chem. Physics *27*, 1156 (1957).

in the atmosphere is a field of research for itself and it is not possible to discuss this matter here.

The values of the rate coefficients for three-body reactions, as measured by different authors, are tabulated in Table I. Although the values are frequently determined by different methods, it can be seen that there is a general agreement of these coefficients within a factor two or less.

It should be noted that the existence of oxygen predominantly as O-atoms in the upper atmosphere above 100 km. is an accepted fact for the following reasons:

I. Experimentation with rockets gave the impressive result that above 100 km. the atmosphere is practically transparent in the wavelength region of 1450 Å. This is only possible if the O_2 is dissociated to a large extent into atoms [21].

II. An NO release by rocket [22] in the 100 km. region gave a luminosity which could only be reasonably attributed to a reaction with O-atoms:

$$NO + O \rightarrow NO_2 + h\nu$$

Since the rate for reaction (1) is now determined, and the UV intensity which strongly dissociates O_2 ($\lambda <$ 1800 Å.) is known to be about 10^{13} quanta per cm^2sec., it can be calculated [23] how far down the O_2 is predominantly dissociated if the transition region due to convection diffusion and the effect of absorption at longer wave lengths is disregarded. The calculation is based on the equation

$$\Sigma h\nu_{(abs)} = \int_{H_0}^{\infty} k\, e^{-3\,Mgj/HRT}\, dH = \Sigma \text{ Recombinations}$$

where $\Sigma h\nu_{(abs)}$ is the amount of light absorbed per cm^2 per second which dissociates the oxygen, H is the altitude at which the oxygen is predominantly dissociated, M is the average molecular weight and g is the gravitational constant. The calculation shows, with these simplifications and using a recombination coefficient of $3 \cdot 10^{-33}$, that during the day the O_2 should be dissociated down to a pressure of 1 micron, corresponding to an altitude of about 95 km.

The solar radiation will also dissociate nitrogen into atoms. At present, however, it is difficult to make reliable estimates concerning the stationary state of N-atoms in the atmosphere. In this regard the role of ion-reactions will be discussed later in this paper. From the absorption spectra of N_2 and O_2, and the intensity distribution of the incident ultraviolet light, a rough estimate can be made showing that the upper limit of primary formed N-atoms is in the order of magnitude of 1 % of the O-atoms formed. The N-atoms may then recombine in three-body combination with O-atoms via:

(4) $O + N + M \rightarrow NO + M$

The N-atoms may also be destroyed by two-body reaction with O_2:

$$N + O_2 \rightarrow NO + O \quad (6)$$

In Figure 1 the lifetime for N-atoms is given considering only the reaction with O_2 dependent on temperature and O_2 particle concentration. In addition, the reaction of N-atoms with NO is very fast (Reaction 7, Table II), so that for each N-atom consumed by reaction (6), a second N-atom may become consumed by reaction (7). At present the stationary N-atom concentration above 100 km. altitude is not known and, therefore, only under various assumptions, can a distribution of the N-atoms be calculated.

The qualitative evidence for the presence of N-atoms is given by the emission of N-atom lines, and from rocket experiments, leading to the observation of the mass-spectroscopic peaks at mass 14. However, an upper limit of the N-atoms is given by the lack of evidence for the emission of the NO bands. In laboratory experiments we have found that the NO formation in three-body collision (Reaction 4) leads mostly to excited NO ($A^2\Sigma$, $B^2\pi$) molecules which emit the β and γ bands of NO. A fraction, (f), containing about $^1/_5$ of this light may be observed. In the chemosphere, the O-atom concentration should be at least 10^{12} atoms per cm^3 and, assuming the stationary amount of N-atoms is 10^{11} particles per cm^3 and the scale height, H, 10^6 cm., then the number of light quanta emitted per cm^2 would be:

$$\Sigma h\nu_{NO} = H k_4 [O] [N] [M] [f].$$
$$= 10^6 \cdot 5 \cdot 10^{-33} \cdot 10^{12} \cdot 10^{11} \cdot 10^{13.1}/_5 = 10^9$$
$$H \quad k_4 \quad [O] \; [N] \; [M] \; [f]$$

The emission of 10^9 light quanta as NO bands would then be observed, and hence the N-atom concentration cannot be as high as the assumed 10^{11} atoms per cm^3.

Bimolecular Reactions

In Table II the bimolecular reactions are listed which play a major role in the upper atmosphere. Reaction 6 gives the reaction rate of N-atoms with O_2 and was partly discussed in the last section. In Figure 1 the lifetime of N-atoms dependent on O_2 particle concentration and temperature is given. It can be seen that, due to the reaction of N-atoms with O_2, the lifetime of the N-atoms is restricted in certain regions of the chemosphere. In addition N-atoms are consumed by reactions (7), (9), and (4). Reaction (7) is very fast and is important, because it is never possible that these two species, N-atoms and NO molecules, could coexist while each has a particle concentration of 10^9 or more under the prevailing conditions in the upper atmosphere. Similarly, reaction (10) is very fast and therefore the stationary NO_2 concentration in the presence of O-atoms is very small. If we take only the most important reactions for NO_2 formation (5) [*] and NO_2 decomposition (10) in consideration, then we get for the ratio

[21] *R. Tousey*, J. opt. Soc. America *43*, 245 (1933).

[22] *J. Pressman, L. M. Aschenbrand, F. F. Marmo, A. S. Jursa,* and *M. Zelikoff* in *M. Zelikoff*: The Threshold of Space. Pergamon Press, London-New York-Paris 1957, p. 235.

[23] This type calculation was first done in detail by *R. Penndorf*, J. geophys. Res. *54*, 7 (1949).

[*] Reaction (14) may contribute substantially in certain regions but is neglected here.

Table II. Bimolecular Reactions

Reaction	k[(cm³/particle) sec⁻¹] at 300 °K	k[(cm³/mole)sec⁻¹] at 300 °K	ΔH activation [kcal/mole]	Ref.	Remarks
(6) $N + O_2 \rightarrow NO + O$	$1 \cdot 10^{-10}$	$6 \cdot 10^{7}$	6	[24, 25]	
	$1 \cdot 10^{-10}$	$6 \cdot 10^{7}$	6.2	[26]	
(7) $N + NO \rightarrow N_2 + O$	$1-3 \cdot 10^{-13}$	$6-18 \cdot 10^{10}$	2	[24, 25]	
	$6.6 \cdot 10^{-13}$	$4 \cdot 10^{11}$		[26]	
	$8 \cdot 10^{-11}$	$5 \cdot 10^{13}$		[27]	
(8a) $2NO$	$5 \cdot 10^{-14}$	$3 \cdot 10^{10}$			Relative rates
(8b) $N + NO_2 \rightarrow N_2O + O$	$3 \cdot 10^{-14}$	$1.8 \cdot 10^{10}$		[25]	of a/b/c/ are
(8c) $N_2 + 2O$	$2 \cdot 10^{-14}$	$1.2 \cdot 10^{10}$			accurate
(9) $N + O_3 \rightarrow NO + O_2$	10^{-14}	$6 \cdot 10^{9}$		[28]	
(10) $NO_2 + O \rightarrow NO + O_2$	$1.6 \cdot 10^{-12}$	10^{12}		[26]	
	$3.5 \cdot 10^{-12}$	$2.1 \cdot 10^{12}$		[29]	
	$8.2 \cdot 10^{-11}$	$5 \cdot 10^{13}$		[27]	
(11) $NO_2 + H \rightarrow NO + OH$	10^{-11}	$6 \cdot 10^{12}$		[30]	
(12) $O_3 + H \rightarrow O_2 + OH$	10^{-11}	$6 \cdot 10^{12}$		[31]	
(13) $O_3 + O \rightarrow 2O_2$	$2.1 \cdot 10^{-15}$	$1.3 \cdot 10^{9}$	6	[3]	
	$3 \cdot 10^{-14}$	$1.8 \cdot 10^{10}$	3.2	[4]	
(14) $O_3 + NO \rightarrow O_2 + NO_2$	$5 \cdot 10^{-14}$	$3 \cdot 10^{10}$		[32]	
	$1.7 \cdot 10^{-14}$	$1 \cdot 10^{10}$		[33]	Extrapolated to room temp. see [32]
(15) $O_3 + NO_2 \rightarrow O_2 + NO_3$	$3.3 \cdot 10^{-17}$	$1.96 \cdot 10^{7}$		[34]	
	$7.5 \cdot 10^{-17}$	$4.5 \cdot 10^{7}$		[35]	see [34]
(16) $N_2 + O(^1D) (+M) \rightarrow N_2O(+M)$				[36]	
(17) $O_2 + H \rightarrow OH + O$	$2 \cdot 10^{-25}$	$1.2 \cdot 10^{-1}$	24	[37]	
(18) $OH + O \rightarrow O_2 + H$	10^{-12}	$6 \cdot 10^{11}$			Reverse of equ. (20)
(19) $H_2 + O \rightarrow OH + H$	$3 \cdot 10^{-17}$	$1.8 \cdot 10^{7}$	6	[38]	
(20) $OH + H \rightarrow H_2 + O$	$3 \cdot 10^{-17}$	$1.8 \cdot 10^{7}$	6	[38]	

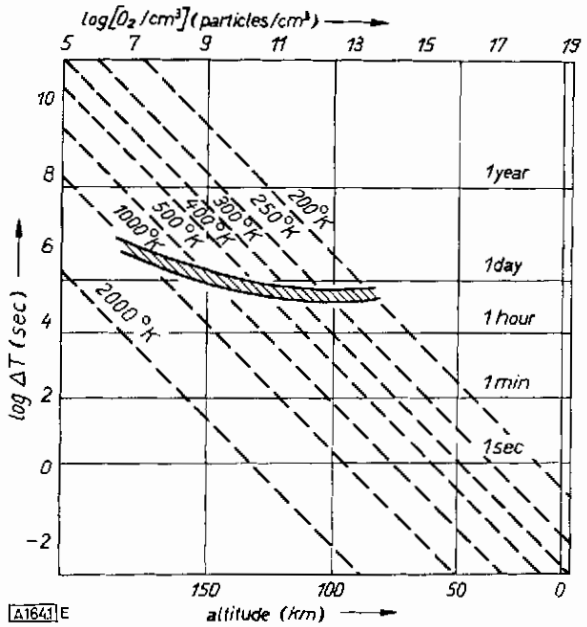


Fig. 1. Average lifetime ΔT of nitrogen atoms. $\Delta T = 1/k_6[O_2]$. Shaded: probable limit of error.

of NO to NO_2 at a particle concentration of $[M] = 10^{13}$ (for three-body collisions):

$$+\frac{d[NO_2]}{dt} = k_5 [NO] [O] [M]$$

$$\frac{d[NO_2]}{dt} = k_{10} [NO_2] [O]$$

Under steady-state conditions

$$\frac{[NO]}{[NO_2]} = \frac{k_{10}}{k_5[M]} = \frac{10^{-12}}{8 \cdot 10^{-32} \cdot 10^{13}} = 1.2 \cdot 10^{6}$$

Since the NO concentration in the chemosphere never reaches values which can be observed by absorption, the NO_2 concentration becomes insignificant even in regions of 200 °K. If the NO_2 concentration is insignificant, then reactions (8a, b, c) can make only a minor contribution to the chemistry of the upper atmosphere. It appears at present, that reaction (8b) cannot be the major source for the N_2O found in the upper atmosphere. It seems more likely that if the N_2O is formed by a photochemical process it must be due to the reaction of excited O-atoms with nitrogen [36], reaction (16). About 10^{15} $O(^1D)$ atoms are produced per cm^2 per second due to photo-decomposition of ozone in the ultraviolet. This is considered sufficient to produce the N_2O observed.

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[26] *G. B. Kistiakowsky* and *G. G. Volpi*, J. chem. Physics *27*, 1141 (1957).

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[34] *H. W. Ford, G. J. Doyle*, and *N. Endow*, J. chem. Physics *26*, 1336 (1957).

[35] *H. S. Johnston*, J. Amer. chem. Soc. *73*, 4542 (1951).

[36] *W. E. Groth* and *H. Schierholz*, J. chem. Physics *27*, 973 (1957).

[37] *B. Lewis* and *G. von Elbe:* Combustion, Flames, and Explosions of Gases. Academic Press, New York, 1951.

[38] *P. Harteck* and *U. Kopsch*, Z. physik. Chem., Abt. B 12, 327 (1931).

Reaction (11) is known to be very fast, but since the NO_2 concentration is only minor it cannot appreciably contribute to the chemistry of the chemosphere. It is also known from rocket experiments [39], that the most abundant negative ion has the mass 46 and if we disregard Na_2, only NO_2^- is possible. It is difficult at present to understand this if such a low NO_2 concentration prevails in the upper atmosphere.

A study of the OH emission in the infrared leads to many interesting conclusions. At present the dominant part of this emission is believed to occur because of the reactions:

$$(12)\quad O_3 + H \rightarrow OH^* + O_2$$
$$OH^* \downarrow$$
$$OH + h\nu$$

$$(18)\quad O + OH \rightarrow O_2 + H$$

The intensity of the observed emission is about 10^{11} photons/cm²·sec., but recent analysis [40] indicates that the number of the primary reactions of $O_3 + H$ per cm²·sec. is in the order of 10^{12} over the entire spectral range (not including radiation by cascading). The total $O_3 + H$ must be greater by at least a factor of two because it occurs with emission in all directions.

Ozone must arise via

$$(2)\quad O + O_2 + M \rightarrow O_3 + M$$

This reaction is then followed by the consecutive reactions (12) and (13) and the H-atom is regenerated by reaction (18). An average rate of O_3 formation by reaction (2) may be calculated for an altitude of 90 km. and a particle concentration $[M] = 10^{14}$ particles/cm³:

$$\frac{d[O_3]}{dt} = k_2\,[O]\,[O_2]\,[M]\,H$$

with

k_2 = $4\cdot10^{-34}$ (cm³/particles)²/sec.
$[O]$ = $3\cdot10^{12}$ (approximate number of O-atoms/cm³)
$[O_2]$ = $2\cdot10^{13}$ (approximate number of O_2 particles/cm³)
$[M]$ = 10^{14} (approximate number of third bodies/cm³)
H = 10^6 (approximate scale height)

$$\frac{d[O_3]}{dt} = 4\cdot10^{-34}\cdot3\cdot10^{12}\cdot2\cdot10^{13}\cdot10^{14}\cdot10^6$$
$$= 2.4\cdot10^{12}\ O_3 \text{ particles/cm}^2\cdot\text{sec.}$$

These conditions can then account for the OH emission if essentially all O_3 formed reacts with H-atoms (Reaction 12).

The reaction

$$(13)\quad O + O_3 \rightarrow 2O_2$$

cannot be predominant over reaction (12), because the amount of OH* formed would be too small to compare with the observed emission of OH bands.

[39] *C. Y. Johnson, E. B. Meadows,* and *J. C. Holmes,* IGY Rocket Report Series No. 1, July 30, 1958, p. 120.

[40] *J. W. Chamberlain* and *C. A. Smith,* J. geophys. Res. *64*, 611 (1959).

Using the approximate values given for the reaction to form O_3, the rate of recombination of O_2 can be estimated:

$$O + O + M \rightarrow O_2 + M \quad (I)$$

$$\frac{d[O_2]}{dt} = k_1\,[O]^2\,[M]\,H, \text{ with } k_1 = 3\cdot10^{-33}$$
$$= 3\cdot10^{-33}\cdot3\cdot10^{12}\cdot3\cdot10^{12}\cdot10^{14}\cdot10^6$$
$$= 2.7\cdot10^{12}\ O_2 \text{ particles per sec.}$$

This means a similar amount of O-atoms may be lost in simple O-atom recombination (Note: *two* O-atoms are lost in the recombination reaction and also *two* in ozone formation when the consecutive reaction (18) is included).

It may be concluded therefore that the consumption of O-atoms may occur by direct recombination in three-body reaction (I) and would be lost in similar quantity by the reaction forming ozone (2). The major part of the ozone formed seems to react with H-atoms giving rise to OH emissions. OH then reacts with a second O-atom giving back the H-atom. This is contrary to what is normally expected, *viz.* that most of the ozone formed is believed to react with an O-atom. If, however, we assume that the two reactions (12 and 13) destroy ozone at an equal rate, then the concentration of H-atoms must have a certain minimum value because:

$$\left(\frac{d[O_3]}{dt}\right)_{13} = \left(\frac{d[O_3]}{dt}\right)_{12}$$

$$-\left(\frac{d[O_3]}{dt}\right)_{13} = k_{13}\,[O]\,[O_3]$$

and

$$-\left(\frac{d[O_3]}{dt}\right)_{12} = k_{12}\,[H]\,[O_3]$$

Under the conditions of the upper atmosphere with $k_{13} = 5\cdot10^{-15}$, $k_{12} = 10^{-11}$, and $[O] = 3\cdot10^{12}$/cm³, the minimum concentration of H-atoms becomes

$$[H] = \frac{[O]k_{13}}{k_{12}} = \frac{3\cdot10^{12}\cdot5\cdot10^{-15}}{10^{-11}} = 1.5\cdot10^9$$

It has to be anticipated that the [H]/[O] ratio will increase with altitude and, therefore, at all higher altitudes any ozone formed will be mainly consumed by the H-atoms.

A further source for ozone formation in the upper atmosphere may arise from the reaction

$$O + O + M \rightarrow O_2(^3\Sigma_u^+) + M \quad (I)$$
$$O_2(^3\Sigma_u^+) + O_2 \rightarrow O_3 + O$$

This reaction is discussed later.

Ion Reactions

The amount of primarily formed ion-pairs and, therefore, the chemical yields by ion reactions, are minor compared with the total amount of uncharged dissociation products formed by the solar radiation. It is possible, however, that the production of nitrogen compounds and nitrogen atoms formed by ion reactions is

larger than by direct photodissociation. Nitrogen is almost transparent until about 800 Å. for solar radiation and since 800 Å. is equivalent to 15.5 eV., which is about the ionization potential of nitrogen, the nitrogen may become only dissociated into $N_2^+ + e^-$ by radiation of wavelengths shorter than 800 Å. [41]. In the older literature it is often erronously stated that $N_2^+ + e^-$ (or negative ions) will react, and that it is by this process that the N_2 will become dissociated into two N-atoms in the upper atmosphere. In the regions of the upper atmosphere, however, where the ion and electron concentrations are orders of magnitudes less than the concentration of the uncharged particles, then it is more probable that reactions involving ions will occur, *i.e.* pure charge transfer reactions and ion-neutral reactions. Reactions (21) and (24) are such charge transfer reactions, whereby a positive ion with higher ionization potential and a particle with lower ionization potential react, the particle giving an electron to the ion (thereby neutralizing it) and becoming itself a positive ion. Obviously the number of possible charge transfer reactions which may occur in the upper atmosphere will be very large; only the important ones are listed here.

Table III. Ion reactions. Pure charge transfer (few examples)

(21) $N_2^+ + O_2 \rightarrow N_2 + O_2^+ + 3.41$ eV
(22) $N_2^+ + N \rightarrow N_2 + N^+ + 1.05$ eV
(23) $N_2^+ + O \rightarrow N_2 + O^+ + 1.99$ eV
(24) $O^+ + O_2 \rightarrow O_2^+ + O + 1.42$ eV

Table IV. Ion reactions. Ion-neutral reactions

(25) $N_2^+ + O_2 \rightarrow NO^+ + NO + 4.44$ eV
(26) $N_2 + O_2^+ \rightarrow NO^+ + NO + 1,03$ eV
(27) $N_2^+ + O \rightarrow NO^+ + N + 3.05$ eV
(28) $N_2 + O^+ \rightarrow NO^+ + N + 1.05$ eV
(29) $N^+ + O_2 \rightarrow NO^+ + O + 6.66$ eV
(30) $N + O_2^+ \rightarrow NO^+ + O + 4.30$ eV
(31) $N^+ + O_2 \rightarrow NO + O^+ + 2.32$ eV
(32) $N + O_2^+ \rightarrow NO + O^+ - 0.04$ eV

Table V. Ionization potentials [eV]

N	14.51	O_3	12.80
O	13.57	H_2	15.42
H	13.54	OH	13.5
Na	5.09	CO_2	13.84
N_2	15.56	CO	13.98
O_2	12.15	CH_4	13.04
NO	9.25 ± 0.2	Xe	12.08
N_2O	11.2 ± 0.5		

In Table V ionization potentials are listed which are of major importance for our consideration. Note that NO is distinguished by the fact that it has the lowest ionization potential in the N_2-O_2 system.

In Table IV a series of ion-neutral reactions is listed where a molecule-ion or atom-ion reacts with an oxygen molecule or atom and *vice-versa*. Unfortunately, at present the relative rates of these reactions are not well known. Since all reactions listed (21 to 33), however, are exothermic it could be expected, that they occur simultaneously, but with different rates. The end product of all reactions where a positive ion is involved in the N_2–O_2 system is NO^+ and NO, O, or N depending upon which particles have been involved in the reaction. If reactions (31) and (32) occur first, then the O^+ formed can react with N_2 forming $NO^+ + N$ (Reaction 28). The NO^+ ion seems to be stable against any chemical reaction. It will react, however, with an electron or a negative ion and by this process may become dissociated, depending upon conditions. If the NO is not dissociated by such a process (*e.g.*: $NO^+ + NO_2^- \rightarrow NO + NO + O$), it may become ionized again by charge transfer or photoionization or may be consumed by reaction with nitrogen [*].

If all ion reactions, which are exothermic, could occur with a high rate coefficient of about 10^{-9}, as assumed from theoretical considerations and from limited experimental knowledge, then obviously there should be no other major concentrations of positive ions in the upper atmosphere except these NO^+ ions. At night all other ions would have ample time to disappear. However, this is not true as can be seen from the results of measurements with ion spectrometers in the upper atmosphere.

We can derive important information from these rocket experiments, where the positive and negative ions are directly measured [**]. As can be seen from Figure 2, during the day there are only O_2^+, O^+, and NO^+ ions at an altitude of 100 km. and no N_2^+ or N^+ ions have been observed in appreciable amounts. At 200 km. altitude the most abundant ion species is O^+, followed by NO^+ and O_2^+. Since no N_2^+ or N^+ ions were observed, they were obviously consumed by charge transfer or ion-neutral reactions according to reactions (21), (25), and (27). The lifetime of the charged particles in the chemsophere during daytime is about 100 seconds, and since no N_2^+ or N^+ were observed (less than 1 %), the lifetimes of N_2^+ or N^+ are less than 1 second. This shows that N_2^+ disappears very fast, even at 200 km. altitudes, probably reacting with each collision, and with a cross section even larger than a normal gas kinetic one. On the other hand the existence of O_2^+ and O^+ ions in high relative concentrations is rather striking. This gives direct evidence that certain exothermic charge transfer and ion-neutral reactions (24, 26, and 28) occur relatively slowly. It can be seen from Figures 2 and 3 that, even at night, the O_2^+ and O^+ ions are not consumed, showing that the heat of activation for reactions (24, 26, and 28) must be at least a few kilocalories; reactions (30 and 32) may be disregarded because we do not know if N-atoms exists in appreciable concentrations at night.

The most reliable conclusions concerning the O_2^+ and O^+ ions may be drawn from the rocket data which is

[41] *G. L. Weissler* in *S. Flügge:* Handbuch der Physik. Springer, Berlin 1956, Vol. 21.

[*] Experiments by *S. Dondes* [42] have shown, that if an N_2–O_2 system is irradiated with ionizing radiation at the pressure range of the chemosphere, the partial pressure of NO at radiation equilibrium is negligible. Since the total chemosphere is equivalent to only a few cm. of air under NPT conditions, it is obvious, that the NO which constitutes only a fraction of 10^{-5} or less is never built up to an amount which could be observed by its absorption spectrum.

[42] *S. Dondes* in *M. Zelikoff:* The Threshold of Space. Pergamon Press, London-New York-Paris 1957, p. 116.

[**] We are greatly obliged to *C. Y. Johnson* and *J. Holmes* of National Research Laboratory who allowed us to use the results given in Figures 2 and 3 for discussion.

given for night time flights. During the day the influx of solar radiation may cause various effects which are not known at this time. From Figures 2 and 3 we can see the relative abundance of mass units 16 (O^+), 30 (NO^+), and 32 (O_2^+). It is immediately apparent that

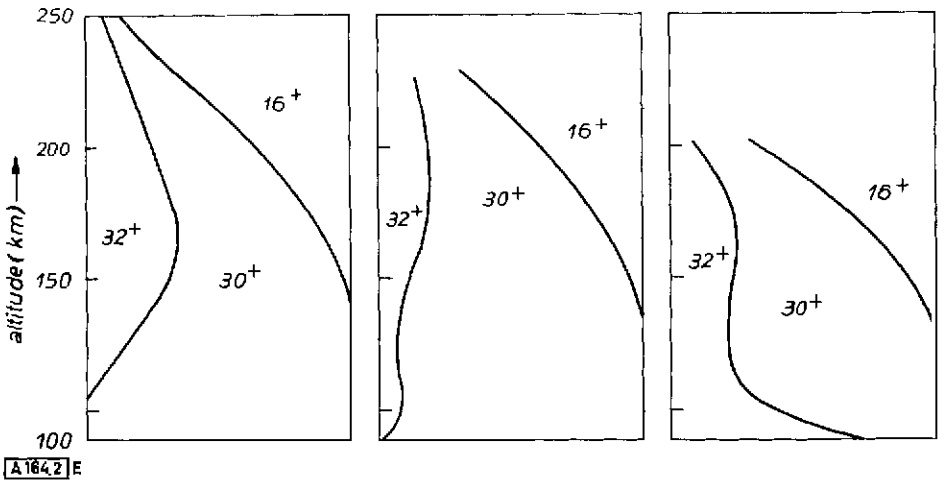


Fig. 2. Distribution of the major positive ions above Fort Churchill, Canada. Rocket Aerobee-HI. Left: November 20, 1956 (night); middle: February 21, 1958 (night); right: March 23, 1958 (day). The numbers indicate masses of positive ions.

O_2^+ is not readily destroyed by an ion-neutral or charge transfer reaction. During the day at 100 km. altitude, the O_2^- concentration is appreciably higher than at night. From these facts it follows that the reaction:

(26) $O_2^+ + N_2 \rightarrow NO + NO^+$

is limited by a rate coefficient of less than 10^{-14}.

Small amounts of NO may transfer charge with O_2^+, but this is difficult to evaluate without a reasonably good estimate of the NO in the 100–150 km. region. The O^+ ion may transfer charge according to

(24) $O^+ + O_2 \rightarrow O_2^- + O$

or react in the ion-neutral reaction

(28) $O^+ + N_2 \rightarrow NO^+ + N$

Again the charge transfer with NO is difficult to evaluate. As can be seen in Figures 2 and 3, there is only a minor decrease of the relative O^+ concentration from day to night, which is direct evidence that reactions (24) and (28) are slow. The O-atoms are considered to have an appreciable concentration down to 100 km.; but no O^+ ions are observed either day or night at 100 km. altitude. O^+ ions are only found down to about 130 km. during the day, and during the night the lower limit is about 145 km. From these facts, however, we can estimate the upper limits of the rates for reactions (24) and for (28). These limits differ by a decade, because at the altitudes concerned the concentration of N_2 is at least an order of magnitude larger than the concentration of O_2. The upper limit for k_{24} can be shown to be about 10^{-12} and for k_{28} to be about 10^{-13} [*].

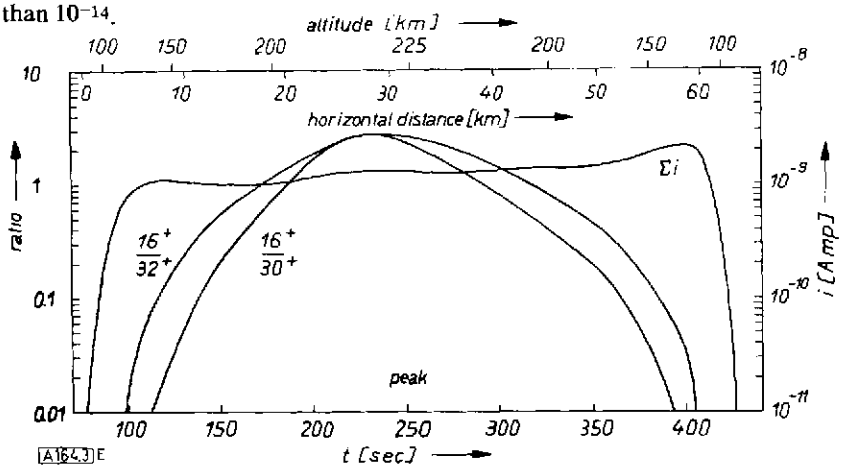


Fig. 3. Ratio of positive ions with mass numbers 16, 30 and 32 above Fort Churchill, Canada. Rocket Aerobee-HI. Experiment made February 21, 1958 (cf. Figure 2, middle).

The point of these particular comments is that all charge transfer and ion-neutral reaction should result in NO^+. During the night, however, appreciable amounts of O_2^+ and O^+ can survive. Therefore, the charge-transfer and ion-neutral reactions, which one normally assumes to have rates equivalent to the collision rate of $k = 10^{-10}$ or higher, must actually have rates in many reactions a few decades lower.

[*] This calculation had been made under the assumption that there is no appreciable ionizing radiation coming from outer space into the upper atmosphere during the night time.

It is well known from laboratory experiments that in the recombination process by three-body collisions, N_2 and NO are formed to a large extent as electronically excited species. Especially in the case of NO it seems from our experimentation that the formation of electronically excited species is by far the most abundant process. It seems to be only reasonable to expect that electronically excited oxygen should be formed to a large extent by three-body recombination [2]. The Herzberg bands are actually emitted very weakly as is known from laboratory experiments with O-atom-O_2 mixtures at about 1 mm. pressure. The atmospheric oxygen bands are somewhat more intense. The observed intensity of these bands is many decades weaker than the light emission from the recombination processes of active nitrogen or from the NO formation under analogous conditions. It must be realized, however, that in the case of N_2 and NO there are electronically excited states from which allowed transitions emitting light can occur, whereas in the case of the O_2 the electronically excited species can only make forbidden or strongly forbidden transitions. Therefore the activated O_2 species may become de-activated before light emission. We have some indication for this. In the night sky radiation, the Herzberg bands are most likely due to the process:

$$O + O + M \rightarrow O_2(^3\Sigma_u^+) + M \text{ and}$$

$$O_2(^3\Sigma_u^+) \rightarrow O_2(^3\Sigma_g^-) + h\nu$$

These are emitted more strongly from altitudes with a prevailing pressure of 1 micron or less, than in laboratory experiments at 1 mm. pressure. This is true even if the sum of recombination processes per cm^2 in the laboratory experiments is orders of magnitudes larger than those of the upper atmosphere.

In our laboratory experiments [44] we were able to enhance the formation of $O_2(^3\Sigma\hat{u})$ by surface catalysis so that it was possible to observe the emission of the Herzberg bands. The luminosity, however, was restricted to the vicinity of the catalyzing surface and faded out at a distance of a few mm. The diffusion time for a distance of 2 mm. at a pressure of 100 microns was about 10^{-5} seconds. In this time interval the excited oxygen molecules may have made in the average only a few collisions with unexcited O_2 molecules. At 1 micron pressure in the upper atmosphere the lifetime of the excited species should be about 100 times as long giving the excited molecules a higher probability of emitting light before becoming deactivated. It seems likely to us, that the excited $O_2(^3\Sigma\hat{u})$ molecules can be destroyed by reaction with O_2 molecules:

$$O_2(^3\Sigma)_u^+) + O_2 \rightarrow O_3 + O$$

Experiments along these lines are already in hand in our laboratory.

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[43] *G. Mannella* and *P. Harteck*, J. chem. Physics, in press.

Phosphorus Nuclear Magnetic Resonance Spectroscopy

BY DR. RICHARD A. Y. JONES [*] AND DR. A. R. KATRITZKY

THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE, ENGLAND

Nuclear magnetic resonance of the ^{31}P nucleus is suitable for the structural elucidation of phosphorus compounds, also for analytical and kinetic studies. In this paper, an attempt has been made towards the presentation of a comprehensive review of all ^{31}P resonances so far determined.

Introduction

Nuclear magnetic resonance spectroscopy has recently become a technique of great importance to the chemist. The main emphasis has rightly been placed on proton resonance, but it has been found that the ^{31}P nucleus gives rise to very useful resonance spectra. This subject was reviewed by *Finegold* [1] in 1958, and a short account is also to be found in the book written by *Pople*, *Bernstein*, and *Schneider* [2a].

Nuclei with odd atomic or mass numbers have magnetic moments. Examples are ^1H, ^{19}F, ^{31}P. In a magnetic field these nuclei precess about the direction of the field with a frequency proportional to the applied field strength; the constant of proportionality depends on the type of nucleus [2b]. The resonance frequency is about 17.2 Mc/sec. for the ^{31}P nucleus in a magnetic field of 10000 gauss. The precession can be perturbed by the application of electromagnetic radiation of the resonance frequency.

[*] Present address: Department of Chemistry, The University, Sheffield, England.

[1] *H. Finegold*, Ann. New York Acad. Sci. *70*, 875 (1958).

[2a] *J. A. Pople*, *W. G. Schneider*, and *H. J. Bernstein*: High Resolution Nuclear Magnetic Resonance, McGraw Hill, New York 1959, p. 347.

[2b] Cf. [2a] or *K. H. Hausser*, Angew. Chem. *68*, 729 (1956).

The ratio of applied field strength to frequency is not quite the same for all nuclei. The electron cloud shields the nucleus from the applied field; thus the field at the nucleus differs from the applied field by a small fraction. Since the electronic distribution depends on the nature of the chemical compound the resonance frequency of two nuclei of the same type, but in different chemical surroundings, will differ. This difference is called a "chemical shift." It is generally measured as parts per million of the applied field or frequency, and thus in a given case it is numerically independent of either. Chemical shifts were first reported for phosphorus compounds by *Knight* [3].

If two different nuclei both having magnetic moments, or two similar nuclei in different chemical environments, are present in the same molecule, there will be an interaction between their magnetic fields which may lead to the splitting of the resonance peaks into multiplets. The degree of splitting depends on the nature of the nuclei involved, and on their proximity to each other. This is called "spin-spin interaction." In phosphorus compounds, splitting of the ^{31}P resonance by ^{1}H or ^{19}F nuclei, and also by other ^{31}P nuclei in some compounds containing more than one phosphorus atom, is frequently observed. A resonance peak split by n equivalent hydrogen or fluorine nuclei will give a multiplet of $n+1$ peaks whose intensities will be proportional to the binomial coefficients. For example, the $P-CH_3$ group will exhibit four peaks with a 1:3:3:1 intensity pattern. In general, two dissimilar phosphorus nuclei in the same molecule will give two doublets which may be further split by hydrogen or fluorine nuclei.

It is easy to discover whether two peaks arise from two nuclei with different chemical shifts or from one nucleus whose resonance is split by spin-spin interaction. Chemical shifts are numerically independent of the applied field or frequency. Spin-spin splitting is proportional to both (thus it is usually measured in cycles per second, or occasionally in gauss, rather than in p.p.m.). Consequently if resonance is observed at two different field strengths, the separation of two peaks, measured in p.p.m., will be the same if they arise from two different nuclei, but different if they arise from spin-spin interaction.

Experimental Methods

The main disadvantage of the ^{31}P nucleus for N.M.R. spectroscopy is that it has a small magnetic moment, and that consequently, atom for atom, the sensitivity is only about 7 % of that for the ^{1}H or ^{19}F nuclei at the same field strength. However, the chemical shifts for ^{31}P cover a range of 500 p.p.m. compared with about 10 p.p.m. for ^{1}H resonance, so that the overlapping of peaks is less important with phosphorus and a lower signal to noise ratio is acceptable. Furthermore, a sample tube of larger diameter may be used with phosphorus since the broadening of the peaks caused by lack of homogeneity of the field throughout the sample is less disadvantageous in the (usually) simple spectra from phosphorus nuclei than in the much more complex spectra derived from protons.

Nevertheless, it has usually been necessary to use a sample which is at least 1 M. in phosphorus, so that the applicability of the method to solid compounds has been limited. The introduction of magnets capable of higher fields is improving this situation to some extent, and recently *Cohn* and *Hughes* [4] have described a technique for measuring the chemical shifts of weak spectra containing broad resonance peaks. These workers have been able to obtain useful results from the spectra of adenosine di- and triphosphate in 0.09 M. solutions and suggest that their method could be extended to solutions as dilute as 0.01 M.

The positions of peaks are determined by reference to a standard substance. In the case of N.M.R. spectroscopic studies with phosphorus this is nearly always an external standard. Calibration is generally carried out by the side-band method, whereby an audiofrequency signal is superimposed onto the radiofrequency oscillator, giving rise to subsidiary resonance peaks on either side of the main one, and separated from it by a distance (in c/sec.) corresponding to the audiofrequency. The standard may be in a small tube inside the sample tube so that the resonance peaks of sample and standard appear on the same spectrum.

If the resonance peak of the sample is weak, and it is necessary not to cause further weakening by adding the standard tube, the sample and standard may be placed alternately into the spectrometer and the side-band of the standard adjusted until it falls in the same place on the oscilloscope screen as the resonance peak of the sample. The use of an external standard introduces a certain error if the diamagnetic susceptibilities of the sample and standard are not the same. For phosphorus resonance this error is small compared with the very wide range of chemical shifts, and it is usually ignored. Errors of $\pm$ 1 p.p.m. are generally quite acceptable for phosphorus resonance, whereas for proton N.M.R. spectroscopy an accuracy of $\pm$ 0.01 p.p.m. may be required.

Chemical Shifts of Phosphorus Compounds

1. Standards

All the chemical shifts which have been reported for phosphorus resonance are given in the appendix. The data are all in the form of parts per million from 85 % aqueous phosphoric acid, which is the universally recognized primary standard. Common secondary standards are recorded in Table 1. For measurements in aqueous solution, a knowledge of the variation of the phosphoric acid peak with the degree of ionisation is important. In contrast to early work, it has recently been shown [28] that the resonance peak decreases smoothly with ionisation, reaching -6 p.p.m. at PO_4^{3-}.

Table 1. Secondary standards

Standard	PBr_3	$(PhO)_3P$	$(o\text{-}MeC_6H_4O)_3PO$
Shift [p.p.m.]	−227	−127	+17

[3] *W. D. Knight*, Physic. Rev. *76*, 1259 (1949).

[4] *M. Cohn* and *T. R. Hughes*, J. biol. Chemistry *235*, 3250 (1960).

2. Chemical Shift Generalizations

Dickinson noticed in 1951 that tri- and pentavalent phosphorus derivatives absorbed at widely different frequencies [5]. Later, several authors [6, 7] pointed out that the trivalent derivatives cause absorption over a very wide range (*ca.* −200 to +200 p.p.m., although the majority are below −100), whereas the phosphoryl (−60 to +40) and thiophosphoryl (−100 to −50) ranges are considerably narrower. However, these ranges are merely guides, and exceptions are known, *e.g.* $PSBr_3$ at +111 p.p.m., $POBr_3$ at +102 p.p.m. The question as to whether the shift in any compound can be predicted from the groups attached to the phosphorus atom, *i.e.* whether "group shifts" exist, has received attention.

Van Wazer, *Shoolery* and their coworkers [7] have concluded that this is possible and have published tables for 3- and 4-coordinated phosphorus compounds; some of their values are reproduced in Table 2. They claimed that predicted values

Table 2. "Group shifts" for trivalent phosphorus compounds [7].

Group	Br	Cl	I	OR	NR_2	OAr	F	S	Ar	R	H
Shift [p.p.m.]	−80	−74	−66	−55	−47	−42	−27	−23	0	+20	+69

were usually correct to ± 10 or 20 p.p.m., but admitted exceptions such as R–PClF: calc. −85, found +20 p.p.m. For 4-coordinated phosphorus compounds, they also gave the following generalizations relating to the effect of substitution:

Substitution of	Shift
R_2N for RO	−11 ± 2 p.p.m.
RS for RO	−25 to −30 p.p.m.
S= for O=	*ca.* −60 p.p.m.

On the other hand, *Muller*, *Lauterbur*, and *Goldenson* [6] have concluded that there is no quantitative correlation between the chemical shift, δ, and the nature of the atom or group bonded to the phosphorus atom. They pointed out that the chemical shifts of A_2BPX were often more negative than those of either A_3PX or B_3PX rather than at intermediate values: *e.g.* $(EtO)_3PS$ −68 p.p.m., $(EtS)_3PS$ −93 p.p.m., but $(EtO)_2(EtS)PS$ −94 p.p.m.

We have examined the suggested "group shift" values of *Van Wazer*, *Shoolery et al.* [7] statistically. For trivalent phosphorus compounds the discrepancies range from −101 to +93 p.p.m., and the standard deviation for forty-one compounds is 37 p.p.m., a far larger figure than they had suggested.

For 4-coordinated compounds we have calculated the means, and standard deviations, for the substitutions they mention as follows:

Substitution of	Shift	
R_2N for RO	−10 ± 10 p.p.m. [*]	(8 compounds)
RS for RO	−20 ± 11 p.p.m.	(13 compounds)
S= for O=	−43 ± 24 p.p.m.	(22 compounds)

[5] *W. C. Dickinson*, Physic. Rev. *81*, 717 (1951).

[6] *N. Muller*, *P. C. Lauterbur*, and *J. Goldenson*, J. Amer. chem. Soc. *78*, 3557 (1956).

[7] *J. R. VanWazer*, *C. F. Callis*, *J. N. Shoolery*, and *R. C. Jones*, J. Amer. chem. Soc. *78*, 5715 (1956).

[*] If one exceptional value is omitted this may be amended to −6 ± 5 p.p.m.

Replacing an alkyl by an aryl group increases the phosphorus resonance frequency; it has been pionted out [4] that this is contrary to expectation for the ring current theory of aromatic systems, and that presumably inductive and mesomeric effects must predominate in this case.

Theoretical Basis for Chemical Shift Variations

Gutowsky and *McCall* [8] have stated that the decreasing shielding $PF_3 > PI_3 > PCl_3 > PBr_3$ (the same order as the proton resonance in the HCX_3 and CH_2X_2 series) indicates two opposing effects, presumably the electronegativity and the ability to form double bonds. The greater shielding in $POCl_3$ than in $PSCl_3$ suggests that PO has more double bond character than PS [8]. In the series $H_2PO(OH)$, $HPO(OH)_2$, $PO(OH)_3$, the shielding increases as H is replaced by OH, contrary to expectation from electronegativity and again suggesting the importance of doubly bonded structures, in this case of the P=ÖH type [8].

Some attempt has been made at relating the ^{31}P chemical shift to the detailed electronic structure of the molecule. However, the mathematical-physical evaluation of the factors influencing the chemical shift cannot usually be made as readily for ^{31}P as for ^{19}F, as has been pointed out by *Finegold* [1].

Muller, *Lauterbur*, and *Goldenson* [6] show that if certain assumptions are made, the relationship

$$\delta = a - bD \quad (1)$$

will hold where D is the number of unbalanced p-electrons and a and b have to be determined empirically. For PX_3 compounds

$$D = {}^{1}\beta^2(1-\varepsilon) \quad (2)$$

where β depends on the bond angle X–P–X and ε is defined by equating (1 + ε) with the number of electrons for each P–X bond that belongs to the P atom. Thus ε may be determined from the electronegativity difference between phosphorus and the neighbouring atom.

The authors show that, with reasonable assumptions, this treatment will account for the gross variations in the chemical shifts of some PX_3 compounds. However, *Parks* [9] pointed out that the above treatment showed a large discrepancy for PF_3 and modified the equations (1) and (2) to:

$$\delta = -230 + 29.0 \times 10^3 \times e^{-46\,D'}$$

$$D' = [0.75 - \beta^2]\,\beta^2(1-\varepsilon)$$

which gave much better agreement.

[8] *H. S. Gutowsky* and *D. W. McCall*, J. chem. Physics *22*, 162 (1954).

[9] *J. R. Parks*, J. Amer. chem. Soc. *79*, 757 (1957).

Effect of Other Structural Features

5- and 6-Coordinated phosphorus compounds [7, 10–15] show large positive chemical shifts; this has been attributed to the involvement of d-orbitals in the bonding [7]. "Bent bonds," as in P_4 and P_4S_3, also give rise to large positive shifts (cf. refs. [6, 7]). Incorporating the phosphorus atom in a 5- or 6-membered ring does not have any constant effect on the resonance position [16].

Effect of Solvents

Although white phosphorus itself is an exception [17], solutions of most phosphorus compounds in carbon disulphide and carbon tetrachloride show little variation of chemical shift with concentration. It has been suggested that shifts in other solvents are due to hydrogen bonding [6]. Values for trimethyl phosphate in various solvents are shown in Table 3 [18].

Table 3. Chemical shift of Me_3PO_4 in various solvents (50 % by volume)

Solvent	Shift [p.p.m.]	Solvent	Shift [p.p.m.]
pure liquid	2.4	Me_2CO	1.9
H_2O	2.7	AcOH	2.1
3 *N* HCl	2.7	AcOEt	1.9
3 *N* NaOH	2.7	$CHCl_3$	2.1
MeOH	2.0	Et_2O	2.0
EtOH	1.7	$Ph-CH_3$	1.9
pyridine	2.3	CCl_4	2.1

Spin-Spin Splitting

Spin-spin splittings of phosphorus resonance peaks were first observed by *Gutowsky* and *McCall* [19, 20] who studied several compounds with one or two fluorine or hydrogen atoms directly attached to phosphorus. They obtained the expected doublet and 1:2:1 triplet patterns. *Gutowsky*, *McCall*, and *Slichter* [21] obtained a signal of seven peaks from HPF_6. It was soon confirmed that the splitting was field independent [22].

For compounds with a hydrogen or fluorine atom directly attached to phosphorus, the splitting is very large.

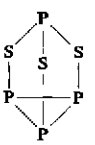
Table 4. Ranges observed for splitting of ^{31}P resonance by adjacent ^{1}H or ^{19}F nuclei.

	P–H		P–F	
	Number of compounds	Splitting c/sec.	Number of compounds	Splitting c/sec.
PIII	3	180–210	5	570–1420
>P=O	13	500–700	5	980–1190
>P=S, Se	3	490–630	0	–

For compounds with one or two other atoms separating the phosphorus and the proton (or fluorine) the splitting is much smaller, but can usually still be seen (*e.g.* eight of the ten peaks expected for $P(OMe)_3$ were resolved [23]). *Finegold* [1] has given the following generalizations for these compounds:

	Splitting	
	P–X–H	P–X–X–H
PIII >P=S	15–20 c/sec.	15–20 c/sec.
>P=O	10 c/sec.	*ca.* 5 c/sec.

The hydroxyl proton in P–OH compounds does not cause splitting, presumably due to rapid exchange [6].



I

Strain appears to increase the degree of splitting: P_4S_3 (I) shows two peaks of area ratio 1:3; the smaller is a quartet and the larger a doublet, as expected with a splitting of 86 c/sec. [7, 23].

Recently the fine structure of the phosphorus resonance has been used to show that the methylene protons in $CH_3PS(OEt)_2$ are not equivalent. This may be due either to preferred ethoxy group orientations, or to unequal P–O bond orders [24a, b].

Structure Determination

The technique is especially suitable for structure determination. It may advantageously be used together with infrared spectroscopy as emphasized by *Finegold* [1].

[10] *M. Becke-Goehring*, Angew. Chem. *73*, 246 (1961).

[11] *G. H. Birum* and *J. L. Dever*, Abstracts of 134th ACS Meeting, Chicago, 1958, p. 101-P.

[12] *E. Fluck*, personal communication.

[13] *F. W. Hofmann, T. C. Simmons*, and *L. J. Glunz*, J. Amer. chem. Soc. *79*, 3570 (1957).

[14] *F. Ramirez* and *N. B. Desai*, J. Amer. chem. Soc. *82*, 2652 (1960).

[15] *Q. E. Thompson*, J. Amer. chem. Soc. *83*, 845 (1961).

[16] *R. A. Y. Jones* and *A. R. Katritzky*, J. chem. Soc. (London) *1960*, 4376.

[17] Bro. *Simon Peter*, Physic. Rev. *93*, 940 (1954).

[18] *R. A. Y. Jones* and *A. R. Katritzky*, unpublished.

[19] *H. S. Gutowsky* and *D. W. McCall*, J. chem. Phyiscs *21*, 279 (1953).

[20] *H. S. Gutowsky* and *D. W. McCall*, Physic. Rev. *82*, 748 (1951).

[21] *H. S. Gutowsky, D. W. McCall*, and *C. P. Slichter*, Physic. Rev. *84*, 589 (1951).

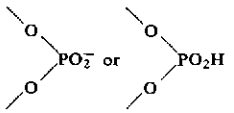
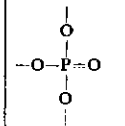
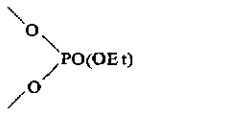
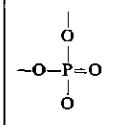
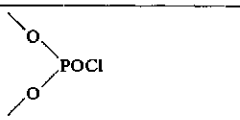
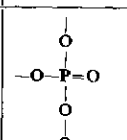
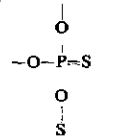
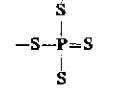
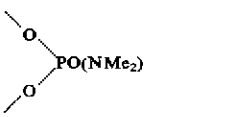
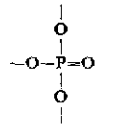
[22] *W. E. Quinn* and *R. M. Brown*, J. chem. Physics *21*, 1605 (1953).

[23] *C. F. Callis, J. R. VanWazer, J. N. Shoolery*, and *W. A. Anderson*, J. Amer. chem. Soc. *78*, 5715 (1956).

[24a] *H. Finegold*, J. Amer. chem. Soc. *82*, 2641 (1960).

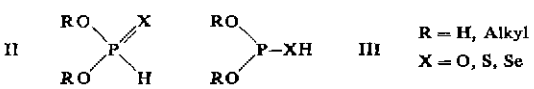
[24b] Footnote added in proof: After this article had been submitted, *J. S. Waugh* and *F. A. Cotton*, J. physic. Chem. *65*, 562 (1961), pointed out that this result is better interpreted by supposing that the hydrogen atoms of each methylene group are nonequivalent rather than that the two methylene groups are in some way different. For a detailed discussion of this point see *L. M. Jackman:* Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry. Pergamon Press, Oxford 1959, p. 99.

Table 5. Chemical shifts [p.p.m.]: condensed phosphates and their derivatives

Isolated	δ	End	δ	Middle	δ	Branching	δ	Ref.
Orthophosphates [28]								
PO_4^{3-}	−6	$-O-PO_3^{2-}$	+5					
HPO_4^{2-}	−3.5	$-O-PO_3H^-$	+10					
$H_2PO_4^-$	−0.5	$-O-PO_3H_2$	+10	in short chains	+18	in alkali metal ultraphosphates	+30 [*]	[7, 23, 29]
H_3PO_4	0			in rings or long chains	+20	in azeotropic phosphoric acid	+34 [*]	
$(EtO)_3PO$	+1	$-O-PO(OEt)_2$	+13		+28		+41 [*]	[30]
$POCl_3$	−2	$-O-POCl_2$	+9		+30		+50 [*]	[31] cf. also [32]
$PSCl_3$	−29	$-O-PSCl_2$	−28					
					−20		−3	
		$-S-POCl_2$	−10				−60	
$(Me_2N)_3PO$	−23	$-O-PO(NMe_2)_2$	−11.5		+12		+40 [*]	[33]

[*] Differences in these values are ascribed to the effect of differing electronegativities on the electronic distribution around the phosphorus atom [30].

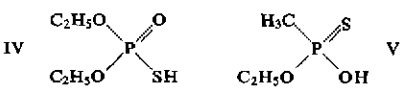
1. Hypophosphorous Acid, Phosphorous Acid, and its Dialkyl Esters and their Thio- and Seleno-Analogues



II III R = H, Alkyl; X = O, S, Se

Phosphorus resonance spectra show conclusively that these compounds exist in the tetracovalent form (II) and not in the tricovalent form (III) [1, 6, 25]. The position of the resonances at once suggest the tetracovalent structure, and the very large splitting observed confirms that a proton must be directly attached to the phosphorus atom (see Table 4).

2. Monothiophosphoric and -Phosphonic Esters

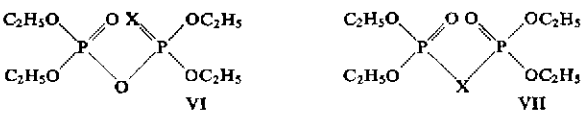


IV V

Chemical shift values suggest that these compounds exist predominantly in the tautomeric forms shown (IV, V) [1].

These conclusions are in excellent agreement with evidence obtained using the *Hammet* equation [26].

3. Monothiopyrophosphates and Related Compounds



VI VII

Rational syntheses of VI and VII (X = S) yield identical products; phosphorus resonance spectra show convincingly that these, and the seleno-analogue, have structure VI (X = S, Se): two peaks are found in the expected positions [27]. Similarly, the unsymmetrical structure

[25] *R. A. Y. Jones, A. R. Katritzky,* and *J. Michalski,* unpublished results..

[26] *M. I. Kabachnik, T. A. Mastrukova, A. E. Shipov,* and *T. A. Melentyeva,* Tetrahedron *9*, 10 (1960).

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

[28] *R. A. Y. Jones* and *A. R. Katritzky,* J. inorg. nucl. Chem. *15*, 193 (1960).

[29] *J. R. VanWazer, C. F. Callis,* and *J. N. Shoolery,* J. Amer. chem. Soc. *77*, 4945 (1955).

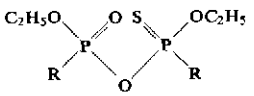
[30] *E. Schwarzmann* and *J. R. VanWazer,* J. Amer. chem. Soc. *83*, 365 (1961).

[31] *L. C. D. Groenweghe, J. H. Payne,* and *J. R. VanWazer,* J. Amer. chem. Soc. *82*, 5305 (1960).

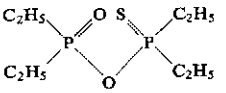
[32] *D. P. Ames, S. Ohashi, C. F. Callis,* and *J. R. VanWazer.* J. amer. Chem. Soc. *81*, 6350 (1959).

[33] *E. Schwarzmann* and *J. R. VanWazer,* J. Amer. chem. Soc. *82*, 6009 (1960).

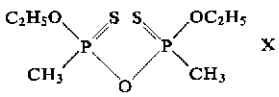
has been demonstrated for VIII and IX [25], whereas X has the symmetrical structure shown [1].



VIII



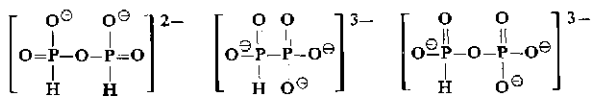
IX



X

4. Oxyacids containing Two Phosphorus Atoms

In addition to the well known pyrophosphates and hypophosphates, three series of salts have been described: pyrophosphites (XI), diphosphites (XII), and isohypophosphates (XIII). *Van Wazer*, *Shoolery* and their coworkers [23] have shown that phosphorus



XI XII XIII

resonance spectra provide powerful support for the structures shown. Pyrophosphites show a doublet with large splitting (due to P–H). The diphosphites show a complex ABX type spectrum (nomenclature of *Pople*, *Bernstein*, and *Schneider* [2]) consistent with structure XII. Isohypophosphates show three main peaks, a singlet due to the phosphorus surrounded by oxygen atoms and a doublet (620 c/sec. splitting) for the phosphorus directly attached to hydrogen. These peaks all show weak splitting (17 c/sec.) due to the non-equivalence of the phosphorus atoms.

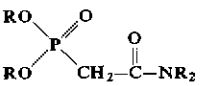
5. Condensed Phosphates and Derivatives

Van Wazer et al. have shown that phosphorus magnetic resonance spectra differentiate terminal, internal and branching point phosphate residues in the polyphosphoric acids and their salts and esters, and in polyphosphoryl halides and dimethylamides. Their results are summarized in Table 5.

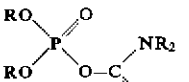
6. Phosphorus-Nitrogen Compounds

Polyphosphoronitrilic chloride, Cl-[-PCl_2=N-]$_n$-H shows two peaks, one due to the terminal phosphorus attached to three chlorine atoms at +7.7 p.p.m. and the other due to the rest of the phosphorus atoms at +16.8 p.p.m. The relative areas of the peaks gave n = 11 in good agreement with other evidence [34]. The spectrum of Cl_3P=N–$POCl_2$ confirms the structure now accepted [35, 36] and is not compatible with the old formulation $P_4O_4Cl_{10}$. The structure of various cyclic triphosphonitriles is supported by NMR spectral data [37–39].

7. Miscellaneous

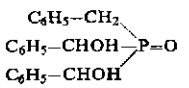


XIV

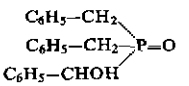


XV

Speziale and *Freeman* [40] used the technique to show that certain phosphorus compounds had structures of type XIV rather than XV by comparison with model compounds of known structure.



XVI



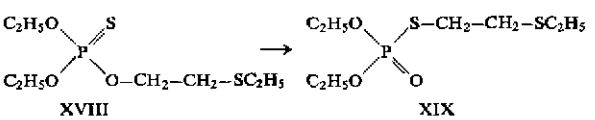
XVII

Phosphine and benzaldehyde react to form a product whose structure XVI was strongly supported by comparison of the phosphorus peak with the authentic compound XVII [41].

Other Applications

1. Kinetics and Reaction Mechanisms

The reaction XVIII → XIX was conveniently followed by observing the fall in the peak at −67.7 p.p.m., and



XVIII XIX

the rise in the peak at −25.9 p.p.m. [42]. The alcoholysis of $EtPCl_3^+AlCl_4^-$ to $EtPO(OEt)_2 \cdot AlCl_3$ was followed by phosphorus resonance and was shown to proceed stepwise via the intermediates $EtPOCl \cdot AlCl_4$ and $EtPO(OEt) \cdot AlCl_4$ by comparison with the authentic spectra of these compounds [13]. This type of measurement is clearly capable of wide application.

2. Analysis of Mixtures

Callis, *Van Wazer*, and *Shoolery* [43] have described the analysis of mixtures of many phosphorus oxy-acids. Provided the solutions are reasonably concentrated analyses of this type are very convenient and rapid.

---

[34] *M. Becke-Goehring* and *G. Koch*, Chem. Ber. *92*, 1188 (1959).

[35] *M. Becke-Goehring*, *A. Debo*, *E. Fluck*, and *W. Goetze*, Chem. Ber. *94*, 1383 (1961).

[36] *E. Fluck*, Chem. Ber. *94*, 1388 (1961).

[37] *M. Becke-Goehring*, *K. Kohn*, and *E. Fluck*, Z. anorg. allg. Chem. *302*, 103 (1959).

[38] *A. C. Chapman*, *D. H. Paine*, *H. T. Searle*, *D. R. Smith*, and *R. F. M. White*, J. chem. Soc. (London) *1961*, 1768.

[39] *M. L. Heffernan* and *R. F. M. White*, J. chem. Soc. (London) *1961*, 1382.

[40] *A. J. Speziale* and *R. C. Freeman*, J. org. Chemistry *23*, 1883 (1958).

[41] *S. A. Buckler*, J. Amer. chem. Soc. *82*, 4215 (1960).

[42] *N. Muller* and *J. Goldenson*, J. Amer. chem. Soc. *78*, 5182 (1956).

[43] *C. F. Callis*, *J. R. VanWazer*, and *J. N. Shoolery*, Analytic. Chem. *28*, 269 (1956).

3. Identification of Reaction Products

Van Wazer has made very extensive use of phosphorus resonance to determine the products of "reorganization reactions" (Table 6).

It was possible to obtain almost all the equilibrium constants for the above systems.

Mixtures of P_2O_5 with $POCl_3$ [31], $PSCl_3$ [31], $(Me_2N)_3PO$ [33], and $(EtO)_3PO$ [30] and of P_2S_5 with $POCl_3$ [31] and $PSCl_3$ [31] gave rise to condensed phosphates (see Table 5). It was also shown that reaction of phosphoric acid with PCl_3 or PBr_3 gave pyrophosphorous acid [49].

Table 6. The products of "reorganization reactions"

Starting materials	Other products detected	Ref.
H_2O–HF–P_2O_5	(HO)POF_2, $(HO)_2POF$, HPF_6, (HO)FPO·O–, H_3PO_4, $(HO)_2PO{\cdot}O-$, –O–PO(OH)–O–	[32]
$POCl_3$–$POBr_3$	$POCl_2Br$, $POClBr_2$	[44]
$PSCl_3$–$PSBr_3$	$PSCl_2Br$, $PSClBr_2$	[44]
$POCl_3$–H_3PO_4	$(HO)_2POCl$, $(HO)POCl_2$, also end and middle groups of polyphosphoryl chlorides, cf. [31]	[45]
PCl_3–PBr_3–$P(OPh)_3$	PCl_2Br, $PClBr_2$, $(PhO)PCl_2$, $(PhO)_2PCl$, (PhO)PClBr, $(PhO)PBr_2$, $(PhO)_2PBr$	[46]
$POCl_3$–PBr_3 / $POBr_3$–PCl_3	$POCl_3$, $POCl_2Br$, $POClBr_2$, $POBr_3$, PBr_3, $PBrCl_2$, PBr_2Cl, PCl_3	[47]
$POCl_3$–$P(OPh)_3$	PCl_3, $PCl_2(OPh)$, $PCl(OPh)_2$, $POCl_2(OPh)$, $POCl(OPh)_2$, $PO(OPh)_3$	[47]
PCl_3–$P(OEt)_3$	$PCl_2(OEt)$, $PCl(OEt)_2$	[48]
$P(OPh)_3$–$P(NEt_2)_3$	$P(OPh)_2(NEt_2)$, $P(OPh)(NEt_2)_2$	[48]

Appendix

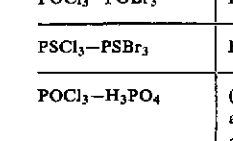
Table of Results for ^{31}P-Nuclear Magnetic Resonance

This table is divided into six sections containing results for:

1. compounds of trivalent phosphorus
2. phosphoryl compounds
3. thiophosphoryl compounds
4. selenophosphoryl compounds
5. other compounds containing one phosphorus atom
6. compounds containing several phosphorus atoms.

It is found that in general, substitution more than two bonds away from the phosphorus atom has little effect on the position of resonance peaks [1]. For this reason a number of results are tabulated by class of compound, particularly those taken from *Finegold*'s table [1], where in many cases the actual compounds measured are not reported. Methyl and isopropyl groups frequently cause anomalous results and are recorded separately wherever possible. In the table, R represents any alkyl group except methyl.

Trivalent Phosphorus Compounds

Ligands			Chemical shift [p.p.m.] [*]	Ref.
CH_3	CH_3	CH_3	+61	[1, 7]
C_2H_5	C_2H_5	C_2H_5	+20.4	[1, 6]
n-C_4H_9	n-C_4H_9	n-C_4H_9	+32.3	[1]
			+21	[41]
C_6H_5	C_6H_5	C_6H_5	+ 7	[1, 6, 7]
CH_3	CH_3	$N(CH_3)_2$	−39	[7]
CH_3	CH_3	H	+98.5 (2; 210)	[7]
C_2H_5	F	F	+30 (3; 980)	[7]
C_2H_5	F	Cl	+20 (2; 570)	[7]
CH_3	Cl	Cl	−191.2	[1, 6]
$Cl(CH_2)_3$–	Cl	Cl	−182	[8]
C_6H_5	Cl	Cl	−162	[1, 6, 7]
C_2H_5	F	i-C_3H_7O–	−29 (2; 980)	[7]
CH_3	OR	OR	−175 ± 2 [a]	[1]
R	OR	OR	−183 [b]	[1]
CH_3	SR	SR	−69.4 [b]	[1]
CH_3	H	H	+163.5 (3; 210)	[7]
F	F	F	−97 (4; 1420)	[8, 19]
Cl	Cl	Cl	−219	[1, 5, 6, 7, 8, 46]
Cl	Cl	Br	−225	[46]
Cl	Br	Br	−228	[46]
Br	Br	Br	−227	[1, 5, 6, 7, 8, 46]
I	I	I	−178	[8]
F	F	OCH_3	−111 (3; 1275)	[8, 19]
Cl	Cl	OCH_3	−181	[1, 6]
Cl	Cl	OC_2H_5	−177	[48]
Cl	Cl	OC_6H_5	−179	[46]
Cl	Br	OC_6H_5	−190	[46]
Br	Br	OC_6H_5	−200	[46]
Cl	OC_2H_5	OC_2H_5	−164	[16, 48]
Cl	$-OCH_2CH_2O-$		−167	[16]
Cl	$-OCH_2CH_2CH_2O-$		−153	[16]
Cl	OC_6H_5	OC_6H_5	−159	[46]
Br	OC_6H_5	OC_6H_5	−177	[46]
OCH_3	OCH_3	OCH_3	−140	[1, 7, 23]
OR	OR	OR	−138 [c]	[1, 6, 7]
OC_2H_5	$-OCH_2CH_2O-$		−131	[16]
OC_2H_5	$-OCH_2CH_2CH_2O-$		−128	[16]
OAr	OAr	OAr	−127 [d]	[1, 6, 7, 46]
OC_6H_5	OC_6H_5	$N(C_2H_5)_2$	−141	[48, 50]
OC_6H_5	$N(C_2H_5)_2$	$N(C_2H_5)_2$	−131	[48, 50]
SC_2H_5	SC_2H_5	SC_2H_5	−115.6	[6]
SC_3H_7	SC_3H_7	SC_3H_7	−118.2	[6]
SR	SR	SR	−117 [b]	[1]
$N(CH_3)_2$	$N(CH_3)_2$	$N(CH_3)_2$	−122	[1, 7]
$N(C_2H_5)_2$	$N(C_2H_5)_2$	$N(C_2H_5)_2$	−118	[1, 6, 7]
H	H	H	+240 (4; 180)	[7, 8, 19]

[44] *L. C. D. Groenweghe* and *J. H. Payne*, J. Amer. chem. Soc. *81*, 6350 (1959).

[45] *J. R. VanWazer* and *E. Fluck*, J. Amer. chem. Soc. *81*, 6360 (1959).

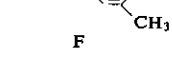
[46] *E. Fluck*, *J. R. VanWazer*, and *L. C. D. Groenweghe*, J. Amer. chem. Soc. *81*, 6363 (1959).

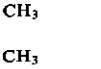
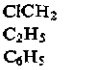
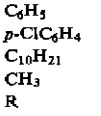
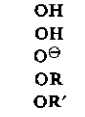
[47] *E. Schwarzmann* and *J. R. VanWazer*, J. Amer. chem. Soc. *81*, 6366 (1959).

[48] *E. Fluck* and *J. R. VanWazer*, Z. anorg. allg. Chem. *307*, 113 (1960).

[49] *E. Schwarzmann* and *J. R. VanWazer*, J. inorg. nucl. Chem. *14*, 296 (1960).

[50] *E. Fluck*, Z. anorg. allgem. Chem. *307*, 38 (1960).

Ligands			Chemical shift [p.p.m.][*]	Ref.
C_2H_5	C_2H_5	C_2H_5	−48.3	[6]
C_4H_9	C_4H_9	C_4H_9	−43.2	[6]
$C_6H_5CH_2$	$C_6H_5CH_2$	C_6H_5CHOH	−41	[41]
$C_6H_5CH_2$	C_6H_5CHOH	C_6H_5CHOH	−43	[41]
R	R	R	−46 ± 3 [b]	[1]
p-Cl-C_6H_4	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4	−23	[1, 7]
CH_3	C_2H_5	Cl	−72	[1]
CH_3	CH_3	OC_2H_5	−50.3	[6]
CH_3	CH_3	OR	−49.5 [b]	[1]
CH_3	CCl_3	OC_2H_5	−40.7	[1]
CH_3	R	OR	−53.0 [b]	[1]
R	R	OR	−54.9 [e]	[1]
p-Cl-C_6H_4	*p*-Cl-C_6H_4	OC_2H_5	−27	[7]
CH_3	F	F	−27.4 (3; ?)	[1, 20]
CH_3	Cl	Cl	−44.5	[1, 6]
$ClCH_2$	Cl	Cl	−38	[7]
C_2H_5	Cl	Cl	−53.0	[1, 13]
C_6H_5	C_6H_5	Cl	−34	[1, 6, 7]
CH_3	F	i-C_3H_7O-	−16.1 (2; ?)	[1]
CH_3	Cl	OR	−40 [f]	[1]
C_2H_5	Cl	OC_2H_5	−45	[1, 13]
CH_3	OC_2H_5	OC_2H_5	−30	[7]
CH_3	OR	OR	−28.4 [g]	[1]
R	OCH_3	OCH_3	−35 [e]	[1]
R	OR	OR	−31.8 ± *1* [h]	[6, 7, 13, 40]
R	OR	OR	−32.8 ± 1.5 [g]	[1]
CH_3COCH_2	OC_2H_5	OC_2H_5	−19.9	[40]
$C_2H_5OOC-CH_2-$	OC_2H_5	OC_2H_5	−19.5	[40]
$(C_2H_5)_2N-CO-CH_2-$	OC_2H_5	OC_2H_5	−21.3	[40]
$(n\text{-}C_3H_7)_2N-CO-CH_2-$	OC_2H_5	OC_2H_5	−22.0	[40]
$ClCH_2$	OC_2H_5	OC_2H_5	−20	[7]
CCl_3	OC_2H_5	OC_2H_5	−6.5	[7]
$C_6H_5-CH_2-SCH_2$	OC_2H_5	OC_2H_5	−24	[7]
$CH_2=CH-$	$-C(CH_2)_2Cl$	$-O(CH_2)_2Cl$	−22	[7]
C_6H_5	$-O(CH_2)_2$	$-O(CH_2)_2$	−19	[7]
	OC_4H_9	$-OC_4H_9$		
Amylnaphthyl	$-OC_4H_9$	$-OC_4H_9$	−22	[7]
X−CO	OC_2H_5	OC_2H_5	+2 [i]	[7]
$(CH_3)_2N-CO-$	OC_2H_5	OC_2H_5	0	[7]
2.4.6-Triazinyl	OC_2H_5	OC_2H_5	0	[7]
CH_3	OC_2H_5	OH	−28.5	[1]
C_2H_5	OC_2H_5	OH	−32.5	[1]
CH_3	OH	OH	−31.1	[1]
$Br(CH_2)_3$	OH	OH	−30	[7]
$n\text{-}C_4H_9$	OH	OH	−32	[7]
$n\text{-}C_5H_{11}$	OH	OH	−33	[7]
p-$C_2H_5-C_6H_4-CH_2-$	OH	OH	−26	[7]
$C_6H_5-CH=CH$	OH	OH	−18	[7]
C_6H_5	OH	OH	−17.5	[7]
p-ClC_6H_4	OH	OH	−14	[7]
$C_{10}H_{21}$	$O^{\ominus}$	$O^{\ominus}$	−27	[7]
CH_3	OR	SR'	−50.5 ± 1.4 [j]	[1]
R	OR'	SR''	−56.5 [b]	[1]
C_6H_5	OC_2H_5	*p*-Cl-C_6H_4-S-	−39	[7]
C_6H_5	OC_2H_5			
CN	OC_2H_5	$N(CH_3)_2$	+10.7	[1]
CH_3	SR	SR	−55.8 [e]	[1]
CH_3	$N(CH_3)_2$	$N(CH_3)_2$	−38.0	[1]
CH_3	OR	H	−32 [f] (2; 530)	[1]
C_6H_5	OH	H	−23 (2; 570)	[7]
	$O^{\ominus}$	H	−20 (2; 500)	[7]
F	F	Cl	+15 (3; 1145)	[8, 19, 20]
F	Cl	Cl	0 (2; 1190)	[8, 19, 20]
Cl	Cl	Cl	−3	[1, 5, 6, 7, 8, 31, 35, 36, 44, 45]
Cl	Cl	Br	+29.6	[44]
Cl	Br	Br	+64.8	[44]
Br	Br	Br	+102	[1, 6, 44]
F	F	OH	+21 (3; 980)	[8, 19, 32]

Ligands			Chemical shift [p.p.m.][*]	Ref.
F	OH	OH	+8 (2; 980)	[32]
Cl	Cl	OC_2H_5	−6.4	[8]
Cl	Cl	OC_6H_5	−1.5	[47]
Cl	Cl	OH	−10	[45]
Cl	OC_2H_5	OC_2H_5	−2.8	[1, 6]
Cl	OC_6H_5	OC_6H_5	+6.2	[47]
Cl	OH	OH	−18?	[45]
Cl	$N(CH_3)_2$	$N(CH_3)_2$	−30.3	[1]
OCH_3	OCH_3	OCH_3	+2.4	[18]
OC_2H_5	$-OCH_2CH_2O-$		17	[16]
OC_2H_5	$-OCH_2CH_2CH_2O-$		+7	[16]
OR	OR	OR	+0.5 ± 1.5 [k]	[1, 6, 7, 18, 40]
	OC_2H_5	OC_2H_5	+7.2	[40]
	OC_2H_5	OC_2H_5	+7.5	[40]
$n\text{-}C_4H_9O$	$n\text{-}C_4H_9O$	OC_6H_5	+4	[7]
OR	OC_6H_5	OC_6H_5	+12 [l]	[1, 7, 18]
OAr	OAr	OAr	+17 [k]	[1, 6, 7, 18]
$OSi(CH_3)_3$	$OSi(CH_3)_3$	$OSi(CH_3)_3$	+26.5	[6]
OR	OR'	OH	+0.5 [m]	[7]
OH	OH	OH	0.0	primary standard
OH	OH	$O^{\ominus}$	−0.5	[28] cf. also
OH	$O^{\ominus}$	$O^{\ominus}$	−3.5	[28] [6, 7,
$O^{\ominus}$	$O^{\ominus}$	$O^{\ominus}$	−6.0	[28] 23, 29, 43]
OCH_3	OCH_3	i-C_3H_7-S-	−31	[1, 7]
OR	OR	SCH_3	−28.4 [e]	[1]
OC_2H_5	OC_2H_5	SR	−26.5 [n]	[1, 6, 42]
OC_2H_5	OC_2H_5	SAr	−21.5 [m]	[1, 7]
OAr	OAr	SAr	−22 [m]	[7]
OC_2H_5	OC_2H_5	SH	−24.0	[1]
OR	OR	$N(CH_3)_2$	−35.0 [e]	[1]
$OCH_2C_6H_5$	$OCH_2C_6H_5$	$N(CH_2\text{-}CH_2)_2O$	−8.4	[18]
$OCH_2C_6H_5$	$OCH_2C_6H_5$	$NCH_3C_6H_5$	−6.2	[18]
OC_6H_5	OC_6H_5	NHC_2H_5	−1	[1, 7]
$OCH_2C_6H_5$	$OCH_2C_6H_5$	$NHCH_2C_6H_5$	−10.0	[18]
$OCH_2C_6H_5$	$OCH_2C_6H_5$	NHC_6H_5	−3.8	[18]
OH	$O^{\ominus}$	NH_2	−3	[7]
$O^{\ominus}$	$O^{\ominus}$	NH_2	−8.9	[51]
OCH_3	OCH_3	H	−11.3 (2; 700)	[1, 7, 23]
OC_2H_5	OC_2H_5	H	−7.5 (2; 670)	[1, 7, 18]
i-C_3H_7O-	i-C_3H_7O-	H	−4.2 (2; 690)	[1, 6]
OC_4H_9	OC_4H_9	H	−8 (2; 670)	[7]
		H	−7 (2; 670)	[7]
OH	OH	H	−5 (2; 700)	[7, 8, 16, 19, 22, 49]
OH	$O^{\ominus}$	H	−4 (2; 620)	[7, 43]
$O^{\ominus}$	$O^{\ominus}$	H	−4 (2; 585)	[7, 43]
OC_2H_5	$N(CH_3)_2$	$N(CH_3)_2$	−16.3	[1, 7]
OH	NH_2	NH_2	+3.5?	[7]
OH	H	H	−13 (3; 570)	[1, 6, 7, 8, 19, 43]
$O^{\ominus}$	H	H	−7 (3; 540)	[7]
SC_2H_5	SC_2H_5	SC_2H_5	−61.3	[1, 6]
$N(CH_3)_2$	$N(CH_3)_2$	$N(CH_3)_2$	−23.4	[1, 6, 33]
			−26.5	[7]
$N(n\text{-}C_4H_9)_2$	$N(n\text{-}C_4H_9)_2$	$N(n\text{-}C_4H_9)_2$	−23.0	[1, 7]

[51] *M. L. Nielsen, R. R. Ferguson,* and *W. S. Coakley,* J. Amer. chem. Soc. *83*, 99 (1961).

Thiophosphoryl Compounds

Ligands			Chemical shift [p.p.m.][*]	Ref.
C_2H_5	C_2H_5	C_2H_5	−54.5	[7]
R	R	R	−51 ± 3 [b]	[1]
CH_3	Cl	Cl	−79.8	[1, 6]
C_2H_5	Cl	Cl	−94.3	[1, 6]
C_6H_5	Cl	Cl	−74.8	[1, 6]
			−80	[7]
CH_3	Cl	OC_2H_5	−94.2	[1]
CH_3	Cl	i-C_3H_7O−	−58.6	[1]
CH_3	OC_2H_5	OC_2H_5	−94.9	[24]
CH_3	OR	OR	−94.5 [o]	[1]
R	OR′	OR′	−101.7 [e]	[1]
CH_3	OC_2H_5	OH	−88.8	[1]
C_2H_5	OC_2H_5	OH	−94.2	[1]
CH_3	OC_2H_5	$O^{\ominus}$	−76.0	[1]
CH_3	i-C_3H_7O−	H	−61.3 (2; 490)	[1]
CH_3	SR	SR	−74 ± 3 [b	[1]
Cl	Cl	Cl	−30	[1, 6, 8, 31, 44]
Cl	Cl	Br	+14.5	[44]
Cl	Br	Br	+61.4	[44]
Br	Br	Br	+112	[6, 44]
Cl	Cl	OR	−56.4 [m]	[1]
Cl	OC_2H_5	OC_2H_5	−68.1	[1, 6]
OCH_3	OCH_3	OCH_3	−73.0	[1]
OR	OR	OR	−68.6 [p]	[6, 42]
			−68.1 ± 1.4 [q]	[1]
OC_2H_5	-O-C_6H_4-NO_2-*p*	-O-C_6H_4-NO_2-*p*	−42	[7]
OAr	OAr	OAr	−53 [p]	[6, 7]
OC_2H_5	OC_2H_5	$O^{\ominus}$	−56	[1, 7]
OC_2H_5	OC_2H_5	SC_2H_5	−95	[1, 6]
OCH_3	OCH_3	-S-S-C_6H_4Cl-*p*	−74	[7]
OC_2H_5	OC_2H_5	SH	−85.7	[1]
OR	OR	NR_2	−75 [e]	[1]
OC_2H_5	OC_2H_5	H	−69.3 (2; 640)	[1, 25]
SC_2H_5	SC_2H_5	SC_2H_5	−92.9	[6]
$N(C_2H_5)_2$	$N(C_2H_5)_2$	$N(C_2H_5)_2$	−77.8	[6]
NR_2	NR_2	NR_2	−76.4 ± 1.4 [b]	[1]

Selenophosphoryl Compounds

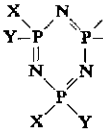
C_2H_5	C_2H_5	C_2H_5	−45.8	[6]
OC_2H_5	OC_2H_5	OC_2H_5	−71	[7]
OC_2H_5	OC_2H_5	H	−71 (2; 630)	[1, 25]

Other Compounds with One Phosphorus Atom

Compounds	Chemical shift [p.p.m.][*]	Ref.
$(N(CH_3)_2)_3(n\text{-}C_4H_9)P^+\ Br^-$	−62	[7]
$(N(CH_3)_2)_3(p\text{-}Cl{-}C_6H_4CH_2)P^+\ Cl^-$	−55.5	[7]
$(N(CH_3)_2)_3(CCl_2F)P^+\ Cl^-$	−44 (2; 85)	[7, 23]
HPF_6	+148 (7; 710)	[19, 22]
	+118	[8, 21]
$PCl_6^{\ominus}$	+300	[10, 12]
PCl_5	+80	[7, 18]
$(o\text{-}C_6H_4O_2)PCl_3$	+26	[18]
$(CH_3O)_3P$ with O−C−X, O−C−X	+53 [i]	[14, 11]
$(CH_3O)_3P$ with O, O	+49	[14, 11]
$(C_6H_5O)_3P{-}O_3$	+63	[15]
$C_2H_5Cl_3P{\cdot}AlCl_4$ / $C_2H_5Cl_3P{\cdot}Al_2Cl_7$	−128.6	[13]
$C_2H_5ClPO{\cdot}AlCl_4$	−77	[13]
$C_2H_5(OC_2H_5)PO{\cdot}AlCl_4$	−54	[13]
$C_2H_5(OC_2H_5)_2PO{\cdot}AlCl_3$	−31	[13]
$(CH_3)_2PH{\cdot}BH_3$	− (2; 350)	[52]

[52] *J. N. Shoolery*, Discuss. Faraday Soc. *19*, 215 (1955).

Compounds with Several Phosphorus Atoms

Compounds	Chemical shift [p.p.m.][*]	Ref.
$[CH_3RO)PO]_2O$	−22.3 [f]	[1]
$[C_2H_5(C_2H_5O)PO]_2O$	−25.0	[1]
$[Cl_2PO]_2O$	+9.5	[31, 35, 36]
$[F(HO)PO]_2O$	+27 (2; 980)	[32]
$[(C_2H_5O)_2PO]_2O$	+13	[1, 27, 30]
adenosin diphosphate, pH 6.9 [**]	α + 11.0	[4]
	β + 8.1	[4]
adenosin triphosphate, pH 7.0 [**]	α + 11.2	[4]
	β + 22.5	[4]
	γ + 8.1	[4]
$[((CH_3)_3SiO)_2PO]_2O$	+32.7	[6]
$[(HO)_2PO]_2O$	+11	[1, 6, 32]
$[(HO)PO_2]_2O^{2\ominus}$	+9.5	[7, 23]
$[PO_3]_2O^{4\ominus}$	+7	[7, 23, 51]
$[(C_6H_5O)_2PO{\cdot}OC_2H_4OC_2H_4OPO{-}(C_6H_5O)]_2O$	+7.5, +12.5	[7]
$[(C_6H_5O)_2PO{\cdot}OC_2H_4OC_2H_4O]_2PO{-}(C_6H_5O)$	+7, +13	[7]
$[((CH_3)_2N)_2PO]_2O$	−11.5	[7, 33]
$(C_2H_5)_2PO{\cdot}O{\cdot}PS(C_2H_5)_2$	−60, −107	[25]
$[CH_3(C_2H_5O)PS]_2O$	−85.4	[1]
$[Cl_2PS]_2O$	−28	[31]
$[Cl_2PO]_2S$	−10	[31]
$C_2H_5(C_2H_5O)PO{-}O{-}PS(C_2H_5O){-}C_2H_5$	−27, −96	[25]
$C_2H_5(i\text{-}C_3H_7O)PO{-}O{-}PS{-}(i\text{-}C_3H_7O)C_2H_5$	−25, −93	[25]
$(C_2H_5O)_2PO{-}O{-}PS(OC_2H_5)_2$	+14.8; −54.0	[27]
$(C_2H_5O)_2PO{-}S{-}PS(OC_2H_5)_2$	−14; −78(?)	[25]
$(C_2H_5O)_2PO{-}O{-}PSe(OC_2H_5)_2$	+14.7; −55.8	[27]
$[(HO)PO_2]_2^{2-}$	−9	[7, 23]
$[(HO)HPO]_2^{2-}$	+4	[23, 49]
	(2; 690)	[23, 49]
	−8	
	(2; 690)	[43]
$(HO)_2PO{-}HPO(OH)$	complex	[23]
P_4 (solid)	+450	[8]
(in CS_2)	+488	[8]
P_4S_3 (2 peaks)	+120 (2; 86)	[7, 23]
	−71 (4; 86)	cf. also [8]
$P_4S_4O_6$	−16	[7]
P_2I_4	−170	[8]
 a) X=Y=Cl	−19	[37]
b) X=Y=$N(CH_3)_2$	−25	
c) X=Cl, Y=N-$(CH_3)_2$	−21	
d) X=Y=$NHCH_3$	−24	
d) X=Y=$NHCH_3$	−24	
Cl-[-$PCl_2{=}N{-}$]$_n$−H (n ≈ 11)	+7.7; +16.8	[34]
$(P_3N_3)Cl_2F_4$ / $(P_3N_3)Cl_3F_3$ / $(P_3N_3)Cl_4F_2$	complex	[38, 39]
$Cl_3P{=}NPOCl_2$ (2 peaks)	+0.1 (2; 15.4)	[35, 36]
	+14.2 (2; 15.4)	
$[(PCl_3)_2N]^+$	−21.4	[10]

[a] 7 unspecified compounds. — [b] 2 unspecified compounds. — [c] 7 compounds from refs. [6] and [7]; 10 unspecified compounds from *ref. [14]*. — [d] Ar = C_6H_5 or *p*-$CH_3C_6H_4$. — [e] 1 unspecified compound. — [f] R = C_2H_5 or *n*-propyl. — [g] 5 unspecified compounds. — [h] 7 compounds. — [i] X = CH_3, C_6H_5. — [j] 9 unspecified compounds. — [k] 5 compounds. — [l] 3 compounds. — [m] 2 compounds. — [n] 5 compounds from refs. [6] and [42]; 6 unspecified compounds from ref. [1]. — [o] 8 unspecified compounds. — [p] 4 compounds. — [q] 11 unspecified compounds.

[*] Figures in brackets beneath or behind a shift value, thus: (*a*, *b*), signify that the peak is split into *a* components by spin-spin interaction and that the separation of the components is *b* c/sec.

[**] Shift varies with pH.

Added in Proof:

Since this review was written the work on reorganisation reactions has been extended to phosphoryl-thiophosphoryl exchange [53]. The reaction product from NH_4Cl and PCl_5 has been identified as $[(Cl_3P)_2N]^+[PCl_6]^-$ (peaks shown at −21.4 and +300 p.p.m.) [54, 55]. Reaction of $POFCl_2$ and P_4O_{10} gave a product $P_2O_3F_2Cl_2$; the phosphorus resonance spectrum (a doublet at +19 p.p.m., splitting: 1120 c/sec.) confirmed the structure as $(FClPO)_2O$ but indicated the presence of a small amount of the unsymmetrical product $F_2PO-O-OPCl_2$ [56]. Tetrameric phosphoronitrilic derivatives of the type $P_4N_4Cl_4(NRR')_4$ [RR′ = Me, Ph and $(CH_2)_5$] have been shown to possess equivalent phosphorus atoms: they show singlets at +1.1 and −1.7 p.p.m. respectively [57]. The phosphorus resonance frequency of complexes of type $R_3PNi(CO)_2$ is *ca.* 40 p.p.m. to lower field than that of the free ligand R_3P, demonstrating that the phosphorus atom is not shielded by the P→Ni bond [58]. The spectrum of sodium salts of $PO_3NH_2^{2-}$ and $(PO_3)_2NH^{4-}$ have been described (singlets at −8.9 and −2.5 p.p.m.) [59].

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Mixed-Phase Pigments with Rutile Structures

BY DR. F. HUND

FORSCHUNGSLABORATORIUM FÜR ANORGANISCHE PIGMENTE, FARBENFABRIKEN BAYER A.G., WERK KREFELD-UERDINGEN

Until the present time, new color pigments have been developed by isotypic and homotypic mixed-phase formation. This paper deals primarily with heterotypic mixed-phase formation for the preparation of new colored and white pigments with the rutile structure. Dioxides and difluorides crystallizing in the rutile lattice-form were chosen as host-lattices for the mixed-phase formation. Hosts of the general formula AB_2 can accommodate, as guests, in the form of solid solutions, oxides and/or fluorides with different structures. Characteristically, the mean statistical cation-radius lies between 0.55 and 0.98 Å, with single radii between 0.46 and 0.98 Å. Relative quantities are so chosen that the cation to anion ratio of 1:2 prescribed by the host lattice, as well as electroneutrality, is maintained.

A) Introduction

By bond formation with itself, or with a few other elements, carbon can form a great number of colored organic pigments and dyes. Other elements form covalent linkages with themselves, or with others, only rarely and then the number of compounds is reduced by several orders of magnitude. In addition to carbon there are more than a 100 other elements; however the number of colored inorganic compounds is surprisingly small. The coloring ability of the elements is, like the atomic radius, the ionization potential etc., a periodic function of its atomic number.

The required characteristics of pigments are numerous and of a physical nature (color-tone and saturation, color, covering, tinting strength, brightening, and brilliance ability, nonreactivity, insolubility or low solubility, chalking resistance, dispersibility, etc.). Furthermore, since, the pigments should be inexpensive to produce there are not many colored inorganic compounds that could be considered. Simple, inorganic compounds of uniform structure, *e.g.* oxides, sulfides, sulfates, carbonates, hydroxides, are listed in Table 1, which is a survey of white pigments. The color pigments are summarized in Table 2. Structural X-ray analysis has clarified the structure of these compounds.

By enlisting the theoretical knowledge derived from crystal chemistry, an attempt was made to increase the small number of technically useful colored pigments by mixed-phase formation. The mixed phases prepared according to this principle are underlined in Table 2. Many of these mixed-phase pigments are used technically. In the mixed-phase pigments that are known so far, both components, designated as host and guest component according to the relative quantity present, are identical in formula and lattice type and present only minor variations of the lattice parameters. They are also chemically very similar. In a mixed phase, host and guest components are dispersed atomically or molecularly in the form of a solid solution and in a statistically uniform manner over the sites required by the space groups; the embedded particles must be of comparable size. There are three possibilities:

Table 1. Survey of the White Pigments

Group	Individual Pigment	Formula	Crystal Class	Space Group
Titanium pigments	Rutile	TiO_2	Ditetragonal-bipyramidal	D_{4h}^{14}
	Anatase	TiO_2	Ditetragonal-bipyramidal	D_{4h}^{19}
Zinc pigments	Zinc sulfide-blende	α-ZnS	Cubic hexakis-tetrahedral	T_d^2
	Zinc sulfide-wurtzite	β-ZnS	Dihexagonal-pyramidal	C_{6v}^4
	Zinc white	ZnO	Dihexagonal-pyramidal	C_{6v}^4
	Lithophone	$ZnS + BaSO_4$	Dihexagonal-pyramidal + orthorhombic-bipyramidal	$C_{6v}^4 + D_{2h}^{16}$
Antimony pigments	Antimony white-senarmontite	Sb_2O_3	Cubic hexakis-octahedral	O_h^7
	Antimony white valentinite	Sb_2O_3	Orthorhombic-bipyramidal	D_{2h}^{10}
Sulfate pigments	Calcium sulfate	$CaSO_4 \cdot 2H_2O$	Monoclinic prismatic	C_{2h}^6
	Barium sulfate	$BaSO_4$	Orthorhombic-bipyramidal	D_{2h}^{16}
	Lead sulfate	$PbSO_4$	Orthorhombic-bipyramidal	D_{2h}^{16}
Carbonate pigments	Calcium carbonate-calcite	$CaCO_3$	Ditrigonal-scalenohedral	D_{3d}^6
	Calcium carbonate-aragonite	$CaCO_3$	Orthorhombic-bipyramidal	D_{2h}^{16}
	Lead carbonate	$PbCO_3$	Orthorhombic-bipyramidal	D_{2h}^{16}
Oxide and hydroxides	Silicic acid-α-quartz	SiO_2	Trigonal-trapezohedral	D_3^4
	Silicic acid-α-high trydimite	SiO_2	Hexagonal	D_{6h}^4
	Silicic acid α- + β-cristobalite	SiO_2	Tetragonal-trapezohedral + cubic-hexakistetrahedral	$D_4^4 + O_h^7$
	Alumina hydrate	γ-AlOOH	Orthorhombic-bipyramidal	D_{2h}^{17}
	Zirconium dioxide	ZrO_2	Monoclinic-prismatic	C_{2h}^5
	Tin dioxide	SnO_2	Ditetragonal-bipyramidal	D_{4h}^{14}

Table 2. Survey of the Colored Pigments

Group	Individual Pigment	Formula	Crystal Class	Space Group
Iron Pigments	Iron oxide yellow	α-FeOOH	Orthorhombic-bipyramidal	D_{2h}^{16}
	Iron oxide red	α-Fe_2O_3	Ditrigonal-scalenohedral	D_{3d}^6
	Iron oxide black	Fe_3O_4-γ-Fe_2O_3	Cubic-hexakisoctahedral	O_h^7
Oxides	Litharge	β-PbO	Orthorhombic-pyramidal	C_{2v}^5
	Minimum	Pb_3O_4	Ditetragonal-bipyramidal	D_{4h}^{13}
	Chrome green	α-Cr_2O_3	Ditrigonal-scalenohedral	D_{3d}^6
	Chrome-green hydrate	γ-CrOOH	Rhombic-bipyramidal	D_{2h}^{17}
	Manganese brown	γ-MnOOH	Monoclinic-prismatic	C_{2h}^5
	Manganese blue	$Ba(S, Mn)O_4$	Rhombic-bipyramidal	D_{2h}^{16}
Sulfides, Selenides	Cadmium yellow blende	α-CdS	Cubic-hexakistetrahedral	T_d^2
	Cadmium yellow-wurtzite	β-CdS	Dihexagonal-pyramidal	C_{6v}^4
	Cadmium red	Cd(S, Se)	Dihexagonal-pyramidal	C_{6v}^4
	Cadmium cinnabar	(Cd, Hg)S	Dihexagonal-pyramidal	C_{6v}^4
	Antimony pentasulfide	Sb_2S_5	Amorphous	–
Silicates	Ultramarine	$Na_8(Al_6Si_6O_{24})S_{(2-4)}$	Cubic-hexakistetrahedral	T_d^4
Aluminates, Spinels	Cobaltblue-spinels	$CoAl_2O_4$	Cubic-hexakis-octahedral	O_h^7
Chromates	Chrome yellow	$Pb(Cr, S)O_4$	Monoclinic-prismatic	C_{2h}^5
	Chrome yellow	$Pb(Cr, S)O_4$	Orthorhombic-bipyramidal	D_{2h}^{16}
	Molybdate red	$Ph(Cr, S, Mo)O_4$	Tetragonal-pyramidal	C_4
Antimonates	Naples yellow	$PbSb_2O_6$	Cubic-hexakisoctahedral	O_h^7
	Naples yellow	$PbSb_2O_6$	Trigonal-trapezohedral	D_3^1

The guest component is identical in its structure, or in one of its structures, with the host component, *i.e.* isotypic mixed-phase formation;

The structure of the guest is very similar to that of the host, *i.e.* homotypic mixed-phase formation;

The structure of the guest is completely unrelated to that of the host; in this case one speaks of heterotypic mixed-phase formation.

B) Host Lattices with Rutile Structures

Figure 1 shows dioxides and difluorides of tetravalent and bivalent metals which crystallize in the rutile-lattice. Thus, for example, the tetragonal cell of titanium dioxide contains two molecules TiO_2, and the two fourfold positively-charged titanium ions occupy the corners and the space center of the tetragonal cell. Six twofold negatively-charged oxygen atoms, which can be shifted in the diagonal plane, surround the titanium ions in a somewhat distorted octahedron. The coordination number of titanium is 6, that of oxygen is 3. In the direction of the c_0-axis there is an infinitely extended chain of octahedra.

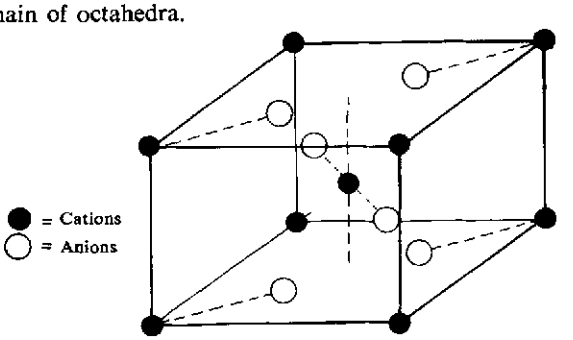


Fig. 1. AB_2-compounds with Rutile Structures
One molecule AB_2 per cell
Difluorides of bivalent metals:
Tig, Mn, Fe, Co, Ni, Pd, Zn
Dioxides of tetravalent metals:
M, V, Nb, Mo, W, Mn, Ru, Os, Ir, Ge, Sn, Pb, Te

C) Methods of Investigation

The starting materials, the pure products prepared as host lattices and the calcined end products were analyzed quantitatively by chemical methods, and the coloration examined visually and, in part, spectrophotometrically. All substances were examined by using the Debye-Scherrer X-ray technique. The rutile-lattices of TiO_2, SnO_2, and of the difluorides, were known from standard substances. The mixed-phase formation, optimum working conditions and solubility limits could be determined by comparing the X-ray diagrams of the reaction products with those of the standard lattices. In general, the position of the lines did not change (or changed only insignificantly) in spite of the uptake of 50 % by weight, and more, of guest component. During the determination of the solubility limits of certain mixed phases with Sb_2O_5, V_2O_5, Nb_2O_5, Ta_2O_5 as one of the guest components, a continuous solid solution was found for the host lattices of TiO_2 and SnO_2. These facts were determined by taking the incorporation equations (cf. Table 3) into account.

Table 3. Incorporation Equations for Rutile Mixed-Phases

Type of incorporation	I:	$Me^{I}_2O + 3\ Me^{V}_2O_5 = 2\ Me^{I}Me^{V}_3O_8$	(1)
Type of incorporation	II:	$Me^{I}F + Me^{V}_2O_5 = Me^{I}Me^{V}_2O_5F$	(2)
Type of incorporation	III:	$Me^{II}O + Me^{V}_2O_5 = Me^{II}Me^{V}_2O_6$	(3)
Type of incorporation	IV:	$Me^{III}_2O_3 + Me^{V}_2O_5 = 2\ Me^{III}Me^{V}O_4$	(4)
Type of incorporation	V:	$Me^{I}_2O + 3\ Me^{VI}O_3 = Me^{I}_2Me^{VI}_3O_{10}$	(5)
Type of incorporation	VI:	$Me^{I}F + Me^{VI}O_3 = Me^{I}Me^{VI}O_3F$	(6)
Type of incorporation	VII:	$Me^{II}O + Me^{VI}O_3 = Me^{II}Me^{VI}O_4$	(7)
Type of incorporation	VIII:	$Me^{III}_2O_3 + Me^{VI}O_3 = Me^{III}_2Me^{VI}O_6$	(8)
Type of incorporation	IX:	$Me^{I}F + Me^{III}F_3 = Me^{I}Me^{III}F_4$	(9)
Type of incorporation	X:	$Me^{I}_2O + 3\ Me^{III}F_3 = Me^{I}_2Me^{III}_2F_9O$	(10)
Type of incorporation	XI:	$Me^{II}O + Me^{III}F_3 = Me^{II}Me^{III}F_3O$	(11)
Type of incorporation	XII:	$Me^{III}_2O_3 + Me^{III}F_3 = Me^{III}_2Me^{III}F_3O_3$	(12)

Me(I) = Li, Cu, Na
Me(II) = Mg, Zn, Mn, Fe, Co, Ni, V, Cu, Pd
Me(III) = Al, Ga, Ti, As, Sb, V, Nb, Ta, Cr, Mn, Fe, Rh, Sc, In
Me(IV) = Mn, Ge, Pb, V, Te, Cr, Ru, Os, Ir, Ti, Sn, Zr, Hf
Me(VI) = Mo, W, U, Te
Anions = O^{2-} und F^{1-}

D) Heterotypic Mixed-Phase Formation in Host Lattices with the Rutile Structure

Individual compounds of non-corresponding structure are incorporated into the host compounds mentioned, which have a rutile structure and the general formula AB_2 (A = cation, B = anion), or into their isotypic solid solutions. They are introduced in such quantities that the 1:2 ratio of cations to anions of the host lattice is unchanged.

The lattice must remain electrically neutral if only in the statistical sense, *i.e.*, the sum of the positive and negative charges must be equal. The guest components incorporated are metal oxides and/or fluorides with a single cation radius between 0.46 and 0.98 Å., and a mean statistical cation radius between 0.55 and 0.98 Å.; the cation radii of the guests and hosts are thus comparable. The conditions for the heterotypic mixed-phase formation yield the 12 incorporation equations presented in Table 3. Among the anions, O^{2-} and F^{-} with radii 1.32 and 1.33 Å., respectively, are practically the only ones with equal radii. By means of the incorporation equations, the statistical mean ionic radii can be calculated from the known single radii. Table 3 lists suitable mono-, bi-, tri-, tetra-, penta-, and hexavalent ions.

In Equation (1) one molecule of Li_2O, for example, is combined with three molecules antimony pentoxide; two molecules of $LiSb_3O_8$ are formed. The sum of the positive charges is +16, that of the negative charges −16; the ratio of the sum of the added cations to that of the added anions is 1:2.

In one example for Equation (2) one molecule of Nb_2O_5 is added to one molecule of NaF; the incorporated guests are three cations with a positive total charge of +11, and 6 anions (5 O^{2-} and 1 F^{-}) with a negative total charge of −11. The AB_2-ratio is also adhered to in this case.

In Equation (3), the addition of one molecule of V_2O_5 to one molecule of MgO may be considered; three cations with a positive total charge of +12 and six oxygen anions with the negative total charge of −12 enter and the AB_2-ratio is satisfied.

One molecule of Al_2O_3 can combine with one molecule of As_2O_5 according to Equation (4); two molecules of the compound $AlAsO_4$ are formed; the total positive charge is +8, the total negative charge is −8; the ratio of the sum of the cations to the sum of the anions is 1:2.

One molecule of Cu_2O, and three molecules WO_3 as the guest components may be selected in Equation (5). Two Cu^{+} and three W^{6+} with a total charge of +20 appear in the lattice. Ten oxygen ions contribute a total charge of −20; the AB_2-ratio is complied with.

In Equation (6) one molecule of WO_3, for example, is added to one molecule of LiF. Two metal ions with the total charge of +7 and three O^{2-} as well as one F^{-} with a total charge of −7 enter the host lattice; the condition AB_2 is satisfied.

As an example in Equation (7), one molecule of ZnO is added per molecule of MoO_3; the two cations have a charge of +8; four oxygen ions contribute eight negative charges. In this example the cation-anion ratio is also 1:2.

Typically in Equation (8), one molecule Fe_2O_3 reacts with one molecule of TeO_3. Three cations with a total charge of +12 and six oxygen ions with a charge of −12 enter the lattice; the ratio of the sum of the cations to that of the anions is 1:2.

According to Equation (9), for example, one molecule of GaF_3 enters the lattice as guest together with one molecule of LiF. Two cations with a total charge of +4 compensate four fluoride ions with a total charge of −4; the cation-anion ratio is 1:2.

In Equation (10) three molecules of AlF_3 can combine with one molecule of LiO_2. Five cations contribute a total charge of +11, the nine fluoride and one oxygen anions have a total charge of −11 and the AB_2-ratio is also established.

In a typical case related to Equation (11), one molecule of NiO couples with one molecule of CrF_3 as guest component. Two metal ions with a positive total charge of +5 compensate four anions (3 F^{-} and 1 O^{2-}) with a total charge of −5; the AB_2-ratio is again established.

According to Equation (12) one molecule of MnF_3, for example, can be introduced into the host lattice together with one molecule of Al_2O_3. Three cations with a total charge of +9 compensate six anions (3 O^{2-} and 3 F^{-}) with a total charge of −9; the cation-anion ratio of 1:2 of the host component is again adhered to.

E) Preparation of the Mixed Phases

Increasing quantities of guest components (up to 70 to 80 % by weight) were added to constant quantities of the host components in the ratios indicated by the formulae. After intensive pulverization, the mixtures were heated at increasing temperatures for 1/2 to 1 hour in air or an atmosphere of dry N_2 or O_2. Instead of the oxide components, heat-labile compounds of the

corresponding elements may be used if they yield the components of the mixed phase upon heating. Thus, instead of titanium dioxide, its hydrate (which yields TiO_2 on heating) can be used as starting material. Alternatively the hydroxides, carbonates, acetates, nitrates, formates, etc. can be chosen instead of the oxides of the metals (*e.g.*, magnesium oxide or zinc oxide).

F) Experimental Results

Mixed-phase formation was considered established when X-ray examination indicated that more than 10 % by weight of the guest component was incorporated as a solid solution. In several cases complete mixed-phase formation was observed, *i.e.*, the host and the guest could interchange their roles. The hosts can also form normal mixed phases with one another, and then, as so-called "mixed hosts", form heterotypic mixed-phases with one or all of the cited guest components. A great number of possible variations are created in this manner. In Figure 2, which is a Periodic Table emphasizing the long periods, elements suitable for the formation of mixed phases with the rutile structure are indicated. Even if one establishes the lower limit of incorporation at more than 10 % by weight, between a half and a third of all elements can be incorporated into these mixed phases (the relatively rare lanthanides, actinides and rare gases are included).

Period	Ia	IIa	IIIb	IVb	Vb	VIb	VIIb	VIIIb			Ib	IIb	IIIa	IVa	Va	VIa	VIIa	VIIIa
1	1 H																1 H	2 He
2	3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
3	11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
4	19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
5	37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
6	55 Cs	56 Ba	57 La	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
7	87 Fr	88 Ra	89 Ac															
	Lanthanides			58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu	
	Actinides			90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 E	100 Fm	101 Mv	102 No		

Fig. 2. Periodic System of the Elements

[A 62.2] E

The properties of ordinary chemical compounds usually change in a discontinuous manner. For typical mixed-phase formation, which is in general restricted to a few components (*e.g.* Cd(S,Se); (Cd,Hg)S; $Pb(S,Cr)O_4$), a continuous color change can indeed be obtained within certain limits. With the new heterotypic mixed phases with the rutile structure one can obtain a continuous change in the color characteristics with practically half of the elements of the Periodic System; this parallels the smooth changes in the characteristics of alloy systems.

Only the color characteristics of the new heterotypic mixed phases with rutile-lattices are examined here; rutile, mixed-phase pigments with TiO_2 as host lattice and NiO as the color-giving component have already attained a large technical application. Figure 3 gives the spectral remission curves (MgO is the white standard) for mixed-phases of titanium dioxide which contain equal quantities of NiO.

In order to satisfy the incorporation equations (1–12), Sb_2O_5, Nb_2O_5 or WO_3 were chosen as the second guest component. A beautiful brilliant lemon yellow pigment is obtained. The coloration, as can be seen from the remission curve, is little affected by the second, colorless, guest component. The remission curves of three systems characteristic for rutile mixed-phase pigments with TiO_2 as the host lattice were chosen for Figure 4. With CuO and Sb_2O_5, one obtains a yellow pigment which is comparable with the above mentioned yellow nickel oxide mixed-phase pigment. With CoO and Sb_2O_5 as guest components a beautiful brown-red pigment can be developed; the combination of Cr_2O_3 with Sb_2O_5 yields a full gold-ochre mixed-phase pigment with rutile structure that has already been used technically.

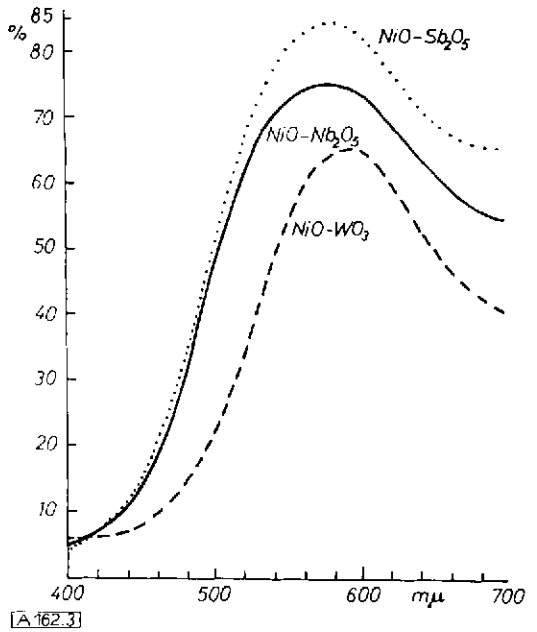


Fig. 3. Spectral Remission of TiO_2 Mixed-Phases (in %)

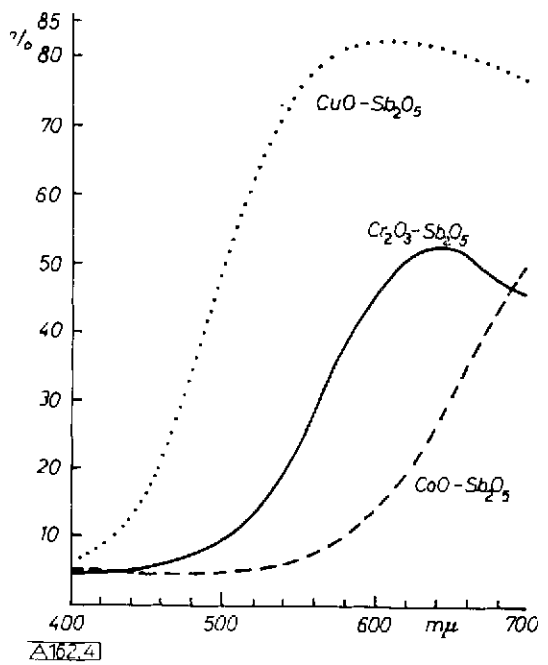


Fig. 4. Spectral Remission of TiO_2 Mixed-Phases (in %)

Figure 5 shows TiO_2 mixed-phases with their remission curves that appear olive-green, black and white to the eye. Inclusion of FeO with WO_3 into TiO_2 yields olive-green, inclusion of Sb_2O_3 with V_2O_5 yields a deep black, and MgO with Sb_2O_5 yields white pigments.

As a final example the spectral remission curves of several mixed-phase pigments with SnO_2 as the host lattice are plotted in Figure 6. With Rh_2O_3 and WO_3 as the guest components, a beautiful, rose-colored mixed-phase pigment with rutile structure is obtained. Bi_2O_3 and V_2O_5 yield a yellow, and $Li_2O/3\ CrF_3$ a purple, pigment.

Many other pigments have been found in addition to those mentioned. Combinations with manganese oxides yield all the desired brown pigments, and combinations with V_2O_5 yield yellow-brown to brown-black pigments. Furthermore, all in-between tones of two mixed-phase pigments can be prepared technically by double mixed-phase formation with one-phase rutile or poly-rutile structures. Known color-producing elements have been incorporated mainly into spinel host lattices for ceramic purposes. If equal amounts of these color-producing elements are incorporated into spinel structures (with

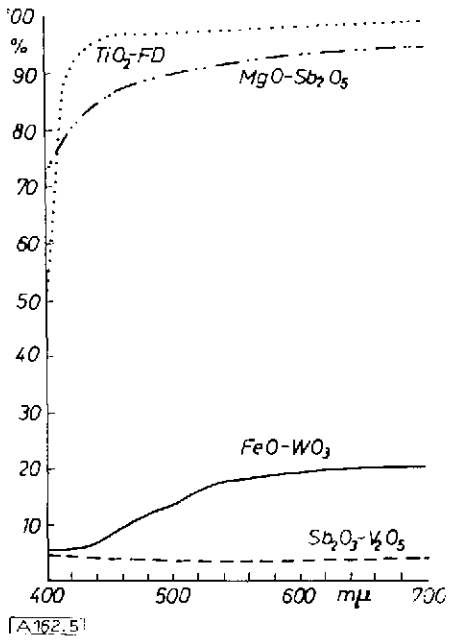


Fig. 5. Spectral Remission of TiO_2 Mixed-Phases (in %)

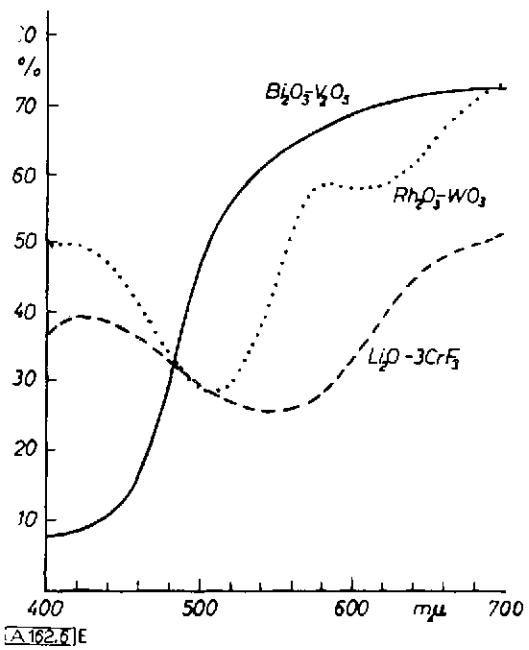


Fig. 6. Spectral Remission of SnO_2 Mixed-Phases (in %)

normal production of mixed phases), or into the rutile lattice of TiO_2 or SnO_2 (with the production of hetero-type mixed-phases), the color-producing effect of the ions is much greater in the latter case. This is probably due to the much higher refractive index of the rutile mixed-phases of TiO_2 or SnO_2 as compared to the refractive index of the spinel phases.

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New Nitrogen-Iodine Compounds

By Doz. Dr. J. Jander, Dipl.-Chem. U. Engelhardt, and Dipl.-Chem. G. Weber

Chemisches Laboratorium der Universität Freiburg/Br. (Germany), Anorganische Abteilung

A new preparative method for an already known [1, 2], red N:I compound has been found. It may be prepared alongside NH_4I as a difficultly soluble, finely divided material from a small quantity of iodine (< 0.1 g.) and an excess of liquid ammonia at −78 °C. The conversion to the green compound $NI_3 \cdot 3\,NH_3$ [1, 3], which is produced directly by starting from more iodine (> 5 g.), takes place via rust-red, brown, and green-brown intermediates. After isolation, the red material turns black while the ammonia is pumped off under high vacuum between −105 and −90 °C. (the process is reversible); the N:I ratio is then equal to 1. An infrared investigation of the structure is being carried out.

The brown $NI_3 \cdot NH_3$ compound [1] yields: 1. An orange-yellow form $CH_3NI_2 \cdot CH_3NH_2$ (confirmed by analysis and its infrared spectrum) which is obtained at −75 °C. with an excess of amine (CH_3NH_2), and which is produced by way of an insoluble, deep-green intermediate. 2. Yellow $(CH_3)_2NI$ at 75 °C. with excess $(CH_3)_2NH$; this compound has been previously prepared by another route [4]. 3. A dark-green solution with excess pyridine at −40 °C. The starting material can be recovered unchanged by pumping off the pyridine at 25 °C.

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[2] *J. Jander* and *E. Schmid*, Angew. Chem. *71*, 31 (1959).

[3] *J. Jander* and *E. Schmid*, Z. anorg. allg. Chem. *292*, 178 (1957).

[4] *F. Raschig*, Liebigs Ann. Chem. *230*, 223 (1885).

Simple Process for Preparing Dialkyl Phosphorus Halides R_2PCl_3 and R_2PBr_5

By Doz. Dr. W. Kuchen and Dipl.-Chem. K. Strolenberg

Institut für Anorganische Chemie und Elektrochemie der T.H. Aachen (Germany)

Dialkylphosphorus trichlorides (II) were obtained in about 80 % yield by reacting the readily available tetraalkyldiphosphine disulfides [1–4] $R_2P(S)-P(S)R_2$ (I) with Cl_2 in CCl_4 according to the reactions

(1) $(I) + Cl_2 \rightarrow 2\,R_2P(S)Cl$

(2) $2\,R_2P(S)Cl + 4\,Cl_2 \rightarrow 2\,R_2PCl_3 + 2\,SCl_2$

The dialkylphosphorus thiochlorides, formed primarily according to Equation (1), could be recovered under suitable conditions. Dialkylphosphorus trichlorides are colorless crystalline substances which liquefy instantaneously on contact with atmospheric moisture. At room temperature, and with the exclusion of moisture, they show no changes even after standing for a month. They are thermally very unstable. For example, $(C_2H_5)_2PCl_3$ decomposes above 65 °C., and $(C_3H_7)_2PCl_3$ above 55 °C. with effervescence, presumably according to the equation

$(II) \rightarrow RPCl_2 + RCl;$

since $C_2H_5PCl_2$ was obtained in the thermal decomposition of $(C_2H_5)_2PCl_3$. Water causes instantaneous hydrolysis:

$(II) + 2\,H_2O \rightarrow R_2P(O)OH + 3\,HCl.$

Attempts to prepare dialkylphosphorus tribromide from (I) led to compounds of the type R_2PBr_5 (III), yield about 80 %), even when the molar ratio (I): Br_2 was varied. Apparently, the reaction

$R_2PBr_3 + Br_2 \rightarrow R_2PBr_5$

proceeds much faster than the reaction of the dialkylphosphorus thiobromides $R_2P(S)Br$ [2] with bromine in an analogous manner to equation (2).

$(C_2H_5)_2PBr_5$, m.p. 103.5 °C, and $(C_3H_7)_2PBr_5$, m.p. 87.5 °C, were obtained as orange-red needles, which melt without decomposing and which are quickly hydrolyzed with water according to

$(III) + 2\,H_2O \rightarrow R_2P(O)OH + 3\,HBr + Br_2$

The solubility of (II) and (III) in polar solvents, as well as the results of conductivity measurements in dimethylformamide, indicate an ionic structure for these substances according to $[R_2PCl_2]^+[R_2PCl_4]^-$ and $[R_2PBr_2]^+Br_3^-$.

Received October 31, 1961 [Z 175/14 IE]

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[3] *P. J. Christen, L. M. van der Linde*, and *F. N. Hooge*, Recueil Trav. chim. Pays-Bas *78*, 161 (1959).

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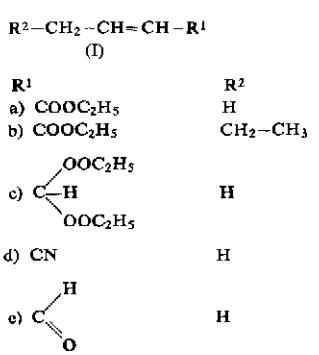
Disubstituted Dithiane Rings

By Dr. B. Hirsch and Dipl.-Chem. H. Fink

Institut für Farbenchemie
der Technischen Universität Dresden (Germany)

R. Tschesche [1] obtained a crystalline product from γ-acetylmercaptopentene-(2) acid ethyl ester by the reaction of methanolic sodium hydroxide solution and described this as 2,5-dimethyl-1,4-dithian-3,6-diacetic acid. We have studied this reaction in more detail.

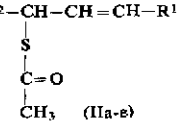
α,β-Unsaturated compounds of the type



(I)

R^1	R^2
a) $COOC_2H_5$	H
b) $COOC_2H_5$	CH_2-CH_3
c) $C(OOC_2H_5)_2H$	H
d) CN	H
e)	H

were brominated in the allyl position with *N*-bromosuccinimide (Wohl-Ziegler method) and allowed to react at room temperature in benzene solution with methanolic potassium thioacetate solution. γ-Acetylmercapto compounds (II) are formed in yields of 90 to 95 %. They are colorless to light yellowish oils with a weak but persistent odor.

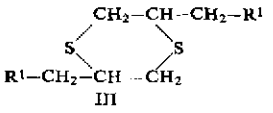


(IIa-e)

Deep red solutions are formed if sufficient methanolic sodium hydroxide to saponify the acetylmercapto group (possibly also R^1 = $COOC_2H_5$) is slowly added to an approximately

30 % methanolic solution of II at room temperature and under a nitrogen atmosphere (pH always < 8–9).

The solutions are allowed to stand overnight and are then diluted with water, acidified with dilute H_2SO_4, ethered out, and the solvent evaporated off. In addition to large quantities of ill-smelling, yellow to red-brown viscous products, colorless crystalline substances are obtained with IIa and IId whose IR-spectra, analyses, and molecular weight determinations point to dithiane substances.



III

IIIa
R^1=COOH
Yield 22.7 %; m.p. (subl.) 180 °C.

IIId
R^1=CN
Yield 22.0 %; m.p. 184 °C.

IIc gives a colorless polymer which is only soluble in dimethylformamide and no longer gives any aldehyde reactions. IIb and IIe yield no crystalline products.

The addition of the intermediary free mercapto group to the double bond of an adjacent molecule with the formation of dithiane rings appears to be favored if; a) a primary mercapto group can form; b) the polarization of the double bond by a carbonyl or nitrile group in a conjugated position is strong enough or; c) if no other reaction course (*e.g.* reaction of the mercapto group and aldehyde group) is possible.

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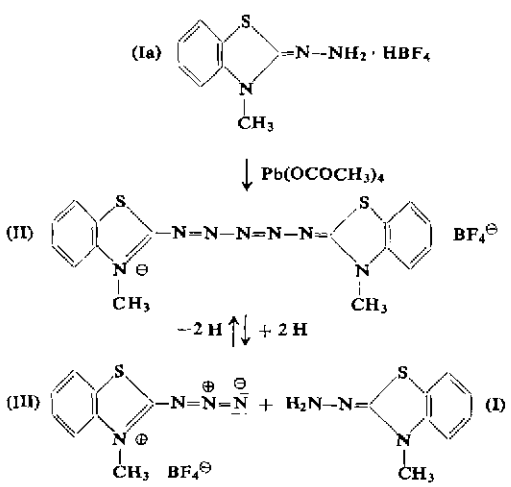
[1] *R. Tschesche, H. Barkemeyer,* and *G. Henschkel,* Chem. Ber. *88,* 1261 (1955).

Penta(aza)-Pentamethine Cyanine Dyes

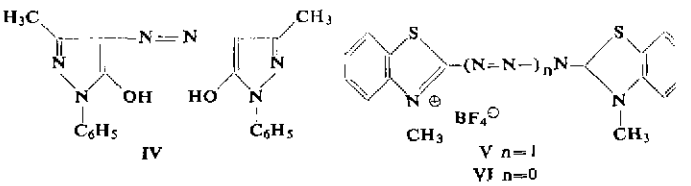
By Prof. Dr. S. Hünig [1], Dozent Dr. H. Balli, and Dipl.-Chem. H. Quast [2]

Chemisches Institut der Universität Marburg
und Institut für Organische Chemie der Universität München (Germany)

It has been possible for some time to synthesize tetra(aza)-pentamethine cyanines [3], and we now report the isolation of the penta(aza)-pentamethine cyanines. The bis-(3-methylbenzthiazol-2-yl)-derivative (II) is formed as a purple dye salt in the oxidation of 3-methylbenzthiazolone-2-hydrazone fluoborate (Ia) with lead tetraacetate in a weakly acidic methanol solution.



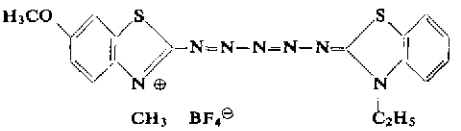
Compound (II) forms metallic, shiny green, needles from acetonitrile at very low temperatures ($\lambda_{max.}$ 552 mμ; ε = 55500 in acetonitrile). If it is titrated with $TiCl_3$ in acetonitrile until colorless, two reduction equivalents are absorbed. The reduction yields 81–87 % (I), isolated as the p-nitrobenzalazine [4], and 57–67 % of the azidinium salt (III) [5] determined optically as dye (IV) which is formed with excess 1-phenyl-3-methylpyrazolone-(5) [5].



IV V n=1 VI n=0

When (II) is heated to 110 °C., the triaza-trimethine cyanine V (55 %) and monoaza-cyanine VI (24 %), each determined optically, are both formed and nitrogen is evolved. This is further support for the structure of (II).

The formation of compound (II) is the cause of the purple color which was obtained by *E. Besthorn* [6] from (I) with $NaNO_2$ in a weakly acidic medium, and which was observed by *G. Hensecke* and *G. Hanisch* [7] when solutions of (I) and (III) were mixed. Presumably, the excess azidinium salt (III) is the dehydrogenating agent [8]. Accordingly, both symmetrical and unsymmetrical penta(aza)-pentamethine cyanines, for example (VII), can be built up from azidinium salts and "hydrazones" having a different heterocyclic ring.



VII $\lambda_{max.}$ = 579 mμ in acetonitrile

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[1] New address: Würzburg, Chemisches Institut der Universität, Röntgenring 11.

[2] From the Diploma-Thesis of *H. Quast,* University of Marburg, 1961.

[3] *S. Hünig* and *K. H. Fritsch,* Liebigs Ann. Chem. *609,* 172 (1957).

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Trithiocarbonic Acid H_2CS_3

By Priv.-Doz. Dr. G. Gattow and cand. chem. B. Krebs

Anorganisch-chemisches Institut der Universität Göttingen (Germany)

Trithiocarbonic acid is formed as a highly refractive red oil when solid $BaCS_3$ is introduced into ice cold 10 % hydrochloric acid [1, 2]. The substance has now been accurately characterized. The molecular weight, determined cryoscopically in bromoform, is 109.9 ± 0.5 (theoretical: 110.2). Molecular weight determinations just above the melting point seem to indicate a partial association. Density, determined with a micropycnometer: d_4^{25} = 1.476 ± 0.003 g./ml.; d_4^{20} = 1.483 ● 0.003 g./ml.; refractive index: n_D^{20} = 1.8225 ± 0.0005; melting point: −26.9 °C. (± 0.2 °); boiling point: +57.8 °C. (extrapolated). The infrared spectra of the free acid as well as of the solution in CCl_4 show strong bands with absorption maxima at 2580, 1508, 1120, 990, 879, 798, and 466 cm^{-1}.

The decomposition pressures of H_2CS_3 were determined by direct measurement (isoteniscope). The decomposition equation [3]

$$H_2CS_{3(liquid)} \longrightarrow H_2S_{(gas)} + CS_{2(dissolved)}$$

was verified by gas-phase molecular weight determination. The H_2S pressure (in mm. Hg) over trithiocarbonic acid between −25 °C. and +15 °C. can be described by the following equation:

$$_{10}\log p_{(H_2S)} = -\frac{2.314\times10^3}{T} + 9.871$$

The evaluation of the measured values gives $\Delta H_R = +10.6 \pm 0.3$ kcal./mole for the heat of reaction, and $\Delta S_R = +32.0 \pm 0.7$ e.u./mole for the reaction entropy. The heat of formation and normal entropy of liquid trithiocarbonic acid is then $\Delta H_f^{298} = +5.6 \pm 1.4$ kcal./mole, and $S^{298} = +53.3 \pm 1.3$ e.u./mole.

The assumption [1] that 1 mole of trithiocarbonic acid dissolves exactly 1 mole of sulfur with the formation of the brown oily tetrathiocarbonic acid H_2CS_4 proved to be incorrect. Rather, a clear temperature dependence of the sulfur absorption was found; it is only coincidental that at 22 °C. 1 mole of S is dissolved (at +25 °C., 1.08 moles and at −10 °C., 0.50 mole of S per mole of H_2CS_3). The IR- and UV-spectra also point to the solution of sulfur in H_2CS_3. On the basis of vapor pressure measurements, the heat of solution of sulfur in H_2CS_3 was determined to be $\Delta H_S = -0.4 \pm 0.5$ kcal./mole.

Received November 8, 1961 [Z 171/10 IE]

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The Constitution of Phosphorus Peroxide

By Prof. Dr. Peter W. Schenk and Dipl. Chem. H. Vietzke

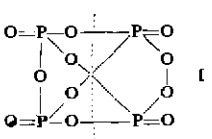
Institut für Anorganische Chemie der
Freien Universität Berlin (Germany)

Violet phosphorus peroxide produced by glow-discharge [1] consists of a violet unstable form, and a colorless form which is stable to temperatures of 120 °C. Both substances yield peroxydiphosphoric acid with water and no H_2O_2 or peroxymonophosphoric acid. The violet form is evidently of a radical nature, but the colorless compound has the formula P_4O_{11}. In addition to $H_4P_2O_8$, $H_4P_2O_7$ is formed according to the equation:

$$P_4O_{11} + 4\,H_2O \longrightarrow H_4P_2O_8 + H_4P_2O_7$$

The latter compound was identified by paper chromatography. Since P_4O_{11} could not be prepared in a pure state, the product of the reaction between P_4O_{10} and water, namely tetrametaphosphoric acid, is always found in addition to the above compounds. This acid constitutes the main reaction product of P_4O_{10} with water because the opposite edges of the P_4O_{10} tetrahedron are first of all broken up [2].

In the structure which we propose (I), all the P–O–P bonds adjacent to the P–O–O–P bond are polarized through the



I

–O–O– group and, therefore, more easily hydrolyzed than the P–O–P bond opposite to the P–O–O–P bond. The latter lies to the left in Formula (I), and remains intact in the reaction with water.

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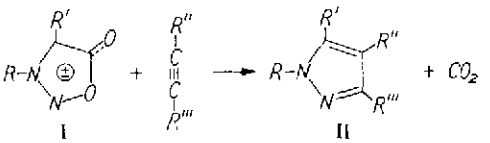
1,3-Dipolar Additions of Sydnones to Alkynes. A New Route into the Pyrazole Series

By Prof. Dr. R. Huisgen, Dr. R. Grashey, Dipl.-Chem. H. Gotthardt, and R. Schmidt

Institut für Organische Chemie der Universität München (Germany)

If *N*-phenyl-*C*-methylsydnone (I, R = C_6H_5, R′ = CH_3) is heated with the dimethyl ester of acetylenedicarboxylic acid in xylene for 1 hr. at 120 °C., 1.0 equivalent of carbon dioxide is released. High vacuum distillation yields 99 % of crystalline dimethyl 1-phenyl-5-methylpyrazole-3,4-dicarboxylate, whose structure is confirmed by saponification, decarboxylation and comparison with authentic 1-phenyl-5-methylpyrazole.

This surprising new pyrazole synthesis can be varied within wide limits (Table 1). The following alkynes react with increasing rate: acetylene, alkylacetylenes < diphenylacetylene < phenylacetylene < propargylaldehyde acetals < propargyl alcohol < phenylpropiolic acid esters < 1-phenyl-2-acylacetylenes < propiolic acid esters < acetylenedicarboxylic acid esters. *N*-Phenyl-, *N*-benzyl- and other sydnones react similarly. Almost all the pyrazoles included in Table 1 were obtained in good to quantitative yields and were structurally determined by degradation or independent synthesis.



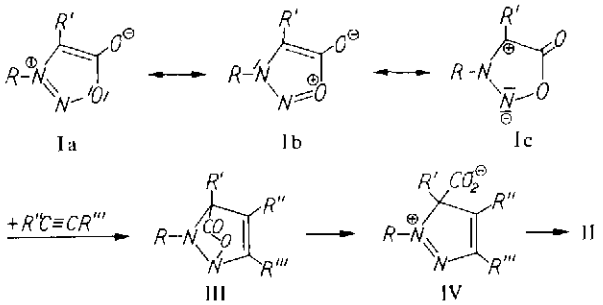
I II

Table 1. Pyrazoles from Sydnones and Alkynes (where the orientation is not certain R″ and R‴ are combined in parentheses).

R	R′	R″	R‴	Reaction conditions °C.	hrs.	Pyrazole (II) % yield
C_6H_5	H	H	H	170	25	75
C_6H_5	CH_3	(H, n-C_6H_{13})		140	30	78
C_6H_5	H	H	C_6H_5	120	20	79
C_6H_5	CH_3	H	C_6H_5	140	12	64
C_6H_5	CH_3	C_6H_5	H			15
$C_6H_5CH_2$	H	H	C_6H_5	140	20	69
C_6H_5	CH_3	C_6H_5	C_6H_5	180	5	97
C_6H_5	H	(CH_3, C_6H_5)		140	20	74
C_6H_5	H	H	CO_2CH_3	100	48	70
C_6H_5	H	CO_2CH_3	H			22
C_6H_5	CH_3	H	CO_2CH_3	140	4	61
C_6H_5	CH_3	CO_2CH_3	H			10
C_6H_5	H	CO_2CH_3	CO_2CH_3	90	4	92
C_6H_5	CH_3	CO_2CH_3	CO_2CH_3	120	1	99
$C_6H_5CH_2$	H	CO_2CH_3	CO_2CH_3	120	5	98
C_6H_5	H	$CO_2C_2H_5$	C_6H_5	95	84	83
C_6H_5	CH_3	$CO_2C_2H_5$	C_6H_5	110	8	82
C_6H_5	H	CO–CH_3	C_6H_5	130	12	100
C_6H_5	H	CO–C_6H_5	C_6H_5	140	16	82
C_6H_5	CH_3	H	$CH(OC_3H_7)_2$	140	15	77
C_6H_5	H	H	CH_2OH	115	24	72

Sydnones [1] are easily accessible aromatic compounds. They can be described only by zwitterionic resonance structures (I, a–c). Formula Ic being a sextet resonance structure undoubtedly contributes little, but permits us to consider the sydnones formally as aromatic azomethine-imines [2] and the primary reaction, induced by the alkyne, as a 1,3-dipolar addition [3]. The spontaneous decomposition of the sydnones occurs only at higher temperatures.

The addition to structure III is followed by a rapid evolution of carbon dioxide with aromatization to the pyrazole II, possibly through the intermediate IV. Analogously, benzyne being a dipolarophile, combines with *N*-phenylsydnone to form 2-phenylindazole + CO_2 [4].



Ia Ib Ic

III IV II

We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for their support of this research program.

Received November 10, 1961 [Z 164/2 IE]

[1] Lit. cited by *W. Baker* and *W. D. Ollis*, Quart. Rev. (Chem. Soc., London) *11*, 15 (1957).

[2] *R. Huisgen*, *R. Fleischmann*, and *A. Eckell*, Tetrahedron Letters No. 12, 1 (1960); *R. Huisgen* and *A. Eckell*, ibid. No. 12, 5 (1960); *R. Huisgen*, *R. Grashey*, *P. Laur*, and *H. Leitermann*, Angew. Chem. *72*, 416 (1960).

[3] Compare *R. Huisgen*, Naturwiss. Rdsch. *14*, 43 (1961); Proc. chem. Soc. (London) 357 (1961).

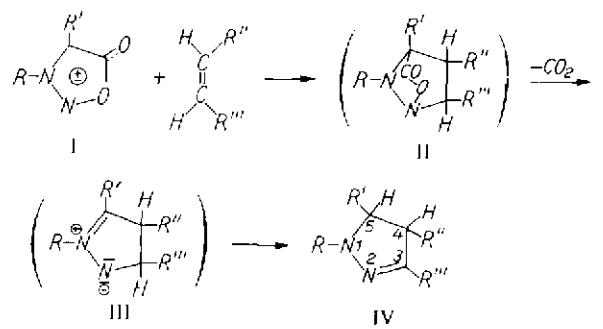
[4] Experiments by Dipl.-Chem. *R. Knorr* in our laboratory.

Reactions of Sydnones with Alkenes

By Prof. Dr. R. Huisgen, Dipl.-Chem. H. Gotthardt, and Dr. R. Grashey

Institut für Organische Chemie der Universität München (Germany)

As with acetylene and its derivatives [1], alkenes can react with sydnones (I), liberating carbon dioxide, but under somewhat more severe conditions. Subsequent to the 1,3-dipolar addition to structure II and decarboxylation (III), stabilization occurs by means of a proton shift and the formation of a Δ^2-pyrazoline (IV). The pyrazolines given in Table 1 were analyzed, characterized spectroscopically and, in part, structurally elucidated by dehydrogenation or independent synthesis.



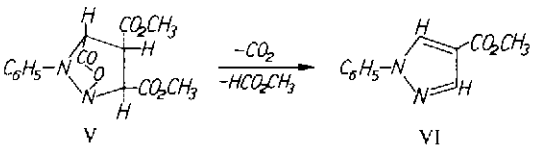
I II III IV

Table 1. Δ^2-Pyrazolines (IV) from Sydnones and Olefins.

Sydnone I R	Sydnone I R'	Olefin	Reaction conditions °C.	Reaction conditions hrs.	Δ^2-Pyrazoline (IV) % yield
C_6H_5	H	Ethylene	180	12	48
C_6H_5	H	Ethyl undecylate	150	15	73
C_6H_5	H	Cyclopentene	145	40	54
C_6H_5	CH_3	Styrene	140	20	79
$C_6H_5CH_2$	H	Styrene	140	24	89
3-Pyridyl	H	Styrene	130	6	79
C_6H_5	H	*p*-Methoxystyrene	140	6	85
C_6H_5	CH_3	Indene	140	5	81
C_6H_5	H	Safrole	150	6	72
C_6H_5	H	Anethole	150	48	42

Alkenes of the styrene type yield pyrazolines which have the aryl radical in the 3-position. Indene yields two structurally isomeric Δ^2-pyrazolines in the ratio 7:1 with the conjugated pyrazoline being the main product.

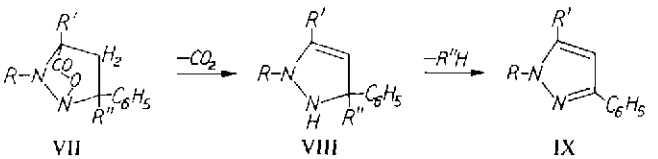
Although the primary adduct V from dimethyl fumarate and *N*-phenylsydnone could, formally, also lead to a Δ^2-pyrazoline, a 60 % yield of VI is isolated, after 50 hrs. at 110 °C., as the result of methyl formate elimination.



V VI

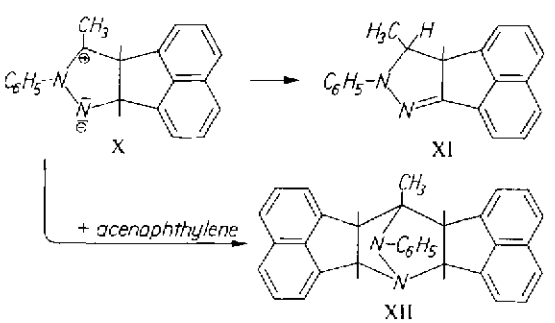
Acrylonitrile and I (R = C_6H_5, R' = CH_3) yield a mixture of 1-phenyl-5-methyl-3-cyano-Δ^2-pyrazoline and 1-phenyl-5-methylpyrazole. In the case of I (R = C_6H_5, R' = H) and in the presence of chloranil, a 84 % yield of 1-phenyl-3-cyanopyrazole is obtained.

Even a quaternary C-atom in the primary adduct VII cannot block the aromatization. If 1,1-diphenylethylene is allowed to react with I (R = C_6H_5, R' = CH_3) in boiling xylene for 24 hours, 99 % (!) of 1,3-diphenyl-5-methylpyrazole (IX, R = C_6H_5, R' = CH_3) is obtained with benzene (determined as *m*-dinitrobenzene) being eliminated. The analogous reaction of I (R = C_6H_5, R' = H) with α-methylstyrene yields IX (R = C_6H_5, R' = H) with the elimination of methane. It is possible that the Δ^4-pyrazolines VIII are intermediates in these unusual eliminations. The reaction of *N*-phenylsydnone with isobutene is also accompanied by aromatization following methane evolution.



VII VIII IX

If I (R = C_6H_5, R' = CH_3) is refluxed with 2 equivalents of acenaphthylene in xylene for 18 hrs., a 47 % yield of a 1:2-adduct is isolated together with 14 % of a 1:1-adduct (XI) of the Δ^2-pyrazoline-type. The ultraviolet absorption spectrum of the 1:2-adduct offers strong support for the polycyclic formula XII.



X XI XII

The hypothetical intermediate X, resulting from 1,3-addition and CO_2-evolution, is again an azomethine-imine similarly to the case of sydnone I; X isomerizes to XI or enters into renewed dipolar addition with acenaphthylene to give XII.

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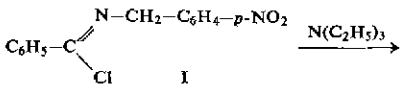
[1] *R. Huisgen*, *R. Grashey*, *H. Gotthardt*, and *R. Schmidt*, Angew. Chem. *73*, 29 (1962); cf. Angew. Chem. internat. Edit. *1*, 48 (1962).

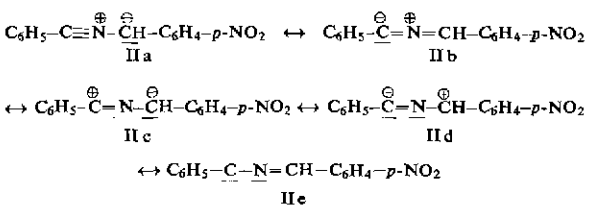
1,3-Dipolar Additions with Nitrile Ylides

By Prof. Dr. R. Huisgen, Dr. H. Stangl, Dr. H. J. Sturm, and H. Wagenhofer

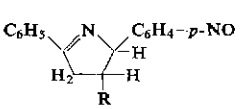
Institut für Organische Chemie der Universität München (Germany)

Nitrile ylides are octet stabilized 1,3-dipoles with a double bond [1]. The first nitrile ylide was obtained by HCl-elimination from the imide chloride I with triethylamine at 0 -20 °C.; triethylammonium chloride separates and a deep violet solution of II (a–e) results.

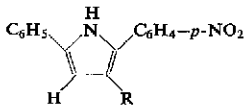




(II) cannot be isolated, but is easily intercepted with dipolarophiles. In the presence of acrylonitrile, the violet color disappears and 86 % of two diastereomeric Δ^1-pyrrolines III are formed. These yield the same carboxylic acid IV with 40 % sulfuric acid. Its methyl ester is identical with the adduct V, isolated in 58 % yield from methyl acrylate and II. Chloranil dehydrogenation of V yields 92 % of the

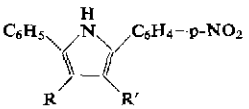


III R = CN
IV R = CO_2H
V R = CO_2CH_3

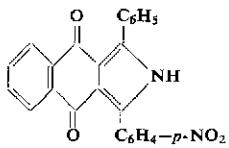


VI R = CO_2CH_3
VII R = CO_2H
VIII R = H

pyrrole derivative VI (NH-band at 3205 $cm.^{-1}$); the same compound is formed in 64 % yield in the 1,3-addition of II to propiolic acid methyl ester. VI may be converted via the carboxylic acid VII to the red 2-(*p*-nitrophenyl)-5-phenylpyrrole (VIII). The independent synthesis of the latter was possible via the structurally known 4-carboxylic acid which is not identical with VII. Compound VII must therefore be the 3-carboxylic acid. This fact determines the orientation of substituents in III–VI.



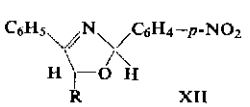
IX R = C_6H_5, R' = CO_2CH_3
X R = R' = CO_2CH_3



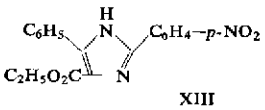
XI

Addition of II to phenylpropiolic acid ester or acetylenedicarboxylic acid ester yields IX and X (49 %). The adduct with acenaphthylene (37 %) still has a Δ^1-pyrroline character, while the aromatic XI (CO-band at 1658 cm^{-1}) is obtained from II and excess 1,4-naphthoquinone.

The aldehyde group is also a suitable dipolarophile with respect to II. With benzaldehyde or acetaldehyde 63 % and 37 % of the Δ^3-oxazolines XII (R = C_6H_5 or CH_3, respectively) are obtained. Their dehydrogenation products clearly agree with the independently synthesized oxazoles. The orientation of addition in the formation of III, V, VI, and XII is accounted for by the resonance structures IIb and d.



XII



XIII

Compound II reacts with the nitrile group of cyanoformic acid ethyl ester to give the imidazole derivative XIII. For the 1:1-adducts of II to carbon disulfide and α-dithionaphthoic acid methylester, the direction of addition has not yet been verified; the adduct from II and the naphthoic ester spontaneously splits off CH_3SH with the formation of a thiazole derivative.

The 1,3-dipolar addition of II to nitrosobenzene is followed by a 1,3-elimination; 38 % of *C*-[*p*-nitrophenyl]-*N*-phenylnitrone are isolated.

Analogous additions were carried out with the nitrile ylide from *N*-[*p*-Nitrobenzyl]-*p*-methoxybenzimide chloride. The phenyl-conjugated double bond of 1,2-dihydronaphthalene also accepts the ylide.

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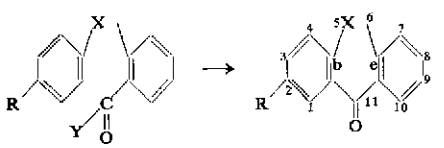
[1] *R. Huisgen*, Naturwiss. Rundschau *14*, 43 (1961); Proc. chem. Soc. (London) *1961*, 357.

New Types of Heterocyclic Ring Systems

By Dr. K. Stach and Dr. H. Spingler

Chemische Forschungslaboratorien der C. F. Boehringer und Soehne G.m.b.H., Mannheim-Waldhof (Germany)

The synthesis of dibenzo[b, e]oxepin-11-one (I; X = O; R = H) and dibenzo[b,e]thiepin-11-one (I; X = S; R = H) and their 2-substituted derivatives takes place in a smooth reaction, and in excellent yields, by dehydration of the *o*-(phenoxymethyl)benzoic acids (II; X = O; Y = OH) with polyphosphoric acid esters (prepared from phosphorus pentoxide in ethanol [1]), or by dehydration of the *o*-(phenylmercaptomethyl)benzoic acids (II; X = S; Y = OH) with polyphosphoric acid at 100–150 °C. over a reaction time of about 30 minutes.



II I

	R	Condensation agent	Reaction temp. [°C.]	Yield [%]	b.p. [°C./mm.Hg]	m.p. [°C.]
I, X = O	H	Polyphosphoric acid ester	100–110	85,5	142–145/0,2	71–72
	CH_3		100–110	82,0	--	108–109
	OCH_3		130–140	81,0	158–162/0,05	93–94
	Cl		130–140	71,5	162–166/0,5	126–127
I, X = S	H	Polyphosphoric acid	100–110	84,5	162–165/0,03	86–88
	CH_3		100–110	86,5	167–175/0,2	119–120
	Cl		130–140	81,0	175–181/0,2	133–134

It is interesting to note that the dibenzo[b,e]oxepin-11-ones are also obtained in good yields by simple heating of the corresponding *o*-(phenoxymethyl)benzoyl chlorides (II; X = O; Y = Cl). The latter are readily obtainable from the acids with thionyl chloride.

The *o*-(phenoxymethyl)- and *o*-(phenylmercaptomethyl)benzoic acids are obtained by the reaction of *ω*-bromo-*o*-toluyl bromide [2] with the sodium salt of the corresponding phenols and thiophenols and subsequent saponification.

The dibenzo[b,e]oxepinones and dibenzo[b,e]thiepinones do not react with ketone reagents. With Grignard compounds, however, such as $ClMg(CH_2)_3N(CH_3)_2$, they form, in very good yields, the corresponding carbinols. These split off water relatively easily. The basic propylidene compounds obtained can be hydrogenated in the customary manner.

Received November 17, 1961 [Z 172/11 IE]

[1] *T. Mukaiyama* and *T. Hata*, Bull. chem. Soc. Jap. *34*, 99 (1961).

[2] *W. Davies* and *W. H. Perkin* Jr., J. chem. Soc. (London) *121*, 2203 (1922).

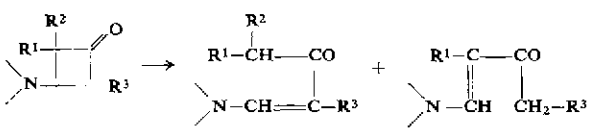
Capture of Ketenes by Cyclo-Addition to Enamines

By Dr. G. Opitz, cand. chem. M. Kleemann, and cand. chem. F. Zimmermann

Chemisches Institut der Universität Tübingen (Germany)

The synthesis [1–3] of 3-dialkylaminocyclobutanone derivatives by cyclo-addition of ketenes to enamines is also possible with ketenes produced *in situ*. A particularly simple route requires only the dropwise addition of an ether solution of an acid chloride (R_2CH-COCl) to a mixture of enamine and triethylamine. After the triethylamine hydrochloride is removed, the solution contains the cyclobutanone base. In this manner, ketenes may be captured which are accessible only with difficulty, or not at all, in monomeric form, *e.g.* methylketene, isopropylketene, butylketene, phenylketene, phenoxyketene, acetoxyketene, chloroketene.

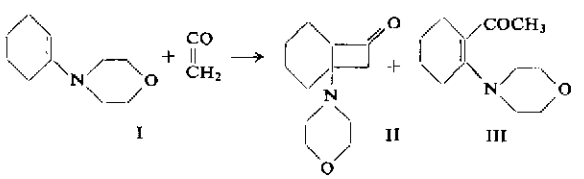
Suitable bases are t-enamines from mono- and di-substituted acetaldehydes. The enolizable cyclobutanone bases suffer ring cleavage on heating and form vinylogous carboxylic acid amides, while the non-enolizable ring bases are thermally stable.



R^2 = H or alkyl R^2 = H

When 1-piperidinopropene is reacted with ketene or acetyl chloride/triethylamine, 2-methyl-3-piperidinocyclobutanone is formed, which, on standing changes to a mixture of 1-piperidino-1-pentene-3-one and 1-piperidino-2-methyl-butenone. Analogous behavior is shown by 2,4-dimethyl-3-piperidinocyclobutanone formed with propionyl chloride/triethylamine, by 2-ethyl-3-piperidinocyclobutanone formed from 1-piperidinobutene and ketene or acetyl chloride/triethylamine, and by 2-ethyl-3-piperidino-4-methyl-cyclobutanone from 1-piperidinobutene and propionyl chloride/triethylamine. Other cyclobutanone bases are summarized in Table 1.

The ring bases have a sharp carbonyl band at 1766–1781 cm^{-1} in the IR-spectrum. In the reaction of 1-morpholinocyclohexene (I) with ketene, the formation of the bicyclic cyclobutanone base II can be detected by IR-spectroscopy. The main product is 1-morpholino-2-acetylcyclohexene (III), which is also formed in the ring cleavage of II.



I II III

Table 1. Synthesis of Cyclobutanone Bases from Enamines and Acid Chlorides in the Presence of Triethylamine

Acid chloride	Cyclobutanone	M.p. [°C.]	Yield [%]
Enamine: 1-Morpholino-isobutene			
Propionyl chloride	2,2,4-Trimethyl-3-morpholino	38–39	
Chloroacetyl chloride	2,2-Dimethyl-3-morpholino-4-chloro-	80–81	30
Phenoxyacetyl chloride	2,2-Dimethyl-3-morpholino-4-phenoxy-	112–113	53
Acetoxyacetyl chloride	2,2-Dimethyl-3-morpholino-4-acetoxy-	95–96	50
Phenylacetyl chloride	2,2-Dimethyl-3-morpholino-4-phenyl-		
Isobutyryl chloride	2,2,4,4-Tetramethyl-3-morpholino-	b.p. 83–85/0.4 mm.Hg	
Diethylacetyl chloride	2,2-Dimethyl-3-morpholino-4,4-diethyl-	39–40	25
Diphenylacetyl chloride	2,2-Dimethyl-3-morpholino-4,4-diphenyl-		
Enamine: 1-Piperidino-isobutene			
Phenoxyacetyl chloride	2,2-Dimethyl-3-piperidino-4-phenoxy-	82–83	78
Isovaleryl chloride	2,2-Dimethyl-3-piperidino-4-isopropyl-		
Caproic acid chloride	2,2-Dimethyl-3-piperidino-4-butyl-		
Stearic acid chloride	2,2-Dimethyl-3-piperidino-4-hexadecyl-		
Enamine: 1-Pyrrolidino-isobutene			
Propionyl chloride	2,2,4-Trimethyl-3-pyrrolidino-		
Ethyl-butyl-acetyl chloride	2,2-Dimethyl-3-pyrrolidino-4-ethyl-4-butyl-	b.p. 111–113/2 mm. Hg	30

Received November 24, 1961 [Z 176/13 IE]

[1] *G. Opitz, H. Adolph, M. Kleemann*, and *F. Zimmermann*, Angew. Chem. *73*, 654 (1961).

[2] *R. H. Hasek* and *J. C. Martin*, J. org. Chemistry, in the press.

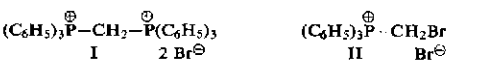
[3] *G. A. Berchtold*, private communication by [2].

Introduction of the Bromomethylene Group using the Wittig Reaction

By Dr. G. Köbrich

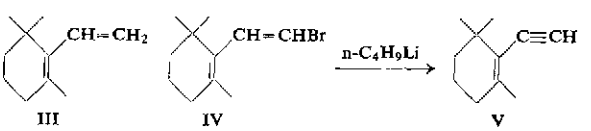
Organisch-Chemisches Institut der Universität Heidelberg (Germany)

Triphenylphosphine reacts with methylene bromide to form a mixture of I and II [1]. Pure II (m.p. 241–242.5 °C.) is obtained in 74 % yield from triphenylhydroxymethylphosphonium bromide and phosphorous pentabromide.



I II

If the chloromethylenation of compound II is attempted by the method of *G. Wittig* and *M. Schlosser* [2], the vinyl compound III (yield 40 %; λ_{max} = 233 mμ; log ε = 3.76) is



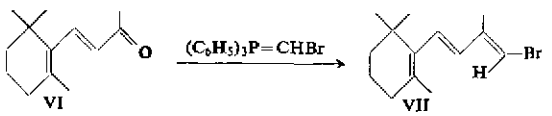
III IV V

formed from n-butyllithium in ether and with β-cyclocitral, rather than the expected product IV; with phenyllithium as base, on the other hand, a mixture of III and IV is formed in the ratio 3:2 (determined by gas chromatography), besides bromobenzene. The bromo compound IV (λ_{max} = 238.5 mμ; log ε = 3.80), which readily polymerizes, may be converted to

V [4] (Hg salt: m.p. 128 to 129 °C.) with n-butyllithium [3]. Thus, it is easier to remove a bromine cation from compound II than a proton [5]:

$$II \xrightarrow{C_6H_5Li} (C_6H_5)_3P{=}CH_2 + (C_6H_5)_3P{=}CHBr$$

The desired bromomethylenation can be realized with lithium piperidide [6] which predominantly removes protons from II; subsequent reaction with β-ionone (VI) gives, after chromatographic purification, the very unstable compound VII in 70 % yield (λ_{max} = 269 mμ; log ε = 4.18).



VI VII

I thank Prof. *G. Wittig* for his assistance in this work.

Received December 4, 1961 [Z 177/15 IE]

[1] Cf. *F. Ramirez, N. B. Desai, B. Hansen,* and *N. McKelvie,* J. Amer. chem. Soc. *83,* 3539 (1961).

[2] Chem. Ber. *94,* 1373 (1961); *D. Seyferth, S. O. Grim,* and *T. O. Read,* J. Amer. chem. Soc. *83,* 1617 (1961).

[3] Cf. ω-bromostyrene: *G. Wittig* and *H. Witt,* Ber. dtsch. chem. Ges. *74,* 1480 (1941).

[4] *H. Sobotka* and *J. D. Shanley,* J. Amer. chem. Soc. *71,* 4136 (1949).

[5] *D. Seyferth* et al. have made the same observation. (Private communication by Prof. *Seyferth.*)

[6] This also gives the best yields in chloromethylenation: *G. Wittig* and *M. Schlosser,* unpublished. I thank Dr. *M. Schlosser* for this communication.

Solubility of Helium in Lithium Silicate Melts

By Priv.-Doz. Dr. H. Scholze and
Dipl.-Chem. H.-O. Mulfinger

Max-Planck-Institut für Silikatforschung, Würzburg (Germany)

The structure of glass is determined essentially by the structure of glass melts. A study of the latter should also be possible by determining the gas solubility in such melts. The solubility of He at 1400 °C. was measured in two lithium silicate melts. For melt 1, with 20.0 mole% of Li_2O, the Ostwald solubility coefficient k_1 = 0.0252. For melt 2, with 24.8 mole% Li_2O, a coefficient k_2 = 0.0200 was found. Thus, the He solubility decreases with increasing Li_2O content.

The molar volumes MV of the glass melts calculated from the data of *Bockris* et al. [1], with each mole containing exactly two oxygen atoms, are almost constant with MV_1 = 27.67 ml. and MV_2 = 27.86 ml., and show that the Li^+ ions are incorporated into cavities present in the melt. (The molar volume for pure SiO_2 glass is 27.30 ml.) If we assume that the He solubility depends only on the volume of the cavities, then the observed decrease of the solubility must correspond to the volume of the additional Li^+ ions, that is the ionic radius of the Li^+ ion can be calculated from the solubility decrease. For a decrease of the He solubility of $k_1MV_1 - k_2MV_2$ = 0.140 ml. and an increase of $0.749 \cdot 10^{23}$ Li^+ ions (per molar volume), we obtain an ionic radius of 0.76 Å for the Li^+ ion. This is in good agreement with literature data on the Li^+ ion radius and the assumption concerning the mechanism of the He solubility is thus verified. The above also provides a better idea regarding the volume of cavities in the glass melts.

The measurement procedure and further data will be reported elsewhere.

Received December 4, 1961 [Z 188/18 IE]

[1] *J. O'M. Bockris, J. W. Tomlinson,* and *J. L. White,* Trans. Far. Soc. *52,* 299 (1956).

The Preparation of Trisilylphosphine

By Dr. E. Amberger and H. Boeters

Institut für Anorganische Chemie der Universität München (Germany)

Trisilylphosphine is prepared in 55 % yield by the reaction of monobromosilane with potassium dihydrophosphide, using a 1:1 molar ratio.

$$3\ SiH_3Br + 3\ KPH_2 \longrightarrow P(SiH_3)_3 + 2\ PH_3 + 3\ KBr.$$

The reaction mixture (solvent: dimethyl ether, frozen) is gradually warmed. The reaction begins at −120 °C. and is finished at −40 °C. Ether, phosphine, and unreacted silylbromide can easily be separated from the trisilylphosphine by high-vacuum distillation.

Trisilylphosphine is a colorless liquid at room temperature and ignites spontaneously in the presence of air. In the range −30 to +11 °C., the following vapor pressure relationship may be applied: log p (mm. Hg) = −(1901.8/T) + 7.792. The molar enthalpy of evaporation amounts to 8697 cal./mole, the extrapolated boiling point is 114 °C. Absorption bands in the infrared region lie at 2164, 1159, 884, 629, 572, and 458 cm^{-1}.

Received December 7, 1961 [Z 183/7 IE]

The Rhenium(I) Tetracarbonyldiethylene Cation

By Prof. Dr. E. O. Fischer and Dr. K. Öfele

Institut für Anorganische Chemie der Universität München (Germany)

In connection with our studies of previously unknown ethylene π-complexes with Mn [1], Fe, Mo, W [2] and Cr [3], we obtained as the first of such complexes with rhenium, the colorless, diamagnetic $[Re(Co)_4(C_2H_4)_2]^+$ cation, prepared under approximately 250 atm. C_2H_4-pressure at 45 °C. in cyclohexane according to the equation

$$Re(CO)_5Cl + AlCl_3 + 2\ C_2H_4 \longrightarrow [Re(CO)_4(C_2H_4)_2]AlCl_4 + CO$$

and isolable by hydrolysis as the difficultly soluble hexafluorophosphate. The recrystallized (acetone/ether) complex salt $[Re(Co)_4(C_2H_4)_2]PF_6$, verified by complete analysis, shows CO bands at 2016, 2053, and 2146 cm^{-1} in its infrared spectrum, as well as the C=C vibration at 1539 cm^{-1} in contrast with 1541 cm^{-1} (corr.) [1b] for $[Mn(CO)_5C_2H_4]AlCl_4$. The cation dissolved in D_2O gives only a proton signal at τ = 6.6 (tetramethylsilane as external standard) [4]. We postulate an octahedral Re(I) covalent complex in which the π-bonded C_2H_4-ligands must lie in *cis*-positions [5], according to the three CO bands.

Since *trans*-$PtCl_2(C_2H_4)_2$ [6] decomposes above −6 °C., this is the first example of a stable diethylene-metal complex.

Received December 12, 1961 [Z 180/6 IE]

[1a] *H. P. Kögler* and *E. O. Fischer,* Z. Naturforsch. *15b,* 676 (1960).

[1b] *E. O. Fischer* and *K. Öfele,* Angew. Chem. *73,* 581 (1961).

[2] *E. O. Fischer* and *K. Fichtel,* Chem. Ber. *94,* 1200 (1961).

[3] *E. O. Fischer* and *P. Kuzel,* Z. Naturforsch. *16b,* 475 (1961).

[4] *H. Keller,* personal communication.

[5] *H. P. Fritz,* personal communication.

[6] *J. Chatt* and *R. G. Wilkins,* J. chem. Soc. (London) 2622 (1952).

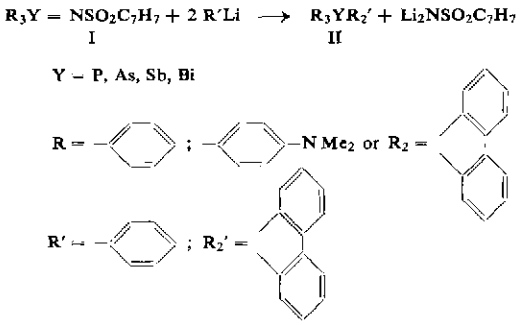
Penta-Aryl Derivatives of the Elements of the Fifth Group

By Prof. Dr. G. Wittig and Dr. D. Hellwinkel

Institut für Organische Chemie der Universität Heidelberg (Germany)

The synthesis of phosphorane derivatives by *G. Wittig* and *E. Kochendörfer* depends upon the reaction of triaryliminophosphorane derivatives with two equivalents of aryllithium [1]. It cannot be applied to the arsenic series since triphenylarsine and derivatives do not react with phenyl azide.

It was established that the triphenyl-*p*-tolylsulphonylimine derivatives (I), which are prepared [2] by the reaction of chloramine-T with triphenylarsine and its analogues, can be converted in good yield to the penta-aryl compounds (II).



A comprehensive publication will be prepared concerning the chemistry of bis(biphenylylene)phenylphosphoranes [1], -arsoranes and -stiboranes.

Received December 12, 1961 [Z 181/4 IE]

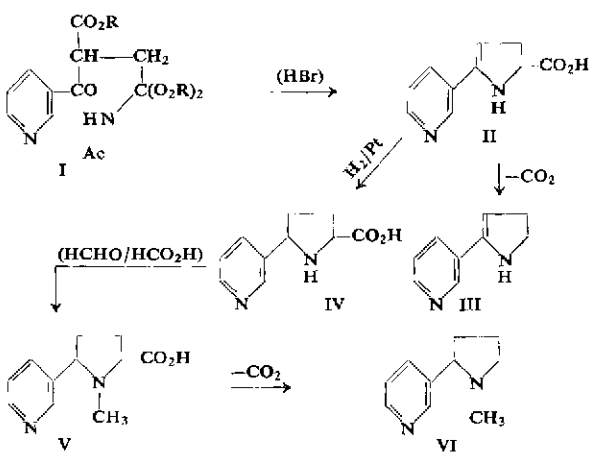
[1] *G. Wittig* and *E. Kochendörfer*, Angew. Chem. *70*, 506 (1958).
[2] *F. G. Mann* and *E. L. Chaplin*, J. chem. Soc. (London) 530, 535 (1937).

Synthesis of Nicotine, Myosmine and Pyridylproline[*]

By Prof. Dr. H. Hellmann and Dr. Dieter Dieterich

Chemisches Institut der Universität Tübingen (Germany)

In the hydrolysis of (I), obtained from nicotinoyl acetic ester, paraformaldehyde and acetaminomalonic ester by asymmetrical three – carbon condensation, 2-(β-pyridyl)-Δ^2-pyrroline-5-carboxylic acid (II) is formed. This can be converted into the tobacco smoke alkaloid, myosmine (III), by decarboxylation and into 5-(β-pyridyl)proline (IV) by hydrogenation.



Compound (IV) can be methylated with formaldehyde/formic acid to 5-(β-pyridyl)hygrinic acid (V) which splits off CO_2 on heating with the formation of nicotine (VI). Total yield: 20 % based on nicotinoyl acetic ester. 5-(γ-Pyridyl)proline can be prepared analogously in 60 % total yield.

Received December 14, 1961 [Z 184/20 IE]

[*] "Asymmetrical Three-Carbon Condensations; XIII". Part XII: *H. Hellmann* and *M. Schröder*, Liebigs Ann. Chem., in the press.

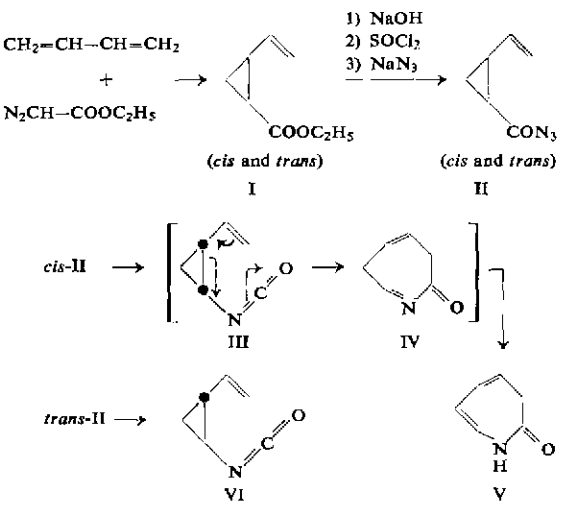
Rearrangement of a Cyclopropane Derivative into a Heterocyclic Seven-Membered Ring Compound

By Prof. Dr. Emanuel Vogel and Dipl.-Chem. Rolf Erb

Institut für Organische Chemie der Universität Köln (Germany)

cis-1,2-Divinylcyclopropane isomerizes even as it is formed (80 °C.), undergoing a Cope rearrangement to form cycloheptadiene-(1,4) [1], while the *trans* isomer is converted to cycloheptadiene-(1,4) only when heated to 190 °C. since it does not fulfil the steric prerequisites for the cyclic transition state of the Cope rearrangement [2]. These results suggest that cyclopropane compounds which are derived from *cis*-1,2-divinylcyclopropane by replacing a vinyl group with another double bond function, for example, –N=C=O, >C=N– or >C=O, should be capable of undergoing an isomerization analogous to the Cope rearrangement.

The reaction of diazoacetic acid ethyl ester (1 mole) with excess butadiene (6 moles) at 100–110 °C. (8 hours) yields 80 % 2-vinylcyclopropane carboxylic acid ethyl ester (I), *cis*: *trans* = 45:55. The mixture was converted into *cis*- and *trans*-2-vinylcyclopropane carboxylic acid azide (II) and the azides were subjected to Curtius degradation at 80 °C. in benzene. Two products with the composition C_6H_7ON were formed: a solid substance (V), m.p. 48–50 °C. (32 % relative to the total quantity of isomeric acid chloride), and a liquid (VI), b.p. 85–86 °C./165 mm. Hg; $n_D^{20} = 1.4630$ (33 %).



The IR spectrum of (V) shows a lactam-like amide group as well as conjugated C=C-bonds, but no vinyl group, and thus points to an unsaturated seven-membered lactam. This was verified by catalytic hydrogenation: (V) absorbs 2 moles of hydrogen with platinum in acetic ester and is converted to caprolactam. The position of the double bonds in the lactam were proven by the IR and UV data ($\lambda_{max} = 255$ mμ; log $\varepsilon = 3.69$ in methanol), as well as by the nuclear magnetic resonance spectrum (adjacency of the CH_2-group to the carbonyl group).

The substance thereby recognized as 1-azacyclohepta-4,6-diene-2-one (V) is apparently formed by valence isomerization of the thermolabile *cis*-2-vinylcyclopropyl isocyanate

(III) to 1-azacyclohepta-4,7-diene-2-one (IV) and prototropic rearrangement [3]. Attempts to convert (V) into the hitherto unknown azepine, or its derivatives, are in progress. For the liquid isomer (VI), the structure of a 2-vinylcyclopropyl isocyanate was proven by IR spectral and nuclear magnetic resonance data. Since (V) is to be considered as the rearrangement product of (III), (VI) must have the *trans* configuration. *trans*-2-Vinylcyclopropyl isocyanate has remarkable thermal stability. Even when heated for 2 hours to 200 °C., it is only slightly polymerized.

Received December 18, 1961 [Z 186/16 IE]

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

[2] *E. Vogel*, Angew. Chem. *72*, 4 (1960).

[3] A similar valence isomerization was recently reported by *W. von E. Doering* and *M. I. Goldstein*, Tetrahedron *5*, 53 (1959).

Plastics from Polyacrylonitrile and Inorganic Nitrates

By Prof. Dr. A. Henglein and Dr. W. Schnabel

Hahn-Meitner-Institut für Kernforschung, Berlin-Wannsee (Germany), and Mellon Institute, Pittsburgh 13, Pa. (U.S.A.)

Acrylonitrile can dissolve up to 2 parts by weight of silver nitrate at 20 °C. Other inorganic nitrates such as copper or cerium(III) nitrate are only slightly dissolved by acrylonitrile; in the presence of silver nitrate, however, large quantities go into solution. In such concentrated solutions of inorganic nitrates, acrylonitrile polymerizes spontaneously and violent explosions may occur in the absence of oxygen and with insufficient cooling. Light, ionizing radiation, and heat accelerate the polymerization. The polyacrylonitrile is cross-linked. When the monomer has been consumed, the mass is hard and transparent and the polymerized acrylonitrile is incorporated in the inorganic nitrate. In the $AgNO_3$-catalyzed polymerization, a portion of acrylonitrile may be replaced with other polymerizable vinyl compounds. The silver nitrate, however, is not interchangeable with other silver salts (nitrite, sulfate, acetate). The substances formed are electrical conductors and have high density. The products prepared with silver nitrate darken in a few weeks because of the separation of silver. In the presence of copper nitrate, deep green transparent products are formed. Under the influence of water stepwise disintegration occurs because the inorganic component is leached out.

The ability of silver nitrate and other nitrates to accelerate the polymerization of acrylonitrile and to cause cross-linkage, as well as to absorb the polymer formed in a clear solid solution, points to considerable mutual interaction between the inorganic "solvent" and the monomeric (or polymeric) acrylonitrile or the growing polymerization chains, respectively. *Bamford* et al. [1] traced the acceleration of the polymerization of acrylonitrile in dimethylformamide with lithium chloride to a complex formation with the growing polymer chains. The kinetics of the polymerization with silver nitrate can be studied if γ-radiation is used for the triggering and the $AgNO_3$ concentration is kept small. It was found that, depending on the concentration, silver nitrate can act as accelerator or inhibitor. In dilute solutions, the polymerization rate decreases with increasing $AgNO_3$ concentration. Only above 10^{-2} moles/liter does the accelerating effect become noticeable.

Received December 18, 1961 [Z 185/19 IE]

[1] *C. H. Bamford, A. D. Jenkins*, and *R. Johnston*, Proc. Roy. Soc. (London), Ser. A, *241*, 364 (1957).

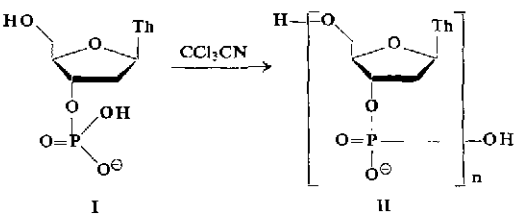
Oligonucleotide Synthesis with Trichloroacetonitrile

By Prof. Dr. F. Cramer, Dr. H. J. Baldauf, and cand. ing. H. Küntzel

Institut für organische Chemie, Technische Hochschule, Darmstadt (Germany)

Trichloroacetonitrile, being a reagent for the esterification of phosphoric acids [1], can be used for the preparation of oligonucleotides of thymidylic acid (I).

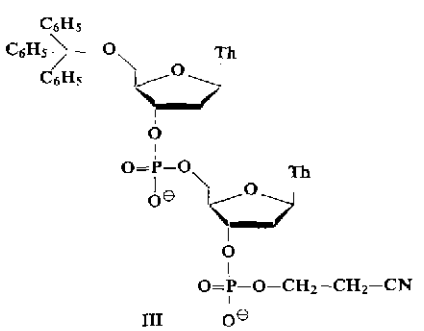
In the direct polycondensation of I ($0.025 \cdot 10^{-3}$ mole (I) as the pyridinium salt; $0.5 \cdot 10^{-3}$ mole CCl_3CN in dimethylformamide; 72 hours at 50 °C.), we obtained a mixture from which a 40 ± 4% oligomer yield could be separated chromatographically [2]. Di-3′-thymidyl pyrophosphate is an intermediate in the polycondensation [3]. Thymidine-3′,5′-cyclophosphate and dimeric cyclonucleotide are also formed.



I II

Stepwise synthesis was possible in the following manner: 5′-*O*-trityl-thymidine-3′-phosphoric acid (Na salt) was condensed with thymidine-3′-β-cyanoethylphosphoric acid [4] to trityl-TPTP-cyanoethyl (III) [5] ($0.5 \cdot 10^{-3}$ mole of both components; 10^{-2} mole trichloroacetonitrile in anhydrous pyridine; 75 °C.; 24 hours, 40 % yield). By detritylation (80 % acetic acid, 20 min. at 100 °C.) and splitting-off the β-cyanoethyl group (9 N ammonia, 60 min. at 60 °C.), the free dinucleotide (II, n = 2) was obtained.

Compound III permits further stepwise synthesis: acetic acid splits off the trityl group and liberates the alcoholic OH; alkali removes the β-cyanoethyl group, so that a renewed condensation at the phosphate end becomes possible.



III

Received December 19, 1961 [Z 187/17 IE]

[1] *F. Cramer* and *G. Weimann*, Chem. and Ind. 46 (1960); Chem. Ber. *94*, 996 (1961).

[2] Vgl. *A. F. Turner* and *H. G. Khorana*, J. Amer. chem. Soc. *81*, 4651 (1959).

[3] *F. Cramer* and *R. Wittmann*, Angew. Chem. *72*, 628 (1960).

[4] *G. M. Tener*, J. Amer. Chem. Soc. *83*, 159 (1961).

[5] The possibility of preparing (III) with carbodiimide has been mentioned by *H. G. Khorana:* Some Recent Developments in the Chemistry of Phosphate Esters Biological Interest. J. Wiley and Sons, New York 1961, p. 112.

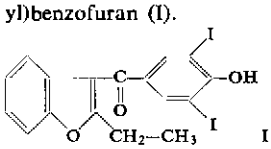
German Therapy Congress and Pharmaceutical Exhibition

Karlsruhe (Germany), August 27 to September 2, 1961

The meeting named 13th Therapeutic Week dealt among other subjects with geriatric psychotherapy, liver, gallbladder, cardiovascular and circulatory disorders, the significance of toxic foci, the intricacy of active vaccination, also with problems of social medicine and occupational diseases, physical therapy and traffic safety.

Approximately 230 drug firms participated in the pharmaceutical exhibition. Only a few of the new natural products and the especially interesting synthetic compounds are presented in this report. The great number of combination products – although they are very valuable for therapeutic purposes – are not considered here.

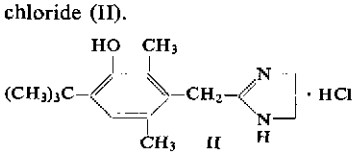
Disorders of the blood supply of the heart muscle, i.e. coronary disorders are among the most frequent causes of death in our times. The firm Woelm-Labaz GmbH. developed Amplivix® which is 2-ethyl-3-(3′,5′-diiodo-4′-hydroxybenzoyl)benzofuran (I).



I

It was shown in many pharmacological and clinical tests that this substance is a specific coronary vasodilator and thus increases the oxygen supply of the heart muscle. The particular advantage of this product compared to the nitrites is its long-lasting effect.

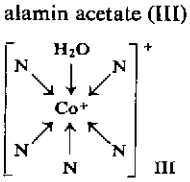
E. Merck recommends Nasivin® for the decongestion of the inflamed mucosa of the nose and the sinuses and for the topical treatment of conjunctivitis. The product is 2-(4′-t-butyl-2′,6′-dimethyl-3′-hydroxybenzyl)-2-imidazoline hydrochloride (II).



II

The almost white crystals melt at 300 °C. and are easily soluble in water and alcobol. The strongly vasoconstricting preparation does not cause undesirable side-effects.

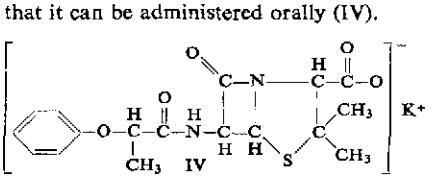
The long search for a fully active physiological depot-form of vitamin B_{12} has been brought to a close by E. Merck with the introduction of Aquo-Cytobion®. This is the aquocobalamin acetate (III) designated as vitamin B_{12a} or B_{12b} in the



III

literature. It is injected intravenously or intramuscularly. The neutral cyanocobalamin used up to now has the disadvantage of being eliminated relatively rapidly from the body. The depotaction of the new preparation is supposed to be due to a firmer tie with the negatively charged serum and tissue proteins and this results in delayed elimination.

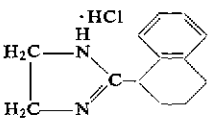
Pfizer GmbH. markets in Germany a synthetically modified penicillin designated as "Pen-200" whose main advantage is that it can be administered orally (IV).



IV

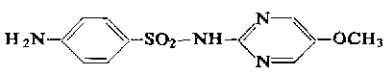
IV is prepared by N-acylation of 6-aminopenicillanic acid with phenoxypropionic acid and is practically non-toxic. Used as the potassium salt in the form of tablets, it is resorbed in the intestinal tract because of its good water solubility and high stability towards acids. Its effective spectrum corresponds to that of the older penicillins.

Yxin®, active ingredient: 2-(1′,2′,3′,4′-tetrahydro-1′-naphthyl)imidazoline hydrochloride (V), 5 % in isotonic solution, is a new ophthalmological drug of Pfizer GmbH. It is recommended for the treatment of conjunctivitis.



V

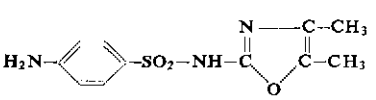
Farbenfabriken Bayer and Schering AG have developed independently of each other a new sulfadiazine derivative. Both firms are introducing the product simultaneously as Durenat®. It is 5-methoxysulfadiazine (VI) and is marketed in tablet and liquid form.



VI

The manufacturers stress that extensive investigations proved its especially long-lasting, intensive effect and its broader spectrum towards gram negative bacteria as compared to penicillin.

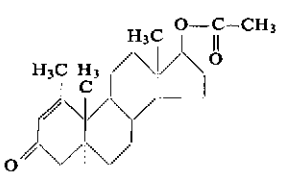
The Nordmark-Werke GmbH. also offer a new type of sulfonamide. Sulfuno is 2-(*p*-aminobenzenesulfonamido)-4,5-dimethyl-oxazole (VII); m.p. 193–194 °C.



VII

Aside from its excellent tolerance the favorable midway position of the drug between the short-term classic sulfonamides with rapid elimination and the repository sulfonamides with delayed resorption and excretion is stressed. Because of accumulation in the gall bladder the preparation is especially indicated for disorders of the gall bladder and the bile duct of the liver.

With Primobolan and Primobolan-Depot, Schering AG put an anabolic steroid for the enhancement of protein build-up onto the market. 1-Methyl-Δ^1-androstenolone acetate or enanthate (VIII) exert a strong anabolic effect without having other undesirable hormonal properties.

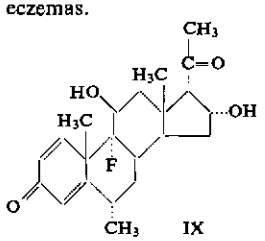


VIII

The nitrogen balance becomes positive during therapy; an additional 22 g. of protein per day are built up by the organism without increasing protein intake.

Farbwerke Hoechst introduced Delmeson®, a skin-specific synthetic steroid. 21-Deoxy-6-methyl-9-fluoroprednisolone

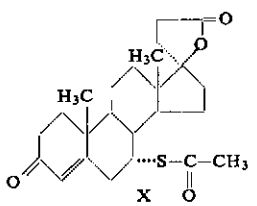
(IX) combined with the antibiotic neomycin is especially suitable for the treatment of inflammatory and allergic eczemas.



IX

Squibb recommends its new preparation Omca® 4-{3-[2-(trifluoromethyl)-10-phenothiazinyl]-propyl}-1-piperazine-ethanol dihydrochloride to influence the complicated vegetative dystonia. The drug is claimed not only to suppress the peripheral symptoms but also the usually present central focus in the brain.

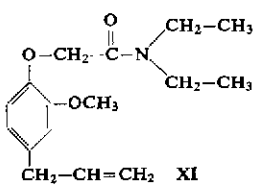
A new type of diuretic is produced by C. F. Boehringer u. Soehne GmbH., Mannheim. Aldactone® belongs to the class of spironolactones and is 3'-(3-oxo-7α-acetylthio-17β-hydroxy-Δ⁴-androsten-17α-yl)propionic acid γ-lactone (X); m.p. 200 °C.; $[\alpha]_D^{20}$ −34 ° in $CHCl_3$.



X

This practically non-toxic substance is an antagonist of the adrenal hormone aldosterone and inhibits the reabsorption of sodium by the kidney which is governed by aldosterone. This results in higher excretion of salt and water.

Chemische Werke Dr. R. Reiss contribute the non-barbiturate, short-term anesthetic Estil® for intravenous administration. 2-Methoxy-4-allylphenoxyacetic acid *N,N*-diethylamide (XI) is a eugenol derivative.

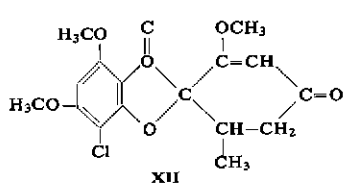


XI

It is an almost odorless oil; b.p. 140–142 °C./0.001 mm. Hg; $n_D^{25} = 1.5300$). Its 5 % aqueous solution is used for anesthesia. Contrary to the usual short-term anesthetics the new preparation is characterized by a stimulation of the respiratory activity and a short recovery time after anesthesia.

The active component of a chemotherapeutic agent of the aromatic diamidine series is 4,4-(hexamethylenedioxy)dibenzamidine bis(β-hydroxyethanesulfonate). It has been introduced on the market by Upha GmbH. as Hexomedin® and is to be used for the treatment of dermatological disorders caused by bacteria or fungi.

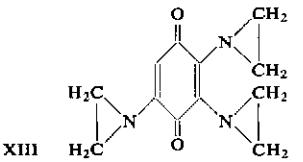
An oral medication for fungus infections of the skin, hair and nails is offered by Imperial Chemical Industries, Ltd. The active component of Fulcin is the antibiotic griseofulvin (XII)



XII

which is obtained from the filtrates of cultures of *Penicillium griseofulvum*. The antimycotic effect is attributed to an infiltration of the substance into the keratin layers.

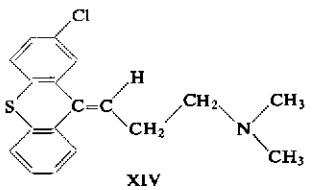
As a further development of the well-known carcinostatic drug E 39 Farbenfabriken Bayer have contributed Trenimon® to medicine. It consists of 2,3,5-tris(ethylene-imino)-benzoquinone-(1,4) (XIII)



XIII

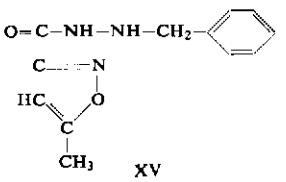
which crystallizes in small purple needles; m.p. 161.6 to 162.5 °C.; somewhat soluble in water. The substance is characterized by a very strong cytostatic effect and was used successfully in extensive experiments in the treatment of chronic leukemia, lymphogranulomatosis, and lymphosarcoma.

The attraction of psychopharmacologic agents has not decreased in the pharmaceutical industry. This is demonstrated by the large number of new preparations. Taractan® of Hoffmann-La Roche AG. and Truxal® of Troponwerke have the *trans*-isomer of 2-chloro-9-(3'-dimethylamino-propylidene)thiaxanthene (XIV) as active component.



XIV

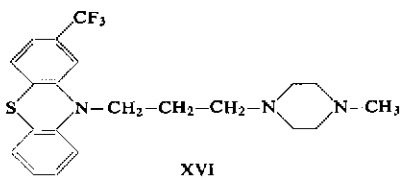
Marplan®, another drug in this field by Hoffmann-La Roche, is 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine (XV).



XV

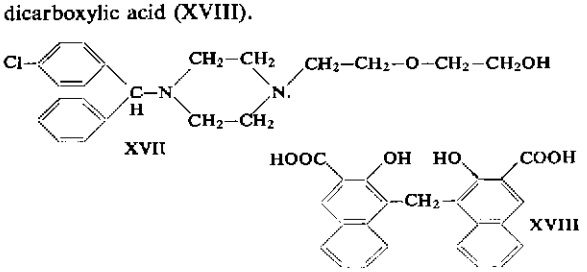
It is supposed to be effective against any kind of depression. Tremaril® of Dr. A. Wander GmbH. consists of 4-(1'-methylpiperidyl-3'-methyl)thiaxanthene hydrochloride and is recommended against Parkison's disease.

Röhm and Haas GmbH. produce Jatroneural® which contains 10-[3-(1-methyl-4-piperazinyl)-propyl]-2-trifluoromethylphenothiazine dihydrochloride (XVI).



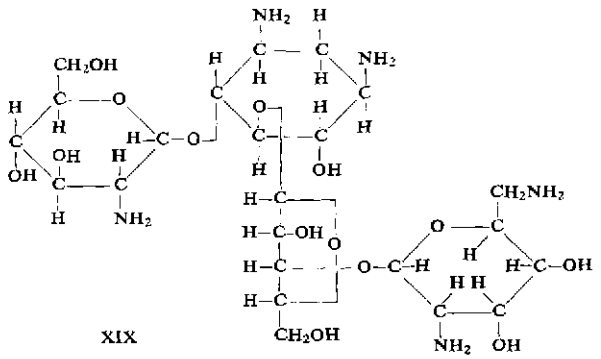
XVI

Masmoran® of Roerig Pharmazeutika (Division of Pfizer GmbH.) is the pamoate of 1-(*p*-chlorobenzhydryl)-4-[2-(2-hydroxyethoxy)ethyl]diethylenediamine (XVII). A pamoate is a salt with 2,2'-dihydroxy-1,1'-dinaphthylmethane-3,3'-dicarboxylic acid (XVIII).



XVII XVIII

Captagon® of Chemiewerk Homburg which consists of 7-[2'-(1''-methyl-2''-phenylethylamino)ethyl]theophylline hydrochloride also belongs in this category.



XIX

Indications for all these medications are fear, states of tension and excitation, psychic and physical exhaustion, climatic distress, etc. These are only a few of the recommendations. Parke-Davis enlarges the therapeutic possibilities with a new effective oral antibiotic. Humatin is paromomycin (XIX) which is obtained from the culture filtrates of *Streptomyces rimosus* forma *paromomycinus*. This active component consists of D-glucosamine, desoxystreptamine, D-ribose, and a diaminohexose, which are linked together according to formula XIX.

The antibiotic is not resorbed from the intestine and has well-defined bactericidal and amebicidal activity.

[VB 535/VB 1 IE]

German Society for Mineral Oil Science and Coal Chemistry

Goslar (Germany), September 27—29, 1961

From the papers:

Utilization of Hydrogen Cyanide from Coke Oven Gas

W. Grimme and *E. Ruschenburg*, Homberg (Germany)

Through hydrogen sulfide wet-washing of coke oven gases, gas concentrates (called "foul gases" or "choke damp") are obtained. These contain 70–80 % by vol. H_2S, 5–7 % by vol. HCN, 10–15 % by vol. CO_2 and about 5 % by vol. of other coke oven gas components. The hydrogen cyanide contained in such gases may be converted at normal pressures directly and continuously, that is, without previous separation from the other gases, to acetone cyanohydrin if the alkali, *e.g.* KCN or KOH, which catalyzes the reaction between HCN and acetone is introduced as a dilute aqueous solution into the washing towers near the plate at which the acetone contains the greatest amount of HCN. By maintaining a water content in the acetone of at least 5 % by vol., the dissolution of H_2S and CO_2 in the acetone is minimized. This in turn reduces the formation of, for example, $KHCO_3$ or KHS. Thus, only a small amount of alkali is needed and the alkali remains catalytically active.

After the separation of excess acetone from the reaction mixture at normal pressure, water is removed at reduced pressure. The acetone cyanohydrin is then obtained by rectification at reduced pressure in a purity which makes it suitable for use in the preparation of methacrylic acid derivatives, *e.g.* methacrylic ester.

Because of the economic utilization of the hydrogen cyanide in the foul gas, as much of the hydrogen cyanide as possible can be transferred from the coke oven gas into the foul gas, thus preventing the hazardous contamination of waste waters and air with hydrocyanic acid. The process is already in use in a commercial plant.

Synthesis of High Melting Paraffins from Carbon Monoxide and Water with Suspended Ruthenium

H. Kölbel, K. K. Bhattacharyya and *W. Müller*, Berlin (Germany)

When metallic ruthenium is suspended in water and carbon monoxide is passed through the suspension at pressures above 50 atm. and temperatures between 150 and 260 °C., straight chain paraffins having melting points up to 131 °C., corresponding to molecular weights of up to about 7000, are formed according to the equation

$$3\,CO + H_2O \rightarrow -CH_2- + 2\,CO_2\ (\Delta H = -58.4\ \text{kcal/mole}).$$

In this process, the water serves simultaneously as reactant, suspension medium, heat transfer medium and direct cooling medium.

The reaction rate is approximately proportional to the CO-partial pressure; the apparent activation energy is 12 kcal/mole at 75 atm. and decreases to 7 kcal/mole at 200 atm. The average molecular weight of the products increases with pressure and decreases with increasing temperature. Up to 95 % of the CO used can be converted into condensed products. As for gaseous hydrocarbons, only small amounts of CH_4 are formed.

Cold Hydrogenation of C_3-Fractions in Liquid Phase

W. Krönig, Leverkusen (Germany)

Propylene, produced by pyrolysis, contains methylacetylene and allene which are troublesome in further processing. The removal of these impurities by selective gas-phase hydrogenation has disadvantages. A process has been worked out in which the C_3-fraction is selectively hydrogenated in large quantities in the liquid phase (or, to be exact, in the trickle phase) between 10 and 20 °C. over fixed, palladium-containing catalyst. The undesirable components are completely removed without any loss of propylene. This process, called "cold hydrogenation", has proven itself in a commercial plant; after more than one year of operation, the activity of the catalyst has not yet diminished. Cold hydrogenation may also be used to advantage for other hydrocarbon fractions.

On the Alkenylation of Aromatics

K. E. Möller, Mülheim/Ruhr (Germany)

At 60 to 65 °C. benzene may be alkenylated with butadiene in the presence of 95 % phosphoric acid giving approximately a 60 % yield (based on butadiene) of an isomeric mixture of phenylbutenes having the following composition:

86.4 % *trans*-1-phenylbutene-(2)

8.0 % *cis*-1-phenylbutene-(2)

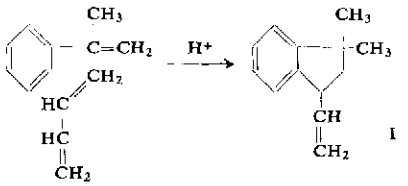
5.5 % 3-phenylbutene-(1)

0.1 % 4-phenylbutene-(1)

The formation of these four isomers may be explained by 1,4- and 1,2-addition of benzene to butadiene. Isomerization of the hydrocarbons formed primarily, for example to 1-phenylbutene-(1), does not take place under the reaction conditions. The alkenylation of toluene or of the xylenes leads to the corresponding *o*- and *p*-substitution products.

In the conversion of styrene or α-methylstyrene, ring closure occurs with the formation of a vinylindane system which is variously substituted depending on the reaction partners which include isoprene in addition to butadiene. For example,

1,1-dimethyl-3-vinylindane (I), b.p. 221.28 °C., $n_D^{20} = 1.5197$ is formed from α-methylstyrene and butadiene.



I

New Esterification Process for Terephthalic Acid in a Fluidized Bed

R. Novotny, Essen (Germany)

A continuous process for the esterification of terephthalic acid with methanol in a fluidized bed and in the presence of catalysts has been developed. The catalyst with the optimum properties was found to be surface active silica gel which, mixed with terephthalic acid, is kept fluidized in the reactor at 280–290 °C. and atmospheric pressure. Superheated methanol is used as the fluidizing and reaction gas. In the two-step catalytic reaction, the terephthalic acid is first converted to the monomethyl ester which is then catalytically reacted in the gas phase to give the dimethyl ester. The gas mixture of dimethyl terephthalate, methanol and reaction water leaving the fluidized bed reactor may be separated by partial condensation into a dimethyl ester fraction and a methanol-water mixture.

The principal advantage of this process lies, above all, in the possibility of a continuous esterification at atmospheric pressure, the high conversion rate of terephthalic acid (1500 g. terephthalic acid per liter contact and per hour), the almost quantitative yield of the dimethyl ester, as well as the extraordinary low content of monoester in the reaction product.

Preparation of Benzene by Dealkylation of Toluene: The Shell-Bextol Process

E. F. Roelofsen, The Hague (Holland)

Benzene production by means of thermal and catalytic hydrodealkylation of toluene was studied in the laboratory and in a pilot plant. The thermal reaction proceeds in the presence of excess hydrogen, primarily according to the following rate equation:

$$\frac{d\,[\text{toluene}]}{dt} = k\,[\text{toluene}]\,[H_2]^{1/2}$$

The catalytic process which appears commercially more advantageous than the thermal process (no carbon deposits, lower quantities of heavy condensation products) was worked out into the large-scale "Bextol-process". A high partial pressure of hydrogen is maintained in the reactor of the large-scale plant by circulating hydrogen-rich gas. The methane formed during the reaction is to a large extent removed from the circulating gas by a simple oil wash. The benzene is purified to nitration grade quality (ASTM and NBA) by treatment with alumina and conventional distillation.

With a hydrogen consumption of only 2 moles/mole of benzene produced, the benzene is obtained in 96 % yield (nitration grade quality) when a toluene fraction from a catalytic reformate is used as the starting material. [VB 545/9 IE]

German Pharmaceutical Society

Munich (Germany), October 19 to 22, 1961

From the papers:

On the Chemical Structure of the Sage Bitter Principle

C. H. Brieskorn and *A. Fuchs*, Würzburg (Germany)

A crystalline substance which is characterized by high sensitivity to light and a bitter taste may be isolated from the petroleum ether extract of the sage leaf. The analytical results give the empirical formula $C_{20}H_{26}O_4$. The sensitivity to light is due to the presence of an *o*-diphenol which was characterized by oxidation, acetylation, and methylation. The two remaining oxygen functional groups originate on a γ-lactone grouping. The corresponding carbonyl band occurs at 5.74 μ. The lactone ring of the methyl ether can be split only by concentrated alkali solutions, the resulting hydroxy acid is stable in the solid form. The melting point of the bitter principle is 224 °C. and melting is accompanied by decarboxylation which no longer occurs after acetylation. This causes considerable difficulties in determining the structure. The basic skeleton of the bitter principle has an isoprenoid structure.

Selenium dehydrogenation yields as main product a crystalline 1,7-disubstituted phenanthrene and a phenanthrol derivative not yet described. In addition to these, slight quantities of an oily naphthalene derivative are obtained. A hypothetical working structure was presented for discussion.

Synthesis of Some Thiophene Derivatives Found in Plants

L. Hörner, Münster (Germany)

2,5-Substituted thiophene derivatives may be prepared in good yield from 1,4-disubstituted butadiynes with hydrogen sulfide in a weakly alkaline medium between 20 and 60 °C. Thus, 2,5-dimethylthiophene is formed from hexadiyne-(2,4); 2,5-diphenylthiophene [1] from 1,4-diphenylbutadiyne; and α-terthienyl, found by *L. Zechmeister* and *W. Sease* [2] in *Tagetes erecta*, from 1,4-dithienylbutadiyne. Thiophene itself may be prepared from diacetylene.

Alkynes with 3 acetylene bonds also enter into this reaction: From decaene-(2)-triyne-(4,6,8)-acid-(1) one obtains β-[5-propynylthienyl-(2)]-acrylic acid, which occurs as methyl ester in *Chrysanthemum vulgare*, according to *E. Guddal* and *N. A. Sörensen* [3].

From octatriyne-(2,4,6)-ol-(1), one obtains 5-propynyl-2-hydroxymethylthiophene, from which the corresponding aldehyde is obtained by oxidation with manganese dioxide. The aldehyde was isolated by *J. H. Birkinshaw* and *P. Chaplen* [4] from Daedalea juniperina and designated as junipal.

Splitting Tertiary Amines with Chloroformic Acid Ethyl Ester

J. Knabe, Braunschweig (Germany)

Chloroformic acid ethyl ester (I) was introduced into alkaloid chemistry in 1921 by *J. Gadamer* and *F. Knoch* as group reagent for tetrahydroisoquinolines. In contrast to the Hofman degradation, which often proceeds non-uniformly, (I) reacts under very mild conditions and ring cleavage occurs always at the benzyl carbon-nitrogen bond with the formation

[1] *K. E. Schulte, J. Reisch*, and *L. Hörner*, Angew. Chem. *72*, 920 (1959).

[2] *L. Zechmeister* and *J. W. Sease*, J. Amer. chem. Soc. *69*, 273 (1947).

[3] *E. Guddal* and *N. A. Sörensen*, Acta chem. scand. *13*, 1185 (1959).

[4] *J. H. Birkinshaw* and *P. Chaplen*, Biochem. J. *60*, 255 (1955).

of a urethane. In spite of this, the cleavage with (I) has been used only rarely, apparently because of the great difficulties which occur in the reconversion of *N*-disubstituted urethanes into amines. After it was found that such urethans can be readily converted into tertiary amines with lithium alanate, the interest in use of the degradation with (I) increased.

According to a previous work, the cleavage of tertiary amines by (I) proceeds smoothly if a benzyl or allylamino group having an electron-donating substituent in the conjugated position is involved. For a number of tertiary benzyl amines with various substituents at the aromatic ring, the author found that this substituent must be an alkoxy group in the *o*- or *p*-position.

Furthermore, the smooth course of the cleavage with (I) depends greatly on the substituent at the nitrogen. For example, compounds of the tetrahydroberberine type are not attacked by (I). Studies on model substances have shown that steric factors are of great importance for the course of the cleavage.

The Enzymatic Oxidation of Rutin

H. Loth, Berlin-Dahlem (Germany)

When peroxydase and hydrogen peroxide act upon rutin, the first reaction step consists of an oxidation of the pyrocatechol side-ring to *o*-quinone. This process could be proved by measuring the light absorption as a function of the reaction time. The measurements show that in the first phase of the reaction two equivalents of hydrogen peroxide are consumed. The substance formed can be reduced with ascorbic acid and titanium trichloride. The reduction product is rutin as indicated by spectrophotometric measurements and analysis via paper chromatography. Thus, the first intermediate product is *o*-quinone and not some semi-quinone of rutin. The *o*-quinone is unstable in aqueous solution; it polymerizes. The polymerization velocity increases with increasing pH. As shown by light absorption measurements, phenolic groups are formed during the polymerization. After the polymerization was completed, rutin could be found by paper chromatography. Thus, the polymerization must be coupled with a redox reaction in which a part of the rutin quinone is reduced to rutin. The measurements of the oxidation of rutin were compared with those of the reaction of peroxydase on pyrocatechol. The reaction process is essentially analogous for the two substances. It is assumed that linking of the rutin molecules between the pyrocatechol rings occurs during the formation of the polymers.

Preparation of Furan and Pyrrole Derivatives from Alkynes

J. Reisch, Münster (Germany)

In the condensation of propargylmalonic ester with α-aminopyridine, cyclization to 2,3-(5-methylfurano)-4-oxo-homopyrimidazole occurs [1]. It was now found that many compounds which have a terminal triple bond in γ-position to an enolizable carbonyl group can be converted into furan derivatives with catalysts such as $ZnCO_3$, conc. H_2SO_4 or conc. H_3PO_4. The reaction is of general importance since it permits, among other things, the synthesis of condensed furan derivatives if the propynyl radical in an alicyclic or heterocyclic compound is in *o*-position with respect to the enolizable carbonyl group. For example, the following compounds could be prepared: methylfuranopyrones from 3-propynyl-4-hydroxypyrones; methylfuranocyclohexene-(2)-one-(3) from 2-propynylcyclohexanedione-(1,3); 2-methylfuranouracil from 5-propynylbarbituric acid; and methylfuranopyrimidine from propynylhydroxypyrimidines.

Pyrrole derivatives may also be prepared from alkyne compounds. Indole-2-carboxylic acid is formed when *o*-amino-phenolpropiolic acid is heated in the presence of small amounts of Cu(I)chloride.

Disubstituted diacetylenes may be converted into 1,2,5-trisubstituted or 2,5-disubstituted pyrroles with primary amines or ammonia under the same conditions [2]. The substituents may be the same or different aliphatic, aromatic, and heterocyclic radicals. The reaction also permits the synthesis of natural substances having di- or tri-substituted pyrrole rings.

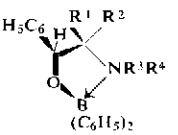
[1] *K. E. Schulte* and *J. Witt*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *291/63*, 298 (1958).

Determination of Configuration with Diphenylborinic Acid

H. J. Roth, Braunschweig (Germany)

The formation of five- or six-membered boron-containing cyclic coordination compounds from 1,2- or 1,3-alkanol amines and diphenylborinic acid (I) is of importance for configuration analysis.

Pseudo-norephedrine, pseudo-ephedrine and pseudo-*N*-methylephedrine react more rapidly with (I) to form horoxazolidines (II), (III), and (IV) than do the corresponding compounds of the ephedrine series: norephedrine, ephedrine and *N*-methylephedrine to form (V), (VI), and (VII). In the hetero-rings (II), (III), and (IV), which are more resistant towards solvolysis, the methyl group at C-4 and the phenyl group at C-5 are in the trans-position; in the less stable hetero-rings (V), (VI), and (VII) they are in the cis-position:



II: $R^1 = R^3 = R^4 = H$; $R^2 = CH_3$
III: $R^1 = R^3 = H$; $R^2 = R^4 = CH_3$
IV: $R^1 = H$; $R^2 = R^3 = R^4 = CH_3$
V: $R^2 = R^3 = R^4 = H$; $R^1 = CH_3$
VI: $R^2 = R^3 = H$; $R^1 = R^4 = CH_3$
VII: $R^2 = H$; $R^3 = R^4 = CH_3$

Boroxazolidines which are resistant against hydrolysis are obtained from cinchonine and quinidine by reaction with (I) and this is a proof of the quasi-cis-position of the OH-group and quinuclidine-nitrogen. Cinchonidine and quinine, with quasi-trans-arrangement of OH and N do not react with (I).

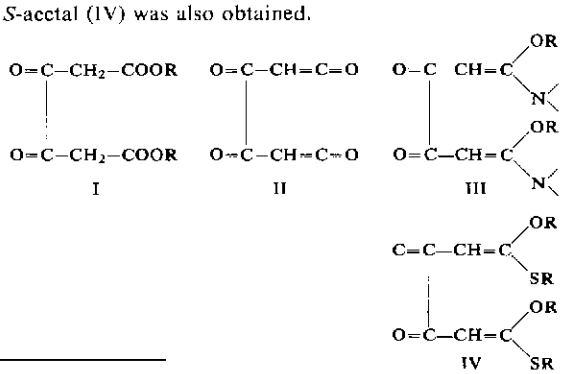
As expected, pseudo-tropine yields a tetrahydroboroxazine with (I). The formation of a corresponding derivative from tropine, in agreement with the trans-position of OH- and *N*-methyl groups, is not possible.

Cevine and veracevine form crystalline reaction products of hitherto unknown ring size with (I). Prerequisite for the formation of a five-membered ring is the axial position of the OH-group at C-20 and, for the formation of a six-membered ring, the axial arrangement of the OH at C-17.

Derivatives of Ketipic Acid

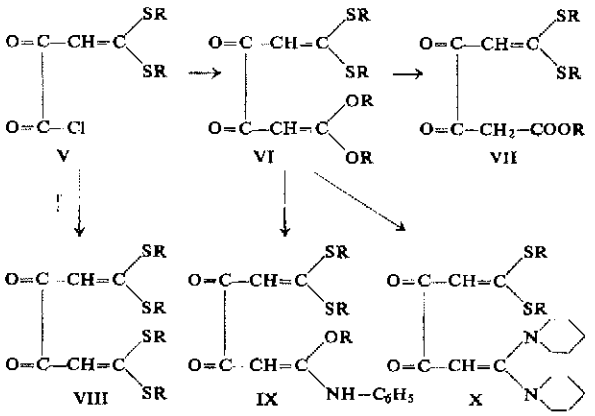
H. D. Stachel, Marburg (Germany)

Only few derivatives of ketipic acid (3,4-diketo-adipic acid, I) have been known so far. New routes to ketipates were found by the synthesis of a few derivatives of oxalyl ketene (II). Oxalylketene itself and the *O,N*-acetal(III)yielded the hitherto unknown amides of ketipic acid. The oxalylketene-*O,S*-acetal (IV) was also obtained.



I II III IV

[2] *J. Reisch* and *K. E. Schulte*, Angew. Chem. *73*, 241 (1961).

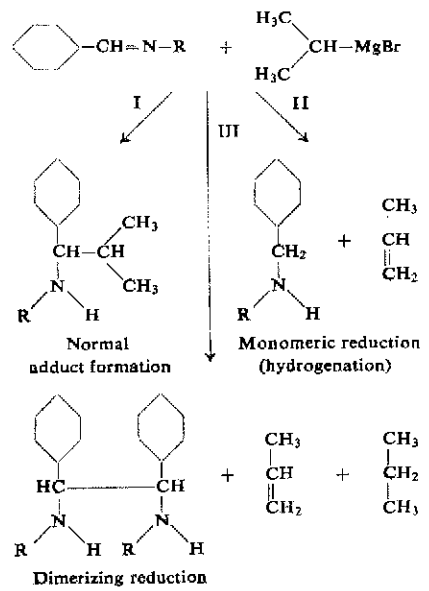


The mercaptal (VIII) is formed in two reaction steps from oxalyl chloride and ketene mercaptal. The first reaction phase yields the acid chloride (V) which can be considered a derivative of pyruvic acid or oxaloacetic acid. With ketene acetal, (V) forms the mixed mercaptal acetal of oxalylketene (VI), from which the *N*-analogs (IX) and (X) can be prepared. The β-keto ester (VII) is obtained on partial hydrolysis of (VI).

Reactions of Schiff Bases with Grignard Compounds and the Influence of Metal Salts

H. Thies, Munich (in collaboration with *H. Schönenberger*, *A. Zeller* and *K. Borah*)

When Schiff bases of the benzylidene alkylamine type are reacted with Grignard compounds in the presence of ions of the transition metals from the 6th, 7th, and 8th groups of the periodic system, the side reactions, *viz.* "monomeric reduction" (II) and "dimerizing reduction" (III), are greatly favored as compared to the normal adduct formation (I).

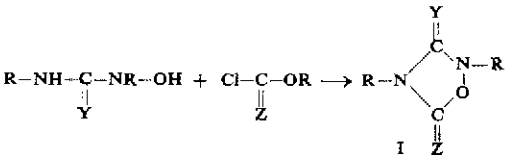


Mn^{2+} exclusively favors the "dimerizing reduction", while Co^{2+} and Fe^{3+}, and to a lesser extent, Ni^{2+} ions promote the "monomeric reduction". Finally, Cr^{3+} promotes both reduction paths. The greatest catalytic action is displayed by Co^{2+} which induces exclusively the formation of "monomeric reduction product", while some normal adduct is always formed with the other ions.

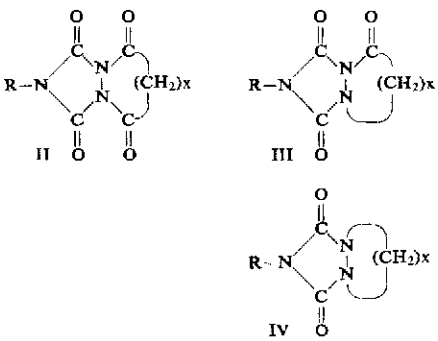
Cyclic Hydroxylamine and Hydrazine Compounds

G. Zinner, Marburg (Germany)

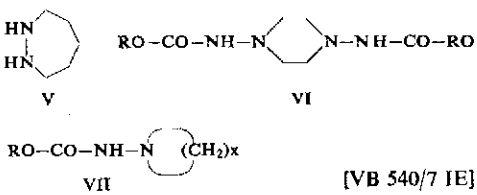
3,5-Dioxo-, 3-oxo-5-thiono-, 3-thiono-5-oxo-, and 3,5-dithiono-1,2,4-oxadiazolidines (I: Y,Z = O,S), which are characterized by "urethane"- and urea-carbonyl bands at short wave length (5.50 and 5.72 μ), in the IR-spectrum were obtained for the first time by the reaction of hydroxyl(thio)-ureas with esters of chloro(thio)formic acid.



In collaboration with *W. Deucker*, the corresponding hydrazine derivatives such as the 3,5-dioxo-1,2,4-triazolidines ("urazoles") were cyclically acylated (II: x = 1,2), alkacylated (III: x = 3) and alkylated (IV: x = 3,4,5) at the hydrazine nitrogen.



By cyclic alkylation of bis-alkoxycarbonyl hydrazines and subsequent hydrolysis, "homopiperidazine" (1,2-diaza-cycloheptane, V; b.p. 59 °C./17 mm. Hg; dibenzoylderivative: m.p. 157.5 °C.; bis-anilinoformyl derivative: m.p. 254 to 255 °C.) was obtained for the first time. Monoalkoxycarbonylhydrazines were cyclically alkylated at the non-acylated nitrogen forming the piperazine- (VI), pyrrolidine- (VII: x = 4), piperidine- (VII: x = 5), and hexahydroazepine derivatives (VII: x = 6).



[VB 540/7 IE]

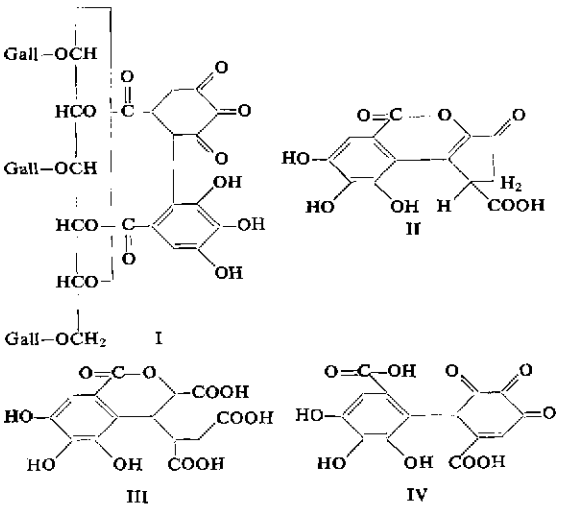
Structure and Formation of Gallotannins and Ellagic Tanning Substances

O. Th. Schmidt, Heidelberg (Germany)

The following new compounds were isolated from myrobalans (*Terminalia chebula*): 1) 1,3,6-trigalloyl-β-glucose; 2) pentagalloyl-β-glucose; 3) a yellow, crystalline tanning substance called "terchebin". Terchebin (I) contains 2 H-atoms less than pentagalloyl glucose and one H_2O less than chebulic acid. In (I), a dicarhoxylic acid $C_{14}H_{10}O_{10}$ is bound to the 1,3,6-trigalloylglucose in the 2- and 4-positions; this dicarboxylic acid is isomeric with hexahydroxydiphenic acid because it contains the cyclohexanetrionecarboxylic acid moiety ("isohexahydroxydiphenic acid") in place of a gallic acid moiety. On heating with water, brevifolin carboxylic acid (II) is formed, among other things, by a "redox disproportionation" [1]. By successive treatment with NaOH and acid, brevifolincarboxylic acid (II) and chebulic acid (III) are formed.

The study of tanning principles from Algarobilla (*Caesalpinia brevifolia*) showed [2] that two molecules of the dicarboxylic acid IV ("dehydrohexahydroxydiphenic acid") are bound to glucose in brevilagin 1. In brevilagin 2, one molecule of (IV) and one molecule of (−)-hexahydroxydiphenic acid are bound to one molecule of glucose.

In view of the hypothesis about the formation of gallotannins and ellagic tanning principles in plants [3, 4], the discovery of the oligogalloylglucoses in myrobalans, the discovery of



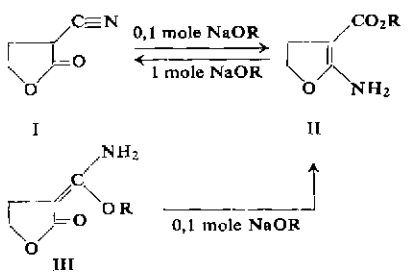
tanning principles which contain isohexahydroxydiphenic acid or (IV) instead of hexahydroxydiphenic acid or (II) or (III), and finally, the conversion of isohexahydroxydiphenic acid into II and III, proven in the test tube, are of great importance.

[Chemische Gesellschaft zu Heidelberg (Germany), November 14, 1961.] [VB 549/6 IE]

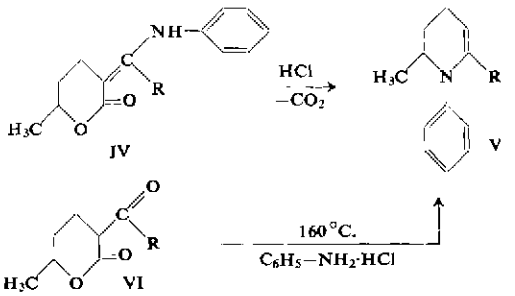
Recent Findings from the Acyl Lactone-Rearrangement

F. Korte, Bonn (Germany)

The proton-catalyzed rearrangement of α-acyllactones is possible also with higher alcohols. The mixtures of tetrahydro- and dihydropyrancarboxylic acid esters of higher alcohols obtained may be separated by distillation. The acyl radical in α-position can be replaced by $-C\equiv N$. Cyclic enamines (II) are obtained from the α-cyano lactones (I) by base-catalyzed rearrangement. The rearrangement is reversible.



α-Carbiminoethoxylactones (III) also rearrange to form (II). The acylradical may be replaced also by an enamine grouping. Thus, (V) is obtained from α-anilinomethylene δ-lactones (IV) by heating them in HCl to 160 °C. According to the findings of *Hünig* and co-workers with dehydroacetic acid, acyl lactones (VI) also yield (V) in the presence of aniline hydrochloride at 160 °C. In some cases, azo compounds of α-keto lactones, which stabilize to hydrazones in rearrangement experiments, are obtained by the coupling of acyl lactones. Some diazo compounds of γ-lactones rearrange to form pyrazoline derivatives. Numerous alkaloids and amino acids may be synthesized by acyl lactone-rearrangement starting with α-acyl-lactams [1].

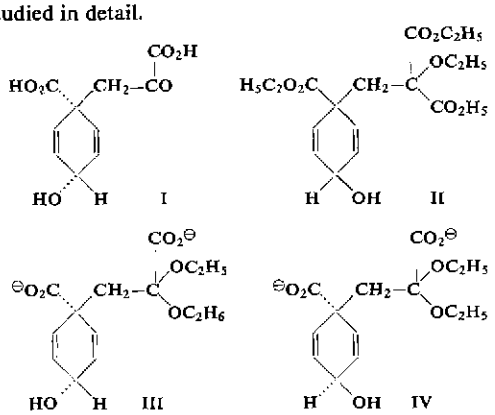


(Münchener Chemische Gesellschaft, November 21, 1961) [VB 550/8 IE]

Prephenic Acid

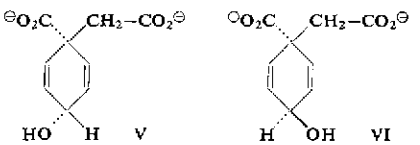
H. Plieninger, Heidelberg

Prephenic acid (I) is a precursor of natural aromatic substances. The acid hydrolysis of the stereoisomeric mixture (III and IV), which was prepared from the ketal ester (II) [2], was studied in detail.



At pH 1.8 in water at 20 °C., ketal hydrolysis and aromatization compete. Prephenic acid is formed from (III), *epi*-prephenic acid from (IV), and phenylpyruvic acid by aromatization. The mixture of the two prephenates was separated from phenylpyruvate over an exchanger, precipitated as the Ba-salt and shown spectroscopically to have a content of 10 % of prephenate and *epi*-prephenate. The proof of the natural prephenate was made by enzymatic aromatization with a crude Coli enzyme.

The two partial steps, the ketal hydrolysis and the aromatization, were studied kinetically on model substances. α-Ketoglutaric acid diethyl ketal has a half-life of 60 min. at pH 1.8 and 20 °C. The rate of aromatization, with CO_2 evolution, was measured on a mixture of the dienoles (V) and (VI) in the Warburg apparatus.



It can be calculated that the reaction proceeds at different rates for (V) and (VI). At pH 2.8 and 20 °C., a half-life of 1.7 min. has been calculated for one compound (presumably V) and 38.4 min. for the other.

(GDCh-Ortsverband Frankfurt/M. (Germany), November 16, 1961) [VB 546/5 IE]

[1] *B. Eistert* et al., Chem. Ber. *93*, 1451 (1960).

[2] Compare *O. Th. Schmidt:* Recent Developments in the Chemistry of Natural Phenolic Compounds. Pergamon Press, London 1961, p. 139.

[3] *O. Th. Schmidt* and *W. Mayer*, Angew. Chem. *68*, 103 (1956).

[4] *L. Zechmeister:* Progress in the Chemistry of Organic Natural Products. Springer Vienna 1956, Vol. XIII, p. 70.

[1] *F. Korte* and *K. H. Büchel*, Paper at the GDCh meeting, Aachen 1961.

[2] *H. Plieninger*, Angew. Chem. *73*, 543 (1961).

Complexes of trivalent silver were obtained by *M. Jenšovský* and *M. Skála* by anodic oxidation of foils of pure silver in alkaline solution in the presence of periodate or tellurate. In order to avoid coatings of low valent silver compounds on the anode, the temperature and current density must be held as low as possible. Depending on the pH, various sodium and potassium salts of the diperiodatoargentate(III)-ion $(Ag(IO_4)_2)^{7-}$ were isolated in the form of brownish red to yellowish red crystals. Ditellurato-argentate(III) was obtained as yellowish crystalline sodium salt $Na_7H_2[Ag(TeO_6)_2]\cdot 24\,H_2O$. Both argentates(III) are diamagnetic. They are very readily reduced to silver(I). / Z. anorg. allg. Chem. *312*, 26 (1961). – Ko. [Rd 990/15 IE]

***N*-Bromotriphenylphosphine imide and a new amino acid synthesis** are discussed by *R. Appel* and *A. Hauss*. *P,P,P*-Triphenylphosphine imide may be brominated with bromine in benzene:

$$2\,(C_6H_5)_3P{=}NH + Br_2 \rightarrow \underset{\text{I}}{(C_6H_5)_3P{-}N{-}Br} + \underset{\text{II}}{(C_6H_5)_3P{-}NH_2^+\,Br^-}$$

The *N*-Bromoimide (I) is soluble in benzene and can therefore readily be separated from the hydrobromide (II). (I), which consists of pale yellow crystals melting at 170 to 172 C., reacts with triphenylphosphine in benzene solution to form bis(triphenylphosphine)imidium bromide (III) whose structure could be proven by the exchangeability of Br^- and NO_3^- and the phosphorus nuclear magnetic resonance spectrum.

$$(C_6H_5)_3P{=}N{-}Br + (C_6H_5)_3P \rightarrow \underset{\text{III}}{[(C_6H_5)_3P{=}N{=}P(C_6H_5)_3]^+\,Br^-}$$

Compound (III) is also formed from dibromotriphenylphosphorane and triphenylphosphine-imide. If (I) is reacted with triphenylarsine or thioethers, compounds (IV) and (V), which are analogous to (III), are obtained.

$$\underset{\text{IV}}{[(C_6H_5)_3P{=}N{=}As(C_6H_5)_3]^+\,Br^-} \qquad \underset{\text{V, R = CH}_3,\,C_2H_5}{[(C_6H_5)_3P{=}N{=}SR_2]^+\,Br^-}$$

The exchange of the NH-group of the *P,P,P*-triphenylphosphineimide with ketone oxygen [1], which is analogous to the Wittig olefin synthesis, may be expanded to an amino acid synthesis: pyruvic acid ester was converted to the α-ketimino ester by treatment with $(C_6H_5)_3P{=}NH$ and then to alanine ester by catalytic hydrogenation. / Z. anorg. allg. Chem. *311*, 290 (1961). – Ko. [Rd 988/16 IE]

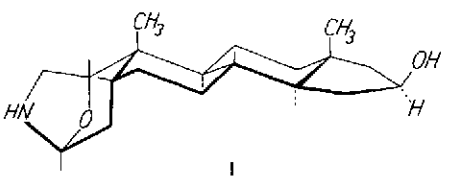
Quinone dehydrogenation, a general method for the preparation of organic cations, has been adapted for the synthesis of stable hydrocarbon cations by *D. H. Reid, M. Fraser, B. B. Molloy, H. A. S. Payne*, and *R. G. Sutherland*. A series of new compounds were obtained by reacting tetrachloro-1,2-benzoquinone (I), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (II) and chloranil (III) with cycloheptatriene: from (II) tropylium 2,3-dichloro-5,6-dicyano-1,4-quinolate, black needles, m.p. 177–178 °C. (d.), 91 %; in the presence of $HClO_4$ tropylium perchlorate; in the presence of oxalic acid dihydrate tropylium tetroxalate, colorless long needles, m.p. 140–145 °C. (d.); with KI ditropylium iodide-triiodide, dark brown needles, m.p. 128.5–129.5 °C.; similarly the hydrogen sulfate, colorless needles decomposing at 175 °C., and the toluene-*p*-sulfonate, platelets, m.p. 125–130 °C. (d.). 1,2,3-Triphenylcyclopropene was converted to the following triphenylcyclopropenylium salts: Perchlorate, colorless needles, m.p. 229–231 °C. (d.), picrate, yellow needles, m.p. 193 to 197 °C., iodide, yellow needles, m.p. 221–224 °C. *Peri*-naphthenylium-, 5-methylphenanthridinium-, acridinium-etc. salts were also be obtained. / Tetrahedron Letters 530 (1961). – De. [Rd 969/5 IE]

Diacetylene compounds of aromatic derivatives of Ge, Sn, Pb, and Sb have been synthesized by *H. Hartmann, E. Dietz, K. Komorniczyk*, and *W. Reiss*. The reaction of triphenyltin chloride, triphenyllead bromide, and diphenylantimony chloride with sodium diacetylide in liquid NH_3 yielded the disubstituted diacetylenes. Triphenylgermanium bromide undergoes a similar reaction in tetrahydrofuran:

$(C_6H_5)_3Ge{-}C{\equiv}C{-}C{\equiv}C{-}Ge(C_6H_5)_3$, m.p. 294 °C.
$(C_6H_5)_3Sn{-}C{\equiv}C{-}C{\equiv}C{-}Sn(C_6H_5)_3$, m.p. 245 °C. (decomp.)
$(C_6H_5)_3Pb{-}C{\equiv}C{-}C{\equiv}C{-}Pb(C_6H_5)_3$, m.p. 187 °C. (decomp.)
$(C_6H_5)_2Sb{-}C{\equiv}C{-}C{\equiv}C{-}Sb(C_6H_5)_2$, m.p. 154 °C. (decomp.)

The compounds are sensitive to air and moisture and crystallize well. The infrared spectra have an intensive $-C{\equiv}C-$ stretching vibration in the 2030 to 2050 cm^{-1} region. / Naturwissenschaften *48*, 570 (1961). – Ma. [Rd 976/10 IE]

The constitution and configuration of Samandarin (I), the main alkaloid from the skin of European Fire and Alpine salamanders, have been elucidated by means of the X-ray investigations of *E. Wölfel, C. Schöpf, G. Weitz*, and *G. Habermehl*. Single crystals of the monoclinic modification of the hydrohalogenides were investigated; the phase problem was solved by the heavy atom and isotypic replacement methods. Refinements, and finally a three-dimensional Fourier synthesis, were calculated for the hydrobromide. A constitutional relationship to the steroids – which had already been suspected earlier as a result of degradation



I

studies – was confirmed. The rings B, C, and D of the steroid skeleton are unchanged. Ring A is enlarged to a seven-membered ring by insertion of a –NH– group between C-2 and C-3; there is an ether bridge between C-1 and C-3 (Formula I). In the crystal, adjacent molecules are joined together by hydrogen bridges between the O-atom of the OH group to the N-atom via the Br^--ion. / Chem. Ber. *94*, 2361 (1961). – Ko. [Rd 987/13 IE]

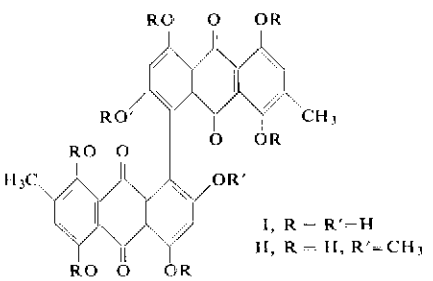
The acylation of aromatic ring systems in the presence of orthophosphate proceeds via mixed phosphoric acid anhydrides according to *C. J. Schoot, J. J. Ponjée*, and *K. H. Klaassens*. Orthophosphates of Ag, Zn, Cd, Sn, Pb, and Al when reacted with acid chlorides at first yield triacylorthophosphates. These disproportionate and lead to mixed phosphoric acid anhydrides which react further with the aromatic compounds. In the presence of Ag_3PO_4 4-methoxybenzophenone is obtained from benzoyl chloride and anisole (60 %); with mesitylene the product is 2,4,6-trimethylbenzophenone (50 %), with diphenylene oxide, 3-benzoyldiphenylene oxide (63 %); with thiophene, 2-benzoylthiophene (60 %) and from 2-chlorobenzoyl chloride and anisole, 2-chloro-4-methoxybenzophenone (60 %). / Rec. Trav. Chim. Pays-Bas *80*, 1084 (1961). – De. [Rd 967/4 IE]

The high toxicity of Toxoflavin (I) an antibiotic formed by *Pseudomonas cocovenans* (LD 50 in mice: intraveneously 1.7 mg./kg.; oral 8.4 mg./kg.) was explained by *H. E. Latuasan* and *W. Berends*. (I) acts as an electron carrier (sidepath of the cytochrome-system) and yields H_2O_2 as the end product of the electron transfer. H_2O_2 is a strong poison for cells deficient in catalase. The ability of (I) to produce H_2O_2 is related the strong antibiotic activity and the poisonous character of the compound. The addition of (I) to anaerobic cultures of *E.coli* and *Str. lactis* did not lead to any H_2O_2 formation and consequently did not cause any damage. / Biochim. biophysica Acta *52*, 502 (1961). – De. [Rd 964/1 IE]

[1] *R. Appel* and *A. Hauss*, Chem. Ber. 405 (1961).

Cadmium poisoning of 17 persons was investigated by *W. Reinl*. In the course of spraying sheet steel with cadmium, the cadmium wire was heated to about 600–700 °C. and a smoke consisting of CdO-particles was produced. (The cadmium concentration in the air of the room was estimated to be at least 40 mg. Cd/m³. This corresponds to a four-fold MAC-value; MAC = Maximum Allowable Concentration.) Although the spray-gun operator was protected by a fresh-air intake mask, a group of employees working at a distance of 100 meters showed discomforts after one hour. They complained mainly of an unbearable cough in conjunction with chest pains and shortness of breath. Weakness, nausea and vomiting were accompanying symptoms. With one exception all workers involved recovered within 10 days. The described symptoms were especially marked in one older worker. In this instance the symptoms included a feeling of suffocation, persistent fever and severe headache. The ECG deviated markedly from the norm. A later examination showed that the heart had been affected as a result of the poisoning. Arch. Toxikologie *19*, 152 (1961). — Re. [Rd 984/11 IE]

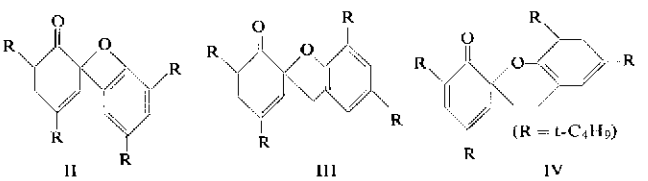
The constitution of Fusaroskyrin, a dye which is the causative agent (*Fusarium* sp.) of the "purple speck" disease found in soja bean, was elucidated by *Shin-ichiro Fujise, Shin-zaburo Hishida, Mannen Shibata,* and *Sumu Matsueda*. The dark-red dye, $C_{32}H_{22}O_{12}$, extracted from the mycelium has a m.p.



I, R = R' = H
II, R = H, R' = CH_3

of 300 °C. and yields a hexaacetate with a m.p. of 264–265 °C. Treatment with HI yields compound I, $C_{28}H_4O_4(CH_3)_2(OH)_8$, m.p. 300 °C., from which a yellow octa-acetate (m.p. 295 to 297 °C.) can be obtained. Erythroglaucine(1,4,5-trihydroxy-7-methoxy-2-methylanthraquinone) is obtained by reduction of fusaroskyrin with $Na_2S_2O_4$ in an alkaline solution. In accordance with spectroscopic findings the dye has the following constitution: 4,4',5,5',8,8'-hexahydro-2,2'-dimethoxy-7,7'-1,1'-dianthraquinone (II). / Chem. and Ind. 1755 (1961). — Ma. [Rd 974/8 IE]

The dehydrogenation of sterically hindered bis-phenols, according to studies by *Eugen Müller, Rudy Mayer, B. Narr, A. Rieker* and *K. Scheffler*, yields inner spiro-quinol ethers. 2,2'-dihydroxy-3,5,3',5'-tetrabutyldiphenyl (I) is dehydrogenated with $K_3Fe(CN)_6$ or with 4-cyano-2,6-di-t.-butylphenoxyl to the inner quinol ether II (m.p. 199 to 201 °C., yield ≈ 70 %). Reduction of (I) with HI or triphenylphosphine yields 1,3,6,8-tetra-t.-butyldibenzofuran; with $LiAlH_4$ (I) is reformed. 2,2'-Dihydroxy-3,5,3',5'-tetra-t.-butyldiphenylmethane may be analogously dehydrogenated to the dihydrofuran derivative III (m.p. 153–155 °C., yield 83 %).



An aroxyl radical is formed as intermediate which can be recognized by its blue color and the electron spin resonance spectrum (three-line signal). The spirocyclic dihydropyran derivative IV is obtained by dehydrogenation of 2-methyl-4,6-di-t.-butylphenol, with 2,2'-dihydroxy-3,5,3',5'-tetra-t.-butyldiphenylethane occuring as intermediate. / Liebigs Ann. Chem. *645*, 25 (1961). —Ko. [Rd 991/17 IE]

Monomethyltaurine and dimethyltaurine were found for the first time in the animal kingdom by *D. Ackermann* and *R. Pant*. These amino acids, which until now had only been known in red algae were shown — by paper chromatography — to be present in the sponge *Calyx nereis*. The monomethyl derivative occurs in large quantities together with taurine. This makes the isolation possible. / Naturwissenschaften *48*, 646 (1961). — De. [Rd 965 / 2 IE]

BOOK REVIEWS

Handbuch der physiologisch- und pathologisch-chemischen Analyse, für Ärzte, Biologen und Chemiker (Encyclopedia of Physiological- and Pathological-Chemical Analysis for Physicians, Biologists and Chemists), by *Hoppe-Seyler-Thierfelder*. Springer-Verlag, Berlin-Göttingen-Heidelberg 1953–1960. 10th Edition, edited by *K. Lang* and *E. Lehnartz*.

Volume I: General Research Methods, 1st Part: XII, 762 pages, 502 figures, Price DM 185.—.

Volume II: General Research Methods, Part 2: XIX, 1096 pages, 534 figures, Price DM 296.—.

Volume III: Components of the Animal Body I (in 2 parts) XVI, XVI, 2142 pages, 200 figures, Prices DM 445.—.

Volume IV: Components of the Animal Body II (in 2 parts) about 1800 pages, 309 figures, Price DM 598.—.

Volume V. Examination of the Organs, Body Fluids and Secretions, IX, 938 pages, 44 figures, Price DM 168.—.

Subscription price for the entire set: DM 1353.60 (about $ 340.—).

The first edition of *Hoppe-Seyler*'s "Handbuch der physiologisch- and pathologisch-chemischen Analyse" was issued more than 100 years ago (1858). It soon proved to be an indispensable reference work and aid for physiological chemists and medical men all over the world. Later editions were published in collaboration with *Thierfelder*, who was in charge until the ninth edition in 1924. Even at that time the material had grown into a heavy, encyclopedic volume and could be managed only with the collaboration of several experts in the field. During the 35 years which have passed since, it had been planned in 1935 to bring out a revised edition, but the finished manuscript fell victim to the war. After 1945, *K. Lang* and *E. Lehnartz* brought together the authors and divided the task, which had grown beyond all expectation. The present "standard work" is one which can hardly be surpassed with respect to contents and quality of press work — unfortunately, also with respect to price. The volume of material which must be covered in an analysis of components important for living organisms has grown to such an extraordinary extent in the past 15 years that the work had to be planned in five imposing volumes.

Now that the "Hoppe-Seyler/Thierfelder" is completed and its value and limitation are immediately apparent to the user, the time has come for a critical evaluation of the changes that took place while the curtain was down. The evaluation has to be different depending on whether the user is more interested in the practical aspects or the principles. It should be noted in advance that he will not find an immediate practical guide suited to his special purpose in every case.

On the other hand, the most outstanding sections give an excellent treatment of the theoretical bases of the methods,

sometimes at a level far beyond the necessary. The entire volume is an unusually competent encyclopedia in the typical sense, but no textbook. The question must be raised whether a series of monographs about branch fields would not be more useful than the creation of a comprehensive methodical "Handbuch" whose individual articles are out-of-date even as it is published and which cannot follow the rapid development in individual fields fast enough because of the multitude of fields treated.

It apparently was the aim of the revised edition to reach a completely new presentation and a completeness far beyond that of the earlier editions, but maintaining the old arrangement. The emphasis was placed on analytical procedures but even boundary fields of biochemical methods – with some exceptions – have not been neglected. While the earlier edition covered the physicochemical fundamentals in about 20 pages, the new edition devotes nearly 1600 pages to them, that is, almost the entire content of the first two volumes.

Volumes 1 and 2 give general methods for the separation, measurement, and examination of body components; volumes 3 and 4 describe the isolation, identification, and determination of the individual substances; volume 5 deals with the examination of the organs, body fluids, and secretions. Without doubt, the first two volumes are the most stimulating ones even though presumably – at least in our case – the three subsequent ones are consulted most frequently.

Volume 1 in 15 chapters covers mostly physical and physicochemical methods for the separation and identification of cell components, such as electrophoresis and the ultracentrifuge, chromatography, optical assay procedures, and electrochemical measurements. Volume 2 covers in 14 sections the means for the characterization and isolation of macromolecular cell components as well as biochemical genetics and the handling of stable and radioactive isotopes. The theoretical basis is always exhaustively clarified, the methodology is described carefully and with clever choice of essentials. Instructional examples and illustrations are aptly chosen. The section by *Rauen* on chromatography deserves special mention in this respect, even though it contains much that is already "outmoded" by today's standards, and almost completely omits paper- and immuno-electrophoresis, gradient-elution and cellulose-exchange chromatography – a sign of the rapid technological development of the individual procedures.

Infrared spectroscopy, polarography, and some other special procedures of molecular chemistry also receive brief treatment. On the other hand, one welcomes the opportunity of being introduced to such remote fields as the methodology of light scattering (*Bücher* and *Möhring*) under expert guidance. The theoretical fundamentals are developed so excellently that they stimulate to use the possibilities which they offer the biochemist for the characterization of macromolecules. On the other hand, the enzyme chemist will miss a detailed treatment of enzymology. Even freeze-drying, the procedures for examining bacteria, as well as general work with microorganisms, and, finally – (one asks why?) – the Warburg technique have been omitted. No reference to it is found, neither in the chapter on gas analysis (*Opitz* and *Bartels*), which should be extremely useful for the practitioner with its added monograms and tables, but which limits itself entirely to the gas analysis of blood. Nor is the Warburg technique mentioned anywhere else while a whole section is devoted, for example, to the Thunberg technique.

It is particularly to be welcomed that numerous chapters are the results of teamwork. By this division of labor, for example the collaboration of a physicist and a biochemist, the basic problems have been worked out more clearly and new points of view have been explored. The section on isotopes was even written by eight authors. It should be pointed out that a large amount of space is devoted to the statistical evaluation of experimental results. The necessity for this and the method are brought close even to those further removed, with the aid of numerous examples.

Basically the same is true of the two volumes which cover the examination of the components of the animal body, from the inorganic mineral substances up to the highly complex proteins, in over 3500 pages, and of the last volume which in more than 800 pages encompasses the special analysis of the organs, body fluids, secretions, etc. In extent and content, some sections are veritable monographs and small masterpieces. This is particularly true of the description of amino acids (*Turba*) enriched by the logical emphasis of modern procedures, the description of steroids (*Reuber*, *Tschesche*, *Schmidt-Thomé*, *Oertel* and *Offe*) which makes an excellent impression with its clear tables, as well as the chapters on metalloproteins (*Bielig*, *Bayer*), pyrrole pigments (*Siedel*) and nucleic acids (*Fischer* and *Dörfel*). The ever-important section on organic phosphoric acid compounds (*Weil-Malherbe*) is excellently summarized and stands out in its excellent and comprehensive treatment.

Overlapping is not found frequently but does exist, for example, between the last-named section (on organic phosphates) and nucleic acids. Cross-references, on the other hand, are sorely missed and, in general, consequential and strong editing so desirable for correct intermeshing of the contributions, is not always realized. In all descriptions, however, comprehensiveness was aimed for and is attained. The specialist is able to copy the procedures and directions and to apply the described methods to his special tasks. The text is illustrated by numerous tables, UV and IR absorption curves and figures.

The articles contain literature – generally, up to 1955 – extensively and critically sorted. The critical attitude of the individual authors with respect to those analytical procedures which often appear to be given only for the sake of completeness and which have almost all been replaced today by simpler and more sensitive colorimetric or spectrophotometric procedures is very welcome, on the whole. This thoroughness, however, makes the text less suitable for obtaining rapid information than for obtaining exhaustive information and it is questionable whether a beginner can make use of the volumes without guidance by a specialist familiar with the field.

The quality and extent of the index should be pointed out. One must be an expert, however, in order to use it properly. It is a small feat to find, say, cholesterol (in German: Cholesterin). This goes as follows: Volume 3 Cholesterin see Steroids. There we find under 35 columns the key word Cholestan(e), to be sure, but not Cholesterin. One discovers that the arrangement may perhaps be by number of carbon atoms and count the 27 C-atoms of the structure. The list, however, ends with C_{21}-steroids. Here we then find – not under C, but under Z – Zoosterine, Cholesterin page 1385. One must have patience, or else one must have read the article first. It is best to use the regular table of contents.

F. Lynen and *L. Jaenicke* [NB 810/4 IE]

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The Path of Carbon in Photosynthesis

NOBEL PRIZE ADDRESS, DECEMBER 11, 1961 [*]

BY PROF. DR. MELVIN CALVIN

DEPARTMENT OF CHEMISTRY AND LAWRENCE RADIATION LABORATORY
UNIVERSITY OF CALIFORNIA, BERKELEY 4, CALIFORNIA

Introduction

It is almost sixty years since *Emil Fischer* was describing on a platform such as this one some of the work which led to the basic knowledge of the structure of glucose and its relatives [1]. Today we will be concerned with a description of the experiments which have led to a knowledge of the principal reactions by which those carbohydrate structures are created by photosynthetic organisms from carbon dioxide and water, using the energy of light.

Speculations on the way in which carbohydrate is built from carbon dioxide began not long after the recognition of the basic reaction and were carried forward, first by *Justus von Liebig*, then by *Adolf von Baeyer* and, finally, by *Richard Willstätter* and *Arthur Stoll*. Actually, the route by which animal organisms performed the reverse reaction, that is, the combustion of carbohydrate to carbon dioxide and water with the utilization of the energy resulting from this combination, turned out to be first one to be successfully mapped, primarily by *Otto Meyerhof* [2] and *Hans Krebs* [3].

Our own interest in the basic process of solar energy conversion by green plants, which is represented by the overall reaction

$$CO_2 + H_2O \xrightarrow[\text{Chlorophyll}]{\text{Light}} (CH_2O)_n + O_2$$

began some time in the years between 1935 and 1937, during my postdoctoral studies with Professor *Michael Polanyi* at Manchester. It was there that I first became conscious of the remarkable properties of co-ordinated metal compounds, particularly metalloporphyrins as represented by heme and chlorophyll. A study was begun at that time (and which is still continuing) on the electronic behavior of such metalloporphyrins. It was extended and generalized by the stimulus of Professor *Gilbert N. Lewis* upon my arrival in Berkeley. I hope these continuing studies may one day contribute to our understanding of the precise way in which chlorophyll and its relatives accomplish the primary quantum conversion into chemical potential which is used to drive the carbohydrate synthesis reaction.

Even before 1940 the idea that the reduction of carbon dioxide to carbohydrate might be a dark reaction separate from the primary quantum conversion act was already extant, stemming most immediately from the comparative biochemical studies of *Cornelis van Niel* and the much earlier work of *F. F. Blackman*, and its interpretation by *Otto Warburg*. The photo-induced production of molecular oxygen had been separated chemically and physically from the reduction of carbon dioxide after the demonstration of oxygen evolution by illuminated chloroplasts. This was done by *Robert Hill* [4] using ferric iron as oxidant in the place of carbon dioxide.

We are thus able to represent in a diagrammatic way (Fig. 1) the overall conversion of light energy into chemical energy in the form of carbohydrate and oxygen. The light energy first absorbed by chlorophyll and related pigments is converted into chemical potential in the

[*] This Address is published in this journal before its appearance in Les Prix Nobel 1961 through the kind co-operation of the Nobel Committee, Stockholm.

[1] *E. Fischer:* Les Prix Nobel. Stockholm 1902.

[2] *O. Meyerhof:* Les Prix Nobel. Stockholm 1923.

[3] *H. A. Krebs:* Les Prix Nobel. Stockholm 1953.

[4] *R. Hill*, Nature (London) *139*, 881 (1937).

form of high energy containing compounds, represented by B in Figure 1. These, in turn, lead to the production of oxygen from water and the simultaneous

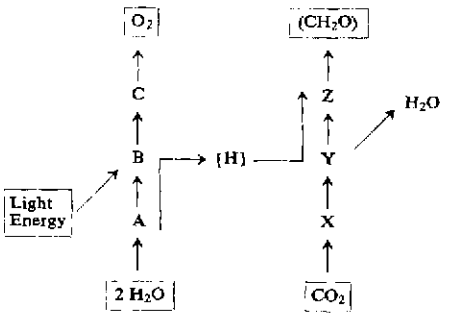


Fig. 1. Diagramatic scheme showing photosynthesis

generation of high level reducing agents which can be used, together with whatever collaborators are required, to carry out the carbon dioxide reduction.

One of the principal difficulties in such an investigation as this, in which the machinery which converts the CO_2 to carbohydrate and the substrate upon which it operates are made with the same atoms, namely, carbon and its near relatives, is that ordinary analytical methods will not allow us to distinguish easily between the machinery and its substrate. However, the discovery of the long-lived isotope of carbon, carbon-14, by *Samuel Ruben* and *Martin Kamen* in 1940 [5] provided the ideal tool for the tracing of the route along which carbon dioxide travels on its way to carbohydrate, represented in Fig. 1 by the series of unknown materials, X, Y, Z, etc.

In 1945 it became apparent to us that carbon-14 would be available cheaply and in large amounts by virtue of the nuclear reactors which had been constructed. With the encouragement and support of Professor *Ernest O. Lawrence*, the Director of the Radiation Laboratory in Berkeley, we undertook to study that part of the energy converting process of photosynthesis represented by the carbon reduction sequence, making use of ^{14}C as our principal tool.

Design of the Experiment

The principle of the experiment was simple. We knew that ultimately the CO_2 which enters the plant appears in all of the plant materials but primarily, and in the first instance, in carbohydrate. It was our intention to shorten the time of travel to such an extent that we might be able to discern the path of carbon from carbon dioxide to carbohydrate as the radioactivity which enters with the CO_2 passes through the successive compounds on its way to carbohydrate.

Preliminary experiments confirmed the idea that the absorption of CO_2 and its incorporation in organic material was indeed a dark reaction. This was easily established by exposing plants which had first been illuminated in the absence of carbon dioxide so as to store some of the intermediate high energy containing compounds, and then noting that these compounds could be used in the dark to incorporate relatively large amounts of CO_2. However, the products did not proceed very far along the reduction scheme under these conditions, and so we undertook to do the experiment in what we call a steady state of photosynthesis.

[5] *S. Ruben* and *M. D. Kamen*, Physic. Rev. *57*, 549 (1940).

Plant Material

As the precision of our experiments increased, the need for more reproducible biological material also increased, and very soon we found it necessary to grow our own plant material in as highly reproducible a manner as possible. A very convenient green plant that had already been the subject of much photosynthetic research was the unicellular green alga, *Chlorella*, a photomicrograph of which is shown in Fig. 2. We developed

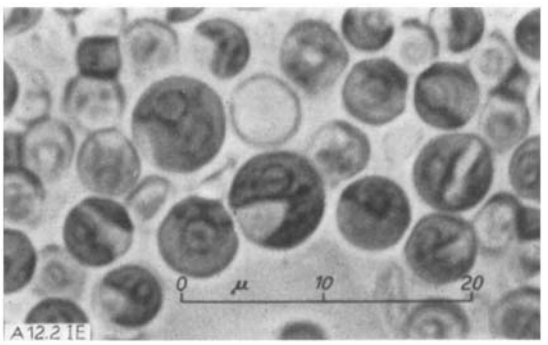


Fig. 2. Photomicrograph of *Chlorella* (Magnification about × 10^5)

methods of growing these organisms in a highly reproducible fashion, both in intermittent and continuous cultures, and it is with organisms such as these that most of our work was done. I hasten to add, however, that the essential features of the cycle with which we finally emerged were demonstrated on a wide variety of photosynthetic organisms, ranging from bacteria to the higher plants.

Apparatus

The exposures were initially performed in a simple apparatus (called a 'Lollipop' because of its shape, Fig. 3) which contained a suspension of the algae under-

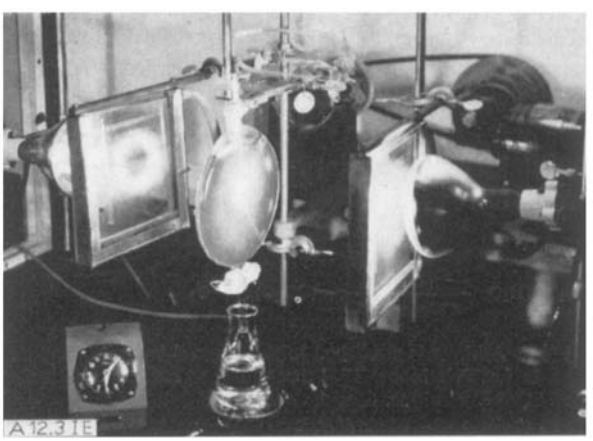


Fig. 3. 'Lollipop', the apparatus in which the photosynthesis experiments are performed

going photosynthesis with normal CO_2. The initiation of our tracer experiment was accomplished by injecting into the nonradioactive carbon dioxide stream, or substituting for it, some ^{14}C labeled CO_2 for a suitable period of time, ranging from fractions of a second to many minutes. At the end of the preselected time period, the organisms were killed by various methods, but principally by dropping the suspension into approximately four volumes of alcohol. This stopped the enzymic reactions and, at the same time, began the extraction of the materials for analysis.

Early Analytical Methods

In the early work, the classical methods of organic chemistry were applied in our isolation and indentification procedures, but it soon became apparent that these were much too slow and would require extremely large amounts of plant material to provide us with the identification of specific labeled compounds. Here, again, we were able to call upon our experience during the war years in which we had used ion exchange columns for the separation of plutonium and other radioactive elements. We made use of both anion and cation exchange columns, and soon discovered that the principal compounds in which we were interested, that is, those which became ^{14}C radioactive in the shorter exposure times, were, indeed, anionic in character.

Because of the peculiar difficulty we found in eluting the principal radioactive components from anion exchange resins, it became apparent that this radioactive material was a strongly acidic material and very likely had more than one anionic point of attachment binding it to the resin. Among these peculiarities was the fact that an ordinary carboxylic acid could be eluted relatively easily while the principal radioactive material would require either very strong acid or very strong base to bring it off. This fact, taken together with a number of other chromatographic properties, led us to the idea that these early products might very well be phosphate esters as well as carboxylic acids.

A more detailed analysis of the precise conditions required to elute the material suggested phosphoglyceric acid as a possibility. To a relatively large amount of algae was added as indicator a small amount of the purified radioactive material obtained from a small sample of algae exposed to radioactive carbon for a few seconds. This led to the direct isolation of slightly over nine milligrams of a barium salt which, by classical organic procedures, we were able to identify as the barium salt of 3-phosphoglyceric acid [6].

Paper Chromatographic Methods

About this time *Martin* and *Synge* [7] had developed their method of partition chromatography which was particularly adapted for amino acid analysis because of the sensitivity of the colorimetric detection method. We turned to this as our principal analytical tool. It was especially suited to our needs because, having spread our unknown material from the plant onto a sheet of filter paper by two-dimensional chromatography, we could then find the particular components which we were seeking, namely the radioactive ones, without knowing their chemical nature beforehand. This was done by placing the paper in contact with photographic film, thus exposing the film at those points of the paper upon which were located the very compounds in which we were interested.

The result of such an experiment in which the algae were exposed to radioactive CO_2 for thirty seconds under what we then thought were steady state conditions, is shown in Fig. 4. The blackened areas on the film indicate the presence of radioactive compounds on the paper at those points. Such a chromatogram and film as shown in Fig. 4 constituted our primary source of information.

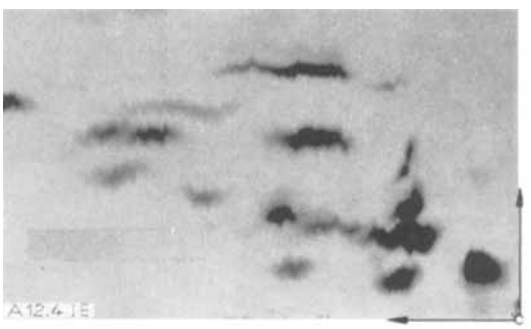


Fig. 4. Two-dimensional chromatogram of extract from algae indicating uptake of radiocarbon from $^{14}CO_2$ during 30 seconds of photosynthesis (using *Chlorella*)

It should be noted that this information resides in the number, position and intensity, *i.e.* radioactivity, of the blackened areas. The paper does not print out the names of these compounds, unfortunately, and our main work during the succeeding ten years was to identify those blackened areas on the film.

The techniques for doing this were many and varied. It was already clear that the co-ordinates of a particular spot in a particular chromatogram could be interpreted in terms of chemical structure in a general way, but this was far from sufficient for identification. Our usual procedure was to seek other properties of the material on the paper, such as fluorescence or ultraviolet absorption. More commonly it was necessary to elute the material from that part of the paper, as defined by the black area of the film, to perform chemical operations on the eluted material, and then rechromatograph the product in order to determine its fate.

From a succession of such operations the chemical nature of the original material could gradually be evolved, and final identification was usually achieved by co-chromatography of the tracer amount of unknown material with carrier, or macroscopic, amounts of an authentic sample of the suspected compound. A suitable chemical test was then performed on the paper and to which the authentic material alone would respond, since

[6] *M. Calvin* and *A. A. Benson*, Science (Washington) *107*, 476 (1948).

[7] *A. J. P. Martin:* Les Prix Nobel. Stockholm 1952; *R. L. M. Synge:* Les Prix Nobel. Stockholm 1952.

it was the only material present in sufficient amount. If the response produced by the authentic material coincided exactly with the radioactivity on the paper in all its details, we could be quite confident of the identity of the radioactive compound with the added carrier.

In this way, after some ten years of work by many students and collaborators and beginning with Dr. *Andrew A. Benson*, we were able to place names on a large number of the black spots on Fig. 4. These are given in

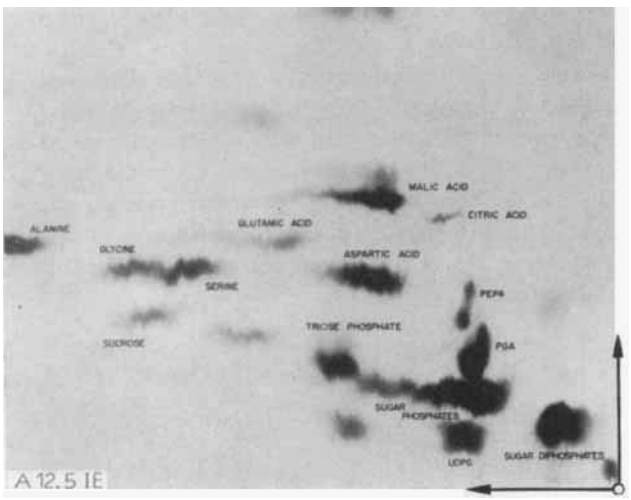


Fig. 5. Two-dimensional chromatogram of extract from *Chlorella* indicating uptake of radioactive carbon during 30 seconds of photosynthesis.
UDPG = Uridine diphosphoglucose; PEPA = Phosphoenolpyruvic acid; PGA = Phosphoglyceric acid

Fig. 5. It is perhaps worth noting that these two chromatograms are duplicate chromatograms of the same extract not simply one chromatogram; the degree of reproducibility of the procedure is thus established [8].

Development of the Carbon Reduction Cycle

Phosphoglyceric Acid as the First Product

It was already clear that in only thirty seconds the carbon has passed into a wide variety of compounds and that we would have to shorten the exposure time in order to get some information regarding the earliest compounds into which CO_2 is incorporated. This we did in a systematic way, and the result of a five second exposure is shown in Fig. 6. Here we began to see the dominance of the sugar- and sugar-acid phosphates. In shortening the exposure time still further, it became

[8] The details of the mapping of the path of carbon in photosynthesis may be found in the following references: a) *M. Calvin*, J. chem. Soc. (London), 1895 (1956); b) *J. A. Bassham* and *M. Calvin:* The Path of Carbon in Photosynthesis, Prentice-Hall, Englewood-Cliffs, New Jersey, 1957; c) *M. Calvin* in *W. D. Claus:* Radiation Biology and Medicine. Addison-Wesley Publishing Co., Reading, Mass., 1958, chapter 31; d) *M. Calvin* et al.: Proceedings 2nd Geneva Conference, on Peaceful Uses of Atomic Energy. Pergamon Press, London 1958, Vol. 24, p. 24 e) *M. Calvin* and *J. A. Bassham* in: Handbuch der Pflanzenphysiologie. Springer-Verlag, Heidelberg 1960, Vol. V, (Part 1), p. 884; f) *J. A. Bassham* and *M. Calvin:* The Photosynthesis of Carbon Compounds. W. A. Benjamin Co., New York 1962.

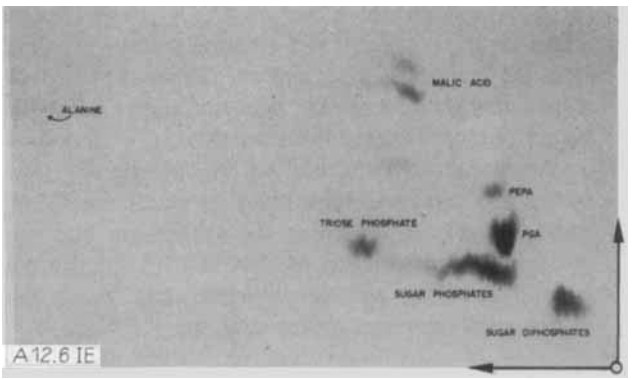


Fig. 6. Two-dimensional chromatogram of extract from *Chlorella* indicating uptake of radiocarbon during 5 seconds of photosynthesis

quite clearly apparent that a single compound dominated the picture in fractions of a second amounting to over eighty or ninety percent of the total fixed radioactive carbon. This compound was phosphoglyceric acid. That the phosphoglyceric acid was not the result of the killing procedure, but was actually present in the living organism, is demonstrated by the fact that when CO_2 is fixed by pre-illuminated algae in the dark under conditions in which not much of the phosphoglyceric acid can be reduced to the sugar level, a good fraction of the three-carbon fragment appears as alanine (Fig. 7).

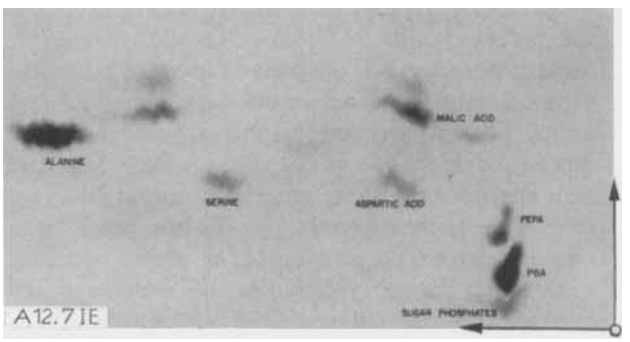


Fig. 7. Two-dimensional chromatogram of extract from *Chlorella*. 20 Seconds dark $^{14}CO_2$ fixation after pre-illumination

Alanine is a stable compound and is not likely to be formed from precursors by merely dropping the algae into the alcohol, and we can be confident that it was present in the living algae. In addition, a wide variety of killing procedures gave the same result. Thus the presence of phosphoglyceric acid itself in the living plant can be confidently presumed.

Labeling of Hexose

Among the earliest sugar phosphates which are shown in Fig. 6 are the triose phosphate and the hexose phosphate, and thus the succession from phosphoglyceric acid to hexose was immediately suggested. The phosphoglyceric acid being a three-carbon compound (and the hexose with its six carbon atoms) meant that further examination was needed in order to determine which carbon atoms were radioactive, and in what order they became so. The same information was, of course, required for the hexose.

The PGA (phosphoglyceric acid) is readily degraded by oxidation following the hydrolysis of the phosphate group, usually with acid. At first, and with periodic acid under conditions which produce the β-carbon as formaldehyde, the latter ean be separated as the dimedone compound. The residual two-carbon fragment may be further oxidized with the same reagent, or better with lead tetraacetate, to produce CO_2 from the carboxyl group and formic acid from α-carbon atom. These are separately collected and counted.

We were, therefore, able to show that in the very shortest times most of the radioactivity appears in the carboxyl group of the PGA and that radioactivity appears in the alpha- and beta-carbon atoms very nearly equally at later times.

A degradation of the hexose sugar showed that the carliest carbon atoms to be labeled were 3 and 4 (and these approximately equally, although not necessarily exactly so) followed by labeling in carbon atoms 1 and 2, and 5 and 6. The obvious relationship, then, between phosphoglyceric aeid and the hexose was the one shown in Fig. 8 in which the PGA, following reduction to phosphoglyceraldehyde and its conversion to the ketone,

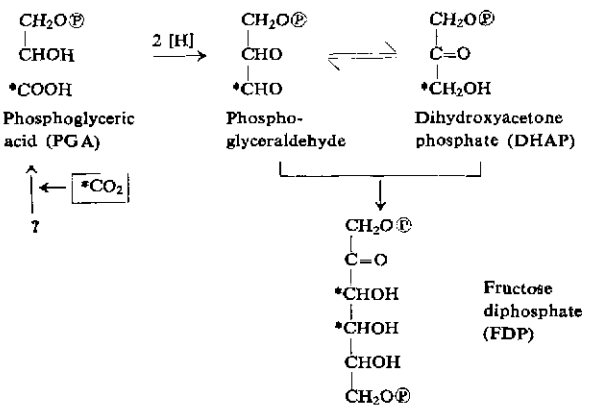


Fig. 8. Carbon pathway to hexose during photosynthesis

undergoes condensation by an aldolase reaction to give fructose diphosphate. This places the labeling of the hexose in the center of the molecule.

It is interesting to note that rather early in the fixation sequence, a compound appeared which moved extremely slowly in both solvents (*i.e.*, remained near the origin,

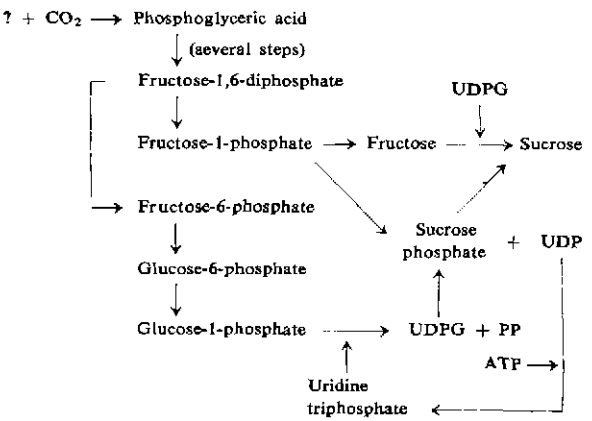


Fig. 9. Relationship between fructose phosphate and sucrose. UDPG = Uridine diphosphoglucose; UDP = Uridine diphosphate; PP = Pyrophosphate; ATP = Adenosine triphosphate

particularly in the acid solvent) and which upon extremely mild hydrolysis produced only labeled glucose. This ease of hydrolysis was even greater than that of glucose-1-phosphate, but the material was not glucose-1-phosphate. It was shown much later to be the nucleoside diphosphoglucose uridine diphosphoglucose, and its part in the synthesis of sucrose itself deduced from the presence of traces of sucrose phosphate, later searched for and found. The relationship between phosphoglyceric acid and sucrose is illustrated in Fig. 9.

Origin of Phosphoglyceric Acid

We now are ready to return to the question of the origin of the PGA itself. Here we were led, by what appeared to be an obvious kind of arithmetic, to seek a compound made of two carbon atoms which acts as a possible acceptor for the radioactive CO_2 to produce the carboxyl-labeled, three-carbon compound, phosphoglyceric acid. This search was a vigorous one and extended over a number of years. (Again, a considerable number of students and laboratory visitors were involved.) While free glycolic acid was found under certain very special conditions, these did not correspond to what would be required of the so-called carbon dioxide acceptor. A good many other compounds were identified in the course of this search; notably a five-carbon sugar, ribulose (as its mono- and diphosphate), and a seven-carbon sugar, sedoheptulose (as its mono- and diphosphate).

While the relationship of the trioses and hexoses to PGA in a time sequence seemed clear, the sequential relationship of the five-carbon and seven-carbon sugars was not readily determined. In fact, attempts to establish this relationship by ordinary kinetic appearance curves of these two sugars resulted in conclusions concerning the order of appearance of the pentose, hexose and heptose which varied from day to day, experiment to experiment, and person to person.

Radioactivity Determination of Pentose and Heptose

The distribution of radioactivity in the pentose and heptose was next determined and this distribution is indicated in Fig. 10 by the number of asterisks on each

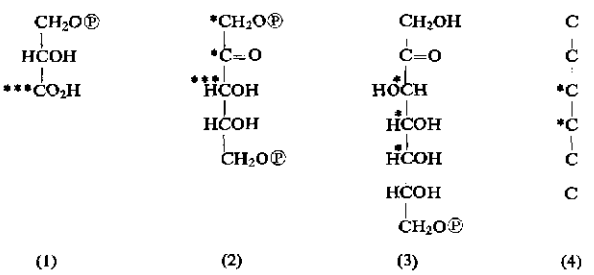


Fig. 10. Distribution of radioactive carbon in (1) phosphoglyceric acid; (2) ribulose diphosphate; (3) sedoheptulose monophosphate; (4) hexose monophosphate

atom. Thus, the 3-carbon atom of the ribulose is the first to be labeled, followed by carbon atoms 1 and 2 and finally carbon atoms 4 and 5. In sedoheptulose, the

center three carbon atoms (3, 4 and 5) were the first to be labeled, followed by carbon atoms 1 and 2, and 6 and 7. Extremely short experiments, of the order of fractions of a second, did show a low value for carbon atom 4 in sedoheptulose.

The peculiar labeling in sedoheptulose, and the absence of any single one carbon atom as dominating over the others, clearly indicates that it is not formed by a $C_6 + C_1$ addition, *i.e.* not directly from the hexose by the addition of a single carbon atom. The only other alternatives for the formation of the sedoheptulose are the combinations of $C_5 + C_2$, or $C_4 + C_3$. Again we call on the apparent but nearly equal distribution of the center three carbon atoms of sedoheptulose to indicate that there is no intact element of the five-carbon ribulose present in the sedoheptulose, since there is no intact group of five carbon atoms which has the same labeling pattern as we see in the ribulose.

We are, therefore, forced to seek a $C_4 + C_3$ method for the construction of sedoheptulose. The availability of the C_3 fragments is clear enough for the phosphoglyceric acid. The hexose seems to be a possible source of the C_4 fragment which, when combined with a C_3 fragment directly related to PGA, will give rise to a C_7 sugar, sedoheptulose, labeled in the manner indicated. This can be done by taking a four-carbon sugar made up from carbon atoms 3, 4, 5 and 6 (*i.e.* the lower four carbon atoms) of fructose, in which the first two (3 and 4) would have the label, and condensing it in an aldol type condensation with the phosphodihydroxyacetone as shown in Fig. 11.

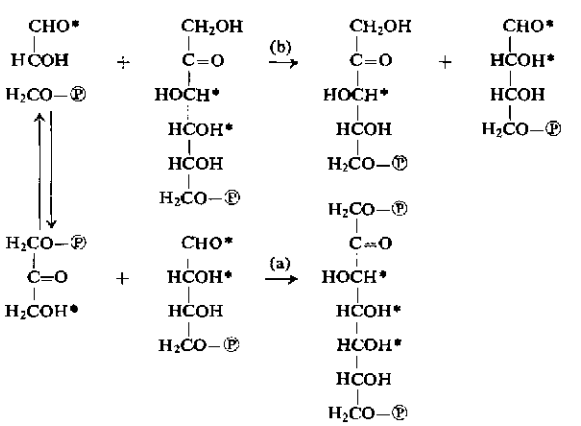


Fig. 11. Formation of a heptose from triose and hexose.
(a) Transketolase; (b) Aldolase

If the pool sizes of the tetrose and triose are very small it should be possible to arrive very quickly at a heptose in which the center three carbon atoms are very nearly equally labeled, although one might expect some differences in the shortest times as we have seen. The top carbon atoms of the hexose, *i.e.* 1 and 2, would be combined with another triose in the same reaction to produce pentose labeled at the 3-position.

Identification of the Two-Carbon Acceptor

Accepting this as the source of the heptose, we are now left with the problem of the source of the pentose with its peculiar and unsymmetric labeling pattern. Again, we call on our simple arithmetic, and discover that the pentose can be made by losing a carbon from the hexose, or by building it up from smaller fragments, *i.e.*, by adding a C_1 to a C_4 fragment, or by adding a C_2 to a C_3 fragment. Once more, we can call upon the lack of relationship between the pentose labeling and any five-carbon sequence in the hexose to eliminate from further consideration the construction of the pentose by loss of a terminal carbon from the hexose. Furthermore this would be a step backwards in our construction program.

We are left with the only remaining alternative for the construction of the pentose, namely, the combination of a C_3 with a C_2 fragment. Again, the source of C_3 fragments is clear enough, but the question of the source of the C_2 fragment to go with it requires some discussion.

At this point it should be remembered that we have already made a C_5 fragment labeled at the 3-carbon atom. The ribulose labeling scheme, as shown in Fig. 10, indicates that the next label to appear was in carbon atoms 1 and 2. Thus, it was not until we realized that the ribulose which we were degrading, and which we obtained from the ribulose diphosphate, actually had its origin in two different reactions, that it became possible for us to devise a scheme for its genesis.

By taking the two-carbon fragment off the top of the sedoheptulose we could make two five-carbon compounds which, taken together with the five-carbon compound already formed, would produce the labeling scheme finally observed in ribulose diphosphate. This is shown in Fig. 12. The enzyme which performs this two-carbon transfer is transketolase and is the same one that we have already used to generate the tetrose required for heptose synthesis.

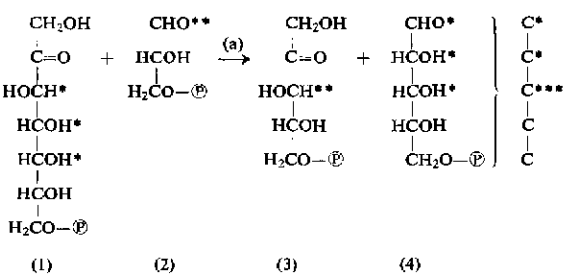


Fig. 12. Proposed scheme for labeling of pentose. (1) Sedoheptulose monophosphate; (2) Phosphoglyceraldehyde; (3) Xylulose monophosphate; (4) Ribose monophosphate; (a) Transketolase

Thus we have devised ways of generating from phosphoglyceric acid all of the sugars which appear on our early chromatograms *i.e.* the triose, the various pentoses, the various hexoses, and the heptose. The earlier failure in selecting a specific sequence amongst these compounds is now understandable, since all of them appear simultaneously following triose. As yet, we had not discovered the compound originally presumed to be the C_2 compound, to which the carbon dioxide may be added in order to produce carboxyl-labeled phosphoglyceric acid.

Carbon-Fourteen Saturation Experiments: Changes in Steady State and Transients

We recognized at quite an early stage that most of the compounds which we have so far mentioned, apart from sucrose, become saturated with radioactivity very quickly, and yet the amount of these materials present in the plant at any one time is small and does not change. This suggested a method for discovering not only how light might operate on PGA, but also how the PGA itself might arise. We could use the radioactivity saturation levels for these compounds (through which carbon was flowing) to measure the total amount of active reservoir of these compounds in the plant. We could then change one or another of the external variables and follow the resultant changes in the size of this reservoir.

The first, most obvious, and easiest external variable to be changed was the light itself. Fig. 13 shows the first set of data taken by *Peter Massini* which not only demonstrates the early saturation but also the effect of the light on the pool transients [9].

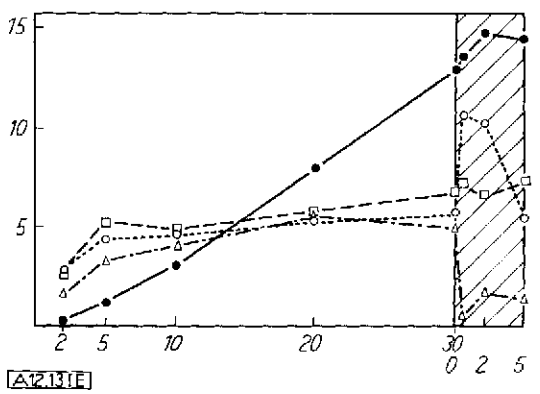


Fig. 13. Effect of light and dark on activities of phosphates and sucrose.
Δ — · — · — Δ Diphosphates
○ · · · · · · ○ Phosphoglyceric acid
□ — — — □ Monophosphates (hexose monophospbate area)
• — · — — • Sucrose
Shaded portion of diagram: dark; unshaded: light
Ordinate: counts/min. on paper × 10^{-3}
Abscissa: time (min.) of exposure to $^{14}CO_2$

Here one can see that the PGA and the sugar phosphate are very quickly saturated, but that the sucrose is not. It is apparent that upon turning off the light there is an immediate and sudden rise in the level of PGA accompanied by a corresponding fall in the level of the diphosphate area, which was primarily ribulose diphosphate.

Here we had our first definitive clue as to the origin of the phosphoglyceric acid. It would appear that it arises as a result of a dark reaction between the ribulose diphosphate and carbon dioxide. Fig. 14 and 15, based upon the work of Dr. *James A. Bassham* [10,11] show what can be achieved with this technique. Here one sees the large number of points obtainable, and the very much smoother curves with their clear saturation points

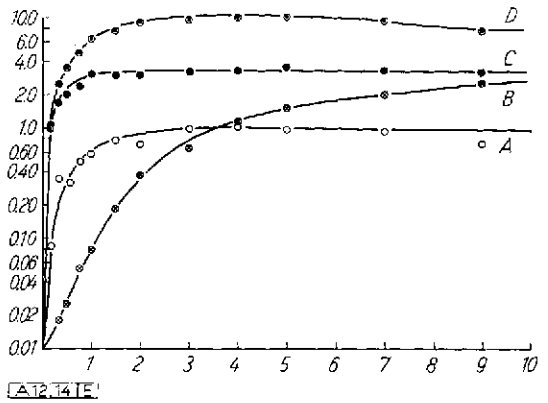


Fig. 14. Appearance of carbon-14 in phosphoglyceric acid and sugar phosphates plotted against time of photosynthesis with $^{14}CO_2$
Curve A = Diphosphates; Curve B = Sucrose; Curve C = Phosphophoglyceric acid; Curve D = Hexose and heptose monophosphates.
Ordinate: μmoles ^{14}C/ml algae.
Abscissa: minutes

well defined. In Fig. 15 the transient rise in the PGA pool size is clearly brought out together with the disappearance of ribulose diphosphate when the light is turned off, thus clearly defining the relationship between these two compounds.

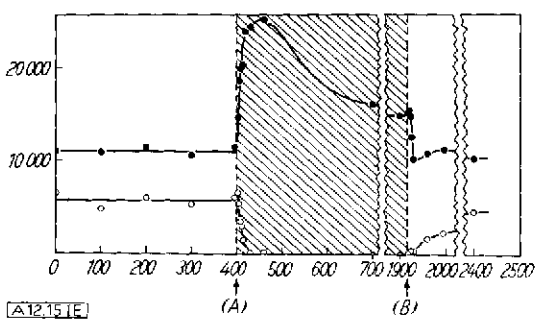


Fig. 15. Light-dark changes in concentrations of phosphoglyceric acid and ribulose diphosphate
Shaded area = darkness
(A) light off, (B) light on.
—○—○— = Ribulose diphosphate
—•—•— Phosphoglyceric acid.
Ordinate: counts/minute.
Abscissa: time (sec.)

We can now formulate the cyclic system driven by high energy compounds produced through the action of light acting upon phosphoglyceric acid which, in turn, results from a reaction between ribulose diphosphate and carbon dioxide (Fig. 16).

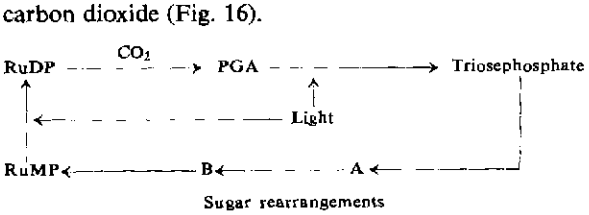


Fig. 16. Formation of 5-carbon sugars from ribulose diphosphate. (See also legend to Fig. 17)

The triose phosphate then undergoes a series of condensations and sugar rearrangements, represented by the letters A and B and including the pentose and heptose

[9] *M. Calvin* and *P. Massini*, Experimentia (Basle) *8*, 445 (1952).

[10] *J. A. Bassham* et al., J. Amer. chem. Soc. *76*, 1760 (1954); *M. Calvin* and *J. A. Bassham*, 1st International Conference on the Peaceful Uses of Atomic Energy, Geneva, Switzerland, 1955. Paper No. A/Conf. 8/P/259.

[11] *J. A. Bassham* and *M. R. Kirk*, Biochim. biophysica Acta (Amsterdam) *43*, 447 (1960).

rearrangement which we have just discussed, leading back again to a ribulose monophosphate which is then phosphorylated to ribulose diphosphate, in order to complete the cycle.

The absence of light has, in effect, blocked the easy conversion of phosphoglyceric acid to triose without any reduction in the rate of formation of PGA from ribulose diphosphate. This should result in an immediate rise in the amount of PGA and an immediate fall in the amount of ribulose, since it no longer can be produced in the dark.

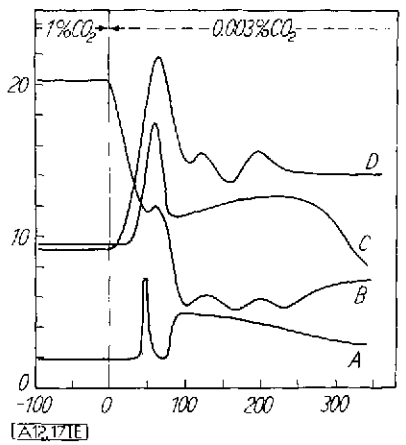
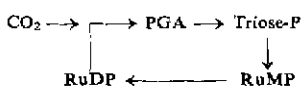


Fig. 17. Transients in the regenerative cycle



Curve A: Triose phosphate x 20; Curve B: Phosphoglyceric acid (PGA); Curve C: Ribulose monophosphate x 10 (RuMP); Curve D: Ribulose diphosphate (RuDP).
Ordinate: relative reservoir sizes
Abscissa: seconds (at 6°C.)

Such a scheme allows us to predict another transient, namely the one which would result if, in the presence of light, *i.e.*, in the presence of the high energy compounds required to drive the cycle, we suddenly diminished the availability of carbon dioxide, putting a block between ribulose and the phosphoglyceric acid. The prediction, which resulted here in the first transients, would be the accumulation of ribulose and the disappearance of PGA. These two transients would then make their way back through the cycle, with the fall in PGA in a clockwise direction and the rise in ribulose in an anti-clockwise direction, thus making for a system of oscillating transients. Such an experiment was performed by Dr. *Alexander T. Wilson* and the results are given in Fig. 17 [12].

Here it is quite clear that the sudden reduction of CO_2 results in a drop in the size of the PGA pool associated with a rise in the ribulose concentration. It is interesting to note that the triose reservoir is the last to rise and the first to fall, as predicted from its position in the cycle.

The Photosynthetic Carbon Cycle

We can now arrange all of the individual steps separately discussed into a sequence which leads to the photosynthetic carbon cycle shown in Fig. 18.

One compound is shown therein as an intermediate lying between ribulose diphosphate and phosphoglyceric acid. This is a branched chain α-hydroxy-β-keto sugar acid. As yet this compound has not been isolated as a separate entity. The enzyme system catalyzing the

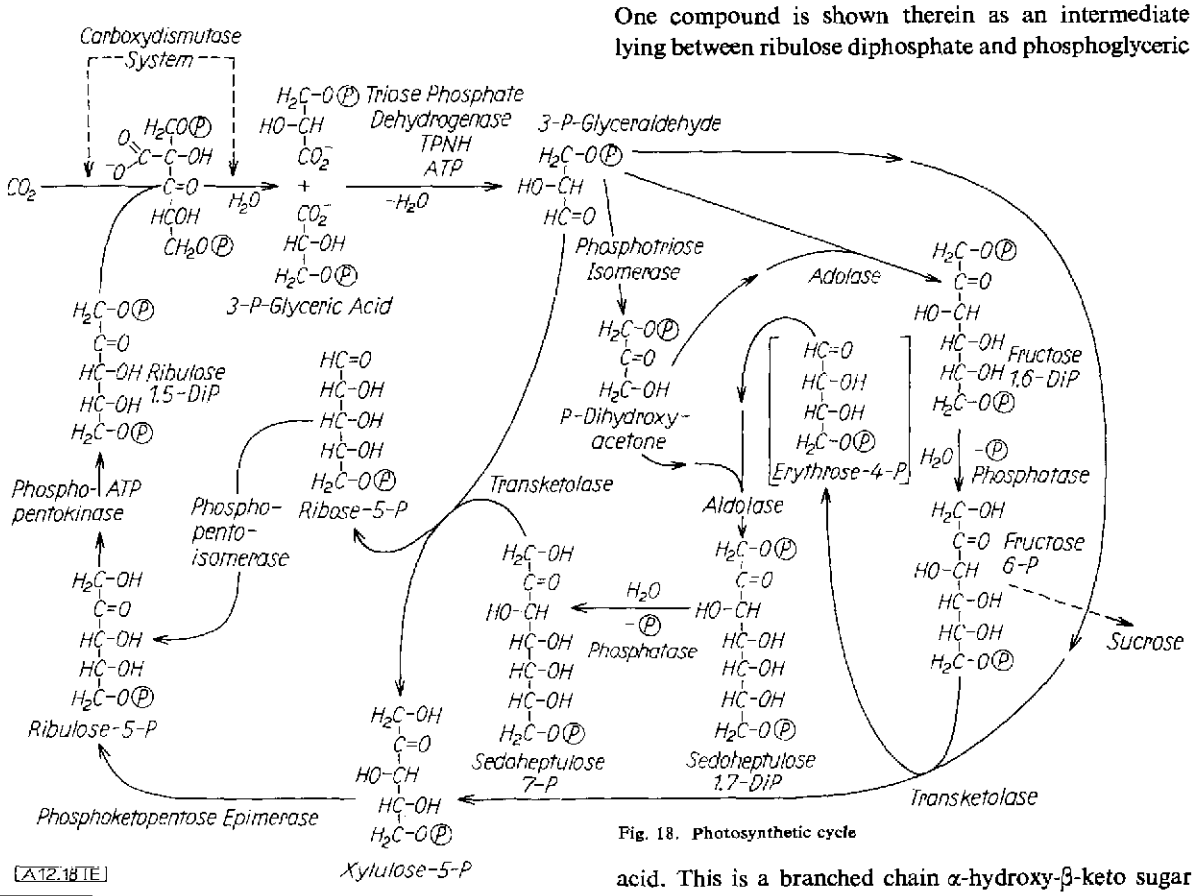


Fig. 18. Photosynthetic cycle

[12] *A. T. Wilson* and *M. Calvin*, J. Amer. chem. Soc. *77*, 5948 (1955).

reaction of ribulose diphosphate to PGA has been isolated and purified, but we have so far been unable to break its reaction down into two steps [13]. If this intermediate is present, it is present only in extremely small amounts as the free compound, if at all, and its hydrolysis to produce two molecules of phosphoglyceric acid takes place extremely rapidly in the isolated enzyme system and even in the living plant itself.

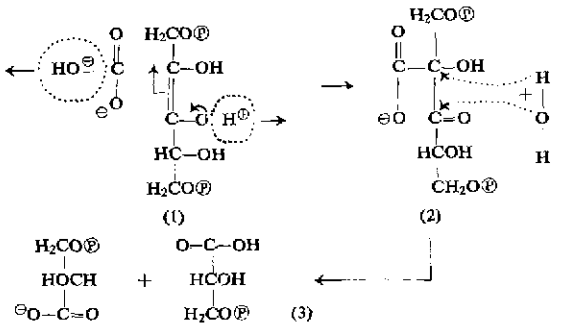


Fig. 19. Mechanism of the carboxydismutase reaction. (1) Ribulose diphosphate (RuDP), ene-diol form; (2) Intermediate; (3) 3-Phosphoglyceric acid

The mechanism for the carboxydismutase (the enzyme responsible for the formation of PGA from ribulose diphosphate) reaction is formulated in Fig. 19.

Here the intermediate is split by hydrolysis to two molecules of phosphoglyceric acid. However, in our earlier work the possibility of a reductive fission at the same point to give one molecule of triose and one molecule of phosphoglyceric acid was considered. It was rejected in favor of the hydrolytic splitting because of our failure to find any evidence for the intermediate. Nevertheless, more recent, very careful, kinetic analysis of the carbon flow rates by Dr. *James A. Bassham* [11, 14] has suggested that the reductive split may indeed participate in the reaction to some extent while the light is actually on. This path is indicated in Fig. 20 by the dotted line from the presumed C_6 keto-acid.

Quantum Conversion in Photosynthesis

As can be seen from the various levels of the schematic drawings of the photosynthetic carbon cycle (Figs. 18 and 20), the energy required to drive the synthetic sequence from carbon dioxide to carbohydrate, and the many other reduced carbon-containing materials which can be derived from the cycle, is delivered in the form of a number of compounds of relatively high chemical potential in the aerobic aqueous system in which the

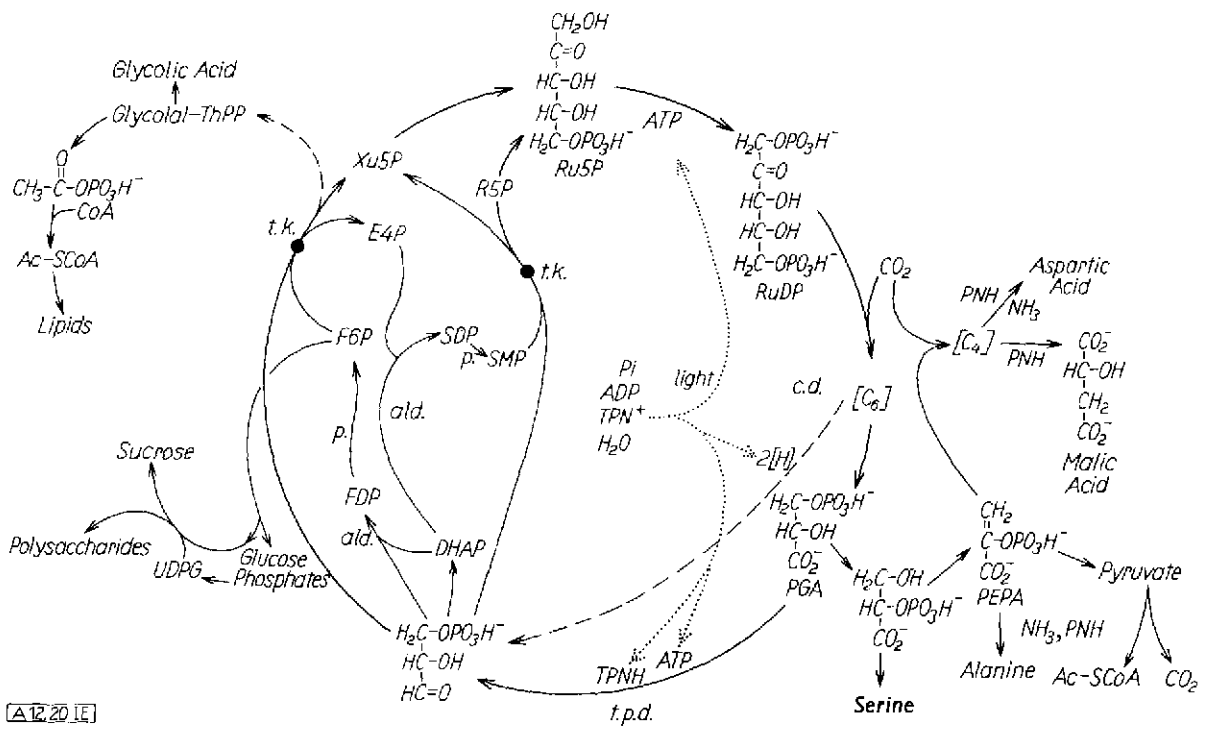


Fig. 20. The photosynthetic carbon cycle and its relation to quantum conversion and to succeeding biosynthesis

Ac-SCoA	= Acetyl coenzyme A
ThPP	= Thiaminpyrophosphate
UDPG	= Uridine diphosphoglucose
Xu5P	= D-Xylulose-5-phosphate
E4P	= Erythrose-4-phosphate
F6P	= Fructose-6-phosphate
FDP	= Fructose-1,6-diphosphate
DHAP	= Dihydroxyacetone phosphate
SDP	= Sedoheptulose-1,7-diphosphate
SMP	= Sedoheptulose-7-monophosphate
R5P	= D-Ribose-5-phosphate
Ru5P	= D-Ribulose-5-phosphate
ATP	= Adenosine triphosphate
RuDP	= Ribulose-1,5-diphosphate
TPNH	= Triphosphopyridine nucleotide (reduced)
PNH	= Reduced pyridine nucleotide
Pi	= Inorganic phosphate
t. k.	= Transketolase
c. d.	= Carboxydismutase
t. p. d.	= Triose phosphate dehydrogenase
p.	= Phosphatase
ald.	= Aldolase

[13] *N. G. Pon*, Thesis, Univ. of California, Berkeley, 1960.

[14] *J. A. Bassham* and *M. Calvin*, Vth International Congress for Biochemistry, Moscow 1961. Symposium VI, Preprint 48.

plant operates. The specific compounds with which we can actually drive the photosynthetic carbon cycle in

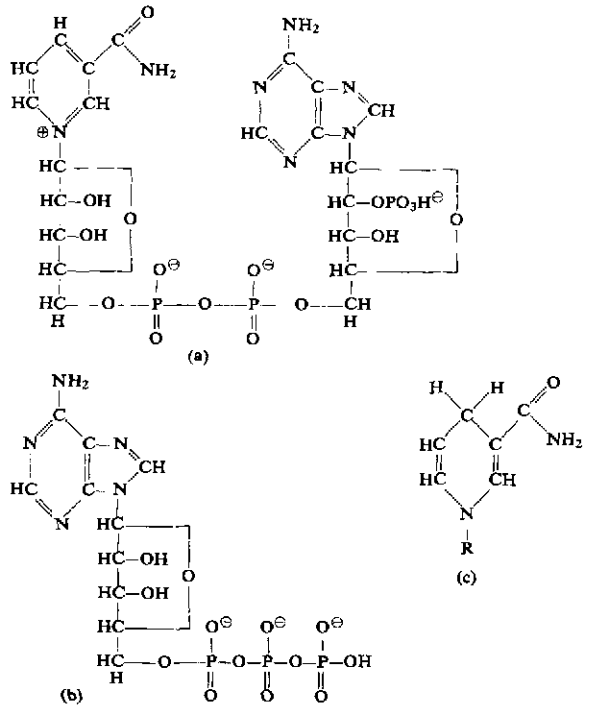


Fig. 21. (a) Triphosphopyridine nucleotide (TPN)
(b) Adenosine triphosphate (ATP). In adenosine diphosphate (ADP), the terminal phosphate is replaced by $-OH$.
(c) Nicotinamide portion of reduced triphosphopyridine nucleotide

the absence of light, but in the presence of all the initial enzymes and substrates [15], are triphosphopyridine nucleotide (TPNH) and adenosine triphosphate (ATP), whose structures are shown in Fig. 21. The primary quantum conversion of the light absorbed by chlorophyll will result in materials which can ultimately give rise to such substances as these.

[15] *E. Racker*, Nature (London) *175*, 249 (1955).

That light energy might be readily converted into chemical potential as ATP, independently of CO_2 reduction and its re-oxidation, was clearly indicated in the whole cell experiments of *Goodman* and *Bradley* [16] and first demonstrated to be independent of oxygen by *Frenkel* [17] who employed bacterial chromatophores. A corresponding anaerobic demonstration of ATP production by green plant chloroplasts was made by *Arnon et al.* [18]. The ability of chloroplasts to photoreduce pyridine nucleotide was demonstrated by *Ochoa* and *Vishniac* [19]. However, the precise nature of the primary quantum conversion act, whose products ultimately give rise in a dark reaction to ATP and TPNH, is still a matter of speculation [20, 21].

The apparatus which performs the quantum conversion act in the plant, together with all of the known carbon reduction enzymes, can be isolated from intact chloroplasts taken from the higher plants. The carbon reduction enzymes are very easily washed off the chloroplasts by water, leaving behind only the chlorophyll-containing quantum conversion matrix. This has a highly ordered structure in which the lamellae are alternating electron-dense and electron-transparent materials, as has been shown in many electron micrographs, a few examples of which are shown in Fig. 22.

The next level of structure within the lamellae is only now becoming visible to us, and an example (spinach chloroplast) is given in Fig. 23 [22]. Here we can see the lamella on its flat side showing a granular structure,

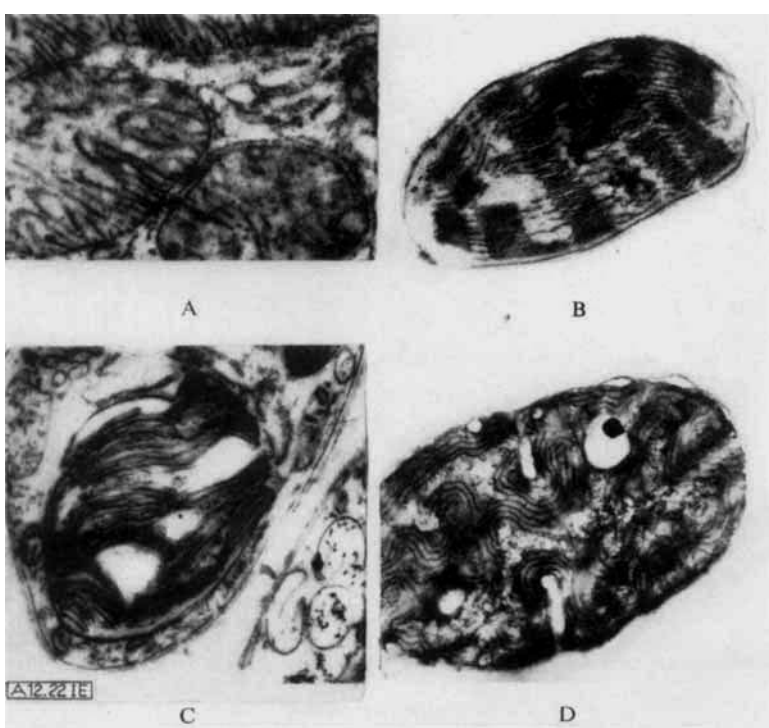


Fig. 22. Electron micrographs.

A. Mitochondria from guinea pig pancreas

B. Tobacco chloroplast maintained 24–36 hrs. in the dark before fixing with permanganate

C. Chloroplast from *Chlamydomonas* with several mitochondria

D. Cell from *Anabena* showing lamellae

[16] *M. Goodman, D. F. Bradley*, and *M. Calvin*, J. Amer. chem. Soc. *75*, 1962 (1953).

[17] *A. Frenkel*, J. Amer. chem. Soc. 76, 5568 (1954).

[18] *F. R. Whatley, M. B. Allen*, and *D. I. Arnon*, Biochim. biophysica Acta (Amsterdam) *16*, 605 (1955).

[19] *W. Vishniac* and *S. Ochoa* in *W. D. McElroy* and *B. Glass:* Phosphorus Metabolism. Johns Hopkins Press, Baltimore, Md., 1952, Vol. II, p. 467.

[20] *M. Calvin*, J. theoretical Biol. *2*, 258 (1961).

[21] *M. Calvin*, Perspectives Biol. and Med., in the press. (1962).

[22] *R. B. Park* and *N. G. Pon*, J. mol. Biol. *3*, 1 (1961).



Fig. 23. "Quantasomes" from spinach chloroplasts; 880 Å diameter polystyrene latex marker molecules

made up of fairly uniform oblate spheroids which we have called "quantasomes"; this work was performed by Drs. *Roderic B. Park* and *Ning G. Pon*. Within these quantosomes the chlorophyll itself is highly organized, as we have been able to demonstrate, particularly by the electric dichroism experiments performed by Dr. *Kenneth H. Sauer* [23].

We are now in the midst of trying to determine precisely what happens after the chlorophyll has absorbed the quantum to become an excited chlorophyll molecule, a problem that involves the physicist and physical chemist as well as organic and biochemists. The determination of the next stage in the energy conversion process is one of our immediate concerns. It is either an electron transfer process [20], and thus comes close in its further stages to the electron transfer processes which are being explored in mitochondria [24], or it is some independent nonredox method of energy conversion [21]. This remains for the future to decide.

Chemical biodynamics, involving as it does the fusion of many scientific disciplines, will play a role in this problem, as it already has done in the elucidation of the carbon cycle. It can be expected to take an increasingly important place towards the understanding on a molecular level of the dynamics of living organisms.

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[23] *K. Sauer* and *M. Calvin*, J. molecul. Biol., in the press.

[24] *D. E. Green*, Vth International Congress for Biochemistry, Moscow 1961. Preprint 176.

Aspects of Nucleophilic Carbene Chemistry

BY DR.-ING. H. W. WANZLICK

ORGANISCH-CHEMISCHES INSTITUT DER TECHNISCHEN UNIVERSITÄT BERLIN [*]

Bis [1,3-diphenyl-2-imidazolidinylidene] shows a considerable tendency towards dissociation into two carbenes. Reactions with this easily accessible carbene source lead to an understanding of nucleophilic carbene chemistry. The question of the existence of particularly stable carbenes is discussed, and it is suggested that a surprisingly large area of preparative possibilities and theoretical knowledge awaits development.

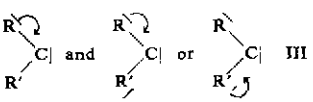
1. Introduction

Carbenes are 1,1-dipoles. The typical carbon atom in a carbene has a free pair of electrons, and at the same time, an electron deficiency. A wealth of data, most of it obtained within the last few years, has shown again and again the electrophilic character of the carbenes so far prepared and studied [1]. The reaction of such a carbene begins with the addition of a pair of electrons donated by the reactant P:



I II

A twofold conclusion may be drawn from the fact that isonitriles exist and are strongly nucleophilic, as shown, for example, in the primary step of an acid hydrolysis (II). In a carbene, which is by its nature, electrophilic, a change to the nucleophilic state, and an increase in stability, will occur whenever the substituents R and R′ are sufficiently strong electron donors (III).



III

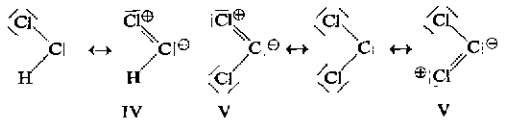
Experience shows that chlorine atoms do not produce such a change. Mono- and dichlorocarbene are, as is carbene itself, markedly electrophilic. Resonance structures (IV) and (V) in which there is no electron deficiency are not very important. The gradual decline of electrophilic reactivity in the series CH_2, $CHCl$, CCl_2 is, however, noticeable [2, 3].

[*] Dedicated to my greatly respected teacher, Prof. *Helmuth Scheibler*, with gratitude on the occasion of his 80th birthday.

[1] *W. Kirmse*, Angew. Chem. *73*, 161 (1961); ibid. references to prior summaries.

[2] *G. L. Closs* and *L. E. Closs*, Tetrahedron Letters No. 10, 38 (1960); ibid. further references.

[3] The ability of the carbenes to exist in the biradical form (triplet stage) is apparently only of use in "hot" carbene chemistry, *e.g.* in carbene itself (cf. J. Amer. chem. Soc. *82*, 3217 (1960)). This phenomenon, which can be no longer observed in chlorocarbene, becomes more improbable with increase in resonance stabilization, and will not be discussed further here.

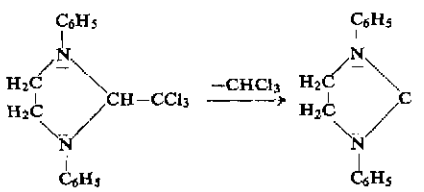


IV V V

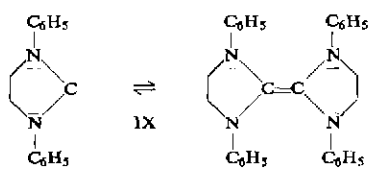
Obviously, the 1,1-dipole of the carbenes can be compared with the potential 1,2-dipole of a C–C double bond. In olefinic double bonds, the range from a nucleophilic to a markedly electrophilic behavior is well known; this may be seen, for example, by comparing tetramethylethylene to tetracyanoethylene. The entire chemistry of carbenes exhibits corresponding, although reverse, characteristics.

2. Bis-[1,3-diphenyl-2-imidazolidinylidene]

Cleavage of hydrochloric acid from 1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl)ethane (DDT) is well known [4]. When we tried to split off HCl from the imidazoline derivative (VI), prepared from dianilinoethane and chloral, chloroform was obtained. This surprising reaction demonstrates the relatively low level of energy in the carbene (VII). The final product of this cleavage reaction is the dimer, (VIII). This colorless, easily crystallized, compound shows a strong band (C=C double bond) in the Raman spectrum [5] at 1640 cm^{-1}. This band is, of course ,absent in the infrared spectrum [6, 7].



VI VII (and mesomeric forms)

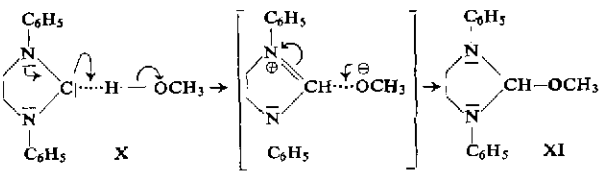


VII IX VIII

The dimer shows a surprisingly high tendency to dissociate (IX). Careful determinations of the molecular weight with exclusion of oxygen, which can only be conducted in camphor (Rast method) because of the poor solubility of the product, seem to indicate that there is approximately 50% dissociation at 170 °C. After the analyses, the dimer (VIII), and only this product, was present [8]. So far, we have not succeeded in performing molecular weight determinations at room temperature. From the chemical properties of the dimer, however, it may be concluded that dissociation also takes place at moderate and normal temperatures, as shown in equation IX. The chemistry of carbenes evolving from the above is based on the dimer (VIII) as starting material.

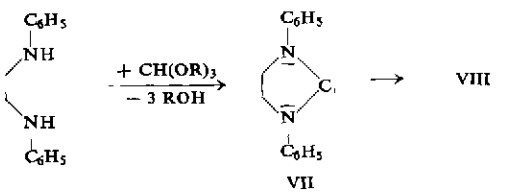
Table 1 contains a selection of the reactions so far carried out. The reaction with methanol is not included; it is given in the following paragraphs, together with a new method for preparing the dimer (VIII).

If methanol is added to the colorless solution of the dimer (VIII) in benzene, a strong purple color develops [9], which disappears on warming. Compound (XI) is formed, probably according to the following mechanism [10]:



X XI

As may be expected from the reactions (VI → VII → VIII) discussed above, compound (XI) can be reconverted to (VIII) via (VII) without difficulty. When (XI) is heated, methanol is split off, and the dimer (VIII) is formed. A new, very simple, synthesis of this compound follows from this discovery: (VIII) may be obtained from dianilinoethane and orthoformic ester in a yield of better than 90 per cent [11].



VII

Carbene (VII) has a distinctly nucleophilic character. The reaction with olefins, typical for previous (electrophilic) carbene reactions, fails. The preparation of (VIII) according to the ortho-ester method just described, can also be carried out, *e.g.* in the presence of a great excess of α-pinene [10]. The strongly electrophilic double bond of tetracyanoethylene, on the other hand, reacts immediately: even at room temperature, adduct (XVIII) shown in Table 1, is obtained within a few minutes.

The mechanism of the reactions summarized above has still to be studied in detail. The nucleophilic character of the carbene (VII), however, is already apparent. It is shown most clearly in reactions with water (XIII) and acids (XIV). Unlike the reaction with water, which is slow even at high temperature, the reaction with acids is fast, even in the cold. The first step – see (X) – is, no doubt, similar in nature to the first step in the acid hydrolysis of isonitriles (II).

[4] *K. Gätzi* and *W. Stammbach*, Helv. chim. Acta *29*, 563 (1946); ibid. further references.

[5] We would like to thank Dr. *B. Schrader* for the spectra. Technique: *B. Schrader*, *F. Nerdel*, and *G. Kresze*, Z. analyt. Chem. *170*, 43 (1959).

[6] *H.-W. Wanzlick* and *E. Schikora*, Angew. Chem. *72*, 494 (1960).

[7] *H.-W. Wanzlick* and *E. Schikora*, Chem. Ber. *94*, 2389 (1961).

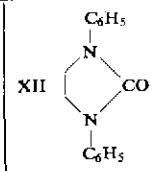
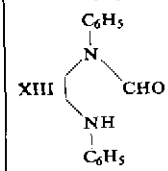
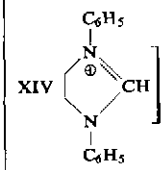
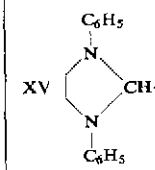
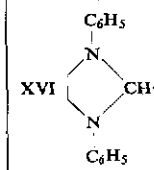
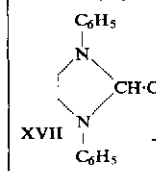
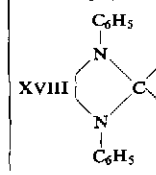
[8] The analyses were made possible by the well known inertness of camphor. See also the reactions of (VII) with ketones.

[9] The nature of this color development, which can be observed in many reactions of the dimer, cannot yet be explained. There are some indications that charge transfer complexes are involved.

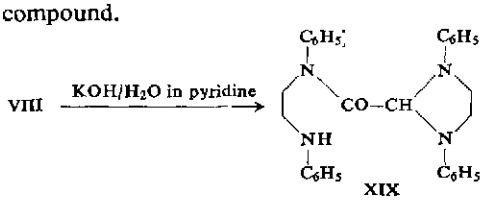
[10] *E. Schikora*, Ph. D.-Thesis, T. U. Berlin 1961.

[11] *H.-W. Wanzlick* and *H.-J. Kleiner*, Angew. Chem. *37*, 493 (1961).

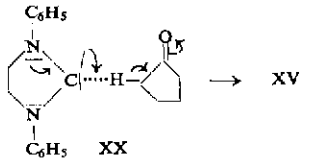
Table 1. Reactions of dimer (VIII) or of carbene (VII)

Reactant	Product	Temp. [°C]	Yield [%]
Oxygen [7]	 XII	25	90
Water [7]	 XIII	110	100
Hydrogen chloride [10]	 XIV	25	100
Cyclopentanone [7, 12]	 XV	130	70
Benzaldehyde [7]	 XVI	130	90
Furfural [13]	 XVII + Furoin	135	80
Tetracyano-ethylene [7, 14]	 XVIII	25	70

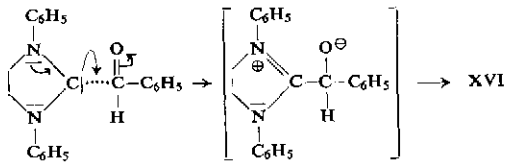
In this connection, it is highly interesting to note that the carbene (VII) does not react with aqueous alkali, but instead a hydration product of the dimer (VIII) is formed in 90% yield. According to analysis and infrared spectral data, formula (XIX) must be assigned to this compound.



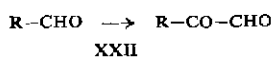
So far, this is the only reaction in which the dimer (VIII) is involved as such and not as a source of carbene. Equation (XX) is the easiest way to formulate the first step of the reaction with cyclopentanone (XV) in conformity with the other reactions. The same applies to other compounds containing "acidic" hydrogen atoms [16].



The reaction with benzaldehyde (XVI), which can be generalized [13, 17], starts with the formation of the "betaine" (XXI).



We believe this reaction to be of interest in preparative chemistry. Since dianilinoethane derivatives can be easily hydrolyzed [18], this reaction makes possible the transformation of an aldehyde to the homologous α-ketoaldehyde in two steps (XXII).



Furfural reacts with the carbene (VII) in the same way as benzaldehyde; compound (XVII) is obtained. Furthermore, appreciable quantities of furoin are formed.

This result is a convincing proof for the nucleophilic nature of the carbene (VII). It shows that this reaction must have been preceded by a dissociation of the dimer (VIII). In this case, the carbene (VII) takes over the role of the classical cyanide ion. The reactions in Diagram 1 are in strict accord with the known mechanism [19].

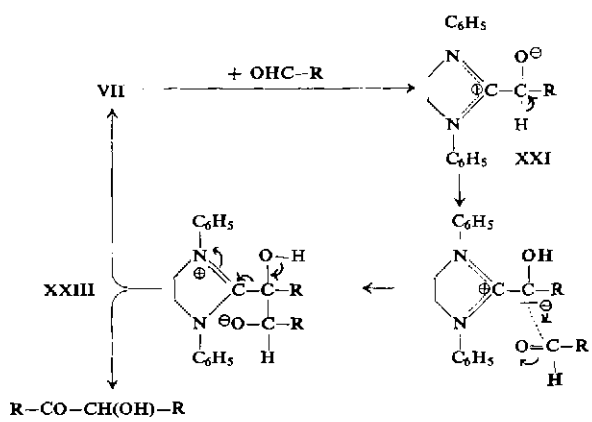


Diagram 1

[12] Other ketones, as well as compounds with active methyl or methylene groups, react in an analogous way. The products appear sometimes as tautomeric forms. Cf. *M. Riccius*, Diploma Thesis, T.U. Berlin 1961, and [15].

[13] *H.-J. Kleiner*, Ph. D.-Thesis, T.U. Berlin 1961.

[14] A polar structure (cf. [7]) as an alternate to (XVIII) is unlikely on the basis of the infrared spectrum. It is known that 1,1,2,2-tetracyanocyclopropane forms most readily. (*R. M. Schibner, G. N. Sausen*, and *W. W. Prichard*, J. org. Chemistry *25*, 1440 (1960).)

[15] *H. Ahrens*, Diploma-Thesis, T.U. Berlin 1961.

[16] α-Picolin does not react with VII, cf. [15].

[17] *M. Riccius*, Diploma-Thesis, T.U. Berlin 1961.

[18] *H.-W. Wanzlick* and *W. Löchel*, Chem. Ber. *86*, 1463 (1953).

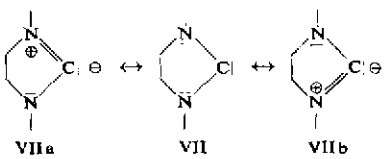
[19] *A. Lapworth*, J. chem. Soc. (London) *83*, 995 (1903); *85*, 1206 (1904).

Obviously the proton in the primary adduct, has the mobility, which is essential for smooth acyloin condensation (XXI). The "catalyst" (VII), released again in step (XXIII), is available for further use, until it is exhausted in the irreversible "side reaction" (XXI → XVII). It was shown in a parallel experiment that the furylglyoxal derivative (XVII) has no catalytic activity [13].

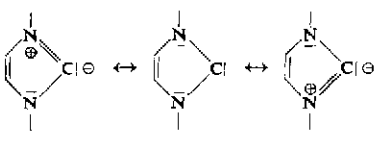
These discoveries raise many new questions, among which the following seems to be the most heuristic: How can stability be improved beyond the degree achieved in carbene (VII)?

One possibility for achieving greater resonance stabilization can be discussed here. We were impressed that what we had considered theoretically had already been achieved in practice.

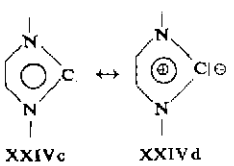
The aromatic system has a great potential for enhancing resonance stability. Inclusion of the carbene carbon atom into a quasi-aromatic system was expected to result in a very efficient stabilization. To the two pairs of electrons, which participate in the resonance of carbene (VII) – *i.e.* according to formula (VII), (VIIa), and (VIIb) – a third pair has to be added. This can result, for example, in the system shown by the formulae (XXIV), (XXIVa), and (XXIVb). This quasi-aromatic resonance stabilization can also be expressed by formulae (XXIVc) and (XXIVd), which conform with a customary manner of presentation.



VIIa VII VIIb



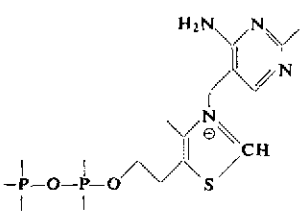
XXIVa XXIV XXIVb



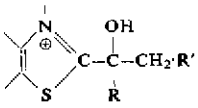
XXIVc XXIVd

3. The Biochemistry of Thiamine

The mechanism of thiamine action is well known. Its pyrophosphate (XXV), known as cocarboxylase, takes part in the decarboxylation of pyruvic acid and, as will be shown here in detail, it has an important function in sugar metabolism as the coenzyme of transketolase [20, 21]. It is known today that the reaction takes place at the C-2 atom of the thiazole ring. The well-established partial formulae (XXVI), (XXVII), and (XXVIII) are assigned to "active pyruvate," "active acetaldehyde," and "active glycolaldehyde," respectively [20, 21].

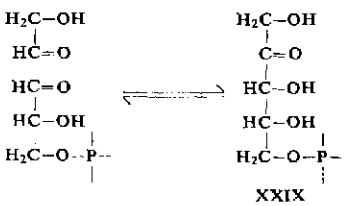


XXV



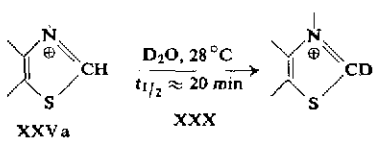
XXVI R = $COO^{\ominus}$ R' = H
XXVII R = H R' = H
XXVIII R = H R' = OH

The combination of glycolaldehyde with phosphoglyceric aldehyde to form ribulose-5-phosphate (XXIX), an acyloin condensation, is based on the preliminary formation of the "active glycolaldehyde" (XXVIII) [22]. It is known that thiazolium salts with an unsubstituted C-2 position also catalyze acyloin condensations *in vitro* [23].



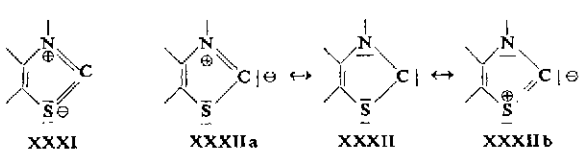
XXIX

An elementary prerequisite for these reactions is the mobility of the proton that is attached to the C-2 carbon atom. This mobility, which *R. Breslow* [20, 24] has proved by replacement with deuterium, is astonishingly great. Thiamine (see partial formula XXVa) has without the addition of base the values shown in equation (XXX). It is therefore comparable to C–H compounds with especially acid hydrogen atoms [25].



XXVa XXX

One would look in vain for a classical explanation of this phenomenon. The resonance structure (XXXI) for the deprotonized thiazolium system which was considered as "geometrically unlikely" by *R. Breslow* [20], is not satisfactory. The resonance structures (XXXIIa) and (XXXIIb), which by themselves fail to explain the stability of the zwitterion obtained from XXV on



XXXI XXXIIa XXXII XXXIIb

removal of a proton because they are feasible with, or without, a hydrogen atom on the C-2 atom [20]; they can, however, be united by the carbene formula (XXXII).

[20] *R. Breslow*, J. Amer. chem. Soc. *80*, 3719 (1958); ibid. further references.

[21] *H. Holzer*, Angew. Chem. *73*, 721 (1961); ibid. further references.

[22] Cf. *E. Baldwin:* Biochemie, Einführung in ihre Dynamik. Verlag Chemie, Weinheim (Germany) 1957, p. 316.

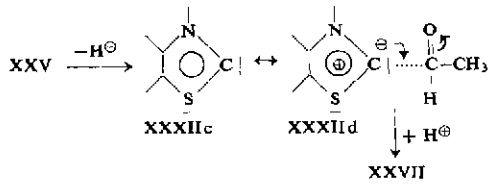
[23] *T. Ugai, S. Tanaka*, and *S. Dokawa*, J. pharmac. Soc. (Japan) *63*, 269 (1943).

[24] *R. Breslow*, J. Amer. chem. Soc. *79*, 1762 (1957).

[25] The hydrogen atoms of acetylene are not exchanged under these conditions, cf. [20].

The case of the carbene with quasi-aromatic resonance stabilization (XXIV and XXIVa–d) thus becomes a reality.

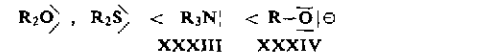
The biochemistry of thiamine is, therefore, in accord with the chemistry of nucleophilic carbenes. For example, the formation of "active acetaldehyde" (XXVII) from thiamine pyrophosphate (XXIV) can be written in the following way:



The formation of furoin, as described above, where the carbene (VII) acts as a catalyst, assumes the character of a model reaction. It could be demonstrated that the catalytic properties of the "thiamine model" (VII) can be enhanced considerably by proper substitution [13].

Nucleophilic carbenes with quasi-aromatic resonance stabilization can also be expected in the case of other heterocyclic compounds. It will be sufficient here to mention the 1,3-dimethylbenzimidazolium system, which can also catalyze acyloin condensations [13, 20]. Additional examples, including cases of obviously lower resonance stabilization, can be found elsewhere [20].

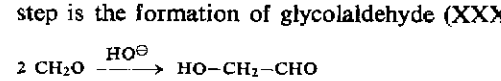
It might be supposed that the properties of nucleophilic carbenes are directly related to the presence and proximity of a strongly basic nitrogen atom. This is, however, not the case. The following observation may be noted: The basicity of the amines (XXXIII) exceeds by far that of the ethers and thioethers. However, on changing to the anion (XXXIV), the basicity of the amines can be exceeded.



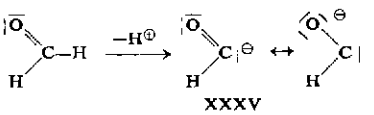
In seeking possible examples of nucleophilic carbene chemistry among the compounds of oxygen, for example, some account must be taken of anionic chemistry.

4. The Butlerow Reaction

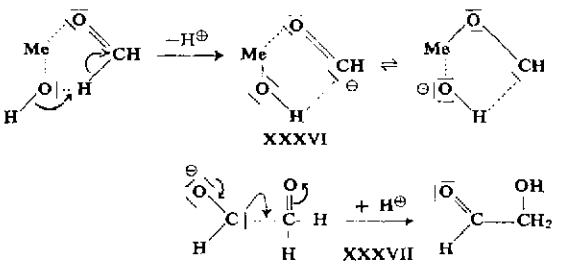
The transformation of formaldehyde into a mixture of sugars under the influence of alkali has been known for 100 years [26], and has been investigated many times [27–29]. There is a consensus of opinion that the first step is the formation of glycolaldehyde (XXXIX) [27].



Once it is formed, glycolaldehyde is a potent autocatalyst for further reaction steps. But clarification of the first step, which cannot be explained according to the classical theory, remains difficult [29]. *R. Breslow*'s reference to a possible relationship with the biochemistry of thiamine [29] suggests the direction in which a solution of the problem may be found. The carbene anion might play a role in this connection (XXXV).

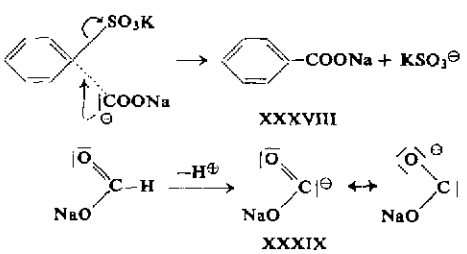


This carbene anion, which is possibly not free, and might appear only in combination with a metal hydroxide (XXXVI), could be capable of a "non-classical aldol-condensation" as the nucleophilic carbene anion (XXXVII).

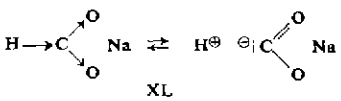


5. Anomalous Reactions of Alkali Formates

The formation of benzoate on melting together potassium benzenesulfonate and sodium formate, previously observed by *V. Meyer* [30], is obviously a nucleophilic aromatic substitution (XXXVIII), and is based upon the detachability of a proton from the formate molecule (XXXIX).



Here again we are in the territory of nucleophilic carbene chemistry. The explanation given by *O. Wichterle* [31] (XL) must be corrected: compounds in group XXXIV exhibit the properties of electron donors, not acceptors.



More important than this example [32], is the carbonylation of aromatic halogen compounds with sodium formate, discovered and studied by *H. Kröper, F. Wirth*, and *O. Huchler* [33]. As a result of their experimental work, the authors exclude a radical mechanism and

[26] *A. Butlerow*, Liebigs Ann. Chem. *120*, 295 (1861).

[27] *R. Mayer* and *L. Jäschke*, Liebigs Ann. Chem. *635*, 145 (1960); ibid. further references.

[28] *E. Pfeil*, Liebigs Ann. Chem. *641*, 121 (1961); ibid. further references.

[29] *R. Breslow*, Tetrahedron Letters No. 21, 22 (1959); ibid. further references.

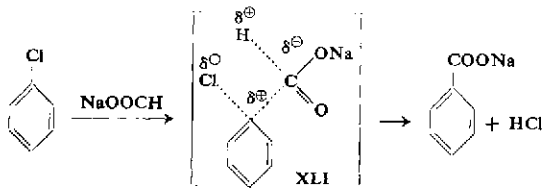
[30] *V. Meyer*, Liebigs Ann. Chem. *156*, 273 (1870).

[31] *O. Wichterle:* Allgemeine Organische Chemie. Akademie-Verlag, Berlin 1955, p. 702.

[32] For further examples see [31].

[33] *H. Kröper, F. Wirth*, and *O. Huchler*, Angew. Chem. *72*, 867 (1960).

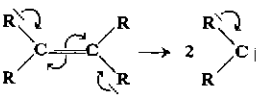
the formation of dehydrobenzene as an intermediate. They conclude that a nucleophilic aromatic substitution (XLI) takes place [34].



Since this subject is once more in the field of nucleophilic carbenes, it is easily understood that the presence of water interferes with the reaction. The sodium formate should not be given an opportunity for electrolytic dissociation because under these circumstances the formate ion will not be able to yield a further proton (which would lead to a di-anion) [31, 33].

6. Final Remarks

The outline given in this paper is intended only to introduce the theme of "nucleophilic carbene chemistry", and to suggest some possibilities. It can be expected that a wide field of synthetic organic chemistry will be opened in the future, and that a wealth of theoretical knowledge will be offered to the organic chemist. One further important question concerns the dissociation of a C–C double bond. Among the two possible explanations of the dissociation mechanism, only one has so far been considered and elaborated: Using tetra-α-naphthylethylene as an example, *V. Franzen* and *H. J. Joschek* [35] have shown that considerable benefit can be derived from the conception of a "mesomeric separate placement of the electrons that are released upon the dissociation of the C–C double bond." The other alternative arises from the considerations dis-



cussed in this paper and can be described in the following way: Dissociation is enhanced by leaving the electron pair released upon dissociation in the free state, and by filling the resulting electron gap as far as possible.

Received November 9, 1961 [A 179/IE 13]

[34] The term "formyl anion" must be assigned to the carbene anion (XXXV) which is discussed in reference to the Butlerow reaction.

[35] *V. Franzen* and *H. J. Joschek*, Liebigs Ann. Chem. *633*, 7 (1960).

The Oxidation of Olefins with Palladium Chloride Catalysts

BY DR. JUERGEN SMIDT [*], DR. W. HAFNER, DR. R. JIRA, DR. R. SIEBER, DR. J. SEDLMEIER, AND DR. A. SABEL

CONSORTIUM FÜR ELEKTROCHEMISCHE INDUSTRIE G.M.B.H., MUNICH (GERMANY)

The oxidation of olefins to carbonyl compounds with palladium compounds, especially the oxidation of ethylene to acetaldehyde, is at present carried out on a technical scale. The reaction takes place via a palladium-olefin complex, the formation of which is inhibited by halide ions. Hydrolysis to the carbonyl compound is inhibited by hydrogen ions. The knowledge gained by studying the reaction of olefins with pure solutions of palladium salts allows important conclusions to be drawn concerning the action of technical catalyst solutions containing copper and palladium chloride.

The oxidation of olefins with palladium compounds has already been reported [1]. In the meantime, technical processes, especially for the oxidation of ethylene to acetaldehyde, have been worked out and large-scale facilities have been in operation for about $1^1/_2$ years.

The reaction of ethylene with palladium chloride proceeds stoichiometrically according to equation 1, with metallic palladium being precipitated. Palladium has to be re-oxidized to the chloride in order to allow its re-use. This is best accomplished by cupric chloride (equation 2). The cuprous chloride which is formed thereby can be reoxidized by oxygen or air, (equation 3) so that, finally, the oxidation of ethylene to acetaldehyde is a catalytic reaction with oxygen according to the summarized equation 4.

$$C_2H_4 + PdCl_2 + H_2O \longrightarrow C_2H_4O + Pd + 2\,HCl \quad (1)$$

$$Pd + 2\,CuCl_2 \longrightarrow PdCl_2 + 2\,CuCl \quad (2)$$

$$2\,CuCl + {}^1/_2\,O_2 + 2\,HCl \longrightarrow 2\,CuCl_2 + H_2O \quad (3)$$

$$C_2H_4 + {}^1/_2\,O_2 \xrightarrow{PdCl_2,\ CuCl_2} C_2H_4O \quad (4)$$

Even though the reaction was first studied with solid catalysts (its discovery originated from these studies), it was soon found that liquid homogeneous solutions of catalysts, which give the same reactions, are more useful for a technical process.

[*] Taken from a lecture given at the GDCh meeting at Aachen (1961). The results are the subject of patents and patent applications.

[1] Angew. Chem. *71*, 176 (1959).

I. Oxidation of Olefins with Palladium Chloride

When ethylene is passed into an aqueous solution of palladium chloride, the originally brown solution turns black, even at room temperature, due to the formation of finely dispersed metallic palladium (equation 1) [2]. Other olefins behave similiarly.

Interestingly enough, no metallic palladium is formed, although aldehydes or ketones are produced, when olefins are reacted with palladium chloride solution containing nitrites; instead, a compound results having the overall composition PdNOCl [3].

The reaction proceeds via a palladium-olefin complex. Such complexes were first described by *Kharasch* et al. [4] as binuclear complexes. The ethylene complex decomposes with water thereby forming acetaldehyde and metallic palladium. Due to its instability in an aqueous medium, it can not as yet be determined whether a binuclear complex of the type described, or a mononuclear complex analogous to Zeise's salt $K(PtCl_3C_2H_4)$, is formed as an intermediate in the direct oxidation. This, however, is of no importance to the following considerations.

Investigations of the reaction of olefins with the palladium salt in aqueous solution with various reagents and under different conditions have led to a thorough understanding of the reactions which take place with the complex. The two main reaction steps, complex formation and complex hydrolysis, occur in aqueous systems simultaneously. Even though intermediates cannot be isolated, fairly safe statements can be made about the course of the reaction. These are based on observations of the effect of changing the variables.

For these investigations, the rate of olefin absorption was measured in solutions containing palladium salts using a shaking apparatus.

Figure 1 shows the absorption of the lower olefins. The quantity of gas absorbed corresponds to the quantity of olefin consumed by oxidation to the carbonyl compound. The rate of reaction decreases in the order ethylene > propylene > butene. The initially fast reaction decreases slowly. Almost exactly one mole of olefin is absorbed and reacted for each mole of palladium chloride. The stoichiometry of equation 1 is thus maintained. Isobutylene deviates distinctly. As shown below, alternative reactions occur here.

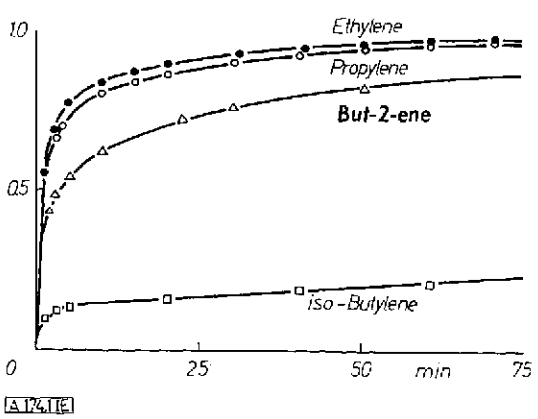


Fig. 1. Rate of adsorption of olefins in $^1/_{10}$ M $PdCl_2$ solution at 20 °C. Ordinate: Olefin absorption, moles olefin/mole $PdCl_2$

The formation of the complex is an equilibrium reaction. The palladium chloride, which could be present in aqueous solution as $[PdCl_2(OH)H_2O]H$, absorbs olefins according to:

$$[PdCl_2(OH)H_2O] + \text{Olefin} \rightleftarrows [PdCl_2(OH)\text{Olefin}]^- + H_2O \qquad (5)$$

With propylene and butene, the equilibrium is shifted more to the left than with ethylene. The lower rate of olefin absorbtion is, as will be discussed later, a consequence of the lower equilibrium concentration.

Effect of Halogenide Ions

If the reaction is carried out in the presence of complexing agents which have a greater affinity towards palladium than hydroxyl ion or water, these complexing agents replace the latter and render exchange with the olefin more difficult.

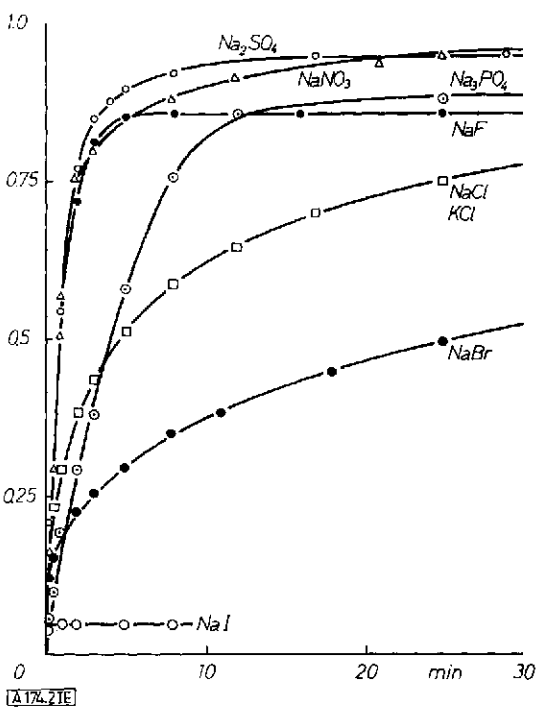


Fig. 2. C_2H_4 absorption in $^1/_{10}$ M $PdCl_2$ solution at 20 °C. Effect of alkali salts (0.4 N). In the ordinate direction the ethylene absorption is plotted in moles C_2H_4/mole $PdCl_2$.

Such complexing agents are, for example, halide ions which form halogeno complexes with palladium (II) [5]. While fluoride ions hardly impede complex formation with the olefin, the chloride, bromide, and iodide ions do so increasingly, *i.e.* they shift the equilibrium of complex formation in the direction of dissociation. This

[2] *F. C. Phillips*, Amer. chem. J. *16*, 255 (1894); *S. C. Ogburn, Jr.* and *W. C. Brastow*, J. Amer. chem. Soc. *55*, 1308 (1933).

[3] *J. Smidt* and *R. Jira*, Chem. Ber. *93*, 162 (1960).

[4] *M. S. Kharasch, R. C. Seyler*, and *F. R. Mayo*, J. Amer. chem. Soc. *60*, 882 (1938).

[5] Compare *H. A. Droll, B. P. Block*, and *W. C. Fernelius*, J. physic. Chem. *61*, 1000 (1957).

complex or substitution equilibrium of the ligands can be formulated as follows:

(6) $[PdCl_4]^{2-} + C_2H_4 \rightleftharpoons [PdCl_3C_2H_4]^- + Cl^-$ ("complex formation")

Other anions, which form complexes less readily, such as sulfate, nitrate, and perchlorate ions, do not interfere in limited concentrations. Phosphate and iodide ions impair absorption because of partial precipitation of their palladium salts.

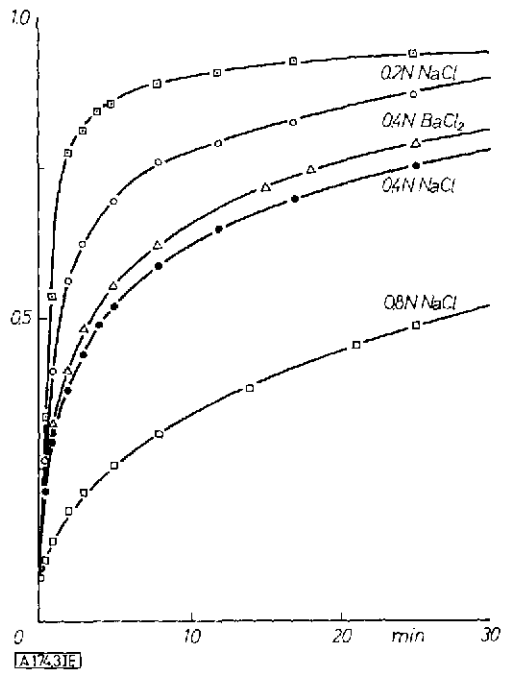


Fig. 3. C_2H_4 absorption in 0.1 M $PdCl_2$ solution at 20 °C. Effect of the Cl^- ion concentration.
Ordinate: ethylene absorption in moles C_2H_4/mole $PdCl_2$.

The influence of increasing concentration of chloride ions is shown in Figure 3.

If solutions of palladium sulfate, nitrate or phosphate are allowed to react with the olefin in place of palladium chloride, the OH^- or water co-ordinated central ion is in a position to take up more than 1 mole of olefin.

This is especially pronounced with palladium sulfate which absorbs more than 1.5 moles of ethylene per mole

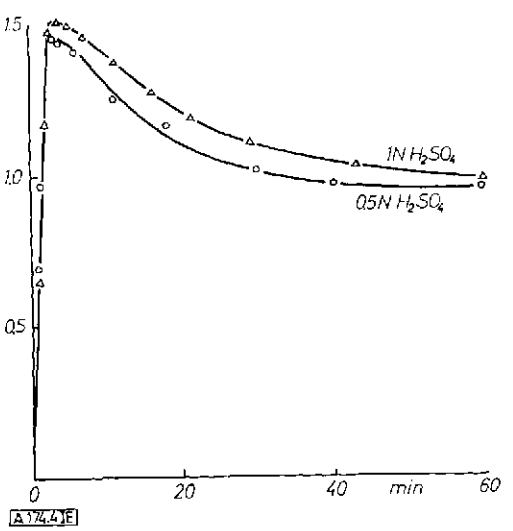


Fig. 4. Ethylene absorption in 0.1 M. $PdSO_4$ solution.
Ordinate: Ethylene absorption in moles C_2H_4/mole $PdSO_4$.

of palladium within a short time. Excess olefin is again desorbed with increasing hydrolysis of the complex and the absorption converges back to the stoichiometric value. Even small amounts of Cl^- ions nullify this phenomenon. The absorption then proceeds as usual.

Effect of Temperature

The overall reaction consists of the two partial reactions, complex formation (equation 6) and hydrolysis of the complex to the carbonyl compound:

$$[PdCl_3C_2H_4]^- + H_2O \longrightarrow C_2H_4O + Pd + 3\,Cl^- + 2\,H^+ \qquad (7)$$
(complex hydrolysis)

The course of the olefin absorption at different temperatures allows a qualitative statement as to which of the two partial reactions is the rate-determining step.

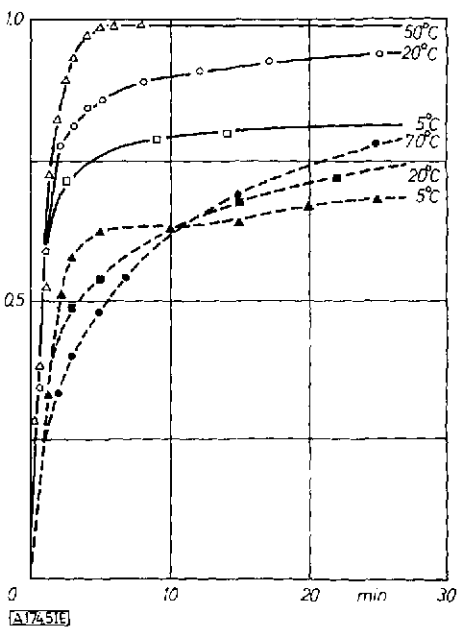


Fig. 5. Olefin absorption in 0.1 M. $PdCl_2$ solution.
Effect of Temperature
— — — = ethylene
------ = butene
Ordinate: Olefin absorption in moles olefin/mole $PdCl_2$.

Ethylene and butene are absorbed very rapidly at low temperatures, for instance, at 5 °C until the equilibrium concentration of olefin is reached according to equ. 6 (see Fig. 5). Subsequent absorption corresponds to the re-formation of the complex and proceeds according to the rate of hydrolysis of the complex. This is very slow at this temperature and therefore determines the rate of the reaction. The absorptions of ethylene and butene differ due to the different stability of their complexes.

Raising the temperature shifts the equilibrium of the complex formation to the left (equation 6), *i.e.* the equilibrium concentration of the olefin complex and the olefin absorption are decreased. Simultaneously, the rate of hydrolysis is increased.

The initially steep curve representing the olefin absorption flattens out due to the decreased concentration of the complex with an increase in temperature, while an increase in the rate of hydrolysis causes the originally flat part of the curve, which represents the hydrolysis,

to rise increasingly. Consequently, the temperature curves for the absorption cross each other. This is clearly seen with butene.

With ethylene both the equilibrium concentration of the complex and the rate of hydrolysis of the complex are higher than with butene. The absorption and reaction is completed within a few minutes. Therefore, the rate of the over-all reaction is determined by the hydrolysis step. At low temperatures, it corresponds to the flat part of the curve; at higher temperatures, it is increasingly represented by the complete curve.

Effect of the Hydrogen Ion Concentration

Figure 6 shows the inhibiting effect of hydrogen ions on this reaction. The absorption decreases with increasing concentration of HCl and stops almost completely with 4 N HCl. Two delaying effects combine;

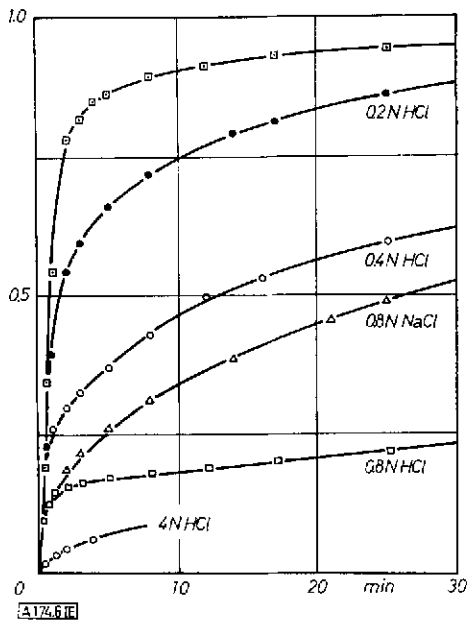


Fig. 6. C_2H_4 absorption in 0.1 M. $PdCl_2$ solution at 20 °C. Effect of the HCl concentration.
Ordinate: Ethylene absorption in moles C_2H_4/mole $PdCl_2$.

the one is that of the Cl^- ions which reduces the concentration of the complex and the other that of the hydrogen ions which reduce the hydrolysis rate of the complex. For comparison, the absorption in the presence of sodium chloride is shown. By analogy with the hydrolytic stability of Zeise's salt in acid solution as observed by *Chernayev* and *Hel'man* [6], we assume that the hydrolysis of the palladium complex is retarded by protons. They impede the nucleophilic attack of OH^- ions which initiate the hydrolytic cleavage [6a].

[6] *I. I. Chernayev* and *A. D. Hel'man*, Izvestiya Sektora Plat. *14*, 96 (1937).

[6a] Added in proof: During the printing of this communication, a publication by *Warhaftig*, *Moiseer*, and *Sirkin* (Doklady Akad. Nauk S.S.S.R. *139*, 1396 (1961)), has come to our notice. The authors found that the rate of oxidation of cyclohexene to cyclohexanone in dilute solutions of $PdCl_2$ and benzoquinone is independent of pH. This stands in contrast to our findings. It is not to be assumed that the reaction mechanism is different in both cases. These differences can be attributed to the nature of the palladium chloride complexes present whereby the effect which is exerted on the reaction rate by the palladium ligands (Cl^-, OH^-, H_2O) must be taken into account.

The hydrolysis of olefin complexes to the carbonyl compounds proceeds at different rates. For instance, it is possible to observe the complex for a short period of time as a brown precipitate which forms when butene is introduced into a hydrochloric acid solution of palladium chloride below room temperature. With ethylene, metallic palladium is precipitated instantly. In heavy water, however, the ethylene complex appears briefly on account of a lower hydrolysis rate due to the kinetic isotope effect. The attempted isolation of these compounds has so far failed due to experimental difficulties. The decreased stability of the complexes of the higher olefins (equilibrium of complex formation) and, on the other hand, the increased resistance of the complexes towards hydrolysis (complex hydrolysis) are essentially the reasons why olefins with increasing chain length react at a decreasing rate with palladium chloride.

Mechanism of the Complex Hydrolysis

Ethylene yields acetaldehyde in this reaction. Other unsaturated compounds yield carbonyl compounds with the oxygen bound to the C atom which takes up the OH group during the acid-catalyzed addition of water according to Markownikoff's rule. Attempts have been made previously to determine the mechanism of the formation of carbonyl compounds in the case of the more stable platinum compound, Zeise's salt. *Chatt* and *Duncanson* [7] assumed that the first step is a dissociation of Zeise's salt into ethylene and platinum chloride whereupon the liberated olefin is hydrated to alcohol. This is subsequently dehydrogenated by the platinum chloride to acetaldehyde. Because ethanol reacts considerably more slowly with palladium chloride than ethylene, and because alcohol is found only in traces in the technical aldehyde process, it is concluded that the hydrolysis of the complex must proceed in a different manner. *Joy* and *Orchin* [8] also arrived at the conclusion that ethanol is not formed as an intermediate in the hydrolytic decomposition of Zeise's salt.

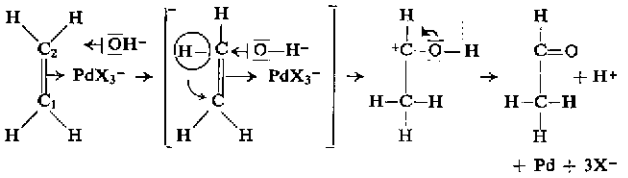
The observation that the hydrolysis is retarded by acids, and considering that the olefin has a partial positive charge within the complex, led to the assumption that the initial step is an addition of an OH^- ion to the complexed olefin [1]. The mechanism can be interpreted as a complete transfer of the π-electron pair of the olefin to the Pd, if there is a possibility for the simultaneous migration of a hydride ion from C-2 into the electron gap formed at C-1. A double bond is then formed between C-2 and oxygen with simultaneous repulsion of the proton from the oxygen atom.

Although the reaction takes place in an acid medium we prefer the formulation with OH^- as the attacking species, because this explains satisfactorily the inhibiting influence of H^+ ions without the necessity of assuming a further intermediate which can interact with the reaction medium. The possibility also exists that the re-

[7] *J. Chatt* and *L. A. Duncanson*, J. chem. Soc. (London) 2942 (1953).

[8] *I. R. Joy* and *M. Orchin*, Z. anorg. allg. Chem. *305*, 236 (1960).

action is initiated by the hydroxo ligands of the palladium which are present at this pH [9]. Nucleophilic attack on the olefin and hydride transfer are characteristic for this reaction.



The oxygen required for the oxidation of the olefin is provided by the water. According to our hypothesis only the oxygen atom of the water is transferred to the olefin while the 4 H atoms originally present in ethylene remain there. Furthermore, this hypothesis concerning the mechanism of the complex hydrolysis was supported by the hitherto unpublished work of Dr. *Krekeler* and coworkers (Farbwerke Hoechst) who found that the binuclear C_2H_4–$PdCl_2$ complex, discovered by *Kharasch*, results in an acetaldehyde, the mass spectrogram of which shows no deuterium after the complex has been hydrolysed with less than stoichiometric amounts of 85 % heavy water.

This result was confirmed by us when we repeated this experiment with 99.7 % D_2O [10]. A certain H–D exchange does take place [11]. This can be largely eliminated by working at a low temperature (5 °C) and by employing short reaction times, attainable by neutralizing the hydrochloric acid being liberated with NaOD in smaller than stoichiometric amounts.

The results of these experiments with deuterium exclude mechanisms with vinyl alcohol as an intermediate as proposed by *Moiseev, Warhaftig* and *Sirkin* [12]. They postulated that one H atom of the acetaldehyde originates from the water, *i.e.* with heavy water the methyl group of the resulting acetaldehyde should carry a deuterium. However, this was not found to be the case.

The results obtained with other unsaturated compounds are also in agreement with our ideas about the mechanism of this reaction.

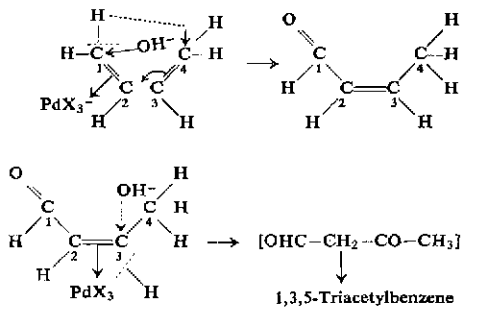
With asymmetrically substituted double bonds, the nucleophilic addition of the OH^- ion takes place predominantly at that C atom of the double bond from which the hydride ion is more readily removable.

Double bonds substituted by alkyl or aryl groups add the OH^- ions predominantly to the C atom which carries either one or the other substituent. In this way, for example, α-olefins react to form methyl ketones, styrene forms acetophenone, etc.

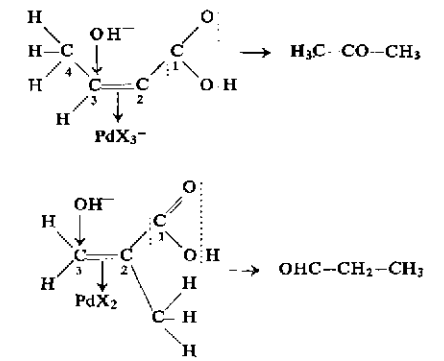
In addition to the methyl ketones, α-olefins also yield the corresponding aldehydes in lower amounts. This reaction can be influenced to a certain extent. With styrene the reaction can be conducted in such a way that phenylacetaldehyde is the main product. This will be reported elsewhere [13].

Groups such as C=C, C=O, COOH and NO_2, on the other hand, direct to the C atom of the double bond which does not carry these groups [14].

Butadiene is typical of a simple olefin with a C=C adjacent to the double bond and which gives crotonaldehyde in the first step (addition to C-1, compare 1,4-addition) [13]. This reacts once more with $PdCl_2$. The newly formed carbonyl group directs the addition of the second OH^- ion to C-3. Consequently 3-ketobutyl aldehyde is formed. This can be isolated as 1,3,5-triacetylbenzene in an acid medium which promotes condensation. The reaction of 2,3-unsaturated acids to keto acids can be explained in the same way with subsequent decarboxylation.



In the case of crotonic acid, both substituents at the double bond, namely, methyl and carboxyl, direct to C-3 which after decarboxylation yields acetone. On the other hand, in the case of the isomeric methacrylic acid, propionaldehyde is formed on decarboxylation since the carboxyl group exerts a directing effect to the C-3 atom and it is only from this site that a hydride ion can be removed.



Most unsaturated compounds react according to this mechanism but not all cases are equally clear. Often the normal course of the reaction is obscured by side-reactions such as hydrolysis, hydrogenation, decarboxylation, condensation, etc. Further examples of the formation of carbonyl compounds can be found under references [1] and [14].

[9] Comp. *I. Landen* and *J. Chatt*, J. chem. Soc. (London) 2936 (1955) and [8].

[10] We are much obliged to Dr. *H. Krekeler* for giving us the opportunity to carry out mass spectrographic investigations at the Farbwerke Hoechst. We also thank Dr. *Kleinpaul* (Consortium für elektrochem. Industrie G.m.b.H.) who did the infrared spectroscopy.

[11] *R. Klar*, Z. physik. Chem. Abt. B *26*, 335 (1934).

[12] *J. J. Moiseev, M. N. Warhaftig*, and *J. H. Sirkin*, Doklady Akad. Nauk UdSSR *130*, 820 (1960); *133*, 377 (1960).

[13] *W. Hafner, R. Jira, J. Sedlmeier*, and *J. Smidt*, Chem. Ber., in the press.

[14] See also *J. Smidt* and *R. Sieber*, Angew. Chem. *71*, 626 (1959).

Side-Reactions

The hydrolysis of the olefin-$PdCl_2$ complex can proceed as discussed only if the carbon atom which is subject to the nucleophilic addition, is linked to a hydrogen atom in order that it may be transferred as a hydride ion to the other carbon atom of the double bond. The normal complex hydrolysis cannot occur if no hydrogen is linked to the carbon atom as, for example, with isobutene and alternative reactions take place. Only the reaction leading to aldehyde and yielding a small amount of isobutyraldehyde follows this mechanism. The main reaction is an acid-catalyzed hydration to t-butanol and $PdCl_2$ has no substantial part in the reaction. Among other compounds some methacrolein is formed.

The formation of acetone as a by-product during the reaction of isobutylene with palladium chloride is surprising. This is favored by low H^+ and Cl^- ion concentrations. Under similar conditions, unbranched α-olefins form, to a small extent, aldehydes having one C atom less than the original olefin. This seems to be a general side-reaction caused by a splitting of the C=C double bond.

II. Non-Oxydative Reactions of Palladium Salts with Unsaturated Compounds

Complex Formation

As mentioned before, the formation of the complex by the absorption of the olefin in the $PdCl_2$-containing solution is subject to a reversible equilibrium. If hydrolysis is impossible due to the absence of water, the olefin can be desorbed by heating of the solution. $PdCl_2$ is not reduced in this case. Use can be made of this fact in order to carry out olefin separations. Olefins which are in contact with such solutions at elevated temperatures for a long time undergo partial polymerisation. Generally dimers are formed.

Another type of complex is obtained by reacting isobutylene with an acetic acid-acetate buffered aqueous palladium chloride solution. Up to 80 % of the palladium salt appears in the form of the methylallyl complex $[C_4H_7PdCl]_2$. This complex contains the olefin as an anion [15]. We produced the same type of complex for the first time from allyl and crotyl alcohol with anhydrous palladium chloride [16].

With cyclopentadiene, a compound having the composition C_5H_5PdCl [17] is obtained, but no carbonyl compound.

Transesterification and Saponification

The group of reactions in which palladium is not reduced, also includes the vinylation of carboxylic acids with vinyl esters of other carboxylic acids and the saponification of vinyl esters. The new vinyl esters are formed within a short time in very good yields when vinyl ester and carboxylic acids are reacted with palladium salts according to equation 8

$$(8)\quad RCOOCH{=}CH_2 + R'COOH \overset{PdX_2}{\rightleftharpoons} RCOOH + R'COOCH{=}C$$

The reaction proceeds well at room temperature. Higher temperatures, of course, accelerate the attainment of the equilibrium. Compounds of the other platinum metals, in particular those of platinum and rhodium, are also good catalysts. Examples for these generally applicable reactions are given in Table 1.

Working with aqueous $PdCl_2$ results in hydrolysis which is faster than with acids of the same concentration. Vinyl esters and vinyl halides yield acetaldehyde; α-methylvinyl esters yield acetone.

Table 1. Preparation of Vinyl Esters by Transvinylation in the Presence of Platinum Metal Salts

Acid	Mole ratio Vinylacetate/ Acid	Moles of catalyst × 10^2 /mole of acid	Temp. [°C]	Time [hrs.]	Conversion [%]	Yield [%]	b.p. [°C/mm. Hg]	Remarks
Propionic acid	3	Pd 0.5	76–80	3	45	96	93/720	$n_D^{20} = 1.4062$
Propionic acid	3	Pt 0.5	76–80	5	38	97		
Lauric acid	3	Pd 1.4	76–80	5	77	98	107–109/2	$n_D^{20} = 1.4439$
Lauric acid	6	Pd 1.4	25	8	55	96		
Lauric acid	3	Rh 1.3	76–80	5	28	99		
α-Chloropropionic acid	3	Pd 0.5	76–80	2	65	95	33/10	$n_D^{21} = 1.4356$
Crotonic acid	3	Pd 0.8	76–80	5	55	90	92/200	
Sorbic acid	3	Pd 1.0	76–80	4	39	92	53–54/1	$n_D^{20} = 1.5145$
Stearic acid	6	Pd 1.4	76–80	3.5	70	90	203/5	
Oleic acid	3	Pd 1.6	76–80	5.5	70		171–175/2	
Benzoic acid	3	Pd 1.2	76–80	3	53	98	81/9	$n_D^{20} = 1.5272$
Adipic acid monoester	4.5	Pd 1.0	80–90	2.5	38	95	127/1.5	m.p. 38 °C
Adipic acid diester					42		89–90/1.5	$n_D^{20} = 1.4541$
ε-Phthalimidocaproic acid	6.5	Pd 0.8	76–80	4	53	98		m.p. 51 °C

In analogy with the formation of carbonyl compounds during the hydrolysis of olefin complexes, we assume here also a nucleophilic attack by a carboxylate or a hydroxyl anion at the complexed vinyl ester.

[15] Unpublished work by Dr. *H. Anselm*, Consortium für elektrochem. Industrie, see note [16]. Compare also *R. Huettel, J. Kratzer*, and *M. Bechter*, Chem. Ber. *94*, 766 (1961).

[16] *J. Smidt* and *W. Hafner*, Angew. Chem. *71*, 284 (1959).

[17] *J. Smidt* and *R. Jira*, Angew. Chem. *71*, 651 (1959).

The increasing retardation of the saponification of vinyl chloride by the hydrogen chloride being liberated may likewise indicate a mechanism via a palladium complex the formation and hydrolysis of which is inhibited by Cl^- and H^+ ions.

III. Olefin Oxidation in the Presence of Cupric Chloride

The palladium metal which is precipitated in a stoichiometric amount during olefin oxidation is reoxidized by cupric chloride in a continuous process.

Besides cupric chloride all other oxidants which have a redox potential higher than the one required for the transition $Pd^0 \rightleftharpoons Pd^{II}$ can be used. However, $CuCl_2$ is best because CuCl can be very easily reoxidized by oxygen.

(1) $C_2H_4 + PdCl_2 + H_2O \longrightarrow C_2H_4O + Pd + 2\,H^+ + 2\,Cl^-$

(2a) $Pd + 2\,Cu^{2+} + 6\,Cl^- \longrightarrow PdCl_2 + 2\,[CuCl_2]^-$

---

(9) $C_2H_4 + 2\,Cu^{2+} + 4\,Cl^- + H_2O \xrightarrow{PdCl_2} C_2H_4O + 2\,H^+ + 2\,[CuCl_2]^-$

During this reaction Cu^{2+} is reduced stoichiometrically according to the amount of carbonyl compound being formed and at lower concentrations remains in solution as the dichloro complex. Substantial reduction results in a precipitation of CuCl which is favored by low Cl^- concentrations. Palladium chloride now functions as a catalyst. Even very low Pd concentrations allow the reaction of large amounts of ethylene per unit time. Due to spontaneous oxidation, metallic Pd is not precipitated at all if there is enough $CuCl_2$ present. This lack of precipitation of Pd is a determining factor for a uniform reaction. In addition it proves that the reaction at the palladium is the slower step which determines the rate of the over-all reaction [9]. Therefore, principally the same aspects hold with regard to the influence of Cl^- or H^+ concentration and temperature for the reaction with $PdCl_2$ in the presence of $CuCl_2$ as is the case for the reaction with $PdCl_2$ alone.

The concentration of $PdCl_2$ remains constant during the reaction of the olefin according to equation 9. However, the concentrations of the H^+ and Cl^- ions change; as mentioned, both retard the reaction considerably.

This effect during the reaction is shown in Figure 7. The upper graph shows the ethylene absorption (absorption per 10 min.), which is here equal to the rate of the reaction, plotted against the degree of oxidation of the solution which is expressed as the mole fraction $[Cu^{2+}]/([Cu^{2+}] + [Cu^+])$.

If the reaction is carried out in the presence of pure $CuCl_2$, the rate decreases rapidly immediately after starting. Reducing the Cl^- concentration in the catalyst solution, for example by partial replacement of $CuCl_2$ with copper acetate or copper oxychloride, causes a considerable increase in the rate of the reaction with decreasing Cl^- concentration. Simultaneously, the pronounced decline is shifted towards lower degrees of oxidation.

The increase in the rate of the reaction cannot be explained merely by a decrease of the Cl^- ion concentration because in the technical catalyst it exceeds the Pd^{II}

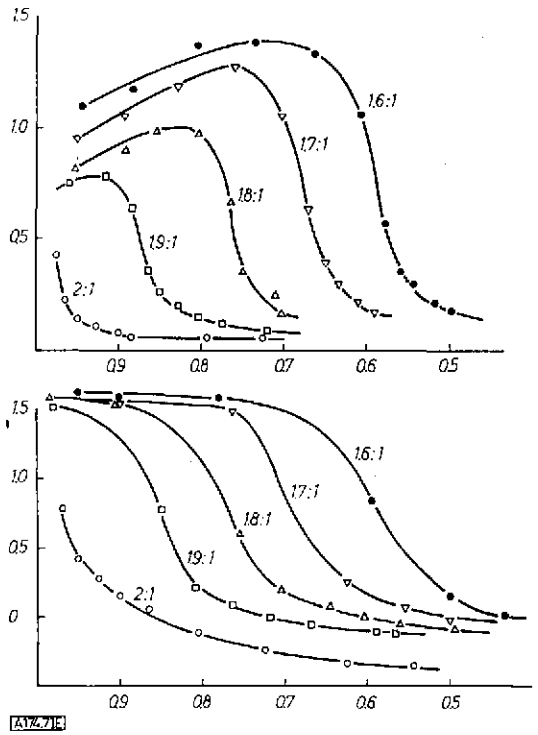


Fig. 7. Relation between rate of reaction and pH value. The figures on the curve indicate the ratio Cl/Cu.
Abscissa : $\frac{Cu^{2+}}{Cu\ total}$
Ordinate in the upper part of the figure : mmoles C_2H_4/10 min.
Ordinate in the lower part of the figure : pH

concentration by a factor of 200–400. A change of the Cl^- concentration by 10 to 20 % cannot produce such an effect.

However, if the pH value during the reaction is considered it becomes apparent that a steep decline, *i.e.* an increase in the H^+ concentration occurs at exactly the same degree of oxidation at which the rate of the reaction falls off.

The pH curves are neutralization curves because of their shape and their significance. The H^+ ions liberated in the reaction neutralize the basic copper salt; the latter is present when the Cl^- concentration is lower than required stoichiometrically for $CuCl_2$. The increase in H^+ ion concentration by one to two powers of ten has a correspondingly strong effect on the rate.

For a technical process the region of high pH value, *i.e.* high reaction rate, is of great importance.

Another factor intervening in this process is that ethylene does not only form complexes with $PdCl_2$ but also with CuCl. The increase of the CuCl concentration during the reaction is accompanied by an increase of the ethylene concentration in the solution. However, the copper complex is less stable than the Pd complex and can transfer its ligands easily to the Pd.

The oxidation of cuprous chloride with oxygen or air according to equation (3a) proceeds rapidly and to completion.

$2\,[CuCl_2]^- + 2\,H^+ + {}^1/_2\,O_2 \longrightarrow 2\,Cu^{2+} + 4\,Cl^- + H_2O$ (3a)

If it is carried out under conditions (pressure, temperature) comparable to the olefin conversion, the reaction rates are of the same order of magnitude.

IV. Technical Processes

There are two possibilities for the combination of both steps, *i.e.* reaction (8) and oxidation (9), to a continuous process.

(1) The one-stage process: Olefin and oxygen are reacted simultaneously with the catalyst solution, and,

(2) The two-stage process: The olefin is first allowed to react with the catalyst solution, then the carbonyl compound formed is separated and finally the reduced solution is oxidized by oxygen or air.

In the two-stage process, the reaction proceeds stoichiometrically with respect to copper according to equation 9. Therefore, a high Cu concentration is advantageous because it allows high ethylene conversion per volume of catalyst. One can select a wide range of high reaction rates as well as a high absolute rate of reaction by using a low Cl/Cu ratio thereby shortening the reaction time which is of importance for an economical process.

However, the Cl/Cu ratio cannot be reduced at random because the useful range, *i.e.* the oxidation capacity of the catalyst, is limited not only by the pH change, but in the case of low chloride content, even more so by the precipitation of cuprous chloride and later on even of metallic Pd. The precipitation of copper oxychloride imposes a limit towards higher degrees of oxidation.

Of course, all measures which decrease the pH value are detrimental to the reaction. The addition of mineral acids in order to avoid precipitation of copper oxychloride reduces the absolute rate as well as the range of high rate. Even acetic acid, which is a by product during the production of acetaldehyde acts as a strong acid due to its strong affinity to copper according to equation 10 and has to be continuously removed from the catalyst.

(10) $CuCl_2 + 2\,CH_3{\cdot}COOH \rightleftharpoons Cu(CH_3{\cdot}COO)_2 + 2\,HCl$

To a certain extent cupric chloride itself interferes due to hydrolysis.

Because ethylene and oxygen react separately, the concentrations of all reactants except $PdCl_2$ change continuously during the reaction and oxidation. Consequently, the two-stage process is characterized by periodic changes in the degree of oxidation of the catalyst solution. The redox potential for the transition of Cu^{II} to Cu^{I} according to equation (11) can be considered a measure of the degree of oxidation of the solution at any time. This is essentially determined by the concentration of Cu^{II} and Cu^{I}.

$$Cu^{2+} + 2\,Cl^- + e^- \rightleftharpoons [CuCl_2]^- \quad (11)$$

Measurement of the potential is a valuable means of controlling the reaction and allows automatic handling of a technical installation.

In the one-stage process, reaction and oxidation occur simultaneously. Depending on the reaction conditions such as pressure and temperature, a steady state is obtained which is characterized by the fact that the reaction and oxidation proceed at an equal rate. The expression "steady state" means that the concentrations of all catalyst components remain constant. Therefore, the one-stage process is characterized by a constant degree of oxidation of catalyst.

It is necessary for the steady state to fall within the range of high reaction rate. This can be achieved by varying the Cl/Cu ratio as well as the gas composition. Because low oxygen concentrations are preferred (due to the explosion limits of the ethylene-oxygen mixture) the one-stage process calls for operation at a higher Cl/Cu ratio than the two-stage process, thereby avoiding a decline of the steady state to degrees of oxidation which cause precipitation of CuCl. In the one-stage process the reaction also proceeds catalytically with respect to the copper in the catalyst and therefore, only a lower total concentration of copper is required.

Both possibilities, namely reacting C_2H_4 and O_2 together or separately, have been worked out as technical processes. We have concerned ourselves with both possibilities but concentrated essentially on the two stage process [18, 19].

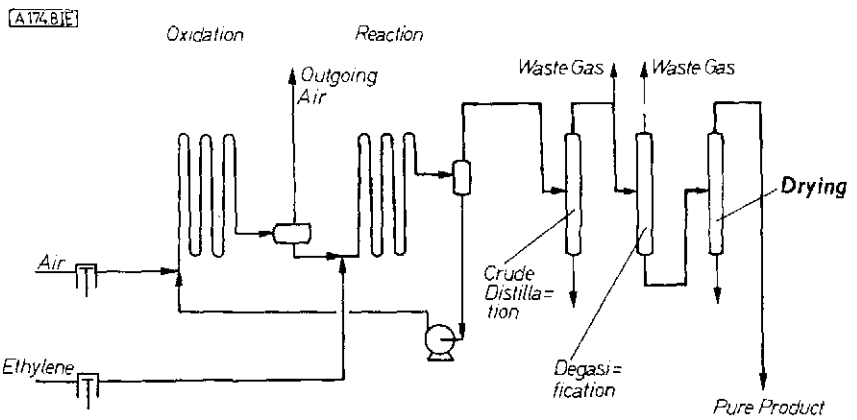


Fig. 8. Diagramatic representation of the two-stage process

Ethylene is more than 99 % converted when passed once (together with the catalyst solution) at moderate pressure and medium temperatures, through a flow reactor. The acetaldehyde formed distills off after releasing the

[18] The "know-how" of the one-stage process has been worked out by Farbwerke Hoechst.

[19] The technical development of the procedure was in the hands of Direktor *W. Fritz*, Obering. *F. Gerstner*, Dr. *J. Poßberg* (Wacker-Chemie, Werk Burghausen) and Dipl.-Ing. *H. Kojer* (Consortium).

pressure because of the heat of reaction stored therein (58 kcal/mole AcH) and is concentrated by partial condensation to a highly concentrated crude product.

The catalyst solution from which the aldehyde has been removed is transferred with a circulating pump into the oxidation reactor. It flows back to the ethylene reactor after treatment with air. The conversion of oxygen from the air occurs to such an extent that the outgoing air can be used as a protective gas. By carrying out the reaction in two separate reactors and abandoning the use of a gas recycle it becomes possible to use ethylene from mixtures with other hydrocarbons.

as insoluble copper oxalate and is decomposed to CO_2 and cuprous chloride by separately heating a partial stream of the catalyst.

The catalyst solution is strongly corrosive to most metals but titanium is permanently resistant. The need to use titanium has resulted in the rapid development of refined machining techniques especially for the lining of the reaction vessels and for the construction of circulating pumps.

The direct oxidation of ethylene is of great interest to the chemical industry. It can be said today without exaggeration that this technique will not only compete

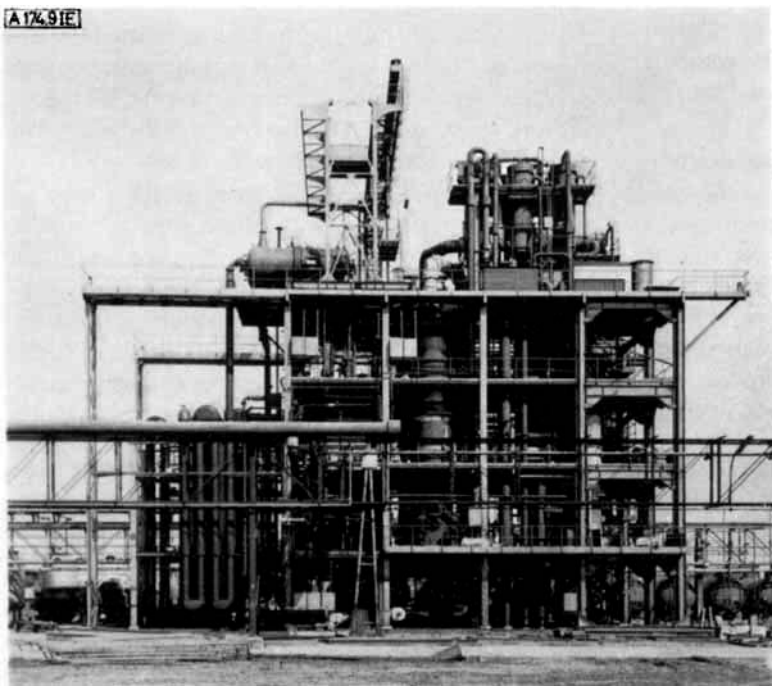


Fig. 9. Production plant for acetaldehyde from ethylene (two-stage process). Capacity per year *ca.* 15000 tons.

The aldehyde is purified in a two-step distillation. In the first, lower boiling by-products (CH_3Cl, C_2H_5Cl, CO_2) are separated; and in the second, higher-boiling by-products (chlorinated acetaldehydes, chloroform, methylene chloride, ethylene chloride, ethylene chlorohydrin, acetic acid, etc.) and water are removed. The purified product is then of the same quality as acetaldehyde from other processes.

In addition to the by-products mentioned, a small amount of oxalic acid is produced. This remains in the solution

favorably with the acetylene process but also more and more favorably with the conventional ethylene process. This is especially due to favorable yields low energy consumption and to the relatively low capital investment factor. At the present time installations are being built all over the world. In the future the complex reaction with $PdCl_2$ will be used for industrial oxidation of the next higher olefins to an ever greater extent.

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Organic N-Sulfinyl Compounds

BY PROF. DR. G. KRESZE, DR. A. MASCHKE, DIPL.-ING. R. ALBRECHT, DIPL.-ING. K. BEDERKE, Dr. H. P. PATZSCHKE, DIPL.-ING. H. SMALLA, AND DIPL.-ING. A. TREDE [*]

ORGANISCH-CHEMISCHES INSTITUT DER TECHNISCHEN UNIVERSITÄT BERLIN UND DER T.H. MÜNCHEN

The nitrogen-sulfur linkage in compounds of the type R–NSO is capable of undergoing addition. For N-sulfinylsulfonamides in particular, the reactivity is increased so greatly that new types of compounds may be obtained by cyclic addition or migration of the sulfinyl group.

In 1890, *Michaelis* and *Herz* [1] identified "thionylaniline" C_6H_5NSO as a product of the reaction of aniline with $SOCl_2$:

(1) $C_6H_5NH_2 + SOCl_2 \rightarrow C_6H_5NSO + 2\,HCl$

This substance has been described earlier by *Böttinger* [2] but with no statement concerning its structure. In a large number of subsequent publications, *Michaelis* has described the preparation of approximately seventy-five N-sulfinylamines of the type R–NSO and their reactions. This thorough exploration of the field, as well as the fact that the described reactions either led back to the amines, or else to products which could be obtained more easily by another route, explains why very little work was done with the N-sulfinyl compounds in the subsequent period. Only in the last few years have various groups made renewed studies of the structure and behavior of the organic *N*-sulfinyl compounds, and it is these studies in particular which are described here. The literature up to June 1958 is summarized in *Houben-Weyl* [3a] and is therefore only treated briefly; a survey of earlier works is also given by *Kennard* [3b]. A summary of the properties of the unsubstituted thionylimide has been given by *Goehring* [4].

A. N-Sulfinylamines and N-Sulfinylhydrazines

Most *N*-sulfinyl compounds known up to the present time are amine or hydrazine derivatives and are prepared from them.

1. Preparation and Properties

In the case of the amines, the preparation is usually carried out by reaction with thionyl chloride according to equation [1], using ether or benzene as solvent. For the aliphatic series, an excess of amine is necessary in order to take up the hydrogen chloride formed. Instead of this excess a tertiary amine may be added [5]. For the less basic aromatic amines, the hydrogen chloride is removed by boiling the reaction solution under reflux. An excess of $SOCl_2$ is generally used for the reaction, and instead of the free amine, its hydrochloride may be employed. For the aniline derivative, the yields are generally almost quantitative; in the case of the less stable aliphatic compounds, they are lower. If pyridine is added, the yield is between 35 and 65 % (based on the amine used).

N-Sulfinylaniline:

Aniline is dissolved in a five fold quantity of dry benzene. With cooling and stirring, a slight excess of $SOCl_2$ in twice its volume of benzene is slowly dripped into the solution. A large amount of finely divided aniline hydrochloride precipitates and the solution turns yellow to orange due to the formation of *N*-sulfinylaniline. The solution is heated under reflux on a water bath until the aniline salt is completely dissolved (3 to 6 hrs.). After the excess $SOCl_2$ and benzene have been distilled off, the *N*-sulfinylaniline is vacuum distilled; b.p. 80 °C/12 mm., yield 95 %.

N-Sulfinylcyclohexylamine [5]:

Thionyl chloride (11.9 g.) is added dropwise to a mixture of cyclohexylamine (9.9 g.) and pyridine (7.9 g.) in anhydrous benzene (50 ml.), and the amine hydrochloride is filtered off. With the customary procedure, 9.5 g. of thionylcyclohexylamine (65.4 %) are obtained; b.p. 78 °C/15 mm.

The method fails in the case of:

a) aromatic amino acids: since there is a partial formation of amides. *N*-Sulfinylamino acid chlorides may be obtained by the reaction of the Pb or Ag salt of the amino acid with $SOCl_2$ [6].

b) benzylamine [7], owing to a secondary redox reaction and the formation of benzaldehyde. (Analogously, benzophenone is obtained from benzhydrylamine [8]).

c) aminophenols [9], although anisidines, react normally [9]. Aniline derivatives in which a +M effect operates

[*] Dedicated with gratitude to Prof. Dr. *Helmut Scheibler* on his 80th birthday.

[1] *A. Michaelis* and *R. Herz*, Ber. dtsch. chem. Ges. *23*, 3480 (1890).

[2] *C. Böttinger*, Ber. dtsch. chem. Ges. *11*, 1407 (1878).

[3] a) Methoden der organischen Chemie (*Houben-Weyl*), 4th ed., Georg Thieme, Stuttgart 1958, Vol. 11/2, p. 738. b) *K. C. Kennard*, Organic Chemical Bull. *27*, No. 2 (1955).

[4] *M. Goehring*: Ergebnisse und Probleme der Schwefel-Stickstoff-Verbindungen. Akademie-Verlag, Berlin 1957.

[5] *D. Klamann, Chr. Sass*, and *M. Zelenka*, Chem. Ber. *92*, 1910 (1959).

[6] *L. Anschütz* and *H. Boedeker*, Ber. dtsch. chem. Ges. *62*, 826 (1929). *L. Anschütz* and *Z. M. Delijski*, Liebigs Ann. Chem. *493*, 241 (1932).

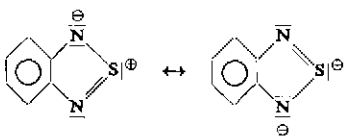
[7] *A. Michaelis* and *O. Storbeck*, Liebigs Ann. Chem. *274*, 197 (1893).

[8] *A. Michaelis*, Ber. dtsch. chem. Ges. *26*, 2162 (1893).

[9] *A. Michaelis* and *E. Haegele*, Liebigs Ann. Chem. *274*, 243 (1893).

react in a manner which gives rise to yields that are generally lower than normal [10].

d) *o*-phenylenediamine and its derivatives. No *N*-sulfinyl compounds are obtained with $SOCl_2$ or even SO_2, but rather "piazthioles" (benzo-2,1,3-thiadiazoles) [11, 12],



which should probably be formulated as mesoionic. Here, also, the yields may be increased by the addition of tertiary bases [13].

For sensitive amines, "trans-sulfinylation" which is based on the equilibrium

(2) $RNH_2 + R'NSO \rightleftharpoons RNSO + R'NH_2$

may be used to advantage. The lower the basicity of the amine $R'NH_2$ and the greater that of RNH_2, the more the equilibrium shifts to the right. Even the 4-hydroxy-, 4-mercapto-, 4-carboxy-, 4-sulfo-, 4-alkyl-, and 4-aminobenzo-2,1,3-thiadiazoles which cannot be obtained by other routes, as well as the corresponding disulfides, can be prepared from the phenylenediamines with *N*-sulfinyl-aniline [14]. Benzylamine reacts anomalously to form benzaldehyde or benzylidene aniline.

Finally, the probable formation of *N*-sulfinylbutylamine from the amine and ethyl ester of chlorosulfinic acid has been described [15].

$RNH_2 + ClSOOC_2H_5 \rightarrow RNSO + HCl + C_2H_5OH$

N-Sulfinylhydrazines RR'N–NSO (where R = aryl, R' = alkyl, H) can be prepared analogously to the *N*-sulfinylamines; their preparation is also possible from hydrazine and SO_2.

Aliphatic *N*-sulfinylamines with short alkyl chains are colorless liquids in the pure state, with a pungent odor. They fume in moist air and gradually decompose even when air and moisture are excluded, taking on a yellow coloration. They can be purified by distillation, the boiling points being about 50–60 °C higher than those of the corresponding amines. *N*-Sulfinyl-laurylamine is wax-like and decomposes in vacuum (0.01 mm.) at 120 °C [16].

The aromatic *N*-sulfinylamines and -hydrazines are yellow to orange-red liquids or well crystallizing solids with a pleasant odor. They may be purified either by distillation (boiling points 10 to 28 °C higher than those of the anilines), or by crystallization from non-polar solvents, and are more stable than the aliphatic derivatives.

[10] *A. Maschke*, Diploma Thesis, T.U. Berlin 1959.

[11] *A. Michaelis* and *A. Buntrock*, Liebigs Ann. Chem. *274*, 259 (1893).

[12] *R. Neef* and *O. Bayer*, Chem. Ber. *90*, 1141 (1957).

[13] *W. G. Pessin, A. M. Chaletzki*, and *Tschshao Tschshi-Tschshun* J. gen. Chem. (Moscow) *27* (*89*), 1570 (1957); Chem. Zbl. *1959*, 6131.

[14] *A. M. Chaletzki, W. G. Pessin*, and *Tschshao Tschshi-Tschshun*, Doklady Acad. Nauk S.S.S.R. *106*, 88 (1956); Chem. Zbl. *1956*, 9990.

[15] *G. Zinner*, Chem. Ber. *91*, 966 (1958).

[16] *R. Albrecht*, Diploma Thesis, T.U. Berlin 1960.

2. Physical Data and Molecular Structure

The structure of the *N*-sulfinyl compounds suggests comparisons with possibly analogous compounds. In this respect the following points are of interest.

a) *Kennard* [3b] pointed out some time ago, that there is a formal similarity between thionylamines and systems possessing cumulated double bonds (isocyanates, ketenes, isothiocyanates). The chemical properties, however, (compare Section A 3) do not indicate such an analogy.

b) A more useful comparison may be made with SO_2, whose organic imido derivatives are *N*-sulfinyl compounds. The latter are well suited for testing bonding conditions at the S atom: By a variation of the organic radical, electron enrichment or depletion will occur at the N–S bond; the influence of such polar effects as well as the conjugating power of the bond with adjacent π-electron systems can be easily studied.

c) It may be shown that *N*-sulfinylamines are comparable with *C*-nitroso compounds. While attempts to prepare the thio-analogs of the nitrosobenzenes, Ar–NS, were unsuccessful [17], the bond between the N atom and the SO group (which is much more strongly electronegative compared with S) is similar to that of the N=O bond.

These analogies are supported by the physical data obtained by studies of *N*-sulfinyl compounds.

Molecular Spectra

Infrared and Raman spectral data on aliphatic *N*-sulfinylamines [16, 18], indicate three bands which can be ascribed to the NSO group:

1245 to 1258 cm^{-1} ν_{as} (NSO)

1110 to 1136 cm^{-1} ν_s (NSO)

575 to 580 cm^{-1} δ (NSO)

The positions and relative intensities of these bands and Raman lines correspond to those of SO_2 (1361, 1151, and 519 cm^{-1}). This suggests a similarly-angled structure for the NSO group. *Glass* and *Pullin* [18] obtained data from measurements with *N*-sulfinyl methyl-, -ethyl-, and -phenylamines and estimate the angle between the NS and SO bond to be about 120 °.

For the aromatic *N*-sulfinylamines, one NSO band is blurred, but the position of the second band (range 1137 to 1178 cm^{-1}) can be clearly evaluated for substituted derivatives [19]. There is a linear relationship between the difference in wave number for compounds which are substituted in the *para*-position of the benzene ring ($\tilde{\nu}_{subst.}$) and the unsubstituted ($\tilde{\nu}_H$) compound, and the Hammett substituent constant σ:

$$\tilde{\nu}_{subst} - \tilde{\nu}_H = (25{,}1 \times \sigma) - 3$$

For *p*-nitro-*N*-sulfinylaniline, the band is at 1175 cm^{-1}, for *p*-dimethylamino-*N*-sulfinylaniline, 1137 cm^{-1}. Such

[17] *R. I. W. Le Fèvre*, J. chem. Soc. (London) *1932*, 2503.

[18] *W. K. Glass* and *A. D. E. Pullin*, Trans. Faraday Soc. *57*, 564 (1961).

[19] *G. Kreße* and *A. Maschke*, Chem. Ber. *94*, 450 (1961).

a strong dependence of the infrared band positions on the polar substituent effects has only been observed up to now for typical π-electron systems, *e.g.* with carbonyl compounds. In these latter compounds the dependence has its origins (at least in part) in the fact that the bond order can be changed relatively easily by a polar effect. Similar conditions may apply to the *N*-sulfinylanilines. Here also, nitrogen-sulphur bonded structures are probable in which the bonding electrons are very mobile and capable of interaction with the remainder of the molecule. This speaks against the concept of the N–S bond as a semi-polar system $R-\overset{\ominus}{\underline{N}}-\underline{\overset{\oplus}{S}}=O$ and for the presence of a "four-electron bond" without the state of the bonding electrons being determined.

Electron-attracting (acceptor-) substituents increase the bonding order of the N–S bonds, electron-repelling (donor) substituents decrease it.

Dipole Moments

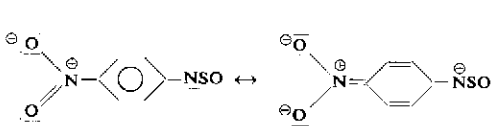
The dipole moments of the *N*-sulfinylanilines verify the assumptions made both with respect to the geometry of the NSO group and the conjugative power of the N–S bond with the aromatic systems: From the permanent moment of the *p*-phenylenediamine derivative it follows that the direction of the partial moment of the NSO group and the C–N bonding direction do not agree [20]; the angle between the two directions (assuming free rotation about the C_{ar}–N axis) is 37.1 ° [21].

Dipole moment data for substituted *N*-sulfinylanilines calculated with this value agree satisfactorily with the measured values for *meta*-substituted derivatives and for the *p*-methyl compound (Table 1), while dipole moments greater than those expeeted occur in *p*-nitro- and *p*-alkoxy-*N*-sulfinylanilines.

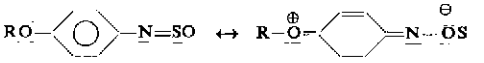
Table 1. Dipole moments of substituted *N*-sulfinylanilines $X-C_6H_4-NSO$ (in Debye units)

Substituent	μC_6H_6 (20 °C)	$\mu_{calc.}$	$\Delta\mu$
H	1.90	–	–
m-CH_3	2.14	2.09	+0.05
m-Cl	1.81; 1.75	1.93	−0.12 to
	1.72 (Dioxane)		−0.21
m-NO_2	3.50	3.66	−0.16
p-CH_3	2.40	2.23	+0.17
p-NO_2	3.20	2.71	+0.49
p-OCH_3	2.90	1.73	+1.17
p-OC_2H_5	3.06	1.73	+1.33

While the customary nitroaniline mesomeric structures can explain the polarity increase in the *p*-nitro derivative,



participation of the N=S-linkage in the conjugation must be assumed for the alkoxy compounds:



if the octet rule for the N atom is not to be violated.

Ultraviolet Spectra

Ultraviolet spectral studies [21–23] show that the conjugative ability of the N–S bond is particularly prominent. Aliphatic *N*-sulfinylamines in hexane solution show a strong absorption at 42500 cm^{-1} (235 mμ), log ε – 3.7, and a weak primary band at 32000 to 33000 cm^{-1} (300 to 310 mμ), log ε = 1.5 to 1.7. This long-wave absorption is much more intensive in the aromatic *N*-sulfinylamines (log ε ≈ 4); it depends on the type of ring substituent in the same way as the 31000 to 35000 cm^{-1} bands of nitrosobenzenes are associated with a $\pi \rightarrow \pi^*$-transition (Table 2).

Table 2. Long-wave absorptions for *N*-sulfinylamines ($X-C_6H_4-NSO$) and nitrosobenzenes ($X-C_6H_4-NO$) in heptane.

X	$X-C_6H_4-NSO$ $\tilde{\nu}_{max}$ [cm^{-1}]	log ε	$X-C_6H_4-NO$ $\tilde{\nu}_{max}$ [cm^{-1}]
m-NO_2	32680	3.92	–
m-Cl	32000	4.00	–
p-NO_2	31850	4.12	35500
H	31750	4.00	35460
m-CH_3	31350	4.00	35460
p-CH_3	30580	4.08	31745
p-CH_3O	27970	4.20	31250

An analogous correlation should therefore also be valid for the long-wave absorption of *N*-sulfinylanilines. The strong bathochromic effect in the *p*-alkoxy compounds then is a sign of mesomeric influence. In the sterically hindered 2,6-dimethyl- and 2,4,6-tribromo-derivatives, this $\pi \rightarrow \pi^*$-absorption is barely recognizable as a shoulder but, instead, an otherwise unobserved band at 27000 cm^{-1} (366 and 367 mμ, respectively) occurs.

In the *N*-sulfinylhydrazines [22b] – as with the nitrosamines – the absorption has changed in comparison to that of the sulfinylamines: The band at 32000 to 33000 cm^{-1} is also intensive for the aliphatic representatives (for $(CH_3)_2N-NSO$, log ε = 4.05); with aromatic radicals there is a strong bathochromic shift (27000 to 29500 cm^{-1}). Polar effects introduced by benzene ring substituents have, as expected, a much lesser (because indirect) influence than in the *N*-sulfinylamines.

Our knowledge of the structure of the NSO group, as obtained from the physical data, may be summarized as follows:

The group has – at least in the N–S bond – an easily polarizable electron system.

The N–S bond may be considered as a four-electron ("double") bond.

This bond may enter into conjugation with π-electron systems and groups which can act as donors. The order of the N–S bond is lowered through conjugation.

Acceptor groups as substituents at the N atom increase the bond order.

[20] *K. A. Jensen* and *N. Hofman Bang*, Liebigs Ann. Chem. *548*, 95 (1941).

[21] *G. Kreße* and *H. Smalla*, Chem. Ber. *92*, 1042 (1959).

[22] *G. Leandri* and *A. Mangini*, a) Ricerca sci. *27*, 1920 (1957); b) Boll. Sci. Fac. chim. Ind. Bologna *17*, 15 (1959); c) Spectrochim. Acta *1959*, 421.

[23] *W. T. Smith Jr.*, *D. Trimnell*, and *L. D. Grinninger*, J. org. Chemistry *24*, 664 (1959).

3. Reactions

Most reactions of *N*-sulfinyl compounds may be considered additions to the nitrogen-sulfur bond, or redox reactions in which the sulfur-oxygen bond participates. In these additions, one must differentiate between reaction with compounds of the type H–X, in which the S=O group is usually split off, and those addition reactions in which one N–S single bond is preserved.

Addition of Proton-Active Compounds to N-Sulfinylamines

Most reactions proceed according to the general scheme given in equation (3).

(3) $R-N=SO + 2\,HX \rightarrow RNH_2 + SOX_2$

where X=OH^-, halogen etc.

a) The simplest of these reactions is hydrolysis, which is apparently catalyzed by acids and bases. Aliphatic *N*-sulfinylamines are extremely sensitive to moisture whereas aromatic *N*-sulfinylamines are more stable in this respect. Compounds in which sterically hindered additions occur at the NSO group, such as is the case with *N*-sulfinylmesidine, may be steam distilled with no appreciable decomposition [24].

Michaelis [25] states that a 1:1:1 adduct is formed from *N*-sulfinylaniline, aniline and H_2O; *Jensen* [20] reports a red crystalline hydrate of *N*-sulfinyl-*p*-nitraniline. These claims, however, have not yet been verified [4, 26].

b) Alcoholysis [23, 27] proceeds analogously to hydrolysis. It has been proved qualitatively that electron-acceptor substituent groups in *N*-sulfinylamines increase the reactivity. The *O*-esters of *N*-substituted aminosulfinic acids, RNH–SOOR, which can be considered the primary products in the alcoholysis, are very unstable and react immediately [15].

c) "Trans-sulfinylation", *viz.* equation (2), can be used for the preparation of *N*-sulfinylamines as well as the -hydrazines [28]. These reactions also belong to the class of HX additions.

d) Reactions with dry hydrogen halide should be mentioned, *i.e.*

$RNSO + 3\,HCl \rightarrow RNH_2{\cdot}HCl + SOCl_2$ [25]

According to studies by *Smith* and *King* [30], this reaction also plays a role in the conversion (*Carré* and *Libermann* [29]) of *N*-sulfinylanilines to acid anilides using acids: pure compounds which are $SOCl_2$- and HCl-free do not react.

While no intermediate products before the cleavage of the two N–S bonds can definitely be characterized in the above additions, it is however possible to isolate a primary product from the reaction with mercaptans [31]:

$$Ar-N=SO + R-SH \rightarrow Ar-\underset{H}{N}-\underset{O}{S}-SR$$

Thioesters of *N*-arylaminosulfinic acid are obtained in an exothermic reaction if thiophenol or *p*-methoxythiophenol in less than stoichiometric quantities are allowed to drip slowly into a well cooled solution of *N*-sulfinyl-*p*-nitraniline; very unstable adducts are also formed in the reaction of ethylmercaptan with *N*-sulfinylaniline itself and with *p*-methoxythiophenol.

S-(p-Nitranilino)-S-(phenylthio)sulfoxide

N-Sulfinyl-*p*-nitraniline (18.5 g.) is dissolved in 40 ml. of dry acetone. With stirring, cooling (internal temperature <5 °C) and the continual passage of N_2, a solution of 11.0 g. of thiophenol in 20 ml. of anhydrous diethyl ether is slowly added over a period of 15 minutes. After another 15 minutes, $^2/_3$ of the solvent are removed, the rest of the reaction solution is added to a mixture of 25 ml. diethyl ether and 75 ml. petroleum ether (b.p. 50–80 °C) and then cooled with an ice/salt mixture. The slowly crystallizing precipitate is filtered with suction under nitrogen and washed with a small amount of cold, dry ethyl ether. It may be recrystallized by dissolving (25 °C) in a small amount of dry acetone, adding a petroleum ether-ethyl ether mixture until precipitation begins and then cooling to −20 °C in a deep-freeze unit (nitrogen atmosphere). Colorless, well-formed crystals are obtained m.p. 93 °C (decomp.); yield: 26.5 g. (90 %).

The N–S single bond in thioesters derived from *N*-substituted aminosulfinic acids is easily split; the reaction with mercaptans may be used for the preparation of asymmetrical alkylaryltrisulfides:

$R-NH-SO-SR' + R''SH \rightarrow RNH_2 + [R''-S-SO-SR']$;

$[R''-S-SO-SR'] + 2\,R''-SH \rightarrow$

$R''-S-S-SR' + H_2O + R''-S-S-R''$

$RNH-SORR' + 3\,R''SH \rightarrow$

$RNH_2 + R''-S-S-S-R' + R''-S-S-R'' + H_2O$

Isolation of the ester is not required.

Ethylphenyltrisulfide [26]

N-Sulfinylaniline (14 g.) is dissolved in dry diethyl ether (100 ml.) and the solution cooled to −15 °C. Thiophenol (11 g. in 25 ml. ether) is then added very slowly under an atmosphere of nitrogen followed after 5 minutes by a solution of ethyl mercaptan (18.6 g.) in acetone (50 ml.). One hour later the mixture is boiled under reflux for 15 minutes, allowed to cool and then shaken with 50 ml. portions of hydrochloric acid and water in a separatory funnel before drying over sodium sulfate. After filtration, the solvent is removed *in vacuo* and the residue fractionally distilled under high vacuum b.p. 67–69 °C/0.01 mm.; yield: 4.8 g. (24 %).

Tolyl trisulfide and disulfide are the products found by *Holmberg* [32] in the reaction of *N*-sulfinylaniline and *p*-thiocresol.

e) In the addition of sulfinic acids to *N*-sulfinylaniline, a complex secondary reaction occurs following a primary reaction which gives rise to a 1:1-adduct which has, so far, not been isolated [33]. "*p*-Toluene sulfinic acid anhydride," *S*-(*p*-tolyl)-*S*-(*p*-tolylsulfinyl)sulfone,

[24] *A. Michaelis* and *G. Junghans*, Liebigs Ann. Chem. *274*, 233 (1893).

[25] *A. Michaelis*, Ber. dtsch. chem. Ges. *24*, 745 (1891).

[26] *H. P. Patzschke*, Diploma Thesis, T.U. Berlin 1959.

[27] *W. T. Smith* and *L. D. Grinninger*, J. org. Chemistry *26*, 2133 (1961).

[28] *A. Michaelis* and *J. Ruhl*, Liebigs Ann. Chem. *270*, 114 (1892).

[29] *P. Carré* and *D. Libermann*, a) Bull. Soc. chim. France *6*, 579 (1939); b) C. R. hebd. Séances Acad. Sci. *194*, 2218 (1932).

[30] *W. T. Smith Jr.* and *G. G. King*, J. org. Chemistry *24*, 976 (1959).

[31] *G. Kreße* and *H. P. Patzschke*, Chem. Ber. *93*, 380 (1960).

[32] *B. Holmberg*. Ber. dtsch. chem. Ges. *43*, 226 (1910).

[33] *K. Bederke*, Diploma Thesis, T.U. Berlin 1961.

is obtained from *p*-nitrothionylaniline and *p*-toluenesulfinic acid in ether at −15 °C:

$$Ar{-}NSO + 2\,R{-}SO_2H \rightarrow ArNH_2 + R{-}SO{-}SO_2{-}R + SO_2$$

Its structure has been clarified by *Bredereck* et al. [34]. The formation of this compound can be explained by a sulfinylation of the sulfinic acid in the OH form:

$$Ar{-}NSO + 2\,HO_2SR \longrightarrow \left[\begin{matrix} R{-}S{-}O{-}S{-}O{-}S{-}R \\ \| \quad\quad \| \quad\quad \| \\ O \quad\quad O \quad\quad O \end{matrix}\right] + ArNH_2$$

$$\downarrow$$

$$\left[R{-}\overset{\oplus}{\underset{O}{\overline{S}}}\right] + SO_2 + \left[\overset{O}{\ominus SR}\right]$$

$$\downarrow$$

$$R{-}\overset{O}{S}{-}\overset{O}{S}{-}R + SO_2$$

The last step corresponds to that assumed by *Bredereck* [35] for the disproportionation of sulfinic acids. Similarly, here, the excess acid in the *p*-nitro-*N*-sulfinylaniline/sulfinic acid reaction mixture reacts with the sulfinyl sulfone at elevated temperature:

$$R{-}SO{-}SO_2{-}R + R{-}SO_2H \longrightarrow R{-}S{-}SO_2R + R{-}SO_3H$$

The corresponding thiolsulfonate and the sulfonic acid salts of *p*-nitraniline may be isolated after reaction in boiling ether.

f) Again, with phenylphosphine and phenylarsine, complex secondary reactions follow the addition:

$$C_6H_5{-}NSO + C_6H_5{-}PH_2 \longrightarrow [C_6H_5{-}NH{-}SO{-}PH{-}C_6H_5] \longrightarrow$$

$$C_6H_5{-}NH{-}\overset{OH}{\underset{\underset{S}{\|}}{P}}{<}_{C_6H_5} \quad \text{or} \quad C_6H_5{-}NH{-}\overset{SH}{\underset{\underset{O}{\|}}{P}}{<}_{C_6H_5} \qquad [36a]$$

$$C_6H_5{-}NSO + C_6H_5{-}AsH_2 \longrightarrow C_6H_5{-}NH_2 + [C_6H_5{-}As{-}SO]$$

$$2\,[C_6H_5{-}As{-}SO] + C_6H_5{-}AsH_2 \longrightarrow 2\,C_6H_5{-}AsS + C_6H_5AsO + H_2O \qquad [36b]$$

Addition of Organometallic Compounds

Both Grignard compounds [5, 37] and organolithium compounds [38] add to the N=S bond of the *N*-sulfinylamines. Careful hydrolysis of the adducts gives the sulfinic acid amides in good yield:

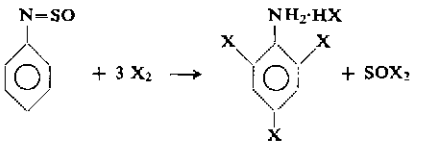
$$R{-}N{=}SO \xrightarrow[2.\ H_2O]{1.\ R'Li \text{ or } R'MgBr} R{-}NH{-}SO{-}R' + LiOH[Mg(OH)Br]$$

Sulfinamides [5]

N-Sulfinylamine (0.1 mole dissolved in ether) is added with stirring and ice cooling to the Grignard compound prepared from 0.11 mole of alkyl halide or aryl bromide and 2.7 g. of magnesium turnings in 100 ml. of absolute ether. The reaction product is best decomposed with ice-cold 10 % NH_4Cl solution. The solid sulfinamides are recrystallized from benzene. Yields are generally in the region of 60 to 90 %.

Addition of Halogens and Halogen-Carriers

The end products of the reaction of *N*-sulfinylaniline with chlorine or bromine are 2,4,6-trihalogenoanilines and thionyl halide:



Since the NSO group has an acceptor character (compare Section A 2), a ring substitution in *o*- and *p*-position is unlikely as a primary step. A cleavage of the N=S bond with the formation of an *N*-bromoaniline derivative which then quickly undergoes the Orton rearrangement must be considered. The behavior of *N*-sulfinyl-*N'*-phenylhydrazine in the presence of bromine [39] also confirms this idea, *viz.*

$$Ar{-}NH{-}N{=}SO + 3\,Br_2 \longrightarrow Ar{-}N_2^{\oplus}Br_3^{\ominus} + HBr + SOBr_2$$

In this reaction the diazonium perbromide is obtained. Analogically benzenediazonium chloride is formed the reactions with $SOCl_2$, PCl_3 or CH_3COCl [28], while *N*-sulfinylaniline with PCl_5 gives *p*-chloroaniline hydrochloride, $POCl_3$ and SCl_2. In the last reaction, $C_6H_5{-}N{=}SCl_2$ is thought to be the intermediate [40]. The fluorine analogs, $Ar{-}N{=}SF_2$, of this compound were recently obtained [41]. In the case of "piazthioles", chlorine or bromine is added to the benzene ring [42] and 4,5,6,7-tetrahalogeno-4,5,6,7-tetrahydrobenzo-2,1,3-thiadiazoles are formed; the chloro derivative yields dichlorobenzo-2,1,3-thiadiazole with alcoholic KOH.

Redox Reactions

Reactions in which the *N*-sulfinyl group first adds one reactant and then the product itself undergoes a disproportionation, have already been described (*viz.* reaction with mercaptans, phosphines, arsines). However, such less well-defined reactions as those of *N*-sulfinylanilines with arylhydroxylamines also belong to this group:

$$2\,C_6H_5{-}N{=}SO + 4\,C_6H_5{-}NHOH \longrightarrow$$

$$2\,[C_6H_5{-}NH_3^{\oplus}]\,[C_6H_5{-}NHSO_3^{\ominus}] + C_6H_5{-}N{=}N{-}C_6H_5$$

If the radicals in the sulfinylamine and the hydroxylamine are different, mixed azo compounds may be formed [43]. Redox reactions of the *N*-sulfinyl compound itself occur in the reaction with hydrazobenzene [40],

$$2\,C_6H_5{-}NSO + 2\,C_6H_5{-}NH{-}NH{-}C_6H_5 \longrightarrow$$

$$3\,C_6H_5{-}N{-}N{-}C_6H_5 + 2\,H_2O + 2\,S,$$

as well as in the reaction of *N*-sulfinyl-*N'*-phenylhydrazine with phenylhydrazine to form diphenyl disulfide

[34] *H. Bredereck, A. Wagner, H. Beck,* and *R.-J. Klein,* Chem. Ber. *93,* 2736 (1960).

[35] *H. Bredereck* et al., Angew. Chem. *70,* 268 (1958).

[36] *L. Anschütz* and *H. Wirth,* a) Naturwissenschaften *43,* 16 (1956); b) ibid. *43,* 59 (1956).

[37] a) *H. Gilman, J. E. Kirby,* and *C. R. Kinney,* J. Amer. chem. Soc. *51,* 2252 (1929). b) *H. Gilman* and *H. L. Morris,* ibid. *48,* 2399 (1926).

[38] *A. Schönberg* et al., Ber. dtsch. chem. Ges. *66,* 237 (1933).

[39] *A. Michaelis,* Ber. dtsch. chem. Ges. *22,* 2228 (1889).

[40] *A. Michaelis* and *H. Banch,* Liebigs Ann. Chem. *274,* 202 (1893).

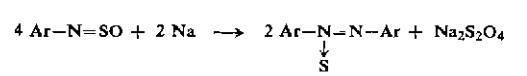
[41] *W. C. Smith* et al., J. Amer. chem. Soc. *82,* 551 (1960).

[42] *A. M. Chaletzki* et al., Doklady Acad. Nauk S.S.S.R. *113,* 627 (1957); Chem. Zbl. *1958,* 11224.

[43] *A. Michaelis* and *K. Petau,* Ber. dtsch. chem. Ges. *31,* 984 (1898).

[44], and in the thermal decomposition of *N*-sulfinyl-*N'*-phenylhydrazine [39] which leads to diphenyl sulfide, diphenyl disulfide, N_2, SO_2, and H_2O.

The reaction of *N*-sulfinylaniline with metallic sodium [45] proceeds relatively smoothly and yields the red azothiobenzenes.



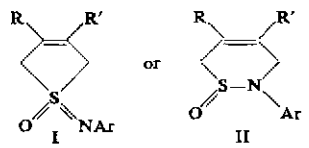
Azothiobenzene

N-Sulfinylaniline (10 g.) in 70 ml. of anhydrous toluene is added to 3.2 g of finely divided Na under xylene and the reaction mixture carefully heated. The exothermic reaction starts at the boiling point of the solution, with the mixture turning red. After the spontaneous boiling has stopped, the solution is heated for 15 minutes longer and is then cooled and filtered. After evacuating the solvent from the filtrate, azothiobenzene is obtained as a red liquid, b.p. 137.5 °C-15 mm.

N-sulfinylanilines, substituted with acceptor groups, (*o*-, *m*-, *p*-NO_2; *p*-C_6H_5CO; *p*-$C_6H_5SO_2$; *p*-NSO) do not give rise to azothiobenzene derivatives. *N*-Aryl-*N'*-sulfinylhydrazines behave differently in the same reaction: they yield the thiophenols Ar–SH and N_2 [45b, c]. Here, too, acceptor group-substituted compounds do not react.

Diels-Alder Reactions

Probably the most important preparative reaction of the *N*-sulfinylamines is the diene synthesis. Both compound types with which the R–NSO derivatives can be compared, namely sulfur dioxide and nitrosobenzenes [46a–c], react readily with dienes. Therefore, two main formulae must be considered for the structure of the adducts which are formed from the N-sulfinylanilines with butadiene or 2,3-dimethylbutadiene:



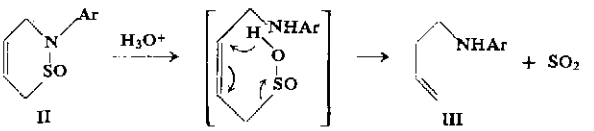
Wichterle and *Rocek* [47a, b], who first discovered the reactivity of the *N*-sulfinylanilines in the Diels-Alder reaction, verified structure II by the reactions and infrared spectra of the adducts. Only aromatic *N*-sulfinylamines react as dienophiles and, indeed, the nitro derivatives (with the relatively highest N=S bond order) do so somewhat better than the parent compound. Aliphatic *N*-sulfinylamines cannot be used as dienophiles.

3,6-Dihydro-4,5-dimethyl-2-phenyl-1,2-thiazine-1-oxide (II, R = R' = CH_3)

Approximately equimolar quantities of *N*-sulfinylaniline and dimethylbutadiene in cyclohexane are heated for 7 hrs. using a water bath (on heating to higher temperatures, violent decomposition occurs sometimes with the formation of asphaltlike sulfur-containing substances). The solvent and excess N-sulfinylaniline are removed in vacuum and the product is recrystallized from cyclohexane; m.p. 79.5 to 80.5 °C, crude yield 72 %.

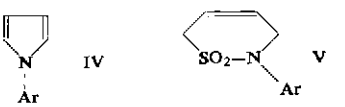
The 3,6-dihydro-1,2-thiazine-1-oxides (II), which are formed in the diene synthesis, may be converted into many new classes of compounds:

a) Acid hydrolysis, with cleavage of the N–S bond and loss of SO_2 leads to Δ^3-*N*-butenylanilines (III); the double bond shift has been formulated as follows [47a]:

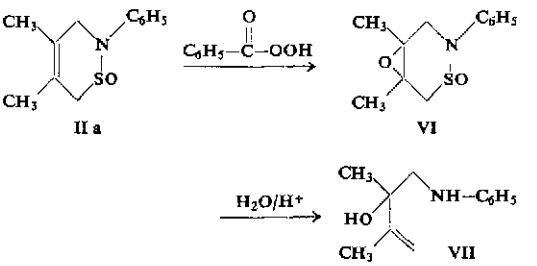


b) Alkaline hydrolysis (as well as treatment with Na ethoxide) yields *N*-aryl pyrroles (IV) [48].

c) Oxidation with H_2O_2 in aqueous alkaline alcohol with prolonged standing yields the sultams (V).

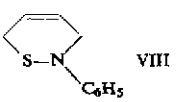


With benzoperacid, on the other hand, the dimethylbutadiene adduct yields a mixture of sultam and epoxide VI of the adduct, which gives 4-phenyl-amino-2,3-dimethylbutene-(1)-ol-(3) (VII) on hydrolysis.



With excess benzoperacid, the epoxide of the sultam is also obtained.

d) Reduction leads to a well-defined product only with $LiAlH_4$. In this case, *N*-phenyl-3,6-dihydro-1,2-thiazine (VIII) is formed.



The versatility of the adducts would be particularly useful if adduct formation were a general reaction. However, the reactivity of the N=S bond in the *N*-sulfinylanilines is much smaller than that of the N=O bond in the nitrosobenzenes (these react already at 0 °C in the course of a few hours). In dienes with less propensity for addition (*e.g.* chloroprene) prolonged heating is therefore required for adduct formation. Because of steric hindrance, severe conditions are necessary for the addition in the case of the 1- and 1,4-substituted dienes [10], and the reactants are consumed in side reactions. No adducts can be isolated with 1-acetoxybutadiene and 1-(*p*-nitrophenyl)butadiene, nor with sorbic acid, its ethyl ester, sorbinol, cyclohexadiene and cyclopentadiene, while the yields are very poor with 1-phenylbutadiene [10].

[44] *A. Michaelis* and *J. Ruhl*, Ber. dtsch. chem. Ges. *23*, 476 (1890).

[45] a) *G. Leandri* and *P. Rebora*, Gazz. chim. ital. *87*, 503 (1957). b) *G. Leandri* and *D. Spinelli*, Ann. Chim. (Rome) *49*, 1689 (1959). c) *G. Leandri* and *D. Spinelli*, Experientia *15*, 9 (1959).

[46] a) *O. Wichterle*, Collect. Trav. chim. tchèques *12*, 292 (1947). b) *Y. A. Arbusow*, Izvestiya Acad. Nauk S.S.S.R. *60*, 993 (1948). c) *G. Kreße* and *G. Schulz*, Tetrahedron *12*, 7 (1961).

[47] *O. Wichterle* and *J. Roček*, a) Chem. Listy *47*, 1768 (1953); b) Czech Pat. 83770 (Jan. 3, 1955), Chem. Abstr. *50*, 7152g (1956).

[48] *J. Roček*, Chem. Listy *47*, 1781 (1953).

In the nitrosobenzenes the dienophile character is reinforced by electron acceptor groups at the benzene ring. For example, the ratio of reaction rates of *p*-nitro- and *p*-methoxynitrosobenzene with cyclohexadiene in ethanol at 10 °C is 4000:1[49]. It should, therefore, be possible to increase the reactivity of the analogous *N*-sulfinyl compounds in the diene synthesis by introducing electron acceptor groups.

The greater reactivity of sulfinylnitroanilines [47a] is not, however, sufficient to allow an addition to 1-substituted dienes [10]. We therefore prepared compounds of the type $R-SO_2-NSO$ for further study.

B. N-Sulfinylsulfonamides

1. Preparation and Properties [10, 50]

Sulfonamides may be reacted with thionyl chloride in benzene solution according to the equation

$$R-SO_2-NH_2 + SOCl_2 \rightarrow R-SO_2-NSO + 2\ HCl$$

The reaction proceeds much more slowly than with the amines but gives good yields if the reaction mixture is heated under reflux for several days.

The sulfinylation is complete when the sulfonamide has dissolved and, except in the case of the *p*-nitrobenzene derivative, the product remains in solution even after the reaction solution has cooled.

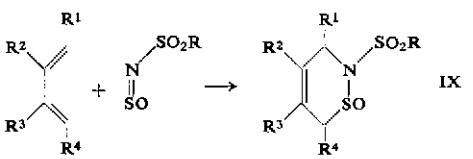
N-Sulfinyl-p-chlorobenzenesulfonamide

p-Chlorobenzenesulfonamide (31 g.) and 13.5 ml. of $SOCl_2$ were heated in 50 ml. of dry benzene under reflux and with exclusion of moisture. After three days the sulfonamide had completely dissolved. The solvent was removed *in vacuo* and the brown, liquid residue distilled under high vacuum. The product is a yellow oil which solidifies on cooling. Yield: 34 g. (88 %), b.p. 122 to 125 °C/10^{-4} mm., m.p. 52 to 53 °C.

The *N*-sulfinylsulfonamides are solid, slightly yellow substances which can be purified in most cases by distillation. The methylsulfonamide derivative is an oil. The compounds are thermally stable up to about 170 °C but may quickly decompose at higher temperatures. They are readily soluble in most inert organic solvents. The infrared spectra show two strong bands at 1090 and 1250 cm^{-1} as well as two $\nu(SO_2)$ bands at 1175 and 1375 cm^{-1}. Most of the reactions described for the *N*-sulfinylamines proceed much faster in the case of the *N*-sulfinylsulfonamides.

2. Diels-Alder Reactions [10, 16, 50]

Reactivity increases and reaction possibilities are widened in the case of diene syntheses. The exothermic reaction



proceeds even at room temperature in a few hours; undiluted 2,3-dimethylbutadiene can react explosively with the *N*-sulfinylsulfonamides.

3,6-Dihydro-N-benzenesulfonyl-1,2-thiazine-1-oxide (*IX*, $R = C_6H_5$, $R^1 = R^2 = R^3 = R^4 = H$)

Butadiene (10 mol.) was condensed in a dry ice/methanol trap and subsequently led into a solution containing 20 g. of *N*-sulfinylbenzenesulfonamide in 50 ml. of dry benzene. (The solution has to be cooled from time to time.) After all the butadiene had been absorbed, the solution was heated for 1 hr. to 50 to 60 °C. The adduct crystallizes from the cooled solution. The crystals were filtered at the pump and washed twice with ether; the colorless crude adduct (24.5 g., m.p. 106 °C) was recrystallized from ethanol. The yield of pure adduct was 23.5 g. (94 %); m.p. 108 to 109 °C.

Yields and properties of a few adducts are summarized in Table 3.

Table 3. 3,6-Dihydro-*N*-arylsulfonyl-1,2-thiazine-1-oxides

Diene	*N*-Sulfinylsulfonamide	M.p. (°C) (from ethanol)	Yield (%)
Butadiene	$C_6H_5-SO_2-NSO$	108–109	90–95
	p-CH_3 $C_6H_4-SO_2-NSO$	97–98	90–95
	p-Cl $C_6H_4-SO_2-NSO$	117–118	90–95
	p-NO_2 $C_6H_4-SO_2-NSO$	158–159	90–95
	CH_3-SO_2-NSO	116–117	90
	$C_6H_5-SO_2-NSO$	112–113	90–95
2,3-Dimethyl-butadiene	$C_6H_5-SO_2-NSO$	107–108	93
	p-$CH_3-C_6H_4-SO_2-NSO$	133–134 (decomp.)	90
Chloroprene	p-$NO_2-C_6H_4-SO_2-NSO$	188 (decomp.) (nitro-methane)	71
Cyclohexadiene	p-$NO_2-C_6H_4-SO_2-NSO$	132–134 (dioxane/ aqueous ethanol)	
2-Chlorocyclo-hexadiene	p-$CH_3-C_6H_4-SO_2-NSO$	158–160	80
1-*p*-Nitrophenyl-butadiene	p-$CH_3-C_6H_4-SO_2-NSO$	96–97 (ether)	63
Ethyl sorbate	p-$NO_2-C_6H_4$ SO_2 NSO	115–116 (ether)	53

As can be seen, the adduct formation also proceeds smoothly for 1- and 1,4-substituted dienes and cyclohexadienes. An adduct of cyclopentadiene isolated at low temperature decomposes at room temperature into its original components since the ring strain in the bicyclic system is too great; the corresponding nitrosobenzene adduct behaves analogously [46c]. The ethyl sorbate adduct is split into its components in boiling ethanol. No addition occurs when hexachlorocyclopentadiene is the diene component. For dienophiles of low electron density, such as the N-sulfinylsulfonamides, an abundance of electrons in the diene is favorable and necessary for the Diels-Alder reaction [51]. Hexachlorocyclopentadiene is therefore unsuitable for the addition.

Properties and Reactions of the Adducts

Most adducts are stable, easily crystallizable substances which can usually be recrystallized from alcohol. In the infrared region they show, besides the strong $\nu(SO_2)$ bands at 1165 and 1350 $cm.^{-1}$, a $\nu(SO)$ band of the cyclic sulfinamide group at 1080 $cm.^{-1}$ which is also very strong.

The reactions of the adducts differ in many ways from those of the *N*-aryl-3,6-dihydro-1,2-thiazine-1-oxide derivatives (Section A 3) derived from *N*-sulfinylanilines. This is due, in part, to the low reactivity of the sulfon-

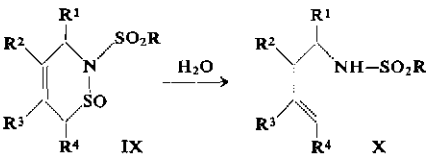
[49] *H. Zimmer*, Ph.D. Thesis, T.U. Berlin 1961.

[50] *A. Maschke*, Ph.D. Thesis, T.U. Berlin 1961.

[51] *G. Kreße, G. Sabuelus, S. Rau*, and *H. Götz*, Liebigs Ann. Chem., *648*, 57 (1961).

amide adduct in all reactions in which the lone electron pair of the sulfonamide nitrogen atom is required.

a) Hydrolysis. The same product is given by both the acid and the alkaline hydrolysis of *N*-arylsulfonyl-3,6-dihydro-1,2-thiazine-1-oxides.



IX X

In the primary product, which cannot be isolated, SO_2 splits off and the C=C double bond undergoes a shift, (indicated by infrared spectroscopy and alternative preparation of the hydrolysis product). In no cases were pyrrole derivatives isolated from alkaline hydrolysis.

N-Buten-3-yl-p-toluenesulfonamide (*X*, $R = p\text{-}CH_3\text{–}C_6H_4$, $R^1 = R^2 = R^3 = R^4 = H$)

Butadiene-*p*-CH_3–C_6H_4–SO_2–NSO adduct (50 g.) was dissolved in 150 ml. of warm concentrated hydrochloric acid. The mixture was allowed to stand for 12 hrs. The separated oily sulfonamide was then dissolved in chloroform, neutralized with sodium carbonate, dried, and the crude product isolated by distilling off the solvent. Crude yield: 39 g. (94%); b.p. 128–130 °C/10^{-3} mm.; $n_D^{20} = 1.5395$.

b) Oxidation with H_2O_2 in alcoholic medium is not possible with *N*-arylsulfonyl-3,6-dihydro-1,2-thiazine-1-oxide derivatives nor does $KMnO_4$ lead to the sultams. The latter are obtained, however, if the oxidation is carried out at low temperatures with H_2O_2 in formic acid-acetic anhydride solution. The N-arylsulfonyl-sultams are substances which crystallize readily and are relatively stable towards acids and alkalis. In the infrared spectra, the difference between the SO_2 groups in the ring and those attached to the ring is evident in the resolution of the $\nu(SO_2)$ bands.

3,6-Dihydro-N-benzenesulfonyl-1,2-thiazine-1,1-dioxide

The butadiene-C_6H_5–SO_2–NSO adduct (8 g.) was dissolved in a mixture of 30 ml. of formic acid and 10 ml. acetic anhydride and mixed, under cooling, with 5 ml. 30% H_2O_2. After standing for one week at room temperature, 3.4 g. of oxidation product separated as colorless crystals. Another 1.4 g. were isolated by dilution with water. The crude sultam was heated for 15 min. with 30 ml. 15% NaOH to 50 °C in order to separate any starting material that might still be present, as well as acidic by-products. The product was subsequently recrystallized from glacial acetic acid. M.p. 150 to 152 °C; yield 4.3 g. (51%).

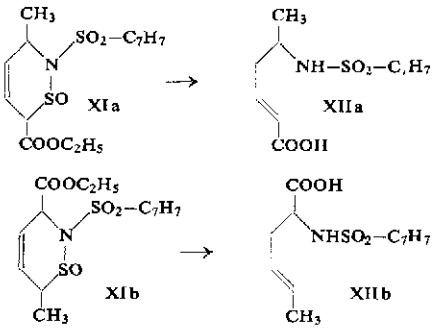
c) Reduction of the *N*-arylsulfonyl-3,6-dihydro-1,2-thiazine 1-oxide derivatives to the thiazines has not as yet been possible.

In all cases (Zn/glacial acetic acid, $LiAlH_4$ in ether, hydrogenation in the presence of Raney nickel) secondary sulfonamides are formed with ring opening.

Structure of the Adducts formed from Asymmetrically Substituted Dienes [50]

In order to determine the reaction path in the Diels-Alder reactions of *N*-sulfinylsulfonamides, the direction

On hydrolysis, the ethyl sorbate yields the tosylate of an amino acid which may have the structure XIIa or XIIb.

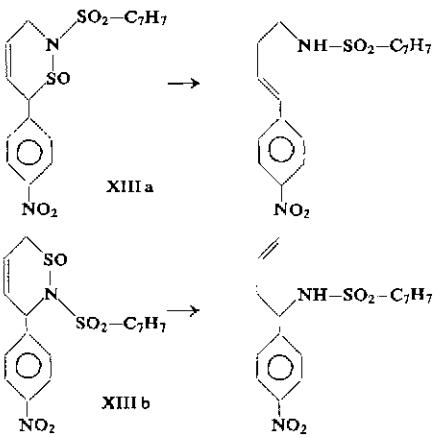


XIa XIIa

XIb XIIb

Hydrogenation of the hydrolysis product yields N-*p*-toluenesulfonyl-δ-aminocaproic acid. Consequently, the adduct has the structure XIa.

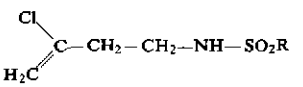
For the *p*-nitrophenylbutadiene adduct, the structure of the hydrolysis product was confirmed spectroscopically:



XIIIa XIIIb

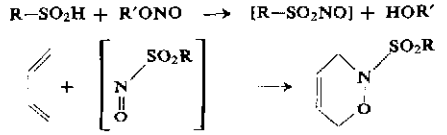
Th. latter showed no vinyl but rather a *trans*-CH=CH band at 970 cm^{-1}; the position of the ultraviolet spectral maximum in ethanol (32500 cm^{-1} = 310 mμ; ε = 13100) corresponds to the *p*-nitrostyrene chromophore (33300 cm^{-1} = 300 mμ; ε = 13900) and not to the *p*-nitrotoluene system (26600 cm^{-1} = 273 mμ; ε = 9500). Accordingly, the adduct should have the formula XIII a.

In both examples, the addition path seems to be determined predominantly by steric factors: The larger radical in the 1-position in the diene goes into the *m*-position with respect to the arylsulfonyl group. In the chloroprene adduct, the chlorine atom is in the 5-position, as is evident from dipole moment measurements [16] and the structures of the hydrolysis products [50].



The homogeneity of these adducts was tested by fractional crystallization. There were no indications of the presence of an isomeric mixture.

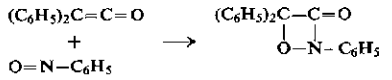
The similarity of the N=O and N=SO group in the diene synthesis suggests that the increase of reactivity due to an adjacent sulfonyl group also occurs in the nitroso compounds. This was confirmed through the capture of the "sulfonylnitrosites" with dienes [52]. Such compounds are assumed to be intermediates in the reaction of sulfinic acids with alkylnitrites in inert solvents.



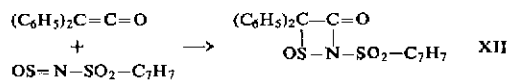
[52] *G. Kreße* and *W. Kort*, Chem. Ber. *94*, 2624 (1961).

3. Addition to Diphenylketene [53]

The similarity between the –N=O and the –N=SO group can also be confirmed by another reaction which in many respects is analogous to the diene synthesis. *Staudinger* and *Jelagin* [54] have shown that under mild conditions, nitrosobenzene combines with diphenylketene to form an oxazetidinone.



N-Sulfinylaniline did not react with diphenylketene. On the other hand, the much more reactive *N*-sulfinyl-*p*-toluenesulfonamide combines with diphenylketene at room temperature in ether-petroleum ether solution to form the moisture-sensitive compound 2-*p*-toluenesulfonyl-4,4-diphenyl-1,2-thiazetidine-3-one-1-oxide (XII), m.p. 140 to 141 °C, in 78% yield.



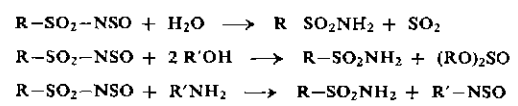
XII

Hydrolysis of the adduct leads to *N*-diphenylacetyl-*p*-toluenesulfonamide, m.p. 176.5 to 177 °C; this compound is also formed from diphenylketene with *p*-toluenesulfonamide in dioxane when pyridine is added.

4. Other Additions: Sulfinylations

The extremely great increase in reactivity found on going from *N*-sulfinylamines to *N*-sulfinylsulfonamides is also exhibited by additions of compounds of the type H–X.

a) Water, alcohols, and amines [10, 50] may react violently with the *N*-sulfinylsulfonamides. In dilute solutions (non-polar solvents) at room temperature, the reactions proceed smoothly and quantitatively.

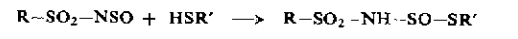


Besides the desired product, only the usually sparingly soluble *p*-toluenesulfonamide is formed. The *N*-sulfinylsulfonamides are therefore suitable agents for preparing sensitive *N*-sulfinyl compounds, as is shown by the following example.

N-Sulfinyl-dimethylaminoaniline [10]

p-Dimethylaminoaniline (0.02 mole) in dry benzene was slowly added to 0.022 mol of thionylamide in dry benzene. The precipitated sulfonamide was filtered with exclusion of moisture, the benzene removed *in vacuo*, and the product distilled; b.p. 115 °C, m.p. 72 °C.

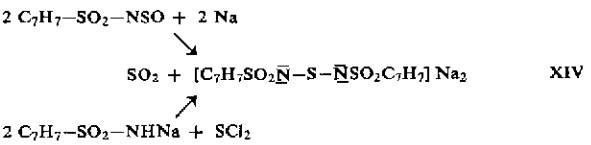
b) In the reaction with thiophenols [33], the very unstable primary adduct may be isolated and can be used,



like the *N*-sulfinylaniline derivative, for the synthesis of mixed aliphatic-aromatic trisulfides.

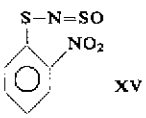
c) The sulfinic acid addition to *N*-sulfinylsulfonamides [33] also proceeds analogously, but faster than with *N*-sulfinyl aniline. The yields of sulfinylsulfones, however, are lower.

d) Qualitatively different, on the other hand, is the course of the reaction of *N*-sulfinyl-*p*-toluenesulfonamide with sodium in toluene [33]. Here, SO_2 is split off on heating and a salt-like product is formed. From the stoichiometry of the reaction, the solubility properties, and the chemical behavior of the product, as well as from the fact that an identical compound is obtained in the reaction of the sodium salt of *p*-toluenesulfonamide with SCl_2, it can be concluded that the probable formula is that given by XIV.



XIV

e) *N*-Sulfinylation with the aid of *N*-sulfinylsulfonamides described under (a) is not limited to amines. Other XNH_2 compounds can also be converted to the *N*-sulfinyl derivatives X–NSO [50]. For example, we prepared the *N*-sulfinyl compound XV from *o*-nitrobenzenesulfenamide. This compound, while similar to the N-sulfinylanilines, is relatively insensitive to moisture; hydrolysis with SO_2 evolution occurs only in the presence of acid.

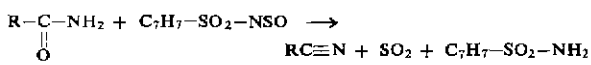


XV

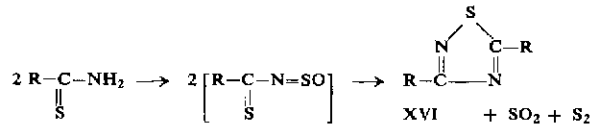
N-Sulfinyl-o-nitrobenzenesulfenamide (XIV)

o-Nitrobenzenesulfenamide (9 g.) and *p*-C_7H_7–SO_2–NSO (11.5 g.) are heated under reflux in 50 ml. of benzene. The *p*-toluenesulfonamide which precipitates on cooling is filtered, extracted with 50 ml. of warm benzene, and again filtered with suction. After the benzene is removed, the combined filtrate leaves 11 g. of crude *N*-sulfinyl compound which is recrystallized twice from acetone. Yellow crystals, m.p. 127 to 128 °C, yield 10 g. (90%).

In some cases, further reaction steps follow the sulfinylation. Thus, nitriles are formed immediately from amides (as well as with $SOCl_2$).



In other cases the subsequent reaction is a disproportionation of the *N*-sulfinyl compound. The reaction of compounds with –CS–NH_2-groups, which leads to 1,2,4-thiadiazoles (XVI), is of preparative importance.



The yields are not only high in the case of thiobenzamide (for which the reaction can also be carried out with $SOCl_2$). Even for thioacetamide, where such substitution is not possible, they are around 45%.

[53] *A. Trede*. Diploma Thesis, T.U. Berlin 1961.

[54] *H. Staudinger* and *S. Jelagin*, Ber. dtsch. chem. Ges. *44*, 365 (1911).

3,5-Dimethyl-1,2,4-thiadiazole (XV, R = CH_3)

p-C_7H_7–SO_2–NSO (100 g.) is dissolved in 200 ml. of dry chloroform and thioacetamide (20 g.) is added to the solution in portions. The reaction proceeds very violently with heat and SO_2-evolution. With each thioacetamide addition, a temporary red coloration occurs. The cooled solution is filtered from the precipitated *p*-toluenesulfonamide, the chloroform completely distilled off and a distillate collected at 50 mm pressure between 80 and 90 °C (120 to 140 °C bath temperature). The crude product may be redistilled at normal pressure, yielding, after a slight forerun, 10 g. (44 %) of 3,5-dimethyl-1,2,4-thiadiazole, b.p. 146 to 148 °C; $n_D^{23} = 1.4985$.

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The Application of Mass Spectrometry in Organic Chemistry: Determination of the Structure of Natural Products

BY PROF. DR. K. BIEMANN

DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE, MASS., USA

Mass spectrometry is a very useful method for the determination of the structure of organic compounds although the technique has not yet been widely employed in this field. Of particular interest is the high sensitivity of the instrument, making possible the use of very small amounts of sample, and the information obtainable regarding the size of the molecule and position of the groups therein. A certain volatility is required and the choice of a suitable derivative is, therefore, sometimes of importance. The fragmentations of the molecules in the ion source may be considered as reactions of "carbonium ions without solvent." The application of the method in the determination of the structure of some natural products is outlined, using lipids, amino acids, peptides and alkaloids as examples.

1. Introduction

Mass spectrometry is generally known as a physical method for the determination of stable isotopes, for the analysis of gases, for the determination of atomic and molecular weights, and in the petroleum industry for the routine analysis of very complex hydrocarbon mixtures. Instrumental methods, such as ultraviolet, infrared, and more recently, nuclear magnetic resonance spectroscopic techniques, have become indispensable in organic chemistry; mass spectrometry, on the other hand, has only very recently been used in the solution of organic chemical problems such as the identification and structure elucidation of organic molecules. As will be shown in the following discussion, the conclusions which can be drawn from the detailed interpretation of a mass spectrum are frequently of quite a different nature from the information obtained by the spectroscopic methods mentioned above. For example, the arrangement of individual groups within the molecule, the size and structure of side chains, the presence (and often the number) of heteroatoms, and in most cases the accurate molecular weight can be deduced from the mass spectrum. The very small sample needed (a fraction of a milligram or, if necessary, a few micrograms) for the determination of a spectrum is certainly of considerable advantage, particularly in the case of natural products. A disadvantage, on the other hand, is the requirement that the sample should have a certain vapor pressure, and it is for this reason that the selection of the most suitable derivative is important.

2. Principle of the Method

The basic working principle of a mass spectrometer is so well known that it need not be discussed here, and the details have been the subject of a number of recent books [1–3]. A few special problems which arise when liquid or solid organic substances are to be investigated will be discussed briefly.

A mass spectrum is a recording of the abundance of the ions formed from the sample on electron impact *versus* increasing mass (Fig. 1). For the formation of such ions the substance to be investigated must be present in the so-called ion source as vapor at a pressure of

[1] *H. Ewald* and *H. Hintenberger:* Methoden und Anwendungen der Massenspektroskopie. Verlag Chemie, Weinheim/Bergstr. 1953.

[2] *L. Jenckel* and *E. Dörnenburg* in *E. Müller:* Methoden der Organischen Chemie (Houben-Weyl). Thieme, Stuttgart 1955, vol. III, part I, p. 693–752.

[3] *J. H. Beynon:* Mass Spectrometry and its Applications to Organic Chemistry. Elsevier Publishing Co., Amsterdam 1960; D. van Nostrand Co., Princeton, N.J., 1960.

about 10^{-5} mm. Hg. For reproducible results this pressure must be kept constant during the recording of the spectrum because the abundance of the ions formed are directly proportional to the concentration of the substance in the ion source. This is most conveniently achieved by keeping the sample in a reservoir at a pressure of about 10^{-2} mm. Hg and by permitting it to diffuse through a small leak directly into the ion source.

Very dilute solutions cannot be measured simply by the use of larger volumes as may be the case if the absorption of light is measured, because in mass spectrometry there is also an upper limit to the amount of sample that can be used. A pressure in the reservoir of more than 1 mm. leads to such a high pressure in the ion source that it ceases to function correctly. Furthermore, the spectrum would be unuseable in tne mass region of the solvent

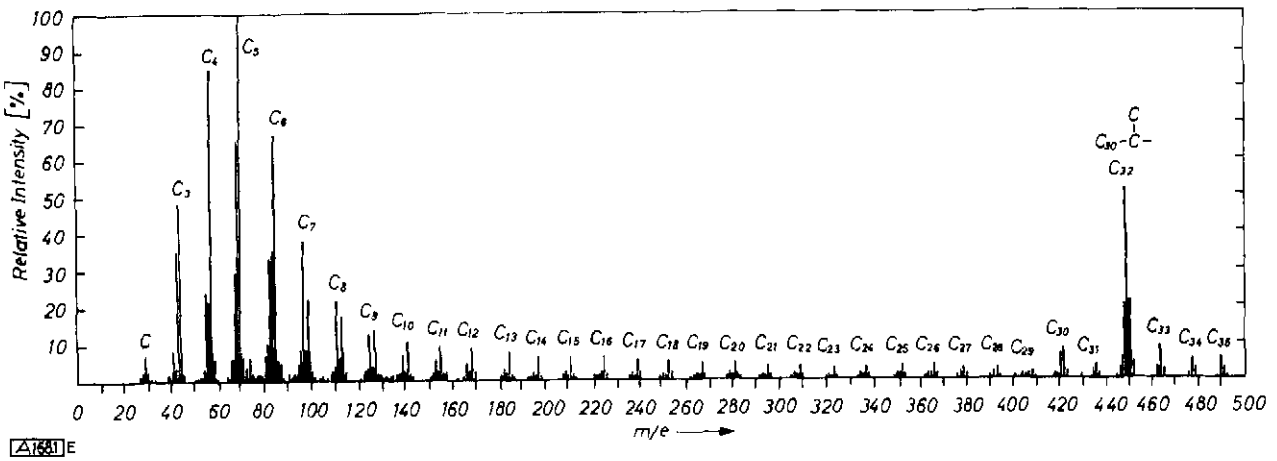


Fig. 1. Mass spectrum of phthiocerane (3-methyl-tetratriacontane) [40b].

The decrease of sample pressure in the reservoir during the time required for scanning the spectrum (five to twenty minutes) can thus be neglected. The vapor pressure requirements for the sample are defined by this technique: The substance must have a vapor pressure of at least 10^{-2} mm. at that temperature at which the reservoir is operated. This container and the necessary valves (the so-called inlet system) must, therefore, be kept at elevated temperatures if the spectra of more complex organic molecules are to be obtained. Temperatures up to 350 °C. are used in the petroleum industry for the analysis of heavy hydrocarbons, but this is too high for more temperature-sensitive compounds; 150 to 250 °C. seems to be the optimum temperature. The volatility of the substance is, of course, important not only for the introduction of the sample but also for its complete removal after the spectrum has been obtained.

The amount of material required for a spectrum depends on the size of the reservoir and on the desired intensity of the spectrum. A sample pressure of $1 \cdot 10^{-2}$ to $2 \cdot 10^{-2}$ mm. Hg is sufficient and requires about 1 to 2 micromoles, *i.e.* a few tenths of a milligram, if a reservoir of three liters capacity is employed in the temperature region discussed above. Although the loss of sample pressure during the run becomes more noticeable if a reservoir of 300 ml. (requiring ten times less substance) is employed, it can be neglected for qualitative purposes. From a practical point of view the lower limit of the sample depends not so much on the sensitivity of the instrument as upon the experimental difficulties in the handling of such small amounts of substance. The unavoidable accumulation of traces of impurities in the solvents used in the experiment, or grease, etc. may lead to considerable difficulties in the interpretation of a spectrum obtained with a very small sample, possibly only of the order of micrograms.

because its contribution cannot be automatically compensated. If the sample is present in the form of a very dilute solution, the solvent must be removed, at least to a large extent, before the spectrum of the solute can be determined.

The introduction of the sample into the instrument is in general quite simple, particularly if it is a pure substance. In the case of a mixture, the possibility of selective fractionation, which could lead to the loss of a component, should be kept in mind. Gases are expanded directly into the evacuated reservoir. Liquids are introduced from a micropipet through a sintered disc covered with gallium to seal it from the atmosphere. It is, however, simpler and more convenient to fill a short length of hypodermic needle with the liquid; after closing off one end of the needle, it is pushed through a silicon rubber diaphragm on the inlet system, thus causing the sample to vaporize into the reservoir. Solid substances may be sublimed directly into the reservoir, for example from a hot glass tube connected to the inlet system by a Teflon gasket.

The upper limit for the molecular size of the sample, which in general is about mass 700 to 800, is given by the mass range of the instrument. Molecules of this size rarely have the required vapor pressure unless they are polyhalogenated compounds. The mass range, therefore, is hardly a limitation, particularly because it can be increased by the use of a stronger magnetic field.

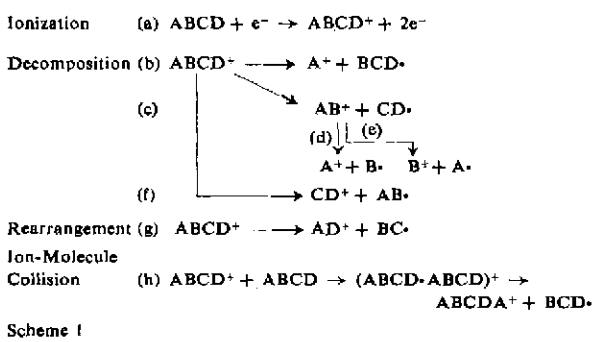
It is of extreme importance for the interpretation to determine the mass of the molecule and of all fragments with an accuracy of better than one mass unit, and the resolution of the instrument must therefore be relatively good. For work with complex organic compounds it is, therefore, required that in the region of about mass 350 to 400, two particles differing only by one mass unit are

recorded as almost completely separated, adjacent peaks resulting in still useable resolution at mass 700.

Finally, it should be pointed out that substances of rather low volatility still yield useful spectra if vaporized directly into the ion source, in which a much lower vapor pressure suffices. This technique requires either the time-consuming venting of the ion source, or a special vacuum lock.

3. The Behavior of Organic Molecules in the Mass Spectrometer

The physical-chemical phenomena occurring in polyatomic molecules on electron impact are necessarily very complex and still mainly unknown. The decomposition of the molecular ion formed on loss of an electron shows, however, many similarities to the reaction of carbonium ions. The following discussion and the interpretation of the spectra is presented in the light of carbonium ion chemistry.



Scheme 1

In Scheme 1 the principal reactions which a hypothetical molecule ABCD may undergo are indicated. On bombardment of a molecule with electrons, the energy of which is equal to or higher than the ionization potential of this molecule, a molecular ion is formed by loss of a valence electron. If this ion remains intact over a sufficiently long period (more than 10^{-4} sec.) *i.e.* long enough to be accelerated in the electric field and deflected in the magnetic field, it will be registered at a mass corresponding to the molecular weight. The ionization potential of organic compounds in general ranges from 7 to 15 eV (for example, 9.24 eV for benzene, 13.1 eV for methane). Electrons of higher energy are able to transfer more energy to the molecule, which may then decompose into fragments, by bond cleavage, sometimes in more than one step. The number of decomposition reactions of type (b)–(g) is considerable for an organic molecule of average size, and leads to the large number of peaks in the mass spectra of such compounds. For this reason mass spectra are very suitable for establishing the identity of two compounds. At a first glance, this complexity would seem to be a disadvantage in the interpretation. The intensities of the peaks are, however, of importance since they are dependent on the probability of formation of the individual fragments. This probability in turn depends on the energy requirements of the decomposition reaction and allows valuable conclusions to be drawn with respect to the structure of the fragment. It would seem that for the interpretation of a mass spectrum it would merely be necessary to deduce the structure of a number of fragments and then formulate a structure for the complete molecule. In simple cases, this is easily possible: The fragments of mass 15 (CH_3), 29 (C_2H_5), 31 (CH_3O), 45 (C_2H_5O), and 46 (C_2H_6O) permit the immediate conclusion that the compound is ethanol, although there are many other peaks present between mass 12 and 48. Their intensity is however, much lower because these particles originate by rupture of more than one bond (a much less favorable process) or they are due to the presence of heavy isotopes.

However, in the spectra of many compounds there are peaks present, the mass of which do not correspond to any group of atoms present as such in the molecule. They are formed by a rearrangement of the molecular ion, or fragment, before or during the decomposition (type g). This phenomenon, first studied in more detail with hydrocarbons, led to the opinion some years ago that mass spectrometry would not be suitable for structure determinations. It turns out however that such rearrangements are rather structure-dependent for non-hydrocarbons. They can be used advantageously in the interpretation once their formation is understood.

Reactions of Type (h) give rise to ions, the mass of which is higher than the molecular weight and could therefore lead to difficulties in its determination. Fortunately, reaction (h) is a bimolecular one and, therefore rather improbable at the low sample pressure in the ion source. The intensities of the corresponding peaks, are not directly proportional to the sample pressure but to the square of this pressure. This behaviour can be used to recognize such peaks. Only one such reaction is of practical importance, and that is the abstraction of a hydrogen atom from a neutral molecule by the molecular ion. This becomes more noticeable if the molecular ion is of low stability while its protonated form is much more stable (for example, amino alcohols, amino esters, etc., see below). These peaks may be easily recognized in spite of their low intensity because of the above-mentioned sensitivity to the sample pressure and the ionization conditions. As such peaks are found one mass unit above the molecular weight ("M+1" peak), they may frequently be used for the unambiguous determination of the molecular weight [4].

The identification of the molecular ion, the mass of which indicates the molecular weight, is not always easy. For pure substances from those classes of compounds which give rise to stable molecular ions, it is represented by the peak of highest mass in the spectrum aside from those found one or two mass units higher and due to the presence of heavy isotopes in the molecule (see below). Many compounds give rise to only a small molecular peak, and in such cases it is possible for a fragment ion of high intensity to be mistaken for the molecular ion. In general, the stability of the molecular ion will be increased by the presence of π-electron systems, and decreased by the presence of bonds which are easily

[4] *F. W. McLafferty*, Analytic. Chem. *29*, 1782 (1957).

cleaved. This is indicated by the following sequence of decreasing stability of molecular ions:

Aromatic compounds > conjugated olefins > olefins > alicyclic compounds > carbonyl compounds > unbranched hydrocarbons > ethers > esters > acids > alcohols > amines > highly branched hydrocarbons.

This property is, to a certain extent, additive; *i.e.* the molecular peak of a polycyclic amine may be more intense than that of an aromatic compound with a highly branched side chain. Some of the spectra which will be discussed in detail later serve as examples for the large differences in the intensities of molecular ions: polyamino alcohols (Fig. 5a), polyamines (Fig. 5b), and amino acid esters (Fig. 3) may easily form stable fragments and the molecular ion is of only low intensity. The somewhat more intense molecular peak in the ethyl ester of methionine, as compared with leucine, indicates the stabilizing influence of the unbranched side chain and the presence of a sulfur atom. The aromatic character of the indole alkaloids, on the other hand, leads to a very intense molecular peak (Fig. 6).

For the differentiation of a molecular ion from fragment ions, a few additional criteria may be used.

(1) The molecular weight of organic compounds is normally an even number unless an odd number of nitrogen atoms are present; the opposite is true for fragments.

(2) The appearance of a fragment of mass 3–14 units less than the peak of highest mass, indicates that the latter is not a molecular ion because the loss of 3–14 hydrogen atoms is a very improbable process. A difference of 3 mass units usually means that the molecular weight is 15 or 18 mass units, higher, respectively, and that the substance is an alcohol losing either CH_3 or H_2O.

(3) It may be necessary to determine whether a peak is due to a molecular ion or to a fragment of a large molecule. Reduction of the electron energy from the normally applied 70 eV to the vicinity of the ionization potential of the compound eliminates peaks due to fragments.

Although the determination of the accurate molecular weight is of considerable value for the identification or structure determination of an organic molecule, additional conclusions can be drawn from the molecular peak; the relationship between its intensity and compound type has already been mentioned. From the number and type of the so-called isotope peaks, it is often possible to deduce the elemental composition, or at least the presence or absence of heteroatoms. The natural abundance of ^{13}C is about 1.1 % and methane, for example, consists of 98.9 % of species of molecular weight 16, but 1.1 % has molecular weight 17 (the natural abundance of deuterium is very small). The ratio of the molecules containing one ^{13}C to those containing only ^{12}C is thus $1.1n$:100 for a compound of n carbon atoms. The peak of mass 311 in the spectrum of ibogaine, $C_{20}H_{26}N_2O$, (Fig. 6) is about 23 % of the intensity of the peak at mass 310 (the actual molecular weight). In this case, nitrogen (natural abundance of ^{15}N is 0.36 %) contributes also to mass 311. The probability of the existence of an ibogaine molecule with two ^{13}C atoms is, of course, much less, and the peak at mass 312 is also much less intense. The isotopes ^{18}O, ^{34}S, ^{37}Cl, and ^{81}Br contribute more to the peak two mass units above the actual (monoisotopic) molecular weight. The natural abundance of ^{18}O is only 0.2 % and therefore not very significant. Heavy sulfur amounts to approximately 4 % of the total sulfur and accounts for the typical appearance of mass spectra of organic sulfur compounds, for which Fig. 3b is a good example: Mass 177 is due to the light molecules, 178 contains either C^{13} or S^{33} (0.7 %), and 179 is mainly due to the molecules containing S^{34}. The intensity of the particle at mass 179 is about 4 % and not 8 % of the intensity at mass 177, and the compound, therefore, can contain only one but not two atoms of sulfur.

An even more charateristic pattern is observed with chloro- or bromo-containing compounds since the ratio of ^{35}Cl:^{37}Cl is 3:1 and ^{79}Br:^{81}Br is 1:1. The appearance of such groups is shown in Fig. 2 which illustrates the

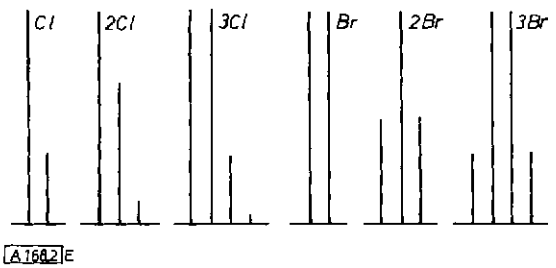


Fig. 2. Multiplets characteristic of the presence of 1–3 chlorine and bromine atoms

typical pattern obtained with compounds containing 1 to 3 chlorine and bromine atoms, respectively. These peaks are always separated by two mass units; observed between the peaks are those due to the presence of ^{13}C. The intensities to be expected for a great number of combinations of atoms have been presented in tabular form by *Beynon* [3].

These conclusions hold also for the elemental composition of fragment ions, although it must be remembered that other fragments may interfere. Fig. 3b is an example of such a situation: mass 61 and 104 contain the sulfur atom as indicated by the intensity of the peaks at mass 63 and 106. Mass 56 does not contain sulfur, and in the case of mass 129 no conclusions can be drawn because of the intense peak at mass 131 which arises through another fragmentation process.

In this discussion the molecular ions have been treated in considerable detail not only because of their importance, but also because the knowledge of the molecular weight and possibly of the elemental composition of the compound is very important for the interpretation of the fragment ions. As already pointed out these are very numerous and the peaks of high intensity are of greatest interest because they arise from a simple decomposition requiring only a moderate amount of energy. In such a case, it may be assumed that the resulting fragment will still bear some relationship to the original molecule. An ion of mass 24 represents, on the

other hand, only two carbon atoms without substituents. This process requires a considerable amount of energy and the intensity of the peak is, therefore, very low but such a peak has also little value for the interpretation.

A low energy requirement, and therefore a high intensity of the resulting peak, depend upon:

(1) the energy of the bond(s) to be broken,

(2) the energy content of the positively charged ion and the neutral fragment (radical or molecule), and in the case of rearrangements,

(3) steric factors.

Consideration of the data obtained from many simple and more complex organic compounds indicate that item (2) is the most important factor; the fragments of appreciable intensity correspond to ions in which the positive charge is particularly stabilized. (It has to be remembered that a conventional mass spectrum records only the positively charged particles); an exception is electron-atachment mass spectrometry [5] in which negative ions are registered.

The more favorable fragmentation reactions can be summarized as follows:

The stability of carbonium ions increases in the series

$$CH_3^+,\ RCH_2^+,\ R_2CH^+,\ R_3C^+ \qquad (A)$$

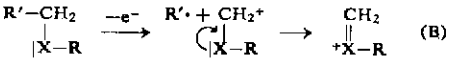
because of the inductive effect of the alkyl groups, and the formation of highly susbtituted fragment ions is therefore favored. Cleavage of a bond at highly substituted carbon atoms and retention of the positive charge at that atom makes it possible to deduce in a hydrocarbon chain the point of branching and the size of the side chains. Fig. 1 shows [40] that phthiocerane, the hydrocarbon containing the basic carbon skeleton of phthiocerol (see below), contains 35 carbon atoms and is substituted at C_{31} with a methyl group. This spectrum also shows that ions of low mass but of comparable stability (with respect to the stabilization of the positive charge) are always of much higher intensity than those of higher mass. This is due in part to instrumental factors and in part to their lack of stability since they contain more bonds which still can fragment.

A positive charge is stabilized if conjugated with a double bond. It is, however, not possible to deduce the position of a double bond based on this factor because it seems that the double bond can migrate both in the molecular ion and also in fragments by a simple hydrogen shift. Methyl oleate and its double bond isomers exhibit very similar spectra except in those compounds in which the double bond is located very close to the ester group as, for example, in methyl-Δ^2-octadecenoate [6].

An aromatic system in conjugation to the positive charge also increases its stabilization; *i.e.* a benzyl bond is easily broken. The resulting ion probably has not the structure of a benzyl ion but rather that of a tropylium ion, as was shown by *Meyerson* [7] using isotopically labelled compounds:



The introduction of heteroatoms in the molecules leads to much more interesting spectra (see for example Figs. 3 to 6) than is the case for hydrocarbons. The free electron pairs of those atoms can very effectively stabilize the positive charge at the neighboring carbon atom:

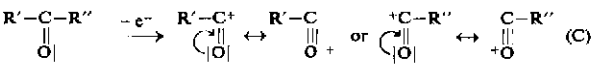


(B)

In alcohols and ethers (X = O), mercaptans and sulfides (X = S), and amines (X = NH), the bond next to the heteroatom is easily cleaved and the positive charge is retained on the fragment containing the hetero element. For the determination of a structure this, is of considerable importance; in an aliphatic alcohol it is possible, for example, to deduce the position of the hydroxyl group from such fragments although the possibility of a further decomposition of the primary fragment has to be kept in mind (see below).

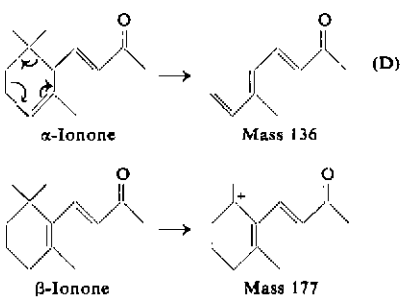
The high intensity of mass 86 in the mass spectra of the ethyl ester of leucine (Fig. 3a) and of mass 104 in the ester of methionine (Fig. 3b) is due to the α-amino group while the high intensity of mass 61 in the latter compound is due to the sulfur atom. The fragment of mass 102 is in both cases much less intense because of the destabilizing influence of the carbonyl group.

Heteroatoms which are part of a double bond are also able to stabilize a carbonium ion:



(C)

In cyclic olefins one can frequently observe a fragmentation involving two bonds simultaneously, which can be viewed as a reverse Diels-Alder reaction [8]. This decomposition seems to be favored in those molecules not containing another easily cleaved bond; the spectra of α- and β-Ionone are a good example:



(D)

The fragment formed by loss of one of the geminal methyl groups from β-ionone is a tertiary allylic carbonium ion giving rise to a very intense peak of mass 177 while the cleavage discussed above would lead to the loss of an ethylene molecule. If such a methyl group is lost from

[5] *M. v. Ardenne, K. Steinfelder,* and *R. Tümmler,* Angew. Chem. *73,* 136 (1961).

[6] *B. Hallgren, R. Ryhage,* and *E. Stenhagen,* Acta chem. scand. *13,* 845 (1959).

[7] *P. N. Rylander, S. Meyerson,* and *H. Grubb,* J. Amer. chem. Soc. *79,* 842 (1957).

[8] *K. Biemann,* unpublished results.

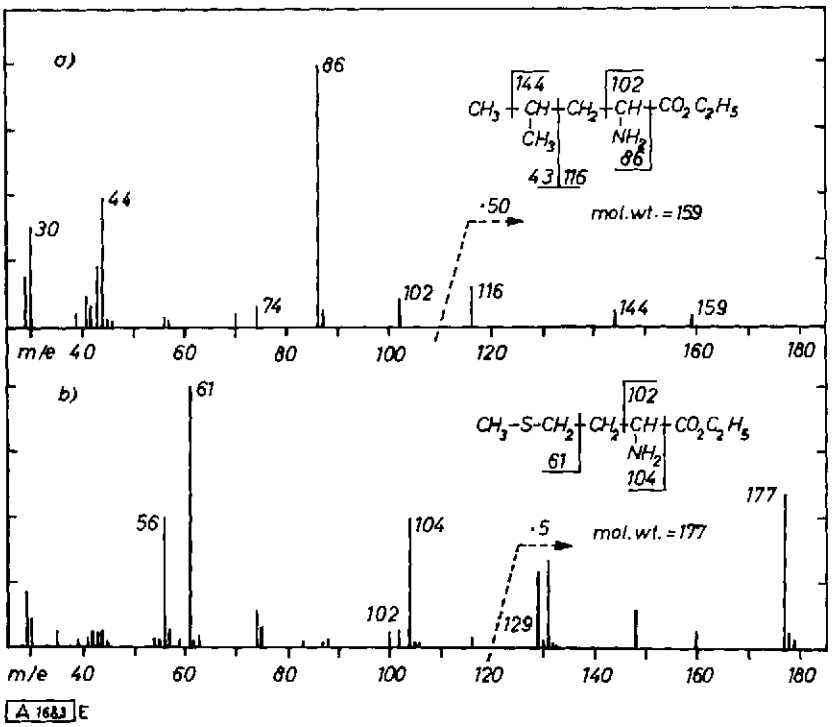
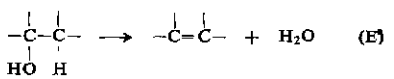


Fig. 3. Mass spectra of amino esters. a) Leucine ethyl ester, b) methionine ethyl ester [*].

α-ionone, a plain tertiary carbonium ion is formed and the fragment of mass 177 is not so intense. The "retro-Diels-Alder reaction" leads, however, to the elimination of a highly substituted and therefore energetically favored olefin as the neutral product; the conjugated olefin ion of mass 136 is very intense in this case.

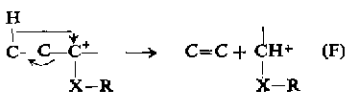
All the fragmentation reactions discussed thus far are simple processes and the resulting ions represent a group of atoms present as such in the molecule. As indicated earlier, fragmentations accompanied by a rearrangement are of considerable importance. These processes, in general, involve the migration of a hydrogen atom with the concomitant formation of a double bond. In such fragmentations the positive charge is retained on the partiele on which it is best stabilized; in the following examples where the positive charge is shown on one particular fragment, it is important to realize that the presence of certain functional groups or substituents on the other fragment may lead to the opposite charge distribution.

The molecular ions of alcohols easily eliminate water and lead to fragments which correspond to olefinic (or cyclic) ions.



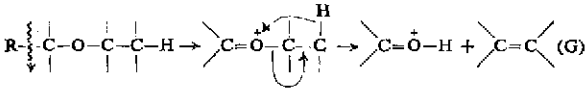
Mercaptans, sulfides, and amines behave in a similar fashion. The fragment of mass 129 in Fig. 3b is formed by the loss of methyl mercaptan (mass 48) from the molecular ion (mass 177). Occasionally fragments themselves may decompose in the same way; elimination of methyl mercaptan from the fragment of mass 104 (Fig. 3b) leads to mass 56.

Portions of molecules which have been formed in a reaction of Type B may eliminate an olefin if the necessary structural requirements indicated in the following scheme are fulfilled:



The fragments of mass 30 (CH_2NH_2) shown in Figs. 3 (a) and (b) are formed in this manner. As can be seen in these spectra the primary fragment is of a much higher intensity and the rearrangement of Type F will hardly lead to the erroneous interpretation that in leucine ester there would be present an H_2N-CH_2-group.

The resonance form of type B ions may undergo a similar decomposition. Ethers show such a cleavage [4].



The most intense peak in the mass spectrum of diethyl ether is found at mass 31 (CH_2OH), representing an example of Type G. Secondary amines [9] and polyamines show an analogous behavior and so do mercaptans [10]. The structural requirements (side chains of at least two carbon atoms bearing a hydrogen atom at Cβ) are shown in the above reaction.

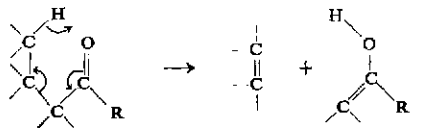
All these rearrangements represent 1,2-elimination, at least in a formal sense, while carbonyl compounds with

[*] In Figs. 3–5 it should be noted that in the region at the right of the arrow all peaks are enlarged by the factor indicated. Because of the wide dynamic range of both the mass spectrometer and the multi-trace recorder commonly used, such relatively small peaks are recorded as accurately as the more intense ones.

[9] *J. Collin*, Bull. Soc. roy. Sci. Liège *21*, 446 (1952).

[10] *E. J. Levy* and *W. H. Stahl*, Analytic. Chem. *33*, 707 (1961).

longer side chains and a γ-hydrogen atom eliminate an olefine molecule via a cyclic six-membered transition state [11]:



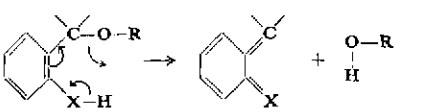
(H)

Aldehydes, methyl ketones, methyl and ethyl esters form fragments of mass 44, 58, 74, and 88, respectively, in such a decomposition. An alkyl group R at C_α increases the mass of the fragment correspondingly by (R−1) mass units. These peaks are rather characteristic because of their intensity and are of value in the identification of α-substituents. The degradation of the antibiotic lagosine led, for example, to an acid, the methyl ester of which had a molecular weight of 312 and its mass spectrum [48 b] showed peaks at mass 158 and 228, indicating a structure such as

$$C_{11}H_{23}-\underset{\displaystyle C_6H_{13}}{\underset{|}{CH}}-COOCH_3$$

which was then shown to be correct by synthesis [12].

Many other groups of compounds, *e.g.* amides [13], alkyl benzenes [14], alkyl heterocyclics [15], arylethanols [16], aryl ethers, vinyl ethers, and olefins [17] lead to rearrangements analogous to that shown for carbonyl compounds in reaction (H) which can be formulated in a more general sense: The carbon atoms may be replaced by heteroatoms and the carbonyl group by other multiple bonds, or an aromatic ring. That, in fact, the γ-hydrogen atom migrates, was shown for esters [18] and alkyl benzenes [19] by isotopic labeling. Finally, it is pertinent to mention a fragmentation exhibited by *ortho*-substituted aromatic compounds of certain structures:



(I)

X = O, NH or CH_2

This process, which also involves the migration of the hydrogen atom, results in considerable differences between *o*-methyl [20], *o*-hydroxyl [21] *o*-amino benzoic esters [8], and *o*-methylbenzyl alcohol [22], on the one hand, and their *m*- and *p*-isomers on the other.

From these fragmentation reactions, it follows that isomers, in general, give rather different mass spectra. Exceptions are: aliphatic diastereomers because in these molecules all bonds are identical; certain olefins (because of the tendency towards migration of the double bond in the ions) as well as certain polysubstituted aromatic compounds where the asymmetry of the original molecule is sometimes lost in the tropylium ion [7]. But even in such cases the different distances of functional groups within the isomeric molecules, such as the "*ortho*-effect" mentioned above, or the rather different resonance stabilization of isomeric cations of substituted heterocycles may lead to appreciable differences in the spectra of such isomers. As an example for the last mentioned group, the isomeric alkyl pyridines may serve as an example. Their spectra clearly indicate the decreasing degree of stabilization of the $-CH_2^+$-group attached to the β-, γ-, or α-position [23]. In this connection it should be mentioned that *McLafferty* has shown [24] that the intensity of certain fragment ions in aromatic carbonyl compounds can be related to the Hammett σ-constant of the substituents present in the aromatic ring.

In the foregoing summary of the favored fragmentation processes of molecular ions, a general picture of the behavior of organic molecules on electron impact in the mass spectrometer has been presented, a knowledge of which is important for correct interpretation. The interested reader is referred to the many original papers which contain the spectra of a variety of compounds:

Alcohols [25]	Ethers [4]
Aldehydes [26]	Amines [9]
Aliphatic ketones [27]	Amino esters [34]
Cyclic ketones [28]	Amino alcohols [35]
Acetals [29]	Mercaptans and sulfides [10]
Aliphatic esters [30–32]	Alkyl benzenes [14]
Polyfunctional esters [33]	Alkyl pyrazines [15]
Aromatic esters [20, 21]	Alkyl pyridines [23]
Amides [13]	Alkyl indoles [36]
	Monoterpenes [37]

[11] *F. W. McLafferty*, Analytic. Chem. *31*, 82 (1959).

[12] *M. L. Dhar, V. Thaller, M. C. Whiting, R. Ryhage, S. Ställberg-Stenhagen*, and *E. Stenhagen*, Proc. chem. Soc. (London) 154 (*1959*).

[13] *J. A. Gilpin*, Analytic. Chem. *31*, 935 (1959).

[14] *S. Meyerson*, Applied Spectroscopy *9*, 120 (1955).

[15] *K. Biemann* and *J. Seibl*, unpublished results.

[16] *J. A. Gilpin*, J. chem. Physics *28*, 521 (1958).

[17] *F. W. McLafferty*, Analytic. Chem. *31*, 2072 (1959).

[18] *Ng. Dinh-Nguyen, R. Ryhage*, and *E. Stenhagen*, ASTM E-14 Meeting on Mass Spectrometry, Atlantic City, June 1960.

[19] *J. D. McCollum* and *S. Meyerson*, J. Amer. chem. Soc. *81*, 4116 (1959).

[20] *F. W. McLafferty* and *R. S. Gohlke*, Analytic. Chem. *31*, 2076 (1959).

[21] *E. M. Emery*, Analytic. Chem. *32*, 1495 (1960).

[22] *T. Aczel* and *H. E. Lumpkin*, Analytic. Chem. *32*, 1819 (1960).

[23] *K. Biemann* and *G. Spiteller*, unpublished results.

[24] *F. W. McLafferty*, Analytic. Chem. *31*, 477 (1959).

[25] *R. A. Friedel, J. L. Shultz*, and *A. C. Sharkey Jr.*, Analytic Chem. *28*, 926 (1956).

[26] *J. A. Gilpin* and *F. W. McLafferty*, Analytic. Chem. *29*, 990 (1957).

[27] *A. G. Sharkey Jr., J. L. Shultz*, and *R. A. Friedel*, Analytic. Chem. *28*, 934 (1956).

[28] *J. H. Beynon, R. A. Saunders*, and *A. E. Williams*, Applied Spectroscopy *14*, 95 (1960).

[29] *R. A. Friedel* and *A. G. Sharkey Jr.*, Analytic. Chem. *28*, 940 (1956).

[30] *A. G. Sharkey Jr.; J. L. Shultz*, and *R. A. Friedel*, Analytic. Chem. *31*, 87 (1959).

[31] *R. Ryhage* and *E. Stenhagen*, Ark. Kemi *13*, 523 (1959); *14*, 483 (1959).

[32] *J. H. Beynon, R. A. Saunders*, and *A. E. Williams*, Analytic. Chem. *33*, 221 (1961).

[33] *R. Ryhage* and *E. Stenhagen*, Ark. Kemi *14*, 497 (1959); *15*, 291, 333, 545 (1960).

[34] *K. Biemann, J. Seibl*, and *F. Gapp*, Biochem. biophysic. Res. Commun. *1*, 307 (1959); J. Amer. chem. Soc. *83*, 3795 (1961).

[35] *K. Biemann, F. Gapp*, and *J. Seibl*, J. Amer. chem. Soc. *81*, 2274 (1959).

[36] *J. H. Beynon* and *A. E. Williams*, Applied Spectroscopy *13*, 101 (1959).

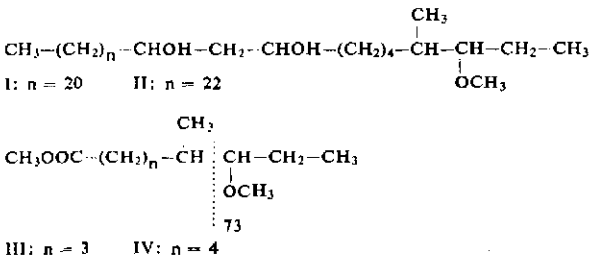
[37] *R. I. Reed* and *T. Gilchrist*, Experientia *16*, 134 (1960).

4. The Determination of the Structure of Natural Products

In recent years, three groups have been active in this field: *E. Stenhagen* and *R. Ryhage* (Göteborg and Stockholm), *R. I. Reed* (Glasgow), and the author's laboratory (Cambridge, Mass.).

The Swedish group has devoted considerable attention to the mass spectrometry of lipids, and this work was the subject of a recent review [38]. Of particular interest is the elucidation of the structure of phthiocerol and mycocerosic acid, both compounds isolated from the lipid fraction of tubercle bacilli [39].

Phthiocerol was shown to be a mixture of I and II on the basis of simple chemical degradation, separation of the products by gas chromatography, and detailed interpretation of the mass spectra of the individual fractions [40]. Both tetracosanoic acid (from II) and docosanoic acid (from I) were isolated, and in addition two alkoxy acids were found. They were assigned structures III and IV on the basis of their molecular weights (as determined on their methyl esters) and the intense peak at mass 73 due to cleavage of the bond between the highly substituted and the oxygen-bearing carbon atom. Such a bond has a high tendency for cleavage as indicated in the earlier discussion (Types A and B).

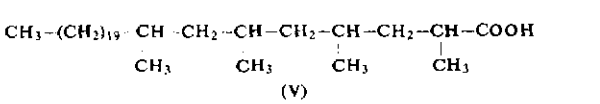


I: n = 20 II: n = 22

III: n = 3 IV: n = 4

The position of the methyl group in the molecule is also shown conclusively by the mass spectrum of phthiocerane (Fig. 1). This material is obtained on exhaustive reduction. The reduction eliminates all the heteroatoms which otherwise dominate the fragmentation of such a molecule, and the only factors remaining are the more highly substituted carbon atoms, making it much easier to deduce the branching points in the molecule. For the unambiguous determination of the structure of an aliphatic carbon sekeleton, substituted by a number of functional groups, the hydrocarbon is the most suitable derivative, if it can be prepared without skeletal rearrangement.

Mycocerosic acid also turned out to be a mixture, the major component of which was attributed to structure V [41].



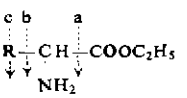
(V)

The mass spectrum of the methyl ester indicated a molecular weight of 494. An intense fragment ion of mass 88 (rearrangement of Type H) indicated an α-methyl group. A higher relative intensity of the fragments containing 5, 8 or 11 carbon atoms in addition to the $COOCH_3$-group indicated an alternating substitution by four methyl groups. This was shown conclusively by the spectrum of the corresponding alcohol which showed all the fragments derived from the hydrocarbon-end of the molecule. Comparison [41] with the isomeric, synthetic product containing only three methyl groups serves as a good example illustrating the fact that in mass spectrometry a synthetic or otherwise easily available comparison sample is of use even if it is only closely related to the molecule being investigated. The differences between the two spectra can frequently be interpreted in terms of the differences between the two structures, a technique that applies less, or not at all, to other criteria (*e.g.* melting point).

Amino Acids, Peptides

The similarity of the various amino acids in their chemical, and also to a certain extent, in their spectroscopic properties, combined with the fact that those compounds are usually available only in small amounts, makes the determination of the structure of new amino acids frequently rather difficult. Mass spectrometry was shown to be a promising technique in this area and also useful for small peptides.

The selection of a suitable derivative is of importance here because of the volatility problem. The ethyl esters of amino acids have been found to be most suitable because they can be prepared easily from a very small sample. An investigation of the mass spectra of a large number of amino esters, of which two are shown in Fig. 3, indicated that almost all the fragments formed belonged to one of three groups [34]: cleavage (type B) of bond (a) gives the "amine fragment," the mass of



which after subtraction of 29 units indicates the size of the group R. This fragment may decompose further depending on its structure and the presence of additional functional groups. Cleavage (Type B) at (b) gives rise to the "ester fragment," the mass of which is 102 in the case of unsubstituted α-amino acids (and is, therefore, absent in the spectrum of proline ester); the ester fragment decomposes further under elimination of ethylene (Type H) to give mass 74. The presence of branched side chains or functional groups in R leads to further fragments, some of which have already been discussed in the esters of leucine and methionine (Fig. 3a and b) or are indicated in the figures.

Based on this experience, the structure of a new amino acid isolated from the gall tissues of various plants was

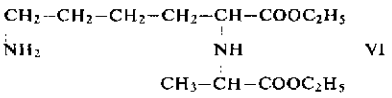
[38] *R. Ryhage* and *E. Stenhagen*, J. Lipid Res. *1*, 361 (1960).

[39] Review of the chemistry of the lipids of mycobacteria: *E. Lederer*, Angew. Chem. *72*, 372 (1960).

[40] [a] *L. Ahlquist*, *R. Ryhage*, *E. Stenhagen*, and *E. v. Sydow*, Ark. Kemi *14*, 211 (1959). [b] *R. Ryhage*, *S. Ställberg-Stenhagen*, and *E. Stenhagen*, ibid. *14*, 247, 259 (1959).

[41] *C. Asselineau*, *J. Asselineau*, *R. Ryhage*, *S. Ställberg-Stenhagen*, and *E. Stenhagen*, Acta chem. scand. *13*, 822 (1959).

recently determined [42]. By the conventional chemical techniques it was not possible to gain any insight into the structure of this molecule aside from the usual analytical data; even its elemental composition was somewhat in doubt. The mass spectrum of the ethyl ester obtained from about half a milligram of the amino acid (Fig. 4) led to the following structure (VI) for the ester:



VI

The even molecular weight (274) indicates the presence of an even number of nitrogen atoms, most probably two. The loss of 73 mass units ($COOC_2H_5$) is analogous to the formation of the amine fragment discussed above

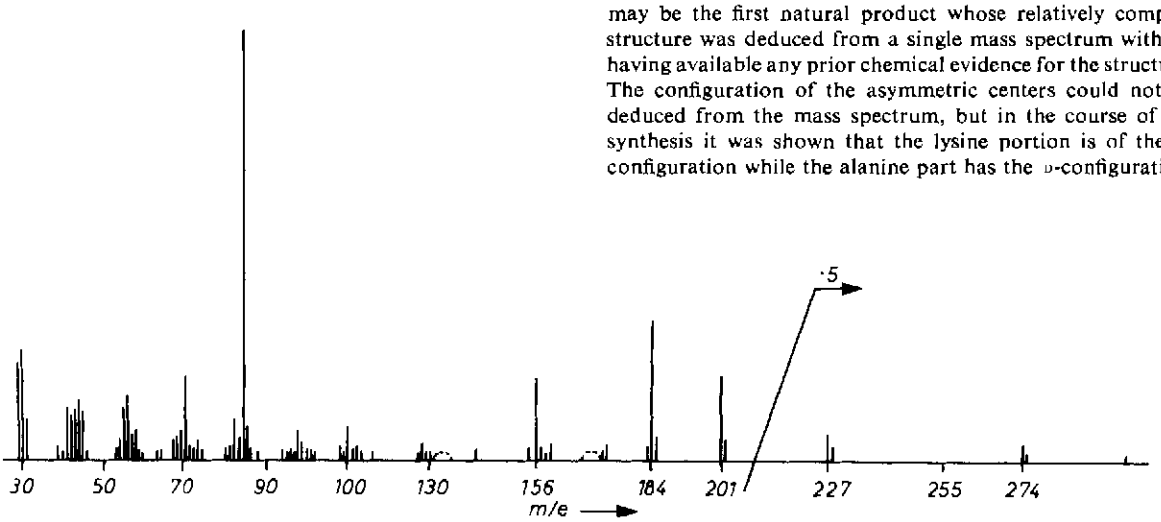


Fig. 4. Mass spectrum of the ethyl ester of lysopine [42]

and indicates an α-amino group (but not $-NH_2$ because of the absence of a fragment of mass 102). The ion of mass 201 formed in this way loses NH_3 leading to mass 184, indicating the presence of an $-NH_2$ group which is lost via elimination of Type E. The fragment of mass 184 eliminates ethylene (Type H, analogous to the formation of mass 74 from mass 102, see above) indicating that there must be present an additional $COOC_2H_5$ group. Most important, however, is the fragment of mass 84; this is also formed from lysine ester [34] where it is due to the elimination of NH_3 from the amine fragment. It was, therefore, concluded that in this new amino acid a C_5-chain connecting the two nitrogen atoms is present. The fact that mass 30 is the most intense aminoalkyl fragment is in agreement with structure VI.

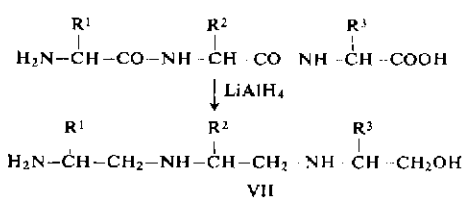
The dotted circles (Fig. 4) indicate so-called "metastable peaks." These are broad peaks of low intensity, spread over a few mass units. Such a peak arises if an ion of mass m_1 is accelerated in the electric field and decomposes to a daughter ion of mass m_2 and a neutral particle before being deflected in the magnetic field. Both these masses are related to the maximum of the metastable peak (m*) by the following expression [43]:

$$m^* = \frac{m_2^2}{m_1}$$

For a decomposition of mass 201 to mass 186, the maximum of the metastable peak (m*) should be at mass 168.4, and is found at mass 169. It is, therefore, a valid assumption that this decomposition in fact takes place, and that mass 184 is not formed, for example, directly from the molecular ion. Similarly, mass 184 decomposes in one step to mass 156 because the metastable peak is found at mass 133 (calculated mass 132.2). The importance of these metastable peaks should not be underestimated as they provide the only information about the mass of the neutral fragments.

The validity of the proposed structure (VI) was shown by synthesis and the amino acid was named lysopine [42]. This may be the first natural product whose relatively complex structure was deduced from a single mass spectrum without having available any prior chemical evidence for the structure. The configuration of the asymmetric centers could not be deduced from the mass spectrum, but in the course of the synthesis it was shown that the lysine portion is of the L-configuration while the alanine part has the D-configuration.

It is also possible to deduce the amino acid sequence in small peptides if they are converted to more volatile derivatives prior to mass spectrometric investigation. The polyamino alcohols (VII) formed by $LiAlH_4$ reduction of such peptides are well suited for this purpose



VII

[35], because they contain a sequence of N–C–C–N bonds which are cleaved with ease (Type B). These fragments are responsible for characteristic peaks in the spectra. Fig. 5 (a) shows the spectrum of the compound obtained on reduction of acetyl-L-leucyl-L-alanyl-L-proline with $LiAlD_4$. The use of deuterium made it possible to prove the correctness of the proposed fragmentation mechanism and also to avoid the otherwise existing symmetry of this particular molecule with respect to the expected mass numbers.

Using a number of synthetic di- to pentapeptides it was shown that the amino acid sequence can be deduced

[42] *K. Biemann, C. Lioret, J. Asselineau, E. Lederer,* and *J. Polonsky,* Biochim. biophysica Acta *40,* 369 (1960); Bull. Soc. Chim. biol. *42,* 979 (1960).

[43] *J. A. Hipple, R. E. Fox,* and *E. U. Condon,* Physic. Rev. *69,* 347 (1946).

from these mass spectra. Gas chromatography can be used successfully [44] for the separation of mixtures of such polyamino alcohols, and this is an example of the extreme usefulness of a combination of the two techniques. In this case, separate collection and determination of the mass spectra is a necessity. Direct coupling of gas chromatograph and mass spectrometer have been suggested [45, 46] for the analysis of mixtures of simple and known compounds of relatively high volatility.

In order to facilitate the separation of the reduction products of peptides containing polyfunctional amino acids, the removal of the polar groups by further reduction (with $LiAlD_4$ via the halides) is suggested. The mass spectra of the polyamines (Fig. 5b) are also well suited for interpretation. In this case, the use of deuterium is even more important because it makes it possible to distinguish the side chains of α-amino butyric acid, threonine, and aspartic acid, which otherwise would become identical [44].

With simple dipeptides, the methyl esters of their N-trifluoroacetates are also sufficiently volatile to be separated by gas chromatography [47, 48b] and investigated by mass spectrometry [48a, b].

Alkaloids

Mass spectrometry can also be used for the determination of the structure of alkaloids. In a molecule consisting of both aromatic and an aliphatic parts, the bonds in the latter will be broken preferentially. Hence it was expected that mass spectra would be particularly suited for the comparison and identification of the alicyclic carbon skeleton of various alkaloids. By this technique it was possible to corroborate the structure of two alkaloids, sarpagine [49a, 50] and ibogaline [51], which had been proposed [49b, 50a] on the basis of biogenetic considerations some time ago. Fig. 6 illustrates this approach using the mass spectra of ibogamine, ibogaine, and

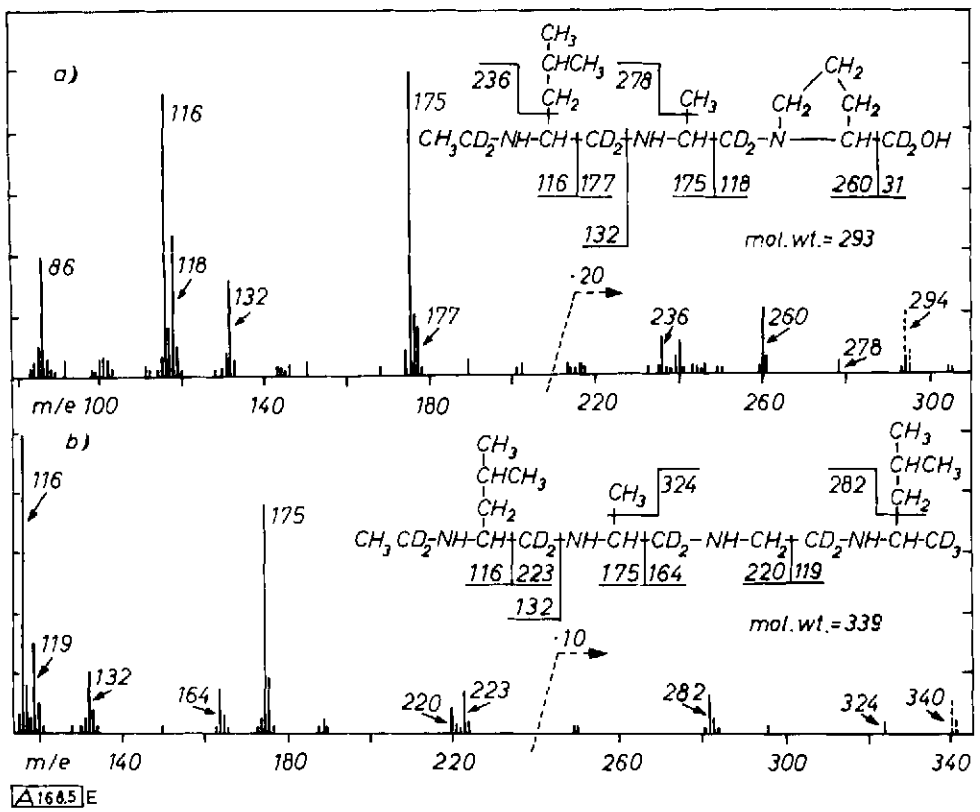


Fig. 5. Mass spectrum (in the region m/e 80–320) of the polyamino alcohol obtained on $LiAlD_4$-reduction of Ac-leu-ala-pro and of the polyamine obtained on two-stage reduction of Ac-leu-ala-gly-leu (in the region of m/e 110–350) [44].

These polyamines and polyamino alcohols give rise to very unstable molecular ions; their corresponding protonated form (ammonium ion) is rather stable. These compounds have, therefore, a considerable tendency to form particles of mass M + 1. The relative intensity of such ions depends on the conditions prevailing in the ion source and the dotted part of the masses 294 and 340 in Fig. 5 indicates this. The molecular weight of these compounds can be deduced accordingly.

[44] *K. Biemann* and *W. Vetter*, Biochem. biophysic. Res. Commun. *3*, 578 (1960).

[45] *R. S. Gohlke*, Analytic. Chem. *31*, 535 (1959).

[46] *L. P. Lindeman* and *J. L. Annis*, Analytic. Chem. *32*, 1742 (1960).

[47] *F. Weygand*, European Peptide Symposium, Basel, September 1960.

[48] [a] *C. O. Andersson*, Acta chem. scand. *12*, 1353 (1958); [b] *E. Stenhagen*, Z. analyt. Chem. *181*, 462 (1961).

[49] [a] *K. Biemann*, Tetrahedron Letters No. 15, 9 (1960); [b] For a review of the chemistry of sarpagine see: *A. R. Battersby* and *H. F. Hodson*, Quart. Revs., *14*, 77 (1960).

[50] *K. Biemann*, International Symposium on the Chemistry of Natural Products, Melbourne, August 1960; J. Amer. chem. Soc. *83*, 4801 (1961).

[50a] *N. Neuss*, J. org. Chemistry *24*, 2047 (1959).

[50b] *M. F. Bartlett, D. F. Dickel*, and *W. J. Taylor*, J. Amer. chem. Soc. *80*, 126 (1958).

[51] *K. Biemann* and *M. Friedmann-Spiteller*, J. Amer. chem. Soc. *83*, 4805 (1961).

ibogaline. Two groups of fragments are clearly indicated: one in the region of mass 120 to 150 and present in all three spectra; the other group of peaks above mass 155 is shifted 30 mass units in ibogaine and 60 mass units in ibogaline compared with the spectrum of ibogamine. This mass difference corresponds to one and two methoxyl groups, respectively. Obviously the fragments of the second group contain the indole nucleus while the rings A, B, and C plus C_{19}. Masses 281 and 285 arise by loss of the ethyl and methyl group, respectively.

On the basis of such considerations, the position of the hydroxyl group in iboxygaine (VIIId) was deduced [52]. Replacement of this group by deuterium led to characteristic shifts of the peaks in the mass spectrum of the ibogaine molecule thus obtained, indicating that the deuterium atom is not located in the methyl group

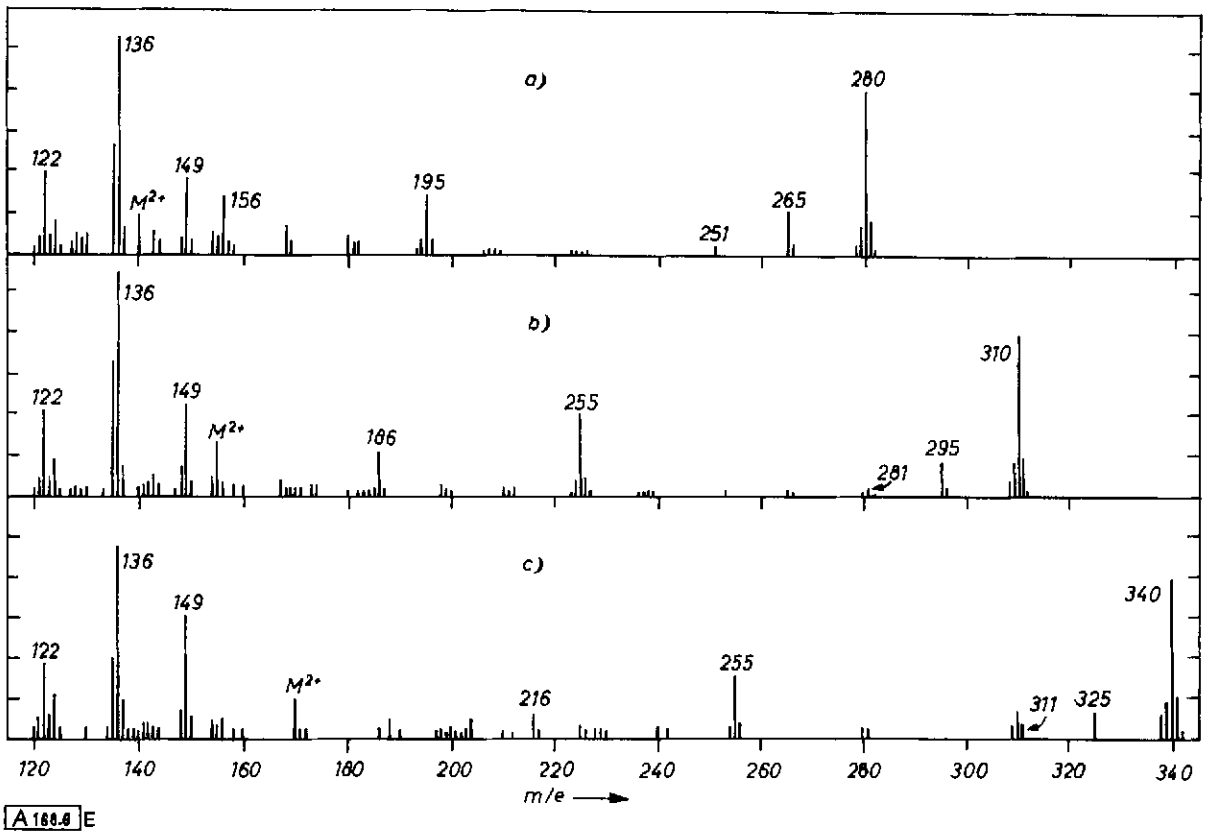
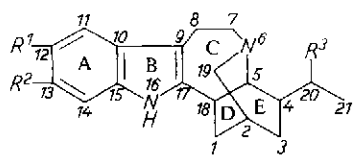


Fig. 6. Mass spectra of iboga alkaloids (in the region of m/e 120–350): ibogamine (VIIIa), ibogaine (VIIIb), and ibogaline (VIIIc) [51]

first group does not. Structures VIIIa and VIIIb for ibogamine and ibogaine had been proved beyond any doubt by chemical degradation [50b]. Thus structure VIIIc follows [51] for ibogaline, the ultraviolet spectrum of which had indicated the presence of a 5,6-dimethoxyindole chromophore [50a].



VIIIa: $R^1 = R^2 = R^3 = H$
VIIIb: $R^1 = OCH_3$, $R^2 = R^3 = H$
VIIIc: $R^1 = R^3 = OCH_3$, $R^2 = H$
VIIId: $R^1 = OCH_3$, $R^2 = H$, $R^3 = OH$

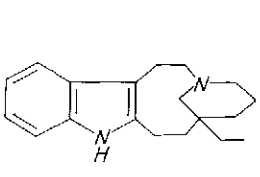
With the aid of deuterium-labelled ibogaine molecules it was possible to trace the formation of the various fragments [51]. The first group mentioned above always contains ring E and the ethyl group, and in mass 122 also C_7, in 136 C_7 and C_8, and in 149 C_{18}, C_1, and C_7. Mass 186, on the other hand, contains rings A and B in addition to C_8, C_{18}, and C_1, while mass 225 represents but is present in the ethyl group: The former was still lost as 15 mass units while the latter was lost as 30 mass units (as indicated by the mass of the peaks, namely 281 and 296); the molecular weight was 311.

The peaks labelled M^{2+} in Fig. 6 are due to doubly charged molecular ions. They are formed by abstraction of two electrons from the molecule and are, therefore, observed in the spectra of those compounds which contain a number of possibly conjugated π-electron systems. The mass spectra of such compounds frequently show a number of peaks of usually low intensity, separated from each other by only one-half of a mass unit. Because doubly charged fragments can be formed, and such particles are always recorded at half the actual mass, the x-axis of a mass spectrum always expresses the mass-to-charge ratio (m/e) rather than mass alone.

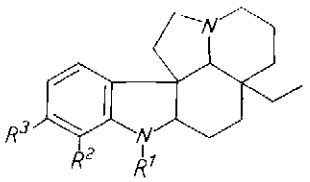
It is thus possible to correlate by mass spectrometry different alkaloids if they contain the same carbon skeleton but differ in the number and type of substituents present in the aromatic moiety of the molecule. This approach was used for the determination of the

[52] *K. Biemann* and *M. Friedmann-Spiteller*, Tetrahedron Letters No. 2, 68 (1961).

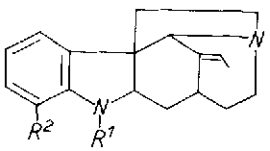
structure of pyrifolidine (X, $R^1 = CH_3CO$, $R^2 = R^3 = CH_3O$) [53], quebrachamine (IX) [53a], and a series of alkaloids of type X and XI [53b] isolated from the bark of *aspidosperma quebracho blanco*.



IX



X



XI

Other Natural Products

The identification of a relatively simple indole derivative, isolated from bovine pineal glands shall be mentioned. The elucidation of the structure of this compound by conventional techniques, and even elemental analysis, was made impossible by the fact that not more than 0.4 milligrams of the material was isolated. It was identified as 5-methoxyindole-3-acetic acid [54] on the basis of ultraviolet fluorescence and infrared spectra combined with the mass spectrum of its methyl ester which indicated a molecular weight of 219 and an intense fragment of mass 160 (loss of the $COOCH_3$ group).

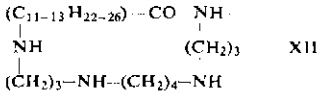
Steroids and triterpenes also yield good mass spectra, but their interpretation is complicated because of the polyalicyclic nature of these compounds. The molecular weight, and frequently also the size and structure of the side chain, can be deduced rather easily [55] but cleavage of the ring system requires fragmentation of at least two bonds and is frequently accompanied by rearrangements. The mass spectra of a number of rather simple representatives of this class (hydrocarbons, alcohols, ketones, and esters) have been determined and several explanations for some of the fragmentation processes have been offered [38, 55–57]. It seems, however, that more detailed investigations, wherever possible accompanied by the mass spectra of isotopically labelled compounds, are required before a clear picture of the detailed fragmentation modes of this class can be presented.

The investigation of the mass spectra of carbohydrates is difficult because of the low volatility of these compounds and the fact that a large number of stereoisomers are possible. The difference in the bond energy of α- and β-glycosidic linkages is said to be borne out by the spectra [58]. The volatility of carbohydrates is increased considerably in certain derivatives; for example, it was possible to obtain a mass spectrum [59] of the oligosaccharide laminarine after permethylation and introduction of the sample directly into the ion source without an intervening leak. A systematic investigation of carbohydrates has not yet been undertaken.

In a few cases it has been already mentioned that the spectra of diastereomers are very similar. A correlation of a number of di- and polycyclic epimeric alcohols showed, however, that the differences in these spectra can be correlated with the stereochemistry of such compounds [60]. Since the fragments obtained from such isomers are the same in both cases, any difference in the steric arrangement in the molecular ion must express itself in the rate of decomposition of this ion and, therefore, in its intensity. Epiandrosterone (equatorial hydroxyl group) exhibits a molecular ion, the intensity of which is 4.58 % of all the ions formed, while this value is 3.53 % for androsterone (axial hydroxyl group). Because of the increased size of an acetoxy group compared with a hydroxyl group, these differences are even larger in the mass spectra of the acetates of these epimers.

Mixtures

The presence of mixtures frequently offers a particular problem. The mass spectra of such a sample often exhibits peaks which cannot be interpreted as the fragments of only one compound. Mixtures of homologs, for example, show differences of 14 mass units from the molecular weight down and are thus easily recognized because a molecular ion never eliminates CH_2 as such. The empirical formula of the alkaloid pithecolobine had been in doubt for some time until it was assumed on the basis of many analyses to contain a C_{12} side chain [61]. The aliphatic acid obtained on degradation of deoxypithecolobine (XII) should, therefore, have been a C_{13}-compound, but the mass spectrum showed that it was a mixture of mainly lauric acid, some myristic acid, and about 5 % tridecanoic acid (as deduced from the molecular weights 200, 214, and 228). This finding was corroborated by fractionating the sample into the mass spectrometer whereupon the series of spectra obtained showed continuously changing behavior. This technique,



XII

[53] *C. Djerassi, B. Gilbert, J. N. Shoolery, L. F. Johnson,* and *K. Biemann,* Experientia *17,* 162 (1961).

[53a] *K. Biemann* and *G. Spiteller,* Tetrahedron Letters No. 9, 299 (1961).

[53b] *K. Biemann, M. Friedmann-Spiteller,* and *G. Spiteller,* Tetrahedron Letters, No. 14, 485 (1961).

[54] *A. B. Lerner, J. D. Case, K. Biemann, R. V. Heinzelman, J. Szmuszkovicz, W. C. Anthony,* and *A. Krivis,* J. Amer. chem. Soc. *81,* 5264 (1959).

[55] *P. de Mayo* and *R. I. Reed,* Chem. and Ind. *1956,* 1481.

[56] *R. I. Reed,* J. chem. Soc. (London) *1958,* 3432.

[57] *S. S. Friedland, G. H. Lane Jr., R. T. Longman, K. E. Train,* and *M. J. O'Neal,* Analytic. Chem. *31,* 169 (1959).

[58] *P. A. Finan, R. I. Reed,* and *W. Snedden,* Chem. and Ind. 1172 (1958).

[59] *P. A. Finan* and *R. I. Reed,* Nature (London) *184,* Suppl. 24, 1866 (1959).

[60] *K. Biemann* and *J. Seibl,* J. Amer. chem. Soc. *81,* 3149 (1959).

[61] *K. Wiesner* et al., Canad. J. Chem. *30,* 761 (1952); J. Amer. chem. Soc. *75,* 6348 (1953).

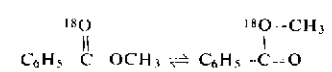
apart from the use of low energy electrons which accentuates the molecular ions, is one of the best for the detection of a mixture. The major component of deoxypithecolobine is, therefore, represented by structure XII containing a C_{11} side chain [62].

Frequently the question of the purity requirements is posed. It cannot be answered in a general way because this depends on the particular problem to be investigated. The presence of water, or low molecular weight solvent does not interfere, for example, in the comparison of the spectra of the iboga alkaloids because only the region of higher masses is used for this purpose (Fig. 6). Similarly, in the determination of deuterium in the undegraded molecule (see below) the presence of heavy water is of no consequence. On the other hand, erroneous results would be obtained in any interpretation requiring the comparison of the intensity of an individual peak with the total intensity of all the ions formed, *e.g.* differentiation of diastereomers. Non-volatile impurities do not, of course, interfere at all as long as they do not find their way into the valves of the instrument.

5. Localization of Stable Isotopes in the Intact Molecule

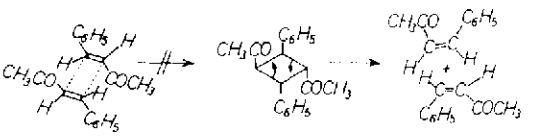
It has already been mentioned repeatedly that the incorporation of deuterium into a molecule leads not only to an increase in its molecular weight but also to characteristic shifts of the peaks in the mass spectrum and that this shift depends on the position of the isotope in the molecule. The application to structural problems has already been discussed. The exchange of hydrogen atoms by deuterium using D_2O or C_2H_5OD in the presence of base, and mass spectrometric determination [8] of the number of exchangeable atoms, has been employed a number of times [63]. Catalytic deuteration of double bonds, on the other hand, often leads to considerable exchange at saturated centers, as was shown, for example, for methyl oleate [64]. The extent of such an exchange seems, however, to depend on the steric environment of the double bond. It was possible to show that the double bond in sarpagine is present in the ethyl group [50].

In the study of reaction mechanisms it is frequently of importance to determine the distribution of the heavy atoms in the reaction product, rather than its total amount. This can be done most easily on the basis of the mass spectrum of the undegraded product. The thermal isomerization of methyl benzoate should be mentioned as an example [65]:



This compound gives a fragment of high intensity at mass 105 corresponding to the Ph–CO group and, therefore, contains the carbonyl oxygen atom. If this is ^{18}O, the peak shifts to mass 107. When methyl benzoate containing 1.5 % ^{18}O in the methoxy group was heated to 250 ° and 400 °C., respectively, it could be shown on the basis of the ratio of the peaks at mass 105 and mass 107 that the rearrangement takes place to an appreciable extent only at the higher temperature. The determination of the heavy oxygen in the usual way (combustion to CO_2) would be useless in this case.

Similarly the possibility of a *trans-cis*-isomerization of benzalacetone via a dimer was investigated [66]:



A mixture of ordinary *trans*-benzalacetone and pentadeutero-benzalacetone (C_6H_5-CD CD CO-CD_3) was subjected to the conditions of isomerization, and the mass spectrum of the product was compared with the spectrum of the starting material. The product did not show any di- and trideuterated molecule. Such species would be expected if a dimeric intermediate were formed, and this mechanism is therefore excluded.

Mass spectrometry is certainly a valuable tool for the investigation of such problems involving the study of a reaction mechanism. The main advantage lies in the ability to observe and monitor the isotope content of the individual components of a mixture. This was recently [67] shown for mixtures of amino acids labelled with ^{15}N.

The mass spectrum shown in Fig. 3 suggests that the presence of heavy nitrogen in the amino group of leucine will lead to a higher intensity of the peak at mass 87 while it would give rise to a peak at mass 105 in methionine. It is thus possible to determine the ^{15}N content of these amino acids not only in their pure form but also in a mixture, since they do not influence each other.

To exclude even small contributions due to other components, it is of advantage to use electrons of low energy (approximately 10 eV) for ionization. Under those conditions the "amine fragment" is still very intense while other fragments are almost eliminated. By this technique it was possible to determine the ^{15}N content of the individual amino acids in a mixture containing eleven components without prior separation [67].

The amount of time and sample required is considerably less compared with the conversion to nitrogen gas, but also the accuracy near the natural abundance of ^{15}N is much lower. This conversion is the usually employed technique and requires a very careful separation of all the components prior to degradation.

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[62] *D. E. Orr* and *K. Wiesner*, Chem. and Ind. *1959*, 672.

[63] See for example *G. Büchi, M. Schach v. Wittenau*, and *D. M. White*, J. Amer. chem. Soc. *81*, 1968 (1959).

[64] *Ng. Dinh-Nguyen* and *R. Ryhage*, J. Res. Inst. Catalysis, Hokkaido Univ. *8*, No. 1, 73 (1960).

[65] *K. B. Wiberg*, J. Amer. chem. Soc. *75*, 2665 (1953).

[66] *H. O. House*, J. org. Chemistry *24*, 1374 (1959).

[67] *K. Biemann* and *G. G. J. Deffner*, Biochem. biophysic. Res. Commun. *4*, 283 (1961).

6. Mass Spectrometers of Extremely High Resolution

Up to this point full mass units have been considered because the previously available mass spectrometers permit only such determinations. If it is possible to measure the mass of a molecule or of a fragment with an accuracy of 0.01 mass units, much additional information can be obtained [68] because of the deviations from integral numbers of the atomic weights. The "monoisotopic" molecular weight (*i.e.*, the molecule containing only the lightest isotopes) of tetralin ($C_{10}H_{12}$) is 132.136; for indanone (C_9H_8O) it is 132.100 while the molecular weight of dihydrobenzpyrazine ($C_8H_{12}N_2$) is 132.110. It is thereby possible not only to determine the molecular weight but also the elemental composition, and with much more certainty than by using the intensity of the isotope peaks discussed earlier. Obviously it is also possible to determine the elemental composition of the fragments, which is very helpful in the interpretation of the spectrum [69]. This factor should however not be overestimated because frequently it is important to find out from which part of the molecule acertain fragment arises, and its elemental composition is of no help if more than one region in the molecule contains the same type of atoms. The use of both high resolution mass spectrometers and isotopically labelled substances will probably evolve as the most useful approach for the mass spectrometry of organic compounds.

7. Conclusion

This review emphasizes primarily some recent mass spectrometric investigations of natural products and other problems in organic chemistry rather than analytical applications. The latter are reviewed elsewhere [70—72], and it is, in part, due to the excellent quantitative results of mass spectrometry that the qualitative potentialities of the technique were until recently very much neglected by the organic chemist. The technique is used for structure determination thus far only in a few research laboratories. This may change if the mass spectrometer is regarded not merely as a complex instrument but rather as a new micro-degradation reaction, the mechanism of which is already elucidated to a certain extent and in which the products are separated automatically, and at the same time subjected to a molecular weight determination and even to elemental analysis.

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[68] *J. H. Beynon* in *J. D. Waldron*: Advances in Mass Spectrometry. Pergamon Press, London 1959, p. 328.

[69] *J. H. Beynon, G. R. Lester*, and *A. E. Williams*, J. physic. Chem. *63*, 1861 (1959).

[70] *V. H. Dibeler* in *J. Mitchell Jr.*: Organic Analysis. Interscience, New York 1956. Vol. III, p. 387.

[71] *V. H. Dibeler* and *R. M. Reese*, Analytic Chem. *32*, 211 R (1960).

[72] *D. W. Stewart* in *A. Weissberger:* Physical Methods of Organic Chemistry. Interscience, New York 1960, Vol. I, Part IV, p. 3449—3539.

COMMUNICATIONS

Reaction of Alkali Amides with Imides of the Elements of Groups III to V

By Prof. Dr. P. W. Schenk and Dr. J. B. P. Tripathi

Institut für Anorganische Chemie
der Freien Universität Berlin (Germany)

Ammonolysis of $SiCl_4$ produces neither $Si(NH_2)_4$ nor $SiNH(NH_2)_2$, $Si(NH)_2$ being formed exclusively even at the melting point of ammonia according to the equation (1):

(1) $SiCl_4 + 6\ NH_3 \rightarrow Si(NH)_2 + 4\ NH_4Cl$

Glemser [1] found that $Si(NH)_2$ is stable up to about 300 °C; we have confirmed this observation. $Si(NH)_2$ is insoluble in hot alkali amide solutions, even under pressure (in contrast to SiO_2 in the aquo-system, where it is soluble in alkali). However, it reacts with melting alkali amide, *e.g.* KNH_2 or $NaNH_2$, in an O_2-free N_2-stream:

(2) $4\ KNH_2 + Si(NH)_2 \rightarrow \underset{\text{I}}{K_4Si(NH)_4} + 2\ NH_3$

Interference lines appear in the X-ray diagram of KNH_2 only when the ratio KNH_2:$Si(NH)_2$ in the reaction mixture exceeds 4:1 mole. Other lines, apparently associated with compound (I), also appear. $Si(NH)_2$ is amorphous to X-rays.

At a ratio of 2 moles of KNH_2 per mole of $Si(NH)_2$, new lines appear. These apparently belong to $K_2Si(NH)_3$ (II):

(3) $2\ KNH_2 + Si(NH)_2 \rightarrow \underset{\text{II}}{K_2Si(NH)_3} + NH_3$

When $NaNH_2$ is used, $Na_2Si_2(NH)_5$ (III) is also formed.

The formation of such compounds was confirmed in conductance measurements by titration with KNH_2 in liquid NH_3. We added a measured quantity of $SiCl_4$ to liquid NH_3 and titrated with an 0.2 N KNH_2 solution. The first break in the conductivity curve occurs after the NH_4Cl, formed according to equation (1), has been neutralized. Two further breaks, at 6 and 8 moles KNH_2 per mole $SiCl_4$, correspond to the equivalence ratios of equations (3) and (2). Addition of $SiCl_4$ to excess of KNH_2 and backtitration with 0.2 N NH_4Cl leads to the same result.

Analogously, we obtained a break in the titration of $AsCl_3$ at 3 moles of KNH_2 per mole of $AsCl_3$ and at 4 moles of KNH_2 per mole of $AsCl_3$. This indicates the formation of $KAs(NH)_2$. Only the titrimetric method was applicable here since, contrary to literature data, $As(NH_2)_3$ does not exist and the $As_2(NH)_3$ formed in the ammonolysis according to equation (4) begins to decompose even below room temperature.

$$2\ AsCl_3 + 9\ NH_3 \rightarrow As_2(NH)_3 + 6\ NH_4Cl \quad (4)$$

Furthermore, we were able to confirm the formation of $KB(NH)_2$, $KP(NH)_2$, and $K_3P(NH)_3$ by conductometric titration of the corresponding chlorides with 0.2 N KNH_2 in liquid NH_3.

It can only be decided after further studies whether the process yields imido compounds (corresponding to oxo compounds), as indicated in the formulae, rather than the amido compounds $KAs(NH_2)_4$, $KB(NH_2)_4$, $KP(NH_2)_4$, and $K_3P(NH_2)_6$ (corresponding to hydroxo compounds).

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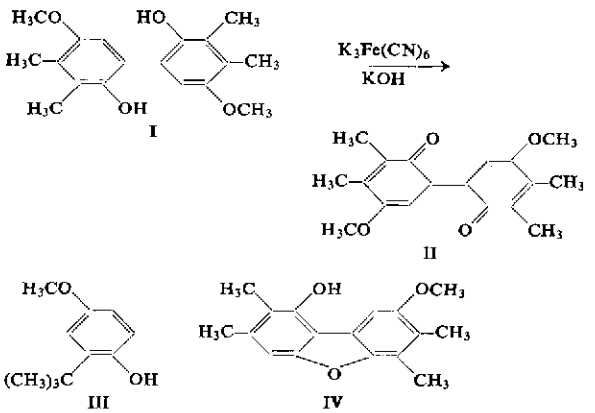
[1] *O. Glemser* and *P. Naumann*, Z. anorg. allg. Chem. *298*, 134 (1959).

A Derivative of o-Diphenoquinone

By Dr. D. Schulte-Frohlinde and Dipl.-Chem. F. Erhardt

Kernforschungszentrum Karlsruhe,
Strahlenchemisches Laboratorium, Karlsruhe (Germany)

The existence of *o*-diphenoquinones is controversial [1]. Derivatives, however, can be prepared provided that the 4,4'-positions as well as the 3,5,3',5'-positions are substituted. Compound (I) yields deep blue crystals of (II) (yield 90 %, decomp. 118 °C, redox potential > + 0.79 V) by oxidation in aqueous alcohol. The oxidation of (III) [2] yields blue solutions, but no *o*-diphenoquinone derivative can be isolated.



The structure of (II) is supported by direct synthesis, by the consumption of two reduction equivalents for the transition (II) → (I) (determined by titration with hydroquinone in benzene/acetone), and by infrared spectral data (C=O band at 1633 cm^{-1}). The ultraviolet spectrum of (II) is similar to that of indigo [indigo in chloroform: λ_{max} = 285 (4.63), 445 (3.0), 610 (4.24) mμ (log ε); (II) in cyclohexane: λ_{max} = 232 (4.42), 375 (3.41), 624 (4.0) mμ (log ε)]. Compound (II) undergoes a photoreaction to give (IV) (quantum yield < 0.001). A similar conversion has previously been found in the case of 4-substituted bis[naphthalene-2]indigoids [3,4]. (II) is converted to (I) when irradiated with ^{60}Co γ-rays in isopropanol with exclusion of air (G = 3.6 molecules/100 eV).

Received December 7, 1961 [Z 198/30 IE]

[1] *E. Müller, R. Mayer, B. Narr, A. Rieker*, and *K. Scheffler*, Liebigs Ann. Chem. *645*, 25 (1961).

[2] *J. Baltes* and *F. Volbert*, Fette, Seifen, Anstrichmittel *57*, 660 (1955).

[3] *D. Schulte-Frohlinde* and *F. Erhardt*, Chem. Ber. *93*, 2880 (1960).

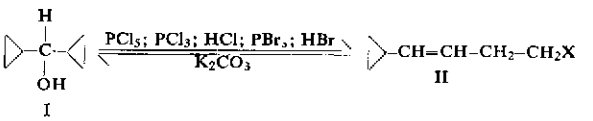
[4] *D. Schulte-Frohlinde* and *L. Klasinc*, Chem. Ber. *94*, 2382 (1961).

Studies with Cyclopropane Derivatives

By Dr. M. Hanack and Dipl.-Chem. H. Eggensperger

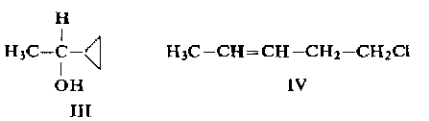
Pharmazeutisch-Chemisches Institut
der Universität Tübingen (Germany)

Dicyclopropylketone [1] was reduced with $LiAlH_4$ to dicyclopropyl carbinol (I). With PCl_5 or PCl_3 at −15 °C, the latter forms 1-cyclopropyl-4-chlorobut-1-ene (II; X = Cl; yield 85 %, b.p. 60–62 °C/12 mm. Hg). 3 % Hydrochloric acid at 80 °C yields 69 % (II; X = Cl) and 11 % of cyclopropylbutadiene as well as 30 % of unconverted dicyclopropyl carbinol. Acetylation of (I) with acetyl chloride in ether yields after 1 hour only 10 % of the acetylated alcohol in addition to 22 % of 1-cyclopropyl-4-chlorobut-1-ene (II; X = Cl) and 68 % of unreacted starting material (I). The pure acetate, however, is easily obtained with acetic anhydride (it yields only I on alkaline saponification). If (I) is reacted with PBr_3 in ether, or with 60 % hydrobromic acid at 0 °C, 1-cyclopropyl-4-bromobut-1-ene is formed in 80 % yield. Owing to homoallyl resonance [2], 1-cyclopropyl-4-chlorobut-1-ene may be hydrolyzed with 10 % K_2CO_3 solution (3 hours, 80 °C) leading to reformation of a three-membered ring and a 35 % yield of (I). Removal of hydrogen chloride from the chloride (II) using sodium amylate gives cyclopropylbutadiene (b.p. 96–97 °C). This compound readily forms a diene adduct (m.p. 84–85 °C) with maleic acid anhydride.



Dicyclopropylmethyl carbinol (b.p. 58 °C/15 mm. Hg), yield *ca.* 70 %) is obtained from dicyclopropyl ketone with methylmagnesium iodide. The amine is readily accessible via the oxime of dicyclopropylketone by reduction with sodium and alcohol.

Methylcyclopropyl carbinol (III) yields (IV) with conc. HCl and $ZnCl_2$ at 0 °C. Hydrolysis with 10 % potassium carbonate solution (3 hours; 80 °C) yields up to 10 % of methylcyclopropyl carbinol because of homoallyl resonance, together with some hydrocarbon and undecomposed chloride.



4-Bromobut-1-ene, on the other hand, yields only butadiene and unreacted bromide under the same conditions.

Received December 12, 1961 [Z 189/23 IE]

[1] *H. Hart* and *O. Curtis*, J. Amer. chem. Soc. *78*, 112 (1956).

[2] Cf. *E. Vogel*, Angew. Chem. *72*, 4 (1960).

Bis(trimethylsilyl)carbodiimide

By Dipl.-Chem. J. Pump and Prof. Dr. U. Wannagat [1]

Institut für Anorganische Chemie und Elektrochemie
der Technischen Hochschule Aachen (Germany)

We have succeeded in preparing bis(trimethylsilyl)carbodiimide $(CH_3)_3Si-\bar{N}=C=\bar{N}-Si(CH_3)_3$ (I) (m.p. −23 °C, b.p. 164 °C, $\log p_{(mm)} = -2320/T + 8.198$, heat of vaporization = 10.6 kcal/mole, Trouton constant = 24.3 cal/mole·degree, n_D^{20} = 1.4351, d_4^{25} = 0.8211) in yields of 60–90 % by the following routes (R=CH_3):

a) from bis(trimethylsilyl)urea with phenyl-lithium and trimethylchlorosilane according to the equation:

$$(R_3SiNH)_2CO + 2\,LiC_6H_5 + 2\,ClSiR_3 \rightarrow 2\,C_6H_6 + 2\,LiCl + O(SiR_3)_2 + (I)$$

b) from sodium bis(trimethylsilyl)amide (II) using phosgene, carbon dioxide or silicon tetra-*N*-cyanate according to the equations.

$$2\,(R_3Si)_2NNa + COCl_2 \rightarrow 2\,NaCl + O(SiR_3)_2 + (I)$$

$$\text{or } 2\,(II) + 2\,CO_2 \rightarrow Na_2CO_3 + O(SiR_3)_2 + (I)$$

$$\text{or } (II) + 2\,Si(NCO)_4 \rightarrow NaNCO + O(Si(NCO)_3)_2 + (I)$$

as well as subsequent reactions, and

c) by analogy with the method of *Ebsworth* and *Mays* [2] from disilver cyanamide and trimethylchlorosilane according to the equation:

$$Ag_2(NCN) + 2\ ClSiR_3 \rightarrow 2\ AgCl + (I)$$

The infrared spectrum supports the carbodiimide structure, since the symmetrical NCN- and the asymmetrical SiNSi vibrations, which should occur for the structural isomer bis(trimethylsilyl)cyanamide($R_3Si\overline{N})_2$- $C\equiv\overline{N}$,are not present.

Received December 15, 1961 [Z 196/27 IE]

[1] 14th Communication on Si-N compounds.

[2] *E. A. V. Ebsworth* and *M. J. Mays*, Angew. Chem. internat. Edit. *1*, 113 (1962).

Silyl-Substituted Sulfur Amides and Imides

By Prof. Dr. U. Wannagat [1] and Dipl.-Chem. H. Kuckertz

Institut für Anorganische Chemie
der Technischen Hochschule Graz (Austria)

Although silyl-substituted alkali amides (I) react almost quantitatively with halogenosilane derivatives according to [2]:

$$(R_3Si)_2NM + XSi\langle \rightarrow MX + (R_3Si)_2N-Si\langle$$

complicated sequences occur in the reaction of (I) with sulfur halides. The following compounds have so far been isolated from the reaction products of SCl_2: sulfur(II)-tetrakis(trimethylsilyl)diamide, $[(CH_3)_3Si]_2\overline{N}-\overline{S}-\overline{N}[Si(CH_3)_3]_2$, m.p. 65 °C, b.p. 142 to 143 °C/15 mm., colorless needles (from methanol); sulfur(IV)-bis(trimethylsilylimide) (II), $(CH_3)_3Si-\overline{N}=\overline{S}=\overline{N}-Si(CH_3)_3$, yellow oil, b.p. 73 to 74 °C/24 mm. Tris-(trimethylsilyl)amine, $N[Si(CH_3)_3]_3$ was also formed, among other products. Disulfur(I)-tetrakis(trimethylsilyl)diamide, $[(CH_3)_3Si]_2\overline{N}-\overline{S}-\overline{S}-\overline{N}[Si(CH_3)_3]_2$, a yellowish oil, b.p. 115 to 116 °C/0.5 mm. was separated from mixtures using S_2Cl_2. However, the expected reactions:

$$2\ (R_3Si)_2NNa + S_nCl_2 \rightarrow 2\ NaCl + [(R_3Si)_2N]_2S_n$$

$n = 1,2$; $R = CH_3$

only play a subordinate role (10 %).

(II) was also formed by reacting SO_2 with (I); the reaction proceeded stoichiometrically, but here, too, the yields were low. In addition to the reaction

$$2\ SO_2 + 2\ NaN(SiR_3)_2 \rightarrow (II) + O(SiR_3)_2 + Na_2SO_3,$$

increased formation of hexamethyldisiloxane and reduction of SO_2 to sulfide occured.

Received December 15, 1961 [Z 197/24 IE]

[1] 15th Communication on Si-N compounds.

[2] *U. Wannagat* and *H. Niederprüm*, Chem. Ber. *94*, 1540 (1961).

The Reaction between Halosilanes and Silver Cyanamide

By Dr. E. A. V. Ebsworth and M. J. Mays

University Chemical Laboratory, Cambridge (England)

The reaction between iodosilane and silver cyanamide yields the compound $(SiH_3)_2CN_2$, m.p. -74.8 ± 0.5 °C., b.p. 84.7 ± 0.5 °C., $\log p_{mm} = -1761/T + 7800$ [1]. The infrared spectrum between 4000 and 400 cm^{-1} shows that there are only two strong bands at 2280 and 795 cm^{-1} which are associated with skeletal stretching modes. They are either missing or very weak in the Raman spectrum. For a molecule of the cyanamide type, $R_2N-C\equiv N$, all four skeletal stretching modes should be both infrared and Raman active, and all are observed in the infrared [2] and Raman [3] spectra of dimethyl cyanamide. However, a molecule of the carbodiimide-type, will have a center of symmetry if the skeleton is linear (as in silyl isothiocyanate [4]); the mutual exclusion rule holds and the infrared active modes will be forbidden in the Raman. Even if the angles are not quite 180 °, the *trans* form will still have a center of symmetry, while vibrations of the *cis* form, which are strong in the infrared, might well give very weak Raman lines. (Since only one peak appears in the proton resonance spectrum, it is unlikely that both *cis* and *trans* forms are present.) Moreover, if the skeleton is almost linear, the molecule approximates to a symmetric top, with one small moment of inertia; parallel and perpendicular bands should have characteristic and different contours, and rotational detail might be observed in the perpendicular bands. The observed gas-phase infrared band contours correspond closely with those expected for such a molecule. Rotational fine structure, with separation of the order of 2–3 cm^{-1}, has been observed in the bands associated with SiH-stretching and SiH_3-deformation modes. This would be difficult to understand if the molecule had the Si_2NCN-configuration. Thus the vibrational spectra, while hard to reconcile with the cyanamide form, are readily explained in terms of the carbodiimide structure.

Received December 15, 1961 [Z 195/21 IE]

[1] *E. A. V. Ebsworth* and *M. J. Mays*, J. chem. Soc. (London) 4879 (1959); see also *J. Pump* and *U. Wannagat*, Angew. Chem. internat. Edit. *1*, 112 (1962).

[2] *M. Davies* and *W. J. Jones*, Trans. Farad. Soc. *54*, 1454 (1958).

[3] *L. Kahovec* and *K. W. F. Kohlrausch*, Z. physik. Chem. *37 B*, 421 (1937).

[4] *D. R. Jenkins*, *R. Kewley*, and *T. M. Sudgen*, Proc. chem. Soc. (London) 220 (1960).

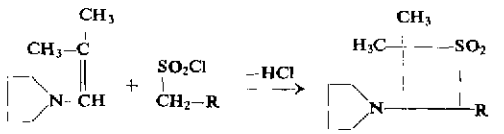
Cycloaddition of Sulfenes to Enamines

By Dr. G. Opitz and Dr. H. Adolph

Chemisches Institut der Universität Tübingen (Germany)

A personal communication from *G. Stork* and *I. J. Borowitz* concerning the reaction of mesyl chloride with 1-morpholinocyclopentene, -cyclohexene, or -propene in the presence of triethylamine, leads us to report our own findings [1].

We have found that the sulfenes, R_2CSO_2, which are formed primarily from aliphatic sulfochlorides R_2CHSO_2Cl and triethylamine, will form substituted 3-aminotrimethylene sulfones with enamines by cycloaddition.



Ia: R = H Ib: R = C_6H_5

If mesyl chloride in ether is allowed to drop into a mixture of triethylamine and 1-pyrrolidinoisobutene at room temperature, triethylamine hydrochloride precipitates immediately. The filtrate yields 2,2-dimethyl-3-pyrrolidinotrimethylenesulfone (Ia, 80 % yield, m.p. 68 °C., mol. wt. calc. 203; found 199). In a similar way, the following trimethylene sulfone bases are obtained from 1-pyrrolidinoisobutene, 1-piperidinopropene, 1-morpholinobutene, or 1-piperidinopentene, and methane-, propane-, and toluene-ω-sulfochlorides.

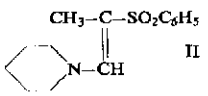
Trimethylenesulfone	M.p. [°C.]	Yield [%]
2,2-Dimethyl-3-pyrrolidino-4-phenyl-(Ib)	161 [*]	70
2-Methyl-3-piperidino-	b.p. 121/10^{-3} mm. Hg [**]	90
2-Ethyl-3-morpholino-	114	83
2-Ethyl-3-morpholino-4-phenyl-	170	65
2-Propyl-3-piperidino-4-ethyl-		88

[*] Mol. wt. calc. 279; found 260.

[**] Hydrochloride, m.p. 210 °C., picrate, m.p. 190 °C., methiodide m.p. 164 °C.

The analytical, spectroscopic, and chemical findings, *e.g.* the correspondence of the base from 1-piperidinopentene and propane sulfochloride with that from 1-piperidinobutene and butane sulfochloride, are in harmony with the cyclic β-aminosulfone structure I. The isomeric cyclic α-aminosulfone structure and the vinylog sulfonic acid amide structure (analogous to II) are eliminated as possibilities because of the absence of reactions characteristic for these classes of substances (acid hydrolysis, reduction with formic acid, formation of immonium salts), as well as the lack of a C=C band in the infrared spectrum.

On the other hand, the vinylog sulfonic acid amide II (m.p. 107 °C.), which has a strong C=C band at 1620 cm^{-1} in the IR spectrum and a λ_{max} value = 282 mμ (ε = 15300) in the ultraviolet spectrum, is formed under the same conditions



II

from 1-piperidinopropene and benzene sulfochloride in 66 % yield. It is readily reduced to 1-piperidino-2-benzenesulfonyl-propane (hydrochloride, m.p. 221 °C.) with formic acid and is hydrolyzed with 2 N HCl to 2-benzenesulfonyl propionaldehyde.

Received December 27, 1961 [Z 190/22 IE]

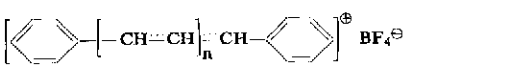
[1] Compare *H. Adolph*, Ph. D.-Thesis, Univ. Tübingen (Germany), 1959.

Polymethine Carbanions

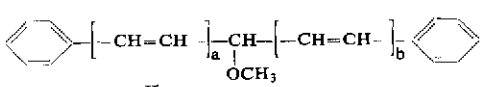
By Doz. Dr. K. Hafner and Dr. K. Goliasch

Chemisches Institut der Universität Marburg (Germany)

We reported recently on polymethine carbonium salts of type I [1]. The corresponding salts (III) of deeply colored polymethine carbanions, some of which were hitherto unknown, were prepared by splitting polyene ethers (II) with metallic sodium. These ethers are obtained by reacting secondary alcohols [1] with methanol.



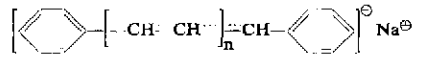
I (n = 0–4)



II

a = 0; b = 0 (b.p. 270–271 °C [2])
a = 1; b = 0 (b.p. 178–180 °C/11 mm. [3])
a = 2; b = 0 (b.p. 185–186 °C/0,8 mm.)
a = 2; b = 1 (b.p. 203 °C/0,8 mm.)
a = 2; b = 2 (b.p. 223–225 °C/0,8 mm.)

The polyene ethers are sensitive to oxygen and light. Their thermal stability decreases with increasing chain length whereas that of the polymethine carbeniate salts increases. The salts can be prepared at room temperature under nitrogen. However, over a longer period of time, they are only stable at −60 °C. They are extremely sensitive to oxygen, carbon dioxide, and atmospheric moisture [4].



III (n = 0–4)

The absorption maxima in the visible region (Table 1) are displaced bathochromically by an average of 33 mμ on lengthening the chain by one C=C-linkage (empirical rule: $\lambda_{max} = 501 + (33 \times n)$, where n = number of C=C-double bonds).

Table 1. Color and absorption maximum of salts of carbanions (III)

n	Color of the solid substance	Color in solution	λ_{max} [mμ] in ether at 20 °C
0 [5]	yellow-orange	orange	501
1 [3]	red	wine-red	535
2	purple	red	568
3	blue, shiny green	blue	600
4	blue-black	deep blue	635

Hydrolysis of the salts leads to the unsaturated parent hydrocarbons which react with alkali metals to reform the salts (III).

Received December 27, 1961 [Z 191/29 IE]

[1] *K. Hafner* and *H. Pelster*, Angew. Chem. *73*, 342 (1961).

[2] *St. v. Konstanecki* and *V. Lampe*, Ber. dtsch. chem. Ges. *39*, 4019 (1906).

[3] *E. Bergmann* and *T. Ukai*, Ber. dtsch. chem. Ges. *66*, 54 (1933).

[4] Added in Proof: *Ch. Jutz* and *H. Amschler*, Angew. Chem. *73*, 806 (1961), reported on of salts polymethine carbanions (III) having a quasi-aromatic anion instead of the phenyl residues.

[5] *K. Ziegler*, Liebigs Ann. Chem. *473*, 18 (1929).

Thin Layer Chromatography of Peptide Intermediates

By Dr. Peter Schellenberg

Institut für Organische Chemie und Organisch-Chemische Technologie der Technischen Hochschule Stuttgart (Germany)

Morin (3,5,7,2′,4′-pentahydroxyflavone) [1] offers possibilities as a spray reagent for quick, convenient and reliable detection of *N*-protected amino acid and peptide derivatives on silica gel thin layer chromatograms. The dried chromatograms are sprayed with a 0.05 % solution of morin in methanol and heated at 100 °C for 2 minutes. Yellow-green fluorescent spots or dark absorption spots on a fluorescent green background can be seen in ultraviolet light. The limit of detection is about 2 μg./spot. Since the silica gel layer has a capacity of more than 1 mg./spot with chloroform-acetone developing mixtures, impurities of down to 0.2 % can be detected with certainty.

Esters of *N*-substituted amino acids, dipeptides and tripeptides run with characteristic R_f-values in chloroform-acetone (9:1, 8:2) or cyclohexane/ethyl acetate (1:1). Higher acyl-oligopeptide esters, as well as acyl-di- and -tripeptide esters with polar groups in the side chain (such as histidine derivatives), require stronger elution with chloroform-methanol (9:1). Compounds not protected at the carboxyl or amino end remain at the starting point in these anhydrous media. The solvent systems conventionally used in thin layer chromatography of amino acids [2] are suitable eluting agents for peptide derivatives with free carboxyl or amino groups.

We have investigated carbobenzoxy-, *p*-nitrocarbobenzoxy-, trifluoroacetyl-, trityl-, tosyl- and phthalyl derivatives of amino acids up to pentapeptides containing glycine, alanine, leucine, valine, glutamic acid, tyrosine and histidine, as well as their methyl-, ethyl-, benzyl- and cyanomethyl esters.

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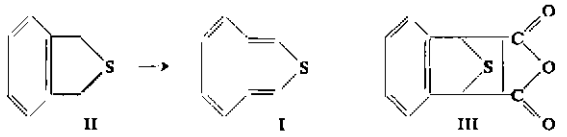
[1] *H. Brockmann* and *F. Volpers*, Chem. Ber. *80*, 77 (1947).
[2] *M. Brenner* and *A. Niederwieser*, Experientia *16*, 378 (1960).

Synthesis of Isothionaphthene [1]

By Prof. Dr. Roland Mayer, cand.-chem. Horst Kleinert, Dipl.-Chem. Swetla Richter, and Dr. Karl Gewald

Institut für Organische Chemie
der Technischen Universität Dresden (Germany)

We have prepared the unsubstituted isothionaphthene (I) in 65 % yield from the known compound II by catalytic vapor phase dehydrogenation over Pd-charcoal at 330 °C in the absence of oxygen.



II I III

(I) is an unstable compound which crystallizes in colorless platelets and can be purified by vacuum sublimation. In the pure state, is melts at 50 to 51 °C, and has an intensive naphthalene-like odor. It can be kept for a few days under nitrogen at −30 °C.

In the presence of a stabilizer, I is stable in solution. (I) gives characteristic addition reactions at the 5-membered ring, forming the benzenoid system. Thus, maleic acid anhydride adds to give III (m.p. 153–154 °C from benzene; λ_{max} in methanol: 205, 270, 280 mμ), which in turn forms naphthalene-2,3-dicarboxylic acid on fusing with NaOH. Because(I) is easily decomposed, the heat of combustion could not be determined. (I) has typical bands at 3110 cm^{-1} and 875 cm^{-1} in the infrared spectrum. Principal maxima in the ultraviolet spectrum (in methanol, given in mμ and log ε): 215 (4.84), 290 (3.97), 303 (4.06).

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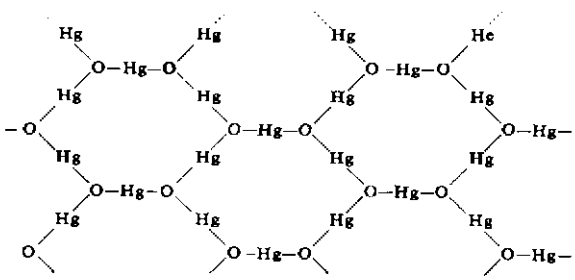
[1] 7th Communication on sulfur-heterocyclics; 6th Communication: *R. Mayer* and *H. Russ*, Chem. Ber. *95*, in press (1962).

The Structure of $HgSO_4 \cdot 2HgO$

By Dr. G. Nagorsen, Dr. S. Lyng, Dr. Alarich Weiss, and Prof. Dr. Armin Weiss [1]

Chemisches Institut der Universität Heidelberg
and Eduard-Zintl-Institut der Technischen Hochschule Darmstadt (Germany)

The mercury salt $HgSO_4 \cdot 2H_2O$ has been known in the literature since 1604 and applied medicinally. X-Ray studies show that it is a mercury oxonium sulphate; the polymeric oxonium cations $(Hg_3O_2)^{2+}$ form slightly undulating two-dimensional infinite layers.



The sulfate ions are enmeshed by the cation lattice. The Hg–O inter-atomic distance, 2.03 Å, is in good agreement with the theoretical value, 2.09 Å, calculated for a homopolar bond. The O–Hg–O valence angles appear to be different for different mercury atoms. According to results obtained so far this angle is about 180° at one Hg atom and about 170° at the other two.

Crystallographic Data:

Trigonal Space Group $P\,3_1\,21\ (D_3^4)$
$a = 7.03$ Å, $c = 9.98$ Å
$d_m = 8.41$ g/cm³, $d_x = 8.52$ g/cm³, $Z = 3$

Atomic coordinates:

6 Hg at 6c with $x = 0.307$, $y = 0.807$, $z = -0.019$;
3 Hg at 3a with $x = 0.693$;
6 O at 6c with $x = 0.474$, $y = 0.141$, $z = 0.000$ (= oxonium oxygen)
3 S at 3a with $x = 0.220$;
6 O at 6c with $x = 0.824$, $y = 0.977$, $z = 0.078$ } (= sulfate
6 O at 6c with $x = 0.724$, $y = 0.597$, $z = 0.094$ } oxygen)

The parameters given above are preliminary. Further work is planned in which more refined intensity measurements will be made taking into consideration the strong absorption.

The compound $HgSeO_4 \cdot 2HgO$ was found to be of the same type as the sulfate ($a = 7.12$ Å, $c = 10.05$ Å).

Received January 8, 1962 [Z 199/38 IE]

[1] 16th Communication on the Chemistry of Mercury. 15th Communication: *A. Weiss* and *E. Michel*, Z. Naturforsch. *15b*, 680 (1960).

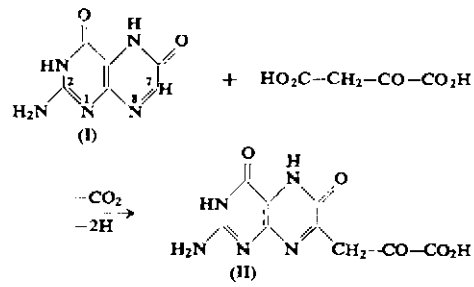
Synthesis of Erythropterin from Xanthopterin

By Prof. Dr. C. Schöpf and Dr. K. H. Gänshirt

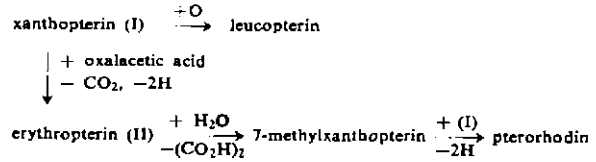
Institut für Organische Chemie der Technischen Hochschule Darmstadt (Germany)

Xanthopterin (I) in dilute aqueous solution reacts with β-keto acids at the 7,8-double bond with decarboxylation. The reaction takes place even at 25 °C and in the pH range 5.8 to 11.5. The expected 7,8-dihydro compounds lose two hydrogen atoms, presumably to atmospheric oxygen [1].

We allowed xanthopterin to react with oxalacetic acid (hydroxymaleic acid) at pH 4.2 and 80 °C and obtained a 35 % yield [2] of erythropterin (II) [3]. Paper chromatography [4] as well as infrared and ultraviolet spectroscopy [4,5] have shown it to be identical with erythropterin isolated from *Catopsilia argante*.



On the basis of hitherto known reactions, it appears possible that xanthopterin is the primary product in the biosynthesis [6] of pteridine butterfly pigments, from which the other pigments may be formed according to the following scheme:



We thank Dr. W. Pfleiderer, Stuttgart, for synthetic xanthopterin and natural erythropterin, as well as for his suggestions on preparations.

Received January 3, 1962 [Z 201/32 IE]

[1] *E. G. Fuchs*, Ph. D. Thesis, T. H. Darmstadt, 1952.

[2] The yield refers to a product which was recrystallized once from 0,5 NHCl and contained traces of xanthopterin, 7-methylxanthopterin and pterorhodin, all of them just barely detectable by paper chromatography. This yield is considerably lower at room temperature.

[3] II should be formulated in the enol-form; *W. Pfleiderer*, Angew. Chem. *73*, 581 (1961).

[4] *W. Pfleiderer*, private communication.

[5] *M. Viscontini* and *H. Stierlin*, Helv. Chim. Acta *44*, 1783 (1961).

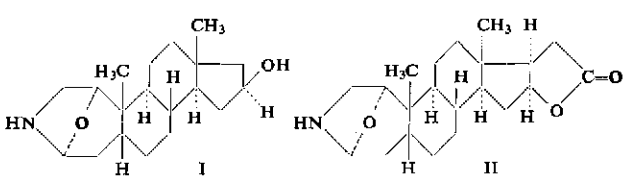
[6] See also *F. Weygand*, et al., Angew. Chem. *73*, 402 (1961).

Structure and Configuration of Samandaridine

By Dr. G. Habermehl

Institut für Organische Chemie der Technischen Hochschule Darmstadt (Germany)

From the skin gland venom of the Fire and Alpine salamanders (*Salamandra maculosa*, *atra* Laur., respectively), *C. Schöpf* and co-workers isolated the major alkaloid samandarine $C_{19}H_{31}NO_2$ (I) [1] as well as 6 minor alkaloids [2]. Among these are samandarone (I; CO instead of CHOH) and samandaridine $C_{21}H_{31}NO_3$. The structure of the latter is now elucidated. A secondary amino group and a γ-lactone ring (band at 1760 cm.$^{-1}$) had already been proved chemically [3]. The double band at 830 and 840 cm.$^{-1}$ indicates an oxazolidine ring. Structure (II) was deduced from the X-ray study of samandaridine hydrobromide [4].



The configuration, too, can be derived from the two-dimensional electron density projection. Molecular models show that only the arrangement of rings given in formula II conforms to this projection. Thus, like samandarine, samandaridine also has the basic framework of 3-aza-A-homo-5-β-androstane a new structural type for natural substances.

Received January 15, 1962 [Z 202/33 IE]

[1] *E. Wölfel, C. Schöpf, G. Weitz*, and *G. Habermehl*, Chem. Ber. *94*, 2361 (1961).

[2] *C. Schöpf*, Experientia *17*, 285 (1961).

[3] *C. Schöpf* and *K. Koch*, Liebigs Ann. Chem. *552*, 37 (1942).

[4] This work will be published in detail in Chem. Ber.

Reaction of Tetracarbonylferrate(-II) with Hydroxylamine-*O*-sulphonic Acid

By Prof. Dr. W. Hieber and Dr. H. Beutner

Anorganisch-Chemisches Laboratorium der Technischen Hochschule, München (Germany)

The reaction of an alkali salt of hydroxylamine-*O*-sulphonic acid with an aqueous alkaline tetracarbonyliron solution at 0 °C results in the instantaneous appearance of a finely crystalline yellow substance which, by analysis, has the formula $Fe(CO)_4NH_3$. According to the normal reactions of hydroxylamine-*O*-sulphonic acid, in which an important role is attributed to the NH radical [1], the following equation may be written:

$$[HFe(CO_4)]^- + NH_2OSO_3^- \longrightarrow HFe(CO)_4NH_2 + SO_4^{2-}$$

From this it appears that the first reaction product is hydrogen tetracarbonylamidoiron, $HFe(CO)_4NH_2$. The compound is soluble in benzene and polar solvents as well as (to a lesser extent) petrol ether and water. It is only stable below 0 °C, but sublimes *in vacuo* at 40 °C with extensive degradation to give big crystals which are coloured ruby red by traces of decomposition products. According to analysis and infrared spectral data, the sublimate is identical with the starting material. It is also diamagnetic and the molecular weight determination indicates a monomer. The infrared spectrum (*W. Beck*) shows two sharp NH valency vibrations at 3399 and 3327 cm.$^{-1}$ in addition to the intensive CO absorptions. Two bands at 1623 and 1256 cm^{-1} may be ascribed to symmetric and antisymmetric NH_3 deformations. This was shown by comparison with the corresponding spectral data (1602 and 1214 cm^{-1}) for the compound $Cr(CO)_5NH_3$ investigated by *H. Behrens* and *W. Kleck* [2]. Therefore the substance is a NH_3-coordination compound, namely tetracarbonyl(ammine)iron(0), $Fe(CO)_4NH_3$. In accordance with its water-solubility and sublimation properties, the structure may given as $(CO)_4\overset{\ominus}{Fe}-\overset{\oplus}{N}H_3$, *i.e.* the betaine form of $HFe(CO)_4NH_2$. The situation corresponds with that for hydroxylamine-*O*-sulphonic acid, for which the betaine structure $H_3\overset{\oplus}{N}-O-\overset{\ominus}{SO_3}$ was similarly established, particularly by infrared studies [3].

Received January 15, 1962 [Z 209/34 IE]

[1] *R. Appel, W. Büchner*, and *G. Guth*, Liebigs Ann. Chem. *618*, 53 (1958) and refs. therein.

[2] *H. Behrens* and *W. Kleck*, Z. anorg. allg. Chem. *292*, 151 (1957).

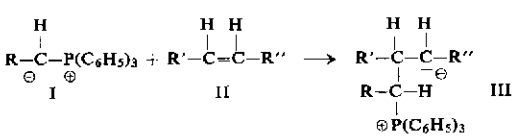
[3] *U. Wannagat* and *P. Pfeiffenschneider*, Z. anorg. allg. Chem. *297*, 151 (1958).

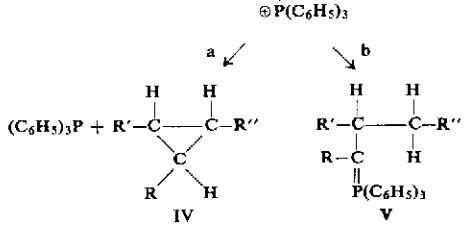
Reaction of Triphenylphosphine Alkylenes with Activated Double Bonds

By Priv.-Doz. Dr. H. J. Bestmann and Dipl.-Chem. F. Seng

Organisch-Chemisches Institut der Technischen Hochschule, München (Germany)

Triphenylphosphine alkylenes (I) react with compounds containing an activated double bond (II):





The polar addition product (III) may stabilize itself in two ways: 1. By formation of a cyclopropane derivative (IV) with loss of triphenylphosphine (path a). This has already been reported [1] in the case of the reaction of triphenylphosphine butylene with 9-n-butylidenefluorene. 2. Through proton migration, giving rise to a new ylide (V) by Michael addition of (I) and (II) (path b). Our preliminary investigations indicate that in the case of phosphine alkylenes with R = alkyl or groups exhibiting a +I effect, path (a) is preferred. Resonance stabilizing groups which introduce a -I effect allow the reaction to proceed extensively by path (b).

We have obtained the ethyl ester of 1,2-dimethylcyclopropane-3-carboxylic acid (IV; R = R′ = CH_3, R″ = CO_2Et; b.p. 167 °C; yield 91 %) and triphenylphosphine by route (a) from ethyl 2-methylacrylate (II; R′ = CH_3, R″ = CO_2Et) and triphenylphosphine ethylene. Route (b) yields triphenylphosphine-[(methoxycarbonyl-2-benzoyl)ethyl]-methoxycarbonylmethylene (V; R = R′ = CO_2Me, R″ = PhCO; m.p. 187 °C; yield 92 %) from methyl benzoylacrylate (II; R′ = CO_2Me, R″ = PhCO) and triphenylphosphine methoxycarbonylmethylene (I; R = CO_2Me).

Received January 22, 1962 [Z 205/35 IE]

[1] *R. Mechoulam* and *F. Sondheimer*, J. Amer. chem. Soc. *80*, 4386 (1958).

Pentamethylcyclopentadienyltitanium Trichloride

By Dr. H. Röhl, Dr. E. Lange, Dr. T. Gössl and Dr. G. Roth

Chemische Werke Hüls AG., Anorganische Abteilung, Marl, Kreis Reklinghausen (Germany)

Pentamethylcyclopentadienyltitanium trichloride (I) can be obtained from $TiCl_4$ and but-1-ene, but-2-ene, isobutene, pentene (mixture of isomers), di-isobutene, tetrapropylene and other unsaturated hydrocarbons. The reactions are carried out with molar ratios of $TiCl_4$ to hydrocarbon from 1:2 to 1:5 at 300 °C and 30 to 60 atm. pressure. After about 2 hrs., the mixture is cooled and decompressed. When isobutene is used, the escaping gas mixture consists of hydrogen, methane, ethane, propane, *n*-butane, isobutane, butenes and hydrogen chloride. The liquid reaction product may be purified by fractional distillation *in vacuo*. Fraction 1 is unreacted $TiCl_4$, fraction 2 a mixture of oligomers of the unsaturated hydrocarbons and their cleavage and rearrangement products, and fraction 3 (boiling range 190 to 220 °C at 4 to 5 mm.) consists of the organotitanium compound (I) (20 to 30 % yield) and higher partially unsaturated hydrocarbons. Compound (I) can be purified by crystallization from organic solvents.

The product (I), reddish-orange crystals, m.p. ≈ 200 °C, is monomeric in solution, stable with respect to moisture and can be heated with water, acids, and alkalis without titanium scission. In aqueous alkaline solutions, only the halogen atoms are split off by hydrolysis and yellow, solid polymer compounds $[C_{10}H_{15}TiO(OH)]_n$, n = 4 to 6, are formed. These are soluble in organic solvents, particularly in tetrahydrofuran. Partial hydrolysis leads to chlorine-containing polymers $(C_{10}H_{15}TiOCl)_n$. The halogen-containing compounds may be esterified to alkoxy titanates, $C_{10}H_{15}Ti(OR)_3$ and $C_{10}H_{15}TiO(OR)$ where denotes an R aliphatic, cycloaliphatic or aromatic hydrocarbon radical. Interchange of ester radicals with higher alcohols occur readily.

The infrared spectrum confirms the presence of CH_3 groups and the nuclear magnetic resonance data show a uniform proton type. A five-fold methylated cyclopentadienyl ring connected with the metal atom through π-bonds as in cyclopentadienyltitanium trichloride [1] appears probable. According to ultraviolet, infrared and mass spectral measurements, the pyrolysis products of $[C_{10}H_{15}TiO(OH)]_n$ (*e.g.* $C_{10}H_{14}$ and $C_{10}H_{16}$) are highly branched olefinic hydrocarbons (CH_3 groups) and contain conjugated double bonds.

Received January, 23, 1962 [Z 204/36 IE]

[1] *C.L. Sloan* and *W.A. Barber*, J. Amer. chem. Soc. *81*, 1364 (1959).

CONFERENCE REPORTS

Fifth International Congress for Biochemistry

Moscow, August 10th to 16th, 1961

Enzymes and Coenzymes

Reduction of Disulfide Bonds with Yeast Enzymes

S. Black, Bethesda, Md. (USA)

Two enzymes which reduce –S–S– groups to SH groups have been isolated from yeast. One of them is a transhydrogenase which transfers the hydrogen of the SH group of glutathione to the –S–S– group of simple disulfides (cystine, oxytocin). The other enzyme consists of two proteins and transfers hydrogen from TPNH to –S–S– groups. The three sulfur bridges of insulin, as well as the –S–S– bridges of simple disulfides, are reduced. Glutathione is not involved in reductions with this enzyme.

The Bond between the Prosthetic Group (Flavin-Adenine-Dinucleotide) and the Apoenzyme in Succinate Dehydrogenase

W. Ying-Lai et al., Shanghai (China)

By simultaneous action of crystalline trypsin and chymotrypsin on purified succinate-dehydrogenase a peptide fragment (FAD peptide) is obtained which carries the prosthetic group of the enzyme. Even though the absorption peak of flavin-mononucleotide (FMN) and of flavin-adenine-dinucleotide (FAD) shifts in alkaline solution from 375 to 355 mμ, the peak of the FAD peptide remains at 350 mμ even at an alkaline pH. In 1 N. HCl the peaks of FMN and FAD at 375 and 450 mμ disappear, and a new peak appears at 385 mμ.

On the other hand, the peaks of the FAD peptide at 350 and 450 mμ remain practically unchanged during acidification. This effect of the peptide chain on the spectrum can best be explained by its attachment to the isoalloxazine ring. During photolysis of the FAD peptide in neutral or alkaline solution one obtains products whose absorption spectra are similar to those of lumichrome or lumiflavin respectively, but which still have the peptide chain. Hydrolysis of FAD peptide, or of its alkaline photolysis product, yields urea and a compound whose UV spectrum has broad peaks at 360 and 305 mμ. These broad peaks correspond to the absorption maxima of 1,2-dihydro-6,7-dimethyl-2-keto-1-D-ribitylquinoxaline-3-carboxylic acid or to 1,2-dihydro-2-keto-1,2,7-trimethylquinoxaline-3-carboxylic acid, *i.e.* the alkaline hydrolysis products of riboflavin or lumiflavin respectively. It follows that the peptide chain in the FAD peptide cannot be attached to the 1-, 2- or 3-positions of the isoalloxazine ring. It is probably attached at the 4-position.

Nature and Geometry of the Surface of Glutamate Dehydrogenase

H. F. Fischer and *E. B. Ford*, Detroit, Mich. (USA)

By means of a plaster cast of the molecular model of L-glutamic acid one can predict, provided the correct surface of the molecular model has been chosen for the cast, whether a given compound can be a substrate for glutamate-dehydro-

genase or not: Compounds whose models fit into the plaster cast of the model of the glutamate molecule are substrates while compounds whose models do not fit are neither substrates nor competitive inhibitors. With the help of the plaster cast it was possible to predict that a substituent on the β-C atom of a L-α-amino acid would affect only to a small degree the velocity of the reaction catalyzed by the enzyme. This was verified experimentally. On the other hand, the steric hindrance of a substituted γ-C atom prohibits such a compound from being a substrate.

Metal-Binding Groups of Carboxypeptidase-A and their Effect on the Activity

J. E. Coleman, B. L. Vallee, and *P. Bent*, Boston, Mass. (USA)

A zinc mercaptide is a part of the active center of carboxypeptidase-A. Potentiometric titrations indicate that the Zn^{2+} ion is in addition attached to a N-atom. Two protons are liberated upon combination of apoenzyme and Zn^{2+}. The pK value of the first is 7.7, that of the second > 9. Investigations on model substances indicate that the value of the first pK is characteristic of a proton on nitrogen (α-amino, or perhaps imidazole-proton) and that of the second is characteristic of an SH group. Bonding of a metal to N and S is also observed when the stability of various enzymatically active metal carboxypeptidases (Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Ph^{2+}) is compared with that of other S–N complexes of the same metals. Among the metal carboxypeptidases, those with Mn^{2+}, Co^{2+}, Ni^{2+} act as both peptidases and esterases; those with Cd^{2+}, Hg^{2+}, and Pb^{2+} act only as esterases.

Enzymatic Reduction of Diphosphopyridine Nucleotide with Gaseous Hydrogen

R. Repaske, Bethesda, Md. (USA)

Cell-free extracts of autotrophically grown *Hydrogenomonas eutropha* (Bovell) rapidly reduce diphosphopyridine nucleotide (DPN) in an atmosphere of hydrogen. The reaction can be followed manometrically or spectrophotometrically at 340 mμ. The presence of flavin mononucleotide (FMN) is required. FMN cannot be replaced by either flavinadenine dinucleotide or riboflavin. Maximum activity is obtained with a FMN concentration of $3.3 \cdot 10^{-7}$ M. The optimum pH is 8. A reducing agent is necessary (mercaptoethanol or, less preferably, cysteine or glutathione) to activate the enzyme. The concentration of the enzyme could be increased sevenfold by precipitation with protamine sulfate and treatment with calcium phosphate gel. It catalyzes the reduction of 12 micromoles of DPN/min. × mg. protein.

Nitrilase, an Enzyme which Hydrolyzes Nitriles to Carboxylic Acids

K. V. Thimann and *S. Mahadevan*, Boston, Mass. (USA)

Indole-3-acetonitrile, which acts in some plant species as a growth substance, is hydrolyzed in the plants to indoleacetic acid. The enzyme responsible for this occurs in the leaves of barley (*Hordeum*), oats (*Avena*), in the *Brassica*-family (cabbage, cauliflower, Brussels sprouts) and in some *Musaceae* (*e.g.* bananas). The presence of the enzyme could not be ascertained in 17 higher plants. However, it was found in several *Fusatia*. It is not specific for indole-3-acetonitrile, but hydrolyzes 32 aromatic and four aliphatic nitriles. In the benzonitrile series, the logarithm of the relative rate of hydrolysis is approximately proportional to the corresponding Hammett constant. It follows that whether a certain nitrile is hydrolyzed by the enzyme or not depends on the negative partial charge on the N atom of the CN group. The amide that is suspected of being an intermediate is not liberated because amides are hydrolyzed by the enzyme to a very small extent only. Starch gel electrophoresis indicates that only one enzyme is involved. This enzyme is named nitrilase.

Effect of Papaverine on the Creatine Kinase in Heart Muscle and in Smooth Muscle

E. P. Chetverikova, Moscow

Papaverine is used medically as an antispasmodic for smooth muscle. Doses of papaverine which cause an enlargement of the coronary vessels, give increased oxygen uptake, increase phosphorylation and cause a greater formation of creatine phosphate in rabbit heart muscle homogenates. Under anaerobic conditions, and in the presence of iodoacetate, more phosphate is transferred from adenosine triphosphate (ATP) to creatine in such homogenates when papaverine is present. Experiments with heart muscle extracts of rabbits which had received papaverine injections indicate that the increased formation of creatine phosphate is caused by a higher creatine kinase activity. The ATPase activity remains unchanged. Papaverine also increases the activity of creatine kinase *in vitro*. The same applies to the activity of creatine kinase in the aorta of rats.

Inhibition of Redox Enzymes by Radical Acceptors

N. M. Emanuel et al., Moscow

n-Propyl gallate, rutin and gallic acid, which act as radical acceptors, inhibit the activity of D-glycerinaldehyde-3-phosphate dehydrogenase, of lactate dehydrogenase and of alcohol dehydrogenase, but do not affect enzymes such as aldolase or enolase whose reactions do not involve radical intermediates. The inhibition increases with the concentration of the radical acceptor. N-Propyl gallate inhibits more strongly than rutin, which in turn is more effective than gallic acid. These compounds do not only influence isolated enzymes but also disturb the glycolysis in normal cells and cancerous tissues. At a concentration of 50 μM. propyl gallate inhibits 50 % of the glycolysis in ascites hepatoma cells at pH 6.8 while it inhibits only 7 % of the glycolysis of normal rat liver homogenates. Addition of citrate has a synergistic effect, *i.e.* it reinforces the effect of propyl gallate. In tumor cells (Ehrlich ascites, acridine sarcoma, leukemic tissue, Brown-Pearce tumor) cytochrome oxidase is also inhibited by propyl gallate. The propyl gallate concentration required for this is not sufficient to inhibit the cytochrome oxidase in normal liver and spleen. 0.3 % Propyl gallate almost completely suppresses the incorporation of 1-^{14}C-glycine into the protein of Yoshida ascites cells. The effect is reversible; protein synthesis is resumed after the radical acceptor is washed out. These results indicate that radical acceptors may make possible a new approach to cancer therapy. Butyl hydroxyanisole (a mixture of 2- and 3-t-butyl-4-hydroxyanisole), Ionol (2,6-di-t-butyl-4-methylphenol), propylgallate and 3,5-di-t-butyl-4-hydroxybenzylamine have an anti-leukemic effect in mice and reduce the growth of sarcoma-180 tumors in mice by 40–60 %.

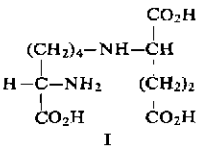
Proteins and Amino Acids

Saccharopin, a New Amino Acid from Yeast

P. O. Larsen and *A. Kjaer*, Aarhus (Denmark)

A new amino acid having the composition $C_{11}H_{20}O_6N_2$ (three carboxyl groups) was isolated from aqueous extracts of baker's and brewer's yeast (hot extraction). Its structure (I) was determined by synthesis from 2-ketoglutaric acid and N^2-(*p*-toluenesulfonyl)-L-lysine. The new amino acid has an

L-configuration in the lysine as well as in the glutamic acid moiety. It is therefore designated as L-saccharopin. The diastereoisomer that is formed together with (I) during the synthesis has a D-configuration in the glutamine acid moiety and is thus designated as D-allosaccharopin.



I

Chemistry of the Botulinus Toxin

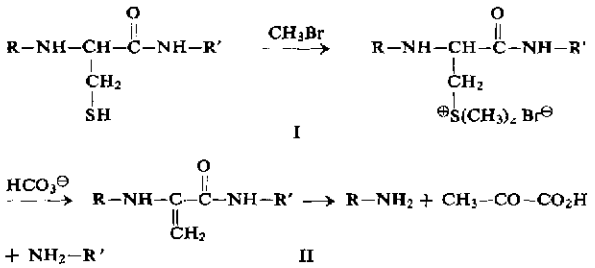
D. A. Boroff and *R. J. Suhadolnik*, Ridgefield, Conn. (USA)

The toxin of *Clostridium botulinum* fluoresces in ultraviolet light. Procedures and reagents which extinguish the fluorescence also affect the toxicity. *Cl. botulinum* requires considerably more tryptophan for synthesis of the toxin than it needs for growth. *N*-Bromosuccinimide, which reacts with the tryptophan contained in the toxin, destroys the fluorescence and the toxicity of the toxin. A 6 M. urea solution also destroys its toxicity, but without affecting the fluorescence. Apparently the urea solution affects the spatial relationship between the tryptophan moieties responsible for the fluorescence and the remainder of the molecule. The toxicity of the toxin is also lost when it is spread out as a monomolecular film. It thus appears that both tryptophan and a specific spatial structure of the protein molecule are required for the toxic effect. *In vivo* the toxin is detoxified by tryptophan and its derivatives (*e.g.*, serotonin).

Chemical Cleavage of Peptides at the Cysteine Residue

A. Patchornik, *M. Sokolovsky*, and *T. Sadeh*, Rehovot (Israel)

The selective splitting of peptide chains at the cysteine residue is possible through the formation of a dehydroalanine residue and subsequent hydrolysis with dilute acid or base. Exhaustive alkylation of the SH group with CH_3Br yields the sulfonium salt (I) which is converted to the olefin (II) upon mild heating with dilute bicarbonate solution. Apparently, compound (II) isomerizes to a Schiff base which is split by hydrolysis.



The SH group can be dinitrophenlyated instead of being methylated. *S*-Dinitrophenylglutathione with 0.2 N. NaOH gives at room temperature in 30 min. the dehydroalanine derivative in 80 % yield which is hydrolyzed to glutamic acid, pyruvate and glycine. Similar reactions could possibly be used for the selective splitting of peptides at a serine residue.

First Stages in the Thermal Denaturation of Serum Albumin

P. Poszwiński, Warsaw

Dissolved serum albumin is relatively heat resistant in the presence of caprylate ions or anions of other fatty acids. A ratio of 6 to 10 moles caprylate per mole of protein are sufficient to prevent the thermal denaturation of albumin, even though the protein carries more than 100 positively charged groups capable of binding the fatty acid ions. If, in addition, the albumin/caprylate solution contains basic amino acids, the stabilizing effect of the caprylate is decreased. Arginine is most effective. Simple amines, especially hydroxylamine and hydrazine, also decrease the stabilizing effect of caprylate. Electrophoretic and viscosimetric investigations indicate that the first stage in the thermal denaturation of albumin is a dimerization. Apparently, positively charged groups of the protein molecule are bound by arginine moieties of other protein chains.

A New Proteolytic Enzyme from Streptomyces Griseus

M. Nomoto and *Y. Narahashi*, Tokyo

A new proteolytic enzyme (molecular weight: 20000; optimum activity at pH 8) was isolated chromatographically from the *Streptomyces griseus* culture medium used for the production of streptomycin. Ca^{2+}-ions stabilize the enzyme whose substrate specificity is very low. Proteins are hydrolyzed to the extent of 70 to 90 % (as compared with acid hydrolysis). Synthetic substrates (di- and tripeptides, amides, esters) are also split. In contrast with trypsin, chymotrypsin, and esterases, the enzyme is not inhibited by di-isopropyl fluorophosphate. Its active center seems to have a structure different from that of comparable enzymes.

Molecular Weight and Amino Acid Content of the Erythrogenic Scarlet Fever Toxin

I. V. Kushko, Moscow

A procedure for the purification of erythrogenic scarlet fever toxin consists essentially of the following steps: (i) precipitation with 62 % saturated ammonium sulfate solution and (ii) isoelectric precipitation at pH 4 followed by five repeated precipitations with two parts by volume of ethanol in the presence of 1.4 % ammonium sulfate. A 100- to 200-fold increase in concentration is attained. The preparations contain $2 \cdot 10^8$ to $3 \cdot 10^8$ skin units of toxin/ml. or $1.2 \cdot 10^8$ to $1.8 \cdot 10^8$ skin units/mg. nitrogen. Colored impurities were removed by chromatography on Al_2O_3; the toxin was eluted with 20 % ammonium sulfate solution. Optimum conditions for the crystallization of the toxin are: High concentration (at least 10 mg. protein/ml. or more), the presence of ammonium sulfate (1 to 20 %, according to the protein concentration), and a temperature between 2 and 6 °C. over a pH range 6.6 to 7.0. The crystalline toxin appears homogeneous during electrophoresis and ultracentrifugation. The sedimentation and diffusion constants are: $S = 2.76 \cdot 10^{-13}$ sec., $D = 8.6 \cdot 10^{-7}$ cm²/sec. According to these values the molecular weight is 29000. Quantitative chromatography indicates that the toxin consists of 16 amino acid residues as follows (the quantities in parentheses indicate the number of amino acid residues/molecule): asparagine (44), glucine (30), leucine and isoleucine (22), glutamic acid (20), alanine (18), serine (16), tyrosine (15), proline (14), valine (11), cystine (10), histidine (7), phenylalanine (7), lysine (5), arginine (5), tryptophan (3).

Nucleic Acids

The Transmission Potential of Acyl Groups to Purine and Pyrimidine Bases

Elizabeth B. Keller and *L. Spector*, Boston, Mass. (USA)

The acyl group of O^4-acetyl-1-methyluracil is non-enzymatically transferred at 37 °C. to glycylglycine ($k_1 = 0.18$ min^{-1}; 0.5 M; pH 6.8) and to imidazole ($k_1 = 0.09$ min^{-1}; 0.05 M; pH 7.0). Under the same conditions O^6-acetyltheo-

bromine glycylglycine (k_1 = 0.11 min^{-1}) and imidazole (k_1 = 0.08 min^{-1}) are acetylated. On the other hand N^4-acetyl-1-methylcytosine and N^6-2′,3′,5′-tetra-acetyladenosine only acetylate glycylglycine (k_1 for N^4-acetyl-1-methylcytosine = $7 \cdot 10^{-3}$ min^{-1}; 1.0 M; pH = 7.9). It is therefore possible to acylate non-enzymatic amino groups in peptides with the *N*-acyl derivatives of all four bases occurring in ribonucleic acid. However, only the transfer potential of *O*-acyl derivatives is sufficient to acylate imidazole.

Metals in Ribonucleic Acid from Tobacco Mosaic Virus

W. Wacker, M. Gordon, and *J. Huff,* Seattle, Washington (USA)

Infectious ribonucleic acid (RNA) obtained by phenol extraction from tobacco mosaic virus (TMV) contains metals. Apart from Mg^{2+}, Ca^{2+}, Fe^{2+}, and Cu^{2+} the following are found (in µg metal/mg. RNA): Sr^{2+} (6), Ra^{2+} (23); Al^{3+} (77), Cr^{3+} (11), Mn^{2+} (6), Ni^{2+} (16). As with RNA from beef liver, TMV–RNA is stabilized by some of these metals: If TMV-RNA is heated between 10 °C. and 50–70 °C. and the extinction followed at 258 mµ, there is an increase in the ratio of the extinction at the elevated temperature to that at 10 °C. Also, the curve of this ratio against temperature reaches a plateau at the ratio value of 1.26. The height of this plateau decreases upon addition of Cr^{2+}, Mn^{2+}, Ni^{2+} or Zn^{2+} to the RNA solution. Apparently, the transition metals of the first large period contribute to the stabilization of the secondary structure of the RNA molecule.

Ribonucleic Acid as a Converting Principle in Bacteria

S. San-Chiun et al., Shanghai (China)

A substance was isolated from a penicillin resistant strain of *Bacillus subtilis* which transforms a penicillin sensitive strain into a genetically resistant strain. That the transforming substance is a ribonucleic acid is evident from the following observations: (i) The activity is destroyed by ribonuclease but not by desoxyribonuclease. Depolymerization of ribonucleic acid and loss of the transforming activity take place at the same time. (ii) The ribonucleic acid isolated from the penicillin resistant bacteria and purified by the phenol procedure exhibits the required activity. (iii) The ribonucleic acid obtained from the converted bacteria also possesses converting activity.

Chemical Basis for the Radiation Sensitivity of Halogenated Desoxyribonucleic Acid

W. Szybalski, Madison, Wis. (USA)

Cultivation of bacteria or mammal cells in the presence of 5-bromodesoxyuridine or its chloro- or iodo-analogs results in the synthesis of a desoxyribonucleic acid (DNA) in which the methyl groups of the thymine residues are replaced by halogen. Halogenated DNA of this type is completely active in the intact cells (as judged by full viability) as well as in the extracted form (genetic transformation in *Bacillus subtilis*). However, cells which contain the hlogenated DNA are sensitive to ultraviolet and X-ray irradiation. It appears that the hydrogen bridges between the strands of a nucleic acid double spiral are practically unaffected by the halogen content. On the other hand, halogen and phosphate groups are spatially so close together in the same strand that the phosphate ester bond is considerably strained. This bond is therefore easily broken under the effect of ultraviolet or X-ray irradiation. Furthermore, during the thermal separation of the two strands of a DNA-spiral, halogenated DNA is degraded more strongly. The bond between 5-bromodesoxyuridine and other pyrimidine nucleotides is sensitive towards both heat and hydrolysis with weak acids. DNA halogenated in both strands is more easily degraded by shearing forces than normal DNA.

Vitamins

Relation between Structure and Vitamin Activity

J. Lowenthal and *J. A. MacFarlane,* Winnipeg (Canada)

All compounds so far described as exhibiting vitamin K activity, are derivatives of 2-methyl-1,4-naphthoquinone. They can be classified into two groups: (i) Compounds which, like vitamin K_3 (2-methyl-1,4-naphthoquinone), are not substituted in the 3-position of the naphthalene skeleton, and (ii) Compounds such as vitamin K_1 (2-methyl-3-phytyl-1,4-naphthoquinone) or vitamin K_2 (2-methyl-3-difarnesyl-1,4-naphthoquinone), which carry a substituent on C-3. Only compounds of the second group destroy the activity of anticoagulants of the coumarin type. Structural prerequisites for this effect on the coagulation are: a) a free or blocked 1,4-naphthoquinone structure, b) a relatively small substituent on C-2 with an inductive or polarizing effect which changes the electron mobility in the naphthalene ring, and c) a substituent on C-3 which increases the lipid solubility. The substituent on C-2 has the greatest specific effect. By changing its size or electronegativity compounds are obtained which possess vitamin K activity and also compounds which are inactive or which act as competitive antagonists. The size of the substituent affects the affinity of the compound for the receptor. Its electronegativity determines the biological effect of the substance. The combined effect of these factors determines whether a compound will have vitamin K activity *in vivo* or not.

Biosynthesis of Vitamin B_{12} and Porphyrins in Propionabacter

G. V. Mantrova, V. N. Bukin, and *V. V. Pchelkina,* Moscow

Bacteria of the genus *Propionobacter* produce porphyrins and vitamin B_{12} in large quantities. According to *Shemin,* both groups of compounds are formed in a similar manner. An attempt was made to influence the synthesis of vitamin B_{12} by inhibiting the porphyrin synthesis or by addition of δ-aminolevulinic acid. δ-Aminolevulinic acid increases the amount of porphyrin three- to sixfold, but does not affect the amount of vitamin B_{12}. Iron salts inhibit the porphyrin synthesis but have no effect on the vitamin B_{12} synthesis. Conversely, the inhibition of vitamin B_{12} biosynthesis with aminopterin and other inhibitors has no effect on porphyrin production. If the biosynthesis of δ-aminolevulinic acid from glycine and activated succinate is interrupted by addition of 4-amino-5-hydroxymethyl-2-methylpyrimidine (a vitamin B_6 antagonist), the formation of porphyrin also comes almost to a halt. It can be reactivated by addition of δ-aminolevulinic acid or, to a lesser degree, of pyridoxal phosphate. However, all these interventions leave the vitamin B_{12}-synthesis unaffected. Consequently, it must branch off at a very early stage of the porphyrine biosynthesis and cannot be an obligatory intermediate for δ-aminolevulinic acid.

Vitamin D and Active Calcium Transport

D. Schachter, New York

The small intestine of several species of mammals can, *in vitro,* transport calcium against an electrochemical potential drop from a solution which bathes the mucosa to a solution which bathes the serosa. This active transport is relatively specific for calcium. Its capacity is limited; it depends on the functioning of the oxidative phosphorylation process and is (for several species) at its maximum in the proximal duodenum. It is stronger in young, growing rats than in older animals and stronger in pregnant than in normal females. A diet, deficient in calcium, increases the transport. However, a vitamin D-free diet disturbs the transport phenomenon considerably after four to five weeks. It can be re-established

by addition of vitamin D_2, vitamin D_3 or dihydrotachysterol to the diet, or by irradiation of the animals with ultraviolet light. The re-establishment of the active Ca transport after a vitamin D-free diet can serve as a biological test for that vitamin.

Hormones

Effect of Steroid Hormones on the Structure and Function of Crystalline Glutamate Dehydrogenase

K. L. Yielding and *G. M. Tomkins*, Bethesda, Md. (USA)

Glutamate dehydrogenase from beef liver is a complex molecule which can dissociate reversibly into four sub-units. The tetrameric form possesses glutamate dehydrogenase activity, while the sub-units act as L-alanine dehydrogenases. Several steroid hormones can promote the dissociation of the enzyme into sub-units. Adenosine diphosphate (ADP), on the contrary, promotes the aggregation of the sub-units. The specificity of structure and the activity of this enzyme can therefore be regulated by the concentration ratio of steroid hormones and adenosine nucleotides. Apart from steroid hormones, other flat molecules effect a reversible dissociation of glutamate dehydrogenase with ADP. On the other hand, the dissociation of the enzyme caused by sodium dodecyl sulfate is not reversible with ADP.

Effect of Thyroid Hormones on the Metabolism of 4-^{14}C-Cortisol [*] in Humans

L. Bradlow et al., New York

The relative abundance in humans of the following metabolic products of cortisol were investigated: 3α,11β,17α,20,21-pentahydroxypregnane (cortol), 3α,17α,20,21-tetrahydroxy-pregnan-11-one (Cortolone), 3α,11β,17α,21-tetrahydroxy-pregnan-20-one (tetrahydrocortisol) and 3α,17α,21 trihydroxypregnane-11,20-dione (tetrahydrocortisone). Hyperthyroid patients eliminate 11-ketones in larger amounts than normal persons. On the other hand, their excretion of 11β-ols is decreased. When persons with a normal thyroid gland are treated with triiodothyronine, the same changes occur. Hypothyroid patients excrete more 11β-ols than normal persons at the expense of the 11-ketones. When both groups of patients are restored to a normal thyroid hormone balance, the quantitative ratio of 11-keto-11β-hydroxy metabolite adjusts itself to that of normal persons. Apparently, the thyroid gland has a specific and reversible effect on this quantitative ratio. Contrary to the metabolism of testosterone, the reduction of the 4,5-double bond of cortisol is apparently not controlled by the thyroid gland because practically the same ratio of 5α-pregnane to 5β-pregnane derivatives can be found in hyperthyroid persons.

Regulation of Amino-Acid Activating Enzymes and Nucleic Acids in Guinea Pig Tissue by Androgens

D. Kochakian et al., Birmingham, Ala. (USA)

When adult male guinea pigs are castrated, the specific activity of the amino acid activating enzymes (ATP/^{32}P-exchange) in the testicles decreases slowly to 40 % of its normal value within 40 days. The specific activity of the enzymes can be restored by administration of testosterone, testosterone propionate or androstan-17β-ol-3-one. However, the required androgen dose is higher than that required for the re-establishment of the normal tissue weight. The ribonucleic acid concentration of the testicles changes with the enzymatic activity. On the other hand the RNA, protein, and amino acid content of the soluble fraction (centrifuged for 60 min. at 105000 g.) changes proportionately with the tissue weight. The enzymatic activity of the prostate gland is not affected by the castration or by androgen administration. However, castration reduces the RNA content of the prostate gland to about 70 % of its normal value. The RNA content can be increased again by administration of androgen.

[*] Also called hydrocortisone.

Further Investigations on the Estrogen-Dependent Nucleotide Transhydrogenase

C. A. Villee and *D. D. Hagerman*, Boston, Mass. (USA)

Estradiol dehydrogenase of the placenta is not a single enzyme with double pyridine nucleotide specificity, as assumed by *Talalay* and *Williams-Ashman*. Rather, it is a system of two enzymes, each of which is specific for a pyridine nucleotide. Both are found in different cells of the placenta. Neither enzyme catalyzes the estrogen-dependent hydrogen transfer alone, nor is this done by a mixture of the two Catalysis is accomplished by a third enzyme. This enzyme has been concentrated to 1/400 of the original. It probably contains flavin-mononucleotide (FMN) as the prosthetic group. 2-Hydroxyestradiol and 2-hydroxyestrone stimulate the enzyme which is not, however, a phenol oxidase. 16-Difluoroestradiol and 16-difluoroestrone inhibit transhydrogenase. The fluorine atoms in this compound probably increase the bond strength between the enzyme and the steroid by enhancing the electropositive nature of the oxygen on C-17. However, they obviously interfere with the activating process. In the placenta, the activation of the transhydrogenase by estrogen causes an increase in the formation of energy-rich compounds (increased incorporation of inorganic ^{32}P-phosphate into adenosine triphosphate). This, in turn, facilitates an increase in the synthesis of proteins, fatty and nucleic acids.

Isolation and Characterization of a New Peptide Hormone: Vasotocin

R. Acher et al., Paris

A hormone with vasopressor as well as oxytocic properties has been isolated from the pituitary of some vertebrates. Purification was carried out by precipitation of the peptide as a complex with a protein, which subsequently was removed by trichloroacetic acid treatment. The active substance was finally chromatographed on Amberlite XE-64. In composition, the new hormone lies between the oxytocin and the arginine-vasopressin. Chemically and biologically, it is identical with the arginine-vasopressin synthesized by *Du Vigneaud* and *Katsoyannis*. (This contains the peptide ring of oxytocin and the side-chain of the arginine-vasotocin.) Vasotocin is found in the lower vertebrates. In mammals it is replaced by the two hormones oxytocin and vasopressin.

Metabolism

Synthesis of Bile Acids from Cholesterol in Humans: Modification of the A Ring

R. S. Rosenfeld and *L. Hellman*, New York

It is possible to form the 3α-OH group of the bile acids from the 3β-OH group of cholesterol via two paths: a) replacement of the 3β-OH group with a 3α-OH group by rear attack of $OH^{\ominus}$ at position C-3; b) oxidation to 3-ketone and its reduction to the alcohol with the opposite configuration on C-3. In order to distinguish between these two possibilities, a patient with a biliary fistula was injected intravenously with 3-^{3}H-cholesterol. Cholesterol was then isolated from blood plasma, faeces, and bile. The bile acids were isolated from

bile. The specific radioactivity of cholesterol from bile and blood plasma agreed and was approximately equivalent to the specific radioactivity of the cholesterol from faeces (corrected for the sterol content of the food). Chenodesoxycholic acid and cholic acid were inactive. It follows that bile acids with a 3α-OH group are formed from cholesterol via a ketonic intermediate step.

Participation of Thioctic Acid in Acetate Activation

G. R. Seaman, Galveston, Texas (USA)

Experiments with crude preparations of aceto-CoA kinase indicated that thioctic acid participates in acetate activation. This is now proven with an enzyme derived from baker's yeast and concentrated to 1/40 of the original. The thioctic acid content of the enzyme is high and the ratio of the co-factor to protein increases during purification. When thioctic acid is split with lipoyl-X hydrolase from *Streptococcus faecalis*, or with thioctic acid-liberating enzyme from yeast, then the said enzyme loses its activity. It can be reactivated by addition of thioctic acid-activating enzyme, ATP and dihydrothioctic acid or thioctic acid, or DPNH and thioctic acid dehydrogenase. The cofactor apparently participates in the acetyl transfer from adenyl acetate to coenzyme A because on its removal the reaction between adenyl acetate and coenzyme A ceases, while the exchange between ATP and pyrophosphate remains unaffected. The following equations can therefore be written for the acetate activation:

(1) ATP + acetate $\rightleftharpoons$ adenyl acetate + pyrophosphate.

(2) Adenyl acetate + dihydrothioctic acid $\rightleftharpoons$ AMP + monoacetylthioctic acid.

(3) Monoacetylthioctic acid + CoA $\rightleftharpoons$ Acetyl-CoA + dihydrothioctic acid.

The formation of AMP from acetate and ATP in the absence of coenzyme A proves the validity of reaction (2).

Ethylene Formation by Cytoplasmic Particles from Apples

M. Lieberman, Beltsville, Md. (USA)

Incubation of cytoplasmic particles from apples with thiomalic or thioglycolic acid gives ethylene. Particle fractions obtained from acid homogenates by centrifuging at 500 g., 16000 g., and 40000 g. are active. Mitochondria are also active. The particles are specific for thiomalic or thioglycolic acid. No ethylene is formed from cysteine, glutathione, methionine, Thiodiglycolic acid, α-monothioglycerol, β-mercaptopropionic acid or carboxymethylmercaptosuccinic acid. If the SH group is blocked, *i.e.* if the thiomalic acid is replaced with acetylthiomalic acid, there is also no ethylene formation. The fact that the reaction is catalyzed enzymatically is apparent from the following facts: The activity of the particles is temperature dependent. It is also destroyed by ethylenediamine tetraacetate and partially restored by the addition of copper. When the system is dialyzed the activity again disappears and is partially restored when concentrated dialyzate is added to the retained portion.

Mode of Action of Some Anesthetics

M. I. Kuzhman and *I. V. Sidorenkov*, Kuibyschev (USSR)

Procaine, Novocaine, Cocaine, Dicaine, Anästhesin (aminobenzoic acid ethyl ester), Xylocaine, and Mesocaine, when used in the usual concentrations required for local anesthesia inhibit the respiration of rat brain homogenates by 10–17 %. Sovcaine (Nupercaine) inhibits it by over 50 %. The compounds interfere with the oxidation of glucose, lactic acid, pyruvic acid, ketoglutaric acid, oxalacetic acid, malic acid, and glutamic acid. The degree of inhibition of the respiration is proportional to the anesthetizing effect of the substance. Apparently the substances block the flavin enzymes because they do not interfere with the cytochrome system, but inhibit the dehydrogenase activity of the brain and the activity of purified α-amino acid oxidase. Glycolysis is somewhat increased by the anesthetics under consideration, but oxygen uptake and oxidative phosphorylation are disturbed.

Biosynthesis of Rhamnose

J. H. Pazur and *E. W. Shuey*, Lincoln, Nebraska (USA)

When micro-organisms whose polysaccharides contain rhamnose are grown in a medium where 1-^{14}C-glucose is the only source of carbon, rhamnose is labelled predominantly in the 1-position. Apparently the hexose molecule is changed into rhamnose without the splitting of its carbon chain. It could be shown that this change consists of several steps and that thymidine diphosphate hexoses participate. First, glucose is phosphorylated by hexokinase to glucose-6-phosphate which, under the influence of mutase, is changed to glucose-1-phosphate. The latter is condensed with thymidine triphosphate to thymidine diphosphate-glucose by a pyrophosphorylase. This hexose nucleotide was isolated. It is isomerized to thymidine diphosphate-rhamnose by an epimerase-dehydrogenase complex with the aid of reduced triphosphorydine nucleotide (TPNH). Thymidine diphosphate-rhamnose apparently acts as a donor of rhamnosyl residues in the polysaccharides synthesis.

Amino Analogs of Mevalonic Acid

J. M. Stewart and *D. W. Woolley*, New York

In a search for mevalonic acid antimetabolites, compounds which carry an amino group instead of the 5-OH group of mevalonic acid were synthesized. By a Reformatsky reaction between bromoacetic acid ethyl ester and 1-phthalimidobutan-3-one (and subsequent hydrolysis), obtained 5-amino-3-hydroxy-3-methylvaleric acid (I) was obtained. The substance has weak mevalonic acid activity (0.04 %) for *Lactobacillus acidophilus* and does not act as an antimetabolite. In order to test whether the behavior is due to the hydrolysis of the 5-amino group 5-amino-2,3-dimethyl-3-hydroxyvaleric acid (II) was prepared. Hydrolytic cleavage of the amino group of (II) should yield 2-methyl-mevalonic acid which is known to be a strong antimetabolite. Surprisingly, (II) has a higher metavalonic acid activity (0.2 %) than (I). 5-Amino-3-methyl-2-pentenic acid (III), which is obtained as a by-product during the synthesis of (I), also has a smaller mevalonic acid activity (0.02 %). However, contrary to the behavior of (I) and (II), which are active both in the presence and absence of mevalonic acid, (III) is active only in the presence of mevalonic acid. It appears that (III) can take over only some of the functions of mevalonic acid.

Further Investigation on the Mode of Action of Carcinolipin

J. Hradec, Prague

Carcinolipin, a carcinogenic substance isolated from biological material, stimulates protein synthesis and particularly, the activation of amino acids in cell-free systems. When carcinolipin alone is incubated with adenosine triphosphate (ATP), pyrophosphate is split off and adenosine monophosphate is formed. Addition of amino acids stimulates the ATP cleavage and the presence of aminoacyl adenylates can be demonstrated. The reaction proceeds linearly for about 20 minutes and can be influenced by Mg^{2+} ions, as well as by SH groups. Many of the characteristics of the reaction (optimum pH, temper-

ature dependence, dependence on the carcinolipin concentration, reversibility) resemble an enzymatic reaction, even though carcinolipin is a lipid and no trace of protein was found in the reaction mixture. Since even very small amounts of cardiolipin (10^{-7} µM.) catalyze the reaction, reaction with the nucleotide must be excluded. It appears to be more likely that carcinolipin acts catalytically.

Endogenous Uncoupling Factor in Swollen Mitochondria

L. Wojtczak and *A. L. Lehninger*, Baltimore, Md. (USA)

During the spontaneous swelling of rat liver mitochondria induced by Ca^{2+} or thyroxine, a substance ("U factor," probably an unesterified fatty acid) is formed. This substance uncouples oxidative phosphorylation. The rate of formation of the substance is proportional to the rate of swelling of the mitochondria. The factor is not formed (or is formed only in very small amounts) when the swelling is induced by phosphate or glutathione. (Beef serum albumin inhibits the spontaneous as well as the Ca^{2+} or thyroxine-induced swelling. However, it does not inhibit the swelling induced by glutathione or phosphate). When swollen mitochondria are in contact with ATP, the endogenous uncoupling factor also disappears very rapidly. The same applies to oleic acid if added to the mitochondria. The rate of mitochondria contraction is proportional to the rate of disappearance of the uncoupling factor. Oleic acid, labeled in the carboxyl group with ^{14}C, is slowly degraded by swollen mitochondria ($^{14}CO_2$ formation). The contraction induced by ATP is accompanied by the rapid incorporation of ^{14}C-oleic acid into the phosphatide acid and cardiolipin fractions. Cane sugar inhibits this incorporation, as well as the ATP-induced contraction of the mitochondria.

Regulation of Cholesterol Biosynthesis

H. E. Eder, *E. Gilon*, and *C. Klein*, New York

Rats fed with cholesterol show inhibition of cholesterol biosynthesis by the liver. As cholesterol is changed in the body into cholic acid (among other things), and the latter is then eliminated in conjugation with taurine, the effect of taurine on the biosynthesis of cholesterol was investigated. Liver slices from rats, whose diet contained 2 % taurine and 0.5 % cholesterol, synthesized five times as much cholesterol from 1-^{14}C-acetate as those from rats whose diet was only augmented with cholesterol. Livers from rats receiving supplementary taurine contained less cholesterol than those from rats on a normal diet, even though the weight of the animals in both groups increased by the same amount. Since in the body taurine is formed from cysteine, the effect of SH compounds on the cholesterol synthesis in liver slices was also considered. If glutathione is added to the incubation medium, the incorporation of 1-^{14}C-acetate and 2-^{14}C-mevalonic acid into cholesterol increases. The fatty acid synthesis is not affected.

Immunochemistry

Biological Effects of Bacterial Polysaccharides

Z. V. Yermol'yeva et al., Moscow

Acetoxan, a polysaccharide obtained from *Acetobacter xylinium*, consists of glucose, mannose, and rhamnose. Its animal toxicity is low, it is practically non-pyrogenic but it does increase the resistance of animals towards pathogenic germs. Animals treated with acetoxan survived blood poisoning caused by *Staphylococcus*, *Cyaneus*-, *Proteus*-, and *Coli* bacteria. Acetoxan increases the survival rate of X-ray irradiated animals. It prevents the formation of pathological changes in mice after injection of a lethal dose of type-A influenza virus (strain PR-8) and delays the death of the animals. In mice, acetoxan also prevents the development of sarcoma 180 and, to a smaller degree, the development of any Ehrlich carcinoma. Parenteral injection of acetoxan affects among other things the reticulo-endothelial and the pituitary-adrenocortical systems. It also increases local tissue immunity. It prevents the development of the exudative inflammation phase and does not adversely affect tissue regeneration.

Differences between Antibodies and Non-Specific γ-Globulins

A. E. Gurvich, *L. M. Guberneva*, and *K. N. Myasoyedova*, Moscow

Pure antibodies were obtained by reaction with protein antigens, which were bound to cellulose with *N*-(*m*-nitrobenzoyloxy)methylpyridinium chloride. Elution was carried out with acid solutions (up to pH 3). Antibodies against horse and human serum albumin, as well as non-specific γ-globulins from rabbit serum were hydrolyzed with trypsin and chymotrypsin. The hydrolyzates were separated electrophoretically. The results indicate a difference in the amino acid content of antibodies with different specificities. There is also a difference in amino acid content between antibodies and non-specific γ-globulins. These differences do not disappear when the proteins are denaturated with trichloracetic acid before enzymatic hydrolysis. These findings contradict the conclusions of *Pauling* and *Horowitz* who suggest that antibodies and non-specific γ-globulins differ only by the folding of the peptide chain.

Comparison of Antibodies and Enzymes Induced by the Same Determinant Groups

S. W. Tannenbaum and *S. M. Beiser*, New York

Antigens containing protocatechuic acid, β-D-glucosyl or β-D-galactosyl groups were coupled to beef serum albumin and injected into rabbits. Antisera free of protein specific antibodies were tested for their specificity towards various haptens and compared with the three enzyme systems induced by protocatechuic acid, β-D-glucoside and β-D-galactoside: protocatechuic oxidase from *Neurospora*, β-D-glucose oxidase from *Rhodotorula* and β-D-galactosidase from *Escherichia*. The specificity for the orientation of the OH group on the ring, the α- and β-configuration on C-1, the ring conformation and the substituent effects were investigated. A good parallelism was found between antibodies and enzymes and it was concluded that the active centers of proteins with different functions but the same inducability have a similar structure.

Microorganisms

Identification, Synthesis and Biological Properties of Several Hydroxystilbenes

D. E. Hathway, Egham, Surrey (England)

Two hydroxystilbenes were isolated from the ether extracts of the heartwood of *Eucalyptus wandoo* using chromatography on cellulose and polyamide. The two compounds were proved by synthesis to be 3,5,4′-trihydroxystilbene and 3,5,4′-trihydroxystilbene-3-β-D-glucoside. Both compounds are strong cellulose inhibitors at a concentration of 10^{-4} M. Apparently they protect the heartwood of dicotyledons from fungus and insect attacks. They were found together with a not yet identified, third, hydroxystilbene in the heartwood of

many other types of *Eucalyptus*. Their detection can be an aid in taxonomic classification. The compounds have a blue fluorescence which facilitates their detection by paper chromatography.

Mode of Action of Streptomycin

F. E. Hahn, Jennie Ciak, and *A. D. Wolfe*, Washington, D.C. (USA)

Addition of streptomycin to a culture of *Escherichia coli* permits the bacterial count to increase by about 50 %, even though the number of viable cells decreases exponentially immediately after the addition of streptomycin. After approximately a third of the generation time, multiplication and protein synthesis cease completely. On the other hand desoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are still synthesized for more than one generation time. However, no material absorbing at 260 mμ appears in the culture medium. Streptomycin does not affect the viability of the bacteria when the medium does not have a source of carbon or protein.

Teichuronic acid, a Mucopolysaccharide from Bacteria Cell Walls

E. Janczura, H. R. Perkins, and *H. J. Rogers*, London

Cell wall preparations from *Bacillus subtilis* contain four polymers: a mucopeptide, an insoluble protein, teichoic acid and a new mucopolysaccharide designated as teichuronic acid. Teichuronic acid can be extracted from the preparations with 5 % trichloroacetic acid and can be purified with cetylpyridinium bromide. The acid is a white solid; its aqueous solutions are clear and somewhat viscous. When hydrolyzed with acid, equimolar quantities of galactosamine and glucuronic acid are formed in total amount corresponding to 80 % of the original substance. Partial acid hydrolysis yields N-acetylgalactosamine and a very small amount of a substance which reacts in *Cifonelli* and *Dorfmann*'s test [1] and must therefore be an amino sugar substituted in position C-3. The velocity of acid and alkaline hydrolysis, the positive optical rotation ($-40°$), the IR spectrum (band at 850 cm^{-1}) and the fact that teichuronic acid is not attacked by hyaluronidase from testicles indicate an α-glycosidic bond, as opposed to chondroitin which has a β-glycosidic bond. Thus it can be assumed that teichuronic acid consists of glucuronic acid and N-acetylgalactosamine which are linked together with α-1 → 3-bonds.

Competitive Relationship between Cell Division and Photosynthesis in Algae of the Genus Chlorella

E. Hase, S. Mihara, and *H. Tamiya*, Tokyo

When young *Chlorella* cells are kept in a sulfur-free medium and are permitted to photosynthesize they grow but are unable to divide. On subsequent transfer to a medium containing sulfate only, the cells will show a different behavior in the light and in the dark. In light, *i.e.* under conditions permitting photosynthesis, the cells grow somewhat, the nucleus divides into four portions, but a division of the cell (formation of four daughter cells from the mother cell) does not take place. In the absence of CO_2, both in the dark and in light, *i.e.* under conditions preventing photosynthesis, the mass of the cells does not increase. However, the cells divide and four smaller daughter cells are formed from each mother cell. Use of ^{35}S-sulfate indicated that the cells form one (or several) sulfur-containing compound(s). This is found in the cell fraction which is soluble in hot acid. This sulfur-containing substance apparently influences cell division since it is found in much lower concentration in cells that do photosynthesize than in those that do not.

[1] J. biol. Chemistry *231*, 11 (1958).

Blood Coagulation

Thromboplastinase, a New Antithrombotic Enzyme

S. Gollub and *A. W. Ulin*, Philadelphia, Pa. (USA)

Bacillus megatherium produces an adaptive enzyme which is excreted into the culture medium and which destroys the enhancing effect upon blood coagulation, shared by all tissues investigated so far, including human blood. A phosphorus-containing substance, which is apparently necessary for the blood-coagulating effect, is split by the enzyme. Thromboplastinase is innocuous when injected intravenously into rabbits (experiments of short duration). The enzyme destroys the detrimental effect of coagulating substances injected intravenously after a thrombosis. A lyophilized enzyme preparation of moderate purity is effective *in vivo* and *in vitro*.

Carboxymethyldextran Sulfate, a Heparinoid based on Dextran

A. Gabert, Leipzig (Germany)

For the clinical use of dextran sulfates in the inhibition of blood coagulation, compounds with a molecular weight of 7500 and a sulfur content of about 17 % have been proposed. The author prepared carboxymethyldextrans of various molecular weights which were converted into carboxymethyldextran sulfates by reaction with pyridine/chlorosulfonic acid. Dextran sulfates were prepared in an analogous manner from these same dextrans. Although the sulfur content of carboxymethyldextran sulfates (about 10.8 % S) is lower than that of dextran sulfates (about 16.5 % S), the two types of compounds inhibit blood coagulation to about the same degree. By introduction of carboxymethyl groups it is thus possible to decrease the sulfur content of dextran sulfates without a significant loss in their activity. This is of importance because the sulfur content of such preparations determines the rate at which they are eliminated from the body.

Trace Elements

Geochemical Ecology of Animals

V. V. Koval'skiy, Moscow

Geochemical ecology is the study of biochemical relationships between living organisms and their surroundings. Several biochemical regions where there was an excess or a deficiency of Co, Cu, Ni, I, B, Mo, Pb, or Sr were investigated. In each case changes in the human or animal metabolism could be observed which are related to the lack or excess of these trace elements, *i.e.* to the deviation of trace elements from the norm. For example, insufficient Co results in an endemic B_{12} avitaminosis. An excess of Mo causes too much xanthine oxidase and uric acid to be formed. The same happens when the ratio Mo:Cu deviates from the norm. This causes endemic gout in humans. In the case of Cu deficiency, wheat acquires an endemic weakness of the stems and animals suffer from endemic ataxia. The activity of several digestive enzymes is decreased when the boron content is too high. In such cases, endemic enteritis is found. A lack of calcium and an excess of strontium results in defective bone formation, with the consequent appearance of Urow's syndrome. In most cases, the majority of individuals adapt themselves to insufficiency or excess of a trace element. The syndrome appears in only 20 % of the cases.

Significance of Boron for the Nucleic Acid Metabolism

M. Y. Shol'nik, A. N. Mayevskaya, and *E. A. Solov'yeva*, Leningrad (USSR)

Wild flowers grown in a boron-deficient soil contain less ribonucleic acid (RNA) in the tips of the stems and roots than normal control flowers. In experiments with sunflowers, addition of RNA to the fertilizer solution eliminated the RNA deficiency in plants that had an initial lack of boron as well as in plants which had been initially grown for a period of 11 days in a boron-containing soil, but which did not receive any boron after that period. It is apparent from these results that boron must have an important role in nucleic acid metabolism. These results probably explain the withering of plants in soils deficient in boron. In any case, the results are in accord with the known need for boron of the meristematic tissue and the known importance of boron for cell division, tissue differentiation and cell membrane formation.

Changes of the Animal and Human Purine Metabolism in Regions Rich in Molybdenum

G. A. Yarovaya and *V. V. Kovalskiy*, Moscow

In rams from regions rich in copper and poor in molybdenum, the xanthine oxidase activity of the small intestine mucosa is 37 %, that of the liver is 34 % and that of the kidneys is 17 % higher than that of animals with normal diets. In regions poor in copper and rich in molybdenum, the xanthine oxidase activity of the above-mentioned tissues increases by 170, 106, and 65 %, respectively; simultaneously, the molybdenum content of the tissues increases. In humans, a molybdenum-rich diet results in an increase of the xanthine oxidase activity of the blood, as well as in an increase in the blood's uric acid content (11 mg.%). This apparently indicates changes in the purine metabolism of some tissues. 31 % of the adult population in regions rich in molybdenum suffer from gout.

New Methods

A New Fatty Acid Synthesis

L. D. Bergel'son, V. A. Vaver, and *M. M. Shemyakin*, Moscow

Acids with the structure $R-CH=CH(CH_2)_n-CO_2H$ are obtained according to the following sequence:

$$Cl-CH_2(CH_2)_n-CO_2R \xrightarrow{NaI} I-CH_2(CH_2)_n-CO_2R \xrightarrow[2.\ RONa]{1.\ (C_6H_5)_3P}$$

$$(C_6H_5)_3P=CH(CH_2)_n-CO_2R \xrightarrow[2.\ OH^{\ominus}]{1.RCHO} R-CH=CH(CH_2)_n-CO_2R$$

A number of acids were prepared by this procedure: Vaccenic acid (trans-Δ^{11}-octadecenoic acid), oleic acid (cis-Δ^{9}-octadecenoic acid), palmitoleic acid (Δ^{8}-hexadecenoic acid), and gadoleic acid (cis-Δ^{9}-eicosenoic acid). The first total syntheses of cetoleic acid (Δ^{10}-docosenoic acid) and of cis-Δ^{11}-eicosenoic acid, both of which occur in the sperm oils of marine mammals, were achieved by this procedure. When a ketone is used instead of the aldehyde for the condensation with ω-phosphorane esters, unsaturated and branched acids are obtained. These can be hydrogenated to saturated compounds. The ω-chloro-carboxylic acids used as the starting materials may be obtained commercially.

Improved Method for the Detection of Tritium-Labelled Substances in Chromatograms

R. P. van Tubergen and *R. Markham*, New York (USA) and Cambridge (England)

The detection of tritium-labelled substances with low specific activity on paper chromatograms can be improved if the chromatograms are sprayed with a suitable solvent and then quickly dried on one side only. A considerable portion of the radioactive substance migrates with the evaporating solvent to the heated surface of the paper. This decreases the absorption of the weak β-rays by the paper. In chromatograms containing ^{3}H-thymidine, which were treated by this procedure (solvent: ethanol; dried with a hair drier), the radioactivity of the heated surface was three times larger then that of the untreated chromatogram.

Measurement of Blood Glucose with a Coupled Glucose-Oxidase Catalase System

F. W. Sunderman Jr. and *F. W. Sunderman*, Philadelphia, Pa. (USA)

The glucose content of protein-free blood or plasma filtrates can be determined in the following manner: Glucose is oxidized by glucose oxidase to gluconic acid and hydrogen peroxide. Catalase then catalyzes the oxidation of methanol by hydrogen peroxide to formaldehyde, which gives a color reaction with chromotropic acid (4,5-dihydroxynaphthalene-2,7-disulfonic acid). The glucose content determined in the venous blood of 38 fasting individuals was found to be 80 ± 1.1 mg./100 ml.

[VB 538/4 IE]

Polynuclear Aromatic Hydrocarbons

A. Sieglitz, München

1-Oxotetralin-3-carboxylic acid and a series of derivatives have been aromatized with air in alkaline solution to 1-hydroxynaphthalene-3-carboxylic acid [1]. The two diastereomeric 1-oxo-1,2,3,4-tetrahydro-4,5-methylenephenanthrene-3-carboxylic acids (I), that are obtained from acenaphthene and maleic anhydride via two diastereomeric acenaphthyl-1-succinic acids by cyclization [2], yield 1-hydroxy-4,5-methylenephenanthrene-3-carboxylic acid (II). Several new derivatives of 4,5-methylenephenanthrene with substituents in the 1- and 3-positions were prepared from (I) and (II), among them amino, hydroxy and carboxyl compounds. In an analogous manner, 3-hydroxyfluoranthene (IV) is obtained from 3-oxo-10b,1,2,3-tetrahydrofluoranthene (III). The method has led to the preparation [3] of numerous previously unknown derivatives of (IV). 1-Carboxyfluorene-9-acetic acid is obtained from (IV) by exposure to light in alkaline solution. 1-Carboxyfluorene-9-malonic acid is similarly prepared from 3-hydroxyfluoranthene-1-carboxylic acid.

Through its 2-oxalic ester derivative, III yields the 3-oxo-10b,1,2,3-tetrahydrofluoranthene-2-carboxylic acid ester. By ring opening 1-carboxyfluorene-9-propionic acid is obtained; this yields 3-oxo-10b,1,2,3-tetrahydrofluoranthene-10-carboxylic acid on ring closure. 3-Hydroxy-fluoranthene-10-carboxylic acid is produced from it by the action of air in alkaline solution, and fluorenone-1,8-dicarboxylic acid by oxydation with bichromate.

By means of the infrared spectra, the color differences of these, and other fluorenone carboxylic acids obtained for the first time by the oxidation of fluoranthen derivatives, can be discussed. In the orange-red compound 7-chlorofluorenone-1-carboxylic acid (from 9-chloro-3-hydroxyfluoranthene), the chelate bonding of fluorenone-1-carboxylic acid (V) remains intact; in the yellow 2-chlorofluorenone-1-carboxylic acid (from 3-chlorofluoranthene) the chelate bonding is eliminated by the Cl atom *ortho* to the carboxyl group. Compound (V) forms a red 1 : 1 complex with (IV) and several of its derivatives.

(GDCh-Ortsverband Marl, Germany; November 24, 1961).

[VB 552/3 IE]

[1] German Patent DBP 1083276 (1960).

[2] German Patent DRP 607380 (1933).

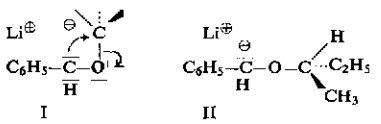
[3] *H. Tröster*, Ph. D. Thesis, Technische Hochschule München, 1961.

Stereochemistry and Reaction Mechanisms of Rearrangements of Ether Anions

U. Schöllkopf, Heidelberg

In the Wittig rearrangement where an aliphatic C-atom is the migrating center we might be dealing with an S_Ni substitution according to (I) with simultaneous ligand exchange "by frontal attack".

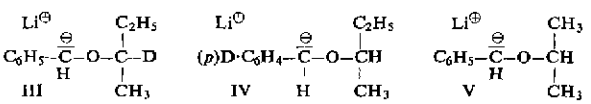
In order to check this, the course of the rearrangement of optically active lithium benzyl s.-butyl ether (II) was studied. Compound (II) isomerizes in various solvents and at different temperatures with 82–67 % racemization; the residual



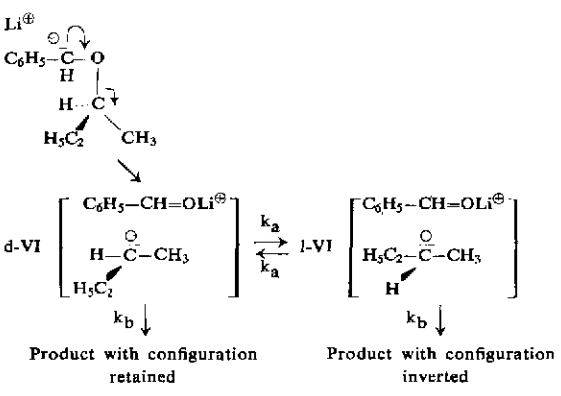
I II

activity is preserved in the sense of a retention of the configuration. Control experiments showed that the activity is lost during the rearrangement rather than before or after. In the isomerization of lithium benzyl 2-D-s.-butyl ether (III), the deuterium at the secondary butyl-C-atom is not replaced by hydrogen.

Cross-over experiments with (IV) and (V) showed that in tetrahydrofuran/ether at −56 °C only about 7 % of the ether anions follow an intermolecular reaction path. Under the same reaction conditions, racemization amounts to approximately 80–82 %. Thus, only a very small portion can be traced to an intermolecular reaction path.



III IV V



A mechanism involving an ion pair d-VI and l-VI should satisfactorily explain the results obtained so far. The extent of racemization would depend on the ratio of the constants k_a and k_b. If the hydrogen in the migrating group is replaced by phenyl, racemization decreases from approximately 80 % to 20 %. This may be explained by assuming that k_a decreases more than k_b with the exchange of H for $-C_6H_5$.

(GDCh-Ortsverband Bonn (Germany), December 5, 1961).

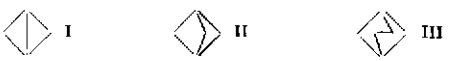
[VB 554/10 IE]

The Chemistry of Bicyclic Small-Ring Compounds

Kenneth B. Wiberg, Seattle, Washington, USA

When the tetrabedral valency angle of a carbon atom becomes smaller (*e.g.* in cyclopropane), bonds which occur in rings retain a larger share of the p-orhital than is the case for normal sp^3-hybridisation. Consequently in the remaining bonds a larger s-share is available; this causes their weakening. Thus a proton should be easier to remove from cyclopropane than from an open-chain hydrocarbon.

In order to test these predictions, it was desirable to prepare the compounds,



I II III

or derivatives thereof.

The ethyl ester of bicyclo[1,1,0]butane-2-carboxylic acid, a derivative of (I), is obtained by the action of the sodium salt of triphenylmethane on the ethyl ester of 3-bromocyclobutane carboxylic acid. This bicyclic ester is very unstable and undergoes all the reactions of an unsaturated compound, yet the nuclear magnetic resonance spectrum clearly supports the proposed structure.

In efforts to prepare a derivative of (II), vain attempts were made to bring about an intramolecular condensation of the ethyl ester of 3-bromoethylcyclobutane carboxylic acid under basic conditions.

In order to obtain (III), a multiple-stage synthesis starting from norcamphor was employed [1]. At the same time a new method of decarboxylation using the t.-butyl ester of the per-acid was worked out. A derivative of (III) was prepared by Cl substitution at the bridgehead [1]. It proved to be very unreactive.

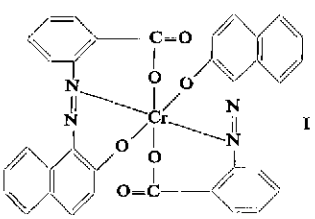
(GDCh-Ortsverband Marburg/Lahn, November 24, 1961).

[VB 551/2 IE]

[1] *K. B. Wiberg*, J. Amer. chem. Soc. *83*, 3998 (1961).

A new class of compounds, azidinium salts – quasi-aromatic azido cyclimonium salts, were prepared by *H. Balli* and *F. Kersting*. They are classified as *N*-diazonium salts because of their reactive behavior. They can be prepared via quaternary halogen salts of aromatic N-heterocyclic compounds. The quaternization can be performed smoothly in ethylene chloride at 50 °C, with triethyloxoniumfluoroborate (yield, 60 to 90 %). The halogen atom in the quaternary salts can be exchanged with azide by reaction with NaN_3 in methanol at 0 to 20 °C to form azidinium fluoroborates in good yields. Their chemical stability is astonishingly high: they are non-explosive at room temperature (*unlike* the perchlorate), stable in neutral and acid media, they conflagrate on heating to about 100 °C and are hydrolyzed by OH^- ions. Heterocyclic azidinium fluoroborates are electrophilic agents. The mesomeric cations can undergo nucleophilic substitution at the carbon atom that bears the N_3 group (*e.g.*, replacement of N_3 by OH), or nucleophilic addition at the terminal N atom (3 - ethyl - 4,5 - dimethylthiazoline - 2 - iminodiazocyanide $C_8H_{11}N_5S$, yellow prisms, m.p. 137 to 139 °C from 2-azido-3-ethyl-4,5-dimethylthiazolium fluoborate and NaCN); as well as redox reactions ($SnCl_2$, H_2SO_3 and I^-), where N_2 is liberated and heterocyclic imines are formed. These can react further with an excess of azidinium salt. In reactions with compounds that contain a reactive methylene group, an azo group can be transferred (*e.g.*, 5-pyrazolones are transformed into symmetrical pyrazole dyes). The high reactivity of the azidinium salts makes them useful for a great number of syntheses. / Liebigs Ann. Chem. *647*, 1, 11 (1961). / –De. [Rd 55/33 IE]

The separation of 1:2 chromium and cobalt complexes of o-hydroxy-o′-carboxy azo dyes into isomers was successfully performed by *G. Schetty* and *W. Kuster*. For example, the complex I on Al_2O_3 was separated into four fractions which differ considerably in their visible absorption spectra. The



I

complexes, isolated in pure form, isomerize easily *e.g.*, upon heating in water. The ratio of isomers depends on the pH. The present theory, namely that the planes of the two ligands in such complexes are vertical to each other, can no longer be sustained. / Helv. chim. Acta *44*, 2193(1961). / –Ko. [Rd 56/34 IE]

The course of a diethylene glycol intoxication was investigated by *H. Patscheider* and *H. Hertzel*. Deep unconsciousness set in rapidly after the drinking of one liter of diethylene glycol, a quantity which represents ten times the lethal dose. All reflex tests were negative. Death occurred after 33 hours. Autopsy indicated damage to the central nervous system in a manner characteristic of lack of oxygen. Considerable odema was found in several parts of the brain. The degree of tissue damage in the brain corresponded to the different degree of sensitivity of the various parts of the brain towards lack of oxygen. These disturbances in the blood supply are probably caused by the lipid solvent action of the diethylene glycol on the walls of the blood vessels. The release of white blood cells in the vicinity of the blood vessels creates odema. The histological changes correspond to a cerebral inflammation. The theory that diethylene glycol causes damage only after its oxydation to oxalic acid could not be confirmed. / Arch. Toxikologie *19*, 143 (1961). – Re. [Rd 985/12 IE]

The separation of chlorine isotopes by chemical exchange methods is described by *K. I. Matveyev*, *O. V. Uvarov*, and *N. M. Shovoronkov*. They have applied the following exchange mechanism:

$$H^{37}Cl_{liq.} + H^{35}Cl_{gas} \rightleftarrows H^{35}Cl_{liq.} + H^{37}Cl_{gas}$$

to the distillation of hydrogen chloride. The low coefficient of separation (1.005) can be increased to 1.014–1.015 by addition of substances which form oxonium compounds.

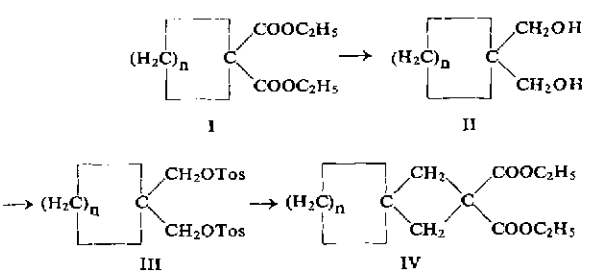
$$RH^{37}Cl_{liq.} + H^{35}Cl_{gas} \rightleftarrows RH^{35}Cl_{liq.} + H^{37}Cl_{gas}$$

R may be diethyl ether, isoamyl alcohol, anisole, *o*-nitrotoluene. Glass columns, 1 meter high, were used; the heavy isotope ^{37}Cl was concentrated in the gas phase, and ^{35}Cl in the liquid phase. / Zhur. Priklad. Khimii *34*, 2563 (1961). / –Bk [Rd 57/35 IE]

The existence of arsonium ions was proved spectroscopically by *A. Heinemann*. The pure hydrides of the elements of the fifth main group were condensed onto a NaCl-plate cooled to 110 °K. and the infrared absorption measured from 1 to 15 μ. This procedure was followed by the condensation of gaseous mixtures XH_3/YH, 1:1 (X = N, P, As, Sb; Y = Cl, Br, I); these were examined between 110 °K. and 230 °K. In the systems PH_3/HCl, (HBr), (HI), and AsH_3/HBr (HI), the bands of the starting material disappeared with an increase in temperature and new, strong, absorption bands appeared which are ascribed to the ions $P^+H_4^-$ and $As^+H_4^-$. Therefore at low temperatures arsonium compounds exist which are analogous to ammonium and phosphonium compounds. / Naturwissenschaften *48*, 568 (1961). – Ma. [Rd 975/9 IE]

The oxidation rate of titanium alloys in air at high temperatures was investigated by *I. S. Anitov* and *S. A. Garbunov*. Constituents of the alloys (5 %) were: Al, Si, Sn, Cu, Fe, Cr, Mo, and V and the temperatures 700 and 1000 °C. Al and Si retarded oxidation; V, Cr, and Fe accelerated oxidation; Sn has practically no influence. Cu increases the oxidation velocity at low temperatures, and decreases it at higher temperatures. Mo behaves in opposite fashion. The V alloys are suddenly and completely destroyed by oxidation above certain temperatures; this can be explained by the great difference in the molecular volumes of V_2O_5 and rutile, and the relatively low melting point of V_2O_5. / Zhur. Priklad. Khimii (Moscow) *34*, 725 (1961). / –Gä. [Rd 54/32 IE]

A systematic synthesis of polynuclear spiranes is described by *E. Buchta* and *K. Geibel*. The diethyl esters of cycloalkane-1,1-dicarboxylic acids (I) are reduced with $LiAlH_4$ to the corresponding 1,1-bis(hydroxymethyl) compounds (II), converted to tosylates (III) and these are then condensed with Na-malonic diethyl ester to give esters of the gem.-spiranedicarboxylic acid.

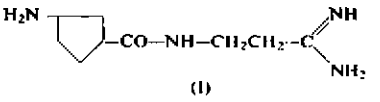


I II

III IV

Repetition of these steps with (IV) yields esters of dispiranedicarboxylic acid and so on. Starting from esters of cyclobutane-, cyclopentane- and cyclohexane-1,1-dicarboxylic acids, spiranes with up to 4 rings have been synthesized. / Liebigs Ann. Chem. *648*, 36 (1961). / –Ko. [Rd 23/29 IE]

Amidinomycin, a new antibiotic which is formed by a *Streptomyces flavochromogenes* strain, has been isolated by *S. Nakamura*, who also established its chemical structure. Amidinomycin (I) inhibits the growth of spore-bearing bacteria such as *B. subtilis*, *B. megatherium* and *C. anthracis* at a concentration of 5–200 γ/ml. It was named „amidinomycin" because it contains an amidino group. The compound forms a sulfate, $C_9H_{18}N_4O \cdot H_2SO_4$, colorless needles or prisms, m.p. 285 to 288 °C $[\alpha]_D^{20}$ 3.9 (c 3; in water), and a reineckate, pink needles, $C_9H_{18}N_4O \cdot 2H[Cr(NH_3)_2(SCN)_4]$, m.p. 208 to 211 °C (decomp.). By hydrolysis, two ninhydrin-positive



(I)

compounds are formed, a new amino acid, cyclopentaminine, $C_6H_{11}NO_2$, m.p. 248 to 251 °C (decomp.); and a base, 2-amidinoethylamine $C_3H_9N_3$. The new antibiotic was identified as *N*-(2-amidinoethyl)-3-aminocyclopentane-1-carboxamide. (Chem. Pharm. Bull. (Japan) 9, 641 (1961) / De. [Rd 52/30 IE]

BOOK REVIEWS

Traité de Biochimie Générale, Vol. I: Composition Chimique des Organismes, (Chemical Composition of Organisms), Parts 1 and 2. Edited by *M. Javillier*, *M. Polonovski*, *M. Florkin*, *P. Boulanger*, *M. Lemoigne*, *J. Roche* and *R. Wurmser*. Masson et Cie., Publishers, Paris 1959. 1st Edition, 1475 pp., 190 figures. Price: 24.50 NF.

A comprehensive "general biochemistry" has now been issued by the publishers who are known for the careful and meticulous "Traité de Chimie Organique". The new book is of the same general standard. Both promoters of this work, *M. Polonovski* and *M. Javillier*, did not live to see its publication. The first part of the work describes (in two volumes) the material composition of organisms, the second part (1 volume) the catalysts of synthesis and decomposition, and the third part (2 volumes), biochemical synthesis and decomposition reactions as well as their coordination. This subdivision of the subject into statics and dynamics is not adhered to as strictly by the French editors as it is in corresponding works in the German or English languages. The authors were apparently granted extensive freedom with respect to the choice of material and the manner of presentation. As always, this produces a welcome subjectivity and a personal character in the individual chapters. On the other hand, this type of presentation also makes for considerable deficiencies. It makes the book more difficult to use, while also causing overlapping and troublesome gaps. The sections on the elementary composition of organisms and mineral components, written by *M. Javillier* and *D. Bertrand*, sometimes deals with details usually reserved for special monographs. There are summaries of the Ni and Co contents found in 30 plants and animals, a small section about the very doubtful gallium content of some organisms and another about silver. On the other hand, selenium is not mentioned at all, although microorganisms can incorporate it into proteins in place of sulfur. There are plants which absorb it from the soil and concentrate it many hundred times. It can alleviate or prevent nutritional liver necrosis.

Subsequent sections deal with natural substances such as sugars (*Ac. Lespagnol*, 128 pp.), fatty acids and glycerides (*M. Naudet*, 64 pp.), phosphoro- and glycolipids (*J. Polonovski*, 37 pp.), waxes and related compounds (*Naudet* and *Polonovski*, 118 pp.), steroids (*D. Bar*, 118 pp.), acids other than fatty acids (*Polonovsky*, 14 pp.) as well as phenols and related compounds (*Lespagnol*, 24 pp.). Depending on the author, these are conventional, short descriptions such as may be found in any textbook of organic chemistry or treatises of wide scope. The chapter, "Amino Acids" (*P. Desnuelle*, 86 pp.), with its exemplary precision and clarity, reveals the expert knowledge of the author with each sentence. A discussion concerning peptides concludes the first volume (*G. Biserte*, 77 pp.).

Judging by the headings of the main sections, the second volume is devoted only to proteins (*P. Boulanger* and *G. Biserte*, 227 pp.) and proteids (glycoproteids, phosphoproteids, nucleoproteids) (*J. Montreuil*, 204 pp.), chromoproteids (*J. Roche*, *D. Bar*, and *G. Biserte*, 132 pp.) and derivatives of proteids (*Nguyen-van Thoai* and *Y. Robin*, 90 pp.). On closer study, however, we also find sections on mucopolysaccharides nucleic acids, nucleotides, nucleosides, purine and pyrimidine bases as well as coenzymes (insofar as these contain these bases), the chemistry of porphyrins and bile pigments, and 54 pages on alkaloids.

It is hoped that particularly important compounds, such as folic acid, biotin, pyridoxine and thiamine, as well as the related coenzymes and others, which were missed because of the loose style of the subdivision, will be treated in the next volume.

Apart from the description of the proteins, there are also sections on physicochemical properties. The one written by *R. Wurmser* on "Combinaisons dissociables des protéines" (28 pp.) will be of great value to all who are concerned with biochemical problems. It gives a systematic arrangement and clear discussion of the various types of association forces, as well as the methods for their determination. The same, and similar, problems are treated once more in a general and less clear description in the final chapter by *F. Tayeau* entitled "Associations entre principes immédiats" (34 pp.). Those familiar with the problem of "hydrophobic bonding" will welcome the careful summary of the fundamental discoveries which were made by *Mâcheboeuf* and his school more than 30 years ago. On the other hand, the sometimes ill-defined formulations can also be a detriment to those for whom this is the first introduction to this field.

Compared to other biochemical handbooks of similar scope, the present work has a national character, since only French authors participated. This has the advantage of bringing into focus some important research results which had not been paid sufficient regard on an international scale. It does, however, labor under the disadvantage that many things were known to the authors only from lectures in a foreign language. The latter is apparently to blame for many misinterpretations and technical errors.

K. Wallenfels [NB 816/5 IE]

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Recent Studies on Fluoroalkyls and Related Compounds

BY PROF. DR. H. J. EMELÉUS [*]

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE, ENGLAND

The discovery of trifluoroiodomethane some 14 years ago opened up a wide range of possibilities for the preparation of new organometallic and organometalloidal compounds containing fluoroalkyl radicals. Simultaneously it offered for the first time the possibility of examining and explaining the differences between such compounds and their alkyl or aryl analogues. A brief recaptiulation of some earlier results is given, followed by a review of recent progress, especially in the chemistry of fluoroalkyls of sulphur and nitrogen as well as certain of the metallic elements.

Preparation and Properties of Trifluoroiodomethane

Trifluoroiodomethane was prepared originally by heating carbon tetraiodide with iodine pentafluoride [1].

$$CI_4 + IF_5 \rightarrow CF_3I \quad (b.p. -22.5\,^\circ C)$$

$$R_FCOOAg + I_2 \rightarrow R_FI + CO_2 + AgI$$

This reaction is not easy to control and does not give good yields. A useful advance, therefore, was the discovery by *Haszeldine* of a more general method involving the thermal interaction of the silver salt of a fully fluorinated organic acid with iodine [2]. Not only does this give excellent yields of trifluoroiodomethane from silver trifluoroacetate, but it is applicable to the preparation of a range of homologues, the main limitation ebing the availability of the fluorinated organic acids.

Trifluoroiodomethane is a typical positive iodine compound which yields fluoroform CF_3H on alkaline hydrolysis rather than the alcohol, CF_3OH. It therefore differs basically from its hydrocarbon analogue, methyl iodide. The two compounds are, however, analogous in that the C-I bond appears to undergo homolytic fission on irradiation with ultraviolet light of wave length about 2800 Å, or on heating to about 250 °C. This fact provided the key to the preparation of a number of new fluoroalkyl derivatives of phosphorus, arsenic, antimony, sulphur, and selenium by the simple procedure of heating trifluoroiodomethane with excess of the element in question in a sealed tube or autoclave. The compounds prepared in this way are listed below (Table 1).

Table 1.

P	$(CF_3)_3P$	b.p. 17.5 °C.
	$(CF_3)_2PI$	73 °C.
	CF_3PI_2	69 °C./29 mm. Hg
As	$(CF_3)_3As$	33.3 °C.
	$(CF_3)_2AsI$	92 °C.
	CF_3AsI_2	154 °C.
Sb	$(CF_3)_3Sb$	72 °C.
	$(CF_3)_2SbI$	109–110 °C.
S	$(CF_3)_2S_2$	35 °C.
	$(CF_3)_2S_3$	86.5 °C.
	$(CF_3)_2S_4$	135 °C.
Se	$(CF_3)_2Se$	−1 °C.
	$(CF_3)_2Se_2$	70 °C.

Much of this earlier work has been reviewed in detail elsewhere [3]. The type of study that has been made can be illustrated by reference to the cases of phosphorus and sulphur.

Reaction of elementary phosphorus with trifluoroiodomethane occurs at 200–220 °C. and there are strong indications of an equilibrium between the products $(CF_3)_3P$, $(CF_3)_2PI$, CF_3PI_2, and PI_3, leading to a preponderance of the tris compound in the product. The chief reactions observed are:

1. Replacement of iodine in the iodoperfluoroalkyl phosphorus compounds by reaction with the corresponding silver salt (*e.g.* AgCN, AgCl) to form compounds such as $(CF_3)_2PCN$ and $(CF_3)_2PCl$.

[*] This paper was presented at the Chemikertreffen in Vienna in October 1961.

[1] *A. A. Banks, H. J. Emeléus, R. N. Haszeldine,* and *V. Kerrigan,* J. chem. Soc. (London) *1948*, 2188.

[2] *R. N. Haszeldine,* J. chem. Soc. (London) *1951*, 584.

[3] *J. J. Lagowski,* Quarterly Reviews *13*, 233 (1959); a full bibliography of earlier work is given.

2. Reduction to the phosphines $(CF_3)_2PH$ and CF_3PH_2.

3. Addition of chlorine to the tris compound and to the two chloro-compounds to form $(CF_3)_3PCl_2$, $(CF_3)_2PCl_3$, and CF_3PCl_4.

4. Hydrolysis of the halogeno-compounds to form very strong acids. The two iodo-compounds mentioned above both yield the phosphonous acid, CF_3PHOOH, one molecule of fluoroform being liberated in the hydrolysis of $(CF_3)_2PI$. This acid is readily oxidised to the phosphonic acid $CF_3PO(OH)_2$, while the second phosphonic acid, $(CF_3)_2PO(OH)$, is formed in the aqueous hydrolysis of $(CF_3)_2PCl_3$.

5. Reaction of iodotrifluoromethylphosphine, or iodobistrifluoromethylphosphine, with mercury yields compounds containing the P–P bond

$$(CF_3)_2PI \rightarrow (CF_3)_2P{-}P(CF_3)_2$$

$$CF_3PI_2 \rightarrow (CF_3P)_4 + (CF_3P)_5$$

Reference may also be made to the reaction of diborane with fluorobistrifluoromethyl phosphine or bistrifluoromethyl phosphine, both of which give the air-stable trimer $[(CF_3)_2P{\cdot}BH_2]_3$.

The behavior of arsenic and antimony is essentially similar to that of phosphorus, a notable difference in the case of antimony being the formation of acids with anions of the type $[Sb(CF_3)_3(OH)_3]^-$.

Fluoroalkyl Derivatives of Sulphur

The derivatives of sulphur are much more varied in type, and in this field there is also substantially more recent progress to record. The main product of the reaction of trifluoroiodomethane with sulphur is the disulphide, $(CF_3)_2S_2$, but this is made more conveniently by the autoclave reaction of carbon disulphide with iodine pentafluoride at 195 °C. [4].

$$CS_2 + IF_5 \xrightarrow{195\,^\circ C.} F_3C{-}S{-}S{-}CF_3\ (76\,\%) + F_3C{-}S{-}S{-}S{-}CF_3\ (7\,\%)$$

Fluorination of carbon disulphide by mercuric fluoride at 300 °C. also yields the disulphide with some monosulphide, the latter being formed also when the disulphide is irradiated [5]. Related compounds are also formed by the addition of fluoro-olefins to sulphur halides, *e.g.* [6]:

$$F_2C{=}CF_2 + S_2Cl_2 \xrightarrow{100-120\,^\circ C} ClF_2C{-}CF_2{-}SCl{-} + (ClF_2C{-}CF_2)_2S_n \quad (n = 1-3)$$

Asymmetrical fluorine-containing sulphides are obtained in the base-catalysed addition of thiols to fluoro-olefins, *e.g.* [7]:

$$RSH + F_2C{=}CFCl \rightarrow R{-}S{-}CF_2{-}CHFCl \quad (R = \text{alkyl})$$

Bistrifluoromethyl disulphide is a liquid, b.p. 34 °C., which is decomposed readily by alkali without liberation of fluoroform. It reacts with mercury in ultraviolet light and the resulting mercurial yields the thiol on treatment with hydrogen chloride [8].

$$F_3C{-}S{-}S{-}CF_3 + Hg \xrightarrow{UV} (F_3CS)_2Hg$$

$$(F_3CS)_2Hg + 2\,HCl \longrightarrow 2\,F_3CSH + HgCl_2$$

The mercurial is a compound of very considerable interest. It is also formed in good yield from carbon disulphide and mercuric fluoride at 250 °C. [9].

$$3\,HgF_2 + 2\,CS_2 \xrightarrow{250\,^\circ C} (F_3CS)_2Hg + 2\,HgS$$

Other salts of this type are known. Thus, the silver derivative F_3CSAg is formed by reaction of aqueous silver nitrate with the mercurial, or better, by heating argentous fluoride with carbon disulphide in an autoclave. The copper(I) salt, F_3CSCu and the mercurial, $(F_3CS)_2Hg$, may be made from the silver salt by metathetical reactions in non-aqueous solution and there is also evidence from conductimetric titrations in non-aqueous solution that similar reactions occur with nickel chloride, cadmium iodide, phosphorus trichloride, arsenic trichloride, stannic iodide, and trimethylsilylchloride [10].

Bistrifluoromethylthiomercury is a reagent for introducing the F_3CS group into other molecules. Thus it reacts readily with alkyl iodides to form compounds of the type RSR_F, and forms $CH_3{-}COS{-}CF_3$ with acetyl chloride and also phosphorus or arsenic derivatives of the types R_3M, R_2MCl, and $RMCl_2$ ($R = SCF_3$) with the trihalides of these two elements [11]. We have also shown recently that it reacts with $(CF_3)_2PI$ and $(CF_3)_2AsI$ to give $(CF_3)_2P{-}SCF_3$ and $(CF_3)_2As{-}SCF_3$. Another interesting reaction is that with chlorine, which yields the sulphenyl chloride, $F_3C{-}SCl$, a substance which behaves as a typical acid chloride in its reaction with ammonia, amines and also, surprisingly, with phosphine. The selenium analogue is also known, as is the trichloride F_3CSeCl_3, although the existence of the sulphur analogue of the latter is doubtful [12].

$$(F_3CS)_2Hg \xrightarrow{Cl_2} F_3C{-}SCl \begin{cases} \xrightarrow{NH_3} F_3C{-}SNH_2 \\ \xrightarrow{R_2NH} F_3C{-}SNR_2 \\ \xrightarrow{PH_3} F_3C{-}SPH_2 \end{cases}$$

Sulphur also forms fluoroalkyl derivatives when in the hexa- or tetra-valent state. The simplest and most

[4] *R. N. Haszeldine* and *J. M. Kidd*, J. chem. Soc. (London) *1953*, 3219.

[5] *E. H. Man, D. D. Coffman*, and *E. L. Muetterties*, J. Amer. chem. Soc. *81*, 3575 (1959).

[6] *I. L. Knunyants* and *A. V. Fokin*, Bull. Acad. Sci. U.S.S.R., Div. chem. Sci. *1955*, 627; *I. L. Knunyants* and *E. G. Bykhovskaya*, ibid. *1955*, 821; *M. S. Raasch*, U.S.-Pat. 2451411 (1948).

[7] *K. E. Rapp, R. L. Pruett, J. T. Barr, J. D. Gibson*, and *R. H. Lafferty*, J. Amer. chem. Soc. *78*, 849 (1956).

[8] *R. N. Haszeldine* and *J. M. Kidd*, J. chem. Soc. (London) *1953*, 3219.

[9] *E. H. Man, D. D. Coffman*, and *E. L. Muetterties*, J. Amer. chem. Soc. *81*, 3575 (1959).

[10] *H. J. Emeléus* and *D. E. MacDuffie*, J. chem. Soc. (London) *1961*, 2597 and unpublished results.

[11] *H. J. Emeléus* and *H. Pugh*, J. chem. Soc. (London) *1960*, 1108.

[12] *J. W. Dale, H. J. Emeléus*, and *R. N. Haszeldine*, J. chem. Soc. (London) *1958*, 2939.

familiar derivatives of S(VI) are F_3C-SF_5 and $(CF_3)_2SF_4$, which have been prepared in various ways [13, 14].

$$CH_3SH \text{ or } CS_2 \xrightarrow[200-250\,^\circ C.]{CoF_3} F_3C-SF_5 + CF_4 + SF_6$$

$$CS_2 \text{ or } CH_3-S-CH_3 \xrightarrow[\text{fluorination}]{\text{electrochem.}} F_3C-SF_5 + (CF_3)_2SF_4$$

Direct fluorination of other sulphur-containing organic compounds has given a number of compounds containing the SF_5 radical, notably pentafluorosulphur nitrile SF_5CN (from methyl thiocyanate) [15]. Direct fluorination of carbon disulphide with fluorine diluted by nitrogen yields a mixture of considerable complexity, viz:- F_3C-SF_5, F_3C-SF_3, $F_5S-CF_2-SF_5$, $F_3S-CF_2-SF_5$, $S{=}CF_2$, CF_4, SF_6, SF_4, and S_2F_{10} [16].

The derivatives containing sulphur in its highest oxidation state show a good deal of the stability to heat and chemical attack which is encountered in sulphur hexafluoride itself. One of the points of current interest is the question of whether it is possible to build up a chemistry of the SF_5 radical which parallels that of the fluorocarbon radicals, and considerable effort has been devoted to exploring this matter. The most hopeful lead so far as been the synthesis of the new compound SF_5Cl. This may be obtained by several routes, the most satisfactory being the interaction of sulphur tetrafluoride with chlorine monofluoride [17]. Both of these substances are now readily available.

$$SF_4 + ClF \rightarrow SF_5Cl \quad (b.p. -21\,^\circ C.)$$

This is a chain reaction, initiated by benzoyl peroxide. Reaction with a hydrocarbon olefin occurs in ultraviolet light, or in an autoclave, *e.g.*

$$CH_3-CH{=}CH_2 + SF_5Cl \rightarrow CH_3-CHCl-CH_2-SF_5$$

Addition of acetylenes has also been observed, *e.g.*

$$CH{\equiv}CH + SF_5Cl \rightarrow F_5S-CH{=}CHCl$$

$$CH_3-C{\equiv}CH + SF_5Cl \rightarrow F_5S-CH{=}CCl-CH_3$$

The products are stable to alkali, except when hydrogen and chlorine are present on adjacent carbon atoms when elimination of hydrogen chloride occurs readily, *e.g.*

$$F_5S-CH{=}CCl-CH_3 \xrightarrow{KOH} F_5S-C{\equiv}C-CH_3$$

Another interesting development in this field is the preparation of aryl sulphur pentafluoride,

$$C_6H_5SF_3 + 2\,AgF_2 \longrightarrow C_6H_5SF_5 + 2\,AgF$$

in which the SF_5 group produces the expected strong deactivating effect on the benzene ring, leading to *meta*-nitration. The second reaction of sulphur chloride pentafluoride which calls for some comment is its photochemical oxidation, which yields two further SF_5 derivatives, SF_5-O-SF_5 and $F_5S-O-O-SF_5$. The first of these compounds is like the perfluoro ethers $(R_F)_2O$ in that it appears to be very inert. It boils at 31 °C. and this again is notable in view of the relatively high molecular weight [17]. The hypofluorite F_5S-OF, on the other hand, is very reactive. The same is true to a lesser extent of the peroxide $F_5S-O-O-SF_5$. Its stability is, however, considerably greater than that of most organic peroxides and it has been shown to be an active polymerisation catalyst.

There are a number of further compounds known which contain the SF_5 radical, although, as already explained, it does not occur, as far as is known, in association with metals or the commoner non-metals (*e.g.* P). One further example which may be mentioned is the product of the electrochemical fluorination of thioglycollic acid [18].

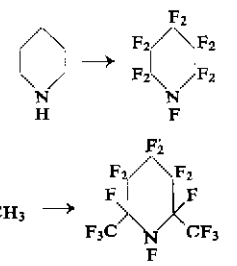
$$\text{Thioglycollic acid} \rightarrow F_5S-CF_2-COOH \rightarrow F_5S-CF_2-COOAg \rightarrow F_5S-CF_2Cl$$

The silver salt undergoes decarboxylation on treatment with chlorine at low temperature to yield F_5S-CF_2Cl.

Fluoroalkyls of Nitrogen

The chemistry of fluoroalkyls of nitrogen is a field in which there is a great deal of current interest. The simple perfluoroamines have been known for a considerable time. They form a substantial group of compounds which includes not only the fluorocarbon analogues of various aliphatic amines but also a number of cyclic structures:

$$(CH_3)_3N \rightarrow (CF_3)_3N,\ (CF_3)_2NF,\ F_3C-NF_2$$



The perfluoroamines are devoid of basic properties and are relatively inert, although they undergo pyrolysis at fairly high temperatures [19], *e.g.*

$$(C_3F_7)_3N \xrightarrow[AlF_3]{660\,^\circ C.} F_7C_3-CF{=}N-CF_3$$

The compound $F_3C-N{=}CF_2$, perfluoromethylene methylamine, has also been made from the reaction product of trifluoroiodomethane and nitric oxide in ultraviolet light, by reaction with tetrafluoroethylene [20].

[13] *G. A. Silvey* and *G. H. Cady*, J. Amer. chem. Soc. *72*, 3624 (1950); *74*, 5792 (1952).

[14] *A. F. Clifford, El-Shamy, H. J. Emeléus*, and *R. N. Haszeldine*, J. chem. Soc. (London) *1953*, 2372.

[15] *J. A. Attaway, R. H. Groth*, and *L. A. Bigelow*, J. Amer. chem. Soc. *81*, 3599 (1959).

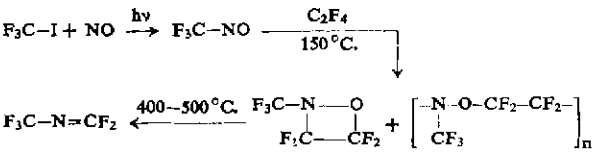
[16] *E. A. Tyckowski* and *L. A. Bigelow*, J. Amer. chem. Soc. *75*, 3523 (1953).

[17] *H. L. Roberts*, Quarterly Reviews *15*, 30 (1961). A full bibliography of recent work on SF_5 derivatives is given.

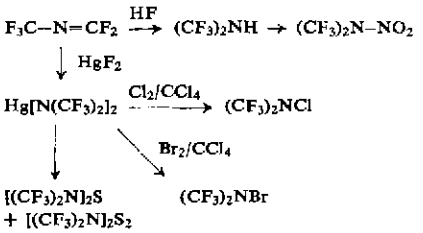
[18] *R. N. Haszeldine* and *F. J. Nyman*, J. chem. Soc. (London) *1956*, 2684.

[19] *W. H. Pearlson* and *L. J. Hals*, U.S.-Pat. 2643267 (1953).

[20] *D. A. Barr* and *R. N. Haszeldine*, Nature (London) *175*, 991 (1955); J. chem. Soc. (London) *1955*, 1881.



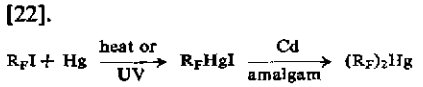
It adds HF to form the amine, $(CF_3)_2NH$ [21], which can be nitrated to $(CF_3)_2N{-}NO_2$, and also reacts with mercuric fluoride to give a new type of mercurial $Hg[N(CF_3)_2]$ from which chloro- and bromo-derivatives are obtained by reaction with the halogens in carbon tetrachloride solution. Reaction of the mercurial with sulphur at 165 °C. also gives the compounds $[(CF_3)_2N]_2S$ and $[(CF_3)_2N]_2S_2$.



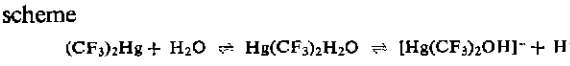
These observations at once open up the possibility of preparing a whole range of metallic and non-metallic compounds containing the relatively unreactive $N(CF_3)_2$ group, and we may expect that substantial progress will be made in this direction. In view of the close similarity of the perfluoroamines and nitrogen trifluoride it is also relevant to consider whether there may not be analogous derivatives which contain the NF_2 group. Here the position is somewhat different. One of the most promising materials for the production of NF_2 radicals is perfluorohydrazine, N_2F_4, which can be made from nitrogen trifluoride by reaction with copper [22]. Little is known at present about its reactions. In particular, it is not known if it will yield derivatives with metals or non-metals, or what the stability of such compounds would be likely to be.

Perfluoralkyl Derivatives of the Metallic Elements

In conclusion, some reference must be made to recent progress in the study of perfluoroalkyl derivatives of the metallic elements. It will be recalled that the first of such compounds to be made were those in which a fluoroalkyl radical was linked to mercury. These were obtained by the reaction of mercury with a perfluoroalkyl iodide under the influence of either heat or light and then treating the product with cadmium amalgam [22].



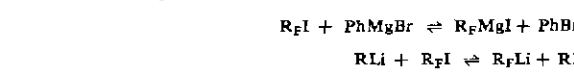
The mercurials have a number of interesting properties. Thus bistrifluoromethyl mercury is a white crystalline solid which is soluble in water, as well as in organic solvents, and which forms a weakly conducting solution in the former. This ionic character, which contrasts sharply with the case of dimethyl mercury, has been attributed to ionisation according to the following scheme



The second equation accounts for the observed liberation of fluoroform at the anode when the aqueous solution is electrolysed. The product $Hg(CF_3)OH$ is itself an electrolyte and accounts for the fluoroform produced at the cathode [23].

The general behaviour of the mercurial suggests that the trifluoromethyl group functions as a pseudo halogen in this type of compound. This is supported by several lines of evidence. Thus the electronegativity has been estimated as intermediate between that of fluorine and chlorine. Trifluoromethyl mercurate anions are also known, the existence of these having first been shown by conductometric titration of aqueous solutions of bistrifluoromethyl mercury and trifluoromethyl mercuric iodide with potassium halides. Discontinuities in the plot of conductivity versus molar ratio of the reactants correspond with the existence of anions of the types $[Hg(CF_3)_2X]^-$, $[Hg(CF_3)_2X_2]^{2-}$, $[Hg(CF_3)IX]^-$, and $[Hg(CF_3)IX_2]^{2-}$; the stability of these decreases in passing from X = I to X = Cl. Furthermore, crystalline derivatives containing these anions have also been prepared, *e.g.* $Zn(en)_3Hg(CF_3)_2I_2$ [24]. Recently it has been shown that perfluoroalkyl mercurials are formed by the interaction of mercuric fluoride with fluoroolefins at 50–150 °C., a route which simplifies the preparation of this group of substances very considerably [25]. On the whole the mercurials have been disappointing as intermediates for the preparation of new perfluoroalkyl compounds of other elements. In particular, they differ from the dialkyl mercurials in that they do not appear to react with other metals or metal halides.

A further approach to the preparation of perfluoro compounds is by the formation of Grignard reagents. It is found that perfluoroalkyl iodides react with magnesium in basic solvents, such as tetrahydrofuran. The products are much less stable than their alkyl and aryl analogues and indeed most of their reactions have had to be studied at below room temperature [26]. Perfluoroalkyl derivatives of zinc have been prepared by analogous methods, but their stability is likewise low [27]. It is also of interest that compounds of this sort may be formed by radical exchanges [28]. Thus:



[21] *D. A. Barr* and *R. N. Haszeldine*, J. chem. Soc. (London) *1955*, 2532. *J. A. Young*, *S. N. Tsonkalas*, and *R. D. Dresdner*, J. Amer. chem. Soc. *80*, 3604 (1958).

(22) *H. J. Emeléus* and *R. N. Haszeldine*, J. chem. Soc. (London) *1949*, 2953.

[23] *J. J. Lagowski*, Quarterly Rev. *153*, 233 (1959).

[24] *H. J. Emeléus* and *J. J. Lagowski*, J. chem. Soc. (London) *1959*, 1497.

[25] *C. G. Krespan*, U.S. pat. 2844614 (1958); J. org. Chemistry *25*, 105 (1960). Cf. J. Amer. chem. Soc. *75*, 992 (1953).

[26] *R. N. Haszeldine*, J. chem. Soc. (London) *1952*, 3423; *1954*, 1273.

[27] *W. T. Miller*, *E. Bergman*, and *A. H. Fainberg*, J. Amer. chem. Soc. *79*, 4159 (1957).

[28] *E. T. McBee*, *C. W. Roberts*, and *A. F. Meiners*, J. Amer. chem. Soc. *79*, 335 (1957).

In spite of the difficulties encountered in the preparation of Grignard-type compounds containing saturated perfluoroalkyl groups, it has been possible to prepare a number of compounds of this type containing the perfluorovinyl group. Thus perfluorovinyl bromide, $F_2C{=}CFBr$, which is available commercially, reacts directly in diethyl ether with magnesium activated with iodine to form $F_2C{=}CFMgBr$, and this magnesium derivative has proved to be extremely valuable in making perfluorovinyl compounds of other elements. Thus reactions with mercuric chloride in ether give bisperfluorovinyl mercury $(F_2C{=}CF)_2Hg$ (b.p. 65 °C./17 mm. Hg) [29].

Reaction of perfluorovinylmagnesium bromide with silicon tetrachloride leads to the preparation of $(F_2C{=}CF)_4Si$ [30]. Dimethyl tin dichloride also reacts with the Grignard reagent to form a perfluorovinyl derivative $(F_2C{=}CF)_2Sn(CH_3)_2$, and this in turn forms one of the few known perfluoro boron compounds, $(F_2C{-}CF)BCl_2$ [31], in its reaction with boron trichloride. Other examples from this interesting and rapidly expanding field might also be quoted. It is evident that the fluorinated vinyl group itself may also be modified very conveniently.

Reverting once more to the reactions of perfluoroalkyl iodides, several other interesting synthetic routes may be noted. These include the cleavage of the Sn–Sn bond in the compound $R_3Sn{-}SnR_3$ in the presence of a perfluoroalkyl iodide and also direct reaction of a fluoroalkyl iodide with a tetra-alkyl lead [32].

$$R_3Sn{-}SnR_3 + R_FI \xrightarrow[UV]{\text{Heat or}} R_3SnR_F + R_3SnI$$

$$R_4Pb + R_FI \xrightarrow[UV]{\text{Heat or}} R_3PbR_F$$

Perfluoroalkyls in which there is a σ-bond between a transition metal and carbon comprise an entirely new group of compounds. It has been suggested on several occasions that the high electronegativity of the perfluoroalkyl groups might enable such bonds to form. Success in this field has so far been limited to the preparation of carbonyl derivatives, though there seems no reason why it should be so restricted. *Stone* and his coworkers [33] first showed that it was possible to obtain a reaction between the alkali metal salts of certain metal carbonyl hydrides and perfluoroaryl halides, leading to the elimination of alkali metal halide.

$$R_F{-}CO{-}Cl + M(CO)_5Na \xrightarrow{\text{Tetrahydrofuran}} R_F{-}CO{-}M(CO)_5 + NaCl$$

$$R_F{-}CO{-}M(CO)_5 \xrightarrow{\text{Heat}} R_FM(CO)_5 + CO \quad (M = Mn \text{ or } Re)$$

Decarbonylation of the initial product serves to establish the R_F-M bond. In certain cases the perfluoroalkyl metal compound is formed directly from the sodium salt in tetrahydrofuran by reaction with a perfluoroacyl chloride, *e.g.*

$$Fe_3(CO)_{12} \xrightarrow[\text{Tetrahydrofuran}]{\text{Na in}} Na_2Fe(CO)_4 \xrightarrow{R_FCOCl} (RF)_2Fe(CO)_4 + 2\,CO + 2\,NaCl$$

Perfluoroalkyl iodides also react directly with metal carbonyls which are able to form metal carbonyl iodides. This is true, for example, for iron pentacarbonyl and also for cyclopentadienyl cobalt dicarbonyl [34].

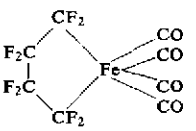
$$Fe(CO)_5 + R_FI \longrightarrow R_FFe(CO)_4I + [R_FFe(CO)_3I]_2$$

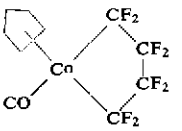
$$C_5H_5Co(CO)_2 + R_FI \xrightarrow[45\,^\circ C.]{\text{Benzene}} C_5H_5Co(CO)R_FI$$

The dimeric perfluoroalkyliron tricarbonyl iodides are better made by the reaction

$$2\,R_FFe(CO)_4I \xrightarrow{50-70\,^\circ C.} [R_FFe(CO)_3I]_2 + 2\,CO$$

A further synthetic method for obtaining σ-bonds of this type is to heat a perfluoro-olefin with the metal carbonyl. The products shown below have been obtained in this way [35]:





It also possible to add a fluorinated olefin to transition metal-hydrogen bonds under mild conditions [36], *e.g.*

$$C_5H_5{-}Mo(CO)_3H + C_2F_4 \longrightarrow C_5H_5{-}Mo(CO)_3C_2F_4H$$

These new compounds are in most cases comparatively stable and volatile and thus contrast sharply with the few known alkyl or aryl derivatives of transition metals. The stability of the σ-bonded perfluoroalkyl groups is well illustrated by the fact that $(C_2F_5)_2Fe(CO)_4$ gives only a trace of C_2F_5H when it is treated with aqueous alkali at 60 °C.

Perhaps the most striking thing about these new transition metal derivatives is the way in which they demonstrate the rapid advances in fluorine chemistry. The subject has moved far and fast in the last twenty years and it is quite certain that we are not yet near the end of what has proved to be a fascinating journey.

Received October 5, 1961 [A 172/9 IE]

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[30] *R. N. Sterlin, I. L. Knunyants, L. N. Purkina*, and *D. R. Yatsenko*, Izvest. Akad. Nauk, S.S.S.R., *1959*, 1492.

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[33] *R. B. King, P. M. Treichel*, and *F. G. A. Stone*, Z. Naturforsch. *15b*, 763 (1960). *R. B. King, P. M. Treichel*, and *F. G. A. Stone*, Proc. chem. Soc. (London) *1961*, 69.

[34] *T. A. Manuel, S. L. Stafford*, and *F. G. A. Stone*, J. Amer. chem. Soc. *83*, 249 (1961).

[35] *T. A. Manuel, S. L. Stafford*, and *F. G. A. Stone*, J. Amer. chem Soc. *83*, 249 (1961).

[36] Paper presented at the Sixth International Conference on Coordination Chemistry, Detroit, August, 1961. I am indebted to Professor *Stone* for permission to refer to results reported in this paper.

Nucleotide Intermediates in the Biosynthesis of Polysaccharides

I. Introduction and Sulfated Polysaccharides [*]

BY PROF. DR. JACK L. STROMINGER

DEPARTMENT OF PHARMACOLOGY. WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST. LOUIS, MISSOURI, USA.

In metabolism, nucleotides play a role not only as the precursors of nucleic acids. Many low molecular weight compounds may be activated for subsequent biosynthesis by forming anhydrides or esters with nucleotides. These nucleotide derivatives function as carriers of the residues attached to them. Frequently the residues become chemically changed while attached to the nucleotide before transfer in a biosynthetic reaction. Following a general survey of nucleotide-types, and their reactions, research into the biosynthesis of sulfated polysaccharides is described.

I. Introduction

A little over 10 years ago, *Leloir* and his collaborators [1] discovered a co-factor for galactose utilization in yeast isolated the compound, and showed that it was uridine diphosphoglucose. Since these pioneering studies, it has become increasingly apparent that, in addition to their role as precursors of nucleic acids, many acid-soluble nucleotides have roles in other metabolic processes. There are four groups of acid-soluble nucleotides related to the four principal ribonucleotides which occur in ribonucleic acid (as well as several, recently discovered, which contain deoxyribonucleotides). The adenosine nucleotides have been known for at least 25 years. Soon after the isolation of uridine diphosphoglucose (UDPG), guanosine and cytidine nucleotides were also discovered as components of the acid-soluble fraction of tissues. Each of these types of nucleotide has a special metabolic function in addition to its role as a nucleic acid precursor. By way of introduction, the general types of compound for each nucleotide and their diverse metabolic functions will be described [**].

Adenosine Nucleotides

In the case of the adenosine nucleotides, there are, first of all, the oxidation-reduction intermediates, DPN, TPN, and FAD. Each of these compounds, as well as most of the others, can be considered as the acid anhydride of a mononucleotide, *i.e.* a substituted phosphoric acid and another acid. For example, DPN is the anhydride of adenylic acid and nicotinamide ribose phosphate, and FAD is the anhydride of adenylic acid and riboflavin phosphate. These compounds are synthesized primarily by reaction between a nucleoside triphosphate (ATP in the case of the adenosine nucleotides) and the acid which is to be activated (Equation 1).

$$\text{XTP} + \text{acid} \rightleftarrows \text{XMP-acid} + \text{PP} \qquad \text{X} = \text{nucleoside} \quad (1)$$

For example, a reaction between ATP and riboflavin phosphate leads to formation of the anhydride, flavin adenine dinucleotide (FAD), with the simulatenous splitting-out of inorganic pyrophosphate. This mechanism for the synthesis of these acid anhydrides by means of displacement of inorganic pyrophosphate from a nucleoside triphosphate by another acid was first discovered by *Kornberg* during studies of DPN metabolism [2].

In addition to the oxidation-reduction intermediates, a number of other types of compounds are activated as derivatives of adenylic acid, *e.g.* amino-acids. In recent years, adenyl amino-acids have been isolated and synthesized, and are believed to be intermediates in the biosynthesis of proteins. Another compound activated in this way is inorganic sulfate. Adenyl sulfate is formed as the product of the primary reaction with ATP (Equation 2). In this latter case, however, the equilibrium is extremely unfavorable and in the living cell it is displaced by the phosphorylation of the adenylic acid moiety (Equation 3). The product is "active sulfate," 3′-phosphoadenosine-5′-phosphosulfate (PAPS). This compound has a role in the biosynthesis of chondroitin sulfates and of other naturally occurring sulfate esters [7] (Equation 4).

$$\text{ATP} + \text{sulfate} \rightleftharpoons \text{AMP-sulfate} + \text{PP} \quad (2)$$

$$\text{AMP-sulfate} + \text{ATP} \rightarrow \text{PAPS} + \text{ADP} \quad (3)$$

$$\text{PAPS} + \text{acceptor} \rightleftharpoons \text{acceptor-sulfate} + \text{PAP} \quad (4)$$

[*] This paper and a second one which is to appear later in this journal are edited transcriptions of two lectures given at Freiburg University in July, 1960, and as the McLaughlin Lectures at the University of Texas in October, 1960. Work in the author's laboratory has been generously supported by the U.S. Public Health Service (Grants NIAMD A-1158 and NIAID E-1902) and by the U.S. National Science Foundation (Grant G-7619), to whom I am greatly indebted.

[**] Documentation of the first half of this paper would require a bibliography of several hundred references. Therefore only a limited number of references are given, but the sources of the work described have been fully covered in several reviews [2–5], including one by the author [6].

[1] *R. Caputto, L. F. Leloir, C. E. Cardini*, and *A. C. Paladini*, J. biol. Chemistry *184*, 333 (1950).

[2] *A. Kornberg*, Advances in Enzymol. *18*, 191 (1957).

Uridine Nucleotides

The second group of compounds is the uridine nucleotides [3, 6]. These compounds are anhydrides of uridylic acid and a sugar phosphate, *i.e.*. UDP-sugar compounds (Equation 5). A very large number of such compounds are now known, and they serve many important metabolic roles in transglycosylation reactions (Equation 6) and in transformations of one sugar to another.

(5) UTP + glucose-1-phosphate $\rightleftharpoons$ UDP-glucose + PP

(6) UDP-glucose + fructose $\rightleftharpoons$ sucrose + UDP

Guanosine Nucleotides

The third group of compounds is the guanosine nucleotides [4, 6]. However, this group has not yet been very extensively studied. Only recently has the isolation of some new compounds stimulated further interest. The earliest isolated was guanosine diphosphomannose (GDP-mannose [8]). Its precise metabolic role is still unknown, but it is presumably an intermediate in the synthesis of mannose-containing polysaccharides. GDP-D-Mannose is also the precursor of GDP-L-fucose [9]. Fucose (6-deoxy-L-galactose) is, therefore, synthesized by living organisms in the form of its nucleotide derivative. Fucose is a very important component of the blood-group substances, as well as of many other types of polysaccharides. GDP-D-Mannose can also be transformed to GDP-colitose [10]. Colitose is a 3,6-dideoxy-hexose (3,6-dideoxy-L-galactose), found in the O-endotoxin of several gramnegative bacteria. For example, it occurs in the O-endotoxin of some pathogenic *E. coli* strains, which are the causative agents of infantile diarrhea. The mechanism involved in the synthesis of O-endotoxins and of their precursors is the subject of very active investigation.

Cytidine Nucleotides

Finally, the compounds which are activated as derivatives of cytidylic acid, are, with one exception, alcohols [5, 6]. One alcohol which is activated as a cytidine nucleotide is choline (Equation 7). CDP-Choline is a key intermediate in phospholipid synthesis (Equation 8) [5]. It may be noted that in the synthetic reaction a phospho-alcohol is transferred (Equation 8) and cytidine monophosphate (CMP) is the second product.

(7) CTP + phosphocholine $\rightleftharpoons$ CDP-choline + PP

(8) CDP-choline + diglyceride $\rightleftharpoons$ lecithin + CMP

This is in contrast to synthetic reactions of uridine nucleotides where the sugar is transferred (Equation 6) and UDP is the second product. Similarly, ethanolamine is activated in this way for the synthesis of ethanolamine lipids. The synthesis of inositol lipids also takes place through a mechanism involving a cytidine nucleotide, although a somewhat more complicated mechanism is used than in the synthesis of choline and ethanolamine lipids [11]. Two compounds which have so far been isolated only from bacteria are CDP-glycerol and CDP-ribitol [12]. They are, presumably, intermediates in the biosynthesis of components of bacterial cell walls and of other bacterial heteropolymers. CMP-N-Acetylneuraminic acid is a very unusual nucleotide in this group [13].

Deoxyribonucleotides

Similar derivatives of nucleotides found in deoxyribonucleic acid have been isolated recently although so far this group of compounds is very limited. Deoxy-CDP-choline and deoxy-CDP-ethanolamine were the first of these to be obtained in a pure state [14, 15]. More recently, thymidine diphosphosugar compounds have been isolated (*e.g.* TDP-L-rhamnose [16, 17], TDP-D-fucose [18, 19], TDP-6-deoxy-D-glucose [18, 19], TDP-4-keto-6-deoxy-D-glucose [19, 20], and TDP-mannose [21]. The occurrence of nucleotide derivatives which are so closely related chemically to deoxyribonucleic acid raises the question as to whether they are related functionally in any way to the genetic material.

II. Reactions of the Nucleotides

A large number of small molecules are activated for synthetic reactions as derivatives of a variety of nucleotides. Acids are activated as adenosine nucleotides, whilst sugars (aldehydes) are activated as guanosine, uridine or thymidine nucleotides and alcohols are activated as cytidine or deoxycytidine nucleotides.

Formula I gives the structure of one of these nucleotides, namely, uridine diphosphoacetylglucosaminc [22]. It

[3] *L. F. Leloir* and *C. E. Cardini* in *P. D. Boyer, H. Lardy*, and *K. Myrback:* The Enzymes. Academic Press, New York, 1960, Volume II, Chapter 2.

[4] *M. F. Utter* in *P. D. Boyer, H. Lardy*, and *K. Myrback:* The Enzymes. Academic Press, New York, 1960, Volume II, Chapter 4.

[5] *E. P. Kennedy* in *P. D. Boyer, H. Lardy*, and *K. Myrback:* The Enzymes. Academic Press, New York, 1960, Volume II, Chapter 3.

[6] *J. L. Strominger*, Physiol. Rev. *40*, 55 (1960).

[7] *F. Lipmann*, Science (Washington) *128*, 575 (1958).

[8] *E. Cabib* and *L. F. Leloir*, J. biol. Chemistry *206*, 779 (1954).

[9] *V. Ginsburg*, J. biol. Chemistry *235*, 2196 (1960).

[10] *E. C. Heath*, Biochim. biophysica Acta *39*, 377 (1960).

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[12] *J. Baddiley*, Proc. chem. Soc. (London) 177 (1959).

[13] *D. G. Comb* and *S. Roseman*, J. Amer. chem. Soc. *80*, 497 (1958).

[14] *Y. Sugino*, J. Amer. chem. Soc. *79*, 5074 (1957).

[15] *W. C. Schneider* and *J. Rotherham*, J. biol. Chemistry *233*, 948 (1958).

[16] *R. Okazaki*, Biochem. biophysical Res. Commun. *1*, 34 (1959).

[17] *R. Okazaki*, Biochim. biophysica Acta *44*, 478 (1960).

[18] *J. L. Strominger* and *S. S. Scott*, Biochim. biophysica Acta *35*, 582 (1959).

[19] *R. Okazaki, T. Okazaki, J. L. Strominger*, and *A. M. Michelson*, (submitted for publication).

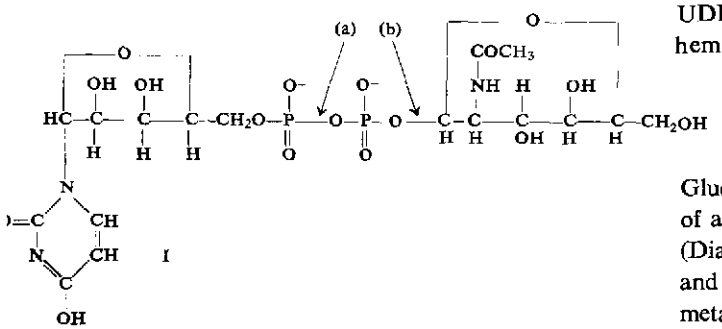
[20] *R. Okazaki, T. Okazaki*, and *J. L. Strominger*, Fed. Proc. *20*, 906 (1961).

[21] *J. Baddiley* and *N. L. Blumson*, Biochim. biophysica Acta *39*, 376 (1960).

[22] *E. Cabib, L. F. Leloir*, and *C. E. Cardini*, J. biol. Chemistry *203*, 1055 (1953)

is a precursor of acetylglucosamine-containing polysaccharides, such as hyaluronic acid. The acid anhydride bond at (a) is formed in the reaction between the nucleoside triphosphate and the sugar phosphate, and the bond at (b) is split in the synthetic reaction involving the transfer of the sugar to a growing polysaccharide chain. The sugar can be considered as a fragment, activated by the nucleotide for some synthetic process.

Many sugars are activated in this way, and in Diagram I, the UDP-sugar compounds related to UDP-glucose are



I

shown. A primary reaction in this scheme is the reaction of glucose-1-phosphate with uridine triphosphate to give UDP-glucose with the formation of inorganic pyrophosphate (Equation 5). Once activated in the form of its nucleotide derivative, the glucose moiety can be modified in a number of ways. UDP-Glucuronic acid, UDP-galacturonic acid, and UDP-galactose are formed through transformation of UDP-glucose. Each of these sugar-containing nucleotides can participate in a synthetic reaction. For example, UDP-glucuronic acid is used in the synthesis of glucuronides. UDP-Glucose is an intermediate in the biosynthesis of sucrose in plants (cf. Equation 6) and in recent years it has been shown that glycogen is not synthesized directly from glucose-1-phosphate but rather from UDP-glucose. UDP-Galactose is used in the synthesis of lactose and of cerebrosides in brain. UDP-Galacturonic acid undoubtedly has many important metabolic roles which have not yet been adequately described. Two congenital defects in uridine nucleotide metabolism occur in man. One of these is a defect in formation of UDP-galactose from galactose-1-phosphate (galactosemia) and the other one is a defect in the transfer of glucuronic acid form UDP-glucuronic acid to bilirubin (congenital non-hemolytic bilirubinemia).

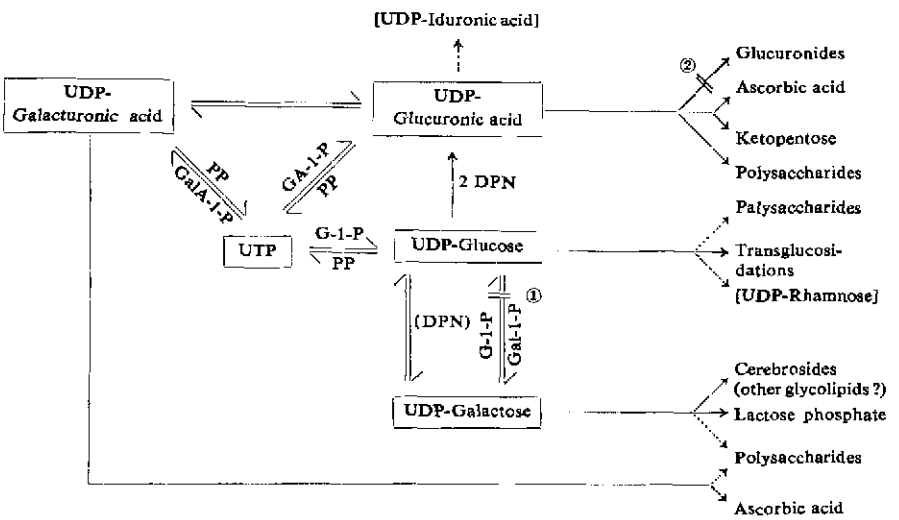


Diagram 1. Uridine Diphosphohexoses

UDP = Uridine diphosphate
UTP = Uridine triphosphate
PP = Pyrophosphate
G-1-P = *Glucose-1-phosphate*
Gal-1-P = Galactose-1-phosphate
GA-1-P = Glucuronic acid-1-phosphate
GalA-1-P = Galacturonic acid-1-phosphate
DPN = Diphosphopyridine nucleotide
(1) Enzymatic defect in congenital galactosemia
(2) Enzymatic defect in congenital non-hemolytic bilirubinemia

Glucuronide Synthesis

Glucuronide synthesis provides an excellent example of a typical reaction cycle for one of these nucleotides (Diagram 2). It is a mechanism by which many drugs and other foreign organic compounds as well as normal metabolites are conjugated prior to excretion. Firstly, uridine triphosphate is formed from uridine diphosphate. Next, glucose-1-phosphate is activated by reaction with UTP. Then the sugar moiety of UDP-glucose is modified, in this case by oxidation, to UDP-glucuronic acid. Finally, the modified sugar is transferred to an acceptor (*e.g.* bilirubin) with formation of a glucuronide. The UDP which is formed as the second product of this reaction can then cycle again. The essential features of this cycle are: 1. phosphorylation, 2. activation of the sugar, 3. modification of the sugar and finally, 4. transfer of the sugar to an acceptor in the synthetic reaction.

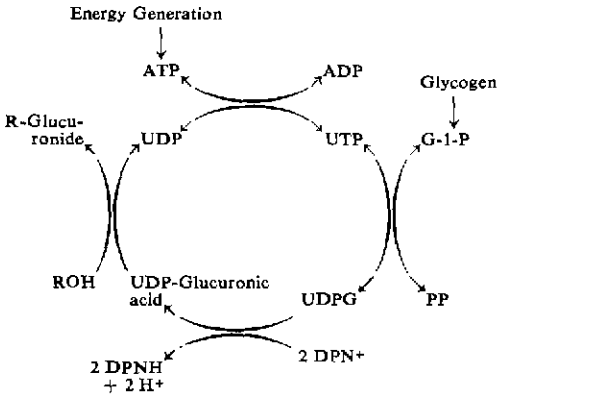
To comment briefly on the reaction by which glucuronic acid is formed from UDP-glucose (Equation 9) [23], it is one of two examples of an oxidation which involves a four electron

(9) UDP-glucose + 2 DPN$^+$ → UDP-glucuronicacid + 2DPNH + 2H$^+$

transfer, and for that reason is of considerable interest. The enzyme which catalyzes the oxidation of the amino alcohol,

[23] *J. L. Strominger, E. S. Maxwell, J. Axelrod,* and *H. M. Kalckar,* J. biol. Chemistry *224*, 79 (1957).

histidinol, to the amino-acid histidine [24], is the only other known example of such an enzyme. All other known biological oxidations involve either one-or two-electron transfers.



Balance:

$$ATP + G\text{-}1\text{-}P + 2\,DPN^+ + ROH \xrightarrow{UDP} ADP + 2\,DPNH + 2\,H^+ + PP + R\text{-}Glucuronide$$

Diagram 2. Cyclic Mechanism of Glucoronide Synthesis
ATP = Adenosine triphosphate
ADP = Adenosine diphosphate
UDP = Uridine triphosphate
G-1-P = Glucose-1-phosphate
PP = Pyrophosphate
UDPG = Uridine diphosphoglucose
DPN = Diphosphopyridine nucleotide
DPNH = Reduced diphosphopyridine nucleotide

The Glucuronic Acid Cycle

In addition to serving as a donor of glucuronic acid for the synthesis of glucuronides, UDP-glucuronic acid has another important metabolic role as a precursor of free glucuronic acid, both for ascorbic acid synthesis and for a third cycle of glucose catabolism which occurs in man as well as in other animals (Diagram 3). This cycle is known both as the "uridine nucleotide shunt" and as the "glucuronic acid pathway."

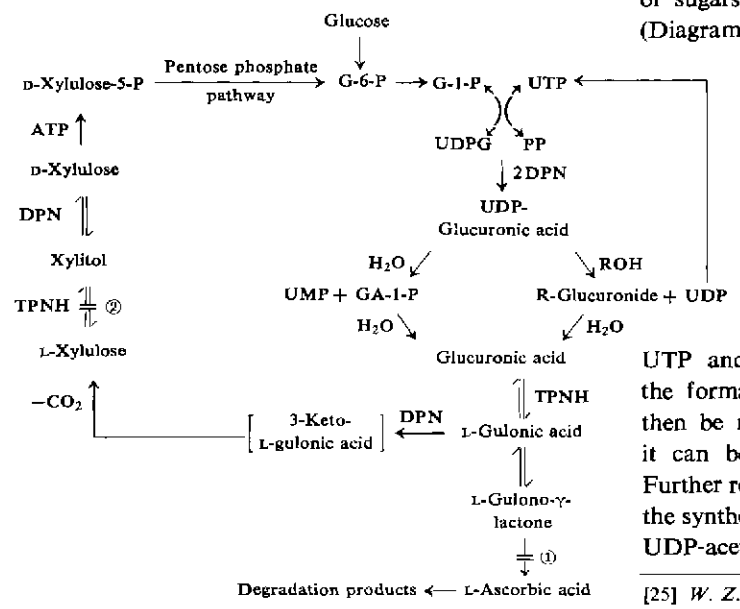


Diagram 3. The Glucuronic Acid Cycle
G-6-P = Glucose-6-phosphate
UMP = Uridine monophosphate
TPNH = Reduced triphosphopyridine nucleotide.
See also keys to Diagrams 1 and 2.

[24] *E. Adams*, J. biol. Chemistry *217*, 325 (1955).

There are two defects in enzymes of this cycle which occur in human beings. One of these is the inability of the species to form ascorbic acid, which man shares with monkeys and guinea pigs. The other defect is in the conversion of L-xylulose to xylitol, a benign condition known as congenital pentosuria. The consequence of this defect is the excretion of very large amounts of L-xylulose. The L-xylulose originates from free glucuronic acid formed from the uridine nucleotide.

Plant Uridine Nucleotides

Plants also have mechanisms for activating sugars as nucleotide derivatives. One of these mechanisms in plants is the activation of the pentoses, xylose and arabinose, as UDP-derivatives for the synthesis of xylans and arabans, important constituents of many plants (Diagram 4) [25].

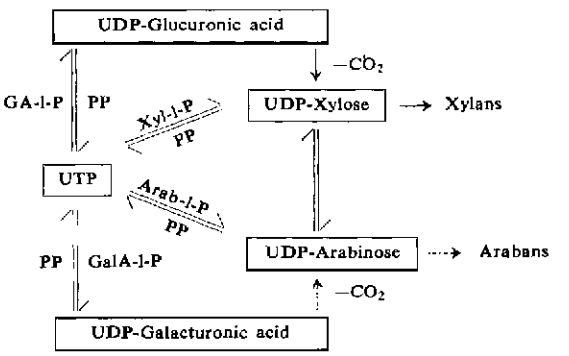


Diagram 4. Uridine Diphosphopentoses.
Xyl-1-P = Xylose-1-phosphate
Arab-1-P = Arabinose-1-phosphate
See also keys to Diagrams 1 and 2

UDP-Acetylamino Sugars

Finally, the acetylamino sugars comprise a third group of sugars which are activated as uridine nucleotides (Diagram 5). An important reaction is that between UTP and acetylglucosamine-1-phosphate, leading to the formation of UDP-acetylglucosamine, which can then be modified in a number of ways. First of all, it can be transformed to UDP-acetylgalactosamine. Further reactions, which are not yet understood, lead to the synthesis of UDP-acetylgalactosamine-4-sulfate and UDP-acetylglucosamine-6-phosphate [*]. These unusual

[25] *W. Z. Hassid, E. F. Neufeld*, and *D. S. Feingold*, Proc. nat. Acad. Sci. U.S.A. *45*, 905 (1959).

[*] It has been found recently that UDP-acetylglucosamine-6-phosphate [26] is a degradation product of the nucleotide actually present in hen oviduct. The structure of this compound, UDP-acetylglucosamine-6-phospho-1-D-galactose was deduced independently in two laboratories [27, 28]. The galactose moiety in the nucleotide is extremely labile.

compounds have been isolated from hen oviduct. Substances of this type, as well as UDP-acetylglucosamine, are presumably precursors of various polysaccharides, including the chondroitin sulfates and hyaluronic acid. The group of compounds which appear at the bottom of Diagram 5 are precursors of bacterial cell walls.

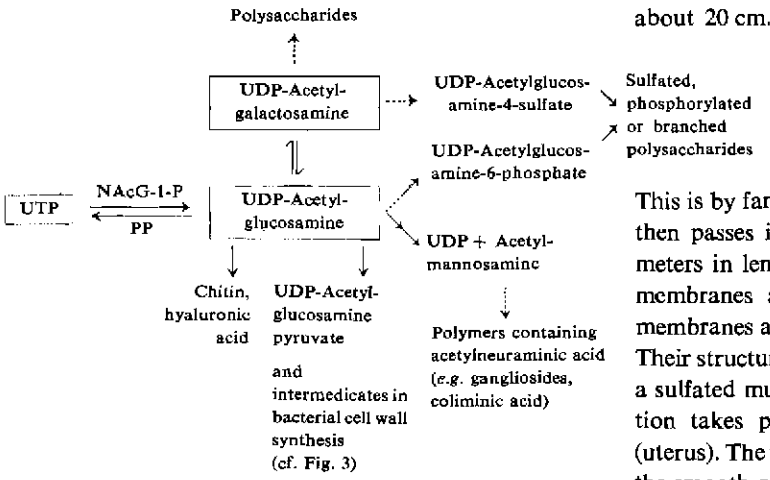


Diagram 5. Uridine Diphosphoacetylamino Sugars
NAcG-1-P = N-Acetylglucosamine-1-phosphate
PP = Pyrophosphate

hens [26]. The acetylgalactosamine-4-sulfate moiety, activated in the form of the uridine nucleotide, is presumably a precursor of some sulfated polysaccharide. In order to consider a possible function of this compound, it is necessary to appreciate the function of the oviduct. The yolk enters from the abdominal cavity through the infundibulum and passes first into a region about 20 cm. in length where the albumin is secreted.

This is by far the largest section of the oviduct. The egg then passes into a very narrow area about two centimeters in length, the isthmus, in which the inner shell membranes are secreted around the albumin. These membranes are secreted over a period of about an hour. Their structures are still not known, but they do contain a sulfated mucopolysaccharide of some kind. Calcification takes place in the third region of the oviduct (uterus). The terminal region (vagina) is the region where the smooth outer surface of the egg (cuticle) is secreted, immediately before the hen lays the egg.

Table 1. Sulfate Metabolism in the Oviduct of the Laying Hen [29]

Segment	Function of Segment	$^{35}SO_4^{2-}$ in Oviduct	$^{35}SO_4^{2-}$ in Egg	UDP-GalNAc-S in Oviduct
Infundibulum				
Albumin Secretion Region	Albumin Formation	0	0	0
Isthmus	Membrane Formation	3+	4+ (membranes)	4+
Uterus	Calcification (including shell matrix formation)	0	?	0
Vagina	Cuticle Formation	4+	2+ (cuticle)	0

III. The Structure and Biosynthesis of Chondroitin Sulfates

With this background, current knowledge of the mechanism of synthesis of the chondroitin sulfates may be discussed and the role of uridine, and other, nucleotides in the biosynthesis of polysaccharides examined. Some interesting data relating to the polysaccharide structure was obtained from studies of the biosynthesis of chondroitin sulfates.

The Nature and Function of the Hen Oviduct

These studies began with the isolation of UDP-acetylgalactosamine-4-sulfate from the oviduct of laying

In order to find out where sulfate metabolism occurred in this complicated route, ^{35}S-inorganic sulfate was given to living hens. It was taken up only in two discrete regions of the oviduct, the isthmus and the vagina, in each of which shell membranes are synthesized (see Table 1). In both of these regions, ^{35}S was located in the glandular epithelium. Eggs laid by these hens were also examined; both the inner shell membranes and the cuticle were radioactive [29].

The distribution of the sulfated uridine nucleotide in the segments of oviduct was examined next. This nucleotide

[26] *J. L. Strominger*, Biochim. biophysica Acta *17*, 283 (1955).
[27] *S. Suzuki*, submitted for publication.
[28] *O. Gabriel* and *G. Ashwell*, submitted for publication.
[29] *J. L. Strominger* and *S. Suzuki*, unpublished observations.

was found only in the isthmus. Its concentration in this region is about 5 micromoles/gram, an extremely high concentration for a nucleotide in a tissue. When a paper chromatogram was prepared from a hot water extract of isthmus, the sulfated uridine nucleotide was the only detectable ultraviolet-absorbing compound. These data suggested that isthmus was an excellent tissue with which to study the synthesis of sulfated mucopolysaccharides.

The Sulfation of Polysaccharides

At about this time *Robbins* and *Lipmann* [30] had isolated phosphoadenosine phosphosulfate (PAPS). It seemed plausible that PAPS might be the sulfate donor for the synthesis of UDP-acetylgalactosamine-sulfate and that the reaction might be a direct sulfation of UDP-acetylgalactosamine. ^{35}S-Labeled phosphoadenosine phosphosulfate was prepared using enzymes isolated from isthmus. Incorporation of ^{35}S from PAP^{35}S into chondroitin sulfate was studied in the belief that the reaction sequence would lead through the sulfated uridine nucleotide. When PAP^{35}S was incubated with enzyme from isthmus, the major reaction was hydrolysis of PAPS to inorganic sulfate. If, however, an acceptor, such as chondroitin sulfate A, was also added, a new sulfated product was formed which remainced at the origin on a paper chromatogram (Figure 1) and which was then recovered and shown to be radioactive chondroitin sulfate A (Table 2) [31].

Table 2. Synthesis of Sulfated Mucopolysaccharides from PAP^{35}S [31]. In these experiments ^{35}S sulfate was transferred from PAP^{35}S of high specific activity to various acceptors, catalyzed by an enzyme preparation from the isthmus of hen oviduct [31]. Data are recorded as c.p.m. incorporated into polysaccharide acceptor under the conditions employed In experiment 1, omission and substitution of various components of the system was studied. In experiment 2, the relative rates of sulfation of various acceptors was examined.

Experiment 1 System with chondroitin sulfate A as acceptor	Radio-activity of the polysaccharide [c.p.m.]
1. Complete	3320
2. Minus chondroitin sulfate A (added after incubation)	30
3. Minus PAP^{35}S (added after incubation)	25
4. Boiled enzyme control	30
5. AP^{35}S substituted for PAP^{35}S	100

Experiment 2 Various acceptors	Radio-activity of the polysaccharide [c.p.m.]
Chondroitin sulfate A	1750
Chondroitin sulfate B	1330
Chondroitin sulfate C	1060
Heparitin sulfate	1000
Heparin, hyaluronic acid, glycogen or charonin sulfate	40 to 50

A number of polysaccharides would serve as acceptors in this system, *viz.* chondroitin, chondroitin sulfate A, chondroitin sulfate B, chondroitin sulfate C, heparitin

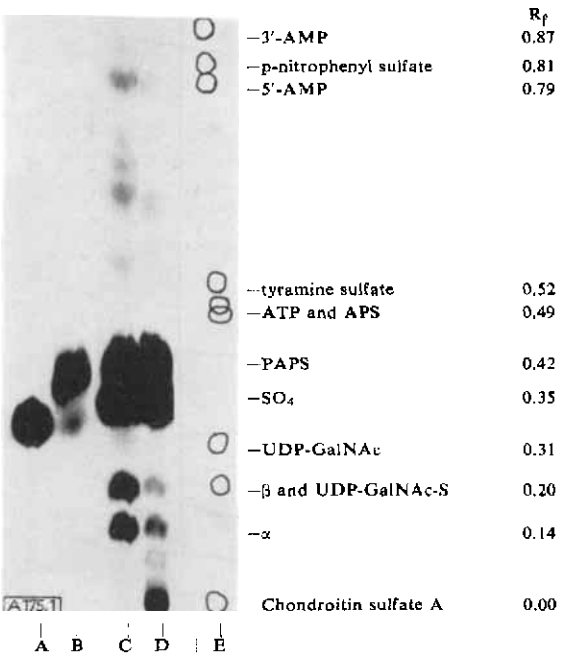


Fig. 1. Radio-autogram of a Chromatogram of Incubation Mixtures Containing PAP^{35}S and an Enzyme Preparation from the Isthmus of Hen Oviduct [31].
A: Inorganic sulfate
B: PAP^{35}S and an enzyme preparation heated before incubation
C: PAP^{35}S and enzyme preparation
D: As C, but with 50 μg chondroitin sulfate A that had been partially hydrolyzed with hyaluronidase. The substance with $R_f = 0$ is the polymer, the spots between $R_f = 0$ and 0.14 correspond to sulfated oligosaccharides. If the polymer is not treated with hyaluronidase before incubation, only the spot at $R_f = 0$ is found.
E: Chromatogram with standard substances
α and β are unidentified radioactive products. β is not UDP-GalNAc-S although it has the same mobility in this solvent.

sulfate, and, finally, a chondroitin sulfate which had been isolated in Japan from shark cartilage and which was believed to be identical to chondroitin sulfate C (Figure 2). However, the apparent K_M and V_{max} for this latter compound were different from those for chondroitin sulfate C. These data suggested that the compound might not be identical with chondroitin sulfate C. Other data (see below) prove that it is, in fact, a novel form of chondroitin sulfate.

The Course of the Sulfation Reaction

In considering the mechanism by which sulfate was incorporated into the polysaccharides in this system, the idea that the sulfated uridine nucleotide (UDP-GalNAc-S) was an intermediate in the incorporation, and that the polysaccharide served as an acceptor for acetyl-galactosamine-sulfate (transferred from the uridine nucleotide), was attractive (Equations 10 and 11). How-

$$\text{UDP-GalNAc} \xrightarrow{\text{PAPS}} \text{UDP-GalNAc-S} \quad (10)$$

$$\text{Polysaccharide} \xrightarrow{\text{UDP-GalNAc-S}} \text{Polysaccharide-GalNAc-S} \quad (11)$$

ever, a second possibility had to be considered, *viz.* that the uridine nucleotide was not an intermediate, but that the polysaccharide itself was the primary acceptor in the trans-sulfation (Equation 12).

$$\text{Polysaccharide} \xrightarrow{\text{PAPS}} \text{Polysaccharide-S} \quad (12)$$

[30] *P. W. Robbins* and *F. Lipmann*, J. biol. Chemistry *233*, 681, 686 (1958).

[31] *S. Suzuki* and *J. L. Strominger*, J. biol. Chemistry *235*, 257, 267, 274 (1960). See also [32].

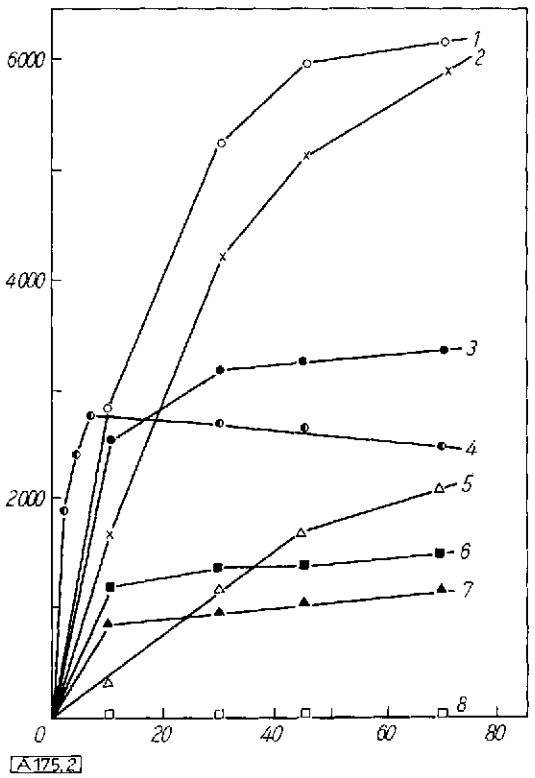


Fig. 2. Relationship between the Concentration of Various Acceptors and Reaction Velocity [31].
Curve 1: Chondroitin sulfate C
Curve 2: Chondroitin from bovine cornea
Curve 3: Chondroitin sulfate A
Curve 4: Chondroitin sulfate B
Curve 5: Chondroitin prepared by chemical desulfation of chondroitin [sulfate
Curve 6: Heparitin sulfate
Curve 7: Chondroitin sulfate from shark cartilage
Curve 8: Glycogen, heparin, keratosulfate, hyaluronic acid or charonin sulfate
Ordinate: Radio-activity of polysaccharides [c.p.m.]
Abscissa: µg. Acceptor per 50 µl. incubation mixture

It was impossible to study this problem using the large polymers as acceptors because the simple addition of ^{35}S-sulfate to these high molecular weight substances could not be distinguished from addition of acetylgalactosamine-^{35}S-sulfate. The sulfation of low molecular weight oligosaccharides derived from chondroitin and from chondroitin sulfate A by enzymatic hydrolysis was, therefore, investigated. In this case, it was relatively easy to distinguish the possible products of sulfation by paper chromatography. For example, if the tetrasaccharide containing no sulfate residues was used as an acceptor the possible products, *tetra*saccharide monosulfate or *penta*saccharide monosulfate, could be easily distinguished. To prepare the sulfated products, enzyme and PAP^{35}S were incubated with various oligosaccharide acceptors. The incubation mixtures were then chromatographed, and in each case a new radioactive product was formed which had a slower mobility than the acceptor itself. This radioactive product was eluted from the chromatogram and its mobility determined during paper chromatography and paper electrophoresis, together with authentic standards. In each case, it was found that the sulfation reaction was a simple transfer of sulfate from the donor to oligosaccharide (corresponding to Equation 12). Acetylgalactosamine and acetylgalactosamine monosulfate were also both sulfated, with the formation of acetylgalactosamine monosulfate or acetylgalactosamine disulfate, respectively, as the products (Figure 3).

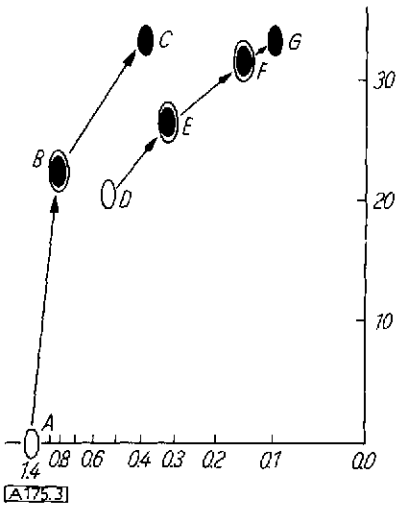


Fig. 3. Sulfation of Mono- and Tetrasaccharides [31].
Positions of the sulfated compounds are derived from paper chromatography (abscissa) and paper electrophoresis (ordinate). The chromatograms were developed with butanol/acetic acid/water.
Open circles: Added as acceptor
Full circles: Radioactive product
Arrows indicate the relationship between acceptors and products.
A: N-Acetylgalactosamine
B: N-Acetylgalactosamine monosulfate
C: N-Acetylgalactosamine disulfate
D: Tetrasaccharide
E: Tetrasaccharide monosulfate
F: Tetrasaccharide disulfate
G: Tetrasaccharide trisulfate
Ordinate: Distance covered during electrophoresis [cm.]
Abscissa: $R_{glucuronic\ acid}$

The relative dependence of the sulfation velocity on the chain length is indicated in Figure 4.

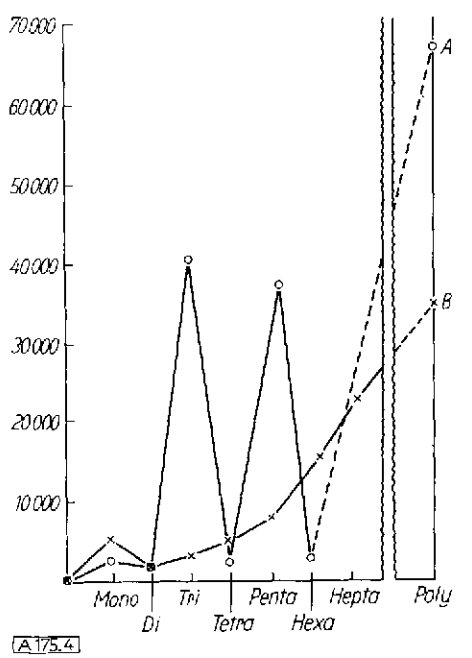


Fig. 4. Relationship between Chain Length of the Acceptor and the Velocity of Sulfate Transfer [31]
-o-o- sulfate-free acceptor
-x-x- sulfated acceptor
A: Chondroitin
B: Chondroitin sulfate A
Ordinate: c.p.m. incorporated.

Although most of these compounds were sulfated at rates which were relatively slow, the trisaccharide (GalNAc-GA-GalNAc) and the pentasaccharide (GalNAc-GA-GalNAc-GA-GalNAc) [*] were sulfated at a rate comparable to that of the polymer itself. This may be an important point. The even-numbered oligosaccharides all contained glucuronic acid on the non-reducing end of the oligosaccharide chain. The odd-numbered oligosaccharides were prepared from the even-numbered compounds by removal of the terminal glucuronic acid residue with a β-glucuronidase, yielding oligosaccharides with an acetylgalactosamine residue on the non-reducing end. These odd-numbered oligosaccharides were extraordinarily efficient as acceptors in the sulfation system. It is possible, therefore, that at least one mechanism for the introduction of sulfate into the polysaccharides is sulfation of an acetylgalactosamine residue on the non-reducing end of a growing polysaccharide chain. However, the role of the sulfated uridine nucleotide still remains to be elucidated, and there may be several mechanisms for the introduction of sugars and of sulfate into polysaccharide chains.

urement of both periodate consumption and formaldehyde liberation distinguishes between all of the possible isomeric acetylgalactosamine sulfates. It has been established that the acetylgalactosamine monosulfate derived from the nucleotide was acetylgalactosamine-4-sulfate while the acetylgalactosamine monosulfate prepared by chemical sulfation is acetylgalactosamine-6-sulfate. The acetylgalactosamine monosulfates were then isolated from several polysaccharides, and by comparison with the now characterized materials, it has been established that the compound from chondroitin sulfate A or B was the 4-sulfate, while that from C was the 6-sulfate, thereby confirming by direct chemical isolation what other investigators had previously concluded from other studies (Table 3).

Table 3. Identification of Acetylgalactosamine Monosulfates [33]

	R_f in Isobutyric acid/NH_4OH	Moles of HCHO formed/mole [*]	ε_{585} in Morgan-Elson reaction	Infrared peaks [**] [cm^{-1}]
1. GalNAc-4-S from uridine nucleotide	0.52	0.92	200	695; 860; 890; 920
2. GalNAc-6-S, chemically synthesized	0.44	0.05	10 000	775; 820; 992
3. GalNAc-S from Chondroitin sulfate A	0.53 (trace at 0.44)	0.62 [+]	1 800 [+]	695; 860; 890; 920
4. GalNAc-S from Chondroitin sulfate B	0.52	0.75 [+]	1 120 [+]	695; 860; 890; 920
5. GalNAc-S from Chondroitin sulfate D	0.44	0.03	10 000	780; 815; 992

[*] With periodate oxidation at 25°C. for 20 hours. GalNAc-4-S consumed 1 mole of periodate while GalNAc-6-S consumed 4 moles.

[**] Peaks in the infrared spectra between 660 and 1000 cm^{-1}.

[+] These values suggest that these samples (predominantly GalNAc-4-S) may contain 10–15 % of GalNAc-6-S.

The Structure of the Chondroitin Sulfates

Two interesting aspects of the structure of chondroitin sulfates arose from these enzymatic studies. Acetylgalactosamine itself is a sulfate acceptor. The product, an acetylgalactosamine monosulfate, was electrophoretically identical to acetylgalactosamine monosulfate derived from the uridine nucleotide by hydrolysis, as well as to acetylgalactosamine sulfate prepared by chemical sulfation of acetylgalactosamine with chlorosulfonic acid. However, examination of these three acetylgalactosamine monosulfates by chromatography indicated that the compound from the uridine nucleotide had a greater mobility than the compound which had been prepared chemically. The enzymatically synthesized product was identical to that derived from the uridine nucleotide.

The structure of these acetylgalactosamine monosulfates has been examined [33]. Periodate oxidation with meas-

The second aspect of this investigation of the mechanism of chondroitin sulfate synthesis was the discovery of a new form of chondroitin sulfate, which was called chondroitin sulfate D, a compound first isolated by *Egami* and co-workers in Japan from shark cartilage [34]. As already mentioned, this compound was not identical to chondroitin sulfate C as an acceptor for the sulfotransferase, and the compound had, furthermore, been found to contain about 22 % sulfate (*i.e.* 1.3 sulfate residues per acetylgalactosamine residue). In order to investigate its structure, *Suzuki* [35] employed an enzyme from *Proteus vulgaris* [36]. This enzyme catalyzes an essentially quantitative degradation of chondroitin sulfates to disaccharides. The reaction is an elimination reaction, rather than a hydrolysis, so that the product is a Δ^4-unsaturated disaccharide [36]. When the degradation products of various chondroitin sulfate preparations were separated by paper chromatography, chondroitin sulfate D yielded an unexpected product which was not formed on degradation of either chondroitin sulfate A or of chondroitin sulfate C. A small amount of a similar product was also formed by degradation of a preparation of chondroitin sulfate B. However, these two compounds could be separated by paper chromatography, and are believed to be isomers. On analysis, each of these compounds contained two sulfate residues per disaccharide unit. This structure is

[*] GalNAc = N-Acetylgalactosamine; GA = Glucuronic acid.

[32] *S. Suzuki, R. H. Threnn,* and *J. L. Strominger,* Biochim. biophysica Acta *50,* 169 (1961).

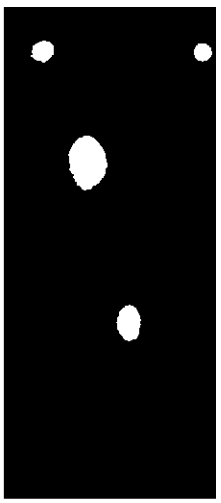
[33] *S. Suzuki* and *J. L. Strominger,* J. biol. Chemistry *235,* 2768 (1960).

[34] *T. Soda, F. Egami,* and *T. Horigome,* J. chem. Soc. (Japan) *16,* 43 (1940).

[35] *S. Suzuki,* J. biol. Chemistry *235,* 3580 (1960).

[36] *K. S. Dodgson* and *A. G. Lloyd,* Biochem. J. *68,* 88 (1958).

in line with the high electrophoretic mobility of the disaccharide (Figure 5). Various data suggest that one sulfate residue of both of these compounds is located on the 2- or 3-position of the uronic acid moiety. For example, the periodate consumptions of the disulfated disaccharides are very much reduced, indicating that the glucuronic acid moieties are substituted in some

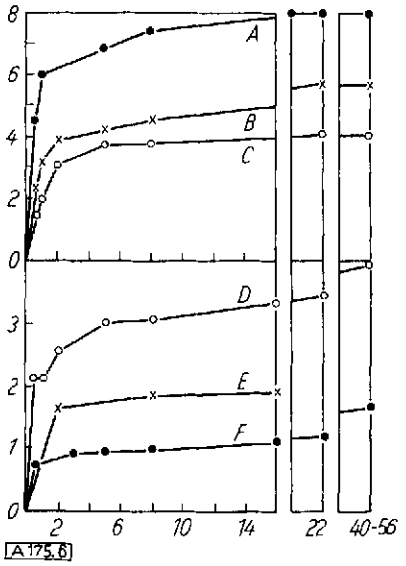


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Fig. 5. Relative Mobilities of Unsaturated Disaccharide from Chondroitin sulfate B and Chondroitin sulfate D [36]
A: Unsaturated disaccharide disulfate from chondroitin sulfate D
B: Unsaturated disaccharide-6-monosulfate
C: Sulfate-free unsaturated disaccharide
D: Unsaturated disaccharide disulfate from chondroitin sulfate B

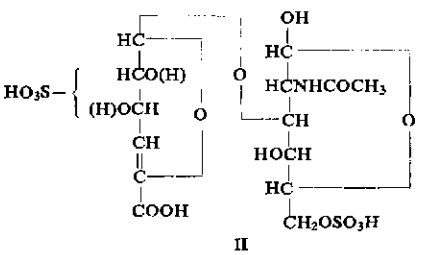
manner, presumably by sulfate (Figure 6). The other sulfate residue is on the acetylgalactosamine. The proposed structures of unsaturated disulfated disaccharides from shark cartilage chondroitin sulfate and from a chondroitin sulfate B preparation [36] are given in Formulae II and III.

The mechanism by which uridine nucleotides and other nucleotides participate in the biosynthesis of sulfated mucopolysaccharides is a very complicated problem. These compounds can contain at least four types of sulfate residues (4-*O*-, 6-*O*- or *N*-sulfate on the amino sugar and sulfate on the uronic acid) as well as several different sugars. Several types of mechanisms undoubtedly exist both for introduction of sulfate and for introduction of sugars into the polysaccharide chains. Undoubtedly there are more surprises to come, both in terms of biosynthetic mechanisms and in terms of structure. With the discovery of a number of nucleotide intermediates, it may be hoped that more rapid progress

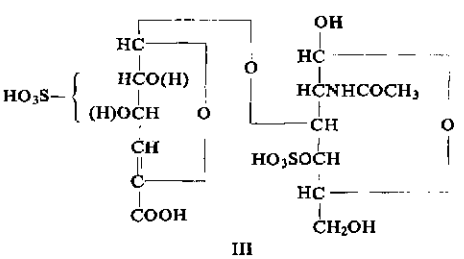


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Fig. 6. Rate of Periodate Consumption of Unsaturated Disaccharides [36]
Curve A: Sulfate-free unsaturated disaccharide
Curve B: Unsaturated disaccharide-4-sulfate
Curve C: Unsaturated disaccharide-6-sulfate
Curve D: Unsaturated disaccharide monosulfate from chondroitin sulfate D
Curve E: Unsaturated disaccharide disulfate from chondroitin sulfate B
Curve F: Unsaturated disaccharide disulfate from chondroitin sulfate D
Note the low periodate consumption of the disulfates (Curves E and F) compared with the periodate consumption of the monosulfates (Curves B to D) and the sulfate-free disaccharide (Curve A).
Ordinate: Moles IO_4^-/mole disaccharide
Abscissa: Time [hours]



II



III

can be made in the study of the biosynthesis of the chondroitin sulfates as well as of other biologically important heteropolymeric substances.

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The Stereochemistry of Organosilicon Compounds

BY PROF. L. H. SOMMER

DEPARTMENT OF CHEMISTRY, THE PENNSYLVANIA STATE UNIVERSITY, UNIVERSITY PARK, PENNSYLVANIA, U.S.A.

Optically active organosilicon compounds having reactive functional groups bonded to asymmetric silicon have recently been synthesized and their study has revealed that many organosilicon reactions are stereospecific.

The present paper deals with the problem of correlation of configuration for six key compounds containing the α-naphthylphenylmethylsilyl group. The solution of this problem by the use of chemical and physical methods is described. In addition the stereochemistry of more than twenty stereospecific reactions of silicon is considered. The probable fundamental relationships between organosilicon stereochemistry and the reaction mechanisms of monofunctional R_3SiY compounds are discussed in a preliminary way.

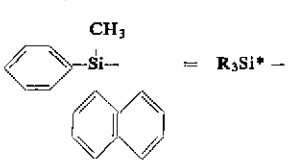
Stereochemistry of Substitution at the Asymmetric Silicon Atom

1. Introduction

In sharp contrast to the presently available detailed knowledge of the stereochemistry of substitution at asymmetric carbon, data on the stereochemistry of substitution at asymmetric silicon have not been presented until very recently.

Prior to 1958 it was not even known whether substitution reactions at silicon atoms are stereospecific. Resolutions of three organosilicon compounds, only two of which contained functions (relatively unreactive) bonded to silicon had been carried out by the pioneer of organosilicon chemistry, *F. S. Kipping*, but the routes to the optically active compounds were so tedious and lengthy, the amounts obtained were so small, and the optical rotations so feeble, that stereochemical studies were not possible with these substances which had the additional disadvantage of sulfonic acid groups bonded to carbon [1, 2].

In October 1958, after two years of abortive effort, we were at last successful in synthesizing optically active organosilicon compounds containing reactive groups bonded to silicon; these compounds contained the α-naphthylphenylmethylsilyl group (designated R_3Si^*- below).



Soon afterwards, a study of the R_3Si^*X compounds yielded the first example of a Walden cycle for silicon [3].

From the above reaction sequence it follows at once that reactions (a) and (b) are highly stereospecific, and that one of these must proceed with essentially pure retention of configuration, and the other with essentially pure inversion of configuration.

$$\underset{[\alpha]_D = +33^\circ}{(+)\text{-}R_3Si^*H} \xrightarrow[(a)]{Cl_2 \text{ in } CCl_4} \underset{[\alpha]_D = -6.8^\circ}{(-)\text{-}R_3Si^*Cl} \xrightarrow[(b)]{LiAlH_4} \underset{[\alpha]_D = -33^\circ}{(-)\text{-}R_3Si^*H}$$

Thus, sixty-three years after the discovery of the first Walden cycle for carbon [4], a similar cycle was discovered for silicon and the problem of the Walden-cycle, *i.e.* deciding which reactions in such a cycle are inversions and which are retentions, confronted us.

In organic chemistry, the problem of the first Walden cycle remained unsolved for at least forty years [5]. In the case of organosilicon stereochemistry, the process has been greatly accelerated by the use of modern chemical and physical methods.

We turn now to a discussion of the stereospecific reactions of R_3Si^*Cl with a wide variety of nucleophilic reagents.

2. A Preferred Common Stereochemistry for Reactions of R_3Si^*Cl

For the reactions of R_3Si^*Cl with diverse nucleophilic reagents, the data given in Table 1 can serve as a general basis for discussion [6].

Following the classical method of chemical correlations of configuration used in organic chemistry to relate carbon-oxygen compounds, the relative configurations of $(-)\text{-}R_3Si^*OH$, $(+)\text{-}R_3Si^*OK$, $(-)\text{-}R_3Si^*OCH_3$, and

[1] *F. S. Kipping* and coworkers, J. chem. Soc. (London) 209 (1917); 2090 (1908); 755 (1910).

[2] Preparation of an optically active organosilicon compound *not* having a reactive functional group, *p*-carboxyphenylmethylethylphenylsilane, has been reported more recently: *C. Eaborn* and *C. Pitt*, Chem. and Ind. 830 (1958).

[3] *L. H. Sommer* and *C. L. Frye*, J. Amer. chem. Soc. *81*, 1013 (1959).

[4] *P. Walden*, Ber. dtsch. chem. Ges. *28*, 1287, 2766 (1895).

[5] Cf. *C. K. Ingold:* Structure and Mechanism in Organic Chemistry. Cornell University Press, Ithaca (New York) 1953, p. 373.

[6] References to all but two of the reactions in Table 1 are given later in the paper. Reactions (6) and (7) are unpublished work of *L. H. Sommer, G. A. Parker*, and *P. G. Rodewald.*

Table 1. Reactions of (−)-R_3Si^*Cl

Reaction	Reagent	Solvent	Product [e]
(1)	$LiAlH_4$	ether	(−)-R_3Si^*H
(2)	H_2O	ether	(−)-R_3Si^*OH
(3) [a]	CH_3OH	pentane	(−)-$R_3Si^*OCH_3$
(4) [b]	KOH(s)	xylene	(−)-R_3Si^*OH
(5)	$NaB(OCH_3)_4$	ether	(−)-$R_3Si^*OCH_3$
(6)	CH_3CO_2Na(s)	benzene	(−)-$R_3Si^*OCOCH_3$
(7)	$(CH_3CO_2)_2Hg$(s)	benzene	(−)-$R_3Si^*OCOCH_3$
(8)	$NaBH_4$	diglyme [c]	(−)-R_3Si^*H
(9) [d]	(+)-R_3Si^*OK	xylene	(−)-$R_3Si^*OSi^*R_3$
(10)	(−)-R_3Si^*OK	xylene	(meso)-$R_3Si^*OSi^*R_3$

[a] Cyclohexylamine or tertiary amines used as acceptor for formed HCl. – [b] The first product, (+)-R_3Si^*OK, gives (−)-R_3Si^*OH upon hydrolysis. – [c] Diethylene glycol dimethyl ether. – [d] It is clear (see below) that (+)-R_3Si^*OK and (−)-R_3Si^*OH have the same configuration. – [e] Reactions (1)–(5) and (9)–(10) are at least 90 % stereospecific; reactions (6)–(8) give products whose optical purity indicates a stereospecificity of only 75 %, but this is too low a figure because: (i) The products in reactions (6) and (7) are racemized by the reagents; and (ii) chloride ion formed in reaction (8) racemizes the (−)-R_3Si^*Cl starting material at a rate which is competitive with reduction.

(−)-$R_3Si^*OCOCH_3$ were shown to be the same by the following reactions which do not involve the central asymmetric silicon atom [7].

$$(-)\text{-}R_3Si^*OH + K_{metal} \xrightarrow{\text{xylene}} (+)\text{-}R_3Si^*OK$$

$$(+)\text{-}R_3Si^*OK + (CH_3)_2SO_4 \xrightarrow{\text{xylene}} (-)\text{-}R_3Si^*OCH_3$$

$$(+)\text{-}R_3Si^*OK + CH_3COCl \xrightarrow{\text{xylene}} (-)\text{-}R_3Si^*OCOCH_3$$

Reaction of potassium metal with (−)-R_3Si^*OH gives (+)-R_3Si^*OK, and the two reactions of (+)-R_3Si^*OK cited above, are unlikely to involve the silicon-oxygen bond. (Independent evidence for the latter conclusion is provided below by the optical rotatory dispersion data.)

The above chemical correlations of configuration show that reactions (2)–(7), (9), and (10) in Table 1, have a common preferred stereochemistry. Furthermore, if we examine reactions (5) and (8) more closely:

$$(-)\text{-}R_3Si^*Cl + NaB(OCH_3)_4 \longrightarrow (-)\text{-}R_3Si^*OCH_3$$

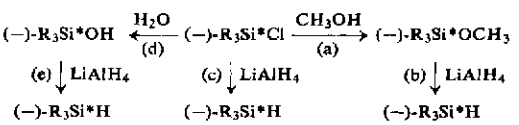
$$(-)\text{-}R_3Si^*Cl + NaBH_4 \longrightarrow (-)\text{-}R_3Si^*H$$

it would appear reasonable (barring an extraordinary degree of stereochemical complexity) to conclude that (−)-$R_3Si^*OCH_3$, and (−)-R_3Si^*H have the same configuration on the grounds that both reactions involve tetravalent boron anions as the source of the attacking nucleophilic species.

Thus, the chemical evidence strongly supports the conclusion that reactions (1)–(10) in Table 1 have a common preferred stereochemistry.

3. Stereochemistry of Substitution Reactions of R_4Si^*Cl: Retention or Inversion?

Although the chemical evidence is fairly convincing concerning a common stereochemistry for the reactions given in Table 1, it cannot by itself indicate the preferred stereochemistry. To illustrate this situation, we may consider the reaction sequences given in Reaction Diagram 1.



Reaction Diagram 1

From examination of Diagram 1, it is clear that the stereochemical relationships pictured therein are consistent with a common stereochemistry for reactions (a), (c), and (d), and also with a retention stereochemistry for reactions (b) and (e). However, even if we assume that these stereochemical relationships are known with certainty, they still do not indicate whether R_3Si^*Cl reacts by a common retention or inversion stereochemistry in reactions (a), (c), and (d).

a) Reactions of the Silicon-Oxygen Bond with Retention and Inversion of Configuration [7].

For certain reactions of the silicon-oxygen bond, the stereochemistry has been determined directly by application of the technique introduced into organic chemistry by *H. Phillips* and *J. Kenyon* [8]. These results can be brought to bear on the problem of the stereochemistry of the reactions of R_3Si^*Cl.

Reaction (11) below is quite an unusual case in stereochemistry. The formation of optically pure potassium silanolate (II), which retains its optical purity for long periods of time in xylene solution and in simultaneous contact with powdered potassium hydroxyde, rigorously proves retention of configuration as the stereochemical path [7].

$$\underset{\text{I}}{(+)\text{-}R_3Si^*OSi^*R_3} \xrightarrow[\text{xylene}]{KOH_{solid}} \underset{\text{II}}{2\,(-)\text{-}R_3Si^*OK} \qquad (11)$$

The optically active disiloxane (I) was prepared from (II) and (+)-R_3Si^*Cl, and compound (II) was obtained from reaction of (+)-R_3Si^*OH with potassium hydroxide.

Retention of configuration in (12) below follows rigorously from the above stereochemical correlation of configuration for (−)-$R_3Si\ OCH_3$ and (+)-R_3SiOK.

$$(-)\text{-}R_3SiOCH_3 \xrightarrow[\text{xylene}]{KOH_{solid}} (+)\text{-}R_3SiOK \qquad (12)$$

Inversion of configuration in (13) and (14) also follows rigorously from the above stereochemical correlation of configuration for (+)-R_3Si^*OK and (−)-$R_3Si^*OCOCH_3$.

$$(+)\text{-}R_3Si^*OCOCH_3 \xrightarrow[\text{xylene}]{KOH_{solid}} (+)\text{-}R_3Si^*OK \qquad (13)$$

$$(+)\text{-}R_3Si^*OCOCH_3 \xrightarrow[\text{pentane; amine}]{CH_3OH} (-)\text{-}R_3Si^*OCH_3 \qquad (14)$$

The change in stereochemistry from retention of configuration for relatively poor leaving groups (*i.e.*

[7] *L. H. Sommer* and *C. L. Frye*, J. Amer. chem. Soc. *82*, 3796 (1960).

[8] *H. Phillips*, J. chem. Soc. (London) *123*, 64 (1923); *J. Kenyon*, *H. Phillips*, and *H. G. Turley*, ibid. *127*, 399 (1925) and subsequent papers.

$-OCH_3$ and $-OSi^*R_3$), to inversion of configuration for a relatively good leaving group ($-OCOCH_3$) suggests, but does not rigorously prove, that a good leaving group such as $-Cl$ would have a preferred inversion stereochemistry. Thus the chemical evidence indicates, but does not prove, that the common stereochemistry for the ten reactions in Table 1 involves inversion of configuration.

To settle the question, it is necessary to consider the use of physical methods for correlating stereochemical configuration.

b) X-Ray Application of the Fredga Method

One of the most widely used methods for correlating configurations of optically active compounds having *similar* structures is the Fredga method based on differences in phase behavior [9], and this technique seemed ideal for comparison of the compounds R_3Si^*H, R_3Si^*F, and R_3Si^*Cl. The fluorosilane is available from treatment of $R_3Si^*OCH_3$ with boron trifluoride etherate.

The Fredga method as applied by *K. Mislow* has provided many fruitful results in recent years, and the pertinent case observed in the present work is his "Case 2" [10] in which pure optical isomers of two different substances that are isomorphous give solid solutions when they are of the same configuration, and a eutectic when they are of opposite configuration. In the present work, x-ray diffraction provided clear and consistent answers [11]:

1. Solid solutions are formed by (−)-R_3Si^*F and (−)-R_3Si^*H; by (−)-R_3Si^*F and (+)-R_3Si^*Cl; and by (−)-R_3Si^*H and (+)-R_3Si^*Cl.

2. Eutectic mixtures are formed by (+)-R_3Si^*F and (−)-R_3SiH; by (+)-R_3Si^*F and (+)-R_3Si^*Cl; and by (+)-R_3Si^*H and (+)-R_3Si^*Cl.

Optically active R_3Si^*H, R_3Si^*F, and R_3Si^*Cl crystallize individually in the orthorhombic system with space group $P2_12_12_1$; an example of perfect isomorphism is observed. The three mixtures (1) also crystallize in the orthorhombic system and are isomorphous with the pure component compounds; no doubling of the unit cell dimensions or change in the symmetry is observed. In Table 2 the crystallographic constants for the pure and mixed crystals [11] are listed.

By comparing the intensities of diffracted x-rays from the mixed crystals with those from the pure component crystals, it is concluded that a random disribution of

Table 2. Crystallographic Constants of the Pure and Mixed Crystals

	a	b	c	Space Group
(−)-R_3Si^*H	8.80	20.19	8.00	$P2_12_12_1$
(−)-R_3Si^*F	8.80	19.85	8.00	$P2_12_12_1$
(−)-R_3Si^*Cl	8.84	19.68	8.10	$P2_12_12_1$
(−)-R_3Si^*H + (−)-R_3Si^*F [a]	9.00	20.22	8.15	$P2_12_12_1$
(−)-R_3Si^*H + (+)-R_3Si^*Cl [a]	8.85	20.20	8.20	$P2_12_12_1$
(−)-R_3Si^*F + (+)-R_3Si^*Cl [a]	8.82	19.80	8.40	$P2_12_12_1$

[a] These data are for equimolar mixtures.

the component molecules in the crystal is observed for each mixture in (1). A partial list of the two-dimensional reflections used for the criteria is given in Table 3.

Table 3. Partial List of Reflections Used for Criteria

For (−)-R_3Si^*H + (−)-R_3Si^*F

Reflections	(−)-Si*H	Mixture	(−)-Si*F
080	strong	medium	weak
600	strong	medium	weak
120	very weak	medium	strong
330	medium	weak	too weak to be observed

For (−)-R_3Si^*H + (+)-R_3Si^*Cl

Reflections	(−)-Si*H	Mixture	(+)-Si*Cl
0,10,2	very strong	medium	very weak
0,11,2	very weak	weak	medium

For (−)-SiF + (+)-SiCl

Reflections	(−)-SiF	Mixture	(+)-SiCl
080	weak	medium	strong
0,10,0	strong	medium	very weak

From the above X-ray evidence it is clear that (−)-R_3Si^*H, (+)-R_3Si^*Cl, and (−)-R_3Si^*F have the same configuration and that the following reactions proceed by the given stereochemical paths:

(15) $R_3Si^*H \xrightarrow[CCl_4]{Cl_2} R_3Si^*Cl$ (retention)
$[\alpha]_D = -33^\circ$ $[\alpha]_D = +6.8^\circ$

(16) $R_3Si^*Cl \xrightarrow[ether]{LiAlH_4} R_3Si^*H$ (inversion)
$[\alpha]_D = +6.8^\circ$ $[\alpha]_D = +33^\circ$

(17) $R_3Si^*F \xrightarrow[ether]{LiAlH_4} R_3Si^*H$ (inversion)
$[\alpha]_D = -47^\circ$ $[\alpha]_D = +33^\circ$

With the above formulation of reactions (15) and (16) the task of elucidating the stereochemistry for the first Walden cycle of reactions at silicon is completed.

c) Optical Rotatory Dispersion

From the following series of stereochemical equations it will be clear that an important additional correlation of configuration now lacking rigorous formulation is that between R_3Si^*H and R_3Si^*OH, or between R_3Si^*OH and R_3Si^*Cl. Only one of these is needed and, if obtained, would not only give the stereochemistry of re-

[9] See *A. Fredga* in: The Svedeberg. Almqvist and Wikesells, Uppsala 1944, p. 261; *J. Timmermans*, J. Chim. Physique *49*, 162 (1952). Conclusions drawn on the basis of a *difference* in phase behavior without exception have proved accurate.

[10] *K. Mislow* and *M. Heffler*, J. Amer. chem. Soc. *74*, 3668 (1952). For a recent application of "Case 2" for determination of the configurational relationships between the pure optical isomers of 3-thiolactanedioic acid and 3-methyloctanedioic acid see *K. Mislow* and *W. C. Meluch*, ibid. *78*, 5920 (1956). For other examples see *J. Timmermans*, ref. [9].

[11] For a preliminary report of the X-ray diffraction data see *L. H. Sommer* et al., J. Amer. chem. Soc. *83*, 2210 (1961); the X-ray data reported in Tables 2 and 3 were kindly furnished by *Y. Okaya* and *R. Pepinsky*, Department of Physics, The Pennsylvania State University, University Park, Pa., U.S.A.

action (b) but (because of chemical correlations of configuration between a considerable number of R_3Si^*O-compounds) would also provide the stereochemical courses of many other substitutions at asymmetric silicon.

$$\underset{[\alpha]_D = -33^\circ}{R_3Si^*H} \xrightarrow[(a)]{Cl_2 + CCl_4} \underset{[\alpha]_D = +6.8^\circ}{R_3Si^*Cl} \xrightarrow[(b)]{H_2O \text{ in } Et_2O} \underset{[\alpha]_D = +20.5^\circ}{R_3Si^*OH}$$

Since the Fredga method, as applied to R_3Si^*H and R_3Si^*Cl, could not be used for either of these correlations (R_3Si^*OH is a liquid at room temperature) optical rotatory dispersion has been applied with success to this problem.

Using a recently developed apparatus [12], the optical rotatory dispersion curves were obtained for (−)-R_3Si^*F, (−)-R_3Si^*H, (−)-R_3Si^*OH, (−)-$R_3Si^*OCH_3$, (−)-$R_3SiOCOCH_3$, and (+)-R_3Si^*Cl. Figure 1 gives the rotatory dispersion curves for these compounds. The conclusions resulting from comparison of these curves and other substantiating lines of evidence for these conclusions are given below:

1. (−)-R_3Si^*F and (−)-R_3Si^*H have the same configuration. This conclusion is the same as that reached from x-ray application of the Fredga method.

2. (−)-R_3Si^*OH and (−)-$R_3Si^*OCH_3$ have the same configuration. This conclusion is rigorously known through the preparation of (−)-$R_3Si^*OCH_3$ from (−)-R_3Si^*OH and dimethyl sulfate utilizing the potassium salt of the silanol in a reaction which does not involve the asymmetric center.

3. Since the four compounds giving the most pronounced Cotton effects are made up of two pairs whose component compounds have been shown to have the same configuration by other methods, and since all four of these optical rotatory dispersion curves are closely similar, it is concluded that (−)-R_3Si^*H, (−)-R_3Si^*OH, (−)-$R_3Si^*OCH_3$ and (−)-R_3Si^*F all have the same configuration.

4. (−)-$R_3Si^*OCOCH_3$ and (−)-R_3Si^*OH have the same configuration. This conclusion is rigorously known to be correct through a chemical correlation of configuration (see above).

5. (−)-R_3Si^*H and (+)-R_3Si^*Cl have the same configuration. This conclusion is the same as that reached from X-ray application of the Fredga method.

The Cotton effects in Figure 1 are all presumed to be negative in sign and the wave-length for the first extremum is reasonably close to the position of the first maximum observed at 317 mμ in the ultraviolet spectra of all of the compounds. This absorption band has $\varepsilon = 310$.

Examination of accurately scaled molecular models clearly shows that the hydrogen atom on the naphthalene nucleus in the *peri*-position relative to the silicon atom causes considerable "crowding" in its vicinity. Maximum freedom of intramolecular motions is attained when the *peri* hydrogen is flanked by the two groups of the remaining three that have the smallest steric requirements. Five of the six compounds

[12] *S. Kirschner, A. J. Sonnessa, D. C. Bhatnagar,* and *D. Moy,* Abstracts of the 138th Meeting of the American Chemical Society, September, 1960, p. 14-N.

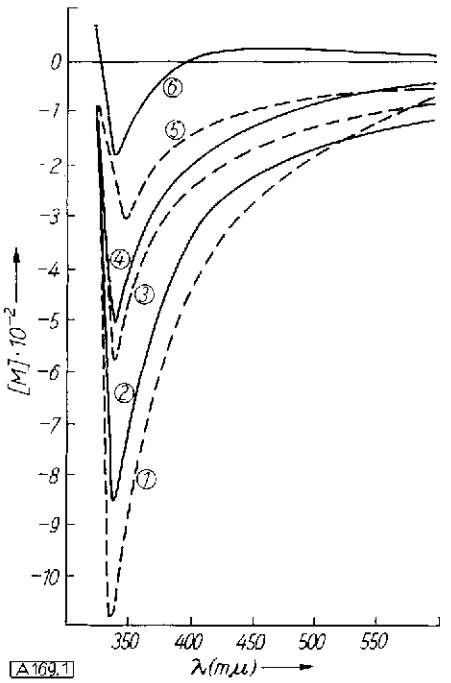


Figure 1. The optical rotatory dispersion [M] of some optically active organosilicon compounds: Curve 1. (−)-R_3Si^*OH; Curve 2. (−)-R_3Si^*F; Curve 3. (−)-R_3Si^*H; Curve 4. (−)-$R_3Si^*OCH_3$; Curve 5. (−)-$R_3Si^*OCOCH_3$; Curve 6. (+)-R_3Si^*Cl

examined by optical rotatory dispersion have a functional group whose steric requirements (for "crowding" about the *peri* hydrogen) are distinctly smaller than those of the methyl group and hence should have approximately the same "conformation" distributions. The fact that the sixth compound, (+)-R_3Si^*Cl, has a functional group only slightly smaller than methyl, and yet is correctly placed in configuration relative to (−)-R_3Si^*H is evidence for the validity of the correlations of configuration given by all six curves [13].

Thus, the curves in Figure 1 lead to assignment of the same configuration to (−)-R_3Si^*F, (−)-R_3Si^*H, (−)-R_3Si^*OH, (−)-$R_3Si^*OCH_3$, (−)-$R_3Si^*OCOCH_3$, and (+)-R_3Si^*Cl, formulate the hydrolysis of R_3Si^*Cl as proceeding with inversion in reaction (2) and provide the means for elucidation of the stereochemistry for some forty reactions of optically active α-naphthylphenylmethylsilyl compounds. In particular, it is concluded that all ten reactions of R_3Si^*Cl listed in Table 1 proceed with inversion of configuration; all of the available evidence strongly supports this conclusion [14].

4. Nucleophilic Displacements on R_3Si^*OR and R_3Si^*OR and R_3Si^*H

The following equations summarize a number of reactions which are highly stereospecific and proceed with *retention of configuration* [7, 14].

[13] As has been pointed out by *C. Djerassi:* Optical Rotatory Dispersion. McGraw-Hill Book Co., New York 1960, p. 102 to 108, correlation between rotatory dispersion curves and configuration must take into account the possibility of free-rotational "conformational" isomerization. However, this kind of uncertainty of interpretation should certainly not obtain for five of the compounds examined, and, in fact does not obtain even the case of R_3Si^*Cl.

[14] *L. H. Sommer, C. L. Frye, M. C. Musolf, G. A. Parker, P. G. Rodewald, K. W. Michael, Y. Okaya,* and *R. Pepinsky,* J. Amer. chem. Soc. *83,* 2210 (1961); *L. H. Sommer* and *C. L. Frye,* ibid. *82,* 4118 (1960).

$$(+)\text{-}R_3Si^*OCH_3 \xrightarrow[\text{ether}]{LiAlH_4} (+)\text{-}R_3Si^*H$$

$$(+)\text{-}R_3Si^*OH \xrightarrow[(n\text{-}Bu)_2O]{LiAlH_4} (+)\text{-}R_3Si^*H$$

$$(+)\text{-}R_3\overset{*}{Si}O\overset{*}{Si}R_3 \xrightarrow[(n\text{-}Bu)_2O]{LiAlH_4} (+)\text{-}R_3Si^*H$$

$$(+)\text{-}R_3Si^*OCH_3 \xrightarrow[\text{xylene}]{KOH_{solid}} (-)\text{-}R_3Si^*OK \xrightarrow{H_2O} (+)\text{-}R_3Si^*OH$$

$$(+)\text{-}R_3\overset{*}{Si}O\overset{*}{Si}R_3 \xrightarrow[\text{xylene}]{KOH_{solid}} 2\,(-)\text{-}R_3Si^*OK \xrightarrow{H_2O} 2\,(+)\text{-}R_3Si^*OH$$

Grignard Reduction:

$$(+)\text{-}R_3Si^*OCH_3 + t\text{-}C_4H_9MgCl \xrightarrow[24\ hrs.]{95\,^\circ C.} (+)\text{-}R_3Si^*H + CH_2=C(CH_3)_2$$

$$(+)\text{-}R_3Si^*H \xrightarrow[\text{xylene}]{KOH_{solid}} (-)\text{-}R_3Si^*OK \xrightarrow{H_2O} (+)\text{-}R_3Si^*OH$$

5. Nucleophilic Displacements on R_3Si^*OCOR

In these reactions there are two possible courses for nucleophilic substitution, illustrated below for reactions with methanol.

$$R_3Si^* \vdots O - COR' + CH_3OH \longrightarrow R_3Si^*OCH_3 + R'COOH \quad (I)$$

$$R_3Si^* - O \vdots COR' + CH_3OH \longrightarrow R_3Si^*OH + R'COOCH_3 \quad (II)$$

In individual cases, the predominant reaction course will depend upon the relative reactivities of silicon and carbonyl as centers for nucleophilic attack. Reactions of type II must proceed with retention of the silicon configuration since the asymmetric center is not involved. In the following reactions, nucleophilic attack at silicon (type I cleavage) leads to *predominant inversion of configuration* [7, 14].

$$(+)\text{-}R_3Si^*\text{-}O\text{-}COCH_3 \xrightarrow[\text{xylene}]{KOH_{solid}} (+)\text{-}R_3Si^*OK \xrightarrow{H_2O} (-)\text{-}R_3Si^*OH$$

$$(+)\text{-}R_3Si^*\text{-}O\text{-}COCH_3 \xrightarrow[\substack{\text{pentane;}\\\text{amine}}]{CH_3OH} (-)\text{-}R_3Si^*OCH_3$$

$$(+)\text{-}R_3Si^*\text{-}O\text{-}COC_6H_5 \xrightarrow[\text{ether}]{LiAlH_4} (-)\text{-}R_3Si^*H$$

$$(+)\text{-}R_3Si^*\text{-}O\text{-}COCH_2Cl \xrightarrow[\substack{\text{pentane;}\\\text{amine}}]{CH_3OH} (-)\text{-}R_3Si^*OCH_3$$

6. Racemization and Inversion Reactions of $R_3Si^*OCH_3$ and R_3Si^*OH

The following three equations show that retention of configuration is not the invariable rule for nucleophilic displacements on these silicon-oxygen bonds [7, 14].

$$(18)\quad (-)\text{-}R_3Si^*OCH_3 + H_2O \xrightarrow[OH^-]{\text{acetone}} (+)\text{-}R_3Si^*OH$$

$$(19)\quad (-)\text{-}R_3Si^*OCH_3 \xrightarrow[CH_3OH]{CH_3ONa(10^{-3}\ M)} \text{racemization; too fast to measure}$$

$$(20)\quad (-)\text{-}R_3Si^*OH + H_2O \xrightarrow[OH^- \text{ or } H^+]{\text{acetone}} \text{rapid racemization}$$

In reaction (18), formation of dextro-silanol is competitive with rapid racemization and is indicated only by a rapid change in the direction of rotation for the reaction which is carried out in a polarimeter tube. Optically active silanol (as indicated in equation 18) is rapidly racemized in aqueous acetone media by small concentrations of base or acid.

The Relationship between Stereochemistry and Reaction Mechanisms

It is becoming more and more evident that silicon compounds exhibit a wide range of reaction mechanisms for nucleophilic substitution reactions. This range of mechanisms is bounded at one extreme by limiting siliconium ion mechanisms, for which kinetic evidence has recently been made available [15]. At the other extreme of this range of mechanisms are reactions which proceed through expanded octets and involve pentacovalent, or hexacovalent silicon mechanisms. Kinetic evidence for expanded-octet organosilicon reaction intermediates has been obtained very recently [16]. Under the circumstances, it seems very probably that S_N2 mechanisms, which fall midway between siliconium ion and expanded-octet mechanisms, represent a third limiting case of mechanism for silicon. Thus, silicon probably has available three limiting mechanisms (in contrast to nucleophilic substitution reactions at saturated carbon, which have only S_N1 and S_N2 mechanisms available as important limiting mechanisms), and this multiplicity of mechanism must be taken into account when considering the theoretical significance of the stereochemical results reported above.

1. Preliminary Correlation of Stereochemistry with Reaction Mechanisms

It is now possible to make several suggestions concerning probable relationships between organosilicon stereochemistry and the reaction mechanisms of monofunctional R_3Si^*Y compounds. Because of the complex nature of these relationships, and despite the hazards involved in drawing conclusions at such an early stage in the development of stereochemical theory in silicon chemistry, it is useful to consider the following possibilities even though they may be highly controversial at the time of writing. The following general remarks concerning stereochemistry-mechanism relationships are followed by some arguments in favor of the validity of the mechanism models which are tentatively assumed:

1. If it is assumed that R_3Si^*Cl and R_3Si^*OCOR' use either an S_N2 mechanism or a somewhat modified S_N2 mechanism in their reactions, and if it is further assumed that in both of these mechanisms the bonds between the entering and leaving groups and the central silicon atom are stretched (*i.e.* relative to the three other bonds in the product-controlling transition state), then the inversion stereochemistry observed for their reactions is simply the result of the same factors which make the Walden Inversion such a common stereochemical path for

[15] *L. H. Sommer* and *G. L. Baughman*, J. Amer. chem. Soc. *83*, 3346 (1961).

[16] *L. H. Sommer* and *G. L. Baughman*, unpublished work.

nucleophilic substitution at saturated carbon. In essence, it may be proposed that the transition states for these reactions greatly resemble S_N2 transition states. The entering and leaving groups are attached to the silicon atom by partial bonds having considerable ionic character, and the three non-reacting groups in the transition state are bonded to the silicon by full bonds which may be formed from either pure sp^2 hybrid orbitals of the silicon, or may use hybrid orbitals of the silicon that involve some contribution from its 3d orbitals.

2. If it is assumed that $R_3Si^*OCH_3$, R_3Si^*H and $R_3Si^*OSi^*R_3$ use an expanded-octet mechanism which proceeds through Si(5) or Si(6) intermediates (these would differ greatly in structure from the transition states proposed in 1 because all five or all six bonds to the silicon atom in these intermediates are full bonds using either sp^3d or sp^3d^2 hybrid orbitals of the silicon), then it would follow that both the retention and the inversion stereochemistry observed in particular cases result from a different preferred geometrical disposition of the entering and leaving groups in the intermediates. If the entering and leaving groups form an angle of 180° with the silicon atom in the trigonal bipyramid or square pyramid formed in Si(5) reactions, inversion of configuration should result. If the entering and leaving groups form an angle of 90° with the central silicon, retention of configuration should result. It is difficult at present to rigorously predict the stereochemical outcome of an angle of 120° between the entering and leaving groups and the central silicon.

3. The larger size and greater polarizability of silicon compared to carbon, as well as its greater multiplicity of mechanism, may cause silicon to become relatively more susceptible to a change in preferred mechanism (and stereochemistry) with a change in the structure of the organosilicon reactant, the nature of the reagent, or the nature of the solvent. In such a case the high reactivity of the bridgehead silicon-chlorine bond in the highly strained structure 1-chloro-1-silabicyclo[2,2,1]heptane [17] is simply the result of a change in mechanism and preferred stereochemistry due to the structural change from acyclic R_3Si^*Cl to strained bridgehead Si–Cl. In particular, a very favorable I-strain factor for formation of an Si(5) or Si(6) intermediate, containing five or six full bonds, exists in 1-chloro-1-silabicyclo[2,2,1]-heptane and is absent in R_3Si^*Cl. Thus a retention (90° angle) stereochemistry is highly favored for the bridgehead compound.

The following arguments may be put forward in favour of the validity of the mechanism models tentatively assumed in 1. and 2., and for the role of an I-strain factor in causing a change in mechanism and preferred stereochemistry for strained cyclic compounds:

(a) R_3Si^*Cl and R_3Si^*OCOR' have good leaving groups, whose conjugate acids have pK_a lower than *ca.* 5. Displacements of such good leaving groups by a pure or somewhat modified S_N2 mechanism should take place readily because of the relatively high capacity of such leaving groups for acceptance of a negative charge.

(b) $R_3Si^*OCH_3$, R_3Si^*H, and $R_3Si^*OSi^*R_3$ have poor leaving groups, whose conjugate acids have pK_a larger than *ca.* 10. Displacements of such poor leaving groups from saturated carbon by strong bases are unknown, except for special cases of carbon-oxygen-carbon reactions involving ring-strained epoxides, and base-catalyzed formation of hydrogen gas from R_3CH has never been observed. For nucleophilic displacement of such groups by strong bases, it is reasonable to assume that silicon must use a mechanism or mechanisms not available to carbon, namely expanded-octet Si(5) or Si(6) mechanisms. Displacement of such poor leaving groups must require relatively high activation of the silicon and very extensive electron-donation to the silicon by the attacking nucleophilic reagent. These requirements for displacement of poor leaving groups can best be met by an Si(5) or Si(6) mechanism, in which full addition of the nucleophilic reagent to the silicon (with formation of five or six full bonds) must precede significant stretching of the bond between the silicon and the poor leaving group.

(c) The role of I-strain as an important factor in causing a change of mechanism and preferred stereochemistry for strained cyclic organosilicon compounds is strikingly confirmed by some very recent work. It has recently been found [18] that the bridgehead silicon-chlorine bonds are very unreactive in 1,3,5,7-tetrachloro-1,3,5,7-tetrasilaadamantane. In this strutcure, which is free from angle and conformational strain, there exists no I-strain factor favorable to a change from an S_N2 to an expanded-octet Si(5) or Si(6) mechanism, and the more usual S_N2 (or modified S_N2) mechanism for hydrolysis of R_3Si^*Cl cannot operate because the bridgehead silicon atoms are unable to undergo Walden Inversion.

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[17] *L. H. Sommer* and *O. F. Bennett*, J. Amer. chem. Soc. *79*, 1008 (1958).

[18] *A. L. Smith* and *H. A. Clark*, J. Amer. chem. Soc. *83*, 3345 (1961).

Liquid Ion-Exchange Technology [*]

BY DR. R. KUNIN, ROHM AND HAAS COMPANY, PHILADELPHIA, PA. (USA),
AND DR. A. G. WINGER, MINOC S. A. R. L., PARIS (FRANCE)

Liquid ion exchangers have certain advantages over conventional solid ion exchange resins. For example, they make possible the removal of ionic species from solutions of relatively high concentration. Because of favorable distribution factors, the number of stages needed for a practical degree of extraction is usually low. Typical liquid ion exchangers are amines or alkyl phosphoric acids in the molecular weight range 250–500.

Introduction

With the continual development of ion exchange technology, new fields of application are uncovered which require ion exchange materials that differ from those in conventional use, not only in their functional groups, but also in physical form. The development of ion exchange perm selective membranes for electrochemical operations and the development of "oversized" ion exchange resin beads for conducting ion exchange operations in viscous media and unfiltered slurries or pulps are examples of this evolutionary process in ion exchange technology.

The need for operating ion exchange systems in a continuous countercurrent system has interested most engineers in this field, especially for applications which involve the recovery or removal of ionic species present in concentrations higher than those normally encountered in conventional ion exchange operations. Although many schemes have been devised for employing conventional ion exchange resin beads in a continuous countercurrent operation, all have some limitations. Resin attrition and transport are but two of several difficulties encountered. In addition to these mechanical difficulties, solid ion exchange materials are not particularly well suited to solutions of high concentration.

The backwash requirements of fixed beds are a problem in short cycles and the void volume in the interstices of beds of solid exchangers results in undesirable dilution effects, reagent losses, and the necessity for recycling portions of the reagents. The design of an ideal solid exchanger demands compromise between optimum hydraulic and kinetic performance. In order to obtain good hydraulic performance, large particles must be used and this results in reduced kinetic performance.

Liquid-liquid extraction is not hindered by the above difficulties associated with the use of solid ion exchangers or other solid adsorbents. The success of liquid-liquid extraction as a unit operation in chemical processing in various atomic energy programs has stimulated much interest on the part of the chemical industries. The problems of hydraulics and kinetics usually encountered with solid exchangers are hardly ever noted in liquid ion exchange technology.

Although various water insoluble acid and basic reagents have been used on occasions as liquid extractants for ionic constituents, their use as liquid ion exchange systems was first proposed by *Smith* and *Page* [1]. These investigators found liquid amines, such as methyldinonylamine, methyldioctylamine, and trioctylamine, very effective for extracting strong acids from their aqueous solutions and considered their systems comparable with solid, weak-base anion exchange resins.

Since this work, various organic liquids have become available commercially and their usefulness as liquid exchangers has been established in several areas of the chemical process industries.

Nature and Properties of Liquid Ion Exchangers

The operation of liquid ion exchangers involves selective transfer of solute between two immiscible phases – an aqueous phase, and an organic phase containing the liquid exchanger. The two immiscible phases are first thoroughly mixed in order to facilitate the transfer of electrolyte and then separated. Depending upon the selectivity or distribution coefficients of the system, several operations may be required. During the transfer of electrolyte, the organic phase containing the liquid exchanger is almost completely anhydrous, in contrast to the behavior of conventional, solid exchangers, which are normally highly hydrated when in contact with aqueous solutions. In view of this, the liquid exchangers are probably undissociated except at the interface between the organic and aqueous phases.

There are several requirements that a liquid exchanger must satisfy before it can be considered for commercial use in chemical processing. The more important characteristics for a useful liquid exchanger are: (1) low solubility, (2) high selectivity, (3) good miscibility with low-cost solvents, (4) freedom from emulsion-forming tendencies, (5) ability to be "stripped" or regenerated with common reagents in cyclic processes, (6) stability towards common reagents under normal conditions, and (7) low cost. Low solubility of the liquid exchanger is important from several points of view. For obvious economic reasons, low solubility in water, acids and bases is a most important characteristic.

Excessive solubility of the exchanger is also objectionable because of the possible impurities it imparts to the solutions being treated. Currently available quaternary ammonium and sulfonic acid compounds have been found unsuitable for most commercial liquid ion exchange

[*] This paper was presented at the 87th Dechema Symposium, Frankfurt am Main (Germany), October 27th, 1961.

[1] *E. L. Smith* and *J. E. Page*, Chem. and Ind. *61*, 47 (1948).

applications. In order to prepare sulfonic acid and quaternary ammonium salt liquid exchangers of low solubility, it would be necessary to prepare compounds of so high an equivalent weight that their commercial use could not be considered.

The importance of selectivity requires very little discussion since it has the same significance as in the case of solid exchangers. However, since liquid ion exchange systems are ideally suited to continuous, countercurrent operation, selectivity is of less importance than in solid ion exchange technology. It is of interest to note that most liquid ion exchange systems exhibit selectivities that are orders of magnitude greater than those exhibited by simple liquid-liquid extraction systems involving solvents that possess no potential ion exchange activity. The miscibility of the liquid exchanger with various solvents is of considerable importance since these exchangers cannot function properly unless diluted with some inert solvent. If employed without dilution, various difficulties such as formation of third phases, precipitates, and emulsions arise. To be of interest to the chemical process industries, the extractant or liquid exchanger should be miscible in high proportions with cheap, inert, and relatively non-volatile solvents.

A critical factor in the operation of a liquid ion exchange system involves the relative ease with which the two phases can be disengaged. This factor depends not only upon the relative densities and viscosities of the individual phases but also upon the formation of emulsions. The formation of emulsions is one of the major disadvantages of liquid-liquid extraction since excessive losses of reagent and product are encountered. Since liquid exchangers usually possess some surface-activity, it is of considerable importance to select those that have a low activity and to operate under conditions which minimize the formation of stable emulsions. Sulfonic, carboxylic, and quaternary type liquid exchangers are usually so surface-active that their use is rather limited.

The regenerative and "stripping" properties of the liquid exchangers are dependent upon the selectivity of the exchanger. Since this behavior is identical to that of solid exchangers, further discussion is unnecessary. The stability of any reagent that must be recycled in chemical processing is always a problem but in the case of liquid exchangers, the problem is much less serious. The contamination of solid exchangers with colloids is always serious because of rate and mechanical difficulties; this is hardly ever a difficulty with liquid exchangers.

Although various organic reagents, including strong and weak acids as well as strong and weak bases, have been investigated as potential liquid extractants, only the weak electrolyte reagents, which come close to satisfying the above requirements for an ideal liquid extractant, have been developed to date. The strong electrolyte liquid exchangers that have been considered, such as quaternary ammonium compounds (*N*,*N*-didodecenyl-*N*,*N*-dimethylammonium chloride) and sulfonic acids (nonyl sulfonic acid) are much too soluble and surface active to be of commercial interest. Even in the weak electrolyte class, practically all of the carboxylic and the phosphoric (also the phosphonic and phosphonous) acid compounds investigated are too soluble and surface active in neutral and alkaline media to be of commercial interest. In acid media, however, these acids are of some importance.

Commercial Liquid Ion Exchangers

Practically all of the useful liquid exchangers are organic compounds having molecular weights in the 250–500 range and are unifunctional; *i.e.* contain only one ionizable group per molecule. The liquid anion exchangers are represented by various primary, secondary, and tertiary amines, and the liquid cation exchangers by a series of alkyl phosphoric acids. Several typical liquid anion and cation exchangers are listed along with their structures in Table 1.

Table 1. Types of liquid ion exchangers commercially available

(A) Anion exchangers

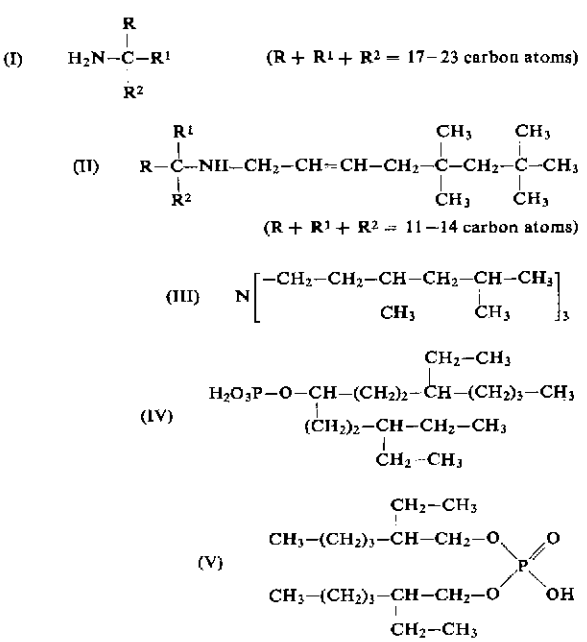
Primary amines	Secondary amines	Tertiary amines
Trialkylmethylamine [a]	*N*-Dodecenyl-*N*-trialkylmethylamine [b]	Trialkylamine
		Tri(iso-octylamine) [c]
	N-Lauryl-*N*-trialkylmethylamine [d]	*N*,*N*-Didodecenyl-*N*-n-butylamine [e]

[a] homologous mixture, 18–24 C-atoms, *e.g.* Primene JM;
[b] mixture, 24–27 C-atoms, *e.g.* Amberlite LA-1;
[c] mixed C_8 radicals;
[d] *e.g.* Amberlite LA-2;
[e] *e.g.* Amberlite XE-204

(B) Cation exchangers; Phosphoric acid derivatives

Monodecyl phosphoric acid
Monoheptadecyl phosphoric acid
Di(2-ethylhexyl)phosphoric acid

Typical structures for some of the pure components listed above are given by formulae I–V.



Some properties of a typical liquid cation and a liquid anion exchanger are listed in Table 2.

Table 2. Properties of typical commercial liquid exchangers

	Amberlite LA-1	Di(2-ethylhexyl)-phosphoric acid
Molecular weight	375	322
Neutral equivalent	390	–
Acid-base binding capacity [meq./g.]	2.6	3.0
Viscosity (25 °C) [cp.]	72	53
Density (25 °C) [g./ml.]	0.84	0.95
Solubility [p.p.m.]	15	100
pK_a	–	3.2
pK_b	10	–

The behavior of liquid ion exchangers may be compared with that of solid ion exchange resins keeping in mind that, in the latter, the organic phase is highly hydrated whereas in the former, the organic phase is practically anhydrous. A liquid anion exchanger, such as a secondary amine, removes acids from aqueous solutions by neutralization, as indicated by the following reactions:

$$R_2NH + HCl \rightarrow R_2\overset{\ominus}{N}H_2\ Cl^{\ominus}$$

$$2\,R_2NH + H_2SO_4 \rightarrow [R_2NH_2]_2^{2+}\ SO_4^{2-}$$

$$[R_2NH_2]_2^{2+}\ SO_4^{2-} + H_2SO_4 \rightarrow 2\,R_2\overset{\oplus}{N}H_2\ HSO_4^{\ominus}$$

The same exchanger may be employed in the salt form for the exchange of anions as indicated by the following reaction:

$$R\overset{\ominus}{N}H_2\ Cl^{\ominus} + NaNO_3 \rightleftharpoons R\overset{\ominus}{N}H_2\ NO_3^{\ominus} + NaCl.$$

As the amines are weak bases, the acid extraction can be reversed and the anion "stripped" by allowing the amine hydrochloride is come into contact with a basic solution.

$$R_2\overset{\ominus}{N}H_2\ Cl^{\ominus} + NH_4OH \rightarrow R_2NH + NH_4Cl + H_2O$$

$$R_2\overset{\oplus}{N}H_2\ Cl^{\ominus} + NaHCO_3 \rightarrow R_2NH + NaCl + CO_2 + H_2O$$

The reactions of a liquid cation exchanger, such as di-(2-ethylhexyl)phosphoric acid, may be depicted as follows:

$$(RO_2)_2PO_2H + NaOH \rightarrow (RO_2)_2PO_2Na + H_2O$$

$$(RO_2)_2PO_2H + NaCl \rightleftharpoons (RO_2)_2PO_2Na + HCl$$

$$2\,(RO_2)_2PO_2Na + CaCl_2 \rightleftharpoons [(RO_2)_2PO_2]_2Ca + 2\,NaCl$$

Although the above reactions may be written formally in this manner, the mechanisms may be, in a sense, more complicated, depending upon the nature of the compounds formed in the organic phase. For example, formation of dimers, trimers, polymers, and micelles may occur in the organic phase when various salts are formed between the liquid exchanger and the electrolytes in question. The formation of these complexes is not only influenced by the nature of the liquid exchanger but also by the nature of the organic diluent and the soluble electrolytes in question.

The behavior of the liquid ion exchangers can best be described in terms of their acid-base strengths and selectivities. Unfortunately, compared to the abundance of data available for solid ion exchange resins, few data are available for the liquid extractants. However, sufficient data are available to indicate that the selectivities of liquid ion exchangers differ little from solid ion exchange resins of similar functionality. The pK_b values show that the liquid amine, weakly basic exchangers are somewhat weaker in basicity than the comparable weakly basic resins [pK_b (liquid) = 9–10 *vs.* pK_b (resins) = 7–9]. The pK_a of the liquid and solid phosphoric acid exchangers are, on the other hand, approximately the same (pK_a 3). The theoretical binding capacities of these materials may be approximated from their titration curves. Figure 1 shows the curves for a typical weakly basic solid and a typical weakly basic liquid ion exchanger.

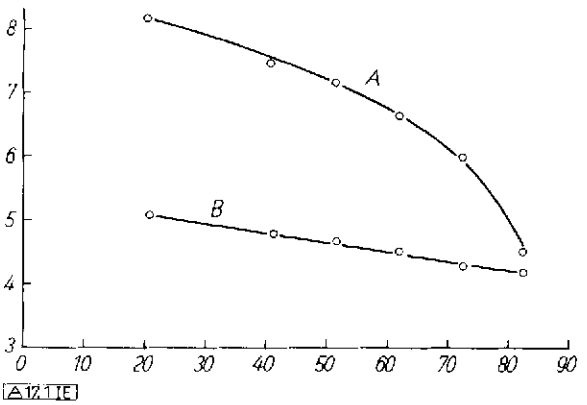


Fig. 1. Titration curves. (A) Solid weak-base exchanger. (B) Liquid weak-base exchanger.
Ordinate: pH
Abscissa: % neutralisation

Because the weakly basic liquid exchangers have a wider scope of utility than the weakly acidic materials, more selectivity data are available for the former than for the latter. In general, the order of preference of the weakly basic amines for various anions follows the sequence,

$$ClO_4^{\ominus} > NO_3^{\ominus} > Cl^{\ominus} > HSO_4^{\ominus} > F^{\ominus}$$

Some quantitative data for the selectivities of two weakly basic amines for various acids are given in Table 3.

Table 3. Relative selectivities of Amberlite LA-1 and Amberlite LA-2 for various acids [*]

Acid	Amberlite LA-1	Amberlite LA-2
Nitric	85.3 %	94.4 %
Hydrochloric	77.3	88.6
Sulfuric	74.5	88.0
Acetic	2.7	8.9
Tartaric	1	44
Azelaic	–	70
Formic	–	50.6
Malic	–	39
Lactic	–	32.5
Glutamic	–	1–2
$RO-SO_3^{\ominus} + NO_3^{\ominus}$ (anion exchange) [**]		82.6

[*] Data refer to per cent acid removed on contacting 1 volume of 0.1 molar amine in kerosene with 1 volume of 0.1 molar acid (in water).
[**] Sulfate form of Amberlite LA-2 contacted with nitric acid.

The selectivities of the above liquid ion exchangers are dependent not only upon their chemical structures but also upon the nature of the diluent. There are no definite trends that can be followed in predicting the effect of the solvent used as the diluent. However, aromatic and polar

diluents improve the selectivity of unbranched liquid amine exchangers for uranium in sulfate systems but decrease that of the highly branched amines. In the case of the liquid cation exchangers, the selectivity of the dialkylphosphoric acids for uranium decreases with the dielectric constant of the organic diluent.

It is interesting to compare the selectivity factor of a liquid ion exchanger with that noted in solid ion exchange technology. Although it is well known that addition of solvents to a solid-liquid ion exchange system has a marked effect upon selectivity, in this case, the solvent is present in both phases. In other words, the effect of solvent in solid-liquid ion exchange systems is normally studied by noting the effect of adding solvents to the solution phase and equilibrating the resin with the same solvent. In the case of liquid exchangers, the solvent is the diluent and this is added to the liquid exchanger phase and normally the other phase contains only a trace of the solvent or diluent. Basically, the effect on selectivity caused by changes in the diluent in liquid ion exchange technology is comparable to the effect of changing the skeletal frame-work poly-styrenes, -acrylates, -phenols) on the selectivity of solid ion exchange resins.

Similarities and differences between liquid and solid exchangers and between liquid and solid exchange operations have been summarized in Table 4.

conventional ion exchange studies. Since rates of exchange during the liquid ion exchange operation are normally quite high, the nature of the equilibrium curve will determine the practicality of the process. Figure 2

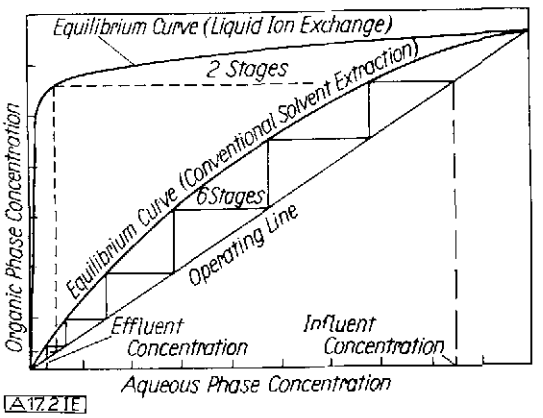


Fig. 2. Liquid ion exchange *vs.* conventional solvent extraction

describes a typical liquid exchanger equilibrium curve a and comparison is also given for a true solvent extraction equilibrium curve. The number of theoretical

Table 4. Comparison of liquid and solid ion exchange technology

	Liquid ion exchangers	Solid ion exchangers
1. Active groups	primarily limited to amines and alkyl phosphoric acids	practically all types available
2. Skeletal structure	diluent serves as carrier of functional groups	rigid, cross-linked, polymeric base
3. Rates of exchange	extremely high	relatively slow
4. Selectivities	varies with functionality, substituent group, and diluent	varies with functionality, degree of cross-linking, substituent groups, and skeletal structure
5. Mode of action	exchange of ions across the liquid-liquid interface into an anhydrous droplet	exchange of ions throughout a hydrated particle
6. Potentialities	adaptable to a variety of engineering techniques and equipment	primarily limited to concurrent columnar operation

Applications

General Considerations

The technique for conducting liquid ion exchange operations is identical to that employed for general solvent extraction operations; the various types of apparatus employed in solvent extraction may be used without modification.

Since the distribution coefficients involved in liquid ion exchange are very high as compared with those encountered in solvent extraction, the number of stages necessary for achieving the degree of extraction required is usually low. In the laboratory, various standard separatory funnels are ideally suited for the study of liquid ion exchange processes. The suitability of liquid exchange for a particular process and the operating conditions can be determined experimentally by measuring the equilibrium curve for the reaction involved.

The determination of the equilibrium curve is similar to the selectivity or adsorption isotherm measurements of extraction stages can be determined from the equilibrium curve by forming steps with horizontal and vertical lines drawn between the equilibrium curve and the operating line with the influent and effluent aqueous phase concentration as limits for the steps.

Experience has shown that it is best to dissolve the extractant in an inert solvent in order to facilitate separation of the organic and aqueous phase and to minimize solubility and entrainment losses. Commercial liquid exchangers are compatible with many inert organic solvents and kerosene has proved to be most satisfactory whenever the exchanger has been used for processing dilute aqueous solutions. Various aromatic solvents such as benzene are also satisfactory. A concentration of 2.5 to 12.5 % by volume is recommended for most systems.

Under certain conditions, emulsions may form, giving rise to difficulties in the separation of the organic and aqueous phases during "stripping" and "loading". When this occurs, the addition of 2 to 3 % of a higher alcohol to the organic phase minimizes the difficulty.

The phase ratio (the volumetric ratio of the aqueous solution to the organic solution) must be considered in the design of the process. The ratio chosen is governed by the concentration of the liquid exchanger in the organic phase and the type of extraction equipment selected. For the treatment of an aqueous 0.1 N acid solution, an equal volume of 0.1 molar liquid anion exchanger in a suitable solvent would be adequate for complete removal of acid under ideal conditions, and the aqueous-to-organic phase ratio of the feed solutions would be 1/1. The greater the concentration of the liquid exchanger in the organic phase relative to the concentration of the component to be removed from the aqueous phase, the greater will be the concentrating effect. While a high concentration of liquid exchanger in the organic phase may be desired because of the high concentrating effect, the high aqueous-to-organic phase ratio that results cannot always be handled adequately. As a rule, a phase ratio greater than 5/1 is not recommended.

The liquid exchanger may be used for ion exchange applications in either batch or continuous operation. The flow pattern in continuous operation may be either concurrent or countercurrent. When using either a batch or a continuous procedure to remove components from an aqueous solution, complete removal should not be expected when a stoichiometric quantity of exchanger is used, because equilibrium conditions prevent completion of the exchange or neutralization reaction. In batch operation, an excess of reagent or exchanger is required if complete removal of a constituent is necessary. However, by employing countercurrent continuous operation, an excess of exchanger is not required for complete extraction provided the number of stages employed is sufficiently large. In a continuous flow system, the relative rates for both aqueous and organic phase will depend primarily on the type of equipment. Some precaution must be taken against flooding (transfer of one phase with the other) at high linear velocities. Since the rate at which ions are transferred from the aqueous to the organic phase is very rapid, the retention time is usually dependent upon the rate at which the phases disengage.

Equipment

Although many different types of equipment have been employed industrially for liquid ion exchange technology, they may be classified into three basic types: (1) mixer-settlers, (2) column contactors, and (3) centrifugal contactors.

Mixer-settlers consist of separate mixing and settling tanks. The organic (liquid exchanger) and aqueous phases are first thoroughly mixed in a tank equipped with baffles and an agitator and the mixture is then fed into a settling tank. Various designs for mixer-settler devices are available and several of these are described in Figure 3. For systems with favorable equilibria, few theoretical plates are required.

Column contactors are employed where one requires more theoretical plates than can be satisfied conveniently with mixer-settlers and where a continuous countercurrent flow is desired. The heavier phase (usually the aqueous phase) is fed into the top of the column and the lighter phase is fed in through the bottom. In this manner, partially loaded liquid exchanger is always in contact with the incoming aqueous phase and the fresh exchanger is in contact with the partially extracted aqueous phase. This mode of operation assures maximum efficiency. There are various column designs

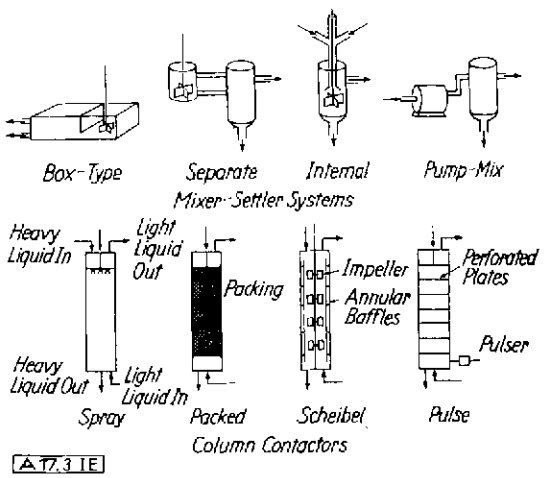


Fig. 3. Typical liquid-liquid contactors

available. The simplest is the spray column in which the phase is introduced at the top of the column as dispersed droplets by means of a series of spray nozzles. The droplets fall through the rising continuous phase. The efficiency of the column can be improved by introducing packing or baffle plates. Further improvement can be achieved by introducing mechanical means for maintaining good dispersion. This is accomplished by means of a rotating central shaft to which impeller blades are attached. Some columns are provided with packing in the regions between the stirring blades. A pulsing device may also be employed. Typical column contactors are also given in Figure 3.

Centrifugal extractors are employed occasionally in liquid ion exchange operations, particularly when a greater driving force is required for proper phase disengagement. These extractors are well suited for systems in which the two phases differ only slightly in density or systems in which emulsions are formed. The extractor normally consists of a long spiral chamber within a cylindrical drum. The chamber is rotated at high speed and the liquids flow in countercurrent through the spiral. A typical centrifugal extractor employed in liquid ion exchange is given in Figure 4.

Basically, the mechanics of a liquid ion exchange operation are simple and the technique offers the following advantages over solid exchangers: (1) rapid rates of exchange, (2) higher selectivity, (3) greater applicability to high concentrations because of the absence of voids and the anhydrous nature of the organic phase, (4) continuous countercurrent operation in simple equipment, (5) processing unaffected by turbidity, (6) liquid exchangers are rarely contaminated or poisoned, (7) "backwashing" is eliminated, and (8) "stripping" (elu-

tion) is accomplished with low reagent consumption, with little dilution, and with extremely low rinse requirements. On the other hand, there are several basic

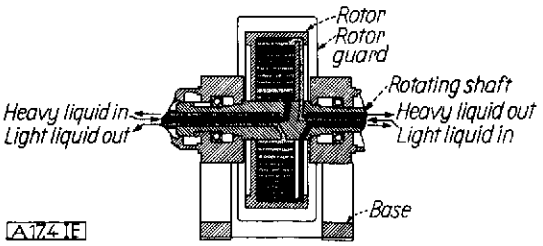


Fig. 4. Schematic diagram showing liquid flow through a Podbielniak extractor

limitations to liquid ion exchange; *e.g.*, (1) emulsion formation increases reagent consumption and exchanger losses, (2) the types of available and useful liquid exchangers are limited, and (3) the solubility of even the least soluble liquid exchanger imparts some contamination to the separated product and results in a steady loss of exchanger.

Specific Applications

Although liquid ion exchangers have been available commercially for only a short period of time, several applications have been developed for these materials and a modest number of plants have been erected in which liquid exchangers are functioning successfully.

Hydrometallurgy

The major application of liquid ion exchange is the recovery and purification of uranium. Both liquid anion and cation exchange processes can be used for recovering uranium from the sulfuric acid leach liquors of low grade ores. Both the anion exchange process and the cation exchange process are basically similar since the optimum conditions and the reagents employed are almost identical.

The technique employed for the anion exchange process is almost identical with that for the recovery of uranium by means of quaternary ammonium anion exchange resins. The uranium present in an acid sulfate leach liquor as the complex uranyl sulfate anion is brought into contact with the liquid amine anion exchanger dissolved in a kerosene diluent. Uranium is recovered from the saturated organic phase by stripping with various salt solutions or an aqueous solution of sodium carbonate. Table 5 summarizes the uranium capacity of

Table 5. Minimum uranium capacity of Amberlite LA-1

Amine concentration (in kerosene)	Organic phase capacity g.U_3O_8/l (amine + kerosene)
0.05 N	1.78
0.10	3.56
0.25	8.88

a typical liquid anion exchanger, for the extraction of uranium from a solution containing 1 g. U_3O_8 and 30 g. sulfate/litre at pH 1.8. The liquid ion exchange process can compete with the conventional process, particularly when the concentration of uranium is above 0.5 g./litre.

The amine process is normally preferred; however, there are occasions when the liquid cation exchange process can be used to advantage, *e.g.* when vanadium is to be recovered along with the uranium. The uranium is extracted by the alkylphosphoric acid at pH 1 and the vanadium is then extracted from the residual solution at pH 2–3. The vanadium can also be extracted by the amine process if it is first oxidized to the pentavalent state; selective elution can be accomplished with an SO_2 solution and liquid exchangers, particularly the amines, are not poisoned by silica, polythionates, cobalticyanides etc., materials which seriously impair the performance of solid exchangers.

Liquid amine anion exchangers can also be employed to recover uranium from concentrated hydrochloric acid solutions. High exchanger capacities are obtained when the uranium is extracted from 6–12 N hydrochloric acid solutions. Since the uranyl chloride complex is unstable at low chloride concentrations, the uranium may be recovered from the organic phase by extraction with water. Other complex metallic chlorides can be extracted from concentrated hydrochloric acid solutions. The use of the liquid amine extractants for removing iron from hydrochloric acid solutions and from aluminum chloride/hydrochloric acid solutions is of considerable interest for the purification of hydrochloric acid and preparing pure aluminum chloride. Although the conventional quaternary ammonium anion exchangers can be used for this application, this is not always satisfactory because of the high concentrations involved. The amine process is ideal because the selectivity for the $FeCl_4^{\ominus}$ complex is extremely high in strong hydrochloric acid solutions, the "stripping" can be accomplished with water. The reactions involved are as follows:

$$FeCl_3 + HCl \rightleftharpoons HFeCl_4 \rightleftharpoons H^{\oplus} + FeCl^{\ominus}_4$$

$$R_2NH{\cdot}HCl + FeCl_3 \xrightarrow{\text{conc. HCl}} \overset{\oplus}{R_2NH_2}[FeCl_4]^{\ominus}$$

$$R_2NH{\cdot}HFeCl_4 + H_2O \rightarrow R_2NH{\cdot}HCl + FeCl_3$$

Cyclic tests have demonstrated that Amberlite LA-1 in kerosene containing 3 % v./v. decyl alcohol is capable of reducing the iron content of a solution containing 10 g. Fe/l, 90 g. Al_2O_3 (as $AlCl_3$)/l, and 10 g. HCl/l to a level of 19 p.p.m. without any loss or dilution of the $AlCl_3$ or HCl.

Recovery and Separation of Acids

The data summarized in Table 3 suggest various applications for the use of weak base liquid exchangers for the removal, recovery, and separation of acids. For example, the separation of sulfuric and nitric acids is possible. Ammonium nitrate may be recovered from nitration wastes, and from nitrate solutions employed during the processing of uranium.

Liquid amine-type ion exchangers are ideally suited for the removal of various acid constituents from process effluents. In many cases, the organic and inorganic acids that constitute waste problems are valuable if they could be concentrated and recovered economically. Extraction

of these acids for recovery can be readily accomplished with amines. Nitric, hydrofluoric, fluosilicic acid, and tartaric acids are a few such examples. Anhydrous extraction agents, such as dry ammonia gas, may be used when it is desired to recover the acid as a solid rather than as a liquid concentrate. The concentrated extractive is treated with anhydrous ammonia and the ammonium salt is filtered from the organic phase. The recovery, as solid ammonium nitrate, of dilute nitric acid present in waste streams can be accomplished by such a procedure.

Several such specific applications for liquid anion exchangers have been developed in the pharmaceutical industry. For example, 6-aminopenicillanic acid can be recovered from fermentation broths by means of this technique. The amine extractant is dissolved in a polar diluent such as butanol or chloroform and the system first buffered with an acetate/acetic acid buffer. Elution can be accomplished with dilute HCl. The extraction and elution, therefore, can be conducted in a buffered system and the entire cycle completed in a short period of time. Conventional solid ion exchangers are, at times, inadequate for sensitive materials because the length of the cycle required for loading and elution is too long.

Liquid anion exchangers have also been employed by the pharmaceutical industry for the removal of nitric acid from the crude nicotinic acid mixture formed during the synthesis of nicotinic acid. A similar application involves the removal of hydrochloric acid from glutamic acid produced in the acid (HCl) hydrolysis of proteins.

Miscellaneous

A primary amine liquid exchanger, is ideal for the recovery of thorium from sulfuric acid liquors. Such materials has also been found useful for the removal of ferric iron and for the recovery of rare earths from sulfate solutions [2].

Di-(2-ethylhexyl)phosphoric acid has been found sufficiently selective for the extraction and separation of the rare earths, actinides, titanium, zirconium and hafnium from sulfuric acid liquors [3]. The solubility and surface activity of the liquid cation exchangers have limited their use to acid solutions.

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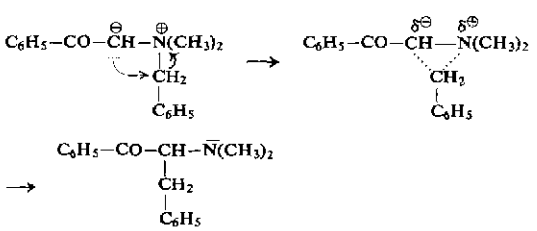
COMMUNICATIONS

On the Mechanism of the Stevens Rearrangement

By Dr. E. F. Jenny and Dr. J. Druey [*]

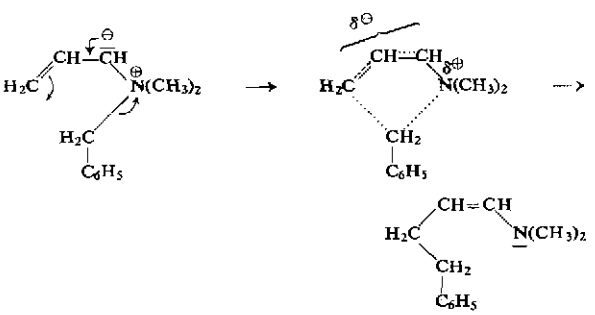
Research Laboratories, Pharmaceutical Division, CIBA, Basel (Switzerland)

The Stevens rearrangement [1] is considered [2] to be an intramolecular, nucleophilic substitution (S_Ni), in which the migrating group, while retaining its configuration, moves without its pair of bonding electrons [3] from a quaternary nitrogen atom to an adjacent carbon atom:



During the rearrangement of allylbenzyldimethylammonium bromide (I; R = H) with sodium amide [4], the benzyl group migrates and not the allyl group, as *Ingold* [2] has stated. It was found that with benzene or liquid ammonia as solvent, the benzyl group underwent a 1,4-shift in addition to the 1,2-shift. The resulting enamine (III) (R = H) can be hydrolyzed to 4-phenylbutyraldehyde [5]. In benzene at 80 °C, the ratio of the 1,2- to the 1,4-migration was about 1.4. In liquid ammonia at −33 °C, a large shift occurred in favor of the 1,2-migration.

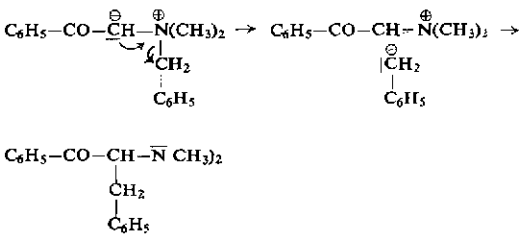
Application of the S_Ni mechanism to the 1,4-migration necessitates postulation of a five-membered cyclic transition state, in which the attacking electron pair no longer displaces the ammonium group at the benzyl residue from the front, as in the 1,2-rearrangement, but from the rear, accompanied by an allylic rearrangement (S_Ni') and Walden inversion of the migrating carbon atom. Models show that the substituting sp orbital of the free electron pair points to the small lobe on the rear of the benzyl carbon atom.



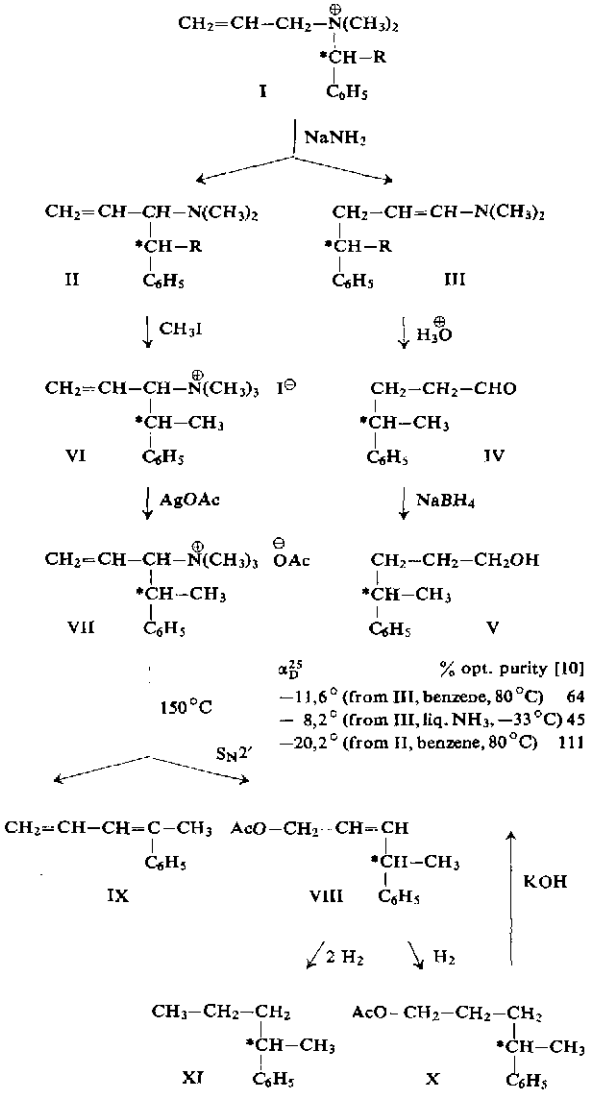
This postulate was tested by reacting optically active allyldimethyl(1-phenylethyl)ammonium bromide (I; R = CH_3) with sodium amide in benzene at 80 °C, or in liquid ammonia at −33 °C, and determining the configuration and optical purity of the migrated 1-phenylethyl group in allylamine (II) and enamine (III) (R = CH_3). In accordance with the results of *Brewster* and *Kline* [3], it was found that in benzene or liquid ammonia the 1,2-rearrangement occured, with at least 90 % retention of configuration. The migrating group moving to the 4-position also retained its configuration, 82 ± 10 % in benzene and 72 ± 10 % in liquid ammonia.

This result contradicts the postulated S_Ni' mechanism. Since we do not believe that the 1,2- and 1,4-rearrangements occur simultaneously while following different mechanisms, we also reject the S_Ni mechanism for the Stevens rearrangement.

Instead, the mechanism previously proposed by *Stevens* [6] seems to apply, *i.e.* the benzyl group migrates with its pair of bonding electrons [7]:



The cation of the intermediate ion pair is related to the carbimonium ion ($R_2\overset{\oplus}{N}=CH_2$), which is the aminomethylating agent of the Mannich reaction [8]. The benzyl anion is situated above the plane of the cation. A similar mechanism was proposed for the Wittig rearrangement by *Schoellkopf* et al. [9].



$\alpha_D^{25} = -15{,}0°$ (from II, liq. NH_3) 100 % opt. purity [11]

The rearrangement of the optically active ammonium salt (I; R = CH_3), obtained from allyl bromide and optically pure (−)-1-phenylethyldimethylamine [3], is formulated in the foregoing chart. It also shows how the configuration and the optical purity of the 1-phenylethyl groups in (II) and (III) were determined. It may be noted that the acetate ion of compound (VII) displaced the trimethylammonium group with allylic rearrangement (S_N2') at about 150 °C, yielding the unsaturated ester of structure (VIII) exclusively. A threefold amount of phenylmethylbutadiene (IX) was also formed. The hydrogenation of (VIII) in cyclohexane or ethanol over palladium on charcoal led to the formation of the saturated ester (X). During hydrogenation under the same conditions very pure fractions suffered hydrogenolytic cleavage of the allylic acetate grouping and were quantitatively converted to 2-phenylpentane (XI).

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[*] A detailed report will not be published elsewhere.

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[3] *J. H. Brewster* and *M. W. Kline,* J. Amer. chem. Soc. *74,* 5179 (1952).

[4] *T. Thomson* and *T. S. Stevens,* J. chem. Soc. (London) 1932 (1932).

[5] *H. Hellmann,* Österr. Chemiker-Ztg. *62,* 315 (1961), also observed this 1,4-migration and utilized it for the synthesis of difficultly accessible aldehydes.

[6] *T. S. Stevens,* J. chem. Soc. (London) 2107 (1930); *T. Thomson* and *T. S. Stevens,* ibid. 55, 2119 (1932).

[7] *o*-Nitrobenzylphenacyldimethylammonium bromide is about 1000 times, and the *p*-isomer about 100 times, as reactive as the unsubstituted benzyl compound. The latter yields *p*-nitrotoluene as a by-product.

[8] *H. Hellmann* and *G. Opitz,* Chem. Ber. *89,* 81 (1956).

[9] *U. Schoellkopf* and *W. Fabian,* Liebigs Ann. Chem. *642,* 1 (1961); *U. Schoellkopf* and *D. Walter,* Angew. Chem. *73,* 545 (1961).

[10] Based on $\alpha_D^{25} = -18.2°$ (maximum value of this alcohol with the same configuration as the starting amine), *P. A. Levene* and *R. E. Marker,* J. Biol. Chem. *110,* 329 (1935).

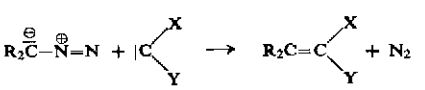
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Reactions of Carbenes with Diazoalkanes

By Dr. H. Reimlinger [*]

Union Carbide European Research Associates, Brussels (Belgium)

In the following reactions haloforms have been utilised for the preparation of halocarbenes[1] and trichloroacetic ester[2] has been used as a source for dichlorocarbene. Diphenyldiazomethane or diazofluorenone were employed as diazo components. The diazoalkane was dissolved in pentane, a suspension of anhydrous potassium t.-butylate in pentane was then added and the haloform or trichloroacetic ester was added dropwise at 10–20 °C with vigorous stirring. Any excess of unreacted diazoalkane was destroyed with acid. For an equimolar ratio of carbene/diazoalkane, the yield of ethylene derivative lies between 20 and 85 %.



X = Y = Cl, X = Cl, Y = Br; X = F, Y = Cl; X = Br, Y = C_6H_5
X = Y = Br; X = F, Y = Br; X = Cl, Y = C_6H_5

The yields given in Table 1 were obtained in test reactions using small quantities. They make no claim to being maximum yields and greatly depend on the concentration of the diazo compound. In the reaction with benzal chloride or benzal bromide, all components were heated in hexane to 70 °C for 12 hrs. By-products are azine (approx. 20 % yield) and polymeric material.

Table 1. Reactions between carbenes and diazoalkanes

Starting Material	Carbene	Diazo-alkane	Reaction product (% yield in brackets)
Chloroform	$:CCl_2$	I	β,β-Dichloro-α,α-diphenyl-ethylene (50). m.p. 80 °C [3]
Trichloro-methylacetate	$:CCl_2$	I	β,β-Dichloro-α,α-diphenyl-ethylene (85). m.p. 80 °C [3]
Chloroform	$:CCl_2$	II	β,β-Dichloro-α,α-diphenyl-ethylene (80). m.p. 132 °C [4]
Fluorodi-chloro-methane	$:CClF$	I	β-Fluoro-β-chloro-α,α-diphenyl-ethylene (50). m.p. 38 °C, b.p. 132 °C/18 mm
Bromoform	$:CBr_2$	I	β,β-Dibromo-α,α-diphenyl-ethylene (20). m.p. 85 °C [5]
Chlorodibro-momethane	$:CClBr$	II	β-Chloro-β-bromo-α,α-diphenyl-ethylene (66). m.p. 132–134 °C
Fluorodibro-momethane	$:CFBr$	II	β-Fluoro-β-bromo-α,α-diphenyl-ethylene (50). m.p. 92–94 °C
Benzalchloride	$:CClC_6H_5$	II	β-Chloro-β-phenyl-α,α-diphenyl-ethylene (40). m.p. 120–122 °C [4]
Benzal-bromide	$:CBrC_6H_5$	II	β-Bromo-β-phenyl-α,α-diphenyl-ethylene (25). m.p. 130 °C [6]

I = Diphenyldiazomethane
II = Diazofluorene

Received, January 10th, 1962 [Z 207/40 IE]

[*] Not published until now by the author's request.

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[2] *W. E. Parham* and *F. C. Loew*, J. org. Chemistry *23*, 1705 (1958).

[3] *H. Biltz*, Ber. dtsch. chem. Ges. *26*, 1952 (1893).

[4] *H. Staudinger* and *I. Siegwart*, Helv. chim. Acta *3*, 847 (1920).

[5] *E. E. Harris* and *G. B. Frankforter*, J. Amer. chem. Soc. *48*, 3144 (1926).

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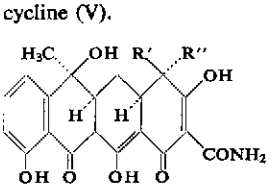
Catalytic Hydroxylation of 12a-Deoxytetracyclines

By Prof. Dr. H. Muxfeldt, cand. chem. G. Buhr, and cand. chem. R. Bangert

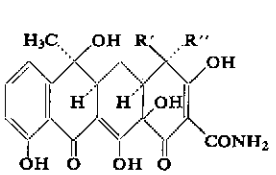
Institut für Organische Chemie, Technische Hochschule, Braunschweig (Germany) and
Department of Chemistry, Univ. of Wisconsin, Madison, Wis. (USA)

The tertiary 12a-OH group, a common feature of all tetracyclines, can be introduced by perbenzoic acid in low yield [1], or by sodium nitrite [2], or microbiologically [3]. We have found that 12a-deoxytetracyclines can be hydroxylated by noble metal catalysts and oxygen [4]. From dedimethylamino-12a-deoxytetracycline (I) and a freshly prehydrogenated platinum oxide catalyst plus oxygen, we obtained a satisfactory yield of crystalline dedimethylaminotetracycline (II). A small amount of dedimethylamino-11a-hydroxy-12a-deoxytetracycline is also formed [m.p. 266–268 °C, λ_{max} = 326 mμ (ε = 19400) and 261 mμ (ε = 18 700) in 0.01 N methanolic HCl; λ_{max} = 346–347 mμ (ε = 23 800), and 256–257 mμ (ε = 12 400) in 0.1 M methanolic $Na_2B_4O_7$ solution].

12a-Deoxytetracycline, prepared according to *A. Green* and *J. H. Boothe* [5], forms 4-epitetracycline (IV) and an 11a-hydroxy compound on oxidation with platinum or palladium and oxygen in dimethylformamide, but no tetracycline(III) [6]. Apparently, the starting material was 12a-deoxy-4-epitetracycline (V).

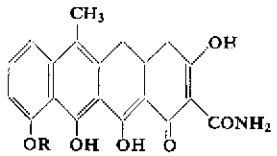


I: R′ = R″ = H
V: R′ = $N(CH_3)_3$; R″ = H

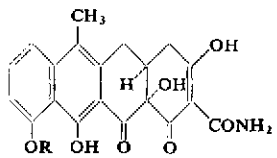


II: R′ = R″ = H
III: R′ = H; R″ = $N(CH_3)_2$
IV: R′ = $N(CH_3)_2$; R″ = H

Anhydrodedimethylaminotetracycline (VII) is the only crystalline product formed when anhydrodimethylamino-12a-deoxytetracycline (VI) is oxidized over a Pt catalyst. The yield is appreciably better than that obtained in the synthesis of compound (IX) by oxidation of the derivative (VIII) with perbenzoic acid [1].



VI: R = H
VIII: R = CH_3



VII: R = H
IX: R = CH_3

Received, January 22nd, 1962 [Z 208/41 IE]

[1] *H. Muxfeldt* and *A. Kreutzer*, Naturwissenschaften *46*, 204 (1959); Chem. Ber. *94*, 881 (1961).

[2] *C. E. Holmlund, W. W. Andres*, and *A. J. Shay*, J. Amer. chem. Soc. *81*, 4748 (1959).

[3] *C. E. Holmlund, W. W. Andres*, and *A. J. Shay*, J. Amer. chem. Soc. *81*, 4750 (1959).

[4] Similar results were obtained in the Medical Research Laboratories of Chas. Pfizer and Co., Inc., *K. J. Brunings*, personal communication.

[5] *A. Green* and *J. H. Boothe*, J. Amer. chem. Soc. *82*, 3950 (1960).

[6] The configuration of III is analogous to that reported by *S. Hirokawa, Y. Okaya, F. M. Lovell*, and *R. Pepinski* for aureomycin, Abstr. Amer. Cryst. Assoc. Meeting, Cornell University-July 1959, p. 44.

Addition of Ketones to Olefins

By Dr. A. Rieche, Dipl.-Chem. E. Gründemann, and Dr. Ernst Schmitz

Institut für Organische Chemie der Deutschen Akademie der Wissenschaften zu Berlin, Berlin-Adlershof (Germany)

We have found that acetone reacts with olefins to form the alkanone (I) via (II) and (III) when heated to 150 °C with a small amount of peroxide [1] such as, for example, di-t.-butyl peroxide or mesityl oxide peroxide [2]:

$$CH_3-CO-CH_3 \xrightarrow{\text{Peroxyde}} \underset{\text{II}}{\dot{C}H_2-CO-CH_3}$$

$$R-CH=CH_2 + (II) \rightarrow R-\underset{\text{III}}{\dot{C}H-CH_2-CH_2-CO-CH_3}$$

$$(III) + CH_3-CO-CH_3 \rightarrow R-\underset{\text{I}}{CH_2-CH_2-CO-CH_3} + (II) \rightarrow (Chain)$$

Besides the 1:1 addition, telomerization occurs:

$$(III) + R-CH=CH_2 \rightarrow R-\dot{C}H-CH_2-\underset{\displaystyle R}{\underset{|}{C}H}-CH_2-CH_2-CO-CH_3 \text{ etc.}$$

From this finding and earlier observations [3], we were able to expand the addition of ketones to olefins into a generally applicable reaction. Methyl ethyl ketone reacts at its α-methylene group. When acetone and ethylene react with di-t.-butyl peroxide, 54 % of pentan-2-one and higher alkanones of type (I) are obtained. Hex-1-ene gives nonan-2-one in 48 % yield, besides 2:1 and 3:1 products.

From dodecene we obtained pentadecan-2-one (b.p. 96 to 100 °C/0.1 mm., m.p. 38–41 °C) in 52 % yield. The methyl ester of 13-ketotetradecanoic acid (m.p. 38–40 °C; b.p. 190–196 °C/15 mm.) is formed in 40 % yield from methyl undecylenate. Methyl ethyl ketone and dec-1-ene gives 3-methyltridecan-2-one (b.p. 88 °C/0.2 mm.).

Received January 22, 1962 [Z 203/37 IE]

[1] *A. Rieche, E. Schmitz* and *E. Gründemann*, Angew. Chem. *73*, 621 (1961).

[2] *A. Rieche, E. Schmitz* and *E. Gründemann*, Chem. Ber. *93*, 2443 (1960).

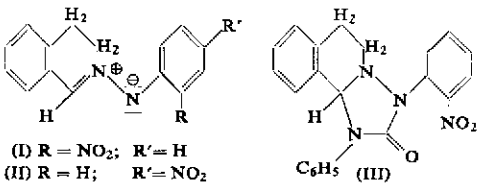
[3] *M. S. Kharash, J. Kuderna*, and *W. Nudenberg*, J. org. Chemistry *18*, 1225 (1953).

The Nitro Group as a 1,3-Dipole in Cycloadditions

By Dr. R. Grashey [1]

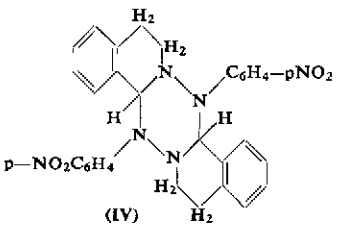
Institut für Organische Chemie der Universität München (Germany)

The reaction of azomethine imines of the 3,4-dihydroisoquinoline series with multiple bonds leads to five-membered heterocyclic rings [2]. Pyridine liberates the 1,3-dipole (I) from 2-(*o*-nitrophenylamino)-3,4-dihydroisoquinolinium bromide. Compound (I) combines quantitatively with phenyl isocyanate *in situ* to form the adduct (III). Whereas (II) dimerizes in the absence of dipolarophiles to form the yellow hexahydrotetrazine derivative (IV), (I) is converted in 86 % yield into a nearly colorless isomer which shows a carbonyl function in its infrared spectrum but no nitro group; its reducing capacity indicates an aldehyde.



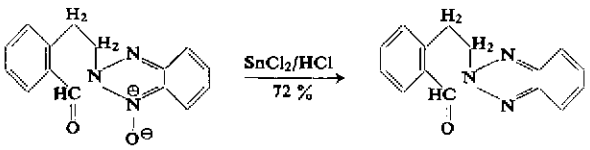
(I) R = NO_2; R' = H
(II) R = H; R' = NO_2

(III)

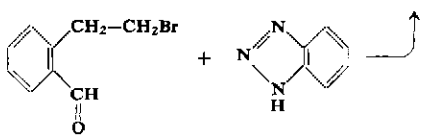


(IV)

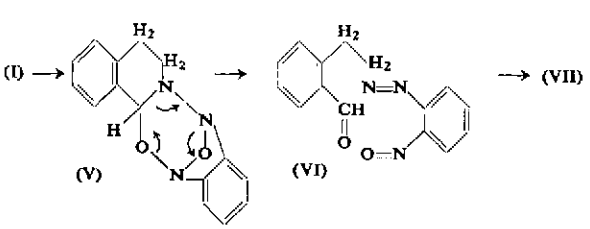
Formula (VII), which was deduced for this product from an assumption concerning the mechanism, was verified as follows: (a) the amino-oxide oxygen can be removed by reduction with stannous chloride and (b) compound VIII was synthesized independently by alkylation of benzotriazole with *o*-(β-bromoethyl)benzaldehyde in the presence of dicyclohexylethylamine. Because of its lower basicity, (VIII) can be separated from the *N*(1)-alkylated isomer which is also formed.



(VII) (VIII)



An intramolecular addition of the nitro group in the *o*-position as a 1,3-dipole [2] probably precedes the rearrangement. The formation of the intermediate (V) is followed by a cyclic electron displacement which leads to (VI); the interaction of the nitroso and azo groups then results in the formation of benzotriazole oxide (VII) [3].



(V) (VI)

Analogously, the nitro derivative of (VII) is obtained in almost quantitative yield by the thermal decomposition of 1-ethoxy-2-(2',4'-dinitrophenylamino)-1,2,3,4-tetrahydroisoquinoline and by the reaction of 2-(2',4'-dinitrophenylamino)-3,4-dihydroisoquinolinium bromide with a tertiary base at about 70 °C.

Received, January 26th, 1962 [Z 206/39 IE]

[1] Presented at the Südwestdeutsche Chemiedozenten-Tagung Munich, May 25–27th. 1961.

[2] *R. Huisgen, R. Grashey, P. Laur,* and *H. Leitermann,* Angew. Chem. *72,* 416 (1960); *R. Huisgen,* Naturwiss. Rundschau *14,* 43 (1961); *R. Huisgen,* Proc. chem. Soc. (London) 357 (1961).

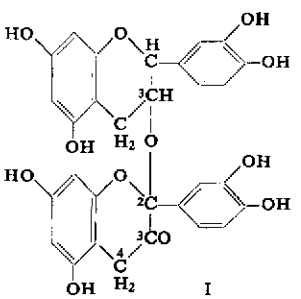
[3] *E. Bamberger* and *R. Hübner,* Ber. dtsch. chem. Ges. *35,* 3822 (1903).

Compound Proanthocyanidins

By Prof. Dr. K. Freudenberg and Dr. K. Weinges

Organisch-Chemisches Institut der Universität und Forschungsinstitut für die Chemie des Holzes und der Polysaccharide, Heidelberg (Germany)

Colorless proanthocyanidins [1] form anthocyanidins upon treatment with acid. Two new compound proanthocyanidins have been found in hawthorn berries (*Crataegus oxyacantha*) [2]. One of them is a combination of epicatechin with 2,3,4-cyanidanetriol; the other is a union of epicatechin with the precursor of another anthocyanidin, presumably delphidin [1]. A proanthocyanidin, which is decomposed by acids into (+)-catechin and cyanidin, has now been isolated from the fruit of *Gleditschia triacanthos.* Hydrolysis and acetylation indicate that the hydroxyl at C-2 of the keto-form of the pseudocyanidin has a ketal linkage with the hydroxyl at C-3 of the (+)-catechin (I).



I

In these three "compound proanthocyanidins", all of which are tannins, the pseudo forms (which in the free state seem to be labile) are stabilized through ketal linkages. A substance found in cacao beans by *W. G. C. Forsyth* and *J. B. Robertson* [3] probably belongs to this new group of natural compounds. The proanthocyanidins known so far are all flavan-3,4-diols; they exist in nature in greater variety than the corresponding anthocyanidins. It has not yet been proved that these proanthocyanidins are the precursors of natural anthocyanidins. In the new proanthocyanidins, however, the coloring components are already at the same level of oxidation as the anthocyanidins formed from them by the action of dilute acid. Anthocyanidins occur in nature only as glycosides – the anthocyans. If they are formed as described, then the last step must be a glycosidation. For other reasons, *H. Reznik* [4] also regards glycosidation as the last step.

Received, February 1st, 1962 [Z 211/45 IE]

[1] Nomenclature: *K. Freudenberg* and *K. Weinges,* Tetrahedron *8,* 336 (1960).

[2] *K. Freudenberg* and *K. Weinges,* Tetrahedron Letters No. 8, 267 (1961); *K. Weinges,* Chem. Ber. *94,* 3032 (1961).

[3] Chem. and Ind. 755 (1958).

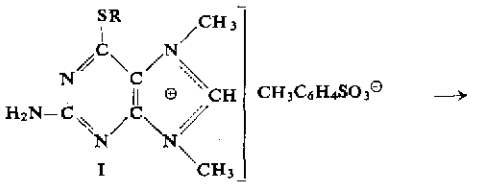
[4] Sitzber. Heidelberger Akad. Wiss., math.-naturwiss. Kl. Nr. 2, 125 (1956).

Synthesis of N,S-Betaines in the Purine Series

By Prof. Dr. H. Bredereck, H. Heise, Dr. O. Christmann and Dr. P. Schellenberg

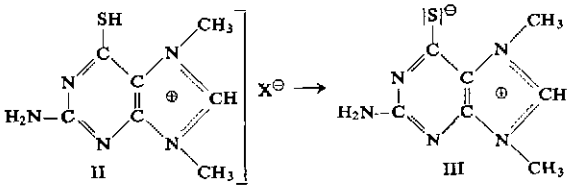
Institut für Organische Chemie und Organisch-Chemische Technologie der Technischen Hochschule Stuttgart (Germany)

Extending our work on xanthinium betaines [1] we aimed to synthesize the previously unknown *N,S*-betaines in the purine series. We prepared the 6-methylmercapto- and 6-benzylmercapto-2-amino-7,9-dimethylpurinium *p*-toluenesulfonates (I) from 6-mercapto- or 6-benzylmercaptoguanine, respectively, and methyl *p*-toluenesulfonate. The methylmercapto group can be replaced by chlorine in the presence of Cl_2, and the chlorine then exchanged for a mercapto group with thiourea, yielding 6-mercapto-2-amino-7,9-dimethylpurinium chloride (II; X = Cl). The benzyl group can be removed with aluminium bromide in toluene, thus forming in a single step the 6-mercapto-2-amino-7,9-dimethylpurinium bromide (II; X = Br). Treatment of the salts (chloride or bromide) with ammonia gave the *N,S*-betaine (III).



I

R = CH_3, $C_6H_5CH_2$



II

X = Cl, Br

Using the aluminum bromide method for splitting off the benzyl group, we obtained other betaines in a similar way, *viz.* the 6-thio-2-hydroxy-, and the 2-thio-6-hydroxy-7,9-dimethylpurinium betaines. The yields in all stages were good, without exception.

Treatment of 6-methylmercapto-2-amino-7,9-dimethylpurinium *p*-toluenesulfonate (I; R = CH_3) with hydrogen iodide in phenol or in a mixture of glacial acetic acid and acetic anhydride also splits off a methyl group.

Received, February 5th, 1962 [Z 210/43 IE]

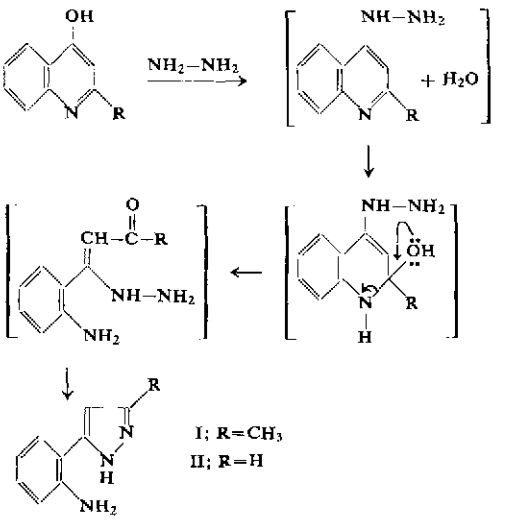
[1] *H. Bredereck, G. Kupsch,* and *H. Wieland,* Chem. Ber. *92,* 566 (1959); *H. Bredereck, O. Christmann* and *W. Koser,* Chem. Ber. *93,* 1206 (1960).

Pyrazolo[1,5-c]quinazoline: A New Heterocycle

By Dr. G. deStevens and Dr. H. M. Blatter

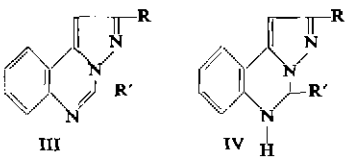
Chemical Research Division, CIBA Pharmaceutical Co., Summit, New Jersey (USA)

3-Methyl-5-(*o*-aminophenyl)pyrazole (I) can be prepared *via* a five-stage synthesis involving *o*-nitrobenzoyl chloride and acetoacetic ester [1]. Good yields of this compound, as well as the unmethylated derivative (II), are easily obtainable by means of a one-stage synthesis involving the hydrazine fission of 2-methyl-4-hydroxyquinoline and 4-hydroxyquinoline [2], respectively. A number of versatile intermediates for the preparation of a new class of heterocycles was made available by the latter route.



I; R=CH_3
II; R=H

We have found that compounds (I) and (II) readily condense with acid chlorides, acid anhydrides and orthoformates to form pyrazolo[1,5-c]quinazolines (III), while condensation with aldehydes and ketones gives rise to 1,2-dihydropyrazolo-[1,5-c]quinazolines (IV). The acid chloride condensation reaction was usually carried out in a dioxane solution con-



III IV

taining an equivalent amount of sodium hydroxide, whereas the aldehyde condensation was effected in refluxing ethyl alcohol. Some representative examples of (III) and (IV) are outlined in the following table [*].

	R	R′	Yield [%]	m.p. [°C]	λ_{max} [mμ] (ε)
III	CH_3	H	68	93–94	255 (37480) 317 (3760)
	H	H	78	83–84	255 (36090) 318 (3680)
	H	CH_3	70	91	253 (31580) 315 (4670)
	H	C_6H_5	72	125–127	255 (39760) 300 (8180)
IV	H	H	15	150	230 (28100) 327 (4355)
	H	$(CH_3)_2$	42	116	224 (19822) 318 (2787)
	H	C_6H_5	40	105–106	228 (25920) 328 (4480)

Acid and aldehyde condensations with other heterocyclic amino-amides and-imides leading to new tricyclic and tetracyclic systems are under investigation.

Received, February 22nd, 1962 [Z 42/IE]

[*] Further derivatives have also been prepared. These will be reported in a later publication.

[1] *E. Koenig* and *J. Freund,* Chem. Ber. *80,* 143 (1947).

[2] *G. Alberti,* Gazz. chim. ital. *87,* 772 (1957).

The Isolation of Substance P from Bovine Brain

By Dr. H. Zuber and Dr. R. Jaques

Forschungslaboratorien der CIBA Aktiengesellschaft, Pharmazeutische Abteilung, Basel (Switzerland)

Substance P [1], which exerts an effect on smooth muscle, and on blood pressure, was isolated on "Sephadex" and carboxymethyl-Sephadex in good yield.

Bovine brain (132 kg.) was extracted according to the method of *Pernow* [2,3]. Precipitation of the extract with ammonium sulfate gave 393 g. crude product (activity [4]: 100 to 150 $\mu g/cm^3$ T. D.). After extraction with acetic acid (residue: 273 g; activity 500 $\mu g/cm^3$ T. D.; soluble fraction: 80 g.; activity 500 $\mu g/cm^3$ T. D.) the active substance was precipitated with ether (39 g.; activity 10–15 $\mu g/cm^3$ T. D.). The precipitate, dissolved in 0.1 N acetic acid, was repeatedly fractionated on Sephadex G-25 [5] (combined active fractions: 3.0 g.; activity 1–2 $\mu g/cm^3$ T. D.). A further, approximately three-fold, enrichment (1.16 g.; activity 0.5–1.0 $\mu g/cm^3$ T. D.) was attained by adsorption of the basic portions of the Sephadex-fractions onto oxycellulose and elution with monochloroacetic acid. The mixture of basic substances (above all, basic polypeptides) was largely separated through repeated chromatography on Carboxymethyl-Sephadex (C-25) [5]:

Column I Starting material 900 mg., activity 0.5–1.0 $\mu g./cm.^3$ T.D.
Main fraction 20 mg. activity 0.03 $\mu g./cm.^3$ T.D.
Column II Main fraction 2.9 mg. activity 5–10 $ng./cm.^3$ T.D. [6]

Further purification was carried out by high-voltage electrophoresis at pH 9.5 (activity 3 ng/cm^3 T. D.).

Substance P, whose biological activity is destroyed by chymotrypsin, behaves during isolation as a basic polypeptide (R_f value = 0,5 in the thin layer chromatogram; silica gel; n-butanol/pyridine/acetic acid/water = 30:20:6:24). On high-voltage electrophoresis (pH 1.9; acetic acid/formic acid/water = 15:3:100) it migrates approximately as far as glutamic acid or serine, and at pH 9.5 (0.25 M triethylammonium carbonate buffer) it behaves in a similar manner to arginine.

Complete hydrolysis of the purified fraction with 6 N HCl gave the following amino acids: lysine, arginine, aspartic acid, threonine, serine, glutamic acid, proline, glycine, alanine, valine, isoleucine, leucine and phenylalanine. If non-peptide materials with typical Substance P activity are absent, and if all the amino acids belong to a single biologically active polypeptide, the calculated activity for this peptide (100 to 130 μg) is 0.5 ng/cm^3 T. D. (150,000–300,000 Euler units) [3,7].

The purest fraction possesses an activity (based on the amount of peptide material) of 0,5 ng/cm^3 T. D. on guinea pig ileum and hen caecum. In the case of rabbits 5 to 10 ng/cm^3 lowers the blood pressure by 11–13 mm. On isolated rat uterus, the threshold dose, even of highly purified fractions, is 50–100 times higher as on guinea pig ileum and hen caecum. In the mouse, highly purified fractions in amounts up to 100,000 units/kg. exhibit no protective effect against strychnine.

Received, February 23rd, 1962 [Z 219/44 IE]

[1] *U. S. v. Euler* and *J. H. Gaddum*, J. Physiology *72*, 74 (1931).

[2] *U. S. v. Euler*, Arch. exp. Pathol. Pharmakol. *181*, 181 (1936).

[3] *B. Pernow*, Acta physiol. scand. *29*, Suppl. 105, 1 (1953).

[4] Contraction of isolated guinea pig ileum in Tyrode's solution at 37 °C. Bath contents: 20 cm^3; atropine and pyribenzamine added: final concentration 2×10^{-8} g. each. T. D. = threshold dose/cm^3 bath liquid.

[5] Pharmacia, Uppsala, Sweden.

[6] 1 ng = 10^{-3} μg = 10^{-9} g.

[7] Since no standard preparation is available, it is not possible to give an accurate estimate in Euler units.

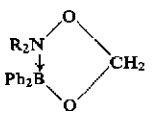
Dihydro-1,2,4,5-boradioxazole and Tetrahydro-1,2,4,6-boradioxazine [*]

By Doz. Dr. G. Zinner and W. Ritter

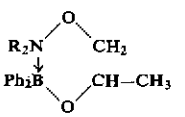
Institut für Pharmazeutische Chemie und Lebensmittelchemie der Universität Marburg (Germany)

The first representatives of the title compounds, botb new ring systems, were obtained by allowing the previously unreported *N*-substituted hydroxylaminoalcohols (I) and (II) to react with tetraphenyldiboroxide:

$R_2N-O-CH_2-OH$ (I) $R_2N-O-CH_2-CH(CH_3)-OH$ (II)



(III)



(IV)

Examples with R_2 = $-(CH_2)_5-$: *O*-Hydroxymethyl-*N,N*-pentamethylenehydroxylamine (I), b.p. 84 °C/12 mm; *O*-[2-hydroxypropyl]-*N,N*-pentamethylenehydroxylamine (II), m. p. 179–181 °C (CCl_4); 1,1-diphenyl-5,5-pentamethylenedihydro-1,2,4,5-boradioxazole (III), m.p. 166 °C (ethanol); 1,1-diphenyl-3-methyl-6,6-pentamethylenetetrahydro-1,2,5,6-boradioxazine (IV); m.p. 150 °C (ethanol).

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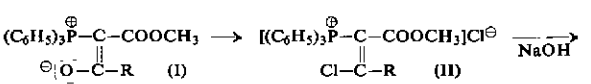
[*] 12th Communication on hydroxylamine derivatives; 11th communication; *G. Zinner*, Arch. Pharmaz. *294*, 765 (1961).

Alk-1-yne-1-carboxylic Acids: A New Synthesis

By Dr. G. Märkl

Chemisches Institut der Universität Würzburg (Germany)

The preparation of alk-1-yne-1-carboxylic acids (III) from the triphenylphosphine-acyl-methoxycarbonyl-methylenes (I) by means of an intramolecular Wittig reaction is known [1,2]. Our investigations have shown that compounds of type (III) are usually obtained in very good yields from (I) by conversion into the chlorinated ylides (II) by means of PCl_5 in $POCl_3$, or with Vilsmeier reagents [3], and subsequent alkali treatment without previous isolation.



(I) (II)



(III)

Procedure: (a) with $PCl_5/POCl_3$: (I), 10^{-2} moles, dissolved in a small quantity of $POCl_3$, is heated for 15 mins. at 80 °C with 12.5×10^{-3} moles PCl_5. The $POCl_3$ is taken off *in vacuo*, the residue taken up in $CHCl_3$ and washed several times with ice-cold water. After removal of the solvent, the product is heated to boiling for 20 mins. with methanolic sodium hydroxide soln.

(b) with dimethylformamide (DMF)/$POCl_3$ [4]: 5×10^{-3} moles (I) are added to a mixture of 2 ml DMF and 4 ml. $POCl_3$ (the mixture is prepared with cooling 30 mins. before use). After 20 hrs. standing at room temperature, the mixture is taken up in $CHCl_3$ and worked-up as described under (a);

(c) with DMF/$SOCl_2$ [4]: 5×10^{-3} moles (I) are allowed to react with 2 ml DMF in 4 ml. $POCl_3$ as described under (b);

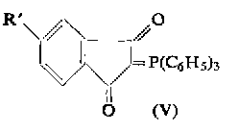
(d) with dimethylformamide hydrochloride $[(CH_3)_2N{=}\overset{\oplus}{C}HCl]\ Cl^{\ominus}$ (IV) [4]: 5×10^{-3} moles (I) are dissolved in a small amount of DMF, allowed to stand for 20 hrs. with 7.5×10^{-3} moles (IV), taken up in $CHCl_3$ and worked-up as described under (a).

The following alk-1-yne-1-carboxylic acids (III) were prepared:

R = phenyl-, m.p. 134–136 °C, yield 73 % (a)
R = *p*-tolyl, m.p. 148 °C, yield 94 % (a), 100 % (b), 100 % (c), 96 % (d)
R = *p*-ClC_6H_4-, m.p. 183–184 °C, yield 90 % (a)

R = *m*-NO_2–C_6H_4-, m.p. 141–142 °C, yield 94 % (a)
R = *m*-$CH_3OC_6H_4$-, m.p. 107 °C yield 39 % (a), 65 % (b), 93,5 % (c), 100 % (d)
R = α-naphthyl-, m.p. 138 °C, yield 10 % (a), 84 % (b), 87 % (c)
R = α-furyl-, m.p. 109–110 °C yield 48 % (a), 56 % (b)
R = methyl-, m.p. 74 °C, yield 17 % (a).

The reaction of (I; R = aryl-) with PCl_5 proceeds in $CHCl_3$ quite differently as in $POCl_3$. The very stable ylides (V) are



(V)

R′ = H-, dark-red crystals with greenish metallic lustre, m.p. 294–296 °C [5], λ_{max} = 508 mμ in benzene
R′ = CH_3-, dark red crystals, m.p. 268–270 °C, λ_{max} = 508 mμ.

formed in 20–40 % yields through intramolecular ring closure. If substituents with a +E-effect (*e.g.* $-OCH_3$) occur in *m*-position, then ring closure takes place even in $POCl_3$ (method a) as a secondary reaction with lowering of the yield of (III).

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[1] *S. T. D. Gough* and *S. Trippett*, Proc. chem. Soc. (London) 302 (1961).
[2] *G. Märkl*, Chem. Ber. *94*, 3005 (1961).
[3] The author thanks Prof. Dr. *S. Hünig* for this suggestion.
[4] *H. H. Bossard* and *H. Zollinger*, Helv. chim. Acta *42*, 1659 (1959).
[5] With the experimental collaboration of Dipl.-Chem. *H. Aman*.

CONFERENCE REPORTS

Meeting of Physicists in Vienna

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Isotope Shifts in Meteorites and the Early History of our Planetary System

W. Gentner, Heidelberg (Germany)

Stony meteorites, which are about twenty times more common than iron meteorites, consist in great measure of chondrites, small spherules the size of a pea, commonly composed of bronzite or olivine. Their origin is unknown. They seem to be drops of melt solidified in a special fashion. All kinds of transitional forms exist, from stony meteorites to pure iron meteorites (*e.g.* sideroliths and lithosiderites). The isotopic abundance of the elements occurring in the meteorites, especially those of the noble gases, deviate greatly from their isotopic abundances in terrestrial material. There are various reasons for this. Thus, the argon present in a meteorite sample can come from four sources:

1. ^{40}Ar arises from the decay of ^{40}K (half-life: 1.3×10^9 years)
2. The stable isotopes ^{36}Ar, ^{38}Ar, ^{40}Ar are formed by spallation through cosmic radiation from the stable iron isotopes.

The available values for neon are:

Atmospheric neon: $^{20}Ne:{}^{21}Ne:{}^{22}Ne = 90.9:0.3:8.8$
Spallation neon: $^{20}Ne:{}^{21}Ne:{}^{22}Ne = 30:34:36$

3. Chondrites contain more or less primal argon, that is, argon which was included by adsorption in the solidifying material during the formation of the protoplanets.

The values available for neon are:

Atmospheric neon: $^{20}Ne:{}^{22}Ne = 10.2$
Primal neon: $^{20}Ne:{}^{22}Ne = 13.0$ (Kapoeta meteor)

In answering the question of the age of the planetary system and the manner of its origin, it is important to determine the particle flux of the cosmic ultraradiation which is responsible for the creation of many radioactive and stable isotopes.

If we compare the ratio of the production rates for the isotopes ^{39}Ar and ^{36}Cl (half-lives: 320 years and 308000 years) in iron meteorites and an iron target bombarded with high-energy protons, we may conclude that the cosmic radiation has remained constant for the last 300000 years. When radioisotopes of still longer half-life are used, this span of time can be extended to 5×10^8 years with fair reliability and if we have data on the track of a meteor, we can follow its path in the planetary system. By further comparison of the rates of production of two isotopes – in the present case ^{37}Ar and ^{39}Ar – in a meteor and on the target of an accelerator, we again find agreement, so that we may conclude that in the planetary space there is no gradient of cosmic radiation. The method ordinarily used to determine age is the potassium argon method. By far the largest number of meteorites show an age of 4×10^9 years and 1×10^9. If we assume a rapid initial condensation, gas loss by outward diffusion may occur due to heating of the matter (passage close to the sun, collision with planetoids); *i.e.* the lower age of 1×10^9 years may be spurious. The irradiation age of meteorites can be determined by the quantity of spallation isotopes present. This is considerably smaller than the "radioactive age". Here stony meteorites and iron meteorites – probably because of differences in mechanical rigidity and in the penetration depth of the radiation – differ by a factor of 10 (stony meteors: *ca.* 25×10^6 years; iron meteors: *ca.* 250×10^6 years).

Information about the time gap between the end of element synthesis and the formation of meteorites would be available if we can interpret the substantial increase in the ^{129}Xe content of stony meteorites relative to the ^{129}Xe content of the air. ^{129}Xe is the end product of the decay of ^{129}I (half-life: 17×10^6 years). In a period following the general process of element synthesis, ^{129}I was formed. When the primitive components of the planetary masses at greater distances from the sun began to condense to the solid phase, ^{129}I must still have been present in considerable amounts, since otherwise we cannot explain such concentrations of the decay product ^{129}Xe in stony meteorites (the figure far exceeds the concentration of xenon in the atmosphere). A similar anomaly is shown by the isotope ^{109}Ag in iron meteorites. This is a product of the decay of ^{109}Pd with a half-life of 7.5×10^6 years. By extrapolation backwards, then, these results give us, for the time gap between element synthesis and meteorite formation (formation of solid matter), a value of *ca.* 5×10^7 years.

Experiments with a K-Ar Method for Determining Ages in the Range from 1×10^5 to 5×10^5 Years

H. J. Lippolt, Heidelberg (Germany)

The problem of adapting the K-Ar method for determination of small ages is bound up with the problem of developing a technique for measuring extremely small quantities of noble gases. An associated problem is that of finding suitable young minerals. It has been shown that biotite contains much atmospheric argon that cannot be driven out by heating without causing troublesome losses of radiogenic argon. Sanidines, however, contains amazingly little atmospheric

argon. Depending on the origin of such sanidines whether from bombs, tuffs, rocks, or sandinites – we must always reckon with the incorporation of considerable extra radiogenic argon during formation of the sample material. Only in a few cases can this be neglected. Every second sample from the Gunz glaciation and the Waal interglacial gave a useful age reading, and on this basis we conclude that the Milankovitch scale is not valid and that the Emiliani curve should be elongated slightly for the glacial periods.

Mass Spectrometers Studies of Potassium from Iron Meteorites

H. Voshage and *H. Hintenberger*, Mainz (Germany)

Since meteorites are exposed to the influence of cosmic radiation during their travel in interplanetary space, "cosmogenic" spallation products are formed from the substance of the meteorite by high-energy nuclear reations. Cosmogenic potassium, among other things, is formed in iron meteorites, where the 39, 40, and 41 isotopes are produced at rates related approximately by the ratio 0,7:0.6:1. Since iron meteorites contain extremely small quantities of primal potassium with a normal isotope ratio, a cosmogenic potassium concentration of about 10^{-9} to 10^{-11} g./g. could constitute a considerable portion of the total potassium concentration. Separation of these small quantities of potassium from a few grams of meteorite material with a yield of about 10 % was possible in high vacuum by fractional vaporization from the iron melt, where a portion of the potassium was freed in the form of positive ions and collected on a high-purity platinum wire with the aid of an electrical field. This platinum wire was used as a thermal surface ion source in the mass-spectrometric isotope frequency analysis of the separated potassium. Because of the natural radioactivity of ^{40}K, it is possible to calculate the time period of the influence of cosmic radiation on meteorites from the potassium mass spectrum (*e.g.* ^{39}K = 42.0 %, ^{40}K = 18.9 %, and ^{41}K = 39.1 % in a meteorite with an extremely low concentration of primal potassium). These "^{41}K–^{40}K radiation ages" lie between 200 and 1400 million years for the eleven meteorites investigated so far.

Light Sources for Spectral Analysis

H. vom Ende, *W. D. Hagenah*, and *K. Laqua*, Dortmund (Germany)

Rotating mirrors (speeds to 40000 rpm) and rapidly revolving discs (to 12000 rpm) were used to study the vapor clouds created from metal electrodes by spark discharges. By breaking down the spectrum (dispersion 10 Å/mm., light intensity 1:6) of the radiation of these vapor clouds, it was possible to make, from single sparks, serial photographs of 25 individual pictures, each exposed for 10 sec. in the light of single spectral lines or narrow spectral ranges. Results:

Vapor from the opposite electrode often may displace the vapor from the analysis electrode way from the spark path and thus reduce the sensitivity of the analysis.

Pulse discharges with constant pulse-current intensity achieved the sensitivity of alternating current break-away arcs of the same current intensity only after combustion periods of 1–5 msec.

The luminosity of the continuous background in the spectrum which has a decisive effect on the sensitivity limit, has a similar spatial distribution to that of the radiation of the analysis lines. Hence blocking out portions of the spark path usually offers no improvement in sensitivity.

The radiation of the so-called diffuse, weakly vaporizing discharge, which occurs especially in a noble gas atmosphere in conjunction with the normal, contracted, evaporating discharge, often disturbs the sensitivity of the analysis and shows a completely different spatial, temporal, and spectral distribution. A weak glow from vaporized electrode material can be observed evenly over the entire space between the electrodes while the discharge burns in the gas of the atmosphere.

Vapor Deposition of Iron by Electron Bombardment and Optical Constants of the Films Formed

Gundolf Meyer, Darmstadt (Germany)

In order to avoid impurities from the crucible or winding material, the iron rod to be vaporized is heated locally by electron bombardment, while its point of support or (the point at which it touches the holder) is kept much colder. By a suitable arrangement we get an Fe vapor source, the vaporization speed of which can be held constant with an accuracy of ± 2 % and which can be reproduced with the same accuracy. An apparatus having the following specifications has proved useful: diameter of the iron rod – 6 m.; spacing between heater winding and rod – 10 mm.; electron current – 120 mA; and accelerating voltage – 1.2 kV. With a distance of 7 cm. between the vapor source and the receiver, a condensation speed of about 1000 Å/min. is obtained.

Optical constants [$\bar{n}^2 = -(k^2-n^2)-2nki$] were determined by Drude's method for opaque layers produced in this way (thickness, 1000 Å). The wavelength of the light was 589 mμ. The optical constants of these layers, for which production conditions were kept constant, are quite reproducible and scatter values are less than 1 %. By means of optical measurements of the growing layer during the vaporization, it is possible to exclude erroneous measurements due to surface films. After the completion of condensation, surface films which might have formed by reaction with the residual gas in the vacuum chamber (pressure 10^{-6} mm. Hg) were on the average thinner than one atomic layer. With variations in the film thickness from 1000 to 9000 Å, the quantity 2nk decreased by a half, and k^2-n^2 remained constant. The cause of this change is still not known. On annealing a 1000 Å. layer, the optical constants in the range from 200 to 400 °C increase markedly with temperature. These changes may be ascribed to the healing of lattice defects.

High-Resolution Preservation of Electron-Optical Images by Polymerization of Organic Substances

L. Binkele and *H. Hamisch*, Berlin-Charlottenburg (Germany)

The change in the solubility of a varnish by electron bombardment may be used to fix the intensity distribution in the image plane of an electron-optical apparatus [1]. The varnish relief obtained is observed (with monochromatic light) in a reflected-light microscope, in order to utilize the lack of grain on the plate. By interference of the light reflected at the upper and lower surfaces of the varnish, differences in thickness of the varnish layer are observable as differences in intensity. In order to have a wide range of contrast, the reflected portions must, insofar as possible, be of the same magnitude. With the help of a thin layer of chromium (approximately equal to 40 Å) on the glass slide under the varnish layer, this was achieved to the extent that decreased contrast was now determined only by the light scatter of the microscope.

In order to obtain a varnish plate with high sensitivity, a small energy requirement for reticulation and a high molecular weight are desirable. High resolution, on the other hand, is obtained only with relatively small molecules which swell only slightly in the solvent. A systematic investigation of different varnishes showed that these requirements are best met through the use of higher unsaturated fatty acid glycerides. Varnish plates made with the dimeric glyceride of

[1] Physik. Verhandlg. *11*, 9 (1960).

eleostearic acid showed, in contrast with Alkydal V 631 previously employed, a decrease in the value of the image point work by some 2 orders of magnitude to 6×10^{-12} watt-seconds for 40 keV electrons. This value lies in the order of magnitude for standard photographic plates.

Up to now the rapid reticulation of the varnish in air has been an obstacle to the convenient use of this method. Addition of hydroquinone (1.5 %) provided stabilization for a short time. It would be desirable, however, to be able to store unexposed plates for at least a few weeks.

A New Electro-Optical Method and its Application

H. Nassenstein, Leverkusen (Germany)

In the electrochemical boundary layers of appropriate solutions, large variations in concentration and optical properties are found, especially in the refractive index. Hence, it is possible to consider the electrochemical boundary layer as an electro-optical element and use it as such. Experiments are reported in which electrochemical boundary layers were created in solubilized systems at a membrane through which current was passed. The changes in the refractive index in the boundary layer were so large (of the order of 0.1) that a convergent beam of light is completely reflected when it strikes the membrane at the proper angle. Depending on the electrical conditions, it is possible to create a sharp limiting edge of total reflection or even to have interference phenomena. A few typical experiments were shown in a motion picture film, as well as the prototype of a new image converter operating on this principle.

Gas Content and Luminescence of a Cavitation Bubble

(Model Tests with Glass Spheres)

Jörg Schmid, Gottingen (Germany)

The glow from vibrating cavitation bubbles (sonoluminescense) is usually considered to be due to thermal radiation from gases diffusing from the cavitated liquid into the bubble where it is heated during implosion by adiabiatic compression to the point of light emission. The temperature reached is determined by the quantity and specific heat of the gas in the bubble. Therefore, it is of interest to know the relationship between gas content and luminescence. Since the gas content of the bubble cannot be measured during ultrasonic cavitation model tests were undertaken with thin-walled glass spheres (Christmas tree balls). The spheres (about 7 cm. in diameter) were placed in a liquid, evacuated, filled with the appropriate gas, and then shattered. Luminescence occured in the last stage of implosion. Measurements were made in pharmaceutical grade glycerin (12 % water) and with different gases. Tests were also made in different liquids with air and krypton. The internal pressure of spheres that glowed well amounted to a few millimeters Hg. As the gas content increases, the radiation intensity of the light pulses generally drops off sharply. The width of the light pulses, which in the case of triatomic and polyatomic gases, as well as in the case of very low gas content in the spheres, lies below the limit of resolution of the oscilloscope (20 mμ sec.) and increases for monatomic and diatomic gases with increasing quantities of gas to values of the order of 10 μsec. (at 10–30 mm. Hg gas pressure). Since helium glows less than krypton, and hydrogen much less than air, it must be concluded that the specific heat is not the only factor governing the glow. Probably the ionization energy is a factor and, perhaps, chemical reactions during implosion (formation of molecules with low ionization energy) and losses due to the heat conductivity of the gas. Measurements in different liquids showed that the radiation intensity of the light pulses changes only slightly, but the width of the pulse under certain conditions is different. The measurements indicate that the vapor pressure of the liquid is a critical factor.

Growth and Properties of Thin Metal Threads ("Whiskers")

P. Svoboda, Vienna (Austria)

Cu and Ag whiskers have been produced by a reduction process from the metal halides. A crystal-rotation X-ray photograph of a helically grown whisker is worthy of note, because it shows an entirely normal monocrystal picture.

Since optical methods for determining the cross section of the whiskers are very inexact, and the results of electrical measurement are not satisfactory either, a new method has been developed in which the whisker was made to vibrate electromagnetically at its fundamental tone. From the frequencies observed with different tensions on the thread, the cross section can be calculated when the density of the material is known. The error of the method does not exceed 2 %.

An apparatus was constructed which makes possible the study of the effect of α-radiation on the resistance of the whisker at 90 °K. In analogy with tests on macroscopic samples and on neutron-irradiated Cu whiskers, we found an increase in resistance of the order of a few hundredths of μΩ cm. after 60–100 hours, using a Po preparation of about 35 mC. The hourly increase in resistance was smaller after a rather long test period than at the beginning.

An apparatus was built to determine stress-strain and flow curves. Here the force applied to the whisker was provided by the weight of a horizontal rod which was suspended at one end on the whisker and had another point of support beyond its center of gravity. The effect of the force on the thread was easily calculated from the geometry of the arrangement. A corresponding arrangement (roller under the rod) made it possible to change the position of the point of support and, therefore the load, without causing forces to appear in the longitudinal direction of the rod. The elongation of the whisker was measured with a micrometer.

While the stress-strain curves showed no special features, the flow tests were of interest because of a clear effect caused by α-radiation. In a number of Cu and Ag whiskers in which the tendency to flow under constant load below and above the yield point was always slight, a clearly defined elongation was immediately noticeable as the specimen was brought close. The velocity of flow at first increased, later declined, and after about 60 minutes the process ceased. The elongation amounted to between 0.4 and 1.2 %. Since in the case of larger crystals, the α-bombardment usually shows a strengthening effect, the explanation must lie in the special structure of the whisker.

Emission of Gas by Solids

R. Jaeckel, H. v. Münchhausen, and *F. J. Schittko*, Bonn (Germany)

Considering the conservation law for a quantity of gas pv in volume V:

$$\frac{d}{dt}(pV) = V\frac{dp}{dt} = S(p-p_0) - K(p)\times F_d$$

Time change of the quantity of gas in V | Quantity pumped out through conductor S with pressure difference $p-p_0$ | Gas emission from the surface Fd

$- L(p_a-p)$ Quantity flowing across L for $p_a > p$ | $+ A(p)\times F_a$ Adsorption on area Fa

neglected

two possibilities are evident for determining the gas loss K by means of pressure measurements and assuming that L and A can be neglected;

a) $S = 0$, measurement of $V\frac{dp}{dt} = -K(p)\times F$

b) S so small that $\frac{Vdp}{dt}$ can be neglected and $S(p-p_0) = k(p)F_\alpha$

Since during measurements, the total amount stored decreases over time t, we may expect that the gas loss K can be described by a law of the form $K = K_0 \exp(-t/t_0)$ or $K\, t^{\beta} = \text{const.}$

For most measurements the values obtained are: $^1/_2$, 1 and 2. In some cases an exponential decrease may also be observed. According to well-known principles, measuring the behavior of the gas loss with time may lead the investigator to the limiting physical process – desorption with and without dissociation or diffusion.

Experiment and theory agree well in most cases but measurements on silicone rubber are an exception. From the measured time curves a desorption process would be expected outtests with sliced samples showed from the very beginning of the test there is also considerable diffusion from the interior. In addition to measurements at room temperature, the temperature-dependence of the gas loss between 300 and 370 °K was investigated. In the pressure region from 10^{-3} to 10^{-6}/mm. Hg, these measurements showed a constant activation energy of about 10 kcal./mole for all samples studied. Since materials of such varying diffusion behavior as plastics and metals have the same activation energy for gas loss, we may conclude that, in the case of the measurements made in this range for the total gas loss, the desorption processes from the surface are limiting.

Reflection of Noble Gas Ions at Metal Surfaces and the Emission of Secondary Ions

V. Walther and *H. Hintenberger*, Mainz (Germany)

Noble gas ions were accelerated to velocities between 100 eV and 30 keV and focused by a lens into a small spot of high ion-current density on a heat-sensitive target. In order to measure the primary ion current, the target was replaced at will by a collector. The secondary ions emitted by bombardment of the target, and the ions reflected at the target, were analyzed in a parabolic spectrograph and the energy distribution determined. In addition, by use of collectors installed around the target, the angular distribution and the yield of ions emitted from the target were measured as a function of the primary energy.

The mass spectrum for the secondary ions consists of distinct mass points lying on a straight line parallel to the direction of magnetic deflection, *i.e.* the ions emitted from the target are predominantly monoenergetic. From their position in the spectrum we infer that they possess only a slight initial energy. Besides the ions of the target material, the mass spectrum contains to a greater or less degree the masses of surface impurities, varying with previous treatment and heating of the target. In addition, we observe reflected noble gas ions which blacken a parabolic area. The position, length, and intensity of the parabolic region depend on the ratio of the mass of the incident ions and the mass of the target atoms. The observed energies of the reflected ions were compared with those based on elastic or inelastic collisions with free target atoms.

Apparatus for Simultaneous Optical and Electrical Determination of the Radii of Aerosol Particles

H. Strauhel, Frankfurt/Main (Germany)

The radii of aerosol particles can be determined optically from light-scattering measurements. In this case, the direction of the maximum intensity of light dispersion depends on the ratio of the particle size to the wavelength of the light. Besides the particle radius, the refractive index and the absorption capacity of the particle play a role. Accumulation of gases on the particles can change the absorption.

A device was developed in which larger particles (up to 0.2 mm. in diameter) can be held fast by alternating electrical fields. The ratio of particle charge to mass can be determined independently by changing the alternating field or changing a superimposed constant field.

By simultaneous observation of the light-scattering intensity as well as the mass change of the particle under study in the presence of different gases, we measured the increase in mass, on the one hand, and the change in light-scattering, on the other.

Isothermal Compressibility of Amorphous and Partially Crystalline High Polymers between 20 and 250 °C

W. Knappe, Darmstadt (Germany)

The isothermal compressibility of polystyrene, polymethylmethacrylate and PVC without plasticizer, as well as high- and low-pressure polyethylene were measured at pressures to 2000 kg./cm.^{2} and temperatures up to 250 °C. A sudden change in compressibility was observed for the amorphous high polymers in the solidification region, and this change is displaced toward higher temperatures with increasing pressure. The results agree with the Ehrenfest equations for a phase transformation of the second order.

In the case of polyethylene, the isothermal compressibility passes a maximum in the melting range. The temperature of the melting material is displaced with increasing pressure toward higher temperatures in satisfactory agreement with the Clausius-Clapeyron equation.

A linear relationship was found between compressibility and density for polyethylene of different types and history, and for polyethylene-terephthalate at room temperature. By way of explanation based on the two-phase model, we find for the compressibility of the amorphous regions a value that approaches that of slightly vulcanized rubber. Correspondingly, we find for the perfectly crystalline polyethylene a value which corresponds approximately to that of long-chain solid paraffins. The two-phase model, therefore, provides a reasonable description of the experiments.

Determination of the Sequential Length Distribution in Tactic Polymers from their Nuclear Resonance Spectra

U. Johnsen, Darmstadt (Germany)

By measurement of the areas of the two methylene resonance triplets in the nuclear-spin resonance spectra of 20 % chlorobenzene solutions of PVC-preparations, the ratio of isotactic to syndiotactic linkages in the chains was determined as a function of the polymerization temperature. The preparations were polymerized in a 1:1 water-methanol mixture in the temperature range from 50 to −35 °C. With polymerizations at 35 °C, both linkages are equally probable and an atactic polymer is obtained. Above this temperature, the isotactic linkages predominate; below 35 °C the isotactic polymerization steps are supressed, while the syndiotactic ratio increases. From the temperature-dependence of the ratio of isotactic to syndiotactic polymerization steps, the difference in activation enthalpy for these two steps was found to be

$$\Delta(\Delta H) = 1750 \pm \text{cal./mole}$$

and the difference in the activation entropy to be

$$\Delta(\Delta S) = 5.6 \pm 0.2 \text{ cal./mole} \times \text{degree}$$

Electrical Properties of Thin Polymeric Benzene Layers and Deposited-Carbon Films

H. Pagnia, Darmstadt (Germany)

Thin polymerized layers were produced by glow discharge in an atmosphere of benzene at voltages between 1 and 9 kV and temperatures of the quartz glass carrier on the anode plate from 300 to 675 °K. Within these preparation limits, the specific electrical resistance of the films lies between 10^{10} and 10^{-2} ohm/cm. Thus, they agree in a range from about 1 to 10^{-2} ohms/cm. with the value of deposited-carbon films,

deposited from a carbon arc *in vacuo* at carrier temperatures between about 300 and 750 °K. Glow discharge polymerizates (of hexane and cyclohexane as well as benzene), which, when produced at small voltages (below 2–3 kV) still show the infrared spectral bands typical for the residues of the parent organic molecules, are practically the same and comparable with the samples produced directly from carbon, when produced at higher voltages *i.e.* they have no remaining characteristic bands in the spectral region from 2.5 to 15 μ. Such layers, which in practice can only be produced from carbon, nevertheless are strikingly different from graphitized samples in their electron diffraction diagram. In both types of films we find only very broad (001) and (hkO) rings (with orthohexagonal indexes). The grid constants are = 2.4 Å, and between 8.6 and 7.2 Å with increasing production temperature. Since no pyramid reflections were observed, the lattice elements of these layers could not have been elementary cells of graphite but only the carbon sextet ring of the basal plane of this unit cell.

Absorption Measurements on Aromatic Ethers in the Microwave Range

F. Hufnagel and *P. Knobloch*, Mainz (Germany)

The shape and position of the absorption curve, and, hence, the basic outlines of the relaxation spectrum, can be determined from dielectric absorption measurements on polar molecules measurements are made in the microwave range and are carried out with dilute solutions in benzene. Because of differing suggested models for the extremely short relaxation time of diphenyl ether [1,2], a further series of ethers was studied. According to these studies, biphenylyl phenyl ether, dinaphthyl ether, biphenylyl hydroquinolyl ether, and diphenyl resorcinolyl ether orient themselves with a mechanism having a speed similar to that of diphenyl ether itself, while diphenylmethane, (contrary to the results of *Smyth* in the pure liquid [2]) is apparently rigid. In the cases of benzyl phenyl ether, dibenzyl ether, and diphenyl carbonate, we also find a short-wave dispersion step of small amplitude. The intramolecular dipole mobility to be inferred from this can be ascribed to the flexibility of the molecules. Diphenylene oxide is rigid, but phenoxathiin has the extremely short relaxation time of 7 μμsec., which can only be explained by a folding process. Consideration of the results obtained for *ortho*- and *meta*-di(nitrophenyl) ethers, as well as for *ortho*- and *para*-pyridyl phenyl ethers leads to the conclusion that in some cases there a folding process is indicated and in others there is a reorientation of mesomeric moment components, so that even in the case of diphenyl ether itself neither of the two mechanisms can be assumed in advance to occur.

[VB 547/12 IE]

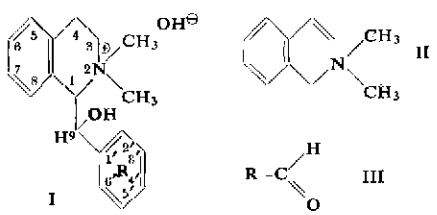
[1] *E. Fischer*, Z. Naturforsch. *9a*, 706 (1949).

[2] *D. M. Roberti, O. F. Kalman*, and *C. P. Smyth*, J. Amer. chem. Soc. *82*, 3523 (1960).

Mechanism of the Hofman Degradation of Tetrahydroisoquinolylphenylcarbinols

W. Wiegrebe, Braunschweig (Germany)

Quaternized tetrahydroisoquinolylphenylcarbinols (I) occur as alkaloid derivatives. They may be cleaved by means of a Hofmann degredation into N-containing and N-free products (I → II + III):



We have observed [1] an analogous cleavage [1,2] to that reported by *King* and *Ecuyer* [3] for 9-hydroxylaudanosine, a 6,7,3′,4′-tetramethoxy derivative of (I). Hofmann degredations were carried out with compounds of type (I) which were synthesized via phenylisoquinolylcarbin-9-ol [4].

The anomalous cleavage reaction can be explained as follows: An internal salt is formed as a result of nucleophilic attack of the OH^- of the quaternary base on the hydrogen atom of the OH-group at C-9. This structure rearranges by electron displacement yielding the preformed aldehyde and an ylide. The latter is converted by protonation and hydroxylation to a quaternary tetrahydroisoquinolinium compound that is not substituted at C-1 and which then splits off the vinyl base (II) by a normal Hofmann degredation. Under strongly alkaline conditions the aldehyde (III) undergoes a Cannizzaro reaction. The mechanism given for the rearrangement of compounds of type (I) also applies to derivatives carrying electronegative substituents.

[GDCh-Ortsverband Braunschweig (Germany), January 8, 1962]

[VB 559/11 IE]

[1] Taken from the *Ph. D. Thesis* of *W. Wiegrebe*, Technische Hochschule Braunschweig 1961; publication by *W. Awe* and *W. Wiegrebe* to follow.

[2] *R. Robinson* and *R. Mirza*, Nature (London) *166*, 271 (1950).

[3] *S. King* and *L. Ecuyer*, J. chem. Soc. (London) 427 (1937).

[4] *P. Dyson* and *D. Hammick*, J. chem. Soc. (London) 1724 (1937).

A Phosphatosilicate Capable of Swelling from Lungs Afflicted with Silicosis

Armin Weiss, Heidelberg

A silicate capable of intracrystalline swelling, which occurs in lungs afflicted with silicosis [1], has been isolated and studied more closely. The chain-type silicate has the formula

$$\underbrace{M^{+}_{1,45}(H_2O)_x}_{\text{Exchangeable cations and swelling water}}\underbrace{\left\{ Fe^{3+}_{0,90}\ Fe^{2+}_{1,10}(OH)\ (Si_{3,36}\ P_{0,64}\ O_{10}) \right\}^{1,45-}}_{\text{Phosphatosilicate anion}}$$

The compound is capable of one-dimensional intracrystalline swelling. This process appears to be influenced to a large extent by the partial replacement of silicon by phosphorus. No similar phosphate-containing silicates are known as minerals.

In animal experiments, the compound was formed from quartz within a few weeks, both after intratracheal or intraperitoneal application. The study of large dust cell sites indicates that the formation occurs only intracellularly.

A compound of this type deserves special interest because chemical reactions which do not occur in free solution under otherwise equal conditions can take place in the interior of such compounds, that is in the liquid layers which are only a few Å thick. Among these reactions are a protease effect, an oxidase effect, and the initiation of folding isomerism in proteins.

[Chemische Gesellschaft zu Heidelberg (Germany), January 9th. 1962]

[VB 558/13 IE]

[1] *A. Weiss*, Hoppe-Seylers Z. physiol. Chem. *324*, 153 (1961).

The Separation of Racemates by Gas Chromatography

G. Karagounis and *E. Lemperle*
Freiburg/Brsg. (Germany)

Gas chromatography was employed in order to eliminate the effect of solvent which, appears to oppose selective adsorption of the optical antipodes. Optically active solids [starch; saccharose; (+)-camphor-10-sulfonic acid, (+)-tris(ethylenediamine)cobalt(III) chloride] or liquids [(+)-ethyl tartrate; (+)isoamyl phthalate; hexamethyl-lactose; hexamethyl-saccharose] were used to cover the optically inactive support (Sterchamol, silica gel etc.).

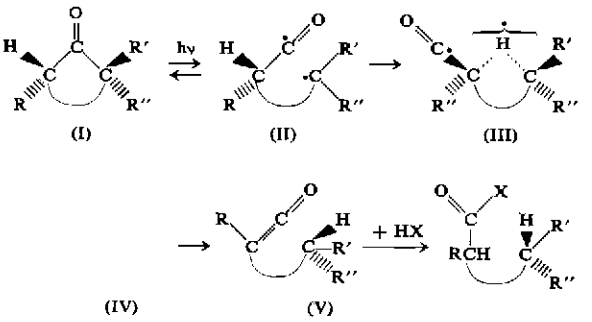
In eight cases [(±)-2-methoxybutane; (+)-1,2-dichlorohexafluorocyclobutane; (+)-methyl bromopropionate; (±)-2-methylbutan-1-ol, (±)-1-acetyl-1-hydroxyethane; (±)-s.-butanol; (±)-2-bromopentane; (±)-ethyl α-bromobutyrate] a clearly discernible splitting of the peaks was observed in the presence of an optically active stationary phase. The time differences between the maxima lie in the range 1–3 minutes so that preparative scale applications of the technique should be possible. A specially prepared rotameter must be employed as a detector, since it appears likely that the use of currently available detectors (heat conductance cells etc.) might induce racemisation. At any given gas-flow velocity through a rotameter, the position of the "swimmer" depends upon density and viscosity of the gas. On passage of organic vapours, the change in height can be used as a signal for the fraction cutter.

[GDCh-Ortsverband Freiburg (Germany), January 27th, 1962]
[VB 562/14 1E]

Photochemical Investigations on Non-Conjugated Ketones in Solution

G. Quinkert, Braunschweig (Germany)

The alkyl/acyl radical-pair (II), formed from the ketone (I) in the primary process of photolysis, undergoes an intramolecular homolytic hydrogen migration from the α-position of the acyl radical towards the alkyl radical (III). By this process both radicals disappear and the ketene (IV) is formed as the actual photochemical reaction product. The hydrogen migration takes place alongside a recombination process which does not result in structural changes. (If the carbonyl chromophore lies in close proximity to an asymmetric centre, photoepimerisation with change of configuration can occur). The band characteristic for the ketene group (2150 cm.$^{-1}$) appears in the infrared spectrum after brief irradiation; in the presence of substances which add to ketenes, this band vanishes. Irradiation in aqueous organic solvents leads to the acids (V; X = OH). Amides (V; X = $-NR_2$) are formed in the presence of primary or secondary amines.

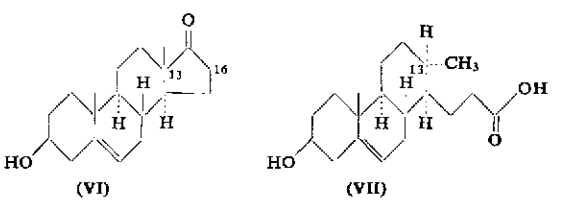


(I) (II) (III) (IV) (V)

No ketene formation takes place if neither of the carbon atoms adjacent to the carbonyl group carries a hydrogen atom.

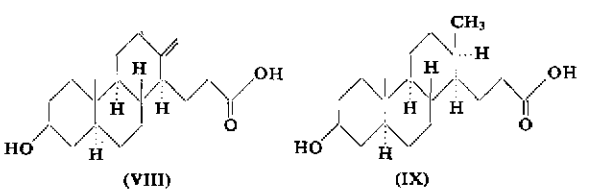
That the homolytic hydrogen migration proceeds via (III) follows from the experimentally detectable ring strain. In the presence of cyclohexylamine, irradiation of camphor yields the corresponding amide in less than 1 % yield; under the same conditions, the amide resulting from homocamphor is isolable in yields higher than 15 %.

The irradiation of Δ^5-androsten-3β-ol-17-one (VI), and its C-13-epimer, in aqueous organic solvents yields only (VII). The reaction is stereospecific and the hydrogen atom migrates from C-16 towards C-13 on the β-side. Proof for the α-configuration of the 13-CH_3 group in (VII) is adduced from the reduction of the exocyclic, isolated, double bond in the C-ring of compound (VIII) with lithium and ethylenediamine. This reduction leads to the thermodynamically more stable product. The catalytic hydrogenation of (VIII) results in the formation of the other epimer (IX).



(VI) (VII)

If the acyl radical of the alkyl/acyl radical-pair can stabilize itself by elimination of CO and the formation of a benzyl or allyl radical, then this radical decomposition is preferred and practically no acid is formed.



(VIII) (IX)

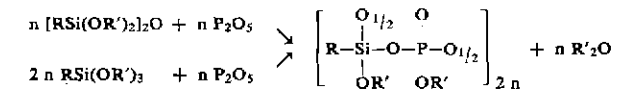
[GDCh-Ortsverband Berlin (Germany), January 29th, 1962]
[VB 567/15 1E]

SELECTED ABSTRACTS

Gaseous SNCl is formed by heating $N_3S_3Cl_3$ in high vacuum to 110 °C. It has a green-yellow color and possesses a band at 1330 cm^{-1} in the NaCl region of the infrared spectrum which is very similar to that of SNF. Upon hydrolysis with NaOH it yields Cl^- and NH_3 ions. SNCl polymerizes rapidly to $N_3S_3Cl_3$ at room temperature. It is also formed during the preparation of $N_3S_3Cl_3$ when Cl_2 is introduced into a solution of S_4N_4 in CCl_4. / Naturwissenschaften *48*, 620 (1961). – Ma. [Rd 973/7 1E]

For separate determination of pyridine and nitrile nitrogen in acrylonitrile-methylvinylpyridine copolymers, a sample is dissolved in a mixture of nitromethane and formic acid, and the pyridine-nitrogen titrated potentiometrically against a glass electrode in dioxane-$HClO_4$ solution. In order to determine the nitrile nitrogen, the sample is dissolved in conc. alcoholic KOH and heated. Ammonia liberated by saponification is taken up in HCl and back-titrated. *J. A. Emelin* et al. Zavod. Lab. (Moscow) *27*, 283 (1961 / –Gä. [Rd 53/31 1E]

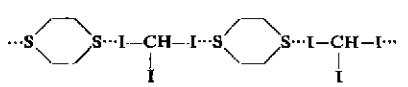
Several organoborosilicon and phosphorosilicon compounds, in which the vinyl groups are linked directly to a silicon atom, were reported by *A. P. Kreshkov, D. A. Karatejev,* and *W. Fjurst.* Vinyltriethoxysilane, divinyltetraethoxydisiloxane and methylvinyldiacetoxysilane were allowed to react with boric acid and phosphoric acid or P_2O_5, respectively:



(where R = $-CH-CH_2$ and R′ = $-C_2H_5$).

Special catalysts and high pressures were used. The structure of the reaction products was ascertained through infrared data. These products are said to improve heat and oil resistance when added to plastic materials and cement mortars (stability against pressure, freezing and moisture). / Zhurnal prikladnoi Khimii (J. applied Chem.) *34*, 2711 (1961). / –Bk.
[Rd 75/38 IE]

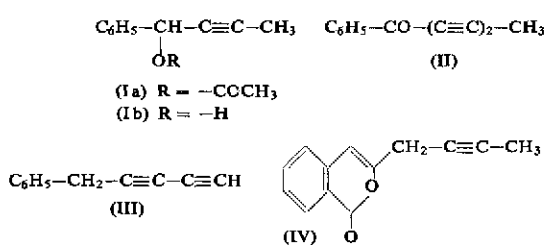
1,5-Dithian and idoform give a 1:1 addition product. It was synthesized by *T. Bjorvatten* and *O. Hassel* and elucidated by X-ray analysis (electron density projection). The colorless, needle-shaped crystals are monoclinic, a = 6.56 Å, b = 21.06 Å, c = 4.47 Å, β = 104.4°, Z = 2, space group P $2_1/m$. Two neighboring dithian molecules are connected by an iodoform bridge whereby two iodine atoms of CHI_3 form charge-transfer bonds with S-atoms. This is shown schematically:



The I-S distance of 3.32 Å is about 0.7 Å shorter than anticipated for a van der Waals bonding. / Acta chem. scand. *15*, 1429 (1961). / –Ko. [Rd 77/39 IE]

The polarographic determination of amino acids has been worked out by *M. Matsuoka* for threonine, serine, methionine, cystine, and cysteine. The method involves oxidation with potassium periodate. KIO_4 reacts with threonine and serine in a ratio of 1:1 (pH 9); with cystine the ratio is 2:1; with cysteine 3:2 (pH 7); and with methionine 1:1 (pH 4). Other amino acids do not interfere. / J. chem. Soc. Japan, Pure Chem. Sect. (Nippon Kagaku Zasshi) *82*, 1193 (1961). – De.
[Rd 966/3 IE]

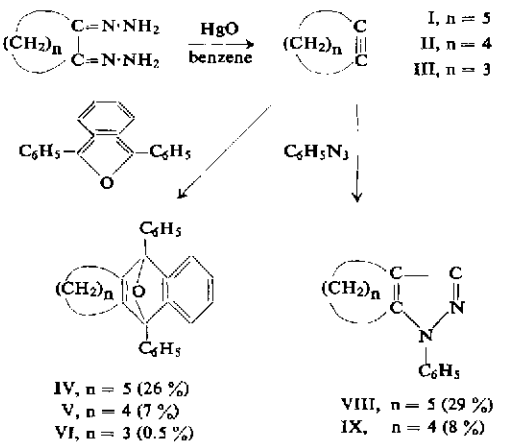
Three new poly(ynes) from plants. *F. Bohlmann* and *K. M. Kleine* have isolated three new poly(ynes) from the roots of *Chrysanthemum frutescens* L. and *Artemisia dracunculus* L. The main poly(yne) (Ia) was isolated from Chrysanthemum with a yield of 0.2 %. Compounds (Ib) and (II) occur in smaller amounts. The poly(yne)ketone (II) is identical with capillol, isolated from *Artemisia capillaris.* Compounds (III) and (IV) occur in the root extract of the wormwood *Artemisia dracunculus.* Compound (III) contains free acetylenic hydrogen. This is the first example of such a compound to be found in higher plants. / Chem. Ber. *95*, 39 (1962). / – R.



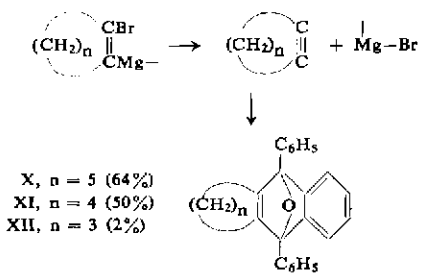
[Rd 72/43 IE]

Isolation and purification of penicillinase was successfully accomplished by *M. K. Muftic.* The enzyme was coprecipitated with benzoic acid from the culture filtrate of *Bacterium smegmatis* and purified by partitioning between n-butanol and water with subsequent precipitation with 2 N phosphoric acid. The enzyme is a white powder, soluble in buffer solutions between pH 6.8 and 7.8. The purity of the preparation was demonstrated by electrophoresis. The infrared spectrum indicates a piperazine structure in the molecule. With tert. ammonium phosphate, the enzyme precipitates as mixed crystals. / Experientia (Basel) *18*, 17 (1962). / –R.
[Rd 73/37 IE]

Cycloheptyne (I), cyclohexyne (II) and cyclopentyne (III) were prepared by *G. Wittig* and *A. Krebs* by oxidation of the bis-hydrazone of the corresponding cycloalkanedione with mercuric oxide. Cycloalkynes could not be isolated, but were trapped with 2,5-diphenyl-3,4-isobenzofuran or phenylazide, forming the addition products (IV to) (VIII):



G. Wittig and *R. Pohlke* also reported that these compounds can be obtained from the corresponding organo magnesium derivatives by splitting-off metal halides. 1,2-Dibromocycloalkenes with magnesium (in tetrahydrofuran) in the presence



of 2,5-diphenyl-3,4-isobenzfuran yield the addition products (X) to (XII), or their conversion products. / Chem. Ber. *94*, 3260 (1962). / –Sk. [Rd 79/42 IE]

The kinetics of hydrogenation of ethylene on nickel at high pressures were investigated by *G. M. Schwab, W. Schmatz,* and *H. Noller.* The measurements allow a choice to be made between the Rideal-Eley mechanism (hydrogen gas reacts with adsorbed ethylene) and the Langmuir-Hinshelwood mechanism (both ingredients react in a mixed adsorbed layer). If the last-named mechanism is correct, the reaction rate at a fixed partial pressure of hydrogen and constant temperature should pass through a maximum (assuming a fixed partial pressure of ethylene). No such maximum was, however, found at pressures up to 10 kg/cm² and temperatures ranging between 60 and 200 °C. The other interpretations of the experiments also support the Rideal-Eley mechanism. / Z. physik. Chem. NF *29*, 356 (1961). / –Ko. [Rd 4/21 IE]

The volatile phytoncides (preferably called phytons, and generally known in the U.S.A. as "higher plant antibiotics"), which the higher plants produce for protection have, in addition to their protistocidal, bactericidal, and fungicidal properties, a growth promoting effect (callus and sprout formation). *H. Schildknecht* and *G. Rauch* succeeded in identifying the active material, isolated from *Robinia pseudacacia*, as pure Δ^2-hexenal. Likewise, they were able to trace the antibiotic effect of oak, alder, lupine, black currant, whortleberry, cranberry, and privet to Δ^2-hexenal. Since in all investigated cases the antibiotic effect is due to the Δ^2-hexenal content, the theory that each leafy plant has its own specific antibiotic agent could not be proved. / Z. Naturforsch. *16b*, 422 (1961). / -Ho. [Rd 1/18 IE]

BOOK REVIEWS

Physikalische Grundlagen der Chemie-Ingenieur-Technik. (The Physical Basis of Chemical Engineering.) By *P. Grassmann*; Vol. 1 of the series Grundlagen der Chemischen Technik (Principles of Chemical Technology). H. R. Sauerlaender & Co., Aarau/Frankfurt (Main) 1961. 1st Ed., 944 pp., 403 fig., bound, DM 80.--. (*ca.* $ 20.--).

This long-needed textbook summarizes the physical principles underlying the chemical process industries.

Using many examples and original comments, the author gives a masterful presentation of the physical laws and their quantitative applications. This book not only enables the student to become familiar with equations but, above all, provides him with a more profound insight into their functional relationship. The fundamental principles presented in the text will serve as a basis for mechanical and process engineers, chemists, physical chemists and physicists in the guidance of their technological work.

The first three chapters deal with physical thermodynamics and kinetic phenomena. In the chapter "Mass and Energy Balances", the author endeavors to give a clear definition of the quantities and units of measure entering into the formulation of energy balances. "The Concept and Application of Entropy" first increases the reader's understanding of the second law of thermodynamics, and then further clarifies the concept of entropy with examples of application. Two examples of thermodynamic analysis, namely, evaporation of salt solutions and liquefaction of air, are particularly interesting. The "Probability Theory and Kinetic Theory of Gases" brings out, among other things, the general significance of statistics and the mathematics of probability in process technology. Problems in construction, of interest to the equipment designer, are found in chapter 4-"Strength of Materials". The important field of materials with large surfaces per unit weight and of finely divided substances is treated in another chapter. More than half of the book deals with flow and transfer phenomena. The principles and applications of flow theory are presented in two sections, which are followed by a section treating "Dimensional Analysis and the Theory of Models". Chapter 9 deals with the analogous momentum, heat and mass transfer phenomena which are related to irreversible thermodynamics. Multiphase flow phenomena, which are of great importance in many fields, are dealt with in chapter 10. Another section is concerned with rheological materials. In the "Summary", the author endeavors, using a few examples, to present a generalized view point with the object of increasing the coherence of the large variety of material presented.

The many references cited (the author index alone contains about 1200 entries) aid in locating the original literature necessary for the solution of special problems. This monograph is very well suited for self-study, as well as for advanced students and those engaged in the process industries; however it assumes a prior knowledge of introductory physics. Approximately 170 problems scattered throughout the text, with solutions given in a special appendix, facilitate self-instruction. The book is recommended to anyone connected with the chemical process industries. The printing is good, as is the presentation of the illustrative material. However, not every interested student will be able to afford the book, and it should therefore be made available in instutional libraries.

K. Hedden [BB 00553/6 IE]

Vitamins and Antivitamins, by *A. Pongratz*. Protoplasmatologia, Handbook of Protoplasm Research, edited by *L. V. Heilbrunn* and *F. Weber*. Vol. II, B2bβ: Published by Springer, Vienna (Austria) 1960. First edition. V, 98 pages. Paperbound DM 35. - (about $ 9.--).

This book is a carelessly compiled collection of abstracts from the older vitamin literature up to about 1954, with only a few references to more recent publications, even though the book was not published until 1960. There is, however, a complete coverage of the author's papers, even where they are of no great significance for the topic. Although the title of the book includes the word "antivitamins", terms like competitive and non-competitive inhibition are never mentioned. *F. Moewus*' data on the biological effects of isorhamnetin and its diglycoside are listed, although they have been disproved several years ago. There are some major errors to be found in the book; *e.g.* vitamin B_{12} is described as a nucleic acid molecule; thioctic acid is supposed to carboxylate α-keto acids by oxidation; in P-vitamins, the 6-hydroxyl is alleged to form ethers with different sugars. To characterize the style, I quote: "Chemical investigation of the structure was aided considerably by the typical form of the B_6-deficiency sickness in rats (B_6-Rattenmangelkrankheit)", or "The reported results concerning the structure and physiological effects of the B_{12} vitamins are based on an unparalled system of logic". After suffering through misprints, obsolete and illogical phrases, errors of fact, biased opinions, monstrosities in word and sentence construction, and much bad German, the reader comes to the following statement on the last page: "This magnificent wealth of ideas, brought about by the cooperation of many disciplines, can be viewed with pride by all mankind". In the opinion of this reviewer, such a statement certainly cannot be applied to the present book.

R. Tschesche [NB 827/71E]

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Isozymes and Heteroenzymes

BY PROF. DR. T. WIELAND AND PROF. DR. G. PFLEIDERER

INSTITUT FÜR ORGANISCHE CHEMIE UND BIOCHEMISCHE ABTEILUNG
UNIVERSITÄT FRANKFURT AM MAIN

"Heteroenzyme" is the term applied to proteins of different origin that differ in their physical, chemical, and biochemical properties, but have the same biological action. Enzymes that have the same origin, and consist of very similar, but distinguishable proteins have been named "isozymes" [*]; they may also be designated as "multiple forms."

Introduction

As a result of the surprising discovery made in the thirties that all the important coenzymes have the same structure regardless of biological origin, biochemists have come to feel that apoenzymes also are identical in structure. Thus, most have continued to speak of "an enzyme" in terms of a well-defined molecular species, as for example in the case of pepsin or catalase. Implicitly, it has been assumed that similar enzymatic properties are due to a similar, though perhaps not identical, structure.

As will be shown in the examples to follow, it has been demonstrated a number of times in recent years that enzymes of similar action, for which the terms "isodynamic" or "homotropic" have been proposed, may differ from one another either chemically or physically, depending on the type of tissue from which they originate. We shall designate such enzymes here as heteroenzymes. At the same time indications are increasing that an enzyme of the same origin may be heterogeneous, *i.e.* that it may consist of different molecular species; these we shall here designate as "multiple forms."

Heteroenzymes

Even today most biochemical handbooks list the important data concerning each enzyme under one category, regardless of its origin. Yet for many years now observations have been made, and attention been called to the fact, that enzymes of similar action but of different origins may be different. Thus, *E. Fischer*, who was probably the first to study the specific action of glycosidases, made the following comment in a footnote written at the end of the last century: "... the various maltases that undoubtedly exist should be termed corn, yeast, *etc.* maltases, depending on their origin" [1].

Nevertheless it was 50 years before *O. Warburg* was able to prove that yeast zymohexase (aldolase) differs from crystalline aldolase of animal origin. Only the former requires heavy metal ions as cofactor [2]. A similarly clear distinction was shown to exist between crystalline alcohol dehydrogenase isolated from horse liver [3] and from yeast [4]. In these instances the properties of enzymes were compared, even though they had been isolated from cells of very different origin. On the other hand, a chemical and biochemical study of enzymes with the same action isolated from the same organ of different species is of particular interest. In this connection attention is called to the fundamental studies of amylases conducted by *K. H. Meyer* and his coworkers [5-11].

[*] An International Commission on nomenclature is now engaged in discussing this concept.

[1] *E. Fischer*, Ber. dtsch. chem. Ges. *28*, 1429 (1895).
[2] *O. Warburg* and *W. Christian*, Biochem. Z. *314*, 149 (1943).
[3] *R. K. Bonnichsen*, Acta chem. scand. *4*, 715 (1950).
[4] *E. Racker*, J. biol. Chemistry *184*, 313 (1950); *E. Negelein* and *H. J. Wulff*, Biochem. Z. *293*, 351 (1937).
[5] *K. H. Meyer, Ed. H. Fischer*, and *P. Bernfeld*, Helv. chim. Acta *30*, 64 (1947); Experientia *3*, 106 (1947).
[6] *K. H. Meyer, Ed. H. Fischer, P. Bernfeld*, and *A. Staub*, Experientia *3*, 455 (1947).
[7] *K.H. Meyer, M. Fuld*, and *P. Bernfeld*, Experientia *3*, 411 (1947).
[8] *P. Bernfeld* and *H. Studer-Pecha*, Helv. chim. Acta *30*, 1904 (1947).
[9] *P. Bernfeld* and *M. Fuld*, Helv. chim. Acta *31*, 1420 (1948).
[10] *P. Bernfeld* and *M. Fuld*, Helv. chim. Acta *31*, 1423 (1948).
[11] *P. Bernfeld, F. Duckert*, and *Ed. H. Fischer*, Helv. chim. Acta *33*, 1064 (1950).

These authors found that crystalline α-amylase isolated from human saliva is identical with that isolated from the human pancreas, but differs significantly from that isolated from hog pancreas. These differences involve both physical and biochemical characteristics (cf. Table 1).

Table 1. Comparison of properties of α-amylase isolated from human and pig pancreas

	Human α-amylase	Hog amylase
Specific activity	1000	630
pH optimum	6.9	6.9
Region of stability	pH 4.5–11	pH 7–8.5
Solubility in H_2O at pH 8.0	0.5 %	4 %
Electrophoretic mobility at pH 10.14 [cm²/sec.]	3.75×10^{-5}	3.55×10^{-5}

At the same time *Bonnichsen* [12] observed that catalase isolated from horse liver can be differentiated immunologically from catalase derived from human liver, but that the catalases isolated from horse blood and liver must be identical. It thus appears that enzymes with the same action isolated from different organs of the same animal may be very similar, but not necessarily identical.

At about the same time, *Warburg*, wondering whether differences in enzymes exist on the basis of their organs of origin, *i.e.* whether enzymes have organ specificity, formulated the problem thus: "If the protoplasm of cells includes their enzymes, one would assume that enzymes of the same action originating in different organs of the same animal differ from one another" [13]. However, no difference was found between the lactate dehydrogenase derived from rat skeletal muscle and that obtained from a Jensen sarcoma [14]. *Pfleiderer* and *Jeckel* were the first to show that the lactate dehydrogenase obtained from rat skeletal muscle differs in many points from that derived from rat heart muscle [15]. To the best of our knowledge this is the first proof for the occurrence of heteroenzymes in the different organs of the same animal.

Multiple Forms of an Enzyme (Isozymes)

Whereas the description of an enzyme type is complicated by the occurrence of heteroenzymes, it becomes considerably more so as a result of the discovery that an enzyme of a single origin may occur in multiple forms. The first definite observation of this type was made by *Neilands* [16] who demonstrated that a previously reported protein component [17] of crystalline beef heart lactate dehydrogenase [*] constituted a second LDH species. These components were designated as A and C (Fig. 1). Shortly thereafter *Krebs* [18] reported that yeast contains four proteins, each with its characteristic migration when subjected to electrophoresis and all four

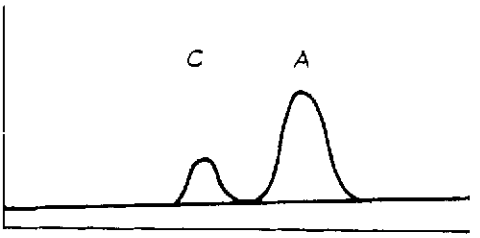


Fig. 1. Schlieren diagram: crystalline LDH from beef heart following electrophoretic separation. Phosphate buffer (pH 5.7); ionic strength: 0.1; descending.
From *J. B. Neilands*, Science (Washington) *115*, 144 (1952).

of which exhibit glyceraldehyde phosphate dehydrogenase activity. Fractional precipitation with nucleic acid allowed fairly complete separation of these four proteins. Using starch block electrophoresis *Vesell* and *Bearn* [19] separated human serum and demonstrated LDH activity in three separate components. At the same time the authors of the present review initiated a study "on the differences of lactate dehydrogenases" [20], previous electrophoretic studies having revealed several proteins with LDH activity derived from a variety of organ extracts [21].

By now the number of reports like this has grown to a point where a special conference held under the auspices of the New York Academy of Sciences was organized to deal with the subject of multiple forms of enzymes [22] and the question of nomenclature has become real. The term "isozymes" has been proposed [23] for enzymes that have the same action, *i.e.*, are isodynamic, and are derived from the same organ, but have different physical and chemical properties.

Differentiation and Separation of Isozymes and Heteroenzymes

Enzymes may be characterized by biochemical, physical, chemical, and immunological methods. The enzyme should be available in maximum purity, preferably in crystalline form.

Biochemical criteria are as follows: (a) turnover number, *i.e.* the number of moles of substrate that react per mole enzyme per minute; (b) optimum pH and (c) substrate and coenzyme affinity, expressed by the Michaelis constant, K_m, *i.e.* the concentration of substrate in moles/liter required for half saturation of the enzyme. Other criteria include the temperature coefficient and the extent to which various substances can interfere with the reaction. Also of importance is the use of

[12] *R. K. Bonnichsen*, Arch. Biochem. Biophysics *12*, 83 (1947).
[13] *O. Warburg:* Wasserstoffübertragende Fermente. Verlag Dr. Werner Sänger G.m.b.H., Berlin 1948, p. 54.
[14] *F. Kubowitz* and *P. Ott*, Biochem. Z. *314*, 94 (1934).
[15] *G. Pfleiderer* and *D. Jeckel*, Biochem. Z. *329*, 371 (1957).
[16] *J. B. Neilands*, Science (Washington) *115*, 143 (1952); J. biol. Chemistry *199*, 373 (1952).
[17] *A. Meister*, J. biol. Chemistry *184*, 117 (1950).
[*] The abbreviation used in this paper is LDH.
[18] *E. G. Krebs*, J. biol. Chemistry *200*, 471 (1953).
[19] *F. S. Vesell* and *A. G. Bearn*, Proc. Soc. exp. Biol. Med. *94*, 96 (1957).
[20] *Th. Wieland* and *G. Pfleiderer*, Biochem. Z. *329*, 112 (1957).
[21] *Th. Wieland* and *G. Pfleiderer*, Angew. Chem. *69*, 199 (1957).
[22] Report, Angew. Chem. *73*, 246 (1961); Ann. N.Y. Acad. Sci. *94*, 655 (1961).
[23] *C. L. Markert* and *Moller*, Proc. nat. Acad. Sci. USA *45*, 753 (1959).

modified coenzymes, as employed by *Kaplan*, for example, in his study of DPN-dependent dehydrogenases [*]. He determined the ratio of $v_{DPN} : v_{DPN(ana)}$ in a reaction catalyzed by the apoenzyme, when its coenzyme is either DPN or a DPN analog (abbreviated as DPN(ana)). If this ratio is the same for two apoenzymes, they are very probably identical. Differences in this ratio, on the other hand, indicate differences in the apoenzyme structure [24].

The following physical methods are available: determination of molecular weight by the ultracentrifuge; light scattering: diffusion or osmometry; determination of solubility and preparation of a salting-out diagram; ultraviolet absorption; potentiometric titration of acidic and basic groups; determination of the isoelectric point and of the electrophoretic mobility; rate of migration on ion-exchange columns or uncharged adsorbers such as calcium phosphate; rotational dispersion; X-ray crystallography.

Chemical determinations can be carried out and data may be obtained concerning: terminal amino groups; functional groups (NH_2, OH, SS, SH, etc.); type and number of component groups (*e.g.* amino acids, coenzyme, heavy metals); primary structure (sequential analysis); oligopeptide mixtures obtained by proteolysis followed by two-dimensional paper chromatography and/or electrophoresis (finger-print technique) [25, 26].

Immunological tests are particularly sensitive for differentiating or identifying two proteins. In principle, an animal is sensitized with one of the enzymes and its serum antibodies are allowed to react with the other enzyme under study. If the two enzymes are identical, they must require the same amount of anti-serum for inactivation; the enzymes differ if quantitative differences arise in this test or, occasionally, if one enzyme does not give rise to any antigen-antibody reaction. As is true of all biological tests, immunological techniques are not as quantitative and reproducible with respect to the detecting of minor differences as generally wished for.

Questions of Definition

When multiple enzyme forms are being studied there is the constant danger that artifacts may result in the course of tissue preparation and purification. Thus, it proved possible to decompose animal cytochrome c, which is a relatively low-molecular weight protein, into several components of varying specific activity by passing it through chromatographic columns containing cationic exchangers. On the other hand, the uniform, purified enzymes could be transformed into a mixture of multiple forms by the use of denaturing reagents. As a result, the occurrence of multiple forms was traced to the extraction with aqueous trichloroacetic acid in the course of the preparation of cytochrome [27]. Such artifacts cannot be included in the term "isozyme."

But where, then, is the difference between artifact and natural product? According to *Trayser* and *Colowick* [28] yeast contains several hexokinases. These can be prepared in two crystalline groups, A and B, depending on the method employed for chromatographic separation on DEAE cellulose. In the presence of glucose, trypsin converts enzyme A into enzyme B. A similar increase in the proportion of B with respect to A can be obtained by extracting yeast for 24 instead of the usual 3 hours. Nevertheless, there is a tendency to label components A and B as isozymes of hexokinase, even though upon further careful chromatography, they can be split into even more components.

Difficulties also arise when an attempt is made to apply the terms "multiple form" or "heteroenzyme" to enzymes with a wide region of specificity. For example, esterases from a single organ that can be differentiated according to the criteria enumerated above, may still be termed multiple forms so long as they are tested by means of a universal substrate. Only detailed consideration of the specificity leads to the recognition that the enzymes involved have different functions, *e.g.* that one is a lipase, the other an acetylcholine esterase, etc. The same is true for proteinases and most phosphatases. It is, therefore, only possible to speak of different forms of an enzyme with certainty when its physiological role and specificity are known thoroughly. The specificity with respect to the coenzyme must also be included. For this reason, for example, the two liver isocitric acid dehydrogenases are not considered as multiple forms, since one requires DPN, whereas the other requires TPN [29].

Differences between Heteroenzymes

Inasmuch as, in principle, all organisms are capable of deriving energy in the same fashion (glycolysis, citric acid cycle), it is reasonable to suppose that each cell has at its disposal similarly acting enzymes. It is not surprising, therefore, that heteroenzymes exhibit marked differences in their amino acid composition and also in other properties. An example is the phosphoglucose isomerase obtained from yeast and the bovine mammary gland [30], the molecular weight of the former being 145000, in contrast to a molecular weight of 48000 for the latter.

On the other hand, it seems surprising that heteroenzymes of very different origin exhibit similar properties. For example, the amino acid composition of glyceraldehyde phosphate dehydrogenase obtained from yeast and mammalian muscle is quite similar [31]. Chemical differences in the α-amylases derived from *Aspergillus oryzae*, *B. subtilis*, pig pancreas and human saliva have been studied by *Stein*, *Junge*, and *Fischer* [32].

Even though all four enzymes have approximately the same molecular weight (50000), the same prosthetic

[*] The abbreviations DPN and DPNH refer to diphosphopyridine nucleotide, and the reduced form, respectively.

[24] *N. O. Kaplan, M. M. Ciotti, M. Hamolsky*, and *R. E. Bieber*, Science (Washington) *131*, 392 (1960).

[25] *Th. Wieland*, Angew. Chem. *71*, 417 (1959).

[26] *H. Tuppy*, Naturwissenschaften *46*, 35 (1959).

[27] *E. Margoliash* and *J. Lustgarten*, Ann. N.Y. Acad. Sci. *94*, 731 (1961).

[28] *K. A. Trayser* and *S. P. Collowick*, Arch. Biochem. Biophysics *94*, 177 (1961).

[29] *A. Kornberg* and *W. Pricer*, J. biol. Chemistry *189*, 123 (1951).

[30] *A. Balch, R. G. Wolfe*, and *F. J. Reithel*, J. biol. Chemistry *235*, 3130 (1960).

[31] *S. F. Velick* and *S. Udenfriend*, J. biol. Chemistry *203*, 575 [1953].

[32] *E. A. Stein, J. M. Junge*, and *E. H. Fischer*, J. biol. Chemistry *235*, 371 (1960).

group (calcium ion) and a similar turnover number, their primary structures are quite different. The chemical difference between enzymes derived from man and hog is as great as that between enzymes from *B. subtilis* and *A. oryzae* (see Table 2).

Table 2. Composition of α-amylases of different origin. (The numbers indicate the number of amino acid molecules per 100000 g protein.)

	α-Amylase from			
	Aspergillus oryzae	*Bacillus subtilis*	Hog pancreas	Human saliva
Lysine	33	51	34	43
Arginine	17	35	33	50
Histidine	12	25	25	21
Aspartic acid + glutamic acid	174	197	180	210
Amide thereof	99	103	94	96
Alanine	66	60	77	50
Cysteine	17	–	19	36
Glycine	75	80	89	91
Isoleucine	48	35	–	44
Leucine	58	47	88	44
Methionine	14	10	14	16
Phenylalanine	25	37	61	44
Proline	37	29	31	31
Serine	58	49	39	74
Threonine	71	47	33	38
Tyrosine	60	49	29	30
Valine	52	51	67	59
Total	836	833	852	916

Frequently, however the differences between heteroenzymes are less obvious. Just as the insulins derived from beef, hog, sheep, horse, and whale differ among each other only in terms of three amino acids between the cysteine residues 7 and 11 of the A chain [26], so the hemopeptides of cytochrome C differ from one another only in a surprisingly small degree, in spite of very different origin [26, 33].

Chromatographic analysis of cytochrome c has shown that its composition is nearly the same, whether extracted from horse heart, whale heart or yeast, but that cytochrome c obtained from *Desulfovibrio desulfuricans* differs materially from all other cytochromes [34]. Recently *Anfinsen* et al. have published comparative studies on the composition of ribonucleases derived from various sources. They report only minor differences between ribonucleases obtained from pig or beef pancreas, but appreciable differences between the latter and those obtained from sheep pancreas [35, 36]. These differences were discovered by means of the fingerprint technique referred to above (Fig. 2).

Using this technique, *Ingram* was able to distinguish between normal human hemoglobin A and the abnormal forms C and S, which are only slightly different from the former. Of the 300 amino acid residues found in one molecule, one glutamic acid residue in hemoglobin A is replaced by a lysine molecule in hemoglobin C, and by valine in hemoglobin S [37, 38].

Similarly, beef, sheep, and pig trypsins, which are quite similar in many respects, differ from one another only in their electrophoretic behavior and in their stability in alkaline medium. At pH 4.8 the pig enzyme migrates

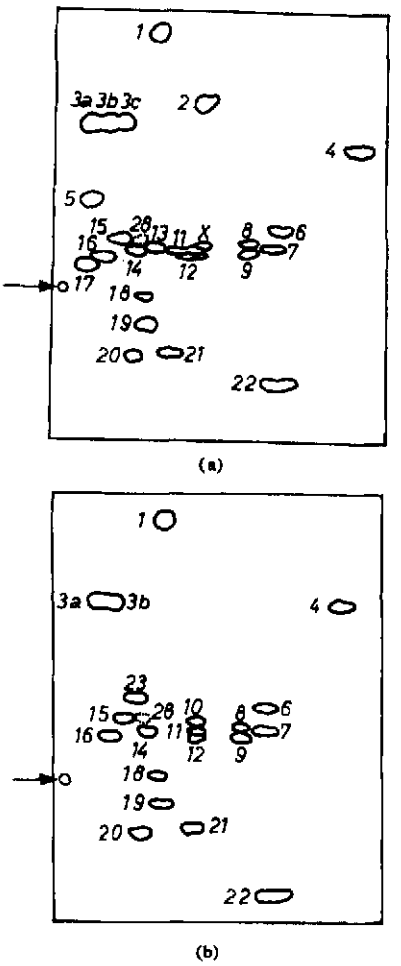


Fig. 2. Two-dimensional chromatographic separation of the products obtained when trypsin and chymotrypsin are allowed to act on oxidized pancreatic ribonuclease. (a) Enzyme derived from beef; (b) Enzyme derived from sheep. Paper chromatography from left to right (origin indicated by an arrow in the left margin). Paper electrophoresis from top (cathode) to bottom (anode).
Anfinsen et al., J. biol. Chemistry *234*, 1118 (1959).

more slowly and is more stable with respect to alkali, than either the more rapidly migrating sheep enzyme or the most rapidly migrating beef enzyme [39]. Our own early studies of LDH dealt with the same problem. We were able to observe differences in electrophoretic mobility between LDH from beef and hog hearts, and between LDH from rabbit and rat skeletal muscles [15]. We were able to cleave these enzymes by means of trypsin and to compare the resulting peptides by means of high-voltage electrophoresis [40]. Small, but clear-cut differences were observed. Amino acid analyses, carried out by Dr. *Weber* in the laboratory of Professor

[33] *J. I. Harris, F. Sanger,* and *M. A. Naughton,* Arch. Biochem. Biophysics *65*, 427 (1956).

[34] *K. Takahashi, K. Titani,* and *S. Minakani,* Biochemistry (Tokyo) *46*, 1323 (1959).

[35] *C. B. Anfinsen, S. E. G. Aqvist, J. P. Cooke,* and *B. Jönsson,* J. biol. Chemistry *234*, 1118 (1959).

[36] *A. M. Katz, J. Dreyer,* and *C. B. Anfinsen,* J. biol. Chemistry *234*, 2897 (1959).

[37] *V. M. Ingram,* Nature (London) *180*, 326 (1957).

[38] *V. M. Ingram,* Lecture, Fourth International Congress of Biochemistry, Vienna 1958.

[39] *A. J. Vithayathil, F. Buck, M. Bier,* and *F. F. Nord,* Arch. Biochem. Biophysics *92*, 532 (1961).

[40] *Th. Wieland, G. Pfleiderer,* and *K. Rajewsky,* Z. Naturforsch. *15b*, 434 (1960).

Brenner in Basle [41], showed that the differences could be attributed to differences in the primary structure. Table 3 lists the differences between LDH obtained from beef and pig heart and from rabbit and rat muscle.

Table 3. Composition of LDH of different origin (Amino acid molecules per 130000 g.protein)

	LDH from						
	Heart muscle				Skeletal muscle		
	Hog (2 det.)		Beef (2 compon.) [16]		Rat (2 extreme values of 4 det.)		Rabbit
	1	2	A	C			
Lysine	87	86	97–98	98	99	103	98
Arginine	28	32	34	36	38	38	35
Histidine	25	27	27–28	28	21	23	37
Aspartic acid	125	125	126–127	125	117	119	108
Glutamic acid	115	116	120	117–118	104	106	106
Alanine	70	70	74	74	71	73	76
Glycine	87	87	91	93	90	91	94
Isoleucine	76	80	79	80	83	87	79
Leucine	128	125	135	134	130	134	130
Methionine	30	33	34–35	31–32	25	26	32
Phenylalanine	19	21	19–20	21	25	26	26
Proline	45	47	43	45	44	47	38
Serine	86	92	90	88	88	94	74
Threonine	55	57	53	52	42	43	41
Tyrosine	25	27	27	27	25	26	26
Valine	139	132	131	132	130	132	126

At first sight, the distribution of all residues seems similar in all four products. This distribution is perhaps characteristic for the "LDH" property of these enzymes. The content of some amino acids, like alanine, isoleucine, tyrosine and cysteine, which were determined in up to 14 residues by a different method in most, but not all, instances, was surprisingly constant. Other residues, notably lysine, aspartic acid, glutamic acid and threonine, occur in the various enzymes in clearly different amounts. Generally speaking the enzymes obtained from the heart muscle of different animals are more like each other than those from skeletal muscle which in turn are similar. The greater mobility of pig heart LDH at pH 8.6 with respect to the anode can be attributed to a lower content of cationic, and a higher content of anionic, residues. Lactate dehydrogenases obtained from skeletal muscle contain fewer anionic side chains and therefore tend to remain behind when subjected to electrophoresis.

Our analytical comparison also included crystalline LDH obtained from different organs of the same animal. LDH derived from rat liver and rat muscle were indistinguishable by electrophoresis, but differed from one another significantly, although only moderately, in their leucine and valine content. The muscle preparation contained, on the average, 3–5 more moles per mole of enzyme than the liver preparation. Differences due to organs of origin are much more clear-cut in the case of LDH derived from rat skeletal muscle and rat heart (Band I). As shown in Table 4, these differences involve all amino acids. In this case as well, the divergence in electrophoretic behavior can be explained by different charges. Heart LDH No. I, which migrates rapidly to the anode, contains much more aspartic acid and less lysine and arginine than the other, electrophoretically less mobile, LDH's derived from liver and skeletal muscle. The pronounced organ specificities

[41] *Th. Wieland* and *G. Pfleiderer*, Ann. N.Y. Acad. Sci. *94*, 691 (1961). Several of the amino acid analyses reported herein were slightly but not significantly different when repeated with more highly purified forms of LDH.

Table 4. Composition of LDH derived from liver, skeletal muscle, and heart muscle of the rat. (Amino acid molecules per 130000 g. protein).

	Rat LDH from				
	Liver (2 extremes of 4 deter.)		Skeletal muscle (2 extreme values of 4 deter.)		Heart (Band I, cf. p. 174)
Lysine	98	100	99	103	95
Arginine	37	40	38	38	34–35
Histidine	23	25	21	23	26
Aspartic acid	113	117	117	119	141
Glutamic acid	106	110	104	106	108–109
Alanine	74	79	71	73	81
Glycine	90	95	90	91	89
Isoleucine	79	82	83	87	83
Leucine	124	129	130	134	130
Methionine	25	26	25	26	33
Phenylalanine	28	30	25	26	21
Proline	48	51	44	47	40
Serine	86	91	88	94	92
Threonine	44	47	42	43	53
Tyrosine	26	27	25	26	27
Valine	116	124	130	132	134

observed here were also confirmed by immunological studies. The antibody produced by the chicken against the rabbit skeletal enzyme, inactivated the rabbit heart enzyme much less than its antigen (*i.e.* the muscle enzyme) [42].

Finally, some reference should be made to the two malate dehydrogenases which occur in the same cell in beef heart and rat liver, but originate in different regions of the cell. A distinction can be drawn between mitochondrial and cytoplasmic malate dehydrogenase[43-45]. This can best be done by electrophoresis on a suitable membrane where, at pH 8.6, the cytoplasmic dehydrogenase migrates to the anode more rapidly than the mitochondrial [46]. The difference seems to be due to the fact that the latter also has a lipoid component. On treatment with n-butanol, one enzyme can be transformed into the other [47]. The question now arises whether in this, so far unique, case the term "heteroenzyme forms" should be applied because the precise intracellular localization is known, or whether they should be designated as "multiple forms," since both enzymes occur in the same cell type.

Differences Between Multiple Forms of an Enzyme (Isozymes)

The most important discoveries with regard to multiple enzyme forms have been described in the preceding sections from a historical point of view. More recently similar observations have been made on many other enzymes, but these cannot be discussed here. The following observations are restricted to examples where multi-

[42] *J. S. Nisselbaum* and *O. Bodansky*, J. biol. Chemistry *234*, 3276 (1959).

[43] *G. S. Christie* and *J. D. Judah*, Proc. Roy. Soc. (London) *141*, 420 (1953).

[44] *A. Delbrück*, *H. Schlmassek*, *K. Bartsch*, and *Th. Bücher*, Biochem. Z. *331*, 297 (1959).

[45] *C. J. R. Thorne*, Biochim. biophysica Acta *42*, 175 (1960).

[46] *Th. Wieland*, *G. Pfleiderer*, *I. Haupt*, and *W. Wörner*, Biochem. Z. *332*, 1 (1959).

[47] *A. J. Sophianopoulos* and *C. S. Vestling*, Biochim. biophysica Acta *45*, 400 (1960).

ple forms have been clearly separated, or where they may have been located by visual tests or even studied in isolated form. In most cases electrophoresis has been the method of choice, particularly zone electrophoresis. It has generally been customary to designate those multiple forms of an enzyme which migrate most rapidly to the anode as I, the next slower ones as II, III, *etc.*

A distinction must be made as to whether the aim is analysis or micropreparation. For the former, paper electrophoresis is most suited. Of decisive significance in this connection was the development of methods by which the separated enzymes could be made visible. Thus, for DPN-dependent enzymes a very sensitive spray test was developed which is based on the disappearance of DPNH fluorescence [21]. Many other enzyme reactions can be coupled with reactions of DPN-specific enzymes, so that the technique has fairly wide application. In the case of redox reactions, identification by means of tetrazolium salts can be very useful; on reduction, strongly colored formazanes are formed [48, 49]. Other enzymes can be detected by means of histochemical procedures. *Hunter* and *Markert* [50] have used the latter to detect enzymes on starch gel electropherograms ("zymograms"). *Vieme* [51] has developed a spectrophotometric method for the detection *in situ* of enzymes. This author allowed the substrate and coenzyme of LDH to react with the separated enzymes on agar and then followed the reactions optically.

One of the disadvantages of paper electrophoresis is that the separated bands of the multiple enzymes cannot be determined quantitatively on the paper nor can they be isolated from the paper without losses. However, elution can be quantitative in the case of synthetic membranes which, in addition, permit an excellent and rapid separation of the LDH components at high voltages (Fig. 3). With this technique 0.01 ml. tissue extract can be separated in about 1 hour by applying

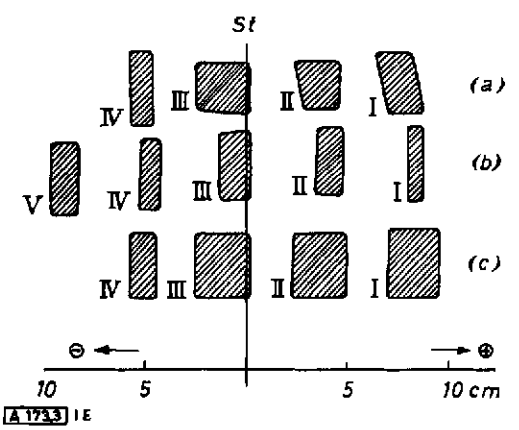


Fig. 3. Electropherogram of purified lactate dehydrogenase from rat: (a) brain, (b) kidney, and (c) heart. Membrane filter; 0.065 M-Veronal buffer, pH 8.6; 30 v/cm.; 90 mins. St. = starting line.
Wieland et al., Biochem. Z. 331, 103 (1959).

about 40 volt/cm. to a filter saturated with Veronal buffer; the separated LDH enzymes can be detected by spraying with a combined coenzyme and substrate solution using a pressure-type sprayer with suitable metal orifice; the enzymes appear as sharp, dark bands and can be eluted directly into cuvettes after the filter sheet has been cut into strips.

The micropreparative electrophoresis technique employs either starch gel (*Smithies* [52]), a starch slurry in a block [53] or a column [54]. When a gel technique is used, it is best to isolate the enzymes by forcing out the previously frozen segment by means of a hypodermic syringe. When working with a starch slurry, the enzymes are allowed to migrate into glass powder [55].

Ion exchange chromatography is also suitable for the separation of multiple forms of enzymes. As early as 1953, *Stein* and *Moore* [56] succeeded in separating a crystalline ribonuclease preparation into two active forms by means of Amberlite IRC-50. Cellulose-type exchangers are more useful in the case of especially sensitive proteins; a good example is diethylaminoethylcellulose, DEAE [57]. According to *Hess* [58] LDH isozymes derived from different organs can be separated on such a cellulose column by means of fractional elution with buffers of varying pH and NaCl content.

On the basis of our collaborative work with *H. Determann* and *F. Ortanderl* we have found that better results are obtained by using DEAE Sephadex exchanger, which has a much higher capacity. Figure 4 shows the separation of a uniformly crystalline rat heart enzyme into

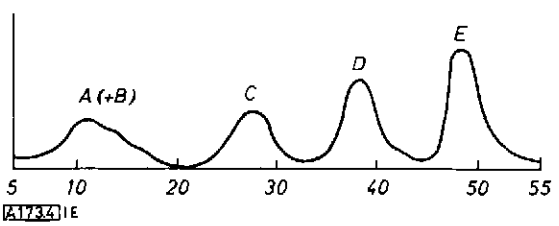


Fig. 4. Chromatographic separation of isozyme from crystalline rat heart LDH by means of DEAE Sephadex. Elution with 0.05 N phosphate buffer (pH 6) in NaCl up to 0.5 M. Component E is the last to appear in the eluate.
Ordinate: Deflection of the recorder in the flow photometer (Uvicord)
Abscissa: Fraction number.

four components. Elution was carried out with a phosphate buffer (pH 6) with increasing NaCl concentration. In accordance with the order of appearance in the eluate, the separate multiple forms obtained on chromatography are designated as A, B, C, etc. This last procedure appears the most suitable for the analytical and preparative separation of multiple enzyme forms.

[48] *R. Kuhn* and *D. Jerchel*, Ber. dtsch.chem. Ges. *74*, 949 (1941).

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[58] *B. Hess* and *S. I. Walter*, Klin. Wschr. *38*, 1080 (1960).

Lactate Dehydrogenases (LDH)

Lactate dehydrogenases have been studied in detail. As early as 1956 we reported five different LDH components isolated from various organs of the rat by means of paper electrophoresis [21]. Subsequently we succeeded in establishing heterogeneity in other enzymes from animals and man [46, 59]. These studies soon led to several questions:

1. Do all organs contain the same number of LDH isozymes?
2. Is the distribution of total activity with respect to the individual components the same in all organs?
3. What are the chemical and physical differences?
4. Is the primary structure of electrophoretically similar lactate dehydrogenases derived from different organs the same?

The answer to the first question is related to the state of development of the analytical technique. Formerly we considered the pig heart LDH as one of the few lactate dehydrogenases which occur in the organ as a single-component enzyme. However, when electrophoresis was carried out on synthetic membranes, a second component was found, even if the preparation was crystalline; this second component amounted to only 1 % of the total. The situation was similar for the LDH from rat skeletal muscle. This enzyme was formerly considered as a pure substance, though quite different from heart muscle LDH. We now know that both LDH preparations contain five isozymes, four of which however contain only a fraction of the total activity present (I–IV). Nevertheless, it is reasonable to assume that the number of LDH components is not the same in all organs of an animal.

Concerning the second question, it may be said that large differences exist in the enzyme distribution patterns of various organs. Table 5 lists the quantities (as percentages) of isozymes in the organs of the rat and of man. As can be seen, there exist undoubtedly two types of distribution in organs, with most of the activity in man or mammal occurring in either the first or the last isozyme. Studies on the age dependence of this distribution have shown that this polarization of distribution does not occur in man while the organs are still in the embryonic stage; rather all multiple forms show a similar distribution with the main emphasis on component II [60]. These differences between the embryonic and the adult stages were also observed in other mammals [23, 61].

Table 5. Distribution of the average activity of LDH components in various organs from man and the rat

	Man (Enzyme no.)				
Organ	I	II	III	IV	V
Heart muscle	60	30	5	3	2
Kidney	28	34	21	11	6
Cerebrum	28	32	19	16	5
Cerebellum	39	34	20	7	–
Erythrocytes	36	35	9	–	–
Liver	0.2	0.8	1	4	94
Skeletal muscle	3	4	7	10	76
Epidermis	0	0	4	17	79
	Rat				
Heart muscle	34	43	15	5	2
Kidney	36	27	7	9	20
Brain	25	23	18	24	10
Skeletal muscle	0.5	1	1.5	3	94
Liver	0	0	0	3	97

[59] *I. Haupt* and *H. Giersberg*, Naturwissenschaften *45*, 268 (1958).

In organs of adults the patterns of distribution are quite constant and characteristic. Heart muscle and liver are extremes. Normally the blood serum contains only a minimal amount of LDH activity, which originates from the rapidly migrating LDH forms of the erythrocytes. If, however, heart muscle or liver has become damaged, the corresponding isozyme will occur in the blood serum in considerably increased amounts. Their analysis may therefore provide a useful diagnostic test [61a]. According to *Hess* and *Walter* [62] it is possible to completely adsorb onto DEAE cellulose (anion exchanger) the heart LDH (I) occuring in blood as a result of a coronary infarct, whereas the liver LDH, freed as a result of hepatitis, cannot be adsorbed by stirring with the anion exchanger [62].

With reference to the third question it may be stated that differences between the isozymes of LDH were first observed in the course of electrophoretic studies. They are therefore the certain result of different net charges of the protein molecule. Moreover, in proteins migrating with different speeds, relationships have been established between electrophoretic behavior and other properties. Thus, in the case of isolated isozymes obtained from rat kidney, the effect of sulfite in inhibiting reactions increases as the negative charges on the proteins increase in number [20]. For example, Band I may, under certain conditions, be inhibited by as much as 80 %, whereas Band V, under the same conditions, may be inhibited by no more than 50 %. This means that the affinity of coenzyme and sulfite for enzyme I is greater than for enzyme V. It was shown subsequently that Bands II to

Table 6. Relationship between electrophoretic mobility and other physical or chemical properties of the five multiple forms of mammalian lactate dehydrogenase

	LDH				
	V	IV	III	II	I
Migration to anode, pH = 8.6 [cm]	0	2	4	6	8
Sulfite inhibition [%]	31–37	42–48	47–53	62–78	69–75
Heat stability (half-time of denaturation at 50 °C) [min.]	3	10	40	ca. 100	nearly ∞
Optimal pyruvate concentration [mole/l.]	$1.2 \cdot 10^{-3}$ ⟶				$0.15 \cdot 10^{-3}$
Increase in reaction rate with 10 °C increase	1.5 ⟶				2.1

[60] *G. Pfleiderer* and *E. D. Wachsmuth*, Biochem. Z. *334*, 185 (1961).

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[61a] For complete description: *F. W. Schmidt* et al. in *H. U. Bergmeyer:* Methoden der enzymatischen Analyse. Verlag Chemie, Weinheim/Bergstr. 1962.

[62] *B. Hess* and *S. I. Walter*, Klin. Wschr. *39*, 213 (1961).

IV, which migrate at intermediate speeds, also have intermediate sensitivity to sulfite [63]. Table 6 reproduces this relationship. At the same time it was observed that other properties of the enzyme also undergo change to the same extent [64, 65]. Thus, the optimum pyruvate concentration for I as compared to V drops by a factor of ten (*i.e.* from 1.2×10^{-3} M to 1.5×10^{-4} M); the temperature coefficient increases uniformly from 1.5 for V to 2.1 for I. The differences are particularly large as far as the heat stability of various proteins is concerned: The half-time value for denaturation at 55 °C amounts to practically infinity for I, 100 mins. for II, 40 mins. for III, 10 mins. for IV, and 3 mins. for V. Perhaps the relationship between such diverse physical data may ultimately provide a deeper insight into the mechanisms of adsorption and reaction with substrate and coenzyme.

The differences in charge between isozymes may be due to the fact that the more rapidly migrating protein contains fewer side chains, perhaps because of acylation of a part of the ε-amino groups of lysine; or they may contain more carboxylate side-chains than the more slowly migrating proteins, where some carboxyl groups have been neutralized by amide formation. Of the several examples of this type attention is called to two mushroom poisons, α- and β-amanitine [66]. The difference in charge may also be due to chemically bound phosphate, sulfate or other polycharged residues.

According to our analyses, differences in phosphate content can be ruled out. Differences in mobility in the electrical field may also be due to differences in heavy metal content. On the other hand, the differences in structures may be much more profound and may go as far as differences in amino acid composition, *i.e.* differences in the primary structure. A clear-cut answer can be given only on the basis of the chemical analysis of components, a procedure so far carried out for only a few compounds. A comparison was made with the LDH isozymes I–III obtained from rat heart by means of preparative starch electrophoresis, or chromatography on DEAE Sephadex. Differences in composition then became more evident. The pronounced drop in aspartic acid content from I to III might explain why these compounds differ in their rate of migration in an electric field (Table 7). On the other hand, no difference is apparent between LDH I and II from beef heart (cf. values in Table 3). As for the molecular weights, no differences were observed in the preparations so far studied. Moreover, the observation that many isozyme mixtures precipitate uniformly in the ultracentrifuge would also seem to suggest a uniform molecular weight. The situation is similar as far as the fourth question is concerned. The only fact that is certain is that the LDH isozymes V from all rat organs behave in the same fashion upon electrophoresis and that they are inhibited by sulfite to the same extent. Notwithstanding this, the LDH isozymes V obtained from skeletal muscle and liver are not identical (cf. Table 4). Comparisons of other isozymes from different organs have not yet been made but are being planned, now that convenient and effective methods for chromatographic separation with DEAE Sephadex are at hand.

Table 7. Composition of lactate dehydrogenases I–III from rat heart. Values in amino acid molecules per 130000 g. protein

	LDH Components		
	I	II	III
Lysine	95	96	94–95
Arginine	34–35	36	40
Histidine	26	25	25–26
Aspartic acid	141	136	130
Glutamic acid	108–109	109	111
Alanine	81	79	81
Glycine	89	89	93
Isoleucine	83	85	83
Leucine	130	131	129
Methionine	33	32	29
Phenylalanine	21	22	26
Proline	40	45	46
Serine	92	87	89
Threonine	52–53	50	49
Tyrosine	27	26	27
Valine	134	134	131

Multiple Forms of Other Enzymes

In recent years the number of times that multiple forms of other enzymes have been reported has risen considerably. In some instances several bands were observed following electrophoretic separation; however, these were neither isolated nor characterized further. We shall now consider some examples where detailed studies have brought to light new points of view.

Among animal enzyme studies mention should be made of a thorough investigation dealing with the heterogeneity of tissue dehydrogenases in the rat. Following zone electrophoresis in starch gel, the strips were incubated in solutions that contained the specific substrate, a tetrazolium salt, methylene blue and the specific pyridine nucleotide. Direct staining led to the identification of the isozymes of lactate, malate, isocitrate, glucose-6-phosphate and α-glycerophosphate dehydrogenases, each of which gave rise to a different number of bands depending on the organ of origin [67].

A recent observation made on pancreatic ribonuclease, the heterogeneity of which has already been referred to, indicates a closer relationship of these isozymes: *Dickman, Morell,* and *Trupin* [68], working with mice and beef pancreas, chromatographed their material on Amberlite IRC-50 and obtained three components when the glands were extracted either with sucrose or phosphate solutions. The two original isozymes were ob-

[63] *Th. Wieland, G. Pfleiderer,* and *F. Ortanderl,* Biochem. Z. *331,* 103 (1959).

[64] *P. W. G. Plagemann, K. F. Gregory,* and *F. Wroblewski,* J. biol. Chemistry *235,* 2288 (1960).

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[68] *S. R. Dickman, G. A. Morrill,* and *K. M. Trupin,* J. biol. Chemistry *235,* 169 (1960).

served when extraction was carried out with 0.25 M sulfuric acid. It turned out that the additional naturally occurring components, which can be obtained by chromatography, were transformed into the other two components by treatment with sulfuric acid; at the same time total activity was enhanced; this suggested the properties of a zymogen or of a ribonuclease modified by an inhibitor.

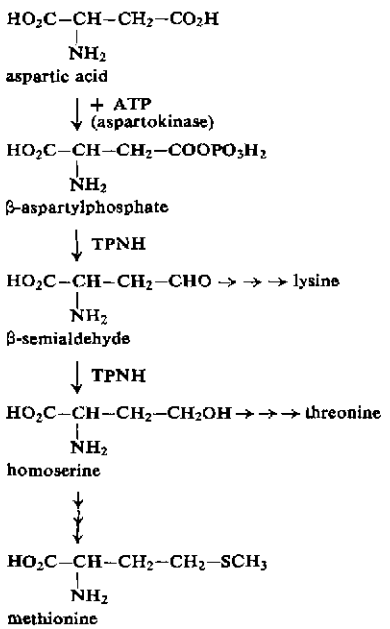
According to *Meister* et al. [69] the crystalline l-amino acid oxidase isolated from snake venom (*Crotalus adamanteus*) consists of two components of equal sedimentation velocity and equal specific activity which can be separated electrophoretically. When pooled venom was worked up, an additional component of equal effectiveness was observed. This indicates quite clearly that comparisons are best carried out with material obtained from the same starting material. The ideal procedure would be to study the products of genetically uniform cells propagated *in vitro*, but present methods of culture do not yet allow this.

Clearer results are obtained from studies with unicellular organimss, as shown below. As early as 1937 *Malmström* [70], using zone electrophoresis and ion exchange chromatography, isolated four proteins with enolase activity from yeast. Similar studies were carried out in our laboratory in recent years. Thus, *Wörner* [71] was able to demonstrate the existence of, and quantitatively determine, five enolase isozymes isolated from brewer's yeast by means of electrophoresis on synthetic membranes. Uniform strains isolated from single-cell culture yielded the same number of enolase components, but with different activity distributions. This contrasts with baker's yeast which contains only a single enolase-like protein component.

Similarly the multiplicity of hexokinases from yeast, described in the very impressive, previously cited studies of *Trayser* and *Colowick* [28], is preserved in uniform single-cell cultures.

In recent years the occurrence of multiple forms of different enzymes has been reported in bacteria, particularly for *E. coli*. Thus, at least two threonine deaminases (TD) were demonstrated in *E. coli* extracts in 1957. The first, the so-called biosynthetic TD which utilizes α-ketobutyric acid, is needed for the biosynthesis of isoleucine. It can be inhibited by l-isoleucine and contains pyridoxal phosphate as coenzyme [72]. The second TD, already described by *Wood* and *Gunsalus* [73], also requires pyridoxal phosphate as well as adenosine triphosphate and glutathione, in order to develop maximum activity. It cannot be inhibited by isoleucine. The question arises here whether these enzymes can in fact be considered multiple forms, since their coenzyme requirement differs.

There can be no doubt, however, of the fact that the recently discovered aspartokinases of *E. coli* [*Stadtman* et al. [74] can be considered as being isozymes, two of which may be isolated by ammonium sulfate precipitation. The phosphorylation of a β-carboxyl group of aspartic acid by ATP and a kinase (aspartokinase) is a fundamental reaction in the biosynthesis of lysine, threonine and methionine in *E. coli*. As shown by the scheme below, this synthesis proceeds by way of two common steps which then diverge. One of these two aspartokinases was inhibited specifically and noncompetitively by L-lysine. When *E. coli* was grown in 10^{-2} M lysine solution, the formation of this enzyme was completely inhibited (repression).



The second aspartokinase is inhibited specifically by L-threonine. The biological significance of these isozymes may be that overproduction is prevented by the specific inhibition due to a given end-product (feed-back control). So far there is no proof for the existence of a similar feed-back function for any of the other isozymes discussed here.

Concluding Remarks

It is necessary to regard the now well-proved chemical differences between many enzymes of similar action as an expression of the development of the organism. Just as organisms are likely to be differentiated into their multiple forms in the course of history, perhaps starting with one cell, so the composition of their proteins may also have undergone differentiation. This fact, in so far as it implies visible and concrete differences, has been known for sometime; an example is mammalian α-globulin, which gives rise to different antibodies in different species, a fact that becomes evident when immunization is carried out improperly. It is also well known that the hemoglobins of the many species studied to-date exhibit distinct differences [75]. The hope that in this domain the fingerprint technique would become

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[70] *B. G. Malmström*, Arch. Biochem. Biophysics *70*, 58 (1957).
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[72] *H. E. Umbarger* and *B. Brown*, J. Bacteriol. *73*, 105 (1957).
[73] *W. A. Wood* and *I. C. Gunsalus*, J. biol. Chemistry *181*, 171 (1949).
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[75] *H. Neurath* and *K. Bailey*: The Proteins. Academic Press, New York 1954, Vol. II, p. 317.

a tool of sharp differentiation has been dampened somewhat by the results of comparative studies carried out by *Pauling* et al. [76]. These investigators were unable to find any difference between the hemoglobins of man, gorilla, and chimpanzee by this method.

Hemoglobin also exhibits heterogeneity, *i.e.* it can be separated into multiple forms by means of zone electrophoresis [77] or chromatography on Amberlite IRC-50 [78, 79]. This has been studied particularly intensively in the ferric cyanohemoglobin of man [79]. Two components, A_I and A_{II}, were regularly produced in an approximate ratio of 1:9. They differ from one another in that A_{II}, does not contain isoleucine. Fetal hemoglobin F can also be separated into two components. The amino acid sequence in myoglobin obtained from the sperm whale has been studied both analytically [80] and by X-ray crystallography [81]. Five components were isolated by chromatography on Amberlite IRC-50. It is believed that these have the same amino acid composition. However, chemical comparisons of proteins should not be restricted merely to a determination of the total number of amino acids present. *Akeson* and *Theorell* [82] have examined two myoglobins isolated from horse muscle and their work shows that only a competent finger-print analysis, or a similarly effective procedure, will ensure that differences in primary structure will be detected in proteins of similar composition.

Thus it can be seen that the occurrence of multiple forms is not restricted to the enzymes discussed in this review. Quite possibly many more natural proteins than have so far been studied exist in isofunctional units. Such proteins can be designated as "homoproteins." Perhaps the concept advanced by geneticists that the formation of each type of protein requires its specific gene may have to be modified if it turns out that differences in composition extend to appreciable deviations in the amino acid sequence. Undoubtedly future biochemical research will have as one of its important aims the clarification of such structural differences and their possible biological significance.

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Conversion of Natural Substances by Microbial Enzymes [*]

BY PROF. DR. CH. TAMM

INSTITUT FÜR ORGANISCHE CHEMIE DER UNIVERSITÄT BASEL, SWITZERLAND

Micro-organisms form enzymes that catalyze many reactions which are difficult to carry out in the laboratory or which involve many steps. Enzymes even react with substances which are normally foreign to them. The frequently high stereospecificity of microbiological reactions is of particular significance. The most important types of reactions are: hydroxylations, dehydrogenations (oxidations), and hydrogenations (reductions), cleavage of ester and C–C bonds, and transglycosidations. The variety of the compounds converted is extremely great.

1. Introduction
2. Methods
3. Steroids
   (a) Hormones of the Androstane and Pregnane Series
   (b) Estrogens
   (c) Bile acids
   (d) Cardenolides and Bufadienolides
4. Terpenes
5. Phenols
6. Carbohydrates
7. Antibiotics
8. Alkaloids
9. Nature of the Enzymes. Reaction Mechanisms
   (a) Hydroxysteroid Dehydrogenases
   (b) Δ-Dehydrogenases and Δ-Reductases
   (c) Δ^5-3-Ketosteroid Isomerase
   (d) Hydroxylases
10. Conclusion

1. Introduction

Micro-organisms seem to compensate for their lack of variety of external forms by specific internal chemism, a criterion which sets them apart from higher plants, which have a differentiated morphology. Their metabolic products (metabolites) cover the entire spectrum of chemical structures; these may be very simple, or very complex, compounds. This is illustrated in a most impressive manner by the numerous antibiotics discovered during the last decades. Studies of mould

[*] Extended version of lectures delivered in Braunschweig (1960), Berlin (1960), and Basel (1961).

metabolites have not only led to the discovery of interesting biological effects which have revolutionized the therapeutic potential in medicine, but have also revealed the paths to novel and remarkable chemical structures.

Apart from low molecular weight metabolic products, micro-organisms also produce very active enzyme systems which are capable of catalyzing chemical reactions with foreign substances when the latter are added for example to a culture solution in which the organism is grown. Ordinarily, these substances are not essential for the growth of the micro organism since sources of carbon and nitrogen are available in the nutrient. The microbial enzymes rather assume the role of chemical reagents characterized by a high degree of selectivity and stereospecifity. Thus, micro-organisms are frequently in a position to carry out reactions in a single step, where as many complicated steps would be required in the laboratory.

The oldest of these reactions is perhaps microbiological oxidation such as has been used for centuries in the production of vinegar. The production of beer is probably almost as old, being also based on a fermentation process. The older methods of indigo dyeing also make use of microbiological reactions.The scientific basis of these purely empirical processes was founded by *Pasteur* about 100 years ago when he studied the oxidation of ethanol to acetic acid by *Acetobacter aceti* [1]. Forty years later, another type of reaction was discovered by *Schradinger*, namely the hydrolysis of starch to dextrins by *Bacillus macerans* [2]. Shortly afterwards, it was possible to carry out reductions with yeast, *e.g.* chloral to trichloroethanol [3]. Up to the middle of the thirties, microbiological reactions were primarily only of academic interest. This situation changed, however, when it was found, as a result of studies *Reichstein*, that L-sorbose, which is required for the synthesis of Vitamin C, can be produced commercially from sorbitol by oxidation with *Acetobacter suboxydans* [4]. The discovery of penicillin, the streptomycins, and other antibiotics during and after the second world war led to the unprecedented development of chemical microbiology in both scientific and industrial respects; this development is not yet concluded. In the course of these investigations, not only new mould metabolites but also numerous reactions with microbial enzymes were discovered. These are tabulated in Table 1 [5].

Table 1. Types of Microbiological Reactions

Oxidation	Cleavage of carbon bonds
Reduction	Decarboxylation
Hydrolysis	Dehydration
Esterification	Amination
Acylation	Deamination
Transglycosidation	Amidation
Methylation	Phosphorylation
Condensation	Halogenation

2. Methods

The micro-organisms required for the reactions may either be isolated or, more commonly, purchased from collections as cultures on agar-agar. The best known are the "American Type Culture Collection" (ATCC) in Washington, D.C., USA; the "Centraalbureau voor Schimmelcultures" (CBS) in Baarn, Netherlands, and the "Agriculture Culture Collection, Northern Utilization Research and Development Division" (NRRL) in Peoria, Illinois, USA.

The organism is cultivated in a suitable medium, generally under aerobic conditions. A solution or suspension of the substrate in a solvent which is miscible with water and non-toxic for the organism (acetone, alcohol, or dioxan) is added under sterile conditions to this culture the mixture is then incubated for several hours or days while aerating by shaking or stirring. Then, the mycelium is separated by suction, adding kieselguhr as filter aid if required and washed thoroughly with alcohol or acetone. The metabolic products are extracted from the culture filtrate with an organic, water-immiscible solvent, separated by column chromatography or countercurrent distribution, isolated, and characterized. Paper chromatography and thin layer chromatography are indispensable tools for the detection and observation of any transformations. In carrying out preliminary experiments, small amounts of material, *e.g.*, 3–5 mg. of substrate and 20 ml. of nutrient in 100 ml. Erlenmeyer flasks, are used before the reactions are attempted on a larger scale, *e.g.*, in fermentation tanks as submerged cultures; on this scale, as much as 1 g. of substrate per liter of nutrient may be used. Adaptation of a reaction to larger vessels often poses additional problems, as the growth conditions may alter significantly for the micro-organism. For reasons to be discussed later, one must still use living – generally growing – cultures; so far cell-free enzyme solutions have only been used in special cases.

Table 2 lists a few micro-organisms, which are used frequently:

Table 2. Micro-organisms frequently used [6]

Fungi:

Phycomycetes:
Cunninghamella, Helicostylum, Mucor, Phycomyces, Rhizopus.

Fungi imperfecti and *Ascomycetes*:
Alteroaria, Aspergillus, Calonectria, Cephalosporium, Cephalothecium, Curvularia, Didymella, Fusarium, Gibberella, Neurospora, Ophiobolus, Penicillium, Pestalotia, Saccharomyces, Septomyxa, Trichothecium.

Basidiomycetes:
Lenzites

Actinomycetes:
Nocardia, Streptomyces

Bacteria:
Bacillus, Corynebacterium, Escherichia, Flavobacterium, Mycobacterium, Pseudomonas.

The following discussion is meant to show the possibilities offered by microbial enzymes for effecting chemical transformations in natural products. No complete

[1] *P. Pasteur:* Memoire sur la Fermentation Acétique (1864).

[2] *F. Schradinger*, Z. Unters. Nahr. Genußm. *6*, 865 (1903); Wiener klin. Wschr. *17*, 207 (1904).

[3] *C. J. Lintner* and *H. Lüers*, Hoppe-Seylers Z. physiol. Chem. *72*, 449 (1911).

[4] Cf. *T. Reichstein* and *A. Grüssner*, Helv. chim. Acta *17*, 311 (1934).

[5] Cf. *F. H. Stodola:* Chemical Transformations by Micro-organisms. John Wiley & Sons, New York (1958), p. 38, where examples of all these types are presented.

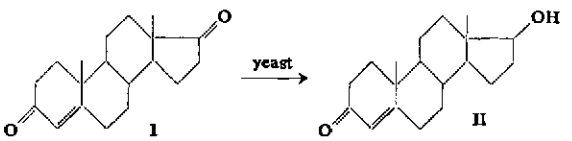
[6] About 40000 species of fungi are known, about 2000 species of bacteria and about 500 species of yeast.

enumeration is attempted, but some recent examples will be discussed in order to illustrate the diversity of the materials and reactions concerned [7]. Problems concerning the nature of the enzymes and reaction mechanisms are discussed at the end of the article.

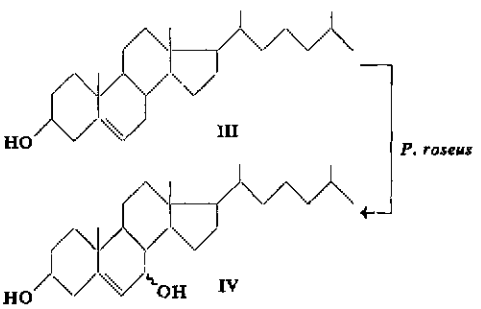
3. Steroids

a) Hormones of the Androstane and Pregnane Series

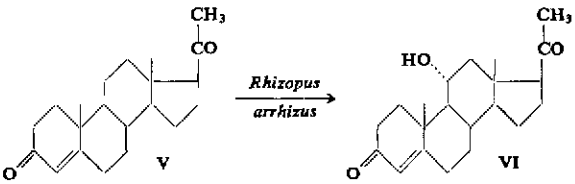
In the steroid field, microbiological reactions, have attained especially great significance and are also used commercially. The first studies were made in 1937 by *Mamoli* and *Vercellone* [8] who converted Δ^4-androstene-3,17-dione (I) to the male sex hormone testosterone (II) by selective reduction of the 17-keto group using yeast.



The first microbiological oxidation of a steroid was described by *Krámli* and *Horváth* [9] 11 years later. They obtained 7 ξ-hydroxycholesterol (IV) from cholesterol (III) by oxidation of the allylic carbon atom with cultures of *Proactinomyces roseus*.



These and similar results were given little attention. The situation changed suddenly however in 1952 when *Peterson* and *Murray* [10] found that progesterone (V) may be converted quantitatively to 11α-hydroxyprogesterone (VI) by incubation with cultures of *Rhizopus*.

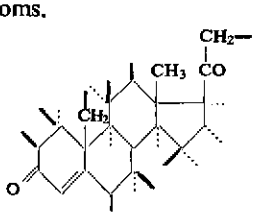


Interest in steroids bearing an oxygen function in the C-11 position was enormously enhanced by the discovery of *Hench* and *Kendall* of the clinical effects of cortisone and cortisol in the treatment of rheumatic arthritis. The mere introduction of this 11-oxygen function during the partial and total syntheses of corticosteroids had previously required numerous complicated chemical operations, which were now replaced by a single microbiological step. Thus, new, less expensive, and more easily accessible starting materials were be made available for the production of these biologically and medically important substances and their derivatives. In subsequent years, the microbiological conversion of steroids was studied over a wide area and numerous new enzymatic reactions were discovered.

Most results have been already discussed in excellent review articles [7, 11–18] hence, the present discussion can be kept short and only some interesting observations of more recent date shall be discussed.

The most frequently occurring reaction by far is oxygenation, *i.e.*, the introduction of an oxygen atom into the steroid skeleton, into the angular methyl groups or in the side chain. Interestingly enough, not only active carbon atoms, such as the allylic C-6 atom in Δ^4-3-ketones, or C-17 and C-21, are attacked, but also non-activated primary, secondary and tertiary C-atoms.

Hydroxylating enzymes are now known for almost all positions of the steroid molecule, not only for those of biological significance. Only C-4, C-8, and C-18 hydroxylations remain unobserved. For a long time, the 9α-hydroxylation was not proved unequivocally. However, later studies [19–21] furnished clear chemical evidence for the 9α-configuration of the OH group in question. Oxygenation at C-3 and C-20 has not been observed so far since all starting materials already had oxygen functions on these C atoms.



Oxygenation by microbial enzymes [21a]: 1α, 2β, 6β, 7α, 7β, 9α, 11α, 11β, 12β, 14α, 15α, 15β, 16α, 17α, 19, 21.
19-Norsteroids: 10β.
Cardenolides: 1β, 5β.

[7] Cf. *Ch. Tamm*, Planta Medica *8*, 331 (1960).

[8] *L. Mamoli* and *A. Vercellone*, Ber. dtsch. chem. Ges. *70*, 470 (1937).

[9] *A. Krámli* and *J. Horváth*, Nature (London) *162*, 619 (1948); *163*, 219 (1949).

[10] *D. H. Peterson* and *H. C. Murray*, J. Amer. chem. Soc. *74*, 1871 (1952).

[11] *J. Fried, R. W. Thoma, D. Perlann, J. E. Herz*, and *A. Bormann*, Recent Progr. Hormone Res. *11*, 149 (1955).

[12] *A. Wettstein*, Experientia *11*, 465 (1955).

[13] *S. H. Eppstein, P. D. Meister, H. C. Murray*, and *D. W. Peterson*, Vitamins and Hormones *14*, 359 (1956).

[14] *G. M. Shull*, Trans. N.Y. Acad. Sci., Ser. II, *19*, 147 (1956).

[15] *P. Talalay*, Physiol. Rev. *37*, 362 (1957).

[16] *E. Vischer* and *A. Wettstein*, Angew. Chem. *69*, 456 (1957).

[17] *E. Vischer* and *A. Wettstein*, Advances in Enzymol. *20*, 237 (1958).

[18] *D. H. Peterson:* Steroid Symposium 4th. Int. Congress on Biochemistry, Vienna, September 1958. Pergamon Press., London, Vol. 4, p. 83.

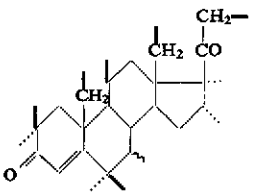
[19] *S. H. Eppstein, P. D. Meister, D. H. Peterson, H. C. Murray, H. M. Leigh Osborn, A. Weintraub, L. M. Reinecke*, and *R. C. Meeks*, J. Amer. chem. Soc. *80*, 3382 (1958).

[20] *R. M. Dodson* and *R. D. Muir*, J. Amer. chem. Soc. *80*, 6148 (1958); *83*, 4631 (1961).

[21] *A. Schubert, D. Onken, R. Siebert*, and *K. Heller*, Chem. Ber. *91*, 2549 (1958).

[21a] A 12α-hydroxylation has until now only been cited in the patent literature: U.S.P. 2914543 concerns a $\Delta^{9,11}$-steroid.

Comparison with enzymes of the mammal organism, in which 16-oxygenation has also been detected, is of interest.

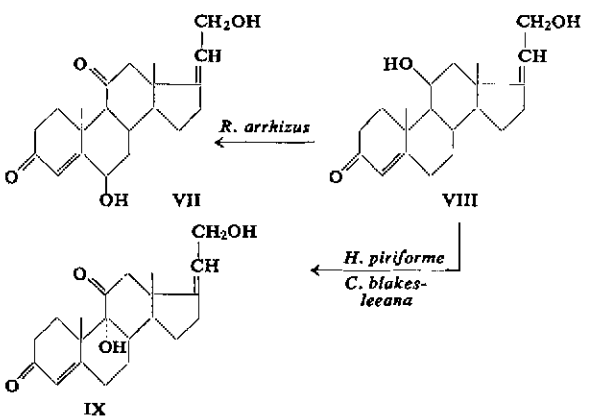


Oxygenation by enzymes from mammals:
Adrenals: 6α, 6β, 11β, 16α, 17α, 18, 19, 21.
Other tissues: 2α, 2β, 6α, 6β, 7ξ, 16α, 21.

Microbial enzymes usually effect the introduction of one oxygen atom, or, more rarely, of two oxygen atoms. Polyhydroxylations have not been observed thus far. As a rule, the more hydroxyl groups already present in the substrate, *e.g.*, the more hydrophilic its character, the more difficult it is to oxygenate it.

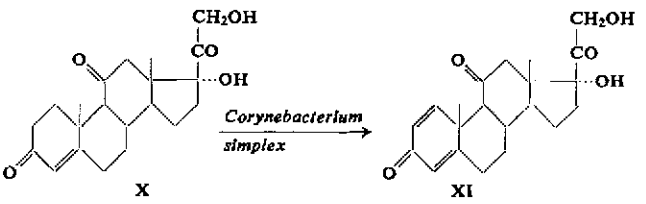
If the starting material has an isolated C=C double bond, organisms, which would introduce an axial hydroxyl group into the hydrogenated compound, may add oxygen at the double bond forming an epoxide (epoxidation).

Dehydrogenation is often encountered together with oxidation. It affects alcoholic hydroxyl groups (especially at C-3 and at C-17), which are converted into keto groups. This reaction is preferentially catalyzed by bacterial enzymes. Using the unsaturated pregnane derivative VIII, *Hanze* et al. [22] recently reported a dehydrogenation of the 11β-hydroxyl group by *Rhizopus arrhizus*, *Helicostylum piriforme* and *Cunninghamella blakesleeana*. Simultaneous hydroxylation occurred at the 6β- and 9α-positions.

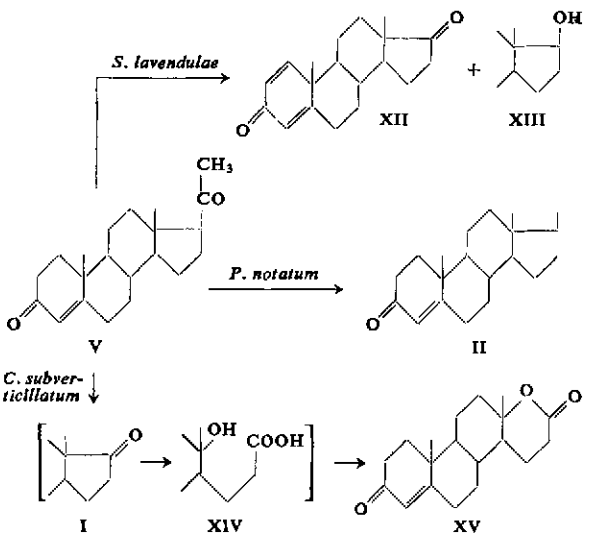


Another type of reaction is exemplified by the dehydrogenation of a saturated carbon chain with formation of an olefinic double bond. The introduction of the Δ^1 double bond into the steroid skeleton has become especially important. Thus, cortisone (X) may be converted into prednisone (XI) by means of a single reaction, *e.g.*, using *Corynebacterium simplex* [23].

In these dehydrogenations, cleavage of a C=C double bond may occur as a side reaction, *e.g.*, a degradation of the side chain in the pregnane series with formation



of androstane derivatives. A mixture of $\Delta^{1,4}$-androstadiene-3,17-dione (XII) and $\Delta^{1,4}$-androstadien-3-on-17β-ol is formed after incubation of progesterone (V) with cultures of *Streptomyces lavendulae*, via Δ^1-dehydroprogesterone as intermediate [24].



However, progesterone gives testosterone (II) [25] in good yield with *Penicillium notatum*, while testololactone (XV) [26] is formed with *Cephalosporium subverticillatum* by a further oxidative opening of ring D and lactonization of the intermediate δ-hydroxycarboxylic acid (XIV).

The lactone of the 11β-hydroxyprogesterone 18-acid (XVI) gave the four products XVII,XVIII, XIX, and XX [26a] with *Fusarium solani*. All of these contain a Δ^1-double bond and have lost their side chains. The 18-norketones XIX and XX may have been formed by decarboxylation of the β-ketocarboxylic acid from which the lactone XVIII is derived. It has not yet been ascertained whether the CO_2 is split off by enzyme action or spontaneously. At any rate, the two 18-norketones have been made more readily accessible by this microbial reaction.

Fonken et al. [27] were able to isolate Δ^4-androstene-3,17-dione (I), testosterone (II), and, especially significantly, testosterone acetate following incubation of progesterone

[22] *A. R. Hanze, O. K. Sebek*, and *H. C. Murray*, J. org. Chemistry *25*, 1968 (1960).

[23] *A. Nobile, W. Charney, P. L. Perlman, H. L. Herzog, C. C. Payne, M. E. Jevnik*, and *E. B. Hershberg*, J. Amer. chem. Soc. *77*, 4184 (1955).

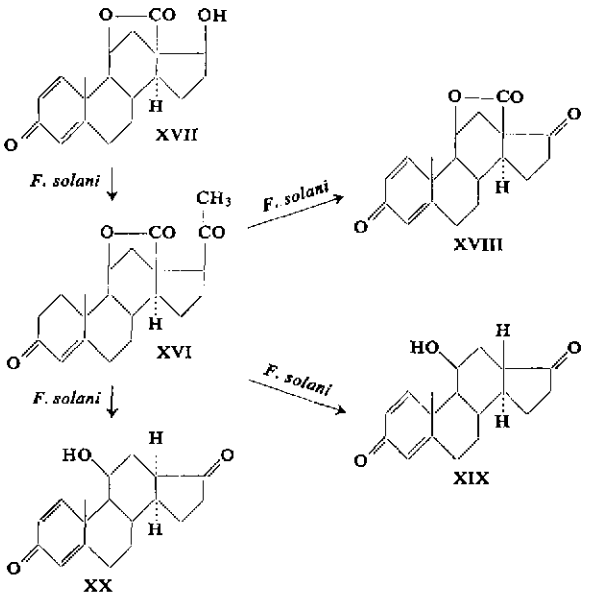
[24] *J. Fried, R. W. Thoma*, and *A. Klingsberg*, J. Amer. chem. Soc. *75*, 5764 (1953); *G. E. Peterson, R. W. Thoma, D. Perlman*, and *J. Fried*, J. Bacteriology *74*, 684 (1957).

[25] *O. Hanč, A. Capek, M. Tadra, K. Macek*, and *A. Simek*, Arzneimittelforsch. *7*, 175 (1957).

[26] *A. Bodánszky, J. Kollonitsch*, and *G. Wix*, Experientia *11*, 384 (1955).

[26a] *J. Urech, E. Vischer*, and *A. Wettstein*, Paper, Meeting Swiss Chemical Society, September 1961.

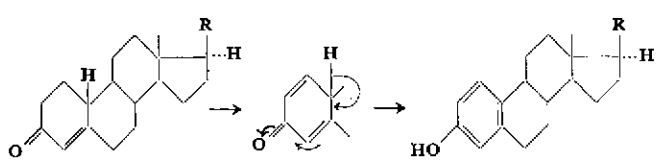
[27] *G. G. Fonken, H. C. Murray*, and *L. M. Reineke*, J. Amer. chem. Soc. *2,8* 5507 (1960).



XVII XVIII XVI XIX XX

(V) with cultures of *Cladiosporum resinae*. When 21-^{14}C labelled progesterone was used, the entire radioactivity was found in the testosterone acetate after the reaction. Since testosterone itself is not acetylated by the organism under identical conditions, Testosterone acetate does not seem to be an acetylation product of II, but an intermediate in the degradation of the side chain of V. It is possible that this reaction is an enzymatic parallel to the degradation of 20-ketosteroids by peracids (see [24]).

The dehydrogenation of 19-norsteroids in the 1-position may be followed by an aromatization reaction, as found by *Bowers* et al. [28] in the conversion of 19-norprogesterone (XXI) and by *Kushinsky* [29] in the reaction of 19-nortestosterone (XXII) with *Corynebacterium simplex* Compound XXI formed the analogue XXIV of the estrogenic hormones and XXII formed estradiol (XXV) as the primary product together with some estrone (XXVI) as secondary product. The intermediate $\Delta^{1,4}$-dien-3-one, corresponding to XXIII, was isolated in traces during the aromatization of XXII alone. Analogous results were obtained by *Peterson* et al. [30] with 2α-methyl- and 4-methyl-19-nortestosterones.



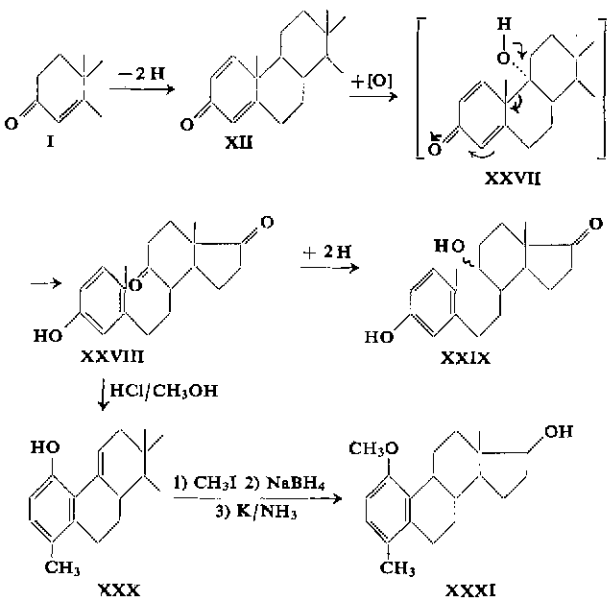
XXI: R = CH_3CO-
XXII: R = HO—

XXIII

XXIV: R = CH_3CO-
XXV: R = HO—
XXVI: R = O=

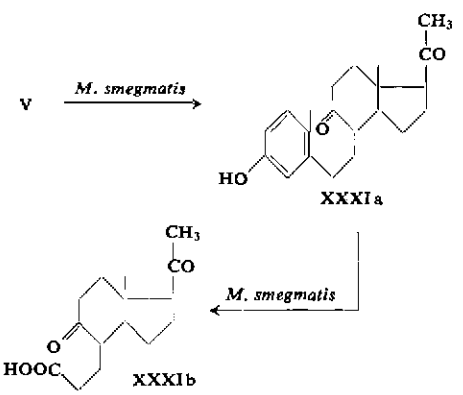
After incubation of Δ^4-androstene-3,17-dione (I) with a *Pseudomonas* type, *Dodson* and *Muir* [31] isolated secophenol (XXVIII) which must have been formed by a whole sequence of microbiological reactions: (1) dehydrogenation at C-1, (2) hydroxylation at C-9, and (3) retroaldol condensation with opening of ring B.

Mycobacterium smegmatis and several other mycobacteria are capable of effecting the same conversion. Besides XXVIII, hydroxysecophenol XXIX was also obtained [32]. In order to elucidate its structure, XXVIII was cyclized with acid to XXX, which was then transformed into the known 1-methoxy-4-methyl derivative XXXI [31] following methylation, $NaBH_4$ reduction of the 17-keto group and saturation of the $\Delta^{9,11}$-double bond using potassium in liquid NH_3. Analogous chemical retroaldol condensations of $\Delta^{1,4}$-3-ketones are known; they are catalyzed by bases and take place even under very mild conditions. The conversion of corticosteroids and of androgens to estrogens in the animal organism probably takes place by the same sequence of reactions.



I XII XXVII XXVIII XXIX XXX XXXI

On incubation of progesterone (V) with *M. smegmatis*, *Schubert* et. al. [32a] were able to isolate the ketocarboxylic acid XXXIb and the phenol ketone XXXIa. The aromatic ring in XXXIa has undergone a considerable oxidative degradation.



XXXIa XXXIb

All the reactions discussed so far have been oxidations. However, there are numerous microbial enzymes which catalyze reductions, *e.g.*, the hydrogenation of carbonyl groups or the saturation of olefinic double bonds in α,β-unsaturated ketones. One instructive example is the reduction of progesterone (V) and cortexone (XXXII) by *Streptomyces griseus*, studied quantitatively by *Vischer* and *Wettstein* [32b]. They found that the C=C

[28] *A. Bowers, C. Casas-Campillo*, and *C. Djerassi*, Tetrahedron *2*, 165 (1958).

[29] *S. Kushinsky*, J. biol. Chemistry *230*, 31 (1958).

[30] *D. H. Peterson, L. M. Reineke, H. C. Murray*, and *O. K. Sebek*, Chem. and Ind. 1301 (1960).

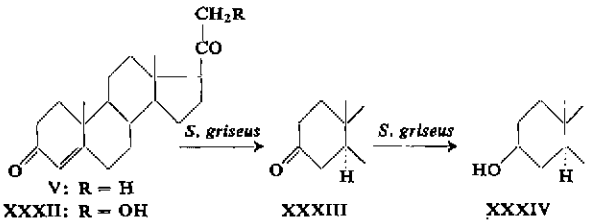
[31] *R. M. Dodson* and *D. Muir*, J. Amer. chem. Soc. *80*, 5004 (1958); *83*, 4627 (1961).

[32] *K. Schubert, K.-H. Böhme*, and *C. Hörhold*, Z. Naturforsch. *15b*, 584 (1960).

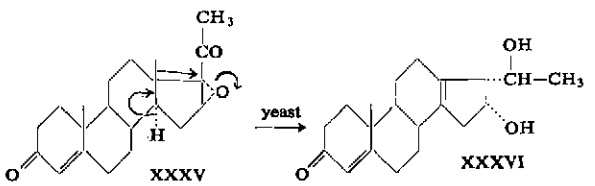
[32a] *K. Schubert, K.-H. Böhme*, and *C. Hörhold*, Hoppe-Seylers Z. physiol. Chem. *325*, 260 (1961).

[32b] *E. Vischer* and *A. Wettstein*, Experientia *16*, 355 (1960).

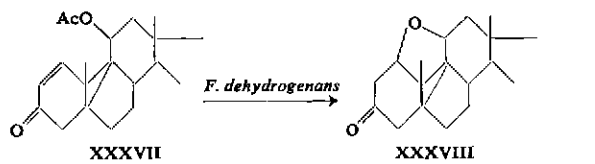
double bond is attacked first (XXXIII) and only thereafter the carbonyl group (XXXIV). With another type of *Streptomyces*, prednisone is selectively reduced at the Δ^4 double bond [32c]. *Carmerino* et al. [33] reported a selective hydrogenation of the 20-keto- group in 16α, 17α-epoxy-20-ketosteroid XXXV by the action of fermenting yeast.



This was followed by a retropinacol rearrangement to form XXXVI. Such *Wagner-Meerwein* rearrangements can also be effected chemically with the aid of acetylating agents and acid catalysts.



Certain micro-organisms have the remarkable ability to smoothly hydrolyze those esters which are difficult to hydrolyze chemically. Thus, *Flavobacterium dehydrogenans var. hydrolyticum* hydrolyzes not only 21-acetoxy groups, a very common phenomenon, but also 11β-acetoxy groups [34]. When the 5,9-cyclosteroid XXXVII was treated with this organism, cleavage of the acetyl group at C-11 was followed by a spontaneous isomerization to the 1β, 11β-oxido-5,9-cyclo derivative XXXVIII [35].



Very recently, ester formation by microbial enzymes was reported for the first time. *McGuire* et al. [36] demonstrated the formation of testosterone acetate from Δ^4-androstene-3,17-dione (I) by the yeast *Saccharomyces fragilis*. A selective 21-acetylation was observed by *Holmlund* et al. [37] in 9α-fluoro-11β-, 21-dihydroxy-16α- and 17α-isopropylidenedioxy-Δ^4-pregnene-3,20-diones with a strain of *Trichoma glauca*. This reaction seems to be highly substrate specific, for it occurred only with starting materials having a 16α, 17α-isopropylidenedioxy grouping.

[32c] *G. Greenspan, C. P. Schaffner, W. Charney, M. J. Gentles,* and *H. L. Herzog*, J. org. Chemistry *26*, 1676 (1961).

[33] *B. Camerino* and *R. Modelli*, Gazz. chim. ital. *86*, 1219 (1956); *B. Camerino, R. Modelli,* and *C. Spalla*, ibid. *86*, 1226 (1956).

[34] *W. Charney, L. Weber,* and *E. Oliveto*, Arch. Biochem. Biophysics *79*, 402 (1959).

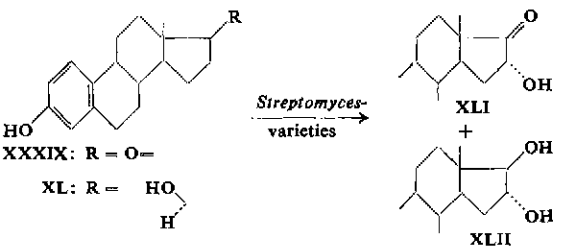
[35] *O. Gnoj, E. P. Oliveto, C. H. Robinson,* and *D. H. R. Barton*, Proc. chem. Soc. (London) 207 (1961).

[36] *J. S. McGuire, E. S. Maxwell,* and *G. M. Tomkins*, Biochim. biophysica Acta *45*, 392 (1960).

[37] *C. E. Holmlund, L. I. Feldman, N. E. Rigler, B. E. Nielsen,* and *R. H. Evans jr.*, J. Amer. chem. Soc. *83*, 2586 (1961).

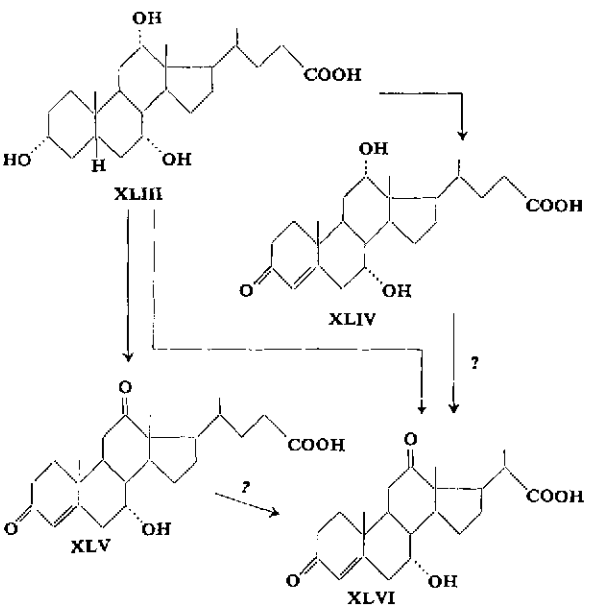
b) Estrogens

Only few studies have been made on microbiological reactions of steroids having an aromatic A ring. Such studies are of most recent date. Strains of *Streptomyces halstedii* and of *Streptomyces mediocidicus* are capable of introducing a 16α-hydroxy group into estrone (XXXIX) as well as into estradiol (XL) [38]. Both substrates were converted to 16α-hydroxyestrone (XLI) and estriol (XLII). In part, an additional hydrogenation of the 17-keto group, and dehydrogenation of the 17β-hydroxyl, respectively, had taken place. The 16α-hydroxylation was also obtained with *Streptomyces bikiniensis* [39] and the hydrogenation and dehydrogenation of the oxygen function at C-17 was achieved by using cultures of *Rhizopus arrhizus* [40] and *Fusarium lini* [40].



c) Bile Acids

A sequence of microbial enzymes appears during incubation of cholic acid (XLIII) with *Streptomyces gelaticus* 1164 in a synthetic medium in which XLIII is the only source of carbon. According to *Hayakawa* et al. [41], the final product is the 7α-hydroxy-3,12-diketo-Δ^4-bis-norcholenic acid (XLVI). It is noteworthy that the side chain degradation stops after the removal of two C atoms. This degradation probably takes place in a later phase of the over all process and presumably requires a substrate having the Δ^4-3-keto-7α-hydroxy



[38] *D. A. Kita, J. L. Sardinas,* and *G. M. Shull*, Nature (London) *190*, 627 (1961).

[39] *B. F. Stimmel, T. E. Bucknell,* and *V. Notcher*, Fed. Proc. 115 (1960).

[40] *Ch. Tamm* and *W. Zürcher*, unpublished results.

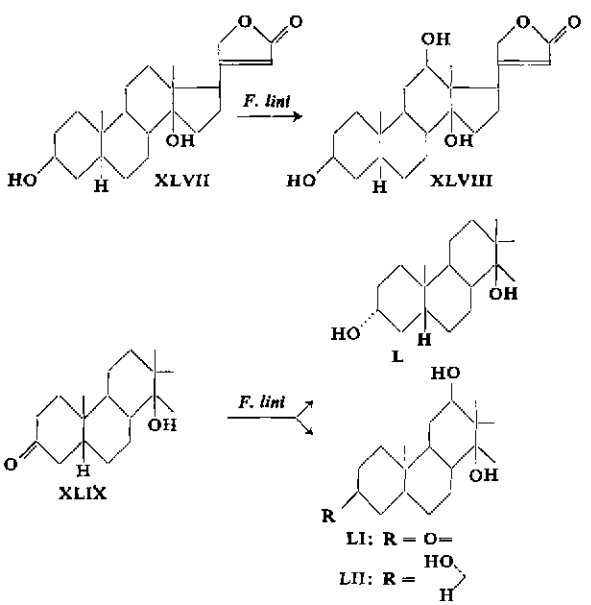
[41] *S. Hayakawa, T. Fuji, Y. Saburi,* and *T. Egudei*, Nature (London) *179*, 537 (1957), references to older literature therein.

grouping, for the reaction stops at the cholic acids XLIV and XLV under different growth conditions or with other *Streptomyces* strains. The 7α-hydroxy group is not dehydrogenated during this reaction.

d) Cardenolides and Bufadienolides

While microbiological reactions (especially of steroids of the androstane and pregnane series) have been studied intensively during the last eight years, the behavior of the structurally closely related cardiac glycosides and aglycones toward microbial enzyme systems had not been previously investigated. We therefore studied the relationship between the constitution of these different types of substrates and the reactivity of the microbial enzymes. At the same time, the structural specifity and stereospecificity of the enzymes with reference to the starting materials and end-products permit the preparation of new and interesting derivatives of cardenolides and bufadienolides, whose synthesis by purely chemical methods is difficult owing to the high degree of lability of these compounds. Microbiological reactions are also useful for solving problems of constitution.

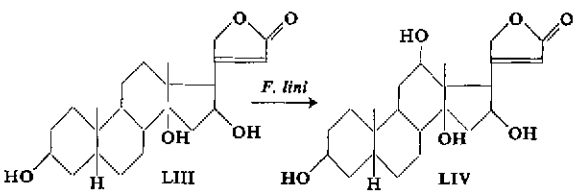
Digitoxigenin (XLVII) is the simplest representative of the cardiotonic digitaloid lactones (basic representative of the cardenolides; aglycone of digitoxin and of



lanatoside A). Its reaction with cultures of *Fusarium lini*, an organism not used previously in steroids studies, gave digoxigenin (XLVIII) in good yield as the only reaction product. Thus, a 12β-hydroxylation had taken place and the butenolide ring, which is sensitive toward chemical reagents remained intact [42,43].

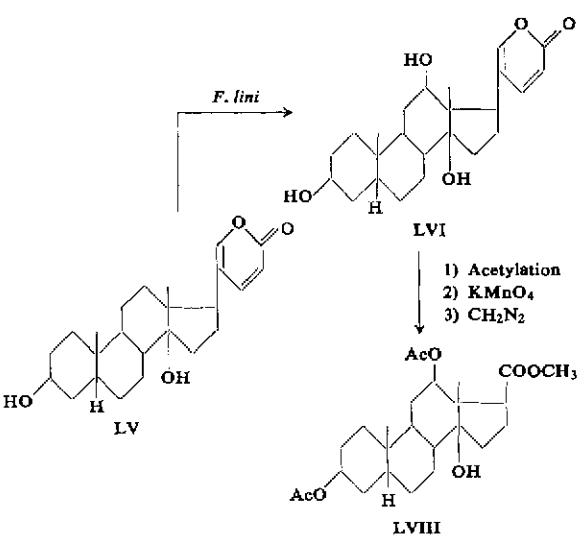
This microbiological reaction has an interesting parallel in the 12β-hydroxylation of digitoxigenin, digitoxin, and gitoxin in the human and animal organism [44,45]. In the formyl and acetyl derivatives of digitoxigenin cleavage of the ester linkage took place besides hydroxylation. Other strains of *Fusaria* are also capable of hydroxylating XLVII in the 12-position [46]. On incubation of 3-dehydrodigitoxigenin (XLIX) as starting material with *F. lini*, 3-epidigitoxigenin (L) was formed as primary product, in addition to 3-dehydrodigoxigenin (LI) and 3-epidigoxigenin (LII) [42,43].

The 12β-hydroxylation of digitoxigenin (XLII) and 3-dehydrodigitoxigenin (XLIX) shows a high substrate specificity, for practically no change took place after systematic modifications of the substrate (reversal of centers of asymmetry, removal or introduction of substituents, hydrogenation of the lactone ring, introduction of a Δ^4-3-ketone grouping [43]). Only gitoxigenin (LIII) could be converted (albeit with great difficulty) to a monohydroxy derivative, which proved to be identical with diginatigenin (LIV) (aglycone of diginatin and lanatoside D) [47]. The structural formula of LIV was still uncertain at that time.



Thus, by relating it to gitoxigenin (LIII), a steroid of known constitution, a single microbiological reaction supplied evidence for the basic skeleton of diginatigenin (LIV), the 17β-positioned butenolide ring, the β-positioned OH groups at C-3, C-14, and C-16; and the 12β-hydroxyl had been shown to be very probable. This supplied evidence for the basic skeleton of diginatigenin (LIV), the 17β-positioned butenolide ring, the β-positioned OH groups at C-3, C-14, and C-16; and the 12β-hydroxyl had been shown to be very probable. This hypothesis was later confirmed [48,49] by relating LIV to digoxigenin (XLVIII) by chemical reactions.

In order to investigate the substrate specificity of the hydroxylase of *F. lini* in more detail the experiments were extended include to the bufadienolides (toad



[42] *A. Gubler* and *Ch. Tamm*, Helv. chim. Acta *41*, 297 (1958).

[43] *Ch. Tamm* and *A. Gubler*, Helv. chim. Acta *42*, 239 (1959).

[44] *B. T. Brown*, *S. E. Wright*, and *G. T. Okita*, Nature (London) *180*, 607 (1957).

[45] *K. Repke*, Naturwissenschaften *45*, 94, 366 (1958).

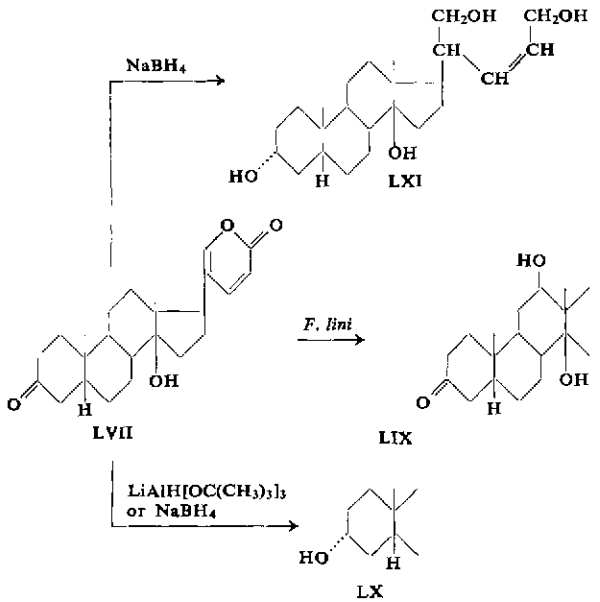
[46] *Ch. Tamm*, *E. Weiss-Berg*, and *G. Juhasz*, unpublished results.

[47] *Ch. Tamm* and *A. Gubler*, Helv. chim. Acta *41*, 1762 (1958).

[48] *H. Linde*, *J. E. Murphy*, and *K. Meyer*, Helv. chim. Acta *42*, 2040, 2753 (1959).

[49] *M. Okada*, *A. Yamada*, and *M. Ishidate*, Chem. Pharm. Bull. (Japan) *8*, 535 (1960).

poisons), in which the butenolide ring attached to C-17 is replaced by a hexadienolide ring. Bufalin, 3β-, 14-dihydroxy-5β-bufa-20,22-dienolide, (LV) gave an unknown monohydroxylation product [50]. It was shown by oxidative degradation to the known etianic acid derivative LVIII [50] that its constitution was that of a



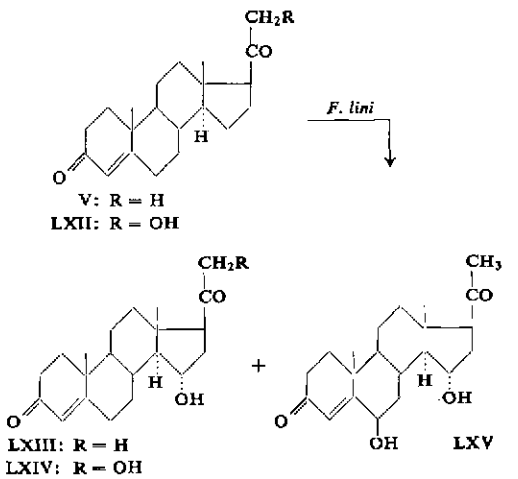
12β-hydroxybufalin (LVI). 3-Dehydrobufalin (LVII) gave only 3-dehydro-12β-hydroxybufalin (LX) and no 3-epibufalin (LIX) [50]. Reduction of the 3-keto group in LVII can be carried out with $LiAlH[OC(CH_3)_3]_3$. Sodium borohydride, surprisingly enough, gives considerable amounts of a by-product LXI, in which, contrary to expectations, the lactone ring had been opened reductively [51].

When the glycosides were used as starting materials instead of the aglycones the results were disappointing, No oxygenations took place, probably because of the strongly hydrophilic character of the substrates. In acetyl derivatives, only the ester bonds were cleaved, in glycosides containing glucose, terminal β-D-glucose residues were removed, regardless of whether they were bound to another sugar or directly to the aglycone [43].

Four enzyme systems were identified in *F. lini* by these studies: (1) a hydroxylase, (2) a hydrogenase, (3) an acylase, and (4) a β-glucosidase.

Previously, *Stoll* et al. [52,53] had observed glycoside cleavages caused by microbial enzymes. These authors were particularly successful in the preparation of intact scillarenin from proscillaridin A and of scillirosidin from scilliroside. They used a modified *Penicillium* strain, whose nutrient contained rhamnose or glucose as the sole source of carbon. Saponins may also be cleaved into aglycone and sugar by enzymatic action. Hydrolysis of digitonin was achieved with a bacterial enzyme [54] and that of heconin with enzymes of various microorganisms [55].

After we had found that cardiac poisons are oxygenated in the 12β-position by *F. lini*, we became interested in the behavior of common androstane and pregnane derivatives toward this organism. The result was surprising: instead of the expected 12β-hydroxylation, 15α-hydroxylation took place [56]; Δ^4-androstene-3,17-dione (I) and testosterone (II) gave the corresponding 15α-hydroxy derivatives. In the case of progesterone (V), besides the 15α-monohydroxylation to LXIII 6β, 15α-dihydroxylation to LXV and saturation of the Δ^4-double bonds were found. Cortexone (LXIII) gave exclusively 15α-hydroxycortexone (LXIV).



How can these results be interpreted? Does the microorganism form two specific hydroxylating enzymes, a 12β- and a 15β-hydroxylase, whose effect is stimulated by the two types of substrate, or is there only a single, relatively non-specific enzyme? Since this raises a fundamental problem of biological oxidation, we undertook some quantitative experiments [57].

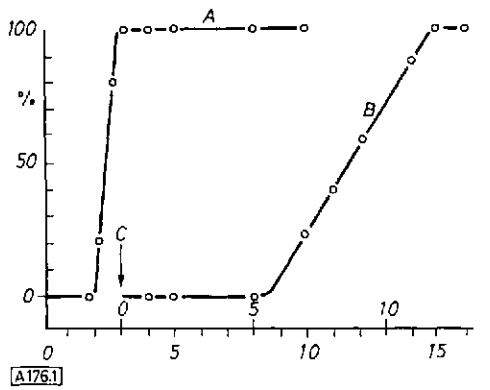


Fig. 1. Experiments on the substrate specificity of the hydroxylase from *F. lini*: Incubation with cortexone (LXII) with subsequent addition of digitoxigenin.

Curve A: Formation of 15α-hydroxycortexone
Curve B: Formation of digoxigenin (12β-hydroxylation)
Curve C: Addition of digitoxigenin
Ordinate: Yield (%)
Abscissa: Days

[50] *Ch. Tamm* and *A. Gubler*, Helv. chim. Acta *42*, 473 (1959).

[51] *Ch. Tamm*, Helv. chim. Acta *43*, 338 (1960).

[52] *A. Stoll*, *J. Renz*, and *A. Brack*, Helv. chim. Acta *34*, 397 (1951).

[53] *A. Stoll*, *J. Renz*, and *A. Brack*, Helv. chim. Acta *34*, 2301 (1951).

[54] *A. Schiesser*, Ricerca sci. *22*, 449 (1952); Chem. Abstr. *49*, 4085 (1955).

[55] *C. H. Hassall* and *B. S. W. Smith*, Chem. and Ind. 1570 (1957).

[56] *A. Gubler* and *Ch. Tamm*, Helv. chim. Acta *41*, 301 (1958).

[57] *Ch. Tamm* and *E. Weiss-Berg*, unpublished results.

The first experiment was based on the hypothesis of enzyme induction. In that period in which one hydroxylase is fully activated by one of the substrate types, the second substrate type is added; the location and rate of hydroxylation are then determined. 15α-Hydroxylation was not observed in digitoxigenin (XLVII) (cf. Fig. 1) nor a 12β-hydroxylation in cortexone (LXII) (cf. Fig. 2). The presence of cortexone (LXII) in the digitoxigenin test even accelerated the normal 12β-hydroxylation of digitoxigenin (XLVII). Figures 1 and 2 show further that the reaction rate in the pregnane series (also in the androstane series) is much higher than that of digitoxigenin (XLVII). This applies to all the cardenolides and bufadienolides investigated by us.

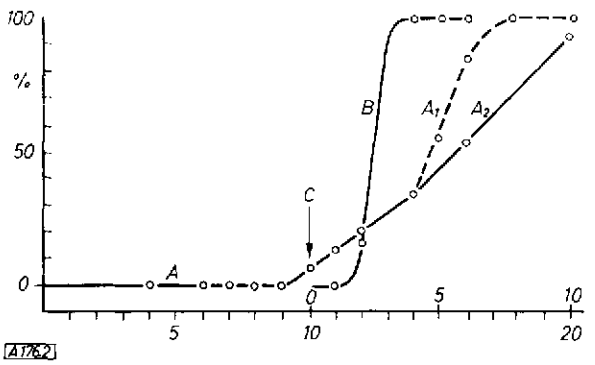


Fig. 2. Experiments on the substrate specificity of the hydroxylase of *F. lini*. Incubation with digitoxigenin (XLVII) with subsequent addition of cortexone (LXII).

Curve A: Formation of digoxigenin (12β-hydroxylation)
Curve A_1: in the presence of cortexone
Curve A_2: in the absence of cortexone
Curve B: Formation of 15α-hydroxycortexone
Curve C: Addition of cortexone
Ordinate: Yield (%)
Abscissa: Days

In the second experiment (cf. Fig. 3), digitoxigenin and cortexone were added simultaneously to the growing culture of the organism and compared with corresponding blank tests.

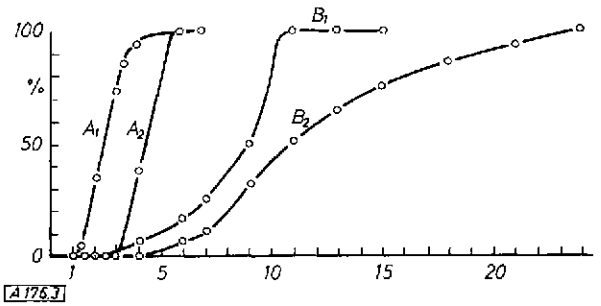


Fig. 3. Experiments on the substrate specificity of the hydroxylase of *F. lini*: Digitoxigenin (XLVII) and cortexone (LXII) incubated together.

Curve A: Formation of 15α-hydroxy-cortexone
Curve A_1: in the absence of digitoxigenin
Curve A_2: in the presence of digitoxigenin
Curve B: Formation of digitoxigenin (12β-hydroxylation)
Curve B_1: in the presence of cortexone
Curve B_2: in the absence of cortexone
Ordinate: Yield (%)
Abscissa: Days

Again, the 12β-position of XLVII and the 15α-position of LXII were hydroxylated. The start of the oxygenation of cortexone (Curve A_1) was somewhat retarded in the presence of digitoxigenin (Curve A_2). The much slower reaction of digitoxigenin (Curve B_2) was significantly accelerated in the presence of cortexone (Curve B_1). These experiments permit the conclusion that *F. lini* forms only one single hydroxylase.

The site of attack of this enzyme is evidently controlled by the stereochemistry of the substrate. This becomes clear by comparing the cardiotonic aglycones (rings A and B, and rings C and D *cis*-fused) with the hormones (Δ^4-3-ketone, rings C and D *trans*-fused – cf. Fig. 4). In the hormones, the steroid skeleton is almost planar and stretched, and the 15-position, especially the pseudo-equatorial 15α-positioned H-atom, is hardly sterically hindered. Enzyme attack at the 15a-position meets with no difficulties. Quantitative measurements have shown that this oxygenation occurs very rapidly. However, it cannot be explained why the enzyme selects the 15-po-

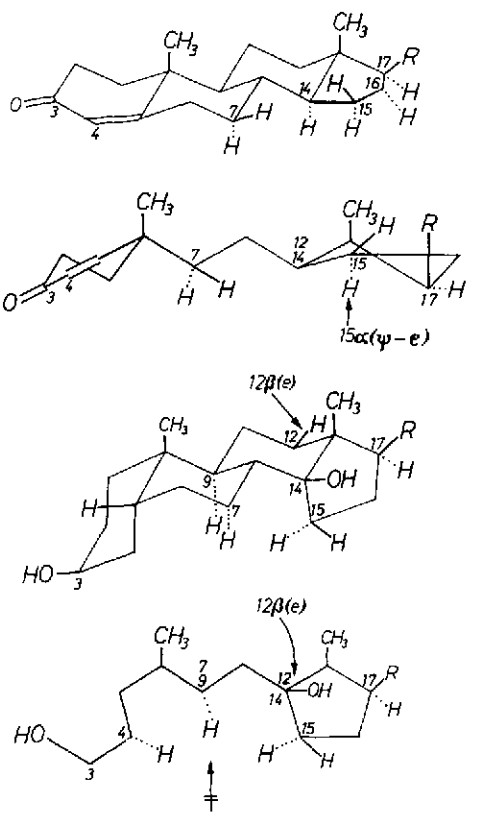
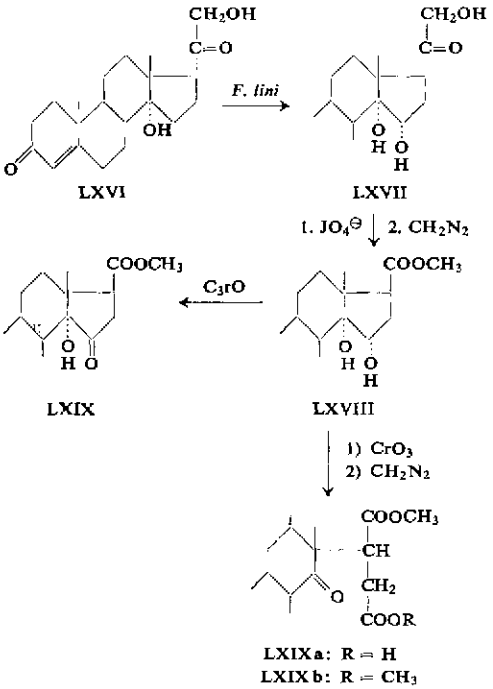


Fig. 4. Perspective representations of the corticoids (Δ^4-3-ketones, C/D-*trans*; upper two lines) and of the cardiac aglycones (A/B-*cis*, C/D-*cis*; lower two lines)

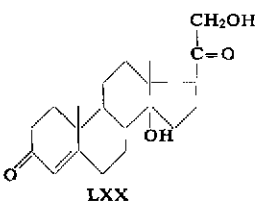
sition. In the case of *cis*-linkage of the rings A/B and C/D, the molecule is twisted considerably on both sides; thus, the 15α-position is strongly hindered, especially by the H atoms in the 4α-, 7α-, and 9α-positions. On the other hand, the equatiorial 12β-H atom is hardly hindered sterically. However, besides the stereochemistry of the ring skeleton, the bulk of the nearby OH group at C-14 is also of importance. The hydroxylation of 14α-hydroxycortexone (LXVI) by *F. lini* took place much more slow than that of cortexone.

In the hydroxylation product LXVII obtained from LXV, the previously introduced OH-group can be acetylated. It is located in the 15α-position although

LXVII consumed only 1 mole IO_4^-; this is needed for the cleavage of the ketol side chain. The secondary-tertiary 14α-, 15α-diol grouping remains intact. The esterified degradation compound LXVIII, formed by



methylation of the acidic cleavage product, gives a neutral keto ester LXIX on treatment with CrO_3 in glacial acetic acid, but mainly the keto acid LXIXa (produced by an oxidative cleavage of the D-ring). The latter can be converted to its dimethyl ester (LXIXb) by the action of CH_2N_2. Infrared spectral examination indicates a keto group in a 6-membered ring. The data, then, suggests 14α, 15α-dihydroxycortexone for the constitution of the hydroxylation product of 14a-hydroxycortexone (LXVI) [58]. The stereoisomeric I4β-hydroxy- derivative (LXX) is hydroxylated much more



slowly than LXVI by *F. lini*. Since this corresponds most closely with the aglycones (rings C and D are *cis*-linked), it is assumed that the 12β-position is hydroxylated [58].

If the additional OH group of the cortexone molecule is spatially removed from the C-15 position, *e.g.*, in the 17α-position as in Rcichsteins Substance S, the hydroxylase again attacks in the 15α-position [59]. Compared with cortexone the reaction rate is substantially lower.

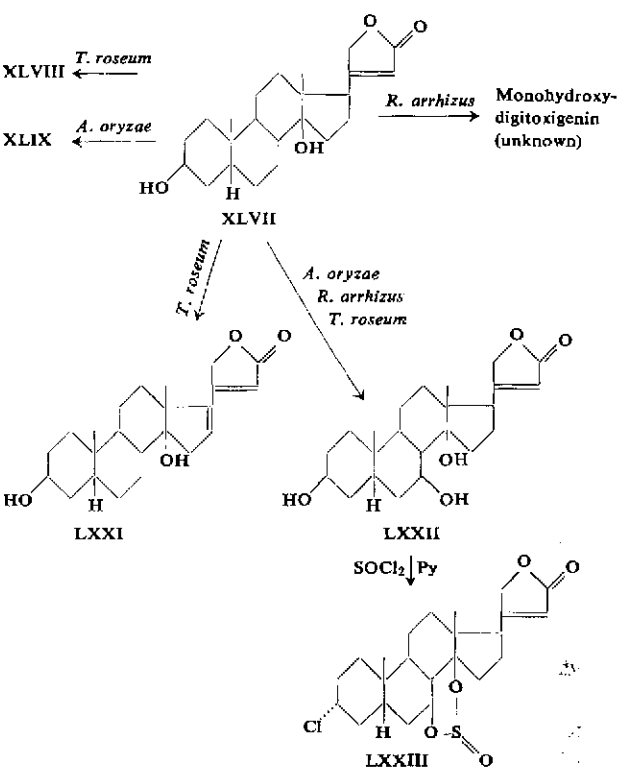
The examples discussed demonstrate that enzymatic reactions may run quite differently in different types of steroids, hence, analogies may only be deduced with caution.

[58] *Ch. Tamm, W. Zürcher*, and *G. Juhasz*, unpublished results.

[59] *Ch. Tamm, E. Weiss-Berg*, and *W. Zürcher*, unpublished results.

In the meantime, other authors, have reached similar conclusions. A few examples will be cited briefly. 4-Methyltestosterone is hydroxylated by *Rhizopus nigricans* predominantly in the 7β-position, to a slight extent in the 11α-, and not at all in the 6β-position, while in the case of testosterone itself the 11α-hydroxy derivative is the primary product and 6β-hydroxytestosterone is the by-product [60]. With *Absidia regnieri*, 17α-hydroxyprogesterone and *Reichstein*'s substance S were hydroxylated in the 11α-position, but cortexone acetate and 11-dehydrocorticosterone in the 14α-position [61]. Cultures of *Botrytis cinera* catalyze 6β- and 15β-hydroxylations. The presence of an 11β-hydroxyl in the substrate inhibits 6β-hydroxylation. If a 17α-hydroxyl group is present, 15β-hydroxylation is suppressed [61]. According to *Urech* et al. [62], *Gibberella saubinettii* causes primarily 15α- and to a lesser extent 6β-hydroxylation in 11β-hydroxy-Δ^4-androstene-3,17-dione. Additional substituents in the 17α-position of the substrate molecule (17α-OH, 17α-CH_3) make the 15α-hydroxylation more difficult, evidently owing to steric factors, thus causing additional 6β-hydroxylation. However, digitoxigenin (XLVII), 3-dehydrodigitoxigenin (XLIX), gitoxigenin (LII), and oleandrigenin are hydroxylated by *G. saubinetti* in the 12β-position [63]; this organism therefore possesses the same properties as *Fusarium lini* as far as its enzymes are concerned.

Nawa et al. [64] have observed other microbiological reactions in the cardenolide series [64a]. Incubation of digitoxigenin (XLVII) with *Helicostylum piriforme* led to digoxigenin (XLVIII) and gitoxigenin (LIII), with *Cunninghamella blakesleeana* to LIII and with *Gibberella fujikuroi* to digoxigenin (XLVIII). 12β-Hydroxylation occurs preferentially with these organisms, too.



[60] *D. N. Kirk, V. Petrow*, and *M. H. Williamson*, J. chem. Soc. (London) 3872 (1960).

[61] *M. Shirasaka*, Chem. Pharm. Bull. (Japan) *9*, 54, 152 (1961).

[62] *J. Urech, E. Vischer*, and *A. Wettstein*, Helv.chim.Acta *43*,1077 (1960).

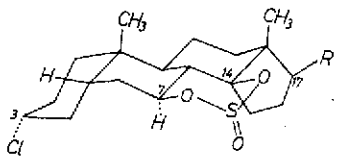
[63] *M. Okada, A. Yamada*, and *M. Ishidate*, Chem. Pharm. Bull. (Japan) *8*, 530 (1960).

[64] *H. Nawa, M. Uchibayashi, T. Kamiya, T. Yamano, H. Arai*, and *M. Abe*, Nature (London) *184*, 469 (1959).

[64a] Cf. *E. Titus*, Adv. applied Microbiol. *3*, 279 (1961).

The simultaneous attack by *H. piriforme* on the 16α-position is noteworthy. We have found that cultures of *Aspergillus oryzae* convert digitoxigenin (XLVII) into 3-dehydrodigitoxigenin (XLIX) as by-product and 7β-hydroxydigitoxigenin (XLII) as primary product [65].

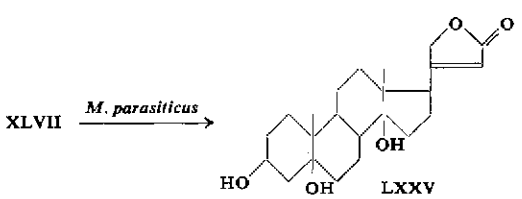
Compound LXXII is a new cardenolide, of which no glycosides have been found in nature so far. It was possible to verify its constitution by the formation of the 3α-chloro-7,14-cyclosulfite LXXIII with $SOCl_2$ in pyridine besides other transformations. Its spatial formula LXXIV shows that the reacting substituents in C-7 and C-14 have equatorial orientation, which is especially favorable for the formation of an additional unstrained 6-membered ring.



LXXIV

Rhizopus arrhizus also gave 7β-hydroxydigitoxigenin [65,66] (LXXII), as well as an isomeric, crystalline monohydroxy-digitoxigenin [65], whose structure has yet not been verified. Numerous other cardenolides used as educts remained unchanged. With androstane and pregnane derivatives containing the Δ^4-3-keto group, hydroxylation with this organism occurs in the 6β- and 11α-position, while saturated pregnanes may also be oxygenated in the 7β-position. The reaction of digitoxigenin (XLVII) with *Trichothecium* (Cephalothecium) *roseum* was studied by *Titus* et al. [67] and by us [65]. The primary product was again 7β-hydroxydigitoxigenin (LXXII) which, however, was considered by the American authors to be the still unknown 6β-isomer. *Titus* et al. [67] identified an additional product as 16-anhydro-digitoxigenin (LXXI), which was possibly formed by 17α-hydroxylation and subsequent dehydration; they also identified sarmentogenin. We did not find any sarmentogenin, but digoxigenin. Tbe reason for this discrepancy has not been found.

Ishii [68] recently reported the formation of periplogenin (LXXV) from digitoxigenin (XLVII) with the aid of *Mucor parasiticus*. This conversion constitutes the first 5β-hydroxylation in the steroid series. *M. parasiticus* hydroxylates representatives of the C_{19}- and C_{21}-series,



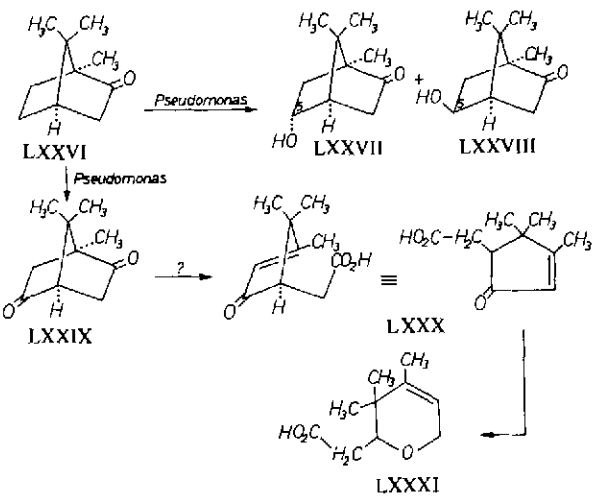
LXXV

which possess a Δ^4-3-keto group, usually in the 14α-position, *i.e.*, again at a tertiary C atom. By incubation of digitoxigenin (XLVII) with representatives of the order *Mucorales*, 7β-hydroxydigitoxigenin is formed together with Acovenosigenin A which occurs as a by-product through 1β-hydroxylation [68a, b]. At the same time, dihydroxylation of XLVII, possibly in the 1β, 7β and 5β, 7β positions, was observed [68a].

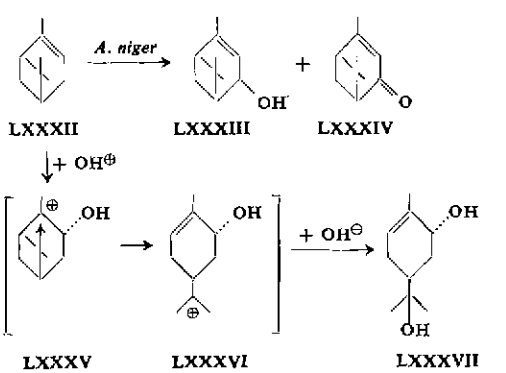
4. Terpenes

The diverse applicability of microbiological reactions in the steroid series provided a motive for the application of such reactions to other classes of natural substances. Thus, *Bradshaw* et al. [69] have studied the enzymatic conversion of (+)-camphor (LXXVI) by a *Pseudomonas* strain; the terpenes are closely related biogenetically to the steroids. In these experiments, camphor was the sole source of carbon.

The following natural substances were obtained: 5-endohydroxy- and 5-exohydroxycamphor (LXXVII and LXXVIII), 2,5-diketocamphor (LXXIX) and the acid LXXX, which was formed by the cleavage of a C–C bond in LXXIX. When complete oxidation is prevented by 2,2′-dipyridine, the dihydropyran derivative LXXXI is formed by cleavage of another C–C bond and ring closure at the oxygen function.



During the incubation of α-pinene (LXXXII) with *Aspergillus niger*, the three oxidation products *cis*-verbanol (LXXXIII-primary product), verbenone (LXXXIV) and *trans*-sobrerol (LXXXVIIby-products) [70] were formed besides CO_2 and



[65] *G. Juhasz* and *Ch. Tamm*, Helv. chim. Acta *44*, 1063 (1961).

[66] *H. Ishii, Y. Nozaki, T. Okumura*, and *D. Satoh*, J. pharmac. Soc. (Japan) *80*, 1150 (1960).

[67] *E. Titus, A. W. Murray*, and *H. E. Spiegel*, J. biol. Chemistry *235*, 3399 (1960).

[68] *H. Ishii*, J. pharmac. Soc. (Japan) *81*, 153 (1961).

[68a] *H. Ishii, Y. Nozaki, T. Okumura*, and *D. Satoh*, J. pharmac. Soc. (Japan) *81*, 1051 (1961).

[68b] *Y. Nozaki* and *T. Okumura*, Agr. biol. Chem. (Japan) *25*, 515 (1961).

[69] *W. H. Bradshaw, H. E. Conrad, E. J. Corey, I. C. Gunsalus*, and *D. Lednicer*, J. Amer. chem. Soc. *81*, 5507 (1959).

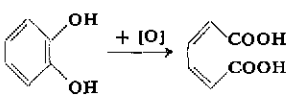
[70] *P. K. Bhattacharyya, B. R. Prema, B. D. Kulkarni*, and *S. K. Pradhan*, Nature (London) *187*, 689 (1960).

H_2O. Whereas LXXXIII and LXXXIV are formed by oxidation of the allyl position, *trans*-sobrerol (LXXXVII) is probably formed by attack of the electrophilic reagent (OH^+) at the double bond, followed by a rearrangement and a subsequent addition of OH^- to the carbonium ion LXXXVI. Thus, two basically different types of reaction probably participate in the formation of LXXXVII; however, this still requires verification. Further microbiological reactions in the terpene series are not known.

5. Phenols

Microbiological oxidations play a conspicuous role in the natural degradation of phenolic substances. They participate, for example, in the formation of lignin during the decay of plants and are recognisable in the brown coloration of sections of plant tissue. A parallel in animal biology is the formation of melanin from tyrosine or of ommochromes from tryptophan. The following types of reactions are found: hydroxylations, dehydrogenations, cleavage of C–C bonds, and demethylations of methyl ethers. According to *Mason* [71], the oxidases may be classified into three groups; one example of each is given in the following paragraphs:

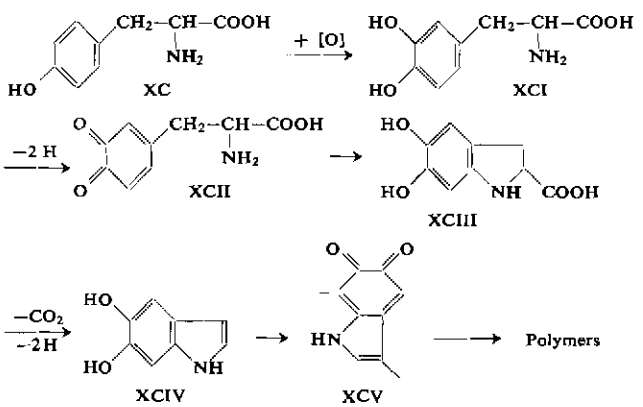
Type I: *Oxygen transferases*: $A + O_2 \rightarrow AO_2$



LXXXVIII LXXXIX

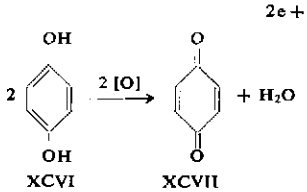
o-Dihydroxybenzene (LXXXVIII) is converted into *cis*, *cis*-muconic acid (LXXXIX) by oxidative cleavage of a C=C bond.

Type II: "*Mixed function oxydases*": $AH + 2e + O_2 \rightarrow AOH + O^{-2}$



In the animal kingdom melanins are formed from tyrosine (XC) through a sequence of several reaction steps (XCI to XCV).

Type III: *Electron transferases*: $4e + O_2 \rightarrow 2\,O^{-2}$ ($2\,H_2O$) or $2e + O_2 \rightarrow O_2^{-2}$ (H_2O_2)

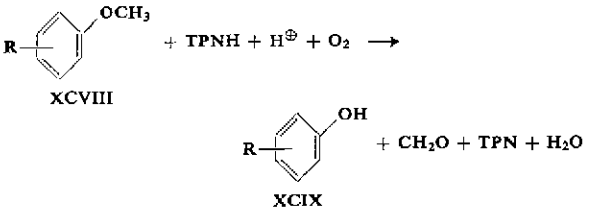


XCVI XCVII

[71] *H. S. Mason*, Advances in Enzymol. *19*, 79 (1957).

p-Benzoquinone (XCVII) is formed from hydroquinone (XCVI) by simple dehydrogenation.

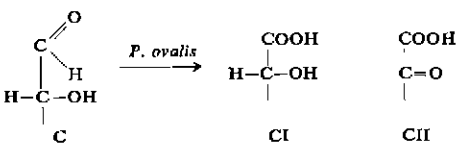
In the animal organism, cleavage of ether bonds takes place by an enzyme dependent on TPNH [72]. The methyl ether XCVIII is converted to the phenol XCIX, formaldehyde and water.



Microbial enzymes possibly act according to the same reaction scheme. The summary published recently by *Flaig* and *Haider* [73] contains numerous additional examples of microbial reactions with phenolic substances.

6. Carbohydrates

Oxidation of reducing sugars with the aid of bacterial enzymes has been studied in detail. For example, *Pseudomonas ovalis* oxidizes glucose (C) to gluconic acid (CI) in 80 % yield; *P. fluorescens* gives the 2-ketogluconic acid (CII) [74].



CI CII

Analogously, reducing disaccharides may be converted to the so-called bionic acids. Selective dehydrogenation reactions on secondary hydroxyl groups of sugar alcohols and cyclitols have been known for a long time.

Microbial transglycosidations in the oligosaccharide and polysaccharide series offer especially extensive possibilities of application. These proceed according to the following scheme:

$$R^1\text{–O–}R^2 + R^3OH \rightleftarrows R^1\text{–O–}R^3 + R^2OH$$

Glycosyl Donor — Glycosyl Acceptor

The glycosyl donor may be a hexose phosphate, a disaccharide, or a polysaccharide. Alcohols, mono- and polysaccharides, and H_3PO_4 assume the role of acceptor. Hexose phosphates, glycosides, di- and polysaccharides are formed together with mono- and polysaccharides and H_3PO_4 [75]. A typical example is the formation of three galactosides from lactose observed by *Pazur* et al. [76]

[72] *J. Axelrod*, Biochem. J. *63*, 634 (1956); *J. Axelrod*, *S. Senoh*, and *B. Witkop*, J. biol. Chemistry *233*, 697 (1958); *J. Axelrod* and *R. Tomchick*, J. biol. Chemistry *233*, 702 (1958).

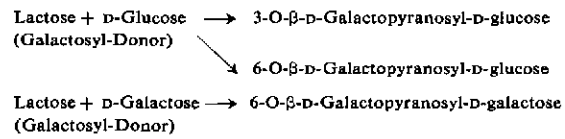
[73] *W. Flaig* and *K. Haider*, Planta Medica *9*, 123 (1961).

[74] *F. H. Stodola:* Chemical Transformations by Micro-organisms John Wiley and Sons, New York 1958, S. 50.

[75] See the summaries in *E. J. Hehre*, Advances in Enzymol. *11*, 297 (1951); *E. J. Hehre* in *S. P. Colowick*, and *N. O. Kaplan:* Methods in Enzymology. Academic Press, New York 1955, Vol. I, p. 178; *F. H. Stodola:* Chemical Transformations by Microorganism. John Wiley and Sons, New York 1958, S. 65ff.

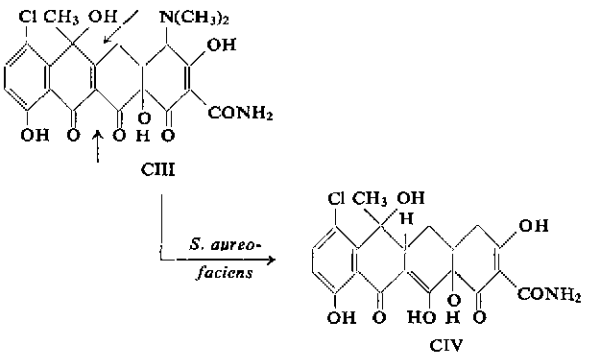
[76] *J. H. Pazur*, *C. L. Tipton*, *T. Budovich*, and *J. M. Marsh*, J. Amer. chem. Soc. *80*, 119 (1958).

during the incubation with cultures of *Saccharomyces fragilis*:

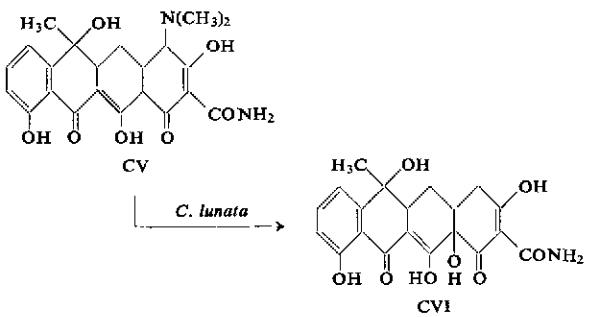


7. Antibiotics

One significant discovery is the microbiological reaction of antibiotic substances which are themselves produced by micro-organisms. *McCormick* et al. [77] converted 7-chloro-5a(11a)-dehydrotetracycline (CIII), which had been isolated from a strain of *Streptomyces aureofaciens*, into Aureomycin® (CIV) by incubation with a mutant of this organism. This involves an enzymatic hydrogenation. These authors were also successful in isolating from the culture filtrate of the organism a new crystalline, yellow active substance, the so-called "Cosynthetic Factor I", which causes the H transfer in this stereospecific reaction [78]. This might be a derivative of pyridine or flavine.

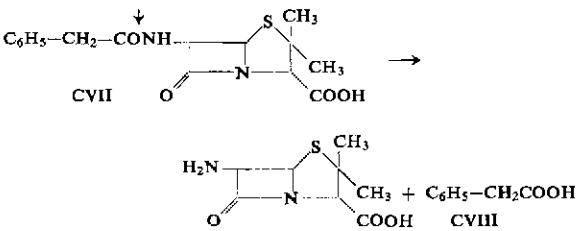


Oxygenation of 12a-desoxytetracycline (CV) was accomplished using *Curvularia lunata*. The OH group was introduced in the 12a-position with formation of tetracycline (CVI) [79].



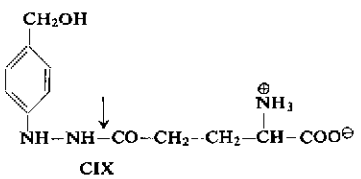
In the biosynthesis of the chlorine-containing tetracyclines, inorganic chloride from the nutrient is built into the tetracycline molecule [80]. *Kollar* and *Jarai* [81] observed that the inorganic chloride of the medium may be replaced by certain chlorinated fatty acids, such as chloroacetic acid or γ-chlorobutyric acid. It seems that the latter case is one of an enzymatic transchlorination. Such reactions have not, so far, been studied to any great extent.

Through the discovery of 6-aminopenicillanic acid (6-APA) (CVIII) in 1959, the field of penicillins has experienced an unexpected renaissance, since 6-APA (CVIII) serves as the starting material for the preparation of semisynthetic penicillins. Controlled enzymatic cleavage of the natural penicillins by acylases from Actinomycetes (*e.g.*, *Streptomyces lavendulae*), fungi, yeasts, and bacteria (*e.g.*, *Escherichia coli*) offers a productive method for preparating 6-APA, *e.g.*, from readily accessible penicillin G (CVII) [82–85].



In contrast to penicillinases these acylases leave the β-lactam ring untouched, *i.e.*, they selectively attack the acid amide bond of the side chain. The reaction is reversible, for example resynthesis of penicillin G from 6-APA (CVIII) and phenylacetic acid may be accomplished by pH variation.

Agaritin (CIX) should be mentioned as a curiosity; it is a phenylhydrazide of L-glutamic acid isolated from the press-juice of *Agaricus bisporus* (*Basidiomycetes*). This press-juice contains a hydrolase which is capable of cleaving the hydrazide group [86]. Occurrence and cleavage of this grouping are uncommon in a natural substance.



Gardner et al. [86a] obtained some clue to the biosynthesis of natural odd-numbered polyacetylenes from even-numbered ones by the observation that the α,β-unsaturated acetylene carboxylic acid CIXa is de-

[77] *J. R. D. McCormick, N. O. Sjolander, P. A. Miller, U. Hirsch, N. H. Arnold*, and *A. P. Doerschuk*, J. Amer. chem. Soc. *80*, 6460 (1958).

[78] *P. A. Miller, N. O. Sjolander, S. Nalesnyk, N. Arnold, S. Johnson, A. P. Doerschuk*, and *J. R. D. McCormick*, J. Amer. chem. Soc. *82*, 5002 (1960); *J. R. D. McCormick, U. Hirsch, N. O. Sjolander*, and *A. P. Doerschuk*, J. Amer. chem. Soc. *82*, 5006 (1960).

[79] *C. H. Holmlund, W. W. Andres*, and *A. J. Shay*, J. Amer. chem. Soc. *81*, 4748 (1959).

[80] *A. P. Doerschuk, J. R. D. McCormick, J. H. Goodman, S. A. Szumsk, J. A. Gorwich, P. A. Miller, B. A. Bitler, E. R. Jensen, M. Matrishin, M. A. Petty*, and *A. S. Phelps*, J. Amer. chem. Soc. *78*, 1508 (1956); *81*, 3069 (1959); *S. J. Kolldr*, and *M. Járai*, Acta microbiol. hung. *7*, 1 (1960).

[81] *S. J. Kollár* and *M. Járai*, Nature (London) *188*, 665 (1960).

[82] *G. N. Robinson, F. R. Batsheior, D. Butterworth, J. Cameron-Wood, M. Cole, G. C. Eustace, M. V. Hart, M. Richards*, and *E. B. Chain*, Nature (London) *187*, 236 (1960).

[83] *C. A. Claridge, A. Gourevitch*, and *J. Lein*, Nature (London) *187*, 237 (1960).

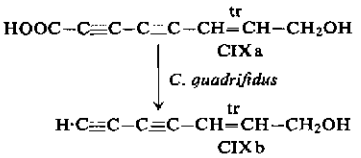
[84] *H. T. Huang, A. R. English, T. A. Seto, G. M. Shull*, and *B. A. Sobin*, J. Amer. chem. Soc. *82*, 3790 (1960).

[85] *W. Kaufmann* and *K. Bauer*, Naturwissenschaften *47*, 474 (1960).

[86] *B. Levenberg*, J. Amer. chem. Soc. *83*, 503 (1961).

[86a] *J. N. Gardner, G. Lowe*, and *G. Read*, J. chem. Soc. (London) 1532 (1961).

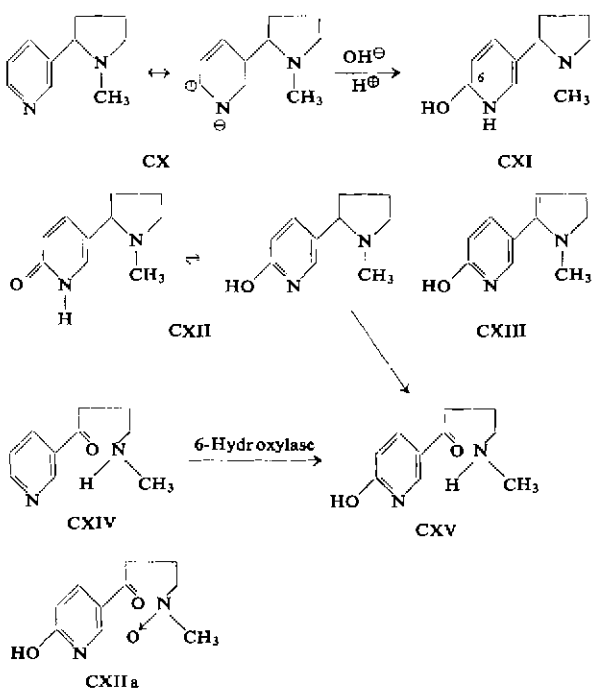
carboxylated by a cell-free extract of *Coprinus quadrifidus* (*Basidiomycetes*) to the acetylene derivative CIXb.



8. Alkaloids

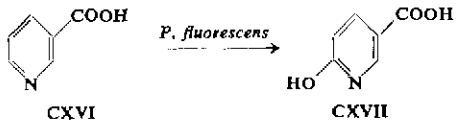
With the exception of the penicillins and agaritin, the microbial reactions discussed so far involved natural substances containing only C, H, and O, but no N. There are only very few reports available dealing with the behavior of basic substrates with N as part of a ring, *i.e.* alkaloids and their precursors toward these enzymes.

Nicotine (CX) was studied in greater detail by *Hochstein* and *Rittenberg* [87]. Three moles of oxygen per mole of nicotine were consumed during the incubation of nicotine with crude cell-free extracts from an unidentified soil bacterium; nicotine was the only source of C and N. The authors observed the formation of three products, two of which were isolated and identified. First, 1-methyl-2[6-hydroxy-3-pyridyl]-pyrrolidine, (CXII), was formed, presumably by nucleophilic attack of OH^- on CX via the pseudobase CXI. In the following step, the pyrrolidine ring is opened by oxidation with formation of 6-hydroxypseudooxonicotine (CXV),which can also be obtained from pseudooxonicotine (CXIV) by 6-hydroxylation with the aid of the same bacteria.

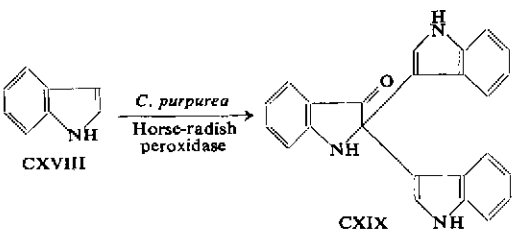


It is not certain whether this ring opening is preceded by a dehydrogenation. At any rate, the corresponding 6-hydroxy-*N*-methylmyosmine (CXIII) has not yet been identified as an intermediate. *Decker* et al. [88] also reported very similar studies with cell-free extracts from *Arthrobacter oxydans*. These authors observed the formation of blue pigments and assumed that CXV is formed through the intermediate *N*-oxide (CXIIa) derived from CXII.

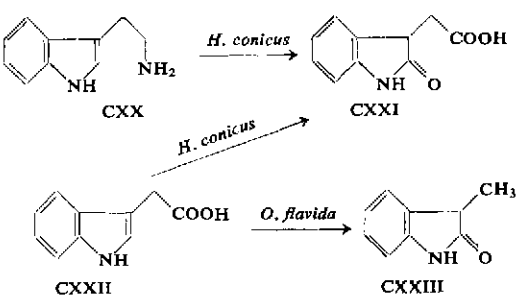
An analogous 6-hydroxylation had already been observed [89] on nicotinic acid (CXVI) using cell-free extracts from bacteria, *e.g.*, *Pseudomonas fluorescens*. An anaerobic soil bacterium which uses CXVI as a source of C and N did not produce 6-hydroxynicotinic acid (CXVII) as final product but decomposed CXVI to propionic acid, acetic acid, CO_2 and NH_3 [90].



In view of the great medicinal significance of the *Rauwolfia* and ergot alkaloids, it is not surprising that attempts were made to obtain new active substances with the aid of microbial enzymes. In contrast to the steroids, the results have not been promising so far, for the reactions took place only very sluggishly, if at all, and gave only poor yields. In the case of the precursor to this series, indole (CXVIII), oxidation with trimerization to CXIX takes place with *Claviceps purpurea* [91]; this was also effected by horse-radish peroxidase [92].



Hygrophorus conicus is capable of converting tryptamine (CXX) as well as indole-3-acetic acid (CXXII) into oxindole-3-acetic acid (CXXI) [93] while CXXII is degraded by oxidation to 3-methyloxindole (CXXIII) through the action of *Omphalia flavida* [94].



[87] *L. I. Hochstein* and *S. C. Rittenberg*, J. biol. Chemistry *234*, 151, 156 (1959); *235*, 795 (1960).

[88] *K. Decker*, *H. Eberwein*, *F. A. Gries*, and *M. Brühmüller*, Hoppe-Seylers Z. physiol. Chem. *319*, 279 (1960); *H. Eberwein*, *F. A. Gries*, and *K. Decker*, ibid. *323*, 236 (1961); *K. Decker*, *F. A. Gries*, and *M. Brühmüller*, ibid. *323*, 249 (1961); *F. A. Gries*, *K. Decker*, and *M. Brühmüller*, ibid. *325*, 229 (1961).

[89] *D. E. Hughes*, Biochem. J. *60*, 303 (1955); *A. L. Hunt*, *D. E. Hughes*, and *J.M.Lowenstein*, ibid.*66*, 2P (1957); *69*, 170 (1958).

[90] *J. Harary*, J. biol. Chemistry *227*, 815 (1957)

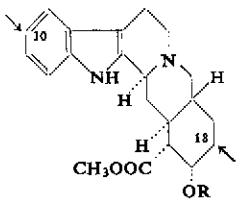
[91] *Y. H. Loo* and *D. O. Woolf*, Chem. and Ind. 1123 (1957).

[92] *A. G. Holmes-Siedle* and *B. C. Saunders*, Chem. and Ind. 265 (1957).

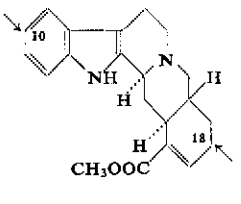
[93] *D. J. Slehr*, J. Amer. chem. Soc. *83*, 2401 (1961).

[94] *P. M. Ray* and *K.V.Thimann*, Arch. Biochem. Biophysics *64*, 175 (1956).

Oxygenations in the 10-position with formation of a phenolic OH group were observed with *Streptomyces platensis* and *Cunninghamella blakesleeana* in alkaloids possessing the yohimbane skeleton, such as 3-epi-α-yohimbane, allo-yohimbine, rauwolcine [95], β-yohimmethyl ether, 3-epi-apoyohimbine, and apoyohimbine [96] (cf. structural types CXXIV and CXXV).



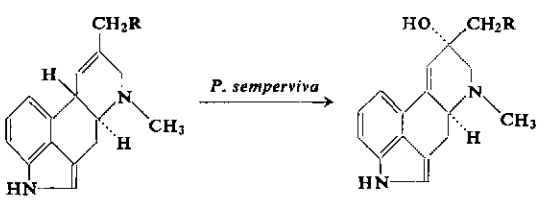
CXXIV



CXXV

C. Blakesleeana also attacked the allylic C-18 atom of apoyohimbine. 18α-Hydroxylation of yohimbine and α-yohimbine has been accomplished with *Streptomyces aureofaciens* and *S. rimosus*, although only in yields of 5 % [97].

A hydroxylation with simultaneous allylic rearrangement was observed by *Brack* et al. [98] after incubation of ergot alkaloids of the clavine type with cultures of *Psilocybe semperviva*. Thus, agroclavine (CXXVI) was largely converted within one to seven days into setoclavine (CXXVII); similarly, elymoclavine (CXXVIII) yields penniclavine (CXXIX).



CXXVI: R = H
CXXVIII: R = OH

CXXVII: R = H
CXXIX: R = OH

Isosetoclavine and isopenniclavine were also formed in small amounts. In the case of ergotamine and ergobasine, only isomerization or an extensive degradation of the ring skeleton was observed under the same conditions.

When colchicine (or thiocolchicine) is incubated with cultures of *Streptomyces griseus*, one of the three methoxy groups attached to ring A is selectively demethylated [99], a reaction which seldom succeeds with chemical reagents. The monodimethyl derivatives differ from the known isomers (substances E and F).

In our experience experiments with tropane derivatives using *Fusarium lini* were disappointing. A positive result was obtained only with tropinone, which was reduced to tropine and ψ-tropine. Dehydrogenation of the two alcohols was not observed [100]. No other publications concerning microbiological reactions in the alkaloid series have appeared.

[95] *Y. H. Loo* and *M. Reidenberg*, Arch. Biochem. Biophysics *79*, 257 (1959).

[96] *W. O. Godtfredsen*, *G. Korsby*, *H. Lorck*, and *S. Vangedal*, Experientia *14*, 88 (1958).

[97] *S. C. Pan* and *F. L. Weisenborn*, J. Amer. chem. Soc. *80*, 4749 (1958).

[98] *A. Brack*, *R. Brunner*, and *H. Kobel*, Helv. chim. Acta *45*, 276 (1962); the author thanks Dr. *Brack* and Dr. *Kobel* for access to unpublished results.

[99] *L. Velluz* and *P. Bellet*, C. R. hebd. Séances Acad. Sci. *248*, 3453 (1959).

[100] *Ch. Tamm*, *H. P. Sigg*, and *W. Zürcher*, unpublished results.

9. Nature of the Enzymes, Reaction Mechanisms

The problem of the nature of the microbial enzymes and the mechanisms of the reactions which they catalyze can now be discussed. It should be emphasized, however, that this examination leads into a field of enzymology investigated but little so far, and is therefore speculative in many aspects. Thus, it is still unknown today what significance the enzymes mentioned here have in microbial metabolism. The substances converted by the micro-organisms are not of vital importance to them. Many organisms even produce steroids themselves *e.g.*, yeast produces ergosterol. However, these sterols are not hydroxylated by the same organism. Nevertheless, if an extraneous steroid is added to the culture, hydroxylation is observed. For this reason, it is assumed that a detoxication reaction might be involved. The extraneous substance is converted into a more water-soluble form by hydroxylation and can thus be removed more rapidly from the closer environments of the organism. The animal organism has the known ability of effecting detoxification in a similar manner; hydroxylation may be followed by the formation of a sulfate or a glucuronide. In favor of this hypothesis is the fact that polyhydroxylated substrates cannot be oxygenated further. Inhibition of fungus growth is often observed after addition of the new substrate. The organism recovers during and after the microbiological reaction. Whether the enzymes are native or whether their formation is induced by the substrate is an unsolved problem. It has been shown that the culture filtrate contained almost only reaction product, while the starting material was enriched in the mycelium [17, 101]. Evidently, the transformation takes place at the lipoid surface of the micro-organism.

a) Hydroxysteroid Dehydrogenases

These are the enzymes studied most. Our knowledge is due principally to studies by *Talalay* [15, 102]. This author isolated two dehydrogenases from a testosterone-adapted *Pseudomonas* strain – a 3α-hydroxysteroid dehydrogenase and a 3β- and 17β-hydroxysteroid dehydrogenase. *Hübener* et al. [103] recently obtained a 20β-hydroxysteroid dehydrogenase (in crystalline form) from extracts of *Streptomyces dehydrogenans*. The reactions catalyzed by these enzymes are reversible and require diphosphopyridine-nucleotide (DPN), or perhaps triphosphopyridine nucleotide (TPN) to act as hydrogen transfer agents. This has been shown by isotope experiments with deuterium. The enzymes are stereospecific *e.g.* β-hydroxysteroid dehydrogenase oxidizes only one of the two enantiomorphic isomers of testosterone prepared by total synthesis [102]. The reactions may be formulated as follows:

$$\text{Hydroxysteroid} + \text{DPN}^{\oplus} \rightleftharpoons \text{Ketosteroid} + \text{DPNH} + \text{H}^{\oplus}$$

[101] *G. Wix* and *K. Albrecht*, Nature (London) *183*, 1279 (1959).

[102] *P. Talalay* and *H. R. Levy* in: Steric Course of Microbiological Reactions. J. A. Churchill, London 1959, S. 53.

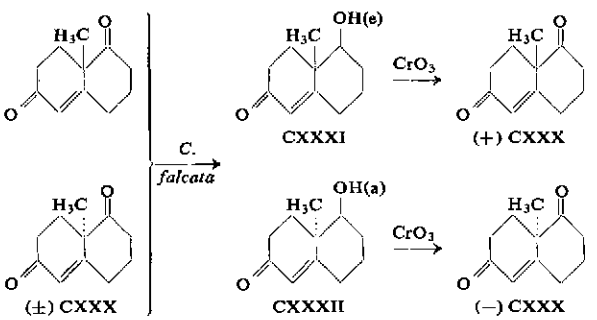
[103] *H. J. Hübener*, *F. G. Sahrholz*, *J. Schmidt-Thomé*, *G. Nesemann*, and *R. Junk*, Biochim. biophysica Acta *35*, 270 (1959).

The folllowing values were found for the equilibrium constants of 3-hydroxysteroid dehydrogenase:

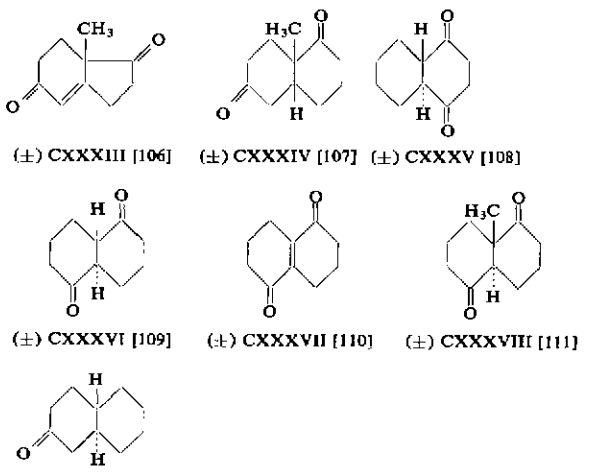
$$K_H = \frac{[\text{Ketone}]\,[\text{DPNH}]\,[H^{\oplus}]}{[\text{Alcohol}]\,[\text{DPN}^{\oplus}]} = 1\times10^{-9} \text{ to } 40\times10^{-9}$$

Purified hydroxysteroid dehydrogenase preparations have proved to be sensitive reagents for the quantitative determination of steroid alcohols and ketones in microanalysis [103a].

Prelog and his co-workers have used racemic derivatives of 1-decalone, 2-decalone, and hydrindanone as substrates since these simple compounds reproduce the most important properties of the steroids. Microorganisms (*Curvularia falcata, Rhizopus migricans, Aspergillus niger*) show no selectivity for the starting material with these model compounds but only product specificity; *C. falcata* in particular exhibits especially high stereospecificity. Steroids are preferentially hydroxylated by these organisms. Thus, (±)-Δ^4-9-methyloctalene-3,8-dione (CXXX) gave only the two Δ^4-8-hydroxyoctal-3-ones (CXXXI) and (CXXXII) with *C. falcata* [104], as each of the two enantiomers of CXXX was stereospecifically reduced to a product with an (8S)-configuration.



Reoxidation of the two products with CrO_3 gave the two antipodes of the starting material, (+)CXXX and (−)CXXX. Since CXXXI and CXXXII may be separated as diastereoisomers, the overall reaction amounts to a racemate separation of CXXX. *Aspergillus niger* [106]



[103a] See *H. J. Hübener* and *W. Rick* in *H. U. Bergmeyer:* Methoden der enzymatischen Analyse. Verlag Chemie, Weinheim-Bergstr. 1962.

[104] *V. Prelog* and *W. Acklin*, Helv. chim. Acta *39*, 748 (1956).

proved to be less product-specific. Analogous reductions, which, however, varied in stereospecificity depending on the micro organism used, were carried out with the ketones CXXXIII to CXXXIX [105–112].

It proved possible to obtain highly enriched hydrogenase from cell-free extracts of *C. falcata*. The process is dependent on TPNH, is activated by cysteine, and is inhibited by traces of chloromercuribenzoate [113]. On the basis of ideas put forward by *Vennesland* and *Westheimer*, *Prelog* interprets his results with the aid of a "two-plane theory", which is a modification of the "three-point theory" of *Ogston* [113]. This states that the dihydropyridine ring and the carbonyl group of the substrate with their two substituents lie in parallel planes during the transition state of the reduction; the larger lipophilic substituent faces the H atom of the coenzyme and the smaller substituent faces the hydrophilic $CONH_2$ group of the coenzyme. An analogous spatial arrangement is postulated for the apoenzyme (protein). An enzyme-substrate complex, in which the hydrophilic (polar) component of the protein, the $CONH_2$ group of the coenzyme, and the smaller substituent in the carbonyl group of the substrate are in closest proximity, while the apolar component of the apoenzyme, the β-hydrogen atom of the coenzyme, and the large lipophilic substituent are arranged in similar (but not identical) manner, ought to be favored from an energy standpoint. The difference in free enthalpy should then be sufficiently great to explain the observed stereospecificity.

b) Δ-Dehydrogenases and Δ-Reductases

Levy and *Talalay* [102,114] isolated and purified two enzymes which introduce Δ^1- and Δ^4-double bonds from cell-free extracts of *Pseudomonas testosteroni*. Phenazine methosulfate is a good electron acceptor in these oxidations. According to studies by *Levy* and *Talalay* and others, these enzymes cause direct dehydrogenation of the steroid, presumably with the participation of a flavine-type prosthetic group. Hydroxylation with subsequent dehydration appears improbable. The 3-keto group must be present. The Δ^1-dehydrogenation is stereospecific, since, when synthetic racemic cortisone or aldosterone is used, only the natural antipode is oxidized [115]. The experiments carried out by *Hayano* et al. [116] with *Bacillus sphaericus* give information about the stereochemical course of the dehydrogenation. Although steroids having a substituent in the 1β- and 2α-positions ($-CH_3$ or $-OH$) are dehydrogenated smoothly, the reaction does not start if the isomers are 1α- and 2β-substituted. This result indicates a direct

[105] *W. Acklin, O. Dütting*, and *V. Prelog*, Helv. chim. Acta *41*, 1424 (1958)

[106] *W. Acklin, V. Prelog*, and *A. P. Prieto*, Helv. chim. Acta *41*, 1416 (1958).

[107] *W. Acklin, V. Prelog*, and *D. Zäch*, Helv. chim. Acta *41*, 1428 (1958).

[108] *P. Baumann* and *V. Prelog*, Helv. chim. Acta *41*, 2362 (1958).

[109] *P. Baumann* and *V. Prelog*, Helv. chim. Acta *41*, 2379 (1958).

[110] *P. Baumann* and *V. Prelog*, Helv. chim. Acta *42*, 736 (1959).

[111] *V. Prelog* and *D. Zäch*, Helv. chim. Acta *42*, 1862 (1959).

[112] *V. Prelog* and *H. E. Smith*, Helv. chim. Acta *42*, 2624 (1959).

[113] *V. Prelog* in: Steric Course of Microbiological Reactions. J. A. Churchill, London 1959, p. 79.

[114] *H. R. Levy* and *P. Talalay*, J. biol. Chemistry *234*, 2014 (1959).

[115] *E. Vischer, J. Schmidlin*, and *A. Wettstein*, Experientia *12*, 50 (1956).

[116] *M. Hayano, H. J. Ringold, V. Stefanovic, M. Gut*, and *R. I. Dorfman*, Biochem. biophys. Res. Commun. *4*, 454 (1961).

axial cleavage of the 1α- and 2β-hydrogen atoms during Δ^1-dehydrogenation. The authors propose the two-step mechanism illustrated in Fig. 5.

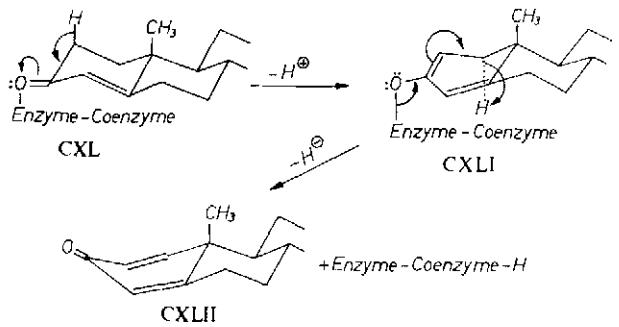


Fig. 5. Two-step reaction in the Δ^1-dehydrogenation of Δ^4-3-ketosteroids [116]

A coordinative complex CXL is formed between the 3-keto group and the enzyme and this is converted into the Δ^2-enol CXLI, the 2β-hydrogenatom being split off as proton. The axial configuration of the H atom is more favorable than the equatorial configuration. In the Δ^2-enol (CXLI), the H atom at C-1 is activated. It is split off as hydride ion and transferred to a still unknown acceptor. Again, an axial 1-H atom is favoured. Oxidation in the presence of ^3H_2O caused an exchange of the activated H atom at C-2 and of the initially non-activated H atom at C-1 [117]. *Holmund* et al. [117a] have confirmed the necessity of the 2β-H atom for Δ^1-dehydrogenation.

The Δ-reductases in animal organisms require TPNH. The reactions seem to be irreversible [102]. It is not known whether this also applies to microbial enzymes.

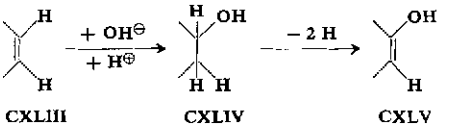
c) Δ^5-3-Ketosteroid Isomerase

Enzymatic isomerization of $\Delta^{5(6)}$ and $\Delta^{5(10)}$-3-ketosteroids to Δ^4-3-ketosteroids presumably occurs by a direct H transfer from C-4 to C-6, since no deuterium or tritium enters into the steroid molecule when, for example, Δ^5-androstene-3,17-dione in D_2O or HTO is converted into Δ^4-androstene-3,17-dione [118]. *Kawahara* and *Talalay* [119] successfully isolated the Δ^5-3-ketosteroid isomerase of *Pseudomonas testosteroni* in crystalline form.

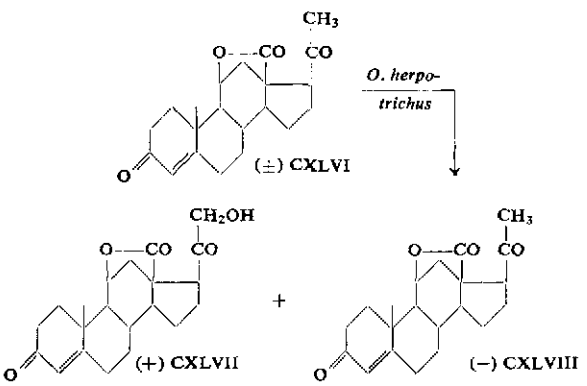
d) Hydroxylases

Hydroxylases have not been obtained cell-free. They must be very sensitive enzyme systems. Presumably the oxygenations take place in the mitochondria; this requires a lipophilic substrate.

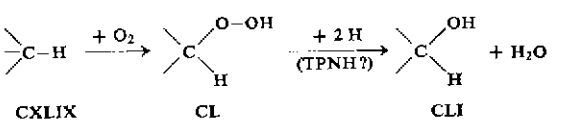
Hydroxylations of aromatic systems follow a basically different reaction mechanism from hydroxylations of saturated hydrocarbons: in the aerobic 6-hydroxylation of nicotinic acid by *Pseudomonas fluorescens* in the presence of $H_2{}^{18}O$ or of $^{18}O_2$, *Hunt* and co-workers [89] found that the oxygen introduced originated from the water of the medium. Water is probably first added to the aromatic substrate CXLIII and then CXLIV is dehydrogenated to the phenol CXLV. Cytochromes possibly play a role in the second step.



Hydroxylations at saturated carbon atoms are stereospecific just as dehydrogenations are. Using the racemic lactone of 11β-hydroxy-18-carboxyprogesterone(CXLV), which was prepared by total synthesis, only the natural antipode was hydroxylated in the 21-position by *Ophiobolus herpotrichus* and the enantiomer CXLVI remained untouched. The optically active ketol CXLVII was converted into natural aldosterone by chemical reduction of the lactone group [115]. Thus, in effect, cleavage of the racemate has been accomplished.



Hydroxylations in the steroid series also require molecular oxygen. Experiments with the ^{18}O oxygen isotope showed that the O atom introduced does not originate from the water of the culture medium but from oxygen in the atmosphere [120]. In the animal organism, the oxygenation is dependent on TPNH. Presumably this is also the case in microorganisms. The reaction probably involves an oxidative and a reductive step in the sense of the formulae CXLIX to CLI:



Respiration measurements indicated that the O_2 absorption of a micro-organism is reduced by steroids when these are used as starting materials, but remains unchanged by the product [121]. Since practically nothing is known about the nature of hydroxylases, correspondingly little is known about their cofactors and inhibitors. Thus, although the 16α-hydroxylase of one strain of *Streptomyces* is inhibited by selenite, arsenite, and azide ions, while fluoride and cyanide

[117] *M. Hayano, V. Stefanovic, Y. Kurosawa, M. Gut,* and *R. I. Dorfman,* Fed. Proc. *20,* 238 (1961).

[117a] *C. E. Holmlund, L. I. Feldman, R. H. Blank, N. Barbacci,* and *B. Nielsen,* Sci. Repts. Ist. Super. Sanità *1,* 289 (1961).

[118] *P. Talalay* and *V. T. Wang,* Biochim. biophysica Acta *18,* 300 (1955).

[119] *F. S. Kawahara* and *P. Talalay,* J. biol. Chemistry *235,* PC 1 (1960).

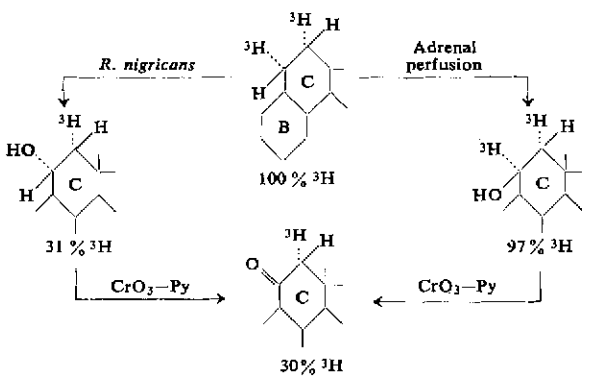
[120] *M. Hayano, N. Saba, R. I. Dorfman,* and *O. Hechter,* Recent Progr. Hormone Res. *12,* 79 (1956); *M. Hayano, A. Saito, D. Stone,* and *R.I.Dorfman,* Biochim. biophysica Acta *21,* 380 (1956).

[121] *A. Capek, H. Pavlu,* and *O. Hanč,* Naturwissenschaften *45,* 89 (1958).

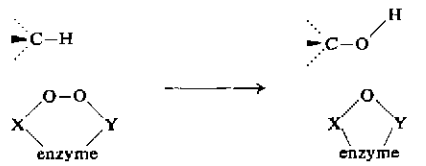
exert no influence [122–124], steroid hydroxylation with *Curvularia lunata* is inhibited by 10^{-3} M NaCN and by 10^{-4} M NaN_3 [125]. Lower concentrations of CN^- promote hydroxylation. There is also a dependence on the concentration of Fe^{++} [125]. 15α-Hydroxylation of cortexone and the 12β-hydroxylation of digitoxigenin with *Fusarium lini* is inhibited by 10^{-2} M KCN, and promoted by 10^{-3} M KCN and 10^{-4}M KCN in the case of digitoxigenin [57]. The 1-dehydrogenation of progesterone by a strain of *Nocardia* is completely suppressed by CN^-; instead 9α-hydroxylation takes place [126]. An interpretation of these results is not possible at the present time.

Experiments with tritium-labelled and deuterated substrates gave further information on the stereochemistry of the oxygenation. Microbial hydroxylation follows the same course as hydroxylation in the animal organism. The isotope experiments – carried out independently in three laboratories – unanimously gave the remarkable result that the hydroxylation at the secondary C atom is a substitution without Walden rearrangement. (In the hydroxylation of the tertiary C-14 atom, the configuration also remains intact.)

Hayano et al. [127] showed this in the following manner using as an example, 11-hydroxylation:



The 11α-hydroxy derivative resulting from incubation of 11α-, 12α-ditritio-5α-pregnane-3,20-dione with *Rhizopus niricans* (11α-hydroxylation) still contained 31 % of the original tritium content. This value did not change after dehydrogenation of the 11α-hydroxy group with CrO_3 in pyridine. On the other hand, the tritium content of the substrate remained practically constant following adrenal perfusion (11β-hydroxylation) and only decreased during the CrO_3-oxidation of the 11β-hydroxy derivate (cf. *Corey* et al. [128]). The same mechanism was found for 7α-hydroxylation in rats [129] and for microbial 12β-hydroxylation [130]. The enzymes which catalyze the hydroxylation at a saturated, nonactivated C atom, are not homolytic but electrophilic reagents, a fact which may be concluded from their stereospecificity. *Corey* and *Gregoriou* [131] postulate the intermediate appearance of an OH^+ species.



An analogy is to be found in the biosynthesis of the steroids and triterpenes, where oxydative cyclization of squalene is also caused by an OH^+ ion (squalene oxidase). The nature of the oxygen-transferring enzyme and the character of the substrate-enzyme complex proper, in which X and Y may be metal ions, are still unknown.

10. Concluding Remarks

In this article an attempt has been made to present a cross-section of current knowledge concerning microbial enzymes. Although considerable success has been achieved in the past many basic problems are still awaiting solution, especially with reference to the nature of the enzymes, their mode of action, and the reaction mechanisms involved. Reactions with micro-organisms may be interpreted as biological models. The study of the behavior of the microbial enzymes towards natural substances and their biogenetic precursors can, therefore, furnish valuable data relating to their biosynthesis and metabolism in the plant and animal kingdoms.

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[124] *D. Perlman,* Abstr. 130th Meeting Amer. chem. Soc. 33 A (1956).

[125] *K. Zetsche,* Naturwissenschaften *47,* 232 (1960).

[126] *C. J. Sih* and *F. L. Weisenborn,* J. Amer. chem. Soc. *82,* 2653 (1960).

[127] *M. Hayano, M. Gut, R. I. Dorfman, O. K. Sebek,* and *O. H. Peterson,* J. Amer. chem. Soc. *80,* 2336 (1958).

[128] *E. J. Corey, G. A. Gregoriou,* and *D. H. Peterson,* J. Amer. chem. Soc. *80,* 2338 (1958).

[129] *S. Bergström, S. Lindstredt, B. Samuelson, E. J. Corey,* and *G. A. Gregoriou,* J. Amer. chem. Soc. *80,* 2337 (1958).

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Inverse Polarography and Voltammetry: New Methods for Trace Analysis

BY PRIV.-DOZ. DR. ROLF NEEB

INSTITUT FÜR ANORGANISCHE CHEMIE UND KERNCHEMIE DER UNIVERSITÄT MAINZ (GERMANY)

Inverse polarographic and voltammetric methods are surveyed. The electrochemical determination procedure is carried out by current reversal after electrolytic concentration on a working electrode. Analyses in the nanogram (ng) region (10^{-9} g.) are possible because the sensitivity is increased by a factor of 100 to 1000 in comparison with the usual polarographic and voltammetric methods. These methods are, therefore, of particular interestin trace analysis.

I. General

Polarographic methods are valuable analytical tools in the region of microgram quantities. Sensitivities greater than 0.2 to 1 μg/ml are generally not attainable. However, particularly sensitive polarographic and voltammetric methods have recently been described [1].

The present paper describes only those methods in which the ion to be determined (*e.g.* by recording a current-voltage curve and determining the diffusion current) is electrolytically preconcentrated. If, after pre-concentration on the working electrode, it is possible to employ a reversible electrochemical process for the determination of the element, a current increase proportional to the concentration factor is obtained. The concentration factor depends upon the conditions during electrolysis and the relationship of the volume of the aqueous solution to the volume (or the surface) of the working electrode.

The principle of inverse voltammetry is described by means of an example in Figure 1: In the reduction of

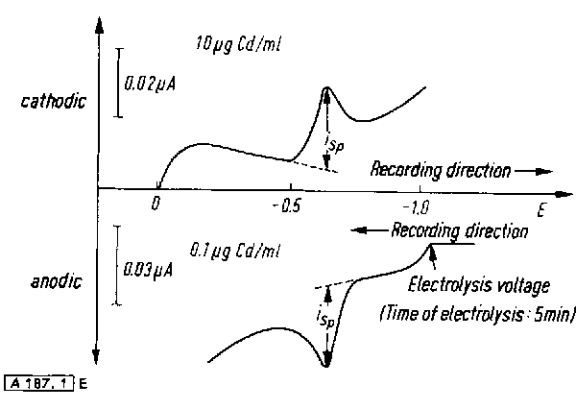


Figure 1. Principle of inverse voltammetry; stationary mercury electrodes (5 mm²), 0.06 V/sec., 0.1 N HCl.

Cd ion at the stationary mercury electrode (*e.g.*, a hanging mercury drop), peak currents are developed [2] which are proportional to the concentration of Cd^{2+} in the aqueous solution.

This peak current is indicated in the upper portion of Figure 1. If the cadmium is electrolytically concentrated (at −1.2 V) on the mercury prior to plotting of the current-voltage curve, then peak currents derived from the oxidation of the cadmium in the mercury are obtained by recording the current-voltage curve in the reverse direction. In an electrolysis of appropriate duration, the concentration of cadmium in mercury is considerably higher than that of the cadmium ion in the aqueous solution. According to *Randles* [2] and *Sevčik* [3] the value of such peak currents is given by the following equation:

$$i_{Sp} = K \cdot O \cdot D^{1/2} n^{3/2} c v^{1/2}$$

where,

D = Diffusion coefficient in mercury or water, c = Concentration in aqueous solution or in amalgam, v = Rate of voltage change (V/sec), n = Valence change, K = Constant, O = Electrode surface area.

Since the diffusion coefficients are of similar order of magnitude and since the equation is also approximately valid for the amalgams, the increase in the peak current is explained by the increase in c.

In this technique the determination takes place when the direction of both the current and diffusion is reversed. The expression "inverse polarography and voltammetry" [*] may therefore be considered justified.

The presently known methods for electrolytic concentration in inverse polarography and voltammetry are shown in Table 1. The concentration process consists of either (a), the electrolytic deposition of a metal on a solid metallic electrode or (b), the production of an amalgam at a mercury electrode, as indicated above.

A third possibility (c) is electrolytic oxidation of the metal of the working electrode in the presence of an anion, which together with the metal ions generated forms a compound which is not readily soluble. This compound is then deposited on the electrode surface in

[1] *M. v. Stackelberg* and *H. Schmidt*, Angew. Chem. *71*, 508 (1959).

[2] *J. E. B. Randles*, Trans. Faraday Soc. *44*, 327 (1947).

[3] *A. Ševčik*, Collect. czechoslov. chem. Commun. *13*, 349 (1948).

[*] In Anglo-American literature the term "stripping technique" is often used. Concerning the term "chronoamperometry" see [5]; concerning the term "voltammetry" see also [4]. The term "inverse polarography" has been used repeatedly in the literature; it is assumed to have originated with *Hickling* et al. [32].

[4] *P. Delahay:* New Instrumental Methods in Electrochemistry. Interscience Publ., New York – London 1954, p. 11.

[5] *P. Delahay, G. Charlot*, and *H. A. Laitinen*, J. elektroanalyt. Chem. *1*, 425 (1959).

Table 1. Basic principles of inverse polarography and voltammetry

Aqueous solution contains	Electrochemical determination; procedure in aqueous solution	Electrolytic preconcentration	Electrochemical determination; procedure of inverse polarography and voltammetry
A) Me^{n+}	$Me^{+} \rightarrow Me^{0}$ (electrochemical reduction)	On metal electrode: $Me^{+} \rightarrow Me^{0}$	$Me^{0} \rightarrow Me^{+}$ (anodic)
B) Me^{n+}	$Me^{+} \rightarrow Me^{0}$ (electrochemical reduction)	On mercury electrode: $Me \rightarrow Me^{0}$ (Hg)	Me^{0} (Hg) $\rightarrow Me^{+}$ (anodic)
C) An^{-}	$A^{-} + Me^{0} \rightarrow MeA$ (electrochemical oxidation)	On metal (also mercury)-electrodes $A^{-} + Me^{0} \rightarrow MeA$	$MeA \rightarrow Me^{0} + A^{-}$ (cathodic)

proportion to the concentration of the anion. The subsequent voltage reversal (cathodic) causes a reduction of the metal ion contained in the deposit. Peak currents, whose values are dependent on the amount and, therefore, on the concentration of the deposited metal ion, are thereby generated.

The concentration of the ion on the working electrode can again be considerably increased by proper selection of the electrolysis conditions. An example of this method is given below for the determination of iodide by means of a silver electrode. (See also Figs. 10 and 11).

II. Equipment

The only factor common to all methods is the electrolytic concentration of ions on the working electrodes. The concentrated substances can be subsequently determined according to the well-known polarographic and voltammetric methods (Table 2).

With the exception of VII, all the methods can also be used for determination of the ion in aqueous solution. The method described under VII is, in reality, a modification of method II. Under certain conditions (slow rate of voltage change, use of platinum electrodes or of amalgamated wire-electrodes), the electrolytically deposited substance dissolves completely within the first voltage sweep. The area under the current curve is then proportional to the quantity of electricity necessary for the redissolution of the deposit and, therefore, to the quantity of deposited material. The second column indicates the current-voltage-time function used for the determination, while the third column shows a schematic representation of the corresponding voltammetric curve.

1) Recording Apparatus and Voltage Source

Generally, commercial equipment can be used. With methods II, III, IV, and VII it is necessary to be able to record rapidly occurring current-voltage curves (II, VII), voltage-time curves (IV), or current-time curves (III). Suitable recorders with fast response time (a maximum of 0.25 sec for full scale deflection) are available and can be used in conjunction with suitable amplifiers. For even higher recording speeds, very sensitive, fast-response galvanometers with photographic recording are required. An installation of this type has been successfully used for several purposes [12]. Oscilloscopes with long-persistence phosphor screens are also used [16, 18]. The so called "Blauschreiber" [26] may well find many applications in analytical methods for the recording of rapid transient phenomena, such as observed in chronopotentiometry with amalgam electrodes. Kohlrausch cylinders or rotary potentiometers, driven by synchronous motors are usually employed for the generation of variable voltages for the recording of current-voltage curves (method II). Electronic voltages sources produce steady voltages which are not subject to disturbances from mechanical contacts even if the voltage change is very rapid. Their principle of operation is based on the use of a well-insulated capacitor which is charged through a large resistor from a constant-voltage source (27–29). The amplification of the input voltage through a cathode amplifier results in a voltage source with a very small internal resistance. (See Fig. 2 for block circuit diagram).

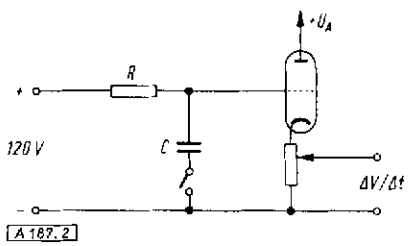


Figure 2. Schematic diagram of an electronic voltage source.
R = 2 to 25 megohms; C = 16 microfarads; $\Delta V/\Delta t$ = 0.08 to 2.0 V/sec.

When only the initial portion of the input curve is considered, the voltage change is seen to be virtually linear. By varying the load resistance one can obtain various voltage change rates. Such electronic voltage generators have recently been incorporated into conventional polarographs [30]. These are the only usable instruments for applications in which the voltage changes rapidly (such as in method II) and also where high sensitivities are required. A polarograph which is particularly suitable for inverse voltammetry (method II) will soon become commercially available [31].

2) Electrodes and Electrolytic Cells

Stationary electrodes with constant surface area are used almost exclusively, while dropping electrodes are used only occasionally.

a) Dropping Amalgam Electrode

While it is analytically of little value, this electrode is used for various polarographic investigations [6]. The amalgams may be produced by electrolysis of aqueous solutions, with the mercury of the drop electrode serving as the cathode.

[6] *N. H. Furman* and *W. Ch. Cooper*, J. Amer. chem. Soc. *720* 5567 (1950).

[7] *A. G. Stromberg* and *A. A. Pyshkina*, Trudy Kom. Anal. Khim; Akad. Nauk. S.S.S.R. *7*, 136 (1956).

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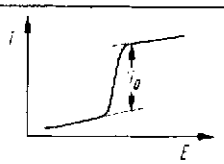
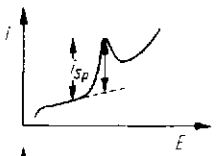
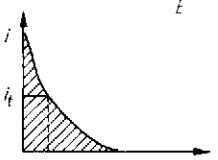
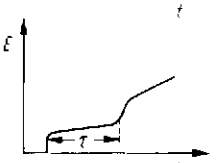
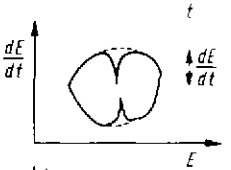
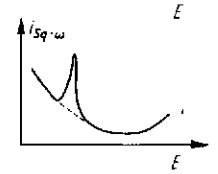
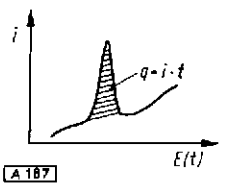
[14] *W. Kemula* and *Z. Kublik*, Analyt. chim. Acta *18*, 104 (1958).

[15] *G. Mamantov, P. Papoff*, and *P. Delahay*, J. Amer. chem. Soc. *79*, 4034 (1957).

[16] *G. Mamantov, P. Papoff*, and *P. Delahay*, Analyt. chim. Acta *18*, 81 (1958).

[17] *R. Neeb*, Z. analyt. Chem., in the press.

Table 2. Analytical methods in inverse polarography and voltammetry

Method	Electrochemical Process	Curve developed	Term used	Calibration curve	Ref.
I	$i = f(E)$ (E = constant)		Amalgam polarography	$c \sim i_D$	[6,7]
II	$i = f(E)$ (E = linearly variable)		Voltammetry "linear sweep voltammetry", chronoamperometry	$c \sim i_{Sp}$	[8–14]
III	$i = f(t)$ (E = const.)		a) Potential-step method (potentiostatic method) b) Coulometry	a) $c \sim i_t$ b) $c \sim \int_0^t i$	[15, 16]
IV	$E = f(t)$ (i = const.)		Current step method (galvanostatic method) Chronopotentiometry	$c \sim \tau$	[15–17]
V	$\frac{dE}{dt} = f(E)$		Micro-oscillopolarography	$c \sim \frac{dE}{dt}$	[18–20]
VI	$i_{Sq.w.} = f(E)$		Square-wave-polarography	$c \sim i_{Sq.w.}$	[21, 22]
VII	$i = f(E)$		Microcoulometry	$c \sim \int i \sim q$	[23–25]

Method I Classical constant voltage polarography: The average current (i) found on the mercury drop is measured as a function of the constant voltage (E). The voltage applied is varied so slowly that "i" is measured at a virtually constant potential.

Method II The applied voltage (E) is changed at a rapid, constant rate of about 0.3 V/sec. Because of the depletion of the material on the electrode surface and the lack of sufficient supply by diffusion, peak currents develop which are proportional to the concentration (i_{Sp}).

Method III The current at a stationary electrode is measured as a function of time at constant potential (in this case more positive than the deposition potential). Either the area below the i/t curve (a) or the current (i_t) after a specific elapsed time (t) are measured for the evaluation.

Method IV After application of a current (i) (decomposition current for amalgams) the potential (E) of the working electrode is measured as a function of time. The transition time (the period of stationary potential) is concentration dependent.

Method V An alternating sinusoidal voltage (E) is applied at a constant current to the mercury electrode. The oscillograph registers the time derivative of the electrode potential $\frac{dE}{dt}$ as a function of (E).

Method VI A square-wave alternating current is superimposed on the current of the usual polarography. The amplitude ($i_{sq.\,wave}$) of the constant voltage is measured at the pulse end where the capacitance current has practically reached zero. This is necessary to eliminate the effect of the capacitance current.

Method VII Similiar to method II (also see text).

[18] *R. Kalvoda*, Collect. czechoslov. chem. Commun. *22*, 139, (1957).

[19] *R. Kalvoda*, Analyt. chim. Acta *18*, 132 (1958).

[20] *R. Kalvoda*, Proc. Intern. Sympos. Microchem. (Birmingham 1958). Pergamon Press, London 1960, p. 288.

[21] *G. C. Barker*, A. E. R. E. Report C/R 1563 (1957).

[22] *G. C. Barker*, Analyt. chim. Acta *18*, 118 (1958).

[23] *S. S. Lord, R. C. O'Neill*, and *L. B. Rogers*, Analytic. Chem. *24*, 209 (1952).

[24] *K. W. Gardiner* and *L. B. Rogers*, Analytic. Chem. *25*, 1393 (1953).

[25] *T. L. Marple* and *L. B. Rogers*, Analyt. chim. Acta *11*, 574 (1954).

[26] Rhode und Schwarz GmbH., München, Germany.

[27] *E. C. Snowden* and *H. T. Page*, Analytic. Chem. *22*, 969 (1950).

[28] *K. Ezr:* Intern. Polarogr. Congress, Prague, *95*, III, 762.

[29] *S. Weidmann*, Thesis, Universität Bern 1942.

[30] *M. T. Kelley, D. J. Fisher*, and *H. C. Jones*, Analytic. Chem. *32*, 1262 (1960).

[31] Analytic. Chem. *33*, No. 3, 70 A (1961).

Figure 3 illustrates the apparatus in which the electrolytic cell is so constructed that the generated amalgam may be used to fill the drop-producing capillary under a nitrogen atmosphere.

When the current-voltage curves are recorded, anodic diffusion currents are generated which are proportional to the concentration of the metal in the amalgam. In the presence of several metals with differing half-wave potentials, separate diffusion currents are generated. The dropping amalgam electrode is of interest in trace analysis only where the diffusion currents, developed from the anodic dissolution (stripping) of the amalgams, are greater than those obtained in an aqueous solution, even at the highest sensitivities. This can be accomplished by the use of minimum amounts of mercury in the electrolysis. In this case, however, the concentration factor is dependent not only on the relationship of the mercury to the volume of the aqueous solution, but also on the duration of the electrolysis. Small amounts of common metals

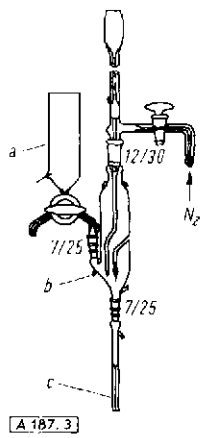


Figure 3. Apparatus for production of dropping amalgam electrodes.
a) Cell with mercury electrode for production of the amalgam;
b) Vessel to "catch" the amalgam in nitrogen atmosphere;
c) Drop capillary. (From: *N. H. Furman* and *W. C. Cooper*, J. Amer. chem. Soc. *72*, 5668, (1950).)

can be determined in the presence of higher concentrations of noble metals by means of the amalgam drop electrodes. This is possible, because, contrary to the case in aqueous solution, the common metal constituents generate their diffusion currents first. It is, however, possible that greater amounts of noble metals, which have been carried into the amalgam during electrolysis, may lead to interference during the anodic dissolution [6, 32]. *Stromberg* [7] reported on the application of the amalgam drop electrode to the analysis of slags and technical amalgams. Determinations of 10^{-3} % of lead in bismuth and 10^{-2} % zinc in cadmium, as well as 10^{-3} % cadmium in lead can be made.

b) Stationary Mercury Electrode

This is the type most commonly used at present. The stationary electrode has almost all the advantages of the dropping mercury electrode but it is important that reproducibility of the surface area can be assured. *Hickling* [32] utilizes a large mercury electrode similar in form to the one used for electrolytic deposition (Hg cathode). The simplest form [9, 15, 33] of small, stationary electrodes consists of one (or several) drops from a drop electrode which are suspended from gold or platinum wires, after having been caught with a small spoon (Fig. 4).

Electrodes of this type consistently deliver mercury drops with a constant surface area. Electrodes in which the mercury drops are not suspended from a platinum wire but collected in a small dish [12], operate in a similar manner.

[32] *A. Hickling, J. Maxwell*, and *J. V. Shennan*, Analyt. chim. Acta *14*, 287 (1956).

[33] *H. Gerischer*, Z. physik. Chem. *202*, 302 (1953).

They improve the mechanical stability of the system, especially when the solution is vigorously stirred.

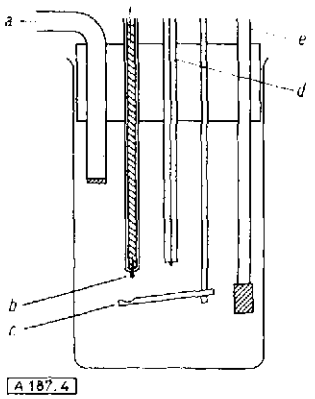


Figure 4. Simple mercury drop electrode: a) Salt bridge in reference electrode; b) Mercury drop electrode; c) Teflon spoon; d) Polarographic capillary; e) N_2 inlet. (From: *J. W. Ross, R. D. DeMars*, and *J. Shain*, Anal. Chem. *28*, 1769 (1956).)

A small mercury meniscus, partially emerging from a capillary of 1 to 3 mm diameter, has also been proposed as an electrode [8]. The electrode surface can be conveniently renewed by the removal of the drop. If the diameter of the capillary is reduced, the quantity of mercury emerging from the capillary can be controlled. In this manner, reproducible and easily renewed mercury drops are produced.

Barker [21] permits the mercury to flow from a capillary of 0.5 mm in diameter with a 0.05 mm diameter neck. The capillary is connected to a mercury reservoir. The mercury flow is interrupted by means of a stopcock or a needle valve (Fig. 5) after a definite time (30 sec). Mercury drops, whose size is reproducible to ± 2 %, were produced. A similar electrode has been recently used for the determination of Cl^- [34]. *Kemula* et al. [10, 11, 13, 14] utilize a screw-type needle piston which forces well-defined mercury drops from capillaries of 0.1 or 0.2 mm in diameter (Fig. 6) [*].

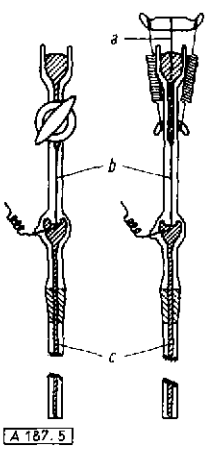


Figure 5. Stationary mercury electrode according to *Barker*. a) Needle valve; b) Neck (0.05 mm. ⌀); c) Capillary (1 mm. ⌀).
(From: *G. C. Barker*, AERE Report C/R 1563 (1957).)

A 90° turn of the piston produces mercury droplets with 0.02 cm^2 of surface area. To avoid variations of electrode size due to the effects of temperature (ther-

[34] *R. G. Ball, D. L. Manning*, and *O. Menis*, Analytic. Chem. *32*, 621 (1961).

[*] The Kemula electrode is manufactured by the Radiometer Co., Copenhagen, Denmark. A similar model is available from Metrohm A.G. Herisau, Switzerland.

mometer effect), both the mercury and the electrolytic cell must be placed in a constant temperature bath.

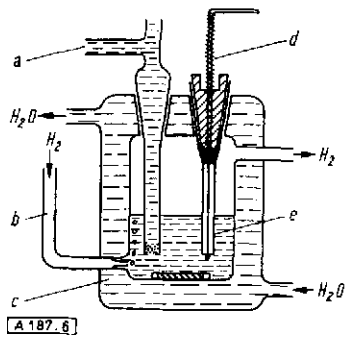


Figure 6. Hanging drop mercury electrode according to *Kemula*. a) To reference electrode; b) Vent; c) Magnetic stirrer; d) Screw needle; e) Capillary (0.018 cm. ⌀). (From: *W. Kemula, Z. Kublik*, and *S. Glodowski*, J. Electroanal. Chem. *1*, 92 (1959).)

Another variation of the stationary mercury electrode [**], in which a silicone-coated capillary (0.5 mm diameter) is inserted from the bottom into the electrolytic cell is given in Fig. 7.

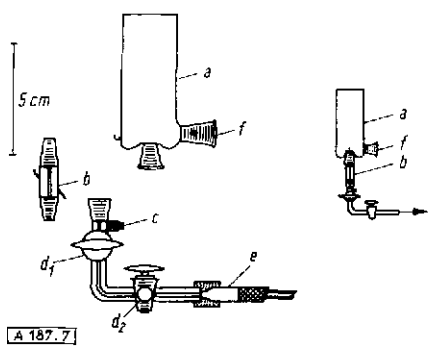


Figure 7. Stationary mercury electrode with micrometer burette (right; full view). a) Electrolysis cell; b) Capillary; c) Current connection; d) d_1 and d_2 stopcocks; e) Glass injection capillary of the microburette; f) Connection to reference electrode. (From: *R. Neeb*; Z. anal. Chem. *180*, 163 (1961).)

This aids in the stabilization of the drop during intensive stirring of the solution [35]. A mercury drop is forced out means of a microburette (piston burette with a micrometer screw). Valve No. 1 is closed after the drop is formed. The capillary now contains only a minute amount of mercury, rendering the entire system less susceptible to temperature changes. A reservoir, attached to the side, permits the refilling of the electrode system. Better control over the quantities of mercury to be delivered is obtained if the glass piston of the microburette is replaced with a steel needle [36] which can be moved by means of the micrometer screw. The measurement of small quantities can thus be improved.

Kalvoda [18,19] describes a larger stationary mercury electrode, applicable to inverse oscillopolarography. Approximately 0.03 ml of mercury are contained in a cup-shaped enlargement of a silicone-coated, bent glass tube of 5 mm. diameter. Additional stirring is possible through vibration of the mercury [20].

[**] Glastechnische Werkstätte G.m.b.H., Rheinallee 28, Mainz, Germany.

[35] *R. Neeb*, Z. analyt. Chem. *180*, 161 (1961).

[36] *P. F. Scholander*, Science (Washington) *95*, 177 (1942).

c) Mercury-coated metal electrodes ("amalgamated electrodes")

Platinum wires of 0.1 to 0.3 mm. in diameter, fused into glass are most commonly used. Gold and silver wire is also employed. *Rogers* et al. [24,25] were the first to use such electrodes for inverse voltammetry. The small amounts of mercury on the electrode (20 to 100 μg), depending on the amalgamation conditions and the electrode size) result in very high amalgam concentrations during electrolysis and, therefore, in high sensitivity. For best results, platinum electrodes should be re-coated with mercury through electrolysis of a mercury-salt solution, prior to each determination [12]. The cleaning and pre-treatment of the electrode exerts a great influence upon the reproducibility of the results [35].

d) Pure metal electrodes

Up to now pure metal electrodes have been used only rarely for the determination of metals. The deposition and stripping of small amounts of metals cause greater difficulties with solid electrodes than with mercury electrodes. *Nicholson* [37] reports on the determination of nickel (10^{-8} M) with platinum or gold electrodes, and on the deposition and stripping of Ag, Pb and Cu (10^{-7} to 10^{-9} M) with a platinum electrode [38]. Also, Ag down to 10^{-10} g. has been determined with a platinum electrode in 20 microliter microcells using the procedure of method VII [23] (Table 2). Small amounts of mercury have been determined after deposition on a platinum electrode by the peak currents developed through current reversal (Method II, Table 2) [39]. The highest currents peaks were obtained after electrolysis at −0.1 V from 0.1 M acids (HNO_3, $HClO_4$). The stripping potential lies at approximately +0.4 V (Fig. 8).

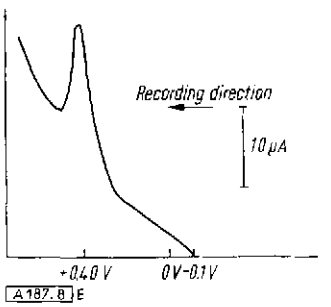


Figure 8. Mercury peak currents on a platinum electrode, 0.50 mg mercury/ml; 0.1 N $HClO_4$ (10 ml); electrolysis period 5 min; Electrolysis voltage — 0.1 V.

Interference by dissolved organic materials is considerable. If the water and acids are stored in polyethylene containers, the generation of peak currents is completely prevented.

The extreme purity of the solutions required in these methods limits their range of applicability in practical analytical work. Solid metal electrodes are more readily usable when the phenomena occurring during the anodic pre-electrolysis (C, Table 1) are utilized for preconcentration. In this manner, small amounts of iodide, for example, may be determined by means of a silver electrode [40]. The AgI, formed at +0.18 V (*vs.* calomel) during electrolysis, is determined either by cathodic stripping with constant potential (method III, Table 2, see also Fig. 9) or by voltammetric recording of the stripping currents (Fig. 10). In the first case, the current is automatically integrated by means of an analog computer integrator circuit.

[37] *M. M. Nicholson*, Analytic. Chem. *32*, 1058 (1960).

[38] *M. M. Nicholson*, J. Amer. chem. Soc. *79*, 7 (1957).

[39] *R. Neeb*, unpublished.

[40] *J. Shain* and *S. P. Perone*, Analytic. Chem. *33*, 325 (1961).

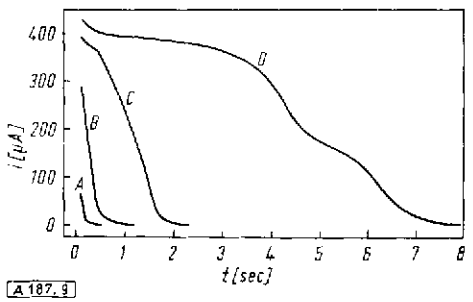


Figure 9. Determination of iodide with a silver electrode: Stripping at constant potential; Stripping potential: −0.40 V (*vs.* total calomel electrode). Iodide concentration and electrolysis time:
a) Blank value; b) 4×10^{-6} M, 10 min.; c) 4×10^{-5} M, 5 min.;
d) 4×10^{-4} M, 2 min. (From: *I. Shain* and *S. P. Perone*, Anal. Chem. *33*, 325 (1961).)

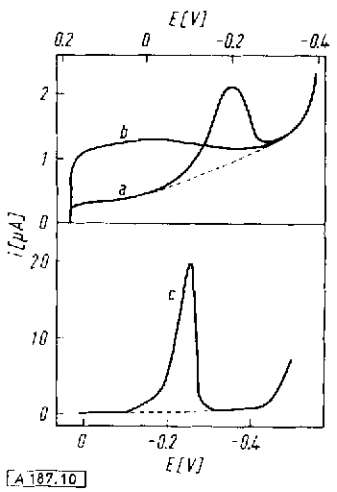


Figure 10. Determination of iodide with a silver electrode: Voltammetry with linearly variable potential. Iodide concentration and electrolysis time: a) 4×10^{-5} M, 30 min.; b) Blank value; c) 4×10^{-6} M, 10 min. (From: *I. Shain* and *S. P. Perone*, Anal. Chem. *33*, 325 (1961).)

III. Determination Procedure

1) Electrolysis and Base Solution

The accuracy attainable depends upon the reproducibility of the electrolytic concentration. The invariant positioning of the electrode and of the stirring mechanism must therefore be carefully considered in the design and construction of the electrolytic cell. For all sensitive determinations stirring of the solution is necessary in order to increase the amount of material deposited during electrolysis. This may be accomplished by means of magnetic stirrers (Fig. 6), by a stirrer introduced from the top [12] or by circulation of the solution [21]. Bubbling of gas [37], or the use of the hydrogen evolved in the electrolysis when stronger negative potentials are encountered [18], vibration [20], as well as rotation of the electrodes [23,24] are also occasionally suggested for stirring the electrolyte.

The extent of the influence of small variations in the mechanical conditions of the electrolysis (*i.e.* stirrer-electrode distance, r.p.m. of the stirrer etc.) on the amount of material deposited during electrolysis must be determined in all cases. If possible, critical conditions should be avoided. It is imperative that the volume of the solution remain constant. In general, one should determine the geometry of the stirrer, the electrode position and the volume of the solution which result in accurate and reproducible conditions for electrolysis.

The duration of electrolysis depends on the type and shape of the electrode and the volume of the solution, as well as on the concentration of the ions to be determined. With a very short electrolysis period and especially with an unstirred solution, the influence of the given conditions on the final result is noticeable. It is then important that the timing of the electrolysis and the stripping cycles be maintained accurately. With small electrodes, larger volumes of aqueous solution and short electrolysis times, the stripping currents are almost linear with the electrolysis period (depending on the method selected – see Table 2). An increase in the electrolysis period contributes to only a small increase of the stripping currents [8,12] (see also Fig. 11). The concentration of the element available on the electrode for stripping (*e.g.* concentration of the amalgam) does not increase noticeably because of the diffusion of the metal into the mercury (in the case of large mercury electrodes), or because of the depletion of the solution (which is especially rapid when small volumes are used).

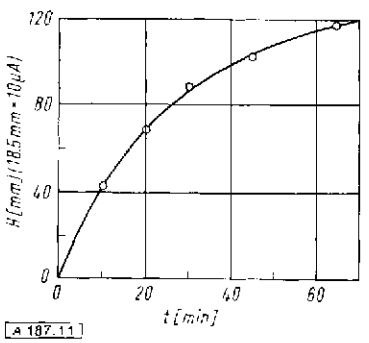


Figure 11. The dependence of stripping currents on time of electrolysis 114 ng Tl/ml; 0.02 M "Titriplex" solution. Volume; 1 ml. Electrode: amalgamated platinum wire (0.3×5 mm.). Electrolysis voltage: −1.1 V.

The electrolysis periods vary from a few minutes to several hours. Thirty minutes appears to be an optimum period for high sensitivity with a stationary mercury electrode (5 mm.² of surface area, 10 ml of electrolyte volume). In general, only a small portion of the element, present in aqueous solution, is deposited during electrolysis. Only 0.25 % of the lead available in 25 ml of solution was deposited on a stationary mercury electrode (4.5 mm.² of surface area) during a five-minute electrolysis period with stirring [8]. However, approximately 25 % of the lead is deposited on an amalgamated platinum electrode (4 to 5 mm.²) during thirty minutes with a 1 ml cell [12]. Naturally, the solution is depleted more rapidly when small sample-volumes are used. In contrast to polarography, therefore, the use of microcells (0.01 to 0.05 ml) does not reduce the absolute amount of determinable material.

The voltage used for electrolysis is normally 0.2 to 0.3 V more negative than the polarographic half-wave potential. Even then (depending on the electrode, element and the solution), maximum deposition rate may occasionally not be attained, since in highly dilute

solutions this will occur only at a considerable overvoltage [41]. A thorough investigation of these conditions is suggested in each particular instance.

Figure 12 shows the slopes of the anodic voltammetric peak currents (on an amalgamated platinum electrode) for Pb, Tl and Bi in the electrolysis of a "Titriplex" solution [12].

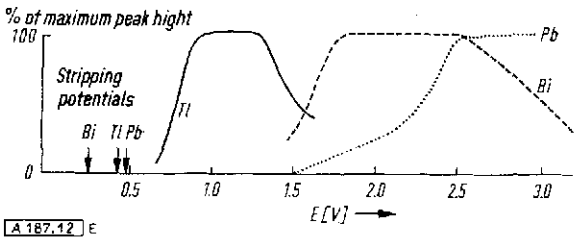


Figure 12. The dependence of the stripping currents on the electrolysis voltage. 0.10 mg Bi, Tl and Pb in 0.02 M "Titriplex" solution. (From: *R. Neeb*, Z. anal. Chem. *17*, 326 (1959).)

According to this graph, the determination of thallium by electrolysis at −1.0 V is possible even in the presence of high concentrations of Pb and Bi, although one would not expect this from the half-wave potentials (Pb: −1.1 V, Bi: −0.70 V), at least in the case of Bi. (In many cases, the anodic peak currents drop off again when higher voltages are used for electrolysis.) Considerable separation is attained by selection of an appropriate supporting solution, as in the case of polarography.

In addition to the variable capability for electrolytic deposition, the "stripping" action caused by different potentials also permits a sharp separation of individual elements. This will be discussed later.

Another example of the importance of the supporting solution is given in the determination of lead in the presence of tin [10]: While both elements are deposited from a strong HCl solution (1.5 N HCl) and even produce coinciding voltammetric stripping peaks, tetravalent tin is not deposited at all from a weakly acid solution (pH = 2 to 3), thus making possible the determination of lead in the presence of large quantities of tin.

The stripping peaks of Tl and Cd (half-wave potentials: −0.51 and −0.58 V, respectively) in 0.1 N KNO_3 and in 1:1 mixture are barely separable [8]. In 0.05 N NH_4Cl/NH_4OH solution, however, the two peaks can be separated, even in mixtures of 1:100. This is because the half-wave potentials, and therefore the peak potentials (see below), are at −0.51 and −0.77 V and are consequently, well resolved.

The stripping methods, while highly sensitive, also are subject to a number of possible errors. These are:

1) the contamination of the supporting solution, and

2) the limited shelf-life of dilute solutions.

Purification of the supporting solution (for example, by extraction) is possible only when no material detrimental to the analytical procedure is thereby introduced. Among the impurities, which must be avoided, are not only metallic contaminants, but also, and primarily, organic materials which may interfere by production of complexes, poisoning of the electrodes, etc. It is therefore important to guard against the presence of impurities with the same amount of care that is applied to ascertaining the absence of the ion to be determined in the solution blank. As an example, NaCl solution extracted with dithizone cannot be utilized as a working solution for the voltammetric determination of lead [12] even if the dithizone and solvents are of the highest purity [42]. The NaCl is re-usable only after evaporation and combustion (methods which, in turn, expose the material to contamination). Surface active compounds, even though they may be intrinsically chemically inert, do interfere particularly with AC methods (Method VI, Table 2), as well as in work involving pure metal electrodes (see above). Methods for the purification of the working solutions *i.e.* in order to remove traces of surface active compounds by means of activated charcoal, silica gel etc., are discussed in reference [21]. In many cases the removal of metallic impurities should be possible by means of their electrolysis on a mercury cathode.

The limited stability of highly dilute solutions necessitates the fresh preparation of standard solutions from concentrated master solutions. Quartz is the only material suitable for vessel construction in high sensitivity work. Slightly acid solutions of lead and cadmium (pH = 3) with metal concentrations of a few ng/ml.can be stored without deterioration in quartz flasks for at least several days [43]. The use of polyethylene containers in connection with highly sensitive polarographic or voltammetric analytical methods is not recommended. The organic materials which are almost always released in noticeable quantities, often produce uncontrollable interferences. Other, "purer", plastics may be more applicable. If glass storage vessels are to be used they should be filled with a portion of the solution to be stored and the contents shaken for an extended period. When adsorption equilibrium between the solution and the container wall is reached, the vessel is refilled with fresh solution which is then said to remain stable [9].

2) Solution process

Redissolution ("stripping") of the deposited materials follows the electrolytic concentration. Because of the relatively high concentrations encountered, interferences, specific to inverse polarography and voltammetry, are observed (see Sect. V). All known polarographic and voltammetric as well as the microcoulometric and potentiostatic methods are, in principle, applicable for use with the stripping process. Voltammetric methods (Method II, Table 2, also called "linear sweep volt-

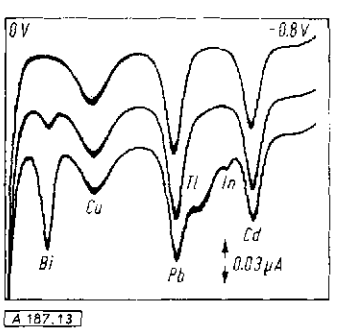


Figure 13. Voltammetric curves for various metals. Hanging drop mercury electrode. Electrolysis period: 3 min, 1.5 N HCl; dE/dt = 0.1 V/min; Concentration (mol/liter).

Curve:	1	2	3 (m)
Bi	—	$2.5\cdot10^{-7}$	$1.5\cdot10^{-6}$
Cu	10^{-6}	10^{-6}	10^{-6}
Pb	$5\cdot10^{-7}$	$5\cdot10^{-7}$	$5\cdot10^{-7}$
Tl	—	$2.5\cdot10^{-7}$	$1.5\cdot10^{-6}$
Cd	$5\cdot10^{-7}$	$5\cdot10^{-7}$	$5\cdot10^{-7}$

(From: *W. Kemula, Z. Kublik*, and *S. Glodowski*, J. electroanal. Chem. *1*, 92 (1959).)

[41] *L. B. Rogers* et al., J. electrochem. Soc. *98*, 447, 452, 457 (1951).

[42] *G. Iwantscheff*: Das Dithizon und seine Anwendungen in der Mikro- und Spurenanalyse. Verlag Chemie GmbH., Weinheim/Bergstr. 1958.

[43] *R. Neeb*, unpublished results.

ammetry") are, however, most commonly used. In the latter case, application of a linearly variable voltage generates peak currents similiar to those found in cathode-ray polarography [2,44]. The peak potentials, in this case, are comparable to the polarographic half-wave potentials [8]. When more than one metal is present in the amalgam, several peaks will be generated during the anodic stripping, providing that their potential difference is at least 0.1 V. The resolution of current peaks is normally better than that encountered with diffusion currents in the case of polarography (Fig. 13). This resolution is a function of the rate of voltage change, v(V/sec), and of the type of electrode used and improves with smaller v, as well as with the use of amalgamated platinum electrodes instead of stationary mercury electrodes [35,60].

The dependence on v(V/sec.), given by the *Randles-Ševčik* equation (see above) for voltammetric methods, also holds for inverse voltammetry in the case of stationary mercury electrodes [8,35]. Amalgamated platinum electrodes, on the other hand, produce a more rapid increase in peak currents with increasing (Fig.14). The circumstances regarding in the redissolution of metals deposited on solid electrodes are apparently similar [37,39].

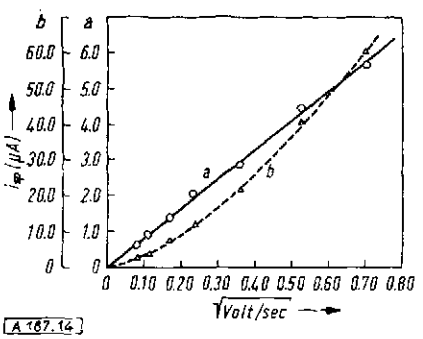


Figure 14. Dependence of the voltammetric peak currents on the rate of voltage change (dE/dt). 0.085 mg Pb/ml; 0.2 M NaCl (pH = 3 to 4). Volume: 10 ml; electrolysis period: 10 min. Electrolysis voltage −1.1 V; Electrodes: a) Stationary mercury electrode; b) Amalgamated platinum electrode. (From: *R. Neeb*, Z. anal. Chem. *180*, 166 (1961).)

When it is necessary to determine a noble constituent, in the overwhelming presence of a less noble constituent, under conditions of unfavorable concentration relations, the less noble constituents may be stripped out from the common deposit by the application of a constant potential. The determination of the more noble constituent can then be carried out undisturbed [10].

3) Calibration curves

Assuming constant and reproducible electrolysis conditions, the various methods of determination shown above yield calibration curves similar to those obtained in the direct analysis of aqueous solutions without electrolytic preconcentration, but with higher concentrations. The majority of the methods result in linear calibration curves, so that extrapolation is possible.

The temperature dependence of the electrolysis as well as of the stripping process require close temperature control of the electrolysis cell for accurate analysis. In the voltammetric determination of Pb or Tl with amalgamated platinum electrodes, positive temperature coefficients of 1.35 % were determined for the over-all process over a temperature range from 20 °C to 40 °C [12]. In a microcoulometric determination of Ni, a temperature increase of 25 °C leads to a threefold increase in the current.

The accuracy attained in inverse polarography and voltammetry will, in general, be lower than that obtained by the usual polarographic methods. The electrolytic preconcentration will always result in an additional error. Standard deviations of 3 % to 5 % can, however, be reached if the electrolysis is carried out carefully [35]. For the determination of very small concentrations, this reduction in accuracy is relatively unimportant, particularly because all the methods discussed here are far superior to any others when applied to trace analysis. As indicated in Table 3, the analysis of 10^{-6} to 10^{-9} M solutions is possible. This indicates a limit of detection lower than 10^{-9} g., since 1 ml. samples are sufficient for the determination. The sensitivity of these methods is not normally limited by instrumentation, but rather by the base current of the supporting solution which masks the very small stripping currents. The application of stationary electrodes now permits the application of differential methods. These were proposed earlier for polarographic analytical methods [45] but have rarely been used because of the hard-to-overcome inherent irregularities of two-drop electrodes.

A schematic diagram for a differential arrangement is shown in Fig. 15. One of the cells contains the solution to be analyzed, while the other contains only the supporting solution. The electrodes in both cells are of identical size. Both reference electrodes must have identical potentials and equal internal resistance.

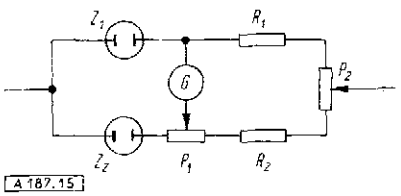


Figure 15. Schematic diagram of a differential arrangement. Z_1 and Z_2 = cells; R_1 and R_2 = internal cell resistance; P_1 and P_2 = potentiometers (G = galvanometer).

Small differences between the cells may be equalized by means of the potentiometers P_1 and P_2. An additional advantage of the carefully equalized differential system may be found in the cancellation of currents generated by impurities in the solution material.

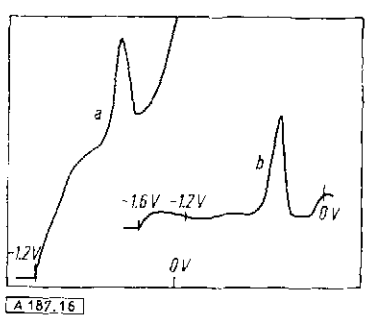


Figure 16. Operation of the differential circuit. 0.02 mg Cd/ml; 0.1 N (slightly acid) NaCl solution. Electrodes: amalgamated platinum; a) Without differential circuit; b) With differential circuit.

[44] *J. E. B. Randles*, Analyst *72*, 301 (1947); *G. F. Reynolds* and *H. M. Davis*, ibid. *78*, 314 (1953).

[45] *G.Semerano* and *L.Riccoboni*, Gazz.chim.ital.*72*, 297 (1942).

The demand for high purity reagents is therefore not too severe. Figure 16 shows the method of operation of the differential circuit. The initial steep increase of the base current is compensated by the reference cell. Small peak currents can now be more readily recognized and evaluated.

IV. Analytical Applications

Table 3 contains the presently known analytical applications of inverse polarography and voltammetry. At least 15 metals and several anions can be detected, but the full scope of these procedures is not yet exhausted.

Table 3. Analytical Applications of Inverse Polarography and Voltammetry.

Element	Method [a]	Ref.
Pb	II	[8, 10–13, 46, 47]
	V	[18]
	VI	[21]
	VII	[25]
Cd	II	[8–13]
	V	[18]
	VI	[21]
	VII	[24]
Zn	II	[9, 11]
	V	[18]
	VII	[24]
Cu	II	[8, 10, 11, 13]
	V	[18]
	VI	[21]
Tl	II	[8–10, 12, 13]
	IV	[17]
	V	[18]
Bi	II	[10, 12, 13]
	V	[18]
In	II	[10]
	V	[18]
Sb	II	[10]
Ni	II	[54]
	VII	[37]
Sn	II	[10, 53]
	V	[18]
Ag	VII	[23]
Ba	V	[18]
Sr	V	[18]
Na	V	[18]
K	V	[18]
NH_4^+	V	[18]
Cl^-	II, III, VII	[34, 40]
J^-	III, VII	[40]

[a] See also Table 2.

For the analysis of highest purity zinc [10], the material is dissolved in 10 N HCl and after dilution to approximately 1.5 N HCl, it is electrolyzed directly on a stationary mercury electrode (hanging mercury drop electrode) at 0.8 V. Pb, Cd, Sn and In may be determined in concentrations down to 10^{-6} %. Similarly, uranium salt can be simply added to the supporting solution (0.1 M K_2CO_3) and analyzed for heavy metals (down to 10^{-5} or 10^{-6} % of Cd, Pb, Tl, Bi and Cu). Thallium can be determined in concentrations down to 10^{-6} % in salts and in potassium minerals when dissolved and added to a "Titriplex" solution [12]. For the analysis of Tl in organic materials [48], a wet oxidation is carried out followed by a bromide extraction. The excess ether is destroyed (H_2SO_4–H_2O_2) and the thallium is determined by means of voltammetry or chronopotentiometry after dissolving in the supporting solutions [17]. Concentrations of 10^{-6} to 10^{-8} % of Tl have been thus determined and the determination of the natural Tl content of various biological materials [49] is possible.

In the analysis of potassium minerals [50] with high Tl content (10^{-5} %) the samples needed for the analysis were so small, because of the sensitivity of the method, that true averages were no longer obtained. Table 4 indicates this for sylvinite. Small amounts of the sample (50 mg.), broken from the sample, as well as some larger powdered samples were analyzed. The variations lie far outside experimental error; they can only be explained by lack of homogeneity in the samples. The difficulty, if not impossibility, of obtaining a true average sample for microanalysis, is indicated by this example.

Table 4. Voltammetric determination of Tl in sylvinite

Sample weight	Thallium (%)	Mean (%)
66.5 mg	$0.4 \cdot 10^{-5}$	
67.9 mg	$0.9 \cdot 10^{-5}$	
59.9 mg	$0.9 \cdot 10^{-5}$	$0.94 \cdot 10^{-5}$
57.7 mg	$1.5 \cdot 10^{-5}$	
61.1 mg	$1.0 \cdot 10^{-5}$	
5 g	$0.8 \cdot 10^{-5}$	$0.8 \cdot 10^{-5}$
5 g	$0.8 \cdot 10^{-5}$	

Pb, Cu and Zn have also been determined in biological materials [20] by (inverse) oscillopolarography. Furthermore, work has been performed on the determination of Pb in blood [51]. Triphenyltin acetate, important as a fungicide, is, after extractive separation from the plant material [52] and mineralization of the extract, determined voltammetrically at a stationary electrode; 0.2 µg Sn/25 ml. can be determined [53].

Cathodic stripping with a mercury electrode has been proposed for the determination of halogens, particularly chloride in uranium sulfate solutions [34]. After addition of citric acid (in order to form the uranium-citrate complex), as little as 0.2 µg Cl^-/ml. can be determined.

V. Interferences

Some of the possibilities for interference should be mentioned. These are caused by the high concentrations of elements to be determined after electrolytic concentration on the working electrode and have been

[46] *E. N. Vinogradova* and *G. V. Prokhorova*, Savodskaja Laboratorija *26*, 41 (1960).

[47] *A. G. Stromberg* and *V. E. Gorodovykh*, Savodskaia Laboratorija *26*, 46 (1960).

[48] *H. Eschnauer* and *R. Neeb*, Z. Lebensmittel-Unters. und -Forsch. *112*, 275 (1960).

[49] *W. Geilmann*, *K. Beyermann*, *K. H. Neeb*, and *R. Neeb*, Biochem. Z. *333*, 62 (1960).

[50] *R. Neeb*, unpublished results.

[51] *O. Rottová-Klaubková*, and *R. Kalvoda*, Pracovni Lekarstvi *12*, 20 (1960) (Analyt. Abstr. *7*, 5349 (1960)).

[52] *S. Gorbach* and *R. Bock*, Z. analyt. Chem. *163*, 429 (1958).

[53] *P. Nangniot* and *P. H. Martens*, Analyt. chem. Acta *24*, 276 (1961).

thoroughly investigated, particularly for mercury as the electrode material. They normally reduce the stripping currents, and may even inhibit the stripping action completely. The three major causes for interference are:

1) the formation of intermetallic compounds
2) the change of diffusion conditions in amalgams of high concentration, and
3) exchange reactions on the amalgam surface.

After electrolytic deposition on mercury, metals may form intermetallic compounds either with the mercury itself or especially with other deposited materials.

Only the formation of such compounds with mercury itself, and in the case of, Co, Ni, and Fe [54], has been described so far. Anode current peaks appear (up to four from cobalt) upon voltammetric stripping of the amalgams of the these elements. Sometimes these peaks are more positive than would be expected from the standard potentials of the metals. They are assumed to be caused by the formation of intermetallic compounds with mercury. Figure 17 shows these phenomena in connection with nickel which produces a well-defined current peak at +0.22 V, particularly after the amalgam has been aged.

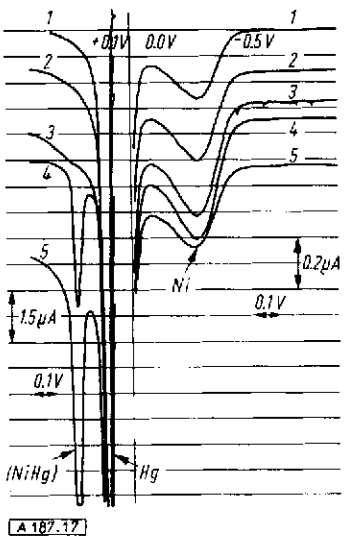


Figure 17. Voltammetric curves obtained from dissolution of nickel-amalgams. 0.1 N KCl = 10^{-4} N $NiCl_2$, hanging-drop mercury electrode. Electrolysis period: 1) 1 min.; 2) 2 min.; 3) 4 min.; 4) 6 min.; 5) 8 min. From: *W. Kemula* and *Z. Galus* Bull. Acad. Polon. Sci., Cl III 7, 732 (1959).

This phenomenon may be useful in the determination of the element even in 10^{-7} M solutions [54, 55]. The stripping of amalgams which are difficult to oxidize, is apparently noticeably influenced by the composition of the supporting solution. In KCNS solutions, nickel, for example, is completely oxidized before mercury [56]. The simultaneous deposition of several elements may cause a reaction by producing intermetallic compounds. The fact that they have been produced, is indicated not only by a decrease of the oxidation currents as compared with pure metal amalgams, but also by the generation of new oxidation currents at other, usually more positive positions. These are due to the redissolution of the intermetallic compounds.

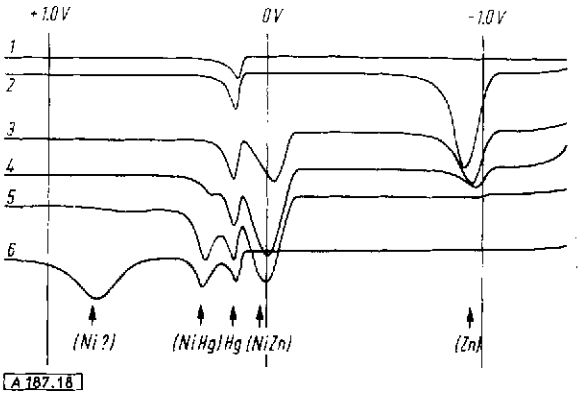


Figure 18. Voltammetric curves from the dissolution of mixed Ni—Zn amalgams. Hanging drop mercury electrode; 2 min electrolysis period at −1.4 V; supporting solution 0.1 M KCl.

Concentration:	$ZnSO_4$	$NiSO_4$
Curve 1	—	—
2	$5 \cdot 10^{-4}$ m	—
3	$5 \cdot 10^{-4}$ m	$2 \cdot 10^{-4}$ m
4	$5 \cdot 10^{-4}$ m	$4 \cdot 10^{-4}$ m
5	$5 \cdot 10^{-4}$ m	$6 \cdot 10^{-4}$ m
6	—	$4 \cdot 10^{-4}$ m

From: *W. Kemula, Z. Galus,* and *Z. Kublik,* Bull. Acad. Polon. Sci., Cl. III *6*, 661 (1958).

Figure 18 indicates the conditions during the determination of zinc in the presence of nickel [57]. A reduction in the peak height for zinc due to the presence of nickel becomes evident, and at the same time a new current peak appears at 0.1 V, which is due to the oxidation of the NiZn compound.

The following systems have been investigated voltammetrically by means of a hanging drop mercury electrode [58]:

Zn/Cu, Cu/Ni, Mn/Cu, Ni/Cr, Ni/Mn, Mn/Fe, Co/Ni, As/Cu, Ni/Sn, Ni/Sb, Ag/Cd, Cd/Cu, and Au/Zn. The interferences caused by the frequent formation of intermetallic compounds limit the applicability of these methods. The interferences can, however, be often eliminated by proper selection of the supporting solutions and electrode conditions, or, in certain cases, by prior chemical separation. Another source of interference through intermetallic compound formation occurs in the use of Pt or Au wires for the suspension of the mercury drops, because of the fact that both gold and platinum are slightly soluble in mercury. It is therefore possible for some of this material to migrate into the mercury and form intermetallic compounds with the deposited metals [59, 61]. Thus, even as little as 0.001 % gold in mercury prevents the oxidation of dilute zinc amalgams because of the formation of ZnAu [61]. Smaller concentrations of gold are of no consequence.

[54] *W. Kemula* and *Z. Galus*, Bull. Acad. Polon. Sci., Cl III 7, 729 (1959).

[55] *W. Kemula, Z. Galus,* and *Z. Kublik*, Nature (London) *182*, 1228 (1958).

[56] *J.T. Porter* and *W. D. Cooke*, J. Amer. chem. Soc. *77*, 1481 (1955).

[57] *W. Kemula, Z. Galus,* and *Z. Kublik*, Bull. Acad. Polon. Sci., Cl. III 6, 661 (1958).

[58] *W. Kemula,* in *J. S. Longmuir:* Advances in Polarography. Pergamon Press, London 1960, vol. 1, p. 105.

[59] *W. Kemula, Z. Kublik,* and *Z. Galus*, Nature (London) *184*, 56 (1959).

[60] *W. Kemula, Z. Galus,* and *Z. Kublik*, Bull. Acad. Polon. Sci., Cl III 7, 723 (1959).

[61] *W. Kemula, Z. Galus,* and *Z. Kublik*, Bull. Acad. Polon Sci., Cl. III 7, 613 (1959).

Gold concentrations above 0.01 % [59] interfere in the determination of Cd. The problems connected with platinum are similiar [60]. Mercury-coated platinum electrodes are, in reality, dilute platinum amalgam electrodes with a variable Pt content. Dissolved platinum markedly interferes with the determination of antimony, tin and zinc [60]. Pb, Cd, Cu and Tl do not, however, form intermetallic compounds under these conditions and can be determined without interference.

A short reference should be made to the importance of voltammetric methods in the study of formation kinetics and the composition of intermetallic compounds [58].

Variations in the diffusion conditions of elements of high concentration in mercury have occasionally been observed but have not so far been investigated in connection with the possibility of interference. In particular, those elements which react, with mercury such as Fe, Co and Ni (see above) could, in high concentrations, cause interference with the diffusion of even those elements which do not form intermetallic compounds. In the oscillopolarographic determination of copper, *e.g.* in the presence of much iron, substantially smaller peaks are observed than in pure copper solutions [18]. After addition of a complexing agent to the supporting solution to prevent the deposition of iron, the original peak height was once more observed.

Reactions on the amalgam surface may well cause changes in the surface concentration of the elements in the amalgam; these, in turn, may cause a change in the stripping currents. In inverse oscillopolarographic determinations of Cd and Zn in uranium salts, peaks which are 20 % to 50 % lower than in solutions of the tetravalent cation U^{4+} occur in UO_2^{2+} solutions. It is assumed that these are caused by the oxidation of the amalgams by the uranium ion together with their electrolytic oxidation [18]. When measuring the stripping currents of mixed Zn-Tl amalgams (as stationary electrodes) considerably higher currents are obtained for the Tl than for the pure thallium-amalgam electrodes. This occurs because the displacement reaction, $2\,Tl^+ + Zn \rightarrow 2\,Tl + Zn^{2+}$, increases the surface concentration of the thallium, thus causing the appearance of the higher diffusion currents [32].

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A New Type of Converter for Ammonia Synthesis

BY DR. H. HINRICHS AND DIPL.-ING. J. NIEDETZKY

ÖSTERREICHISCHE STICKSTOFFWERKE AG., LINZ, AUSTRIA

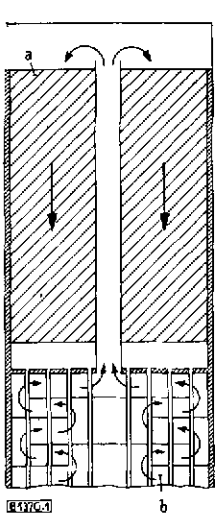
A comparison of known types of converters used for the synthesis of ammonia, and an evaluation of their respective advantages and disadvantages are given. A new type of converter is described, in which catalyst contact beds alternate with heat exchange regions. This arrangement permits both close control of the operating temperature at or near optimum conditions and utilization of the excess heat of reaction for preheating the reaction gases.

For over 40 years, the production of ammonia has been based on the Haber-Bosch process developed in Germany during World War I. Although the converters in use at the present time are still based on the original principle of the invention – combination of hydrogen and nitrogen at high pressure in the presence of suitable catalysts – the choice of a particular type of converter depends on local conditions. In the last few years, a fundamentally new converter has been developed at the Österreichische Stickstoffwerke AG, Linz, Austria. It has several advantages over other converters available at present. Calculations made on electronic computers by the engineering firm Haldor Topsøe of Hellerup, Denmark, and by our own departments, have indicated a high economic potential for this converters and patents have been applied for in several industrial countries.

The most important types of converters known today may be classified as follows:

1) Continuous packed converters (Fig. 1).

2) Packed converters, subdivided into several sections: the heat of formation of ammonia, liberated in each packed stage, increases the gas temperature sharply; the gas temperature is then reduced by direct injection of a cold nitrogen-hydrogen mixture into the free spaces between the packed stages (Quench converters, Fig. 2).



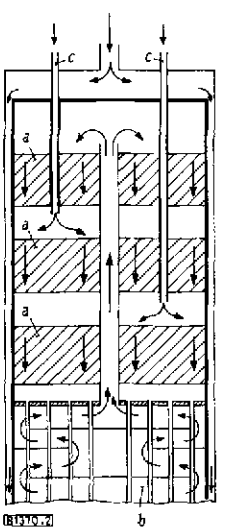
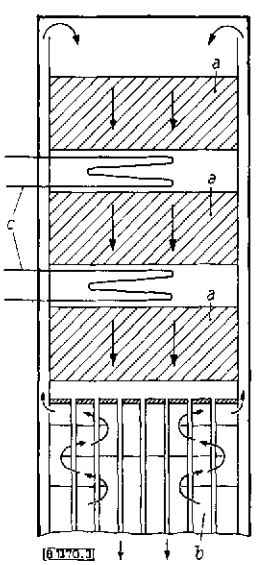


Fig. 1. Packed converter with a single continuous catalyst bed
a) Catalyst zone, b) Heat recovery section

Fig. 2. Packed converter with subdivided catalyst beds and injection of cold gas into free spaces between catalyst zones (quench converter)
a) Catalyst zone, b) Heat recovery section, c) Cooling coils or tubes

3) Packed converters, subdivided into several stages: here, the gas temperature is also sharply raised in packed zones by the heat of formation of ammonia but is then cooled indirectly with water in intermediate free spaces (Fig. 3).



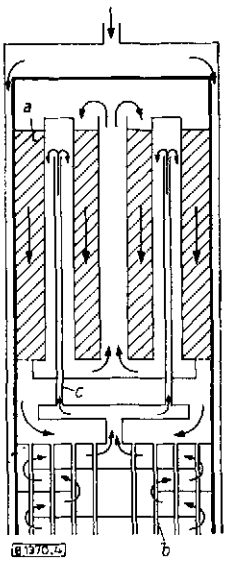
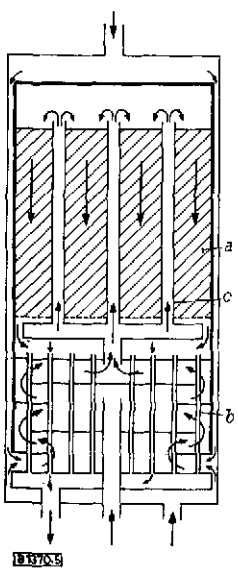


Fig. 3. Packed converter with subdivided catalyst bed and indirect reactor cooling of gases between the catalyst zones
a) Catalyst zone, b) Heat recovery section, c) Cooling coils or tubes

Fig. 4. Tubular converter with multipass parallel gas flow
a) Catalyst zone, b) Heat recovery section, c) Cooling coils or tubes

4) Tubular converter, in which the catalyst is arranged in or around tubes (Figs. 4 to 6).



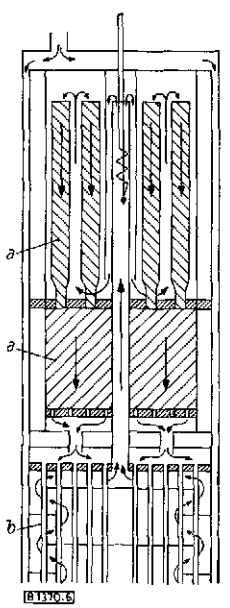


Fig. 5. Tubular converter with multipass counter current gas flow
a) Catalyst zone, b) Heat recovery section, c) Cooling coils or tubes

Fig. 6. Tubular and packed converter combination
a) Catalyst zone, b) Heat recovery section

Various combinations of these four basic concepts are, of course, also possible. For example, in quench converters, the lowest catalyst chamber is sometimes arranged as a tubular section. Furthermore, tubular and packed reactor designs may be combined, so that a packed catalyst section is connected with a tubular section. Each of the above types or their combinations possesses both advantages and disadvantages; thus, the selection of the preferred type will have to be based on local conditions. The method of gas mixing, the utilization of waste heat, the overall pressure in the unit, the purity of the gas, the design of the cooling system, the inert gas content of the recycled gas, as well as many other factors and conditions will play a significant role in the selection of the most economical converter type.

Operating Temperature Profile and Optimum Rate of Formation of Ammonia [1]

In addition to the effects of catalyst poisons, the most important factor influencing the life of the catalyst is the operating temperature. Generally, 550 °C is considered to be the maximum permissible temperature. Various sources mention 520 °C as the upper temperature limit for continuous operation. If the catalyst is used over prolonged periods of time at temperatures above the latter value, it becomes prematurely inactive and its particle structure breaks down.

The rate of formation of ammonia at a given pressure and corresponding ammonia concentration exhibits a maximum at a very definite temperature. This is illustrated in Fig. 7 by the curve of the optimum production rate. The equilibrium curve, also shown, indicates only the concentration level of ammonia that can be reached with an infinite contact time between the nitrogen-hydrogen mixture and the catalyst. The curve holds for a working pressure of 300 atm., and approximately 25000 m^3 process gas/m^3 catalyst.

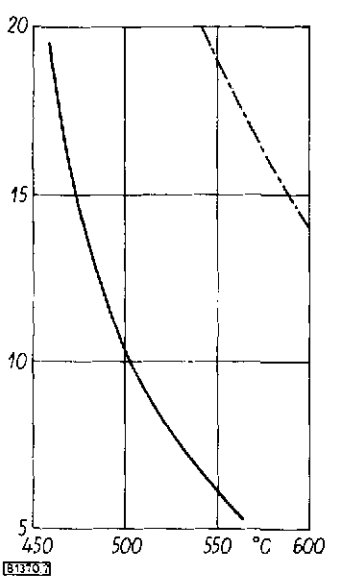


Fig. 7. Curve for the optimum ammonia production rate (———) and the equilibrium curve for the ammonia formation reaction (– – – –).
Ordinate: NH_3 content [% by volume]
Abscissa: Temperature

In general, it may be said that the closer the temperature in the catalyst chamber approaches the curve of optimum production rate, the greater will be the production of

[1] *K. Schönemann*, Chemiker-Ztg. *83*, 365 (1959).

ammonia and consequently, the higher the capacity of the converter. Nevertheless, in the lower concentration range, i.e. below approximately 6% (by vol.) of ammonia, it is necessary to forego the somewhat higher optimum rate of reaction (which in this range lies above 550 °C) in order to preserve the catalyst. However, this consideration is of little practical importance, since at such a low ammonia concentration range, the reaction rates are very high not only at 550 °C but even at somewhat lower temperatures. For optimum production of ammonia an idealized, but practically unattainable converter may be visualized: the nitrogen-hydrogen mixture enters the first catalyst layer at a temperature of 550 °C and is held at that temperature by a high (in practice unattainable) rate of heat removal until the gas reaches an ammonia content of 6 % by volume. The gas is then cooled at such a rate that the loci of intersection of the temperature and ammonia concentration curves move along the curve of optimum reaction rate.

The Most Important Types of Converters

The continuous packed converter (Fig. 1) is by far the simplest type of converter. The nitrogen-hydrogen mixture fed into the catalyst chamber becomes very hot, because the heat released by ammonia formation is not removed (over 13 kcal are liberated per mole of ammonia). If a nitrogen-hydrogen mixture with an initial ammonia content of 2 % enters the catalyst bed at 440 °C, the reaction will cease when the ammonia concentration reaches 11–12 % between 575 and 590 °C. However, it is seen from Fig. 7 that for optimum reaction conditions, this ammonia content should be reached at temperatures of 480–500 °C. Furthermore, a high working temperature, such as 590 °C, leads to an appreciable drop in catalyst activity after only a few months of operation, causing even further reduction in the ammonia yield from this type of converter.

In the quench converter, i.e. a packed converter cooled by injection of cold gas between the separate catalyst sections (Fig. 2), the nitrogen-hydrogen mixture with an ammonia content of 2 % is introduced to the catalyst at 430 °C. The reaction gas reaches a temperature of approximately 540 °C and an ammonia content of approximately 9 % in the first catalyst section. It is then cooled to approximately 460–470 °C by injection of cold synthesis gas containing 2 % ammonia. The ammonia content of the reacted gas is thereby lowered from 9 to 8 % (see Fig. 8); however, the conversions obtained from Fig. 8 cannot be used for comparison of the actual production of ammonia in the two converters, since they operate under very different conditions.

The cooled converter gases then enter the second catalyst section, where they are again heated by further formation of ammonia. Cooling of the reaction gases is then alternated with heating, by the formation of ammonia in the subsequent sections of the converter. This very widespread type of reactor offers a very good solution to the problems discussed by preventing overheating of the catalyst and yet maintaining satisfactory efficiency of the converter. However, the dilution of ammonia in the reacting gases passing into the subsequent catalyst sections constitutes a disadvantage as far as maximum production of ammonia is concerned. The size of the recuperative heat exchanger is a further drawback

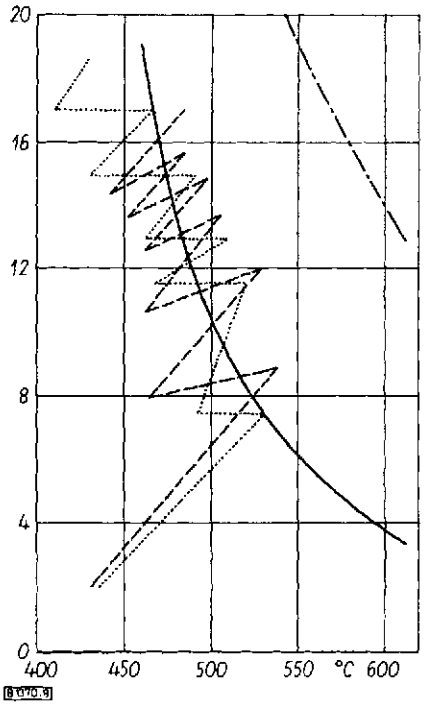


Fig. 8. Temperature profile and ammonia formation in the quench converter of Fig. 2 (- - - - - -) and in the packed reactor with indirect water cooling of Fig. 3 (·····). Optimum production rate of ammonia (——); equilibrium curve for the reaction (——·——).
Ordinate: NH_3 content [% by volume]
Abscissa: Temperature

of this type of reactor. The heat exchanger, situated in the lower part of the reactor, must be very large in order to preheat the entering nitrogen-hydrogen mixture to approximately 430 °C. The preheating must be accomplished with the reacted gases leaving the last catalyst section and having a temperature of only about 500 °C. The large size of the heat exchanger makes the possible size of the catalyst chamber in this type of reactor relatively small compared to that of other installations of equal overall length. The sum effect is that the relative capacity of this converter is lower than that of other converters of the same overall length.

In packed converters with indirect water cooling between separate catalyst sections (Fig. 3), the feed gases enter the catalyst chamber at a temperature of 435 °C with an ammonia content of 2 %. The feed gases are heated to approximately 530 °C in the first catalyst section. The gas stream is then indirectly cooled by water to approximately 490 °C before entering the next catalyst section. Formation of ammonia with attendant rise in temperature alternates with water cooling. The number of times this cycle can be repeated is a function of the length of the available high pressure vessel (see Fig. 8). Apart from the technical difficulties involved, particularly safeguarding against leakage from the tubes carrying water into the high pressure vessel, this reactor system represents an entirely satisfactory solution to the

problem of controlling the converter temperature profile for maximum ammonia formation. However, there is also the drawback that a very long heat exchanger is needed to preheat the feed gas to 435 °C using the reaction gases leaving the last catalyst section. When compared with other reactors of equal volume, this means a reduction in the volume of catalyst available for ammonia conversion and therefore a reduced capacity. On the other hand, by providing this type of converter with an auxiliary heat recovery installation, it is possible to obtain about 0.8 ton of high pressure steam per ton of ammonia produced.

In tubular converters the catalyst is either placed in tubes or distributed around the cooling coils. The nitrogen-hydrogen mixture to be preheated flows either countercurrently to or concurrently with the reacting gases, which pass through the catalyst bed proper (see Figs. 4 to 6). Heat exchange takes place in the catalyst chamber. The recuperative heat exchanger, located underneath the catalyst section, may therefore be comparatively short. The temperature profile of the reactor and consequently the formation of ammonia, will deviate (sometimes appreciably) from the optimum curve along the entire length of the catalyst section. It is particularly difficult to keep the operating temperature from rising above 550 °C in the upper third of the catalyst bed. Here, it is necessary to work with very active catalysts in order to assure a sufficiently high rate of reaction even at temperatures as low as 400 to 410 °C (at an ammonia content of 2 % by volume). If the heat exchange area in the catalyst chamber is sufficiently large, the temperature can be maintained below 550 °C even in the upper third of the bed. However, if insufficient attention is paid to catalyst quality and the layout of the heat exchange surfaces, the temperature in the catalyst chamber (especially in countercurrent reactors) may rise to 580 °C and higher. This causes not only premature destruction of the catalyst, but also reduction in the yield of ammonia because of excessively large deviation from the curve of optimum reaction rate. Furthermore, it is not possible to effect changes in the temperature profile inside the catalyst chamber of the converter. Although this arrangement simplifies the operation of such a converter, it also reduces the flexibility of operation since no adjustment to the optimum reaction rate curve can be made.

The New Converter [2]

The Österreichische Stickstoffwerke AG now considered the possibility of developing a converter in which packed sections alternated with zones of heat exchange. In the heat exchange zones, the partially converted gases were to be indirectly cooled by the nitrogen-hydrogen mixture being preheated. As in the case of baffled reactors, the temperature of the reaction gases entering and leaving a packed catalyst section were to be as close as possible to the optimum reaction rate curve. The advantage of this type of reactor over the quench converter would lie in the fact that cooling would not involve dilution of the ammonia content by the addition of cold gas. The use of heat exchange surfaces between the various packed catalyst sections should also reduce the overall heat exchange area requirements, as compared to quench converters.

In such a system, the nitrogen-hydrogen mixture enters the reactor through the upper cover plate and passes through the annular gap between the pressure jacket and the reactor core to the main heat exchanger b_I (see Fig. 9). Here, the first stage of preheating takes place.

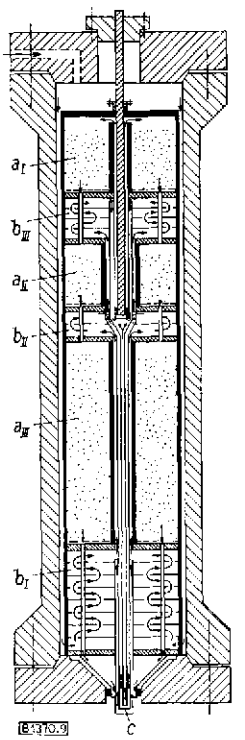


Fig. 9. New converter
a_I, a_{II}, a_{III} = catalyst beds:
b_I, b_{II}, b_{III} = heat exchangers;
c = cold gas inlet

Through a concentric annular gap situated in the lowest catalyst bed, the warm nitrogen-hydrogen mixture now enters the intermediate heat exchanger b_{II}, located between the second and third contact beds. There the mixture is heated further, while at the same time it cools the hot reaction gases flowing from the second to the third catalyst section. After passing through the annular gap in the center of the second catalyst bed, the gas flows into the heat exchanger b_{III}, located between the first and second catalyst beds. There it is heated to the feed temperature specified for the uppermost catalyst bed. The reaction gases, leaving this catalyst bed are thus cooled by the countercurrent gas stream to the temperature desired at the inlet to the second catalyst bed.

The nitrogen-hydrogen mixture, which is now at the optimum temperature for reaction in the topmost catalyst bed, is led downwards through another annular passage and then flows upwards along an electrical heater provided for starting purposes. The gases now pass through the successive catalyst bed heat-exchanger sequences in such a way that they always reach the following catalyst bed at the optimum temperature.

[2] Austrian Patent 215436 (Nov. 15, 1960); 216533 (Jan. 15, 1961); German Patent Application L 33611 IVa/12g (July 1, 1959); L 37594 IVa/12g (Nov. 22, 1960); Dutch Patent Application 257966 (Nov. 15, 1960); Belgian Patent 597362 (Nov. 22, 1960); French Patent Application 844995 (Nov. 25, 1960).

Fig. 10 shows the production of ammonia in the various sections, and the resulting total production capacity of the converter.

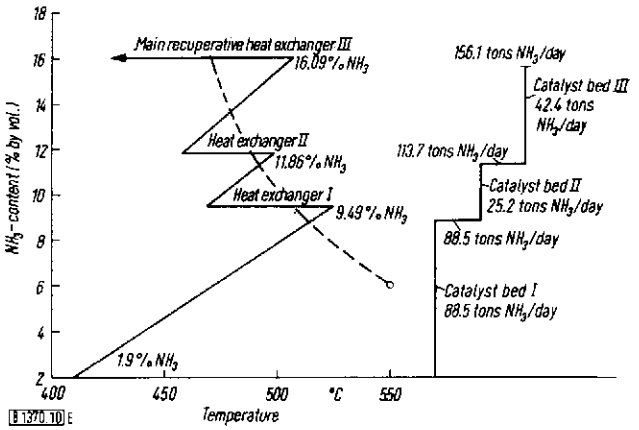


Fig. 10. Temperature profile and ammonia production in the new converter

In addition, a series of concentric tubes passing through the lower cover plate of the reactor (Fig. 9) allows the injection of cold gas into the nitrogen-hydrogen mixture being preheated at the various levels of the converter. At the start of a run, the catalyst possesses very high activity. Thus, the preheated gas stream may have to be diluted with a relatively large proportion of cold gas. As the activity of the catalyst drops off, the quantity of cold gas injected is correspondingly reduced.

The basic principle of this converter, therefore, consists of indirect preheating of the nitrogen-hydrogen mixture with hot reaction gases leaving the various successive catalyst sections. Appropriate choice of dimensions for the heat exchange surfaces and addition of a suitable amount of cold gas allow the hot reaction gases to be cooled to a temperature most favorable for optimum ammonia production on entering the following catalyst bed. Extensive adjustments of the reaction profile to the curve of optimum production rate are therefore possible.

The number of catalyst stages necessary has to be calculated for each individual case. Theoretically, a large number of catalyst stages favor maximum yields of ammonia, since in such a case the operating temperatures deviate only slightly from the optimum production rate curve. However, since structural considerations dictate an appreciable thickness (about 6 to 10 cm.) for the bottom plates of the catalyst containers and the heat exchangers, excessive sub-division would cause too great a reduction in the catalyst volume available. For example, it has been shown that for a given set of operating conditions, sub-division of the converter into four catalyst sections results, from a practical point of view, in no significant production increase over sub-division into three sections. However, division into five sections would result in a reduced production of ammonia, owing to the significantly smaller volume of catalyst.

The converter described above is a special arrangement of certain structural elements, all of which have been used for decades in ammonia synthesis. Catalyst containers alternate with heat exchangers. At the start of a run, the stream of gas is heated by an electrical resistance heater (rod burner). Cold gas is added, as needed, through concentric tubes.

Calculation of the optimum conditions required for a pressure vessel 12 m. long and with an internal diameter of 800 mm. was performed on electronic computers with the following result: at a throughput of 70000 m^3 (STP) of gas per hour at a pressure of 315 atm., an output of 156 tons of ammonia per 24 hours is obtained, with a maximum catalyst temperature of 525.4 °C. The calculations also yielded information on the lengths of the catalyst sections and the areas of the heat exchange surface required. The feed gas had the composition (in % by volume): NH_3–1.9; Ar–4.0; CH_4–4.0; CO–4 ppm; the remainder was H_2 and N_2 in a 3:1 ratio.

This converter arrangement may be justified wherever production factors demand most efficient utilization of available high pressure vessels. The low operating temperature (maximum 525 °C) guarantees a considerably longer life for the catalyst than that obtained in reactors with higher catalyst temperatures.

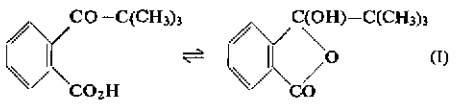
Received, July 3rd. 1961 [B 1370/20 IE]
German version: Chemie-Ing.-Techn. 34, 88 (1962).

On the Structure of the Optically Active Cumulenes [1]

By Prof. Dr. Richard Kuhn and Bernhard Schulz

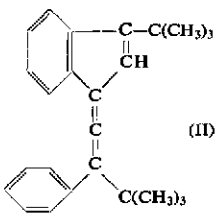
Max-Planck-Institut für Medizinische Forschung, Institut für Chemie, Heidelberg (Germany)

By means of oxidative degradation we have obtained *o*-trimethylacetylbenzoic acid (I) from the hydrocarbon described in the literature [2] as 1,5-di(t.-butyl)-1,5-diphenylpentatetraene (m.p. 100–101 °C). The keto-acid (I) (m.p. and mixed m.p. 119 °C; infrared spectrum) can also be prepared in good yield from phthalic anhydride and t.-butylmagnesium bromide



(I)

The above-named hydrocarbon is therefore an isomer of the expected cumulene and arises by cyclisation; most probably it is the indene derivative (II) [3].



(II)

Formula (II) is in agreement with the uptake of 3 moles of hydrogen on catalytic hydrogenation [2] and the strong infrared band at 1940 cm^{-1}. The existence of stable optical antipodes of pentatetraenes would have been surprising [4]. The existence of optical antipodes [2] of type (II) cumulenes, however, corresponds to the situation with the known allenes and does not signify an experimental realisation of *J. H. van't Hoff*'s prediction, according to which substituted pentatetraenes should exist in D- and L-forms.

Received, March 20th. 1962 [Z 243/69 IE]

[1] Cumulenes: XIV. XIIIth. communication. *R. Kuhn* and *H. Fischer*, Chem. Ber. *94*, 3060 (1961).

[2] *M. Nakagawa, K. Shingu*, and *K. Naemura*, Tetrahedron Letters No. 22, 802 (1961).

[3] See *K. Brand* et al., Ber. dtsch. chem. Ges. *54*, 1987 (1921); *54*, 2007 (1921); *57*, 846 (1924); J. prakt. Chem. *115*, 335 (1927); *115*, 351 (1927).

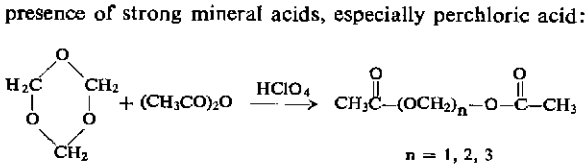
[4] No monomeric pentatetraenes are yet known; see *R. Kuhn* and *H. Fischer*, Chem. Ber. *92*, 1849 (1959); *R. Kuhn, H. Fischer*, and *F. A. Neugebauer*, Liebigs Ann. Chem., in the press.

Low-Molecular Polyoxymethylene Diacetates from Trioxane

By Ing. CSc. J. Tomiška and Ing. E. Spousta

Institute for Research in Macromolecular Chemistry, Brno (Czechoslovakia)

We have found that mono-, di-, and trioxymethylene diacetates (I, II, III) are formed easily, and almost quantitatively, by cleavage of trioxane in acetic anhydride solution in the presence of strong mineral acids, especially perchloric acid:



n = 1, 2, 3

For example, 1 mole of acetic anhydride and 0.2 ml of 60 % perchloric acid are heated to 60 °C and 0.22 moles of trioxane are added within 10 minutes (vigorous exothermic reaction). The excess of anhydride is then destroyed by pouring the reaction mixture into an aqueous suspension of sodium bicarbonate. The mixture is subsequently extracted with ether; an oily, yellowish product (62 g.) is obtained after evaporation. The anhydride content (saponification number, calculated as acetic anhydride content according to *Staudinger* [1]) amounts to 69.7 %, which corresponds exactly to an equimolar mixture of I and II (69.4 % theory); the yield is 94 %. Separation of the products is easily achieved by fractional distillation at atmospheric pressure. The physical constants for (I) and (II) agree with those reported by *Staudinger* [1, 2]. The composition of the product remains constant within a wide range of experimental temperature and concentration.

Below −20 °C, compound (III) is formed in addition to (I) and (II) (theoretical anhydride content 53,12 %). At −65 °C (III) constitutes 80 % of the reaction product. Its separation was achieved in the manner described above. Other anhydrides, such as butyric or benzoic anhydride, may be used instead of acetic anhydride.

Presumably a cationic cleavage of the trioxane ring is taking place in combination with the acylation of products resulting from this cleavage.

Received, January 26th. 1962 [Z 220/51E]

[1] *H. Staudinger* and *M. Lüthy*, Helv. Chim. Acta *8*, 41 (1925).

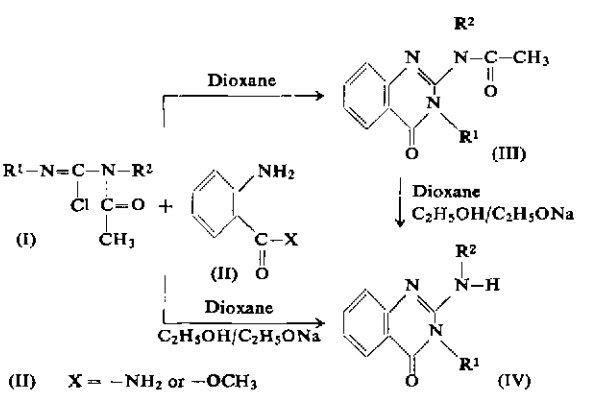
[2] *H. Staudinger, R. Signer, H. Johner, M. Lüthy, W. Kern, R. Russidis*, and *O. Schweitzer*, Liebigs Ann. Chem. *474*, 145 (1929).

Ring Closures with Acylated Carbodiimides

By Dr. K. Hartke and Quim. Farm. J. Bartulin

Central Institute of Chemistry, University of Concepción (Chile)

Aliphatic carbodiimides easily add carbonyl halides at room temperature. However, the adducts, which tend to decompose into the starting compounds, can be isolated in the pure form only in special cases [1]. In solution, acylated carbodiimides react very readily with nucleophilic reagents and can be used for the synthesis of heterocyclic compounds.



(II) X = $-NH_2$ or $-OCH_3$
(III) $R^1 = R^2$ = isopropyl; m.p. 140 °C
(IV) a: $R^1 = R^2$ = isopropyl; m.p. 81 °C
b: $R^1 = R^2$ = cyclohexyl; m.p. 122 °C
c: R^1 = t.-butyl; R^2 = methyl (also possible R^1 = methyl, R^2 = t.-butyl); m.p. 132 °C

Acetylated aliphatic carbodiimides (*e.g.* I) react with anthranilamide or methyl anthranilate (II) to form 4-quinazolones (III, IV). The yields amount to approximately 65%.

Received, February 5th. 1962 [Z 212/49 IE]

[1] *H. D. Stachel*, Angew. Chemie *71*, 246 (1959); *73*, 64 (1961).

Elimination of Hydrogen Sulfide with Acylated Carbodiimides:

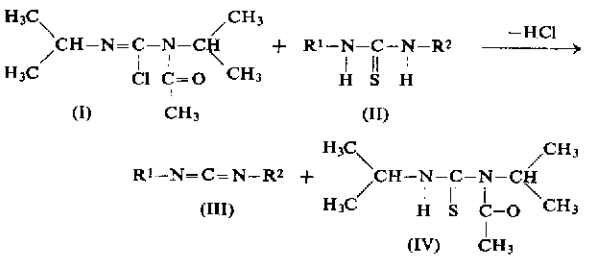
General Synthesis of Aromatic and Aliphatic Carbodiimides

By Dr. K. Hartke

Central Institute of Chemistry,
University of Concepción (Chile)

Under extremely mild conditions, acylated, aliphatic carbodiimides (I) [1] react with many thioamides with the elimination of hydrogen sulfide. The aliphatic carbodiimide is mixed with the acid halide in absolute ether and is allowed to stand for several hours. Equivalent amounts of triethylamine and thioamide are added and the mixture stirred at room temperature for 3 to 4 hours. Triethylamine hydrochloride is filtered off and acylated thiourea (IV), a by-product, is shaken out with aqueous sodium hydroxide. The reaction product is isolated from the ether phase in very pure form.

Benzonitrile is obtained from thiobenzamide with a yield of 75 %; benzyl cyanide from phenylthioacetamide with a yield of 74 %. Likewise, thiourea compounds (II) can be converted into the corresponding carbodiimides (III).



(III)	R^1	R^2	% Yield of (III) [a]	Physical Constants of (III)	% Yield of (IV)
A [2]	phenyl-	phenyl-	67	b.p. 160—162 °C/0.2 mm. Hg	82
B [3]	*p*-tolyl-	*p*-tolyl-	65	m.p. 55—56 °C	74
C	phenyl-	isopropyl-	77	b.p. 106 °C/0.3 mm. Hg	86
D	phenyl-	methyl-	33 [b]		81
E	cyclohexyl-	methyl-	65	b.p. 93 °C/16 mm. Hg	84

[a] Yields refer to pure distilled products; 0.02—0.03 mole used for the experiment; hence with larger amounts, higher yields can be expected.

[b] Polymerizes during distillation; yield refers to urea obtained by hydrolysis.

The experiments are being continued; among others, the elimination of water from suitable compounds with the aid of acylated carbodiimides is under investigation.

Received, February 5th. 1962 [Z 213/50 IE]

[1] *K. Hartke* and *J. Bartulin*, Angew. Chem. internat. Edit. *1*, 211 (1962).

[2] *C. Schall* and *S. Paschkowetzky*, Ber. dtsch. chem. Ges. *25*, 2886 (1892); *R. Stollé*, ibid. *41*, 1125 (1908).

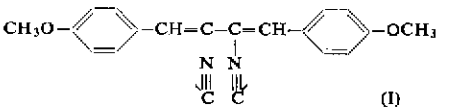
[3] *F. Zetzsche* et al., Ber. dtsch. chem. Ges. *71*, 1513 (1938); *72*, 364 (1939); *73*, 474 (1940).

Synthesis of Xanthocillin Dimethyl Ether

By Dr. Ilse Hagedorn and Dr. U. Eholzer [*]

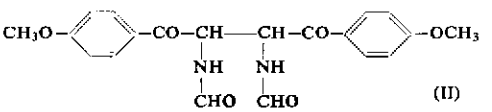
Chemisches Laboratorium der Universität Freiburg/Brsg. (Germany)

The structure of the surface antibiotic xanthocillin has been established through its more stable dimethyl ether (I), [1]. The total synthesis, to which *H. Etling* [2] has contributed valuable preliminary studies, was accomplished by the following route: 4 - methoxy - ω - formylaminoacetophenone (m.p.



93 °C) can be metalated at the methylene group with potassium t.-butoxide at and oxidatively dimerized to (II) (m.p. 241 °C) with iodine. The 1,4-diketone was reduced with sodium borohydride to the 1,4-diol (m.p. 227 °C) and the latter was converted with phosphorus oxychloride in pyridine to the β,β′-dichlorodiisonitrile. Thereafter, the butadiene derivative was formed by double HCl elimination with KOH in pyridine.

The chemical and physical properties of the compound prepared in this manner correspond to those of (I) and the infrared spectra are identical in every respect.



[Z 215/55 IE]

[*] Reported at the Südwestdeutsche Chemie-Dozenten-Tagung, Munich, May 24th. 1961. At the authors' request, the report was not published. Received as a communication on February 7th., 1962.

[1] *I. Hagedorn* and *H. Tönjes*, Pharmazie *12*, 567 (1957).

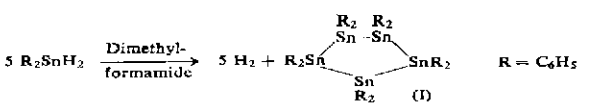
[2] *H. Etling*, Diploma Thesis, Universität Freiburg i. Brsg. 1960; *I. Hagedorn* and *H. Etling*, Angew. Chem. *73*, 33 (1961).

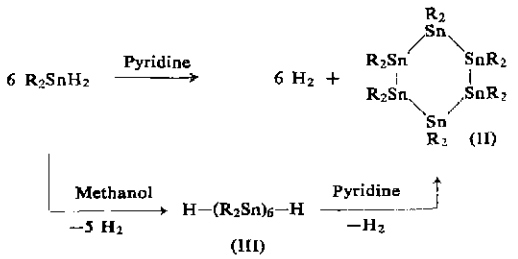
Preparation and Structure of Diphenyltin

By Priv.-Doz. Dr. W. P. Neumann and cand. chem. K. König

Chemisches Institut der Universität Gießen (Germany)

It has been recently reported that "diethyltin" has a ring structure [1]. We have now been able to show that polymeric diphenyltin, formed in the reaction of numerous amines with diphenyltin dihydride, also has a ring structure. At 20 °C the pentamer (I) is obtained in a good yield with dimethylformamide, while the hexamer (II) is the predominant product in the reaction with pyridine. Compounds (I) and (II) crystallize from toluene as colorless, rectangular plates which release the bound solvent on heating *in vacuo* and which decompose above 270 °C. Correct molecular weight determinations were carried out using a thermistor osmometer. $(C_6H_5)_2Sn$ groupings are the only components, as shown by degradation with iodine and analysis of the cleavage products [2,3]. The predominant product formed from diphenyltin dihydride in methanol is the solid linear organotin hydride (III) (Sn—H absorption at 1790 $cm.^{-1}$), rather than a modification of diphenyltin [4]. At 20 °C the hydride (III) looses H_2 and is converted into (II) by the action of pyridine or other amines.





Although the yellow product, which is obtained from tin dichloride with phenylmagnesium bromide [5,6], and the red product obtained with phenyl-lithium [4,7] have empirical formulae similar to that of diphenyltin, they are very inhomogenous. They are mostly branched and consist of phenyltin and diphenyltin groupings, in addition to 25–30 mole % and about 40 mole %, respectively, of terminal triphenyltin groups.

Received, February 12th. 1962 [Z 214/54 IE]

[1] *W. P. Neumann*, Lecture, Chemikertreffen Vienna, Oct. 12th. 1961; reported in Angew. Chem. *74*, 22 (1962).

[2] *R. Bock, S. Gorbach*, and *H. Oeser*, Angew. Chem. *70*, 272 (1958).

[3] *K. Bürger*, Z. Lebensm.-Untersuch. *114*, 1 (1961).

[4] *H. G. Kuivila* et al., J. org. Chemistry *26*, 1426 (1961).

[5] *E. Krause* et al., Ber. dtsch. chem. Ges. *53*, 173 (1920).

[6] *K. A. Jensen* et. al., Z. anorg. allg. Chem. *250*, 277 (1943).

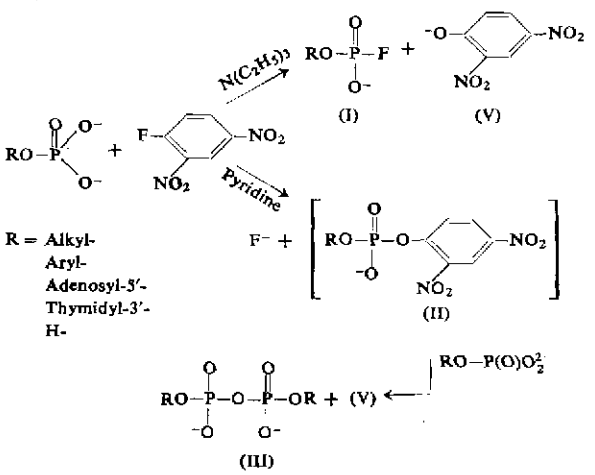
[7] *G. Wittig* et al., Liebigs Ann. Chem. *571*, 169, 193 (1951).

A New Synthesis of Monoesters of Monofluorophosphoric Acid

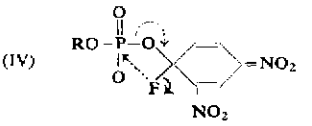
By Dr. R. Wittmann

Institut für Organische Chemie
der Technischen Hochschule Darmstadt (Germany)

Depending on the type of base added, 2,4-dinitrofluorobenzene undergoes two different reactions with phosphoric acids. In the presence of strong tertiary bases, such as triethylamine, derivatives of monofluorophosphoric acid (I) and 2,4-dinitrophenolate (V) are formed quantitatively, while in the presence of pyridine normal phosphorylation takes place, *e.g.* to form the symmetrical diester pyrophosphates (III).



In the reaction with pyridine, 2,4-dinitrophenyl esters of the phosphoric acids (II) are assumed to be the active intermediates. In the presence of strong, tertiary bases, a quinoid intermediate (IV) is postulated which reacts by an intramolecular four-center mechanism. Structure (IV) has been proved by aminolysis and by observation of the visible spectrum. The reaction proceeds at room temperature and is quantitative. Nucleotides, such as adenosine-5′- and thymidine-3′-phosphoric acids, can also be converted to the monofluoro-derivatives in this manner.



The following compounds were prepared:

1) The potassium salts of phenyl hydrogen phosphorofluoridate (I, R=C_6H_5; m.p. 214–216 °C, 91 % yield), of *p*-chlorophenyl hydrogen phosphorofluoridate (I, R=*p*-Cl-C_6H_4 m.p. 238–239 °C, 93 %), and of methyl hydrogen phosphorofluoridate (I, R=CH_3; m.p. 166 °C, 70 %);

2) the ammonium salts of 5′-adenosyl hydrogen phosphorofluoridate (m.p. 170 °C, 76 %), of 3′-thymidyl hydrogen phosphorofluoridate (m.p. 181 °C, 82 %), as well as the tri-n-butylammonium salt of adenosine-2′, 3′-cyclophosphoric acid (m.p. 144 °C, 70 %).

3′-Ribonucleotides, on the other hand, quantitatively form the 2′, 3′-cyclophosphates with 2,4-dinitrofluorobenzene and tri-n-butylamine [1].

Orthophosphoric acid yields a mixture of monofluoro- and difluorophosphate.

The reaction should be suitable for sequence analysis of polynucleotides.

Received, February 15th. 1962 [Z 216/57 IE]

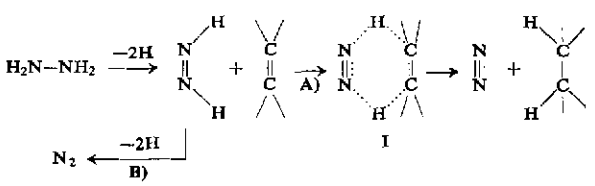
[1] We have learned recently that an analogous formation of 2′,3′-cyclophosphates in approximately 20 % yield has been described by *J. Stockx*, Bull. Soc. chim. belg. *70*, 125 (1961).

Reductions with Diimide [1]

By Prof. Dr. S. Hünig and Dipl.-Chem. Hans Richard Müller

Chemisches Institut der Universität Würzburg (Germany)

Diimide is formed as an intermediate in the oxidation of hydrazine [1–3], the decomposition of *p*-toluenesulfohydrazide [1,4], of azodicarboxylic acid [1,2,5] and of anthracene-9,10-bisimine [6], as well as from chloramine [7] and hydroxylamine-*o*-sulfonic acid [8]. The diimide is primarily active in the hydrogenation of carbon-carbon multiple bonds. The transfer of both hydrogen atoms proceeds stereospecifically as a *cis*-addition, which indicates a cyclic transition-state [1,9].



The ratio of the rates of the competitive reactions A and B can be determined when potassium hexacyanoferrate(III) is used as dehydrogenating agent [1]. Under standardized reaction conditions, the evaluation of the hydrogenation curves of various olefins yields the relative rates of hydrogenation which are compiled in Table 1. These results support

Table 1

No.	Olefin	Rel. rate
1	fumaric acid	100
2	undecenoic acid	40
3	maleic acid	10
4	methylfumaric acid	3
5	methylmaleic acid	0.7
6	*trans*-cinnamic acid	10
7	*cis*-cinnamic acid	3
8	*p*-dimethylaminocinnamic acid	8
9	*p*-methoxycinnamic acid	8
10	*p*-chlorocinnamic acid	8–9
11	*p*-nitrocinnamic acid	7–11
12	*o*-chlorocinnamic acid	11
13	α-methylcinnamic acid	1.4
14	β-methylcinnamic acid	1.4

the postulate of a weakly polar multiple-center reaction (1) for the following reasons:

a) Alkyl substituents at the double-bond considerably decrease the rate of hydrogenation (see 1 and 4; 3 and 5; 6 and 13 or 14).

b) *trans*-Olefins are hydrogenated at a faster rate than *cis*-olefins because in the transition-state the mutual interference of *cis*-olefin substituents increases as the bond angles contract toward 109° (see 1 and 3; 6 and 7). This does not happen in the case of *trans*-olefins. As expected, the substituent effects in the diimide reduction are therefore similar to those in the diene synthesis [10].

c) *p*-Substituents on cinnamic acid have practically no effect on the rate of hydrogenation (see 8–12). This is understandable if the transition state is assumed to be weakly polar and much more similar to the starting components than to the products. This would be expected from *Hammond*'s principle [11] for strongly exothermic reactions (in this case the heat of reaction is approximately 70 kcal/mole [2]).

Received, February 19th. 1962 [Z 221/52 IE]

[1] 2nd. Communication; 1st. communication, see *S. Hünig, H. R. Müller*, and *W. Thier*, Tetrahedron Letters No. 11, 353 (1961).

[2] *E. J. Corey, W. L. Mock*, and *D. J. Pasto*, Tetrahedron Letters No. 11, 347 (1961).

[3] *F. Aylward* and *M. Savistovska*, Chem. and Ind. *404*, 433 (1961).

[4] *E. E. van Tamelen, R. S. Dewey*, and *R. J. Timmons*, J. Amer. chem. Soc. *83*, 3725 (1961).

[5] *R. S. Dewey* and *E. E. van Tamelen*, J. Amer. chem. Soc. *83*, 3729 (1961).

[6] *E. J. Corey* and *W. L. Mock*, personal communication; J. Amer. chem. Soc., accepted for publication.

[7] *E. Schmitz* and *R. Ohme*, Angew. Chem. *73*, 807 (1961).

[8] *R. Appel* and *W. Büchner*, Angew. Chem. *73*, 807 (1961).

[9] *E. J. Gorey, D. J. Pasto*, and *W. L. Mock*, J. Amer. chem. Soc. *83*, 2957 (1961).

[10] *R. Huisgen, H. J. Sturm*, and *H. Wagenhofer*, Z. Naturforsch., in the press.

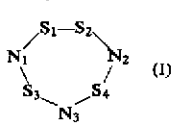
[11] *G. S. Hammond*, J. Amer. chem. Soc. *77*, 334 (1955).

The Structure of Thiotrithiazyl Nitrate

By Doz. Dr. Johannes Weiss

Anorganisch-Chemisches Institut
der Universität Heidelberg (Germany)

The structure of the thiotrithiazyl cation, $S_4N_3^+$ [1], has been determined by X-ray analysis of thiotrithiazyl nitrate. The nitrate, $S_4N_3NO_3$, crystallizes in a monoclinic form, space group C_{2h}^5–$P2_1/c$. The lattice constants are: a = 5.81 Å, b = 10.42 Å, c = 12.47 Å, β = 108°; there are four formula units per unit cell. The structure was deduced from three-dimensional Patterson and Fourier syntheses. According to these, the $S_4N_3^+$ cation forms a seven-membered ring (I). It is not yet certain whether this ring is completely planar.



(I)

The S–N distances were found to be 1.67 Å on the average, and the distance S_1–S_2 is 1.94 Å.

Preliminary parameters:

S_1	0,937	0,058	0,124
S_2	0,312	0,614	0,311
S_3	0,023	0,316	0,004
S_4	0,648	0,385	0,125
N_1	0,026	0,173	0,049
N_2	0,648	0,268	0,180
N_3	0,854	0,396	0,046

NO_3^-:

N	0,340	0,218	0,833
O_1	0,533	0,167	0,944
O_2	0,254	0,130	0,783
O_3	0,313	0,175	0,338

Received, February 21st, 1962 [Z 217/58 IE]

[1] Regarding thiotrithiazyl compounds, see *M. Goehring*: Ergebnisse und Probleme der Chemie der Schwefelstickstoff-Verbindungen. Scientia Chimica, Vol. 9, Akademie-Verlag Berlin, 1957.

Reductive Dehalogenations with Sodium Hydrazide and Hydrazine

By Dr. Th. Kauffmann, Dipl.-Ing. H. Henkler, and cand.-Ing. H. Zengel

Institut für Organische Chemie
der Technischen Hochschule Darmstadt (Germany)

In contrast to the monohalogenobenzenes [1], the aromatic halogeno compounds listed in Table 1 react either completely, or to a considerable extent, with sodium hydrazide in the presence of hydrazine. In these reactions, halogen is exchanged for hydrogen. The dehalogenation reactions, which usually proceed rapidly in ether or benzene even below room temperature, follow the general equation

$$RHal + 2\ NaNH{-}NH_2 + H_2N{-}NH_2 \rightarrow RH + NaHal{\cdot}NaNH{-}NH_2 + 2\ NH_3 + N_2.$$

The reductive dehalogenation can thus be followed by the evolution of gas. An excess of sodium hydrazide should be used, since it forms addition compounds with sodium halides in a molar ratio of 1:1 in which the activity of the hydrazide is greatly reduced.

Table 1

Halogeno compound	Temp. [°C]	Product	Yield [%]
Bromomesitylene	25	Mesitylene	82
o-, *m*-, *p*-Bromoanisole	20	Anisole [2]	58, 30 and 38, resp.
1- or 2-Bromonaphthalene	0	Naphthalene [3]	75 and 52, resp.
1- or 2-Chloronaphthalene	0	Naphthalene [3]	65 and 75, resp.
1- or 2-Fluoronaphthalene	25; 0	Naphthalene [3]	39 and 60, resp.
9-Bromoanthracene	0	Anthracene	90
2,3-Dibromocoumarone	0	Coumarone	85
2,3-Dibromobenzo[b]thiophen	45	Benzo[b]thiophen	74
4-Bromoisoquinoline	0	Isoquinoline	57
1-Chloroferrocene	30	Ferrocene	97

Received, February 23rd. 1962 [Z 222/56 IE]

[1] See *Th. Kauffmann* et al., Angew. Chem. *73*, 540 (1961).

[2] In addition, hydrazinoanisoles are formed by substitution according to the aryne mechanism.

[3] In addition, hydrazinonaphthalenes are formed by substitution according to an additive mechanism.

The Conversion of Dienes into Azines, Pyrazoles, and Pyrazolines with Sodium Hydrazide and Hydrazine

By Doz. Dr. Th. Kauffmann, Dipl.-Ing. Horst Müller, and Dipl.-Ing. Ch. Kosel

Institut für Organische Chemie der Technischen Hochschule Darmstadt (Germany)

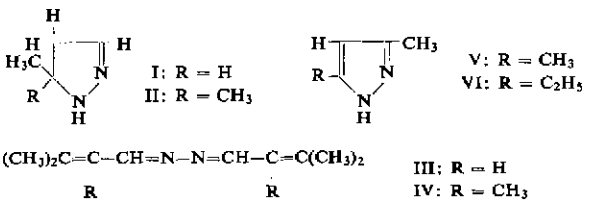
Ether solutions of buta-1,3-diene, its 2-methyl and 2,3-dimethyl derivatives, as well as penta-1,3-diene, react with sodium hydrazide in the presence of hydrazine [1] with vigorous evolution of ammonia. The reaction takes place even at temperatures below 20 °C. By contrast, the corresponding conversion of hexa-2,4-diene requires heating to 50–60 °C. The products isolated from the reaction mixtures are given in Table 1. The pyrazoline, azine or pyrazole structures of the bases (I) – (VI) show that under the action of sodium hydrazide and hydrazine on the dienes investigated, dehydrogenation reactions always follow the addition of hydrazide. The single exception is the non-dehydrated addition

Table 1

Diene	Products	Yield (%)
Buta-1,3-diene [2]	*N,N*-dicrotylhydrazine and	32
	5-methyl-Δ^2-pyrazoline [3] (I)	25
2-Methylbuta-1,3-diene	5,5'-dimethyl-Δ^2-pyrazoline (II; b.p. 42–43 °C/15 mm.Hg) and	15
	β,β'-dimethylcrotonaldazine (III; m.p. 108 °C)	63
2,3-Dimethyl-buta-1,3-diene	α,β,α',β'-tetramethylcrotonal-dazine (IV; m.p. 110 °C)	70
Penta-1,3-diene	3,5-dimethylpyrazole [3] (V)	54
Hexa-2,4-diene	3-methyl-5-ethylpyrazole (VI; b.p. 79–80 °C/0.2 mm. Hg)	53

product *N,N*-dicrotylhydrazine, isolated together with the pyrazoline (I) from the reaction with buta-1,3-diene [2].

Compounds (II), (III), (IV) and (VI) apparently have not been described before.



The structure of (VI) was proved by synthesis from hydrazine and hexane-2,4-dione; the structure of the bases(II)-(IV) is deduced from their spectra and from degradation reactions.

Received, February 23rd. 1962 [Z 223/53 IE]

[1] Caution! Explosion danger when working with sodium hydrazide.

[2] Reaction with sodium hydrazide in the absence of hydrazine yields exclusively the di-addition product *N,N*-dicrotylhydrazine; see Angew. Chem. *73*, 540 (1961).

[3] *R. von Rothenburg*, J. prakt. Chem. *52*, 45 (1895).

Proton Resonance and Infrared Spectra of Substituted Quinolines

By Dipl.-Chem. W. Seiffert

Physikalisch-Chemisches Institut der Technischen Hochschule München (Germany)

The chemical shift δ in proton resonance is determined by the magnetic screening of the hydrogen nucleus and therefore by the electron arrangement in its environment. In valence and deformation vibration, the electronic grouping in the bonds of the atoms involved and the energy are inter-dependent. Therefore, some relationship between the CH vibrational energy and the chemical shift of the corresponding protons is to be expected. Such a relation should be seen most clearly in the out-of-plane deformation vibrations of aromatic CH groups which lie between two substituted C atoms, or between one substituted C-atom and a point of ring closure in the molecule. In these cases only one infrared vibration band, whose frequency can be unambiguously correlated with an experimentally determined δ-value for the proton, is expected.

The infrared spectra of 35 substituted quinolines, iodethylquinolines, and quinolinium perchlorates were examined and the CH bands of the out-of-plane vibrations assigned by the usual methods [1]. The proton resonance spectra of 15 quinoline bases in the liquid state, or in supercooled melts, were determined and interpreted (H_0 = 25 Mc). The results show that a linear relation exists between the chemical shift of an isolated hydrogen atom in a ring and the deformation energy of its out-of-plane vibration (Fig. 1).

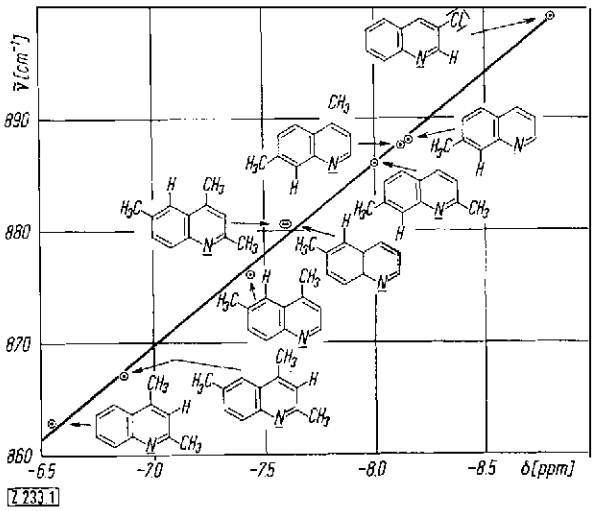


Fig. 1. Chemical shift (tetramethylsilane as internal standard) and CH deformation frequency of substituted quinolines

In the pure liquid phase the chemical shift δ is due to the magnetic screening which is produced by the electrons in the investigated molecule and those of neighbouring molecules. With regard to the out-of-plane vibrations. Fig. 1 shows that weakly screened protons lie in a somewhat steeper potential well than strongly shielded protons. The potential curves can be calculated from the CH vibration frequencies.

In dilute solutions using an inert solvent (*e.g.* hexane) a proton is screened primarily by the electrons in its own molecule. For this reason the spectra of such solutions can be examined for an estimate of the π-electron density in the ring. This procedure has been applied independently to azulenes by *Spiesecke* and *Schneider*, and to substituted benzenes by *Fraenkel* et al. [2]. The heterocyclic quinoline ring shows an electron deficiency in the 2- and 4-positions and an electron excess in the 3-position; this is consistent with its chemical behavior. From a comparison of the infrared frequencies, it may be concluded that the deformation energy of a hydrogen atom in the 3-position is less than that of a proton in the 2-position.

Received, February 26th. 1962 [Z 233/68 IE]

[1] See also *L. J. Bellamy:* The Infrared Spectra of Complex Molecules. Methuen and Co., Ltd. London, and John Wiley and Sons, New York, 1958; *H. H. Perkampus* and *E. Baumgarten*, Z. Electrochem. *64*, 951 (1960).

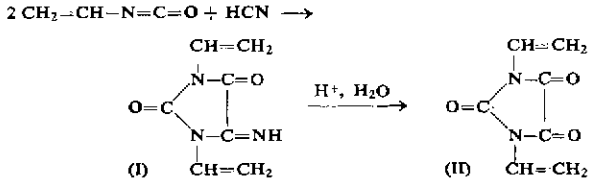
[2] *H. Spiesecke* and *W. G. Schneider*, Tetrahedron Letters No. 14, 468 (1961); *G. Fraenkel* et al., J. Amer. chem. Soc. *82*, 5846 (1960).

The Preparation of 1,3-Divinylparabanic Acid (1,3-Divinylimidazoletrione) and its 4-Imino Derivative

By Priv.-Doz. Dr. Rolf C. Schulz and Dr. H. Hartmann

Institut für Organische Chemie der Universität Mainz (Germany)

Vinyl isocyanate [1], reacting at 0 °C with liquid hydrogen cyanide in inert solvents (benzene or petroleum ether) and in the presence of a small quantity of pyridine, does not yield the expected 1:1 addition product [2], *N*-vinyl cyanamide. Instead, 1,3-divinyl-4-iminoparabanic acid (I; b.p. 87–89 °C/0.3–0.4 mm. Hg; m.p. 36 °C (after sublimation); mol. wt.



(*Rast*) 160 (calc. 165.2); λ_{max} = 247 mμ (log ε = 3.89); 222 mμ (log ε = 4.38) [3]) is obtained in 79 % yield.

Further proof for the structure of compound (I) is provided by hydrolysis with dilute aqueous acids. This results in a nearly quantitative conversion to divinylparabanic acid [11; m.p. 116–117 °C after sublimation. λ_{max} = 308–310 mμ (log ε = 2.75); 247 mμ (log ε = 3.80); 214–215 mμ (log ε = 4.39)].

Received, March 2nd. 1962 [Z 227/63 IE]

[1] *R. Hart*, Bull. Soc. chim. belges *65*, 291 (1956).

[2] *S. Petersen*, Liebigs Ann. Chem. *562*, 205 (1949); *W. Dieckmann* and *H. Kämmerer*, Ber. dtsch. chem. Ges. *38*, 2977(1905); *40*, 3737 (1907).

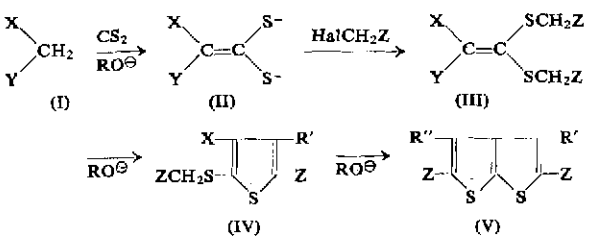
[3] For further ultraviolet spectral data on *N*-vinyl compounds see *R. C. Schulz* and *H. Hartmann*, Mh. Chemie *92*, 303 (1961).

New Thiophens and Thieno[2,3-b]thiophens

By Doz. Dr. R. Gompper and cand. chem. E. Kutter

Institut für Organische Chemie und Organisch-chemische Technologie der TechnischenHochschule Stuttgart (Germany)

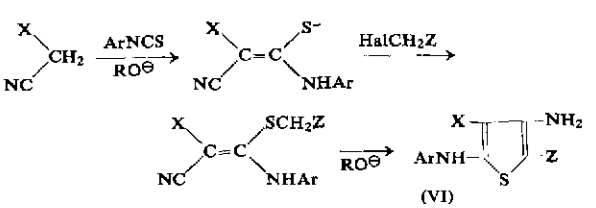
Substituted 1,1-dimercaptoethylene derivatives (III) are easily converted into amino- and hydroxythiophens (IV) [1,2]; the former are accessible by the action of halogenoacetic acid derivatives on the dithiocarboxylic acid salts (II) prepared from active methylene compounds (I) and carbon disulfide. We have now succeeded in preparing the thieno-[2,3-b]thiophens (V) in good yields, either from compounds of the type (IV), or directly from (I) without isolation of (II), (III) and (IV).



	X	Y	R′	R″	
a:	CN	CN	NH_2	NH_2	Z = CN
b:	CO_2R	CN	NH_2	OH	CO_2R
c:	CO_2R	CO_2R	OH	OH	$CONH_2$
d:	$CONH_2$	CN	NH_2	–	
e:	C_6H_5	CN	NH_2	–	

At the same time, the synthesis of dihydroxythieno[2,3-b]-thiophen (Vc) establishes that the compound obtained by partial cyclisation from malonic ester is the hydroxythiophen derivative (IVc) and not 2-[bis(ethoxycarbonyl)methylene]-4-ethoxycarbonyl-5-keto-1,3-dithiacyclohexane [3].

The aminothiophens (IV) and the aminothieno[2,3-b]-thiophens (V) behave as aromatic amines; for example, they can be diazotised, acylated and condensed with aldehydes. Although compound (Va) may be formally compared with 1,8-diaminonaphthalene, differences in reactivity nevertheless exist on account of the different bond angles. On heating with orthoformic ester the *N*,*N*′-bis(ethoxymethylene) derivative is formed from (Va).



Compound (Vc) can be converted with H_2SO_4 into 3,4-dihydroxythieno[2,3-b]thiophen (Vc; Z = H); the latter undergoes reactions similar to those of 3-hydroxythionaphthene and, according to infrared spectral data, exists predominantly in the diketo-form.

If isothiocyanates are employed in the reaction sequence (I) → (IV) instead of carbon disulfide, 2,4-diaminothiophens (VI) are obtained in good yields.

Received, March 5th. 1962 [Z 226/47 IE]

[1] Angew. Chem. *73*, 537 (1961).

[2] *W. Töpfl*, Ph. D. Thesis, Technische Hochschule Stuttgart, 1961.

[3] British Patent 597446 (1948); Chem. Abstr. *42*, 4604 (1948).

Preparation and Properties of Diazopropyne

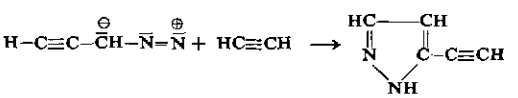
By Dr. H. Reimlinger

Union Carbide European Research Associates, Brussels (Belgium)

We have used *N*-acetylpropargylamine (I) [2,3] as the starting material for the synthesis of diazopropyne [1]. In order to obtain *N*-nitroso-*N*-acetylpropargylamine, the amine (30 g.) was treated with glacial acetic acid (300 ml) at 0 °C [4]. Ice-cold water was then added to the acetic acid solution, and the red oil which separated was dissolved in ether. After neutralisation, the ether was evaporated, and the liquid residue distilled in a high vacuum; b.p. 23 °C/10^{-4} mm. (Distillation of the nitroso compound in a water-pump vaccum can lead to explosions [5].)

The crude product (6.3 g.) was dissolved in a mixture of carbon tetrachloride (80 ml) and methanol (20 ml) and a solution of sodium methylate in absolute methanol (2 g. Na in 20 ml of methanol) added at −15 °C. The Liebermann test was negative after 15 min. Ethereal diazopropyne solutions split off nitrogen in the presence of *p*-nitrobenzoic acid. The propargyl ester (m.p. 89 °C [6]) is the only reaction product so far isolated.

Diazopropyne in ether solution forms 3(5)-ethynylpyrazole (m.p. 55 °C) when shaken for several hours with acetylene in an autoclave [7] (12–15 atm.).



The nitroso compound (12.5 g.) was added to a suspension of barium oxide (5 g.) and barium hydroxide (10 g.) in *n*-decanol (50 ml) and the diazo compound distilled into a cold trap at 0 °C and 10^{-1} mm. nitrogen pressure. A solid, brown substance (m.p. −65 °C), which gave the propargyl ester (m.p. 89 °C) when allowed to react with *p*-nitrobenzoic acid in dichloromethane solution, was isolated.

In contrast to diazomethane solutions, solutions of diazopropyne in ether or dichloromethane are stable for prolonged periods at room temperature without decomposition.

The infrared spectrum of diazopropyne in CCl_4 shows the bands characteristic for the diazo group (2075 $cm.^{-1}$) as well as for the monosubstituted acetylene derivative (2140 $cm.^{-1}$ and 3330 $cm.^{-1}$).

Received, March 6th. 1962 [Z 228/60 IE]

[1] *P. S. Skell* and *J. Klebe*, J. Amer. chem. Soc. *82*, 247 (1960).

[2] *A. Marszak-Fleury*, Ann. Chim. *3*, 656 (1958).

[3] *R. A. Raphael*, personal communication.

[4] *O. Fischer*, Ber. dtsch. chem. Ges. *9*, 463 (1876); *R. Huisgen* and *J. Reinertshofer*, Liebigs Ann. Chem. *574*, 157 (1951); *H. France*, *I. M. Heilbron*, and *D. H. Hey*, J. chem. Soc. (London) *1940*, 369; *E. H. White*, J. Amer. chem. Soc. *77*, 6008 (1955).

[5] *P. S. Skell*, personal communication.

[6] *W. Reppe* and Mitarb., Liebigs Ann. Chem. *596*, 38 (1955).

[7] *H. Reimlinger*, Chem. Ber. *92*, 970 (1959).

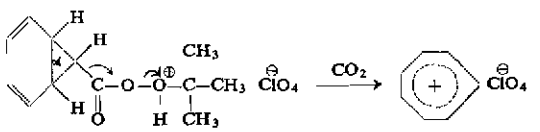
Acid-Catalyzed Fragmentation of t.-Butyl Norcaradiene Percarboxylate: A Novel Type of Perester Degradation

By Dr. C. Rüchardt and cand. chem. H. Schwarzer

Institut für Organische Chemie
der Universität München (Germany)

When 70 per cent perchloric acid (2 mole equivalents) is added to a solution of t-butyl norcaradiene percarboxylate at −30 °C, CO_2 (67 % of the theorctical amount) is evolved. After evaporating the solvent at −30 °C and treatment of the residue with ethyl acetate, crystalline tropylium perchlorate (60 % theor.) is obtained. This compound was identified by its explosion point at 280 °C, by the characteristic precipitation reaction with sodium tetraphenylborate, and by its infrared spectrum [1]. t-Butanol (33 % theor.) was identified in the mother liquor by gas chromatography.

The results are best interpreted by an electrophilic fragmentation [2] of the perester. Similar fragmentations with formation of tropylium salts have been described by *K. Conrow* [1].



+ $(CH_3)_3COH$

While degradation reactions of peresters R−CO−O−O−C−$(CH_3)_3$ by radical [3] or ionic [4] scission of the peroxide bond, as well as by simultaneous radical scission of the peroxide and the R−CO-bonds [5] are known, this is the first example of an ionic perester fragmentation. Studies are in progress to determine whether this reaction can take place with other peresters. Also, the transformations of peresters, the residues R of which have aromatic character when they become carbonium ions or carbanions, are under study.

t.-Butyl norcaradiene percarboxylate (m.p. −5 to −8 °C with decomposition; CO band at 1765 cm.$^{-1}$ [6]) was obtained from the acid chloride and t.-butyl hydroperoxide with stoichiometric amounts of pyridine in petroleum ether at −50 °C. Purification was achieved by chromatography on neutral aluminum oxide at −50 °C. The compound decomposes violently when warmed to room temperature; its half-life on thermal decomposition at 10 °C is about 25 to 30 minutes in chlorobenzene, and 8 to 10 minutes in methanol. This t.-butyl perester therefore has the greatest decomposition tendency.

Received, March 8th. 1962 [Z 230/59 IE]

[1] *K. Conrow*, J. Amer. chem. Soc. *81*, 546 (1959).

[2] *C. A. Grob* in: Theoretical Organic Chemistry (Kekulé Symposium, London 1958). Butterworths Scientific Publications, London 1959, p. 114.

[3] *A. T. Blomquist* and *I. A. Berstein*, J. Amer. chem. Soc. *73*, 5546 (1951).

[4] *R. Criegee* u. *R. Kaspar*, Liebigs Ann. Chem. *560*, 127 (1948); *P. D. Bartlett* and *T. G. Traylor*, J. Amer. chem. Soc. *83*, 856 (1961).

[5] *P. D. Bartlett* and *R. E. Pincock*, J. Amer. chem. Soc. *82*, 1753 (1960) and earlier publications.

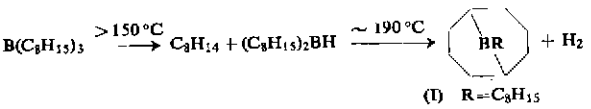
[6] *P. D. Bartlett* and *R. R. Hiatt*, J. Amer. chem. Soc. *80*, 1398 (1958).

Heterocyclic Boron Compounds by Pyrolysis of Cycloalkylboranes

By Dr. R. Köster and Dipl.-Chem. G. Rotermund

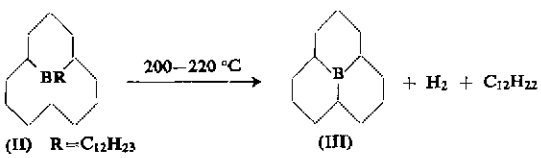
Max-Planck-Institut für Kohlenforschung,
Mülheim/Ruhr (Germany)

Tricycloalkylboranes and cycloalkyldiboranes consisting of rings with at least 8 carbon atoms yield heterocyclic boron compounds upon pyrolysis. These results are similar to those obtained with trialkylboranes [1] and alkyldiboranes [1]. Tri(cyclo-octyl)borane is quantitatively converted into *B*-cyclo-octyl-9-borabicyclo[3,3,1]-nonane (I), with elimination of one mole of *cis*-cyclo-octene (96.5 %, the remainder being cyclo-octane) and one mole of hydrogen.



(I) R = C_8H_{15}

The pyrolysis of tricyclododecylborane proceeds similarly. *B*-cyclododecyl-13-borabicyclo[7,3,1]tridecane (II) is obtained following the cleavage of one mole of cyclic C_{12}-hydrocarbons (28 % *cis* and 64 % *trans*-cyclododecene, 8 % cyclododecane) and one mole of hydrogen. However, on further heating above 200 °C, compound (II) loses an additional one mole of hydrogen and one mole of cyclo-olefin and is converted into perhydro-9^b-boraphenalene [2] (III). The yield of the latter amounts to 70–80 %. The remainder consists of polymeric substances.



(II) R = $C_{12}H_{23}$ (III)

Pyrolysis of tricyclohexylborane does not yield *B*-cyclohexyl-7-borabicyclo[2,2,1]heptane. An equimolar mixture of cyclohexene and cyclohexane is split off, and dark-brown boron-containing polymers with the composition $(BC_6H_{11})_x$ are formed. There is practically no formation of hydrogen.

$$xB(C_5H_{11})_3 \xrightarrow{250\,^\circ C} (BC_6H_{11})_x + xC_6H_{10} + xC_5H_{12}$$

Received, March 8th. 1962 [Z 231/64 IE]

[1] *R. Köster* and *G. Rotermund*, Angew. Chem. *72*, 138, 563 (1960).

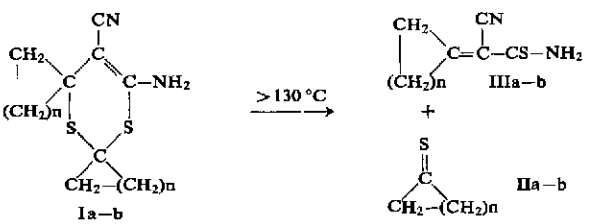
[2] *R. Köster*, Angew. Chem. *69*, 684 (1957).

Simple Synthesis of Monomeric Thioketones [1]

By Prof. Dr. Roland Mayer and Dipl.-Chem. J. Jentzsch

Institut für Organische Chemie der Technischen Universität
Dresden (Germany)

gem-Dithiols, now easily available by synthesis [2], react almost quantitatively with malonic dinitrile forming the novel 1,3-dithiacyclohex-4-enes (Ia–b) [1]. On heating above their melting points, these compounds decompose completely, yielding the specific thioketone (IIa–b) and the corresponding thioamide (IIIa–b).



a: n = 3; b: n = 4

The relatively unstable, monomeric, deep-red, thioketones have a disagreeable odour. They are readily recovered in a higher state of purity, and in 70–90 per cent yields, by distillation. Cyclopentanethione (IIa), b.p. 56 °C/11 mm., is obtained from (Ia) (m.p. 105–107 °C) at 130 °C, and cyclohexanethione (IIb), b.p. 74 °C/11 mm., from (Ib) (m.p. 118 °C at 135 °C.

The thioketones were identified by analysis, preparation of derivatives, spectroscopic studies and characteristic reactions.

The infrared spectrum of compound (IIa) was identical with that of another sample which we had obtained by a different route [3].

The cleavage reaction outlined here is variable within wide limits and has been elaborated further. Spectral data relating to the now more accessible thioketones, and other properties, will be described in detail elsewhere.

Received, March 9th. 1962 [Z 234/61 IE]

[1] X th. Communication on Sulfur Heterocycles. – IX th. Communication: *J. Jentzsch* and *R. Mayer*, J. prakt. Chem., in press.

[2] *J. Jentzsch, J. Fabian*, and *R. Mayer*, Chem. Ber. in press.

[3] *R. Mayer* and *P. Barthel*, Chem. Ber. *93*, 428 (1960); further elaboration with confirmation of structure: *G. Wenschuh*, Ph. D. Thesis, Technische Universität Dresden (not yet completed).

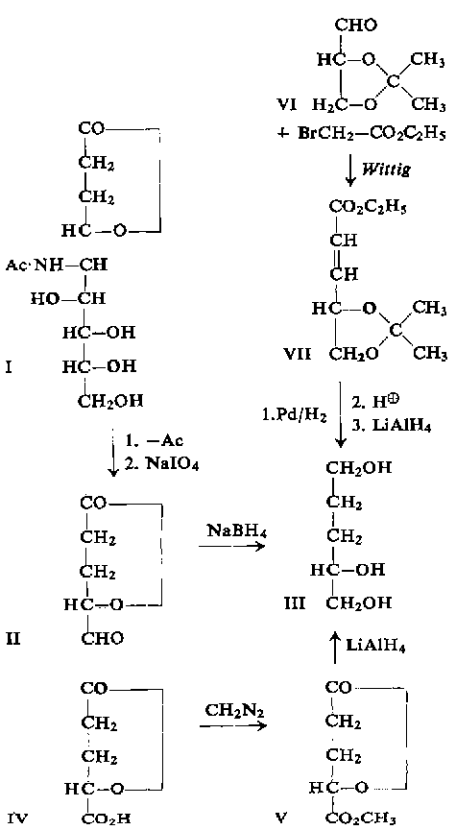
The Configuration of Sialic Acids

By Prof. Dr. Richard Kuhn and Dr. R. Brossmer

Max-Planck-Institut für Medizinische Forschung, Institut für Chemie, Heidelberg (Germany)

The assumption that the OH group at *C*-4 in sialic acids is on the left (*E. Fischer*'s terminology) was based on the lactone rule of *C. S. Hudson*: Both the lactaminic acid lactone diethylmercaptal [1] ($[\alpha]_D = -83°$), and the desthiolactone [2] (I) ($[\alpha]_D = -35°$) prepared from it, were laevorotatory. The degradation of compound (I) to *R*-(−)-pentane-1,4,5-triol, which we have now carried out, proves that this conclusion was incorrect. The hydroxyl group at *C*-4 in sialic acid is on the right.

Pentane-1,4,5-triol from	$[\alpha]_D$ in CH_3OH	$[\alpha]_D$ in Borate [3]
lactaminic acid	−12.5°	+3.5°
L-glutamic acid	−11.5°	+3.5°
D-glyceraldehyde	−12.7°	+4.5°



We have obtained proof through preparation of the *R*-(−)-pentane-1,4,5-triol (III) by three methods:

1. The desthiolactone (I), prepared from lactaminic acid (*N*-acetylneuraminic acid) was deacetylated with $Ba(OH)_2$ and subsequently cleaved with $NaIO_4$. The resulting solution of the lactone aldehyde (II) was reduced with $NaBH_4$ to give the triol (III) (total yield, 50 %).

2. L-(+)-Glutamic acid was converted to L-(−)-α-hydroxyglutaric acid with nitrous acid; the methyl ester (V) of its lactone (IV) was hydrogenated by $LiAlH_4$ to form (III) in 80 % yield.

3. Acetone-D-glyceraldehyde (VI) was converted by Wittig synthesis to the α,β-unsaturated dihydroxy ester (VII) in 75 % yield. From this, the laevo rotatory triol (III) was obtained by catalytic hydrogenation, cleavage of the isopropylidene group with dilute acid, and subsequent reduction with $LiAlH_4$. The tris(phenylurethane) melts at 105–107 °C $[\alpha]_D^{20} = -18°$ (in pyridine).

The revision of the sialic acid formula is in agreement with the results of *R. Kuhn* and *G. Baschang* [4], who succeeded on the one hand in converting an α,β-unsaturated lactone, obtained from *N*-acetyl-D-mannosamine and oxalacetic ester, into lactaminic acid by $H^⊕$ attack, and on the other hand by ozonolysis to 3-acetylamino-3-desoxy-D-manno-D-galaheptose [5] whose structure is well established.

Received, March 12th. 1962 [Z 235/65 IE]

[1] *R. Kuhn* and *R. Brossmer*, Angew. Chem. *69*, 534 (1957).

[2] *R. Kuhn* and *R. Brossmer*, Liebigs Ann. Chem. *624*, 137 (1959).

[3] Triol in CH_3OH, plus an equal volume of saturated aqueous $Na_2B_4O_7$ solution.

[4] Unpublished results.

[5] *R. Kuhn* and *G. Baschang*, Liebigs Ann. Chem. *636*, 164 (1960).

Explosion during the Uncatalyzed Addition of Trichlorobromomethane to Ethylene

By Dr. H. Elsner and Dr. S. Saure

Wissenschaftliches Laboratorium der Dynamit Nobel AG., Troisdorf (Germany)

In the laboratory preparation of 1,1,1-trichloro-3-bromopropane according to the method of *W. A. Skinner* et al. [1], the high-pressure autoclave exploded with great force in the fourth run, following three incident-free experiments. The circumstances under which the explosion occurred may stand as a warning to chemists using this reaction, which has not previously been considered dangerous.

The pressure vessel was designed for an operating temperature of 350 °C and an operating pressure of 300 gauge-atm. (test-pressure 420 gauge-atm.). It had a volume of about 900 ml., and was provided with an electromagnetic stirrer, external resistance heating, a manometer, a thermometer connection, and gas inlet and outlet valves. The values recommended in the literature for the initial pressure (approximately 50 gauge-atm.) and for the reaction temperature (120 °C), were observed. The trichlorobromomethane was freshly distilled; its purity had been confirmed by boiling point, refractive index, and density measurements.

Our fourth run proceeded normally for about $1-1/2$ hours, that is, for more than one-third of the prescribed time (4 hours), when, suddenly, a strong explosion occurred, shattering the 12 mm. thick wall of the autoclave. The manometer (with a scale maximum of 400 atm.) was also shattered. The laboratory walls were covered with soot. As far as can be determined, no failure of the ancillary equipment had occurred.

A query directed to the authors of the method elicited the response that they had never at any time observed an explosion during the course of this reaction.

It must be assumed that a previously unknown side reaction suddenly occurred.

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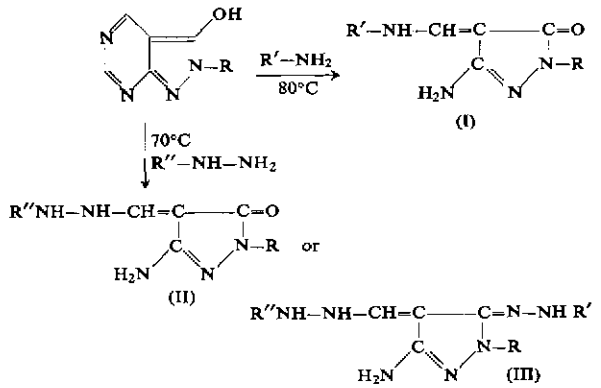
[1] J. org. Chemistry *23*, 1710 (1958).

Cleavage of the Pyrimidine Ring with Amines and Hydrazines

By Prof. Dr. H. Bredereck, Dr. F. Effenberger, and Dipl.-Chem. W. Resemann

Institut für Organische Chemie und Organisch-chemische Technologie derTechnischen Hochschule Stuttgart (Germany)

In the course of our investigations of the heterocyclic series, we found a new reaction, which, according to our experiences so far, has general applicability. 2-Substituted 3-hydroxypyrazolo-[3,4d]-pyrimidines [1] react with amines and



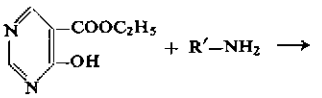
(I)

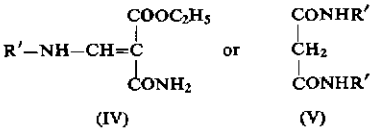
(II)

(III)

hydrazines under very mild conditions, evolving ammonia. Thus, the pyrimidine ring is opened and undergoes partial degradation.

In the reaction with aniline (R'=phenyl), *N,N'*-diphenylformamidine was isolated as well as the pyrazolone derivative (I). 2-Substituted 3-mercaptopyrazolo-[3,4d]-pyrimidines are also cleaved, forming the corresponding pyrazolonethiones. Reactions with hydrazines lead to (II) or (III) depending on the conditions and the hydrazine derivative used. This novel cleavage reaction can even be applied to simple pyrimidines.





(IV) (V)

Whether (IV) or (V) is formed depends only on the amine. Aniline (R'=phenyl) yields (IV); benzylamine ($R'=C_6H_5CH_2$) yields (V).

The structural prerequisites for this cleavage reaction are the topic of further investigations.

E. C. Taylor [2] has reported the cleavage of pteridines by means of amines and hydrazines.

Received, March 14th. 1962 [Z 237/66 IE]

[1] *H. Bredereck, F. Effenberger,* and *W. Resemann,* Chem. Ber., in the press.

[2] *E. C. Taylor,* J. Amer chem. Soc. *74,* 1651 (1952).

CONFERENCE REPORTS

Determination of the Electron Distribution in Solids by X-Rays and its Relation to Chemical Bonding

H. Witte, Darmstadt (Germany)

The distribution of the valence electrons particularly influences the diffraction pattern at small and medium glancing angles. It is, therefore, important to measure such diffraction intensities as accurately as possible. By means of a combination of measurements on single crystals and on powders it has, in most cases, been possible to obtain absolute values for structure amplitudes with an accuracy of about 1%. By avoidance of termination effects, Fourier series have been used to calculate electron distributions along those planes which permit conclusions concerning the bonding conditions. Fourier series were also applied to the errors of the structure amplitudes so that both the value of the electron density and the measurement error function could be reported.

The deviations from spherical symmetry due to bonding in NaCl, LiF, and CaF_2 have little effect on the intensity of the X-ray reflections. The deviations found are not substantially larger than the error function. Characteristic for these materials is the bridging between the Cl^--ions in NaCl or the F^--ions in LiF and CaF_2 in which the electron density is reduced to 0.2 el/Å^3. There exists in NaCl an area between Na^+ and Cl^- which is virtually free of any charge. On the other hand, the electron densities between Li^+ and F^- in LiF and Ca^{2+} and F^- in CaF_2 never fall to zero.

If the distances between the points of minimum electron density on the line joining the cations and anions are compared with the conventional radii according to *Goldschmidt* and *Pauling*, the radii of the cations, thus defined, are much larger, while those of the anions are much smaller. Thus, in NaCl, the value for Na^+ is 0.98 Å according to *Goldschmidt*, and 0.95 Å according to *Pauling*. The value of 1.19 Å, obtained by *Fumi* and *Tosi*, who used Born's approximations, however, agrees well with our own values.

Only in the case of aluminum was no deviation from the spherically symmetrical charge distribution observed. (The virtually constant electron density of 0.2 el/Å^3 between the ions is in approximate agreement with the expected value of 3 conducting electrons/atom.)

Valence electron distribution strongly influences some reflections in diamond and silicon and, at the same time, the "forbidden" reflection (222). The same systematic deviations from the theoretical values of the structure amplitudes have been found in both substances. (The theoretical values were calculated according to the method of *Hartree* on the basis of a spherically symmetrical charge distribution of free atoms.) These deviations can be detected in the whole temperature range between −170 °C and +450 °C.

All of these deviations cause an increase in electron density between neighboring atoms. At the midpoint of the line joining the two atoms values of 1.70 el/Å^3 for diamond and 0.65 el/Å^3 for silicon have been found (calculated: 1.16 el/Å^3, and 0.35 el/Å^3, respectively). The density values between neighboring atoms are virtually independent of temperature.

The experimentally determined electron distribution between neighboring atoms agrees well with that calculated on a wave mechanical basis by *Ewald* and *Hönl* (calculated: 1.50 el/Å^3, measured: 1.70 el/Å^3).

[Chemische Gesellschaft zu Heidelberg (Germany), January 23rd. 1962].

[VB 566/19 IE]

Investigations on Isopolytungstate and Isopolymolybdate Anions in Aqueous Solution

By *O. Glemser* and *W. Holznagel*, Göttingen (Germany)

Isopolytungstate and isopolymolybdate anions exist in differing stages of condensation according to the pH value. We have found:

1. For isomolybdate solutions: The octamolybdate anion, $Mo_8O_{26}^{4-}\cdot xH_2O$, occurs as the highest stage of condensation in "metamolybdate solutions" (pH ≈ 3; $H^+/MoO_4^{2-} = 1.5$). The dependence of the degree of hydrolysis of the octamolybdate on concentration was calculated, and a complex stability constant for the octa-ion arrived at. In "paramolybdate solutions" (pH ≈ 8; $H^+/MoO_4^{2-} = 1.143$), the occurrence of a heptamolybdate anion $Mo_7O_{24}^{6-}\cdot xH_2O$ is very probable. The existence of hydrogen paramolybdate anions can be established indirectly. There is a high probability that aggregation stages with a degree of condensation under 6 are excluded. Establishment of the equilibrium in polymolybdate solutions takes place instantaneously.

2. For isopolytungstate solutions: In contrast to the earlier statements of other authors, the degree of polymerisation of isopolytungstate anions is not 6 but 12. Solutions in equilibrium at a degree of protonation $<1.5\ H^+/WO_4^{2-}$ and pH >5 contain the so-called "paratungstate" anion, $W_{12}O_{41}^{10-}\cdot xH_2O$, and the so-called" metatung state" anion, $W_{12}O_{39}^{6-}\cdot xH_2O$. Solutions with a pH value <5 contain only metatungstate as polyanion. Approximate stability constants were obtained for both polyanions.

The protracted aging process in freshly prepared solutions comprises the slow formation of metatungstate and an associated decrease in the concentration of the already existing protonated products. Even in solutions with pH >5 – and in opposition to reports in the literature – the metatungstate ion is formed at the expense of the primarily formed para-ion.

[Colloquium, Anorganisch-Chemisches Institut der Universität Göttingen (Germany), January 29th. 1962]

[VB 571/16 IE]

Recent Investigations on Oxometallates and Double Oxides

R. Scholder, Karlsruhe (Germany)

Compounds of the so-called β-alumina type were formulated as $M_2^{(I)}O\cdot 11\,M_2^{(III)}O_3$ ($M^{(I)}$ = alkali metal, $M^{(III)}$ = Al, Ga, Fe). X-Ray and chemical methods (action of acids on $M_2O\cdot nM_2O_3$, volatalisation of K_2O from $K_2O\cdot 2.5\ Fe_2O_3$ at 1000–1100 °C) showed that β-alumina has the composition $M_2O\cdot 6\,M_2O_3$. Pure $K_2O\cdot 6Fe_2O_3$ can be prepared in a coarse crystalline form from a KF melt and Fe_2O_3-A phase $M_2O\cdot 11\,M_2O_3$ was not observed in any of the oxide systems that were investigated [1].

Alkaline earth rhenates$^{(VI)}$ of the types M_3ReO_6, M_2ReO_5 and $M_3Re_2O_9$ can be prepared from rhenates$^{(VII)}$ [2], rhenium metal and alkaline earth oxides by mixing together in the correct proportions. The Li compounds, Li_6ReO_6 and Li_4ReO_5, can be prepared similarly. The powder photograph of $M_3Re_2O_9$ is very similar to photographs of the alkaline earth orthophosphates; this clearly suggests formulation as $M_3(ReO_{4,5}^{-})_2$ with an excess of oxygen when compared with $M_3(PO_4)_2$. Oxorhenate containing $Re^{(V)}$ was first observed in the compounds $BaRe_{0,5}^{(V)}La_{0,5}^{(III)}O_3$ and $BaRe_{0.5}^{(V)}\text{-}In_{0.5}^{(III)}O_3$ which crystallise as super-lattices with the Perovskite type of structure. Corresponding compounds containing $Re^{(VI)}$ and $M^{(II)}$ were obtained by *Ward* [3] and by us, using different methods, at about the same time. The easily obtainable rhenate$^{(V)}$ Li_3ReO_4 does not have the rock-salt structure of the corresponding osmate$^{(V)}$ Li_3OsO_4 but the structure described by Lang for the $A_2^{(I)}B^{(IV)}O_3$. Therefore, Li_3ReO_4 can be considered structurally as $Li_2(Re_{0,75}\text{-}Li_{0.25})O_3$.

In experimental attempts to prepare rhenates$^{(IV)}$ by thermal methods, disproportionation of ReO_2 invariably occurred. It is only in the equilibrium system attained at fairly high temperatures that the Na_2ReO_3 coexists with Na-rhenate (VII) and metallic rhenium. $LiReO_2$ containing trivalent Re has the NaCl structure as do the corresponding compounds of $Mo^{(III)}$ and $W^{(III)}$.

The potassium ferrate that was prepared by *Klemm* [4] is also produced, together with $KFeO_2$, by the thermal decomposition of K_2FeO_4. With a longer reaction time and at a higher temperature pure $KFeO_2$ is eventually produced as a result of the evaporation of K_2O. The most useful temperatures for the preparation of pure K_3FeO_4 from Fe_2O_3 and KO_x in O_2 are those in the range 750–780 °C if at the same time the reaction time is chosen to be as short as possible. The K_3FeO_4 thus produced disproportionates in alkali and 65.6–66.1 % of the total Fe is present as $Fe^{(VI)}$ (calc. 66.67 %)·K_3FeO_4 decomposes gradually into $KFeO_2$ and potassium superoxide at 400–500 °C. According to the first experiments K_3FeO_4 dissolves in cold, conc., sodium hydroxide evidently without disproportionation. The solution gave the ratio Fe:O act. as 1:1.50 within the limits of experimental error. A residue of Fe_2O_3·aq. was not observed on filtration.

[GDCh-Ortsverband Hannover (Germany), February 1st. 1962]

[VB 568/18 IE]

[1] Cf. *R. Scholder* and *M. Mansmann*, Z. Naturforsch. *15b*, 681 (1960).

[2] *R. Scholder*, Angew. Chem. *70*, 583 (1958).

[3] *R. Ward* et al., J. Amer. chem. Soc. *83*, 1088, 2816 (1961).

[4] *K. Wahl*, *W. Klemm*, and *G. Wehrmeyer*, Z. anorg. allg. Chem. *285*, 322 (1956).

Mechanisms of Chromic Acid Oxidation

Kenneth B. Wiberg, Seattle, Washington (USA)

The rates of oxidation of both aliphatic hydrocarbons and the side chains of aromatic hydrocarbons parallel the rates of free radical hydrogen abstraction from these compounds, and are quite different from the relative rates of solvolysis of the corresponding chlorides. This, and other evidence, suggests that the first step involves the abstraction of a hydrogen atom from the hydrocarbon giving the alkyl or benzylic radical which reacts further.

The oxidation of a hydrocarbon with an optically active tertiary center gave a tertiary alcohol with 80 % retention of configuration. This suggests that the second step involves recombination of the alkyl radical with chromium (V) in the solvent cage to give a chromium (IV) ester. The latter is then hydrolyzed with chromium - oxygen bond cleavage. This is in accord with the mode of hydrolysis of tetra-t-butoxychromium.

The Etard reaction of the hydrocarbons is somewhat different. The oxidation of n-propylbenzene gives propiophenone and benzyl methyl ketone in a 1:3 ratio. The latter product arises from an initial α-attack followed by a rearrangement, as shown by deuterium labeling in the α- and β-positions. The product ratio is affected by the chromyl chloride concentration. High concentrations favor the formation of propiophenone. This indicates that the propiophenone is formed by two successive normal oxidations, and that benzyl methyl ketone arises by elimination following the initial oxidation, and then, finally, reaction of the alkene with chromyl chloride.

[GDCh-Ortsverband Darmstadt (Germany), January 16th. 1962]

[VB 570/17 IE]

Polyacetylenes in Medicinal Plants

K. E. Schulte, Münster (Germany)

Six polyacetylenes were isolated from the air-dried roots of *Arnica montana*. Four of them were identified as C_{13} hydrocarbons by perhydrogenation and gas chromatography: tridec-1-en-3,5,7,9,11-pentayne (the largest portion of the alkyne mixture; LD_{50} = 15 mg/kg mouse, orally); tridec-1,11-dien-3,5,7,9-tetrayne, a substance with a tetraynene chromophore and another with a pentaenyne chromophore (based on optical properties). In addition to a phenol fraction, containing thymol among other substances, there are associated with the polyacetylenes: thymol methyl ether, 3,6-dihydroxythymol dimethyl ether and Δ^8-dehydro-3,6-dihydroxythymol dimethyl ether.

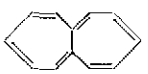
Some alkynes were also found in the fresh roots of *A. longifolia* and *A. foliosa*, and some were found in the blossoms of *A. montana*. Seven polyacetylenes were found in the fresh roots of *Pulicaria dysenterica*, which is rarely used for therapeutic purposes nowadays, and five of them were identical with those found in *A. montana*. The aromatic compounds named above also occur in these plants. Other medicinal plants containing alkynes are: *Calendula officinalis*, *Grindelia robusta*, *Helichrysum arenarium*, *Hydrocotyle asiatica*, *Ricinus communis*, *Valeriana officinalis*. In *Tagetes erecta* a water-soluble polyacetylene was found. From the same plant *L. Zechmeister* et al. isolated α-terthienyl and *J. H. Uhlenbrock* et al. isolated 5-[but-3-en-1-ynyl]-2,2′-bithienyl. The occurrence of polyacetylenes together with thiophene derivatives suggested the possibility of preparing the latter from the former, since it is known that di-, tri- and tetra-ynes, in weakly alkaline solution, add H_2S with formation of a thiophene ring [1]. In this fashion, junipal (5-propynyl-2-formylthiophene) was prepared from octa-2,4,6-triyn-1-ol, α-terthienyl was prepared from dithienylbutadiyne and *cis*- and *trans*-β-(5-propynylthien-2-yl)acrylates were produced from the esters of *cis*- and *trans*- n-dec-2-en-4.6,8-triynoic acid (dehydromatricaria acid).

[GDCh-Ortsverband Bielefeld (Germany), January 30th. 1962] [VB 565/20 IE]

[1] *K. E. Schulte, J. Reisch*, and *L. Hörner*, Angew. Chem. *72*, 920 (1959).

SELECTED ABSTRACTS

Heptalene (I), the long sought bicyclic compound with $4n\ \pi$ electrons (n = 3), has been prepared by *H. J. Dauben* and *D. J. Bertelli*. An ice-cooled, approximately 0.005 molar solution of 1-heptalenium tetrafluoroborate [1] in $CHCl_3$ was treated with an excess of trimethylamine also dissolved in $CHCl_3$. After filtration of the trimethylammonium tetrafluoroborate and chromatographic separation, (I) was isolated as a dark yellowish to reddish brown viscous oil, which failed to crystallize when cooled to −78 °C. The compound polymerizes in air or on slight heating, but it is relatively stable when protected from air in solid form at −78 °C, or in dilute solution at +25 °C.

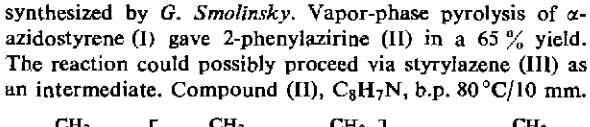


I

The structure was confirmed by the nuclear magnetic resonance spectrum (typical AB_2X_2 spectrum showing absorptions only in the "vinylic region") and by re-protonation to the 1-heptalenium ion by treatment of the cyclohexane solution with concentrated sulfuric acid. Further proof was established by catalytic hydrogenation to bicyclo[5,5,0]-dodecane. With bromine, compound (I) rapidly forms a water-soluble, yellow precipitate, probably bromoheptalenium bromide. The properties investigated thus far indicate that (I) is more similar to a cyclic polyene than to an aromatic system. / J. Amer. chem. Soc. *83*, 4659 (1961). / −Ko. [Rd 19/25 IE]

[1] *H. J. Dauben* and *D. J. Bertelli*, J. Amer. chem. Soc. *83*, 4657 (1961).

2-Phenylazirine, an azacyclopropene derivative, has been synthesized by *G. Smolinsky*. Vapor-phase pyrolysis of α-azidostyrene (I) gave 2-phenylazirine (II) in a 65 % yield. The reaction could possibly proceed via styrylazene (III) as an intermediate. Compound (II), C_8H_7N, b.p. 80 °C/10 mm.



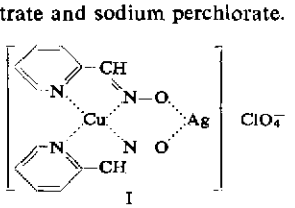
I III II

is a colorless, thermally unstable liquid, which is transformed into 2,5-diphenylpyrazine in 30 % yield by boiling with acidic aqueous ethanol. α-Azidostyrene was obtained from styrene dibromide and one mole of NaN_3 in dimethylformamide with subsequent dehydrobromination of the resulting bromoazide with potassium t-butylate in benzene. / J. Amer. chem. Soc. *83*, 4483 (1961). −Ma. [Rd 22/28 IE]

Certain photosensitized cycloaddition reactions of dienes have been reported by *G. S. Hammond, N. J. Turro*, and *A. Fisher*. Butadiene yields *cis*- and *trans*-1,2-divinylcyclobutane and 4-vinylcyclohexene when irradiated with ultraviolet light in the presence of benzil, 2,3-pentanedione, acetophenone, and other sensitizers. The ratio of the products formed depends largely on the sensitizer. The method is especially useful as a preparative procedure for *trans*-1,2-divinylcyclobutane. The reaction is carried out at −10 °C using 2,3-pentanedione as a sensitizer. After separation of the sensitizer, the mixture is heated for 3 hrs. at 120 °C to convert the *cis*-isomer to 1,5-cyclobutane, and then fractionated (yield ca. 37 %). Norbornadiene (I) can be converted by an inner addition under similar conditions (isopentane solution; acetone, acetophenone or benzophenone as sensitizers) to quadricyclene (II). Compound (II), b.p. 108 °C/740 mm., $n_D^{26.5}$ = 1,4830 was characterized primarily by its nuclear magnetic resonance spectrum. At 140 °C it reconverts slowly to norbornadiene. / J. Amer. chem. Soc. *83*, 4674 (1961). / −Ko. [Rd 20/26 IE]

β-Isopropyltropolone, which occurs in some woody plants in a concentration up to 4 %, can be used for extracting metal ions, as was shown by investigations in the system: $CHCl_3$ 0.1 M aqueous perchlorate solution. At pH < 1 it is possible to extract: Sc(III), Fe(III), Cu(II), In(III), Th(IV), U(VI) [probably also Al(III), and Ga(III)]; between pH 2 and 6: Co(II), Ni(II), Zn(II), Cd(II), Y(III), lanthanide ions and Am(III); further, at pH > 7: Ca, Ba, Sr, and partly Ag. In some cases, the extraction is improved by adding quinoline or laurylamine. / Acta chem. scand. *15*, 1614 (1961). / −Ma. [Rd 76/40 IE]

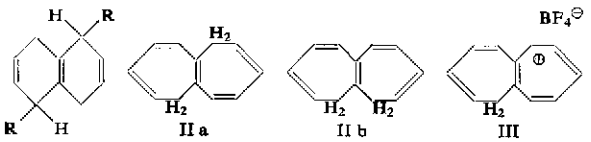
A heterobinuclear chelate with silver(I) and copper(II) was synthesized by *C. H. Liu* and *Ch. F. Liu*. Bis(pyridine-2-aldoxime)copper(II) was allowed to react in aqueous solution with a small excess of silver nitrate and sodium perchlorate.



I

After heating and slow neutralization with NaOH (final pH 7.2), the binuclear complex (I) was formed as a green precipitate. / J. Amer. chem. Soc. *83*, 4167 (1961). / −Ko. [Rd 7/24 IE]

The 1-heptalonium ion was synthesized as the tetrafluoroborate by *H. J. Dauben* Jr. and *D. J. Bertelli*. 1,5-Naphthalenedicarboxylic acid was reduced with Na/C_2H_5OH in liquid NH_3 at −78 °C to 1,4,5,8-tetrahydronaphthalene-1,5-dicarboxylic acid (Ia). Further reduction with $LiAlH_4$ yielded the diol (Ib; m.p. 73–75 °C) which was converted to the ditosylate Ic (m.p. 114–117 °C, decomp.). Solvolytic rearrangement of Ic in pure acetic acid and in the presence of NaH_2PO_4, was carried out by the ring-expansion route developed by *Nelson* et al. [1].

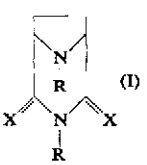


Ia: R = COOH, Ib: R = CH_2OH, Ic: R = CH_2OTos

A mixture of 1,5- and 1,10-dihydroheptalene (IIa and b) was obtained in the form of a yellowish oil which polymerized when exposed to air. When treated with triphenylmethyltetrafluoroborate, the mixture of IIa and IIb is rapidly converted with loss of a hydride ion to 1-heptalenium tetrafluoroborate (III); bright yellow cubes, moderately stable in air. The structure is confirmed by its nuclear magnetic resonance spectrum. The 1-heptalenium ion ($pK_a \geq 7$) is considerably more stable than the related azulenium ion. ($pK_a = 1$). / J. Amer. chem. Soc. *83*, 4567 (1961). / —Ko. [Rd 21/27 IE]

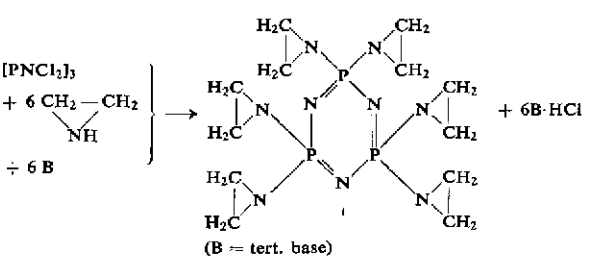
[1] *N. A. Nelson, J. H. Fassnacht*, and *J. U. Piper*, J. Amer. chem. Soc. *83*, 206 (1961).

A new ring system, 3,8-diazobicyclo[3.2.1]octane (I), was obtained by *E. Schipper* and *W. R. Boehme* by condensation of α,α'-dibromoadipic acid esters (II) with amines. 3,8-Dimethyl-3,8-diazabicyclo[3,2,1]octane-2,4-dione (R = CH_3, X = O), b.p. 145–150 °C./13 mm., m.p. 114–115 °C., crystals



from pentane) is obtained from the dimethyl ester of (II) and methylamine in 3 % yield, and from the diethyl ester in a 5 % yield. However, it is obtained from 1-methyl-2-carbethoxy-5-pyrrolidine-*N*-methylcarboxamide in 53 % yield after heating for 5 days at 160–180 °C. The 3,8-di(2-diethylaminoethyl) derivative of I, b.p. 175–180 °C./0.03 mm., n_D^{26} 1.4840, can be obtained from the diethyl ester of II with benzylamine in 16 % yield. / J. Org. Chemistry *26*, 3599 (1961). — De. [Rd 970/6 IE]

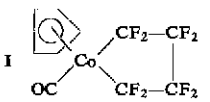
Hexakis(1-aziridinyl)triphosphonitrile sterilizes insects [1]. This compound and its homologs were first synthesized by *R. Rätz* and *Ch. Grundmann*. Hexakis(1-aziridinyl)triphosphonitrile was obtained in high purity, when one mole of trimeric phosphonitrilic chloride was reacted in the presence of a tertiary base with an excess of ethyleneimine in benzene solution. After removal of the hydrochloride, the substance



crystallizes from benzene as colorless crystals, m.p. 147.5 °C (recrystallization from heptane). The melting point is reproducible if the substance is heated on a Fisher-Johns block at a speed of 5 °C per minute. The tetramer, octakis(1-azidirinyl) tetraphosphonitrile, melts at 262 °C. In order to avoid autopolymerization, the melting point block must be preheated. The azidirinyl phosphonitriles are very reactive, water-soluble compounds. Their carbon-nitrogen rings can be opened with reagents such as hydrogen sulfide, hydrogen chloride, sulfurous acid, etc. / *R. Rätz* and *Ch. Grundmann*, U.S.-Patent 2858306; *R. Rätz*, "Contributions to the Chemistry of Cyclic Phosphonitrilic Compounds", Gordon Research Conference on Inorganic Chemistry, 1960, New Hampton, N.H., U.S.A. / —R. [Rd 3/20 IE]

[1] cf. Nachr. Chem. Techn. *9*, 357 (1962).

A novel heterocyclic cobalt compound was obtained by *T. D. Coyle, R. B. King, E. Pitcher, S. L. Stafford, P. Treichel*, and *F. G. A. Stone*, in the reaction between cyclopentadienylcobalt dicarbonyl and tetrafluoroethylene. The reaction was carried out in an autoclave with cyclohexane as solvent (20 hrs. at 160 °C). Structure (I) was proved by infrared studies and also especially from the ^{19}F and ^{1}H nuclear resonance



data. The ^{19}F spectrum consists of a group of two lines (+ 67.5 and + 135 p.p.m. on the high field site of $CFCl_3$). The 67.5 p.p.m. multiplet, attributable to the α-fluorine atoms, indicates that the asymmetrical arrangement of ligands around the cobalt atom produces non-equivalence between the fluorine atoms on opposite sides of the ring. The ^{1}H spectrum has only a single line, *i.e.* all protons are equivalent./ J. inorg. nucl. Chem. *20*, 172 (1961). / —Ko. [Rd 6/23 IE]

Homopolymers of α-vinylnaphthalene and its copolymers with styrene can be metalated with alkali metals in tetrahydrofuran, provided air and moisture are carefully excluded. Dark-green products, which have a polycarbanion base, are formed. The number of metalated nuclei can be determined acidimetrically after precipitating the polymer with water or by determining the acid groups following reaction with CO_2, during which each nucleus is converted to a dihydronaphthalene dicarboxylic acid residue. / Comptes rendus hebd. seances Acad. Sci. *254*, 1067 (1962 / —Ma. [Rd 96/48 IE]

Polycyclic hydrocarbons of the 3,4-benzpyrene type were found as impurities in soils, e.g., forest soils, grass soils, etc., far away from cities. Even in the Soil of tundras north of the artic circle, 1 μg. of benzpyrene/100 g. could be detected. Such compounds are apparently decomposed only very slowly in the soil, while they are destroyed more rapidly in the atmosphere due to the action of air, ultraviolet radiation and ozone. The question of endogeneous formation of such compounds by micro-organisms remains to be investigated. / Comptes rendus hebd. séances Acad. Sci. *254*, No. 5 (1962) / —Ma. [Rd 97/49 IE]

The polymerization of vinylbutyl ether by ultrasonics was studied by *V. V. Salnikov, Z. K. Panshina, E. A. Druyan* and *F. H. Makarova*. The ultrasonic source was a low-power laboratory generator. The vibration frequency was 24 kilocycles, the acoustic power 2 W/cm². The ultrasonic energy causes an immediate and intensive distribution of the catalyst in the monomer. The course of the polymerization is influenced only by the degree of saturation of the monomer with catalyst. Ferric chloride (2.5–5 g./100 ml. ether) was used as catalyst. Additions of butanol to the monomer increased the degree of polymerization (maximum values for additions of 0.1 % butanol and 20 °C). / Zhurnal Prikladnoi Khimii ./ J. Applied Chem. U.S.S.R. *35*, 214 (1962) / —Bk. [Rd 98/50 IE]

α,β-Acetylenecarboxylic acids can be prepared by an intramolecular Wittig-synthesis. *G. Märkl* has reported that triphenylphosphine carboxymethylene (I) reacts with acid chlorides as shown in equation (1):

$$(1)\quad 2\,(C_6H_5)_3P{=}CH{-}COOCH_3 + R{-}COCl \rightarrow$$
$$\rightarrow\ (C_6H_5)_3P{=}\underset{\underset{O-C-R}{|}}{C}{-}COOCH_3 + [(C_6H_5)_3\overset{\oplus}{P}{-}CH_2{-}COOCH_3]Cl^{\ominus}$$
$$\text{I} \qquad\qquad \text{II}$$

Triphenylphosphine acylcarbomethoxymethylenes (II) are colorless, well crystallized compounds which are quite resistant to hydrolysis. Pyrolysis at 220 to 250 °C yields triphenylphosphine oxide and the substituted methyl esters of propiolic acid:

$$(2)\quad (II) \xrightarrow{> 220\,^{\circ}C} R{-}C{\equiv}C{-}COOCH_3 + (C_6H_5)_3P{=}O$$

Chem. Ber. *94*, 3003 (1961). / –Ko. [Rd 78/41 IE]

The cage effect, which in a solvent holds reactive molecules together, was proved by *R. K. Lyon* and *D. H. Levy*. Mixtures of azomethane and hexadeutero azomethane were photolyzed and the reaction products analyzed by mass spectrometry. In a random reaction involving methyl and trideutero methyl radicals, the expected product ratio is given by the equation:

$$Q = \frac{[CH_3CD_3]^2}{[C_2H_6][C_2D_6]} = 4$$

This value was closely approximated in gas phase photolysis (Q = 4.1 ± 0.8). On the other hand, photolysis in iso-octane solution, yielded practically no CH_3CD_3 (less than 0.3 % of the total ethane), but almost exclusively C_2H_6 and C_2D_6. / J. Amer. chem. Soc. *83*, 4290 (1961). / –Ko. [Rd 5/22 IE]

The hydroborination of acetylenes at first yields substituted vinylboranes according to *H. C. Brown* and *G. Zweifel*. On protonolysis, these are conveted to *cis*-olefins in high yield and purity. Oxidation of the vinylboranes with hydrogen peroxide in weakly alkaline solution leads to the corresponding ketones or, if terminal acetylenes are used as starting materials, aldehydes. If the acetylenes are treated with a large excess of boranes showing no steric hindrance, double hydroborination occurs. The two boron atoms attach themselves predominantly to the same C-atom: after the addition of the borane to 1-hexyne, oxidation yields hexanal and only little 1,2-hexanediol. / J. Amer. chem. Soc. *83*, 3834 (1961). –Ko. [Rd 989/14 IE]

A new enzymological method for the diagnosis of myocardial infarction. *W. Stich* and *A. Tsirimbas* have examined the activity of the muscle-specific creatinephosphokinase (CPK) which in heart and skeletal muscle has a concentration 10 to 30-times higher than in other organs. The authors studied the activity of CPK in the serum of normal persons and those suffering from myocardial infarctions and other illnesses. The normal value was 1.96 to 0.17 CPK units/ml. of serum in 15 healthy individuals but in myocardial infarction, an increase in the CPK activity of the serum occurs, even after a few hours, reaching a maximum after 18 to 30 hours. The increase over the normal value is 3 to 20-fold. The diagnostically significant increase in CPK occurs practically only in myocardial infarction and in muscular diseases that can be clinically distinguished (progressive muscular dystrophy, Erb-, Crush-syndromes). Consequently, the CPK test – in contrast to existing enzyme tests – makes possible the biochemical differentiation between myocardial infarction and clinically similar diseases such as pulmonary infarction, gallbladder and liver diseases, among others. / Klin. Wschr. *40*, 115 (1962). / –A. [Rd 74/36 IE]

BOOK REVIEWS

Kinetik der Gasreaktionen (Kinetics of Gas Reactions), by *E. Cremer* and *M. Pahl*. Walter De Gruyter & Co., Berlin 1961. 1st Ed., XVI, 129 pp., 48 diagrams, 17 tables. Price DM 28.–.

This book originated from a suggestion made by *K. F. Bonhoeffer* and is dedicated to the memory of *M. Bodenstein*, under whose guidance the author completed, in 1927, her doctoral thesis on the hydrogen-chlorine reaction. This thesis discussed mechanisms involving branching chain-reactions and explosions due to branching chain-reactions before the publication of *Semenov*'s fundamental papers. The fact that *Bodenstein* himself did not recognize the full import of the results, was one of the reasons why the implications of *Cremer*'s thesis were not pursued further. In referring to her previous work, Dr. *Cremer* is modest enough not to mention these facts.

She praises *Bodenstein* as the "father of reaction kinetics", a name he deserves as far as gas reactions are concerned. Clear and straightforward experimentation, in which he pioneered, is one of the prerequisites for success in this field, a fact which is unfortunately often forgotten today.

His second achievement was the discovery of the "chain reaction" (a name given to this phenomenon by *Cristiansen* 7 years later). As his third achievement, one may mention his introduction of the concept of the "quasi-stationary state". It is perhaps typical of *Bodenstein*, that the mathematical foundations of his method were wrong (a fact that he himself came to recognize in later years) but that in this case, as in others, he never erred in the application of the mathematical reasoning. This should, perhaps, have been brought out in the presentation of the subject.

The authors deserve praise for including a few ion-molecule reactions at the end of the book. In keeping with the introductory nature of the book, the theoretical discussion of recent developments is avoided. Thus, for example, in the case of unimolecular reactions no mention is made of developments more recent than the work of *Lindemann* and *Hinshelwood*.

The descriptive treatment of reaction mechanisms and a short discussion of the theoretical principles involved are followed by a discussion of a few selected examples. The strength of the book lies in its limited scope which is confined to a discussion of the principles and the results of the experiments. Probably no other book is capable of introducing the reader to practical reaction kinetics in so few pages.

W. Jost [NB 825/8 IE]

The Enzymes, Vols. 4 and 5: Hydrolytic Cleavage (Part A and B), edited by *P. D. Boyer*, *H. Lardy*, and *K. Myrbäck*. Academic Press, Inc., New York-London, 1960/61. 2nd edition, Vol. 4: XX, 631 pages, price: $18.–, Vol. 5: XIX, 645 pages, price: $20.–.

While the first three volumes of the revision of "The Enzymes" deal with the fundamentals of enzyme chemistry, Volumes 4 and 5 discuss certain hydrolytic enzymes, peptide bond cleavage, other C-N bond cleavage, glycoside cleavage, esterases, hydrolysis of ester and amide phosphates, synthesis and cleavage of the C-C bonds, isomerases, hydratases, and dehydratases. The material is arranged according to functions, not by metabolic relationships. For example, enolase, crotonase, and fumarase are found among the hydrolases. Special attention is given to the catalytic mechanisms and the facts associated with these. Methods of preparation and activity measurements are mentioned only in passing since well known, specialized treatises exist for these. On the other hand, information about the protein

structure, the amino acid composition, and the groups responsible for the activity are presented with a completeness not found elsewhere to date. The inductive and metabolic regulation of enzyme formation is also discussed where indicated.

By this arrangement, the properties of enzymes and the relations to the catalytic functions are excellently brought out. However, this arrangement does not do full justice to the importance of enzymes as metabolic catalysts and to their role in the organism.

It was therefore the plan of the editors to devote individual chapters to such enzymes only about which considerable information is available concerning either the properties of the enzyme molecule or the nature of the process catalyzed and to preface the individual groups with survey chapters containing the relationships and generalizations (but describing also less well characterized enzymes). This was done by competent authors who extracted the literature, at least up to 1959 and sometimes even up to 1960 (that is, immediately before going to press), as well as their own unpublished material. They have adapted themselves to the general plan, written comprehensive and complete chapters, and, together with the good editorial staff, have created an extremely useful and modern handbook. Frequently, the existing material does not as yet permit a complete representation of the catalytic process; in these cases, particularly, one finds stimulating discussions and considerations, for example, about the activation and mechanism of various peptidases and glucosidases, or the substrate specificity of cholinesterase. Some survey chapters, such as that about peptidases (*E. L. Smith*), phosphatases (*G. Schmidt* and *M. Laskowski*), phosphorylases (*M. Cohn*) or isomerases (*Y. J. Topper*) are particularly well done.

Frequently, however, the plan demands too much of the authors since unified viewpoints can be brought into the material only by force. Generalized predictions can hardly ever be expected. All in all, the biochemist finds a book which is clearly arranged, critically oriented, penetratingly analyzed and most up-to-date. As always, the publishers have brought out an excellent edition and complemented its usefulness by careful author and subject indexes.

L. Jaenicke [NB 797/1 IE]

Wandlungen in den Grundlagen der Naturwissenschaft (Changes in the Fundamental Concepts of Natural Sciences). Ten Lectures by *W. Heisenberg*. S. Hirzel Co., Stuttgart, 9th edition, 1959, 183 pp. DM 12. . ($ 3.) .

Ten lectures, given before various audiences between the years 1932 and 1958, were combined in this ninth edition of *Heisenberg*'s book. Their main purpose was to present the more important, newer concepts of contemporary physics to a larger circle of laymen. For this reason the mathematical complexities of the discipline have been omitted (only in two lectures is some familiarity with quantum mechanics required for perfect understanding). For the same reasons of simplicity, this collection of lectures deals essentially with a single theme, rather than with a sequence of cumulative concepts. Each lecture is a self-contained unit. Monotony of repetition is avoided by discussing the same basic problem from different points of view. The treatment varies with the premise and purpose of the question asked. Mindful of the fact that one can speak meaningfully about "change" only in the light of an existing historical background, the author devotes several lectures to a description of the historical development of physical concepts. In this discussion, it becomes apparent that from the days of antiquity there has been a clear tendency in physics, astronomy, and chemistry to unify and simplify the understanding of nature by postulating an ordered universe. In such an orderly universe, it is possible to seek the constant and the immutable which underlies the changing multiplicity of natural processes perceived by the senses, and reveal them through mathematical structures depicting reality. The reduction of sensible qualities to the quantities in the atomic theory of *Democritus* represented the first step on the road leading to analytical "explanations" and the first attempt to discover causative relationships between natural phenomena. This analytical view takes the place of the direct cognition, intuitive "understanding" and interpretations of nature. Thus, even the very earliest statements of science were bought at the price of renouncing the evidence of the senses and the direct experience of nature. Later, this seriously disturbed *Goethe*, whose oft-cited disagreement with *Newton* is critically discussed by the author.

Nevertheless, modern science continues to pursue this self-defeating course. Instead of "explaining" it modestly aims at "describing" nature. While strictly abstaining from any judgment on the "why's" of natural phenomena, science aims exclusively at the "how" of the event. Since an event is defined solely in terms of mathematical functions, the concept of "description" acquires, as a consequence, a meaning considerably different from the original connotation.

But these generalized intellectual constructions, made up as they are of mere hypotheses, are so far from giving a true picture of nature, that each individual event requires further verification. Furthermore, no single experiment can ever quite exactly conform to the predictions of these ideal limiting laws.

The youngest phase of physics emerges as a continuation, in purpose and method, of this centuries-old scientific thinking. Results of quantum mechanics thus appear as the logical consequence of the chain of thought begun by *Democritus* in deriving perceptible qualities from mathematical calculations. Carrying this reasoning to its logical extreme (whereby a particle of mass is ultimately reduced to a differential equation) leads to a situation where all imagery is *ipso facto* erroneous. In the strictest sense, atoms are, therefore, no longer regarded as real corporal structures.

That notwithstanding all the continuity of methodological progress we are dealing here with a profound change is illustrated by the changing concepts of matter, space and causality. The change affects not only individual ideas and results, but also the very "foundations" of physical science. This becomes most apparent when modern atomic physicists abandon the view, held by their predecessors, that the observation of natural phenomena can be independent of the preconceptions of the investigator. In fact, every observation made in the microphysical realm is inevitably accompanied by a disturbance of the observation, leading physicists to reject the classical demand for objectivity, and thereby forcing upon them a new scientific philosophy.

The author shows careful restraint in dealing with philosophical problems and his statements do not go beyond the present state of science. The problems are not ignored, but are displayed intact in their entire theoretical form and import. This will be particularly appreciated by the reader whose interests involve more than the quest for purely factual information.

E. Stroeker [NB 826/9 IE]

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The Mechanism of Bimolecular β-Elimination Reactions [*]

BY PROF. DR. J. F. BUNNETT

INSTITUT FÜR ORGANISCHE CHEMIE DER UNIVERSITÄT MÜNCHEN (GERMANY) AND DEPARTMENT OF CHEMISTRY, BROWN UNIVERSITY, PROVIDENCE, RHODE ISLAND (U.S.A.)

In bimolecular β-elimination (E 2 mechanism), several bonds are ruptured or formed in one concerted reaction step. However, the various aspects of bond-making or -breaking need not be completely synchronous. In the E 2 transition state for elimination of HX, rupture of the C-X bond may be more advanced than that of the C-H linkage, or vice versa. Factors influencing the relative extents of rupture of these two bonds at the transition state are discussed, and the consequences of non-synchroneity in one sense or the other are developed from theory and illustrated from experiment. This treatment provides an understanding of the Hofmann-vs.-Saytzeff orientation problem.

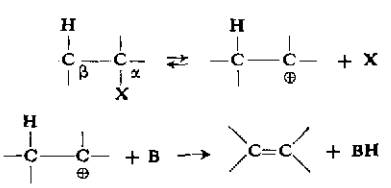
Introduction

β-Eliminations are reactions in which two atoms or groups situated on adjacent carbon atoms are split off with formation of a new multiple linkage. In the most familiar cases, with which this article is concerned, H and some other atom or group X are removed from vicinal saturated carbon atoms to form olefins. The "leaving group" X may be, for example, a halogen atom or a sulfonoxy (RSO_2O-), sulfonio (R_2S^+-) or ammonio (R_3N^+-) group.

Owing chiefly to the perspicacity of *Hughes* and *Ingold* [1–3] three principal mechanisms of β-elimination of HX have been recognized:

The E 1 Mechanism

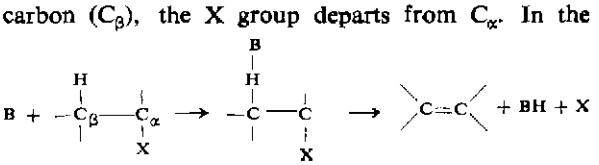
The C–H and C–X bonds are broken in separate steps. First heterolysis of the C–X linkage occurs, forming a carbonium ion intermediate, which then loses a β-hydrogen to a solvent molecule or other base [**]:



The carbonium intermediate may in part recapture X, regenerating the substrate, or it may proceed entirely to products. This is controlled by the relative rates of X recapture and proton loss.

The E 2 Mechanism

The C–H and C–X bonds are ruptured in the same single step. As the base removes a proton from the β-carbon (C_β), the X group departs from C_α. In the transition state



[*] Based on lectures presented in February–July, 1961, at University College, London, University College, Dublin, the University of Bologna and the University of Munich.

[1] *E. D. Hughes* and *C. K. Ingold*, Trans. Faraday Soc. *37*, 657 (1941).

[2] *M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw*, and *L. I. Woolf*, J. chem. Soc. (London) 2093 (1948).

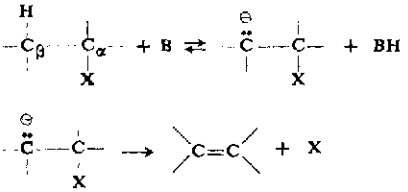
[3] *C. K. Ingold*; Structure and Mechanism in Organic Chemistry, Cornell University Press, Ithaca, N.Y., 1953, Chapter VIII.

[**] Charge designations are intentionally omitted from X and B, in the interest of generality of notation. Thus the byproduct X of the first step will be an anion or a neutral molecule according as X in the original substrate is neutral (*e.g.* halogen in an alkyl halide) or positive (the R_3N^+-group in a quaternary ammonium salt). The base B may be an anion or a neutral molecule.

transition state, the C–H and C–X bonds are both partially broken, and the new C–C bond is partially formed.

The E 1 cb or Carbanion Mechanism

First the base removes hydrogen from C_β, forming a carbanion intermediate. In a subsequent step, X departs from C_α.



The three mechanisms differ in the temporal sequence of the C–X and C–H bond rupture. They represent, respectively, C–X breaking before, during or after C–H breaking.

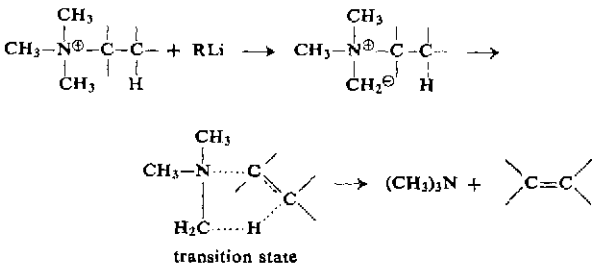
The E 1 and E 2 mechanisms were recognized, not only in principle but also from experimental evidence for particular reactions, over a quarter of a century ago [4,5]. Criteria for distinguishing them and factors determining the incidence of each have been discussed by *Ingold* [3]. The carbanion mechanism [6], however, remained in the realm of speculation. Only recently was it convincingly identified for an olefin-forming elimination [7]. As might have been expected, the case is one in which the leaving group (X) is poor (*i.e.* slow to depart) and there is good stabilization of the β-carbanion. In the reaction of methanolic $NaOCH_3$ with $CDCl_2CF_3$, hydrogen isotope exchange is much faster than methoxide consumption. The latter represents an elimination reaction forming $CCl_2{=}CF_2$, which is transformed into other products under the reaction conditions. These observations indicate initial deuteron removal to form $CF_3CCl_2^\ominus$, which captures a proton to form $CHCl_2CF_3$ far more often than it loses fluoride ion to form the olefin.

Reactions which, judging from reactant and product structures appear to be β-eliminations may in fact be initiated by proton removal from an α-carbon. In α-elimination, X departs from C_α after or during removal of H from the same carbon, and a carbene is generated [8–10]. Migration of hydrogen from C_β to C_α can then form an olefin. The carbene may simultaneously follow other reaction paths, giving rise to a mixture of products.

$$CH_3CH_2CH_2CH_2Cl + C_6H_5Na \rightarrow \underset{\text{n-propylcarbene}}{CH_3CH_2CH_2CH} \rightarrow$$

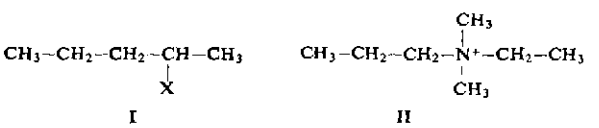
$$CH_3CH_2CH{=}CH_2 + CH_3{-}\langle\!\rangle$$

In α',β-elimination from quaternary ammonium or tertiary sulfonium salts, hydrogen is first removed from one α-carbon. The resulting α-carbanion (ylide) then reaches across to abstract a β-hydrogen from another branch, presumably with concerted rupture of the C-N or C-S bond [11–14]. Efforts to detect this mechanism in reactions of onium salts with hydroxide or alkoxide ions in hydroxylic solvents have been unsuccessful [12, 14, 14a].



Orientation in E 2 Reactions

An unsymmetrical substrate, such as I or II, may in principle progress to two (or rarely more) olefins. Thus I may give 1- or 2-pentene, and II ethylene or propylene.



In some reactions, elimination occurs preferentially towards that β-carbon which carries the fewer β-alkyl substituents, and therefore the more β-hydrogen atoms. Such are said to obey the *Hofmann* rule [15]. In others, which follow the *Saytzeff* rule [16], double bond formation at the more alkylated β-carbon, which carries the fewer β-hydrogens, is favored. The story of how these rules came to be formulated, and of how their apparent contradiction was recognised, and of their respective zones of authority, has been related in detail by *Ingold* [3]. In general, the *Hofmann* rule governs E 2 reactions in which X is an ammonio, sulfonio or sulfonyl group, while the *Saytzeff* rule prevails in E 2 reactions of alkyl halides and alkyl sulfonate esters as well as in all E 1 reactions.

Two subsidiary questions of definition arise. The *Hofmann* rule is sometimes stated as favoring formation of the least-alkylated ethylene. This is equivalent to the definition given above insofar as it refers to the effects of β-alkyl substituents. However, it breaks down even in the simplest cases when the effects of α-alkyl groups are at issue. Thus pyrolyses of

[4] *W. Hanhart* and *C. K. Ingold*, J. chem. Soc. (London) 997 (1927).

[5] *E. D. Hughes*, J. Amer. chem. Soc. *57*, 708 (1935).

[6] *S. J. Cristol*, J. Amer. chem. Soc. *69*, 338 (1947).

[7] *J. Hine, R. Wiesboeck*, and *O. B. Ramsay*, J. Amer. chem. Soc. *83*, 1222 (1961).

[8] *D. G. Hill, W. A. Judge, P. S. Skell, S. W. Kantor*, and *C. R. Hauser*, J. Amer. chem. Soc. *74*, 5599 (1952).

[9] *L. Friedman* and *J. G. Berger*, J. Amer. chem. Soc. *83*, 492 (1961).

[10] *V. Franzen, H.-J. Schmidt*, and *C. Mertz*, Chem. Ber. *94*, 2942 (1961).

[11] *G. Wittig* and *T. F. Burger*, Liebigs Ann. Chem. *632*, 85 (1960).

[12] *F. Weygand, H. Daniel*, and *H. Simon*, personal communication.

[13] *V. Franzen* and *C. Mertz*, Chem. Ber. *93*, 2819 (1960); *V. Franzen* and *H.-J. Schmidt*, ibid. *94*, 2937 (1961).

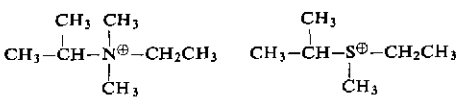
[14] *A. C. Cope, N. A. LeBel, P. T. Moore*, and *W. R. Moore*, J. Amer. chem. Soc. *83*, 3861 (1961).

[14a] *G. Ayrey, E. Buncel*, and *A. N. Bourns*, Proc. chem. Soc. (London) 458 (1961).

[15] *A. W. Hofmann*, Liebigs Ann. Chem. *78*, 253 (1851); *79*, 11 (1851).

[16] *A. Saytzeff*, Liebigs Ann. Chem. *179*, 296 (1875).

ethylisopropyldimethylammonium and ethylisopropylmethylsulfonium hydroxides afford principally propylene [17].



The labels "*Hofmann*" and "*Saytzeff*" are therefore reserved to describe the effects of β-substituents, α-substituents being held constant.

The second question is how, or whether, these labels should be applied with respect to the influence of a β-substituent other than an alkyl group (*e.g.* phenyl or halogen). One possibility is that they be used to describe the polar, steric or other factors responsible for the orientation obtained; thus, an elimination would be designated as a "*Hofmann*" if the dominant factors were those which in ordinary cases repel the new double bond from a β-alkyl group. In this article, a less ambiguous, phenomenological definition is used: an elimination is considered to obey the *Hofmann* rule when the new double bond is repelled from a β-substituent, and the *Saytzeff* rule when it is drawn towards a β-substituent, regardless of what the β-substituent is or what factors are responsible.

The *Saytzeff* rule is generally interpreted as a consequence of conjugative or hyperconjugative interaction of unsaturated β-substituents or β-alkyl groups with the double bond developing in the E 2 transition state (or in the transition state at the second step of the E 1 mechanism).

Hughes and *Ingold* have attributed *Hofmann*-rule behavior to the strong inductive effect of 'onium leaving groups, which increases the acidity of β-hydrogens so much that this becomes the controlling factor: the more acidic β-hydrogen is preferentially eliminated. Since, owing to their electron-releasing inductive effect, β-alkyl groups reduce the acidity of β-hydrogens, formation of the least-substituted ethylene is favored. *H. C. Brown*, on the other hand, has averred that the *Hofmann* rule represents steric control of orientation [18, 19]. Observing that leaving groups which bring the *Hofmann* rule into operation are all quite bulky, *Brown* reasoned that they caused such crowding in the transition state as to oblige elimination to occur into the less substituted branch. The disagreement between the *Hughes-Ingold* and *Brown* views is perhaps the most spectacular problem in the field of elimination reactions today.

Although *Ingold* foresaw in 1927 the possibility that C–X and C–H breaking might not be fully synchronous [4], these two aspects of an E 2 reaction were for many years treated as though they had made about equal progress at the transition state. In 1956, *Cram*, *Greene*, and *DePuy* [20] published experiments which called for the modified view that the transition states of diverse bimolecular eliminations may differ in detail of geometry, and therefore in the relative extents of C–H breaking, C–X breaking, and C=C formation. Subsequently a number of other authors have, on experimental grounds, embraced the view that the E 2 mechanism, though concerted, need not be entirely synchronous [17, 21–29].

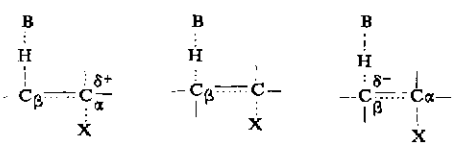
It is the purpose of this paper to take the ideas of these several authors, each of whom has dealt experimentally with a part of the whole problem, and to combine them into a full and consistent theory. The full theory has perhaps not been visualized before in its entirety. It provides not only an understanding of the experimental findings from which it sprung, but also of several others including the *Hofmann* and *Saytzeff* rules.

Our procedure shall be to construct a model, starting with a basic premise and elements of well-accepted theory, then to deduce how this model should respond to certain changes in reaction conditions, and finally to see how it operates when applied to specific experimental data. Although experimental evidence will not be mentioned in developing this model, it is admitted that important parts of it were fashioned to meet the challenge of empirical fact.

A Model of the E 2 Mechanism

The basic premise is that bimolecular β-eliminations on the whole differ in the relative extents of C–X and C–H bond rupture at the transition state. At one extreme, which approaches the transition state for the first step in E 1 reactions, C–X breaking is far advanced while the C–H bond is but slightly disturbed. There is only a small degree of double bond character, and the α-carbon carries a great deal of positive charge. The base (B) is stoichiometrically present, but has acquired the β-hydrogen only to a small extent. This "nearly E 1" transition state is symbolized by structure III.

At the other extreme, represented by structure V, the base has nearly severed the C–H bond while the C–X bond is almost intact. The incipient double bond is but slightly formed, and the β-carbon carries considerable



III IV V

[17] *D. V. Banthorpe, E. D. Hughes*, and *C. Ingold*, J. chem. Soc. (London) 4054 (1960).

[18] *H. C. Brown* and *I. Moritani*, J. Amer. chem. Soc. *78*, 2203 (1956).

[19] *H. C. Brown*, J. chem. Soc. (London) 1248 (1956).

[20] *D. J. Cram, F. D. Greene*, and *C. H. DePuy*, J. Amer. chem. Soc. *78*, 790 (1956).

[21] *D. J. Cram* in *M. S. Newman:* Steric Effects in Organic Chemistry. John Wiley and Sons, New York 1956, Chapter 6.

[22] *J. Weinstock, R. G. Pearson*, and *F. G. Bordwell*, J. Amer. chem. Soc. *78*, 3473 (1956).

[23] *W. H. Saunders*, Jr. and *R. A. Williams*, J. Amer. chem. Soc. *79*, 3712 (1957).

[24] *V. J. Shiner*, Jr. and *M. L. Smith*, J. Amer. chem. Soc. *80* 4095 (1958).

[25] *W. H. Saunders*, Jr. and *D. H. Edison*, J. Amer. chem. Soc. *82*, 138 (1960).

[26] *S. J. Cristol* and *R. S. Bly*, Jr., J. Amer. chem. Soc. *82*, 142 (1960).

[27] *C. H. DePuy* and *C. A. Bishop*, J. Amer. chem. Soc. *82*, 2532, 2535 (1960).

[28] *E. D. Hughes* and *J. C. Maynard*, J. chem. Soc. (London) 4087 (1960).

[29] *E. D. Hughes* and *J. Wilby*, J. chem. Soc. (London) 4094 (1960).

negative charge. This extreme approaches in bonding character the transition state for the first step of the carbanion mechanism.

(The heavy dashed lines stand for bonds largely intact, and the faint dotted lines for bonds almost broken.)

Between these extremes, a gradual change through an infinite number of intermediate possibilities can be visualized. At the central position, C–X and C–H rupture have made equal progress. A large degree of C=C double bond character is possible. Structure IV symbolizes a "central" transition state.

In principle, a diversity of "central" transition states is also conceivable. Even when the fractional degress of C-X and C-H breaking are equal, the fraction may vary from nearly zero to nearly one. Thus if C-X and C-H are only one-quarter broken in the transition state, the double bond can be no more than one-quarter formed. But if they are three-quarters broken, as much as three-quarters C=C character is possible. Moreover, the degree of C=C formation need not equal the degree of C-X (and C-H) rupture; if the latter is three-quarters, the former may be only one-quarter, with C_α and C_β carrying half a positive and half a negative charge, respectively. For present purposes, we shall assume that such variations in the "central" type of transition state are of secondary consequence and may be neglected in first-approximation discussions.

Factors Affecting the Quality of the Transition State

Let us now consider how various changes in the structure of the substrate or in the conditions of the reaction may affect the quality of the transition state.

1. *Introduction of an α-aryl substituent.* Since such substituents stabilize carbonium ions, they will shift the mechanism towards the "nearly E 1" (III) extreme when the transition state lies to the "left" side of center. The stabilizing effect of conjugation with the more highly developed double bond in a "central" transition state should tend to shift all mechanisms towards the center, but this influence is presumably outweighed by the carbonium ion stabilization for reactions left of center. Overall, a uniform "left" shift towards the "nearly E 1" extreme is predicted.

2. *Introduction of an α-alkyl substituent.* These also stabilize carbonium ions and interact favorably with olefinic bonds, so a uniform shift to the left is again forecast.

3. *Change to a better leaving group* will allow C–X rupture to take a more advanced position, and therefore cause a shift towards the "nearly E 1" extreme.

4. *Change to a leaving group of greater electron-attracting character.* Inductive electron-attraction by X will oppose α-carbonium but favor β-carbanion character. A shift towards the "right" or "nearly carbanion" extreme should result.

5. *Introduction of a β-aryl substituent.* Such groups should stabilize β-carbanion character, and therefore cause a shift towards the "nearly carbanion" extreme when the transition state is right of center. Conjugation with the developing double bond should cause a shift towards the center from either side, but this is presumably overpowered by the effect of β-carbanion stabilization for reactions on the "right" side. Overall, a uniform shift to the right is predicted.

6. *Introduction of a β-alkyl substituent.* For reactions with C–H breaking in the lead, both an adverse effect on β-carbanion character and benign interaction with the developing olefinic bond should cause a shift towards the center (*e.g.* left). For reactions with C–X severance in the lead, a special kind of inductive stabilization of the α-carbonium center, discussed below, appears to overcome interaction with the developing olefinic linkage so as to cause a net displacement towards the "nearly E 1" extreme. In all cases, β-alkyl groups should cause a "left" shift.

7. *Introduction of an electron-attracting β-substituent* should stabilize β-carbanion character, oppose α-carbonium character, and therefore cause a universal shift towards the "nearly carbanion" extreme.

8. *Change to a more polar solvent* should, in the common case where B is initially negative and X initially neutral, move the mechanism towards the "nearly E 1" extreme. Poorer solvation of X makes it loath to depart as an anion, and poorer solvation of B makes it a more aggressive reagent [30]. Also, transition states left of center are characterized by increasing degrees of charge separation.

9. *Change to a stronger base.* No prediction is ventured because of uncertainty as to what measure of base strength to heed and as to whether a stronger base would call for a transition state with increased or decreased C–H rupture. RS^- ions are known to be kinetically stronger bases than RO^- in effecting bimolecular elimination, though of course they are weaker bases thermodynamically [31,32 and Table 2].

Chart 1 summarizes the foregoing conclusions as to how diverse influences should affect the quality of the transition state.

Chart 1. Influences of diverse factors on the quality of the E2 transition state

Factor	Transition state "Nearly E1"	"Central"	"Nearly carbanion"
1. α-Aryl group	←	←	←
2. α-Alkyl group	←	←	←
3. Better leaving group	←	←	←
4. Leaving group more electron-attracting	→	→	→
5. β-Aryl group	→	→	→
6. β-Alkyl group	←	←	→
7. Electron-attracting β-substituent	→	→	→
8. Better solvent for ions (X initially neutral, B negative)	←	←	←
9. Stronger base	?	?	?

[30] *S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens,* and *J. S. Gall,* Tetrahedron Letters No. 9, 24 (1960).

[31] *P. B. D. de la Mare* and *C. A. Vernon,* J. chem. Soc. (London) 41 (1956).

[32] *E. L. Eliel* and *R. S. Ro,* J. Amer. chem. Soc. *79,* 5995 (1957).

Consequences (Criteria) of the Quality of the Transition State

Certain kinetic consequences of changing transition state character can be forecast. These may appear in the form of rate coefficients or, in favorable cases, as the relative yields of two or more products formed competitively. Some of these consequences, *viz.* those in which one has the most theoretical confidence, can alternatively be regarded as criteria of mechanism.

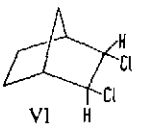
A) *X isotope effects.* When two or more isotopes are represented in the first atom of the leaving group, lighter X groups should be eliminated faster [33]. The isotope effect should be greater the more the C–X bond is broken in the transition state, *i.e.* strong for reactions near the "nearly E 1" extreme, weak for those near the other extreme.

B) *H isotope effects.* Modern theory [34] calls for the isotope effect (k_H/k_D) for a proton transfer reaction, A–H + B → A + H–B, to be maximum when the proton is half transferred at the transition state. If at that point on the reaction coordinate H is more tightly bonded to A than to B, or more to B than to A, the isotope effect should be lower.

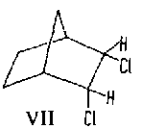
One does not know to what extent the C–H bond is ruptured in the transition state of a fully synchronous E 2 reaction. Certainly there is no requirement that the hydrogen be equally held by carbon and the base. It is probable, however, that transition states near the extremes will have hydrogen more tightly bonded to carbon (at the left) or to the base (at the right), with resultant lower hydrogen isotope effects than for reactions of more central character.

C) *The stereoelectronic preference for trans-elimination.* It is known [21] that *trans*-elimination of H and X is favored over *cis*-elimination, and that the best geometry for the E 2 transition state is anti-coplanar (the H–C, C–C, and C–X bonds all in one plane, and arranged as shown in Structure IV). However such an arrangement is not absolutely essential; instances of *cis*-elimination are known, as are eliminations from rigid substrates in which attainment of anti-coplanar geometry is impossible.

trans-2,3-Dichloronorbornane (VI) loses HCl under the influence of sodium 1-pentoxide eight times faster than does its isomer, *endo-cis*-2,3-dichloronorbornane (VII), *i.e. cis*-elimination is faster: *Cristol* [6,35–37] advocated the carbanion mechanism for these and related reactions, although he has acknowledged that convincing evidence for this view is lacking. Nor is there evidence requiring the E2 mechanism [38].



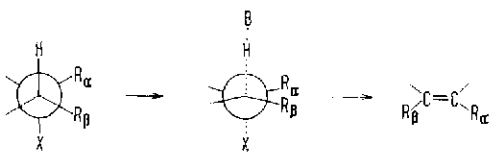
VI



VII

It is not well understood from theory why this geometry is so good. Presumably there is a favored pathway for a synchronous electronic shift whereby the electrons released from the C–H bond can enter the octet of C_α on the back side with respect to the departing X group [2]. If so, the "requirement" for an anti-coplanar conformation should be less stringent, the less synchronous the mechanism. If release of X by C_α is nearly independent of the compensating supply of electrons from the C–H bond (the "nearly E 1" extreme), or if the electrons of the C–H bond accumulate on C_β with only meagre relay to C_α in the transition state (the "nearly carbanion" extreme), it should make less difference whether the stereoelectronic pathway is optimum or not.

D) *Eclipsing effects* [20]. As a saturated system passes into the β-elimination transition state, substituents on C_α and C_β destined to be *cis* in the eventual olefin are brought closer together. The degree of eclipse in the



transition state will be greater, the greater the C=C double bond character of the transition state, *i.e.* greater for "central" mechanisms than for those at either extreme.

The approach of R_α to R_β may affect transition state free energy and therefore elimination rate. Crowding of one group against the other should be an adverse effect; it may, however, tilt an unsaturated R group out of the plane of the developing double bond, disrupting mesomeric interaction and ultimately causing either an increase or decrease in the activation energy. Conceivably, if R_α and R_β are groups of high polarizability, *London* forces might actually reduce transition state free energy as the groups approach more closely [39].

These effects will not materialize when R_α and R_β are destined for a *trans*-relationship. Therefore eclipsing effects can be assessed in favorable cases from the relative rates of elimination of *threo* and *erythro* diastereomers [20], or from the proportions of *cis* and *trans* olefins formed from a substrate with two β-hydrogens.

E) *Effects of β-substituents on reaction rate, or on the proportions of elimination into the branches of an unsymmetrical substrate.* This section deals with the question of whether a *Hofmann* or *Saytzeff* product will predominate. The conclusions drawn are sketched in Fig. 1. Note that *Hofmann* territory is below the null line, *Saytzeff* above.

(i) β-Aryl groups. For transition states near the "nearly carbanion" extreme, β-aryl groups should help

[33] *W. H. Saunders*, Jr., in *S. L. Friess, E. S. Lewis* and *A. Weissberger:* Investigation of Rates and Mechanisms of Reactions. 2nd ed., Interscience Publishers, New York 1961, Part I, Chapter IX.

[34] *F. H. Westheimer*, Chem. Reviews *61*, 265 (1961).

[35] *S. J. Cristol* and *E. F. Hoegger*, J. Amer. chem. Soc. *79*, 3438 (1957).

[36] *S. J. Cristol* and *R. P. Arganbright*, J. Amer. chem. Soc. *79*, 3441 (1957).

[37] *S. J. Cristol* and *N. L. Hause*, J. Amer. chem. Soc. *74*, 2193 (1952).

[38] Cf. *D. J. Cram, D. A. Scott*, and *W. D. Nielsen*, J. Amer. chem. Soc. *83*, 3706 (1961).

[39] *K. S. Pitzer:* Quantum Chemistry, Prentice-Hall, New York 1953, p. 198.

to stabilize the β-negative charge and thereby accelerate elimination. For "central" reactions, conjugation with the incipient double bond should again be a beneficial influence, but whether more or less so than the foregoing factor of β-carbanion stabilization is hard to say. For reactions near the "nearly E 1" extreme, conjugation with the forming double bond should be a weak promoting influence, more or less offset by inductive interaction with the (remote) α-carbonium center. Overall, strong acceleration is forecast for "central" and "right-of-center" reactions, and weak acceleration or even weak retardation for reactions near the "nearly E 1" extreme. This is symbolized by the dashed line in Fig. 1.

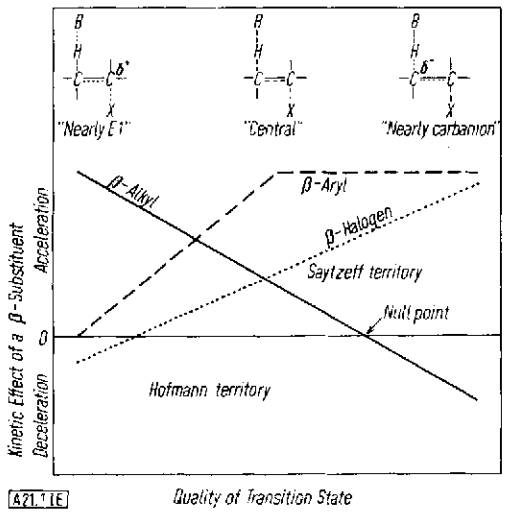
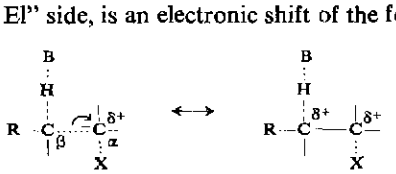


Fig. 1. Kinetic Effects of β-Substituents as a Function of the Quality of the Transition State

(ii) β-Halogen atoms. Because of a strong stabilizing influence on a β-negative charge, weak mesomerism with the developing double bond and an unfavorable effect on α-carbonium ion character, one predicts strong acceleration of reactions at the far right, slight acceleration of "central" reactions and retardation of "nearly E 1" reactions. This is depicted by the dotted line in Fig. 1.

(iii) β-Alkyl groups. For reactions near the "nearly carbanion" extreme, deceleration owing to inductive effect on β-negative charge is expected. For fully synchronous reactions, the stabilizing effect of alkyl groups on the adjacent ethylenic linkage should cause an increase in rate. At the far left, the same effect should operate but to a smaller extent.

Another factor, important for reactions on the "nearly El" side, is an electronic shift of the following sort:



The small fraction of an electron pair available for the developing π-bond is relinquished to the α-carbonium center, where it enters the orbital of the C–X bond. Concomitantly, C_β acquires some carbonium character. By stabilizing the β-positive charge, β-alkyl groups facilitate the π-bond electron shift.

A priori, one cannot predict whether this effect would be greater or less as the "nearly El" extreme is approached. The lesser degree of π-bond formation might be more or less important than the greater C_α carbonium character in determining the magnitude of this shift. The fact that *Saytzeff* control by β-alkyl groups is most pronounced in true E 1 reactions [2] indicates that the degree of carbonium character is the dominant consideration.

The predicted effects of β-alkyl groups on the various transition states are represented by the unbroken line in Fig. 1. The "null point" about midway along the right-of-center region should be noted. This is the boundary between *Saytzeff* and *Hofmann* territories. Another null point occurs left-of-center in respect to β-halogen substituents.

Specific Reactions with Respect to the Scheme

Eliminations from β-Phenylethyl Halides and Similar Compounds

Data for a number of reactions, concerning dependence of measurable kinetic effects on the leaving group, are given in Table 1. If the overall reaction rate is taken as a measure of "leaving" tendency, the higher X groups in this table are the better leaving groups.

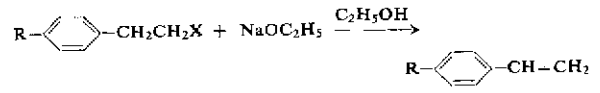
With respect to the effect of *para*-substituents, all of these reaction series have positive *Hammett* ρ values [41], *i.e.* they are all accelerated by electron-attracting *para*-substituents, an outcome to be expected if all the transition states bear some negative charge on the β-carbon atom (the atom next the ring). These reactions are therefore thought to have transition states on the "nearly carbanion" side, with C–H rupture in advance of C–X breaking. If so (factor 3, above), change to poorer leaving groups should shift the mechanism farther to the right, to transition states of increasingly pronounced β-carbanion character, with resultant greater dependence on the electron-attracting capacity of *para*-substituents. The predicted steady increase in ρ matches the experimental fact (Table 1).

Moreover (consequence B, above), it is expected that beyond some point of half-transfer of β-hydrogen from C_β to base, change to poorer leaving groups should cause a steady decrease in hydrogen isotope effect. The isotope effect (k_H/k_D = 7.1) for X = Br is about the maximum predicted by the *Bigeleisen* theory, and suggests that hydrogen is half transferred in the transition state of this reaction. The rest of the measured isotope effects (Table 1) fall in the predicted sequence. If the transition state for elimination from the sulfonium salt (X = SMe_2^+) is correctly judged to lie rather far towards the "nearly carbanion" extreme, the sulfur isotope effect (k_{S-32}/k_{S-34}) should be quite small (con-

[40] *C. H. DePuy* and *D. H. Froemsdorf*, J. Amer. chem. Soc. *79*, 3710 (1957).

[41] *L. P. Hammett:* Physical Organic Chemistry. McGraw-Hill Book Co., New York 1940, p. 186.

Table 1. Dependence of kinetic effects on the leaving group [23,25,27,40]



X	Relative rate (R = H)	*Hammett* ρ	k_H/k_D [a]
I	26600	+ 2.07	
Br	4100	+ 2.14	7.1
OTs [b]	392	+ 2.27	5.7
Cl	68	+ 2.61	
SMe_2^+	7.7 [c]	+ 2.75	5.1
F	1	+ 3.12	
NMe_3^+		+ 3.77 [d]	3.0 [e]

[a] Ratio of rates at 30 °C, when R = H, of the ordinary compound to the derivative with two β-deuteriums (α to the ring).

[b] *p*-Toluenesulfonoxy group.

[c] The measnred relative rate of 37900 has been corrected for a 4900-fold exaltation due to unusually high entropy of activation originating from its unusual charge character.

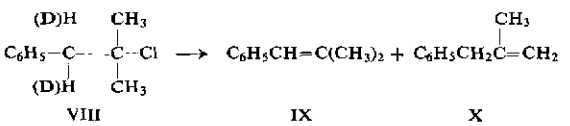
[d] *W. H. Saunders, Jr.* and *D. G. Bushman*, unpublished work.

[e] 50 °C.

sequence A, above). It is in fact small, only 1.0015 compared to *ca.* 1.018 for the S_N1 decomposition of t-butyldimethylsulfonium ion in water [42]. The latter reaction should, from the theory of S_N1 reactions, have a nearly maximum sulfur isotope effect, and indeed the measured effect is close to the maximum calculated from theory.

Elimination from Benzyldimethylcarbinyl Chloride (VIII)

In methanol with either CH_3O^- or $C_2H_5S^-$ as the base, this substrate gives two olefins, IX and X [43]. Dissected bimolecular rate coefficients for the partial



VIII IX X

reactions leading to the two olefins are displayed in Table 2. It is noteworthy that the mercaptide ion is the more effective reagent by a wide margin [31,32].

Table 2. Elimination from benzyldimethylcarbinyl chloride (VIII) [43]

	$NaOCH_3$	$NaSC_2H_5$
k_{IX} [a]	1.52	9.85
k_{IX}(D cpd.) [a]	0.58	4.14
k_X [a]	0.38	4.35
$k_{IX(H)}/k_{IX(D)}$	2.6	2.4
$6\,k_{IX}/2\,k_X$	12.0	6.7

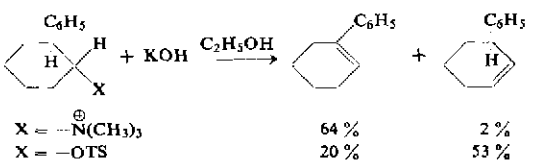
[a] Units of $l \times mole^{-1}\ sec.^{-1} \times 10^{-4}$; temperature 76 °C; solvent: methanol

The decrease in rate caused by introduction of two β-deuterium atoms is about 2.5-fold, with either reagent. This isotope effect is much less than those noted in Table 1, and only a small part of the decrease can be ascribed to the difference in temperature (76 °C *vs.* 30 °C). From consequence (criterion) B above, this indicates an off-center mechanism. Since there are two α-methyl substituents (factor 2), the mechanism is judged to lean towards the "nearly E 1" extreme.

The ratio $6\,k_{IX}/2\,k_X$ represents the acceleration caused by introduction of a β-phenyl substituent, statistically adjusted for the differing numbers of β-hydrogen atoms in the benzyl *vs.* methyl branches. The acceleration observed in these experiments, 6.7- or 12-fold, is much less than the 526-fold (statistically adjusted) enhancement of elimination rate on insertion of a β-phenyl group into ethyl bromide [44]. That only a small acceleration should be observed in a reaction with a left-of-center mechanism is expected [effect (i), above]. These observations of small hydrogen isotope and small β-substituent effects combine, then, to place eliminations from VIII on the left side of the E 2 spectrum, where C–X breaking is more advanced than C–H rupture.

The β-phenyl substituent effect is less definitive than the hydrogen isotope effect. The former certainly arises in part from steric interference of β-phenyl with α-methyl in the transition state leading to IX. Besides the adverse effect of simple crowding, this could tilt the phenyl group out of the plane of the developing double bond, interfering with conjugative stabilization. However, neither steric influence should come significantly into play if the new double bond is but slightly formed, as the hydrogen isotope effects suggest.

Elimination from trans-2-Phenylcyclohexyl Tosylates, etc.



$X = -\overset{\oplus}{N}(CH_3)_3$	64 %	2 %
X = –OTS	20 %	53 %

The reaction of *trans*-2-phenylcyclohexyltrimethylammonium ion with KOH in ethanol gives predominantly 1-phenylcyclohexene, a product of *cis*-elimination [45]. It has been shown that the alternative product, 3-phenylcyclohexene, is not isomerized under the conditions of the reaction. This substrate, with its poor leaving group (factor 3) and its β-aryl substituent (factor 5), should lie far towards the "nearly carbanion" extreme. Accordingly (consequence C), the stereoelectronic preference for *trans*-elimination should be much lower than usual. The experiment shows that the beneficial effect of a β-aryl group [effect (i)] is sufficient to overcome the stereoelectronic barrier.

Change to the much better tosylate leaving group, however, shifts the mechanism sharply towards the left (factor 3), presumably to a more-or-less "central" position where *trans*-elimination should be much more strongly required. In fact, the principal product is now 3-phenylcyclohexene.

The reaction of *trans*-2-phenylcyclohexyl tosylate with *ca.* 0.2 M ethanolic KOH did not show clear cut second order kinetics [45]; 17 % substitution products (replacement of

[42] *W. H. Saunders*, Jr. and *S. Asperger*, J. Amer. chem. Soc. *79*, 1612 (1957).

[43] *J. F. Bunnett, G. T. Davis*, and *H. Tanida*, J. Amer. chem. Soc., in press.

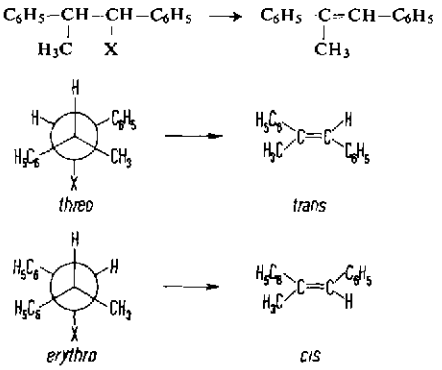
[44] *M. L. Dhar, E. D. Hughes, C. K. Ingold*, and *S. Masterman*, J. chem. Soc. (London) 2055 (1948).

[45] *S. J. Cristol* and *F. R. Stermitz*, J. Amer. chem. Soc. *82*, 4692 (1960); *R. T. Arnold* and *P. N. Richardson*, ibid. *76*, 3649 (1954) *J. Weinstock* and *F. G. Bordwell*, ibid. *77*, 6706 (1955); *A. C. Cope, G. A. Berchtold* and *D. L. Ross*, ibid. *83*, 3859 (1961).

–OTs by –OH or $-OC_2H_5$), characteristic of an S_N1-El solvolysis mechanism, were formed. It is certain, however, that 3-phenylcyclohexene is not formed to any large extent via the El route, since El eliminations obey the *Saytzeff* rule [2,3,43]. Indeed, to the extent that olefins were formed via the El mechanism, the predominance of 3-phenylcyclohexene in the products of E2 elimination is greater than indicated by the figures shown.

Elimination from 1,2-Diphenylpropyl Halides and Related Compounds

There are two asymmetric carbon atoms in the 1–X-1,2-diphenylpropane system. There is only one β-hydrogen with respect to X, and *trans*-eliminations from the *threo* and *erythro* diastereomers give stereoisomeric olefins.



As discussed above, eclipsing interactions betwen α-phenyl and β-methyl (in the *threo* series) or between α-phenyl and β-phenyl (in the *erythro* series) can affect transition-state free energy. Since the phenyl group is larger than methyl, and since the mesomeric effects of both α- and β-phenyl groups assist elimination, eclipsing effects should depress the elimination rate in the *erythro* series more seriously. The rate ratio, $k_{threo}/k_{erythro}$, can then be taken as a measure of the extent to which eclipsing effects come into play, that is to say, as a measure of the "flatness" of the transition state [20].

Selected $k_{threo}/k_{erythro}$ values are shown in Table 3. In view of the α-phenyl group, a strong factor (factor 1 above) for a mechanism leaning towards the "nearly

Table 3. Elimination from isomeric 1-X-1,2-diphenyl propanes [20]

Base	X	$k_{threo}/k_{erythro}$
$C_2H_5O^-$ in C_2H_5OH	Cl	1.1
	$N(CH_3)_3^+$	57
$(CH_3)_3CO^-$ in $(CH_3)_3COH$	Br	5.4
	Cl	15

E 1", and the β-methyl and β-phenyl groups which somewhat offset each other (factors 5 and 6), a mechanism rather far to the "left" might be expected. Eclipsing effects should then be small, as they are when X = Cl ($k_{threo}/k_{erythro}$ = 1.1). Change to such a poor leaving group as trimethylammonio should (factors 3 and 4) displace the mechanism strongly to the "right", conceivably to a near-"central" position where the rate ratio should be high, as it is [57].

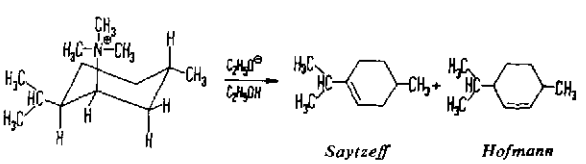
With X = Cl, change to a poorer solvent for ions should shift the mechanism from a "left" to a more "central" position (factor 8), causing $k_{threo}/k_{erythro}$ to increase. It does indeed increase, from 1.1 in ethanol to 15 in t-butyl alcohol. Changing to a better leaving group (factor 3) should shift it back again; the ratio for X = Br in t-butyl alcohol is 5.4.

This discussion is substantially the same as that originally given by *Cram, Greene,* and *DePuy* [20]. A point of difference is that those authors attributed part of the change in mechanism in going from $C_2H_5O^-$ in C_2H_5OH to $(CH_3)_3CO^-$ in $(CH_3)_3COH$ to the change in the base. In the present discussion, the effect of changing the base has been considered unpredictable. It is not meant to infer, however, that it is inconsequential.

A further change in the substrate and conditions is embodied in the work of *Cristol* and *Bly* [26], who studied reactions of *meso*- and (±)-1,2-dichloro-1,2-diphenylethanes with sodium hydroxide in 92.6 % (w/w) ethanol. Replacement of β-CH_3 by β-Cl (factors 6 and 7) should favor a transition state closer to the "nearly carbanion" extreme, but introduction of 7 % water into the solvent should (factor 8) have the opposite influence. The transformation of a fraction of base ions from ethoxide to hydroxide [46] is presumed, as a first approximation, to have little effect on the quality of the transition state. In fact, k_{dl}/k_{meso} (the equivalent of $k_{threo}/k_{erythro}$) was 6.1 (at 53 °C) with β-Cl, compared to 1.1 (for X = Cl, solvent ethanol) with β-CH_3. A more "central" mechanism is indicated, and the change in the β-substituent appears to be the principal cause.

Elimination from 2-Alkylcyclohexyltrimethylammonium Ions

The principal olefin formed from bimolecular reaction of neomenthyl-trimethylammonium ion with hydroxide or ethoxide ion is 3-menthene [29,47], a *Saytzeff* product



XI

from a quaternary ammonium base! Since there are *trans*-hydrogens in both the 2- and 4-positions, the stereoelectronic factor is not responsible for this violation of the *Hofmann* rule.

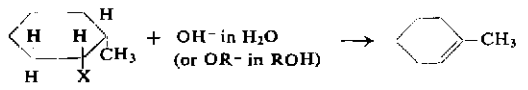
The explanation appears to lie in the considerable steric compression contained in conformation XI for the neomenthyl-trimethylammonium ion. This conformation, with its $-N(CH_3)_3^+$ axial and anti-coplanar with the 2- and 4-hydrogens, is the favored one to undergo elimination. In XI, there is such compression of the trimethylammonio group against the cyclohexane framework as to constitute a considerable driving force for its ejection. This makes $-N(CH_3)_3^+$ a much better

[46] *R. G. Burns* and *B. D. England*, Tetrahedron Letters No. 24, 1 (1960).

[47] *W. Hückel, W. Tappe,* and *G. Legutke*, Liebigs Ann. Chem. *543*, 191 (1940); *N. L. McNiven* and *J. Read*, J. chem. Soc. (London) 153 (1952).

leaving group than usual, pushing the mechanism from its usual location in *Hofmann* territory (owing to factors 3 and 4) across the null point (Fig. 1) into *Saytzeff* territory where a β-alkyl group is beneficial [effect (iii)]. This is essentially the explanation of *Hughes* and *Wilby* [29].

cis-2-Methylcyclohexyltrimethylammonium ion likewise affords a *Saytzeff* product in reactions with aqueous alkali or alcoholic alkoxides [48]. The olefinic product is



$X = -\overset{\oplus}{N}(CH_3)_3$	94–97 %
$X = -OTS$	40–76 %

94–97 % 1-methylcyclohexene. The corresponding tosylate ester, which gives 40–76 % of the same product, is actually less faithful in adherance to the *Saytzeff* rule! The explanation [48], insofar as the quaternary ammonium salt is concerned, is again steric enhancement of the leaving tendency of the trimethylammonio group. The effect is so great that this normally sluggish leaving group surpasses the tosyloxy group. The latter does not experience the same "push" because it occupies less space near the cyclohexane ring.

Elimination from 2-Pentyl Halides

Using vapor phase chromatography, *Saunders*, *Fahrenholtz*, and *Lowe* [49] determined the olefin proportions from elimination induced by $NaOC_2H_5$ in ethanol to be as follows:

$$CH_3CH_2CH_2\underset{\displaystyle X}{\underset{|}{C}}H-CH_3 \xrightarrow[C_2H_5OH]{NaOC_2H_5} CH_3CH_2CH_2-CH=CH_2 + CH_3CH_2CH=CH-CH_3$$

	Hofmann product	*Saytzeff* product
X = Cl	37 %	63 %
Br	25 %	75 %
I	20 %	80 %

Saytzeff control is strongest with the largest leaving group, iodine, contrary to *H. C. Brown*'s hypothesis that a larger X group favors *Hofmann* elimination [18,19]. With respect to the present scheme, these substrates with good leaving groups (factor 3) attached to secondary carbon (factor 2) may be expected to undergo E 2 elimination by mechanisms more or less "central" or perhaps with C–X breaking somewhat in the lead. "Nearly E 1" character should be greatest for the iodide and least for the chloride (factor 3). With reference to effect (iii), reactions farther to the "left" should give a greater proportion of *Saytzeff* products, as observed. *Saunders* et al. [49] observed a parallel trend in reactions of t-amyl chloride and bromide, for which a similar interpretation can be given. Carbonium character at C_α would of course be greater in tertiary halide transition states.

[48] *T. H. Brownlee* and *W. H. Saunders*, Jr., Proc. chem. Soc. (London) 314 (1961).

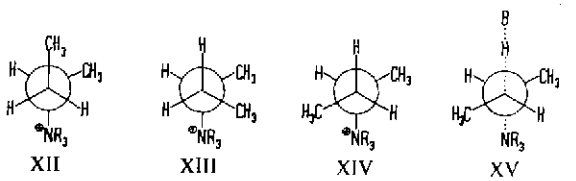
[49] *W. H. Saunders*, Jr., *S. R. Fahrenholtz*, and *J. P. Lowe*, Tetrahedron Letters No. 18, 1 (1960).

In the first stage of this paper, a mechanistic model for bimolecular β-eliminations was constructed, based on the premise that the relative extents of C–H and C–X breaking in the transition state may vary, and elaborated with reference to standard concepts of theory. Several sets of experimental observations were then examined to see how they fit the model, and it was shown that correspondence of experiment with theory is excellent. There are many other data which could also be discussed and which fit equally well, but those which have been treated are sufficient to demonstrate the value of the theory in correlating experimental observations of diverse sorts.

It is well to define the position of this theory with respect to the old problem of *Saytzeff vs. Hofmann* orientation. Whether a β-alkyl group favors or opposes elimination into its branch is considered to depend on the character of the transition state. Only for reactions rather far over on the "nearly carbanion" side, to the right of the nullpoint in Fig. 1, is *Hofmann* elimination held to occur. The kind of transition state a reaction has is governed by a number of factors, of which the most pertinent are the identities of α-substituents, the quality of X as a leaving group, and the inductive effect of X.

The present theory does not grant steric effects a major role in determining *Hofmann* orientation at least in the majority of cases involving substrates and reagents of "normal" size. It is universally acknowledged that steric effects may be decisive when extraordinarily large bases or β-alkyl groups are involved. It is noteworthy that *H. C. Brown*'s only convincing evidence for steric control concerns such outsize reagents.

Let us consider *Brown*'s argument for steric control insofar as it concerns the size of the leaving group, with attention to the example of s-butyltrimethylammonium ion which the leaving group is quite large. Three staggered conformations, representing rotation about the bond between carbons 2 and 3 of the butyl group, are XII, XIII and XIV. XII, which has β-CH_3 *anti* to NMe_3^+, is the most favored. Of those with β-H *anti* to NMe_3^+ (XIII and XIV), a feature necessary in the



XII XIII XIV XV

elimination transition state, XIV is preferred because it avoids methyl-methyl skew interaction. XV represents the elimination transition state related to XIV.

Brown has pointed out that the skew interaction between the β-CH_3 and NMe_3^+ present in XIV persists to some extent in the transition state and will tend to raise its free energy. Since in the transition state (not shown) for elimination into the methyl branch it is possible for β-CH_3 and NMe_3^+ to have the relationship of conformation XII, this steric factor will retard elimination

into the ethyl branch and therefore work for *Hofmann* orientation.

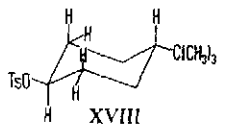
However, this theoretical argument that steric interaction between β-alkyl substituents and the X group will favor elimination into the methyl branch does not establish that it is the main factor responsible for such an elimination. Experimental evidence to the contrary [17] is the fact that XVI undergoes elimination, on treatment with ethanolic sodium ethoxide, 10-fold slower than XVII. In the ground state of XVI, β-CH_3 must always be skew to either NMe_3^+ or t-butyl (groups of equivalent size), whereas in the transition state resembling XV, skew interaction between β-CH_3 and NMe_3^+ is reduced. Thus a small acceleration might have been predicted were steric effects predominant. The fact that introduction of β-methyl retarded elimination by more than the statistical factor of three shows that there is a genuine non-steric factor favoring *Hofmann* elimination from quaternary ammonium salts. The fact that the magnitude of deceleration was nearly the same as on introduction of β-methyl into $CH_3CH_2NMe_3^+$ shows that this non-steric factor is able to account for nearly the whole of the deceleration in a more "normal" case. This matter has been examined at length, both from experiment and from theory, by *Banthorpe*, *Hughes*, and *Ingold* [17].

$CH_3-CH_2-CH-C(CH_3)_3$ (⊕NMe_3) — XVI

$H-CH_2-CH-C(CH_3)_3$ (⊕NMe_3) — XVII

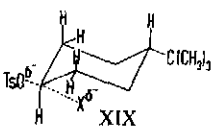
The Merged Mechanism

trans-4-t-Butylcyclohexyl *p*-toluenesulfonate (XVIII), in which the *p*-toluenesulfonate group is almost "frozen"



XVIII

equatorially, undergoes a considerable fraction (25-30%) of elimination in reactions with halide ions in acetone [50]. Because the reagents are such weak bases (in the thermodynamic sense) and because attainment of the preferred anti-coplanar geometry was inconceivable, it was postulated [50] that the halide ions mount a nucleophilic attack upon carbon, forming an intermediate pictured as XIX. This intermediate was visualized to undergo either expulsion of tosylate ion, forming a substitution product, or expulsion of both anions plus



XIX

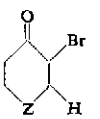
a β-hydrogen, forming an olefin. The tosylate ion was thought most likely to accept the proton. This mechanism was subsequently endorsed by other authors [51–54].

The justification of this mechanism lies basically in the intuitive feeling that straightforward β-elimination should be forbidden both for stereoelectronic reasons and by the weakness of the bases available. In the intervening five years several infractions of the stereoelectronic rule have come to light. Also, it has come to be recognized, at least in principle, that basicity in the kinetic sense may more nearly parallel kinetic nucleophilicity than thermodynamic basicity [55]. Moreover, it is now recognized that halide ions in non-hydroxylic solvents are kinetically much more reactive than in water or in alcohols [30]. All of these developments tend to weaken the intuitive argument.

In the 4-t-butylcyclohexyl X system, the measured superiority in elimination rate of axial-X over equatorial X compounds is 14- to 65-fold. These figures correspond to differences in ΔF^* of 1.8 to 2.5 kcal./mole. Such $\Delta\Delta F^*$ values do indicate a substantial preference for elimination from substrates in which both the H and X fragments to be eliminated are *trans*-axial rather than *trans*-equatorial. The $\Delta\Delta F^*$ values are not incompatible with preparative evidence to the same point [56], especially if it is allowed that changes in the reagent may alter in degree the geometry of the transition state and therefore the sensitivity of the reaction to substrate conformation.

The "merged" mechanism has been advocated for dehydrobromination of α-bromo-ketones effected by

XX



reagents such as amines and bromide ion [57]. Elimination occurs with considerable ease, especially from cyclic ketones of type XX, where $-\overline{Z}-$ is an atom such as sulfur or nitrogen bearing an unshared electron pair [58, 59]. Substitution in which the base-nucleophile displaces bromine occasionally accompanies or supersedes elimination.

Something like the "merged" mechanism is superficially attractive because α-bromo-ketones are quite reactive with nucleophiles at C_α and because the carbonyl substituent should oppose the development of C_α

[50] *S. Winstein, D. Darwish,* and *N. J. Holness,* J. Amer. chem. Soc. *78,* 2915 (1956).

[51] *E. L. Eliel* and *R. S. Ro,* Tetrahedron *2,* 353 (1958).

[52] *E. L. Eliel* and *R. G. Haber,* J. Amer. chem. Soc. *81,* 1249 (1959).

[53] *D. S. Noyce* and *B. N. Bastian,* J. Amer. chem. Soc. *82,* 1246 (1960).

[54] *G. A. Gregorian,* Chimika Chronika *23,* 174 (1958).

[55] *J. F. Bunnett, C. F. Hauser,* and *K. V. Nahabedian,* Proc. chem. Soc. (London) 305 (1961).

[56] *D. H. R. Barton,* J. chem. Soc. (London) 1027 (1953).

[57] *N. H. Cromwell* and coworkers, J. Amer. chem. Soc. 79, 230 (1957); *80,* 901 (1958); *82,* 130, 133, 136 (1960); *83,* 1237, 3812, 3815 (1961).

[58] *F. Krollpfeiffer, H. Schultze, E. Schlumbohm,* and *E. Sommermeyer,* Chem. Ber. *58,* 1654 (1925).

[59] *M. Harfenist,* personal communication.

carbonium character. However, conjugation of the carbonyl group with the developing double bond should, in terms of the E 2 mechanism, provide a strong driving force. This should be especially powerful in elimination from XX because conjugation of $-\overline{Z}-$ with $-CO-$ would be established in the transition state. Moreover, these reactions conform to the *trans*-stereoelectronic pattern characteristic of E 2 reactions [60, 61].

[60] *H. B. Alther* and *T. Reichstein*, Helv. Chim. Acta *26*, 492 (1943); *E. Seebeck* and *T. Reichstein*, ibid. *26*, 536 (1943).

[61] *N. L. Wendler, D. Taub*, and *H. Kuo*, J. Amer. chem. Soc. *82*, 5701 (1960).

In view of the absence of compelling experimental evidence for the "merged" mechanism, it seems best regarded as an interesting speculation.

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Recent Developments in Non-Mercurial Diuretics [*]

BY PROF. DR. E. SCHLITTLER, DR. G. DESTEVENS, AND DR. L. WERNER

RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS INC., SUMMIT, NEW JERSEY (USA)

Mercurial diuretics today are still the drugs of choice when a prompt and full diuretic response is needed. However, most mercurial diuretics are effective only when given parenterally. This factor, plus the toxicity usually associated with organic mercurials, has prompted the search for non-toxic, orally active, non-mercurial diuretic drugs. The most important group of organic compounds found to date which fulfills these conditions is the sulfonamides. Among these, derivatives of chlorothiazide and hydrochlorothiazide are most effective. In the following report these compounds are described in detail. Aldosterone antagonists and blockers of aldosterone excretion play only a minor role.

I. Introduction

The formation of adequate amounts of urine in the kidneys is essential to life. By the excretion of urine, electrolyte balance is maintained and fluid and nitrogenous end products are removed. It is therefore readily understood that the search for diuretics, *i.e.* drugs which promote the formation of urine [1], has long been a goal of medicinal chemistry.

The term diuretic is usually reserved for those drugs which have a major action on the kidney itself when applied clinically. Thus, to understand the action of a diuretic agent, it is best initially to consider briefly renal function.

Each of the two human kidneys contains approximately one million similar secretory units. Such a unit is called a nephron and may be considered representative of the action of the kidney as a whole (see Figure 1). Each of these nephrons consists of a glomerulus, tubuli (both proximal and distal), the loop of Henle and the collecting tubule, all of which participate in the elaboration

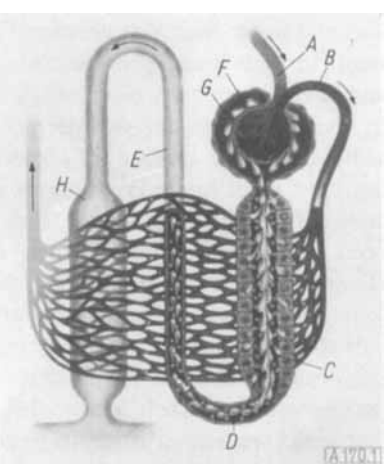


Fig. 1. Anatomy and function of a nephron

A: afferent arteriole	E: distal tubule
B: efferent arteriole	F: Bowman's capsule
C: proximal tubule	G: glomerulus
D: loop of Henle	H: collecting tubule

The small grey circles symbolize sodium ions.

[*] Recent reviews on diuretics:

a) *K. H. Beyer* and *J. E. Baer* in *E. Jucker:* Progress in Drug Research. Birkhäuser-Verlag, Basel and Stuttgart, 1960, Vol. II, p. 9.

b) *H. Heller* and *M. Ginsburg* in *G. P. Ellis* and *G. B. West:* Progress in Medicinal Chemistry. Butterworths, London, 1961, Vol. I, p. 132.

c) *J. H. Moyer* and *M. Fuchs:* Hahnemann Symposium on Edema. Saunders Co., Philadelphia and London, 1960.

[1] *A. Grollman:* Pharmacology and Therapeutics. 4th Ed., Lea and Febiger, Philadelphia, Pa., 1960, p. 516.

of urine. Therefore, the important factors which determine the volume and composition of urine are:

1. glomerular filtration
2. proximal and distal tubular re-absorption
3. tubular secretion

Within a twenty-four hour period, approximately 1700 liters of blood flow through the human kidneys [2]. This blood enters the nephrons through the arterioles and is filtered by the glomeruli at the rate of 140 liters per day, or approximately 100 milliliters per minute. The energy to run this filtration pump is supplied by the beating heart. The components that are filtered or pass through the glomerulus into the tubuli are water, electrolytes ($NaCl$, $(NH_4)_2HPO_4$, KCl etc.) and low molecular weight organic substances such as glucose and urea. The filtrate passes through the proximal tubulus, the loop of Henle and the distal tubulus and it is in these areas of the nephron that the major re-absorption of the filtrate takes place. In addition it is now recognized that in the collecting ducts additional re-absorption of water and perhaps other substances occurs.

In total 98–99 % of the water of the glomerular filtrate plus a great number of inorganic ions and organic compounds are re-absorbed through the cell walls of the tubuli and ducts and returned to the blood stream. The re-absorption process, the energy of which is supplied by the kidney cells, serves to accomplish two purposes; namely to control electrolyte balance and to maintain a constant hydrostatic pressure. Of prime importance is the re-absorption of physiologically necessary amounts of sodium, potassium and chloride ions and the rejection of urea, uric acid and creatinine. Thus, the residue of the filtrate which is not re-absorbed enters the collecting tube and is eventually eliminated as urine.

Changes in the glomerular or tubular functions arising either as a result of pathology of the kidney itself or from disturbance of cardiac output can reduce the capacity of the body to excrete sodium and chloride ions and water. Such serious physiological changes may result in high blood pressure, congestive heart failure and edema (retention of excess fluids in the body). It is, therefore, essential to interrupt this vicious cycle somewhere. One method of alleviating this condition has been to facilitate the removal of the excess water and sodium and chloride ions from the body. This has been accomplished with the use of diuretic agents. Diuretic drugs serve to decrease the re-absorption of water, electrolytes and low molecular weight compounds into the blood stream and, as a consequence, promote the formation of urine. As stated previously 98–99 % of the glomerular filtrate is re-absorbed. It is thus apparent that a slight reduction in tubular re-absorption will result in a large increase in urine volume. Generally it is believed that these drugs act somewhere in the tubuli, but no definitive knowledge as to the specific area is, as yet, forthcoming.

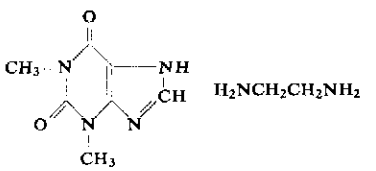
[2] *J. S. Goodman* and *A. Gilman*: The Parmacological Basis of Therapeutics. 2nd Ed., Macmillan, New York, 1955, p. 863

II. Chemistry of Diuretics

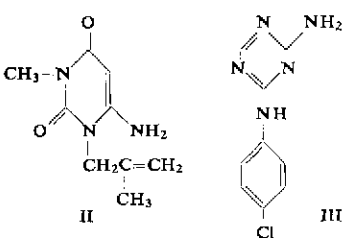
The diuretics have been classified in six major groups:

a) Water
b) Osmotic diuretics
c) Xanthines, triazines, pyrimidines
d) Mercurials
e) Sulfonamides
f) Aldosterone antagonists and inhibitors of aldosterone secretion

Groups a) and b) will not be discussed; with regard to group c) it may suffice to say that they are mild diuretics. Representative members of this group are aminophylline (I), aminoisometradine (II) (Rolicton®), and chlorazanil (III) (Daquin®, Orpidan®).



I



II III

Starting with the clinical demonstration of the efficacy of caffeine in promoting diuresis [3], the leaders of the German classical organic chemistry school, *Emil Fischer*, *Wilhelm Traube*, and others, attacked the problem with great vigor by devising methods for the synthesis of a large number of purines and pyrimidines structurally related to caffeine and theophylline. This approach to the problem has persisted to modern times. However, research in this area of heterocyclic chemistry has not led, as yet, to a diuretic drug with wide and effective clinical application and low toxicity.

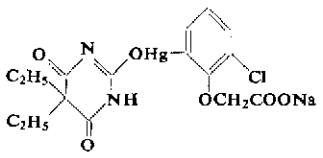
During the period of the past forty years, until 1957, only one class of compounds, the mercurial diuretics had been of major clinical importance. Emphasis has been placed on the past four decades, since before that time the clinical control of congestive heart failure and edema with the use of drugs was quite insignificant.

Mercurial Diuretics (Group d)

Mercurial diuretics today are still the drugs of choice when a prompt and copious diuretic response, such as treatment of advanced congestive heart failure [4], is needed. The history of mercurial diuretics can be traced from the 16th century (when *Paracelsus* used calomel) to "Guy's Hospital Pill" (calomel, squill, and digitalis) and finally to the modern organomercurials. However, the discovery of modern mercurial diuretics was made by chance [5] when a young syphilitic patient was

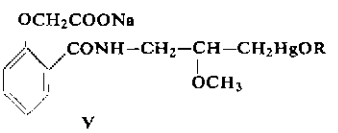
[3] *W. von Schröder*, Arch. exp. Pathol. Pharmakol. *22*, 39 (1887).
[4] *A. Vogl*, Amer. J. Cardiology *6*, 1078 (1960).
[5] *A. Vogl* described his early experience many years later in Amer. Heart Journal *39*, 881 [1950].

treated with a salicylate of mercury instead of an arseno-compound. This compound was merbaphen (IV) which was followed four years later by the less toxic compound mersalyl (V).



IV

1920: Merbaphen (Novasural®, Bayer)



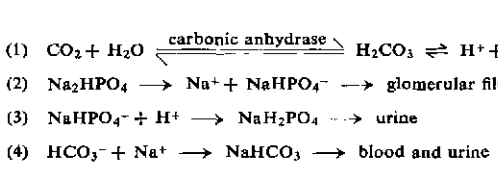
V

1924: Mersalyl (Salyrgan®, Bayer)

There are a number of interesting reviews [6] available on mercurial diuretics, to which the reader should turn for information. The field of mercurial diuretics was investigated very actively between 1920 and 1945 and considerable progress has been made in reducing toxicity and irritation at the site of injection. However, most mercurial diuretics are effective only when given parenterally. This factor, plus the toxicity usually associated with organic mercurials, has prompted the search for non-toxic, orally active, non-mercurial diuretic drugs. The most important group of organic compounds found to date which fulfills these conditions is the sulfonamides.

Sulfonamides (Group e)

The exploration of sulfonamide chemistry has yielded a rich return in drugs of therapeutic value. Their role in the diuretic field began in 1940 in connection with a study of the side effects of certain sulfa drugs. Clinical studies revealed that some patients treated with sulfanilamide (VI) (see Table 1) developed acidosis. Shortly thereafter *Mann* and *Keilin* [7] ascertained that this side effect resulted from inhibition of carbonic anhydrase, the enzyme responsible for bicarbonate formation from CO_2 and water:



(1) $CO_2 + H_2O \xrightleftharpoons{\text{carbonic anhydrase}} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

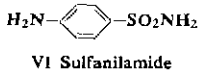
(2) $Na_2HPO_4 \longrightarrow Na^+ + NaHPO_4^- \longrightarrow$ glomerular filtrate

(3) $NaHPO_4^- + H^+ \longrightarrow NaH_2PO_4 \longrightarrow$ urine

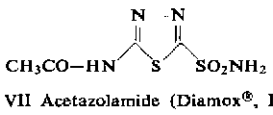
(4) $HCO_3^- + Na^+ \longrightarrow NaHCO_3 \longrightarrow$ blood and urine

In 1949, *Schwartz* [8] pointed out that the inhibition of carbonic anhydrase should lead to a decrease in the rate of conversion of carbon dioxide to hydrogen and bicarbonate ions (Equation 1). Therefore, the transformation of disodium phosphate (Na_2HPO_4) into monosodium phosphate (NaH_2PO_4) (Equation 2) is slowed down due to the non-availability of hydrogen ions which usually are exchanged for sodium ions by the cells of the kidney tubuli. As a result, it was postulated that carbonic anhydrase inhibition necessarily leads to excretion of a greater than normal amount of sodium ions in the form of Na_2HPO_4 (instead of NaH_2PO_4). *Schwartz* [8] was able to show clinically that the diuretic action of sulfanilamide (VI, Table 1) was in fact due to its inhibition of carbonic anhydrase. He also pointed out that chronic use of sulfanilamide led to excessive excretion of sodium and bicarbonate ions and concomitant metabolic acidosis rendering the carbonic anhydrase inhibitor ineffective for further diuretic action. *Roblin* and *Clapp* [9] capitalized on this lead and proceeded to prepare a large number of heterocyclic compounds containing a sulfonamide grouping for evaluation as carbonic anhydrase inhibitors [10]. This work led to the synthesis in 1950 of acetazolamide (VII) (see Table 1).

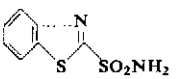
Table 1. Carbonic anhydrase inhibitors



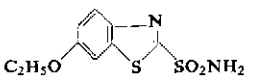
VI Sulfanilamide



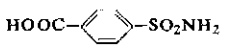
VII Acetazolamide (Diamox®, Lederle)



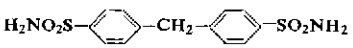
VIII Benzothiazole-2-sulfonamide



IX Ethoxzolamide (Cardrase®, Upjohn)



X Carzenide (Dirnate®, Merck)



XI (Nirexon®, Bayer)

Acetazolamide was considered an important accomplishment in diuretic therapy since it was the first clinically effective, non-mercurial, orally active diuretic drug [11]. *Roblin* and co-workers found benzothiazole-2-sulfonamide (VIII) to be even more potent than acetazolamide as a carbonic anhydrase inhibitor when tested *in vitro*; but when given intravenously to dogs it had little effect upon electrolyte or water excretion. *Clapp* [12] has presented evidence indicating that this heterocyclic sulfonamide is metabolized very rapidly in animals to 2-mercaptobenzothiazole which in turn is excreted in the urine as the glucuronide. Recently, 6-ethoxybenzothiazole-2-sulfonamide (IX) [13] has been introduced as a carbonic anhydrase inhibitor. It is believed that the 6-ethoxy group renders the compound more resistant to metabolic degradation than VIII. Also, Dirnate® (X), a structural modification of sulfanilamide, was tested in man, but its diuretic activity was found to be low. In 1957, Nirexon® (XI) [14] was introduced in Germany and was claimed to be several times more active than acetazolamide as a carbonic anhydrase inhibitor.

[6] See e.g. *H. L. Friedman*, Ann. N.Y. Acad. Sci. *65*, 461 (1957) or *A. Burger:* Medicinal Chemistry. 2nd Ed., Interscience Publishers Inc., New York and London, 1960, p. 641.

[7] *T. Mann* and *D. Keilin*, Nature (London) *146*, 164 (1940).

[8] *W. B. Schwartz*, New England J. Med. *240*, 173 (1949).

[9] *R. O. Roblin* and *J. W. Clapp*, J. Amer. chem. Soc. *72*, 4890 (1950).

[10] *R. W. Berliner* and *J. Orloff*, Pharmacol. Rev. *8*, 137 (1956).

[11] E.g. *J. R. Cummings*, *E. Tabachnik*, and *M. Seelig* in *J. H. Moyer* and *M. Fuchs:* Hahnemann Symposium on Edema. Saunders Co., Philadelphia and London, 1960, p. 252; *C. K. Friedberg*, ibid., p. 258.

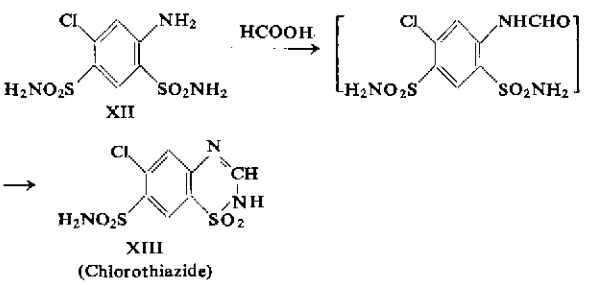
[12] *J. W. Clapp*, J. biol. Chemistry *223*, 207 (1956).

[13] *J. Korman*, U.S. pat. 2,868,800 (Jan. 13, 1959).

[14] *W. Modell*, Amer. J. med. Sci *231*, 564 (1956).

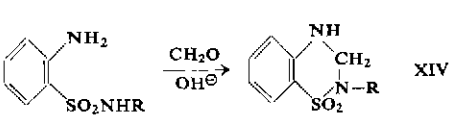
Meanwhile, a group of chemists led by *Sprague* of the Merck, Sharp and Dohme Research Laboratories was engaged in the preparation of benzene disulfonamides [15]. They found that *p*-benzenedisulfonamides showed some diuretic activity in experimental animals, but it was actually the benzene-1,3-disulfonamides which were of much greater interest. Already at that time it was noticed that additional substituents in the benzene ring markedly influenced diuretic activity. The most promising compounds in this series were the N-acyl (CH_3CO to $C_5H_{11}CO$) derivatives of 4-amino-6-chlorobenzene-*m*-disulfonamide (XII), the diuretic activity increasing from CH_3 to C_5H_{11} [16].

Then a most important development took place. Following an old publication of *Ekbom* [17] on the condensation of orthanilamide with formic acid, *Novello* and *Sprague* treated compound XII with this acid. The formylamino intermediate appears to have only transitory existence, since the product isolated was the cyclic derivative, 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (XIII) (chlorothiazide) [18]. Chlorothiazide showed an unusually high degree of diuretic activity



with low toxicity when tested orally in humans. The daily dose was found to be from 500 mg. to 2.0 g. Chlorothiazide marks the great breakthrough in the search for potent non-mercurial diuretics. Unlike the carbonic anhydrase inhibitors this compound resembles the mercurial diuretics in its action, *i.e.* approximately equivalent amounts of sodium and chloride ion are excreted. Continued administration does not lead to acidosis and full effectiveness is maintained.

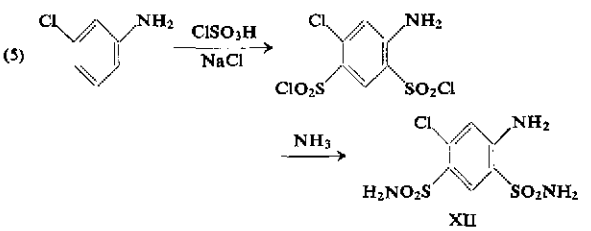
In 1951 *Freeman* and *Wagner* [19] reported that substituted *o*-aminobenzenemonosulfonamides react with formaldehyde in alkaline solution to yield *N*(2)-substituted dihydrobenzothiadiazine-1,1-dioxides (XIV). When this reaction was carried out in our laboratories with unsubstituted o-aminobenzenesulfonamide, and various aldehydes in non-polar solvents with catalytic



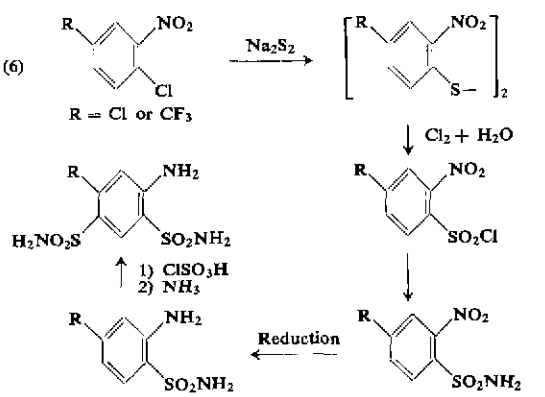
R = Phenyl or substituted phenyl

amounts of hydrogen chloride [20], analogous compounds were obtained. Condensation of 4-amino-6-chloro-1,3-benzenedisulfonamide (XII) with para-formaldehyde yielded 6-chloro-3,4-dihydro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (XVI) in spite of the presence of a second sulfamyl group. The structure of XVI was confirmed by sodium borohydride reduction of chlorothiazide (XIII) to XVI (see page 239). Compound XVI (hydrochlorothiazide) proved to be 10–15 times more potent than chlorothiazide as a diuretic agent in laboratory animals and humans. This observation of the increased activity of the dihydro compounds was confirmed later in many hundred of compounds prepared as diuretics. It was one of the major findings in this field after the initial work of *Novello* and *Sprague*.

Before going into detailed discussion of the great number of thiazide diuretics prepared by many different laboratories within the last three years, it might be appropriate to give an outline of the preparation of the starting materials for this class of diuretics. Chlorosulfonation of aniline leads to an aminobenzenemono- or trisulfonamide. To obtain an aminobenzenedisulfonamide, it is necessary to block one of the positions *meta* to the amino group [21]. The most direct method for the preparation of XII is that of *Lustig* and *Katscher* [22] and consists of heating *m*-chloroaniline with chlorosulfonic acid and sodium chloride, followed by amidation of the resulting benzene disulfonylchloride.



Modifications of this procedure have been studied; *e.g.* the use of an organic solvent such as tetrachloroethane as a diluent, and replacement of sodium chloride by thionyl chloride [21]. In some cases the use of a large excess of chlorosulfonic acid alone may suffice to introduce two sulfonylchloride groups [23].



[15] *J. M. Sprague*, N.Y. Acad. Sci. Biol., Lecture on Nov. 8, 1957.

[16] *J. M. Sprague* et al., Ann. N.Y. Acad. Sci. *71*, 328 (1958).

[17] *A. Ekbom*, Bih. Svenska, Vet.-Akad. Handl. *27*, II (No. 1), p. 22 (1902); Beilstein, 4th Ed. *27*, 570; *14*, 682.

[18] *F. C. Novello* and *J. M. Sprague*, J. Amer. chem. Soc. *79*, 2028 (1957); U.S. pat. 2,809,194 (Oct. 8, 1957).

[19] *J. H. Freeman* and *E. C. Wagner*, J. org. Chemistry *16*, 815 (1951).

[20] *G. deStevens, L. H. Werner, A. Halamandaris*, and *S. Ricca*, Experientia *14*, 463 (1958).

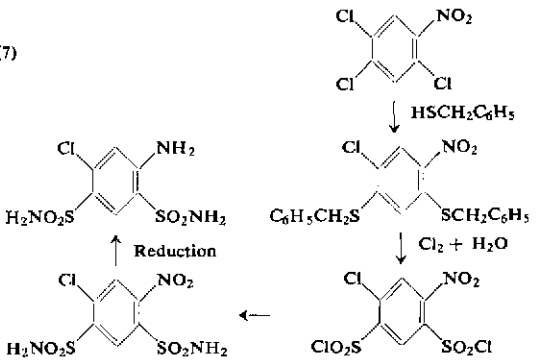
[21] *F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler*, and *J. M. Sprague*, J. org. Chemistry *25*, 965 (1960).

[22] *O. Lustig* and *E. Katscher*, Mh. Chem. *48*, 87 (1927).

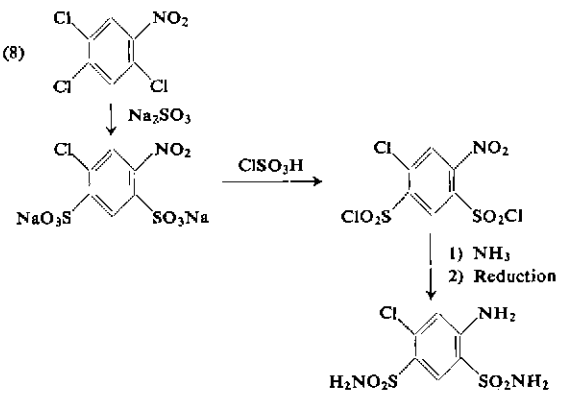
[23] *W. Logemann, P. Giraldi*, and *S. Galimberti*, Liebigs Ann. Chem. *623*, 157 (1959).

Alternate approaches [24] have also been studied. Some of these procedures are outlined in Equations (6)–(8).

(7)

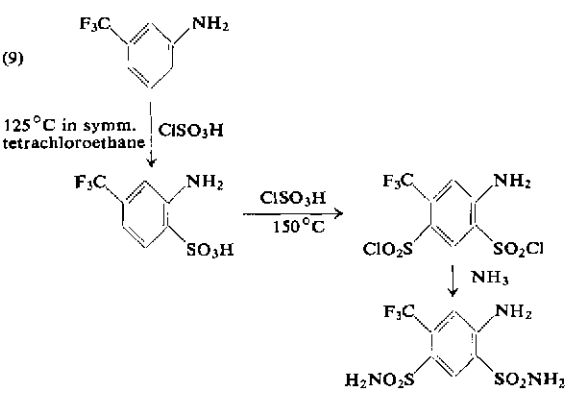


(8)



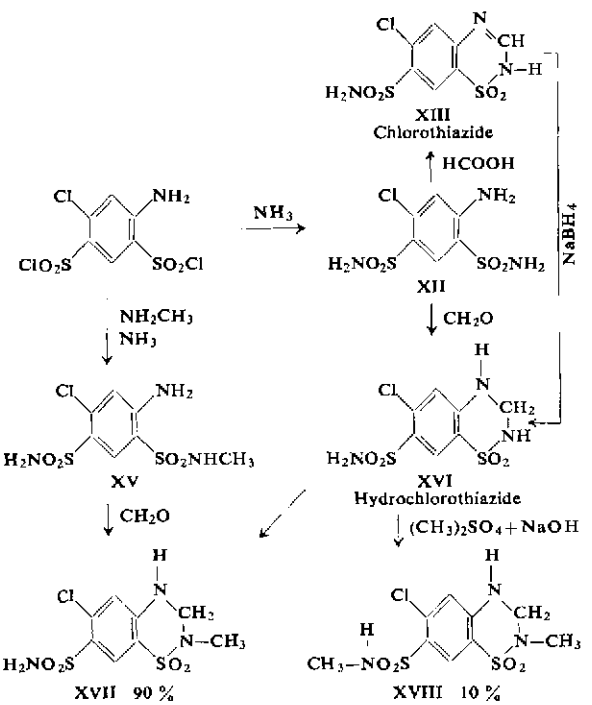
Procedure (5) usually gives good yields of the desired benzenedisulfonylchlorides. However, when applied to *m*-trifluoromethylaniline low yields are obtained [25]. Two procedures for the preparation of this material have been reported, the one using the corresponding trifluoromethyl compound as starting material follows Equation (6) [26] while the other is outlined below [21].

(9)



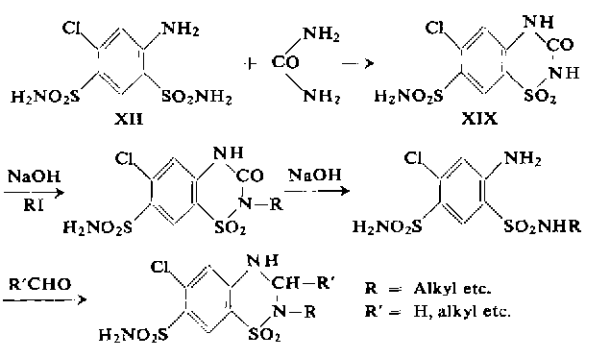
Thus, procedures for the preparation of the significant intermediate disulfonamide XII (the trifluoromethyl analog (CF_3 in place of Cl) has been widely used lately for the same purpose) which serves as the important starting material for the preparation of the highly potent chlorothiazides and hydrochlorothiazides have been well worked out.

The discovery of these drugs, which belong to a virtually unexplored group of heterocyclic compounds, has led a number of investigators to synthesize and biologically evaluate a vast number of benzothiadiazines, a considerable number of which are substituted at position 3 due to the ready availability of the corresponding acids, aldehydes and ketones. For introduction of alkyl groups in position 2 either the correspondingly alkylated sulfonamide (XV) can be condensed with an aldehyde (see below), or the heterocyclic ring can be alkylated after its formation.



Methylation of XVI with one mole of dimethyl sulfate gave a 90 % yield of monomethyl derivative (XVII) and 10 % of the dimethyl compound (XVIII). That the methyl group in XVII was at position 2 rather than at 4 or at the 7-sulfamyl group was unequivocally demonstrated by reductive cleavage experiments. The structure of XVIII was proven by ring closure of the corresponding *N,N'*-dimethyldisulfonamide [27].

Close and co-workers [28] have developed a method for obtaining only the 2-alkyl substituted dihydrobenzothiadiazine-1,1-dioxides (see Table IV). Compound XII was condensed with urea to yield 6-chloro-3-keto-7-



[24] *F. C. Novello*, U.S. pat. 2,910,475 (Oct. 27, 1959); 2,965,656 (Dec. 20, 1960); *C. T. Holdrege, R. B. Babel*, and *L. C. Cheney*, J. Amer. chem. Soc. *81*, 4807 (1959).

[25] *R. Selleri* and *O. Caldini*, Ann. Chimica *50*, 170 (1960).

[26] *H. Kracker* and *F. Herrlein*, U.S. pat. 2,119,882 (June 6, 1938).

[27] *L. H. Werner, A. Halamandaris, S. Ricca, L. Dorfman*, and *G. deStevens*, J. Amer. chem. Soc. *82*, 1161 (1960).

[28] *W. J. Close, L. R. Swett, L. E. Brady, J. H. Short*, and *M. Vernsten*, J. Amer. chem. Soc. *82*, 1132 (1960).

sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (XIX). Since the cyclic sulfonamide grouping is more acidic than the 7-sulfamyl group, alkylation resulted only in the formation of the 2-substituted derivative, which was hydrolyzed and re-cyclized with the appropriate aldehyde to form the 2-mono-substituted or the 2,3-disubstituted dihydrobenzothiadiazine-1,1-dioxides. The overall yield of 2-substituted compounds by this four-step procedure is not better than that obtained by the direct alkylation of hydrochlorothiazide.

Stability of Thiazide Diuretics in Aqueous Solutions

Chlorothiazide and hydrochlorothiazide are slowly hydrolyzed in aqueous, neutral, acidic or alkaline solutions. Stability studies and analytical procedures for chlorothiazide have been reported by *Charnicki* et al. [29], and for hydrochlorothiazide by *Rehm* and *Smith* [30].

The relative stabilities of chlorothiazide and hydrochlorothiazide as calculated from kinetic data obtained in our Analytical Research Laboratories are as follows:

Hydrolysis of chlorothiazide and hydrochlorothiazide in 0.1 N sodium hydroxide at 25 °C.

hydrochlorothiazide	approximately 1 % per 300 hours
chlorothiazide	approximately 1 % per hour

It has been found generally that 3-substituted hydrochlorothiazide derivatives are less stable than the parent compound.

The relative stabilities of chlorothiazide and hydrochlorothiazide at other conditions of *pH* and temperature are probably somewhat different due to differences in dependency of the hydrolytic process to hydrogen and hydroxyl ion catalysis. For the photometric determination of hydrochlorothiazide and its hydrolysis products see Reference [30].

Biologic Assay Procedures for Diuretic Activity

The rapid development in the field of the thiazide diuretics was in part due to reliable biological assay methods for diuretic activity. Preliminary screening was done in rats and the methodology has been reported by *Renzi* et al. [31]. Fasted rats were given, by stomach tube, 5 ml. of 0.2 or 0.9 % saline per 100 g. body weight plus the drug to be tested. The rats were then placed in metabolism cages and the urine excretion measured at intervals over a 3-hour period. The urine was analyzed for sodium, potassium and chloride ions.

Determination of the diuretic activity in dogs gave a more accurate picture of the effect that might be expected clinically and allowed a better comparison with chlorothiazide or hydrochlorothiazide. Procedures have been described by *Barrett* et al. [32], and *Baer* et al. [33].

Groups of six dogs received a subcutaneous injection of 100 ml. of 0.9 % saline. Immediately before the saline injection they received by capsule the compound to be tested orally. The urine was collected by catheterization at 2, 4, and 6 hour intervals and analyzed for sodium, potassium, and chloride ions.

Structure-Activity-Relationships

The great number of compounds prepared as possible diuretics within the last few years can be grouped into the following two classes:

A) Disulfonamides and related compounds without a benzothiadiazine ring

B) Multi-ring compounds with a benzothiadiazine or a dihydrobenzothiadiazine ring.

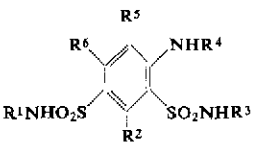
Each of these two classes contains the following three groups:

a) derivatives of *m*-benzenedisulfonamides
b) derivatives of heterocyclic sulfonamides
c) derivatives of benzenecarboxamidesulfonamides.

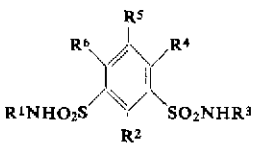
Aa) *m*-Benzenedisulfonamides without a benzothiadiazine-1,1-dioxide ring:

A large number of *m*-benzenedisulfonamides have been prepared by *Novello* et al. [21], *Lund* and *Kobinger* [34], *Close* et al. [28], *Petrow* et al. [35], and in our Laboratories [27]. Many of these compounds have diuretic activity. In order to facilitate discussion we differentiate between 1,3-disulfonamides with an amino-or-substituted amino group in position 4 (XX) and compounds which have other substituents (including H) in position 4 (XXI).

In compounds of group XX maximum pharmacological activity is obtained when R^6 is chlorine, bromine, trifluormethyl or nitro and R^1 to R^5 are hydrogen. 6-Fluoro-, amino-, methyl-, and methoxy-substitution



XX



XXI

diminish activity. Surprisingly, when R^1 to R^6 is equivalent to hydrogen, an inactive compound results. This is also true when R^5 is $-SO_2NH_2$ and R^1 to R^6 is hydrogen. The introduction of additional substituents at R^4 and R^5 with R^6 equal to Cl lowers the activity. It is of interest that substitution of the sulfonamide nitrogens, *e.g.* R^1

[29] *W. F. Charnicki, F. A. Bacher, S. A. Freeman,* and *D. H. DeCesare,* J. Amer. pharmac. Assoc., sci. Edit. *48,* 656 (1959).

[30] *C. R. Rehm* and *J. B. Smith,* J. Amer. pharmac. Assoc., sci. Edit. *49,* 386 (1960).

[31] *A. A. Renzi, J. J. Chart,* and *R. Gaunt,* Toxicol. appl. Pharmacol. *1,* 406 (1959).

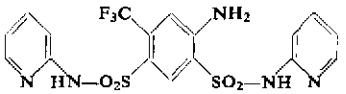
[32] *W. E. Barrett, R. A. Rutledge, H. Sheppard,* and *A. J. Plummer,* Toxicol. appl. Pharmacol. *1,* 333 (1959).

[33] *J. E. Baer, H. F. Russo,* and *K. H. Beyer,* Proc. Soc. exp. Biol. Med. *100,* 442 (1959).

[34] *F. J. Lund* and *W. Kobinger,* Acta pharmacol. toxicol. (Kopenhagen) *16,* 297 (1960).

[35] *B. G. Boggiano, V. Petrow, O. Stephenson,* and *A. M. Wild,* J. Pharmacy Pharmacol. *12,* 497 (1960); *G. B. Jackman, V. Petrow, O. Stephenson,* and *A. M. Wild,* ibid., *12,* 648 (1960); *V. Petrow, O. Stephenson,* and *A. M. Wild,* ibid. *12,* 705 (1960).

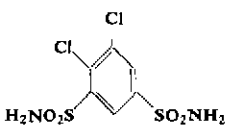
and R^3 equal methyl or ethyl, does not seem to lower the activity. Compound XXII [36] has been claimed to have high diuretic activity. The substituents R^1 to R^6



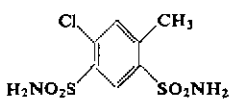
XXII

have been widely varied, especially R^6. XII has been introduced as a diuretic under the trade name Salamid (Ferrosan) [37]. Also its 1,3-dimethyl derivative (R^1, $R^3 = CH_3$; R^2, R^4, $R^5 = H$; $R^6 = Cl$) is highly active [38].

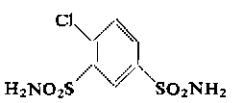
A number of active preparations have been obtained also from structure XXI and several compounds have been introduced as diuretics and for other purposes, *e.g.* XXIII [39], XXIV [40], and XXV [41].



XXIII
Dichlorphenamide
Daranide®
(Merck & Co., Inc.)



XXIV
Disulphamide
Disamide® (British Drug Houses)

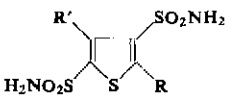


XXV
Haflutan® (Curta)

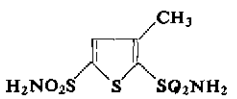
Daranide is a potent carbonic anhydrase inhibitor (more highly active than acetazolamide) and therefore it is less suitable as a diuretic; its main application is in the treatment of glaucoma [42].

Ab) Heterocyclic Disulfonamides

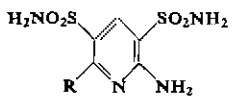
In this group, disulfonamides of thiophene [43] and pyridine [44] have been prepared. The 5-chloro- and 5-lower alkyl-2,4-thiophenedisulfonamides have been found to be about 2–4 times as potent as 4-amino-6-chloro-1,3-benzenedisulfonamide (XII). The 3-methyl-2,5-thiophenedisulfonamide (XXVII) was somewhat more active. However, the 3-ethyl-5-methyl-2,4-thiophenedisulfonamide (XVI) ($R = CH_3$; $R^1 = C_2H_5$) was only weakly active. These compounds, when tested in laboratory animals not only increased the sodium output but also raised the output of potassium substantially.



XXVI
R = Halogen, alkyl, $NHCOCH_3$
R' = H, C_2H_5



XXVII

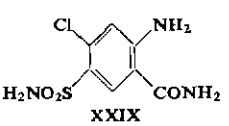


XXVIII R = H, NH_2, CH_3

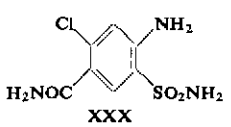
This is an indication of their potent carbonic anhydrase inhibitory action. These facts make this type of compound less desirable as a diuretic. In the pyridine series, 2-aminopyridine (XXVIII) (R = H) and 2,6-diaminopyridine-3,5-disulfonamide (XXVIII) ($R = NH_2$) were very weakly active; 2-amino-6-methyl-3,5-pyridinedisulfonamide (XXVIII) ($R = CH_3$) showed greater activity but was still less active than 4-amino-6-chloro-1,3-benzenedisulfonamide (XII).

Ac) Benzenesulfonamides Containing a Carboxamide Group

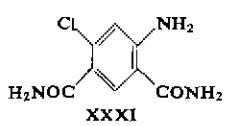
Compounds of this type have been prepared by *Cohen* [45], *Novello* [46], and in our Laboratories. Compounds of the type XXIX have shown some diuretic action, but are weaker than the corresponding benzenedisulfonamides, compounds of type XXX and XXXI being inactive as diuretics.



XXIX



XXX



XXXI

Ba) Thiazide and Hydrothiazide Derivatives

Among the three classes of Group B this is by far the most important group and from a practical view-point this is the only group from which therapeutically important compounds are derived. Since structure-activity relationships show some differences in the thiazide and hydrothiazide group, the two groups are dealt with separately.

Thiazides: 6-Chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (chlorothiazide) exists in two tautomeric

[36] *L. C. Cheney* and *C. T. Holdrege*, U.S. pat. 2,947,742 (Aug. 2, 1960).

[37] *A. Lund* and *K. Storling*, Acta pharmacol. toxicol. (Kopenhagen) *15*, 300 (1959); *T. A. Hilden* et al., Ugeskr. Laeger *121*, 454 (1959).

[38] *W. Logemann*, *P. N. Giraldi*, and *M. A. Parenti*, Nature (London) *182*, 1510 (1958); *W. Logemann*, *P. Giraldi*, and *S. Galimberti*, Liebigs Ann. Chem. *623*, 157 (1959).

[39] *J. B. Rochelle*, *J. H. Moyer*, and *R. V. Ford*, Amer. J. med. Sci. *235*, 168 (1958).

[40] *B. G. Boggiano*, *S. Condon*, *M. T. Davies*, *G. B. Jackman*, *B. G. Overell*, *V. Petrow*, *O. Stephenson*, and *A. M. Wild*, J. Pharmacy Pharmacol. *12*, 419 (1960); *A. David* and *K. P. Fellowes*, ibid., *12*, 65 (1960).

[41] *H. Düster*, Med. Klinik *54*, 2044 (1959); *G. Kabisch*, Die Medizinische *1959*, 2179.

[42] *J. E. Harris*, *O. Beaudreau*, and *G. Hoskinon*, Amer. J. Ophthalmol. *45*, 120 (1958); see also [39].

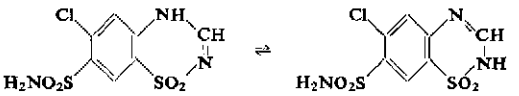
[43] *G. deStevens*, *A. Halamandaris*, *S. Ricca*, and *L. H. Werner*: Abstracts, 136th National Meeting of the Amer. chem. Soc. Sept. 1959, p. 13–0; *W. Siedel* and *K. Sturm*, German patent applications (Hoechst) 1,059,921; 1,088,508; 1,088,509; 1,096,916.

[44] *L. H. Werner*, *S. Ricca*, *A. Halamandaris*, and *G. deStevens*, Meeting-in-Miniature, Amer. chem. Soc. North Jersey Section, Feb. 1960; *H. L. Yale* and *J. T. Sheehan*, Abstracts, 138th National Meeting of the Amer. chem. Soc. Sept. 1960, p. 49–0; *H. L. Yale*, *K. Losee*, and *J. Bernstein*, J. Amer. chem. Soc. *82*, 2042 (1960).

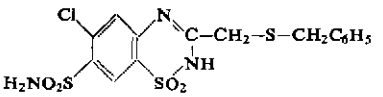
[45] *E. Cohen*, *B. Klarberg*, and *J. R. Vaughan*, J. Amer. chem. Soc. *82*, 2731 (1960).

[46] *F. C. Novello*, U.S. pat. 2,952,680 (Sept. 13, 1960).

forms [21]. It is possible to introduce substituents at the 2:3 or 3:4 positions.



Substitution in the benzene ring is possible at positions 5, 6, 7, and 8, the same naturally also applies to hydrochlorothiazides. A free sulfamyl group in position 7 is essential for high activity. Alkylation or acylation of the sulfamyl group lowers it considerably. Compounds without this sulfamyl group are inactive as diuretics [47]. For maximal activity an additional substituent must be present in position 6. Compounds with chlorine, bromine, trifluoromethyl, and nitro groups in this position are highly active. The trifluoromethyl derivative has been introduced as flumethiazide; it is as active as the chloro derivative (chlorothiazide). Methyl, fluorine, methoxy and amino groups are less effective. Introduction of a chloro or methyl group in position 5, in addition to the chlorine in the 6-position, lowers the activity. Alkylation of either nitrogen atoms in the heterocyclic ring gives rise to compounds with lower activity. Compounds with an alkyl group in the 3-position retain a high order of activity, whereas the 3-phenyl derivatives are less active. It has, however, been found that the introduction of a benzylthiomethyl group at the 3-position of chlorothiazide increases the potency approximately 10 times. This compound is known as benzthiazide.



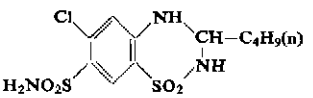
Benzthiazide [48]
Naclex® (Robins)

Hydrothiazides: Previously it had been stated that hydrogenation of the 3,4-double bond of chlorothiazide leads to a 10–20 fold increase in activity. The hydrogenated ring system allows for more possibilities for substitution and as a consequence, the structure-activity relations have been studied more intensively with hydrochlorothiazide. Most of the examples cited below come from our own Laboratories. The effects of the substitution of the benzene ring run parallel with those in the chlorothiazide series and do not necessitate further comments. In this series, the 6-trifluoromethyl derivative has been introduced as hydroflumethiazide. Its activity is comparable to the activity hydrochlorothiazide.

Contrary to the effects of substitution in the heterocyclic ring of chlorothiazide, substitution in the 2- and 3-position of the 3,4-dihydrobenzothiadiazine ring has led to many compounds with greatly increased activity and also with qualitative differences as compared to the parent compound. These modifications are discussed in detail below. At the end of each paragraph the structure of representative members and their activity compared to hydrochlorothiazide are given (HCT = hydrochlorothiazide).

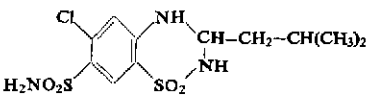
α) Substitution in Position 3

a) Straight chain alkyl groups: Substitution with a straight chain alkyl group in the 3-position gives rise to an increase in activity which becomes greater as the chain is lengthened from methyl to butyl and then slowly decreases again. The 3-butyl derivative is approximately 5–10 times as active as hydrochlorothiazide. The 3-heptyl derivative has the same order of activity as hydrochlorothiazide.



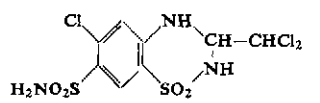
Su 6254 5–10 × HCT

b) Branched chain alkyl groups: The lowest member in this group, the 3-isopropyl derivative is less active than hydrochlorothiazide. The 3-isobutyl and the 3-(1-methylpropyl) derivatives are approximately 20 times as potent as hydrochlorothiazide, whereas the 3-(1-methylbutyl), the 3-(1-ethylpropyl), and the 3-(1-ethylpentyl) derivatives are less active than the parent substance.



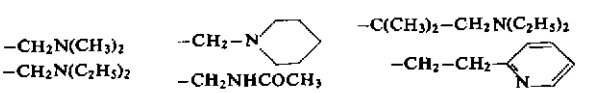
Su-6187 [*] 20 x HCT
Thiabutazide, Saltucin® (Boehringer, Mannheim)

c) Halogeno-alkyl groups: Halogeno-alkyl groups in the 3-position also increase the diuretic activity. The 3-chloromethyl derivative is approximately 7 times as active, the 3-dichloromethyl derivative is approximately 20 times as active as hydrochlorothiazide, the latter has been assigned the generic name trichloromethiazide. On the other hand, the 3-trichloromethyl and the 3-(1,2-dichloroethyl) analogues are only as active as hydrochlorothiazide. The 3-(2-chloroethyl) and the 3-(1,1,2-trichloroethyl) derivatives are ten times as active as hydrochlorothiazide.



Su-7037 Trichloromethiazide [49] 20 x HCT
Naqua® (Schering, USA)
Esmarin® (E. Merck)
Fluitran®

d) Amino-alkyl groups: Substitution in the 3-position with alkylamino groups resulted generally in compounds with no increase in activity. Some of the 3-alkylamino substituents investigated are shown below.



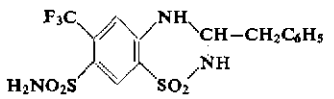
[47] *W. Logemann, P. N. Giraldi,* and *M. A. Parenti,* Nature (London) *182,* 1510 (1958); *J. H. Short* and *U. Biermacher,* J. Amer. chem. Soc. *82,* 1135 (1960). Cf. *J. G. Topliss, N. Sperber,* and *A. A. Rubin,* U.S. pat. 2,986,573 (June 30, 1961) and *A. A. Rubin, F. E. Roth, M. M. Winbury, J. G. Topliss, M. H. Sherlock, N. Sperber,* and *J. Black,* Science (Washington) *133,* 2067 (1961), where antihypertensive, non-diuretic compounds are reported which lack this sulfamyl group.

[48] *S. Y. P'An, A. Scriabine, D. E. McKersie,* and *W. McLamore,* J. Pharmacol. exp. Therap. *128,* 122 (1960).

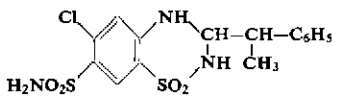
[*] The prefix Su- refers to compounds prepared at CIBA, Summit, N.J.

[49] *R. M. Taylor* and *M. M. Winbury,* Nature (London) *187,* 603 (1960); *G. deStevens, L. H. Werner, W. E. Barrett, J. J. Chart,* and *A. A. Renzi,* Experientia *16,* 113 (1960); *M. H. Sherlock, N. Sperber,* and *J. Topliss,* ibid., *16,* 184 (1960).

e) Aralkyl groups: The introduction of aralkyl groups in the 3-position had a favorable influence. The 3-benzyl and the 3-(1-phenethyl) derivatives are approximately 20 times as active as hydrochlorothiazide. The 6-trifluoromethyl-3-benzyl analogue shown below has been introduced as benzhydroflumethiazide. Branching of the side chain, as in the 3-(2-phenethyl) derivative Su-7078, resulted in still higher activity. This compound is approximately 100 times as active as hydrochlorothiazide.



Benzhydroflumethiazide, Naturetin® (Squibb) 20 x HCT [34,50]

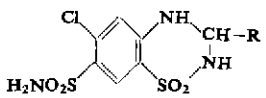


Su-7078: 100 x HCT

f) Phenyl and substituted phenyl groups: The introduction of phenyl or substituted phenyl groups in the 3-position shows no advantage as compared with the introduction of aralkyl groups. Some of the substituents investigated include: -phenyl, *o*- and *m*-tolyl, *m*- and *o*-fluorophenyl, *o*-carboxyphenyl, *m*-hydroxyphenyl, *o*-, *m*-, and *p*-chlorophenyl. Heterocyclic groups such as 2-thienyl, 2-furfuryl and 4-pyridyl in the 3-position have similar effects. Recently the 3-(2-thienyl)methyl derivative has been reported to be highly active.

g) Cycloalkyl groups: A number of compounds in this series has shown extremely high activity. Amongst the many substances prepared in this series, the 3-cyclopentyl derivative was found to be five times as active as hydrochlorothiazide, whereas the 3-cyclohexyl, 3-cycloheptyl, and 3-cyclo-octyl are approximately twenty times as active as hydrochlorothiazide. The 3-Δ^2-cyclohexenyl was somewhat more potent, being about forty times as active as hydrochlorothiazide.

The introduction of a methylene group between the heterocyclic ring and the cycloalkyl group led to a further increase in activity. The 3-cyclopropylmethyl and 3-cyclobutylmethyl derivatives are twenty times as active as hydrochlorothiazide. Increasing the ring size to the 3-cyclopentylmethyl group resulted in a significant increase in activity. *This compound is one hundred and sixty times as potent as hydrochlorothiazide.* On the other hand, the 3-cyclopentylethyl derivative is only twenty times as active as hydrochlorothiazide. The 3-cyclohexylmethyl derivative again is less active than the 3-cyclopentylmethyl analogue. It is fifty to one hundred times as potent as hydrochlorothiazide. Thus it is apparent that the requirements for maximum activity in this group are quite specific with regard to the size of the cycloalkyl group and to its distance from the benzothiadiazine ring.



Su-8341: R = $-CH_2-$⟨⟩; 160 x HCT
Cyclopenthiazide [51], Navidrix® (CIBA)

Su-8395: R = $-CH_2-$⟨⟩; 50–100 x HCT

Su-7526: R = −⟨⟩; 5 x HCT

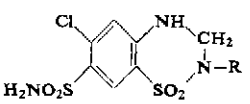
Su-8740: R = $-CH_2-CH_2-$⟨⟩; 20 x HCT

[50] *C. T. Holdrege, R. B. Babel,* and *L. C. Cheney,* J. Amer. chem. Soc. *81,* 4807 (1959).

[51] *W. E. Barrett, J. J. Chart,* and *A. A. Renzi,* Arch. int. Pharmacodynam. Thérap. *131,* 325 (1961); *B. Truniger* and *W. Siegenthaler,* Schweiz. med. Wschr. *91,* 87 (1961).

β) *Substitution in Position 2*

Unlike the conditions prevailing in the chlorothiazide series, alkylation in the 2-position of the hydrochlorothiazide molecule increased the activity and yielded compounds of high potency. Substituents investigated were lower alkyl, cyclopentyl, allyl, and benzyl. The 2-ethyl derivative was the most active member of this group, being approximately one hundred times as active as hydrochlorothiazide. With higher alkyl groups and with benzyl, the activity drops off but the compounds were still considerably more active than hydrochlorothiazide. Here again, for maximum activity, the requirements are quite specific.



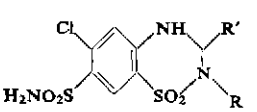
R = CH_3; Su-6441: 3 x HCT
R = C_2H_5; Su-6835: 100 x HCT
R = C_3H_7; Su-8305: 65 x HCT
R = $CH_2C_6H_5$; Su-8066: 20 x HCT

γ) *Substitution in Position 4*

Methylation in the 4-position decreased the activity considerably. Substitution in this position does not appear to be very fruitful and no reports of highly active compounds in this series have appeared. 4-Methylhydrochlorothiazide (Su-6247) is less effective than hydrochlorothiazide.

δ) *Simultaneous Substitutions in Positions 2 and 3*

Substitution in both the 2- and 3-positions resulted in compounds which were as active, or more active, than hydrochlorothiazide.

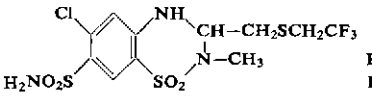


Su-6694: R = R′ = CH_3: equal to HCT
Su-6938: R = CH_3; R′ = n−C_4H_9: 20 x HCT
Su-7272: R = CH_3; R′ = CH_2Cl: 10 x HCT
Methyclothiazide, Enduron® (Abbott) [52]
Su-8293: R = $CH_2C_6H_5$; R′ = CH_2Cl: 20 x HCT

It is remarkable that the introduction of a bulky group such as a benzyl group in the 2-position in addition to the chloromethyl group in position 3 as in Su-8293 does not lower the activity but actually increases it. One compound (methyclothiazide) from this group has been

[52] *R. V. Ford,* Current Therap. Res. *2,* 422, 430 (1960).

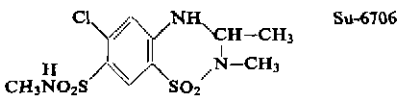
introduced whereas a second one, polythiazide [53], has recently been evaluated and is now also commercially available.



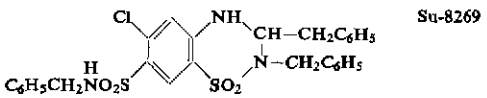
Polythiazide
Renese® (Pfizer) 50 x HCT

ε) *Simultaneous Substitutions in Positions 2 and 3 and at the 7-Sulfamyl Group*

Substitution in all three positions did not give uniform activity changes.



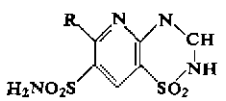
Su-6706



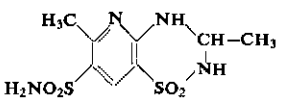
Su-8269

Bb) Thiazide with a Heterocyclic Aromatic Ring [54]

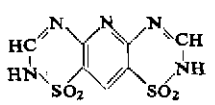
In this group, mainly pyridine derivatives have been prepared. These compounds have virtually the same activity as chlorothiazide.



Su-5938: R = H: inactive
Su-5939: R = CH_3: equal to CT
Su-5919: R = NH_2: inactive



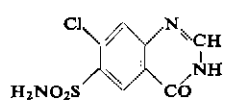
Su-6857: equal to HCT



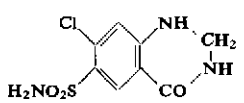
Su-5922: inactive

Bc) Heterocyclic Derivatives of Benzene Carboxamide Sulfonamides

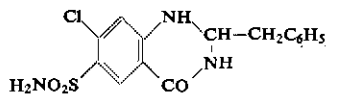
The first two of the following three compounds have been reported to possess diuretic activity. Compound Su-8427 was prepared in our Laboratories and possessed good activity.



Merck, Sharp & Dohme[56]



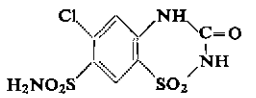
Lederle[55]



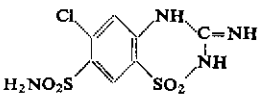
Su-8427

Miscellaneous Derivatives

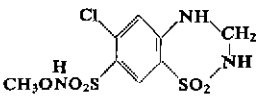
The first of the following three compounds is only weakly active, whereas the second is reputed to be comparable to chlorothiazide, and the third shows activity in the range of hydrochlorothiazide.



Merck, Sharp & Dohme[57]

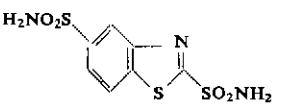


Lepetit[58]

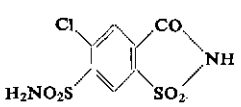


Hoffmann-LaRoche[59]

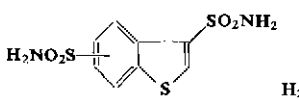
A number of benzothiazoles, saccharin-like compounds, benzothiophenes and large ring compounds with thiazide-like structure have been synthesized in our Laboratories. All these compounds proved to be inactive. The following examples might be mentioned.



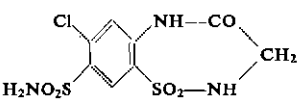
Su-5789



Su-5923



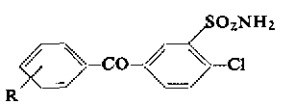
Su-6207



Su-6264

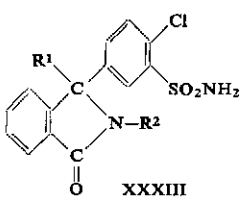
Diuretic Activity of Benzophenone Derivatives

A series of sulfonamides derived from benzophenone and of the general structure XXXII and XXXIII was prepared by a group working with *Stoll* [60] at the Geigy Laboratories.



XXXII

R = COOH
R = $-COOC_2H_5$
R = $-CONH_2$
R = $-SO_2NH_2$



XXXIII

R^1 = —OH
R^2 = —H, alkyl

A member of this group, chlorthalidone (Hygroton®) (XXXIII) (R^1 = OH, R^2 = H) has shown pronounced

[53] *J. M. McManus, A. Scriabine,* and *W. M. McLamore,* Fed. Proc. *20,* 411 (1961); *R. V. Ford,* Current Therap. Res. *3,* 320 (1196).

[54] See also *H. L. Yale* and *J. T. Sheehan:* Abstracts, 138th National Meeting of the Amer. chem. Soc. Sept. 1960, p. 49—0; *H. L. Yale, K. Losee,* and *J. Bernstein,* J. Amer. chem. Soc. *82,* 2042 (1960).

[55] *E. Cohen, B. Clarberg, J. R. Vaughan,* J. Amer. chem. Soc. *81,* 5508 (1959); see also [41].

[56] *F. C. Novello,* U.S. pat. 2,952,680 (Sept. 13, 1960).

[57] *F. C. Novello,* U. S. pat. 2,886,566 (May 12, 1959); J. org. Chemistry *25,* 977 (1960).

[58] Lepetit S.p.A., Brit. pat. 847,176 (May 22, 1958).

[59] Hoffmann-La Roche, Belg. pat. 593,790 (Aug. 4, 1960).

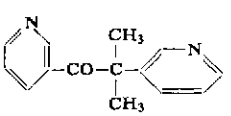
[60] *W. Graf, E. Girod, E. Schmid,* and *W. G. Stoll,* Helv. chim. Acta *42,* 1085 (1959).

diuretic activity in the clinic [61] and has been introduced. This drug is characterized by a long duration of action.

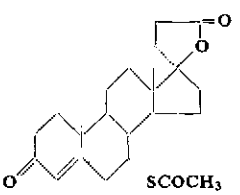
Aldosterone Antagonists (Group f)

It is now an accepted fact that, under certain circumstances, aldosterone plays a major role in provoking and prolonging edema. Aldosterone inhibits excretion of sodium and promotes that of potassium. In diseases associated with edema, such as congestive heart failure, liver cirrhosis and the nephrotic syndrome, the adrenal cortex often produces excessive quantities of aldosterone This leads to increased sodium retention and potassium excretion and therefore tends to aggravate the existing edema. However, it is possible to resolve the edema by blocking the action of aldosterone on the renal tubuli.

The effect of aldosterone can be blocked at two sites, *i.e.* by blocking its secretion in the adrenal cortex or its action in the distal tubulus. By administering substances which inhibit adrenocortical secretion, *e.g.* Metopirone [62] Su-4885, it is possible to suppress the production of aldosterone. Metopirone, however, also interferes with the biosynthesis of corticosterone and cortisol. This results in an increased output of ACTH and hence in stimulation of the adrenal cortex. However, the blocking effect of Metopirone on hydroxylation in position 11, causes only the precursors of cortisol and corticosterone to be synthesized in larger quantities. These precursors have a strong sodium retaining effect and therefore encourage the formation of edema. To prevent this, ACTH secretion also must be inhibited and this is accomplished by administering prednisone or dexamethasone together with Metopirone. This combined treatment with Metopirone and a corticosteroid not only counteracts salt and water retention but induces diuresis [63].

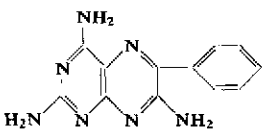


Su-4885, Methopyrapone
Metopirone® (CIBA)



Spironolactone
Aldactone® (Searle)

An alternate method involves a direct blockage of the action of aldosterone on the renal tubuli. This has been done with the aid of the spirolactones [64]. These are steroids with a spirolactone group incorporated into their structure at carbon 17. A preparation of this type is Aldactone. When this drug is administered to a patient with hyperaldosteronism, sodium and water output is increased and potassium is retained. A compound of this type, has been shown to be clinically effective only in patients in which the presence of aldosterone is a contributing factor to the disease. Metopirone and Aldactone, however, have been found to be effective in cases resistant to the thiazide diuretics. Combinations of Metopirone, Aldactone and corticosteroid proved beneficial in such cases. Recently clinical reports [65] on a new aldosterone blocking agent, SKF 8542, have appeared. Especially good results were obtained in cirrhosis of the liver. The compound is considerably more active than Aldactone, but whether its action is due strictly to a blocking effect on aldosterone remains open.



SKF 8542

In conclusion we can say that many different types of compounds act as diuretics. However, none of them have achieved the wide applicability, lack of toxicity and side effects as is the case for the thiazide and hydrothiazide derivatives.

III. Commercial Aspects of the Market for Diuretics

Early in 1961 the following non-mercurial diuretics were on the world market:

16 sulfonamides, 4 triazines, 2 aminouracils and the spironolactone. The leading product was hydrochlorothiazide, sold by 66 companies, followed by chlorothiazide (40 companies), hydroflumethiazide (20 companies), benzhydroflumethiazide (11 companies), acetazolamide (10 companies), and 11 additional sulfonamides of lesser importance. In Italy alone, which is often the leading country in the number of brands, hydrochlorothiazide was sold under 27 (!) different names early in 1961. The estimated total sales for these preparations amount to about 45 million dollars (inside U.S.A. only).

Received, October 16th. 1961 [A 170/A 5 IE]

[61] *F. Reutter* and *F. Schaub*, Schweiz. med. Wschr. *89*, 1158 (1959); *M. Fuchs*, *J. H. Meyer*, and *B. E. Newman*, Ann. N.Y. Acad. Sci. *88*, 795 (1960); *S. Mach* and *R. Veyrat*, ibid., *88*, 841 (1960); *W. K. Stewart* and *L. W. Constable*, Lancet No. 7176, 523 (1961).

[62] *W. L. Bencze* and *M. J. Allen*, J. Amer. chem. Soc. *81*, 4015 (1959).

[63] *D. A. Holub* and *J. W. Jailer*, Ann. intern. Med. *53*, 425 (1960).

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Mechanical and Dielectric Relaxation Phenomena and their Molecular-Physical Interpretation

BY DR. WERNER ZEIL

INSTITUT FÜR PHYSIKALISCHE CHEMIE UND ELEKTROCHEMIE DER TECHNISCHEN HOCHSCHULE KARLSRUHE (GERMANY)

Measurement of mechanical and dielectric relaxation phenomena provides some information concerning intermolecular interactions. These have been thoroughly elucidated for gases, whereas with liquids and amorphous solids (high polymers), we are limited to simplified representations by models. Although at present the main emphasis in applied technology is placed on relaxation investigations of high polymers, it seems appropriate to present here the general physical principles of mechanical and dielectric relaxation phenomena. Furthermore, a review of the relaxation behavior of gases, liquids, and amorphous solids (high polymers) is given. These problems were the main topic of the Sixtieth Congress of the "Deutsche Bunsen Gesellschaft für Physikalische Chemie" [1]. Relaxation phenomena dependent upon chemical equilibria and the field of magnetic relaxation phenomena are not discussed.

1. Basic Theory

In physics the elongation of a body as the result of a stress is described by Hooke's Law:

$$B = \frac{1}{M} \cdot \sigma \qquad (1)$$

B = strain, *i.e.* the relative change in length $\frac{\Delta l}{l}$

σ = stress, expressed as force per unit area

M = modulus of elasticity

Equation (1) holds rigorously only for the static case and includes no information regarding the interim between the moment a mechanical stress is applied to a body and the moment the strain process is completed. That is, the equation contains no statement about the speed with which mechanical strain occurs.

In practically all cases, a measurable period of time must elapse before the above values are attained. If one applies a definite stress σ to a body, then the final strain B_0 is attained only after a definite time. An analogous phenomenon is as follows: if one stretches a piece of rubber very quickly from its originally tension-free state to a new length, then the stress corresponding to Hooke's Law,

$$\sigma_0 = M_0 \cdot B_0 \qquad (2)$$

is reached only after a certain time. Immediately after stretching, a maximum stress σ_∞ is observed. In time, this stress decreases and approaches the constant value σ_0 which is given by Hooke's Law. This specific process whereby the original maximum stress decreases to the value corresponding to Hooke's Law is termed relaxation. The above described process delays the attainment of a deformation or elongation after the sudden application of a stress and is called retardation. However, it is common usage to call relaxation phenomena proper, as well as retardation phenomena, by the common name of relaxation phenomena. This is justified, since both phenomena are causally connected and can be mutually inter-converted if necessary. A measure of the time of adjustment to the final state is the so-called relaxation time, or retardation time.

In Figure 1a, it is shown how a retarded deformation changes with time after application of a stress, whose course time dependence is given. Similarly, the relaxation behavior is represented in Figure 1b. The curve is drawn so that the value of the final stress corresponds to the value of the stress applied for the retardation case.

Here, and in what follows, the mechanical stress σ may be replaced by the electrical field strength E. In an analogous manner, the strain B may be replaced by the electric polarization P, or the electric displacement D, so that Eq. (1) can be written:

$$D = \varepsilon E \qquad (3a) \qquad \text{or} \qquad P = \chi E \qquad (3b)$$

E = electric field strength
D = electric displacement vector
P = electrical polarization vector
ε = dielectric constant
χ = susceptibility, given as $\frac{\varepsilon - 1}{4\pi}$.

[1] 60. Hauptversammlung der Deutschen Bunsen-Gesellschaft für physikalische Chemie, May 11th.–14th. 1961, in Karlsruhe, with the main topic "Relaxation Behavior and the Molecular Structure of Matter", together with the Spring 1961 joint meeting of the technical committees on "Acoustics" and "High Polymers" of the Verband Deutscher Physikalischer Gesellschaften. See particularly the main lectures:
H. O. Kneser: Fundamentals of Dielectric and Mechanical Relaxation Phenomena. (Grundlagen der dielektrischen und mechanischen Relaxationserscheinungen)
W. Maier: Dielectric and Mechanical Relaxation in Liquids. (Die dielektrische und mechanische Relaxation in Flüssigkeiten)
K. A. Wolf: Relaxation Investigations of Molecular Processes in High Polymers. (Relaxationsuntersuchungen zum Studium der molekularen Vorgänge in Hochpolymeren)
For a report see Z. Elektrochem. *65*, 718 (1961).

Similar phenomena apply also in the field of paramagnetism; but these will not be treated in this article. The meaning which the quantities σ, B, and M can assume are shown in Table 1.

Table 1. Variables in Mechanical and Dielectric Relaxation

External force	Reaction of system	Modulus
Stress, σ	Strain, B	Reciprocal of the elastic modulus $\frac{1}{M}$ [*]
Electric field strength, E	Electric displacement, D	Dielectric constant, ε

[*] Frequently, for experimental reasons, another modulus, *e.g.* torsion modulus, compression modulus, or longitudinalwave modulus, is determined. For comparison, see *H. Oberst*, "Grundlagen und Begriffe der elastischen und plastischen Stoffeigenschaften bei statischer und schwingender Beanspruchung".

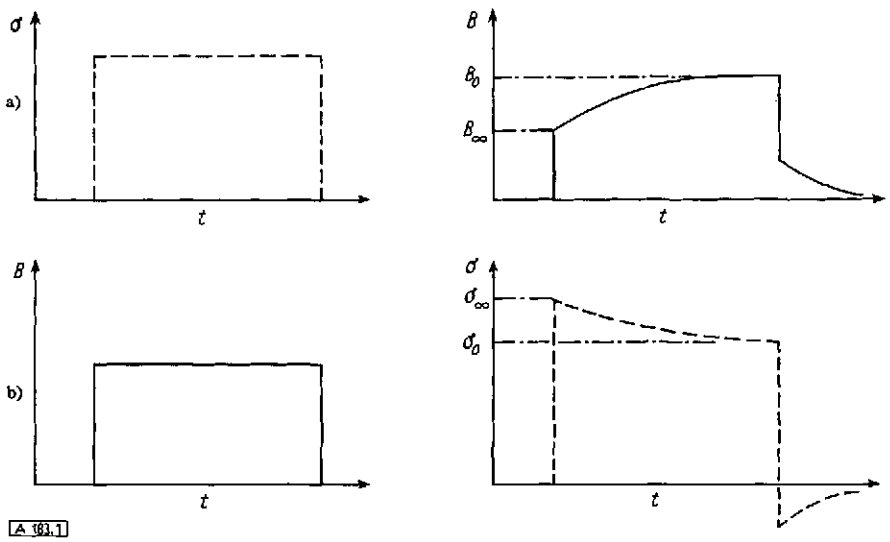


Fig. 1. Stress and strain *versus* time a) for retardation behavior, b) for relaxation behavior

With the aid of some simple considerations which are based on experimental facts, basic equations for relaxation behavior can be formulated thereby making plausible the frequeney dependence of the modulus observed experimentally. We assume that the rates of approach to the final value for the strain in the case of retardation and to the final value of stress in the case of relaxation, increase with the deviation from the final value. That is, the rate of change of the strain under constant stress, or that of the stress under constant strain, is set proportional to the deviation of the strain or the stress from the final value (linearization of the problem). This can be expressed by the following equations:

$$\left(\frac{\partial B}{\partial t}\right)_\sigma = \dot{B}_\sigma = \frac{1}{\tau_\sigma}(B_0 - B) \tag{4}$$

$$\left(\frac{\partial \sigma}{\partial t}\right)_\varepsilon = \dot{\sigma}_\varepsilon = \frac{1}{\tau_B}(\sigma_0 - \sigma) \tag{5}$$

The equations are in agreement with the exponential variation of σ and B observed experimentally. The proportionality constant must then be expressed in units of reciprocal time; these times τ_σ and τ_B are called retardation time and relaxation time and are – as already mentioned – a measure of the delay in attaining the final state. For the following analysis, both these times are still distinct; in the course of this paper we shall speak only more generally of relaxation times and – analogously – of relaxation phenomena.

Equations (4) and (5) resemble equations in chemical kinetics. If, for example, we replace σ by a reaction rate $\frac{dc}{dt}$, $(\sigma_0 - \sigma)$ by a concentration c, and $1/\tau$ by the reaction rate constant k, then we obtain the equation for a first-order reaction. This similarity in formalism is no accident. It is also observed on comparison of relaxation phenomena with the rate of approach to a thermodynamic equilibrium. Almost all theories of relaxation phenomena are based on this analogy. We can therefore formulate relaxation phenomena as gradual adjustments, after a disturbance of a previously existing state of thermodynamic equilibrium, to a new state of equilibrium caused by the disturbance.

We now assume that the final values of the strain B_0, and the stress σ_0 are proportional, the proportionality constant being the elastic modulus of Hooke's Law. In this case, it is designated by M_0, because the operation is allowed to occur only once, *i.e.* no periodic change of state is involved. The quantity M_0 is therefore a characteristic constant for each material. This assumption in mechanical cases implies applicability of Hooke's Law. If we confine ourselves to small elongations (linearity), this is always attained to a good approximation. In dielectrics, also, the assumption of proportionality is always valid.

This assumption, as well as the assumption of proportionality of the rate and the deviation from the final state, are the conditions for the linear relaxation behavior, to which we will limit ourselves here. With the aid of equation (2), we can now eliminate the quantities B_0 and σ_0 from Eqs. (4) and (5) and thereby obtain equation (6).

$$\sigma + \tau_B \frac{d\sigma}{dt} = M_0 \left(B + \tau_\sigma \frac{dB}{dt}\right) \tag{6}$$

This is the basic equation for describing simple relaxation behavior or – using *Kneser*'s terminology – a "simple

relaxation body." The characteristic of a simple relaxation body is that it possesses only a single relaxation or retardation time.

In general, for technical reasons, experiments [2] for determining relaxation time should, be carried out by allowing the change of state to vary periodically:

$$\sigma(t) = \sigma_0 \cos \omega t \qquad \omega = 2\pi\nu \tag{7}$$

or, in complex notation [3]:

$$\underline{\sigma}(t) = \sigma^0 \cdot e^{i\omega t} \tag{7a}$$

$$\underline{B}(t) = B^0 \cdot e^{i(\omega t - \delta)} \tag{7b}$$

where:

σ^0 = amplitude
B^0 = amplitude
δ = phase shift between σ and B

As is well known:

$$e^{i\omega t} = \cos \omega t + i \sin \omega t$$

$\underline{\sigma}$ and analogously $\underline{B}$ are complex quantities.

Calculation using complex quantities permits a mathematical treatment of the phase shift between applied stress and strain. With the aid of these quantities and equation (6), the following relationship is obtained:

$$\delta^0(1 + i\omega\tau_B)e^{i\omega t} = M_0 B^0(1 + i\omega\tau_\sigma)e^{i(\omega t - \delta)} \tag{8}$$

For very high frequencies, *i.e.* for $\omega \gg \frac{1}{\tau_B}$ and $\omega \gg \frac{1}{\tau_\sigma}$, Equation (8) becomes

$$\frac{\sigma_\infty}{B_\infty} = M_0 \frac{\tau_\sigma}{\tau_B} = M_\infty \tag{9}$$

From this, it follows that

$$\sigma_\infty = M_0 \frac{\tau_\sigma}{\tau_B} B_\infty = M_\infty \cdot B_\infty \tag{10}$$

We see that M_∞, *i.e.* the modulus for very high frequencies, is different from the modulus for the limiting case of zero frequency. Figs. 2 and 3 show the frequency dependence or – expressed differently – the dispersion of the modulus or the reciprocal dielectric constant, as derived by experiment. We see that $M_\infty > M_0$ and $\varepsilon_\infty < \varepsilon_0$. This can be generalized, as can be shown theoretically, by saying that $M_\infty > M_0$ and $\frac{1}{\varepsilon_\infty} > \frac{1}{\varepsilon_0}$. The difference $\Delta M = M_\infty - M_0$, which is always positive, is called by Kneser the "Relaxationsbetrag". Analogously: $\Delta\varepsilon = \varepsilon_0 - \varepsilon_\infty > 0$. Furthermore, it follows from equation (9) that $\tau_\sigma > \tau_B$, *i.e.* the retardation time is greater than the relaxation time. If the amount of relaxation (Relaxationsbetrag) is small, as for example in the case of dilute solutions of dipolar molecules in nonpolar solvents, the difference between retardation and relaxation time can be neglected. Then, as shown later, the general expression for „relaxation time" can be used.

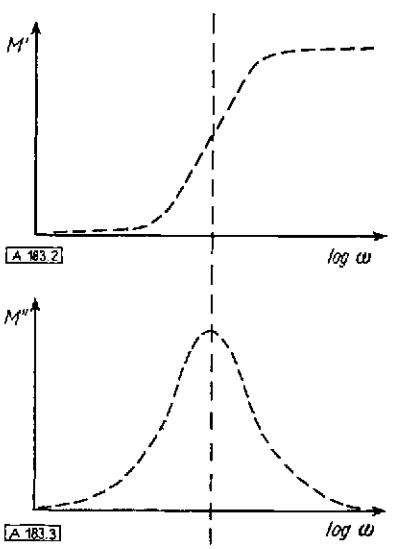


Fig. 2. (above) and Fig. 3. (below). Frequency dependence of the real part M' and imaginary part M'' of the modulus of elasticity

In the course of our simplified considerations on the existence of a dependence of the elastic modulus on the frequency of the induced deformation or strain, we have considered only the limiting cases of static behavior and the behavior at extremely high frequencies as well. For arbitrary frequencies, we must apply complex values to the elastic modulus or the corresponding reciprocal dielectric constant, as is usually done when dealing with a phase shift between an external influence and the attainment of its corresponding value [*].

$$\underline{M_{(\omega)}} = \frac{\sigma}{B} = M' + iM'' \tag{11}$$

M' represents the real part, M'' the imaginary part of the complex modulus.

By a separation of the real and imaginary parts it follows from equations, (11), (7a), (7b), (8) and (9), that

$$M' = M_0 + \Delta M \frac{\omega^2\tau_B^2}{1 + \omega^2\tau_B^2} \text{ and } M'' = \Delta M \frac{\omega\tau_B}{1 + \omega^2\tau_B^2} \tag{12}$$

In the dielectric case we obtain

$$\varepsilon_{(\omega)} = \frac{D}{E} = \varepsilon' + i\varepsilon'' \tag{13}$$

whereby

$$\varepsilon' = \varepsilon_0 - \Delta\varepsilon \frac{\omega^2\tau_E^2}{1 + \omega^2\tau_E^2}; \quad \varepsilon'' = -\Delta\varepsilon \frac{\omega\tau_E}{1 + \omega^2\tau_E^2} \tag{14}$$

and $\Delta\varepsilon = \varepsilon_0 - \varepsilon_\infty$.

It is characteristic of the equations, that both the real and the imaginary parts depend on the relaxation value. The relaxation behavior is therefore described by the relaxation time, the amount of relaxation, and the modulus for the static case. A lucid representation of this relation is obtained by plotting the modulus or the dielectric constant at different frequencies in the complex plane. In both cases the result is a semicircle whose centre lies on the real axis. This representation was first chosen for dielectric behavior by *Cole* and *Cole* [5]. The description was introduced by *Kneser* [6] for mechanical relaxation. Such circles are called "*Cole* circles."

Elimination of $\omega\tau$ from equations (12) or (14) gives

$$\left[M' - \frac{M_0 + M_\infty}{2}\right]^2 + M''^2 = \left[\frac{M_\infty - M_0}{2}\right]^2 \tag{15}$$

[2] For methods of measurement see, *e. g. R. Nitsche* and *V. A. Wolf:* Kunststoffe. Springer, Heidelberg 1962, Vol. II.

[3] Regarding the application of calculations with complex quantities to the treatment of vibrations, see *e.g.* DIN (German Industrial Standards) 5483, "Character of Complex Numbers," and DIN (German Industrial Standards) 1302.

[*] Cf. *e.g.* the complex impedances in alternating-current and high-frequency circuits which permit treatment of the correlation of voltage and current as well as their phase shift. The impedance representation of relaxation behavior depends on this analogy [4].

[4] *J. Meixner*, Nederl. Tijdschr. Natuurkunde *26*, 259 (1960).

[5] *K. S. Cole* and *R. H. Cole*, J. chem. Physics *9*, 341 (1941).

[6] *H. O. Kneser*, Ann. Physik *43*, 465 (1943).

This is the equation of a circle obtained by plotting M'' as a function of M'. The diameter of the circle is given by the amount of relaxation.

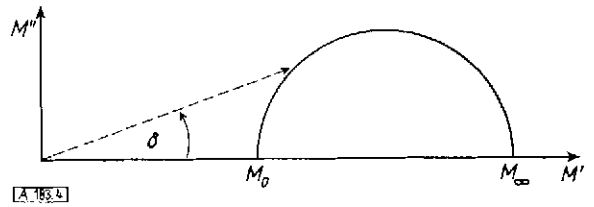


Fig. 4. Circular plot of $\underline{M} = M' + i\,M''$

In Figure 4, the complex representation is shown as a vector diagram. Above all, it may be noted from the figure that the phase-shift δ between the corresponding quantities increases, and later decreases, with frequency. As is known, such a phase shift leads to the irreversible conversion of a fraction ΔW of the expended energy W into heat during each cycle. It follows that:

$$\frac{\Delta W}{W} = 2\,\pi \sin\delta \qquad (16)$$

where δ cannot exceed a definite value. This value depends upon the amount of relaxation.

It can be shown, furthermore, that the imaginary part of M or ε always has its maximum at the relaxation frequency $\omega = \frac{1}{\tau_B}$ or $\frac{1}{\tau_E}$.

On the other hand, the frequency at which the angle δ and, therefore, its tangent, tan δ, is greatest also depends essentially on the amount of relaxation. This means that the quantity tan δ, generally taken as a measure of the loss, reaches its maximum not at the relaxation frequency $1/\tau_\varepsilon$, but at a frequency $\omega = \frac{1}{\tau_\varepsilon}\sqrt{\frac{\varepsilon_0}{\varepsilon_\infty}}$ (see also Fig. 14). In most cases this distinction is admittedly insignificant, but it should always be kept in mind in more precise discussions of relaxation curves.

Two general theories apply to the treatment of relaxation phenomena. Neither contains any assumption concerning the molecular-physical event forming the basis of the phenomena. Conversely, by means of these theories, there is no possibility of obtaining information about the molecular event from relaxation measurements. These theories are:

1. The thermodynamic theory of relaxation phenomena, based on irreversible thermodynamics and due to *Meixner* [7]. We will meet some principles of this theory by way of an example.

2. The after-effect theory of relaxation phenomena. This theory is more general, but also more formal than the thermodynamic theory; it will not be discussed in detail here (cf. *e.g. Meixner* [8]).

A third representation is the kinetic, or statistical, theory, developed in its general form by *De Kronig* [9]. It utilizes a statistical approach and can thus tender some knowledge of molecular-physical events from relaxation measurements. However, it is necessary to use models because it is impossible to draw a direct conclusion concerning these events from relaxation phenomena alone.

[7] *J. Meixner*, Z. Naturforsch. *4a*, 594 (1949).

[8] *J. Meixner*, Kolloid-Z. *134*, 3 (1953).

[9] *R. De Kronig*, Z. techn. Physik *19*, 509 (1938).

From the theories mentioned above, we also expect to be able to interpret the phenomenon of dispersion, *i.e.* the frequency dependence of the elastic modulus or the dielectric constant, and the energy absorption always associated with it.

Thermodynamic Theory

We shall now derive the dynamic equation of state for a simple relaxation system with the aid of the thermodynamic theory of relaxation. Using an example taken from a paper by *Meixner* [4], we will simultaneously become acquainted with the method of the thermodynamic theory and its application to relaxation processes.

The differential of the free energy f of a system subject to a one-dimensional deformation leading to a stress σ as a consequence, is

$$df = \sigma \cdot dB - A \cdot d\xi \qquad (17)$$

σ = the stress resulting from a strain B. It is equal to the partial derivative $\left(\frac{\partial f}{\partial B}\right)_\xi$

A = affinity, in the sense of irreversible thermodynamics [10]. It is given by the partial derivative $-\left(\frac{\partial f}{\partial \xi}\right)_B$

ξ = an intrinsic variable; it can signify the degree of advancement of the reaction [10] or the concentration of some component in the system subject to a change of state.

Figure 5 shows the free energy f as a function of the intrinsic variable ξ at constant strain B. At the minimum of the curve, *i.e.* $\left(\frac{\partial f}{\partial \xi}\right)_B = 0$, the affinity is zero. The minimum in f means that the system is in a state of

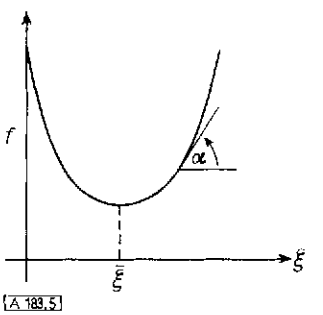


Fig. 5. Free energy f as a function of the intrinsic variable ξ at constant strain B

thermodynamic equilibrium. $\bar{\xi}$ represents the equilibrium value of the intrinsic variable ξ. The affinity is equal to $-\tan\alpha$, where α represents the slope of the tangent to the curve describing the dependence of the free energy f on the variable ξ. The affinity is therefore a measure of the deviation of the system from equilibrium. We now make the assumption that, for sufficiently small values of B and ξ, the variation in ξ with time, *i.e.* the derivative $\frac{d\xi}{dt}$, is proportional to the affinity A. Thereby, the affinity A simultaneously becomes a measure of the reaction rate [10] with which the system restores itself to thermo-

[10] *Ulich-Jost:* Kurzes Lehrbuch der Physikalischen Chemie. 9th. Ed., Steinkopff, Darmstadt 1956; *S. R. De Groot:* Thermodynamik irreversibler Prozesse. Hochschultaschenbücher. Bibliographisches Institut, Mannheim 1960, Vol. I.

dynamic equilibrium after a disturbance – in our case after a deformation. We designate the proportionality constant by $1/C$. Therefore the following equation applies to the relation between affinity and the reaction rate v:

$$v = \frac{d\xi}{dt} = \frac{1}{C} \cdot A \tag{18}$$

We assume isothermal behavior, *i.e.* the temperature remains constant during the experiment, and we expand the free energy (which then depends only on the strain B and the intrinsic variable ξ) in powers of B and ξ. Furthermore, we define ξ such that, at thermodynamic equilibrium and, therefore, in the initial state, when the stress B is equal to zero, ξ is also equal to zero. As a consequence, there are no linear terms the exponential series. The expansion for small B and ξ then reads as follows:

$$f(B;\xi) = f(0;0) + \frac{1}{2} M_\infty B^2 + bB\xi + \frac{1}{2} c \cdot \xi^2 \tag{19}$$

M_∞ is the modulus of elasticity for very rapid deformation. A comparison of Eq. (19) with Eq. (17) leads to the following relation for the stress:

$$\sigma = M_\infty \cdot B + b \cdot \xi \tag{20}$$

By analogy, for the affinity we get:

$$-A = b \cdot B + c \cdot \xi \tag{21}$$

Equations (20) and (21) describe the thermodynamic properties of matter, assuming constant temperature. For $A = 0$, *i.e.* for the equilibrium state, we obtain the following relationship between stress and strain:

$$\sigma = \left(M_\infty - \frac{b^2}{c}\right) \cdot B \tag{22}$$

This relation holds – since it was derived for $A = 0$ – only under the assumption of continuous establishment of equilibrium conditions. Under this assumption, however, *Hooke*'s Law applies:

$$\sigma = M_0 \cdot B \tag{23}$$

We therefore obtain a relationship between the modulus of elasticity in the case of equilibrium M_0 and the modulus of elasticity for very fast deformation, the "instantaneous modulus of elasticity."

$$M_0 = M_\infty - \frac{b^2}{c} \tag{24}$$

From further considerations, which will not be examined here, it follows that $M_\infty > 0$, $c > 0$ and $cM_\infty > b^2$. From this we obtain $M_\infty > M_0$. It follows from equation (20), by solving for ξ and differentiating with respect to time, that for $\frac{d\xi}{dt}$:

$$\frac{d\xi}{dt} = \frac{1}{b}(\dot{\sigma} - M_\infty \cdot \dot{B}) \tag{25}$$

By elimination of b, A, ξ and $\frac{d\xi}{dt}$ from equations (21) to (25)

$$\sigma + \frac{C}{c}\frac{d\sigma}{dt} = M_0 \cdot \left(B + \frac{C}{c}\frac{M_\infty}{M_0}\frac{dB}{dt}\right) \tag{26}$$

If we now replace $\frac{C}{c}$ by τ_B and $\frac{C}{c} \cdot \frac{M_\infty}{M_0}$ by τ_σ, then equation (26) is transformed into equation (6), the equation of dynamic state with which we are already acquainted. The ratio of the relaxation time at constant strain τ_B to the relaxation time at constant stress τ_σ, *i.e.* the ratio of relaxation time and retardation time, is equal to the fraction $\frac{M_\infty}{M_0}$. We have thus derived the dynamic equation of state thermodynamically.

This same approach is applicable to all other linear relaxation processes, as well as in cases involving several intrinsic variables. A more complete treatment is given by *Meixner* [7, 8].

The after-effect theory ("Nachwirkungsdarstellung") of relaxation phenomena obtained by integration of the dynamic equation of state, shows how the stress $\sigma(t)$ depends on the instantaneous values of the deformation $\varepsilon(t)$ and on the previous history before deformation. For our special case compare *Meixner* [4]. *Müller* [11] has presented a treatment of the after-effect theory for dielectric relaxation phenomena.

Statistical Theory

We have thus derived the dynamic equation of state using thermodynamics. The frequeney dependence (dispersion) of the modulus can be derived from this equation. We shall now derive directly, with the help of the statistical theory of *De Kronig*, the equations given above concerning the frequency dependence of the real and imaginary parts of the modulus of elasticity or the dielectric constant. This theory is not as free from postulates as the thermodynamic theory; on the basis of its assumptions and on this basis alone can we make some statements concerning special molecular-physical processes. *De Kronig*'s theory attempts to describe relaxation phenomena from a common molecular-physical point of view. In a publication which appeared in 1938, *De Kronig* [9] formulates the problem as follows:

"A total system consists of a large number of mostly similar partial systems which are independent of one another to a first approximation, and each of which is capable of a series of states l with energy W_l. At thermodynamic equilibrium, the partial systems are distributed with respect to the energy value W_l according to *Boltzmann*'s Law, and the population corresponding to each state is

$$N_l = N \frac{e^{-\frac{W_l}{kT}}}{\sum e^{-\frac{W_l}{kT}}} \tag{27}$$

where N is the total number of partial systems, k is the *Boltzmann* constant, and T is the absolute temperature. It follows then that

$$N = \sum N_l$$

while T is unequivocally defined through fixation of the total energy

$$W = \sum W_l N_l$$

If the distribution at a given instant is made to differ from *Boltzmann*'s distribution, then the problem reduces to a matter of determining the order of

[11] *F. H. Müller* and *Chr. Schmelzer*, Ergebn. exakt. Naturwiss. *25*, 357 (1951).

magnitude of the time in which a suitably defined mean of the deviation from the population N_l decreases from its equilibrium value to a certain fraction of its original value, *e.g.* to the *e*-th part." [*]

The *De Kronig* theory therefore makes special assumptions about the energy distribution in the system exhibiting relaxation phenomena. *De Kronig* also explains what he means by partial systems: these are the atoms or molecules of the gases, liquids, or solids in question. The energy values of which *De Kronig* speaks consist of contributions from translational, rotational, and vibrational energy, whereby the first fluctuates continuously while the rotational and vibrational energies, because of quantum condition, can assume only a series of discrete values. These statements hold particularly for the problem of mechanical-(acoustical) relaxation phenomena. In dielectric relaxation phenomena, the partial systems are the permanent electrical dipoles of the molecules. Their energy is the interaction energy with the electric field, which in general will be an external field.

However, we must keep in mind that there are also perturbations in this field, which may originate from neighboring molecules or ions. In this case, the orientation is assumed to be continuously changeable. The energy of interaction can also assume continuously any value between the limiting values of parallel and antiparallel orientations. It is therefore a prerequisite for the establishment of a new thermodynamic equilibrium after applying a disturbance that transitions between the various states of the partial systems are possible, *i.e.* there must be a finite probability of transition A_{lm} between the states l and m. This probability of transition may be dependent not only on the energy of the various states, but also on pressure, temperature, and external electric fields. *De Kronig* formulates the following differential equation which specifies the rate of change of population number N_l.

$$\dot{N}_l = \sum_{m \neq l} (N_m A_{ml} - N_l A_{lm}) \tag{28}$$

[*] Original text from reference [9]: „Ein Gesamtsystem besteht aus einer großen Anzahl von meistens gleichartigen Teilsystemen, die in erster Näherung voneinander unabhängig sind und deren jedes einer Reihe von Zuständen l mit der Energie W_l fähig ist. Im thermodynamischen Gleichgewicht sind die Teilsysteme über die Energiewerte W_l nach dem *Boltzmann*schen Gesetz verteilt mit den Besetzungszahlen

$$N_l = N \frac{e^{\frac{W_l}{kT}}}{\sum e^{\frac{W_l}{kT}}} \tag{27}$$

wo N die Gesamtzahl der Teilsysteme, k die *Boltzmann*sche Konstante, T die absolute Temperatur bedeuten. Es gilt dann

$$N = \sum N_l$$

während durch Vorgabe der Gesamtenergie

$$W = \sum W_l N_l$$

T eindeutig festgelegt wird. Bewirkt man irgendwie, daß die Verteilung in einem gegebenen Augenblick von der *Boltzmann*schen verschieden ist, so handelt es sich darum, die Größenordnung der Zeit zu bestimmen, in der ein geeignet definiertes Mittel der Abweichungen der Besetzungszahlen N_l von ihren Gleichgewichtswerten auf einen gewissen Bruchteil seines ursprünglichen Betrages, z. B. auf den e-ten Teil, abnimmt."

This equation indicates that the rate of change of N_l with time has two causes:

1. the influx of partial systems from state m with a transition probability A_{ml} and

2. the outflow of partial systems from the state l with the probability of transition A_{lm}.

De Kronig then assumes that the external disturbance, which results in the relaxing change in state, is small and that the population, which alters as a result of the external disturbance, varies linearly with the disturbance F. The respective difference of population is designated by n_l. The distribution after the disturbance is then

$$N_l = N_l^0 + n_l \tag{29}$$

N_l^0 signifies the population of the states at equilibrium. As already mentioned, the probability of transition A_{lm} also depends on F. We expand A_{lm} in terms of F and break off the series after the linear term:

$$A_{lm} = A_{lm}^0 + \left(\frac{\partial A_{lm}}{\partial F}\right)_0 F \tag{30}$$

A_{lm}^0 then signifies the value of the probability of transition in the absence of a disturbance F. In the equilibrium state, the following must apply:

$$N_l^0 A_{lm}^0 = N_m^0 A_{ml}^0 \tag{31}$$

In this case the number of transitions, which is equal to the product of the numerical distribution and the probability of transition, is by definition equal in both directions. In consideration of equation (27), we then obtain the following relationship:

$$A_{lm}^0 = e^{\frac{\left(W_l^0 - W_m^0\right)}{kT}} A_{ml}^0 \tag{32}$$

We now differentiate with respect to F and get

$$\left(\frac{\partial A_{lm}}{\partial F}\right)_0 = e^{\frac{\left(W_l^0 - W_m^0\right)}{kT}} A_{ml}^0 \left(\frac{\partial}{\partial F}\frac{W_l - W_m}{kT}\right)_0 + e^{\frac{\left(W_l^0 - W_m^0\right)}{kT}} \left(\frac{\partial A_{ml}}{\partial F}\right)_0 \tag{33}$$

Considering again equation (27), then we obtain

$$N_l^0 \left(\frac{\partial A_{lm}}{\partial F}\right)_0 = N_m^0 A_{ml}^0 \left(\frac{\partial}{\partial F}\frac{W_l - W_m}{kT}\right)_0 + N_m^0 \left(\frac{\partial A_{ml}}{\partial F}\right)_0 \tag{34}$$

Referring to equations of (31) and (34) and substituting equations (29) and (30) in equation (28), we then get the following system of linear differential equations:

$$\dot{n}_l = \sum_{m \neq l} \left\{ n_m A_{ml}^0 - n_l A_{lm}^0 - N_m^0 A_{ml}^0 \left(\frac{\partial}{\partial F}\frac{W_l - W_m}{kT}\right)_0 F \right\} \tag{35}$$

If F is a known function of time, then n_l can be derived as a function of t. If the external disturbance F is periodic in nature, which for technical reasons is almost always the case, then, by analogy to the assumption made above concerning the linear relationship between n and F,

$$n = n_0 \cdot e^{i\omega t} \tag{36}$$

We shall now assume, for the sake of simplicity, that l can assume only two values, *viz*, the values 1 and 2. This means that there are only two states between which participate in equilibrium. For example this is valid to a very close approximation in the case of vibrational relaxation of a diatomic molecule, (considered later), where only the vibrational ground state and the first excited state are occupied to an appreciable extent. In this case, the solution consists of two linear differential equations:

$$n_1 = -n_2 = \frac{C}{1 + i\rho\nu} F \tag{37}$$

where

$$C = -\frac{N}{2\left[1+\cosh\frac{W_1^0 - W_2^0}{kT}\right]}\left(\frac{\partial}{\partial F}\frac{W_1 - W_2}{kT}\right)_0 \quad (38)$$

$$\rho = \frac{2\pi}{A_{12}^0 + A_{21}^0} \quad (39)$$

If we now consider n_1 as a complex quantity

$$n_1 = n_1' - i\,n_1'' \quad (40)$$

then we obtain the following relationship for its real and imaginary parts:

$$n_1' = -n_2' = \frac{C}{1+\rho^2\nu^2}F \quad (41)$$

$$n_1'' = -n_2'' = \frac{C\rho\nu}{1+\rho^2\nu^2}F \quad (42)$$

If we compare the equations regarding the frequency dependence of the population of a state, derived from the statistical postulate using *Boltzmann*'s Law, with the equations obtained from the phenomenological approach, then we see that the relaxation time corresponds to the reciprocal of the sum of the transition probabilities in the equilibrium state:

$$\tau = \frac{1}{A_{lm}^0 + A_{ml}^0} \quad (43)$$

The amount of relaxation corresponds to the quantity C in the *De Kronig* theory. The real part n' of the additional numerical distribution related to the disturbance of magnitude 1 corresponds to $M'-M_0$ or $\varepsilon'-\varepsilon_\infty$, and the imaginary part n'' corresponds to M'' or ε''.

To summarize the first section regarding the theoretical treatment of the relaxation phenomena: The experimental retardation or relaxation curves, which lead to equations (4) and (5) and from which both the basic equation for a simple relaxation body, (*i.e.* the dynamic equation of state) as well as the frequency dependence of the real and imaginary parts of the modulus of elasticity or dielectric constant can be ascertained, are obtainable both by a purely thermodynamic approach, *i.e.* using a continuous-process theory, and also from a statistical approach based on the distribution of energy in different states according to *Boltzmann*'s ratio and finite probabilities of transition between these states. The thermodynamic theory is more general and is based on fewer assumptions. This freedom from assumptions, however, is connected with the fact that no statements can be made about the molecular mechanism effecting relaxation behavior. The statistical-kinetic theory is less general but is based on atomic and molecular-physical principles regarding the existence of partial systems and the distribution of energy associated with these partial systems. With adequate certainty of the identity of these partial systems with atomic or molecular parts of the total system, and of the possible states in which these systems can exist, it is possible to draw conclusions from relaxation measurements regarding the molecular processes involved and their energetic relationships.

It is common to both theories, to assume that the establishment of a thermodynamic equilibrium after an initial disturbance is the cause of relaxation phenomena. Up to now, in both the thermodynamic and the statistical-kinetic theories, we have spoken of the free energy and its dependence on variables or of the distribution of atomic or molecular units in the various states of free energy f. On the basis of the *Gibbs-Helmholtz* equation we can now divide the free energy into an internal energy term and an entropy term. We can therefore also write for the population of a given state

$$N_i = Const \cdot e^{-\frac{f_i}{kT}} = Const \cdot e^{-\frac{E_i - TS_i}{kT}} \quad (44)$$

From Equation (44) we find that, in order to investigate relaxation phenomena, the system can be disturbed in principle in three ways: either we change the temperature or the energy of the possible states or we increase the order of the system, *i.e.* we decrease the entropy. The experimental possibilities are:

An increase in temperature can be brought about by subjecting a gas or a liquid to a rapid adiabatic compression. This is easily done by passing a sound wave of sufficiently high frequency through the substance. A change in the entropy is thought to be possible only by mechanical deformation. On the other hand the increase in internal energy can be caused by mechanical stress as well as by electric or magnetic fields (the latter will not be discussed here). The most important relaxation phenomena to be discussed are enumerated below:

1. Acoustic relaxation phenomena in gases and liquids, known as sound dispersion.

2. Mechanical relaxation phenomena in plastics (high polymers);

3. Dielectric relaxation phenomena in liquids and plastics (high polymers).

We will not go into the broad range of relaxation phenomena in which a chemical equilibrium is disturbed and whose investigations, currently known as the kinetics of rapid reactions, form a specific field of research in chemical reaction kinetics [*]. Furthermore – as already mentioned at the beginning – magnetic relaxation phenomena and the closely connected phenomenon of nuclear relaxation will not be discussed, since, for their comprehension, extensive details concerning the interaction of spin-systems and neighboring fields must be included. This would be far beyond the scope of this paper.

2. Mechanical Relaxation Phenomena in Gases (Sound Relaxation)

In gases, mechanical relaxation phenomena are perceptible in the dispersion of sound and in the corresponding absorption of sound. *Kneser* [12] summarized experimental methods for investigating molecular ab-

[*] See *e.g.* the report on the Discussions of the Deutsche Bunsen-Gesellschaft für Physikalische Chemie concerning rapid reactions in solutions (Z. Elektrochem. *64*, No. 1 (1960)).

[12] *H. O. Kneser*, Handbuch der Physik. Springer, Berlin-Göttingen-Heidelberg 1961, Vol. XI/1, p. 129.

sorption and dispersion of sound in gases and liquids. Measurements are made of the dependence of the velocity of sound on frequency (sound dispersion) and the dependence of the absorption of sound on frequency. The equation for the velocity of sound is

$$c^2 = \frac{M}{\rho} \tag{45}$$

Here again M represents the modulus of elasticity which, in the special case of the propagation of longitudinal waves in gases, equals the ratio of specific heats at constant pressure and volume multiplied by the reciprocal isothermal compressibility. For an ideal gas, this is equal to $1/p$. It follows then that

$$c^2 = \frac{p \cdot \gamma}{\rho} \tag{46}$$

where $\gamma = \frac{C_p}{C_v}$, $M = \frac{\gamma}{\varkappa_{\text{isotherm}}}$.

One can now assume the following as the cause of sound dispersion and, therefore, of relaxation phenomena [12]: on adiabatic compression of a portion of the volume of a gas, caused by the passage of a sound wave, the temperature of this portion of the volume increases. If all the degrees of freedom of the energy are newly distributed in a way corresponding to this rise in temperature, as is the case at low sound frequencies, we always have an equilibrated system. At very high sound frequencies a portion of the degrees of freedom cannot assume the energy corresponding to the equilibrium distribution in the short time available. This is equivalent to a decrease in specific heat, which is composed additively of the translational, rotational, and vibrational energies per unit degree. It will now be assumed that at very high frequencies, a certain number of the degrees of freedom is always excited according to an equilibrium state. The specific heat corresponding to these degrees of freedom we call C_a; the specific heat which is caused by degrees of freedom whose adjustment require a certain time we call C_i. In the statistical case then

$$C_v = C_a + C_i$$

The equation for the dependence of the complex speed of sound, $\underline{c}$, on the sound frequency now reads [12]:

$$\frac{1}{\underline{c}^2} = \varkappa_{\text{isotherm}} \cdot \rho \frac{C_v}{C_p} = \varkappa_{\text{isotherm}} \cdot \rho \frac{C_a + \frac{C_i}{1 + i\omega\tau}}{\Delta + C_a \frac{C_i^0}{1 + i\omega\tau}} \tag{47}$$

with $\Delta = C_p - C_v$ ($= R$ in the case of an ideal gas). The relaxation time corresponds, in *De Kronig*'s sense, to the reciprocal sum of the transition probabilities:

$$\tau = \frac{1}{A_{12} + A_{21}}.$$

In our case $\frac{A_{12}}{A_{21}} \ll 1$ [12]. That is, τ is approximately equal to $1/A_{21}$. In this case, the relaxation time is equal to the transition time of vibrational energy into translational energy on collision. This corresponds to the lifetime of a "vibrational quantum" and must not be confused with the lifetime of an "excited vibrational state".

Transformation of Equation (47) produces the formula for the propagation of sound, where c_0 represents the propagation for the limiting case of zero frequency and the new relaxation time τ' thus introduced is slightly different from the relaxation time τ defined above:

$$\frac{c_0^2}{c^2} = 1 - \varepsilon \frac{\omega^2\tau'^2}{1 + \omega^2\tau'^2} \tag{48a}$$

$$\tau' = \tau \frac{C_a + \Delta}{C_a + C_i + \Delta} \tag{48b}$$

The quantity ε represents the "relaxationbetrag". It is given by

$$\varepsilon = \frac{\Delta \cdot C_i}{(C_a + C_i)(C_a + \Delta)} \tag{48c}$$

(Confusion of this quantity ε with the dielectric constant appearing later seems not likely). On examination of equation (48) we find that the complex speed of sound assumes real values for the limiting cases of frequency = 0 and ∞: in the former case the value c_0, in the latter case the value $c_\infty = c_0/\sqrt{1-\varepsilon}$. From the last relationship we can obtain a new definition for ε:

$$\varepsilon = \frac{c_\infty^2 - c_0^2}{c_\infty^2} = 1 - \frac{\varkappa_\infty^{\text{adiab.}}}{\varkappa_0^{\text{adiab.}}} \tag{49}$$

Since the complex sound velocity in the case of a plane wave is connected with the phase velocity c and the absorption coefficient per centimeter α by the relationship

$$\frac{1}{\underline{c}} = \frac{1}{c} + i\frac{\alpha}{\omega} \tag{50}$$

then by separating real and imaginary parts and neglecting second- and third-order terms of ε, in the formula for sound propagation, an approximate dependence of the sound velocity on the frequency, the relaxation time τ' and the relaxation value ε is obtained:

$$\frac{c^2}{c_0^2} \approx \frac{1 + \omega^2\tau'^2}{1 + \omega^2\tau'^2(1 + \varepsilon)} \tag{51}$$

Without neglecting terms the absorption coefficient then reduces to:

$$\alpha = \frac{1}{2}\frac{c}{c_0^2}\frac{\varepsilon\omega^2\tau'}{1 + \omega^2\tau'^2} \tag{52}$$

α is therefore a function of the amount of relaxation ("relaxationsbetrag"), relaxation time, frequency, and sound velocity. Sometimes the absorption coefficient will be represented by a dimensionless coefficient for each wavelength. This leads to

$$\mu = \alpha \cdot \lambda = \frac{1}{2}\frac{c^2}{c_0^2}\frac{2\pi\varepsilon\omega\tau'}{1 + \omega^2\tau'^2} \approx \frac{\pi\varepsilon\omega\tau'}{1 + \omega^2\tau'^2} \tag{53}$$

It is possible to represent relaxation behavior in the sound propagation in four ways as shown in Figs. 6 (a), (b), (c) and (d). A circular (complex plane) plot, first suggested by *Kneser* [6], is also possible in the case of sound absorption. The real part is given by $\frac{c_0^2}{c^2}$ and the imaginary part by $-\frac{\mu}{\pi}\frac{c_0^2}{c^2}$. This circular plot is analogous to the *Cole-Cole* plot for the dielectric constant. The problem evolved here following *Kneser*'s method and by application of the *De Kronig*'s concept can also be treated with the aid of thermodynamic theory. This

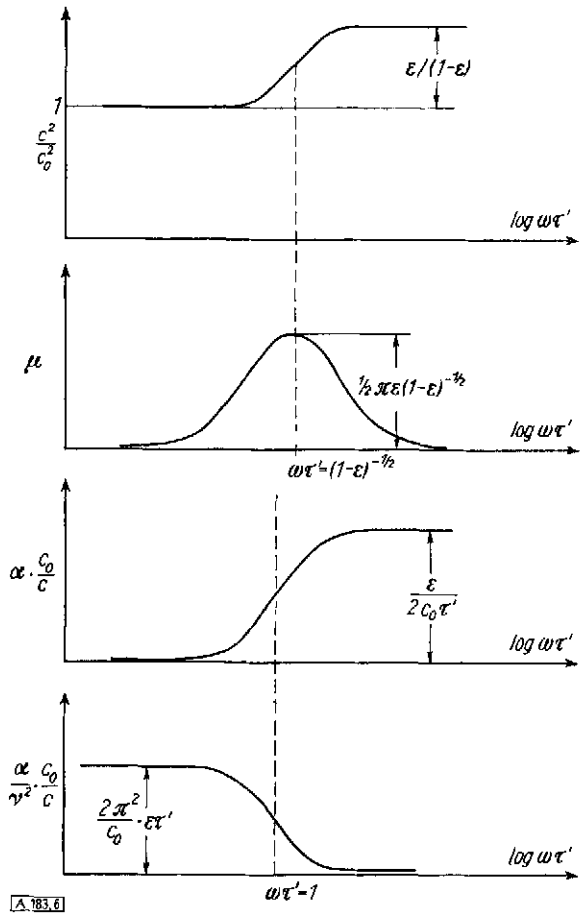


Fig. 6. Representation of relaxation behavior in sound propagation (*Kneser* [12], p. 146)

has been shown by *Meixner*, who also made allowance for viscosity, thermal conductivity and diffusion [13].

The question is: Which molecular-physical processes take place during the occurrence of relaxation phenomena in gases? In most cases, relaxation of vibrational energy is observed. Figure 7 shows measurements of

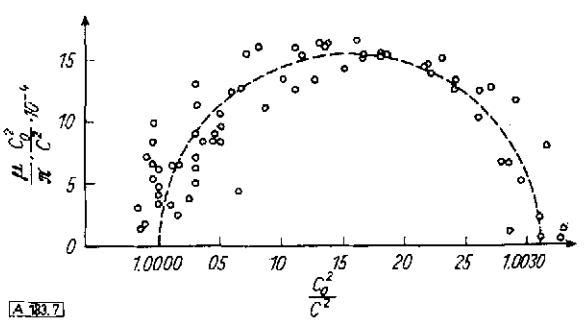


Fig. 7. Dependence of the sound absorption on its velocity: O_2 gas. (*Kneser* [15], p. 149)

sound absorption in oxygen, given in a circular plot. The behavior required by theory is very nearly attained. This means that there exists only one single relaxation time, *i.e.* one simple relaxation body. From the radius of the circle, the value of the relaxing portion of the specific heat C_i can be determined using Eq. (48). This value agrees well with the vibrational energy of oxygen calculated from spectroscopic measurements (valence vibration in the Raman spectrum) of oxygen by means of characteristic temperature. A well-defined correlation of relaxation phenomena to excitation of vibrational energy is thereby obtained. The absorption curves of CO_2 too, are explained by the relaxation of vibrational energy. Also in this case only one relaxation time appears. A relaxation of rotational energy has been found un-

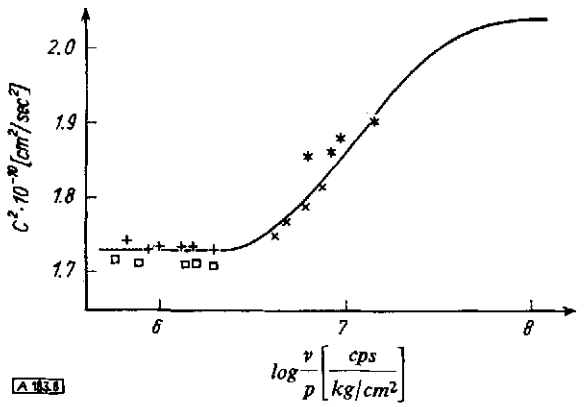


Fig. 8. Sound dispersion in H_2 gas resulting from rotational relaxation. Values given by *E. S. Stewart*, Physic. Rev. *69*, 632 (1946). (*Kneser* [15], p. 151.)

equivocally in the case of H_2 (Fig. 8). Rotational relaxation can also be observed in oxygen as well. Since the relaxation times are quite different for the excitation of vibrational and rotational energy, two separate circles

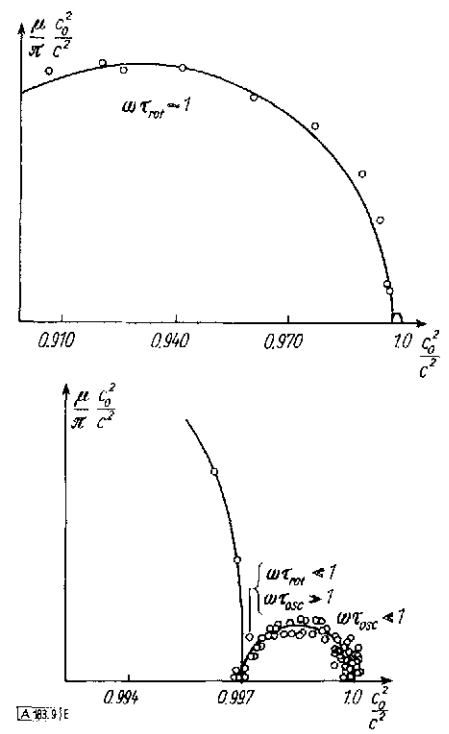


Fig. 9. Circular plot of vibrational and rotational relaxation for O_2 (*Kneser* [12], p. 178).

can be established in the circular plot in the case of oxygen. Figure 9 shows the smaller circle, which corresponds to the vibrational relaxation, as well as a portion of a larger circle corresponding to the rotational relaxation.

[13] *J. Meixner*, Ann. Physik *43*, 244 (1944).

What conclusions can now be drawn from measurements of sound absorption? We observe immediately that the excitation of vibrational energy requires a certain time lapse. Since an exchange of energy between gas molecules can occur only in the relatively very short period of time involved in collision of two molecules with one another, we are led to the question, how often must one gas molecule collide with another until vibrational energy is exchanged? This means that by measuring the relaxation time and from a knowledge of the collision number (given by the kinetic theory of gases) we can obtain the number of collisions and thereby the answer to the above question through the relation

$$\tau = t \cdot z \qquad (54)$$

where t represents the reciprocal of the collisions number, *i.e.*, the average duration of impact, and z is the number of collisions survived by a vibrational quantum before being transformed into translational energy. As an example of the order of magnitude of z some values may be indicated:

Cl_2	$z_{osc.} = 4.2 \times 10^4$	(20 °C)
O_2	$z_{osc.} = 2 \times 10^7$	(20 °C)
N_2	$z_{osc.} = 2.7 \times 10^3$	(20 °C)

For rotational relaxation, z lies between 3 and 10 for diatomic molecules. Investigations to date have shown, furthermore, that neither rotational nor vibrational maxima show great deviations from the theoretically expected behavior. This means that only one relaxation time occurs, *i.e.* only one relaxing process is observed. In the case of molecules with several degrees of freedom*, of the vibration energy, experiments have shown that the excitations which occur practically always involve the vibrational degree of freedom corresponding to the frequency.

Here we may consider briefly the relaxation phenomena involved in the exchange of rotational and vibrational energy, factors which today have gained great importance. Hot combustion gases stream from rocket combustion chambers through a Laval-nozzle so quickly that, to a great extent, no exchange of energy can occur, *i.e.* the temperature adjustment of the individual degrees of freedom can no longer follow the changing pressure conditions in the nozzle. These processes are of importance for the calculation of thrust data.

Investigations in the gaseous state can be facilitated if instead of varying the frequency over a large range (this requires rather complicated apparatus), the relaxation time can itself be altered by increasing the density of the gas or its pressure. Since vibrational relaxation is essentially a question of the collisions number required to exchange vibrational energy, the relaxation time can be decreased by increasing the collisions number (as is always possible by increasing the pressure). It is quite easy, to accumulate extensive experimental data which can be converted to standard pressure. Strangely enough, the relationship, that the reciprocal relaxation time is proportional to the pressure, holds time not only in the gaseous state, but also in the liquid state. In this sense at least, the liquid can be interpreted as highly compressed gases. We thus arrive at a discussion of relaxation phenomena in liquids.

3. Mechanical and Dielectric Relaxation Phenomena in Liquids

In this section we will discuss first of all the results of mechanical relaxation phenomena and then deal with dielectric relaxation phenomena in liquids. The experimental methods for investigating mechanical relaxation properties of liquids are analogous to those used for gases [12].

Whereas relaxation phenomena in gases generally involve simple relaxation processes, which can be described by a single relaxation time, or in which the individual relaxation processes were independent of one another and correspond to a definite relaxation time (*e.g.* in the case of oxygen where rotational and vibrational relaxation correspond to separate relaxation), in liquids it is very frequently observed, in mechanical and more particularly in dielectric relaxation, that the relaxation curves are no longer characterized by a single relaxation time. Here we have in general to deal with phenomena which cannot be interpreted without assuming a large number of relaxation times; even with a continuous distribution. In this case, we can no longer postulate with certainty that the relaxation times and the corresponding processes are independent of one another. Although these phenomena are actually treated as if this were the case, in more detailed treatments of the distribution of relaxation times, the question of independence of the individual processes should either be examined or the assumption of independence should always be borne in mind.

The relaxation curves for liquids can be represented in a manner analogous to those for the gaseous state. After absorption measurements have been made, the relaxation value can be determined expediently from the maximum value of the absorption μ, and the relaxation time can be determined from the frequency of the maximum of the μ curve. The analogous equations for the case of relaxation phenomena in gases are valid [*].

We will now discuss some examples in which it was possible to find a well-defined correlation between the molecular physical processes and the observed relaxation curves and the relaxation times calculated from the latter. Disregarding processes in which chemical reactions (such as dissociation and solvation processes) occur, and which in general will not be treated here, essentially two processes have been observed. In the one case, analogous to the processes in the gaseous state, there is the process of relaxation of vibrational energy (vibrational relaxation). Following a proposal by *Herzfeld* [14], liquids, in which vibrational relaxation is observed and which can be treated by analogy to relaxation phenomena in the gaseous state, can be designated as "Kneser-liquids," since *Kneser* was the first to apply the theory developed for gases to the case of liquids [15]. The theoretical treatment, similar to the theory of vibrational relaxation in gases, proceeds from the assumption that only bimole-

[*] $\mu_{max} = \frac{\pi}{2} \cdot \frac{\varepsilon}{\sqrt{1-\varepsilon}}$ (55) $\qquad \nu_{max} = \frac{1}{2\pi\tau\sqrt{1-\varepsilon}}$ (56)

[14] *K. F. Herzfeld* and *T. A. Litovitz:* Absorption and Dispersion of Ultrasonic Waves. Academic Press, New York 1959.

[15] *H. O. Kneser*, Ergebn. exakt. Naturwiss. 22, 121 (1949).

cular and to a limited extent, trimolecular collisions, are involved in the exchange of vibrational energy. Thus, the collision number in the liquid is considered proportional to the number of collisions in the gas times the density of the liquid. Cooperative behavior of a large group of molecules does not appear to be essentially connected with relaxation behavior. *Litovitz* [16] carried out a theoretical treatment of the temperature and pressure dependence of relaxation behavior; this stands in very good agreement with experiment.

Carbon disulfide, for example, has been thoroughly investigated. Figure 10 shows the absorption of sound in CS_2 at two temperatures. Table 2 shows the qualitative

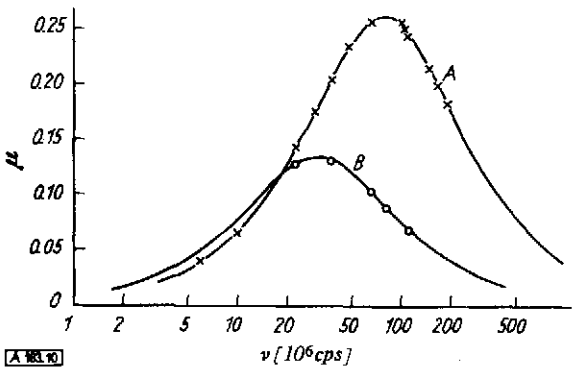


Fig. 10. Sound absorption in CS_2. A at 25 °C; B at 63 °C (*Davies* and *Lamb* [17], p. 155)

agreement of the relaxation times for vibrational relaxation in the liquid and in the gaseous state, taking into account the ratio of densities, and simultaneously confirms the idea that a retarded attainment of the vibration temperature is the cause of sound relaxation phenomena in liquids.

Table 2. Relaxation times and density ratios of several compounds in the gaseous state (τ_g) and liquid state (τ_l) (after *Herzfeld*)

Compound	$\tau_g \times 10^8$[sec]	$\tau_l \times 10^{10}$ [sec]	τ_g/τ_l	ρ_l/ρ_g
CH_3Br	7.5	1.26	600	460
$CHCl_3$	1.35	1.3	105	320
CCl_4	2.1	1.26	170	260
$(CH_2Cl)_2$	0.5	0.495	100	320
C_6H_6	5	2.7	180	280
CS_2	72.7	28.3	260	420

The other cause for the appearance of relaxation phenomena is observed in liquids whose molecules can occur in two or more forms. This is the case, for example, with cyclohexane derivatives, which can exist in two different chair forms (Fig. 11) or for rotational isomers, *e.g.* triethylamine (Fig. 12) or 2-methylbutane. The condition for the occurrence of ultrasonic relaxation in these isomers is related to the fact that both forms possess a noticeable difference in energy. Actually it is a

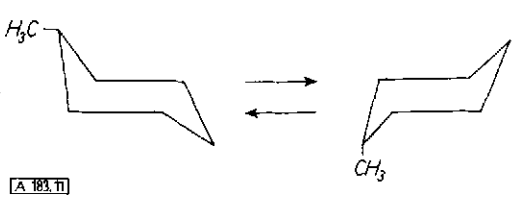


Fig. 11. The two chair forms of methylcyclohexane

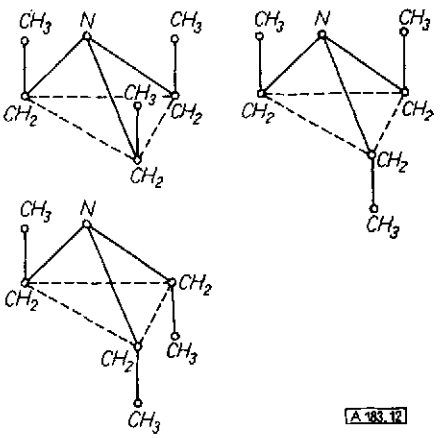


Fig. 12. Rotational isomers of triethylamine (schematic); (*Davies* and *Lamb* [17] p. 153)

phenomenon completely analogous to vibrational relaxation except that the "vibration" corresponds to a "flop-over" of the one form into the other, involving the crossing of a potential barrier, associated with a hindrance potential, or, (in the language of reaction kinetics) an activation energy. This causes an important difference in the temperature dependence of the collision number necessary in order to accomplish intramolecular conversion or inversion. In general one expects an exponential temperature dependence of the collision number z necessary for conversion.

$$z = z_0 \cdot e^{-V/RT} \qquad (57)$$

Here V is the hindrance potential. In the case of the cyclohexane derivatives or the indicated rotational isomers it amounts to the order of magnitude of some kcal/mole The difference compared with vibrational relaxation, for which the same process is principally responsible, lies in the fact that here the quantity V is generally very much smaller than the thermal energy RT. This results in the weak temperature dependence of the collisions number necessary for vibrational excitation. Whereas pure cyclohexane shows no relaxation phenomena, since both chair forms possess the same energy, relaxation investigations of methylcyclohexane reveal an energy difference of 1.6 kcal./mol between the two forms. In the case of triethylamine, shown in Fig. 12, three rotational isomers between which transitions can occur are possible. Figure 13 shows the temperature dependence of ultrasonic wave absorption.

We will not discuss here the results which can be obtained from mechanical relaxation measurements on solutions and the various types of relaxation curves which thereby result. The reader is referred to reviews by *Davies* and *Lamb* [17] and *Sette* [18]. With regard to liquids, which contain larger molecular aggregates, and to the consequent temperature-dependent structural effects and their influence on mechanical

[16] *T. A. Litovitz*, J. chem. Physics *26*, 469 (1957).

[17] *R. O. Davies* and *J. Lamb*, Quart. Rev. (Chem. Soc., London) *11*, 134 (1957).

[18] *D. Sette:* Handbuch der Physik. Springer, Berlin-Göttingen-Heidelberg 1961, Vol. XI/1, p. 275.

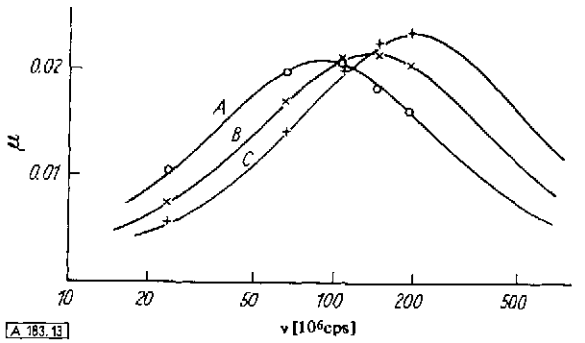


Fig. 13. Ultrasonic wave absorption in triethylamine: A at 25 °C, B at 35 °C, C at 45 °C. (*Davies* and *Lamb* [17], p. 153)

relaxation behavior, reference should be made to *Sette*'s review [18]. In the same paper, results of studies of the pressure-dependent relaxation behavior of water are to be found. Investigations concerning sound absorption in electrolytes, have been summarized by *Tamm* [19]. This topic is of significance in the theory of electrolyte solutions.

The first theoretical treatment [*] of dielectric relaxation phenomena of liquids is connected with the name of *Debye* [20]. He derived the following equations for the frequency dependence of the real and imaginary parts of the dielectric constant:

$$\varepsilon' = \varepsilon_\infty + \frac{\varepsilon_0 - \varepsilon_\infty}{1 + \omega^2 \tau^2} \tag{58}$$

$$\varepsilon'' = \frac{(\varepsilon_0 - \varepsilon_\infty)\,\omega\tau}{1 + \omega^2 \tau^2} \tag{59}$$

Figure 14 shows typical curves for the dependence of the real and imaginary parts of the dielectric constant on the frequency. Furthermore, Figure 14 shows the dependence of tan δ on the frequency.

Here it can be seen that the maximum of the tan δ curve does not coincide with the maximum of the ε'' curve. Eqs. (58) and (59) can also be obtained from the general relaxation equation (14), indicated in the first section, by a simple transformation. The *Debye* equations can also be represented in the *Cole-Cole* plot by eliminating ωτ. The equations are only valid for systems which possess a single relaxation time and are, therefore characterized by a single relaxation process.

Debye has already given a molecular physical interpretation of the dielectric relaxation phenomena. A sphere (with its solvation shell) possessing a dipole moment and moving within a viscous medium in accordance with *Stoke*'s Law serves as a model. Here, the viscosity of the solvent is used for the viscosity term. (However, *Debye* always speaks of an intrinsic or microscopic viscosity, in contrast to the macroscopic viscosity measured by the usual viscosimetric methods. This problem is treated by *Smyth* [21]). The relation between the

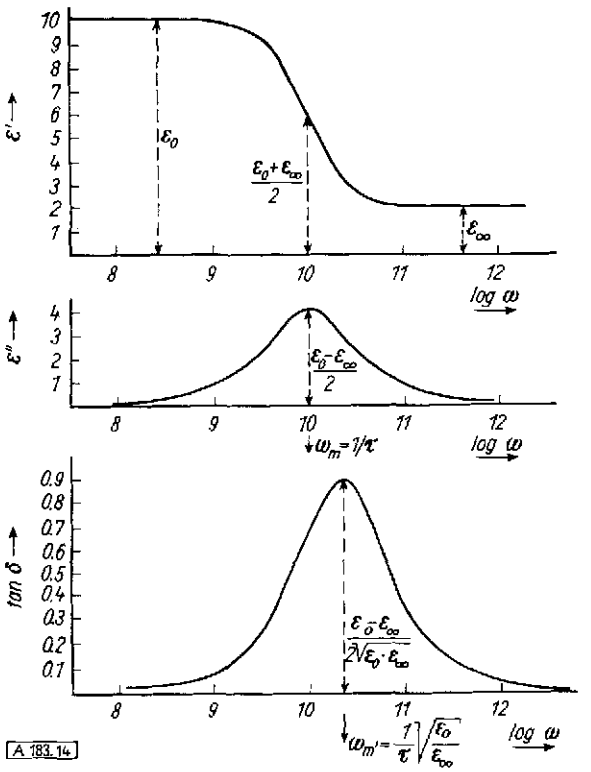


Fig. 14. Dependence of the real and imaginary parts of the dielectric constant as well as tan δ on the frequency (*Böttcher* [33])

relaxation time τ, the viscosity η of the solvent, and the dimension of the sphere, *i.e.* of the dipole molecule is given, according to *Debye* by the following relationship

$$\tau = \frac{4\pi a^3 \eta}{kT} \tag{60}$$

(a = radius of the sphere). This model has been used many times for the interpretation of dielectric relaxation measurements. However, it soon became evident that the resulting molecular diameters very often did not coincide with values for molecular diameters obtained by other ways. Nevertheless, *Meakins* [22] was able to show that the *Debye* equation acquired a higher degree of validity when the dipole molecule is larger in comparison to the solvent molecule.

Eyring and *Kauzman* [23] have proposed a quite different approach to the molecular-physical interpretation of dielectric relaxation times. They regard the relaxation process as being caused by a "jump" process of orientation in the sense of the theory for absolute reaction rates developed by *Eyring*.

The Eyring-Kauzman concept is as follows: The molecular dipole occurs in a potential trough. A "rotation" into the direction of an applied electric field, or reorientation into the position corresponding to the thermodynamic state of equilibrium after removing the field, is only possible by overcoming a potential barrier $\Delta G^{\neq}$. The height of this potential barrier is regarded as the activation energy for the "reaction" rotation of the dipole. The dipole oscillates back and forth in the potential trough with a certain frequency which, according to Eyring-Kauzman, is equal to $\frac{kT}{h}$. At

[19] *K. Tamm*, Handbuch der Physik. Springer, Berlin-Göttingen-Heidelberg 1961, Vol. XI/1, p. 202.

[*] Concerning methods of measurement in the high-frequency and microwave range for the determination of the real and imaginary parts of the dielectric constant, see: Discussions of the Faraday Society, "Dielectrics" (1946); *F. H. Müller* and *C. Schmelzer*, Naturwissenschaften *25*, 359 (1951); Handbuch der Physik. Springer, Berlin-Göttingen-Heidelberg 1956, Vol. XVII; *C. G. Montgomery:* Technique of Microwave Measurements. McGraw-Hill 1947; and other publications cited.

[20] *P. Debye:* Polare Molekeln. Hirzel, Leipzig 1929.

[21] *C. P. Smyth:* Dielectric Behavior and Structure. McGraw-Hill, New York-Toronto-London *1955*; J. physic. Chem. *58*, 580 (1954).

[22] *R. J. Meakins*, Trans. Faraday Soc. *54*, 1160 (1958).

[23] *S. Glasstone, K. J. Laidler*, and *H. Eyring:* Theory of Rate Processes. McGraw-Hill, New York *1941*; *W. Kauzman*, Rev. mod. Physics *14*, 12 (1942).

each $e^{\Delta G^{\neq}/RT}$-th oscillation, it is able to jump over the potential barrier $\Delta G^{\neq}$ and assume a new orientation. The potential trough, which corresponds to a directed orientation, lies lower than that of the random orientation. As a consequence, the potential barrier to be overcome is greater for the deorientation in the case of an applied field and thus the probability of deorientation is smaller when the electric field is applied. On the average, there results an excess of orientated molecules and thus causing polarization of the dielectric. After turning off the field, reorientation is caused only by the difference in the population at each position, since the potential barrier is equal in both directions. The temperature dependence of the relaxation time then follows from the Eyring-Kauzman theory as:

$$\tau = \frac{h}{k \cdot T} \cdot e^{\Delta G^{\neq}/RT} = \frac{h}{k \cdot T} \cdot e^{\Delta H^{\neq}/RT} \cdot e^{-\Delta S^{\neq}/R} \quad (61)$$

Taking logarithms, and by transposing, we get:

$$\ln \tau \cdot T = \frac{\Delta H^{\neq}}{R} \frac{1}{T} + \ln \frac{h}{k} - \frac{\Delta S^{\neq}}{R} \quad (62)$$

From which it is evident that from a knowledge of the temperature dependence of the relaxation time, not only does the quantitiy $\Delta G^{\neq}$ correspond to the free enthalpy of activation of the orientation process and is a measure of the height of the potential barrier, but also that the activation enthalpy and the activation entropy for the orientation process can be calculated. The Eyring-Kauzman concept contains two hypotheses, whose validities are doubtful:

1. The heights of the potential barriers may not fluctuate during an orientation process. The basis of a theory which allows for the fluctuation of the potential trough has been attempted by *Holzmüller* [24].

2. The validity of the frequency factor $\frac{k \cdot T}{h}$ without which calculation of the activation entropy is impossible. This factor, which arises from the Eyring theory for calculating rate constants of gas reactions, was adopted in the theory of an orientation process in which an initially unknown factor $\varkappa$ was set equal to unity [23]. Up till now, no agreement has been reached regarding the validity of this frequency factor for an orientation process, although *Schallamach* [25] argues for its validity.

In many cases, the experimentally observed relaxation curves, *i.e.* the frequency dependence of the real and imaginary parts of the dielectric constant, cannot be described by the *Debye* equations. A leveling off of the dispersion curve and a broadening of the absorption curve is observed. In the circular plot (Fig. 15), the

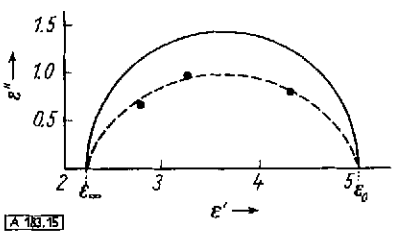


Fig. 15. *Cole* circle for n-octylbromide at 25 °C (*E. J. Hennelly, W. M. Heston*, and *C. P. Smyth*, J. Amer. Chem. Soc. 70, 4102 (1948))

values still lie on the arc of a circle, but its centre no longer lies on the abscissa. *Cole* and *Cole* [26], who deal with this behavior, modify the *Debye* equations and the corresponding equation for circular plot in the following way:

$$\underline{\varepsilon} = \varepsilon_{\infty} \frac{\varepsilon_0 - \varepsilon_{\infty}}{1 + (i\omega\tau)^{(1-\alpha)}} \quad (63)$$

The parameter α is meant to be a measure of the distribution of relaxation times, and can be derived from the circular plot. Therefore, the broadening of the absorption curve is interpreted by the assumption of a distribution of the relaxation times. So far, the *Cole-Cole* interpretation of the distribution of relaxation times has been applied mostly to the evaluation of relaxation curves. However, there are a whole series of other proposals for interpretating the deviation from the Debye behavior. *Wagner* [27a] was the first who attempted to explain deviations from normal dispersion behavior by considering the distribution of relaxation times about a focal point. His distribution function for the relaxation times is

$$f(\tau)\, d\tau = \frac{(\varepsilon_0 - \varepsilon_{\infty})}{\varepsilon_{\infty}\sqrt{\pi}} e^{-b^2 z^2} dz \quad (64)$$

where $z = \ln \tau/\tau_0$

Corresponding to this distribution function, or to the parameter b determining the extent of distribution, we obtain (Figs. 16 and 17) the dependence of the real and imaginary parts of the dielectric constants on the logarithm of the frequency. The distribution of the relaxation time itself is given in Fig. 18.

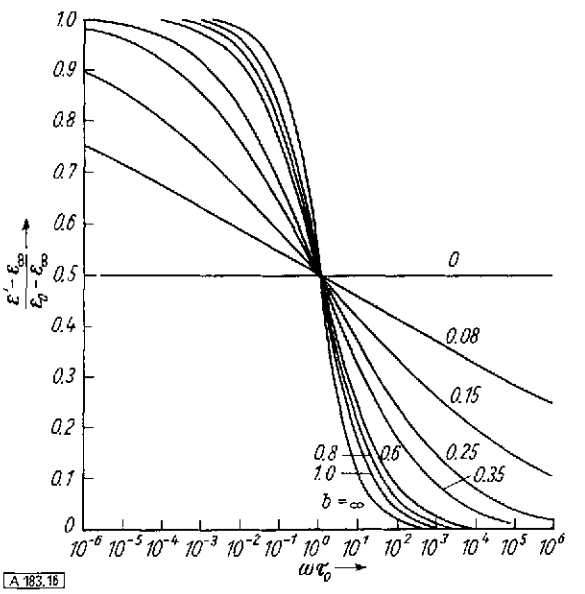


Fig. 16. Graphical representation of the dependence of the leveling off of the dielectric constant on the distribution constant b (*Wagner* and *Yager* [27b])

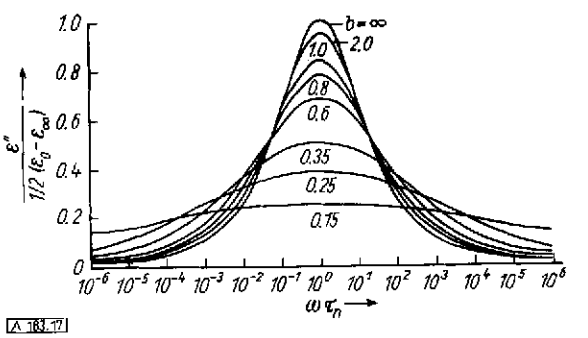


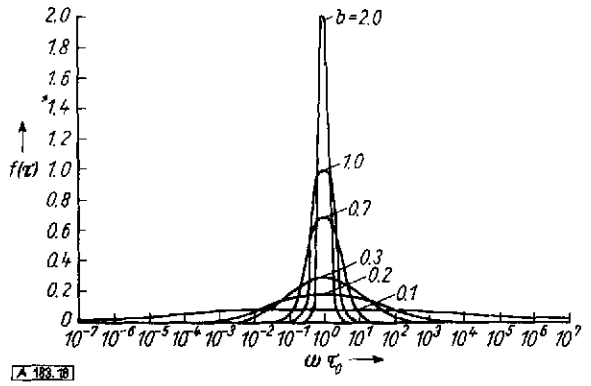
Fig. 17. Graphical representation of the dependence of the leveling off of the angle of loss on the distribution constant b (*Wagner* and *Yager* [27b])

[24] *W. Holzmüller*, Physik. Z. *41*, 499 (1940).

[25] *A. Schallamach*, Trans. Faraday Soc. *42A*, 166 (1946).

[26] *K. S. Cole* and *R. H. Cole*, J. chem. Physics *9*, 341 (1941).

[27] (a) *K. W. Wagner*, Ann. Physik *40*, 817 (1913);
(b) *K. W. Wagner* and *W. A. Yager* Physics *7*, 434 (1936).



A 183.18

Fig. 18. The influence of the distribution constant b on the density of distribution of relaxation times (*Wagner* and *Yager* [27b])

Gevers [28] and *Fröhlich* [29] suggest a different distribution, in which the distribution function has a practically constant value between two τ values, but has the value zero outside this interval. If, in the sense of the Eyring theory, the potential barrier related to τ_0 is designated by H_0, then the τ values for homogeneous distribution, disregarding dipole interactions, vary between τ_1 and τ_0:

$$\tau_1 = \tau_0 \cdot e^{V_0/k \cdot T} \tag{65}$$

$$\tau_0 = \frac{h}{k \cdot T} \cdot e^{-\Delta S/k} \cdot e^{H_0/k \cdot T} \tag{66}$$

The height of the potential barrier therefore fluctuates between H_0 and $H_0 + V_0$. The distribution function is then:

$$f(\tau) = (\varepsilon_0 - \varepsilon_\infty)\frac{k \cdot T}{V_0} \cdot \frac{1}{\tau} \text{ für } \tau_0 < \tau < \tau_1 \tag{67}$$

In this distribution, the *Debye* equations now have following forms:

$$\varepsilon'(\omega) - \varepsilon_\infty = (\varepsilon_0 - \varepsilon_\infty)\left(1 - \frac{kT}{2V_0} \ln \frac{1+\omega^2\tau_1^2}{1+\omega^2\tau_0^2}\right);$$

$$\varepsilon''(\omega) = (\varepsilon_0 - \varepsilon_\infty)\frac{kT}{V_0}\left[\arctan \omega\tau_1 - \arctan \omega\tau_0\right] \tag{68}$$

The deviation range of the potential barrier, *i.e.* V_0, can be obtained from the value of the maximum of ε'' using the following equation:

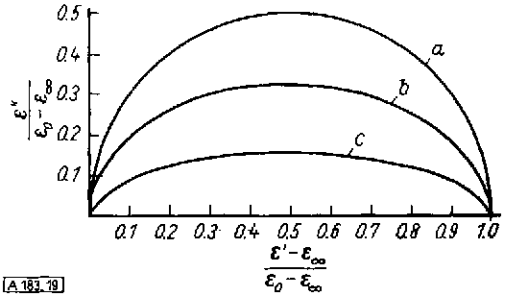
$$\varepsilon''_{max} = (\varepsilon_0 - \varepsilon_\infty)\frac{kT}{V_0}\left[\arctan e^{\frac{1}{2}\frac{V_0}{kT}} - \arctan e^{-\frac{1}{2}\frac{V_0}{kT}}\right] \tag{69}$$

The ratio of both limiting relaxation times can be determined from the equation:

$$\frac{\varepsilon''(\omega)}{\varepsilon''_{max}} = \frac{\arctan \frac{\omega}{\omega_m}\sqrt{\frac{\tau_1}{\tau_0}} - \arctan \frac{\omega}{\omega_m}\sqrt{\frac{\tau_0}{\tau_1}}}{\arctan \sqrt{\frac{\tau_1}{\tau_0}} - \arctan \sqrt{\frac{\tau_0}{\tau_1}}} \tag{70}$$

It is interesting that this representation is only affected outside the range of main absorption by changes in the pattern of the barrier height H. Figure 19 shows the normalized ε'' curve as a function of ε' for three values of V_0.

Bergmann [30a] was able to show that the Fröhlich curve can be approximated closely by an ellipse. On this assumption, *Higasy*, *Bergmann*, and *Smyth* [30b] derived a relationship between the *Fröhlich* parameter V_0 and the *Cole* parameter α.



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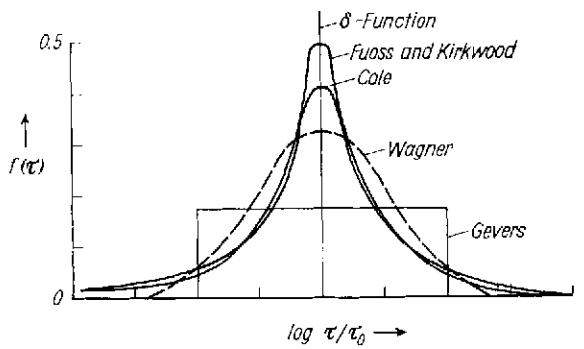
Fig. 19. Normalized Fröhlich curves for a) $V_0 = 0$ kT, (Debye circle) b) $V_0 = 4$ kT c) $V_0 = 10$ kT

An additional distribution function for relaxation times was specified by *Fuoss* and *Kirkwood* [31], whose equation reads:

$$\varepsilon''(\omega) = \varepsilon''_{max}\frac{1}{\cosh \ln \frac{\omega_{max}}{\omega}} \tag{71}$$

It leads to:

$$\frac{\varepsilon^* - \varepsilon_\infty}{\varepsilon_0 - \varepsilon_\infty} = \frac{1}{1 + i(\omega\tau_0)^\beta} \tag{72}$$



A 183.20

Fig. 20. Various distribution functions. Density of the relaxation times on a logarithmic scale (*Müller* and *Schmelzer* [11], p. 384)

The various distribution functions proposed are compiled in Fig. 20. *Poley* [32] related the distribution parameter β of the Fuoss-Kirkwood equation and the parameter α of the Cole-Cole distribution. It holds to a first approximation [33]:

$$\beta \cdot \sqrt{2} = 1 - \alpha / \cos \frac{(1-\alpha) \cdot \pi}{4} \tag{73}$$

A further attempt to describe the deviation from Debye behavior was undertaken by *Perrin* [34]. He considers nonspherical molecules as ellipsoids and introduced three relaxation times corresponding to the three major axes of an ellipsoid. According to *Fischer* [35], the relationship between the relaxation time and molecular dimensions is given by

$$\tau = \frac{4\pi\eta^* f a b c}{kT} \tag{74}$$

where a, b and c are the semiaxes of the ellipsoid, f is a structure coefficient and $\eta^* = 0.36\ \eta$. In the case of α,ω-dibromoalkanes, the dielectric relaxation behavior has been

[28] *M. Gevers*, Philips Research Rep. *1*, 279 (1946).

[29] *H. Fröhlich:* Theory of Dielectrics. Oxford University Press, Oxford 1958.

[30a] *K. Bergmann*, Ph. D. Thesis, Universität Freiburg 1957.

[30b] *K. Higasy*, *K. Bergmann*, and *C. P. Smyth*, J. physic. Chem. *64*, 880 (1960).

[31] *R. M. Fuoss* and *J. G. Kirkwood*, J. Amer. chem. Soc. *63*, 385 (1941).

[32] *J. Ph. Poley*, quoted after *C. J. F. Böttcher* [33], p. 371.

[33] *C. J. F. Böttcher:* Theory of Electric Polarization. Elsevier Publ. Co., Amsterdam 1952.

[34] *F. Perrin*, J. Physique Radium *5*, 497 (1934).

[35] *E. Fischer*, Physik. Z. *40*, 645 (1939).

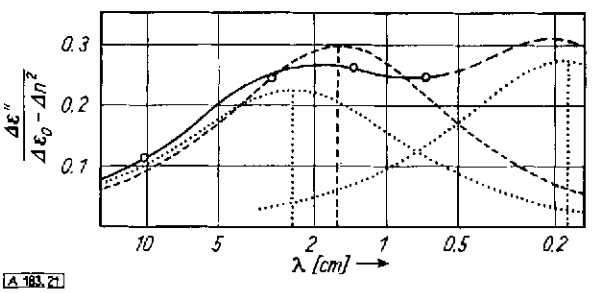
described by *Price* with the aid of a Fuoss-Kirkwood distribution [36].

Having now discussed the general attempts for the treatment of dielectric relaxation phenomena in liquids, some experimental results will now be considered. Evaluation of the temperature dependence of the relaxation times obtained from dielectric measurements according to *Eyring* and *Kauzman* almost invariably indicates negative activation entropy (this holds only if the factor $\frac{k \cdot T}{b}$ is valid). Since, in line with the model, one associates the orientation process in the Eyring-Kauzman concept with a liberation of the dipole molecule from its solvation shell, the occurrence of negative activation entropy (corresponding to an increase in the order of the activated state) was hard to understand. *Müller* [37] and independently *Levi* [38] have given a qualitative explanation. They assume that in order that the dipole can rotate, the solvent molecules they have to make room by "crowding together." This "crowding together" corresponds to a state of higher order and therefore furnishes an explanation of the occurrence of negative activation entropy.

Although at present, the Eyring-Kauzman theory offers the best basis for a model interpretation of the dielectric relaxation processes in liquids, it has not been possible to obtain results of general validity on the basis of this theory. The primary reason for this may be that the model is oversimplified and that, so far, no theory of liquids exists which involves all physical phenomena. Despite the difficulties, however, in individual cases, model interpretation of τ-values resulting from dielectric relaxation measurements have been successful.

In dilute solutions, in which a dipole-dipole interaction is probably largely non-existent, *Zeil* and co-workers [39] were able to point out qualitative relationships between the activation quantities derived from the temperature dependence of the relaxation time and the intermolecular forces between solvent molecules and dipole molecules on the one hand, and the state of order, described by the free volume of the solvent, on the other hand. The activation enthalpy is augmented with an increase in the London and Debye forces between solvent molecule and dipole molecule. The magnitude of the negative activation entropy increases with increasing free volume of the solvent. The following model representation was proposed: In the activated state, the dipole molecule is desolvated and the solvate molecules occupy free space (holes) in the solvent. The energy necessary for the liberation of the solvate molecules, reduced by a value involving by the inclusion of solvate molecules in the holes, corresponds to the activation enthalpy. The increase in order derived from incorporation of solvate molecules into the holes of the solution will be all the greater, the more holes available. This model holds for densely packed solvents and for dipole molecules which are very large compared to the solvent molecules in the Debye model of viscous rotating spheres, in which only the translational process in the solvent, and thus the viscosity, play decisive roles.

Klages et al. [40] succeeded in various cases in satisfactorily interpreting a broadeuing of the relaxation maxima by assuming two discrete relaxation times. By superposition of two Debye curves and thus of two discrete relaxation times, they were able to satisfactorily explain measurements made on aliphatic chlorinated hydrocarbons. Experimental results with aniline derivatives were also explained by this method. Figure 21 shows how the data can be interpreted by superposition of two Debye terms. One relaxation time corresponds to an intrinsic mobility of the NH_2 group, the greater relaxation time to overall rotation of the molecule. In addition,



A 183.21

Fig. 21. Approximation to the absorption behavior of *p*-toluidine by a Debye-term (- - - - -) or by two Debye terms (————) (*Kramer* [40], p. 976)

the dipole moment can be resolved into partial moments, *i.e.* the dipole component closely associated with the rigid part of the molecule can be separated from the dipole component of the mobile group.

A very interesting attempt to interpret the extremely short relaxation times and the deviation from Debye behavior of dilute solutions of diphenyl compounds through a superposition of a Debye term by a Fröhlich term has been reported by *Hufnagel* [41].

A very comprehensive analysis of a relaxation time distribution originated with *Schroeder* [42]. *Meckbach* [43] investigated pure α-bromonaphthalene and interpreted the deviation from Debye behavior by superposition of several relaxation times, conditioned by the ellipsoid structure of the molecule according to *Perrin* [34], but *Schroeder* showed that the broadening of the ε'' curves for α-bromonaphthalene in carbon tetrachloride is dependent on concentration. His extensive measurements embrace practically the whole dispersion region. The results (Table 3) can be very well represented by a Fröhlich distribution.

Table 3. Concentration dependence of the width of the "ε" curves as well as the V_0 values of α-bromonaphthalene in CCl_4

Concentration, weight percentage	$\frac{\log(\omega_0/\omega_1)}{1.14}$	τ_1/τ_0	V_0
1	1.02 ± 0.02	1.5 ± 0.5	0.4 kT
5	1.04 ± 0.02	2.2 ± 0.5	0.8 kT
10	1.05 ± 0.01	2.5 ± 0.2	0.9 kT
20	1.09 ± 0.03	3.5 ± 0.7	1.2 kT

[36] *A. H. Price*, Bull. Groupment AMPERE (C. R. IX Coll.) *1960*, 71.

[37] *F. H. Müller*, Kolloid-Z. *134*, 215 (1953).

[38] *D. L. Levi*, Trans. Faraday Soc. *42A*, 152 (1947).

[39] *W. Zeil, H. Fischer, W. Metzger, K. Wagner*, and *J. Haase*, Z. Elektrochem. *63*, 1110 (1959); *W. Zeil, J. Haase*, and *O. Stiefvater*, ibid., *65*, 616 (1961).

[40] *O. Kramer*, Z. Naturforsch. *15a*, 974 (1960).

[41] *F. Hufnagel*, Z. Naturforsch. *15a*, 733 (1960).

[42] *R. Schröder*, Z. Naturforsch. *12a*, 731 (1957).

[43] *W. Meckbach*, Z. Physik *131*, 331 (1952).

Table 3 contains the relative broadening compared with a Debye curve. The value log (ω_0/ω_1) is a measure of the width of an ε'' curve. In the Debye case, it is 1.14. The table also contains the ratio of the two relaxation times, between which a continuous spectrum of relaxation times exists, as well as the range of variation V_0 of the height of the potential barrier. It shows that with increasing concentration, the variation of the potential barrier increases. *Schroeder* explains this as being due to an increasing interaction between dipole molecules without of association, since in such a case, the value of τ/η (η = viscosity) would have to increase with increasing concentration. Experimentally, the contrary was observed.

We will not go into individual investigations of systems which involve hydrogen bonding. One should refer to works by *Fröhlich* [29] or *Brown* [44] regarding the possibility of the occurrence of resonance absorption. The publications of *Müller* [37] and *Gross* [45] are recommended regarding the difficulties confronting analysis of relaxation curves where no Debye behaviour exists.

The topic of dielectric relaxation in electrolytic solutions will not be described here. In this case there occurs a further loss through ohmic conduction and the conductivity also shows dispersion. A summary is given by *Falkenhagen* [46]. More recent measurements in this area are due to *Weber* [47].

Regarding the structure of anisotropic liquids, there are interesting investigations by *Maier* and co-workers [48] on the dielectric behavior of liquid crystals (anisotropic liquids).

4. Mechanical and Dielectric Relaxation Phenomena in High Polymers [*]

Dielectric and mechanical relaxation phenomena in plastics (high polymers) will be treated together since, in contrast to the case of liquids, there are no completely different mechanisms to account for both relaxation phenomena. It is generally assumed that both the dielectric as well as the mechanical losses are caused by the same molecular physical phenomena.

If the extent of relaxation in the mechanical or dielectric region is investigated then it is evident – in contrast to gases and many low-molecular weight liquids – from the order of magnitude of the loss M'' or ε'' compared with the frequency, that a Debye curve is not obtained. The half-width of a Debye absorption curve amounts to about 1.14 frequency-decades. With high polymers, the absorption curves are considerably broader. Thus, for example, with polyoxymethylene, $[-CH_2-O-]_n$, a half-width two to two-and-a-half times as large is observed [49]. Figures 22 and 23 show the

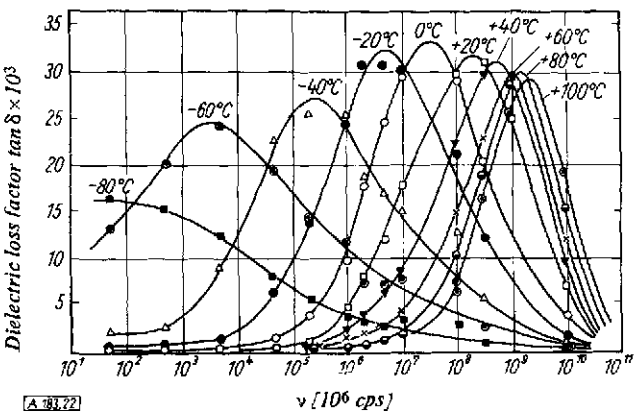


Fig. 22. Frequency curves for the dielectric loss factor (tan δ) of polyoxymethylene at various temperatures (°C) (*Thurn* [49], p. 324)

dielectric loss factor tan δ, measured with polyoxymethylene, plotted against the frequency for various temperatures and the temperature for various frequencies. One finds such more or less broad absorption curves for almost all high polymer materials. At an early stage,

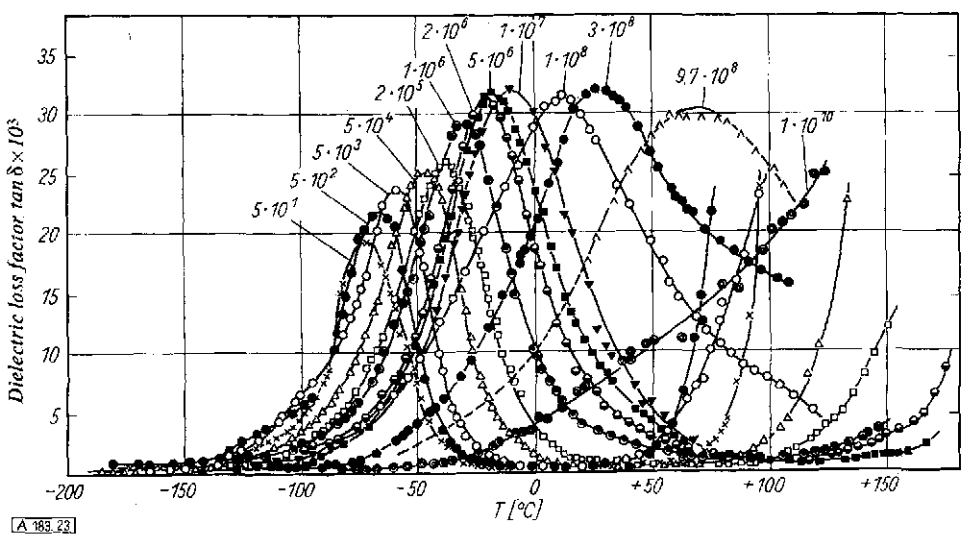


Fig. 23. Temperature curves for the dielectric loss factor (tan δ) of polyoxymethylene at different frequencies (*Thurn* [49], p. 324)

Kuhn [50] and *Smekal* [51] reached the conclusion that the cause of this is a continuous distribution of relaxation times covering a certain range, *i.e.* a continuous relaxation time spectrum. Moreover materials of more

[44] *W. Fuller Brown jr.:* Handbuch der Physik. Springer, Berlin-Göttingen-Heidelberg 1956, Vol. XVII, p. 131.

[45] *B. Gross*, Kolloid-Z. *134*, 65 (1953).

[46] *H. Falkenhagen:* Elektrolyte. 2nd. Ed., Hirzel, Leipzig 1953.

[47] *G. Weber*, Ph. D. Thesis, Universität Tübingen 1961.

[48] *W. Maier* and *G. Meier*, Bull. Groupment AMPERE (C. R. IX Coll.) *1960*, 38.

[*] For the methods of measurement consult the original literature.

[49] *H. Thurn:* Festschrift C. Wurster. Ludwigshafen 1960, p. 321.

[50] *W. Kuhn*, Z. physik. Chem. *42*, 1 (1939); Helv. chim. Acta *30*, 487 (1947); *31*, 1259 (1948).

[51] *A. Smekal*, Z. physik. Chem. *44*, 461 (1939).

complex structure, show two, or in many cases even more, maxima in the loss curves obtained by dielectric as well as mechanical relaxation measurements; we then speak of the appearance of a primary maximum and a secondary maximum. It can be concluded, therefore, that different processes, caused by a continuous distribution of relaxation times, account for this relaxation behavior. The focal points must therefore lie sufficiently far apart. If one the half-width of the loss curve of polyoxymethylene is plotted against temperature, then it is seen that it becomes smaller at increasing temperatures. This can only be explained by a temperature-dependent distribution of the spectrum of relaxation times.

If the measurements cover the total frequency range of relaxation, the distribution function for the relaxation times can be determined, in principle, using complex methods of calculation which we will not described here. Such a procedure involves great experimental difficulties in many cases. Whereas a relatively large range of frequencies can be applied in dielectric relaxation, this is scarcely possible in the case of mechanical relaxation. Comparison of the curves obtained at constant temperature and varying frequencies with those obtained at varying temperatures but at constant frequency now shows, however, that in the first case, about 8 to 12 frequency decades must be covered experimentally in order to gain a rather complete understanding of a relaxation curve, while in the second case a variation in temperature of only about 100 °C is necessary. The large frequency intervals required to evaluate the spectrum of relaxation times are necessary, because the wings of the absorption curves enter very strongly into the calculation of the distribution of relaxation times. Since only in rare cases can more than a two-decade range of frequencies be covered using the same apparatus, it is normal to investigate experimentally, the more easily accessible temperature variation of relaxation at constant frequency. However, theoretical treatment shows that for a quantitative interpretation, only the frequency variation at constant temperature may be chosen as the starting point; here, of course, for a complete understanding of the relaxation phenomena, the dependence of these curves on the temperature must also be known. *Ferry* et al. [52] developed a procedure whereby, *e.g.* from measurements of the stress relaxation or of the dynamic modulus, one can convert mathematically from an experimentally limited range of frequencies at varying temperatures to a much more extensive range of frequencies at constant temperature. This method is frequently used to deduce the relaxation-time spectrum from temperature-variation curves. It is only applicable, however, if the relaxation-time spectrum does not change with temperature. In the case of polyoxymethylene (Fig. 23), this does not apply. Furthermore, the method is not applicable if the regions of different relaxation mechanisms overlap. For example, the results of *Müller* and *Broens* [53] could not be evaluated meaningfully by Ferry's conversion procedure.

[52] *J. D. Ferry* et al., J. appl. Physics *22*, 717 (1950); J. Amer. chem. Soc. *77*, 3701 (1955).

[53] *F. H. Müller* and *O. Broens*, Kolloid-Z. *140*, 121 (1955); *141*, 20 (1955).

Because of experimental and theoretical difficulties encountered in the interpretation of the loss maxima of high polymers, another, more qualitative, method has therefore been adopted and has already indicated significant correlations between the constitution of high polymers (structure, degree of branching, polarity, partial crystallinity, etc.) and relaxation phenomena. Relaxation phenomena, and the underlying relaxation times corresponding to them, are considered to be caused by delayed orientation movements of the molecules, or of parts of the molecules, of high polymers. Molecules, or parts thereof, therefore follow the oscillation of an external field with a phase lag in both dielectric and mechanical cases. Causes of the delay in the adjusting motion are steric effects and internal fields, due to partial dipole moments or bonding moments, since the loss maxima always occur when the duration of the periods of applied field or of the applied mechanical strain becomes comparable to the relaxation time of molecular motion. One considers, therefore, the appearance of a loss maximum as an indication of a possible molecular motion [54]. From this viewpoint, measurements at constant frequency and varying temperature can be interpreted quite clearly. At a definite temperature, parts of molecules or entire molecules become mobile and can follow the applied alternating field. The temperature at which this mobility is sufficient to follow the oscillating field will depend on the frequency. The higher the frequency of the oscillating field, the more mobile the molecules or parts of molecules must be, *i.e.* the loss maxima shift to higher temperatures with increasing measurement frequency.

From the foregoing, it follows that generally, loss-maximum curves can be interpreted, although, in principle, the real parts (elastic modulus and dielectric constant) can also be utilized for evaluation. Frequently the results

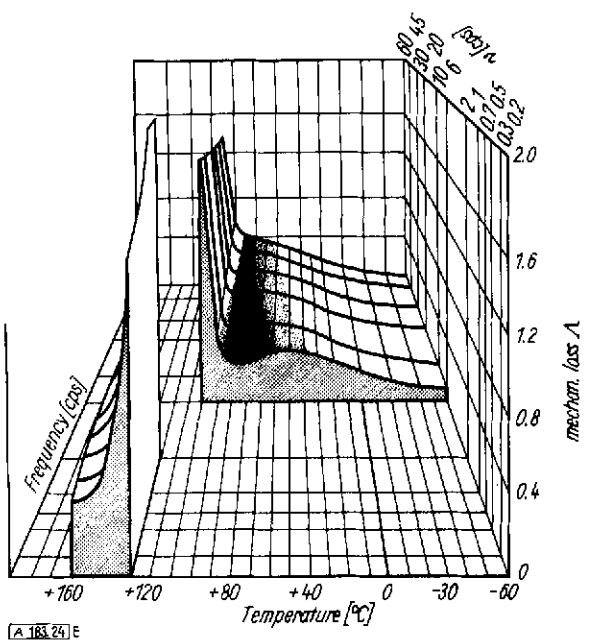


Fig. 24. Three-dimensional representation of mechanical loss of *poly*(methyl methacrylate) (*Schmieder* and *Wolf* [55])

[54] *H. Hendus, G. Schnell, H. Thurn*, and *K. A. Wolf*, Ergebn. exakt. Naturwiss. *31*, 220 (1959).

are recorded as a three-dimensional graph, *e.g.* the measurements of mechanical loss of *poly*(methyl methacrylate) by *Schmieder* and *Wolf* in Fig. 24 [55]. The results can also be interpreted in part by a sort of contour diagram: see Fig. 25.

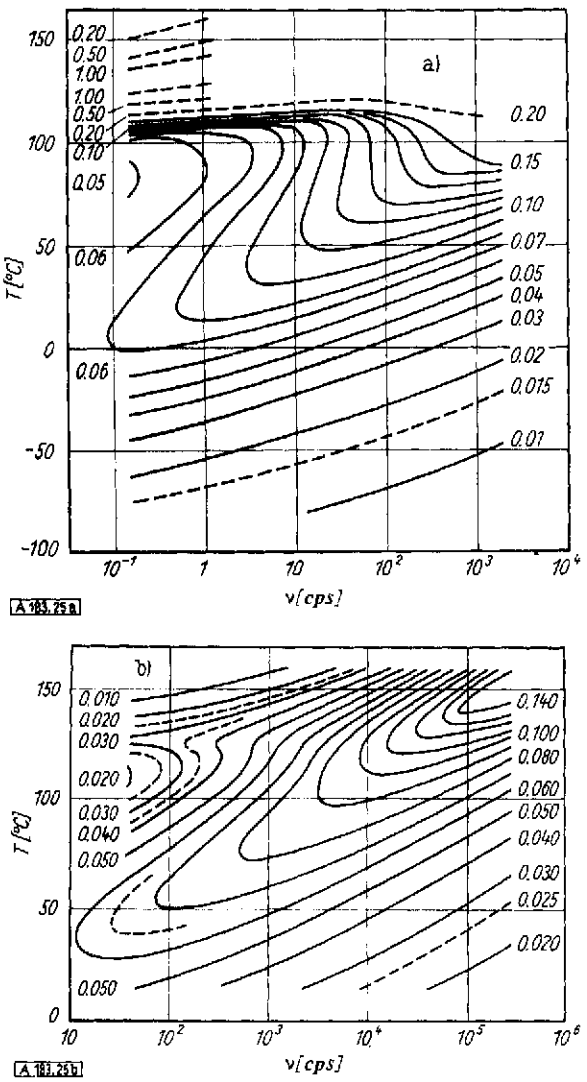


Fig. 25. Contour diagram of mechanical loss (a) and dielectric loss (b) in *poly*(methyl methacrylate); (*J. Heijboer, P. Dekking,* and *A. J. Staverman,* Kolloid Z. 148, 36 (1956))

We now wish to consider several examples, with the aid of models, where it was possible to correlate individual loss maxima with the mobility of specific parts of molecules by varying the chemical structure of the high polymers systematically.

The results obtained so far exhibit the following regularities. The shift of the loss maxima in relation to temperature and frequency shows that there are two groups of maxima: the group of so-called primary maxima has a slight temperature and frequency shift; the group of secondary maxima, which always appears at lower temperatures or at higher frequencies as the primary maxima, show a large temperature and frequency shift. In general, the primary maxima are attributed to the mobility of the main chains of the high polymers, whereas the secondary maxima are supposed to correspond to the motion of small parts of the molecule *e.g.* side-chains. Figure 26 shows how steric influences affect the temperature at which the primary maxima occur and records the measurements of *Schmieder* and *Wolf* [56] on *poly*(isobutylene) (I), *poly*(styrene) (II) and *poly*(vinylcarbazole) (III).

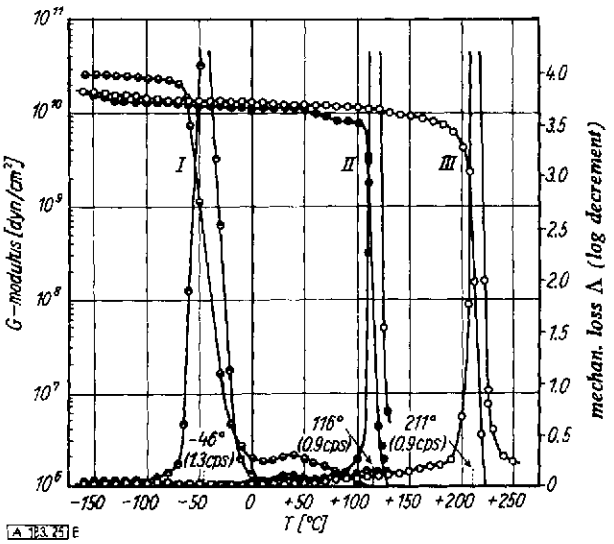
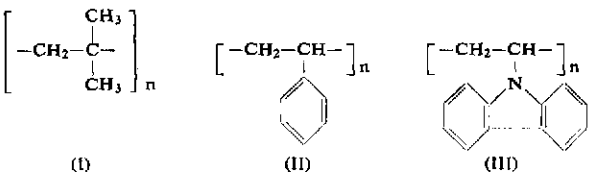


Fig. 26. Steric influence on the temperature pattern of the primary maxima, measured in *poly*(isobutylene) I, *poly*(styrene) II, and *poly*(vinylcarbazole) III (*Schmieder* and *Wolf* [56])



It is seen that, with increasing extension of the side groups, the mobility of the molecular chain, which is responsible for the loss maxima, is hindered more and more; this leads to a displacement of the maxima to higher temperatures at constant measuring frequency. At constant temperature a corresponding shift of the maxima to lower frequencies is observed.

The influence of polarity on the mobility of the main chain is seen in Table 4.

Table 4. Influence of polarity on the mobility of the main chain

	Poly(iso-butylene)	*Poly*-(vinyl methyl ether)	*Poly*-(vinyl acetate)	*Poly*-(vinyl chloride)
Dipole moment (debyes)	0	1.2	1.8	2.0
Mechanical measurement T_{max} (°C) at about 2 cps	−48 [57]	−10 [57]	+33 [57]	+90 [57]
Dielectric measurement T_{max} (°C) at 2×10^6 cps	unpolarized no maximum	+37 [58]	+122 [58]	+139 [59]

With increasing dipole moment, the maxima shift to higher temperatures, corresponding to a decrease in

[55] *K. Schmieder* and *K. Wolf*, Kolloid-Z. *127*, 65 (1952).
[56] *K. Schmieder* and *K. Wolf*, Kolloid-Z. *148*, 136 (1956).
[57] *K. Schmieder* and *K. Wolf*, Kolloid-Z. *134*, 149 (1953).
[58] *H. Thurn* and *K. Wolf*, Kolloid-Z. *148*, 16 (1956).
[59] *H. Thurn* and *F. Würstlin*, Kolloid-Z. *156*, 21 (1958).

mobility with increasing polarity. From the last two examples, one can conclude that with increasing steric hindrance and increasing polarity, the mobility of the main chain is shifted to higher temperatures. For practically equal dipole moments, the influence of the length of the side-chains is such that a shift of the maximum to lower temperature occurs with increasing length of the side-chains[60]. The literature should be consulted for information regarding cross-linked high polymers; *e.g. Wolf* et al. [54]. There the molecular weight effect is related to the temperature dependence of the primary loss maxima.

In some cases it has been possible to assign definite molecular motion to individual loss maxima in materials with several loss maxima. Besides its primary maximum of mechanical loss, *poly*(methyl methacrylate) possesses a secondary maximum lying at a lower temperature. It is interesting that in dielectric measurements, the height of the primary and secondary peaks are just the opposite of those found in mechanical measurements. This is related to the fact that in dielectric experiments the height of the maxima, *i.e.* the magnitude of loss, is dependent on the polarity (dipole moment) of the moving parts of molecules whereas in the mechanical case the mobile mass determines the height of the maximum. *Poly*-(methyl methacrylate) has the main chain with the methyl groups as the nonpolar part and the methyl ester groups as the polar part. The dielectric primary maximum must therefore be due to the motion of the methyl ester groups, while the mechanical primary maximum must be associated with the motion of the primary chain. It turns out that the mechanical secondary maximum possesses an activation energy of 18 kcal./mole and, in good agreement, the corresponding dielectric primary maximum possesses an activation energy of 21 kcal./mole, thus confirming the correlation. Several maxima were also observed for *poly*(isobutylene) [54]. The low temperature maximum is attributed to a motion of the CH_3 group. Its activation energy amounts to about 4 kcal./mole. An internal rotation or torsional vibration of the CH_3 group is considered to be the cause. A maximum at intermediate temperatures is explained by the onset mobility of the segments of the main chain. A third maximum observed at high temperatures, occurs only for very large molecular weights. It has a relatively small activation energy.

As a last example of analysis of relaxation processes in high polymers we will now consider *poly*(ethylene) *Thurn* and *Wolf* [61] measured the dielectric loss of unoxidized *poly*(ethylene) from −190 °C to + 160 °C, at frequencies between 5×10^3 and 1×10^5 cps. With the aid of a special method, they were able to measure loss factors down to 1×10^{-5}. This was necessary because only very slight partial dipole moments occur in *poly*-(ethylene), the dielectric loss thus becoming very small. At low temperatures, a loss maximum is observed in linear as well as branched *poly*(ethylene). It is not large and is attributed to a motion of the CH_2 groups. In addition, for branched *poly*(ethylene) a very intense maximum is observed at 0 °C. that is strongly dependent on molecular weight. This maximum is caused by double bonding, especially at the side chains. An important contribution can be attributed to small polarities associated with molecular assymetry, particularly at the branch points. *Thurn* and *Wolf* have also measured mechanical loss maxima of *poly*(ethylene) at a comparable frequency. Corresponding loss maxima were found; in addition, at the same frequency, the temperature patterns of the dielectric and mechanical loss maxima were largely consistent.

The examples cited were intended to show that relaxation investigations on high polymers are able to provide clues as to the molecular structure of plastics (high polymers). Furthermore, these investigations afford valuable knowledge concerning the relation between the molecular structure of materials and their technically interesting mechanical and dielectric properties.

Dielectric relaxation phenomena in crystals cannot be discussed here. A theory of dielectric relaxation in molecular crystals has, however, been developed [62]. Additional work has been done on relaxation phenomena in crystals, semiconductors and in absorbed water, *q.v.*, Conference Reports of the Groupment AMPERE for recent years. The phenomenon of molecular rotational relaxation in solids is under investigation by *Davies* [63].

Received, September 19th. 1961 [A 183/29 IE]

[60] *B. L. Funt* and *Th. Sutherland*, Canad. J. Chemistry *30*, 940 (1952); *Th. Sutherland* and *B. L. Funt*, J. Polymer Sci. *11*, 177 (1953); reviewed in [54], p. 236.

[61] *H. Thurn* and *K. Wolf*, Paper No. 247, Meeting of the Verband Deutscher Physikalischer Gesellschaften, Vienna, October 20th., 1961.

[62] *J. D. Hoffman*, Maxwell-Ampere-Conference, VIII. Coll. Ampere, Kundig, Genf 1959, p. 36.

[63] *M. Davies* et al., Bull. Groupment AMPERE (C. R. IX. Coll.) Kundig, Genf, 1960 p. 77.

COMMUNICATIONS

N-Azidodimethylamine [1]

By Dr. H. Bock and cand. chem. K. L. Kompa

Institut für Anorganische Chemie der Universität München

In the course of experiments directed towards a new synthesis of tetrazene according to the general equation

$$2\ R_2NCl + 2\ MeN_3 \rightarrow R_2N{-}N{=}N{-}NR_2 + 2\ N_2 + 2\ MeCl,$$

sodium azide was added to *N*-chlorodimethylamine in an inert solvent. After stirring the solution for several days at room temperature, we were able to isolate a 25 % yield of *N*-azidodimethylamine (1,1-dimethyltetrazadiene), which was originally expected be an unstable intermediate

$$\left\{(CH_3)_2\overset{\ominus}{\underline{N}}{=}\underline{N}{-}\underline{N}{=}\overset{\ominus}{\underline{N}} \leftrightarrow (CH_3)_2\overline{N}{-}\underline{N}{=}\overset{\oplus}{\underline{N}}{=}\overset{\ominus}{\underline{N}} \leftrightarrow (CH_3)_2\overline{N}{-}\overset{\ominus}{\underline{N}}{-}\overset{\oplus}{\underline{N}}{\equiv}N|\right\}$$

The highly explosive compound (b.p. 32 °C/11 mm.) was characterized by its molecular weight (in the gaseous state), its azide absorption bands in the infrared spectrum [2110 cm^{-1} (vs) and 1210 cm^{-1} (vs)], and by an approximate nitrogen analysis.

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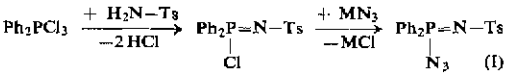
[1] 1st. Communication on inorganic azides.

A Phosphazene Azide [1]

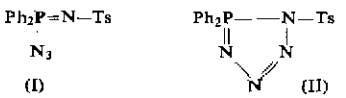
By Dr. H. Bock and Dipl.-Chem. W. Wiegräbe

Institut für anorganische Chemie
der Universität München (Germany)

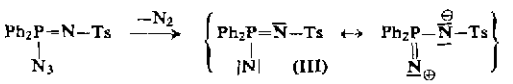
In the course of our investigations on the reactivity of the phosphorus-nitrogen double bond we have isolated *P*-diphenyl-*N*-tosylphosphazene azide (I) in 83 % yield.



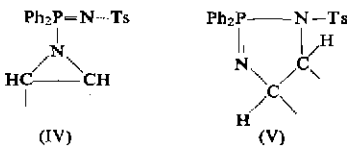
In contrast to the formal analogy with the tetrazole-azidoazomethine equilibrium [2], the infrared spectrum indicates the exclusive existence of the azide form (I); no indication was found for the phosphatetrazole structure (II).



P-Diphenyl-*N*-tosylphosphazene azide (m.p. 86 °C) decomposes above 220 °C with release of the calculated amount of nitrogen; copper as catalyst lowers the decomposition point to 120 °C. The unstable azene intermediate (III) formed on thermal decomposition can be formulated as a 1,3-dipole in a mesomeric structure [3]:



Reaction with the strained double bond of dicyclopentadiene yields a crystalline 1:1 adduct (m.p. 144 °C). Whether this compound is the aziridine (IV) formed through azene attack or the Δ^1-1,2,5-phosphadiazoline (V) formed by 1,3-dipolar addition is still undecided.



Received, November 21st, 1961 [Z 252/72 IE]

[1] 2nd. Communication on inorganic azides. 1st. Communication: *H. Bock* and *K. L. Kompa*, Angew. Chem. internat. Edit. *1*, 264 (1962).

[2] See *W. G. Finnegan, R. A. Henry*, and *E. Lieber*, J. org. Chemistry *18*, 779 (1953); *J. H. Boyer* and *E. J. Miller*, J. Amer. chem. Soc. *80*, 4671 (1959).

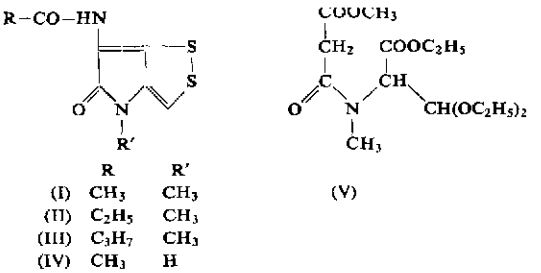
[3] See *R. Huisgen*, Naturw. Rundschau *14*, 43 (1961).

Total Synthesis of the Antibiotics Thiolutin, Aureothricin, and Holomycin

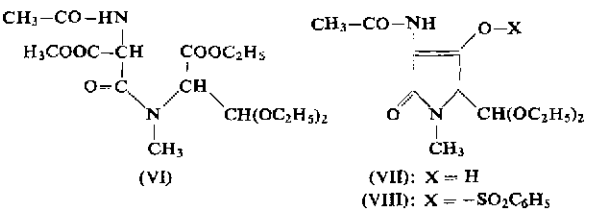
By Dr. U. Schmidt and Dipl.-Chem. F. Geiger

Chemisches Laboratorium
der Universität Freiburg/Breisgau (Germany)

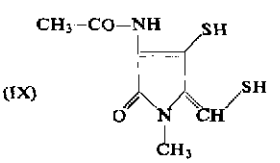
Thiolutin® (I) [1] and *aureothricin* (II) [2] are antibiotics which are active against pathogenic fungi, and Gram-negative and Gram-positive bacteria. Recently, two other closely related antibiotics, isobutyrylpyrrothin (III) [3] and holomycin (IV) [4], were isolated from *Streptomyces* species by *Bhate* et al. and by *Prelog* and a Ciba research team. Total syntheses of this group of antibiotics, which contain condensed pyrrolonedithiol ring systems, have not yet been reported.



We have carried out a total synthesis of Thiolutin®, starting from *N*-methyl-1-ethoxycarbonyl-2-diethoxyethylamine. Treating this with methoxycarbonylacetyl chloride led to the amide (V), Nitrosation and acetylative reduction led to the peptide (VI), which formed the pyrrolone (VII) on ester condensation with elimination of the methoxy carbonyl group. The enolic hydroxyl group in the 4-position reacted smoothly with benzenesulfonyl chloride to form (VIII).



When the sulfonate (VIII) was allowed to react with NaSH in alcohol, dihydrothiolutin (IX) was formed and was then dehydrated with iodine to yield Thiolutin (I). The conversion of natural Thiolutin into aureothricin and isobutyropyrrothin by hydrolysis of the amide group and acylation has already been reported [5]. Holomycin was synthetized analogously starting from 1-ethoxycarbonyl-2-diethoxyethylamine.



Received, February 21st, 1962 [Z 242/79 IE]

[1] *W. D. Celmer* and *J. A. Solomons*, J. Amer. chem. Soc. *77*, 2861 (1955). Angew. Chem. *66*, 745 (1954). Synopsis: The Merck Index. 7th. Ed., Rahway, N. J., U.S.A. 1961, p. 1038.

[2] *H. Umezawa* et al., Jap. Med. J. *1*, 512 (1948). Synopsis: The Merck Index. 7th. Ed., Rahway, N. J., U.S.A. 1961, p. 112.

[3] *D. S. Bhate* et al., Experientia (Basel) *16*, 504 (1960).

[4] *L. Ettlinger, E. Gäumann, R. Hütter, W. Keller-Schierlein, F. Kradolfer, L. Neipp, V. Prelog*, and *H. Zähner*, Helv. chim. Acta *42*, 563 (1959).

[5] *W. D. Celmer* and *J. A. Solomons*, Antibiotics Annual *1953–1954*, 622;

Experimental Methods for Estimating π-Electron Densities, π-Moments, and Atomic Dipole Moments of Aromatic Heterocyclics

By W. Seiffert, Dr. H. Zimmermann, and Dr. G. Scheibe

Physikalisch-Chemisches Institut der
Technischen Hochschule Munich (Germany)

Proton magnetic resonance spectra of aromatic heterocyclics in dilute solution in nonpolar solvents (4 mole-% in hexane) were used for estimating the π-electron densitities in the molecular ground state. A reference spectrum, based on the ring current model of *Waugh* and *Fessender* [1], is calculated first. This applies to a molecule with a fictitious π-electron density of $q = 1$ per ring atom as occurs for example, in the case of benzene. Any difference ($\Delta\delta$) in the chemical shift of

a proton signal between the spectrum determined experimentally and the reference spectrum is to be attributed to a difference between the shielding of the proton in the real molecule and that in the model with $q = 1$. $\Delta\delta$ is therefore a measure of the deviation from $q = 1$ of the π-electron density on the carbon atom in the ring carrying the hydrogen atom investigated. The proportionality factor between $\Delta\delta$ and the π-electron density can be determined from the chemical shift of the signals of the cyclopentadienyl anion, the tropylium cation, and benzene. The π-electron density per carbon atom is $q = 1$ for benzene, $q \approx 6/5$, for the cyclopentadienylanion, and $q \approx 6/7$ for the tropylium cation. A calibration curve indicating the quantitative relationship between $1\text{-}q$ and $\Delta\delta$ can be constructed using these values [2].

This calibration permits calculation of $1\text{-}q$ for pyrimidine from the experimental $\Delta\delta$ values, and hence of the π-electron density distribution in the ground state. Table 1 gives the values of the densities determined experimentally and the corresponding values derived by quantum mechanics. The π-electron density of the nitrogen atoms was determined from the equation $\Sigma_i\,(1\text{-}q_i) = 0$ (i = total number of atoms).

Table 1. Calculated and measured values of q for pyrimidine

Ring atom	q_i (calc.) $\delta_N = 0.6$	$\delta_N = 0{,}5$	$\delta_N = 0.4$	q_i (exp.)
1 N	1.244	1,200	1.160	1.20_4
2 C	0.811	0,842	0.875	0.83_0
3 N	1.244	1,200	1.160	1.20_4
4 C	0.844	0,873	0.898	0.87_5
5 C	1.011	1,011	1.007	1.01_1
6 C	0.844	0,873	0.898	0.87_5

The π-electron densities in column 2 were calculated by *Löwdin* [3], using the electronegativity factor $\delta_N = 0.6$; the values in column 4 are from *Hameka* and *Liquori* [4], who used $\delta_N = 0.4$. The smaller the value of δ_N selected, the closer the value of q approaches unity. Our experimental values favor $\delta_N \approx 0.5$.

The π-moment derived from the experimental values of q_i is 1.0 D. The resulting σ-moment of pyrimidine is calculated from the CH-bond moments to be 0.6 D by assuming the CC- and CN-bond moments to be zero. This value has been postulated for the CN-bond moment [4]. The figures given in the literature for the CN-moment are generally too high, since they may contain portions of the atomic dipole moment of the N atom. From the dipole moment of pyrimidine of 2.42 D [3], the atomic dipole moment of the nitrogen atoms can be estimated at ca. 0.8 D. If a $\overset{\oplus}{C}\text{–}\overset{\ominus}{N}$ bond moment differing from zero does exist, the value of 0.8 D represents the upper limit of the atomic moment of the free electron pair on the nitrogen.

Received, February 26th. 1962 [Z 232/77 IE]

[1] *J. S. Waugh* and *R. W. Fessender*, J. Amer. chem. Soc. 79, 846 (1957).

[2] This procedure was applied to azulene independently by *H. Spiesecke* and *W. G. Schneider*, Tetrahedron Letters *14*, 468 (1961), and by *G. Fraenkel et al.*, J. Amer. chem. Soc. *82*, 5846 (1960).

[3] *P. Löwdin*, J. Chem. Phys. *19*, 1323 (1951).

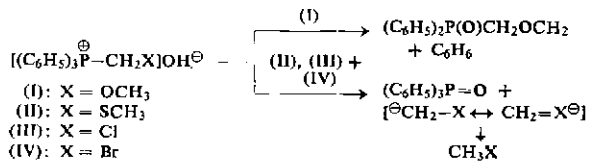
[4] *H. F. Hameka* and *A. M. Liquori*, Molec. Phys. *1*, 9 (1958).

Rearrangement and Degradation of α-Heterofunctionally Substituted Phosphonium Salts

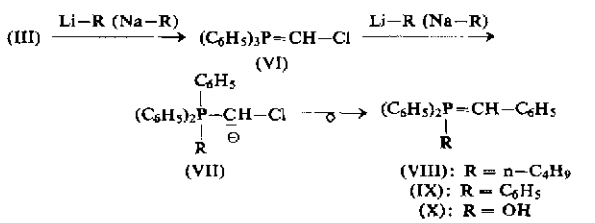
By Dr. M. Schlosser

Organisch-Chemisches Institut
der Universität Heidelberg (Germany)

On degradation of phosphonium salts with alkalis to form phosphine oxides, the ligand which is the most stable anion is split off. In the case of methoxymethyltriphenylphosphonium chloride (I) [1], a phenyl group is eliminated [2]. However, the aliphatic group is stabilized as an anion, and its elimination is therefore favored, if the oxygen in (I) is replaced by a heteroatom capable of d-orbital resonance (II [1], III [1], and IV [4]):



Whereas, in dilute alkalis, (I) only decomposes on boiling, addition of 1 N NaOH to a cold aqueous solution of II causes immediate quantitative separation of triphenylphosphine oxide and dimethyl sulfide. A novel, intra-anionic phenyl migration [5] leading to benzyldiphenylphosphine oxide (V) (17 % from III, 33 % from IV) competes with the elimination of methyl halide from (III) and (IV). This phenyl migration can also be brought about in anhydrous medium by the action of excess *n*-butyl-lithium or phenyl-lithium on III. The organometallic reagent first releases the ylene (VI) [1]:



The benzylidenephosphoranes (VIII) and (IX) can be detected by the Wittig reaction (VIII + benzaldehyde → stilbene) or by hydrolysis (IX + HBr → 62 % benzyltriphenylphosphonium bromide). Triphenylphosphine is formed in a side reaction in the aqueous alkaline degradation (10 % from III, 3 % from IV), but is not formed in the non-aqueous medium.

In contrast to the formulation given by *Hellmann* and *Bader*, who also observed the phenyl migration in aqueous alkaline solution [6], these results seem to indicate that the NaOH, too, probably first deprotonizes (III) to the ylene (VI) [3]. Addition of a further hydroxyl ion produces the anion (VII) (R = OH), which then rearranges to (X). Compound (X) tautomerizes to (V).

Received, March 5th. 1962 [Z 240/80 IE]

[1] *G. Wittig* and *M. Schlosser*, Chem. Ber. *94*, 1373 (1961).

[2] *C. K. Ingold*, J. Chem. Soc. (London) 2342 (1929); 531 (1933).

[3] *W. von E. Doering* and *A. K. Hoffmann*, J. Amer. chem. Soc. *77*, 521 (1955).

[4] *G. Köbrich*, Angew. Chem. internat. Edit. *1*, 51 (1962). I wish to thank Dr. *Köbrich* for the starting material.

[5] Cf. similar rearrangements observed by *G. Wittig* and *H. Laib*, Liebigs Ann. Chem. *580*, 57 (1953); *A. W. Johnson* and *J. C. Tebbe*, J. chem. Soc. (London) 2126 (1961).

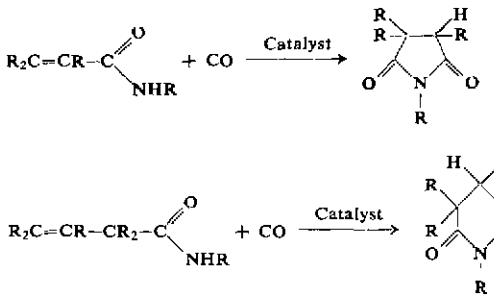
[6] *H. Hellmann* and *J. Bader*, Tetrahedron Letters 724 (1961).

Imides by the Reaction of Unsaturated Amides with Carbon Monoxide

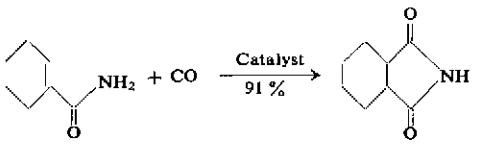
By Dr. J. Falbe and Prof. Dr. F. Korte

Shell Grundlagenforschung-GmbH.,
Schloss Birlinghoven (Germany)

Aliphatic and alicyclic α,β- and β,γ-unsaturated carbonamides react with carbon monoxide in the presence of Raney cobalt, cobalt salts, and cobalt carbonyls at 160–280 °C and 100 to 300 atm. to produce succinimides or glutarimides in 65–95 % yield. For example, acrylamide gives succinimide in 81 % yield.



With longer-chain carbonamides, partial isomerization occurs. For example, crotonamide yields 68 % α-methylsuccinimide and 19 % glutarimide. Alicyclic unsaturated carbonamides form bicyclic imides.



Cyclohexenecarbonamide forms hexahydrophthalimide in 91 % yield.

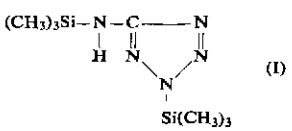
Received, March 19th, 1962 [Z 239/78 IE]

Preparation of Trimethylsilyl Azide

By Prof. Dr. L. Birkofer, Dr. A. Ritter, and Dipl.-Chem. P. Richter [1]

Institut für Organische Chemie
der Universität Köln (Germany)

A hydrazoic acid derivative containing an organosilicon moiety – *viz.* trimethylsilyl azide $(CH_3)_3SiN_3$ (III) – was synthesized for the first time by thermolysis of 1-(*N*-trimethylsilylamino)-3-trimethylsilyltetrazole (I), which was obtained in 60 % yield as white prismatic crystals, m.p. 69–70 °C, by boiling 1-aminotetrazole with hexamethyldisilazane, $(CH_3)_3Si{-}NH{-}Si(CH_3)_3$ (II). Compound III is a colorless, easily hydrolyzed liquid, b.p. 92–93 °C/760 mm Hg.



(I)

In our experience so far, the product possesses remarkable thermal stability. This indicates a higher degree of stabilization by mesomerism, compared to purely organic azides. An attempt to synthesize III from anhydrous hydrazoic acid and II gave a 62 % yield of the desired product, identical in every respect with that obtained from I by thermolysis.

$$3\,HN_3 + (CH_3)_3Si{-}NH{-}Si(CH_3)_3 \rightarrow 2\,(CH_3)_3SiN_3 + NH_4N_3$$
(II) (III)

Besides III, the thermolysis of I afforded bis(trimethylsilyl)-carbodiimide, $(CH_3)_3Si{-}N{=}C{=}N{-}Si(CH_3)_3$, described by *Pump* and *Wannagat* [2] and by the present authors [3].

Received, March 23rd, 1962 [Z 244/75 IE]

[1] Communication XIV on organosilicon compounds; Communication XIII: *L. Birkofer, A. Ritter,* and *P. Richter*, Tetrahedron Letters, in press.

[2] *J. Pump* and *U. Wannagat*, Angew. Chem. internat. Edit. *1*, 112 (1962).

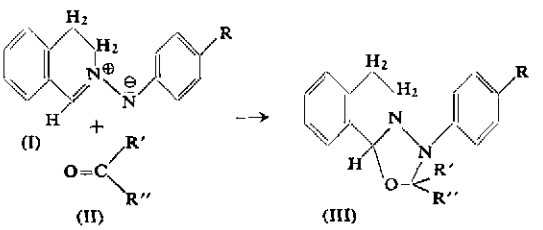
[3] *L. Birkofer, A. Ritter,* and *P. Richter*, Tetrahedron Letters, in press.

Synthesis of 1,3,4-Oxadiazolidines by 1,3-Dipolar Addition of Azomethine Imines to Carbonyl Compounds

By Dr. R. Grashey and cand. chem. K. Adelsberger

Institut für Organische Chemie
der Universität München (Germany)

Azomethine imines of the 3,4-dihydroisoquinoline series (I) form five-membered heterocycles with alkenes, alkynes, and compounds containing C=N- or C=S-double bonds [1]. With carbonyl compounds as dipolarophiles, 1,3,4-oxadiazolidines (III) are obtained in good yields (Table 1). Derivatives of this ring system have not yet been described.



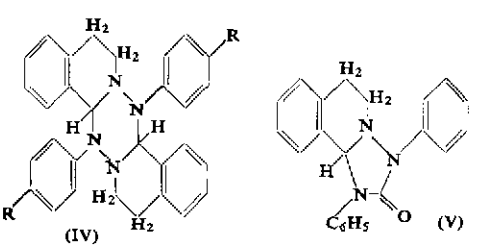
(I) (II) (III)

Table 1. List of 1.3.4-oxadiazolidines prepared

R	R′	R″	Yield [%]
H	H	H	88
H	CH_3	H	79
H	CCl_3	H	84
NO_2	CCl_3	H	99
H	C_6H_5	H	93
H	p-CH_3O-C_6H_4	H	92
H	o-Cl-C_6H_4	H	90
H	p-Cl-C_6H_4	H	92
H	p-NO_2-C_6H_4	H	84
H	2-Pyridyl	H	98
H	4-Pyridyl	H	87
H	2-Furyl	H	85
H	$COOC_2H_5$	$COOC_2H_5$	88
NO_2	$COOC_2H_5$	$COOC_2H_5$	98
H	$COOC_2H_5$	H	93
NO_2	$COOC_2H_5$	H	100

Compound I is produced *in situ* by dissociation of hexahydrotetrazines (IV) at 50–80 °C. It can be reacted with aliphatic, aromatic, and heterocyclic aldehydes; and ketones such as mesoxalic ester.

Acid hydrolysis of III smoothly affords the carbonyl compound II and the hydrazonium salt corresponding to I. Adducts of type III are thermally unstable and decompose, reverting to the starting compounds. Thus, with phenylisocyanate at 100 °C, III (R=H; R′ = p-O_2N-C_6H_4; R″ = H) affords the isocyanate adduct V in 94 % yield. Establishment



(IV) (V)

of an equilibrium III ⇌ I + II is also indicated by thermochromism: a red-brown to dark red color characteristic of I is formed on heating III in inert solvents. Adducts with R = NO_2, in particular, are so unstable that their preparation in the pure state is only possible in exceptional cases. These findings indicate that 1,3-dipolar additions are basically reversible.

If R′ and R″ themselves do not contain carbonyl functional groups, the IR spectra of III do not show any carbonyl

bands. Oxadiazolidine III (R = R′ = R″ = H) was reduced with $LiAlH_4$ to 2-(*N*-phenyl-*N*-methylamino)-1,2,3,4-tetrahydroisoquinoline (95 %), which was also synthesized by an independent route.

Received, March 24th. 1962 [Z 245/76 IE]

[1] *R. Huisgen, R. Grashey, P. Laur*, and *H. Leitermann*, Angew. Chem. *72*, 416 (1960); *R. Huisgen*, Naturwiss. Rundschau *14*, 43 (1961); *R. Huisgen*, Proc. chem. Soc. (London) 357 (1961).

Preparation and Properties of Trisilylarsine

By Dr. E. Amberger and Dr. H. Boeters

Institut für Anorganische Chemie
der Universität München (Germany)

Trisilylarsine is formed in 48 % yield by the reaction of monobromosilane with potassium arsinedihydride in a 1:1 molar ratio:

$$3\,SiH_3Br + 3\,KAsH_2 \rightarrow As(SiH_3)_3 + 2\,AsH_3 + 3\,KBr$$

In this preparation, the two reactants are allowed to warm up slowly together in the previously frozen reaction medium, dimethyl ether. The reaction begins at −122 °C and is completed at −38 °C (after 2 hours). Arsine, ether, and reacted silyl bromide are separated from the trisilylarsine by vacuum distillation.

At room temperature, trisilylarsine is a colorless liquid, which burns in air. Within the range −15 to + 14 °C, the following equation holds for its vapor pressure:

$$\log p\,[mm.] = -(2142{,}6/T) + 8{,}333.$$

The molar enthalpy of vaporization is 9798 cal/mole; the extrapolated boiling point is 120 °C. $As(SiH_3)_3$ exhibits an infrared absorption spectrum analogous to that of $P(SiH_3)_3$ [1], with bands at 2165, 930, 874, 598, 546, and 456 cm^{-1}.

Received, March 24th. 1962 [Z 246/82 IE]

[1] *E. Amberger* and *H. Boeters*, Angew. Chem. *74*, 32 (1962). An infrared band of $P(SiH_3)_3$ which was previously given at 1159 cm^{-1} should be corrected to read 941 cm^{-1}.

Thiohydroxylamine-*S*-monothiocarboxylates

By Dr. R. Gösl

Institut für Anorganische Chemie
der Universität Erlangen-Nürnberg (Germany)

In aqueous solution, and at temperatures in the range 0 to 10 °C, xanthates react rapidly with hydroxylamine-*O*-sulfonate or monochloramine to give almost quantitative yields of thiohydroxylamine derivatives, *viz.* thiohydroxylamine-*S*-monothiocarboxylates (I) [1].

$$RO-\underset{\underset{S}{\|}}{C}-S^- + H_2NOSO_3^- \rightarrow H_2N-S-\underset{\underset{S}{\|}}{C}-OR + SO_4^{2-}$$

(+ H_2NCl) (I) (+ Cl^-)

The thiohydroxylamine-*S*-monothiocarboxylates (I) listed in the table are light yellow liquids, sparingly soluble in water and readily soluble in organic solvents.

	I		II
R	b.p. [°C/mm. Hg]	d^{25}	m.p. [°C]
CH_3	41/0.15	1.29	96
C_2H_5	54/0.4	1.21	73
$n-C_3H_7$	62/0.4	1.15	101
$i-C_3H_7$	49/0.1	1.13	67
$n-C_4H_9$	78/0.5	1.12	72

On standing for a few days at room temperature, they change into thio- *O*-alkyl carbamates, $H_2N-CS-OR$ by loss of sulfur. Thiohydroxylamine-*S*-monothiocarboxylates oxidize HI and in dimethylformamide, acetone, or alcohol form transient blue-to-red solutions with bases (OR^-, OH^-, CO_3^{2-}, amine). The amino group can condense with aldehydes. Readily crystallizing, stable, thio-oxime derivatives of salicylaldehyde, $RO-CS-S-N=CH-C_6H_4-OH$ (II), are obtained especially easily.

Received, March 27th. 1962 [Z 249/83 IE]

[1] Nomenclature analogous to that of the thiohydroxylamine-*S*-sulfonates, $H_2N-S-SO_3^-$, obtained from thiosulfates; *R. Gösl* and *A. Meuwsen*, Z. anorg. allg. Chem. *314*, 334 (1962).

The Order of Reactivity of Dienes towards Maleic Anhydride in the Diels-Alder Reaction

By Dr. J. Sauer, D. Lang, and A. Mielert

Institut für Organische Chemie
der Universität München (Germany)

Kinetic investigations, using ultraviolet spectroscopy or dilatometry in dioxan, on the addition of maleic anhydride to dienes allow, for the first time, a comparison of the reactivities of a large number of dienes. Since the dienophiles studied by us so far show similar orders of reactivity, the data contained in Tables 1 and 2 give important general indications as to the rates of Diels-Alder reactions.

Table 1. Reaction rate constants (at 30 °C in dioxan) and Arrhenius parameters of Diels-Alder additions of maleic anhydride to dienes

Diene	$10^8 \times k_2$ (liters/mole × sec)	E_A (kcal/mole)	log *A*
1. Cyclopentadiene	9210000	8.93	5.40
2. 9,10-Dimethylanthracene	1600000	10.9	6.04
3. 1,2-Bis(*exo*methylene)-cyclohexane	755000	—	—
4. 1,1′-Bicyclopentenyl	118000	—	—
5. 1-Methoxybutadiene	84100	—	—
6. 2-Phenylbutadiene	*ca.* 60000	—	—
7. 1,1′-Bicyclohexenyl	39100	—	—
8. 2,3-Dimethylbutadiene	33600	12.0	5.21
9. *trans*-1-Methylbutadiene	22700	—	—
10. 2-Methylbutadiene	15400	—	—
11. 2,3-Bis(exomethylene) bicyclo [2.2.1] heptane	14800	—	—
12. Cyclohexadiene	13200	12.6	5.22
13. Butadiene	6830	—	—
14. *trans*-1-Phenylbutadiene	4280	13.9	5.63
15. Tetracyclone	1670	—	—
16. 2-Chlorobutadiene	690	—	—
17. *trans,trans*-1.4-Diphenyl butadiene	296	13.3	4.08
18. Hexachlorocyclopentadiene	1.14	19.1	5.80

The k_2 values permit the following conclusions, for example:

1. The reactivities of cyclic and quasi-cyclic dienes (Table 1, Nos. 1, 2, 3) considerably exceed the reactivities of acyclic dienes. The influence of steric factors is great (Table 1, Nos. 3, 11). Electron-donating substituents on the diene usually accelerate the reaction whereas electron acceptors retard it.

Bulky, electron-attracting, ligands in the 2-position of acyclic dienes also accelerate the reaction, since they favor the quasi *cis*-conformation required for the reaction [1]. − 2. The k_2 values for the anthracene derivatives in Table 2 are influenced to an unexpectedly high degree by substituents in the 9- and 10-positions [2]; the increase in rate produced by methoxy groups is smaller than that of alkyl groups because of the impaired coplanarity (*peri*-hydrogens). Ligands in the 2-position have only small influence on the reaction rate in

Table 2. Reaction rate constants (at 130 °C in dioxan) and Arrhenius parameters in t he Diels-Alder addition of maleic anhydride to anthracene derivatives

Anthracene derivative	$10^5 \times k_2$ (liters/mole×sec)	E_A (kcal/mole)	log A
1. 9,10-Dimethyl-	141000	10.9	6.04
2. 9,10-Diethyl-	24200	11.9	5.84
3. 9-Methyl-	11200	13.3	6.24
4. 9-Ethyl-	4420	13.1	5.76
5. 9-Methoxy-	1630	14.8	6.25
6. Anthracene	646	16.3	6.67
7. 9-Chloro-	192	16.8	6.41
8. 9,10-Dimethoxy-	191	14.8	5.29
9. 9-Bromo-	152	—	—
10. 9-Phenyl-	49.0	16.7	5.74
11. 9,10-Dichloro-	*ca.* 28	—	—
12. 9-Nitro-	5.89	18.8	5.99
13. 9-Cyano-	*ca.* 4.2	—	—
14. 2-Dimethyl-amino-	1680	14.9	6.32
15. 2-Methyl-	664	15.6	6.26

additions involving maleic anhydride (Table 2, Nos. 14, 15).– 3. Differences in reactivity of the dienes are primarily caused by changes in E_A; the extremely low log A value is remarkably constant. In combination with the rate phenomena observed with *cis-trans* isomeric dienophiles [3] and the low solvent effect, we consider our results as an additional argument in favor of a concerted mechanism for the Diels-Alder addition.

Received, March 27th. 1962 [Z 253/85 IE]

[1] See also *D. Craig, J. J. Shipman,* and *R. B. Fowler,* J. Amer. chem. Soc. *83,* 2885 (1961).

[2] *L. J. Andrews* and *R. M. Keefer,* J. Amer. chem. Soc. *77,* 6284 (1955).

[3] *J. Sauer, H. Wiest,* and *A. Mielert,* Z. Naturforsch., in the press; *J. Sauer, D. Lang,* and *H. Wiest, ibid.,* in the press.

Diels-Alder Additions with "Inverse" Electron Demand

By Dr. J. Sauer and H. Wiest

Institut für Organische Chemie der Universität München

The rate of reaction of normal Diels-Alder additions is increased by electron attracting ligands in the dienophile and decreased by electron donating ligands. In the formal sense the dienophile reacts as the electron deficient component, the diene as the electron rich component.

The data in Table 1 show for the first time the existence of Diels-Alder additions with "inverse" electron demand and simultaneously eliminate uncertainties existing in the literature [1]. In these cases, the diene acts as the electron deficient component and the dienophile as the component with excess electrons.

From the data in Table 1 the following conclusions are obtained:

1. Simple olefins (Nos. 7, 6, 3) surpass maleic anhydride in their rate of addition to hexachloropentadiene; however, maleic anhydride adds to 9,10-dimethylanthracene about 200,000 times faster than cyclopentene. While tetracyanoethylene, the most active dienophile, reacts with the anthracene derivative almost immeasurably fast – even at 20 °C [2] – it has not yet been possible to add it to hexachlorocyclopentadiene. – 2. Conjugation of the olefinic double bond with electron donating ligands (Nos. 7, 5, 1 and 3, 2) promotes the addition to hexachlorocyclopentadiene, but retards the addition to 9,10-dimethylanthracene (Nos. 3, 2). – 3. The low degree of dependence of the rate of addition [3] on substituents, also observed in other diene additions, the extremely low log A values, and the significant influence of steric factors (Nos. 3, 9, 11) suggest that diene additions with "inverse" electron demand also proceed by a concerted mechanism.

A search for further examples of diene additions with "inverse" electron demand involving other electron deficient dienes and electron rich dienophiles is being conducted at present.

Received, March 27th. 1962 [Z 254/87 IE]

[1] Cf. *R. Riemschneider* and *B. E. Grabitz,* Mh. Chemie *91,* 22 (1960).

[2] Unpublished experiments in collaboration with *R. Wiemer,* Munich.

[3] *E.g., E. J. DeWitt, C.T. Lester,* and *G. A. Ropp,* J. Amer. chem. Soc. *78,* 2101 (1956); *I. Benghiat* and *E. I. Becker,* J. org. Chem. *23,* 885 (1958).

Table 1. Rate constants and Arrhenius parameters for Diels-Alder additions of hexachlorocyclopentadiene and 9,10-dimethylanthracene at 130 °C in dioxan

Dienophile	Hexachlorocyclopentadiene			9,10-Dimethylanthracene		
	$10^6 \times k_2$ [liters/mole×sec]	E_A [kcal/mole]	log A	$10^6 \times k_2$ [liters/mole×sec]	E_A [kcal/mole]	log A
1. Cyclopentadiene ..	15200	14.0	5.77	—	—	—
2. *p*-Methoxystyrene .	1580	—	—	50.0	—	—
3. Styrene	750	15.2	5.14	70.1	17.9	5.56
4. *p*-Nitrostyrene	538	—	—	602	—	—
5. 2,3-Dihydrofuran .	333	—	—	—	—	—
6. Norbornene	70.8	—	—	36.2	—	—
7. Cyclopentene	59.0	16.2	4.54	7.80	17.6	4.44
8. Maleic anhydride .	29.1	19.1	5.80	1410000	10.9	6.04
9. α-Methylstyrene ..	8.2	—	—	—	—	—
10. Cyclohexene	3.0	—	—	—	—	—
11. β-Methylstyrene ..	*ca.* 2.8	—	—	—	—	—

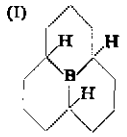
Isomers of Perhydro-9^b-boraphenalene

By Dipl.-Chem. G. Rotermund and Dr. R. Köster

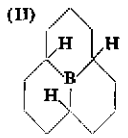
Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr (Germany)

We have prepared three pure isomers of perhydro-9^b-boraphenalene [1], of formula $C_{12}H_{21}B$. The compounds can be separated by distillation and differ in their physical (see table) and also in some of their chemical properties.

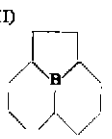
Compound (I) is obtained either by hydroboration of all-*trans*-cyclododeca-1,5,9-triene with *N*-triethylamineborane [1] or ethyldiborane [2] or by pyrolysis of tricyclododecylboran [3]. Compound (II) is formed quantitatively on thermal isomerization of I in the presence of trialkylamines (*e.g.* triethylamine) and hydrogen, using pressure and temperatures above 200 °C (hydrogenation/dehydrogenation equilibria). Small amounts of II are also formed on pyrolysis of polymeric by-products formed during hydroboration of cyclododecatrienes (dehydroboration/hydroboration equilibria).



all-*cis*-perhydro-9b-boraphenalene (centroboron I)



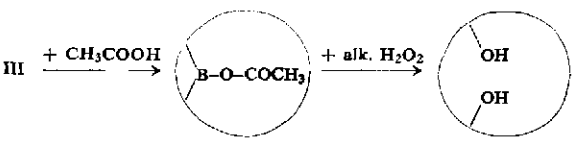
cis,cis,trans-perhydro-9b-boraphenalene (centroboron II)



13-boratricyclo[6,4,1,0^{4,13}]tridecane (centroboron III)

Compounds (I) and (II) have characteristically different infrared spectra and undergo auto-oxidation. However, (II) is more stable toward various reagents than (I). Thus, (II), remains virtually unattacked by ethylene at 150–200 °C (displacement reaction) [4] and is attacked only slowly by hydrogen under pressure (hydrogenation of the B–C bonds) [5], whereas I reacts in essentially the same manner as trialkylboranes BR_3.

About 30–40 % (III) is formed along side (I) from *trans, trans,cis*-cyclododeca-1,5,9-triene and triethylamineborane [1,6]. At about 200 °C, III isomerizes in to (I). On partial acetolysis [7] and subsequent oxidation with alkaline H_2O_2, three cyclododecanediols are obtained from (III); these were separated as their diacetates by gas chromatography.



three isomers

We suspect that III is the all-*cis* form of the four possible *cis-trans* isomers.

Table 1. $C_{12}H_{21}B$ Isomers

Centroboron compound	b.p. [°C/mm.Hg]	m.p.[°C]	d_4^{35}	n_D^{35}
I	115/10	–	0.9377_1	1.5100
II	113.5/10	+ 31	0.9220	1.5027
III	113/10	–	0.9219_6	1.5058

Received, April 2nd. 1962 [Z 250/84 IE]

[1] *R. Köster*, Angew. Chem. *69*, 684 (1957).

[2] *R. Köster* and *G. Griaznov*, Angew. Chem. *73*, 171 (1961).

[3] *R. Köster* and *G. Rotermund*, Angew. Chem. internat. Edit. *1*, 217 (1962).

[4] *R. Köster*, Liebigs Ann. Chem. *618*, 31 (1958).

[5] *R. Köster, G. Bruno*, and *P. Binger*, Liebigs Ann. Chem. *644*, 1 (1961).

[6] *N. N. Greenwood* and *J. H. Morris* (J. chem. Soc. (London) *1960*, 2922; Proc. chem. Soc. (London) *1960*, 25) therefore did not have a pure centroboron compound for their investigations; cf. Angew. Chem. *72*, 328, 792 (1960).

[7] *P. Heimbach*, Ph. D. Thesis, Technische Hochschule, Aachen 1960.

C-Acylation of Alkylenephosphines

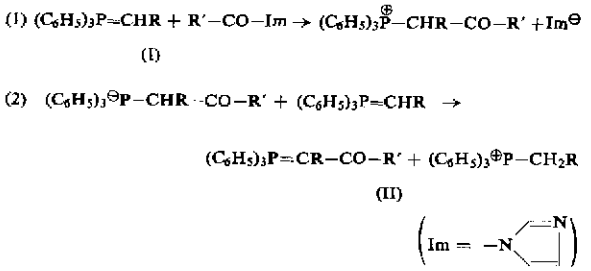
By Dr. H. J. Bestmann

Organisch-chemisches Institut der Technischen Hochschule München (Germany)

Dipl.-Chem. N. Sommer and Prof. Dr. H. A. Staab,

Organisch-chemisches Institut der Universität Heidelberg (Germany)

Independent studies in Munich and Heidelberg have shown that alkylenetriphenylphosphines (I; R = H or alkyl; 2 moles) can be *C*-acylated with *N*-acylimidazoles (1 mole) in benzene or benzene/tetrahydrofuran. Good yields are obtained at room temperature. The second mole of alkylene (I) serves as a proton acceptor [1] in the "transylidation" (2), and forms the corresponding phosphonium bromide if the reaction is carried out, as is usual, in the presence of LiBr (imidazole-lithium is formed at the same time; this can be shown by reaction with ethyl bromide leading to *N*-ethylimidazole).



Example: α-Benzoylmethylene-triphenylphosphine (II, R = H; R' = C_6H_5): *N*-Benzoylimidazole (0.52 g.; 3 mmoles) dissolved in benzene (50 ml.) is added dropwise, and at room temperature, to a solution of (I) prepared from triphenylphosphonium bromide (2.14 g.; 6 mmoles) in benzene (150 ml.) and 6 mmoles standardized (*ca.* 1 N) phenyllithium in ether. The usual working-up procedure gives (II) in 99 % yield (1.13 g.), m.p. 181–185 °C (Lit.: 181 ° C); after recrystallization from acetone m.p. 186–187 °C.

Received, March 30th. 1962 [Z 247/70 IE]

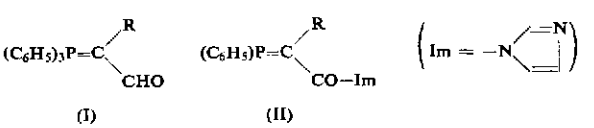
[1] See *H. J. Bestmann*, Chem. Ber. *95*, 58 (1962).

α-Formylalkylenetriphenylphosphines and α-Imidazolylcarbonylalkylenetriphenylphosphines

By Prof. Dr. H. A. Staab and Dipl.-Chem. N. Sommer

Organisch-chemisches Institut der Universität Heidelberg (Germany)

Analogously to the *C*-acylation of alkylenephosphines described above [1], the α-formyl derivatives (I) can be prepared by use of *N*-formylimidazole [2], *e.g.* α-formylmethylene triphenylphosphine (I; R = H) is obtained in 81 % yield. The α-formyl derivatives yield α,β-unsaturated aldehydes [3] in the Wittig reaction and the aldehydes R-CH_2-CHO are formed on hydrolysis.



α - Imidazolylcarbonylalkylenetriphenylphosphines (II; R = H, m.p. 184–186 °C, 81 % yield; R = CH_3; m.p. 172–175 °C, 60 % yield) result from reaction with N,N'-carbonyldiimidazole at room temperature [4]. When the imidazolyl compounds (II) are hydrolysed, the corresponding carboxylic acids R–CH_2–COOH are obtained in good yields. Despite more vigorous reaction conditions, the Wittig reaction with compounds (II) leads to α,β-unsaturated carboxylic acids (*via* α,β-unsaturated imidazolides only in moderate yields.

Received, March 30th. 1962 [Z 248/71 IE]

[1] *H. J. Bestmann, N. Sommer*, and *H. A. Staab*, Angew. Chem. internat. Edit. *1*, 270 (1962).

[2] *H. A. Staab* and *B. Polenski*, Liebigs Ann. Chem., in the press.

[3] See *S. Trippett* and *M. Walker*, J. chem. Soc. (London) 1266 (1961).

[4] *H. A. Staab*, Liebigs Ann. Chem. *609*, 75 (1957).

Symposium on Co-ordination Compounds

Swiss Chemical Society, Berne, February 17th, 1962

Structure and Light Absorption of the Hydroxides, Halides and Hydroxyhalides of Cobalt

A. Ludi, H. R. Oswald, and *W. Feitknecht,* Berne

As is known, the spectra of the transition metal complexes consist of two regions. The absorption between 400 and 2000 mμ originates in electron transitions within the d shell of the central atom. Transitions between ligand and central atom (charge transfer) cause absorptions below 400 mμ.

The writers measured the diffraction spectra of the solid cobalt(II) halides, hydroxyhalides and the hydroxide. In these compounds, the cation is always surrounded by 6 ligands: either H_2O, halogen, OH^- and halogen, or OH^- alone. The absorption bands generally correspond to those predicted from the ligand field theory, giving the following series of increasing ligand field: I^-, Br^-, Cl^-, F^-, OH^-, and OH_2. Only a strong distortion of the co-ordination octahedron (hydroxyhalides) causes the occurrence of new absorption bands.

In the corresponding nickel and copper compounds, the positions of OH^- and OH_2 in the spectrochemical series are interchanged.

Crystal Structure of the β-Form of Zinc Hydroxide-2,4-Dinitrophenolate

W. Nowacki, H. Bürki, and *S. Locchi,* Berne

The compound has the composition:

$Zn(DnPh)_{0.32}(OH, H_2O)_{2.347}$; (where DnPh = dinitrophenolate).

About 2000 X-ray diffraction photographs of single-crystal samples were evaluated. This permitted elucidation of the structure as a single-layer lattice of the C_6 type which is rhombohedrally distorted. Thirteen formula units are required per unit cell: $Zn_9(OH)_{22}Zn_4(OH, H_2O)_8(DnPh)_4$. The nine zinc atoms of one layer are octahedrally surrounded by twenty-two hydroxyl ions which belong to two parallel layers of eleven ions each. Outside these hydroxyl layers, there are also four zinc atoms which are tetrahedrally surrounded by oxygen atoms, some of which belong to the phenolate structures. The dinitrophenolate frameworks lie outside the tetrahedrally surrounded zinc atoms. The color of the crystals is caused by the dinitrophenolate ion.

Structure of the Nickel Complex of 1,2,3,4-Tetramethylcyclobutadiene

H. Ch. Mez and *J. D. Dunitz,* Zurich

The fact that cyclobutadiene should exist within metal complexes was predicted in 1954 by *Orgel* and *Longuet-Higgins* on the basis of a highly simplified version of the molecular orbital theory and was proved by *Criegee* in 1959. This was the first cyclobutadiene compound to be readily and definitely elucidated by X-ray spectroscopy.

The evaluation of the X-ray patterns with two- and three-dimensional Fourier analysis suggests a dimeric structure for $NiCl_2{\cdot}C_4(CH_3)_4$. The two nickel atoms are interconnected *via* two common chlorine atoms. There is a cyclobutadiene molecule above and below the nickel atom. The two four-membered rings are completely planar but are slightly distorted into a shape and for steric reasons the four methyl groups protrude slightly from the plane of the ring.

On the Stability of Alcoholate Complexes

R. Gut, Zurich

In contrast to the case of metal hydroxides in water, most metal alcoholates are soluble in alcohol. While the solid hydroxides are formed *via* a complicated series of mono- and polynuclear hydroxo complexes (*Sillen*), the formation of alcoholates in alcoholic solution is less involved. An attempt can be made towards a quantitative explanation of this process. Preliminary results have been obtained for the following reactions:

$$B(OCH_3)_3 + OCH_3^- \rightarrow B(OCH_3)_4^- \quad \log K = 5.47$$
$$Nb(OCH_3)_5 + OCH_3^- \rightarrow Nb(OCH_3)_6^- \quad \log K = 5.39$$
$$Ta(OCH_3)_5 + OCH_3^- \rightarrow Ta(OCH_3)_6^- \quad \log K = 6.65$$
$$CH_3COOH + OCH_3^- \rightarrow CH_3COO^- \quad \log K = 7.68$$

The solvent was methyl alcohol to which tetramethylammonium chloride had been added in order to maintain an ionic strength at $\mu = 1$ (temperature 20 °C).

The data to the right of the equations have been derived from titration curves, obtained by measuring the pH value of the solution (and thus the concentration of alcoholate) with a hydrogen electrode while titrating the metal alcoholate with lithium methylate. The ion product was found to be

$$[H^+]\,[OCH_3^-] = 10^{-16{,}62} \quad (\mu = 1,\ 20\ °C)$$

The sensitivity of the system to water caused great difficulties. The water content must be less than 1 % of the metal alcoholate concentration of 10^{-2} M, *i. e.* less than 10^{-4} mole liter = 2 mg./liter. Such small quantities cannot be detected with Karl Fischer reagent.

Determination of the Relative Exchange Coefficients and the Complex-Formation Constants of Rare Earths by Use of Ion-Exchange Procedures

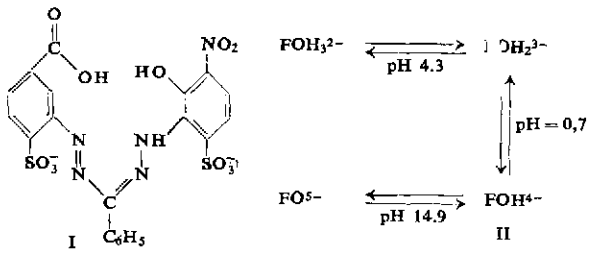
M. Randin and *G. Brunisholz,* Lausanne

It is a known fact that the rare earths can be separated if their EDTA complexes are passed through a column filled with an ion-exchanger containing Cu^{2+} ions. The relative exchange coefficients, which are proportional to the complex-formation constants, can be calculated from the length of column required for complete separation. The values found agree approximately with those found by *Schwarzenbach.* The authors used the same method for explanation of the neodymium-NTA complex and came to the conclusion that 2:3 complexes, having the formula $(Nd_2(NTA)_3)^{3-}$, besides the 1:1 and 1:2 complexes, are capable of existence.

Kinetics and Mechanism of Complex-Formation Reactions with Formazans

K. Treszer and *S. Fallab,* Basel

The formation of complexes of Fe^{II}, Fe^{III} and Ni^{II} with the formazan dye I (FOH_3^{2-}) was studied from a kinetic view point. With increasing pH, the protons at the carboxyl, phenol, and imino groups are split off (II).



The stability constant can usually only be estimated. For the complexes listed below, they are:

$CuFO^{3-}$, $NiFO^{3-}$	log K ≥ 28
$FeFO^{2-}$	log K ≥ 25
$FeFOH^{2-}$	log K ≥ 10
$ZnFO^{3-}$	log K = 13.6 (accurately determined)
$PbFOH^{2-}$	log K ≈ 8
$CdFOH^{2-}$, $BeFOH^{2-}$, $MgFOH^{2-}$	log K ≥ 2

The differences in stability between copper or nickel complexes when compared with those of lead, cadmium, beryllium, and magnesium, point to a planar tetragonal structure, since the electron structures of Cu^{2+} and Ni^{2+} favor this arrangement. Kinetic measurements were possible only with Fe^{2+}, Fe^{3+}, and Ni^{2+} in acid solution since the formation of complexes with other metal ions proceeds too rapidly to be measured. The reaction takes place in two steps: 1) the instantaneous dissociation of the complex-forming substance and 2) the coordination of the metal ion with subsequent cleavage of the imino proton. The reaction of Cu^{2+} with the formazan complexes of Fe^{II}, Fe^{III} and Ni^{II}, which results in a metal exchange, is of the S_N1 type.

Donor-Acceptor Properties of Nickel Chelate Complexes

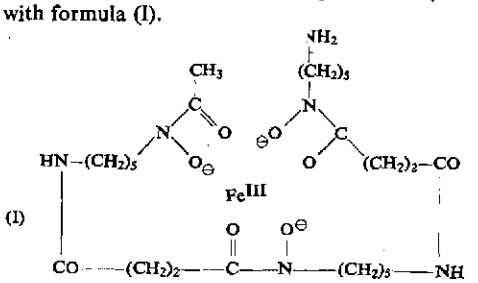
W. Ludwig, Zurich

The absorption spectra of toluene solutions of bis(*N*-methyl-, cyclohexyl- or -phenylsalicylaldiminato)nickel were studied in the visible region. The spectra as well as the molecular weights, cryoscopically determined in benzene, point to an equilibrium between the monomeric and dimeric forms of the complex which is highly temperature-dependent. The dimerization appears to be due to a mutual interaction of Ni–Ni. This interaction also makes itself felt in the anomalous paramagnetism observed with this compound in solution. The arrangement of the associated groups in solution is probably similar to that in the crystal of the β-modification of bis(*N*-methylsalicylaldiminato)nickel.

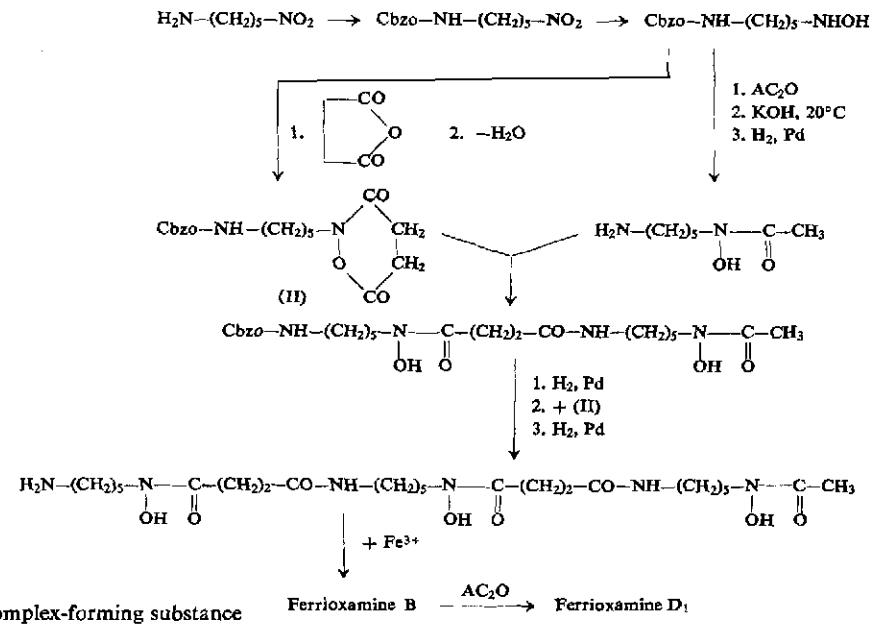
Biologically Active Iron(III) Trihydroxamate Complexes from Micro-organisms

W. Keller-Schierlein, Zurich

A biologically active iron(III) trihydroxamate complex can be isolated from the metabolic products of actinomycetes by means of ion-exchangers. Ferrioxamine B is stable in a pH region of 3 to approximately 10. Acid hydrolysis results in 1 mole acetic acid, 2 moles succinic acid, and 3 moles 5-aminopentylhydroxylamine. Since the molecule contains only one basic group, it must be a chain structure. In order to coordinate the iron octahedrally, the hydroxamic acid groups must be separated by large distances. This is possible only in accordance with formula (I).



The synthesis was carried out as follows:



Synthetic ferrioxamine B has exactly the same properties as the natural product. Besides ferrioxamine B, other, only slightly different, accompanying substances were found and partially synthesized. The ferrioxamines play an important role in iron transport within the body.

The Ultraviolet Absorption of Addition Compounds of Ketones with Lewis Acids

D. Janjic and *P. Chalendon*, Geneva

The separate addition of the Lewis acids $AlCl_3$ and $HgCl_2$ to acetophenone was studied optically in the ultraviolet and in the infrared regions. The ketone bands at 1700 $cm.^{-1}$ are displaced toward lower frequencies, by 120 $cm.^{-1}$ in the case of $AlCl_3$ and by 20 $cm.^{-1}$ in the case of $HgCl_2$. In both cases new bands, characteristic for the complex, occur in the ultraviolet at 2740 Å. This band disappears again in the $HgCl_2$ complex, that is, the complex decomposes again. Absorptions between 2700 and 2800 Å are characteristic of a charge transfer.

Sequestration *in vivo* of Radioactive or Toxic Metal Ions with Chelating Agents

A. Catsch, Karlsruhe

Metal poisoning can be treated with multidentate chelating agents which combine with the troublesome metal. The complex is then excreted through the kidneys. The complexing agents must fulfill the following requirements: they must not be toxic, nor must they decompose rapidly in the body; they should have a high specific affinity for the metal ions foreign to the body and yet should not combine with normal body ions, particularly calcium. The biological efficiency of a complexing agent can be predicted quite well on the basis of the formation constant of the complexes of the metal to be removed and that of calcium.

Radioactive rare-earth cations and plutonium can be readily removed from the body with amino(*poly*)acetic acids (*e.g.* EDTA). Of these compounds, diethylenetriaminepentaäcetic acid and triethylenetetraäminehexaäcetic acid are the most effective. Lead can also be removed with such amino(*poly*)-acetic acids. However, better extractions of lead, and of mercury as well, are obtained with complexing agents containing the mercapto group, mercaptoethyliminodiacetic acid and cystaminediacetic acid being especially effective. The removal of radioactive strontium from the body is difficult because there are no complexing agents which combine more readily with Sr^{2+} than with the physiologically necessary Ca^{2+}. Sequestration of metals which form inert complexes is also difficult. For instance, Ru^{106} can be separated only if the treatment is started immediately.

The lipid-soluble esters and lactones of amino(*poly*)acetic acids proved to be superior in some cases to the free acids or their salts.

[VB 572/21 IE]

Colloquium on Macromolecules

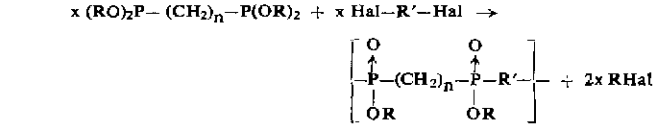
Freiburg/Brsg. (Germany), March 8th.—10th. 1962

From the agenda:

Preparation of Polyphosphinic Esters by the Arbuzov Reaction

M. Sander and *E. Steininger*, Frankfurt (Germany)

Linear polyphosphinic esters of a molecular weight of 2000–5000 can be synthesized by polycondensation of diphosphonous esters with aliphatic or arylaliphatic dihalides.

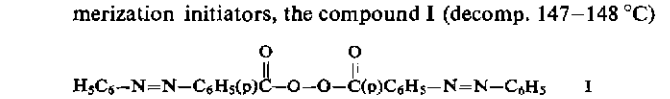


By varying R,R′ and n, their effect on the course of reaction was studied. At higher temperatures, or with very reactive dihalides, cross-linking takes place as a result of an alkyl interchange at the ester group. The polymeric esters can be hydrolyzed to linear polyphosphinic acids. Owing to the polar P → O group, polyphosphinic esters absorb up to 20 % of water when exposed to air. Possibilities of increasing molecular weight and decreasing water absorption were discussed.

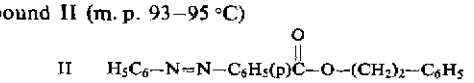
Incorporation of a Catalyst Labeled with Azobenzene Groups in the Polymerization of Styrene

H. Kämmerer, Mainz (Germany)

The incorporation of fragments of halogen-labeled peroxide initiators in the polymerization of vinyl compounds is known. Quantitative terminal group analyses are limited by the accuracy of the usual methods of halogen determination (± 0.3 %). In comparison, radioactive labeling is far more sensitive. In searching for a better method of labeling polymerization initiators, the compound I (decomp. 147–148 °C)



was prepared, among others. Purified polystyrene, prepared with this peroxide, contains covalently bound, colored terminal groups. It was separated into fractions. Equally concentrated solutions, arranged according to visually rated color intensity, were also found to be arranged according to the Staudinger index (intrinsic viscosity), indicating that a colorimetric molecular weight determination should be possible. Based on preliminary experiments, absorption measurements at 450 and 326 mμ are suitable for this purpose. The absorption (at 1724 cm^{-1}) of 4 % polymer solutions in CCl_4 was also used for the quantitative determination of end-groups. A calibration curve was constructed with the aid of a series of CCl_4 solutions containing varyous concentrations of the compound II (m. p. 93–95 °C)



and using the same IR bands for calculation. Up to a value of 70000, molecular weights computed from the terminal group content are in agreement with values obtained by other methods. Computation of the ratio of molecular weight obtained by other methods to that determined by infrared spectrophotometry shows that this ratio increases to 2.3 as the molecular weight increases to 200000.

Polymerization of Styrene in Liquid Sulfur Dioxide

Rolf C. Schulz and *A. Banihaschemi*, Mainz (Germany)

The effect of peroxides on the polymerization of 2-methyl-4-pentene (I), cyclohexene (II), hexene (III), and styrene (IV) in liquid sulfur dioxide below −20 °C was studied. Compounds (I), (II), and (III) give polysulfones with t.-butyl hydroperoxide or perlauric acid. Compound (IV) does not give a copolymer, but polystyrene. Polymerization leads to almost complete conversion in a few minutes; it was not inhibited by hydroquinone or m-dinitrobenzene. Furthermore, since a mixture of styrene and methyl methacrylate yields a copolymer which predominantly consists of styrene repeating units, a cationic mechanism was postulated. In agreement with this mechanism, polymerization inhibition by water has been observed. The possible reactions between liquid sulfur dioxide and hydroperoxides were discussed. Model experiments showed that sulfur trioxide, sulfuric hemi-esters or sulfuric acid, formed as intermediates, might be considered as catalysts. The polymerizations are strongly affected by solvents.

Anionic Graft Polymerizations

G. Greber, *G. Egle*, and *J. Tölle*, Freiburg/Brsg. (Germany)

The addition of diethylaluminum hydride to polymers containing unsaturated C=C bonds affords macromolecular organoaluminum compounds which give reactions typical of this class of compounds. With transition metal compounds, they form macromolecular complex catalysts for the graft polymerization of ethylene and propylene. Propylene affords a graft polymer with isotactic side chains.

If organometallic reagents are reacted with copolymers containing nitrile groups, macromolecules with N-metal

bonds are formed. These bonds make possible the grafting of acrylonitrile, methyl methacrylate and vinylpyridine onto these macromolecules.

We obtained macromolecular ion-radicals or carbanions by electron transfer from metals to the C=O, C=N, and C=C bonds of suitable macromolecules (for example, in the case of the C=O group, polyketyls are formed). These, too, lend themselves to grafting with acrylonitrile, methyl methacrylate, vinyl pyridine and styrene. Moreover, it was found that halogen-containing polymers (*e.g.* poly-*p*-chlorostyrene) can be metalated rapidly and quantitatively under mild conditions with complexes formed between an alkali metal and an aromatic compound. No excess of metalating agent was found. These organometallic macromolecules can then be grafted with all above-cited monomers.

New Method for the Low-Pressure Polymerization of Ethylene [1]

By *G. Bier* and *G. Messwarb*, Höchst (Germany)

Aqueous solutions containing medium and high concentrations of silver salts, such as $AgNO_3$, $AgBF_4$, $AgClO_4$, exhibit a marked dissolving power for ethylene and the higher olefins, even at low pressures. Solution takes place by way of a silver salt-olefin complex. With the aid of organic and inorganic peroxides, ethylene can be converted in these solutions, and under mild conditions, to high molecular weight products.

It is advantageous to feed the peroxide and the ethylene continuously, as fast as they are consumed.

The most favorable experimental range lies between 10 and 40 °C and 5 and 50 gauge atm.

The silver salt apparently has the following functions:

a) It makes possible a relatively high ethylene concentration (in the solution);

b) Presumably, it enhances the reactivity of the double bond;

c) It forms a metal-redox system with the peroxide.

The ethylene/silver salt molar ratio is important. A large excess of silver salt leads to low polymerization rates, because a considerable amount of activator is consumed in the reaction between the silver salt and the peroxide. For ethylene/silver salt ratios $\lesssim 1$, the polymerization rate is approximately proportional to the first power of the ethylene concentration and to the square root of the catalyst concentration. For ethylene/silver ratios $\gg 1$ (*e.g.* at pressures > 50 atm. at 30 °C), an increase in pressure does not increase the polymerization rate. Free, non-complexed ethylene apparently has a slight chain-cleaving effect.

Polymerization initiation may also be promoted by high-energy radiation. In this case, the quantum yield is very high compared to that obtained in previous investigations in the field of ethylene polymerization.

Polyethylene of a wide molecular weight distribution was prepared. Its density is in the lower range of Ziegler-type polyethylene. Various observations point to the presence of long side chains.

Steric Effects and Tacticity in the Free Radical Polymerization of Methacrylic Acid

G. Schröder, Darmstadt (Germany)

Methacrylic acid in aqueous solution was polymerized at different temperatures both as the free acid, at pH 2.5, and as the sodium salt, at pH 7–8. The tacticity was determined following methylation to polymethyl methacrylate. In both cases, the syndiotactic fractions decreased with increasing temperature. Syndiotacticity was substantially greater in the polymerization of the salt than in that of the free acid.

Polymerization of methacrylic acid in organic solvents afforded considerably less syndiotactic polymerizates. The cation size had no, or at the most only a slight, effect on the polymerization of several methacrylic salts, whereas the solvent effect was strong.

To explain this, it was assumed that the addition of a new monomer to the growing macroradical is favored for the conformation displaying the least steric and electrostatic interaction. It was found that the different space requirements and electrostatic interactions of the substituents cannot be the only factors determining tacticity, but that, at least in the case of the methacrylic acid and its salts, the solvate shell also must be considered.

Branching of Polyvinyl Acetate

G. V. Schulz and *D. Stein*, Mainz (Germany)

The degree of branching of polyvinyl acetate is determined by the transfer constant C_p and the degree of conversion. The authors obtained a value for C_p by the α-polymer method (*Schulz, Henrici, Olivé*, 1955). Result: $C_p \times 10^4 = 2.5 \pm 0.5$. This value is not essentially higher than that for polystyrene. In the preparation of α-polymers, it was found that special precautionary measures were necessary, *i.e.* the careful exclusion of oxygen and the avoidance of higher temperatures. Oxygen leads to high chain transfer constants (*Stein* and *Schulz*, 1960) and incorrect results; the use of too high a temperature results in the formation of allyl groups which even in low concentrations exert a strong inhibiting effect.

In addition, the absolute values of the constants k_w and k_{ab} were re-determined for this purpose making use of the experiments of *Mattheson* (1949) and *Bartlett* (1950) which were based on intermittent irradiation. It was found that both constants are considerably higher than the still generally accepted literature values. For example, at 60 °C, $k_{ab} = 5 \times 10^8$. This suggests that, even in the absence of the Trommsdorff effect, diffusion processes control the course of polymerization (at least in part).

Changes in Entropy and Energy on Elastic Extension of Swelled Polyvinyl Alcohol Model Filaments

H. Abe and *W. Prins*, Delft (Holland)

Isotropic, cylindrical model filaments were prepared from an aqueous polyvinyl alcohol gel containing 20 % polyvinyl alcohol (completely hydrolyzed polyvinyl alcohol; < 1 % acetyl groups) using a methyl alcohol coagulating bath. The swelled filaments were cross-linked at varying temperatures with monothiodiacetaldehyde in an acidified, aqueous Na_2SO_4 bath. In this fashion, filaments (0.5 to 0.8 mm in diameter) of different degrees of cross-linking (from 1 to 11 % of reacted OH groups) and of swelling (from 2 to 9) were obtained. Another type of filament was spun from a 40 % solution of partially hydrolyzed polyvinyl alcohols (13 % acetyl groups) and treated with formaldehyde. In this case, only intramolecular rings were formed (36 % of the hydroxyl groups reacted). The two types of filaments are no longer soluble in boiling water.

Stress-strain and stress-temperature curves for filaments in swelling equilibrium with water (from 20 to 90 °C) were obtained. A complete thermodynamic analysis of elasticity also requires measurements of the filament volume (microscopically) as a function of extension and temperature [1, 2]. The analysis shows that the elasticity of the formaldehyde fiber is in agreement with the generalized rubber theory [3] (among other things, the extension energy is negative and approximately as large as the negative extension entropy).

[1] Belg. Patent 602153, issued to Farbwerke Hoechst AG. (Inventors: *E. Nölken, G. Messwarb, G. Bier*, and *M. Lederer*). In addition to the inventors the following are named as collaborators: *W. Eichhorn, K. Hofmann, St. Müllner, S. Rösinger, O. Fuchs, and H. J. Leugering*.

[1] *A. Ciferri, C. A. J. Hoeve*, and *P. J. Flory*, J. Amer. chem. Soc. *83*, 1015 (1961).

[2] *S. Gabrail* and *W. Prins*, J. polymer Sci. *51*, 279 (1961).

[3] *A. Ciferri*, J. polymer Sci. *54*, 149 (1961).

Above 70 °C, the dialdehyde fibers behave almost like ideal rubber (no extension energy). However, they show large positive extension energies and extension entropies below 70 °C. This behavior at low temperatures probably is a result of the tendency of completely hydrolyzed polyvinyl alcohols to crystallize partially, or of the tendency of its chains to form partial helices.

Association of High Polymers in Solution

J. Hengstenberg and *E. Schuch*, Ludwigshafen (Germany)

The presence of aggregates in solutions of high polymers has been established many times. The formation of these aggregates is often reversible and affects the behavior of the solutions especially during fractionation and molecular weight determinations.

In the case of polyvinyl chloride, the authors have thoroughly examined the prerequisites for the formation of aggregates as well as their behavior. Investigations with the aid of the ultracentrifuge showed the aggregates to consist of a certain number of individual molecules. They form discrete particles, the amounts of which may correspond to as much as 50 % of the dissolved substance. Polyvinyl chloride aggregates are formed in dioxane, methyl ethyl ketone, dimethylformamide, tetrahydrofuran and in alcohol-containing solvents. In general, no aggregate formation has been observed in cyclohexanone. Their formation in solvent mixtures depends on the procedure used for dissolution.

The molecular weight exerts a strong influence on association. The proportion of aggregates increases markedly with increasing molecular weight. In solutions of high polymer fractions, it may amount to 50 % (this amount is considerably lower for non-fractionated products). The dependence of the amount of aggregates on concentration is slight; association is still evident for c = 0.1 g/100 ml.

In most systems, the aggregates dissociate at higher temperatures, but re-form on cooling, although very slowly.

The particle weight of the aggregates can be estimated from their sedimentation coefficient. For the aggregates (extrapolating to a concentration of c = 0), the sedimentation constant is approximately 4 to 6 times greater than for the individual molecules. The particle diameter, determined with the electron microscope, was found to be 158 Å.

[VB 564/27 IE]

On the Mechanism of Photosynthesis

Alexander Müller, *B. Rumberg*, and *H.T. Witt*, Marburg/L. (Germany)

Green plant cells have been examined by flash photometry and, so far, eight different types of absorption changes have been found. These changes were measured by means of very sensitive methods and their time course was recorded. They are caused:

1) by the formation of the π–π^* triplet states of chlorophyll-a and b (Chl–a_0 and Chl–b_0); 2) by the formation of a probably metastable state of chlorophyll-a (Chl–a_1); 3) by photooxidation of chlorophyll-a (Chl–a); or a compound similar to chlorophyll-a 4) by oxidation of cytochrome (Cyt); 5) by photo-reduction of a substance X (some properties of X were investigated); 6) by reduction of plastoquinone (Pl) (statically measured); 7) by reduction of added "2,6-dichlorophenol indophenol" (In); 8) by reaction of an unknown compound with changes in absorption at 420 mμ.

Reactions 1) and 2) are not directly connected with photosynthesis. Investigation of the relationship of reactions 3)–7) to numerous physical and chemical parameters resulted – in comparison with [1] – in an extended reaction scheme which is presented in Fig. 1 in a simplified form.

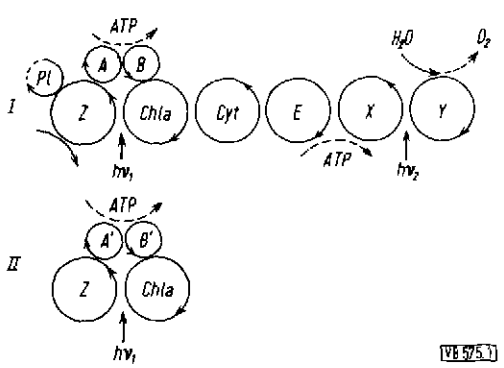


Fig. 1

The solid arrows indicate the direction of the flow of electrons. In the reaction system I triphosphopyridine nucleotide (TPN) is reduced by transfer of electrons from water, at least, *via* Y, X, E, Cyt, Chl-a, and Z. Probably Z can also reduce plastoquinone [2]. The electron transfer between Chl-a and Z, and the transfer between X and Y (which are both endergonic in the dark) are made possible by two light absorptions $h\nu_1$ and $h\nu_2$. Very probably, only a cyclic e-transport takes place in system (II).

$$\text{Chl–a} \xrightarrow{h\nu_1} \text{Z} \rightarrow \text{A}' \rightarrow \text{B}' \rightarrow \text{Chl–a}.$$

This also occurs in (I) but only then when A is the only electron acceptor available to Z. Altogether, at least 3 light reactions are involved in photosynthesis. From the redox potentials of the substances, it follows that phosphorylation of ADP to ATP can be coupled with the reactions indicated in Fig. 1. With ATP and $TPNH_2$, carbon dioxide can be reduced to sugar *via* the Calvin cycle [3]. – Concerning 2 light reactions in photosynthesis cf. [4]. The reaction mechanism described in Fig. 1 can be separated in the case of chloroplasts (spinach) into seven partial reactions (diagrammatically represented in Fig. 2) by the following stages:

(1) Overall sequence as in Fig. 1.

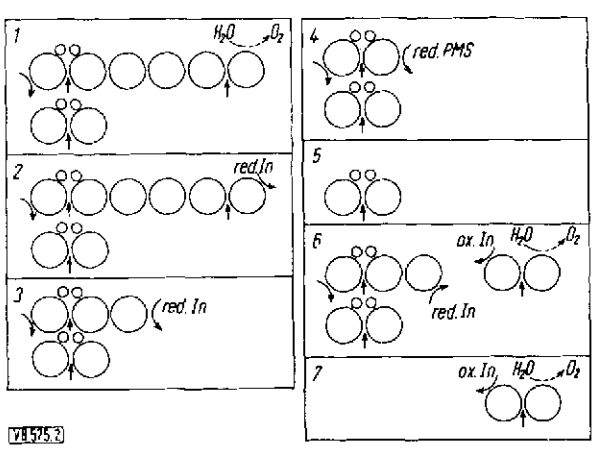


Fig. 2

[1] *H.T. Witt*, *A. Müller*, and *B. Rumberg*, Nature (London) *191*, 194 (1961); *192*, 967 (1961); Angew. Chem. *73*, 507 (1961).

[2] *M. Klingenberg*, *A. Müller*, *P. Schmidt-Mende*, and *H.T. Witt*, Nature (London) (1962), in press.

[3] *M. Calvin*, Angew. Chem. *74*, 165 (1962).

[4] *H. Kautsky et al.*, Biochem. Z. *332*, 277 (1960); *B. Kok et al.*: Light and Life. John Hopkins Press, Baltimore 1961, p. 397; *M. B. Allen et al.*, Biochem. biophys. Res. Commun. *4*, 271 (1961); *L. N. M. Duysens et al.*, Nature (London) *190*, 510 (1961); *M. Losada et al.*, ibid. *190*, 606 (1961).

(2) Reversible blocking of water splitting by Chlorophenyl-dimethylurea (CMU); reduced dichloroindophenol (red. In) acts as electron donor to Y instead of H_2O.

(3) Irreversible blocking of the temperature sensitive reactions of X and Y on warming to 50–60 °C; the electron donor for cytochrome is reduced In. Reversible blocking of X and Y is possible by illumination at −150 °C, or by exclusive irradiation with $h\nu_I$ ($\lambda > 700$ mμ) or by extraction with petroleum ether.

(4) Blocking of X and Y as in (3) for example by warming to 50–60 °C. Cytochrome is by-passed by the action of reduced phenazine methosulfate (red. PMS) which at higher concentrations > 10^{-5} mole/litre) acts as an electron donor to Chl-a.

(5) Isolation of system II. For this purpose, cyclic electron transport in I is blocked by addition of, for example, oxidized indigocarmine which operates as electron acceptor to Z. Non-cyclic electron transfer in I is suppressed by the blocking of water splitting with CMU.

(6) Uncoupling of the two light reactions in I by addition of oxidized In and reduced In. Oxidized In acts as an electron acceptor to X, reduced In. acts as e-donor to cytochrome.

(7) Blocking of the light reactions $h\nu_I$ in I and $h\nu_I$ in II so that only the light reaction $h\nu_2$ can take place. This can be achieved by chemical oxidation of Chl-a with ferricyanide. Oxidized In. accepts electrons from X. Details see [5].

[GDCh-Ortsverbände München and Berlin (Germany), February 15th. and 22nd. 1962, respectively]

[VB 575/26 *IE*]

[5] *B. Rumberg, A. Müller*, and *H.T. Witt*, Nature (London), in the press.

X-Ray Structure Analyses of Phenyl-Substituted Acetylene Compounds of Group V Elements

D. Mootz, Braunschweig (Germany)

X-Ray crystal structure determinations were reported for the following compounds

$(C_6H_5)_2As{-}C{\equiv}C{-}As(C_6H_5)_2$ (I)

$(C_6H_6)_2P{-}C{\equiv}C{-}P(C_6H_5)_2$ (II)

$(C_6H_5{-}C{\equiv}C{-})_3P$ (III)

$(C_6H_5{-}C{\equiv}C{-})_3As$ (IV)

$(C_6H_5{-}C{\equiv}C{-})_3Sb$ (V),

$(C_6H_5{-}C{\equiv}C{-})_3P \rightarrow S$ (VI)

Molecule (I) possesses a center of symmetry. Compounds (III), (IV), and (V) are isomorphous; their molecules show threefold rotational symmetry, a pyramidal configuration, and propeller-type twisting of the rings. The molecules of (VI), and perhaps also of (II) belong to general point locations and therefore do not necessarily possess a characteristic symmetry in the crystal.

Preliminary phase sets were obtained by the use of the heavy atom method, partly in combination with Patterson syntheses. Refinements for (I) by the use of Fourier syntheses have shown essentially an intramolecular arrangement of the atoms in two planes such that the four benzene rings form, in pairs, two approximately planar partial structures, each of which contains the grouping As–C≡C–As in the center. The mesomerism that is made possible by this arrangement can also be detected by a certain equalization of the bond lengths.

Analogous situations occur in the cases of (III), (IV), and (V). The rings are twisted into the surface planes of the pyramid, so that three planar partial structures result. Each plane contains the heteroatom with two acetylene groups and one benzene ring. The bond lengths again indicate an increased capacity for mesomeric behaviour.

H. Hartmann et al. explained the weak basicity of these compounds by an extensive involvement of the so-called free electron pair of the heteroatom in the resonance states of the entire molecule; this is in good agreement with the results obtained by X-ray structural analysis.

[Chemisches Kolloquium, Technische Hochschule Braunschweig (Germany), February 19th, 1962] [VB 573/23 IE]

Recent Findings in the Chemistry of Complex Acetylides

R. Nast, Hamburg (Germany)

Following a review of the complex 3d-metal acetylides, the preparation and properties of tetra(alkynyl) complexes of Cd (II) and Hg (II) were described. The latter complexes can be precipitated from liquid ammonia as pure, colorless, crystalline barium salts, according to the equation:

$$M(SCN)_2 + 4\ KC{\equiv}CR \rightarrow K_2[M(C{\equiv}CR)_4] + 2\ KSCN$$
$$(M = Cd, Hg;\ R = H, C_6H_5) \qquad \downarrow + Ba(SCN)_2$$
$$Ba[M(C{\equiv}CR)_4]$$

One or two phenyl groups of diphenylzinc can be split off through protolysis by allowing an ether solution of diphenylzinc to react with phenylacetylene in the molar ratio of 1:1, or 1:2, whereby the crystalline, moisture-sensitive compounds $C_6H_5ZnC{\equiv}CC_6H_5$ and $Zn(C{\equiv}CC_6H_5)_2$ are formed, respectively. The latter is soluble in liquid ammonia in the form of a non electrolyte, $[Zn(C_2C_6H_5)_2 \cdot 2NH_3]$. Phenylzinc phenylacetylide displays a tendency toward dismutation in the solid as well as in the dissolved state, whereby, for example, zinc *bis*(phenylacetylide) and diphenylzinc are formed in liquid ammonia, according to the reaction

$$2\ C_6H_5ZnC{\equiv}CC_6H_5 + 2\ NH_3 \rightarrow [Zn(C{\equiv}CC_6H_5)_2 \cdot 2\ NH_3] + Zn(C_6H_5)_2$$

Diphenylzinc is first ammonolyzed to reactive zincamide by evaporation of the NH_3, and the zincamide can then be converted with gaseous acetylene to $[Zn(C{\equiv}CH)_2 \cdot 2NH_3]$ as follows:

$$Zn(NH_2)_2 + C_2H_2 \rightarrow [Zn(C{\equiv}CH)_2 \cdot 2\ NH_3]$$

Finally, by reacting the acetylides of Ag(I) and Au(I) in liquid ammonia, dialkynyl argentate (I), or aurate (I) can be isolated.

$$MC{\equiv}CR + KC{\equiv}CR \rightarrow K[M(C{\equiv}CR)_2]$$
$$(M = Ag, Au)$$

Complex acetylides of the type *cis*-$Ba[Pd(CN)_2(C{\equiv}CR)_2]$, or $K_2[Pt(C{\equiv}CR)_4]$, which are diamagnetic and without doubt contain anions with a planar structure, can be prepared in pure form by reacting alkali acetylides in liquid NH_3 with $K_2[Pd(CN)_4]$ or $K_2[Pt(SCN)_4]$. By reducing acetylide-containing solutions of the tetracyano complexes of Pd(II) and Pt(II) with potassium in liquid ammonia according to the reaction

$$K_2[M(CN)_4] + 2\ KC{\equiv}CR + 2\ K \rightarrow K_2[M(C{\equiv}CR)_2]\downarrow + 4\ KCN$$
$$(M = Pd, Pt;\ R = H, CH_3, C_6H_5)$$

yellow diamagnetic crystals of dialkynyl complexes of Pd(O) and Pt(O) can be precipitated, which, although not explosive, are pyrophoric. The particular ability of alkynyl ligands to stabilize the lower oxidation states of the central metal atom is further underlined by the reaction

$$[M(CO)_3(NH_3)_3] + 3\ KC{\equiv}CR \xrightarrow{\text{liq. } NH_3}$$
$$K_3[M(CO)_3(C{\equiv}CR)_3]\downarrow + 3\ NH_3$$
$$(M = Cr, Mo, W;\ R = H, CH_3, C_6H_5)$$

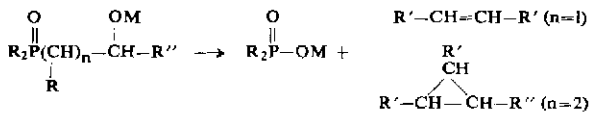
which permits the preparation of pure diamagnetic potassium tricarbonyl(trialkynyl)-metalates (O) of Cr, Mo and W.

[Chemische Gesellschaft Heidelberg (Germany), February 20th. 1962]

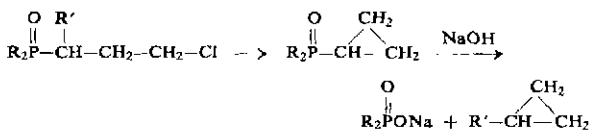
[VB 574/25 IE]

SELECTED ABSTRACTS

Cyclopropane derivatives from metalated phosphine oxides and olefin oxides were obtained by *L. Horner, H. Hoffmann,* and *V. G. Toscano.* Potassium and sodium salts of β-hydroxyphosphine oxides decompose into olefins and phosphinates (P=O-activated vinylation). Similarly, cyclopropane derivatives are formed from γ-hydroxyphosphine oxides (yield about 60 %). Both reactions are based on a common mechanism:

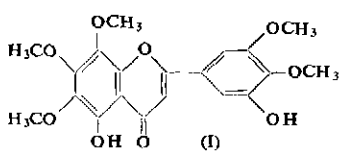


In the vinylation reaction, R can be C_6H_5 (phosphine oxides); alkoxy (phosphonic ester); C_6H_5 and alkoxy together (phosphinic esters). In the formation of cyclopropane, R = C_6H_5. γ-Hydroxyphosphine oxides may be obtained by condensation of α-metalated phosphine oxides with olefin oxides (yield 60–90 %), and can be converted into γ-chlorophosphine oxides (yield about 80 %). From the latter, cyclopropyl



phosphine oxides are formed by internal alkylation via the action of metalating agents. Cyclopropylphosphine oxides undergo scission into cyclopropane and phosphinates when heated with NaOH. / Chem. Ber. *95*, 536 (1962). / —Ho. [Rd 127/51 IE]

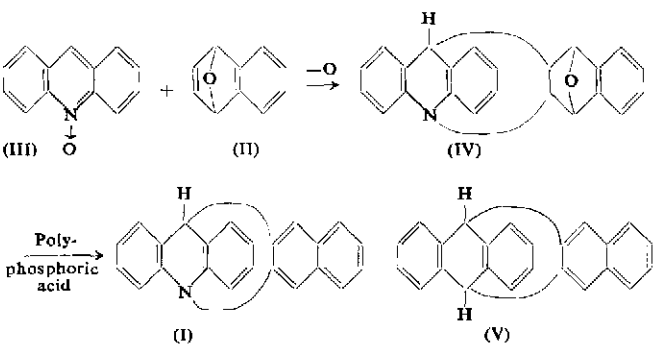
Digicitrin, a new flavone from the leaves of the red foxglove (*Digitalis purpurea L.*) was isolated in 0.002 % yield from air-dried leaves by *A. Fürst* et al. by benzene extraction and chromatographic separation on Al_2O_3. Digicitrin (I), yellow-orange crystals, m.p. 178–179 °C (from glacial acetic acid and by sublimation at 150–160 °/0.01 mm.), $[\alpha]_D^{20} = 0°$ (c = 1, $CHCl_3$), $C_{21}H_{22}O_{10}$, forms a dimethyl ether which yields



only one phenolic compound ($C_{13}H_{18}O_7$) besides tri-*O*-methylgallic acid during alkaline cleavage. This phenolic compound was identified as 2-hydroxy-ω,3,4,5,6-pentamethoxyacetophenone. Compound (I) was found to have the structure represented by 5,3′-dihydroxy-3,6,7,8,4′,5′-hexamethoxyflavone. It is the richest in oxygen of the flavones so far found in nature. / Helv. chim. Acta *45*, 232 (1962) / —De. [Rd 94/46 IE]

A novel synthesis of heavy acetone, using only 1.5 times the stoichiometric quantity of D_2O, is reported by *H. Hunziker, W. Good, R. Meyer,* and *H. H. Günthard.* Mg_2C, obtained by treating Mg with pentane at 690 °C, reacts with D_2O at 150 °C and pressures of 0.05 to 1 atm. to give perdeuterated propyne C_3D_4, which is then converted to perdeuterated acetone CD_3COCD_3, in the presence of $HgSO_4$ as catalyst. Since heavy water present in excess such as that bound in the $Mg(OD)_2$ can be easily recovered, essentially pure fully deuterated acetone is obtained in a process which requires only 5 to 10 % excess over the theoretical amount of D_2O. / Helv. chim. Acta *45*, 59 (1962). / —De. [Rd 132/56 IE]

Benzoazatriptycene (I) was synthesized by *G. Wittig* and *G. Steinhoff* by the reaction of dihydronaphthalene endoxide (II) with acridine *N*-oxide (III) and dehydration of the primary adduct (IV) with polyphosphoric acid.



The ultravioletspectrum of benzoazatriptycene agrees with that of benzotriptycene (V); benzoazatriptycene is more basic than triphenylamine. / Chem. Ber. *95*, 203 (1962) / —Sk. [Rd 93/45 IE]

BOOK REVIEWS

Gmelins Handbuch der anorganischen Chemie (Gmelin's Handbook of Inorganic Chemistry), 8th edition, new and completely revised. Published by the Gmelin-Institut für anorganische Chemie und Grenzgebiete in der Max-Planck-Gesellschaft zur Förderung der Wissenschaften. Begun by *R. J. Meyer* and continued by *Erich Pietsch,* Verlag Chemie, GmbH., Weinheim/Bergstraße, Germany.

The burden of other assignments compelled the reviewer to interrupt for quite some time the discussion of the Gmelin volumes. On the other hand, this circumstance now permits him to make a summary report covering a long time interval and thus allows an evaluation of the work of the Gmelin editorial staff over the entire period. At the present time the number of signature sheets in the fascicles published per year lies between 150 and 200. Thus, in 1958 six fascicles appeared (Copper B 1, Oxygen 3, Germanium Supplement, Zirconium, Hafnium Supplement, Silicon C), with 2690 pages of text and 547 figures (total price: 1670 DM); in 1959, five fascicles (Fluorine Supplement, Iron D Supplement, Cadmium Supplement, Silicon B, Arrangement of the Indices and the Code), with 2672 pages of text and 711 figures (total price: 1629 DM); in 1960, six fascicles (Barium Supplement, Strontium Supplement, Oxygen 4, Sulfur B 2, Mercury 1, Lithium Supplement), with 2990 pages of text and 463 figures (total price: 1846 DM), and in 1961, three fascicles (Copper B 2, Calcium B 3, Cobalt A Supplement), with 2150 pages of text and 359 figures (total price: 1355 DM). For the current year 1962, six additional fascicles (Oxygen 5, Sulfur B 3, Mercury 2, Chromium B, Cobalt B Supplement, Iron A Supplement), containing approximately 200 signature sheets, corresponding to around 3000 pages of text, are envisioned. This impressive task was, and is, carried out by a relatively small working staff, including, at the present time, 59 scientific contributing editors who, together with a staff of scientific-technical and technical collaborators, under the direction of six group and section leaders, evaluate and prepare for publication a mass of factual material which has been abstracted from more than 5500 domestic and foreign journals and placed in a subject file containing, at the latest count, 2300000 index cards.

The total, beginning with the appearance of the first issue of the 8th edition of "Gmelin" (Zink, 1924), including the "Gmelin Patent Collection," consists of more than 60000 pages of text; obviously, there will never be an end to this edition, since the chemical literature is increasing alarmingly from year to year, so that, whenever a new volume appears,

the volumes that are oldest at that time are again hopelessly obsolete, and, therefore, once more require supplementation.

Among the innovations introduced during the period under review may be mentioned: a) the expansion of the index by the addition of an English-language section, first introduced in 1958 in the supplementary volume on germanium, b) the addition of marginal notes in English, first introduced in the same year in the supplementary volume on hafnium, and c) the resolution, passed in 1961 by the Gmelin editorial board, to rescind again the cutoff date previously set for the end of 1949 for all volumes appearing after 1950, and to bring up to date the evaluation of the literature in all future issues, so far as technically possible. Plainly, this latter resolution will be greeted with special satisfaction by the users of "Gmelin", since the latest issues of the Handbuch of necessity have displayed a painfully obvious gap of as much as ten years, which can hardly be bridged by an occasional reference to more recent work.

The individual fascicles will be reviewed in the forementioned order of their appearance. This discussion continues the last review [1], beginning with the six fascicles for 1958.

System No. 60: Copper. Part B, fascicle 1 (Compounds to Copper Tellurate), 1958, XXVII, 624 pages with 58 illustrations, index. Paperbound 387 DM. – Edited by *Olga Angern, Hildegard Banse, A. Hirsch, Erna Hoffmann, G. Kirschstein, P. Koch, A. Kunze, Margarete Lehl-Thalinger, Ellen von Lindeiner-Schön, Gertrud Pietsch-Wilcke, L. Roth, Hildegard Wendt*, and *H.-G. Wuttge*.

Three parts are envisioned for the complete discussion of copper (Part A: History, Occurrence, The Element. Part B: Compounds of Copper. Part C: Alloys of Copper). Of these, Part A (1955), with 1465 pages and 425 figures, already exists in completed form. No fascicle from Part C has been published up to the present time. From Part B, there appeared in 1958 fascicle 1 (to be discussed here), comprising the compounds of copper with elements up to System No. 11 (tellurium), and, in 1961, Volume 2 (to be reviewed later), comprising the compounds of copper with elements of System No. 13 (boron) up to System No. 19 (bismuth).

Among the compounds of copper with hydrogen, oxygen, nitrogen, fluorine, chlorine, bromine, iodine, sulfur, selenium, and tellurium, treated in the present fascicle B 1, especially comprehensive coverages of the following compounds are given: Cu_2O (30 pages), CuO (32 pages), $Cu(OH)_2$ (35 pages), $Cu(NO_3)_2$ (30 pages), CuCl (48 pages), $CuCl_2$ (73 pages), CuBr (23 pages), $CuBr_2$ (18 pages), CuI (27 pages), Cu_2S (36 pages), and $CuSO_4$ (100 pages). These alone occupy more than 70 % of the total number of pages in the issue. The properties of the copper compounds that also occur as minerals are mentioned at times in conjunction with the properties of the synthetic compounds, in departure from established custom. In addition to the compounds themselves, their complex addition compounds (basic salts, hydrates, ammoniates, etc.) are also on occasion described, while the chemistry of the inner complex salts will be treated within the framework of fascicle B 3. On glancing through the table of contents, the preparative inorganic chemist comes upon numerous compounds still designated with a question mark, which deserve a fuller investigation in the interest of complete systemization. The contradictory data on the copper(III) oxide, Cu_2O_3, particularly suggest further research.

The literature is complete to the end of 1949, and in special cases it is covered up to 1954.

System No. 3: Oxygen, Fascicle 3 (Elementary Oxygen), 1958, XI, 518 pages with 100 illustrations, index. Paper bound 316 DM. Edited by *M. Atterer, Krista von Baczko, Hildegard Banse, Anna Bohne-Neuber, H. Gedschold, R. Glauner, G. Hantke, Erna Hoffmann, G. Kirschstein, H. K. Kugler, Margarete Lehl-Thalinger, Imberta Leitner, Gertrud Pietsch-Wilcke, K. Rumpf*, and *F. Seuferling*.

[1] Angew. Chem. *71*, 347 (1959).

Fascicles 1 and 2 (a total of 300 pages of text with 32 figures), which appeared in 1943 (reprinted in 1953) and 1951, dealt, respectively, with the history, and the occurrence and technology, of oxygen and its compounds with hydrogen. The present fascicle 3 is devoted to elementary oxygen, and begins with a 17-page review on the preparation and purification of oxygen in the laboratory, including the production of liquid and solid oxygen, and the concentration and isolation of oxygen isotopes, especially isotope ^{18}O. In the 275 pages following, the physical properties of oxygen are discussed.

Here, under the heading "Atom," the major part is devoted to a compilation of the extensive numerical data on the atomic and ionic radius, and on the atomic volume of oxygen, as well as a discussion of their dependence on the other atoms forming the bond. Under the section on the atomic weight, the century-and-a-half-old controversy concerning the use of H or O as a basis for the atomic weights is covered in a historical survey with numerous references. Through a comparison of the physical and the chemical scales of atomic weight the problems involved in the existence of two such scales are demonstrated. These differences were, however, brought to an end in 1961 by the agreement made between physicists and chemists to use $^{12}C = 12.0000$ as the basis for the relative atomic weights. The statement on the bonding of oxygen, which concludes the "Atom" section and according to which, the oxygen atom, after forming bonds with two H atoms, stoichiometrically univalent groups, or radicals, can bring into play "one of the two unpaired electrons" (by this is meant one of the two free electron pairs) for binding a proton, and therefore can become trivalent is somewhat surprising. Also, the acetate ion CH_3COO (instead of the much simpler, inorganic hydroxyl ion OH^-) is given here as an example of the univalence of oxygen.

The section "Molecule" deals exhaustively with the existence, the structure and the properties of the normal state as well as with numerous excited states of atomic and molecular oxygen.

From the point of view of the crystallographic properties, the sections on the three O_2 modifications and on the atomic structure factors of oxygen are of special interest. Among the thermo-mechanical properties, the data on the weight of a liter of oxygen under standard conditions are of great interest as reference quantities for the density of gases. Also of interest are the data on the boiling point of oxygen as a fixed point of the temperature scale, and on the solubility and sorption of oxygen. The extensive data extending over the range of oxygen optics (line spectra, X-ray spectra, microwave spectra, band systems, etc.), and on the electrical properties of oxygen (electron affinities of the reactions $O + e^- \rightarrow O^-$, $O + 2e^- \rightarrow O^{2-}$, $O_2 + e^- \rightarrow O_2^-$, $O_2 + 2e^- \rightarrow O_2^{2-}$), should also be emphasized.

In the chapter "Electrochemical Behavior" (30 pages), model forms and potentials of the oxygen electrode are treated. These data are of special interest in view of the still unsolved problem of a practical fuel cell.

According to the Gmelin system of classification (the "principle of the last place"), only the reaction of oxygen (System No. 3) with hydrogen (System No. 2) is treated in the chapter on the chemical properties (196 pages). Especially praiseworthy here is the introductory survey, which, together with preliminary remarks for the separate sections, gives information in condensed form to the user who is only slightly familiar with the subject. The introduction also joins together subjects that are necessarily separated from each other by the classification, and facilitates the use of the volume by functioning as an expanded table of contents. In particular, the following subject is treated: the triggering of reactions by O and H atoms foreign to the reaction, by ionizing radiation, by static electric discharges, by photochemical processes, and by surface catalysis. The most extensive section of the chapter is devoted to thermal reactions. Among the headings, those dealing with the limits of explosive and non-explosive reactions, reaction mechanisms, and the effect of the dimensions and material of the container and of foreign matter may be noted here. Data on the special use of this information

in the area of hydrogen flames are found in the last section, in which all the literature data on spectra, mechanisms, chain propagators, intermediate products, flame temperature, flame velocities, ignition limits, and ignition temperature are brought together.

All in all, this is an exceedingly worthwhile work in every respect, and gives a complete survey of the literature up to the end of 1949.

System No. 45: Germanium. Supplementary Volume, 1958, XLIV, 576 pages with 290 illustrations, index. Paperbound 359 DM. Edited by *Frauke E. Cirkler-Trettin, H. Gedschold, A. Hirsch, Erna Hoffmann, W. A. von Meyeren, W. Müller, L. Roth, F. Seuferling* and *Hildegard Wendt.*

The turbulent development in the area of germanium in recent times is expressed in the fact that the main volume "Germanium," which appeared in 1931 (reprinted in 1935), contained only 62 pages and two figures, while the present supplementary volume, describing the advances in the years 1931–1953, requires nearly ten times as much space, *i.e.*, 576 pages and 290 figures.

After the report on the occurrence of germanium (26 pages), the physics of germanium, requiring 414 pages, occupies by far the greatest amount of space, that is, three-quarters of the total number of pages in the volume; within this chapter on physics, the optical (38 pages), electrical (255 pages), and photoelectric properties (68 pages), with a total of 361 pages, significantly take up the greatest amount of space (in the main volume, the electrical and photoelectric data were compressed into a single page!). Here we see documented the increasing importance and use of germanium in the form of semi-conductor diodes, transistors, and photo-transistors. Notice should be made of the successful efforts of the two collaborators responsible for this section (*Frauke E. Cirkler-Trettin* and *Wilhelm A. von Meyeren*) to bring this extensive and complicated material within the range of the non-specialist.

In the chapter on the optical properties, the absorption and emission spectra in the total spectral range from the short-wave ultraviolet, through the visible, up to the long-wave infrared, as well as the X-ray spectra, recombination phenomena and energy band theory, are extensively discussed; the latter, for its part, is of importance in describing the electrical and photo-electric behavior.

The chapter on the electrical properties is divided into two subchapters: germanium free of barrier layers and germanium with barrier layers. In the first subchapter, the conduction phenomena in the pure, intrinsic conductor material (intrinsic semi-conductor) is first discussed, and then conduction process in impurity conductor germanium (extrinsic semi-conductor), in which the various methods of "doping" the germanium with donor and acceptor impurities are also gone into extensively. The second subchapter is devoted to the physics of germanium barrier layers, and reports first on the theory of germanium diodes (rectifiers) and transistors (amplifiers), in order then to go into the technology, *i.e.* into the processes for the production of good rectifying and amplifying devices and the common electrical circuits and technical applications of these diodes and transistors.

The chapter on photo-electric properties considers both the surface and internal photo-electric effect. In the latter case, within the framework of a section on the internal intrinsic photo-effect, the photo-electric phenomena occurring in homogeneous germanium free of barrier layers and in non-homogeneous germanium with barrier layers are first considered. This leads to a discussion of the photo-effects observed at barrier layers in photo-diodes, photo-transistors, and photo-elements – processes which already have practical significance. An additional section on the internal extrinsic photo-effect reports on the "impurity photo-effect" of "doped" germanium crystals, followed by briefer sections on the photo-diffusion effect and the Hall photo-effect.

Taken all in all, this part of the germanium supplementary volume forms an especially impressive monograph, completely covering also the entire difficultly accessible literature up to the end of 1954. It is of extraordinary value not only to the chemist, but also to the physicist and engineer.

In comparison with the material on the physical properties, the chemical part of the germanium volume (preparation of germanium and germanium compounds, chemical and electrochemical behavior of germanium, detection and determination, alloys, compounds), with a total of 136 pages, is of far lesser dimensions. Compounds and alloys of germanium (System No. 45) with the elements of System No. < 45, occupy the largest part here (101 pages). Half of the section is devoted to the germanium hydrides (12 pages), germanium oxides (14 pages), germanium chlorides (14 pages), and organic germanium compounds (12 pages). Here are found data on the hydrides $(GeH)_x$, $(GeH_2)_x$, GeH_4, Ge_2H_6, and Ge_3H_8, and references to the (also recently isolated) higher hydrides, Ge_4H_{10} and Ge_5H_{12}, data on the oxides, GeO and GeO_2, and their "hydrates" [2]: germanium hydroxide, $Ge(OH)_2$, and germanium acid, H_2GeO_3, as well as data on the germanium chlorides $(GeCl)_x$, $GeCl_2$, $GeCl_4$, GeH_nCl_{4-n}, Ge_2Cl_6, $GeOCl_2$, and Ge_2OCl_6. The chapter on organic compounds with Ge–C bonds is especially valuable; it includes almost 300 compounds, partially with chain and ring structure,. These compounds together with the organic esters $Ge(OR)_4$, thioesters $(Ge(SR)_4$, and amines $Ge(NR_2)_4$[3] are summarized in a table.

System No. 42: Zirconium. 1958, XXXVII, 448 pages with 57 illustrations, index. Paper bound 280 DM. – Edited by *M. Atterer, H. Balters, Hildegard Banse, K.-Ch. Buschbeck, H. Gedschold, R. Glauner, A. Hirsch, Isa Kubach, W. Müller, J. Nägler, Anne-Lise Neumann, Gertrud Pietsch Wilcke, N. Polutoff, K. Rumpf, F. Seuferling, K. Swars,* and *Hildegard Wendt.*

The present completed 448-page volume on zirconium of this, the (current) 8th edition of Gmelin, takes the place of a 206-page chapter in the volume, "Zirconium, Hafnium, Thorium, Niobium, Tantalum, Rare Earths" of the 7th edition, which appeared 34 years ago (1928), and surveys the literature up to the end of 1949.

After a brief (1 page) outline of the history of the element, discovered 173 years ago (1789) by *M. H. Klaproth* in the mineral zircon, from which it takes its name, the volume deals, in the usual thorough and complete way (48 pages), with the occurrence of zirconium. The separation of the zirconium mineral from the other useful minerals occurring with it usually requires extensive dressing processes, purification procedures, processes for removal of other metals, and methods of separation, which are discussed summarily in a 34-page chapter, together with data on the technical preparation of special zirconium compounds and on the uses of zirconium (as an industrial raw material, in vacuum technology and electrical engineering, in pyrotechnics, and as a constituent of alloys) and of zirconium compounds (for example, zirconium dioxide, zirconium silicate, and other compounds used in the manufacture of refractory substances and glass, as an opaque material for enamels and glazes, as fillers and pigments, catalysts and sorbents, and in illumination and electronics technology). The additional 108-page discussion on elementary zirconium is divided, as usual, into the preparation (18 pages), the physical properties (55 pages), and the electrochemical and chemical behavior (35 pages) of the element. In the latter section, the summarizing description, "General Reactions of Zirconium Salts", in which the analytical reactions of zirconium are also extensively considered, should be given special mention.

The five-page chapter that follows, on the alloys of zirconium known up to the present, covers the alloys of zirconium

[2] On page 493, a typographical error occurs: instead of the correct heading, "Germanium and Oxygen", the heading "Germanium and Hydrogen" mistakenly appears.

[3] The amino group NR_2 is frequently given erroneously in the table as NR, for example: $Ge(NCH_3)_4$ instead of the correct $Ge[N(CH_3)_2]_4$.

(System No. 42) with the metals from System No. 18 (antimony) to 41 (titanium), and therefore includes the alloys of Zr with Sb, Be, Cu, Zn, Cd, Hg, Ga, and Ti. The alloys with the metals Mg (System No. 27) and Al (System No. 35), which also belong here, have already been treated (contrary to the usually followed "principle of the last place") in the fascicles Magnesium A 4 (1952) and Aluminum A 5 (1937; reprinted in 1953). The alloys of zirconium with elements of lower system numbers than Sb are treated in the following 252-page chapter on compounds of zirconium with elements up to System No. 41 (titanium).

From this last chapter, the sections on solutions of hydrogen in zirconium and the hydride ZrH_2 (12 pages), solutions of oxygen in zirconium and the zirconium dioxide ZrO_2 and its hydrates (53 pages), solutions of nitrogen in zirconium and the compounds ZrN and $Zr(NO_3)_4$ (15 pages), the zirconium chlorides, $ZrCl_2$, $ZrCl_3$, $ZrCl_4$, and $ZrOCl_2$ (30 pages), the zirconium sulfides, sulfites, and sulfates (27 pages), zirconium carbide, ZrC, and zirconium organic compounds (18 pages), the zirconium silicides and silicates (11 pages), the zirconium phosphides and phosphates (10 pages) and the zirconates of the alkali and alkaline earth metals, together with their derivatives (41 pages), may be singled out. All this material takes up a total of almost 90 % of the space devoted to the zirconium compounds.

Because of the recent use of zirconium in reactor technology, the appearance of the present volume which evaluates all the available original literature, including difficultly accessible material, will be greeted with appreciation not only by chemists, but also by physicists and engineers.

System No. 43: Hafnium. Supplementary Volume, 1958, II, 23 pages with 1 illustration, index. Paperbound 19 DM. -- Edited by *H. Balters, R. Glauner, W. Müller, J. Nägler, Gertrud Pietsch-Wilcke, K. Rumpf, F. Seuferling, K. Swars,* and *Hildegard Wendt.*

With this 23-page supplement, which continues the 62-page main volume that appeared in 1941 (reprinted in 1955) and covers the period 1940–1949, the treatment of Subgroup IVb of the periodic system, comprising the elements titanium (1951), zirconium (1958), hafnium (1958), and thorium (1955), is concluded with Gmelin's standard literature cutoff date the end of 1949. Thus, altogether, the subgroup fills up an imposing space of 1420 pages with 194 figures.

The small size of the present supplementary volume shows that very little subsequent work has been done on hafnium since the appearance of the main volume. After giving data on the occurrence of zirconium and the presence of elements which are always associated with zirconium (4.5 pages) and on the preparation and uses of hafnium and its compounds (4 pages), the volume reports on the physics of hafnium (7.5 pages), as well as on the chemical and analytical behavior of hafnium salts (3 pages). The remaining 4 pages are devoted to recent data on compounds of hafnium with hydrogen, oxygen, nitrogen, fluorine, chlorine, bromine, boron, carbon, phosphorus, and strontium.

System No. 15: Silicon. Part C (Organic Silicon Compounds), 1958, XII, 501 pages with 41 illustrations, index. Paperbound 309 DM. Edited by *G. Huschke* and *U. Krüerke* under the direction of *G. Hantke.*

A total of three parts is envisaged for consideration of silicon (Part A: History, Occurrence. Part B: The Element and the Inorganic Compounds of Silicon. Part C: Organic Silicon Compounds). Of these, Part A is still due. The 923-page Part B appeared in 1959. The 501-page Part C to be referred to here deals exclusively with organic Silicon compounds, and considers the literature to the end of 1953 and, in special cases, even beyond that date. It represents the imposing work of two co-workers of the Gmelin Institute, one of whom (*Ulrich Krüerke* as outside collaborator) was responsible for the chapters on compounds with a direct Si–C bond (326 pages) and silicones (78 pages), while the second (*Gerd Huschke*) wrote the chapter on compounds lacking direct Si–C bonds (82 pages). Although this volume of Gmelin fits in, in essentials, with the Gmelin format for handling the material, in comparison with other volumes it appears to be more closely knit, which can certainly be attributed to the smaller number of workers.

The large size of the volume impressively documents the rapid growth of the chemistry of organic silicon compounds in the last decades. In the 7th edition of "Gmelin", which appeared 50 years ago (1912), a single page sufficed for the treatment of organic compounds of silicon with a direct Si–C bond.

After an introduction on the systematics, nomenclature, and history of organiosilicon compounds with Si–C bonds (8 pages), there follows a description of tetraalkylsilanes, SiR_4 (94 pages), alkylhydrogensilanes, R_nSiH_{4-n} (13 pages), alkylhalogenosilanes, R_nSiX_{4-n} (68 pages), alkylsilyl esters $(R_3Si)_nY$ (6 pages), alkylalkoxysilanes, $R_nSi(OR)_{4-n}$ (11 pages), alkylsilanols, $R_nSi(OH)_{4-n}$ (42 pages), alkyl siloxanes "$R_nSiO_{2-n/2}$" (63 pages), alkylthiosilanes, $R_nSi(SR)_{4-n}$ and "$R_nSiS_{2-n/2}$" (1 page), alkylaminosilanes and alkylsilazanes, $R_nSi(NR_2)_{4-n}$ and "$R_nSi(NR)_{2-n_2}$", respectively (9 pages), alkylpolysilanes Si_nR_{2n+2} (10 pages), and trialkylsilylmetal compounds, R_3SiM (1 page).

To this section, totalling 326 pages, on compounds with at least one direct Si–C bond, there is added an 82-page report on organic silicon compounds without a direct Si–C bond. This latter report, after an introductory section on systematics, history, and general chemistry (2 pages), deals both with esters of monosilicic acid, $Si(OR)_4$ or $SiO(OR)_2$ (63 pages) and with esters of polysilicic acids "$(RO)_nSiO_{2-n/2}$" (17 pages), together with their derivatives.

In all, therefore, more than 3000 compounds are described, in part individually, and in part in groups, in 146 extensive tables (with data on preparation and properties). In order to facilitate finding individual compounds in these tables, to each compound is given a code number, the significance of which can be found in the section entitled "Systematics".

The description of these silicon compounds, then, forms the groundwork for the 78-page report on silicones of increasing technical significance. In this report the general methods for the preparation of silicones (17 pages) and the special technology of the silicones (55 pages) are treated, following an introductory synopsis (6 pages) devoted especially to the structure of the silicone framework. In this part, all types of silicones, together with their possible uses, are discussed -- not only silicone oils, therefore, but also silicone pastes, greases, resins, rubbers, cements, foams, films, and impregnating materials.

An additional 15-page alphabetical subject index, together with the system of code numbers previously mentioned, facilitates the location of any compound in this volume, one which has no equal as a reference work, in spite of other new publications in this field, and for which the Gmelin editorial staff can be congratulated. *E. Wiberg* [NB 833/10 IE]

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Phosphonitrilic Chlorides from Phosphorus Pentachloride

BY PROF. DR. MARGOT BECKE-GOEHRING AND DR. EKKEHARD FLUCK

ANORGANISCH-CHEMISCHES INSTITUT DER UNIVERSITÄT HEIDELBERG (GERMANY)

Under suitable conditions, PCl_5 reacts rapidly and quantitatively with NH_4Cl to form $[Cl_3P = N–PCl_3]$ $[PCl_6]$, which, with additional PCl_5 and NH_4Cl, is transformed to $[Cl_3P = N–PCl_2 = N–PCl_3]$ $[PCl_6]$. The cation of the latter compound and the NH_4^+ ion react with ring closure to form $[NPCl_2]_3$, together with longer chains which can yield with NH_4^+ either $[NPCl_2]_4$ or, for example, $Cl_3P = N–(PCl_2 = N)_n–PCl_2 = NH$. The salt-like intermediates of the phosphonitrilic chloride synthesis react with SO_2 to form the oxygen-containing products, $Cl_3P = N–P(O)Cl_2$ and $Cl_3P = N–PCl_2 = N–P(O)Cl_2$. Sulfur analogs are also easily obtained. The constitution of the compounds was determined by nuclear magnetic reasonance spectroscopy.

Introduction

In 1834, *J. von Liebig* [1] discovered that chlorine-containing phosphorus-nitrogen compounds are formed in the reaction of PCl_5 with ammonia, but their composition remained uncertain. Later, it was shown [2] that the reaction products consisted of compounds of the type $[NPCl_2]_n$. The first established member of the series was the trimeric chloride $[NPCl_2]_3$ [2]. The fact that higher degrees of polymerisation (n>3) also occur was proved by *Stokes* [3]. In the following years, various methods [3, 4] were developed for the production of phosphonitrilic chlorides. These depend entirely on the interaction of PCl_5 and NH_4Cl (as NH_3 donor) but the mode of formation of this class of compounds remained unknown.

Phosphorus Pentachloride

In the gaseous state, phosphorus pentachloride exists in the form of PCl_5 molecules, envisioned as trigonal bipyramids with five Cl atoms at the corners [5]. The ions $[PCl_4]^+$ and $[PCl_6]^-$ occur in the solid state [6]. Ions are apparently also present in solution if the solvent is highly polar [7]. It may be assumed, therefore, that PCl_5 is capable of reacting through an ionic mechanism and, in particular, ionic reactions ought to take place in solvents which possess large dielectric constants.

Reaction Between PCl_5 and Acid Amides

It has been known for a long time that phosphorus pentachloride reacts with acid amides in such a way that two H atoms of the amide are replaced by the PCl_3 group. For example, the compound $Cl_3P = N–SO_2Cl$ is readily formed from sulfamic acid, $H_2N–SO_3H$ [8] and the same product is formed when sulfamic acid chloride is used as starting material [8a].

$$H_2N–SO_3H + 2\,PCl_5 \rightarrow Cl_3P{=}N–SO_2Cl + 3\,HCl + OPCl_3$$

$$H_2N–SO_2Cl + PCl_5 \rightarrow Cl_3P{=}N–SO_2Cl + 2\,HCl$$

[1] *J. v. Liebig*, Ann. Chem. Pharmaz. *11*, 139 (1834).

[2] *C. Gerhardt*, Ann. Chimie Physique [3] *18*, 188 (1846); C. R. hebd. Séances Acad. Sci. *22*, 858 (1846); *M. Laurent*, ibid. *31*, 356 (1850); *J. H. Gladstone* u. *J. D. Holmes*, J. chem. Soc. (London) *17*, 225 (1864); Ann. Chimie Physique [4] *3*, 465 (1864); Bull. Soc. chim. France [2] *3*, 113 (1865); *H. Wichelhaus*, Ber. dtsch. chem. Ges. *3*, 163 (1870).

[3] *H. N. Stokes*, Amer. Chem. *17*, 275 (1895); *19*, 782 (1897).

[4] *R. Schenck* u. *G. Römer*, Ber. dtsch. chem. Ges. *57 B*, 1343 (1917); *R. Steinmann, F. B. Schirmer* u. *L. F. Audrieth*, J. Amer. chem. Soc. *64*, 2377 (1942).

[5] Cf., *e.g.*, *J. R. Van Wazer:* Phosphorus and its Compounds, Interscience Publ., New York 1958, vol. I, p. 236 et seq.

[6] *D. Clark, H. M. Powell*, and *A. F. Wells*, J. chem. Soc. (London) 642 (1942).

[7] Cf. *D. S. Payne*, J. chem. Soc. (London) 1052 (1953); *V. Gutmann*, Mh. Chem. *83*, 583 (1952); *J. H. Simons* u. *H. Jessop*, J. Amer. chem. Soc. *53*, 1263 (1931).

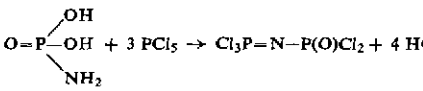
[8] *F. Ephraim* u. *M. Gurewitsch*, Ber. dtsch. chem. Ges. *43*, 138 (1910); *A. V. Kirsanov*, Bull. Acad. Sci. USSR, Chem. Sect. 426 (1950).

[8a] *Th. Mann*, Ph. D. Thesis, Heidelberg 1960.

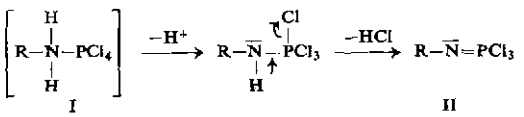
Analogously, $Cl_3P{=}N{-}SO_2{-}N{=}PCl_3$ is obtained [9] from sulfurylamide

$$H_2N{-}SO_2{-}NH_2 + 2\ PCl_5 \rightarrow Cl_3P{=}N{-}SO_2{-}N{=}PCl_3 + 4\ HCl$$

and $Cl_3P{=}N{-}P(O)Cl_2$ [10] may be prepared from phosphoramidic acid $(HO)_2P(O)NH_2$.



It may be mentioned in passing that amides of organic acids react analogously. For example, $Cl_3P{=}N{-}CO{-}N{=}PCl_3$ is formed from urea [11]. We believe that this "Kirsanov reaction" takes place in such a manner that $[PCl_4]^+$, acting as an electrophilic reagent, reacts with the amide to produce adduct (I) which stabilises itself in forming the reaction product (II) by deprotonization and subsequent loss of HCl. It seems to be important that the residue R should be sufficiently electronegative [10].

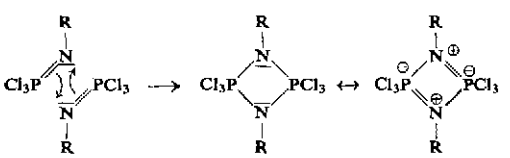


I II

Scheme A

Reaction Between PCl_5 and Amines

Phosphorus pentachloride reacts with primary amines in the same way as with acid amides. Monomeric compounds of the type $R{-}N{=}PCl_3$ can only be obtained when the amine $R{-}NH_2$ is a weak base [12]. With stronger bases (in water $K_B > 10^{-10}$) dimeric compounds of type III are obtained, the phosphorus atoms having a coordination number of 5 [13]:

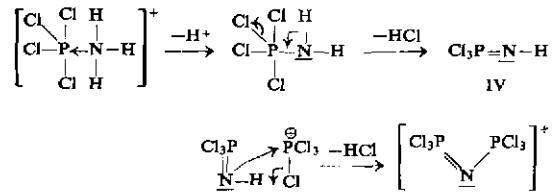


III

Reaction Between PCl_5 and Ammonia

If the reaction of phosphorus pentachloride with NH_3 is analogous to reactions with ammonia derivatives, then the following mechanism would be expected:

The $[PCl_4]^+$ion and NH_3 should combine in a Kirsanov reaction to form the intermediate compound (IV), an unstable monomer. With an excess of $[PCl_4]^+$, compound (IV) should either form $[NPCl_2]_n$ – with polymerization and cleavage of HCl – or react with more $[PCl_4]^+$ to give the cation (V). This cation would then form salt (VI) with the $[PCl_6]^-$ anion present in phosphorus pentachloride. This reaction actually takes place.



$[Cl_3P{=}N{-}PCl_3]\ [PCl_6]$ V

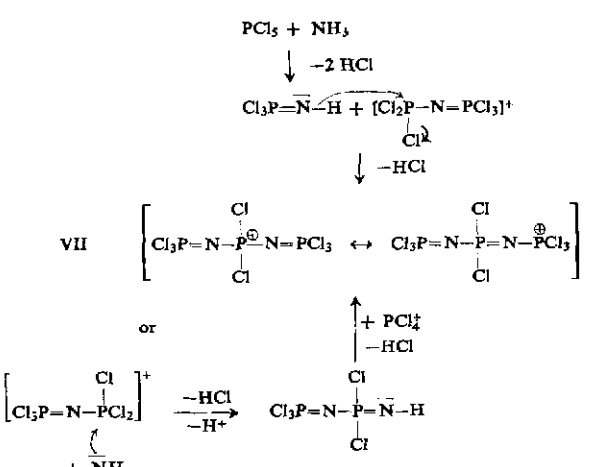
VI, m.p. 310–315 °C (decomp.)

Scheme B

We have studied the interaction between excess PCl_5 and NH_4Cl; the latter serving as NH_3 donor. It was noted [14] that these compounds react according to Scheme B, even at 45–60 °C, when a polar solvent such as nitrobenzene is used. Compound (VI), P_3NCl_{12}, is obtained with a yield of 80–90 %. It crystallizes well and melts with decomposition at 310–315 °C. (VI) can also be obtained in good yield from PCl_3 and NCl_3 [16]. It was to be expected that the intermediate compound (IV) would not react only with $[PCl_4^+]$. Rather, it should be able to react with every analogous Lewis acid, forming addition products accompanied by cleavage of HCl. Cation (V) may be compared wich $[PCl_4]^+$ inasmuch as in both cases a P atom exists with a formal positive charge. Consequently, a further reaction was, above all, to be expected with the cation $[Cl_3P{=}N{-}PCl_3]^+$. Indeed, salt (VI) reacted in tetrachloroethane at about 150 °C with additional PCl_5 and NH_4Cl (molar ratio 1:1) and the crystalline compound $P_4N_2Cl_{14}$, m.p. 161 °C [15] was obtained in good yield.

$$P_3NCl_{12} + PCl_5 + NH_4Cl \rightarrow P_4N_2Cl_{14} + 4\ HCl$$

This reaction is illustrated in scheme C:



Scheme C

[9] *A. V. Kirsanov*, J. gen. Chem. (Russ.) *22*, 1346 (1952); Chem. Abstr. *1956*, 1242.

[10] *M. Becke-Goehring, Th. Mann*, and *H. D. Euler*, Chem. Ber. *94*, 193 (1961).

[11] *A. V. Kirsanov*, Bull. Acad. Sci. USSR, Chem. Sect. 646 (1954).

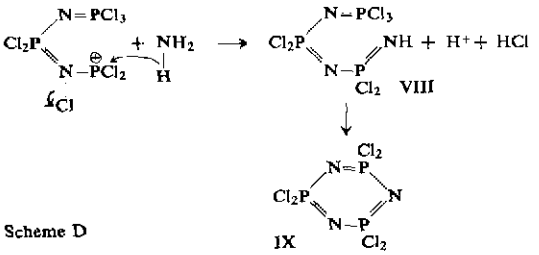
[12] *I. N. Zhmurova* and *A. V. Kirsanov*, J. appl. Chem. (Russ.) *30*, 3044 (1960); Chem. Abstr. *55*, 17551 (1961).

[13] *A. C. Chapman, W. S. Holmes, N. L. Paddock*, and *H. T. Searle*, J. chem. Soc. (London) 1825 (1961); *P. A. Fowell* and *C. T. Mortimer*, Chem. and Ind. 444 (1960).

[14] *M. Becke-Goehring* and *W. Lehr*, Chem. Ber. *94*, 1591 (1961).

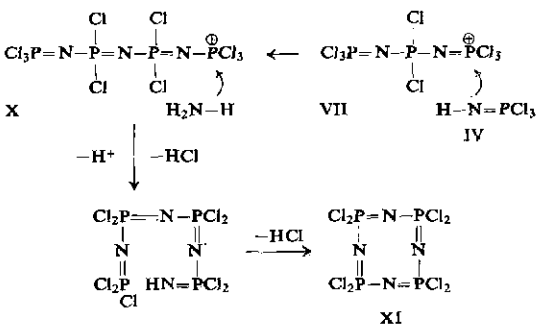
[15] Cf. *M. Becke-Goehring, E. Fluck*, and *W. Lehr*, Z. Naturforsch., in the press.

Starting with compound (VII) and an excess of NH_4Cl in tetrachloro ethane at 150 °C, triphosphonitrilic chloride (IX, scheme D) is easily obtainable via intermediate (VIII):



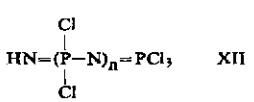
Scheme D

The yield of (IX), based on the cation of (VII) [16], amounts to about 80 %. The chain-forming reaction described in schemes B and C does not stop at VII. Besides the intermediate (VII), cations with more than one $-N{=}PCl_2-$ group are also formed. For example, cation (X) is formed from (VII) and the intermediate (IV). Tetrameric phosphonitrilic chloride (XI) can be produced from (X) with NH_3 (from NH_4Cl) according to scheme E.



Scheme E

On the other hand cation (X) and additional $HN{=}PCl_3$ (IV) form long chains. Eventually, cations of the composition $[Cl_3P{=}N\text{-}(PCl_2{=}N)_nPCl_3]^+$ appear. These cations can react again with NH_3. With higher values of n, ring closure no longer occurs. Much more phosphonitrilic chloride is produced with $NPCl_2$ centergroups and HN= or $Cl_3P{=}$, respectively, as endgroups. Such linear phosphonitrilic chlorides are noncrystalline. In an earlier investigation [17], a fraction with $n \approx 10$, formula (XII), was isolated from the oily residue of the reaction product from PCl_5 and NH_4Cl:



Constitution of the Products Formed from PCl_5 and NH_3

1) P_3NCl_{12}

As shown above, the salt $[Cl_3P{=}N{-}PCl_3]\,[PCl_6]$ (VI) was the first successfully isolated product of the reaction between PCl_5 and NH_3. The constitution of this compound was demonstrated in the following manner.

The cryoscopically determined molecular weight in nitrobenzene was found to be 289 [14]. This led to the assumption that P_3NCl_{12} dissociates into two components in this solvent. If the intermediate (VI) is dissolved in nitromethane and conductance measurements are carried out it follows from the results that (VI) must be dissociated into two monovalent ions [14]. These results are in good agreement with formula (VI).

The structure of (VI) was confirmed by its nuclear magnetic resonance spectrum [18]. The spectrum (Figure 1) shows two isolated singlets with chemical shifts of $a = -21.4\times10^{-6}$ and $b = 305\times10^{-6}$.

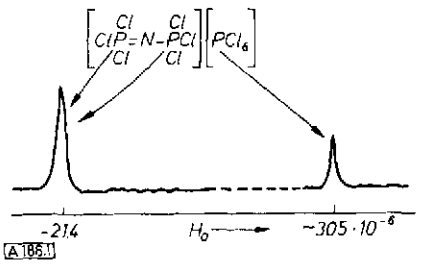
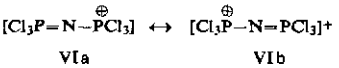
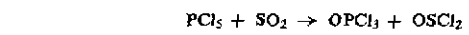


Figure 1. Nuclear magnetic resonance spectrum of P_3NCl_{12}

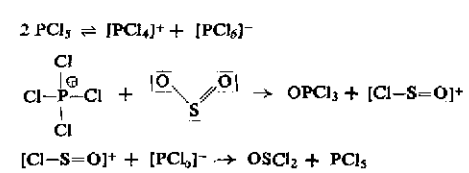
Singlet a arises from the chemically equivalent P atoms present in the cation. The resonance maximum b is caused by the strongly shielded P atom of the anion. The spectrum clearly reveals that the cation is resonance stabilised and should be written according to formulae VIa and VIb.



An additional indication of the structure of salt (VI) is given by the reaction with sulfur dioxide. As is known, SO_2 reacts readily with PCl_5:

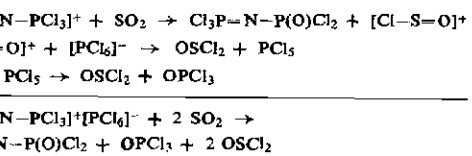


This reaction presumably involves a nucleophilic attack on the $[PCl_4]^+$ ion by SO_2. The complete reaction can be written according to scheme F:



Scheme F

Salt (VI) is a derivative of PCl_5 with the same anion as phosphorus pentachloride, but with a different cation. It should undergo a reaction with SO_2 which ought to be completely analogous to the case of phosphorus pentachloride.



[16] *M. Becke-Goehring* and *W. Lehr*, unpublished results.

[17] *M. Becke-Goehring* and *G. Koch*, Chem. Ber. *92*, 1188 (1959).

[18] *E. Fluck*, Z. allg. anorg. Chem., in the press.

This reaction was actually quantitatively observed [14]. Compound (XIII), formed from the cation of (VI), is identical with a substance already obtained earlier from the amides of phosphoric acid and PCl_5 [10]. Furthermore, it is identical with the main reaction product between PCl_5 and hydroxylammonium salts [19]; it is also identical with a reaction product obtained from PCl_3 and N_2O_4 [20]. The imidodiphosphate (XIV) is easily obtained by the hydrolysis of (XIII).

$$Cl_3P{=}N{-}P(O)Cl_2 + OH^- \rightarrow {}^{2-}O_3P{-}NH{-}PO_3^{2-}$$

XIII XIV

This reaction shows that a P–N–P grouping is present in the compound. The structure of compound (XIII) is also indicated by the nuclear magnetic resonance spectrum. As shown in Figure 2, two doublets can be observed [21]:

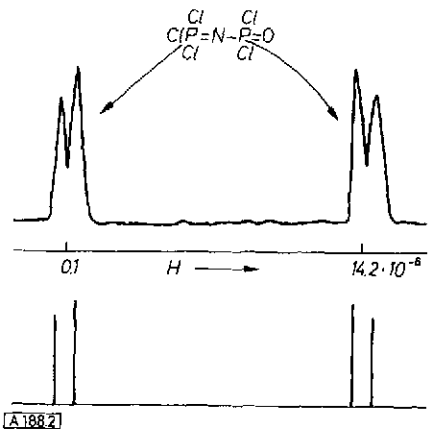
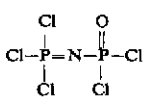


Figure 2. Nuclear magnetic resonance spectrum of $Cl_3P{=}N{-}P(O)Cl_2$ (XIII) and the theoretical spectrum of a molecule of the type A B with the ratio $J/\nu_0\delta = 0.07$

These resonance maxima originate from two P nuclei bonded to different atoms. Both phosphorus atoms are connected with one another through nitrogen and have coupled spins:



XIII, m. p. 35 °C

2) $P_4N_2Cl_{14}$

The structure of salt VII can be determined in the same way as was the case for salt VI. The apparent molecular weight, cryoscopically determined with nitrobenzene as solvent, is 330 [15]. In nitromethane, electrolytic conductivity was again observed and which also indicated a dissociation into two monovalent ions [16]. These observations indicate a salt-like structure as shown in formula VII. This is confirmed (Figure 3) by the nuclear magnetic resonance spectral data [15].

Band a which shows a doublet, was produced by the end-group P atoms of the cation. Band b, a triplet,

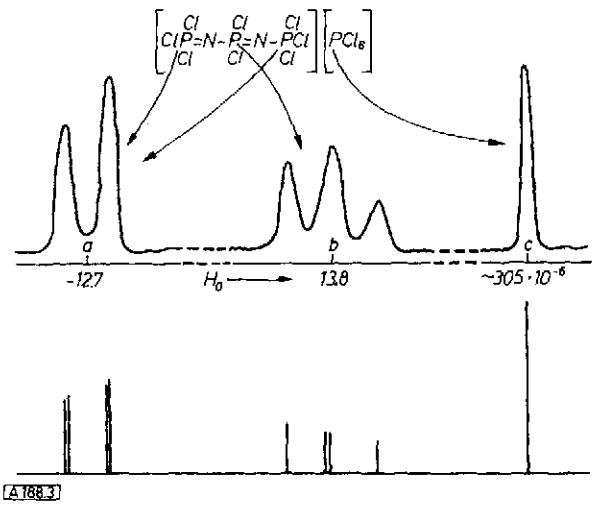


Figure 3. Nuclear magnetic resonance spectrum of $P_4N_2Cl_{14}$ and the theoretical AB_2 spectrum for the ratio $J/\nu_0\delta = 0.106$

was produced by the center-group P atom of the cation. The singlet at about 305×10^{-6} is again assigned to the anion $[PCl_6]^-$ [18].

The following reaction takes place between (VII) and SO_2 [16]:

$$[Cl_3P{=}N{-}PCl_2{=}N{-}PCl_3]\,[PCl_6] + 2\,SO_2 \rightarrow Cl_3P{=}N{-}PCl_2{=}N{-}P(O)Cl_2 + OPCl_3 + 2\,OSCl_2$$

XV

The structural formula (XV) of the reaction product again follows from the nuclear magnetic resonance spectral data (Figure 4). The distribution of the spectral bands with respect to the various P atoms of (XV) can be recognized from Figure 4.

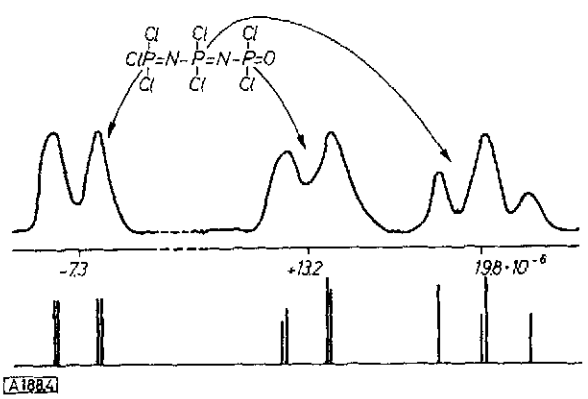
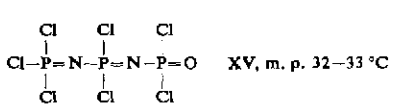


Figure 4. Nuclear magnetic resonance spectrum of $P_3N_2Cl_9O$ and the theoretical spectrum of the type ABX (for calculations see [18])

The sulfur analogs of (XIII) and (XV) can be obtained by allowing (VI) and (VII), respectively, to react with H_2S.



XV, m. p. 32–33 °C

3) $[NPCl_2]_3$

Triphosphoronitrilic chloride, represented by the six-membered ring system in formula (IX), has been known for a long time. The crystal analysis carried out by *Wil-*

[19] *E. J. Kahler*, U. S. Patent 2925320 (1960).

[20] Cf. *M. Becke-Goehring, A. Debo, E. Fluck*; and *W. Goetze*, Chem. Ber. *94*, 1383 (1961).

[21] *E. Fluck*, Chem. Ber. *94*, 1388 (1961).

son and *Carroll* [22] shows discrete molecules in the solid state. The ring is not exactly planar, but the deviations are so small, that they appear to be caused by crystal forces; it is assumed to be planar in the gaseous state. This is in conformity with electron-diffraction studies [23]. The Cl atoms lie perpendicular to the plane the ring. It is interesting to note that all P–N distances are equal (1.57 to 1.61 Å). The angles at phosphorus (opposite N) and at nitrogen deviate only slightly from 120°. The Cl–P–Cl angles, found to be 101.77° and 102.05°, are markedly different from the expected tetrahedral values. The results indicate that the ring system is stabilized by mesomerism. It is very probable, that $p\pi-d\pi$ bonding plays a part [24]. Exactly which type of delocalisation occurs is, however, still an open question [25].

4) $[NPCl_2]_4$

Tetrameric phosphonitrilic chloride is apparently non-planar [26]. In this substance, also, the P–N distances are equal but they are shorter than would be expected for a single P–N bond. Again, a delocalization of π-electrons is to be assumed, either in the form of delocalization over the entire ring or as three-centered π-bonds extending over one N atom and two adjoining P atoms. Determination of the heat of formation indicates, perhaps, a stronger P–N linkage in tetrameric phosphonitrilic chloride than that existing in the trimeric form [27].

Linear Phosphonitrilic Chlorides

Nuclear magnetic resonance spectral investigations carried out with an oily phosphonitrilic chloride show that formula XII is a possibility [17]. So far, however, only a middle fraction from an oily residue (prepared by the method of *Schenck* and *Römer* [4]) has been studied.

Since step-wise reactions between PCl_5 and NH_4Cl take place through well-defined intermediate compounds to give the phosphonitrilic chlorides as end-products, it is possible to guide the reaction in various directions. If controlled quantities of PCl_5 are employed, the salt with P–N–P chains in the cation, and with $[PCl_6]^-$ as anion, is formed preferentially. When an excess of PCl_5 is used at low temperatures, mainly $[Cl_3P = N-PCl_3][PCl_6]$ is produced. With more NH_4Cl, the longer-chain cation $[Cl_3P{=}N{-}PCl_2{=}N{-}PCl_3]^+$ is formed. Triphosphonitrilic chloride arises from this ion in the presence of additional NH_4Cl. However, with further $[PCl_4]^+$ and NH_3, longer chains and the tetrameric compounds are also formed from this cation. Evidently, chain-formation and ring-closure reactions proceed at rates of comparable magnitude.

The stable homologues $[NPCl_2]_3$ and $[NPCl_2]_4$ can be converted one into one another or into other phosphonitrilic chlorides. *Schmitz-Dumont* [28] has demonstrated that on heating to about 600 °C an equilibrium is established between the various phosphonitrilic chlorides, with accompanying depolymerization and polymerization. However, the trimeric ring system $[NPCl_2]_3$ is opened even at about 300 °C and polymerization leading to the formation of longer chains takes place [29].

The ring-opening reaction is entirely different in the presence of PCl_5. Even at temperatures of 200–220 °C [30] a reaction occurs (in a sealed tube) between PCl_5 and trimeric or tetrameric phosphonitrilic chloride. If the molar ratio of PCl_5:$[NPCl_2]$ is at least 1:1, a homogeneous melt appears; this solidifies only slowly on cooling. On addition of more PCl_5, two layers are formed, the upper containing unreacted PCl_5 [31]. Nuclear magnetic resonance data showed that $[PCl_6]^-$ is always present in the homogeneous melt (resonance maximum at $+ 305\times10^{-6}$). Moreover, a cation of the type $[Cl_3P{=}(N{-}PCl_2)_n{=}N{-}PCl_3]^+$ is found [31]. The existence of branched chains, or of chains of the type $Cl{-}PCl_2{=}(N{-}PCl_2)_n{=}N{-}PCl_4$, could not be demonstrated [32]. Salt-like intermediates containing $[PCl_6]^-$ anions, play an important role in both the synthesis and degradation of phosphonitrilic chloride via PCl_5.

Received, December 13th, 1961. [A 188/22 IE]

[22] *A. Wilson* and *D. F. Carroll*, J. chem. Soc. (London) 2548 (1960).

[23] *L. O. Brockway* and *W. M. Bright*, J. Amer. chem. Soc. *65*, 1551 (1943).

[24] Cf., *e.g.*, *L. E. Sutton:* Chemische Bindung und Molekülstruktur. Springer, Berlin-Göttingen-Heidelberg 1961, p. 78 et seq.

[25] Cf., *e.g.*, *D. P. Craig*, Chem. Soc. (London) Spec. Publ. No. 12, 343 (1958); J. chem. Soc. (London) 997 (1959); *D. P. Craig* and *N. L. Paddock*, Nature (London) *181*, 1052 (1958); *M. J. S. Dewar*, *E. A. C. Lucken*, and *M. A. Whitehead*, J. chem. Soc. (London) 2423 (1960).

[26] *J. A. Ketelaar* and *T. A. de Vries*, Recueil Trav. chim. Pays-Bas *58*, 1081 (1939); see also *G. J. Bullen*, J. chem. Soc. (London) 425 (1960).

[27] *S.B. Hartley*, *N.L. Paddock*, and *H. T. Searle*, J. chem. Soc. (London) 430 (1961).

[28] *O. Schmitz-Dumont*, Z. Elektrochem. *45*, 651 (1939).

[29] *K. H. Meyer*, *W. Lotmar*, and *G. W. Pankow*, Helv. chim. Acta *19*, 930 (1936).

[30] *L. G. Lund*, *N. L. Paddock*, *J. E. Proctor*, and *H. T. Searle*, J. chem. Soc. (London) 2542 (1960), thought a temperature between 300 and 350 °C is necessary; this is not the case.

[31] *E. Fluck*, Z. anorg. allg. Chem., in the press.

[32] Assumed by *X. Bilger*, French Patent 1157097.

Advances in the Chemistry of Organic Ring Systems with Adamantane Type Structures

BY PROF. DR. H. STETTER

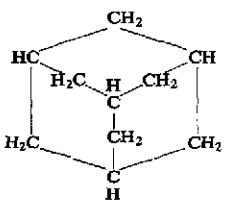
INSTITUT FÜR ORGANISCHE CHEMIE, TECHNISCHE HOCHSCHULE, AACHEN (GERMANY)

Since the last review of the topic in 1954 [1], *the chemistry of organic compounds with the adamantane type structures has been considerably advanced in scope and significance by the work of the author and of others. Since 1954, the number of ring systems of this type known has risen from 13 to 22. At the same time, the number of compounds with adamantane type structures known has been more than tripled. Summary of recent advances is therefore justified. As before, the emphasis in this review is placed on complete coverage.*

1. Adamantane

a) Isolation and Synthesis

Landa and *Hala* [2] have considerably improved the isolation of adamantane from crude petroleum; the original process involving fractional distillation and subsequent purification by freezing led to incomplete separation. These investigators obtained a beautifully

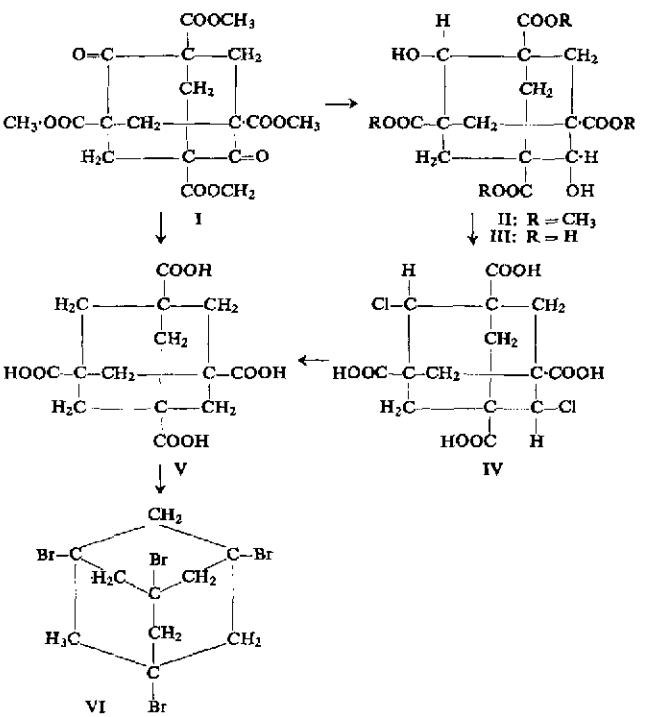


Adamantane

crystalline "channel"-type inclusion compound of adamantane, with thiourea; this adduct is particularly suitable for separating adamantane from petroleum fractions. *Landa* and *Hala* [3] even developed this separation method into a procedure for estimating adamantane in petroleum. Adamantane was also isolated from petroleum by azeotropic distillation [3a].

The original synthesis developed by *Prelog* and *Seiwerth* [4], starting from tetramethyl adamantane-2,6-dione-1,3,5,7-tetracarboxylate (I), which is readily obtained from Meerwein ester according to *Böttger* [5], has been modified to give a yield three times as great [6]. The known compound tetramethyl 2,6-dihydroxyadamantane-1,3,5,7-tetracarboxylate (II) was easily obtained by catalytic hydrogenation of (I). The acid (III), obtained by hydrolysis of the ester, reacted with phosphorus pentachloride to yield the acid chloride (IV). This compound exhibited molecular asymmetry. Salt formation with cinchonine made it possible to separate it into its antipodes [7]. Catalytic hydrogenation of (VI) in alkaline solution produced adamantanetetracarboxylic acid (V). Degradation of its silver salt with bromine by the method of *Hunsdiecker* yielded 1,3,5,7-tetrabromoadamantane (VI), from which adamantane itself can be obtained by catalytic hydrogenation in the presence of alkali.

Larda and *Kamycek* [8] obtained (V) in high yields by direct reduction of I using a modified Wolff-Kishner reduction.



Despite these improvements on the original synthesis, the preparation of larger amounts of adamantane remained difficult.

A decisive change was brought about by an observation of *Schleyer* [9]; on attempting to rearrange *endo*-tri-

[1] *H. Stetter*, Angew. Chem. *66*, 217–229 (1954); an outline of the methods of synthesis of such ring systems and a discussion of the nomenclature are given therein.

[2] *S. Landa* and *S. Hala*, Chem. Listy *51*, 2325 (1957); Collection Czechoslov. Chem. Commun. *24*, 93 (1959).

[3] *S. Landa* and *S. Hala*, Erdöl u. Kohle *11*, 698 (1958).

[3a] *R. L. Martin et al.*, Analytic. Chem. *31*, 2082 (1959).

[4] *V. Prelog et al.*, Ber. dtsch. chem. Ges. *74*, 1644, 1769 (1941).

[5] *O. Böttger*, Ber. dtsch. chem. Ges. *70*, 314 (1937).

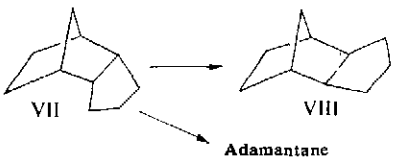
[6] *H. Stetter, et. al.*, Chem. Ber. *89*, 1922 (1956).

[7] *H. Stetter* and *O. E. Bänder*, Chem. Ber. *88*, 1535 (1955).

[8] *S. Landa* and *Z. Kamycek*, Collection Czechoslov. Chem. Commun. *24*, 4004 (1959).

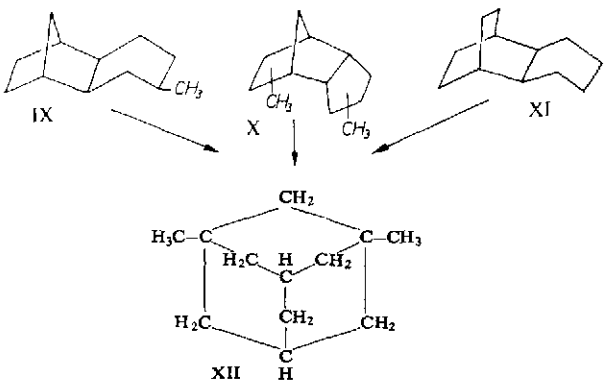
[9] *P.v. R. Schleyer*, J. Amer. chem. Soc. *79*, 3292 (1957).

methylenenorbornane (tetrahydrodicyclopentadiene; VII) with aluminum bromide or chloride, he obtained the expected *exo*-trimethylene-norbornane (VIII) plus a 12% yield of a crystalline hydrocarbon, which he identified as adamantane.

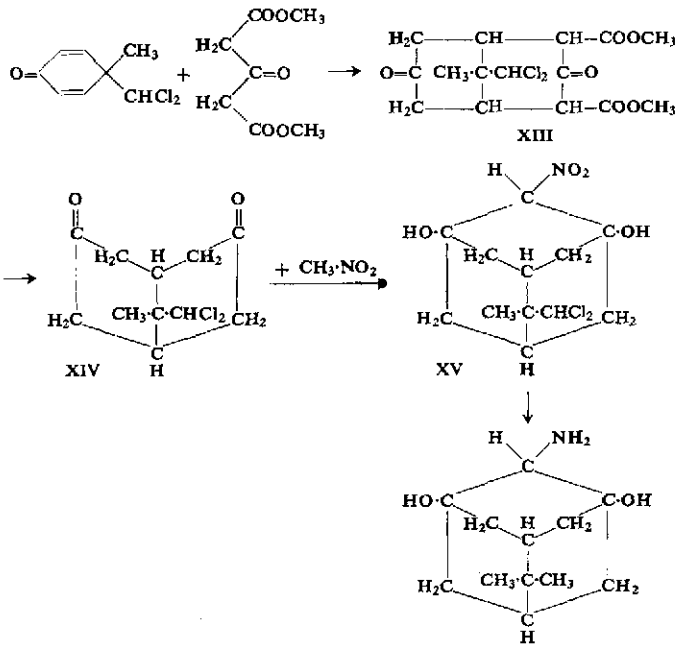


Schleyer and *Donaldson* [10] studied this carbonium rearrangement in greater detail and proposed a mechanism. By increasing the amount of aluminum bromide, adding a small quantity of t.-butyl bromide, and passing hydrogen bromide through the resulting solution, they succeeded in raising the yield of adamantane to 18.8%. According to a Du Pont patent [11], the yield can be increased to 30% by carrying out the isomerization with a mixture of hydrogen fluoride and boron-trifluoride.

Schleyer and *Nicholas* [12] were able to show that various methyl derivatives of trimethylenenorbornane isomerize much more easily and in considerably better yields into mixtures of 1-methyl- and 2-methyl-adamantane. *exo*-Tetramethylenenorbornane can also be isomerized almost quantitatively to 1-methyladamantane. Furthermore, the ease of isomerization of the hydrocarbons IX, X, and XI to 1,3-dimethyladamantane (XII) indicated that the adamantane ring system was the stable product of isomerization in every case



Another synthesis of the adamantane ring system, based on a new principle, renders certain specific derivatives available [13]. Dimethyl 9-methyl-9-dichloromethyl-bicyclo[3,3,1]-nona-3,7-dione-2,4-dicarboxylate (XIII) can be prepared by Michael addition of dimethyl acetonedicarboxylate onto 4-methyl-4-dichloromethyl-cyclohexa-2,5-diene-1-one; the latter is readily obtainable by the action of chloroform and alkali on *p*-cresol. Ketonic hydrolysis of (XIII) yielded (XIV). 1,3-Dihydroxy-2-nitro-6-methyl-6-dichloromethyladamantane (XV) is formed in a smooth ring closure reaction, when nitromethane is allowed to react with (XIV) in the presence of alkoxide. Catalytic hydrogenation of (XV) gives 1,3-dihydroxy-2-amino-6,6-dimethyladamantane, with elimination of the halogen.



b) Direct Substitutions

Landa et al. [13a] observed that the action of bromine on adamantane produced a single monobromoadamantane, which yielded a monohydroxyadamantane on hydrolysis. The proton nuclear magnetic resonance spectra and the stability of the hydroxyadamantane toward oxidizing agents indicate that this compound is 1-bromoadamantane (XVI) [14].

Investigation of the course of the bromination [15] showed that is is very easily accomplished at room temperature. In contrast, introduction of a second bromine atom is more difficult. The usual radical chain mechanism of paraffin halogenation cannot be reconciled with these results. Therefore, an ionic mechanism for the halogenation was postulated; here positively charged halogen and adamantyl-1-carbonium ions are supposed to assume the role of chain propagators in the usual halogenation mechanism. The strongest support for this mechanism has come from the observation that the halogenation is strongly catalyzed by Friedel-Crafts catalysts. Depending on the catalyst and the reaction conditions, various highly brominated adamantane derivatives can be obtained [16]. Homogeneous 1,3-dibromoadamantane may be obtained by using boron tribromide as catalyst, while 1,3,5-tribromoadamantane is produced by aluminum bromide or ferric bromide

[10] *P.v. R. Schleyer* and *M. M. Donaldson*, J. Amer. chem. Soc. *82*, 4645 (1960).

[11] E. J. Du Pont De Nemours Co., Belgian Patent 583519 (1959); German Patent Application 1097438 (1959) by *R. E. Ludwig*.

[12] *P.v. Schleyer* and *R. D. Nicholas*, Tetrahedron Letters 305 (1961).

[13] *H. Stetter* and *J. Mayer*, Angew. Chem. *71*, 430 (1959).

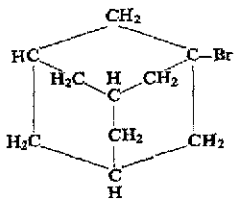
[13a] *S. Landa*, *S. Kriebel*, and *E. Knobloch*, Chem. Listy *48*, 61 (1954).

[14] *H. Stetter*, *M. Schwarz*, and *A. Hirschhorn*, Angew. Chem. *71*, 429 (1959); Chem. Ber. *92*, 1629 (1959).

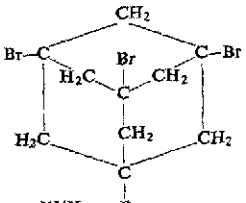
[15] *H. Stetter*, *J. Mayer*, *M. Schwarz*, and *C. Wulff*, Chem. Ber. *93*, 226 (1960).

[16] *H. Stetter* and *C. Wulff*, Chem. Ber. *93*, 1366 (1960).

catalysts. With the same catalysts, further bromination can be achieved above 150 °C. 1,3,5,7-Tetrabromoadamantane (XVII) produced in this case was obtained in an earlier unequivocal synthesis [6]. Similar results were obtained from chlorinations with Friedel-Crafts catalysts [17,19]. It is not possible to introduce more than four halogens into the adamantane molecule in this way. The high degree of selectivity of this reaction is very surprising; substitution proceeds exclusively at the tertiary hydrogen atoms.

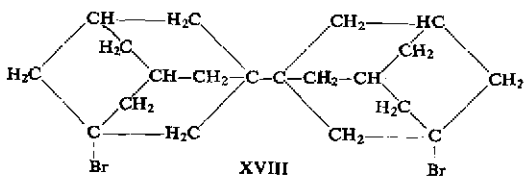


XVI



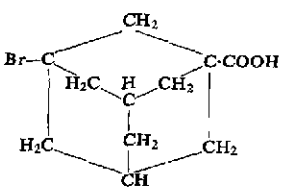
XVII

1,1'-Biadamantyl is just as easy to brominate as adamantane itself, forming exclusively 3,3'-dibromo-1,1'-biadamantyl (XVIII) in a highly selective reaction. Here, too, further bromination does not occur in the absence of catalysts [18,19].



XVIII

Adamantane-1-carboxylic acid can also be brominated readily by using aluminum bromide as catalyst, yielding 3-bromoadamantane-1-carboxylic acid (XIX) in high yield. Halogenation did not take place without a catalyst [20].



XIX

When the usual conditions for radical-type halogenation are employed, halogenation of adamantane follows a nonspecific course. *G. W. Smith* and *Williams* [21] chlorinated adamantane by illuminating it in various solvents. They were able to confirm with adamantane the solvent effect previously observed in other experiments [22]. Two monochloroadamantanes as well as polychlorinated adamantanes of unknown constitution were obtained. Similar polychloroadamantane compounds, also obtained under conditions for radical halogenation, are described in a patent by Shell [23].

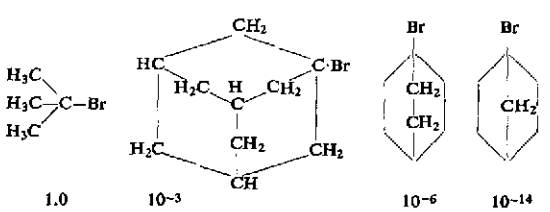
Oxidation of adamantane follows a course similar to halogenation; 1-hydroxyadamantane is obtained by the action of fuming sulfuric acid or of chromium trioxide in glacial acetic acid [19]; *Schleyer* and *Nicholas* [24] obtained a mixture of 1- and 2-hydroxyadamantanes by radical hydroxylation using peracetic acid with illumination. A similar nonspecific course was observed in the oxidation of adamantane with oxygen in the presence of cobalt salts and organic peroxides [21]. 1-Hydroxyadamantane and adamantan-2-one were obtained, together with other unidentified oxidation products.

From a preparative point of view, nitration with nitric acid in glacial acetic acid is of particular importance [21]. Depending on the reaction conditions, 1-nitroadamantane and 1,3-dinitroadamantane are obtained selectively and in good yields.

Among other direct-substitution reactions of adamantane, the synthesis of a still incompletely identified adamantanesulfonic acid – obtained by the action of sulfur dioxide and oxygen – and the formation of hydroxymethyladamantane by radical addition onto formaldehyde [21] are worthy of mention.

c) Reactivity of Substituents on the Adamantane Ring System

In investigations of the reactivity of halogenated adamantanes, it was noted with surprise that – contrary to theoretical predictions – 1-bromoadamantane is highly reactive in nucleophilic substitutions. This reactivity of the halogen on the bridge carbon atom of the rigid ring system was wholly unexpected. Since there is no possibility of attack from the rear, nucleophilic substitution via an S_N2 mechanism is excluded. Even an S_N1 mechanism ought to be very unlikely, because the formation of a planar carbonium ion is only possible with considerable distortion of the rigid ring system [25,26]. Measurements of the solvolysis constants of 1-bromoadamantane [15,27] indicates the following values for 1-bromobicyclo[2,2,2]octane and 1-bromonorbornane relative to t.-butylbromide:



1.0 10^{-3} 10^{-6} 10^{-14}

The experimental observation that 1-bromoadamantane reacts about 1000 times faster than 1-bromobicyclo-[2,2,2]octane, is especially remarkable, because the ring system of the latter has no Baeyer strain, just like that of adamantane. *Schleyer* and *Nicholas* [27] attempted to give a theoretical explanation of this vast difference in

[17] German Patent Application by *H. Stetter* and *C. Wulff*.

[18] *H. F. Reinhardt*, personal communication.

[19] *C. Wulff*, Ph. D. Thesis, Technische Hochschule Aachen 1961.

[20] *H. Stetter* and *J. Mayer*, Chem. Ber. *95*, 667 (1962).

[21] *G. W. Smith* and *H. D. Williams*, J. org. Chemistry *26*, 2207 (1961).

[22] *G. A. Russell*, J. Amer. chem. Soc. *79*, 2977 (1957); *80*, 4987, 4997, 5002 (1958).

[23] Brit. Patent 819240 (1959) by *W. C. Webber* u. *P. A. Harthoorn*.

[24] *P. v. R. Schleyer* and *R. D. Nicholas*, J. Amer. chem. Soc. *83*, 182 (1961).

[25] *E. L. Eliel* in *M. S. Newman*: Steric Effects in organ. Chemistry. J. Wiley & Sons, New York 1956, p. 135–138.

[26] *U. Schöllkopf*, Angew. Chem. *72*, 147 (1960).

[27] *P. v. R. Schleyer* and *R. D. Nicholas*, J. Amer. chem. Soc. *83*, 2700 (1961).

reactivity of the two halogen compounds. Whereas adamantane is completely free from both Baeyer and conformational (Pitzer) strain, bicyclo[2,2,2]octane does have Pitzer strain because of its unfavorable conformation. This conformational strain appears to offer greater resistance to the formation of a carbonium ion than the adamantane ring system.

In contrast to adamantyl-1-carbonium ion, adamantyl-2-carbonium ion shows very little stability. Measurements of acetolysis rates indicated that adamantyl-1-tosylate solvolyzes 10^5 times faster than adamantyl-2-tosylate [24, 27]. This extremely large difference explains why in all ionic substitutions of adamantane, the 1-position is very strongly favored over the 2-position. *Schleyer* and *Nicholas* [24] discuss the extent to which increase in the tetrahedral bond angle during the formation of the carbonium ion in this rigid ring system contributes to its strongly decreased reactivity.

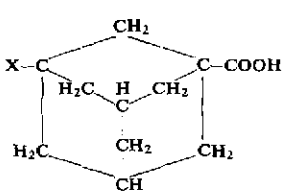
The series 1-bromoadamantane, 1,3-dibromoadamantane, 1,3,5-tribromoadamantane, and 1,3,5,7-tetrabromoadamantane shows a marked decline in reactivity in nucleophilic substitutions [16]. This decrease of reactivity with increasing halogen content can only be explained by an inductive effect of the halogen substituents on the formation of a carbonium ion. Measurements of the solvolysis constants of 1-bromoadamantane, 3-bromoadamantane-1-carboxylic acid, and 1,3-dibromoadamantane in 70 % dioxan at 100 °C gave the following values [20]:

1-bromadamantane:	$k_1 = 7.89 \cdot 10^{-4}$ [sec^{-1}]
3-bromadamantane-1-carboxylic acid:	$k_1 = 1.32 \cdot 10^{-5}$ [sec^{-1}]
1.3-dibromadamantane:	$k_1 = 2.31 \cdot 10^{-6}$ [sec^{-1}]

These values and their order confirm the existence of a strong inductive effect. The results of this also become apparent in measurements of the dissociation constants of adamantane-1-carboxylic acid, substituted in the 3-position and of general formula A [20].

The values are shown in Table 1.

Table 1. Dissociation constants of adamantane-1-carboxylic acids, substituted in the 3-position



A

Carboxylic Acid	X	$K_A \cdot 10^7$ (Mean values)
XX	H	1.55
XXI	C_6H_5	1.71
XXII	OH	4.86
XXIII	OCH_3	5.07
XXIV	I	5.50
XXV	Br	6.46
XXVI	Cl	7.13
XXVII	F	10.00

These values are of the same order of magnitude as those obtained by *Roberts* and *Moreland* [28] with substituted carboxylic acids of the bicyclo[2,2,2]octane series.

The high reactivity of 1-bromoadamantane makes it possible to prepare many 1-substituted adamantanes; in particular, the smooth synthesis of adamantane-1-carboxylic acid following the method of *Koch* and *Haaf* [14, 29], and the preparation of 1-acylaminoadamantane by the Ritter reaction [14]. In the presence of t.-butanol, both products are obtainable directly from adamantane [30, 31]. In this case, the t.-butylcarbonium ion initially formed is in equilibrium with the adamantyl-1-carbonium ion formed by hydride transfer.

Catalysis with aluminum bromide [32] effects addition of 1-bromoadamantane onto olefins as well as Friedel-Crafts alkylation with benzene [14]. It is remarkable that 1-(*p*-methoxyphenyl)adamantane is produced on heating 1-bromoadamantane with anisole even without addition of catalysts [18].

Analogously, all the substitution reactions described above are possible with 3,3′-dibromo-1,1′-biadamantyl (XVIII) [18, 19]. However, as already mentioned, substitution reactions with 1,3-dibromoadamantane occur only under more drastic conditions [16].

A large number of other adamantane derivatives has been produced by starting out from adamantane-1-carboxylic acid which is readily obtainable in high yields [29, 33].

It would exceed the scope of this review to discuss individually the numerous reactions of the adamantane series. Instead, all the adamantane derivatives described since 1954 are listed in Table 2.

d) Physical Studies

With regard to physical measurements on adamantane *Mecke* and *Spiesecke* [36] discussed its infrared and Raman spectra, and *McCall* and *Douglass* [37] reported on the proton nuclear magnetic resonance spectrum of solid adamantane. *Haberditzl* et al. [38] described magnetochemical investigations. Measurements of the magnetic susceptibility of adamantane and hexamethylenetetramine yielded surprisingly high, positive values for the diamagnetic exaltation, *viz.* +12.6 and +20.5 °, respectively, probably occasioned by the highly symmetrical atomic arrangement.

The heat capacity of adamantane and hexamethylenetetramine was determined by *Shu-Sing Chang* and *Westrum* [39] using adiabatic calorimetry in the range 5 to 350 °K. Additional thermodynamic data were also obtained.

[28] *J. D. Roberts* and *W.T. Moreland*, J. Amer. chem. Soc. *75*, 2167 (1953).

[29] *H. Stetter* and *E. Rauscher*, Chem. Ber. *93*, 1161 (1960).

[30] *H. Koch* and *W. Haaf*, Angew. Chem. *72*, 628 (1960).

[31] *W. Haaf*, Angew. Chem. *73*, 144 (1961).

[32] *H. Stetter* and *P. Goebel*, Chem. Ber. *95*, 1093 (1962).

[33] *H. Stetter* and *E. Rauscher*, Chem. Ber. *93*, 2054 (1960).

[34] *S. Landa* and *Z. Kamýcek*, Collection Czechoslov. Chem. Commun. *21*, 772 (1956); *24*, 1320 (1959).

[35] *S. Hála* and *S. Landa*, Collection Czechoslov. Chem. Commun. *25*, 2692 (1960).

[36] *R. Mecke* and *H. Spiesecke*, Chem. Ber. *88*, 1997 (1955).

[37] *D.W. McCall* and *D. C. Douglas*, J. chem. Physics *33*, 777 (1960).

[38] *W. Haberditzl*, *R. Havemann*, and *H. Köppel*, Naturwissenschaften *48*, 300 (1961).

[39] *Shu-Sing Chang* and *E. F. Westrum*, J. physic. Chem. *64*, 1547 (1960).

Table 2. Derivatives of adamantane described since 1954

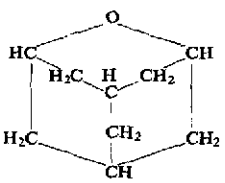
Compound	M.p. (b.p.) [°C]	Ref.
1-methyladamantane	103	[14, 12]
2-methyladamantane	143.8—146	[12, 24]
methylenadamantane	135.8—136.5	[24]
1,3-dimethyladamantane	(210)	[34, 12]
1,3,5,7-tetramethyl-adamantane	66—67	[8]
1-ethyladamantane	(240)	[2, 35]
1-propyladamantane	(251)	[2]
1,3-diisopropyladamantane	(294—296)	[34]
1,3-diisopropenyl-adamantane	(155—158/15 mm.Hg)	[34]
1-cyclohexyladamantane	104.5	[2]
1-Ethynyladamantane	83	[32]
1-phenyladamantane	87—89; 82	[2, 14]
1-chloroadamantane	165	[14, 15, 17, 19, 21]
1,3-dichloroadamantane	133	[17, 19]
1,3-bis(chloromethyl)-adamantane	63.8—65.3	[34]
1,3-bis(α-methyl-α-chloroethyl)adamantane	71.5—72.5	[34]
1,3,5-trichloroadamantane	115—116	[17, 19]
1,3,5,7-tetrakis-(chloromethyl)adamantane	165—166.5	[8]
1-(diphenylchloromethyl)-adamantane	150—152	[29]
1-bromoadamantane	119—120; 118	[13a, 14]
1,3-dibromoadamantane	112—113	[14, 16]
1,3,5-tribromoadamantane	126—127	[16]
1,3,5,7-tetrabromo-adamantane	246—247	[6, 16]
1,3-bis(bromomethyl)-adamantane	85.5—87	[34]
1-(β-bromoethyl)-adamantane	68—69	[32]
1-(β,β-dibromoethyl)-adamantane	(117—118/2 mm.Hg)	[32]
1-(β-bromoethenyl)-adamantane	117—118	[32]
1-iodoadamantane	75.3—76.4	[27]
1,3-bis(iodomethyl)-adamantane	85.5—86.5	[34]
1-hydroxyadamantane	288.5—290; 282	[13a, 14, 21, 24]
—, *p*-nitrobenzoate	185.8—186.1	[24]
—, *p*-toluenesulfonate	63—85	[27]
2-hydroxyadamantane	296.2—297.7	[24]
—, *p*-toulenesulfonate	82.7—83.7	[24]
1,3-dihydroxyadamantane	315	[16]
1,3,5-trihydroxyadamantane	> 360	[16]
2-methyl-2-hydroxy-adamantane	207.8—209	[24]
—, *p*-nitrobenzoate	133.1—133.7	[24]
1-hydroxymethyl-adamantane	115	[14, 21]
—, *p*-toluenesulfonate	76	[14]
1-(α-hydroxyethyl)-adamantane	75—76	[33]
1,3-dimethyloladamantane (hydroxymethyl)	180.5—182	[34]
1,3,5,7-tetramethyloladamantane (hydroxymethyl)	231—232	[8]
1,3-bis(α-methyl-α-hydroxyethyl)adamantane	164—167	[34]
diphenyl-1-adamantyl-methanol	127—128	[29]
2-hydroxy-2-methyl-3-(1-adamantyl)but-4-yne	80—81	[32]
1-hydroxy-1,1-diphenyl-3-(1-adamantyl)prop-3-yne	—	[32]
diphenyl-1-(adamantyl)-methylmethyl ether	202	[29]
1-(*p*-methoxyphenyl)-adamantane	—	[18]
adamantane-1-carbox-aldehyde	—	[29]
—, 2,4-dinitrophenyl-hydrazone	225	[29]
adamantanone	224—225; 281.2—282.8	[24, 21]
—, oxime	162.8—163.6	[21]
—, 2,4-dinitrophenyl-hydrazone	213.5—214.5, 221—221.5	[21, 24]
methyl-1-adamantylketone	54	[32, 33, 35]
—, oxime	182—184	[33]
—, 2,4-dinitrophenyl-hydrazone	219—220	[33]
—, methyl enol ether	(69—71/1.5 mm.Hg)	[32]
bromomethyl-1-adamantyl-ketone	78—79	[33]
phenyl-1-adamantylketone	55—56	[29]
—, oxime	224	[29]
—, 2,4-dinitrophenyl-hydrazone	242—244	[29]
1-oxo-1-(1-adamantyl)-3,3-diphenylprop-2-ene	119—121	[32]
adamantane-1-carboxylic acid	181	[14, 29, 30]
—, ethyl ester	(122—123/9 mm.Hg)	[14]
—, acid chloride	—	[14, 29]
—, anhydride	229	[29]
—, amide	189	[15]
—, anilide	197	[29]
—, hydrazide	156—157	[29]
N,N'-bis-(adamantane-1-carboxy)hydrazide	255—256	[29]
N-(*p*-toluenesulfonyl)-*N'*-(adamantane-1-carboxy)-hydrazide	192	[29]
3-fluoroadamantane-1-carboxylic acid	152	[20]
—, methyl ester	32—34	[20]
3-chloroadamantane-1-carboxylic acid	149	[20]
3-bromoadamantane-1-carboxylic acid	146.5	[20]
—, methyl ester	32	[20]
3-iodoadamantane-1-carboxylic acid	165	[20]
3-hydroxyadamantane-1-carboxylic acid	202—203	[20]
3-methoxyadamantane-1-carboxylic acid	126	[20]
3-phenyladamantane-1-carboxylic acid	168	[20]
adamantane-1,3-dicarboxylic acid	279.5—280.5; 276	[16, 20, 34]
—, dimethyl ester	57	[16, 34]
—, dipiperidide	162—163	[16]
adamantane-2,6-dione-1,5-dicarboxylic acid		
—, dimethyl ester-bis-ethylene mercaptal	212—215	[34]
adamantane-1,3,5,7-tetracarboxylic acid	395 (decomp.)	[6, 8]
—, tetramethyl ester	168—169	[6, 8]
—, tetraethyl ester	56—57	[8]
2,6-dichloroadamantane-1,3,5,7-tetracarboxylic acid	331	[7, 6]
—, tetramethyl ester	197—199	[6, 7]
2,6-dihydroxyadamantane-1,3,5,7-tetracarboxylic acid	300 (decomp.)	[7]
—, tetramethyl ester	237—239	[7]
adamantane-2,6-dione-1,3,5,7-tetracarboxylic acid	283.5—284.5	[8]
—, tetramethyl ester		
1-adamantyl-acetic acid	136	[14]
1-adamantylpropiolic acid	130—131	[32]
ethyl-β-(1-adamantyl)-β-oxopropionate	(108—110/0.06 mm.Hg)	[33]
1-nitroadamantane	173; 158.5—159	[15, 21]
1,3-dinitroadamantane	213.5—214	[21]
1,3-dihydroxy-2-nitro-6-methyl-6-dichloromethyl-adamantane	172	[13]
1-aminoadamantane	160—190	[15]
1-formaminoadamantane	140	[31]
1-acetaminoadamantane	148	[14, 15]
N-(1-adamantyl) methyl urethane	119	[15]

Table 2 (continued)

Compound	M.p. (b.p.) [°C]	Ref.
1-(*p*-toluenesulfonyl-amino)adamantane	166	[15]
2-aminoadamantane	–	[21]
1,3-dihydroxy-2-amino-6,6-dimethyladamantane	–	[13]
1,3-diaminoadamantane	–	[16, 21]
(1,3-bis-acetamino)-adamantane	226–227	[16]
adamantanesulfonic acid(?)	174.7–175.9	[21]
1,1'-biadamantyl	296; 288–290	[2, 18, 19]
3,3'-dibromo-1,1'-biadamantyl	236–237; 231–233	[18, 19]
3,3'-dihydroxy-1,1'-biadamantyl	271–272	[18]
3,3'-dihydroxymethyl-1,1'-biadamantyl	217–218	[18]
1,1'-biadamantyl-3,3'-dicarboxylic acid	352–355; 368–370	[18, 19]
–, *dimethyl ester*	144	[19]
3,3'-dicyano-1,1'-biadamantyl	261–262	[18]
3,3'-bis(aminomethyl)1,1'-biadamantyl	–	[18]
3,3'-diphenyl-1,1'-biadamantyl	270–271	[18]
3,3'-di(*p*-hydroxyphenyl) 1,1'-biadamantyl	343–344	[18]
3,3'-di(*p*-anisyl)-1,1'-biadamantyl	263	[18]
1,2-di-1-adamantylethylene glycol	257–265	[29]
1,2-di-1-adamantyl-1-oxo ethane	277–278	[29]
1,2-di-1-(adamantyl)-1-oxo-2-hydroxy ethane	223–224	[29]
1,2-di-1-(adamantyl)-1,2-dioxoethane	219	[29]
1,4-di-1-(adamantyl)butane	130–132	[32]
1,4-di-1-(adamantyl)-diacetylene	348–350 (decomp.)	[32]
1,4-di-1-(adamantyl)-buta-1,4-dione	132–133	[33]
1-phenyl-3-1-(adamantyl)-pyrazol-5-one	138–139	[33]
2,5-di-1-(adamantyl)furan	217	[33]
2,5-di-1-(adamantyl)-pyrrole	227–228	[33]

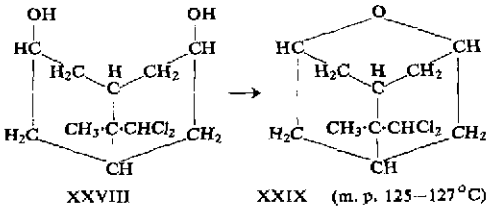
2. 2-Oxa-adamantane

This ring system was prepared in 1959 starting from 9-methyl-9-dichloromethyl-bicyclo[3,3,1]nonane-3,7-dione (XIV) [40]. Lithium aluminum hydride reduction of (XIV)

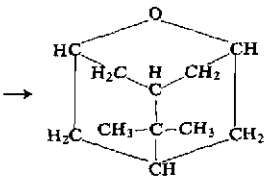


yielded 9-methyl-9-dichloromethylbicyclo[3,3,1]nonane-3,7-diol (XXVIII) which was converted in to the cyclic ether, 6-methyl-6-dichloromethyl-2-oxa-adamantane (XXIX), with sulfuric acid. Catalytic hydrogenation in the presence of alkali eliminated the halogen and highly volatile 6,6-dimethyl-2-oxa-adamantane (XXX) was formed.

[40] *H. Stetter* and *J. Mayer*, Chem. Ber. *92*, 2664 (1959).

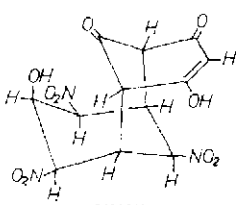


XXVIII XXIX (m. p. 125–127 °C)

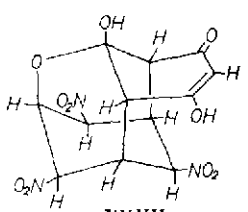


XXX (m. p. 180 °C)

On the basis of its infrared spectrum, *Severin* [41], suggested that the adduct XXXI obtained from 1,3,5-trinitrobenzene and phloroglucinol formed a cyclic semiketal (XXXII) corresponding to the ring system of 2-oxa-adamantane. The same structure was also postulated for the corresponding adducts of 1,3,5-trinitrobenzene onto nitrophloroglucinol and of picric acid onto phloroglucinol.



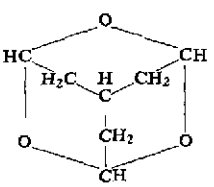
XXXI



XXXII

3. 2,4,9-Trioxa-adamantane

"Intramolecular trimerization" of branched tricarbonyl compounds to form the ring system of 2,4,9-trioxa-adamantane [42] was investigated more thoroughly on further examples [43]. Methanetriacetyl chloride (XXXIII) was treated with diazomethane and yielded



the tris-diazoketone XXXIV. When the latter was treated with hydrochloric acid or hydrogen bromide, 1,3,5-tris-(chloromethyl)-2,4,9-trioxa-adamantane (XXXVI) or the corresponding bromo compound XXXVII was formed instead of the anticipated triketone XXXV. "Intramolecular trimerization" of the carbonyl groups of the triketone XXXV initially formed led to XXXVI and XXXVII. In contrast, Friedel-Crafts reaction of methanetriacetyl chloride with benzene produced a triketone XXXVIII, which did not isomerize to the ring system of 2,4,9-trioxa-adamantane. In this case,

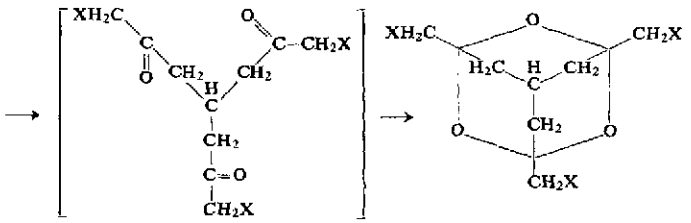
[41] *T. Severin*, Chem. Ber. *92*, 1517 (1959).

[42] *H. Stetter* and *M. Dohr*, Chem. Ber. *86*, 589 (1953).

[43] *H. Stetter* and *H. Stark*, Chem. Ber. *92*, 732 (1959).

"intramolecular trimerization" was prevented by the diminished reactivity of the aromatic carbonyl groups owing to mesomerism with the benzene nucleus.

$HC(CH_2{\cdot}CO{\cdot}C_6H_5)_3$ ← $HC(CH_2{\cdot}COCl)_3$ → $HC(CH_2{\cdot}CO{\cdot}CHN_2)$
XXXVIII XXXIII XXXIV

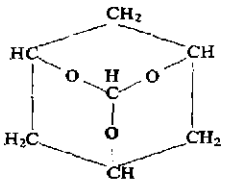


XXXV

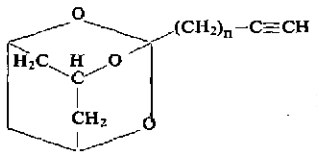
XXXVI: X = Cl (m.p 114°C)
XXXVII: X = Br(m.p 129°C)

4. 2,4,10-Trioxa-adamantane

Ortho-ester formation with *cis*-phloroglucitol, leading to formation of 2,4,10-trioxa-adamantane, was once proposed for protecting carboxyl groups from the action of organometallic reagents [44]. *Osbond* et al. [45]



utilized this protecting technique in the synthesis of long-chain carboxylic acids of the acetylene series; starting out from 5-cyanopent-1-yne and 6-cyanohex-1-yne, they prepared 3-(pent-4′-ynyl)-2,4,10-trioxa-adamantane (XXXIX) and 3-(hex-5′-ynyl)-2,4,10-trioxa-adamantane (XL).

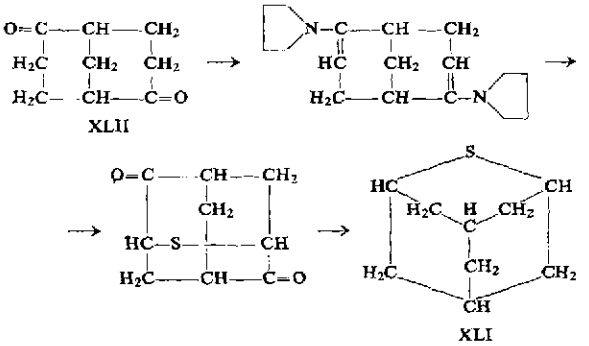


XXXIX: n = 3 (m.p. 53–54°C)
XL: n = 4 (m.p. 47–49°C)

Their Grignard compounds were condensed with 1-bromotetradeca-2,5,8-triyne and 1-bromoundeca-2,5-diyne, respectively. Subsequent hydrolysis produced octadeca-6,9,12-trynic acid and eicosa-5,8,11,14-tetraynic acid, neither of which was isolated.

5. 2-Thia-adamantane

2-Thia-adamantane (XLI), discovered in South Iranian petroleum in 1952[46] has been synthesized for the first time [47]. The synthesis started from bicyclo-[3,3,1]-nonane-2,6-dione (XLII) which was readily available from Meerwein ester by ketonic hydrolysis. The bis-(enamine) derivative was obtained in the usual fashion, with pyrrolidine. When the bis(enamine) was reacted with sulfur dichloride, ring closure occurred with formation of 2-thia-adamantane-4,8-dione, from which 2-thia-adamantane was obtained by Wolff-Kishner reduction.

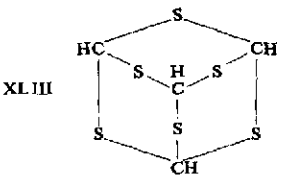


XLII XLI

The heat of combustion of (XLI) was determined by *Lacina et. al.* [47a].

6. 2,4,6,8,9,10-Hexathia-adamantane

Although tetra-alkyl derivatives of this ring system have been known for a long time [1], unsubstituted 2,4,6,8,9,10-hexathia-adamantane (XLIII) was first synthesized in 1956. *Fredga* and *Olsson* [48] obtained crystals of



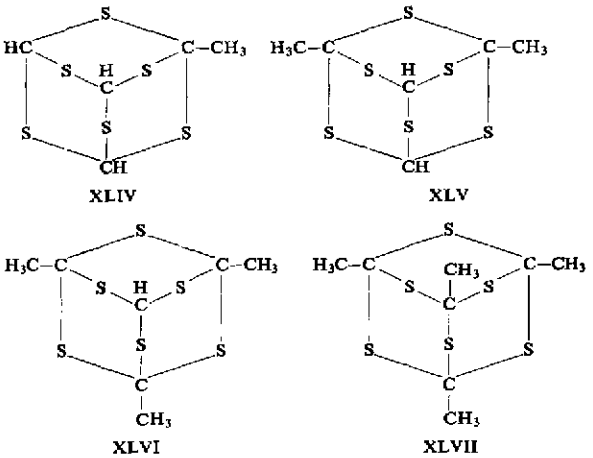
XLIII

(XLIII) when formic acid in nitrobenzene was saturated with hydrogen chloride and allowed to stand for several weeks in an atmosphere of hydrogen sulfide. The preparation was also successful in ether solution with boron trifluoride. Application of the dilution principle was important in both cases because, otherwise, only high-molecular weight polymers were formed. Surprising properties of (XLIII) were its non-volatility and extreme insolubility in common solvents. The explanation assumed was that very strong intermolecular forces exist between the sulfur atoms; such forces cannot come into play in tetra-alkyl derivatives of the ring system, because the alkyl groups prevent approach of the sulfur atoms in the crystal lattice.

Investigations of the crystal structure by *Andersen* and *Lindquist* [49] confirmed this view and elucidated the molecular structure. The molecules in the crystal are densely packed and the intermolecular distances between the sulfur atoms are unusually short. The short distances between the sulfur atoms indicate the presence of strong Van der Waals forces. This is supported by the investigations and discussions of the infrared spectra by *Spiesecke* and *Mecke* [50].

[44] *H. Stetter* and *K. H. Steinacker*, Chem. Ber. *87*, 205 (1954).
[45] *J. M. Osbond et. al.*, J. chem. Soc. (London) 2779 (1961).
[46] *S.F.Birch, T.V.Cullum, R.A.Dean*, and *R.L.Denyer*, Nature (London) *170*, 629 (1952); Ind. Engng. Chem. *47*, 240 (1955).
[47] *H. Stetter* and *H. Held*, Angew. Chem. *73*, 114 (1961).
[47a] *J. L. Lacina et. al.*, J. physic. Chem. *65*, 1026 (1961).
[48] *A. Fredga* and *K. Olsson*, Arkiv för Kemi *9*, 163 (1956).
[49] *E. K. Andersen* and *I. Lindquist*, Arkiv för Kemi *9*, 169 (1956).
[50] *H. Spiesecke* and *R. Mecke*, J. chem. Physics *25*, 577 (1956).

By treating a mixture of (XLIII), thioacetic acid, and formic acid with zinc chloride, *Olsson* [51] prepared a mixture containing 1 - methylhexathia - adamantane (XLIV), 1,3 - dimethylhexathia - adamantane (XLV), 1,3,5-trimethylhexathia-adamantane (XLVI), and 1,3,5,7-tetramethylhexathia-adamantane (XLVII) and isolated the individual compounds.



XLIV XLV

XLVI XLVII

A series of more highly alkylated hexathia-adamantanes was prepared by applying thiopropionic acid and thiobutyric acid analogously. It is remarkable that in every case, the solubility increased and the melting point decreased with increase in the number of alkyl groups, in good agreement with the influence of the alkyl groups on the intermolecular forces in the crystal described above.

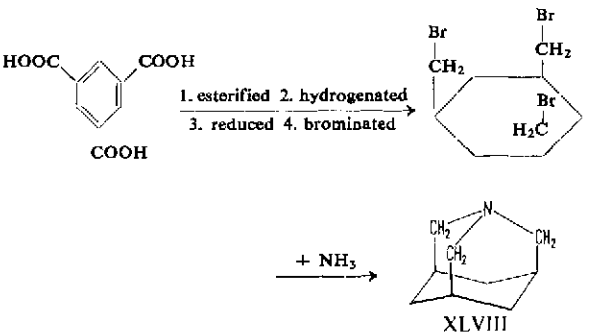
A summary of the derivatives of the hexathia-adamantane series is shown in Table 3.

Table 3. Compounds of the hexathia-adamantane series

Compounds	m.p. [°C]
2,4,6,8,9,10-hexathia-adamantane	*ca.* 330 (decomp.)
1-methyl-2,4,6,8,9,10-hexathia-adamantane	*ca.* 300 (decomp.)
1,3-dimethyl-2,4,6,8,9,10-hexathia-adamantane	*ca.* 300 (decomp.)
1,3,5-trimethyl-2,4,6,8,9,10-hexathia-adamantane	*ca.* 300 (decomp.)
1,3,5,7-tetramethyl-2,4,6,8,9,10-hexathia-adamantane	224—225
1-ethyl-2,4,6,8,9,10-hexathia-adamantane	*ca.* 300 (decomp.)
1,3-diethyl-2,4,6,8,9,10-hexathia-adamantane	*ca.* 250 (decomp.)
1,3-diethyl-2,4,6,8,9,10-hexathia-adamantane	*ca.* 250 (decomp.)
1,3,5-triethyl-2,4,6,8,9,10-hexathia-adamantane	209—210
1-propyl-2,4,6,8,9,10-hexathia-adamantane	*ca.* 300 (decomp.)
1,3-dipropyl-2,4,6,8,9,10-hexathia-adamantane	179—182
1,3,5-tripropyl-2,4,6,8,9,10-hexathia-adamantane	198—199
1,3,5,7-tetraphenylethyl-2,4,6,8,9,10-hexathia-adamantane [51a]	183—183,5

7. 1-Aza-adamantane

1-Aza-adamantane (XLVIII) was synthesized for the first time in 1953 by *Fusco* and *Bianchetti* [52]. The synthesis started with trimesic acid, which was converted into *cis*-cyclohexane-1,3,5-tricarboxylic acid by catalytic hydrogenation. The methyl ester of this acid was reduced with lithium aluminum hydride to form 1,3,5 - tris(hydroxymethyl)cyclohexane, which yielded *cis*-1,3,5-tris(bromomethyl)cyclohexane with hydrogen bromide. When this compound was heated to 180 to 200 °C with alcoholic ammonia, a moderate yield of 1-aza-adamantane (XLVIII) m.p. 258 °C, was obtained.

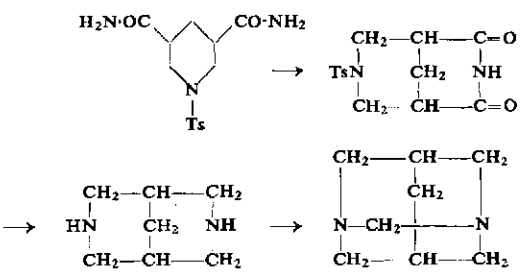


XLVIII

Shortly afterwards, *Lukes* and *Galik* [53] independently reported the same method of synthesis. The method used by *Newman* and *Lowric* [54] proved less successful; they reacted the methanesulfonate of 1,3,5-tris(hydroxymethyl) cyclohexane with ammonia instead of *cis*-1,3,5-tris(bromomethyl)cyclohexane, and were able to isolate only a very small amount of an impure preparation. The crystal structure was determined by *Bauer* [55].

8. 1,3-Diaza-adamantane

1,3-Diaza-adamantane (XLIX) was synthesized for the first time in 1955 [56]. The synthesis started from diethyl pyridine-3,5-dicarboxylate, which was converted by hydrogenation of the nucleus to diethyl piperidine-3,5-dicarboxylate. The latter was hydrolyzed and converted to *N*-tosyl piperidine-3,5-dicarboxylic acid with *p*-toluenesulfonyl chloride. The diamide of this acid (see formula) was heated in α-methylnaphthalene and lost ammonia to yield 2,4-dioxo-7-tosylbispidine. Lithium aluminum hydride reduction yielded bispidine with simultaneous reductive elimination of the *p*-toluenesulfonyl residue. The bispidine was then condensed with formaldehyde to give 1,3-diaza-adamantane.



Ts = p-toluenesulfonyl- XLIX

Later, this synthesis was simplified and improved [57]. The key factor was the discovery that when the cyclic imide was formed from the *N*-tosylpiperidine-3,5-di-

[51] *K. Olsson*, Acta chem. scand. *12*, 366 (1958); Arkiv för Kemi *14*, 371 (1959).

[51a] *H. Behringer et al.*, Liebigs Ann. Chem. *600*, 23 (1956).

[52] *R. Fusco* and *G. Bianchetti*, Atti Accad. Lincei (8) XV, 420 (1953); Gaz. chim. Italiana *86*, 500 (1956).

[53] *R. Lukes* and *V. Galik*, Collection Czechoslov. Chem. Commun. *19*, 712 (1954); Chem. Listy *48*, 858 (1954).

[54] *M. S. Newman* and *H. S. Lowric*, J. Amer. chem. Soc. *76*, 4598 (1954).

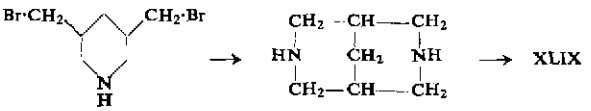
[55] *J. Bauer*, Chem. Listy *48*, 861 (1954).

[56] *H. Stetter* and *H. Hennig*, Chem. Ber. *88*, 789 (1955).

[57] *H. Stetter* and *R. Merten*, Chem. Ber. *90*, 868 (1957).

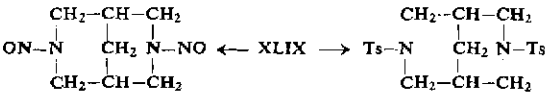
carbonamide, the *trans* form also reacted, following rearrangement.

Shortly afterwards, *Galinowsky* and *Langer* [58] used piperidine-3,5-dicarboxylic acid as starting material and reduced its ester to 3,5-bis(hydroxymethylpiperidine). 3,5-Bis(bromomethyl)piperidine, obtained from the latter, was converted to bispidine by condensation with ammonia. 1,3-Diaza-adamantane was obtained by condensation with formaldehyde, as well as by condensation with methylene iodide.



Another method for preparing bispidine is afforded by direct catalytic hydrogenation of pyridine-3,5-dicarbonitrile [59].

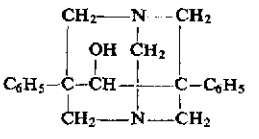
The N–C–N linkage in 1,3-diaza-adamantane is stable to hydrolysis by aqueous mineral acids, analogously to the ring system of 1,3,5-triaza-adamantane [60]. With nitric acid and *p*-toluenesulfonyl chloride, however, formaldehyde is split off and *N,N'*-dinitrosobispidine and *N,N'*-ditosylbispidine are formed [61].



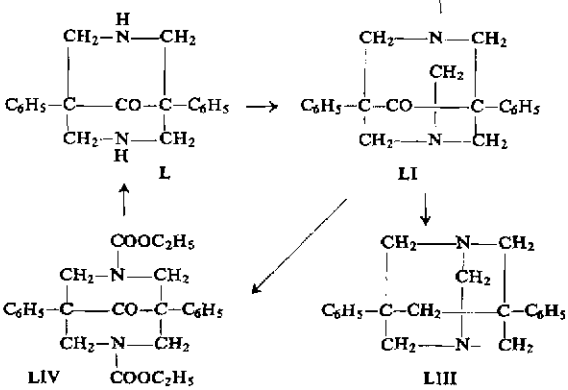
Another rather simple preparative pathway to the 1,3-diaza-adamantane ring system was provided by the Mannich condensation in the presence of dibenzyl ketone. *Zu-Yoong-Kyi* and *Wilson* [62] described a Mannich condensation of dibenzyl ketone with formaldehyde and ammonium acetate, whereby 1,5-diphenylbispid-9-one(L) is supposed to have been formed as reaction product. The formation of this bispidone in the presence of free formaldehyde appeared strange, since bispidine itself reacts smoothly with formaldehyde, forming 1,3-diaza-adamantane. The reaction of (L) with *p*-toluenesulfonyl chloride and acetic anhydride, leading to *N,N'*-ditosyl-1,5-diphenylbispid-9-one and *N,N'*-diacetyl-1,5-diphenylbispid-9-one was used by these authors as a proof of their structure, but cannot be accepted as a proof for the bispidone structure because, as mentioned above, 1,3-diaza-adamantane also produces derivatives of bispidine under the same conditions with elimination of formaldehyde.

It has been demonstrated that the compound obtained by *Zu-Yoong-Kyi* and *Wilson* was in fact 5,7-diphenyl-1,3-diaza-adamantan-6-one (LI) [63]. Its structure was determined by its elementary analysis, negative Zerevitinoff test, and the absence of NH absorption in its infrared spectrum.

6-Hydroxy-5,7-diphenyl-1,3-diaza-adamantane (LII) has been obtained by reduction of (LI) with lithium aluminum hydride and by heating (LI) to 180 °C with alkali in alcoholic solution corresponding to a Meerwein-Ponndorf reduction. The ease of this reduction makes Wolff-Kishner reduction in the conventional form impossible. Reduction of (LI) to 5,7-diphenyl-1,3-diaza-adamantane (LIII) only succeeded when sodium acetate and hydrazine were used instead of alkali and hydrazine.

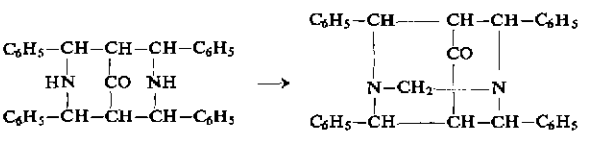


LII [*]



Shortly afterwards, *Chiavarelli* and *Settimj* [64] were also able to prove the structure of (LI) and succeeded also in preparing 1,5-diphenylbispid-9-one (L) itself. Treatment of (LI) with chloroformic acid ester yielded *N,N'*-diethoxycarbonyl-1,5-diphenylbispid-9-one (LIV) from which 1,5-diphenylbispid-9-one (L) was obtained by alkaline hydrolysis. The compound reacted immediately in the presence of formaldehyde to form (LI).

Chiavarelli et al. [65] were able to use acetone instead of dibenzyl ketone in this Mannich condensation by using benzaldehyde as the aldehyde component. The 2,4,6,8-Tetraphenylbispid-9-one (LV) produced was converted to 4,8,9,10-tetraphenyl-1,3-diaza-adamantan-6-one (LVI) by condensation with formaldehyde.



The same sequence of reactions was also performed with methyl ethyl ketone and substituted benzaldehydes.

Instead of dibenzyl ketone, bis(phenylthio)acetone can also be used in the Mannich condensation with formaldehyde and ammonium acetate, 5,7-bis(phenylthio)-1,3-diaza-adamantan-6-one (LVII) being obtained [66].

[58] *F. Galinowsky* and *H. Langer*, Mh. Chem. *86*, 449 (1955); *87*, 100 (1956).

[59] *F. Bohlmann, N. Ottawa*, and *R. Keller*, Liebigs Ann. Chem. *587*, 162 (1954); *F. Bohlmann* and *N. Ottawa*, Chem. Ber. *88*, 1828 (1955).

[60] *H. Stetter* and *W. Böckmann*, Chem. Ber. *84*, 834 (1951).

[61] *H. Stetter* and *R. Merten*, Chem. Ber. *90*, 868 (1957).

[62] J. chem. Soc. (London) 1706 (1951).

[63] *H. Stetter, J. Schäfer*, and *K. Dieminger*, Chem. Ber. *91*, 598 (1958); Angew. Chem. *70*, 52 (1958).

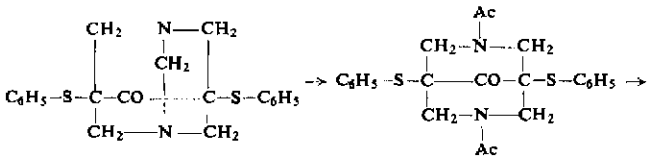
[*] Exhibits strong convulsant activity similar to that of strychnine in mice, rats, and rabbits. *V. G. Longo et. al.*, J. Pharmacol. exp. Therapeut. *126*, 41 (1959).

[64] *S. Chiavarelli et al.*, Gaz. chim. Italiana *88*, 1234 (1958).

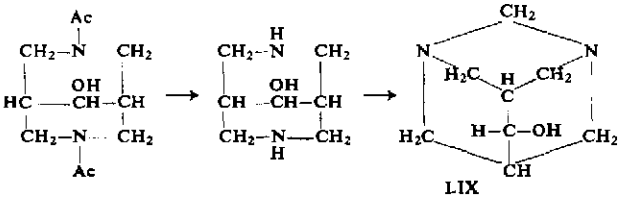
[65] *S. Chiavarelli et al.*, Gaz. chim. Italiana *90*, 311 (1960).

[66] *H. Stetter et el.*, Chem. Ber. *92*, 2057 (1959).

Elimination of the residues containing sulfur can be effected by first splitting the compound into *N,N'*-diacetyl-1,5-bis(phenylthio)bispid-9-one (LVIII) by acetylation and then desulfurizing with Raney nickel. The bispidin-9-ol, obtained in this way, condensed with formaldehyde to form 1,3-diaza-adamantan-8-ol (LIX). *Bis*(benzenesulfonyl)acetone can also be converted into 5,7-bis(benzenesulfonyl)-1,3-diaza-adamantan-6-one in an identical Mannich condensation.

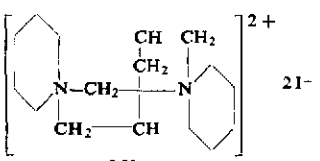


LVII LVIII



LIX

The adduct LX obtained by condensation of sparteine with methyl iodide is worthy of mention here. It also contains the 1,3-diaza-adamantane ring system which is important for the structural determination of this alkaloid. The same ring closure is also possible with α-isosparteine [67].



LX

Compounds of the 1,3-diaza-adamantane series are listed in Table 4.

Table 4. The 1,3-diaza-adamantane series

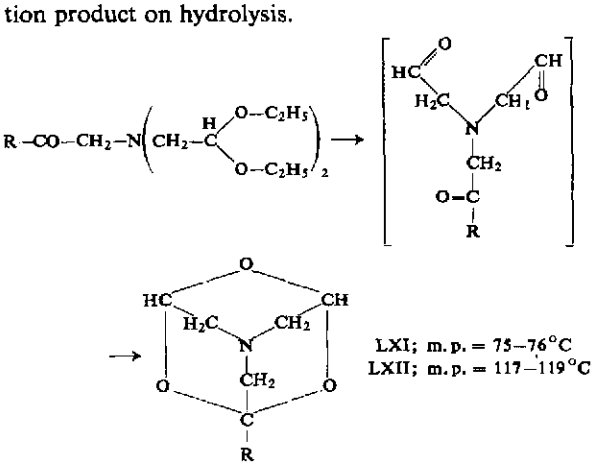
Compound	M.p. [°C]	Ref.
1,3-diaza-adamantane	260–262, 264–265	[56, 58]
5,7-diphenyl-1,3-diaza-adamantane	217–219	[63]
4,8,9,10-tetraphenyl-1,3-diaza-adamantane	268–269	[65]
1,3-diaza-adamantan-6-ol	270	[66]
5,7-diphenyl-1,3-diaza-adamantan-6-ol	274; 278–279	[63, 64]
4,8,9,10-tetraphenyl-1,3-diaza-adamantan-6-ol	260–261	[65]
4,8,9,10-tetraphenyl-5-methyl-1,3-diaza-adamantan-6-ol	251–253	[65]
5,7-bis-phenylmercapto-1,3-diaza-adamantan-6-ol	190–191	[66]
5,7-diphenyl-1,3-diaza-adamantan-6-one	257; 263–264	[63, 64]
4,8,9,10-tetraphenyl-1,3-diaza-adamantan-6-one	229–230	[65]
4,8,9,10-tetraphenyl-5-methyl-1,3-diaza-adamantan-6-one	264–266	[65]
5,7-bis phenylthio-1,3-diaza-adamantan-6-one	245	[66]
5,7-bis benzenesulfonyl-1,3-diaza-adamantan-6-one	337 (decomp.)	[66]
adduct sparteine + methylene iodide	345	[67]
adduct α-isosparteine + methylene iodide	351	[67]

[67] *F. Galinovsky, P. Knoth,* and *W. Fischer,* Mh. Chem. *86,* 1014 (1955).

9. 1-Aza-4,6,10-trioxa-adamantane (Trimorpholine)

This ring system is formed analogously to the ring system of 2,4,9-trioxa-adamantane by "intramolecular trimerization" of branched tricarbonyl compounds with nitrogen atoms at the branching points [1]. As already mentioned in the section on 2,4,9-trioxa-adamantane, trimerization does not occur when the reactivity of the carbonyl groups is reduced through mesomerism with neighboring groups. Studies have been made on the extent to which such carbonyl groups with reduced reactivity can undergo "intramolecular trimerization" with reactive carbonyl groups [68].

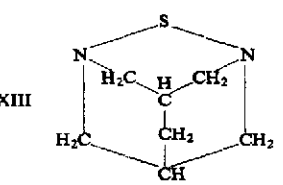
It was shown that such a "mixed trimerization" is at all possible using the example of bis(diethoxyethyl)acetonylamine, produced from bis(diethoxyethyl)amine and bromoacetone (see next set of formulae; R = CH_3). Hydrolysis of the acetal groups yielded 3-methyl-1-aza-4,6,10-trioxa-adamantane (LXI) in a smooth reaction. The corresponding bis(diethoxyethyl)phenacylamine (R = C_6H_5), accessible from bis(diethoxyethyl)amine and phenacyl bromide also underwent cyclization when hydrolyzed to give 3-phenyl-1-aza-4,6,10-trioxa-adamantane (LXII). These results clearly indicate that the unreactive carbonyl group in conjugation with the benzene nucleus underwent an "intramolecular trimerization" with the two aldehyde groups, while three α-aryl-keto groups alone could not undergo this reaction, as shown by the example of tris phenacyl methane. Although an α-aryl-keto group can participate in the trimerization, ester carbonyl groups cannot. *N,N'*-diacetalylglycine ethyl ester did not yield a uniform reaction product on hydrolysis.



LXI; m.p. = 75–76°C
LXII; m.p. = 117–119°C

10. 2-Thia-1,3-diaza-adamantane

2-Thia-1,3-diaza-adamantane (LXIII) was obtained in 1955 by condensation of ethyl sulfoxylate with bispidine [57]. This material exhibited the characteristic volatility



LXIII

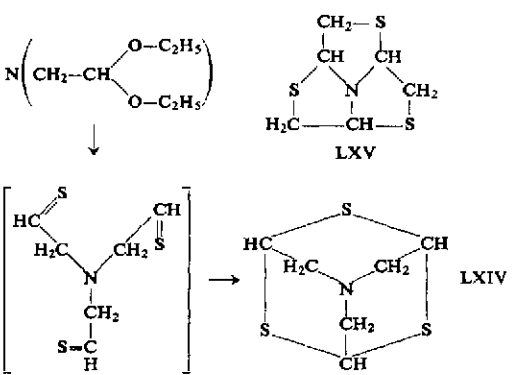
[68] *H. Stetter* and *H. Stark,* Chem. Ber. *95,* 574 (1962).

of compounds of this structure and melted at 160 °C with decomposition. The sulfur-nitrogen linkage of the ring system was not stable in either acid or alkaline aqueous media. Furthermore, the ring system underwent oxidative degradation when an oxidation of the sulfide sulfur atom to form a sulfone group was attempted.

11. 1-Aza-4,6,10-trithia-adamantane

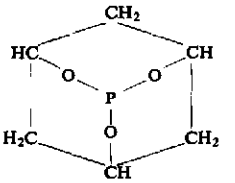
Craig et al. [69] allowed ammonium dithiocarbamate and chloroacetaldehyde to react and obtained a by-product in ca. 8 % yield in the form of a crystalline compound, m.p. 147–148 °C, which they identified on the basis of its analysis and physical properties as 1-aza-4,6-10-trithia-adamantane (LXIV). The same compound was later obtained when mercaptoacetaldehyde was treated with ammonium chloride [70]. *Thiel* et al. [71] obtained the same compound when gaseous ammonia was passed through a solution of thioacetaldehyde. They were able to prove definitively that the compound was 1,4,7-trithia-2,5,8-*endo*-azacyclononane (LXV).

In 1960 *Thiel* et al. [72] achieved an unequivocal synthesis of 1-aza-4,6,10-trithia-adamantane (LXIV). Similar to the preparation of the oxygen analogue, trimorpholine, they started out from triacetalylamine, which was treated at 30–40 °C in a sealed tube with liquid hydrogen sulfide, containing hydrogen bromide. Compound LXIV sublimes above 100 °C and decomposes above 285 °C. With methyl iodide, the iodomethylate was obtained.



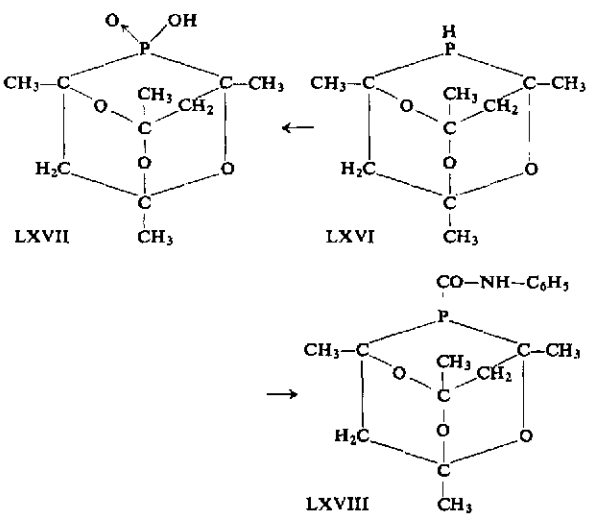
12. 1-Phospha-2,8,9-trioxa-adamantane

Andersen and *Hjortaas* [74] subjected phosphoric acid ester and thiophosphoric acid ester of *cis*-phloroglucitol, *viz.* 1-phospha-2,8,9-trioxa-adamantane-1-oxide and 1-phospha-2,8,9-trioxa-adamantane-1-sulfide synthetized previously [73] to an X-ray structural analysis. The first compound has the space group Cc. Its lattice dimensions are a = 11.37 Å, b = 6.25 Å, c = 11.74 Å, and $\beta = 118°$, with four molecules per unit cell. The sulfide has the space group $Pna2_1$ and the lattice dimensions a = 11.45 ± 0.05 Å, b = 7.28 ± 0.04 Å, and c = 47 ± 0.05 Å, with four molecules per unit cell.

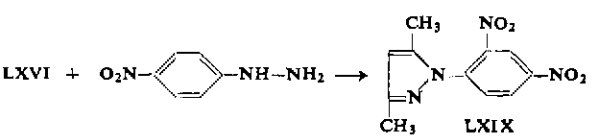


13. 2,4,6-Trioxa-8-phospha-adamantane

Epstein and *Buckler* [75] permitted phosphine to react with acetylacetone acidified with hydrochloric acid and obtained a crystalline compound to which they assigned the structure of 1,3,5,7-tetramethyl-2,4,6-trioxa-8-phospha-adamantane (LXVI) on the basis of its analytical results, infrared and NMR spectra and chemical behavior. The secondary phosphine structure can be demonstrated by characteristic reactions. For example, oxidation produces the phosphinic acid LXVII, and reaction with phenyl isocyanate produces the phenylcarbamic acid derivative LXVIII.



Reaction with 2,4-dinitrophenylhydrazine produced the pyrazole LXIX derived from acetylacetone in a yield of over 50 %. This resplitting of the ring system indicated that no alteration of the carbon skeleton had occured in LXVI.



[69] *D. Craig, J. J. Shipman, A. Hawthorne,* and *R. Fowler,* J. Amer. chem. Soc. *77*, 1283 (1955).

[70] *R. Haberl* and *O. Hromatka,* Mh. Chem. *88*, 998 (1957).

[71] Liebigs Ann. Chem. *611*, 121 (1958).

[72] *M. Thiel, F. Asinger,* and *K. Schmiedel,* Mh. Chem. *91*, 473 (1960).

[73] *H. Stetter* and *K. H. Steinacker,* Chem. Ber. *85*, 451 (1952).

[74] *P. Andersen* and *K. E. Hjortaas,* Acta chem. scand. *14*, 829 (1960).

[75] *M. Epstein* and *S. A. Buckler,* J. Amer. chem. Soc. *83*, 3279 (1961).

Under identical conditions, primary phosphines also yield compounds with the same type of structure on reaction with acetylacetone. Additional crystalline by-products, with two or three phosphorus atoms per molecule, were isolated. It is assumed that these compounds also have an adamantane type skeleton.

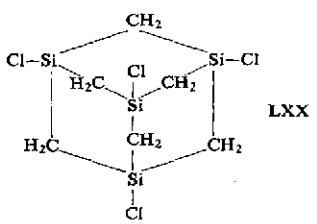
Compounds with the 2,4,6-trioxa-8-phospha-adamantane structure mentioned in this paper are summarized in Table 5.

Table 5. Compounds with a 2,4,6-trioxa-8-phospha-adamantane structure

Compound	m.p. [°C]
1,3,5,7-tetramethyl-2,4,6-trioxa-8-phospha-adamantane	88–90
1,3,5,7-tetramethyl-2,4,6-trioxa-8-phospha-adamantane-8-phosphinic acid	220–222
1,3,5,7-tetramethyl-2,4,6-trioxa-8-phospha-adamantane-8-dithio acid ammonium salt	212–214
9-phenylcarbamyl-1,3,5,7-tetramethyl-2,4,6-trioxa-8-phospha-adamantane	108–109
N,N'-(4-methyl-*m*-phenylene)-bis-1,3,5,7-tetramethyl-2,4,6-trioxa-8-phospha-adamantane-8-carbonamide	217–219
1,3,5,7,8,8-hexamethyl-2,4,6-trioxa-8-phosphonia-adamantane	243–244 (decomp.)
1,3,5,7-tetramethyl-8,8-dibutyl-2,4,6-trioxa-8-phosphonia-adamantane iodide	209–211 (decomp.)
8,8-dihydroxymethyl-1,3,5,7-tetramethyl-2,4,6-trioxa-8-phosphonia-adamantane chloride	161–162
1,3,5,7-tetramethyl-8-octyl-2,4,6-trioxa-8-phospha-adamantane	42–43
1,3,5,7-tetramethyl-8-isobutyl-2,4,6-trioxa-8-phospha-adamantane	75–77
1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phospha-adamantane	105–107

14. 1,3,5,7-Tetrasila-adamantane

A. L. Smith and *Clark* [76] allowed silicon tetrachloride and trimethylchlorosilane to react together in the presence of aluminum chloride under high pressure and at temperatures of up to 500 °C and obtained very small amounts of a crystalline, volatile by-product, to which they assigned the structure of 1,3,5,7-tetrachloro-1,3,5,7-tetrasila-adamantane (LXX) on the basis of its infrared



LXX

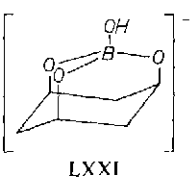
spectrum and chemical analysis. Resistance to hydrolysis was taken as an additional proof of the adamantane type structure of this compound, as it can be explained satisfactorily by the position of the halogen on the bridge atoms.

[76] *A. L. Smith* and *H. A. Clark*, J. Amer. chem. Soc. *83*, 3345 (1961).

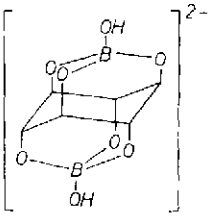
15. Boric Acid Complexes with Adamantane-type Structures

Angyal and *McHugh* [77] demonstrated by paper onophoresis that the cyclohexane derivatives of the *cis*-1,3,5-trihydroxycyclohexane structure can form complexes with boric acid, having the structure shown in LXXI. In structure determinations this type of complex formation must be considered along side that derived from the *cis*-1,2-dihydroxy structure.

Weissbach [78] isolated a corresponding double complex of boric acid with the structure LXXII in the case of scyllitol.



LXXI

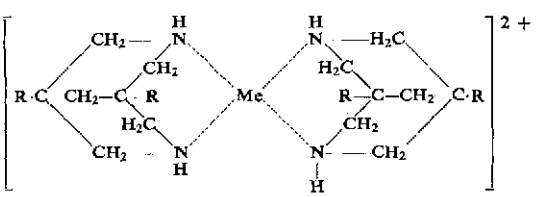


LXXII

16. Metal Complexes with Adamantane Type Structures

In the past few years, several complex salts with adamantane type structures have become known; here the metal atom assumes the role of an atom of the ring. Such complex salts were derived from either bispidine or *cis*-triaminocyclohexane or their derivatives.

Complex salts of general formula (LXXIII) were obtained from bispidine [57] and 1,5-diphenylbispidine [63] with Cu(II) and Ni(II) salts. The copper complex of bispidine has about ten times the stability of the corresponding copper complex of ethylenediamine.



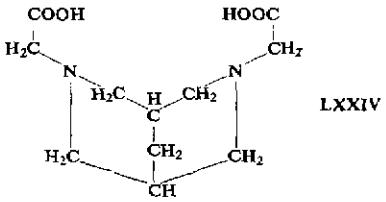
LXXIII R=H, C_6H_5

Bispidine - *N,N'*- diacetic acid (LXXIV) readily obtainable from bispidine (LXXIII) was also able to form very stable chelate complexes with adamantane type structures of formula (LXXIV), which were isolated in crystalline form [79]. The constants of complex formation (log K_c) are of the same order of magnitude as those obtained for nitrilotriacetic acid. They were: $Ca^{2+} = 4.22$, $Cu^{2+} = 14.45$, $Ni^{2+} = 8.58$, and $Co^{2+} = 10.55$.

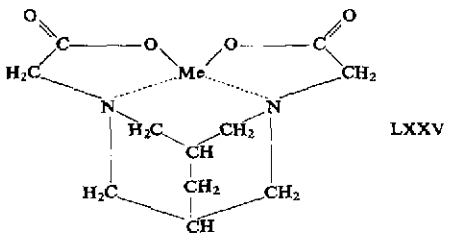
[77] *S. J. Angyal* and *D. J. McHugh*, J. chem. Soc. (London) 1423 (1957).

[78] *A. Weissbach*, J. org. Chemistry *23*, 329 (1958).

[79] *H. Stetter* and *K. Dieminger*, Chem. Ber. *92*, 2658 (1959).

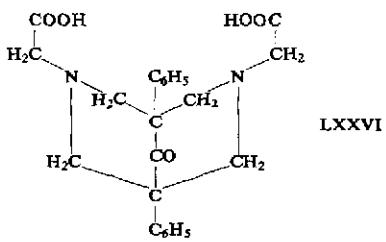


LXXIV



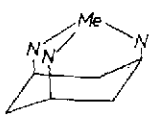
LXXV

1,5-Diphenylbispid-9-one-3,7-diacetic acid (LXXVI), a complexing agent of the same structure, was obtained in a simple manner by Mannich condensation of dibenzyl ketone with formaldehyde and glycine. The complex-formation constants for this agent were: Cu^{2+} = 16.02, Ni^{2+} = 8.11 and Co^{2+} = 9.48.



LXXVI

Lions and *Martin* [80] reported on complex salts with hexamethylenetetramine type structures derived from *cis*-1,3,5-triamino-cyclohexane, to which they assigned the general formula LXXVII with regard to their ring



LXXVII

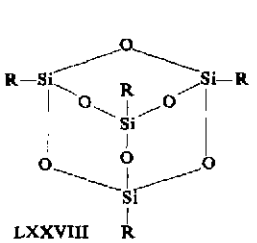
system. The complexing agents were condensation products of the triamine LXXVII with salicylaldehyde, naphth-2-ol-1-carboxaldehyde and pyridine-2-carboxaldehyde. Complexes of Co^{2+}, Co^{3+}, Fe^{2+}, and Rh^{3+} with the coordination number 6 were isolated in crystalline form.

[80] *F. Lions* and *K. V. Martin* J. Amer. chem. Soc. *79* 1572 (1957).

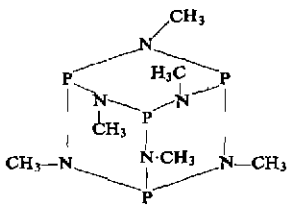
17. Concluding Remarks

As in the first review, the literature on hexamethylenetetramine itself has not been considered in the present article.

Although only organic ring systems with adamantane type structures have been covered in this literature survey, a few compounds with purely inorganic ring systems should be mentioned in conclusion. For example, on hydrolyzing alkyltrichlorosilanes, *Wiberg* and *Simmler* [81], obtained 2,4,6,8,9,10-hexaoxa-1,3,5,7-tetra-alkylsilamantanes of general formula LXXVIII, and on condensing phosphorus trichloride with excess methyl amine, *Holmes* [82], obtained compound (LXXIX). *Nöth* and *Vetter* [83] prepared similar compounds from arsenic trichloride and methylamine.



LXXVIII



LXXIX

It can be stated in conclusion that, because of the extremely rapid advances made in the chemistry of compounds with adamantane type structures during the last few years, many more interesting results are to be expected in the future. The scope and methods of organic chemistry will thereby be enriched.

Received, November 10th. 1961 [A 181/32 IE]

[81] *E. Wiberg* and *W. Simmler*, Z. anorg. allg. Chem. *282*, 330 (1955); *283*, 401 (1956). For elucidation of structure, see: *G.-M. Schwab*, *J. Grabmaier*, and *W. Simmler*, Z. physikal. Chem., N.F. *6*, 376 (1956).

[82] *R. R. Holmes*, J. Amer. chem. Soc. *83*, 1334 (1961).

[83] Naturwissenschaften *48*, 553 (1961).

Some Organic Sulfur Compounds in Vegetables and Fodder Plants and their Significance in Human Nutrition

BY PROF. DR. ARTTURI I. VIRTANEN [*]

LABORATORY OF THE FOUNDATION FOR CHEMICAL RESEARCH, BIOCHEMICAL INSTITUTE, HELSINKI, (FINLAND)

Many plants that serve for human nutritional purposes contain compounds from which physiologically active substances are formed by enzymic reactions. Usually such compounds, and the enzymes which react with them, are located in different cells, so that the active substances are formed only on crushing the plant. Examples are the lachrymatory factor and the antimicrobial substances formed from the different cysteine-S-oxides of the onion and garlic, as well as the goitrogenic compounds formed from the thioglucosides occurring in the Brassica species.

Introduction

Belief in the preventive or curative effect of vegetables towards disease has persisted for thousands of years. Garlic, onion, cress, and cabbage are examples. In Eastern Europe and Asia Minor, large amounts of raw onion or garlic are a normal feature of the diet. The science of nutrition has paid but little serious attention to these beliefs, since, to some extent, they can be explained on the basis of the vitamins and minerals contained in these vegetables, and because other alleged effects, if they exist, seem to be connected with substances better regarded as drugs than foods.

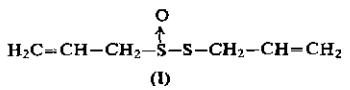
Many vegetables contain precursors from which physiologically active substances (such as flavor compounds, antibiotics or anti-thyroid substances) are formed enzymically when the plants are crushed. In the intact plant, precursor and enzyme are separated from each other in different cells [1]; the enzymic reaction is not possible before the cells are crushed. If the enzymes in intact plants are destroyed by heating, or by placing the plants for some time in cold alcohol, the active substances are no longer formed upon crushing and it is possible to isolate the precursor from the plant. Fresh and cooked vegetables thus differ essentially. This is the situation, for example, with regard to the onion and its relations, and in plants of the *Cruciferae* family.

Sulphur Compounds from the Onion and Garlic

Allicin and Alliin

At the end of last century, the ill-smelling oils obtained by steam distillation from various *Allium* species were investigated and found to contain alkyl sulfides.

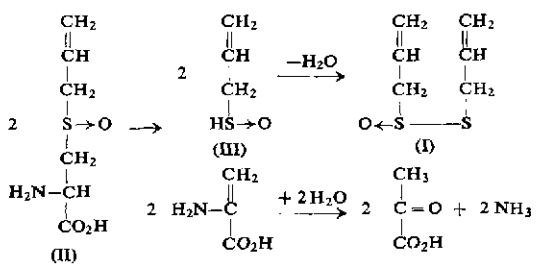
Eighteen years ago, *Cavallito* et al. [2] succeeded in elucidating the chemical nature of an antibiotic factor formed in crushed garlic as a result of enzyme action. They proposed the structure (I) and called the product allicin:



(I)

The substance has only a mild, not too unpleasant garlic odour. It is relatively unstable. The allyl disulfide and trisulfide present in garlic oil, are formed from it by secondary reactions.

Some years later, *Stoll* and *Seebeck* [3] succeeded in isolating the precursor of allicin from garlic. This proved to be (+)-*S*-allylcysteine-*S*-oxide or alliin (II); it is decomposed by the alliinase present in garlic as follows:



Scheme 1. Formation of allicin from alliin by alliinase

We found no peak of mass 90 corresponding to allylsulfenic acid in mass-spectral studies of the degradation products of crushed garlic. It is therefore possible that allylsulfenic acid (III) disproportionates immediately to allylsulfinic acid (IV) and allyl mercaptan (V). Allicin (I) might then be formed from these compounds by elimination of water (Scheme 2). *Challenger* [4] has also considered this kind of reaction possible.

According to *Stoll* and *Seebeck*, prerequisites for the activity of alliinase are that the cysteine derivative

[*] Lecture held on October 12th. 1961 at the Fifth Organic Chemistry Conference on Organic Sulfur Compounds at Natick, Massachusetts. (Sponsored by the National Academy of Sciences – National Research Council).

The investigations reported in the lecture are part of a research project under U. S. Public Law No. 480, 83rd. Congress. The investigations on the composition of onion were first supported by a grant from the Rockefeller Foundation.

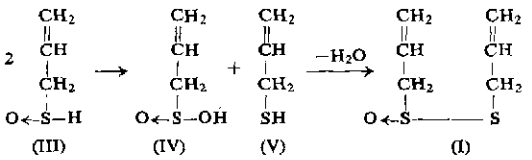
[1] *L. Guignard*, C. R. hebd. Séances Acad. Sci. *111*, 249 (1890).

[2] *C. J. Cavallito, J. S. Buck*, and *C. M. Suter*, J. Amer. chem. Soc. *66*, 1952 (1944).

[3] *A. Stoll* and *E. Seebeck*, Helv. chim. Acta *32*, 197 (1949); Advances in Enzymol. *11*, 377 (1951).

[4] *F. Challenger:* Aspects of the Organic Chemistry of Sulfur. Butterworths, London 1959, p. 56.

should be in the form of the *S*-oxide, and that the group linked to the sulfur atom should be aliphatic. *S*-Benzylcysteine-*S*-oxide is not degraded. In experiments in our laboratory, *S*-benzylcysteine-*S*-oxide has been degraded with a purified enzyme preparation from onion. The



(III) (IV) (V) (I)

Scheme 2. Formation of allicin (I) from allylsulfenic acid (III)

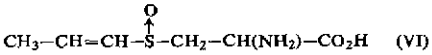
enzymes from garlic and onion differ somewhat with regard to the influence of pH on their activity and stability, but both show the highest degree of reactivity with the allyl derivative as substrate, and both split only *S*-oxides. Pyridoxal phosphate stimulates both enzymes. An enzyme which splits *S*-alkylcysteines as well as *S*-oxides has been isolated by *Gmelin* et. al. [5] from the seeds of *Albizzia lophanta*.

Synthetic *S*-allyl-L-cysteine-*S*-oxide is racemic at the sulfur atom and *Stoll* and *Seebeck* have separated the diastereoisomers by fractional crystallization. The dextrorotatory component proved to be identical with natural alliin and was quantitatively and rapidly degraded by the enzyme, whereas the laevo isomer was decomposed much more slowly. Derivatives of D-cysteine were not attacked.

Matikkala and *Virtanen* [6] found *S*-methyl and *S*-n-propyl-L-cysteine-*S*-oxides to be precursors of alkylthio alkylsulfinates corresponding to (I). These sulfinates also exert an antibiotic effect on many gram-positive and – negative bacteria, yeasts, and fungi [7]. Their effect is, however, not so great as that of allicin. No allylcysteine-*S*-oxide could be found in onion.

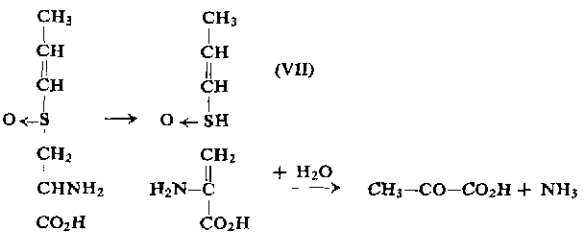
The Lachrymatory Substance of the Onion

Recently, *Spåre* and *Virtanen* [8] found that the crystalline precursor of the lachrymatory factor in the onion is also an *S*-alkenyl-cysteine-*S*-oxide. On paper chromatograms the compound behaved like alliin, and had the same elementary composition, but no lachrymatory factor was formed enzymically from alliin. Present data indicate that the precursor of the lachrymatory factor in the onion is (+)-*S*-(prop-1-enyl)-L-cysteine-*S*-oxide (VI).



(VI)

Pyruvic acid and ammonia were observed in equivalent amounts as end-products of the enzymic cleavage of (VI). In mass-spectral studies of an aqueous solution of (VI) and a dialyzed enzyme preparation from onion, a strong peak of mass 90 was observed, but no peak of higher mass [9]. A weaker peak of mass 73 was also found. This could have arisen through cleavage of a hydroxyl group from the compound of mass 90. In this connection, it ought to be mentioned that a peak of mass 61 is formed from dimethyl sulfoxide (mass 78). The lachrymatory factor may thus be prop-1-enylsulfenic acid (VII) (mass 90), formed from *S*-(prop-1-enyl)-L-cysteine-*S*-oxide (Scheme 3).

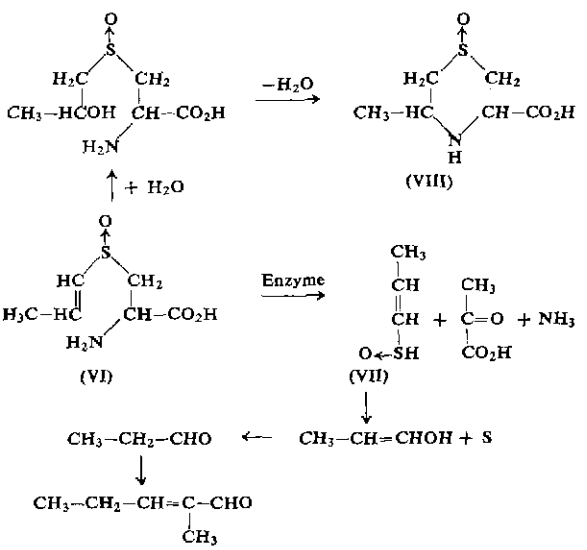


Scheme 3. Formation of *S*-propenylsulfenic acid from *S*-(prop-1-enyl)-L-cysteine-S-oxide

No aliphatic sulfenic acids are known, but the position of the double bond in (VII) is a possible stabilizing factor. The lifetime of the lachrymatory factor is short and hence its chemical investigation is difficult.

In their earlier mass-spectral analysis of flavor compounds in onion *Niegisch* and *Stahl* [10] observed a peak of mass 90 in the −80 °C cold traps and proposed the structure $HO-CH_2-CH_2-CHS$ (β-hydroxypropanthial). The lachrymatory precursor is now characterized chemically as (VI), hence the older structure is untenable.

A large amount of propionaldehyde is formed in the enzymic cleavage of (VI), probably spontaneously from the first decomposition product, prop-1-enylsulfenic acid. 2-Methyl-2-pentenal was also formed in smaller amounts in crushed onion, probably from propionaldehyde [11]. The products of enzymic and chemical cleavage of *S*-(prop-1-enyl)-cysteine-*S*-oxide are presented in Scheme 4.



Scheme 4. Products of enzymatic and chemical cleavage of *S*-propenylcysteine-*S*-oxide (VI)

[5] *R. Gmelin, G. Hasenmaier*, and *G. Strauss*, Z. Naturforsch. *12b* 687 (1957).

[6] *A. I. Virtanen* and *E. J. Matikkala*, Acta chem. scand. *13*, 1898 (1959).

[7] *L. V. Small, J. H. Bailey*, and *C. J. Cavallito*, J. Amer. chem. Soc. *69*, 1710 (1947).

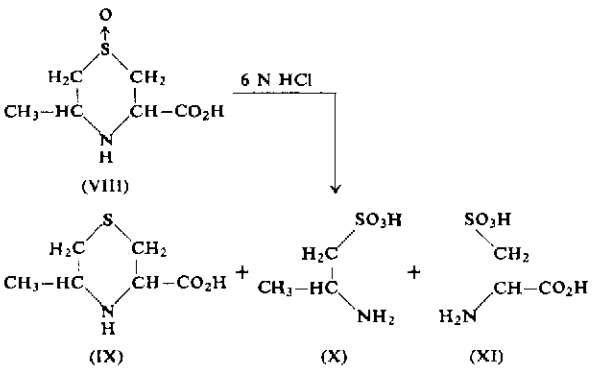
[8] *A. I. Virtanen* and *C.-G. Spåre*, Suomen Kemistilehti B *34*, 72 (1961).

[9] *T. Moisio, C.-G. Spåre*, and *A. I. Virtanen*, Suomen Kemistilehti B *35*, 29 (1962).

[10] *W. D. Niegisch* and *W. H. Stahl*, Food Res. *21*, 657 (1956).

[11] *A. I. Virtanen* and *C.-G. Spåre*, Suomen Kemistilehti B *34*, 18 (1961); *C.-G. Spåre* and *A. I. Virtanen*, Acta chem. scand. *15*, 1280 (1961).

Some years ago a new cyclic sulfoxide, $C_6H_{11}O_3NS$ (VIII), was isolated from onion by *Matikkala* and *Virtanen* [12, 13]. When heated with 6 N HCl, it disproportionates to give 2-methyltaurine (X) and cysteic acid (XI) as oxidation products; as well as the thioether (IX) as reduction product (Scheme 5).

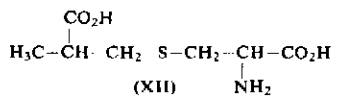


Scheme 5. Disproportionation of cycloalliin (VIII)

On the basis of these and other findings, it was inferred that the compound is 3-methyl-1,4-thiazane-5-carboxylic acid-1-oxide (VIII) [14, 15]. This structure was confirmed by synthesis from *S*-allylcysteine [15]. Because (VIII) has the same elementary composition as alliin, the name cycloalliin was proposed. At that time, the isomer (VI) of alliin – the precursor of the lachrymatory factor – was not yet known, and it was thought that (VIII) might be formed in onion from alliin [15]. Later it was shown that the lachrymatory precursor cyclizes to cycloalliin when the pH of its solution is raised above 7. It is, therefore, probable that the lachrymatory precursor in the onion is the precursor of cycloalliin (see Scheme 4) [8]. Cycloalliin can be formed during the isolation but it is present even in intact onions, as was proved by boiling the vegetable material in 6 N hydrochloric acid whereupon the thioether (IX) is formed [16]. *S*-(Prop-1-enyl)-cysteine-*S*-oxide (VI) decomposes even in 0.5 N hydrochloric acid, and is not cyclized in acid solution.

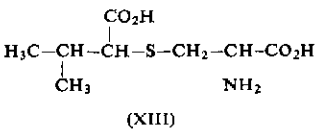
γ-Glutamyl-Peptides

Another type of cysteine derivative was found in the γ-glutamyl peptide isolated from onion by *Matikkala* and *Virtanen* [17]. Its structure was proved to be (−)-*S*-[β-carboxyprop-1-yl]-L-cysteine (XII).



(XII)

This was confirmed by synthesis from L-cysteine and β-bromoisobutyric acid. *Mizuhara* and *Oomori* [18] have since found this compound in human urine in both the free and bound forms. According to their private communication the presence of the amino acid in urine cannot be traced back to the consumption of onions. The same authors [19] have isolated another cysteine derivative, *S*-(1-carboxy-2-methylprop-1-yl)-cysteine (XIII), from the urine of hyper-cholesterolemic patients suffering from arteriosclerosis or myxodema.



(XIII)

Some years ago, our attention was attracted to the presence of numerous peptides in onions. These were hydrolyzed even with dilute hydrochloric acid (0.5–1 N) at 100 °C. All proved to be γ-glutamyl peptides. Ten years ago the only known representative of this group was glutathione. The peptides were fractionated on a Dowex 1 column with 1 N acetic acid followed by 1 N hydrochloric acid. Isolation of individual peptides was accomplished on a cellulose powder column with butanol-acetic acid-water. So far, nine γ-glutamyl peptides have been isolated in crystalline form from onion and their structures have been elucidated [20, 21]. In the order of elution, from Dowex 1, these peptides are:

1. γ-L-Glutamyl-L-valine
2. γ-L-Glutamyl-L-isoleucine
3. γ-L-Glutamyl-leucine
4. γ-L-Glutamyl-*S*-(prop-1-enyl)-cysteine-*S*-oxide
5. Ethyl ester of γ-glutamyl peptide No. 9 (possibly artifact)
6. γ-L-Glutamyl-L-methionine
7. γ-L-Glutamyl-*S*-methylcysteine
8. γ-L-Glutamyl-L-phenylalanine
9. γ-L-Glutamyl-*S*-(2-carboxyprop-1-yl)-cysteinylglycine.

Some difficulty was experienced in determining the structure of peptide No. 4. Its cysteine residue was decomposed by even the mildest acid hydrolysis. However hydrolysis of the peptide was eventually affected with an enzyme preparation from calf kidney and the cysteine derivative isolated in crystalline form identified as *S*-(prop-1-enyl)-cysteine-*S*-oxide (VI) [21]. It had the same dextrorotation as the sulfoxide (VI), which occurs in free form in onions. Hence it was not formed from the thioether by oxidation during isolation.

[12] *A. I. Virtanen* and *E. J. Matikkala*, Suomen Kemistilehti B *29*, 134 (1956).

[13] *E. J. Matikkala* and *A. I. Virtanen*, Suomen Kemistilehti B *30*, 219 (1957).

[14] *A. I. Virtanen* and *E. J. Matikkala*, Suomen Kemistilehti B *31*, 191 (1958).

[15] *A. I. Virtanen* and *E. J. Matikkala*, Acta chem. scand. *13*, 623 (1959).

[16] *A. I. Virtanen* and *E. J. Matikkala*, Suomen Kemistilehti B *34*, 114 (1961).

[17] *A. I. Virtanen* and *E. J. Matikkala*, Hoppe-Seylers Z. physiol. Chem. *322*, 8 (1960).

[18] *S. Mizuhara* and *S. Oomori*, Arch. Biochem. Biophysics *92*, 53 (1961).

[19] *S. Oomori* and *S. Mizuhara*, Biochem. biophysical Res. Commun. *3*, 343 (1960), and personal communication.

[20] *A. I. Virtanen* and *E. J. Matikkala*, Suomen Kemistilehti B *34*, 53 (1961).

[21] *A. I. Virtanen* and *E. J. Matikkala*, Suomen Kemistilehti B *34*, 84 (1961).

Numerous γ-glutamyl peptides are also present in garlic, many being the same as those from onion. However, some other peptides are also present. We have isolated one of these as a crystalline compound and shown it to be γ-glutamyl-*S*-allyl-L-cysteine [22]. It was later isolated independently by *Suzuki* [23].

The function of the γ-glutamyl peptides in onion and garlic is not well understood. Since the peptides are present in both bulbs and seeds, but not, or only scantily, in the green parts of the plants, they are probably reserve substances. When the green leaves push out from the bulbs, the γ-glutamyl peptides disappear rapidly and thus probably take part in nitrogen metabolism. There is, therefore, even a physiological similarity between glutamine and γ-glutamyl peptides. It is peculiar that in onions we have found neither γ-glutamyl transferase nor an enzyme able to hydrolyze the γ-peptide bond. Enzymes of both types are present in kidney and liver [24].

Meister [25] demonstrated the existence of a transaminase specific for glutamine. We obtained small amounts of alannei from pyruvate and γ-glutamyl-*S*-(prop-1-enyl)-cysteine by the action of a dialyzed enzyme preparation from onion leaves at pH 7.4 [26]. An enzyme preparation made from rat liver had a stronger effect than the onion preparation [25]. It is still uncertain, however, whether this is the principal pathway for the metabolism of γ-glutamyl peptides in onions.

Biological Action of Cysteine-S-Oxides

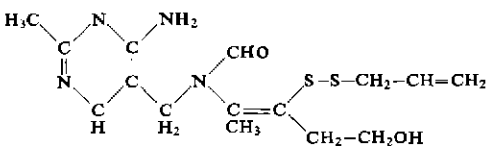
At least three of the cysteine-*S*-oxide derivatives, *S*-methyl-, *S*-propyl-, and *S*-allyl-, may act as antibiotics in animals and humans because of the antimicrobial properties of the alkyl and alkenyl thiosulfinates formed from them. These compounds inhibit the growth of *Staphylococcus* and many other bacteria in dilutions of 1:10000 to 1:100000. The allyl compound has the highest activity.

The antibiotic effects of onions vary greatly depending especially on the variety, but also on climatic conditions. Homogenates of onions grown in Finland can be diluted with 10 to 15 volumes of water and still inhibit the growth of *Staphylococcus* for 24 hours; garlic homogenates have an activity ten to twenty times higher. However, the antibiotic potency of these vegetables in the human organism cannot be calculated solely on the basis of the results of experiments *in vitro* because of the incomplete decomposition of the alkyl sulfoxides by chewing and the ease with which the alkyl thiosulfinates are reduced to disulfides. Although these also have an antibiotic effect against *Staphylococcus*, it is weaker than that of the corresponding thiosulfinates. A large part of the *S*-alkyl sulfoxides probably pass unchanged into the intestinal canal. It is possible that they are decomposed there, forming thiosulfinates and disulfides. In our experiments with *Coli*-type intestinal bacteria, cleavage of *S*-allyl- and *S*-propylcysteine-*S*-oxide was demonstrated [27] by the presence of the corresponding disulfides. It is therefore probable that regular consumption of garlic and onion may have an antibiotic and regulative effect on the bacterial flora of the intestinal canal. This might then account for their curative or preventive effect on intestinal disturbances.

No antibiotic effect is exhibited by aqueous solutions of the lachrymatory factor (VI) from onions. If raw onions are eaten, this factor will also be formed in the mouth and some even in the stomach and intestinal canal. Irritating and stimulating effects on the mucous membrane are then possible.

Nearly thirty years ago, *v. Kokas* and *v. Ludány* [28] found in experiments with dogs and pigeons that the rhythm of the intestinal villi was greatly increased by crushed garlic and onion in concentrations of 1:1000. At the same time glucose resorption was enhanced by 15 to 20 %. Cloves, paprika, and pepper had a similar effect. These unique experiments were performed *in vivo* as well as with pieces of intestine. Unfortunately they have never been repeated. *Von Euler* has reported that an intratumoural injection of allin in Jensen and benzpyrene sarcomas in rats even leads, in some cases, to the disappearance of the tumour [28a].

Fujiwara et al. [29] have reported that allithiamine and its propyl homologue are more active than thiamine when given to rats on a vitamin B_1-free diet and more curative when given to B_1-deficient animals. *Yurugi* [29] has found that allithiamine (XIV) is formed in the reaction between thiamine and allicin. Methyl- and propyl thiosulfinates react similarly with thiamine. Because allithiamine and its homologues are more readily absorbed from the intestine than thiamine, alkyl- and alkenyl thiosulfinates may be of some importance in the "activation" of thiamine in the intestines.



(XIV)

The amounts of sulfur compounds isolated to date in this laboratory from the onion are given in Table 1. Taken together, they amount to some 80–90 % of the soluble sulfur content.

Table 1. Approximate concentrations of the sulfur compounds so far isolated from the onion [mg./kg. fresh-weight]

S-Propylcysteine-*S*-oxide	50
S-Methylcysteine-*S*-oxide	200
S-Propenylcysteine-S-oxide	40
Cycloallin [a]	2500
γ-L-Glutamyl-(+)-*S*-propenyl-cysteine-*S*-oxide	1300
γ-L-Glutamyl-*S*-methylcysteine	50
γ-L-Glutamylmethionine	50
S-(2-Carboxyprop-1-yl)glutathione	330

[a] A part of the cycloallin may be formed from *S*-propenylcysteine-*S*-oxide during elution of amino acids with ammonia from the Amberlite column.

[22] *A. I. Virtanen* and *I. Mattila*, Suomen Kemistilehti B *34*, 44 (1961).

[23] *T. Suzuki, M. Sugii*, and *T. Kakimoto*, unpublished.

[24] *C. S. Hanes, F. J. Hird*, and *F. A. Isherwood*, Biochem. J. *51*, 25 (1952); *F. J. Hird* and *P. H. Springell*, ibid. *56*, 417 (1954).

[25] *A. Meister* and *S. V. Tice*, J. biol. Chemistry *187*, 173 (1950).

[26] *A. I. Virtanen* and *E. J. Matikkala*, unpublished.

[27] *M. Saarivirta* and *A. I. Virtanen*, unpublished.

[28] *E. v. Kokas* and *G. v. Ludány*, Arch. exp. Pathol. Pharmakol. *169*, 140 (1933).

[28a] Cf. *A. Stoll* and *E. Seebeck*, Advances in Enzymol. *2*, 377 (1951).

[29] Cf. *B. C. Johnson*, Ann. Rev. Biochem. *24*, 419 (1955).

Sulfur Compounds from Cruciferae

Mustard Oil Glucosides

Mustard oil glucosides are characteristic of many plants, especially the *Cruciferae*, but also *Tropaeolaceae*, *Resedaceae*, and certain other families. Many of the mustard oils (isothiocyanates) formed enzymically from these glucosides when the plants are crushed have a characteristic, pungent, but not unpleasant, flavor. The antimicrobial activity of some mustard oils is high with respect to molds and fungi and fairly high against many bacteria (see Figure 1) [30].

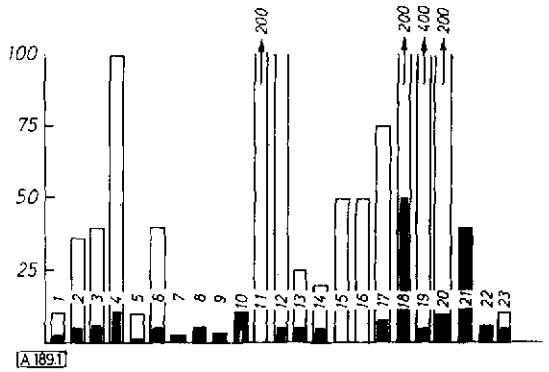


Fig. 1. Lowest inhibition-concentrations (μg./ml.) of different mustard oils, some of their precursors, and other compounds.
White area: Activity against *Staphylococcus aureus* 209 Innsbruck
Black area: Activity against *Penicillium glaucum*.
Ordinate: Minimum concentration required for inhibition [μg/ml].

Isothiocyanates:

1. Methyl-
2. Ethyl-
3. Propyl-
4. Isopropyl-
5. Allyl-
6. Phenyl-
7. Benzyl-
8. Ethylphenyl-
9. *m*-Methoxybenzyl-
10. *p*-Methoxybenzyl-
11. *p*-Hydroxybenzyl- (Sinalbin)
12. Methylthiopropyl-
13. Methylthiobutyl-
14. Methylthiopentyl-
15. Methylsulfinylpropyl- (Glucoiberin)
16. Methylsulfonyl
17. Methylsulfonylbutyl-

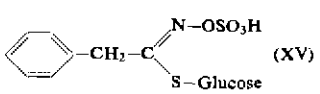
Thiocyanates:

18. Isopropyl-
19. Benzyl-
20. Ethylphenyl-

Other sulfur compounds:

21. Dibenzylcarbothialdin
22. Na-Benzyldithiocarbamate
23. Benzylammonium-benzyldithiocarbamate

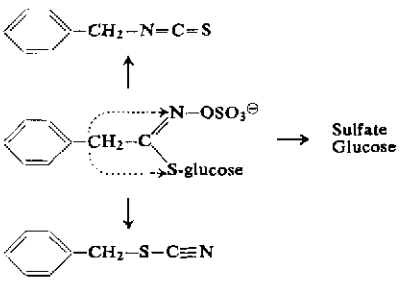
Benzyl isothiocyanate has the highest antibiotic effect of all the known mustard oils when the activity against both fungi and bacteria is considered. Its precursor, glucotropaeolin (XV), occursin *Lepidium sativum* and *Tropaeolum majus*, both used as vegetables in Western Europe.



(XV)

Winter [31] studied their antibiotic effect in the human organism and found that even 20 to 30 g causes a high antibiotic activity in the urine for many hours against *Staphylococcus* and *E. coli*. An extract of *Tropaeolum* is used as a remedy against infections.

In the course of further investigations on an isothiocyanate fraction from crushed moist *Lepidium sativum* seeds, *Gmelin* and *Virtanen* [32] separated the fraction into benzyl isothiocyanate and benzyl thiocyanate. Mainly benzyl thiocyanate is found in crushed seeds of *Lepidium ruderale* but only benzyl isothiocyanate in those of *Tropaeolum majus*. In all cases glucotropaeolin (XV) was decomposed during the enzymic cleavage. In the green parts of *Lepidium* species benzyl isothiocyanate and thiocyanate are also formed enzymically. The formation of benzyl thiocyanate suggests that after enzymic liberation of glucose and sulfate, rearrangement of the remainder of the molecule can take place in two ways, *i.e.* the benzyl group can migrate to either the nitrogen or the sulfur atom (Scheme 6).



Scheme 6. Enzymatic degradation of glucotropaeolin (XV)

Benzyl isothiocyanate and benzyl thiocyanate differ greatly in their properties. The latter has a very slight antibiotic effect upon bacteria, but affects the iodide uptake of the thyroid gland, whereas benzyl isothiocyanate has no such effect.

The seeds of *Thlaspi arvense*, *Peltaria* species, and *Brassica nigra*, which contain the allyl thioglucoside sinigrin form only allyl thiocyanate after crushing [32].

It is not yet clear why the enzymic cleavage of the mustard oil glucosides by myrosinase leads to the formation of isothiocyanates in most plants and thiocyanates, or both, in others. *Gaines* and *Goehring* [33] have shown that myrosinase is a mixture of two enzymes, one of which splits off glucose and the other sulfate. The possibility that the relative activities of these enzymes in different plants might not be the same seems to offer, at first sight, a plausible explanation to our findings. However, a preparation of myrosinase (purified only by dialysis) formed benzyl isothiocyanate alone from crystalline glucotropaeolin, whereas the crushed and moistened seeds of *Lepidium ruderale* gave mainly benzyl thiocyanate.

Cabbage plants, and many other *Cruciferae*, contain *S*-methylcysteine-*S*-oxide [34, 35] but lack an enzyme like alliinase. Hence, no thiosulfinate is formed in these plants after crushing. Degradation of methylcysteine-*S*-oxide is, however, possible in the intestinal canal.

Glucobrassicin

Over thirty years ago, *Chesney* et al. [36] observed that rabbits fed on a diet of cabbage developed enormous goiters which were largely reversible with iodide. In some

[30] *M. Saarivirta*, unpublished.

[31] *A. G. Winter*, Hippokrates *28*, 695 (1957).

[32] *R. Gmelin* and *A. I. Virtanen*, Acta chem. scand. *13*, 1474 (1959).

[33] *R. D. Gaines* and *K. J. Goehring*, Biochem. biophysical Res. Commun. *2*, 207 (1960).

[34] *C. J. Morris* and *J. F. Thompson*, Chem. and Ind. (London) 951 (1955).

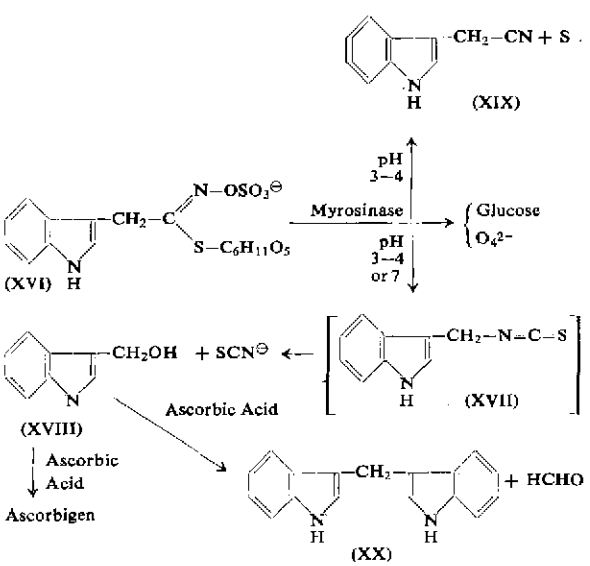
[35] *R. L. M. Synge* and *J. C. Wood*, Biochem. J. *60*, 15 (1955).

[36] *A. M. Chesney*, *T. A. Clawson*, and *B. Webster*, John Hopkins Hosp. Bull. *43*, 261 (1928).

regions, where sections of the community regularly consume large amounts of cabbage, this type of goiter is not uncommon. The goitrogenic factor was unknown for many years.

Barker's [37] discovery that goiters developed in two patients who had undergone prolonged treatment with potassium thiocyanate for hypertension drew the attention of investigators to the thiocyanate ion (SCN^-) as a goitrogenic factor. Until recently it was thought that this ion must be formed endogenously in the human organism, *i.e.* from organic cyanides, nitriles, and cyanogenic glucosides in food. In 1958, *Michajlovskij* and *Langer* [38] found considerable amounts of thiocyanate in cabbage and the authors regarded this anion in food as the cause of the goitrogenic effect. Somewhat later, *Gmelin* and *Virtanen* [39] showed that intact cabbage contains no thiocyanate but a precursor which liberates SCN^- when cabbage is crushed. The precursor was isolated in crystalline form from *Brassica oleracea sabauda* and *gongyloides* as the tetramethylammonium salt [40,41]. The chemical composition as well as the nature of enzymic and chemical decomposition products demonstrate the presence of a thioglucoside which we call glucobrassicin; this proved to be an indole derivative (XVI) [41,42].

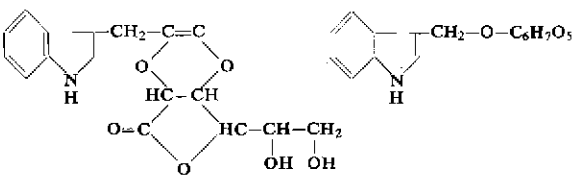
Glucobrassicin is the first mustard oil glucoside with an indole group in the molecule and is the precursor of many biologically interesting compounds (Scheme 7). 3-Indolylmethyl isothiocyanate (XVII), which should be formed from glucobrassicin by the action of myrosinase at a neutral pH, is immediately split into two fragments, SCN^- and 3-hydroxymethylindole (XVII). The formation of indolylacetonitrile (XIX) and sulfur at pH 3.5 is probably due to the occurrence of a chemical reaction after the enzymic liberation of glucose and sulfate. This reaction explains the chemical nature of the



Scheme 7. Products formed by the enzymatic degradation of glucobrassicin (XVI)

"bound growth-hormones" in *Brassica* plants studied by many earlier investigators [43]. 3-Indolylacetic acid is formed in the acid and alkaline hydrolysis of glucobrassicin.

3,3'-Diindolylmethane (XX) is formed from two molecules of 3-hydroxymethylindole by splitting off one molecule of formaldehyde. The 3-hydroxymethylindole can also react with ascorbic acid present in cabbage to form ascorbigen. This compound has been isolated by *Procházka* et al. [44] from cabbage and is believed to be an original substance in this plant. The formula (XXI) previously proposed for ascorbigen has to be corrected. The synthesis of ascorbigen [42] from 3-hydroxymethylindole and ascorbic acid shows that the ascorbic acid in ascorbigen is linked with the hydroxymethyl group of the indole compound, probably by an ether bridge (XXIa). Ascorbic acid is split off during hydrolysis with dilute hydrochloric acid. Ascorbigen administered orally to guinea pigs, or man, has an antiscorbutic effect [45].



Nagashima et al. [46] have reported that ascorbic acid strongly stimulates the activity of myrosinase.

In addition to glucobrassicin, we [42] recently isolated *N*(1)-methoxy-glucobrassicin (neoglucobrassicin) from rutabaga. It is also present in small amounts in some cabbage species. Thiocyanate ion is split off quantitatively from this compound by the action of myrosinase at pH 7. Table 2 illustrates the amounts of thiocyanate formed by myrosinase in some *Brassica* species [39].

Table 2. SCN^- content in cabbage species after myrosinase treatment

Brassica species	SCN^- formation per 100 g. fresh plants
Brassica oleracea [*] var. *sabauda* ssp. *Ulmer*	27–31 mg.
Brassica oleracea [*] var. *gemmifera*	10 mg.
Brassica oleracea [*] var. *capitata*	4 mg.
Brassica oleracea [*] var. *cretica*	4 mg.
Brassica napus [+] var. *rapifera* [+]	8.8 mg.
Brassica napus [*] var. spring rape	2.5 mg.
Brassica rapa [*] var. winter turnip rape	1.7 mg.

[*] leaves [+] root.

[37] *M. H. Barker*, J. Amer. med. Assoc. *106*, 762 (1936).

[38] *N. Michajlovskij* and *P. Langer*, Hoppe-Seylers Z. physiol. Chem. *312*, 26 (1958); *P. Langer* and *N. Michajlovskij*, ibid. *312*, 31 (1958).

[39] *R. Gmelin* and *A. I. Virtanen*, Acta chem. scand. *14*, 507 (1960).

[40] *R. Gmelin*, *M. Saarivirta*, and *A. I. Virtanen*, Suomen Kemistilehti B *33*, 172 (1960).

[41] *R. Gmelin* and *A. I. Virtanen*, Suomen Kemistilehti B *34*, 15 (1961).

[42] *R. Gmelin* and *A. I. Virtanen*, Ann. Acad. Sci. fennicae Ser. A. II., No. 107 (1961).

[43] *H. Linser*, Planta *29*, 392 (1939); *J. A. Bentley*, Ann. Rev. Plant Physiol. *9*, 47 (1958).

[44] *Ž. Procházka*, *V. Šanda*, and *F. Šorm*, F. Coll. czech. chem. Commun. *22*, 654 (1957).

[45] *M. Kiesvaara* and *A. I. Virtanen*, Acta chem. scand. *16*, 510 (1962).

[46] *Z. Nagashima* and *M. Uchiyama*, Bull. agric. Soc. Japan *23*, 555 (1959).

When large amounts of cabbage are regularly consumed, the iodine content of the diet should be higher. Some SCN^- is split off from glucobrassicin even on boiling in water (Fig. 2) [42].

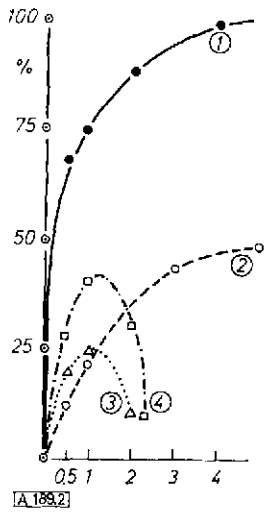
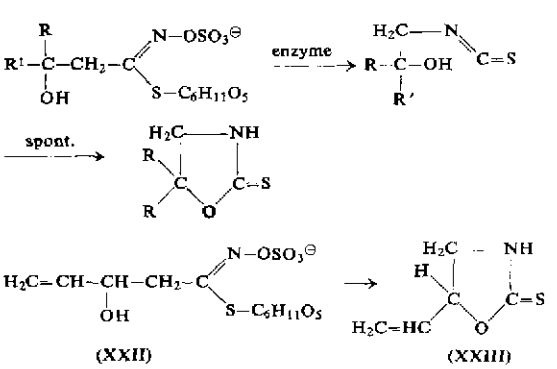


Fig. 2. Formation of thiocyanate from glucobrassicin (1) through enzymatic splitting, (2) through the action of boiling water, (3) by boiling in 0.1 N HCl and (4) by boiling in 0.1 N NaOH. Ordinate: liberated SCN^- [% of theoretically possible amount] Abscissa: Time [hours]

Goitrin and Progoitrin

The thiooxazolidones represent another type of antithyroid substances formed enzymically from precursors in cruciferous plants. They inhibit the synthesis of thyroid hormones and this inhibition is not reversed by iodine. More than ten years ago, *Astwood, Greer* and *Ettlinger* [48] isolated goitrin, L-5-vinyl-2-thiooxazolidone, from moistened, crushed *Brassica* seeds as well as from crushed rutabaga. This compound had about the same antithyroid acitivity as the drug propylthiouracil, used therapeutically against hyperthyroidism.

Thiooxazolidones are cyclic derivatives of isothiocyanates containing a hydroxyl group at the C-2 position. After *Ettlinger* and *Lundeen* [49] had shown the correct structure of the mustard oil glucosides it was at once possible to see that goitrin is formed from its precursor, progoitrin (isolated by *Greer* [50]), as shown in Scheme 8.



Scheme 8. Formation of thiooxazolidone from mustard oil glucosid and of goitrin (XXIII) from progoitrin (XXII)

The relatively abundant occurrence of progoitrin in many *Brassica* seeds is the explanation of the finding[51] that seeds of cabbage and rape are goitrogenic to rats. Progoitrin could, at first, not be found in the green parts of *Brassica* plants, *e.g.* cabbage or kale. Some years ago, however, the formation of goitrin in crushed cabbage, kale, green rape, *etc.* [52–54] was demonstrated.

The amount of progoitrin in cabbage is so low – the highest value found in our laboratory was about 20 μg./g. of fresh plants – that goitrin cannot influence the function of the thyroid gland if cabbage is used as a vegetable in reasonable quantities. Higher values have, however, been found [53] in various fodder plants belonging to the genus *Brassica*.

Because of the large amounts of fodder which cows eat daily, cruciferous plants in feedstuffs could conceivably make milk goitrogenic. *Clements* and *Wishart* [55] alleged that in Tasmania, and some other parts of Australia, milk produced on a feed composed largely of marrow kale actually has goitrogenic properties which cannot be prevented by iodine. Because of the far-reaching implications of this statement, we have studied the problem more thoroughly. The transfer of goitrin from fodder to milk was found to be very low. Feeding experiments were carried out using crystalline goitrin, crushed and moistened rape seed, green rape, and marrow kale [47,56] and, at the most, only 0.05 % of the goitrin fed was to be found in the milk. When crystalline progoitrin was administered without *Brassica* plants, only traces of goitrin were to be found in the milk. The goitrin content of the milk could not be raised to a level anywhere near that needed to make milk goitrogenic.

The transfer of thiocyanate to milk was also studied [57]. It seems impossible to raise the SCN^- content of cow's milk over approximately 10 mg. per liter even with large amounts of *Brassica* plants in the feed. With cows fed on grass, hay, and cereals, the SCN^- content of the milk varies between 2 and 5 mg./liter.

Our experiments with both volunteers and rats [47] led us to the conclusion that milk has no goitrogenic properties even when cows are on widely different diets, including mainly various *Brassica* plants.

Benzoxazinone Glucosides from Grain Seedlings

Brief reference should be made to a new group of substances found in young rye, wheat and maize plants. These compounds do not contain sulfur, but they are

[47] Cf. *A. I. Virtanen*, Experientia *17*, 241 (1961).

[48] *E. B. Astwood, M. A. Greer*, and *M. G. Ettlinger*, J. biol. Chemistry *181*, 121 (1949).

[49] *M. G. Ettlinger* and *A. J. Lundeen*, J. Amer. chem. Soc. *78*, 4172 (1956).

[50] *M. A. Greer*, J. Amer. chem. Soc. *78*, 1260 (1956).

[51] *C. E. Hercus* and *H. D. Purves*, J. of Hyg. *36*, 182 (1936).

[52] *A. I. Virtanen, M. Kreula*, and *M. Kiesvaara*, Acta chem. scand. *12*, 580 (1959).

[53] *M. Kreula* and *M. Kiesvaara*, Actachem. scand. *13*, 1375 (1959).

[54] *M. R. Altamura, L. Long*, and *T. Hasselstrom*, J. biol. Chemistry *234*, 1847 (1959).

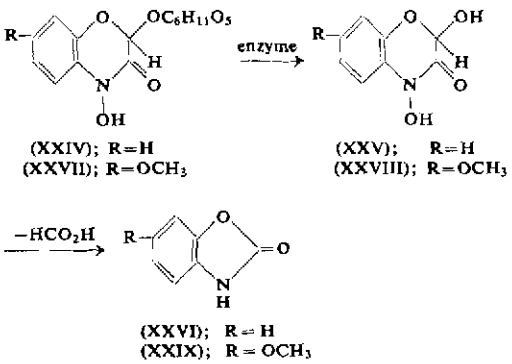
[55] *F. W. Clements* and *J. W. Wishart*, Metabolism *5*, 623 (1956).

[56] *A. I. Virtanen, M. Kreula*, and *M. Kiesvaara*, Acta chem. scand. *13*, 1043 (1959).

[57] *A. I. Virtanen* and *R. Gmelin*, Acta chem. scand. *14*, 941 (1960).

hydroxylamine derivatives (like the mustard oil glucosides). Because they are not present in seeds they do not occur in human, but only in animal nutrition.

Relatively large amounts of glucoside (XXIV) [58–61] are present in young rye plants, and of glucoside (XXVII [62] in wheat and maize plants. The glucosides are rapidly hydrolyzed when the plants are crushed, and the aglucones (XXV) and (XXVIII) are formed. Both have an antifungal and antibacterial effect. Experiments with ^{14}C-labelled compounds have shown that an intramolecular redox reaction occurs, in which formic acid is split off and the six-membered heterocycle is converted into a five-membered ring with a reduced nitrogen atom [63]. This reaction only takes place if the hydroxyl group is linked to the nitrogen atom, and if the bond between the carbon and oxygen atoms in the heterocyclic ring is weak (see Scheme 9).



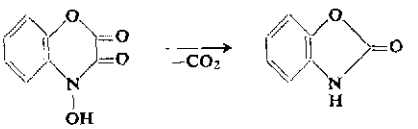
(XXIV); R=H
(XXVII); R=OCH_3

(XXV); R=H
(XXVIII); R=OCH_3

(XXVI); R=H
(XXIX); R=OCH_3

Scheme 9. Benzoxazinone glucosides from rye (XXIV) and wheat or maize plants (XXVII)

Accordingly, benzoxazolinone (XXVI) is formed from 2,4-dihydroxy-1,4-benzoxazin-3-one (XXV) and, with liberation of CO_2, from 4-hydroxy-1,4-benzoxazine-2,3-dione (XXX).



(XXX) (XXVI)

The isolation of this new group of compounds shows how easily mistakes may arise in work of this nature. While investigating the rye plant for substances which might explain the different resistance of several rye varieties to *Fusarium nivale*, benzoxazolinone (XXVI) was isolated by *Hietala* and *Virtanen* [64]. The corresponding 6-methoxy derivative (XXIX) was isolated [65] from maize and wheat plants. At first we believed, erroneously, that these compounds existed as such in the plants, since they cannot form *O*-glucosides. This error was later corrected and the precursors were isolated. Many compounds in the literature believed to be present in the intact plants, may in reality be artifacts formed during the crushing of the plants or, in some cases, at a later stage of the isolation process.

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[58] *A. I. Virtanen* and *P. K. Hietala*, Suomen Kemistilehti B *32*, 38, 138, 252 (1959).

[59] *A. I. Virtanen* and *P. K. Hietala*, Acta chem. scand. *14*, 499 (1960).

[60] *P. K. Hietala* and *A. I. Virtanen*, Acta chem. scand. *14*, 502 (1960).

[61] *E. Honkanen* and *A. I. Virtanen*, Acta chem. scand. *14*, 504 1214 (1960).

[62] *Ö. Wahlroos* and *A. I. Virtanen*, Acta chem. scand. *13*, 1906 (1959).

[63] *E. Honkanen* and *A. I. Virtanen*, Acta chem. scand. *15*, 221 (1961).

[64] *A. I. Virtanen* and *P. K. Hietala*, Acta chem. scand. *9*, 1543 (1955).

[65] *A. I. Virtanen*, *P. K. Hietala*, and *Ö. Wahlroos*, Suomen Kemistilehti B *29*, 143, 171 (1956).

Chemical Reactions and Microtacticity of High Polymers[*]

BY PROF. DR. G. SMETS

UNIVERSITY OF LOUVAIN, BELGIUM

The reaction course and kinetics of interfunctional reactions with polymers are determined by the microtacticity of the polymer chain. Among other things, this is shown by the hydrolysis of ester and amide polymers of different tacticities, and by ring-closure reactions (anhydride formation). The physical and physico-chemical properties are also governed by the tacticity.

Introduction

When reactions are carried out with *poly*(vinyl)-derivatives, it is often found that the yields are much lower than those obtained with lower molecular weight homologues; sometimes the course of reaction may be completely modified by neighbouring group interactions. The question therefore arises as to the origin of these differences, and conversely, in what manner the limitations of these reactions can be avoided. In this paper, possible effects due to heterogeneous reaction conditions are neglected; indeed under these conditions swelling of the polymer and the degree of accessibility to the reactive sites become rate determining factors.

[*] Presented at the GDCh-Hauptversammlung Aachen, Sept. 21st. 1961.

The characteristics of polymer reactions are best observed by correlating the internal structure of the polymer either with the course of the reactions themselves, *i.e.* by kinetic studies, or with some fundamental physical properties.

Monofunctional Reactions

When reactions on high polymers take place at monofunctional sites, the activation energies are usually identical with those of low molecular weight compounds; small differences in rates may be due to steric effects. The latter are more pronounced with high polymers (Tables 1 (a), (b), and 2) and may become predominant.

Table 1. Comparative data from the hydrolysis of high polymers and related low molecular weight compounds [1]

(a) Polymer	Activation Energy E_a (kcal/mole)	log PZ
poly(*N*-vinylpyrrolidone)	25 ± 1	11.7
68-vinylpyrrolidone/ 32 maleic acid copolymer [*]	16 ± 1	6.3
(b) Unpolymerized Lactams		
N-Isopropyl-2-methylpyrrolidone	27 ± 0.5	12.3
N-methoxycarbonylpyrrolidone	17 ± 0.5	7.3

[*] 68 : 32 mole per cent composition.

Table 2. Comparative data from the alkaline hydrolysis of *poly*(acrylamide) and acrylamide copolymers [2]

Polymer	$K_1 \times 10^5$				E_a kcal/mole	log PZ
	35 °C	50 °C	65 °C	80 °C		
poly(Acrylamide) 1 st.	44	1.2	2.5	—	14.16	5.63
58-Vinylpyrrolidone/ 42-acrylamide copolymer	61	2.02	4.94	—	14.5	5.55
Isobutyramide					14.2	5.56
poly(Acrylamide) 2nd.		13	32	77	13.71	4.4
36-Acrylic acid/64-acrylamide copolymer		14	27	89	13.75	4.1

These effects are responsible for a strong limitation of the final degree of conversion; in exceptional cases, reactions may be almost completely hindered. A typical example is the alkaline hydrolysis of *poly*(methyl methacrylate), which should take place by means of an S_N2 mechanism. Nevertheless, a rearward attack by OH-ions is hindered by the substituents. However, when acidic functions are present in the polymer chain, as in the case of copolymers of methyl methacrylate with differing amounts of methacrylic acid (28.9, 49.5, 58.5 and 72 mole-%) hydrolysis in 1 N NaOH proceeds slowly and all the copolymers approach the same final percentage conversion (about 83–85 %) asymptotically. It can be seen that the various conversion curves can be made to overlap by a suitable horizontal shift (Fig. 1). This means that with respect to hydroxyl ion concentration there is no difference between these copolymers.

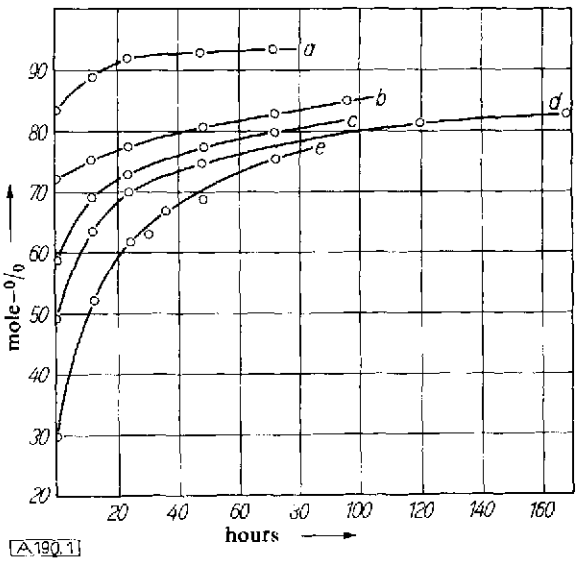


Fig. 1. Hydrolysis of methacrylic acid/methyl methacrylate copolymers in 1 N NaOH. Acid content (a) 83 %, (b) 72 %, (c) 58.5 %, (d) 49.5 %, (e) 28.9 % [3]

The limited extent of the hydrolysis is due to electrostatic repulsion, which prevents further attack by hydroxyl-ions when the number of charges attains a given value.

Interfunctional Reactions

Under milder reaction conditions, *e.g.* in a buffered acid media or at a pH between 10 and 12.5, the monofunctional character of the reaction disappears; all the reactions become interfunctional. In this case, the tacticity of the systems is very important and becomes a rate-determining factor.

Hydrolysis takes place mainly because of the interaction of neighbouring groups, either carboxylic or carboxylate, with the ester group [4]. The intramolecular nature of the reaction mechanism has been demonstrated by reference to the hydrolysis of a water-soluble methyl methacrylate/vinylpyrrolidone copolymer. Owing to its relatively low methacrylate content (13,5 %), each ester group in this copolymer is surrounded by a number of vinylpyrrolidone units.

Experiments were carried out with methyl methacrylate/methacrylic acid copolymers containing 50 and 28 mole per cent of the ester. Acetic (or polymethacrylic) acid was added and the ratio of free acid: carboxylate groups was adjusted to a pre-determined value, for example 1:1, by neutralisation. The experimental rate constants for the hydrolysis of the acid-ester copolymers were of the order 10^{-6} sec.$^{-1}$ while those for methyl methacrylate/vinyl pyrrolidone copolymer are only about 10^{-8} sec.$^{-1}$ *i.e.* approximately one hundred times lower.

[1] *A. Conix, G. Smets,* and *J. Moens,* Ricerea Scientifica *25,* 1 (1955).

[2] *J. Moens* and *G. Smets,* J. Polymer Sci. *23,* 931 (1957).

[3] *G. Smets* and *W. De Loecker,* J. Polymer Sci. *41,* 375 (1959).

[4] *W. De Loecker* and *G. Smets,* J. Polymer Sci. *40,* 203 (1959).

When due allowance is made for the fact that acetic acid is much stronger than either polymethacrylic acid or the copolymer, these differences are even more pronounced. The experiments show unambiguously that the intermolecular functional reactions are practically negligible in comparison to intramolecular functional interactions in which the ester groups react with a vicinal acid or carboxylate groups.

A second argument favoring an intramolecular reaction mechanism follows from experiments carried out at twice the above concentrations (see Table 3). With doubled amounts of copolymer, and employing concentrations of acid and ester that are twice as high as

Table 3. Influence of copolymer concentration on the rate of hydrolysis of methacrylic acid-methyl methacrylate copoymer at 110 °C

Ratio acid groups: alkoxycarbonyl groups	Acid content (mole-%)	Rate (mole/l.) sec. $^{-1} \times 10^8$	
		ester concn. 0.0312 mole/l.	ester concn. 0.0624 mole/l.
1	72	3.0	
	83	5.8	
2	72	3.5	
	83	6.3	
3	72	7.6	15.5
	83	13.6	26.5
7	72	3.5	7.4
	83	6.9	13.0

previously, the rate of hydrolysis is only doubled. This fact demonstrates that an acid-ester pair functions as a kinetic entity and that the reaction occurs between neighbouring groups. From Table 3 it can be seen that the rate of hydrolysis is twice as high when the ratio of neutralization (r) is equal to 3, than at any other ratio. Moreover, on the basis of structural probability calculations, it can be shown that vicinal location is an insufficient explanation for the limited percentage of hydrolyzable ester groups; the percentage is always appreciably lower than the total amount of 1,2-configurations. For example, in a copolymer with 86.5 mole per cent of the acid component theoretically 75 % of the reactive groups are present as 1,2-pairs and should therefore be hydrolyzable. However, it was found by experiment that only 45 % hydrolyze.

Stereospecificity

Direct evidence for the stereospecificity of this functional interaction can be given as follows:

If a copolymer consisting of methyl methacrylate and 60 mole per cent of methacrylic acid is hydrolysed until the ratio of acid groups to alkoxycarbonyl groups is 1:1, hydrolysis is at first rapid but then slows down before attaining a final value of 72 mole per cent acid groups.

If a copolymer containing 72 mole per cent of methacrylic acid is hydrolysed a rapid stage is observed in which the rate is higher than that found for the copolymer containing only 60 mole per cent of the acid. The actual

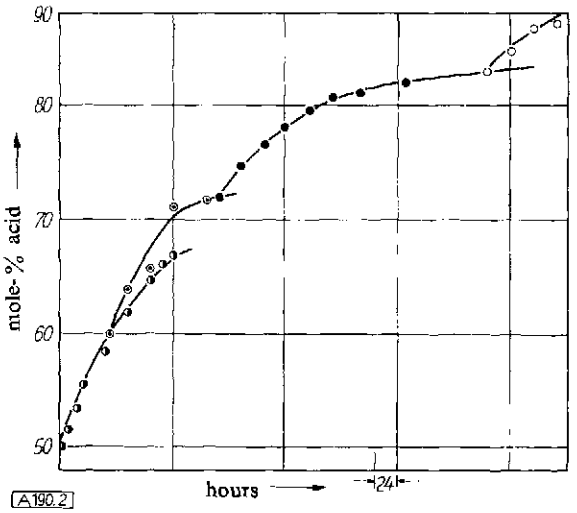


Fig. 2. Successive hydrolysis of different methacrylic acid-ester copolymers. Influence of the stereochemical composition. (◑) 50 mole-% acid, (○) 60 mole-% acid, (●) 72 mole-% acid, (○) 80 mole-% acid.

rate of hydrolysis of the former also drops progressively; when 83 mole per cent of the acid is present the rate is again comparable to that found for the hydrolysis of the corresponding 83-copolymer which is again higher than that of the preceding copolymer with 72 mole per cent acid.

This type of behavior is illustrated in Fig. 2, which shows that even when the chemical compositions of any two copolymers are identical, their kinetic behavior may differ largely. Similar relationships were obtained for acrylic acid/methyl acrylate copolymers and confirm the broad validity of this statement.

From these experiments it must be concluded that the stereochemical structure of such copolymers plays a fundamental role in the hydrolysis reaction. These assumptions were supported by results obtained by the alkaline hydrolysis of *poly*(methyl methacrylate) i.e. samples of various tacticities as well as those obtained from methyl methacrylate/methacrylic acid copolymers of differing tacticities. On the basis of conversion *versus* time data, *Glavis* [5] has shown that conventional atactic *poly*(methyl methacrylate) and syndiotactic polymers are hydrolyzed relatively slowly, while the hydrolysis of isotactic polymer proceeds very rapidly and to higher final conversion. This difference in behavior has been used for the separation of mixtures of polymers of different types. Although these experiments were carried out in heterogeneous media, acid-catalyzed reactions in homogeneous solutions showed similar differences. It is therefore very likely that these differences in chemical reactivity are attributable to differences in the internal structure of the copolymers. We have measured the rate of hydrolysis of methacrylic acid/methyl methacrylate copolymers of the same chemical composition but different tacticity in order to obtain a direct verification of the previous assumptions. The experiments were carried out in an aqueous medium. The direct synthesis of such copolymers of different tacticity has not yet been reported, and consequently they were prepared by partial hydrolysis

[5] *F. J. Glavis*, J. Polymer Sci. *36*, 547 (1959).

of the parent *poly*(methyl methacrylates). The structure of the polymers had been investigated by *Fox et al.* [6–10]. It is assumed that the tacticity of the polymeric chain remains unchanged during the course of hydrolysis [11].

The syndiotactic copolymer, prepared by sulfuric acid hydrolysis of *poly*(methyl methacrylate) and initiated by phenylmagnesiumbromide, hydrolyzes 4 to 5 times as fast as the conventional copolymers; on the other hand, copolymers from *poly*(methyl methacrylate) prepared at −20 °C by photoinitiation in the presence of benzoin exhibit very slow rates of hydrolysis, and at high acid content they cannot be hydrolyzed further. The data are given in Table 4.

Table 4. Hydrolytic rate constants at 110 °C for methacrylic acid/methacrylate ester copolymers of different tacticities

PMMe-OM = prepared from *poly*(methyl methacrylate) initiated with organomagnesium compd.

PMMe-B = prepared from *poly*(methyl methacrylate) photoinitiated with benzoin at −20 °C

Moles per cent methacrylic acid	ratio $\frac{(COOH)}{(COO)}$	$K_1 \times 10^6$		
		Conventional	PMMe-OM	PMMe-B
40.6	1			0.8
	3			0.8
50	1	1.3		
	3	1.0		
60	1	1.3		0.3
	3			0.3
72	1	0.9	4.2	
	3	2.6		
78.3	1		5.3	
83	1	1.1	5.6	0
	3	3.0	16.8	0

Similar results were obtained for conventional and isotactic acrylic acid/methyl acrylate copolymers [12]. The conventional polymer was prepared in the presence of azobis(isobutyronitrile) by direct copolymerization of acrylic acid and methyl acrylate in benzene. The isotactic copolymer was obtained by hydrolysis of isotactic *poly*(t-butyl acrylate); the isotactic polyacrylic acid was partially methylated by treatment with diazomethane. In this series, the rates are 3 to 5 times higher for the isotactic copolymers than for the conventional ones (Table 5).

The same interpretation is valid for the hydrolysis of *poly*(acrylamide) [13]; indeed it can be shown that *poly*-

Table 5. Hydrolysis rate constants for isotactic and conventional acrylic acid/methyl acrylate) copolymers at 103 °C

Isotactic			Conventional		
Acrylic acid (mole per cent)	ratio $\frac{(COOH)}{(COO^-)}$	$k \times 10^6$ sec.$^{-1}$	Acrylic acid (mole per cent)	ratio $\frac{(COOH)}{(COO^-)}$	$k \times 10^6$ sec.$^{-1}$
80	0	14	80.5	0	3.1
	1	16.5		1	5.8
	2	19		2	7.9
				3	9.2
67	0	14	64.5	0	5.1
	1	15		1	5.4
	2	17		2	6.7

(acrylamide) can be easily hydrolyzed, and in acid medium behaves just like its homologue, isobutyramide. However in buffered acid solution, autocatalytic acceleration of the reaction was observed, as soon as about 3 per cent of the amide groups had been hydrolyzed. This behaviour is again explained by intramolecular interactions between carboxylic acid and neighbouring amide groups (Fig. 3).

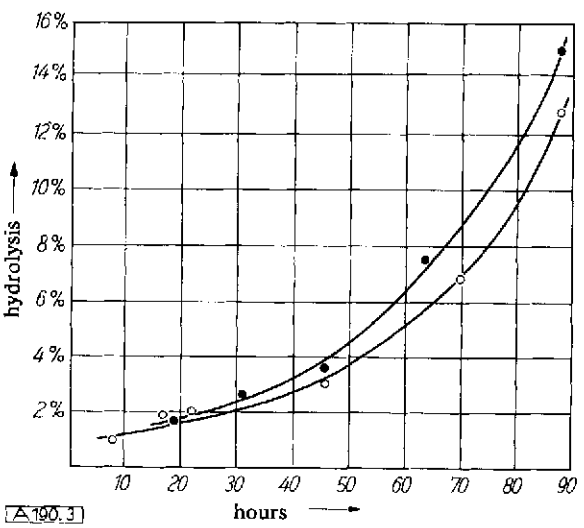


Fig. 3. Autoacceleration in the hydrolysis of *poly*(acrylamide) in the presence of maleic acid (○) or acetic acid (●)

Copolymers of acrylamide and acrylic acid hydrolyze in two successive steps; a rapid hydrolysis occurs during the first step but only 40 % of the −CO−NH-linkages situated near the carboxyl groups hydrolyze. Because of the favorable stereochemical configuration the rate constant is about 3000 times higher than that of polyacrylamide in buffered acetic acid solution at the same pH. The second step proceeds very slowly. The stereospecificity of the reaction was demonstrated by the differences in behaviour of two copolymers of the same overall composition but of different internal structures. After the initially rapid step, the hydrolysis of a copolymer containing 85 mole per cent of acrylic acid slows down before 90 per cent of the potentially available acid groups are reformed, while a copolymer containing 90 mole per cent of the acid and prepared by direct copolymerization hydrolyzes much more rapidly (Fig. 4).

[6] *R. G. J. Miller, B. Mills, P. A. Small, A. Turner-Jones,* and *D. G. M. Wood,* Chem. and Ind. 1323 (1958).

[7] *T. G. Fox, W. E. Goode,* and *J. D. Strobe* (Röhm and Haas), U.S.-Pat. 652267 April 11th. 1957 (57–87).

[8] *T. G. Fox, B. S. Garrett, W. E. Goode, S. Gratch, J. F. Kincaid, A. Spell,* and *J. D. Stroupe,* J. Amer. chem. Soc. *80,* 1768 (1958).

[9] *J. D. Stroupe* and *R. E. Hughes,* J. Amer. chem. Soc. *80,* 2341 (1958).

[10] *T. G. Fox, W. E. Goode, S. Gratch, G. M. Huggett, J. F. Kincaid, A. Spell,* and *J. D. Stroupe,* J. polymer Sci. *31,* 173 (1958).

[11] *G. Smets* and *W. De Loecker,* J. polymer Sci. *45,* 461 (1960).

[12] *G. Smets* and *W. Van Humbeeck,* J. polymer Sci., in the press.

[13] *G. Smets* and *A. M. Hesbain,* J. polymer Sci. *40,* 217 (1959).

Studies made by *Morawetz* et al. [14–17] on the hydrolysis of copolymers of acrylic or methacrylic acid containing 1–2 mole per cent of an acrylic or methacrylic *p*-nitrophenyl ester can also be interpreted by considering the microtacticity of the polymeric chain. At pH 6, the p-nitrophenyl methacrylate units, incorporated into the polyacrylic acid chain hydrolyze

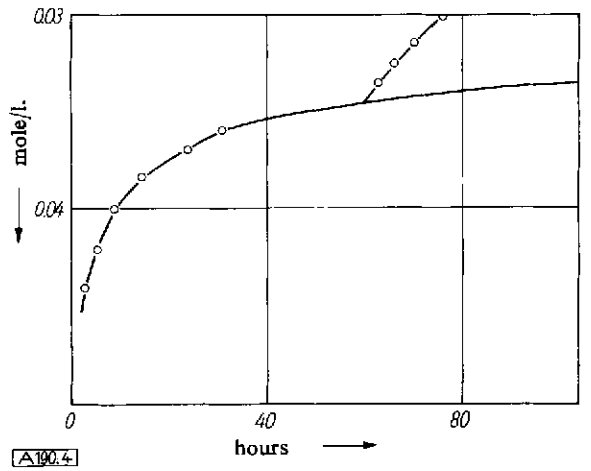


Fig. 4. Rate of hydrolysis of acrylamide acrylic acid copolymers. Influence of stereospecificity.
Upper curve: 90 % acid; Lower curve: 85 % acid

about 10^6 times more rapidly than the homologue, p-nitrophenyl pivalate. Copolymers containing methacrylate esters in a methacrylic acid chain gave first-order plots with a pronounced downward curvature and behave as if they contain ester groups of widely divergent reactivity, the ratio of both rate constants being about 1:1.4. These authors assumed a reaction mechanism based upon attack of carboxylate at the ester group site, with intermediate formation of an acid anhydride. This cyclization must be subject to steric influences, the effects of which may be the same, or in opposition.

In order to clarify the situation, the hydrolysis rates of monoesters of meso- and racemic 2,3-dialkylsuccinic acids were compared in a pH range where the rate is controlled by neighbouring carboxylate attack; these phenomena are directly related to the intramolecularly catalyzed reactions, recently described by *Bender* et al. [18] in the case of methylhydrogen phthalate, acetyl salicylate, *p*-nitrophenyl glutarate, phthalic acid monoamide and *o*-carboxyphthalimide.

In our opinion this argument is not necessarily conclusive, because the monoesters of 2,4-dialkylglutaric acid are in fact, the corresponding homologue, and not the succinic derivatives. Moreover, no direct demonstration of the influence of the microtacticity was given, although polyacrylic and polymethacrylic systems of different tacticities can be synthesized. Recent nuclear magnetic resonance measurements by *Bovey* [19], show that *poly*(methyl methacrylate) and *poly*(methacrylic acid) prepared by radical polymerization contain approximately 8–12 % isotactic triads, 55 % syndiotactic triads. (nearest neighbours with opposite configuration) and the remaining groups are heterotactic structures (one nearest neighbour with the same, and one with the opposite configuration). It is evident that these different steric configurations can easily explain the data reported by *Morawetz* et al.

Cyclisation

In connection with these experiments, it must pointed out from a purely organic point of view that any cyclization reaction carried out along a polymeric chain must be strongly dependent on the stereochemical structure of the polymer skeleton.

In this field, only few data are so far available, but some very recent results obtained in a study of the dehydration of polyacrylic and polymethacrylic acids to their corresponding polyanhydrides may be briefly described. Polyacrylic anhydride can be prepared for example by polymerization of acrylic anhydride using the cyclopolymerization process, described by *Butler* [20] and *Jones* [20a]. The polymer prepared at 35 °C contains a large number of intact rings (60 to 80 per cent of the theoretical maximum) and has a syndiotactic structure, *i.e.* nearest neighbours are of opposite configuration. On heating for several hours in dimethylformamide, or in the presence of pyridine, the syndiotactic system isomerizes into the isotactic form, probably by an enolization mechanism. The change of configuration was followed by comparing the relevant infrared spectra with those obtained for the corresponding racemic and meso-2,4-dimethylglutaric anhydrides, and the results were compared with nuclear magnetic resonance data [21].

On hydrolysis in the cold, the *poly*(acrylic anhydrides) give the corresponding acids with the same tacticity as the parent polymer. On treatment with thionyl chloride the syndiotactic polyacrylic acid does not cyclize; this means that it cannot revert to the original cyclopolymer. In contrast, conventional polyacrylic acid prepared by radical polymerization cyclizes progressively by two distinct steps, the second being about 5 to 6 times slower than the first. The interpretation of this difference in behavior is again based on the presence of a given amount (about 36–40 %) of isotactic pairs, which are responsible for the rapid cyclization.

At a later stage the reaction proceeds only very slowly on account of the syndiotactic configuration. This necessitates a slow preliminary isomerization [22].

[14] *H. Morawetz* and *P. E. Zimmering*, J. physic. Chem. *58*, 753 (1954).
[15] *H. Morawetz* and *E. W. Westhead*, J. Polymer Sci. *16*, 273 (1955).
[16] *H. Morawetz* and *I. Oreskes*, J. Amer. chem. Soc. *80*, 2591 (1958).
[17] *H. Morawetz* and *E. Gaetjens*, J. Polymer. Sci. *32*, 526 (1958).
[18] *M. L. Bender*, Chem. Reviews *60*, 1 (1960).
[19] *F. A. Bovey* and *G. V. D. Tiers*, J. Polymer Sci. *44*, 173 (1960).
[20] *G. B. Butler* and *A. Crawshaw*, J. Amer. chem. Soc. *80*, 5464 (1958).
[20a] *J. F. Jones*, J. Polymer Sci. *33*, 15 (1958).
[21] *J. Mercier* and *G. Smets*, J. Polymer Sci. *57*, 763 (1962).
[22] *A. Poot*, personal communication.

On the other hand, treatment of polymethacrylic acids of different tacticities with acetic anhydride gives rise to a cyclization process which occurs very rapidly in each case and without noticeable rate differences. Moreover, polymerization of the mixed anhydride derived from methacrylic and acetic acids gives practically pure *poly*-(methacrylic anhydride) accompanied by the simultaneous formation of acetic anhydride.

The nature and the yield of most reactions for which an intramolecular mechanism has been demonstrated depend up on the microtacticity of the chain. For example, it is possible that hydrolysis of *poly*(vinyl acetals), a process which is strongly influenced by the presence of neighbouring alcohol residues is dependant upon the tacticity of the starting material; at the present time, however, no experimental results are available.

Physical Properties and Tacticity

The microtacticity of the chain must exert a pronounced influence on the physical and physicochemical properties of the polymers. Some data recently obtained by *Loebl* [23] on polyacids are of interest in this connection in addition to its influence on the reaction kinetics.

It is well known that for the explanation of results obtained from potentiometric titrations of polyacids first, and, possibly, second neighbouring group interaction must be considered. It is therefore interesting to compare the behavior of polyacids differing only in their stereochemistry. Although no difference could be found between stereoregular and atactic polyacrylic acid [24], significant differences were observed in the case of the polymethacrylic acids. The isotactic acid is a weaker acid than the atactic form; the apparent acid dissociation constants differ by about 0.3 pK units independently of the degree of neutralization, and practically also of the presence of added salt. The enthalpy of dissociation of the isotactic acid is about zero at all degrees of neutralization, while that of the atactic acid is negative and decreases with increasing neutralization

$$(\Delta H_{d.iso}) = -7 \times 10^2 \text{ cal./ degree of neutralization}$$

$$\frac{d}{dx}(H_{d.\,iso}) = -3 \times 10^2 \text{ cal./degree of neutralization}$$

Equilibrium measurements have shown that the isotactic acid binds Cu^{++}-ions much stronger than the atactic form. The persistence of the difference in ion-binding (proton and Cu^{II}) at high salt concentrations undoubtedly indicates the importance of close neighbour interaction.

Future Prospects

It may be concluded that the microtacticity of the polymeric chains constitutes a new fundamental aspect of polymer chemistry. In the light of these findings it follows that several reactions and fundamental properties stand in need of re-interpretation. Furthermore, the possibilities for the synthesis of polymers of different tacticities affords a new field for research in high polymer chemistry.

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Ring Substitutions and Secondary Reaktions of Aromatic-Metal π-Complexes, Part I

BY DR. KLAUS PLESSKE

INSTITUT FÜR ANORGANISCHE CHEMIE DER UNIVERSITÄT MÜNCHEN [*]

π-Complexes of aromatic compounds with transition metals display aromatic characteristics. This is shown, among other things, by the fact that many such compounds undergo aromatic substitution reactions. A survey of substitutions and secondary reactions in such systems is given.

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Introduction

Since the discovery of dicyclopentadienyliron, $Fe(C_5H_5)_2$ [1,2], the development of metallic π-complex chemistry has introduced novel reaction possibilities and unexpected types of compounds. Apart from having developed compounds in which five- and six-membered aromatic rings and a large number of olefins are linked preferentially to transition metals by π-bonds [3], *Woodward*, *Rosenblum*, and *Whiting* [4] also observed that ferrocene can be substituted by means of the Friedel-Crafts reaction. This discovery opened up a new branch of π-complex chemistry involving substitutions and secondary reactions of metallic ring compounds. The majority of derivatives prepared have involved ferrocene. In addition, higher homologues such as dicyclopentadienylruthenium ("ruthenocene"), dicyclopentadienylosmium ("osmocene") as well as "mixed" five- and six-membered ring metal carbonyls such as tricarbonyl(cyclopentadienyl)manganese, $C_5H_5Mn(CO)_3$, tricarbonyl(cyclopentadienyl)vanadium, $C_5H_5V(CO)_4$, dicarbonyl(cyclopentadienyl)nitrosylchromium, $C_5H_5Cr(CO)_2NO$, benzenetricarbonylchromium, $C_6H_6Cr(CO)_3$, and dibenzenechromium, $Cr(C_6H_6)_2$, are able to participate in organic substitution reactions. This "organic" branch of metallic π-complex chemistry exclusively encompasses well-known organic substitutions of ring hydrogen atoms by other groups, whereby the original metal-ring π-bond is preserved, as well as secondary reactions of the functional derivatives thus obtained. In view of the vast volume of investigated material hitherto, a summarized presentation seems appropriate. Methods

[*] Present adress: California Institute of Technology, Gates and Crellin Laboratories of Chemistry, Pasadena, Calif. USA.

[1] *T. J. Kealy* and *P. L. Pauson*, Nature (London) *168*, 1039 (1951).

[2] *S. A. Miller*, *J. A. Tebboth*, and *J. F. Tremain*, J. chem. Soc. (London) 632 (1952).

[3] Review articles: *E. O. Fischer*, Angew. Chem. *67*, 475 (1955); *P. L. Pauson*, Quart. Rev. (Chem. Soc., London) *9*, 391 (1955); *K. Schlögl*, Österr. Chemiker-Ztg. *59*, 93 (1958); *A. N. Nesmeyanov* and *E. G. Perewalova*, Uspekhi khim., *27*, 3 (1958); *M. E. Dyatkina*, ibid. *17*, 57 (1958); *E. O. Fischer* and *H. P. Fritz*: Recent Advances in Inorganic Chemistry and Radiochemistry. Academic Press, New York 1959, vol. 1, p. 55; *G. Wilkinson* and *F. A. Cotton*: Progress in Inorganic Chemistry. Interscience Publishers, Inc., New York 1959, vol. *1*, p. 1; *P. L. Pauson*: Non-Benzenoid Aromatic Compounds. Interscience Publishers, Inc., New York 1959, p. 107; *P. L. Pauson* and *H. Zeiss* in *H. Zeiss*: Organometallic Chemistry. Reinhold Publishing Corp., New York 1960, pp. 346, 380; *E. O. Fischer* and *H. P. Fritz*, Angew. Chem. *73*, 353 (1961).

[4] *R. B. Woodward*, *M. Rosenblum*, and *M. C. Whiting*, J. Amer. chem. Soc. *74*, 3458 (1952).

used to link preformed five- or six-membered cyclic derivatives to central metallic atoms in a subsequent reaction step have not been included in the summary.

The nomenclature is based on the following: The ten ring positions of ferrocene, ruthenocene and osmocene are labelled 1 to 5 and 1′ to 5′, respectively as shown in Fig. 1. Under normal conditions, the two rings in the ferrocene crystal are "displaced" with respect to each other, while they are superposed in both ruthenocene and osmocene. At higher temperatures in solution, the ferrocene rings are free to rotate with respect to one another. So far, there are no data available concerning the ring rotation in ruthenocene, osmocene and dibenzenechromium.

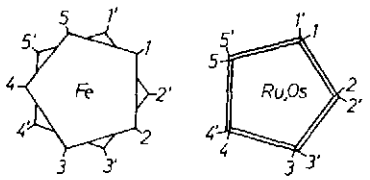


Fig. 1. Position of the rings in the crystal lattice

While the ring positions are designated with Arabic numerals, positions in the side-chains are indicated by Greek letters, whenever possible. Furthermore, ferrocenyl stands for $C_5H_5FeC_5H_4-$ and 1,1′-ferrocenylene stands for $-C_5H_4FeC_5H_4-$.

1. Alkyl Derivatives

Direct Friedel-Crafts alkylation of the π-complexes with alkyl halides, olefins, or alcohols in the presence of aluminum chloride or phosphoric acid as catalyst leads to mixtures of position isomers consisting of mono- and poly-alkylated products which are difficult to separate. The yields are generally low. According to *Nesmeyanov*, reaction of ferrocene with ethyl bromide and aluminum chloride gives ethylferrocene, a liquid in 4 % yield (boiling at 107–108.5 °C/5 mm. Hg.) together with diethylferrocene (3.5 %) and a mixture of various triethylferrocenes (3.5 %) [5]. When the reaction is carried out in n-pentane at a slightly higher temperature, the yield of ethylferrocene increases to 18.5 %; concurrently, two homoannular isomers (i.e., substituted in the same ring) of diethylferrocene have been isolated [6].

Analogous Friedel-Crafts reactions of ferrocene with methyl chloride (from HCl, ZnCl and CH_3OH) [6], isopropyl chloride [6], n-butyl chloride [5], and benzyl chloride [5] result in low yields of methylferrocene, dimethylferrocene (homoannular), isopropylferrocene, diisopropylferrocene (homoannular), n-butylferrocene, di-n-butylferrocene and penta-n-butylferrocene, and benzylferrocene respectively. t.-Butyl chloride and t.-amyl chloride react with ferrocene in petroleum ether, even in the absence of aluminum chloride to give t.-butylferrocene and di-t.-butylferrocene, or t.-amylferrocene and di-t.-amylferrocene [7]. In the reaction of 1,2-dichloroethane with ferrocene in the presence of aluminum chloride, *Nesmeyanov* and *Kochetkova* [5,8] obtained diferrocenylethane along with a high polymer material (Section 16), and by multiple interlinking of two ferrocene molecules, pentaethylenediferrocene and dodecaethylenetetraferrocene. Later, *Rinehart* [9] proved that the "diferrocenylethane" was really the unsymmetrical rearrangement product, 1,1-diferrocenylethane. In a normal course of reaction, 1,2-diferrocenylethane would be expected.

Tricarbonyl(cyclopentadienyl)manganese, $C_5H_5Mn(CO)_3$, and its methyl derivative, $CH_3-C_5H_4Mn(CO)_3$, also react with alkyl halides, similarly to ferrocene. Tricarbonylcyclohexyl(cyclopentadienyl)manganese or tricarbonyldicyclohexyl(cyclopentadienyl)manganese can thus be obtained concurrently as liquid compounds, also in low yields by using cyclohexyl chloride [10]. Isolable mono-, di-, and tri-ethylated derivatives [11] are also obtained as distillable liquids by treating tricarbonylmethyl(cyclopentadienyl)manganese with ethyl bromide.

The yields of alkyl derivatives are higher in the reaction of ferrocene with olefins under pressure in the presence of aluminum chloride. Ethylene at 100–150 °C and 30–40 atm. pressure gives ethylferrocene in a 20.5 % yield, together with lesser amounts of diethylferrocene and a mixture of various polymethylated products [12]. The yields of isopropylferrocene, diisopropylferrocene and a polyisopropyl-ferrocene mixtures are higher in the analogous pressure reaction of ferrocene with propylene [12]. Isobutylene gives t.-butylferrocene at room temperature, together with homoannular di-t.-butylferrocene, while at 100–150 °C crystalline tri-n-butylferrocene with a heteroannular configuration of the substituents is formed in 43.5 % yield alongside smaller quantities of liquid tetra-t.-butylferrocene [7]. Tricarbonyl(cyclopentadienyl)manganese can be alkylated with isobutylene, even at ambient pressure to form t.-butyl-, di-t.-butyl-, and tri-t.-butyltricarbonyl(cyclopentadienyl)manganese, which can be separated by distillation [10].

The reaction of ferrocene with alcohols under the influence of condensation catalysts such as phosphoric acid or aluminum chloride was reported by *Rausch* et al. [13] as totally unsuitable for obtaining alkylferrocenes. The alkylated products formed in very low yields could not be separated in a satisfactory manner by distillation or chromatography.

The problem of the multiple substitution which occurs in direct Friedel-Crafts alkylation will now be discussed. As in the alkylation of benzene, in metal-bonded ring systems the first entering alkyl group increases the ring reactivity by induction effects to a level where second and third substitutions are facilitated. With monocyclopentadienyl compounds, such as $C_5H_5Mn(CO)_3$ these substituents can occupy the α- or β-positions (relative to the first substituent), or both positions,

[5] *A. N. Nesmeyanov* and *N. S. Kotschetkova*, Doklady Akad. Nauk. S.S.S.R. *109*, 543 (1956).

[6] *A. N. Nesmeyanov* u. *N. S. Kotschetkova*, Doklady Akad. Nauk. S.S.S.R. *114*, 800 (1957).

[7] *A. N. Nesmeyanov* and *N. S. Kotschetkova*, Doklady Akad. Nauk. S.S.S.R. *117*, 92 (1957).

[8] *A. N. Nesmeyanov* and *N. S. Kotschetkova*, Doklady Akad. Nauk. S.S.S.R. *126*, 307 (1959).

[9] *K. L. Rinehart* et al., J. Amer. chem. Soc. *82*, 2082 (1960).

[10] *J. Kozikovski, R. E. Maginn* et al., J. Amer. chem. Soc. *81*, 2995 (1959).

[11] *R. Riemschneider* and *H. G. Kassahn*, Z. Naturforsch. *14b*, 348 (1959).

[12] *A. N. Nesmeyanov* and *N. S. Kotschetkova*, Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk 242 (1958).

[13] *M. Vogel, M. D. Rausch* et al., J. org. Chemistry *22*, 1016 (1957).

depending upon steric factors. In addition, hydrogen atoms of the second ring in the dicyclopentadienyls, ferrocene, ruthenocene and osmocene, can be replaced as well. This is the case with first-order entering substituents, such as alkyl groups, where the latter can only enter the still unoccupied ring owing to steric effects. The t.-butylation of ferrocene with isobutylene mentioned above [7] may serve as an example. While both substituents in di-t.-butylferrocene are located in the same ring (*i.e.* homoannular disubstitution), tri-t.-butylferrocene and tetra-t.-butylferrocene, are substituted for steric reasons, in a heteroannular manner.

However, when a second order substituent, such as an acyl group or a metal, enters a dicyclopentadienyl compound, the substituted ring becomes so deactivated that a second substitution in the same ring is largely prevented. In such a case, heteroannular substitution is extremely favored. Hence, all acylations and metalations, heteroannular disubstituted compounds are always encountered together with monosubstitution products; homoannular disubstitution is only observed in a few instances.

These simple rules have hitherto only been worked out for cyclopentadienyl complexes. Orientation experiments disclosed that different rules apply for six-membered ring compounds (Section 8a). While so far conclusions regarding the mutual positions of substituents in homoannular polysubstitution of both mono- and dicyclopentadienyls can be drawn in only few instances, the decision whether homo- or hetero-annular substitution has taken place in a two-ring compound is plainly possible with the help of infrared spectroscopy. π-Bonded cyclopentadienyl-metal rings show strong characteristic bands at 1000 and 1100 $cm.^{-1}$ which disappear when a side-chain is present [14].

Alkylferrocenes are also formed by condensation of ferrocene with formaldehyde or benzaldehyde in concentrated sulfuric acid [15] or liquid hydrogen fluoride [16]. In contradiction to the earlier opinions of *Nesmeyanov* [17,18], *Rinehart* has shown that the formaldehyde condensation of ferrocene gives sym-diferrocenylethane, which can be obtained in 27 % yield in liquid hydrogen fluoride as high-melting yellow crystals. The reaction with benzaldehyde leads to sym-diferrocenyl-diphenylethane, which can also be obtained in two stereoisomeric forms, together with ferrocene aldehyde, aniline, benzoylferrocene and phenylferrocenylcarbinol, by acid-catalyzed decomposition of phenylferrocenyl-carbinyl azide [21,22].

Ferrocene aldehyde itself, in analogy to formaldehyde and benzaldehyde, also condenses with one molecule of ferrocene whereby, however, a dark blue diferrocenylmethine cation is formed [19].

Nesmeyanov [20] found that diferrocenylmercury reacts with triphenylchloromethane, giving (triphenylmethyl)ferrocene in low yield. However, there are no indications up to now that this method of reaction might be of more general application.

Considerably more important than these direct substitution methods are procedures by which secondary reactions on already substituted derivatives lead to well defined alkyl compounds in a very convenient preparative manner and in high yields. The methyl ester of ferrocenemonocarboxylic acid and ferrocene-1,1′-dicarboxylic acid dimethyl ester are reduced with lithium aluminum hydride (molar ratio ester: $LiAlH_4$ = 1:6) in ether through the intermediate alcohol step to methylferrocene [23], and 1,1′-dimethylferrocene, respectively [24] [*]. Methylferrocene is also obtained in 94 % yield (m.p. 118–119 °C) by reductive cleavage of ferrocenylmethyltrimethylammonium iodide (III) with sodium amalgam.

$$C_5H_5FeC_5H_4{-}CH_2{-}\overset{\oplus}{N}(CH_3)_3\,I^{\ominus} \qquad \text{(III)}$$

Clemmensen reduction was shown to be very suitable for the synthesis of higher alkylferrocenes. Acetylferrocene and 1,1′-diacetylferrocene are converted into ethylferrocene and 1,1′-diethylferrocene, respectively, by amalgamated zinc and hydrochloric acid [13,25,26]. 1,1′-Dipropionylferrocene and 1,1′-dibutyrylferrocene can likewise be transformed into 1,1′-dipropylferrocene and 1,1′-dibutylferrocene [25]. Syntheses of long-chain alkylferrocenes, such as 1,1′-didodecyl-, 1,1′-ditridecyl-, 1,1′-dihexadecyl-, and hexadecylferrocene were achieved for the first time by Clemmensen reduction of the corresponding α-keto compounds [13]. Benzylferrocene can be prepared in a similar manner from benzoylferrocene [27,28], phenylbenzoyldiferrocenylmethane being formed in small quantities as by-product. The latter, originates as the main product, however, when benzoylferrocene is treated in alcoholic solution with zinc, alcoholic hydrochloric acid and mercuric chloride [28].

Benzylferrocene and 1,1′-dibenzylferrocene have been prepared in excellent yields by reducing the corresponding ketones with sodium in ethanol [27], or by using

[14] Cf. e.g. *A. N. Nesmeyanov* et al., Doklady Akad. Nauk. S.S.S.R. *125*, 1037 (1959); *H. P. Fritz*, Chem. Ber. *92*, 780 (1959); *M. Rosenblum* and *R. B. Woodward*, J. Amer. chem. Soc. *80*, 5443 (1958); *G. R. Knox* and *P. L. Pauson*, J. chem, Soc. (London) 692 (1958); *A. N. Nesmeyanov* et al., Doklady Akad. Nauk. S.S.S.R. *117*, 433 (1957); *K. L. Rinehart* et al., J. Amer. chem. Soc. *79*, 3420 (1957).

[15] *A. N. Nesmeyanov* and *I. I. Kritskaja*, Izvest. Akad. Nauk. S.S.R., Otdel. Khim. Nauk. 253 (1956); *A. N. Nesmeyanov* et al., (Chem. Abstr. *50*, 13886f (1956).

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[17] *K. L. Rinehart* et al., J. Amer. chem. Soc. *81*, 3126 (1959); *K. L. Rinehart* et al., XVII. Internat. Congress Pure and Applied Chemistry, Munich 1959, Abstracts Vol. 1, p. 29; see Angew. Chem. *72*, 38 (1960).

[18] *A. N. Nesmeyanov* et al., Doklady Akad. Nauk. S.S.S.R. *117*, 433 (1957).

[19] *C. Jutz*, Tetrahedron Letters Nr. 21, 1 (1959).

[20] *A. N. Nesmeyanov*, *E. G. Perewalowa* et al., Doklady Akad. Nauk. S.S.S.R. *119*, 288 (1958).

[21] *A. Berger*, *J. Kleinberg* et al., Chem. and Ind. 204 (1960).

[22] *A. Berger*, *J. Kleinberg* et al., Chem. and Ind. 1245 (1960).

[23] *A. N. Nesmeyanov* and *E. G. Perewalova*, Doklady Akad. Nauk. S.S.S.R. *121*, 117 (1958).

[24] *A. N. Nesmeyanov* and *E. G. Perewalova*, Doklady Akad. Nauk. S.S.S.R. *112*, 439 (1957).

[*] Note added in proof: Reaction occurs only in the presence of both, $LiAlH_4$ and $AlCl_3$. For further information on reductions with $LiAlH_4/AlCl_3$ see *K. Schlögl* et al., Mh. Chem. *92*, 921 (1961).

[25] *A. N. Nesmeyanov* and *N. A. Wolkenau*, Doklady Akad. Nauk. S.S.S.R. *107*, 262 (1956).

[26] *F. S. Arimoto* and *A. C. Haven*, J. Amer. chem. Soc. *77*, 6295 (1955).

[27] *M. D. Rausch*, *M. Vogel* et al., J. org. Chemistry *22*, 903 (1957).

[28] *N. Weliky* and *E. S. Gould*, J. Amer. chem. Soc. *79*, 2742 (1957).

catalytically activated hydrogen under pressure [27]. 1,1′-Diacetylferrocene can be converted into 1,1′-diethylferrocene by pressure hydrogenation. Raney nickel [25] and PtO_2 [13] have been found to be good catalysts. While long-chain ferrocenyl ketones such as 1,1′-dicaprylylferrocene could not be transformed into alkyl compounds with hydrogen/platinum oxide [13], 2-acetyl-1,1′-dimethylferrocene[29] and "*cis*-" and "*trans*-" 3,3′-diacetyl-1,1′-dimethylferrocene [30] are easily converted into the ethyl compounds.

Interesting materials also originate from reductive treatment of cyclic π-complex ketones. For example, bis(tetrahydroindenyl)iron, usually prepared by catalytic hydrogenation of bis(indenyl)iron [31], was synthesized by Clemmensen reduction of bis(α-ketotetrahydroindenyl)iron [32]. Analogously, tricarbonyl-1,2-trimethylene-(cyclopentadienyl)manganese, also designated as tricarbonyl(tetrahydropentalenyl)manganese is formed from tricarbonyl-1,2-α-ketotrimethylene(cyclopentadienyl)manganese [33,34]. 1,1′-Trimethyleneferrocene, which is bridged by three methylene groups, is obtainable by hydrogenation of 1,1′-α-ketotrimethyleneferrocene with platinum oxide [35].

π-Complexes with fused saturated rings are also available through catalytic hydrogenation of unsaturated derivatives. Besides the synthesis of bis(tetrahydroindenyl)iron from bis(indenyl)iron mentioned above [31], tricarbonyl(dihydropentalenyl)manganese can similarly be converted to tricarbonyl(tetrahydropentalenyl)manganese with hydrogen and *Raney* nickel [33,34]. Likewise, the ferrocene derivatives cyclopentylferrocene [16], unsym.-di(ferrocenyl)ethane [9], 1-dimethylaminoethyl-2-ethylferrocene, 2-cyano-1-ethylferrocene and 1-hydroxymethyl-2-ethylferrocene [36] have been made available by catalytic hydrogenation of the corresponding alkenyl compounds.

2. Aryl Derivatives

To date, aryl derivatives are known to have been obtained only from ferrocene. According to the reaction

$$n\ R{-}C_6H_4{-}N_2^{\oplus} + C_{10}H_{10}Fe \rightarrow n\ N_2 + n\ H^{\oplus} + (R{-}C_6H_4)_nC_{10}H_{10-n}Fe$$

they can be prepared by treating ferrocene with diazonium salts. Generally, this type of substitution, developed by three research groups[37–41], gives mixtures of mono-, di-, and poly-arylated derivatives, which can be separated easily. By altering the nature of diazonium component, a potential method of preparing diverse arylferrocenes is available. In practice, the aqueous diazonium salt solution is treated with solutions of ferrocene in dilute sulfuric acid [37], in water ether mixtures [39–41], or in concentrated acetic acid [38]. The reaction products are deeply colored, crystalline, and usually stable in air. The aryl derivatives of ferrocene are tabulated in Table 1.

Table 1. Aryl derivatives of ferrocene

R	n	Reference
H	1	[37,38,42]
	2	[37,38,42]
	3	[38]
H	5	[40]
p-Cl	1	[37]
	2	[37]
m-Cl	1	[38]
	2	[38]
p-NO_2	1	[37–40]
	2	[37,39,40]
m-NO_2	1	[41]
o-NO_2	1	[38]
p-CH_3	1	[40]
o-CH_3	1	[38]
p-C_6H_5	3	[37]
o-COOH	2	[37]
	mixture 3,4	[37]
	1	[38]
p-OH	1	[37,41]
p-OCH_3	1	[38,40]
	2	[38]
8-Carboxynaphth-1-yl	1	[37]
	3	[37]
p-SO_3H	1	[38]
p-O-C_6H_5	1	[43]
m-O-C_6H_5	2	[43]
p-$COCH_3$	1	[42]

The di- and poly-substituted compounds (n = 2,3...) are always heteroannularly arylated derivatives. An interesting application of this procedure was found by *Schlögl* [44] in the preparation of diethyl *p*-ferrocenylbenzylformamidomalonate (IV), an important intermediate for making the amino acid, DL-*p*-ferrocenylphenylalanine (see under 12a).

$$H_2N{-}C_6H_4{-}CH_2{-}C(COOC_2H_5)_2 \xrightarrow[2.\ +\ \text{Ferrocene}]{1.\ \text{Diazotization}} FeC_{10}H_9{-}C_6H_4{-}CH_2{-}C(COOC_2H_5)_2$$
$$\text{NHCOH} \qquad\qquad\qquad\qquad\qquad\qquad \text{NHCOH}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \text{(IV)}$$

Further similar arylations with diazonium salts have hitherto been carried out with ruthenocene only; in this case, however,

[29] *K. L. Rinehart, K. L. Motz* et al., J. Amer. chem. Soc. *79*, 2749 (1957).

[30] *K. L. Rinehart* u. *K. L. Motz*, Chem. and Ind. 1150 (1957).

[31] *E. O. Fischer* and *D. Seus*, Z. Naturforsch. *9b*, 386 (1954).

[32] *A. N. Nesmeyanov, N. A. Wolkenau* et al., Doklady Akad. Nauk. S.S.S.R. *111*, 362 (1956).

[33] *T. H. Coffield, K. G. Ihrman* et al., J. Amer. chem. Soc. *82*, 1251 (1956).

[34] *T. H. Coffield, K. G. Ihrman* et al., J. Amer. chem. Soc. *82*, 4209 (1960).

[35] *K. Schlögl* and *H. Seiler*, Mh. Chem. *91*, 79 (1960).

[36] *D. Lednicer* u. *C. R. Hauser*, J. org. Chemistry *24*, 43 (1959).

[37] *V. Weinmayr*, J. Amer. chem. Soc. *77*, 3012 (1955).

[38] *G. D. Broadhead* and *P. L. Pauson*, J. chem. Soc. (London) 367 (1955).

[39] *A. N. Nesmeyanov* et al., Doklady Akad. Nauk. S.S.S.R. *97*, 459 (1954).

[40] *A. N. Nesmeyanov* et al., Doklady Akad. Nauk. S.S.S.R. *99*, 539 (1954).

[41] *A. N. Nesmeyanov* et al., Doklady Akad. Nauk. S.S.S.R. *102*, 535 (1955).

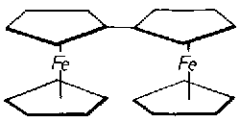
[42] *M. Rosenblum*, J. Amer. chem. Soc. *81*, 4530 (1959).

[43] *S. I. Goldberg*, J. org. Chemistry *25*, 482 (1960).

[44] *K. Schlögl*, Mh. Chem. *88*, 601 (1957).

the preparation of the products in pure form seems to meet with difficulties [45].

Diferrocenyl, in which the ferrocene itself figures as the "aryl" component, also belongs to the arylferrocene class. A small quantity of this dark-orange material, m.p. 239–240 °C, whose structure (V) was proved by infrared and ultraviolet spectra, was obtained as a by-product in the reaction of tri-*n*-hexylsilylbromide with a ferrocene metalation mixture [46,47].



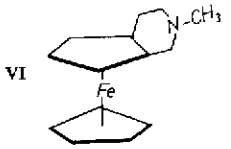
V

Better yields were obtained in the reaction of diferrocenylmercury with palladium [48] or finely divided silver [49]. Ferrocenyl radicals are formed under the influence of the metal and disproportionate to ferrocene and diferrocenyl; this has been firmly established, especially by *Rausch* [49]. *Nesmeyanov* et al. [50,51] report that diferrocenyl is also formed in the reaction of ferrocenylboronic acid with silver oxide or copper salts such as copper acetate or copper propionate, or, according to *Shechter* and *Helling* [75], in the treatment of ferrocenyl-magnesium bromide with $CoCl_2$. The method giving the highest yields is that due to *Rausch*. Diferrocenyl can thus be obtained in nearly quantitative yield by Ullmann diaryl-coupling of iodoferrocene with activated copper-bronze [49] [*].

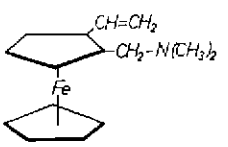
3. Alkylene Derivatives

Vinylferrocene, the simplest member of this class of compounds, was first prepared from α-hydroxyethylferrocene by *Arimoto* and *Haven* using a thermal dehydration reaction. Substantially higher yields are obtained in the pyrolysis of the corresponding ester, α-acetoxyethylferrocene [26]. A further preparative method involves treatment of β-trimethylammoniumethylferrocene iodide (see Section 12b) with potassamide in liquid ammonia, whereby the compound is easily converted by β-elimination into vinylferrocene [52,53]. A derivative of vinylferrocene is also formed in an interesting manner by an elimination reaction. On treatment with formaldehyde and formic acid, β-aminoethylferrocene is transformed in an abnormal Leuckart-Eschweiler-Clarke reaction into a cyclic compound (VI) [53,54,62], whose quaternary ammonium iodide forms 1-dimethylaminomethyl-2-vinylferrocene (VII) when treated with strong alkali [62].

This reaction is of considerable interest, as it renders 1,2-disubstituted ferrocenes available.



VI



VII

Vinylferrocene can be polymerized with various catalysts [26] (see Section 16), and has an astoundingly great affinity for protons, as expressed by the ease of formation of α-azidoethylferrocene and α-acetoxyethylferrocene when vinylferrocene is treated with hydrazoic acid, or acetic acid in benzene solution [56]. The energetically favored carbonium ion (VIII), which also plays a decisive role in a number of other reactions, is probably formed as an intermediate [36–59,62].

$$C_5H_5FeC_5H_4-\overset{\oplus}{C}H-CH_3 \qquad \text{VIII}$$

α,α-Diferrocenylethanol and 1,1′-di(α-hydroxy-α-methyl)-propylferrocene can also be subjected to thermal dehydration; α,α-diferrocenylethylene [9] and 1,1′-di(but-2-en-2-yl)-ferrocene [60] are obtained. Alkylene derivatives of tricarbonyl(methylcyclopentadienyl)manganese are also available in a similar manner. At 200 °C, water can be eliminated from tricarbonyl[(α-hydroxy-α-methylethyl)methylcyclopentadienyl]manganese, from tricarbonyl[(α-hydroxy-α-phenylethyl)methylcyclopentadienyl]manganese, and from tricarbonyl[(α-hydroxy-α-methylpropyl)methylcyclopentadienyl]manganese to give tricarbonyl[(isopropenyl)methylcyclopentadienyl]manganese, tricarbonyl(α-styrylmethylcyclopentadienyl)manganese and tricarbonyl(but-2-en-2-ylmethylcyclopentadienyl)manganese respectively [61].

Ferrocene chemistry also exhibits a remarkable autoalkenylation in liquid hydrogen fluoride at 100 °C, by which crystalline cyclopentenylferrocene [16] is formed. The stability of the alkenyl in this reaction is surprisingly high, since other olefins undergo fluorination and polymerization under similar conditions.

4. Hydroxyl Derivatives and Alcohols

Compounds analogous to phenols, *viz.* hydroxyferrocene and 1,1′-dihydroxyferrocene, have been obtained in good yields from alkaline hydrolysis of their acetates

[45] *M. D. Rausch, E. O. Fischer,* and *H. Grubert,* J. Amer. chem. Soc. *82,* 76 (1960).

[46] *S. I. Goldberg* and *D. W. Mayo,* Chem. and Ind. 671 (1959).

[47] *S. I. Goldberg, D. W. Mayo* et al., J. org. Chemistry *24,* 824 (1959).

[48] *O. A. Nesmeyanova* and *E. G. Perevalova,* Doklady Akad. Nauk. S.S.S.R. *126,* 1007 (1959).

[49] *M. D. Rausch,* J. Amer. chem. Soc. *82,* 2080 (1960).

[*] Note added in proof: This reaction was independently found by *E. G. Perevolova* and *O. A. Nesmeyanov,* Doklady Akad. Nauk. S. S. S. R. *132,* 1093 (1960).

[50] *A. N. Nesmeyanov* et al., Doklady Akad. Nauk. S.S.S.R. *126,* 1004 (1959).

[51] *A. N. Nesmeyanov* et al., Chem. Ber. *93,* 2717 (1960).

[52] *C. R. Hauser, J. K. Lindsay* et al., J. org. Chemistry *23,* 358 (1958).

[53] *D. Lednicer, K. Lindsay* et al., J. org. Chemistry *23,* 653 (1958).

[54] *J. M. Osgerby* and *P. L. Pauson,* Chem. and Ind. 196 (1958).

[55] *C. R. Hauser, J. K. Lindsay* et al., J. org. Chemistry *22,* 717 (1957).

[56] *G. R. Buell, E. McEven* et al., Tetrahedron Letters Nr. 5, 16 (1959).

[57] *J. H. Richards,* Abstracts of Papers, 135th Meet. Amer. Chem. Soc., Boston 1959, p. 87.

[58] *J. H. Richards,* XVII. Internat. Congress Pure and Applied Chemistry Munich 1959, Abstracts Vol. 1, p. 31.

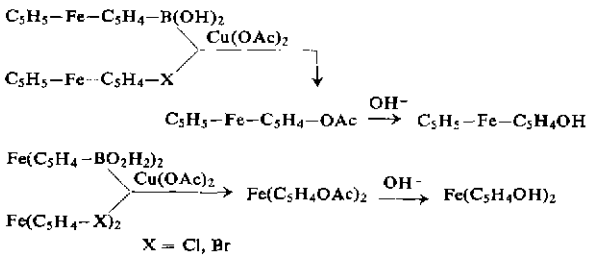
[59] *J. H. Richards* and *E. A. Hill,* J. Amer. chem. Soc. *81,* 3484 (1959).

[60] *R. Riemschneider* and *D. Helm,* Chem. Ber. *89,* 155 (1956).

[61] *R. Riemschneider* and *H. G. Kassahn,* Chem. Ber. *92,* 3208 (1959).

[62] *D. S. Trifan* u. *R. Bacskai,* Tetrahedron Letters Nr. 13, 1 (1960).

[50,51,63]. The starting materials, ferrocenyl acetate and ferrocenylene-1,1′-diacetate can be prepared from ferrocenylboronic acid and ferrocenylene-1,1′-diboronic acid, or from mono- and disubstituted halogenoferrocenes with cupric acetate [50,51].

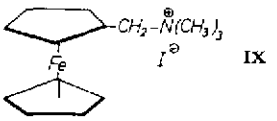


Contrary to most ferrocene derivatives, the yellow crystalline hydroxyferrocene obtained, m.p. 166–170 °C, is sensitive to air and can only be stored under pure nitrogen. Like phenol, it is readily soluble in aqueous alkali and can be reprecipitated from these solutions with carbon dioxide. As the dissociation constants show [50,51], hydroxyferrocene ($K = 6.9 \times 10^{-11}$) is a weaker acid than phenol ($K = 1.2 \times 10^{-10}$). The disubstituted derivative, 1,1′-dihydroxyferrocene, is very unstable and can only be stored for a limited time, *i.e.* is similar to 1,1′-dihydroxy-3,3′-dimethylferrocene [64], obtained by hydrolysis of 1,1′-dibenzoyloxy-3,3′-dimethylferrocene. Oxidation in air gives a cyclopentadienone dimer, and the metal is split off [50,51].

Hydroxyferrocene and 1,1′-dihydroxyferrocene form methyl ethers (see Section 11.5) which are stable in air. Mono- or disubstituted esters or can be prepared with benzoyl chloride or benzenesulfonyl chloride by the Schotten-Baumann method [50,51,63].

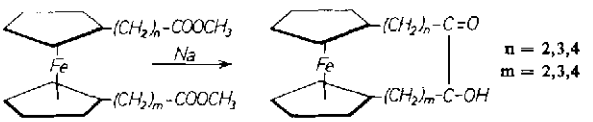
Ester cleavage of ferrocenylacetate is also possible using phenylmagnesium bromide, hydroxyferrocene can be isolated, after hydrolysis, along with diphenylmethylcarbinol [50,51,63].

In addition to hydroxyl derivatives with a direct ring-oxygen bond, π-complexes with an alcohol group in a side-chain are also known. Reductions of carboxylic acids, esters, aldehydes, and ketones with complex hydrides, and Grignard reactions with keto groups have been proved feasible for their production. β-Ferrocenylethanol [53,65], γ-ferrocenylallyl alcohol and γ-ferrocenylpropan-1-ol [44] have been synthesized in good yields by $LiAlH_4$ reduction of ferrocenylacetic acid, ferrocenylacrylic acid, and β-ferrocenylpropionic acid respectively. The methyl ester of ferrocene carboxylic acid and the dimethyl ester of ferrocene-1,1′-dicarboxylic acid react with $LiAlH_4$ in the molar ratio ester:$LiAlH_4$ = 1:3 in ether, giving hydroxymethylferrocene [24,44], and 1,1′-dihydroxymethylferrocene respectively [24] (contrast formation of methyl- and 1,1′-dimethyl-ferrocene, Section 1.). Hydroxymethylferrocene is also obtained from the reaction of ferrocenealdehyde with either $LiAlH_4$ in ether [44,66] (90 % yield), or with $NaBH_4$ in methanol [67] (85 % yield). The same product can also be obtained in excellent yields by alkaline hydrolysis of ferrocenylmethyltrimethylammonium iodide(IX) [70,72].



IX

The acyloin condensations, carried out successfully [35] by reacting finely dispersed sodium with the dimethyl esters of long-chain ω-ferrocenylene-1,1′-dicarboxylic acid (X), should be mentioned in connection with the ester reductions.



X XI

Bridged ferrocene derivatives are formed in this reaction, 9-, 11-, and 13-membered cyclic acyloins (including the central iron atom) were thus obtained from the dimethyl esters of ω-ferrocenylene-1,1′-dipropionic acid, ω-ferrocenylene-1,1′-dibutyric acid and ω-ferrocenylene-1,1′-valeric acid (n = m = 2,3,4). When dimethyl ω-ferrocenylene-1-butyrate-1′-valerate (n = 3, m = 4) was subjected to the same reaction, a 12-membered compound was formed. The possibility of investigating medium-size rings containing ferrocene has thus been brought closer to realization.

As expected, π-complex ketones can also be reduced with hydrides to give secondary alcohols. Thus, acetylferrocene and 1,1′-diacetylferrocene are converted with $LiAlH_4$ into α-hydroxyethylferrocene [26], and 1,1′-di-α-hydroxyethylferrocene, respectively [66]. Acetylcyclopentadienyl(tetracarbonyl)vanadium is converted by $LiBH_4$ into relatively unstable tetracarbonyl-(α-hydroxyethylcyclopentadienyl)vanadium which forms a more stable α-acetoxyethylcyclopentadienyl(tetracarbonyl)vanadium upon esterification with acetic anhydride [68]. Benzoylferrocene, 1,1′-dibenzoylferrocene, and benzoylruthenocene can be converted in a similar manner into α-hydroxybenzylferrocene [28,30], 1,1′-di-α-hydroxybenzylferrocene [30], and α-hydroxybenzylruthenocene [69].

α-Hydroxyethylferrocene can also be obtained from methylmagnesium iodide and formyl-ferrocene [70]. The Grignard reaction with keto compounds (to give tertiary alcohols) can also be applied to π-complex ketones. The tertiary alcohols, 1,1′-di-α-hydroxyisopropylferrocene, 1,1′-di-α-hydroxyisobutylferrocene and 1,1′-dihydroxydiphenylmethylferrocene, were thus prepared by the reaction of 1,1′-diacetylferrocene and 1,1′-dibenzoylferrocene with methylmagnesium iodide, ethylmagnesium bromide and phenyl-magnesium iodide, respectively. The anticipated stereoisomers were sep-

[63] *A. N. Nesmeyanov* et al., Tetrahedron Letters No. 17, 13 (1959).

[64] *R. E. Benson* and *R. V. Lindsay*, J. Amer. chem. Soc. *79*, 5471 (1957).

[65] *K. L. Rinehart, R. J. Curby* et al., J. Amer. chem. Soc. *79*, 3420 (1957).

[66] *P. J. Graham* et al., J. Amer. chem. Soc. *79*, 3416 (1957).

[67] *G. D. Broadhead, J. M. Osgerby*, and *P. L. Pauson*, J. chem. Soc. (London) 650 (1958).

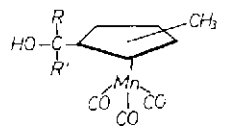
[68] *K. Plesske*, Ph. D. Thesis, Universität München 1960.

[69] *D. E. Bublitz, J. Kleinberg* et al., Chem. and Ind. 936 (1960).

[70] *C. R. Hauser* and *J. K. Lindsay*, J. org. Chemistry *22*, 906 (1957).

arated in the case of 1,1′-di-α-hydroxyisobutylferrocene [60]. α,α-Diferrocenylethanol was obtained by the reaction of methylmagnesium iodide with diferrocenylketone [9].

Similar reactions are known in the chemistry of tricarbonyl-(cyclopentadienyl)manganese. Tricarbonyl (benzoylcyclopentadienyl)manganese reacts with phenylmagnesium bromide to give tricarbonyl(hydroxydiphenylmethylcyclopentadienyl)manganese which shows halochromism in concentrated sulfuric acid [68, 71]. *Riemschneider* et al. [61] obtained the carbinols XIIa–d from acetyl- and tricarbonyl(benzoylmethylcyclopentadienyl)manganese and CH_3MgI, C_2H_5MgBr, and C_6H_5MgBr respectively.

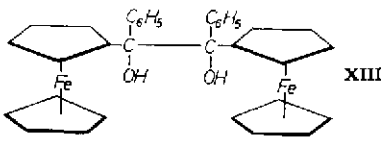


XII

a: R = R′ = CH_3 c: R = CH_3, R′ = C_6H_5
b: R = CH_3, R′ = C_2H_5 d: R = R′ = C_6H_5

The alternatively possible action of Grignard reagents on the three CO ligands does not take place.

sym-Diferrocenyldiphenylethanediol (XIII), the only polyvalent alcohol containing ferrocene, discovered so far, was obtained by simultaneous reaction of benzoylferrocene with methylmagnesium bromide and anhydrous cobalt chloride [28].



XIII

5. Ethers

Methoxyferrocene and 1,1′-dimethoxyferrocene are most conveniently prepared by the reaction of ferrocenylacetate and ferrocenylene-1,1′-diacetate with dimethyl sulfate [50, 51, 73]. Both compounds are stable to air, in contrast to the hydroxyl derivatives. Ferrocenyl allyl ether, prepared by direct reaction of hydroxyferrocene with allyl bromide, surprisingly did not participate in the *Claisen* rearrangement [50, 51] [*].

Nesmeyanov et al. [50, 51] obtained *O*-ferrocenylglycolic acid and *O*,*O*′-(ferrocenylene-1,1′)diglycolic acid from hydroxyferrocene and 1,1′-dihydroxyferrocene with monochloroacetic acid in alkaline medium. 1,1′-Dihydroxy-3,3′-dimethylferrocene similarly gives *O*,*O*′-(3,3′-dimethyl-1,1′-ferrocenylene)diglycolic acid [64].

Ether formation also takes place in the reaction of PBr_3 with hydroxymethylferrocene, diferrocenylmethyl ether being formed. When the more reactive PCl_3 is used, the former compound is obtained in only small amounts, besides the normal chlorination product chloromethylferrocene [44].

α-Hydroxybenzylferrocene and diferrocenylphenyl carbinol can readily be converted into the corresponding ethers with methanol [28]. The high reactivity of the hydroxyl group in α-hydroxybenzylferrocene can also be demonstrated by Meerwein-Ponndorf reduction of benzoylferrocene. The α-hydroxybenzylferrocene formed first immediately reacts further with excess isopropyl alcohol to give α-isopropoxybenzylferrocene [28]. In these etherifications, α-ferrocenylcarbonium ions are again formed in the transition state (see Section 3).

Tricarbonyl(anisole)chromium is obtainable by treating tricarbonyl(chlorobenzeno)chromium with sodium methoxide [139].

6. Halogeno Compounds

Direct halogenation of ferrocene rings has not yet proved successful. In halogenation experiments with elementary iodine, bromine, or chlorine, under certain conditions, deeply colored ferrocene-halogen adducts are formed, *e.g.* with iodine, $C_{10}H_{10}Fe \cdot I_{20}$ and $C_{10}H_{10}Fe \cdot I_6$; the halogen can be removed again with reducing agents with reformation of the unchanged ferrocene [60, 74]. Under severe conditions, the complex is degraded to halogenated cyclopentanes via a ferricinium cation step. Feasible preparative methods for obtaining halogen derivatives of ferrocene (only ferrocene has such derivatives) were first discovered through ligand exchange reactions.

Chloromercuri-ferrocenes react with elementary iodine or bromine in xylene or chloroform according to the

$$ClHg{-}C_5H_4{-}Fe{-}C_5H_5 + X_2 \rightarrow X{-}C_5H_4{-}Fe{-}C_5H_5 + ClHgX$$

$$ClHg{-}C_5H_4{-}Fe{-}C_5H_4{-}HgCl + 2\,X_2 \rightarrow X{-}C_5H_4{-}Fe{-}C_5H_4{-}X + 2\,ClHgX \quad (X=I, Br)$$

equations to give mono- or di-substituted iodo- or bromo-ferrocenes, which can be isolated as stable yellow to orange solids [74]. The yield of iodoferrocene is 64%, while 1,1′-diiodoferrocene, bromoferrocene, and 1,1′-dibromoferrocene are obtained in only relatively small yields. By reacting 1-chloro-1′-chloromercuri-ferrocene and 1-bromo-1′-chloromercuriferrocene-, obtained from 1-halogenoferrocenyl-1′-boronic acids and $HgCl_2$ (see Section 14d) – with iodine, the mixed dihalogenoferrocenes 1-chloro-1′-iodoferrocene and 1-bromo-1′-iodoferrocene have been obtained [50, 51].

A second procedure consists in the reaction of the ferrocenylboronic acid derivatives with copper halides in aqueous solution.

$$C_5H_5{-}Fe{-}C_5H_4{-}B(OH)_2 \xrightarrow{2\,CuX_2} C_5H_5{-}Fe{-}C_5H_4{-}X$$

$$(HO)_2B{-}C_5H_4{-}Fe{-}C_5H_4{-}B(OH)_2 \begin{cases} \xrightarrow{2\,CuX_2} X{-}C_5H_4{-}Fe{-}C_5H_4{-}B(OH)_2 \\ \xrightarrow{4\,CuX_2} X{-}C_5H_4{-}Fe{-}C_5H_4{-}X \end{cases} \quad X = Cl, Br$$

The yields are more favorable in this instance [50, 51]. In the reaction of small amounts of CuX_2 with ferrocenylene-1,1′-diboronic acid, only one $B(OH)_2$ group is exchanged for halogen, and 1-halogenoferrocenyl-1′-boronic acids are obtained. These compounds are of interest for further reactions. Table 2 lists the halogenoferrocenes prepared so far.

[71] *E. O. Fischer* and *K. Plesske*, Chem. Ber. *91*, 2719 (1958).

[72] *J. K. Lindsay* and *C. R. Hauser*, J. org. Chemistry *22*, 355 (1957).

[73] *A. N. Nesmeyanov* et al., Doklady Akad. Nauk. S.S.S.R. *129*, 1060 (1959).

[*] Note added in proof: Cleavage of ferrocene ethers with lithium see *A. N. Nesmeyanov et. al.*, Doklady Akad. Nauk. S.S.S.R. *133*, 1105 (1960).

[74] *A. N. Nesmeyanov*, *E. G. Perevalova* et al., Doklady Akad. Nauk. S.S.S.R. *100*, 1099 (1955).

Table 2. Halogenoferrocenes

Halogeno Derivative	Appearance	M.p. [°C]	Reference
Chloroferrocene	Yellow crystals	59–60	[50,51]
Bromoferrocene	Canary-yellow cryst.	32–33	[74]
Iodoferrocene	Orange-yellow cryst.	44–45	[74]
1,1'-Dichloroferrocene	Yellow crystals	75–77	[50,51]
1,1'-Dibromoferrocene	Yellow crystals	50–51	[50,51,74]
1,1'-Diiodoferrocene	Brown-red liquid $n = 1.682$; $d = 2.286$ g/cm³	—	[74]
1-Chloro-1'-iodoferrocene	—	42–44	[50,51]
1-Bromo-1'-iodoferrocene	—	28–30	[50,51]

The reactions of some of these compounds are rather interesting. While nucleophilic exchange reactions with KOH or CH_3COOK do not occur, bromo- and chloro-ferrocenes react with cupric acetate to give ferrocenylacetate and ferrocenylene-1,1'-diacetate (see Section 14) [50,51]. After initial failures [74], Grignard reactions were successfully accomplished very recently [75] (see Section 14). Furthermore, iodoferrocene has become important for use in the Ullmann reaction; by this means diferrocenyl can now be obtained in larger quantities [49] (see Section 2).

7. Pseudohalogen Compounds

Pseudohalogen derivatives in which one or two ring positions are replaced by CN or SCN groups, have also only been obtained so far with ferrocene. Ferrocenecarbonitrile $C_5H_5-Fe-C_5H_4-CN$ is available by various preparative methods. Friedel-Crafts reaction of cyanogen bromide with ferrocene in the presence of $AlCl_3$ yields only small traces of the compound [67]. Considerably better results were obtained by *Nesmeyanov, Perevalova* et al. [76] by direct cyanation of the ferricinium cation with KCN, or better, with liquid hydrocyanic acid. When ferricinium-tetrabromoferrate $[(C_5H_5)_2Fe]^{\oplus}FeBr_4^{\ominus}$ is treated with potassium cyanide in aqueous alkali, ferrocenecarbonitrile is formed directly, although only in 3 % yield. However, a yield of 86 % can be obtained when liquid HCN in tetrahydrofuran is reacted with a mixture of ferrocene and anhydrous $FeCl_3$ (intermediate ferricinium salt formation). The product collects in the form of stable crystals, melting at 107–108 °C, which can be conveniently purified by chromatography. This reaction also represents the first known substitution on the ferricinium cation, which had hitherto resisted electrophilic attack.

Methylferrocene, ethylferrocene, chloroferrocene and ferrocenecarbonitrile can also be cyanated in a secondary substitution step using this procedure. It is interesting that with alkyl-substituted ferrocenes, the CN group enters the same ring, while with chloroferrocene and ferrocenecarbonitrile, heteroannular-substituted derivatives are formed.

Ferrocenecarbonitrile can be prepared in good yield by subjecting chloro- or bromo-ferrocene to a nucleophilic exchange reaction with cuprous cyanide [50,51]. The same product is also obtained by dehydration of ferrocenealdoxime, which is readily available from the reaction of ferrocene carboxaldehyde with hydroxylamine. The dehydration is effected with acetic anhydride/P_2O_5 [66], acetic anhydride, PCl_5, *N,N'*-dicyclohexylcarbodiimide, or *Raney* nickel [67]. According to *Nesmeyanov* and *Reutov* [77] ferrocene-1,1'-dicarboxamide and ferrocene-carboxamide can also be dehydrated with acetic anhydride, to give ferrocene-1,1'-dicarbonitrile and ferrocenecarbonitrile. Ferrocenylacetonitrile $C_5H_5-Fe-C_5H_4-CH_2-CN$ is formed in the reaction of KCN and ferrocenylmethyl-trimethylammonium iodide (IX) [53,54,78]. 1-Vinylferrocenyl-2-acetonitrile can be prepared from (1-vinylferrocenyl-2-methyl)trimethylammonium iodide in an analogous manner [36]. Thiocyanoferrocene $NCS-C_{10}H_9Fe$ is presumably formed as an intermediate in the reaction between diferrocenylmercury and dithiocyanogen [20]. It has not yet been isolated.

8. Carboxylic Acids and their Derivatives

a) Carboxylic Acids

π-Complex carboxylic acids with the carboxyl group attached directly to the ring have hitherto been identified with ferrocene, ruthenocene, osmocene, the cobalticenium cation, tricarbonyl(cyclopentadienyl)manganese and dibenzenechromium. In principle, they can be prepared either by metalation followed by carboxylation, or by oxidation of acetyl and methyl derivatives, or by hydrolysis of nitriles and carboxamides. *Benkeser* et al. [79] and independently *Nesmeyanov, Perevalova* et al. [39] discovered, the metalation of ferrocene with butyllithium, according to the equation:

$$C_{10}H_{10}Fe + n\ LiC_4H_9 \rightarrow Li_nC_{10}H_{10-n}Fe + n\ C_4H_{10} \qquad n = 1,2$$

whereby a novel substitution principle of the metallic π-complexes was found, which was later applied to ruthenocene, osmocene [45] and dibenzenechromium [80]. Besides butyl-lithium [39,45,47,79,81,82] phenyl sodium [24,47] and amylsodium [80,83] have been confirmed as metalating agents, capable of reacting with the complexes in inert solvents. The reaction solutions can be treated with CO_2; isolation of the alkali derivatives formed is unnecessary (see Section 14b). The carboxylic acids are obtained by subsequent acidification.

$$Li_nC_{10}H_{10-n}Fe + n\ CO_2 \rightarrow (LiOOC)_nC_{10}H_{10-n}Fe \xrightarrow{H^+} (HOOC)_nC_{10}H_{10-n}Fe \qquad n = 1,2$$

[75] *H. Shechter* and *J. F. Helling*, J. org. Chemistry *26*, 1034 (1961).

[76] *A. N. Nesmeyanov, E. G. Perevalova* et al., Chem. Ber. *93*, 2729 (1960).

[77] *N. A. Nesmeyanov* and *O. A. Reutov*, Doklady Akad. Nauk. S.S.S.R. *120*, 1267 (1958).

[78] *J. M. Osgerby* and *P. L. Pauson*, J. chem. Soc. (London) 656 (1958).

[79] *R. A. Benkeser, D. Goggin*, and *G. Schroll*, J. Amer. chem. Soc. *76*, 4025 (1954).

[80] *E. O. Fischer* and *H. Brunner*, Z. Naturforsch. *16b*, 406 (1961).

[81] *M. D. Rausch, M. Vogel* et al., J. org. Chemistry *22*, 900 (1957).

[82] *D. W. Mayo, P. Shaw* et al., Chem. and Ind. 1388 (1957).

[83] *A. N. Nesmeyanov, E. G. Perewalova* et al., Doklady Akad. Nauk. S.S.S.R. *120*, 1263 (1958).

In the metalation of ferrocene, ruthenocene, and osmocene with butyl-lithium, both mono substitution and heteroannular disubstitution are possible, so that mono- and dicarboxylic acids are always found together. The ferrocene- and ruthenocene-carboxylic acids can be readily separated because of their solubility characteristics; however, separation of the osmocene derivatives is not yet possible. Following the ferrocene metalation process originally reported by *Benkeser* [79], using LiC_4H_9 in ether with subsequent carboxylation, whereby ferrocenecarboxylic acid was obtained in 4.5 % yield, and ferrocene-1,1′-dicarboxylic acid in a mere 1.6 % yield, considerable yield improvements were obtained by the adaptation of *Mayo* [82]. Ferrocenecarboxylic acid and ferrocene-1,1′-dicarboxylic acid are stable, yellow compounds, melting at 225–230 °C and 250 °C, respectively. Ruthenocenecarboxylic acid and ruthenocene-1,1′-dicarboxylic acid are also crystalline, stable substances, which can be prepared by reacting LiC_4H_9 with ruthenocene in ether or in an ether/tetrahydrofuran mixture with subsequent carboxylation [45].

The carboxylic acid mixture obtained from osmocene in an analogous reaction consists of approximately equal parts of osmocenecarboxylic acid and osmocene-1,1′-dicarboxylic acid [45], as shown by analyses.

An interesting sequence is observed on comparing the dissociation constants of benzoic acid, ferrocenecarboxylic acid, and ruthenocenecarboxylic acid:

C_6H_5—COOH $\quad K_s = 6{,}93\cdot10^{-6}$ (in 41% C_2H_5OH) [84]

$C_5H_5FeC_5H_4$—COOH $\quad K_s = 1{,}89 \pm 0{,}04\cdot10^{-6}$ (in 38% CH_3OH)[45]

$C_5H_5RuC_5H_4$—COOH $\quad K_s = 3{,}71 \pm 0{,}15\cdot10^{-6}$ (in 38% CH_3OH) [45]

In alcoholic solution, ferrocenecarboxylic acid and ruthenocenecarboxylic acid are weaker acids than benzoic acid. The slightly higher acidity of ruthenocenecarboxylic acid, as compared with ferrocenecarboxylic acid can probably be explained by the increasing metal-ring bond strength in the series ferrocene-ruthenocene-osmocene. The resulting decreasing π-electron density in the rings leads to the increasing acidity of the carboxylic acids, owing to mesomeric and inductive effects.

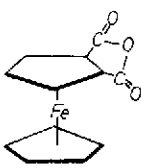
Of interest is the fact that only dimetalation occurs when ferrocene is treated with phenylsodium [24] or amylsodium [83], so that only ferrocene-1,1′-dicarboxylic acid can be prepared by this method. The yields are fairly good – 42 % and 68 %. Amylsodium treatment followed by carboxylation also converts dimethylferrocene into a 1,1′-dimethylferrocenecarboxylic acid of hitherto unresolved constitution [83].

Surprising results were obtained in investigations of the metalation and carboxylation of bis-benzene-chromium by *E. O. Fischer* and *H. Brunner* [80]. This compound, which was long thought to be largely nonreactive [68,85] can be metalated with amylsodium in alkanes, subsequently reacted with CO_2, and esterified with dimethyl sulfate, converting it into a mixture of mono-, di-, and poly-substituted dibenzenechromium carboxylic acid (methyl esters). The dimethyl ester of dibenzenechromium dicarboxylic acid separated from the above reaction mixture comprises a mixture of homoannularly disubstituted isomers, detected by gas chromatography [86]; the mixture is extremely difficult to separate, but the *m*-isomer is the main component. The situation with $Cr(C_6H_6)_2$ is therefore basically different from that with the dicyclopentadienyls of Fe, Ru, and Os which, besides monocarboxylic acids, all give exclusively heteroannularly disubstituted dicarboxylic acids. Homoannular secondary substitution is obviously a strongly favored reaction in the six-membered rings of dibenzenechromium; furthermore, there are indications that tri- and poly-carboxylated derivatives are present; these have not yet been observed with five-membered ring compounds.

Ferrocenecarboxylic acid and ferrocene-1,1′-dicarboxylic acid are also formed, as expected, in the reaction of CO_2 with Grignard compounds of ferrocene [75].

A further method for preparing π-complex carboxylic compounds is the oxidation of the readily accessible acetyl derivatives with hypohalites or iodine in pyridine. The procedure was used by *Woodward* [4] in preparing ferrocene-1,1′-dicarboxylic acid by hypoiodite oxidation of 1,1′-diacetylferrocene. Similarly acetylferrocene can be converted into ferrocene carboxylic acid in 50 % yield by using iodine in pyridine solution [16,29,87].

Richards and *Curphey* [88] used this reaction to provide a very elegant proof of the structure of 1,2-diacetylferrocene, which is formed in small amounts during acetylation of ferrocene. They oxidized the compound with NaOCl to ferrocene-1,2-dicarboxylic acid; dehydration with *N,N′*-dicyclohexylcarbodiimide produced the anhydride XIV.



XIV

1,1′-Dimethylferrocene-2-carboxylic acid, and 1,1′-dimethylferrocene-3-carboxylic acid can be obtained in low yields by iodine oxidation of 1,1′-dimethyl-2-acetylferrocene and 1,1′-dimethyl-3-acetylferrocene [29]. The preparation of carboxylic acids of both tricarbonyl(cyclopentadienyl)manganese and its methyl derivative became possible for the first time by using this procedure. A previously attempted synthesis by means of metalation and carboxylation was unsuccessful, as reactions of $C_5H_5Mn(CO)_3$ with butyl-lithium always destroyed the expected product [68]. However, when tricarbonyl(acetylcyclopentadienyl)manganese and tricarbonyl(acetylmethylcyclopentadienyl)manganese are oxidized by iodine in pyridine, the corresponding carboxylic acids are obtained in 87 % and 65 % yield [89], respectively.

Methyl groups can be oxidized to carboxyl groups with alkaline permanganate, as demonstrated by *E. O. Fischer* and *Herberich* [90] with the 1,1′-dimethylcobalticinium cation. The following compounds have been obtained in good yields:

$Co(C_5H_4COOH)_2^+Br^-$

$Co(C_5H_4COOH)_2^+ ClO_4^-$

$Co(C_5H_4COO)_2^- Ag^+\cdot 0{,}5\ AgClO_4$

The preparation of functional derivatives of the cobalticinium cation, which, despite an electron distribution similar to ferrocene, had previously resisted all substitution attempts, was successfully accomplished for the first time by this method.

[84] *W. Fröhlich*, Ph. D. Thesis, Universität München 1960.

[85] *E. O. Fischer* and *H. P. Fritz*, Z. Naturforsch. *12b*, 67 (1957).

[86] *E. O. Fischer* and *H. Brunner*, unpublished results.

[87] *V. Weinmayr*, U.S.-Patent 2683157 (1954); Chem. Abstr. *49*, 10364a (1955).

[88] *J. H. Richards* and *T. J. Curphey*, Chem. and Ind. 1456 (1956).

[89] *R. Riemschneider* and *K. Petzold*, Z. Naturforsch. *15b*, 627 (1960).

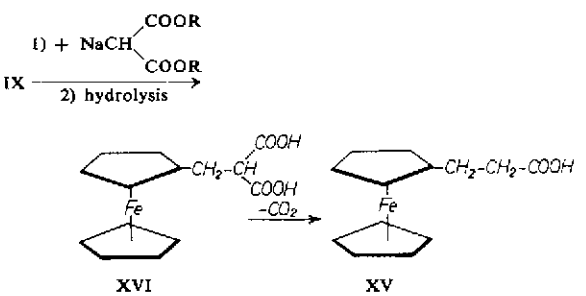
[90] *E. O. Fischer* and *G. E. Herberich*, Chem. Ber. *94*, 1517 (1961).

Ferrocenecarboxylic acid derivatives can also be prepared by alkaline hydrolysis of amides and nitriles. Ferrocenecarboxylic acid is obtained by alcoholic KOH treatment of ferrocenecarboxamide and *N,N*-diphenylferrocenecarboxamide, which are both available by *Friedel-Crafts* reactions. 1-Acetylferrocene-1′-carboxylic acid and 1-benzoylferrocene-1′-carboxylic acid can be obtained in a similar way by hydrolysis of 1-acetylferrocene-1′-*N,N*-diphenylcarboxamide, and 1-benzoylferrocene-1′-*N,N*-diphenylcarboxamide, respectively[91]. (For the preparation of the starting materials, see Section 8d). Contrary to expectations, the *N*-monosubstituted ferrocenecarboxamides prepared by *Rausch* [92] could not be hydrolyzed to ferrocenecarboxylic acid, even under relatively drastic conditions. Ethylferrocenecarbonitrile is the only nitrile to have hitherto been converted into an acid, it gives ethylferrocenecarboxylic acid (homoannular) in good yield by boiling for several hours in aqueous-alcoholic NaOH [76]. Ferrocenecarboxylic acid is also formed along with hydroxymethylferrocene by the Cannizzaro reaction of ferrocenealdehyde [67,72], or by decarboxylation of ferrocene-1′,1-dicarboxylic acid with trichloroacetic acid in nitrobenzene at 120–130 °C [77].

Tricarbonyl(benzoic acid)chromium was obtained as stable orange crystals melting at 201–202 °C by hydrolysis of tricarbonyl(methylbenzoate)chromium. Potentiometric determinations of the dissociation constant indicated a considerably higher acidity than that of benzoic acid (factor of 20) [138].

A series of π-complex carboxylic acids are known, in which the complex-bound ring is separated from the carboxyl group by one or more CH_2 groups. Ferrocenylacetic acid is available in good yield by hydrolysis of ferrocenylacetonitrile [53,78], or by a Willgerodt reaction from acetylferrocene [65,66,78]. Ferrocenylene-1,1′-diacetic acid can be prepared from 1,1′-diacetylferrocene by a Willgerodt reaction [65].

The production of β-carboxyethylferrocene (XV) is possible in different ways. Thermal decarboxylation of ferrocenylmethylmalonic acid (XVI) forms XV in good yield [93]. The starting compound can be obtained by the reaction of ferrocenylmethyltrimethylammonium iodide (IX) with sodio malonic ester, followed by hydrolysis.



XVI XV

β-Ferrocenylacrylic acid, prepared from malonic acid and ferrocencarboxealdehyde [44,67,94] can be hydrogenated with H_2/Pd, also to give XV. Tricarbonyl(β-carboxyethylcyclopentadienyl)manganese is obtained in analogous fashion by hydrogenation of tricarbonyl-(β-carboxyvinylcyclopentadienyl)manganese [33,34,95].

The compound (XV) can also be prepared by hydrolysis of β-ethoxycarbonylethylferrocene [65], by Clemmensen reduction of ethoxycarbonylacetylferrocene [96], and by high pressure hydrogenation of oxalylferrocene with a PtO_2 catalyst [65]. Long-chain ω-ferrocenylcarboxylic acids (γ-carboxypropylferrocene, δ-carboxybutylferrocene, and ε-carboxyvalerylferrocene) are prepared by the action of H_2/PtO_2 on the corresponding keto-carboxylic acids (preparation, see section 11) [65], or by hydrolysis of the ethyl ester, as in the case of δ-carboxyvalerylferrocene [65]. Tricarbonyl(γ-carboxypropylcyclopentadienyl)manganese is formed by Clemmensen reduction of the keto-acid, tricarbonyl(β-carboxypropionylcyclopentadienyl)manganese [95]. The disubstituted ferrocenecarboxylic acids, 1,1′-di-(β-carboxyethyl)-ferrocene, 1,1′-di-(γ-carboxypropyl)ferrocene, and 1-(β-carboxypropionyl)-1′-(γ-carboxypropyl)ferrocene, can be prepared by hydrolysis of their esters [35]. (See Section 8b for preparation of the starting materials).

b) Esters

Ferrocenecarboxylic acid reacts with anhydrous ethanol in benzene, in the presence of concentrated HCl to give a stable ethyl ester [16]. The methyl ester and the dimethyl ester of ferrocene-1,1′-dicarboxylic acid are obtained in a similar way by the reaction of methanol with the corresponding acids [79,4]. 1,1′-Di-(β-carboxypropionyl)ferrocene can be esterified with ethanol and H_2SO_4 with equal ease [66].

The more elegant reaction of acids with diazomethane in ether solution is especially applicable to acid-sensitive compounds. This method was used to obtain the methyl ester of ferrocenecarboxylic acid[44], 1,1′-di-(δ-methoxycarbonylbutyl)ferrocene [35], the methyl ester of ferrocenesulfonic acid [97], and tricarbonyl(ethoxycarbonylmethylcyclopentadienyl)manganese [89]. The synthesis of dibenzenechromium dicarboxylic acid dimethyl ester (see Section 8a) was only accomplished by treatment of the carboxylation mixture with dimethyl sulfate. The ester yields are rather poor (caused by the instability to air and acid). The ester itself is surprisingly stable in air, even when in solution [80,96]. Ferrocene-1,1′-dicarboxylic acid dimethyl ester is prepared in very good yield from ferrocene-1,1′-dicarbonyl dichloride and methanol [43].

Keto-esters have been successfully prepared by Friedel-Crafts acylation using half-ester acid chlorides, such as succinic acid chloride methyl ester (n = 2), glutaric acid chloride methyl ester (n = 3), and adipic acid methyl ester (n = 4) with ferrocene [32,35,65]. Depending on

$$C_{10}H_{10}Fe + x\ ClCO-(CH_2)_n-COOCH_3 \xrightarrow{AlCl_3} [CH_3OOC-(CH_2)_n-CO]_x-C_{10}H_{10-x}Fe + x\ HCl$$

x = 1; 2
n = 2; 3; 4

the molar ratio of the reactants and on the amount of $AlCl_3$, either mono- or di-substitution predominates.

[91] *W. F. Little* and *R. Eisenthal*, J. Amer. chem. Soc. *82*, 1577 (1960).

[92] *M. D. Rausch*, *P. Shaw* et al., J. org. Chemistry *23*, 505 (1958).

[93] *C. R. Hauser* and *J. K. Lindsay*, J. org. Chemistry *22*, 1246 (1957).

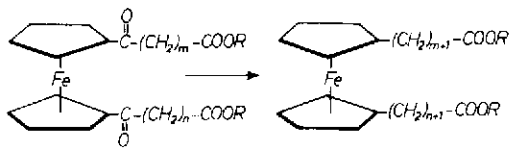
[94] *G. D. Broadhead*, *J. M. Osgerby*, and *P. L. Pauson*, Chem. and Ind. 209 (1957).

[95] *M. Cais* et al., Chem. and Ind. 202 (1960).

[96] *J. B. Thomson*, Chem. and Ind. 1122 (1959).

[97] *G. R. Knox* and *P. L. Pauson*, J. chem. Soc. (London) 692 (1958).

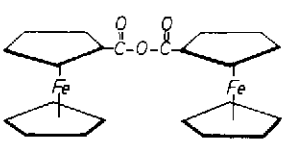
The keto-esters with one CH_2 group less, ethoxycarbonyl acetylferrocene (n = 1, x = 1) and 1,1′-bis(ethoxycarbonylacetyl)ferrocene (n = 1, x = 2), have been made available by ethoxycarbonylation of acetylferrocene [65,98] and 1,1′-diacetylferrocene with methyl carbonate. These keto-esters can be reduced. Clemmensen reduction with amalgamated zinc and HCl, and concurrent hydrolysis, converts ethoxycarbonylacetylferrocene into β-ethoxycarbonylferrocene [96]. Pressure hydrogenation with PtO_2 converts 1,1′-bis(ethoxycarbonylacetyl)ferrocene (a = b = 1), 1,1′-bis(β-methoxycarbonylpropionyl)-ferrocene (m = n = 2) (Clemmensen reduction is also possible [32]), 1,1′-bis(γ-methoxycarbonylbutyryl)ferrocene (m = n = 3), and 1-(β-methoxycarbonylpropionyl)-1-(β-methoxycarbonylbutyryl)ferrocene (m = 2, n = 3) into their saturated esters [35].



Compounds are also known in which the π-complex group is located in the alcohol component of the ester. Examples are ferrocenylacetate and ferrocenylene-1,1′-diacetate mentioned [50,51] above. These are of special interest in the preparation of hydroxyferrocenes. Benzoyloxyferrocene, 1,1′-di(benzoyloxy)ferrocene, benzenesulfonyloxyferrocene and 1,1′-di(benzenesulfonyloxy)ferrocene were synthesized as stable, crystalline compounds by a Schotten-Baumann reaction [50,51] of hydroxyferrocene, or 1,1′-dihydroxyferrocene with benzoyl chloride and benzenesulfonyl chloride. 1,1′-Dimethyl-3,3′-di(benzoyloxy)ferrocene and 1,1′-dimethyl-3,3′-di(benzenesulfonyloxy)ferrocene are formed similarly [64]. These hydroxyferrocenes are fairly sensitive to air but become totally resistant to air oxidation when esterified and can therefore be handled more conveniently as their esters. Moreover benzoyloxymethylferrocene [72], tetracarbonyl(α-acetoxyethylcyclopentadienyl)vanadium [68], phenylferrocenylcarbinylazide and phenylruthenocenylcarbinylazide [21,69]. have been prepared from the corresponding π-complex alcohols.

c) Acid Anhydrides

Ferrocenecarboxylic anhydride (XVII) can be prepared in good yields by the reaction of pyridine and traces of water with ferroceneoyl chloride [77,99].



XVII

Its formation was also observed, instead of the expected peroxide, in the reaction of ferrocenoyl chloride and Na_2O_2 [100]. Dehydration of ferrocene-1,2-dicarboxylic acid gives the intramolecular anhydride [88].

[98] *C. R. Hauser* and *J. K. Lindsay*, J. org. Chemistry *22*, 482 (1957).

[99] *E. M. Acton* and *R. M. Silverstein*, J. org. Chemistry *24*, 1487 (1959).

[100] *H. H. Lau* and *H. Hart*, J. org. Chemistry *24*, 280 (1959).

d) Carboxamides

Only the carboxamides of the two ferrocenecarboxylic acids and of ruthenocenecarboxylic acid have been hitherto described. Ferrocene reacts with isocyanates in a process, catalyzed by $AlCl_3$, according to the reaction:

$$R-NCO + C_5H_5-Fe-C_5H_5 \xrightarrow{AlCl_3} R-NH-CO-C_5H_4-Fe-C_5H_5$$

to give *N*-substituted ferrocenecarboxamides; this finding was first reported by *Weliky* and *Gould* [28], and later by *Rausch* et al. [92]. Only monoderivatives are obtained, in fairly good yields, even when excess isocyanate is used. To date, ferrocenecarboxamides with R = phenyl, *p*-bromophenyl, *p*-diphenyl-, 1-naphthyl-, ethyl and *n*-octadecyl have been synthesized as crystalline, stable substances. This method was also applied to ruthenocene; a stable ruthenocenecarboxanilide was obtained in good yield, starting from phenylisocyanate [45].

Thus, ferrocenecarboxanilide is obtained in a relatively low yield by treating the ferrocene metalation mixture [92] with phenylisocyanate, and also by a Beckmann rearrangement of benzoylferrocene oxime [28].

N-Substituted ferrocenecarboxamides are also obtained in the reaction of ferrocenoyl chloride with ammonia [26], aniline [92], hydrazine [44], 2-aminothiazole, morpholine, *N*-phenyl-α-naphthylamine, phenothiazine and aminoferrocene [99]. Ferrocene-1,1′-dicarboxamide is formed from ferrocene-1,1′-dicarbonyl dichloride and NH_3 [77].

A further reaction of the Friedel-Crafts type, the treatment of ferrocene with carbamyl chloride or *N,N*-diphenylcarbamyl chloride, gave ferrocenecarboxamide or *N,N*-diphenylferrocenecarboxamide [91]. In this case too, substitution occurs preferentially on one ring only;

$$R_2N-CO-Cl + C_{10}H_{10}Fe \xrightarrow{AlCl_3} R_2N-CO-C_{10}H_9Fe + HCl$$
$$R = H, C_6H_5$$

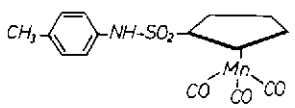
when excess *N,N*-diphenylcarbamyl chloride was used, small amounts of diacylated product were obtained. The remaining unsubstituted ring can, however, be acylated or benzoylated with ease. As mentioned previously, hydrolysis of these compounds allows 1-acylferrocene-1′-carboxylic acids to be prepared (see Section 8a).

e) Carbonyl and Sulfonyl Chlorides

Acid chlorides can be produced by the action of PCl_3, $POCl_3$ or PCl_5 on carboxylic or sulfonic acid derivatives of π-complexes. Thus, with PCl_5, ferrocenecarboxylic acid yields ferrocenecarbonyl chloride, a dark red crystalline compound [22,44,45,92,99,100]. However, PCl_3, was better suited for the chlorination of ferrocene-1,1′-dicarboxylic acid [43,77].

Similarly, ferrocenesulfonic acid and ferrocene-1-sulfo-1′-carboxylic acid, when treated with PCl_3 give ferrocenesulfonyl chloride [97] and 1-chlorosulfoferrocene-1′-carbonyl chloride, the latter being a mixed acid chloride

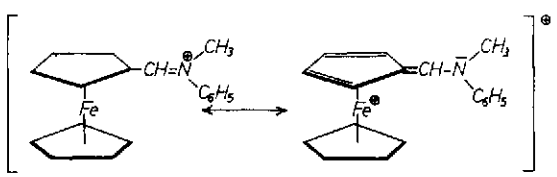
[101]. Ferrocene-1,1′-disulfonic acid is chlorinated preferably in the form of its lead salt. Treatment with PCl_3 produces the monochloride, 1-chlorosulfoferrocene-1′-sulfonic acid, while $POCl_3$ gives the dichloride, ferrocene-1,1′-disulfonyl dichloride [102]. Tricarbonyl-(cyclopentadienyl)manganese sulfonylchloride is obtained in practically quantitative yield by the reaction of the *p*-toluidide of tricarbonyl(cyclopentadienyl)-manganese sulfonic acid (XVIII) with PCl_5 [103].



XVIII

9. Aldehydes

In this class of substances, derivatives of ferrocene, ruthenocene, tricarbonyl(cyclopentadienyl)manganese and tricarbonyl(benzene)chromium are known. Ferrocenecarboxaldehyde has been investigated particularly well. Several investigators [66, 67, 104] demonstrated that Vilsmeier formylation with *N*-methylformamide, in the presence of $POCl_3$ is applicable to ferrocene. Ferrocenecarboxaldehyde was prepared by this method. This elegant formylation procedure, which has found application in organic chemistry, particularly with reactive aromatic compounds such as anthracene, phenol ethers and dialkylanilines but which is not applicable to benzene or its alkyl derivatives, confirms the "aromatic" character of ferrocene. The Vilsmeier process has been improved further [44, 66, 67], so that the aldehyde can now be obtained in 78 % yield in the form of red-brown crystals melting at 121–122 °C. According to *Jutz* [105a] a resonance-stabilized ferrocenecarboxaldehyde-methylanil cation (XIX) is formed first in the reaction mixture; it can be precipitated as its perchlorate. The cation, when hydrolyzed, yields ferrocenecarboxaldehyde and methylaniline.

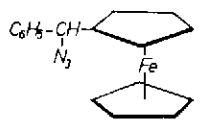


XIX

Ferrocenecarboxaldehyde can also be obtained by the Sommelet reaction of ferrocenylmethyltrimethylammonium iodide (IX) with hexamethylenetetramine in glacial acetic acid [67, 94]. The yield (approximately 40 %) is relatively low. *Rinehart* succeeded in oxidizing methylferrocene to ferrocenecarboxaldehyde in 23 % yield with activated MnO_2. An attempted oxidation of 1,1′-dimethylferrocene, however, did not give the expected ferrocene-1,1′-dicarboxaldehyde, but stopped at the intermediate 1-methylferrocene-1′-carboxaldehyde [106]. Infrared spectral data indicates, however, that the dialdehyde is formed by reduction of ferrocene-1,1′-dicarbonyl dichloride with lithium-tri-t.-butoxyaluminum hydride. Its preparation in pure form has, however, been hitherto hindered by several limitations [43].

Activated MnO_2 has also been found useful in the oxidation of hydroxymethylferrocene to ferrocenecarboxaldehyde [55, 70, 72]. The yield is excellent (98 %); however, direct formylation is probably still the method preferred, as the synthesis of the starting material itself is only possible in several steps (see Section 4).

The formation of ferrocenecarboxaldehyde alongside aniline, benzoylferrocene, *sym*-diferrocenyldiphenylethane, and phenylferrocenylcarbinol in the acid-catalyzed decomposition of phenylferrocenylcarbinyl azide (XX) is of more theoretical interest.



XX

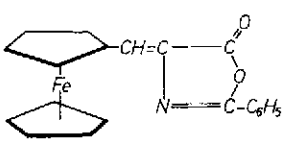
Several decomposition mechanisms have been discussed [21, 22, 107]. Analogous decomposition of phenylruthenocenylcarbinylazide gave ruthenocenecarboxaldehyde [69]. A similar possibility also seems to exist in osmocene chemistry [107].

Tricarbonyl(formylcyclopentadienyl)manganese was obtained in good yield as a distillable reddish oil by reduction of tricarbonyl(cyclopentadienyl)manganesecarbonyl chloride with $LiAlH(OC_4H_9)_3$ [33, 34, 95].

However, there are no details available on the preparation of the acid chloride.

Tricarbonyl(benzaldehyde)chromium was obtained by hydrolysis of tricarbonyl(benzaldehyde diethylacetal)-chromium, which is formed from benzaldehyde diethylacetal and $Cr(CO)_6$. The complex aldehyde undergoes the Cannizzaro reaction [108].

The chemical behavior of ferrocenecarboxaldehyde is similar to that of aromatic aldehydes, hence it undergoes a Cannizzaro reaction in aqueous alcoholic solution with strong alkali to form ferrocenecarboxylic acid and hydroxymethylferrocene [67, 72]. Condensation reactions with C–H acidic compounds and esters are also known. Malonic acid reacts with ferrocenecarboxaldehyde in pyridine/piperidine solution to give β-ferrocenylacrylic acid [44, 67, 94], which can also be produced in several intermediate steps by the Claisen reaction of the aldehyde with acetic acid-t.-butyl ester, in the presence of $LiNH_2$ [70]. When condensed with hippuric acid, the aldehyde forms the azlactone, 2-phenyl-4-(ferrocenylmethylene)oxazol-5-one (XXI) [44, 78, 94].



XXI

[101] *A. N. Nesmeyanov* and *O. A. Reutov*, Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk. 926 (1959).

[102] *A. N. Nesmeyanov, E. G. Perevalova* et al., Doklady Akad. Nauk. S.S.S.R. *119*, 949 (1958).

[103] *M. Cais* u. *J. Kozikowski*, J. Amer. chem. Soc. *82*, 5667 (1960).

[104] *M. Rosenblum*, Chem. and Ind. 72 (1957).

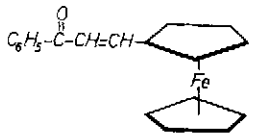
[105] (a) *C. Jutz*, Tetrahedron Letters Nr. 21, 1 (1959); (b) *A. Treibs* and *R. Zimmer-Galler*, Chem. Ber. *93*, 2539 (1960).

[106] *K. L. Rinehart* et al., J. Amer. chem. Soc. *82*, 4112 (1960).

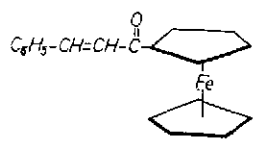
[107] *A. Berger, W. E. McEven* et al., J. Amer. chem. Soc. *83*, 2274 (1961).

[108] *E. Moshardini, F. Calderazzo*, and *R. Ercoli*, Chem. e Industria (Milan) *42*, 1231 (1960).

The first known barbituric acid containing ferrocene, 5-(ferrocenylmethylene)barbituric acid, was synthesized by *Graham* et al. from ferrocenecarboxaldehyde and barbituric acid [66]. In the presence of a little alkali the aldehyde gives a typical Claisen-Schmidt condensation with acetophenone and after dehydration, β-ferrocenylacryloylbenzene (XXII) [44, 70] is obtained. This is isomeric with cinnamoylferrocene (XXIII), obtained by another method (see Section 10b).



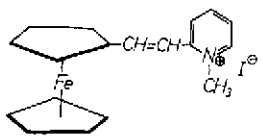
XXII



XXIII

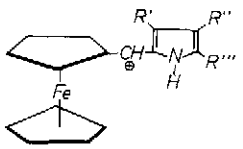
The two compounds only differ essentially in their infrared spectra [44].

While ferrocenecarboxaldehyde does not form an acyloin with cyanide, it does react with benzaldehyde in a "mixed" benzoin condensation, leading to 1-phenyl-2-ferrocenylethan-1-ol-2-one (mandeloylferrocene) [67]. Heterocyclic C–H acids also react with ferrocene carbox aldehyde. Thus, 1,2-dimethylpyridinium iodide forms the "stilbazole" derivative XXIV [67].



XXIV

A. Treibs et al. used condensations with pyrrole derivatives to prepare deeply colored methine salts of the type XXV, which can be precipitated with perchlorate [105b].



$R' = R''' = CH_3$
$R'' = H, C_2H_5, COOC_2H_5$

XXV (one of three mesomeric forms)

A similar compound is diferrocenylmethine perchlorate, a jet-black resonance stabilized material, which can be prepared either from ferrocenecarboxaldehyde and ferrocene, or directly from ferrocene and formic acid in the presence of *Lewis* acids, such as $POCl_3$ [105a].

Its analogue tricarbonyl(formylcyclopentadienyl)manganese, also seems to be accessible through condensation reactions, as exemplified by the preparation of tricarbonyl(β-carboxyvinylcyclopentadienyl)manganese from the aldehyde and malonic acid [33, 34, 95].

Ferrocenecarboxaldehyde can also be converted into α-ferrocenylethanol with CH_3MgI [70]. Like all aldehydes, ferrocenecarboxaldehyde forms a bisulfite compound [66, 104], a cyanohydrin [66], and an acetal [67]. The latter hydrolyzes with extreme ease. Oximes, semicarbazones, hydrazones and azines of aldehydes are referred to in Section 12f.

10. Ketones

a) Preparative Methods

Friedel-Crafts acylation has been found particularly suitable for the synthesis of metallic π-complex ketones. Using acid chlorides and anhydrides, it has been applied in the preparation of ketones of ruthenocene, osmocene, tricarbonyl(cyclopentadienyl)manganese tetracarbonyl(cyclopentadienyl)vanadium dicarbonyl-nitrosyl(cyclopentadienyl)chromium and tricarbonyl(benzene)chromium, in addition to ferrocene. Moreover, acylation also permits observations on the reactivity of ferrocene [67] and tricarbonyl(cyclopentadienyl)manganese [10] compared to that of organic aromatic compounds. Concurrent acetylations resulted in the following sequence of decreasing reactivity:

Phenol ≈ ferrocene > anisole > $CH_3-C_5H_4Mn(CO)_3$ > $C_5H_5Mn(CO)_3$ > benzene

The practical preparative procedure does not greatly differ from the established methods of organic chemistry; however the work generally has to be carried out under exclusion of air in totally air-free solvents. Methylene chloride and carbon disulfide, or less frequently chloroform, ethylene chloride, acetic anhydride or liquid hydrogen fluoride have been found suitable as solvents. Boron fluoride [67, 98], stannic chloride [39], phosphoric acid [66], and liquid hydrogen fluoride [16] can some-times serve advantageously as acylation catalysts, in other instances $AlCl_3$ was used for this purpose.

Numerous keto compounds are available by the Friedel-Crafts method (as shown in Table 3). Although an intramolecular resonance relation between the two five-membered rings of the dicyclopentadienyls is to be assumed, the first entering acyl group does not deactivate the second ring strongly enough to hinder the secondary substitution markedly. In the presence of sufficient acylating agent and an excess of $AlCl_3$ diacylation in heteroannular ring positions almost always occurs. The only homoannularly disubstituted ferrocene derivative discovered so far is 1,2-diacetylferrocene which was isolated in 1.2 % yield, along with 76 % 1,1′-diacetylferrocene and 2.4 % acetylferrocene, from the reaction of ferrocene with acetyl chloride and $AlCl_3$ in the mole ratio ferrocene: $CH_3COCl:AlCl_3$ = 1:2.5:2.5 [109] (very recently, a new homoannular dibenzoylruthenocene of unknown substituent location has also been reported [69]). The yield of acetylferrocene may be increased to 86 % if the reactants are brought together in the ratio ferrocene: $CH_3COCl:AlCl_3$ = 1:1:1. The disubstituted product is not formed at all here [67]. Acetylferrocene alone (yield up to 90 %) [98] is also obtained if boron fluoride [67, 98], phosphoric acid [66], stannic chloride [39], or hydrogen fluoride [16] are used as catalysts instead of $AlCl_3$, with acetic anhydride as the acylating agent.

Acetylferrocene forms orange needles, melting at 85–86 °C, while 1,1′-diacetylferrocene crystals are ruby-red and melt at 131 °C. Both compounds are stable substances, as are all the ketones enumerated in Table 3, which are purified by distillation, sublimation, recrystallization or chromatography.

Acetyl and benzoyl derivatives of diferrocenyl (Section 2) have also been prepared by *Rausch* [49].

The acylation of ruthenocene and osmocene, which was successfully accomplished for the first time by *Rausch*, *Fischer*, and *Grubert* [45, 120] revealed some interesting differences (Table 4). Friedel-Crafts acetylation and benzoylation of ruthenocene forms preferentially the monosubstituted derivatives. 1,1′-Diacetylruthenocene and 1,1′-dibenzoylruthenocene are obtained only in low

Table 3. Ferrocene ketones prepared by *Friedel-Crafts* acylation
(Literature references in italics: best preparative methods)

Substituents	Reference
Acetyl-	[16, 29, 39, 66, *67, 98*, 109]
1,1-Diacetyl-	[*13, 45*, 60, 67, 110]
1,2-Diacetyl-	[88, *109*]
2-Acetyl-1,1'-dimethyl-	[*29*, 83]
3-Acetyl-1,1'-dimethyl-	[29]
Acetyl-1,1'-dimethyl- (constitution unknown)	[66]
2,2'-Diacetyl-1,1'-dimethyl (2 *cis-trans* isomers)	[30, 83]
3,3'-Diacetyl-1,1'-dimethyl- (2 *cis-trans* isomers)	[30] [109]
1-Acetyl-2-ethyl-	[109]
1-Acetyl-1'-ethyl-	[109]
1-Acetyl-3-ethyl-	[109]
Diacetyldiethyl- (const. unknown) (2 isomers)	[110]
2-Acetyl-1,1'-diisopropyl-	[29]
3-Acetyl-1,1'-diisopropyl-	[29]
1-Acetyl-2-phenyl-	[42]
1-Acetyl-3-phenyl-	[42]
1-Acetyl-1'-phenyl-	[42]
1-Acetyl-2,2'-diphenyl-	[42]
1-Acetyl-3,3'-diphenyl-	[42]
Chloroacetyl-	[44]
1-Acetyl-1'-benzoyl-	[110]
1-Acetyl-1-carbamyl-	[91]
1-Acetyl-1'-(*N,N*-diphenylcarbamyl)-	[91]
Propionyl-	[65, *98*, 111]
1,1'-Dipropionyl-	[25]
β-Phenylpropionyl-	[*112*]
Di-(β-chloropropionyl)-	[4]
1,1'-Diacryloyl-	[4]
Cinnamoyl-	[111]
1,1'-Dibutyryl-	[25]
1,1'-Dicaprylyl-	[13]
1,1'-Dicaprinoyl-	[13]
1,1'-Dilauroyl-	[13]
1,1'-Di-tridecanoyl-	[13]
Palmitoyl-	[13]
1,1'-Dipalmitoyl-	[13]
Benzoyl-	[*27, 28*]
1,1-Dibenzoyl-	[*25, 27*, 45, 60]
1-Benzoyl-1'-(*N,N*-diphenylcarbamyl)-	[91]
Anisoyl-	[28]
Ferrocenoyl-	[45]
Ruthenocenoyl-	[45]

yields, even when large amounts of acetyl chloride and $AlCl_3$ are used. Only monoacyl derivatives of osmocene have so far been obtained. For example, osmocene benzoylation, under conditions used in the preparation of 1,1'-dibenzoylferrocene in 70 % yield, only resulted in a 62 % yield of benzoylosmocene [45, 120, 121]. The increasing strenght of the ring-metal bond in the sequence ferrocene – ruthenocene – osmocene causes an increasing intramolecular action between the two rings, so that the deactivating influence of the first substituent upon the second ring becomes stronger.

Table 4. Ruthenocene and osmocene ketones prepared by Friedel-Crafts acylation.
(Literature references in italics: best preparative methods)

Starting Materials	Substituents	References
Ruthenocene	Acetyl-	[45]
	1,1'-Diacetyl-	[*45*, 120]
	Benzoyl-	[*45*, 120]
	1,1'-Dibenzoyl-	[*45*, 120]
	Dibenzoyl-(homoannular)	[69]
	Ferrocenoyl-	[45]
Osmocene	Acetyl-	[*45*, 120]
	Benzoyl-	[*45*, 121]

Keto compounds of monocyclopentadienyl-metal compounds have also been made available by Friedel-Crafts acylations (Table 5), thus demonstrating that such rings can be substituted.

Table 5. Ketones of aromatic-metal carbonyls prepared by Friedel-Crafts Acylation
(Literature references in italics: best preparative methods)

Starting Material	Substituents	Reference
$C_5H_5Mn(CO)_3$	Acetyl-	[10, *71*, 113]
	Benzoyl-	[10, *71*]
	Acetylmethyl-	[11]
	Benzoylmethyl- (2 isomers)	[11, *61*]
	p-Chlorobenzoylmethyl- (2 isomers)	[61]
	Acryloylmethyl-	[61]
	Adipinoyldimethyl-	[61]
	p-Terephthaloyldimethyl-	[61]
$C_5H_5V(CO)_4$	Acetyl-	[114, 115, *116*]
	Propionyl-	[*68*, 115]
	Acetylmethyl-	[115]
	Propionylmethyl-	[115]
$C_5H_5Cr(CO)_2NO$	Acetyl-	[117]
$C_6H_6Cr(CO)_3$	Acetyl-	[118, *119*]
	Acetylmethyl-	[118]
	Acetylethyl-	[118]

Tricarbonyl(cyclopentadienyl)manganese can be acetylated and benzoylated in good yields [10, 68, 71, 113]. Tricarbonyl-acetyl-, and -benzoyl(cyclopentadienyl)manganese are crystalline, stable compounds, melting at 41.5–42.5 °C and 73.5–74.5 °C, respectively. The keto derivatives of tricarbonyl(methylcyclopentadienyl)-manganese can also be synthesized in a smooth reaction [11, 61]. However, the determination of the position of the substituents has not yet been achieved. It is of interest that tetracarbonyl cyclopentadienylvanadium, which is fairly sensitive to oxygen, can be markedly stabilized by acetylation [114–116]. Dicarbonyl-nitrosyl(cyclopentadienyl)chromium can be acetylated, as we have demonstrated by preparing the dark red dicarbonyl - nitrosyl(acetylcyclopentadienyl)chromium, which melts at 27–28 °C [68, 117]. Acetyl derivatives of tricarbonyl(dibenzene)chromium [118, 119] and its methyl and ethyl homologues [118], prepared by a subsequent ring substitution are known.

So far, only monosubstituted products have been isolated by these acylations on aromatic metal carbonyls. A second substitution is probably hindered by the deactivating effect of

[109] *M. Rosenblum* and *R. B. Woodward*, J. Amer. chem. Soc. *80*, 5443 (1958).

[110] *A. N. Nesmeyanov* and *N. A. Volkenau*, Doklady Akad. Nauk. S.S.S.R. *111*, 605 (1956).

[111] *M. D. Rausch* and *L. L. Coleman*, J. org. Chemistry *23*, 107 (1958).

[112] *T. A. Mashburn, C. R. Hauser* et al., J. org. Chemistry *25*, 1982 (1960).

[113] *F. A. Cotton* and *J. R. Leto*, Chem. and Ind. *1958*, 1368.

[114] *F. Calderazzo, R. Ercoli* et al., Chim. e Industria (Milan) *42*, 52 (1960).

[115] *R. Riemschneider* et al., Mh. Chem. *91*, 307 (1960).

[116] *E. O. Fischer* and *K. Plesske*, Chem. Ber. *93*, 1006 (1960).

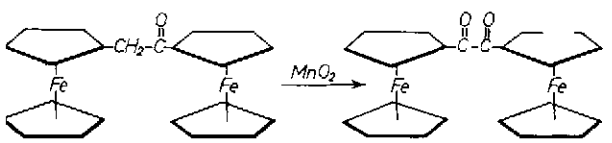
[117] *E. O. Fischer* and *K. Plesske*, Chem. Ber. *94*, 93 (1961).

[118] *R. Riemschneider* et al., Mh. Chem. *90*, 571 (1959).

[119] *R. Ercoli, F. Calderazzo* et al., Chim. e Industria (Milan) *41*, 404 (1959).

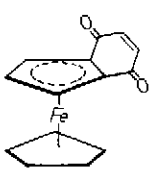
the electrophilic primary substituent, as is the case with aromatic compounds, and the dicyclopentadienyls of Fe, Ru, and Os.

Methods other than the Friedel-Crafts acylation are of little importance for the manufacture of π-complex ketones. *Nesmeyanov* et al. [20] found that by treating diferrocenylmercury with acetyl chloride, acetylferrocene is obtained in a yield of only 1%. β-Phenylpropionylferrocene, 1,1'-di-(β-phenylpropionyl)ferrocene, and β-benzoylethylferrocene can be prepared by catalytic hydrogenation of the unsaturated compounds cinnamoylferrocene [111], 1,1'-dicinnamoylferrocene [112], and β-benzoylvinylferrocene, respectively [44]. Oxidation of methylene groups to keto groups with activated MnO_2 is only interesting in isolated instances. Ethylferrocene, diferrocenylmethane, and ferrocenylacetylferrocene ("deoxyferrocoïn", XXVI) can thus be converted under mild reaction conditions into acetylferrocene (15% yield), diferrocenylketone, and "ferrocil" (XXVII), respectively.



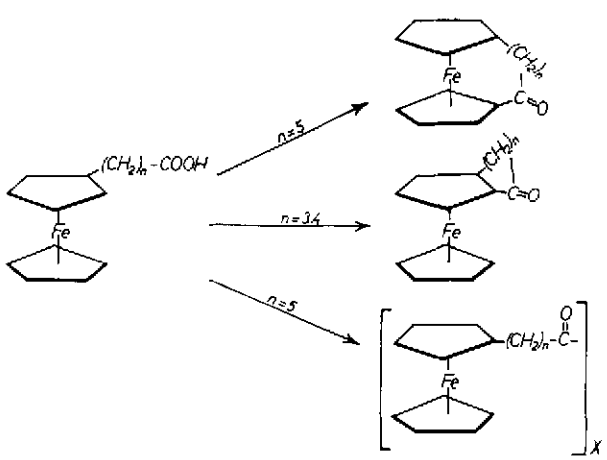
XXVI XXVII

The synthesis of purple ferrocenobenzoquinone (XXVIII) [106] was successfully accomplished by applying this method to 1,2-(α-ketotrimethylene)ferrocene.

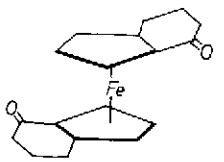


XXVIII

Ring ketones, too, are known in the chemistry of ferrocene and tricarbonyl(cyclopentadienyl)manganese. They are formed by ring-closure of carboxylic acids with a terminal complex group, by dehydration with polyphosphoric acid or trifluoroacetic anhydride. According to *Rinehart* [65,122], monosubstituted ω-ferrocenylcarboxylic acids can react in three ways, depending on their chain length. Heteroannularly bridged 1,1'-α-ketotrimethyleneferrocene is obtained when n = 2, the homoannular ring ketones 1,2-α-ketotetramethyleneferrocene (n = 3) and 1,2-α-ketopentamethyleneferrocene (n = 4) are formed accordingly; intermolecularly bridged polymeric keto compounds result when n = 5.

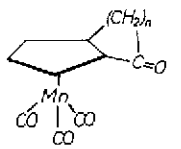


The disubstituted derivative 1,1'-di(γ-carboxypropyl)ferrocene follows the second alternative and gives a double homoannular ring-closure forming di(α-ketotetrahydroindenyl)-iron (XXIX) [32]. This structure was proved by carrying out a Clemmensen reduction to give bis(tetrahydroindenyl)iron, which was compared with authentic compound obtained by another method [123].



XXIX

Tricarbonyl(cyclopentadienyl)manganese ring ketones of type XXX can be isolated after an similar reaction of the corresponding carboxylic acids with phosphoric acid. Tricarbonyl-(1,2-α-ketotrimethylene-cyclopentadienyl)manganese (n = 2) [33,34], tricarbonyl-(1,2-α-ketotetramethylene-cyclopentadienyl)manganese (n = 3) and tricarbonyl-(1,2-α-ketopentamethylene-cyclopentadienyl)manganese (n = 4) [95] have been prepared in this way.



XXX

b) Reactions

As in organic chemistry, π-complex ketones can also form new derivatives. Oxidation (Section 8a) and reduction (Sections 1 and 4) methods, yielding carboxylic acids, or alcohols and alkyl derivatives as well as aminomethylation (Section 12b) are mentioned elsewhere in this article. A few more reactions will be mentioned here, especially those of acetyl derivatives. Owing to the C–H acidity of their methyl group, they are, like all other ketones, able to enter into base-catalyzed condensations with carbonyl compounds. Acetylferrocene reacts with benzaldehyde and traces of alkali to give (benzylideneacetyl)ferrocene (cinnamoylferrocene) [44,98,111]. Crystalline tricarbonyl(cinnamoylcyclopentadienyl)manganese[124] and tetracarbonyl(cinnamoylcyclopentadienyl)vanadium [68] can be prepared in a similar way. 1,1'-Diacetylferrocene, treated with an excess of benzaldehyde, gives a red 1,1'-dicinnamoylferrocene [112]. When less benzaldehyde is used, however, the expected 1-acetyl-1'-cinnamoylferrocene is not formed. The infrared spectrum of the yellow material obtained indicated several possible structures, which may be formed by inter- or intra-molecular ring-closures between still active acetyl groups and C=C double bonds of cinnamoyl groupings. A complete explanation is not yet available [112].

β-Diketones of ferrocene can be prepared by ester condensation of acetyl ferrocene or 1,1'-diacetylferrocene with esters of acetic, propionic, or benzoic acids in the

[120] *M. D. Rausch, E. O. Fischer,* and *H. Grubert,* Chem. and Ind. 756 (1958).

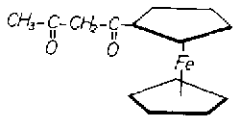
[121] *R. Riemschneider,* Mh. Chem. *90,* 658 (1959).

[122] *K. L. Rinehart* and *R. J. Curby,* J. Amer. chem. Soc. *79,* 2390 (1957).

[123] *E. O. Fischer* and *D. Seus,* Z. Naturforsch. *9b,* 386 (1954).

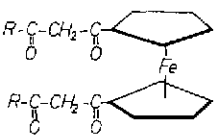
[124] *E. O. Fischer* and *K. Plesske,* Chem. Ber. *92,* 2841 (1959).

presence of alkali alcoholates or alkali amides. Ferrocenoylacetone (XXXI) [125,128], ferrocenoyltrifluoroacetone [125] and ferrocenoylacetophenone [98,128] have thus been prepared from acetylferrocene and ethyl acetate, ethyl trifluoroacetate and methyl benzoate, respectively.



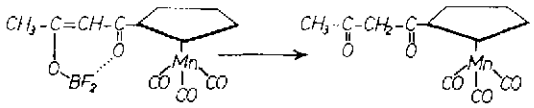
XXXI

Compound XXXI can also be obtained from ferrocenecarboxylic acid methyl ester and acetone in the presence of $NaNH_2$ [127]. The bis-β-diketones, 1,1'-bis-(benzoylacetyl)ferrocene (XXXIIa) [126, 128], 1,1'-bis-(β-ketobutyryl)ferrocene (XXXIIb) and 1,1'-bis-(β-ketovaleryl)ferrocene (XXXIIc) [128] can be prepared from 1,1'-diacetylferrocene and methyl benzoate, ethyl acetate and ethyl, propionate, respectively.



XXXII a) R = C_6H_5
b: R = CH_3
c) R = C_2H_5

In contrast, tricarbonyl(acetylcyclopentadienyl)manganese does not condense with esters under similar conditions. However, the action of acetic anhydride and gaseous boron trifluoride gave a very stable red difluoroboric acid enol ester of tricarbonyl(β-ketobutyrylcyclopentadienyl)manganese (XXXIII); when treated with NaF in boiling methanol, this gave the desired tricarbonyl(β-ketobutyrylcyclopentadienyl)manganese (XXXIV) [124].



XXXIII XXXIV

Being typical β-diketones, ferrocenoylacetone [127], ferrocenoylacetophenone [98], 1,1'-bis(benzoylacetyl)-ferrocene [126] and tricarbonyl(βketobutyryl)cyclopentadienylmanganese [124] form chelate compounds with metals, such as Cu, Al and Th.

11. Keto-Acids

The keto-acids of ferrocene and tricarbonyl(cyclopentadienyl)manganese, which have already been mentioned in connection with long-chain carboxylic acids (Section 8a) are obtained, generally in good yields, by Friedel-Crafts reaction of the π-complexes with cyclic anhydrides. Ferrocene can form mono- and di-substituted products, whose yield can be controlled by both variation of the molar ratios and the quantity of $AlCl_3$. Succinic anhydride reacts with ferrocene with ring opening to form β-carboxypropionylferrocene [65] and 1,1'-di(β-carboxypropionyl)ferrocene [32,66]; only monosubstituted γ-carboxybutyrylferrocene [65] has been isolated so far after analogous reaction with glutaric anhydride. Phthalic anhydride reacts with ferrocene to give *o*-carboxybenzoylferrocene [32] or 1,1'-di-(*o*-carboxybenzoyl)ferrocene [4].

Tricarbonyl(cyclopentadienyl)manganese reacts similarly with succinic and glutaric anhydrides, tricarbonyl(β-carboxypropionylcyclopentadienyl)manganese and tricarbonyl-(γ-carboxybutyrylcyclopentadienyl)manganese [95] being obtained in very good yields as stable crystals. Keto-esters of ferrocene were mentioned in Section 8b.

Part II of this paper will be published in July.

[125] *V. Weinmayr*, Naturwissenschaften *45*, 311 (1958).

[126] *C. R. Hauser* and *C. E. Cain*, J. org. Chemistry *23*, 1142 (1958).

[127] *L. Wolf* and *M. Beer*, Naturwissenschaften *44*, 442 (1957).

[128] *C. R. Cain*, *T. A. Mashburn* et al., J. org. Chemistry *26*, 1030 (1961).

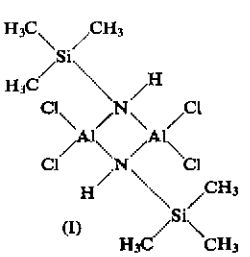
COMMUNICATIONS

Alkylsilazalanes [1]

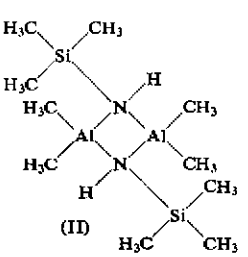
By Dr. H. Schmidbaur and Dr. M. Schmidt

Institut für Anorganische Chemie der Universität München (Germany)

The remarkable properties of alkylsiloxalanes [1] prompted us to prepare the analogous alkylsilazalanes. We started with trialkylsilazadihaloalanes [2]. Trimethylsilazadichloroalane is formed as a dimer (I) from hexamethyldisilazane and aluminum trichloride and can be recrystallized from benzene (m.p. 163 °C, decomp.). Compound (I) can be methylated in ether solution with four moles of methyl-lithium to give the dimeric pentamethylsilazalane (II).

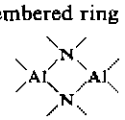


(I)



(II)

The product (II) is easily purified by vacuum sublimation and recrystallization. (m.p. 78—79 °C). This compound attains a remarkable thermal stability through a coordinative saturation of the reactive centers in a planar four-membered ring



and is surprisingly inert. Besides the chemical analysis, the molecular weight determination (cryoscopically in benzene) and the infrared spectrum, especially the proton magnetic resonance spectrum affords an insight into the type of bonding.

Table 1. Chemical shifts in the ^{1}H-NMR spectrum of silazanes and silazalanes

	Chem. shift [in ppm] [3]	
	$(CH_3)_3Si-$	$(CH_3)_2Al-$
$(CH_3)_4Si$	0	–
$(CH_3)_3SiNHSi(CH_3)_3$	−0.033	–
$[(CH_3)_3SiNHAl(CH_3)_2]_2$	−0.200	+0.870
$[(CH_3)_3SiNHAlCl_2]_2$	−0.420	–

The ^{1}H-NMR spectrum of (II) shows two signals with areas in the ratio 3:2 [4]. In comparison with hexamethyldisilazane and tetramethylsilane (Table 1) there is little shielding of the protons in the silyl group, indicating the extinction of the $d_\pi p_\pi$-portion of the Si—N bond due to the fact that the free electron pairs on the nitrogen are used for co-ordination with aluminum. In the case of (I) this effect is overlapped by the inductive effect of the two chlorine atoms.

Received, February 21st. 1962 [Z 257/89 IE]

[1] Heterosiloxanes VII. Communication VI: *H. Schmidbaur* and *M. Schmidt*, J. Amer. chem. Soc. *84*, 1069 (1962).

[2] *M. Becke-Goehring* and *H. Krill*. Chem. Ber. *94*, 1059 (1961). Our compounds had to some extent different properties from those reported in this paper.

[3] Varian A 60 (60 Mc). All compounds in CCl_4 solution at concentrations of 1–5%. Tetramethylsilane as external standard, hexamethyldisilazane as additional internal standard.

[4] The signal of the protons on nitrogen is not considered.

^{1}H-NMR Investigation of the tris-Trimethylsiloxy Compounds of Boron, Aluminum and Gallium [1]

By Dr. H. Schmidbaur and Priv.-Doz. Dr. Max Schmidt

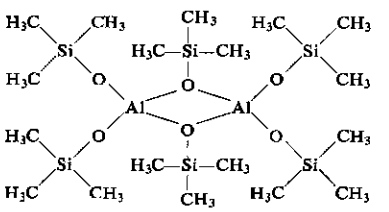
Institut für Anorganische Chemie der Universität München (Germany)

The reactions of sodium trimethylsiloxide with aluminum or gallium trichloride in the molar ratio of 3:1 according to

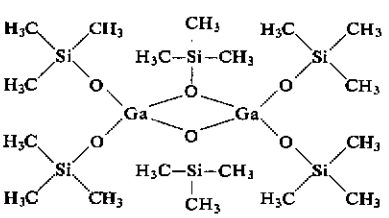
$$3\,(CH_3)_3SiONa + AlCl_3 \rightarrow [[(CH_3)_3SiO]_3Al]_2 + 3\,NaCl$$

$$3\,(CH_3)_3SiONa + GaCl_3 \rightarrow [[(CH_3)_3SiO]_3Ga]_2 + 3\,NaCl$$

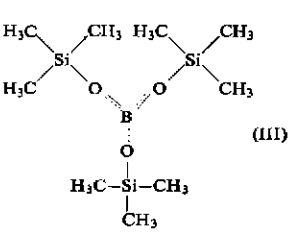
afford good yields of the colorless, crystalline, waxlike compounds, $(Me_3SiO)_3Al$ [2] and $(Me_3SiO)_3Ga$, respectively. Both are high melting, sublimable solids of strikingly low chemical reactivity, high thermal stability and excellent solubility in all organic solvents. Cryoscopic molecular weight determinations for both (I) and (II) give the dimeric molecular weight.



(I)



(II)



(III)

The infrared spectra [3] of the compounds (in solution and in Nujol mull) are in agreement with this structure, as are the ^{1}H-NMR spectra. Compounds (I) and (II) each show two sharp resonance singlets with relatively high chemical shift differences (Table 1) [4], and areas in the ratio of 2:1. The astonishingly small shielding of the protons of the bridge siloxy groups indicates the extinction of the $d_\pi p_\pi$-portion of these Si—O bonds through coordination [1, 5].

Table 1. Physical Data and Chemical Shift Values [4]

	m.p. [°C]	subl. temp. [°C/mm. Hg]	Chem. shift of the siloxy groups (terminal) [ppm]	(bridge) [ppm]
III	− 35	34/1	−0.120	–
I	+238	155/1	−0.058	−0.275
II	+208	135/1	−0.070	−0.283

In contrast to (I) and (II), the known compound (III) [6] is a volatile, monomeric substance. As expected, its NMR spectrum, as determined by us, shows only one sharp signal whose position indicates the presence of Si–O bonds in which the d_π—p_π portions are only partially cancelled by mesomeric π bonding between boron and oxygen.

Received, February 21st. 1962 [Z 258/88 IE]

[1] Heterosiloxanes VIII. Communication VII: preceding.

[2] We were unable to verify earlier reports concerning these compounds: *K. A. Andrianov, A. A. Zhdanov*, and *K. Kazakova*, Izvestiya Akad. Nauk SSSR, Otdel. Tekh. Nauk 466 (1959); Chem. Abstr. *53*, 17561 (1959).

[3] Cf. *C. G. Barraclough, D. C. Bradley, J. Lewis*, and *J. M. Thomas*, J. chem. Soc. (London) 2601 (1961).

[4] Varian A 60 (60 Mc). All compounds in CCl_4 solution at concentrations of 3–5%, trimethylsilane as internal standard.

[5] *H. Schmidbaur* and *H. Schmidt*, J. Amer. chem. Soc., in the press.

[6] *W. E. Abel* and *Apar Singh*, J. chem. Soc. (London) 690 (1959), and references cited therein.

Aromatic Compounds from Leaf Alcohol

By Dr. A. Hatanaka, Prof. Dr. M. Ohno, and Assist. Prof. Dr. Y. Inoue

Institute for Chemical Research, University of Kyoto (Japan)

In 1935 *S. Takei* et al. [1] obtained compound (I), b.p. 240 °C, by heating leaf alcohol (*cis*-hex-3-en-1-ol) with sodium at 160 to 170 °C under reflux; the compound has an orange-like aroma. The structure of (I) was assumed to be 3-propyl-3-nonen-1-ol or 3-propyl-3,5-nonadien-1-ol, since it forms a urethane (m.p. 145 °C) and a 3,5-dinitrobenzoate (m.p. 78 °C). We assume that compound (I) (b.p. 138–139 °C/12 mm. Hg; n_D^{20} 1.5150; 3,5-dinitrobenzoate, m.p. 78 °C [2]) has an aromatic structure for the following reasons: (1) It does not absorb hydrogen in the presence of platinum oxide; (2) it does not decolorize a potassium permanganate solution at room temperature; (3) it does not react with bromine, and (4) the infrared spectrum has the sharp bands characteristic of aromatic compounds. Furthermore, the ultraviolet spectra of 2,5-dimethylbenzyl alcohol and of compound (I) both show a strong maximum at 268 mμ. Oxidation with potassium permanganate gives benzene-1,2,4-tricarboxylic acid [3] (m.p. 208 °C) in quantitative yield. Compound (I) was obtained not only from *cis*-hex-3-en-1-ol, but from *trans*-hex-3-en-, *cis*-hex-2-en- and *trans*-hex-2-en-1-ols, as well as from *trans*-hex-2-en-1-al (leaf aldehyde); n-hexan-1-ol and n-caproic acid were obtained as by-products in every case.

The structure of the aromatic compound (I) obtained from leaf alcohol or leaf aldehyde should therefore be 2-propyl-5-ethylbenzyl alcohol, since from *cis*- and *trans*-hex-2-en-1-ols and from *trans*-hex-2-en-1-al, we obtained (I) and from *trans*-but-2-en-1-ol we obtained 2-methylbenzyl alcohol [4] (b.p. 115–117 °C/17 mm. Hg; n_D^{20} 1.5082; 3,5-dinitrobenzoate

m.p. 128–129 °C). An aromatic compound, presumably 2-ethyl-5-methylbenzyl alcohol (b.p. 110–120 °C/11 mm. Hg; n_D^{20} 1.5080); 3,5-dinitrobenzoate m.p. 76 °C), was obtained from pent-3-en-1-ol.

Received, February 23rd. 1962 [Z 238/73 IE]

[1] *S. Takei, Y. Sakato*, and *M. Ohno*, J. agric. chem. Soc. Japan *14*, 303 (1935).

[2] According to *S. Takei* [1], no melting point depression when mixed with the 3,5-dinitrobenzoate of compound (I).

[3] No melting point depression when mixed with authentic benzene-1,2,4-tricarboxylic acid.

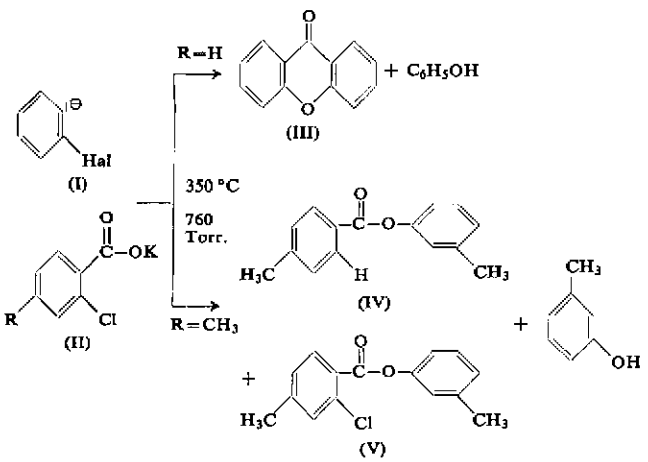
[4] Identified in the form of *o*-toluic acid.

A New Route to Benzyne

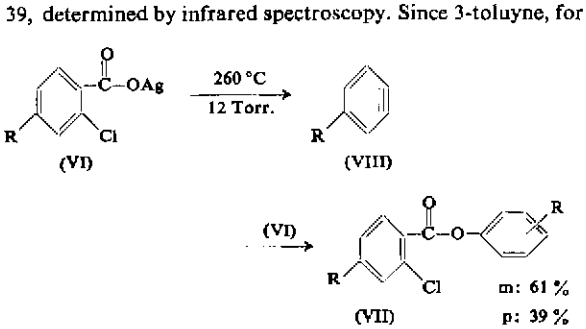
By Dr. G. Köbrich [*]

Organisch-Chemisches Institut
der Universität Heidelberg (Germany)

Decarboxylation of salts of *o*-halogenobenzoic acids in non-alkaline reaction medium should proceed via the intermediate (I) and provide a convenient approach to benzyne (VIII, R = H) [1]. Although pyrolysis of potassium *o*-chlorobenzoate (II, R = H) produces a 52 % yield of xanthone (III) and a small quantity of phenol [2], pyrolysis of the *p*-methyl compound (II, R = CH_3) gives some *m*-cresol and a mixture of esters (IV) and (V), both containing *m*-cresol as phenol component. This result is in agreement with the assumption of nucleophilic substitution of the halogen induced by the carboxylate anion, but not with formation of a benzyne intermediate.



The silver salt VI (R = H), in which the nucleophilicity is depressed by increased homopolarity of the bond between cation and the carboxylate group, pyrolyzes smoothly to give chlorobenzene and phenyl *o*-chlorobenzoate (VII, R = H). Proof for the existence of the intermediate VIII, which was postulated earlier for this reaction [2], but which could not be trapped using tetracyclone, is furnished by decarboxylating VI (R = CH_3); this produces a mixture of esters (VII, R = CH_3) which have a uniform acid component and which on hydrolysis gave *m*- and *p*-cresol in a ratio of 61 : 39, determined by infrared spectroscopy. Since 3-toluyne, for example, adds on 53 to 62 % of various amines in the *m*-position [3], it seems that, besides aryne formation, S_N2 reaction of the carboxylate group can only play a very small part in the formation of the above products.



Received, February 23rd. 1962 [Z 241/81 IE]

[*] Dedicated in admiration and gratitude to Prof. Dr. *G. Wittig* on the occasion of his 65th. birthday.

[1] Cf. *G. Wittig* and *R. W. Hoffman*, Angew. Chem. *73*, 435 (1961); *G. Wittig* and *H. F. Ebel*, ibid. *72*, 564 (1960); *M. Stiles* and *R. G. Miller*, J. Amer. chem. Soc. *82*, 3802 (1960).

[2] *G. Köbrich*, Chem. Ber. *92*, 2985 (1959); cf. *H. E. Simmons*, J. org. Chemistry, *25*, 691 (1960); *J. K. Kochi*, ibid. *26*, 932 (1961); *E. I. McNelis*, Abstr. Papers Fall Meeting Amer. chem. Soc. 1961, p. 89.

[3] *R. Huisgen* and *J. Sauer*, Chem. Ber. *91*, 1453 (1958); Angew. Chem. *72*, 91 (1960); *F. Scardiglia* and *J. D. Roberts*, J. org. Chemistry *23*, 629 (1958).

Ternary Uranium(V) Oxides [1]

By Prof. Dr. W. Rüdorff, Dipl.-Chem. S. Kemmler, and Dr. H. Leutner

Laboratorium für anorganische und analytische Chemie, Universität Tübingen (Germany) [*]

Reaction of uranates (VI) with UO_2, if necessary in the presence of UO_3 or $Me^{II}O$, gave the uranium(V) compounds shown in Table 1. The reaction between zinc as well as nickel(II)-uranate (VI) and UO_2 gave only mixtures of U_3O_8, $UO_{2.25}$, and $Me^{II}O$.

Table 1. Ternary Uranium(V) Oxides

Compound	Lattice Constants	Structure Type
$Li_2O \cdot U_2O_5 = LiUO_3$	rhombohedral $a = 5{,}90_1$ Å $\alpha = 54°36'$	Ilmenit or $LiNbO_3$
$Li_2O \cdot 2\,U_2O_5 = LiU_2O_{5,5}$	cubic $a = 10{,}7_0$ Å	CaF_2 – Superstructure
$Na_2O \cdot U_2O_5 = NaUO_3$	rhombic $a = 5{,}77_5$ Å, $b = 5{,}90_5$ Å $c = 8{,}25$ Å	$GdFeO_3$
$K_2O \cdot U_2O_5 = KUO_3$	cubic $a = 4{,}29_0$ Å	Perovskite
$Rb_2O \cdot U_2O_5 = RbUO_3$	cubic $a = 4{,}32_3$ Å	Perovskite
$MgO \cdot U_2O_5 = Mg(UO_3)_2$	cubic $a = 5{,}27_5$ Å	CaF_2
$CdO \cdot U_2O_5 = Cd(UO_3)_2$	cubic $a = 5{,}35_7$ Å	CaF_2
$2\,CdO \cdot U_2O_5 = Cd_2U_2O_7$	rhombohedral $a = 10{,}71_5$ Å $\alpha = 91°18'$	?
$2\,PbO \cdot U_2O_5 = Pb_2U_2O_7$	cubic $a = 11{,}1_8$ Å	CaF_2 – Superstructure
$2{,}5\,PbO \cdot U_2O_5 = Pb_{2,5}U_2O_{7,5}$	rhombohedral $a = 11{,}2_0$ Å, $\alpha = 90°18'$	?

In the alkali-uranium (V) oxides series, only the compounds Li_7UO_6, Li_3UO_4, Na_3UO_4 [2], $LiUO_3$, and $NaUO_3$ [1] were previously known. The structures of the two latter compounds have now been determined. The brown-violet compounds KUO_3 and $RbUO_3$, which crystallize in a cubic perovskite-type lattice, were prepared for the first time. Furthermore, the existence of a cubic phase $Li_2O \cdot 2\,U_2O_5$ in the system $Li_2O - U_2O_5$ has been demonstrated. It possesses a CaF_2 superstructure with empty spaces in the anion positions. On further reduction of the Li_2O content, a hexagonal phase appears in addition to the cubic phase. Its lattice constants ($a = 6.81_5$ Å, $c = 4.13_0$ Å) are practically the same as those of the "U_3O_8" modification which is stable between 400–600 °C [3]; the oxygen content of the latter, however, is less than that of this structure [4]. Since the hexagonal phase was

observed at ordinary temperatures only in the $Li_2O-U_2O_5$ system, it may be assumed that in this case stabilized U_2O_5 is present due to incorporation of very small amounts of Li_2O. With very low amounts of Li_2O (1 Li_2O : 15–20 U_2O_5), the lines of the hexagonal modification diverge in the direction of the lines of the orthorhombic α-U_3O_8 modification, and at the same time $UO_{2.25}$ lines make their appearance in the X-ray photograph.

The compounds $MgO \cdot U_2O_5$ and $CdO \cdot U_2O_5$ crystallize in a fluorite-type lattice with statistical distribution of the cations $(Me^{2+}_{0.33}U^{5+}_{0.67})O_2$. The cadmium compound reacts with additional CdO to give a rhombohedral phase, the upper phase limit of which lies near 2 $CdO \cdot U_2O_5$.

No 1 : 1 compound appears in the system $PbO-U_2O_5$. On the other hand, two phases richer in PbO exist; a cubic phase, whose homogeneity range extends from approximately 1.6 $PbO \cdot U_2O_5$ to 2.25 $PbO \cdot U_2O_5$, and a rhombohedral phase with the approximate composition 2.5 $PbO \cdot U_2O_5$.

Received, March 7th. 1962 [Z 229/62 IE]

[*] Dedicated to Prof. Dr. *G. Wittig* on his 65th. birthday.

[1] 1st. Communication: *W. Rüdorff* and *H. Leutner*, Z. anorg. allg. Chem. *292*, 193 (1957).

[2] *R. Scholder*, Angew. Chem. *72*, 120 (1960).

[3] *S. Siegel*, Acta Crystallogr. *8*, 617 (1955).

[4] *H. R. Hoekstra* and *S. Siegel*, J. inorg. nucl. Chem. *18*, 154 (1961).

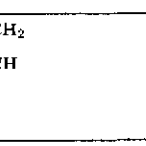
The Catalytic Activity of Thiourea and Thiourea Analogues in the Rearrangement of Maleic Acid to Fumaric Acid

By Dr. W. Schliesser

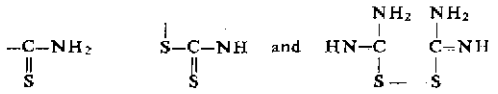
Badische Anilin- & Soda-Fabrik, Ludwigshafen/Rh. (Germany) [*]

In 1938, *K. Huttner* [1] observed the rearrangement of maleic acid to fumaric acid in the presence of thiourea. A few patents [2] have also dealt with this technically useful isomerization. The organic sulfur- and nitrogen-containing catalysts for the rearrangement are derived from the tautomeric forms of thiourea.

(I) $H_2N-C(=S)-NH_2 \rightleftharpoons HN=C(-SH)-NH_2$

	Compound	Conc. (rel. to maleic acid) %	Yield fumaric acid %
1	$H_2N-C(=S)-NH_2$	1.86	89
2	$H_2N-NH-C(=S)-NH_2$	2	17.3
3	$H_2N-C(=S)-NH-NH-C(=S)-NH_2$	3.45	14.7
4	$H_2N-C(=S)-NH-CH_2-CH=CH_2$	2	79
5		2	66.5
6	$H_2N-C(-S-COCH_3)=NH$	1.86	72.6
7	$H_2N-C(-S-C(OH)(CH_3)_2)=NH$	1.86	83.3
8	$HN=C(-S-CH_3)-NH_2 \cdot H_2SO_4$	2	–
9	$HN=C(-S-(CH_2)_2-COOH)-NH_2 \cdot HCl$	2	–

They are, for instance, the thiocarbamides, mercaptothiazolines, and formamidine disulfide with their characteristic groupings:



In connection with the preparation of fumaric acid, we investigated thiourea [2], thiourea analogs [2], and isothiourea derivatives with respect to their catalytic behavior toward maleic acid during the *cis-trans* isomerization in aqueous solution.

The results, summarized in the Table show clearly the influence of the equilibrium, shifted forward in the manner of (I) [3,4], as a necessary first step for the formation of a reactive site on the second $-NH_2$ group which does not take part in the tautomerism. No *cis-trans* rearrangement is observed in extreme cases as with compounds 8 (sulfate) and 9 (hydrochloride) where, besides a fixed –C–S–C bond, the $-NH_2$ group is additionally involved in salt formation [5].

Received, March 10th. 1962 [Z 256/92 IE]

[*] Dedicated to Prof. Dr. *G. Wittig* on his 65th birthday.

[1] IG-Farbenindustrie AG, Ludwigshafen/Rh., unpublished.

[2] Wingfoot Corp., US 2414066 (1943); Chem. Abstr. 1947, 2437. US Rubber Corp., US 2454385/87 (1946); Chem. Abstr. 1949, 1798. Allied Chemical & Dye Corp., US 2483576 (1947); Chem. Abstr. 2553 (1950); US 2548687 (1947); Chem. Abstr. 8552 (1951).

[3] *H. Lechner* and *C. Heuck*, Liebigs Ann. Chem. *438*, 169 (1924); *445*, 77 (1925). *L. Ebert*, Chem. Ber. *64*, 679 (1931). *A. Clow*, Trans. Faraday Soc. *34*, 459 (1938). *J. E. Stewart*, J.chem. Physics *26*, 249 (1957).

[4] Compare *D. Schulte-Frohlinde*, Liebigs Ann. Chem. *612*, 131 (1958).

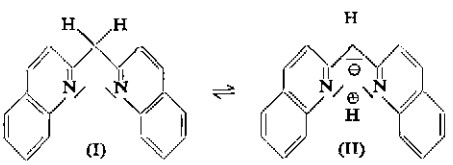
[5] Rearrangements at 50 °C with 30–31 % maleic acid solutions; reaction time 2 hours.

Alkali Compounds of Di(2-quinolyl)methane: Chelation Complexes with Di(2-quinolyl)methane[1]

By Dr. H. J. Friedrich and Dipl.-Phys. G. Hohlneicher

Physikalisch-Chemisches Institut der Technischen Hochschule München (Germany)

Di(2-quinolyl)methane occurs in the colourless form (I) and as the tautomeric, red, hydrogen-bridged chelate (II) [2].



Salts of Zn^{2+}, Co^{2+} or Be^{2+} can be incorporated into (II) instead of the proton [3].

Both the base and the complexes enter into prototropic equilibria in solution. If the proton in (II) is substituted by alkali ions, the pure, red form corresponding to (II) is obtained. The alkali compounds are deep-red, extremely sensitive to hydrolysis and possess characteristic absorption spectra [3] (see table).

The long-wave absorption bands are bathochromically displaced with increasing size of the alkali-metal ion. Accordingly, the metal ion must stand in a close inter-relation with the anion and, as the proton in (II), must be localised between the N-atoms ("metal-bridge bonding").

The di(*cis*)-configuration can be deduced from the oscillation intensity of the colour bands [4].

If the positions of the absorption maxima are plotted against the ionic radii of the alkali ions, a straight line is obtained and,

assuming that the relationship may be linearly extrapolated, the radius of the proton in (II) is almost zero. The correlation between the location of the absorption band and the ionic radius of the central ion points to a steric effect. We assume that the molecule is spread in the plane so that the valency angle at the *meso* C-atom becomes larger than normal.

An analogous situation exists in the case of aza-compounds, in which the *meso*-methine group is substituted by a trigonal N-atom.

	Ionic radius [Å]	$\tilde{\nu}_{max}$ [cm^{-1}] in dioxane	λ_{max} [mμ] in dioxane
$H^{\oplus}$	–	19600	510
$Li^{\oplus}$	0.60	18900	530
$Na^{\oplus}$	0.95	18400	543
$K^{\oplus}$	1.33	17900	558
$Cs^{\oplus}$	1.69	17500	572

Received, March 14th. 1962 [Z 265/91 IE]

[1] 3rd. Communication. – 2nd. Communication: *G. Scheibe* et al., Angew. Chem. *73*, 273 (1961).

[2] *G. Scheibe* and *W. Riess*, Chem. Ber. *92*, 2189 (1959).

[3] *G. Scheibe* and *H. J. Friedrich*, Z. Elektrochem. *64*, 720 (1960); *65*, 851 (1961).

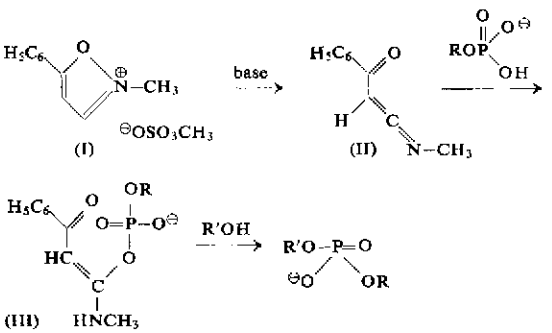
[4] *G. Scheibe*, Angew. Chem. *73*, 383 (1961).

New Phosphorylation Reactions and Protecting Groups for Nucleotides

By Prof. Dr. F. Cramer, Dipl.-Chem. H. Neunhoeffer, Dipl.-Chem. K. H. Scheit, cand. ing. G. Schneider, and cand. ing. J. Tennigkeit [*]

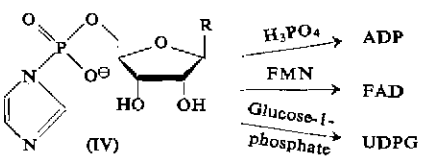
Institut für Organische Chemie
der Technischen Hochschule Darmstadt (Germany)

N-Methyl-5-phenylisoxazolium methyl sulphate (I) [1] in the presence of a base yields compound (II), which combines with phosphoric acid to form (III), an excellent phosphorylating agent of the enol-phosphate type.



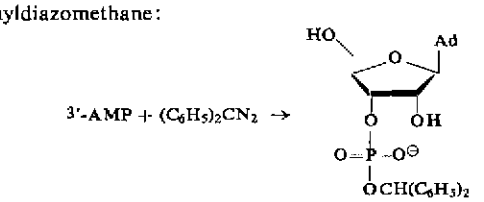
The following compounds were prepared: methyl phenyl phosphate (89% yield), ethyl phenyl phosphate (70%), isopropyl phenyl phosphate (73%), benzyl phenyl phosphate (81%). The reaction can also be applied to the synthesis of nucleotide esters and hence to oligonucleotide synthesis.

Nucleotide imidazolides [2] are starting materials for the synthesis of nucleotide derivatives. AMP imidazolide (IV, R = adenine) reacts with orthophosphate to give ADP (95%) and with flavin mononucleotide to give flavin adenine dinucleotide, FAD (67%). UMP imidazolide (IV, R = uracil) with glucose-1-phosphate yields the coenzyme uridine diphosphoglucose UDPG (67%). IMP imidazolide leads to the corresponding thymidine diphosphoglucose (70%).



The t-butyl group was introduced as a new protecting group for phosphoric acid in nucleotides. t-Butyl nucleotides are obtainable by the trichloroacetonitrile method [3], *e.g.* the t-butyl esters of 5′-AMP (60% yield) and of 3′-thymidylic acid (75%). The protecting group can be removed with 20% acetic acid in 45 min at 60 °C.

Nucleotides protected by other means were obtained in 60% yields by the reaction of 3′-adenylic acid or 3′-uridylic acid with diphenyldiazomethane:



Received, March 27th. 1962 [Z 270/102 IE]

[*] From a paper delivered to the Basler Chemische Gesellschaft (Basle Chemical Society) on Dec. 21st. 1962.

[1] *R. B. Woodward* and *R. A. Olofson*, J. Amer. chem. Soc. *83*, 1010 (1961).

[2] *F. Cramer, H. Schaller*, and *H. A. Staab*, Chem. Ber. *94*, 1612 (1961).

[3] *F. Cramer* and *G. Weimann*, Chem. Ber. *94*, 996 (1961).

New Syntheses of 2,4-Disubstituted s-Triazines

By Prof. Dr. H. Bredereck, Dr. F. Effenberger, and Dipl.-Chem. A. E. Hofmann

Institut für Organische Chemie und Organisch-Chemische Technologie, Technische Hochschule, Stuttgart (Germany)

With the syntheses of s-triazine and *N*-substituted s-triazines [1], we have also described the preparation of 2,4-diamino-s-triazine from guanidine carbonate and formamide. We have now succeeded in obtaining, in good yields, numerous 2,4-disubstituted triazines by reacting urea, guanidine, suhstituted guanidines, benzamidine, and *S*-methylisothiourea with formylating agents (trisformaminomethane, orthoformic ester, dimethylformamide diethylacetal).

Heating urea with trisformaminomethane or orthoformic ester led to 2,4-dihydroxy-s-triazine, which until now has been very difficult to prepare [2]. Guanidine formed 2,4-diamino-s-triazine with dimethylformamide diethylacetal; likewise, butylguanidine gave 2,4-bisbutylamino-s-triazine, phenylguanidine gave 2,4-dianilino-s-triazine, and *p*-tolylguanidine formed 2,4-di-*p*-toluidino-s-triazine.

The reaction of benzamidine with ethyl formate or dimethylformamide diethylacetal yielded 2,4-diphenyl-s-triazine. Finally, 2-methylmercapto-4-amino-s-triazine, a compound which we have previously reported, was obtained by heating *S*-methylisothiourea with dimethylformamide diethylacetal.

Received, April 2nd. 1962 [Z 260/95 IE]

[1] *H. Bredereck, O. Smerz*, and *R. Gompper*, Chem. Ber. *94*, 1883 (1961).

[2] *I. Flament, R. Promel*, and *R. H. Martin*, Helv. chim. Acta *42*, 487 (1959); *H. Biltz* and *E. Gieseler*, Ber. dtsch. chem. Ges. *46*, 3410 (1913).

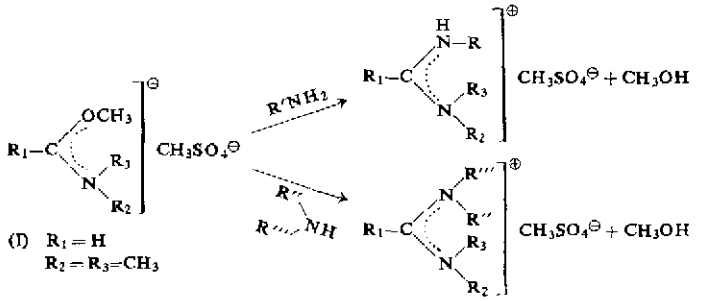
Synthesis of N,N,N′-Trisubstituted Amidines, Quaternary Amidinium Salts and Aminal Esters

By Prof. Dr. H. Bredereck, Dr. F. Effenberger, and Dipl.-Chem. G. Simchen

Institut für Organische Chemie und Organisch-Chemische Technologie, Technische Hochschule, Stuttgart (Germany)

Complexes of *N,N*-disubstituted acid amides with dialkyl sulfates [1] can, under mild conditions, be converted to *N,N,N′*-trisubstituted amidinium salts [2] by reaction with primary

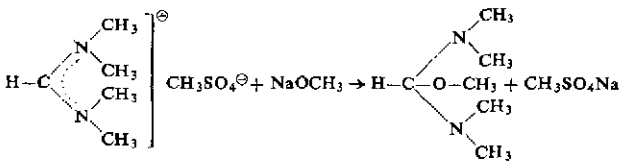
amines, and to quaternary amidinium salts [3–6] by reaction with secondary amines.



(I) $R_1 = H$, $R_2 = R_3 = CH_3$

Thus, compound (I) with methylamine gave *N,N,N'*-trimethylformamidinium methyl sulfate (90 % yield), from which the hitherto unknown, free trimethylformamidine (b.p. 108 °C/740 mm.; $n_D^{20} = 1.4490$) can be obtained in good yields.

Compound (I) and dimethylamine form *N,N,N',N'*-tetramethylformamidinium methyl sulfate (94 % yield). Using sodium methylate, this compound can be converted in equally good yields into the highly reactive bis(dimethylamino)-methoxymethane (b.p. 128 °C; $n_D^{20} = 1.4158$), which is an aminal ester [5].



These reactions also take place with dialkyl sulfate complexes of higher acid amides, as well as with other amines.

Received, April 2nd, 1962 [Z 259/94 IE]

[1] *H. Bredereck, F. Effenberger,* and *G. Simchen,* Angew. Chem. *73,* 493 (1961).

[2] *H. Bredereck, R. Gompper, K. Klemm,* and *H. Rempfer,* Chem. Ber. *92,* 837 (1959).

[3] *Z. Arnold,* Coll. czech. chem. Commun. *24,* 760 (1959).

[4] *Z. Arnold* and *F. Sorm,* Coll. czech. chem. Commun. *23,* 452 (1958).

[5] *D. H. Clemens* and *W. D. Emmons,* J. Amer. chem. Soc. *83,* 2588 (1961).

[6] *H. Böhme* and *F. Soldan,* Chem. Ber. *94,* 3109 (1961).

Anisotropy of the Triplet-Singlet Phosphorescence of Aromatic Compounds

By Priv.-Doz. Dr. F. Dörr and Dipl.-Chem. H. Gropper

Physikalisch-chemisches Institut der Technischen Hochschule München (Germany)

It is found that the oscillators responsible for phosphorescence in dyes do not lie in the same plane as the absorption and fluorescence oscillators.

While the phosphorescence spectra of numerous compounds have been accurately investigated, little has been known up to the present time concerning polarization of this luminescence in dyes [1,2], phenanthrene and naphthalene [3], and dibenzoylmethane [4] complexes. We used a well-known method [5,6] for the determination of the relative positions of the electron oscillators for the investigation the phosphorescence polarization of aromatic compounds. Frozen solutions of phenanthrene, 5,6-benzoquinoline, 7,8-benzoquinoline, *o*-, *m*-, *p*-phenanthroline, benzoquinoxaline, triphenylene, coronene, and quinoline were investigated (10^{-4} to 10^{-3} M in ethanol, temperature approximately 105 °K). They were excited to luminescence by linearly polarized light in the different absorption bands. Then the relative degree of polarization of the phosphorescence was measured and compared with that of the fluorescence. In the same way, the polarization of the spectrally resolved luminescence was determined at constant excitation wavelength as a function of wavelength. The apparatus will be described in greater detail in the Zeitschrift für Angewandte Physik.

The phosphorescence of phenanthrene and its derivatives, of triphenylene, and of coronene is strongly negatively polarized for all absorption bands. The numerical value of the degree of polarization is only slightly dependent upon the particular compound and upon the conditions of measurement; it lies between − 0.15 and − 0.20. For quinoline, the value is only − 0.08 and at higher concentrations it approaches zero. The degree of polarization of the phosphorescence is for all the compounds investigated independent of the absorption wavelength and almost constant.

The curve for the degree of polarization of the spectrally resolved phosphorescence shows that the O-O-transitions of the phosphorescence are negatively polarized with respect to the O-O-transitions in the long-wave absorption band. No essential change is introduced into the degree of polarization by superposition of vibration bands.

The results indicate that, for the substances investigated so far, the electron oscillators of triplet-singlet phosphorescence are nearly perpendicular to the oscillators of the singlet system. Since the latter, from all the evidence gathered so far, lie in the plane of the molecule, it follows that the triplet-singlet phosphorescence of these compounds is polarized perpendicular to the molecular plane. It has been shown by *Weissman* [6] that dipole transitions are involved.

Further investigations are being made to elucidate these findings.

Received, April 6th 1962 [Z 261/98 IE]

[1] *Th. Förster:* Fluoreszenz organischer Verbindungen. Vandenhoeck und Rupprecht, Göttingen 1951.

[2] *V. A. Pilipovich,* Opt. and Spectr. *10,* 104 (1961).

[3] *R. Williams,* J. chem. Physics *30,* 319 (1961).

[4] *S. J. Weissman,* J. chem. Physics *8,* 1258 (1950).

[5] *F. Dörr* and *M. Held,* Angew. Chem. *72,* 287 (1960).

[6] *S. Freed* and *S. J. Weissman,* Physic. Review *60,* 440 (1941).

Pyrroline by the 1.4-Addition of Imene to Butadiene [*]

By Prof. Dr. R. Appel and Dr. O. Büchner

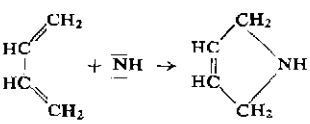
Anorganisch-Chemisches Institut der Universität Heidelberg (Germany)

A recent report by *V. Franzen* [1] on the 1,4-addition of methylene to butadiene prompts us to communicate results that we obtained in 1960 [2] on the 1,4-addition of imene [3] to butadiene. The former is isolectronic with methylene. Hydroxylamine-*O*-sulphonic acid was treated with sodium methylate in methanol into which butadiene had previously been passed over a long period of time. On working-up by steam and fractional distillation, a small amount of distillate coming over in the range 65–93 °C, and consisting principally of methanol and a little pyrroline was obtained. The pyrroline was identified by gas chromatography through comparison with an authentic sample prepared by reduction of pyrrole.

We assume that the imene, formed according to equation (1),

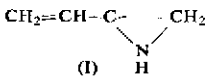
$$H_2N{-}O{-}SO_3^{\ominus} \xrightarrow[-CH_3OH]{+CH_3O^{\ominus}} \overline{\underline{N}}H + SO_4^{2-} \qquad (1)$$

reacts directly with butadiene (equation 2) in a 1,4-addition.



(2)

Whether or not the imene acts as a diradical, or as an electrophilic agent, cannot yet be decided [4]. It is unlikely that pyrroline formation occurs through the isomerisation of a vinylethylene imine (I) formed by 1,2-addition since we have



(I)

never found aziridines in the reaction of olefines with the imene produced according to equation (1); on the contrary, hydrogenation alone is always observed [5]. The 1,4-addition that we have noted is a further important argument for the appearance of the imene as an intermediate in the alkaline break-down of hydroxylamine-*O*-sulphonic acid and chloramine [4].

Received, April 6th. 1962 [Z 255/74 IE]

[*] Dedicated to Prof. Dr. *G. Wittig* on the occasion of his 65th birthday.

[1] *V. Franzen*, Chem. Ber. *95*, 571 (1962).

[2] *O. Büchner*, Diploma Thesis, Universität Heidelberg (1960).

[3] According to nomenclature proposals by *A. Lüttringhaus, J. Jander*, and *R. Schneider*, Chem. Ber. *92*, 1756 (1959), the name "imene" (Imen) for NH should be applied in place of "imine" (Imin) (German nomenclature in brackets).

[4] See also: *R. Appel* and *W. Büchner*, Liebigs Ann. Chem., in press.

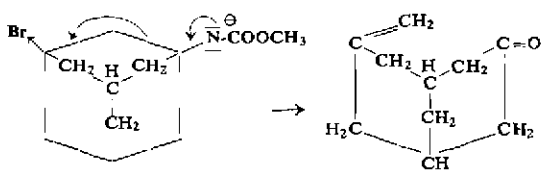
[5] *O. Büchner*, Ph. D. Thesis, Universität Heidelberg (1962).

A Fragmentation Reaction in the Adamantane Series

By Prof. Dr. H. Stetter and Dipl.-Chem. P. Tacke

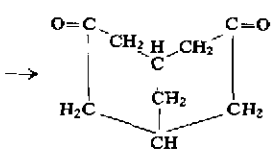
Institut für Organische Chemie, Technische Hochschule, Aachen (Germany)

3-Bromoadamantane-1-carboxylic acid [1], which is easily obtained by direct bromination of adamantane-1-carboxylic acid, was converted to the amide by way of its acid chloride. Hofmann degradation yields *N*-[3-bromo-1-adamantyl]-methylurethane (I), which on alkali treatment undergoes fragmentation, whereby 3-methylenebicyclo[1,3,3]nonan-7-one (II) is formed in high yield. Ozonolysis gives the previously unknown bicyclo[1,3,3]nonane-3,7-dione (III), which on Wolff-Kishner reduction gives rise to bicyclo[1,3,3]nonane.

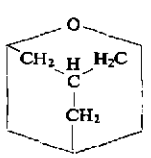


I m.p. 80—81 °C

II m.p. 160 °C



III m.p. 249 °C, decomp.



IV m.p. 225 °C

On reducing (III) with lithium aluminum hydride, bicyclo-[1,3,3]nonane-3,7-diol (m.p. 231—234 °C) was isolated as an isomeric mixture. Analogous to the preparation of 6,6-dimethyl-2-oxa-adamantane [2], treatment with sulfuric acid gave the hitherto unknown cyclic ether, 2-oxa-adamantane (IV). On condensation with nitromethane [2] compound (III) gives 1,3-dihydroxy-2-nitroadamantane (m.p. 167 °C).

Received, April 11th. 1962 [Z 262/90 IE]

[1] *H. Stetter* and *J. Mayer*, Chem. Ber. *95*, 667 (1962).

[2] *H. Stetter* and *J. Mayer*, Angew. Chem. *71*, 430 (1959); Chem. Ber. *92*, 2664 (1959).

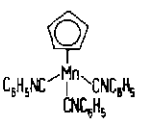
Isonitrile Complexes of Manganese, Iron and Nickel

By Prof. Dr. P. L. Pauson and Dr. W. H. Stubbs

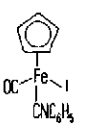
Department of Chemistry, The Royal College of Science and Technology, Glasgow (Scotland)

Despite the widespread current interest in both hydrocarbon [1] and isonitrile derivatives [2] of transition metals, no complexes have been described which contain both types of group. We now report cyclopentadienyl metal isonitriles of manganese, iron and nickel, analogous to the corresponding hydrocarbon metal carbonyls.

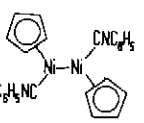
Tris(phenyl isocyanide) cyclopentadienylmanganese (I) was obtained in 20% yield as yellow crystals, m.p. 97 °C (from pentane), when a solution of hexakis(phenyl isocyanide)manganese iodide in dimethylformamide was added to cyclopentadienylsodium in tetrahydrofuran.



(I)



(II)



(III)

The iron complex (II) was formed by direct displacement of one molecule of carbon monoxide when dicarbonylcyclopentadienyliron iodide was treated with phenyl isocyanide in tetrahydrofuran solution. This behaviour contrasts with the reaction of the corresponding chloride with triphenylphosphine, whereby the halide ion is displaced rather than a carbonyl group [3]. The product (II) was isolated by chromatography and formed black crystals m.p. 89 °C, from methylene chloride and ligroin; $\nu_{max.}$ in the CNR and CO stretching region: 2137 cm^{-1}, 2058 cm^{-1} and 2000 cm^{-1}.

Like carbon monoxide, phenyl isocyanide displaces both cyclopentadienyl groups from dicyclopentadienylnickel, but the desired mixed-complex was formed (again by analogy to the corresponding carbonyl [4]) when dicyclopentadienylnickel and tetrakis(phenyl isocyanide)nickel were allowed to react together in refluxing benzene. The product, deep red plates, m.p. 91 °C (from pentane), shows a single band at 2174 cm^{-1}, *i.e.* the normal region for isonitrile groupings bonded to single metal atoms [1,5]. No isonitrile-bridged complexes appear to be known, but they would be expected to absorb at lower frequency. The nickel complex is, therefore, formulated as having structure (III), whereas its carbonyl analogue has two bridging CO groups.

Received, April 16th. 1962 [277/106 IE]

[1] *H. Zeiss:* Organometallic Chemistry. Reinhold, New York 1960.

[2] *L. Malatesta* in *F. A. Cotton:* Progress in Inorganic Chemistry. Interscience, New York 1959, Vol. I, p. 283.

[3] *A. Davison, M. L. H. Green* and *G. Wilkinson*, J. chem. Soc. (London) 3172 (1961).

[4] *E. O. Fischer* and *C. Palm*, Chem. Ber. *91*, 1725 (1958).

[5] *F. A. Cotton* and *R. V. Parish*, J. chem. Soc. (London) 1440 (1960); *F. A. Cotton* and *F. Zingales*, J. Amer. chem. Soc. *83*, 351 (1961).

Carbon-Free Metal Chelate Rings Containing Boron

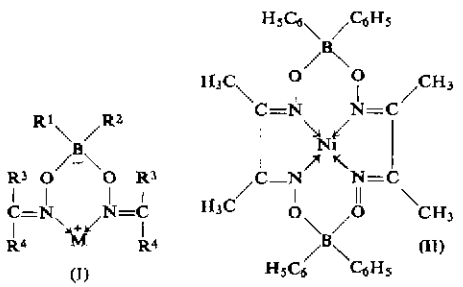
By Priv.-Doz. Dr. F. Umland and Dipl.-Chem. D. Thierig

Institut für Anorganische Chemie, Technische Hochschule Hannover (Germany)

Chelate rings with the basic structure (I) are obtained by the reaction of borinic acid esters or anhydrides with certain metal salts and oximes [1].

Example: An aqueous solution of a nickel salt, amyl alcohol, and methanolic solutions of dimethylglyoxime and of

Flavognost® [diphenylborinic acid aminoethyl ester complex (Heyl and Co., Hildesheim, West Germany)] are mixed in the volume ratio 1:3:1:1, and the mixture is boiled for 1 to 2 minutes. A yellow solution of (II) results. The reaction can be carried out on a microanalytical scale. On a preparative scale, it is better to fuse nickel dimethylglyoximate with excess Flavognost for a short time at approximately 200 °C. Compound (II) is then extracted from the solidified melt with benzene and, for further purification, recrystallized from a methanol-chloroform mixture. Depending on the proportions of this mixture, fine yellow-orange needles or coarse red-orange rods are obtained. Compound (II) is readily soluble in non-polar solvents, sparingly soluble in polar solvents, and insoluble in water. Even in the presence of wetting agents it is not perceptibly saponified by hot water. After



(I) (II)

M = metal
R^1, R^2 = aryl, halogen (F, Cl)
R^3, R^4 = alkyl, aryl

dissolving (II) in concentrated sulfuric acid, followed by neutralization, nickel dimethylglyoximate is regenerated. On heating to 305–310 °C, the compound turns dark and decomposes.

The corresponding olive-green palladium chelate, the violet copper(II) chelate, and the reddish iron(II) chelate are obtained similarly.

Received, April 16th. 1962 [Z 264/103 IE]

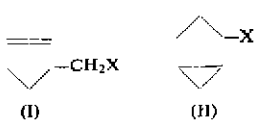
[1] *G. N. Schrauzer* has prepared similar compounds (personal communication; Chem. Ber. in the press).

Rearrangements of Δ^2-Cyclopentenylmethane Derivatives

By Priv.-Doz. Dr. M. Hanack
and cand. chem. H. J. Schneider

Pharmazeutisch-chemisches Institut
der Universität Tübingen (Germany)

As a result of homoallyl resonance, Δ^2 cyclopentenylmethylamine (I; X = NH_2) forms a three-membered ring on reaction with HNO_2 (in 10% acetic acid, 60 °C, 5 hrs.). A mixture composed of the stereoisomers (58%) of bicyclo[3,1,0]-hexan-2-ol (II; X = OH), 12% Δ^2-cyclopentenylmethanol (I; X = OH) and 12% Δ^3-cyclohexenol is obtained alongside the acetates (18%). The nuclear magnetic resonance spectrum of (II) shows a three-membered ring; the infrared spectra of the alcohols separated by preparative gas chromatography are identical with independent preparations [1].



(I) (II)

For the preparation of (I; X = NH_2), Δ^2-cyclopentenyl chloride (in aqueous acetone) is allowed to react with KCN [2] and, after removal of Δ^2-cyclopentenol (*ca.* 20%), the Δ^2-cyclopentenyl nitrile (yield 50%; b.p. 55–57 °C/12 mm.) is reduced with $LiAlH_4$ to give the required product in 50% yield (b.p. 48–50 °C/12 mm.). The amine is pure by gas chromatography. Benzoyl compound, m. p. 120–104°C.

Tosylated Δ^2-cyclopentenylmethanol (I; X = OTs), m.p. 3–4 °C, likewise reacts to form a three-membered ring through solvolysis in abs. methanol with the addition of $CaCO_3$. A mixture of the stereoisomers of methyl bicyclo-[3,1,0]hex-2-yl ether (II; X = OCH_3), b.p. 60 °C/50 mm., is formed in 80% yield, alongside other products.

Δ^2-Cyclopentenylmethanol (I; X = OH) was prepared both by reaction of Δ^2-cyclopentenyl chloride with Mg and paraformaldehyde (yield 20%, b.p. 50–51 °C/12 mm., alongside 50% hydrocarbon), and through reduction of ethyl Δ^2-cyclopentenylcarboxylate (I; X = $CO_2C_2H_5$) with $LiAlH_4$. The ethyl ester (I; X = $CO_2C_2H_5$) is accessible from the nitrile (I; X = CN) *via* the iminoether chloride.

Received, April 19th, 1962 [Z 271/100 IE]

[1] *M. Hanack* and *H. Allmendinger*, unpublished results.

[2] Cf. *N. P. Buu-Hoi* and *P. Caignant*, Bull. Soc. chim. France *12*, 978 (1945).

Dialkylaminoisocyanides

By Prof. Dr. H. Bredereck, Dr. B. Föhlisch
and cand. chem. K. Walz

Institut für Organische Chemie and Organisch-Chemische Technologie der Technischen Hochschule Stuttgart (Germany)

In the course of our investigations on acid amide-acid chloride complexes, we have synthesised representatives of the previously unknown dialkylaminoisocyanides (II). The action of phosgene on an ice-cooled solution of *N,N*-disubstituted formylhydrazine (I) in methylene chloride and in the presence of a tertiary amine, preferably trimethylamine, leads to the formation of dialkylaminoisocyanides (II; R = C_2H_5, b.p. 39 °C/16 mm.; R = n-C_4H_9, b.p. 42 °C/0.1 mm.).

$$\underset{\text{(I)}}{R_2N{-}NH{-}CHO} + COCl_2 + 2\,(CH_3)_3N \rightarrow \underset{\text{(II)}}{R_2N{-}\overset{\oplus}{N}{\equiv}\overset{\ominus}{C}} + CO_2 + 2\,(CH_3)_3N{\cdot}HCl$$

Dialkylaminoisocyanides – which can formally be considered as dialkylamides of fulminic acid – are highly reactive, unstable, evil-smelling liquids. If a solution of formic acid in ethyl acetate is added, compound (I) is re-formed with evolution of carbon monoxide. The infrared spectra of (II) show a characteristic band at 2100 cm^{-1}.

Received, April 24th. 1962 [Z 269/99 IE]

Stereospecific Formation of Cyclopropanes by Reaction of Diphenyldibromomethane with Methyllithium and Olefins

By Prof. Dr. Gerhard L. Closs and Dr. Liselotte E. Closs [*]

Department of Chemistry, The University of Chicago, Chicago, Illinois (USA)

According to *Skell* et al. [1], the photolysis of diphenyldiazomethane leads to a carbene whose addition to olefins is not stereospecific [2]. Accordingly, a triplet ground-state was ascribed to diphenylmethylene.

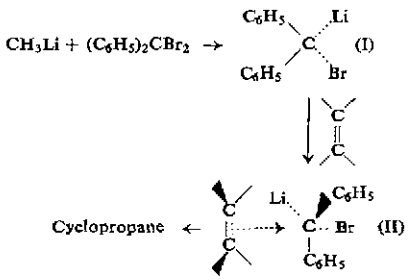
While investigating the reactivity of carbenes as a function of their method of preparation, it was of interest to prepare diphenylcarbene by another route.

Reaction of diphenyldibromomethane with methyllithium at –10 °C in the presence of olefins [3] leads to 1,1-diphenylcyclopropane in moderate yields (10–15%), alongside larger amounts of tetraphenylethylene.

Mixtures resulting from reaction with *trans*- and *cis*-but-2-enes were analysed by gas chromatography; this showed that the additions are completely stereospecific. Both isomers of 1,1-diphenyl-2,3-dimethylcyclopropane were characterised

through their infrared and nuclear magnetic resonance spectra. A further difference between these reactions and the photolysis of diphenyldiazomethane is that diphenylmethyl-substituted olefins and tetraphenylethane cannot be detected. The latter compounds arise during photolysis of the diazo-compound through hydrogen transfer from the allyl position of the olefin to the triplet methylene followed by combination of the resultant, resonance-stabilised radicals [4, 5].

These findings show unequivocally that photolysis of diphenyldiazomethane and the splitting-off of lithium bromide from the corresponding halogeno compound do not proceed *via* the same intermediate. They are comprehensible if it is assumed that complex formation with lithium bromide leads to an energy poor "carbenoid" molecule (I).



Hence, the transition state in the reaction of (I) with olefins can be formulated as (II) in analogy with a nucleophilic substitution (S_N2) [6].

Received, April 30th. 1962 [Z 266/93 IE]

[*] Dedicated to Prof. Dr. *G. Wittig* on the occasion of his 65th birthday. — For financial support we gratefully acknowledge the Petroleum Research Fund, administered by the American Chemical Society.

[1] *R. M. Etter* et al., J. Amer. chem. Soc. *81*, 1008 (1959).

[2] Repitition of *Skells'* work [1] led only to qualitative agreement. In our laboratory the addition of diphenylmethylene to *trans*-but-2-ene was 96% stereospecific; to *cis*-but-2-en, 87%.

[3] For the application of the halogen-metal exchange method in carbene chemistry, see: *W. T. Millar Jr.* and *C. S. Y. Kim*, J. Amer. chem. Soc. *81*, 5008 (1959).

[4] Cf. *W. Kirmse, L. Horner*, and *H. Hoffmann*, Liebigs Ann. Chem. *614*, 19 (1958).

[5] *G. L. Closs*, unpublished results.

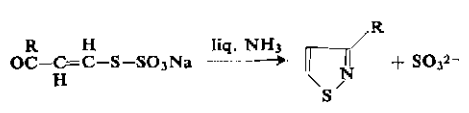
[6] A similar transition state has been proposed in the reaction of benzal bromide, alkyllithium and olefins: *G. L. Closs*, Carbene Symposium Washington, D. C., March 1962.

The Preparation of Isothiazole and 3-Methylisothiazole: A New Route in to the Isothiazole Series

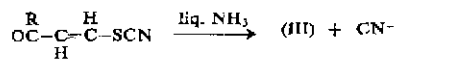
By Prof. Dr. F. Wille, Dipl.-Chem. L. Capeller, and A. Steiner

Institut für Anorganische Chemie
der Universität München (Germany)

If sodium acrolein 3-thiosulphate (I, R=H) or acrolein-3-thiocyanate are allowed to react with liquid ammonia, isothiazole (III, R=H) is formed in approximately 25 and 55% yield, respectively. Both reactions proceed with cleavage of sulfurous or hydrocyanic acid respectively.



(I) (III)



(II)

Correspondingly, 3-methylisothiazole (III, R=CH_3) can be obtained (in approx. 25% yield) either from but-1-en-3-one-1-thiosulphate (I, R=CH_3), or from the thiocyanate (II, R=CH_3). The starting materials (I) and (II) are prepared in good yields by the addition of sodium thiosulphate or thiocyanic acid to propynal or but-1-yn-3-one respectively. Isothiazole and 3-methylisothiazole were reported several years ago [1]. Both heterocyclics are now easily accessible by the route described above.

Received, April 24th. 1962 [Z 273/105 IE]

[1] *A. Adams* and *R. Slack*, Chem. and Ind. 1232 (1956); J. chem. Soc. (London) 3061 (1959).

Preparation and Properties of Triphenylsilylazide

By Dr. Nils Wiberg, cand. chem. F. Raschig and cand. chem. R. Sustmann

Institut für Anorganische Chemie
der Universität München (Germany)

The reaction of triphenylchlorosilane, Ph_3SiCl, with excess lithium azide in tetrahydrofuran leads to almost quantitative yields of triphenylsilylazide, Ph_3SiN_3 (I), after about 24 hrs. Long, well-crystallising, moisture-sensitive needles (m.p. 79–80 °C) are formed from petroleum ether. Correspondingly, trimethylsilylazide, Me_3SiN_3 [1], is also accessible[2]. Compound (I) is characterised by extreme thermal stability (even in the presence of Cu-powder). No nitrogen evolution was detected during long periods of heating at 400 °C. Slow decomposition takes place in benzene at 50°C in the presence of tripbenylphosphine according to the equation:



(II)

The loss of nitrogen does not follow first order kinetics.

(Triphenylsilyl)triphenylphosphine-imine (II), the first example of an *N*-silylated phosphine-imine, is obtained in well formed colourless rhombic crystals (m.p. 213–215 °C). It is soluble in tetrahydrofuran, insoluble in petroleum ether, benzene and ether.

Received, May 2nd. 1962 [Z 268/97 IE]

[1] Cf. *L. Birkhofer, A. Ritter*, and *P. Richter*, Angew. Chem. internat. Edit. *1*, 267 (1962).

[2] It was not possible to prepare organosilicon azides with more than one azide group using the method described above. However, we have recently succeeded in preparing pure diazidodiphenylsilane $Ph_2Si(N_3)_2$ by another route.

N-Methyl-N-tetrahydropyran-2-ylhydroxylamine: A Stable Hydroxylaminoacetal

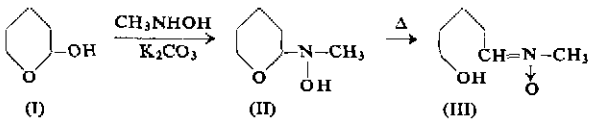
By Dr. H. Ulrich and Dr. A. A. Sayigh

The Carwin Co., North Haven, Conn. (USA)

Hydroxylaminoacetals are unstable compounds which readily isomerize to the stable oximes or nitrones. Although several hydroxylaminoacetals of formaldehyde are reported in the literature [1], hydroxylaminoacetals of the higher homologs are not known.

We obtained *N*-methyl-*N*-(tetrahydropyran-2-yl)hydroxylamine (II) (b.p. 110–113 °C/0.3 mm; n_D^{23} = 1.4882; yield: 75%) from 2-hydroxytetrahydropyran (I) and *N*-methylhydroxylamine in the presence of potassium carbonate. The infrared spectrum of (II) shows no absorption in the C=N region, the compound gives a positive hydroxylamine test with triphenyltetrazolium chloride [2], and silver halide is reduced in the cold.

The cyclic *N*-hydroxylaminoacetal of 5-hydroxypentanal (II) is remarkably stable. On standing for several months at room temperature no change could be observed. However, on



(I) (II) (III)

distillation *in vacuo* a considerable amount (*ca.* 40%) isomerized to the tautomeric *N*-oxide of 5-hydroxy-1-(*N*-methylimino)pentane (III) (b.p. 150 °C/0.3 mm.; $n_D^{23} = 1.4858$). The structure of (III) was elucidated by analysis and infrared spectroscopy (C=N: 6.0 μ; N → O: 6.6 μ). The physical data for (III) are in agreement with those of its higher homologs [3].

Received, May 10th. 1962 [Z 274/104 IE]

[1] *E. Bamberger*, Ber. dtsch. chem. Ges. *33*, 941 (1900); *H. Hellmann* and *K. Teichmann*, Chem. Ber. *89*, 1134 (1956).
[2] *G. A. Snow*, J. chem. Soc. (London) 2588 (1954).
[3] *A. A. Sayigh* and *H. Ulrich*, unpublished.

CONFERENCE REPORTS

Luminescence Amplification and Extinction by Electric Fields

H. E. Gumlich, Berlin-Dahlem (Germany) and Newark, Del. (USA)

The amplification and extinction of the luminescence of powdered manganese-activated ZnS- and ZnS–CdS phosphors by electric fields depends on the field strength, field frequency, intensity and wavelength of the exciting radiation, the emission wavelength, and the temperature. Of particular interest are phosphors whose luminescence can also be amplified by infrared and red light and those in which the number of radiationless electronic recombinations is increased by the additional inclusion of cobalt. An investigation of these phosphors reveals that the maximum amplification is produced by infrared and red light of wavelength 1350 and 770 mμ, respectively. The field amplification attains a maximum for field frequency between 10 and 100 cps. If the exciting radiation, the stimulating light and the electric field all act simultaneously on these phosphors, then the effect of the electric field and of the stimulating radiation is not equal to the sum of the individual effects, i.e. the infrared amplification and the field amplification are not independent of one another. The nature of the interaction depends on the field strength, the field frequency and the intensity of the stimulating radiation but not, however, on the cobalt content.

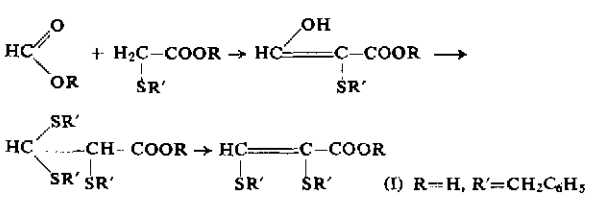
The cobalt content of the phosphor does have a marked effect on the field amplification. The luminescence amplification in its dependence on the cobalt content passes through a maximum: low cobalt concentrations cause an amplification greater than, and high cobalt concentrations cause an amplification smaller than is the case in the absence of cobalt. With a cobalt addition of 10^{-6} parts by weight and at low field frequencies, the electric field can effect an eighteenfold increase in luminescence. The luminescence amplification observed for powdered phosphors was compared with the field amplification effects measured in the red bands for CdS single crystals.

[GDCh-Ortsverband Berlin (Germany), February 20th. 1962] [VB 577/22 IE]

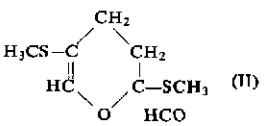
The Chemistry of Mercaptoacrylic Acid Derivatives

K.-D. Gundermann, Münster (Germany)

Following a survey of α- and β-alkylmercaptoacrylic acid derivatives [1] a new, generally applicable, method for the preparation of α,β-bis[alkylmercapto]acrylic acid derivatives was presented: Mercaptalization of formylalkylmercaptoacetate followed by removal of one mole of mercaptan from the mercaptals by means of $KHSO_4$ yields esters of α,β-bis-[alkylmercapto]acrylic acid.



The easily accessible α,β-bis-[benzylmercapto]acrylic acid (I) can then be converted to 1,4-dithi-2-ene-2-carboxylic acid as well as to the higher melting α,β-bis[methylmercapto]acrylic acid [2] by debenzylation with sodium or lithium in liquid ammonia and subsequent realkylation with 1,2-dichloroethane or methyl iodide. Thus their steric assignment is confirmed.



(II)

The relatively high dibenzyl formation of up to 50% of the theoretical amount, during the reductive debenzylation, also supports the *cis*-configuration of both benzylmercapto groups in (I); this is explained by the spatial proximity of the two benzylmercapto groups (fixation by the double bond). The characteristic dimerization tendency of α-alkylmercaptoacrylonitrile and ester is also found with α-alkylmercaptoacroleins; the α-methylmercaptoacrolein synthesized from thioglycidaldehyde diethylacetal [3] by way of β-diethylamino-α-mercaptopropionaldehyde diethyl acetal has, up to the present time, only been obtained as the semicarbazone of dimer (II).

The peculiar reactivity of α-alkylmercaptoacrylic acid derivatives is explained by the fact that thioether groups can act as electron donors as well as acceptors [4].

[GDCh-Ortsverband Ruhr, Mülheim/Ruhr (Germany), March 28th. 1962] [VB 578/29 IE]

[1] *K. D. Gundermann* and *R. Huchting*, Chem. Ber. *95*, 632 (1962) and earlier communications.
[2] *K. D. Gundermann* and *R. Thomas*, Chem. Ber. *91*, 1330 (1958).
[3] *J. B. Wright*, J. Amer. chem. Soc. *79*, 1694 (1957).
[4] *G. Cilento*, Chem. Reviews *60*, 147 (1960); *H. C. Volger* and *J. F. Arens*, Rec. trav. chim. Pays-Bas *77*, 1170 (1958).

Application of Electron Paramagnetic Resonance Spectroscopy in Studies on Oxidizing Enzymes

Helmut Beinert, Madison, Wisc. (USA)

Although electron resonances (EPR) spectroscopy has many potential applications in the study of biological problems. One of the most serious handicaps of the method is its relative insensitivity in aqueous media, owing to the strong background absorption of microwave energy by water. Nevertheless, recent experimental work has shown that in problems of enzyme chemistry, EPR spectroscopy may yield answers which cannot at present be obtained by other methods. Thus, for example, a new group of oxidation-reduction catalysts were discovered in beef heart mitochondria, that can only be recognized by their characteristic EPR signals [1]. Typical asymmetrie signals ($g_{||} = 2.00$, $g_{\perp} = 1.94$) are observed even with samples of freshly frozen whole heart or liver and are also

found in isolated mitochondria and submitochondrial particles obtained by sonic disintegration of mitochondria. The signals appear when the oxidation-reduction catalysts are in the reduced state and show some differences depending on the reducing substrate added. When a dehydrogenase specific for a particular substrate (*e.g.* succinate, DPNH) is isolated, the signal characteristic for reduction by this substrate is found in the isolated enzyme. Signals of the same general type have also been found in bacteria, in xanthine oxidase from milk, aldehyde oxidase from liver, and dihydroorotic dehydrogenase. The new catalysts are thought to be protein-bound iron complexes, which do not involve porphorin. Chemical and spectroscopic analyses exclude other metals. Direct evidence that iron is responsible for the signals was obtained in experiments with ^{57}Fe. Kinetic studies were carried out in which the redox state of the cytochrome components was assessed by optical reflectance spectroscopy on the same frozen samples, which were then subjected to EPR spectroscopy. Thus, the new catalysts and the cytochromes could be observed at the the same state by both methods. The rate of reduction and reoxidation of the new catalysts did not differ from that of the cytochromes. In addition, reduction of the copper of cytochrome oxidase could be observed under these conditions. It is possible to assess the state of the copper in this enzyme during isolation procedures. A change in the ligand environment of the copper is easily recognized. Quantitative evaluation of the spectra indicates that there may be a pair of vicinal copper atoms in cytochrome oxidase. The possibility of reaction of this pair of copper atoms with oxygen forms an attractive hypothesis. Experiments with dihydroorotic dehydrogenase – again applying combined optical and EPR spectroscopy – confirmed a previous suggestion [2] that semiquinoid forms of flavoproteins have absorption bands at about 600 mμ and that flavoproteins are not necessarily reduced to their leuco-forms by their substrates, but rather to the semiquinoid level only, so that during active catalysis one would expect turnover mainly between oxidized and semiquinoid forms.

[Max-Planck-Institut Heidelberg (Germany),
March 26th. 1962] [VB 579/28 IE]

[1] Cf. *H. Beinert* and *W. Lee*, Biochem. Biophys. Res. Commun. *5*, 40 (1961).

[2] *H. Beinert*, J. biol. Chemistry *225*, 465 (1957).

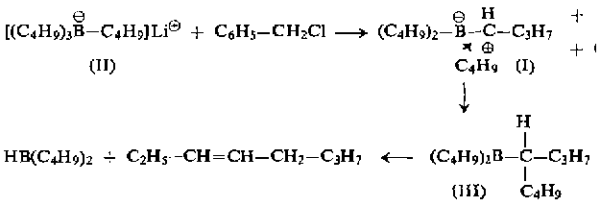
SELECTED ABSTRACTS

Stereospecific polymerization of isoprene with calcium-zinc alkyl and titanium salts was studied by *W. Marconi, A. Mazzei, S. Cucinella*, and *M. De Malde*. A polyisoprene with about 70 % 1,4-*trans*- and 22 % 3,4-linkages is obtained with the catalyst complex $(CaH_2)_x Ca(C_2H_5)_2{}_y Zn(C_2H_5)_2$, available from the reaction of metallic Ca with $Zn(C_2H_5)_2$. However, the reaction in benzene tends to be more stereospecific if small additions of $TiCl_4$ are made. The structure of the polymer depends to a large extent on the ratio (Ca + Zn)/Ti. At a ratio of 0.5 or less, one obtains primarily the 1,4-*trans* compound, while the 1,4-*cis* structure predominates at ratios between 0.6 and 0.9. A mixture of 1,4-*cis*-, 1,4-*trans*-, and 3,4-isomer is obtained only after a ratio of about 2 is reached. The activity of the catalytic system is affected by the ratio of Ca/Zn. The best results, with regard to yield and stereospecificity, are obtained with a Ca/Zn mole ratio between 0.3 and 1.88 and a (Ca + Zn)/Ti ratio between 0.6 and 0.9. / Chim. e Ind. *44*, 121 (1962). / —Pf. [Rd 129/53 IE]

Thin-layer chromatographic separation methods can be scaled up to column size by means of horizontal chromatography in cellophane tubing. *H. Dahn* and *H. Fuchs* pressed gypsum-free adsorbents suitable for thin-layer chromatography into a dialysis tube with the aid of a rod and carried out horizontal chromatography using a special flow tank. About 250–300 mg. of mixture can be separated on silica gel or aluminum oxide columns having a length of 40 to 45 cm. and a diameter of 3.6 cm. The zones representing different substances are observed in visible or ultraviolet light (to which the cellophane tubing is transparent), with addition of fluorescent substances to the column packing when necessary. If fluids of low volatility are used, R_F values obtained from the layers can be used directly in column calculations. The zones containing the substances may be separated simply by cutting the chromatogram. / Helv. chim. Acta *45*, 261 (1962) / —Ra. [Rd 92/44 IE]

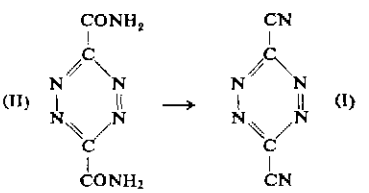
The synthesis of santene in a two-step reaction with an overall yield of 40 %, has been accomplished by *H. J. Ache*. In the first step, cyclopentadienylsodium was alkylated with methyl bromide in liquid ammonia. This reaction is applicable for the synthesis of mono- or di-substituted cyclopentadienes in general and gives excellent yields. Diels-Alder addition of eythlene to give santene (I) was achieved at 250 °C and 200 atm. The reaction product thus formed also contained methylnorcamphene (II) and its isomers, and was separated into its components by distillation using a spinning-band column. / Chem. Ber. *45*, 503 (1962) / —Re. [Rd 130/54 IE]

A **boron ylide (I)**, bearing a negative charge on the boron atom and a positive charge on the carbon atom, is postulated by *H. Jäger* and *G. Hesse* as an intermediate in the reaction between lithium tetrabutyl boron (II) and alkylating agents such as benzyl chloride:



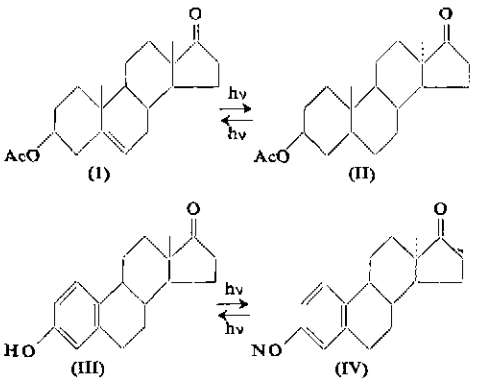
The existence of (I) as an intermediate is suggested especially by the formation of octene (51.3 % yield) which, in the opinion of the authors, is formed from (I) by anionotropic migration of a butyl group and subsequent elimination of $HB(C_4H_9)_2$ from di-(n-butyl)-4-octylboron (III). If the lithium tetrabutyl boron is oxidized before working up and the borate ester thus formed is hydrolyzed, a mixture of octanols containing predominantly octan-1-ol is obtained in 9 % yield. The rearrangement (I) → (III) is the counterpart of the Stevens rearrangement in the chemistry of the nitrogen ylides. / Chem. Ber. *95*, 345 (1962). / —Sk. [Rd 128/52 IE]

A new carbon-nitrogen compound, 3,6-dicyano-1,2,4,5-tetrazine, C_4N_6, has been synthesized by *E. Gryskiewicz-Trochimowski* and *M. Bousquet*. The compound (I) was obtained by dehydration of 1,2,4,5-tetrazinedicarbonamide (II) with P_2O_5 at 140–170 °C at 0.1 mm. Hg (Ar atmosphere), the reaction product subliming off (yield 12–18 %). The compound is



unstable and can be stored in Ar for a few hours only. It forms ruby-red prisms, which dissolve in organic solvents (with the exception of petroleum ether), yielding strongly colored solutions. Water and mineral acids decompose the compound, which rapidly splits off HCN and N_2. / Compt. Rend. hebd. Séances Acad. Sci. *253*, 2992 (1961). / —Ma. [Rd 134/58 IE]

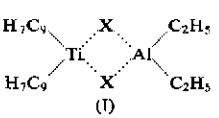
The reversibility of photoepimerization of 17-oxo steroids at C-13 was demonstrated by *H. Wehrli* and *K. Schäffner*. The isomeric 13α-compound (II), accessible photochemically from 3β-acetoxy-17-oxo-Δ^5-androstene (I), reverted in dioxan solution to (I) on irradiation with the full spectrum of high-pressure mercury-vapor lamp (Hanau Q 81, quartz vessel). The yield was low (about 7 % at 90 °C in 60 min.; about 2 % at 20 °C). The formation of lumiestrone (IV) from estrone



(III) was also shown to be reversible under identical conditions. Apart from amorphous decomposition products, only the unchanged 13α-ketones were recovered in both cases. In previous studies by *A. Butenandt*, lumiestrone was shown to be stable towards radiation of the 313 mμ Hg-line (absorption by the C=O group). / Helv. chim. Acta 45, 385 (1962). / —Ku. [Rd 131/55 IE]

Monofluoroacetylene (I) has been prepared by *H. G. Viehe* and *E. Franchimont* It is formed by bromine cleavage from 1-fluoro-1,2-dibromoethylene (80 % yield) or 1-fluoro-1,1,2,2-tetrabromoethane (60 % yield) with magnesium in tetrahydrofuran. The gas (b.p. −104 °C) is neither explosive nor self-igniting. Its reaction with triphenylphosphine in ether gives ethynyltriphenylphosphonium fluoride, $[(C_6H_5)_3P{-}C{\equiv}CH]^{\oplus}F^{\ominus}$, in 73 % yield. Only small amounts of butyl- or phenyl-acetylene are formed in the reaction of (I) with butyl- or phenyl-lithium. / Chem. Ber. *95*, 319 (1962). / —Re. [Rd 195/62 IE]

The synthesis of bisindenyl derivatives of titanium and their complexes with aluminium alkyls is reported by *W. Marconi*, *M. L. Santostasi*, and *M. De Maldè*. Bisindenyltitanium dihalides, $(C_9H_7)_2TiX_2$ (X = Cl, Br, I), are formed in ethereal solution by reaction of indenyl-lithium with titanium tetrahalides (molar ratios 2:1). The dark-green (Cl, Br) to brown-black (I) powders, which are crystallisable from toluene, are permanently stable under pure N_2 but are hydrolysed in a moist atmosphere. The rate of hydrolysis increases from the chlorine to the iodine compound. In suspension the dihalides react very rapidly with $Al(C_2H_5)_3$ (ratio Al/Ti = 2), even at room temperature, forming a clear-green solution from which green, needle-like, crystals may be separated by strong cooling. Analysis gives the formula $(C_9H_7)_2TiX_2Al(C_2H_5)_2$ (I). Magnetic measurements show that, in the complexes, the titanium is trivalent. These compounds are also permanently stable when fused in ampoules under dry., O_2-free nitrogen.



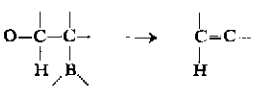
(I)

Probably, the Al and Ti atoms are bound through halogen-bridges. Chemically, and in their infrared spectra, the dihalides show a noticeable similarity with the corresponding cyclopentadienyl compounds. It seems very probable that a "sandwich" structure exists.

On addition of an excess of ether or trimethylamine to a solution of (I) in petroleum ether, red-brown crystals, crystallisable from toluene, appear. They analyse for $(C_9H_7)TiX$. / Chim. e Ind. *44*, 229 (1962). / —Pf. [Rd 197/64 IE]

The catalytic hydrogenation of organic compounds with pentacyanocobaltate(II) is possible. *J. Kwiatek*, *L. J. Mador*, and *J. K. Seyler* were able to reduce aliphatic dienes, conjugated aromatic olefins, α,β-unsaturated acids (in the form of esters or salts), aldehydes, 1,2-diketones, epoxides and azoxybenzenes in aqueous solution in the presence of this Co(II) co-ordination compound, $[Co^{III}(CN)_5H]^{3-}$, at room temperature and normal pressure. Water-insoluble substances were used either directly or dissolved in non-polar solvents such as benzene. Propionaldehyde yields the dimeric aldehyde, α-methyl valeraldehyde (*via* base-catalyzed aldole condensation). Hydrogen peroxide and a series of inorganic salts were also reduced. / J. Amer. chem. Soc. *84*, 304 (1962). / —Dc. [Rd 95/47 IE]

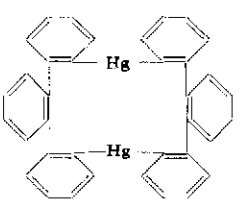
A new method for preparing olefins was found by *L. Caglioti*, *G. Cainelli*, and *A. Selva*. Organoboron compounds with an oxide function in the β-position are treated at elevated temperatures with propionic acid or acetic anhydride, in order to effect an elimination of the boron and oxygen atoms with formation of a double bond. The requisite organoboron



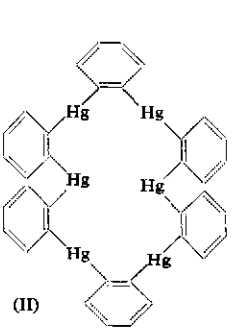
compounds are obtained by hydroboration of enol esters or ethers of α,β-unsaturated ketones in diethylene glycol dimethyl ether. For example, $\Delta^{3,5}$-5α-cholestene is formed in 60 % yield from Δ^4-3-ketocholestene in acetic anhydride. The reaction also takes place when the unsaturated ketones have an electronegative function, such as Cl or OCH_3, in the α-position and one or two alkyl groups in the β-position. / Chim. e Ind. *44*, 36 (1962). / —Pf. [Rd 135/59 IE]

Waterproof adhesives for glass, which are also resistant to solvents such as nitrobenzene, nitrotoluene, alcohol, ether, and carbon tetrachloride, can be obtained from Perlon®. To cement the glass, the Perlon® mass is heated and applied to the surfaces to be joined, which are also preheated, and the glass is then annealed carefully to avoid stresses. Perlon® intermediates are also suitable for cementing glass. / Naturwissenschaften *49*, 8 (1962). / —Ma. [Rd 133/57 IE]

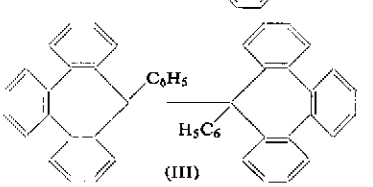
o-Terphenylmercury (I), prepared by shaking *o*-dibromobenzene with lithium- sodium- or potassium-amalgam in tetrahydrofuran or 1,2-dimethoxyethane, has been reported by *G. Wittig*, *E. Hahn*, and *W. Tochtermann*. Compound (II) is formed as a by-product.



(I)



(II)



(III)

In the presence of lithium, compound (I) yields *o,o'*-dilithium-*o*-terphenyl, which was converted *via* several steps into bis[1-phenyltribenzoheptatrienyl] (III). Compound (III) on warming dissociates into two phenyltribenzocycloheptatrienyl radicals. It dissociates less readily than the bis[1-phenyldibenzocycloheptatrienyl]. / Chem. Ber. *95*, 431 (1962) / —Sk. [Rd 193/60 IE]

Das Dithizon und seine Anwendung in der Mikro- und Spurenanalyse (Dithizone and Its Use in Micro- and Trace Anylysis) by *G. Iwantscheff*. Verlag Chemie GmbH., Weinheim/Bergstr. (Germany) 1958. 1st Ed. 272 pp., 41 figures, 24 tables. Cloth bound DM 29.80.

In modern chemical analysis, diphenylthiocarbazone has become the most important single reagent for the isolation and determination of traces of metals. Its use requires careful technique and extensive experience. The author has thoroughly checked laboratory directions culled from more than 500 publications and supplemented them with his own experience, and has thus evolved a text that presents complete tested directions to those who are unfamiliar with dithizone, while those experienced in its use will be stimulated to make more extensive application of the reagent.

The text is divided into five sections. After discussing the theoretical fundamentals, the author describes the general technique of working with dithizone, devoting as much space to a discussion of the requirements with respect to laboratory facilities, equipment, and reagents as to description of the actual methods of separation and determination. The third and longest chapter deals with the application of dithizone to quantitative determinations of all the 18 metals involved in selective reactions with this reagent. For each element the chapter presents clearly the general basis for the respective determination procedure, interfering factors, practical directions, and some typical applications. The last two chapters discuss the use of dithizone for qualitative analysis and some specialized applications, *e.g.* as an indicator for metals in volumetric analysis.

The bibliography covers 523 references to the original literature. Numerous diagrams and tables add to the value of this excellent book which will quickly become indispensable in every laboratory doing trace analysis.

C. Mahr [NB 854/12 1E]

Toxicology and Biochemistry of Aromatic Hydrocarbons, by *H. W. Gerarde*. Elsevier Monographs on Toxic Agents. Elsevier Publishing Co., Amsterdam-London-New York-Princeton, 1960. 1st edition, XII, 320 pages, 89 figures, 63 tables. Price: hfl. 16. . (Price in the USA: $ 6.–).

This book, appearing in the series Elsevier Monographs dealing with industrial toxicology, is by *H. W. Gerarde*, the toxicologist of the medical research division of Esso whose own research in this field (alkylbenzene metabolisms, neurotoxic effect of *p*-t.-butyltoluene, etc.) are well known. On the basis of his own experiences the author is in a position to critically evaluate the most recent (up to the end of 1959) and sometimes quite inaccessible literature, *e.g.* on diphenyl, cataract production by naphthalene, etc. Supported by 59 tables and 89 figures, formulae and sketches, truly everything is mentioned that is important in industrial toxicology of aromatic hydrocarbons. After a general survey about their chemistry, application, and biology, the 20 most important mono-, di-, and polyalkyl derivatives of benzene, as well as the di- and tricyclic aromatic hydrocarbons, are described and their chemistry and physical chemistry, preparation, use, and possible exposure are described. Directions for the analysis of alkylbenzenes in air and in the organism are given with detailed descriptions of the conversion of various hydrocarbons in the organism. The importance of the excretion of free and bound sulfate for the diagnosis of a benzene exposure in comparison with other hydroxcarbons is shown. The "official" MAC (maximum allowable concentration) values are criticized and MAC values for substances which have not yet been officially fixed, are proposed. [Regrettable typographical error: Table 23 (page 81), the MAC value for styrene is equated with that for *p*-t.-butyltoluene (10 ppm = 60 mg/m^3), while it is correctly given on page 140 as 100 ppm 420 mg/m^3].

The polycyclic hydrocarbons and their carcinogenic representatives are discussed briefly, and the problem of carcinogenicity is stated clearly, in agrement with the excellent biography of *Eckardt*. The last chapter concerns mixtures of aromatic hydrocarbons and their use as solvents, fuels, or lubricants, with a short glossary of the terminology used in petrochemistry.

The book is enjoyable and useful, written clearly and critically. It is recommended to all who deal experimentally with the toxicology of aromatic hydrocarbons as well as for those who have to give expert testimony, and who, unfortunately, still frequently equate the effects of the "homologs of benzene" with those of benzene. *H. Oettel* [NB 808/3 1E]

Landolt-Börnstein, Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik und Technik. Band IV: Technik, Teil 3: **Elektrotechnik, Lichttechnik, Röntgentechnik** (Landolt-Börnstein, Numerical Data and Functions pertaining to Physics, Chemistry, Astronomy, Geophysics, and Technology. Volume IV: Technology, Part 3: Electrical, Light, and X-Ray Technology). Edited by *E. Schmidt*. Springer-Verlag, Berlin-Göttingen-Heidelberg 1957. Sixth edition, XV, 1076 pp., 2117 figures. Cloth bound DM 396.—.

This new edition of Volume IV of the Landolt-Börnstein handbook covering the field of technology ("Numerical Data and Functions Pertaining to Technology") is certainly no mean undertaking. Besides numerous organizational and other problems, the selection of material presents an additional difficulty.

It has been impossible to avoid some overlapping between the "technology" and "pure science" volumes. For example, Figs. 35—37, pp. 25–26, Section 4414, of the present volume are identical with Figs. 4—6 of Vol. II, Part 6, pp. 92–93, Section 27114. Much that is given on pp. 332ff. of Vol. IV, Part 1 is found in a more modern and complete form in Vol. IV, Part 3, pp. 1045ff. Repetitions within Vol. IV itself ought to be eliminated; however, the overlapping with sections of Vol. II, Part 6 can only be avoided with difficulty and this, inded, gives some indication of the principal difficulty of the task. If Vol. IV is intended for use on its own, *i.e.* without having the other volumes available – and that pertains particularly to private purchasers –, the repetition is desirable. If, however, it is expected that basic information on substances under consideration should be principally sought first in Vol. II, then the repetitions should be eliminated, first, in order to make the search for information as direct and unambiguous as possible and, secondly, to avoid unnecessarily bulky and expensive volumes.

The volume under discussion deals with three important fields: electrical engineering, light technology, and X-ray technology. The section on electrical engineering lists mainly data on electrical conductivity of solids and liquids (*A. Schulze*), thermoelements (*A. Schulze*), transmission of electricity through gases (*P. Schulz* and *H. Lau*) insulating materials (*W. Claussnitzer*), and magnetic materials (*R. Ochsenfeld* and *K. H. Klitzing*). The section on electrical conductivity naturally also lists the temperature coefficients of resistance, the effect of mechanical treatment on conductivity, skin effects, and the resistances of thin layers and semiconductors. Very extensive tables deal with the resistances of materials used in resistance thermometers (for ultrapure Pt, values to six-places are given for every degree of temperature). The chapter on thermoelements contains data on all the ordinary combinations of materials and the changes in thermoelectric force brought about by changes in ambient pressure and by cold-forming. A 120 page section on the transmission of electricity through gases deals with electrical conductivity in gases and all related subjects [ionization and excitation numbers, cathode drop, gradients of the positive column, properties of plasma, breakdown voltages, including those in inhomogenous fields (sphere-sphere, point-plate, and

point-point), in the environment of cylinders as well as along insulators]. This is followed by the longest and most ramified chapter, that dealing with electrical insulators (526 pages). Numerous tables deal with the most diverse insulating materials, whose number is being continuously increased by the plastics industry. Besides organic insulators, inorganic ones, such as mica, quartz, glass, and ceramics, are treated (*C. Schusterius*). The section on magnetic materials (more than 100 pages) lists data on permeability, coercive force, magnetic induction, and hysteresis loss for all important magnetic materials, including the ferrites. The data are often presented in the form of graphs which are extremely clear and easy to read, even in complicated cases.

The section on light technology (*E. Lax, A. Schleede, P. Schulz, A. Lompe, W. Geffcken*, and *W. Meidinger*) presents data on the sensitivity of the human eye to radiation, on fluorescent materials, light sources, light filters, and photographic emulsions. The section on the sensitivity of the eye also contains graphs showing the dependence of erythema formation on the wavelength of the incident radiation. With regard to fluorescent materials, there are tables summarizing chemical composition, lattice type, incandescent temperature, excitation thresholds for cathode rays and light, fluorescence colors, spectral distribution of the emission and extinction regions, and radiation yield after excitation with cathode rays and the form of the decay curves. Data on energy yield, thermoluminescence and scintillation are also listed. Comprehensive pertinent data for daylight, black bodies, incandescent lamps, Nernst glowers, Welsbach mantles, electronic flash lamps, low- and high-pressure gas-discharge lamps, carbon arcs, and fluorescent lamps are presented in the section on light sources. The data in the section on light filters deals not only with the passbands and the transmittance of commercially available short- and long-wave filters but also gives much desirable information on the suppliers of these filters and their code designations for the items. This information is absolutely necessary here since the data listed in the tables are, in general, based on measurements made in the laboratories of the manufacturers. Here too, the tables are further supplemented by clear drawings. A summary of combinations of liquid filters for passing narrow spectral regions ought to prove of special value. Interference and dispersion filters are also discussed. The section is concluded with a chapter dealing with photographic emulsions. It contains a table for compounding emulsions for various purposes. Data on the sensitivity, energy yield and changes in dimensions of the emulsions as a function of temperature and humidity are presented.

Each chapter — and, when necessary, each table — is preceded by introductory remarks in which the properties tabulated are defined, and general aspects, including the reliability of the data and particularities involved in the measurements, are discussed. These explanations are valuable additions to the tables and justify the claim made in the introduction that the immense amount of material presented is intended to be nevertheless accessible to non-specialists.

A special section deals with "General X-Ray technology" (*R. Jaeger, R. Glocker, R. Berthold, O. Vaupel, H. Weyerer, V. Schmid*, and *W. Kast*). Here Landolt-Börnstein partly abandons its tradition. The section sometimes comes close to being an abridged texthook (of applied physics) in that experimental set-ups and measurement procedures are rather extensively described. Furthermore, the explanations are presented in an unusual form. For instance, some "tables" consist of only a single sentence: under the caption "4612 Units of Accelerating Voltage (plate voltage)" one finds only the sentence "*The plate voltage of X-ray tubes is given either in volts (V), kilovolts (kV), or megavolts (MV).*" This obviously trivial statement — and there are many like it to be found needs no table number. Such explanations — if at all necessary — can be given as elsewhere in the text, without a heading. Table 46211, "Inductor Circuit for Ionic Tubes," 46212, "Transformer Circuits using Rectifying Tubes," 46213, "Transformer Circuit using Rectifying Tubes and Capacitors," 46214, "Surge Voltage Circuit According to Marx," 46215, Belt Generator and Acceleration Device" do not belong in Landolt-Börnstein, in the reviewer's opinion. Neither physicists nor technicians will require such tables, and furthermore they would not search for such information here. Chemists and physicians are wont to use commercial apparatus, and in the event of breakdowns, they would not be helped much by knowledge of these circuit diagrams.

In addition to information on radiation protection, Table 4624 gives data on radiation shielding materials (lead equivalents). Moseley's law for K radiation is admittedly presented, but there is no indication as to where the exact wavelengths for the entire series are given. Apparatus for measuring X-ray intensities is briefly described, and pertinent bibliography is listed. Dosage units are defined in the chapter on medical X-ray techniques; information on surface and deep doses as a function of hardness of the rays and distance from the cathode are given. This is followed by sections dealing with investigations of fine-structure. These sections also include details on methods which is unusual for Landolt-Börnstein.

A table with data on the phases in phase diagrams of binary alloys is followed by about 30 pages of an excellent summary of the structure of natural and synthetic high molecular-weight organic compounds. This table actually should have been placed in Vol. I, Part 4, at the end of the table on the structure of organic molecules, for even though their molecular weights are not strictly defined, these substances are sufficiently well characterized by the data on their unit cells dimensions and atomic arrangements. In the section on X-ray technique, the chapter on the texture of metals and alloys is also very worthwhile.

It may be concluded from examination of the entire section that this is a first attempt to cover a field which is perhaps a little difficult to handle. As a matter of fact, the material presented here as "X-Ray Technology" is, in essence, not technology at all. Medical diagnostic methods are not technical procedures; the same may be said of investigations of fine-structure, even when they are applied to technical problems. However, if the purpose of this section is not merely to present results of technological importance (such as texture as a function of mechanical treatment) but also to describe the principles of experimental procedures, then a table of wavelengths, absorption edges, and absorption coefficients for X-rays of technologically important materials should also be included, so that Vol. IV might be used indepently of the other volumes.

The survey of the contents of Vol. IV, Part 3 given above indicates the wide scope of the material covered. The book will be an important tool not only for engineers, but also for those of purely scientific interests as well, and thus it fulfills its aim. One is obliged to thank the editors and authors very much for their painstaking work.

R. Brill [NB 852/14 1E]

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The Chemical Basis of Ancient Greek Vase Painting [*]

BY PROF. DR. U. HOFMANN
ANORGANISCH-CHEMISCHES INSTITUT DER UNIVERSITAT HEIDELBERG (GERMANY)

Dedicated to Prof. Dr. Georg Wittig on his 65th birthday

In classical times, black- and red-figured vases were an important Greek export article, balancing payments resulting from grain import. This was especially true in Athens. The red pigment was always Fe_2O_3, and the black Fe_3O_4. A carefully chosen clay containing iron, which could be formed by hand with a simple potter's wheel, was used for the vessels. The fired ceramic usually provided the red of the vessels. For the black painting, and for the occasionally used red painting (Intentional Red), a layer of finely elutriated clay was painted on. The vessel was fired between 800 and 900 °C, first under oxidizing conditions, then under reducing, and finally again under oxidizing conditions. From the reproductions of Adam Winter it may be concluded that an illitic clay was used for the black figure painting. During the reductive firing, the painted layer became impervious by sintering owing to the K_2O content of the clay. A kaolinitic clay, poorer in K_2O, served for the red painting. This clay remained porous on reduction and was reoxidized, like the ceramic of the vessel, in the second oxidation. For the terra sigillata of the Romans, the entire surface of the vessel was covered with a clay slip, which, on firing under oxidizing conditions at higher temperatures, gave a hard surface, so that the vessels could be used as table utensils.

Economic Significance of Grecian Vases

While still studying classics at an early age, I wondered why most of the battles of the Third Peloponnesian War, in which Sparta eventually forced Athens to capitulate, were fought at the Hellespont (Dardanelles) (Fig. 1).

The Athenians won a sea battle near Abydos in 411 B.C. At Kyzikos, in 410 B.C., Alcibiades won a great victory for Athens, but Lysander of Sparta destroyed the last Athenian fleet at Aigospotamoi in 405 B.C. Within a year, Athens capitulated. Why?

Athens was, of course, protected by its huge walls on the land side and was connected with its harbor, Piraeus. The Spartans could, indeed, lay waste to Attica, but they could never storm the city of Athens itself. Furthermore, they could not strike a decisive blow against the strong Athenian battle fleet while its rear was protected by Piraeus. Why then did they attack far away, at the Hellespont? Today, the explanation is given in school books. The great city of Athens was utterly dependent on grain supplies from southern Russia, from the Ukraine and from the region near the river Hypanis (Kuban). When Lysander succeeded in closing the

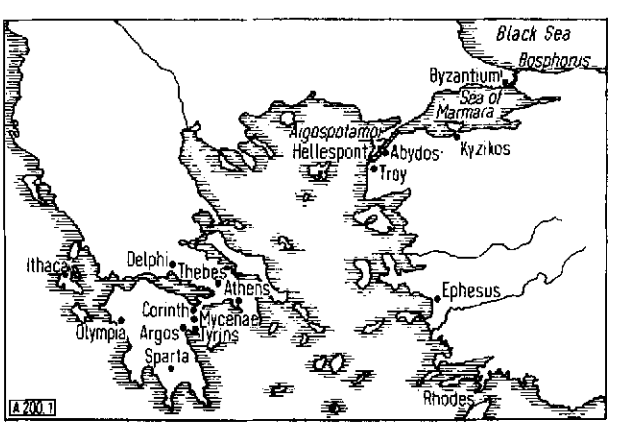


Fig. 1. Ancient Greece and the Black Sea region (Pontus Exinus).

[*] From lectures given before the German Ceramics Society in Cologne on October 2nd, 1961, and before the Heidelberg Academy of Sciences on January 13th, 1962.

Hellespont, he thereby cut off the grain supply of Athens, and the city had to surrender or starve.

Before the Hellespont lay Troy. When *Schliemann* excavated Troy he found, to his surprise, that not one, but many Troys had existed. Perhaps there had been as many as nine. Since 2500 B.C., Troy had been repeatedly devastated and repeatedly rebuilt. Why? The Greeks of that time were already wont to trade with the lands around the Pontus Euxinus (Black Sea). The saga of the Argonauts is a clear example of this; the myth of Iphigenia is another [1]. At this time, too, the Greeks were already buying grain from the lands around the Black Sea. The cargo ships at their disposal were insufficiently equipped with oars to be able to sail through safely to the northeast against the strong current of the Hellespont. Their wares therefore had to be transshipped before passing through the strait. Thus, at the point of transshipment, a city always arose again. The city became rich and powerful from the tolls and transfer taxes, and continually increased its takings, until the Achaians (Greeks) finally came to the conclusion that a war would be cheaper. The Trojan War, which Homer sang in the Iliad, might have come about in this way. It probably concerned Troy VII in the years *ca.* 1200 B.C. However, then as today, the Achaians needed a popular *casus belli*, and they found it in Helen!

Figure 2 shows Helen [2] after the city of Troy had been overrun by the Achaians (Greeks). Helen has fled to the Palladium, the wooden statue of Pallas Athena, and is clasping it. Menelaus rushes in with drawn sword. But Helen's robe has fallen from her shoulders, and Menelaus, beholding her loveliness, forgives her.



Fig. 2. "Menelaus and Helen." Red-figured hydria (water pot) attributed to Cleophrades, Attic painter *ca.* 480 B.C., in the Museum at Naples (Italy)

The red-figured vase painting is attributed to Cleophrades, a painter at the time of the Persian wars, about 480 B.C. In order to appreciate the beauty of the painting, one need only observe the difference between the fixed expression on the face of the wooden statue of Pallas and the living expression of entreaty on the face of Helen.

However, back to history. How did the Athenians pay for the grain imports from the area around the Black Sea? They paid for them with oil and wine, and with handicraft products, but, above all, with their vases. Many of the most beautiful Attic vases have been found in southern Russia. One can well imagine that for such a vase a Scythian prince would not only fill the whole ship of some 200 tons with grain, but would also supply it with oarsmen, for slaves were also an important export article of the lands around the Black Sea.

At the time of the Persian wars and of Pericles, the trade with the area around the Black Sea, of course, was no longer conducted directly by the ship masters and the Scythian princes, but was carried on through the merchants of the Greek cities, who had settled as "colonists" on the shores of the Black Sea. The existence of these cities and their large number again reflect the extent of the commercial traffic through the Hellespont.

Some economic data may be introduced here by way of illustration [3]:

In the Golden Age of Athens, the classical period before the beginning of the Peloponnesian War around 431 B.C., Attica contained approximately 315000 inhabitants. Of these, 175000 were free citizens, 110000 were slaves, and 30000 were serfs (μετοικοι). Serfs were the free denizens of foreign extraction, who had no political rights.

The city of Athens had approximately 100000 inhabitants. After the start of the war, this number may have doubled owing to the influx of country people fleeing to the city.

In estimating the economic situation at that time, it is interesting to note that the taxable property of the Athenians at the beginning of the Peloponnesian War in 428 B.C. amounted to 7000 to 10000 talents. On conversion according to the exchange rate for gold [*], this corresponds to 17 to 25 million

[1] See *F. Grillparzer:* "Das goldene Vliess" (The Golden Fleece), and *G. Hauptmann:* "Atridentetralogie" (Tetralogy of the Atrides).

[2] Unfortunately, the author must confess here that, although the official description of the portrait on the vase is "Menelaus and Helen", the Helen is probably Cassandra, and the Atrid is really Ajax of Locris, the son of Oileus.

[3] Most of the data comes from the book by *Rostovtzeff:* Wirtschaftsgeschichte der Hellenistischen Welt (Economic History of the Hellenistic World). Darmstadt 1955, Vol. I, and from *Busolt* in: Handbuch der klassischen Altertumswissenschaft (Handbook of Studies on Classical Antiquity). Verlag C. H. Beck, Munich 1926, Vol. IV/1, 1.

[*] 1 Attic talent = 6,000 drachmas = 26.2 kg. silver. Rate of exchange at the time, gold:silver = 11.5:1; present price of gold, 1 g = $1.25.

dollars today. Conversion according to the price of wheat then and now would be more correct, for wheat was usually imported. One hundred kg. of wheat cost 7.7 drachmas in Athens in 390 B.C.; today, on the New York Produce Exchange, this quantity costs $8.40. Accordingly, the 7000 to 10000 talents would correspond today to 46 to 66 million dollars.

The taxes were fixed from year to year, according to the needs of the polis (city-state). For example, the revenue from taxes in Athens at the time of Demetrius Phalereus (310 B.C.) is known. It was unusually high and amounted to 1200 talents per year, corresponding to 3.1 million dollars according to the gold rate of exchange, or about 8 million dollars according to the price of wheat. In 431 B.C., the taxes were not so high. The revenue amounted to 500 talents. In addition, considerable income came from the silver mines of Laurium and, before the Peloponnesian War, from the payment of tribute by the allied cities amounting to around 450 talents per year.

The principal food of the Athenians in the classical age consisted of bread, beans, oil, and fish. Salted and dried fish were imported from abroad, again to a considerable extent from the countries around the Black Sea. Meat was a luxury. The period of the joints of beef and roast pigs of the Homeric feasts was long past.

A consumption of 0.8–1.5 kg. of flour per person per day is estimated. This means that Attica had an annual requirement of 100000 to 165000 metric tons of grains, of which most had to be imported. The agriculture of Attica at that time was keyed to the production of wine and oil, which, as has previously been mentioned, were in part exported. If imports of 100000 metric tons of wheat per year are assumed, this corresponds to 3.25 million dollars (gold basis). Added to this were the imports of fish, iron, flax, hides, hemp and slaves, again mostly from the Black Sea regions. The value of the total imports into Attica can therefore be estimated to be at least 5 million dollars per year (gold basis) or to at least 11.5 million dollars per year (wheat basis).

Further evidence of the extent of this foreign trade is given by the known toll collections of the island of Rhodes, which in the second century B.C. came to rival Athens. These receipts were approximately 1 million drachmas per year, corresponding to 425 thousand dollars on the gold basis or about one million dollars on the wheat basis. These figures are in reasonable ratio to the assumed import volume.

The volume of the foreign trade of Attica may thus have been 2-3 times that of the revenue from taxes.

In comparison, it may be observed that the revenue from taxes of the German Federal Republic (54 million people) from April to December, 1960, amounted to 7.1 billion dollars. The exports of the German Federal Republic had in 1960 a value of 12 billion dollars; the imports amounted to 10.6 billion dollars [*].

For overseas transport, an efficient merchant fleet was available. It is estimated that it amounted certainly to several hundred, and perhaps to almost a thousand ships. The cost of the imports had to be covered by the exports. For this purpose, in addition to oil, wine and handicraft products, the vases, especially, could be offered. The prices of the vases are not known. As far as the black- and red-figured vases are concerned, these are works of art, which might have brought fantastic prices. Certainly, we will not go wrong if we assume that the vases accounted for more than half of the value of the exports of Athens.

Attic ceramics at this time dominated the overseas market. The extent of the ceramics industry in Athens is shown by the fact that it took up an entire section of the city, which was appropriately called "Keramaikos."

[*] Fischer World Almanac 1962. Fischer-Bücherei, Frankfurt-Main.

Nevertheless, the production of ceramics was a true handicraft industry. Only after the Peloponnesian War did it develop into an industry of capitalistic nature and begin to utilize slaves to a great extent. However, at the time, slave labor was much more expensive and of poorer quality than that of the free workers (see *Rostovtzeff* [3]). That the labor of slaves played no great role in the classical age of Athens is shown by their small number. They were used predominantly as household servants.

The individual artistry of each black- or red-figured vase shows that these are not factory products, but original creations by master craftsmen.

The Technique of the Greek Potter and Vase Painter

Greek vases are classified as pottery. The body is porous and has a limited strength. The red pigment used for painting is Fe_2O_3 (for example, the terra cotta red of the red-figured vessel in the color plate). The black pigment is Fe_3O_4. Both come from the iron contained in the clay used for the vase and its painting. The white that is often applied (see the sail of the Exekias cup on the color plate) is a white-firing clay. For the occasional crimson ornamentation, terra di siena was used, which is also Fe_2O_3, but of a different shade. The chief colors, however, are the terra cotta red and the velvety black.

Recently the Heidelberg archeologist *Roland Hampe* [4] has successfully investigated the technique of the Greek potter. He sought out the potters of Crete and Cyprus, who today still produce ceramic storage vessels called pithoi using the same techniques as their ancestors 2500 years ago.

For the first fundamental studies in the techniques of the vase painter, we must thank *T. Schumann* [5] and *A. J. Rijken* [6]. Further valuable contributions were made by *Oberlies* and *Köppen* [7] and by American investigators [8]. The sculptor *Adam Winter* from Mainz [9] is to be especially commended for elucidation of the relationships involved. With *Hampe*, he searched in Greece for the clays that might have been used by the ancient Greeks. Among other deposits, these investigators found a deposit near Krora in Attica that definitely had been used by the Athenians in classical times. *Winter* then searched for, and found, similar clays in Germany. An expert ceramist, he worked out under experimental conditions, which lay well within the capabilities of the ancient Greeks, the manner in which they may have shaped and

[4] *R. Hampe:* Bei Töpfern und Töpferinnen in Kreta, Messenien und Cypern. R. Habelt Verlag, Bonn 1962.

[5] *Th. Schumann*, Ber. dtsch. ceram. Ges. *23*, 408 (1942).

[6] *A. J. Rijken* and *J. Ch. L. Favejee*, Chem. Weekbl. *38*, 262 (1941).

[7] *F. Oberlies* and *N. Köppen*, Ber. dtsch. ceram. Ges. *30*, 102 (1953); *31*, 287 (1954); *39*, 19 (1962).

[8] *M. Farnsworth* and *H. Wisely*, Amer. J. Archaeol. *62*, 165 (1958); *J. V. Noble*, *ibid. 64*, 307 (1960).

[9] *Adam Winter:* Technische Beiträge zur Archäologie. Römisch-Germanisches Zentralmuseum, Mainz 1959.

painted with these clays. With the practiced eye of a painter, he matched his colors exactly with the colors of the ancient vases.

Our own work, stimulated by that of *Hampe* and *Winter*, extended to an investigation of the clays and paint slips empirically selected by *Winter*, and to an electron-microscopic investigation of the surfaces of antique vases and shards, as well as of *Winter*'s reproductions. Up to the present time, we have investigated 12 clays and paint slips produced from them, as well as 40 vases and shards. We shall give some typical examples here.

The direct investigation of the antique vases and fragments is naturally indispensable. Since the paint layer is only 20 to 40 μ thick, it is difficult to study it without removing some material from the body itself, along with it. In addition, paint layers and bodies exist only as fired material and thus give but little information about the clay that was used. The prior history of these vases and potsherds must also be kept in mind. If they have lain in the earth without protection, they have been exposed to weathering, so that previously impervious paint layers may have become porous, or may have flaked off. On the other hand, the vases and fragments may have been the victims of a fire, which, at the high temperatures of a burning house or a burning city, would cause additional alterations in the structure of the paint layer. It was therefore of inestimable aid to have at our disposal *Winter*'s copies, which we could investigate in the finished, fired state and whose clays and paint slips we could also analyze before firing.

From our own and earlier investigations, the following picture of the production of the vases and of their painting emerges:

Based on experience passed down through the ages, the Cretan potters of today still know of, and seek out, deposits of the very plastic and firm clay which first made it possible to form, using simple tools, vessels that were frequently taller than a man. Today, as of yore, the clay that is cut from the deposits is dried in air, pulverized, moistened, trodden with the feet and, finally, squeezed by hand until the mass is sufficiently homogeneous. Then the potter shapes the vessel by hand on a primitive potter's wheel. Handles, when they are required, are added to the moist vessel. Simple storage vessels, such as the pithoi, or other finds, for example, from Pompeii, are not painted; after shaping, they were dried in the air and then fired.

The procedure for producing painted vases was more refined.

The first production step involved not only careful choice of the clay, but also elutriation. Figure 3, derived from *Winter*, shows this in schematic form. The coarse sediment was discarded. The more compact sediment deposited above could be used as a working clay for the vases, unless, as with the pithoi, an unelutriated clay was used. Only the finest part of the suspension, which did not settle out, yielded the material for the paint slip. The paint slip material was sometimes the only product of the elutriation.

In order to prepare paint slips, the Greek potters had to peptize the clay. They had at their disposal for this purpose both potash from wood ashes, and also soda in the form of ash from seaweeds. The peptizing action of potas-

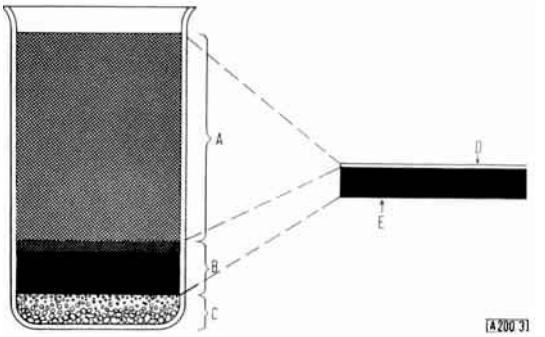


Fig. 3. Greek elutriation art (according to *A. Winter*)
A = color slip
B = working clay
C = sediment (unusable)
D = paint layer
E = base ceramic

sium or sodium carbonate depends on ion exchange [10]. The exchangeable ions of clays in the natural deposits are mainly those of calcium and, to a lesser extent, magnesium. These bivalent cations cause the clay to flocculate when it is shaken with water. In the flocculated, often very voluminous sediment, the crystal platelets of the clay mineral and the quartz grains are held together in a framework similar to that of a house of cards and the separation of the fine and coarse constituents is prevented (Fig. 4, right). Calcium and magnesium ions are exchanged for potassium or sodium ions from potassium or sodium carbonate, since the alkaline earth ions form sparingly soluble carbonates. The alkali ions form a diffuse ionic cloud around the crystals of the clay minerals, which affords a separation of these clays from one another and also from the quartz. Then, after shaking in water, the quartz particles and the platelets of clay minerals settle out according to their weights and sizes, in agreement with Stokes' law (Fig. 4, left).

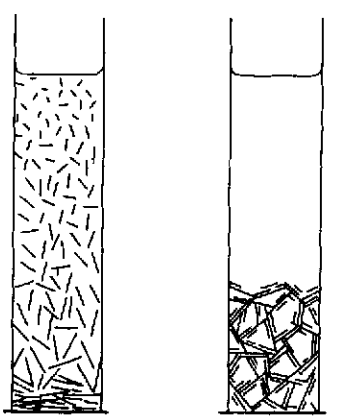


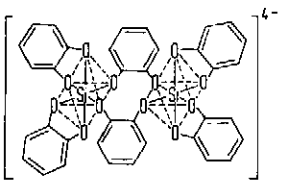
Fig. 4. Sedimentation and flocculation of a clay suspension. Left, separation by sedimentation with alkali ions; right, flocculation by alkaline earth ions. The lines represent the platelets of the clay minerals. Granular minerals, such as quartz, are not shown in the drawing.

The Greeks, however, peptized in a still more sophisticated way by adding tannins. Tannins, of course, are derivatives of gallic acid. Gallic acid is esterified through

[10] *U. Hofmann*, Kolloid-Z. *169*, 58 (1960); 3rd Int. Congress for Surface Active Materials. Universitätsdruckerei Mainz, 1960. Vol. II, p. 658; *K. Frühauf*, *W. Burck*, and *U. Hofmann*, Kolloid-Z. *180*, 150 (1962).

its carboxyl groups with other molecules of gallic acid or with glucose, as for example, in tannin from Chinese nut-galls.

Armin Weiss [11] has thoroughly investigated the ester complexes of silicic acid with *o*-diphenols, such as pyrocatechol, which were first prepared by *Rosenheim*. In these, the silicon has an unusual coordination number, being surrounded by six oxygens (Fig. 5). While the previously known esters of silicic acid hydrolyze in water,



A200.5

Fig. 5. Constitution of the ester complexes of silicic acid with *o*-diphenols (according to *Armin Weiss*).

the *o*-diphenol ester complexes are stable in aqueous solution. Pyrocatechol is so readily bound to silicic acid that it can dissolve even quartz at pH 8.2. Gallic acid, with its *ortho*-hydroxyl groups, and tannins form analogous ester complexes.

In peptization by tannins the process does not proceed so far that the silicates or the quartz of the clay are dissolved. The hydroxyl groups of the gallic acid are probably bound to the oxygen atoms by hydrogen bonds or by esterification to the surface OH groups of the clay minerals and of the quartz (Fig. 6).

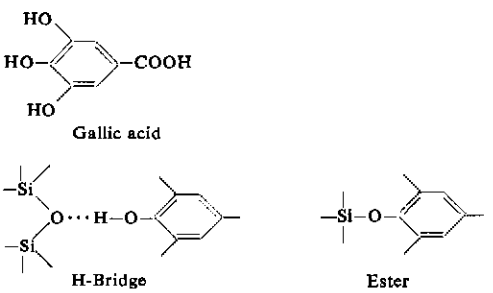


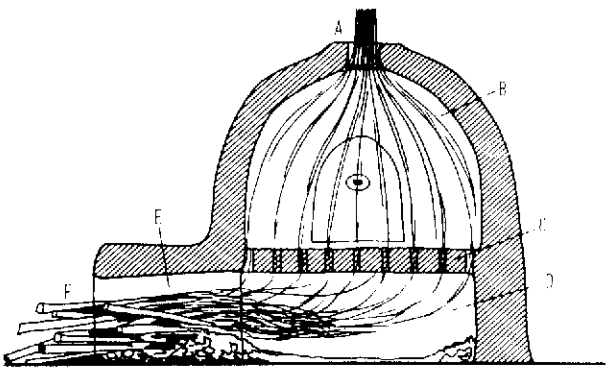
Fig. 6. Peptization by tannins

Since the tannin molecules are soluble in water, they tend to hold the platelets of clay minerals and the quartz particles in suspension in the water. This results in an intensification of the peptization.

The second production step consisted in shaping the vessel, as already described. The vessel was then dried until it was "leathery", as the ceramists call it. Next, the surface was polished. Only a smoothly polished surface beneath the paint layer would yield the beautiful, velvety luster obtained after firing. The paint layer of the black painting must have been relatively thin since, after firing, it was only 20–40 μ thick. The unpainted "body" of the vessel provided the normal terra cotta red of the red painting. Occasionally the unpainted bodies were also covered with a very thin coating made from a dilute paint slip.

[11] *A. Rosenheim, B. Raibmann*, and *G. Schendel*, Z. anorg. allg. Chem. *196*, 160 (1941); *Armin Weiss, G. Reiff*, and *Alarich Weiss*, *ibid. 311*, 151 (1961).

The third and most interesting production step was the firing. The sketch of Fig. 7, again by *Winter*, shows a kiln which may have been used by the Greek potters. One must not imagine this kiln as being necessarily



A200.7

Fig. 7. Attic potter's kiln (according to *A. Winter*)
A = vent
B = firing chamber with door for insertion of the vases
C = grating
D = fire pit
E = combustion zone
F = opening for stoking

small. The height could be as much as three meters. At the bottom was the firebox, which was stoked with wood; above it lay the grate, through which the flames and the hot kiln-gases rose, and above that, the firing chamber. In this chamber the vases were tightly packed, as is still the practice in ceramic kilns today. The potter could observe the firing from the outside through a peephole. The firing was carried out between 800 and 900 °C. The trained eye can recognize this temperature range simply by the color.

The firing took place in three stages. First, under oxidizing conditions, *i.e.* with an excess of air, at 840 °C. At this stage, the entire surface, the vessel and its paint layer were red. The potter then obstructed the air supply with woods rich in resin and, if necessary, also closed the vent. Now the firing was continued under reducing conditions at approximately 840 °C for 5–10 minutes. The combustion produced carbon monoxide, which reduced the iron oxide in the body and in the paint layer to Fe_3O_4. After this firing under reducing conditions, the entire surface of the vase was black. The potter then opened the air supply and the vent and continued the firing once more under oxidizing conditions, while increasing the temperature up to 860 °C or higher. In this "reoxidation" stage what was intended to be black became black, and what was intended to be red became red.

How was this possible? Figure 8 shows electron microscopic photographs of replicas [*] of the surfaces of ancient red and ancient black. They show that the surface of the terracotta red, and therefore of the body, occasionally covered with a thin coating, is rough and remained porous on firing. The oxygen was able to penetrate through the pores during reoxidation and oxidized the black Fe_3O_4 again to red Fe_2O_3. The

[*] Replicas on Triafol film, shadow-cast at 30 ° with WO_3 and at 90 ° with C.

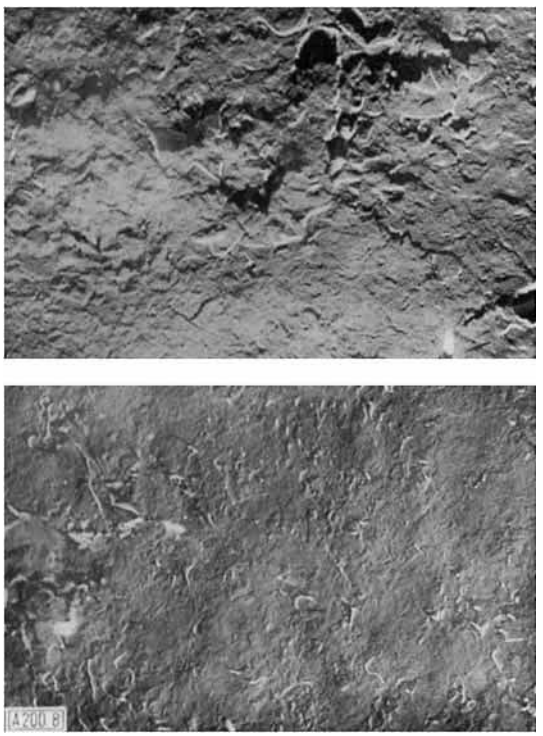


Fig. 8. Replicas of the surface of Attic terracotta red (above) and black (below). Magnification: 15000 times.

surface of the black paint layer is fine-grained; it has sintered to form a more impervious layer. The black paint layer therefore withstood the reoxidation.

The thin coating over the red body was also reoxidized since it was very much thinner than the black paint layer. Occasionally, at the edges, where the black layer is very thin, the red color reappears, indicating a reoxidation.

Why did the black paint layer sinter to form an impervious layer, while the body remained porous?

The most immediate answer that comes to mind is the fact that the clay for the body was coarser and lean, while that for the paint layer was fine. The finer state of dispersion would favour sintering. But is this explanation sufficient?

ing the model of an Attic drinking cup and which was painted with black and intentional red. The color of the intentional red is the same in *Winter*'s reproduction as in the ancient model, except that in the latter case the intentional red has partly flaked off.

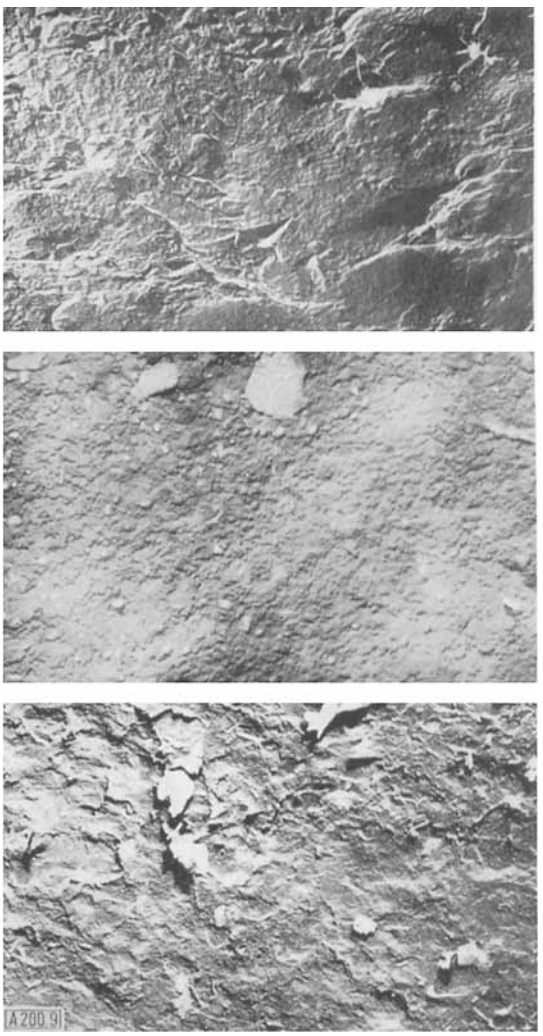


Fig. 9. Replicas of the surface of *Winter*'s reproduction. Terracotta red (above), black (center), intentional red (below). Magnification: 15000 times

Table 1. Paint slips for black and intentional red

The iron content of the three paint slips was between 9.5 and 10.5 % Fe_2O_3; besides the clay minerals and iron oxides, the paint slips contained only a small percentage of quartz.

Paint slips	Clay mineral	Content of K_2O	Grain size, equivalent diameter	Color after firing 820–840 °C reducing 860 °C reoxidized	Color corresponds to
Wirbelau	Illite	5.9 %	< 0.8 μ	Black	Attic black
Eisenberg	Predominantly illite	4.4 %	< 0.5 μ	Black	Attic black
Dehrn	Very predominantly kaolinite	0.8 %	< 0.5 μ	Red	Intentional red

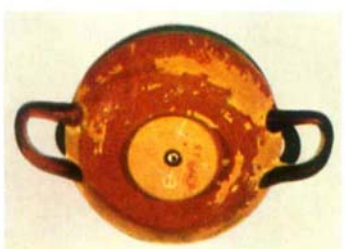
The color plate shows the Dionysus cup of Exekias from the time of the tyrant Pisistratus, around 530 B.C. Here, the bright coral red of this cup is not that of the body; rather, it is painted on, like the black. This red is called "intentional red." It is painted on approximately as thickly as the black paint layer. The red pigment of the intentional red is also Fe_2O_3.

Winter succeeded in reconstructing intentional red. The color plate shows a vessel which *Winter* produced following the model of an Attic drinking cup and which was painted with black and intentional red. The color of the intentional red is the same in *Winter*'s reproduction as in the ancient model, except that in the latter case the intentional red has partly flaked off.

For the black, *Winter* took a mixture of paint slips made from the clays of Eisenberg and Wirbelau. For the intentional red, he chose a paint slip made from the clay of Dehrn (Table 1). The electron microscope photographs (Fig. 9) show that although *Winter*'s black sintered to form an impervious layer, not only the terracotta red surface at the base of the cup, but also *Winter*'s intentional red remained porous. The intentional red was therefore reoxidized along with the base ceramic.



Dionysus cup of Exekias, *ca.* 530 B. C., Munich (Germany).
Black-figured painting and intentional red painting.
The white of the sail painted on the black is almost entirely flaked off.



drinking cup, 500 B. C., Berlin (Germany),
rtly flaked intentional red painting.



Reproduction of the Attic drinking cup (Berlin) by *A. Winter*.
The handles of the cup have been omitted.



Roman *terra sigillata* vessels, Treves (Germany).



Red-figured cup, around 470 B. C., Munich (Germany).

Table 1 shows that the paint slip from Eisenberg was not more finely elutriated than the paint slip from Dehrn used for the intentional red. The paint slip from Wirbelau was even coarser. The fact that the black paint layer sintered to an impervious layer on firing under reducing conditions cannot, therefore, be attributed to a finer structure.

The mineral composition of the clays clearly offers the explanation. The paint slips from Eisenberg and Wirbelau contain predominantly the clay mineral illite. The clay from Dehrn predominantly contains the mineral kaolinite.

Table 2 shows the formulae of these two abundant and important clay minerals. While the formula for kaolinite describes it with satisfactory accuracy, the composition of illite varies considerably from deposit to

Table 2. Formulae of the clay minerals kaolinite and illite

Kaolinite	$Al_2(OH)_4\,[Si_2O_5]$
Micaceous clay minerals or illite	$\sim K^+_{0,7} \cdot \{(Al_2, Mg_3)(OH)_2\,[Si_{3,3}Al_{0,7}O_{10}]\}^{-0.7}$
	Octahedral layer / Tetrahedral layer

deposit. Thus, the illite formula is "idealized." The illite varies with respect to the content of K ions and with respect to the isomorphic substitution of Si by Al in the tetrahedral layer. Besides Al and Mg, Fe can occur in the octahedral layer. In the clay from Eisenberg, for example, the iron is bound in the illite and not admixed as iron oxide. It is important to note, however, that the illite contains a significant amount of potassium, which is lacking in kaolinite.

Accordingly, the clays from Wirbelau and Eisenberg have a high potassium content, while the clay from Dehrn contains practically none at all. Potassium oxide, acting as a flux, and the clay mineral, whether illite or kaolinite, determine whether the applied paint layer will sinter so imperviously during the firing under reducing conditions (approximately 840 °C for 5 to 10 minutes) that it cannot again be oxidized in the reoxidation step, or whether it will remain porous.

By investigation of numerous intentional red paint layers from the classical age, it has been shown that the intentional red sometimes remained porous and sometimes was rendered impervious by the firing. The electron microscope photographs in Fig. 10 show this for intentional red samples from one and the same Attic cup. How is this to be interpreted?

Table 3 again shows *Winter*'s results. If an illitic clay is fired under reducing conditions, it sinters imperviously at approximately 830 °C. If it is fired under oxidizing conditions, it sinters imperviously only at 920 °C. This difference of almost 100 °C depends on the fact that the clays contain iron. The Fe^{2+} ions act as a flux by formation of iron(II) silicates, while, on the other hand, Fe_2O_3 tends to separate from the silicate and has poorer properties as a flux.

Table 3 further shows that a predominantly kaolinite clay first sinters imperviously at 920 °C on firing under reducing conditions, and that it also sinters imperviously on firing under oxidizing conditions, but only at a considerably higher temperature.

Table 3. Sintering of iron-containing clays on firing

	Reducing conditions	Oxidizing conditions
Illitic clay	Sinters imperviously at 830 °C	Sinters imperviously at 920 °C
Kaolinitic clay	Sinters imperviously at 920 °C	Sinters imperviously at 990 °C

It may be that the Greek potter inserted so many pine chips at the time of the firing under reducing conditions that he still had a great deal of charcoal in the kiln after this firing had ended. In the reoxidation this charcoal

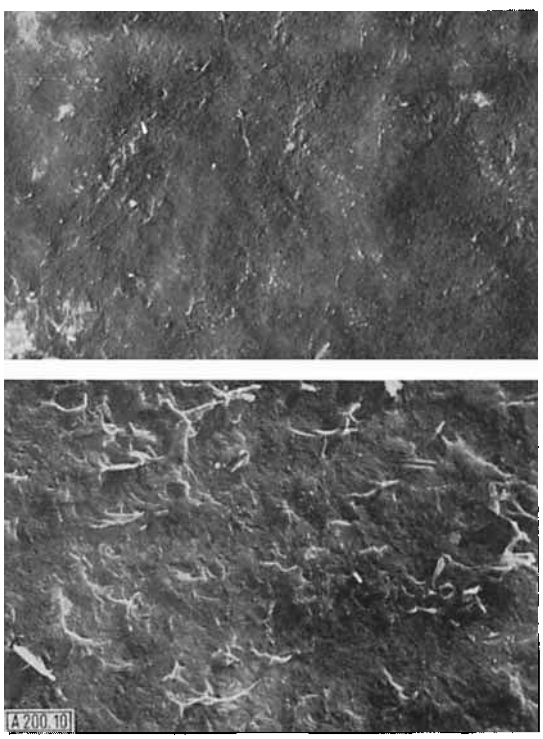


Fig. 10. Replicas of the surface of Attic intentional red, Berlin, Cup CXVIII. Impervious (above) and porous (below). Magnification: 15 000 times

would burn and cause the temperature to rise. If the temperature rose very high, the intentional red also would sinter to form an impervious layer under the oxidizing conditions of the reoxidation stage. Depending on the position of the vase in the kiln, only a portion of its intentional red paint layer might have become so hot that an impervious layer was formed by sintering, while another portion remained porous. An accidental fire in the building where the vases stood (*e.g.* during devastation of the city in wartime) could produce the same effect. The black paint layer could resist the reoxidation in both cases because of its sintered condition.

Another interpretation that may be brought forward is that the intentional red was not applied until after the first firing and then, depending on whether an illitic or a kaolinitic clay was used, was fired a second time under oxidizing conditions to give a more or less impervious red. In this way, owing to its sintered condition, the black paint layer would again survive the firing under oxidizing conditions.

Terra Sigillata

Another type of ceramic with an impervious red coating, formed under oxidizing conditions, comes down to us from classical antiquity: it is the *terra sigillata* which the Romans produced from the first century B.C., and which they exported from Arretium (Fig. 11). The color plate shows several vessels of *terra sigillata*. The Romans were an extremely practical people. Although the *terra sigillata* vessels do not approach the beauty of the Greek vases, their nonporous surfaces made them suitable for kitchen and dining ware. They were produced in quantity for daily use so that a great many of them have been discovered, for example, in the Neuenheim field near Heidelberg, in front of the gates of the Chemical Institute. The vessels were not painted, but were coated by dipping or sprinkling with a clay slip, which sintered to form an impervious layer on firing. One may imagine that dessert was eaten from the small dishes, and the black Spartan soup from the soup plates. This black soup probably did not have too Spartan a taste, for it was considered a delicacy in the best Roman cuisine, just like bouillabaisse today.

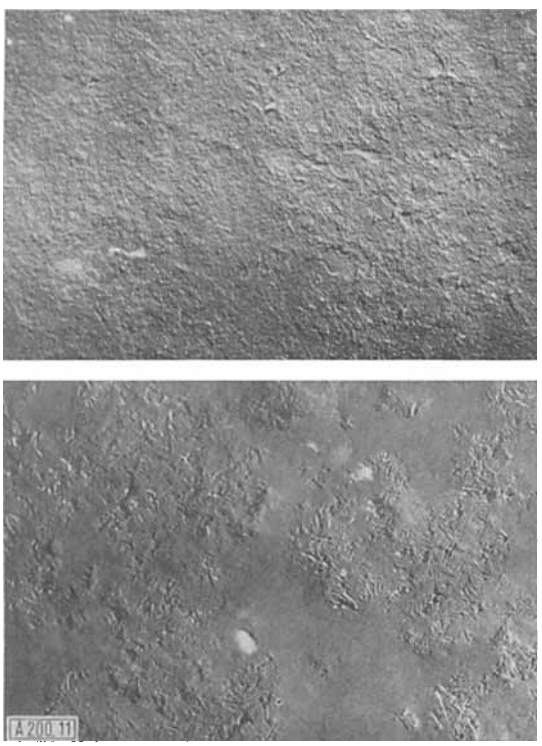


Fig. 11. Replicas of the surface of *terra sigillata*. Roman, Heidelberg (above) and *Winter*'s reproduction (below). Magnification: 15 000 times

However, the Greeks also coated their craters (mixing vessels) on the inside with impervious black paint layers, so that they could be used for mixing wine.

The shades of red from the bright coral intentional red through the medium tone of terra cotta to the reddish brown of *terra sigillata* stem from differences in the fineness and purity of the iron oxide formed on firing.

Terra sigillata, intentional red and the black paint layer are not glazes, as used today, since they are fired clay and not at all vitreous materials. Therefore, the black paint layer and the other Greek paint layers soften only at considerably higher temperatures than the glazes of porcelain and earthenware. In practical use, however, the imperviously sintered coating of *terra sigillata* filled the same purpose as the glaze of earthenware.

I should like to thank Prof. Hampe and Dr. Gropengiesser, Heidelberg, Drs. Greifenhagen and Diehl, Berlin, as well as Drs. Lullies, Ohly, and Sachtleben and Fräulein Vogelpohl of Munich for permission to take color photographs and replicas of the surfaces of the ancient vases in the Heidelberg, Berlin and Munich collections. I should also like to thank Drs. Gose (Treves) and Stadler (Munich) for color slides of terra sigillata. I am also indebted to Dr. Boehm for color photographs, to Fräulein Heideklang for the electron microscopy work, and to Fräulein Lierow for assistance in the mineral analyses.

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New Methods of Preparative Organic Chemistry IV.

Syntheses Using Heterocyclic Amides (Azolides) [*]

BY PROF. DR. H. A. STAAB

ORGANISCH-CHEMISCHES INSTITUT DER UNIVERSITÄT HEIDELBERG (GERMANY)

Dedicated to Prof. Dr. Georg Wittig on his 65th birthday

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2. Preparation and properties of azolides of carboxylic acids
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   c) Other azolides
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Introduction

Syntheses using reactive heterocyclic amides (azolides) apply a principle of activation of chemical compounds that has been systematically studied and whose general applicability has been recognized only in recent years, despite the fact that a few isolated observations in this direction had been made some time ago.

Our interest in this class of compounds was generated by biochemical deliberations and was concentrated at first on kinetic investigations of azolide reactions. Although in our first publication relating to these compounds, we already indicated their "potential application for preparative transacylations" [1], their utilization for preparative purposes was not the primary goal of these studies. Meanwhile, however, interest in the new preparative methods originating from these kinetic investigations has been increasing.

[*] This contribution will be published with extensive procedural details in "Neuere Methoden der präparativen organischen Chemie" [New Methods of Preparative Organic Chemistry], Vol. IV, Verlag Chemie, Weinheim/Bergstr.

[1] *H. A. Staab*, Chem. Ber. *89*, 1927 (1956).

1. Reactivity of Heterocyclic Amides

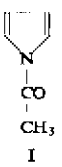
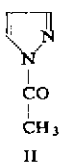
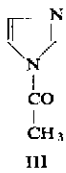
The term reactive heterocyclic amides or "azolides" implies amides whose amide nitrogen is a member of a quasi-aromatic five-membered ring containing at least two nitrogen atoms, *i.e.* "azoles" [2]. Since normal amides are characterized by particularly low reactivity in nucleophilic reactions (*e.g.* hydrolysis or alcoholysis), the high degree of reactivity of azolides in nucleophilic reactions is certainly surprising at a first glance; it places these compounds on the same level as acyl halides and anhydrides.

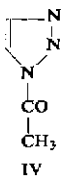
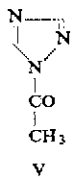
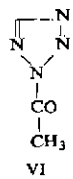
This is shown in Table 1 for the hydrolysis of *N*-acetylazoles in water at pH 7 and room temperature. Whereas *N*-acetylpyrrole (I) like other carboxamides is not hydrolyzed at a measurable rate in neutral aqueous media, the half-life of the hydrolysis of *N*-acetylimidazole (III) at 25 °C is already 41 min. Under identical conditions, *N*-acetyl-1,2,4-triazole (V) is hydrolyzed with a half-life of only 6.4 min., and *N*-acetyltetrazole (VI) decomposes so rapidly into tetrazole and

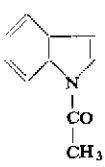
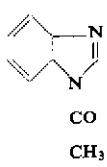
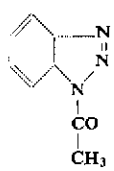
[2] The "azoles" include imidazole, pyrazole, the triazoles, benzimidazole, benzotriazole, and their substituted derivatives.

acetic acid on dissolving in pure water at 25 °C that the rate of hydrolysis cannot be determined by the usual kinetic methods.

Table 1. Values of k′ and the half-lives $\tau_{1/2}$ for the hydrolysis of *N*-acetylazoles in conductivity water at 25 °C at pH 7.0 ($\nu'_{C=O}$ values refer to infrared spectra measured in chloroform) [1, 3]

	 I	 II	 III
$k' \cdot 10^5$ [sec^{-1}]	→ 0	1.27 [4]	28.1
$\tau_{1/2}$ [min]	→ ∞	908	41
$\nu'_{C=O}$ [cm^{-1}]	1732		1747

	 IV	 V	 VI
$k' \cdot 10^5$ [sec^{-1}]	43.5 [4]	180	> 2000
$\tau_{1/2}$ [min]	26.6	6.4	< 0.5
$\nu'_{C=O}$ [cm^{-1}]		1765	1779

	 VII	 VIII	 IX
$k' \cdot 10^5$ [sec^{-1}]	→ 0	1.75	10.1
$\tau_{1/2}$ [min]	→ ∞	760	115
$\nu'_{C=O}$ [cm^{-1}]	1711	1729	1735

The high degree of reactivity of azolides and the order of reactivity in this group are connected with the quasi-aromatic character of azoles [1,5]. As a result of the participation of the electron pair on the amide nitrogen in the π-electron system of the ring, this nitrogen becomes more positive, exerting an attraction towards the ring of the electrons of the exocyclic bond of this nitrogen. In the case of unsubstituted heterocycles, this electron attraction leads to the known acidity of the N–H bond and in the case of azolides increases the rate of nucleophilic reactions involving the carbonyl group, regardless of whether the mechanism is of the S_N1 or the addition-elimination type. The increase in reactivity with an increasing number of nitrogen atoms in the ring is explained by assuming that the delocalization of the lone electron of the amide nitrogen – and, hence, also the electron attraction by the ring – increases with the number of CH groups replaced by more electronegative nitrogen atoms. Of the isomeric azolides with the same number of nitrogen atoms in the ring, those with the greater number of adjacent nitrogen atoms show lower reactivity. Thus, pyrazolides (II) are hydrolyzed more slowly than imidazolides [4, 6], and 1,2,3-triazolides (IV) more slowly than 1,2,4-triazolides (V) [4]. In the case of these compounds, the amide nitrogen obviously becomes less positive, because two neighboring nitrogen atoms cannot assume the same π-electron density as two nitrogens separated by a carbon atom.

In the series *N*-acetylindole (VII), *N*-acetylbenzimidazole (VIII), *N*-acetylbenzotriazole (IX), too, the rate of hydrolysis increases with the number of nitrogen atoms in the ring [3]. However, in each case the reactivity is lower than that of the monocyclic azolide having the same number and arrangement of ring nitrogens. This again is in agreement with theoretical considerations [7].

The same order of reactivity that is observed for the hydrolysis of azolides of carboxylic acids (Table 1) is found for other nucleophilic reactions, *e.g.* alcoholysis and aminolysis, involving the carbonyl group of these compounds. All these reactions can be followed spectrophotometrically, since azolides exhibit characteristic intense absorption bands which, as a rule, are found at longer wavelengths than those for the products of hydrolysis, alcoholysis, and aminolysis. For example, Fig. 1 shows the change in the absorption spectrum during neutral hydrolysis of *N*-(4-methylbenzoyl)-imidazole at 21 °C in water/tetrahydrofuran (3:1). Such kinetic investigations have shown that aminolysis and alcoholysis of azolides take place by a bimolecular addition-elimination (AE) mechanism. Neutral hydrolysis of azolides of aromatic carboxylic acids also follows this mechanism, as indicated for imidazolides in Fig. 2 by the Hammett diagram with reaction constant ρ = +1.85 [5]. On the other hand, hydrolysis of azolides of sterically hindered aliphatic carboxylic acids in pure water seems to occur by an S_N1 mechanism [8,9]. Essentially, these conclusions are based upon the investigation of the dependence of rate constants and activation energies on the nature of the acyl residue. Differences in reactivity with varying acyl residues are quite pronounced within the individual azolide groups. In the imidazolide series, for example, imidazolides of substituted aromatic carboxylic acids, such as *N*-(*p*-dimethylaminobenzoyl)imidazole, are hydrolyzed by water at room temperature with half-lives of several weeks, while under identical conditions, *N*-(trifluoroacetyl)imidazole and *N*-(trichloroacetyl)imidazole are decomposed practically instantly in a very vigorous re-

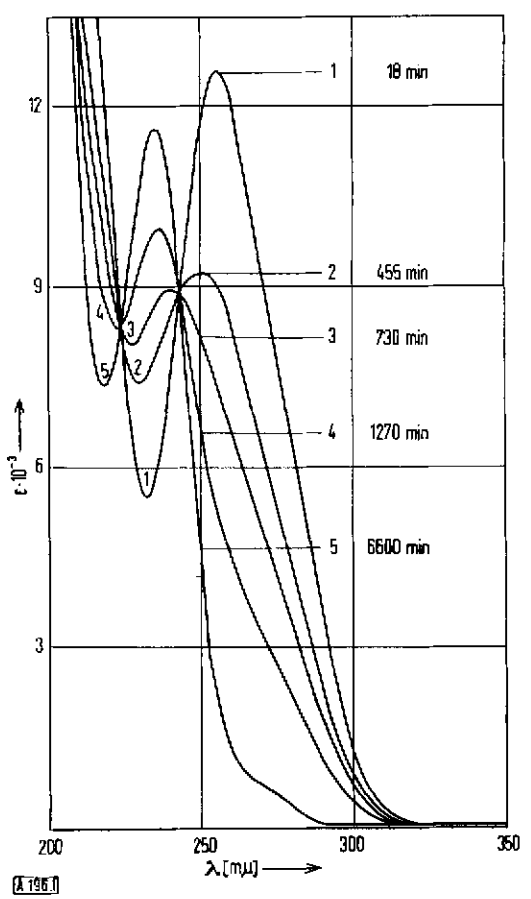


Fig. 1. Hydrolysis of *N*-(4-methylbenzoyl)imidazole in water/tetrahydrofuran (3:1) at 21 °C

[3] *H. A. Staab*, Chem. Ber. *90*, 1320 (1957).

[4] *R. Hüttel* and *J. Kratzer*, Chem. Ber. *92*, 2014 (1959).

[5] *H. A. Staab*, *W. Otting*, and *A. Ueberle*, Z. Elektrochem. *61*, 1000 (1957).

[6] *H. A. Staab*, Liebigs Ann. Chem. *622*, 31 (1959).

[7] Cf. *C. A. Coulson* and *H. C. Longuet-Higgins*, Trans. Faraday Soc. *43*, 87 (1947).

action [10]. One of the most reactive imidazolides is *N*-formylimidazole; its rate of hydrolysis exceeds that for *N*-acetylimidazole by a factor of about 100 (Table 1) [11].

As shown in Table 1 for *N*-acetylazoles, the increased reactivity in nucleophilic reactions involving the carbonyl group is paralleled by a marked shift of the infrared absorption of the carbonyl bands toward shorter wavelengths. For more reactive compounds, such as *N*-acetyltetrazole, this band is found in a frequency range (1780 cm^{-1}) quite unusual

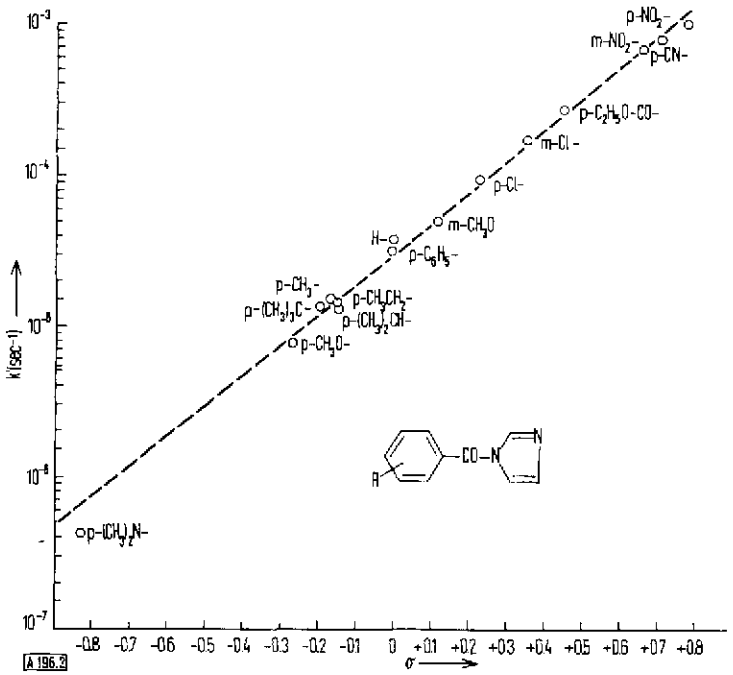


Fig. 2. Hammett diagram for the hydrolysis of imidazolides of aromatic carboxylic acids in water/tetrahydrofuran (3:1) at 21 °C

for amides [1, 12]. This shift of the carbonyl band toward shorter wavelengths, *i.e.* the increase in the C···O force constant, can also be attributed to increased electron attraction by the heterocycles [5]. It was found that the carbonyl wave number ν_{C-O} for both imidazolides and 1,2,4-triazolides of substituted benzoic acids is so closely proportional to log *k* for neutral hydrolysis that the hydrolysis rates of numerous members of this series could be predicted, within the range of accuracy of the kinetic method, from the infrared spectra [5]. Furthermore, the occurrence of azolide carbonyl bands at unusually short wavelengths is of interest for identifying compounds of this structural type [13].

2. Preparation and Properties of Azolides of Carboxylic Acids

a) Imidazolides

Although imidazolides are not the most reactive group among heterocyclic amides (cf. Table 1), they are most interesting for preparative purposes, because of the availability of imidazole. As shown in Table 2, nearly all imidazolides are crystalline compounds, and with very few exceptions, they can be conveniently handled.

Previous to the beginning of our work, the literature contained but few references to imidazolides. In 1892, *Bamberger* [14] observed that imidazoles undergo ring scission when attempts are made to acylate them in alkaline solution with acid chlorides. Nevertheless, in 1913 *Gerngross* [15] showed that *N*-benzoylimidazole, which according to our kinetic findings, however, is substantially more stable than imidazolides of aliphatic carboxylic acids, may be obtained by reacting benzoyl chloride with imidazole in a 1:2 molar ratio in benzene. The first imidazolide of an aliphatic carboxylic acid – the only other compound among the imidazolides of carboxylic acids listed in Table 2 that was previously known –, was prepared, after earlier unsuccessful attempts, by *Boyer* in 1952 [16], starting from imidazole and isopropenyl acetate. Somewhat later, *Wieland* and *Schneider* [17] prepared the same compound by *Gerngross*' method. These workers were also the first to carry out a few experiments on the hydrolytic and aminolytic reactivity of *N*-acetylimidazole. On the basis of the results obtained, they classified the imidazolides as energy-rich acetyl derivatives. However, as early as 1928, *Bergmann* and *Zervas* [18] had shown that the analogous *N*-aminoacyl derivatives of histidine react with amino acids to form dipeptides and discussed the question of whether such reactions might play a role in biological protein synthesis.

The imidazolides listed in Table 2 may be prepared by two very simple methods, both of which usually give practically quantitative yields [19].

[8] *H. A. Staab*, Chem. Ber. *89*, 2088 (1956).

[9] *H. A. Staab* and *D. Wurmb-Gerlich*, unpublished data.

[10] *H. A. Staab* and *G. Walther*, Chem. Ber., in press.

[11] *H. A. Staab* and *B. Polenski*, Liebigs Ann. Chem., in press.

[12] *W. Otting*, Chem. Ber. *89*, 1940 (1956).

[13] See, for example, *R. Gompper*, *E. Hoyer*, and *H. Herlinger*, Chem. Ber. *92*, 550 (1959); *H. A. Staab* and *G. Seel*, Chem. Ber. *92*, 1302 (1959).

[14] *E. Bamberger* and *B. Berlé*, Liebigs Ann. Chem. *273*, 342 (1892); cf. also *O. Gerngross*, Ber. dtsch. chem. Ges. *46*, 1913 (1913).

[15] *O. Gerngross*, Ber. dtsch. chem. Ges. *46*, 1908 (1913).

[16] *J. H. Boyer*, J. Amer. chem. Soc. *74*, 6274 (1952).

[17] *T. Wieland* and *G. Schneider*, Liebigs Ann. Chem. *580*, 159 (1953).

[18] *M. Bergmann* and *L. Zervas*, Hoppe Seyler's Z. physiol. Chem. *175*, 145 (1928).

[19] *H. A. Staab*, *M. Lüking*, and *F. H. Dürr*, Chem. Ber. *95*, 1275 (1962); additional literature references are to be found therein.

Table 2. Some imidazolides of carboxylic and carbonic acids (Im = *N*-imidazolyl)

	m.p. (b.p.) [°C]	Ref.
I. *Imidazolides of carboxylic acids*		
a) Monoimidazolides		
H–CO–Im	54–55	[11]
CH_3–CO–Im	104	[1, 16, 17]
CH_3–CH_2–CO–Im	38	[1]
CH_3–$(CH_2)_2$–CO–Im	19	[1]
CH_3–$(CH_2)_3$–CO–Im	(100/18 mm.)	[1]
CH_3–$(CH_2)_4$–CO–Im	35	[1]
CH_3–$(CH_2)_6$–CO–Im	47	[1]
CH_3–$(CH_2)_8$–CO–Im	63	[1]
CH_3–$(CH_2)_{10}$–CO–Im	70.5–71	[45]
CH_3–$(CH_2)_{14}$–CO–Im	83	[1]
$(CH_3)_2CH$–CO–Im	(92/18 Torr)	[8]
$(CH_3)_3C$–CO–Im	56	[8]
C_6H_5–CH_2–CO–Im	53	[9]
$(C_6H_5)_2CH$–CO–Im	126–128	[9]
$(C_6H_5)_3C$–CO–Im	148	[9]
C_6H_5–CH=CH–CO–Im	133–134	[19]
CH_3–CH=CH–CH=CH–CO–Im	86	[51]
$C_{19}H_{17}$–CO–Im (Vitamin A acid imidazolide)	112–113	[48]
CF_3–CO–Im	(137–138)	[10]
CCl_3–CO–Im	39–40	[10]
CH_3O–CO–$(CH_2)_4$–CO–Im	63–64	[49]
C_6H_5–CH(OCOCH$_3$)–CO–Im	100–102	[50]
$(C_6H_5)_3P$=CH–CO–Im	184–186	[42]
$(C_6H_5)_3P$=C(CH_3)–CO–Im	172–175	[42]
C_6H_5–CO–Im	20–21	[15, 19]
2–Cl–C_6H_4–CO–Im	68–69	[52]
2–Br–C_6H_4–CO–Im	(107-110/10^{-3} mm.)	[52]
2–CH_3CO–C_6H_4–CO–Im	89	[52]
2–CH_3OCO–C_6H_4–CO–Im	110–111.5	[50]
3–Cl–C_6H_4–CO–Im	44–45	[52]
3–Br–C_6H_4–CO–Im	59–61	[52]
3–CH_3O–C_6H_4–CO–Im	(100/10^{-2} mm.)	[19]
3–NO_2–C_6H_4–CO–Im	89	[19]
3–CH_3OCO–C_6H_4–CO–Im	97–99	[50]
4–CH_3–C_6H_4–CO–Im	75	[19]
4–C_2H_5–C_6H_4–CO–Im	22–24	[19]
4–$(CH_3)_2CH$–C_6H_4–CO–Im	53.5–54.5	[19]
4–$(CH_3)_3C$–C_6H_4–CO–Im	110	[19]
4–C_6H_5–C_6H_4–CO–Im	120–121.5	[19]
4–CH_3O–C_6H_4–CO–Im	68–69	[19]
4–Cl–C_6H_4–CO–Im	86.5–87.5	[19]
4–Br–C_6H_4–CO–Im	94	[19]
4–$(CH_3)_2N$–C_6H_4–CO–Im	109	[19]
4–CH_3CONH–C_6H_4–CO–Im	179–180	[50]
4'–$(CH_3)_2N$–C_6H_4–N=N–C_6H_4–CO–Im	97–100	[19]
4–NO_2–C_6H_4–CO–Im	123	[19]
4–C_2H_5OCO–C_6H_4–CO–Im	77–78	[49]
4–C_5H_4N–CO–Im	95	[19]
2.6–$(CH_3O)_2C_6H_3$–CO–Im	86–87	[9]
2.4.6–$(CH_3)_3C_6H_2$–CO–Im	46	[51]
b) Diimidazolides		
Im–CO–$(CH_2)_2$–CO–Im	166	[34]
Im–CO–$(CH_2)_4$–CO–Im	158	[34]
Im–CO–$C(CH_3)_2$–CO–Im	147	[19]
Im–CO–C_6H_4–CO–Im–(1.4)	202	[34]
Im–CO–C_6H_4–CO–Im–(1.3)	148–149	[50]
II. *Imidazolides of carbonic acid derivatives*		
Im–CO–Im	116–118	[53]
n–C_4H_9NH–CO–Im	74–75.5	[57]
$C_6H_{11}NH$–CO–Im	95.5–97	[57]
C_6H_5NH–CO–Im	117	[56]
$(C_2H_5)_2N$–CO–Im	48–49.5	[57]
$(C_6H_5)_2N$–CO–Im	123–124	[31]
$(C_6H_5)(CH_3)N$–CO–Im	69–72.5	[57]
$C_6H_5CH_2ONH$–CO–Im	90 (decomp.)	[60]
$(C_6H_5CH_2)(C_6H_5CH_2O)N$–CO–Im	59.5–61.5	[61]
C_2H_5O–CO–Im	(105-107/16-17mm.)	[56]
$(CH_3)_3CO$–CO–Im	46–47.5	[19, 63]
Im–CS–Im	105–106	[65]
n–C_4H_9NH–CS–Im	55–56.5	[66]
$(C_2H_5)_2N$–CS–Im	80.5–81.5	[65]
C_6H_5–CH_2O–NH–CS–Im	116–117 (decomp.)	[66]
C_2H_5O–CS–Im	29–30.5	[65]
C_6H_5O–CS–Im	96.5–97.5	[65]
β–$C_{10}H_7O$–CS–Im	113–114.5	[65]
Im–C(NC_6H_5)–Im	135–136	[67]

1. In a modification of the old method according to *Gerngross*, acid chloride and imidazole are caused to react in a 1:2 molar ratio at room temperature in tetrahydrofuran or another inert solvent, in which imidazolium chloride is insoluble. After filtering off the imidazolium chloride, imidazolides of good purity are obtained directly in most cases by evaporating off the solvent. Purification may be effected by vacuum sublimation or crystallization from tetrahydrofuran, benzene, or similar solvents.

2. The reaction of free carboxylic acids with *N,N'*-carbonyldiimidazole at room temperature, described in Section 3, leads to imidazolides, with evolution of CO_2. This reaction constitutes the preferred method for preparing imidazolides of carboxylic acids whose acid chlorides cannot be prepared at all or only with difficulty, *e.g.* the imidazolide of formic acid or vitamin A acid. As a rule, separation of the imidazole formed in this reaction presents no difficulty [19]. However, in most reactions involving imidazolides, separation of the imidazole and isolation of the imidazolide are not at all necessary. Instead, the imidazolide solutions obtained from the reaction of the free carboxylic acid with *N,N'*-carbonyldiimidazole may be used directly, *i.e.* esters, amides, peptides, aldehydes, *etc.* may be obtained from carboxylic acids by two reactions carried out without isolating the intermediates (hereinafter referred to as a "two-in-one-reaction").

Imidazolides may also be prepared from *N,N'*-thiocarbonyldiimidazole and carboxylic acids, in a reaction analogous to that involving *N,N'*-carbonyldiimidazole. In this reaction, carbonyl sulfide is formed in addition to imidazole (see Section 8a). Similarly, *N,N'*-thionyldiimidazole reacts with carboxylic acids with evolution of SO_2 to form imidazolides in practically quantitative yields (see Section 11).

To obtain imidazolides, *Birkofer*, *Richter*, and *Ritter* [20] treated *N*-(trimethylsilyl)imidazole with acid chlorides. The former was prepared by heating a mixture of hexamethyldisilazane and imidazole for several hours. This reaction is noteworthy because of the particularly high rate at which it takes place, but, compared to the above methods, it seems to offer no advantages to justify its more extensive preparative effort.

b) Pyrazolides

Following our investigations of azolide reactions, *Ried* and *Schleimer* [21] reported analogous reactions of *N*-acyl-3,5-dimethylpyrazoles, which are easily prepared from hydrazides

[20] *L. Birkofer, P. Richter*, and *A. Ritter*, Chem. Ber. *93*, 2804 (1950).

[21] *W. Ried* and *B. Schleimer*, Liebigs Ann. Chem. *626*, 98 (1959); see also *W. Ried* and *B. Schleimer*, *ibid. 619*, 43 (1958); *W. Ried* and *F. J. Königstein*, *ibid. 622*, 37 (1959); *625*, 53 (1959); *W. Ried* and *P. Pfaender*, *ibid. 640*, 111 (1961).

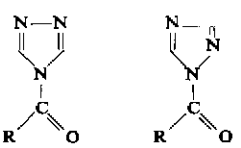
of the corresponding acids and acetylacetone. However, since pyrazolides are much less reactive than imidazolides in nucleophilic reactions involving the carbonyl group [4, 7], the former are not suitable for some of the reactions described below and, in the others, they do not seem to offer any advantages over imidazolides.

c) Other Azolides

Triazolides, benzimidazolides, and benzotriazolides can be prepared by procedures analogous to those described for the preparation of imidazolides.

The first example of a tetrazolide was prepared from the Ag salt of tetrazole, by reaction with an acid chloride in inert, anhydrous solvents [1]. Because of their extreme sensitivity to hydrolysis tetrazolides are not suitable for preparative transacylations. The preparation of other *N*-acyl derivatives in the tetrazole series was reported by *Huisgen* et al. [22], who discovered the interesting formation of, 1,3,4-oxadiazoles during acylation of 5-substituted tetrazoles.

As to *N*-acyl-1,2,4-triazoles, of which to our knowledge also no representatives were known until now, both isomeric structures X and XI are possible, but on the basis of physical properties, the symmetrical structure X was at first believed to be more probable [1]. This structural problem could not be resolved by chemical methods. However, it has been solved recently with the aid of proton magnetic resonance in favor



(X) (XI)

of the nonsymmetrical structure XI. For the symmetrical *N*-acetyl-1,2,4-triazole, only a single signal was to be expected in the absorption region of aromatic C–H protons. However, in addition to the resonance of methyl protons (τ = 7.27), the spectrum (in $CDCl_3$) shows two absorptions at τ = 1.94 and at τ = 1.02. The intensity ratio of the peaks is 3:1:1, as is to be expected for XI [23].

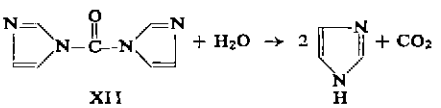
Although 1,2,3- and 1,2,4-triazolides are more reactive than imidazolides in nucleophilic reactions involving the carbonyl group, from a preparative standpoint, they and the less reactive pyrazolides, benzimidazolides, and benzotriazolides are less important than the imidazolides. Hence, the following discussion will be restricted to imidazolides without constantly reaffirming that in most cases other azolides may also be used. In special preparative problems, however, it may be of practical interest that the azolides constitute an entire series of compounds whose transacylation potential varies step by step.

3. Preparation and Properties of Diazolides of Carbonic Acid

a) N,N'-Carbonyldiimidazole and Other N,N'-Carbonyldiazoles

The explanation given in Section 1 for the reactivity of azolides, led to the synthesis of *N,N'*-carbonyldiimidazole (XII) and other *N,N'*-carbonyldiazoles[24,25] which form a new class of compounds with a wide range of preparative applications. These compounds are obtained in nearly quantitative yield by reacting azoles with phosgene in a 4:1 molar ratio in tetrahydrofuran or benzene. They may also be prepared in a satisfactory state of purity and in nearly quantitative yields from *N*-trimethylsilyl derivatives of heterocycles, by the method of *Birkofer* et al. [20].

As expected, these diazolides of carbonic acid exhibit very high reactivity toward nucleophilic reagents, because of the electron attraction exerted from both sides on the carbonyl group by the heterocycles. For example, pure water hydrolyzes XII at room temperature within seconds, with vigorous evolution of CO_2:



XII

On the other hand, these *N,N'*-carbonyldiazoles (Table 3) are crystalline compounds and, compared, for example, with phosgene, which possesses similar reactivity, they can be conveniently handled provided care is taken to exclude moisture.

Table 3. Some *N,N'*-carbonyldiazoles

	m.p. [°C]
N,N'-Carbonyldi-(1,2,4-triazole) [24]	134–136
N,N'-Carbonyldiimidazole (XII) [24]	116–118
N,N'-Carbonyldibenzotriazole [25]	183–185
N,N'-Carbonyldibenzimidazole [25]	182–183
N,N'-Carbonyldi-(3,5-dimethylpyrazole) [6]	89–90

The reactions of *N,N'*-carbonyldiazoles with alcohols and amines, which are analogous to those of phosgene and in which the order of reactivity was found to be the same as that shown by azolides of carboxylic acid (Table 1), are discussed in Section 7.

b) Reaction of N,N'-Carbonyldiimidazole with Carboxylic Acids to Form Imidazolides

N,N'-Carbonyldiimidazole (XII) reacts with carboxylic acids in equimolar proportions at room temperature in tetrahydrofuran, chloroform, or similar inert solvents to form imidazolides in practically quantitative yields, with liberation of CO_2 and formation of one mole of imidazole [19]. In agreement with the proposal of *Paul* and *Anderson* [26], we assume that a mixed anhydride (XIII) of imidazole-*N*-carboxylic acid and the carboxylic acid is formed first; however, the anhydride could not be isolated even at −50 °C. The extremely fast formation of imidazolides, even at low temperatures, is understandable if it is assumed that at stage XIII, an intramolecular nucleophilic substitution takes place at the

[22] *R. Huisgen, J. Sauer, H. J. Sturm,* and *J. H. Marggraf,* Chem. Ber. *93,* 2106 (1960).

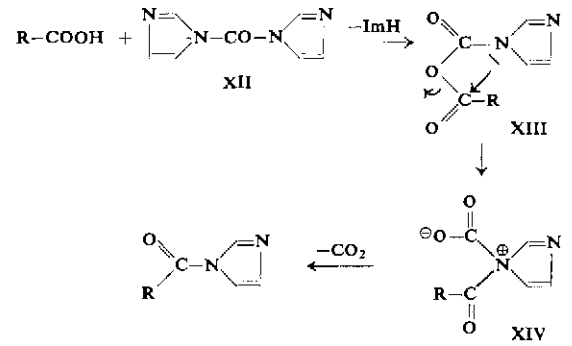
[23] *H. A. Staab* and *A. Mannschreck,* unpublished data.

[24] *H. A. Staab,* Liebigs Ann. Chem. *609,* 75 (1957); for an improved method of preparing XII see *H. A. Staab* and *K. Wendel,* Chem. Ber. *93,* 2910 (1960).

[25] *H. A. Staab* and *G. Seel,* Liebigs Ann. Chem. *612,* 187 (1958).

[26] *R. Paul* and *G. W. Anderson,* J. Amer. chem. Soc. *82,* 4596 (1960).

acyl carbonyl group, followed by the then strongly favored elimination of CO_2 via XIV.



XII XIII XIV

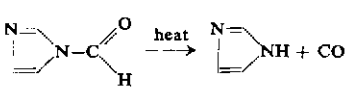
Experiments are in progress with ^{14}C-imidazole to exclude the possibility of a second reaction pathway, *viz.* that of bimolecular acylation of an imidazole molecule by XIII.

This reaction of carboxylic acids with XII, which leads to imidazolides and, hence, to very reactive carboxylic acid derivatives under mildest conditions, has a wide range of applicability. It takes place with aliphatic, aromatic, and heterocyclic carboxylic acids and is not affected by the presence of other functional groups, unless they react with XII as, for example, primary or secondary amines do. Hydroxycarboxylic acids can also be converted to imidazolides in this manner, since XIII reacts faster with the carboxyl than with the hydroxyl group. For further syntheses, however, the two-in-one-reaction procedure (see below) is preferred in this case, since the isolation of imidazolides of hydroxycarboxylic acids presents difficulties because of the possibility of inter- and intra-molecular esterification [27]. With XII, dicarboxylic acids afford diimidazolides. It is only in the case of malonic acids that decarboxylation of the intermediate monoimidazolide competes with further reaction to give the diimidazolide (even at low temperatures) so that imidazolides of the correspondingly substituted acetic acids are generally the major products [19].

By analogy to the reaction of XII with carboxylic acids to yield imidazolides, reaction of other *N,N'*-carbonyldiazoles with carboxylic acids yields the corresponding azolides.

In the reaction of formic acid with *N,N'*-carbonyldiimidazole, *N,N'*-carbonyldibenzimidazole, and *N,N'*-carbonyldibenzotriazole, it was observed that the azolide reactivity does not follow the order usually observed for nucleophilic reactions, but the order of basicity instead [11]; this indicates that in this case the *N,N'*-carbonyldiazoles participate in the reaction in their protonated form.

The imidazolides of formic acid obtained in these reactions are very effective formylating agents. Above their melting points, they decompose practically quantitatively, with evolution of carbon monoxide, forming the unsubstituted heterocycles:

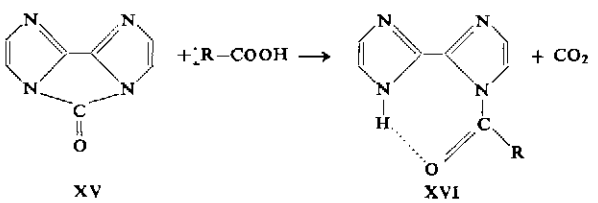


m.p. = 53 –55 °C

[27] See, for example, *H. A. Staab* and *H. Bräunling*, Liebigs Ann. Chem. *654*, 119 (1962).

c) N,N'-Carbonyl-2,2'-biimidazyl (XV)

In contrast to the reaction of *N,N'*-carbonyldiazoles with carboxylic acids, where formation of azolide is accompanied by that of one mole of CO_2 and one mole of azole, in the reaction of XV with carboxylic acids, the azole resulting from nucleophilic substitution is hooked up to the azolide. Thus, apart from the azolide XVI, only CO_2 would be expected as a product. Azolide XVI ought to be particularly reactive in nucleophilic transacylations because of its intramolecular hydrogen bond.



XV XVI

In contrast to non-cyclic *N,N'*carbonyldiazoles, XV (prepared from 2,2'-biimidazyl and phosgene) is an intensely yellow substance (λ_1 = 380 mμ; ε_1 = 1900) exhibiting an infrared carbonyl band at an unusually short wavelength (1820 cm^{-1}). Its hydrolysis by water is slower than that of *N,N'*-carbonyldiimidazole, and it also shows a reduced reactivity in reactions with carboxylic acids. This and the increased reactivity of XVI cause the reaction XV → XVI to be followed by other reactions: carboxylic anhydrides are formed (see Section 4c), and transacylation to yield *N,N'*-diacyl-2,2'-biimidazyl takes place. This reaction is facilitated by the simultaneous formation of 2,2'-biimidazyl, which is insoluble in nearly all organic solvents [28].

4. Transacylation Reactions of Imidazolides

a) Synthesis of Esters

The reaction of a carboxylic acid with *N,N'*-carbonyldiimidazole, described in Section 3b, combined with alcoholysis of the imidazolides constitutes a new synthesis of esters, which differs from conventional methods by virtue of its particularly mild reaction conditions. Equimolar amounts of carboxylic acid, alcohol, and *N,N'*-carbonyldiimidazole are allowed to react together in tetrahydrofuran, benzene, chloroform, dimethylformamide or similar inert solvents:

$$R{-}COOH + R'{-}OH + Im{-}CO{-}Im \rightarrow R{-}CO{-}OR' + CO_2 + 2\,ImH$$

(Im = N-Imidazolyl)

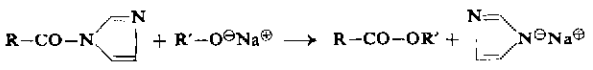
In contrast to aminolysis of imidazolides (Section 4b), their alcoholysis – the second step in the ester synthesis – is quite slow at room temperature. Hence, the reaction mixture must be heated at 60–70 °C for some time [29]. However, it has been found recently that catalytic amounts of sodium ethoxide accelerate the ester synthesis to such an extent that even at room temperature, esterification is complete after a short time, usually within a few minutes [30]. This catalysis is a

[28] *H. A. Staab, K. Wendel,* and *B. Polenski,* unpublished data.

[29] *H. A. Staab,* Angew. Chem. *71*, 194 (1959).

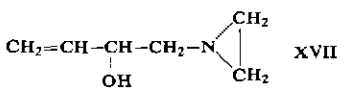
[30] *H. A. Staab, W. Rohr,* and *A. Mannschreck,* Angew. Chem. *73*, 143 (1961); *H. A. Staab* and *A. Mannschreck,* Chem. Ber. *95*, 1284 (1962).

result of the fact that ethoxide is a strongly nucleophilic agent and reacts with the imidazolide very rapidly, forming the ester:



Simultaneously, imidazolylsodium is formed; it is in equilibrium with the alcohol because the acidity constants of alcohols and imidazole are of the same order of magnitude. Hence, ethoxide is constantly reformed as long as it is used up by its reaction with the imidazolide. In agreement with this explanation, imidazolylsodium or other alkali metal compounds capable of converting alcohols to alkoxides, *e.g.* sodamide, may be used in place of ethoxide to initiate the catalytic cycle. Since in the presence of these catalysts, *N,N'*-carbonyldiimidazole itself reacts with alcohols to give carbonic esters (Section 7b), in the ester synthesis following the two-in-one-reaction procedure, the catalyst may only be added after the reaction of *N,N'*-carbonyldiimidazole with the carboxylic acid has proceeded to the imidazolide stage. This is indicated by the subsidence of the CO_2 evolution. An approximately 0.05 mole% solution of sodium ethoxide or imidazolylsodium, prepared easily by dissolving sodium in alcohol or in a tetrahydrofuran solution of imidazole, respectively, is used.

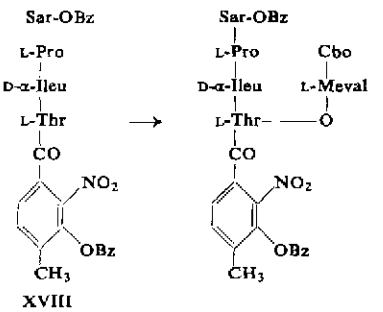
Table 4 contains a few examples of esters synthetized by the imidazolide method. "E" indicates that the esters were prepared directly from the free carboxylic acid and alcohol by the two-in-one-reaction procedure. The yields are based on carboxylic acid. It is noteworthy that even esters of polyunsaturated alcohols and carboxylic acids, *e.g.* esters of the vitamin A series, may be obtained in excellent yields. The same is usually true for esters of tertiary alcohols, whose synthesis by conventional methods presents difficulties. However, esters of tertiary alcohols cannot be prepared in this manner



XVII

from carboxylic acids containing "acidic" hydrogen atoms on the α-C atom, because C-C condensations, described in Section 4c, take place. Cytostatic esters of 1-ethyleneimino-2-hydroxybut-3-ene (XVII) were synthetized in excellent yields by the imidazolide method at room temperature and with reaction times of only a few minutes [31]. Their synthesis by conventional methods is difficult because of the high sensitivity of this unsaturated ethyleneiminoalcohol.

Brockmann and *Lackner*[32] used the imidazolide method for ester synthesis in their total synthesis of actinomycin C_3. Working with carbobenzoxy-L-*N*-methylvaline and *N,N'*-carbonyldiimidazole, they succeeded in esterifying the hydroxyl group on the threonine residue in XVIII; this could not be accomplished by any of the conventional methods.

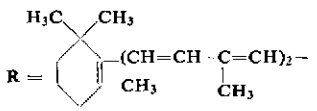


XVIII

Thus the use of the imidazolide method is advantageous when highly labile carboxylic acids or alcohols must be esterified under very mild conditions. Because of its nearly quantitative course, this reaction has also been used for the synthesis of isotope-labelled esters [33].

With diols, diimidazolides of dicarboxylic acids, such as terephthalic acid or adipic acid, yield the corresponding polyesters [34].

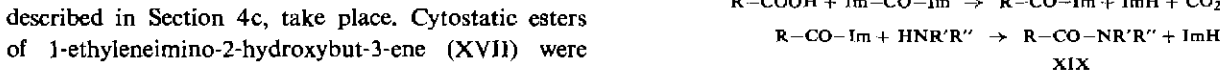
Table 4. Esters synthetized by the imidazolide method [30]



Ester	Yield [%]
$C_6H_5-CO-O-CH_2-C_6H_5$	89 (E)
$C_6H_5-CO-O-CH_2-CH=CH-C_6H_5$	77 (E)
	85
$C_{15}H_{31}-CO-O-CH_2-CH=CH-C_6H_5$	80
$C_6H_5-CH=CH-CO-O-CH_3$	83 (E)
$CH_3-CO-O-CH_2-R$	91; 66 (E)
$R-CO-O-CH_3$	91; 70 (E)
$R-CO-O-C_2H_5$	88; 50 (E)
$R-CO-O-CH_2-R$	73
$C_6H_5-CO-O-C(CH_3)_3$	91 (E)
$(CH_3)_3C-C_6H_4-CO-O-C(CH_3)_3$	75
$(CH_3)_2CH-CO-O-C(CH_3)_3$	70
$(CH_3)_3C-CO-O-C(CH_3)_3$	64

b) Synthesis of Amides, Peptides, Hydrazides, and Hydroxamic Acids

Amides are prepared by the imidazolide method [19] by reacting the free carboxylic acid at room temperature with *N,N'*-carbonyldiimidazole in a 1:1 molar ratio and adding an equimolar amount of amine after the CO_2 evolution has subsided:



XIX

The reaction is complete after 1 to 2 hours at room temperature. After filtering off the imidazole, the amide is obtained, usually in very good yields. Suitable solvents are tetrahydrofuran, chloroform, dimethylformamide, *etc.* High molecular weight polyamides may be obtained without the use of solvents by heating an equimolar mixture of the diimidazolide of a dicarboxylic acid and a diamine such as hexamethylenediamine [34].

The use of *N,N'*-carbonyldiimidazole for the synthesis of peptide linkages was first recommended by *Anderson*

[31] *H. A. Staab* and *W. Rohr*, Chem. Ber. *95*, 1298 (1962).

[32] *H. Brockmann* and *H. Lackner*, Naturwissenschaften *47*, 230 (1960); also see *H. Brockmann*, Angew. Chem. *72*, 939 (1960).

[33] Cf. *A. R. Ronzio* and *T. J. De Cino*, Microchem. J. *4*, 531 (1960).

[34] *H. A. Staab*, Chem. Ber. *90*, 1326 (1957).

and *Paul* [35]. The acylamino acid is reacted in tetrahydrofuran at room temperature with an equimolar amount of *N,N'*-carbonyldiimidazole, and after 1 hour, the ester of the desired amino acid or peptide is added. In this second step, hydrochlorides of the ester of the amino acid may also be used. Although the yields are lower, it is possible to use even aqueous solutions of salts of amino acid. The first reaction step, *i.e.*, the reaction with *N,N'*-carbonyldiimidazole, must be carried out under anhydrous conditions, however, since otherwise hydrolysis of the carbonyldiimidazole competes with the conversion of the latter into the imidazolide [36]. An excess of *N,N'*-carbonyldiimidazole must be avoided, because it would react with the amine component to give urea derivatives [37].

Besides its favorable yields and simple experimental procedure, the peptide synthesis with *N,N'*carbonyldiimidazole also has the advantage that racemization of the amino acids is minimized because of the mild reaction conditions. *Paul* and *Anderson* [35] indicate that racemization amounts to less than 0.5 % if both reaction steps are performed in dimethylformamide at −10 °C. *Kappeler* and *Schwyzer* [38] used the method to synthetize a heptapeptide closely related to the adrenocorticotropic hormone (ACTH) and the two melanophore-stimulating hormones (α- and β-MSH).

Hydrazides of carboxylic acids can be prepared by the imidazolide method in a similar fashion [19]. For example, the hydrazide of isonicotinic acid is obtained in very good yield from isonicotinic acid and hydrazine hydrate by the two-in-one-reaction procedure at room temperature. Diimidazolides of dicarboxylic acids react with hydrazines in a 1:1 molar ratio to form cyclic hydrazides, *e.g.* the diimidazolide of 2,2-dimethylmalonic acid and phenylhydrazine afford 1-phenyl-4,4-dimethyl-3,5-dioxopyrazolidine.

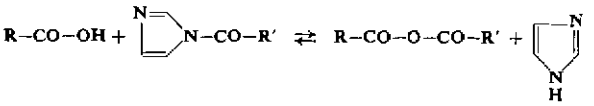
Hydroxamic acids are formed from carboxylic acids when imidazolide solutions in tetrahydrofuran are shaken with hydroxylammonium chloride at room temperature [19]. The formation of hydroxamic acids is complete within a few minutes, as indicated by the colorimetric test with $FeCl_3$. If an isolated imidazolide is used, the hydroxamic acid (XX) is accompanied by tetrahydrofuran-insoluble imidazolium chloride, as shown by the following equation:

$$R{-}CO{-}Im + [NH_3OH]^{\oplus}Cl^{\ominus} \rightarrow R{-}CO{-}NHOH + ImH_2^{\oplus}Cl^{\ominus}$$
(XX)

Thus, after filtration and evaporation of the solvent, the hydroxamic acid is directly obtained.

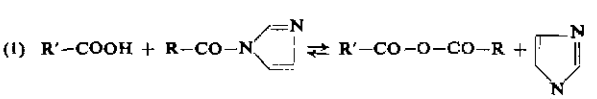
c) Synthesis of Anhydrides of Carboxylic Acids

It is characteristic of the high "transacylation potential" of imidazolides that they can be used to acylate carboxylic acids to form anhydrides [39]. However, an anhydride synthesis of preparative significance is only possible if the equilibrium

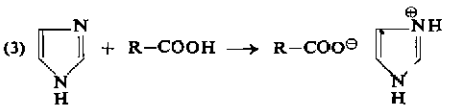


can be affected in favor of the anhydride formation. Hence, an anhydride is obtained if an imidazolide is reacted at room temperature in a 1:2 molar ratio with a carboxylic acid which forms a salt with the imidazole (formed by transacylation) that is insoluble in the solvent used (ether, tetrahydrofuran, benzene). Thus, trifluoroacetic acid and *N*-(trifluoroacetyl)imidazole afford trifluoroacetic anhydride in good yield [40]. Similarly, maleic and phthalic anhydrides are obtained from the corresponding acids via the monoimidazolide step, by treating the acid in a 3:1 molar ratio with *N,N'*-carbonyldiimidazole in tetrahydrofuran at room temperature. Two moles of the insoluble monoimidazolium salt of the dicarboxylic acids are also formed in this reaction.

However, with the aid of *N*-(trifluoroacetyl)- or *N*-(trichloroacetyl)-imidazole, it is possible to obtain symmetrical anhydrides even from carboxylic acids which do not form salts insoluble in benzene, ether, or tetrahydrofuran. This is accomplished by treating the acid with one of these imidazolides in a 2:1 molar ratio [40]. In this case, equilibria (1) and (2) are followed by irreversible formation (3) of insoluble imidazole trifluoro- or trichloro-acetate:



(2) $R'{-}COOH + R{-}CO{-}O{-}CO{-}R' \rightleftarrows R'{-}CO{-}O{-}CO{-}R' + R{-}COOH$



($R = -CF_3$ or $-CCl_3$)

This reaction with *N*-(trifluoroacetyl)- or *N*-(trichloroacetyl)-imidazole may be used to synthetize symmetrical aliphatic and aromatic anhydrides from free carboxylic acids (yields: benzoic anhydride 81%, phthalic anhydride 89 %, palmitic anhydride 54 %). It fails with carboxylic acids which by "transimidazolation" form an imidazo-

[35] *R. Paul* and *G. W. Anderson*, J. Amer. chem. Soc. *82*, 4596 (1960); J. org. Chemistry *27*, 2094 (1962); preliminary communication: *G. W. Anderson* and *R. Paul*, J. Amer. chem. Soc. *80*, 4423 (1958).

[36] Lack of attention to this competing reaction explains the negative result obtained by *J. C. Sheehan* and *K. R. Menery-Logan*, [J. Amer. chem. Soc. *81*, 3089 (1959)] in their attempt, in the total synthesis of penicillin V, to form the β-lactam ring using *N,N'*-carbonyldiimidazole in aqueous solution.

[37] Cf. *H. Giesemann* and *D. Braun*, J. prakt. Chem. *8*, 39 (1959); on reacting DL-phenylalanine with an excess of *N,N'*-carbonyldiimidazole, these authors obtained no peptide formation; instead they observed the formation of *N,N'*-carbonyl-bis-DL-phenylalanine.

[38] *H. Kappeler* and *R. Schwyzer*, Helv. Chim. Acta *43*, 1453 (1960); for further applications, see *H. Kappeler*, Helv. Chim. Acta *44*, 476 (1961); *L. Birkofer*, *W. Konkol*, and *A. Ritter*, Chem. Ber. *94*, 1263 (1961); see also *H. C. Beyerman* and *W. Maassen van den Brink*, Recueil Trav. chim. Pays-Bas *80*, 1372 (1961), who used *N.N'*-carbonyldi-(1,2,4-triazole) as peptide forming reagent.

[39] *H. A. Staab*, *G. Walther*, and *W. Rohr*, Chem. Ber., in press.

[40] *H. A. Staab* and *G. Walther*, Chem. Ber., in press.

lide which itself gives an insoluble trichloro- or trifluoroacetate. For example, the reaction of cinnamic acid with *N*-(trichloroacetyl)imidazole does not yield cinnamic anhydride Instead, the trichloroacetate of *N*-cinnamoylimidazole is obtained in 95 % yield.

d) C-Acylation of Alkylenephosphoranes

Triphenylalkylenephosphoranes (XXI, R = H or alkyl) can be *C*-acylated in excellent yields by reaction with imidazolides in a 2:1 molar ratio at room temperature in benzene or benzene/tetrahydrofuran [41]. In the "transylidation" which follows this reaction, the second mole of XXI acts as proton acceptor.

$$(C_6H_5)_3P{=}CHR + R'{-}CO{-}Im \rightarrow (C_6H_5)_3P^{\oplus}{-}CHR{-}CO{-}R' + Im^{\ominus}$$

XXI

$$(C_6H_5)_3P^{\oplus}{-}CHR{-}CO{-}R + (C_6H_5)_3P{=}CHR \rightarrow (C_6H_5)_3P{=}CR{-}CO{-}R' + (C_6H_5)_3{}^{\oplus}P{-}CH_2R$$

XXII

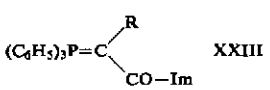
R=H, R'=C_6H_5: 99 % Yield

R=CH_3, R'=C_6H_5: 77 % Yield

R=H, R'=CH_3: 70 % Yield

Most interesting is the *C*-formylation of alkylenephosphoranes to yield α-formyl derivatives such as XXII, where R = R' = H (81 % yield) [42]. In the Wittig reaction, these triphenyl-α-formylalkylenephosphoranes afford α,β-unsaturated aldehydes [43], while hydrolysis gives aldehydes RCH_2CHO.

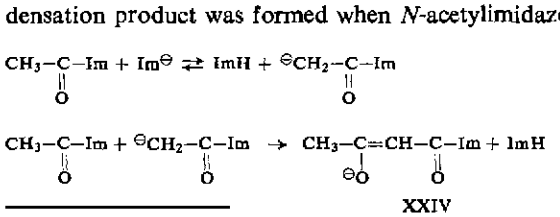
Triphenylalkylenephosphoranes (XXI) react with *N*,*N*'-carbonyldiimidazole at room temperature to form triphenyl (α-carboxylalkylene)phosphorane imidazolides (XXIII, R = H, yield = 81 %; XXIII, R = CH_3, yield = 60 %). Hydrolysis of these compounds gives carboxylic acids RCH_2COOH in good yields. The Wittig reaction proceeds via the imidazolides to give α,β-unsaturated carboxylic acids in moderate yields.



XXIII

e) Other C-Acylations [44]

When an attempt was made to prepare t-butyl acetate by reacting *N*-acetylimidazole with t-butanol in the presence of sodium t-butoxide, the sodium enolate of *N*-acetoacetylimidazole (XXIV) was obtained. The same condensation product was formed when *N*-acetylimidazole



XXIV

was reacted with imidazolylsodium in a 2:1 molar ratio at room temperature in tetrahydrofuran. In other words, a reaction similar to a Claisen ester condensation results. The fact that such C-C condensations have not been observed during the esterification of aliphatic carboxylic acids by the imidazolide method with primary and secondary alcohols in the presence of an alkoxide or imidazolylsodium catalyst (cf. Table 4) is attributed to the unusually fast formation of ester in this case. Only with tertiary alcohols the alcoholysis of the imidazolide is slow enough for C-C condensation to take place, provided that an acidic hydrogen is present on the α-carbon atom. Another example of C-acylation by means of imidazolides is the reaction of *N*-benzoylimidazole with ethyl sodiomalonate, yielding ethyl benzoylmalonate.

f) Acylation of Peroxides with Imidazolides [45]

Imidazolides acylate hydrogen peroxide to form peroxycarboxylic acids, which in turn can react further with imidazolides to give diacyl peroxides. Thus, if H_2O_2 is treated with imidazolides in a 1:2 molar ratio, symmetrical diacyl peroxides are obtained:

$$R{-}CO{-}Im + HO{-}OH \rightarrow R{-}CO{-}O{-}OH + ImH$$

$$R{-}CO{-}Im + HO{-}O{-}CO{-}R \rightarrow R{-}CO{-}O{-}O{-}CO{-}R + ImH$$

The reaction is carried out at room temperature in tetrahydrofuran and affords diacyl peroxides in very good yields (Table 5). Use of anhydrous hydrogen peroxide solution is not necessary, since it was found that the yields with 34 % and 17 % aqueous hydrogen peroxide solutions are no worse than those obtained with anhydrous ether solutions of H_2O_2. Because of the stronger nucleophilic character of hydrogen peroxide, hydrolysis of the imidazolides is completely suppressed.

Table 5. Preparation of diacyl peroxides

Diacyl peroxide	Yield [%]
Dibenzoyl-peroxide	88
Di-p-toluyl-peroxide	91
Di-[*p*-chlorobenzoyl]-peroxide	85
Di-[*p*-nitrobenzoyl]-peroxide	87
Dicinnamoyl-peroxide	63
Dilauroyl-peroxide	88
Dipalmitoyl-peroxide	67

In this case, too, it is possible to start directly from the free carboxylic acid and use a two-in-one-reaction procedure. The acid is treated with *N*,*N*'-carbonyldiimidazole to form the imidazolide, which in turn is allowed to react with hydrogen peroxide without being isolated.

The two steps required to produce diacyl peroxides from H_2O_2 and imidazolides may also be accomplished separately. With a great excess of H_2O_2, imidazolides afford peroxycarboxylic acids, and the latter react with imidazolides to give diacyl peroxides in excellent yields. The latter reaction may be used to prepare unsymmetrical diacyl peroxides (*e.g.* *p*-nitrobenzoyl benzoyl peroxide,

[41] *H. J. Bestmann, N. Sommer,* and *H. A. Staab,* Angew. Chem., Internat. Edit. *1*, 270 (1962).

[42] *H. A. Staab* and *N. Sommer,* Angew. Chem., Internat. Edit. *1*, 270 (1962).

[43] Cf. *S. Trippett* and *M. Walker,* J. chem. Soc. (London) *1961*, 1266.

[44] *H. A. Staab* and *A. Mannschreck,* unpublished data.

[45] *H. A. Staab* and *W. Rohr,* unpublished data.

yield = 74 %; *p*-chlorobenzoyl benzoyl peroxide, yield = 79 %). However, one special precaution must be taken: even at room temperature, imidazole is capable of converting unsymmetrical diacyl peroxides by transacylation into a mixture of all three possible diacyl peroxides (*N*-alkylimidazoles cannot do this). To prevent this rearrangement, the imidazole formed in the reaction between the imidazolide and the peroxy-acid must be separated immediately in the form of its maleate, which is insoluble in tetrahydrofuran.

5. Synthesis of Aldehydes from Carboxylic Acids via Imidazolides

The reduction of azolides to aldehydes with $LiAlH_4$ is closely related to the transacylations discussed up to this point, insofar as it is also primarily a nucleophilic reaction, *i.e.* a nucleophilic attack of a hydride anion on the carbonyl group. $LiAlH_4$ reduces normal amides to amines with the same number of carbon atoms or to alcohols. Prevention of this further reduction should be easier, the faster the first reaction step takes place, *i.e.* the faster the nucleophilic addition of hydride anion onto the carbonyl group occurs. Taking this into consideration, *Wittig* and *Hornberger* [46] reduced *N*-acylcarbazoles with $LiAlH_4$ and obtained aldehydes in good yields. The carbonyl groups of all other carboxamides, from which aldehydes have been prepared in recent years by reduction with $LiAlH_4$, were similarly activated for nucleophilic reactions. These amides include *N*-methylanilides [47] and pyrazolides [48]. Since imidazolides are more reactive in nucleophilic reactions than even these carboxamides, and since they can be readily prepared from the free carboxylic acids and *N,N'*-carbonyldiimidazole, reduction of carboxylic acids to aldehydes via imidazolides seemed to be particularly promising.

Table 6 contains some results [49]. Optimum reaction conditions vary somewhat. Reductions were usually carried out in ether or tetrahydrofuran, with a little more than 0.25 mole of $LiAlH_4$ per mole of imidazolide, and at −20 °C for 30 to 60 min. The good results obtained in the reduction of unsaturated imidazolides, for example in the synthesis of vitamin A aldheyde (retinene) from vitamin A acid (68 % yield), are noteworthy. Diimidazolides of dicarboxylic acids give dialdehydes. Imidazolides of monoesters of dicarboxylic acids yield monoester aldehydes, and *N*-acylaminocarboxylic imidazolides form *N*-acylaminoaldehydes [50]. Thus, because of its great reactivity, the imidazolide group can be selectively reduced with $LiAlH_4$.

It is particularly advantageous that a two-in-one-reaction process, involving no isolation of the imidazolide, is possible in this case, too. Hence, aldehydes are obtained directly from free carboxylic acids by reacting the latter in tetrahydrofuran or ether with *N,N'*-carbonyldiimidazole in a 1:1 molar ratio, and immediately treat-

Table 6. Aldehydes prepared from imidazolides

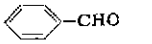
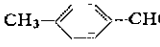
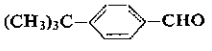
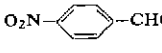
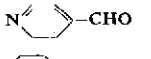
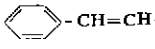
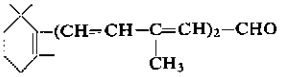
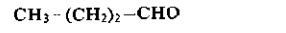
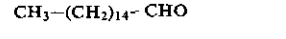
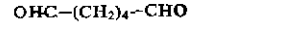
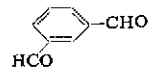
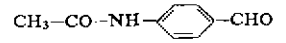
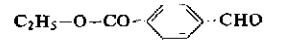
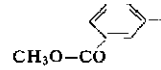
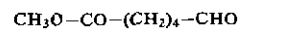
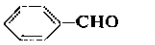
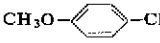
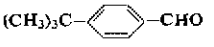
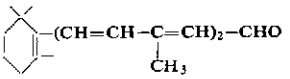
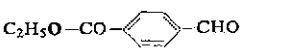
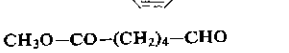
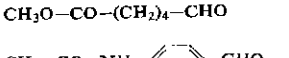
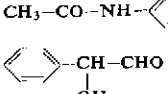
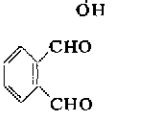
Aldehyde	Yield [%]
	77.5
	79
	76
	87.5
	82
	69.5
	68
	60
	84
	65
	69.5
	53
	72
	51
	71

Table 7. Aldehydes prepared directly from carboxylic acids by the two-in-one-reaction process

Aldehyde	Yield [%]
	83
	65
	67
	77
	56
	78.5
	59
	55
	33.5
	29.5

[46] *G. Wittig* and *P. Hornberger*, Liebigs Ann. Chem. *577*, 511 (1952).

[47] *F. Weygand, G. Eberhardt, H. Linden, F. Schäfer*, and *I. Eigen*, Angew. Chem. *65*, 525 (1953).

[48] *W. Ried* and *F. J. Königstein*, Liebigs Ann. Chem. *622*, 37 (1959); see also *W. Ried, G. Deuschel*, and *A. Kotelko*, *ibid. 642*, 121 (1961).

[49] *H. A. Staab* and *H. Bräunling*, Liebigs Ann. Chem. *654*, 119 (1962).

[50] *H. A. Staab* and *H. Bräunling*, unpublished data.

ing the imidazolide solution with $LiAlH_4$. However, in this case, an additional 0.25 mole of $LiAlH_4$ must be used, because the imidazolide solution resulting from the reaction of *N,N'*-carbonyldiimidazole with the carboxylic acid contains 1 mole of imidazole with active hydrogen per mole of imidazolide. The yields of aldehyde given in Table 7 refer to this two-in-one-reaction procedure and are based directly on the amount of carboxylic acid used. Hydroxycarboxylic acids with unprotected hydroxyl groups have also been reduced to hydroxyaldehydes by this two-in-one-reaction procedure, although in moderate yields. For example, mandelic acid gave mandelaldehyde in 33.5 % yield.

6. Synthesis of Ketones from Carboxylic Acids via Imidazolides

In the reaction of carboxylic acid derivatives with Grignard reagents, the yields of ketones are usually low owing to further reaction to give the corresponding tertiary alcohols, and to other side reactions. For reasons similar to those discussed in Section 5 with regard to the reduction to aldehydes with $LiAlH_4$, the preparation of ketones by reaction of imidazolides with organomagnesium reagents appeared to be promising. Table 8 [51] illustrates the preparation of purely aromatic, aromatic aliphatic, and purely aliphatic ketones by the reaction of imidazolides of aromatic or aliphatic carboxylic acids with aromatic or aliphatic Grignard reagents. The yields are very satisfactory, even for purely aliphatic ketones, since in this case too, alcohol formation is completely suppressed. The unfavorable result obtained in the synthesis of sorbophenone, whose preparation by other methods also results in poor yields [52], can be attributed to the instability of this compound.

Table 8. Ketones prepared from imidazolides and Grignard reagents [51]

Imidazolide	Grignard-reagent	Ketone	Yield [%]
C_6H_5–CO–Im	C_6H_5–MgBr	C_6H_5–CO–C_6H_5	72
3–Cl–C_6H_4–CO–Im	C_6H_5–MgBr	3–Cl–C_6H_4–CO–C_6H_5	94
4–Cl–C_6H_4–CO–Im	C_6H_5–MgBr	4–Cl–C_6H_4–CO–C_6H_5	91
3–Br–C_6H_4–CO–Im	C_6H_5–MgBr	3–Br–C_6H_4–CO–C_6H_5	87
4–Br–C_6H_4–CO–Im	C_6H_5–MgBr	4–Br–C_6H_4–CO–C_6H_5	88
CH_3–CO–Im	C_6H_5–MgBr	CH_3–CO–C_6H_5	50
CH_3–$(CH_2)_4$–CO–Im	C_6H_5–MgBr	CH_3–$(CH_2)_4$–CO–C_6H_5	69
CH_3–$(CH{=}CH)_2$–CO–Im	C_6H_5–MgBr	CH_3–$(CH{=}CH)_2$–CO–C_6H_5	5
CH_3–$(CH_2)_4$–CO–Im	C_2H_5–MgBr	CH_3–$(CH_2)_4$–CO–C_2H_5	64
CH_3–$(CH_2)_4$–CO–Im	CH_3–MgBr	CH_3–$(CH_2)_4$–CO–CH_3	73.5

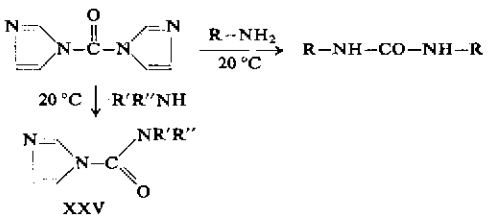
7. Reactions of N,N'-Carbonyldiimidazole Analogous to Those of Phosgene

a) Reaction with Amines

In reactions with amines and alcohols, *N,N'*-carbonyldiimidazole shows about the same reactivity as phosgene. The fact that it can be prepared in such good yields from phosgene and imidazole can be ascribed to the insolubility of imidazolium chloride in tetrahydrofuran, benzene, and chloroform (as for the preparation of imidazolides from acid chlorides and imidazole).

Naturally, the preparative use of *N,N'*-carbonyldiimidazole in reactions in which phosgene is normally used is of practical interest only in special cases where the following advantages are important: 1. carbonyldiimidazole reactions take place in neutral media without formation of HCl; the reaction product is accompanied only by imidazole which is markedly inert and which can usually be removed readily; 2. once prepared, *N,N'*-carbonyldiimidazole is a non-toxic, crystalline substance and is more convenient to handle and easier to measure out than toxic, gaseous phosgene.

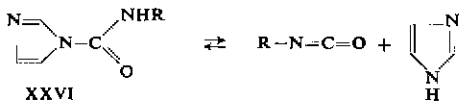
In inert solvents, *N,N'*-carbonyldiimidazole reacts quantitatively with primary aliphatic and aromatic amines within a few minutes even at room temperature to yield ureas [53]. Ureas may also be obtained without using solvent, by heating a mixture of the components; where diamines are used, high molecular weight polyamides of carbonic acid (polyureas) are formed.



XXV

At room temperature, the reaction with secondary amines occurs on one side only, and imidazole-*N*-carboxamides (XXV) are formed.

By using primary amines in a 1:1 molar ratio, primary imidazole-*N*-carboxamides (XXVI) are obtained. These compounds are interesting for their ability to dissociate into isocyanates and imidazole, even at room temperature.



XXVI

It was determined by infrared spectrophotometry from the extinction of the very characteristic isocyanate band at 2250 cm^{-1}, that XXVI (R = C_6H_5) in chloroform is dissociated to the extent of 16.1 % at 20 °C and 36.7 % at 45 °C [54–56].

[51] *H. A. Staab* and *E. Jost*, Liebigs Ann. Chem., in press.

[52] *R. Kuhn* and *H. A. Staab*, Chem. Ber. *87*, 262 (1954).

[53] *H. A. Staab*, Liebigs Ann. Chem. *609*, 75 (1957).

[54] *W. Otting* and *H. A. Staab*, Liebigs Ann. Chem. *622*, 23 (1959).

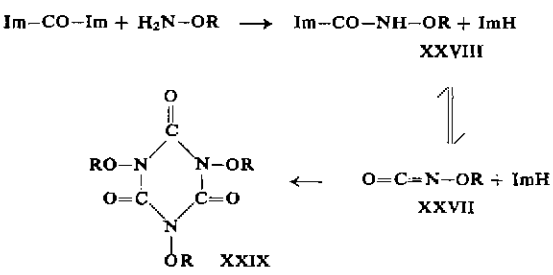
[55] *J. Derkosch*, *K. Schlögl*, and *H. Woidich*, Monatsh. Chem. *88*, 35 (1957).

[56] *H. A. Staab*, Liebigs Ann. Chem. *609*, 83 (1957).

This dissociation forms the basis for a simple method of preparing isocyanates from aliphatic, alicyclic, and aromatic amines [57]. One mole of amine is added dropwise at room temperature to a solution of one mole of *N,N'*-carbonyldiimidazole. Distillation of the mixture then produces pure isocyanate in good yield. The mixture may also be treated directly with an alcohol to produce a carbamate (urethane), or with another amine, to produce an unsymmetrical urea. Because of their great tendency to dissociate, imidazole-*N*-carboxamides are at the head of the list of "masked isocyanates". Whereas, as a rule, the dissociation of urethanes and trisubstituted ureas requires rather high temperatures [58], imidazole-*N*-carboxamide solutions practically behave like isocyanate solutions even at room temperature. In the solid state, however, imidazole-*N*-carboxamides are crystalline, stable compounds, free of the toxic side effects of isocyanates.

The behavior of benzimidazole-*N*-carboxamides is similar to that of the imidazole derivatives. On the other hand, dissociation into isocyanates at room temperature could not be detected in the case of 1,2,3-triazole, 1,2,4-triazole, and benzotriazole derivatives, which are more reactive than the imidazole analogues in direct nucleophilic reactions involving the carbonyl group, nor in the case of the pyrazole and indazole compounds [54, 57, 59].

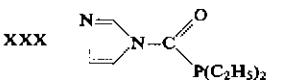
The dissociation of imidazole-*N*-carboxamides into isocyanates prompted us to attempt the preparation of alkoxyisocyanates (XXVII), *i.e.* representatives of hitherto unknown monoximes of carbon dioxide. These compounds should form from the product (XXVIII) of the reaction between *N,N'*-carbonyldiimidazole and *O*-alkylhydroxylamines. In fact, when XXVIII (R = CH_2–C_6H_5) is heated, the corresponding trialkoxyisocyanuric acid (XXIX) is formed by trimerization of XXVII [60]. It also appeared very probable that aminolysis of XXVIII, which, for example, gives *N*-benzoxyurea with cyclohexylamine in a few minutes at room temperature, also proceeds through stage XXVII. This is supported by the fact that compounds



of type XXVIII, in which the amide hydrogen is substituted by an alkyl and which therefore are no longer able to dissociate into alkoxyisocyanates, do not aminolyze under these conditions [61]. The results obtained to date suggest that compounds of type XXVII can be formed. However, their tendency to trimerize is apparently so great that their direct detection is difficult. The same is also true for aminoisocyanates, which may be regarded as monohydrazones of carbon dioxide. These, however, do not trimerize but, according to preliminary findings, form dimers with four-membered rings [61].

The difference cited above between reactions of *N,N'*-carbonyldiimidazole with primary and secondary amines, too, is based on the ability of imidazole-*N*-carboxamides of primary amines to dissociate. The imidazole-*N*-carboxamides XXV formed in the reaction with secondary amines can react further with nucleophilic reagents only if the carbonyl group is directly attacked; this requires more vigorous conditions than those encountered in the reaction involving an isocyanate intermediate. In this case, to obtain the carbamates, equimolar amounts of alkoxide must be added and the solution heated. In this way, carbamates of cytostatically active 1-ethyleneimino-2-hydroxy-3-butene were obtained [31].

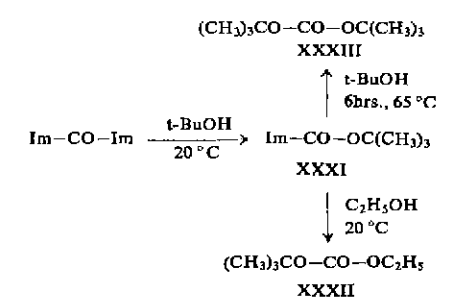
The reaction of *N,N'*-carbonyldiimidazole with phosphines is analogous to that with amines. Thus compound



XXX is formed with diethylphosphine, but its imidazole residue cannot be replaced even by prolonged heating with an excess of diethylphosphine [62].

b) Reaction with Alcohols

On heating, *N,N'*-carbonyldiimidazole reacts with alcohols and phenols, forming diesters of carbonic acid [53]. As in the case of alcoholysis of imidazolides, the reaction can be accelerated so effectively with catalytic amounts of sodium ethoxide or imidazolylsodium that it takes place, in most cases exothermically, even at room temperature [30]. Under these conditions, only t-butanol, even when in excess, reacts with *N,N'*-carbonyldiimidazole only to form t-butyl imidazole-*N*-carboxylate (XXXI). The latter compound was recently proposed by *Brenner* and *Klee* [63] as a reagent for the t-butyloxycarbonylation of amino acids. Whereas, by using the catalytic method at room temperature, XXXI and ethanol react smoothly to give ethyl t-butyl carbonate (XXXII), the catalyzed reaction with t-butanol yields di-t-butyl carbonate (XXXIII) only on heating at 65 °C for several hours.



The reaction of *N,N'*-carbonyldiimidazole with only one mole of alcohol yields imidazole-*N*-carboxylic esters, which can also be prepared from imidazole and

[57] *H. A. Staab* and *W. Benz*, Liebigs Ann. Chem. *648*, 72 (1961).

[58] Cf. *S. Petersen* in *Houben-Weyl-Müller:* Methoden der organischen Chemie. 4th ed., G. Thieme Verlag, Stuttgart 1952, Vol. 8, p. 119.

[59] *H. A. Staab* and *G. Seel*, Liebigs Ann. Chem. *612*, 187 (1958).

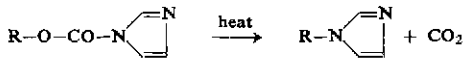
[60] *H. A. Staab* and *W. Benz*, Angew. Chem. *73*, 657 (1961).

[61] *H. A. Staab* and *W. Benz*, unpublished data.

[62] *H. A. Staab* and *D. W. Müller*, unpublished data.

[63] *W. Klee* and *M. Brenner*, Helv. Chim. Acta *44*, 2151 (1961).

chloroformates [64]. As already mentioned for XXXI, unsymmetrical carbonates may be prepared via these compounds; with amines, carbamates are formed. By analogy to the corresponding chloroformates, benzyl and benzhydryl esters of imidazole-*N*-carboxylic acid are thermally not very stable and are transformed into substituted imidazoles, with evolution of CO_2:

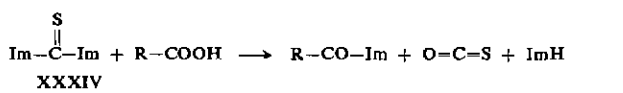


XXXI decomposes at 160–170 °C into CO_2, isobutylene, and imidazole.

With bifunctional co-reactants, *N,N'*-carbonyldiimidazole yields polycarbonates [54] or polyurethanes.

8. Reactions of N,N'-Thiocarbonyldiimidazole Analogous to Those of Thiophosgene [65]

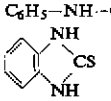
The behavior of *N,N'*-thiocarbonyldiimidazole (XXIV), which is easily prepared from thiophosgene and imidazole, is similar to that of carbonyldiimidazole, except that it is somewhat less reactive. With water, it hydrolyzes slowly at room temperature to form imidazole and carbonyl sulfide. With carboxylic acids, imidazolides are formed, with liberation of COS:



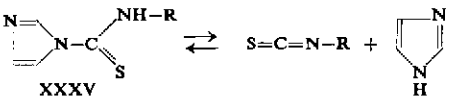
XXXIV

With primary aliphatic and aromatic amines in a 2:1 molar ratio, a quantitative yield of thioureas is obtained at room temperature (Table 9). Secondary amines,

Table 9. Thioureas prepared from XXIV and primary amines [65]

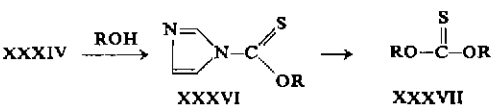
Thiourea	Yield [%]
C_4H_9–NH–CS–NH–C_4H_9	91
C_6H_{11}–NH–CS–NH–C_6H_{11}	94
C_6H_5–NH–CS–NH–C_6H_5	90
	90

even if used in excess, only form imidazole-*N*-thiocarboxamides with XXXIV. This indicates that in the reaction with primary amines, the formation of thiourea occurs via the isothiocyanate. In fact, by analogy to the synthesis of isocyanates, isothiocyanates (mustard oils) are obtained in very good yields by reacting XXXIV with primary aliphatic or aromatic amines in equimolar amounts at room temperature. It is noteworthy that even at room temperature, the dissociation equilibrium of imidazole-*N*-thiocarboxamides (XXXV) is completely shifted to the right hand side [66].



XXXV

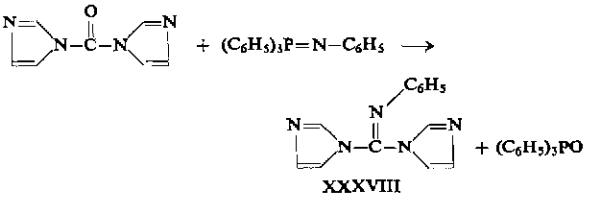
XXXIV smoothly reacts with alcohols and phenols to give imidazole-*N*-thiocarboxylic *O*-esters (XXXVI), which on prolonged heating react further with a second mole of alcohol or phenol forming *O,O*-diesters of thiocarbonic acid (XXXVII).



XXXVI XXXVII

9. Imino Derivatives of N,N'-Carbonyldiimidazole and Imidazolides [67]

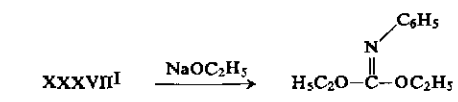
In order to obtain the *N*-phenylimino derivative of *N,N'*-carbonyldiimidazole (XXXVIII), the reaction with triphenylphosphine *N*-phenylimide, applied previously by *Staudinger* and *Hauser* [68] to ketenes, isocyanates, ketones, and aldehydes, was used with *N,N'*-carbonyldiimidazole as carbonyl component giving good yields.



XXXVIII

XXXVIII is a crystalline compound, m.p. 135–136 °C, and compared to *N,N'*-carbonyldiimidazole, is remarkably unreactive: it dissolves in 2 N HCl and can be reprecipitated with ammonia. Concentrated hydrochloric acid cleaves XXXVIII into CO_2, aniline, and imidazole. Stable salts are formed with carboxylic acids in a 2:1 molar ratio. Heavy metal salts ($FeCl_3$, $CuCl_2$) give sparingly soluble, stable 1:1 complexes.

On heating, XXXVIII reacts with sodium ethoxide in ethanol to form the diethyl ester of *N*-phenyliminocarbonic acid (yield: 82 %).



XXXIX

Unsubstituted *N,N'*-carbiminodiimidazole cannot be obtained by an analogous reaction from carbonyldiimidazole and unsubstituted triphenylphosphine imide [69]. In this reaction, the triphenylphosphine imide undergoes acylation with substitution of an imidazole residue, yielding XL, a crystalline compound, m.p. = 200–201 °C. Compound XL is stable

[64] *H. A. Staab*, Liebigs Ann. Chem. *609*, 83 (1957); *A. Patchornik, A. Berger*, and *E. Katchalski*, J. Amer. chem. Soc. *79*, 6416 (1957); cf. *W. John*, Ber. dtsch. chem. Ges. *68*, 2283 (1935).

[65] *H. A. Staab*, Angew. Chem. *73*, 148 (1961); *H. A. Staab* and *G. Walther*, Liebigs Ann. Chem., in press; *W. Ried* and *B. M. Beck*, Liebigs Ann. Chem. *646*, 96 (1961).

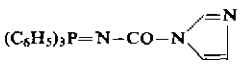
[66] *H. A. Staab* and *G. Walther*, Liebigs Ann. Chem., in press.

[67] *H. A. Staab* and *D. W. Müller*, unpublished data.

[68] *H. Staudinger* and *F. Hauser*, Helv. Chim. Acta *4*, 867 (1921).

[69] *R. Appel* and *A. Hauss*, Chem. Ber. *93*, 405 (1906).

towards water, but is cleaved by 2 *N* HCl at room temperature into triphenylphosphine oxide, ammonia, CO_2, and imidazole [70].



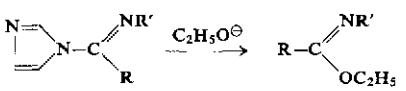
XL

Imidazolides of carboxylic acids react with triphenylphosphine *N*-phenyl imide to form the corresponding iminoacylimidazoles (XLI) in good yields. The latter can generally be prepared from one mole of an imido-

Table 10. Some iminoacylimidazoles and the yields of iminoesters (XLII) obtained therefrom [67]

	m.p. [°C]	Iminoester Yield
$C_6H_5-C(=N-CH_3)-Im$	61–63	53
$C_6H_5-C(=N-C_6H_5)-Im$	111–112	83
$CH_3-C(=N-C_6H_5)-Im$	108–110	83
$C_6H_5-CH=CH-C(=N-C_6H_5)-Im$	138–141	80

chloride and two moles of imidazole in tetrahydrofuran (see Table 10). In this case, too, with alkoxides, alcoholysis takes place in which iminoesters (XLII) are formed in good yields (Table 10):



XLI XLII

10. Imidazolides of Sulfonic Acids

The preparation and the most important reactions of imidazolides of carboxylic acids can also be applied in the sulfonic acid series [71].

a) Preparation and Properties

The preparation of imidazolides of sulfonic acids is analogous to that of the carboxylic derivatives (Section 2a). It can be accomplished in nearly quantitative yields by reacting either imidazole with sulfonyl chlorides, or sulfonic acids with *N,N'*-carbonyldiimidazole (at a higher temperature and in a 2:1 molar ratio, however). Sulfonic anhydrides also react with imidazole in a 1:2 molar ratio in tetrahydrofuran to form imidazolides and, simultaneously, insoluble imidazole sulfonates. The imidazolide of sulfanilic acid is of pharmacological interest; its preparation had been unsuccessfully attempted several years ago by Russian investigators [72]. It was now obtained via the fluoride of sulfanilic acid and also by hydrogenation of the imidazolide of azobenzene-4-sulfonic acid with Raney nickel.

At room temperature, the imidazolides of sulfonic acids (Table 11) are relatively stable to hydrolysis. However, they hydrolyze on heating in water alone. Under alkaline conditions, hydrolysis takes place rapidly even at room

[70] *R. Appel* and *H. A. Staab*, unpublished data.

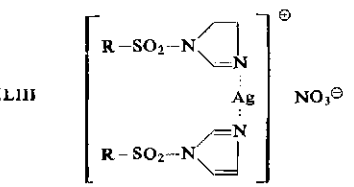
[71] *H. A. Staab* and *K. Wendel*, Chem. Ber. *93*, 2902 (1960).

[72] *S. I. Lur'e*, *M. G. Kuleshova*, and *N. K. Kochetkov*, Zhur. Obshch. Khim. (USSR) *9*, 1933 (1939); Chem. Abstr. *34*, 4388 (1940).

Table 11. Some imidazolides of aromatic sulfonic acids

	m.p. [°C]
$C_6H_5-SO_2-Im$	83–84
$4-CH_3-C_6H_4-SO_2-Im$	78–78.5
$4-H_2N-C_6H_4-SO_2-Im$	182–183 (decomp.)
$4-CH_3-CO-NH-C_6H_4-SO_2-Im$ [72]	167
$C_6H_5-N=N-C_6H_4-SO_2-Im$	168–168.5
$C_6H_5-NH-NH-C_6H_4-SO_2-Im$	140–141 (decomp.)

temperature; this is in contrast to normal sulfonamides, which are extremely stable to alkaline hydrolysis. Imidazolides of aromatic sulfonic acids form very sparingly soluble 2:1 complexes with $AgNO_3$, probably of structure XLIII. These are of interest because they undergo

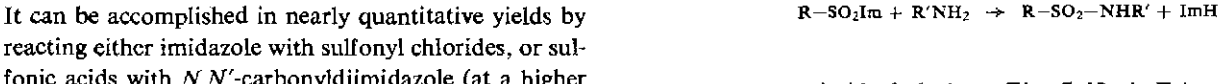


XLIII

aminolysis to give sulfonamides much more rapidly than the imidazolides of sulfonic acids themselves [73]. Thus, as in the protonation of *N*-acylimidazoles in acid solution, the binding of the lone electron pair on the nitrogen by the complex formation results in increased reactivity, attributable to the increased electronegativity of the ring nitrogens involved.

b) Aminolysis to Give Sulfonamides

Aminolysis of imidazolides of sulfonic acids requires prolonged heating at temperatures above 100 °C but usually gives good yields. In this case, too, it is possible to start out from the free sulfonic acid directly. The acid is treated with *N,N'*-carbonyldiimidazole to form the imidazolide, and the latter, without purification, is aminolyzed to the sulfonamide.



c) Alcoholysis to Give Sulfonic Esters

In alcoholysis reactions, too, imidazolides of sulfonic acids exhibit much lower reactivity than the correponding carboxylic derivatives. Although they do react quantitatively with phenols when a melt is heated at 100 °C for several hours, with alcohols under these conditions only very slight alcoholysis is observed. It was therefore very remarkable to find that, in the presence of 0.05 equivalents of sodium ethoxide or imidazolylsodium, imidazolides of sulfonic acids react with alcohols practically quantitatively and exothermically at room temperature in a very short time to form sulfonic esters (*e.g.* ethyl azobenzene-4-sulfonate in 91 % yield after 2 min. at 20 °C). The mechanism of this catalysis by bases corresponds to that operative in the synthesis of carboxylic esters by the imidazolide method (Section 4a). Because of the more pronounced nucleophilic character

[73] *H. A. Staab* and *K. Wendel*, unpublished data.

of alkoxide ions, sulfonate esters can also be prepared in good yields by alcoholysis of their imidazolides in the presence of hydroxyl ions, *i.e.* with aqueous-alcoholic sodium hydroxide.

d) Etherification Using Imidazolides of Sulfonic Acids

Addition at room temperature of a solution in benzene of the imidazolide of *p*-toluenesulfonic acid in a 1:2 molar ratio to a suspension in benzene of sodium cinnamoxide affords the dicinnamyl ether in 71 % yield [73, 74]. Apparently, a highly reactive, so far unisolated sulfonate of cinnamyl alcohol is formed first (a), which then reacts further with a second mole of alkoxide to form the ether according to (b):

(a) $R-SO_2-Im + R'-O^{\ominus}Na^{\oplus} \rightarrow R-SO_2-O-R' + Im^{\ominus}Na^{\oplus}$

(b) $R-SO_2-O-R' + R'-O^{\ominus}Na^{\oplus} \rightarrow R'-O-R' + R-SO_3^{\ominus}Na^{\oplus}$

With the sodium derivative of benzyl alcohol, the dibenzyl ether was obtained in 63 % yield, accompanied by 24 % *N*-benzylimidazole. The formation of the latter compound results from the reaction of the sulfonate ester with the imidazolylsodium formed in step (*a*). This competes with the second step of the ether synthesis (b) according to (c):

(c) $R-SO_2-O-R' + Im^{\ominus}Na^{\oplus} \rightarrow R'-Im + R-SO_3^{\ominus}Na^{\oplus}$

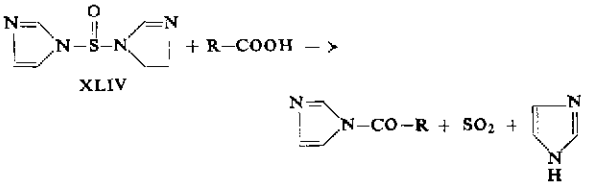
Thus, the reaction may be directed to effect predominantly *N*-alkylation of the imidazole, if low alkoxide and high imidazolylsodium concentrations are used. Under these conditions, *N*-benzylimidazole, for example, may be obtained in 90 % yield.

11. N,N'-Thionyldiimidazole and N,N'-Sulfuryldiimidazole

a) N,N'-Thionyldiimidazole [75]

Thionyl chloride and imidazole react together in a 1:4 molar ratio under anhydrous conditions, by a method analogous to that used for the synthesis of *N,N'*-carbonyldiimidazole; the resulting *N,N'*-thionyldiimidazole (XLIV) is rather difficult to purify. It is obtained in the pure state (m.p. 78–79 °C) in the reaction of thionyl chloride with *N*-trimethylsilylimidazole [76]. Compound XLIV is extremely hygroscopic and reacts with water at room temperature with considerable evolution of heat. It does not have to be purified for use in further reactions. After filtering off the imidazolium chloride, the solution of XLIV resulting from the reaction of imidazole with $SOCl_2$ may be used directly.

Compound XLIV reacts exothermically with alcohols and phenols at room temperature to form esters of sulfurous acid, *e.g.* the dimenthyl ester in 94 % and the di-α-naphthyl ester in 91 % yield. With carboxylic acids, imidazolides are formed at room temperature in nearly quantitative yield with evolution of SO_2 [75]:



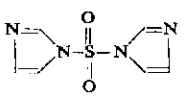
XLIV

Hence, XLIV, like carbonyldiimidazole, may be used to synthetize esters, amides, and peptides by the imidazolide method. Recently, *Wieland* and *Vogeler* used XLIV for the synthesis of peptides [77].

The greater reactivity of XLIV compared to that of *N,N'*-carbonyldiimidazole can be observed particularly well in the reaction with sulfonic acids, which with XLIV yield imidazolides of sulfonic acids even at room temperature.

b) N,N'-Sulfuryldiimidazole [78]

The preparation of *N,N'*-sulfuryldiimidazole (XLV) can be accomplished, in a manner analogous to that of XLIV, from sulfuryl chloride and imidazole. Compound XLV is much less reactive than XLIV; it can be crystallized from ethanol (m. p. 141 °C) and is hydrolyzed by

XLV 

dilute hydrochloric acid only on boiling. Even if heated, it does not react with carboxylic acids to form imidazolides. However, the imidazolide of *p*-toluenesulfonic acid was prepared in 87 % yield by reacting *p*-toluenesulfonic acid with XLV in a 2:1 molar ratio at 90 °C in the absence of solvent.

12. Imidazolides of Phosphoric Acid

The synthetic methods obtained as a result of applying imidazolide reactions in phosphoric acid chemistry are particularly interesting in view of the importance of phosphoric acid derivatives in biochemistry. It could be shown that the reactions developed are suitable for the synthesis of nucleotide coenzymes and other biochemically important phosphoric acid derivatives.

a) Preparation and Properties

Monoesters of phosphoric acid and orthophosphoric acid itself react with *N,N'*-carbonyldiimidazole in acetone at room temperature, with evolution of CO_2, to form imidazolium salts of imidazolides (XLVI) in very good yields [79, 80].

[74] *H. A. Staab* and *K. Wendel*, Angew. Chem. *72*, 708 (1960).

[75] *H. A. Staab* and *K. Wendel*, Angew. Chem. *73*, 26 (1961).

[76] *L. Birkofer, W. Gilgenberg*, and *A. Ritter*, Angew. Chem. *73*, 143 (1961).

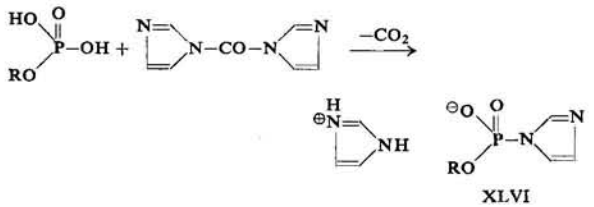
[77] *T. Wieland* and *K. Vogeler*, Angew. Chem. *73*, 435 (1961).

[78] *H. A. Staab* and *K. Wendel*, unpublished data.

[79] *H. A. Staab, H. Schaller*, and *F. Cramer*, Angew. Chem. *71*, 736 (1959).

[80] *F. Cramer, H. Schaller*, and *H. A. Staab*, Chem. Ber. *94*, 1612 (1961).

Salts of type XLVI are soluble in acetone and the solutions can be used directly for phosphorylations. However, the imidazolides may be isolated as insoluble sodium or cyclohexylammonium salts (Table 12).

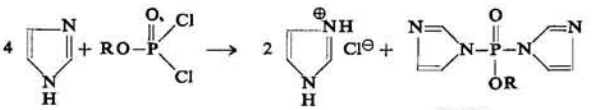


XLVI

Table 12. Imidazolides of phosphoric acids (XLVI) prepared from phosphoric acids and *N,N'*-carbonyldiimidazole

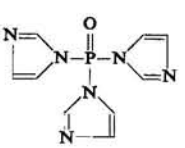
R	Cation	Yield [%]
C_6H_5-	$Na^{\oplus}$	98
	$CHA^{\oplus}$	100
$p-Cl-C_6H_4-$	$Na^{\oplus}$	94
$\beta-C_{10}H_7-$	$Na^{\oplus}$	94
	$CHA^{\oplus}$	95
$C_6H_5-CH_2-$	$Na^{\oplus}$	96
$CH_3O-CH_2-CH_2-$	$Na^{\oplus}$	70
5-Adenosyl-	$Na^{\oplus}$	67
H-	$Na^{\oplus}$	92

Diesters of phosphoric acid do not react with carbonyldiimidazole under these conditions because of the low nucleophilicity of secondary phosphate ester anions. However, imidazolides of diesters of phosphoric acid can be prepared from the corresponding acid chlorides and imidazole [81, 82]. Correspondingly, diimidazolides of monoesters of phosphoric acid (XLVII) are obtained according to the equation:



XLVII

The triimidazolide of phosphoric acid (triimidazolyloxophosphorane, XLVIII) is formed from phosphorus oxychloride and imidazole [80, 83].



XLVIII

Imidazolides of monoesters of phosphoric acid are stable in aqueous solution but the diester derivatives are rapidly hydrolyzed by water. The di- and triimidazolides of phosphoric acid are particularly sensitive to hydrolysis. The latter react violently with water and generally exhibit a reactivity corresponding to that of *N,N'*-thionyldiimidazole [80, 84].

[81] *T. Wagner-Jauregg* and *B. E. Hackley*, J. Amer. chem. Soc. *75*, 2125 (1953).

[82] *J. Baddiley, J. G. Buchanan*, and *R. Letters*, J. chem. Soc. (London) 2812 (1956).

[83] *L. Birkofer, W. Gilgenberg*, and *A. Ritter*, Angew. Chem. *73*, 143 (1961).

[84] *F. Cramer* and *H. Schaller*, Chem. Ber. *94*, 1634 (1961).

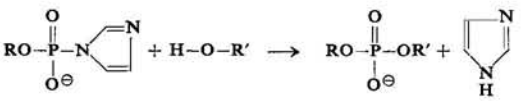
[85] *H. Schaller, H. A. Staab*, and *F. Cramer*, Chem. Ber. *94*, 1621 (1961).

b) Phosphorylations Using Imidazolides of Phosphoric Acid [85]

Aminolysis of imidazolides of phosphoric acid affords phosphoramidic acids in good yield. For example, when treated with aqueous ammonia, the imidazolide of adenosine monophosphate (AMP), which can be prepared from AMP and *N,N'*-carbonyldiimidazole, gives the amide of AMP in 86 % yield [86].

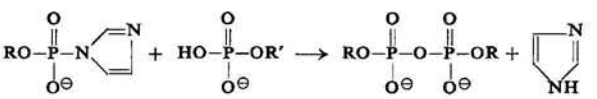
Alcoholysis of imidazolides of monoesters of phosphoric acid yields diesters of phosphoric acid in a smooth reaction. A few examples of these are given in Table 13.

Table 13. Preparation of some diesters of phosphoric acid [80, 87]



R	R'	Yield [%]
C_6H_5-	CH_3-	95
C_6H_5-	C_2H_5-	75
C_6H_5-	$i-C_3H_5-$	80
C_6H_5-	$n-C_4H_9-$	79
C_6H_5-	$n-C_5H_{11}-$	95
C_7H_7-	CH_3-	74
5-Adenosyl-	$C_6H_5-CH_2-$	93
5-Adenosyl-	$p-NO_2-C_6H_4-$	62

Imidazolides of phosphoric acids react with one mole of phosphoric acids nearly quantitatively even at room temperature to form pyrophosphates:



By this method it has been possible, for example, to prepare adenosine diphosphate (ADP) [86, 87] by converting adenosine monophosphate into its imidazolide and reacting the latter with orthophosphate. The coenzyme flavin adenine dinucleotide (FAD) was synthetized from riboflavin phosphate and the imidazolide of AMP [87]. Other dinucleotides were also obtained, and it is therefore to be expected that the use of this reaction in the nucleotide field will be extended.

Imidazolides of phosphoric acids react with carboxylic acids to form primarily acylphosphates, which, in the sense of biochemical terminology, are energy-rich acyl compounds. The acylphosphates are in transacylation equilibrium with the imidazolides of the carboxylic acid that are formed by transfer of the acyl residue to imidazole, which is produced in the first step [80, 84].

13. Imidazolides in Biochemistry

In general, the synthetic pathways in nature and the routes followed by the organic chemist differ very markedly. Most preparative methods in organic chem-

[86] *L. Goldman, J. W. Marsico*, and *G. W. Anderson*, J. Amer. chem. Soc. *82*, 2969 (1960).

[87] *F. Cramer* and *H. Neunhoeffer* Chem. Ber., in press.

istry require such reaction conditions and reactants that it is improbable *a priori* that nature follows the same paths in building up the same compounds. The syntheses via imidazolides described above are characterized by particularly mild conditions and seem to be an exception to this rule. Moreover, there are indications that imidazolides play a role in nature by participating in enzymic transacylations and transphosphorylations. The extensive literature published on this subject [88] cannot be further discussed here.

[88] Cf. review article by *E. A. Barnard* and *W. D. Stein*, Adv. Enzymology *20*, 51 (1958).

The author's own investigations reported in this review were carried out in collaboration with W. Benz, H. Bräunling, Dr. F. H. Dürr, Dr. E. Jost, Dr. F. Lüking, A. Mannschreck, D. W. Müller, B. Polenski, Dr. W. Rohr, Miss G. Seel, N. Sommer, G. Walther, Dr. K. Wendel, and Mrs. D. Wurmb-Gerlich, to whom thanks are expressed. Moreover, thanks are due to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and to the Badische Anilin- und Soda-Fabrik A.G., Ludwigshafen/Rhein for their generous financial support.

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Prephenic Acid: Properties and the Present Status of its Synthesis

BY PROF. DR. H. PLIENINGER

ORGANISCH-CHEMISCHES INSTITUT DER UNIVERSITÄT HEIDELBERG (GERMANY)

Dedicated to Prof. Dr. G. Wittig on his 65th birthday

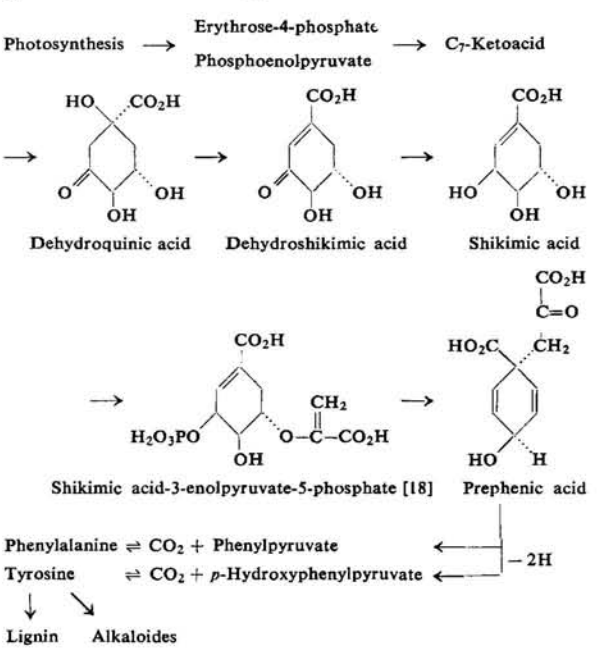
Prephenic acid is an intermediate in the biosynthesis of aromatic compounds. Its synthesis is made difficult by the fact that it is a cyclohexadienol which is easily aromatized by acids and bases. Experiments aimed at its synthesis have led to an as yet inseparable mixture of a little prephenic acid, epiprephenic acid and dihydroprephenic acid (as Ba-salt). Comparison with model compounds indicated that the tertiary carboxyl group and the hydroxyl group are in cis relationship.

Nature makes use of two pathways for the synthesis of aromatic compounds. In one, acetate is the elementary unit from which long chains are built up in a manner similar to the synthesis via β-keto acids of fatty acid, and are then cyclized to aromatic rings bearing hydroxyl groups (generally with *meta* orientation). Little is known about the intermediate steps [*].

The other path has been elucidated almost completely using mutants of micro-organisms [1, 2]. It is outlined in Scheme 1.

The compound designated as prephenic acid was isolated as its barium salt from culture filtrates of certain *Escherichia coli* mutants no longer capable of synthetizing phenylpyruvate [3–6]. Mutants of *Neurospora crassa* can also produce prephenate, when cultured under neutral conditions [7].

Normally, under the conditions of its biosynthesis, prephenate is converted enzymatically into phenylpyruvate, from which phenylalanine is formed by transamination. Recently, an enzymatic conversion into *p*-hydroxyphenylpyruvate was discovered [8]. This must be associated with a



Scheme 1. Biosynthesis of aromatic compounds *via* prephenic acid

[*] Cf. the review by *A. J. Birch*, Proc. chem. Soc. (London) 3 (1962).

[1] *B. D. Davis*, Adv. Enzymology *16*, 247 (1955).

[2] *B. D. Davis* in *W. D. McElroy* and *H. B. Glass:* A Symposium on Amino Acid Metabolism. John Hopkins Press, Baltimore 1955, p. 799.

[3] *S. Simmonds*, J. biol. Chemistry *185*, 755 (1950).

[4] *B. D. Davis*, Science (Washington) *118*, 251 (1953).

[5] *M. Katagiri* and *R. Sato*, Science (Washington) *118*, 250 (1953).

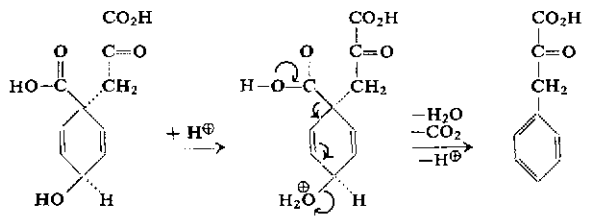
[6] *U. Weiss, C. Gilvare, E. S. Mingioli*, and *B. D. Davis*, Science (Washington) *119*, 774 (1954).

[7] *R. L. Metzenberg* and *H. K. Mitchell*, Arch. Biochem. Biophysics *64*, 51 (1956).

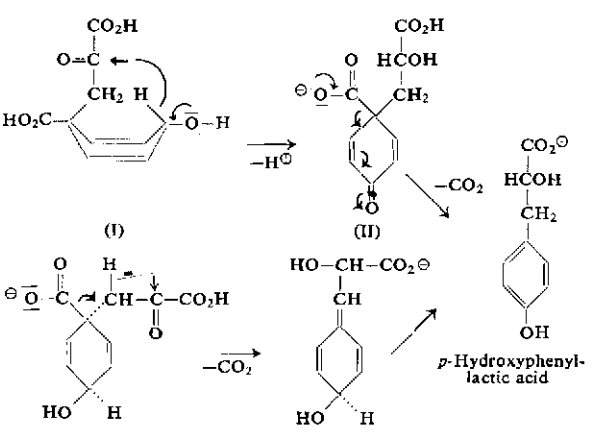
[8] *J. Schwinck* and *E. Adams*, Biochim. biophysica Acta *36*, 102 (1959).

dehydrogenation. Several natural products including lignin and several alkaloids, are derived, from the phenylpyruvic acid or phenylalanine. Prephenate has not yet been detected in higher plants, but it may be assumed that the conversions shown in Scheme 1 also take place here, since shikimic acid is an intermediate in the formation of coumarin [9] and lignin [10, 11].

The structural formula of prephenic acid [6, 13] was deduced from analysis of its barium salt $C_{10}H_8O_6Ba \cdot H_2O$, the absorption of 3–4 moles of hydrogen during catalytic hydrogenation on platinum, the absence of absorption between 240 and 260 mμ, and the conversion (with acid or an enzyme from a strain of *Escherichia coli*) into phenylpyruvic acid and CO_2. The hydroxyl group could not be detected at first. The establishment of the correct formula for prephenic acid on the basis of these data is a masterpiece of research, considering that cyclahexadienols of a similar type and their tendency to aromatize became known only much later [12]. The acid-catalyzed conversion of prephenic acid into phenylpyruvic acid can be represented plausibly in the following manner [13]:



Prephenic acid is somewhat more stable towards alkali than towards acid, but on heating or prolonged standing in dilute alkali, it is converted into *p*-hydroxyphenyllactic acid. Two mechanisms may be assumed for this conversion [13, 14]. The first is only possible if the keto-acid group and the hydrogen atom at C-4 of the prephenic acid ring are *cis* (which is actually the case). In both instances, the reaction begins with an intramolecular hydride shift.



[9] *F. Weygand* and *H. Wendt*, Z. Naturforsch. *14b*, 421 (1959).

[10] *St. A. Brown* and *A. C. Neish*, Nature (London) *175*, 688 (1955).

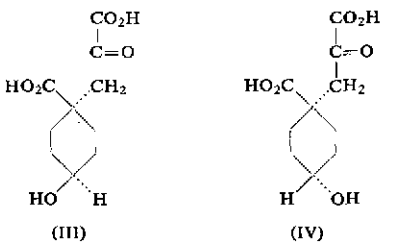
[11] *G. Eberhardt* and *W. J. Schubert*, J. Amer. chem. Soc. *78*, 2835 (1955).

[12] *H. Plieninger* and *G. Keilich*, Chem. Ber. *91*, 1891 (1958).

[13] *U. Weiss*, personal communication.

[14] *C. Gilvarg* in *W. D. McElroy* and *H. B. Glass*: A Symposium on Amino Acid Metabolism. John Hopkins Press, Baltimore 1955, p. 812.

Prephenic acid has a plane of symmetry (perpendicular to the plane of the paper) and is therefore optically inactive; however, it can have *cis* and *trans* isomers (prephenic and epiprephenic acid). We arrived at the explanation of the steric arangement of the naturally occurring product in the following manner [15]. Barium prephenate was hydrogenated over Pd/barium sulfate so that only the double bonds became saturated; no aromatization and no hydrogenolysis of the allylic OH group occurred. The dinitrophenylhydrazone of the tetrahydroprephenic acid thus obtained was compared chromatographically on borate buffered paper with the dinitrophenylhydrazones of the two synthetic tetrahydroprephenic acids (III) and (IV) of known steric configuration [16, 17].



Tetrahydroprephenic acid corresponds to (III), in which the t.-carboxyl group and the hydroxyl group are *cis* (Fig. 1).

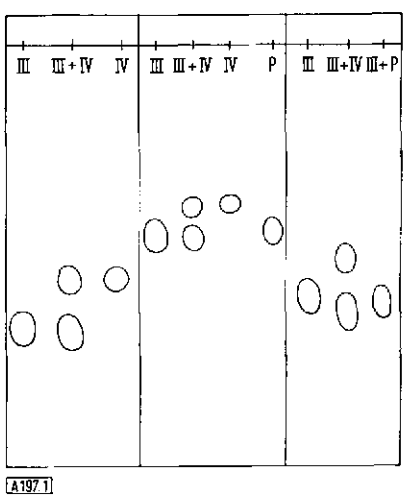
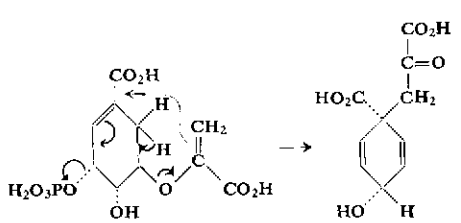


Fig. 1. Paper-chromatographic comparison of hydrogenated naturally-occurring prephenic acid (P) with synthetic isomeric tetrahydroprephenic acids (III) and (IV) (as dinitrophenylhydrazones)

The steric arrangement of the substituents corresponds to the mechanism [18] that was suggested for the formation of prephenic acid from shikimic acid 3-enolpyruvate-5-phosphate:



[15] *H. Plieninger* and *G. Keilich*, Z. Naturforsch. *16b*, 81 (1961).

[16] *H. Plieninger* and *H. J. Grasshoff*, Chem. Ber. *90*, 1973 (1957).

[17] *H. Plieninger* and *G. Keilich*, Chem. Ber. *92*, 2897 (1959).

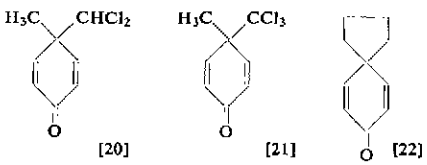
[18] *J. G. Levine* and *D. B. Sprinson*, Biochem. biophys. Res. Commun. *3*, 157 (1960).

Synthesis

The synthesis of prephenic acid is as intriguing as it is difficult since the compound has a tendency to aromatize at acid as well as at alkaline pH. Its synthesis is important as the final proof of its structure and for the preparation of labelled compounds to be used to determine whether there are biosynthetic pathways which proceed directly from prephenic acid without prior aromatization to phenylpyruvic acid [19].

The synthesis of cyclohexadienols of the prephenic acid type must start out with cyclohexadienones, which can be reduced with sodium borohydride or aluminium isopropoxide [12]. Theoretically, cyclohexadienones can be synthetized by four methods:

1. Introduction of a second substituent in the 4-position of a 4-substituted phenol (cresol + chloroform + alkali [20]; cresol + $AlCl_3$ + CCl_4 [21]; or after the fashion of an aryl neighboring group effect [22]).



[20] [21] [22]

2. Dibromination of a saturated ketone and removal of HBr with collidine or with $LiCl/Li_2CO_3$ in dimethylformamide [23].

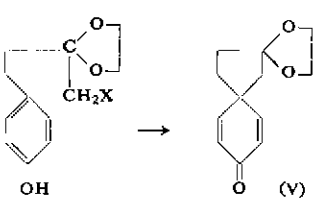
3. Introduction of a second double bond into a substituted cyclohexenone

a) with SeO_2 in t.-butanol [24];

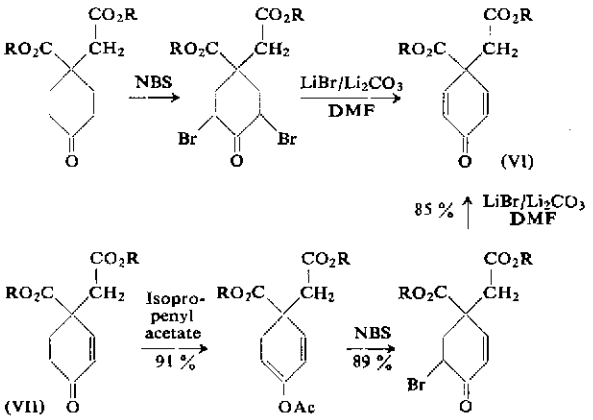
b) *via* the enol acetate with bromosuccinimide followed by elimination of HBr [25, 26].

4. Introduction of a keto group into a correspondingly substituted cyclohexadiene by oxidation.

No compounds resembling prephenic acid have been prepared to date *via* the first method. The synthesis of compound (V) [28] could be a first step.



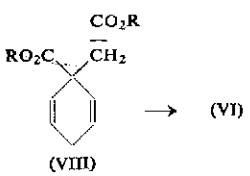
Using the second method, the dienone (VI) [*] can be obtained from the saturated ketone. Better yields are obtained by method 3b, when the unsaturated ketone (VII) [29] is the starting material [30].



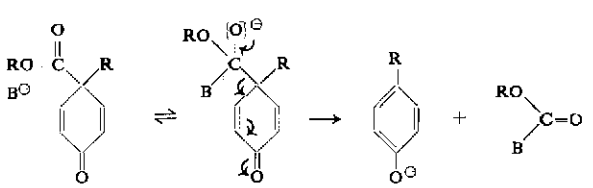
R = C_2H_5; NBS = *N*-Bromosuccinimide

DMF = Dimethylformamide

The enone (VII) can also be dehydrogenated with SeO_2 to give (VI), but the yields are low [30]. Finally, the dienone (VI) can also be obtained by oxidation of the cyclohexadiene derivative (VIII) [31] with t.-butyl chromate [27]. The product is purified *via* its semicarbazone.



The dienone (VI) shows an unexpected property: Attempts at alkaline saponification yield *p*-hydroxyphenylacetic acid; with alkoxides, the ester of this compound plus carbonic ester result. Here a kind of "ketone splitting" of a vinylogous β-keto ester occurs, which does not occur with ordinary β-keto esters, but which has been observed recently with derivatives of 2-ethoxycarbonylindol-3-one [32]. With cyclohexadienones, the reaction proceeds as follows [33]:



B = $C_2H_5O^{\ominus}$; $H^{\ominus}$

When sodium borohydride is employed, this reaction also takes place to some extent, and formic acid ester is split off [33]. The main product, however, is a mix-

[19] *E. Wenkert*, Experientia (Basel) *15*, 165 (1959).

[20] *K. v. Auwers* and *F. Winternitz*, Ber. dtsch. chem. Ges. *35*, 465, 4207 (1902).

[21] *Th. Zincke* and *R. Suhl*, Ber. dtsch. chem. Ges. *39*, 4148 (1960).

[22] *S. Winstein* and *R. Baird*, J. Amer. chem. Soc. *79*, 756 (1957).

[23] *R. P. Holysz*, J. Amer. chem. Soc. *75*, 4432 (1953).

[24] *Ch. Meystre, H. Frey, W. Voser*, and *A. Wettstein*, Helv. chim. Acta *39*, 734 (1956).

[25] *C. Djerassi* and *C. T. Lenk*, J. Amer. chem. Soc. *75*, 3493 (1953).

[26] *H. Plieninger* and *T. Suehiro*, Chem. Ber. *89*, 2789 (1956).

[27] *R. V. Oppenauer* and *H. Oberrauch*, Annales Assoc. Quim. Argentina *37*, 246 (1949); Chem. Abstr. *44*, 3871 (1950); *K. Heusler* and *A. Wettstein*, Helv. chim. Acta *35*, 284 (1952); *W. Logemann* and *P. Giraldi*, Gazz. chim. Ital. *81*, 548 (1951).

[28] *S. Dorling* and *J. Harley-Mason*, Chem. and Ind. 1551 (1959).

[*] The dinitrophenylhydrazone of (VI) was also obtained by a different route by *S. Dorling* and *J. Harley-Mason*, Chem. and Ind. 495 (1960).

[29] *H. Plieninger, G. Ege, R. Fischer*, and *W. Hoffmann*, Chem. Ber. *94*, 2106 (1961).

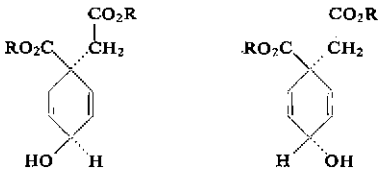
[30] *H. Plieninger, G. Ege, H. J. Grasshoff, G. Keilich*, and *W. Hoffmann*, Chem. Ber. *94*, 2115 (1961).

[31] *H. Plieninger* and *G. Ege*, Chem. Ber. *94*, 2095 (1961).

[32] *O. Neunhoeffer* and *G. Lehmann*, Chem. Ber. *94*, 2960 (1961).

[33] *H. Plieninger* et al., Angew. Chem. *73*, 543 (1961).

ture of the dienols (IX) and (X) when the reduction is carried out with aluminum isopropoxide.



(IX) R = C_2H_5 (X) R = C_2H_5
(XI) R = H (XII) R = H

The dienols are stable to alkali and can be saponified to the dicarboxylic acids (XI) and (XII). Both acids are easily aromatized to form phenylacetic acid. The rate of decarboxylation at pH 2.8 and 20 °C was followed by pressure readings on a Warburg manometer; the results are shown in Fig. 2 [34].

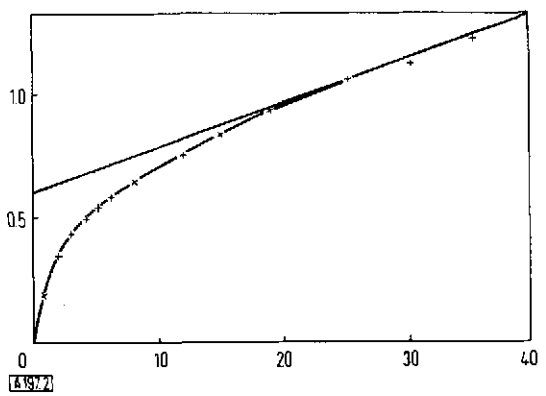
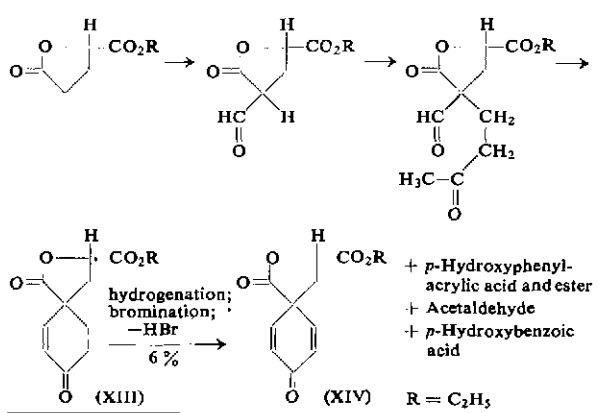


Fig. 2. Rate of decarboxylation of a mixture of (XI) and (XII) (measured manometrically).
Ordinate: ln c_0/c
Abscissa: time [min.]

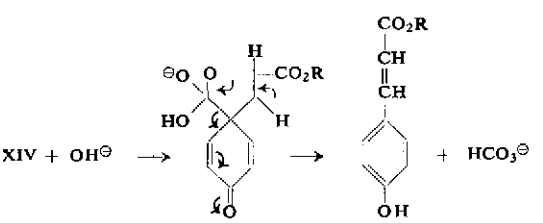
It is evident from the graph that two separate rates corresponding to the two stereoisomers exist. The half-lives were calculated to be 1.7 and 38 minutes. According to the mechanism postulated on page 368, it is to be expected that (XI) is decarboxylated more quickly than (XII), since in (XI), CO_2 and H_2O leave the ring from the same side. Obviously an "internal" S_N2 reaction is involved [35].

For the synthesis of cyclohexadienones with the "correct" substituents, (–COOH and $-CH_2-CO-COOH$), the route *via* the spirocyclic enone (XIII) was most suitable [29]. Starting from (XIII), a compound with a lactic acid side-chain was synthetized, in the hope that it could be dehydrogenated biochemically to give an α-keto acid. This synthesis proceeded to the enone (XIII) with reasonable yields [28].



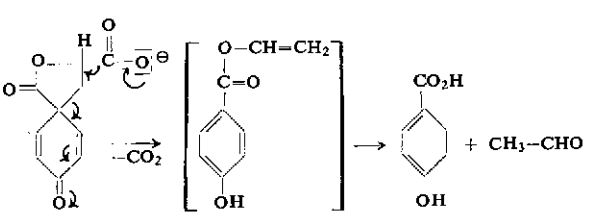
Compound (XIII) has an unusually intense absorption band at 293 mμ (log ε = 3.17) and a normal band at 233 mμ (log ε = 3.85). The spatial proximity of the lactone carbonyl group (as electron donor) to the asymmetrical conjugated ketone carbonyl group is evidently responsible for this spectrum. This is an interesting n → π* transition which is under further investigation.

The introduction of a second double bond into the spirocyclic enone is difficult; it succeeded using method 2 (see above) with poor yields; with method 3b only traces are obtained. Under sufficiently drastic conditions during the HBr elimination with $LiCl/Li_2CO_3$ in boiling dimethylformamide, most of the spirocyclic dienone (XIV) undergoes further transformations forming primarily *p*-hydroxyphenylacrylic acid and its ester. The dienone-lactone (XIV) can be freed of these phenols (with large losses) by extractions with cold sodium hydroxide solution. The pure dienone has only one absorption maximum, *viz.* at 267 mμ (log ε = 4.05). After alkaline hydrolysis followed by acidification, *p*-hydroxyphenyllactic acid and *p*-hydroxyphenylacrylic acid were obtained (shown by paper chromatography). The first product warrants no further explanation; the unsaturated acid might be formed by the following mechanism if an olefinic double bond is formed simultaneously with the aromatization (*p*-hydroxyphenyllactic acid does not split off water under the conditions of the alkaline hydrolysis).



The ethyl ester of *p*-hydroxyphenylacrylic acid is formed quantitatively from the dienone (XIV) and sodium ethylate.

In the synthesis of the dienone (XIV) (splitting off HBr by boiling with LiBr and Li_2CO_3 in dimethylformamide), (XIV) obviously becomes partially saponified and is subject to a different fragmentation reaction in which acetaldehyde (identified through its dinitrophenylhydrazone) and *p*-hydroxybenzoic acid (identified by paper chromatography) are formed. The following mechanism is postulated:

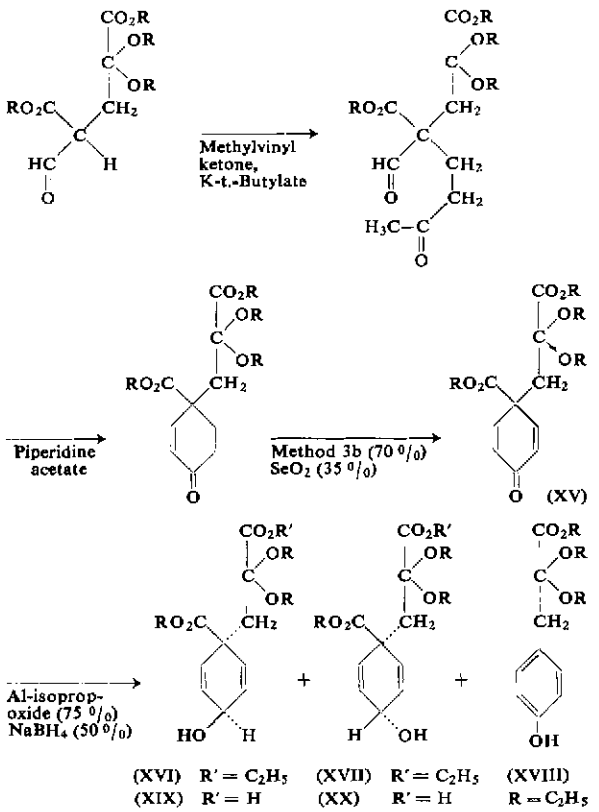


The reduction of the dienone XIV with sodium borohydride leads to *p*-hydroxyphenylacrylic acid and to a compound which yields phenylacetic acid on acidification. The poor yields do not permit utilization of the above reactions for preparative purposes.

[34] *H. Plieninger* and *L. Arnold*, unpublished.

[35] *G. Stork* and *W. N. White*, J. Amer. chem. Soc. 75, 4119 (1953).

The synthesis of the dienone (XV), a compound with the desired side chain (as the diethyl ketal), can be achieved in relatively good yield [29, 36].



The reduction of the keto group leads to dienols (XVI and XVII) as well as phenol (XVIII), and the latter can be readily separated. The stereoisomeric dienols are formed in approximately equal amounts, which can be proved by catalytic hydrogenation and paper chromatographic comparison with the two synthetic tetrahydroprephenic acids [33].

The acid hydrolysis of the ketal group succeeds only with simultaneous aromatization, *i.e.* under vigorous conditions, since ketals of α-keto acid esters are stable in acid [37]. We therefore investigated the behavior of ketals of free keto acids, starting with simple model compounds. Half-lives of 67 and 56 minutes were obtained for the hydrolysis of the diethyl ketal and dimethyl ketal of ketoglutaric acid [33]. The diethyl ketal of phenylpyruvic acid was hydrolyzed with a half-life of 63 minutes (all experiments at pH 1.8 and 20 °C). The rate of aromatization of naturally occurring prephenic acid is also known. The half-life at pH 2 and 0 °C is 300 minutes; at pH 1 and 0 °C it is 60 minutes.

It should therefore be possible to obtain phenylpyruvic acid, prephenic acid, and epiprephenic acid by acid hydrolysis of the free keto acids (XIX) and (XX).

By alkaline saponification of the esters (XVII) and (XVIII), a solution of the salts of (XIX) and (XX) was obtained without aromatization. This solution was kept for 6.5 hours at pH 1.8 at 20 °C, during which time simultaneous ketal hydrolysis and aromatization took place. After neutralization phenylpyruvic acid was separated from the prephenates by means of a basic ion exchanger, followed by precipitation as barium salts. The amount of prephenate in the barium salt was determined by conversion into phenylpyruvic acid and quantitative measurement of the absorption at 320 mμ (pH 14) (Fig. 3).

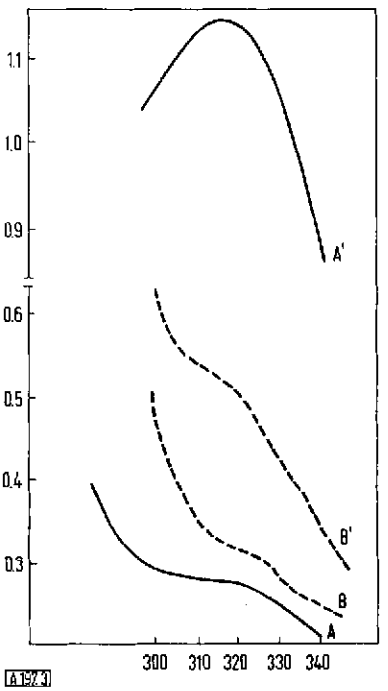


Fig. 3. Acid conversion of a mixture of barium prephenate and barium epiprephenate (A) in phenylpyruvic acid (A') and enzymatic conversion of a mixture of barium prephenate and barium epiprephenate (R) in phenylpyruvic acid (B') with enzymes from a strain of *Escherichia coli* at pH 7. Measurements at pH 14.
Ordinate: Extinction
Abscissa: Wavelength [mμ]

It turned out that the barium salt consists of 10% barium prephenate plus barium epiprephenate. The bulk of the precipitate is dihydroprephenic acid, obtained from the incomplete dehydrogenation during the synthesis of (XV) [*]. The content of naturally occurring prephenic acid has not yet been determined exactly. The measurement of the rate of decarboxylation in a Warburg apparatus showed that the barium salt consists of two compounds, one of which splits off CO_2 at a faster rate. This should be the naturally occurring prephenic acid. Further proof that the natural product was obtained in addition to epiprephenate was seen in the fact that a partial aromatization of the mixture could be achieved (Fig. 3) with a crude enzyme from a strain of *Escherichia coli* at pH 7. It cannot be assumed that the crude enzyme contains a component which catalyzes the aromatization of epiprephenic acid. After heating of the prephenates with sodium hydroxide, the presence of *p*-hydroxyphenyllactic acid can be demonstrated by paper chromatography.

Thus, the synthesis of prephenic acid as a mixture with epiprephenic acid has been achieved [38]. Further efforts

[36] *H. Plieninger* et al., unpublished.

[37] *E. Vogel* and *H. Schinz*, Helv. chim. Acta *23*, 116 (1950).

[*] The yield of prephenic acid and epiprephenic acid was raised to 20% by using method 3b for the preparation of the intermediate XV.

[38] *H. Plieninger*, Angew. Chem. internat. Edit. *1*, 61 (1962).

will be required to obtain pure barium prephenate (not contaminated with epiprephenate) in such quantities that tracer experiments can be performed.

We are grateful to Dr. U. Weiss, National Institutes of Health, Bethesda, Md., USA, for his always stimulating remarks. Valuable advice in the biochemical and analytical experiments was obtained from Dr. J. Knappe. We obtained a Neurospora mutant for the synthesis of prephenate from Dr. H. K. Mitchell, Pasadena, Calif., USA, to whom we are grateful. This investigation was generously aided by the Deutsche Forschungsgemeinschaft and we are indebted to the Verband der Chemischen Industrie (Fonds der Chemie) for financial assistance. We have been also helped with gifts of chemicals by the Badische Anilin- und Sodafabrik, Ludwigshafen am Rhein.

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Syntheses in the Tetracycline Series

BY PROF. DR. H. MUXFELDT [*]

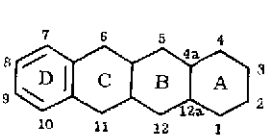
DEPARTMENT OF CHEMISTRY UNIVERSITY OF WISCONSIN, MADISON, WIS. (U. S. A.)

Tetracyclines are antibiotics used most frequently in the chemotherapy of infectious diseases. Numerous degradation and transformation products of natural tetracyclines have been prepared and their biological properties tested. Furthermore, workers in several laboratories have been engaged in synthetizing tetracyclines or their biologically active degradation products. Some investigations carried out by the author and collaborators in this connection will be reported.

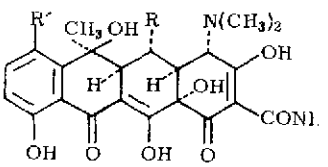
Introduction

Tetracyclines are pale yellow crystalline antibiotics produced by strains of *Streptomyces*. They are characterized by particularly advantageous chemotherapeutic properties, and represent a new class of structurally interesting natural products whose chemical and physical properties have been thoroughly investigated during the last decade.

Since *Duggar*'s isolation in 1948 of Aureomycin® from cultures of *Streptomyces aureofaciens* [1], seven additional members of this class have been obtained from naturally occurring streptomycetes or from artificial mutants of tetracycline-producing organisms. Terramycin®, which was isolated in 1950 in the laboratories of Chas. Pfizer and Co. [2], was the first tetracycline, whose structure, was completely elucidated in collaboration with *Woodward* [3]. Shortly afterwards, these same workers as well as those from the Lederle Laboratories showed [4, 5] that Aureomycin and Terramycin are very closely related substitution products of the also naturally occurring tetracycline (I): Terramycin is a 5-hydroxytetracycline (II) and Aureomycin is 7-chlorotetracycline (III).

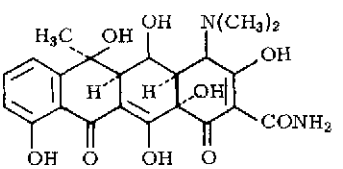


Numbering [3]



Tetracycline (I); R=R'=H
Terramycin (II); R=OH, R'=H
Aureomycin (III); R=H, R'=Cl

From the results obtained during the elucidation of the structure of Terramycin (II), it was possible to state the configurations at the six asymmetric centers [3].



IV

X-ray analysis confirmed the structure proposed in IV to a major extent and indicated the configuration shown

[*] From reports presented at the IUPAC Symposium in Munich, September 4th. 1959, the General Meeting of the GDCh in Stuttgart, April 30th. 1960, and the Gordon Research Conference in New Hampton, August 4th. 1960, and from the Karl Folkers Lectures delivered at the University of Wisconsin, October 19th. and 20th. 1960.

[1] *B. M. Duggar*, Ann. N.Y. Acad. Sci. *51*, 175 (1948); US-Patent 2482055 (1949); *R. W. Broschard, A. C. Dornbush, S. Gordon, B. L. Hutchings, A. R. Kohler, G. Krupta, S. Kusher, D. V. Lefemine*, and *C. Pidacks*, Science (Washington) *109*, 199 (1949).

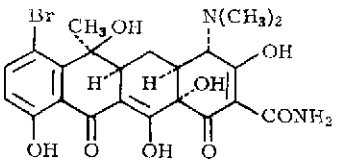
[2] *A. C. Finlay, G. L. Hobby, S. Y. Plan, P. P. Regna, J. B. Routien, D. B. Seeley, G. M. Shull, B. A. Sobin, I. A. Solomons, J. W. Vinson*, and *J. H. Kane*, Science (Washington) *111*, 85 (1950).

[3] *F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings*, and *R. B. Woodward*, J. Amer. chem. Soc. *75*, 5455 (1953).

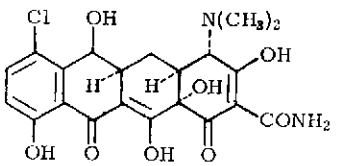
[4] *C. R. Stephens, L. H. Conover, R. Paternack, F. A. Hochstein, W. T. Moreland, P. P. Regan, F. J. Pilgrim, K. J. Brunings*, and *R. B. Woodward*, J. Amer. chem. Soc. *76*, 3568 (1954).

[5] *C. W. Waller, W. L. Hutchings, R. W. Broschard, A. A. Goldmann, W. J. Stein, C. F. Wolf*, and *J. A. Williams*, J. Amer. chem. Soc. *74*, 4981 (1952).

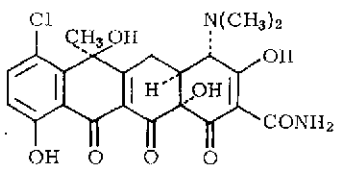
in II [6,7]. X-ray structural analysis showed further [8] that Aureomycin (III) and Terramycin (II) possess the same configurations at all common asymmetric centers, as may also be assumed probable for all the other tetracyclines (V–IX) isolated from streptomycetes.



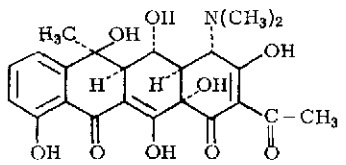
7-Bromotetracycline (V) [9]



6-Demethyltetracycline (VI, H instead of Cl) [10]
6-Demethyl-7-chlorotetracycline (VII) [10]



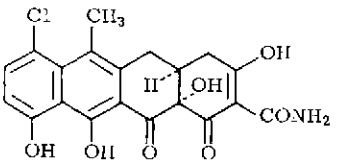
Dehydro-7-chlorotetracycline (VIII) [11]



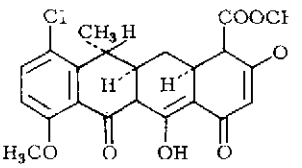
Decarbamoyl-2-acetyl-5-hydroxytetracycline (IX) [12]

The investigations carried out over the last decade in the tetracycline field, can be divided into three groups: 1. isolation and determination of the structures of new tetracyclines; 2. synthesis of degradation and transformation products of naturally occurring tetracyclines for the purpose of obtaining compounds with new chemotherapeutic properties; 3. attempts at the total synthesis of tetracyclines or their biologically active derivatives.

We have been occupied primarily with the synthesis of tetracyclines, and here describe those experiments which led to the synthesis of dedimethylamino-anhydro-aureomycin (X) [13] in 1959 and to the stereospecific synthesis of the tetracyclic compound XI [14] in the spring of 1960.

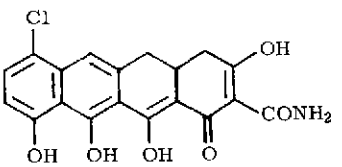


X

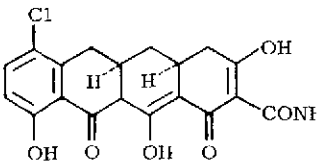


XI

The extensive investigations in the Lederle Laboratories which resulted in the synthesis of dedimethylamino-12a-deoxy-demethyl-17-chloro-anhydrotetracycline (XII)[15] and dedimethylamino - 6,12a - bis(deoxy) - demethyl - 7-chloro-tetracycline (XIII) [16] will not be discussed.



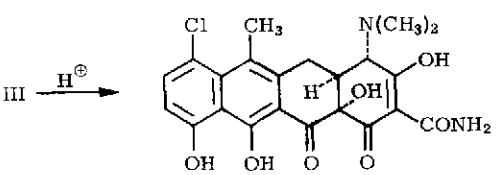
XII



XIII

Some Chemical Properties of Tetracyclines

The numerous substituents on the tetracycline ring system and their positions relative to each other make these compounds highly reactive toward acids, bases, and reducing agents. While reactions in strong alkali are of a complex nature, most tetracyclines are dehydrated only to anhydrotetracyclines by acids. Thus, aureomycin (III) is converted into anhydro-aureomycin (XIV) [4] by mild treatment with mineral acids.



XIV

Treatment with 5 % $NaHCO_3$ solution converts aureomycin (III) into *iso*-aureomycin (XV). The half-life time of aureomycine under these conditions is two

[6] *Y. Takeuchi* and *M. J. Buerger*, Proc. nat. Acad. Sci. USA *46*, 1366 (1960).

[7] The chemical properties of Terramycin and a few degradation products are more compatible with structure IV than with structure II. However, as long as the results of the X-ray analysis are not clearly disproved, we will use formulae derived from II to describe the configuration of the tetracyclines.

[8] *S. Hirokawa, Y. O. Okawa, F. M. Lovell*, and *R. Pepinsky*: Paper presented at the Meeting of the American Crystallographer's Association, July 1959, Abstracts, p. 44.

[9] *A. P. Doerschuk, B. A. Bittler*, and *J. R. D. McCormick*, J. Amer. chem. Soc. *77*, 4687 (1955); *P. Sensi, G. A. DeFerrari, G. G. Gallo*, and *G. Rolland*, Farmaco (Pavia), Ed. sci. *10*, 337 (1955).

[10] *J. R. D. McCormick, N. O. Sjolander, U. Hirsch, E. R. Jensen*, and *A. P. Doerschuk*, J. Amer. Chem. Soc. *79*, 4561 (1957).

[11] *J. R. D. McCormick, P. A. Miller, J. A. Growich, N. O. Sjolander*, and *A. P. Doerschuk*, J. Amer. chem. Soc. *80*, 5572 (1958).

[12] *F. A. Hochstein, M. Schach von Wittenau, F. W. Tanner*, and *K. Murai*, J. Amer. chem. Soc. *82*, 5934 (1960).

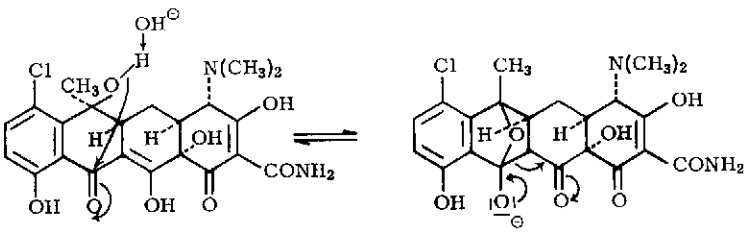
[13] *H. Muxfeldt*, Chem. Ber. *92*, 3122 (1959); *H. Muxfeldt* and *A. Kreutzer*, Chem. Ber. *94*, 881 (1961); preliminary communication: Naturwissenschaften *46*, 204 (1959) and Abstracts, 17th. International Congress of Pure and Applied Chemistry, Munich, Sept., 1959, Vol. II, p. 19.

[14] *H. Muxfeldt, W. Rogalski*, and *K. Striegler*, Angew. Chem. *72*, 170 (1960).

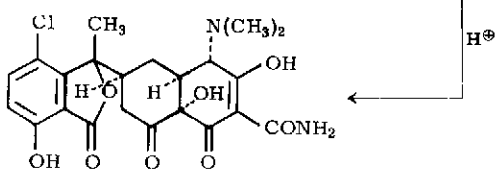
[15] *A. S. Kende, T. L. Fields, J. H. Boothe*, and *S. Kushner*, J. Amer. chem. Soc. *83*, 439 (1961); preliminary communication: *J. H. Boothe, A. S. Kende, T. L. Fields*, and *R. G. Wilkinson*, J. Amer. chem. Soc. *81*, 1006 (1959).

[16] *T. L. Fields, A. S. Kende*, and *J. H. Boothe*, J. Amer. chem. Soc. *82*, 1250 (1960); *83*, 4612 (1961).

hours at room temperature [4]. The fact that this selective cleavage of one carbon-carbon bond in a system of four β-positioned carbonyl groups can occur, together with many other observations, makes it clear that the 6-hydroxyl group is involved in the alkali cleavage.

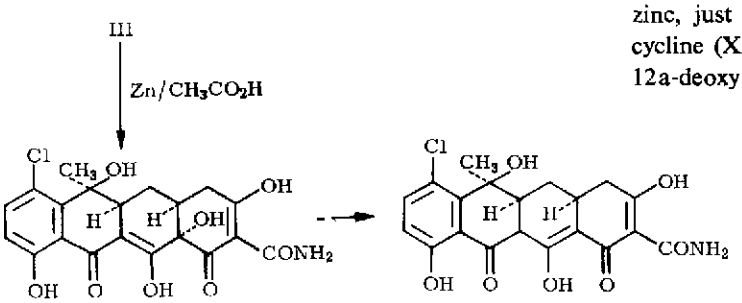


III



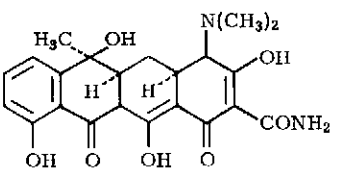
XV

The dimethylamino group as well as the 12a-hydroxyl group, can be removed with zinc in various media; with zinc in acetic acid, depending on the duration of the reaction, either the dimethylamino group can be removed selectively (XVI) [4,17], or dedimethylamino-12a-deoxytetracycline can be obtained (XVI → XVII) [3,4].



XVI XVII

In ammonia, the 12a-hydroxyl group is first reduced. Thus, tetracycline (I) yields 12a-deoxy-4-epitetracycline (XVIII) [18,29] by simultaneous epimerization at carbon-4.

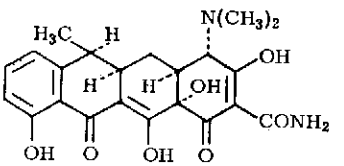


XVIII

[17] Excellent yields of dedimethylaminotetracyclines are obtained when the tetracyclines are first quaternized with CH_3I and then treated with zinc in dilute acetic acid. *J. H. Boothe, G. E. Bonvicino, C. W. Waller, J. P. Petisi, R. W. Wilkinson,* and *R. B. Broschard,* J. Amer. chem. Soc. *80,* 1654 (1958).

[18] *A. Green* and *J. H. Boothe,* J. Amer. chem. Soc. *82,* 3950 (1960).

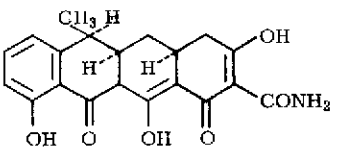
All the degradation products mentioned so far possess either very little antibiotic activity *in vivo*, or none at all. This is not true of the compounds obtained by catalytic hydrogenation [19] (removal of the 6-hydroxy group). In this process, the configuration at carbon-6 is inverted (see below). Thus, hydrogenation of tetracycline (I) yields 6-deoxy-6-epitetracycline (XIX).



XIX

6-Deoxytetracyclines differ from naturally occurring tetracyclines in their higher stability toward acids and bases (the 6-hydroxy group which causes the acid lability and raises the alkali lability is missing).

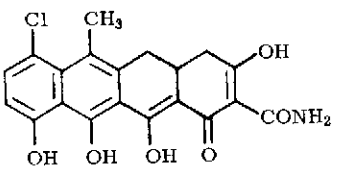
Of course, 6-deoxytetracyclines can be reduced with zinc, just like tetracyclines. From 6-deoxy-6-epitetracycline (XIX), one thus obtains the dedimethylamino-12a-deoxy compound (XX).



XX

Syntheses

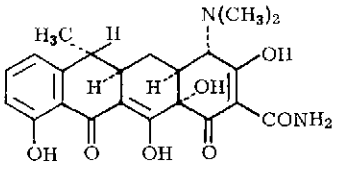
Our first aim was the synthesis of dedimethylamino-12a-deoxy-anhydro-aureomycin (XXI). This compound is easily obtained by degradation of Aureomycin (III) and can also be used as starting material for studies in partial syntheses, which have led to the preparation of dedimethylamino-anhydro-aureomycin (X).



XXI

[19] *C. R. Stephens, K. Muray, H. H. Rennhard, L. H. Conover,* and *K. J. Brunings,* J. Amer. chem. Soc. *80,* 5324 (1958).

Later, we worked on the synthesis of 6-deoxytetracycline (XXII). These investigations gave us valuable experience

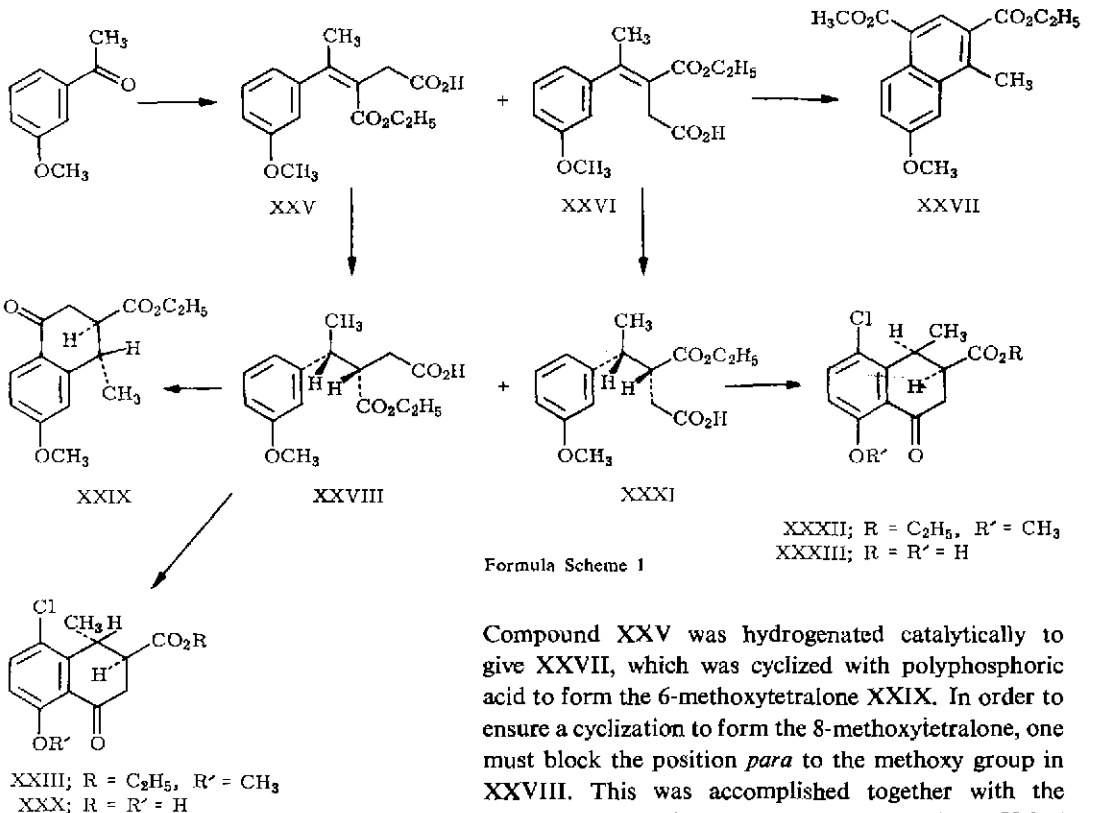


XXII

for the synthesis of Terramycin (II). A synthesis of the basic ring system of XXII is described in the last section of this paper.

Thus, it seemed expedient to prepare XXIII first, in order to obtain an intermediate for both syntheses.

Stobbe condensation of 3-methoxyacetophenone with diethyl succinate gave a good yield of a mixture of the *cis* and *trans* isomers of the mono-esters XXV and XXVI (Formula Scheme 1). Since only one of the esters crystallizes, their separation was accomplished easily. In order to determine the configuration of the esters, we treated them with sodium acetate in acetic anhydride [20]. In this manner, the oily mono-ester formed the naphthalene derivative XXVII in high yield, while the crystalline mono-ester remained unchanged. We therefore assigned the configuration XXV to the crystalline mono-ester and the configuration XXVI to the oil.

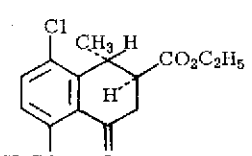


XXV XXVI XXVII XXIX XXVIII XXXI XXXII; R = C_2H_5, R′ = CH_3 XXXIII; R = R′ = H XXIII; R = C_2H_5, R′ = CH_3 XXX; R = R′ = H

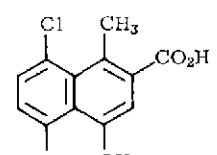
Formula Scheme 1

Synthesis of Dedimethylamino-anhydro-aureomycin (X)

The starting material for the construction of the ring system of 6-deoxytetracycline (XXII) was *trans*-3-ethoxycarbonyl-4-methyl-5-chloro-8-methoxy-1-tetralone (XXIII). Aromatization of this compound should give the naphthalene derivative XXIV, which we thought to be a suitable compound for transformation to dimethylamino-12a-deoxy-anhydrotetracycline.



XXIII



XXIV

Compound XXV was hydrogenated catalytically to give XXVII, which was cyclized with polyphosphoric acid to form the 6-methoxytetralone XXIX. In order to ensure a cyclization to form the 8-methoxytetralone, one must block the position *para* to the methoxy group in XXVIII. This was accomplished together with the cyclization in a single operation, by treating XXVIII with one equivalent of chlorine and then with polyphosphoric acid. A compound is formed in good yield, whose UV-spectrum is very similar to that of *o*-hydroxyacetophenone but differs from that of *p*-hydroxyacetophenone (Fig. 1).

This shows that the cyclization must have given a compound of structure XXIII, which is also evident from comparison of the IR-spectra of XXIII and the 8-hydroxytetralone (XXX). This compound can be obtained by dealkylation of XXIII with hydrobromic acid. As compared to XXIII, it shows even in dilute solution a bathochromic shift of 0.13 μ in the absorption of the ketonic carbonyl at 6.09 μ, thus proving the position of the hydroxyl group.

The configurations of the tetralones XXIII and XXX follow from the configuration of the starting material XXV, provided that no isomerization occurred during

[20] *W. S. Johnson* and *A. Goldman*, J. Amer. chem. Soc. *66*, 1030 (1944).

the reactions. In order to establish the configuration of XXIII and XXX unequivocally the mono-ester XXVI (the oil) was treated just like the crystalline mono-ester XXV. Judging from their spectra, the products are 8-hydroxytetralones but are not identical with XXIII and

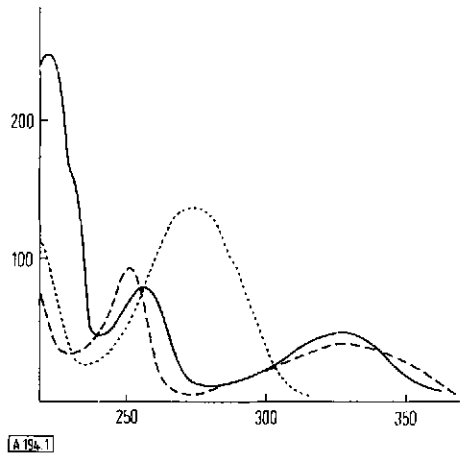
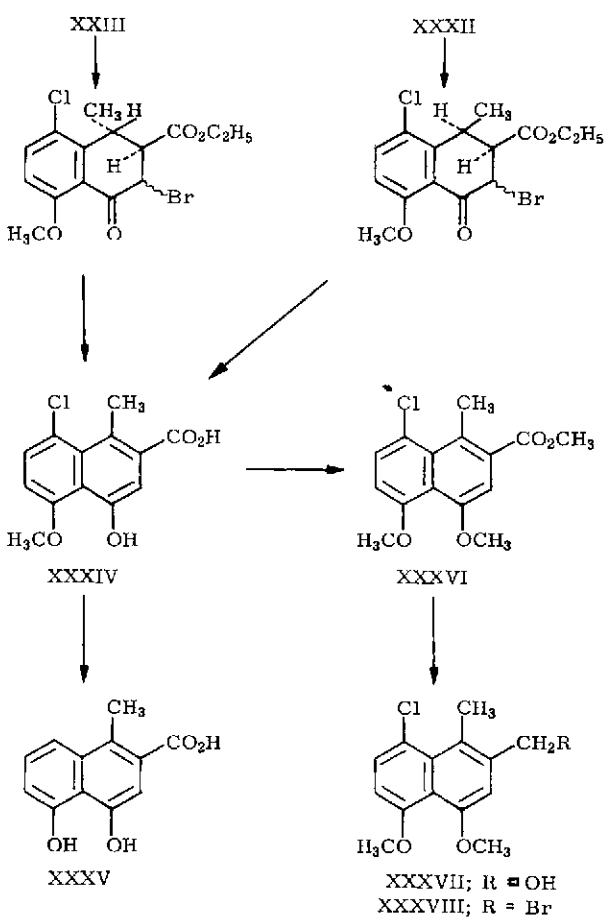


Fig. 1. UV-Spectra of (- - -)*o*-hydroxyacetophenone, (. . . . .)*p*-hydroxyacetophenone, and (——) *trans*-3-ethoxycarbonyl-4-methyl-5-chloro-8-methoxy-1-tetralone (XXIII) in methanol.
Abscissa: Wavelength [mμ].
Ordinate: Extinction coefficient, $\varepsilon \times 10^{-2}$ [cm.²/mole].

XXX. Consequently, they must be compounds XXXII and XXXIII containing *cis* substituents; this also proves the configuration of the 8-hydroxytetralone derivatives XXIII and XXX.



Formula Scheme 2

The aromatization of the tetralones XXIII and XXXII necessary for the synthesis of dedimethylamino-12a-deoxy-anhydro-aureomycin (XXI) was effected by photocatalyzed bromination, followed by elimination of hydrobromic acid with 10% sodium hydroxide (Formula Scheme 2). An 88% yield of the monomethyl ester of chloroterranaphthoic acid (XXXIV) is obtained. Treatment of XXXIV with hydriodic acid gives terranaphthoic acid (XXXV) [21], which was earlier obtained by degradation of terramycine (II) with alkali [3].

When the crystalline potassium salt of the monomethyl ester of chloroterranaphthoic acid (XXXIV) is allowed to react with dimethyl sulfate in acetone, its dimethyl ether-methyl ester (XXXVI) is obtained in good yield. $LiAlH_4$ reduces XXXVI to the terranaphthol derivative XXXVII, and the latter forms the bromide XXXVIII with PBr_3 in chloroform.

For the addition of the B-ring, XXXVIII was treated in boiling toluene with the sodio derivative of di-t.-butyl ethoxycarbonylmethylmalonate (Formula Scheme 3). It was possible to hydrolyze the ethoxycarbonyl group of the condensation product XXXIX selectively. Cyclization of the acid XL yields the tricyclic compound XLI [22]. The t.-butyl ester groups are extremely easily saponified because of the neighboring group effect of the newly formed carbonyl group in XLI. The dicarboxylic acid XLII is formed in almost quantitative yield when the ester XLI is boiled for 5 minutes with 5% sodium hydroxide. To decarboxylate XLII, it was heated for a short time at 170 °C in diethyl phthalate, thus giving a high yield of the tricyclic monocarboxylic acid XLIII. Experiments aimed at effecting the necessary lengthening of the side chain using the *Arndt-Eistert* reaction were at first unsuccessful, since the diazoketone XLIV, obtained easily from XLIII, did not react under the usual conditions for a *Wolff* rearrangement. Thermal decomposition of XLIV by the method of *Wilds* and *Meader* [23] in a mixture of dimethylaniline and benzyl alcohol at 180 °C yielded the ketol ether XLV. The product of a *Wolff* rearrangement was only formed when the diazoketone XLIV was decomposed by heating in pure benzyl alcohol or preferably, in cyclohexanol.

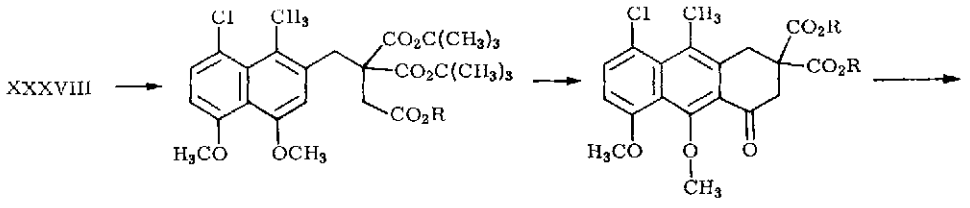
To obtain the starting material XLVII for the last cyclization, esters XLVIa or XLVIb had to be hydrolyzed to the carboxylic acid XLVIc, and the latter converted with malonic ester via its acid chloride into the acylmalonic ester XLVII. This reaction succeeded easily, but many experiments were necessary to cyclize XLVII with basic condensation reagents. Only treatment with sodium hydride in anisole or 1,4-dimethoxybenzene yielded the crystalline yellow tetracyclic compound XLVIII.

[21] Terranaphthoic acid has been synthesized in the laboratory of *R. B. Woodward* by *E. F. Ullmann* (Ph. D. Thesis, Harvard University), private communication. Another synthesis has been reported by *Zen-ichi Horii*, *Ichiya Ninomiya*, and *Yasumitsu Tamura*, Chem. pharmac. Bull. (Japan) 7, 444 (1959).

[22] Contrary to our first communication [13], this compound and some of its subsequent products have proved to be mixtures of mono- and di-methyl ethers. The physical and chemical properties of the pure compounds will be described elsewhere.

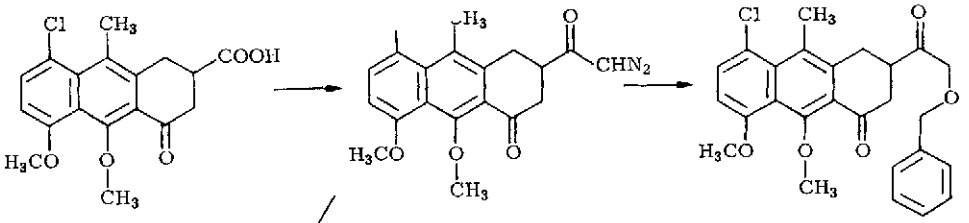
[23] *A. L. Wilds* and *A. L. Meader*, J. org. Chemistry *13*, 763 (1948).

The remaining task, the conversion of the ethoxycarbonyl group in XLVIII into a carbamoyl group, could only be accomplished in a less satisfactory manner. It was not possible to obtain the amide IL in more



XXXIX; R = C_2H_5
XL; R = H

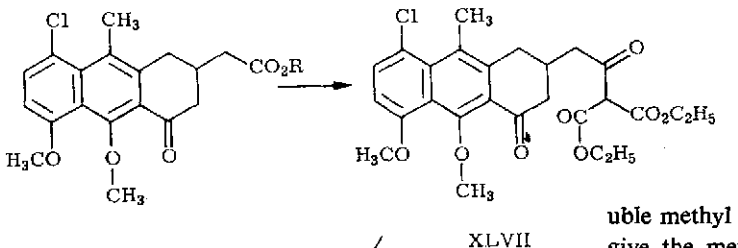
XLI; R = $C(CH_3)_3$
XLII; R = H



XLIII

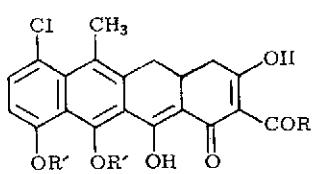
XLIV

XLV



XLVIa; R = Benzyl
b; R = Cyclohexyl
c; R = H

XLVII



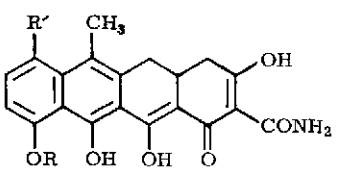
XLVIII; R = OC_2H_5, R′ = CH_3
IL; R = NH_2, R′ = CH_3
XXI; R = NH_2, R′ = H

Formula Scheme 3

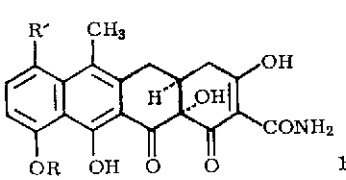
than 6% yield by warming XLVIII in methanolic ammonia containing catalytic amounts of sodium methoxide. However, it was possible to prepare quantities of crystalline IL sufficient to establish the identity of its ultraviolet and infrared spectra with those of a comparison preparation obtained from Aureomycin (III) and to convert it with hydrochloric acid/glacial acetic acid into crystalline (±)-dedimethylamino-12a-deoxy-anhydro-aureomycin (XXI), the ultraviolet spectrum of which also coincided with that of the aureomycin degradation product XXI.

The conversion of XXI into dedimethylamino-anhydro-aureomycin (X) succeeded at first only in a three-stage reaction sequence, with unsatisfactory yields: *viz.* methylation with diazomethane to give the more soluble methyl ether L, oxidation with perbenzoic acid to give the methyl ether LI (poor yield), and treatment with acid. The main product from the peroxyacid oxidation was the monomethyl ester of dedimethylamino-12a-epianhydro-aureomycin (LII).

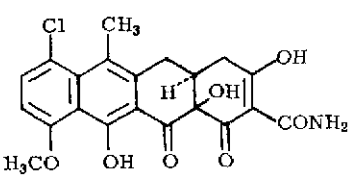
Hydroxylation leading exclusively to dedimethylamino-anhydrotetracycline succeeded by means of a platinum-catalyzed oxidation of dedimethylamino-12a-deoxy-



XXI; R = H, R′ = Cl
L; R = CH_3, R′ = Cl
LIII; R = H, R′ = H



X; R = H, R′ = Cl
LI; R = CH_3, R′ = Cl
LIV; R = H, R′ = H

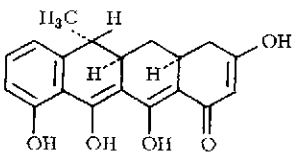


LII

anhydrotetracycline with oxygen. One thus obtains dedimethylamino-anhydrotetracycline (LIV) as the only crystallizable product from dedimethylamino-12a-deoxy-anhydrotetracycline (LIII) and in much better yield.

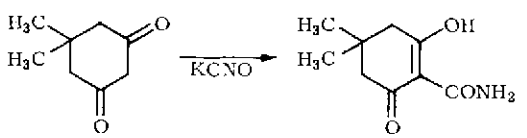
Synthesis of 6-Deoxytetracyclines

In addition to the synthesis of dedimethylamino-decarbamoyl-6,12a-bisdeoxytetracycline (LV), we searched for reactions permitting the introduction of a carbamoyl group into position 12a, a dimethylamino group into position 4, and a hydroxyl group into position 12a.



LV

A method for the synthesis of compounds of the 2-carbamoylcyclohexan-1,3-dione type, such as occur in the A-ring of most tetracyclines, was first worked out by *Shemaykin* et al. [24]. They obtained carbamoyldimedone (LVII) by treatment of dimedone (LVI) with ethoxycarbonyl- or acetyl-isocyanate, and saponification of the product with ammonia. We obtained the same compound when solutions of dimedone in dimethylformamide and water or in acetonitrile were treated with metal cyanates (potassium cyanate or lead cyanate). Dimedone can also be converted into carbamoyldimedone by warming with a mixture of urea and dimethylformamide [25,26]. These reactions proceed under conditions such that their applicability to the synthesis of tetracyclines with a carbamoyl group in position 2 is to be expected.



LVI LVII

The synthesis of tetracyclines from 12a-deoxytetracyclines has been carried out microbiologically [27], or using sodium nitrite [28], or via oxidation with oxygen catalyzed by noble metals [29] (see above).

[24] *M. M. Shemyakin, J. A. Arbuzov, M. N. Kolosov, G. A. Shatenshteyn, W. W. Onoprienko*, and *J. V. Konnova*, Zhur. Obshchey Khim. *30*, 542 (1960).

[25] *G. Grethe*, Ph. D. Thesis, Technische Hochschule Braunschweig, 1960.

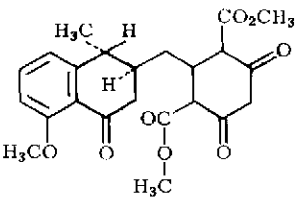
[26] The synthesis of LVII using urea was described by *H. C. Scarborough* and *W. A. Gould*, J. org. Chemistry *26*, 3720 (1961), while this manuscript was under preparation.

[27] *C. E. Holmlund, W. W. Andres* and *A. J. Shay*, J. Amer. chem. Soc. *81*, 4748 (1959).

[28] *C. E. Holmlund, W. W. Andres* and *A. J. Shay*, J. Amer. chem. Soc. *81*, 4750 (1959).

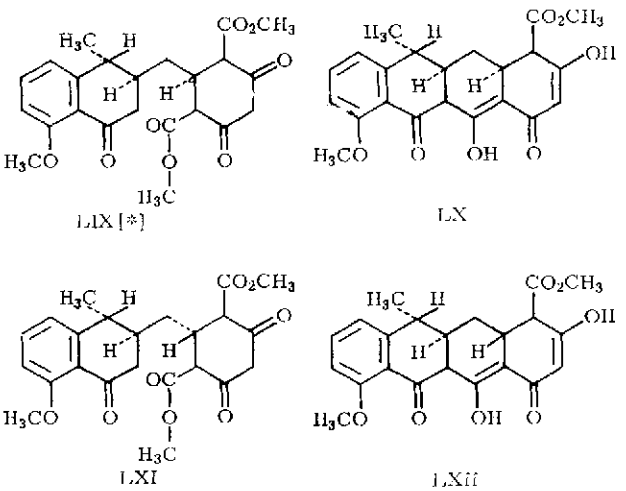
[29] *H. Muxfeldt, G. Buhr*, and *R. Bangert*, Angew. Chem. internat. Edit. *1*, 157 (1962). The same reaction was discovered in the laboratories of Chas. Pfizer and Co. (*K. J. Brunings*, private communication).

The *trans*-3-ethoxycarbonyl-4-methyl-5-chloro-8-methoxy-1-tetralone (XXIII) previously described was available for the synthesis of the tetracyclic compound LV. We intended to synthetize compound LVIII which contains the tricyclic ring A and then to close ring B.



LVIII

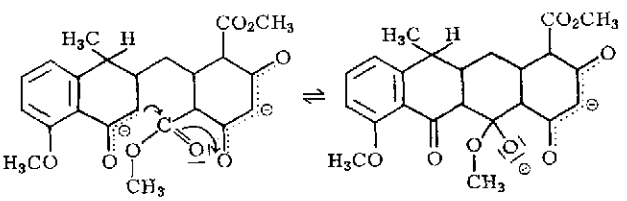
This approach seemed to offer several advantages: one could expect that LVIII might be obtained from the tetralone in relatively few steps, and that cyclization of LVIII would favor formation of a compound LX with the same configuration as 6-deoxytetracycline (XXII). This assumption is based on the following considerations: There are two possible modes of cyclization of LVIII: LIX → LX and LXI → LXII. Compounds LX and LXII have different configurations at carbon-4a.



LIX [*] LX

LXI LXII

If it is assumed that the formation of a new carbon-carbon bond is the rate-determining step of a *Dieckmann* condensation and that the geometries of the transition states are similar to the intermediates of type LXIII, then deductions can be made from the relative stabilities of the intermediates concerning their rates of formation and therefore the rates of the reactions leading to LX and LXII.



LXIII

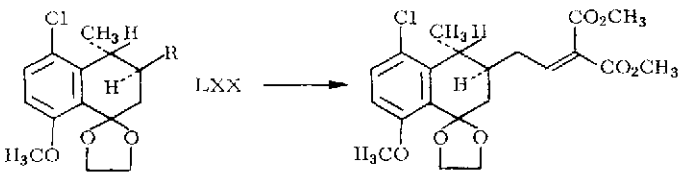
Conformational analysis of all the intermediates conceivable shows that the most stable intermediate on the pathway leading to LX has an energy level several kcal

[*] In all the formulae, the configuration at equilibrable asymmetric centers has been drawn arbitrarily, unless otherwise noted.

less than that of the most stable intermediate on the path to LXII. In the intermediate LXIV, the nonbonded interactions between the oxygen at carbon-12 and the substituent on carbon-4a are much smaller than those in the intermediate LXV.

Therefore the basic ring structure of the tetracyclines should be constructable in a stereospecific manner from LVIII, provided the *Dieckmann* condensation can be kinetically controlled.

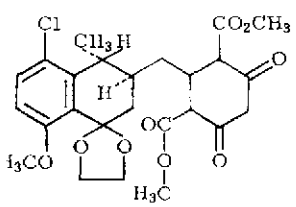
In order to synthesize LVIII, the tetralonecarboxylic ester XXIII was converted into the alkylidene malonic ester LXXI (Formula Scheme 4), which was subjected to a combined *Michael-Dieckmann* condensation with sodio acetoacetic ester. Ketalysis of the carbonyl function was necessary since a free carbonyl group would have made the synthesis impossible by the pathway to be discussed, and because an alkylidenemalonic ester with a free keto group is not stable to alkali.



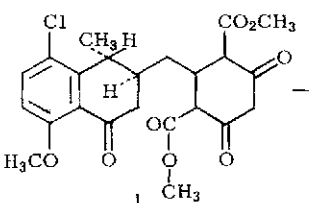
LXX

LXVI; R = $-CO_2C_2H_5$
LXVII; R = $-CH_2OH$
LXVIII; R = $-CH_2OSO_2CH_3$
LXIX; R = $-CH_2CN$
LXX; R = $-CH_2CHO$

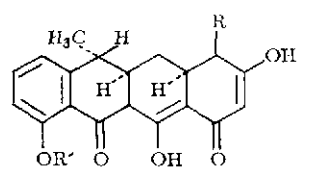
LXXI



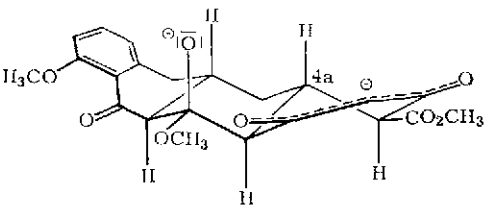
LXXII



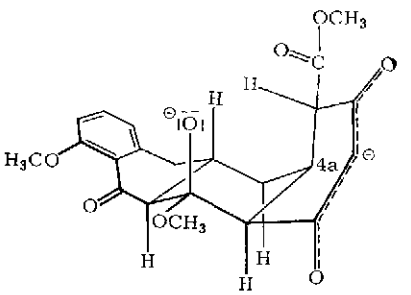
LXXIII



LX; R = CO_2CH_3, R′ = CH_3
LXXIV; R = H, R′ = CH_3
LV; R = H, R′ = H



LXIV



LXV

Formula Scheme 4

The ketalysis was effected with ethylene glycol and catalytic amounts of *p*-toluenesulfonic acid in boiling alcohol. The extremely acid-labile ketal LXVI was reduced with $LiAlH_4$ to the alcohol LXVII, which yielded the mesylate LXVIII with mesyl chloride in pyridine. Solvolysis with potassium cyanide, dimethylformamide, and water yielded the nitrile LXIX, which was reduced to the aldehyde with lithium triethoxyaluminumhydride as described by *H. C. Brown* et al. [30]. This aldehyde was condensed with malonic ester in a boiling mixture of benzene, piperidine, and acetic acid. The crystalline alkylidenemalonic ester LXXI, obtained in good yield, was converted into the crystalline alkali salt of compound LXXII with either sodio or potassio methyl acetoacetate in methanol and ether. For a long time it was impossible to obtain the free compound LXXII in crystalline form. The reason for this seems to be that even in relatively nonpolar solvents, a very quick tautomeric equilibrium sets in, in which obviously many of the 21 possible tautomers of LXXII are present. Crystallization of one tautomer was successfully accomplished when the crystalline potassium salt was dissolved in water and the solution extracted with ether immediately after acidification. However, the crystals which formed spontaneously could not be recrystallized because of the rapid equilibration. That the crystalline material had in fact the structure of a tautomer of LXXII follows from its analysis and ultraviolet spectrum. As shown in Fig. 2, the ultraviolet spectrum of LXXII corresponds very well to the spec-

[30] *H. C. Brown, C. S. Shoaf,* and *C. P. Garg,* Tetrahedron Letters No. 3, p. 9 (1959).

trum of a mixture of equivalent amounts of LXIX and 5-phenyl-4,6-dimethoxycarbonylcyclohexane-1,3-dione [31,32].

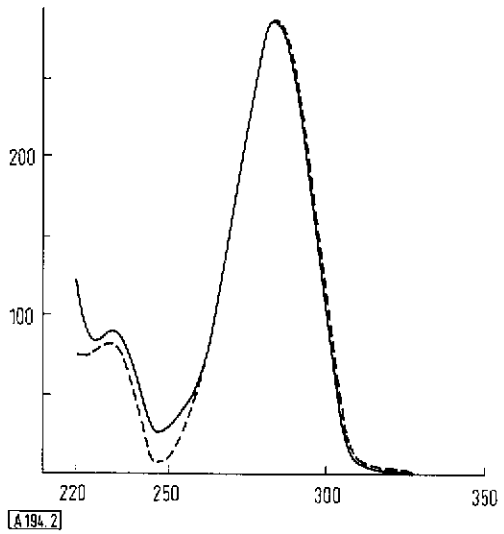


Fig. 2. Ultraviolet spectra of LXXII (——) and of a mixture (- - -) of equivalent amounts of LXIX and 5-phenyl-4.6-dimethoxycarbonyl-cyclohexane-1,3-dione in 0.01 N methanolic sodium hydroxide.
Abscissa: Wavelength [mμ].
Ordinate: Extinction coefficient $\varepsilon \times 10^{-2}$ [cm.²/mole].

To prepare the tricyclic compound LVIII, required for the last cyclization, it was merely necessary to cleave the ketal group in LXXII and to remove the chlorine from the aromatic ring by hydrogenolysis. Both reactions proceeded without difficulty. LXXII was treated with traces of *p*-toluenesulfonic acid in acetone at room temperature, and the amorphous precipitate LXXIII obtained in almost quantitative yield, hydrogenated catalytically. LVIII was then cyclized with sodium hydride in anisole, giving a single tetracyclic compound (LX) in 41 % yield. The ultraviolet spectrum of this substance, measured in sodium tetraborate solution, is similar to the spectrum of dedimethylamino-6,12a-bis-deoxy-6-epitetracycline (XX) (Fig. 3). The differences between the absorption curves of XX and LV are even smaller (Fig. 3); LV was obtained from LX with glacial acetic acid and hydrobromic acid.

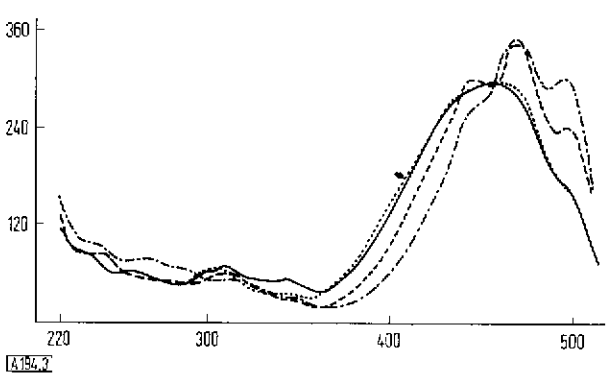


Fig. 3. Ultraviolet spectra of (-.-.-) dedimethylamino-6,12a-bis-(deoxy)-6-epitetracycline (XX), (——) 10-methyl ether of dedimethylamino-decarbamoyl-6,12a-bis(deoxy)-4-methoxycarbonyltetracycline (LX), (·····) 10-methyl ether of dedimethylamino-decabamoyl-6,12a-bis-(deoxy)tetracycline (LXXIV), and (- - - -) dedimethylamino-decarbamoyl-6,12a-bis(deoxy)tetracycline (LV) in 0.1 M methanolic sodium tetraborate solution after attainment of tautomeric equilibrium.
Abscissa: Wavelength [mμ].
Ordinate: Extinction coefficient $\varepsilon \times 10^{-2}$ [cm.²/mole].

These curves correspond to absorptions of borate complexes, which contain a chromophore conjugated over all four rings because of enolization of the carbonyl groups. The relatively long wavelength of absorption therefore is a criterion of C-11a being able to become trigonal [33]. This is the case, according to their ultraviolet spectra, with all the 12a-deoxytetracyclines so far prepared from naturally occurring tetracyclines. It was therefore surprising that after cyclization, the chlorine-containing tricyclic compound LXXIII yielded a product with a spectrum which did not show absorption at 460 mμ in sodium tetraborate solution (Fig. 4). This product is the chlorine-containing tetracyclic compound XI, since it can be converted by catalytic hydrogenation into the dechloro-compound LX. The chlorine atom at C-7 therefore prevents any detectable enolization in the direction of carbon-11a, which also follows from the fact that the spectrum of XI is similar to that of dedimethylamino-11a-hydroxy-12a-deoxytetracycline [29] (Fig. 4).

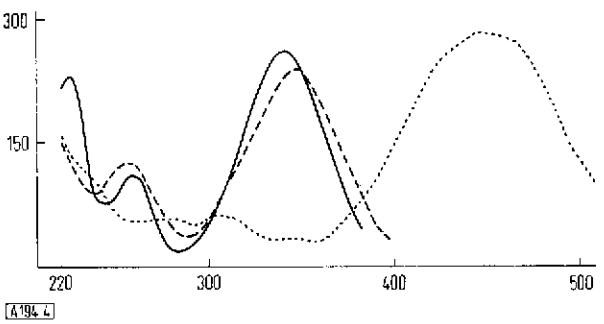
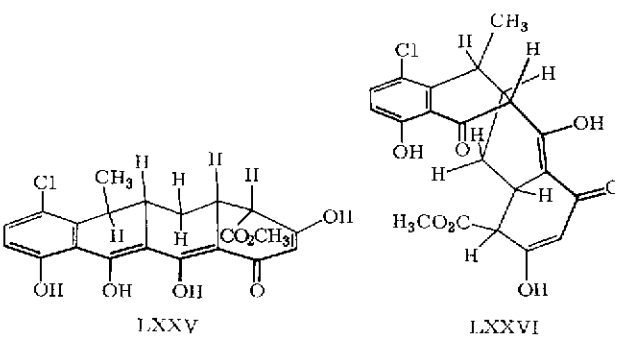


Fig. 4. Ultraviolet spectra of the 10-methyl ether of dedimethylamino-decarbamoyl-6,12a-bis(deoxy)-4-methoxycarbonyl-7-chlorotetracycline (XI), dedimethylamino-11a-hydroxy-12a-deoxytetracycline, and the 10-methyl ether of dedimethylaminodecarbamoyl-6,12a-bis(deoxy)-4-methoxycarbonyl-7-chloro-6-epitetracycline (LXXIX) in 0.1 M methanolic sodium tetraborate solution, after attainment of tautomeric equilibrium.
Abscissa: Wavelength [mμ].
Ordinate: Extinction coefficient $\varepsilon \times 10^{-2}$ [cm.²/mole].

The reason that the chlorine atom prevents sp^2 hybridization of carbon-11a is obtained from conformational analysis of all the possible tautomers of XI. In all



[31] *H. Beylich*, Diploma Thesis, Technische Hochschule Braunschweig 1961.

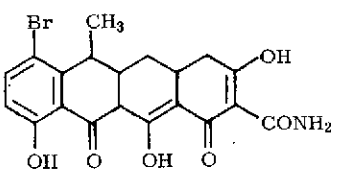
[32] *G. Grethe*, Ph. D. Thesis, Technische Hochschule Braunschweig, 1961.

[33] The measurement of the ultraviolet spectra of the 12a-deoxytetracyclines in sodium tetraborate solution was suggested by *T. L. Fields, A. S. Kende*, and *J. H. Boothe*.

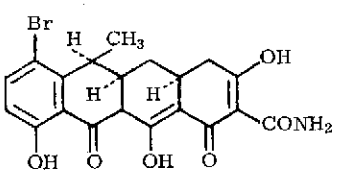
tautomers with tetrahedral 11a-carbons, for example in LXXVI, the 6-methyl group is located quasi-equatorially and thus the distance between this group and the chlorine atom is minimal. To obtain a maximum distance between the chlorine atom and the methyl group, a tetrahedral carbon at 11a is necessary. If rings B and C are *cis* to each other, the methyl group in LXXVI can assume a quasi-axial conformation.

The spectral behavior and conformational analysis of the tautomers of XI therefore show that the nonbonded interactions between the chlorine atom and the methyl group permit only a tetrahedral carbon at 11a.

Compound LXXVII was obtained by *Kende* [*] by degradation of tetracycline (I) (*e.g.* by hydrogenolytic removal of the 6-hydroxyl group). Despite its bromine atom in the 7-position, this compound does not possess a spectrum similar to our compound XI, but in alkaline solution shows the long wavelength absorption of a chromophore which is conjugated over all four rings. Hydrogenolysis of the 6-hydroxyl group must therefore proceed with inversion of configuration, since it is only when LXXVII possesses the configuration of a 6-deoxy-6-epitetracycline (LXXIII) that the methyl group in tautomers with a tetrahedral carbon atom at 11a is quasi-axial, *i.e.* only then is enolization in the direction of carbon-11a unhindered by the bromine atom in the 7-position.

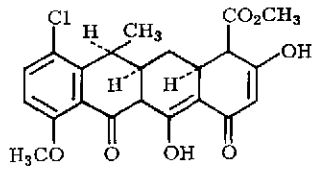


LXXVII

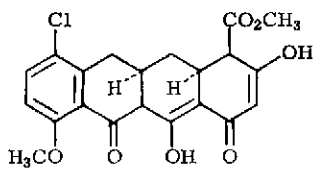


LXXVIII

We therefore reached the conclusion that our synthesis would not lead to compounds which are obtained from tetracyclines by catalytic hydrogenation. We had in fact to synthetize compounds of the 6-desoxy-6-epitetracycline series. To this end, *cis*-3-ethoxycarbonyl-4-methyl-5-chloro-8-methoxy-1-tetralone (XXXII) was converted into the tetracyclic compound LXXIX, by analogy to the synthesis of XI. The borate complex of LXXIX exhibits the absorption of a conjugated chromophore at long wavelengths (Fig. 4) [34]. Since the tetracyclic compound LXXX, obtained from 3-methoxy-



LXXIX



LXXX

carbonyl-5-chloro-8-methoxy-1-tetralone, also shows an absorption maximum at 450 mμ in sodium tetraborate solution [35], the hypothesis concerning the influence of a chlorine atom on the hybridization of carbon atom 11a in XI is thus confirmed.

Conclusion

We have shown that the β-tetracarbonyl system of tetracyclines can be synthetized in 12 steps. The conditions of the reactions are such that, in principle, the synthesis can probably be used for the preparation of compounds that are derived from Terramycin (II) and that have the two hydroxyl groups in the 5- and 6-positions.

The results described here were obtained in collaboration with Dr. Armin Kreutzer, Dr. Klaus Striegler, Dr. Werner Rogalski, Dr. Guenter Grethe, Konrad Uhlig, Eckkardt Jacobs, Renate Bangert, Gerhard Buhr and Heiner Beylich. We are pleased to acknowledge the generous and extensive support of Prof. H. H. Inhoffen, the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and Farbwerke Hoechst.

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Electrophilic Substitutions at Saturated Carbon Atoms

BY DR. G. KÖBRICH

INSTITUT FÜR ORGANISCHE CHEMIE DER UNIVERSITÄT HEIDELBERG (GERMANY)

The results obtained in recent years from investigations into the mechanisms of electrophilic substitution reactions at sp^3-hybridized carbon atoms are reviewed.

1. Introduction

Nucleophilic reactions at saturated carbon atoms [1] and electrophilic substitutions at aromatically bonded carbon atoms, the classical representatives of heterolytic mechanisms, are long known and have been extensively investigated. Excellent surveys dealing with nucleophilic aromatic substitution are available [2]. Electrophilic substitution at saturated carbon atoms is related formally to nucleophilic aromatic substitution in the same manner as the two "classical" mechanisms are related to each other.

2. Summary of Possible Mechanisms

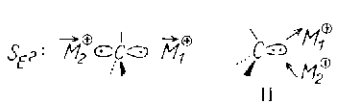
According to *Charman*, *Hughes*, and *Ingold* [3], three reaction routes, analogous to those of nucleophilic reactions [1], can be postulated for electrophilic substitutions at saturated carbon atoms.

An S_E1 reaction, such as in Eq. (1), should be favored by both an ionizing medium and a polar $R-M_1$ bond and should follow first-order kinetics, if the first step is irreversible. Optically active compounds are expected to undergo racemization, at least partially.

$$(1)\quad S_E1:\ R-M_1 \xrightarrow{\text{slow}} R^{\ominus} + M_1^{\oplus}$$

$$R^{\ominus} + M_2^{\oplus} \xrightarrow{\text{fast}} R-M_2$$

One can conceive of S_E2 reactions with second-order kinetics, in which the configuration of the optically active substrates is either retained or inverted. Whether such reactions can take place depends on the bond-stretching capacity of the center orbital. The transition states are represented by I and II. I corresponds to the transition taking place in S_N2 reactions, with *Walden* inversion, although with the significant difference that the participating orbitals exhibit only two reacting electrons.



II

On the other hand, the route involving II leads to the retention of the configuration in the final product. This also holds in the case of S_Ei reaction with a cyclic transition state, shown in Eq. (2) below, to which second order kinetics should also apply:

$$(2)\quad S_Ei:\ R-M_1 + M_2X \longrightarrow \begin{matrix} M_1 \\ R \\ M_2 \end{matrix}\!\!\!

greater stability in nonpolar solvents indicates an ionic racemization mechanism.

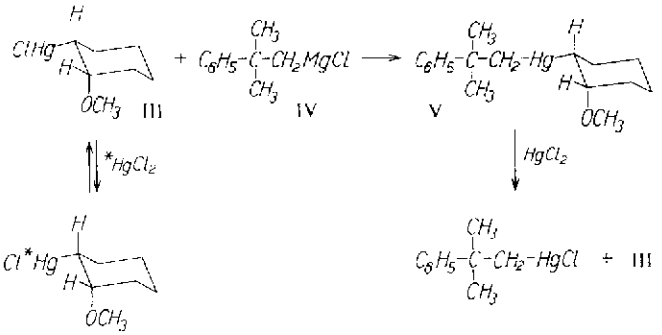
The cyclopropyl system, whose bond relationships occupy position intermediate between alkyl and alkenyl compounds [*] produces more stable metal derivatives. Several cyclopropyl-lithium compounds have been converted into carboxylic acids of 100 % optical purity [6,7]. Recently, the first optically active *Grignard* compound of the same ring system [8] was synthetized. However, no clear-cut definition of the stereochemical course of a reaction is possible as long as only the starting compound for the organo-metallic substrate is available for comparison of configuration with the subsequent (*e.g.* a carboxylation) product. This problem arises from the fact that the retention of configuration generally observed can be the result of either retention or inversion of configuration in both of the partial reactions. The stable, isolable heavy metal compounds have proved helpful in this respect, especially mercury compounds, a number of which with optically active aliphatic substituents have been described in recent years [3,9–12].

Bimolecular Reactions

4. Reactions with Alicyclic Compounds

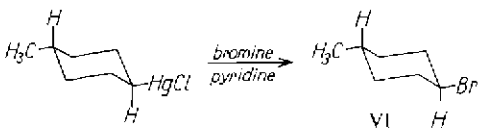
The results obtained with this class of compounds, can in most cases be included in the reaction scheme described in the next section. For the sake of clarity however, they will be considered separately. In this class of compounds, substances of definite configurations can be prepared with relative ease.

According to *Winstein* et al., the mercury compound V, obtained *in situ* from *cis*-2-methoxycyclohexylmercuric chloride (III) and neophylmagnesium chloride (IV), when treated with radioactive $^{203}HgCl_2$ again yields 2-methoxycyclohexyl-mercuric chloride, which contains at least 99.7 % of the *cis* isomer (III) [13,14]. The cleavage thus occurs with retention of the configuration. The measured radioactivity of the final products shows that both the neophyl and the cyclohexyl bonds are broken to an extent of approximately 50 %.



Alkylmercury halides are also capable of reacting with mercury salts. The radioactive organomercury compound is formed with complete retention of configuration both from III and from the corresponding *trans* compound by the reaction of either of these with radioactive mercuric chloride [15]. *Reutov* et al. studied the rate determining factors of this reaction using alicyclic mercury compounds [12].

Both stereoisomers of 4-methylcyclohexylmercuric bromide can be converted into the bromo-derivative VI by reaction with bromine in polar solvents (pyridine). Only one isomer is formed in each case. According to spectroscopic findings [16], it is the one with the same configuration as the starting compound.



The symmetrization of organomercury halides with magnesium also proceeds with virtually complete retention of configuration, as *Jensen* and *Landgrebe* [17] found during investigation of *cis*- and *trans*-4-methylcyclohexylmercuric bromide. Some indication of the mechanism of the reaction (cf. p. 386) is given by the fact that under those conditions, III (with Br instead of Cl) yields only cyclohexene by β-elimination.

The fact that electrophilic substitutions at bridgehead carbon atoms of bicyclic compounds are so easily accomplished [18] strongly indicates that, in contrast to S_N2 reactions, these processes involve frontal attack. The rate of solvolysis of 4-camphylmercuric chloride (VIII) in glacial acetic acid lies between those observed for n-butyl- and neophyl-mercuric chlorides [19]. Thus, there is no reason for assuming that another, normally

[*] The high configurational stability of the alkenyl-lithium compounds is well-known; see, *e.g.*, *B. L. Crombie*, Quart. Reviews *6*, 137 (1952); *D. Y. Curtin, H. W. Johnson*, and *E. G. Steiner*, J. Amer. chem. Soc. *77*, 4566 (1955); *F. G. Bordwell* and *P. S. Landis*, ibid. *79*, 1593 (1957); *N. I. Allinger* and *R. B. Hermann*, J. org. Chemistry *26*, 1040 (1961).

[6] *H. M. Walborsky* and *F. J. Impastato*, J. Amer. chem. Soc. *81*, 5835 (1959).

[7] *D. E. Applequist* and *A. H. Peterson*, J. Amer. chem. Soc. *83* 862 (1961).

[8] *H. M. Walborsky* and *A. E. Young*, J. Amer. chem. Soc. *83*, 2594 (1961).

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[10] *F. R. Jensen, L. D. Whipple, D. K. Wedegaertner*, and *J. A. Landgrebe*, J. Amer. chem. Soc. *81*, 1262 (1959); *82*, 2466 (1960).

[11] *O. A. Reutov* and *E. V. Uglova*, Izv. Acad. Nauk USSR, Otd. Khim. Nauk, 757 (1959); Chem. Abstr. *53*, 21, 626 (1959).

[12] Summary of Russian work see *O. A. Reutov*, Angew. Chem. *72*, 202 (1960).

[13] *S. Winstein, T. G. Traylor*, and *C. S. Garner*, J. Amer. chem. Soc. *77*, 3741 (1955).

[14] *G. F. Wright*, Canad. J. Chem. *30*, 268 (1952).

[15] *O. A. Reutov, P. Knoll*, and *Yan-Tsei U*, Dokl. Acad. Nauk USSR *120*, 1052 (1958); Chem. Abstr. *52*, 20003 (1958).

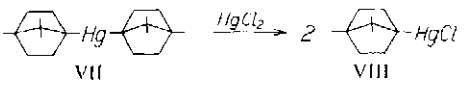
[16] *F. R. Jensen* and *L. H. Gale*, J. Amer. chem. Soc. *81*, 1261 (1959).

[17] *F. R. Jensen* and *J. A. Landgrebe*, J. Amer. chem. Soc. *82*, 1004 (1960).

[18] For a review, see *U. Schöllkopf*, Angew. Chem. *72*, 147(1960).

[19] *S. Winstein* and *T. G. Traylor*, J. Amer. chem. Soc. *78*, 2597 (1956).

preferred mechanism was suppressed by steric hindrance at the bridgehead [19]. Carboxylation of 4-camphyllithium, syn proportionation of bis-4-camphylmercury (VII) with $HgCl_2$ to give VIII, reduction of VIII by lithium alanate to camphane, and the reaction of the iodide of VIII (with I instead of Cl) to 4-iodo-camphane [19] all proceed smoothly and inavoidably with retention of configuration, in exactly the same way as similar reactions at the bridgehead of triptycene [20, 21].



VII VIII

5. Alkyl Exchange in Organomercury Compounds

Hughes and *Ingold* [3] distinguished three classes of reactions between organo-mercury compounds, depending on whether the two reacting molecules carry a total of one, two, or three aliphatic substituents:

(3) $X_2Hg + RHgX \rightleftharpoons XHgR + HgX_2$

(4) $XHgR + RHgX \rightleftharpoons RHgR + HgX_2$

(5) $XRHg + RHgR \rightleftharpoons RHgR + HgRX$

R = alkyl
X = acid anion

It is obvious that when R and X are the same, the initial and final products differ chemically only in Eq. (4). Information for the other reactions has to be obtained by means of labelling the molecule.

The fourth possibility, the exchange between two dialkylmercury compounds according to Eq. (6), can only be achieved by catalysis with aluminum chloride [22], since the mercury atoms lose their ease of reactivity owing to the electron releasing influence of the ligands.

(6) $R_2Hg + RHgR \overset{AlCl_3}{\rightleftharpoons} RHgR + HgR_2$

a) Alkyl Exchange between HgX_2 and RHgX

Nefedov et al. obtained an isotope-exchange between methylmercury bromide and radioactive mercury bromide, but they incorrectly assumed a two-stage mechanism for the reaction [23].

$CH_3HgBr + {}^{203}HgBr_2 \rightleftharpoons CH_3{}^{203}HgBr + HgBr_2$

Hughes, *Ingold* et al. [24] were able to demonstrate in careful kinetic investigations, that a one-step bimolecular reaction takes place and that with an optically active alkyl group, it proceeds with complete retention of configuration. The increase in rate in the sequence of increasingly ionic derivatives $CH_3HgBr < CH_3HgI \ll CH_3HgOCOCH_3 \ll CH_3HgNO_3$ suggests a polar transition state, as does the positive salt-effect caused by lithium acetate or nitrate. Therefore, according to these authors, an S_E2 reaction is more probable than one following the S_E1 path [24].

This exchange is catalytically accelerated by alkali halides [25]. Such an effect is attributed to the formation of a complex, which can create an energetically favored, bridged transition state (IX) with the organic compound.

$$HgX_2 + LiX \rightleftharpoons Li^{\oplus}HgX_3^{\ominus}$$

If the concentration of extraneous salt exceeds that of the reactants, a second type of catalysis, with a different reaction rate, comes into effect. This is apparent from a break in the straight line obtained on plotting the salt concentration against the reaction rate. The corresponding transition state X can be written as follows [25]:



IX X

As the bulk of the transition state grows with increase in the number of bromine atoms, the catalysis becomes less efficient, when branched alkyl groups R are involved. In particular, the "two-anion catalysis", although usually faster, can then lag behind the "one-anion catalysis" [26].

In the reactions discussed here, the solvent exerts a decisive effect, as *Reutov* et al. [26a] were able to show by means of isotope exchange in the ester XI (with C_2H_5 instead of $C_{10}H_{19}$). The exchange in pyridine follows second order kinetics, whereas in 70 % aqueous dioxan, it is of the first order with respect to substrate and of zero-th order with respect to mercuric bromide. Alterations in the rate of reaction occasioned by substituents in the *para*-position in the phenyl substituent are in accordance with an S_E1 mechanism – the first therefore to be identified among mercury derivatives.

b) Alkyl Exchange between R_2Hg and HgX_2

Such reactions [27] are designated as syn-proportionations, when written as in Eq. (4); read in the reverse direction, they describe symmetrization reactions of organo-mercury compounds. When extended to other organometallic compounds, this is what is known as the "*Schlenk* equilibrium" which, incidentally, does not exist in the case of derivatives of magnesium [28], zinc,

[20] *G. Wittig* and *U. Schöllkopf*, Tetrahedron *3*, 91 (1958).

[21] *G. Wittig* and *W. Tochtermann*, unpublished results.

[22] *G. Calingaert*, *H. Soroos*, and *V. Hnizda*, J. Amer. chem. Soc. *62*, 1107 (1940).

[23] *V. D. Nefedov*, *E. N. Sinotova*, and *N. Ya Frolov*, Zhur. Fiz. Khim. *30*, 2356 (1956); Chem. Abstr. *51*, 9271 (1957).

[24] *E. D. Hughes*, *C. Ingold*, *F. G. Thorpe*, and *H. C. Volger*, J. chem. Soc. (London) 1133 (1961).

[25] *H. B. Charman*, *E. D. Hughes*, *C. Ingold*, and *H. C. Volger*, J. chem. Soc. (London) 1142 (1961).

[26] *E. D. Hughes* and *H. C. Volger*, J. chem. Soc. (London) 2359 (1961).

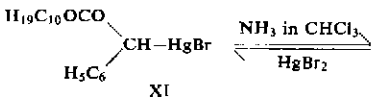
[26a] *O. Reutov*, *U. I. Sokolov*, and *I. P. Beletskaja*, Dokl. Acad. Nauk USSR *136*, 631 (1961); Chem. Abstr. *55*, 17557 (1961).

[27] *E. Krause* and *A. von Grosse*: Chemie der metallorganischen Verbindungen. Verlag Gebr. Borntraeger, Berlin 1937, p. 127.

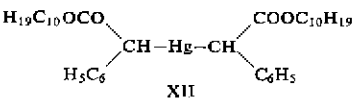
[28] *R. E. Dessy* and *G. S. Handler*, J. Amer. chem. Soc. *80*, 5824 (1958); *R. E. Dessy*, *G. S. Handler*, *J. H. Wotiz* and *C. A. Hollingsworth*, ibid. *79*, 3476 (1957).

cadmium [29], and beryllium [30] and which has been definitely established only for the case of mercury.

Reactions of the type, shown by Eq. (4) are basically reversible and always proceed with retention of configuration. (An observation to the contrary [31] was later corrected [12,32]). Thus, on symmetrization with ammonia, each of the two diastereoisomeric L-menthyl esters of α-bromomercuriphenylacetic acid (XI) yields only one isomer XII, which reforms compound XI when treated with mercuric bromide or hydrogen bromide [31–33].



XI



XII

Fifty percent of the C-Hg bonds are newly formed in the partial reaction step XI → XII, and the recovered XI is stereochemically homogeneous. Therefore, the step XI → XII must have taken place with retention of configuration. The fact that the initial product is identical with the final one proves the retention of configuration in the second step XII → XI.

In experiments with diastereoisomers there is, however, a possibility that the second asymmetric carbon atom exerts a stabilizing influence upon the reaction center. The identification of optically active lithium and magnesium compounds in the presence of an optically active solvent [34] is an example of this, since racemization takes place when an optically inactive solvent is used under the same conditions. The syn-proportionation was therefore also investigated with compounds having substituents with only one asymmetric carbon atom. *Reutov* [11,12] investigated bis(2-methyl-5-hexyl)-mercury, while *Hughes* and *Ingold* [35], and independently, *Jensen* [36] studied bis(s.-butyl-mercury). The latter contained one optically active group, according to Eq. (7), and with mercury bromide in acetone or alcohol

(7) (−)-R−HgBr + (±)-R−MgCl ⟶ (−)-R−Hg−(±)-R

$\xrightarrow{HgBr_2}$ (−)-R−HgBr + (±)-R−HgBr R = s-butyl

yielded s.-butylmercury bromide, with half the rotation of the starting material [35,36]. The syn-proportionation must, therefore have taken place with retention of configuration. The reaction is bimolecular and its rate increases in the sequence:

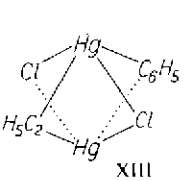
$$HgBr_2 < Hg(OCOCH_3)_2 < Hg(NO_3)_2,$$

that is, proportionally to increase in the cationic character of the Hg atom. An S_E2 mechanism was, therefore, preferred to an S_Ei mechanism [35]. The $LiHgBr_2$ complex, formed by addition of lithium bromide, is obviously incapable of reacting, unlike the one in the reaction discussed in a).

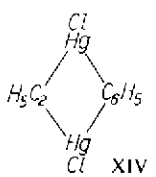
Dessy et al. [37] report that the syn-proportionation of diphenyl-mercury proceeds according to Eq. (8) and is several orders of magnitude faster than the reaction with diethylmercury. It would, therefore, be expected that the phenyl-mercury bond in unsymmetrical phenyl-ethyl-mercury (C_6H_5–Hg–C_2H_5) would be preferentially severed.

(8) R−Hg−R′ + HgI_2 ⟶ R−HgI + R′−HgI

However, in the reaction with radioactive mercuric iodide, both cleavage products display approximately the same activity and this distribution does not originate from a subsequent isomerization. One would conclude from this that both mercury atoms must be equivalent in the transition state. It is believed [37] that, of the two configurations (XIII and XIV) possible, the octahedral one (XIII) can be excluded, since cyclic compounds, such as XV and XVI, in which a transition state of the type XIII would be very unfavorable, show kinetic data very similar to those of acylic substances.



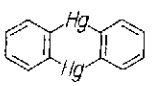
XIII



XIV



XV



XVI

The conclusion is not valid with respect to compound XVI, however, since the latter actually exists as the trimer [38].

In order to be able to include aromatically substituted mercury derivatives in reactions of this type, avoidance of interchange of substituents before the reaction in accordance with Eq. 6, which can occur here without a catalyst [38a] and which would necessarily lead to a statistical distribution of the isotopes in the final products after the subsequent reaction with labelled mercuric halide, is essential. According to *Brodersen* and *Schlenker* [38b], starting from unsymmetrical organomercury compounds and labelled mercuric bromide in ether at −20 °C, a distribution of activity in the final

[29] *A. B. Garrett, A. Sweet, W. L. Marshall, D. Riley*, and *A. Touma*, Record chem. Progr. *13*, 155 (1952); Chem. Abstr. *48*, 2575 (1954).

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[31] *A. N. Nesmeyanov, O. A. Reutov*, and *S. S. Poddubnaya*, Dokl. Acad. Nauk USSR *88*, 479 (1953); Chem. Zbl. 5474 (1953).

[32] *O. A. Reutov*, Angew. Chem. *69*, 688 (1957).

[33] *A. N. Nesmeyanov, O. A. Reutov, Yan-Tsei U*, and *Tsin-Tschu Lu*, Izv. Acad. Nauk USSR, Otcl. Khim. Nauk. 1327 (1958); Chem. Abstr. *53*, 7224 (1959).

[34] *H. L. Cohen* and *G. F. Wright*, J. org. Chemistry *18*, 432 (1953); *A. G. Brook, H. L. Cohen*, and *G. F. Wright*, ibid. *18*, 447 (1953).

[35] *H. B. Charman, E. D. Hughes*, and *C. Ingold*, J. chem. Soc. (London) 2530 (1959).

[36] *F. R. Jensen*, J. Amer. chem. Soc. *82*, 2469 (1960).

[37] *R. E. Dessy, Y. K. Lee*, and *Yin-Young Kim*, J. Amer. chem. Soc. *83*, 1163 (1961).

[38] *G. Wittig* and *F. Bickelhaupt*, Chem. Ber. *91*, 883 (1958); *D. Grdenic*, ibid. *92*, 231 (1959).

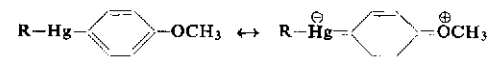
[38a] *O. A. Reutov* et al., Tetrahedron Letters No. 19, p. 6 (1960).

[38b] *K. Brodersen* and *U. Schlenker*, Chem. Ber. *94*, 3304 (1961).

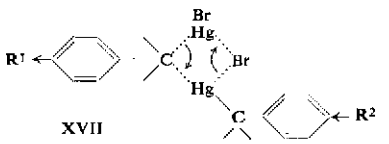
products is obtained that indicates a decrease in the readiness of the R–Hg bond to break along the series

$$CH_3 > C_2H_5 > n\text{-}C_3H_7 \text{ and } n\text{-}C_4H_9 \gg C_6H_5 > p\text{-}H_3COC_6H_4,\ p\text{-}BrC_6H_4$$

These results are in agreement with the assumption of increasing polarity of the C–Hg bond with increasing chain length of aliphatic substituents and of a π-bond participation leading to an increase in the strength of attachment of aromatic substituents.



According to *Reutov* [12], the likelihood of an S_Ei mechanism is supported by the fact that disproportionation of esters of α-bromomercury (II)-phenylacetic acid (corresponding to XI) proceeds more rapidly when different substituents are present in the *para*-position of the aromatic ring than with each component alone. Assuming that the reaction proceeds through a transition state of the type XVII [12] and that the portion containing the electron-attracting substituent serves to cleave the C-Hg bond, while the portion with donating substituents serves to cleave the Hg-Br bond, it would necessarily follow that if one reactant labelled with radioactive mercury were introduced, the distribution of activity in the final products would be non-statistical. This experiment has not yet been carried out.



XVII

The symmetrization reaction, which is normally at a disadvantage with respect to the reverse syn-proportionation [39], can be forced to go with reducing agents, as well as with reagents capable of complexing the HgX_2 formed (Eq. 4). While the reaction obviously proceeds via radicals with hydrazine [14,40,41], and sodium stannite [42], it is stereospecific with sodium thiosulfate [13,40], or magnesium [17]. In the latter case neither radicals (with styrene), nor a carboxylic acid (in a CO_2 atmosphere), both of which should appear with intermediates such as $R^{\ominus}$ or RMgBr could be detected. The course of reaction has been interpreted by *Jensen* and *Landgrebe* [17] as follows:

$$R\text{–}HgBr + Mg \longrightarrow R\text{–}Hg^{\ominus} + {}^{\oplus}MgBr$$

$$R\text{–}Hg^{\ominus} + R\text{–}HgBr \longrightarrow R\text{–}HgHg\text{–}R + Br^{\ominus}$$

$$R\text{–}HgHg\text{–}R \longrightarrow \underset{\displaystyle R}{\underset{|}{R\text{–}HgHg}} \quad \text{(Retention!)}$$

$$\underset{\displaystyle R}{\underset{|}{R\text{–}HgHg}} \longrightarrow R_2Hg + Hg \qquad R = \text{L-(–)-s-butyl}$$

The inversion shown in the last two equations furnishes an explanation for the homolytic isotope exchange with metallic mercury, which can proceed stereospecifically [15,43,44].

c) Alkyl Exchange between R_2Hg and RHgX

Three mechanisms are possible for this reaction type [45]:

$$(9)\quad {}^{0}R^{*}HgBr + R_2Hg \longrightarrow {}^{0}RR^{*}Hg + RHgBr \qquad {}^{0}R:\ Hg = 1:1$$

$$(10)\quad {}^{0}R^{*}HgBr + R_2Hg \longrightarrow R^{*}HgBr + {}^{0}RRHg \qquad {}^{0}R:\ Hg = 1:0$$

$$(11)\quad 2\,{}^{0}R^{*}HgBr \longrightarrow {}^{0}R_2{}^{*}Hg + {}^{*}HgBr_2 \qquad {}^{0}R:\ Hg = 2:1$$

$$^{*}HgBr_2 + R_2Hg \longrightarrow R^{*}HgBr + RHgBr$$

According to *Hughes, Ingold* et al. differentiation between these is possible by simultaneous use of an optically compound ($^{\circ}R$ = s.-butyl) and labelled mercury ($^{*}Hg$), since the resulting bis(s.-butyl)mercury must exhibit the various ratios of labelled atoms indicated to the right of the equations. The measurements gave a ratio of Hg: $^{\circ}R = 0.96$, thus favoring Eq. (9) [45]. The same result was obtained by *Reutov* and co-workers [38a] (R = 2-methyl-5-hexyl). The reaction proceeds with retention of configuration and second-order kinetics. It is only slightly accelerated by lithium salts. In this case, too, an S_E2 reaction is more likely than S_Ei, because of the increase in the rate of reaction with increasingly ionizing anions [45].

d) Summary

The exchange reactions between the two reacting mercury atoms apparently proceed the faster, the greater the difference in the polarization induced by their substituents. It is possible that the substitution is preceded

$$R\text{–}Hg\text{–}A + B\text{–}Hg\text{–}X \rightleftharpoons \underset{\displaystyle A\ B}{\underset{|}{R\text{–}HgHg}}\text{–}X$$

A, B = alkyl or acyl

by the formation of a complex, from which the alkyl exchange proceeds in a concerted mechanism. *Wright* [46] has shown from dipole measurements that the required angles and deformabilities of the mercury valences are possible even in the ground state of molecules in solution.

6. Cleavage of Alkylmercury Compounds with Acids

This reaction has been extensively studied even at an early vantage [47]. Very little is known about its mechanism, originally formulated as an S_E1 reaction [48].

[39] *I. B. Johns* and *R. M. Hixon*, J. physic. Chemistry *34*, 2226 (1930).

[40] *O. A. Reutov* and *Tsin-Tschu Lu*, Dokl. Acad. Nauk. USSR *110*, 575 (1956); Chem. Abstr. *51*, 8042 (1957); Zh. Obschye Khimii *29*, 182 (1959); Chem. Abstr. *53*, 22058 (1959).

[41] *O. A. Reutov* and *Tsin-Tschu Lu*, Zh. Obschey Khimii *29*, 1207 (1959); Chem. Abstr. *54*, 1586 (1960); compare, however, ibid. *29*, 1617 (1959); Chem. Abstr. *54*, 8884 (1960).

[42] *T. G. Traylor* and *S. Winstein*, J. org. Chemistry *23*, 1796 (1958).

[43] *O. A. Reutov*, Izv. Akad. Nauk. USSR, Otcl. Khim. Nauk. 684 (1959); Chem. Abstr. *52*, 20004 (1958).

[44] See [12] p. 206.

[45] *H. B. Charman*, *E. D. Hughes*, *C. Ingold*, and *F. G. Thorpe*, J. chem. Soc. (London) 1121 (1961).

[46] *H. Sawatzky* and *G. F. Wright*, Canad. J. Chem. *36*, 1555 (1958).

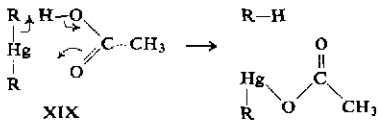
[47] *M. S. Kharasch* and *R. Marker*, J. Amer. chem. Soc. *48*, 3130 (1926); *F. C. Whitmore* and *H. Bernstein*, ibid. *60*, 2626 (1938).

[48] *M. S. Kharasch* and *A. L. Flenner*, J. Amer. chem. Soc. *54*, 674 (1932).

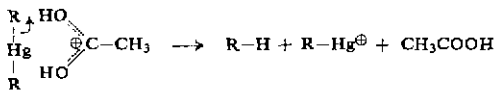
According to *Winstein* [49], pseudo first order acetolysis proceeds with decreasing rate in the sequence

$C_6H_5 > s\text{-}C_4H_9 > n\text{-}C_4H_9 >$ neophyl (for R_2Hg).

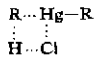
The cleavage proceeds much faster when perchloric acid is added, and stringently follows first-order kinetics with respect to substrate and perchloric acid. It has been discussed that an S_Ei mechanism applies in the first case (XIX), while the second proceeds via an S_E2 mechanism (XX):



XIX



XX



XXI

Participation of the anion appears probable from results of *Dessy* [50], who found that cleavage of symmetrical organomercury compounds with hydrogen chloride is accelerated by all factors which suppress dissociation of the HCl molecules. The bimolecular reaction has therefore been formulated as a concerted reaction, in accordance with XXI. The influence of the substituents upon the reaction rate is reflected in the sequence:

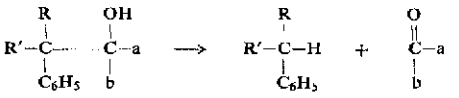
cyclopropyl > vinyl > phenyl > ethyl > isopropyl > n-propyl > methyl.

Interestingly, the greater ease of cleavage of unsaturated organometallic compounds, also observed, for example, with organotin [51] and organosilicon [52] compounds, is contrary to the increase in reactivity of alkyl- compared to vinyl- and aryl-lithium derivatives, principally due to the basicity of the organic anion involved.

Reactions Including Carbanions [*]

7. Cleavage of Alkoxides

According to experiments by *Cram* et al. [53–61], the base-inhibited decomposition of optically active alcohols of the type XXII is caused by an S_E1 mechanism. The cleavages take place, for example, with potassium-*N*-methylanilide in *N*-methylaniline, with predominant



XXII XXIII XXIV

retention of configuration [**] [53]. The extent of racemization depends on the reaction temperature, while the readiness to undergo cleavage depends mainly on the substituents *a* and *b*, so that heterolysis is accelerated with increase in bulk because of steric stresses. In solvents of low dielectric constant, cleavage of (−)-3,4-dimethyl-4-phenyl-3-hexanol occurs with a maximum retention of configuration of 93 % (*e.g.* with KOH in t.-butanol, or potassium-t.-butoxide in benzene). In solvents of high dielectric constant, the cleavage proceeds chiefly with an inversion of configuration in the reaction product (corresponding to XXIII) up to a maximum of 51 % (*e.g.* with potassium glycolate in glycol) [54]. Consequently, in mixtures of two solvents, any ratio of the enantiomorphs in the final product can be obtained, within the limits dictated by the pure solvents [55].

It is obvious that several mechanisms are in play: which one comes into effect depends on the solvent. Two reaction paths are conceivable, one proceeding exclusively with retention of configuration, the other exclusively with inversion of configuration. The fraction of racemate would then originate by superposition of both those processes. This possibility is, however, improbable. In the corresponding solvents at higher temperatures, both retention and inversion decrease in favor of the racemic product [55, 59]. The ratio of the reaction rate constants, k_{ret}/k_{inv}, would therefore have to have a negative temperature coefficient in media favoring retention and on the other hand, media favoring inversion would have to exhibit a positive temperature coefficient.

Accordingly, besides the two stereospecific mechanisms, a third one must be in effect, yielding a racemic cleavage product, the proportion of which increases with increasing temperature [55]. Homolysis or racemization preceding cleavage may be excluded [56, 57].

The stereochemical course of the cleavage is nearly independent of the nature of the leaving group XXIV. This is especially true for some diastereoisomeric pairs, such as XXV, investigated in solvents favoring retention. Under identical conditions, these compounds

[*] A few elimination reactions of interest in this connection are included.

[49] *S. Winstein* and *T. G. Traylor*, J. Amer. chem. Soc. *77*, 3747 (1955).

[50] *R. E. Dessy, G. F. Reynolds*, and *Jin-Young Kim*, J. Amer. chem. Soc. *81*, 2683 (1959); cf. *R. E. Dessy* and *Jin-Young Kim*, ibid. *82*, 686 (1960); *83*, 1167 (1961).

[51] *D. Seyferth*, J. Amer. chem. Soc. *79*, 2133 (1957).

[52] *R. A. Benkeser, D. I. Hoke*, and *R. A. Hickner*, J. Amer. chem. Soc. *80*, 5294 (1958).

[53] *D. J. Cram, A. Langemann, J. Allinger*, and *K. R. Kopecky*, J. Amer. chem. Soc. *81*, 5740 (1959).

[54] *D. J. Cram, A. L. Langemann*, and *F. Hauck*, J. Amer. chem. Soc. *81*, 5750 (1959).

[**] The absolute configurations of the initial and final products are known.

[55] *D. J. Cram, K. R. Kopecky, F. Hauck*, and *A. Langemann*, J. Amer. chem. Soc. *81*, 5754 (1959).

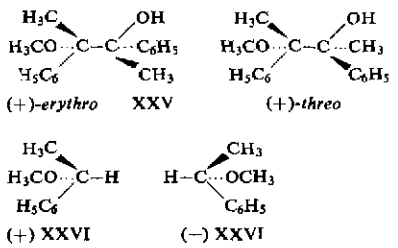
[56] *D. J. Cram, A. Langemann, W. Lwowski*, and *K. R. Kopecky*, J. Amer. chem. Soc. *81*, 5760 (1959).

[57] *D. J. Cram, F. Hauck, K. R. Kopecky*, and *W. D. Nielsen*, J. Amer. chem. Soc. *81*, 5767 (1959).

[58] *D. J. Cram, J. L. Mateos, F. Hauck, A. Langemann, K. R. Kopecky, W. D. Nielsen*, and *J. Allinger*, J. Amer. chem. Soc. *81*, 5774 (1959).

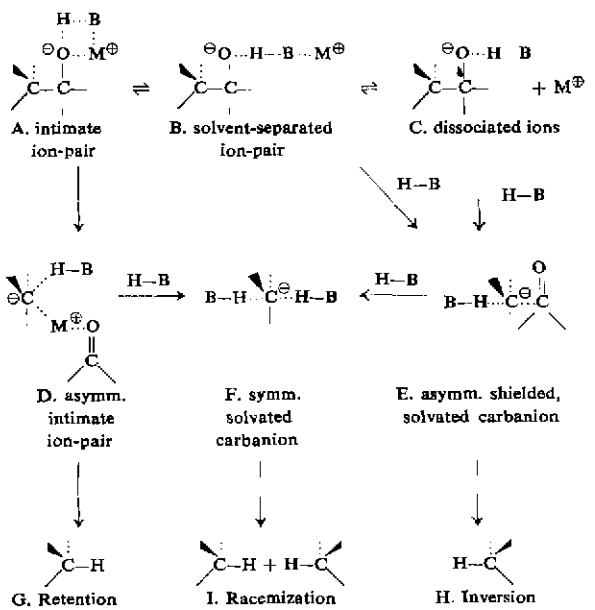
[59] *D. J. Cram* and *W. D. Nielsen*, J. Amer. chem. Soc. *83*, 2174 (1961).

yield, within the limits of error, the enantiomorphs XXVI of the cleavage products in an equal ratio [57]. This is to be expected in an S_E1 reaction, in which the breaking of the C–C bond and formation of the C–H linkage takes place in two consecutive steps, whereas in



a one-step process, less uniform results would be expected owing to the difference in energy content in the transition state – even in the case of enantiomorphs. Moreover, it must be considered that the cleavage in medium favoring retention is influenced neither by the concentration nor by the acidity of the proton donor [54–56], and that deuterated enantiomorphs are produced from deuterium ion donors in the same ratio as protonated compounds are produced by the corresponding proton donors [60].

Heterolysis and protonation therefore proceed through different transition states. The carbanion figures as an intermediate in between, lying in a depression in the energy profile. The scheme proposed by *Cram* et al. [58] reflects the experimental findings.



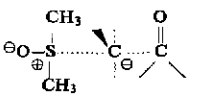
Reaction scheme by *Cram* et al.

The internal ion-pair A, enclosed in a common solvent cage, is in equilibrium with the dissociated ions C, via a solvent-separated ion pair B. Only A is capable of cleaving with retention of configuration, whereby it passes through a state D, into which the H atom of the proton (H–B) enters from the front. A slight spatial separation between anion and cation is the prerequisite for A. If this is not possible for steric reasons, the reaction must proceed via a different path. Complete racemization was in fact observed with tetrasubstituted ammonium salts in t.-butanol.

While the states B and C are of only minor importance in nonpolar media, they become significant in solvents which possess a great dissociating power, either because of their polar structure or in addition (as in glycols) because of their chelating ability. The cleavage then proceeds through a transition state E, in which the leaving group shields the carbanion from the front, so that the proton donor H–B has to attack from the rear, resulting in inversion of configuration. The increasingly effective shielding ability of the leaving group XXIV with increase in its bulk, can be seen from the increase in stereospecificity. A strong argument in favor of this inversion mechanism is the fact that tetrasubstituted ammonium salts, in comparison with those of alkali metals, do not cause a loss of stereospecificity [58], as can be seen from formulae B and C.

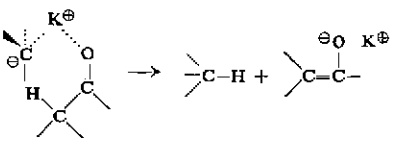
With the addition of a second H–B molecule, D as well as E can be transformed into the symmetrical state F, which from symmetry considerations necessarily leads to a racemic product. Since this process is a polymolecular reaction, it should be favored by high temperatures, a fact which has been proved experimentally (cf. p. 387).

In strongly dissociating solvents which are not H-donors (dimethyl sulfoxide) the transition state is XXVII, corresponding to E. Because of dipole stabilization, the anion therein is sufficiently long-lived to become imbedded in a symmetrical solvate shell. In this case, too, a racemic final product results exclusively.



XXVII

The proton may be abstracted from the leaving group, if no proton donor whatsoever is present in the solution.



In this case, the cleavage proceeds much less stereospecifically and is only of importance when external proton donors are absent. The cleavage product found in deuterated alcohols is chiefly deuterated and is only protonated to an extent of a few percent [61, 62].

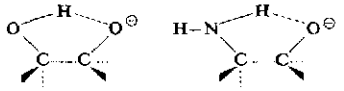
Conditions are different in the cleavage of glycols [61]. Here, a hydrogen bridge can be assumed between the alkoxide anion and the hydroxyl group (XXVIII), so that protonation from the "front side" is preferred, regardless of whether an intimate or a solvent-separated ion-pair is involved. Therefore, retention of configuration predominates even in solvents favoring inversion. On the other hand, with the corresponding amino compounds,

[60] *D. J. Cram* and *B. Rickborn*, J. Amer. chem. Soc. *83*, 2178 (1961).

[61] *D. J. Cram, L. K. Gaston*, and *H. Jäger*, J. Amer. chem. Soc. *83*, 2183 (1961).

[62] Cf. *D. J. Cram, C. C. Kingsbury*, and *B. Rickborn*, J. Amer. chem. Soc. *81*, 5835 (1959).

a proton is also available for the attack from the rear (XXIX). The stereochemical result is strongly dependent



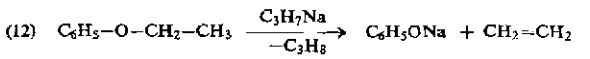
XXVIII XXIX

on temperature and is probably determined by subtle changes in the conformation of the molecule. Again, when dimethyl sulfoxide is used racemization takes place [61].

8. Reactions of Metalated Ethers

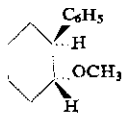
a) Eliminations

The cleavage of alkyl ethers [63] with organometallic compounds is effected by a metalation of the β-carbon and a β-elimination, in accordance with Eq. (12).



(12) $C_6H_5-O-CH_2-CH_3 \xrightarrow[-C_3H_8]{C_3H_7Na} C_6H_5ONa + CH_2=CH_2$

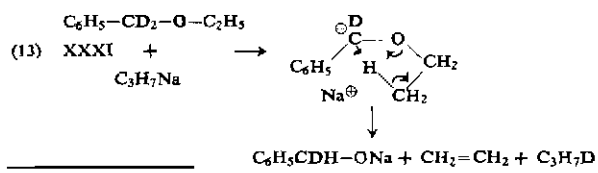
cis-Elimination from *trans*-phenyl-2-methoxycyclohexane (XXX) proceeds faster than *trans*-elimination from the *cis*-compound [65]. Activation of the α-position, especially by phenyl groups, promotes metalation in this



XXX

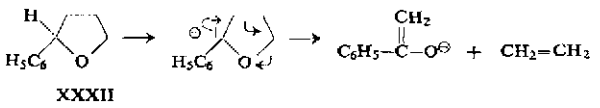
position [64,66,67]. The further fate of the α-metalated ether is dependent upon the reaction conditions and the substituents and is characterized by the tendency of the molecule to discharge the carbanion.

According to *Letsinger* [64,67], deuterated benzyl ether (XXXI) is cleaved by propyl sodium in accordance with Eq. (13). This type of reaction, referred to as an α', β-elimination [68–70] generally occurs preferentially to other cleavages. However, the Wittig rearrangement (see below) can supersede it when more than one



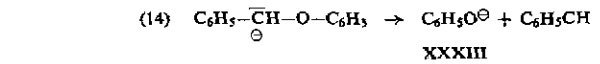
(13) $C_6H_5-CD_2-O-C_2H_5$ XXXI + C_3H_7Na → $C_6H_5CDH-ONa + CH_2=CH_2 + C_3H_7D$

phenyl group is attached to the α-carbon atom (*e.g.* in benzhydryl ethyl ether [64]). If the α',β-elimination becomes impossible for steric reasons, as in XXXII, fragmentation occurs [64]:



XXXII

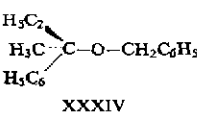
The α-elimination, originally expected here, can be achieved with benzyl phenyl ether; the carbene XXXIII is formed when the latter reacts with n-butyl-lithium [71].



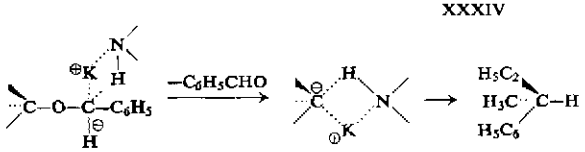
(14) $C_6H_5-\overset{\ominus}{\underset{}{C}}H-O-C_6H_5 \rightarrow C_6H_5O^{\ominus} + C_6H_5CH$

XXXIII

β-Elimination from benzyl t.-alkyl ethers in a proton-active medium is another reaction type. Cleavage of the optically active ether XXXIV with potassium-*N*-methylanilide in *N*-methylaniline yields s.-butylbenzene(XXXV) with at least 29 % retention of configuration [72]. This result may be explained as a protonation of the intimate ion pair XXXVI from the front [72]. The first step of this reaction is related to the *Wittig* rearrangement in inert solvents.



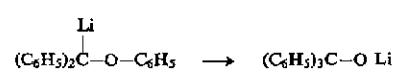
XXXIV



XXXVI XXXV

b) Wittig Rearrangement

α-Metalated ethers can rearrange to alkoxides, according to *Wittig* et al. [73–78].



$(C_6H_5)_2\overset{Li}{\underset{|}{C}}-O-C_6H_5 \longrightarrow (C_6H_5)_3C-O\,Li$

When aryl groups migrate, the isomerization is enhanced by electron attracting substituents [78,68]. The rearrangement of fluorenyl benzyl- and fluorenyl allyl ethers with potassium-*n*-butoxide in *n*-butanol proceeds in high yields. At the same time, optically active substrate is racemized [79], however, racemisation before

[63] *P. Schorigin*, Ber. dtsch. chem. Ges. *43*, 1931 (1910); further references see [65].

[64] *R. L. Leisinger* and *D. F. Pollart*, J. Amer. chem. Soc. *78*, 6079 (1956).

[65] *R. L. Letsinger* and *E. Bobko*, J. Amer. chem. Soc. *75*, 2649 (1953).

[66] *G. Wittig* and *R. Polster*, Liebigs Ann. Chem. *599*, 13 (1956).

[67] *R. L. Letsinger*, Angew. Chem. *70*, 151 (1958).

[68] *G. Wittig*, Experientia *14*, 393 (1958).

[69] *G. Wittig*, Angew. Chem. *70*, 69 (1958).

[70] *F. Weygand*, *H. Daniel*, and *H. Simon*, Chem. Ber. *91*, 1691 (1958).

[71] *U. Schöllkopf* and *M. Eisert*, Angew. Chem. *72*, 349 (1960).

[72] *D. J. Cram*, *C. A. Kingsbury*, and *A. Langemann*, J. Amer. chem. Soc. *81*, 5785 (1959).

[73] *G. Wittig* u. *L. Löhmann*, Liebigs Ann. Chem. *550*, 260 (1942).

[74] *G. Wittig* and *W. Happe*, Liebigs Ann. Chem. *557*, 205 (1947).

[75] *G. Wittig*, *H. Döser*, and *I. Lorenz*, Liebigs Ann. Chem. *562*, 192 (1949).

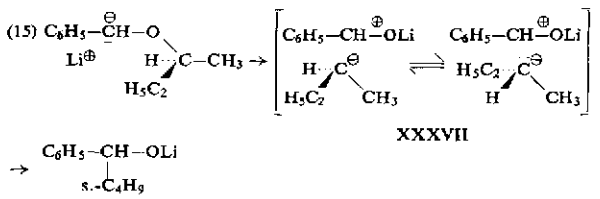
[76] *G. Wittig* and *R. Clausnizer*, Liebigs Ann. Chem. *588*, 145 (1954).

[77] *G. Wittig* and *E. Stahnecker*, Liebigs Ann. Chem. *605*, 69 (1957).

[78] *G. Wittig* and *H. Schlör*, Suomen Kemistilehti B *31*, 2 (1958).

[79] *J. Cast*, *T. S. Stevens*, and *J. Holmes*, J. chem. Soc. (London) 3521 (1960).

and/or after the reaction was not taken into account in these experiments. The optical antipodes of benzyl s.-butyl ether with *n*-butyl-lithium yield a product with partial retention of configuration but predominantly a racemate in proton-inactive media [80]. It is presumed that two cleavage fragments are formed as intermediates, and which subsequently recombine to the rearranged product but which do not exist as free ions [73,74,79,81]. Crossing experiments using metalated benzyl ethers of similar constitution showed that intermolecular reaction takes place to a limited extent only (approx. 7%). *Schöllkopf* et al. [80,82] concluded that the Wittig rearrangement occurs by β-elimination via an intimate ion pair (XXXVII).

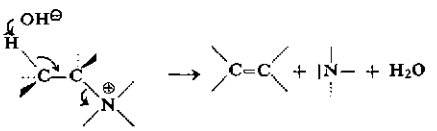


XXXVII

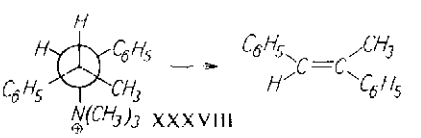
9. Reactions of Amines and Ammonium Compounds with Bases

a) Eliminations

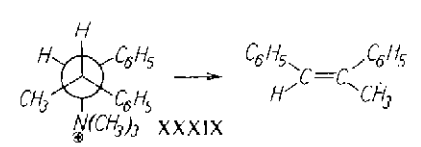
The cleavage known as the Hofmann elimination, of quaternary ammonium hydroxides, into an amine, olefin, and water, usually proceeds as a concerted reaction (*E* 2 mechanism) via a *trans*-β-elimination, as proposed by *Hughes* and *Ingold* [83].



Cram et al.[84] were thus able to show that the *threo*-(1,2-diphenyl-2-methyl)-ethyl-trimethylammonium compound with conformation XXXVIII is converted into *trans*-1,2-diphenylmethylethylene with sodium ethylate in ethanol, while the *erythro* compound (XXXIX) yields the *cis* isomer.



XXXVIII



XXXIX

[80] *U. Schöllkopf* and *W. Fabian*, Liebigs Ann. Chem. *642*, 1 (1961).

[81] *C. R. Hauser* and *S. W. Kantor*, J. Amer. chem. Soc. *73*, 1437 (1951).

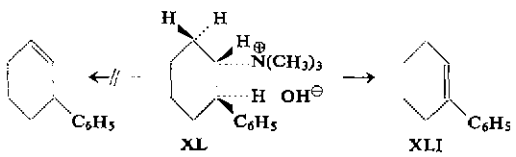
[82] *U. Schöllkopf* and *D. Walter*, Angew. Chem. *73*, 545 (1961).

[83] *E. D. Hughes*, *C. K. Ingold*, and *C. S. Patel*, J. chem. Soc. (London) (1933); Review: *A. C. Cope* and *E. R. Trumbull*, Org. Reactions *11*, 317 (1960).

[84] *D. J. Cram*, *F. D. Greene*, and *C. H. Depuy*, J. Amer. chem. Soc. *78*, 790 (1956).

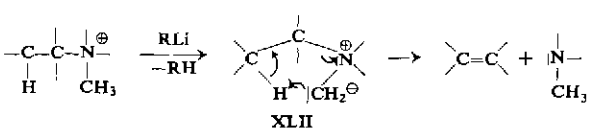
Experiments with deuterium [85a] and tritium labels [85b] in the β-position have shown that the ammonium hydroxides can be deprotonated only in the β-position, and not in the α-position.

However, with a favorable combination of steric and electronic factors, *cis*-β-elimination can predominate over the *trans*-cleavage. Hofmann degradation of XL thus gives exclusively 1-phenylcyclohexene (XLI), and not 3-phenylcyclohexene, which would be expected from the *trans*-elimination [86].



XL XLI

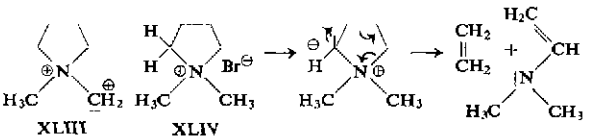
A modification of the Hofmann degradation became known from studies of *Wittig*, where ylides XLII [87], formed from ammonium salts and strong bases (especially phenyl-, and *n*-butyl-lithium), undergo an intramolecular *cis*-elimination, via the conformation of a planar five-membered ring, to give the final products [88] (α',β-elimination [69,70]).



XLII

This concept of the course of reaction implies that predominantly *cis*-cyclooctene would be formed [89] from cyclo-octyltrimethylammonium salts, while normal Hofmann degredation gives the *trans*-product, and that the reaction would stop at the ylide step, when the proton transfer in formula XLII becomes impossible for steric reasons, as in XLIII [90,91]. Experiments using salts with suitable deuterium [85] and tritium labels [92] have confirmed this mechanism, which also seems to play a part in the pyrolysis of amine oxides [92a].

N,N-Dimethylpyrrolidinium bromide (XLIV) splits into ethylene and vinyldimethylamine [93,91], via a frag-



XLIII XLIV

[85] a) *A. C. Cope*, *N. A. LeBel*, *P. T. Moore*, and *W. R. Moore*, J. Amer. chem. Soc. *83*, 3861 (1961). b) *E. M. Hodnett* and *J. J. Flynn*, J. Amer. chem. Soc. *79*, 2300 (1957).

[86] *R. T. Arnold* and *P. N. Richardson*, J. Amer. chem. Soc. *76*, 3649 (1954); *J. Weinstock* and *F. G. Bordwell*, J. Amer. chem. Soc. *77*, 6706 (1955); *A. C. Cope*, *G. A. Berchtold*, and *D. L. Ross*, J. Amer. chem. Soc. *83*, 3859 (1961); *G. Ayrey*, *E. Buncel*, and *A. N. Bourns*, Proc. chem. Soc. (London) 458 (1961); *S. J. Christol* and *D. J. Davies*, J. org. Chemistry *27*, 293 (1962).

[87] Reviews: *G. Wittig*, Angew. Chem. *63*, 15 (1951); *66*, 10 (1954); Acta chim. Acad. Sci. hung. *12*, 347 (1957); and [68].

[88] *G. Wittig* and *R. Polster*, Liebigs Ann. Chem. *599*, 13 (1956).

[89] *G. Wittig* and *R. Polster*, Liebigs Ann. Chem. *612*, 102 (1958).

[90] *G. Wittig* and *T. F. Burger*, Liebigs Ann. Chem. *632*, 85 (1960).

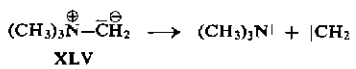
[91] *G. Wittig* and *W. Tochtermann*, Chem. Ber. *94*, 1092 (1961).

[92] *F. Weygand*, *H. Daniel*, and *H. Simon*, Chem. Ber. *91*, 1691 (1958); – a) *A. C. Cope* and *D. L. Ross*, J. Amer. chem. Soc. *83*, 3854 (1961).

[93] *F. Weygand* and *H. Daniel*, Chem. Ber. *94*, 1688 (1961).

mentation reaction with organolithium compounds. This is similar to the reaction of the tetrahydrofuran system XXXII.

The appearance of *N*-methylpyrrolidine in the reaction product is perhaps an indication of an α-elimination originating in the ylide XLIII. The ylide XLV, prepared with phenyl-lithium/phenylsodium can also be split into trimethylamine and carbene, according to *Franzen* and *Wittig* [94]:

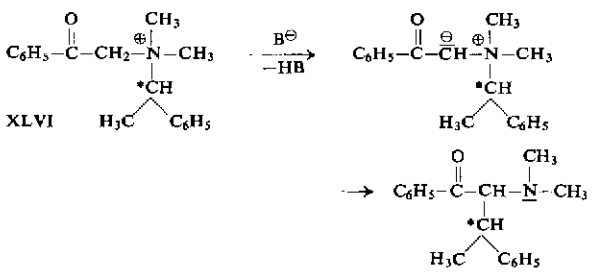


XLV

Tertiary sulfonium compounds, being related to the ammonium salts, can undergo analogous reactions [95].

b) Stevens Rearrangement

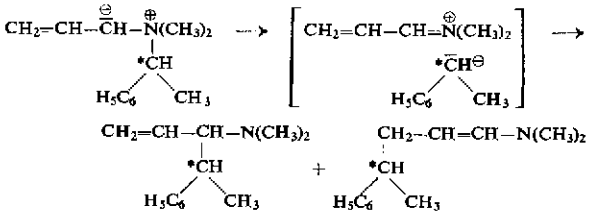
The rearrangement of quarternary ammonium compounds under the influence of strong bases, discovered by *Stevens* [96], and later studied thoroughly from another viewpoint by *Wittig* [87], involves migration of a mobile nitrogen ligand to an ylide carbon atom initially formed:



XLVI

Joint rearrangement of two compounds with nearly equal isomerization rates, both brominated at the nucleus, did not result in "cross-products" [97]. Labelling of one benzyl group with ^{14}C did not result in detectable radioactivity in the second rearrangement product [98]. The optically active compound XLVI survives the rearrangement with 97 % retention of optical activity [99], by a retention of configuration [100].

On the basis of these findings, it was hitherto assumed that the *Stevens* rearrangement involves an S_Ni type intramolecular reaction. However, it was recently observed that with *N*-(1-phenyl)ethyl-*N*-allyl-*N*,*N*-dimethylammonium bromide, under certain conditions, besides the normal 1,2-shift, a 1,4-migration of the benzyl group occurs with accompanying allyl rearrangement, and, furthermore, with retention of configuration whereas a rear side attack producing inversion of configuration would be expected for a five-membered ring transition state [100a]. Thus the 1,4-, and hence probably the 1,2-shift as well, more likely pass through the stage of an internal ion pair. Because of the strongly electrophilic character of the immonium group, the latter is so short lived that inversion of configuration at



the carbanion does not occur [80]. Whether a rearrangement involving an internal ion pair should be called intramolecular is merely a question of definition.

Under drastic conditions, certain amines can also undergo a *Stevens* rearrangement [101]. This process takes place without the appearance of free ions [102].



The *Sommelet* isomerisation [87, 102a], which is related to the *Stevens* rearrangement requires the presence of aromatic nuclei and may, therefore, be regarded as belonging to the field of nucleophilic aromatic substitution reactions [2]. Little is known about the mechanism of the isomerisation of aralkyl-metal compounds [103].

10. Hydrogen and Deuterium Exchange in Activated Methylene Compounds

Base-catalyzed deprotonations of enolizable methylene compounds can be studied in deuterated solvents [104–107]. Regardless of the nature of the solvent, complete racemization takes place with ketones, nitriles, and carboxylic acid derivatives with an optically active α-carbon atom. The racemization proceeds at the same rate as bromination (which is independent of the halogen concentration [108]) and deuterium exchange [105, 109]. Deuterated compounds are brominated at a slower

[94] *V. Franzen* and *G. Wittig*, Angew. Chem. *72*, 417 (1961).

[95] Hofmann elimination: *W. H. Saunders* and *R. A. Williams*, J. Amer. chem. Soc. *79*, 3712 (1957); α- and α′, β-elimination: *V. Franzen* and *H.-J. Schmidt*, Chem. Ber. *94*, 2937 (1961), *V. Franzen*, *H.-J. Schmidt* and *C. Mertz*, Chem. Ber. *94*, 2942 (1961); fragmentation: *F. Weygand* and *H. Daniel*, Chem. Ber. *94*, 3145 (1961).

[96] *T. Thomson* and *T. S. Stevens*, J. chem. Soc. (London) 69 (1932) and previous papers, cited in this reference.

[97] *T. S. Stevens*, J. chem. Soc. (London) 2107 (1930).

[98] *R. A. W. Johnstone* and *T. S. Stevens*, J. chem. Soc. (London) 4487 (1955).

[99] *A. Campbell* and *A. H. J. Houston*, and *J. Kenyon*, J. chem. Soc. (London) 93 (1947).

[100] *J. H. Brewster* and *M. W. Kline*, J. Amer. chem. Soc. *74*, 5179 (1952).

[100a] *E. F. Jenny* and *J. Druey*, Angew. Chem. internat. Edit. *1*, 155 (1962).

[101] *W. F. Cockburn*, *R. A. W. Johnstone*, and *T. S. Stevens*, J. chem. Soc. (London) 3340 (1960).

[102] *R. A. W. Johnstone* and *T. S. Stevens*, J. chem. Soc. (London) 3346 (1960).

[102a] *F. N. Jones* and *C. R. Hauser*, J. org. Chemistry *26*, 2979 (1961).

[103] *H. E. Zimmerman* and *A. Zweig*, J. Amer. chem. Soc. *83*, 1196 (1961); *E. Grovenstein* and *L. P. Williams*, ibid. *83*, 412, 2537 (1961).

[104] *W. D. Walters* and *K. F. Bonhoeffer*, Z. physik. Chem. *A 182*, 265 (1938).

[105] *S. K. Hsü*, *C. K. Ingold* and *C. L. Wilson*, J. chem. Soc. (London) 78 (1938).

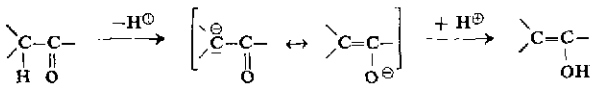
[106] *D. J. G. Ives*, J. chem. Soc. (London) 81 (1938).

[107] *D. J. Cram*, *B. Rickborn*, *C. A. Kingsbury*, and *P. Haberfield*, J. Amer. chem. Soc. *83*, 3678 (1961).

[108] *S. K. Hsu* and *C. L. Wilson*, J. chem. Soc. (London) 623 (1936).

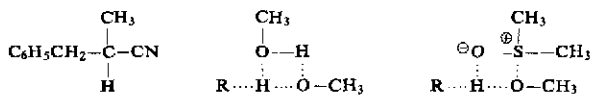
[109] *D. J. G. Ives* and *G. C. Wilkes*, J. chem. Soc. (London) 1455 (1938).

rate than the corresponding hydrogen compounds [110, 111]. Deprotonation to give the ambivalent anion XLVII, which is subsequently protonated at the more



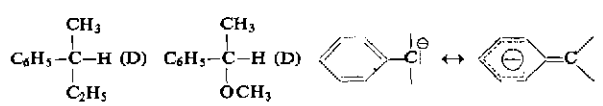
XLVII

electronegative oxygen atom, is thus the rate-determining step in these reactions [105, 107]. The non-stereospecific reaction of (+)-α-benzylpropionitrile (XLVIII) with sodium methoxide in dimethyl sulfoxide proceeds approximately 10^9 times faster than in methanol, presumably because the transition state XLIX is more stabilized than L, owing to the presence of a dipole in the solvent [107].



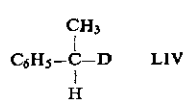
XLVIII L XLIX

On the other hand, *Cram* et al. [112] found the same regularities with regard to dependence on the solvent of the stereochemical path as in the H–D exchange between deuterated and nondeuterated 2-phenylbutane (LI) and the methoxy-compound LII, as observed in the cleavage reactions, previously mentioned (Section 7), *viz.* predominant retention of configuration in butanol, racemization in dimethyl sulfoxide, and presumably, slight inversion of configuration in glycol. The stereospecificity of the reaction in solvents favoring retention is supposed to depend on asymmetrical solvation [112] cf. p. 388), since, on the basis of the resonance LIII a ↔ b, the intermediate carbanion is assigned an approximately planar configuration [113].



LI LII a LIII b

Streitwieser et al. [114] carried out an elegant determination of the stereochemical path of the deprotonation of optically active ethylbenzene-1-D (LIV) with lithium cyclohexylamide in cyclohexylamine. Since the race-



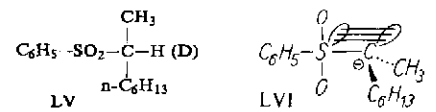
LIV

mic portion of the reaction product is formed by D - H exchange (rate constant k_D) and by the nonstereospecific fraction λ of the H–H exchange (constant k_H), the following relationship results:

$$k_{rac} = k_D + \lambda\, k_H.$$

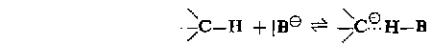
k_{rac} and k_D can be measured directly; k_H is obtained by incorporating a tritium-labelled substrate (k_T), according to a formula given by *Swain* [115]. The value 0.17 found for λ represents an 83 % retention of configuration. This is in accord with the concept of *Cram* [53], whereby amines are retention-favoring solvents.

A third reaction type was found by *Cram* and co-workers [116] in an optically active sulfone (LV). Here, the configuration was always largely retained in H–D exchange, regardless of the reaction medium. The gradual change observed with solvents favoring retention, inversion, or racemization, respectively, indicates that, again, solvated asymmetrical carbanions participate in the case of solvents favoring retention. The decisive factor is, however the retention of the original configuration of the molecule due to the interaction of the



LV LVI

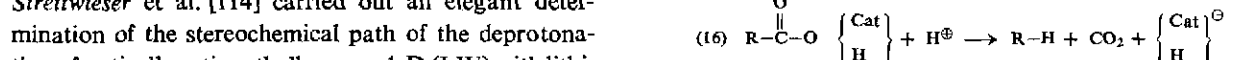
carbanion-doublet with a sulfur d-orbital, most probably in accordance with formula LVI. The measured isotope effect is low, because in all probability, the exchange is preceded by a rapidly established equilibrium, so that



separation of a proton is not the rate-determining step in this reaction [116] Racemization of the molecule is also catalyzed by base and originates in the anion LVI; protonation predominates by a factor of about 80 [117].

11. Decarboxylations

Decarboxylation reactions have been widely investigated [118]. *Schenkel* and *Schenkel-Rudin* [119] have proposed S_E1 and S_E2 mechanisms. A reaction rate directly proportional to the acidity of the medium is characteristic of the S_E2 mechanism, in accordance with Eq. (16).



(16)

The existence of an S_E2 mechanism has been demonstrated in this manner with certain (mainly aromatic) carboxylic acids, whose α-C atoms had to be made sufficiently electronegative for proton attack [120–122]

[110] *C. L. Wilson*, J. chem. Soc. (London) 1550 (1936).

[111] *O. Reitz*, Z. physik. Chem. *A 176*, 363 (1936).

[112] *D. J. Cram, C. A. Kingsbury*, and *B. Rickborn*, J. Amer. chem. Soc. *83*, 3688 (1961).

[113] Cf. *G. A. Russel*, J. Amer. chem. Soc. *81*, 2017 (1959).

[114] *A. Streitwieser, D. E. VanSickle*, and *L. Reif*, J. Amer. chem. Soc. *82*, 1513 (1960); *84*, 258 (1962).

[115] *C. G. Swain, E. C. Stivers, J. F. Reuwer*, and *L. J. Schaad*, J. Amer. chem. Soc. *80*, 5888 (1958).

[116] *D. J. Cram, D. A. Scott*, and *W. D. Nielsen*, J. Amer. chem. Soc. *83*, 3696 (1961).

[117] *E. J. Corey*, Angew. Chem. *74*, 88 (1962).

[118] Reviews: *B. R. Brown*, Quart. Rev. (chem. Soc., London) *5*, 131 (1951); *V. Franzen:* Reaktionsmechanismen. Dr. Alfred Hüthig Verlag, Heidelberg 1958, p. 154; *J. Hine:* Reaktivität und Mechanismus in der organischen Chemie. Georg Thieme Verlag, Stuttgart 1960, p. 275; *E. S. Gould:* Mechanismus und Struktur in der organischen Chemie. Verlag Chemie, Weinheim-Bergstr. 1962.

[119] *H. Schenkel* and *M. Schenkel-Rudin*, Helv. chim. Acta *31*, 514 (1948).

[120] *H. Schenkel*, Helv. chim. Acta *29*, 436 (1946).

[121] *W. M. Schubert*, J. Amer. chem. Soc. *71*, 2639 (1949).

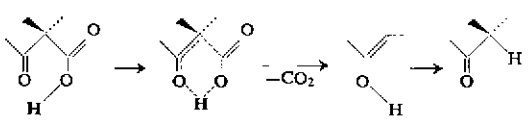
[122] *B. R. Brown, D. I. Hammick*, and *A. J. B. Scholefield*, J. chem. Soc. (London) 778 (1950).

by appropriate substituents. An example of decarboxylation occuring at a saturated carbon atom in which a S_E2-mechanism at least participates was given by *Pressmann* and *Lucas* [123] in the case of β-hydroxyisovaleric acid.

Decarboxylations, normally originate from carboxylate ion [124,125] and seem to occur much more frequently as monomolecular reactions. The carbanions which occur as intermediates in this case were successfully captured in some heterocyclics, using carbonyl compounds [126]. *Hine* et al. [127] found that a close relationship exists between the rate of decarboxylation of various trihalogenoacetates and the rate of deprotonation by alkali, of the corresponding haloforms. This finding can best be explained by assuming the existence of a common intermediate, the haloform anion [127].

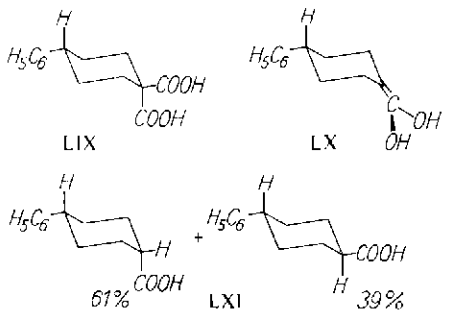
Decarboxylation of optically active compounds has been frequently investigated. This reaction is generally enormously accelerated by amines [128,119] and proceeds at a variable rate with antipodes of optically active acids, when an optically active amine is used. Thus, D-camphocarboxylic acid decomposes 13 % faster than the L-acid in the presence of L-nicotine [128]. This effect is even greater with (−)-*threo*-1-*p*-nitrophenyl-2-aminopropanediol as catalyst, while on the other hand, the (+)-*threo*-isomer promotes the decomposition of the L-acid [129].

Substituted optically active alkoxycarbonylacetic acids decarboxylate with complete racemization, according to *Kenyon* and *Ross* [130]. This is in accordance with the assumption of *Pedersen* [131] that β-keto-carboxylic acids generally decompose by a special mechanism, which leads to enols LVIII [132] via the transition state LVII.



LVII LVIII

These are protonated randomly at the α-carbon by attack from both sides, *i.e.* optically active substances are converted into racemic final products. However, one of the isomers is preferentially formed when the approach of the proton donor is hindered from one side owing to steric factors. Thus, *Zimmermann* and *Giallombardo* [133] obtained predominantly the *cis* form of LXI (61 %) from 4-phenylcyclohexane-1,1-dicarboxylic acid (LIX) and concluded that the intermediate LX is preferentially protonated from an equatorial direction.

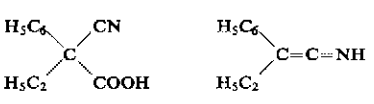


LIX LX

61% LXI 39%

Taylor and *Verhoek* [134] obtained optically active s.-butyl phenyl sulfone by pyrolysis of (−)-2-methyl-2-benzenesulfonylbutyric acid. The conclusion that this decarboxylation is a bimolecular process must be revised in view of the strong increase in the positive character of the α-C atom caused by the sulfo-group. Stabilization by a sulfur d-orbital of a carbanion, formed in an S_Ei reaction, seems to be more probable (cf. p. 392).

According to *Cram* [135], salts of optically active 1-ethyl-1-phenyl-1-cyanoacetic acid (LXII) give enantiomorphic decarboxylation products in such a ratio that a comparison with the S_Ei mechanism previously discussed (Section 7) is invited. Thus, predominantly retention occurs in t.-butanol (racemization with potassium and lithium salts, however) and inversion in glycol, whose magnitude does not depend significantly upon on the cation. It has therefore been postulated for the stereospecific parts of the reactions that the cleavage is caused by the intimate ion pair in the first case, and by the solvent-separated ion pair in the second instance (cf. p. 388). The observed effects are slight, since the intermediate anion, being stabilized by a phenyl and a nitrile group, is sufficiently long-lived to surround itself to a considerable degree with a symmetrical solvate shell, and therefore forms a racemic end-product. (Less



LXII LXIII

activated molecules require more stringent reaction conditions, in which the decarboxylation product is configuratively unstable [13]. Alternatively an intermediate product LXIII, corresponding to the enol LVIII, may be responsible for the racemization [135].

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[126] *P. Dyson* and *D. L. Hammick*, J. chem. Soc. (London) 1724 (1937); cf. [118].

[127] *J. Hine, N. W. Burske, M. Hine*, and *P. B. Langford*, J. Amer. chem. Soc. *79*, 1406 (1957).

[128] *G. Bredig* and *K. Fajans*, Ber. dtsch. chem. Ges. *41*, 752 (1908); *K. Fajans*, Z. physik. Chem. *73*, 25 (1910).

[129] *P. Pratesi, L. Arpesella*, and *A. LaManná*, J. Amer. chem. Soc. *75*, 5476 (1953); Chem. Abstr. *50*, 13800 (1956).

[130] *J. Kenyon* and *W. A. Ross*, J. chem. Soc. (London) 3407 (1951).

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[132] Cf. *W. von E. Doering* and *V. Z. Pasternak*, J. Amer. chem. Soc. *72*, 143 (1950).

[133] *H. E. Zimmermann* and *H. J. Giallombardo*, J. Amer. chem. Soc. *78*, 6259 (1956); further examples: *W. Goodwin* and *W. H. Perkin*, J. chem. Soc. (London) 119 (1895); cf. *V. P. Golmov*, J. gen. Chem. (USSR) *23*, 1152 (1953); Chem. Abstr. *47*, 12255 (1953); *F. S. Kipping* and *W. H. Perkin*, J. chem. Soc. (London) 304 (1890).

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Ring Substitutions and Secondary Reactions of Aromatic-Metal π-Complexes, Part II

BY DR. KLAUS PLESSKE

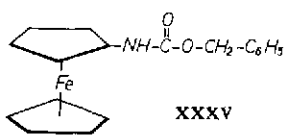
INSTITUT FUR ANORGANISCHE CHEMIE DER UNIVERSITÄT MÜNCHEN (GERMANY)

Part I: Angewandte Chemie, International Edition *1*, 312 (1962)

12. Nitrogen Containing Derivatives

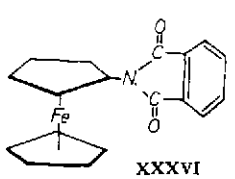
a) Aminoferrocene and Ferrocene Amino Acids

Aminoferrocene is the only metallic π-complex derivative known at present with the NH_2 group located directly on a ring. Its preparation is possible by different routes. It is formed in low yield by the action of *o*-benzylhydroxylamine [129], or preferably *o*-methylhydroxylamine [99] on the metalation mixture of ferrocene and butyl-lithium. In this reaction 1,1'-diaminoferrocene is thought to be formed, too, in an extremely small yield [*]. As expected nitroferrocene [130, 131] and azoferrocene [132] can be converted into aminoferrocene with HCl and iron or by catalytic hydrogenation. *N*-Ferrocenylbenzylurethan (XXXV), which is formed by a Curtius rearrangement of ferrocenecarbonyl azide (from $C_5H_5FeC_5H_4$–COCl and NaN_3) in benzyl alcohol [26], can be transformed into aminoferrocene by reductive cleavage with hydrogen [26, 99], or by alkaline hydrolysis [26].



XXXV

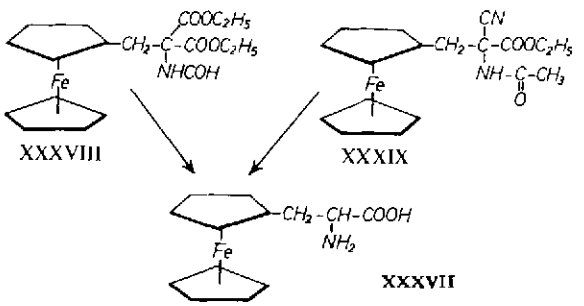
Nesmeyanov [50, 51] has reported yet another method – the cleavage of *N*-ferrocenylphthalimide (XXXVI) with hydrazine giving aminoferrocene in 82 % yield. Compound XXXVI, on the other hand, can be obtained from the reaction of copper phthalimide with chloro- or bromo-ferrocene [50, 51].



XXXVI

Aminoferrocene is a yellow-brown compound, which melts at 153–155 °C and which also sublimes. It is soluble in acids and can be reprecipitated with bases. The basicity constant is 1.55×10^{-9} [129] (aniline: 7.2×10^{-11}). Aminoferrocene reacts with acetic anhydride, *p*-toluenesulfonyl chloride and ferrocenecarbonyl chloride in a Schotten-Baumann reaction to give *N*-acetylaminoferrocene [133], *N*-ferrocenyl-*p*-toluenesulfonamide [99], and *N*-ferrocenylferrocenecarboxamide [99], respectively.

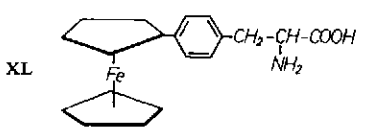
So far, only ferrocene has been found to form π-complex amino acids. *Schlögl* [44] treated ferrocenecarbonyl chloride with amino esters, such as those of glycine, leucine, phenylalanine and methionine, and obtained *N*-ferrocenylamino esters, which were then hydrolyzed to the *N*-ferrocenoylamino acids. Besides these *N*-substituted amino acids, β-ferrocenylalanine (XXXVII), a *C*-ferrocenylated amino acid, is now known. The compound is obtained in a single step from diethyl ferrocenylmethylformaminomalonate (XXXVIII) (simultaneous decarboxylation) [44, 78], or from ethyl ferrocenylmethylacetamidocyanoacetate (XXXIX) [93].



XXXVIII XXXIX XXXVII

Compound XXXVIII is obtained from chloromethylferrocene and potassio diethyl formamidomalonate [44], or from ferrocenylmethyltrimethylammonium iodide (IX) and sodio diethyl formamidomalonate [78]. Substance XXXIX is prepared analogously from IX and ethyl acetamidocyanoacetate [93].

The preparation of diethyl *p*-ferrocenylbenzylformamidomalonate has been described in Section 2. Hydrolysis and decarboxylation of this compound result in DL-*p*-ferrocenylphenylalanine (XL) [44].



XL

b) Aminomethyl and Aminoethyl

Carbon atoms which display strong C–H acidity due to neighboring group effects can be aminomethylated with

[129] *A. N. Nesmeyanov, E. G. Perevalova* et al., Doklady Akad. Nauk. S.S.S.R. *102*, 535 (1955).

[130] *H. Grubert* and *K. L. Rinehart*, Tetrahedron Letters Nr. 12, 16 (1959).

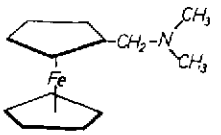
[131] *J. F. Helling* and *H. Shechter*, Chem. and Ind. 1157 (1959).

[132] *A. N. Nesmeyanov, E. G. Pervalova* et al., Tetrahedron Letters No. 1, 1 (1960).

[*] Note added in proof: Aminoferrocene and 1,1'-diaminoferrocene were also obtained by reduction of azoferrocenes: *G. R. Knox*, Proc. chem. Soc. (London) 56 (1959).

[133] *K. Schlögl* and *H. Seiler*, Naturwissenschaften *45*, 337 (1958).

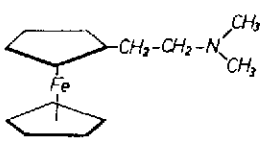
formaldehyde and ammonia or secondary amines. *Lindsay* and *Hauser* [72,134] were the first to show that ferrocene, is reactive enough to undergo aminomethylation. Thus, reaction of ferrocene and paraformaldehyde or, preferably *N,N,N',N'*-tetramethyldiaminomethane and dimethylamine gave a stable, distillable liquid, *N,N*-dimethylaminoferrocene (XLI) [72,134].



XLI

The compound can also be obtained by aminomethylation with *N,N,N',N'*-tetramethyldiaminomethane alone, with phosphoric acid as condensing agent [78]. Piperidinomethylferrocene [78] was prepared similarly. Furthermore, XLI can be obtained in good yield by reductive amination of ferrocenecarboxaldehyde [66]. CH_3I is used to convert XLI into ferrocenylmethyltrimethylammonium iodide (IX) [72,134]. Unsubstituted aminomethylferrocene was prepared by *Schlögl* [44] in excellent yield as a distillable oil by $LiAlH_4$-reduction of ferrocenecarboxamide.

β-Aminoethyl compounds can be obtained in various ways. For example, ferrocenylmethyltrimethylammonium iodide (IX) is converted into β-dimethylaminoethylferrocene (XLII), with chain-extension when treated with KNH_2 in liquid NH_3 [52,54,55].



XLII

β-Aminoethylferrocene itself can be prepared from ferrocenylacetonitrile (see Section 7) by $LiAlH_4$ reduction [53,54] and conversion to the quaternary ammonium salt with excess CH_3 I [53].

α-Aminoethylferrocene can be obtained by reductive amination either of ferrocenecarboxaldehyde [66], or less conveniently, of acetylferrocene [66]. Acetylferrocene gives a normal Mannich condensation with paraformaldehyde and dimethylamine forming the β-aminoketone, β-dimethylaminopropionylferrocene in good yields [111].

c) Isocyanates, Urea Derivatives and Urethans of Ferrocene

Ferrocenyl isocyanate $OCN-C_{10}H_9Fe$ can be prepared either from aminoferrocene and phosgene (mole ratio 1:1) [133], or by brief heating of ferrocenecarbonyl azide in toluene [133]. Similar reaction of aminomethylferrocene and $COCl_2$ yields ferrocenylmethyl isocyanate [44]. *N*-Methylaminoferrocene [133] is obtained when ferrocenyl isocyanate is reduced with $LiAlH_4$.

When aminoferrocene is reacted with phosgene in a 2:1 molar ratio, *N,N'*-diferrocenylurea is obtained [99]. This compound can also be prepared from ferrocenyl isocyanate by reaction with water or aminoferrocene [133]. Moreover, addition of ammonia or aniline to ferrocenyl isocyanate yields *N*-ferrocenylurea or *N*-ferrocenyl-*N'*-phenylurea [133]. The latter compound can also be obtained from phenyl isocyanate and aminoferrocene. *N,N'*-Dicyclohexyl-*N*-ferrocenoylurea is formed by addition of ferrocenecarboxylic acid to *N,N'*-dicyclohexylcarbodiimide [100].

N-Ferrocenylbenzylurethan, the important starting material for the aminoferrocene synthesis (Section 12a) is formed by decomposition of ferrocenecarbonyl azide in benzyl alcohol at 200 °C [26,99]. Other urethans have been obtained by the additions of alcohols to ferrocenylisocyanate [133].

d) Nitroferrocene

Nitroferrocene is the only known representative of metallic π-complex nitro-compounds. Its synthesis was achieved independently by *Grubert* and *Rinehart* [130], and *Helling* and *Shechter* [131], who reacted ferrocenyllithium with *n*-propyl nitrate and N_2O_4, respectively. Only mono-metalated ferrocene undergoes the $Li-NO_2$ exchange. The extremely stable substance obtained forms sublimable, deep red needles, melting at 130 °C and decomposing at approximately 190 °C.

e) Azoferrocene

Azoferrocene is also a stable, deep violet compound, melting at 256–258 °C, and was first prepared by *Nesmeyanov, Perevalova* et al. [132], by introducing N_2O into the metalation mixture of ferrocene with butyl-lithium. This compound can be converted into aminoferrocene by catalytic hydrogenation. Azoferrocene cannot be prepared by direct coupling, since diazotization of aminoferrocene has not yet been achieved.

f) Oximes, Hydrazones, Semicarbazones and Azines

In π-complex chemistry, as elsewhere, reactions with typical aldehyde and ketone reagents can be used to characterize carbonyl groups. The following derivatives are known:

Oximes of:
Ferrocenecarboxaldehyde [66,67,72,104]
Acetylferrocene [26,39]
1,1'-Diacetylferrocene [4]
Tricarbonyl(acetylcyclopentadienyl)manganese [68]
Tricarbonyl(benzoylcyclopentadienyl)manganese [68]
Benzoylferrocene [27,28]
1,1'-Dibenzoylferrocene [27]

Semicarbazones of:
Ferrocenecarboxaldehyde [66,72,104]
Acetylferrocene [39]
Ruthenocenecarboxaldehyde [69]

2,4-Dinitrophenylhydrazones of:
Ferrocenecarboxaldehyde [104]
Tricarbonyl(acetylcyclopentadienyl)manganese [71]
Tricarbonyl(benzoylcyclopentadienyl)manganese [71]
Ruthenocenecarboxaldehyde [69]
Tetracarbonyl(acetylcyclopentadienyl)vanadium [114]
Dicarbonyl-nitrosyl(acetylcyclopentadienyl)chromium [117]

Hydrazones of:
Tricarbonyl(acetylcyclopentadienyl)manganese [135]
Tricarbonyl(acetylmethylcyclopentadienyl)manganese [135]

Isonicotinylhydrazone of:
Ferrocenecarboxaldehyde [66]

[134] *C. R. Hauser* and *J. K. Lindsay*, J. org. Chemistry *21*, 382 (1956).

[135] *R. Riemschneider*, Z. Naturforsch. *16b*, 78 (1961).

Azines of:
Ferrocenecarboxaldehyde [66]
Tricarbonyl(acetylmethylcyclopentadienyl)manganese [135]

13. Sulfur Containing Derivatives

a) Sulfonic Acids and Sulfonamides

Only ferrocene and tricarbonyl(cyclopentadienyl)-manganese are known to form sulfonic acids and their derivatives. *Weinmayr* [16] succeeded in sulfonating ferrocene with concentrated sulfnric acid in acetic anhydride solution. Chlorosulfonic acid in acetic anhydride [97], and pyridine, or dioxane-sulfur trioxide in dichloroethane [25, 110, 136] were later used in this reaction. Either mono- or heteroannular disubstitution takes place, depending on the mole ratio of the components. The SO_3 method has given the best yields so far [110, 136] (both ferrocenesulfonic acid and ferrocene-1,1′-disulfonic acid in approximately 85% yield). The two ferrocenesulfonic acids are yellow, crystalline compounds, which absorb water in moist air and slowly decompose by oxidation (ferrocenesulfonic acid dihydrate: m.p. 103–104 °C). For this reason, immediate conversion into their stable ammonium salts is of advantage.

A difficultly soluble ferrous salt of ferrocenesulfonic acid, $[O_3S{-}C_{10}H_9Fe]_2^-\ Fe^{2+}.\ 4\ H_2O$, which melts with decomposition, has been found to occur as a by-product of all sulfonations. Free Fe(II) ions are formed by partial decomposition of this ferrocene by excess sulfonating agent. Extension of direct sulfonation to less stable π-complexes should therefore be subject to certain limitations. Ferrocenecarboxylic acid is also convertible into 1-carboxyferrocene-1′-sulfonic acid [101], like ferrocene itself, by the action of SO_3/dioxane. Tricarbonyl(cyclopentadienyl)manganese sulfonic acid can be prepared by treating $C_5H_5Mn(CO)_3$ with concentrated sulfuric acid in acetic anhydride [103]. In this case, the conversion of the sulfonic acid into its yellow- p-toluidide, m.p. 204–207 °C, is advantageous.

Sulfonamides of π-complexes are available by reacting sulfonyl chlorides (their preparation is given on page 322) with ammonia or amines. Ferrocenesulfonamide can thus be obtained from ferrocenesulfonyl chloride and ammonia [97]. Ferrocenesulfonyl diethylamide, and ferrocene-1,1′-disulfonyl bis(diethylamide) are prepared by reacting diethylamine with ferrocenesulfonyl chloride and ferrocene-1,1′-disulfonyl dichloride [102]. Tricarbonyl(cyclopentadienyl)manganese sulfonyl chloride reacts with *p*-toluidine to give the *p*-toluidide of tricarbonyl(cyclopentadienyl)manganese sulfonic acid (XVIII), mentioned in Sections 8e and 13a [103].

b) Sulfinic Acids

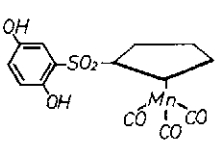
Ferrocenesulfonyl chloride and ferrocene-1,1′-disulfonyl dichloride have been reduced with metallic zinc to the sulfinic acids [136a]. With $LiAlH_4$ ferrocenesulfonyl chloride yields ferrocenethiol [97]. Tricarbonyl(cyclopentadienyl)manganese sulfonyl chloride can be readily converted in aqueous solution with sodium sulfite into the corresponding sulfinic acid [103]. The compound is of importance in the preparation mercury(II) derivatives of $C_5H_5Mn(CO)_3$ (Section 14a).

c) Thiol and Disulfide Compounds of Ferrocene

Ferrocenethiol is formed in nearly quantitative yield by $LiAlH_4$ reduction of ferrocenesulfonyl chloride [97]. Air oxidizes it to diferrocenyl disulfide, which can be reconverted into the thiol with $LiAlH_4$ [97]. Diferrocenyl disulfide has also been obtained by sodium thiosulfate reduction of the product resulting from the reaction of dithiocyanogen and diferrocenylmercury [20].

d) Sulfones

Sulfones of ferrocene have so far only been obtained in low yields by the reaction of benzenesulfonyl chloride or ferrocenesulfonyl chloride with diferrocenylmercury [20]. Phenylferrocenylsulfone and diferrocenylsulfone are stable, crystalline compounds, melting at 145–146 °C and 270–275 °C (decomp.), respectively. In addition sulfones of tricarbonyl(cyclopentadienyl)manganese have been prepared. According to *Cais* [103], tricarbonyl(cyclopentadienyl)manganese sulfonyl chloride can be reacted with anisole, under Friedel-Crafts conditions, whereby isomeric (probably *ortho*- and *para*-) methoxyphenylsulfonyl(cyclopentadienyl)manganese tricarbonyls are formed. Tricarbonyl(cyclopentadienyl)manganese sulfinic acid, like other sulfinic acids, adds easily to quinones. This reaction, is described, using benzoquinone, which gives LXIII.

LXIII 

Further sulfones of $C_5H_5Mn(CO)_3$ have been prepared by reacting the sulfonic acid salt of tricarbonyl(cyclopentadienyl)manganese sulfonic acid with aliphatic halides [103].

14. Metal Derivatives

a) Mercury Derivatives

Nesmeyanov, Perevalova et al. [39] were the first to find that mercury derivatives of ferrocene could be easily prepared. In contrast to the relatively severe conditions necessary for mercuration of benzene, ferrocene reacts even at room temperature with $Hg(OOCCH_3)_2$ in ether alcohol or benzene alcohol, according to the reaction

$$n\ Hg(CH_3COO)_2 + C_{10}H_{10}Fe \rightarrow (CH_3COO{-}Hg{-})_nC_{10}H_{10-n}Fe + n\ CH_3COOH$$

$n = 1,2$

[136] *A. N. Nesmeyanov, E. G. Perewalova* et al., Doklady Akad. Nauk. S.S.S.R. *114*, 335 (1957).

[136a] *A. N. Nesmeyanov* et al., Doklady Akad. Nauk. S.S.S.R. *119*, 949 (1958); *132*, 853 (1960).

The mono- and di-substituted acetatomercuri derivatives formed simultaneously can be converted into (chloromercuri)ferrocene and 1,1′-di(chloromercuri)ferrocene by treatment with KCl or LiCl solution. The two ferrocenes can be easily separated by using the difference in their solubilities, especially in n-butanol.

The optimum reaction conditions were investigated later [81]. Chloromercuriferrocene has also been obtained from ferrocenylboronic acid with $HgCl_2$ [50,51]. As the yield is rather low (approximately 20 %), direct mercuration should be preferred. The 1-halogeno-1′-chloromercuriferrocenes are listed in Table 6.

The chloromercuriferrocenes have become of greater interest for secondary reactions; attention is called to the preparation of halogeno derivatives (Section 6).

Diferrocenylmercury is formed, with symmetrization, from chloromercuriferrocene and sodium thiosulfate [39], sodium stannite, sodium iodide, or by careful low-temperature hydrolysis [81].

Mercuration of ruthenocene with $Hg(OOCCH_3)_2$ is also possible [45]. The mixture of chloromercuriruthenocene and 1,1′-di(chloromercuri)ruthenocene obtained could not be separated into its components.

Tricarbonyl(cyclopentadienyl)manganese could not be mercurated directly. Tricarbonyl(chloromercuricyclopentadienyl)-manganese can, however, be obtained in good yields by an exchange reaction between tricarbonyl(cyclopentadienyl)-manganese sulfinic acid and $HgCl_2$ [103]. It is crystalline and melts at 135–136 °C.

In attempts to prepare the lithium derivative of $C_5H_5Mn(CO)_3$, unobtainable in a direct manner, by a metal interchange reaction with butyl-lithium, only a symmetrization giving bis tricarbonyl(cyclopentadienyl)manganese mercury(II) resulted.

All the presently known mercury derivatives of π-complexes are listed in Table 6.

Table 6. π-Complex mercury derivatives

Compound	Appearance	M.p. [°C]
Chloromercuriferrocene [39, 50, 51, 81]	Gold-yellow platelets	194–196
1,1′-Di(chloromercuri)ferrocene [39, 81]	Light yellow powder	300 (decomp.)
Diferrocenylmercury [39, 81]	Orange-yellow cryst. (2 stable forms)	235–236 245–248
Mixture of chloromercuri and 1,1′-di(chloromercuri)-ruthenocene [45]	Yellow needles	217–218 (decomp.)
Tricarbonyl-chloromercuri-cyclopentadienylmanganese [103]	Yellow crystals	135–136
Bis(cyclopentadienylmanganese)-tricarbonylmercury(II) [103]	Crystals	178–179

b) Alkali Metal Derivatives

The lithium and sodium derivatives of ferrocene, ruthenocene, osmocene and dibenzenechromium are extremely sensitive to air and moisture and are preferably not isolated, but simply subjected to further reactions in the original metalation solution. Table 7 lists some reactions of this class of compounds.

Table 7. Some reactions of π-complex alkali metal derivatives

Alkali Metal Derivative of	Reacted with	Reaction Product
Ferrocene [24, 39, 79, 82, 83] Ruthenocene [45] Osmocene [45] Dibenzenechromium [80, 86]	CO_2	Carboxylic Acids
Ferrocene [47, 79, 81]	$R_3Si—Hal$	Silylferrocenes (Diferrocenyl)
Ferrocene [50, 51]	$B(OR)_3$	Ferrocenyl-boronic acids
Ferrocene [92]	R—NCO	Ferrocene-carboxamide
Ferrocene [99, 129]	$R—CH_2—ONH_2$	Aminoferrocene
Ferrocene [130, 131]	$N_2O_4, C_3H_7ONO_2$	Nitroferrocene
Ferrocene [132]	N_2O	Azoferrocene

c) Silylferrocenes

Ferrocenyl-lithium and ferrocenylene-1,1′-di(lithium) react with triphenylsilyl chloride, giving good yields of triphenylsilylferrocene, and 1,1′-bis(triphenylsilyl)ferrocene. Both were isolated in stable, crystalline forms [79]. A slight amount of diferrocenyl is formed as by-product (see Section 2). Trimethylsilylferrocene, 1,1′-bis(trimethylsilyl)ferrocene [81], tri-n-hexylsilylferrocene and 1,1′-bis(tri-n-hexylsilyl)ferrocene [47] were obtained in like manner, as distillable liquids with an aromatic odor. Use of the corresponding sodium ferrocene derivatives is not recommended for preparative procedures [47]. Table 8 lists the silylferrocene derivatives.

Table 8. Silylferrocenes

Residue	B.p. [°C/mm, Hg]	M.p. [°C]	n_D^{20}	Reference
Triphenylsilyl-	—	142–143	—	[79]
1,1′-Bis-(triphenylsilyl)-	—	253–254	—	[79]
Trimethylsilyl-	64–65/0,045	23	1,5696	[81]
1,1′-Bis-(trimethylsilyl)-	87–88/0,06	16	1,5454	[81]
Tri-n-hexylsilyl-	180–198/0,20	—	1,5202	[47]
1,1′-Bis-(tri-n-hexylsilyl)-	—	—	1,5054	[47]

d) Boric Acid Derivatives of Ferrocene

Nesmeyanov [50,51] prepared ferrocenylboronic acid (m.p. 143–148 °C) and ferrocenylene-1,1′-diboronic acid (m.p. 180 °C, decomp.) by the reaction of borate esters with ferrocenyl-lithium derivatives, subsequent acidification and separation by fractionated alkaline extraction. These compounds are crystalline (yellow) and both acids can be hydrolyzed (cf. purely organic boronic acids) to give ferrocene when boiled with $ZnCl_2$. Table 9 lists secondary reactions of ferroceneboronic acids.

Table 9. Secondary reactions of ferroceneboronic acids [50, 51] (fc = ferrocene)

	Reaction with	Product
Ferrocenyl-boronic acid	$HgCl_2$	Chloromercuri-fc
	$Cu(OOCCH_3)_2$	Ferrocenylacetate Hydrolysis → Hydroxy-fc
	$Cu(OOCC_2H_5)_2$	Ferrocenylpropionate
	AgO, $Cu(OOCR)_2$	Diferrocenyl
	$CuCl_2$, $CuBr_2$	Chloro-fc, Bromo-fc
Ferrocenylene-1,1'-diboronic acid	4 $CuCl_2$, 4 $CuBr_2$	1,1'-Dichloro-fc 1,1'-Dibromo-fc
	2 $CuCl_2$, 2 $CuBr_2$	1-Chloroferrocenyl-1'-boronic acid 1-Bromoferrocenyl-1'-boronic acid
	$Cu(OOCCH_3)_2$	Ferrocenylene-1,1'-diacetate Hydrolysis → 1,1'-Dihydroxy-fc
1-Chloroferrocenyl-1'-boronic acid	$HgCl_2$	1-Chloro-1'-chloromercuri-fc → mixed dihalogeno-fc
1-Bromoferrocenyl-1'-boronic acid	$HgCl_2$	1-Bromo-1'-chloromercuri-fc → mixed dihalogeno-fc

e) Diferrocenylselenium

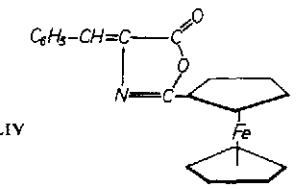
Diferrocenylmercury reacts with $SeBr_4$ in chloroform. Diferrocenylselenium can be isolated from the reaction solution by hydrolysis and subsequent reduction with $Na_2S_2O_3$, as a stable, crystalline product in 21 % yield (m.p. 151–153 °C) [20].

f) Grignard Compounds of Ferrocene

After initial experimental failures [74], *Shechter* and *Helling* [75] succeeded in obtaining ferrocenyl Grignard compounds and ferrocenylene-1,1'-di-Grignard compounds. Chloro-, bromo-, and iodo-ferrocene, as well as 1,1'-dibromoferrocene have been reacted with magnesium powder and CH_3I in tetrahydrofuran. The corresponding Grignard compounds were obtained in satisfactory yields. The CH_3I initiates the reaction, even when used in minute amounts. Proof that the Grignard reaction occurs was furnished by conversion into the carboxylic acids of ferrocene. Diferrocenyl is formed in increasing amounts under more energetic reaction conditions, especially when ethylene bromide is added. A radical mechanism is proposed in this case. Diferrocenyl is obtained in 80 % yield by reaction of ferrocenylmagnesium bromide with cobalt(II) chloride.

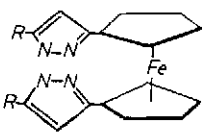
15. Heterocyclic Derivatives

Ferrocene derivatives with heterocyclic side-chains have been mentioned previously in this review. Attention is called to 5-(ferrocenylmethylene)barbituric acid (Section 9), 1-ferrocenyl-2-[α-*N*-methylpyridilium]ethylene iodide (XXIV) (Section 9), the ferrocenyl(pyrryl)methylene salts (XXV) (Section 9) and 2-phenyl-4-(ferrocenylmethylene)oxazol-5-one (XXI) (Section 9). An isomer of XXI was obtained by an azlactone cyclization of *N*-ferrocenoylglycine, followed by condensation with benzaldehyde to give XLIX [44].



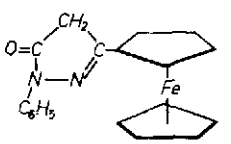
XLIV

Derivatives of pyrazole and pyrazolone have been obtained by condensing β-diketones or β-keto-esters with hydrazine or phenylhydrazine. Thus, ferrocenoylacetophenone readily forms 5-phenyl-3-ferrocenylpyrazole with hydrazine in ethanolic solution [98]. The disubstituted β-diketones (1,1'-benzoylacetyl)ferrocene (XXXIIa), 1,1'-di-(β-ketobutyryl)ferrocene (XXXIIb), and 1,1'-di-(β-ketovaleryl)ferrocene (XXXIIc) (Section 10b) are transformed into bis-pyrazolylferrocenes (XLV) [126, 128].



XLV a) R = C_6H_5; b) R = CH_3; c) R = C_2H_5

A yellow, stable, crystalline tricarbonyl-(5-methyl pyrazol-3-yl)-cyclopentadienylmanganese is obtained in analogous manner from tricarbonyl-β-ketobutyrylcyclopentadienylmanganese (XXXIV) and hydrazine [124]. Ethoxycarbonylacetylferrocene reacts with phenylhydrazine, to give 1-phenyl-3-ferrocenylpyrazol-5-one (XLVI) [98].



XLVI

16. Polymers

Nesmeyanov et al. [5, 8] studied the Friedel-Crafts reaction of dichloroethane with ferrocene, besides unsymmetrical *asym.*-diferrocenylethane, pentaethylenediferrocene and dodecaethylene-tetraferrocene (Section 1), a high polymer material, representing the first iron-organic electron-exchange resin was obtained. Another polymeric product containing ferrocene of empirical formula $(C_{16}H_{18}O_{1.5}Fe)_x$ is formed, according to *Riemschneider* et al. [60], in the dehydration of 1,1'-di-(α-hydroxy-α-methylethyl)ferrocene.

So far, controlled polymerizations have only been carried out with vinyl and cinnamoyl derivatives of ferrocene and tricarbonyl(cyclopentadienyl)manganese. Further development of such electron-exchangers seems promising for practical applications. The marked oxidation and reduction properties of the ferrocene polymer is of considerable interest. Vinylferrocene can

be reacted with phosphoric acid, azodiisobutyric acid nitrile, and $K_2S_2O_8$ to give polymers of various consistencies. Moreover, copolymerizations with methyl methacrylate, styrene, chloroprene and formaldehyde [26] have also proved successful. Further copolymerizations have been carried out between cinnamoylferrocene and styrene, acrylonitrile, methyl methacrylate, ethyl acrylate, 1,1'-dihydroperfluorobutylacrylate, butadiene and isoprene [137], as well as between tricarbonyl(cinnamoylcyclopentadienyl)manganese and styrene [124].

Sincere thanks are due to my teacher, Prof. Dr. E. O. Fischer, for his interest in this work and for valuable discussions and suggestions.

Received, August 22nd. 1961 [A 182/23 IE]

[137] *L. E. Coleman* and *M. D. Rausch*, J. Polymer Sci. *28*, 207 (1958).

[138] *E. O. Fischer, K. Öfele* et al., Chem. Ber. *91*, 2763 (1958).

[139] *B. Nicholls* and *M. C. Whiting*, J. chem. Soc. (London) 551 (1959).

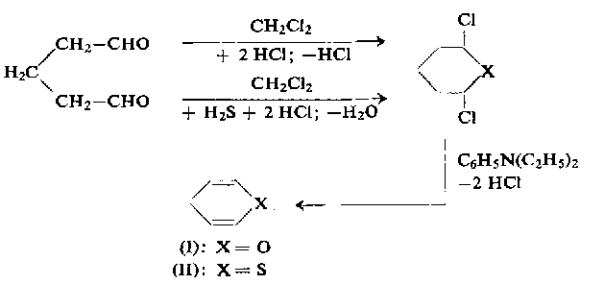
COMMUNICATIONS

γ-Pyran and γ-Thiopyran

By Dr. J. Strating, cand. chem. J. H. Keijer, cand. chem. E. Molenaar, and Dr. L. Brandsma

Organic Chemistry Department, University of Groningen (Holland)

The hitherto unknown parent heterocyclic systems γ-pyran (I) and γ-thiopyran (II) can be synthesised from glutardialdehyde by application of *Brandsma* and *Arens'* method [1].



(I): X = O
(II): X = S

γ-Pyran (I) was obtained as a 90% pure product by vacuum distillation (40–15 mm. Hg) of the reaction mixture at 9 °C (59 g. from 100 g. glutardialdehyde). Purification by fractional distillation at normal pressure gave 15 g. of pure colourless γ-pyran (b.p. 80 °C/760 mm., $n_D^{20} = 1.4559$). The product quickly turns brown in contact with air. The 2,4-dinitrophenylhydrazone derivative of glutardialdehyde forms rapidly on addition of 2,4-dinitrophenylhydrazine in ethanol/H_2SO_4. The ultraviolet absorption spectrum of the pure γ-pyran in methanol showed peaks at 222 mμ (ε = 7035) and 238 mμ (ε = 5125); infrared bands lie at 3170 cm^{-1} (C–H), 1700 cm^{-1} (C=C) [2], 1660 cm^{-1} (C=C), and 1280 1260 cm^{-1} (C–O–C).

Crude γ-thiopyran distilled on heating the reaction mixture to 120 °C (60–15 mm. Hg). A 20% over-all yield of the pure substance (II; b.p. 30 °C/12 mm., $n_D^{20} = 1.5623$) was obtained by fractional distillation *in vacuo*. The compound darkens rapidly in the air at room temperature, but is much more stable in the solid state (m.p. –28 °C). Reaction of (II) with 2,4-dinitrophenylhydrazine reagent (as above) takes place much more slowly than in the case of (I) but yields the same product; H_2S is evolved. The ultraviolet spectrum of the pure γ-thiopyran in petroleum ether has a peak at 278 mμ (ε = 2430) and a shoulder at 236–238 mμ (ε = 5265); the infrared spectrum shows characteristic bands at 3100 cm^{-1} (C–H), 1640 and 1600 cm^{-1} (C=C) and 750 cm^{-1} (C–S).

Received, March 26th. 1962 [Z 272/101 1E]

[1] *L. Brandsma* and *J. F. Arens*, Recueil Trav. chim. Pays-Bas *81*, 33 (1961).

[2] *R. Gompper* and *O. Christman*, Chem. Ber. *94*, 1784 (1961).

4-(Dimethylallyl)tryptophan, a Precursor of Clavine Alkaloids

By Prof. Dr. H. Plieninger, Dr. R. Fischer, and Dipl.-Chem. V. Liede [*]

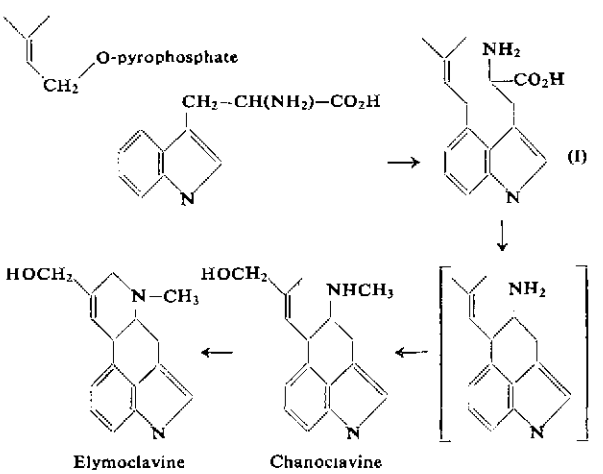
Organisch-Chemisches Institut der Universität Heidelberg (Germany)

In the living cell clavine and ergot alkaloids are synthetised from tryptophan and 3,5-dihydroxy-3-methylvaleric acid (mevalonic acid) or isopentenyl pyrophosphate [1]. We wished to ascertain whether the isoprenoid residue condenses with the tryptophan in the 4-position to give 4-(dimethyallyl)-tryptophan (I), or whether it first combines with the alanine side-chain of the tryptophan.

Using radio-active formaldehyde, we obtained β-^{14}C labelled 4-(dimethylallyl)tryptophan with a specific activity of 89 μC/mmole; the synthesis of 4-(dimethylallyl)tryptophan starting from 4-bromoindole-2-carboxylic acid will be published elsewhere. The tryptophan derivative (100 mg) was added to a 10-day old saprophytic culture of the ergot fungus of African millet (*Pennisetum typhoideum Rich.*) [2] in 250 ml. nutrient medium. After working-up [3], the crude alkaloid mixture showed a very high activity. Elymoclavine (200 mg) was added to the mixture and the total elmyoclavine present recrystallised to constant specific activity (0.64 μC/mmole). Allowing for the elymoclavine yields normally obtained (400 mg per litre culture filtrate) and the additional inactive elymoclavine, the incorporation rate is at least 5%.

An amine, which after acetylation can no longer be extracted with 2 N HCl, is present among the crude radio-active alkaloids. This compound is either 4-(dimethylallyl)tryptamine or chanoclavine.

This work shows that the clavine alkaloids, and therefore probably all ergot alkaloids, are formed according to the following reaction scheme:



Elymoclavine Chanoclavine

The evidently electrophilic attack of dimethylallyl pyrophosphate at the weakly reactive 4-position of the indole nucleus is surprising. The formation of the C ring by linking of an allylic C-atom with the α-position of an amino-acid is equally unusual. Whether this linkage takes place in (I) or (after decarboxylation) in the amine remains to be proved.

Received, April 16th. 1962 [Z 278/109 IE]

[*] Dedicated to Prof. Dr. *G. Wittig* on the occasion of his 65th. birthday.

[1] For literature summaries see: *A. J. Birch* et al., J. chem. Soc. (London) 421 (1962); *H. Plieninger* et al., Liebigs Ann. Chem. *642*, 214 (1961).

[2] Grateful acknowledgement is tendered to the Sandoz AG., Basel (Switzerland), for the supply of the fungus strain and advice on its culture.

[3] *A. Stoll* et al., Helv. chim. Acta *37*, 1815 (1954).

Combination of Thin-Layer Chromatography and Mass Spectrography

By Prof. Dr. K. Heyns and Dr. H. F. Grützmacher

Institut für Organische Chemie, Universität Hamburg (Germany)

Mass spectra can be obtained directly from samples of thin-layer chromatograms of condensed aromatic compounds, heterocycles, steroids, carbohydrate derivatives, amino acids and peptides.

In the structural analysis of organic compounds, mass spectrometry [1] with the usual experimental set-up (introduction of the test sample into the ion-source from a storage vessel, with or without an injection mechanism) can be applied only to substances of relatively high volatility. Less volatile compounds must be directly introduced into the ion source, where they are vaporized. However, this latter procedure [2] leads to strong "memory" effects and to a reduction in the resolving power of the mass spectrometer. In a CH-4 mass spectrometer [*] with a solid ionsource the ionization chamber of the ion-source can be interchanged by means of a vacuum lock. The substance to be examined is placed in a small glass tube, 10 mm long and about 1 mm in diameter, and the open end is drawn into a capillary. The tube is fastened in the ionization chamber in such a manner that the substance sublimes directly into the electron beam. Thus, the resolving power is unaffected. Contamination of the ion source is mainly restricted to the easily cleaned ionization chamber. It is however a disadvantage that the temperature of the ion-source cannot be regulated and that the normal operating temperature is 150–200 °C. The method can be applied to substances which are thermally stable at 150–200 °C, and at this temperature possess a vapor pressure of about 10^{-7} mm Hg. We were able to obtain mass spectra of alicyclic carboxylic acids, sugar derivatives, and acylated amino acids and peptides [3]. Substances adsorbed on silica gel may be used directly. The background spectrum caused by silica gel and residual solvent does not interfere in the region of high masses, important for structure determinations. Several μg of substance is required; however, the ratio of substance to silica gel must be at least 1:100. This ratio is achieved in the sharp and intense spots of thin-layer chromatograms.

Received, April 16th. 1962 [Z 263/107 IE]

[*] Made by the Atlas Mess- und Analysen-Technik GmbH., Bremen (Germany).

[1] *K. Biemann*, Angew. Chem. *74*, 102 (1962).

[2] *R. I. Reed, W. K. Reid* and *J. M. Wilson:* Symposium on Mass Spectrometry. Oxford 1961.

[3] The experiments were carried out in collaboration with Dipl.-Chem. *H. Scharmann*. The results will be reported in detail elsewhere.

The Reaction of Chlorosilanes with Divers' Solutions

By Prof. Dr. K. Rühlmann [1]

Hochschule für Verkehrswesen, Dresden (Germany)

Silyl derivatives of NH_3, methylamine or dimethylamine are mostly obtained by the reaction of halogenosilanes with the amines in an inert solvent [2]; hexamethyldisilazane, too, can be prepared by addition of trimethylchlorosilane to liquid NH_3 [3]. It is more convenient, however, to allow chlorosilane to react with Divers' solutions (ammonium salts in amines) [4] at normal pressure and in an ice-water bath. Two layers are obtained; the upper is nearly pure aminosilane, the lower contains the ammonium salts dissolved in excess amine. The silylamine can be recovered by decantation, or separation of the layers in a funnel. Using this very simple method, hexamethyldisilazane, the trimethylsilyl derivatives of methylamine and trimethylsilyldimethylamine were obtained in yields amounting to 80 %, 83 % and 84 %, respectively.

Received, April 24th. 1962 [Z 279/108 IE]

[1] 11th. Communication on the Si-N bond. 10th. Communication: *K. Rühlmann, U. Kaufmann*, and *D. Knopf*, J. prakt. Chem., in press.

[2] *R. O. Sauer*, J. Amer. chem. Soc. *66*, 1707 (1944).

[3] *R. O. Sauer* and *R. H. Hasek*, J. Amer. chem. Soc. *68*, 243 (1946); *J. E. Noll, J. L. Speier*, and *B. F. Daubert*, *ibid.* *73*, 3867 (1951).

[4] *E. Divers*, Philos. Trans. Roy. Soc. (London) *163*, 359 (1873).

Bistrifluoromethylphosphorus Derivatives of Transition Metal Carbonyls

By Prof. H. J. Emeleus and Dr. J. Grobe

Department of Inorganic Chemistry, University Chemical Laboratory, Cambridge (England)

Perfluoroalkylphosphorus derivatives of transition metals have been previously described only with respect to nickel tetracarbonyl [1], *e.g.*, $(CF_3)_3PNi(CO)_3$, $[(CF_3)_3P]_2Ni(CO)_2$ and $(CO)_3NiP(CF_3)_2{-}P(CF_3)_2Ni(CO)_3$. In these compounds, and by analogy to the bonding of the carbonyl groups, a phosphorus-nickel donor σ-bond through the phosphorus 3s-electron pair, and additional back-donation between the 3d-level of the nickel and the empty 3d-shell of the phosphorus (dπ-dπ portion), are assumed [2].

By reaction of bistrifluoromethyliodophosphine with transition metal carbonyls, we have now succeeded in preparing perfluoromethylphosphorus derivatives which evidently contain a pure phosphorus-metal σ-bond (*cf.*, alkyl- and aryl-phosphine complexes of palladium, nickel and cobalt [3]).

The compound $Mn_2(CO)_8P(CF_3)_2I$ (orange-red crystals) was isolated as the only reaction product resulting from the interaction of manganese carbonyl (1 mole) with bistrifluoromethyliodophosphine (1 mole) at 120 °C in a sealed tube and in the absence of solvent. The product was separated, together with a small amount of $Mn_2(CO)_{10}$, when the yellow-red crystalline mass resulting from an 18 hr. reaction was fractionally sublimed in high vacuum at 40–50 °C. During the reaction, 1.8 moles of CO were liberated for each mole of manganese carbonyl.

The infrared spectrum shows carbonyl frequencies at 2101 cm^{-1} (s) [*], 2045 cm^{-1} (vs), 2009 cm^{-1} (s) and 1985 cm^{-1} (sh) as well as CF-absorptions at 1175 cm^{-1} (s), 1138 cm^{-1} (s), 1127 cm^{-1} (s) and 1102 cm^{-1} (m) which in contrast with those of bistrifluoromethyliodophosphine are shifted to lower wavenumbers. Phosphorus and iodine are envisaged as bridging atoms in the binuclear complex since the spectrum excludes

carbonyl-bridging. The ultraviolet spectrum contains a maximum at 417 mμ (ε = 950), a minimum at 382 mμ (ε = 670) and a point of inflection at 310 mμ (ε = 2940).

Pentacarbonyliron reacts with bistrifluoromethyliodophosphine in a sealed tube, and without solvent, to give a dark-red crystalline mass, at the same time releasing 2 moles of CO for each mole of $Fe(CO)_5$. Reaction occurs even at room temperature, but is faster (*ca.* 12 hrs) at 60–70 °C. A finely crystalline, brick-red compound, $[(CF_3)_2PFe(CO)_3I]_2$, soluble in almost all organic solvents and relatively stable to air and light, was isolated by high-vacuum sublimation at 80–90 °C. With longer exposure to air, light, and above all water, the compound decomposes. Its infrared spectrum shows carbonyl frequencies at 2127 cm^{-1} (m) and 2088 cm^{-1} (s), and suggests a symmetrical disposition of the ligands. The CF-absorptions at 1187 cm^{-1} (vs), 1157 cm^{-1} (vs), 1137 cm^{-1} (s) and 1122 cm^{-1} (vs) are also displaced to lower wave-numbers in comparison with bistrifluoromethyliodophosphine. The binuclear complex is bridged either by iodine atoms or with $(CF_3)_2P$-groups. A more detailed investigation of the possible structural isomers by means of dipole and ^{19}F nuclear resonance measurements, as well as by cleavage reactions, is planned. The ultraviolet spectrum shows maxima at 353 mμ (ε = 3800) and 264 mμ (ε = 21550); minima at 338 mμ (ε = 3560) and 244 mμ (ε = 18600).

Received, May 3rd. 1962 [Z 267/96 IE]

[*] vs = very strong, s = strong, m = medium, sh = shoulder.

[1] *H. J. Emeléus* and *J. D. Smith*, J. chem. Soc. (London) 527 (1958); *A. B. Burg* and *W. Mahler*, J. Amer. chem. Soc. *80*, 2334 (1958).

[2] *L. S. Meriwether* and *M. L. Fiene*, J. Amer. chem. Soc. *81*, 4200 (1959).

[3] *R. G. Hayter*, Nature (London) *193*, 872 (1962); *K. Issleib* et al., Z. anorg. allg. Chem. *305*, 15 (1960); *312*, 287 (1961).

Dichlorocarbene from Methyl Trichloromethanesulfinate and Trichloromethanesulfonyl Chloride

By Doz. Dr. U. Schöllkopf and cand. chem. P. Hilbert [*]

Organisch-Chemisches Institut der Universität Heidelberg (Germany)

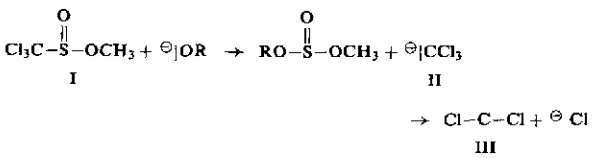
While in search of new ways leading to carbenes, we found a further route to dichlorocarbene. If potassium t-butoxide or sodium methoxide is allowed to react with methyl trichloromethanesulfinate (I) in the presence of an olefin, dichlorocyclopropane compounds are formed (Table 1).

Table 1. Cyclopropane adducts obtained from methyl trichloromethanesulfinate, bases, and olefins. [a] 0.1 mole I in 50 cc. of olefin was added dropwise to a suspension of the base in 100 cc. olefin

[b] 0.2 mole base
[c] 0.28 mole base
[d] 0.1 mole base
[e] 0.2 mole base
[f] I in ether added dropwise

Olefin	Base	Temp. [°C]	Adduct	Yield [%]
cyclohexene [a]	K t-butoxide [b]	82	dichloronorcarane	40
cyclohexene [a]	K t-butoxide [c]	82	dichloronorcarane	48
cyclohexene [a]	K t-butoxide [d]	−10 to +25	dichloronorcarane	37
cyclohexene [a]	CH_3ONa [c]	82	dichloronorcarane	32
isobutene [f]	K t-butoxide [c]	−6	1,1-dichloro-2,2-dimethylcyclopropane	15

Presumably, the alkoxide ion attacks the sulfur atom of the sulfinic ester and displaces the trichloromethyl anion (II), which then dissociates into dichlorocarbene (III) and a chloride ion. III adds onto the double bond of the olefin in a known manner [1].



I (b. p. 38–40 °C/1 mm.) is obtained from trichloromethanesulfinic acid [2] and diazomethane, or from trichloromethanesulfinyl chloride and methanol in the presence of potassium carbonate.

Thermal decomposition of sodium trichloromethanesulfinate, Cl_3C-SO_2Na, in cyclohexene does not lead to dichloronorcarane. Instead, cyclohexyl chloride, benzene, chloroform, and other products are formed. However, dichloronorcarane is formed when trichloromethanesulfonyl chloride in cyclohexene is treated with potassium t-butoxide (yield 35 %).

Dichloronorcarane from methyl trichloromethanesulfinate. Methyl trichloromethanesulfinate (0.1 mole) in 50 cc. cyclohexene was added dropwise over 20 min. to a vigorously stirred suspension of 0.28 Mol K t-butoxide in 100 cc. cyclohexene, and the mixture then boiled for further 30 min. After hydrolysis, the cyclohexene layer was dried and on distillation yielded (48 %) dichloronorcarane, b. p. 78 to 80 °C/15 mm., n_D^{23} 1.5005.

Received, May 11th. 1962 [Z 275/122 IE]

[*] Dedicated to Prof. Dr. *G. Wittig* on the occasion of his 65th birthday.

[1] *W. v. E. Doering* and *A. K. Hoffmann*, J. Amer. chem. Soc. *76*, 6162 (1954).

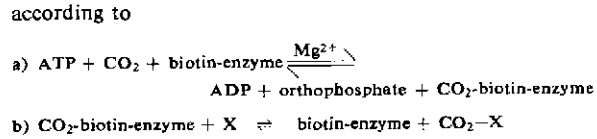
[2] Prepared according to the directions of *O. Loew*, Z. für Chemie *12*, 82 (1869) by reduction of trichloromethanesulfonyl chloride with H_2S in methanol (b. p. 71–72 °C/0.05 mm., m. p. of anilinium salt 143–143.5 °C).

On the Structure of CO_2-Biotin Enzymes[*]

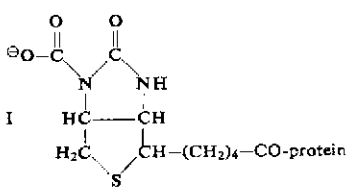
By Dr. J. Knappe, cand. chem. K. Biederbick and cand. chem. W. Brümmer

Organisch-chemisches Institut der Universität Heidelberg (Germany)

Carboxylation reactions catalysed by biotin enzymes proceed according to



via a CO_2-biotin-enzyme compound which acts as a carbonic acid donor and in which CO_2 is bonded to biotin. This was recognised during investigations on methylcrotonyl carboxylase (X = β-methylcrotonyl-CoA) [1].



By enzymatic hydrolysis of the biotin-protein bond in CO_2-[methylcrotonyl carboxylase], we have now proved the allophanate structure (I) assumed by *Lynen* et al.

β-Methylcrotonyl carboxylase [2] from *Achromobacter* [1] (18 mg; specific activity 2.4 μmoles substrate/min × mg) was converted into the $^{14}CO_2$-compound with ATP and

$KH^{14}CO_3$ (2×10^7 counts per min/μmole) according to equation (a); the complex (10.8×10^5 counts per minute) was separated from the reaction mixture by filtration on "Sephadex". Brief treatment with trypsin, followed by methylation of the cleavage products with CH_2N_2 at pH 6.5–7, yielded a mixture of stable methoxy-^{14}C-carbonyl compounds (9.6×10^{-5} counts per minute). *N*(1)-methoxy-^{14}C-carbonyl-(+)-biotin was obtained in 93 % yield (calculated on radio-activity) by hydrolysis of the water-soluble fraction (6×10^5 counts/min) with biotinidase [3]. The compound was identified, for example, as its dimethyl ester by chromatographic comparison with the methyl ester of *N*(1)-methoxycarbonylbiotin and the methyl ester of *N*(3)-methoxycarbonylbiotin [4].

We used biotinidase that had been enriched 200 times from pig kidney extract. The enzyme, which is inhibited by iodoacetamide and diisopropylfluorophosphate, specifically hydrolyses amides and esters of (+)-biotin; to a small extent also their carboxy-derivatives. K_M for *N*-(biotinyl)aminobenzoate 5×10^{-6} M, for *N*-[*N*(1)-methoxycarbonylbiotinyl]-aminobenzoate 8×10^{-4} M.

Our attempts to obtain the apoenzyme of methylcrotonyl carboxylase by elimination of biotin were unsuccessful. The bond between vitamin and protein can be attacked only after denaturation or degradation of the enzyme protein.

Received, May 14th. 1962 [Z 276/116 IE]

[*] Dedicated to Prof. Dr. *G. Wittig* on the occasion of his 65th. birthday.

[1] *F. Lynen* et al., Biochem. Z. *335*, 123 (1961).

[2] We are grateful to Prof. *Lynen* for the communication of an improved isolation technique.

[3] *R. W. Thoma* and *W. H. Peterson*, J. biol. Chemistry *210*, 569 (1954).

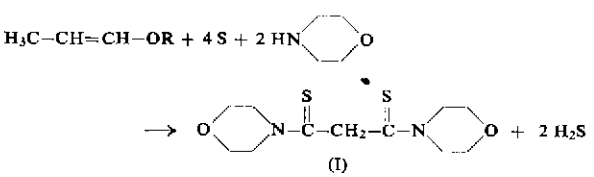
[4] *J. Knappe*, *E. Ringelmann*, and *F. Lynen*, Biochem. Z. *335*, 168 (1961).

On the Preparation of the Dimorpholide of Dithiomalonic Acid

By Dr. B. Brähler, Dr. J. Reese and Dr. Rolf Zimmermann

Chemische Werke Albert, Abteilung Allgemeine Organica Wiesbaden-Biebrich (Germany)

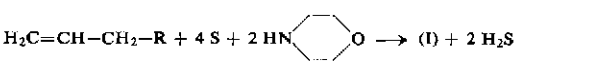
A method for the preparation of the dimorpholide (I) from propenyl alkyl ethers, morpholine and sulfur is already known [1]:



R = alkyl

This is a special case of the Willgerodt-Kindler reaction with attack at both ends of the C_3-chain [2].

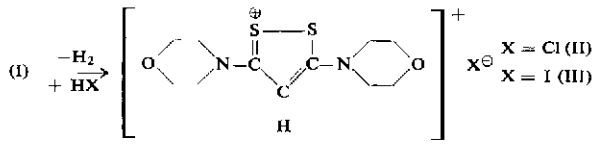
We have now found that a similar reaction occurs with the more easily accessible allyl compounds. The preparation of (I) can be carried out even with simple compounds such as allyl alcohol or allyl chloride, and with better yields as when working with allyl ethers or esters:



(R' = OH, Cl *etc.*)

The smooth course of the reaction is surprising. Compound (I), m.p. 208 °C, is obtained in yields up to 47 %.

In analogy to the work by *U. Schmidt* [3], we have subjected (I) to cyclising oxidation and obtained 3,5-dimorpholino-1,2-dithiacyclopentadienylium halides (II, III).



(II): yellowish needles, m.p. 250–260 °C (decomp.)
(III): yellow-brown needles, m.p. 250 °C.

Received, May 16th. 1962 [Z 282/117 IE]

[1] German Patent 1003212 (*H. Feichtinger*, Ruhrchemie A.G.).

[2] *R. Wegler* et al., Angew. Chem. *70*, 351 (1958).

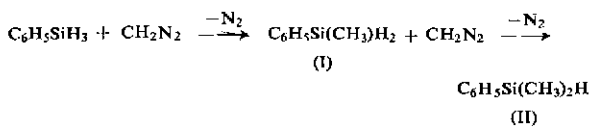
[3] *U. Schmidt*, Chem. Ber. *92*, 1171 (1959).

The Reaction of Diazomethane with Silanes

By Dr. K. Kramer and Dr. A. Wright

Shell Research Ltd., Thornton Research Centre, Chester, (Great Britain)

By the reaction of phenylsilane with excess diazomethane we have obtained phenylmethylsilane (I) as the major product, together with phenyldimethylsilane (II).



The products (I and II) were characterized by gas chromatography, mass and infrared spectroscopy and (I) also by microanalysis. No reaction occurred in the absence of catalysts or light, although phenyltrichlorosilane reacts readily with diazomethane, in the same way as silicon tetrachloride [1, 2], giving phenylchloromethyldichlorosilane and phenyl-bis-(chloromethyl)chlorosilane. Low yields of (I) were obtained when a copper catalyst was used. When the reaction mixture was photolysed with a "Hanau" mercury arc lamp in a quartz dip-tube, up to 70 % (I) and 5 % (II) were formed. No phenyltrimethylsilane could be detected by mass spectrometry or gas chromatography. In all the photolyses in diethyl ether solutions, n-propyl and iso-propyl ethyl ethers were also formed [3], as is to be expected in a reaction involving free carbene. However, methylenation of the phenyl group did not occur, as was shown by gas chromatography and the infra-red spectrum.

Under the same conditions, diphenylsilane gave diphenylmethylsilane (50 %) as the only product. Triphenylsilane did not react readily, although a mass spectrometric examination suggested that traces of triphenylmethylsilane were formed. Germanes also react similarly. Diphenylgermane gives both diphenylmethylgermane and diphenyldimethylgermane. Triethylgermane gives 9 % triethylmethylgermane on photolysis, but none is formed in the presence of a copper catalyst of the type used in the preparation of organogermanium esters from diazoacetic ester [4].

Received, May 16th. 1962 [Z 290/121 IE]

[1] *A. Ya. Yakubovitch* et al., Dokl. Akad. Nauk S.S.S.R. *72*, 69 (1950).

[2] *D. Seyferth* and *E. G. Rochow*, J. Amer. chem. Soc. *77*, 907 (1955).

[3] *H. Meerwein*, *H. Rathjen*, and *H. Werner*, Ber. dtsch. chem. Ges. *75*, 1610 (1942).

[4] *M. Lesbre* and *J. Satge*, C. r. hebd. Séances Acad. Sci. *247*, 471 (1958).

Explosion Resulting from the Oxidation of Mesitylene with Nitric Acid

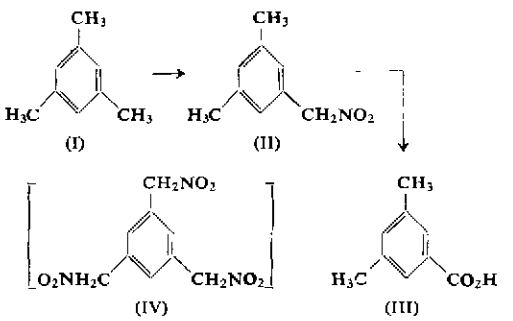
By Dr. H. Wilms and Dr. A. Dorlars

Wissenschaftliches Hauptlaboratorium der Farbenfabriken Bayer A.-G., Leverkusen (Germany)

The oxidation of mesitylene (I) to 3,5-dimethylbenzoic acid (III) by boiling with dilute nitric acid has been widely reported [1]. In order to reduce the reaction time (60 hrs.), the mesitylene (240 g.), water (1,2 litres) and conc. nitric acid (690 g.) were to be heated together to 115 °C in a 3-litre stirring autoclave (300 °C operating temperature, 100 gauge-atm. operating pressure).

Several minutes after reaching 115 °C and 10 gauge-atm. a powerful explosion took place. The autoclave was torn apart lengthwise and widely scattered, together with the steel doors of a safety cover.

Starting materials and the technical installation were in order. Other alkyl aromatics had previously been frequently oxidised with nitric acid under more rigorous conditions, and without particular difficulty, in autoclaves. Furthermore, later oxidation experiments with mesitylene proceeded smoothly in a 0.3 litre autoclave at 115 °C. Depending on the experimental conditions, predominantly 3,5-dimethylbenzoic acid, 3-methylisophthalic and or benzene-1,3,5-tricarboxylic acid (trimesic acid) were obtained. However, if these smaller reaction mixtures were removed after 2–3 hours and worked-up, it was found that the hydrocarbon layer contained up to 30 % α-nitromesitylene (II).



3,5-Dimethylbenzoic acid (III) is then formed from (II), probably *via* the hydroxamic acid [2]. It may be assumed, therefore, that in the case of the mesitylene reaction at a temperature a little above 115 °C, as may occur temporarily with larger amounts of reaction mixture because of the relatively lower heat radiation from the autoclave, an unexpected side-reaction takes place. Under these conditions, side-chain nitration proceeds more quickly than the further reaction to carboxylic acid. α,α′,α″-Trinitromesitylene (IV) is finally formed, which accounts for the highly shattering effect of the explosion.

Received, May 17th. 1962 [Z 281/114 IE]

[1] *R. Fittig*, Liebigs Ann. Chem. *141*, 144 (1867); *H. R. Synder* et al., J. Amer. chem. Soc. *63*, 3281 (1941); *E. Gryskiewicz-Trochimowski* et al., Bull. Soc. chim. France 595 (1948).

[2] *Houben-Weyl:* Methoden der organischen Chemie. G.Thieme, Stuttgart 1952, vol. VIII, p. 441.

Diazomethane via the Forster Reaction

By Dr. W. Rundel

Chemisches Institut
der Universität Tübingen (Germany)

The Forster reaction [1] (action of chloramine on α-oximino-ketones with the formation of α-diazoketones) has hitherto only been applied for the preparation of aryl-substituted diazoalkanes (*e.g.* diazofluorene, diphenyldiazomethane, small amounts of phenyldiazomethane) [2]. Simple, unsubstituted diazoalkanes have not been obtained [2, 3].

We have found that a variation of this reaction produces diazomethane from formaldehyde oxime in yields of 70–75 % (based on NH_2Cl). A solution of 40–50 mmoles $CH_2{=}NONa$ in absolute ether and the exact amount of absolute methanol is combined with an etheral chloramine solution at 0 °C. Within an hour, NaCl separates, and diazomethane can be isolated by distillation:

$$CH_2{=}NONa + NH_2Cl \longrightarrow NaCl + CH_2N_2 + H_2O \quad [4]$$

The reaction is also possible with hydroxylamine-*O*-sulphonic acid. However, the yields in this case suffer from the introduction of the strong acid; very considerable reductions in yield (right down to a few per cent) are also observed when other aliphatic oximes are used.

Received, May 17th. 1962 [Z 283/113 IE]

[1] *M. O. Forster*, J. chem. Soc. (London) *107*, 260 (1915).

[2] *J. Meinwald* et al., J. Amer. chem. Soc. *81*, 4751 (1959).

[3] *L. A. Carpino* et al., J. Amer. chem. Soc. *81*, 955 (1959).

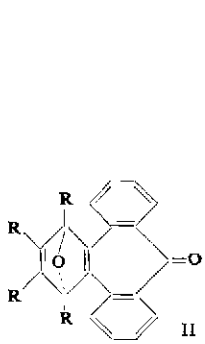
[4] *E. Bamberger*, Ber. dtsch. chem. Ges. *28*, 1682 (1895), prepared diazomethane similarly, but from other components (*N,N*-dichloromethylamine and hydroxylamine.)

The Intermediate Occurrence of 4,5-Dehydro-2,3,6,7-dibenzotropone

By Dr. W. Tochtermann [*]

Institut für Organische Chemie
der Universität Heidelberg (Germany)

After allowing an etheral suspension of K-t-butoxide to act on 4-bromo-2,3,6,7-dibenzotropone [1] for many hours, 95 % of the bromine can be detected as silver bromide in the aqueous phase following hydrolysis. In the presence of furan or tetramethylfuran this reaction leads to the Diels-Alder adducts IIa (67 % yield) and IIb (30 % yield), respectively. In the presence of tetraphenylcyclopentadienone tetraphenyltribenzotropone (III) (45 % yield) is formed with loss of carbon monoxide. These facts suggest the intermediate occurrence of 4,5-dehydro-2,3,6,7-dibenzotropone (I) [2].



IIa: R = H; m.p. 204–206 °C
IIb: R = CH_3; m.p. 261–262 °C

III: m.p. 375–378 °C

The constitution of compounds (II) and (III) is based on analyses, spectral data, and chemical behaviour.

These investigations, which have led to the otherwise difficultly accessible tribenzotropone system [3], are being continued, with a view to the preparation of the benzotropylium radicals [4], *etc.*

Received, May 17th. 1962 [Z 280/110 IE]

[*] Dedicated to Prof. Dr. *G. Wittig* on the occasion of his 65th. birthday.

[1] *W. Treibs* and *H.-J. Klinkhammer*, Chem. Ber. *84*, 671 (1951).

[2] See *G. Wittig*, Angew. Chem. internat.Edit. *1* (1962), in the press.

[3] *M. Stiles* and *A. J. Libbey*, J. org. Chemistry *22*, 1243 (1957); *E. D. Bergmann* and *J. Klein*, *ibid. 23*, 512 (1958).

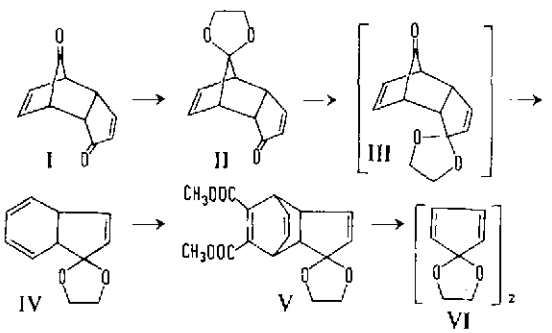
[4] *G. Wittig*, *E. Hahn*, and *W. Tochtermann*, Chem. Ber. *95*, 431 (1962).

Ethylene Ketal of Cyclopentadienone

By Prof. Dr. E. Vogel and chem. E.-G. Wyes

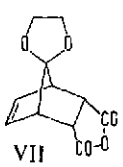
Institut für Organische Chemie
der Universität Köln (Germany)

Cyclopentadienone [1] dimerises in the nascent state at 5 °C. The reaction is not reversible and gives the product (I) (*endo*-configuration [2]). In the presence of excess ethylene glycol in benzene, the dimer (I) yields the monoketal (II), m.p. 94–95 °C, crude yield 94 %. The position of the keto group follows from the ultraviolet and infrared spectra. If (II) is subjected to pyrolysis at 400 °C *in vacuo*, it is converted almost quantitatively into the ethylene ketal (IV) of the unknown 8,9-dihydroindenone. Carbon monoxide is evolved. The product (IV) exhibits the typical ultraviolet spectrum of 8,9-dihydroindene [3]; on catalytic hydrogenation it takes up 3 moles of hydrogen.



We assume that, in analogy with the reversible Cope rearrangement of α-1-hydroxydicyclopentadiene into syn-8-hydroxydicyclopentadiene [4], the pyrolysis of (II) leads primarily to (III). In agreement with the thermal behaviour of compound (I), compound (III) should, under the conditions of pyrolysis decompose into carbon monoxide and (IV).

Compound (IV) reacts with maleic anhydride, even at room temperature (m.p. of the adduct: 151 °C). It also combines readily with the dimethyl ester of acetylene dicarboxylic acid to give (V), m.p. 72–73 °C, yield 90 %. The cyclopentadienone ethylene ketal formed in an Alder-Rickert thermal cleavage of (V) at 160 °C proved to be considerably more reactive than supposed and, similarly to cyclopentadienone, could only be isolated in the form of its dimer (VI), m.p. 92 °C, yield 72 % [5]. Hydrolysis of the dimer to (I) shows that it has the *endo*-configuration.



By pyrolysis of (V) in the presence of maleic anhydride (50 % excess) it was possible to capture the ethylene ketal of cyclopentadienone as the adduct (VII), m.p. 148–9 °C, yield 73 %.

Received, May 21st. 1962 [Z 286/115 IE]

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

[2] The configurational proof of (I) was carried out by catalytic hydrogenation to 1,8-diketotetrahydrodicyclopentadiene which was then reduced (Wolff-Kishner) to *endo*-tetrahydrodicyclopentadiene.

[3] *K. Alder* and *F. H. Flock*, Chem. Ber. *87*, 1916 (1954); *E. Vogel* Angew. Chem. *73*, 548 (1961).

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

[5] The dimeric ethylene ketal of cyclopentadienone has also been prepared in the meantime by *C. H. DePuy, B. W. Ponder* and *J. D. Fitzpatrick*, Angew. Chem. internat. Edit. *1*, 404 (1962). By agreement with Prof. *DePuy*, both syntheses are published simultaneously.

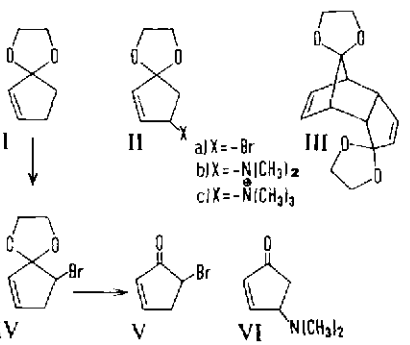
Ethylene Ketal of Cyclopentadienone

By Prof. C. H. DePuy, Dr. B. W. Ponder and J. D. Fitzpatrick

Department of Chemistry, Iowa State University,
Ames, Iowa (USA)

It has not been possible to isolate cyclopentadienone [1] in the form of its monomer. However, it seemed reasonable to suppose that the ethylene ketal of cyclopentadienone would be more likely to remain monomeric.

With this view in mind, the cyclic ethylene ketal of cyclopentenone (I) [2] was allowed to react with *N*-bromosuccinimide in carbon tetrachloride solution. Depending on the reaction conditions, different products are obtained. In the presence of an initiator (azobisisobutyronitrile), the expected 4-bromocyclopentenone ketal (IIa) was formed. This allylic halide reacts with dimethylamine to give compound (IIb);



overall yield from the eneketal: 64 %. In the presence of an inhibitor (di-t.-butyl-*p*-cresol) and HBr, the 5-bromocyclopentenone ketal (IV, 62 % yield) was formed, probably by an elimination-addition mechanism [3]. Compound (IV) does not react with dimethylamine, and hydrolyzes easily to give 5-bromocyclopentenone (V).

Hofmann elimination from (IIc) gives, under a wide variety of conditions, only the dimer (III) of the ketal. This dimer is extremely stable, and could not be cracked to monomeric cyclopentadienone ketal. Apparently, the inductive effect of the oxygen atoms is sufficient to induce an electron deficiency into the cyclopentadiene ring [4].

The 4-substituted amino ketal (IIb) readily hydrolyzes to 4-dimethylaminocyclopentenone (VI). The extension of these reactions to the synthesis of a variety of cyclopentenones is under investigation.

Received, May 21st. 1962 [Z 287/111 IE]

[1] *C. H. DePuy* and *C. E. Lyons*, J. Amer. chem. Soc. *82*, 631 (1960); *K. Hafner* and *K. Goliasch*, Chem. Ber. *94*, 2909 (1961); *C. H. DePuy, M. Isaks*, and *K. L. Eilers*, Chem. and Ind. 429, 1961.

[2] *H. W. Wanzlick* et al., Chem. Ber. *88*, 69 (1955).

[3] *A. Marquet* et al., C. R. hebd. Séances Acad. Sci. *248*, 984 (1959).

[4] *C. H. DePuy* and *E. F. Zaweski*, J. Amer. chem. Soc. *81*, 4920 (1959).

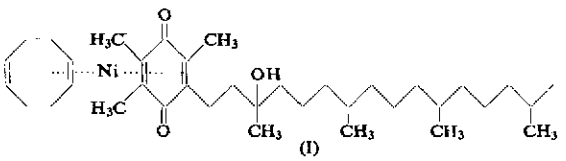
Vitamin E-quinone-nickel(0)-cycloocta-1,5-diene

By Dr. G. N. Schrauzer and Dipl.-Chem. H. Thyret [1]

Institut für Anorganische Chemie der Universität München
(Germany)

In the course of related work [2], we found that vitamin E-quinone and nickel carbonyl yield a nickel(0) "sandwich" complex at 70–80 °C in the presence of an excess of cycloocta-1,5-diene. Vitamin E-quinone-Ni(0)-cycloocta-1,5-diene was isolated as a deep-red, highly viscous oil, which was stable up to 150 °C. Its structure (I) follows clearly from

its composition, and its IR, UV, and H^1-NMR spectra. On complex formation, the C=O band of tocoquinone



(I)

is displaced by 114 cm^{-1} from 1647 to 1533 cm^{-1} and bands at 779, 824, and 860 cm^{-1} characteristic of symmetrically π-complexed cyclooctа-1,5-diene appear. The UV spectrum closely resembles that of cycloocta-1,5-diene-Ni(0)-duroquinone. In the proton resonance spectrum, the signal due to the four olefinic protons of the π-complexed cyclooctadiene appears at $\tau = 2.28$, while that due to aliphatic protons of the diene is found at $\tau = 1.90$ (40×10^6 cps). The remainder of the NMR spectrum resembles that of DL-α-tocoquinone. The compound, which is stable in air for considerable periods, is soluble in benzene, halogenated hydrocarbons, alcohols, ethers, and acetone, but is insoluble in water. It is the first well-defined π-complex of a transition metal with a natural product; in view of the possible carcinogenic properties of nickel, the physiological evaluation of (I), which is in progress, promises to be of considerable interest.

Received, May 21st. 1962 [Z 289/120 IE]

[1] Part 4 of a series on complexes of the bis-duroquinone-nickel(0) type. Part 3: *G. N. Schrauzer* and *H. Thyret*, Z. Naturforsch. *17b*, 73 (1962).

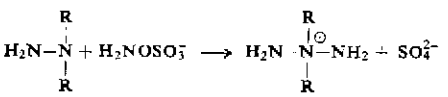
[2] *G. N. Schrauzer* and *H. Thyret*, J. Amer. chem. Soc. *82*, 6420 (1960); Z. Naturforsch. *16b*, 353 (1961). — Interaction of DL-α-tocoquinone and nickel carbonyl yields paramagnetic, salt-like, insoluble compounds incorporating divalent nickel (as in the reaction product of benzoquinone and nickel carbonyl).

2,2-Dialkyltriazanium Salts

By Dr. R. Gosl

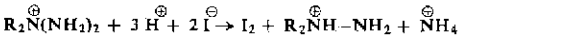
Institut für Anorganische Chemie
der Universität Erlangen-Nürnberg (Germany)

1,1-Dialkylhydrazines form quaternary ammonium salts with hydroxylamine-*O*-sulfonic acid (I); these salts contain the triazane structure:



The amination of the hydrazine nitrogen provides a route into the still little explored class of "paraffin aza-compounds" and suggests that, in the Raschig synthesis, the oxidative destruction of hydrazine or mono-substituted hydrazine by the acid (I) or monochloramine also takes place *via* amination [1].

The colourless and crystalline 2,2-dimethyltriazanium sulfate $[(CH_3)_2N(NH_2)_2]_2SO_4$ (II), obtainable from 1,1-dimethylhydrazine with yields of 70–80 %, is stable up to approximately 115 °C. A dilute aqueous and neutral solution is stable at room temperature, whilst the action of alkali or acid results in rapid decomposition. $Ag(NH_3)_2^+$ is reduced only after a certain time or on heating. On the other hand, free iodine is quickly liberated from acidified iodide solution.



This reaction makes possible the simple determination of the triazanium portion of such salts.

The infrared spectrum of the 2,2-dimethyltriazanium ion shows a striking similarity with that of the tetramethylammonium ion [2]. Some bands can be assigned to the NH_2-groups.

The corresponding oxalate, as well as tetraphenylborate, were prepared from (II). The borate is difficultly soluble in water. A salt of composition $[C_5H_5N(NH_2)_2][C_5H_{10}NH-NH_2]SO_4$ was obtained from *N*-aminopiperidine and (I).

Received, May 21st. 1962 [Z 284/118 IE]

[1] Cf. *R. Gösl* and *A. Meuwsen*, Chem. Ber. *92*, 2525 (1959); *J. W. Cahn* and *R. E. Powell*, J. Amer. chem. Soc. *76*, 2565 (1954).

[2] *F. Nerdel* and *W. Lehmann*, Chem. Ber. *92*, 2460 (1959).

An Explosion of Tropylium Perchlorate

By Dr. P. G. Ferrini and Priv.-Doz. Dr. A. Marxer

Forschungslaboratorien der CIBA Aktiengesellschaft,
Pharmazeutische Abteilung, Basel (Switzerland)

A chemist was seriously injured, and a laboratory assistant dangerously wounded, by a violent explosion of tropylium perchlorate. This compound has been described frequently in the literature and is often used as a starting material for syntheses. After normal reactions on a 0.1 molar scale, a larger amount (80 g.) was being transferred into a round-bottomed flask via a powder funnel. It was intended to push the compound that had heaped up in the funnel through the relatively wide mouth of the funnel using a glass rod. On coming into contact with the glass rod (static electricity?), the tropylium perchlorate detonated. The force of the explosion shattered the bench-top and broke solvent bottles stored beneath it. The spilt solvents caught fire. A paper by *A. P. ter Borg* et al. (Shell Laboratoires, Amsterdam) [1], received after the explosion, mentions the explosive nature of tropylium perchlorate in the experimental section. Since this unobtrusive notice, based on observations by *A. Dreiding* (University of Zurich), might be overlooked, we consider it essential to draw attention to the dangerous nature of this substance.

Received, May 25th. 1962 [Z 292/123 IE]

[1] Rec. Trav. chim. Pays-Bas *81*, 164 (1962).

β-Asp[1],Val[5]-Hypertensin II, a Hypertensin Analogue of Extremely High Biological Activity

By Dr. B. Riniker, Dr. H. Brunner [1], and
Prof. Dr. R. Schwyzer

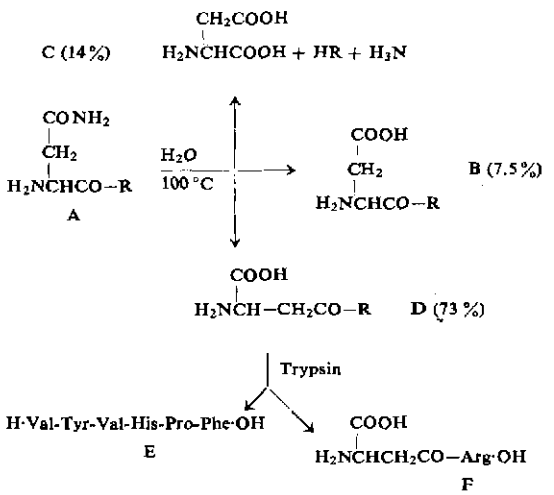
Pharmazeutische Abteilung, Forschungslaboratorium der
CIBA Aktiengesellschaft, Basel (Switzerland)

Acid hydrolysis of $Asp(NH_2)^1$,Val^5-hypertensin II (A) results in a good yield of Val^5-hypertensin II (Val^5-angiotensin II, B) [2]; an analogous reaction occurs on heating in aqueous solution [3]. Detailed study of the preparative value of this latter reaction has shown however that it yields appreciable amounts of an isomeric octapeptide D in addition to product B and the heptapeptide C. None of the solvents studied by us were capable of distinguishing D from B by either thin-layer or paper chromatography. Separation was achieved, however, by using basic eluents on aluminum oxide layers, or by electrophoresis on a carrier at either pH 2.1 or 9.1.

Quantitative separation of D from B was achieved by means of chromatography on neutral Al_2O_3, using methanol/2 M-ammonia (1:1, v/v). Analysis of the products of digestion with trypsin indicated the constitution of compound D. These products were the hexapeptide (E) and the dipeptide (F); the latter was identified by comparison with a synthetic prepara-

tion. Studies are now in progress to determine the degree of racemization of the aspartic acid residue effected by the transpeptidation.

When D was tested for its hypertensive effects on nephrectomized rats, its activity proved to be 50 % higher than that of B.



α → β shift R = –Arg-Val-Tyr-Val-His-Pro-Phe · OH
Yields are given in brackets

	B	D
Thin-layer chromatography on Al_2O_3: s-butanol/3 % NH_3 [100:44 v/v]	$R_F = 0.39$	0.21
Paper electrophoresis		
pH = 2.1; 5 hrs.; 7.5 v/cm distance traveled	–17.3 cm	–15.7 cm
pH = 4.75; 16 hrs.; 5 v/cm	–9.7 cm	–9.7 cm
pH = 9.1; 15 hrs.; 5 v/cm	+3.8 cm	+0.9 cm

Received May 28, 1962 [Z 291/126 IE]

[1] Responsible for the biological studies.

[2] *R. Schwyzer* et al., Helv. Chem. Acta, *41*, 1287 (1958); Chimia *11*, 335 (1957).

[3] *B. Riniker* and *R. Schwyzer*, Helv. Chim. Acta *44*, 685 (1961); *R. Schwyzer*, Circulation *25*, 175 (1962).

Tetrakisdimethylamino-ethylene, a Strong Electron Donor

By Dr. Nils Wiberg and Dipl.-Chem. J. W. Buchler

Institut für Anorganische Chemie der Universität München (Germany)

Tetrakis(dimethylamino)ethylene (I)[1] is a strong electron donor which gives up two electrons to certain oxidizing agents [2] forming the stable colourless cation II, in contrast to tetracyanoethylene, which is a strong electron acceptor. Further light is thrown on the structure of II by the infrared and nuclear magnetic resonance spectra of compounds I–IV (Table 1).

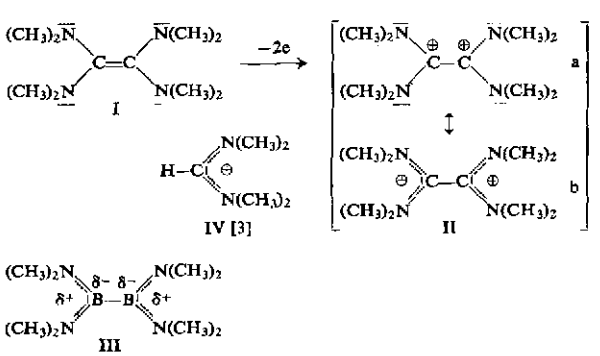


Table 1

	ν_{as} CN_2 [cm^{-1}] or ν_{as} BN_2 [cm^{-1}]	Chemical shift [ppm] ($(CH_3)_4Si$ as external standard)	Integrated intensity ratio
I	?	2.32	–
II	1670 very strong	2.87/3.15	1:1
III	1367 strong [4]	2.40	–
IV	1720 very strong	2.95 7.16 [5]	12:1

The high wave-number of 1670 cm^{-1} for the CN_2 group in II indicates a high double bond character. Whereas I, III, and IV [5] give only a single methyl proton signal, II gives two separate peaks with an integrated intensity ratio of 1 : 1; thus there might be no rotation about the C–N$(CH_3)_2$ bond. In this compound, therefore, in comparison with III and IV the amino electron pairs play a more substantial part in the mesomerism of the cation – a conclusion supported by the large chemical shift. This is understandable because in this way the two mutually repelling positive charges are as far apart as possible.

II has been isolated as its bromide [1] (m.p. 252 °C), hexafluorophosphate (m.p. 278 °C), tetrafluoroborate (m.p. 273 °C), picrate (m.p. 200 °C), and impure chloride and iodide. All these salts melt with decomposition.

I also forms electron donor-acceptor complexes, *e.g.* with trinitrobenzene (m.p. ca. 35 °C decomp., reddish-black, sensitive to air, λ_{max} 550, 475, 437 mμ), nitrobenzene (deep violet, ethersoluble, colorless at –180 °C), tetracyanoethylene (violet-black at first, soon decomposing to a brown powder).

Received, May 28th. 1962 [Z 296/127 IE]

[1] *R. L. Pruett* et al., J. Amer. chem. Soc. *72*, 3646 (1950).

[2] *E.g.* bromine. Reaction with oxygen proceeds under pale green luminescence at room temperature; oxidation in this case does not give II, but mainly tetramethylurea, tetramethyloxamide, and dimethylamine.

[3] IV was prepared from $HCCl_2F$ and $(CH_3)_2NH$. The hexafluorophosphate melts at 182–183 °C.

[4] *H. J. Becher* et al., Z. anorg. Chem. *314*, 226 (1962).

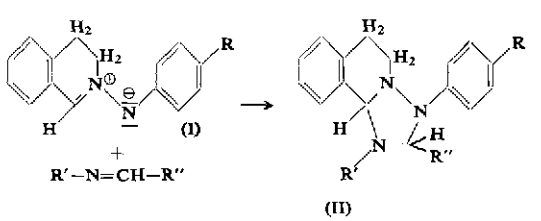
[5] The signal at 7.16 originates from the centrally bound formamide hydrogen.

1,3-Dipolar Addition of Azomethine-imines onto Alkylidene-imines, Nitriles, and Thiocyanates

By Dr. R. Grashey, H. Leitermann, R. Schmidt, and cand. chem. K. Adelsberger

Institut für Organische Chemie der Universität München (Germany)

Azomethine-imines of the 3,4-dihydroisoquinoline series (I) react with C–C double and triple bonds as well as with carbonyl groups to give 5-membered heterocycles in good yields [1–3]. Compounds of type I also react with the C=N double bond of Schiff bases and azines with equal ease to form substituted 1,2,4-triazolidines (II) (Tab. 1).



The dissociation of hexahydrotetrazines (formula IV of ref. [3]), which takes place at 50–80 °C, serves to prepare I *in situ*; I (R = NO_2), is generated just as easily by elimination of

Table 1. 1,2,4-Triazolidines

R	R′	R″	Yield [%]
NO_2	CH_3	C_6H_5	95
Cl	CH_3	C_6H_5	91
H	CH_3	C_6H_5	97
H	CH_3	p-Cl-C_6H_4	96
H	CH_3	p-CH_3O-C_6H_4	91
H	$C_6H_5CH_2$	C_6H_5	83
H	C_6H_5	C_6H_5	80
H	$C(CH_3)_3$	H	72
H	$N{=}CHC_6H_5$	C_6H_5	53

methanol from 1-methoxy-2-(*p*-nitrophenylamino)-1,2,3,4-tetrahydroisoquinoline in boiling benzene.

Acid hydrolysis opens up the triazolidine ring: II (R = H; R′ = CH_3; R″ = C_6H_5) yields 96 % benzaldehyde (as its 2,4-dinitrophenylhydrazone), 65 % methylamine (as its hydrochloride), and the hydrazonium salt corresponding to I, which was identified as the carbon disulphide adduct (formula XII of ref. [1]) (86 %).

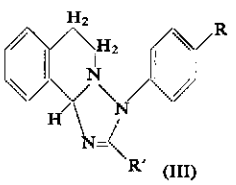
The thermolability of the triazolidines II, is less than that of the 1,3,4-oxadiazolidines [3]. Nevertheless, by heating II (R = H; R′ = CH_3; R″ = p-Cl-C_6H_4) with phenyl isothiocyanate to 90 °C, one obtains quantitative yield of the mustard-oil adduct (formula X of ref. [1]). This finding, as well as the reversible thermochromism observed on heating II in

Table 2. Δ^3-1,2,4-Triazolines

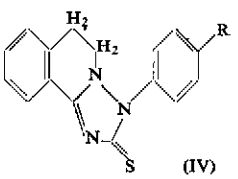
R	R′	Yield [%]	R	R′	Yield [%]
NO_2	$CO_2C_2H_5$	83	NO_2	$SCH_2C_6H_5$	91
NO_2	C_6H_5	55	H	$SCH_2C_6H_5$	91
NO_2	o-NO_2-C_6H_4	45	NO_2	SCH_2-p-Cl-C_6H_4	77
NO_2	p-NO_2-C_6H_4	69	NO_2	S-cyclohexyl	66
NO_2	o-CN-C_6H_4	87	NO_2	$SCH(CH_3)_2$	73
NO_2	SC_6H_5	91	NO_2	$SCH(CH_3)CO_2C_2H_5$	20 + IV

solution, shows that the 1,3-addition leading to II is reversible. If I is prepared in the presence of nitriles or thiocyanates Δ^3-1,2,4-triazolines (III) (Tab. 2) are produced.

Acid hydrolysis of III (R = NO_2; R′ = p-$C_6H_4NO_2$) produces *p*-nitrobenzoic acid, ammonia, and the hydrazonium salt



(III)



(IV)

corresponding to I. On heating above their melting points, the thiocyanate adducts III (R′ = S-Alkyl) undergo fragmentation and are transformed into triazolethiones (IV).

Received, May 29th. 1962 [Z 293/125 IE]

[1] *R. Huisgen, R. Grashey, P. Laur*, and *H. Leitermann*, Angew. Chem. *72*, 416 (1960).

[2] *R. Huisgen*, Naturwiss. Rundschau *14*, 43 (1961); *R. Huisgen*, Proc. Chem. Soc. (London) *1961*, 357.

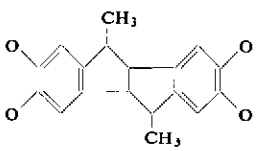
[3] *R. Grashey* and *K. Adelsberger*, Angew. Chem. Internat. Edit. *1*, 267 (1962).

2,3,6,7-Tetrahydroxy-9,10-dimethyl-9,10-ethanoanthracene

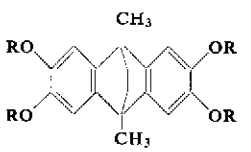
By Dr. E. Le Goff

Mellon Institute, Pittsburgh, Pa. (USA)

Niederl and *Nagel* [1] reported the isolation of a white compound (m.p. 300 °C) from the reaction of 1,2-dihydroxybenzene and 2,5-hexanedione in 70 % sulfuric acid. On the basis of its elemental analysis and conversion to a tetraacetate (mp.. 238–240 °C) this compound was assigned structure I.



I



IIa, R = H IIb, R = CH_3CO–

Another formulation, 2,3,6,7-tetrahydroxy-9,10-dimethyl-9,10-ethanoanthracene (IIa) seemed from a mechanistic standpoint to be a probable choice for the structure of this condensation product. The N.M.R. spectrum of the tetraacetate of the condensation product (m.p. 243–244.5 °C) is in complete agreement with the structure IIb. It exhibits a four-proton singlet at τ = 2.95 (aromatic =CH), a twelve-proton singlet at τ = 7.75 (CH_3CO–), a six-proton singlet at τ = 8.13 (–$\overset{|}{\underset{|}{C}}$–$CH_3$), and a four-proton singlet at τ = 8.37 (–CH_2–) [2].

Received, June 4th. 1962 [Z 298/124 IE]

[1] *J. B. Niederl* and *R. H. Nagel*, J. Amer. chem. Soc. *62*, 3070 (1940).

[2] N.M.R. spectra were obtained on a Varian A-60 spectrometer in deuterochloroform. The author thanks Dr. *B. L. Shapiro* for obtaining these spectra.

CONFERENCE REPORTS

Meeting of the German Pharmacological Society

April 8th to 11th, 1962 in Mainz (Germany)

From the papers:

A Quinazolinone Derivative with Strong Anticonvulsant Properties

Karl-Heinz Boltze, Dietrich Lorenz and *Maria Rüberg-Schweer*, Köln-Mülheim (Germany)

Among compounds of the quinazolinone series, 2-(2-pyridyl-vinyl)-3-*o*-tolyl-3,4-dihydroquinazolin-4-one (experimental code B 169) is distinguished by its particularly strong anticonvulsant action.

After maximum electrical shock, the effective dose ED_{50} in mice was $14.5^{+6.7}_{-4.6}$ mg/kg (single administration *per os*). Thus, B 169 is just as effective as phenobarbital, diphenylhydantoin, and phenacetylurea, definitely more effective than primidone, and about twice as effective as phenylchloroacetylurea, methsuximide, and *N*-(4-sulfamoylphenyl) butane-1,4-sultam.

After pentylenetetrazole shock, the ED_{50} *per os* for mice was 145^{+18}_{-13} mg/kg (*i.e.* dose which doubles the intravenous pentylenetetrazol administration required for the convulsion threshold to be reached). In strychnine convulsion, we found an ED_{50} of 200^{+48}_{-39} mg/kg (dose which counteracts the toxicity of strychnine in 50 % of the animals). From these tests, it would appear that B 169 is in some ways more and in some ways less effective than the reference compounds mentioned above.

The sedative action of B 169 was tested on mice by means of the balancing test on a horizontal rod and by observing their reactions in the rotating squirrel cage. In the balancing test, the ED_{50} was 120 mg/kg (dose at which 50 % of the animals fall from the rod within 5 minutes); in the treadmill test, it was 57.5 mg/kg (dose at which the performance of trained mice is decreased by 50 %). Thus, like other reference substances which have proved effective in grand mal epilepsy, B 169 shows a relatively strong action in these tests. On the other hand, its hypnotic effect is considerably less than that of other anticonvulsant drugs. For this particular effect, the ED_{50} for B 169 determined on mice was 1600 mg/kg (dose at which 50 % of the animals lie dormant in the lateral position for one hour).

The toxicity of B 169 is so low that no LD_{50} could be determined after oral administration; even doses of 6000 mg/kg were tolerated. The index of > 414 after electrical shock and > 41 after pentylenetetrazol shock, calculated from the quotient LD_{50}/ED_{50}, is not even approached by any of the reference compounds.

In chronic feeding experiments, rats showed no toxic symptoms whatever after a 13-week period during which their average daily consumption was 500 to 600 mg/kg.

Clinical reports on B 169 are not yet available.

Pharmacological Analysis of Acetylpyridine Poisoning

H. Coper and *H. Herken*, Berlin-Dahlem (Germany)

After injection of 3-acetylpyridine, a very peculiar toxicological picture develops in rats, the most prominent feature being the disturbance of neurological functions. On investigating tumors, *Kaplan* et al. found that DPN-nucleosidase catalyzes an exchange of nicotinamide for acetylpyridine in DPN, so that an abnormal DPN structure is formed. Previous attempts to isolate this acetylpyridine-DPN from brain tissues failed. We have now detected this compound in the brains of animals suffering from acetylpyridine poisoning. After separating the DPN zone from the remaining free nucleotides of the brain by ion-exchange chromatography, paper-chromatographical analysis showed that the DPN zone from acetylpyridine-poisoned animals was nonuniform. Chemical and spectrophotometric investigations revealed that the second substance in the DPN zone was 3-acetylpyridine-DPN. The spectra obtained after reduction of the compound with alcohol dehydrogenase and subsequent treatment with KCN were identical with those reported by *Kaplan* et al. The proportion of 3-acetylpyridinenucleotide in the total DPN of the brain was between 6 and 10 %. It must be taken into account, however, that the acetylpyridine compound concentrates mainly in those areas of the brain in which DPN-ase activity is particularly high. This is primarily the case in the hypothalamus and apparently also in the hippocampus. The enzyme is not very active in the cerebral cortex. Since acetylpyridine-DPN behaves differently from DPN in various dehydrogenase systems, replacement of nicotinamide with 3-acetylpyridine in DPN may have far-reaching consequences upon tissue metabolism. Intoxication with 3-acetylpyridine demonstrates the damage that may occur when an important enzyme of the central nervous system becomes non-specific.

Thin Layer Chromatography in the Toxicological Detection of Hypnotics

H. Eberhardt and *K. J. Freundt*, Tübingen (Germany)

First, the hypnotics are extracted from body fluids with ether in a Kutscher-Steudel extractor. The concentrate is then applied to silica gel plates impregnated with eosine. Piperidine/petroleum ether (1:5) serves as eluent. The spots on the chromatogram become visible under UV light against the background by intensification or extinction of fluorescence. In addition, mercuric nitrate may be sprayed on in order to increase the contrast of the spots. The hypnotics bearing the proprietary names Veronal, Luminal, Phanodorm, Medomin, Adalin, Bromural, Persedon, Noludar, Doriden, Valamin, and Revonal distribute themselves along the strip from $R_F = 0.1$ to $R_F = 0.9$. Several hypnotics, when ingested in therapeutic doses, are excreted only in the form of their metabolites. In the piperidine/petroleum ether system, however, characteristic metabolite distributions are also obtained.

Amine Formation by X-Ray Irradiation

K. Flemming, Heiligenberg/Baden (Germany)

Pharmacologically active amines are formed in solutions of certain aromatic amino acids by ultraviolet irradiation. Such amine formation is also feasible with X-rays, as has been confirmed by the detection of histamine in histidine solutions irradiated by X-rays. In the extracts of solutions of phenylalanine, tryptophan, and tyrosine irradiated with X-rays, the corresponding amines, phenylethylamine, tryptamine, and tyramine were found. – The presence of oxygen inhibits the formation of amines by X-rays, but the presence of cysteine and other reducing agents (homocysteine, thioglycerol, ascorbic acid) enhances it. The adjuvant effect of reducing compounds is also evident in solutions free from oxygen; the effect is even greater than in the presence of oxygen. – It could be shown that the formation of amine was due to OH radicals. In histidine solutions, in which such radicals were produced by a means other than X-rays (photochemical cleavage of H_2O_2), histamine was also detected. The radical mechanism permits a unified interpretation to be made of the influence of oxygen and of the reducing agents, if it is assumed that HO_2 radicals inhibit the amine formation and that the ratio of the OH and HO_2 radicals formed is shifted by oxygen in favor of the HO_2 radicals, and by reducing substances in favor of OH radicals.

Liberation of Catecholamines by Calcium

A. Philippu and *H. J. Schümann*, Frankfurt/Main (Germany)

In perfusion experiments on isolated adrenal glands of cats, *Douglas* and *Rubin* showed that acetylcholine liberates catecholamines only in the presence of calcium. Our experiments with perfused isolated adrenals of cattle showed that in contrast to acetylcholine, the action of the indirectly acting sympathomimetic amines tyramine and β-phenylethylamine is independent of calcium.

In incubation experiments with isolated cytoplasmic particles, the storage granules of the medullary hormones epinephrine and norepinephrine, the authors found that calcium as well as tyramine and phenylethylamine liberate catecholamines. Even the physiological calcium concentration of blood plasma (2.5 μ moles/ml.) proved to be effective. However, the action of calcium differs in two respects from the action of the sympathomimetic amines investigated: 1. besides amines, calcium liberates ATP in almost equal proportion; tyramine and phenylethylamine, on the other hand, liberate only catecholamines; 2. calcium-induced amine liberation occurs at 37 °C as well as at 0 °C, while the sympathomimetic amines are ineffective at 0 °C.

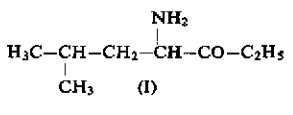
Acetylcholine, the physiological liberator of the catecholamines from the medullary cells, cannot liberate any of these amines from storage granules isolated from the same cells, even in the presence of calcium.

The following picture can be drawn up of the physiological processes which lead to the liberation of the medullary hormones. Acetylcholine, which is released during excitation of the splanchnic nerve, depolarizes the membrane of the chromaffine cell and thus creates conditions leading to increased calcium influx, as is indicated by ^{45}Ca experiments of *Douglas* and *Poisner*. The calcium then liberates hormones and ATP from the storage granules. Any calcium entering the cytoplasm is probably removed from the cell by active transport.

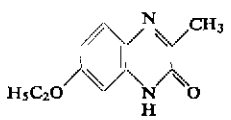
[VB 581/32 IE]

This year the 13th. Mosbacher Colloquium (May 3rd–5th) was held under the theme "Induction and Morphogenesis". In his introduction, *E. Klenck*, Cologne (Germany), recalled that this borderline field between biology and chemistry has hitherto been regarded, above all, from a morphological stand-point, but that recently progress has come about through a more chemical approach.

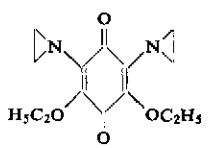
This was clearly shown in the first paper: *F. Lehmann*, Bern (Switzerland), spoke on "Biological and Biochemical Problems in Morphogenesis". First structure-forming and segregation processes can take place even in the undivided ovum (*Ascidia*). With other species (vertebrates, echinoderms), morphogenesis begins after the division of the ovum. Until the present time, however, only few relationships were recognized between morphogenetic and biochemical segregation. *Gustafson*, *Lenicque* and *Hörstadius* have found that in the case of young sea-urchin embryos the region of a given redox potential (detected by staining with a redox dyestuff) lies at different distances from the vegetative pole depending upon the stage of vegetative development. Here, a region of marked biochemical activity appears to be displaced in the same sense as a region of particular morphological activity. Regenerating tissues can also give information concerning the relationship between the formation of morphological and biochemical patterns. Substances have been discovered which inhibit the regeneration of the tails of *Xenopus* larvae without essentially impairing the vitality of the larvae themselves. Such compounds (morphostatics) comprise, among others; colchicine, β-mercaptoethanol, 1-amino-3-methylbutyl ethyl ketone (I), 2-methyl-3-oxo-6-ethoxyquinoline (II), 2,6-diethyleneimino-3,5-ethoxy-*p*-benzoquinone (III) as well as the heterocycle (IV). 5-(1,2-Dithiolan-3-yl)valeric acid (thioctic acid) (V) and nicotinamide are also capable of morphostatic action.



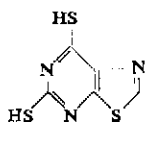
(I)



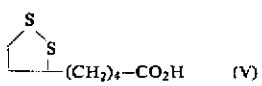
(II)



(III)



(IV)



(V)

With normal regeneration of the tail, the cathepsin activity increases and later falls of to a normal level. Cathepsins are proteolytic enzymes and the raising of their activity during regeneration might be related to the formation of peptides necessary for the regeneration processes. The aminoketone (I) raises the cathepsin activity quite considerably, which perhaps leads to such an extensive decrease of the tail proteins that regeneration of the tail ceases. On the other hand a combination of quinoxaline (II) (1:250000) + colchicine ($1:10^6$) inhibits the regeneration by 40 % without changing the cathepsin activity. Evidently, therefore, several enzymes of which the cathepsin activity is only a part, are responsible for morphogenesis. It is to be assumed that different morphostatics influence different parts of this enzyme system.

J. Brachet, Brussels (Belgium), dealt with "The Influence of Free -SH Groups on Morphogenesis". β-Mercaptoethanol in low concentrations (10^{-3} to 3×10^{-3} M) retards the development of *Xenopus* embryos; in its presence, the heads are too small and the tails too short. Melanine formation is completely inhibited. Dithiodiglycol, the oxidation product of mercaptoethanol, has the inverse effect (it does not influence pigment formation), so that it is to be assumed that the above-mentioned developments depend upon the state of the sulphydryl/disulphide equilibrium in the cells.

In higher concentrations (3×10^{-3} to 10^{-2} M), β-mercaptoethanol also inhibits the development of the nervous system; the cavity containing the neural plate fails to close. This effect can be reversed with adenosine triphosphate (0.1 mg/ml), although ATP has no influence on the inhibition of tail development and melanine formation.

In the fungiform algae *Acetabularia mediterranea*, β-mercaptoethanol (3×10^{-3} to 5×10^{-3} M) interferes with the formation of the pileus. In contrast, sterile whorls, from which the pileus would normally grow, are formed without inhibition. Here, too, dithiodiglycol (10^{-4} M) has an opposite effect; it promotes pileus formation and inhibits whorl formation. By use of reagents which react with –SH groups (*p*-chloromercuribenzoate, 10^{-7} M, and *p*-iodosobenzoate, 10^{-5} M) it can be confirmed that free –SH groups are detrimental to pileus formation.

In the case of the embryos of amphibia, thioctic acid in minute concentrations (5 μg/ml) inhibits only the tail growth (to an extent of *ca.* 30 %). In higher concentrations (15–30 μg/ml) it exhibits the same effect as mercaptoethanol at higher concentration levels but does not influence pigment formation. Here also, the development of the nervous system can be normalised with ATP. This compound has no influence on tail growth. Furthermore, oxaloacetate or succinate reverse the under-development of tails in embryos which have been treated with thioctic acid This is not so with embryos which have been treated with mercaptoerhanol. The formation of the nervous system and the differentiation of the tail tissue are therefore based on different biochemical mechanisms.

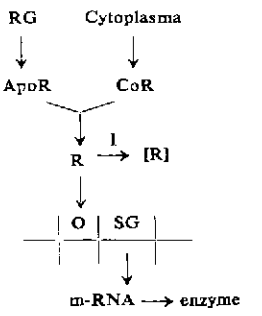
Experiments with ^{35}S-mercaptoethanol showed that 25 % of the radio-activity entering the cell becomes protein-bound, presumably by formation of mixed disulphides. It seems, therefore, that proteins are a point of attack for mercaptoethanol.

The topic discussed by *H. O. Halvarson*, Madison, Wis. (USA), was "The Control of Enzyme Synthesis in Microorganisms". Three possibilities for the regulation of enzymatic activity in the cells of *Escherichia coli* were referred to:

a) An enzyme is inhibited through the end-product of a synthetic chain. Example: *E. coli* contains two β-aspartokinases of which one is inhibited by threonine, and the other by lysine.

b) The structure of an enzyme is so altered that its specificity changes. Example: the hormone-influenced conversion of glutamate dehydrogenase into alanine dehydrogenase.

c) The inhibition of enzyme synthesis by means of a repressor. A regulator gene (RG) governs the synthesis of an apo-repressor (Apo-R, presumably ribonucleic acid). This combines with a cytoplasmic co-repressor (Co-R) to give the complete repressor, which reversibly blocks the operator



gene (O). As a consequence of this blockage the structure genes (SG), which lie adjacent to the operator genes, are not able to promote the synthesis of messenger-RNA which is indispensable for the synthesis of protein. Inductors (I) in-

activate the repressor, *e.g.* by forming an inactive complex with the co-repressor [1].

In this diagram, constitutive enzyme synthesis is the result either of a mutation of the regulator gene (synthesis of an inactive apo-repressor) or of the operator gene (no pairing of the gene with repressor).

Hitherto, the hypothesis given under c) has only been proved for bacteria. It has now been shown on yeast cells that other organisms can contain several identical and independent structure genes for the same enzyme. Presumably, then, every structural gene has its own operator gene. A structure gene can be controlled through a number of regulator genes.

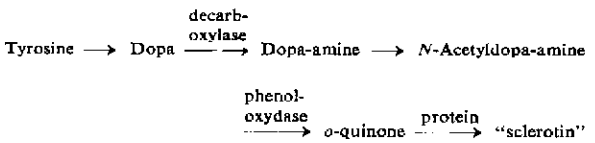
In the case of yeast there is, evidently, a fourth possibility for regulating enzymatic activity; in this case the removal of the ready synthesized enzyme from the ribosome is affected.

W. Berrman, Tübingen, reported on "Cytological Aspects of the Transfer of Information from the Chromosomes to the Cytoplasm". Giant chromosomes, which are formed by a combination of many thousands of single chromosomes, are found in the cell nuclei of *Diptera* larvae. These giant chromosomes display a disc-like pattern (chromomere pattern) that arises through the alternating sequence of DNA-rich and DNA-poor layers. At several points the giant chromosomes are swelled out to double normal thickness ("puffs"). The previously compact oblique discs become spongy at these positions and DNA can usually only be detected by autoradiography and no longer by staining. Staining with light-green is positive, *i.e.* the "puffs" contain protein.

Whereas the chromomere pattern is, to a considerable extent, similar for different organs, the puff pattern changes in a specific manner from organ to organ and also alters during metamorphosis. Using radio-actively labelled uridine it can be shown that RNA is synthesized in these puffs. Possibly this RNA is related to the messenger-RNA which serves, in a later phase, as a matrix for the synthesis of protein. It appears that the size of a "puff" is proportional to the amount of RNA synthesized in it. Evidently the puff pattern changing from organ to organ and from metamorphological phase to metamorphological phase is an expression of different genetic activity leading to the synthesis of enzymes typical for an organ or for a stage in the metamorphosis. This relationship was demonstrated genetically for a "puff" in the salivary gland chromosome of *Chironomus*.

The formation and retrogression of the "puffs" can be brought about by several means (incubation medium, temperature change, transplantation). The observation that the injection of the hormone ecdysone into *Chironomus* larvae induces the formation of two puffs is of particular interest. The earliest signs of metamorphosis are visible only several hours after the puff formation.

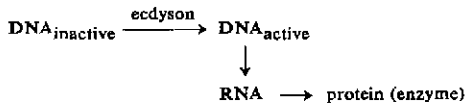
One of the effects brought about by ecdysone is sclerotisation (hardening) of the skin during the transformation of the larvae into pupae. According to *P. Karlson*, Munich (Germany), this process is comparable to an *o*-quinone tannage: *o*-quinone arising from tyrosine cross-links the skin protein by reaction with free amino-groups. Ecdysone so changes the



[1] *F. Jacob* and *J. Monod*, Cold Spring Harbor Sympos. quantitat. Biol. *26*, 193 (1962).

tyrosine metabolism of the larvae (through formation of a decarboxylase and a phenoloxidase) that an *o*-quinone is finally produced *via* dihydroxyphenylalanine (Dopa) and Dopa-amine.

The phenoloxidase could be crystallised. It is formed (under the influence of ecdysone) from inactive intermediates contained in the larvae. This activation appears to consist of a limited hydrolysis and it was shown that ecdysone causes the formation of the necessary proteolytic enzyme. Together with the observation that puffs form on the chromosomes under the influence of ecdysone (cf. paper delivered by *Beerman*) the following scheme can be given for the action of ecdysone in sclerotisation.



H. Holtzer, Philadelphia (USA), has found that the spinal chord of chick embryo induces undifferentiated mesenchyme cells (somites) of the same embryo to develop into cartilage cells. This applies *in vivo* (transplantation of spinal chord into the mesenchyme tissue) as well as *in vitro*, *i.e.* in a tissue culture. If the mesenchyme tissue and spinal chord are separated *in vitro* through a fine filter (pore size *ca.* 40 μ), induction still takes place. Three days pass between the commencement of the mutual incubation, and the first appearance of cartilage cells. Presumably this period is required for the synthesis of the enzymes and co-factors necessary for cartilage formation.

A substance which induces the development of somites (from chick embryo) into cartilage cells was isolated from the spinal chords of 4 day-old chick embryos by *F. Zilliken*, Nijmegen (Holland). The spinal chords were homogenised with 0.25 M $HClO_4$ at 0 °C, neutralised and centrifuged. The supernatant was treated with charcoal which was then eluted with 10 % pyridine. Further purification was carried out on Dowex 1-X8 by gradient elution with formic acid and ammonium formate. The substance purified in this manner is most stable at pH 5.5–6.0, and is neither found in yeast nor in tissues which are not able to promote the development of cartilage cells. It consists of guanosine monophosphate (GMP), glucose, galactose, mannose, ribose and an unidentified sugar which migrates rapidly on chromatography (idose?). Furthermore it contains two uronic acids, glucosamine, *N*-acetylneuraminic acid and a peptide residue comprised of 15 types of amino-acids, (asp., thr., ser., glu., pro., hydroxy-pro., glyc., ala., val., meth., ileu., leu., tyr., phe.). Up to the present time, only hypothetical arguments can be put forward concerning the mutual linkages of these building units.

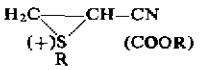
Materials which are able to cause induction of fore-heads (fore-brain, middle-brain and eyes), hind-heads (bind-brain, auditory capsules and head muscles), or trunks and tails of salamander embryos were obtained from 9 day-old chick embryos by *H. Tiedemann*, Heiligenberg (Germany). The trunk-and tail-inducing "mesodermal factor" is a protein of mol. wt. 50000 to 100000. Fore-heads are induced by the "neural factor" which is a nucleoproteide. Both factors are inactivated by trypsin or pepsin. In the presence of thioglycollic acid or performic acid, or when the temperature is raised, both factors behave differently. The mesodermal factor is quickly inactivated in all cases. Evidently a combination of both factors is necessary for the induction of the hind-heads.

[VB 583/30 IE]

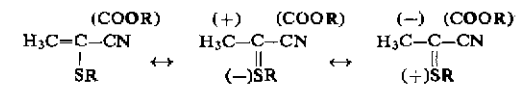
Effects of Neighbouring Groups and of Substituents in Organic Sulfur Compounds

K. D. Gundermann, Münster/Westf. (Germany)

The intermediate formation of ethylenesulfonium ions of the type



explains why the addition of alkylsulfenyl chlorides (RSCl) to derivatives of acrylic acid [1] gives not only α-alkylmercapto-β-chloropropionic acid derivatives, which are to be expected on the basis of the polarity of the reactants, but isomeric α-chloro-β-alkylmercaptopropionic acid derivatives as well. On the other hand, α-dialkylaminoacrylic acid derivatives, which should react like the corresponding thioether derivatives, could not be made to add mercaptans, malonic ester or diazomethane in a preparatively useful manner. Considering the capability of the S atom to undergo octet expansion [2], the following extreme mesomeric structures, which make possible a polar mechanism for "head-to-head" dimerization, were discussed.



Attempts to propare α-nitroacrylic esters (in order to study the effect of a particularly strong electron-attracting substituent in the α-position of the acrylic acid bond system) from α-bromo-β-methoxypropionic ester according to the method of *Kornblum* [3] lead to α,α'-dinitro-α-methoxymethylglutaric ester. This compound arises by a Michael addition of α-nitro-β-methoxypropionic ester to α-nitroacrylic ester, which is formed in the course of the reaction; its structure was proved by energetic reduction to α-methyl-α,α'-diaminoglutaric acid.

[GDCh-Ortsverband Krefeld (Germany), April 5th, 1962]

[VB 580/31 IE]

[1] *H. Brintzinger* and *M. Langheck*, Chem. Ber. *87*, 325 (1954).

[2] *G. Cilento*, Chem. Revs. *60*, 147 (1960).

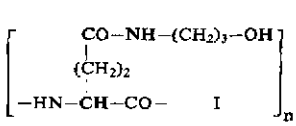
[3] *N. Kornblum*, J. Amer. chem. Soc. *79*, 2507 (1957).

Synthetic Polypeptides as Models for Proteins

M. Sela, Rehovoth (Israel)

Of the many syntheses for poly(α-amino acids), polymerization of anhydrides of *N* carboxy-α-amino acids (Leuchs anhydrides) proved particularly advantageous. This procedure yields high-molecular weight materials with very narrow distribution of molecular weights. The polymerization succeeds even in aqueous solution. With polyvalent amines (*e.g.* polylysine) as initiators, branched poly(amino acids) are obtained. By the same process, proteins can be converted into polypeptidyl proteins.

Simple water-soluble protein models should help in the study of the helical content of proteins in aqueous solution. If 1,3-propanolamine is treated with poly-(γ-benzyl-L-glutamate), a product designated as poly-[N^5-(3-hydroxypropyl)-L-glutamine] (I) results. It is soluble in water and in several organic solvents and contains neither free amino groups nor free carboxyl groups in its chain.



From optical rotation measurements, it can be shown that in dimethylformamide and methanol, I occurs essentially as a helix. Addition of water reduces the portion of the helical structure. In distilled water, the helical structure amounts to only 50 %, and addition of urea results in complete "denaturation" of the molecule.

With polyproline, the presence in *Escherichia coli* of a previously unknown proline iminopeptidase was demonstrated. The enzyme splits the bond between the imino nitrogen of the five-membered ring and the carbonyl group of the next pyroline residue. Polyalanyl ribonuclease containing 40 alanine residues per molecule and polyalanyl trypsin are as active enzymatically as the native enzymes. If all four disulfide bridges in polyalanyl ribonuclease are reduced and reoxidized, all the enzymatic activity is regained. Polyalanyl ribonuclease also has three free amino groups in the RNase chain (unchanged RNase has 11). Among these three free amino groups is the ε-amino group of lysine residue No. 41, which is considered to be part of the active center.

Gelatin is normally a very weak antigen. If this protein is condensed with tyrosine, tryptophan, phenylalanine, cyclohexylalanine, or cysteine peptides, it becomes a strong antigen. At a tyrosine content of 2 % (w/w), primarily antibodies against gelatin result. With a tyrosine content of 10 %, the antibodies are almost completely directed against the polytyrosyl residues attached to the gelatin. Since in this case gelatin apparently only plays the role of an inert carrier, it was replaced by multichain poly-(DL-alanine). Tyrosylation of this polypeptide resulted in a strong antigen. It produced antibodies primarily directed against tyrosine. Among numerous linear and branched polypeptides, consisting of one or more of the amino acids tyrosine, glutamic acid, lysine, or alanine, only those containing tyrosine proved to be antigens. Thus, these synthetic polypeptides allow immunological investigations on well-defined models which can be altered in a controlled fashion.

[GDCh-Ortsverband Freiburg-Südbaden (Germany), May 18th, 1962]

[VB 587/33 IE]

Ternary Compounds of Mercury Halides with Elements of Groups 5B and 6B

H. Puff, Kiel (Germany)

The reaction of PH_3 with $HgCl_2$ yields various different precipitates depending on the experimental conditions:

a) in aqueous solutions at pH < 1, in ether, dioxan, or tetrahydrofuran, a yellow substance Hg_3PCl_3 is obtained

b) in aqueous solutions at pH > 5 or in pyridine, a black precipitate in which Hg:P = 3:2, frequently contaminated with elemental mercury, is formed

c) in aqueous solutions at pH 2–3, as well as in methanol, ethanol, or isopropanol, mixtures of the above two substances of brown appearance are obtained.

All the precipitates are amorphous, judging by X ray analysis. From its properties and reactions, it is concluded that Hg_3PCl_3, analogous to the chloride of Millon's base $(Hg_2N)Cl$, has a spatial lattice cation of 2-coordinate mercury and 4-coordinate phosphorus, the positive charge being balanced by $HgCl_3^{\ominus}$ ions, *i.e.* $(Hg_2P)(HgCl_3)$.

When phosphonium halides are allowed to react with salts of mercury and cadmium, PH_4HgBr_3, PH_4HgI_3, PH_4CdBr_3, and PH_4CdI_3 are obtained. These substances are very sensitive towards moisture and heat. PH_4HgBr_3 crystals have the perovskite structure.

By annealing mercurous halides with red phosphorus or arsenic, the following almost insoluble and very stable compounds were formed: Hg_2PCl_2, Hg_2AsCl_2, Hg_2PBr_2, Hg_2AsBr_2, $Hg_3P_2Cl_2$, $Hg_3As_2Cl_2$, and $Hg_4As_2Cl_3$. The latter compound crystallizes in the cubic system, the others in the

monoclinic system. It is assumed that these substances are derived from diphosphine or diarsine respectively.

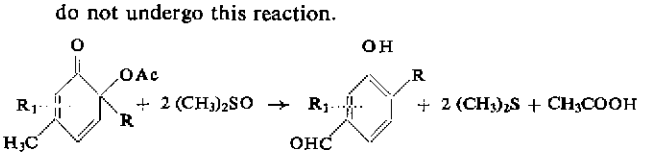
Compounds of formula $Hg_3Y_2X_2$, where Y = S, Se, or Te and X = Cl, Br, or I, were prepared and examined; they are sparingly soluble and resistant to acids. X-ray structure analysis of the substances $Hg_3S_2Cl_2$, $Hg_3Se_2Cl_2$, $Hg_3Te_2Cl_2$, and $Hg_3Te_2Br_2$, which crystallize in the cubic system, indicated spatial lattice-type cations with 2-coordinate mercury and 3-coordinate chalcogen as well as discrete halide ions.

[Technische Hochschule Aachen (Germany),
May 15th, 1962] [VB 593/35 IE]

SELECTED ABSTRACTS

The synthesis of tricycloisoazalenes is described by *W. Treibs* and *J. Beger*. 2-Azafluorenes, obtainable from 4-aryl-3-carboxypyridines, give tricycloisoazalenes (I) on quaternization and subsequent treatment with alkali. Some of these compounds are quite unstable in solution, but some are surprisingly stable in the crystalline state. Aryl groups on the nitrogenous six-membered ring exert a hypsochromic and on the five-membered ring a bathochromic effect. Compared to the benzo group, the thieno group exerts a strong hypsochromic effect. Examples: 5,6,7-trimethyl-1-phenyl-2,3-benzisoazalane, $C_{21}H_{19}N$, m.p. 212–216 °C, black crystals, solution: blue-purple; 5,6,7-trimethyl-1-phenylthieno[3′2′:2,3]-isoazalene (II), $C_{19}H_{17}NS$, m.p. 188–191 °C, red-purple crystals, solution: purple-red. / Liebigs Ann. Chem. *652*, 192, 204, 212 (1962) / –Ma. [Rd 211/68 IE]

A new synthesis of substituted *m*-hydroxybenzaldehydes was developed by *J. Leitich* and *F. Wessely*. On heating in dimethyl sulfoxide at 80 °C for several hours, 5-methyl-1-quinol-2-acetates give (preferably in the presence of $NaHCO_3$) *m*-hydroxybenzaldehydes in about 50 % yield. The presence of catalytic amounts of atmospheric oxygen is necessary. Benzyl alcohols are formed as by-products in 10–15 % yields. *o*-Quinol acetates which are not substituted in the 5-position do not undergo this reaction.



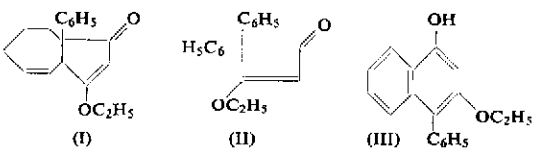
Examples: 2,5-Dimethyl-1-quinol-2-acetate → 3-hydroxy-4-methylbenzaldehyde; m.p. 73–74 °C; 2,3,5-trimethyl . . . . → 3-hydroxy-4,5-dimethylbenzaldehyde, m.p. 100–101.5 °C; 2-isopropyl-5-methyl . . . . → 3-hydroxy-4-isopropylbenzaldehyde, m.p. 40–42.5 °C. Ketones can be prepared in a similar manner: 2,4-dimethyl-5-(β-phenylethyl) . . . . → 2,4-dimethyl-5-(phenylacetyl)phenol, m.p. 127.5–129 °C. / Mh. Chem. *93*, 566 (1962) / –Ma. [Rd 212/69 IE]

A new method for the preparation of primary phosphines has been reported by *F. Pass* et al. The method is simple and inexpensive and yields pure products. Aluminium chloride and phosphine together form a salt-like complex $[H_3\overset{\ominus}{P} \rightarrow \overset{\ominus}{Al}Cl_3]$ in which the bonding of a hydrogen atom is so weakened that subsequent reaction with alkyl halides takes place under conditions in which phosphine alone does not react. By hydrolytic cleavage of the complex

$$[H{-}(CH_2)_{2n}{-}H_2\overset{\oplus}{P} \rightarrow \overset{\ominus}{Al}Cl_3],\ n = 3{-}9$$

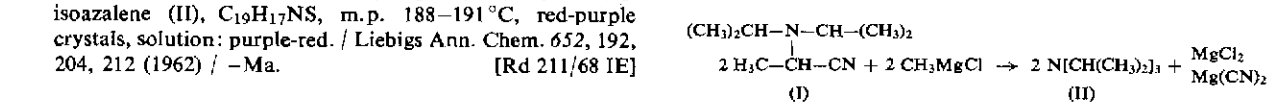
primary phosphines are obtained in average yields of 60 %. / Mh. Chem. *93*, 230 (1962). / –Re. [Rd 196/63 IE]

The cycloaddition of ethoxyacetylene to diphenylketene has been reported by *J. Druey, E. F. Jenny, K. Schenker*, and *R. B. Woodward*. 1-Ethoxy-3-oxo-3a-phenyl-3,3a-dihydroazulene (I, m.p. 160–161 °C) and 1,1-diphenyl-2-ethoxycyclobut-2-en-4-one (II, m.p. 94–96 °C) are formed in approximately equal amounts when the reaction is carried out at 25 °C.



Compound (II) rearranges into the α-naphthol (III) on gentle warming. The constitution of (I) was established by conversion into 1-oxo-3a-phenylperhydroazulene and 1-phenylcycloheptene. / Helv. chim. Acta *45*, 600 (1962). / –Ma. [Rd 199/66 IE]

Triisopropylamine (II), until now difficult to prepare, was obtained in 54 % yield by *F. Kuffner* and *W. Koechlin*. α-Diisopropylaminopropionitrile (I) is treated with methylmagnesium chloride in ether.



Steam distillation and extraction with ether yields II, b.p. 160–162 °C. Compound I was obtained in 40 % yield from diisopropylamine, acetaldehyde, and KCN by the Strecker synthesis. The substance is of pharmaceutical interest. / Mh. Chem. *93*, 476 (1962) / –Re [Rd 213/70 IE]

To alkylate nitriles, *L. Horner* and *H. Güsten* used naphthylsodium as a reactive metalation agent to attack the acidic α-hydrogen. At –60 °C under highly purified nitrogen, diphenylacetonitrile and phenylacetonitrile can be titrated accurately with the green solution of naphthylsodium [prepared from equivalent amounts of naphthalene and sodium in absolute tetrahydrofuran; cf. *N. D. Scott* et al., J. Amer. chem. Soc. *58*, 2442 (1936)]. The metalated nitrile is then alkylated in the usual manner. Thus, two different alkyl residues can be introduced into phenylacetonitrile one after the other without isolating the monoalkyl intermediate. Since no by-products are formed, the use of naphthylsodium is more convenient than that of the sodamide commonly employed. The yields obtained with naphthylsodium are as high as those with sodamide or phenylsodium. Among other compounds, the well-known spasmolytic agent Polamidon® was synthesized in this manner. / Liebigs Ann. Chem. *652*, 99 (1962). / –H. [Rd 216/73 IE]

The inhibition of corrosion of titanium in sulfuric acid effected by organic compounds was investigated by *A. P. Brynza* and *L. J. Gerasyutina*. Surface attack on titanium is prevented or strongly reduced by the addition of small amounts of *p*-nitroaniline, *m*-nitroaniline, *p*-aminophenol, *p*-nitrophenol, 2,4-dinitrophenol, nitrobenzene, or *o*-nitroanisole to 5 N H_2SO_4. Presumably, a protective film is formed on the surface of the titanium. The lowest effective concentration was, in all cases, 3 mmole/liter. Experiment duration was 16–24 hours. / J. appl. Chem. USSR *35*, 683 (1962) / –Bk. [Rd 215/72 IE]

Bis(trimethylsilyl)carbodiimide, the first representative of a new class of compounds, was synthetized by *J. Pump* and *U. Wannagat*. Metalation of *N,N'*-bis(trimethylsilyl)urea (obtained by silylation of urea with hexamethyldisilazane) with LiC_6H_5 or $NaNH_2$, and reaction with $(CH_3)_3SiCl$ gave the unusually stable bis(trimethylsilyl)carbodiimide, $C_7H_{18}N_2Si_2$, a colorless, highly mobile liquid, b.p. 164 °C, $n_D^{20} = 1.4351$, $d_{25}^{25} = 0.8211$ g/ml, Trouton's constant: 24.3 cal/mole × degree (yield = 80 % and 12 %). The infrared spectrum is in agreement with the structure. The remarkable stability can be explained on the basis of resonance stabilization due to several limiting mesomeric structures, of which I probably exerts a dominating influence.

$$R_3Si-\overset{\ominus}{N}-C\equiv\overset{\oplus}{N}-SiR_3 \quad (I) \quad (R = CH_3)$$

The chemical reactions of I differ from those of organic carbodiimides. The stability of the compound towards water is greater than that of its organic analogue; the compound has unlimited storage stability at room temperature and does not react with H_2S, NH_3, aniline, or catalytically activated H_2. H_2O and HCl split off the silyl group:

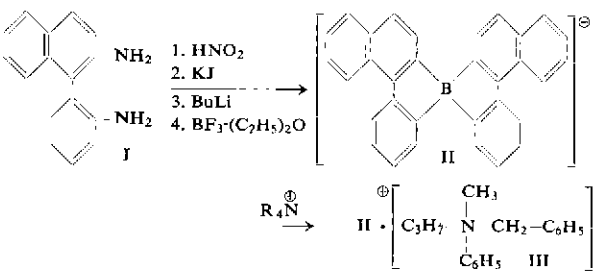
$$I + H_2O \longrightarrow (R_3Si)_2O + H_2N-CN,$$

$$I + 4\,HCl \longrightarrow 2\,R_3SiCl + Cl^{\ominus}[H_2\overset{\oplus}{N}=C=\overset{\oplus}{N}H_2]^{\ominus}Cl$$

Compound I can also be prepared in 60 % yield from bis(trimethylsilyl)sodamide and phosgene or in 20 % yield from Si tetraisocyanate, or in 90 % crude yield from di-Ag-cyanamide and trimethylchlorosilane. / Liebigs Ann. Chem. *652*, 21 (1962) / -Ma. [Rd 210/67 IE]

Lead tetraalkyls and other metal alkyls resistant to hydrolysis can be prepared according to *K. Ziegler* and *O.-W. Steudel* by electrolysis of aqueous solutions of sodium tetraalkylboranates using an anode of the desired metal (Pb, Sb, Bi, Hg) and a mercury cathode. Compared to the electrochemical synthesis of tetraethyllead in molten sodium aluminium tetraethylene, the preparation of the compound by this procedure has the disadvantage that a maximum current density of only 3.5 amp. per square decimetre can be used for prolonged periods, since at higher current densities the oily reaction product, $Pb(C_2H_5) \cdot 4\,B(C_2H_5)_3$, forms an electrically insulating coating on the anode. / Liebigs Ann. Chem. *652*, 1 (1962) / -L. [Rd 214/71 IE]

An optically active borospiran was obtained by *K. Torsell*. The diamine (I) was converted into the di-iodide by a Sandmeyer reaction and then into the dilithium compound by reaction with butyl-lithium. The dilithium compound yields the anion (II) with BF_3. Compound (II) in methanol and in the presence of the optically active benzylmethylpropylphenylammonium salt of bromo-(+)camphor-π-sulphonic acid, gave the difficultly soluble salt(III). Crystallisation from nitromethane leads to optically pure (III) with constant rotation $[M]_D = -596°$.



Since the rotation of the benzylmethylpropylphenylammonium ion ($[M]_D$ approx. −259 °) is largely independent of the nature of the anion, it is calculated that the optically pure boron-containing anion has the large rotation $[M]_D$ approx. −338 °. /Acta chem. scand. *16*, 87 (1962). / -Sk. [Rd 194/61 IE]

Indenyl derivatives of titanium, in combination with metal alkyls, catalyse the polymerisation of mono- and di-olefins. Investigations have been reported by *W. Marconi, M. L. Santostasi*, and *M. de Maldè*. Highmolecular weight linear poly-(ethylene), poly(butadiene) with predominantly 1,4-*cis*- and 1,4-*trans*-structures, and poly(isoprene) in the 1,4-*trans* form are obtained by the reaction of bis(indenyl)titanium dihalides with aluminium trialkyls, dialkylaluminium halides or Grignard compounds. Catalysis occurs under homogeneous conditions and possesses in itself a certain stereospecificity, *e.g.* a poly(butadiene) with a high 1,4-*cis* content is obtained with dialkylaluminium halide and bis(indenyl)titanium diiodide while the corresponding bromo compound leads mainly to 1,4-*trans*-poly(butadiene) and -poly(isoprene). In the polymerisation of ethylene, the activity of the catalyst system diminishes in the order $AlR_2I > AlR_2Br > AlR_2Cl > AlR_3$ corresponding to the changed Al/Ti ratio; in the case of poly(butadiene) and -(isoprene) the structure of the polymer is influenced in addition to the catalytic activity and yields. / Chim. e Ind. *44*, 235 (1962). / -Pf. [Rd 198/65 IE]

BOOK REVIEWS

Ionenaustauscher (Ion Exchangers), Volume I: Fundamentals. Structure Manufacture Theory, by *F. Helfferich*. Verlag Chemie GmbH., Weinheim/Bergstr., 1959, VIII, 520 pages, 153 figures, 14 tables. DM 48.— ($ 12.00).

Several books on ion exchangers have been written in recent years. Most of these entailed summaries of studies and reviews of opinions published up to the corresponding periods. A valuable contribution has been made by *F. Helfferich* in perusing the numerous theoretical analyses scattered throughout the literature, and presenting these from a single point of view. The various processes and physical relationships occurring in ion exchange are presented clearly in easily understandable fashion, by avoiding a detailed and complete description of all of the various published theories. The clarity of the treatment is possibly also due to the fact that the author has worked in the field of ion exchangers since the beginning of his scientific career and was himself directly involved in the development of the physicochemical concepts of ion exchange, in both Germany and the USA. Furthermore, in the preparation of the manuscript, the author has leaned on the experience of the leading experts in the field of ion exchange.

The book [1] deals first with the structure and properties of various types of ion exchangers. The manufacture of ion exchange resins is also described in detail. Next, the fundamental theories required for the calculation of capacity, exchange equilibria, and kinetics of ion exchange are individually explained. The electrochemical properties of ion exchange resins, ion exchange membranes, ion exchange beds, the behavior of ion exchangers in non-aqueous and in mixed solvents, the catalytic properties of ion exchangers, electron exchangers (redox resins), and redox ion exchangers are dealt with in subsequent separate chapters.

In order to facilitate the understanding of the individual chapters, in addition to a quantitative mathematical derivation, the author presents a qualitative, non-mathematical picture of the ion exchange processes involved.

In addition to the theoretical treatment, a description of the experimental methods, as well as a clearly formulated summary are to be found at the end of each chapter. The summary is particularly helpful because only essentials are emphasized. The book may be recommended to persons interested in de-

[1] A revised English translation is being published by McGraw-Hill, New York.

tailed information on the theory of ion exchange, as well as to those who would like to acquire a practical knowledge of the quantitative relationships involved in the application of ion exchangers, in order to optimize process conditions.

The book is the first independent volume of a three-volume work and can be purchased separately. We can only express our hope that the editor will be able to find authors, who will be equally successful in preparing the next two volumes, which are to describe applications of ion exchangers in the laboratory and in technology. *G. Manecke* [NB 881/21 IE]

Chemische Technologie (Chemical Technology) in five volumes, edited by *K. Winnacker* and *L. Küchler*. Volume 3: Organische Technologie 1 (Organic Technology 1). Carl Hanser Verlag, Munich 1959. Second Edition, XX, 912 pages, 347 figures, 226 tables, price cloth bound DM 98.– (about $24.50).

In this new edition of *Winnacker-Weingaertner*, the editors have tried to incorporate the continuous changes and the mass of new accomplishment in this particular field, while still maintaining as far as possible the original setup of the book. The present volume deals with organic technology of raw materials; the table below gives a comparison of the number of pages included in the individual chapters of the new and old editions. Organic technology has undergone a striking transformation, as a consequence of the removal on Jan. 2nd, 1953 of import duty on crude oils imported for chemical utilization in new processes set in operation after that date. This introduced a new source of raw materials and made true petrochemistry possible in Germany for the first time. It has not only led to unusually rapid development of new processes but has also had a sustaining effect on the

Table 1

	Pages new	Pages old
Chemical utilization of coal	111	120
Chemical utilization of lignite, etc.	65	113
Chemical technology of petroleum (including high pressure hydrogenation and lubricating oil refining)	209	183
Methanol and isobutyl oil syntheses	53	51
Fischer-Tropsch synthesis	82	124
Wood and its chemical technological processing	129	141
Aliphatic chemicals and intermediates	134	96
Aromatic intermediates	113	—
Synthetic fibers	—	69
	896	897

economic importance of already existing processes. The publishers have succeeded in taking this development into account by making extensive abridgements in the text (*e.g.* in the Fischer-Tropsch process, high pressure hydrogenation, isobutyl synthesis, and the saccharification of wood) as well as by using a more concise style, while carefully maintaining the total coverage. Those who have observed these technological developments, *e.g.* in high pressure hydrogenation and the Fischer-Tropsch processes, can imagine how difficult such deletions must be, since the technological information pertaining to the basic methods retains a certain value independent of the economic importance of the process itself. Thus, it was necessary to revise the entire text. The number of collaborators has increased from 26 for the first edition to 34, of whom 24 were new to this task; of the eight authors who signed and were responsible for the chapters, only two collaborated in the first edition. Thus, the material has been revised much more thoroughly than is apparent at a first glance. The more concise style is evident also in the more uniform subdivision of chapters, and the extensive bibliography at the end of each main chapter is a great improvement. The two chapters on the chemical utilization of coal and lignite are condensed, have excellent review tables, and are free of certain obsolete expressions, so that now more is contained in less space. A welcome addition is the multilingual glossary of terms dealing with petrographic and other properties of coal, which greatly facilitates orientation for the nonspecialist. Gasification of coal and lignite are treated separately, each within its own chapter. Here, combining the two gasification processes would have meant a simplification. In the lignite chapter, the production of montan wax by the extraction method is given only rather cursory treatment. A more detailed bibliography would also be desirable here.

The chapter on "Chemical Technology of Petroleum" by *Zorn*, in which previous chapters on high pressure hydrogenation and lubricating oil refining have been incorporated, is considerably enlarged. Special mention should be made of the good presentation of the properties of petroleum, the distribution of trace metals in crude oils of various origin, the compositions, yields, and consumption requirements of fuels (the question of octane number with instructive tables and illustrations). Even a picture of a jet engine is included. The section on lubricants is particularly well done. It is probably unavoidable that in such a presentation certain areas must be slighted. The increasing importance of fuel oils is only briefly mentioned; only two pages are devoted to fuel oils themselves, barely one to petroleum bitumen. The section, "Petroleum and Natural Gas as Raw Materials for the Chemical Industry" (8 pages), is also surprisingly short. In such a small space, no more than a summary listing is possible, with no claim to completeness. In view of the key position of the olefins, especially ethylene, in the chemical industry, a more detailed description of their preparative processes would be very desirable.

In the chapter on the Fischer-Tropsch processes by *Kolbel*, the essential results of the recent extensive development are deftly worked out. The developments during the last war and our present competitive industrial economy system have had the effect that an extremely large volume of literature and reference material on the Fischer-Tropsch processes is available, so that the author deserves praise for his condensed survey. In the section on wood, wood processing, wood coking, wood saccharification, and the preparation of cellulose and paper have been combined into a single chapter. Despite the abridgements the informational content has increased. The subsection on cellulose and paper is up-to-date in every respect, and it is gratifying that the techniques involved, which are of general interest, have finally found their way into a modern textbook on chemical technology. In keeping with its importance, the chapter on aliphatic chemicals and intermediates by *Horn* and *Bestian* has also been expanded.

Winnacker-Küchler bridges the gap in the literature between textbooks on the one hand, and technological encyclopedias on the other. We pay tribute to the publishers and authors, most of whom are active in industry, for allocating their time and effort not only to collecting the material, but also to compiling, classifying, and condensing it. Especially in view of the rapid pace of current developments, their didactic approach becomes increasingly important.

We wish them continued success in their work.

H. Sachsse [NB 856/18 IE]

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Small Rings with Carbon-Carbon Triple Bonds

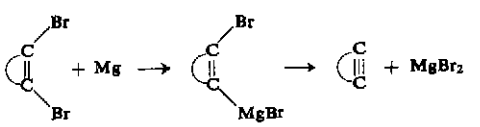
BY PROF. DR. G. WITTIG [*]

INSTITUT FÜR ORGANISCHE CHEMIE DER UNIVERSITÄT HEIDELBERG (GERMANY)

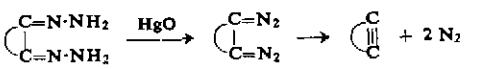
Over the last few years, numerous hydrocarbon ring structures with triple bonds have been studied, e.g. cycloalkynes, heterocyclic compounds with triple bonds, and particularly dehydrobenzene (better known in the Anglo-American literature as benzyne). Dehydrobenzene has not yet been isolated. The prospects of doing so are discussed.

Ring Strain and Stability

The chemistry of the cycloalkenes, down to highly strained cyclopropene, has been thoroughly investigated, but relatively little is known about small rings with carbon-carbon triple bonds, even though many attempts have been made to prepare lower cycloalkynes [1]. Failure to isolate these compounds is a consequence of the extremely high strain exerted on the ring by *sp*-hybridization of the σ-bonds, which forces any $-CH_2-C\equiv C-CH_2$-system into an extended linear arrangement. Thus, cyclononyne, prepared by *Prelog* et al. [2], is unstrained, judging from its model, whereas cyclo-octyne, prepared by *Blomquist* and *Liu* [3], has quite a significant strain in its structure. Since the likelihood of actually preparing cycloalkynes with even fewer ring members is rather small, *Wittig* et al. [4] attempted to demonstrate the occurence of these cyclic acetylenes in capture reactions. Two routes following known principles were used to produce the compounds. 1,2-Dibromocycloalkenes were treated with magnesium in tetrahydrofuran; a cycloalkyne should be the principal product:

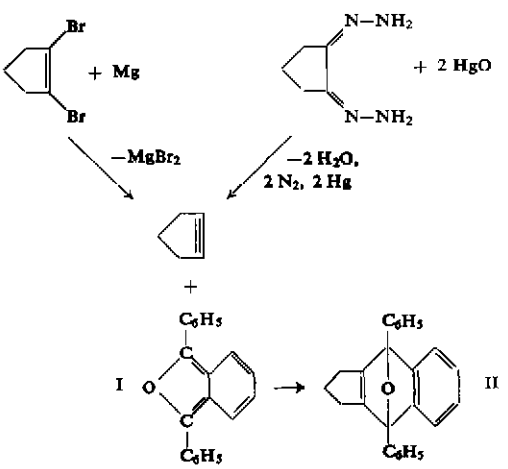


Alternatively, bishydrazones of 1,2-cycloalkanediones were oxidized with mercuric oxide to give cycloalkynes:



In no experiment could cycloalkynes be isolated.

The experiments were, therefore, repeated in the presence of cyclic dienes, in the hope of capturing cycloalkynes formed as intermediates in the form of *Diels-Alder* adducts. Although furan and cyclopentadiene proved unsuitable, success was attained with 2,5-diphenyl-3,4-benzofuran (I), because in this case, the diene addition was favored by the simultaneous aromatization of (I). It was thus possible to demonstrate the occurrence, albeit short-lived, of cycloheptyne, cyclohexyne, and cyclopentyne. An example is presented in the reaction sequence for cyclopentyne:



[*] From a lecture delivered at the Butlerov Jubilee in Leningrad 1961.

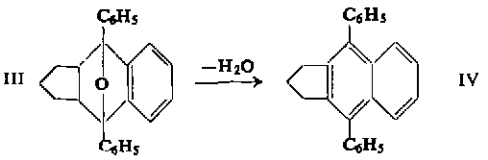
[1] For literature review by *G. Wittig* and *A. Krebs* see: Chem. Ber. *94*, 3261 (1961).

[2] *V. Prelog, K. Schenker*, and *W. Kueng*, Helv. Chim. Acta *36*, 471 (1953).

[3] *A. T. Blomquist* and *Liang Huang Liu*, J. Amer. chem. Soc. *75*, 2153 (1953).

[4] *G. Wittig* and *A. Krebs*, Chem. Ber. *94*, 3260 (1961); *G. Wittig* and *R. Pohlke*, Chem. Ber. *94*, 3276 (1961).

Adduct II was obtained by both routes. Hydrogenation of II yielded III, which led by dehydration to IV, a compound previously prepared by a different route [5]:



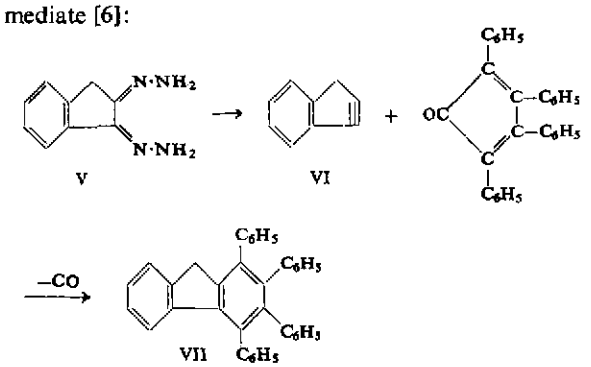
The yields of the various adducts, obtained under identical conditions, are shown in Table 1.

Table 1. Yields of cycloalkyne/2,5-diphenyl-3,4-benzofuran adducts

Method Material	Grignard reaction	Bishydrazone oxidation
Cycloheptyne	64 %	26 %
Cyclohexyne	50.5 %	7.0 %
Cyclopentyne	2.1 %	0.5 %

The two entirely different procedures both give yields which decrease proportionately with decreasing ring size, hence the presence of side-reactions, which might occur preferentially to the formation of cycloalkynes, may be ruled out. It is more likely that the cycloalkynes are true intermediates which decompose faster, the fewer the number of members in the rings and thus, their life spans decrease in the same order. Reactions leading to decomposition of the cycloalkynes include rearrangement to cycloallenes and cycloalkanedienes, as already noted by Russian investigators [1], and trimerization to benzene derivatives. All of these reactions are favored by the rapidly increasing ring strain.

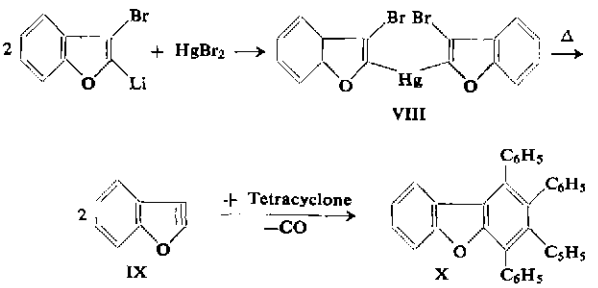
An additional increase in the strain of cyclopentyne is to be expected if another C = C bond is introduced into the five-membered ring. Although there appeared to be no prospect of establishing the occurrence of a derivative of cyclopentyne, an effort was made to prepare its relative, indyne (VI), by oxidizing the corresponding bishydrazone with manganese dioxide and to capture the latter in the presence of tetracyclone. Surprisingly enough, it was possible to isolate an adduct (VII) in 2 % yield. Consequently, VI must have been an intermediate [6]:



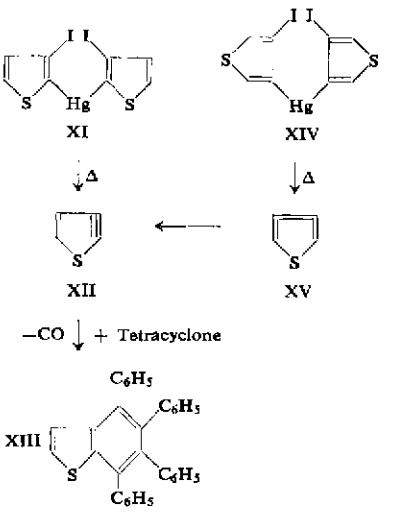
[5] *G. Wittig* and *T. F. Burger*, Liebigs Ann. Chem. *632*, 99 (1960).

[6] *G. Wittig* and *H. Heyn*, unpublished experiments.

This discovery prompted us to introduce triple bonds into heterocyclic five-membered rings. Being dehydroaromatic compounds – similar to benzyne to be discussed below – it may be expected that these would have relatively longer lives. Here, 2,3-dehydrocoumarone, postulated as a possible intermediate by *Stoermer* [7] in 1902 seemed of particular interest. 2-Lithium-3-bromocoumarone, although relatively stable at room temperature [8], proved to be unsuitable for preparing IX, but its mercury derivative VIII gave the adduct X in 70 % yield, when fused with tetracyclone, thus indicating the transient existence of dehydrocoumarone [9]:



2,3-Dehydrothiophene has also been obtained in this manner. Again, 2-lithium-3-iodothiophene proved to be surprisingly unreactive, but the bis-3-(iodothienyl-2-) mercury (XI) prepared from it combined on heating with tetracyclone to form tetraphenylthionaphthene (XIII) via its precursor dehydrothiophene (XII) [10]:



Interestingly enough, compound XIV, an isomer of XI, yielded the same adduct (XIII) under these conditions. Since rearrangement of XIV into XI was ruled out with a considerable degree of certainty, it may be assumed that the 3,4-dehydrothiophene (XV) initially formed,

[7] *R. Stoermer* and *B. Kahlert*, Ber. dtsch. chem. Ges. *35*, 1633 (1902).

[8] *G. Wittig* and *G. Kolb*, unpublished.

[9] *G. Wittig* and *H. Boos*, unpublished; according to Anglo-American nomenclature, compound IX would be named "coumaryne".

[10] *G. Witfig* and *V. Wahl*, Angew. Chem. *73*, 492 (1961).

having cumulative double bonds in a five-membered ring, isomerizes into XII, which is less strained, and then gives a Diels-Alder reaction [10]. These studies have not yet been completed.

Dehydrobenzene (Benzyne)

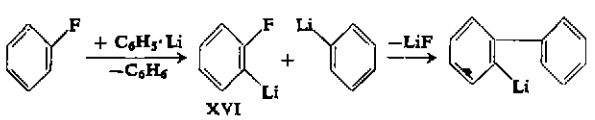
In its capacity as an aromatic system, thiophene has properties resembling those of benzene, which can also be dehydrogenated. Dehydrobenzene (XVII) and its derivatives have been studied in several laboratories. In retrospect, three phases of experimentation emerge:

1. Studies extending over a number of years by *Wittig* [11] on the action of organolithium compounds on halides led to the discovery of *ortho*-metalation, and the highly increased reactivity of the halide anion. As early as 1942, this effect suggested the concept of "dehydrobenzene" in the field of aromatic compounds; "dehydrobenzene" ought to appear following *ortho*-metalation. Related to this problem is the knowledge, gained using aliphatics, that anionization of the halide is accompanied by elimination of the halogen to yield a carbene [12].

2. Between 1954 and 1959, the symmetrisation effect of the "aryne" linkage was demonstrated experimentally, thus helping to explain the isomerizations observed during metalation of aromatic halides [13].

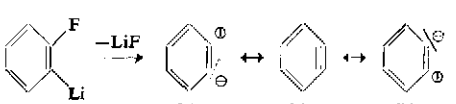
3. During the last few years, efforts have been directed at finding out whether dehydrobenzene really occurs as a true intermediate, or whether it is merely a transition state of one of the reaction components.

We shall now discuss the chemistry of the processes, insofar as they seem to be related to the dehydrobenzene problem. Fluorobenzene reacts much faster with phenyl-lithium than the other halobenzenes to form diphenyl, because the fluorine ligand favors *ortho*-metalation because of its particularly strong inductive effect:



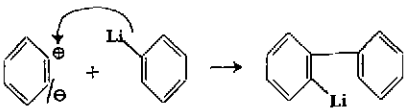
XVI

The conspicuous feature of the process was the fact that the fluorine in XVI becomes so highly anionically mobile that in the subsequent condensation *o*-lithium

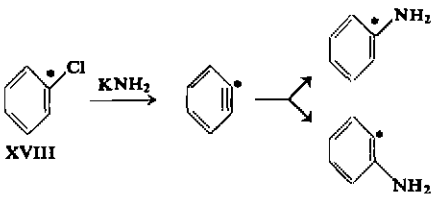


XVII

diphenyl is formed rapidly as identified product. This may be explained by considering that an energy-releasing mesomerization between the two dipolar extremes (a) and (b) facilitates elimination of lithium fluoride and that the remaining phenyl-lithium combines with dehydrobenzene in a nucleophilic addition:



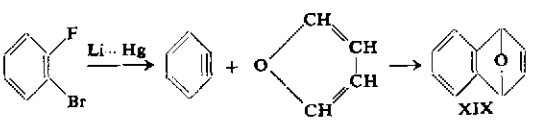
This hypothesis requires that, in accordance with the mesomerization XVIIa ↔ XVIIb ↔ XVIIc, the nucleophilic agent must attack both *ortho* positions involved in the resonance, distributing itself symmetrically. As early as 1953, in independent studies, *Roberts* et al. [14] caused C^{14}-labelled chlorobenzene (XVIII) to react with potassamide and proved that a 50 % yield of each of the expected anilines was produced.



XVIII

Huisgen and *Rist* [15] demonstrated in 1955 that in the case of 1- and 2-fluoronaphthalene, reaction between fluoroaromatics and phenyl-lithium involves symmetric addition of the phenyl anion onto two vicinal carbon atoms (*ortho* to each other). Dehydronaphthalene is very probably an intermediate.

If dehydrobenzene does actually occur as a reaction intermediate, then it should possess dienophilic properties because of its reactive triple bond in the strained aromatic ring. That this was actually the case was shown by *Wittig* and *Pohmer* [16], when *o*-fluorobromobenzene was reacted with lithium amalgam in furan. 1,4-Dihydronaphthalene-1,4-endoxide (XIX) was produced:



XIX

Using *o*-fluorobromobenzene and magnesium in tetrahydrofuran as dehydrobenzene source, it was possible to carry out a series of *Diels-Alder* reactions; for example, the synthesis of triptycene, which was first prepared by

[11] *G. Wittig*, Naturwissenschaften *30*, 696 (1942); Angew. Chem. *69*, 245 (1957).

[12] *J. Hine*, J. Amer. chem. Soc. *72*, 2438 (1950); *W. v. E. Doering* and *A. K. Hoffmann*, ibid. *76*, 6162 (1954).

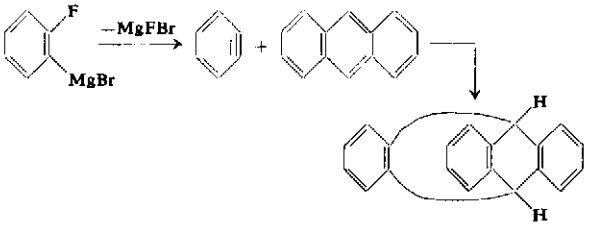
[13] *J. D. Roberts* et al., J. Amer. chem. Soc. *78*, 601 (1956); *J. F. Bunnett* and *T. K. Brotherton*, ibid. *78*, 6265 (1956); *R. Huisgen* and *J. Sauer*, Chem. Ber. *91*, 1453 (1958).

[14] *J. D. Roberts* et al., J. Amer. chem. Soc. *75*, 3290 (1953); *Roberts* proved analogously (Tetrahedron *1*, 343 (1957); J. Amer. chem. Soc. *82*, 4750 (1960)) that the C≡C linkage in cycloalkynes with small rings has symmetrizing properties.

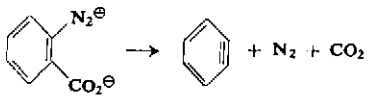
[15] *R. Huisgen* and *H. Rist*, Liebigs Ann. Chem. *594*, 137 (1955).

[16] *G. Wittig* and *L. Pohmer*, Chem. Ber. *89*, 1334 (1956); since then, intermediate occurrence of 3,4-dehydropyridine and 3,4-dehydroquinoline via addition of furan has been demonstrated by *T. Kauffmann* and *F. P. Boettcher*, Angew. Chem. *73*, 65 (1961); *T. Kauffmann*, *F. P. Boettcher*, and *J. Hansen*, ibid. *73*, 341 (1961).

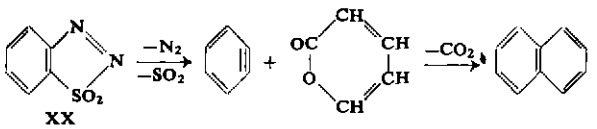
Bartlett et al. [17] using a seven-stage reaction scheme [17]:



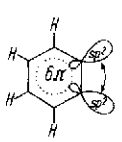
Subsequently, new reactions involving formation of dehydrobenzene were found. *Stiles* and *Miller* [18] degraded the long known compound benzenediazonium-2-carboxylate to the endoxide XIX by heating it in furan:



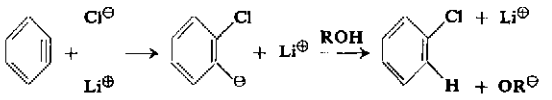
Benzothiadiazole dioxide (XX), prepared by *Wittig* and *Hoffmann* [19], proved more effective; it is converted into dehydrobenzene even at 0 °C, with elimination of nitrogen and sulfur dioxide. With furan, XX forms XIX and with anthracene, it forms triptycene. Furthermore, this method of preparation permits reactions which do not occur with the organometallic compounds described above. In ethanol, phenetol is formed; phenylazide gives 1-phenylbenzotriazole, and reaction with coumalin gives naphthalene:



The ester group in coumalin is not attacked by organometals, as would be expected in the reaction with *o*-fluorophenyl-lithium or from an influence of the dipolar extreme of dehydrobenzene (XVIIa). This indicates that XVIIa or XVIIb only comes into play under the influence of the nucleophilic partners (*e.g.*, the phenyl or amide anion), that there is a carbon-to-carbon triple bond in the ground state of dehydrobenzene, and that, because of ring strain, there is only a sparse overlap of the sp^2 orbitals entering into the aromatic 6 π-electron system, as suggested by *R. Huisgen* and *J. Sauer* [20]:

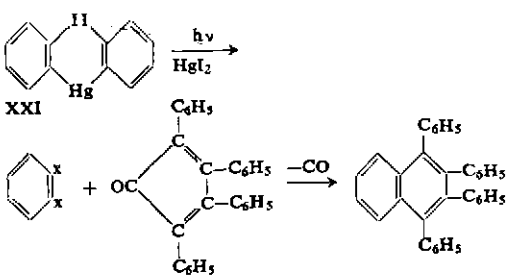


Dehydrobenzene prepared from XX forms phenetole in ethanol, but in solutions containing lithium chloride mainly chlorobenzene, and only a little phenetole, are formed. The chlorobenzene arises from nucleophilic attack of the chlorine anion upon XVIIa with subsequent alcoholysis of the anion being formed:

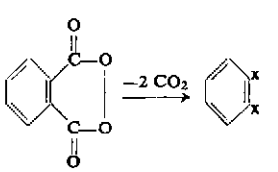


It may be assumed that the elimination of lithium halide to give dehydrobenzene following the metalation of aromatic halides [XVI (Cl instead of F) → XVII] is reversible [21]. An ethanolic solution of XX, to which equimolar amounts of lithium chloride, bromide, and iodide were added, formed only a little phenetole, and chloro-, bromo- and iodobenzene in the ratios 1:8:66, with a total yield of about 50 %, based on the original equimolar quantity of XX. These yields reflect the increasing nucleophilic nature of the halide partners up to the iodide anion.

Dehydrobenzene is also formed under conditions in which a short-lived biradical – whether in the singulet or triplet state – is to be expected, as follows from the decomposition of bis-*o*-iodophenylmercury (XXI) in benzene solution, which can only be brought about by photolysis and which leads to the formation of tetraphenyl-naphthalene in the presence of tetracyclone [22]:



The same transformation occurs when phthaloyl peroxide replaces XXI [23]:



All these reactions probably involve dehydrobenzene as an intermediate and together, they infer that a compound with the impermissible name "cyclohexadienyne" [*] does make a brief appearance. However, a strict proof would require the preparation and identification of "naked" i.e. gaseous dehydrobenzene. As soon as a sufficiently large number of stable starting compounds became available, we tried to produce this gaseous form of dehydrobenzene.

In order to prepare gaseous dehydrobenzene by thermal means, a recycling apparatus was constructed, where the

[17] *P. D. Bartlett* et al., J. Amer. chem. Soc. *64*, 2649 (1942).

[18] *M. Stiles* and *R. G. Miller*, J. Amer. chem. Soc. *82*, 3802 (1960).

[19] *G. Wittig* and *R. W. Hoffmann*, Angew. Chem. *73*, 435 (1961).

[20] *R. Huisgen* and *J. Sauer*, Angew. Chem. *72*, 91 (1960).

[21] *G. Wittig* and *R. W. Hoffmann*, unpublished; *H. Dürr* (thesis p. 34–36, Heidelberg, 1961) isolated 3–4 per cent chlorobenzene from a reaction of *o*-fluorobromobenzene with magnesium in tetrahydrofuran in the presence of lithium chloride; this is another proof of the reversibility of the elimination and addition of metal halides in the dehydrobenzene system.

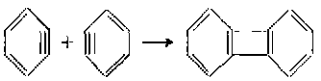
[22] *G. Wittig* and *H. F. Ebel*, Angew. Chem. *72*, 564 (1960).

[23] *F. D. Greene*, J. Amer. chem. Soc. *78*, 2246 (1956).

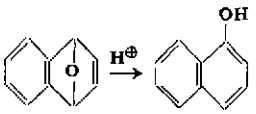
[*] Just as benzene is not "cyclohexatriene".

intermediate product was synthesized and subsequently captured under high vacuum in argon [24].

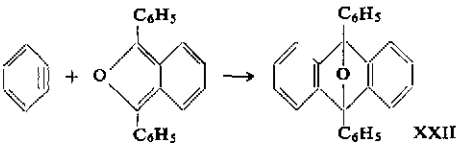
First of all, we studied the mercury derivative XXI and phthaloyl peroxide, which sublimed without decomposition at 5 mm. Hg and 90 °C and which gave off mercuric iodide and carbon dioxide, respectively, at 600 °C. Nearly pure biphenylene, accompanied by traces of triphenylene (identified by gas chromatography), appeared in the cooled receiver at the outlet from the quartz tube. Apparently, dehydrobenzene was formed, but it combined to form biphenylene by collision of two gaseous molecules:



A further proof of the intermediate occurrence of gaseous dehydrobenzene was obtained from the fact that furan, admitted into the tube behind the decomposition zone, combined with dehydrobenzene to form the endoxide XIX. The latter could not be identified directly, but only via its isomerization product, α-naphthol, which was identified by its 3,5-dinitrobenzoate. The isomerization of the endoxide in the presence of acids was already known [15]:



Having proved the existence of gaseous dehydrobenzene, the possibility of examining the compound physically was brought closer. Dehydrobenzene, formed from *o*-fluorobromobenzene with magnesium in tetrahydrofuran under the conditions given above for 1,2-dibromocycloalkenes, reacts with diphenylbenzofuran to give the adduct XXII in high yield (85 %) [25]:



One may therefore speculate that the increased stability and lifetime might somehow be connected with resonance – perhaps only slight – between the aromatic 6-π-electron system and the two sp^2 orbitals of the triple bond lying in the plane of the benzene nucleus.

Meanwhile, *Berry*, *Spokes* and *Stiles* [26] succeeded in decomposing benzenediazonium carboxylate by short wave ultraviolet irradiation and in delineating the UV spectrum of dehydrobenzene. Details of the interpretation of the spectrum are still lacking however.

We must therefore wait until physical investigations can provide more information about the form and lifetime of gaseous dehydrobenzene. We find ourselves in exactly the same situation that exists with carbene. Perhaps a better understanding of the subject – but this is still wishful thinking – may even enable us to describe and elucidate the resonance states of (bis-dehydro)-benzene C_6H_2, – an attempt in which we have long been unsuccessful [27] – and ultimately, even of (tris-dehydro)benzene, C_6, as a unit of graphite.

Received, February 20th, 1962 [A 193/25 IE]

[24] *G. Wittig* and *H. F. Ebel*, Liebigs Ann. Chem. *650*, 20 (1961), see p. 25.

[25] *G. Wittig* and *E. Knauss*, Chem. Ber. *91*, 902 (1958).

[26] *R. S. Berry*, *G. N. Spokes* and *R. M. Stiles*, J. Amer. chem. Soc. *82*, 5240 (1960).

[27] *G. Wittig* and *H. Haerle*, Liebigs Ann. Chem. *623*, 23ff. (1959).

Elastomeric Fibers Based on Polyurethanes [*]

BY DR. H. RINKE

FARBENFABRIKEN BAYER AG., LEVERKUSEN (GERMANY)

Highly elastic polyurethanes suitable for fiber production can be obtained by various synthetic routes based on diisocyanate polyaddition processes. Macrodiisocyanates obtained from long chain diols and diisocyanates are allowed to react with polyamines during fiber formation (chemical spinning process) or the macrodiisocyanates are treated in solvents (e.g. dimethylformamide) with polyamines to give highly viscous, spinnable solutions of polymer. Both methods yield highly elastic polymers with wide-mesh network structures. The production of polyurethane fibers and their structures and physical properties are described.

Introduction

Up to the present, elastic threads have either been cut from vulcanized rubber sheets or spun from latex or rubber solutions containing sulfur, fillers, and vulcanization accelerators; the solutions were spun through spinnerets into baths and finally vulcanized. The starting material in every case, however, was rubber. In this age of completely synthetic fibers, it was inevitable that chemists would attempt to develop highly elastic fibers with properties possibly better than those of natural rubber.

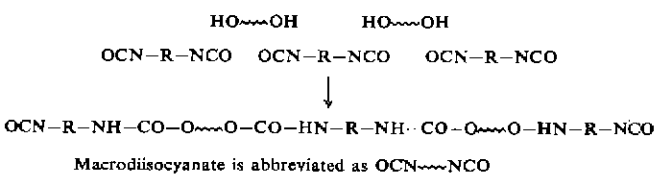
An important beginning was provided by the "Vulkollan principle" based on the polyaddition of diisocyanates

[*] From a report delivered on April 10th, 1962 at the meeting of the GDCh-Fachgruppe "Kunststoffe und Kautschuk" (Plastics and Rubber Group of the German Chemical Society) in Bad Nauheim.

developed by *O. Bayer* and co-workers. According to the Vulkollan principle, elastomers can be prepared which are distinguished from diene polymers by their high tensile strength and tear resistance (notch test), *etc.* The starting materials are long chain dialcohols, diisocyanates, and so-called "extenders". The products are high polymers with a crosslinked structure, which possess more or less high rubber like elasticity, depending on the degree and type of crosslinking. In order to obtain an elastomer with the best possible properties, it is indispensable to have as uniform a network as possible.

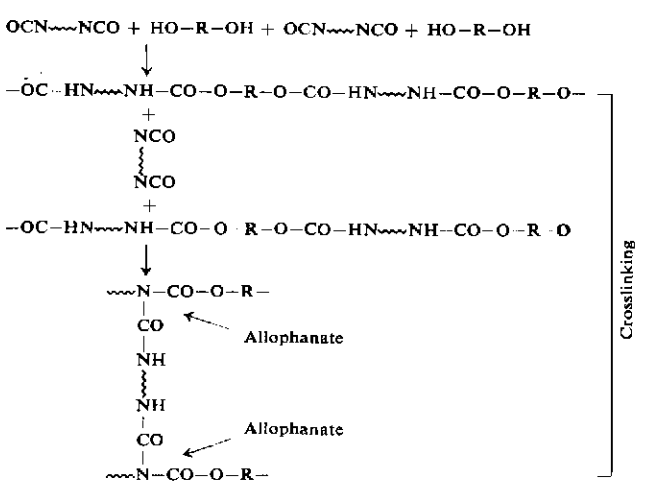
Synthesis of Polyurethanes

Chain formation is brought about in the following way: a linear polyester of adipic acid and ethylene glycol of an average molecular weight of 2000–3000 and with a free OH group at each chain end, is reacted with a diisocyanate in a molar ratio of about 2:3. An essentially linear macrodiisocyanate with an average molecular weight of 4000–6000 is formed. Naturally, a mixture of homologous polymers is obtained.



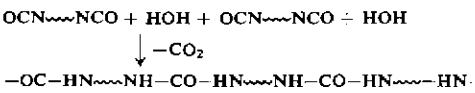
Macrodiisocyanate is abbreviated as OCN~~NCO

In order to secure the highest molecular weights possible the macrodiisocyanate is allowed to react with a bifunctional, low molecular weight substance, such as a glycol, in an amount somewhat less than the quantity corresponding to the number of free isocyanate groups, so that free isocyanate groups will still be available for crosslinking.

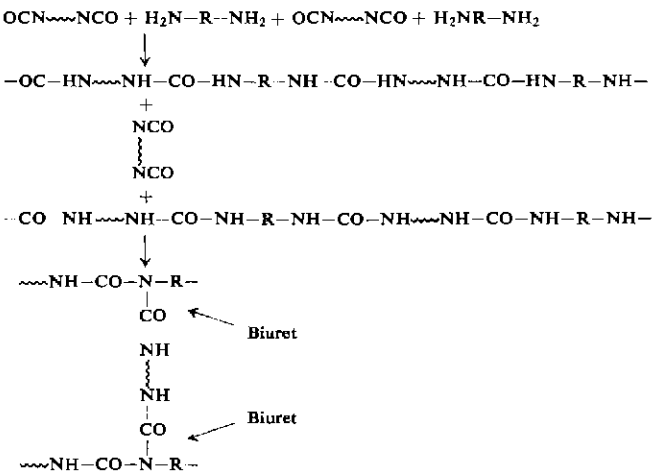


During crosslinking, the remaining free isocyanate groups react with the hydrogen atoms in the urethane linkages formed during the polyaddition of the macrodiisocyanates onto glycol to form allophanate groupings. Since the same macrodiisocyanate forms both the chains and the crosslinks, the network must possess a fairly regular mesh structure.

Water can also cause formation of high molecular substances with evolution of CO_2; these are then linked through urea groupings:



The macrodiisocyanates can also be extended with diamines. This reaction, however, is much more vigorous than the extension with glycols or water. Primarily urea groups are

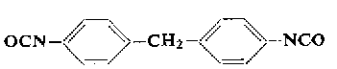


likewise formed, whose hydrogen atoms are quite easily substituted. The chain-building reaction with the bulk of the isocyanate groups is followed by the branching or crosslinking reaction with the remainder of the isocyanate groups. Networks are thus formed which are linked through biuret groups and have a uniform mesh structure. These elastomers possess the highest strengths and the lowest abrasion losses yet measured in rubbery elastic materials.

Polyurethanes with pendant reactive groups can also be crosslinked by vulcanization after having been shaped into fibers (see below).

Preparation of Highly Elastic Fibers

In order to prepare highly elastic fibers, amine crosslinking, which proceeds very rapid was used in our laboratory for the first time in 1949 [1]. In this "chemical" spinning method, the macrodiisocyanate melt is spun through nozzles into a bath of aqueous piperazine We used principally macrodiisocyanates made from polyesters and aliphatic diisocyanates; however, because of their rather low reactivity – particularly during crosslinking – too long a hardening time was required for the resulting threads. Later, a similar spinning method was developed by the U. S. Rubber Corp. [2] utilizing macromolecules of aromatic diisocyanates. The fibers are formed in baths containing diprimary aliphatic diamines. For this reaction, diphenylmethane-4,4′-diisocyanate (I) appears to be most suitable.

(I) 

[1] German Pat. 826641 (1949), Farbenfabriken Bayer; Inventor: *E. Windemuth.*

[2] French Pat. 1185093 (1957), U.S. Rubber; Inventors: *R. C. Kohrn, D. G. Plovin,* and *F. L. Bliven.*

On spinning the macrodiisocyanate into the amine bath, a relatively tough skin forms at once on the surface of the filament because of the rapid formation of a polyurea. This makes it possible to wind the filament after only a short reaction time. Since the polyurea skin inhibits further penetration of diamine, the wound filament is treated with warm water for a long time in order to make the interior of the freshly spun fiber equally hard. In this way, any portion of the macrodiisocyanate that is still not crosslinked is converted by the water into polyurea, with evolution of CO_2 (see above).

The elastic properties of the fiber can be increased in this "chemical" spinning process of macrodiisocyanates are used which have been heated for a lengthy period at about 100 °C in the absence of water [3]. Since such macrodiisocyanates contain substantially fewer free isocyanate groups than would be expected from the quantities of isocyanate and diol employed, it is assumed that isocyanate groups are used up in side reactions, as a result of which branching or crosslinking can then occur even more readily. It has, in fact, been found that the degree of crosslinking in fibers pretreated by spinning into diamine is considetably increased. This has a particularly favorable effect on the restoring force which returns a stretched fiber to the unstretched condition.

A further increase in the degree of crosslinking is achieved by hardening the macrodiisocyanate with polyfunctional amines, *e.g.*, diethylenetriamine. The fraction of this polyamine in the hardening bath must not be too great, however, lest the extensibility and the flexibility of the fibers be reduced.

"Chemical" spinning thus allows the preparation of highly crosslinked filaments, which cannot be obtained directly, for example, by extrusion of a highly prepolymerized mass. The elastomeric fiber produced according to this principle by the U. S. Rubber Corp. is called Vyrene®.

In 1951, we observed that, despite their crosslinked structure, polyurethane elastomers can be dissolved in highly polar solvents such as dimethylformamide [4]. Admitted, the elastomers must not be too strongly crosslinked. By injecting such an elastomer solution into a precipitating medium such as water, threads can be obtained whose elastic properties are practically identical with those of the original elastomer. This method, however, fails to give reproducible results and hence has not gained popularity. Nonetheless, the information derived from this work has made valuable contributions to the synthesis of spinnable elastomeric polyurethanes in solvents.

Chemists at DuPont utilized polytetrahydrofurans with hydroxyl end-groups, as synthetized by *Meerwein* [4a] in place of the hydroxy polyesters. These are naturally less susceptible to attack by hydrolytic agents. It was further observed that highly elastic polyurethanes are obtained on direct reaction of macrodiisocyanates with diamines in highly polar solvents such as dimethylformamide or dimethyl sulfoxide [5]; however, the quantity of diamine must correspond exactly to the quantity of isocyanate present. In principle, only a linear extension of the chains can occur in this manner, since no more free isocyanate groups are available for crosslinking. Polyurethanes prepared in this manner remain soluble and can be formed into films and fibers. The reaction with diamines, which takes place rapidly even at room temperature, occurs with both polyester- and polyether macrodiisocyanates. For its Lycra® fiber, DuPont prefers dihydroxypolyethers with a molecular weight of about 1000, which are then extended with a mixture of isomeric toluenediisocyanates, so that dihydroxy polyethers are produced, which contain urethane groups and which have an average molecular weight of 2000. The extended chains are probably sterically more irregularly constructed; this sometimes leads to improved elastic properties.

The macrodiisocyanate is formed by the action of two moles of diphenylmethanediisocyanate on one mole of previously extended polyether at approximately 100 °C. The duration of the reaction and the activity of the polyether are of special importance, since there is a tendency for branch formation to occur during this reaction *e.g.*, through allophanate linkages. The macrodiisocyanate is then dissolved in anhydrous dimethylformamide and, after a determination of the free isocyanate groups, the calculated quantity of an aliphatic diamine is added. Hydrazine is also suitable here. It is clear that the high velocity of this reaction demands a particularly intensive mixing of the components, but few details are known. Very viscous solutions of high polymeric materials containing a considerable quantity of urea groupings along with urethane groups are produced. Such solutions can be spun into very fine, highly elastic fibers, using spinning processes similar to those used for poly(acrylonitrile) or cellulose acetate fibers. The preparation and handling of these soft, highly elastic filaments pose many new problems in processing technology, which can only be solved with difficulty if currently available spinning apparatus is to be used.

Makrodiisocyanate

$$\underset{\text{Extender}}{\overset{\text{OCN}\sim\text{NCO} + \text{OCN}\sim\text{NCO} + \text{OCN}\sim\text{NCO}}{\overset{\text{H}_2\text{N}-\text{R}-\text{NH}_2 \qquad \text{H}_2\text{N}-\text{R}-\text{NH}_2}{\downarrow}}}$$

$$[\text{OC}-\text{HN}\sim\text{NH}-\text{CO}-\text{NH}-\text{R}-\text{NH}-\text{CO}-\text{NH}\sim\text{NH}-\text{CO}-\text{NH}-\text{R}-\text{NH}-\text{CO}-\text{NH}\sim\text{NH}-\text{CO}]_n$$

Structure of Polyurethane Filaments

The filaments obtained in the dry spinning process have a dumbbell-shaped cross section (Fig. 1), by which they can be distinguished from other filaments, *e.g.* from polyacrylonitrile, spun by the same method.

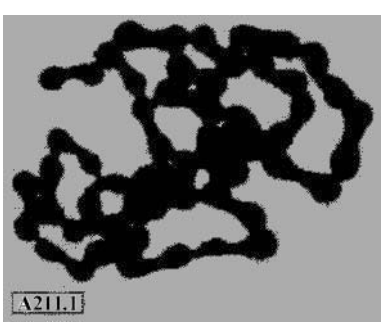


Fig. 1.
Cross section of a dry-spun polyurethane filament

[3] Belgian Pat. 587060 (1960), U.S. Rubber; Inventor: *V. S. Urs.*

[4] German Pat. 888766 (1951), Farbenfabriken Bayer; Inventor: *W. Brenschede.*

[4a] *H. Meerwein, D. Delfs,* and *H. Morschel,* Angew. Chem. *72,* 927 (1960).

[5] U.S.-Pat. 2929804 (1955), DuPont; Inventor: *N. Steuber*; Belgian Pat. 574488 (1959), DuPont; Inventor: *R. J. Schilit.*

The filaments so produced have remarkable physical properties (Fig. 2). In particular, the tensile strength and the force required for stretching may be as much as double the values obtained previously for vulcanized rubber.

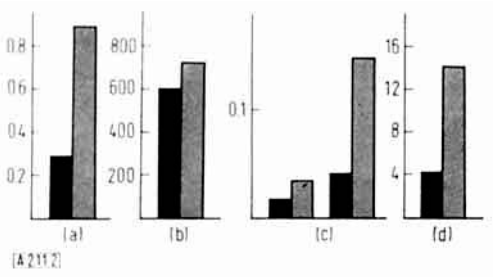


Fig. 2. Physical properties of dry-spun polyurethane filaments (hatched areas) in comparison with vulcanized rubber filaments (solid areas).

(a) Tensile strength [g/den]; (b) Elongation [%] at breaking point; (c) Modulus of elasticity [g/den] left, at 150 % elongation, right, at 300 % elongation; (d) Permament elongation [%] after 300 % stretch.

The comparison of the physical properties raises the question of how to explain the strong elasticity, since the preparation of the polymers in a solvent and their shaping therein do not permit (to any significant extent) the kind of crosslinking called for in the previous discussion of Vulkollan.

Just as strong hydrogen bridges form in polyamide fibers between the CO and NH groups of neighboring molecular chains (Fig. 3), the urea groups occurring regularly along the polymer chain provide an opportunity for formation of hydrogen bridges. In place of chemical crosslinking through sulfur bridges of known diene polymers, here crystalline regions occur (at least in part) whose strong residual valence forces provide, so to speak, physical crosslinks. It is therefore possible to dissolve these polymers in polar solvents, which themselves can form strong hydrogen bonds.

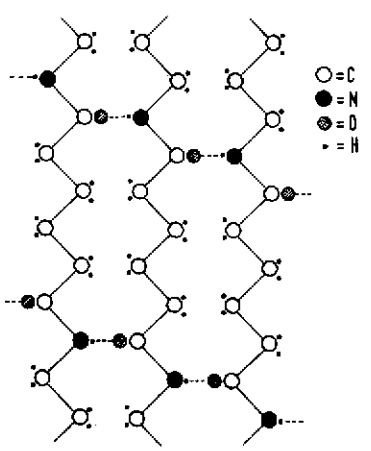
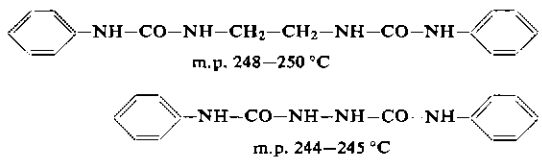


Fig. 3. Structure of a polyamide (schematic)

These crystalline regions appear also to be of importance for the heat resistance of these elastomeric fibers. Since at least 75 % of the mass of the filament consists of polyesters or polyethers melting at 20–50 °C, the crystalline regions must exhibit very high melting points if they are to impart to the elastomers a resistance to temperatures of 170–200 °C sufficient for practical use. That this is actually the case can be shown on comparing the melting points of some diphenylureas which can be looked upon as representing the urea bridges separated out of the polymer chains.



X-ray investigations have shown that particularly elastomer filaments containing polyether components and exhibiting practically no crystallinity in the unstretched condition become oriented on stretching, whereupon a pseudocrystalline structure arises [6] which can be photographed with a monochromatic beam (Fig. 4).

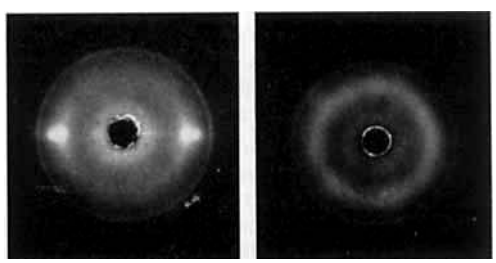


Fig. 4. X-ray diffraction of polyurethane elastomers (a) unstretched; (b) stretched.

In these pseudocrystalline regions, the chain segments which contain urea groups lie parallel to each other and are bound laterally – *i.e.* approximately at right angles to the molecular chains – by forces which may be of the same order of magnitude as those in perfect crystal lattices.

From consideration of the high reactivity of the isocyanate groups, it must be assumed that, besides the linear alternation of polyester or polyether and urea bonds, the polymers undergo a certain degree of crosslinking even in solution. Naturally, this crosslinking

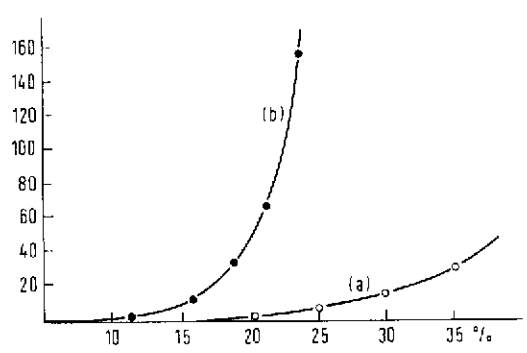


Fig. 5. Viscosity of polyurethane elastomers as a function of concentration.

Curve a: $[PE + 44]_n$; Curve b: $[44 + PE + 44 + H_2N{-}NH_2]_n$.
PE = Poly(ethylene adipate), molecular weight 2000
44 = Diphenylmethane-4,4'-diisocyanate

Ordinate: Viscosity [poise]
Abscissa: Concentration [%] by wt. in dimethylformamide

[6] *H. G. Kilian*, private communication.

must not lead to gel formation, because spinning would thus be made difficult or even impossible. That such crosslinking does indeed exist may be seen from the viscosity-concentration curves (Fig. 5).

In Fig. 5, Curve refers to a polyurethane prepared under mild conditions from one mole of polyester and one mole of diphenylmethanediisocyanate. Curve refers to a macrodiisocyanate from the same substances, which has been extended with hydrazine in dimethylformamide It is very striking that the viscosity of polymer increases much more rapidly with concentration than the viscosity of the polyurethane a. This rheological difference may be due to entanglements of the coils of molecules caused by very wide mesh crosslinking within the elastomer solution.

These differences appear even more distinctly if the viscosity of dilute solutions of these polymers in hexamethylphosphoramide is considered (Fig. 6). One per cent solutions of polymers a and have similar viscosities at room temperature. These viscosities do not change on prolonged standing at room temperature.

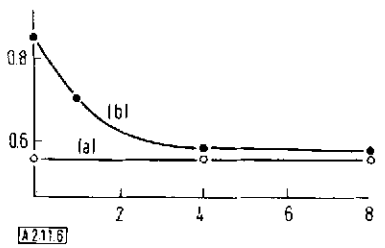


Fig. 6. Viscosity of dilute polyurethane solutions, warmed to 80 °C, as a function of time.

Solvent: $OP[N(CH_3)_2]_3$. Concentration: 10 g/liter

Explanation of a and b: see caption to Fig. 5.

Ordinate: Viscosity $[\eta] = \frac{\ln \eta_r}{c}$

Abscissa: Time [hours]

If these solutions are heated for several hours at 80 °C, however, the viscosity of solution a is not, or only slightly, changed whereas that of elastomer b is considerably lowered and reaches a constant value only after about four hours from the start of heating.

This behavior is easily explained if it is assumed that the urethane bonds forming the main chains in both polymers are not attacked, but that elastomer b contains thermolabile bonds, *e.g.* allophanate-type crosslinks, which are opened by the combined action of heat and the solvent. If the macrodiisocyanate is treated with an aliphatic diamine instead of with hydrazine, then somewhat more thermostable, probably biuret-type crosslinks are formed, which begin to break at 100 °C and then only slowly.

By comparing the molecular weights of fractionated portions of elastomeric polyurethanes some of which had undergone degradation on heating at 80 °C in a polar solvent, it was shown that the average molecular weight of a chain segment between two branching sites is probably 30000 to 40000. Polymers prepared according to this method therefore possess, a very wide mesh network, which explains the rheological properties of the spinning solution.

Du Pont's Lycra fibers are probably synthetized according to the scheme just discussed using a polar solvent, polybutylene ether with hydroxyl end-groups, toluenediisocyanate, diphenylmethanediisocyanate, and hydrazine [7]. Some further properties of this fiber will be presented below.

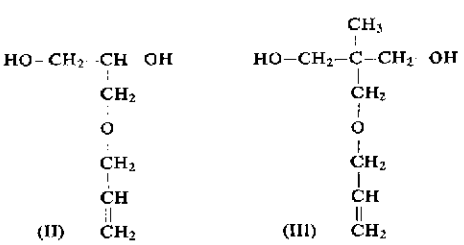
Preparation via Stable Intermediates

In addition to the methods described above, where elastomers which are suitable for filament production are prepared in solution or where the filaments are produced in several stages, methods have been developed whereby polyurethane intermediates which are stable enough to be stored can be transformed into highly elastic filaments by thermoplastic forming. In these intermediates, the macromolecules must exist in a kind of borderline condition between linear and crosslinked structures. This can be attained, for example, if the relative quantities of polyester, diisocyanate, and glycol are so selected during the chain-extending with glycol, that after this extension step only very few free isocyanate groups [8]. In this way, high molecular weight linear products are obtained which are very stable on storage, and whose residual isocyanate groups react only during or after a brief thermoplastic deformation upon prolonged heating at about 110 °C. As a consequence of this vulcanization-like process, the degree of crosslinking is increased and the elastic properties are significantly improved [9].

Crosslinking by Vulcanization

Finally, crosslinking which leads to elastomeric filaments can occur by a vulcanization process independent of the fiber's basic material. When sulfur is used, the storable intermediates must contain reactive double bonds. This is achieved by employment of the polyester of unsaturated components such as maleic or fumaric acids during the preparation. The polyester is then converted into a high molecular weight polyurethane by means of an equimolar quantity of a diisocyanate [10].

Another possibility is the polyaddition of toluenediisocyanate onto a mixture comprising polybutylene ether and a branched diol containing a reactive double bond



[7] U.S.-Pat. 2957852 (1955), DuPont; Inventors: *P. E. Frankenburg* and *A. H. Frazer*.

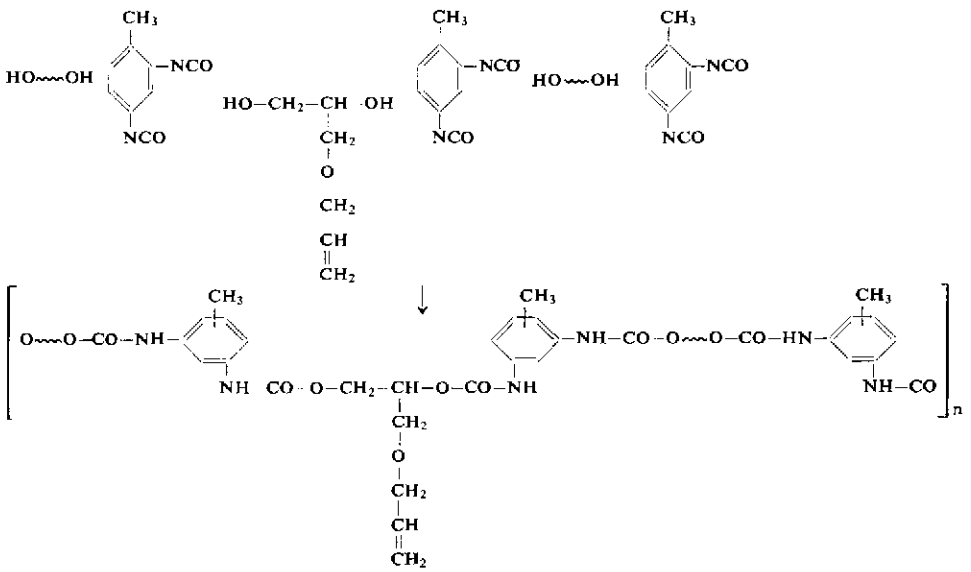
[8] German Pat. 831772 (1959), Farbenfabriken Bayer; Inventors: *E. Müller, H. F. Piepenbrink, F. Schmidt*, and *E. Weinbrenner*.

[9] Modern Plastics, March 1961, p. 88.

[10] German Pat. 863403 (1944), Farbenfabriken Bayer; Inventors: *E. Müller, O. Bayer*, and *H. F. Piepenbrink*.

in the side chain [11]. Such diols are, for example, glycerol-1-allyl ether (II) or 2-allyloxymethyl-2-methyl-1,3-propanediol (III).

The product evidently has optimum properties if two moles of polybutylene ether, one mole of diol with a side-chain double bond, and three moles of toluene-diisocyanate are permitted to undergo polyaddition at 80–100 °C. The resulting plasto-elastic product can be processed further by the customary methods of the rubber industry: it is treated with sulfur and the conventional auxiliaries by passing through rubber rollers,



plasticized in compounders with a readily volatile solvent, and, in the form of a viscous fluid mass, forced through spinnerets in extruders. The filaments are then heated for a long time at 120–140 °C, so that vulcanization can take place.

It can be calculated from the formulation that there is a chain segment with an average molecular weight of about 3000 between successive vulcanizable double bonds. The degree of crosslinking can be enhanced by increasing the double bonds, but the products are then generally harder and less elastic. The vulcanized filaments have good elastic properties, closely approaching those of rubber. It is conceivable that the strong chemical crosslinks are primarily responsible for this.

Properties of Polyurethane Fibers

The tensile strengths of polyether and polyester filaments lie, on the average, between 0.5 and 0.8 g/den (600–900 kg/cm²; rubber fibers are about 300 kg/cm²) with an extensibility of 600 to 700 %. The force required to extend these filaments is two to four times that required for rubber. This has the advantage that even relatively thin filaments may possess the same tensile strength as thicker rubber fibers. The elastic recovery is generally good, although that of rubber filaments is somewhat better. The two types of fiber differ in their resistance to hydrolysis, such as that caused by too intensive washing. Since the elastomers containing polyester are less resistant to this type of attack.

Changes occurring in the synthetic elastomer filaments on exposure to sunlight (discoloration, loss of strength) are caused primarily by the sensitivity of the methylene group in diphenylmethanediisocyanate. Photostabilizers which are added to the spinning solutions, absorb the destructive portion of ultraviolet light (between 3500 and 4000 Å), thereby increasing the fiber's resistance to light. In aging tests, especially aging under oxygen, all polyurethane elastomers prove to be remarkably resistant.

With the aid of new spinning methods, the denier of polyurethane fibers can be reduced to a range inaccessible with the older processes used in the manufacture of rubber fibers; such fineness would have had but little significance for rubber fibers any way, in view of their low elastic moduli. Since the polyurethane filaments are outwardly similar to fully synthetic fibers and can be readily dyed with many dyestuffs, there is a possibility of dyeing them together with other fiber constituents of a finished fabric in a single process. In this way, the problem of the unpleasant whitened appearance which is observed on stretching colored textiles containing undyed rubber threads can be overcome. Because of their dyeability, abrasion resistance, and resistance to perspiration and cosmetic oils, polyurethane filaments – in contrast to rubber ones – can be processed without first being coated or braided.

[11] German Pat. Application 1109363 (1956), DuPont; Inventor: *D. B. Pattison*.

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Copolymers and Fibers from Vinylidenedicarbonitrile [*]

BY B. S. SPRAGUE, H. E. GREENE, L. F. REUTER, AND R. D. SMITH

CELANESE FIBERS COMP., CHARLOTTE, N. C., U. S. A.

Vinylidenedicarbonitrile (Vinylidene cyanide) on free radical catalyzed copolymerization shows a much stronger tendency to form 1:1 alternating copolymers than acrylonitrile. While bulk poly(vinylidene cyanide) fails to crystallize, despite its molecular symmetry, several alternating copolymers are readily crystallizable, notably those containing butadiene, isoprene, isobutylene, or vinylidene chloride. Fibers have been prepared from a number of the higher melting copolymers and examined for physical properties. Fibers from the vinyl acetate and vinyl chloride copolymers show exceptional elastic behavior both when dry and wet The fiber from the vinylidene cyanide/vinyl acetate alternating copolymer (Darvan® nytril fiber) is only moderately oriented and is characterized by exceptional softness and excellent elastic recovery and resilience, both when dry and wet.

Introduction

Vinylidenedicarbonitrile (vinylidene cyanide) was first synthesized in the laboratories of the B. F. Goodrich Company in 1947 [1], and its synthesis and properties have been described by *Ardis* and co-workers [2]. It is a colorless liquid which boils at 150 °C and freezes at 9 °C; for comparison, acrylonitrile boils at 89 °C and freezes at −82 °C. The monomer is rather unusual in that it will polymerize readily by an ionic mechanism in the presence of very weak bases [3]. Any source of hydroxyl ion causes almost instantaneous conversion into low molecular weight poly(vinylidene cyanide). If properly stabilized, however, the monomer may be stored for long periods of time.

This paper will discuss the structure and properties of a series of copolymers prepared from vinylidene cyanide, and of fibers prepared from these copolymers. Appropriate comparisons will be made with acrylonitrile copolymers. Properties of a vinylidene cyanide/vinyl acetate alternating copolymer, and the fiber Darvan® will be considered in some detail.

Copolymerization Characteristics

The free radical catalyzed copolymerization of vinylidene cyanide with other monomers gives a striking demonstration of the unusual behavior of this material as compared to acrylonitrile [4]. With many comonomers, vinylidene cyanide shows a strong tendency to form alternating copolymers, rather than the random copolymers associated with the free radical copolymerization of acrylonitrile. The product of the reactivity ratios ($r_1 \times r_2$), as proposed by *Mayo* and *Lewis* [5], has been used to determine the tendency to form alternating copolymers, as shown in Table 1. As the product of the reactivity ratios approaches zero, the structure approaches perfect alternation, and conversely, as their product approaches unity, the copolymer approaches a completely random structure. The strong tendency of vinylidene cyanide to form alternating polymers with common comonomers is quite apparent.

Table 1. Reactivity ratio products of copolymer systems

Comonomer	$r_1 \times r_2$ with Vinylidene cyanide	$r_1 \times r_2$ with Acrylonitrile
Styrene	5×10^{-6}	9×10^{-3}
Butadiene	1×10^{-5}	2×10^{-2}
2-Chlorobuta-1,3-diene	7.7×10^{-5}	6.1×10^{-2}
Vinylidene chloride	5.9×10^{-5}	3.3×10^{-1}
Vinyl acetate	5.9×10^{-5}	4.2×10^{-1}
Methyl methacrylate	1.4×10^{-4}	2.4×10^{-1}
Vinyl chloride	1×10^{-2}	1×10^{-2}

$r_1 \times r_2 \rightarrow 1$: random
$r_1 \times r_2 \rightarrow 0$: alternating

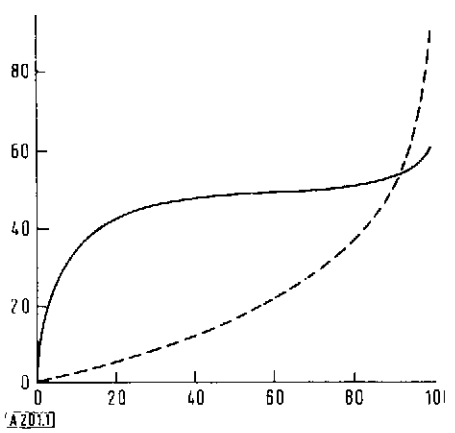


Fig. 1. Composition of copolymers from vinyl acetate and (——) vinylidene cyanide or (- - -) acrylonitrile.
Ordinate: Mole% vinyl acetate in polymer
Abscissa: Mole% vinyl acetate charged

[*] Lecture at the Meeting of the Gesellschaft Deutscher Chemiker, Section "Kunststoffe und Kautschuk", on April 10th. 1962 at Bad Nauheim (Germany).

[1] *H. Gilbert*, U.S.Patent 2514387 (1950).

[2] *A. E. Ardis* et al., J. Amer. chem. Soc. *72*, 1305 (1950).

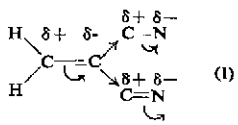
[3] *H. Gilbert* et al., J. Amer. chem. Soc. *76*, 1074 (1954).

[4] *H. Gilbert* et al., J. Amer. chem. Soc. *78*, 1669 (1956).

[5] *F. R. Mayo* and *F. M. Lewis*, J. Amer. chem. Soc. *66*, 1954 (1944).

The tendency of vinylidene cyanide to form copolymers of equimolar composition is also demonstrated by the relatively constant composition of vinylidene cyanide/vinyl acetate copolymers over a very wide range of monomer ratios in the starting mixture. This contrasts strongly, for instance, with the behavior of the acrylonitrile/vinyl acetate system, where the polymer's composition is very dependent upon the monomer ratio charged (Figure 1).

Gilbert [3] has ascribed the unusual polymerization properties of vinylidene cyanide to polarization of the π-electrons of the double bond and the C≡N triple bond (I).



(I)

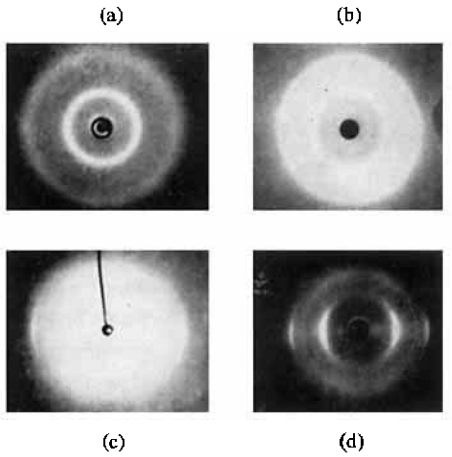
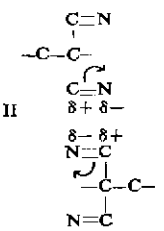


Fig. 2. X-Ray diffraction diagrams of bulk homopolymers and drawn fibers
a) Bulk poly(vinylidene cyanide)
b) Bulk poly(acrylonitrile)
c) Poly(vinylidene cyanide), drawn film
d) Poly(acrylonitrile), drawn fiber

Structure and Physical Properties of Copolymers

The symmetry of vinylidene cyanide might be expected to result in strong crystallization of the homopolymer, but surprisingly, X-ray diffraction powder diagrams indicate that poly(vinylidene cyanide) is less ordered than poly(acrylonitrile) (Figure 2). Even when highly drawn fibers or films are made from the homopolymers, the poly(vinylidene cyanide) behaves similarly to poly(acrylonitrile), displaying only high lateral order but no crystallinity, as indicated by the lack of reflections other than equatorial (Figure 2) [6]. It is probable that the low degree of crystallinity of poly(vinylidene cyanide) polymer and fiber results from the inability of the molecules to arrange themselves with sufficient 3-dimensional regularity, owing to the occurrence of numerous extremely strong intermolecular attractions, which set up a highly stable random network of chains, leading to an extremely high glass transition temperature. It is believed that the intermolecular attractive forces concerned are principally dipole-pair bonds such as have been described by *Saum* [7] for alkyl cyanides and dicyanides (II).



II

The ability to crystallize seems to be improved considerably with certain alternating copolymers. A series of such copolymers and their softening or crystalline melting points are given in Table 2. Comonomers such as butadiene, isoprene, chloroprene, and piperylene (which react by 1,4-*trans* additions), isobutylene and vinylidene chloride give rise to strong crystallinity in the bulk copolymer, whereas unsymmetrical comonomers such as styrene, vinyl chloride, and vinyl acetate do not (see Figures 3 and 4). It appears that overall symmetry of the copolymer molecule, together with some modification or reduction of the tendency of

Table 2. Properties of copolymers of vinylidene cyanide

Comonomer	Mole % comonomer in the copolymer	Crystallizable	Softening or melting pt. [°C]	Soluble in	Melt	
					Viscosity	Stability
Styrene	50	no	190	ketones	very high	good
Propylene	50	no	110	ketones	high	good
Isobutylene	50	yes	115	ketones	high	good
Butadiene	50	yes	270	hot dimethylformamide	low	very poor
Chloroprene	50	yes	155	dimethylformamide	low	poor
Isoprene	50	yes	180	hot dimethylformamide	low	very poor
Piperylene	50	moderate	110	ketones	low	good
Vinyl chloride	50	no	220	dimethylformamide	high	poor
Vinylidene chloride	50	yes	205	dimethylformamide	high	poor
Vinyl acetate	50	no	180	dimethylformamide	high	poor
Methyl methacrylate	55	no	130	ketones	high	excellent
Vinyl formate	50	no	175	dimethylformamide	high	poor

[6] *C. R. Bohn, J. R. Schaefgen,* and *W. O. Statton,* J. Polymer Sci. *55,* 531 (1961).

[7] *A. M. Saum,* J. Polymer Sci. *42,* 57 (1960).

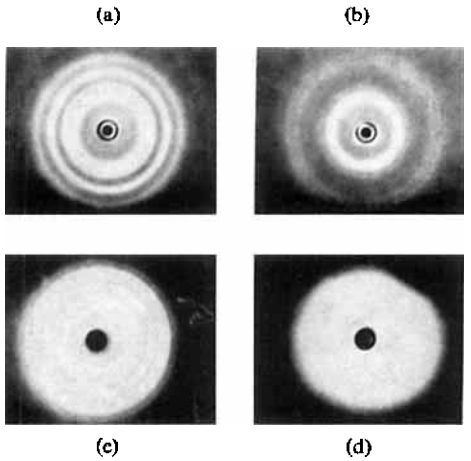


Fig. 3. X-Ray diagrams of symmetrical or stereoregular copolymers of vinylidene cyanide
a) Copolymer with butadien
b) Copolymer with vinylidene chloride
c) Copolymer with isoprene
d) Copolymer with piperylene

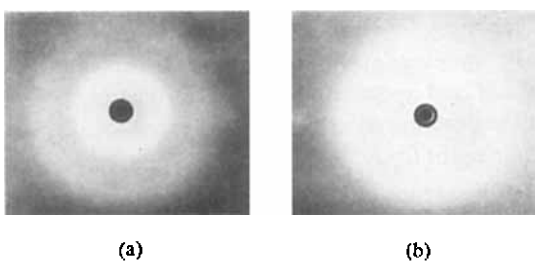


Fig. 4. X-Ray diagrams of unsymmetrical copolymers of vinylidene cyanide
a) Copolymer with vinyl acetate
b) Copolymer with styrene

vinylidene cyanide to form dipole-pair bonds, is required to promote crystallization in the bulk polymer. In no case do the corresponding 50 % acrylonitrile copolymers display crystallinity, although some lateral order is observed with the acrylonitrile/vinyl chloride copolymer (Dynel®) in fiber form. The butadiene/vinylidene cyanide copolymer has an exceptionally high melting point (270 °C), in contrast to the corresponding copolymer based on acrylonitrile. The latter is a rubber at room temperature, as are the other acrylonitrile/diene copolymers. A 50/40/10 vinylidene cyanide/butadiene/styrene terpolymer also crystallizes but has a significantly lower melting point. X-ray diffraction studies indicate that its crystallinity is associated only with the vinylidene cyanide/butadiene portions of the molecule.

It is of interest that the inclusion of a methyl group, as in copolymers with isoprene or piperylene, or a chlorine substituent, as with chloroprene copolymers, drastically modifies the crystalline melting point, even though sufficient stereoregularity is maintained to provide a crystallizable polymer.

Even with the non-crystallizable copolymers, very high softening points are attained as compared to the corresponding copolymers based on acrylonitrile. For example, the vinylidene cyanide/styrene copolymer softens at 190 °C, and the vinylidene cyanide/vinyl acetate copolymer at 180 °C, whereas the corresponding copolymers based on acrylonitrile are rubbery above 60–80 °C. The fact that copolymers with methyl methacrylate and vinyl formate soften at a somewhat lower temperature than the vinyl acetate copolymer is unexpected; this suggests that some interaction may occur between the cyanide group and adjacent group on the same chain.

Fibers from Vinylidene Cyanide Copolymers

While all of the copolymers discussed above are potential fiber formers, those with melting or softening points lower than 170–180 °C have been eliminated as being of little practical interest. In addition, poor melt stability and difficulty in obtaining sufficiently concentrated solutions for satisfactory solution spinning resulted in elimination of the butadiene and isoprene copolymers, while low yields eliminated the styrene copolymer from serious consideration. Fibers have been spun from the copolymers of vinylidene cyanide with vinyl chloride, vinylidene chloride, and vinyl acetate by solution techniques, and from the vinylidene cyanide/butadiene/styrene terpolymer by a modified melt spinning technique and assessed for mechanical properties, as shown in Table 3. Typical properties of a polyacrylonitrile fiber are listed for comparison.

While these small scale spinning experiments did not yield optimum fibers, the data obtained were sufficiently typical to indicate the most desirable copolymers for further study. In spite of the crystallizability of the vinylidene cyanide/vinylidene chloride copolymer, the fiber elongation is poor and its elastic behavior is not outstanding. In contrast, fibers from the vinylidene cyanide/vinyl chloride and vinylidene cyanide/vinyl acetate copolymers show remarkably good elastic behavior both when dry and wet. In fact, the wet elastic behavior is so important with respect to end-use performance that these two copolymers are by far the most

Table 3. Mechanical properties of fibers prepared from copolymers of vinylidene cyanide

Comonomer	Mole % comonomer in the copolymer	Tenacity [g./den.]	Elong. [%]	Modulus of elasticity [g./den.]	Elastic recovery from 3 % elongation [*]			
					dry		wet	
					TSR [%]	WR [%]	TSR [%]	WR [%]
Butadiene/styrene	40/10	3.0	14	40	51	37	43	28
Vinylidene chloride	50	2.8	6.5	34	55	33	—	—
Vinyl chloride	50	1.6	19	45	79	45	68	38
Vinyl acetate	50	2.0	30	34	70	35	70	34
Poly(acrylonitril)	100	2.7	30	47	64	25	35	16

[*] Method of *Beste & Hoffman*
TSR-tensile strain recovery
WR-work recovery (resilience)

interesting for further study. It has been found that the vinyl chloride copolymer is somewhat unstable at high temperatures, since it tends to lose HCl. Accordingly, detailed examination of fiber properties will be limited to the vinylidene cyanide/vinyl acetate copolymer.

Fiber from Vinylidene Cyanide/Vinyl Acetate Copolymer

The fiber from the 1:1 alternating copolymer of vinylidene cyanide and vinyl acetate has been studied extensively in comparison with other acrylic and modified acrylic fibers [*].

The specific fibers utilized for comparison are identified in generic terms, as follows:

a) Nytril – a fiber composed of a 1:1 alternating copolymer of vinylidene cyanide and vinyl acetate.

b) Acrylic I – a fiber composed of acrylonitrile with less than 10 % polar vinyl comonomers – cationic dyeable.

c) Acrylic II – a fiber composed of acrylonitrile with not more than 10 % polar vinyl comonomers – acid dyeable.

d) Modacrylic – a fiber composed of an approximately 1:1 copolymer of acrylonitrile and vinyl chloride.

The nytril fiber, produced by a solution spinning and drawing technique, has only low orientation and no crystallinity, as seen in the X-ray diagram of Figure 5,

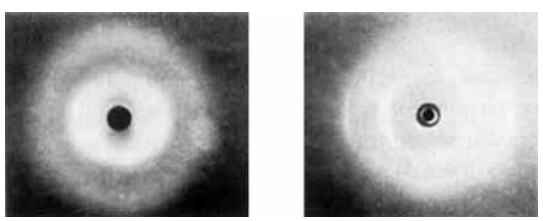


Fig. 5. X-Ray diffraction of (a) nytril and (b) acrylic I fibers

the diffraction being produced by a small amount of lateral order only. Acrylic I, in contrast, has somewhat higher orientation, although it too displays only lateral order. This may be noted by observing the absence of any non-equatorial diffraction in Figure 5. The specific gravity of the fiber is 1.21 as compared to 1.19 for acrylic I and 1.31 for the modacrylic fiber [8]. The nytril fiber becomes sticky at 170 °C compared to 235 °C for acrylics I and II. The modacrylic fiber shrinks drastically at temperatures above 135 °C [9].

Other physical properties of the nytril fiber are compared with those of acrylic and modacrylic fibers in Table 4.

The strength of the nytril fiber, while somewhat lower than that of the acrylic and modacrylic fibers, is adequate for textile applications, and under hot wet conditions is distinctly superior to that of the acrylics. The initial relatively low level of the modulus of elasticity, which is, however, maintained to a high degree in the presence of heat and moisture, as well as the low level of uncrimping energy, contributes to the exceptionally soft feel of the nytril fiber.

Table 4. Mechanical properties of fibers

	nytril	nytril steam set	acrylic I	acrylic II	modacrylic
Tenacity [g./den.]					
23 °C, 65 % r. h.	2.2	2.1	3.0	2.4	3.0
23 °C, wet	1.8	1.8	2.3	1.8	3.0
70 °C, wet	1.5	1.4	0.7	0.9	2.1
Elongation [%]					
23 °C, 65 % r. h.	26	35	33	42	36
23 °C, wet	30	36	40	44	37
70 °C, wet	31	40	77	65	50
Modulus [g./den.]					
23 °C, 65 % r. h.	25	22	46	27	35
23 °C, wet	20	17	41	26	28
70 °C, wet	11	10	4	4	16
Energy to uncrimp [g.×cm./den.×cm.] × 10⁴	1.8	0.8	3.6	5.4	4.0

The high resistance of the fiber to hot water may also be noted in Figure 6, where modulus is plotted as a

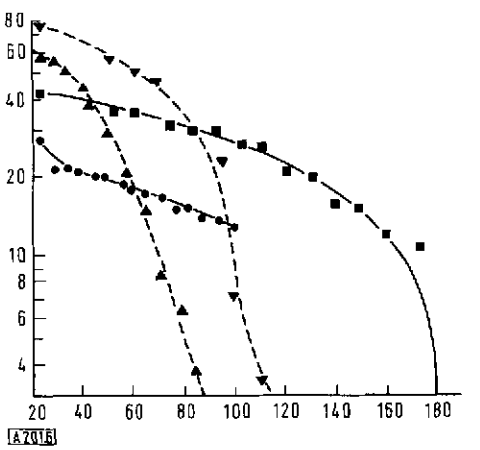


Fig. 6. Modulus temperature relationship (measured at 1 % strain)
—●—●— wet nytril fiber
—■—■— dry nytril fiber
—▲—▲— wet acrylic fiber I
—▼—▼— dry acrylic fiber I
Ordinate: Modulus of elasticity [g./den.]
Abscissa: Temperature [°C]

function of temperature both dry and wet, in comparison to acrylic I. These data suggest the presence of a major wet glass transition temperature (Tg) in the region of 50 °C for acrylic I, but no detectable wet glass transition temperature below 100 ° for the nytril fiber. Treatment of the nytril fiber in saturated steam reveals that considerable shrinkage sets in at temperatures of 120–130 °C, indicating the presence of a wet glass transition temperature in this region. This is reinforced by the fact that dye penetration (to be discussed below) is highly accelerated by pressure dyeing above 120 °C.

[*] The fiber, known commercially as Darvan®, was developed by the B. F. Goodrich Co. However, the rights to the fiber are now owned by the Celanese Corporation of America, and the data cited below were obtained through the joint efforts of Goodrich and Celanese personnel.

[8] *E. R. Kaswell:* Textile Fibers, Yarns, and Fabrics. Reinhold, New York 1953, p. 11.

[9] See [8], p. 112.

The setting of impressed configurational geometry such as crimp can be achieved best by treatment in steam at a pressure of 20 lbs./sq. in. (127 °C), in contrast to the acrylic and modacrylic fibers, where the low wet glass transition temperature allows configurational

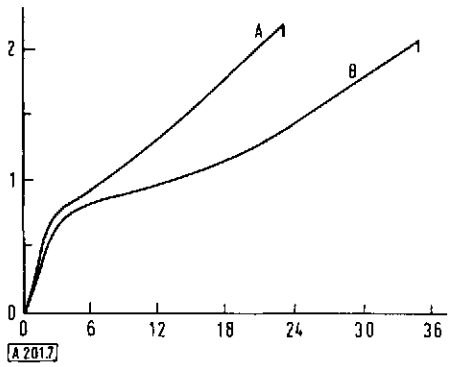


Fig. 7. Effect of steam setting on the stress-strain behavior of nytril fiber
Curve A: untreated
Curve B: steam set
Ordinate: Stress [g./den.]
Abscissa: Strain [%]

setting to be effected during the drying of wet fiber. This hot setting procedure also provides some relaxation of internal stresses in the nytril fiber, resulting in a slightly "softer" stress-strain curve (Figure 7). The setting procedure has a considerable effect on the elastic

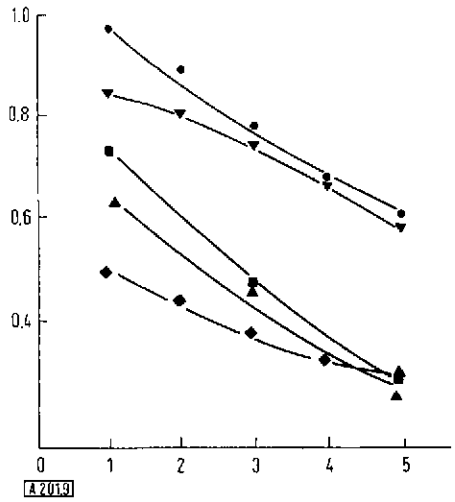


Fig. 9. Proportion of strain energy immediately recoverable
—▲—▲— nytril fiber
—■—■— nytril fiber, steam set
—●—●— silk
—▼—▼— wool
—◆—◆— acrylic fiber I
Ordinate: Energy index of elasticity
Abscissa: Extension [%]

behavior of the fiber, as seen in Table 5; it improves both work recovery (resilience) and permanent set well above the level of acrylic I under all conditions examined. This elastic behavior is one of the most important attributes of the nytril fiber, resulting in retention of

Table 5. Elastic properties of nytril, acrylic I, and modacrylic fibers [*]

Conditions	nytril		nytril steam set		acrylic I		modacrylic	
	WR [%]	PS [%]	WR [%]	PS [%]	WR [%]	PS [%]	WR [%]	PS [%]
23 °C, 56 % r. h.	22	24	30	14	12	34	16	33
23 °C, wet	16	34	33	15	9	39	17	33
70 °C, wet	16	43	35	9	20	17	—	—

[*] ASTM method D-1774-61-T, 5 % Extension. WR = work recovery PS = permanent set

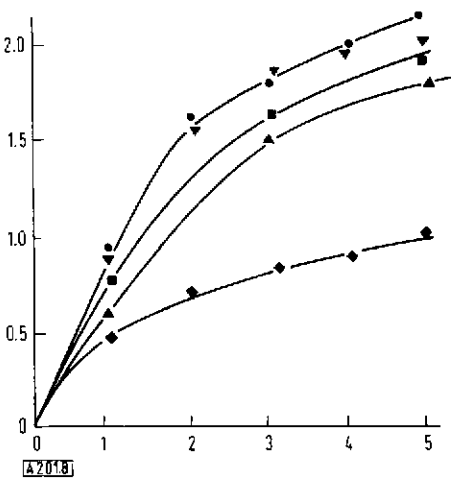


Fig. 8. Proportion of strain immediately recoverable
—▲—▲— nytril fiber
—■—■— nytril fiber, steam set
—●—●— silk
—▼—▼— wool
—◆—◆— acrylic fiber I
Ordinate: Immediate elastic deflection [%]
Abscissa: Extension [%]

shape and appearance throughout the wearing and laundering of garments. The elastic behavior has also been examined by sonic modulus techniques, using methods developed by *Hamburger* [10]. The data shown in Figure 8 indicate the proportion of strain immediately recoverable, while the energy available for immediate recovery from strain is given in Figure 9. The nytril fiber is seen to compare very favorably with silk and wool, in contrast to the acrylic fiber. Steam setting improves the performance slightly.

Dyeing behavior of the nytril fiber is a broad subject and will be discussed only briefly here. The fiber displays affinity primarily for disperse (non-ionic) dyes and is only penetrated with difficulty without the use of carriers or elevated pressure and temperature. In fact, such conditions must be used to build up heavy shades. As discussed above, it appears likely that the improvement in dyeability experienced under pressure above 120 °C results from a major increase in the diffusion rate which is brought about by exceeding the wet glass transition temperature. The mechanism by which

[10] *W. J. Hamburger* et al., Textile Res. J. *22*, 695 (1952).

carriers promote disperse dyeability of the nytril fiber at 100 °C is not completely understood but may involve an increase in both affinity and diffusion rate. Typical carriers such as methyl *p*-toluate and *o*-phenylphenol combine strongly with many disperse dyes and, when inside the fiber, may act as temporary dye sites. In addition, these compounds are strong solvating agents for sites of dipole interaction and thus may be expected to lower the wet glass transition temperature to some degree, resulting in improved diffusion rate.

While a discussion of the properties and performance of fabrics made from Darvan® nytril fiber is beyond the scope of this paper, it should be stated that the postulates concerning performance which have been derived from fiber properties have been borne out by extensive fabric trials. Soft texture, resilience, shape retention throughout wearing and laundering, and a high degree of resistance to wrinkling have been experienced with such fabrics.

Relationship of Properties to Fiber Structure

The outstanding features of softness, elasticity, resilience, and resistance to moisture displayed by the nytril fiber may be traced directly to its chemical constitution and fine structure. The relatively low degree of orientation and lateral order, together with the large number of points of intermolecular attraction provided by the polarized cyano groups, result in a strong, flexible network of molecules. This, in turn, is responsible for the soft, resilient texture of the fiber. The strength of the dipole-pair intermolecular bond, which is of the order of 8–10 kcal./mol. for alkyl cyanides [7] and which is probably much higher for vinylidene cyanide, owing to resonance, together with the large number of such bonds, probably accounts for the high degree of elastic recovery, the good wrinkle resistance, and the relative insensitivity to hot water. These same factors, of course, would tend to increase the wet glass transition temperature and reduce the dye diffusion rate.

It is impossible to give individual credit for specific aspects of the work in a project of such broad scope. The staffs of the Research Center, B. F. Goodrich Co. Brecksville, Ohio; the Development Center, B. F. Goodrich Chemical Co., Avon Lake, Ohio; the Summit Research Laboratories, Celanese Corporation of America, Summit, N. J.; and the Application and Product Development Dept., Celanese Fibers Co., Charlotte, N. C. have all made significant contributions to the work reported here.

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Pyrrolidone, Capryllactam and Laurolactam as new Monomers for Polyamide Fibers [*]

BY DR. K. DACHS AND DR. E. SCHWARTZ

BADISCHE ANILIN- & SODA-FABRIK A.G., LUDWIGSHAFEN AM RHEIN (GERMANY)

The industrial production of capryllactam (1-azacyclononan-2-one) and of laurolactam (1-azacyclotridecan-2-one) starts with cyclization of acetylene or butadiene to give cyclooctatetraene or cyclooctadiene, or cyclization of butadiene to give cyclododecatriene. Further steps are: oxidation of the cyclic hydrocarbon to the ketone, formation of the oxime, and rearrangement of the latter with sulfuric acid. Pyrrolidone can be prepared from acetylene and formaldehyde by way of butyrolactone. The behavior of the lactams during polycondensation is described and the properties of the resulting fibers are compared with those of the known polyamide fibers.

I. Introduction

Of the great number of aliphatic homopolyamides known, 33 of which are listed in Table 1, only two are of substantial importance in the fiber industry. Apart from Nylon-6.6, the polyamide made from hexamethylenediamine and adipic acid (production in 1961, approx. 350000 tons), Nylon-6, a polyamide made from ε-caprolactam, is gaining importance. The ease of polymerization of caprolactam, the good thermal stability of the polymer, and its suitability as a raw material for fibers were recognized by *P. Schlack* in 1938. In 1962, an annual production of approximately 250000 tons of this lactam polymer should be available in the Western world. A third polyamide, Nylon-11, made from ω-aminoundecanoic acid, is relatively unimportant, its annual production, including that used for plastics, being only approximately 1 % of Nylon-6 and Nylon-6.6 production combined.

Technically feasible syntheses have recently been found for other lactams, too, for instance, pyrrolidone, enantholactam, capryllactam and laurolactam. The example of Nylon-11 shows that fibers from other polymers of the lactam series may also be of interest. However, considering that there is little difference in the

[*] From a lecture delivered at the meeting of the Plastics and Rubber Section of the Gesellschaft Deutscher Chemiker on April 9th, 1962, in Bad Nauheim (Germany).

Table 1. Aliphatic homopolyamides [1]

$NH-(CH_2)_n-CO-NH-(CH_2)_n-CO-$

Polyamide made from	n	m.p. [°C]
Pyrrolidone	3	260
Caprolactam	5	223
Enantholactam	6	233
Capryllactam	7	200
ω-Aminopelargonic acid	8	209
Azacycloundecan-2-one	9	188
ω-Aminoundecanoic acid	10	190
Laurolactam	11	179

$-NH-(CH_2)_x-NH\ CO-(CH_2)_y-CO-$

Polyamide made from	x	y	m.p. [°C]
Ethylenediamine and			
Sebacic acid	2	8	276
Dodecanedioic acid	2	10	261
Hexamethylenediamine and			
Adipic acid	6	4	265
Pimelic acid	6	5	228
Suberic acid	6	6	232
Azelaic acid	6	7	226
Sebacic acid	6	8	223
Dodecanedioic acid	6	10	217
Eicosanedioic acid	6	18	189
Heptamethylenediamine and			
Adipic acid	7	4	250
Pimelic acid	7	5	214
Suberic acid	7	6	230
Azelaic acid	7	7	201
Sebacic acid	7	8	208
Octamethylenediamine and			
Adipic acid	8	4	250
Suberic acid	8	6	225
Azelaic acid	8	7	206
Sebacic acid	8	8	210
Dodecanedioic acid	8	10	202
Eicosanedioic acid	8	18	179
Decamethylenediamine and			
Adipic acid	10	4	236
Suberic acid	10	6	217
Sebacic acid	10	8	203
Dodecanedioic acid	10	10	191
Eicosanedioic acid	10	18	171

properties of the various aliphatic homopolyamides, it is important for the economic feasibility of a fiber of this class that the higher production costs incurred in the monomer synthesis, polymerization, or spinning should be outweighed by improved fiber properties. We shall discuss below favorable industrial procedues for monomer synthesis, polymerization, and spinning for the three fibers mentioned above, and compare these processes with those employed in the production of other commercially available polyamide fibers.

II. Syntheses of the Lactam Monomers

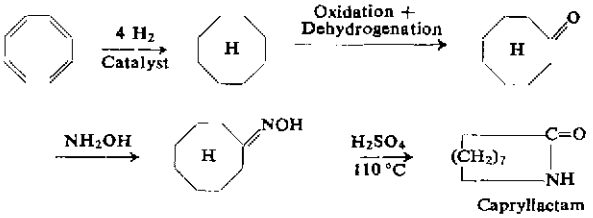
The process for the preparation of pyrrolidone (C_4) differs from that for capryllactam (C_8) and laurolactam (C_{12}), both of which can be obtained from cyclic hydrocarbons that are readily available from commercial sources.

[1] *M. Paul* and *E. Schwartz*; Festschrift für Karl Wurster, Badische Anilin- & Soda-Fabrik, Ludwigshafen am Rhein, 1960, p. 333.

1. Industrial Syntheses of Capryllactam and Laurolactam

The industrial preparation of capryllactam starts either with the cyclization of acetylene to cyclooctatetraene by the method of *Reppe* [2] or with the cyclization of butadiene to cyclooctadiene by the method of *Ziegler* [3]. In the preparation of azacyclotridecan-2-one, cyclododecatriene is first synthetized from butadiene by the method of *Wilke* [4]. Starting from these unsaturated cyclic hydrocarbons, the following routes lead to the lactams:

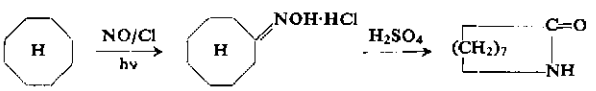
a) Hydrogenation to give the saturated compound, oxidation to the ketone, which is then treated with hydroxylamine to yield the ketoxime, and a final rearrangement in sulfuric acid to give the lactam:



Capryllactam

Oxidation of hydrocarbons by air is well-known from its use in the production of caprolactam. It can be used for the preparation of all lactams with more than seven members in the ring;

b) The photocatalytic reaction of nitrosyl chloride [5] or a mixture of chlorine and nitric oxide [6] with saturated cyclic hydrocarbons. The oxime hydrochlorides, are formed directly and are rearranged with sulfuric acid [7]:



c) Another reaction for the conversion of a twelve-membered ring into its lactam is due to *Wilke* [8] and involves epoxidation of the unsaturated hydrocarbon, for instance, with peracetic acid or acetaldehyde peracetate, followed by hydrogenation and rearrangement of the saturated epoxide to the ketone with magnesium iodide. The lactam is then obtained, for example, via the ketoxime:

[2] *W. Reppe, O. Schlichtung, K. Klager*, and *T. Toepel*, Liebigs Ann. Chem. *560*, 1 (1948).

[3] *K. Ziegler* and *W. Wilms*, Angew. Chem. *59*, 177 (1947).

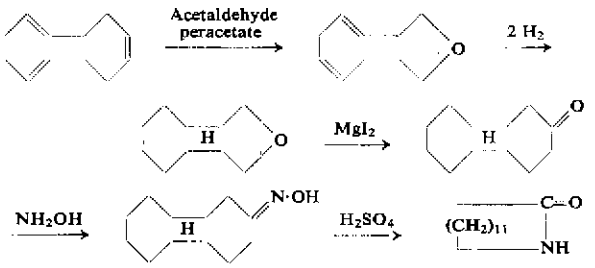
[4] *G. Wilke*, J. Polymer Sci. *38*, 45 (1959); German Patents 555180 and 564175 (Studiengesellschaft Kohle, by *G. Wilke*).

[5] *M. A. Nylor* and *A. W. Anderson*; J. Org. Chemistry, *18*, 115 (1953); *Y. Ito*; Bull. Chem. Soc. Japan *29*, 227 (1956); German Patent 973677 (BASF, by *W. Reppe, H. J. Riefl*, and *O. von Schickh*); *V. Martello, G. Lametre, G. Capara*, and *V. Giolitti*, Chem. e Ind. *38*, 932 (1956); German Patent 1 079 036 (BASF, by *O. von Schickh* and *H. Metzger*).

[6] *E. Müller* and *H. Metzger*, Angew. Chem. *71*, 229 (1959).

[7] German Patent 1 024 515 (BASF, by *O. von Schickh* and *H. Metzger*); German Patent 1 094 263 (BASF, by *O. von Schickh* and *H. Metzger*).

[8] German Patent 1 075 601 and 1 085 601 (Studiengesellschaft Kohle, by *G. Wilke*).



2. Industrial Synthesis of 2-Pyrrolidone

Synthetic routes leading to the C_4 lactam almost exclusively involve butyrolactone as an intermediate. In the best and, as far as we know, the only process being used industrially at present, formaldehyde and acetylene are reacted according to *Reppe* [9]. Butyrolactone is formed through butynediol and butanediol intermediate steps. The butyrolactone in turn reacts with ammonia to yield the pyrrolidone:

$$2\,CH_2O + HC{\equiv}CH \rightarrow HOCH_2{-}C{\equiv}C{-}CH_2OH \xrightarrow[Cat.]{+\,2\,H_2}$$

$$HO(CH_2)_4OH \xrightarrow{-\,2\,H_2} \underset{O}{\square}{=}O \xrightarrow[200\,^\circ C]{NH_3} \underset{NH}{\square}{=}O$$

III. Polycondensation

While polycondensation of C_8 and C_{12} lactams to spinnable material can be carried out in the melt in the presence of water or salts that liberate water, that is, at temperatures above the melting point of the polymers, pyrrolidone cannot be polymerized under these conditions. For pyrrolidone, the equilibrium

$$\text{monomer} \rightleftharpoons \text{polymer}$$

in the melt is shifted completely towards the monomer.

1. Polycondensation of Capryllactam and Laurolactam

The average chain length of the polymer and the concentration ratio of polymer to monomer are determined mainly by two equilibria [10]: the condensation equilibrium

$$H[HN{-}(CH_2)_n{-}CO]_xOH + H[HN{-}(CH_2)_n{-}CO]_yOH \rightleftharpoons H[HN{-}(CH_2)_n{-}CO]_{x+y}OH + H_2O$$

and the addition equilibrium

$$H[HN{-}(CH_2)_n{-}CO]_xOH + HN{-}(CH_2)_n{-}CO \rightleftharpoons H[HN{-}(CH_2)n{-}CO]_{x+1}OH$$

In the case of caprolactam, appreciable amounts of monomer are in equilibrium with the polymer at temperatures above 200 °C (at 230 °C: 7 %; at 280 °C: 9.5 %) [11]. In this temperature range, poly(pyrrolidone) is not stable; in the case of reactions with enantholactam and higher homologs, only the polymer is stable.

This behavior is attributed to the fact that the five-membered ring is unstrained and at higher temperatures is energetically favored over the free chain; on the other hand, conformational strain occurs in seven-membered caprolactam [12]. This increases in eight-membered enantholactam and higher homologs so that the equilibrium permits only low concentrations of monomer in the melt.

The ring of capryllactam is already so labile that the *cis*-relationship of the CH_2 groups adjacent to the amide bond, which is mandatory in smaller rings, tends to convert to the *trans*-form, which is always present in non-cyclic amides and which has been shown to be the preferred form in higher lactams [13]. However, after the polycondensation, large and probably nearly unstrained lactams, such as azacyclotridecan-2-one, contain only small amounts of methanol-soluble (monomeric) material (< 1.5 %). This might be due to the fact that the probability of the reverse reaction polymer → monomer at the end of a polymer chain must decrease with increasing chain length of the monomer.

The heats of polymerization, $\Delta H_{(liquid\text{-}liquid)}$, which can be regarded as measures of chain strain, are shown in Table 2.

Table 2. Enthalpies of polymerization

Monomer	$\xrightarrow{\Delta H}$ Lactam (liq.) → Polymer (liq.)
Caprolactam	−3.2 kcal/mole [14]
Enantholactam	−5.2 kcal/mole [14]
Capryllactam	about −9.6 kcal/mole [*]
Laurolactam	about −1.4 kcal/mole [*]

[*] Estimated from the temperature rise during rapid adiabatic alkaline polymerization.

The rate of polymerization in the presence of the free aminocarboxylic acid as a catalyst, measured by the decrease of monomer content, is higher with capryllactam than with caprolactam and efficient removal of the great quantity of heat evolved in the reaction has to be effected. In the case of laurolactam, polymerization proceeds much more slowly than with these two short-chain lactams. However, the thermal stability of laurolactam permits the use of higher temperatures to assure an adequate rate.

2. Polymerization of 2-Pyrrolidone

Because of the unfavorable position of the monomer ⇌ polymer equilibrium, for a long time it was considered impossible to polymerize the C_4 lactam. In 1951, *Ney* [15] found that an insoluble polymeric powder separates out when a solution of pyrrolidone is allowed to stand for some time in the presence of alkali. The yield after two to three weeks is only about 2 %. Organic acyl compounds (acid chlorides, anhydrides, esters, lactams) considerably accelerate the alkali-initiated polymerization of pyrrolidone [16]. The mechanism of this activated ionic polymerization of lactams – without

[9] *W. Keppe:* "Neue Entwicklungen auf dem Gebeit des Acetylens und Kohlenoxyds", Springer Verlag, Heidelberg, 1949, p. 27ff., 46, 47.

[10] *P. H. Hermans*, J. Appl. Chem. *5*, 493 (1955).

[11] *H. K. Reimschussel*, J. Polymer Sci. *41*, 457 (1959).

[12] *A. B. Meggy*, J. Appl. Chem. *4*, 154 (1954).

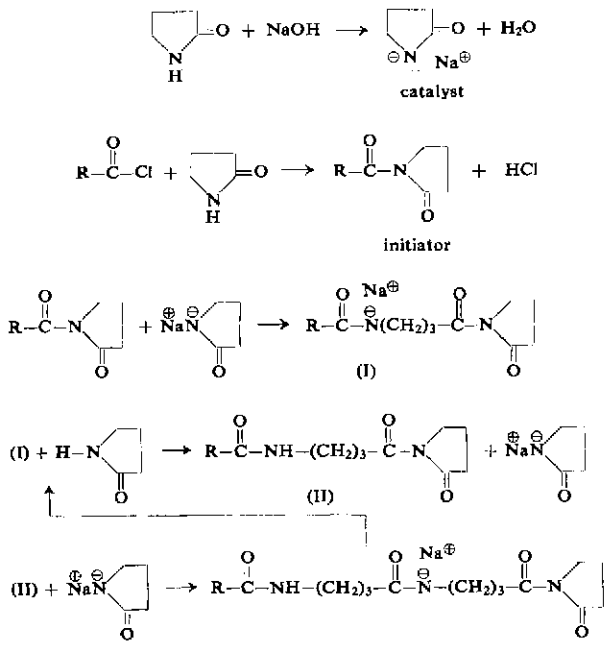
[13] *R. Huisgen*, Angew. Chem. *69*, 341 (1957).

[14] *S. M. Skuratov* et al., Doklady Akad. Nauk. SSSR *95*, 591 (1954).

[15] U.S. Patent 2 638 463 (Dec. 7th, 1951).

[16] U.S. Patent 2 739 959 (Feb. 24th, 1953).

considering side and termination reactions – can be represented roughly as follows [17]:



Using this process, it is possible to polymerize pyrrolidone below 60 °C in yields of 80–85 % at economically acceptable rates. In liquid phase and in the presence of inert compounds (*e.g.* hydrocarbons) which are not miscible with pyrrolidone, finely dispersed polymer suspensions are obtained which are well adapted to further treatment. The monomer must be removed from the polymer and the alkali carefully washed out, since it accelerates decomposition at elevated temperatures. The molecular weights that can be attained are sufficiently high to ensure good mechanical properties.

IV. Properties of the Polymers

The melting point and the amount of water that can be absorbed by a polyamide are significant for the properties of the resulting fiber. Table 3 gives these values for lactam polymers. With increasing chain length, the melting point of the lactam decreases. A polyamide with an even number of carbon atoms in the monomer has a lower melting point than either of its two odd-numbered neighbors. Thus, poly(capryllactam) and poly(laurolactam) are worse off in this respect than their neighbors.

In its absorption of water, the pyrrolidone polymer is similar to cotton (Fig. 1). Thus, it is unique in this respect.

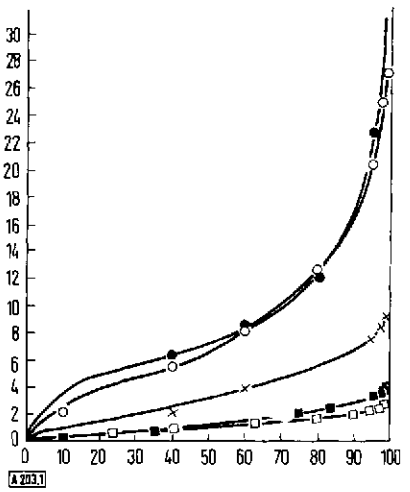


Fig. 1. Water absorption of (●–●–●) cotton, (○-○-○) poly(pyrrolidone), (×–×–×) poly(caprolactam), (■-■-■) poly(capryllactam), and (□–□–□) poly(laurolactam)
Ordinate: g water/100 g. dry substance
Abscissa: % relative humidity

V. Spinning of the Polymers

Poly(capryllactam) and poly(laurolactam) have a high thermal stability and contain only small amounts of monomer and oligomer in the melt. They can therefore be spun directly from the polymerization vessel, even at long holding times. There is no need to extract the filament. In the case of poly(pyrrolidone), however, because of its thermal instability, spinning from the melt is very difficult. Therefore, the decomposition of poly(pyrrolidone) will be briefly considered in the following.

If poly(pyrrolidone) is kept under pure nitrogen for various periods of time at *e.g.* 240 °C. Determination of the decrease in weight and the viscosity $\left(\eta_{c=1} = \frac{\ln \eta_r}{c}\right)$ of a solution of the residue remaining after removal of monomer indicates a first-order decomposition mecha-

[17] See, for example, *H. K. Hall*, J. Amer. chem. Soc. *80*, 6407 (1958).

Table 3. Melting points and water absorption of polymers made from lactams

Polyamide made from	Number of		m.p. [°C]	Water absorption of polymers at		Species present in equilibrium at m.p.
	C atoms	CH_2 groups		65 % rel. humidity	99 % rel. humidity	
Pyrrolidone	4	3	ca. 265	9.1	28	monomer
Caprolactam	6	5	223	4.3	9.5	polymer and a lot of monomer
Enantholactam	7	6	233	2.8	5.0	polymer and a little monomer
Capryllactam	8	7	200	1.7	3.9	
ω-Aminopelargonic acid	9	8	209	1.5	3.3	
Azacycloundecan-2-one	10	9	188	1.4	1.9	
ω-Aminoundecanoic acid	11	10	190	1.3	2.8	
Azacyclotridecan-2-one	12	11	179	1.3	2.7	

nism with respect to the loss of mass (Fig. 2). Thus, where a = amount of polymer at time zero and x = quantity decomposed after time t

$$\ln \frac{(a-x)}{a} = -kat$$

It can be seen from Fig. 2 that after an initial rapid decomposition, during which approximately 25 % of the mass is lost, the decomposition proceeds much more slowly. At the same time, the upper curve shows that during the first 80 minutes chain ruptures are taking place causing a drop in the viscosity of the solution. Following that period, however, the viscosity slowly rises again (from $\eta = 1.18$ to $\eta = 1.25$).

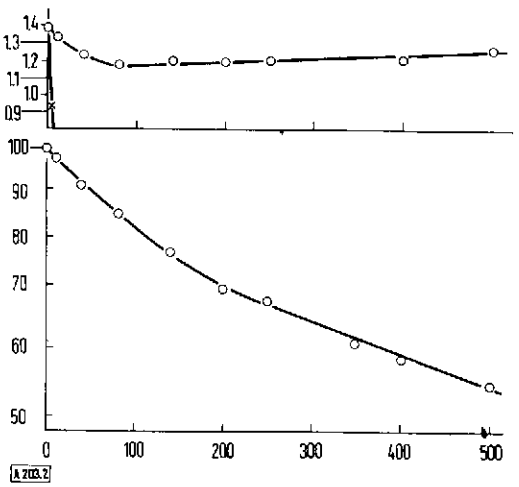


Fig. 2. Viscosity of a solution (upper curve) and loss of mass (lower curve) in thermal decomposition (240 °C) of poly(pyrrolidone).

(○-○-○) - - Under pure nitrogen, (x-x-x) - - in air.

Ordinate: upper curve: Viscosity [$\eta_{c=1}$].

lower curve: Quantity of poly(pyrrolidone) [% of initial amount] remaining after a time t.

Abscissa: Time [min].

The initial high loss of mass and the chain scissions might be due to occluded air or moisture and the subsequent increase in viscosity might be due to preferential decomposition of short-chain fractions. The almost constant average molecular weight during the decomposition might be explained by assuming that cleavage of a monomer from the end of a chain is followed by disintegration of the whole chain, which thus disappears from the system.

On melting, poly(pyrrolidone) decomposes above 265 °C, with partial formation of gaseous monomer. The lactam vapor hinders heat transfer between the hot walls and the solid. The polymer should therefore be pressed against a hot well-conducting surface from which the melt can flow off [18].

Since the melt holding times of poly(pyrrolidone) may only be very short, it is spun in the laboratory by the rod-melting process: A pressed rod of well dried poly(pyrrolidone) is forced through a heated cone at such a temperature (270 °C), that a melt is formed which gives a smooth unbroken filament when passed through the spinneret. In this way, the holding time can be reduced to less than a minute. Since homogenization of the melt is not possible, the filaments are not uniform.

Poly(pyrrolidone) fibers can also be obtained by the dry-spinning process from a 45 % solution in concentrated form ic acid.

The tensile strength of filaments from melt spinning is superior to that of filaments obtained from solutions (Table 4).

Table 4. Tensile strength and viscosity (initial value $\eta_{c=1} = 1.38$) of poly(pyrrolidone) fibers

	Melt spinning					Dry spinning			
$\eta_{c=1}$	Tensile strength dry	Tensile strength wet	Elongation [%] dry	Titer [den.]	$\eta_{c=1}$	Tensile strength dry	Tensile strength wet	Elongation [%] dry	Titer [den.]
1.08	51	33	51	2.8	1.35	34	24	71	4.0
1.00	51	31	42	2.3	1.35	30	18	63	4.5

VI. Properties of the Fiber

Fibres made from poly(pyrrolidone), poly(caprylactam), and poly(laurolactam) exhibit tensile elongation behavior characteristic of polyamide fibers. Even at a ratio of 11 CH_2 groups per CONH group, the mechanical properties of the fiber are determined to a great extent by the amide groups.

The moduli of elasticity of polyamides are relatively small at small elongations; they increase with increasing elongation but fall again when the region of strong plastic deformation is reached.

The initial modulus of elasticity can be used as a measure of the stiffness of the fiber. Polyamide fibers are relatively soft. With increasing stretching, *i.e.* with decreasing elongation required to break the stretched filament, the initial modulus increases. In order to compare the modulus of elasticity, polyamide fibers of similar breaking elongation should be used. It was found that polyamide fibers become somewhat stiffer with increasing length of the CH_2 chain. Besides the dependence of the melting point on the CH_2 chain length, the effect of water absorption, which increases

[18] French Patent 1,221,478 (Minnesota Mining and Manufacturing Company).

Table 5. Mechanical properties of polyamide fibers [*]

Fiber made from	Dry			Wet			Relative wet strength [%]	Relative humidity modulus [%]
	Tensile strength	Elongation [%]	Titer [den.]	Tensile strength	Elongation [%]	Titer [den.]		
Poly(pyrrolidone)	41.4	31	3.03	31.2	32	3.03	70–80	45–65
Poly(caprolactam)	83.1	30	5.97	71.0	29	5.97	85–90	55–70
Nylon-6.6	78.0	20	5.98	67.29	17	5.89	85–90	55–70
Poly(caprillactam)	74.8	24	5.56	70.8	22	5.56	93–97	90–95
Poly(laurolactam)	72.2	24	5.10	72.5	24	5.10	100	90–95

[*] The values of the tensile strength [except for poly(pyrrolidone)] were measured on tire-cord material, while the values of relative wet strength and the relative humidity modulus refer to fibers of lower strength.

as the chain length decreases, is of interest. Water only slightly affects the mechanical properties of filaments with low hygroscopicity, such as those made from laurolactam or C_{11}lactam. The relative humidity modulus ranges from 90–95 % (Table 5).

The relative wet strength of even the poly(capryllactam) fibers (with a hygroscopicity of 4 % at 100 % relative humidity), is still about 95 % and the relative humidity modulus is 90–95 %, while for Perlon and Nylon, these values decrease to about 85 % and 55–70 %, respectively. Poly(pyrrolidone) fibers give only slightly lower values.

VII. Future Prospects

The properties of poly(capryllactam) fibers were tested at every stage right up to the finished textile. With respect to their rich hand and their capacity for retaining their shape, the textiles are more like Nylon-11 than like Nylon-6. However, in spite of the economy of its polycondensation compared with that of caprolactam and the low-cost spinning process, acetylene and butadiene are too expensive as starting materials, so that the fiber cannot be expected to find a very wide market.

Fibers made from poly(laurolactam) have an advantage over those made from ω-aminoundecanoic acid in the more stable price of its petrochemical raw material, and the disadvantage of a 10 °C lower melting point. Its manufacturing cost is higher than that of poly(caprolactam) fiber.

Pyrrolidone is an inexpensive raw material. However, it is certainly no cheaper than caprolactam, its polycondensation proceeds more slowly, and it gives lower yields. A further disadvantage is the fact that the polycondensation cannot be carried out continuously through a homogeneous equilibrium. In order to spin the polymers directly from the melt and to obtain uniform fibers, non-coloring oxidation inhibitors and end-group stabilizers must be found and tested. Difficulties may also arise from the ease of penetration into the interior of the fiber, as evidenced by its high water absorption. The danger of discoloring might be more troublesome. Finely dispersed dirt might be adsorbed more easily, and damage from oxidizing bleaching agents or oxygen in the air may be higher than in fibers with lower water absorption.

As long as caprolactam is the cheapest raw material for polyamide fibers, its use in the fiber industry will be expanded, and all the more expensive polyamide fibers with certain superior qualities will be limited to those applications where their better properties are absolutely needed.

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Thin-Layer Chromatography of Nucleotides

BY DR. K. RANDERATH [*]

INSTITUT FÜR ORGANISCHE CHEMIE DER TECHNISCHEN HOCHSCHULE DARMSTADT (GERMANY)

Thin-layer chromatography of nucleotides on DEAE- and ECTEOLA-cellulose is superior to the methods of separation in use up to the present. Using dilute hydrochloric acid, and without a gradient elution technique, it is possible to achieve a group separation of mono-, di-, and tri-phosphates as well as subfractionation within these groups depending on the basicity of the nucleobases. Thin-layer chromatography is appreciably more sensitive than paper chromatography; 5×10^{-4} μmole adenine nucleotides can still be detected. The total quantity of material that can be chromatographed without tailing is greater in this procedure than that with paper chromatography; a mixture consisting of 1 μmole ATP and ADP per starting spot can be resolved with ease. Hence, the procedure can also be applied for micro-scale preparative separations. A mixture of 10^{-2} μmole ADP and ATP, respectively, can be separated completely in four to ten minutes.

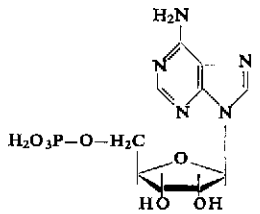
Introduction

Nucleotides are constituents of the high molecular weight nucleic acids. They are made up of a nucleobase, a pentose – ribose in the case of RNA and 2′-deoxyribose in the case of DNA – and a phosphate residue esterified with the pentose [**]. The principal nucleobases of RNA are the purines, adenine and guanine, and the pyrimidines, cytosine and uracil. DNA contains thymine (5-methyluracil) in place of uracil.

In the nucleic acids, nucleotides, *e.g.* 5′-AMP (I), are connected together by 3′,5′-phosphate diester bonds.

[*] A book on Thin-Layer Chromatography by K. Randerath about 200 pp.) will be publisbed shortly by Verlag Chemie GmbH, Weinheim/Bergstr., Germany.

[**] The following abbreviations will be used: RNA: ribonucleic acid; DNA: deoxyribonucleic acid; AMP, ADP, ATP: adenosine mono-, di-, and tri-phosphate, respectively; GMP, GDP, GTP; CMP, CDP, CTP; UMP, UDP, UTP: the corresponding phosphate compounds of guanosine, cytidine, and uridine, respectively; 5′-AMP: adenosine-5′-monophosphate; DEAE-cellulose: diethylaminoethylcellulose; ECTEOLA-cellulose: cellulose linked to triethanolamine (TEOLA) via epichlorhydrin (EC).



Also, many coenzymes possess the nucleotide structure. These are esters of di- and tri-phosphoric acid.

Chromatography of Nucleotides

Paper chromatographic separation of nucleotides lasts 15 to 24 hours for one-dimensional procedures and two to three days for two-dimensional procedures. High-voltage electrophoresis requires relatively complicated and expensive apparatus.

Difficulties arise in thin-layer chromatography of extremely hydrophilic compounds, such as nucleoside polyphosphates [1–4], if the usual inorganic supporting materials are used. These difficulties cannot be overcome even by using highly polar solvents. Di- and tri-phosphates in particular tend to tail and are difficult to separate. The $CaSO_4$ content of inorganic adsorbents interferes with the chromatography with alkaline, *i.e.* ammoniacal eluting agents [1,2]. Moreover, the inorganic materials absorb strongly in the 250–260 mμ region, thus interfering with the usual UV tests for the presence of nucleotides [5]. It is possible to lower the limit of detection for nucleotides by incorporating fluorescent materials in the layer [6,7] or by subsequently spraying the plates with fluorescein solution [8,9], but even then, the limit of detection is higher than that achieved by using organic layers.

Because ion-exchange chromatography is suitable for the preparative separation of nucleotides [10, 11], it occurred to us that equally effective resolution might be achieved by using these exchangers in thin-layer chromatography. In ion-exchange procedures the rate of migration is essentially a function of the total charge, which in turn is pH-dependent. The total charge can be calculated by multiplying the number of ionized groups by their respective degrees of dissociation and summing them. Figure 1 [10] shows the relationship between total charge and pH in the case of the four most important nucleoside monophosphates. It can be seen that the negative charge at a given pH increases as follows: CMP < AMP < GMP < UMP. This order remains the same for the di- and tri-phosphates. This suggests that CMP can be eluted most easily and UMP least easily with dilute acids from an anion-exchange column. However, the order of elution for guanine and uracil derivatives is often reversed. This is due to the presence of adsorption forces. Purines are generally adsorbed more strongly than pyrimidines. This effect is particularly pronounced in ion-exchange chromatography using

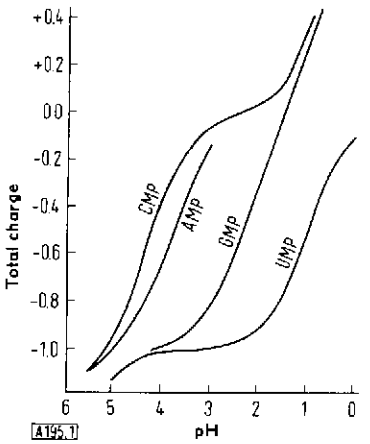


Fig. 1. Relationship between total charge and pH of the solvent for CMP, AMP, GMP, and UMP [cf. [10]]

neutral electrolyte eluents: although all nucleotides of the same type have the same total charge – the bases carry no charge under these conditions – cytosine and uracil derivatives are eluted ahead of adenine and guanine derivatives.

Preliminary experiments, made on layers consisting of conventional resin exchangers, showed that nucleotides can be separated on ion-exchanger layers, but the results were unsatisfactory. Detection of the nucleotides was rendered difficult, as the layer absorbed strongly in the ultraviolet region. On the other hand, the use of cellulose exchangers [12] for thin-layer chromatography led to results superior to those achieved by other methods [1,2].

Up to the present, cellulose ion-exchangers were used almost exclusively for separating high molecular weight materials, such as oligonucleotides, polynucleotides, peptides, proteins, and polysaccharides. Almost nothing was known about their ability to separate low molecular weight compounds. Our results show that these materials are also suitable for the chromatography of low molecular weight materials. We have succeeded in obtaining separations on thin layers of cellulose ion-exchangers without applying gradients (changes in ionic strength and/or pH of the eluent during chromatography) such as have hitherto only been achieved on resin exchanger columns by means of gradient elution. It may well be that, in the course of the chromatographic separation, a gradient is formed within the layer itself as a result of a "frontal analysis" of the solvent, and that this is in part responsible for the good separation.

Cellulose exchangers intended for column chromatography are not directly suitable for thin-layer chromatography; for example, their grain size may be too large [2]. Mechanical disintegration alone is insufficient in many cases. Products prepared in this fashion often have properties (high swelling power, poor adhesion to glass *etc.*) which preclude their use in thin-layer chromatography. Commercially available modified celluloses

[1] *K. Randerath*, Angew. Chem. *73*, 436 (1961).

[2] *K. Randerath*, Angew. Chem. *73*, 674 (1961).

[3] *K. Randerath* and *H. Struck*, J. Chromatogr. *6*, 365 (1961).

[4] *K. Randerath*, Biochem. biophys. Res. Commun. *6*, 452 (1961/1962).

[5] *E. R. Holiday* and *E. A. Johnson*, Nature (London) *163*, 216 (1949).

[6] *J. G. Kirchner*, *J. M. Miller* and *G. E. Keller*, Analytic. Chem. *23*, 420 (1951).

[7] *H. Gänshirt* and *A. Malzacher*, Arch. Pharmaz. *293/65*, 925 (1960).

[8] *T. Wieland* and *L. Bauer*, Angew. Chem. *63*, 511 (1951).

[9] *T. Wieland* and *B. Heinke*, Liebigs Ann. Chem. *615*, 193 (1958).

[10] *W. E. Cohn* in *E. Chargaff* and *J. N. Davidson:* The Nucleic Acids. Academic Press, New York 1955, Vol. 1, p. 211 *et seq.*

[11] *W. E. Cohn*, J. Amer. chem. Soc. *72*, 1471 (1950).

[12] *E. A. Peterson* and *H. A. Sober*, J. Amer. chem. Soc. *78*, 751 (1956).

differ so widely in their behavior in thin-layer chromatography tests that it became necessary to standardize them first [13].

The following requirements must be met:

1. The layer must be mechanically stable. It must not swell to any considerable extent in the course of chromatography with dilute electrolytes. No fissures must develop as the chromatogram dries.

2. It must be possible to separate mono-, di-, and triphosphates of the same nucleobase without gradient elution, but simply by using 0.01 N to 0.03 N HCl with DEAE-cellulose, or 0.02 to 0.04 N HCl with ECTEOLA-cellulose. In the case of DEAE-cellulose, tailing must be suppressed even when the layer has been loaded with as much as 1 μmole ADP or ATP per starting point. When ECTEOLA-cellulose is used, a mixture consisting of 10^{-2} μmole ADP and 10^{-2} μmole ATP must be separated completely within 5 min. with 0.05 to 0.07 N HCl as eluent.

3. It must be possible to separate 10^{-2} μmole each of CTP, ATP, GTP, and UTP by using 0.03 to 0.05 N HCl on DEAE-cellulose or 0.05 to 0.07 N HCl on ECTEOLA-cellulose. In such a procedure CTP and ATP do not need to be completely separated.

4. It must be possible to separate cytosine and adenine derivatives of the same type with 0.05 to 0.12 *M* NaCl solutions [*].

5. The exchanger must not absorb short-wave UV light to any significant extent. As little as 5×10^{-4} μmole ATP on DEAE-cellulose should be detectable in incident light.

Layers made of unmodified cellulose, as first used by *Teichert* et al. [14] for thin-layer chromatography, can also result in satisfactory separation of nucleobases, nucleosides, and nucleotides [3, 4]. In this case solvents that have been used with success in paper chromatography can be used in thin-layer chromatography as well, perhaps with slight modification. Even when unmodified cellulose is used, the advantages of thin-layer chromatography are preserved (*i.e.* more rapid development, more sharply delineated spots).

Results

1. Preparation of the Layer and Chromatography

Ten grams of cellulose exchanger or unmodified cellulose are shaken vigorously with 60–70 ml. of distilled water in a closed Erlenmeyer flask for a period of 30 to 45 sec., and the suspension is then spread on glass plates in the usual fashion (thickness of layer approx. 250 μ) [15]. When the suspension is prepared in an electric mixer, the resulting layer appears more homogeneous. However, in our experience, shaking is sufficient. Ten grams of powder are sufficient for seven to ten 10×20 cm² plates. The layers are mechanically most stable if they are left to dry at room temperature overnight. They should be stored according to the same principles as chromatography paper.

Chromatography on ion-exchanger layers is carried out in open vessels in ascending fashion. The vessels are filled to a depth of about 1.2 cm. with solvent. The materials are applied to the layer with a micropipette at about 3 cm. from the lower edge of the plate. The progress of the chromatographic separation can be followed in incident short-wave ultraviolet light. In general, it is not necessary to darken the room in which the separation is carried out. The plates are dried in a stream of warm air. The chromatograms can be copied onto cellophane in incident UV light.

2. Chromatography on DEAE-Cellulose

As shown in Figs. 2 to 4, nucleotides can be separated quite well with dilute HCl on DEAE-cellulose layers.

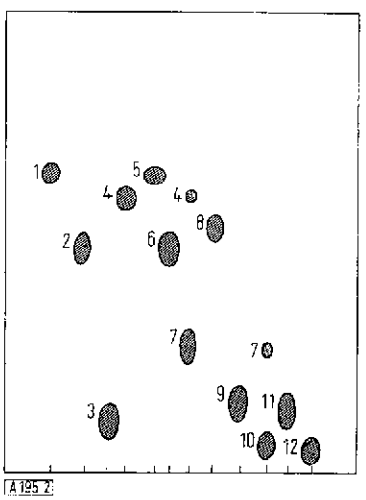


Fig. 2. Thin-layer chromatogram of nucleotides (10^{-2} μmole of each) on DEAE-cellulose. Solvent: 0.02 N HCl. Distance covered: 9.2 cm. in 40 min.

1 = 5'-AMP; 2 = ADP; 3 = ATP; 4 = 5'-GMP; 5 = 5'-CMP; 6 = 5'-UMP; 7 = GDP; 8 = CDP; 9 = UDP; 10 = GTP; 11 = CTP; 12 = UTP

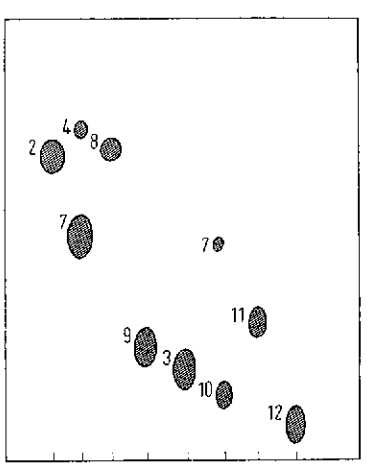


Fig. 3. Thin-layer chromatogram of nucleotides (10^{-2} μmole of each) on DEAE-cellulose. Solvent: 0.03 N HCl. Distance covered: 8.8 cm. in 40 min. For code, see caption of Fig. 2

[13] DEAE- and ECTEOLA-celluloses suitable for thin-layer chromatography are obtainable from Serva-Entwicklungslabor, Heidelberg, Germany.

[*] A previous specification [2], *viz.* the resolution of mono-, di-, and tri-phosphates by means of dilute salt solutions on ECTEOLA-cellulose, has been rejected. Separations using dilute acids are superior.

[14] *K. Teichert, E. Mutschler,* and *H. Rochelmeyer,* Dtsch. Apotheker-Ztg. *100,* 283 (1960).

[15] *E. Stahl,* Chemiker-Ztg. *82,* 323 (1958).

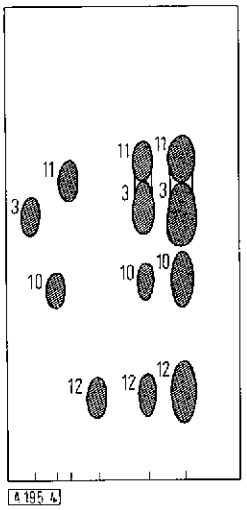


Fig. 4. Thin-layer chromatogram of nucleoside triphosphates (10^{-2} µmole of each; outer right: 5×10^{-2} µmole of each) on DEAE-cellulose; Solvent: 0.04 N HCl; Distance covered: 12.8 cm. in 100 min. For code see caption of Fig. 2

The rate of migration of the compounds is determined primarily by:

a) the difference in negative charge of mono-, di-, and tri-phosphates; monophosphates migrate faster than diphosphates, which in turn migrate faster than triphosphates.

b) differences in ionization of the bases. The rate of migration decreases in the following order: cytosine > adenine > guanine > uracil derivatives.

Hence, the relationship shown in Fig. 1 also recurs in thin-layer chromatography. The separations of diphosphates obtained with 0.02 to 0.03 N HCl (Figs. 2 and 3) and of triphosphates with 0.04 N HCl (Fig. 4) are particularly noteworthy. No other method leads to equally good and rapid separations with comparably simple experimental conditions.

Adenine and cytosine derivatives of the same type which cannot be completely separated [*] can be separated by means of 0.05 to 0.12 *M* NaCl solution. The resulting spots are less sharp than when the chromatography is done with dilute HCl. Solutions of alkaline buffers do not achieve good resolution of the mononucleotides.

In the chromatography of ATP with 0.03 N HCl on DEAE-cellulose, the lower limit of detection is in the neighborhood of 5×10^{-4} µmole. Short-wave UV light (approx. 260 mµ) [**] is thrown on the layer in a completely darkened room. When testing for larger quantities, it is not necessary to darken the room; the UV lamp is held close to the chromatogram so as to screen off a portion of the incident daylight. Compounds of adenine, cytosine, and uracil appear as dark-blue, whereas guanine compounds appear as light-blue fluorescent spots. Traces of GMP in GDP solutions and of GDP in GTP solutions are particularly easy to recognize (cf. Figs. 2 and 3).

DEAE-cellulose is also suitable for micro-scale preparative separations. The three starting points on the chromatogram shown in Fig. 5 were loaded (from l. to r.) with 0.8, 1.4, and 2.0 µmole, respectively, of a mixture of ADP and ATP (molar ratio 1:1). Complete separation of the two components was achieved with 0.03 N HCl within 80 to 100 min.

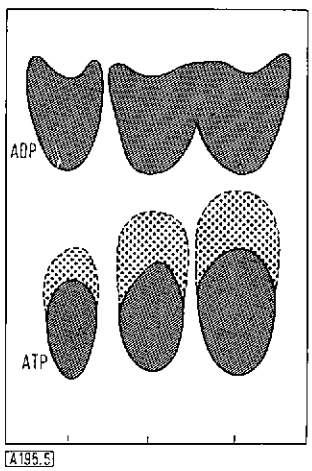


Fig. 5. Micro-scale preparative separation of ADP and ATP on a thin-layer chromatogram of DEAE-cellulose.
Solvent: 0.03 N HCl. Distance covered: 11.7 cm. in 90 min.
The following quantities of ADP and ATP were applied: 0.4 µmole to the left hand spot, 0.7 µmole to the middle spot, and 1 µmole to the right hand spot. Approximate area of the starting spots, in terms of UV absorption: (from left to right) 1×1 cm², 1.5×1.5 cm², 2.5×1.5 cm² (width × height). The front of the ADP spot is in a zone which is visible in ultraviolet light and which is frequently observed in chromatography carried out with dilute acids on DEAE- and ECTEOLA-cellulose layers. The rate of migration of this zone increases as the concentration of the acid increases. Resolution is unaffected, however

A usual paper chromatogram cannot be charged with 1 µmole nucleotide/starting point. A rough calculation shows that with a 20×20 cm² thin-layer chromatogram made of DEAE-cellulose, it would be possible to separate 2 mg. ADP from 2 mg. ATP. The spots can be scraped out with a scalpel and the nucleotides eluted, *e.g.* with 0.2 N HCl.

Analytical quantities of ADP and ATP (10^{-2} µmole or less) can be separated completely in seven to ten minutes. Table 1 lists some R_F values. Of particular interest are the vast differences in the R_F values of the di- and triphosphates with 0.02 and 0.03 N HCl as solvents.

Table 1. R_F Values of nucleotides on DEAE-cellulose (thin-layer chromatogram with 10^{-2} µmole/starting point)

Compound	Solvent			
	0.01 N HCl	0.02 N HCl	0.03 N HCl	0.04 N HCl
5'-AMP	0.45	0.65		
ADP	0.24	0.48	0.68	
ATP	0.06	0.11	0.20	0.56
5'-GMP	0.36	0.60	0.75	
GDP	0.09	0.27	0.51	
GTP	0.05	0.07	0.14	0.41
5'-CMP	0.46	0.65		
CDP	0.31	0.53		
CTP	0.09	0.13	0.31	0.64
5'-UMP	0.31	0.49		
UDP	0.07	0.15	0.25	
UTP	0.04	0.04	0.08	0.18

[*] Two overlapping spots can best be detected in transmitted light in the arrangement: UV lamp → thin layer → glass support → protective glasses → eyes.

[**] *E.g.* from a Mineralight lamp made by Ultraviolet Products, Inc., San Gabriel, Calif., USA.

3. Chromatography on ECTEOLA-Cellulose

When the thin layer is made of ECTEOLA-cellulose, dilute acids are also more suitable for chromatographing mononucleotides than neutral salt solutions [2] or alkaline buffers. Differences from chromatography on DEAE-cellulose are relatively minor. Triphosphates can be separated with 0.06 N HCl in about 60 min.; the chromatogram obtained is very much like that on DEAE-cellulose (Fig. 4). Whereas CTP, GTP, and UTP, or ATP, GTP, and UTP can be separated completely, CTP and ATP can be separated only incompletely, just as with DEAE-cellulose. Complete separation can only be achieved with dilute NaCl [2]; this also applies to the corresponding di- and mono-phosphates.

As shown in Fig. 1, the distances run by nucleotides on chromatograms developed with HCl depend on the type of nucleobase in question. The time required to cover the same distance is smaller on ECTEOLA-cellulose than on DEAE-cellulose. For example, a mixture made up of 10^{-2} μmole ADP and 10^{-2} μmole ATP can be separated on ECTEOLA-cellulose with 0.05 to 0.07 N HCl in as little as 4 to 5 min. No other method can be used to separate such chemically similar compounds in so short a time. Paper chromatography requires 15 to 20 hours; even electrophoretic separation requires several hours.

4. Chromatography with Unmodified Cellulose

When thin-layer chromatography is carried out with unmodified cellulose, the same solvents can usually be used as for paper chromatography. Hence, the two methods can be compared in detail [4]. Under identical conditions, the spots obtained on thin-layer chromatograms are appreciably smaller and sharper than on paper [4] (cf. Figs. 6 and 7). Ion exchangers are, however, clearly superior to simple cellulose in the chromatography of nucleotides.

Nucleobases and nucleosides can be separated on layers consisting of unmodified cellulose by means of distilled water or dilute sodium chloride solutions [3, 4], just as in paper chromatography [16]. Separation by means of aqueous solvents can also be obtained on DEAE- and ECTEOLA-cellulose layers. The R_F values obtained in different procedures are in remarkable agreement [2].

[16] *C. Tamm, H. S. Shapiro, R. Lipshitz,* and *E. Chargaff,* J. biol. Chemistry *203*, 673 (1953).

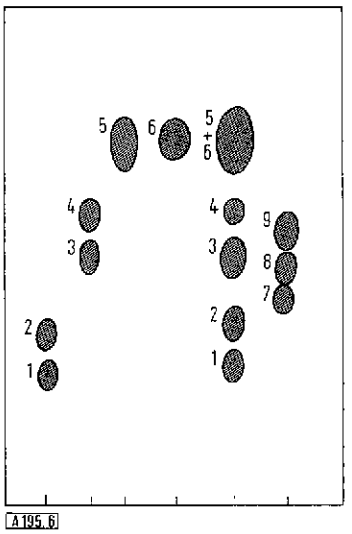


Fig. 6. Thin-layer chromatogram of nucleotides [4] on unmodified cellulose. Solvents: saturated ammonium sulfate/1 M sodium acetate/isopropanol 80:18:2 (v/v) [17]. Distance run: 10 cm, in about 90 min. 1 = 3'-AMP; 2 = 2'-AMP; 3 = 3'-GMP; 4 = 2'-GMP; 5 = 2'- and 3'-CMP; 6 = 2'-and 3'-UMP; 7 = 5'-AMP; 8 = ADP; 9 = ATP

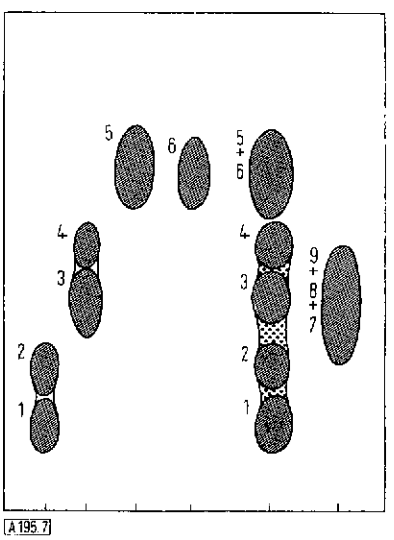


Fig. 7. Paper chromatogram of nucleotides run under the same conditions as the thin-layer chromatogram shown in Fig. 6 [4]. Paper: 2043 b (Schleicher and Schüll). Distance run: 10 cm. in about 130 min. For code, see caption of Fig. 6.

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Theories of Ion-Exchange Column Performance: A Critical Study

BY DR. F. HELFFERICH

SHELL DEVELOPMENT COMPANY, EMERYVILLE, CALIFORNIA (U.S.A.)

Many theories of ion-exchange column performance, differing widely in their simplifying assumptions and their results, have been advanced. For successful application it is vital to choose, in each particular case, the most appropriate theory. This requires a thorough general understanding of the phenomena and a precise knowledge of the consequences of the simplifying assumptions. The most important qualitative characteristics of ion-exchange columns are outlined, especially the formation of self-sharpening and non-sharpening boundaries and of constant and proportionate patterns. The commonly used quantitative theories and calculation methods are then discussed and their adequacy, their shortcomings, and the ranges of their applicability are critically studied.

Introduction

Plant-scale ion-exchange columns have been operated successfully for more than half a century. The plant engineer is familiar with all questions of operation, and the technical literature on this subject is voluminous [1]. The same is true for the literature on column-performance theories, which are, of course, of utmost importance for design purposes. But despite, or perhaps just because of, the abundance of literature, the task of the process engineer's designing a plant-scale unit is not an easy one. He is beset less by mathematical difficulties than by the confusing multiplicity of theories from which to choose. Contrary to occasional claims, a universal and rigorous theory of column performance does not exist and would be of unmanageable complexity, if ever developed. Instead, a wide variety of theories, many of them mutually exclusive, have been derived with different sets of simplifying assumptions, often without discussing the consequences of the latter. Since even seemingly harmless assumptions may lead far astray, the process engineer needs a sound general understanding of column phenomena to choose, for any particular case, the theory which yields a maximum amount of correct information with a minimum of effort. Indeed, the choice of the proper theory is perhaps the most important step in any performance calculation. In the present study, a qualitative picture is outlined and is used in the subsequent discussion of the most common mathematical theories and their ranges of validity. For theoretical details and derivations the reader is referred to the cited literature [2]. Furthermore, problems of construction [1], methods for predicting optimum operating conditions [3,4], and processes in other than fixed beds will not be discussed. With minor modifications the arguments and theories also apply to adsorption processes.

Qualitative Aspects

As a rule, ion-exchange columns are used to remove one or more ionic species (hereafter designated as B) from a solution in exchange for another ionic species (hereafter designated as A). For this purpose the solution is passed through a column filled with an ion-exchanger in A form. The column effluent will then contain a quantity of A equivalent to the removed B. When "breakthrough" of B is reached, the column must be regenerated with a solution containing A.

While on stream, the ion-exchange bed is exhausted (*i.e.*, converted from A to B form) progressively from the inlet to the outlet end. The boundary between the exhausted and the still unconverted ion-exchanger is not ideally sharp so that, at breakthrough of B, the bottom layers of the bed still contain some A. The more diffuse the boundary, the sooner breakthrough occurs and the lower are the breakthrough capacity and the degree of column utilization. Similarly, the more diffuse the boundary in the regeneration step, the more regenerant is required to reconvert the bed to the A form. The sharpness of the boundary thus is of paramount importance in any ion-exchange operation.

The sharpness of the boundary depends primarily on the "favorable" or "unfavorable" effects of ion-exchange equilibrium. Equilibrium is said to be "favorable" if the ion exchanger takes up the ion from the feed (B) in preference to the ion initially in the bed (A), that is, if the separation factor [5]

$$\alpha_B^A \equiv \frac{\overline{C}_A \, C_B}{\overline{C}_B \, C_A} \qquad (1)$$

[1] See *e.g.* literature cited in *F. C. Nachod* and *J. Schubert:* Ion-Exchange Technology. Academic Press, New York 1956; *E. H. Becker-Boost*, Chemie-Ing.-Techn. *27*, 579 (1955); *28*, 411, 532 (1956); Ullmanns Encyklopädie der technischen Chemie. 3rd. Ed., Urban und Schwarzenberg, Munich 1957, vol. 8, p. 823.

[2] See also the excellent review by *T. Vermeulen*, Advances Chem. Engng. *2*, 147 (1958).

[3] *E. Glueckauf*, in Ion-Exchange and Its Applications. Soc. Chem. Ind., London 1955, p. 34.

[4] *F. Helfferich:* Ion-Exchange. McGraw-Hill. New York 1962, chapter 9.

[5] Note the differences between the separation factor and other similar quantities involving, in their definitions, the ionic valences as exponents; for column-performance calculations the separation factor is the most convenient quantity. The quantity α_B^A is equivalent to r in *Vermeulen*'s [2] and 1/K in *Gilliland*'s papers [44].

is less than unity. In this case, A ions lagging behind the boundary are preferentially displaced by B from the stationary ion exchanger into the moving solution and thus catch up with the boundary, while B ions having moved ahead of the boundary are preferentially retained by the ion exchanger until the boundary reaches them again. Therefore the boundary remains relatively sharp. Conversely, equilibrium is said to be "unfavorable" if the ion exchanger retains its original counterion (A) in preference to that from the feed (B), *i.e.* if $\alpha_B^A > 1$.

In that case, A ions behind the boundary are selectively retained and thus keep falling farther behind, while B ions ahead of the boundary stay preferentially in the solution and thus increase their lead. Accordingly, the boundary spreads rapidly.

The difference between favorable and unfavorable equilibria is a fundamental one and not just a matter of degree. With favorable equilibrium, the sharpening effect of equilibrium and the spreading effects of any disturbances counteract one another. The boundary attains a steady-state form, the so-called "constant pattern", in which the opposing effects compensate one another so that the pattern remains unchanged as the boundary travels farther down the column. Such boundaries are called "self-sharpening" boundaries. With unfavorable equilibrium, on the other hand, there is no sharpening effect, and the boundary keeps spreading. Eventually, a "proportionate pattern" is attained in which the boundary spread increases linearly with the distance travelled. Such boundaries are called "non-sharpening" boundaries.

Typical self-sharpening and non-sharpening boundaries and the corresponding ion-exchange isotherms are shown in Fig. 1. The isotherms give the equivalent

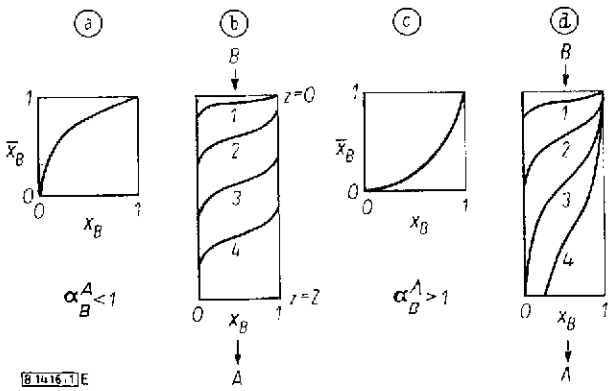


Fig. 1. Ion-exchange isotherms and boundary shapes for favorable and unfavorable equilibria (schematic). Axial concentration profiles in the column are shown for four consecutive times (numbered 1 to 4)

fraction of B in the ion exchanger as a function of this fraction in the solution, at equilibrium and for a specified constant total concentration (in equivalents) of the solution. The equivalent fraction is defined by

$$x_B \equiv \frac{z_B C_B}{z_A C_A + z_B C_B} \qquad (2)$$

(z = ionic valence)

If $\alpha_B^A < 1$, the isotherm of B has negative curvature, and the boundary is self-sharpening; if $\alpha_B^A > 1$, the isotherm of B has positive curvature, and the boundary is non-sharpening [6]. A linear isotherm, as assumed in many theories, can exist only if $\alpha_B^A = 1$, that is, if the ion exchanger has no preference for one ion over the other [7]. A linear isotherm leads to a non-sharpening boundary, but not to a proportionate pattern.

In addition to unfavorable equilibrium, the following effects can act as disturbances tending to spread the boundary:

1. The ion-exchange rate is finite and thus cannot completely keep pace with the rapid change in composition of the solution in a layer through which a sharp boundary passes. This effect is most pronounced if the ion-exchange rate is low and the sharpness and migration rate of the boundary are high.

2. The so-called longitudinal diffusion (*i.e.* diffusion in the direction of the column axis) tends to level out concentration differences within the bed. This effect is most pronounced if the boundary is sharp and its residence time in the column is long (*i.e.* the migration rate is low). This effect, though being considerable in gas adsorption and gas chromatography, is usually insignificant in ion exchange.

3. Hydrodynamic effects may cause back-mixing (eddy dispersion, eddy diffusion) and can also distort rather than spread the boundary. These effects, too, affect mainly sharp boundaries (see page 449).

The constant pattern of a self-sharpening boundary is determined by the balance of forces between the sharpening effect of favorable equilibrium and the spreading effects of the disturbances; accordingly, the shape of such a boundary depends decisively on the extent of the disturbances. The opposite holds for non-sharpening boundaries; as the boundary becomes sufficiently diffuse, the disturbances lose their influence, and the proportionate pattern from then on depends on the ion-exchange equilibrium only.

For more extensive coverage, a few more complex ion-exchange processes of practical interest are included in the discussion:

Ion exchange followed by neutralization or other consecutive reactions occurs, for example, in deionization with cation- and anion-exchange columns in series. The effluent of the first (cation-exchange) column is acidic. Therefore, the exchange of anions for OH^- in the subsequent anion-exchange column is accompanied by neutralization of OH^- by H^+ in the solution. This elimination of the OH^- ions released by the ion exchanger renders the anion-exchange equilibrium "favorable" and thus makes the boundary self-sharpening. As H^+ is used up, however, this favorable effect becomes weaker and may disappear altogether. An analogous situation is encountered in cation exchange between an alkaline feed and a cation exchanger in H^+-form and, quite generally, in processes in which the ion released by the ion exchanger is

[6] In adsorption columns the situation is similar. Adsorption isotherms are usually negatively curved and, hence, "favorable" for adsorption and "unfavorable" for desorption. Therefore, front boundaries in adsorption are usually self-sharpening and rear boundaries in desorption (elution) non-sharpening.

[7] This is true for the processes discussed in this paper, in which x_B varies from 0 to 1, but not for elution chromatography of a trace ion B where always $x_B \ll 1$. In the latter case, only a short segment of the isotherm is needed which, as a reasonable approximation, may be considered linear even if $\alpha_B^A \neq 1$ (here, A = eluting ion).

consumed by a consecutive reaction (complex formation, association, *etc.*).

In mixed-bed deionization, cation and anion exchange take place simultaneously on adjacent ion-exchanger particles, and the H^+ and OH^- ions released by the ion exchangers are consumed at once by neutralization. Equilibrium thus remains "favorable" and unchanged for both ion-exchange processes until the bed is completely exhausted.

If the feed contains several counterion species, the ions with higher affinities for the ion exchanger migrate more slowly than the others. With favorable equilibrium, a band containing only the ion with the least affinity for the ion exchanger will thus build up behind the front boundary. Hence, the sharpness of this boundary is unaffected by the ions with higher affinities.

In displacement development – used, for example, in commercial rare-earth separations [8] – the mixture containing several counterion species is introduced at the top of the bed and is then "developed" by a solution containing a counterion which the ion exchanger prefers to those of the mixture. The developing agent thus displaces the mixture with a self-sharpening boundary. The counterion originally present in the bed is chosen in such a way that the front boundary of the mixture is also self-sharpening. While the mixture migrates through the bed between the two self-sharpening boundaries, its components arrange themselves into bands between which further self-sharpening boundaries arise. Eventually, a constant pattern is attained, *i.e.*, all bands and boundaries then migrate at equal rate and maintain their shapes. The individual counterion species of the mixture can be collected as separate fractions in the effluent where they emerge in the sequence of increasing affinity. The sharpness of a boundary between two adjacent bands depends on the separation factor of the counterions on either side, but is not affected by the counterions in other, more distant bands. Optimum separation is achieved with a column that is long enough to permit the constant pattern to be attained; a further increase in column length does not improve the sharpness of separation, but only adds to the separation time.

Quantitative Approaches and Theories

The foremost aim of column-performance calculations is to predict effluent concentration histories (effluent concentrations as a function of time or of the effluent volume) of the species involved, for specified operating conditions and from known or experimentally determined data on ion-exchange equilibria and rates.

For such calculations, equations representing ion-exchange equilibria and rates are required. Unfortunately, however, ion-exchange equilibria and rates are too complex to be expressed by equations that are simple and yet universal and rigorous. For example, the separation factor defined in Eq. (1) is usually not constant but depends on the solution concentration and even on the equivalent fractions of the ions involved, and thus varies in the course of ion exchange. Also, the rate of ion exchange obeys nonlinear differential equations which, even for very simple boundary conditions, have been solved so far only by numerical computation [9]. Column-performance calculations therefore require idealizations such as, for example, the assumption of a constant separation factor and the postulation of mathematically more manageable rate laws. A sacrifice in rigor at this stage is not necessarily detrimental since a completely rigorous treatment is impossible because of hydrodynamic effects, for which no accurate theory exists. Care must be taken, however, that no relevant feature of the system is lost; as a striking example, a theory which postulates a linear isotherm and thus leads invariably to a non-sharpening boundary must give answers which will not even be qualitatively correct when applied to self-sharpening boundaries.

In the discussion below an attempt is made to classify the most common theories according to their simplifying assumptions, to study critically their adequacy and shortcomings, and to delineate their ranges of applicability. For the sake of simplicity, the effects of longitudinal diffusion and of hydrodynamic and electrochemical disturbances are discussed separately (see p. 448). A uniform set of symbols will be used, and the equations of the various authors are modified accordingly.

The Martin-Synge Model

One of the earliest approaches to column performance is based on a concept which originated from the theory of distillation. This concept was first adapted to gas chromatography by *Martin* and *Synge* [10], and was later applied to ion-exchange chromatography by *Mayer* and *Tompkins* [11]. The basic idea is that the actually continuous operation can be represented, in reasonable approximation, by a discontinuous one in which the solution remains in an "effective plate" of the column until equilibrium with the ion exchanger is established, then passes on to the next plate to undergo another equilibration, and so forth. In the actual column, in which the flow of solution is continuous, local equilibrium between ion exchanger and solution is usually not attained. Nevertheless, the Martin-Synge model can be applied since deviations from local equilibrium as well as any other disturbances are approximately accounted for by a suitable choice of the plate height. (In other words, the model substitutes complete mixing within the plates for other disturbances as the cause of boundary spreading). The plate height, however, is a purely empirical quantity. Its dependence on the operating conditions – required for theoretical predictions – can only be established by correlation with other, more accurate theories.

Theories based on this model have been developed mainly for elution development, but the model can also be applied to processes as discussed here. Because of its simplicity the model can be used to obtain very crude approximations in a relatively short time and may still be manageable in cases in which more accurate theories become too complex. Even if analytical solutions cannot be found, the model may still be used for numerical evaluation.

[8] *F. H. Spedding* and *J. E. Powell* in *F. C. Nachod* and *J. Schubert:* Ion-Exchange Technology. Academic Press, New York 1956, p. 359.

[9] For detailed discussions of equilibria and rates see *e.g. F. Helfferich:* Ion-Exchange. McGraw-Hill, New York 1962, chapters 5 and 6.

[10] *A. J. P. Martin* and *R. L. M. Synge*, Biochem. J. *35*, 1358 (1941).

[11] *S. W. Mayer* and *E. R. Tompkins*, J. Amer. chem. Soc. *69*, 2866 (1947).

DeVault's Equilibrium Theory and Its Limiting Cases

A more accurate way of describing column performance is by a "continuous" treatment rather than by the "discontinuous" Martin-Synge model. The continuous treatment is based on material balances in a differential layer of the bed. The material balance for an arbitrary species i states that the change in content of the layer equals inflow minus outflow, and can be written as

$$q \frac{\partial}{\partial V}(\overline{X}_i + \beta C_i) + \frac{\partial C_i}{\partial z} = 0 \qquad (3)$$

[q = column cross section; z = space coordinate downstream (distance from column inlet); V = solution volume that has passed through layer; β = fractional void volume of bed; C_i = concentration of i in solution per unit volume of solution; $\overline{X}_i$ = concentration of i in ion exchanger per unit volume of bed (insterstitial void included)].

In the simplest theories of this type, local equilibrium between ion exchanger and solution is assumed to exist everywhere in the bed. In this case, of course, the relation between $\overline{X}_i$ and C_i is solely determined by the isotherm. Solutions of Eq. (3) with the condition of local equilibrium were first given by *DeVault* [12,13]. This author also showed that, quite generally, isotherms with positive curvature give spreading boundaries whereas isotherms with negative curvature give boundaries which remain ideally sharp (or become ideally sharp, if initially diffuse). With linear isotherms, the shape of the boundary remains unchanged as the boundary migrates. With unfavorable equilibrium, the pattern is proportionate from the very beginning if the initial composition of the bed is uniform and the composition of the feed is constant. For the particular case of a constant separation factor $\alpha_B^A > 1$, a bed initially in A form, and B as feed, *Walter* [15] obtained the relationship

$$x_B = \frac{\alpha_B^A - (\alpha_B^A/\mathfrak{T})^{1/2}}{\alpha_B^A - 1} \qquad (4)$$

where the "throughput ratio" $\mathfrak{T}$ is defined by [16]

$$\mathfrak{T} \equiv \frac{V - \beta V_b}{V_{stoi}} \qquad (5)$$

[V_b = bed volume and $V_{stoi} \equiv V_b\overline{X}/C$ = solution volume which is stoichiometrically equivalent to the ion-exchange capacity of the bed; Eq. (4) applies within the limits $1/\alpha_B^A \leq \mathfrak{T} \leq \alpha_B^A$ (for lower and higher values of $\mathfrak{T}$, x_B is zero or unity, respectively)].

Solutions or calculation methods for other initial conditions and restrictions, as well as for systems with more than two counterion species, have been given by *DeVault* [12] and later authors [2,15,17–23].

Figure 2 (upper part) shows schematically the behavior of the boundary for favorable and unfavorable equilibria. Values of constant x_B fall on straight lines in the system z, V, x_B, provided that local equilibrium is not disturbed. This facilitates the computation in more complex cases.

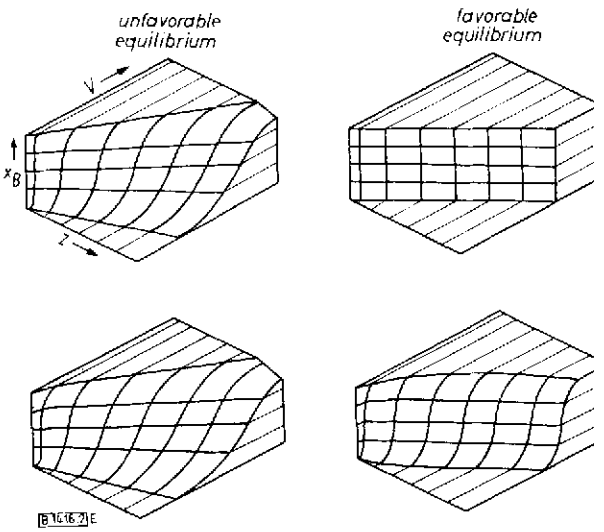


Fig. 2. Boundary shapes with unfavorable and favorable equilibria, calculated from *DeVault*'s equilibrium theory (top) and *Thomas*' rate theory (bottom). Note that the lines of constant x_B values are straight in the equilibrium theory and are curved near their origin in the rate theory

The assumption of local equilibrium is justified only if the finite ion-exchange rate does not cause significant deviations. It will be seen later that this condition is met if equilibrium is unfavorable and the (non-sharpening) boundary has become sufficiently diffuse. In contrast, if equilibrium is favorable, the boundary shape continues to depend decisively on the ion-exchange rate, and equilibrium theories are inapplicable.

The Rate Theories of Furnas and Thomas, Their Limiting Cases and Extensions

In contrast to the "equilibrium theories", the "rate theories" drop the assumption of local equilibrium and attempt to account quantitatively for the effect of the finite ion-exchange rate. The material balance, Eq. (3), is retained, but $\overline{X}_i$ now depends not only on C_i but also on the ion-exchange rate. Quite generally, the problem is to solve a set of equations of the type

[12] *D. DeVault*, J. Amer. chem. Soc. *65*, 532 (1943).

[13] Differential material balances have been used by others before *DeVault*, particularly by *Bohart* [72], *Wicke* [74], and *Wilson* [14]. The non-equilibrium theories of Bohart and Wicke are discussed later. *Wilson* assumes local equilibrium but neglects the insterstitial void (*i.e.* $\beta = 0$), limits himself to linear isotherms, and thus obtains boundaries which retain their initial sharpness.

[14] *J. N. Wilson*, J. Amer. chem. Soc. *62*, 1583 (1940).

[15] *J. E. Walter*, J. chem. Physics *13*, 229 (1945).

[16] The throughput ratio is a useful parameter; it is linear in the feed (or effluent) volume and defined in such a way that it is zero when one void volume has passed the bed, and is unity when the solution volume which has passed through is stoichiometrically equivalent to the ion-exchange capacity of the bed.

[17] *J. I. Coates* and *E. Glueckauf*, J. chem. Soc. (London) 1308 (1947).

[18] *E. N. Gapon* and *T. B. Gapon*, Zhur. Priklad. Khim. *21*, 937 (1948).

[19] *E. Glückauf*, Nature (London) *156*, 748 (1945); Proc. Roy. Soc. (London) *A 186*, 35 (1946); J. chem. Soc. (London) 1302, 1321 (1947).

[20] *A. C. Offord* and *J. Weiss*, Discuss. Faraday Soc. *7*, 26 (1949); see also discussion by *E. Glueckauf*.

[21] *V. V. Rachinskii*, Zhur. Priklad. Khim. *27*, 831 (1954).

[22] *A. P. Tudge*, Canadian J. Physics. *11*, 1600, 1611 (1961).

[23] *J. Weiss*, J. chem. Soc. (London) 297 (1943).

$$q\frac{\partial}{\partial V}(\bar{X}_i + \beta C_i) + \frac{\partial C_i}{\partial z} = 0 \qquad \text{(material balance)} \quad (3)$$

$$\bar{X}_i^* = f(C_i) \qquad \text{(isotherm)} \quad (6)$$

$$\frac{\partial \bar{X}_i}{\partial t} = f(\bar{X}_i^*, \bar{X}_i, C_i^*, C_i) \qquad \text{(rate law of ion exchange)} \quad (7)$$

(quantities with asterisks are equilibrium values: $\bar{X}_i^*$ = concentration of i in ion exchanger in equilibrium with solution of concentration C_i; C_i^* = concentration of i in solution in equilibrium with ion exchanger of concentration $\bar{X}_i$).

The various theories differ in their postulated isotherms and rate laws. A general objection, that can be raised against any such set of equations, will be discussed later. Most rate theories operate with height equivalents of effective plates, or similar quantities that are reminiscent of the Martin-Synge model. In the rate theories, however, these quantities are not empirical but are well-defined functions of the operating conditions and constitute convenient, but by no means indispensable, auxiliaries.

The J function. A set of equations analogous to Eqs. (3), (6), and (7) applies to heat transfer in heat exchangers. A solution for this analogous problem was derived by *Anzelius* [24], *Schumann* [25], *Nusselt* [26], and *Furnas* [27], and was later adapted to mass-transfer processes by *Beaton* and *Furnas* [28]. This solution is valid for a linear isotherm and a simple rate law:

$$\bar{X}_i^* = aC_i \qquad (a = \text{const.}) \quad (8)$$

$$\frac{\partial \bar{X}_i}{\partial t} = k(\bar{X}_i^* - \bar{X}_i) = ak(C_i - C_i^*) \quad (9)$$

(k = first-order rate constant)

The effluent history of a bed initially in A form with B as feed may be written as

$$x_B = J(\mathfrak{N}, \mathfrak{T}\mathfrak{N}) \quad (10)$$

where the function J is defined by

$$J(x, y) \equiv 1 - \int_0^x \exp(-x-\xi)\, I_0(2\sqrt{y\xi})\, d\xi \quad (11)$$

and $\mathfrak{N}$ is the "number of mass-transfer units", defined by

$$\mathfrak{N} \equiv \frac{akZ}{v} \quad (12)$$

(Z = column length; v = linear flow rate = volume of solution passing through unit cross section of bed per unit time; I_0 = modified Bessel function of first order).

The mass-transfer unit can be visualized as some kind of effective plate. Its height equivalent, however, is only about half that of the effective plates in the Martin-Synge model and in the standard theories of gas chromatography.

The J function is shown in Fig. 3. The effluent histories, normally S-shaped, come out as almost straight lines in this log-probability plot, a fact which facilitates interpolation between tabulated values. Extensive tables of the function $g(x,y) \equiv 1 - J(x,y)$ have been published by the U.S.Bureau of Mines [29]; shorter tables and graphical representations have been given by *Hougen* [30], *Furnas* [27,28], *Klinkenberg* [31], and *Goldstein* [32]. *Klinkenberg* also gives various simpler approximations [31,33].

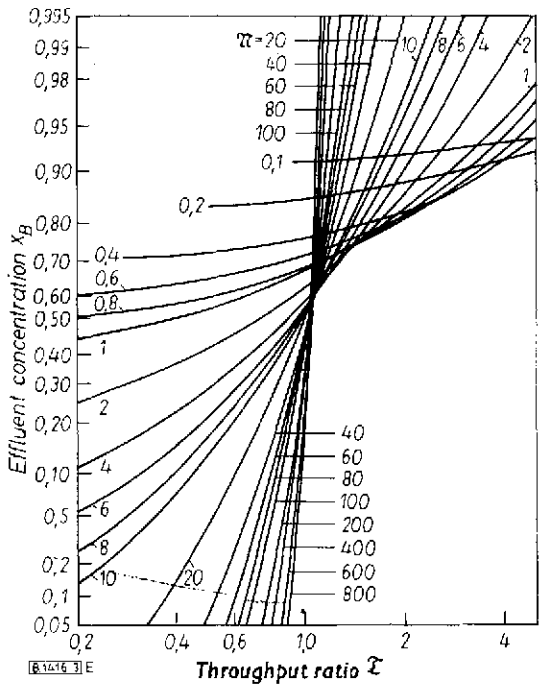


Fig. 3. The "J" function. The diagram shows x_B as a function of $\mathfrak{T}$ with $\mathfrak{N}$ as the parameter (from *N. K. Hiester* and *T. Vermeulen* [42])

The J function, because of its restriction to a linear isotherm, is not in itself a very useful solution, but is of importance in the evaluation of other solutions. For example, this function appears in Thomas' solution (see below) and can also be used in theories of elution development [34].

Various limiting cases of the J function have been discussed by *Klinkenberg* [31], *Goldstein* [32], and *Ver-*

[24] *A. Anzelius*, Z. angew. Math. Mech. *6*, 291 (1926).

[25] *T. E.W. Schumann*, J. Franklin Inst. *208*, 405 (1929).

[26] *W. Nusselt*, Tech. Mech. u. Thermodyn. *1*, 417 (1930).

[27] *C. C. Furnas*, Trans. Amer. Inst. Chem. Eng. *24*, 142 (1930).

[28] *R. H. Beaton* and *C. C. Furnas*, Ind. Engng. *33*, 1500 (1941).

[29] *S. R. Brinkley*, Jr., Report 3172, U.S.Dept. of the Interior, U.S.Bureau of Mines, Explosives and Physical Sciences Div., Pittsburgh, Pa., 1951; *S. R. Brinkley*, Jr., *H. E. Edwards*, and *R. W. Smith*, Jr., Math. Tables Aids Computation *6*, 40 (1952).

[30] *O. A. Hougen* and *W. R. Marshall*, Jr., Chem. Engng. Progress *43*, 197 (1947).

[31] *A. Klinkenberg*, Ind. Engng. Chem. *46*, 2285 (1954).

[32] *S. Goldstein*, Proc. Roy. Soc. (London) *A 219*, 151, 171 (1953).

[33] *A. Klinkenberg*, De Ingenieur, in the press.

[34] In elution development, the assumption of a linear isotherm is a reasonable approximation (see [7]). As shown by *Vermeulen* [2,35] the band shape as a function of sample size can be obtained by subtracting two J functions from one another (see also *Rosen* [36] and *Stene* [37] for the prerequisites of such simple superpositions). In the limiting case of sufficiently small sample size, this treatment reduces to the standard theories of *van Deemter* [38] and *Glueckauf* [39,40].

[35] *T. Vermeulen* and *N. K. Hiester*, Ind. Engng. Chem. *44*, 636 (1952).

[36] *J. B. Rosen* and *W. E. Winsche*, J. chem. Physics *18*, 1587 (1950).

[37] *S. Stene*, Arkiv Kemi Mineral. Geol. *A 18*, No. 18 (1945).

[38] *J. J. van Deemter*, *F. J. Zuiderweg*, and *A. Klinkenberg*, Chem. Engng. Sci. *5*, 271 (1956).

[39] *E. Glueckauf*, Discuss. Faraday Soc. *7*, 12 (1949).

[40] *E. Glueckauf*, Trans. Faraday Soc. *51*, 34 (1955).

meulen [2]. For $\mathfrak{N}\sqrt{\mathfrak{T}} > 60$, that is, for sufficiently long columns, Eq. (10) reduces to

$$x_B \cong {}^1/_2\left[1 + \operatorname{erf}\left(\sqrt{\mathfrak{T}\mathfrak{N}} - \sqrt{\mathfrak{N}}\right)\right] \tag{13}$$

The Thomas Theory and its Limiting Cases. H. C. Thomas [41] was the first to find a solution of Eq. (3) for non-equilibrium conditions and a non-linear isotherm. He assumes a constant separation factor and a rate law which formally corresponds to a reversible chemical reaction of second order:

$$\frac{\partial \bar{X}_B}{\partial t} = kC_B(\bar{X}-\bar{X}_B) - k\alpha_B^A \bar{X}_B (C-C_B) \tag{14}$$

(stoichiometric exchange of ions of equal valence is assumed; $\bar{X} \equiv \bar{X}_A + \bar{X}_B$ = total concentration in ion exchanger; $C \equiv C_A + C_B$ = total concentration in solution; k = second-order rate constant. For exchange of ions of different valences, Eq. (14) can be used with equivalent instead of molar concentrations).

Thomas' solution is for the effluent of a bed in A form, with B as feed, and may be written as [2,42]:

$$x_B = \frac{J(\alpha_B^A \mathfrak{N}, \mathfrak{T}\mathfrak{N})}{J(\alpha_B^A \mathfrak{N}, \mathfrak{T}\mathfrak{N}) + \left[1-J(\mathfrak{N}, \alpha_B^A \mathfrak{T}\mathfrak{N})\right]\exp\left[(\alpha_B^A-1)\mathfrak{N}(\mathfrak{T}-1)\right]} \tag{15}$$

where

$$\mathfrak{N} \equiv \frac{k\bar{X}Z}{v} \tag{16}$$

This solution has been tabulated by the Stanford Research Institute for a great number of sets of the parameters α_B^A, $\mathfrak{N}$, and $\mathfrak{T}$ [43].

The following limiting cases of the Thomas solution are of interest [2,32,42,44,45]. For $\alpha_B^A = 1$ (linear isotherm), Eq. (15) reduces to the simple J function, Eq. (10). For $\alpha_B^A > 1$ (unfavorable equilibrium) and long columns, Eq. (15) reduces to *Walter*'s Eq. (4), i.e. to a proportionate pattern. In contrast, for $\alpha_B^A < 1$ (favorable equilibrium) and long columns, Eq. (15) reduces to

$$x_B = \frac{1}{1 + \exp\left[(\alpha_B^A-1)\mathfrak{N}(\mathfrak{T}-1)\right]} \tag{17}$$

This latter equation gives a constant pattern [46] and has been derived by *Walter* [47] and *Sillén* [48] by an independent and simpler method postulating such a pattern.

Typical non-sharpening and self-sharpening boundaries obtained from Eq. (15) are shown schematically in Fig. 2 (bottom). By comparison with the boundaries obtained from the equilibrium theory one can recognize the effect of the finite ion-exchange rate; with unfavorable equilibrium this effect is noticeable in the early stages only, whereas with favorable equilibrium it remains significant indefinitely.

The Thomas solution has its shortcomings which will soon become apparent. Nevertheless, this solution is of great significance as the most general – though not exact – treatment providing a logical framework which permits more accurate solutions for particular cases to be classified. Thus, the Thomas solution provided the first mathematical proof that boundaries indeed attain constant or proportionate patterns; beyond that, one can use the Thomas solution to estimate, for any specified separation factor, how many mass-transfer units are needed to attain such a pattern.

Extensions and Modifications of the Thomas Theory. The Thomas theory is extended without great difficulties to other initial and boundary conditions – at least as long as the initial bed composition is uniform, the feed is constant, and not more than two counterion species are involved [2,45,49]. Several solutions for more complex entry conditions (*e.g.*, for regeneration of an incompletely exhausted bed) and for certain cases involving three counterion species have been worked out by *Hiester* [50], *Goldstein* [32,45], *Baddour* [51], and *Cornaz* [52]. All these solutions, however, are based on the somewhat controversial rate equation (14).

Objections against Eq. (14), which is the rate law of a reversible chemical reaction, can be raised because ion exchange is known to be controlled by ionic diffusion in the ion-exchanger beads or adherent films rather than by a chemical reaction [9,53]. To reconcile *Thomas*' treatment with diffusion-controlled ion exchange, *Gilliland* [44] and others [51] correlate the rate constant in Eq. (14) with mass-transfer coefficients or "diffusion resistances":

$$k = \frac{1}{\bar{X}R_p + CR_f/\alpha_B^A} \tag{18}$$

where R_p and R_f are the diffusion resistances in the particle and the film, respectively, and are assumed to be constant. Unfortunately, a closer examination reveals that the rate equation (14), even with Gilliland's definition of the rate constant, does not provide a satisfactory approximation. The reason is that film diffusion and particle diffusion affect the shape of a boundary in different places. Let us consider a self-sharpening boundary. Slow film diffusion results mainly in "leakage" of small amounts of the displacing ion far ahead of the main boundary (Fig. 4, top), whereas slow particle diffusion results mainly in "tailing" of small amounts

[41] *H. C. Thomas*, J. Amer. chem. Soc. *66*, 1664 (1944); Ann. N.Y. Acad. Sci. *49*, 601 (1948); in *F. C. Nachod:* Ion-Exchange. Academic Press, New York 1949, p. 29.

[42] *N. K. Hiester* and *T. Vermeulen*, Chem. Engng. Progress *48*, 505 (1952).

[43] *A. Opler* and *N. K. Hiester:* Tables for Predicting the Performance of Fixed-bed Ion-exchange and similar Mass-transfer Processes. Report, Stanford Research Institute, 1954.

[44] *E. R. Gilliland* and *R. F. Baddour*, Ind. Engng. Chem. *45*, 330 (1953).

[45] *S. Goldstein* and *J. D. Murray*, Proc. Roy. Soc. (London) *A 252*, 334, 348, 360 (1959).

[46] It is readily shown that a constant pattern is obtained from any equation in which the parameters $\mathfrak{N}$ and $\mathfrak{T}$ appear only in the combination $\mathfrak{N}(\mathfrak{T}-1)$.

[47] *J. E. Walter*, J. chem. Physics *13*, 332 (1945).

[48] *L. G. Sillén*, Arkiv Kemi Mineral. Geol. *A 22*, No. 15 (1946); Nature (London) *166*, 722 (1950); *E. Ekedahl*, *E. Högfeldt*, and *L. G. Sillén*, Nature (London) *166*, 723 (1950).

[49] *T. Vermeulen* and *N. K. Hiester*, J. chem. Physics *22*, 96(1954).

[50] *N. K. Hiester* and *T. Vermeulen*, J. chem. Physics *16*, 1087 (1948).

[51] *R. F. Baddour*, *D. J. Goldstein*, and *P. Epstein*, Ind. Engng. Chem. *46*, 2192 (1954); *R. F. Baddour* and *R. D. Hawthorn*, *ibid.* *47*, 2517 (1955).

[52] *J. P. Cornaz* and *N. K. Hiester*, unpublished (1957).

[53] Rate control by a chemical reaction has been observed in an exceptional case by *R. Turse* and *W. Rieman* III, J. physic. Chem. *65*, 1821 (1961).

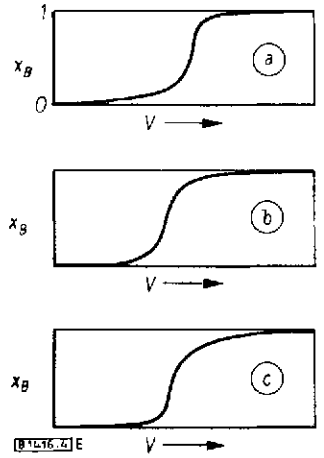


Fig. 4. Typical effluent concentration histories of self-sharpening boundaries; a) with film-diffusion control ($k_f \ll k_p$; "leakage"); b) intermediate case ($k_f = k_p$; symmetrical curve), and c) with particle-diffusion control ($k_f \gg k_p$; "tailing"). The Thomas theory always gives a symmetrical curve.

of the displaced ion far behind the main boundary (Fig. 4, bottom). In contrast, the rate equation (14) leads invariably to a "symmetrical" boundary (Fig. 4, middle). Thus the concept of constant and additive diffusion resistances fails [54]. In particular, calculated breakthrough capacities or degrees of column utilization may be badly in error since leakage can cause a much earlier breakthrough than *Gilliland*'s treatment would predict.

More satisfactory approximations for the ion-exchange rate are [2,3,38–40,55–60]:

$$\frac{\partial \bar{X}_i}{\partial t} \simeq k_p(\bar{X}_i^* - X_i) \qquad \text{for particle-diffusion control} \qquad (19)$$

$$\frac{\partial \bar{X}_i}{\partial t} \simeq k_f(C_i - C_i^*) \qquad \text{for film-diffusion control} \qquad (20)$$

In these "linear-driving-force relations" it is assumed that the rate is always proportional to the distance from equilibrium. Correlations between the rate constants k_p and k_f in these equations and other physical quantities can be obtained by curve fitting with more accurate rate equations [2,3,44]. For example, *Glueckauf* [3] uses

$$k_p = \frac{\bar{D}}{0.071\, r_o^2}; \qquad k_f = \frac{D(1 + 70\, r_o v)}{0.133\, r_o^2} \qquad (21)$$

($\bar{D}$ = average diffusion coefficient in ion exchanger; D = average diffusion coefficient in solution; r_0 = particle radius [61]).

It has been shown by *Vermeulen* [2,42] that *Thomas*' solution, Eq. (15), can still be used with the more appropriate rate equations (19) and (20); now, however, $\mathfrak{N}$ is no longer constant but changes with the variable x_B and thus has different values at different parts of the boundary:

$$\mathfrak{N} = \frac{k_g Z\bar{X}/Cv}{\alpha_B^A - (\alpha_B^A - 1)\bar{x}_B} \qquad \text{for particle-diffusion control} \qquad (22)$$

$$\mathfrak{N} = \frac{k_f Z/v}{1 + (\alpha_B^A - 1)x_B} \qquad \text{for film-diffusion control} \qquad (23)$$

The desired effluent history $x_B(\mathfrak{T})$ must therefore be composed by a rather lengthy procedure, piecing together curve segments corresponding to various constant $\mathfrak{N}$ values [2,42]. This method does, however, at least reflect the characteristic effects of particle- and film-diffusion control (tailing and leakage).

The ion-exchange rate may be affected, in certain cases, by both particle and film diffusion. As a first approximation, the boundary spreads caused by the two processes may then be regarded as additive [3]. For better accuracy corrections must be applied [2,62,63].

Another simplifying and not always justified assumption in these theories is the constancy of the separation factor. If the latter depends noticeably on x_B, it may again be necessary to compose the effluent curve by piecing together individual curve segments [2].

Other solutions of the general set of equations (3), (6), and (7) have also been worked out with a number of other rate laws and isotherms [2,41,55,64–71]. The principal objection that can be raised against any such set of equations applies to all these solutions also (see p. 447).

Simpler Solution for Proportionate and Constant Patterns

In practice, the number of mass-transfer units or effective plates in a column is usually large enough for attainment of a proportionate or constant pattern. This is particularly true if the selectivity is high, as in most industrial processes, since then a relatively small number of plates is sufficient. The calculation of these patterns is comparatively simple and does not require the use of the more elaborate theories discussed above.

Proportionate pattern. With unfavorable equilibrium, the effect of the finite ion-exchange rate disappears as the boundary spreads and attains the propor-

[54] This concept holds only for linear isotherms. (Additivity of plate-height contributions or variances in theories of elution development is the consequence of the assumptions of linear isotherms). Similarly, longitudinal diffusion is a non-additive disturbance unless the isotherm is linear (see p. 448). For the mathematically analogous situation in columns with inert packing, see *R. Sizmann*, Chem.-Ing.-Technik *33*, 659 (1961).

[55] *E. Glueckauf* and *J. I. Coates*, J. chem. Soc. (London) 1315 (1947).

[56] *E. Glueckauf*, J. chem. Soc. (London) 3280 (1949).

[57] *A. S. Michaels*, Ind. Engng. Chem. *44*, 1922 (1952).

[58] *L. Lapidus* and *J. B. Rosen*, Chem. Engng. Progress Symp. Ser. *50*, No. 14, 97 (1954).

[59] *N. R. Amundson*, Ind. Engng. Chem. *48*, 26, 35 (1956).

[60] *A. Klinkenberg* and *F. Sjenitzer*, Chem. Engng. Sci. *5*, 258 (1956).

[61] For spherical particles; otherwise radius of "equivalent sphere", i.e., of the sphere which has the same surface-to-volume ratio as the ion-exchange material (cf. *R. Aris*, Chem. Engng. Sci. *6*, 262 (1957)).

[62] *N. K. Hiester, S. B. Radding, R. L. Nelson*, Jr., and *T. Vermeulen*, A. I. Ch. E. Journal *2*, 404 (1956).

[63] *K. Klamer, C. van Heerden*, and *D. W. van Krevelen*, Chem. Engng. Sci. *9*, 1 (1958).

[64] *J. DuDomaine, R. L. Swain*, and *O. A. Hougen*, Ind. Engng. Chem. *35*, 546 (1943).

[65] *N. R. Amundson*, J. physic. Chem. *52*, 1153 (1948); *54*, 812 (1950).

[66] *W. A. Selke* and *H. Bliss*, Chem. Engng. Progr. *46*, 509 (1951).

[67] *T. Vermeulen*, Ind. Engng. Chem. *45*, 1664 (1953).

[68] *M. V. Tovbin* and *F. G. Dyatlovitskaya*, Zhur. Fiz. Khim. *28*, 1539 (1954).

[69] *E. Glueckauf*, Trans. Faraday Soc. *51*, 1540 (1955).

[70] *C. Tien* and *G. Thodos*, A. I. Ch. E. Journal *5*, 373 (1959).

[71] *Ç. Tien* and *G. Thodos*, A. I. Ch. E. Journal *6*, 364 (1960); Chem. Engng. Sci. *13*, 120 (1961).

tionate pattern (see p. 445). Therefore, equilibrium theories are adequate for calculating such patterns. For a constant separation factor *Walter*'s Eq. (4) can be used. For variable separation factors and more complex conditions effluent histories can be constructed as indicated by *DeVault* [12].

Constant pattern. It is practical for calculating constant patterns to use a gliding rather than a stationary frame of reference by placing the origin of the space co-ordinate into, say, the center of gravity of the boundary. As the constant pattern is attained, the variable x_B then becomes a function only of the new space co-ordinate (distance from center of gravity) and no longer of time. This greatly simplifies the mathematics.

Solutions for various rate laws can be derived without much difficulty. With a constant separation factor and Thomas' rate equation (14), the effluent history of a bed in A form, with B as feed, is given by *Walter*'s Eq. (17) and is "symmetrical" (see Fig. 4, middle). In contrast, with the rate equations (19) and (20) one obtains, according to *Glueckauf* [3], for the effluent volume $V(x_B)$ at which the concentration x_B emerges:

$$V(x_B) = V_b \left(\frac{\bar{X}}{C} + \beta\right) \left\{1 - \frac{\bar{X}/C}{(\bar{X}/C + \beta)^2} \frac{v}{k_p Z} \left[\frac{1}{1-\alpha_B^A} \ln (1-x_B) - \frac{\alpha_B^A}{1-\alpha_B^A} \ln x_B + 1\right]\right\} \text{ for particle-diffusion control;} \quad (24)$$

$$V(x_B) = V_b \left(\frac{\bar{X}}{C} + \beta\right) \left\{1 - \left(\frac{\bar{X}/C}{\bar{X}/C + \beta}\right)^2 \frac{v}{k_f Z} \left[\frac{\alpha_B^A}{1-\alpha_B^A} \ln (1-x_B) - \frac{1}{1-\alpha_B^A} \ln x_B + 1\right]\right\} \text{ for film-diffusion control.} \quad (25)$$

Equation (25), in a slightly different form, had been derived earlier by *Michaels* [57]. These equations, in contrast to Eq. (17), reflect "leakage" and "tailing". The form given is particularly convenient for computing breakthrough capacities at specified maximum permissible effluent concentrations. If both particle and film diffusion affect the ion-exchange rate, the boundary spreads caused are often considered as additive; for better accuracy, however, a correction must be applied [2,62]. In addition to Eqs. (24) and (25), solutions for various other entry conditions have been derived [2].

Solutions for the simple limiting case of irreversible sorption or ion exchange ($\alpha_B^A = 0$) were derived much earlier. With the rate law of a second-order reaction (Eq. (14) without the second term), *Bohart* [72] obtained, as early as 1920:

$$x_B = \frac{1}{1 + \exp[-\mathfrak{R}(\mathfrak{T}-1)]} \quad (26)$$

that is, *Walter*'s Eq. (17) with $\alpha_B^A = 0$. With the rate equation (20) for film-diffusion control, *Drew* [73] obtained

$$x_B = \exp[\mathfrak{R}(\mathfrak{T}-1)-1] \quad (27)$$

($\mathfrak{R} \equiv k_f Z/v$; Eq. (27) is valid for $1/\mathfrak{R} \leq \mathfrak{T} \leq 1 + 1/\mathfrak{R}$; $x_B = 1/\mathfrak{R}$ for lower values of $\mathfrak{T}$, and $x_B = 1$ for higher values of $\mathfrak{T}$).

On the other hand, the rate equation (19) for particle-diffusion control leads to

$$x_B = 1 - \exp[-\mathfrak{R}(\mathfrak{T}-1)-1] \quad (28)$$

($\mathfrak{R} = k_p Z\bar{X}/Cv$; Eq. (28) is valid for $\mathfrak{T} \leq 1 - 1/\mathfrak{R}$; with $x_B = 0$ for lower values of $\mathfrak{T}$).

[72] *G. S. Bohart* and *E. Q. Adams*, J. Amer. chem. Soc. *42*, 523 (1920).

[73] Quoted by *I. M. Klotz*, Chem. Reviews *39*, 241 (1946).

It can be shown that Eqs. (24) and (25) reduce to the simpler Eqs. (28) and (27) under the following conditions. For $0 < \alpha_B^A \ll 1$ (very favorable equilibrium) and $\bar{X}/C \gg \beta$, film-diffusion control leads to Eq. (27) as long as $x_B \ll 1$, and particle-diffusion control leads to Eq. (28) as soon as $(1-x_B) \ll 1$. In other words, with film-diffusion control, Eq. (27) is a good approximation for the early part of the effluent history, and with particle-diffusion control, Eq. (28) is a good approximation for the late part. It is interesting to see that, with highly favorable equilibrium, the "leakage" with film-diffusion control and the "tailing" with particle-diffusion control depend on the kinetics only (*i.e.* on $\mathfrak{R}$) and not on the separation factor and not even on the particular shape of the isotherm.

Several other constant-pattern solutions for other isotherms, rate laws, and particular conditions have been derived [2, 55, 58, 65, 71]. *Wicke*'s solution for irreversible sorption [74] will be discussed later.

Two more complex, but interesting constant-pattern cases will be noted briefly. In *mixed-bed de-ionization* of dilute solutions, one may safely assume film-diffusion control; also, equilibrium is highly favorable, and the breakthrough concentration that can be tolerated is usually quite low (*i.e.* $x_B \ll 1$). Accordingly, the simple Eq. (27) can be used [2,75]. Here, x_B should be defined as the ratio of effluent concentration to feed concentration.

In *displacement development*, the shapes of the boundaries between the individual bands and, hence, the cross contamination by band overlap can be calculated from Eqs. (24) and (25). In addition, the column length required for attainment of the constant pattern must be calculated. For displacement development of two species B and C (with $\alpha_C^B < 1$), Spedding [76] obtained

$$Z_{sep} \simeq Z_{B+C} \frac{Q_B + \alpha_C^B Q_C}{(Q_B + Q_C)(1-\alpha_C^B)} \quad (29)$$

where Z_{sep} is the length the mixed band must travel to attain the constant pattern, Z_{B+C} is the length of the mixed band, and Q_B and Q_C are the amounts of B and C in equivalents. If more than two species are separated, one may apply Eq. (29) to the pair which is most difficult to resolve [4].

The Rate Theories of Wicke and Rosen

All rate theories discussed so far are based on sets of equations such as Eqs. (3), (6), and (7) or, for constant patterns, on analogous sets derived for a gliding frame of reference. One might believe that it should be possible, at least in principle, to obtain rigorous solutions from such sets of equations by using exact isotherms and rate laws and, if necessary, by including further effects. Un-

[74] *E. Wicke*, Kolloid-Z. *86*, 295 (1939).

[75] *N. W. Frisch* and *R. Kunin*, A.I.Ch.E. Journal *6*, 640 (1960).

[76] *F. H. Spedding*, *J. E. Powell*, and *H. J. Svec*, J. Amer. chem. Soc. *77*, 6125 (1955).

fortunately, this is not the case. The reason is that the rate of particle-diffusion controlled ion exchange is not an unequivocal function of the instantaneous values of C_i (solution concentration) and $\overline{X}_i$ (average intraparticle concentration), but also depends on the intraparticle concentration profiles and thus on the particle history. Therefore, it is inherently impossible to express the ion-exchange rate by a rate law of the form

$$\frac{\partial \overline{X}_i}{\partial t} = f(\overline{X}_i^*, \overline{X}_i, C_i^*, C_i) \qquad (7)$$

Any such rate law, as complex as it may be, can only be valid for a particular set of initial and boundary conditions. Hence, it is impossible to obtain rigorous solutions from a set of equations involving such a rate law.

An example may serve to illustrate the effect of particle history. While ion exchange is in progress, the ion exchanger may be separated from the solution and later reimmersed ("interruption test"). During the interruption the intraparticle concentration profiles level out; ions taken up in the outer shells of the particle find time to migrate into the interior. Consequently, the ion-exchange rate after interruption is higher than before [77], although the average concentrations C_i and $\overline{X}_i$ have not changed. Similarly, interruption of the feed may affect column-effluent concentrations. Rate laws of the form of Eq. (7) are unable to account for any such effects.

A more rigorous treatment which includes the effects of intraparticle concentration profiles is much more difficult. For spherical particles, for example, the rate must be expressed by [59, 74, 78, 79]:

$$\frac{\partial \overline{C}_i}{\partial t} = \frac{1}{r_o^2} \frac{\partial}{\partial r}\left(r^2 \overline{D} \frac{\partial C_i}{\partial r}\right)$$

$$\overline{X}_i = \frac{3}{r_o^3 (1-\beta)} \int_0^{r_o} \overline{C}_i r^2 \, dr \qquad (30)$$

Here, $\overline{C}_i$ is the local concentration in the ion exchanger (per unit volume of ion exchanger not including insterstitial void) at the distance r from the bead center, and $\overline{X}_i$ is the average concentration in the ion exchanger (per unit volume of bed including void) as used before.

With this rate law, *Wicke* [74], *Rosen* [78], and *Amundson* [59, 79] have derived solutions assuming a linear isotherm and a constant intraparticle diffusion coefficient $\overline{D}$. *Wicke*,'s approximation [74] for the effluent of a sufficiently long bed in A form, with B as feed, may be written as

$$x_B \cong \tfrac{1}{2}\left[1 + \operatorname{erf}\left(\tfrac{1}{2}\mathfrak{T}\sqrt{\mathfrak{R}} - \tfrac{1}{2}\sqrt{\mathfrak{R}}\right)\right] \qquad (\mathfrak{R} > 10) \quad (31)$$

where

$$\mathfrak{R} = 15 \frac{\overline{D}\overline{X}Z}{Cr_o^2 v}$$

Rosen's solution is the most accurate and general one and also includes film diffusion, for which a rate law of the type of Eq. (20) is assumed. The solution is in the form of an integral which is difficult to evaluate, but which has been tabulated for various sets of parameter values [80]. For complete particle-diffusion control and sufficiently long columns, *Wicke*'s Eq. (31) is obtained as a limiting case. Note that this limiting equation is similar to, but not identical with, the approximation (13) which is obtained from the J function. Rosen also gives extensions for various other entry conditions [78].

Rosen's theory is undoubtedly the most exact mathematical treatment of column performance. Its practical application, however, is severely limited by the assumption of a linear isotherm. Even minor deviations from linearity of the isotherm affect column performance profoundly; for example, with $\alpha_B^A < 1$ they result in a constant pattern to which *Rosen*'s theory cannot be applied. Another, less obvious and less serious idealization is the assumption of a constant intraparticle diffusion coefficient; actually, this coefficient varies with $\overline{C}_B$ if the exchanging ions have different mobilities [9, 81]. These effects cannot be included by applying simple corrections, because non-linearities would be introduced and would prevent the use of *Rosen*'s ingenious solution method. On the other hand, *Rosen*'s solution is useful for estimating (for a linear isotherm and a constant diffusion coefficient) the errors introduced by the use of less accurate rate laws.

No solutions have been found for the general case of a non-linear isotherm. The limiting case of irreversible sorption or exchange ($\alpha_B^A = 0$), however, has been solved by *Wicke* [74]:

$$x_B = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left\{-n^2\left[\frac{\pi^2}{15}\mathfrak{R}(\mathfrak{T}-1) + 0.97\right]\right\} \qquad (32)$$

where, again, $\mathfrak{R} = 15\,\overline{D}\overline{X}Z/Cr_0^2 v$, and $\overline{D}$ is assumed to be constant.

Longitudinal Diffusion: Hydrodynamic, Thermochemical, and Electrochemical Effects

The theories discussed in the previous sections cover the effects of ion-exchange equilibrium and of the finite ion-exchange rate, but do not include the effects of longitudinal diffusion and of hydrodynamic, thermochemical, and electrochemical disturbances. A brief account of these additional effects follows.

Longitudinal Diffusion

Longitudinal diffusion (or axial diffusion) is diffusion in the interstitial solution parallel to the column axis. To account for this effect, the material balance (3) must be modified to include changes in content by diffusion into and out of the layer under consideration. One obtains

$$q \frac{\partial}{\partial V}(\overline{X}_i + \beta C_i) + \frac{\partial C_i}{\partial z} - \frac{D\beta}{v\varnothing} \frac{\partial^2 C_i}{\partial z^2} = 0 \qquad (33)$$

($\varnothing$ is a "labyrinth factor" which accounts for the fact that the diffusion path between the particles is tortuous; *Glueckauf* [3, 39] uses $\varnothing = \sqrt{2}$).

[77] *T. R. E. Kressman* and *J. A. Kitchener*, Discuss. Faraday Soc. *7*, 90 (1949).

[78] *J. B. Rosen*, J. chem. Physics *20*, 387 (1952).

[79] *P. R. Kasten, L. Lapidus*, and *N. R. Amundson*, J. physic. Chem. *56*, 683 (1952).

[80] *J. B. Rosen*, Ind. Engng. Chem. *46*, 1590 (1954).

[81] *O. P. Fedoseeva, E. P. Cherneva*, and *N. N. Tunitskii*, Zhur. Fiz. Khim. *33*, 936, 1140 (1959).

The additional third term resulting from longitudinal diffusion involves the flow rate in the denominator and is noticeable only at very low flow rates. For most purposes longitudinal diffusion can thus be disregarded [82].

Solutions of Eq. (33) for several limiting cases have been given by various authors [2,58,59,83–92]. Calculations with $\alpha_B^A > 1$ (non-sharpening boundaries) show that the effect of longitudinal diffusion disappears, as do the other disturbances, when the boundary has become sufficiently diffuse. Calculations with $\alpha_B^A < 1$ show that longitudinal diffusion does not prevent attainment of the constant pattern, but that its effect and those of other disturbances are not additive [93]. Note that, in a consistent treatment which includes longitudinal diffusion, rather complicated boundary conditions for the inlet and outlet ends of the bed must be introduced to account for diffusion (or absence of diffusion) into and out of the liquid above and below the bed [94].

Hydrodynamic Effects

In all theories discussed so far, "ideal plug flow" in the column is assumed, that is, distortion of flow lines and velocity differences within the bed are disregarded. In reality, however, the following deviations from ideality occur:

1. The continuous branching and rejoining of flow lines and velocity differences between neighboring flow lines cause so-called eddy dispersion [95], that is, backmixing of the solution.

2. In irregularly packed beds the flow rate is higher in regions of lower packing density; this "channeling" distorts boundaries and bands.

3. Density and viscosity differences between adjacent bands may cause hydrodynamic instabilities that distort the boundaries between such bands.

Eddy dispersion results from the geometry of the flow pattern. Since the flow lines branch and rejoin over distances of the order of one to several particle diameters, it seems plausible that eddy dispersion also is effective over similar distances. Indeed, various models and statistical theories of eddy dispersion in packed beds yield contributions to the effective plate height amounting to one to three particle diameters [3,38,39,60,86,96–98]. In plant-scale operations, the plate-height contributions from other effects are usually much greater, so that eddy dispersion can often be disregarded.

Channeling and the resulting distortion of the boundary may seriously impair column performance. Theoretical and experimental studies are hampered by the fact that the disturbance arises from random irregularities which are difficult to estimate and to reproduce. So far, there is no unanimity even as to the effects of flow rate and column length and shape on boundary distortion by channeling.

More is known about a particular type of channeling at the walls of uniformly packed beds [89,91,92,99–102]. The flow rate is lowest directly at the column wall and highest at a distance of about one particle diameter from the wall. This effect, however, is of little consequence for the effluent history if the column diameter is larger than about 20 particle diameters.

Channeling is particularly serious if the ion-exchanger shrinks during the operation so that crevices form in the interior of the bed and especially at the column wall [100]. Swelling of the ion exchanger, on the other hand, does not lead to channeling but may greatly increase the flow resistance of the bed.

Hydrodynamic instabilities ("Taylor instabilities"), caused by density and viscosity differences when highly concentrated solutions are processed, have so far not received due attention. The phenomenon as such, however, is known from displacement of liquids in porous media and is theoretically well understood [103–107]. Its occurence in ion-exchange columns has been demonstrated [105,108].

It is obvious that gravity may cause instability of a boundary between two liquid layers if the upper layer has the higher density, and helps to stabilize the boundary in the opposite case. The effect of viscosity differences is also readily understood. Packing irregularities, random disturbances, etc., continually cause small bulges in the migrating boundary. If the displacing liquid is the less viscous one, then the flow resistance in such bulges, where the boundary is farther advanced, is

[82] In gas adsorption and gas chromatography, the diffusion coefficient is several orders of magnitude higher; accordingly, longitudinal diffusion is significant even at relatively high flow rates.

[83] *C. N. Hinshelwood et al.*, J. chem. Soc. (London) 401 (1947).

[84] *E. Ledoux*, J. physic. Chem. *53*, 960 (1949).

[85] *L. Lapidus* and *N. R. Amundson*, J. physic. Chem. *56*, 984 (1952).

[86] *H. Kramers* and *G. Alberda*, Chem. Engng. Sci. *2*, 173 (1953).

[87] *W. C. Bastian* and *L. Lapidus*, J. physic. Chem. *60*, 816(1956).

[88] *E. N. Lightfoot*, Jr., J. physic. Chem. *61*, 1686 (1957).

[89] *V. P. Dorweiler* and *R. W. Fahien*, A.I.Ch.E. Journal *5*, 139 (1959).

[90] *A. Acrivos*, Chem. Engng. Sci. *13*, 1 (1960).

[91] *E. J. Cairns* and *J. M. Prausnitz*, Chem. Engng. Sci. *12*, 20 (1960).

[92] *A.W. Liles* and *C. J. Geankoplis*, A.I.Ch.E. Journal *6*, 591 (1960).

[93] Disturbances are additive for linear isotherms only; see also [54].

[94] See, for example, *Bastian* [87] and *J. F.Wehner* and *R. H. Wilhelm*, Chem. Engng. Sci. *6*, 89 (1956).

[95] Also called eddy diffusion; neither term is appropriate since the effect arises even with laminar flow in uniformly packed beds, *i.e.* in the absence of actual eddies.

[96] *M. J. Beran*, J. chem. Physics *27*, 270 (1957).

[97] *J. C. Giddings*, Nature (London) *184*, 357 (1959).

[98] Most theories lead to plate-height contributions which depend on the particle size only. An exception is *Gidding*'s treatment [97] which leads to a contribution that decreases at very low flow rates.

[99] *C. E. Schwartz* and *J. M. Smith*, Ind. Engng. Chem. *45*, 1209 (1953).

[100] *E. B. Byrne* and *L. Lapidus*, J. Amer. chem. Soc. *77*, 6506 (1955).

[101] *R.W. Fahien* and *J. M. Smith*, A.I.Ch.E. Journal *1*, 28 (1955).

[102] *M. B. Sheridan* and *M. B. Donald*, Ind. Chemist 439, 487 (1959).

[103] *H. Lamb:* Hydrodynamics. 6th Ed., Cambridge University Press 1932, chapters 9 and 11.

[104] *G.Taylor*, Proc. Roy. Soc. (London) *A 201*, 192 (1950).

[105] *S. Hill*, Chem. Engng. Sci. *1*, 247 (1952).

[106] *P. G. Saffman* and *G.Taylor*, Proc. Roy. Soc. (London) *A 245*, 312 (1958).

[107] *R. L. Chuoke*, *P.van Meurs*, and *C.van der Poel*, Petroleum Trans. Amer. Inst. mech. Engnr. *216*, 188 (1959).

[108] *F. Helfferich*, J. Amer. chem. Soc., in the press.

less than in the vicinity. Consequently, the bulge tends to grow, and the boundary thus is unstable (unless a favorable gravity effect predominates and stabilizes the boundary). Conversely, if the displacing liquid is the more viscous one, then the flow resistance in the bulges is higher than in the vicinity; the bulges therefore tend to disappear, and the boundary thus is stable (unless an unfavorable gravity effect predominates and makes the boundary unstable). High flow rate enhances the viscosity effect. A quantitative treatment leads to the following hydrodynamic stability criterion [105–107]:

$$\begin{aligned} &(\mu_1-\mu_2)pv_{\downarrow} + (\rho_2-\rho_1)g > 0 \qquad \text{stable} \\ &(\mu_1-\mu_2)pv_{\downarrow} + (\rho_2-\rho_1)g < 0 \qquad \text{unstable} \end{aligned} \tag{34}$$

(μ = absolute viscosity, ρ = density, subscripts 1 and 2 refer to the upper and lower layer, respectively; p = permeability coefficient of bed (pressure gradient required to produce unit flow rate of a liquid having unit viscosity); $v_{\downarrow}$ = average linear flow rate, positive for downflow and negative for upflow).

Hydrodynamic instability often leads to a characteristic "finger pattern", with long fingers of surprisingly uniform thickness and spacing penetrating deeply into the liquid being displaced (see Fig. 5). Statistical hydrodynamics even permits the finger size to be predicted with reasonable accuracy [103, 104, 107].

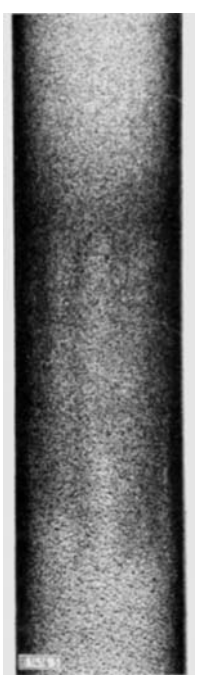


Fig. 5. Typical "fingering" pattern of a hydrodynamically unstable boundary. The operation is a ligand-exchange displacement of a diamine by concentrated ammonia [108]. The dark diamine zone has an unstable, strongly fingering front boundary and a stable, relatively sharp rear boundary

Density and viscosity differences that are large enough to produce such hydrodynamic effects can occur only when highly concentrated solutions are processed or when one solvent is displaced by another. In such cases, however, hydrodynamics are of paramount importance because fingering may drastically reduce the efficiency of the column.

A practical example may serve to illustrate the consequences of hydrodynamic effects. Water-softening columns are usually regenerated with concentrated brine. The brine is the displacing liquid and has a higher density and higher viscosity than the interstitial water being displaced. If regeneration is carried out with upflow, the front boundary of the brine thus is stable with respect to both gravity and viscosity. If regeneration is carried out in downflow, however, the boundary is gravitationally unstable and can only be stabilized by a flow rate which is high enough to make the viscosity effect the predominant one.

Thermochemical Effects

The common theories of column performance either imply tacitly or state explicitly that operation is isothermal. For most purposes, this assumption is a reasonable approximation since the heat of ion exchange is usually low in comparison with the specific heat of the bed. Exceptions are those cases in which ion exchange is followed by a consecutive reaction with significant evolution of heat. For example, the heat of neutralization is released when an alkaline solution is fed to a cation-exchange bed in H^+ form, or an acidic solution to an anion-exchange bed in OH^- form. In such cases, a "hot spot" travels with the boundary through the column [109]. The effluent history may be affected since both rate and equilibrium of ion exchange depend on temperature. It seems that, apart from calculations for special cases [110], such effects have been taken into account only by *Wicke* [74].

Electrochemical Effects

The flow of electrolyte solution in an ionexchange bed produces a streaming potential. One should expect that this electric-potential gradient transfers counterions in upstream direction and that, at boundaries, the counterion of higher mobility is transferred at a higher rate. It is conceivable that the sharpness of the boundary might be affected by this electrochemical effect. No theories have so far been worked out for this phenomenon. The results of the few investigations of streaming potentials in ion-exchange beds [111,112] are insufficient for estimating the magnitude and importance of this effect.

Numerical Evaluation Methods

A standard procedure in column-performance calculations, as in other fields, is to resort to numerical evaluation methods when simple and explicit analytical

[109] *J. F. Short, P. G. Smith,* and *G. H.Twigg,* J. appl. Chem. *3,* 198 (1953).

[110] *Short*'s simple theory [109] neglects heat transfer to the environment and gives only the adiabatic temperature rise in the bed. A theory for elution development of carrier-free radioelements (temperature rise by released heat of radiation) has been worked out by *E. Glueckauf* in *D. H. Desty:* Gas Chromatography. Academic Press, New York 1958, p. 69. Equations for calculating "burn-off" of carbonaceous residues on molecular sieves have been made available by the U.S. Linde Company: Design Manual for Octane Improvement, Book II, page D-74, 1959.

[111] *Ya. A. Epshtein,* Issled. Oblasti Khromatog., Trudy Vsesy. Soveshchaniya Khromatog., Acad. Nauk SSSR, Otdel. Khim. Nauk 211 (1950); see Chem. Abstr. *48,* 2443 (1954).

[112] *A. S. Michaels* and *C. S. Lin,* Ind. Engng. Chem. *47,* 1249 (1955).

solutions cannot be found [65,70,113–116]. Certain analytical solutions, for example, those of *Thomas* and *Rosen* and even the simpler J function, are so complex that their evaluation with pencil and paper is very laborious; therefore, digital computers have been used to tabulate these functions for various sets of arguments [29,43,80]. A more diversified and more important field of application of numerical methods, however, is that of complicated systems for which analytical solutions have not been found. For example, no general analytical solutions are so far available for processes involving more than two counterion species, for variable flow rate and feed composition, and for non-uniform initial bed composition. The last case is of practical importance for the calculation of regeneration of beds which have been on stream only until breakthrough [117].

With simple means, *e.g.* with a slide rule or a desk calculator, crude approximations can be obtained by using the Martin-Synge model. Such calculations are carried out "plate by plate", that is, equilibrium is computed for the first portion of solution in the first plate, to obtain the composition of the solution passing on into the second plate; equilibrium is then computed in that plate, and so forth for all plates; the procedure is then repeated for all subsequent portions of the feed until the desired effluent history is obtained. The plate height must be estimated beforehand by use of a rate theory. (If the flow rate varies, the plate height must, of course, be changed accordingly in the course of the calculation). The procedure is not overly lengthy, provided that the number of plates in the column is small.

More accurate results can be obtained by numerical integration of the differential material balances, Eqs. (3) or (33). If more than two counterion species are involved, the simultaneous balances for all species must be integrated. Such integrations, even for only two species, exceed the scope of simple calculators and can only be handled by electronic computers. A relatively simple computer program, developed by *Dranoff* and *Lapidus* [115], may serve as a typical example for calculations of this type. The program is for three counterion species and assumes constant binary separation factors α_B^A, α_C^A, and $\alpha_C^B = \alpha_C^A/\alpha_B^A$ and simultaneous rate laws of the form of Eq. (14) (simultaneous second-order reversible reactions). The results thus constitute an extension of the *Thomas* theory to three counterion species and have the same merits and shortcomings as that theory. The computation time (IBM 704, 709, or 7090) is several minutes per case.

Calculations involving rate laws of the general type of Eq. (7) are usually programmed as follows. The calculation is carried out in a network of the time and space co-ordinates, t and z [118] (see Fig. 6). The concentrations at the mesh points along the lines t = 0 (initial bed composition) and z = 0 (feed composition as a function of time) are given as initial and boundary conditions. The material balances and rate laws are approximated by finite-difference equations; the finite

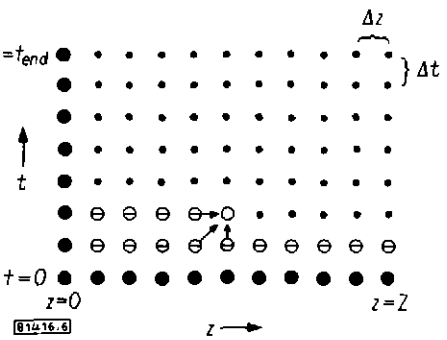


Fig. 6. Numerical calculation in the network of the coordinates z and t. The moment of calculation of the concentrations at the point ○ is shown. Entry conditions ●; previously calculated values ⊙

differences Δz and Δt correspond to the mesh widths of the network. By use of the finite-difference equations and an equation for ion-exchange equilibrium, the concentrations of the species at a mesh point (z+Δz, t+Δt) can be calculated from those at the points (z+Δz, t), (z, t), and (z, t+Δt); in other words, one proceeds by calculating, at any stage, the concentrations at the corner of a mesh-point rectangle for which the concentrations at the three other corners are already known (see Fig. 6). In this way one obtains, step by step, the concentrations at all mesh points and thus, eventually, the effluent concentration history (concentrations along the line z = Z) and the final bed composition at the time t_{end}, when feed is discontinued (concentrations along the line t = t_{end}). To achieve the desired accuracy, the mesh widths Δz and Δt must be made sufficiently small; decreasing the mesh width, however, increases the number of mesh points and thus adds to the computation time and to the memory capacity requirements.

In principle, such calculations can also be made with the more rigorous rate laws of the type of Eq. (30). The time and memory-capacity requirements, however, are thereby increased by at least one order of magnitude. It does not seem practical to work out a general program of this type, even for the fastest computers. On the other hand, it should be possible to develop efficient and not overly lengthy programs for particular cases by taking all short cuts that the respective case permits. The same is true for calculations which include thermochemical effects or other additional disturbances.

The main reason for the much greater time and memory-capacity requirements in calculations with rate laws such as Eq. (30) is that, at each mesh point and for each species, a whole array of intraparticle concentrations $\overline{C}_i(r)$ for a series of r values must be computed and stored, whereas a single value $\overline{X}_i$ suffices for the simpler rate laws. Also, of course, the greater number of equations results in a longer program.

Numerical evaluation methods in general have several advantages over analytical solutions. First, they can be applied to systems with more than two counterion species – admittedly at a substantial expense in calculation time. Second, they can be applied to systems with almost any kind of initial and boundary conditions,

[113] *A. Opler*, Ind. Engng. Chem. *45*, 2621 (1953); in *F. C. Nachod* and *J. Schubert*: Ion-Exchange Technology. Academic Press, New York 1956, p. 219.

[114] *A. Acrivos*, Ind. Engng. Chem. *48*, 703 (1956).

[115] *J. S. Dranoff* and *L. Lapidus*, Ind. Engng. Chem. *50*, 1648 (1958); *53*, 71 (1961).

[116] *J. E. Funk* and *G. Houghton*, Nature (London) *188*, 389 (1960).

[117] An analytical solution which, however, is complex and restricted to certain conditions, was derived by *Cornaz* [52], but has so far not been published.

[118] Instead of the time co-ordinate, the effluent volume V can be used. If longitudinal diffusion is not included, it is more practical to use a reduced time or volume co-ordinate (such as θ = t−βz/v; see *Thomas* [41], *Rosen* [78], *Acrivos* [114], and *Dranoff* [115]).

isotherms, and rate laws without much increase in calculation time. To the digital computer it makes little difference whether or not the initial bed composition is uniform, the feed is constant, the separation factor is constant, or the rate law is linear. With non-uniform entry conditions, one merely has to feed to the computer a series of values instead of single constants, and with variable separation factors, diffusion coefficients, etc., the only additional operation of the computer is to calculate the values of these quantities at each mesh point from programmed equations instead of taking them as constants from memory. In this way, for example, one can readily take into account the concentration dependence of the diffusion coefficient in the rate law Eq. (30). For analytical solutions, in contrast, the linearity of the system and the simplicity of the entry conditions usually are prerequisites. On the other hand, analytical solutions have the advantage of giving the effects of the various parameters in the form of general explicit equations, whereas numerical evaluation can only give results that are valid merely for the particular parameter values and conditions chosen. To assess the effect of a parameter in a quantitative way by numerical calculations, a series of calculations must be made in which this parameter is varied systematically while all others are kept constant – and even then the result is valid only for those particular values of the other parameters. In view of the many degrees of freedom in ion-exchange column performance, it appears hardly worth while to use computer programs for systematic tabulations. On the other hand, flexible programs can be of great value in obtaining results for particular cases of immediate practical interest.

The use of analog instead of digital computers is an obvious alternative which is actively pursued by several groups [119]. However, the more complex cases, which cannot be solved analytically (systems with more than two counterions, non-constant entry conditions, rate laws such as Eq. (30), etc.), pose problems for analog computation also, mainly because simultaneous nonlinear differential equations must be solved and a large number of values must be stored in memory in the course of the computation.

Conclusions and Summary

The conclusions that can be drawn from the critical study of the various theories can be briefly summarized as follows.

When developing new theories or testing existing theories as to their accuracy and range of applicability, one should keep the following points in mind:

1. The assumption of a linear isotherm – tempting because of its mathematical convenience – is inadmissible (except for elution development). Even minor deviations from linearity result in a fundamentally different column behavior rather than merely in perturbations which could be neglected in approximations or could be taken into account by simple corrections.

2. The concept of constant and additive diffusion resistances in the particle and the film, although cherrished by the process engineer, fails if the isotherm is non-linear. A universal rate law (*i.e.* applicable to both particle- and film-diffusion control) with only one constant over-all mass-transfer coefficient cannot be more than a poor approximation because slow film diffusion and slow particle diffusion affect the boundary shape in different places.

3. With particle-diffusion control, the momentary ion-exchange rate depends on the shape of the intraparticle concentration profiles and thus on the particle history. Therefore, the rate cannot be accurately expressed by an equation of the type of Eq. (7). To obtain rigorous solutions, the diffusion equation within the particle must be integrated.

4. The separation factor and the intraparticle diffusion coefficient are, as a rule, variable. The use of constant values for these quantities is admissible for approximations only.

5. Longitudinal diffusion, eddy dispersion, thermochemical and electrochemical effects are usually insignificant in plant-scale operations, but channeling and hydrodynamic instabilities of boundaries may act as serious disturbances. Omission of these latter effects at least limits the validity range of a theory.

In any practical application, the first and most important step is the choice of the most appropriate theory or solution method, as has been stressed at the outset. Since a rigorous and universally valid theory does not exist, one must select, for each particular case, that approximation which adequately accounts for the relevant characteristics of the system without being unnecessarily complex. Since even the most sophisticated theories involve idealizations and thus cannot yield accurate results, one can often use simpler theories to obtain almost equally useful results much faster and with much less effort. In practice, rather simple theories are usually sufficient for crude approximations, whereas really reliable results can only be obtained by electronic computers. Even simple approximations, however, should adequately reflect these features:

1. If equilibrium is unfavorable, the boundary attains a proportionate pattern which depends primarily on the ion-exchange isotherm and is not significantly affected by the finite ion-exchange rate and other disturbances. Equilibrium theories are admissible as approximations. To obtain more accurate results by including the effects of disturbances, it suffices to use rather crude approximations (*e.g.* a very simple ion-exchange rate law) for estimating such effects since they result in only minor corrections.

2. If equilibrium is favorable, the boundary attains a constant pattern which depends decisively on both the ion-exchange isotherm and the ion-exchange rate. Equilibrium theories are inadmissible, and, even for crude approximations, adequate ion-exchange rate laws must be used which, in particular, properly reflect the characteristic differences between particle- and film-diffusion control. Furthermore, all other disturbances

[119] *S. H. Jury* and *J. M. Andrews*, Ind. Engng. Chem. *53*, 883 (1961).

such as channeling, hydrodynamic instabilities, *etc.* are more serious here than with unfavorable equilibria. If the column is long enough for attainment of the constant pattern, the mathematical treatment can be simplified by restricting the calculation to this steady-state pattern.

The common theories do not include boundary distortion by channeling, wall effects, or hydrodynamic instability. The best solution for these problems is to avoid them as far as possible. For example, one should choose an ion exchanger which does not swell or shrink while in operation; one should take care to achieve a reasonably uniform packing and provide for "backwashing" (*i.e.* expanding the bed in upflow) before each cycle; and one should avoid "fingering" by choosing operating conditions which guarantee hydrodynamic stability of the boundary (note the criterion Eq. (34)).

So far, only the problem of predicting column performance on the basis of known ion-exchange isotherms, ion-exchange rates, and other relevant data has been discussed. Often, however, the procedure is reversed, that is, attempts are made to obtain information about ion-exchange equilibria, kinetics, and rates by evaluating experimental effluent concentration histories. Here, one is on dangerous ground indeed. The effluent histories can only be evaluated with theories involving simplifying assumptions which cannot be checked by column experiments alone. Moreover, all effluent histories are, in any event, more or less S-shaped so that the evaluation must be based on the often minor deviations from the standard form. For example, it is difficult to discern whether "tailing" of a self-sharpening boundary is due to slow intraparticle diffusion or to the shape of the isotherm (increase of α_B^A with increasing x_B). The task of interpreting effluent histories requires judgement and experience, and it may happen that the conclusions are more characteristic of the theory than of the actual conditions.

C_i	Concentration of species i in solution	mmoles per cm³ solution
$\overline{C}_i$	Concentration of i in ion exchanger	mmoles per cm³ swollen ion exchanger
C_i^*	Concentration of i in solution in equilibrium with ion exchanger of concentration X_i	mmoles per cm³ solution
C	Total concentration in solution	meq per cm³ solution
D_i	Diffusion coefficient of i in solution	cm²/sec
D_i	Diffusion coefficient of i in ion exchanger	cm²/sec
k	Rate constant	sec^{-1} or $cm^3 mmole^{-1} sec^{-1}$
k_f	Rate coefficient in film	sec^{-1}
k_p	Rate coefficient in particle	sec^{-1}
$\mathfrak{N}$	Number of mass-transfer units	dimensionless
q	Column cross section	cm²
r	Distance from particle center	cm
r_0	Particle radius	cm
t	Time	sec
$\mathfrak{R}$	Throughput ratio (see Eq. (5))	dimensionless
v	Linear (superficial) flow rate (see Eq. (12))	cm/sec
V	Effluent volume	cm³
V_b	Bed volume (including interstitial void)	cm³
x_i	Equivalent ionic fraction of i (see Eq. (2))	dimensionless
$\overline{X}_i$	Concentration of i in ion exchanger	mmoles per cm³ bed incl. interstitial void
$\overline{X}_i^*$	Concentration of i in ion exchanger in equilibrium with solution of concentration C_i	mmoles per cm³ bed incl. interstitial void
X	Total concentration in ion exchanger	meq per cm³ bed incl. interstitial void
z	Distance from column inlet	cm
z_i	Valence of ion i	dimensionless
Z	Column length	cm
α_B^A	Separation factor of counter ions A and B (see Eq. (1))	dimensionless
β	fractional void volume	dimensionless

$$\exp(x) = e^x$$

$$\mathrm{erf}(x) = \frac{2}{\sqrt{\pi}} \int_0^x \exp(-y^2)\,dy$$

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German version: Chem.-Ing.-Techn. *34*, 269 (1962).

COMMUNICATIONS

The Preparation of Complex Salts on Cation-Exchangers

By Dr. B. Sansoni, cand. chem. H. Axt and cand. chem. H. J. Hansen

Chemisches Institut der Universität Marburg/Lahn (Germany)

The preparation of salts with complex anions can be carried out in one step from the cation-exchanger salt of the metal cation according to

$$Ni^{2+}\text{-resin} + 4\ KCN \rightleftharpoons K_2[Ni(CN)_4] + K^+\text{-resin-}K^+$$

The metal-ion (Ni^{2+}) is quantitatively eluted as the anion by the ligand-containing solution (4 KCN) and, in its place, cation (2 K^+) corresponding to the Donnan-Guggenheim membrane equilibrium [1] is held on the resin. The eluate contains only $K_2[Ni(CN)_4]$, which can be precipitated with alcohol/ether or can be obtained in the pure state by evaporation. A prerequisite is that the capacity of the resin for K^+ is no less than it is for the metal cation (Ni^{2+}). However, alkali capacities mostly lie somewhat higher.

The simple method is generally applicable to anionic complexes with high to medium stability constants [2] and low activation energies. We have so far obtained, among others, $K_2[Ni(CN)_4]$, $K_4[Co_2(CN)_{10}]$, $K_2[Cd(CN)_4]$, $K_2[Zn(CN)_4]$, $K_2[HgI_4]$, $K[BiI_4]$, $K_3[Fe(C_2O_2)_3]$, $H_2[Ca(EDTA)]$, $H_2[Mg(EDTA)]$, $H_2[Ni(EDTA)]$. Semi-automatic column operation is valuable for the preparation of complexes with radio-active metal cations [3], easily permits exclusion of air and with a series-connected redox-exchange column [4] allows complete exclusion of oxygen from the starting solution. The batch technique can be applied to strong complexes with definite co-ordination numbers and gives somewhat higher yields. Titration of the Ni^{2+}-resin with KCN solution gives $K_2[Ni(CN)_4]$; the preparation takes only 10–20 minutes. More stable complexes can also be obtained at higher temperatures.

Received, April 24th, 1962 [Z 285/112 IE]

[1] *F. Helfferich:* Ionenaustauscher. Verlag Chemie, Weinheim-Bergstr. 1958, vol. 1.

[2] *J. Bjerrum, G. Schwarzenbach,* and *L. G. Sillen:* Stability Constants. The Chemical Society, London 1958.

[3] *B. Sansoni,* unpublished results.

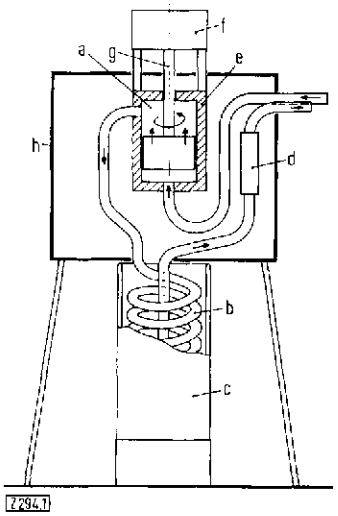
[4] *B. Sansoni,* Ph. D. Thesis, Universität München 1956.

Cryostat for Low Temperatures

By Dipl.-Ing. G. Hohlneicher

Physikalisch-Chemisches und Elektrochemisches Institut der Technischen Hochschule, München (Germany)

The cryostat described here operates with a closed loop gas circulation and without a heat exchanger. Liquid air or helium is used as refrigerant. With this cryostat, the temperature of the object under study can be maintained within a range of 1 °C. A freely suspended rotary pump (a) produces a gas stream in the closed circuit, the rate of flow being dependent on the speed of the pump. The pump forces the



gas through a copper coil (b) placed in the Dewar vessel (c) containing the refrigerant. In passing through the coil, the gas is cooled down almost to the temperature of the refrigerant. As the cold gas flows from the cooling coil to the measuring cell, it passes over a heating coil in unit (d) by means of which its temperature may be raised somewhat, if desired. Following passage through the measuring cell, the gas returns to the pump inlet. The pump housing (e) is made of a plastic material of low thermal conductivity. The drive shaft seal in the pump casing is frictionless. The motor (f) and the shaft bearings (g) are at ambient temperature outside the thermostat housing (h), which is insulated with polystyrene foam. This housing (h) also contains all the instrumentation necessary for adjustment of the temperature [1].

Received, April 27th. 1962 [Z 294/130 IE]

[1] Details are included in a paper which will appear shortly in "Chemie-Ing.-Technik".

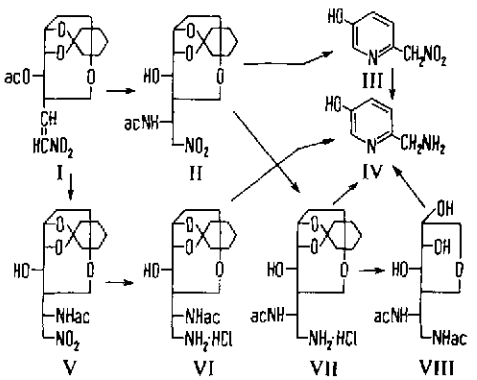
The Preparation of 5-Amino Sugars and their Transformation into Pyridine Derivatives

By Dr. Hans Paulsen

Chemisches Staatsinstitut, Institut für Organische Chemie, Universität Hamburg (Germany)

5-Amino sugars are of special interest on account of the possibility of an "oxo-cyclo tautomerism" to "piperidinoses". The nitro-olefin I easily adds on ammonia and, by synchronous acyl transfer, a mixture of the 5-acetamido-6-nitro-sugars II and V is formed and can easily be separated on silicagel. Hydrogenation of II and V gives VII and VI; *N*-acetylation of VII and mild hydrolysis affords the free 5,6-diacetamidosugar VIII, which crystallises in the furanose form.

Mild hydrolysis of VII first yields the free sugar by elimination of the cyclohexylidene group; the sugar invariably reacts further by fracture of the acetamido group and consequent spontaneous elimination of three molecules of water and aromatisation to give 2-aminomethyl-5-hydroxypyridine (IV). With 2N HCl, VII and VIII are converted directly into IV. The gluco-compound VI is also convertible into IV by acid hydrolysis. Hydrolysis of the nitro-sugar II results in conversion of the free sugar into the pyridine derivative III, hydrogenation of which affords IV.



These experiments show that 5-acetamido-sugars (*e.g.* VIII) exist in the furanose form but that on saponifaction of the 5-acetamido group, interaction of the carbonyl group with the amino group at C-5 takes place. The "piperidinoses", which are assumed to be intermediate products, immediately lose three molecules of water – presumably via a Δ^1-piperideine and subsequent enolisation – and aromatise to form 3-hydroxypyridine derivatives. Compounds which for steric reasons cannot form a 6-membered cyclic acetal, such as 5-amino-3,6-anhydro-5-deoxy-L-idose [1] (obtained from VII by deamination), do not give this transformation.

Received, May 14th, 1962. [Z 297/129 IE]

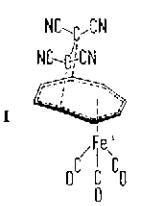
[1] Cf. *M. L. Wolfrom* et al., Abstr. Papers Amer. Chem. Soc. *141*, 7 D (1962).

New Reactions of Cyclooctatetraene-iron Tricarbonyl

By Dr. G. N. Schrauzer and Dipl.-Chem. S. Eichler

Institut für Anorganische Chemie der Universität München (Germany)

The two non-complexed double bonds of cyclooctatetraene-iron tricarbonyl are relatively inert. However, tetracyanoethylene reacts with them in benzene solution even at room temperature to yield a sparingly soluble, pale yellow 1:1 adduct (I), m.p. 176 °C with decomposition [1].



Irradiation of solutions of $C_8H_8Fe(CO)_3$ in benzene, in the presence of an excess of cyclooctatetraene [2], gives rise to a yellow complex (II), m. p. 118 °C, together with traces of (III), m. p. 172 °C, decomp. Prolonged irradiation [3] of $Fe(CO)_5$ in a mixture containing excessive cyclooctatetraene also produces II and III. These substances are $Fe(CO)_3$ adducts of hitherto unknown cyclooctatetraene dimers. Their proton magnetic resonance spectra indicate that the two C_8H_8 molecules are linked by two C–C bonds and that apparently a 1,4-addition onto the two free double bonds in $C_8H_8Fe(CO)_3$ has occurred. Presumably, the cyclo-

octatetraene added photochemically occurs in II as a bicyclo[4,2,0]octa-1,3-diene and in III as a cycloocta-1,3,5-triene unit. If irradiated in the presence of $Fe(CO)_5$, both II and III lose benzene, and a new yellow-red binuclear complex (IV) of formula $C_{10}H_{10}Fe_2(CO)_6$ and m. p. 170 °C (decomposition) is formed.

Received, May 21st, 1962 [Z 288/119 IE]

[1] Compound (I) has also been described by *A. Davison* et al., Chem. and Ind. 820 (1962).

[2] Performed in Jena glass vessels, using a 200 watt mercury vapour lamp as light source.

[3] Irradiation for shorter periods of time results in $C_8H_8Fe(CO)_3$, together with a small amount of $C_8H_8Fe_2(CO)_6$; *M. D. Rausch* and *G. N. Schrauzer*, Chem. and Ind. 957 (1962).

Wurtz Syntheses with Naphthalene-sodium

By Dipl-Chem. H. Güsten and Prof. Dr. L. Horner

Institut für Organische Chemie
der Universität Mainz (Germany)

During our investigations of the possibilities of employing naphthalene-sodium in organic syntheses [1, 2], we used this reagent introduced by *Scott* [3] virtually as "dissolved sodium". Exceptionally good results were obtained in the Wurtz synthesis [4].

If the green solution of naphthalene-sodium, prepared in the apparatus previously described [2], is added dropwise at 60 °C to a solution of an aromatic halide, the drops are immediately decolorized. The solution quickly becomes turbid owing to precipitation of sodium halide. If the reaction is carried out under pure nitrogen in absolute tetrahydrofuran using pure, dry starting materials, the end point can be determined exactly by titration. In order to isolate the reaction product, the solvent is distilled off and the naphthalene formed is removed by steam distillation. When benzyl halides are used, the residue from the steam distillation primarily contains the dimerization product in a very pure state. Catalytic quantities of naphthalene may also be used; the steam distillation can then be omitted. The yields of crude material are better than 90%. Similar experiments with tetraphenylethylene disodium were recently reported by *Müller* and *Roscheisen* [5].

The reaction between naphthalene-sodium and benzyl halides proceeds according to the following equation:

$$2\,RCH_2Cl + 2\,Na(naphthalene) \rightarrow RCH_2CH_2R + 2\,NaCl + (naphthalene).$$

The following compounds were used as starting materials (the first number indicates the melting point [°C] the second the yield [%]: R = phenyl (51, 80); α-naphthyl (163, 71); benzhydryl (211, 71); 3,4-dichlorophenyl (184, 6); 9-bromofluorene (240, 64). Dichlorodiphenylmethane yields tetraphenylethylene (220, *ca.* 50).

As can be seen in the case of 3,4-dichlorobenzylchloride, naphthalene-sodium does not react very selectively with organically bound halogen. Only 6% of the expected 3,3′,4,4′-tetrachlorodibenzyl, in addition to unknown reaction products and 50% unchanged starting material, are obtained.

The conversion of α,ω-dicarboxylic esters into cyclic acyloins, in analogy to the method of *Hansley*, *Prelog*, and *Stoll* [6], cannot be achieved using naphthalene-sodium. Once more the theory is confirmed that this acyloin ring closure occurs on the surface of metallic sodium.

Received, May 30th, 1962 [Z 299/131 IE]

[1] *L. Horner*, *P. Beck*, and *H. Hoffman*, Chem. Ber. *92*, 208 (1959).

[2] *L. Horner* and *H. Güsten*, Liebigs Ann. Chem. *652*, 99 (1962).

[3] U.S. Patent 2027000; Chem. Abstr. *30*, 1392 (1936).

[4] *N. D. Scott*, *J. F. Walker*, and *V. L. Hansley*, J. Amer. chem. Soc. *58*, 2442 (1936).

[5] *E. Müller* and *G. Roscheisen*, Chem. Ber. *90*, 543 (1957).

[6] *V. Prelog* et al., Helv. chim. Acta *30*, 1741 (1947).

Structure of the Main Component of Gamboge Resin

By Prof. Dr. H. Auterhoff, H. Fraudendorf, W. Liesenklas, and Dr. C. Schwandt

Institut für Pharmazeutische Chemie
der Technischen Hochschule Braunschweig (Germany)

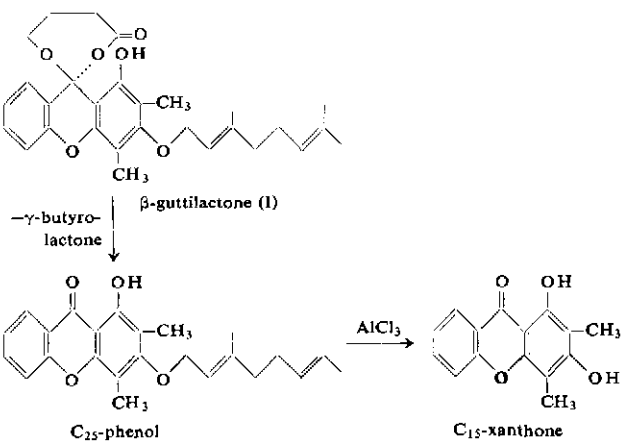
Seventy-five per cent of gamboge resin (*gummi gutti*), the dried milky exudate of *Garcinia* species from Southern Asia, is an ether-soluble material, the main component of which is β-guttilactone (sometimes called β-guttic acid). This can be isolated as its pyridine [1] or α-picoline complex. The acidity of the compound is due to its phenolic character. Acetyl-β-guttilactone is obtained by acetylation with acetic anhydride in the presence of perchloric acid. If the acetylated material is heated with 5% ethanolic potassium hydroxide, a phenolic substance of formula $C_{25}H_{32}O_4$ is obtained, and in the mother liquor, γ-butyrolactone can be found. If the C_{25}-phenol is heated with $AlCl_3$ to 160–170 °C, a substance of empirical formula $C_{15}H_{12}O_4$ is produced which is identical with synthetic 1,3-dihydroxy-2,4-dimethylxanthone (m. p. 247 °C) and which crystallizes after methylation in the 3-position (m. p. 184 °C). In the natural product, the hydroxyl at C-3 forms an ether linkage with geraniol. This is clearly evidenced from identification by gas-chromatography of the following cleavage products from the C_{25}-phenol:

Heating with 50% KOH → 2-methylhept-2-en-6-one

Heating with CH_3COOH in a sealed tube → geranyl acetate

Hydrogenation with 1 mole H_2/PtO_2, then cleavage with 50% KOH → 2-methylheptan-6-one

Exhaustive hydrogenation, then cleavage with $AlCl_3$ → 3,7-dimethyloctanol



The reactions permit the structural formula (I) to be written for β-guttilactone.

β-Guttilactone is optically active; the pyridine complex has a specific optical rotation $[\alpha]_D^{22} = -560°$ (c = 2.4 mg/ml, methanol). In accordance with its formula, the C_{25}-phenol does not rotate the plane of polarized light

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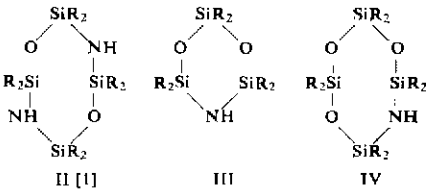
[1] *N. Amorosa*, Ann. Chimica *45*, 40 (1955); Chem. Zbl. 11378 (1958).

Mixed Siloxane/Silazane Compounds

By Dr. Carl R. Krüger and Prof. Dr. Eugene G. Rochow

Department of Chemistry, Harvard University, Cambridge, Massachusetts (U.S.A.)

Dihalogenopolysiloxanes $Cl(SiR_2O)_n-SiR_2Cl$ (I) (n = 1,2,3) react with ammonia in etheral solution to form the ring compounds II, III, and IV besides thermally unstable polymers $[(SiR_2O)_nSiR_2NH]_x$.



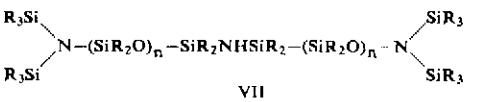
R = CH_3

	II [1]	III	IV
b.p./760 mm Hg	206–208 °C	151–151.5 °C	190–191 °C
b.p./9 mm Hg	82–83 °C	—	—
m.p.	37 °C (sublimes readily)	9.5–10.5 °C	20–20.5 °C
n_D^{20}	—	1.4068	1.4151
sp. gravity	—	0.9895 (25 °C)	0.9921 (26 °C)

Compounds II, III, and IV are readily soluble in non-polar solvents and can be hydrolyzed in acidic media. With sodamide or phenyl-lithium, fission of the Si–O bond occurs.

With I under similar conditions, methylamine yields only monomeric compounds of the general formula $RNH-(SiR_2O)_n-SiR_2NHR$ (V) (n = 1, b.p. 50–51 °C/11 mm Hg, $n_D^{20} = 1.4105$; n = 2, b.p. 78–79 °C/11 mm Hg, $n_D^{20} = 1.4089$), which do not condense thermally to form ring compounds.

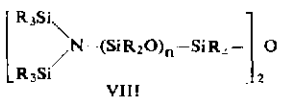
Treatment of I with sodium bis(trimethylsilyl)amide [2] in benzene solution in a 1:1 molar ratio produces good yields of easily hydrolyzable oils $(R_3Si)_2N-(SiR_2O)_n-SiR_2-Cl$ (VI), *e.g.* n = 3, b.p. 122–125 °C/2 mm Hg, $n_D^{20} = 1.4323$, which in etheral solution with gaseous ammonia at 0 °C yield silylamines, *e.g.* n = 3, b.p. 98–99 °C/1 mm Hg, $n_D^{20} = 1.4317$, sp. gravity = 0.9886 at 27 °C. By thermal elimination of ammonia, these can be converted into disilazanes, *e.g.*



VII

(n = 3, b.p. 196–198 °C / 1 mm Hg, $n_D^{20} = 1.4437$).

Partial hydrolysis of the halogensiloxanes VI in ether with pyridine as hydrogen halide acceptor yields silanols (*e.g.* n = 3, b.p. 103–104 °C/1.5 mm Hg, $n_D^{20} = 1.4308$) or disiloxanes (VIII):



VIII

(*e.g.* n = 3 b.p. 214–215 °C / 1 mm Hg, $n_D^{20} = 1.4339$, sp. gravity = 0.9905 at 26 °C).

The disiloxanes obtained are thermally stable oils; *e.g.* compound VIII, when n is 3, can be heated under normal pressure almost to 400 °C without decomposition. They are readily soluble in non-polar organic solvents, but are hydrolysed in acidic media.

Received, June 7th, 1962 [Z 295/128 IE]

[1] *N. N. Skolow*, J. Gen. Chem. U.S.S.R. *29*, 258 (1959), cf. Chem. Abstr. *53*, 21622 (1959).

[2] *U. Wannagat* and *H. Niederprüm*, Z. anorg. allg. Chem. *308*, 357 (1961); Chem. Ber. *94*, 1540 (1961).

Preparation of p-Quinol Ethers with Boron Trifluoride as Catalyst

By Priv.-Doz. Dr. E. Hecker and Dr. R. Lattrell

Max-Planck-Institut für Biochemie, München (Germany)

The ethers of *p*-quinols are of considerable interest [1], yet a general method for their preparation has been hitherto unknown. If *p*-alkylphenols are oxidised with lead tetracetate or thallium triacetate in methanol, *p*-quinol methyl ethers are obtained: *e.g.* tolu-*p*-quinol methyl ether (m.p. 62–63 °C), tetralin-*p*-quinol methyl ether (m.p. 42–43 °C), or 17β-acetoxy-estra-*p*-quinol-(10β)-methyl ether (m.p. 152–154 °C, $[\alpha]_D^{21}$ −44 °). By using ethanol or butanol as solvent, the corresponding ethyl or butyl ethers are obtained: *e.g.* tetralin-*p*-quinol ethyl ether (liquid at room temperature) or tetralin-*p*-quinol n-butyl ether (liquid at room temperature). The reaction is strongly catalyzed by boron trifluoride, the degree depending on the *p*-alkyl substituents (Table 1). Thallium triacetate generally gives lower yields than lead tetracetate. *p*-Quinol acetates are formed only in traces. These findings are interpreted as supporting an ionic mechanism for the oxidation.

Table 1. Yields from the reaction of *p*-alkylphenols with thallium triacetate or lead tetracetate in methanol, catalyzed by boron trifluoride etherate. The yields are determined by the DNPH-method [2]. Limits of error ± 2 %. Values in parentheses: yields without addition of BF_3

p-Alkylphenol	Yields with $Tl(OAc)_3$ [%]	$Pb(OAc)_4$ [%]
p-Cresol	16	36
Ethyl *p*-hydroxyphenylacetate	0	20 (2)
6-Tetralol	56 (6)	42 (39)
Estradiol-17β-acetate	29	29

Received, July 7th, 1962 [Z 312/143 IE]

[1] *E. Hecker* and *R. Lattrell*, Chem. Ber., in press.

[2] *E. Hecker*, Chem. Ber. *92*, 3198 (1959); *93*, 2928 (1960).

Splitting C-C Double Bonds with Sodium Hydrazide

By Doz. Dr. Th. Kauffmann, Dipl.-Ing. H. Henkler, Dr. C. Kosel, cand. Ing. E. Rauch, Jutta Schulz, and Reingard Weber

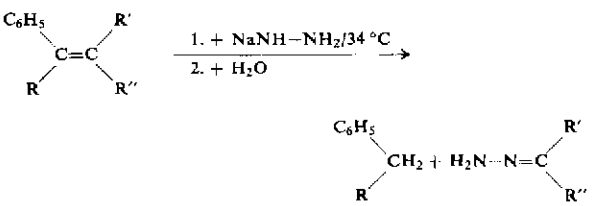
Institut für Organische Chemie der Technischen Hochschule Darmstadt (Germany)

In boiling ether under pure nitrogen, sodium hydrazide splits the alkenes shown below at their olefinic double bond, each yielding a nitrogen-free and a nitrogen-containing fragment. Free hydrazine in the reaction mixture generally facilitates the fission, but suppresses it with stilbene by promoting the competitive reaction of reduction to dibenzyl. The nitrogen free fragment was isolated in every instance, the yields being, as a rule, over 80 %.

Experimental results:

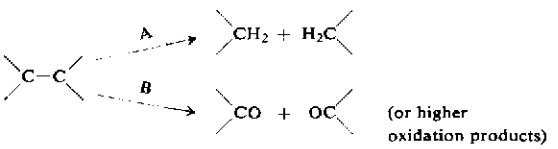
styrene [1] → toluene (3 hours, 81 %)
β-methylstyrene → toluene (8 hours, 86 %)
β-ethylstyrene → toluene (6 hours, 83 %)
trans-stilbene → toluene [2] (1 hour, 32 %)
α-methylstyrene → phenylethane (6 hours, 84 %)
α-phenylstyrene → diphenylmethane (6 hours, 97 %)
β,β-dimethylstyrene → toluene (6 hours, 74 %).

In the experiments with stilbene and β,β-dimethylstyrene, in addition to the nitrogen-free fragment, the nitrogenous fragments could also be isolated, being identified as the hydrazone of benzaldehyde and acetone, respectively (28 % and 53 %, respectively). In the other fission reactions, acid hydrolysis of the nitrogenous fragment, which was not isolated [3], afforded formaldehyde (from styrene), acetaldehyde (from



β-methylstyrene; 78 %), or propionaldehyde (from β-ethylstyrene; 94 %). In general, therefore, the fission very probably follows the above scheme; the fact that only a very small quantity of formaldehyde could be detected can well be attributed to secondary reactions of formaldehyde hydrazone [4]. Phenyl-ethylenes therefore behave towards sodium hydrazide like carbonyl groups [5a] and azomethine [6] groups. (O and RN, respectively, instead of $C_6H_5(R)C$ in the above scheme.) Our findings up to the present indicate that isolated C-C double bonds, are not attacked by sodium hydrazide. One exception is the double bond of allylbenzene in the β,γ-position to the phenyl residue, which is split by sodium hydrazide in boiling ether to give toluene (70 %), and a compound which gives acetaldehyde on acid hydrolysis. Under the influence of sodium hydrazide, which is strongly basic, the β,γ-double bond is evidently shifted to the α,β-position and then ruptured.

With compounds in which splitting with sodium hydrazide leads to a hydrazone or an azine, this can be combined in a two- in-one reaction with the Huang-Minlon modification [7] of the Wolff-Kischner reduction to give a reductive fission according to scheme A, as was confirmed by an experiment with stilbene.



Fission with a reagent which is a strong reducing agent is of special interest because, in all the known methods of rupture of C-C double bonds using oxidising agents, splitting according to scheme B occurs.

Received, June 18th, 1962 [Z 310/141 IE]

[1] Cf. adduct formation at 0 °C: *Th. Kauffmann*, *Ch. Kosel*, and *D. Wolf*, Chem. Ber. *95*, 1540 (1962).

[2] Dibenzyl is also formed.

[3] To our knowledge, no monomeric hydrazone of formaldehyde, of propionaldehyde has ever been described.

[4] In a control experiment, after reaction of formaldehyde and hydrazine at 20 °C, only very little of the aldehyde used could be distilled off from the acidified reaction mixture.

[5] *Th. Kauffmann* et al.: a) Angew. Chem. *72*, 918 (1960); b) ibid. *74*, 248 (1960).

[6] Sodium hydrazide is an excellent reagent for splitting C-N double bonds; cf. the decomposition of quinoxaline at 0 °C. *Th. Kauffmann* et al., Angew. Chem. *73*, 540 (1961).

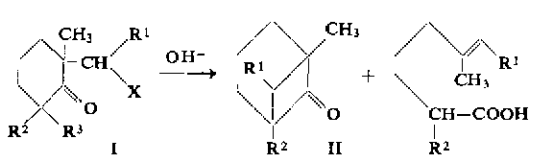
[7] J. Amer. chem. Soc. *68*, 2487 (1946).

A Synthesis of Bicyclo[3.1.1]heptanones

By Prof. Dr. F. Nerdel, Dipl.-Ing. D. Frank, and Dipl.-Ing. H. Marschall

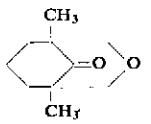
Institut für Organische Chemie
der Technischen Universität Berlin (Germany)

A communication [1] on the preparation of 1-methylbicyclo-[3.1.1]heptan-6-one prompts us also to report on the solvolysis of ketones of structure I. When boiled in aqueous or aqueous-alcoholic alkali, ketones such as I give bicyclic ketones (II) in 24–74 % yield along with the corresponding hept-6-enoic acids (1–26 % yield):



(X = OTs; $^+N(CH_3)_3\,J^-$; R^1=H, CH_3; R^2=H, CH_3; R^3=H, CH_2OTs)

2,6-Dimethyl-2,6-bis-(*p*-toluenesulfonyloxymethyl)cylcohexan-1-one (I, $R^1 = H$, $R^2 = CH_3$, $R^3 = CH_2OTs$, X = OTs) affords a 30 % yield of 1,5-dimethylbicyclo[3.1.1]heptan-6-one along with 30 % of the corresponding 6-heptanol and about 1 % of a bicyclic keto ether with the following structure:



Received, June 12th, 1962 [Z 302/135 IE]

[1] *E. Wenkert* and *D. P. Strike*, J. org. Chemistry *27*, 1883 (1962).

Monomeric Phosphinoboranes [1]

By Priv.-Doz. Dr. H. Nöth and Dipl.-Chem. W. Schrägle

Institut für Anorganische Chemie
der Universität München (Germany)

Monomeric phosphinoboranes (R_2P-BX_2) are not very well known [2]. They are to be expected when the electron deficiency of the boron atom becomes saturated by the formation of a $p_\pi-p_\pi$ double bond. We therefore attempted to prepare bis(dialkylamino)dialkylphosphinoboranes, since the dialkylamino group very readily affords this type of bond formation. The phosphinoboranes I and II were obtained in ether according to the following reactions:

$$[(H_3C)_2N]_2BCl + LiP(C_2H_5)_2 \rightarrow LiCl + [(H_3C)_2N]_2B-P(C_2H_5)_2 \quad (I)$$

$$(H_5C_2)_2NBCl_2 + 2\,LiP(C_2H_5)_2 \rightarrow 2\,LiCl + (H_5C_2)_2N-B[P(C_2H_5)_2]_2 \quad (II)$$

They are oily liquids which are readily oxidized and hydrolyzed and which dissolve in benzene with retention of their formula weight: Compound I: b.p. 134–136 °C/53 mm, Mol. Wt. calc. 188.1; found, 184.4; Compound II: b.p. 79–81 °C/0.001 mm; Mol. Wt. calc. 261.2; found 256.7.

Compounds I and II are highly reactive. Reactions take place at the dialkylphosphino group rather than at the dialkylamino group. This indicates that the free electron pair of the phosphorus atom, in contrast to that of the nitrogen atom, either does not participate in recoordination at the p_z-orbital of the boron atom, or does so only to a minor extent.

The phosphonium salts, $[((CH_3)_2N)_2B-P(C_2H_5)_2(CH_3)]I$ and $[(C_2H_5)_2N-B[P(C_2H_5)_2(CH_3)]_2]I_2$, can be precipitated as unstable compounds from ether with methyl iodide. Hydrogen chloride instantly cleaves the B–P bond of I and II:

$$(H_5C_2)_2N-B[P(C_2H_5)_2]_2 + HCl \rightarrow HP(C_2H_5)_2 + (H_5C_2)_2N-\underset{\displaystyle Cl}{\underset{|}{B}}-P(C_2H_5)_2 \quad (III)$$

Compound III, b.p. 45–48 °C/0.001 mm, can be dehalogenated with Na–K alloy in petroleum ether; from two molecules of III, the diboro compound,

$$(H_5C_2)_2N\ N(C_2H_5)_2$$
$$(H_5C_2)_2P-B-B-P(C_2H_5)_2$$

b.p. 160–170 °C/0.001 mm is obtained.

Alcohols or primary or secondary amines rapidly liberate diethylphosphine from I and II. Only then is the B–N linkage attacked.

Reaction of BCl_3 with $LiP(C_2H_5)_2$ in an equimolar ratio gives dimeric diethylphosphinodichloroborane, $[(H_5C_2)_2PBCl_2]_2$, m.p. 136–138 °C.

Received, June 19th, 1962 [Z 303/136 IE]

[1] Communication XVIII: "Contributions to the Chemistry of Boron".

[2] *G. E. Coates* and *J. G. Livingstone*, J. chem. Soc. (London) *1961*, 1000.

Decarboxylation of Diacyl Peroxides to Give Carboxylic Esters

By Prof. Dr. R. Huisgen and Dipl.-Chem. W. Edl [1]

Institut für Organische Chemie
der Universität München (Germany)

The statement by *Reynhart* [2] that dibenzoyl peroxide can benzoxylate benzene in the presence of $AlCl_3$ is incorrect. In both toluene and nonaromatic solvents, phenyl benzoate is obtained. An especially suitable electrophilic catalyst for this decarboxylative intramolecular ester formation is boron trifluoride, which in methylene cloride as solvent converts dibenzoyl peroxide into phenyl benzoate at 0–20 °C in 89 % yield. The even more rapid formation of an ester from di-(*p*-toluoyl) peroxide and the resistance exhibited by di-(*p*-nitrobenzoyl) peroxide to boron trifluoride suggest that an intramolecular electrophilic substitution on the aromatic ring takes place. In mixed aroyl-benzoyl or alkoyl-benzoyl peroxides, the two reaction paths leading to I and II compete (Table 1; the time data refer to the disappearance of the peroxide titer and give a rough measure of the rate of reaction).

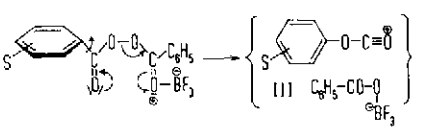
Table 1. Carboxylic esters from mixed diacyl peroxides with BF_3 in methylene chloride at 0–20 °C

$$R{-}CO{-}O{-}O{-}CO{-}C_6H_5 \xrightarrow[-CO_2]{BF_3} \underset{(I)}{R{-}CO{-}O{-}C_6H_5} + \underset{(II)}{R{-}O{-}CO{-}C_6H_5}$$

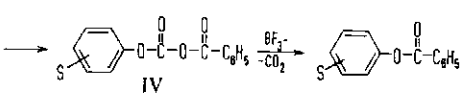
R	Reaction time	% Ester	Ratio I:II
p-$CH_3OC_6H_4$	10 min.	66	0:100
p-$CH_3C_6H_4$	10 min.	92	11:89
C_6H_5	3 hrs.	89	50:50
p-ClC_6H_4	2 hrs.	95	50:50
p-BrC_6H_4	2 hrs.	94	45:55
p-$NO_2C_6H_4$	16 hrs.	59	100:0
o-$CH_3OC_6H_4$	10 min.	68	0:100
o-$CH_3C_6H_4$	10 min.	87	0:100
o-ClC_6H_4	30 min.	76	0:100
o-$NO_2C_6H_4$	34 hrs.	11	100:0
CH_3	20 min.	77	100:0
$ClCH_2$	70 min.	53	100:0
C_2H_5	50 min.	88	100:0
$C_6H_5{\cdot}CH_2$ [*]	40 hrs.	75	0:100
$C_6H_5{\cdot}CH_2{\cdot}CH_2$	90 min.	63	66:34

[*] Without boron trifluoride; at 30 °C.

We propose the following mechanism analogous to that of the formation of an acyl carbonate from *p*-methoxy-*p'*-nitrobenzoyl peroxide in thionyl chloride [3]:



Ion pair



IV

According to this mechanism, heterolysis of the peroxide bond is coupled with an electrophilic substitution at the aromatic ring, which, in the course of a rearrangement, leads to the carboxonium ion III. The acyl carbonate IV cannot be isolated under the reaction conditions; with compound IV, S = H as an example, we observed 92 % rapid ester formation at 0 °C in the presence of BF_3. This mechanism also fits an experiment [4] carried out with dibenzoyl peroxide-[$C^{18}O$], $AlCl_3$, and benzene[5].

Table 1 shows an interesting violation of the Hammett equation for *p*-chloro- and *p*-bromo-dibenzoyl peroxides, which suggests competition of several simultaneous mechanisms. The preferential participation of *o*-substituted phenyl groups in the rearrangement is striking. The steric hindrance of resonance in the ground state of such compounds helps to meet the activation requirements of the electrophilic substitution on the aromatig ring.

Received, June 20th, 1962 [Z 306/140 IE]

[1] *W. Edl*, Diploma Thesis, Universität München, 1960.

[2] *A. F. A. Reynhart*, Rec. Trav. chim. Pays-Bas *46*, 54 (1927).

[3] *J. E. Leffler*, J. Amer. chem. Soc. *72*, 67 (1950); cf. the work with labelled ^{18}O by *D. B. Denney*, ibid. *78*, 590 (1956); *79*, 4806 (1957).

[4] *D. B. Denney* and *H. M. Weiss*, Chem. and Ind. *1962*, 818. These authors still proceed on the assumption of an intermolecular ester formation, which has meanwhile become invalidated.

[5] Note added in proof (July 14th, 1962): according to *J. T. Edwards, H. S. Chang*, and *S. A. Samad*, Canad. J. Chem. *40*, 804 (1962), ester formation from dibenzoyl peroxide and $AlCl_3$ is an intramolecular reaction.

Polymerisation of Cyclosilazanes

By Dr. C. R. Krüger and Prof. Dr. E. G. Rochow

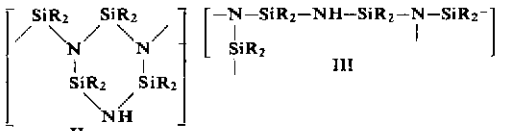
Department of Chemistry, Harvard University,
Cambridge, Massachusetts (U.S.A.)

Cyclosiloxanes are polymerised to linear polysiloxanes in strongly acidic media [1]. We performed an analogous reaction with cyclosilazanes by usipg ammonium halides as acidic catalysts. Contrary to the behavior of cyclosiloxanes, with cyclosilazanes, cross-linking through tertiary nitrogen with evolution of ammonia is preferred to linear polymerisation.

Thermo-polymerisation of hexamethylcyclotrisilazane (190 to 300 °C, 1–10% ammonium bromide) yielded 70% ammonia, calculated according to equation I, in 200–300 minutes, 27–32% distillable oligomers and 57–67% of high polymeric materials being obtained as reaction products.

$$n(R_2SiNH)_3 \rightarrow 2\,[(R_2Si)_{3/2}N]_n + nNH_3 \quad (I)$$

These materials are waxes or elastomers, depending on their degree of polymerisation. They show high stability to alkalies, low resistance to concentrated acids, and are soluble in nonpolar organic solvents. Slight decomposition occurs only above 495 °C/2 mm Hg; Si_3N_4 can be used as filling material Analyses, infrared and NMR spectra, and a quantitative investigation of the addition of phenyl isocyanate onto the remaining NH-groups [2], show that nearly $^2/_3$ of the nitrogen atoms are completely silyl-substituted. These results indicate approximately the structures II or III:



II III

The NH-groups of the substances can be metallated by butyl-lithium in petroleum ether, and the resulting *N*-metallic compounds react with halosilanes. Modifications of the described polymerisation reactions by addition of chain-stoppers (hexamethyldisilazane) and other applications will be reported elsewhere.

Received, June 20th, 1962 [Z 307/134 IE]

[1] *D. W. Scott*, J. Amer. chem. Soc. *68*, 2294 (1946); *D.T. Hurd*, J. Amer. chem. Soc. *77*, 2998 (1955).

[2] *U. Wannagat, C. Krüger*, and *J. Pump*, Z. anorg. allg. Chem. (to be published).

Photochemical Syntheses with Iodo Compounds [*]

By Prof. Dr. Norman Kharasch and Dr. L. Göthlich

Chemistry Department, University of Southern California, Los Angeles, California (U.S.A.)

The photolysis of various iodoarenes for the synthesis of polyaryl compounds, in good yields, has been reported recently [1]. By extending this reaction to a series of various iodo compounds the further general applicability could be shown.

Iodo Compound	Time [hrs.]	Product	Yield [%]
1-Iodo-2-phenylacetylene	12	Diphenylacetylene	50
1-Iodo-2-tolylacetylene	12	Tolylphenylacetylene	62
Benzoyl iodide	60	Benzophenone	12 [a]
2-Iodobenzaldehyde	48	2-Phenylbenzaldehyde	95 [a]
4-Iodobenzaldehyde	48	4-Phenylbenzaldehyde	90 [a]
Monoiodoacetic acid	24	Phenylacetic acid	67
Cyanogen iodide	10	Benzonitrile	50 [b]

[a] as 2,4-Dinitrophenylhydrazone; [b] as benzoic acid.

As light sourcea low-pressure mercury lamp, "Vycor" 7900, with water-cooled electrodes, was used which provides light of the wavelength 2537 Å. The formation of tarry decomposition products in noticeable amounts was observed only when irradiation was continued for a period of more than 48 hours.

We are now extending the investigation systematically to other iodo compounds, to studies involving ring closures and to reduction reactions, such as ArI → ArH and ArI → ArD. These results, as well as studies of the photolysis of iodo compounds in carbon tetrachloride (which leads, among other products, to hexachloroethane) and studies on the mechanism of the general reaction will be reported in the near future.

Received, June 26th, 1962 [Z 308/132 IE]

[*] Work supported by the National Science Foundation U.S.A.

[1] *W. Wolf* and *N. Kharasch*, J. org. Chemistry *26*, 283 (1961); and succeeding papers.

CONFERENCE REPORTS

Société Chimique de France

On May 18th and 19th, 1962, the Société Chimique de France held its annual meeting at the University of Rennes

From the agenda:

A Basic Iron Chloride

E. Quéméneur, Caen (France)

Basic iron chloride $Fe_2Cl_6 \cdot 25\ FeOOH$ has been obtained by the hydrolysis of iron chloride solutions between 50 and 175 °C, and by the action of sodium carbonate on these solutions.

The changes occurring in the liquid phase were followed by pH measurements, and those in the solid phase were detected by X-ray analysis; the composition of the liquid and solid phases was then determined by difference.

The formation of a precipitate began at 85 °C. After boiling the solutions for one hour at 100–105 °C and subsequent cooling, the solid and liquid phases were investigated. The solid phase corresponds to the formula $Fe_2Cl_6 \cdot 25\ FeOOH$. Hydrolysis experiments at 75 and 50 °C gave similar results. At 125 °C, the basic compound is still formed but is rapidly converted into α-Fe_2O_3. The rate of this conversion, which first occurs perceptibly at 100 °C, increases with temperature. Thus, α-Fe_2O_3 makes its appearance in the basic oxide diagram after 70 hours at 100 °C, 3 hours at 125 °C, or 1 hour at 175 °C. At this last temperature, pure oxide is obtained after 5 hours. During the hydrolysis at 100 °C, the pH changes from 2.25 to 1.34 in the most dilute solutions (0.03 mole/1000 g.) and from 0.6 to 0.25 in the most concentrated solutions (2 moles/1000 g.).

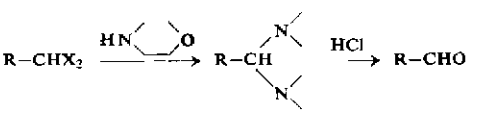
Under the same conditions of pH and concentration as in the hydrolysis of the iron chloride solutions, addition of sodium carbonate also brings about the precipitation of the basic oxide.

The amorphous hydroxide obtained by precipitation with NH_3 in the presence of ammonium salts and drying in air, is also converted into α-Fe_2O_3 on boiling for 24 hours in a solution of $FeCl_3$, but this precipitate is less well crystallized than that obtained from the basic salt.

Preparation of Aldehydes by the Action of Morpholine on gem-Dihalogeno Compounds

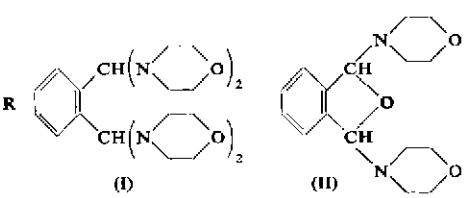
M. Kerfanto, Rennes (France)

Geminal dihalogeno compounds are converted to aldehydes by first preparing *gem*-diamino compounds, using anhydrous secondary bases such as morpholine; hydrolysis of these compounds with hydrochloric acid then leads to the aldehydes.



The yields of benzaldehyde, *p*-nitrobenzaldehyde, 3,5-dichlorobenzaldehyde, ethyl glyoxylate, and phenylglyoxal range from 60 to 90%.

In this manner, ring-substituted $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylenes, obtainable from *o*-xylenes by bromination in ultraviolet light, can be converted to *o*-phthalaldehydes. Intermediates of type I were isolated in this reaction



(I) (II)

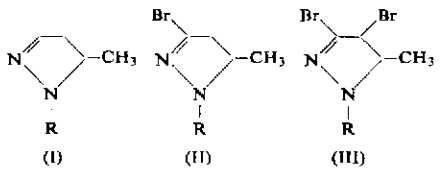
The product obtained when water was allowed to react with $\alpha,\alpha,\alpha',\alpha'$-tetra-(*N*-morpholino)-*o*-xylene (I, R=H) or when moist morpholine was used, contains only two morpholino groups. Judging from the absence of a carbonyl band in its infrared spectrum, a 1,3-dimorpholinophthalane structure(II) was assigned to this compound. On hydrolysis with hydrochloric acid, I and II afford *o*-phthalaldehyde.

In addition to *o*-phthalaldehyde, its 4-nitro, 4-chloro, and 4-bromo derivatives have been prepared by this method.

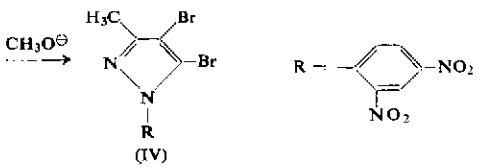
Bromination and Isomerization of 2-Pyrazolines

J. Elguero, Montpellier (France)

In the bromination of 1-(2,4-dinitrophenyl)-5-methylpyrazoline (I) with *N*-bromosuccinimide, it was demonstrated that the bromine attacks at the 3-position of the pyrazoline ring (II).



(I) (II) (III)



(IV)

The action of Br_2 in glacial acetic acid on II afforded III, which reacted with sodium methoxide in the known manner, giving IV.

Analogous results were obtained with pyrazoline, 4-methylpyrazoline, and 5-phenyl-pyrazoline and with their *N*-(2,4-dinitrophenyl)-, *N*-(*p*-nitrophenyl)- and *N*-(2,4,6-trinitrophenyl) derivatives. Chlorination was found to proceed in a similar manner.

The fact that the action of one mole of Br_2 on 5-methylpyrazoline gave 3- and 5-methylpyrazole hydrobromides, whereas two moles of Br_2 gave the hydrobromides of 4-bromo-3- and 4-bromo-5-methylpyrazoles, led to the conclusion that, initially, an *N*-bromo derivative is formed which immediately gives the pyrazole by elimination of HBr. This mechanism prevents attack at the 3-position. The *N*-bromo derivative was isolated in the case of 3,5,5-trimethylpyrazoline.

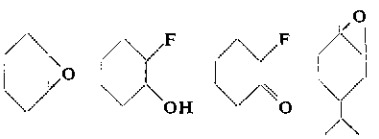
By means of NMR measurements, the isomerization of 5-methylpyrazoline (V) into 3-methylpyrazoline (VI) was studied by observation of the signals arising from the methyl group. No isomerization was found to take place during preparation or on refluxing. On the other hand, nearly complete isomerization occurred on heating with 1% powdered KOH or on refluxing with conc. HCl.

The cyclization of acetaldazine with formic acid to form 1-formyl-5-methylpyrazoline (VII) is described in the literature. The NMR spectrum shows that the product obtained is free of isomers. The author has now found that acid hydrolysis of VII affords a mixture of isomers containing about 30% of the 3-methyl compound (VI), and hydrolysis with 20% KOH gives almost exclusively the 3-methyl compound (VI). Hence, any preparation of pure 5-methylpyrazoline (V) by this method seems questionable.

Preparation of New Fluoroalcohols by the Action of Anhydrous Hydrofluoric Acid on Epoxides

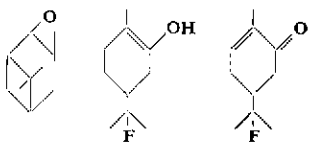
G. Farges, Clermont-Ferrand (France)

With HF, cyclohexene oxide (I), afforded 2-fluorocyclohexanol (II), characterized as its 3,5-dinitrobenzoate and the *p*-nitrobenzoate. Oxidation of the latter with chromosulfuric acid gave 2-fluorocyclohexanone (III), characterized as its 2,4-dinitrophenylhydrazone.



(I) (II) (III) (IV)

Analogous reactions of carvomenthene oxide (IV) showed that the C-F bond of the ketone is weaker than that of the alcohol. Similarly, limonene oxide gave a fluoroalcohol, which, because of its instability, could not be purified and oxidized. It was, however, characterized via its ester.



(V) (VI) (VII)

Pinene oxide (V) gave fluorocarvotanacetol (VI). This indicates that the action of anhydrous hydrofluoric acid on pinene oxide causes an allylic rearrangement with ring opening, a fact known from other examples. Oxidation of VI with chromosulfuric acid gives the ketone VII.

[VB 595/40 IE]

International Society for Fat Research

London, April 9th–13th, 1962

The lectures delivered at the VIth I.S.F. Congress were primarily concerned with autoxidation of fats, the investigation of substances which accompany fats in nature, and oleochemicals, *i.e.* synthetic products with a fat or fatty acid basis. *Swern* (Philadelphia, U.S.A.) and *Kaufmann* (Münster, Germany) were among those who spoke on this last topic. Both naturally occuring fatty acids and fatty alcohols can serve as dienes for *Diels-Alder* syntheses in the field of fats. They may be obtained *e.g.* by catalytic conjugation or total synthesis. Conjugated fatty acids may themselves act as dienophile components, but in this connection many other olefinic compounds can be considered. Diene syntheses in the fat field serve 1. for analytical purposes and/or structural determinations, 2. for the manufacture of technical products (stand oils, modified oil paints, *etc.*), and 3. to prepare new substituted hydroaromatic compounds, from which the corresponding benzene derivatives may be obtained by dehydrogenation, and carboxylic acids by subsequent oxidation. *Richert-Mellier* (Paris, France) reported on the acylation of phenols by palmitic acid in the presence of boron trifluoride. He prepared several mono- and dihydroxyphenyl ketones, their most important derivatives (oximes, dinitrophenylhydrazones, acetates), and by reduction, the secondary alcohols, all in good yield.

The mechanisms of radical reactions of unsaturated fatty acids and associated radical prototropic rearrangements have by now been extensively clarified; ionic reactions, on the other hand, still require investigation, and in this respect appear to merit at least equal importance, as was shown by *Baltes* (Hamburg, Germany) by illustration with typical ionic reaction mechanisms.

By stereospecific hydroxylation of the double bonds in fatty acids using iodine and silver acetate according to *Woodward*, combined with chromatography on silicic acid or alumina, *Fedeli* and *Valentini* (Milan, Italy) were able to obtain di- and tetrahydroxy fatty acids in remarkable purity. Conversely it was possible to prepare very pure oleic acid.

for example, from dihydroxystearic acid via the bromine compound.

In the preparation of pure symmetrical triglycerides from mixed fatty acids by the action of the chloride of one acid upon the 1,3-diglyceride of the other acid, it is important to prevent the formation of side products by acyl migration. *Crossley* and *Padley* (Port Sunlight, England) succeeded in obtaining pure triglycerides by performing the reaction at room temperature in chloroform/pyridine. By this method, the formation of 2-oleodistearin is virtually complete 30 seconds after addition of the oleyl chloride.

With regard to the associates of fats in nature, the accent was placed upon lecithin. In the food stuffs industry, lecithin from soya beans is chiefly used. In Poland, soya lecithin has been successfully replaced by rape seed lecithin on economic grounds. The technology of the production of rape seed lecithin is very similar to that of the soya bean product, but the hydrogenation step is somewhat more difficult. According to *Jakubowski* (Warsaw, Poland), a continuous hydrogenation process has been developed which will permit the production in 1962 to rise to 400 tons. Rape seed lecithin is used in Poland in the margarine, chocolate, and bread-making industries. Rape seed lipase shows two regions of optimum activity, one under acid conditions (pH 5) and the other under alkaline conditions (pH 8). Rape seed lipase displays its greatest activity at 37 °C; it is inactivated between 60 and 70 °C.

Pardun (Kleve, Germany) described a new method of preparing pure lecithin from crude plant lecithin. According to this procedure, crude lecithin is treated with a ternary solvent mixture, consisting of hydrocarbons, acetone, and water; two liquid phases are formed; the lower contains mainly the phosphatides, and the upper the crude oil and free fatty acid. Multistage application of the solvent mixture, *e.g.* in a counter-current apparatus, results in isolation of pure lecithin in a yield of *ca.* 95 % with only 1–2 % residual oil content.

A new submicro method for analysis and structure determination of lecithins and triglycerides was described by *Privett* and *Blank* (Austin, Minn., U.S.A.). Completely saturated, partially saturated, and unsaturated lecithins and triglycerides in admixture can each be quantitatively determined. The method depends on reductive ozonolysis of the unsaturated fatty acids and subsequent separation of the cleavage products by thin layer chromatography and gas chromatography. Whilst the mixture of short-chain aldehydes which arise from the 'free ends' of the unsaturated fatty acids on reductive ozonolysis is removed by distillation and analysed by gas chromatography, the residues from the 'glyceride ends' of the lecithins and triglycerides are fractionated by thin layer chromatography and the fractions estimated by quantitative photodensitometry.

The paraffin and olefin hydrocarbons present in the unsaponifiable portion of oils and fats can be separated from polyenes, such as squalene, by chromatography on silica gel. The hydrocarbon mixture can be resolved further by fractional crystallisation from acetone followed by gas chromatography. In the unsaponifiable fraction of linseed oil, all the n-hydrocarbons from C_{12} to C_{35}, all the iso-members from C_{11} to C_{22} as well as the members from C_{14} to C_{20} of a still unidentified series, *i.e.* a total of 43 hydrocarbons, could be detected. With the exception of olive oil, whose unsaponifiable portion contains only some 20 to 25 hydrocarbons, other oils such as peanut, rapeseed, and corn oil show a picture similar to that of linseed oil.

The volatile components of butter fat contain free fatty acids, carbonyl compounds, and lactones. By removal of the carbonyl compounds with Girard reagent, and extraction of the residue with petroleum ether and subsequent chromatography of the extract on alumina, the enol lactone of 2,3-dimethyl-4-ketonon-2-enoic acid ($C_{11}H_{16}O_2$) was successfully isolated. This γ-lactone is characterised by a strong odour of celery and was named 'bovolide' by its discoverers. By heating butterfat in the presence of water, a series of methyl ketones with odd numbers of carbon atoms (C_5 to C_{15}) was formed. In the absence of water no ketone formation occurs. Non-volatile β-keto esters in the butter (concentration *ca.* 0.03 %) are the precursors of these methyl ketones.

Paquot and *Mercier* (Paris, France) dealt with the primary stages of autoxidation of unsaturated fatty acids. They proved successfully that autoxidation of methyl esters of fatty acids containing one, two, or three *cis* double bonds (oleic, erucic, linoleic, and linolenic acids), one *trans* double bond (elaidic acid), or one double bond at the end of the chain (undecylenic acid) produces in every case hydroperoxides which are polarographically determinable. At room temperature, both double bond attack and subsequent hydroperoxide decomposition proceed most rapidly with esters containing terminal double bonds.

Skellon (London, England) discussed the mechanisms of the lesser known secondary changes which occur during autoxidation of simple unsaturated fatty acids. He showed that the primary hydroperoxides undergo homolytic scission to yield free hydroxyl radicals, dihydroxy derivatives, ketols, and aldehydo-acids. In the later stages of the reaction, the last two compounds may undergo condensation or polymerisation. For mono-unsaturated fatty acids, one can predict the formation of four isomeric hydroperoxides, which must give four aldehydes and four aldehydo-esters as degradation products. The 'predicted' aldehydes and also the related aldehydo-esters were isolated from autoxidised petroselinic esters. Cleavage products of shorter chain length were also found.

A report on the autoxidation of linoleic acid, particularly in the presence of metal-porphyrin catalysts was given by *N. Uri* (Waltham Abbey, England).

Octamethyltetraza-porphyrins and phthalocyanines of iron, cobalt, manganese, and copper were investigated. The copper complex was found to be inactive, whereas the others proved to be highly active autoxidation catalysts in homogeneous systems. The catalyst is obviously able to react with both the substrate and the peroxides formed. The formation of an oxygen-complex appears equally possible. In metal-porphyrin catalysis, some 50 % of the peroxides formed are converted into carbonyl compounds. Whereas chelating agents, such as hydroxy acids and certain amines, did not influence catalytic activity, free radical acceptors, *e.g.* a series of polyphenolic compounds, proved to be active antioxidants. The activity of the porphyrins, like that of the heavy metal stearates, is influenced by the polarity of the medium.

It is well known that free unsaturated fatty acids and their ethyl esters are protected against autoxidation by formation of complexes with urea. However this only applies at lower reaction temperatures. Even at 60 °C, the stability of the urea adducts is rather unsatisfactory.

Krog and *Tolboe* (Aarhus, Denmark) fractionated soya lecithin with acetone, ethanol, acetic acid, and chloroform/ethanol (1:2) and found that the fraction soluble in ethanol is rich in phosphatidyl choline and has a relatively low copper content, whilst the fraction insoluble in chloroform/ethanol contains the phosphoinositides in concentrated form and have a high copper content. Model experiments with citrate buffer and citrate buffer + ethylenediamine-tetra-acetic acid showed that the ethanol-soluble phosphatidyl choline fraction gave up a considerable portion of its copper content to the buffer, whereas in the case of the insoluble phosphoinositide fraction, the effect was very limited. No influence of pH on the release of copper could be detected between pH 3.0 and 6.6. Whilst the phosphatidyl choline fraction proved to have an antioxidant effect in margarine, the phosphoinositide fraction showed neither an antioxidant nor (despite its high copper content) a pro-oxidant effect.

Wissebach (Emmerich, Germany) discussed high pressure hydrogenation of commercial oils and refinery fatty acids. Under normal conditions (4 atms.), the hydrogenation lasts many hours and requires up to several percent nickel (on the basis of the starting material) as catalyst. A relatively mod-

erate increase in hydrogen pressure to 30 atms. shortened the hydrogenation time considerably and reduced the catalyst requirement by 30 to 50 %. The results obtained in laboratory experiments were confirmed on a factory scale. By using pure hydrogen, still further advances in the hydrogenation of commercial oils and fatty acids may be expected.

Owing to its high carotene content, palm oil requires more intensive decolourisation than is necessary for other oils and fats. The bleachability of the raw oil is chiefly influenced by its free fatty acid content, preoxidation, and heavy metal contamination. The above factors can be favourably influenced by suitable control over the harvesting, recovery, storage, and transport of the raw oil. These investigations have already found practical application in the Congo, where so-called 'SPB Palm Oil' is now produced, which is characterised by first-class bleachability and, as a result, reasonably good stability of the finished product.

Treatment of 3-pentachlorphenoxy-1,2-epoxypropane with adipic acid produces 3-pentachlorphenoxy-2-hydroxypropyl mono-adipate, which possesses antibacterial and antimycotic activity and hence may be used as an additive for dressings and bacteria- and fungus-resistant coatings.

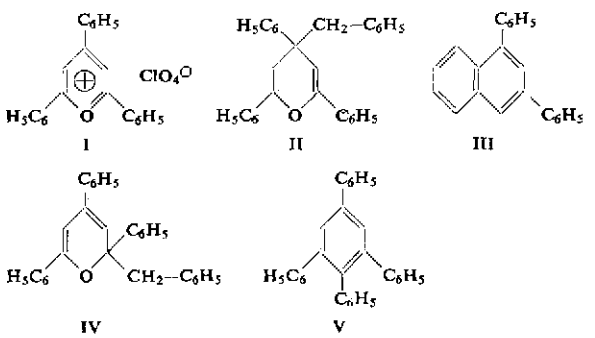
[VB 590/37 IE]

Reactions with Pyrylium Salts

K. Dimroth, Marburg/Lahn (Germany)

Pyrylium salts are oxonium-carbonium salts which are stabilised by mesomerism as aromatic 6π cations and which add on nucleophilic reagents at C-2, C-6, or C-4 [1]. The site at which primary addition occurs appears to depend on the type of reaction involved. Detailed examination of the reaction of 2,4,6 substituted pyrylium salts with benzylmagnesium chloride showed that, in this case, primary addition takes place at C-4.

2,4,6-Triphenylpyrylium perchlorate (I) yields the 4*H*-pyran derivative II, which, on treatment with perchloric acid, is converted with loss of acetophenone into 1,3 diphenylnaphthalene (III) in 90 % yield [2]. Under the influence of bases, such as CaO or preferably disodium oxydiethoxide, II undergoes an allyl rearrangement to give the 2*H*-pyran derivative (IV), which under the reaction conditions is converted immediately into 1,2,3,5-tetraphenylbenzene (V). It is possible to isolate IV on irradiating II with ultraviolet light [3]. Although IV is converted into the benzene derivative V by bases, it does not form a naphthalene derivative III under the influence of perchloric acid. Thus the reverse rearrangement of IV into II by acids does not occur.



I II III

IV V

Isomeric 2*H*- and 4*H*-heterocyclics were also isolated in the thiopyran series. In contrast, pyridinium salts yield with benzylmagnesium chloride only *N*-Alkyl-1,4-dihydropyridine derivatives corresponding to the 4*H*-compounds, as shown unequivocally by comparison of their absorption spectra; these cannot be rearranged into 1,2-dihydropyridine derivatives.

A report will be published elsewhere on reactions of pyrylium salts with methylenetriphenyl-phosphorane, which, after addition at C-2 (or C-6), produce benzene derivatives and which yield 1,3,4,6,8-pentaphenyl-5-benzoylazulene in an interesting sequence of changes [4].

[Chemische Gesellschaft Karlsruhe (Germany),
May 24th, 1962]

[VB 597/36 IE]

[1] *K. Dimroth*, Angew. Chem. *72*, 331 (1960).

[2] *K. Dimroth* and *K. H. Wolf*, Angew. Chem. *72*, 778 (1960).

[3] *H. Kroke*, Ph. D. Thesis, Marburg/Lahn 1962.

[4] *K. H. Wolf* and *K. Dimroth*, unpublished results.

Collagen

M. Brenner, Basel (Switzerland)

Soluble tropocollagen has been reported to be converted into acid and alkali insoluble collagen via a procollagen step [1]. This process is thougt to involve a nonenzymatic curing process (aggregation, chemical crosslinking) which goes on throughout life, at later stages assuming the form of ageing. In an investigation of this process *F. Verzar* (Basel) and the author studied the different forms of collagen and the products formed in the course of its thermal contraction [2]. As experimental material, tail tendons from rats of different ages were used. Results: 1. Tropocollagen from 3 months old rats contains significantly more lipophilic amino acids and less of the amino acids characteristic of collagen than either procollagen or collagen does [3]. 2. During thermal shrinkage (64 °C in water), tendons from young (7 months) and old (30 months) animals break down into water-soluble gelatin of high molecular weight and an elastic thread; the older the animals, the slower the rate of degradation. However, the proportion of the products of decomposition remains roughly constant (5–10% insoluble product in the form of the elastic thread).– 3. Surprisingly, the amino acid composition of the insoluble material, whose hydrolysis products contain increasing amounts of amino sugars as the age of the experimental animals increases, is similar to that of tropocollagen, particularly of its α_2 component [4].

Conclusion: Collagen is not merely cross-linked tropocollagen. In the course of its development, either a chemical transformation of the tropocollagen peptide chain or a linking of the tropocollagen onto a second independent collagen intermediate (pro-collagen?) must occur. The results show how essential it is to consider the solid state of collagen in chemical investigations of this material.

[GDCh-Ortsverband Frankfurt/Main (Germany),
May 24th, 1962].

[VB 594/39 IE]

[1] See, for example, *E. Budecke*, Angew. Chem. *72*, 663 (1960).

[2] *A. Meyer*, Ph. D. Thesis, Universität Basel 1962.

[3] Compare: *D. S. Jackson et al.*, Biochim. biophysica Acta *27*, 418 (1958).

[4] *K. A. Piez et al.*, Biochem. Biophys. Acta *53*, 596 (1961).

Anisotropy of Electronic and Physical Properties of Graphite and its Crystal Compounds

A. R. Ubbelohde, London (England)

Large single crystals of graphite for investigations of anisotropy were obtained from metallic melts, but were never quite pure. A more suitable product was obtained by pyrolysis of CH_4 or C_3H_8 at 1600–2300 °C; this graphite was deposited in the form of plates about 1 mm thick having the carbon layers orientated parallel to the supporting surface of polycrystalline graphite, *i.e.* the c-axes lie perpendicular to the support. Lat-

tice defects in this pyrolytic graphite were eliminated to a great extent by annealing at 3000 °C. Their amount at concentrations $< 10^{-5}$ was determined from the Hall Effect and the change in conductivity in a magnetic field. Graphite almost free from defects is bright silver in color, but slowly darkens on exposure to air.

Contradictory values in the literature for the ratio ρ_a/ρ_c of the specific resistance in the direction of the a-axis and the c-axis respectively were explained. With decreasing concentration of defects, ρ_a (ca. $10^{-4}\Omega$·cm) falls slightly, whilst ρ_c, after an initial rise, shows a characteristic decrease from 1 to $10^{-2}\Omega$·cm in the case of crystals entirely free from defects. The number of charge carriers is greatly influenced by the presence of defects or foreign atoms.

Orientated graphite shows a positive thermoelectric power along the c-axes; in the a-direction, the effect is either slightly positive or negative depending on the concentration of defects. This makes it possible to use orientated graphite to construct thermo-elements capable of use up to 2400 °C.

The thermal conductivity parallel to the layers is three times that of Cu; in the c-direction it is 0.01 times that of Cu. The unusual anisotropy of the thermal conductivity of pyrolytic graphite makes it possible to construct inductively heated crucibles, which, with a wall thickness of only 3 mm, may have a temperature of 3000 °C inside and only 2000 °C on the outside.

Graphite compounds with electron donors (*e.g.* C_8K) or acceptors (*e.g.* $C_{24}^{+}HSO_4^{-}\cdot 2H_2SO_4$) are better electrical conductors than graphite, because electrons are added to an unoccupied conductivity band, or are withdrawn from an occupied band. The carbon layers are to be regarded as macro-anions or macro-cations.

[Chemische Gesellschaft zu Heidelberg (Germany), May 28th, 1962] [VB 596/34 IE]

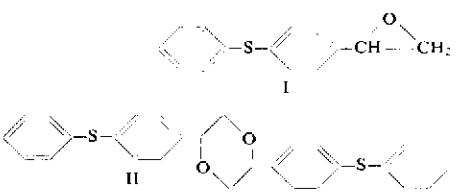
SELECTED ABSTRACTS

A correlation between the autumnal coloration of green leaves and the kind and quantity of yellow coloring matter formed in this process was established by *W. Eichenberger* and *C. A. Grab* on the basis of studies of the carotenoids from green, yellowing, and yellowed leaves. Using chromatographic and spectroscopic methods, they found that during yellowing the number of different carotenoids increases while their total quantity decreases. When distributed between petrol ether and methanol, the newly formed additional compounds are found more abundantly in the upper phase (epiphase). They exhibit, however, the same chromophoric system as the green leaves. New formation of carotenoids during yellowing seems improbable. The epiphase compounds are presumably phytoxanthine esters. A change in the chloroplasts and the consequent change in their synthetic abilities are proposed as reasons for the transformation of the summer carotenoids. / Helv. chim. Acta *45*, 974 (1962) / Bs. [Rd 220/77 IE]

Alkyl **hydroperoxides** were synthesized by *G. Wilke* and *P. Heimbach* from olefins via trialkylborines. With olefins *N*-triethylborazan gave trialkylborines which autoxidized to $RB(OOR)_2$; further oxidation with peracids gave compounds of the type $ROB(OOR)_2$, which were then hydrolyzed to the hydroperoxides. For example, the following hydroperoxides were thus prepared: cyclododecyl, cyclooctyl, undecyl, 2-ethylhexyl, 2-phenethyl, and 1- and 2-indanyl hydroperoxides. / Liebigs Ann. Chem. *652*, 7 (1962) / Wi. [Rd 217/76 IE]

The pharmacological properties of Haemaccel, a new colloidal plasma substitute, have been investigated by *R. Muschaweck* and *W. Benoit*. Animal experiments have shown that Haemaccel, a 3.5 % solution of a polymerized gelatin hydrolyzate with added electrolytes, is tolerable as a plasma expander and can replace 70–80 % of the circulating blood plasma in rats without ill effect. No disturbances in circulatory or renal functions were observed. Histological examination failed to reveal tissue deposits or secondary tissue reactions. The time of retention in the body (as determined by testing the urinary excretion of hydroxyproline, of which Haemaccel contains approx. 1.5 %) depends on the species investigated. The half-life in the serum of rats and dogs is 4–5 hours, only 5–10 % remaining after 24 hours; in man, 74 % of any Haemaccel administered is excreted in the urine in four days. Haemaccel meets all the requirements for a good plasma expander, namely, adequate retention before decomposition or excretion by the organism, the absence of antigenic or pyrogenic properties or of effects on serological reactions, and compatibility with whole and citrated blood. / Arzneimittelforsch. *12*, 380 (1962) / –De. [Rd 223/80 IE]

A series of new, aromatically substituted, mostly sulfur-containing mono- and diepoxides, *e.g.* di-(4-epoxyethylphenyl)-sulfide, were obtained by *H. Hopff* and *R. Wandeler* from the also previously unknown chlorohydrins. The compounds exhibited variable stability, as is typical of epoxides. Particularly unstable products were obtained (in an analytically pure state) directly from carefully purified chlorohydrins. On heating to 100 °C in 50 % aqueous sulfuric acid, 4-epoxyethylphenyl phenyl sulfide (I) gave, among other products, a dimer which was assigned the dioxan structure II.



Fusing I with hexamethylenediamine or phthalic anhydride gave polyadducts which were, however, not homogeneous because of the high melting points and the high rate of reaction. / Helv. chim. Acta *45*, 982 (1962) / Bs. [Rd 222/781E]

BOOK REVIEWS

Gmelins Handbuch der anorganischen Chemie (Gmelin's Handbook of Inorganic Chemistry), 8th completely new edition. Published by the Gmelin-Institut für Anorganische Chemie und Grenzgebiete in der Max-Planck-Gesellschaft zur Förderung der Wissenschaften. Begun by *R. J. Meyer*, continued by *Erich Pietsch*. Verlag Chemie, GmbH., Weinheim/Bergstr. (Germany).

System No. 5: Fluorine. Supplement Volume, 1959, XVIII, 258 pages with 31 illustrations, German-English table of contents, English headings and subheadings on the margins of the text, paperbound DM 162.– ($ 40.50), clothbound DM 167.– ($ 42.–). Edited by *A. Hirsch*, *A. Kunze*, *W. Lippert*, *W. Müller*, *Gertrud Pietsch-Wilcke*, *F. Seuferling*, *L. Thaler*, and *Hildegard Wendt*.

The supplementary volume on fluorine (dedicated on the occasion of his 80th birthday to Prof. Dr. *Otto Hahn*, then president of the Max Planck Gesellschaft) is a continuation of the main volume on fluorine (which appeared 36 years ago

in 1926) for the 25-year period 1926–1950. In contrast to the mere 86 pages (with 4 illustrations) of the main volume, the present supplementary volume contains 258 pages (with 31 illustrations). From this fact itself one can infer the great strides in research and technology of fluorine (System No. 5) and its compounds with hydrogen, oxygen, and nitrogen (Systems Nos. 2, 3, and 4, respectively), which are solely discussed in the present volume in accordance with the Gmelin principle of the last place.

The 65-page chapter "Occurrence" treats both the extraterrestrial occurrence of the element in stars and meteorites and the terrestrial occurrence in the lithosphere, hydrosphere, atmosphere and biosphere. The complete data on fluorite are not included in the discussion of minerals containing fluorine, since mineral deposits and mineralogy of fluorite have already been amply treated in the Calcium Volume A 2 (1957).

In the 76-page section on elemental fluorine, the preparation of fluorine (15 pages) is treated first. Special emphasis is placed on the commercial production via electrolysis of KF:n HF melts (equipment, electrodes, decomposition voltage, yield, tests for purity, handling, storage, transportation). This section is of special value, since elemental fluorine was not produced in industrial quantities before the Second World War. In fact, the commercial production of fluorine was first established during the last war (with the possibility of use as an oxidizing agent in rocket propulsion, for example). This section of the volume presents, therefore, more recent data. The treatment of the physical properties of fluorine (17 pages) follows the usual Gmelin classification. The recent data on the energy of dissociation should be especially mentioned here. These show that F_2, contrary to earlier ideas, readily dissociates into atoms on heating (at 1250 °C and 1 atm., for example, the degree of dissociation is 80%). Its tendency to dissociate, therefore, surpasses very considerably that of the easily cleaved I_2 (whose degree of dissociation at 1250 °C is close to 60%). In the concluding section on the chemical properties (44 pages), the electrochemical, chemical, physiological, and analytical behavior of fluorine is treated in the usual complete manner.

The 117-page section on compounds of fluorine, which occupies nearly half of the supplementary volume, is devoted to hydrogen (79 pages), oxygen (14 pages), and nitrogen (24 pages) compounds of fluorine. Of special interest are sections on the association of hydrogen fluoride and the behavior of anhydrous liquid hydrogen fluoride as a solvent, as well as the sections on the preparation, structure, and properties of compounds that were discovered since the appearance in 1926 of the main volume on fluorine. These are the oxygen fluorides OF_2 (1927) and O_2F_2 (1933), nitrogen fluorides NF_3 (1928), N_2F_2 (1942), and N_3F (1942), and nitrogen oxyfluorides NOF (1931), NO_2F (1931), and NO_3F (1934). The cut-off date for the literature survey (end of 1950) is especially regrettable here. This is because the last decade, here with a few exceptions neglected, brought about substantial new data in this field.

This supplementary volume on fluorine contains for the first time both a German-English table of contents and an index system in the form of English margin notes. These innovations offer the German reader a welcome bridge to English technical terminology and facilitate the use of the handbook by the foreign reader.

System No. 59: Iron. 2. Supplement Volume to Iron, Part D ("Magnetic Materials"), 1959, XXXVIII, 580 pages with 308 illustrations, German-English table of contents, English headings and subheadings on the margins of the text, paperbound DM 359.– (\$ 90), clothbound DM 364.– (\$ 91.–). Edited by *U. Dehlinger, J. v. Harlem* (deceased), *W. Heister, G. Kirschstein, K. H.v. Klitzing, A. Kussmann*, and *K. Merkle*.

Seven parts of the Gmelin Handbook are devoted to the treatment of iron. Of Part A (Historical, Occurrence, The Element, Its Metallurgy and Its Alloys), Section I in 5 fascicles (1929–1933; 1166 pages with 421 illustrations) and Section II in 4 fascicles (1934–1939; 781 pages with 416 illustrations) have been completed up to this time, while the last section (III) is still to appear. Part B (Compounds of Iron) in 5 fascicles (1929–1932; 1166 pages with 62 illustrations) and Part C (Assay Methods, Mechanical and Engineering Properties of Carbon Steels and of Steel Alloys) in 2 fascicles (1937–1939; 450 pages with 313 illustrations + 8 full-page illustrations) are complete. Part D, which appeared in 1936 (Magnetic and Electrical Properties of Industrial Alloys; 466 pages with 342 illustrations) was augmented in 1955 by a first supplementary volume (148 pages with 166 illustrations), and in 1959 by a Second supplementary volume (580 pages with 308 illustrations). The latter will be discussed here. Part E (Corrosion and Its Prevention with Alloy Steels) is still to appear. Part F (Detection and Determination of Foreign Elements in Iron and Steel) was concluded in two sections (Section I in 2 fascicles: 1939–1941, reprinted in 1955; 430 pages with 36 illustrations + 4 full-page illustrations. Section II with 2 fascicles: 1939, reprinted in 1955; 388 pages with 19 illustrations). Part G (Cast Iron) is still to appear. The treatment of the element iron is therefore covered up to now in 5575 pages with 2083 illustrations plus 12 full-page illustrations, at a total price of 3670 DM (about \$920.–). The reviewer is forced to pose the question whether this is not too much of a good thing within the framework of a handbook of inorganic chemistry. Certainly, the complete treatment of the metallurgy of iron, of assay methods, of the mechanical and engineering properties of carbon and alloy steels, of the magnetic and electrical properties of alloy steel, of corrosion and its prevention using alloy steels, of cast iron, etc., is of primary significance for workers in the field. Certainly, these subjects should be dealt with in an appropriate text if the presently available pertinent standard works do not already fulfill this function. However, the reviewer doubts that Gmelins Handbook of Inorganic Chemistry is the proper place for such a broad and complete treatment of all these technical problems, especially if this results in undue postponement of initial volumes on such important elements as carbon, tin and lead, phosphorus, vanadium, niobium and tantalum, manganese, nickel, silver, and the transuranium elements.

From this point of view, the present Supplement 2 to the main volume Iron D, entitled "Magnetic Materials", is certainly very meritorious and admirable in its completeness, but its conception falls outside of the proper function of the "Gmelin". As far as the reviewer was able to determine from numerous conversations, the majority of inorganic chemists, to whom the Gmelin Handbook is directed, would in most cases be better satisfied if extensive volumes, such as the present one, could either be postponed in favor of the more rapid issuance of the System Numbers that are still lacking and a quicker completion of the present System Numbers or, still better, could be abandoned to other, thematically more suitable handbooks.

And now to the discussion of the present Supplement 2 to the volume Iron, Part D (System No. 59), which as a special volume entitled "Magnetic Materials", also serves to supplement the System Nos. 52 (chromium), 56 (maganese), 57 (nickel), and 58 (cobalt). Of these, a major part (Cr, Mn, Ni) is still not covered by a principal volume of the 8th edition of Gmelin.

The volume begins with a 34-page introductory chapter, which defines and classifies the material to be treated, discusses the general literature, and the terminology and the symbols used, and deals in a general way with the contemporary theoretical concepts concerning ferromagnetism and the behavior of ferromagnetic substances.

The 307-page chapter on "Ferromagnetic Elements and Alloys" which follows, contains an introductory statement on the literature and systematics (3 pages) and then deals with the magnetic properties of iron and its alloys (147 pages), of cobalt and its alloys (24 pages), of nickel and its alloys (106 pages), of alloys of manganese (21 pages) and chromium (2 pages), as well as with the composition and the properties of the permanently magnetic alloys (4 pages). In the case of alloys of iron, cobalt, nickel, manganese, and chromium, alloys with elements of higher System Nos. than that of the

main element are also considered, so far as data on their magnetic properties exist, contrary to the Gmelin principle of the last place that is usually followed.

After a brief survey of nomenclature (1 page), the subsequent 120-page chapter, "Ferromagnetic Semiconductors," deals with the magnetic and electrical properties of oxides and mixed oxides of iron (110 pages), of chromium, manganese, and cobalt (5 pages), as well as those of ferromagnetic sulfides, selenides, and hexacyano complexes (5 pages).

The next, 67-page chapter on "Patents" compiles all the 800 patents which have appeared from the time of the publication of volume Iron D (1936) and its Supplementary Volume 1 (1937) up to June 30, 1957 and which deal with materials for permanent magnets, weakly magnetic materials, nonmagnetic materials, conductors, and resistors.

A final 51-page "Material Index" gives information about all the alloy systems (45 pages) and oxide systems (4 pages) which have been discussed. It also gives trade names of alloys and oxides (2 pages) and therefore facilitates orientation within the book.

All in all, the present supplementary volume undoubtedly represents an impressive achievement. It surveys the literature up to the end of 1949, and in special instances up to the end of 1955 (manganese and chromium alloys, ferromagnetic semiconductors) or the middle of 1957 (patents). Because of its subject matter, it is of greater interest to the electronics engineer and the physicist working with metals than to the inorganic chemist.

System No. 33: Cadmium. Supplement Volume, 1959, XCIV, 802 pages with 218 illustrations, German-English table of contents, English headings and subheadings on the margins of the text, paperbound DM 508.– (\$ 127.–), clothbound DM 513.– (\$ 128.50). Edited by *M. Atterer, H. Balters, Marianne Drössmar-Wolf, R. Gagarin, H. Gedschold, Gertrud Glauner-Breitinger, R. Glauner, G. Hantke, A. Hirsch, Erna Hoffmann, G. Huschke, H. Lehl, Margarete Lehl-Thalinger, Imberta Leitner, W. Müller, J. Nägler, Gertrud Pietsch-Wilcke, F. Plessmann, K. Rumpf, F. Seuferling, Ph. Stiess, K. Swars, E. Uhlein,* and *Hildegard Wendt.*

while the main volume on cadmium, which appeared 37 year ago (1925), contained only 214 pages (23 illustrations), the present supplementary volume requires nearly four times as many pages [802 pages (218 illustrations)] in order to cover the 25-year period 1924–1949 alone.

This supplementary volume begins with a 19-page section on the occurrence of cadmium and ends with a 10-page index of ligands or addends contained in the complex compounds of cadmium treated in the volume. The remainder of the text (773 pages) is devoted approximately one third to the physics and two thirds to the chemistry of cadmium.

The chapter on the physics of cadmium (268 pages) is subdivided in the usual way under the headings of atom and molecule, and crystallographic, mechanical, thermal, optical, magnetic, electrical, and electrochemical properties. The electrochemistry section is notable since it occupies approximately half (127 pages) of the physics part. Here the reader is familiarized with all the recent work on the standard potential of cadmium, the electromotive force of cells with cadmium and cadmium amalgam electrodes, the manufacture, properties, and uses of the cadmium-mercury cell (Weston cell) and the increasingly important nickel-cadmium battery, the overvoltage of cadmium electrodes, the behavior of cadmium in cathodes and anodes, and the electrolytic deposition of cadmium.

The chemical part (505 pages) reports first the industrial production of cadmium (23 pages) and the general chemical behavior both of elemental cadmium (21 pages) and of the cadmium ion (21 pages). It then deals with alloys and compounds of cadmium (440 pages).

The chapter on cadmium alloys (60 pages) encompasses all the alloys of cadmium (System No. 33) with the elements of System Nos. 18 (antimony) through 32 (zinc). Excluded here are only alloys with magnesium (System No. 27), which, contrary to the Gmelin last place principle, have already been described in the Magnesium Volume A 4 (1952). Cadmium alloys with elements of System Nos. lower than 18 are considered with the cadmium compounds. Almost half the chapter on cadmium alloys is devoted to cadmium-zinc alloys (28 pages). These latter have been extensively cited in the newer literature, especially with reference to their structure and their electrolytic preparation.

The chapter on cadmium compounds (380 pages) discusses cadmium compounds with elements up to System No. 32. That is, the chapter treats cadmium compounds with hydrogen, with elements of the seventh (F, Cl, Br, I), sixth (O, S, Se, Te), fifth (N, P, As, Sb, Bi), fourth (C, Si), third (B), second (Be, Mg, Ca, Sr, Ba), and first principal group (Li, Na, K, Rb, Cs, NH_4) and those with Zn. Especially thorough treatment is accorded here to the oxygen compounds CdO and $Cd(OH)_2$ (26 pages), cadmium chloride $CdCl_2$ (50 pages), cadmium bromide $CdBr_2$ (23 pages), cadmium iodide CdI_2 (39 pages), cadmium sulfide CdS (24 pages), cadmium sulfate $CdSO_4$ (24 pages), and complex compounds of cadmium (80 pages). Their description alone requires 70 % of the space devoted to cadmium compounds. The discussions in this part emphasize the data on the crystallographic properties of the basic cadmium salts (some of which crystallize in complicated layer lattices), the polymorphism of cadmium iodide (32 modifications of which have already been described), the manufacture of cadmium sulfide pigments (cadmium yellow), the photoconductivity of cadmium chalcogenides, and the cationic complexes of cadmium with O, N, S, P, and As compounds. Plainly, the discussion of the cationic complexes is of especial value to the chemist interested in the field, since nowhere else can one find such a complete general survey of this part of cadmium chemistry. It is regrettable that the anionic complexes of cadmium are not similarly collected in one specific section; they must be individually searched for since they are scattered under the respective metals concerned (for example, under "Cadmium and Potassium", "Cadmium and Ammonium", Cadmium and Organic Bases"). To be sure, this deficiency is partially corrected by the previously mentioned index of the complex compounds of cadmium, which includes not only the cationic, but also the anionic complexes, insofar as the latter are derived from organic bases.

The subject of detection and determination of cadium is excluded since the analytical chemistry of cadmium is already treated in detail in Volume II, 2 (1955) and III, 2b (1945) of the Handbook of Analytical Chemistry by *W. Fresenius* and *G. Jander*, and a repetitious compilation of the factual material is unnecessary.

The literature has been consulted up to the end of 1949, but for certain important developments it is considered beyond this date, even up to 1958.

The value of the supplementary volume is increased by a comprehensive German and English table of contents that is no less than 94 pages long. This table also includes the contents of the main volume and thus greatly facilitates the location of any particular piece of information.

System No. 15: Silicon. Part B, The Element and the Inorganic Compounds of Silicon, 1959, LIX, 923 pages with 154 illustrations, German-English table of contents, English headings and subheadings on the margins of the text, paperbound DM 570.– (\$ 142.50), clothbound DM 575.– (\$ 144.–). Edited by *M. Atterer, H. Balters, Marianne Drössmar-Wolf, H. Gedschold, Gertrud Glauner-Breitinger, G. Hantke, A. Hirsch, Erna Hoffmann, G. Kirschstein, H. K. Kugler, A. Kunze, H. Lehl, Imberta Leitner, Gertrud Pietsch-Wilcke, K. Rumpf, Renate Schmieder-Jancke, F. Seuferling, K. Swars.*

The present volume, Silicon B, which considers, in 923 pages (154 illustrations), the element silicon and the inorganic compounds of silicon, has long been eagerly awaited by the users of the Gmelin Handbook. Only the 288-page chapter in Volume III, 1 of the 7th edition of Gmelin, which appeared a half-century ago (1912) and is therefore hopelessly out of date, has been available up to this time as a reference on silicon.

The pertinent literature up to the end of 1949 is completely surveyed in the present volume. This arbitrary cut-off date of course interrupts the continuity of development of several significant problems of silicon chemistry in awkward places. For example, the discovery of the semi-conductor properties of silicon (as diodes and transistors) and the solution of the corresponding manufacturing and engineering problems occurred mainly in the last decade. In order to make up at least partially for this deficiency, a limited three-page selection from the review literature on silicon and its inorganic compounds for the years 1950–1959 is appended at the end of the volume. This compilation obviously contains only a small fraction of the literature which has appeared since 1950. It is supplemented in various other locations of the volume by further literature references. The silicon case clearly shows the praiseworthiness of the recent decision of the Gmelin advisory board. According to that decision, in the future the evaluation of the literature will be brought up to date.

One fourth of the 920-page text of the present volume is devoted to elemental silicon, and three fourths to compounds of silicon (System No. 15) with elements up to System No. 14 (carbon).

The chapter "Elemental Silicon" (226 pages) discusses first the preparation of silicon in the laboratory and in industry (15 pages). Here, under the heading of "Purification," one misses the processes for manufacturing extrapure silicon which were, of course, developed after the cut-off date for the review of the literature. In the following sections on the physical (95 pages), electrochemical (5 pages), chemical (14 pages), and physiological (5 pages) properties of silicon, the literature which appeared up to the end of 1949 is evaluated in the usual careful way and, where necessary, is supplemented by references to more recent work. The section on "Detection and Determination" (92 pages) is also complete, since the pertinent volumes of the Handbook of Analytical Chemistry by *Fresenius* and *Jander* have not yet appeared. Indeed, from the abundance of available material, preference has been given here to recent literature, since, currently, the old established methods are being re-examined in detail in the light of modern knowledge.

The chapter "The Compounds of Silicon" (694 pages) deals with compounds of silicon with hydrogen, with the halogens and chalcogens, and with nitrogen, boron, and carbon. By far the largest part of this chapter (nearly 60%) is devoted to oxygen compounds of silicon (silicon monoxide, silicon dioxide, silicic acids, silanols, siloxanes, siloxenes, glass electrodes – a total of 402 pages), corresponding to their importance.

Some significant examples from the chapter on the compounds of silicon may be chosen at random for description. The 30-page section on silanes gives an imposing picture of the pioneer work of *Alfred Stock*, and represents, indeed, the most comprehensive description available of the entire literature in this special area. The same can be said of the 12-page section on silicon monoxide. The 313-page chapter on silicon dioxide includes both silicic anhydride SiO_2 and silicic acid hydrates $SiO_2 \cdot x\,H_2O$ (acids, sols, gels), and discusses, among other subjects, the lattice structures of the various modifications of SiO_2, the optical, electrical, and piezoelectric behavior of quartz and its future technical applications, the structures of the various silicic acids, as well as the commercial preparation of silicic acid gels. The subsequent 20-page section on silanols, siloxanes, and siloxenes contains only substances that are basic in these classes of compounds and their inorganic derivatives, since the organic derivatives are treated in Silicon Volume C (1958), which was previously reviewed [1]. The section on the analogous silicon-nitrogen compounds (9 pages) is considerably shorter than the chapter on the silicon-oxygen compounds; work on the former compounds has stagnated for a long time, and has only recently begun to increase. On the other hands, for the treatment of the silicon-carbon compounds (excluding the extensive area of the organic Si–C compounds, which are reserved for the Silicon Volume C [1]), 103 pages are necessary (96 pages for silicon carbide SiC and its numerous modifications alone). The 57-page chapter on the properties and behavior of glass electrodes, which closes the present volume, is of particular value. Here, under headings such as forms of electrodes, methods of measurement, potentials, reaction mechanisms, and use, factual material from widely scattered sources is clearly arranged in a comprehensive report, the study of which can be recommended to all interested chemists, physical chemists, and physicists.

Systematic Subject Index, Alphabetic Series. 1959. IV, 109 pages, Text in German and English, paperbound DM 30 ($ 7.50), clothbound DM 35.– ($ 9.–). Edited by the Documentation Section of the Gmelin Institute.

The 109-page special volume, "Alphabetische Folge zur Systematik der Sachverhalte," is a supplement to the 116-page special volume, "Systematics of the Subject Index," which appeared two years ago, and which has already been discussed in this journal [2]. It contains, in alphabetical order (both in German and in English), approximately 5000 key words, together with the pertinent combinations, for a suitable documentation and arrangement of the individual concepts found in the index system of the Gmelin Handbook. It differs fundamentally from the first special volume only in regard to the arrangement of the key words, which in the present volume are arranged alphabetically, whereas in the previous volume the systematic classification into collective groups, principal groups, sub-groups, and special cases predominated However, the supplementary volume is a praiseworthy improvement, since it greatly increases the value and usefulness of the first special volume in several ways. Thus, it expands the 2000 concepts contained in the latter by an additional 3000 key words, and makes it possible, by means of the number-letter combinations introduced, for even a non-specialist to arrange, positively and without uncertainty, subjects which are difficult to classify because they are named after their discoverers ("Bullard-Dunn process", "de Haas-van Alphen effect", "Olsen test"), because they involve abbreviations ("BDS process," "TTT curves", "LS coupling"), or because their names are synthetic ("alitize", "alumitize," "sherardize"). Thus, for example, the key combination "35.21.42.B" signifies the concept, "Alclad process", which deals with a surface treatment by coating with metallic aluminum by means of rolled plating (collective group 35: surface treatment; principal group 21: metallic coating; subgroup 42: aluminum; special case B: rolled plating).

The price of the present special volume is 30 DM (about $7.50); the reviewer notes this with satisfaction, since he objected to the high price (72 DM, about $18.00) of the first special volume [2] which was no larger.

E. Wiberg [NB 855/15 IE]

[1] Angew. Chem. internat. Edit. *1*, 277 (1962).

[2] Angew. Chem. *71*, 348 (1959).

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The Chemistry of Sulfur Tetrafluoride [*]

BY DR. WILLIAM C. SMITH

FABRICS AND FINISHES DEPARTMENT, EXPERIMENTAL STATION,
E. I. DU PONT DE NEMOURS & COMPANY, WILMINGTON, DELAWARE (U.S.A.)

Current knowledge regarding the chemical and physical properties of sulfur tetrafluoride is reviewed. The structural features of the compound are discussed, and its toxicological properties are presented. Particular attention is given to its reactions as a fluorinating agent in view of the widespread interest in this facet of its chemistry.

Introduction

Sulfur tetrafluoride (SF_4) is a novel and extremely useful reagent and reaction intermediate; yet its ability to exist was questioned as late as 1950. In that same year, however, the compound was first isolated and identified and since 1954, its chemical and physical characterization has been the subject of intensive study. These investigations have shown that SF_4 possesses an unusual combination of physical, structural, and chemical characteristics. The discovery that SF_4 is a unique and specific fluorinating agent has been of particular value in synthetic work. The compound has also been employed in the synthesis of other simple sulfur fluoride derivatives (*e.g.* SF_5Cl and SOF_4), which themselves undergo a number of interesting and potentially useful reactions. Investigation of the chemistry of SF_4 has clearly shown that this reagent provides a route to a variety of new fluoro compounds as well as a convenient method for preparing many known substances that were only obtained with difficulty by earlier fluorination techniques.

Synthesis

The first specific attempt to prepare SF_4 was reported by *Ruff* and *Thiel* [1]. These investigators tried unsuccessfully to obtain the compound by the interaction of hydrogen fluoride with tetrasulfur tetranitride and sulfur tetrachloride, as well as by fluorination of the latter with stannic fluoride and arsenic trifluoride. Elemental sulfur and many sulfur-containing compounds have since been treated with a variety of fluorinating agents under a wide range of experimental conditions. *Ruff* and *Heinzelmann* [2] apparently were the first to prepare and isolate an impure sample of SF_4, judging by the properties of a low-boiling material they obtained, but they did not recognize it as such. The first reasonable claim to a synthesis of this compound was published by *Fischer* and *Jaenckner* [3] who obtained it in a state of questionable purity by the reaction of elemental sulfur with cobalt trifluoride. Studies of numerous other investigators [4–8] led to mixtures of sulfur fluorides that undoubtedly contained SF_4, but the latter was not isolated and identified in these studies.

The first unequivocal synthesis of SF_4 was that of *Silvey* and *Cady* [9], who isolated it from the products formed in the decomposition of CF_3SF_5 in an electrical discharge [10].

$$CF_3SF_5 \rightarrow CF_4 + SF_4$$

[*] A joint contribution from the Central Research Department and the Fabrics and Finishes Department, E. I. du Pont de Nemours & Co., Inc.

[1] *O. Ruff* and *C. Thiel*, Ber. dtsch. chem. Ges. *38*, 549 (1905).

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[3] *J. Fischer* and *W. Jaenckner*, Angew. Chem. *42*, 810 (1929).

[4] *O. Ruff* and *G. Bahlau*, Ber. dtsch. chem. Ges. *51*, 1752 (1918).

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[9] *G. A. Silvey* and *G. H. Cady*, J. Amer. chem. Soc. *72*, 3624 (1950).

[10] *R. Geballe* and *F. S. Linn*, J. appl. Phys. *21*, 592 (1950).

Several other reliable but inconvenient routes to SF_4 have been reported in the literature. Thermal decomposition of disulfur decafluoride was shown to give SF_4 and SF_6 in equimolar amounts [11]. Mild fluorination of carbon disulfide with elemental fluorine gave SF_4 as a reaction product [12, 13]. The reaction of elemental sulfur with elemental fluorine at −75 °C provided the SF_4 utilized by *Brown* and *Robinson* for their excellent physical studies of the compound [14]. *Schmidt* [15] indicated that a yellow solid obtained by the reaction of sulfur monobromide (S_2Br_2) with iodine pentafluoride yielded SF_4 on subsequent treatment with copper turnings, but reinvestigation of this reaction [16] showed that the interaction of S_2Br_2 with IF_5 yielded SF_4 directly. A related method, that is particularly useful if product of high purity is desired, involves the oxidative fluorination of elemental sulfur with IF_5 at 200–300 °C [17]:

$$5\,S + 4\,IF_5 \rightarrow 5\,SF_4 + 2\,I_2$$

The action of chlorine trifluoride on elemental sulfur also gives SF_4 as one of the oxidative fluorination products [18].

The most convenient routes to SF_4 are based on (1) reactions of sulfur or sulfur-containing compounds with elemental chlorine and a metal fluoride, or (2) fluorination of sulfur dichloride with a metal fluoride in an inert medium of high dielectric constant. In both of these methods, finely divided sodium fluoride serves conveniently as the fluorinating agent. The first procedure involves heating a sulfur source with chlorine and a metal fluoride such as sodium fluoride. Sulfur dichloride is a particularly useful reactant [17], giving overall reaction:

$$SCl_2 + Cl_2 + 4\,NaF \rightarrow SF_4 + 4\,NaCl$$

Other sulfur-containing reactants which may be used include elemental sulfur, metal sulfides and sulfur monochloride, and it is reasonable to assume that in each of these cases SCl_2 is formed prior to reaction with the other constituents of the system. Carbon disulfide may also be employed as the sulfur source [19]; the volatile reaction products consist of SF_4 and halomethanes. The most practical laboratory synthesis is the unique procedure discovered by *Tullock* [17]; sulfur dichloride is heated at atmospheric pressure in a medium of high dielectric constant with a metal fluoride such as sodium fluoride. The volatile sulfur fluoride escapes from the reaction mixture as soon as it is formed and is collected conveniently in a trap cooled in acetone/solid carbon dioxide. Acetonitrile is a particularly convenient reaction medium, and the reaction is carried out at the reflux temperature (68–72 °C) in conventional glass equipment. The use of dry, finely divided sodium fluoride and redistilled sulfur dichloride are prerequisites if maximum purity and yields are desired.

[11] *W. R. Trost* and *R. L. McIntosh*, Canad. J. Chem. *29*, 508 (1951).

[12] *G. A. Silvey* and *G. H. Cady*, J. Amer. chem. Soc. *74*, 5792 (1952).

[13] *E. A. Tyczkowski* and *L. A. Bigelow*, J. Amer. chem. Soc. *75*, 3523 (1953).

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[15] *W. Schmidt*, Mh. Chem. *85*, 452 (1954).

[16] *E. L. Muetterties*, unpublished results.

[17] *C. W. Tullock*, *F. S. Fawcett*, *W. C. Smith*, and *D. D. Coffman*, J. Amer. chem. Soc. *82*, 539 (1960).

[18] *H. L. Roberts*, Canadian Patent 634 467 (January 9, 1962).

[19] *W. A. Sheppard*, U. S. Patent 2 972 518 (February 21, 1961).

Structure

The structure of the SF_4 molecule is essentially a trigonal bipyramid, in which two fluorine atoms and the unshared electron pair are in the equatorial positions and the other fluorine atoms in the polar positions. This conclusion was first reached on the basis of infrared and Raman studies, which indicated that SF_4 has C_{2v} symmetry, and was subsequently supported by nuclear magnetic resonance spectroscopic studies. This structure is basically the same as that of other halides of the group V, VI and VII elements, *e.g.* that found by electron diffraction for $TeCl_4$ [20]. The nuclear magnetic resonance studies established that there are two pairs of nonequivalent fluorine atoms in the molecule, and that the atoms in the apical and equatorial positions undergo rapid exchange at room temperature [21]. The rate of fluorine exchange at low temperatures is sufficiently slow to permit a meaningful study of the variation of the nuclear magnetic resonance spectrum with temperature. The activation energy of fluorine exchange was found to be 4.5 ± 0.8 kcal/mole.

Microwave spectral studies carried out recently have shown that one FSF angle is 101 °33′ ± 30′ and the opposite one is 186 °56′ ± 30′. The bond length of the nearly linear bonds is 1.646 ± 0.003 Å; for the equatorial pair it is 1.545 ± 0.003 Å [22].

It was first proposed that the bonding in SF_4 – like that in PF_5 – is sp^3d. However, more recently it has been suggested that a completely analogous situation would not be expected, because the sulfur orbitals in SF_4 should have different hybridization ratios owing to the presence of the unshared electron pair and the fact that the s, p, and d sulfur orbitals have large energy differences. It was therefore proposed that the three equatorial bonds are formed with sp^2 hybrids and that the apical bonds consist of p and d orbitals. This concept is consistent with the structural data. The equatorial bonds (1.545 Å) have the length of a normal S–F bond, while the polar bonds (1.646 Å) are quite long; and in addition, the equatorial angle is only 101 °33′ compared to 120 ° in a true trigonal bipyramid [22].

The presence of an unshared electron pair in the SF_4 molecule suggests that the compound should have some basic character. Similarly, the presence of an unoccupied 3d-orbital in the molecule, together with the known

[20] *D. P. Stevenson* and *V. Schomaker*, J. Amer. chem. Soc. *62*, 1267 (1940).

[21] *E. L. Muetterties* and *W. D. Phillips*, J. Amer. chem. Soc. *81*, 1084 (1959); *F. A. Cotton*, *J. W. George*, and *J. S. Waugh*, J. chem. Physics *28*, 994 (1958).

[22] *W. M. Tolles* and *W. D. Gwinn*, J. chem. Physics *36*, 1119 (1962).

ability of the sulfur atom to be hexacoordinate (*e.g.* in SF_6), suggests that SF_4 should also be an electron pair acceptor. Studies described in the following sections have established that SF_4 can act as a weak acid and suggest that it can also function as a weak base.

Physical Properties

The known physical properties of SF_4 are given in Table 1. The values for the heat of formation are based on studies of the heats of hydrogenation and hydrolysis, respectively.

Table 1. Physical properties of sulfur tetrafluoride

	Ref.
Melting Point = −121.0 ± 0.5 °C	[14]
Boiling Point = −38 °C	[14]
Density at 200 °K = 1.9191 g/cm³	[14]
Density at T °K (170–200 °K) = 2.5471−0.00314 T	[14]
Critical Temperature = 90.9 ± 0.2 °C	[17]
Surface Tension at 200 °K = 25.70 dynes/cm	[14]
Surface Tension at T °K (190–230 °K) = 61.36−0.1783 T	[14]
Heat of Formation = −171.7 ± 2.5 kcal/mole	[23]
−176 kcal/mole	[24]
Molar Heat of Vaporization = 6.32 kcal	[14]
Trouton's Constant = 27.1	[14]
Vapor pressure [mm] at T °K (160–224 °K), log P = 8.8126−1381/T	[14]
Coeff. of cubical expansion [cm³/cm³/ °C] (170–200 °K) = 0.00170	[14]
Dipole Moment = 0.632 ± 0.003 Debye; 1.0 ± 0.1 Debye	[22; 25]
S–F bond energy *ca.* 78 kcal/mole	[23]

Purification

Sulfur tetrafluoride can be obtained in a state of purity suitable for many reactions by distillation in an efficient low-temperature still [17]. Small amounts of dissolved chlorine introduced as the result of synthetic techniques involving sulfur chlorides and/or elemental chlorine can be removed by treatment with finely divided sulfur at room temperature. The SF_4 isolated in this way is at least 90–95 % pure; the principal impurity is thionyl fluoride. This relatively unreactive fluoride does not normally interfere with reactions of SF_4 and is usually a by-product of SF_4 fluorination reactions involving oxygen replacement in any case. Gas chromatography can be employed to separate thionyl fluoride from SF_4 if higher purity is required. The use of sodium fluoride coated with either tetramethylene sulfone or the dimethyl ether of tetraethylene glycol is a particularly effective absorbent and gives SF_4 with a purity of 98 % or more in a single pass through a preparative scale column [26]. The use of "Kel-F" [*] on "Chromosorb" [**] as absorbent is suggested by a recent publication, which describes the gas chromatographic separation of sulfur fluoride mixtures [27].

Adducts with certain Lewis acids (*e.g.* $SF_4 \cdot BF_3$) have also been employed successfully in the purification of SF_4. The nature of these adducts and the method by which SF_4 is regenerated from them is discussed in a later section.

Toxicity and Hazards

Sulfur tetrafluoride is of the same order of toxicity as phosgene, as judged by acute inhalation toxicity tests with mice [28]. Four hour exposure to a concentration of 19.4 ppm was lethal to one of two animals exposed. All animals, including those exposed to 10 ppm for one hour, showed irregular breathing and signs of irritation. At the higher concentrations, the clinical signs were severe and consisted of rapid, labored breathing, weakness, cyanosis, and discharges from the nose. Animals receiving lethal amounts showed pulmonary edema on autopsy. Animals subjected to sublethal exposure showed no pathological changes when sacrificed 14 days after exposure. The toxicity of SF_4 and the ease with which it hydrolyzes to give hydrogen fluoride on contact with moisture make extreme care a prerequisite in working with this fluoride.

Sulfur tetrafluoride hydrolyzes very rapidly but can be handled in glass equipment that has been dried thoroughly under vacuum. It is convenient to store the fluoride in stainless steel cylinders; the vapor pressure of SF_4 at 25 °C is about 10 atms. For carrying out reactions of SF_4 at elevated temperatures, stainless steel or "Hastelloy C"-lined bombs have been used satisfactorily. Care must be taken to avoid overloading such bombs to prevent excessive pressures being generated at elevated temperatures [28].

Fluorination Reactions of SF_4

The selective replacement of oxygen and sulfur atoms by fluorine in many types of organic compounds has been shown to be a general and particularly useful reaction of SF_4. These and the other reactions of SF_4 discussed in the paragraphs below provide direct syntheses of many new and hitherto inaccessible compounds containing fluorine.

Fluorination of Organic Carbonyl and Hydroxyl Compounds

Sulfur tetrafluoride is a remarkably effective reagent for the selective replacement by fluorine of carbonyl oxygen in organic compounds [29].

$$>C=O + SF_4 \rightarrow >CF_2 + SOF_2$$

[23] *J. D. Vaughan* and *E. L. Muetterties*, J. physic. Chem. *64*, 1787 (1960).

[24] *Nicholls*, Ph. D. Thesis, Durham University, 1958.

[25] *R. E. Dodd* and *R. Little*, Nature (London) *188*, 737 (1960).

[26] *J. W. Robson* and *W. B. Askew*, J. Chromatog. *7*, 409 (1962).

[*] Trademark of M. W. Kellogg Co., Jersey City, N. J.

[**] Trademark of Johns-Manville Corp.

[27] *R. H. Campbell* and *B. J. Gudzinowicz*, Analytic. Chem. *33*, 842 (1961).

[28] New Product Information Bulletin 2b, "Sulfur Tetrafluoride Technical", Organic Chemicals Department, E. I. du Pont de Nemours & Co., Inc., 1961.

[29] *W. R. Hasek*, *W. C. Smith*, and *V. A. Engelhardt*, J. Amer. chem. Soc. *82*, 543 (1960).

The reaction has broad scope and is effective with a variety of carbonyl compounds including aldehydes, ketones, and carboxylic acids.

a) Carboxylic Acids

In the reaction of a carboxylic acid with SF_4, the carboxyl group is converted to a trifluoromethyl group. This is the most general and direct method for synthesizing compounds with $-CF_3$ groups. Although a trifluoromethyl derivative can be obtained directly from a carboxylic acid, the reaction, illustrated below for benzoic acid, proceeds in two steps – formation of the acyl fluoride, and replacement of the carbonyl oxygen.

$$C_6H_5COOH + SF_4 \rightarrow C_6H_5COF + HF + SOF_2$$

$$C_6H_5COF + SF_4 \rightarrow C_6H_5CF_3 + SOF_2$$

The first step normally occurs at or below room temperature, while the second step requires elevated temperatures. The effectiveness of this reaction for the fluorination of a wide variety of aliphatic and aromatic carboxylic acids is described in the literature [29]. With polybasic acids, the degree of fluorination may be controlled by the amount of SF_4 used. Thus, from sebacic acid, either 1,1,1,10,10,10-hexafluorodecane or 10,10,10-trifluorodecanoyl fluoride may be obtained as the principal product.

$$HOOC(CH_2)_8COOH \xrightarrow{6\ SF_4} CF_3(CH_2)_8CF_3 \quad (87\,\%)$$

$$\downarrow 3\ SF_4$$

$$CF_3(CH_2)_8COF + CF_3(CH_2)_8CF_3 + FCO(CH_2)_8COF$$

45 % 27 % 21 %

That the reaction of SF_4 with carbonyl groups is unusually specific is shown by the fact that olefinic and acetylenic bonds are unaffected. As a result, trifluoromethylethylene and trifluoromethylacetylene are easily accessible in good yield from acrylic and propiolic acids, respectively.

$$CH_2{=}CHCOOH \xrightarrow{SF_4} CH_2{=}CHCF_3$$

$$CH{\equiv}CCOOH \xrightarrow{SF_4} CH{\equiv}CCF_3$$

Other functional groups including fluoro, chloro, bromo, nitro, and methoxycarbonyl usually are unaffected by SF_4 at temperatures up to 160 °C.

In some cases $\alpha,\alpha;\alpha',\alpha'$-tetrafluoro ethers have been isolated from reactions of carboxylic acids and SF_4. For example, diglycolic acid yielded 2,2,6,6-tetrafluorodioxan as well as 2,2,2-trifluoroethyl ether.

$$HOOCCH_2OCH_2COOH \xrightarrow{SF_4} CF_3CH_2OCH_2CF_3 + \text{tetrafluorodioxan}$$

Fluorination can also be carried out successfully when the carboxyl group is attached to a heterocyclic ring. For example, 2-trifluoromethyl-5-nitrofuran was obtained from 5-nitro-2-furoic acid [30].

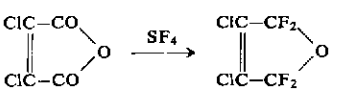
The introduction of a trifluoromethyl group into a steroid by this method was reported recently [31]. The conversion of lithocholic acid 3-acetate into its trifluoromethyl derivative in modest yield was accomplished at room temperature in methylene chloride as solvent but only in the presence of a substantial amount of hydrogen fluoride.

Modification of the Lewis acid concentration, reaction medium, and other reaction conditions were shown to afford a clean and convenient method for the selective fluorination of formyl and ketone groups in steroids that also contain acetate and α,β-unsaturated ketone functions.

Another recent application of this technique is the fluorination of amino acids [32]. The conditions required for the direct reaction of SF_4 with compounds containing primary or secondary amino groups often lead to generation of hydrogen fluoride, with subsequent degradation of the organic compound at the required reaction temperatures. By carrying out the reaction in liquid hydrogen fluoride, however, the amino group is successfully protected from attack by SF_4; the latter can then fluorinate the carboxylic acid group in the normal manner. The reaction has been carried out on many aliphatic amino acids in modest yields; when an optically active amino acid was employed, optical activity was retained in the resultant fluoroamine. Amino acids employed in this work include glycine, DL-alanine, DL-phenylalanine and L-leucine. The hydrogen fluoride solvent system was also shown to be useful in obtaining moderate to good yields of fluorination products from such heterocyclic compounds as picolinic, isonicotinic, quinaldic, and 4,5-imidazoledicarboxylic acids with SF_4.

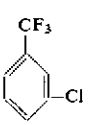
b) Acid Anhydrides, Salts, and Acyl Halides

Carboxylic anhydrides, salts, and acyl halides react with SF_4 to give products like those from the acids, but more vigorous conditions are required [29]. Whereas phthalic acid yielded a mixture of 43 % *o*-bis(trifluoromethyl)benzene and 23 % *o*-trifluoromethylbenzoyl fluoride at 120 °C, the anhydride yielded only phthaloyl fluoride (92 % yield) at 180 °C and required a temperature of 350 °C for conversion to *o*-bis(trifluoromethyl)benzene (45 % yield). The anhydride ring may react without loss of the ring oxygen atom, however. For example, dichloromaleic anhydride and SF_4 give 3,4-dichloro-2,2,5,5-tetrafluoro-2,5-dihydrofuran.



The reaction of an acyl fluoride with SF_4 proceeds in the expected manner to give a trifluoromethyl compound. The reaction of an acyl chloride and SF_4 is not so straightforward, however. With benzoyl chloride, the initial reaction appears to be exchange of Cl by F. This is followed by replacement of the carbonyl oxygen with two fluorine atoms and also by chlorination of the ring. The nature of the chlorinating agent is unknown.

$$C_6H_5COCl + SF_4 \rightarrow C_6H_5COF \rightarrow$$



c) Esters

Carboxylic esters require vigorous conditions for uncatalyzed reaction with SF_4. The products usually are

[30] *W. R. Sherman, M. Freifelder,* and *G. R. Stone,* J. org. Chemistry *25,* 2048 (1960).

[31] *F. Kagan* and *D. G. Martin,* Abstracts of 140th Meeting of the American Chemical Society, Chicago, Ill., September, 1961 page 30 M.

[32] *M. S. Raasch,* J. org. Chemistry *27,* 1406 (1962).

trifluoromethyl compounds, and evidence that α,α-difluoro ethers and acyl fluorides are reaction intermediates has been obtained [29]. Thus, methyl benzoate did not react at 250 °C but fluorination at 300 °C gave benzotrifluoride and methyl fluoride.

$$C_6H_5COOCH_3 + 2\,SF_4 \rightarrow C_6H_5CF_3 + CH_3F + 2\,SOF_2$$

The fluorination of esters can, as for acid anhydrides, be catalyzed effectively by certain binary inorganic fluorides and markedly lower reaction temperatures can then be used. Recent work has clearly established that in certain instances, direct replacement of the carbonyl oxygen atom in esters with fluorine can be accomplished with formation of the corresponding α,α-difluoro ethers. This has led to a general and direct synthesis of aryl perfluoroalkyl ethers based on the reaction of SF_4 with perfluoroalkyl esters and aryl fluorocarbonates in the presence of hydrogen fluoride as catalyst [33].

$$ArO\overset{\overset{O}{\|}}{C}X + SF_4 \xrightarrow{HF} ArOCF_2X \quad \text{(where X = F or perfluoroalkyl)}$$

d) Amides

In contrast to the sluggish behavior of the ester group with SF_4, the amide group is quite sensitive. Two types of amides may be distinguished: those in which there is at least one N–H bond and those without an N–H bond. In the first group, the carbonyl-nitrogen bond breaks to give an acyl fluoride, which may then undergo further reaction. Thus, benzamide and *N*-methylbenzamide both yield benzotrifluoride and benzoyl fluoride. With amides having no N-H bond the carbonyl-nitrogen bond may or may not be broken. While replacement of the carbonyl oxygen with fluorine atoms in such molecules can be accomplished, it is difficult to prepare α,α-difluoro amines reproducibly by this method. The primary reason for this appears to be the chemical instability of the fluorination products.

e) Aldehydes and Ketones

The action of SF_4 on aldehydes is typified by the preparation of benzal fluoride from benzaldehyde.

$$C_6H_5CHO \xrightarrow{SF_4} C_6H_5CHF_2$$

In general, aldehydes having no α-hydrogen atoms give high yields of the expected difluorides. Aliphatic aldehydes containing α-hydrogens are somewhat sensitive to SF_4, and yields of their difluorides are correspondingly lower [29].

Sulfur tetrafluoride has been employed successfully in the fluorination of a number of ketones. Although ketones containing α-hydrogen are also sensitive toward SF_4, acetone can be converted to 2,2-difluoropropane in good yield. This fluorination can in fact be carried out at atmospheric pressure under reflux if a cold trap is employed to keep the reactants contained in the reaction vessel. Cyclohexane derivatives are particularly sensitive, but cyclohexanone can be converted successfully to 1,1-difluorocyclohexane at reaction temperatures below 50 °C.

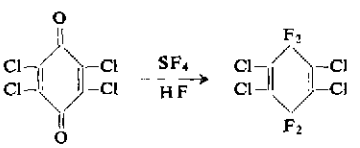
[33] *W. A. Sheppard*, J. Amer. chem. Soc. *83*, 4860 (1961).

Benzophenone is quite resistant to reaction with SF_4 – even at temperatures considerably higher than those employed for other ketones – probably because of steric hindrance of the carbonyl group. However, high yields of diphenyldifluoromethane were obtained from benzophenone and SF_4 when a catalyst was employed. When the catalyst was BF_3, AsF_3, or TiF_4, the temperature had to be moderated to prevent complete charring of the benzophenone. With vicinal polyketones, such as benzil and diphenyltriketone, all of the ketonic oxygen atoms are replaced.

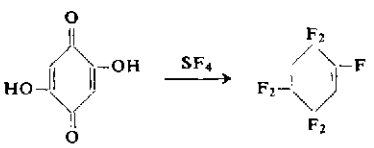
The preparation of several new types of fluorosteroids by replacement of ketonic oxygen atoms with fluorine has also been accomplished. Both 3,3-difluoro and 17,17-difluoro compounds in the androstane series, as well as 3,3-difluoro and 20,20-difluoro derivatives of C_{21} steroids, have been prepared in this manner. As expected, the ease of fluorination, as reflected in the yields of products, was greatly dependent on the site and nature of the carbonyl function undergoing reaction [34]. The report that such fluorinations can be carried out selectively and conveniently in the presence of excess hydrogen fluoride was discussed earlier in the section dealing with the fluorination of a steroid containing a carboxylic acid group [31].

f) Quinones

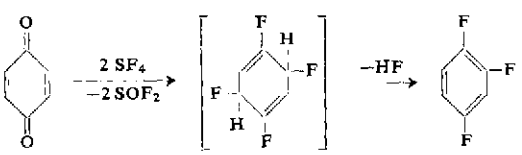
Some quinones, such as anthraquinone and chloranil, react in the same fashion as ketones to yield products in which each carbonyl oxygen atom has been replaced



by two fluorine atoms. Other quinones behave irregularly with SF_4. Some hydroxyquinones yield substances in which HF addition to an unsaturated bond of the initial product has also occurred. Thus, 1,3,3,4,4,6,6-heptafluorocyclohexene is obtained from 2,5-dihydroxyquinone.



Quinone reacts with SF_4 and HF at 200 °C to give a 30 % yield of 1,2,4-trifluorobenzene. This reaction may proceed by 1,4-fluorination of the α,β-unsaturated carbonyl groups followed by loss of a molecule of hydrogen fluoride [29].

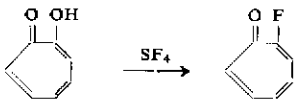


g) Hydroxylic Compounds

Compounds containing hydroxy
with SF_4, a fluorine atom being i
the hydroxyl group. As expec
correlation between the acidity
and the yield of product. Carbo
which possess very acidic hydı
converted in high yields to the ac
Polyfluorinated alcohols of th
have the requisite acidity and

[34] *J. Tadanier* and *W. Cole*, J. org

the polyfluoroalkanes $H(CF_2)_nCH_2F$ [35]. Moderate yields of fluorinated products are given by less acidic compounds such as tropolone, which is converted to α-fluorotropone.



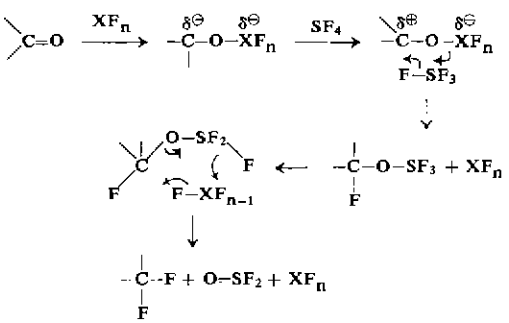
Compounds that are even less acidic, such as methyl, ethyl, and isopropyl alcohols, give the corresponding alkyl fluorides, but a major by-product is the alkyl ether.

Treatment of polymeric materials containing hydroxylic groups with SF_4 has been reported to improve their water-repellency substantially [36].

h) Catalysis and Mechanism

The greater ease of reaction of a carboxylic acid with SF_4, as compared to its anhydride, to give a trifluoromethyl compound led to the discovery of catalysis of the reaction by hydrogen fluoride. That hydrogen fluoride is actually a catalyst was proved when the yield of diphenyldifluoromethane from benzophenone and SF_4 was increased from 10 to 97 % by addition of less than a stoichiometric amount of HF. Other fluorides such as BF_3, AsF_3, PF_5, and TiF_4 are even more potent catalysts.

A possible route by which an oxygen atom is replaced by two fluorine atoms is indicated in the scheme:



The initial step is thought to be coordination of the fluoride XF_n with the carbonyl compound to bring about polarization of the carbonyl group. The complex may then react with SF_4 in the manner depicted. An alcohol probably reacts with SF_4 by elimination of HF to give an intermediate, $R-O-SF_3$, which may react further with XF_n in a manner like that shown for $>CF-O-SF_3$. Although the role of XF_n may be assumed by SF_4, reactions proceed under milder conditions when XF_n is one of the catalysts, HF, BF_3, AsF_3, TiF_4, or PF_5. The ability of a substance to act as a catalyst can be correlated with its strength as a Lewis acid, *i.e.* the greater the Lewis acid strength of the inorganic fluoride with respect to a carbonyl group, the more pronounced the catalytic activity.

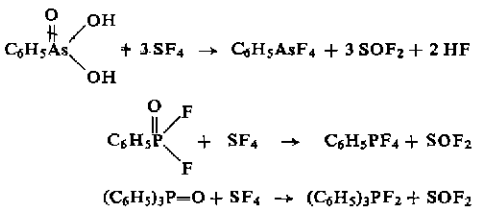
Additional evidence that the reaction may be initiated by coordination of a Lewis acid with the carbonyl group is provided by the behavior of compounds having two strongly electron-attracting groups attached to the carbonyl group. In such compounds, the Lewis base character of the carbonyl group is so greatly reduced that coordination with the Lewis acid is significantly decreased. Reactions of such compounds should therefore require more vigorous conditions than compounds without electron-attracting groups, and such is found to be the case. Compounds having fluoroalkyl groups or fluorine atoms attached to the carbonyl group are very sluggish in reactions with SF_4. A temperature of 250 °C and use of BF_3 as a catalyst was required to convert 2,2,3,3-tetrafluoropropionyl fluoride to 1(*H*)-perfluoropropane. Carbonyl fluoride similarly requires vigorous conditions for transformation into carbon tetrafluoride. The reaction conditions required are far more vigorous than those necessary for acyl fluorides and ketones with electron-releasing groups attached to the carbonyl group [29].

[35] *W. R. Hasek* and *A. C. Haven*, U.S. Patent 2980740 (April 18, 1961).

[36] *A. K. Schneider* and *J. C. Thomas*, U.S. Patent 2983626 (May 9, 1961).

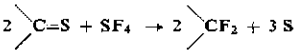
Fluorination of Organophosphorus and Organoarsenic Compounds Containing Oxo Groups

Sulfur tetrafluoride is a useful reagent for the replacement by two fluorine atoms of oxygen doubly bonded to phosphorus or arsenic [37]. The reaction is formally similar to the fluorination of carbonyl compounds. Any hydroxyl groups bonded to the metalloid can also be replaced by fluorine and, as with compounds containing carboxylic acid groups, this replacement takes place at a somewhat lower temperature than that required for replacement of a doubly bonded oxygen atom. Examples of these replacement reactions are illustrated by the equations:



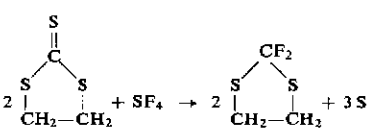
Fluorination of Organic Thiocarbonyl Compounds

The thiocarbonyl group in organic compounds is fluorinated by SF_4 in a manner similar to the fluorination of the carbonyl group. This reaction differs from that of SF_4 with carbonyl compounds, however, in that a formal oxidation-reduction of the sulfur atoms in the thiocarbonyl compound and the SF_4 occurs, resulting in the formation of free sulfur and the complete utilization of the fluorine atoms in SF_4 [38].



The course of the reaction parallels that of SF_4 with inorganic sulfides, which is discussed in a later section and which leads to the corresponding inorganic fluorides and elemental sulfur.

While this reaction has not received the attention given to that with carbonyl compounds, it is a very useful synthetic technique. Thus, ethylene trithiocarbonate reacts smoothly with SF_4 at 110 °C in the absence of a catalyst to give 2,2-difluoro-1,3-dithiolane in high yield.



[37] *W. C. Smith*, J. Amer. chem. Soc. *82*, 6176 (1960).

[38] *R. J. Harder* and *W. C. Smith*, J. Amer. chem. Soc. *83*, 3422 (1961).

Similarly, thiouram disulfides have been fluorinated to give a novel series of new compounds, the dialkyltrifluoromethylamines.

Fluorination of Compounds Containing Carbon-Nitrogen Multiple Bonds

The reaction of SF_4 with organic and inorganic compounds having carbon-nitrogen multiple bonds leads to organoiminosulfur difluorides. These compounds contain tetravalent sulfur and have the general formula $RN{=}SF_2$, as shown by chemical and physical studies[39].

Routes based on SF_4 leading to three types of organoiminosulfur difluorides are available. Compounds of the type $RN{=}SF_2$ are obtained by the reaction of organic isocyanates with SF_4 (equation 1). Products of the type $RCF_2N{=}SF_2$ are prepared from nitriles and SF_4 (equation 2). The compound $CF_3N{=}SF_2$ is the product of the reaction between SF_4 and inorganic substances containing one carbon-nitrogen multiple bond. However, the reactions of SF_4 with compounds having the requisite carbon-nitrogen unsaturation are not limited to these broad classes. Organoiminosulfur difluorides have also been obtained by the reaction of SF_4 with such compounds as benzalaniline and cyanuric acid. Cyanogen reacts with SF_4 at 350 °C to give both the mono- and bis (iminosulfur difluorides) (equation 3) [39].

(1) $RN{=}C{=}O + SF_4 \rightarrow RN{=}SF_2 + COF_2$

(2) $RC{\equiv}N + SF_4 \rightarrow RCF_2N{=}SF_2$

(3) $N{\equiv}C{-}C{\equiv}N + SF_4 \rightarrow N{\equiv}C{-}CF_2N{=}SF_2 + F_2S{=}N{-}CF_2CF_2N{=}SF_2$

The reaction of isocyanates with SF_4 gives an iminosulfur difluoride derivative, and carbonyl fluoride is formed as a byeproduct. A speculative mechanism has been suggested, in which the first step involves addition of the elements of SF_4 across the carbon-nitrogen bond, followed by an intramolecular rearrangement and elimination of carbonyl fluoride [39].

$$R{-}N{=}C{=}O + SF_4 \rightarrow \left[R{-}N(=O){-}CF(F){-}SF_2{-}F \right] \rightarrow RN{=}SF_2 + COF$$

The reaction of nitriles with SF_4 has been postulated to proceed by a similar mechanism, *i.e.*:

$$R{-}C{\equiv}N + SF_4 \rightarrow \left[R{-}C(F){=}N{-}SF_2{-}F \right] \rightarrow RCF_2N{=}SF_2$$

Fluorination of Organic Chlorides and Bromides

Sulfur tetrafluoride undergoes halogen exchange with chloro- and bromo-methanes, chloroalkenes, halobenzenes, cyanuric chloride and chloropyrimidines [40]. Normally, only partial substitution of fluorine for chlorine or bromine takes place. At the reaction temperatures investigated, chloroalkenes and hexachlorobenzene underwent oxidative fluorination to give chlorofluoroalkanes and chlorofluorocyclohexenes, respectively. Studies of the fluorination of carbon tetrachloride and tetrabromide indicate that replacement of bromine by fluorine is easier than replacement of chlorine. The use of SF_4 in such halogen exchange reactions is somewhat limited, as mixtures of partially fluorinated products sometimes result. However, certain classes of compounds containing chlorine can be fluorinated readily in high yield. A synthesis of particular interest is the preparation of fluoropyrimidines from their corresponding chloro derivatives.

Fluorination of Inorganic Oxides, Sulfides, and Carbonyls

Sulfur tetrafluoride is a versatile reagent for preparing a wide range of inorganic fluorides by replacement of oxygen or sulfur in inorganic compounds [41]. Examples of binary fluorides prepared from oxides and SF_4 include UF_6, WF_6, IF_5, SeF_4, and GeF_4.

$$I_2O_5 + 5\,SF_4 \rightarrow 2\,IF_5 + 5\,SOF_2$$

In these reactions, thionyl fluoride is usually the principal by-product, but with sulfides, elemental sulfur is the other reaction product.

$$SF_4 + SnS_2 \rightarrow SnF_4 + 3\,S$$

The preparation of selenium tetrafluoride and molybdenum and tungsten hexafluorides from the corresponding oxides and SF_4 is the most convenient method known for the synthesis of these compounds; similarly, pure anhydrous SnF_4 is most conveniently prepared from the sulfide. This fluorination technique is also useful for the preparation of certain oxyfluorides. Thus, chromyl fluoride (CrO_2F_2) is readily obtained by passing SF_4 over anhydrous CrO_3 at 5 °C [42].

The synthesis of ternary fluorides based on SF_4 reactions has been examined in a preliminary way and offers an attractive route to a variety of new inorganic fluorides [43,44]. The reactions were carried out by treating mixtures of monovalent metal fluorides and metal oxides, sulfides, or carbonyls with SF_4. Typical reactions are illustrated by the equations below:

$$NaF + Nb_2O_5 \xrightarrow[350\,^\circ C]{SF_4} NaNbF_6$$

$$2\,NaF + WO_3 \xrightarrow[250\,^\circ C]{SF_4} Na_2WF_8$$

$$CsF + W(CO)_6 \xrightarrow[200\,^\circ C]{SF_4} CsWF_6$$

$$TlF + Mo(CO)_6 \xrightarrow[165\,^\circ C]{SF_4} TlMoF_6$$

Normally, no valence change is encountered in the formation of the complex fluoride. However, reactions of tungsten and molybdenum carbonyls invariably gave products in which these metals were oxidized to the pentavalent state. It is apparent that much remains to be learned about this aspect of SF_4 chemistry.

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[39] *W. C. Smith, C. W. Tullock, R. D. Smith,* and *V. A. Engelhardt,* J. Amer. chem. Soc. *82,* 551 (1960).

[40] *C. W. Tullock, R. A. Carboni, R. J. Harder, W. C. Smith,* and *D. D. Coffman,* J. Amer. chem. Soc. *82,* 5107 (1960).

[41] *A. L. Oppegard, W. C. Smith, E. L. Muetterties,* and *V. A. Engelhardt,* J. Amer. chem. Soc. *82,* 3835 (1960).

[42] *H. L. Krauss* and *F. Schwarzbach,* Chem. Ber. *94,* 1205 (1961).

[43] *R. D. W. Kemmitt* and *D. W. A. Sharp,* J. chem. Soc. (London) 2496 (1961).

[44] *W. C. Smith,* U.S. Patent 2904398 (September 15, 1959).

The reaction of SF_4 with uranium(VI) oxide offers a convenient method for the synthesis of uranium hexafluoride in the laboratory [41,45]. Plutonium tetrafluoride can also be prepared readily by fluorination of the corresponding oxide with SF_4 at 500 °C.

Oxidation of Sulfur Tetrafluoride

Oxidation by Selected Inorganic Oxides and Oxyfluorides

Inorganic oxides which are strong oxidizing agents will convert SF_4 into sulfur oxytetrafluoride (SOF_4). The need for a very strong oxidizing agent is clearly shown by the fact that selenium dioxide undergoes an exchange reaction with SF_4 and is incapable of oxidizing it. Such oxidations have been carried out only at elevated temperatures in closed reaction vessels, using metal oxides such as CrO_3 and CeO_2 [46]. As noted earlier, treatment of CrO_3 with SF_4 at atmospheric pressure only leads to formation of the volatile chromyl fluoride.

The above metal oxides are not useful as specific reagents for the oxidation of SF_4 to SOF_4 in that appreciable amounts of thionyl fluoride (SOF_2), sulfuryl fluoride (SO_2F_2), and sulfur hexafluoride are normally formed. The formation of the latter two compounds is presumably due largely to disproportionation of SOF_4 [47] under the vigorous conditions required. Certain oxides of nitrogen and their salts are more effective oxidizing agents, since the formation of these by-products is minimized; but in these systems, a substantial amount of SOF_4 is incorporated in a corrosive solid of unknown structure, from which it can be recovered only with difficulty. The most convenient specific route to SOF_4 is the reaction of SF_4 with oxygen at 200 °C in the presence of NO_2 as catalyst [46]. This route leads to SOF_4 routinely in 75–80% yield and conversion. Evidence has been cited to show that this process involves oxidation of the SF_4 by the NO_2 and that the latter is in fact a true reaction catalyst. Recent publications [48,49] suggest that SOF_4 is a potentially useful chemical reagent.

Sulfur tetrafluoride is oxidized by peroxydisulfuryl difluoride (FSO_2OOSO_2F) at 128 °C to give a single product incorporating both reactants. The compound is reported to be tetrafluoro bis (fluorosulfonato) sulfur-(VI), $SF_4(OSO_2F)_2$, [52] and represents the only known hexacoordinate sulfur fluoride derivative in which sulfur is bonded to two oxygen atoms. The preparation and characterization of additional compounds containing this novel arrangement of atoms about hexavalent sulfur will undoubtedly be the subject of further study.

[45] *C. E. Johnson, J. Fischer,* and *M. J. Steindler,* J. Amer. chem. Soc. *83,* 1620 (1961).

[46] *W. C. Smith* and *V. A. Engelhardt,* J. Amer. chem. Soc. *82,* 3838 (1960).

[47] *W. J. Middleton,* U.S. Patent 2912307 (November 10, 1959).

[48] *F. Seel* and *G. Simon,* Angew. Chem. *72,* 709 (1960).

[49] *R. Cramer* and *D. D. Coffman,* J. org. Chemistry *26,* 4164 (1961).

Oxidation by Selected Metal Fluorides

A limited number of metal fluorides are capable of oxidizing SF_4 to SF_6. The reactions are not of value for the synthesis of the latter compound but in some instances do provide convenient routes to lower-valent metal fluorides formed as reduction products [45, 50, 51]. Known reactions of this type are illustrated below:

$$IrF_4 \xrightarrow[350\,^\circ C]{SF_4} IrF_3$$

$$PuF_6 \xrightarrow[30\,^\circ C]{SF_4} PuF_4$$

$$PdF_3 \xrightarrow[250\,^\circ C]{SF_4} PdF_2$$

Oxidation by Electrolytic Means

A liquid mixture of sulfur tetrafluoride and hydrogen fluoride can be electrolyzed readily to give sulfur hexafluoride in high yield [53].

$$SF_4 + 2\,HF \xrightarrow{e^\ominus} SF_6 + H_2$$

The electrolysis is carried out efficiently at a temperatures below −40 °C with a direct current of 0.5–1.1 amperes at 34–72 volts.

Addition of Sulfur Tetrafluoride to Selected Fluoro-olefins

The general synthesis of organoiminosulfur difluorides by the addition of the elements of SF_4 to compounds containing carbon-nitrogen double bonds was discussed in an earlier section. By contrast, SF_4 apparently adds to olefinic linkages only in very specific instances. The three known reactions of this type are represented by the equations below [54,55]:

$$CH_3OCF{=}CF_2 + SF_4 \xrightarrow{120\,^\circ C} CH_3OCF_2CF_2SF_3$$

$$CH_3CH_2OCF{=}CF_2 + SF_4 \xrightarrow{120\,^\circ C} CH_3CH_2OCF_2CF_2SF_3$$

$$CF_2{=}CF(CF_3) + SF_4 \xrightarrow[CsF]{150\,^\circ C} (CF_3)_2CF{-}SF_3$$

These studies represent significant contributions to the rapidly expanding and recently reviewed [56] area of sulfur fluoride derivative chemistry.

[50] *N. Bartlett* and *M. A. Hepworth,* Chem. and Ind. (London) 1425 (1956).

[51] *P. L. Robinson* and *G. J. Westland,* J. chem. Soc.(London) 4481 (1956).

[52] *J. M. Shreeve* and *G. H. Cady,* J. Amer. chem. Soc. *83,* 4521 (1961).

[53] *E. H. Man,* U.S. Patent 2964476 (September 15, 1959).

[54] *W. R. Hasek,* U.S. Patent 2928870 (March 15, 1960).

[55] *R. M. Rosenberg* and *E. L. Muetterties,* J. inorg. Chem., to be published.

[56] *H. L. Roberts,* Quart. Revs. (chem. Soc. London) *15,* 30 (1961).

Adducts of Sulfur Tetrafluoride with Inorganic Fluorides

Sulfur tetrafluoride interacts with certain inorganic fluorides that are Lewis acids to form solid "adducts" [22,41,51,57–61]. The known adducts in approximate order of decreasing stability are $SbF_5 \cdot SF_4$, $AsF_5 \cdot SF_4$, $IrF_5 \cdot SF_4$, $BF_3 \cdot SF_4$, $PF_5 \cdot SF_4$, $GeF_4 \cdot 2\,SF_4$, and $AsF_3 \cdot SF_4$. The wide range of thermal stability in this class of compounds is seen from the fact that the first member melts at 253 °C while the last dissociates readily at temperatures above about −20 °C.

Early investigators [57] suggested that these substances were simple Lewis acid → Lewis base complexes of the type $SF_4 \rightarrow BF_3$. This postulate was criticized by *Cotton* and *George* [60], who pointed out that phosphorus trifluoride does not react with boron trifluoride and that SF_4 in turn should be a poorer electron donor than PF_3, since the extra fluorine atom would decrease the basicity of the unshared electron pair. This fact and the well known ability of BF_3, ASF_5, SBF_5, etc. to accept fluoride ion (*e.g.* to give BF_4^-), prompted them to suggest a formulation of the type $SF_3^+BF_4^-$. *Seel* and *Detmer* [59] have provided more positive evidence for this structure by obtaining the infrared spectrum of a thin film of the SF_4–BF_3 adduct on a rock-salt plate. The spectrum shows a strong band at 1050 cm^{-1} typical of BF_4^-. Furthermore, a doublet was observed at 908 and 940 cm^{-1}, which was assigned to the SF_3^+ ion by comparison with the isoelectronic phosphorus trifluoride molecule. Structural determination of the SbF_5 adduct is as yet incomplete, but the symmetry is suggestive of the ionic formulation $SF_3^+SbF_6^-$ [61].

While the explanation given above supports the concept that the solid adducts are ionic in nature, it is equally apparent that essentially nothing is known about the character of these materials in solution. Unfortunately, there is no simple method for studying such systems; the solid adducts are extremely reactive toward many potential solvents and are insoluble in most materials which are chemically inert toward them. The only system which has so far received any attention involves a solution of the $SF_4 \cdot AsF_3$ adduct in liquid arsenic trifluoride. Nuclear magnetic resonance studies did not indicate that AsF_4^- ion persisted in solution, nor was there any new band in the S–F region which could be ascribed to the SF_3^+ ion. On the basis of this meagre evidence, it would appear that in this particular solvent system, the SF_4–AsF_3 adduct is present as a weakly associated material in which the constituent molecules of the adduct are bonded either by Lewis acid → Lewis base interaction or through fluorine atom bridging.

All of the adducts prepared so far are completely dissociated in the gas phase. A study of the vapor pressure *v.s.* temperature relationship for the SF_4–BF_3 system [58] led to the conclusion that the heat of dissociation of $SF_3^+BF_4^-$ is 24.83 kcal/mole.

Very little is known about the chemical properties of these SF_4 adducts. Their use in the purification of SF_4 has been reported. For example, SF_4 can be regenerated from its solid SF_4–BF_3 adduct by treatment with reagents such as SeF_4 and NaF, which in turn have a greater affinity for BF_3 than SF_4 does [57,61]. Thionyl fluoride does not form such adducts at ordinary temperatures, and this technique provides a particularly effective way of separating it from SF_4. These SF_4 adducts are also of possible significance in the catalytic fluorination of oxygenated materials by SF_4 in the presence of selected inorganic fluorides. The ability of metal fluorides to function as catalysts for SF_4 fluorination reactions seems to be directly related to the thermal stability of their respective adducts with SF_4 [29].

Electron Acceptor Properties of Sulfur Tetrafluoride

Sulfur tetrafluoride is a very weak acceptor molecule. Although it has a heat of reaction or solution with many bases such as ethers and amides, only tertiary amines proved sufficiently basic to perturb the characteristic F^{19} resonance spectrum of SF_4 [62]. The F^{19} spectra of SF_4 solutions in amines consist of single resonances and are essentially temperature insensitive. Pressure *v.s.* composition studies indicate that amines containing one tertiary nitrogen atom combine with SF_4 in a 1:1 molar ratio [63], the products presumably having pseudooctahedral structures. The instability of these complexes may be seen from the fact that they all have appreciable dissociation pressures, even at 0 °C. Other investigators have reported that sulfur tetrafluoride is too poor an acceptor to form complexes with platinum dichloride, cesium fluoride, or nitryl fluoride [58].

Miscellaneous

Carbon monoxide only reacts with SF_4 in a metal reactor under pressure in the presence of a suitable catalyst and at elevated temperatures to give carbon tetrafluoride, sulfur, and carbonyl sulfide [29]. More recently, it has been shown that slow reaction occurs at ordinary temperatures on irradiation with ultraviolet light to give considerable amounts of carbonyl fluoride and sulfur hexafluoride, together with traces of carbonyl sulfide [64]. This technique may lead to a variety of as yet unknown fluorination reactions of SF_4.

The reaction of two equivalents of aniline with SF_4 yields bis(phenylimino)sulfur, $C_6H_5N{=}S{=}NC_6H_5$ [65]. The reaction presumably goes in the two steps shown below; the second step has been demonstrated separately.

$$C_6H_5NH_2 + SF_4 + 2(CH_3)_3N \rightarrow C_6H_5N{=}SF_2 + 2(CH_3)_3N{\cdot}HF$$

$$C_6H_5N{=}SF_2 + C_6H_5NH_2 + 2(CH_3)_3N \rightarrow C_6H_5N{=}S{=}NC_6H_5 + 2(CH_3)_3N{\cdot}HF$$

This reaction should be capable of extension to a variety of other primary amines.

Received, May 25th, 1962 [A 218/38 IE]

[57] *N. Bartlett* and *P. L. Robinson*, Chem. and Ind. (London); 1351 (1956); Proc. chem. Soc. (London) 230 (1957).

[58] *N. Bartlett* and *P. L. Robinson*, J. chem. Soc. (London) 3417 (1961).

[59] *F. Seel* and *O. Detmer*, Z. anorg. allg. Chem. *301*, 113 (1959).

[60] *W. C. Smith* and *E. L. Muetterties*, U.S. Patent 3000694 (September 19, 1961).

[61] *F. A. Cotton* and *J. W. George*, J. inorg. nucl. Chem. *7*, 397 (1958).

[62] *E. L. Muetterties*, J. Amer. chem. Soc. *82*, 1082 (1960).

[63] *E. L. Muetterties*, *W. D. Phillips*, and *W. C. Smith*, U.S. Patent 2897055 (July 28, 1959).

[64] *A. G. Massey* and *K. J. Packer*, J. chem. Soc. (London) 5554 (1961).

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The Synthesis of Nucleosides

BY DR. T. L. V. ULBRICHT [1]

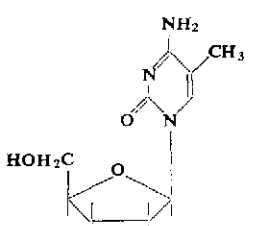
TWYFORD LABORATORIES LTD., LONDON (ENGLAND)

The most important developments in nucleoside synthesis in the last few years have been the application of the mercury salt procedure to both purines and pyrimidines, and the isolation of relatively stable, crystalline 2-deoxyribofuranosyl halides; as a result, almost any nucleoside may now be synthesized. Earlier syntheses, based on older methods or on the conversion of one nucleoside to another, played an essential part in establishing the structure of the nucleosides (and hence of the nucleic acids).

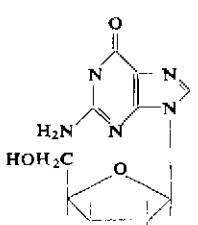
Introduction

It has been shown that in the nucleic acids, the sugar, D-ribose or 2-deoxy-D-ribose, is attached to the pyrimidines at *N-3* (*e. g.* 5-methylcytidine, I) and to the purines at *N-9* (*e. g.* 2'-deoxy-guanosine, II) by a β-glycosidic linkage [2].

The proof of the structure of these compounds and their synthesis constituted major steps in the elucidation of the structure of the nucleic acids themselves. New methods of synthesis have been developed in the last few years, making possible the preparation of the natural 2'-deoxyribonucleosides and of a variety of analogues and labelled compounds for biological studies. The emphasis in this review is placed on those methods which have either proved to be most useful in practice, or have thrown light on the chemistry of the nucleosides.



(I)

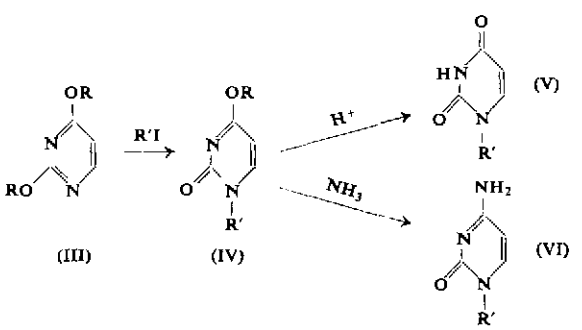


(II)

1. Synthesis of Ribonucleosides

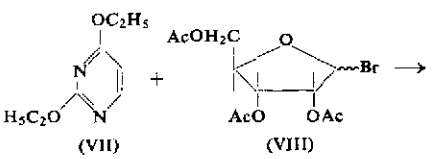
1.1. Hilbert-Johnson Method

The first synthesis of a natural nucleoside was that of cytidine by *Todd* and co-workers in 1947 [3]. They used the method of *Hilbert* and *Johnson*, who had found [4] that a dialkoxypyrimidine (III) reacts at room temperature with one mole of an alkyl iodide, R'I, to give an *N(3)*-alkylpyrimidine (IV), *i. e.* the new alkyl group is bound to the same nitrogen atom as that to which the sugar is attached in nucleosides. On treatment with acid, the pyrimidine (IV) is converted to the uracil (V), and with alcoholic ammonia the corresponding cytosine (VI) is formed.

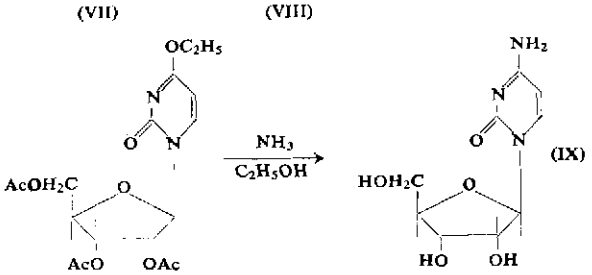


(III) (IV) (V) (VI)

Using the halogenosugar acetobromoglucose in place of an alkyl iodide, a completely analogous reaction takes place, and the β-D-glucopyranosides of uracil [5] and cytosine [6] were obtained. In the synthesis of cytidine [3], the reactants were the diethoxypyrimidine (VII) and triacetylribofuranosyl bromide (VIII). Deacetylation of the product with alcoholic ammonia gave cytidine (IX).



(VII) (VIII)



(IX)

(~~~ indicates that the configuration is not known; probably both forms are present)

[1] Based on a lecture at the Max-Planck-Institut für Virusforschung, Tübingen (Germany), September 1961.

[2] For a comprehensive review, see *D. M. Brown* and *T. L. V. Ulbricht* in *M. Florkin* and *E. Stolz:* Comprehensive Biochemistry, Elsevier, Amsterdam, Vol. 2, in press.

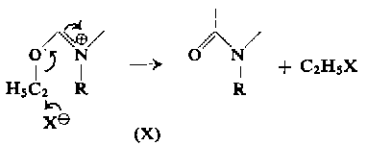
[3] *G. A. Howard, B. Lythgoe*, and *A. R. Todd*, J. chem. Soc. (London) 1052 (1947).

[4] *G. E. Hilbert* and *T. B. Johnson*, J. Amer. chem. Soc. *52*, 2001 (1930).

[5] *G. E. Hilbert* and *T. B. Johnson*, J. Amer. chem. Soc. *52*, 4489 (1930).

[6] *G. E. Hilbert* and *E. F. Jansen*, J. Amer. chem. Soc. *58*, 60 (1936).

The mechanism of the reaction of dialkoxypyrimidines with halogeno compounds and with acids (dealkylation) is fundamentally the same [7]. The first step is the addition of a proton or alkyl or glycosyl group to the nitrogen, followed by attack by the halide ion (X).

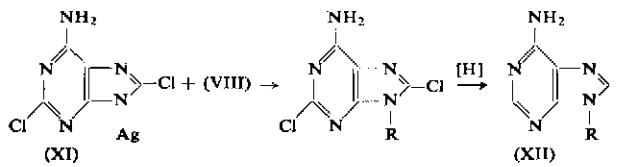


(X)

It is not necessary to use strong acids to hydrolyse alkoxypyrimidines; the reaction proceeds readily with sodium iodide in acetic acid [7]. It will be remembered that the reaction of *O*,2'-cyclouridine (also an alkoxypyrimidine) with iodide ion requires the presence of acid [8] (cf. Section 3.2.).

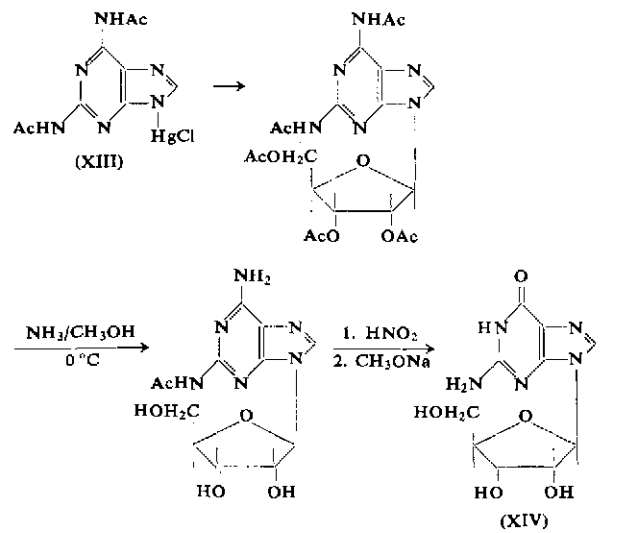
1.2. Fischer-Helferich Synthesis

It was shown by Fischer and Helferich [9] that purine nucleosides may be synthesized by the reaction of the silver salt of 2,8-dichloroadenine (XI) with a halogenosugar. *Todd* et al. [10] used the ribofuranose (VIII); deacetylation followed by catalytic dehalogenation gave adenosine (XII).



(R = β-D-ribofuranosyl).

The reason for using dichloroadenine is that adenine itself is sufficiently basic to dehydrohalogenate the sugar derivative. *Davoll* [11] found that it was simpler to acylate the amino group and use, for example, *N*-benzoyladenine. He showed further that better yields were obtained using purine chloromercury rather than silver salts. The reaction with these modifications, which still constitutes the best general method for synthesizing purine nucleosides, is illustrated by the synthesis of guanosine (XIV) from the chloromercury salt of diacetylamino purine (XIII) [10].



(XIV)

1.3. Mercury Procedure with Pyrimidines

Fischer's attempts to synthesize pyrimidine nucleosides using pyrimidine silver salts [9] led to the formation of very labile products which were, undoubtedly, *O*-glycosides. The successful synthesis of purine nucleosides using mercury salts prompted the investigation of such derivatives of pyrimidines, which in fact proved to be very useful. However, in each case it is necessary to investigate which particular mercury derivative can be used: for the synthesis of thymine riboside it is dithyminylmercury [12]; for cytidine, *N(6)*-acetylcytosinemercury [13]. Uracil does not give a suitable derivative and uridine has not been synthesized by this route. The mechanism of this reaction, which has also been used to synthesize deoxyribonucleosides, is discussed in Section 3.3. (p. 479).

2. Stereochemistry of Nucleoside Synthesis [14]

That syntheses of nucleosides using acetobromoglucose, known to have the α-configuration, lead to compounds having the β-configuration is readily explicable on the assumption that the reaction proceeds with a single, normal inversion at *C-1* of the sugar. However, the synthesis of the natural β-nucleosides just described all used syrupy ribofuranosyl halides which almost certainly are a mixture of α- and β-forms, and in the synthesis of puromycin [15] a crystalline halogenosugar known to have the β-configuration also gave only the β-nucleoside. To account for these results, *Baker* [16] has proposed that condensation of a heavy-metal salt of a purine with an acylated glycosyl halide will form a nucleoside with a 1,2-*trans*-configuration in the sugar (*i. e.* a β-riboside), regardless of the original configuration at *C-1*–*C-2*. If the halogenosugar has the 1,2-*cis*-configuration, the purine will enter by a single S_N2 reaction with inversion at *C-1*, giving a nucleoside with

[7] *T. L. V. Ulbricht*, J. chem. Soc. (London) 3345 (1961).

[8] *D. M. Brown, D. B. Parihar*, and (Sir) *A. Todd*, J. chem. Soc. (London) 4242 (1958).

[9] *E. Fischer* and *B. Helferich*, Ber. dtsch. chem. Ges. *47*, 210 (1914).

[10] *J. Davoll, B. Lythgoe*, and *A. R. Todd*, J. chem. Soc. (London) 967 (1948).

[11] *J. Davoll* and *B. A. Lowy*, J. Amer. chem. Soc. *73*, 1650 (1951).

[12] *J. J. Fox, N. Yung, J. Davoll*, and *G. B. Brown*, J. Amer. chem. Soc. *78*, 2117 (1956).

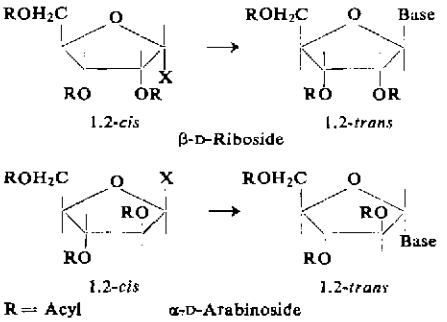
[13] *J. J. Fox, N. Yung, I. Wempen*, and *I. L. Doerr*, J. Amer. chem. Soc. *79*, 5060 (1957).

[14] For other examples and a more complete discussion see ref. [2].

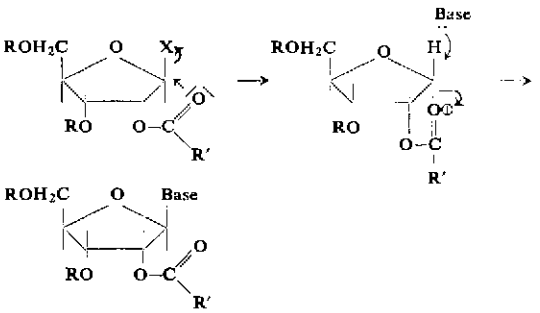
[15] *B. R. Baker, J. P. Joseph*, and *R. E. Schaub*, J. Amer. chem. Soc. *77*, 5905, 5911 (1955).

[16] *B. R. Baker* in *G. E. W. Wolstenholme* and *C. M. O'Connor*: The Ciba Foundation Symposium on the Chemistry and Biology of the Purines. J. and A. Churchill, London 1957, p. 120.

the 1,2-*trans*-configuration, and which may be α or β depending on the sugar:



Halogenosugars with a 1,2-*trans*-configuration undergo two S_N2 reactions, the first of which is intramolecular, with participation of the 2-acyloxy group:



Thus the formation of β-ribosides from β-ribose derivatives is seen to depend on the neighbouring group participation of the 2-acyloxy group; if such a group is missing or sterically hindered a mixture of products is to be expected. This was found, for example, in the adenosine synthesis using 5-*O*-benzoyl-D-ribofuranosyl bromide-2,3-cyclic carbonate, which gave both natural adenosine and its α-anomer [17], and in the synthesis of 2'-deoxyribosides from 2-deoxyribose (see below).

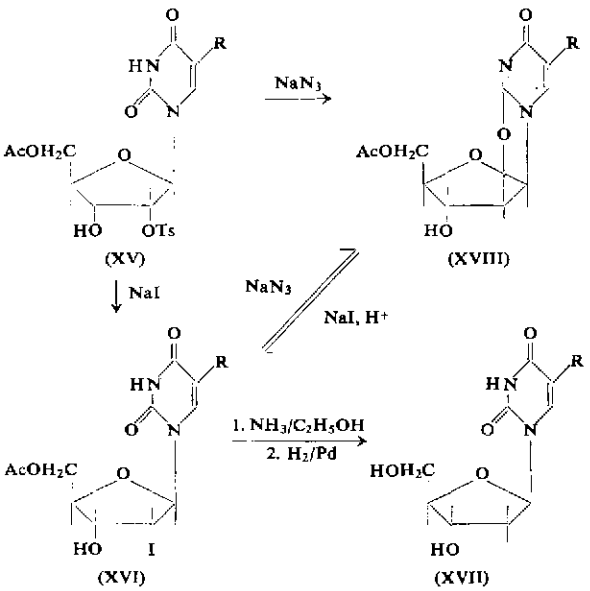
3. Synthesis of Deoxyribonucleosides

3.1. Special Problems

One special problem is that any synthesis proceeding from a derivative of 2-deoxyribose would not be stereospecific and would yield a mixture of α- and β-derivatives. In addition, it was anticipated that a deoxyribofuranosyl halide would be unstable and be readily dehydrohalogenated, as shown by early attempts along these lines [2]. Since 2-deoxyribose itself was such a difficultly assessible compound, work in some laboratories was concentrated on trying to synthesize deoxyribonucleosides from the corresponding ribonucleosides.

3.2. Synthesis by Nucleoside Conversion

In 1957–1958 2'-deoxyuridine, thymidine and 3'-deoxyadenosine were synthesized from ribonucleoside sulphonyl esters. Sugar secondary sulphonyloxy groups are usually regarded as unreactive; *Oldham* and *Rutherford*'s Rule [18] states that such groups will not react with sodium iodide in acetone at 100 °C – the reaction is used to distinguish them from the more reactive primary sulphonyloxy groups. However, in the first experiment in which the 2'-*O*-tosyluridine (XV, R=H) was allowed to react with sodium iodide in acetonylacetone at 100 °C, a high yield of a crystalline deoxyiodo derivative (XVI, R=H) was obtained, which after deacetylation and catalytic reduction gave 2'-deoxyuridine (XVII, R=H) [19]. In a similar manner, the corresponding derivative of thymine (XV, R=CH_3) was converted to thymidine (XVII, R=CH_3) [20].



Normally one would expect the iodo derivative to have been formed by a single S_N2 reaction, and consequently to have the arabo configuration, but elucidation of the reaction mechanism [8] showed that the iodide was a ribose compound (XVI). Treatment of the tosylate with sodium azide in acetonitrile gave the *O*,2'-cyclouridine (XVIII), which with sodium iodide in acetic acid (cf. Section 1.1) yielded the same iodide (XVI), obtained directly from (XV). Reaction of the iodide with sodium azide reformed the cyclonucleoside. The reaction of the tosylate (XV) with iodide ion must, therefore, have involved the cyclonucleoside as an intermediate, thus yielding a product (XVI) with the ribo configuration. *Varadarajan* suggested the possibility of synthesizing thymidine by conversion of 5-methyl-2-thiouridine [21] to a thiocyclonucleoside followed by hydrolysis and desulphurisation with Raney Nickel; this method gives small yields [22].

Although the reactivity of 2'-*O*-tosyluridine derivatives is obviously due to cyclonucleoside formation, similar

[17] *R. S. Wright, G. M. Tener.* and *H. G. Khorana*, J. Amer. chem. Soc. *80*, 2004 (1958).

[18] *J. W. H. Oldham* and *J. K. Rutherford*, J. Amer. chem. Soc. *54*, 366 (1932).

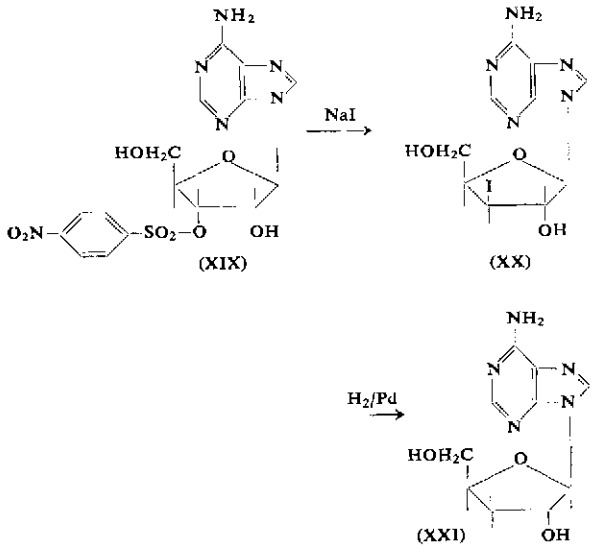
[19] *D. M. Brown, D. B. Parihar, C. B. Reese*, and (Sir) *A. Todd*, Proc. chem. Soc. (London) 321 (1957).

[20] *D. M. Brown, D. B. Parihar, C. B. Reese*, and (Sir) *A. Todd*, J. chem. Soc. (London) 3035 (1958).

[21] *D. M. Brown, D. B. Parihar*, (Sir) *A. Todd*, and *S. Varadarajan*, J. chem. Soc. (London) 3028 (1958).

[22] *G. Shaw* and *R. N. Warrener*, J. chem. Soc. (London) 50 (1959).

reactions of secondary sulphonyloxy groups in other nucleosides might proceed if esters more susceptible to nucleophilic displacement were used. Reaction of *p*-nitrobenzenesulphonyl chloride with 5′-*O*-acetyladenosine gave, after deactylation, two isomeric mono-*p*-nitrobenzenesulphonyladenosines. One of these (XIX) reacted with sodium iodide to yield a crystalline deoxyiodo derivative which was reduced in quantitative yield to a new deoxynucleoside, shown to be 3′-deoxyadenosine (XXI) [23], and the reaction sequence must



be as shown. The 2′-isomer of (XIX) does not react with iodide or bromide ion below its decomposition temperature; this may be due to the steric inaccessibility of the 2′-carbon atom in such compounds.

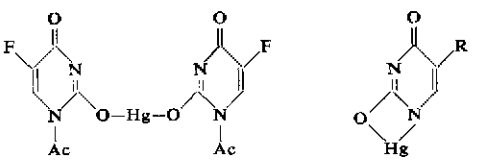
The first synthesis of 2′-deoxyadenosine [24] involved an ingenious series of rearrangements with an adenine xyloside, but the yield was very low and direct synthesis soon followed (see Section 3.3). An alternative synthesis of 3′-deoxyadenosine has been described [25].

3.3. Direct Synthesis, and the Mechanism of the Mercury Procedure

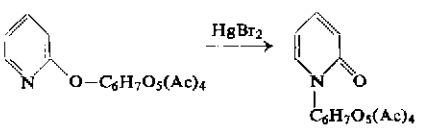
The development of a practicable method for preparing 2-deoxy-D-ribose [26] led to syntheses using deoxyribofuranosyl halides. When the adenosine synthesis (see Section 1.2) was carried out with crude 3,5-di-*p*-nitrobenzoyl-2-deoxyribofuranosyl chloride (later obtained in crystalline form), 2′-deoxyadenosine (10 %) and its α-anomer (19 %) were obtained [27]. In a synthesis using the old Fischer-Helferich procedure with crude 3,5-di-*O*-acetyl-2-deoxyribofuranosyl chloride, only the natural β-isomer of 2′-deoxyadenosine was isolated [28]. By appropriate manipulation of the purine substituents, the latter method was also used to synthesize 2′-deoxyguanosine and 2′-deoxyinosine.

The discovery that it is possible to obtain crystalline 3,5-di-*O*-*p*-chloro- (or *p*-methyl-) benzoyl-2-deoxyribofuranosyl chlorides has led to a practicable synthesis of pyrimidine deoxyribosides using the mercury procedure [29–31], a mixture of α- and β-thymidine, 2′-deoxycytidine and other compounds being obtained. The mechanism of these reactions using mercury derivatives of pyrimidines is of considerable interest, since it is curious that silver and mercury salts should give different products (cf. p. 477). The following results appear to the reviewer to be of particular importance:

(i) *Hoffer* [30] found that the dithyminylmercury, successfully used in the synthesis of thymine riboside, gave an *O*-glycoside with a deoxyribosyl halide. For the synthesis of thymidine, it is necessary to use a monothyminemercury, $C_5H_4N_2O_2Hg$, in which two hydrogens of thymine have been replaced by mercury. This compound is prepared by the reaction of *N(3)*-acetylthymine with mercuric acetate. In the preparation of the corresponding compound from 5-fluorouracil, an intermediate was isolated for which structure (XXII) was proposed. Further reaction, in methanol, gives methyl acetate and the product, for which structure (XXIII) was suggested.



(ii) *Wagner* and *Pischel* studied the reaction of chloromercury-α-pyridone and acetobromoglucose and obtained an *O*-glucoside as the initial product. If the reaction was allowed to proceed for several hours, or if the *O*-glucoside (XXIV) was isolated and then heated with mercuric bromide in toluene, the *N*-glucoside (XXV) was formed [32].



(iii) Rearrangements of *O*- to *N*-alkylpyrimidines are known, and may be readily carried out by heating an alkoxypyrimidine with sodium iodide in acetonylacetone at 100 °C [7].

[23] (Sir) *A. Todd* and *T. L. V. Ulbricht*, J. chem. Soc. (London) 3275 (1960).

[24] *C. D. Anderson, L. Goodman*, and *B. R. Baker*, J. Amer. chem. Soc. *81*, 3967 (1959).

[25] *W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman* and *B. R. Baker*, J. Amer. chem. Soc. *83*, 1906 (1961).

[26] *H. W. Diehl* and *H. G. Fletcher*, Jr., Arch. Biochem. Biophysics *78*, 386 (1958).

[27] *R. K. Ness, D. L. MacDonald*, and *H. G. Fletcher*, Jr., J. Amer. chem. Soc. *82*, 3434 (1960).

[28] *H. Venner*, Chem. Ber. *93*, 140 (1960).

[29] *M. Hoffer, R. Duschinsky, J. J. Fox*, and *N. Yung*, J. Amer. chem. Soc. *81*, 4112 (1959).

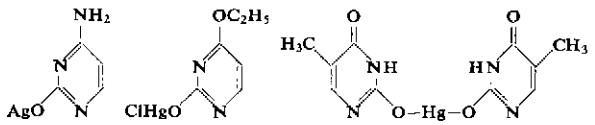
[30] *M. Hoffer*, Chem. Ber. *93*, 2777 (1960).

[31] *J. J. Fox, N. C. Yung, I. Wempen*, and *M. Hoffer*, J. Amer. chem. Soc. *83*, 4066 (1961).

[32] *G. Wagner* and *H. Pischel*, Naturwissenschaften *48*, 454 (1961).

On the basis of the foregoing, it is here proposed that:

(a) chloromercurypyrimidines and dipyrimidylmercury compounds are, like pyrimidine silver salts, oxygen derivatives (*e. g.* XXVI–XXVIII);



(XXVI) (XXVII) (XXVIII)

(b) these derivatives react with glycosyl halides to give, initially, *O*-glycosides, but under the conditions of the reaction, many of these compounds are rearranged, more or less rapidly, to the *N*-glycosides;

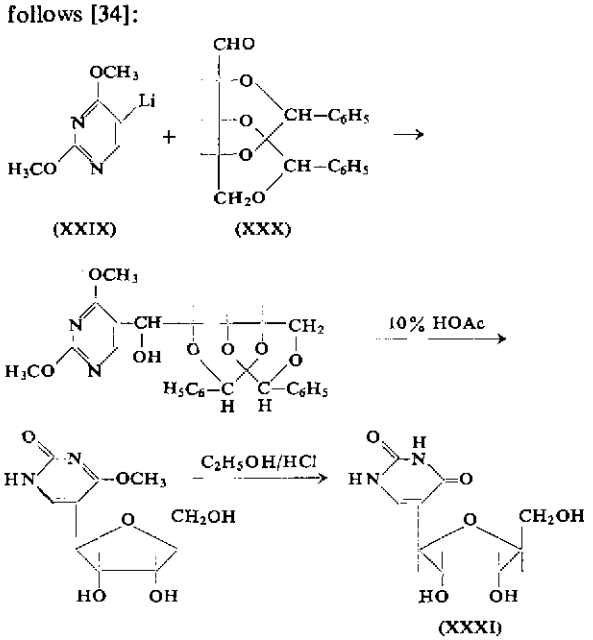
(c) monopyrimidinemercury compounds probably have a structure in which mercury is attached to nitrogen and may give *N*-glycosides directly;

(d) as already suggested [7], it should be possible to rearrange pyrimidine *O*- to *N*-glycosides. This is under investigation [*].

4. Special Synthetic Methods

4.1. Pseudouridine

It has been suggested that pyrimidine *C*-glycosides might be prepared by the reaction of a pyrimidine-lithium compound and a suitable glycosyl halide [33]. As experiments along these lines using the lithium derivative (XXIX) and triacetylribofuranosyl halides were not promising, a protected aldehydoribose (XXX) was used instead, and pseudouridine (XXXI) synthesized as follows [34]:



(XXIX) (XXX)

(XXXI)

[33] *T. L. V. Ulbricht*, Tetrahedron *6*, 225 (1959).

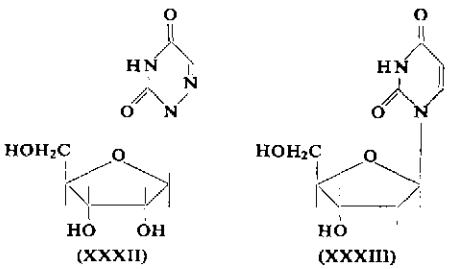
[34] *D. M. Brown, P. Slatcher*, (Lord) *Todd*, and *T. L. V. Ulbricht*, unpublished.

[*] *Note added in proof*: Recent work by the author has shown that the condensation of pyrimidine silver salts with halogenosugars gives *O*-glycosides, which rearrange to *N*-glycosides with mercuric bromide.

Other workers, knowing of the early Cambridge experiments, tried a tribenzoyl ribofuranosyl halide and obtained a 2 % yield of pseudouridine by the original method [35].

4.2. Azauridine

Azauracil itself is readily available [36] but conversion to the riboside (XXXII) using the mercury procedure gave only a 14 % yield of (XXXII), the major product being an isomer presumed to be the 1-riboside [37]. This is apparently due to the fact that in azauracil it is the hydrogen at *N-1* which is most acidic. An unambiguous synthesis of the 3-riboside has been devised, using a derivative blocked at *N-1* [38]; the yield is 25 %, but six steps are required in place of two.



(XXXII) (XXXIII)

4.3. Spongonucleosides

Two of the unusual nucleosides isolated from *Cryptotethia* sponges are 3-β-D-arabinosides of uracil and thymine [39]. From our discussion of the stereochemistry of nucleoside synthesis it is clear that such compounds cannot be synthesized from arabinosyl halides. Spongouridine (XXXIII) was synthesized by the hydrolysis of *O*,2′-cyclouridine (XVIII, R=H, no acetyl at 5′) [40]; spongothymidine has been obtained in an analogous manner [41].

4.4. Labelled Compounds

Labelled nucleosides are almost always synthesized from previously labelled bases and/or sugars by standard methods. The conversion of 5-bromodeoxyuridine to thymidine using a lithium intermediate and methyl iodide permits specific labelling of the methyl group in thymidine [33].

4.5. Analogues and other Methods of Synthesis

It is beyond the scope of this review to describe the numerous syntheses of analogues, with variations in the

[35] *R. Shapiro* and *R. W. Chambers*, J. Amer. chem. Soc. *83*, 3921 (1961).

[36] *P. K. Chang* and *T. L. V. Ulbricht*, J. Amer. chem. Soc. *80*, 976 (1958).

[37] *R. E. Handschumacher*, J. biol. Chemistry *235*, 764 (1960).

[38] *M. Prystas, J. Gut*, and *F. Sorm*, Chem. and Ind. 947 (1961).

[39] *W. Bergmann* and *D. F. Burke*, J. org. Chemistry *20*, 201 (1955).

[40] *D. M. Brown*, (Sir) *A. Todd*, and *S. Varadarajan*, J. chem. Soc. (London) 2388 (1956).

[41] *J. J. Fox, N. Yung*, and *A. Bendich*, J. Amer. chem. Soc. *79*, 2775 (1957).

structure of both the base and the sugar compounds, that have been carried out in recent years, particularly by *B. R. Baker* and by *J. J. Fox* and their respective coworkers. These analogues as well as other synthetic methods, such as that of *Shaw*, using glycosylamines, are discussed in other reviews [42, 43].

Schramm [44, 45] has described the use of ethyl polymetaphosphate to effect the condensation of purine bases with unprotected sugars to give nucleosides, *e. g.* 2'-deoxyadenosine (30 %) and adenosine (25–37 %) [46]. Pyrimidine nucleosides are formed less readily; perhaps because the pyrimidine-glycosyl bond is more stable, it is also harder to form [47]. It will be interesting to see how adaptable this method proves, as its simplicity and apparent stereospecificity (only the natural β-furanosides have been reported) have obvious appeal. The fact that only 2'-β-deoxyadenosine is formed from 2-deoxyribose and without any of the α-anomer, seems impossible to explain at present.

Received, May 14th, 1962 [A 35 IE]

[42] *J. J. Fox* and *I. Wempen*, Advances Carbohydrate Chem. *14*, 283 (1959).

[43] *A. M. Michelson*, Annu. Rev. Biochem. *30*, 133 (1961).

[44] *G. Schramm*, Colloquium on Ribonucleic acids and Polyphosphates, Strasbourg, July 1961.

[45] *G. Schramm*, *H. Grötsch*, and *W. Pollmann*, Angew. Chem. internat. Edit. *1*, 1 (1962).

[46] *W. Pollmann*, personal communication.

[47] The stability of nucleosides to acid hydrolysis will be the subject of a separate review.

β-Lactams, Their Polymerization and Use as Raw Materials for Fibers [*]

BY DR. R. GRAF, DR. G. LOHAUS, DR. K. BÖRNER, DR. ERWIN SCHMIDT AND DR. H. BESTIAN

FARBWERKE HOECHST AG., FRANKFURT/MAIN (GERMANY)

β-Lactams can be prepared by cyclization of β-amino acid esters. Recently they have become available also from olefins by addition of N-carbonylsulfamyl chloride (isocyanatosulfonyl chloride) and from aldehydes by reaction with N-carbonylsulfamyl chloride and ketene. Condensative or anionic polymerization results in polyamides the chains of which contain many more amide groups than the chains of polyamides of the nylon-6 type. Hence the new polymers resemble silk more closely. Fibers and films can be prepared from solution.

Introduction

Following the discovery of the polymerization of lactams by *P. Schlack* [1] in 1938, lactams with rings containing more than six-members – expecially ε-caprolactam – were at first the main subject of the scientific and technical development effort. Only within recent years has it become possible to prepare analogues of polycaprolactam (Nylon-6) with longer carbon chains in the monomers, thanks to the development of new syntheses of lactams with eight and twelve carbon atoms in the ring (Nylon-8, Nylon-12).

New drive was given to the development of lactam polymerization when it became possible to polymerize α-pyrrolidinone – a 5-membered ring lactam – to give a high molecular-weight fiber-forming polyamide (Nylon-4) [2, 3], using alkaline catalysts known for a long time for caprolactam but rarely used.

The development in our laboratory of new synthetic methods for preparing β-lactams made it possible to work on the polymerization of these four membered lactams and to examine polyamides of the Nylon-3 type. With the synthesis of such polyamide fibers with almost double the number of amide groups of Nylon-6, materials approaching the model of natural silk have become available.

1. Preparation of the β-Lactams

β-Lactams (azetidin-2-ones), discovered by *Staudinger* [4], have remained relatively difficult to prepare despite the momentum given to their synthesis by research on penicillins [5]. There was a dire need for simple methods of preparing lactams which are not substituted on the nitrogen atom. This gap was bridged by *R. Graf* [6,7].

[*] From a lecture delivered on April 9th, 1962 at a meeting of the GDCh-Fachgruppe "Kunststoffe und Kautschuk" (Plastics and Rubber Division of the German Chemical Society) in Bad Nauheim.

[1] German Pat. 748253 (11th June, 1938), IG-Farbenidustrie AG.

[2] U.S.-Pat. 2638463 (7th Dec., 1951), Arnold, Hoffmann & Co.

[3] U.S.-Pat. 2809958 (24th Febr., 1953), General Anilin & Film Corp.

[4] *H. Staudinger*, Liebigs Ann. Chem. *356*, 51 (1907); Ber. dtsch. chem. Ges. *40*, 1145 (1907).

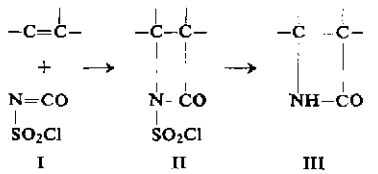
[5] *J. C. Sheehan* and *E. J. Corey*, Org. Reactions *9*, 388 (1957); *Th. Wieland* in Houben-Weyl: Methoden der organischen Chemie. G. Thieme, Stuttgart 1958, Vol. 11/2, p. 518; *G. Ehrhart*, Arzneimittel-Forsch. *7*, 397 (1957).

[6] German Pat. 941847 (18th Dec., 1953), Farbwerke Hoechst AG.; Chem. Zbl. 1297 (1957).

[7] German Pat. 1086234 (22nd Mar., 1958), Farbwerke Hoechst AG.; German Pat. 1116228 (12th Aug., 1959), Farbwerke Hoechst AG.

a) Preparation from Olefins and *N*-Carbonylsulfamyl-Chloride

N-Carbonylsulfamyl chloride (isocyanatosulfonyl chloride, I) [8], which is readily available from cyanogen chloride and sulfur trioxide, adds on to olefins even under mild conditions. The β-lactam-*N*-sulfonyl chlorides (II) formed are hydrolyzed under weakly acidic condition to give the free β-lactams (III).

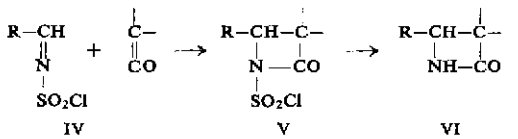


I II III

This method works particularly well with olefins of the following types $RR^1C{=}CH_2$, $RR^1C{=}CHR^2$, and $RR^1C{=}CR^2R^3$, as well as with styrene.

b) Preparation from Aldehydes, N-Carbonylsulfamyl Chloride, and Ketene

Aldehydes react with *N*-carbonylsulfamyl chloride (I) to yield *N*-alkylene-sulfamyl chlorides (IV) [9], from which β-lactam-N-sulfonyl chlorides (V) may be prepared by reaction with ketene or dimethylketene. Removal of the chlorosulfonyl group yields lactams of type VI.

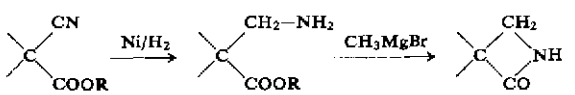


IV V VI

This method can be used to prepare 4-substituted azetidin-2-ones. The latter may also have two methyl groups in the 3-position.

c) Cyclization of β-Amino Esters

A further method for the preparation of β-lactams still bearing a hydrogen atom on the nitrogen is the cyclization of β-amino esters with Grignard reagents [10,11]. We have employed this method to produce 3,3-dimethylazeditin-2-one, starting with dimethylcyanoacetic ester.



Recently, *Testa et al.* [12] prepared 3-substituted azetidin-2-ones by this method. The use of this procedure is limited by the fact that only the 3-substituted compounds can be prepared in good yields. Moreover, the starting materials are not readily available and Grignard reagents must be employed.

The parent compound of the β-lactams, azetidin-2-one itself, can be prepared only with considerable difficulties in this way: cyclization of β-alanine ester with a Grignard reagent gives very poor yields. Even the use of high dilution techniques results in yields of only 0.76 % [11].

2. Polymerization of β-Lactams

Surprisingly, all the substituted β-lactams prepared so far can be polymerized as long as the nitrogen carries a hydrogen atom. However, considerable differences exist in their reactivities. In contrast to the β-lactams, substituted α-pyrrolidinones (for example 3-, 4-, or 5-methylpyrrolidinone) cannot be polymerized [13].

a) Condensative Polymerization

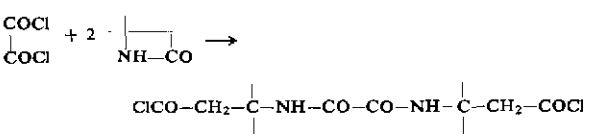
It is known that lactams with seven- or higher-membered rings can be converted into fiber-forming polymers by hydrolytically acting catalysts in the melt at 230–280 °C. When β-lactams were thus employed, a few examples showed that they already polymerize at 150–200 °C. The degrees of polymerization of 3,3-dimethylazetidinone and 4,4-dimethylazeitdinone are quite different (Table 1).

Table 1. Condensative polymerization of ε-caprolactam and β-lactams (catalyst: hexamethylenediamine salt of adipic acid)

Monomer	Temp. [°C]	Reaction time [hrs]	Specific viscosity (1 % solution in H_2SO_4; 20 °C)
ε-Caprolactam	250	6	1.5
3,3-Dimethylazetidinone	200	6	1.06
4,4-Dimethylazetidinone	200	6	0.40

3,3-Dimethylazetidinone was converted at 200 °C into a polyamide which had a viscosity close to that of the polyamide prepared from caprolactam at 250 °C. Under the same conditions, 4,4-dimethylazetidinone yields products which do not yet have fiber-forming properties. This difference in behavior between the two dimethylazetidinones can probably be explained by the fact that the polyamide from the 4,4-dimethyl compound precipitates out at low degrees of polymerization. The use of higher temperatures is precluded by the fact that both the monomer and the polyamide decompose as a result of the instability of the β-amino group.

An interesting variant, which is useful only for the polymerization of β-lactams, involves the use of acid chlorides as catalysts. Thus, 4,4-dimethylazetidinone can be polymerized with oxalyl chloride above about 60 °C. The initiation reaction is the addition of the acid chloride onto the β-lactam with ring opening and



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

[9] German Pat. 1109667 (22nd Jan., 1960), Farbwerke Hoechst AG.

[10] *W. Bestian*, Ph. D. Thesis, Technische Hochschule Hannover, 1944.

[11] *R. W. Holley* and *A. D. Holley*, J. Amer. chem. Soc. *71*, 2129 (1949).

[12] *E. Testa* et al., Liebigs Ann. Chem. *614*, 158, 167 (1958); *625*, 95 (1959); *647*, 93 (1961).

[13] *H. K. Hall*, J. Amer. chem. Soc. *80*, 6404 (1958).

formation of a new COCl group at the end of the chain. ε-Caprolactam and α-pyrrolidinone react with acid chlorides to form only rather stable *N*-acyllactams.

In summary, it can be said that in the β-lactam series condensative polymerization appears to be useful only for 3,3-dimethylazetidinone, which is difficult to prepare. For the preparation of high molecular weight, fiber-forming polyamides from β-lactams based on olefins, basic catalysts are better suited.

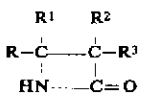
b) Anionic Polymerization

Owing to ring strain, the tendency of the β-lactams, to polymerize is particularly pronounced under the mild conditions of fast alkaline polymerization. While at relatively low temperatures, ε-caprolactam and α-pyrrolidinone can normally be polymerized only in bulk, it is possible to polymerize many β-lactams at −15 to +20 °C in solution [14].

α) Influence of Substituents on Polymerizability

The lactams VII to XX (Table 2) were polymerized to give linear polyamides in the presence of basic catalysts. The most readily available lactam, 4,4-dimethylazetidinone (VII), was investigated in detail. As the table shows, the tendency to polymerize decreases with increased substitution of the lactam ring. The positions of the substituents also influence the ease of polymerization of the monomers. 3,3-Dimethylazetidinone is the more reactive of the two dimethyl-β-lactams XII and XIII.

Table 2. Influence of substituents on the polymerization of β-lactams



	R	R^1	R^2	R^3	Polymerizability [*]	Relative viscosity of polymer (1 % solution in H_2SO_4; 20 °C)
VII	C_6H_5-	H	H	H	1	100
VIII	$p-CH_3C_6H_4-$	H	H	H	1	10
IX	$p-Cl-C_6H_4-$	H	H	H	1	–
X	CH_3-	H	H	H	1	9.5
XI	H_3C, H_3C >CH−	H	H	H	2	3.5
XII	H	H	CH_3-	CH_3-	2	4.0
XIII	CH_3-	CH_3-	H	H	3	21.0
XIV	$n-C_3H_7-$	CH_3-	H	H	3	6.0
XV	CH_3-	H	CH_3-	CH_3-	4	1.3
XVI	C_6H_5-	H	CH_3-	CH_3-	4	2.3
XVII	CH_3-	CH_3-	H	CH_3-	4	1.7
XVIII	H_3C, H_3C >CH−	H	CH_3-	CH_3-	5	1.5
XIX	CH_3-	CH_3-	CH_3-	CH_3-	5	1.5
XX	$-(CH_2)_5-$		$-(CH_2)_5-$		6	–

[*] Polymerizabilities classified by numbers 1 through 6; 1: polymerizes very readily; 6: polymerizes only with great difficulty.

[14] *P. Schlack* and *G. Lohaus*, unpublished data.

The degree of polymerization is determined not only by the polymerization tendency of the monomer, but also by the solubility or swelling tendency of the polymer, as well as by the monomer purity. The classification of the polymerizability in Table 2 can therefore be used only as a rough guide.

β) Copolymerization

As can be expected from the qualitative data on polymerizability given in Table 2, not all β-lactams undergo unlimited copolymerization with each other. Components with corresponding rates of polymerization must be used. 4,4-Dimethylazetidin-2-one (XIII) and 4-methyl-4-propylazetidin-2-one (XIV) copolymerize with particular ease and apparently in every ratio. 3,3-Dimethylazetidin-2-one (XII) can be copolymerized with 4,4-dimethylazetidin-2-one (XIII) as well as 4-phenylazetidinone (VII) in almost any ratio, while only small amounts of 4,4-dimethylazetidinone (XIII) copolymerize with 4-phenylazetidinone (VII). Much better results may be obtained however, if the more reactive phenyllactam is added dropwise, *e.g.*, as a solution in dimethylsulfoxide, to the less reactive dimethyllactam during the polymerization, so that the former is always present in relatively low concentration.Copolymerization of three or more components is also possible.

A few of the β-lactams in the table may be copolymerized easily with α-pyrrolidinone, but only in bulk. The growing β-lactam chains simultaneously accelerate the polymerization of the pyrrolidinone.

γ) Factors Influencing the Course of Polymerization

For systematic investigations of the factors influencing the course of the polymerization, we used primarily 4,4-dimethylazetidin-2-one which is readily prepared and, to a smaller degree, the readily available highly pure lactams 4-methyl-4-propylazetidin-2-one and 4-phenylazetidin-2-one.

High purity of the monomers and solvents, and the exclusion of water and other compounds with reactive hydrogen atoms, are prerequisites for a reproducible and optimal course of the polymerization.

Reaction Temperature

Increase in temperature accelerates the polymerization but simultaneously decreases the average molecular weight of the polyamide. Figure 1 demonstrates this for the polymerization of 4,4-dimethylazetidin-2-one. A little 4-methyl-4-propyl-azetidin-2-one, which polymerizes at approximately the same rate, was added to the reaction mixture in order to improve the solubility of the polyamide and thus assure a homogeneous course of reaction throughout the reaction time. Even at room temperature appreciable reaction rates are observed. Under the same conditions, 4-phenylazetidinone polymerizes quantitatively at 20 °C within a few minutes.

Since the polymerization of β-lactams is strongly exothermic, it is important to have good cooling arrangements during

the reaction in order to obtain a high degree of polymerization. Dissipation of the heat of reaction can become difficult when larger quantities are to be polymerized in bulk.

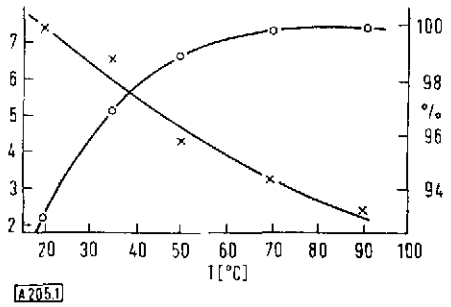


Fig. 1. Influence of reaction temperature on viscosity (—x—x—) and yield (—o—o—). Lactam concentration: 31 % (w/v). Catalyst: 3.7×10^{-3} mole pyrrolidinone-Na/mole lactam. Starting material: 9 parts by weight 4,4-dimethylazetidin-2-one + 1 part 4-methyl-4-propylazetidin-2-one. Reaction time: 25 hrs. Solvent: dimethylsulfoxide.

Ordinate: left, relative viscosity; right, percentage conversion.
Abscissa: Temperature [°C].

Reaction Time

Reaction time and temperature can really only be considered together. If, however, a certain temperature range is predetermined by the properties of the polymers desired, then the reaction time assumes importance as an isolated parameter (Fig. 2).

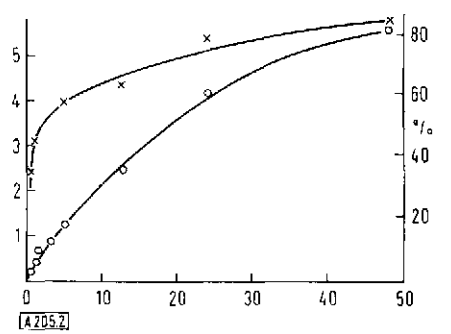


Fig. 2. Polymerization of 4,4-dimethylazetidinone (30.8 % w/w) in dimethylsulfoxide at 20 °C. Catalyst: 3.7×10^{-3} mole pyrrolidinone-Na/mole lactam.

(—x—x—) and left ordinate: relative viscosity.
(—o—o—) and right ordinate: percentage conversion.
Abscissa: Time [hrs.]

The curve shows the absence of a noticeable induction period even without the use of a cocatalyst. The steady increase in viscosity, even at high conversions where the polymer becomes insoluble in dimethylsulfoxide and separates out as a swollen mass, can be explained by assuming that the precipitated polymer is still reactive and continues to grow by addition of monomer.

Solvent

The solvent has a considerable influence on the course of the reaction. In principle, any solvent without active hydrogen atoms can be used.

It is advantageous technologically to use solvents which boil between 30 and 200 °C at atmospheric pressure. Distillation of a portion of the solvent under reduced pressure simultaneously removes any water present which would inhibit the polymerization reaction; only traces of the high boiling lactam distill off under these conditions.

Solvents which dissolve or at least swell the polymer, *e.g.* dimethylsulfoxide or hexamethylphosphoramide, are particularly desirable for high-quality products. For example, the polymer from 4,4-dimethylazetidin-2-one precipitates from dimethylsulfoxide solution only at relatively high degrees of polymerization. Kinetic measurements indicate that even afterwards the polymerization continues, homogeneously, apparently because the product is present in a highly swollen state. The use of these solvents, which strongly swell the polymer, differentiates our polymerization procedure considerably from the polymcrization of α-pyrrolidinone and ε-caprolactam. These solvents allow the polymcrization to proceed to practically quantitative yields under mild conditions.

It is also possible to polymerize in two-phase systems, in which the lactam is dispersed, either alone or with a polymer-swelling solvent, in a diluent in which it does not dissolve.

Monomer Concentration

In the polymerization of 4,4-dimethylazetidin-2-one in dimethylsulfoxide, best results are obtained when the concentration is one part of monomer in 2 to 4 parts by weight of solvent. Naturally, higher concentrations give higher space-time yields, but these are attained at the expense of a lower degree of polymerization. One reason for this situation, though certainly not the only one, may be the poorer heat transfer at higher concentrations. Higher dilution of the reaction mixture results in poorer yields as well as lower viscosities. Presumably, the relatively larger quantities of chain-terminating impurities are responsible for this.

Catalysts

Suitable catalysts are strongly basic compounds which yield an adequate concentration of lactam anion in equilibrium with the β-lactam (alkali and alkaline earth salts of various lactams and open-chain carbonamides, alkali alkoxides, alkali hydrides, alkali organometallic compounds, Grignard reagents, and in some cases even alkali and alkaline earth hydroxides, alkali carbonates, and cyanides). A particularly good catalyst is pyrrolidinyl potassium, which can be readily prepared as a fine, anhydrous powder and which can be measured out exactly. It is also rapidly soluble in the polymerization medium at low temperatures. The reaction rate is proportional to the catalyst concentration. We use 0.3 to 3 mole-% catalyst (based on monomer).

Cocatalysts

The polymerization of β-lactams in the presence of alkaline catalysts generally starts spontaneously. The polymerization reaction can be speeded up appreciably by the use of cocatalysts, in a manner similar to the polymerization of α-pyrrolidinone and ε-caprolactam. Acylating compounds which form *N*-acyl-β-lactams in the initiation reaction are useful as cocatalysts. Besides acyllactams themselves, compounds such as *N*-acyl-*N*-alkyl carbonamide, isocyanates, acyl chlorides, and anhydrides are useful as accelerators. If high molecular

weight products are desired, then these additives may be used in small quantities only (usually less than 0.1 mole %, based on lactam). Apart from shortening the

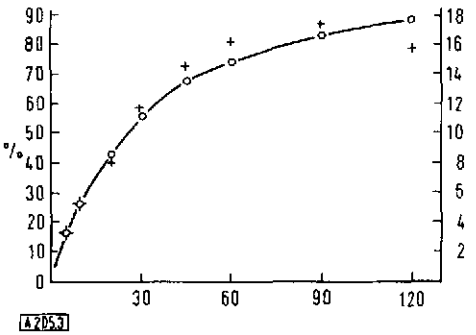
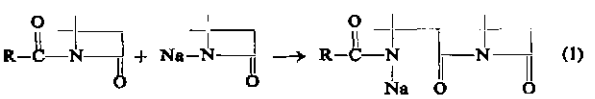


Fig. 3. Polymerization of 4,4-dimethylazetidinone (16 % w/w) in dimethylsulfoxide at 20 °C. Catalyst: 3.25×10^{-2} mole pyrrolidinone-K/mole lactam; Cocatalyst: 4×10^{-5} mole oxalylpyrrolidinone/mole lactam.
(—x—x—) and right ordinate: reduced viscosity [dl/g].
(—o—o—) and left ordinate: percentage conversion.
Abscissa: Time [min.]

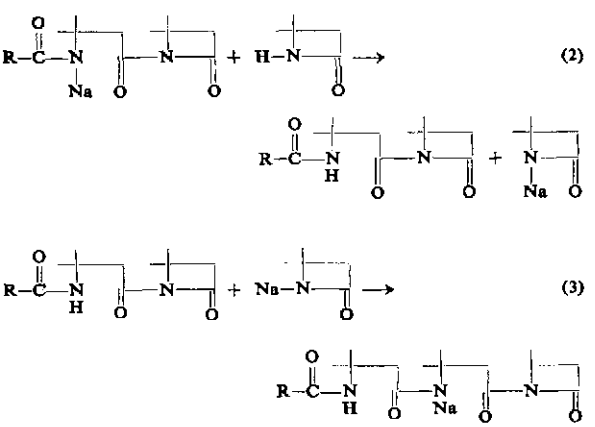
reaction time, these cocatalysts have an additional advantage: if sufficiently reactive bifunctional activators are present, it is possible to raise the average molecular weight of the product appreciably (compare Figure 2 with Figure 3).

δ) Mechanism of the Polymerization

In the presence of cocatalysts, the reaction begins with the addition of the alkali lactamate onto the acyllactam, accompanied by the opening of the ring of the acyllactam (1).



The sodium ion shifts to another lactam molecule (2), which in turn reacts (3) in the same manner with the acyllactam group formed in reaction (1)



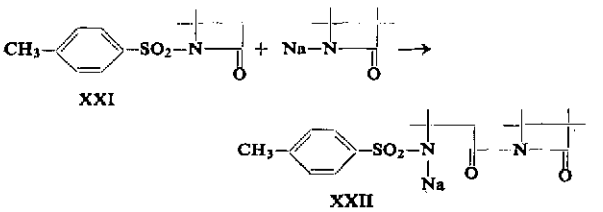
Similar concepts were advanced by other authors [13, 15–17].

[15] *G. Champetier* and *H. Šekiguchi*, J. Polymer Sci. *48*, 309 (1960).

[16] *O. Wichterle, J. Šebenda*, and *J. Králíček*, Fortschr. Hochpolymer-Forsch. *2*, 578 (1961).

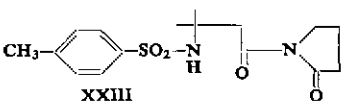
[17] *N. Yoda* and *A. Miyake*, J. Polymer Sci. *43*, 117 (1960).

Tosyllactams (XXI) are also useful as chain initiators. In this case it was possible to obtain the intermediates of each reaction step:

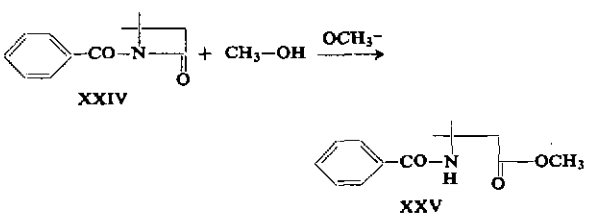


The sodium salt (XXII) precipitates after a few minutes and can be isolated in good yield. It could be demonstrated that the tosyllactam (XXI) is built into the polymer.

The potassium salt of compound XXIII can be isolated as a reaction product of pyrrolidylonyl potassium with *N*-tosyl-4,4-dimethylazetidinone.



Since alcohols and water serve as chain terminators, we examined the behavior of acyllactams with alcohols. *N*-benzoyl-4,4-dimethylazetidinone (XXIV) reacts vigorously with methanol in the presence of catalytic amounts of sodium methoxide. The reaction is accompanied by ring opening and formation of *N*-benzoyl-β-valine ester (XXV).



Alongside the polymerization initiated by acyllactam there is a considerably slower spontaneous initiation step. This results in polymers with amino end groups, which were estimated colorimetrically with 2,4-dinitrofluorobenzene [18].

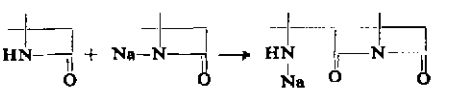


Figure 4 shows the conversion at equal reaction times as a function of cocatalyst concentration. The resulting straight lines do not pass through the origin. The intercept with the ordinate gives the fraction of the conversion derived from the spontaneous reaction.

ε) Viscosity and Molecular Weight, Behavior in Solution

Relative viscosities of the polymers were found to be highest in concentrated sulfuric acid (Table 3). The lower viscosities in phosphoric acid trisdimethylamide, *m*-cresol, and particularly $Ca(CNS)_2$/methanol are probably due to the fact that the polymers are coiled to a higher degree in these poor solvents. An increase in the

[18] *H. Zahn* and *P. Rathgeber*, Melliand Textilber. *34*, 749 (1953).

Table 3. Dependence of the viscosity of poly(4,4-dimethylazetidin-2-one) on the solvent

Solvent	Relative viscosity (1 % solution)			
	0 °C	25 °C	50 °C	80 °C
Conc. sulfuric acid	12.0	11.1	–	–
Phosphoric acid trisdimethylamide	7.32	6.38	–	4.48
m-Cresol	7.0	6.26	–	4.75
$Ca(CNS)_2$/Methanol	2.31	2.48	2.46	–

relative viscosity with temperature, usually observed in poor solvents, was not found here. This is probably due to the fact that any increase in temperature decreases the solvation and hinders the disentanglement of the coiled molecules.

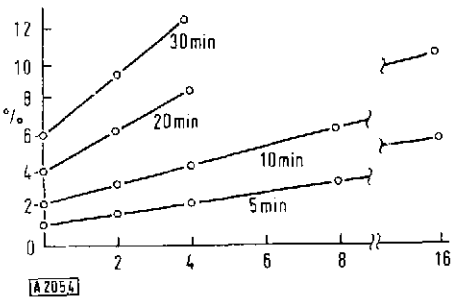


Fig. 4. Polymerization of 4,4-dimethylazetidin-2-one in dimethylsulfoxide at 20 °C. Catalyst: 6.4×10^{-3} mole pyrrolidinonyl-K/mole lactam.

Cocatalyst: Oxalylpyrrolidone.
Ordinate: Percentage conversion after times given on the curves.
Abscissa: Cocatalyst concentration (10^{-5} mole oxalylpyrrolidinone/mole lactam).

The infrared spectrum of the copolymer from 4,4-dimethylazetidinone and 4-metbyl-4-propylazetidinone in chloroform also gives evidence of this coiling of the molecules in poor solvents. The copolymer has a relatively low viscosity in this solvent and the infrared spectrum contains a band indicative of concentration-independent, *i.e.* intramolecular, hydrogen bonds.

The following relationship exists between the viscosity number in conc. sulfuric acid and the weight-average molecular weight of poly(4,4-dimethylazetidin-2-one) in trifluoroethanol as determined by light scattering [19]:

$$[\eta] = 4{,}53 \cdot 10^{-4} \cdot \overline{M}_w^{0{,}7} \qquad (4)$$

According to this, polymers of viscosity number 4.5, which we use for spinning experiments, have a weight-average molecular weight of about 500000.

The number-average molecular weight of the poly (4,4-dimethylazetidinone) could not be determined because most solvents attacked the cellulose membranes of the osmotic cells. However, osmotic measurements in methanol solution could be carried out on the copolymer of 4,4-dimethylazetidinone (50 %) and 4-methyl-4-propylazetidinone (50 %) [20]. These resulted (Figure 5) in the relationship

$$[\eta] = 1{,}36 \cdot 10^{-3} \cdot \overline{M}_n^{0{,}63} \qquad (5)$$

The equations (4) and (5) are valid for polymers produced in cocatalyzed fast alkaline polymerizations, in other words, for products having no uniform molecular weight. An idea of the heterogeneity of the polymers

[19] *E. Duch*, unpublished data.

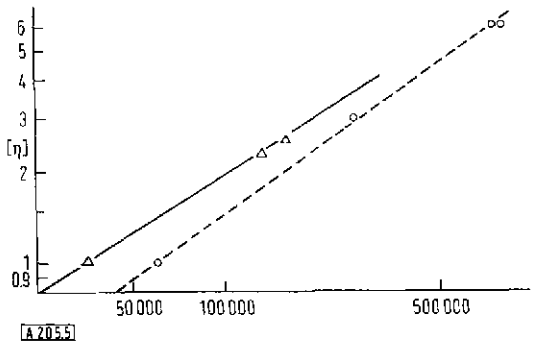


Fig. 5. Relationship between viscosity number and weight-average molecular weight $\overline{M}_w$ (—o—o—), determined by light scattering on poly(4,4-dimethylazetidinone). Curve (—Δ—Δ—): Number-average molecular weight $\overline{M}_n$, determined by osmotic measurements on copolymers of 4,4-dimethylazetidinone (50 %) and 4-methyl-4-propylazetidinone.

Ordinate: Viscosity number in conc. H_2SO_4 at 20 °C; [dl/g].
Abscissa: Molecular weight.

is obtained by fractionation with a mixture of 38.5 % (by weight) phenol and 61.5 % carbon tetrachloride as solvent and with normal hexane as precipitating agent [20] (Figure 6).

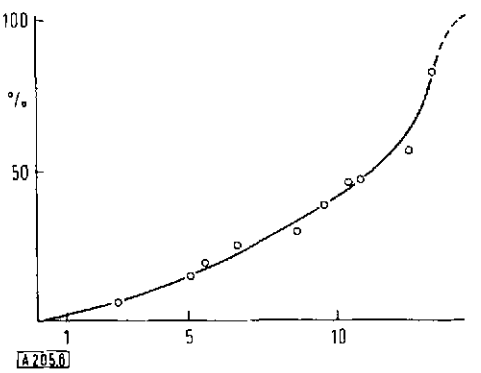


Fig. 6. Fractionation of poly (4,4-dimethylazetidine-2-one) by precipitation with n-hexane from phenol/carbon tetrachloride 38.5:61.5 (w/w). Reduced viscosity of the starting material: 8.0 dl/g. Temperature: 25 °C.

Ordinate: % of total material
Abscissa: Reduced viscosity of a solution of 1 % polymer in phenol/carbon tetrachloride 21.1:78.9 (w/w) at 25 °C; [dl/g]

From the course of the distribution curve it can be seen that about 40 % of the polymer have a uniform molecular weight. This portion is due to the chains initiated by acyllactam at the start of the polymerization. The low molecular weight portion is due to chain terminations and chains which started later.

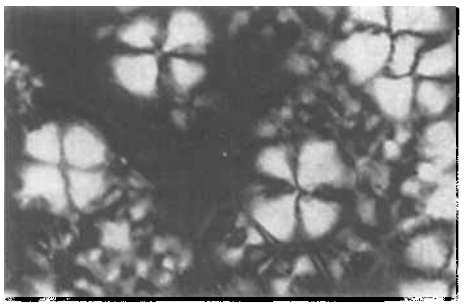
ζ) Structure of Poly(4,4-dimethylazetidinone)

Poly(4,4-dimethylazetidinone) is highly crystalline even in the unstretched condition. Thus, during polymerization in dimethylsulfoxide, the polymer precipitates as swollen spherulites (Figure 7). These spherulites disappear on drying, but the powdered polymer, as well as unstretched films prepared from it, give well defined X-ray patterns.

X-ray patterns of stretched fibers show the expected high degree of orientation of the crystallites. The identity period along the fiber is much larger than with Nylon-6. The exact crystal structure is currently being investigated [21].

[20] *W. Schmieder*, unpublished data.
[21] *A. Pebler*, unpublished data.

The infrared spectrum indicates that almost all the amide groups have formed hydrogen bonds with carbonyl oxygens on neighboring chains. One would expect, therefore, that adequate tensile strengths would be obtained even with molecular weights in the 10000–20000 range, as for



A 205.7

Fig. 7. Spherulites of poly (4,4-dimethylazetidinone), from polymerization in dimethylsulfoxide. Magnification: 500 times.

Nylon-6. Surprisingly, however, stretched fibers made from poly(4,4-dimethylazetidinone) are of sufficient strength for textile applications only when the weight-average molecular weight is above 200000. In this connection, it is worth noting that, contrary to Nylon-6, stretched films of poly(4,4-dimethylazetidinone) show no dichroism of the CO and NH bands in polarized infrared radiation. Since such dichroism appears in other absorption bands, we are forced to conclude that in poly(4,4-dimethylazetidinone), the CO and NH bonds are not normal to the fiber's axis of length, as is the case with Nylon-6. These investigations are also still in progress [22].

3. Fiber Preparation

The preparation of fibers and films from β-lactam polymers is encumbered by their insolubilities and high melting points (Table 4). In particular, polymers of the 4-substituted β-lactams melt only at about 300 °C and then with decomposition. Prolonged heating even at 200–250 °C reduces the viscosity of the polymer.

Table 4. Melting points and solubilities (20 °C) of several β-lactam polymers (+ soluble, – insoluble, ± swells)

	Polymer obtained from									
	4-Methyl-	4-Isopropyl-	4-Phenyl-	3,3-Dimethyl-	4,4-Dimethyl-	3,3-Dimethyl-4-methyl-	3,3-Dimethyl-4-isopropyl-	3,3-Dimethyl-4-phenyl-	3,3,4,4-Tetramethyl-	4,4-Dimethyl- and 4-Methyl-4-propyl- (1:1)
	-azetidin-2-one									
M. p. (decomp.) [°C]	328	330	330	250	296	360	330	360	330	130–160
Solubility in										
Methanol	–	–	–	–	–	–	–	–	–	+
Chloroform	–	–	–	–	–	–	–	–	–	+
Phosphoric acid trisdimethylamide	–	–	–	+	+	–	–	–	–	+
Trifluoroethanol	–	–	–	+	+	+	+	+	+	+
Phenol	+	+	±	+	+	+	+	+	+	+
Conc. H_2SO_4	+	+	+	+	+	+	+	+	+	+
$Ca(CNS)_2$/ methanol	+	+	–	+	+	+	–	–	–	+

Because of this poor thermal stability of the β-lactam polymers, it is hardly possible to prepare products from the melt. One exception is poly(3,3-dimethylazetidinone), which is sufficiently stable to allow melt spinning to stretchable fibers of good quality.

Dry spinning from solutions is difficult because the polymers have such low solubilities in common solvents. Trifluoroethanol and trichloroethanol are two of the few solvents which have sufficient solvent power to dissolve the polyamides and are volatile enough to be useful for the dry spinning process. Dimethylsulfoxide dissolves poly(4,4-dimethylazetidinone) only above 100 °C. Poly-(4,4-dimethylazetidinone) and poly(3,3-dimethylazetidinone) dissolve in phosphoric acid trisdimethylamide, but this solvent is too involatile to be useful for dry spinning. Naturally there is a pos ibility for improving the solubilities by copolymerization, but then the good fiber properties normally suffer.

Some of our polyamides are soluble in methanolic calcium thiocyanate. Wet spinning of these polyamide solutions into water results in fibers with good textile properties [23]. This process was worked out in detail for poly(4,4-dimethylazetidinone), which appeared to be a particularly interesting product for fiber production because of the accessibility of the raw-material and because of its favorable properties. The ease with which the methanolic calcium thiocyanate dissolves the poly-β-lactams even at room temperature is surprising, since it acts as a precipitating agent for poly-ε-caprolatam.

The viscosity of the spinning solution depends upon the poly-β-lactam concentration and the viscosity of the polymer. Polymers of viscosity numbers between 3 and 6 can be readily spun in 12 to 15 % solutions.

4. Fiber Properties

It is not yet possible to make a final statement on the properties of fibers of poly-β-lactams, in particular those of poly(4,4-dimethylazetidinone), because work on the spinning process has not yet been completed. Preliminary data show that hopes are justified that useful fibers can be prepared from these new materials (Table 5).

[22] *H. H. Suhr*, unpublished data.

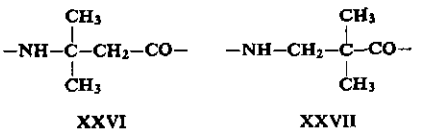
[23] *H. Hoyer, H. Behrenbruch*, and *K. Börner*, unpublished data.

Table 5. Fiber properties of poly(4,4-dimethylazetidinone) in comparison with Nylon-6 and silk

Physical and mechanical properties	Poly(4,4-dimethyl-azetidinone)	Nylon 6 (normal) [*]	Silk [*]
M.p. of crystallite [°C]	296	215	-
Specific gravity	1,11	1,14	1,37
Tensile strength, dry [g/den]	2–3	4,1–5,8	3,3–5,5
Elongation to break, dry [%]	30–55	26–40	13–25
Relative tensile strength, wet [%]	70	85–90	80
Tenacity (knot), [%]	95	ca. 80	80–85
Moisture uptake (65 % rel. humidity, 20 °C) [%]	4,5	4–4,5	9

[*] Fasertafel des Deutschen Forschungsinstituts für Textilindustrie (Fiber Table of the German Textile Research Institute), Reutlingen (Values from Sept. 1960).

In comparison to other polyamides, fibers made from poly(4,4-dimethylazetidinone) are characterized by their remarkable stability to oxidative attack, which prevents yellowing of the fiber on heating. This stability is apparently due to the two methyl groups in the monomer unit (XXVI) which shield the neighboring atoms from attack by oxidizing agents. The poly-β-lactam with the isomeric monomer unit (XXVII) discolors on heating just like normal polyamides.



XXVI XXVII

Fibers made from poly(4,4-dimethylazetidinone) can be dyed like those from poly-ε-caprolactam, but they have a poorer affinity for most of the dyestuffs tested so far. The best results were obtained with dispersion dyestuffs.

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Long Periods in Drawn Polyethylene [*]

BY DR. E. W. FISCHER AND DR. G. F. SCHMIDT

LABORATORIUM FÜR PHYSIK DER HOCHPOLYMEREN
AM INSTITUT FÜR PHYSIKALISCHE CHEMIE DER UNIVERSITÄT MAINZ (GERMANY)

Meridional reflections appearing in small-angle X-ray diffraction diagrams of drawn polyethylene are caused by a nearly periodic arrangement of crystalline and disordered regions. The long period, which is determined by the average distance between two consecutive crystallites, depends on the method of preparing the sample. The time and temperature dependences of the positions of the small-angle reflections have been investigated. The growth of the long period of unoriented bulk polyethylene and polyethylene single crystals follows the same time dependence as that of stretched films. However, characteristic differences were observed in the relationship between density and long period; they are attributed to the fact that in single crystals and in material crystallized from the melt, the chains are folded at the boundaries of the crystallites, whereas this is not the case in stretched polyethylene.

I. Introduction

The properties of high polymeric solids depend not only on the chemical structure of the macromolecules but also on the thermal and mechanical treatment of the samples. This is especially true for crystallizable high polymers, where the pretreatment affects the relative arrangement of the chains; for example, one may obtain samples with different lattice modifications or different degrees of crystallinity. These effects can be measured by wideangle scattering of X-rays and other methods. In addition, pretreatment also has an effect on the size of the crystallites, on their relative arrangement, and on their structural relationship to disordered regions. These three structural characteristics are grouped together under the term "microstructure". Their characteristic linear dimensions are in the order of magnitude of 100 to 1000 Å; suitable methods of investigating them are, therefore, measurements of the small-angle diffraction of X-rays and electron microscopy.

Hess and *Kiessig* [1] were the first to recognize the importance of small-angle diffraction of X-rays for determinating the relative arrangement of the crystallites. They found long periods of the order of magnitude of 100 Å for stretched polyamides and polyesters; these could not be associated with the structure of the molecular chains, so they, therefore, considered the positions of these small-angle reflections on the meridian as a measure of the relative distance between the centers of gravity of two consecutive crystallites lying along the fiber's axis. This interpretation is still accepted today, although certain aspects of the original model appear to be questionable in the light of more recent investigations.

[*] From a lecture delivered on Apr. 11th 1962 at the meeting of the GDCh-Fachgruppe "Kunststoffe und Kautschuk" (Plastics and Rubber Division of the German Chemical Society) in Bad Nauheim.

[1] *K. Hess* and *H. Kiessig*, Z. physik. Chem. (A) *193*, 196 (1944); Kolloid-Z. *130*, 10 (1953).

Since the discovery of these long periods in polyamides, similar effects have been observed in many other synthetic high polymers. It can therefore be assumed that the nearly periodic arrangement of approximately equally large crystallites in the chain direction indicated by the small-angle period is a general and typical structural characteristic of crystalline polymers. The as yet unexplained process leading to this structure is designated as "periodic crystallization" [2].

In order to interpret the small-angle effect, two points must be clarified: the structure, responsible for the observed diffraction phenomena has to be determined; and the cause of the formation of these structures must be sought.

To clarify to the first issue, a number of structural models have been proposed. These will be discussed below and compared with electron microscopic observations.

The second point is more difficult to clarify, because until now only few systematic investigations of the dependence of microstructure on the conditions of formation are available. Therefore, it is desirable to have measurements of the dependence of the long period on the crystallization or annealing temperature, the annealing time, the chemical nature of the polymer, and other parameters.

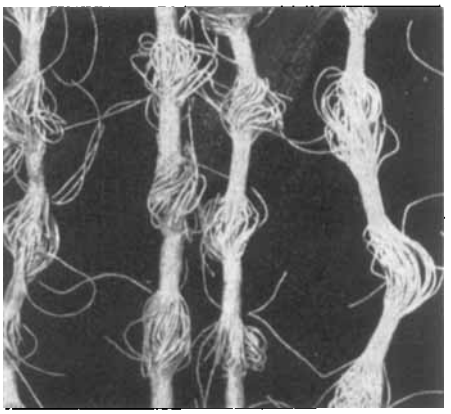
We limited our initial measurements to annealing experiments on polyethylene. This substance was chosen because of its relative stability toward degradation and chemical changes during long annealing times and because it can easily be prepared in the form of single crystals. Their structure is well known, thus simplifying interpretation of the changes that take place during annealing. Other high polymers appear to behave in much the same manner as polyethylene, with regard to the effects measured by us.

The dependence of the long period on the annealing time and temperature, as well as the density, birefringence, and wideangle X-ray diffraction were measured for the annealed samples. We attached special significance to a comparison of observations on drawn material with observations on polyethylene single crystals and on isotropic films crystallized from the melt.

II. Microstructure of Drawn Fibers and Films

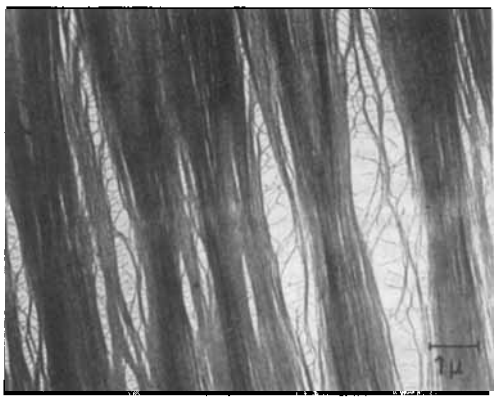
The structural model of *Hess* and *Kiessig* [1] assumes that the drawn polymer is composed of thin elementary fibrils, in which amorphous and crystalline regions alternate more or less regularly along the length of the fiber (Fig. 1). In electron microscopic investigations, structures similar to the fibrillar structure of the model are frequently found. Fig. 2a shows the stretched zone of a thin polyethylene film. In the fibrils appearing there, the chain molecules are predominantly oriented parallel to the fiber axis, as can be seen from the position of the (002) reflection of the corresponding electron diffraction pattern (Fig. 2b).

With a structure according to Fig. 1 or Fig. 2a, in addition to the meridional reflections caused by the disordered regions, an intense equatorial scattering should be expected as a result of the extended voids between the fibrils. Such small-angle patterns have actually been observed (Fig. 3a). This however, is not normally the case but usually only occurs with "overstretched" films. The opaque, milky appearance of these samples and their anomalously low densities indicate that voids of considerable size can occur. By pressing the



A202.1

Fig. 1. String model of a drawn fiber. The elementary fibrils are composed of crystalline and disordered regions in a practically periodical arrangement (after [3])



A202.2a

Fig. 2a. Electron microscopic photograph by transmitted radiation of the stretched zone of a thin film of polyethylene, which was composed of spherulites before drawing



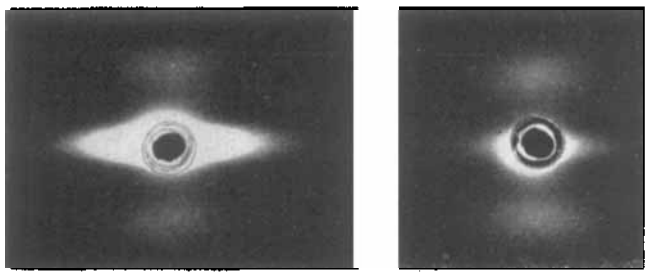
A202.2b a

Fig. 2b. Electron diffraction photograph of the same region as in Fig. 2a. The position of the (002) reflection shows that the chains are oriented parallel to the direction of the fibrils

[2] *E. W. Fischer*, Ann. N.Y. Acad. Sci. *89*, 620 (1961).

[3] *W. O. Statton*, J. Polymer Sci. *41*, 143 (1959).

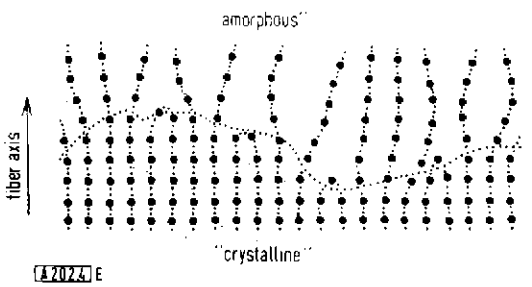
voids can be made to disappear partially and the equatorial scattering decreases [4], as can be understood from Fig. 2a.



A 202.3 (a) (b)

Fig. 3. Small-angle reflections of drawn polyethylene:
a) With intense equatorial scattering; drawn at room temperature;
b) Drawn at 70 °C

If the stretching is done under normal conditions, *i.e.*, at elevated temperature and with moderate elongation, then small-angle patterns are obtained such as are shown in Fig. 3b. Here, only the meridional reflections caused by the long periods along the length of the fiber appear. In this case, interpretation of the diagram in terms of the model shown in Fig. 1 can present difficulties [5]. This is partly due to the fact that the dilatation chains in the amorphous regions of Fig. 1 would prevent close packing of the fibrils and would therefore tend to prevent the disappearance of the equatorial scattering. *Bonart* and *Hosemann* [5] therefore proposed a structural model in which the difference in electron density between the disordered and crystalline regions that is necessary to produce the observed diffraction effect is obtained by folding some of the chains at the boundary of the crystalline regions (Fig.4).



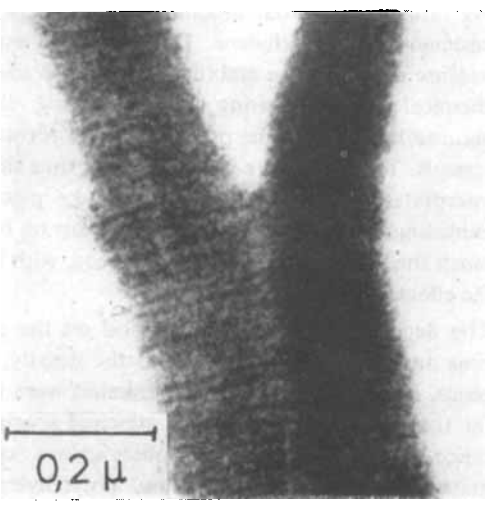
A 2024 E

Fig. 4. Model proposed for the transition region between the crystalline and amorphous regions in drawn fibers. Some chains are folded at the crystallite boundary (after [4])

Keller [6] also expressed the idea that just as in single crystals, a large part of the chains in the drawn material does not connect consecutive crystallites but is folded at the boundary surfaces.

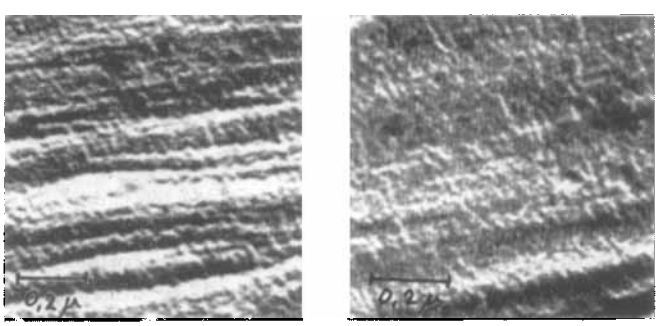
A decision in favor of one or the other of the two models, *i.e.* whether the chains are folded or not, does not appear to us to be possible on the basis of X-ray measurements alone. In particular, the space requirement of the amorphous regions in the model of *Hess* and *Kiessig* can easily be estimated, but then it is found that the voids caused by these regions cannot be correlated with the equatorial diffractions such as shown for example in Fig. 3b. Furthermore, other characteristics of the small-angle patterns can be explained using either model. According to the model of Fig. 1, any broadening of the meridional reflections in the direction of the layer lines would depend on the cross-sectional dimensions of the fibrils and on the relative longitudinal displacement of the crystalline regions. *Bonart* and *Hosemann* conceive the cause of the broadening to be the bending of the crystalline regions indicated in Fig. 4.

To solve this problem, other methods of investigation must be brought into play. For example, certain conclusions can be drawn by observing the behavior of drawn materials during annealing (see below). Electron microscopic investigations can also be used to obtain further information. Thus, the periods of cellulose, poly(vinyl alcohol), and Perlon determined by X-ray techniques can also be verified by electron microscopy by embedding substances of sufficiently high electron contrast in the amorphous regions [7, 8]. Fig. 5 shows an example of a hydrocellulose fibril with a clearly discernible periodic structure [8]. Naturally, embedding (in this case, of iodine) is possible with



A 202.5

Fig. 5. Electron microscopic photograph of a hydrocellulose fibril with embedded iodine [8].



A 202.6 (a) (b)

Fig. 6. Shadowed replica of drawn low-pressure polyethylene. Obliquely shadowed with Au/Pd at an angle of 25 °, reinforced by carbon

[4] *R. Bonart* and *R. Hosemann*, personal communication.

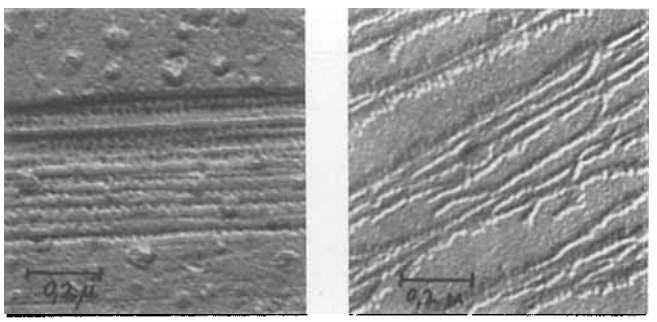
[5] *R. Bonart* and *R. Hosemann*; Makromolekulare Chem. *39*, 105 (1960).

[6] *A. Keller*, Kolloid-Z. *165*, 34 (1959).

[7] *K. Hess* and *H. Mahl*, Naturwissenschaften *41*, 86 (1954).

[8] *K. Hess*, *H. Mahl*, and *E. Gütter*, Kolloid-Z. *155*, 1 (1957); *168*, 37 (1960).

both of the models mentioned above. On the other hand, oblique shadowing of stretched samples should only expose the dilated regions. By using this method, we have in fact found periodicities with the electron microscope, these being of the order of magnitude of 150 to 400 Å. This is shown in the replicas of low-pressure polyethylene (Figs. 6a and 6b), which was stretched at a temperature of about 50 °C. The periodicity along the length of the fibrils is clearly recognizable. Systematic investigations of appropriate shadowing materials and methods of pretreating the samples are currently in progress. In Figs. 7a and 7b, individual



A 202.7 (a) (b)

Fig. 7. Polyethylene fibrils obtained by drawing of single crystals. Obliquely shadowed with Au/Pd at an angle of 25 °

polyethylene fibrils, which were obtained by stretching polyethylene single c ystals are reproduced. Periodicities of the expected order of magnitude are also encountered here. In addition, in these experiments, another long period of ca. 600 Å was also found [9].

The results of electron microscopic investigations obtained so far do not allow an unequivocal answer to the question whether the chains are folded or laterally dilated. Nevertheless, these experiments, particularly those of *Hess*, *Mahl* and *Guetter*, offer strong support to the assumption that the long-period diffractions are caused by alternation of crystalline and amorphous regions. Without going further into the divergent assumptions concerning the structure of the amorphous regions, we will base the following considerations and evaluations of measurements on this common feature of the two models. Other possibilities, such as the existence of helical structural elements, whose pitch is supposed to determine the position of the small-angle reflections, will be excluded [10, 11].

Our assumption is also supported by other investigations. If one integrates the total region of small-angle diffraction, then one obtains the "diffraction power" [12] of the samples, which is dependent only on the composition of the diffracting system and not on its geometric structure. By comparing the diffraction power with the density of the samples, it could be shown that in polyethylene the small-angle diffraction is caused only by the "crystalline" and "amorphous" phases [13, 14].

It should also be mentioned that, in consideration of this result, still another structural model is possible, *viz.* the small-angle diffraction can be considered as pure particle diffraction [14]. The maxima would then no longer be measures of the distances between the crystallites, but would provide information about their size and shape. However, we do not consider this concept – at least for polyethylene – to be sufficiently well established as yet.

III. Periods of the Small-angle Diffraction of Drawn Polyethylene as a Function of Thermal Treatment

The positions of the reflections of small-angle diffraction of polyamides and polyesters change on annealing [1]. This is also true for polyurethane [15], poly(ethylene glycol terephthalate) [16], and polyethylene. For example, during thermal shrinking of fibers of low-pressure polyethylene, the long period initially increases with increasing contraction rate, and then decreases [17]. *Belbeoch* and *Guinier* [14] described the effect of annealing on four-point patterns obtained by them with branched polyethylene. In both cases the annealing effects overlap with relaxation phenomena, so that it becomes very difficult to interpret the changes in the period of the small-angle diffraction. For our measurements on highly oriented low-pressure polyethylene, we selected a temperature range in which no relaxation can be noticed. Up to temperatures of 133 °C, even at annealing times of 24 hours, the length of the stretched samples remained constant, and no desorientation could be observed in wide-angle X-ray patterns. The samples could therefore be annealed without holding them under tension; measurements on samples annealed

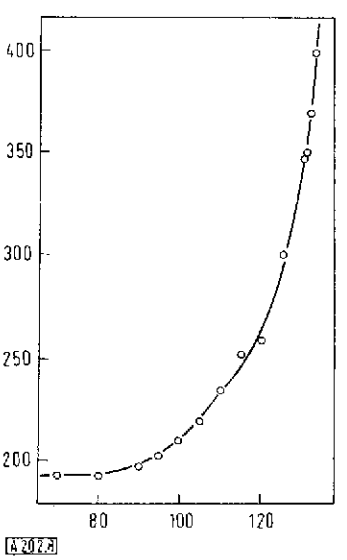


Fig. 8. Temperature dependence of the long period of drawn polyethylene. The initial samples were stretched approximately 16-fold at 70 °C

Annealing time: 24 hrs.
Ordinate: Length of the long period [Å]
Abscissa: Temperature [°C]

[9] *H. A. Stuart*, Ann. N.Y. Acad. Sci. *83*, 3 (1959).

[10] *L. B. Morgan, A. Keller* et al., Philos. Trans. Roy. Soc. London, Ser. A *247*, 1 (1954).

[11] *W. Cochran, F. A. C. Crick*, and *V. Vand*, Acta crystallogr. *5*, 581 (1952).

[12] *G. Porod*, Fortschr. Hochpolym. Forsch. *2*, 363 (1961).

[13] *Herrmann* and *Weidinger*, MakromolekulareChem. *39*, 67 (1960).

[14] *B. Belbéoch* and *A. Guinier*, Makromolekulare Chem. *31*, 1 (1959).

[15] *H. Zahn* and *U. Winter*, Kolloid-Z. *128*, 142 (1952).

[16] *W. O. Statton*, J. Polymer Sci. *41*, 143 (1959).

[17] *A. S. Posner, L. Mandelkern, C. R. Worthington*, and *A. F. Diorio*, J. appl. Phys. *31*, 536 (1960).

at constant length gave no difference in the long periods within the temperature range selected by us.

Fig. 8 shows the temperature dependence of the long period at constant annealing time. As with other polymers, the long period increases with increase in temperature. It doubles after annealing for 24 hours at 133 °C. Obviously, such a change in size cannot be explained by growth of crystallites at the expense of the interstitial amorphous regions. The expansion of the long period associated with this would be far too small. On the contrary, it must be assumed that the microstructure breaks down completely, with concomitant new crystallization.

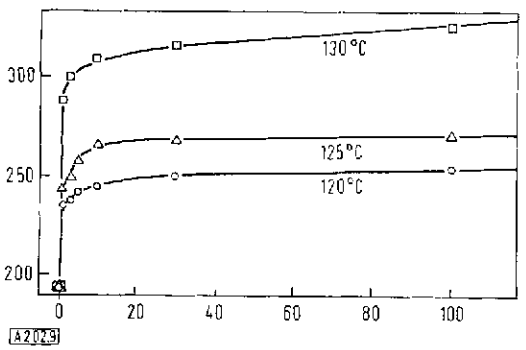


Fig. 9. Dependence of the long period of drawn polyethylene on the annealing time.
Ordinate: Length of the long period [Å]
Abscissa: Time [min]

As our measurements of the time dependence show, this process goes on continuously. In Fig. 9, the dependence of the long period on the annealing time at three different temperatures is plotted. At first, the long period increases very rapidly, but thereafter changes very little. Figure 10 shows

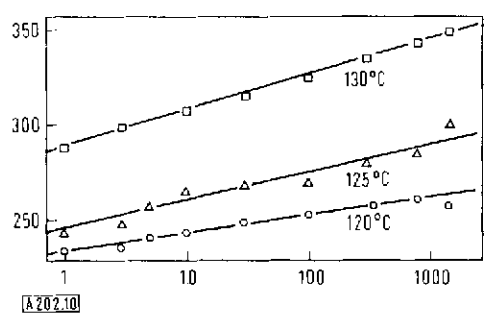


Fig. 10. Dependence of the long period on the logarithm of the annealing time.
Ordinate: Length of the long period [Å]
Abscissa: Time [min.]

that the long period is linearly dependent on the logarithm of the annealing time, *i.e.*, the variation can be described by the relationship

$$P = K \log t + p \qquad (1)$$

where K is the gradient of the straight line and p is its intercept on the ordinate. Eq. 1 can also be written in the form

$$P = K \log t/t_0 + P_0 \approx K \log (t/t_0 + 1) + P_0 \qquad (2)$$

where P_0 is the long period of the unannealed sample and t_0 is the time obtained by extrapolating to the starting period P_0. This is of the order of magnitude of 10^{-2} to 10^{-6} minutes, so that at the times measured by us, $\log t/t_0$ may be approximated by using $\log (t/t_0 + 1)$. This takes the fact into account that at time $t = 0$, the long period is $P = P_0$.

According to Eq. 1, the long period should change only very little after long annealing times. Apparently, this has often led to the view that the value of the long period is dependent only on the temperature. Therefore annealing times are frequently not given in the literature. Furthermore, measurements on the time dependence of other polymers are unavailable. According to our investigations, the long period still increases even after very long periods of time. Only after 500 hrs., does the long period become constant at elevated temperatures (130 and 132 °C); however, under these conditions, chemical changes in the samples may come into play. Investigations of this matter are in progress.

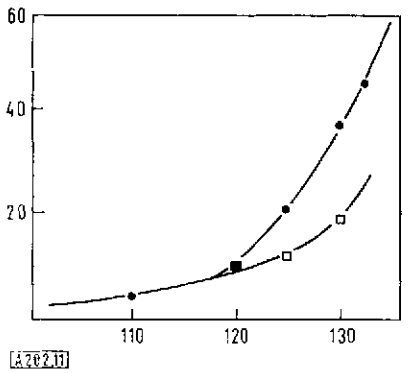


Fig. 11. Temperature dependence of the gradients K of the logarithmic curves from Eq. 1 for drawn low-pressure polyethylene
(—●—●—) drawn approximately 10-fold
(—□—□—) drawn approximately 16-fold
Ordinate: K values from Eq. 1 [Å]
Abscissa: Temperature [°C]

The gradient K of the logarithmic straight line depends on the temperatures as is shown in Fig. 11 for two series of experiments. From this it can be seen that the rate of growth of the long period depends on the temperature and pretreatment of the sample. Moreover, it appears that the predominant effect depends on the degree of drawing; the smaller the elongation, the more rapidly K increases with temperature. In agreement with this, undrawn polyethylene and polyethylene single crystals show a much sharper increase of the gradient constant K with temperature (cf. Fig. 18).

The dependence of the growth of the period on the extent of drawing is also shown in Fig. 12. The change of the long period after annealing for 24 hours at 125 °C

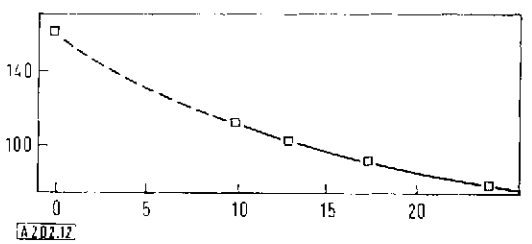


Fig. 12. Dependence of the increase of the long period on the drawing ratio after annealing for 24 hours at 125 °C.
Ordinate: Length of the long period [Å]
Abscissa: Drawing ratio

is plotted here for samples of different degrees of drawing. Surprisingly, the value measured for the unstretched sample fits well into the curve.

However, the long period increases not only with the temperature during annealing but, in much the same sense, it also depends on the temperature during stretching [14]. This dependence is shown in Fig. 13. It is apparent that the curves for branched and unbranched polyethylene exhibit much the same behavior and are merely shifted about 55 Å relative to one another along the ordinate. This appears to us to furnish evidence that the frequently expressed viewpoint that the long period is in branched polyethylene determined by the average length between neighboring branch points is incorrect.

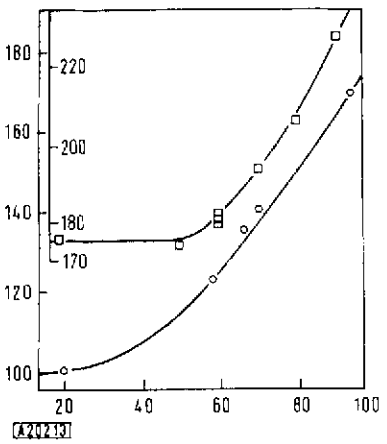


Fig. 13. Dependence of the long period on the drawing temperature for branched (—o—o— and left ordinate)[14] and unbranched (—□—□— and right ordinate) polyethylene.

Ordinate: Length of the long period [Å]

Abscissa: Temperature [°C]

Summarizing, it can be said that: 1. in stretched polyethylene, the long period increases as the stretching temperature increases; 2. during annealing, the long period increases with the logarithm of time, and it increases more rapidly, the higher the annealing temperature; and 3. the greater the degree of drawing, the smaller the gradient of the logarithmic time curve.

IV. Changes in the Long Period of Unoriented Polyethylene and Polyethylene Single Crystals during Annealing

Up to the present, very little data have been presented concerning the variation of the long period during annealing of unoriented bulk polyethylene. They show that, here, as with the drawn material, the long period increases with increasing temperature [14, 18, 19] and that the annealing time is also important [20]. In addition, the degree of branching has some effect on the increase of the period during annealing [21].

After these effects were noted by *Keller* and *O'Connor* [23], the temperature dependence of small-angle diffraction patterns of polyethylene single crystals were thoroughly investigated by *Statton* and *Geil* [22]. *Hirai* et al. [24] have drawn attention to the time dependence of this process. *Statton* [25] observed that the growth of the long period proceeds much faster in liquids than in air.

We have measured the time and temperature dependence of the growth of the long period during annealing of unoriented polyethylene and polyethylene single crystals.

Low-pressure polyethylene was melted and then quenched in ice water. The samples were annealed at different temperatures and subsequently again quenched in ice water. For measuring the period of the small-angle scattering, a camera according to *Kratky* was used [*]. Polyethylene single crystals were prepared from dilute solution at various temperatures. The aggregates of superimposed crystal lamellae obtained by slow sedimentation were dried carefully in a vacuum and then annealed and investigated in the manner described above.

The dependence of the long periods of these samples on the annealing temperature at constant annealing time (24 hours) is shown in Figs. 14 and 15. Curves similar to those with drawn polyethylene are obtained (cf. Fig. 8). One striking difference occurs. With stretched material, the long period increases continuously with temperature, whereas in the case of single crystals there is a sharp inflection at 105–110 °C. Below this temperature, the long period increases only slightly. *Statton* and *Geil* [22] also found changes in the long period only at temperatures above 110 °C [**].

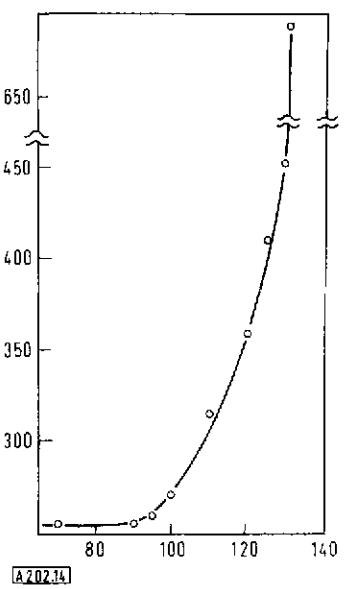


Fig. 14. Temperature dependence of the long period of unstretched polyethylene. The starting samples were quenched at 0 °C from the melt. Annealing time: 24 hrs.

Ordinate: Length of the long period [Å]

Abscissa: Temperature [°C]

[18] *H. Hendus*, Ergebn. exakt. Naturwiss. *31*, 331 (1959).

[19] *D. H. Geil*, personal communication.

[20] *L. Mandelkern, A. S. Posner, A. F. Diorio*, and *D. E. Roberts*, J. appl. Physics *32*, 1509 (1961).

[21] *C. Sella*, Lecture, IUPAC-Symposium on Macromolecules Wiesbaden (Germany) 1959.

[22] *W. O. Statton* and *P. H. Geil*, J. appl. Polymer Sci. *3*, 357 (1960).

[23] *A. Keller* and *A. O'Connor*, Discuss. Faraday Soc. *25*, 114 (1958).

[24] *N. Hirai, Y. Yamashita, T. Mitsuhata*, and *Y. Tamura*, Rep. Res. Lab. Surface Sci. Okayama University *2*, 1 (1961).

[25] *W. O. Statton*, J. appl. Physics *32*, 2332 (1961).

[*] Details of the experimental technique and evaluation of the data will be reported elsewhere.

[**] With crystals with a smaller folding period, a stronger increase in the period also occurs below this inflection (cf. [26]).

[26] *E. W. Fischer* and *G. F. Schmidt*, unpublished.

There may be a connection with the results of nuclear magnetic resonance measurements [27], according to which the mobility of the segments starts within this temperature range. It should be mentioned that, in order to exclude any possible effect of the cooling

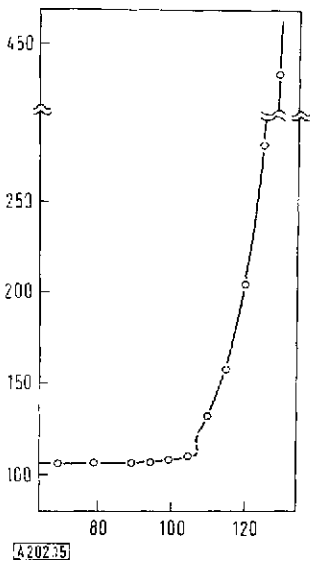


Fig. 15. Temperature dependence of the long period of polyethylene single crystals crystallized at 70 °C from a dilute solution in tetrachloroethylene. Annealing time: 24 hrs.
Ordinate: Length of the long period [Å]
Abscissa: Temperature [°C]

process on the long period, we recorded the small-angle diffraction at the annealing temperature with a camera according to *Kiessig*. The values obtained from these experiments are in good agreement with the values obtained with samples at room temperature, especially with regard to the time dependence of the long period. Still, these values were all a few ångstroms higher (about 10%). At present we are unable to offer an unambiguous explanation for this.

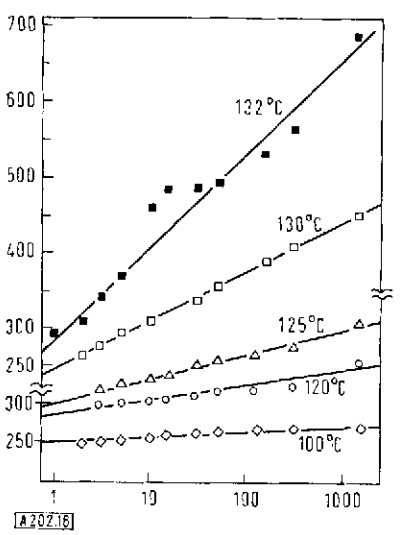


Fig. 16. Dependence of the long period of the quenched and subsequently annealed polyethylene on the annealing time.
Ordinate: Length of the long period [Å]
Abscissa: Time [min].

[27] *W. P. Slichter*, J. appl. Physics *32*, 2339 (1961).

The time dependence of the long period at different annealing temperatures is shown in Figs. 16 and 17. In both quenched bulk polyethylene and single crystals, the long period again increases linearly with the logarithm of the time. Large deviations only with the

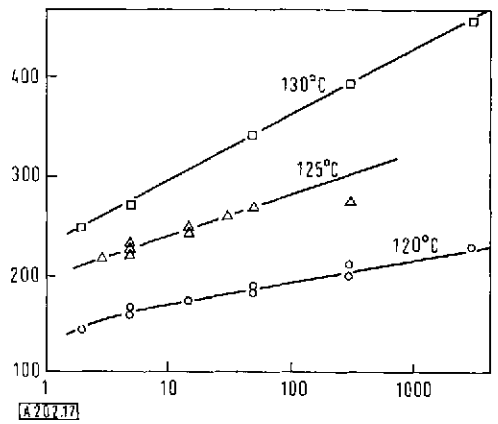


Fig. 17. Dependence of the long period on the annealing time for polyethylene single crystals precipitated at 80 °C from a solution in xylene
Ordinate: Length of the long period [Å]
Abscissa: Time [min]

quenched polyethylene at 132 °C. At the present time we are unable to offer an explanation for this. According to *Hirai* [24], the long periods of polyethylene single crystals increase stepwise. We have so far been unable to observe this effect and assume that it was produced by the latter's measurement method (the same sample was repeatedly cooled and reheated for photographing the diffraction pattern).

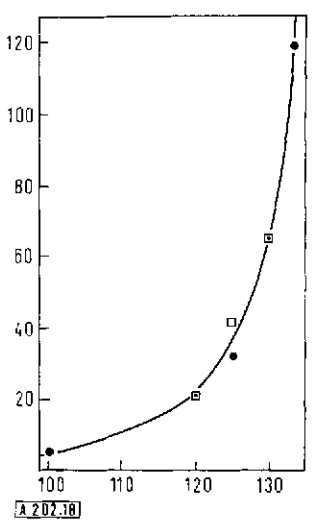


Fig. 18. Temperature dependence of the gradients K of the logarithmic curves from Eq. 1 for unstretched, annealed polyethylene (—●—●—) and for polyethylene single crystals (—□—□—).
Ordinate: K values from Eq. 1 [Å]
Abscissa: Temperature [°C]

In both unorientated bulk material and single crystals, the long period increases at a much greater rate than in stretched polyethylene. The temperature dependence of the constant K from Eqs. 1 and 2 is shown in Fig. 18. To a good approximation, the same value is found for quenched material and single crystals. This again is

evidence that both preparations behave very similarly during annealing and are quite different from stretched material.

V. Changes in Crystallinity during Annealing

The growth of the long periods described in the preceding sections occurs within a temperature range which approximately corresponds to the so-called "melting range" of polyethylene. In this range, one observes a decrease in the degree of crystallinity, which is dependent on the temperature and any thermal pretreatment of the sample; this phenomenon is called "partial melting". Since one must assume that the growth of the long period necessitates a complete transformation of the microstructure, the question arises whether some sort of relationship exists between this recrystallization and the partial melting. It is in fact to be expected that two processes are necessary for the growth of the long period: at least partial melting of the original structure, and recrystallization, which leads to new crystallite dimensions and therefore to a new long period. The superposition of the two processes should be observable from the manner in which the crystallinity changes with time. As will be shown, this is so with single crystals and with unstretched polyethylene. Because of the overlapping of the two processes, at a certain time, the crystallinity is at a minimum. With orientated polyethylene, such an effect does not occur or only occurs to a very small extent.

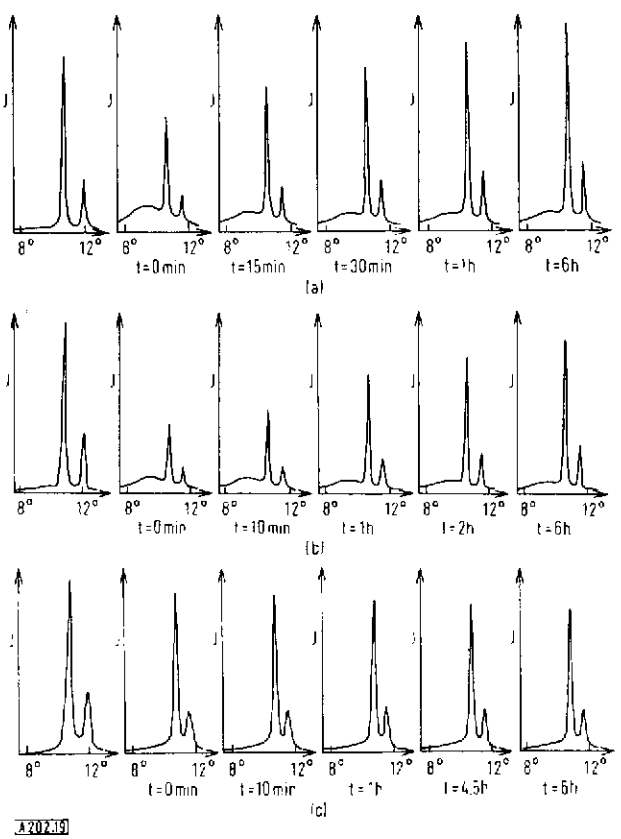


Fig. 19. Time dependence of the X-ray diffraction pattern of several polyethylene preparations during annealing. The first diagram of each series was obtained at room temperature.

a) polyethylene single crystals crystallized at 80 °C from a solution in xylene, annealed at 130 °C
b) polyethylene quenched from the melt, annealed at 130 °C
c) drawn polyethylene, annealed at 132 °C
Ordinate: Intensity of the X-ray reflections
Abscissa: Scattering angle

The melting of polyethylene single crystals during annealing can be demonstrated by means of wide-angle X-ray diffraction [2]. In Figs. 19a–c, the change with time of the X-ray patterns of three samples is shown. With single crystals and samples quenched from the melt, the first two crystalline reflections (110) and (220) nearly disappear and are replaced by an amorphous halo. On further annealing, their intensity increases again. In stretched polyethylene the intensity decreases somewhat because of the raise in temperature, but it remains constant with time. Only after cooling to room temperature does the higher crystallinity (relative to the starting sample) resulting from the annealing process become detectable.

In these experiments, it was not possible to bring the samples instantaneously up to the annealing temperature. Since the samples are already changing during the heating up, no quantitative comparisons with density measurements can be made.

For density measurements, the annealed samples were quenched in ice water. The density was measured at 30 °C in a gradient tube [*]. The dependence of the density on the annealing time at various temperatures is shown in Figs. 20a–c. For the single crystals, the density first decreases rapidly and then slowly increases again. The higher the annealing temperature, the lower the minimum. Annealing for longer times leads to a further increase in density, which soon exceeds the value for the unannealed sample [28].

A density minimum also occurs at higher temperatures with quenched polyethylene albeit somewhat later (Fig. 20b). These results are in agreement with observations of *Kovacs* and *Gubler* [29] and of *Rabesiaka* and *Kovacs* [30]. The latter authors measured the effect of annealing on the specific volume of the quenched samples dilatometrically at the annealing temperature. The density minima occur at the same times but are much more pronounced, since during the quenching the partially molten state can only be partially frozen. This could also be the reason why we did not observe minima at lower temperatures.

Stretched polyethylene behaves differently. The density increases continuously with the annealing time, without passing through a minimum (Fig. 20c).

This different behavior was also observed during measurements of optical birefringence, for which the

[*] We have not yet undertaken dilatometric experiments because only a very small amount of material is obtained during the preparation of the single crystals from very dilute solution, and besides, the effects of interest to us occur within relatively short time periods. The construction of a dilatometer for these investigations is planned.

[28] The density of the unannealed single crystals depends on the temperature of crystallization [26].

[29] *A. J. Kovacs* and *M. G. Gubler*, Lecture, IUPAC-Symposium on Macromolecules, Wiesbaden (Germany) 1959.

[30] *J. Rabisiaka* and *A. J. Kovacs*, personal communication by *A. J. Kovacs*.

samples were not quenched after annealing, but were measured at the annealing temperature. In contrast to the X-ray measurements, because of the small volumes of the samples investigated, here it was possible to use a relatively high rate of heating; the samples could be

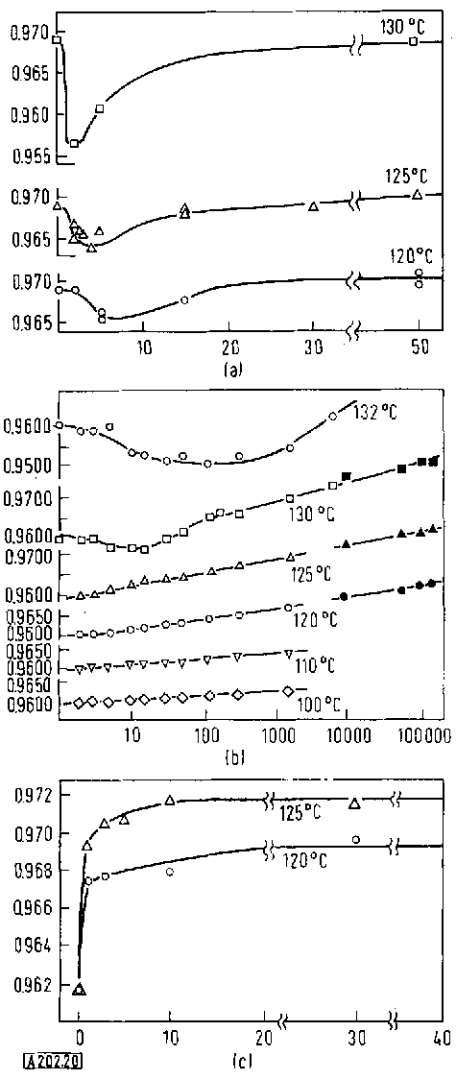


Fig. 20. Dependence of density on the annealing time. After annealing the samples were quenched in ice water and the density was measured at 30 °C.

a) polyethylene single crystals crystallized at 80 °C from a solution in xylene.

b) polyethylene quenched out of the melt (values in bold-faced type after [20])

c) polyethylene drawn at 70 °C.

Ordinate: Density [g/cc]

Abscissa: Time [min]

brought up to the annealing temperature in 10 to 15 sec. For these experiments, cross sections perpendicular to the planes of the crystal lamellae were prepared with a microtome from the single crystal aggregates, so that the birefringence could be measured in the direction of and transverse to the direction of the chains. The dependence of the percent change of birefringence with time is plotted in Fig. 21 for single crystals and for stretched polyethylene. Again, one observes in the first case a well-defined minimum which is progressively lower at higher temperatures.

Summarizing, it may be stated that, during annealing the crystallinity of the single crystals as well as of the isotropic polyethylene quenched from the melt passes through a minimum relative to the time, whereas in drawn samples it increases, albeit more slowly.

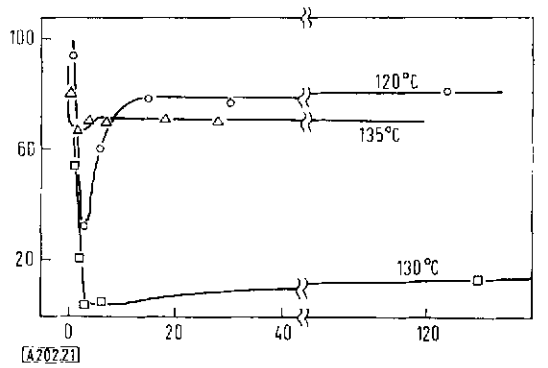


Fig. 21. Dependence of the percent change in birefringence on the annealing time, measured at the annealing temperature. (—o—o—) and (—□—□—) single crystals, (—Δ—Δ—) drawn polyethylene.

Ordinate: Percentage

Abscissa: Time [min]

VI. Relationship between Density and the Long Period of Annealed Polyethylene

As previously mentioned, the minimum in the density can be thought of as arising from superposition of partial melting and recrystallization. If comparisons are made between the densities of the samples and their long periods, an interesting relationship is observed. First, let us consider only samples whose annealing times are greater than the times which correspond to the minima in Figs. 20a and 20b.

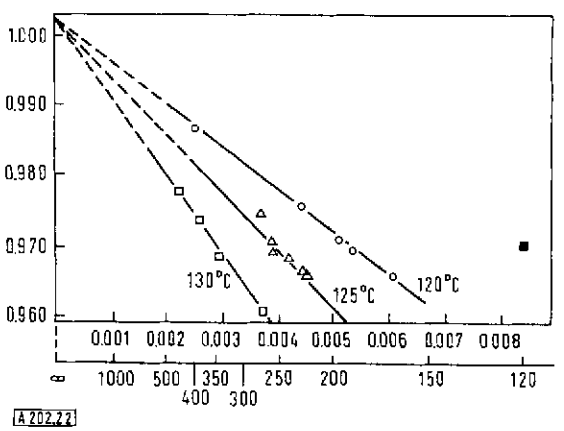


Fig. 22. Relationship between density and long period for polyethylene single crystals annealed at constant temperatures for various lengths of time. (The black square represents the unannealed sample).

Ordinate: Density [g/cc]

Abscissa: Top: reciprocal length of the long period [Å^{-1}];
Bottom: length of the long period [Å]

In Fig. 22, densities *vs* the reciprocal values of the long period are plotted for several single-crystal aggregates annealed for various lengths of time. For each annealing temperature, to a good approximation, a straight line is obtained, so that the relationship between the density ρ and the long period P may be represented by the equation

$$\rho = \rho_k - \frac{A}{P} \qquad (3)$$

where A is a constant dependent upon temperature, defined as the gradient of the straight lines in the ρ *vs* l/P diagram. ρ_k is the density that a single crystal of infinitely long period would possess. This figure shows that ρ_k is independent of the temperature and has a value of

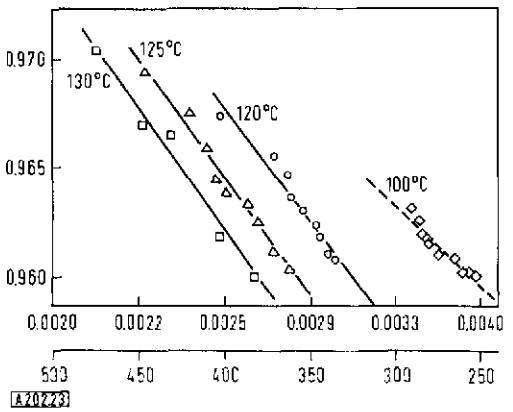


Fig. 23. Relationship between density and long period of annealed undrawn polyethylene.
Ordinate: Density [g/cc]
Abscissa: Top: reciprocal length of the long period [Å^{-1}]
Bottom: length of the long period [Å]

1.002 g/ml. Interestingly, this density of an infinitely large crystal is in good agreement with the density calculated from X-ray data for an ideal crystal. The literature values (after conversion to 30 °C) lie between 1.000 and 1.008 g/ml. The discrepancies probably result from differences in the types of polyethylene, and are of no further concern [*].

The relationship between density and long period in bulk polyethylene is also given by Eq. 3. The values are shown in Fig. 23. At 100 °C, the changes of ρ and P are extremely small for the annealing times used so far. Therefore, we have not made further use of the points at that temperature. At the other temperatures, the gradient and the intercept on the ordinate of the straight lines were calculated according to the method of least squares.

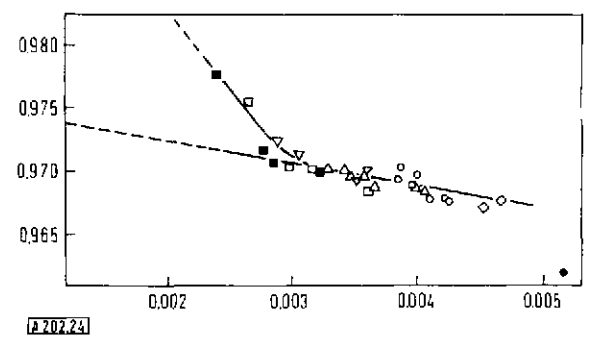


Fig. 24. Relationship between density and long period of drawn polyethylene.
● at 70 °C, drawn *ca.* 16-fold, unannealed
○ at 70 °C, drawn *ca.* 16-fold, annealed at 120 °C
△ at 70 °C, drawn *ca.* 16-fold, annealed at 125 °C
◇ at 50 °C, drawn *ca.* 10-fold, annealed at 100 °C
▽ at 50 °C, drawn *ca.* 10-fold, annealed at 125 °C
□ at 50 °C, drawn *ca.* 10-fold, annealed at 130 °C
■ at 50 °C, drawn *ca.* 10-fold, annealed at 132 °C
Ordinate: Density [g/cc]
Abscissa: Reciprocal length of the long period [Å^{-1}]

[*] These deviations correspond to variations of only about ± 0.02 Å in the lattice constants.

A value for ρ_k of 1.0033 ± 0.0010 g/cc was obtained, in excellent agreement with the value found for single crystals. Thus it was confirmed experimentally that there is a simple reciprocal relationship between density and long period. Extrapolation to infinitely large crystals gives the density of the polyethylene crystals.

With drawn samples (Fig. 24), despite deviations in the points measured, two fundamental differences, from the other two preparations are found: first, the measured points do not lie on a straight line that gives an intercept on the ordinate ρ equal to the ideal density as determined by the X-ray method, and, second, the position of the measured points on the stretched-sample curve do not permit identification of the corresponding annealing temperatures.

VII. Discussion of the Results

Although our measurements and the theoretical interpretation of our results have not yet been completed, we would like to point out some consequences which may be of significance for understanding the thermal behavior of crystalline high polymers.

The relationship between density and long period of the annealed samples is considered first, utilizing the simple and obvious model of Fig. 25. Laterally extended crystallites of density ρ_k with a distance P between their centers of gravity are separated by an amorphous boundary layer of thickness d and density ρ_a. One obtains for the average density ρ of this arrangement

$$\rho P = \rho_k(P - d) + \rho_a d$$

or

$$\rho = \rho_k - \frac{d(\rho_k - \rho_a)}{P} \qquad (4)$$

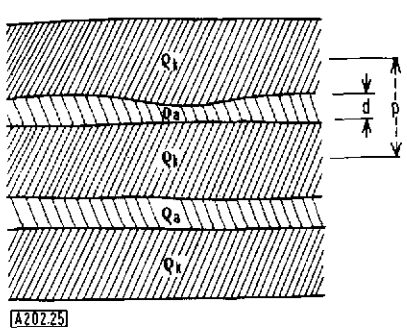


Fig. 25. Schematic representation of the structure of crystalline high polymers with interval P between the crystallites and thickness d of the amorphous boundary layer.

This relationship is identical with Eq. 3, which was determined experimentally, if we set

$$A = d(\rho_k - \rho_a) \qquad (5)$$

Thus, our findings may be interpreted easily using a crystalline/amorphous two-phase model with the following properties: 1. the so-called "amorphous" region is identical with the boundary layer between two crystalline lamellae, and 2) the product of the thickness d of the boundary layer times the difference in density

($\rho_k - \rho_a$) between it and the crystalline phase is constant for a given temperature. In other words, this means that the entire difference between the density of the annealed samples and the X-ray density is caused by the lower density of the crystal boundary layers, the thickness of these grain boundaries between the consecutively stacked crystals being dependant on the temperature.

This temperature dependence suggests that there may be some relationship between the group of straight lines plotted in Figs. 22 and 23 and the partial melting effect generally observed in high polymers. In this connection, attention is called to the value obtained for unnanealed single crystals in Fig. 22. If the temperature of the single-crystal aggregate is raised, at first the density defect caused by the boundary layer increases, until it attains a value appropriate for the particular annealing temperature. As a result, the density decreases. Simultaneously, the long period begins to increase, the measured point moves along the line belonging to the corresponding temperature, and the density again slowly increases.

The same considerations apply to bulk polyethylene (Fig. 23). If we also plot in Fig. 23 the values of samples with annealing times before the density minimum, then these points lie on a curve joining the point for the unannealed sample to the straight line corresponding to the annealing temperature. The higher the annealing temperature, the lower the density of the sample becomes.

Stretched polyethylene behaves completely differently. In this case, straight lines corresponding to some specific temperature are not obtained on plotting ρ *vs* (1/P) (Fig. 24). Not only does the long period increase during annealing, but there is also a corresponding continuous increase in the density (cf. Fig. 20c). No partial melting occurs.

Although our measurements urgently require supplementation by dilatometric experiments in order to exclude density changes during the quenching, we may present the following tentative interpretation of our results. It can be show that at constant long period P, the number of chain members per loop of a folded chain depends on the temperature [31]. This number increases with increasing temperature so that crystallite melts upon heating, starting from the surface areas containing the loops, and the thickness, d of the boundary layer increases. This is not the case with continuous chains such as are shown in Fig. 1, as calculations show [*]. Hence, the differences exhibited in Figs. 22–24 between the single crystals and quenched polyethylene on the one hand, and the stretched material on the other, can be interpreted in the following manner: in the first two materials, the chains are folded at the boundary areas of the crystallites, whereas, in the stretched material, the crystallites are interconnected by chains which pass through the amorphous region. Furthermore, the uniform value obtained for the constant K (Fig. 18), which governs the rate of growth of the periods, permits the conjecture that the single crystals and polyethylene crystallized from melt have basically the same structure. The increase of the long period in unstretched polyethylene up to values of 650 or 1000 Å [20] does not exclude the possibility of chain folding, which might otherwise be assumed not to exist, since the folding period in this case approaches the same order of magnitude as the chain length. The experiments of *Hess* and *Kiessig* [32] on mixtures of soaps of different chain length, and especially the work of *Zahn* et al. [33] and of *Kern* et al. [34] on the long periods of oligomers, clearly demonstrate that chain folding is also possibile when the chain length is only slightly larger than the folding period. Attention was already called above to relevance of this fact to the theory of chain folding [2].

Now we turn our attention to the growth of the long period. With all of the three materials investigated by us, the long period increased continuously with the logarithm of the time (cf. Figs. 10, 16, and 17). By differentiation of Eq. 2, it is easily found that the rate $(\delta P/\delta t)_T$ of the growth of the period is given by the relationship

$$\frac{\delta P}{\delta t} = Ce^{-BP} \quad (6)$$

The rate therefore decreases exponentially with increasing long period. The constants C and B are dependent on temperature and may be calculated from the quantities t_0, K, and P_0 in Eq. 2.

We have not yet found a satisfactory explanation for the relationship formulated in Eq. 4; however, we do believe that we can eliminate a few possible explanations for the growth of the long periods. For example, it is often assumed that the long period grows during annealing in the melt owing to melting of the smaller crystallites whereby, the average size of the crystallite increases. With single crystals, this is certainly not the case, since *Hosemann* et al. [35] found by analysis of the breadths of the small-angle X-ray diffractions, that the average relative variation in thickness of the crystal lamellae was no greater than 4 %. However, we consider this explanation to be improbable for polyethylene crystallized from the melt, too.

Hirai et al. [24] suggested another interpretation for single crystals. They assumed that the increase of the long period proceeds by a repeated secondary nucleation, the nucleation energy being dependent on the long period P. The constant B in Eq. 6 would then vary only slightly with temperature. According to the results of *Hirai* et al., this is actually the case, whereas our measurements gave a strong temperature dependence (cf. Figs. 11 and 18). Again, we believe that this discrepancy results from the fact that *Hirai* et al. cooled the samples between the two annealing times used for the measurement of the long period.

The dependence of the long period on time according to Eq. 2 also precludes the assumption that the long period is related to the size of the critical nucleus, as was postulated by *Mandelkern* et al. [20] for primary iso-

[31] *E. W. Fischer*, unpublished.

[*] Here it is assumed that the ratio of the length of the chain segments in the amorphous region to the distance between the crystallite boundary layers does not exceed a certain value which can be dealt with in calculations, *i.e.*, the chain may not form loops of unlimited size.

[32] *K. Hess* and *H. Kiessig*, Chem. Ber. *81*, 327 (1928).

[33] *H. Zahn* and *W. Pieper*, Kolloid-Z. *180*, 97 (1962).

[34] *W. Kern, I. Davidovits, K. J. Rauterkus*, and *G. F. Schmidt*, Makromolekulare Chem. *53*, 106 (1961).

[35] *R. Hosemann, R. Bonart*, and *M. Klein*, Physik. Verh. *11*, 162 (1960).

thermal crystallization of polyethylene. Furthermore, the dependence of the long period on the stretching temperature cannot be explained by this assumption because the temperature dependence shown in Fig. 13 does not agree with it. This will be discussed in detail elsewhere. It should be mentioned here, however, that the long periods obtained at different stretching temperatures only differ by an added constant from those obtained at the same temperature for single crystals obtained from dilute solution. Therefore, the temperature dependence can be explained in terms of the theory of thermodynamic stability of macromolecular crystals developed by us [36]. From this theory, it follows that, above a certain temperature which according to *Reinhold* [36] lies between 100 and 120 °C, the size of the crystallite in the chain direction is no longer determined by a minimum in the density of free energy. Above this temperature, only infinitely large crystals (in the direction of the chain) are thermodynamically stable. During annealing, the system tends towards this state.

In conclusion, attention is called to a possible relationship of the growth of the periods to the phenomenon of "secondary crystallization". This term designates the process during the isothermal crystallization of high polymers, which follows the main crystallization associated with the growth of morphological entities (spherulites). Secondary crystallization is observed as an increase in density of long duration. If the time dependence of the long period according to Eq. 2 is substituted in Eq. 3, then curves are obtained for the dependence of the density on time which qualitatively agree with the measured curves [37]. It can therefore be assumed that the increase in density observed during secondary crystallization is caused by the growth of the long period.

Thanks are due to Prof. Dr. H. A. Stuart for his many valuable suggestions and advice, to our co-workers for their aid in the experiments, and to the Deutsche Forschungsgemeinschaft for providing equipment.

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[36] *A. Peterlin, E. W. Fischer,* and *R. Reinhold,* J. Polymer Sci., in press.

[37] *S. Buckser* and *L. H. Tung* J,. physic. Chem. *63*, 763 (1959).

The Patenting of Chemical Inventions in the Federal Republic of Germany

BY DR. V. VOSSIUS, PATENTANWALT, MÜNCHEN (GERMANY)

Under German Patent Law, the patenting of chemical inventions is subject to special rules which need not be observed with inventions in the mechanical field. These rules will be discussed in detail.

I. Exceptional Provisions of Section 1, § 2 of the Patent Act

Under German Patent Law, the following inventions are excepted from patent protection:

1. Inventions, the exploitation of which would be contrary to law or public policy, unless the provisions of law only restrict the offering for sale or trading of the subject matter of the invention or, if the subject matter of the invention is a process, of the product directly produced by the process;

2. Inventions of foodstuffs, luxury foods, medicaments, and materials produced by chemical means, unless the inventions concern only a specific process for producing the products.

Owing to this provision, the claim under public law of an inventor or applicant to the granting of a patent for his invention is considerably restricted. In all other fields, the new products themselves may be patented, whereas in the case of foodstuffs, luxury foods, medicaments, and materials produced by chemical means, exclusively the processes for producing these products are patentable. Without mentioning the reasons which prompted the legislator to draft these exceptional provisions, the consequences resulting from this regulation of the patent protection of chemical inventions in the Federal Republic of Germany will now be discussed.

According to Sec. 1, § 2, No. 1 of the Patent Act of 1953, inventions, the exploitation of which would be contrary to law or public policy, were excepted from patent protection. In accordance with the new Patent Act effective as of July 1st, 1961, patents are also granted for new inventions concerning materials, the sale of which is restricted by German law (*e.g.* Act for Amending and Supplementing the Foodstuff Act, of December 21st, 1958; the decree on tobacco and tobacco products of December 19th, 1959). Such inventions are, for example, processes for the preservation of foodstuffs with specific preserving agents, processes for treating foodstuffs with high-energy radiation, treatments for increasing the yield in meat of useful animals by means of *e.g.* anabolic steroids, and other inventions relating to the production and treatment of foodstuffs; these inventions may now be patented without difficulties. The products obtained from these processes cannot, however, be offered for sale or sold in Germany, since or if they do not correspond to the legal provisions on foodstuffs. However, no objections are made on the German side against exporting these products.

II. The Effect of a Process Patent

In order to prevent the circumvention by import of products produced in patent-free countries abroad of patents on processes for the production of foodstuffs, luxury foods, medicaments, or a material produced by chemical means, it is stipulated in Sec. 6, sentence 2, of the Patent Act, that a patent which is granted on a process also covers the product directly produced according to this process. This provision is of great importance in practice.

According to Sec. 6, sentence 1, of the Patent Act, the patent entitles the patent holder alone to produce the product of the invention commercially, to market it, to offer it for sale, and to use it. If a patented process is used by another person in Germany, both this other user of the process and the commercial user of the product directly produced according to the process infringe the patent. If the process patented in Germany is used in patent free countries abroad, this does not interfere with the German Patent Law since it is applicable in the Federal Republic of Germany only. According to Sec. 6, sentence 2, of the Patent Act, however, the products directly produced by this process must not be imported into Germany.

On the basis of this same sentence from the Patent Act, the patent holder has the advantage of being able to designate not only the process, but also the direct product thereof as being patented, *e.g.* by "protected by German Patent".

Sec. 6, sentence 2, of the Patent Act is also applicable to the actually unpatentable foodstuffs, luxury foods, medicaments, and materials produced by chemical means insofar as these products are the "direct" products of the patented process.

The question as to what is to be regarded as a "direct" process product can best be answered by stating some concrete cases.

The word "direct" allows of various interpretations:

a) The different production steps from the raw products to the finished products may be meant. One may say then that the remoter the production step is from the raw product, the less one can speak of a direct product in the sense of Section 6, sentence 2, of the Patent Act.

b) One may also say, however, that the different production steps are inessential and that the important point is rather the main market value of the raw product obtained from the process and imparting the peculiar character to the finished product.

Legal practice is not uniform in this respect. In some decisions, the word "direct" is understood in the sense mentioned under a), other decisions are based on the interpretation under b).

The decision of the Supreme Court of the German Reich of May 24th, 1909 in criminal procedures [1] states that the finished product is not a direct product if it has been produced from the raw product or semimanufactured product obtained from the patented process. Other decisions consider the "main market value" of the finished product or its "peculiar character" to be decisive. In the decision of the Supreme Court of the German Reich of May 13th, 1916 [2] it is stated:

"the very properties (*i.e.* resistance to water, acids, alkalis, heat, and coldness), the creation of which is the pronounced object of the patented process, are transferred to the plaintiff's paints in which he uses his binder and are so embodied that they impart to the paints, *i.e.* to the new product, a peculiar character and the main market value, compared to which the light and decorating effect of the paint is of secondary importance. If in Section 6 of the Patent Act the patent protection is restricted to the "direct product" of the patented process, by no means will any purely chemical change render the product unprotected; rather is it to be avoided that an article be regarded as the product of a patented process even if it no longer shows those features, in the creation of which the commercial importance of the patented process resides".

The Supreme Court of the German Reich [3] decreed that

a) there is no direct product if the patented process leads to a raw product or semifinished product first and another process must be applied to produce the finished product;

b) there is a direct product if a material that had already been subjected to a different process is now processed according to the patented process or if, for producing the product, two or several processes are applied, of which the patented process formed an essential part.

According to a decision of the German Federal Supreme Court of February 16th, 1951 [4], a patented repairing process does not include protection of a repaired machine part. This machine part is not a product of the process in the sense of Sec. 6, sentence 2.

From the above statements, it may be concluded that each case can only be decided individually as to whether or not a product is to be regarded as a "direct" one in the sense of Sec. 6, sentence 2, of the Patent Act. There is no general rule. There is a direct product in all those cases where the patented process has exclusively or predominantly led to the formation of the product. There is a direct product when this product has not been altered decisively in its properties and its market value by other process steps. As a rule, subsequent chemical reactions of a chemical material would alter this product to such an extent that it is no longer a direct product. In the case of mechanical processing, however, *i.e.* the transfer into a specific shaped structure (*e.g.* the shaping of synthetic materials), the situation may be different. The manufacture of film from a plastic produced according to a patented process using a calendar does not abolish the directness of the product, since its properties and market value have not been changed by this processing. However, the import of tires which contain carbon black as a filling material and which have been produced according to a process patented in

[1] Blatt für Patent-, Muster- und Zeichenwesen *1909*, 8.

[2] Blatt für Patent-, Muster- und Zeichenwesen *1916*, 135.

[3] Blatt für Patent-, Muster- und Zeichenwesen *1937*, 29.

[4] Blatt für Patent-, Muster- und Zeichenwesen *1951*, 314.

Germany would appear not to be regarded as a patent infringement, since, according to usage, the carbon black (in contrast to the rubber, for example) is not the decisive component of the tires. If a medicament produced according to a patented process is mixed with other substances for producing, for example, suppositaries, ointments, tablets, *etc.*, the final product is still a direct one, even if several process steps are required for making it. According to a decision of the Provincial Court of Düsseldorf (4/0/333/60 of March 21st, 1961; this decision has not yet become legally valid), the import of suppositaries containing the antibiotic chloramphenicol is an infringement of a patent covering the production of chloramphenicol by chemical means, because the conversion of the antibiotic into a special form for application and the mixing with other substance do not alter its character as a direct process product. The market value of the suppositaries resides in their content of the chemical substance chloramphenicol, which is protected by the process patent [4a].

The conditional product protection, *i.e.* the product protection connected to the production process as provided for in Sec. 6, sentence 2, of the Patent Act, thus enables the patent holder to forbid the import, the offering for sale, and the sale of a product produced according to the patented process in patent-free foreign countries, provided the patent holder can prove that these products are, in fact, produced according to the patented process. It is often very difficult for the patent holder to furnish such proof. Hence, Sec. 47, § 3 of the Patent Act rules that, in the case of an invention concerning a process for producing a new product, any product of equal character is regarded as produced according to the patented process until the contrary is proven. In civil proceedings, it is up to the defendant to convince the court of the fact that his product has been produced according to a different process not interfering with the scope of protection of other patents.

III. Materials Produced by Chemical Means

Materials produced by chemical means in the sense of Sec. 1, § 2, of the Patent Act comprise only uniform compounds, *i.e.* defined chemical individuals, the direct formation of which was caused by a chemical reaction, *e.g.* a salt formation, condensation, polymerization, complex formation, or the like. Since chemistry is the study of materials and changes of materials (physics, the twin science, is the study of states and the change of states), artificial elements and isotopes are to be regarded as materials produced by physical-chemical means. Therefore, a claim of approximately the following wording:

"Radiator of hard gamma-rays having a half-life of 14.3 days, characterized as radiophosphorus and having an atomic weight of 32"

appears to be impermissable in view of the exceptional provision of Sec. 1 of the Patent Act, since this claim characterizes a chemically uniform material. As far as I know, the question of allowability of product claims in the field of the production of artificial radioactive elements has not yet been the subject of a decision of a Senate of the Patent Office or of the Federal Patent Court.

Owing to the non-patentability of products produced chemically, the Patent Office even rejects product claims directed to a specific purpose, such as:

"Nematicide consisting of the substance X";

however, it allows claims which show that the product is not a uniform compound, but a mixture suitable for a specific technical purpose, for example:

"Nematicide, characterized by a content of the compound X as active constituent".

Technically utilizable mixtures of chemical products in correlation with their purpose of use are thus patentable, except for mixtures of foodstuffs, luxury foods, and medicaments, since the patenting thereof would mean nothing other than the protection of products as such, and this is forbidden by law.

IV. The Patentability of Chemical Processes

Patent jurisdiction distinguishes between two groups of chemical processes:

a) processes of analogy, *i.e.* processes based on known methods which are within the ability of those skilled in the art and which in all probability would lead to the expected result of the reaction.

b) chemically peculiar processes, *i.e.* processes in which one could not foresee that the compounds, means, or measures used in this process would bring about the specific effect. Peculiar modifications of known methods also belong to this group.

Processes for producing chemical products may lead to intermediates or finished products. The production of most chemical materials takes place in multi-stage processes. The products formed in each of these stages are in the proper sense designated as intermediates. However, intermediates are obtained not only in multi-stage processes, but may also be obtained in a one-stage reaction. Reference is made in this context *e.g.* to, the production of nitrobenzene, an important intermediate in organic chemistry obtained by one-stage nitration of benzene. In the case of nitrobenzene, the designation "intermediate" is justified for reasons of organization, operation, or economy, which are of importance to the producer or the person processing the intermediate.

As with any other invention in the field of industry, a process for producing a chemical product must fulfil the following conditions required for patenting:

1. It must be novel as compared to the knowledge of those skilled in the respective art;

2. It must not be self-evident, *i.e.* a certain degree of inventive effort must have been made to find it;

[4a] *E. v. Pechmann*, Gewerbl. Rechtsschutz, Urheberrecht *64*, 8 (1962).

3. It must bring about a technical advance,

4. It must be commercially utilizable.

In Table 1, the patentability of some possible variations of chemical processes is indicated:

Table 1. Patentability of production processes

Process	Patentability of the production process for:			
	Intermediate		Final Product	
	new	known	new	known
A. Process of analogy: Starting compound known	no	no	yes	no
B. Process of analogy: Starting compound new	no	no	yes	yes
C. Peculiar process: Starting compound known	yes	yes	yes	yes
D. Peculiar process: Starting compound new	yes	yes	yes	yes

Table 1 shows that a production process for either an intermediate or a final product is patentable if the process itself represents an advance in the art, *i.e.* if the invention resides in the new mode of operation (Processes C and D).

However, the Processes A and B of the table, *i.e.* processes making use of so-called trivial modes of operation, are of special interest. These processes are especially important for the chemical industry because it is becoming increasingly seldom that basically new and/or peculiar reactions are found in chemistry. These types of processes and their patentability will now be discussed in more detail.

A. a) Process of Analogy; Starting Compound Known, Reaction Product New

This case is probably the most important one, since it occurs most frequently. New substances are formed starting from known substances and using known methods. The question of whether such a process, which does not differ from the known art in the type of the process, but only in the substances employed, and whose result can be foreseen with certainty by a chemist, is patentable at all was decided for the first time by the Supreme Court of the German Reich in 1889 in the case of a process for producing a new azo dye, Congo red. It was foreseeable at that time that by reacting benzidine, which was diazotized in the usual manner, with 1-naphthylamine-4-sulfonic acid an azo dye would be produced and that the coupling would occur at the 2-position of the naphthalene system. However, the characteristic of the resulting product of dying cotton directly, *i.e.* without mordant, were not foreseeable and were surprising since they became obvious first when the product was employed. The Supreme Court of the German Reich confirmed the patentability of the production process, which was actually trivial, because of these surprising technically valuable characteristics of the new product. These characteristics, inherent in the new product, radiate figuratively back to the production process and make it appear to be inventive.

In judging the patentability of processes for the production of new medicaments according to analogous processes, the therapeutic effect has been put on a par with the technical effect. Therefore, such processes are patentable in spite of their triviality if the new product is more effective pharmacologically than other known products.

In the case of analogous processes whose patentability is based only on the surprising, technically valuable characteristics of the new process products, numerous examining departments of the German Patent Office request the inclusion of this "technical effect" in the preamble to the claim, for example "process for the production of an anti-knock compound for gasoline engines, characterized in that X is made to react with Y according to methods known *per se*". Objections raised by some applicants to the effect that this wording would largely restrict the scope of protection of the patent, that merely the use of the product produced according to the process of analogy as an anti-knock compound would be protected, and that third parties would be allowed to use the product for other purposes, are unjustified. In view of Sec. 6, sentence 1 of the Patent Act any use for all other purposes is protected provided the product is produced according to the claimed process. The statement of valuable physical, pharmacological, or other technological properties in the preamble to a claim does not impair the right to forbid the use of the patented products, it is to be regarded merely as a statement on the industrial utilizability of the process product.

Processes of analogy for producing new intermediates are excepted from patent protection according to German Patent Office practice (see, *e.g.* the action of the 5th Senate of Appeal of the German Patent Office of March 19th, 1957 [5]) since, they do not meet one of the basic requirements for patenting, namely they do not constitute a "novel invention". A process of analogy leading to an intermediate is not an invention either of a process or of a material. Moreover, the possibly valuable properties of the final product produced from the intermediate do not make the production process of the intermediate patentable.

A. b) Process of Analogy; Starting Compound Known, Reaction Product Known

A process which, starting from known compounds, leads to a known reaction product or intermediate is not patentable if the formation of the reaction product is foreseeable in all probability. A new purpose of use found for this product cannot be adduced in support of the trivial process, for this purpose of use has nothing to do with the means of the process. Invention of an application of a known product in a specific industrial field merely allows the grant of a use patent; a therapeutical use, however, cannot be protected in view of the exceptional provisions for medicaments according to Sec. 1, § 2 of the Patent Act. If a surprising effect, (a "process effect") is attained in a *per se* known trivial

[5] Mitt. dtsch. Patentanw. *1957*, 116.

process *e.g.* a surprisingly high yield of a known reaction product, or if a general technical prejudice of those skilled in the art is overcome, *e.g.* by use of an especially cheap starting compound, then according to patent jurisdiction, this constitutes not a process of analogy but a chemically peculiar process.

B. a) Process of Analogy; Starting Compound New, Reaction Product New

According to the practice of the German Patent Office, a chemical process, the starting materials and end products of which had been unknown on the filing date of the application and the problem associated with which did not exist at all in view of the state of art, is not considered to be a typical process of analogy self-apparent to those skilled in the art, even if the reaction underlying the claimed process is one of analog, *e.g.* employment of a generally known method (5th Senate of Appeal of October 7th, 1952 [6]. Consequently, a special effect of the final product need not be claimed for the patentability of such a process. The production of the new starting materials, however, must be stated in the specification in a way such that it can be repeated

B. b) Process of Analogy; Starting Compound New, Reaction Product Known

According to a decision of the 5th Senate of Appeal of the German Patent Office [7], a process whose starting material is new but whose final product is known cannot be regarded as a process of analogy, because, in the case of a material unknown from the very beginning, statements on the practicability of a reaction cannot be made, even if in the reaction a generally known process in employed.

When applying this legal judgement to processes for producing intermediates, in my opinion, it logically follows that in cases involving new starting materials or new starting materials and new end products, the processes as such ought to be patentable.

V. The Arrangement of Patents for Chemical Inventions by Choosing the Wording of Specific Types of Claims

Sec. 26, § 1, sentence 5, of the Patent Act stipulates that, at the end of the specification of an application, it should be stated what is to be protected as patentable (claims). The selection of the types of claims for a patent in order to protect the patented invention to the greatest possible extent from circumvention is of great significance in practice. The significance resides in the fact that the claims – as will be discussed in greater detail under VI – are the first and foremost means of interpretation for determining the inventive idea of a patent. Careful attention has to be paid to the wording of the claims since anything which cannot be gathered from the claims, if necessary with the help of the statements in the specification and perhaps of accompanying drawings, cannot be protected. In a patent, four types (categories) of claims may be used:

a) process claims,
b) use claims,
c) product claims,
d) apparatus (device) claims.

It is not fully within the discretion of the applicant to choose one of these types of claims. The decision on the form of a patent rather depends on objective points of view, *e.g.* the state of the art. In each case, the essence of the invention has to be ascertained and the claims are then worded accordingly.

For chemical inventions, the categories a–c, *i.e.* process claims, use claims, and product claims, are primarily used; however claims directed to an apparatus for carrying out specific chemical reactions are also encountered occasionally. In view of the exceptional provisions of Sec. 1, § 2, of the Patent Act, inventions of materials produced by chemical means (see under III) can be protected only by the categories a and b, process patents and use patents. Owing to the prohibition of product patents on foodstuffs, luxury foods, and medicaments, however, the grant of a use patent on these products is not possible. Mixtures of chemical substances suitable for specific technical purposes of use, *e.g.* fuel mixtures, polymer mixtures for the production of shaped structures, specific catalysts *etc.*, in the formation of which a chemical reaction does not take place, may be protected by the product patent category.

The legal consequences of a patent's belonging to a specific category are different. As already discussed, if the claims are directed to a production process, the scope of protection of the patent, according to Sec. 6, sentence 2, of the Patent Act (see under II), also covers the products directly produced by this process. Another legal consequence is the facilitation of furnishing proof of the production of a new material, *i.e.* a reversal of the burden of proof provided for in Sec.47 § 3, of the Patent Act in the case of patents for new products. Again, if a production process for a new dye is protected by patent, other parties may not produce this dye, offer it for sale, or use it in the Federal Republic of Germany if made by the same method, but goods colored with this dye in patent-free foreign countries may be imported into the Federal Republic of Germany, since they are not direct products of the production process. Of course, the dye may also be produced by a different independent method and may then be applied or sold, *etc.*

When choosing the process patent category, as already discussed above, the scope of protection covers not only the disclosed use on which the invention is based (in processes of analogy), but also includes any use for any other purpose, provided the product has been produced according to the claimed process, even if other patents for specific purposes of use are granted at a later date.

[6] Blatt für Patent-, Muster- und Zeichenwesen *1954*, 477.

[7] Mitt. dtsch. Patentanw. *1957*, 94; this decision cannot be generalized.

Selection of the use patent category – in which case examination by the Patent Office as to whether or not the material to be used is new is inessential – automatically effects that the material itself – including all the possibilities of its production and use – is no longer covered by patent protection; merely its use for producing specific articles or attaining specific technical effects is protected. Consequently, merely the use of the material for the protected or a similar purpose falls under the scope of protection of the patent. Applied to the above example of the dye, this would mean that, in the case of a use patent on the dye, the dyed goods are protected, *i.e.* other parties may not use the dye in Germany, although the dye itself may be produced in Germany by other firms and may be exported.

In the case of a patent claim directed to a product, the scope of the patent covers all types of production and is not restricted to a specific type of production. It is understood that the product must not be a product prepared by chemical means but only a product, in the production of which a chemical reaction does not occur.

Of course, a new process (or an apparatus or a device) for producing an product already patented may be patented, but such a younger patent is then dependent on the earlier product patent (or apparatus patent). The same applies to a use patent, if the subject matter thereof makes use of an earlier patented process or product or apparatus.

Several Categories of Claims in One Application

The problem of whether or not several claim categories may be granted in one application depends on whether or not an inventive complex may be combined under certain aspects to form a uniform invention. Sec. 26, § 1, sentence 2, of the Patent Act stipulates that for each invention a special application is required.

It is the current practice of the German Patent Office to regard an application as being uniform if the application comprises process claims and claims directed to an apparatus for carrying out the process. A process and product, or a process, apparatus, and product may also be claimed in one application, provided there is a uniform complex, *i.e.* provided the application resides in one inventive idea.

There is agreement in legal practice and literature that there are two different patentable inventions if the production process and the use lie in two different fields. In this case, the inventions can be protected only by two separate patents independent of each other. The legal situation is different in every respect, however, if the production and use reside in the same field, *i.e.* if the product obtained from the production process is used "according to determination". The problem becomes complicated when the production process is a chemical process of analogy which can be patented according to current practice of the Patent Office only because the product obtained exhibits surprising technological properties. The same problem arises if a product claim directed to a purpose, and this is to be considered equivalent to a use claim, is drawn up side by side with such a process claim directed to a certain purpose. Objections are raised to drawing up such claims in a single application on the grounds that inadmissible protection is claimed for the production as well as for the use of a chemical invention within the framework of one application and that therefore the subject matter of the application would lack unity. The use of a chemical material for a specific purpose or a mixture containing the material does not necessarily have a technical connection with the production process of the material. Finally, permissibility of these claims together is not possible, because the patentability of both the material and the process of analogy for producing the material is based on the same technological properties of the material and this effect would have to be regarded as being exhausted by one type of claim alone.

It is the practice of the German Patent Office and presumably it will also be the practice of the chemical Senates of Appeal of the Federal Patent Court that, in addition to either a product claim directed to a certain purpose or a use claim, *e.g.* "Insecticides, characterized by a content of the compound X as the active substance", a process claim directed to the process of analogy for producing this active substance cannot be protected by one application, since both the claims do not only relate to the same problem, but also concern the same inventive idea expressed in different terms.

As regards the objection mentioned above about exhausting the technical effect, the following is pointed out: in the examination of a younger application, the concept of exhausted technical effect can be adduced in view of an earlier application in specific cases according to Sec. 4, § 2, of the Patent Act, in order to avoid double patenting. This concept cannot be applied to applications or inventive subject matters in applications of the same date. In the case of the same convention date or filing date, *i.e.* when two identical inventions are received in the Patent Office at the same time, the possibility of protection is not exhausted by one of the applications, but a patent is granted for both applications.

VI. The Scope of Protection of Chemical Process Patents

German Patent Law does not mention the concept of scope of protection. In Sec. 4, § 2 relating to the prohibition of double patenting – and in Sec. 6, § 1 which deals with the patent holder's rights to forbid the use of the patent – mention is made only of the "subject matter of the invention". Sec. 26, § 1, sentence 5, states that, what is to be protected as patentable (claims) is to be defined at the end of the specification of the application. One may say that scope of protection entails matter that goes beyond the characterized direct inventive subject matter of the patent, which is thus surrounded, as it were, by a protectable area of radiation emanating from the essential inventive idea.

The legal practice of the German Federal Supreme Court distinguishes between:

1. The direct subject matter of the invention

which may be derived from the wording of the claims, if necessary with the help of statements in the specification and drawings, but without any further interpretation.

2. The subject matter of the invention

which is the technical idea derived by those skilled in the art from the wording of the claims as a basis and from the patent specification, the drawings and their general technical knowledge of the entire art in the field concerned. The subject matter of the invention also includes plain technical and patent law equivalents as well as patent law and technical equivalents which are not plain.

Plain equivalents in the sense of the Patent Law are means which, instead of equivalent means, are available to those skilled in the art on the basis of their technical knowledge in the respective individual case for solving the problem in question immediately without special consideration. These plain equivalents in the sense of the Patent Law may also be designated as "means most comparable to the wording of the claims".

Equivalents which are not plain also belong to the subject matter of the invention. Equivalents that are not plain are those equivalents which those skilled in the art may find only after special considerations on the basis of their technical knowledge, but without having an inventive idea, *e.g.* by searching the literature.

3. The general inventive idea

The general inventive idea is the idea which those skilled in the respective art and of average ability and knowledge at the moment of the application could derive from the patent without being attached to the wording thereof and without limiting their views to the most contiguous but also without adding inventive matter of their own.

Since the general inventive idea, as compared to the wording of the claims, is neither contiguous – for that is the subject matter of the invention (item 2) – nor resides in an inventive effort, the general inventive idea is any idea which is still close, relative to the wording of the claim.

When ascertaining the scope of protection of a patent in an infringement suit, the subject matter of the invention and the general inventive idea are opposed to each other, since a patent infringer will, as a rule, avoid using the "direct subject matter of the invention", *i.e.* he will avoid working according to the wording of the claims of the patent.

As already stated above, the subject matter of the invention is the technical information which those skilled in the art and possessing average technical knowledge at the filing date of the application could, without inventive effort, gather from the claims when interpreting the claims properly in the light of the specification, the drawings, the general technical knowledge, and the hypothetical knowledge of the state of the art which are considered to be known. In any case, a judge in an infringement suit will, in the first place, have to ascertain the subject matter of the invention. Once the subject matter of the invention has been ascertained, the question may be answered regarding the extent to which the contested infringement makes use of the same or similar (equivalent) means and, therefore, comes within the scope of protection of the patent.

In principle, the judge in an infringement suit need not examine whether the subject matter of the invention is novel, advanced, or inventive over the known prior art. Instead he has to consider the patent as it has been granted. Only if, in an exceptional case, it should prove that the subject matter of the invention is fully anticipated by the known prior art or is anticipated in a technically separable part or if it is fully or partially identical with an earlier right that does not belong to the state of the art, the judge, although he cannot plainly refuse protection on the granted patent, has to avoid gross injustice and, therefore, has to restrict the scope of protection of the patent to the narrowest limit possible which forms an inviolable remainder. This means that, the judge will have to restrict the scope of protection to the mere wording of the claims, in other words to the socalled "direct subject matter of the invention". Therefore, in order to destroy this inviolable remainder, the plaintiff or the defendant has to file a nullity suit at the Federal Patent Court.

The question as to whether or not a patentable "general inventive idea" may be gathered from a patent, in the event of a given case of infringement, is raised only if the contested embodiment does not fall directly under the "subject matter of the invention". In contrast to the case of finding the "subject matter of the invention", the ascertaining of a "general inventive idea" has to be directed specifically to the contested form of infringement. In this case, it need not be considered whether any kind of a general inventive idea may gathered from the patent in suit, but it has to be considered whether or not there is a general inventive idea common to the patent in suit and the contested form of infringement; furthermore, it has to be examined whether or not this common inventive idea comprises the embodiment of the invention expressed in the claims as well as the form of infringement in question and whether or not this general inventive idea may be derived from one of the claims and is disclosed in the patent so that it can be repeated by anyone skilled in the art without any inventive effort. If this is the case, it has further to be considered whether or not the general inventive idea disclosed in this patent in suit is patentable, *i.e.* especially novel, advanced and inventive and whether the applicant did not pronounce a disclaimer or a corresponding restriction excluding the broader scope of protection in the course of examining or nullity proceedings. If the court answers these questions in the affirmative, the question concerning the infringement of the patent in suit by the contested embodiment is answered in the affirmative, too, since, according to the preconditions made, this embodiment is based on the same general

inventive idea underlying this embodiment and the patent in suit.

VII. The Scope of Protection of Patents on Chemical Inventions

Neither the Supreme Court of the German Reich nor the Federal Supreme Court has decreed that protection of chemical inventions by patents is to be judged differently from the patent protection of other types of inventions. In infringement suits, the courts always consider the patents with a view to the presence of a general inventive idea and possibly acknowledge this.

Those skilled in the respective field of art and having the average ability and knowledge at the moment of the application gather from the chemical process patent, without any effort of their own, the constitution of the new compound, at least one way of producing the compound, and specific technical or pharmacological properties of the compound. Since the synthesis of most chemical compounds may be effected in various ways, it very often happens that, when looking at a constitutional formula, those skilled in the art can think of a number of different, actually known processes which also may lead to the new compound described in the patent. Those skilled in the art have only to carry out these processes and find out whether the desired compound will be obtained in good yields.

The question is: in what case do such different ways of producing the compound, which are not described in the patent but which are known to those skilled in the art without any inventive effort of their own, come within the scope of protection of the patent?

In the case of a chemically peculiar process described in a patent as well as in the case of a process of analogy, these different *per se* known methods of producing the new compound come within the scope of protection of the patent, since they belong to the general inventive idea of the patent. However, processes which could not be found without an independent inventive effort on the part of those skilled in the art, *i.e.* in the case of chemically peculiar processes, which are based on a method that so far had not been known in chemistry, do not come under the scope of the patent.

If, in applying a *per se* known mode of operation for producing a patented compound, a surprising technical effect is attained over the patented process, *e.g.* a very high yield, a so-called "process effect" occurs [see IV, A. b) above], this process might very well be patentable. The holder of a patent on such a process would be in a position to forbid third parties, including the owner of the earlier patent, to use the inventive idea that had been patented for him. In using his patent, however, he is dependent on the authorization of the owner of the earlier patent, because the invention protected by the younger patent cannot be employed without making use of the inventive idea of the earlier patent.

Examination as to whether or not a patent is independent of another is not conducted by the German Patent Office, but by ordinary courts in the way outlined above in connection with the proceedings in infringement cases.

Another possibility of modifying a patented process resides in its application according to the same method, but with different starting compounds, thus obtaining a different end-product. If a product with completely different technical or pharmacological properties is obtained, such a process does not come under the scope of protection of a previous patent.

However, if there is a great similarity between the products obtained and those of the patented process, the modification comes under the scope of protection of the existing patent, especially if the patented process is a so-called chemically peculiar process. In the case of a process of analogy, however, the scope of protection with respect to the modification of the end-product will be a narrower one, since the actual inventive idea does not reside in the mode of operation, but in the surprising properties of the new products. If, for example, instead of a analgetically active propylate, an amyl ester is produced, the pharmacological effects of which are practically the same, this modification would appear to fall within the scope of protection of the patent of analogy. In the case of examining dependency, it is decisive in such cases to find out to what extent the prior art comes close to the process and whether or not those skilled in the art could foresee the properties of the modified process products.

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COMMUNICATIONS

Syntheses in the Griseofulvin Series: 6'-Demethylgriseofulvin

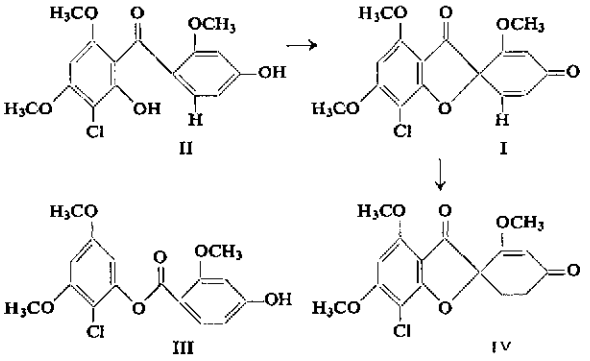
By Dr. D. Taub and Dr. N. L. Wendler

Merck, Sharp & Dohme Research Laboratories
Merck & Co., Inc., Rahway, N.J. (U.S.A.)

The possibility of synthesizing 6'-demethyldehydrogriseofulvin (I) from the phenol II appeared to be of interest. The latter was prepared by condensation of 2-chloro-3,5-dimethoxyphenol with 2-methoxy-4-acetoxybenzoic acid in trifluoroacetic anhydride at 20 °C [1] and separated from the products of the condensation by extraction with 2% aqueous potassium hydroxide. On mild saponification, the neutral fraction afforded III (m.p. 192–196 °C), which was submitted to a Fries rearrangement using $TiCl_4$ in nitrobenzene [2], thereby providing additional amounts of II.

Attempts to convert II into 6'-demethyldehydrogriseofulvin (I) with potassium ferricyanide resulted in yields of only about 1%. By means of lead dioxide in 50% ether-acetone [3], however, II was converted smoothly into I in 80–90% (m.p. 345–350 °C).

The 6′-demethyldehydrogriseofulvin (I) was hydrogenated over palladium on charcoal followed by treatment with zinc and acetic acid [4]. The resulting product was separated into 35 % of the alkali soluble benzophenone derivative II and a



neutral moiety, which was chromatographed on alumina and which yielded 70–80 % of pure 6′-demethylgriseofulvin (IV, m.p. 227–228 °C) as the major component, together with a minor amount of 6′-demethyl-2′,3′-dihydrogriseofulvin.

Received, June 12th. 1962 [Z 304/137 IE]

[1] *D. Taub* et al., Chem. and Ind. *1962*, 557.

[2] *N. M. Cullinane* and *B. F. R. Edwards*, J. chem. Soc. (London) *1957*, 3016.

[3] *C. H. Hassall* and *J. R. Lewis*, J. chem. Soc. (London) *1961*, 2312.

[4] *C. H. Kuo* et al., Chem. and Ind. *1960*, 1627.

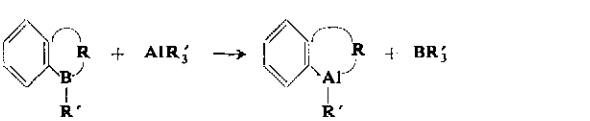
Organic Aluminum Heterocycles

By Dr. R. Köster and Dr. G. Benedikt

Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr (Germany)

Five- and six-membered organic aluminum heterocycles [1, 2] have been obtained in exchange reactions involving boron- and aluminum-alkyls [3].

When one mole of *B*-ethylboraindane or -tetralin [4] is heated (not above 100 °C) with 1 to 1.5 mole of triethylaluminum and all the boron removed as triethylborane by distillation under reduced pressure, 1-ethylaluminaindanes or -tetralins are obtained. Numerous new aluminum heterocycles were obtained as colorless crystals.

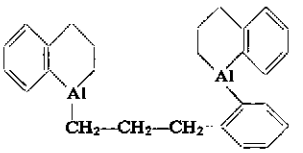


e.g. R = $-CH_2CH_2-$, $-CH_2CHMe-CH_2-$, $-CH_2CH_2CH_2-$ R′ = C_2H_5, C_3H_7

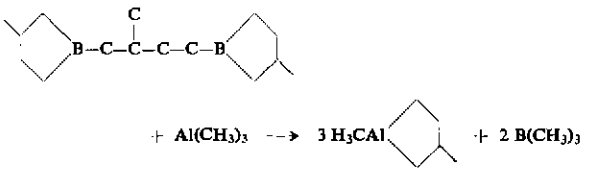
Table 1. 1-Alkylaluminaindanes and -tetralins

Compound	M.p. [°C]
1-Propylaluminaindane	52
1-Ethyl-3-methylaluminaindane	102
1-Propyl-3-methylaluminaindane	103
1-Propylaluminatetralin	liquid

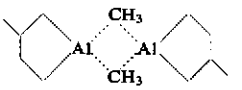
In solution in cyclohexane or benzene, these compounds are dimeric but are capable of producing donor complexes (etherates, pyridinates) derived from the monomeric form (*e.g.* pyridinate of 1-propyl-3-methylaluminaindane, m.p. 93.5 °C). When heated at 120–140 °C under reduced pressure, 1-propylaluminatetralin splits off tripropylaluminum, but no metallic aluminum is deposited. A highly viscous residue is obtained from which crystalline $Al_2(CH_2CH_2CH_2C_6H_4)_3$ (m.p. 137–139 °C) can be isolated on treatment with pentane. On deuterolysis, this yields *o*-deutero-3-deuteropropylbenzene as the only hydrocarbon and is thus likely to have the structure:



Alkyl-exchange reactions between bis-boryl-alkanes [5] and trialkylaluminum in molar proportions of 1:3 to 1:4 produce 1-alkylaluminacyclopentanes which are distillable *in vacuo*:



These liquids are colorless and can be distilled under reduced pressure; in cyclohexane, they exist as dimers but are



converted above 100 °C into polymeric compounds, which solidify to glass-like substances at room-temperature.

Received, July 3rd. 1962 [Z 309/138 IE]

[1] Cf. *J. J. Eisch* and *W. C. Kaska*, J. Amer. chem. Soc. *84*, 1501 (1962).

[2] Cf. *R. Polster*, Liebigs Ann. Chem. *654*, 20 (1962).

[3] Cf. *R. Köster* and *G. Bruno*, Liebigs Ann. Chem. *629*, 89 (1960).

[4] *R. Köster* and *K. Reinert*, Angew. Chem. *71*, 521 (1959).

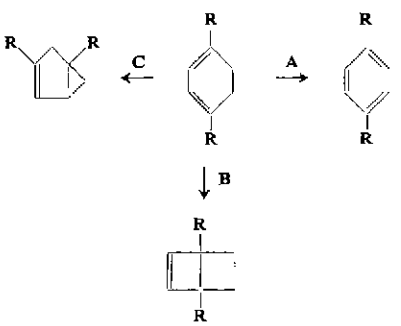
[5] *R. Köster*, Angew. Chem. *71*, 520 (1959).

Photoisomerisation of 1.3-Cyclohexadienes

By Dr. H. Prinzbach and Dipl.-Chem. J. H. Hartenstein

Chemisches Laboratorium der Universität Freiburg/Brsg. (Germany)

Photochemically excited derivatives of 1.3-cyclohexadiene are usually stabilised by ring fission according to A [1].



Up to the present, intramolecular isomerisations according to B have only been observed with two polycyclic systems [2], and according to C only in the cases of dehydroergosterol acetate [1] and of pentaphenylcyclohexadiene [3]. While investigating the conjugated addition of photochemically produced carbenes onto dienes [4], we observed that isomerisation according to B is also possible with simply substituted 1.3-cyclohexadienes. On irradiation (Hg high pressure arc, S 81 Hanau) in etheral solution, in the presence of CH_2N_2 as sensitiser, I [R = CO_2CH_3, λ_{max}(ethanol) = 309 mμ (ε = 13000); proton magnetic resonance spectrum: one singlet each at τ = 2.42 (2

protons), τ = 5.95 (6 protons) and τ = 7.27 (4 protons)] gives rise to II (R = CO_2CH_3) in approximately 70 % yield (colorless oil, b.p. 75–80 °C at 0.001 mm Hg). For a bicyclo[2.2.0]-hexene derivative, II is remarkably stable. It shows only end absorption in the ultraviolet (210 mμ). Its PMR spectrum consists of a two-proton singlet (τ = 4.15), a six-proton singlet (τ = 6.23) and a four-proton A_2B_2-multiplet (τ = 8.87). Hydrolysis of II yields a dicarboxylic acid (R = CO_2H; m.p. 175–179 °C). This can be hydrogenated to give bicyclo[2.2.0]-hexanedicarboxylic acid without disturbing the ring structure. Oxidation of II (R = CO_2CH_3) with periodate/permanganate finally leads to *cis/trans*-cyclobutane-1.2-dicarboxylic acid via a double decarboxylation.

Received, July 6th, 1962 [Z 311/142 IE]

[1] *D. H. R. Barton*, Helv. chim. Acta *42*, 2604 (1959).

[2] *W. G. Dauben* and *G. J. Fonken*, J. Amer. chem. Soc. *81*, 4060 (1959); *W. H. Schuller*, *R. N. Moore*, *J. E. Hawkins*, and *R. V. Lawrence*, J. org. Chemistry *27*, 1178 (1962).

[3] *G. R. Evanega*, *W. Bergmann*, and *J. English*, J. org. Chemistry *27*, 13 (1962).

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Preparation and Properties of Cyclopropylboranes

By Dr. P. Binger and Dr. R. Köster

Max-Planck-Institut für Kohlenforschung,
Mülheim/Ruhr (Germany)

1,1-Bis(dialkylboryl)-3-chloropropanes (II) may be prepared in 65–70 % yield from tetra-alkyldiboranes (*e.g.* tetraethyldiborane) and propargyl chloride via dialkyl-(3-chloroprop-1-enyl)boranes (I):

$$B_2H_2R_4 + 2\ HC{\equiv}C{-}CH_2Cl \rightarrow 2\ R_2B{-}CH{=}CHCH_2Cl \quad (I)$$

$$R_2B{-}CH{=}CHCH_2Cl + {}^1/_2\ B_2H_2R_4 \rightarrow (R_2B)_2CHCH_2CH_2Cl \quad (II)$$

A small part of the borohydride derivative adds on in the first stage in an inverse manner, a reaction course which is increased in extent if diborane itself is used. The addition product then changes rapidly according to:

$$\rangle BH + HC{\equiv}C{-}CH_2Cl \rightarrow \rangle B{-}\underset{\displaystyle CH_2Cl}{\underset{|}{C}}{=}CH_2 \rightarrow$$

$$\rangle BCl + C_3H_4 \xrightarrow{+\ 2\ \rangle BH} \left(\rangle B\right)_2C_3H_6$$

Thus, an alkylboron chloride is split off and bis(dialkylboryl)-propanes arise via an intermediate C_3H_4 (allene?) by addition of further borohydride.

Allene (95 %) and 5 % propyne are formed from I with alkaline reagents (*e.g.* aqueous sodium hydroxide [1] or sodium tetra-alkylborons [2]) by loss of chlorine.

$$\rangle B{-}CH{=}CH{-}CH_2Cl + NaBR_4 \rightarrow$$

$$NaCl + \rangle BR + BR_3 + C_3H_4$$

1,1-Bis(dialkylboryl)-3-chloropropanes (II) give dialkylcyclopropylboranes (III) with sodium tetra-alkylborons in non-aqueous solvents in 80 % yield.

$$\begin{matrix} R_2B \\ \diagdown \\ \quad CH{-}CH_2{-}CH_2Cl \\ \diagup \\ R_2B \end{matrix} + NaBR_4 \xrightarrow{120-130\ ^\circ C}$$

$$R_2B{-}\langle\ + 2\ BR_3 + NaCl \quad (III)$$

III can be isolated by fractional distillation (*e.g.* diethylcyclopropylborane, b.p. = 75–76 °C/150 mm.). In the presence of catalytic amounts of BH-compounds, tricyclopropylborane (b.p. = 65–66 °C/10mm) can be prepared from III on account of alkyl group interchange [3]. This compound is obtained directly if a sodium trialkylborohydride is used instead of sodium tetra-alkylboron, because the catalyst for the *trans*-alkylation is present right from the beginning.

$$6\ (R_2B)_2CHCH_2CH_2Cl + 6\ NaBR_3H \rightarrow$$

$$2\ B\left(\langle\right)_3 + 10\ BR_3 + 3\ B_2H_2R_4 + 6\ NaCl$$

Cyclopropyl groups attached to boron are surprisingly stable toward borohydride compounds. The C-C bonds of the cyclopropane ring are not split even at 100 °C. Besides, the cyclopropyl residue in the cyclopropylboranes is not displaced by olefins. Tricyclopropylborane and triethylaluminum yield cyclopropylaluminum compounds, from which monodeuterocyclopropane is formed by deuterolysis.

$$b{-}\langle\ + al{-}C_2H_5 \rightarrow b{-}C_2H_5 + al{-}\langle \xrightarrow{+\ D_2O} D{-}\langle$$

Received, July 11th, 1962 [Z 313/144 IE]

[1] *M. F. Hawthorne* and *J. A. Dupont*, J. Amer. chem. Soc. *80*, 5830 (1958).

[2] *P. Binger* and *R. Köster*, Tetrahedron Letters *1961*, 156.

[3] *R. Köster* and *G. Griaznow*, Angew. Chem. *73*, 171 (1961).

Isothiazoles [*]

By Dr. F. Hübenett, Dr. F. H. Flock, and Hd. Hofmann

Forschungslaboratorium
der Hans J. Zimmer Verfahrenstechnik,
Frankfurt/Main (Germany)

In the course of our work on the simultaneous action of sulphur dioxide and ammonia on organic compounds (which affords, for example, benzonitrile from toluene) [1], we have found a simple method of synthesis of the isothiazole ring-system [2]. Thus, on passing propylene together with ammonia and sulphur dioxide over catalysts [3] (such as activated aluminum oxide) at temperatures above 200 °C one obtains isothiazole (b.p. 114 °C; n_D^{20} = 1.5308; d_4^{20} = 1.1706), according to the overall equation:

$$3\ CH_2{=}CH{-}CH_3 + 4\ SO_2 + 3\ NH_3 \rightarrow 3\ \begin{matrix} HC & CH \\ \| & \| \\ HC & N \\ \diagdown & \diagup \\ & S \end{matrix} + 8\ H_2O + H_2S$$

In the same way, isobutylene furnishes 4-methylisothiazole (b.p. 147 °C; n_D^{20} = 1.5239; d_4^{20} = 1.0872), while but-1-ene, as well as but-2-ene yield mixtures of 3-methylisothiazole (b.p. 134 °C; n_D^{20} = 1.5180; d_4^{20} = 1.0924) and 5-methylisothiazole (b.p. 145 °C; n_D^{20} = 1.5215; d_4^{20} = 1.1010), which may be separated by fractional distillation. Depending on the olefins used, the yields vary between 25 and 60 %. Isothiazole and its methyl derivatives are water-clear, neutral liquids with good solvent properties and a pyridine-like odor. They are miscible with the common solvents except water. Isothiazole is much more poisonous than pyridine.

Received, July 12th, 1962 [Z 315/145 IE]

[*] 1st Communication.

[1] German patent application Az. Z 8871 IVb/12o.

[2] *S. Goerdeler* and *H. W. Pohland*, Angew. Chem. *72*, 77 (1959); *F. Wille*, *L. Capeller*, and *A. Steiner*, Angew. Chem. internat. Edit. *1*, 335 (1962).

[3] German patent application Az. Z 9032 IVd/12p.

Effect of Ultraviolet Light on the Biosynthesis of Polyphenylalanine

By Prof. Dr. A. Wacker, Priv.-Doz. Dr. D. Jacherts, and Dr. Blanda Jacherts

Institut für Therapeutische Biochemie der Universität Frankfurt/Main (Germany)

The preferential dimerisation of adjacent uracil molecules in a polynucleotide chain on irradiation with ultraviolet light [1] may serve as the basis of a sequence analysis of code triplets necessary for protein synthesis [2], insofar as these contain two uracil molecules. With this method we can also test whether the code of the messenger ribonucleic acid (m-RNA) is complementary to that of the deoxyribonucleic acid and the transfer ribonucleic acid (transfer-RNA). Uracil should have adenine, which is resistant to ultraviolet radiation, as its complementary base. To test this we investigated the sensitivity of incorporation of phenylalanine, which is dependent on the code triplet uracil-uracil-uracil [3] (Table 1).

Table 1. Dependence of incorporation of phenylalanine-[3-^{14}C] on ultraviolet irradiation of different fractions of the biosynthetic system [3]. DL-Phenylalanine-[3-^{14}C], specific activity 1 mC/mmole. UV-dose = 3.5×10^4 erg/mm^2. A polynucleotidephosphorylase from HeLa-cells was used for polymerizing the uridine-diphosphate

Experimental system	Phenylalanine-[3-^{14}C] incorporated after 20 min. [counts/min.]
1. Complete system	6728
2. System without polyuridylic acid	1847
3. System + polyuridylic acid, UV-irradiated	2393
4. System + 100-S-fraction, UV-irradiated	7664
5. System + ribosomes, UV-irradiated	3021

As may be seen from Table 1, the m-RNA [4] and the ribosomes are inactive after irradiation, whereas the transfer-RNA is resistant to ultraviolet light. Hence, it may be concluded that the adjacent uracil molecules in the code triplet of the m-RNA are altered (dimerised) photochemically. The hypothesis of the complementary code adenine-adenine-adenine in the transfer-RNA appears to be valid, since the transfer-RNA, as expected, is resistant to ultraviolet irradiation.

Received, July 16th, 1962 [Z 314/149 IE]

[1] *A. Wacker, H. Dellweg,* and *E. Lodemann,* Angew. Chem. *73,* 64 (1961); *A. Wacker, L. Träger,* and *D. Weinblum, ibid. 73,* 65 (1961); *A. Wacker, D. Weinblum, L. Träger,* and *Z. H. Moustafa,* J. molec. Biology *3,* 790 (1961).

[2] *M. W. Nirenberg* and *J. H. Matthaei,* Proc. nat. Acad. Sci. U.S.A. *47,* 1588 (1961); *P. Lengyel, J. F. Speyer,* and *S. Ochoa, ibid. 47,* 1936 (1961).

[3] *M. W. Nirenberg* and *J. H. Matthaei,* Proc. nat. Acad. Sci. U.S.A. *47,* 1588 (1961).

[4] *L. Grossmann* (personal communication) independently also found inhibition of polyphenylalanine synthesis after ultraviolet irradiation of polyuridylic acid.

Cross-linked Poly-(p-lithiumstyrene), a Reagent for the Preparation of Organo-lithium Compounds

By Dr. D. Braun and Dipl.-Ing. E. Seelig

Deutsches Kunststoff-Institut Darmstadt (Germany)

Treatment of linear poly-(*p*-iodostyrene) with butyl-lithium yields poly-(*p*-lithiumstyrene) [1], a polymeric organometallic compound whose reactivity is similar to that of phenyl-lithium [2].

Cross-linked homopolymers and copolymers based on *p*-iodostyrene can be obtained by pearl polymerisation of *p*-iodostyrene, styrene and divinylbenzene in the molar ratio 1:1:0.02 (the polymerisation is initiated with benzoyl peroxide). The resultant polymers can be converted almost quantitatively into cross-linked poly-(*p*-lithiumstyrene) by stirring for several hours, at room temperature, with a benzene solution of butyl-lithium (in 3- to 4-fold molar excess). Addition of ether facilitates filtration of the polymer which is somewhat swollen in benzene. By repeated washing and filtration in a nitrogen atmosphere it can be obtained pure and free from soluble organo-lithium compounds of low molecular weight.

Cross-linked poly-(*p*-lithiumstyrene) also corresponds to phenyl-lithium in reactivity. It can serve as a starting material for the synthesis of ion-exchange resins containing special functional groups [3], or it may be used in place of butyl-lithium for metallation and halogen-lithium exchange reactions. Benzene is a suitable solvent; ether or tetrahydrofuran are better. Cross-linked poly-(*p*-lithiumstyrene) does not react in aliphatic hydrocarbons.

With the new reagent one can, for example, convert fluorene into fluorene-9-carboxylic acid, phenylacetylene, *p*-bromophenylacetylene and *p*-vinylphenylacetylene into the corresponding phenylpropiolic acids, and diphenylene oxide into diphenylene oxide-4-carboxylic acid. Halogen-lithium exchange reactions may be illustrated by *e.g.* the conversion of 1-iodonaphthalene into 1-naphthoic acid and of *p*-iododiphenyl ether into *p*-phenoxybenzoic acid.

The preparative value of cross-linked poly-(*p*-lithiumstyrene) lies in its insolubility, which simplifies the separation of reaction products from excess reagent.

Received, July 30th, 1962 [Z 319/151 IE]

[1] *D. Braun,* Makromolekulare Chem. *30,* 85 (1959).

[2] Cf. *D. Braun,* Angew. Chem. *73,* 197 (1961).

[3] *D. Braun,* Lecture at the Symposium on Anomalous Reactions on Exchange Adsorbents, Weimar (Germany) April 1961.

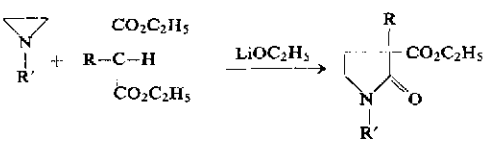
β-Aminoethylation of Malonic Esters with Aziridines

By Dr. H. Stamm

Institut für Pharmazeutische Chemie und Lebensmittelchemie der Universität Marburg (Germany)

In contrast to the numerous aminoethylations with aziridines on hetero-atoms, only a few examples of aminoethylations on carbon are known [1, 2].

By heating 1-phenethylaziridine (I, R′ = C_6H_5–C_2H_4–) and $LiOC_2H_5$ with a large excess of diethyl malonate (II, R=H) to 100–130 °C, 1-phenethyl-3-ethoxycarbonyl-2-pyrrolidone



(I) (II) (III)

	R	R′
IIIa	H	C_6H_5–CH_2–CH_2–
IIIb	CH_3	C_6H_5–CH_2–CH_2–
IIIc	H	C_6H_5–

(IIIa) is formed, infrared bands at 1689–1691 cm^{-1} (lactam-carbonyl, weakly split) and at 1735 cm^{-1} (ester-carbonyl), yield: 20–25 %. Likewise, but with lower yield, IIIb can be obtained from diethyl methylmalonate (II, R=CH_3), and 1-phenyl-3-ethoxycarbonyl-2-pyrrolidone (IIIc) from diethyl malonate and 1-phenyl-aziridine. Compound IIIc crystallised after about 3 months, m.p. 57.5 °C. The carbonyl bands of

the solid compound occurred at 1686 cm^{-1} and 1727 cm^{-1} and before crystallisation (measured as film) at 1703 cm^{-1} and 1735 cm^{-1}.

Compounds IIIa–c were isolated by distillation at bath temperatures of 70–120 °C and pressures of about 10^{-2} mm Hg.

Received, July 30th, 1962 [Z 318/147 IE]

[1] Reaction of benzene with aziridines in the presence of $AlCl_3$: *G. I. Bras*, Doklady Acad. Nauk S.S.S.R. *87*, 599, 747 (1952); cf. Chem. Zbl. *1953*, 7278, 9136.

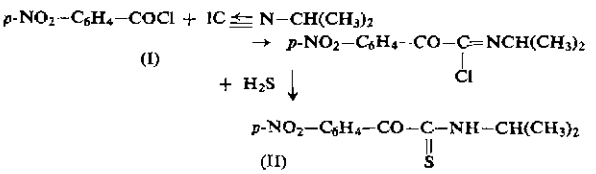
[2] Reaction of indole with ethyleneimine using the Grignard compound of indole: *R. Bucourt* and *M. Vignau*, Bull. Soc. chim. France *1961*, 1190.

A New Synthesis of α-Ketothiocarboxamides

By Priv.-Doz. Dr. W. Walter and Dipl.-Chem. K.-D. Bode

Chemisches Staatsinstitut, Institut für Organische Chemie der Universität Hamburg (Germany)

N-Substituted α-ketothiocarboxamides (II) are only difficultly accessible by the usual thioamide syntheses. We were able to prepare *N*-substituted α-ketothiocarboxamides, *e.g.* *p*-nitrophenylthioglyoxyl-*N*-isopropylamide (II), in good yield by reacting H_2S with substituted glyoxylimidoyl chlorides, *e.g.* (I), which are easily accessible [1] from acid chlorides and isonitriles:



10 g. *p*-Nitrophenylglyoxyl-*N*-isopropylimidoyl chloride (I), m.p. 56–62 °C, were dissolved in 50 ml. benzene and 50 ml. chloroform and the solution was saturated with H_2S. After pouring into water, washing of the organic phase with $NaHCO_3$-solution and water and evaporation of the solvents, a red oil remained, which crystallised in the cold. Orange-red crystals from benzene/light petroleum, m.p. 76–78 °C. Yield: 87 %. In the same way pyruv-*N*-isopropylthioamide (b.p. = 104 °C/11 mm.) was prepared.

Received, July 30th, 1962 [Z 317/146 IE]

[1] *I. Ugi* and *V. Fetzer*, Chem. Ber. *94*, 1116 (1961).

A New Method for the Synthesis of Ribo-oligonucleotides:

The Preparation of Uridyl-(3′→5′)-uridine-3-phosphate

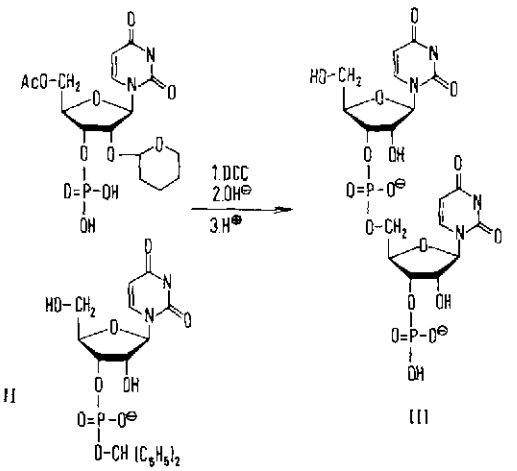
By Prof. Dr. F. Cramer and Dipl.-Chem. K. H. Scheit

Institut für Organische Chemie der Technischen Hochschule Darmstadt (Germany)

Several methods are known for the step-wise synthesis of deoxyribo-oligonucleotides [1,2]; in the ribooligonucleotide series, on the other hand, only a dinucleoside phosphate has been prepared [3,4]. We now wish to report the first step-wise synthesis of a dinucleotide of the ribose series:

One of the starting-materials is the pyridinium salt of 5′-*O*-acetyl-2′-*O*-tetrahydropyranyluridine-3′-phosphate (I) [4]. The position of the substituents in I was proved by esterification with methanol, removal of the protecting groups and subsequent enzymatic hydrolysis with ribonuclease, which gave exclusively uridine-3′-phosphate. The second component is the benzhydryl ester of uridine-3′-phosphate [5] (II, NH_4^+ salt).

The phosphate group in II is protected by substitution, and the 2′-OH group cannot be acylated because of the size of the benzhydryl residue. Compounds I and II (10^{-4} mole of each) in pyridine (1 ml.) were condensed to the protected dinucleotide using a seven-fold excess of dicyclohexylcarbodiimide (DCC). After 4 days the acetyl group was removed by treatment with a solution of concentrated ammonia (5 ml.) in 50 % aqueous dioxane (5 ml.), and the benzhydryl and tetrahydropyranyl groups were hydrolysed by treatment at 20 °C with 80 % acetic acid (5 ml.) for 15 hours.



The dinucleotide III was purified by chromatography. Yield: 30 μmole (30 %), R_F-value (isopropanol/NH_3/H_2O, 7:1:2): 0.05. At pH 8.3 (37 °C, 6 hrs.) III was degraded by ribonuclease to the extent of 95 % to mainly uridine-3′-phosphate (R_F 0.11); found also was some cyclic uridine-2′,3′-phosphate (R_F 0.31), proving that 95 % of the dinucleotide (III) had had the correct 3′→5′ inter-nucleotidic linkage [6].

Received, August 8th, 1962 [Z 325/152 IE]

[1] *H. G. Khorana*: Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest. Wiley, New York 1960.

[2] *F. Cramer, H. J. Baldauf*, and *H. Küntzel*, Angew. Chem. internat. Edit. *1*, 54 (1962).

[3] *M. Smith, D. H. Rammler, I. H. Goldberg*, and *H. G. Khorana*, J. Amer. chem. Soc. *84*, 430 (1962).

[4] *J. Smrt* and *F. Sorm*, Collect. czechoslov. chem. Commun. *27*, 83 (1962).

[5] *F. Cramer, H. Neunhoeffer, K. H. Scheit, G. Schneider*, and *J. Tennigkeit*, Angew. Chem. internat. Edit. *1*, 331 (1962).

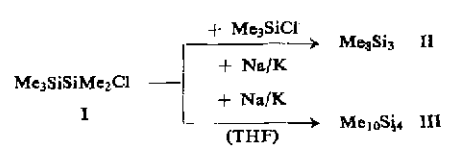
[6] Note added in proof (August 30th, 1962): Meanwhile we have prepared by the same method a mixed dinucleotide, uridyl-(3′→5′)-adenosine-3′-phosphate, with 39 % yield.

Octamethyltrisilane and Decamethyltetrasilane

By Dr. U. Graf zu Stolberg

Institut für Anorganische Chemie der Universität München (Germany)

Octamethyltrisilane (II) and decamethyltetrasilane (III) were hitherto not readily prepared. Only the formation of a mixture of II and III, by the reaction of aluminum on bis-(trimethylsilyl)mercury, was reported [1]. The condensation of trimethylchlorosilane and dimethyldichlorosilane with sodium was tried unsuccessfully [2]. It was now found that II and III can be synthesised from pentamethylmonochlorodisilane (I) [3].



By reacting a Na–K alloy (0.75 mole Na, 1.5 mole K) with a mixture of trimethylchlorosilane (4.6 mole) and I (0.19 mole) a 95 % yield of II (with respect to I), together with hexamethyldisilane, is obtained. Therefore, the dehalogenation of I is substantially more rapid than that of trimethylchlorosilane. Compound III is formed in good yield by the reaction of I with Na–K alloy in tetrahydrofuran.

Compounds II and III are water-clear liquids and stable to air (II: m.p. −46 °C, b.p. 180 °C, $n_D^{20} = 1.4599$, $d_4^{20} = 0.7595$; III: m.p. −4 °C, b.p. 242 °C, $n_D^{20} = 1.4876$, $d_4^{20} = 0.7889$).

By reaction with excess bromine in CCl_4, II and III are completely degraded to Me_3SiBr and Me_2SiBr_2, respectively, even at room temperature. Analysis of the compounds is therefore possible by determination of their bromine uptake.

Received, August 8th, 1962 [Z 329/155 IE]

[1] *L. Kreuzbichler*, Ph. D. Thesis, Munich University, 1961.

[2] *W. Sundermeyer*, Z. anorg. allg. Chem. *310*, 50 (1961).

[3] *M. Kumada, M. Yamaguchi, Y. Yamamoto, J. Nakajima*, and *K. Shiina*, J. org. Chemistry *21*, 1264 (1956).

Synthesis of Aromatic Compounds by an Intramolecular Wittig Reaction

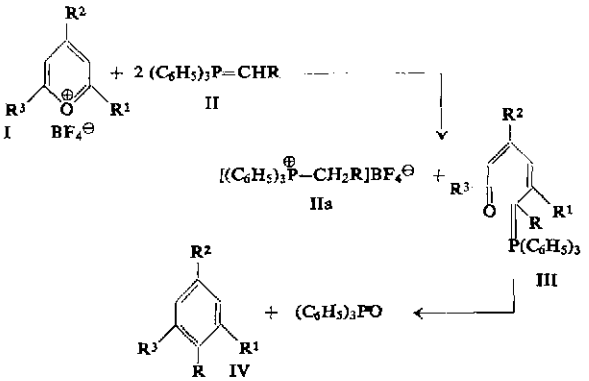
By Dr. G. Märkl

Chemisches Institut der Universität Würzburg (Germany)

Pyrylium salts (I) react with triphenylphosphinemethylene derivatives (II) to give the vinylogous phosphine-acylmethylenes (III), which – depending on the nature of the substituents – can be isolated or converted directly to the substituted aromatic compounds IV by an intramolecular Wittig alkenation.

Example: A solution of I ($R^1=R^2=R^3=C_6H_5$; 10 mmole) [1] in a little acetonitrile was added to a boiling solution of the phosphinemethylene II (R=H; 20 mmole) in toluene (100ml.) in the course of one hour. The violet colour which appeared at the place of mixing disappeared immediately.

After completion of the addition the brown solution was boiled for 30 minutes, then it was concentrated to 30 ml. and precipitation of IIa was completed by the addition of ether (100 ml.). The filtrate was evaporated to dryness, some methanol was added to the residue and after some time the 1,3,5-triphenylbenzene (m.p. 170–172 °C [2], yield 59 %) was filtered off.



With $R^1=R^3=p\text{-}CH_3\text{-}C_6H_4$, $R^2=C_6H_5$ and R=H the yield of IV (m.p.138-140 °C) amounted to 72 %. I ($R^1=R^2=R^3=C_6H_5$) and II ($R=CO_2CH_3$) after 24 hours in boiling chloroform gave III in the form of garnet-red crystals (m.p. 178–180 °C, yield 64 %, $\lambda_{max} = 462$ mμ, C=O bands at 1639 and 1628 cm^{-1}).

This exchange of the oxygen atom in the ring of the pyrylium salts for the –CH= group supplements the existing methods for the preparation of aromatic hydrocarbons from pyrylium salts [1,3,4] and α-pyrones [5].

Received, August 10th, 1962 [Z 330/156 IE]

[1] *K. Dimroth*, Angew. Chem. *72*, 331 (1960).

[2] *C. Engler* and *H. E. Berthold*, Ber. dtsch. chem. Ges. *7*, 1123 (1874).

[3] *K. Dimroth* and *G. Neubauer*, Chem. Ber. *92*, 2042 (1959).

[4] See also *G. Köbrich* and *D. Wunder*, Liebigs Ann. Chem. *654*, 131 (1962).

[5] *R. Gompper* and *O. Christmann*, Angew. Chem. *71*, 32, 378 (1959).

CONFERENCE REPORTS

Meeting of German Chemistry Lecturers

April 25th—28th, 1962 in Bonn (Germany)

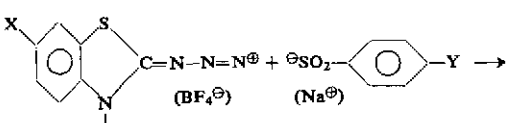
From the agenda:

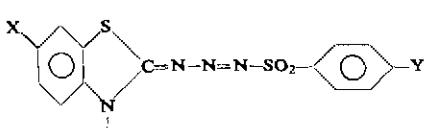
Transfer of Azo Groups to Compounds with Active Methylene Groups by Means of Heterocyclic Iminodiazosulfones

H. Balli and *R. Gipp*, Marburg/Lahn (Germany)

Heterocyclic iminodiazosulfones, *e.g.* III, prepared from azidinium salts (I) and aryl sulfinates (II), can transfer their azo group almost quantitatively to *e.g.* 1-phenyl-3-methyl-pyrazol-5-one, forming the symmetric dyestuff 5,5'-dihydroxy-3,3'-dimethyl-1,1'-diphenyl-4,4'-azopyrazole, 6-X-3-ethyl-2-iminobenzothiazoline, and arylsulfinic acid, 1-phenyl-3-methyl-4-diazopyrazol-5-one being an intermediate.

The kinetics of this coupling reaction were investigated by spectrophotometry. It was possible to show that the dissociation of the iminodiazosulfone III can be made to determine the rate of the complex reaction. The effect of the substituents X and Y on the rate of dissociation of III can be determined under these conditions by measuring k_D. It fits the Hammett relationship giving $\rho_X = -1.59$ and $\rho_Y = +1.43$ (at 25.0 °C in 1:1 dimethylformamide/water, $\mu = 0.10$).





X: CF_3, $COOC_2H_5$, Cl, H, CH_3, CH_3O
Y: NO_2, $COOC_2H_5$, Cl, H, CH_3, CH_3CONH, CH_3O, $(CH_3)_2N$

New Phosphorus-Halogeno Compounds

Marianne Baudler, Köln (Germany)

According to dipole, infrared, and Raman spectral studies, diphosphorus tetraiodide has a different molecular configuration in CS_2 than in the crystal lattice, where the two PI_2 groups are arranged in a *trans* configuration [1], while in solution they are rotated through 90° into C_2 symmetry.

The yellow phosphorus oxyiodide of average composition $P_3I_2O_6$ [2], recently prepared by the reaction of P_2I_4 with oxygen at 20 °C, was shown to be amorphous by X-ray analysis. It is insoluble in inert organic solvents and all its properties suggest it is a high polymer. It is hydrolyzed with extreme ease, forming hypophosphoric, phosphorous, and phosphoric acids, as well as some pyrophosphorous acid and phosphine. The infrared spectrum of $P_3I_2O_6$ shows considerable similarity to that of P_4O_{10}. These findings permit the assumption of a structural element composed of six-membered P_3O_3 rings, joined to one another by single P-P bonds. Under suitable conditions, the analogous reaction P_2I_4 with sulfur yields as primary product orange colored $P_2I_4S_2$, which decomposes after a short time at room temperature with evolution of iodine. At higher reaction temperatures, P_4S_7, PI_3, and I_2 are formed. The corresponding oxygen compound, $P_2Cl_4O_2$, can be prepared by the reaction of $P(O)Cl_2Br$ with magnesium, either without solvent or in ether; the products of the reaction form adducts through the oxygen of the phosphoryl group.

The reactions of diphosphine with bromine or of phosphonium iodide with phosphorus pentachloride form orange-red, insoluble highly polymeric P_3X (X = Br, I) of reproducible stoichiometric composition. Its structure very probably consists of bifunctional three-membered phosphorus rings with substituent halogen atoms. In contrast to the three-membered rings in the P_4 tetrahedron, the formation of a polymeric structure is favored by the energy relationships in the molecule, since in this case only one of the valence angles of the phosphorus is deformed to 60°, while the two others can assume the normal value of approximately 100°.

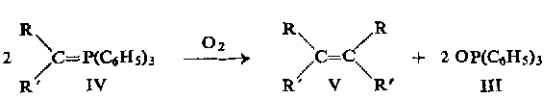
Autoxidation of Alkylenephosphines and its Preparative Uses [3]

H. J. Bestmann and *O. Kratzer*, Munich (Germany)

Autoxidation of alkylenephosphines of structure I yields olefins (II) and triphenyloxophosphorane (III)

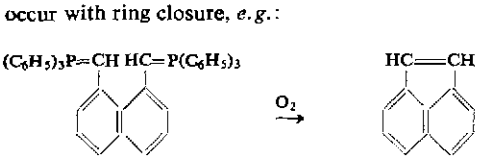
$$2\ R{-}CH{=}P(C_6H_5)_3 + O_2 \rightarrow R{-}CH{=}CH{-}R + 2\ OP(C_6H_5)_3$$
$$\text{I} \qquad\qquad \text{II} \qquad\qquad \text{III}$$

Autoxidation of ylides of structure IV leads to ketones and triphenyloxophosphorane



If the autoxidation of IV is interrupted when $^1/_2$ O_2 has been absorbed, the ketone formed reacts with unoxidized ylide IV to give the olefin V by the Wittig reaction.

Autoxidation of bis(alkylenetriphenylphosphoranes) can occur with ring closure, *e.g.*:



[1] *Y. C. Leung* and *J. Waser*, J. physic. Chem. *60*, 539 (1956).

[2] *M. Baudler*, Angew. Chem. *73*, 761 (1961).

[3] Cf. Angew. Chem. internat. Edit. *1*, 270 (1962).

A New Method of Preparing Oxyfluorides

K. Dehnicke, Stuttgart (Germany)

In a reaction similar to one already used in the preparation of oxychlorides and oxybromides [4], it is now possible to prepare oxyfluorides smoothly by treatment of chlorofluorides with excess Cl_2O:

$$TiF_2Cl_2 + Cl_2O \rightarrow TiOF_2 + 2\ Cl_2$$

The chlorofluorides TiF_2Cl_2 and SnF_2Cl_2 can be obtained by reaction of ClF_3 with $TiCl_4$ and $SnCl_4$, respectively. Since SnF_2Cl_2 reacts only very slowly with Cl_2O, it was thought advisable to use more strongly polar chlorine nitrate [5], which leads to the stable intermediate, tin (IV) fluoronitrate:

$$SnF_2Cl_2 + 2\ ClNO_3 \rightarrow SnF_2(NO_3)_2 + 2\ Cl_2\,.$$

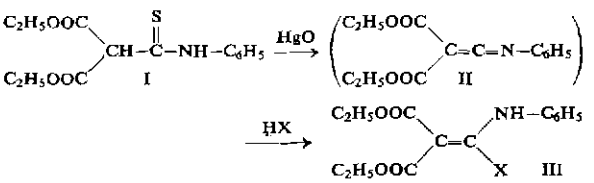
Thermal decomposition of $SnF_2(NO_3)_2$ at 250 °C gives pure, cubic crystals of $SnOF_2$. While TiF_2Cl_2 (yellow) and SnF_2Cl_2 (white) are readily volatile, very hygroscopic, thermolabile solids that are soluble in polar solvents, the oxyfluorides $TiOF_2$ and $SnOF_2$ have greater thermal stability and show no tendency to form adducts; their low solubility results from this latter fact.

On the Preparation of Reactive Iminoketenes

F. Effenberger, Stuttgart (Germany)

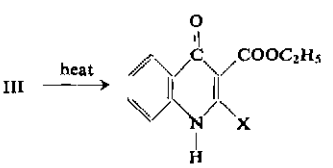
The synthesis of reactive iminoketenes by elimination of H_2S from substituted thioamides using mercuric oxide was investigated by analogy to the preparation of carbodi-imides from substituted thioureas with heavy metal oxides.

Anilinothiocarbonylmalonic ester (I), which is produced from sodiomalonic ester and phenyl isothiocyanate serves as a typical example. The expected diethyl ester of *N*-phenyliminoketene-2,2-dicarboxylic acid (II) [6], could not be isolated. Anilinocarbonylmalonic ester was always formed. If the desulfurisation is carried out in the presence of a reactive partner HX, addition products (III) of HX onto the iminoketene (II) primarily formed are produced.



X = OCH_3; OC_2H_5; $OCH_2C_6H_5$; $NHCH_3$; $N(CH_3)_2$.

Compounds III are particularly suitable for the synthesis of heterocycles; by simply heating, γ-quinolones (IV) are obtained in good yields.



X = OCH_3; OC_2H_5; $OCH_2{-}C_6H_5$; $NHCH_3$; $N(CH_3)_2$.

Properties of Sulfur Iodides (Iodosulfanes)

F. Fehér and *H. Münzner*, Köln (Germany)

The sulfur iodides S_2I_2, S_3I_2, S_4I_2, S_5I_2, and S_6I_2 were prepared by forcing a cyclohexane solution of the corresponding chlor des (10^{-3} to 10^{-4} mole/l) through a layer of powdered

[4] *K. Dehnicke*, Angew. Chem. *73*, 535 (1961); *73*, 763 (1961).

[5] *M. Schmeisser*, Angew. Chem. *73*, 388 (1961).

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

potassium iodide approximately 1 cm thick. Reaction: $S_nCl_2 + 2KI \rightarrow S_nI_2 + 2KCl$. In this manner, prolonged contact between the nascent sulfur iodide and potassium iodide is prevented. Such contact accelerates decomposition of the unstable sulfur iodides.

Sulfur iodides have characteristic absorption spectra (with three or two maxima) which differ from those of the starting materials and from those of the decomposition products and which are hardly, if at all, affected by the latter. The maxima appearing at the longest wavelength are following: S_2I_2: 350 mμ; S_3I_2: 300 mμ; S_4I_2: 297 mμ; S_5I_2: 292 mμ; S_6I_2: 290 mμ. Comparison of the main absorption maxima for the compounds S_2Cl_2 (265 mμ), S_2Br_2 (296 mμ), and S_2I_2 (350 mμ) shows a regular shift toward longer wavelengths, from chloride to bromide to iodide.

The decomposition constants were obtained from the variation of the extinction at 400 mμ with time. For S_2I_2, the half life is 9.5 hr. (first-order decomposition) and for higher sulfur iodides from 1 to 2.5 hr. at starting concentrations of about 10^{-4} mole/l (second-order decomposition).

Decomposition of the products yields sulfur and iodine. The latter was determined photometrically, thus demonstrating the quantitative course of the synthesis.

Effect of Substituents on Double Bond Isomerization during Hydroformylation of Substituted n-Olefins

B. Fell and *A. Jankowski*, Aachen (Germany)

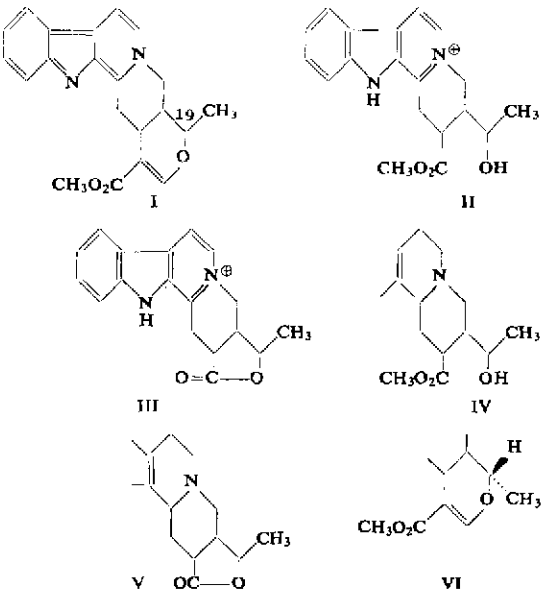
In many reactions of olefinic hydrocarbons catalyzed by metal carbonyls, *e.g.* hydroformylation, the catalyst causes a more or less pronounced isomerization of the olefinic double bond. This often leads to equlibrium mixtures of the bond position isomers. In the case of 1-undecenoic acid and its methyl ester it was shown that the metal carbonyl-catalyzed double bond shift is definitely hindered by the carboxyl substituents. We have investigated the results of isomerization of these substituted olefins with cobalt tetracarbonyl hydride and iron pentacarbonyl, as well as the composition of unreacted olefin on partial hydroformylation. Treatment of methyl 1-undecenoate and a mixture of methyl 8-undecenoate and 9-undecenoate with iron pentacarbonyl at 175 °C resulted in identical double bond isomer mixtures. Surprisingly, this isomeric mixture contains only very small amounts of methyl 8-undecenoate and, particularly, 9-undecenoate. Being an α,β-unsaturated compound, the latter should be thermodynamically favored. It is possible that there is an analogy between this isomerization and the "contrathermodynamic" double bond isomerization of isoalkylboranes to the thermodynamically less favored n-alkylboranes observed by *H. C. Brown* and co-workers.

The Configuration at C-19 in Serpentine; A Contribution to the Knowledge of the Lactone Rule

Helmut Fritz, Frankfurt/Main (Germany)

To elucidate the still unknown configuration at C-19 in serpentine (I), the latter was degraded to the derivatives II and III. Application of the lactone rule as the displacement rule of optical rotation results in a high, positive value for Δ [M], which would indicate an *R*-configuration for C-19. However, if II and III are converted into IV and V, which contain a tetrahydrogenated pyridine nucleus, comparison of rotation gives a negative Δ[M] value, indicating an S-configuration for the asymmetric center at C-19. Comparison of the rotation for derivatives II and III is not permissible because of the strong ultraviolet absorbtion of the β-carbolinium chromphore. Hence, the result obtained for the tetrahydrogenated derivatives indicates an *S*-configuration at C-19 (VI).

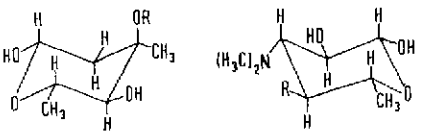
The observation that II and III, which still contain the β-carbolinium chromophore that absorbs in the region of longer wavelengths, give a positive value for Δ[M], despite their *S*-configuration at C-19, constitutes the first clear exception to the lactone rule applied as the displacement principle [7].



The Stereochemistry of Macrolide Sugars

H. Grisebach and *W. Hofheinz*, Freiburg/Breisgau (Germany)

In the course of studies on the biosynthesis of macrolides [8], the authors investigated the hitherto unknown configuration of the following macrolide sugars: mycarose (I), cladinose (II), mycaminose (III) and desosamine (IV). The nuclear magnetic resonance spectrum of diacetylmycarose indicates an *erythro*-configuration at C-4 and C-5. By comparison with the NMR spectrum of synthetic 3-epi-mycarose [9], a *ribo*-configuration was assigned to I. The NMR spectrum of more strongly levorotatory methyl mycaroside suggests an α-configuration for this compound and hence an L-configuration for mycarose. Moreover, NMR spectra indicate identical conformations for mycarose and cladinose. Compound II can be converted into I with boron trichloride. The formation of a cyclic carbonate from 1-methylmycarose and phosgene, the kinetics of the periodic acid oxidation of I, and the formation of complexes of I with borates are compatible with the *ribo*-configuration. The borate complexes were established by paper electrophoresis with borate buffer. Hence, mycarose is a 2,6-dideoxy-3-*C*-methyl-L-ribohexose, and cladinose is its 3-methyl ether [10]. The NMR spectrum of its more strongly levorotatory triacetate suggests that mycaminose is 3,6-dideoxy-3-dimethylamino-D-*gluco*-hexose [11]. Similarly, a D-*xylo*-configuration has been assigned to desosamine [12]. Based on their NMR spectra, the sugars have the following conformations:



I, R = H
II, R = CH_3

III, R = OH
IV R = H

[7] Cf. *W. Klyne*, Chem. and Ind. *1954*, 1198.

[8] *H. Grisebach, H. Achenbach*, and *W. Hofheinz*, Tetrahedron Letters *1961*, 234, and preceding communications.

[9] *F. Korte, U. Claussen*, and *K. Göhring*, Tetrahedron, in the press; *D. M. Lemal, P. D. Pacht*, and *R. B. Woodward*, Tetrahedron, in the press.

[10] *W. Hofheinz, H. Grisebach*, and (in part) *H. Friebolin*, Tetrahedron, in the press.

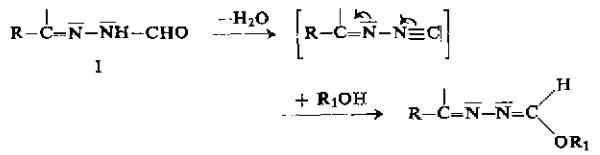
[11] *W. Hofheinz* and *H. Grisebach*, Z. Naturforschg. *17b*, 355 (1962).

[12] *W. Hofheinz* and *H. Grisebach*, Tetrahedron Letters *1962*, 377.

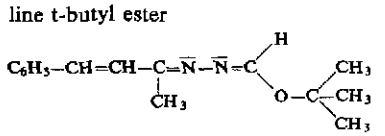
N-Isonitriles and Hydrazonoformates

Ilse Hagedorn and *U. Eholzer*, Freiburg/Breisgau (Germany)

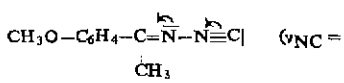
Xanthocillin ether adds on alkoxide ion [13] at its α,β-unsaturated isonitrile groups to give mono- and di-formimido esters. Until now, it had not been possible to apply this reaction to saturated isonitriles. However, if formylhydrazones (I) are dehydrated at 0–10 °C (analogous to the synthesis of isonitriles from formamides, by elimination of water [13–15]), in the presence of alkoxide, an instantaneous addition of alcohol onto the *N*-isonitrile formed as an intermediate occurs. This leads to formhydrazono esters (II)



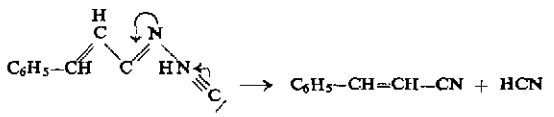
With the formylhydrazone of benzylideneacetone as the starting material, it was even possible to prepare the crystalline t-butyl ester



In some cases, it was possible to isolate crystals of *N*-isonitriles, which also are a new class of materials, for example, those of



The limit of stability for *N*-isonitriles of this type seems to be reached with *N*-isonitrilocinnamylidenimine, which decomposes even at room temperature into cinnamonitrile and HCN.



New Reactions for the Photometric Determination of Molybdenum

H. Hartkamp, Dortmund (Germany)

In the reduction of weakly acidic molybdate solutions with stannous chloride, intensely colored, unstable compounds are formed in the presence of picolinic acid, lutidinic acid, 1,10-phenanthroline, 2-aldoximino-pyridine, or 2,3-pyrazinedicarboxylic acid. If the solutions also contain a sufficient excess of thioglycolic acid, stable reddish-brown solutions are obtained, whose light absorption at *ca.* 400 mμ and *ca.* 500 mμ can be used for the determination of molybdenum in the concentration range from 1–20 μg Mo/ml. These solutions contain molybdenum (V) complexes, which, in addition to the pyridine derivatives mentioned above, also contain thioglycolic acid as a ligand. On addition of ammonia, the complexes are converted into characteristically colored compounds, whose formulae are as yet undefined.

When solutions of molybdenum(VI) compounds are strongly acidified with hydrochloric acid and reduced with titanous chloride or stannous chloride in the presence of 2,3-pyrazinedicarboxylic acid, a trivalent molybdenum compound is obtained, which has an intense violet color and is diamagnetic in its crystalline state. It contains 2,3-pyrazinedicarboxylic acid and chloride ions as ligands. A binuclear complex containing a Mo-Mo bond is postulated for the compound on the basis of its composition and properties. The reaction leading to its formation is well reproducible. The light absorption of the resulting solutions is insensitive to changes in the concentrations of the 2,3-pyrazinedicarboxylic acid, stannous chloride, and hydrochloric acid; the extinction coefficients are constant over long periods of time, and are not affected by most cations. This procedure is as sensitive as the detection of molybdenum using thiocyanate and can therefore be used for the photometric determination of molybdenum in the concentration range from 0.1 to 10 μg Mo/ml. It is superior to the thiocyanate method with respect to accuracy and specificity.

[13] *I. Hagedorn* and *H. Tönjes*, Pharmazie *12*, 567 (1957).

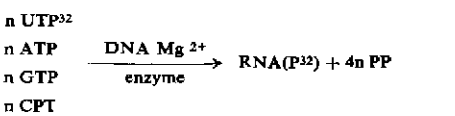
[14] *W. R. Hertler* and *E. J. Corey*, J. Org. Chem. *23*, 1221 (1958).

[15] *J. Ugi* and *R. Meyr*, Chem. Ber. *93*, 239 (1960).

The Biological Mode of Action of the Actinomycins

G. Hartmann and *U. Coy*, Munich (Germany)

Although the cytostatic actinomycins suppress ribonucleic acid synthesis *in vivo*, formation of cellular deoxyribonucleic acid and virus protein can continue (*E. Reich*). In order to elucidate the mechanism, we have investigated the effect of the actinomycins on an enzyme from *Escherichia coli B*, which synthetizes ribonucleic acids by the following reaction.

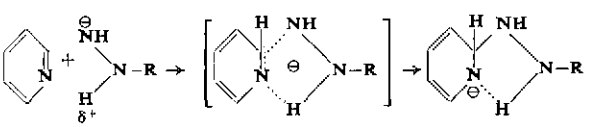


It was found that the presence of even $4 \cdot 10^{-6}$ mole/actinomycin C_2 results in a 50 % reduction of the nucleotide incorporation. The same inhibition was shown by actinomycins C_1, C_3, F_1, F_2, F_3, F_4, E_1, and X. The point of attack of the actinomycins is not at the enzyme protein, since the inhibition is not diminished at higher enzyme concentrations. The inhibition is caused by an inactive DNA-actinomycin compound and, as expected, is abolished by increasing the DNA concentration. This explanation of the mechanism of actinomycin action through the formation of an inactive DNA-actinomycin compound is supported by the observation of *Rauen* et al. that DNA can form complexes with actinomycin. These compexes can be isolated by gel filtration. They dissociate in the presence of urea.

Does Hydrazide Ion Add onto Multiple Bonds as a 1,3-Dipole in a Synchronous Process?

Th. Kauffmann, *H. Henkler*, and *Jutta Schulz*, Darmstadt (Germany)

In toluene, sodium hydrazide and sodium methylhydrazide add onto pyridine even at 10–15 °C, whereas sodamide and sodium *N,N*-dimethylhydrazide react only upon heating to 80–90 °C. This is surprising in view of the weak basicity of hydrazide and methylhydrazide ions compared to amide and *N,N*-dimethylhydrazide ions. The unexpected capacity of hydrazide and methylhydrazide ions to undergo addition becomes understandable, if the assumption is made that these ions add across the pyridine double bond as 1,3-dipoles



I: R = H
II: R = CH_3



III IV

in a synchronous process, as shown below. Because of the delocalization of the negative charge in a 5-membered ring, the transition states I and II should have lower energy than the possible transitions states III and IV[R = H or $N(CH_3)_2$] during addition of an amide or an *N,N*-dimethylhydrazide ion.

This addition mechanism also readily explains why sodium hydrazide and sodium methylhydrazide react with *p*-fluorotoluene in benzene at 30 °C via the additive mechanism of aromatic nucleophilic substitution, whereas the reaction of *p*-fluorotoluene with sodium *N,N*-dimethylhydrazide only occurs on heating at 80 °C and proceeds according to the aryne mechanism.

Synthesis of Dialkylphosphorus Compounds

W. Kuchen, Aachen (Germany)

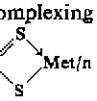
Dialkylphosphorus compounds were synthetized from tetraalkyl(biphosphine sulfides) $R_2P(S)-P(S)R_2$ (I) (R = n-alkyl). The reaction of I with HgO, which in the presence of moisture leads to dialkylphosphinic acids, proceeds via dialkylphosphinic anhydrides, according to the equations

$$R_2P(S)-P(S)R_2 + 3\,HgO \rightarrow R_2P(O)-O-P(O)R_2 + 2\,HgS + Hg$$

$$R_2P(O)-O-P(O)R_2 + H_2O \rightarrow 2\,R_2P(O)OH$$

The anhydrides can be isolated by working with careful exclusion of moisture. Reaction of I according to the equation

$$R_2P(S)-P(S)R_2 + Na_2S \cdot 9\,H_2O + S \rightarrow 2\,R_2P(S)SNa \cdot 2\,H_2O + 5\,H_2O$$

leads smoothly to Na dialkyldithiophosphinates, which occur as stable, crystallizing dihydrates. These are of synthetic interest and are useful as complexing agents (they form inner complexes of formula  with numerous metals).

With alkyl halides they give esters of dialkyldithiophosphinic acids, according to the equation

$$R_2P(S)SNa + RX \rightarrow R_2P(S)SR + NaX$$

With gaseous HCl in dioxan, they give the diakyldithiophosphinic acids $R_2P(S)SH$ in over 90 % yield. Bis(dialkylthiophosphoryl) disulfides were obtained according to the equations

$$2\,R_2P(S)SH \xrightarrow{+\,I_2,\,-2\,HI} R_2P(S)-S-S-P(S)R_2$$

$$2\,R_2P(S)SNa \xrightarrow{+\,KI_3,\,-2\,NaI} R_2P(S)-S-S-P(S)R_2$$

and bis(diethyldithiophosphoryl) trisulfides, according to the equation

$$2\,(C_2H_5)_2P(S)SH + SCl_2 \xrightarrow{\text{pyridine}} (C_2H_5)_2P(S)-S-S-S-P(S)(C_2H_5)_2 + 2\,Py \cdot HCl$$

A comparison of the rate of hydrolysis of $R_2P(O)-O-P(O)R_2$ (II), $R_2P(S)-O-P(S)R_2$ (III) and $R_2P(S)-S-P(S)R_2$ (IV) gave the following sequence: II $\gg$ IV > III, R = C_3H_7 > R = C_2H_5. III was prepared from $R_2P(S)Br$ and Ag_2O, and IV was obtained from $R_2P(S)Br + R_2P(S)SNa$.

The Formation of Silver Isotopes on Irradiating Cadmium with Pile Neutrons

Franz Lux, Munich (Germany)

The formation of radioactive silver isotopes during the reaction of neutrons from an atomic reactor with cadmium was investigated in connection with work on the determination of silver by activation analysis of substances of high cadmium content. Of the longer-lived silver isotopes, the nuclides Ag^{106}, Ag^{110m}, and Ag^{111} are formed by (n, p) reactions. As was shown by measurement of the Ag^{105} activities arising during and after irradiation, Ag^{105} is almost exclusively formed by way of the reaction

$$Cd^{106}(n,\,2n)Cd^{105} \xrightarrow{\beta^+,\,K} Ag^{105}$$

and not from Cd^{106} by an (n,pn) reaction. Based on the reaction $S^{32}(n,p)P^{32}$, the following effective cross sections are obtained for fission-spectrum neutrons:

$Cd^{106}(n,2n)Cd^{105}$, 0.24 mb; $Cd^{106}(n,p)Ag^{106}$, 0.51 mb; $Cd^{110}(n,p)\,Ag^{110m}$, 0.009 mb (*R. S. Rochlin* gives 0.1 mb; no detailed experimental conditions are given); and $Cd^{111}(n,p)\,Ag^{111}$, 0.053 mb. These studies show that, in the determination of silver in materials containing cadmium via activation analysis, the conventional procedure of irradiating the untreated sample by neutrons is impractical at silver contents of 10^{-5} g or less per gramme of cadmium, owing to the high Ag^{106} activities produced. Thus, the electrolytic separation of silver prior to neutron activation previously described is required at higher silver contents than was expected from earlier calculations.

A Curtius Rearrangement of Boron Compounds

P. Paetzold, Munich (Germany)

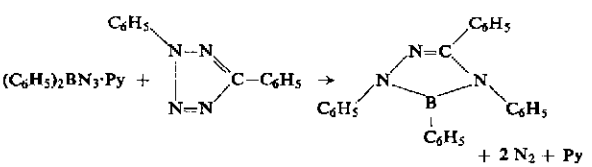
Diphenylboron chloride was stirred with sodium azide in pyridine for several days at room temperature to give a 90 % yield of colorless, stable crystals of diphenylborazidopyridine $(C_6H_5)_2BN_3 \cdot Py$ (I). Heating solvent-free I at 200 °C in a sealed tube produces a nearly quantitative conversion into hexaphenylborazole with migration of a phenyl anion. Pyridine and nitrogen are split off.

$$3\,(C_6H_5)_2BN_3 \cdot Py \rightarrow (C_6H_5B-NC_6H_5)_3 + 3\,N_2 + 3\,Py$$

With an excess of dimethylamine in a sealed tube at 250 °C, compound I gives 1-diphenylboron-2,2-dimethylhydrazine in low yield.

$$(C_6H_5)_2BN_3 \cdot Py + NH(CH_3)_2 \rightarrow (C_6H_5)_2B-NH-N(CH_3)_2 + N_2 + Py$$

This indicates that diphenylborazene, $(C_6H_5)_2B\text{-}N$, is an intermediate in the decomposition of I. At 210 °C, I reacts with 2,5-diphenyltetrazole in a sealed tube to give tetraphenyl-1-bora-2,3,5-triaza-3-cyclopentene:



The reaction product indicates that phenylimidophenylborane, $C_6H_5B=NC_6H_5$, is another intermediate in the thermal decomposition of I.

Effect of Substituents on Radical Rearrangements

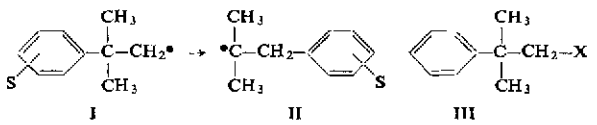
C. Rüchardt, Munich (Germany)

Relative migration rates of substituted phenyl groups in the isomerization of β-arylisobutyl radicals (I) to aryl-butyl radicals (II) were determined by competition methods. With a few exceptions, the rate values (Table 1) are independent of whether the β-arylisobutyl radicals (I) are formed by decarbonylation of β-arylisovaleraldehydes (III, X = CHO) [16], by thermal decomposition of t-butyl β-arylperisovalerates (III, X = COO–O–t-Bu), or from β-arylisobutyl chlorides (III, X = Cl) by the Kharasch reaction [17].

[16] *C. Rüchardt*, Chem. Ber. *94*, 2599, 2609 (1961); *C. Rüchardt* and *S. Eichler*, Chem. Ber., in the press.

[17] *W. H. Urry* and *M. S. Kharasch*, J. Amer. chem. Soc. *66*, 1438 (1944).

The effect of substituents on this intramolecular radical alkylation is ten times larger than that in intermolecular phenylations and depends in part on a polar substituent



I II III

Table 1. Relative micration rates

Substance	Aldehyde decarbonylation	Perester composition	Karasch reaction
p–CH_3O	0,35	0,36	0,78
p–F	0,38	0,40	0,28
p–CH_3	0 65	0,76	
o–Cl	0,90	0,9	
unsubst.	=1,00	=1,00	=1,00
o–COH_3	1,10	–	0,40
m–F	1,45	–	1,27
m–Cl	1,55	1,33	
m–Br	1,70	1,58	
p–Br	1,79	1,90	
p–Cl	1,82	1,88	1,78
p–CN	19		

effect [18]. The relative rates of migration may be used as criterion for differentiation between carbonium, carbanion, and radical rearrangements.

Photochemical Reactions Involving Cycloheptatriene

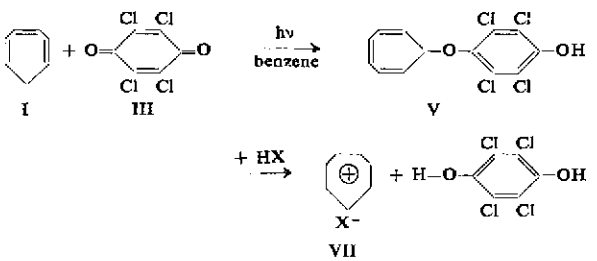
G. O. Schenck, E. Koerner von Gustorf, B. Kim, G. v. Bünau, and *G. Pfundt*, Mülheim/Ruhr (Germany)

Cycloheptatriene (I) photochemically adds onto maleic anhydride (II) to give a Diels-Alder adduct [19]. With phenanthrenequinone, I forms a Schönberg adduct [20]. Photo-induced dehydrogenative dimerization of I with Bengal Rose or duroquinone in the absence of oxygen leads to Doering's dicycloheptatrienyl. On the other hand, photochemical reaction of I with $Y = O_2$, chloranil (III), or azodicarboxylic acid diethyl ester (IV) proceeds *via* substitutive addition, as shown below:

$$C_7H_8 + Y \xrightarrow{h\nu} C_7H_7{-}Y{-}H.$$

Photosensitized addition of O_2 [21] onto I yields an unstable cycloheptatrienyl hydroperoxide, which undergoes conversion into tropone.

By acid cleavage of V and VI any tropylium salt VII (*e.g.* X = Cl, Br, ClO_4) can be prepared.



I III V

VII

Compound VI is formed in thermal and photochemical reactions from I + IV (by addition onto I of a phototropically isomeric biradical derived from IV) [22, 23]. It adds to II and IV like a norcaradiene derivative.

[18] *P. D. Bartlett* and *C. Rüchardt*, J. Amer. chem. Soc. *82*, 2646 (1960).

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

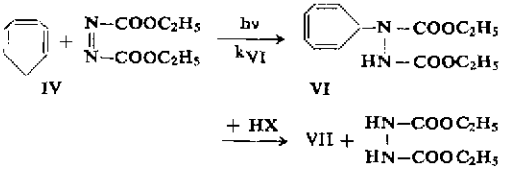
[20] *G. O. Schenck*, Z. Elektrochem. *64*, 997 (1960).

[21] *G. O. Schenck*, Angew. Chem. *69*, 579 (1957).

[22] *G. O. Schenck*, Plenary lecture, Uppsala, July 6–7th, 1961, Naturwissenschaften, in the press.

[23] *J. M. Cinnamon* and *K. Weiss*, J. org. Chemistry *26*, 2644 (1961).

Acrylonitrile and azo-bis-isobutyronitrile have no effect on the rate of formation of VI; the dependence on the polarity of the solvent is slight (in toluene: $k_{VI}^{40} = 2.9 \cdot 10^{-5}$ liters/mole·sec; $E_A = 14.7$ kcal/mole; $\Delta S = -34$ cal/degree·mole;



IV VI

in acetonitrile: $k_{VI}^{40} = 12.9 \cdot 10^{-5}$ liters/mole·sec; $E_A = 9.6$ kcal/mole; $\Delta S = -48$ cal/degree·mole). These findings can be readily explained on assumption of a concerted reaction occurring through a cyclic transition state according to *Huisgen* and *Pohl* [24].

Acid cleavage of a 1:1 adduct obtained from IV and 1,1′-dicylcoheptatrienylferrocene leads via initially formed tropylium ions to substituted ferricinium salts, with oxidation of the central Fe(II).

New Studies on the Etard Reaction

H. Schildknecht and *W. Föttinger*, Erlangen-Nürnberg (Germany)

In an attempt to prevent the formation of byproducts containing halogen, chromyl acetate was used in place of chromyl chloride for the oxidation of olefins. However, chromyl acetate oxidizes the aldehydes initially formed further to give carboxylic acids. Better results were obtained with chromyl benzoate, but even in this case, epoxides *etc.* are formed alongside the desired dialdehydes; *e.g.*, cyclooctene gave only a 6 % yield of suberaldehyde, while the yield of cyclooctene oxide was 25 %.

From considerations of electronic theory, chromyl trichloroacetate should be particularly well suited for the preparation of carbonyl compounds from olefins. The reagent was prepared from chromium trioxide and trichloroacetic anhydride in CCl_4; it can be stored at room temperature for a long time. With chromyl trichloroacetate, it was possible to oxidize cyclooctene to suberaldehyde (68 %), cycloheptene to pimealdehyde (58 %), cyclohexene to adipaldehyde (46 %), and cyclopentene to glutaraldehyde (32.5 %). There are indications that the oxidation proceeds via the carbonium ion of a 1:1 complex, from which a 1:2 complex (1 mole of olefin to 2 moles of chromyl compound) is formed.

The Crystal Structure of $Na[Zn(OH)_3]$

H. G. von Schnering, Münster (Germany)

Hitherto nothing was known of the structure of the solid ternary hydroxides. The first X-ray study of a representative of this class, *viz.* $Na[Zn(OH)_3]$ has now been made. The results indicate that the formula $Na[Zn(OH)_3]$ represents not only the composition, but also to a great extent the structure of this compound in the solid state: each Zn atom is surrounded by three O atoms coplanar with the Zn. Two more distant O atoms complete the coordination polyhedron giving an elongated trigonal bipyramid. Each Na is surrounded by six O atoms, forming a distorted octahedron. Short O–O distances indicate the presence of hydrogen bridge bonding. The position of the hydrogen atoms could not yet be determined.

In addition to the strong bands of the Na_2CO_3 invariably present [~ 3000, 1440, 878, 705, and 700 cm^{-1}] and H_2O in the region of the bending vibration δ (OH), the infrared spectrum shows a series of well resolved bands, which are assigned to the $Na[Zn(OH)_3]$. These are at (~ 3000), 1072,

[24] *R. Huisgen* and *H. Pohl*, Chem. Ber. *93*, 527 (1960).

968, 922, 850, and 799 cm^{-1}. The possibility of the presence of $ZnCO_3$, basic $ZnCO_3$ or $Zn(OH)_2$ can be excluded. In approximately 2N alkaline sodium zincate solutions, no absorptions were observed in these regions.

Cleavage Reactions with the Chlorosilanes Si_2Cl_6, Si_3Cl_8, and Si_5Cl_{12}

E. Wiberg and *A. Neumaier*, Munich (Germany)

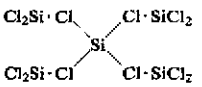
Under the catalytic influence of trimethylamine, hexachlorodisilane should disproportionate into $SiCl_4$ and $SiCl_2$ [25]. A re-examination showed that only 0.75 mole $SiCl_4$ is formed per mole Si_2Cl_6 and that the silicon subchloride has the empirical formula "$SiCl_{2.40}$". Its mulecular formula is Si_5Cl_{12} [26]. The disproportionation equation is therefore

$$4\,Si_2Cl_6 \rightarrow 3\,SiCl_4 + Si_5Cl_{12}$$

Si_5Cl_{12}, which is formed by allowing Si_2Cl_6 to stand for three hours at room temperature in the presence of catalytic amounts of trimethylamine, forms colorless moisture sensitive crystals, m.p. 306 °C (decomp.). They are readily soluble in ether and benzene, difficultly soluble in carbon tetrachloride. In a high vacuum above 50 °C they can be sublimed without decomposition. Si_3Cl_8 also forms Si_5Cl_{12}:

$$2\,Si_3Cl_8 \rightarrow SiCl_4 + Si_5Cl_{12}$$

With HCl at 50–70 °C, Si_5Cl_{12} forms $SiCl_4$ + 4 $HSiCl_3$. In an ether solution at −100 °C, excess lithium aluminum hydride hydrogenates Si_5Cl_{12} in one hour to give a mixture of 1 mole of SiH_4 and 4 moles of SiH_2. Chlorine converts Si_5Cl_{12} into 5 moles $SiCl_4$ at 200 °C but the reaction is slow and takes several days. The reaction of Si_5Cl_{12} indicate the structure



They do not agree with a "n-pentane", "isopentane" or "neopentane" structure.

Treatment with trimethylamine for several days at room temperature or higher leads to disproportionation of Si_5Cl_{12} ("$SiCl_{2.40}$") into $SiCl_4$ and subchlorides containing less chlorine, "$SiCl_{<2.40}$". Similarly, in an analogous reaction between trimethylamine and Si_2Cl_6 over several days, products poorer in chlorine, "$SiCl_{<2.40}$", are obtained besides the disproportionation compound "$SiCl_{2.40}$". The chlorine content of the "$SiCl_{<2.40}$" product can fall even below the value $SiCl_2$, especially on heating.

[VB 588/38 IE]

[25] *C. J. Wilkins*, J. chem. Soc. (London) *1953*, 3409.

[26] *Cf. G. Urry* and *A. Kaczmarczyk*, J. Amer. chem. Soc. *82*, 751 (1960); J. inorg. nucl. Chem. *17*, 186 (1961).

SELECTED ABSTRACTS

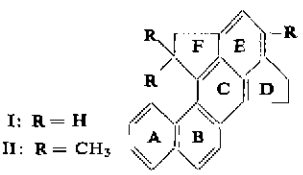
The continuous purification of air contaminated with tetraethyl-lead by means of activated carbon was studied by *I. F. Zemskov*, using a countercurrent, multi-stage fluid bed adsorber. The adsorber column contains four perforated plates. Air is fed in below the bottom plate and flows upward at a rate of 1.2 to 1.5 m/sec. Fresh carbon is continuously fed onto the top plate. The activated charcoal passes from plate to plate through overflows, a fluid bed 80 mm high being maintained on each tray. A countercurrent flow of activated carbon and contaminated air is thus established. The four-stage adsorption process achieves more than 85 % removal of TEL from the air. Ninety nine percent of the activated carbon entrained by the air is removed in a cyclone separator. The carbon leaving the bottom of the adsorber is continously treated with an air chlorine mixture, thus converting the TEL into $PbCl_2$. The latter is extracted from the carbon with hot water and the water extract treated with Na_2SO_4 to precipitate $PbSO_4$. The carbon is continuously dried in a fluid bed and recycled to the adsorber. / Zh. Prikl. Khimii *35*, 536 (1962). [Rd 218/74 IE]

Metallo-organic syntheses involving aryl compounds have been reported by *D. Wittenberg*. When aluminum is ground together with small quantities of aluminum chloride, a metal preparation is obtained which reacts with bromobenzene at 100 °C or with chlorobenzene at its boiling point to produce phenylaluminum sesquihalides in good yields.

$$3\,C_6H_5X + 2\,Al \rightarrow C_6H_5AlX_2\cdot(C_6H_5)_2AlX \qquad X = Cl, Br$$

Non-activated aluminum fails to react with aryl halides or affords merely undefined products. Phenylaluminum sesquichloride, in contrast to phenylsodium and phenylmagnesium chloride, is readily soluble in aromatic compounds. It may be employed, like its Grignard analogues, as an arylating agent. With phosphorus trichloride, it yields 93 % triphenylphosphine; with stannic chloride, depending on the proportions employed, it produces, phenyltin trichloride, diphenyltin dichloride, triphenyltin chloride, or tetraphenyltin. / Liebigs Ann. Chem. *654*, 24 (1962) / −Sk. [Rd 295/86 IE]

F-Nor-steranthrene (I) has been obtained by *E. Buchta* and *D. Kiessling* from 2a,3,4,4a-tetrahydropyracene by way of 1′-oxo-1′,2′,3′,4′-tetrahydro-7,8-benzo-2a,3,4,4a-tetrahydropyracene (colorless platelets from petroleum ether, m.p. 103–104 °C) in an eight-stage synthesis. I forms yellow platelets m.p. 209–210 °C (from ligroin/benzene) and, like



I: R = H
II: R = CH_3

its 3,6,6-trimethyl derivative II, represents, a ring system derived from cholesterol. The *in vivo* conversion of cholesterol in to II is theoretically possible. / Naturwissenschaften *49*, 280 (1962 / −De. [Rd 288/82 IE]

BOOK REVIEWS

Encyclopedia of Chemical Technology, by *R. E. Kirk* and *D. F. Othmer*, Second Supplementary Volume, edited by *Anthony Standen*. Interscience Publishers, Inc., New York, 1960. XV, 970 pp. Numerous Illustrations. Bound in black buckram: $ 25.00 [1].

The second supplement has now appeared three years after the publication of the first supplement. This volume has been edited by *Anthony Standen*, who was an assistant editor of the main work. The volume contains 60 individual articles that average approximately 15 pages each. The articles emphasize the technological progress of recent years. Technological developments in the USA are given the most thorough treatment; this is to be expected since all of the 80 authors, except one, are Americans. Because 65 authors are active in American industry, the new volume retains its conventional emphasis on practical applications. Basic problems, such as the thermodynamics of irreversible processes, the solid

[1] See previous reviews in Angew. Chem. *66*, 343 (1954); *72*, 426 (1960); *72*, 356 (1960).

state and the dislocation theory, constitute 13.7 % of the text (compared to 12 % in the main work and 21 % in the first supplementary volume). A larger portion of the text, 32.5 %, is devoted to industrial processing methods and equipment, such as nitric acid concentration and tool materials for machining (compared to 13.3 % in the main work and 24.8 % in the first supplementary volume). The remaining text deals with chemical substances from an engineering point of view.

In this short review it is possible to consider only a few details, selected from the numerous diverse articles.

Acetylene (35 pp.): The preparation of acetylene from hydrocarbons is treated extensively for the first time in this work. The article is a good presentation of this topic and one can gradually acquire an overall view of the field. The Phillips and Tennessee-Eastman methods should have been mentioned in the section on the two-stage flame process. Also, a more critical comparison of the individual methods with greater emphasis on their advantages and disadvantages would have been desirable. The excellent description of the explosive properties and the industrial methods of handling acetylene is of considerable value.

Cells, electric (34 pp.), Fuel cells (22 pp.): The new developments in galvanic cells (dry cells, wet cells, reserve cells, and fuels cells) are extensively treated. The tendency to reduce the size of portable electronic equipment has considerably influenced these recent developments. Reserve cells are units that can be stored in their inactive state for a very long time and can be activated before use, *e.g.* by flooding with ammonia gas. These cells are capable of delivering a single electric discharge which is high in relationship to the cell's weight and volume. They are of great importance in rocket technology. For military reasons, new interest has developed in fuel cells, which provide a noiseless and portable source of electric power.

Ceramics (28 pp.), Glass (19 pp.): The material in these two articles informs the reader about new developments for special applications, *e.g.* ceramics for electronic instruments, new enamelling processes, ceramic tools, radiation-barrier glass for observation parts weighing up to six tons, photosensitive glasses, from which articles can be prepared by irradiation and a chemical machining process that cannot be manufactured by ordinary mechanical methods, *etc.* The articles give numerous worthwhile details.

Chemical coding (29 pp.): This concept is defined as "An analysis of chemical information for concise recording to facilitate its transmission, utilization, and correlation." It is expected that substantial savings in the cost of research will be achieved as a result of these efforts, since too many experiments are duplicated owing to lack of knowledge of the literature. The author of this article expresses a significant opinion that it is as unreasonable to expect the busy experimental scientist to attend to his own literature search as it would be to expect him to do his own glass blowing. The article conveys a good impression of the current American attitude regarding documentation.

Cryogenics (10 pp.): Methods of attaining low temperatures (below −100 °C) are covered briefly and the application of products obtained in these processes, especially nitrogen, is described. The article is too short to do even remotely justice to the great importance of low-temperature techniques, particularly in the field of hydrocarbon fractionation. It is written more from the point of view of the steel industry's need for oxygen. However, the article does not impart any essentially new technical view points even in the field of liquefaction of air.

Geochemical Prospecting (21 pp.): A good survey is given of the chemical methods and the organization of field experimentation for predicting geological deposits. A description is given of special techniques for analyzing rock formations, soil, water, sediments, and plants, using the above approach. These working methods have attained great importance. For example, the North Rhodesian copper companies process more than one million samples per year.

Nonionic Surfactants (33 pp.): The field of nonionic surface active agents is covered extensively. A list giving approximately 600 trade names is, on account of its size, very unsuitable for an encyclopedia, particularly if one considers the fact that these trade names change very quickly.

Polymethylbenzenes (45 pp.): This does not refer to polymers but to dimethyl-, trimethyl-, and tetramethylbenzenes. The article is a careful, comprehensive, chemical study of the yields of the various compounds and isomers obtained in the petroleum industry, together with their properties, analytical determination, and the chemistry of their reactions.

Polypropylene (11 pp.): The article covers the essential facts about the properties, preparation, and application of this new synthetic material. A good detailed table gives a comparison between the properties of polypropylene and high density polyethylene; another table illustrates the chemical resistance of polypropylene. The stability to light and oxygen might have been covered more extensively.

Gas Chromatography (37 pp.): Since the entire subject of chromatography was treated only very briefly in the main work (a total of 7 pages), this is the first time that gas chromatography is presented here in a complete unit. The various types of detectors are compared according to their fields of application. A separate section covers theoretical principles. The applications of gas chromatography to process control are mentioned.

Synthesis Gas (5 pp.): This short article provides data primarily on the Texaco Synthesis Gas Process. A more thorough comparison of all the existing processes would have been desirable, since this topic was only briefly touched upon in the main work.

The above examples of the individual articles should be sufficient to indicate the scope of the volume.

Summarily, it can be stated that the volume is a good supplement to the main work. Moreover, the volume is a stimulating and interesting collection of industrial progress reports. The work provides an insight into the current ideas and trends of the American industry. Obviously, such a picture still only indicates parts of the whole. The development of special products, particularly for the communication and nuclear industries, appears to be preponderant in many places of the volume. The plastics industry and petrochemistry are less well covered. Heavy inorganic industry (with the exception of the articles on glass and ceramics) is not covered at all. One must nevertheless agree with the point of view of the editor that in the supplementary volumes, it is important to describe in full those subjects which have recently undergone changes of a more fundamental character, rather than to make minor additions to existing articles. Good indexes, with references to the main work, facilitate the use of the supplementary volume. We wish the book great success.

H. Sachsse [NB 872/19 IE]

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Attempts to Synthetize Tetramethylcyclobutadiene

BY PROF. DR. R. CRIEGEE

INSTITUT FÜR ORGANISCHE CHEMIE DER TECHNISCHEN HOCHSCHULE, KARLSRUHE (GERMANY)

Dedicated with friendship to Professor C. H. Nenitzescu on the occasion of his 60th birthday.

Attempts to prepare cyclobutadiene, which is primarily of theoretical interest, or one of its derivatives have so far led only to products structurally closely related to tetramethylcyclobutadiene. It has not been possible to prepare the compound itself nor to establish unequivocally that it occurs as a reaction intermediate.

Introduction

The following is a review of investigations begun by us about eight years ago, which were aimed at achieving the synthesis of a cyclobutadiene derivative. Originally, a comprehensive study was planned, but we soon found out that other research teams were working on the same problem. Partly as a result of agreement and partly on our own initiative, we divided the work.

For example, *C. D. Nenitzescu* [1] in Bucharest studied unsubstituted cyclobutadiene, *M. C. Cava* and his co-workers [2] investigated benzocyclobutadiene, *E. H. White* worked on diphenylcyclobutadiene [3], and *H. H. Freedman* [4] and others, studied derivatives of tetraphenylcyclobutadiene. As time went on, we came to concentrate all our efforts on the tetramethyl compound.

According to the theorists, our chances of success were doubtful. For example, in 1958, *M. J. S. Dewar* wrote the following [5]: "In fact, cyclobutadiene would have a negative resonance energy and I cannot encourage anyone to try to make it." Nevertheless, we continued our investigations in spite of this, firstly, because we, as experimenters, doubted the reliability of theoretical computations, which are necessarily based on approximations and simplifications. Furthermore, we thought that it would be interesting to see what actually happens in reactions which, from a rational point of view, could be expected to afford cyclobutadiene. Finally, it seemed to us that it should be possible to demonstrate the existence of a cyclobutadiene derivative, at least as some short-lived intermediate, and to learn something about its properties from the course of its subsequent reactions.

It is not intended to discuss here the findings of other research teams and the early work in this field, because both have been adequately reviewed elsewhere [6]. However, we will touch up on certain aspects of our own work which, although not directly related to the cyclobutadiene problem, may still, in a manner of speaking, be considered as a by-product.

The study of tetramethyl derivatives offered some advantages over investigations of the unsubstituted compound. First, tetramethylcyclobutadiene should be more stable than cyclobutadiene. If, as predicted by the theorists, the latter behaves as a biradical, then the substituted compound should be a ditertiary radical and hence should have a lower energy content than the disecondary radical represented by the parent compound. Second, more favorable physical properties (higher boiling point of the monomer, better crystallization of the possible dimers) are to be expected of the methylated compound. However, the decisive factor was the ready availability of the starting material (see below).

On the other hand, some disadvantages were also apparent. These include steric hindrance caused by crowding of the methyl groups, which could prevent some "normal" reactions from occurring and interfere with certain

[1] Cf. *M. Avram, E. Marica,* and *C. D. Nenitzescu,* Chem. Ber. *92,* 1088 (1959).

[2] *M. P. Cava* and *D. R. Napier,* J. Amer. chem. Soc. *79,* 1701 (1957).

[3] *E. H. White* and *H. C. Dunathan,* Abstracts of Papers of the ACS-Congress, Chicago, *1958,* 41P.

[4] *H. H. Freedman,* J. Amer. chem. Soc. *83,* 2194, 2195 (1961).

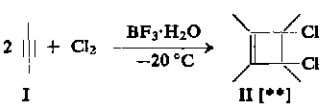
[5] *W. Baker* and *J. F. W. McOmie,* The Chemical Society Special Publication *12,* 49 (1958); *M. J. S. Dewar,* ibid., p. 108.

[6] Cf. *E. Vogel,* Angew. Chem. *72,* 4 (1960), in particular p. 17.

structure determinations. More serious was the fact that the presence of the side chain offered the possibility of double bond migration from the ring to one of the side chains, so that undesirable side reactions had to be considered. Finally, if cyclobutadiene were actually obtained, the presence of substituents on all four carbon atoms would prevent determination of the compound's ability to undergo substitution, and thus no light would be shed on at least this one facet of its aromatic character.

Starting Material

The starting material for all the substances described below was dichlorotetramethylcyclobutene (II), which was discovered in 1952 by *Smirnov-Samkov* [7]. This compound is obtained in a one-step reaction from 2-butyne (I) [*] with either chlorine or sulfuryl chloride. The yield obtained in this synthesis, the mechanism of which has not as yet been elucidated, was increased by *Moschel* [8] to 50 % by using boron trifluoride as catalyst. Attempts by both ourselves and the Russian worker to apply this synthesis to other acetylenic compounds failed. The dichloride II (m.p. 57 °C) is a highly reactive



I II [**]

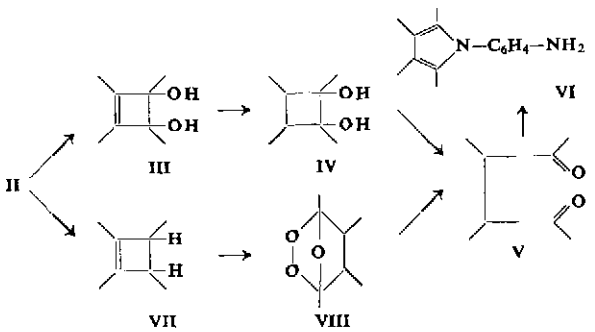
and versatile compound. It owes its reactivity to the two tertiary, and at the same time, allylic chlorine atoms, to the double bond, and to the strained unsaturated ring system.

Structure and Configuration of Dichlorotetramethylcyclobutene

The structure of the dichloride was established on the basis of two degradation sequences both yielding the same aliphatic diketone (V). This compound was characterized as the crystalline pyrrole derivative VI obtained by reaction with *p*-phenylenediamine.

Degradation Route 1 [7,9]

The dichloride is very readily hydrolyzed to the unsaturated diol (III), which may be isolated in two polymorphous forms (m.p. 92 and 126 °C) [10]. Tetrahydrofuran was found to be a better solvent for this hydrolysis than the acetone initially used, because the latter tends to hold part of the diol in solution as an acetone adduct [11]. Because of this and because the diol readily rearranges in the presence of acids, into another unsaturated diol (m.p. = 133 °C), the hydrochloric acid formed must be neutralized with bicarbonate. Judging from its reaction with potassium triacetylosmate, and in view of the easy formation of its adduct with acetone, the low-melting diol must be assigned the *cis*- and the high-melting diol, the *trans*-configuration. In contrast to the *trans*-isomer, which cannot be hydrogenated, the *cis*-diol is readily converted into the saturated *cis*-diol (IV, m.p. 60–61 °C). The elevated rate at which this compound is cleaved by lead tetraacetate (k_{20}, in 99.5 % glacial acetic acid, is 350,000; time in minutes) [12] confirms the *cis*-configuration of its hydroxyl groups. Preparative scale oxidation of this diol with lead tetraacetate affords the diketone V, from which the pyrrole derivative VI is obtained.



Degradation Route 2 [13]

Hydrogenolysis of the dichloride with lithium aluminum hydride affords a mixture of two stereoisomeric tetramethylcyclobutenes (VII), which are readily separated by distillation. On ozonolysis, both give relatively stable, isolable ozonides (VIII). On hydrogenation, these yield the two possible stereoisomeric diketones V, both of which were converted into the same pyrrole derivative VI. The fact that the opening of the cyclobutene ring on either side leads to the same end-product proves the high symmetry of the ring system.

The dichloride II most probably has the *cis*-configuration, as indicated by its high dipole moment of 2.38 D. Despite considerable effort, we have been unable to prepare the stereoisomeric dichloride. Thus, with hydrogen chloride, the *cis*- and *trans*-diol III give the same dichloride II; with hydrogen bromide, too, only one dibromide (m.p. 61–62 °C) is formed [13,14]. Its dipole moment of 2.35 D indicates that the latter must also be the *cis* compound. The same is true for the di-iodide (m.p. 79–80 °C), which is readily prepared from III and hydrogen iodide [11,14]. The fact that mild hydrolysis of the dichloride yields exclusively *cis*-diol cannot be considered as confirming evidence for the configuration of the dichloride, because the detailed mechanism of the reaction is not known.

[7] *I. V. Smirnov-Samkov*, Doklady Akad. Nauk SSSR *83*, 869 (1952); Chem. Zbl. 1939 (1954).

[*] The 2-butyne used was in part a product furnished by Chemische Werke Hüls and in part a product repeatedly prepared from methyl ethyl ketone on a 5-kg scale in facilities kindly provided by Farbwerke Hoechst.

[8] *R. Criegee* and *A. Moschel*, Chem. Ber. *92*, 2181 (1959).

[**] Here and hereinafter, the lines denote methyl groups.

[9] *R. Criegee* and *G. Louis*, Chem. Ber. *90*, 417 (1957).

[10] *C. Jahn*, Diploma Thesis, Technische Hochschule, Karlsruhe, 1960.

[11] *H. Kristinsson*, Diploma Thesis, Technische Hochschule, Karlsruhe, 1962.

[12] *H. Fiedler*, Ph. D. Thesis, Technische Hochschule, Karlsruhe, 1959.

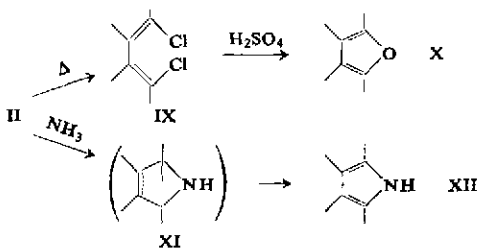
[13] *R. Criegee* and *K. Noll*, Liebigs Ann. Chem. *627*, 1 (1959).

[14] *R. Riemschneider* and *D. Becker*, Mh. Chem. *90*, 524 (1959).

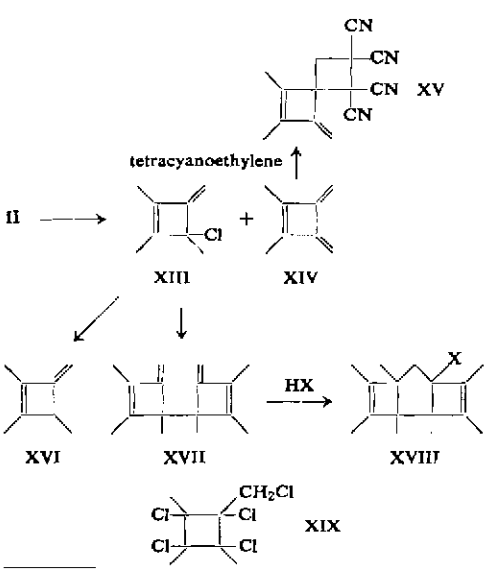
Other Simple Reactions of the Dichloride

Like all cyclobutene derivatives, the dichloride II is thermally unstable. At about 190 °C, it is converted, with bond isomerization, in 61 % yield into a 2,5-dichloro-3,4-dimethyl-2,4-hexadiene (IX) of unknown steric configuration at the double bonds. Its structure was determined from its reaction with concentrated sulfuric acid, which affords the known tetramethylfuran X.

Another simple route, leading from the dichloride II to heterocycles such as tetramethylpyrrole (XII) and its *N*-alkyl derivatives [16], is the reaction at room temperature of compound II with ammonia or primary aliphatic amines. The assumption follows readily that this reaction proceeds through an intermediate of the ethylenimine type (*e.g.*, XI). The bond isomerization XI → XII must occur particularly readily here, because the double bond in the four-membered ring would tend to weaken further the already very strained bond between the two rings and because the transition state is favored by the low energy level of the aromatic system being formed.



On heating in quinoline, II is converted into a mixture of the chlorodiene XIII and the triene XIV, with loss of hydrogen chloride [17]. Hydrogenolysis of chlorodiene XIII with lithium aluminum hydride affords the diene XVI, which may also be obtained by partial hydrogenation of triene XIV. As *Blomquist* found previously for simpler compounds [18], the diene and the triene give a 1,2-1,2-addition with tetracyanoethylene, to yield derivatives of spiro[3.3]heptane, *e.g.* compound XV. The inability of triene XIV to undergo a normal diene synthesis again indicates the high energy content of the cyclobutadiene system.

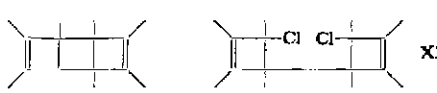


With lithium amalgam, the chlorodiene XIII undergoes a Wurtz reaction to form the dimeric hydrocarbon XVII. This highly reactive compound [17], also obtainable from II by dehalogenation of a pentachlorocyclobutane (presumably XIX), gives with acids, even in the cold, crystalline derivatives of the tricyclic system XVIII, which will not be discussed further here.

Dehalogenation of Dichloride II

Dehalogenation of the dichloride II should yield tetramethylcyclobutadiene. Actually, however, it proved to be very difficult to split off the two chlorine atoms. The Finkelstein reaction with sodium iodide [19], as well as many other applicable reactions, failed. Only the use of lithium amalgam, which had been employed shortly before by *G. Wittig* for the preparation of dehydrobenzene, led to partial success of some significance: *Louis* [9] obtained a hydrocarbon, m. p. 196 °C (decomp.), in yields exceeding 90 %. Analysis and molecular weight determination led to the formula $C_{16}H_{24}$, indicating that the compound was a dimer of tetramethylcyclobutadiene C_8H_{12}.

Since the compound could not be hydrogenated because of the strong steric hindrance caused by the crowding of the methyl groups mentioned above, and since this hindrance caused other reactions to take an anomalous course, the structure of the compound was determined first by a combination of physical methods. Nuclear magnetic resonance was particularly useful. The NMR spectrum of the substance showed only two sharp, unsplit signals of equal intensity, indicating by their position the presence of protons from paraffinic and allylic methyl groups. However, the presence of four allylic methyl groups requires (at least) two double bonds. This and the empirical formula indicate a tricyclic system. The infrared spectrum showed a band at 1680 cm^{-1}, which is typical for the disubstituted cyclobutene double bond. This indicates that, as in the starting material, the double bonds are located in the four-membered ring. The absence of absorption in the ultraviolet in the region above 210 mμ proves the absence of a conjugated system. All this suggests formula XX for *Louis*' hydrocarbon. At first, only the high stability of the new compound seemed incompatible with the structure assumed, which might be expected to be highly strained. However, heating the compound above its melting point brought about a strongly exothermic reaction, with quantitative formation of a "liquid isomer", the structure of which will be discussed later.



[15] *W. Engel*, Ph. D. Thesis, Technische Hochschule, Karlsruhe, 1962.

[16] *M. Krieger*, Diploma Thesis, Technische Hochschule, Karlsruhe, 1962

[17] *J. Dekker*, Ph. D. Thesis, Technische Hochschule, Karlsruhe, 1961.

[18] *A. T. Blomquist* and *Y. C. Meinwald*, J. Amer. chem. Soc. *79*, 5316 (1957).

[19] *H. Finkelstein*, Chem. Ber. *92*, xxxvii (1959).

It would seem obvious to explain the formation of XX by spontaneous dimerization of tetramethylcyclobutadiene. However, a twofold Wurtz reaction, presumably involving the dichloride XXI as an intermediate, is also quite possible. Although the preparation of compound XXI has not yet been accomplished, the reaction cited above of the chlorodiene XIII with lithium amalgam suggests that the corresponding reaction with II should also be possible. By dehalogenation, the second step of such a reaction sequence should then lead to the formation of the middle four-membered ring. Normally, the reaction of 1,4-dihalides with metals, if it takes place at all, gives cyclobutane only in moderate amounts [20]. In the case of XXI, however, the otherwise common side-reaction, *i.e.*, fragmentation with formation of two olefin molecules, is probably not favored, since it would have to lead to the cyclobutadiene system.

Nickel Chloride Complex

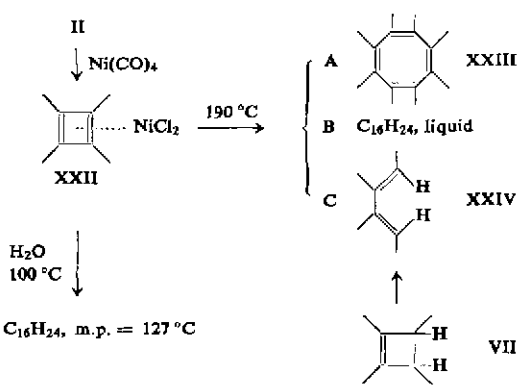
In 1956, *Longuet-Higgins* and *Orgel* [21] predicted the possibility of the existence of a C_4H_4–$NiCl_2$ complex of cyclobutadiene. Later, *Schröder* [22] treated the dichloride II with nickel carbonyl in benzene, acetone, and ether, and obtained an almost quantitative yield of a purple nickel complex of empirical formula $C_8H_{12}NiCl_2$. This compound is stable up to 180 °C, even if exposed to air; its solution, for example, in chloroform or methylene chloride, is darkpurple. It dissolves very readily in water to give a blood-red solution. Evaporation of aqueous solutions, in which the compound is apparently present in a hydrated form, again yields the purple salt. With silver nitrate, instantaneous precipitation of silver chloride takes place, but with dimethylglyoxime, separation of the nickel salt is slow, beginning only after about an hour.

Cryosopic measurements indicated strong association but did not resolve the question whether, in the complex, tetramethylcyclobutadiene is bound to one nickel atom, or whether one of its dimers is bound to two nickel atoms. However, chemical degradation reactions unequivocally pointed to the monomeric structure. Catalytic hydrogenation in aqueous solution quickly destroyed the complex and, along with nickel, tetramethylcyclobutane was formed, 90 % of which was in the all-*cis* form. The hydrocarbon was identical with the product of catalytic hydrogenation of *cis*-tetramethylcyclobutene (VII) [13]. This compound was also prepared by treating the complex with zinc and hydrochloric acid. Finally, reaction of an aqueous solution of the complex with sodium nitrite in the cold gave a good yield of *cis*-tetramethylcyclobutenediol (III). This indicates unequivocally that the monomeric four-membered ring is present in the complex. The NMR spectrum is also in agreement with structure XXII as it shows a single signal, proving the equivalence of all four methyl groups. X-ray structural investigations by *Dunitz* [23] offered the best evidence for the formula assumed and, in addition, showed that the nickel atom was situated above the center of the four-membered ring. It is noteworthy that the crystals consist of double molecules held together by chlorine atoms. Obviously, the 16-electron shell of the nickel (*dsp*² structure) as it occurs in the single molecules is completed to form an 18-electron shell by addition of an electron pair from the chlorine atom of an adjacent molecule.

In solution, solvent molecules seem to play the role of the third chlorine ligand. Strong electron donors such as triphenylphosphine or *o*-phenanthroline give new complexes of composition $C_8H_{12}NiCl_{12}{\cdot}P(C_6H_5)_3$ and $C_8H_{12}NiCl_{12}{\cdot}$phenanthroline, respectively, in which, however, the bond with the new ligands is relatively weak.

Decomposition of the Complex

Since the nickel chloride complex was proved to be a structural derivative of tetramethylcyclobutadiene, it seemed promising to attempt to obtain the desired hydrocarbon from its complex with the metal. First, thermal decomposition *in vacuo* was studied [22]. This reaction took place at about 190°C and gave three volatile products, A, B, and C along with nickel chloride. Small amounts of A were deposited in the distillation bridge in the form of very long, colorless needles, m.p. 113 °C. Its empirical formula, $C_{16}H_{24}$, showed it to be a new dimer of tetramethylcyclobutadiene. Its NMR spectrum exhibited only a single, sharp signal. A satisfactory explanation of both the equivalence of all the methyl groups and the unsaturated character of the compound was obtained only on assumption of the octamethylcyclooctatetraene structure (XXIII). Its ultraviolet absorption spectrum resembles that of the unsubstituted tetraene. The main product, B, was liquid and was found to be identical with the "liquid dimer" obtained by thermal decomposition of hydrocarbon XX. The cold trap contained a small amount of the very volatile compound C. This material was found to be a hydrocarbon, C_8H_{14}, identified as tetramethylbutadiene (XXIV) by its spectrum and reactions. It was probably formed by thermolysis of tetramethylcyclobutene (VII), which in turn was formed by thermal hydrogenation of tetramethylcyclobutadiene or of the nickel complex. In fact, thermal cleavage of the cyclobutene derivative VII to give XXIV was readily accomplished [13].



[20] *W. B. Smith*, J. Org. Chemistry *23*, 509 (1958).

[21] *H. C. Longuet-Higgins* and *L. E. Orgel*, J. chem. Soc. (London) 1969 (1956).

[22] *R. Criegee* and *G. Schröder*, Liebigs Ann. Chem. *633*, 1 (1959).

[23] *J. D. Dunitz* et al., Angew. Chem. *72*, 755 (1960); Helv. chim. Acta *45*, 647 (1962).

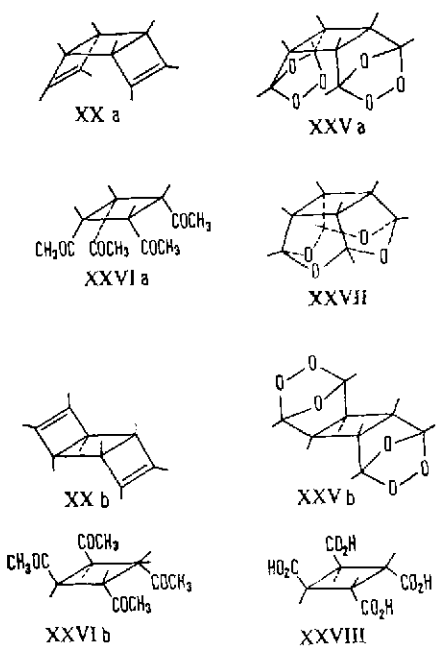
According to *G. Schröder*, the behavior of the nickel complex, on prolonged refluxing of its aqueous solution, was entirely different. Gradually, colorless crystals (m.p. 127 °C) formed in the reflux condenser, a 50 % yield being obtained. This yield was increased to 70–80 % by using ethylene glycol as solvent. The new hydrocarbon is also a dimer of tetramethylcyclobutadiene; it is, however, different from XX, XXIII, and the "liquid dimer". Spectral data for this compound and XX are surprisingly similar, indicating that the compound is possibily a stereoisomer of *Louis*' hydrocarbon. This supposition was confirmed [24].

syn- and *anti*-Tricyclooctadiene

For a compound of the type of *Louis*' hydrocarbon (XX), theory predicts two steric forms, *i.e.* the *syn*-(XXa) and the *anti*-form (XXb). It was possible to show that the isomer melting at 196 °C possesses the *syn*-, and that melting at 127 °C the *anti*-configuration.

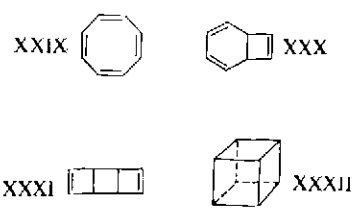
This assignment is supported by their dipole moments: *viz.* 0 and 0.63 ± 0.2 D, respectively. Decisive evidence was obtained from oxidative degradation, which is relatively easy to effect via isolable diozonides. Hydrogenation of the two diozonides (XXVa and XXVb) gave two products of formula $C_{16}H_{24}O_4$. Only one product (that from XXVb) proved to be a tetraketone (XXVIb); the latter was oxidized further with hypobromite to a tetracarboxylic acid (XXVIII), whose anhydride was identical with a compound obtained by photodimerization from dimethylmaleic anhydride [25, 26].

By contrast, the compound obtained from XXVa contained no carbonyl, hydroxyl, or perhydroxyl groups. Hence, the four oxygen atoms necessarily formed ether linkages. The supposition that the hypothetical all-*cis* tetraketone XXVIa underwent spontaneous cyclization to a tetraketal (XXVII) was verified by the NMR spectrum of the new compound. This spectrum showed only two proton signals of equal intensity. The formation of this tetraketal proves that both double bonds in XXa are in the *syn*-form.



Valence Isomerism of the $C_{16}H_{24}$ Hydrocarbons

Theoretically, five bond isomers are possible for a hydrocarbon $(CH)_8$, the methyl-free parent compound of hydrocarbons XXa, XXb, and XXIII. These are: monocyclic cyclooctatetraene (XXIX), bicyclo[4.2.0] octatriene (XXX), containing a four-membered and a six-membered ring, the *syn*- and *anti*-isomers of tricyclooctadiene (XXXI), and pentacyclooctane ("cubane", XXXII). Of these compounds, XXIX is well known and seems to be related by bond tautomerism to XXX; at any rate all efforts to prepare XXX have so far failed. One of the tricyclic compounds (XXXI) seems to have been found among the decomposition products of the silver complex $C_4H_4 \cdot AgNO_3$, prepared by *Nenitzescu* [27]. Cubane is still unknown [*].



The compounds missing in the series of permethylated compounds were octamethylcubane (attempts to prepare this compound by sensitized irradiation of XXa were unsuccessful) and the bicyclic isomer XXX. *Wirth* [28] succeeded in preparing the latter by subjecting *Louis*' hydrocarbon (XXa) to thermal decomposition in the presence of a small amount of sodium ethoxide. In the absence of base, the "liquid isomer" $C_{16}H_{24}$ mentioned above is formed. This compound is not a bond isomer, because it is certain that it contains a semicyclic methylene group formed by a proton shift. Isomerization of XXa into the "liquid isomer" may be accomplished not only thermally, but also at 0 °C using conc. sulfuric acid. Hence, the thermal isomerization could logically also be ascribed to the presence of traces of acids or acid sites on the reactor wall. As already mentioned, the isomerization does in fact take a different course in the absence of acids and yields exclusively a hydrocarbon (XXXIII), m.p. 23 °C Under identical conditions, both the *anti*-compound XXb and, interestingly, also the cyclooctatetraene derivative XXIII

[24] *R. Criegee, G. Schröder, G. Maier*, and *H. G. Fischer*, Chem. Ber. *93*, 1553 (1960).

[25] *D. Erickson*, unpublished data.

[26] *G. O. Schenck* et al., Chem. Ber. *95* (1962), in press.

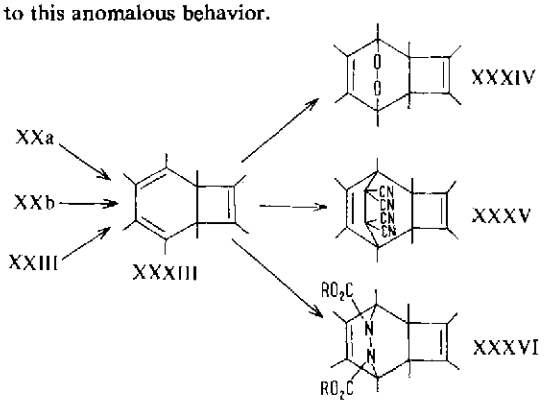
[27] *M. Avram, G. Mateescu, J. G. Dinulescu, E. Marica*, and *C. D. Nenitzescu*, Tetrahedron Letters 21 (1961).

[*] Addition in proof: In a paper just published *H. H. Freedman* and *D. R. Petersen* ascribe the structure of octaphenylcubane to a hydrocarbon $C_{56}H_{40}$: J. Amer. chem. Soc. *84*, 2837 (1962).

[28] *W. D. Wirth*, Ph. D. Thesis, Technische Hochschule, Karlsruhe, 1960.

are isomerized to the bicyclic compound XXXIII. Of the four isomers, XXXIII is obviously the most stable thermodynamically.

The structure of the new isomer was determined from its physical properties and chemical behavior. Its NMRspectrum reveals an 18:6 value for the ratio of allylic to paraffinic protons, indicating the presence of three double bonds and, hence, two rings. The strong ultraviolet absorption between 225 and 250 mμ (log ε = 3.6 to 3.7) indicates that two of these double bonds are conjugated. The absence of the expected maximum at 270–280 mμ might be due to the fact that a planar arrangement of the six-membered ring is impossible owing to crowding of the methyl groups. A transannular interaction of the double bond in the four-membered ring with the conjugated system could also lead to this anomalous behavior.



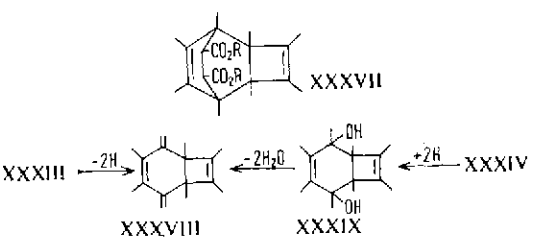
The isolation of XXXIII thus indicates that the permethylated compounds are capable of forming such bond isomers (these even possess relatively high stability), which are unknown so far for the unsubstituted compounds. It would be worthwhile to determine whether in other cases, too, an accumulation of methyl groups can stabilize the structure of bond isomers.

The behavior of XXXIII towards oxygen is unusual [28]. The hydrocarbon autoxidizes so readily that its preparation is possible only with complete exclusion of oxygen. On exposure to air for a few hours, it is quantitatively transformed into a crystalline peroxide. On shaking its methanolic solution with oxygen, exactly one mole of oxygen is absorbed in 20 minutes. The rate of peroxide formation is independent of illumination; it occurs equally rapidly in the dark and is also independent of the presence of inhibitors. Since physical and chemical analysis of the compound indicates the absence of –OOH groups, the compound must be a transannular peroxide of structure XXXIV. Its infrared, ultraviolet, and NMR spectra are compatible with this structure. It is known that cyclohexadienes can form endoperoxides; this, however, seems to be the first example where such a peroxide is formed in the dark. The presence of methyl groups on the unsaturated system cannot be the only reason for such behavior, considering that hexamethylcyclohexadiene, synthetized to check this point [29], is not appreciably oxidized in the dark. Rather, it appears that the unsaturated four-membered ring of the condensed system is required for this unusual behavior.

Compound XXXIII also acts as a diene with tetracyanoethylene [15] and azodicarboxylic esters [30], the adducts XXXV and XXXVI being readily prepared. By contrast, it is unusual that no reaction takes place with maleic anhydride and acetylenedicarboxylic esters even at 140 °C [15]. At higher temperatures, the compound simply rearranges to the "liquid isomer". This inertness towards maleic anhydride is even more unusual in view of the recent finding of *Cookson* [31] that *Louis'* hydrocarbon (XXa) reacts with acetylenedicarboxylic esters at 125 °C to give an adduct which seems to have structure XXXVII. Hence, either this structure must be revised or XXXVII cannot be obtained via XXXIII.

Most unusual, however, is the behavior of XXXIII toward dehydrogenating agents. On shaking its solution in ether with aqueous silver nitrate, silver is deposited, and a hydrocarbon, $C_{16}H_{22}$ (m.p. 55 °C), can be isolated from the ether solution [28]. The same reaction may be achieved with chloranil in the cold or with benzoquinone on heating.

The two detached hydrogen atoms must originate from two methyl groups since no other possibility exists. In agreement with this, the infrared and NMR spectra of the new compound, which was first prepared by *Maier* [32], indicate the presence of two semicyclic methylene groups. These cannot be directly conjugated with each other, since the new hydrocarbon does not undergo diene syntheses with dienophiles. However, a conjugated system is present, as indicated by the ultraviolet absorption spectrum showing maxima at 226 mμ (log ε = 4.33) and 255 mμ (log ε = 4.29). Since, judging from the NMR spectrum two paraffinic methyl groups must be



present, the only possible structure remaining for *Maier's* hydrocarbon is XXXVIII [15]. This structure also explains why diol XXXIX, formed by reduction of peroxide XXXIV, also yields XXXVIII on elimination of water. Energetically, the hydrocarbon must be very much favored, as indicated by the fact that it is formed as the main product of thermal decomposition, with loss of water, of the epoxides of XXa and XXIII [32].

Structure of the "Liquid Isomer" [9, 15, 28]

The "liquid isomer" is the product of stabilization of all four $C_{16}H_{24}$ bond isomers, *viz.* XXa, XXb, XXIII, and XXXIII; it is formed from these either thermally or by the action of acids. The "compound" has a semicyclic double bond and a system of conjugated double bonds (λ_{max} = 241 mμ; log ε = 4.26). This conjugation is either absent in the other isomers or, because of their nonplanar structure, is not fully effective and must be the reason for the greater stability. On hydrogenation, the "compound" adds on two atoms of hydrogen and loses its semicyclic double bond, giving rise to a mixture of $C_{16}H_{26}$ hydrocarbons. These can be separated by gas

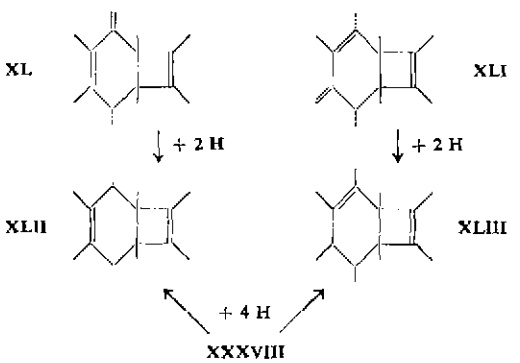
[29] *W. Trieselt*, Ph. D. Thesis, Technische Hochschule, Karlsruhe, 1961.

[30] *A. Ludwig*, unpublished data.

[31] *C. E. Berkoff*, *R. C. Cookson*, *J. Hudec*, and *R. O. Williams*, Proc. chem. Soc. (London) 312 (1961).

[32] *G. Maier*, Ph. D. Thesis, Technische Hochschule, Karlsruhe, 1959.

chromatography into five very similar components, two of which are crystalline at room temperature. A mixture of the same products in different proportions is obtained on hydrogenation of *Maier*'s hydrocarbon. Adding four hydrogen atoms, this compound also loses its two semicyclic double bonds, while the cyclobutene double bond, which can be easily identified, by its characteristic infrared spectrum, remains unaltered. This certainly indicates that the "liquid isomer" and XXXVIII are closely related. Thus, we can assume that the former has the structure XL, and that the common hydrogenation product has the structure XLII. However, if the four- and six-membered rings are assumed to be joined in a *cis*-configuration, then only three stereoisomers are possible for XLII, whereas five were found. Hence, it is probable that the "liquid isomer" is a nonseparable mixture of the two similar hydrocarbons XL and XLI, and that the dihydro compounds are mixtures of the stereoisomers XLII and XLIII. If this is so, it must be assumed that a partial 1,4-addition of hydrogen takes place in the conversion of XXXVIII into XLIII. Both XL and XLI could have been easily formed from XXXIII as a result of a prototropy, and their formation from the other three isomeric $C_{16}H_{24}$ hydrocarbons can also be readily explained. Thus, the preliminary structure of the "liquid isomer" previously proposed, *i.e.*, a condensed three- and seven-membered ring system [9,22], is not tenable.



Thermolysis of the C_8H_{12}·$NiCl_2$·Phenanthroline Complex [33]

Having discussed the dimers of tetramethylcyclobutadiene and their various reactions, let us again consider the monomer. Since thermolysis of the simple nickel chloride complex did not give the desired result, and attempts to displace the four-membered ring system from the nickel by the use of other ligands failed, thermal decomposition of adducts of the nickel complex with electron donors was investigated. The triphenylphosphine complex revealed no new information. By contrast, decomposition of the phenanthroline complex proceeded somewhat differently. In this case, too, the "liquid isomer" XL plus XLI was the main reaction product. However, in place of octamethylcyclooctatetraene (XXIII) the *anti*-form of the tricyclic hydrocarbon XXb was obtained. A relatively large amount of a monomer (yields of up to 30 %) was found in the cold trap. However, this material was neither tetramethylcyclobutadiene nor tetramethylbutadiene (XXIV) but methylenetrimethylcyclobutene (XVI), an isomer of the cyclobutadiene derivative. This indicated that the undesirable side reaction discussed earlier, *viz.* the double bond shift to the side chain, had taken place. Possibly, this shift is similar to the acid-catalyzed double bond migration observed in the case of the dimers. This migration might be caused by the small amount of hydrogen chloride which is formed in all thermolyses of nickel chloride complexes and the formation of which could so far not be prevented. The occurrence of the side reaction indicates that methylenecyclobutene is more stable than methylcyclobutadiene, whereas, normally, in a four-membered ring, an endocyclic double bond is favored over an exocyclic one [34].

[33] *P. Ludwig* and *K. Noll*, unpublished data.

Reaction of the Nickel Chloride Complex with Cyclopentadienylsodium [35]

The chlorine atoms in the nickel chloride complex XXII can be replaced easily by other ligands [36]. For example, it was possible to prepare the bromide, iodide, periodide, azide, nitrate, sulfate, trichloroacetate, and oxylate. Reaction of XXII in aqueous solution with the sodium salt of dimercaptodicyanoethylene, described by *G. Bähr* [37], gave a crystalline precipitate, which may be used for the quantitative determination of the $C_8H_{12}Ni^{2+}$ cation.

The reaction of the nickel complex with cyclopentadienylsodium was also investigated in connection with these reactions A new, red, beautifully crystalline nickel complex was obtained in tetrahydrofuran according to the equation:

$$C_8H_{12}NiCl_2 + 2\ C_5H_5Na \rightleftharpoons 2\ NaCl + C_{18}H_{22}Ni$$

This complex is soluble in hydrocarbons, insoluble in water, and sublimes undecomposed *in vacuo*; in the solid state, it is fairly resistent to atmospheric oxygen but is quite sensitive solution.

On hydrogenation, the compound adds on four atoms of hydrogen without undergoing any appreciable color change. A tetrahydro complex, $C_{18}H_{26}Ni$, very similar to the unreduced complex, may thus be isolated. Nickel is split off only on further vigorous hydrogenation, and a saturated hydrocarbon, $C_{13}H_{24}$, is obtained, along with cyclopentane. An unsaturated C_{13} hydrocarbon is obtained on treatment of the unhydrogenated complex with two moles of acid, with simultaneous formation of one mole of cyclopentadiene, as shown in the equation:

$$C_{18}H_{22}Ni + 2\ HX \rightleftharpoons NiX_2 + C_5H_6 + C_{13}H_{18}$$

The $C_{13}H_{18}$ hydrocarbon contains three double bonds and, on hydrogenation, affords the saturated bicyclic $C_{13}H_{24}$ hydrocarbon. Two double bonds are conjugated, as indicated by the fact that the compound forms an adduct with acetylenedicarboxylic esters. At 300 °C, this adduct undergoes decomposition into cyclopentadiene and tetramethylphthalic ester XLVIII. This is best explained by assuming structure XLVII. The hydrocarbon may then be represented by formula XLVI,

[34] *F. F. Caserio, S. H. Parker, R. Piccolini*, and *J. D. Roberts*, J. Amer. chem. Soc. *80*, 5507 (1958); *E. Gil-Av* and *J. Herling*, Tetrahedron Letters *27* (1961).

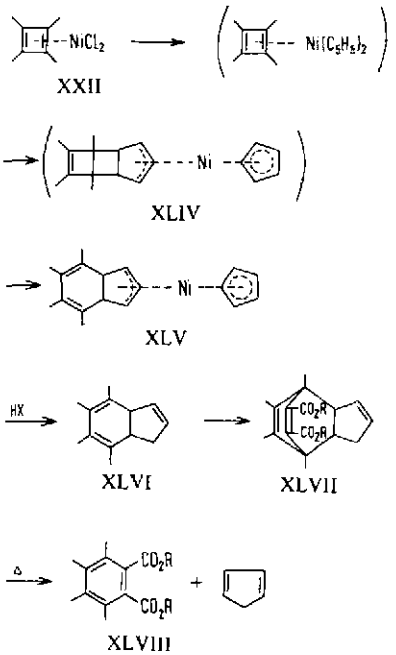
[35] *R. Criegee* and *P. Ludwig*, Chem. Ber. *94*, 2038 (1961).

[36] *J. F. Pfrommer*, Ph. D. Thesis, Technische Hochschule, Karlsruhe, 1961.

[37] *G. Bähr* and *G. Schleitzer*, Chem. Ber. *90*, 441 (1957).

whereas the complex must be of the π-allyl-π-cyclopentadienyl type, as indicated by formula XLV. As can be seen, the two double bonds in the six-membered ring are not necessary to hold the complex together. Thus, they may be hydrogenated without ill effects.

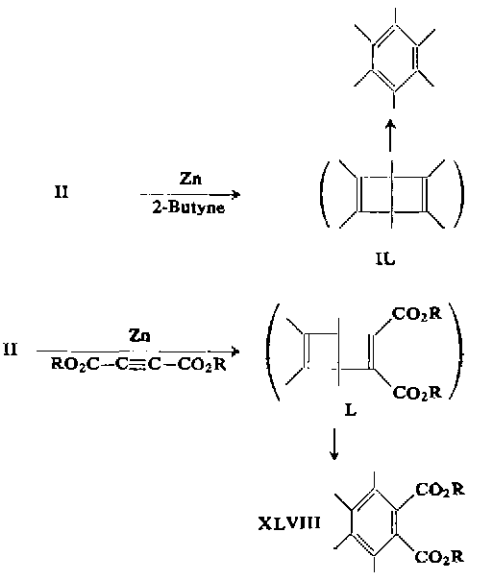
In the formation of complex XLV from the original nickel complex XXII, tetramethylcyclobutadiene must have added onto one of the cyclopentadienyl residues bound to the nickel. The tricyclic intermediate XLIV then rearranged to XLV with bond isomerization. The synthesis of the indane skeleton is reminiscent of the synthesis of tetrametyhlnaphthalene involving a chromium complex, as carried out by *Zeiss* [38].



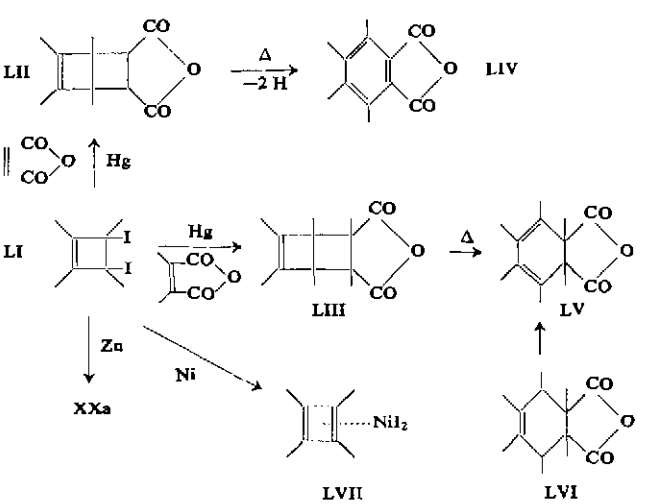
Dehalogenation of Diiodotetramethylcyclobutene

Efforts to prepare tetramethylcyclobutadiene have recently received new stimuli from two sides. First, *Cookson* [31] investigated the dehalogenation of dichlorotetramethylcyclobutene (II) in the presence of acetylene derivatives. Whereas with lithium amalgam, independent of such additives, he always obtained *Louis'* hydrocarbon (XXa), with zinc and 2-butyne, he obtained hexamethylbenzene as well. The interpretation of this reaction as an addition of tetramethylcyclobutadiene onto the butyne to give the bond isomer of hexamethylbenzene (IL) with simultaneous, spontaneous isomerization, found support in the corresponding reaction carried out in the presence of an acetylenedicarboxylic ester, which led to a tetramethylphthalic ester (XLVIII) via the bicyclic compound L.

Independently, *Kristinsson* [11] carried out some preliminary experiments on the dehalogenation of the diiodide (LI) corresponding to the dichloride II, hoping that the former would loose its halogen under milder conditions than those required for the dichloride. Whereas, with zinc, *Louis'* hydrocarbon (XXa) was obtained nearly quantitatively, shaking with mercury or silver produced



colorless solutions, which deposited dark resins on exposure to air. Additions of cyclopentadiene or furan had no effect on this phenomenon. However, when the reaction was conducted in the presence of maleic or dimethylmaleic anhydride, the adducts LII and LIII were obtained, sometimes in excellent yields. In contrast to IL and L, these adducts are stable, since simple bond isomerization cannot produce a low-energy, aromatic system. The bicyclic compound is cleaved only upon thermal treatment. In the case of LII, this simultaneously causes dehydrogenation to give tetramethylphthalic anhydride (LIV), whereas LIII affords the cyclohexadiene derivative LV, which does not undergo dehydrogenation. This derivative had been previously synthesized by *Trieselt* [29] from tetramethylbutadiene (XXIV) via its adduct with dimethylmaleic anhydride (LVI).

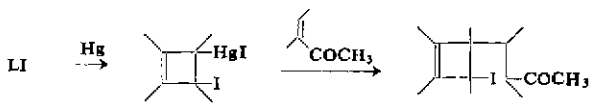


While at first sight these experiments seem to prove the formation of tetramethylcyclobutadiene as an intermediate a corresponding experiment with addition of 3-methylpentenone suggests caution. This experiment afforded a 10 %

[38] *W. Herwig, W. Metlesics,* and *H. Zeiss,* J. Amer. chem. Soc. *81,* 6203 (1959).

yield of the iodine-containing compound LIX, which must have been formed by the action of the monomercury compound LVIII on the ketone. Whether an organometal synthesis or a free-radical addition on to the C=C double bond has taken place in this case still remains to be seen.

Shaking the diiodide with degassed Raney nickel smoothly afforded tetramethylcyclobutadiene-nickel iodide (LVII).



LVIII LIX

Conclusions

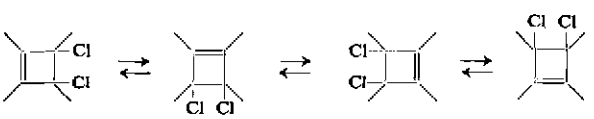
The experiments described dealt with compounds which are structurally closely related to tetramethylcyclobutadiene; these compounds can be arranged into the three following groups:

1. Compounds of the C_8 series:
   Tetramethylbutadiene (XXIV)
   Methylenetrimethylcyclobutene (XVI)
   Nickel complexes $C_8H_{12}NiHal_2$ (XXII, LVII)
2. Dimeric, $C_{16}H_{24}$ hydrocarbons:
   syn-Tricyclooctadiene (XXa)
   anti-Tricyclooctadiene (XXb)
   Octamethylcyclooctatetraene (XXIII)
   "Liquid isomer" (XL plus XLI)
3. Condensation products:
   Nickel complex $C_{18}H_{22}Ni$ (XLIV)
   Hexamethylbenzene
   Tetramethylphthalic ester (XLVIII)
   Tetramethylbicyclohexenedicarboxylic anhydride (LII)
   Hexamethylbicyclohexenedicarboxylic anhydride (LIII)

In particular, the following should also be noted. In most instances, the type of product formed is highly specific. For example, the reaction of the dichloride with lithium amalgam affords only the *syn*-dimer (XXa), the decomposition of the nickel complex with water only the *anti*-dimer (XXb). Thermal decomposition of the nickel chloride complex gives, apart from the "liquid dimer", only octamethylcyclooctatetraene, while the apparently very similar decomposition of the phenanthroline complex yields, apart from the "liquid dimer" only the tricyclic *anti*-compound XXb. The dichloride yields the tricyclic *syn*-compound (XXa) not only when it is reacted with lithium amalgam, but also (although in markedly lower yields) in the reaction with zinc. In the first instance, the reaction cannot be influenced by addition of an acetylenic compound, in the second, it can. With zinc, the diiodide LI yields the tricyclic *syn*-compound XXa in nearly quantitative yield, whereas, with mercury or silver, not more than traces are formed. With nickel, only a nickel iodide complex is formed, but no dimer.

Do these experiments, or at least some of them, constitute evidence for the occurrence of tetramethylcyclobutadiene as an intermediate? We should like to answer this question in the negative. Certainly the formation of all the products cited can be postulated to involve a cyclobutadiene derivative as an intermediate, which then undergoes stabilization by dimerization, complex formation, reaction with dienophiles, double bond migration to a side chain, or addition of two hydrogen atoms supplied by other molecules. Some postulates of this type even appear quite plausible. The specificity mentioned above, however, suggests caution. If the same intermediate were in fact involved in all the reactions, the products obtained would form a more uniform picture. Moreover, all the reactions can be interpreted by assuming a mechanism involving products similar to cyclobutadiene, but not this compound itself.

The use of labelled compounds would hardly afford the desired proof, either. For example, if it were possible to label the two methyl groups adjacent to the chlorine atoms in dichloride II, then it could be expected that, in reactions proceeding via free tetramethylcyclobutadiene, the labelled isotope in *Louis'* hydrocarbon XXa for example would be distributed over all four methyl groups. However, since other possible mechanisms involve the occurrence of ions or free radicals (or at least cryptoions or cryptoradicals), interaction of these with the allylic cyclobutene double bond could be expected, and this, too, would lead to a uniform distribution of the labelled carbon. Because of the high reactivity of dichloride II, it is even doubtful that specific labelling of this compound is possible, since tautomerism of the following type certainly takes place very rapidly.



Hence, in future, other routes will have to be taken to demonstrate the existence of cyclobutadiene. Our studies certainly prove that tetramethylcyclobutadiene, if it exists at all, not only has nonaromatic properties but must also be a compound of high energy content.

Received, March 9th, 1962 [A 222/48 IE]

The Isomerization of Aziridine Derivatives

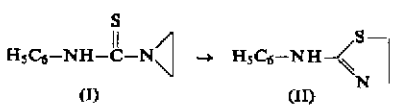
BY PROF. DR. H. W. HEINE [*]

BUCKNELL UNIVERSITY, LEWISBURG, PENNSYLVANIA (U.S.A.)

Derivatives of aziridine or ethylenimine are isomerized by acids, nucleophilic reagents, or pyrolysis. All of the isomerizations reported so far are ring-opening reactions, predominantly involving cleavage of the carbon-nitrogen bond of the ring, although a few isomerizations are known in which the carbon-carbon bond of the ring is broken. Isomerization of appropriate aziridine derivatives provides useful synthetic pathways leading to heterocyclic systems such as oxazolines, imidazolines (and related systems), imidazolidinones, thiazolines, pyrazolines, and triazolines. Other isomerizations form N-unsaturated amides, anils, and isocyanates.

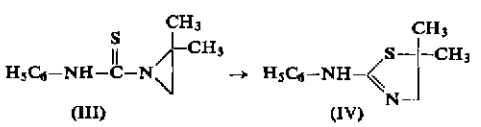
Acid Catalyzed Isomerizations of Aziridine Derivatives

The earliest example of an acid catalyzed isomerization of an aziridine was described by *Gabriel* and *Stelzner* [1] in 1895. These investigators converted 1-aziridinethiocarboxanilide (I) into 2-anilino-Δ^2-thiazoline (II) by heating it in concentrated hydrochloric acid. Subsequent work has shown that this isomerization occurs in 90% yield [2]. The reaction was extended to a number of substituted 1-aziridinethiocarboxanilides [3] as well as to 1-(*N*-cyclohexylthiocarbamyl)aziridine [4] and 1-(*N*-benzylthiocarbamyl)aziridine [3]. It was further shown



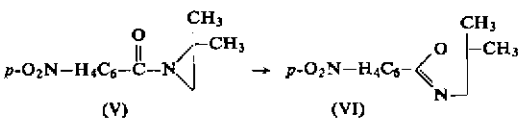
(I) (II)

that aqueous sulfuric acid or phosphoric acid also catalyze analogous isomerizations of 1-(*N*-*m*-tolylthiocarbamyl)aziridine and 1-(*N*-cyclohexylthiocarbamyl)-aziridine [3]. Treatment of unsymmetrical 1-(*N*-phenylthiocarbamyl)-2,2-dimethylaziridine (III) with hot concentrated hydrochloric acid gave a 30% yield of 2-anilino-5,5-dimethyl-Δ^2-thiazoline (IV) along with some phenylthiourea and 2-methylpropanal [2].



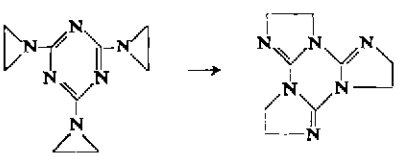
(III) (IV)

1-Aroylaziridines are isomerized into 2-aryl-Δ^2-oxazolines by aluminum halides in refluxing heptane [5] or by concentrated sulfuric acid at room temperature [6]. Dissolution of 1-(*p*-nitrobenzoyl)-2,2-dimethylaziridine (V) in concentrated sulfuric acid formed 2-(*p*-nitrophenyl)-5,5-dimethyl-Δ^2-oxazoline (VI) in 97% yield [6]. Analogously, 1-(*p*-nitrobenzoyl)-2-methylaziridine and 1-(*p*-nitrobenzoyl)-2-ethylaziridine rearrange to the corresponding 2-(*p*-nitrophenyl)-5-alkyl-Δ^2-oxazolines in concentrated sulfuric acid [7].



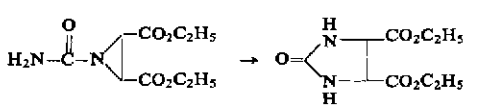
(V) (VI)

A study of the reaction of 2,4,6-tris-(1-aziridinyl)-*s*-triazine (VII) and 2,4-diamino-6-(1-aziridinyl)-*s*-triazine with triethylamine hydrochloride in boiling acetonitrile revealed that conversion into 2,3,6,7,10,11-hexahydrotrisimidazo-[1,2-*a*; 1′,2′-*c*; 1″,2″-*e*]-*s*-triazine (VIII) and 5,7-diamino-2,3-dihydroimidazo[1,2-*a*]-*s*-triazine respectively had occurred [8].

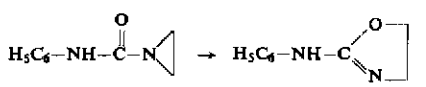


(VII) (VIII)

Two reports on the isomerization of 1-carbamylaziridines by acid catalysts have appeared. When heated with dilute hydrochloric acid, 1-carbamyl-2,3-diethoxycarbonylaziridine (IX) rearranged into 4,5-diethoxycarbonyl-2-imidazolidinone (X) [9]. In contrast, 1-



(IX) (X)



(XI) (XII)

[*] National Science Foundation Faculty Fellow 1961–1962 at the Chemisches Institut der Universität Köln (Germany).

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[7] *H. W. Heine* and *E. M. Johnson*, unpublished results.

[8] *F. C. Schaefer*, J. Amer. chem. Soc. *77*, 5922 (1955).

[9] *T. Curtius* and *W. Dörr*, J. prakt. Chem. *125*, 425 (1930)

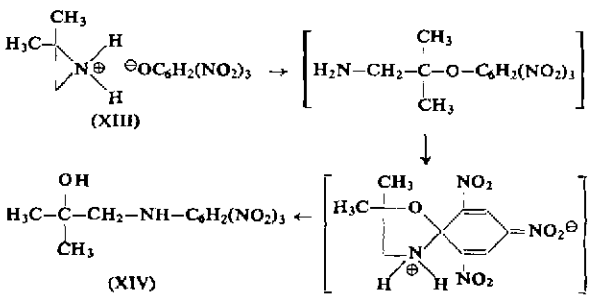
aziridinecarboxanilide (XI) is isomerized into the picrate of 2-anilino-Δ^2-oxazoline (XII) in refluxing ethyl acetate containing picric acid [4].

The acid catalyzed isomerizations cited so far – especially those occurring in sulfuric acid – can be rationalized by mechanisms involving protonation of the aziridinyl nitrogen followed by ring opening to form a carbonium ion with subsequent ring closure to give the various five-membered heterocyclic systems. In the case of V, ring opening is postulated [6] to yield the tertiary carbonium ion:

$$Ar{-}CO{-}NH{-}CH_2{-}\overset{\ominus}{C}(CH_3)_2$$

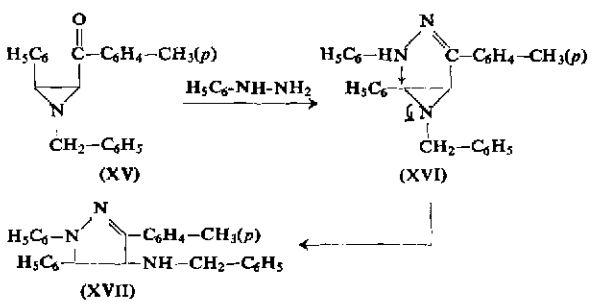
A similar mechanism had been proposed previously [2] for the isomerization of III by hydrochloric acid, although prior formation of *N*-(2-chloro-2-methylpropyl)-*N'*-phenylthiourea followed by ionization of chloride ion to give a tertiary carbonium ion is not ruled out.

A rather unusual isomerization occurred when the picrate of 2,2-dimethylaziridine (XIII) was heated in solvents such as acetonitrile or nitromethane. The picramide of 1-amino-2-methyl-2-propanol (XIV) was obtained in 40 % yield [10]. The following mechanism has been suggested for this transformation:



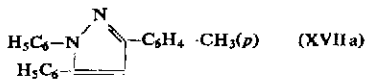
(XIII) (XIV)

The reaction of presumably the *trans* form of 1-benzyl-2-phenyl-3-(*p*-toluyl)aziridine (XV) with phenyl-hydrazine in glacial acetic acid to give 1,5-diphenyl-3-(*p*-tolyl)-4-benzylaminopyrazoline (XVII) may be regarded as an acid catalyzed isomerization of the non-isolated phenylhydrazone (XVI) [11a, b].



(XV) (XVI) (XVII)

The *cis* form of XV as well as the presumed *cis* forms of 1-benzyl-2-phenyl-3-benzoylaziridine and 1-benzyl-2-(*p*-tolyl)-3-benzoylaziridine reacted under analogous conditions to give the corresponding pyrazoles. These are probably formed from pyrazolines of the type XVII by *trans* elimination of the hydrogen on C-5 and the benzylamino group on C-4. Formula XVIIa depicts the pyrazole derived from the *cis* form of XV.

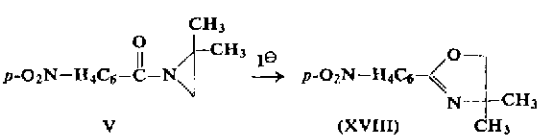


(XVIIa)

Isomerization of Aziridine Derivatives by Nucleophiles

The isomerization of aziridines by nucleophilic reagents such as iodide ion or thiocyanate ion was first observed in 1959. These reagents are effective catalysts for the rearrangement of 1-aroylaziridines, 1-(*N*-arylbenzimidoyl)aziridines (and similar systems), 1-aziridinecarboxanilides, 1-aziridinethiocarboxanilides, and 1-arylazoaziridines. Iodide ion also brings about dimerization of a number of aziridines which are substituted at position one with electron-withdrawing groups. Reaction of primary or secondary amines with aziridines usually gives addition products rather than isomerized substances.

1-Aroylaziridines are easily isomerized into 2-aryl-Δ^2-oxazolines in acetone solutions containing sodium iodide or potassium thiocyanate [6, 12]. The rearrangement proceeds in high yields for various 1-aroylaziridines studied, *e.g.* 1-(*p*-nitrobenzoyl)-, 1-(*p*-chlorobenzoyl)-, 1-(*p*-ethoxybenzoyl)- and 1-(3,5-dinitrobenzoyl)-aziridines. 1-Aroyl-2-alkylaziridines such as 1-(*p*-nitrobenzoyl)-2-methylaziridine, 1-(*p*-nitrobenzoyl)-2-ethylaziridine, and 1-(*p*-nitrobenzoyl)-2,2-dimethylaziridine (V) form selectively the corresponding 2-(*p*-nitrobenzoyl)-4-alkyl-Δ^2-oxazolines *e.g.* (XVIII) when treated with iodide ion in acetone [6, 12]. In contrast, ring opening in the acid catalyzed isomerization of V occurs at the carbon of the aziridine ring with the largest number of alkyl groups to give 2-(p-nitrophenyl)-5,5-dimethyl-Δ^2-oxazoline (VI) as the only product.



V (XVIII)

In acetonitrile as solvent 1-(*p*-Nitrobenzoyl)aziridine is also rearranged by iodide ion whereas in methanol, it is quickly converted by iodide ion or methoxide ion into methyl *p*-nitrobenzoate. Interestingly, other amides such as *p*-nitroacetanilide, *p*-nitrobenzamide, *N*-(*p*-nitrobenzoyl)piperidine or *N,N*-dimethyl-*p*-nitrobenzamide may be refluxed for several hours in methanol containing iodide ion without methanolysis taking place.

1-(*N*-Arylbenzimidoyl)aziridines (XIX) and the similar systems 2,4,6-tris-(1-aziridinyl)-*s*-triazine (VII) and 2-

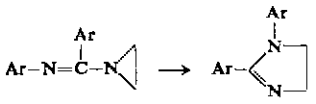
[10] *L. B. Clapp, E. A. Rick, W. B. Moniz,* and *V. B. Schatz,* J. Amer. chem. Soc. *77*, 5116 (1955).

[11a] *N. H. Cromwell, N. G. Barker, R. A. Wankel, P. J. Vanderhorst, F. W. Olson,* and *J. H. Anglin,* Jr., J. Amer. chem. Soc. *73*, 1044 (1951).

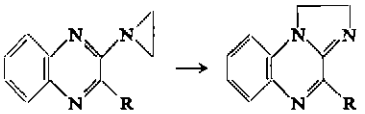
[11b] *N. H. Cromwell* and *H. Hoeksema,* J. Amer. chem. Soc. *71*, 716 (1949).

[12] *H. W. Heine, W. G. Kenyon,* and *E. M. Johnson,* J. Amer. chem. Soc. *83*, 2570 (1961).

(1-aziridinyl)quinoxalines (XX) are easily isomerized by iodide ion or thiocyanate ion into 1,2-diaryl-2-imidazolines (XXI) [13], 2,3,6,7,10,11-hexahydrotrisimidazo [1,2-*a*; 1′,2′-*c*; 1″,2″-*e*]-*s*-triazine (VIII) [12] and 1,2-dihydroimidazo[1,2-*a*]quinoxalines (XXII) [14], respectively.



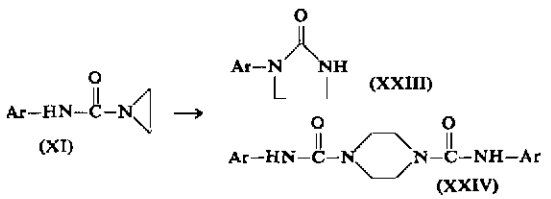
(XIX) (XXI)



(XX) (XXII)

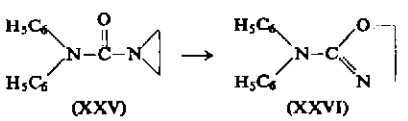
In each of these examples, the aziridinyl moiety is converted by the nucleophile into an effective alkylating agent for a neighboring nitrogen. It appears that this reaction might be quite general and might be employed for the synthesis of novel heterocyclic compounds.

In the presence of sodium iodide and acetone, 1-aziridinecarboxanilide (XI) is transformed into several products [12]. Employment of large quantities of sodium iodide and very small amounts of acetone gave an 85 % yield of 1-phenylimidazolidin-2-one (XXIII). Smaller quantities of sodium iodide and larger volumes of acetone resulted in the formation of as much as 22 % of the dimer, *N,N′*-bisphenylcarbamylpiperazine (XXIV), as well as XXIII and some 2-anilino-Δ^2-oxazoline (XII). Control runs without sodium iodide resulted in recovery of unchanged 1-aziridinecarboxanilide.



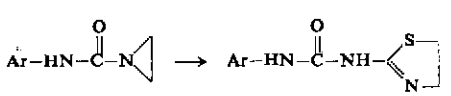
(XI) (XXIII) (XXIV)

The conversion of 1-aziridinecarboxanilides into 1-arylimidazolidin-2-ones by iodide ion in acetone has been observed to be a general reaction [15]. 1-(*N,N*-Diphenylaminocarbonyl)-aziridine (XXV), in which the hydrogen



(XXV) (XXVI)

of the N–H bond of 1-aziridinecarboxanilide has been replaced by a phenyl group, isomerizes under analogous conditions to give 2-diphenylamino-Δ^2-oxazoline(XXVI)



(XI) (XXVII)

[13] *H. W. Heine* and *H. S. Bender*, J. org. Chemistry *25*, 461 (1960).

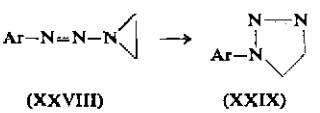
[14] *H. W. Heine* and *A. C. Brooker*, J. org. Chemistry *27*, 2943 (1962).

[15] *H. Najer, R. Giudicelli, J. Menin*, and *C. Morel*, C. R. hebd. Séances Acad. Sci. *253*, 2369 (1961).

[12]. When 1-aziridinecarboxanilides (XI) are treated with potassium thiocyanate in place of sodium iodide in acetone solution, 2-(3-arylureido)-Δ^2-thiazolines(XXVII) are obtained instead of isomerized products [15].

In contrast to the 1-aziridinecarboxanilide system, 1-aziridinethiocarboxanilide (I) isomerized into 2-anilino-Δ^2-thiazoline (II) in 95 % yield when heated with iodide ion in acetone [12]. It is reported that 1-aziridinethiocarboxanilide is isomerized by sodium ethoxide in ethanol and by hydrazine hydrate in 96 % ethanol to give 2-anilino-Δ^2-thiazoline in yields of 16 % and 8.4 %, respectively [3]. 1 - (Cyclohexylthiocarbamyl)aziridine and 1-(2,5-dimethylphenylcarbamyl)aziridine are likewise isomerized in ethanolic sodium ethoxide solutions into the corresponding 2-thiazolines in 10 % and 15 % yield, respectively [3]. It is quite possible that these rearrangements are not due to the ethoxide ion or hydrazine at all, since 1-(cyclohexylthiocarbamyl)-aziridine was observed to isomerize into 2-cyclohexyl-Δ^2-thiazoline in 11 % yield by merely heating in ethanol [4].

Isomerization of 1-arylazoaziridines (XXVIII) into 1-aryl-Δ^2-1,2,3-triazolines (XXIX) is achieved by treating the azoaziridines with acetone solutions of sodium

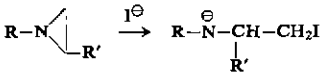


(XXVIII) (XXIX)

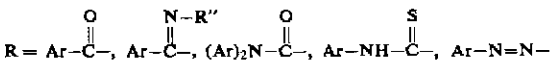
iodide [16]. This isomerization represents the first general method for synthetizing monosubstituted Δ^2-1,2,3-triazolines.

1-Arylazoaziridines containing an *ortho* substituent on the aryl moiety, such as 1-(2-methyl-4-bromophenylazo)-aziridine or 1-(2-methyl-5-nitrophenylazo)aziridine, explode violently a short time after having been isolated. Other 1-arylazoaziridines decompose vigorously when exposed to fumes of hydrogen bromide or chloride.

No experimental evidence is available to lend credence to any particular mechanistic pathway for the isomerizations of aziridines by nucleophiles. The isomerizations can be explained by reaction schemes having a common first step, *viz.* attack by a nucleophile, such as iodide ion, on one of the carbon atoms of the aziridine ring to form a 2-iodoethylamine anion (XXX):



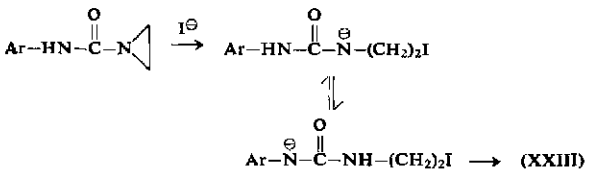
(XXX)



This step is followed by an expulsion of the nucleophile catalyst due to internal *O*- or *N*- or *S*-alkylation to yield the isomerized product. With 1-aroyl-2-alkylaziridines, the iodide ion reacts exclusively at the less substituted carbon atom to form an *N*-(1-alkyl-2-iodoethyl)benzamido ion.

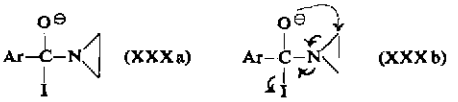
[16] *H. W. Heine* and *D. A. Tomalia*, J. Amer. chem. Soc. *84*, 993 (1962).

In the isomerization of the 1-aziridinecarboxanilides, it is suggested that the ring-opening step is followed by a tautomerization prior to the displacement of the iodide ion, thus producing an imidazolidinone instead of an oxazoline [12, 15]:



If, however, the hydrogen on the nitrogen of 1-aziridinecarboxanilide is replaced by a phenyl group, *e.g.* as in XXV, tautomerization is precluded and oxazoline formation is observed.

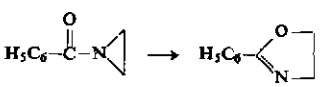
Alternate proposals can be envisaged for the isomerizations. Thus, rearrangement of the 1-aroylaziridines might involve an amide addition complex (XXXa) followed by formation of the oxazoline (XXXb).



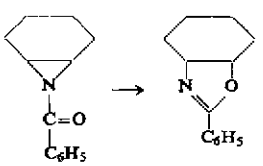
Similar intermediates can be conceived for other aziridine systems that undergo rearrangement with nucleophiles.

Thermal Isomerizations of Aziridine Derivatives

Gabriel and *Stelzner* were the first to report a thermal isomerization of an aziridine. They observed that 1-benzoylaziridine (XXXI) isomerized to 2-phenyl-Δ^2-oxazoline (XXXII) upon distillation at 240 °C and atmospheric pressure [1]. Later workers noted that the distillate obtained by distilling 1-benzoylaziridine at 125 °C/12 mm. consisted approximately of 70 % 2-phenyl-Δ^2-oxazoline and 30 % 1-benzoylaziridine [17]. More recently, it was shown that pyrolysis of *N*-benzoyl-

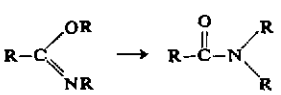


(XXXI) (XXXII)



(XXXIII) (XXXIV)

cis-cyclohexenimine (XXXIII) gave (±)-*trans*-2-phenyl-4,5-tetramethylene-Δ^2-oxazoline (XXXIV) in 20 % yield [18]. These pyrolytic isomerizations represent examples

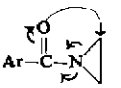


(XXXIVa)

[17] *A. A. Goldberg* and *W. Kelley*, J. chem. Soc. (London) 1919 (1948).

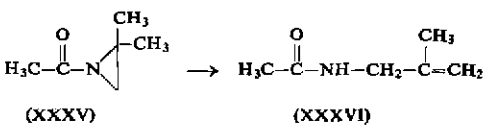
[18] *F. Winternitz, M. Mousseron*, and *R. Dennilauler*, Bull. Soc. chim. France 382 (1956).

of the reverse of the reaction on pyrolysis of imido esters (XXXIVa) and may involve a cyclic four-membered transition state:

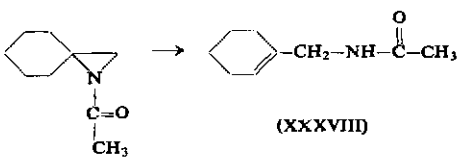


Similarly, 1-aziridinethiocarboxanilide (I) and *N,N*-ethylenethiourea have been converted into the corresponding thiazoline derivatives by heating in decalin [4].

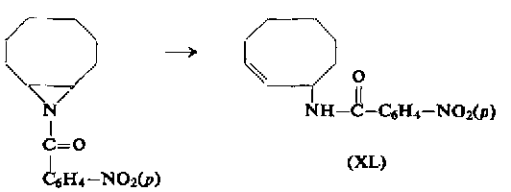
Fanta et al. have discovered and studied extensively pyrolytic isomerizations of suitably substituted 1-acyl-2-alkylaziridines into unsaturated amides. 1-Acetyl-2,2-dimethylaziridine (XXXV) undergoes pyrolytic rearrangement to *N*-(β-methallyl)acetamide (XXXVI) in high yield [19] as does 7-acetyl-7-azaspiro[5.2]octane (XXXVII) to *N* - (1 - cyclohexenylmethyl)acetamide (XXXVIII) [20]. Other examples include the isomerization of 1-(*p*-nitrobenzoyl)-2,2-dimethylaziridine (V) in refluxing heptane into *N*-(β-methallyl)-*p*-nitrobenzamide [6] and of *N*-(*p*-nitrobenzoyl)cycloöctenimine (XXXIX) into *cis*-*N*-(*p*-nitrobenzoyl)-3-cycloöctenylamine (XL) in toluene solution at 170–180 °C [21].



(XXXV) (XXXVI)

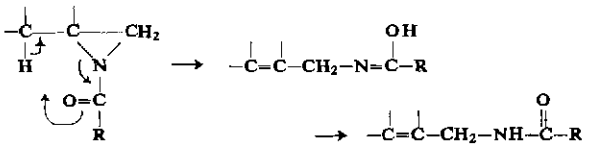


(XXXVII) (XXXVIII)



(XXXIX) (XL)

The conversion of 1-(*p*-nitrobenzoyl)-2-benzylaziridine in refluxing toluene into *N*-(*trans*)-cinnamyl-*p*-nitrobenzamide demonstrates the stereospecificity of these isomerizations [22] and suggests that the pyrolytic rearrangement of 1-acyl-2-alkylaziridines occurs by an intramolecular, concerted and stereospecific transfer of a proton from the alkyl group to the oxygen, as formulated below:



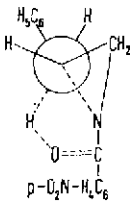
[19] *P. E. Fanta* and *A. S. Deutsch*, J. org. Chemistry *23*, 72 (1958).

[20] *P. B. Talukdar* and *P. E. Fanta*, J. org. Chemistry *24*, 526 (1959).

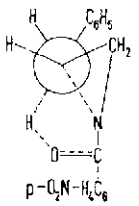
[21] *D. V. Kashelikar* and *P. E. Fanta*, J. Amer. chem. Soc. *82*, 4927 (1960).

[22] *D. V. Kashelikar* and *P. E. Fanta*, J. Amer. chem. Soc. *82*, 4930 (1960).

With regard to the isomerization of 1-(*p*-nitrobenzoyl)-2-benzylaziridine, the *trans* isomer is thought to arise from a transition state (XLI) which does not require eclipsing of the relatively bulky phenyl group and the methylene group of the aziridine ring in contrast to the transition state XLII.



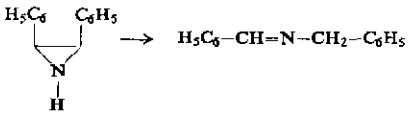
(XLI)



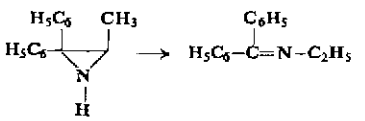
(XLII)

1-(*p*-Bromobenzenesulfonyl)-2,2-dimethylaziridine also reacted at 150 °C in toluene forming *N*-(β-methallyl)-*p*-bromobenzenesulfonamide in 15 % yield [23].

The pyrolytic isomerizations of 2,3-diphenylaziridine (XLIII) into benzalbenzylamine (XLIV) [24a, b] and of 2,2-diphenyl-3-methylaziridine (XLV) into ethyliminobenzophenone (XLVI) [25] at 175–205 °C are of interest, since they involve scission of the carbon-carbon bond of the aziridine ring rather than the usual cleavage of the carbon-nitrogen bond of the ring.

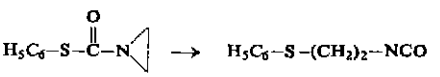


(XLIII) (XLIV)



(XLV) (XLVI)

The isomerization of 1-phenylthiocarbamylaziridine (XLVII) in refluxing toluene or xylene into the isocyanate (XLVIII) has recently been observed [26].



(XLVII) (XLVIII)

Sufficient evidence is not available to decide what is the mechanism of this transformation.

Received, June 14th, 1962 [A 228/44 IE]

[23] *D. V. Kashelikar* and *P. E. Fanta*, J. org. Chemistry *26*, 1841 (1961).

[24a] *G. H. Coleman* and *G. P. Waugh*, Proc. Iowa Acad. Sci. *40*, 115 (1935).

[24b] *G. H. Coleman* and *C. S. Nicholopoulos*, Proc. Iowa Acad. Sci. *49*, 286 (1942).

[25] *B. K. Campbell* and *K. N. Campbell*, J. org. Chemistry *9*, 178 (1944).

[26] *H. W. Heine* and *D. A. Tomalia*, unpublished results.

Dyeing of Poly(acrylonitrile) Fibers with Azatrimethinecyanines

BY DR. JACQUES VOLTZ

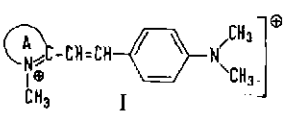
WISSENSCHAFTLICHE LABORATORIEN DER J. R. GEIGY AG., FARBSTOFFABTEILUNG
BASEL (SWITZERLAND)

Like all basic dyes, azatrimethinecyanines possess a good dyeing affinity for acrylic fibers. Compounds with isolated nitrogen atoms in the trimethine chain show insufficient light fastness, whereas good to excellent fastness to light is displayed by compounds having neighboring nitrogen atoms in the chain. Thus, a working hypothesis stating that the light fastness of trimethinecyanines on acrylic fibers is improved by progressive replacement of methine groups by nitrogen atoms has been partially confirmed.

Introduction

Soon after the appearance of the acrylic fibers on the textiles market, it became evident that representatives of old, well-known basic dyestuffs, *e.g.* of the di- and tri-phenylmethane, oxazine, and methine series, *etc.*, are particularly well-suited for dyeing polyacrylonitrile. However, most of the products in these dyestuff classes do not satisfy the light fastness requirements of the dyer.

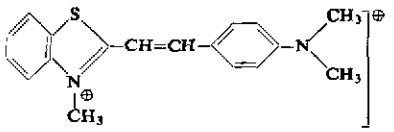
During investigations of cationic salts (I) of the hemicyanine series, in which A is an aromatic heterocycle (a thiazole, thiodiazole, triazole, imidazole, pyrazole,



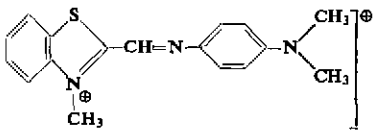
I

or indazole ring), it was found that the light fastness of dyeings made with such compounds increases with in-

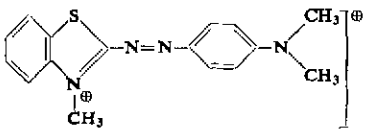
crease in the number of methine groups replaced by nitrogen atoms. Thus, dyeings made with methine (II) and monoazamethine (III), *e.g.*, on Orlon® (Du Pont) or Dralon® (Bayer), display light fastness values of approximately 2, while those made with diazamethine (IV)



II



III

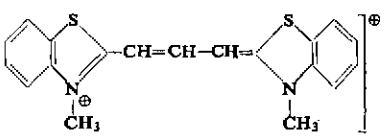


IV

exhibit light fastness of 6–7 [1]. This behavior may be due to the stability to oxidation displayed by the dye salts [2].

While conventional basic dyestuffs are readily attacked by oxygen and water in the presence of light, diazahemicyanines are stable under these conditions. However, they are extremely unstable in the presence of nitrogen and water and in the absence of oxygen. Simultaneously, they are unstable to reducing agents in aqueous solution and are difficult to remove from the dyed fiber with oxidizing agents. No satisfactory explanation for this remarkable behavior of the diazahemicyanines could be given up to now.

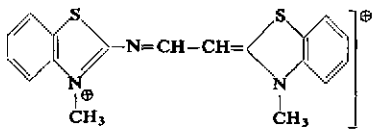
It therefore seemed a good proposition to investigate the effect of replacing methine groups in methinecyanines with nitrogen atoms. The readily obtainable carmine trimethinecyanine dye V was used as standard



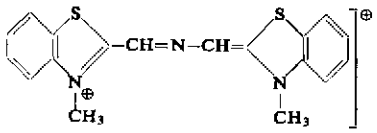
V

for comparison; although it dyes acrylics well, its dyeings display a low fastness to light (light fastness of 2).

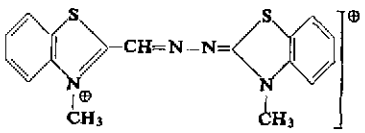
Azatrimethinecyanines have already been described in the literature. Their sensitizing and desensitizing properties in photographic films have been thoroughly studied, and attempts have been made to evolve a theoretical explanation of these properties [3,4]. Their dyeing properties, however, have never been properly evaluated. This discussion is thus concerned with the compounds VI through X.



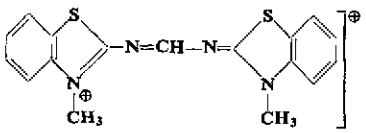
VI [5]



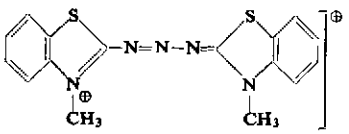
VII, [6]



VIII [7,8]



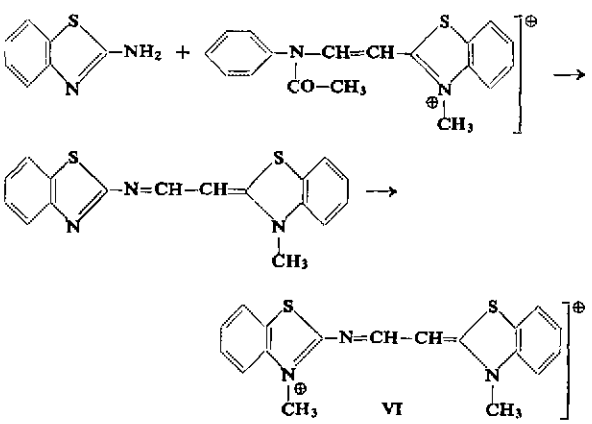
IX [9]



X [10]

Monoazatrimethinecyanines

Unsymmetrical monoazatrimethinecyanines can be formed as follows [5]:



VI

The dye cation VI shows an absorption at 466 mμ in methanol – a much shorter wavelength than that of the absorption of the trimethinecyanine V (522 mμ in

[1] Cf. *H. Baumann*, Chimia *15*, 163 (1961); *J. Voltz*, *ibid. 15*, 168 (1961).

[2] *G. Schwen* and *G. Schmidt*, J. Soc. Dyers Colourists *75*, 101 (1959).

[3] Cf. *L. G. S. Brooker* in *C. E, K. Mees:* The Theory of Photographic Processes. McMillan, New York 1952, pp. 1025, 1043 *et seq.*

[4] *K. Venkataraman:* Synthetic Dyes, Academic Press, New York 1952, vol. II, p. 1183 *et seq.*

[5] *J. D. Kendall*, US.-Pat. 2080050.

[6] *L. G. S. Brooker* [3], p. 1043. To our knowledge nothing else has been published on preparation and properties of these compounds.

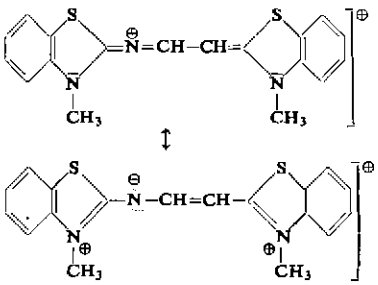
[7] *K. Fuchs* and *E. Grauaug*, Ber. dtsch. chem. Ges. *61*, 57 (1928).

[8] *N. I. Fisher* and *F. M. Hamer*, J. chem. Soc. (London) 907 (1937).

[9] *J. D. Kendall*, US.-Pat. 2080049.

[10] *A. I. Kiprianow*, Ukrain. Khim. Zh. *15*, 460 (1949); *20*, 204 (1954).

methanol). *Brooker* [11] interprets this absorption shift by assuming the resonance structures VIa and VIb. The nitrogen atom in the chain



VIa

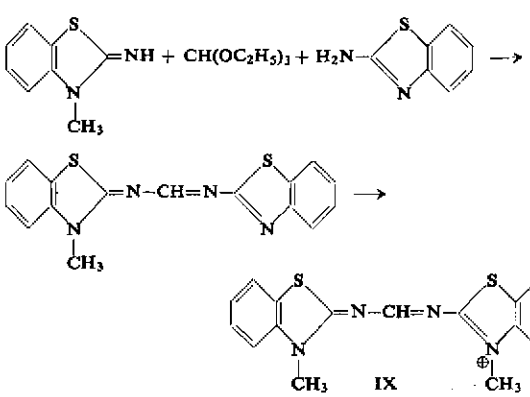
VIb

carries either a positive or a negative charge. However, the resonance structure VIa is probably of only slight importance, since the nitrogen sp^3-bond is tetrahedral, and both terminal heterocycles must then be located in planes lying perpendicular to each other. The resonance system of the trimethinecyanine dye is divided into two shorter resonance systems (terminal ammonium-nitrogen – azeniate-nitrogen within the chain) under the influence of the negatively charged nitrogen atom in the chain of VIb, which acts as an auxochrome. At shorter wavelengths, the shorter conjugated systems must show a lower absorption intensity than the longer conjugated system, situated between the two terminal nitrogen atoms.

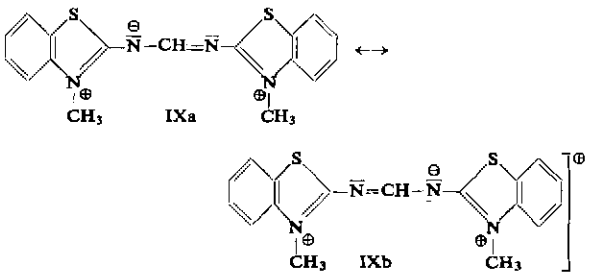
In spite of their being Schiff's bases, compounds of type VI are very stable toward hot dilute acids; this may be due to their resonance stabilization. They can, therefore, be used for dyeing poly(acrylonitrile) fibers in a boiling acetic acid bath. The dye salt VI shows a high affinity for acrylics and gives green fluorescent dyeings. However, they have only low light fastness, approximately 2.

Diazatrimethinecyanines

Symmetrical diazatrimethinecyanines of type IX can be prepared in the following manner [9]:

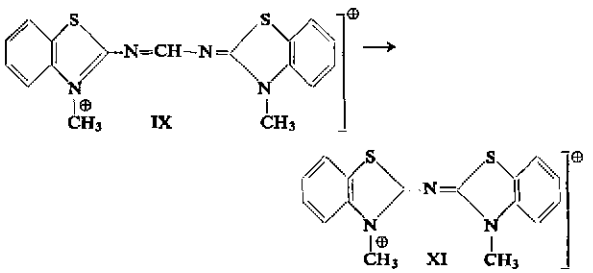


Compound IX is a green-tinged yellow substance of low coloring strength, which shows an absorption maximum at 412 mμ in 1,2-dichloroethane. Compared to trimethinecyanine (V; $\lambda_{max} = 522$ mμ in methanol), the maximum absorption peak is thus located at a shorter wavelength. According to *Brooker* [11], this may be explained by resonance structures of types IXa and IXb, in which the nitrogen atoms in the chain become additional auxochromes.

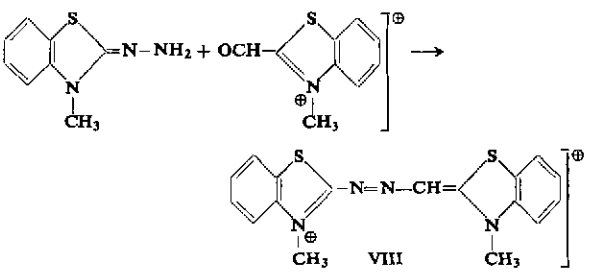


The dye is thereby divided (at least formally) into two resonance systems of small chain length (terminal ammonium-nitrogen – azeniate-nitrogen within the chain); this results in a short-wave, lower intensity absorption.

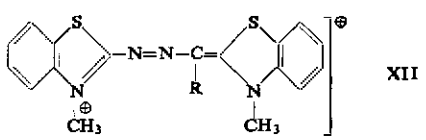
Dye salts of type IX are not suitable for dyeing poly(acrylonitrile), as they hydrolyze when boiled in weakly acidic aqueous solution, yielding basic fragments which also have an affinity for the fiber. By a still obscure mechanism, the fluorescent azamonocyanine XI is formed, among others products, from the cation IX [12,13].



Unsymmetrical diazatrimethinecyanines of type VIII are obtained in the following way [7, 8]:



Branched-chain diazatrimethinecyanines (XII) are obtained when heterocyclic ketones are used instead of heterocyclic aldehydes:



Heterocyclic dichloromethyl or carbonyl compounds can be also condensed with the hydrazone to give the dye base (XIII), which is then alkylated to the dye salt

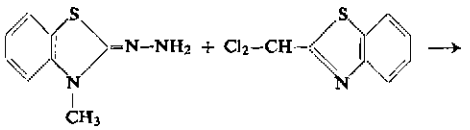
[11] *L. G. S. Brooker*, J. Amer. chem. Soc. *73*, 1087 (1951).

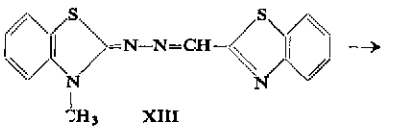
[12] *F. M. Hamer*, J. chem. Soc. (London) 1348 (1924); *N. I. Fisher* and *F. M. Hamer*, *ibid.* 907 (1937).

[13] Badische Anilin- & Sodafabrik, Belgian Pat. 589006.

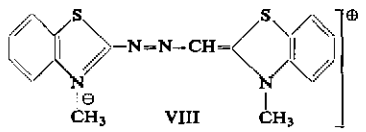
(VIII). The alkylation occurs exclusively on the tertiary nitrogen atom of the non-alkylated heterocycle [14, 15].

A wide range of unsymmetrical diazatrimethinecyanines can thus be synthetized by varying the heterocyclic hydrazones and carbonyl compounds. The industrial manufacture of these dyestuffs is hindered by the lack of suitable heterocyclic carbonyl compounds. Imidazole-2-aldehyde is an exception, as it can be prepared easily from *o*-phenylenediamine and dichloroacetyl chloride [16].



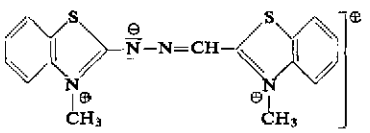


XIII



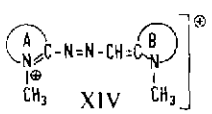
VIII

The absorption maximum of compound VIII (479 mμ in methanol) is found at a shorter wavelength than that of the corresponding trimethinecyanine (552 mμ), but at a longer wavelength than the maximum of the symmetrical diazatrimethinecyanine IX (412 mμ). According to *Brooker* [11], this must be related to the formation of the resonance structure VIIIa, in which the cyanine dye is divided into two short-chain resonance systems, which



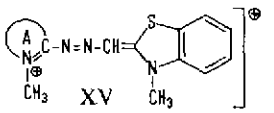
VIIIa

individually display lower absorption intensities at shorter wavelengths than the trimethinecyanine V. While compound IX can have two resonance structures, in each of which a chain nitrogen becomes an auxochrome, compound VIII can only have one such resonance structure. Resonance structures with relatively long resonance systems prevail, therefore, in VIII, so that, during the transition of IX into VIII, an absorption shift towards longer wavelengths becomes plausible. The location of the absorption maximum of unsymmetrical diazatrimethinecyanines of type XIV depends greatly on the nature of the aromatic heterocycles.



XIV

The color of these compounds ranges from a green-tinged yellow to a yellow-tinged red. If the heterocycle A in XV for example, is altered, the bathochrome series listed in Table 1 is observed. Branched-chain diazatrimethinecyanines (XII) absorb at somewhat shorter wavelengths and with much lower intensities than straight-chain diazatrimethinecyanines (VIII). This becomes



XV

clear on examining a model of the molecule: with increasing bulk of the substituent R in the chain ($H < CH_3 < C_6H_5$), the conjugated system is forced more and more out of plane [17].

Table 1. Diazatrimethinecyanines (XV) with various heterocycles A

Ring A in XV	Color	Light fastness on poly(acrylonitrile)
2-Imidazolyl	green-tinged yellow	7
3-Pyridyl	green tinged yellow	approx. 6
2-Pyridyl	red-tinged yellow	6–7
4-Pyridyl	orange	6–7
2-Quinolyl	red-tinged orange	4–5
2-Benzthiazolyl	red-tinged orange	7
6-Methoxybenzthiazol-2-yl	scarlet	7

The stability of unsymmetrical diazatrimethinecyanines of type VIII to hot dilute acids is remarkable, even though azines usually hydrolyze easily in acid solution. These dye salts do not undergo any significant hydrolysis even on prolonged boiling in a pH range of 4 to 8. Slow hydrolysis begins to take place only at pH < 3. These substances are, therefore, suited for dyeing poly(acrylonitrile), *i.e.* Orlon® and Acrilan®, in a pH range of 2 to 8.

Compounds of type VIII display remarkable dyeing properties on acrylics. Apart from their superior affinity and brilliant shades, their dyeings possess excellent wet fastness and, in part, outstanding light fastness [13, 14] (see Table 1). The only drawback of these basic dyestuffs is their relatively weak dye strength compared to carbocyanine dyes.

Branched-chain diazatrimethinecyanines (XII; R = *e.g.* CH_3 or C_6H_5) are less stable in aqueous solution than the salts with an unbranched chain. They are stable towards hydrolysis only in the pH range of 3 to 6. Their light fastness is also lower than that of the unbranched diazatrimethinecyanines.

Salts of the dye bases (XIII) can also be used together with strong acids for dyeing acrylic fibers, instead of diazatrimethinecyanines (VIII). Naturally, the working pH range is then 2 to 3. The dyeings are weak, since, even under those conditions, the concentration of the dye salt is fairly low. During the dyeing process, the protonated dye base is gradually removed from the dyeing bath, and new dye salt is constantly reformed. Since the sparingly water-soluble free dye base (XIII) behaves like a dispersed dye, it also adheres to the fiber. For this reason, at pH values above 2, these dye bases give different shades of dyeings, depending on the acid concentration in the bath. The dyeings are sensitive to base

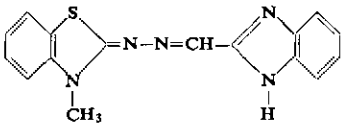
[14] Ilford, French Pat. 1227962; French Pat. 1235612.

[15] Badische Anilin- & Sodafabrik, French Pat. 1178178

[16] Badische Anilin- & Sodafabrik, German Patent Application 1025415.

[17] Cf. *L. G. S. Brooker*, Chem. Rev. *41*, 325 (1947).

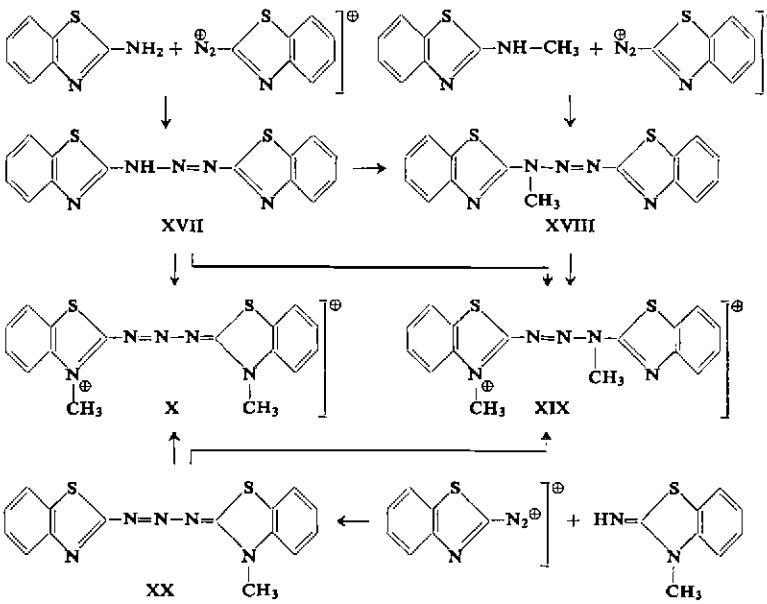
and their light fastness does not compare well with dyeings of salts of type VIII. The light fastness ranges between 1 and 4. The strongly basic compound XVI is an exception, as it provides usable dyeings even from acetic acid solution.



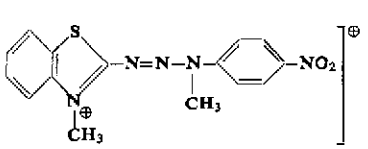
XVI

Triazatrimethinecyanines

Triazatrimethinecyanines (X) can be prepared as follows:



1,3-Dibenzthiazolyltriazene (XVII), which forms red metal salts with alkalies, is obtained by coupling 2-benzthiazolyldiazonium salts with 2-aminobenzthiazole. When XVII is alkylated in alkaline solution, a uniform monoalkyl derivative is obtained, which proves to be identical to the coupling product (XVIII) of 2-benzthiazolyldiazonium sulfate with 2-methylaminobenzthiazole. It is isomeric with the triazene derivative XX obtained from the reaction of 2-benzthiazolyldiazonium salt with 2-imino-3-methyl-2,3-dihydrobenzthiazole. Further alkylation of XVIII yields a yellow dye salt (XIX; λ_{max} = 374 mμ in methanol), the constitution of which probably corresponds to the diazahemicyanine XXI described earlier (λ_{max} = 379 mμ in methanol) [18]. A mixture of XIX and the symmetrical triazatrimethinecyanine X is prepared by vigorous alkylation of XVIII, *e.g.* in a dialkyl sulfate melt. The same mixture is obtained by alkylating the diazoimino compound XX in an inert solvent [10]. The separation of the isomeric dye cations X and XIX can be achieved by chromatography on neutral alumina. *Balli* [19] synthetized compound X by way of the 2-benzthiazolylazidinium salt.



XXI

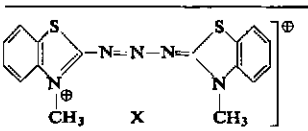
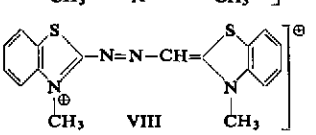
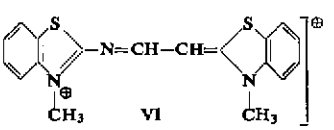
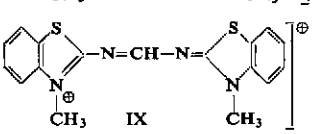
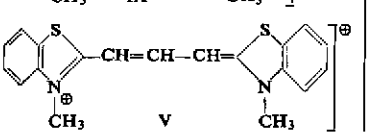
[18] J. R. Geigy AG, French Pat. 1226828.

[19] *H. Balli*, Angew. Chem. *70*, 442 (1950); *71*, 374 (1957); Liebigs Ann. Chem. *647*, 15 (1961).

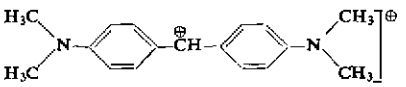
If the triazatrimethinecyanines are compared with the corresponding carbocyanines (V), it becomes evident that the former compounds absorb at shorter wavelengths and with much lower intensities. The absorption maxima of corresponding mono- (VI), di- (VIII, IX), and tri-azatrimethinecyanines (X) are listed together for comparison in Table 2.

On first consideration, the long-wave absorption of the symmetrical triazatrimethinecyanine X (483 mμ) may be surprising when compared with that of the symmetrical diazatrimethinecyanine IX (412 mμ). An effect similar to that observed in the transition of Hydrol Blue (XXII; λ_{max} = 610 mμ) into Bindschedler's Green (XXIII; λ_{max} = 725 mμ) seems to exist here: The central azenium-chromophore in XXIII or in the resonance structure Xa is much more effective than the more electrophilic

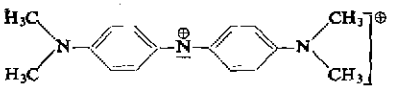
Table 2. Maximum absorptions of mono-, di-, and triazatrimethinecyanines

	λ_{max}
 X	483 mμ in methanol
 VIII	479 mμ in methanol
 VI	466 mμ in methanol
 IX	412 mμ in 1,2-dichloroethane
 V	552 mμ in methanol

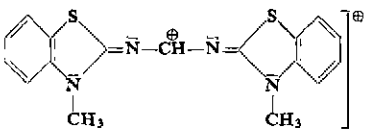
central carbonium-ion chromophore in XXII or in the resonance structure IXa. In comparison to the trimethinecarbocyanine V, two effects therefore counteract



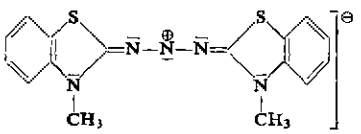
XXII



XXIII



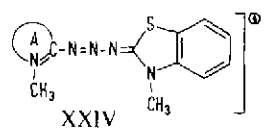
IXa



Xa

each other in X: The hypsochromic influence of the two α-nitrogen atoms of the methine chain, which act as auxochromes, and the bathochromic influence of the central nitrogen atom, which acts as a chromophore.

If the nature of the heterocycle A in the dye cation XXIV is altered, then a bathochromic effect is observed



XXIV

similar to that observed in the diazahemicyanine series in the transition from triazole by way of pyridine to 6-methoxybenzthiazole [2]: The color changes from green-tinged yellow to red-orange (Table 3).

Table 3. Triazamethinecyanines (XXIV) with different heterocycles A

Ring A in (XXIV)	Color	Light fastness on polyacrylonitrile
1,2,4-Triazol-2-yl	green-tinged yellow	2—3
1,2,4-Thiodiazol-2-yl	yellow	2—3
2-Thiazol-yl	red-tinged yellow	6
2-Benzthiazol-yl	orange	6
6-Methoxybenzthiazol-2-yl	scarlet	7

The triazatrimethinecyanines are surprisingly stable in acidic aqueous solution, but they are less stable to hydrolysis than the unsymmetrical diazatrimethinecyanines. Like the azahemicyanines (XXI) they decompose rapidly in water at pH > 7, giving colorless products of unknown constitution. They also undergo appreciable hydrolysis at pH values < 4.

The triazatrimethinecyanines show a very good affinity for Orlon® and give bright green-tinged yellow to red dyeings. The wet fastness is usually excellent. The light fastness of individual representatives of this class is outstanding. Even in very pale dyeings, individual dyes display light fastness values of 7 to 8. These are the highest values observed so far with basic dyestuffs [20]. Peculiarly, the light fastness decreases when azole rings with more than one nitrogen atom are selected for the heterocycle A in XXIV.

We would like to thank Dr. J. D. Kendall of Minnesota Mining and Manufacturing Co. for valuable criticisms and the supply of samples.

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[20] J. R. Geigy AG., French Pat. 1228047.

Biology and Biochemistry of Reproduction and Contraception

BY DR. W. JÖCHLE

HAUPTLABORATORIUM DER SCHERING AG., BERLIN (GERMANY)

Maturation of sperm and ovum are not autonomous processes. Rather, germ cell activity is controlled by a regulatory center in the hypothalamus. This assures germ cell maturation, fertilization, and development of the fetus until birth. Command, functional release, and feedback take place by humoral paths which involve gonadotropin releasers, gonadotropins, and sex hormones. Even in antiquity, attempts at birth control involved a search for substances which might inhibit the essential physiological and biochemical reproductive processes. This report deals with more recent efforts along these lines.

I. Physiology of Reproduction

Successful conception requires the presence of male germ cells capable of fertilization and of female cells that can be fertilized. These cells are present at certain ages only. From puberty on, their presence at all times can be demonstrated only in males, provided the individual is healthy and in a satisfactory nutritional state [1]. In females, on the other hand, germ cells capable of fertilization are present only at periodic intervals. Their periodicity is reflected in the menstrual cycle, which can be considered as resulting from the failure of a mature ovum to have become fertilized.

[1] C. *Lutwak-Mann*, Vitamins and Hormones *16*, 35 (1958).

Constant maturation of the semen and periodic maturation of ova do not take place autonomously, *i.e.* independently of what occurs in the rest of the organism. Rather, the activity of the organs giving rise to the germ cells, *i.e.* of the gonads (testes and ovaries), is subject to central control and exerts feedback effects on all other central controls.

The hypophysis-hypothalamus constitutes the *regulatory center* of both males and females. The hypophysis with its anterior lobe is located on or within the base of the cranium. Its commands are issued in response to orders that originate in the diencephalon (hypothalamus), located directly above the hypophysis. The sexual nerve center is located there. Throughout the entire reproductive system, the preferred path for the transmission of commands, release or initiation of functions, as well as feedback, is humoral in nature.

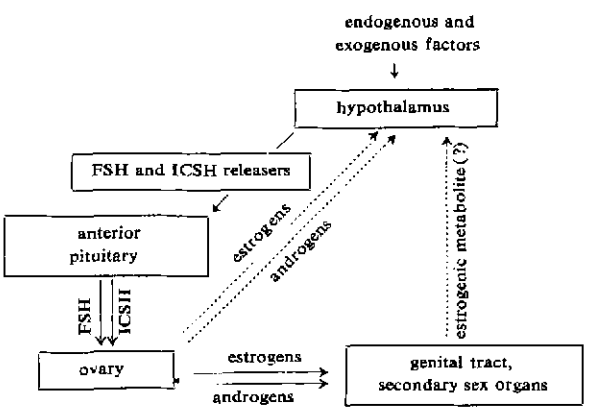
In all likelihood, *functional release* of pituitary activity occurs by way of short-chain peptides, the gonadotropin releasers. The substances released in time by the pituitary are water-soluble protein hormones of as yet unknown structure, *i.e.* the gonadotropins. The structure of the substances released by the gonads in response to the gonadotropins is known: both male and female sex hormones are steroids. The latter can be classified in terms of C_{18}-steroids (estrone derivatives, or estrogens), C_{19}-steroids (androstane derivatives, or androgens) and C_{21}-steroids (pregnane derivatives, or gestagens). On the one hand, these sex hormones feed back information on started secretions in the neuroendocrine system; on the other hand, they induce the necessary preparation of the germ-cell transporting and protecting portions of the genital system. In other words, they cause the secretions of the secondary sex glands to be ready for ejaculation in the male; in the female they stimulate development of the endometrium to receive the fertilized ovum.

The neuroendocrine regulation of the maturation of the ovum consists of two regulatory cycles [1a], which are interrelated through a feedback mechanism [2].

The pivotal element in both cycles is the hypothalamic sex center, which is affected by environmental factors, the autonomic nervous system, and psychological factors, all of which influence sexuality. The regulatory center is not set at a given degree of sensitivity; rather, its sensitivity varies throughout life. Thus, in childhood even small quantities of sex hormones have a pronounced antigonadotropic action; *i.e.* they inhibit the production of gonadotropins by the anterior pituitary gland [3,4]. With the advent of puberty, the control center becomes less sensitive to the sex hormones, until then probably originating from the adrenal. Even relatively large doses of sex hormones appear to have only little antigonadotropic action. This means that gonadotropin releasers are secreted, and gonadotropins which are formed in the anterior lobe of the pituitary are now capable of inducing gonadal maturation and the production of sex hormones. Sexual maturity therefore involves a certain sensitivity of the sex center and the function of a feedback system according to the following scheme:

Phase 1: Induction of Ovulation

The sex center, freed from the effects of a preceding ovulation or pregnancy, induces the release in the anterior pituitary of two gonadotropins, *viz.* FSH (follicle-stimulating hormone) and ICSH (the interstitial-cell stimulating or luteinizing hormone). These in time act to cause a primary ovarian follicle, which had remained quiescent until now, to mature into a Graafian follicle; they also induce production of sex hormones. Estrogens and androgens act on the genital tract in such a manner as to cause it to develop an optimum milieu for fertilization (proliferative phase of the endometrium). As soon as the follicle has released the ovum (ovulation = release of the mature ovum into the oviduct), these same hormones inhibit FSH and apparently also ICSH production in the regulatory center. This blocking reduces gonadotropin production but does not shut it off completely. From the point of view of cybernetics, a minimum level of gonadotropin secretion is necessary to provide residual stimulation (see Scheme 1). The ovum released from the ovary is capable of being fertilized for 12 hours. In contrast, semen released remains viable for up to 72 hours following coitus.



Scheme 1. First regulatory cycle: Ovulation phase (maturation and rupture of follicle, development of endometrium).

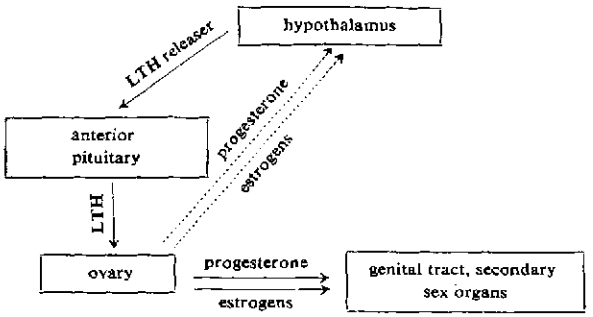
.....→ stimulation
–––––→ inhibition
FSH = follicle stimulating hormone
ICSH = interstitial-cell stimulating hormone

Phase 2: Preparation for Nidation

The rise in estrogen level in the blood in Phase 1, in addition to causing the temporary inhibition of FSH and ICSH, also causes the release of a third gonadotropin, LTH (luteotropic hormone). Under its influence the cavity of the ovarian follicle becomes transformed into the yellow body or *corpus luteum*. The ICSH had already initiated this development at the end of Phase 1. LTH induces and temporarily maintains the production of estrogens and gestagens in the *corpus luteum*. Gestagens and estrogens act to provide the ovum with optimum paths in the oviduct, as well as optimum nutritional and nidational conditions in the uterus (transformation and secretion phases of the endometrium). Moreover, they block in the center the release of FSH and of ICSH and, increasingly, that of LTH (see Scheme 2). If the ovum remains unfertilized, the *corpus luteum* loses its function. Functionally this means: a) desquamation of the endometrium that was ready for nidation (menstruation or monthly period); on the average this occurs 28–30 days after the previous menstrual period; b) restarting of the

[1a] *W. Hohlweg* and *K. Junkmann*, Klin. Wschr. *33*, 321 (1932).
[2] *R. Wagner*, Münchener med. Wschr. *103*, 717 (1961).
[3] *W. Hohlweg* in: 2. Symp. Dtsch. Ges. Endokrinologie, Goslar 1954. Springer, Berlin-Göttingen-Heidelberg.
[4] *W. Hohlweg*, Wiener klin. Wschr. *71*, 445 (1961).

functions of the first regulatory cycle, leading to another ovulation, which normally occurs 12–14 days after the beginning of the past menstrual period.

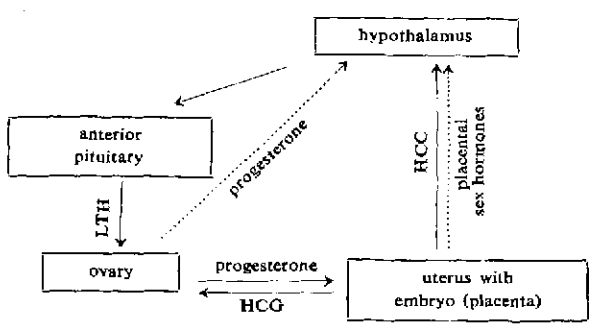


Scheme 2. Second regulatory cycle: Preparation for nidation (formation of *corpus luteum*, maturation of *corpus luteum*, transformation of endometrium; if fertilization does not occur: *corpus luteum* degenerates, endometrium is desquamated = menstruation).
——→ stimulation
·····→ inhibition
LTH = luteotropic hormone

In addition to the regulatory mechanisms outlined so far, antagonistic relations between estrogens and gestagens may exist in the ovary [4a, b]. Similarly, ovary and genital tract seem to form a regulatory cycle in which ovariogenic steroid metabolites, after passing the uterus, act synergistically with the ovary function during the first half of the second phase and antagonistically during its second half [4c]

Phase 3: Pregnancy

If fertilization has occurred, the fertilized ovum will produce within a few days, *i.e.* before nidation, choriogenic gonadotropic hormone (HCG), which maintains the function of the *corpus luteum*, perhaps by preventing the release of LTH from ceasing. A direct effect of HCG on the ovary cannot be excluded. This then inhibits the functioning of the first regulatory cycle (*i.e.* the cycle is at rest during pregnancy). In the course of pregnancy, gestagens and estrogens are formed primarily by the placenta, which can be considered as an accessory organ of the embryo or fetus. These in turn affect the metabolism of the maternal organism, cause the mammary glands to develop, and protect the uterus and its content from the labor-inducing activity of the oxytocin secreted by the hypothalamus (see Scheme 3).



Scheme 3. Phase 3: Pregnancy.
—→ stimulation
·→ inhibition
LTH = luteotropic hormone
HCG = choriogenic gonadotropin

[4a] *Fr. Hoffmann*, Geburtsh. Frauenheilk. *22*, 433 (1962).
[4b] *S. Kullander*, Acta endocrinol. *38*, 598 (1961).
[4c] *I. W. Rowlands*, J. Endocrinology *24*, 105 (1962).

In Phase 2, progesterone and estrogen lead to an active secretion on the part of the endometrium [5]; the latter is ready for nidation but cannot effect it under the influence of progesterone alone. A temporary rise in the estrogen level, due to estradiol secreted by the *corpus luteum*, releases histamine and initiates the deciduous reaction of the uterus [5]. The simultaneous rise in cytolytic activity in the lumen of the uterus enables the trophoblast, *i.e.* the fertilized ovum in its early developmental stage, to become embedded in the adjoining endometrium, which has been growing outward as a decidua. This process completes nidation [5].

In addition to this well regulated sequence of ovulation, it appears to be possible that ovulation can be induced in sexually mature individuals at other times by nervous stimulation [5a–c].

So far, similar phaselike processes involving regulation and feedback have not been observed in human males. Nevertheless, they may well occur, as is known from animal studies. In any event, there is a feedback-controlled equilibrium in males between gonadotropism and sex hormone production: high doses of sex hormones inhibit FSH and ICSH in the regulatory center; these latter gonadotropins in turn induce spermatogenesis. LTH does not appear to have a function in the male. It is uncertain whether the androgens formed in the testes are necessary for sperm maturation *in situ* [4] or whether they are needed only for the formation of secretions in the accessory sex organs (prostate gland, seminal vesicle) [*]. It should be added that, morphological maturity notwithstanding, the sperm cells formed in the testes are sterile until they undergo several weeks of maturation in the epididymis; a functional ejaculate contains only mature sperm from the epididymis.

II. Biochemistry of Conception

It is characteristic of the sperm cell that it does not obtain its energy for life and motility from aerobic respiration but from anaerobic glycolysis [6, 7]. Sperm cells do possess a complete cytochrome system which would permit them to use oxygen directly [8, 9, 15]. However,

[5] *M. E. Shelesnyak* in: Proc. Sixth internat. Conf. Planned Parenthood. London 1959, p. 151.
[5a] *W. Bickenbach, G. K. Döring*, and *C. Hossfeldt*, Arch. Gynäkol. *192*, 412 (1960).
[5b] *W. Foellmer*, Arch. Gynäkol. *194*, 355 (1961).
[5c] *J. Amreich*, Wiener med. Wschr. *112*, 9 (1962).
[*] The similarity in the neuroendocrine regulation of sexual activity that prevails in the higher vertebrates has made these the preferred models of study. Results obtained and observations made there are frequently transferred to man without regard for their species-specificity. This is not valid. Similarly, our knowledge of biochemical events is largely derived from experiments with animals. It appears more justifiable to apply these results to human studies, at least until reactions have been found that are specific for man.
[6] *T. Mann* in: Mammalian Germ Cells. Ciba Foundation Symposium. Little and Brown, Boston 1954, p. 1.
[7] *T. Mann:* The Biochemistry of Semen. Wiley, New York 1954.
[8] *H. Elftman* in Egle E.T.: Studies on Testes and Ovary, Eggs and Sperm. Thomas, Springfield, Ill., 1952, p. 26.
[9] *T. Mann*, Biochem. J. *48*, 386 (1951).

they behave like anaerobic malignant tumor cells [6, 10, 11]. They differ from the latter, however, in being anaerobic not because of a mutation involving a loss of potential but by virtue of having adapted to the milieu of fertilization, which is poorly supplied by the vasculature and hence poor in oxygen [12–15]. Moreover, as a result of the action of estrogens, the metabolism of the female genital tract is largely anaerobic and glycolytic [16–21].

It is in such a milieu that the sperms must travel a considerable distance, approximately 2000 times their own length [22]. Motility, length of life, and fertility of the sperm are therefore at a maximum under anaerobic conditions and are considerably less so under aerobic conditions [7, 10, 23–28]. The anaerobic source of energy is fructolysis. In addition, energy may be generated by oxidation of lactic acid and intracellular plasmalogens, if the very low oxygen pressure allows such oxidations to take place [28a].

The metabolism of the maturing sperm in the epididymis is less glycolytic than that of sperm in the ejaculate [29]. Apparently, enzymes occur in seminal glands and the prostate which cause uncoupling of the cytochrome and phosphorylating systems.

Conceivably, the ability to obtain energy by way of oxidative metabolism is of more significance for fertilization [30]. Nevertheless it seems doubtful that the observation made on a phylogenetically primitive animal cell (sea urchin egg) also applies to mammalia. In mammalia, fertilization and initial development of the fertilized ovum through nidation are probably also mainly anaerobic. Only when the fertilized ovum has become implanted in the uterus is its oxygen supply assured. This in turn makes aerobic metabolism possible.

The metabolic processes that accompany ovulation in the female genital tract serve two purposes: they induce anaerobiosis and produce optimum conditions for the sojourn of the sperm in the tract and for fertilization. Under the influence of estrogens the cervical mucus becomes more liquid and increases in quantity, and its NaCl content increases. This facilitates penetration and survival of the sperm. The pH becomes more alkaline [30]. The glycolytic metabolism becomes more intense as the endometrium proliferates, and reaches its peak at the time of ovulation [30]. Simultaneously, estrogens increase the activities of the following enzymes: alkaline phosphatase [31–35], adenosinetriphosphatase [36, 37], β-glucuronidase [32], sulfatase [32], serine aldolase [40], peroxidase [42], hexokinase [22], and various dehydrogenases [42, 43]. This milieu [44] possibly induces the so-called capacitation of the sperm. This term refers to a maturation process of the sperm that occurs *in utero* and without which fertilization does not occur [30].

In the secretory phase, which is under progesterone domination, oxidative glycolysis is again predominant. Acid phosphatase [45], succinic dehydrogenase [46], lactic dehydrogenase [47], and carbonic anhydrase [48] occur in high activities. Whereas estrogens cause glycogen storage [49–51], progesterone leads to glycogen secretion [24]. In the secretory phase, sperm capacitation does not take place and the reduced amount of toughened cervical mucus becomes again an agglutinin-containing barrier warding off sperm [30].

Sperm agglutinins, which effect head-to-head agglutination of spermatozoa, are always found in the genital tracts of both men and women. Though they have similar action, they appear to differ in the two sexes [52]. They occur in the secretions of the sperm glands in males but are neutralized there by epididymal and

[10] *J. MacLeod*, Amer. J. Physiol. *118*, 512 (1943).

[11] *T. Mann*, Nature (London) *156*, 80 (1945).

[12] *R. S. Hotchkiss:* Etiology and Diagnosis in the Treatment of Infertility in Man. Thomas, Springfield, Ill., 1952.

[13] *J. MacLeod*, J. gen. Physiol. *34*, 705 (1951).

[13a] *M. Kerly*, Biochem. J. *31*, 1544 (1937).

[14] *R. Moricard*, Nature (London) *165*, 763 (1950).

[15] *R. Moricard* in: Mammalian Germ Cells. Ciba Foundation Symposium. Little and Brown, Boston 1954, p. 187.

[16] *W. Dirscherl, H. Schriefers*, and *H. Brehrer*, Acta Endocrinol. *20*, 181 (1955).

[17] *W. Eschbach*, Arch. Gynäkol. *187*, 337 (1956).

[18] *W. Eschbach* and *E. Negelein*, Arch. Gynäkol. *188*, 84 (1956).

[19] *M. Kerly*, Biochem. J. *31*, 1544 (1937).

[20] *V. M. Stuermer* and *R. J. Stern*, Amer. J. Obstetr. Gynecol. *63*, 359 (1952).

[21] *O. Walaas, E. Walaas*, and *F. Loken*, Acta endocrinol. *10*, 201 (1952).

[22] *S. H. Sturgis*, Fertil. Sterility *7*, 468 (1956).

[23] *D. W. Bishop* in: *E. T. Engle:* Studies on Testes and Ovary, Eggs and Sperm. Thomas, Springfield, Ill., 1952, p. 95.

[24] *E. C. Hughes*, Amer. J. Obstetr. Gynec. *49*, 10 (1945).

[25] *H. A. Lardy, D. Ghosh*, and *G. W. E. Plant*, Science (Washington) *109*, 365 (1949).

[26] *J. MacLeod*, Fertil. Sterility *7*, 368 (1956).

[27] *G. W. Salisbury* and *N. L. Vandemark*, Nature (London) *180*, 989 (1957).

[28] *H. Shapiro*, Physiol. Zoology *21*, 218 (1948).

[28a] *T. Mann*, Schweiz. Arch. Tierheilk. *103*, 359 (1961).

[29] *I. G. White* and *R. G. Wales*, J. Reprod. Fertility *2*, 225 (1961).

[30] *M. Gross*, Fertil Sterility *12*, 245 (1961).

[31] *W. B. Atkinson* and *E. T. Engle*, Endocrinology *40*, 327 (1947).

[32] *J. E. Hall*, Amer. J. Obstetr. Gynecol. *60*, 212 (1950).

[33] *G. T. Hedberg*, Gynaecologia *129*, 239 (1950).

[34] *H. Leeb* and *U. Ploberger*, Enzymologia *16*, 317 (1954).

[35] *H. G. Sturz*, Stanford med. Bull. *11*, 210 (1953).

[36] *A. Csapo*, Amer. J. Physiol. *162*, 406 (1950).

[37] *H. W. Jones, Jr., R. Wade*, and *B. Goldberg*, Amer. J. Obstetr. Gynecol. *64*, 1118 (1952).

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[40] *A. Herranen* and *G. C. Mueller*, Biochem. biophysica Acta *24*, 223 (1957).

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[43] *C. G. Rosa* and *J. T. Velardo*, Ann. N.Y. Acad. Sci. *83*, 122 (1959).

[44] *D. Olds* and *N. L. Van Denmark*, Fertil. Sterility *8*, 345 (1957).

[45] *B. Goldberg* and *H. W. Jones, Jr.*, Obstetr. Gynecol. *7*, 542 (1956).

[46] *M. L. Telfer* and *F. L. Hisaw, Jr.*, Acta endocrinol. *25*, 390 (1957).

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[48] *C. Lutwag-Mann*, J. Endocrinology *13*, 26 (1955).

[49] *B. Lapan* and *M. M. Friedman*, Amer. J. Obstetr. Gynecol. *59*, 921 (1950).

[50] *H. W. Payne* and *J. P. A. Latour*, J. clin. Endocrinol. *15*, 1106 (1955).

[51] *O. Walaas*, Acta endocrinol. *10*, 175 (1952).

[52] *P. E. Lindahl* and *A. Nilsson*, Biochim. biophysica Acta *25*, 22 (1957).

prostatic antiagglutinins. Antiagglutinins occur in the female genital tract at the same time as estrogen secretion is stimulated by follicle maturation. Their maximum concentration occurs in the fluids of the follicles and oviducts [52]. Both ova and spermatozoa are bathed by fluids that contain antiagglutinins. Thus protected from clotting, a spermatozoon, thanks to its mobility and its hyaluronidase activity, can begin its migration through the granulosa cells surrounding the ovum, passing through the intercellular spaces of the cellular *corona radiata* and through the thick mucoprotein membrane of the *zona pellucida*. The sperm cell then remains in the perivitelline space for a short time. There it is protected from other sperm cells, which are kept from penetrating the outer layer of the ovum as a result of an unknown biochemical block. Finally the sperm penetrates into the cytoplasm of the ovum [53].

Although fertilization *in vitro* has repeatedly been achieved, it is not yet possible to give exact information about the biochemistry of or the optimum conditions for this process [53a]. After ovulation the egg cell is protected from clotting with coagulating plasma by a heparin-like substance [53b]. In the Fallopian tube the egg cell awaits the sperm cells. Survival, fertilization and transport of the egg towards the uterus as well as development of the embryo depend on different estrogen-gestagen relationships the occurrence of which corresponds in time exactly to the necessity for different optimum conditions [53c]. This is true in particular for the stage when the embryo reaches the uterus and nidation starts: a short-time increase in estrogen concentration [53d] makes possible the contact between the embryo and the gestagen-primed endometrium. The embryo is lured by the resorptive activity of the endome-

Table 1. Contraceptive plants and minerals used in antiquity

	Mode of application	Origin or area where used	Authors
Plants or Plant Products			
Cedar resin	vaginal	Ancient Greece	*Soranus* (Sorani Ed. Ermerins, Traj. ad Rhen., 1869)
Honey	vaginal		
Artemisia arborescens (rue, mugwort, or wormwood)	vaginal	Ancient Greece	
Crocus sativus (crocus)	oral		*Hippocrates* [54], cited by [59]
Ferula opoponax	oral		
Laurel	oral		
Nettle seeds	oral		
Myrrh	vaginal		
Peony roots	oral		
Peucedanum officinalis	oral		
Ruta graveolens	vaginal		
Cypress fruit	vaginal		
Artemisia arborescens (see above)	vaginal	Ancient Greece	*Dioscorides* [60], cited by [59]
Cheiranthus cheiri (wallflower)	oral		
Lithospora purpureocoeruleum	oral		
Aspidium filix/mas	oral	Ancient Rome	*Pliny* (Plinii Historiae mundi, Basel 1554, LXXVIII, CIX, p. 485)
Pteridium aquilinum	oral		
Centaurium majus (centaury)	oral	Byzantine, 6th century A.D.	Aetii Amidensis, Libri med. sedec., Venice 1534
Ammi copticum L.	oral	Byzantine 7th century A.D.	Pauli Aeginetae Medici Opera, Lugduni 1551, p. 233
Ammi visnaga	oral		
Aristolochia	oral		
Ruta graveolens (see above)	oral		
Veratrum album (gerber)	oral		
Anchusa tinctoria (ox-tongue)	oral and vaginal	Arabian, 13th century A.D.	*Ebn Baithar*, (*Sontheimer's* translation of Collectio magna, 1840)
Artemisia arborescens (see above)	in bath		
Epimedium alpinum	oral		
Gummi ammoniacum	vaginal		
Iris florentina (sword lily)	oral		
Juniperus sabina (juniper)	oral		
Lupinus termes (lupin)	oral		
Pinus cedrus (cedar)	vaginal		
Sesamum orientale (sesame)			
Seseli tortuosum (sessil)	oral		
Stachys germanica (hedge nettle)	oral		
Minerals			
Misy (μισυ)	oral	Ancient Greece	*Hippocrates* [54]
White lead	vaginal		*Soranus*
Alum	vaginal		*Soranus* and *Dioscorides* [60]

[53] *M. C. Chang* in: Proc. Sixth internat. Conf. Planned Parenthood London 1959, p. 129.

[53a] *J. M. Bedford* and *M. C. Chang*, Nature (London) *193*, 898 (1962).

[53b] *J. E. Stangroom* and *R. de G. Weevers*, J. Reprod. Fertility *3*, 269 (1962).

[53c] *E. S. E. Hafez*, J. Reprod. Fertility *3*, 14 (1962).

[53d] *A. Psychoyos*, C. r. hebd. Séances Acad. Sci. *253*, 1616 (1961).

trium [53e]. Under the influence of histamine [5], heparin [53f], and acetylcholine [53g] a deciduoma develops at the point of contact, which is similar to granulation tissue and which finally surrounds the embryo.

III. Contraceptive Agents

Contraceptives are substances used before or after coitus in order to inhibit fertilization or further development of the fertilized ovum. They are intended to suppress germ cell maturation or to keep the germ cells from being fertilized, or to inhibit as soon as possible the further development of the embryo. Such agents should not interfere with libido or the inclination to have coitus. When no longer used, there should be no further interference with the development of healthy germ cells. Contraceptives occupy a central role in birth control measures, whether they are taken on an individual basis for the purposes of family planning, on a community basis (*e.g.* in India and China) or to reduce the frightening rise in the number of illegal abortions.

Long surrounded by taboos, the discovery and testing of contraceptives in the past was mostly empirical. Transmission of such knowledge was a matter of tribal or family custom. Hence the knowledge of effective principles frequently was restricted either to certain areas or in the number or kinds of people involved. Only in recent times have medicine and biology begun to devote attention to contraceptive agents.

1. Historical and Ethnological Aspects

The writings of the Hippocratic physicians already contain detailed indications for contraceptives and directions for contraceptive activities [54]. Though making no claim to completeness, Table 1 lists minerals and plants which the ancients described as contraceptives. They culminate in a "patent medicine", mentioned several times by Hippocrates; a single ingestion is said to have produced sterility lasting for one year [54]. Named μισυ, its constitution and action are unknown. The following compounds have been implicated: $CuSO_4$, $FeSO_3$, or $FeSO_4$; all of these have chronic toxic efforts.

Several detailed publications summarize on a worldwide basis plant materials used for contraceptive purposes [55, 58]. These, together with data from *Lewin*'s book "Abortion with Poisons" [59], are shown in Table 2.

[53e] *R. Vokaer* and *F. Leroy*, Amer. J. Obstetr. Gynecol. *83*, 141 (1962).

[53f] *C. A. Finn* and *P. M. Keen*, Lecture, Annual Conference Soc. Study of Fertility, London 1962.

[53g] *Y. Chambon*, C. r. Soc. Biol. (Paris) *155*, 1351 (1961).

[54] *Hippocrates*: Opera omnia. Ed. van den Linden, Lugd. Bat. 1665.

[55] *R. D. C. Casey*, Indian J. med. Sci. *14*, 590 (1960).

[56] *R. D. C. Casey*, Indian J. med. Sci. *15*, 431 (1961).

[57] *H. De Laszlo* and *P. S. Henshaw*, Science (Washington) *119*, 626 (1954).

[58] *R. H. Dreisbach*, cited by [56].

[59] *L. Lewin*: Die Fruchtabtreibung durch Gifte und andere Mittel. 4th ed., Georg Stilke, Berlin, 1925.

The plant materials listed have not only an abortive but also seem to have a clearcut contraceptive action.

Table 2. Contraceptive plants [59]

Species	Mode of application	Geographical Area
Geranium pratense	oral	Siberia
Juniperus sabina	oral	Central Europe
Lathraea squamaria	oral	Russia
Lycopodium annotinum	oral	Russia
Nerium oleander L.	oral	Balkans
Taxus baccata L.	oral	Europe

As opposed to the large number of supposedly or actually contraceptive plant species, only few plant materials are known to be effective on the basis of clinical or experimental studies (Table 5). Chemically they are mostly ill-defined. A systematic search for such materials is made difficult by numerous imponderables. Thus the content of the active ingredient varies with location, season of harvest, storage, portion of the plant used, and methods of preparing and storing the extract. So far, elucidation of structure and synthesis of contraceptive plant materials have been achieved in only one case: *m*-xylohydroquinone was extracted from peas, purified and tested (cf. Table 5). The application of plant materials is further restricted by toxic side-effects; it is not yet clear whether these must be attributed to impurities or to the contraceptives themselves.

2. Mechanism of Action and Structure of Modern Contraceptives

Two classes of contraceptives are differentiated:

a) materials that act selectively on either male or female germ cells or on their stages of maturation, or those which act on the fertilized ovum;

b) materials that affect other physiological or biochemical processes concerned with conception.

In the following, regardless the footnote on p. 539, results of animal studies will also be considered, even where their results cannot be applied to man. This is done to provide a measure of the extent of pertinent studies.

a) *Materials that act selectively on either male or female germ cells or on the fertilized ovum*

α) Spermatozoa (see Scheme 4)

With the exception of spermicidal materials (Table 4), the only promising compound for human application in this group is bis(dichloroacetyl)diamine. It causes reversible but as yet unexplained arrest of spermatogenesis in the testes [61]. In contrast to what happens when derivatives of nitrofuran are taken, which have a similar effect, the administration of effective doses of bis(dichloracetyl)diamine is without side effects [61].

[60] *Dioskorides:* Comm. ab Eguatio. Veneto 1516.

[61] *C. G. Heller, D. J. Moore, Y. Clermond*, and *C. A. Paulsen*, 43rd Meeting endocrinol. Soc., New York 1961. No. 37, p. 21.

The cell and mitotic poisons listed in Table 3 are very toxic, just as are the antimetabolites. Because of a special characteristic of spermatogenesis, these compounds may nevertheless find application in minimal doses: mitosis in the course of spermatogenesis, including meiotic division, which reduces the number of chromosomes to half, takes place very slowly. Hence even minimal doses of these compounds may have an optimum period in which to act [62].

The azoospermia due to cadmium can be overcome by the simultaneous administration of zinc. Apparently, cadmium acts as a competitive enzyme inhibitor [62].

Table 3. Contraceptives with selective action on either male or female germ cells or on the fertilized ovum (for symbols see caption to Scheme 4)

Agent	Category	Effect on spermatozoa	Ref.	Category	Effect on ova	Ref.	Category	Effect on fertilized ovum	Ref.
Cadmium salts	D	destroy male germ cell epithelium	[63]				D	prevent implantation of fertilized ovum in uterus	[65]
	D	inhibit spermatogenesis	[64—66]						
Selenium				D	damages ova	[84]			
Bis(dichloroacetyl)diamine	B	inhibits spermatogenesis	[61]						
Cell Poisons									
BAL derivatives	D	inhibit spermatogenesis	[67, 68]				D		[91—93]
Ethyleneimino compounds	C, D		[69, 70]						
Sulfuric acid alkyl esters (*e.g.* Myleran)	D	inhibit spermatogenesis and sperm maturation in testes and epididymis	[71]	D	kill ova	[85]	D	kill fertilized ovum	[85]
Nitrofuran derivatives	C, D	inhibit spermatogenesis	[72—78]						
2-Chloro-2-acetylthiophene	D		[79]						
Triethylenemelamine	D		[79a]				D	kill fertilized ovum	[94—96]
6-Azauridine							D		[97]
Mitotic Inhibitors									
Colchicine (and derivatives)	D	inhibit spermatogenesis	[80—82]				D	kill fertilized ovum	[98, 99]
Podophyllotoxin							D		[99—103]
β-Aminopropionitrile							D		[104]
Methylcholanthrene							D		[105]
MER-25				C, D	damages ovum in tube, inhibits fertilization by estrogen antagonism	[70, 77, 86—90]			
Antimetabolites									
Ethionine	D	inhibits spermatogenesis	[83]						
6-Mercaptopurine, thioguanine							D	kill fertilized ovum	[106]
Aminopterine (folic acid antagonist)							D		[95, 107]
Antibiotics									
Azaserine							D	kill fertilized ovum	[93, 99, 106—110]
Diazooxonorleucine							D		[70, 99, 111]
Diazoacetylserine							D		[112]
Spermicidal Agents: see Table 4									

[62] *T. Mann:* Proc. Sixth internat. Conf. Planned Parenthood. London 1959, p. 122.

[63] *M. Allanson* and *R. Deanesly*, J. Reprod. Fert. *2*, 510 (1961).

[64] *A. B. Kar* and *R. P. Das*, Acta biol. med. germanica *5*, 153. (1960).

[65] *A. B. Kar*, cited by [56].

[66] *J. Parizek*, J. Reprod. Fertil *1*, 294 (1960).

[67] *J. Freund, M. M. Lipton*, and *G. E. Thompson*, J. exper. Med. *97*, 711 (1953).

[68] *B. H. Landing, A. Goldin*, and *H. A. Noe*, Cancer *2*, 1075 (1949).

[69] *H. Jackson*, Pharmacol. Rev. *11*, 135 (1959).

[70] *W. O. Nelson*, Fertil. Sterility *12*, 109 (1961).

[71] *H. Jackson, B. W. Fox*, and *A. W. Craig*, J. Reprod. Fert. *2*, 447 (1961).

[72] *H. Harmsen*, Arztl. Mittlg. *46*, 145 (1961).

[73] *W. O. Nelson*, Acta endocrinol., Suppl. *28*, 7 (1956).

[74] *W. O. Nelson* and *E. Steinberger*, Fed. Proc. *12*, 103 (1953).

[75] *W. O. Nelson* and *R. G. Bunge*, J. Urology *77*, 275 (1957).

[76] *J. T. Prior* and *J. H. Ferguson*, Cancer *3*, 1063 (1950).

[77] *S. J. Segal*, cited by [56].

[78] *H. E. Paul, M. F. Paul, F. Kopko, R. C. Bender*, and *G. Everett*, Endocrinology *53*, 585 (1953).

[79] *E. Steinberger, A. Boccabella*, and *W. O. Nelson*, cited by [56].

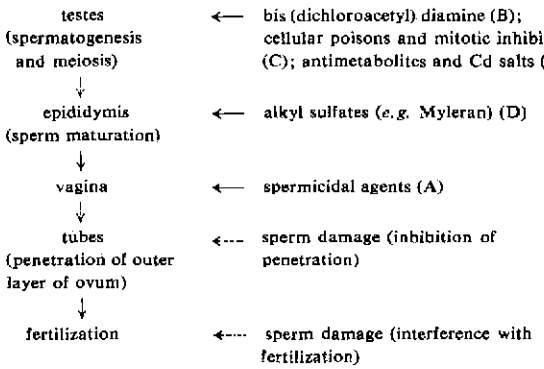
[79a] *E. Steinberger*, J. Reprod. Fert. *3*, 250 (1962).

[80] *H. Barsoum*, J. Pharmacol. *115*, 319 (1955).

[81] *A. D. Bergner*, Cancer *3*, 134 (1950).

[82] *W. Fleischmann* and *G. E. Ullyot*, Cancer *3*, 130 (1950).

[83] *N. Kaufman, J. V. Klavins*, and *T. D. Kinney*, Amer. J. Pathol. *32*, 105 (1956).



Scheme 4. Contraception by selective action on the sperm cell.

A = tested in humans, commercially available
B = tested in humans, application possible
C = tested in humans, of uncertain promise or has undesirable side effects
D = tested in animals, use in humans uncertain or impossible
←··· = suggested application

Sulfuric acid alkyl esters, depending on their chemical structure [71], not only interfere with the early stages of spermatogenesis, *i. e.* spermatogonia and spermatocytes, but also act on the maturing sperm cells in the epididymis and the testes [85, 113, 114]. This opens up the possibility of not only systematically blocking spermatogenesis but also of affecting the sperm depot [71].

With the single exception referred to, all methods designed to act systemically on sperm cells are characterized by the dangers of poor toleration or toxicity. Vaginally applied spermicidal agents, on the other hand, are safe, easily applied and relatively reliable (see Table 4); hence they dominate the contraceptive market. Applied as pastes, jellies, suppositories, foams or tablets and inserted just at the mouth of the cervix, they act to immobilize the sperm [115, 116]. Table 4 lists a number

Table 4. Spermicidal materials to be applied vaginally

Material	Trade name	Manufacturer
Lactic and boric acids	Contraceptalene	Lamberts Ltd., Dalstone, England
Boric acid, aluminum acetotartrate, formaldehyde, and chlorocarvacrol	Patentex	Patentex GmbH., Frankfurt
Mercuric phenylacetate and lactic acid	Prophylcols	Labopharma, Berlin
Boric acid, lactic acid, methyl- and propyl-*p*-hydroxybenzoic acids, hydroxycinchonine	Confidol	Pharmasal, Hannover
Mercuric phenylacetate	Volpar, Mycon	British Drug Houses Ltd., London Allied Laboratories Ltd., London
Mercuric phenyl-dinaphthyl-methanedisulfonate	Penotrane	Ward Blenkinsopp and Co. Ltd., London
Castor oil and sodium lauryl sulfate	Ortho Creme	Ortho Pharmacy Ltd., High Wycombe, Bucks., England
Castor oil and *p*-diisobutyl phenoxypolyethoxyethanol	Ortho Jelly	Ortho Pharmacy Ltd.
Nonylphenoxypolyethoxyethanol, potassium ricinoleate, and sodium lauryl sulfate	Staycept cream	Stayne Laboratories, Ltd., Wakingham, Bucks., England
Nonylphenoxypolyethoxyethanol and benzylethonium chloride	Emko Foam	Emko Co., St. Louis, USA
Hexylresorcinol	C. P. Ointment, Jelly Prentif Gels	Gilmont Products, London; Prentif Ltd London
o-Hydroxyquinol sulfate	Semori	Luitpold-Werke, Munich
Triisopropylphenoxypolyethoxyethanol	Vol Fam Creme	Aries Ltd., London
Dioctyl sodium sulfosuccinate and paraformaldehyde	Antemin	Coates and Cooper Ltd., London
Chloramine	Gynamin	Coates and Cooper Ltd., London
Chloramine and zinc phenol sulfate	Bymeston	Lamberts Ltd., Dalstone, England
Zinc phenol sulfate	Rendell Foam	W. J. Rendell Ltd.
Cellulose sulfate	A-Gen	Dr. Herbrand, Gengenbach/Baden, Germany

[84] *I. Rosenfeld* and *O. A. Beath*, Proc. Soc. exp. Biol. Med. *87*, 295 (1954).
[85] *W. Bollag*, Schweiz. med. Wschr. *84*, 393 (1954).
[86] *M. C. Chang:* Proceedings Sixth internat. Conf. Planned Parenthood. London 1959, p. 129.
[87] *C. W. Emmens:* Proceedings Sixth internat. Conf. Planned Parenthood. London 1959, p. 325.
[88] *S. J. Segal*, Eugenic Quarterly *6*, 94 (1959).
[89] *S. J. Segal* and *W. O. Nelson*, Proc. Soc. exp. Biol. Med. *98*, 431 (1958).
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[91] *C. H. Danforth* and *E. Cater*, Proc. Soc. exp. Biol. Med. *86*, 705 (1954).
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[93] *M. L. Murphy*, *D. A. Karnofsky*, and *J. Roddy*, Proc. Amer. Assoc. Cancer Res. *1*, 34 (1954).
[94] *H. Jackson* and *M. Bock*, Nature (London) *175*, 1037 (1955).
[95] *J. B. Thiersch*, Acta endocrinol., Suppl. *28*, 37 (1956).
[96] *J. B. Thiersch*, Proc. Soc. exp. Biol. Med. *94*, 36 (1957).
[97] *M. A. Sanders*, *B. P. Wiener*, and *J. Yudkin*, Nature(London) *180*, 1015 (1961).
[98] *J. B. Thiersch*, Proc. Soc. exp. Biol. Med. *98*, 479 (1958).
[99] *J. B. Thiersch* in: Proc. Sixth internat. Conf. Planned Parenthood. London 1959, p. 157.
[100] *K. Didcock*, *D. Jackson*, and *J. M. Robson*, Brit. J. Pharmacol. Chemotherapy *11*, 437 (1958).
[101] *M. G. Kelley* and *J. L. Hartwell*, J. nat. Cancer Inst. *14*, 967 (1954).
[102] *A. Tyler* in: Proc. Sixth internat. Conf. Planned Parenthood. London 1959, p. 138.
[103] *B. P. Wiesner*, *M. Wolfe*, and *J. Yudkin*, Stud. Fertil. *9*, 129 (1958).
[104] *F. W. Stamler*, Proc. Soc. exp. Biol Med. *90*, 294 (1955).
[105] *D. Jackson* and *J. M. Robson*, Brit. J. exp. Pathol. *39*, 133 (1958).
[106] *J. B. Thiersch*, Ann. N.Y. Acad. Sci. *60*, 220 (1954).
[107] *J. B. Thiersch*, Amer. J. Obstetr. Gynecol. *63*, 1298 (1952).
[108] *S. C. Hartmann*, *B. Levenberg*, and *J. M. Buchanan*, J. biol. Chemistry *221*, 1057 (1956).
[109] *M. L. Murphy* and *D. A. Karnofsky*, Cancer *9*, 954 (1956).
[110] *J. B. Thiersch*, Proc. Soc. exp. Biol. Med. *94*, 27 (1957).
[111] *J. B. Thiersch*, Proc. Soc. exp. Biol. Med. *94*, 33 (1957).
[112] *J. B. Thiersch*, Proc. exp. Biol. Med. *97*, 888 (1958).
[113] *A. W. Craig*, *B. W. Fox*, and *H. Jackson*, Nature (London) *181*, 353 (1958).
[114] *H. Jackson*, J. Faculty Radiologists *9*, 217 (1958).
[115] *J. MacLeod*, *A. Sorbrero*, and *W. Inglis*, J. Amer. med. Asoc. *176*, 427 (1961).
[116] *M. E. Paniagua*, *P. R. Rio Piedras*, *A. B. Vaillant*, and *C. J. Gamble*, J. Amer. med. Assoc. *177*, 125 (1961).

of compounds that have been tested for spermicidal effect and have also been tested extensively for how well they are tolerated in the vagina. Under the stimulus of the Planned Parenthood Association, test methods for spermicidal preparations were developed [116a–c] and regular lists of useful preparations are published (Approved List of Contraceptives by the Family Planning Association, London SW 1; last available edition: 1959). Using these methods, the spermicidal activities of numerous compounds, mainly detergents [116d], were tested *in vitro*.

Finally, it is conceivable to treat the male partner so as to damage his sperm (without effecting any apparent morphological defects) in such a way as to prevent it from penetrating the ovum and thus consummating fertilization. So far this has not been observed. However, male sterility caused by autoantibodies against sperm has been described [116e]. Treatment of semen with artificially produced serum antibodies prevented conception [116f].

β) Ova (see Scheme 5)

It is considerably more difficult to affect either the unfertilized or the fertilized ovum (see Scheme 5 and Table 3). So far no entirely harmless procedure has been developed for humans,

ovary (phase of follicle maturation)	←	Myleran, selenium (D)
	⇠	mitotic inhibitors, antimetabolites
↓		
tubes (maturation processes)	←	MER-25 (D)
	⇠	mitotic inhibitors, antimetabolites
↓		
tubes (fertilization)		
↓		
tubes and uterus (development of trophoblast prior to nidation)	←	cell poisons, mitotic inhibitors, antimetabolites, Cd salts (D)
↓		
uterus (development of embryo following nidation)	←	cell poisons (D)

Scheme 5. Prevention of pregnancy by selective action on the ovum or the fertilized ovum. Symbols as in Scheme 4

nor are such procedures known from animal experiments. Myleran is the only compound with which it was possible to demonstrate an ovicidal action preceding ovulation [85]. Selenium, added to the drinking water, appears to damage the ovum to the point where fertilization can no longer take place. Of interest is the action ascribed to MER 25, 1-(*p*-2-diethylaminoethoxyphenyl)-1-phenyl-2-*p*-anisylethanol; this compound is said to change the outer layer of the ovum to the point where sperm penetration is prevented [86].

γ) Fertilized ovum (see Table 3)

Extensive studies are being carried out to test the possibility of providing the mother with embryotoxic materials that are harmless to her (selective embryotoxicity). These should be applicable either before or after nidation. The danger exists, however, that an insufficient dose may result in the birth of a live but malformed baby [*]. Hence such compounds seem unsuitable for contraceptive purposes.

b) *Materials that affect other physiological or biochemical processes concerned with conception*

Numerous discussions and systematic investigations have been concerned with the question whether or not the fundamental physiological and biochemical processes concerned with conception can be affected in such a way as to inhibit conception. Practical results have been obtained in either sex only by the use of compounds that act directly on the regulatory center.

In principal, two possibilities can be considered for use in women: sustained morphine medication is known to cause a reversible blocking of the hypothalamic sex regulatory center [117]. In chickens and rats, this method has been applied with success but has not been pursued further [118,119]. Similarly, the antiovulatory effect of neuroplegic and sedative agents observed in animal experiments has not been tested in humans. It seems possible to develop a morphine analogue that is not addictive and is also free of other side effects.

Another possibility is to simulate the central inhibition of the periodicity of ovarian function by the use of ovariogenic and placental steroids. *Pincus* et al. [120–122] have proved the applicability of gestagenic steroids taken by mouth for this purpose. Functional and psychological considerations led to the combination of a gestagen with an estrogen, to be taken daily. When taken in the prescribed cycle of 20 days on and 10 days off the medication, this combination not only inhibits ovulation but also induces a cyclelike growth and sloughing off of the endometrium. Studies have shown that the drug does not suppres the basic secretion of gonadotropin but merely inhibits the rise in the blood level, which induces ovulation and which is normally part of the first phase of the cycle [123]. On interrupting the treatment, the normal cycle returns, and fertility reappears [124, 125]. Of the estrogen-gestagen combinations listed in Table 5, Enovid® is the oldest.

Attempts at improving effectiveness, questions of tolerance, and price have led to the development of other similar preparations, among which Anovlar® seems to be particularly well tolerated [124, 125, 170a–c]. After treatment with ovulation-inhibiting steroid combina-

[*] This is the only possibility where the use of contraceptives can give rise to malformations. Malformations due to the use of other type of contraceptives have often been claimed, but such claims have not so far been conclusively substantiated. However, none of these methods seems applicable without affecting the mother.

[116a] *J. MacLeod, A. J. Sobrero*, and *W. Inglis*, J. Amer. med. Assoc. *176*, 427 (1961).

[116b] *W. N. Harris*, J. Reprod. Fertility *3*, 105 (1962).

[116c] *Cl. Harvey* and *R. E. Stuckey*, J. Reprod. Fertility *3*, 132 (1962).

[116d] *Cl. Harvey* and *R. E. Stuckey*, J. Reprod. Fertility *3*, 124 (1962). [116e] *A. S. Parkes*, J. Reprod. Fertility *3*, 160 (1962).

[116f] *A. C. Menge, W. H. Stone, W. J. Tyler*, and *L. E. Casida*, Reprod. J. Fertility *3*, 331 (1962).

[117] *M. F. Meyer*, Zbl. Gynäkol. *60*, 47 (1936).

[118] *G. Dörner* and *W. Hohlweg*, Arch. Gynäkol. *91*, 463 (1959).

[119] *G. Knappe* and *G. Doerner*, Zbl. Gynäkol. *81*, 2073 (1951).

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[121] *G. Pincus, J. Rock*, and *C. R. Garcia*, Amer. J. Obstetr. Gynecol. *75*, 1333 (1958).

[122] *G. Pincus, C. R. Garcia*, and *J. Rock*, Science (Washington) *130*, 81 (1959).

[123] *R. Buchholz*, Lecture, Meeting of the Nordwestdtsch. Ges. Gynäkologie, Kiel, 1961.

[124] *F. Peeters*, Lecture, Meeting of the Nordwestdtsch. Ges. Gynäkologie, Kiel, 1961.

[125] *F. Peeters, M. van Roy*, and *H. Oeyen*, Med. Klin. *56*, 1679 (1961).

Table 5. Contraceptives that act on other processes that are necessary for conception (for symbols see caption of Scheme 4)

Material	Supposed or proven mode of action					
	Category	In the male	Ref.	Category	In the female	Ref.
Steroid hormones						
Ethynyl-19-nortestosterone acetate (Primolut (N)® Schering)				A		[70]
Ethynyl-19-nortestosterone and ethynyl-estradiol (Anovlar®, Schering)				A		[124, 125]
Ethyl-19-nortestosterone (Nilevar®, Searle)				B		[70]
Ethynyl-$\Delta^{5,10}$-19-nortestosterone and ethynylestradiol-3-methyl ether (Enovid®, Enavid®, Conovid®; Searle)				A	inhibit ovulation by action on diencephalon	[70, 122, 133] [134]
Ethynyl-19-nortestosterone and ethynyl-estradiol-3-methyl ether (Orthonovum; Ortho)				A		[135]
Ethynyl-Δ^4-estren-17-ol (ethynyl-3-deoxo-19-nortestosterone) and ethynylestradiol-3-methyl ether (Lyndiol; Organon)				A		
6α-Methyl-17-hydroxyprogesterone acetate and ethynylestradiol (Protex; Leo)				A		
Testosterone	B	inhibits spermatogenesis	[130–132]	B		[127, 136, 137]
Estrogens (steroids or stilbenes)	C, D	inhibit spermatogenesis	[128]	B D	in small doses they accelerate transport of the ovum through the tubes, thereby preventing nidation; in large doses they block transport through the tubes and thus prevent nidation	[138] [139, 140]
Gestagens (19-norprogesterone, gestagens)	B	inhibit spermatogenesis	[70, 126]	D	prevent nidation by acting on endometrium	[144–148]
19-Norgestagens				D	act on cervical mucus (preventing the passage of the sperm); inhibit nidation in endometrium	[77, 14–150]
Antihormones						
Antigonadotropines	D	inhibit spermatogenesis	[132a]	D	induce hypotrophy of ovaries and genital tract	[150a]
Pituitary inhibitors (nonsteroids)				D	chemical blocking of gonadotropin releasers or of gonadotropin production	[151]
Dithiocarbamoyl hydrazines (particularly 1-methylallylthiocarbamoyl-2-methyl-thiocarbamoylhydrazine)				D		
MER-25				D	decreases secretion in the tubes	[151a]
Anti-inflammatory agents						
Antihistaminics Monoaminooxidase inhibitors	D	diminish male fertility (sperm damage?)	[132a]	D D	inhibit nidation by diminishing the effect of estrogens and gestagens	[69] [5, 152]
5-Hydroxytryptamine				D D	ditto and estrus inhibition kills fetus in 2nd half of pregnancy	[153, 154] [153, 155]
So-called hyaluronidase inhibitors						
Hesperidine phosphate				C, D	prevents fertilization	[102]
Cirantin (pyrone derivative)				C	inhibits ovulation	[156, 157]
Neuroplegic materials and sedatives						
Reserpine Chloropromazine Morphine				D D C, D	inhibit ovulation by acting on diencephalon	[158, 159] [160] [117–119]

[126] *M. Apostolakis*, Acta Endocrinol. *37*, 75 (1961).

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Material	Supposed or proven mode of action					
	Category	In the male	Ref.	Category	In the female	Ref.
Parasympaticomimetics						
Pilocarpin				D		
Physostiguin				D		
Sympaticolytics					inhibit nidation by	[160a, b]
Ergot alkaloids (Neo-gynergen)					stimulating unphysiological mobility of the genital tract	
Contact insecticides						
Thiophosphonic ester [E 625]				D	toxic to embryo	[160b]
Hexachlorocyclohexane				D	after nidation	[160b]
Plant hormones					inhibit nidation,	[160b]
Indolyl-3-acetic acid				D	toxic to embryo	
Plants and plant materials						
Lithospermum ruderale, Lithospermum officinale				C, D	inactivate gonadotropins	[161, 162]
Lycopus virginale				D		[163]
Polygonum hydropiper L.				D	inhibits gonadotropins in anterior pituitary	[162, 164]
Ergotoxins (active components: ergocornin and ergocryptin)				D	prevent nidation by inhibiting gestagens	[165, 166]
m-Xylohydroquinone				C, D	estrogen and progesterone antagonist	[70, 120, 167–170]
					peripheral gonadotropin inhibition	[70, 167]
Embelia ribes, Piper longum and *asafetida*				D, (B)	block estrogen-induced enzyme activation	[172]

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tions, thromboses were observed in some cases who had previously suffered from thrombophlebitis and/or thromboembolism. There is, however, no direct connection between medication and thrombosis [170 d]. Nevertheless, these cases are not ignored: preparations of the kind mentioned should not be given to women with a tendency to develop thrombosis.

In males, too, orally administered gestagens can inhibit sperm cell maturation by blocking the central regulatory control [126]. Of interest is the suppression of libido in males in the course of medication, whereas this is not true in women.

Both estrogens and androgens block the hypothalamic regulatory center in men and women, but their side effects are such as to prohibit administration of the necessary doses [127,128].

In addition to methods affecting the diencephalon region, it is also conceivable to inhibit the initial stages of the regulatory cycles in both sexes by means of antigonadotropins and by blocking the anterior pituitary by antireleasing agents (see Schemes 6 and 7 and also Table 5).

hypothalamus (sex center in diencephalon)	←	gestagens and androgens (B); estrogens (C)
↓		
gonadotropin releaser	←···	antireleaser hormone
↓		
anterior pituitary	←	*Polygonum hydropiper* (D)
↓	←	chemical block of gonadotropin production (D)
gonadotropins (FSH, ICSH)	←	*m*-xylohydroquinone (C)
	←···	antihormones; *Lithospermum* species
↓		
testes	←	estrogens (D)
↓	←···	monoaminooxidase inhibitors (D)
epididymis	←···	effect on antigaglutinin formation and sperm maturation
↓		
secondary sex glands (prostate, seminal vesicles)	←···	effect on agglutinin or antiagglutinin formation; inducers for transforming sperm metabolism to aerobic

Scheme 6. Prevention of pregnancy by interfering with processes in the male that are essential for conception.
For symbols see caption of Scheme 4

hypothalamus (sex center in diencephalon)	←	gestagens (A); androgens and estrogens (B); morphine (C); neuroplegic psychic inhibition(D)
↓		
gonadotropin releaser	←···	antireleaser hormone
↓		
anterior pituitary	←	*Polygonum hydropiper*
↓	←	chemical blocking of gonadotropin production (D)
gonadotropins (FSH, ICSH, LTH)	←··	*Lithospermum* species, antihormones (C); *Lycopus virginale* (D)
↓		
ovary (follicle maturation and ovulation)	←	hyaluronidase inhibitors, monoamine oxidase inhibitors (D)
↓		
tubes (transport of ovum and sperm, milieu of fertilization)	←	*m*-xylohydroquinone (C); estrogens (D)
↓	←···	effect on antiagglutinin formation or anaerobic metabolism or motility (D)
uterus (preparation for nidation and nidation)	←	*m*-xylohydroquinone (C); gestagens, estrogens, antihistaminic agents, antiinflammatory agents, ergotoxins (D)
↓	←···	induction of sperm antibodies and antibodies to gestagen proteins
cervix (sperm penetration)	←	gestagens (C)

Schema 7. Prevention of pregnancy by interfering with processes in the female that are essential for conception.
For Symbols, see caption of Scheme 4

Observations have been made in humans on the transitory accumulation of antigonadotropin and the resulting inactivation of gonadotropin [129]. However, major difficulties oppose the widespread use of these antihormones.

Greater success seemed possible with plant derivatives which apparently act as gonadotropin inactivators by way of a pituitary block. On the basis of popular officinal medicine, *Polygonum hydropiper*, *Lithospermum* species, *Lycopus virginicus* and *Pisum sativum* have been studied intensively. A stable and defined product was obtained only from the pea plant, *viz. m*-xylohydroquinone [70,167,168,171]. Widespread clinical trials notwithstanding, its contraceptive qualities have not been definitely established, and the claim for its mechanism of action remains unproven. Preparations made from other than the above mentioned plants have been tested with positive results in animal experiments and, in some instances, clinically [161]. Until now they have proved impractical because they lack stability and are tolerated poorly, and because it is difficult to obtain enough starting material [162,163].

There has been some discussion concerning the use of sperm agglutinins. An increased agglutinin titer might render the sperm incapable of fertilization. No work has been done as yet concerning the possible effect of changes in epididymal metabolism on sperm maturation with the aim of rendering the sperm sterile. Such a procedure would not exclude the possibility of malformations.

In the female more succes is likely to be achieved by interrupting the regular cycle in order to prevent conception: thus in regulatory cycle I (see Scheme 1) inhibitors of monoaminooxidase and hyaluronidase have been shown in animal experiments to prevent the rupture of the follicles induced by ICSH. The ovum dies and the follicle either atrophies or luteinizes [156,157].

In the case of regulatory cycle II (see Scheme 2) it has been shown in animal experiments – and quite possibly only because of species-specific mechanisms – that small doses of estrogens accelerate the movement of the ovum through the follicles and thereby inhibit fertilization or nidation. Large doses of estrogens under similar circumstances block movement of the ovum in the oviduct; this causes the arrival of the fertilized ovum to be out of phase with nidation. Thus nidation can be prevented by interference with the physiological relationship between estrogens and gestagens.

Function of the *corpus luteum*, fertilization, and nidation are so delicately adjusted in time that interference with one of these factors makes it impossible for nidation of the fertilized ovum to occur. It might be possible to do in humans what has been done in dogs, *i.e.* to inject estrogens just after copulation. However, this would require the injection to be given within a few days after conception had occurred. Moreover, diagnosis of pregnancy can be made only at a time when steroids can no longer affect nidation.

If done at the right moment, nidation can also be prevented by the administration of anti-inflammatory substances (Table 5 and Scheme 7). Apparently these compounds block the development of the decidua in the endometrium as induced by estrogens and gestagens; this development closely resembles an acute inflammation [5].

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A combination of plant materials, discussed in ancient Indian medical literature, blocks the estrogen-induced increase in enzyme activity [172]. Experiments with mice have shown that nidation can also be prevented by upsetting the endocrine equilibrium needed for this process [173]. Induction of unphysiological motility of the genital tract before nidation has occurred greatly decreases the viability of the embryo (cf. Table 5).

The question remains whether the anaerobic metabolism which prevails at the beginning of the second regulatory cycle and which provides an optimum milieu for fertilization can be affected in any way. This in turn would modify some of the functions in the female genital tract needed to effect conception; for example, the production of antiagglutinins and "fertilisins" needed for capacitation of the sperm might be affected.

It has been possible to produce an antigen from sperm and also antiserum against spermatozoa of different species [174].

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It is not yet possible to foretell the practical significance of the many measures discussed in this article. As yet there is competition on the one hand between contraceptive measures that interfere with certain of the mechanisms of conception and mechanical devices, and, on the other, between these and attempts to determine the nonfertile period in the second regulatory cycle (*e.g.* by means of the *Knaus* and *Ogino* calendar, by measuring the vaginal temperature in the morning in order to determine the postovulatory rise in temperature caused by progesterone, or by pregnanediol determination according to *Reimann-Hunziker* and *Wild* [175]). On the basis of statistics, it can be asserted that, when properly used, gestagens that inhibit the sex center and thereby prevent ovulation have the greatest contraceptive potentialities and reliability (practically 100 %).

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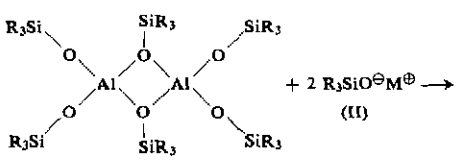
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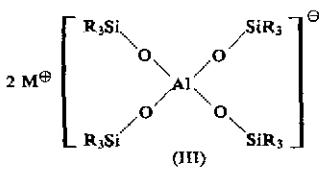
Anionic Heterosiloxanes [1]

By Dr. H. Schmidbaur and Prof. Dr. Max Schmidt

Institut für Anorganische Chemie
der Universität Marburg/Lahn (Germany)

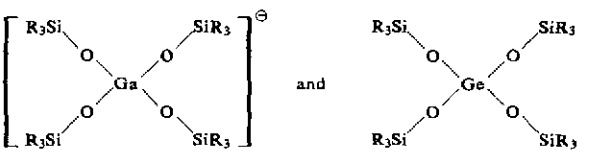
The siloxyl groups forming coordination bridges between two metal atoms in the dimeric tris-trimethylsiloxy compounds (I) of Al and Ga [2] account for the great readiness with which these compounds add on metal siloxides (II). Even at room temperature, equimolar mixtures of solutions of $\{[(CH_3)_3SiO]_3Al\}_2$ or $\{[(CH_3)_3SiO]_3Ga\}_2$ and $NaOSi(CH_3)_3$ or $KOSi(CH_3)_3$ in CCl_4 yield white precipitates of the sodium or potassium tetrakis-trimethylsiloxy-alanates (III) or -gallanates (IV) in an exothermic reaction, *e.g.*





(M = Na or K; R = CH_3). These sodium and potassium salts are insoluble in organic solvents, and begin to decompose slowly at temperatures above 250 °C. Their infrared spectra in Nujol show bands, whose positions prove the existence of discrete anions (ν Si–O–Al at 10.35 μ and ν Si–O–Ga at 10.80 μ). Analogously prepared lithium salts are soluble in organic solvents, are fusible, sublime *in vacuo*, and have infrared spectra unlike those of the Na and K salts. The spectra of the Li compounds indicate a strong homopolar linkage of the metal to the anion, as well as the presence of molecular association, which is further confirmed by molecular weight determinations. The proton magnetic resonance spectra in CCl_4 show only one sharp resonance singlet, which is an impressive proof of the equivalence of all four siloxyl groups (chemical shift for $Li\{Al[OSi(CH_3)_3]_4\}$, −0.125 ppm; for $Li\{Ga[OSi(CH_3)_3]_4\}$, −0.165 ppm [3].

The anions of III and IV are isosteric with the neutral siloxanes $Si[OSi(CH_3)_3]_4$ and $Ge[OSi(CH_3)_3]_4$, for example:



B.p. 59–60 °C/1 mm.; m.p. −59 °C [4]

Their infrared and proton magnetic resonance spectra show the complete structural identity of the tetrahedral ionic and neutral siloxane compounds. With analogous "complex silicones", where iron was the heteroatom, we obtained similar results [1].

Received, June 22nd. 1962 [Z 305/139 IE]

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[2] *H. Schmidbaur* and *M. Schmidt*, Angew. Chem. internat. Edit. *1*, 328 (1962).

[3] Varian A 60 (60 Mc); solutions of all substances in CCl_4 at c = 5 ± 1 %, with tetramethylsilane as internal standard.

[4] First prepared by us from $GeCl_4$ and four moles of $NaOSi(CH_3)_3$ in anhydrous ether.

Bis(triphenylphosphine)-ethylene-nickel and Analogous Complexes

By Priv.-Doz. Dr. G. Wilke and Dipl.-Chem. G. Herrmann

Max-Planck-Institut für Kohlenforschung
Mülheim/Ruhr (Germany)

By the interaction, at approx. 20 °C, of nickel acetylacetonate with $(C_2H_5)_2AlOC_2H_5$ in the presence of triphenylphosphine (TPP) (Ni:P = 1:2) in benzene, bis(triphenylphosphine)-ethylene-nickel, $(TPP)_2Ni{\cdot}C_2H_4$) is produced in yellow

crystalline form in a yield of about 75 % [1]. Gaseous reaction products are a little ethylene, but chiefly ethane and hydrogen. Therefore, the reduction proceeds, at least partially, as follows:

a) $Ni(C_5H_7O_2)_2 + 2\,Al(C_2H_5)_2OC_2H_5 \rightarrow Ni(C_2H_5)_2 + 2\,Al(C_5H_7O_2)(OC_2H_5)(C_2H_5)$

$Ni(C_2H_5)_2 \rightarrow NiH_2 + 2\,C_2H_4$

$NiH_2 \rightarrow Ni + H_2$

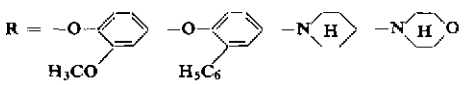
The evolution of ethane may arise from a side reaction hydrogenation of ethylene or from radical formation by decomposition of the intermediate $Ni(C_2H_5)_2$:

b) $Ni(C_2H_5)_2 \rightarrow Ni + 2 \bullet C_2H_5$

$2 \bullet C_2H_5 \rightarrow C_2H_4 + C_2H_6$

The yield of $(TPP)_2Ni{\cdot}C_2H_4$ can be raised to 90–95 % if a solution initially saturated with ethylene is employed. Molecular weight determinations in benzene showed that the compound is monomeric in solution, *i.e.* it behaves again as a nickel complex of coordination number 3 [2]. Similarly, the following compounds $(R_3P)_2Ni{\cdot}C_2H_4$ were prepared:

R	Yield [%]	Form
Ethyl	70	Yellow oil
Cyclohexyl	92	Yellow crystals



62 % 68 % 80 % 60 %

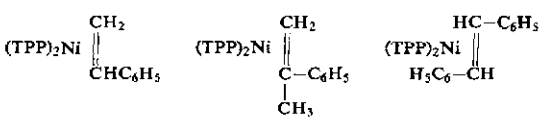
Yellow, crystalline compounds.

Ethylene is expelled by the action of other electron donors. By volumetric determination of ethylene the progress of the expulsion can be followed. In all cases over 90 % of ethylene are obtained.

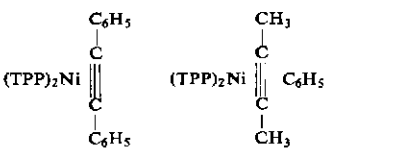
By splitting-off ethylene from $(TPP)_2Ni{\cdot}C_2H_4$ according to the general equation:

c) $(TPP)_2Ni{\cdot}C_2H_4 + Donor \rightarrow (TPP)_2Ni{\cdot}Donor + C_2H_4$

the following crystalline compounds were obtained among others:



88 %, yellow orange 86 %, yellow 83 %, dark red



60 %, yellow 90 %, yellow, crystallizes with 1 molecule of benzene

Investigations are in progress on the infrared and proton resonance spectra of the described new compounds to determine the effect of different donors on the bond between nickel and the CCC multiple linkages.

Received, July 27th. 1962 [Z 316/150 IE]

[1] Previously, this compound was erroneously considered to be $[(C_6H_5)_3P]_2Ni(0)$: *G. Wilke, E. W. Müller*, and *M. Kröner*, Angew. Chem. *73*, 33 (1961).

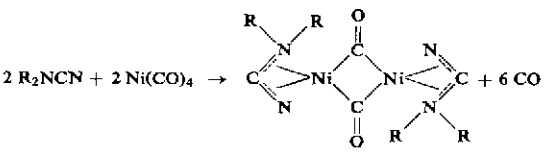
[2] *G. Wilke*, Angew. Chem. *72*, 581 (1960).

Nickel(0)-dialkylcyanamide-carbonyl

By Dr. H. Bock

Institut für Anorganische Chemie
der Universität München (Germany)

Nickel(0)-dialkylcyanamide-carbonyls (I) are formed by the reaction of dialkylcyanamides with an excess of $Ni(CO)_4$ as analytically pure, air-sensitive orange coloured crystals: Ia, R = CH_3, Decompn. pt. 98 °C; Ib, R = $-(CH_2)_5-$, Decompn. pt. 118 °C.



(I)

The structure follows from elemental analysis, molecular weight determination, diamagnetism and infrared spectra [1] between 2300 and 1700 cm^{-1}. There are three equally strong bands (Ia: 2037(a), 2004(b), and 1790(c) cm^{-1}; Ib: 2037(a), 1980(b), and 1790(c) cm^{-1}). These bands can be attributed to the N=C=N skeleton, the vibrations of which are shifted to lower frequencies by complex formation (a and b), and to the bridge carbonyl group (c). The nitrile bands of the free cyanamides occur at 2217 cm^{-1}

An additional confirmation of the proposed structure is provided by the quantitative thermal decomposition at 10^{-4} mm Hg:

$[Ni(R_2NCN)(CO)]_2 \rightarrow 2\,Ni + 2\,R_2NCN + 2\,CO$

Received, August 1st. 1962 [Z 320/164 IE]

[1] For a discussion of the infrared spectra I am indebted to Dr. *H. P. Fritz*; the magnetic measurements were carried out by cand. phys. *H. Mödl*, Physikalisches Institut der Technischen Hochschule München.

The Intermediate Product of the Wackenroder Reaction

By Prof. Dr. P.W. Schenk and cand. chem. W. Kretschmer

Institut für Anorganische Chemie
der Freien Universität Berlin (Germany)

According to present concepts the treatment of H_2S with SO_2 in aqueous medium results in two simultaneous reactions:

1) $2\,H_2S + SO_2 \rightarrow 3\,S + 2\,H_2O$

2) $H_2S + 3\,SO_2 \rightarrow H_2S_4O_6$ $(H_2S_nO_6)$

The formation of the different polythionic acids can be interpreted by the equation:

3) $H_2S_4O_6 + H_2SO_3 \rightleftharpoons H_2S_3O_6 + H_2S_2O_3$

Whereas it is generally accepted that equation 3 is valid, opinions regarding the initial reactions differ [1]. Since a major role is sometimes attributed [2] to the sulphur formed according to equation 1, we tested whether it is in fact elementary sulphur that precipitates in the reaction of H_2S with SO_2. The remarkable golden-yellow colour of the precipitate could be due to polysulphur oxides [3,4], although monomeric S_2O is extremely sensitive to water [5].

We passed H_2S into an ice-cold solution of sulphurous acid to which some NaCl and HCl had been added to permit a ready flocculation. The golden-yellow precipitate was sucked off quickly and dried in high vacuum. It was then decomposed it by quick heating. The abundantly evolved gases, which were pumped off, condensed in liquid air to a cherry red condensate. The ultraviolet spectrum of the gases showed the bands of S_2O.

Thus it is confirmed that $H_2S_2O_2$ is formed primarily in the course of the Wackenroder reaction:

4) $H-S-H + HO-\overset{\overset{O}{\|}}{S}-OH \rightarrow HS-\overset{\overset{O}{\|}}{S}-OH + H_2O$

It can react further to polysulphur oxides, whose composition approaches the ideal formula $(S_2O)_n$:

5) $H-\overset{\overset{O}{\|}}{S}-\overset{\overset{O}{\|}}{S}-OH + H-\overset{\overset{O}{\|}}{S}-\overset{\overset{O}{\|}}{S}-OH \rightarrow H-\overset{\overset{O}{\|}}{S}-\overset{\overset{O}{\|}}{S}-\overset{\overset{O}{\|}}{S}-\overset{\overset{O}{\|}}{S}-OH \rightarrow (S_2O)_n \cdot H_2O$

The formation of the polysulphur oxides cannot be ascribed to polymerisation of the anhydride of $H_2S_2O_2$, as monomeric S_2O quickly reacts with water to form $H_2S + SO_2$.

Received, August 2nd, 1962 [Z 326/163 IE]

[1] *H. Stamm, M. Becke-Goehring*, and *M. Schmidt*, Angew. Chem. *72*, 34 (1960).

[2] *M. Schmidt* and *H. Heinrich*, Angew. Chem. *70*, 572 (1958).

[3] *M. Becke-Goehring*, Z. anorg. allg. Chem. *257*, 227 (1948).

[4] *P. W. Schenk*, Z. anorg. allg. Chem. *265*, 177 (1951).

[5] *P. W. Schenk* and *H. Platz*, Z. anorg. allg. Chem. *215*, 126 (1933).

Alkylated Disulphur(IV) Nitride

By Prof. Dr. Margot Becke-Goehring and Dipl.-Chem. H. P. Latscha

Anorganisch-chemisches Institut der Universität Heidelberg (Germany)

A new type of sulphur-nitrogen compound with the cation $[(CH_3)_2S-N=S(CH_3)_2]^+$ was obtained by the interaction of trithiazyl chloride, $[NSCl]_3$, with dimethylsulphoxide:

$$[NSCl]_3 + 6\,(CH_3)_2SO \rightarrow 3\,[(CH_3)_2S-N=S(CH_3)_2]Cl + 3\,SO_2$$

I

The yield of compound (I) is about 60 %. It crystallises in colourless needles, which decompose at about 80 °C. It is soluble in dimethylsulphoxide, and on heating in tetrachloroethane, acetonitrile and nitrobenzene; it is insoluble in benzene, petroleum ether and carbon tetrachloride.

The solution in dimethylsulphoxide is electrically conductive. Cryoscopic molecular weight determination in dimethylsulphoxide indicates about 70 % dissociation (1.4 % solution).

Received, August 2nd, 1962 [Z 322/159 IE]

Hydrolytic Fission of the Higher Oxides of Praseodymium and Terbium

By Prof. Dr. G. Brauer and Dipl.-Chem. B. Pfeiffer

Chemisches Laboratorium der Universität Freiburg/Brsg. (Germany)

Higher praseodymium oxides of a composition between $PrO_{1.05}$ and $PrO_{1,83}$ hydrolize in moist air at room temperature with valency disproportionation. Thus $Pr(OH)_3$ (lattice constants a = 6.47, c = 3.78 Å) and PrO_2 (a = 5.394 Å) are obtained in a heterogeneous mixture and well crystallized. The reaction is accelerated by boiling with water under reflux. It can be utilized for a new preparation of PrO_2; by extracting Pr_6O_{11} with boiling 90 % acetic acid pure PrO_2 is obtained.

The hydrolysis of the higher oxides of terbium is much slower and less simple. A temperature of 200 °C is required. One obtains the crystalline phases $Tb(OH)_3$ (a = 6.31, c = 3.59 Å) $TbO_{1.823}$ [1] (a = 5.28 Å) and TbO_2 (a = 5.220 Å). Pure TbO_2 with a composition strictly in accord with its formula can be obtained by extracting Tb_4O_7 with a boiling mixture of equal parts by volume of conc. hydrochloric acid and glacial acetic acid. Hitherto TbO_2 was available only by the use of atomic oxygen [1,2].

Received, August 6th, 1962 [Z 323/157 IE]

[1] *N. C. Baenziger, H. A. Eick, H. S. Schuldt*, and *L. Eyring*, J. Amer. chem. Soc. *83*, 2219 (1961).

[2] *D. M. Gruen, W. C. Koehler*, and *J. J. Katz*, J. Amer. chem. Soc. *73*, 1475 (1951).

Triphenylazidosilane and Diphenyldiazidosilane [1]

By Dr. N. Wiberg, cand. chem. F. Raschig, and cand. chem. R. Sustmann

Institut für Anorganische Chemie der Universität München (Germany)

To prepare triphenylazidosilane, Ph_3SiN_3 (I), [1,2] and diphenyldiazidosilane, $Ph_2Si(N_3)_2$ (II), excess NaN_3 in pyridine was allowed to react at room temperature with triphenylchlorosilane and diphenyldichlorosilane, respectively [3]. The progress of the reaction was measured by titrimetric determination of the salts formed (NaN_3, NaCl). After three days the reaction was almost quantitative. II is a water-clear liquid (b.p. 85 to 90 °C/10^{-3} mm. Hg, n_D^{20} = 1.5887) and, like I, thermally extremely stable [4]. No nitrogen is evolved on heating for two hours at 300 °C. Sunlight and, more strongly, ultraviolet irradiation modify II.

I and II react with a 1:1 molar ratio of triphenylphosphine in ether at 100 °C with evolution of nitrogen to give *N*-silylphosphinimines (III) and (IV).

$Ph_3Si-N=PPh_3$ — III, m.p. 215—216 °C

$Ph_3P=N-SiPh_2-N=PPh_3$ — IV, m.p. 190—191 °C

In both cases a maximum of only 50 % of the expected amount of nitrogen is evolved. Consequently a side-reaction must take place forming further nitrogen-containing compounds (*e.g.* triphenylphosphinimonium azide, $[Ph_3P=NH_2]^+N_3^-$, can be isolated). At room temperature the reaction of PPh_3 with compound I takes place without nitrogen evolution. Ph_6SiNP (V), isomeric with III, was found to be one reaction product. (The infrared spectrum of V does not contain the band due to the P=N double bond). The structures of III and IV were confirmed by degradation with dry hydrogen chloride in benzene.

Received, August 7th, 1962 [Z 328/154 IE]

[1] 2nd Communication on silyl azides. 1st Communication: *N. Wiberg* et al., Angew. Chem. internat. Edit. *1*, 335 (1962).

[2] *R. West* et al., J. Amer. chem. Soc. *84*, 1763 (1962).

[3] Phenyltrichlorosilane also reacts in this manner. The azide obtained is, however, still impure.

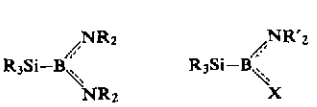
[4] The ^1H-resonance spectrum of the phenyl groups of I indicates a marked degree of sharing of the d-orbitals of the silicon atom with the π-electron system of the benzene rings.

Compounds Containing a Silicon-Boron Bond [1]

By Priv.-Doz. Dr. H. Nöth and Dipl.-Chem. G. Höllerer

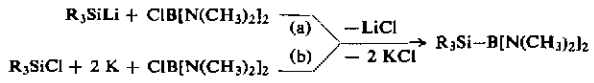
Institut für Anorganische Chemie der Universität München (Germany)

The synthesis of compounds with stable silicon-boron bonds is made possible by π-bonds between nitrogen and boron atoms [2]:



I II

Triorganosilyldialkylaminoboranes of Type I are accessible by one of the following routes:



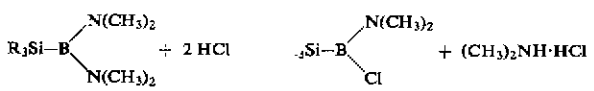
By route (a) $Ph_3Si-B[N(CH_3)_2]C_4H_9$ can also be prepared, but not however $Ph_3Si-B(C_4H_9)_2$; this underlines the importances of the π-bonds for the stability of the Si–B bond.

The hydrolysis of $Ph_3Si-B[N(CH_3)_2]_2$ proceeds quantitatively according to

$$Ph_3Si-B[N(CH_3)_2]_2 + 3\,H_2O \rightarrow Ph_3SiH + B(OH)_3 + 2\,HN(CH_3)_2.$$

Methanolic potassium hydroxide reacts with all silylboranes with the evolution of hydrogen, *i.e.* with hydrolysis of the initially formed Si–H bond. Silylboranes reduce silver salts to silver.

HCl in ether attacks I only at the B–N bond, not at the Si–B bond. Reaction in the molar proportions of 2:1 leads to triorganosilyldimethylaminochloroboranes of Type II (X=Cl:



The physical constants of the compounds which have been characterised by analysis and infrared spectroscopy are:

	M.p. (°C)	B.p. (°C)
$Ph_3Si-B[N(CH_3)_2]_2$	50	150–160/HV [3]
$Ph_3Si-B[N(CH_3)_2]Cl$	135	150–160/HV [3]
$Ph_3Si-B[N(CH_3)_2]C_4H_9$	–	155–165/HV [3]
$(CH_3)_3Si-B[N(CH_3)_2]_2$	–	65/9 mm Hg
$(CH_3)_3Si-B[N(CH_3)_2]Cl$	–	42/9 mm Hg

The trimethylsilyl compounds are spontaneously inflammable in air.

Received, August 15th, 1962 [Z 331/160 IE]

[1] XIXth Communication on "Contributions to the Chemistry of Boron".

[2] A similar system exists in *B*-tris(triphenylsilyl)-*N*-trimethylborazole; *D. Seyferth* and *H. P. Kögler*, J. inorg. nucl. Chem. *15*, 99 (1960).

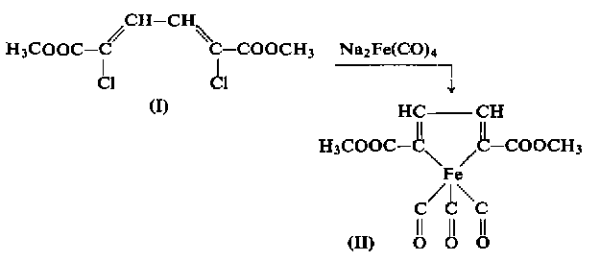
[3] Oil bath temperature. HV = high vacuum.

Synthesis of Ferrole Derivatives

By Doz. Dr. Ernst Bayer, Dr. H. A. Brune, and Dipl.-Chem. K. L. Hock

Institut für Organische Chemie der Technischen Hochschule Karlsruhe (Germany)

Derivatives of ferrole, *i.e.* of the 5-membered heterocycle with iron as the hetero-atom, can be synthesised from sodium iron carbonyl and 1,4-dichlorobutadiene derivatives. In this way dichlormuconic acid dimethyl ester (I) yields an orange-yellow tricarbonyl compound (II) of ferrole dicarboxylic acid dimethyl ester.



Tri-irondodecacarbonyl (5 g) in liquid ammonia (100 ml) at −78 °C and under oxygen-free nitrogen is converted to $Na_2Fe(CO)_4$ by the addition of metallic sodium (1.37 g). The ammonia is then evaporated in a stream of nitrogen and the cooling bath (methanol/solid CO_2) removed. Compound I (5 g) in dry, peroxide-free ether (250 ml) is now added dropwise and the mixture refluxed, with stirring, for 24 hours. The filtered solution is evaporated to dryness *in vacuo*, the residue taken up in benzene and chromatographed on a column (1.5 cm diameter, 50 cm long) of silica (Merck, 0.02–0.05 mm diameter). A green, a red and a yellow-orange zone are eluted. The green compound is $[Fe(CO)_4]_3$; the yellow-orange the ferrole derivative (II), which is further purified by vacuum sublimation (0.1 Torr) at 50 °C. Yield: 80 mg (II), m.p. 57 °C.

With its unsubstituted β-C-atoms (II) is suitable for electron distribution investigation, and is especially suited to answer the problem of whether or not there is present in ferrole a cyclic conjugation similar to that of the quasi-aromatic heterocycles pyrrole and thiophen. In its NMR-spectrum (Varian A 60) the proton bands of the β-CH-groups show a chemical shift of $\delta = 6.54$ ppm. This value is in the region of those found for analogous furan-, thiophen- and pyrrole derivatives. In addition the iron complex prepared from thiophen by *Stone* et al. [1] and claimed as a π-complex of ferrole is found to have a value for δ of 6.48 ppm [2].

Received, August 15th, 1962 [Z 332/161 IE]

[1] *F. G. A. Stone, H. D. Kaesz*, and *R. B. King*, J. Amer. chem. Soc. *82*, 4749 (1960).

[2] *M. L. H. Green, L. Pratt*, and *G. Wilkinson*, J. chem. Soc. (London) *1960*, 989.

Dimethyldiazidosilane

By Dr. W. Sundermeyer

Anorganisch-wissenschaftliches Laboratorium der Farbenfabriken Bayer AG., Leverkusen (Germany)

The previously reported method for the preparation of pseudo-halogen compounds of silicon from alkali pseudo-halogenides and chlorosilanes in fused salts as solvents [1] could also be used for the preparation of azides. Trimethylchlorosilane reacts with sodium azide, dissolved for example in an anhydrous $ZnCl_2$–KCl melt, at 230–250 °C to give a good yield of trimethylazidosilane (I) [2] (b.p. 96 °C corr.).

Similarly, an approximately 60 % yield of dimethyldiazidosilane (II) [3,4] was obtained.

$$(CH_3)_2SiCl_2 + 2\,NaN_3 \rightarrow \underset{\text{II}}{(CH_3)_2Si(N_3)_2} + 2\,NaCl$$

Whereas with phenylazidosilanes – analagous to the phenylsilylamines and phenylsilanols – stability due to contributions from mesomerism and the strong double bond character of the Si–N bond would be expected, the existence of II is surprising. The compound boils, without decomposition, at 144.3 °C (corr.) and is, like I and like triorganoazidosilanes containing phenyl groups [5,6], remarkably stable thermally.

II is not sensitive to percussion, but in contrast to I burns with deflagration when ignited on an open spoon. Atmospheric moisture quickly hydrolyses the compound to dimethylpolysiloxanes and hydrazoic acid. Its infrared spectrum resembles that of dimethyldichlorosilane and in addition shows characteristic bands at 3436 (w), 2619 (w), 2146 (vs), 1322 (vs), 1157 (w), 1073 (w), and 1020 (w) cm^{-1} [*].

II is also obtained in almost quantitative yield by the reaction of I with dimethyldichlorsilane.

$$2\,(CH_3)_3SiN_3 + (CH_3)_2SiCl_2 \xrightarrow{AlCl_3} \text{II} + 2\,(CH_3)_3SiCl$$

The reactants are heated with aluminium chloride under reflux, and the trimethylchlorosilane formed is continuously removed.

Received, August 20th, 1962 [Z 333/162 IE]

[1] *W. Sundermeyer*, Z. anorg. allg. Chem. *313*, 290 (1962).

[2] *L. Birkofer, A. Ritter*, and *P. Richter*, Angew. Chem. internat. Edit. *1*, 267 (1962); cf. [5].

[3] Cf. *E. Wiberg* and *H. Michaud*, Z. Naturforsch. *9b*, 500 (1954).

[4] During publication *N. Wiberg, F. Raschig*, and *R. Sustmann* reported the successful preparation of diphenyldiazidosilane: Angew. Chem. internat. Edit. *1*, 551 (1962).

[5] *R. West* and *J. S. Thayer*, J. Amer. chem. Soc. *84*, 1763 (1962).

[6] *N. Wiberg* and *F. Raschig*, Angew. Chem. internat. Edit. *1*, 335 (1962).

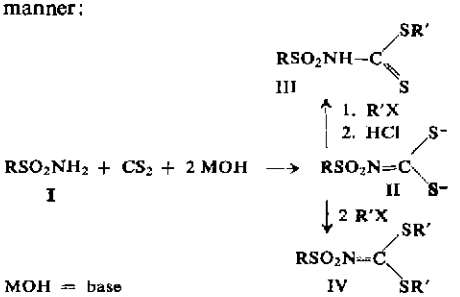
[*] w = weak, vs = very strong.

N-Sulphonyliminodithiocarbonic esters and *N*-Sulphonyldithiourethanes

By Doz. Dr. R. Gompper and Dipl.-Chem. W. Hägele

Institut für Organische Chemie und Organisch-chemische Technologie der Technischen Hochschule Stuttgart (Germany)

The reaction of sulphonamides with carbon disulphide has not been described previously. It may proceed in the following manner:



Suitable solvents include dimethylformamide, *N*-methylpyrrolidone, and dimethylsulphoxide, while conc. sodium or potassium hydroxide may be used as base.

The salts II may be isolated or converted directly into III and IV. Good yields can be obtained only if MOH and CS_2 are added in portions to the solution of I (at first 1 equivalent of MOH and $^1/_2$ equivalent CS_2, then $^1/_2$ MOH and $^1/_4$ CS_2, and so on). The alkylthio groups in III and IV undergo nucleophilic substitution readily. As coreactants we have so far used alcohols, ammonia, primary and secondary amines, diamines, aminoalcohols, ethyleneimine, hydrazine, guanidine, and CH-acid compounds. Replacement of the second alkylthio group in IV proceeds only under more vigorous conditions (*e.g.* with NH_3 in phenol at 100 °C).

Oxidation of III gives *N,N'*-disulphonylisothiuram disulphides. Heating III in an inert solvent eliminates an alkylthiol; perhaps sulphonyl-mustard oils are also formed as intermediates on heating in alcohol; these then react further to form *N*-sulphonylthiocarbamic esters.

Received, August 30th, 1962 [Z 335/166 IE]

A Simple Method for Preparing Cellulose Anion-exchanger Powders and Papers

By Dr. K. Randerath

Institut für Organische Chemie der Technischen Hochschule, Darmstadt (Germany)

We have found that cellulose powder and chromatography paper can be impregnated with polyethyleneimine [1] to produce anion-exchanger materials which give excellent resolution. These exchangers are markedly superior to celluloses with basic substituents used hitherto. This may be mainly attributed to the fact that a considerably higher nitrogen content (and hence capacity) can be achieved by impregnation of the cellulose rather than by substitution.

For example, a strip of Whatman No. 1 paper is soaked for 1–2 sec. in a 1–5 % solution of polyethyleneimine neutralised with hydrochloric acid, air-dried, washed with distilled water, and dried in a current of warm air.

The anion-exchanger paper thus obtained is excellently suited for separating nucleotides and other phosphoric esters, for example, AMP, ADP, and ATP can be separated in 12 min. on polyethyleneimine-paper with 0.8 M sodium chloride solution. This takes 15 to 20 hrs. on untreated paper (partition chromatography), and on commercial ion-exchanger papers (substituted celluloses) they cannot be separated at all with neutral electrolytes.

Impregnated celluloses are also suitable for column and thin-layer chromatography, separations being particularly sharp in the latter case. A mixture of AMP, ADP, and ATP can be completely resolved in 3–4 min. on a polyethyleneimine-cellulose layer with 0.8 M sodium chloride solution.

The mild conditions of these separations seem particularly noteworthy.

Received, August 30th, 1962 [Z 336/168 IE]

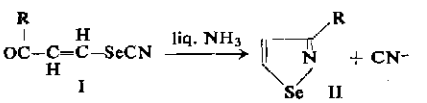
[1] Prepared by Badische Anilin- & Soda-Fabrik, Ludwigshafen/Rhein (Germany).

Isoselenazole and 3-Methylisoselenazole

By Prof. Dr. F. Wille, A. Ascherl, G. Kaupp, and L. Capeller

Institut für Anorganische Chemie der Universität München (Germany)

We recently reported that on treatment with ammonia 3-thiocyano-acrolein is converted into isothiazole [1]. An analogous cyclization occurs when 3-cyanoseleno-acrolein (I, R=H) is treated with liquid ammonia. The product is the hitherto unknown isoselenazole (II, R=H), a colorless liquid with a pyridine-like odour (b.p. = 68 °C/46 mm.; n_D^{20} = 1.603; λ_{max} = 266 mμ; ε = 4680, in dioxane)



Ammonia and 3-cyanoselenobutenone (I, R=CH_3) yield the analogous 3-methylisoselenazole (II, R=CH_3; b.p. = 51 to 51.5 °C/13 mm; n_D^{20} = 1.575; λ_{max} = 268 mμ; ε = 3630, in dioxane).

Cyanoseleno-acrolein (I, R = H; m.p. = 73–75 °C) is prepared by the addition of selenocyanic acid to propynal; 3-cyanoseleno-butenone (I, R = CH_3; m.p. = 50–53 °C) is obtained similarly from butynone.

Received, September 7th, 1962 [Z 337/167 IE]

[1] *F. Wille, L. Capeller*, and *A. Steiner*, Angew. Chem. Internat. Edit. *1*, 335 (1962).

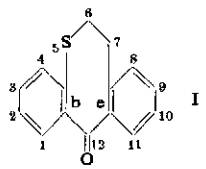
New Heterocyclic Ring Systems

By Dr. K. Stach and Dr. F. Bickelhaupt

C. F. Boehringer & Söhne G.m.b.H., Mannheim-Waldhof (Germany)

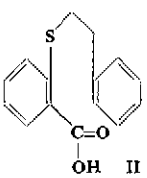
7,12-Dihydro-6*H*-dibenzo[b,e]thiocin-12-one (I) (m.p. 149 to 149.5 °C, from diethyl ketone) is prepared smoothly in 70 % yield within 30 min by dehydration with polyphosphoric

acid at 110 °C of *o*-(β-phenylethylmercapto)benzoic acid (II), which is obtained by treatment of the sodium salt of methyl thiosalicylate with β-phenylethyl bromide in boiling methanol, followed by hydrolysis (m.p. 123 °C; yield: 85 %, based on methyl thiosalicylate). I is also obtained in 45 % yield by cyclisation of *o*-(phenylethylmercapto)benzoyl chloride (b.p. 191–196 °C/0.2 mm, obtained by treatment of II with thionyl chloride) with aluminium chloride in a carbon disulfide-nitrobenzene mixture.

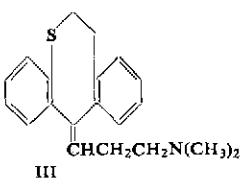


I

The action of polyphosphoric acid on *o*-(β-phenyl-mercapto-ethyl)benzoic acid – an isomer of II – affords only a 10 % yield of I. This is remarkable, because ring systems containing one methylene group less, *viz.* 6.11-dihydro[b,e]-thiepin-11-one [1–3] or -oxepin-11-one [1] are produced in 80–90 % yield by cyclising *o*-(phenylmercaptomethyl)- or *o*-(phenoxymethyl)-benzoic acid or their derivatives, respectively.



II



III

Reaction of I with Grignard reagents, *e.g.* $ClMg(CH_2)_3N(CH_3)_2$, in tetrahydrofuran produces, as in the cyclooctene [1c], thiepine [1c,2,3], and oxepine series [1c], the corresponding carbinol (m.p. 138.5 – 140 °C; 93 %), which is convertible by dehydration (*e.g.* with alcoholic hydrochloric acid) into 12-(3-dimethylaminopropylidene)-7.12-dihydro-6*H*-dibenzo[b,e]thiocine (b.p. 184–185 °C/0.3 mm; 83 %).

Received, August 31st, 1962 [Z 334/165 IE]

[1] a) *K. Stach* and *H. Spingler*, Angew. Chem. *74*, 31 (1962).
b) *K. Stach* and *H. Spingler*, Monatsh. Chem., in press; c) *K. Stach* and *F. Bickelhaupt*, Monatsh. Chem., in press.

[2] *M. Protiva, M. Rajšner, V. Seidlová, E. Adlerová*, and *Z. J. Vejdělek*, Experentia *18*, 326 (1962).

[3] *Sandoz*, Belg. Pat. 607503 (Aug. 24th, 1961; published, Febr. 26th, 1962).

Inorganic Redoxites [*]

By Dr. B. Sansoni and Dipl.-Chem. O. Sigmund

Chemisches Institut der Universität Marburg/L. (Germany)

As the first purely inorganic counterpart to organic redox resins the clay mineral Nontronit [1] was examined [2]. Aluminium in the rigid double-octahedron layers is partially and isomorphously replaced by $Fe^{2+/3+}$ ions. These are capable, according to *Weiss* and *Hofmann* [3], of being partially reduced or oxidised by sulphite or hydrogen peroxide, respectively. This is therefore a redox ite according to our definition [4].

Brittle, friable, greenish yellow aggregates from the pit at Ficht/Opf. (Germany) were crushed, screened to 0.5–0.6 mm and washed. Analysis: 3.83 % Fe_2O_3; 94.8 % SiO_2; about 1.1 % CaO and 0.6 % MgO; traces of Al^{3+}, K^+, Cl^-. According to Debye-Scherrer diagrams the substance contains large amounts of quartz. After reduction with aqueous dithionite solution it is dark green, after oxidation with highly dilute H_2O_2 it is honey yellow. The reflection spectra of both forms show weakly marked bands, which correspond approximately to solid Fe(II) or Fe(III) sulphate.

The redox capacity determined with a 0.2 M solution of Fe(II) sulphate in 0.01 N sulphuric acid is 0.16 mequiv./g or 0.19 mequiv./ml, corresponding to about $^1/_3$ of the total iron. It strongly decreases during five successive reductions and oxidations owing to the partial extraction of the iron. By potentiometric titration with a 0.1 N solution of titanium(III) chloride and ceric(IV) sulfate in 1 N H_2SO_4 the E_{50} %-potential was found to be 654 ± 10 mV, *i.e.* about 27 mV lower than the potential of $Fe^{2+/3+}$ in the same solution. A third method gave somewhat higher values [5]. During the determination slight decomposition occurs.

The exchange capacity of the reduced form for anions is < 0.005 mequiv. Cl^-/g. The exchange capacity for cations (about 0.085 mequiv. $^{60}Co^{2+}$/g) is approximately the same for both the reduced and the oxidized forms. The low exchange capacity of the Fe^{3+} form for anions is surprising: it is < 0.005 mequiv. Cl^-/g, 0.00004 mequiv. $^{131}J^-$/g (partially bound as I_2?) and 0.000009 mequiv. $^{87}Br^-$/g [5].

Advantages as compared with organic redox resins are the absence of irreversible oxidations, a relatively high reduction rate (no gel diffusion), high temperature and radiation stability; basic disadvantages are inferior redox capacity and instability in strongly acidic or alkaline solution.

As further redoxites sodium polyvanadate and silicic acid phenolic esters are being studied. The latter can be reduced and oxidized on the surface in water free solvents [6]. Crystalline ammonium phosphomolybdate was reduced in benzene by phenylhydrazine to a deep blue form, without molybdenum blue going into solution, and was then reoxidized.

Received, August 6th, 1962 [Z 324/158 IE]

[*] XIIth Communication on "Redox-Exchangers".

[1] *K. Jasmund:* Die silikatischen Tonminerale. 2nd ed., Verlag Chemie, Weinheim/Bergstr. 1955, p. 122.

[2] *B. Sansoni*, Lecture, GDCh-Hauptversammlung Stuttgart (Germany) 1960; prediction of inorganic redoxites: lecture, Institute of Technology, Stockholm (Sweden) 1957.

[3] *A. Weiss, U. Hofmann* et al., Ber. dtsch. keram. Ges. *31*, 301 (1954); Z. anorgan. allg. Chem. *284*, 247 (1956).

[4] *B. Sansoni*, Naturwissenschaften *39*, 281 (1952); *Ph. D. Thesis*, University Munich (Germany) 1956; Chem. Technik *10*, 580 (1958).

[5] For a discussion of error see full publication.

[6] *B. Sansoni* and *W. Schmidt*, Abschlußarbeit, Regensburg 1953.

Deutsche Gesellschaft für Metallkunde

(German Metallurgical Society)

June 19th—22nd, 1962, in Munich

The Internal Oxidation of Iron-Silicon Alloys

K. Bohnenkamp and *H. J. Engell*, Düsseldorf (Germany)

Exposure of alloys to gases containing oxygen results in diffusion of oxygen into the metal. Less noble constituent elements may thereby separate out in the form of their oxides; this process is described as 'internal oxidation'.

Internal oxidation of silicon in iron-silicon alloys containing 0.14 to 1.76 % Si was investigated in the temperature range 820 to 1100 °C. The alloys were oxidised in water-vapor/hydrogen mixtures, in which the partial pressure of oxygen was below the dissociation pressure of iron(II) oxide. The diffusion constant for silicon and the "oxygen transport" could be calculated from the increase in weight of the samples and the depth of the zone containing precipitated silica. The increase in weight was proportional to the square root of the time of exposure. The microsection and the weight *vs.* time curves indicated uniform diffusion of the oxygen. The oxygen transport is proportional to the product of the solubility at equilibrium with the external partial pressure (p_0) and the diffusion coefficient (D_0).

$$c_0 D_0 \sim (pH_2O/pH_2) \times \exp(-A/RT)$$

It was found that in ferrite, A = 51 ± 2 kcal/mole and in austenite A = 61 ± 4 kcal/mole. Assuming that the diffusion coefficient of oxygen into iron is equal to that of nitrogen, the maximum solubility of oxygen is about 1.5×10^{-4} % at 890 °C and about 3×10^{-3} % at 1100 °C. The diffusion coefficient of silicon is about 10^{-10} $cm^2 sec^{-1}$ at 890 °C in ferrite and 1100 °C in austenite. Both D_{Si} and D_0C_0 show a sharp drop at the α-γ-transition.

Electron Microscopic studies on precipitations in an Aluminum-Copper Alloy

M. v. Heimendahl and *G. Wassermann*, Clausthal-Zellerfeld (Germany)

The Guinier-Preston GP (II)-zones, and the Θ′ and Θ phases were investigated for an aluminum-4 % copper alloy using transmission electron microscopy. Examination of definite areas under the microscope before and after periods of heat treatment explained in particular the hitherto open question, how interconversions among the three phases occur in detail. It was found that, in the conversion GP (II) → Θ′, the Θ crystals appeared frequently in the positions previously occupied by GP (II)-zones. Moreover, the Θ′ plates are then of the same diameter as but are thicker than the zones from which they were derived.

In contrast to this, the metastable Θ' crystals are transformed into the equilibrium Θ phase by disappearance of the Θ' crystals and growth of Θ crystals. The Θ nuclei appeared in every case either at points formerly occupied by the disappearing Θ' crystals or at grain boundaries. The two types of crystals have quite different forms. The Θ' crystals are very thin plates lying on the cube faces (three different systems), while the Θ crystals have in general a more compact droplike form.

The Wrought Zinc Alloy (Zn-Cu-Ti)

E. Pelzel, Stolberg/Rheinland (Germany)

The creep resistance of the wrought zinc alloys (1 % extension per year at a stress of 2–3 kg/mm²) is too unfavourable for practical use. The corresponding properties of the cast zinc alloys are much more favourable and it is reasonable to expect that an improvement of the creep resistance of the wrought alloys could be obtained by suitable heat treatment.

The annealing treatment however initiates recrystallisation which leads, particularly in the case of rolled material, to a greatly decreased formability, especially across the direction of rolling, and consequently the treatment can only be applied to finished parts. Small additions of titanium below the eutectic content of 0.18 % inhibit graingrowth during annealing at 350 °C.

The structure of the billet is dependent on the rate of cooling and markedly affects the technological properties of the material on the rolled state. The stability to heat treatment was determined by measurement of the elongation at the fractures of the test pieces and by examination of the onset of cracking in samples bent through 180°. Alloys containing titanium gave practically constant elongation after annealing between 150 and 350 °C. and satisfactory bend tests. At constant titanium content the strength increased with increasing copper content while elongation and bendability remained in the useful region. The creep resistance is defined as that stress which produces a permanent extension at the rate of 1 % per year. For annealed Zn-Cu-Ti alloys values of 7–8 kg/mm² parallel to the rolling direction were obtained, and values of 8–9 kg/mm² were found across the direction of rolling.

An After-Melting Effect in Pure Metals

B. Predel, Münster (Germany)

Heating curves obtained with pure metals by differential thermal analysis have been found to deviate from the behaviour to be expected from a first order phase transformation. The deviations are caused by heat absorbtion immediately after the melting process. Impurities and possible defects in the apparatus cannot be responsible for the anomalies since only metals of high purity have been used and the results have been confirmed with different experimental arrangements.

This after-melting phenomenon can possibly be explained on the basis that the breaking down of the lattice at the melting point yields a melt which is not exclusively mono-atomic, but in which some aggregates of atoms persist with a short-range order similar to that in the solid state. These aggregates disperse with rising temperature. Ga, In, Sn, Bi, Tl, Cd, Pb, Zn, Sb and Al all show this effect. It was least in magnitude (about 4 % of the melting enthalpy) with In, Al and Cd and greatest with Sb and Bi (13 and 14 % of the melting enthalpy, respectively). A similar effect during cooling could not be detected and it is concluded that the process which causes after-melting is irreversible.

Some Results of Diffusion Experiments in the System Ti-Ag

R. Reinbach and *D. Fischmann*, Hanau (Germany)

Diffusion between titanium and silver, at 600–900 °C initially produces only the intermetallic phase TiAg, the breadth of which does not however increase parabolically with time. Examination of diffusion between Ti and TiAg discloses the formation of a Ti_3Ag phase. Other phases, especially phases

richer in silver could not be detected. These diffusion experiments gave some new information on the solubility of silver in α-titanium. At 750 °C it is about 10 %, falling off to about 9 % at 700 °C and to about 6 % at 600 °C, being thus markedly temperature dependent.

Precipitation in a Nickel-Chromium Alloy Containing Titanium and Aluminum

P. Schwab and *K. Hagen*, Duisburg (Germany)

It is well established that nickel alloys containing titanium and aluminium have age-hardening properties. Although it is generally agreed that the presence of titanium and aluminium are responsible for these properties, there are conflicting opinions regarding the mechanism by which the hardness is produced. Some assume on evidence obtained by X-ray diffraction that it is caused by the development of zones similar to those found in Duralumin, others assert that the precipitation of finely dispersed Ni_3Al (γ'phase) is the cause. Precipitation processes were therefore investigated. The alloy used had the composition: carbon 0.2 %; nickel 70.5 %; chromium 16.6 %; iron 6.8 %; titanium 3.2 %; aluminum 0.3 %. The samples were heat-treated at 1150 °C and annealed for periods varying from 5 minutes to 1600 hours between 600 and 900 °C. The hardness of the annealed samples was then determined and the structure examined under the microscope. In addition electron microscopic examinations of extraction replicas and of thin films prepared by electrolytic polishing were also made.

The results showed that in the above alloy, apart from the carbide $M_{23}C_6$, the only stable separated phase is the η-phase Ni_3Ti, which precipitates discontinuously. At the same time or slightly before this phase appears, extremely fine particles of the metastable γ'-phase Ni_3Al separate and these cause the increase in hardness. However there is no simple relation between the number and size of the γ'-particles and the increase in hardness. With the continued precipitation of the η-phase the metastable γ' particles disappear after long annealing. At low annealing temperatures also the carbide $M_{23}C_6$ separates discontinuously.

Anomalies of Diffusion in the Hume-Rothery Phases of the System Copper-Tin

E. Starke and *H. Wever*, Berlin (Germany)

Diffusion experiments in the γ- and δ-phases (Hume-Rothery's β- and γ-phases) of the system copper-tin showed the high mobility typical of Hume-Rothery phases. In the δ-phase the activation energy of the diffusion process is not as is usual independent of temperature. Because of the concentration gradient it is possible to attempt an explanation of this unexpected result by supposing that the thermodynamic factor is strongly temperature dependent. It turns out however that this assumption is not sufficient. Perhaps the migration energy of structure controlled lattice defects varies with temperature. Copper is in both phases much more mobile than tin, so that the transport is not continuous but involves a defect transfer mechanism. Evidence from other sources suggests that actually a vacancy transfer mechanism is involved and there is evidence that the mean free path of diffusion of the vacancies is unexpectedly long. In the γ-phase the diffusion coefficient is strongly dependent on concentration and increases with increasing tin content.

[VB 616/46 IE]

International Symposium on Gas Chromatography

Organized by the Analytical Chemistry Group of the Gesellschaft Deutscher Chemiker and the Gas Chromatography Discussion Group, under the auspices of the Hydrocarbon Research Group of the Institute of Petroleum, the symposium was held in Hamburg, in conjunction with the 41st Assembly of the Europäische Föderation für Chemie-Ingenieur-Wesen, from the 13th to 16th of June of this year.

From the agenda:

Programmed Low-Temperature Gas Chromatography

F. Baumann, *R. F. Klaver*, and *J. F. Johnson*, Richmond, Calif. (U.S.A.)

The researchers described a programmed low-temperature gas chromatograph, employing liquid carbon dioxide as coolant. The coolant is injected into the column thermostat through a valve. The cooling system is connected, through an electromagnetically operated valve, with a temperature-control device, which permits linear programming of the column thermostat from −75 to +400 °C.

The low-temperature region can be used with excellent results in gas chromatography under programmed temperature conditions. Samples that contain gases and cover a broad range of boiling points can be conveniently analyzed. The possibility of obtaining fixed initial temperatures lying below and in the vicinity of the ambient temperature leads to more reproducible retention times in programmed gas chromatography. The carbon dioxide cooling apparatus can also be used for rapid coniolg of the column.

Silicone polymers have proved to be most satisfactory as liquid phases. General Electric silicone oil SF-96 (50) can be used from −60 to +270 °C. Polar liquid phases that can be used at low temperatures are Dow Corning fluorosilicone oil QF 1-0065 (−20 to +220 °C) and General Electric nitrile-silicone oil XF-1112 (−40 to +200 °C).

Investigations, in which the wide temperature range of this instrument was fully exploited, show that the retention temperature is more a function of the boiling point than of the number of carbon atoms. Methods of introducing pressure corrections into the calculation of retention temperatures were explained. In addition, methods of calculation of retention temperatures, using parameters obtained from isothermal data, were pointed out. These were illustrated for homologous series of normal paraffins, aromatic compounds, and primary alcohols.

Reaction Gas Chromatography

F. Drawert, Siebeldingen/Pfalz (Germany)

The investigation of aqueous biological solutions that are very dilute with respect to certain components is an example of one specialized use of gas chromatography. Reaction gas chromatography solves such problems as, for example, the quantitative determination of alcohols in the range of a few parts per thousand, by the use of chemical reactions that are carried out either before or after the column separation [1]. Thus, blood alcohol, for example, may be quantitatively determined with ethylene in a 0.1 to 0.01 ml volume of untreated blood within a few minutes following esterification. Fatty acids can be quantitatively esterified and are separated and analyzed as the fatty acid esters.

For gas-chromatographic analysis of weakly radioactive, ^{14}C-labeled fractions obtained from biological material, a

[1] Angew. Chem. *72*, 555 (1960).

combination of a gas chromatograph with the usual detector and a proportional flow tube counter is used. In this case, the analysis can be carried out in a stream of hydrogen. After registration and exit from the gas chromatograph, the separated fractions are cracked to methane in a Raney nickel furnace, and the radioactive count in the flow, is determined. Properties of hydrogenation catalysts at various temperatures can also be readily investigated in this experimental arrangement consisting of a reactor, a gas chromatograph and a system for detecting ^{14}C-labeled compounds.

Frequently, changes in substances take place to a considerable extent in the injection and evaporation systems connected to the analytical separation column, and it is then preferable to separate complex mixtures before the gas chromatography, or to carry out chemical reactions in combination with gas chromatography.

Mass-Spectrometric Identification in Gas Chromatography with Capillary Columns

D. Henneberg and *G. Schomburg*, Mülheim/Ruhr (Germany)

It is possible to identify by means of a mass spectrometer the individual components of mixtures separable in capillary columns. The use of a mass spectrometer as a detector provides structure-specific data; it can be used for practically all classes of substances that can be chromatographed. In a continuous process using a combination of a gas chromatograph and a mass spectrometer, a portion of the eluate is continuously introduced into the mass spectrometer. Since the carrier gas concentration changes when a peak is passing through, the mass spectrum must be scanned very rapidly, within approximately $^1/_{10}$ sec. However, the mass-spectroscopic data necessary for the identification can also be obtained if a fixed reference mass is used. This method was demonstrated analysing a complex petroleum fraction.

The mass spectrometer is adjusted for a definite mass, and this adjustment is maintained during an entire chromatogram. The instrument then records each peak on a "mass chromatogram" with a sensitivity which follows from the mass spectrum of the substance under consideration. The influence of concentration is eliminated by the use of a nonspecific detector, running in parallel.

For the identification, 3 to 12 mass chromatograms, using various selected masses, are usually required. The sensitivities from several mass chromatograms are combined and compared with standard spectra.

Identification of the class of a substance can be accomplished with as few as 1 to 3 mass chromatograms, as was shown by using mass 91, characteristic for alkylbenzenes, as the reference.

In a mixture of over 70 components (paraffins, aromatic compounds, traces of cycloparaffins) 37 were identified; these totalled 97–98 % of the mixture. This demonstrates the special advantage of the method with a fixed reference mass for the identification of traces and in the case of partial overlapping of the peaks.

Non-linear Ideal Chromatography and the Potentialities of Linear Gas-solid Chromatography

J. F. K. Huber and *A. I. M. Keulemans*, Eindhoven (Holland)

The basic prerequisits for high separating efficiency in gas-liquid and gas-solid chromatography were discussed, and a comparison was made to what extent these requirements are met in the two techniques. The conclusion is reached that excellent separation should be attainable in both cases. The nonvolatility of the stationary phase in gas-solid chromatography was cited as an advantage important in work at higher temperatures and in the detection of trace constituents. Disadvantages are a contingent catalytic action of the adsorbent and the difficulty of reproducing the adsorptive properties of a solid surface.

The theory of ideal chromatography was applied to elution techniques with small samples, and the influence of the type of adsorption isotherms on the shapes of the peaks, and therefore on the separation, was investigated. It was shown that under certain operating conditions the experimental results are adequately described by this simplifying theory. From this study a simple, rapid, and sufficiently accurate procedure ensues for the determination of adsorption isotherms in the range of small concentrations.

In addition, the preparation of an adsorbent by thermal treatment of silica gel was described. On this material adsorption isotherms for hydrocarbons are practically linear even at low temperatures and up to sufficiently high concentrations. With respect to its separating capacity, a column filled with a material of this type is equivalent to a good gas-liquid chromatographic column of comparable dimensions.

Trace Analysis by Means of Gas-solid Chromatography

F. H. Huyten, G. W. A. Rijnders, and *W. van Beersum*, Amsterdam (Holland)

In gas-liquid chromatography, the irregularities in the base line depend to a great extent on the vapor pressure of the stationary liquid phase. In principle, therefore, the detection limits attainable with gas-solid chromatography should exceed those obtained with gas-liquid chromatography.

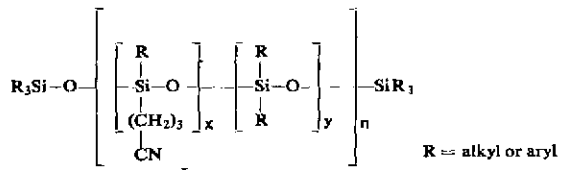
Using aluminum oxide (treated to reduce its adsorptive capacity) as stationary phase, trace analyses of low-boiling hydrocarbons (up to C_6) in concentrations of 100–0.01 p.p.m. were carried out with the aid of a very sensitive flame ionization detector without stepwise pre-enrichment. For this analysis, the sample mixtures were prepared in a so-called dynamic dilution apparatus, with which a dilution of $1:10^8$ could be attained reproducibly. Difficulties arose in the analysis of acetylene because of the irreversibility of the adsorption; however, these difficulties could be overcome by preliminary treatment of the column with acetylene. The experimental apparatus, as well as a specially constructed burner, make it possible to use various carrier gases, among them air; this should be especially interesting in connection with problems of air pollution.

The separation capacity of the columns could be held constant over a long period of time by saturating the carrier gas with water. In an analysis of 10 to 30 minutes duration it was possible to detect components present in the sample to an extent of a few thousandths of a p.p.m.

New Polar Partition Liquids with Graded Selectivity Coefficients

H. Rotzsche, Radebeul-Dresden (Germany)

The silicone oils often used in gas chromatography as partition liquids are in general not very selective because of their low polarity. Polarity and selectivity can be increased considerably by the introduction of cyanoalkyl groups into the silicone molecule and can be varied by varying the ratio x:y in I between the limits x = 0 (II) (conventional silicone



I

oil, for example, DC 703, MS 550, OE 4011, *etc.*) and y = 0 (V) [strongly polar silicone oil, which, for example, retains naphthalene (b.p. 217.9 °C) in a 1.5 m column at 200 °C more than three times as long as it retains n-hexadecane

(b.p. 287.5 °C)]. Selectivity coefficients of 1.2 [x = 0 (II)], 3.0 [x:y = 1:1 (III)], 4.1 [x:y = 3:1 (IV)] and 6.1 [y = 0 (V)], were found for the separation of alkylbenzenes from n-paraffins at 100 °C. The following selectivity coefficients were found:

for the separation of	between
alkylbenzenes/cyclohexanes	1.1 and 3.0
primary alcohols/ethers	0.4 and 2.1
ketones/ethers	0.8 and 2.8

The shift in retention volume on transition to a silicone oil with higher polarity can be easily estimated since here, in contrast to the stationary phases of different polarity heretofore known, the basic chemical structure (I) remains unchanged and only the number of cyanoalkyl groups contained in the molecule is altered. As these oils also possess a great range of selectivity, they can be used as standard partition liquids. The four oils (II)–(V) alone suffice for the solution of many separation problems. Since they are effective both at elevated temperatures (up to 150 °C, and in some cases, above 200 °C) and at room temperature, they are suitable for use as selective stationary phases in temperature-programmed columns.

Rational Integration Procedures for Gas Chromatography Using Novel Apparatus Combinations

H. Kelker, H. Rohleder, and *O. Weber,* Höchst (Germany)

Integration is almost always indispensible to quantitative gas-chromatographic analyses. Therefore, it seemed important to rationalize this step. Procedures of integration heretofore suffered from the fact that intermediate units, *e.g.* the compensograph, exerted a limiting and delaying effect or even decreased the accuracy. In addition, the integration step is coupled in time with the separation process. The present solution of the problem differs therefrom as follows:

a) Use of an analog digital converter (Hewlett-Packard Co. "Dymec" Type DY 2210) at the output of the measuring apparatus (flame ionization detector; in principle, also feasible with thermal conductivity cells). In this way, greater precision, wider range of measurement, and excellent linearity are attained and changes in range are avoided. The converter gives a pulse frequency proportional to the DC signal which comes from the detector.

b) Storage of the pulse-form chromatogram from the converter on commercial magnetic tape. In this way, greater flexibility of operation is attained: the detection and evaluation processes may be run at different times. Chromatograms, independently obtained at various times, can be more economically evaluated by a central system.

c) Evaluation of the magnetic tapes. The integration of the stored pulses is carried out by means of an electronic counter. A limiting-value detector starts and a maximum-minimum detector terminates the integration. Both detectors are completely digital and thus differ from similar systems using "analog" elements. The integration is coupled with measurement of the retention time.

d) On a second tape track, a 100-cycle signal, synchronized with the detection process, is recorded, and it is used to measure the retention time. A "logical circuit" registers the maximum of each peak and controls the readout of the corresponding time on a printer (ADDO® X-41 E). Each time the limiting value or a minimum is reached, the area integrals are also printed. By virtue of this arrangement the retention-time and peak-area counters can be actuated. In the evaluation of the tapes, the time pulses can be counted either forward or backward, which offers some advantages in the evaluation.

e) With the aid of a curve follower, ordinary paper strip chromatograms can also be handeled; that is, they can be evaluated by planimetry. The DC voltage produced by the tracer is transformed by means of the apparatus described under a) and evaluated by feeding the resulting pulses to the counter and printer. In this case, the only additional equipment required is the tracer. In our experience a magnetic-head recorder has proven satisfactory. The development of an optical system will be finished in the near future.

The entire apparatus is cheap since commercial digital units [*], converters, tape recorders and printers are used. The recording system costs approximately $1100 and the central evaluation system approximately $2500. The evaluating unit for graphically recorded chromatograms costs approximately an additional $3500.

Experiences with a Catalytic Combustion Cell for the Determination of Small Quantities of Substances

G. Schay, Gy. Székely, and *G. Traply,* Budapest (Hungary)

Because of the considerable heats of combustion of organic substances, considerable increase in the recording sensitivity can be attained when the heater filament of a katharometer cell is used for catalytic combustion in the usual circuit. The cell was a glass tube 10 cm long and 0.18 ml internal volume, with an axially stretched 50 μ Pt wire covered with Pt – Pd as catalyst. The combustion generally proceeded well even at a filament temperature of 150 °C and was always smooth and rapid at 200 °C.

The detection properties of the cell were first tested with single substances in an O_2 current. Complete linearity (of cell output) with the concentration at constant flow rate, or with the rate (up to approximately 90 ml/min) at constant concentration, resulted. Using a Wheatstone bridge and a recording potentiometer with a full scale deflection at 50 mv, no additional amplification was required to obtain a sensitivity of 12.5 mv μg^{-1} sec^{-1} (corresponding to 1.39 v cal^{-1} sec^{-1}) in the case of amyl alcohol.

Likewise, excellent linearity between area and quantity introduced, over a wide range, was obtained in the investigation of elution peaks.

Since the rubber hose coupling of the glass cell to an analytical column can readily result in contamination of the catalyst, a metal cell was later constructed. As an example, the analysis of a commercial xylene (99.5 % xylene isomers, 0.38 % toluene, 0.12 % benzene) was carried out. The saturated xylene vapor (approximately 30 g) was introduced into the column in an O_2 stream. The peak areas (for the principal component 5.13 mv μg^{-1} sec^{-1}, recording potentiometer with 2 mv for full scale deflection, no additional amplification) had to be corrected because of the differences in the heats of combustion; however, the evaluation of the chromatogram then gave excellent agreement with the known composition of the mixture.

Combustion cells are simple to make, and the usual katharometer circuit, without special amplification, gives a sensitivity that is only about 1-2 orders of magnitude lower than that obtained with flame ionization detectors.

The Importance of Gas-Chromatographic Methods for the Chemistry of Boroalkyls and Borohydrides

G. Schomburg, Mülheim/Ruhr (Germany)

Both classes of compounds are characterized by their high reactivity with oxygen and, to some extent, also with water. Therefore, in addition to considerations of thermal stability and volatility, special precautions are required in adapting gas-chromatographic techniques for the separation of these substances.

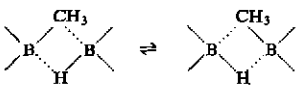
For the identification of many substances that can be isolated only by gas chromatography, both mass spectrometry as well as infrared spectroscopy (especially for the borohydrides) were used.

[*] "Estacord" units from Akkord-Radio, Herxheim/Pfalz (Germany).

The solutions of the following problems were accomplished with the use of gas chromatography:

Rapid separation of equilibrium mixtures of boroalkyls, borohydrides, and oxygen-containing boroalkyls.

Determination of the rates of reactions that occur by way of hydrogen or alkyl bridges. For example:



Separation of isomeric boroalkyls (normal, branched, cyclic).

Separation of compounds that are associated by hydrogen bridges, such as mono-, di-, tri-, and tetraalkylboranes and their isomers, for example, separation of the *cis*- and *trans* isomers of *sym*-dimethyldiborane.

Determination of the retention volumes of homologous mixed boroalkyls and borohydrides and the relationship between these data and the structure and number of carbon atoms. The influence of the formation of donor-acceptor complexes between the stationary phase and the boron compound.

Identification of boroalkyls and borohydrides in simple and complicated mixtures by mass spectrometry and infrared spectroscopy.

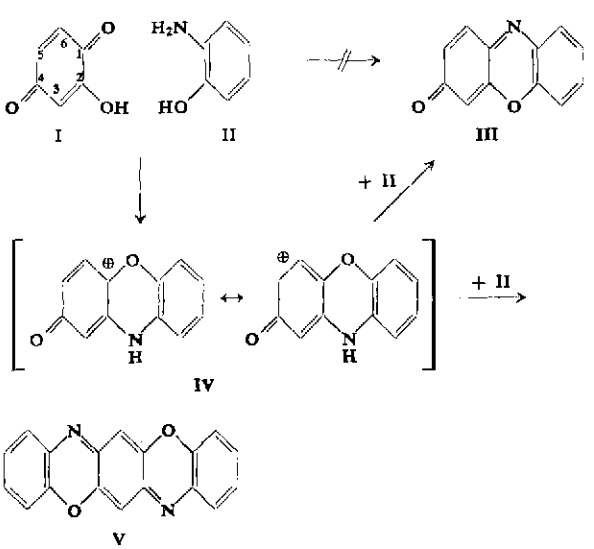
Quantitative analysis of boroalkyl mixtures. [VB 615/51 IE]

The Synthesis of Phenoxazines and Phenoxazones

H. Musso, Marburg/Lahn (Germany)

Reaction in glacial acetic acid of hydroxyquinones (I) that are unsubstituted in the 5-position and *o*-aminophenols (II) yields only traces of the phenoxazones (III) that are to be expected according to *Kehrmann* [1]; the main products (60–70 %) are triphendioxazines (V).

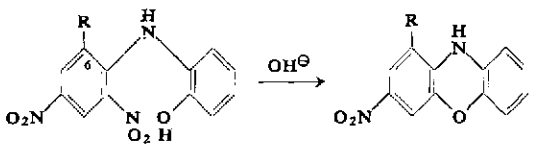
In collaboration with *J. Kuhls*, it has been shown that the formation of V from I and II proceeds about one hundred times as fast as its formation from II and III and that no ammonia is evolved. Therefore, V cannot be formed from I and II via the intermediate III or by oxidation of II by I via 3-aminophenoxaz-2-one, as was previously assumed. These experiments support the mechanism postulated recently [2] that the formation of III and V occurs in competing reactions from the same intermediate cation IV.



[1] *F. Kehrmann*, Ber. dtsch. chem. Ges. *28*, 353 (1955) and later publications.

[2] *H. Beecken* and *H. Musso*, Chem. Ber. *94*, 601 (1961).

The synthesis of nitrophenoxazines (VII) from 2,4-dinitro-2′-hydroxydiphenylamines (VI) in aqueous-alcoholic alkali only proceeds in good yield when the 6-position in VI is substituted. Kinetic data show that a methyl group in the 6-position reduces the undesired hydrolysis to the dinitrophenol by a factor of thirteen, while cyclization is increased by a factor of 26.



VI VII

This can be explained by a steric effect that is evidenced in the infrared spectra. In the transition state of the ring closure, the nitro group moves out of the plane of the benzene ring, thus reducing the steric strain between the methyl and the amino group.

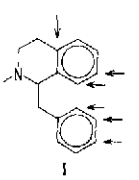
[GDCh-Ortsverband Marburg/Lahn (Germany), June 1st, 1962] [VB 603/48 IE]

Oxidative Condensations in Alkaloid Biosynthesis

B. Franck, Göttingen (Germany)

(From work done in collaboration with *G. Blaschke*, *G. Schlingloff*, and *H.-G. Reinhardt*)

Oxidative condensations of hydroxylated phenyl residues, besides the Mannich condensation, are involved in the biosynthesis of numerous alkaloids. A description was given of how 130 benzyltetrahydroisoquinoline alkaloids, 60 *Amaryllidaceae* alkaloids, 14 *Erythrina* alkaloids, and 13 colchicine alkaloids may arise in the plant cell by oxidative condensation of simple phenolic precursors. The role of oxidative condensation is especially versatile in relation to the benzyltetrahydroisoquinoline alkaloids; the 16 basic structures identified so far in this group arise by intra- or bi-molecular condensation at the six positions indicated in 1. By oxidizing 18 benzyl-



I

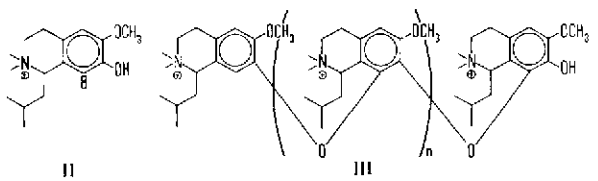
and alkyl-tetrahydroisoquinolines with systematically graded oxidizability under various conditions, the following results were obtained:

1) Secondary, tertiary and *N*-acylated bases of type I were dehydrogenated – even under mild conditions – via aminocarbinols to give isoquinoline derivatives. This course of oxidation, which is undesirable in the sense of a biogenetic-type condensation, does not take place with quaternary bases.

2) Phenyl residues of quaternary benzyltetrahydroisoquinolines condense in good yields on oxidation with potassium ferricyanide or ferric chloride so long as they contain an *o*-dihydroxy or an *o*-methoxybenol grouping. Whether the mesomeric radical which is formed from the phenolate anion condenses at the phenol oxygen or in the position *ortho* or *para* to it, depends on the steric accessibility of the positions of the radical. Sterically hindered *C*-radical positions such as C-8 of II condense preferentially with aryloxy radicals to give diphenyl ethers. The condensation proceeds similarly in biosynthesis.

These findings make it possible to carry out simple biogenetic-like syntheses of numerous alkaloids; apomorphine as well as

bisbenzyltetrahydroisoquinoline alkaloids were prepared in good yield [1]. Oxidation of *N,N*-dimethyl-1-isobutyl-6-methoxy-7-hydroxyisoquinolinium iodide (II) gave polymeric



II III

compounds III, alongside the dimeric condensation product III (n = 0), whose structure corresponds to that of the cactusalkaloid pilocerein III, (n = 0, $>N-CH_3$ instead of $>\overset{\oplus}{N}(CH_3)_2$) [2]. It seems possible that quaternary bases also serve as precursors in syntheses in the plant cell.

[Organisch-chemisches Kolloquium,
Universität Münster (Germany), June 28th, 1962]

[VB 612/44 IE]

Microsomal Oxidation-Reduction Enzymes

Hj. Staudinger, Giessen (Germany)

Microsomes are fragments of endoplasmic reticulum. Besides many other enzymes, one also finds enzymes concerned with hydrogen or electron transport in this cell fraction. The enzymes that transport electrons from reduced pyridine nucleotides to oxygen can, at least in theory, be arranged in a kind of electron transport chain on the basis of their normal potentials. A terminal oxidase of the cytochrome type which is sensitive to carbon monoxide, cytochrome b_5 (or cytochromes related to it) and several different "cytochrome reductases" are components of this "microsomal electron transport" chain. An enzyme which is dependent on ascorbic acid and which transfers hydrogen from reduced DPNH to the monodehydroascorbic acid radical belongs to this latter group. This enzyme has recently been extracted from microsomes and concentrated. The importance of the various microsomal electron transport mechanisms from the point of view of cell physiology is not fully understood. They have only a very small share in the total oxygen turnover of the cell. The affinity of the microsomes for oxygen is one-hundredth of that of the mitochondria (or cytochrome a_3). When saturated with oxygen, the microsomal turnover per mg of protein is about one-third that of the mitochondria. At the low intracellular partial pressure of oxygen, the microsomal oxygen turnover represents only about 1 % of the total respiration of a cell. The microsomal electron transport is of importance for diverse hydroxylation reactions (of aromatic compounds, steroids, *etc.*) that also occur within the microsomes. A preliminary mechanism for the hydroxylation reaction was discussed. Besides microsomal "electron transport", one also finds hydrogen transfer by enzymes in microsomes, for instance enzymes that reduce the Δ^4-3 keto group of steroid hormones and thereby inactivate the hormones. The "doctrine" that only TPNH can act as hydrogen donor for this reaction is incorrect. DPNH is also a suitable hydrogen donor, provided that orthophosphate is also present. The reaction velocity of the dissolved microsomal enzyme is dependent on the concentration of orthophosphate and approaches a saturation value at about 10^{-1} M phosphate. Orthophosphate can be replaced by arsenate; other anions, such as pyrophosphate, sulfate a. o., are ineffective. The possibilities of a transhydrogenation onto endogenous TPN^+ and of a transphosphorylation converting DPNH into TPNH were excluded with certainty by means of various control experiments. The phosphate alters V_{max}, but does not alter K_M for the enzyme + DPNH + testosterone.

[Biochemisches Colloquium, Giessen (Germany),
July 6th, 1962] [VB 613/45 IE]

[1] *B. Franck, G. Blaschke*, and *G. Schlingloff*, Tetrahedron Letters 439 (1962).

[2] *C. Djerassi, S. K. Figdor, J. M. Bobbit*, and *F. X. Markley*, J. Amer. chem. Soc. *78*, 3862 (1956).

SELECTED ABSTRACTS

The action of hydrogen on metallo-organic compounds has been examined by *K. Clauss* and *H. Bestian*. Organolithium compounds yield lithium hydride and hydrocarbons; the reaction is promoted by polar solvents such as tetrahydrofuran or triethylamine. Organomanganese compounds are reduced to manganese and hydrocarbons, *e.g.* diphenylmanganese gives manganese and 2 moles of benzene. Certain organotitanium compounds are not attacked by hydrogen, others undergo hydrogenolysis (*e.g.* dicyclopentadienyldimethyltitanium → dicyclopentadienyltitanium and 2 moles of titanium). Reactions of organotitanium and organoaluminum compounds may be accelerated by hydrogen. Thus, for example, the interaction of dicyclopentadienyltitanium dichloride (I) with excess dimethylaluminum chloride, which yields successively the complex II and then III plus methane, occurs only at 80–100 °C in an inert atmosphere, but at room temperature in the presence of hydrogen.

(I) $(C_5H_5)_2TiCl_2$ (II) $\left[(CH_3)AlCl_2{\cdot}(C_5H_5)_2Ti\begin{matrix}Cl\\CH_3\end{matrix}\right]$

(III) $[(CH_3)_n\,Al(Cl)_{3-n}{\cdot}(C_5H_5)Ti-Cl] + CH_4$

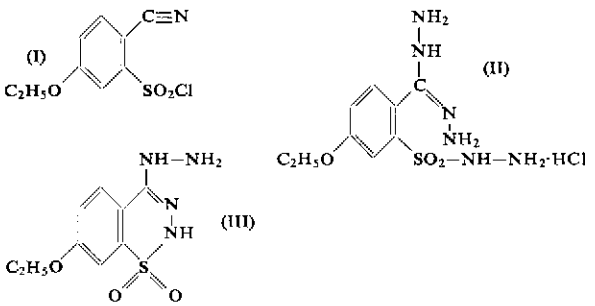
It appears that the bydrogen facilitates the removal of the methyl radical from the titanium at the stage II → III. Mixed catalysts comprising organoaluminum and organotitanium compounds with tetravalent titanium are discussed; they polymerize in the presence of hydrogen/ethylene to give unbranched paraffins with molecular weights of 1000–1500. In this reaction, the hydrogen obviously detaches the growing alkyl chain prematurely from the titanium, leading to a diminished molecular weight. The tetravalent titanium is simultaneously reduced to its catalytically less effective trivalents state; thus the effective catalyst concentration is decreased. / Liebigs Ann. Chem. *654*, 8 (1962) / –Sk. [Rd 296/87 IE]

Sodium sulfite and sodium pyrosulfite have been prepared by *I. G. Blyakher* and *A. G. Laryushkina* from sodium carbonate and an SO_2-air mixture having a definite moisture content, using a fluid bed technique.

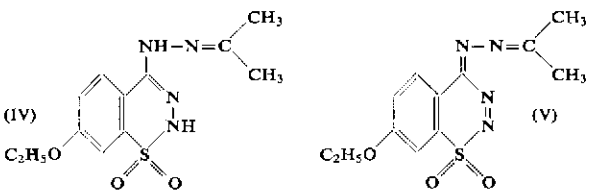
$Na_2CO_3 + SO_2 \rightarrow Na_2SO_3 + CO_2$; $Na_2SO_3 + SO_2 \rightarrow Na_2S_2O_5$

The SO_2-air mixture was saturated with steam and passed through a preheater, flowing upwards into a reactor filled with a moist, fluidized layer of soda. The following factors affect the reaction: a) the moisture content of the soda (maximum allowable – 13 %), b) the saturation temperature of the gas (15–57 °C), c) the concentration of SO_2 (7 % optimum), d) the gas velocity (0.3 m/sec. optimum), and e) the height of the fluid bed. The addition of 0.03 % of an inhibitor (metol) increases the yield. During the course of the reaction, the temperature in the fluidized bed ranged from 40 to 75 °C; the SO_2 conversion ranged from 95–97 % at the beginning of the cycle to 10–20 % at the end. / Zh. Priklad. Khim. *35*, 503 (1962). [Rd 219/75 IE]

4-Hydrazino-7-ethoxybenzo-1,2,3-thiadiazin-1,1-dioxide (III), discovered by P. *Schmidt*, *K. Eichenberger* and *M. Wilhelm*, is a compound with marked hypotensive and diuretic activity. The compound can be obtained from 2-cyano-5-ethoxybenzenesulfonyl chloride (I) by converting it into II with an excess of hydrazine. Compound II can be cyclized to give III by splitting out the hydrazine in the presence of HCl.

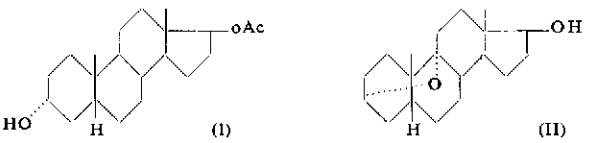


Compound III gives the usual reactions of monosubstituted hydrazines. The reaction with acetone leads to a colorless isopropylidene compound (IV) which can be converted into

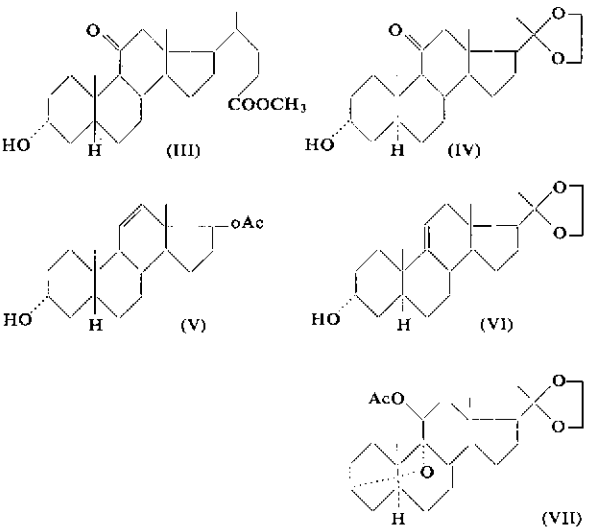


the stable, yellow azine V by treating with the required quantity of H_2O_2. / Helv. chim. Acta *45*, 996 (1962) – Bs. [Rd 221/79 IE]

The mechanism of oxidation of primary alcohols with lead tetraacetate has been studied by *H. Immer*, *M. L. J. Mihailović*, *K. Schaffner*, *D. Arigoni*, and *O. Jeger* in the formation of six-membered cycloethers (3α,9-oxides) from 3α-hydroxysteroids with $Pb(OAc)_4$. The 3α,9-oxide II is formed from I in a maximum yield of 4 %. This low yield is attributed to the unfavorable geometry of the transition state (the formation of furan derivatives is substantially more favored); among other factors bearing on the result of the reaction, an intermediate with an electron deficient oxygen atom (radical or cation) is discussed, and from this viewpoint, a comparison is made with the decomposition *via* a radical of secondary *N*-chloromethylamines to *N*-methylpyrrolidines (*Hofmann-Löffler-Freytag* reaction).



Yields of ethers with six-membered rings depend greatly on the situation in ring C. Treatment for sixteen hours with $Pb(OAc)_4$ of the methyl ester of 3α-hydroxy-11-oxo-5β-cholanic acid (III), 3α-hydroxy-11-oxo-20-ethylenedioxy-5β-pregnane (IV), and 3α-hydroxy-17-acetoxy-Δ^{11}-5β-androstene (V) gave the corresponding 3α,9-oxides in 45, 71, and 65 % yield, respectively. VI gave among other products 18 % of



VII, which demonstrates stereospecific formation of the 11β-compound. The corresponding 3α-acetoxy derivatives are not altered by the $Pb(OAc)_4$ treatment. / Helv. Chim. Acta *45*, 753 (1962) / – Bs. [Rd 286/81 IE]

BOOK REVIEWS

Anorganisches Grundpraktikum (Basic Laboratory Manual of Inorganic Chemistry) by *C. Mahr*, Verlag Chemie GmbH., Weinheim/Bergstr. 1961. 2nd Edition, XVI, 421 pages, 82 illustrations, numerous tables, bound in cardboard, DM 28. (about $7.00).

This latest edition of the manual has been extensively revised and enlarged by 50 %. The fresh approach to a practical introductory text on chemistry found in the first edition has been retained and even improved upon.

The first hundred pages present in an orderly fashion a number of interesting experiments together with theoretical considerations; these are designed for a five- to six week's (24 half-days) survey course in the general fundamentals of chemistry. The 200 experiments in the second part cover reactions of compounds of all the important elements and basic analytical methods including semimicro preparative separations; this section ends with experimental procedures for 27 preparations. The last 60 pages of the book constitutes a special section on semimicro qualitative analysis, with extensive use of organic reagents.

The basic idea of the book – to use the largest possible variety of reactions for all sorts of purposes, applying the most important physicochemical facts instead of the usual introduction to chemistry by way of qualitative analysis, which only involves a small segment of all reaction processes – is an extremely welcome change. The design and text of the book are excellent, and it would appear that anyone who would not be delighted to use this book in a first year laboratory course should hardly be studying chemistry. Conscientious completion of the course will give more practical experience and more comprehensive theoretical knowledge in less time than is required by the usual methods.

In any subsequent third edition, besides the few minor corrections required, it is suggested that the concept of acids and bases in the strict sense be confined to appropriate substances, and that the Brönsted and Lewis concepts which attempt to relate definite facts of chemistry using ambiguous terms from everyday language be omitted, and instead, only the simple, clear-cut ideas – proton, hydroxyl, and electron donor or acceptor – be used. The designation of the OH ion as the "conjugate base of the acid, water", or of caustic soda as a "salt solution" proves that concepts resting on weak foundations take away more understanding than they give.

Otherwise, the theoretical sections are clear and up-to-date. The survey of paper chromatography, the introduction of new

subdivisions into the analytical schemes, and the large number of valuable individual references, are worthy of note.

Because of its practical design and its significantly new approach, this book can be heartily recommended, but with the one qualification that a rather large number of laboratory demonstrators must be available for its completely effective use (a condition which, it is hoped, is becoming easier to realize).

E. Hayek [NB 880/20 IE]

Integraltafeln zur Quantenchemie (Tables of Integrals for Quantum Chemistry) Vol. III [1], by *H. Preuss*, Springer-Verlag, Berlin-Heidelberg-Göttingen, 1961, 1st edition, VIII + 563 pp., clothbound, DM 144.– (about $35.–).

As is well known, overlap integrals, Coulomb integrals, and exchange integrals have always to be determined in quantum mechanical calculations of the gain in energy accompanying the combination of several atoms to form a molecule. Evaluation of these integrals is very tedious and requires many separate integrations since, in general, their solutions involve series expansions. In particular, excessive computational difficulties are encountered in evaluating integrals representing the averaging of the repulsion potential between two valence electrons via the individual electron distributions in the neighborhood of their respective nuclei. To evaluate these integrals, the reciprocal distance between the valence electrons is customarily expanded into a series of spherical harmonics; it is expedient to express the positions of the valence electrons in the vicinity of their nuclei in terms of elliptical coordinates. Integrals of products of these harmonics with unperturbed electron wave functions ψ still remain to be evaluated. Usually, functions of the form $\psi = r^n e^{-r}$, sometimes multiplied by spherical harmonics when the valence electrons are not of the *s*-type, are used.

Finally, integrals of the type

$$\int_1^{\infty}\int_1^{\infty} Q_\tau^{(\nu)}(\mu_1)\; P_\tau^{(\nu)}(\mu_2)\; e^{-R(\alpha\mu_1+\beta\mu_2)}\left[(\mu_1^2-1)(\mu_2^2-1)\right]^{\nu/2} \mu_1^m \mu_2^n\, d\mu_1\, d\mu_2 \qquad \mu_1 < \mu_2 \tag{1}$$

$$\int_1^{\infty}\int_1^{\infty} Q_\tau^{(\nu)}(\mu_2)\cdot P_\tau^{(\nu)}(\mu_1)\; e^{-R(\alpha\mu_1+\beta\mu_2)}\left[(\mu_1^2-1)(\mu_2^2-1)\right]^{\nu/2} \mu_1^m \mu_2^n\, d\mu_1\, d\mu_2 \qquad \mu_2 > \mu_1$$

remain, in which $P_\tau^{(\nu)}$ and $Q_\tau^{(\nu)}$ are spherical harmonics (and associated spherical harmonics) of the first and second kind, μ_i is the elliptical coordinate of the i-th valence electron, and R is the distance between the centers.

There are also simpler integrals of the type

$$\int_{-1}^{+1} e^{\alpha x}\, P_\tau^{(\nu)}(x)\,(1-x^2)^{\nu/2}\, x^m\, dx \tag{2}$$

These two types of integrals are tabulated for electron wave functions in which, for the first case, αR and βR vary between 3 and 20, and the other values are chosen so that $\nu \le \tau \le 6+\nu$ and $0 \le m$; $n \le 8 \le \nu$. For the second case, α is tabulated from 0 up to 20 times the reciprocal of the Bohr radius; some values for $\alpha = \beta$ are omitted, since they already have been given in the literature by other authors.

The values are given to ten places. Although such precision is not needed in quantum mechanical calculations, the tables will greatly reduce the effort involved in these calculations. This, the third volume completes the series "Tables for Quantum Chemistry".

K. Schäfer [NB 879/22 IE]

Die Naturwissenschaftler und ihre Philosophie – Geistesgeschichte der Chemie (Scientists and their Philosophy – A Philosophical History of Chemistry). By *W. Böhm*. Verlag Herder KG., Wien-Freiburg-Basel 1961. First Ed., XVI, 315 pp, clothbound DM 20.–.

The author carries over the "phase scheme" of *Dempf*'s concept of history to a developmental history of chemistry. According to an *a priori* number system, philosophical concepts of a certain period are compared with the chronologically corresponding concepts in chemistry. The intellectual contents of the individual "phases" from both disciplines are compared, and from all this emerges a "proof" – or so we are assured eleven times – that every chemical theory has its origins in a definite metaphysical system. Thus, it would appear that there is "*no basic difference between a scientific and a metaphysical hypothesis*" and that "*the problem of induction in a theory of natural science becomes superfluous.*" (p. 5). Experiments serve basically only for the verification of a theory (p. 75), and, since the latter is of metaphysical origin, they serve only to confirm the corresponding metaphysics; this thus "*deals a death blow*" to positivism. (pp. 1, 207). Astonishing results in an astonishingly simple way.

Böhm has spared no pains in sorting the historical material of the two disciplines to correspond with this theory. The history of chemistry is forced here into a mould in which it can only be maintained through loss of the distinction between the historically meaningful and the insignificant, and there are distortions to be found which do not lack an element of the grotesque. The pages are filled with disconnected juxtapositions of individual facts. These "must" be introduced to illustrate the individual phases. Biographical details, edifying, but irrelevant from the metaphysical-historical point of view, plug the gaps where achievements must be passed over because they do not fit into the postulated scheme. *Van Helmont*, the founder of gas chemistry, is placed in the shadow of "Mystics"; *Richter* appears under "Ethics"; even that stroke of genius that befell *Wöhler* – the urea synthesis – is credited to "Mystical Influences" – the philosophy of *Fichte!*

The reader is encumbered with such burdens not only in the history of chemistry. What poses here as "philosophy" is simply a shame – especially in "Antiquity" and "Modern Times" – both from the point of view of facts as well as from the point of view of good literature. It is painful even if one's eyes could be closed to the factual errors. Protestations of one's own "intellectual level" (p. xiii) are not convincing in an historical treatise in which an elementary study of the source materials is completely absent.

"Philosophical History of Chemistry"? A premature and pitifully inadequate attempt to deal with a subject which still awaits a careful and serious study.

Elisabeth Ströker [NB 851/111E]

[1] Cf. also Angew. Chem. 69, 279 (1957).

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The Structure of Ice

BY PROF. DR. R. BRILL

FRITZ-HABER-INSTITUT DER MAX-PLANCK-GESELLSCHAFT, BERLIN-DAHLEM (GERMANY)

Of the seven modifications of ice that are stable at temperatures above −80 °C, modification I has so far been investigated in especially great detail. An eighth modification (ice Ic) which is stable only below −80 °C is also well known. In the following, the crystal lattice structures of these modifications and the formation of mixed crystals are discussed.

Introduction

According to studies carried out by *Tammann* [1] and *Bridgman* [2], there are seven known modifications of ice; their phase boundaries are shown in Fig. 1. There is, however, an additional eighth modification, which is designated as Ic. It is metastable below −80 °C and stable below −120 °C. Its phase boundaries are thus not comprised in Fig. 1. Of these modifications, ice I and

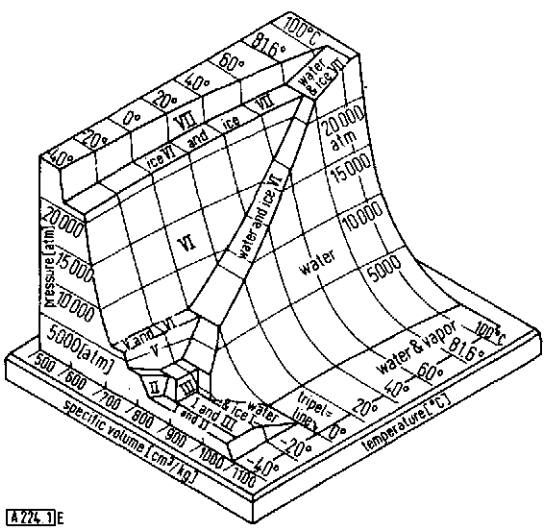


Fig. 1. Phase diagram of ice

ice Ic are the best known. The first is "ordinary" ice, obtained by cooling water below its freezing point at atmospheric pressure. Modification Ic cannot, however, be obtained from I by cooling; it can only be condensed from the vapor phase or be obtained from amorphous ice [*]. Above −80 °C it is irreversibly transformed into ice I. Crystallographic data for the various ice modifications insofar as they are known, are summarized in Table 1. The subscripts (H) and (D) refer to H_2O and

Table 1. Crystallographic data for some modifications of ice

Modification	Crystal system	Unit cell dimensions
I (H)	hexagonal	a = 4.523 Å (0 °C) c = 7.367 Å
I (D)	hexagonal	a = 4.526 Å (0 °C) c = 7.369 Å
Ic (H)	cubic	a = 6.350 Å (−130 °C)
Ic (D)	cubic	a = 6.351 Å
II (H)	cubic	a = 11.25 Å (−190 °C)
III (H)	tetragonal	a = 6.75 Å (−190 °C) c = 6.79 Å

D_2O. The crystal structure of modification II is not yet known with certainty. In all the other structures, the mode of packing is the same: each oxygen of the water molecule is tetrahedrally surrounded by four others. These tetrahedrons are, to a very close approximation, regular. Only in ice III, which is obtained under pressure and which has a density of 1.14 g/cm³, are they somewhat deformed [3]. Figures 2 and 3 show the crystal lattices of ice I and ice Ic; only the oxygen atoms are shown. The similarity of the two structures is evident. In both cases the loose packing of the molecules leads to extensive holes, which pervade the lattice. At equal temperatures, the distance between two neighboring oxygens is the same in the hexagonal

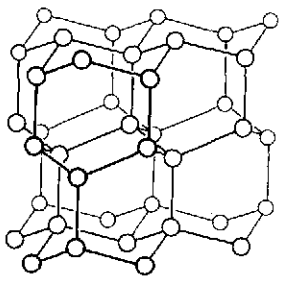
[1] *G. Tamann*, Ann. Physik *2*, 1 (1900).

[2] *P. W. Bridgman*, Proc. nat. Acad. Sci. U.S.A. *47*, 441 (1912); J. chem. Physics *3*, 597 (1935); *5*, 964 (1937).

[*] Amorphous ice is obtained by condensation of water vapour below −140 °C.

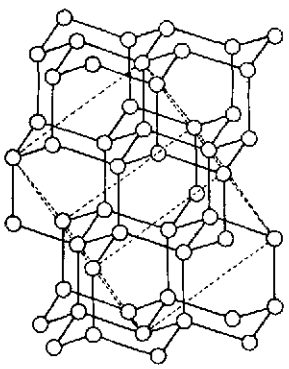
[3] *W. B. Kamb* and *S. K. Datta*, Nature (London) *187*, 140 (1960).

and in the cubic ice I modifications, being 2.75 Å in both cases at −80 °C and 2.76 Å in the hexagonal ice modification in the vicinity of the melting point. This value is characteristic for a hydrogen bridge; this leads to



A 224.2

Fig. 2. Structure of ice I



A 224.3

Fig. 3. Structure of ice Ic

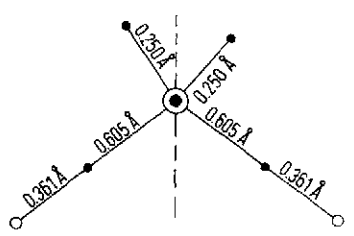
the conclusion that the hydrogens must lie between the oxygen atoms. This hypothesis was confirmed by neutron diffraction studies [4] but has recently been disputed [5]. It seems that the neutron diffraction results admit a position of the hydrogen atoms on the line connecting two oxygens (bond angle at the oxygen atom 109.5 °) as well as somewhat besides this line (bond angle at the oxygen atom 104.5 ° as in water vapor).

Hydrogen Bridges

The hydrogen bridges in ice are directional. According to *Schneider* [6] the formation of hydrogen bonds with oxygen leads to the formation of tetrahedral orbitals around the oxygen atoms. Each vertex of the tetrahedron would thus correspond to a pair of electrons according to the following schematic representation:



Since hydrogen atoms are covalently bound only to two vertices of the tetrahedron, the tetrahedron is not regular. This deformation is characterized by the location of the centers of the electron charge -2e between the center and the vertices of the tetrahedron (Fig. 4).



A 224.4

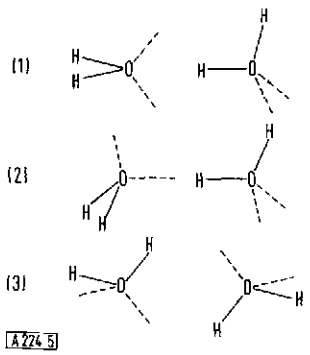
Fig. 4. Position of the charge centers for pairs of valence electrons (black circles) in the water molecule [6]. The hydrogen atoms are indicated by unshaded circles, the oxygen by an unshaded circle with a black center

[4] *E. O. Wollan, W. L. Davidson*, and *C. G. Shull*, Physical. Rev. *75*, 1348 (1949); *S. W. Peterson* and *H. A. Levy*, Acta crystallogr. *10*, 70 (1957).

[5] *R. Chidembaram*, Acta crystallogr. *14*, 467 (1961).

[6] *W. G. Schneider*, J. chem. Physics *23*, 26 (1955).

Schneider [6] applied this model in order to compute the energy of interaction between two neighboring molecules, 2.76 Å apart, as a function of their orientation. He found that the most stable configuration is that in which hydrogen atom lies on the axis between two neighboring oxygens. Of the various possible arrangements shown in Fig. 5, energy considerations favor the one on the second line [*].



A 224.5

Fig. 5. Possible arrangements of neighboring water molecules in ice [6]

The hydrogen bridge bonds are responsible for the anomalous physicochemical properties of ice and water. Because of them, the density of ice at 0 °C is less than that of water at the same temperature, and the density of water increases up to +4 °C. The tetrahedral coordination of each water molecule with four neighbors, caused by hydrogen bonding, results in a very loosely packed structure. On melting ice, some of the hydrogen bonds break. Thus, the molecules are able to assume a denser packing, resulting in increased density. Since no single molecules are formed on melting, however, further compacting by further rupture of hydrogen bonds occurs until a point is reached where any increase in density is more than compensated by thermal expansion.

In Table 2, oxygen-oxygen distances are given for compounds containing hydrogen bridges. The bond lengths

Table 2. Distances between oxygen atoms connected *via* hydrogen bridges in various compounds

Compound	Distance [Å]
Nickel dimethylglyoxime	2.43
Maleic acid	2.47
Palladium dimethylglyoxime	2.49
Potassium dihydrogen phosphate	2.49
Urea oxalate (strong bond)	2.50
Oxalic acid dihydrate (strong bond)	2.52
Sodium bicarbonate	2.55
N-Acetylglycine	2.56
Succinic acid	2.64
Adipic acid	2.68
Resorcinol	2.68
Pentaerythritol	2.69
Ice	2.76
Urea oxalate (weak bond)	2.80
1-Hydroxyproline	2.82
Oxalic acid dihydrate (weak bond)	2.87

themselves are inversely proportional to the strength of the hydrogen bridges. The table shows that, even though they are so important for the structures of ice, the hydro-

[*] Only electrostatic interactions were taken into account in this calculation; however, this is adequate for a first approximation.

gen bridge bonds in ice are not very strong *per se*. This, however, is compensated for by the fact that each molecule is bound to its neighbors by four hydrogen bridges.

Disorder in the Crystal Structure

If we accept the premise that ice consists of hydrogen-bonded H_2O molecules, then a completely ordered lattice of coordination number 4 must result, which is schematically projected onto a plane in Fig. 6.

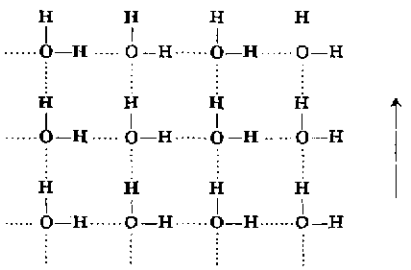


Fig. 6. Schematic diagram of the bonding arrangement in an ideal ice crystal

Such an ordered arrangement, however, is found in ice only as an exception and then only for periods of short duration. This follows, on the one hand, from the fact that crystals of ice I, for example, ordinarily do not show any polarity in the direction of the c-axis. The arrangement shown in Fig. 6 ought to be polar in the direction of the arrow, for example. (The direction of the arrow would be reversed if the covalently bonded hydrogen atoms – here drawn above the oxygen atoms – were found below the oxygen atoms.) On the other hand, neutron diffraction experiments with ice I show two hydrogen density peaks of half height, each about 1 Å from the nearest oxygen [4], instead of a single hydrogen peak on the line joining the two oxygens. This result is best explained by *Pauling*'s hypothesis of a statistical distribution of hydrogen atoms in ice. According to this hypothesis, the atomic structure of ice is characterized only by the constraints that each oxygen must form a primary bond with two hydrogens and be joined via hydrogen bridges with two other oxygens, and that only one hydrogen may be located on the axis between two neighboring oxygens [7]. Fig. 7 presents a schematic diagram of this type of lattice disorder. This model of

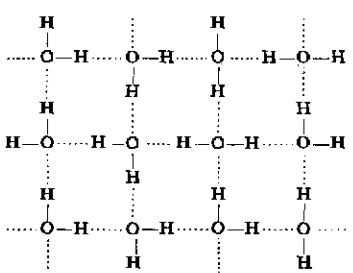


Fig. 7. Schematic diagram of the bonding arrangement in a real ice crystal; note the irregularity in the arrangement of the H atoms

[7] *L. Pauling:* Nature of the Chemical Bond. Cornell University Press, Ithaca 1960.

limited disorder leads quite precisely to the experimental value of the entropy of ice at 0 °K, *viz.* 0.8 e.u.

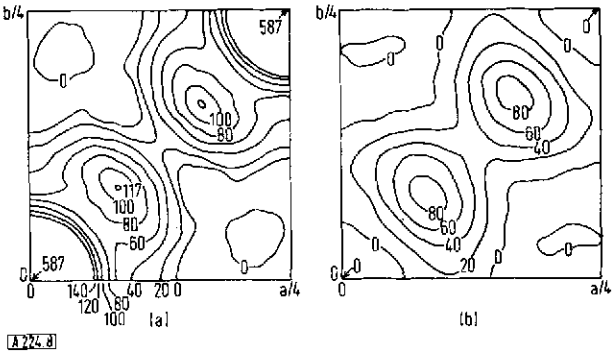


Fig. 8. Fourier projection of ice Ic (see text)

Such disorder is found not only in ice I but also in ice Ic. Fig. 8a shows results obtained from electron diffraction studies [8] carried out with this modification. In the lower left and upper right hand corners of the diagram, there is an oxygen atom. Both half hydrogens between the oxygen atoms are clearly discernible. In Fig. 8b, the contributions of the oxygen atoms have been subtracted in order to make the results stand out more clearly [8]. A similar investigation of other ice modifications has thus far not been reported.

The reason for this disorder in the ice lattice appears to be the exceedingly large mobility of the protons, found by *M. Eigen*; these, of course are present as H_3O^+ ions, just as in water. One of the three hydrogen atoms of the H_3O^+ ion is easily transferred as a proton to the neighboring molecule, and from that to the next, *etc.* Since each of the three hydrogen atoms can migrate with equal likelihood, they distribute themselves rather randomly throughout the lattice. In this way, a statistical distribution is obtained (Fig. 7). This is also the reason that almost all efforts to find a piezoelectric effect in ice have failed; this effect should occur if the c-axis were polar owing to a regular array of hydrogen atoms in the lattice (see Fig. 6). Recently, a piezoelectric effect parallel to the c-axis was found by *Deubner* et al. [9] in hexagonal ice. Thin platelets obtained from slightly supercooled water were investigated. The piezoelectric effect vanished with aging of the crystals. It disappeared within three to four days at the latest even at −20 °C. This result demonstrates the effect of proton migration in ice.

In Fig. 9, the lattice constants of hexagonal ice I are shown as a function of temperature. It can be seen that there are no differences between ordinary ice (H_2O) and heavy ice (D_2O). However, the deviations due to the different vibrational amplitudes of D and H are of the order of a few thousandths of an Ångstrom [10]; *i.e.* they lie within the limits of experimental error of the data shown in Fig. 9. Special attention is called to the crosses drawn in the upper half of the diagram. These

[8] *G. Honjo* and *K. Shimaoka*, Acta crystallogr. *10*, 710 (1957).

[9] *A. Deubner*, *R. Heise*, and *K. Wenzel*, Naturwissenschaften *47*, 600 (1960).

[10] See, *e.g. L. S. Bartell*, *K. Kuchitsu*, and *J. D. Neui*, J. chem. Physics *35*, 1211 (1961). The relationships found with solid methane also hold for ice since the valence vibration frequencies are practically the same.

show the lengths of the a-axis which would be observed if the axial ratios in ice were c/a = 1.6330, the same as for ideal close packing of spheres. This axial ratio is to be expected if all the oxygen-oxygen distances in the ice

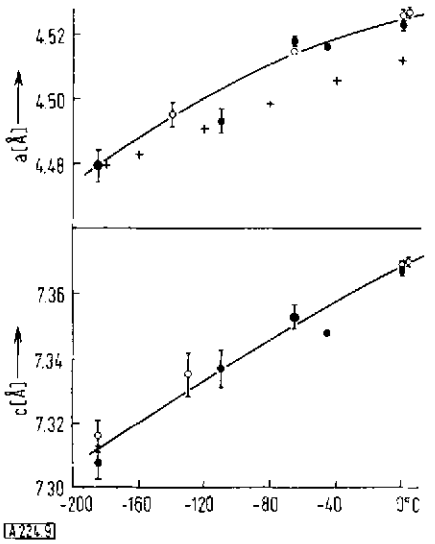


Fig. 9. Lattice constants of ice I as a function of temperature (after measurements by *H. D. Megan, L. Vegard,* and *S. Hilles,* and *M. Blackman* and *N. D. Lisgarten*).
● = H_2O; ○ = D_2O; + for a = c/1.633

lattice are equal. According to these measurements, this appears to be the case only at very low temperatures. However, findings of *La Placa* and *Post* [11] suggest, in contrast, that the axial ratio between 0 °C and −180 °C is independent of temperature. Additional experiments will be required to determine which of the results is correct. Under these circumstances, it seems hardly worthwhile, at present, to discuss the older measurements. However, it is interesting that the more recent data agree with the older on one point: the axial ratio does deviate from the ideal at higher temperatures. This deviation may be interpreted to mean that either 1) all four hydrogen bridges between a molecule and its neighbors are still of equal length, but the bond angle at the oxygen has departed from the ideal tetrahedral value (109.47 °) [*], and deviates from it by ± 0.16 °, the negative sign applying to bonds parallel to the c-axis and the positive sign applying to all others; in this case the parameter z = 1/16, which defines positions of the oxygen atoms in the unit cell, must also be decreased by 0.0004; or 2) differences in the bond lengths must be assumed. In the latter case, the oxygen parameter would remain z = 1/16, and the bond angles at the oxygen would deviate from the ideal tetrahedral angle by only 0.05 °. The distances between neighboring oxygens parallel to the c-axis, would then be 2.76 Å, while all others would be 2.77 Å.

The second interpretation is more likely. The reason is that only perpendicular to bonds which are parallel to c, a mirror plane exists with respect to the bond direction of the oxygen atoms. Hereby, a configuration of local charges can be created which effects, parallel to c, a bond that is stronger than all the other ones. Thus, the oxygen-oxygen distances parallel to the c-axis should be somewhat smaller than those in other directions.

[11] *S. La Placa* and *B. Post*, Acta crystallogr. *13*, 503 (1960).
[*] Assuming that the H atoms lie exactly on the O–O line.

Mixed Crystals

Because of its tendency to form hydrogen bridges, water has a definite propensity to form many occlusion compounds. In this connection the question arises whether or not water is able to form mixed crystals in the solid state. For example, it could be thought to replace a water molecule in ice by a hydroxyl group, and to compensate the residual charges by inclusion of small positive ions in the lattice holes. The smallest ion to fit would be Li^+. However, when ice is crystallized from LiOH solutions and then separated from the mother liquor and washed, the water obtained from these crystals does not impart even a trace of color to a flame. Thus, the experiment gives a negative result. In an analogous manner it can be shown that H_2O molecules in ice cannot be replaced by NH_3, even in traces. Positive results are obtained with HF and NH_4F. However, only very small quantities of HF are absorbed. The formation of mixed crystals can be demonstrated by means of a simple experiment: a small quantity of CsF is dissolved in a large volume of water, half of the water is frozen, and the solid part is separated from the solution. After melting, the liquid from the frozen part reacts acid, while the mother liquor reacts alkaline [12]. Thus:

$$Cs^+ + F^- + H^+ + OH^- \rightarrow \underset{\text{in the aqueous portion}}{CsOH} + \underset{\text{in the ice}}{HF}$$

It is much easier to replace two water molecules by one (isoelectronic) NH_4F molecule [13]. The relevant phase diagram is shown in Fig. 10. Dielectric measurements

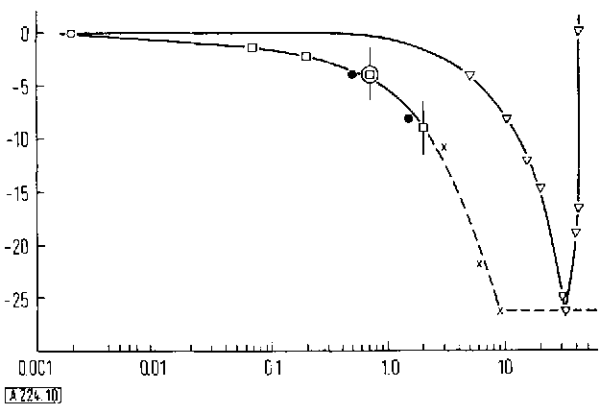


Fig. 10. Part of the phase diagram of the system H_2O/NH_4F.
Lower curve: solidus curve; upper curve: liquidus curve.
Ordinate: Melting point [°C]
Abscissa: % NH_4F by weight

with such mixed crystals show that NH_4F reduces the activation energy for the rotation of molecular dipoles in ice quite considerably (from 13.5 to about 4 kcal/mole). Figure 11 illustrates schematically how the NH_4F molecule may fit into the ice lattice.

[12] *R. Brill* and *H. Ender*, Nature (London) *176*, 935 (1955).
[13] *R. Brill* and *S. Zaromb*, Nature (London) *173*, 316 (1954); J. chem. Physics *24*, 895 (1956).

The strong fields of the ions present in the lattice of these mixed crystals interact with neighboring water dipoles and generate lattice defects in the surroundings. These are healed out within a short distance. In the region

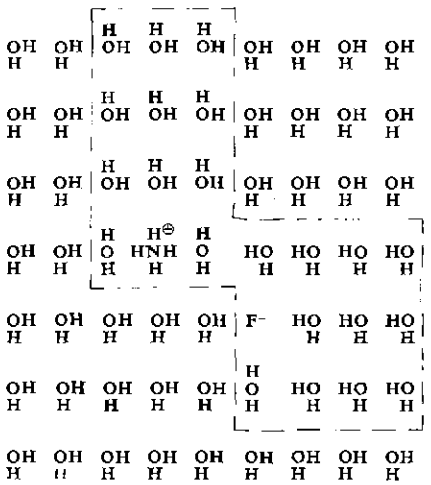


Fig. 11. Schematic representation of the incorporation of NH_4F within an ice lattice. The principle that there can be only one hydrogen between two non-hydrogen atoms or ions is complied with. The order of the H atoms could be perturbed even further, in the sense of Fig. 7

intermediate between the defect and the normal lattices, the dipoles are more mobile, thus requiring less activation energy for rotation [14]. Obviously, not all dipoles have their activation energies reduced by the same extent. It is rather to be expected that the activation energies will be distributed over a whole "spectrum" of values, the maximum value being that which corresponds to the activation energy of pure ice. This spectral distribution can be proved in the following way:

Dielectric constants ε can be measured either in a stationary field or in an alternating field of frequency ν. (The first is really a special case of the second, with $\nu = 0$.) In a completely general way then $\varepsilon = \varepsilon' - i\varepsilon''$, where ε' is the real part and ε'' the imaginary part of the complex dielectric constant. The magnitudes of both parts depend upon the frequency. Each may be measured separately. For $\nu = 0$, we have $\varepsilon'' = 0$; the imaginary part thus vanishes.

Cole and *Cole* [15] have shown that in a diagram with axes ε' and ε'', all the points measured must lie on a semicircle whose center is on the ε' axis insofar as only one relaxation time [*] for the dipole rotation is involved. However, if there is a variety of relaxation times, then the center of the semicircle no longer lies on the ε' axis but below it. This applies to the ice-NH_4F mixed crystals but not to pure ice (see Fig. 12). The reciprocal of the dielectric relaxation time (τ) for mixed crystals corresponds to a rate constant. Its temperature dependence thus obeys Arrhenius' Law:

$$\frac{1}{\tau} \sim \nu = k e^{-Q/RT}$$

[14] *R. Brill, H. Ender* and *A. Feuersanger*, Z. Elektrochem. *61*, 1071 (1957).

[15] *K. S. Cole* and *R. H. Cole*, J. chem. Physics *9*, 341 (1941).

[*] The relaxation time $\tau = 1/\omega$, where ω is that frequency for which ε'' is a maximum. It is a measure of the inertia with which a dipole follows the electric field.

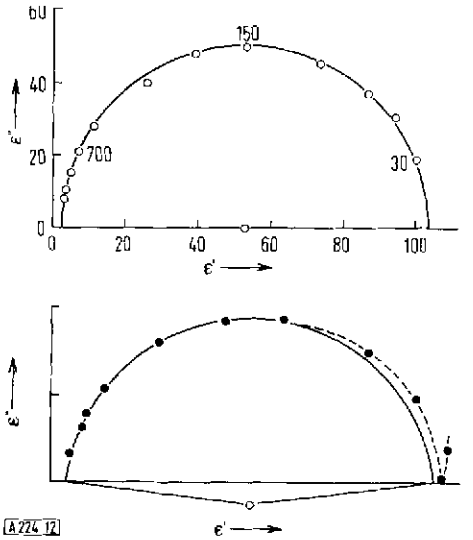


Fig. 12. Cole Diagram of ice (above) and ice-NH_4F (below). The center of the semicircle lies on the abscissa for ice and below the abscissa for NH_4F-ice. The deviation of a few experimental points from the semicircle, shown by the dotted line, is due to polarization at low frequencies. The numbers shown on the semicircle in the upper figure are the frequencies pertaining to the measured points (in cycles/sec)

and to the spectrum of relaxation times, therefore, corresponds a spectrum of activation energies Q. This fact is implicit in the dependence of k on Q (compensation effect). This means that $1/\tau$ may be described by an expression similar to that given by *Cremer* [16] for catalysts with a "spectral" distribution of the activity of their "active sites." The difference here is that with ice all the constants appearing in the equation may be represented quantitatively by physically defined magnitudes. Thus, for the relaxation time in the concentration range of 0 to 0.7 %:

$$\frac{1}{\tau} = \nu \cdot \exp\left[(\Delta S/R) - (Q - Q')/RT_0 - Q/RT\right]$$

where: ν = frequency of vibration of the water molecules in ice; ΔS = entropy change associated with the rotation (≈ 9 e.u.); Q, and Q' = activation energy for the dipole rotation in mixed crystals and in pure ice, respectively; T_0 = melting point of ice; and T = temperature at which the measurements are carried out.

Thus, we find not only the compensation effect frequently observed in catalysts, but also a virtual temperature T_0 which here corresponds to the highest temperature assumed by the substance during its formation. Since for pure ice we have Q = Q', the factor containing T_0 in the expression above disappears. This means that the compensation effect vanishes. The value of Q depends upon the manner in which the mixed crystals were prepared (*e.g.*, upon the rate of crystallization). However, since T_0 is independent of the mode of preparation, we conclude that the distribution statistics for "sites" with different activation energies is also independent of it.

The present report was not intended to be exhaustive. If, for those less familiar with the subject, it has contributed to an understanding of the structural problems and certain related questions connected with such a "well known" substance as ice, then it will have fulfilled its objective.

Received, April 26th, 1962 [A 224/54 IE]

[16] *E. Cremer*: Advances in Catalysis and Related Subjects. Academic Press, New York 1955, vol. VII, p. 73.

Reactivity of Dichloro- and Trichloropyrimidyl Dyes and the Sensitivity of their Dyeings to Hydrolysis

BY DR. O. THUMM AND DR. J. BENZ

SANDOZ AG., BASEL (SWITZERLAND)

Several examples are used to show that the reactivity of dichloro- and trichloropyrimidyl dyes and the sensitivity of their dyeings to hydrolysis are determined by the nature of the bridge unit between the chromophore and the reactive system. The tendency of the dyeings to hydrolyze in acid and, more particularly, in alkaline media increases with increasing reactivity of the dyes. In alkaline media, dyeings made with dyes containing oxygen bridges are cleaved mainly between the reactive system and the chromophore, while in dyeings made with dyes containing imino or methylimino bridges, the linkage between the reactive system and the cellulose is hydrolyzed.

Reactive dyes are those that react with a textile substrate with formation of a homopolar bond. In 1956, I.C.I. introduced the Procions®, the first reactive dyes for cellulose. Reactive dyes for wool (Remalan® and Cibalan Brilliant® dyes) had appeared earlier. However, the rapid development of this class of dyes, which is still in full swing today, came into effect only after the appearance of the Procions®.

Advances have also been made in the application of reactive dyes to other textile substrates. As a result of this research the Procinyl® dyes, a class of reactive disperse dyes for polyamide fibers, and others, were created. At the present time, however, reactive dyes for cellulose claim the greatest interest.

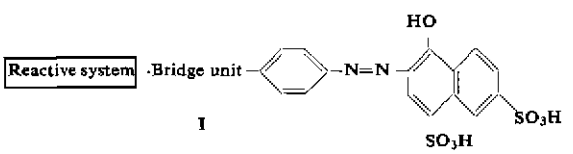
The success of the reactive dyes for cellulose fibers is chiefly due to the brilliance and high wet fastness properties of their dyeings. The brilliance of reactive dyeings, which often cannot be matched by dyes of other classes, is due to the uncomplicated, narrow absorption bands displayed by the simple structure of the dye molecules, while the good wet fastness is the result of the stable linkage between the dye and the cellulose.

Certain fastness properties of reactive dyeings are governed by the reactive system. These are the properties given by the resistance of the dyeing to hydrolysis. To be of commercial interest, a reactive dyeing must exhibit a certain minimum stability to alkaline and acid hydrolysis. The stability required depends on the intended use of the dyed material.

Furthermore, the resistance of a reactive dyeing to alkali has to be correlated with the reactivity of the dyestuff. All the reactive dyes known so far must be fixed on cellulose in alkaline medium. Hence it is possible that during the course of fixation a part of the dye which has already reacted with the fiber may be hydrolyzed. The prerequisite for a reactive dye that can be used under alkaline fixing conditions is that the rate of hydrolysis of the dyeing under the fixing conditions must be negligible in comparison to the rate of fixation.

The stability of reactive dyeings to acid hydrolysis is also of great practical importance. Most dyed cellulose fabrics receive a resin finish, which is applied with an acid catalyst. Furthermore, the acidic atmosphere prevalent in many industrial areas is likely to attack reactive dyeings that are easily hydrolyzable. Even when such acid hydrolysis proceeds very slowly, definite deterioration of the dyed goods may be observed after long storage. With the growing use of blended fabrics of cellulose and synthetic fibers, the fastness of the dyed cellulose component to acid cross-dyeing is of increasing importance.

The present paper describes a study of the sensitivity of the dyeings of dichloro- and trichloropyrimidyl dyes to alkaline and acid hydrolysis and of the fixation rate of the corresponding dyestuffs. Since these properties were to be examined as a function of the reactive system, dyes with one and the same chromophore were prepared (I).



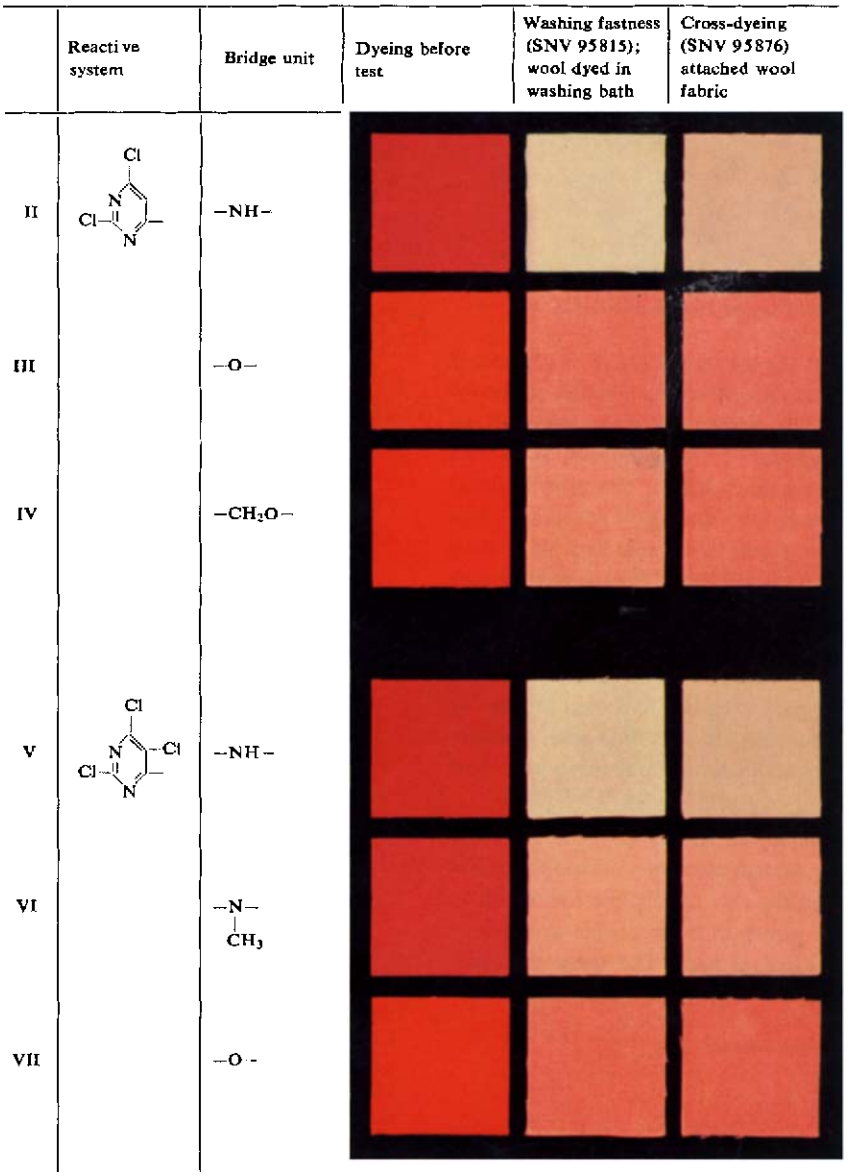
I

Depending on the type of bond formed at the pyrimidine ring, the bridge unit may affect to a great extent the reactivity of the dye and the tendency of the corresponding dyeing to hydrolyze. The combinations of type I used in our work are listed in the color table. The formulae of the dichloro- and trichloropyrimidyl radicals require that symmetrical trichloro- and tetrachloropyrimidine exchange their halogen atoms at position 4 for the bridge radical during condensation [1].

Besides the combinations listed in the color table, we examined a large number of similar dyes and observed essentially the same pattern of behavior. Some of these findings have been included in the present paper.

All the dyes were applied to mercerized cotton in standard depth by the thermal fixation process and the dyeings carefully washed. The sensitivity to hydrolysis was then examined. We tested the stability of the dyeings in alkaline medium by using the washing fastness test No. 5 (SNV 95815); the fabric was mechanically agitated for 4 hours at 95 °C in a bath containing soap and 2 g of sodium carbonate per liter

[1] *H. Ackermann* and *P. Dussy*, Melliand Textilber. *42*, 1167 (1961).



of approximately pH 10. The dye that bled into the washing bath was applied to wool by acidifying the bath; this is necessary because, owing to the nature of their chromophores, all the dyes have only very slight substantivity and are not directly adsorbed on cellulose.

Adapting the work of *van der Eltz* [2], we studied the tendency to hydrolyze with acid by observing the fastness to cross-dyeing with sulfuric acid (SNV 95876). The dyeings were agitated for 90 minutes at 98 °C in a bath containing sodium sulfate and 0.08 % by weight of sulfuric acid; its pH was approximately 2. The stripped dye was adsorbed by the wool fabric attached to the dyeing.

The relative stability of the dyeings was determined by comparison of the dyeings on the wool pieces attached to the test samples. The findings are largely in accordance with those communicated in an earlier paper [3].

An insight into the mechanism of hydrolysis was obtained by chromatography of the hydrolysates. By permitting identification of the cleavage products, this method makes it possible to determine whether the linkage between the cellulose and the reactive system or that between the reactive system and the chromophore is hydrolyzed.

The reactivity of the dyes, which is of significance here chiefly because of its relation to the sensitivity of dyeings to alkaline hydrolysis, was tested in most cases by the pad-jig method at room temperature with caustic soda as alkali. The fixation yields of the dyes were determined as a function of the fixation time by the method of *Michie* and *Thornton* [4], which was first applied to reactive dyes by *Dawson* et al. [5].

The color table shows that dye II with the imino bridge linkage is practically unhydrolyzed under the alkaline conditions chosen. The dyeings of dyes III and IV with oxygen bridges are distinctly less stable.

Chromatographic examination of hydrolysates obtained under more severe conditions revealed cleavage at the positions shown in Table 1.

The results shown in Table 1 are easily understood if symmetrical trichloropyrimidine is regarded as the chloride of barbituric acid. The reactive system of dye II is linked to the chromophore through an amide linkage. It is to be expected that this linkage would be more stable to alkali than the ester linkage between the reactive component and the cellulose. The situation is

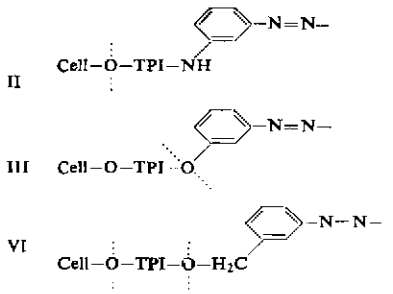
[2] *H. U. van der Eltz*, Melliand Textilber. *42*, 929 (1961).

[3] *J. Benz*, J. Soc. Dyers Colorists *77*, 734 (1961).

[4] *A. G. H. Michie* and *R. Thornton*, J. Soc. Dyers Colorists *69*, 629 (1953).

[5] *T. L. Dawson*, *A. S. Fern*, and *C. Preston*, J. Soc. Dyers Colorists *76*, 210 (1960).

Table 1. Hydrolysis of dyeings of dichloropyrimidyl dyes



TPI = Bivalent radical of symmetrical trichloropyrimidine

different with dye III: the pyrimidyl group is connected on the one side to the chromophore through a phenol ester bond and on the other it is esterified with an aliphatic hydroxyl group of the cellulose. It is not surprising that, on alkaline attack, the ester linkage with the phenol is the first to undergo hydrolysis, since phenol esters are more prone to alkaline hydrolysis than those of primary alcohols. Similarly, the pyrimidine ring in the dyeing of dye IV is esterified both by the cellulose and the chromophore. Aliphatic hydroxyl groups are involved in both ester linkages. If the cellulose reacts predominantly through its primary hydroxyl groups, as is likely [6], it is to be expected that both ester linkages will be hydrolyzed by alkali to approximately the same extent.

In the three examples above, the nature of the linkage between the reactive system and the chromophore has a marked influence on the rate of alkaline hydrolysis of the dyeing. Figure 1 shows that the bridge unit affects the reactivity of the dye as well. The three dichloro-

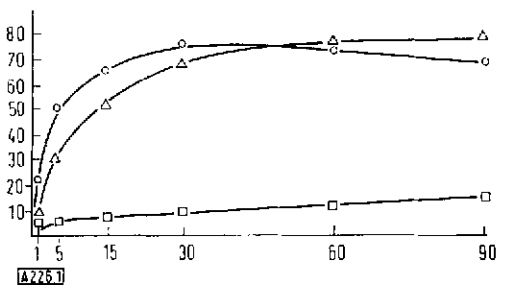


Fig. 1. Reactivity of dyes II (□), III (○), and IV (△)
Ordinate: Fixation yield [%]
Abscissa: Time [min.]

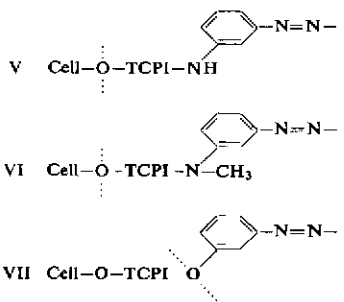
pyrimidyl dyes were applied under identical conditions by the pad-jig process at room temperature with the addition of alkali. After the times given, samples of the dyeing were taken, and the fixation yield was determined. The reactivity of the dichloropyrimidyl dyes increases with increase in the positive charge of the carbon atom in the pyrimidine ring to which the mobile halogen atom is attached. Dyes III and IV, in which the reactive component is linked to the chromophore through an oxygen atom, accordingly react much more rapidly than dye II, which contains an imino bridge.

Under the conditions chosen, dye III reaches its maximum fixation yield within approximately 30 minutes. With longer fixation times, marked rehydrolysis of the alkali-sensitive dyeing occurs. In contrast, dye II with the imino bridge gives dyeings with high resistance to alkaline hydrolysis, although under identical conditions, this dye requires about 50 hours to attain its maximum fixation yield.

The color table shows that under our conditions the susceptibility to acid hydrolysis of the three dichloropyrimidyl dyes II, III, and IV runs roughly parallel to their sensitivity to alkaline hydrolysis. The Drimarene® type, represented by dye II, displays not only very good stability to alkali but also excellent resistance to acid hydrolysis, while dyes III and IV with the oxygen bridges give considerably poorer results.

The results of the alkaline washing fastness tests with the trichloropyrimidyl dyes V, VI, and VII indicate that dyes with an imino or, to a somewhat lesser degree, a methylimino linkage between the reactive component and the chromophore also give dyeings of higher alkaline stability than those with a phenol ester linkage. Chromatography of the hydrolysates obtained under severe conditions gave the results shown in Table 2.

Table 2. Hydrolysis of dyeings of trichloropyrimidyl dyes



TCPI = Bivalent radical of tetrachloropyrimidine

Dyes V and VI, which are linked with the reactive radical through an imino and a methylimino bridge, respectively, hydrolyze in alkaline medium in such a way that cleavage occurs mainly at the linkage between the dye and the cellulose. However, in dyeings with dye VII, the linkage between the pyrimidine ring and the chromophore is split. Thus, dyes V and VII behave in the same way as dichloropyrimidyl derivatives of analogous structure.

The effect of the bridge unit on the reactivity of the dyes is shown in Fig. 2.

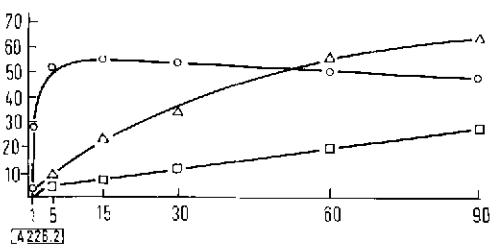


Fig. 2. Reactivity of dyes V (□), VI (△), and VII (○)
Ordinate: Fixation yield [%]
Abscissa: Time [min.]

The transition from an imino to an oxygen bridge in the trichloropyrimidyl dyes results in an increase in reactivity, just as with the dichloropyrimidyl dyes II and III. This behaviour can once more be explained as resulting from the influence exerted by the bridge member on the positive partial charge of the pyrimidine nucleus. With the trichloropyrimidyl dye VII, as with dye III, fixation extended beyond the optimum time results in re-saponification of the alkali-sensitive dyeing.

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

The increase in reactivity obtained when an imino group is replaced by a methylimino group is illustrated in Fig. 3, using a pair of dyes containing a different chromophore.

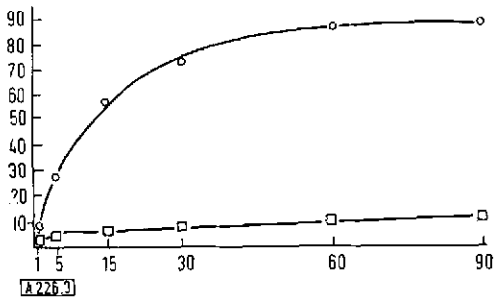
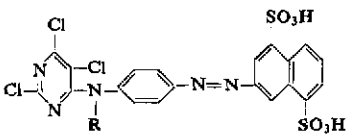


Fig. 3. Increase in reactivity on transition from an imino bridge t methylimino bridge in dyes of the type



(□) R=H
(○) R=CH_3

Ordinate: Fixation yield [%]
Abscissa: Time [min.]

It has been shown that the slower rate of reaction of trichloropyrimidyl compounds of primary aromatic amines compared with that of the corresponding *N*-methyl compounds is due to the more acidic character of the former type [1]. In a caustic alkaline fixing medium, the protons from the imino groups are almost completely dissociated and the rate of reaction is determined by the relatively low concentration of reactive, undissociated compound.

Since replacement of an imino group by a methylimino group results in increased reactivity, it might be expected that the reactivities of trichloropyrimidyl dyes bearing imino groups would depend on the basicity of these groups and on the pH value of the fixation medium.

This hypothesis is not easy to prove by coloristic means, because, in most cases, as the basicity of the reactive amino group is changed, other properties that may affect the dyeing behavior, such as substantivity and salt sensitivity, are changed at the same time.

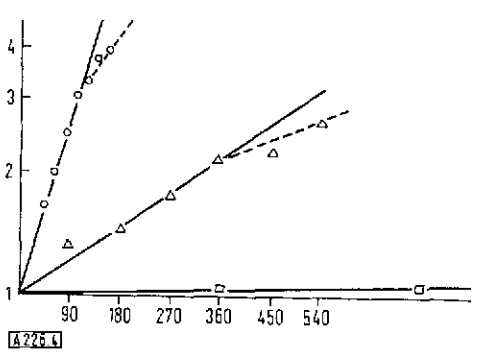
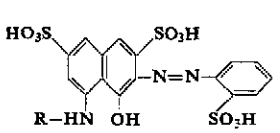


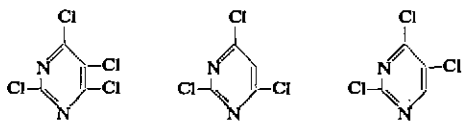
Fig. 4. Reactivity of dyestuffs of type



(○) R = Monovalent radical of tetrachloropyrimidine (VIII)
(△) R = Monovalent radical of symmetrical trichloropyrimidine (IX)
(□) R = Monovalent radical of asymmetrical trichloropyrimidine (X)
Ordinate: $c_0/(c_0-c_t)$
Abscissa: Time [min]

Figure 4 shows that trichloropyrimidyl dyes, compared to dichloropyrimidyl dyes of analogous structure, show a slightly greater lability toward alkaline and acid hydrolysis, and significantly higher reactivity.

Dyes containing the radicals of symmetrical (IX) and asymmetrical (X) trichloropyrimidine, and of tetrachloropyrimidine (VIII) were applied by the pad-batch process at 50 °C.



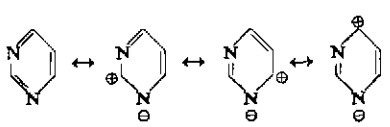
VIII IX X

The fixation of all three dyes is a first-order reaction, at least initially. *Ackermann* and *Dussy* [1] made the same observation in the fixation of trichloropyrimidyl dyes. Under the fixing conditions chosen, we obtained the rate constants listed in Table 3.

Table 3. Rate constants for fixation of the dyes described in Fig. 4

Dyes with the radical of	k [min^{-1}]
VIII	$11{,}4 \cdot 10^{-3}$
IX	$2{,}16 \cdot 10^{-3}$
X	$0{,}109 \cdot 10^{-3}$

The decrease in reactivity on passing from the trichloropyrimidyl group (VIII) to the radicals of symmetrical (IX) and asymmetrical (X) trichloropyrimidine can be explained by the properties of the pyrimidine ring. As a result of the difference in the affinity for electrons exhibited by the nitrogen and carbon atoms, the following resonance forms are possible:



The electron deficiencies in positions 2, 4, and 6 of the pyrimidine ring make the halogens in these positions mobile. In contrast, position 5 is only slightly affected by the two heteroatoms. A halogen atom in position 5 of the pyrimidine ring thus reacts as slowly as one that is aromatically bonded. However, it leads to marked activation of the other halogen atoms at positions 2, 4, and 6. This activating effect of a chlorine atom in position 5 is the reason for the better reactivity of dyes containing the monovalent radical of tetrachloropyrimidine (VIII). A nitro group in position 5 increases the mobility of the halogen atoms at positions 2, 4, and 6 much more than an identically positioned chlorine atom. Accordingly, dyes with the radical of 5-nitro-2,4,6-trichloropyrimidine display still greater reactivity than dyes with the radical of tetrachloropyrimidine. On the other hand, the reactivity of dyes containing the radical of 5-methyl-2,4,6-trichloropyrimidine is somewhat lower.

Dyes with the radical of 2,4,5-trichloropyrimidine (X) are less reactive than dyes of analogous structure containing the radical of symmetrical trichloropyrimidine (IX). This is due to the fact that, even with a chlorine atom in position 5, the chlorines in positions 2 and 6 of (X) are not as reactive as those at position 4 in (IX), since they lack the enhancing effect of resonance in the pyrimidine ring.

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Special Properties of the Sugars in Cardioactive Glycosides

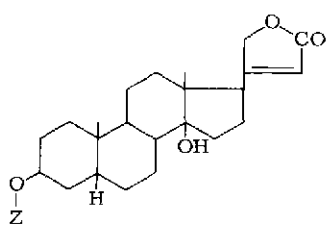
BY PROF. DR. T. REICHSTEIN [1]

INSTITUT FÜR ORGANISCHE CHEMIE DER UNIVERSITÄT BASEL (SWITZERLAND)

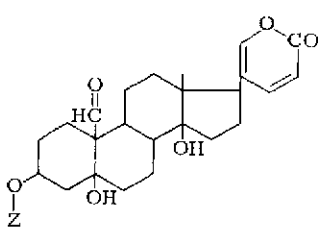
Striking differences are observed when the sugar components of digitaloid lactones (as well as of two additional minor groups of substances) are compared with those of the other glycosides in higher plants: non-digitaloid glycosides almost always contain one or more of the following eight sugars as a structural unit: D-glucose, D-glucuronic acid, D-xylose, L-arabinose, D-galactose, D-galacturonic acid, L-fucose, and L-rhamnose. Oligosaccharide moieties almost always contain hexoses "on the inside", i.e. linked directly onto the aglycone, and pentoses and methyl pentoses "on the outside". Oligosaccharide moieties containing more than two sugars often appear to be branched. Cardioactive glycosides (and two related minor groups of substances) chiefly contain only two sugars of the eight listed, viz. D-glucose and L-rhamnose. Very often numerous other sugars are found, particularly hexamethyloses. Oligosaccharide moieties always contain the hexose (D-glucose) "on the outside". As far as is known, oligosaccharide moieties with more than two sugars are always built up linearly.

1. Definitions and Formulation of the Problem

Cardioactive glycosides are sterol derivatives found in many higher plants [2]. They received their name on account of their specific "digitalis-like" action on cardiac muscle. Depending on the structure of the aglycone, they can be divided chemically into two main groups, cardenolides *(1)* with C_{23}-genins and bufadienolides (2) with C_{24}-genins.



(1) Example of a cardenolide with digitoxigenin ($C_{23}H_{34}O_4$) as aglycone. Z = sugar residue



(2) Example of a bufadienolide with hellebrigenin (bufotalidin) ($C_{24}H_{32}O_6$) as aglycone

This aglycone or genin (the steroid moiety) is coupled with one or more sugars by a glycosidic linkage. The cardiac glycosides therefore differ from other glycosides only in the special structure of the genin component; and from other steroid glycosides, only in the "side chain," which in this case is present as a lactone ring. It is surprising that this slight distinction strongly affects the nature of the sugars attached at the other end of the molecule. However, this narrowly limited group of substances contains a very large variety of sugars, including many which are seldom found in other natural products from higher plants or animals [3]. These differences in the sugars will constitute the principal topic of this paper.

Table 1. Sugars in group A glycosides (see text)

D-Glucose	D-Glucuronic acid	D-Xylose	L-Fucose
D-Galactose	D-Galacturonic acid	L-Arabinose	L-Rhamnose

In order to illustrate the differences we include arbitrarily in group A all the important types of sugar derivatives of higher plants [4] and animals, excluding the cardioactive glycosides and two other minor groups. It follows from the examples given below that, quantitatively, the eight sugars listed in Table 1 are by far the most preponderant in group A. This is particularly true for regular glycosides.

[1] From lectures delivered at Lindau (June 25th, 1961) and Marburg (July 14th, 1961).

[2] Comprehensive texts: [a] *R. Tschesche* in *H. Lettré, H. H, Inhoffen*, and *R. Tschesche*: Über Sterine, Gallensäuren und verwandte Naturstoffe (Sterols, Bile Acids and Related Natural Products). F. Enke, Stuttgart 1954, vol. 1, p. 287. [b] *C. Tamm*, Fortschr. Chem. org. Naturstoffe *13*, 137 (1956); *14*, 71 (1957). [c] *L. F. Fieser* and *M. Fieser*: Steroids. Reinhold Publishing Corp., New York 1959, p. 727

[3] Review: *T. Reichstein* and *E. Weiss*, Advances in Carbohydrate Chemistry, Vol. 17 (1962) in press.

[4] Bacteria and other microorganisms often have more complicated metabolisms and are not considered here.

In contrast to this, we have group B, which includes cardioactive glycosides and the two minor classes of substances mentioned, *viz.* the digitanol glycosides [5] and the ester glycosides, which presumably contain the C-nor-D-homosteroid skeleton. The latter are found in various *Asclepiadaceae*. In the group B compounds, most of the sugars present differ from those listed in Table 1.

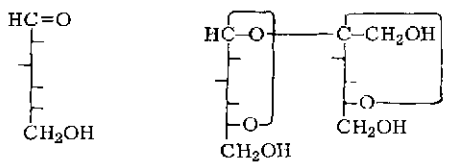
2. Examples of Group A

In nature, sugars are most often encountered in one of three forms: as free sugars (mono-, oligo-, and polysaccharides [6]), as esters, or as glycosides. The latter can be divided into *N*-, *S*-, and *O*-glycosides. In addition, there are *C*-glycosyl compounds which, however, are actually derivatives of sugar alcohols.

2.1. Free Sugars

Examples:

Monosaccharides *Oligosaccharides*:



D-Glucose Saccharose

Polysaccharides: Cellulose, starch, glycogen, pentosans, pectins, gums, chitin, mucopolysaccharides.

Free sugars exhibit the greatest diversity of all the substances in group A. The eight sugars listed in Table 1 are those most often found. The additional six sugars listed in Table 2 are relatively abundant [7]; their relationship to D-glucose and D-galactose, with which they are also biogenetically connected, is obvious [8].

Table 2. Sugars other than those listed in Table 1 frequently found in mono-, oligo-, and polysaccharides

D-Mannose	D-Glucosamine	D-Mannosamine
D-Fructose	D-Galactosamine	D-Neuraminic acid (Sialic acid)

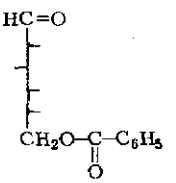
Only in specific instances were the following sugars observed [9]: L-galactose (linseed, red algae), D-sedoheptulose, D-mannoheptulose, D-arabinose (lichens), D-mannuronic acid, L-iduronic acid [10], 2-*O*-methyl-L-fucose (*Prunus*), 3-*O*-methyl-D-galactose (*Ulmus*), muramic acid (bacteria), L-acofriose (*Picea nigra*).

There are at least two ways in which the biosynthesis of oligo- and polysaccharides can occur: by way of sugar-1-phosphates with phosphorylases [11] or by way of nucleotide derivatives, especially uridine-diphosphate D-glucose [12] with special enzymes. Common glycosides seem to be formed almost exclusively by the latter method [13]. Possibly the diversity of sugars participating in polysaccharide formation is connected with the fact that these sugars originate in different ways.

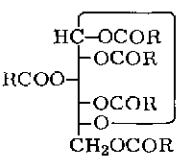
The diversity of the sugars in the other classes of substances of group A is much less.

2.2. Sugar Esters

Examples:

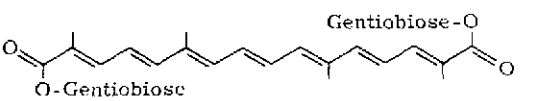


Vacciniin (in *Ericaceae*)



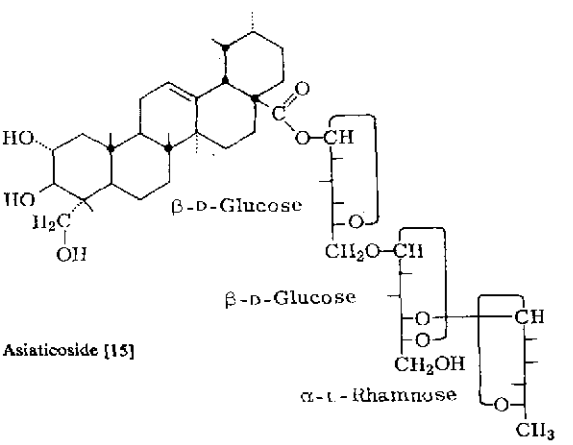
Tannin-type substances (α- and β-configuration)

Inorganic esters, especially with H_3PO_4, H_2SO_4



Crocin (in *Crocus sativus* [14])

Stevioside (see formula *(14)* in Section 2.343): contains 1 D-glucose (linked as ester) and 1 sophorose (linked as a glycoside)



Asiaticoside [15]

Sugar esters are abundant in tannins. So far only D-glucose and L-rhamnose have been found in organic esters.

[5] Name given by *R. Tschesche* and *G. Buschauer*, Liebigs Ann. Chem. *603*, 59 (1957).

[6] Of these, the oligo- and polysaccharides are also glycosides. Their biosynthesis, however, follows paths only partly similar to that of the biosynthesis of glycosides of phenols or steroids.

[7] Distribution of amino sugars: *R. Kuhn*, Angew. Chem. *69*, 23 (1957).

[8] *S. Roseman*, Ann. Rev. Biochem. *28*, 559 (1959); *P. Kohn, R. J. Winzler*, and *R. C. Hoffman*, J. biolog. Chemistry *237*, 304 (1962) and literature cited therein.

[9] Relatively stable end-products are understood. Short-lived intermediate products, *e.g.* of photosynthesis, cannot be considered here. It is quite likely that with modern methods still more sugars will be detected in the future. The fact that the eight sugars listed in Table 1 are predominant will hardly be altered on account of this.

[10] Probable biosynthesis in rabbits: *B. Jacobson* and *E. A. Davidson*, J. biol. Chemistry *237*, 638 (1962).

[11] See for example, *F. Leuthardt*: Lehrbuch der physiologischen Chemie (Textbook of Physiological Chemistry). 14th ed., W. de Gruyter & Co., Berlin 1961, p. 298, 308.

[12] *W. Z. Hassid*, Biochem. Soc. Symposia *21*, 63 (1962).

[13] Synthesis of phenol glucuronides: *G. J. Dutton* and *I. D. E. Storey*, Biochem. J. *53*, xxxvii (1953); Biosynthesis of rutin: *G. A. Barber* and *E. F. Neufeld*, Biochem. biophys. Research Commun. *6*, 44 (1961).

[14a] *P. Karrer, F. Benz*, and *M. Stoll*, Helv. chim. Acta *16*, 297 (1933).

[14b] *R. Kuhn* and *A. Winterstein*, Ber. dtsch. chem. Ges. *67*, 344 (1934) and literature cited therein.

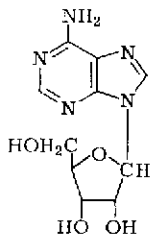
[15] *P. Boiteau, A. Buzas, E. Lederer*, and *J. Polonsky*, Nature (London) *163*, 258 (1949); Bull. Soc. Chim. biol. *31*, 46 (1949); Chem. Abstr. *43*, 8053 (1949); *M. Frèrejacque*, Bull. Soc. Chim. biol. *31*, 1510 (1949); Chem. Abstr. *44*, 6584 (1950); *J. Polonsky, E. Sach*, and *E. Lederer*, Bull. Soc. chim. France *1959*, 880; *J. Polonsky* and *J. Zylber*, *ibid.* *1961*, 1586.

2.3. Glycosides

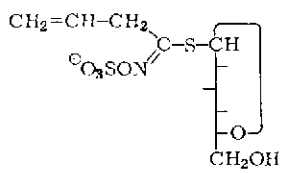
The actual glycosides of group A, especially the *O*-glycosides, are of prime importance for comparison with the compounds of group B.

2.31. *N*-Glycosides

Example: Adenosine, formula *(3)*. *N*-Glycosides play a significant role as nucleotides in the cell function. So far only the sugars D-ribose and 2-deoxy-D-ribose have been found in this class of substances. The biosynthesis of these sugars from D-glucose [16] occurs by way of 5-phospho-D-ribulose, which is formed *de novo* also in photosynthesis [17, 18]. The D-ribose-5-phosphate ultimately formed is suitable for the biosynthesis of nucleotides [16], but apparently not for the formation of *O*-glycosides. Presumably for this reason D-ribose is rarely found in *O*-glycosides.



(3) Adenosine
Example of an *N*-glycoside



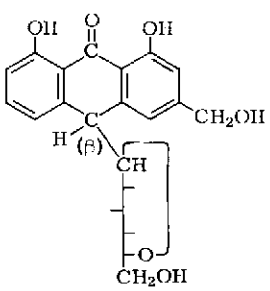
(4) Sinigrin [19]
Example of an *S*-glycoside

2.32. *S*-Glycosides

Example: Sinigrin, formula *(4)*. Mustard oil glycosides belong to this class of substances [20]. So far only the sugar D-glucose has been found in this class of compounds.

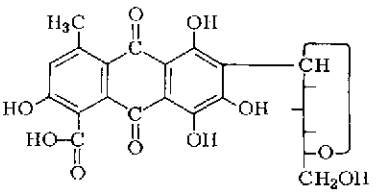
2.33. *C*-Glycosyl Compounds

Examples: Barbaloin *(5)* and carminic acid *(6)*.



(5) Barbaloin [21] (in *Liliaceae*)

Bergenin (from *Bergenia crassifolia* etc.) [23], homonataloin [24], vitexin (flavone derivative from *Vitex littoralis* (*Verbenaceae*) and *Polygonum orientale*) [25] also belong to this interesting group of substances. Substances of this type are



(6) Carminic acid [22] (in *Coccus cacti*)

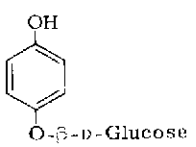
perhaps much more prevalent than it is presently known, since special methods are required for their detection and structural determination. So far only D-glucosyl residues have been observed in these substances.

2.34. *O*-Glycosides

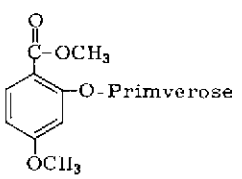
This class of substances, which is very abundant in nature, can be subdivided into phenolic, aliphatic, and alicyclic glycosides, depending on the nature of the aglycone. Only rarely are sugars found that are not listed in Table 1 [25a].

2.341. Phenol Glycosides

These glycosides are very abundant in the plant kingdom (flavones, anthocyanins, anthraquinone derivatives). Two simple examples are given in formulae *(7)* and *(8)*.



(7) Arbutin



(8) Primverin

D-Glucose, D-galactose, D-xylose, L-arabinose, L-rhamnose, and in rare cases apiose (in *Umbelliferae*) have been observed in this class of glycosides. Excluding the latter, these are again sugars listed in Table 1. It is of interest to establish the type of linkage in the disaccharides. It always corresponds to diagram *(9)* (in cardioactive glycosides the opposite sequence is always observed); the glucose is directly linked to the aglycone, and the pentose or methylpentose remains on the outside. The

[16] *J. N. Davidson:* The Biochemistry of the Nucleic Acids. 4th Ed., Methuen and Co. Ltd., London 1960, p. 171, 191.

[17] *H. A. Krebs* and *H. L. Kornberg*, Ergebn. Physiol. biol. exp. Pharmakol. *49*, 212 (1957).

[18] *J. A. Bassham* and *M. Calvin:* The Path of Carbon in Photosynthesis. Prentice Hall Inc., Englewood Cliffs, N.J., 1957; see also the collective review in *W. Ruhland:* Handbuch der Pflanzenphysiologie (Handbook of Plant Physiology). Springer, Berlin-Göttingen-Heidelberg 1960, vol. 5.

[19] New formula according to *M. G. Ettlinger* and *A. J. Lundeen*, J. Amer. chem. Soc. *78*, 4172 (1956).

[20] Mustard oil glycosides, review: *A. Kjaer*, Fortschr. Chem. org. Naturstoffe 18, 122 (1960).

[21] Formula and partial synthesis by *N. Mühlemann*, Pharm. Acta. Helv. *27*, 17 (1952); *J. E. Hay* and *L. J. Haynes*, J. chem. Soc. (London) *1956*, 3141; also see *H. Böhme* and *J. Bertram*, Arch. Pharm. Ber. dtsch. pharmaz. Ges. *288*, 510 (1955); *R. A. Barnes* and *W. Holfeld*, Chem. and Ind. (London) *1956*, 873.

[22] *O. Dimroth* and *H. Kämmerer*, Ber. dtsch. chem. Ges. *53*, 471 (1920); *M. A. Ali* and *L. J. Haynes*, J. chem. Soc. (London) *1959*, 1033.

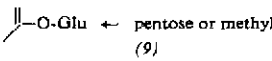
[23] *J. E. Hay* and *L. J. Haynes*, J. chem. Soc. (London) *1958*, 2231.

[24] *L. J. Haynes, J. I. Henderson*, and *J. M. Tyler*, Chem. and Ind. *1960*, 50; J. chem. Soc. (London) *1960*, 4879.

[25] *W. H. Evans, A. McGookin, L. Jurd, A. Robertson*, and *W. R. N. Williamson*, J. chem. Soc. (London) *1957*, 3510; *L. Jurd, T. A. Geissman*, and *M. K. Seikel*, Arch. Biochem. Biophysics *57*, 284 (1957); *L. Hörhammer, H. Wagner, H. Nieschlag*, and *G. Wildi*, Arch. Pharm. Ber. dtsch. pharmaz. Ges. *292*, 380 (1959).

[25a] *E.g.* D-glucomethylose in α- and β-chinovin and in purgic acid, D-fucose in convolvulin and jalapin, Literature: *T. Reichstein* and *E. Weiss* [3].

bonding follows the Klyne rule [26], which states that an α-L- or β-D-glycosidic configuration is favored.



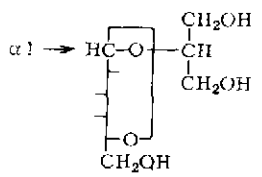
(9)

Thus, in phenol glycosides, the following biosides were found:

Primverose = 6-[β-D-xylosido]-D-glucose
Vicianose = 6-[α-L-arabinosido]-D-glucose [27]
Rutinose = 6-[α-L-rhamnosido]-D-glucose [28]
Apiosido-D-glucose (in *Umbelliferae*) [29]
Robinobiose = 6-[α-L-rhamnosido]-D-galactose [30].

2.342. Aliphatic Glycosides

Glycosides of pure aliphatic alcohols are rare in plants. *Examples*: floridoside *(10)* and 3-[α-D-mannosido]-floridoside in red algae. α- and β-D-glucosides of ribitol are also found as components of teichoic acid in bacteria, *etc.* [31]. Cerebrosides in particular should be mentioned for the animal kingdom [32]. D-Galactose is the sugar of these biologically important substances, while the closely related gangliosides [33] contain D-glucose, *N*-acetylgalactosamine and *N*-acetylneuraminic acid (sialic acid) in addition to D-galactose.

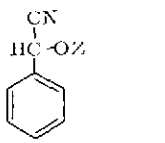


(10) Floridoside (Red algae)

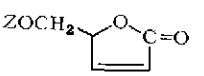
2.343. Alicyclic Glycosides

These glycosides are very abundant in plants. Some examples are given in formulas *(11)* to *(16)*. Except for the occasional occurrence of D-glucomethylose, the sugar units throughout are again those listed in Table 1. Saponins of the triterpene and spirostane series usually contain several (up to 4 or 6) sugars. The configuration of the glycoside linkage is not certain in any case. Better information is available on the structure of the sugar chain in some steroid alkaloid glycosides, *e.g.* formulas *(17)* and *(18)*. The structures of their sugar chains were elucidated by methylation. The extensive branching is noteworthy.

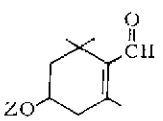
Pentoses and methylpentoses are "on the outside", just as in phenylglycosides. It is possible that the sugar chains of the triterpene and spirostane saponins may often have similar structures.



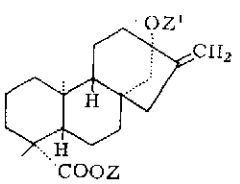
(11)
HCN-glycosides [34]
Z = D-glucose, gentiobiose, vicianose



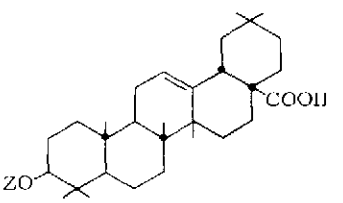
(12)
Ranunculin [35]
Z = D-glucose



(13)
Picrocrocin [14b]
Z = D-glucose



(14)
Stevioside (*Stevia rebaudiana, Compositae* [36]
300 times sweeter than cane sugar
Z = D-glucose (esterified!)
Z' = sophorose (2-β-D-glucosidoglucose), linked glycosidically



(15)
Example of triterpene-saponins [37] with oleanolic acid as genin (C_{30}-genin) and up to 4 sugars per molecule
Z = D-glucose
D-galactose
D-glucuronic acid
L-arabinose
L-rhamnose
D-glucomethylose (α-chinovin)

[26] *W. Klyne*, Biochem. J. *47*, xli (1950). The rule states that in cardioactive glycosides D-sugars are connected by β-glycosidic linkages and L-sugars by α-glycosidic linkages. It is usually valid also for other glycosides of higher plants but not for substances from bacteria and other microorganisms and not for polysaccharides (*cf.* for example, starch).

[27] Enzymatic synthesis: *K. Wallenfels* and *D. Beck*, Liebigs Ann. Chem. *630*, 46 (1960) and literature cited therein.

[28] *G. Zemplen* and *A. Gerecs*, Ber. dtsch. chem. Ges. *68*, 1318 (1935), formulated this as a β-L-derivative on the basis of its synthesis [*ibid. 67*, 2049 (1934)]. The molecular rotation clearly indicates that the α-configuration actually occurs.

[29] Review: *C. S. Hudson*, Adv. Carbohydrate Chem. *4*, 57 (1949); Synthesis of D-apiose: *P. A. J. Gorin* and *A. S. Perlin*, Canad. J. Chem. *36*, 480 (1958); Chem. Abstr. *52*, 12772 (1958); L-Apiose: *F. Weygand* and *R. Schmiechen*, Chem. Ber. *92*, 535 (1959).

[30] Identified by *G. Zemplen*, *A. Gerecs*, and *H. Flesch*, Ber. dtsch. chem. Ges. *71*, 774 (1938), on the basis of its synthesis by *G. Zemplen* and *A. Gerecs*, *ibid. 68*, 2054 (1935). Claimed to be a 6-β-L-rhamnopyranoside by *G. Zemplen* and *R. Bognar*, *ibid. 74*, 1783 (1941). According to the molecular rotation of the derivative, in this case also an α-L-rhamnopyranoside is undoubtedly actually present.

[31] *J. Baddiley*, *J. G. Buchanan*, and *F. E. Hardy*, J. chem. Soc. (London) *1961*, 2180; *A. R. Archibald*, *J. J. Armstrong*, *J. Baddiley*, and *J. B. Hay*, Nature (London) *191*, 570 (1961); *J. Baddiley*, *J. G. Buchanan*, *U. L. RajBhandary*, and *A. R. Sanderson*, Biochem. J. *82*, 439 (1962) and literature cited therein.

[32] See for example *H. Thierfelder* and *E. Klenk:* Die Chemie der Cerebroside und Phosphatide (The Chemistry of Cerebrosides and Phosphatides). J. Springer, Berlin 1930; *E. Klenk*, Naturwiss. *40*, 449 (1953).

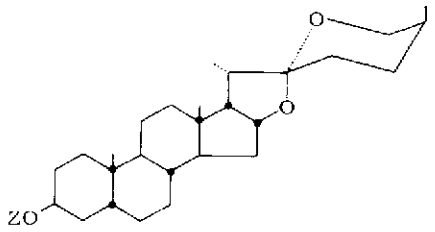
[33] *R. Kuhn* et al., Angew. Chem. *72*, 805 (1960); *73*, 580 (1961); *E. Klenk* and *W. Gielen*, Hoppe-Seylers Z. physiol. Chem. *326*, 158 (1961) and literature cited therein.

[34] *P. Seifert* in *K. Paech*, and *M. V. Tracey:* Modern Methods of Plant Analysis, Springer, Berlin 1955, vol. 4, p. 676.

[35] *R. Hill* and *R. van Heyningen*, Biochem. J. *49*, 332 (1951).

[36] Isolation: *M. Bridel* and *R. Lavieille*, Bull. Soc. Chim. biol. *13*, 781 (1931); J. Pharm. Chim. *14*, 99, 154 (1931).
Sugar: *H. B. Wood Jr.*, *R. Allerton*, *H. W. Diehl*, and *H. G. Fletcher Jr.*, J. org. Chem. *20*, 875 (1955); *E. Vis* and *H. G. Fletcher Jr.*, J. Amer. chem. Soc. *78*, 4709 (1956).
Aglycone: *E. Mosettig* and *W. R. Nes*, J. org. Chemistry *20*, 884 (1955); *F. Dolder*, *H. Lichti*, *E. Mosettig*, and *P. Quitt*, J. Amer. chem. Soc. *82*, 246 (1960); *E. Mosettig*, *P. Quitt*, *U. Beglinger*, *J. A. Waters*, *H. Vorbrueggen*, and *C. Djerassi*, *ibid. 83*, 3163 (1961); *C. Djerassi*, *P. Quitt*, *E. Mosettig*, *R. C. Cambie*, *P. S. Rutledge*, and *L. H. Briggs*, *ibid. 83*, 3720 (1961).

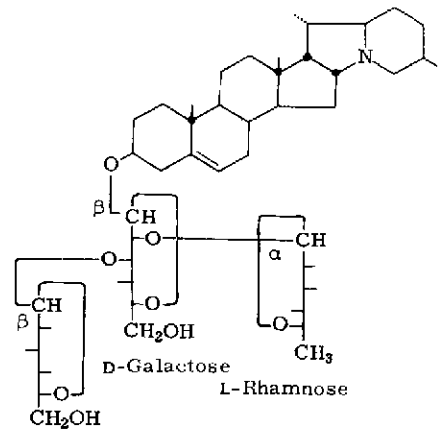
[37] *M. Steiner* and *H. Holtzem* in *K. Paech* and *M. V. Tracey:* Modern Methods of Plant Analysis. Springer, Berlin 1955, vol. 3, p. 58.



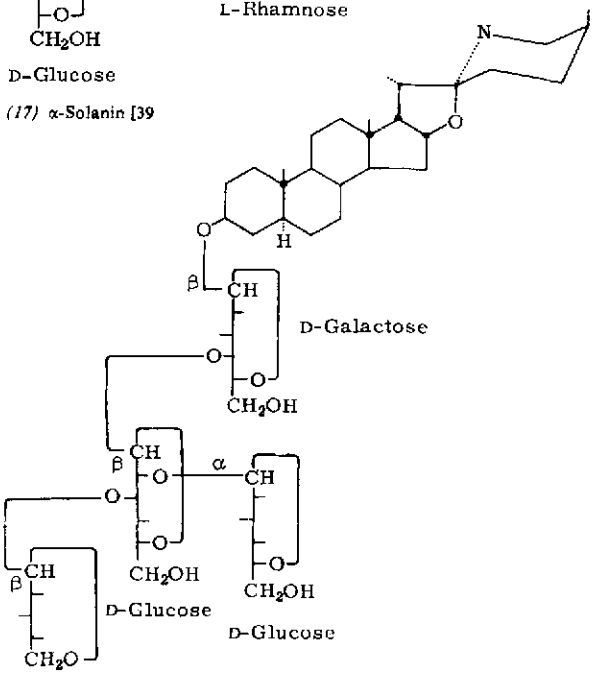
(16)

Example of spirostane-saponins [38] with sarsasapogenin as genin (C_{27}-genin) and up to 6 sugars per molecule

Z = D-glucose
D-galactose
D-glucuronic acid
L-rhamnose
D-xylose (digitonin)



(17) α-Solanin [39]



(18) Tomatin [40]

2.344. Holothurin A

Finally, a glycoside of animal origin, holothurin (there is a group of related substances of this name), should be mentioned. The structure of its aglycone is not definitely known, but the structure of its sugar chain is approximately known. According to *Chanley* et al. [41], it is built as shown in diagram *(19)*. The substance is distinguished physiologically by its high toxicity and chemically by its two anomalous sugars.

Genin: $C_{27}H_{47}O_5SO_3$
↑
D-xylose
↑
D-glucose
↑
3-*O*-methyl-D-glucose
↑
D-glucomethylose

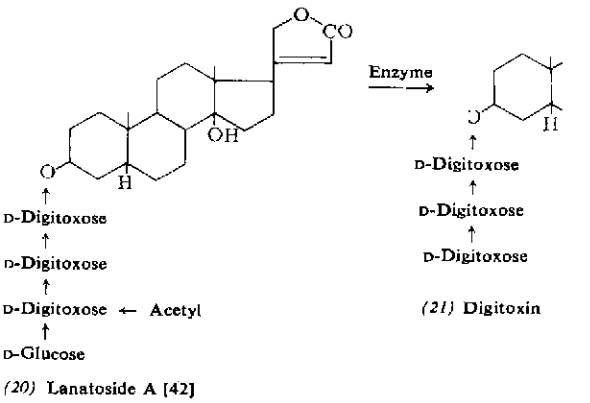
(19) Holothurin A from *Actinopyga agassizi (Echinodermae)*

3. Examples of Group B

Group B includes cardenolides *(1)*, bufadienolides *(2)*, digitanolglycosides, *e.g. (25)* and *(26)*, as well as the ester glycosides of C-nor-D-homosteroids, *e.g. (27)* and *(28)*. The sugars of these substances have been thoroughly discussed in a recent review [3]. Here only their differences from group A can be emphasized.

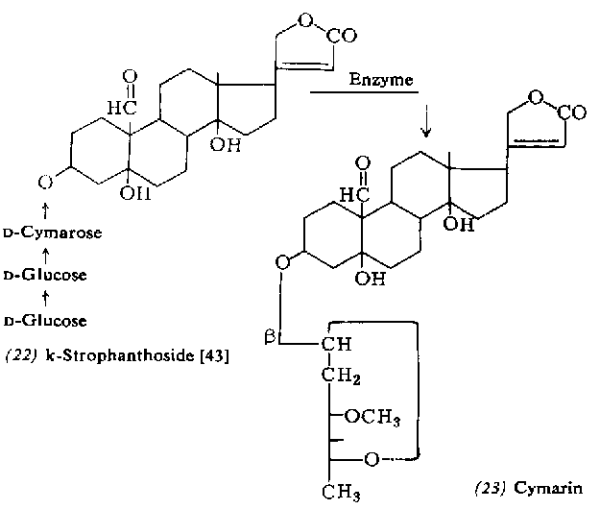
3.1. Cardenolides

Examples:



(20) Lanatoside A [42]

(21) Digitoxin



(22) k-Strophanthoside [43]

(23) Cymarin

[38] *L. F. Fieser* and *M. Fieser:* Steroids. Reinhold Publishing Corp., New York 1959, p. 810.

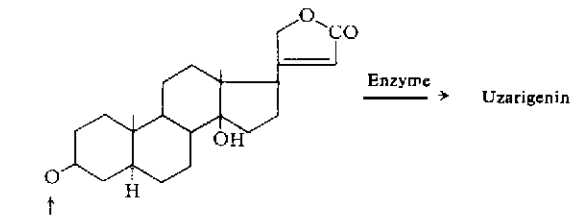
[39] *R. Kuhn* and *I. Löw*, Angew. Chem. *66*, 639 (1954).

[40] *R. Kuhn, I. Löw*, and *H. Trischmann*, Chem. Ber. *86*, 1027 (1953); Angew. Chem. *68*, 212 (1956); Chem. Ber. *90*, 203 (1957); Summary: *V. Prelog* and *O. Jeger* in *R. H. F. Manske:* The Alkaloids. Academic Press, Inc., New York 1960, vol. 7, p. 346.

[41] *J. D. Chanley, J. Perlstein, R. F. Nigrelli*, and *H. Sobotka*, Ann. New. York Acad. Sci. *90*, 902 (1960); Chem. Abstr. *55*, 12671g (1961) and literature cited therein.

[42] For details see *A. Stoll* and *W. Kreis*, Helv. chim. Acta *16*, 1049 (1933); *17*, 592 (1934); *H. Lichti, M. Kuhn*, and *A. von Wartburg, ibid. 45*, 868 (1962); *M. Kuhn, H. Lichti*, and *A. von Wartburg, ibid. 45*, 881 (1962) and literature cited therein.

[43] For details see *A. Stoll, J. Renz* and *W. Kreis*, Helv. chim. Acta *20*, 1484 (1937) and literature cited therein.



(24) Uzarin [44]

Lanatoside A *(20)* is an example of the digitalis glycosides. The linear arrangement of three digitoxose residues is common in these glycosides; an additional glucose unit is "on the outside" and therefore can be easily separated by glucosidases *(21)*. *Okano* et al. [45] recently described a glycoside of similar structure, *viz.* gitoxincellobioside, which contains 5 sugar structural units. It contains an additional D-glucose molecule which is also linearly connected.

k-Strophanthoside *(22)* is an example of a type of glycoside which is widely distributed in several species of plants. Here there is only one "anomalous" sugar directly linked to the aglycone and two D-glucose residues "on the outside", which can be split off with enzymes *(23)*.

Finally, uzarin *(24)* contains only D-glucose; it can be enzymatically degraded to its genin.

The monosaccharides listed in Table 3 have so far been discovered as sugars in cardenolides.

Table 3. Sugars present in cardenolides.
Sugars in square brackets were identified only by paper chromatography. It is therefore uncertain whether they are present in the D- or L-form.

Hexoses and 6-deoxyhexoses

D-Glucose	D-Gulomethylose
D-Allomethylose	L-Rhamnose
D-Glucomethylose	L-Talomethylose
D-Fucose	[Altromethylose]

Methyl ethers of hexoses and 6-deoxyhexoses

[3-*O*-Methylglucose]
2,3-Di-*O*-methyl-D-glucose
D-Thevetose (= 3-*O*-Methyl-D-glucomethylose)
L-Thevetose
L-Acofriose (= 3-*O*-Methyl-L-rhamnose)
L-Acovenose (= 3-*O*-Methyl-L-talomethylose)
D-Digitalose (= 3-*O*-Methyl-D-fucose)
2,3-Di-*O*-methyl-D-fucose
[2-*O*-Methyl-fucose]
[3-*O*-Methyl-altromethylose]

2-Deoxysugars

D-Arabo-2-deoxyhexose (= 2-Deoxy-D-glucose)
[Xylo-2-deoxyhexose (= 2-Deoxygulose)]
D-Digitoxose (= D-Ribo-2,6-bisdeoxyhexose)
D-Boivinose (= D-Xylo-2,6-bisdesoxyhexose)
D-Canarose (probably D-Arabo-2,6-bisdesoxyhexose) [45a]
D-Cymarose (= 3-*O*-Methyl-D-ribo-2,6-bisdeoxyhexose)
L-Cymarose
L-Oleandrose (= 3-*O*-Methyl-L-arabo-2,6-bisdeoxyhexose)
D-Sarmentose (= 3-*O*-Methyl-D-xylo-2,6-bisdeoxyhexose)
D-Diginose (= 3-*O*-Methyl-D-lyxo-2,6-bisdeoxyhexose)
L-Diginose

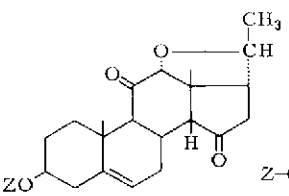
The sugars of the *Calotropis* cardenolides could not be isolated unaltered so far. According to *Hesse* et al. [46], they are carbocyclic hexoses (some containing N and S) which are presumably connected to the aglycones through ether linkages. Upon thermal cleavage, the respective glycosides yield methylreductic acid or hydroxymethylreductic acid. Similarly a very characteristic sugar residue was found in gomphoside [47]. According to *Coombe* and *Watson* [48], it has a 4,6-bisdeoxyhexosone structure.

3.2. Bufadienolides

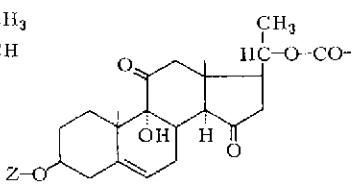
Bufadienolides *(2)* are much less widely distributed in the plant kingdom than the cardenolides. So far they have been discovered only in *Liliaceae* and *Ranunculaceae*. The sugars found in them are: D-glucose, L-rhamnose, and L-thevetose. In disaccharides, the deoxysugar is directly linked with the aglycone, and D-glucose is "on the outside." It may be possible that the bufadienolides also contain *C*-glycosyl compounds.

3.3. Digitanolglycosides [5,49]

Digitanolglycosides have so far been isolated only from *Digitalis* species; biologically they do not exhibit any digitalis-like effect. *Diginin* [50] has been known longest. According to *Shopee* et al. [51], it has the formula *(25)*. Other digitanolglycosides – insofar as they have been identified structurally – are also pregnane derivatives (C_{21}-genins). Up to now the following sugars have been found: D-diginose, D-oleandrose (as opposed to cardenolides which contain L-oleandrose), D-digitoxose (in



Z = D-Diginose
(25) Diginin [51]



Z = Three D-Digitoxoses, one mono-acetyl
(26) Digacetinin [52]

digacetinin *(26)*, three digitoxose residues are linked linearly with one another; one of these is a mono-*O*-acetyl derivative just as in lanatoside A), and D-digitalose.

[44] For details see *R. Tschesche* and *K. Bohle*, Ber. dtsch. chem. Ges. *68*, 2252 (1935); *R. Tschesche* and *K. H. Brathge*, Chem. Ber. *85*, 1042 (1952) and literature cited therein.

[45] *A. Okano, K. Hoji, T. Miki*, and *A. Sakashita*, Chem. pharm. Bull. (Tokyo) *7*, 226 (1959).

[45a] Recently isolated from a glycoside of *Digitalis canariensis*; Prof. *K. Meyer*, Basel, personal communication.

[46] *G. Hesse* and *K. W. F. Böckmann*, Liebigs Ann. Chem. *563*, 37 (1949); *G. Hesse, L. J. Heuser, E. Hütz*, and *F. Reicheneder*, *ibid. 566*, 130 (1950); *G. Hesse* and *G. Lettenbauèr*, *ibid. 623*, 142 (1959); *G. Hesse* and *K. Mix*, *ibid. 625*, 146 (1959); *G. Hesse, H. Fasold*, and *W. Geiger*, *ibid. 625*, 157 (1959); *G. Hesse* and *W. Geiger*, *ibid. 625*, 161 (1959); *G. Hesse, H. Hertel*, and *K. Mix*, *ibid. 625*, 174 (1959).

[47] *T. R. Watson* and *S. E. Wright*, Austral. J. Chem. *10*, 79 (1957); Chem. Abstr. *51*, 10550 (1957).

[48] *R. G. Coombe* and *T. R. Watson*, Proc. chem. Soc. (London) *1962*, 214.

[49] Recent review: *R. Tschesche*, Angew. Chem. *73*, 727 (1961).

[50] *W. Karrer:* Festschrift für *E. Barell* (*E. Barell* Jubilee Volume), p. 238, Basel 1936; Chem. Zbl. *1936*, II, 2727.

[51] *C. W. Shoppee, R. Lack*, and *A. V. Robertson*, Proc. chem. Soc. (London) *1962*, 65.

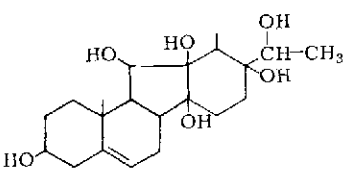
[52] *R. Tschesche, W. Hammerschmidt*, and *G. Snatzke*, Liebigs Ann. Chem. *642*, 199 (1961).

3.4. Glycosides of C-Nor-D-homosteroids

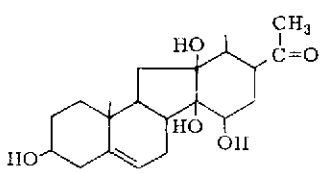
Ester glycosides are found in *Asclepiadaceae*; they are derived from C_{21}-genins and presumably possess the C-nor-D-homosteroid skeleton [see formula *(27)*] [53]. This was first observed with *Veratrum* alkaloids [54], recently also with *Fritillaria* alkaloids [55]. Biologically, the substances of this group too do not show any digitalis-like action. *Cornforth* [56] proposed formula *(27)* for sarcostin (the aglycone of glycosides from *Sarcostemma* species [53] as well as from *Pachycarpus lineolatus* and *Asclepias glaucophylla* [53]). *Mitsuhashi* and *Shimizu* [53] assigned formula *(28)* to lineolone (= deacylcynanchogenin). Recently [57] they were able to relate sarcostin directly to lineolone, so that at least one of the formulae *(27)* or *(28)* requires further modification.

The other substances belonging to this group must be structurally similar, although their exact structures are not known.

In plants, these genins are present in combination with various sugars and as esters of different acids. Up to the present, none of the genuine glycosides has been described in a pure form [58]. The sugars thus far observed are: D-digitoxose, D-cymarose (oleandrose), D-thevetose (digitalose) and D-glucose.



(27) Sarcostin [56], $C_{21}H_{34}O_6$



(28) Lineolone [53] (= Deacylcynanchogenin), $C_{21}H_{32}O_5$

[53] The drevosides from *Dregea volubilis* (*R. E. Winkler* and *T. Reichstein*, Helv. chim. Acta *37*, 721 (1954)), the glycosides from *Sarcostemma australe* (*J. W. Cornforth* and *J. C. Earl*, J. chem. Soc. (London) *1939*, 737; *1940*, 1443), "condurangin" from *Marsdenia condurango* (*F. Korte* and *H. Weitkamp*, Chem. Ber. *89*, 2669 (1956); *F. Korte* and *J. Ripphahn*, Liebigs Ann. chem. *621*, 58, (1959)), perhaps "vincetoxin" from *Vincetoxicum officinale* (see the last-named publication), certain glycosides from *Asclepias glaucophylla* (*J. M. Nascimento*, Ph.D. Thesis, Universität Basel, 1959), from *Pachycarpus lineolatus* (*E. Abisch, C. Tamm*, and *T. Reichstein*, Helv. chim. Acta *42*, 1014 (1959)), and from *Cynanchum caudatum* (*H. Mitsuhashi* and *Y. Shimizu*, Chem. pharm. Bull. (Tokyo) *7*, 749, 949 (1959); *8*, 313, 318, 738 (1960)), belong to this group.

[54] Veratramine, jervine, and cevine [see *K. J. Morgan* and *J. A. Barltrop*, Quart. Reviews *12*, 34 (1958)] belong to this group; they occur in plants partly as β-D-glucosides, and partly as esters.

[55] *Fritillaria roylei* (*Liliaceae*): *T. T. Chu, W. K. Hwang*, and *J. Y. Loh*, Acta chim. Sinicia *21*, 227, 232 (1955); Chem. Abstr. *51*, 444 (1957); *F. imperialis* (imperialin): *T. T. Chu, J. Y. Loh*, and *W. K. Hwang*, Acta chim. Sinicia *21*, 401 (1955); Chem. Abstr. *51*, 445 (1957); *H. Morimoto* and *S. Kimata*, Chem. pharm. Bull. (Tokyo) *8*, 302 (1960).

[56] *J. W. Cornforth*, Chem. and Ind. *1959*, 602.

[57] *H. Mitsuhashi* and *Y. Shimizu*, Chem. pharm. Bull. (Tokyo) *10* ,433 (1962).

[58] Very recently *K. Jaeggi* (Ph. D. Thesis, Universität Basel, 1963) was able to isolate glycosides from *Gongronema Taylorii* (*Asclepiadaceae*), which belong to this group. They are amorphous but pure according to thin-layer chromatography, and contain dihydro-sarcostin, thevetose, digitoxose, and cymarose as well as benzoic acid and cinnamic acid.

4. Summary of Results

Of the eight sugars listed in Table 1 that are predominant in group A and that participate almost exclusively in the formation of *O*-glycosides of group A, we find only D-glucose and L-rhamnose frequently in group B; in one case, D-xylose was also found. Instead, a large number of special sugars is found in group B; these are either altogether absent in group A or are found only in a very few cases [25a]. The presence of both fucoses is also noteworthy. In group A, the L-form is almost always found, while in group B, so far only D-fucose has been observed.

If several sugars, inclusing glucose, take part in the formation of the glycosides of group B then the glucose is always found "on the outside". The hexamethylose is therefore directly linked with the aglycone. Oligosaccharides with more than two sugars are always built linearly.

5. Discussion of Results

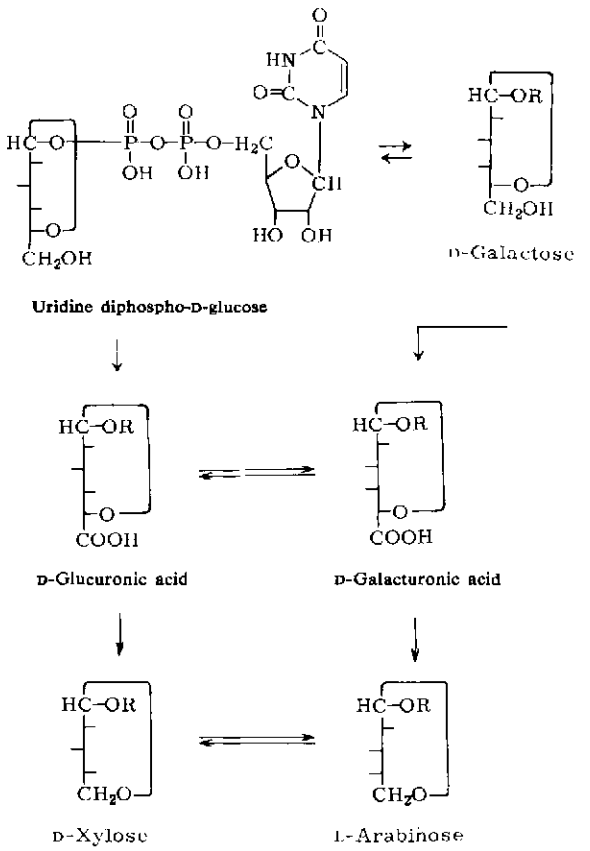
The striking difference in the structure of the sugars of groups A and B must be due to their different modes of biogenesis.

For the present, the preferential incorporation of the sugars listed in Table 1 into the glycosides of group A is the only factor well understood. These sugars are biogenetically related, probably in such a manner that the seven others originate from D-glucose. The conversion of D-glucose into D-galactose, D-glucuronic acid, D-galacturonic acid, D-xylose, and L-arabinose is well known and occurs by way of uridine pyrophosphate derivatives. The formula diagram 1 shows the reactions involved in mung bean seedlings (*Phaseolus aureus*) according to *Hassid* et al. [59]. It should be observed that the new sugars are formed as uridine pyrophosphate derivatives, in a form which is especially suited for transglycosidation onto a genin. The formation of D-ribose from D-glucose follows another path [16] which leads to D-ribose-5-phosphate. The latter is suited for the formation of nucleotides but not for the formation of glycosides. Recently, *Ginsburg* [60] found the probable path (see formula diagram 2) for the formation of L-fucose from D-glucose with enzymes from either *Aerobacter aerogenes* or mammalian tissue. Guanosine diphospho-

[59] *W. Z. Hassid, E. F. Neufeld*, and *D. S. Feingold*, Proc. nat. Acad. Sci. USA *45*, 905 (1959); see *E. F. Neufeld, V. Ginsburg, E. W. Putman, D. Fanshier*, and *W. Z. Hassid*, Arch. Biochem. Biophysics *69*, 602 (1957); *E. F. Neufeld, D. S. Feingold*, and *W. Z. Hassid*, J. biol. Chemistry *235*, 906 (1960); *D. S. Feingold, E. F. Neufeld*, and *W. Z. Hassid, ibid. 235*, 910 (1960); *G. Kessler, E. F. Neufeld, D. S. Feingold*, and *W. Z. Hassid, ibid. 236*, 308 (1961); *E. F. Neufeld* and *D. S. Feingold*, Biochim. biophysica Acta *53*, 589 (1691).

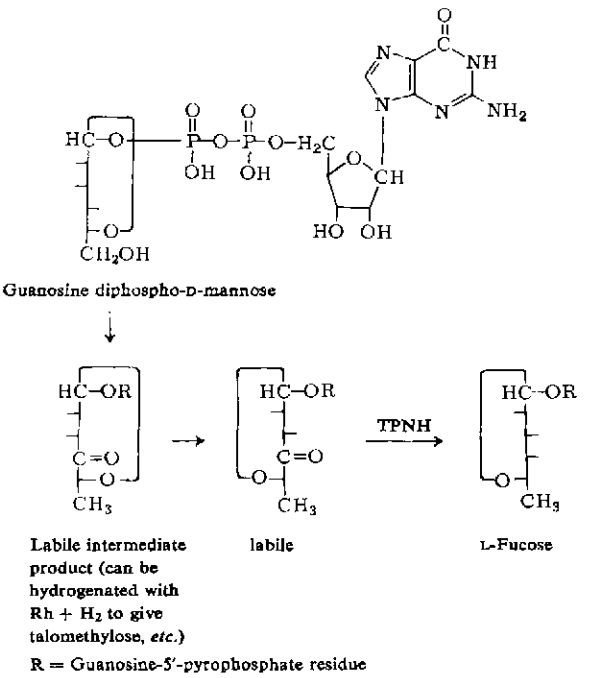
[60] *V. Ginsburg*, J. biol. Chemistry *235*, 2196 (1960); *236*, 2389 (1961); *D. W. Foster* and *V. Ginsburg*, Biochim. biophysica Acta *54*, 376 (1961) and the literature cited therein.

D-mannose is the starting material which was previously found in yeast [61] and red algae [62]. Earlier, guanosine diphospho-L-fucose was found in the milk of various animals [63]. Probably a similar path is followed in higher plants. As shown in formula diagram 2, L-fucose also arises in the form of a nucleotide derivative from which it can be transferred onto genins.



Formula diagram 1. Formation of hexoses and pentoses from uridine diphospho-glucose

Watkin and *Neish* [64] discuss an essentially similar path way for the formation of L-rhamnose in buckwheat (*Fagopyrum tataricum Gaertn.*). They were able to demonstrate that L-rhamnose of rutin in these plants arises from D-glucose without rearrangement of the carbon skeleton. They postulate that nucleotides are intermediate products and that the resulting L-rhamnose nucleotide transfers the sugar onto the aglycone. Free L-rhamnose is not incorporated into rutin. *Kornfeld* and *Glaser* [65] as well as *Pazur* and *Shuey* [65] described an enzyme which converts thymidine diphospho-D-glucose into thymidine diphospho-L-rhamnose. This compound too is able to transfer its L-rhamnose residue further, *e.g.* onto 3-quercetin-D-glucoside with formation of rutin [66].



Formula diagram 2. Formation of L-fucose from D-mannose

The preferential formation of group A glycosides with the eight sugars listed in Table 1 is understandable if it is assumed that other pentoses or deoxyhexoses do not originate in plants in an exactly corresponding manner [67]. A convincing explanation of the formation of group B glycosides is not possible at the present time, because their biogenesis, especially the biogenesis of their sugars, is still unknown. We must expect that it follows a different course from that of the biogenesis of the sugars which occur very frequently in group A. It is striking that the formation of digitoxose derivatives in *Digitalis* is limited to the cardenolides. In addition to the digitoxose derivatives of cardenolides, the same plant also forms large quantities of digitonin and other spirostane glycosides which contain normal sugars, *i.e.* sugars which are listed in Table 1. In the biogenesis of the glycosides which are included here in group B, the formation of anomalous sugars must be connected in some way with the side chains which are present or originating at the other end of the steroid molecule.

Received, June 29th, 1962 [A 231/51 IE]

[61] *E. Cabib* and *L. F. Leloir*, J. biol. Chemistry *206*, 779 (1954).

[62] *J. C. Su* and *W. Z. Hassid*, J. biol. Chem. *235*, PC 36 (1960). In red algae, *Porphyra perforata*, in addition to guanosine diphospho-L-galactose and guanosine diphospho-D-mannose, uridine diphospho-D-glucose, uridine diphospho-D-glucuronic acid and uridine diphospho-D-galactose were also present. It is noteworthy that L-galactose was present only as a guanosine derivative and D-galactose only as a uridine derivative.

[63] *R. Denamur*, *G. Fauconneau*, and *G. Guntz*, C. r. hebd: Séances Acad. Sci. *246*, 2820 (1958); *R. Denamur*, *G. Fauconneau*, and *G. Jarrige-Guntz*, Ann. Biol. anim. Biochem. Biophys. *1*, 74 (1961); *D. M. Carlson* and *R. G. Hansen*, Fed. Proc. *20*, 84 (1961).

[64] *J. E. Watkin* and *A. C. Neish*, Phytochemistry *1*, 52 (1961) and literature cited therein on similar reactions in microorganisms.

[65] *S. Kornfeld* and *L. Glaser*, Biochim. biophysica Acta *42*, 548 (1960); *L. Glaser* and *S. Kornfeld*, J. biol. Chemistry, *236*, 1795 (1961); see also *J. H. Pazur* and *E. W. Shuey*, J. Amer. chem. Soc. *82*, 5009 (1960); J. biol. Chemistry *236*, 1780 (1961); *R. Okazaki*, *T. Okazaki*, and *J. L. Strominger*, Fed. Proc. *20*, 85 (1961).

[66] *G. A. Barber* and *E. F. Neufeld*, Biochem. biophys. Research Commun. *6*, 44 (1961).

[67] It has been demonstrated repeatedly that 2-deoxy-D-glucose inhibits glycolysis in yeast and in various animal tissues, see *S. Barban* and *H. O. Schulze*, J. biol. Chemistry *236*, 1887 (1961) and literature cited therein, also *S. Barban*, *ibid. 237*, 291 (1962).

Automatic Activity Measurements during the Separation of Radioactive Compounds by Thin-Layer Chromatography

BY DR. P.-E. SCHULZE AND DR. M. WENZEL

HAUPTLABORATORIUM DER SCHERING AG., BERLIN (GERMANY)
AND PHYSIOLOGISCH-CHEMISCHES INSTITUT DER FREIEN UNIVERSITÄT, BERLIN (GERMANY)

A method was developed for continuous automatic measurement of the radioactivity distribution of weak β-emitters on open columns, for example, thin-layer chromatograms. It may be used for analytical separations, as well as for preparative separations on a semi-micro scale. During the measurements the substances are not contaminated by addition of other materials.

Introduction

Since its rediscovery by *Stahl* [1-4], thin-layer chromatography has been used principally for the solution of analytical problems [4a]. This paper will demonstrate the utility of this method for checking the purity of labelled compounds and for the preparative separation of substances labelled with tritium by the gas exchange procedure of *Wilzbach* [5,6]. In addition, chemically synthetized compounds labelled with radioactive elements that emit soft β-rays, for example ^{14}C-labelled steroids or ^{35}S-labelled sulfonamides, can be measured directly and separated from impurities on the thin-layer plates.

Formerly, paper chromatography, gas chromatography, and partition processes were used to check the purity of such compounds. In the latter two cases, however, accurate measurement of the radioactivity requires complicated apparatus. In some cases, paper chromatography has also been used for the preparative separation of labelled compounds; however, this procedure is not well adapted for this purpose owing to the low capacity of the paper sheets, especially for lipophilic substances [6].

Principles

a) Analytical Methods

Since thin-layer chromatography is essentially a separation on an open column, it offers the possibility of direct measurement of radioactive substances. For this purpose, a proportional gas-flow counter [*] tube with an extremely flat aperture plate was developed (Fig. 1).

The aperture has no projecting parts, hence, the chromatogram can be guided along on a carriage situated directly below the aperture slit (distance from the surface of the layer to the interior of the counter tube: 1–3 mm).

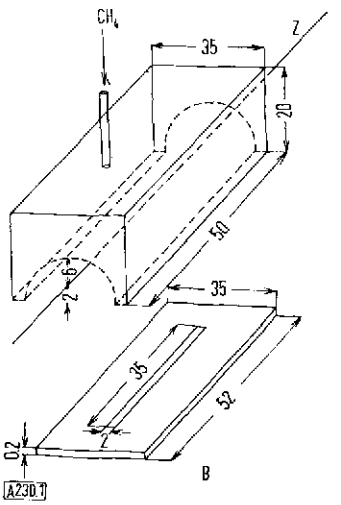


Fig. 1. Gas flow counter with an extremely flat aperture plate (B) for measurement of weak β-emitters on thin-layer chromatograms. The aperture plate is attached to the counter tube without projecting parts. Z = counter wire (30 μ diameter). The measurements are given in mm.

With this arrangement, soft β-ray emitters – including tritium – can be measured with high radiation yields. The distribution of the radioactivity is recorded via a cathode follower (connected to the counter tube) and a scaling unit with a synchronized recorder [**].

Calibration curves for ^{14}C and ^{3}H were prepared using thin-layer plates with a layer 0.25 mm thick of Silica Gel G (E. Merck) as layer material. Testosterone labelled with ^{14}C in the 4-position (specific activity 0.016 mc/mg), and estradiol labelled with ^{3}H in the 6- and 7-positions (specific activity 1.3 mc/mg) were used as standard substances. Fig. 2 shows the calibration curve for ^{3}H. With the lowest activity measured, the error is naturally at a maximum; *e.g.* for 0.0001 μc ^{14}C $\sigma_M = \pm$ 8 % and for 0.1 μc ^{3}H $\sigma_M = \pm$ 9.3 %. For activities

$$\sigma_M = \pm \sqrt{\frac{\Sigma\Delta^2}{n-1}} \quad ; n = 10$$

[1] *E. Stahl*, Chemiker-Ztg. *82*, 323 (1958).

[2] *E. Stahl*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *292*, 411 (1959).

[3] *E. Stahl*, Angew. Chem. *73*, 646 (1961).

[4] Dünnschicht-Chromatographie. Brochure of E. Merck, Darmstadt (Germany) 1960.

[4a] Compare also *K. Randerath*: Dünnschicht-Chromatographie. Verlag Chemie, Weinheim/Bergstr. 1962.

[5] *K. E. Wilzbach*, J. Amer. chem. Soc. *79*, 1013 (1957).

[6] *M. Wenzel* and *E. Schulze*: Tritium-Markierung. W. de Gruyter, Berlin 1962.

[*] We wish to thank Mr. *Bust*, precision mechanic at the Physiologisches Institut der Freien Universität, for the manufacture of the counter tube (patent applied for on December 7th, 1961).

[**] Manufactured by Laboratorium Prof. Berthold, Wildbad/Schwarzwald (Germany).

greater than 0.1 μc for ^3H, and 0.001 μc for ^{14}C, the error is less than ± 3 %.

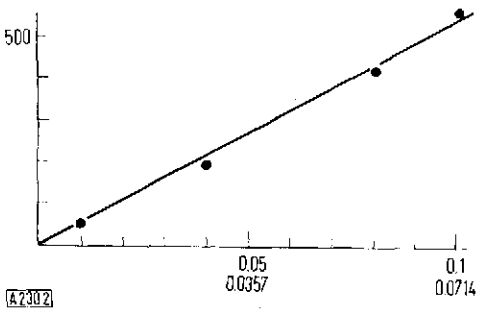


Fig. 2. Dependence of the radioactivity measured (average of 10 measurements) on the amount of radioactivity applied. Layer material: Silica Gel G (E. Merck). Layer thickness: 0.25 mm. Developing agent: cyclohexane/ethyl acetate (90:60, by volume). Increasing amounts of a methanolic solution of estra-6,7-diol-$^3H_2$ were initially applied as spots at intervals of approximately 15 mm. Ordinate: counts/min. at the activity maximum. Abscissa: Upper numbers: radioactivity applied [μc]; lower numbers: amount of substance applied [μg].

If several substances of different R_f values are present on a thin-layer chromatogram, the determination of their relative radioactivities is even more accurate, since changes in the distance between plate and counter tube aperture are more readily obviated in a single measurement using a single plate than when different plates are inserted in sequence. With tritium, a small change in the plate-counter distance causes an especially large error, because of the low average range of its β-particles in air (approximately 4.5 mm). With layer thicknesses of 0.25 mm, the efficiency of the measurement is approximately 40 % for ^{14}C and approximately 0.3 % for tritium. For tritium this is less than the efficiency attainable by the use of liquid scintillation spectrometry described by *Scharpenseel* [7], but the simplicity of the present method compensates for this disadvantage, especially since the sample is not contaminated in the measurement and can be recovered.

[7] *H. W. Scharpenseel* et al., Z. analyt. Chem. *180*, 81 (1961); *182*, 1 (1961); Angew. Chem. *73*, 615 (1961).

b) Preparative Separations

In labelling by gas exchange according to the method of *Wilzbach*, sometimes radioactive impurities appear, which are negligible in weight, although their specific activities are greater than that of the main product. These by-products (*e.g.* compounds where double bonds have been hydrogenated with tritium) can often be removed only with difficulty by reprecipitation or recrystallization. Purification is best carried out by recrystallization and chromatography. The separation of impurities from a nucleoside labelled with ^3H according to *Wilzbach* by thin-layer chromatography [8] has proved satisfactory.

In combination with the present method of measurement, preparative thin-layer chromatography offers the possibility of combining easy measurement with sharp separations. A slight increase in the thickness of the layer does not alter the excellent separating properties of normal thin-layer plates and permits separations on a preparative scale [9]. Examples are given in Table 1 and Fig. 3. The fact that the counting efficiency decreases with increasing layer thickness is not important, since, in the separation of mg quantities, large activities are to be expected anyway.

Table 1. Compounds separated by thin-layer chromatography on a preparative scale. Layer material: Kieselgel G, Merck (Germany)

Substance applied	Amount added [mg.]	Developing agent	Substance isolated	Amount isolated [mg.]	Specific activity [μg/mg.] [*]
Δ^1-Androsten-17β-ol-3-one-^3H [+]	20	[a]	Δ^1-Androsten-17β-ol-3-one-^3H	12	0.6
			Androstan-17β-ol-3-one-^3H	3 [**]	1.1 [**]
1-Methyl-Δ^1-androsten-17β-ol-3-one-^3H [+]	20	[a]	1-Methyl-Δ^1-androsten-17β-ol-3-one-^3H	10	22.4
			1β-Methyl-androstan-17β-ol-3-one-^3H	2.7 [**]	5.7 [**]
Androstane-3,17-dione-^3H [+]	20	[a]	Androstane-3,17-dione-^3H	15	2.5
Sulfanilamido-*N'*-5-methoxypyrimidine-^{35}S [++]	40	[b]	Sulfanilamido-*N'*-5-methoxypyrimidine-^{35}S	30	—
N-Methylthiourea-^{35}S [++]	40	[b]	*N*-methylthiourea-^{35}S	28	—

[*] Measurement of the radioactivity of an infinitely thin layer (1 γ/sq. cm.) of pure substances on a planchet, using a methane flow counter (FH 407) with a 44 % efficiency and an average error of ± 6 % [6, 10].

[**] In the elution, small amounts of carrier substance were added.

[+] Labelled by the *Wilzbach* procedure.

[++] Highly impure synthesis residues.

[a] Cyclohexane/ethyl acetate (3:2 v/v).

[b] Butanol saturated with conc. NH_3.

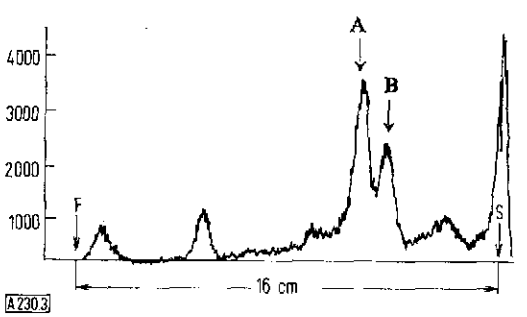


Fig. 3. Chromatography of crude Δ^1-androsten-17β-ol-3-one-^3H on Silica Gel G (E. Merck). Layer thickness: 0.9 mm. Developing agent: cyclohexane/ethyl acetate (90:60, v/v). On scratching off zones A and B no mixtures of A and B were obtained, as was shown by test-chromatograms. That the radioactivity between A and B does not return to zero is partly due to the geometry of the flow counter.
S = start F = front
A = androstan-17β-ol-3-one-^3H
B = Δ^1-androsten-17β-ol-3-one-^3H
Ordinate: counts/min.

[8] *M. Wenzel* and *H. P. Körtge*, Naturwissenschaften *48*, 431 (1961).

[9] *P. Schmialeck* succeeded in separating 250 mg. of a lipoid ester mixture on a silicagel layer 20 cm^2 in size and *ca.* 1 mm. thick (personal communication).

[10] *J. Rydberg*, Acta chem. scand. *12*, 399 (1958).

Material labelled with tritium by the *Wilzbach* procedure [6] can be applied without preliminary purification. Only loosely attached tritium is previously removed. After chromatography and measurement of the radioactivity, the width of radioactive band given by the recorder are transcribed onto the chromatogram, and the silica gel of the different bands is scraped off; the sample is eluted and worked up. Then an aliquot portion is tested for radioactive homogeneity on a further chromatogram and purified, if necessary, by sublimation or recrystallization.

The distribution of radioactivity can also be determined by autoradiography. For the determination of tritium by this procedure, scintillators such as 1,4-diphenylbenzene or 1,4-di-(5-phenyloxazol-2-yl)benzene are admixed with the developing liquid. Subsequent spraying of the chromatogram with a solution of scintillator is also possible [11]. The darkening of superposed film plate is evaluated photometrically. This method of recording, however, requires considerable time.

Experimental Procedure

Commercial counting apparatus supplied by Frieseke and Höpfner Co. (FH 49) was used as scaler and H.T.-unit, together with cathode follower FH 484; the gas flow counter was attached directly to the latter.

The counter tube potential was 2100 volts; methane was used as counter gas. The flow velocity was one bubble per second; the background counting rate attained in this standardization not more than 30 counts/min. For the measurement of the radioactivity distribution, the thin-layer plate was placed on a small carriage moving on a rail. By means of a water-level and screw adjustment, the carriage with the plate is adjusted to the horizontal. The carriage was drawn along by means of a cord coiled around the conveyor cylinder of a paper chromatogram scanning apparatus FH 552 (Frieseke and Höpfner), and the activity recorded by a synchronized recorder. The distance from the surface of the layer to the counter tube aperture was not greater than 1 mm. Stepwise measurement by means of a preset count device and a time recorder is also possible.

In order to prepare uniformly coated glass plates, the coating apparatus shown in Fig. 4 was used. By placing aluminum foil on the poly(vinyl chloride) support to the right and left of the glass plate, the thickness of the layer can be varied. To make the coating, the sliding bar is placed in front of the glass plate, the slurry is poured on, and the sliding bar is drawn slowly and uniformly over the glass plate. The plates are dried for one hour at 120 °C, and then stored in a desiccator over calcium chloride.

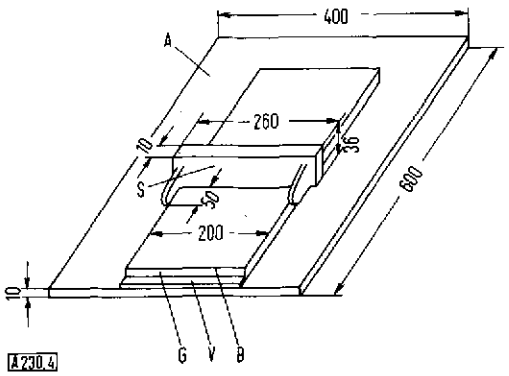


Fig. 4. Apparatus for coating glass plates for thin-layer chromatography. The bottom plate (A) and the coating apparatus (S) are made of poly(vinyl chloride). The measurements are given in mm. See text for details.

G = glass plate, 4 mm. thick
B = layer material. V = plastic ledge

The substances to be chromatographed were dissolved in enough methanol or benzene so that a strip of about 3 cm broad could be applied across the whole width of the plate. In order not to disturb the layer, the solution was applied with a capillary in drops, at intervals of 3 mm. The capillary opening should be at least 0.6 to 0.8 mm in diameter in order to avoid clogging. Ten to forty mg of the substance were applied.

After development, the chromatograms were dried at 60 °C (in some cases in a vacuum drying oven), and the radioactivity was measured as described. The radioactive zones were marked on the basis of the distribution of radioactivity given by the recorder, and were scraped off. Instead, the non-radioactive zones can also be scraped off, and the radioactive substance can be eluted with a solvent from the remaining bands. It is frequently expedient to measure the right and the left edge of the plate in order to determine whether the bands have run uniformly.

For elution of steroids, ethyl acetate which had been washed with water and dried over sodium sulfate was used. After concentration of the solvent *in vacuo*, frequently more of the crude material was obtained than had been added (calcium sulfate from binder?).

This possibly can be avoided by pretreating the layer material with the eluting solvent.

We wish to thank Miss D. Muchow and Miss G. Fischer for their interested and diligent cooperation.

[11] *P. Schmialeck*, personal communication.

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Problems in the Theoretical Treatment of Reactions Occurring at Easily Passivated Metal Anodes [*]

BY PROF. DR. K. J. VETTER

FRITZ-HABER-INSTITUT DER MAX-PLANCK-GESELLSCHAFT, BERLIN-DAHLEM (GERMANY)

Industrial anode materials should show small tendency to corrode in order to have a long life and, from energy considerations, should give low anodic overvoltages. The maximum corrosion in the active state in the presence and absence of complex formation is discussed on the basis that diffusion processes are limiting. The discussion also considers the formation of porous outer films of more difficultly soluble corrosion products. Corrosion in the passive state is treated as a property of the nonporous passive layer; several examples are presented, and the Flade potential for transitions from the active to the passive state and its properties are discussed. The influence of pH and complexing agents on passive corrosion is treated. – Anode processes or, as treated here, redox processes such as the evolution of oxygen or chlorine can take place at passive electrodes only if the passive film has a sufficiently high electron conductivity. This is not the case with films on aluminum, titanium, and tantalum, for example. The overvoltage on passive anodes is a property of the passive film at the electrolyte side of the phase boundary. – Semiconducting materials and graphite as anode materials are discussed separately.

In industrial anodic processes one of the most important demands placed upon the anodic material is that it should be attacked either not at all or at least only to a small degree during the reaction, since this leads to erosion of the electrode. Moreover, even on gradual anodic dissolution of the anode material, the electrolyte becomes contaminated with the products of this reaction. Furthermore, a definite amount of current is consumed in such corrosion processes, although, admittedly, this may not be critical from an economic point of view. This then presents the problem of preventing corrosion of anode materials.

The industrial anode process to be discussed is the electrochemical oxidation of an electrolyte constituent, *i.e.*, an anodic redox process. Examples are:

the oxidation of Cl^- to Cl_2 gas:

$$2\,Cl^- \rightarrow Cl_2 + 2e^-$$

the formation of oxygen, according to the equation:

$$2\,H_2O \rightarrow O_2 + 4\,H^+ + 4e^-$$

or the same thing in alkaline solution:

$$4\,OH^- \rightarrow O_2 + 2\,H_2O + 4e^-$$

The rates of both electrode processes, *i.e.*, anodic corrosion and the anodic oxidation-reduction process, depend in general upon the relative potential of the anode in comparison to a reference electrode (*e.g.*, normal hydrogen electrode) and upon the composition of the electrolyte. Otherwise, both processes take place completely independently of one another. The only connecting factor is the electrode potential, which controls the rate of the two independent processes. The two rates, the corrosion rate of the anode material and the oxidation rate of the redox process, can be expressed according to Faraday's Law by a corrosion current density i_c and an oxidation current density i_a. Both current densities are strictly proportional to the corresponding rates. The total current density i, which is measured in an external circuit, is the sum of the two partial current densities:

$$i = i_a + i_c$$

as is seen in Fig. 1. For industrially utilizable anodes, i_c is very much smaller than i_a over the normal working potential range, so that i_a is practically identical with i. Nevertheless, the complete process must be discussed on the basis of Fig. 1.

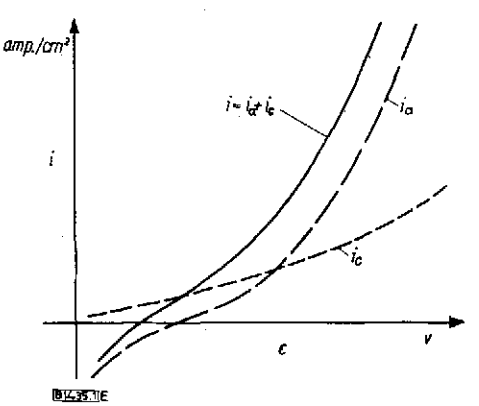


Fig. 1. Superposition of the corrosion current density, i_c and the oxidation current density i_a of an anodic process to give the total current I on the basis of the schematic curve of current density *vs* potential

Electrolytic Corrosion of Anode Materials

Potential-dependent corrosion of anodic material in the active state [$i_c(\varepsilon)$], where the anode surface is not covered by a protective film must be differentiated from passive corrosion, where the anode is covered with a

[*] Presented at a meeting of the GDCh-Fachgruppe Angewandte Elektrochemie (Applied Electrochemistry Division of the German Chemical Society) Oct. 5th–6th 1961, in Frankfurt-Höchst, Germany.

thin passive layer that prevents direct contact between the metal and the electrolyte. The dependence of the corrosion current density i_c on the potential can, in general, be represented by a characteristic curve such as is shown schematically in Fig. 2. Above the Flade potential ε_F, which is characteristic for each metal, the metal surface becomes covered with a protective, nonporous film. Dissolution of the active metal according to the equation

$$Me \rightarrow Me^{z+} \cdot aq + z \cdot e^-$$

then ceases. The metal is passivated.

Active Corrosion

Active metals have no industrial importance at the high positive operating potentials which are generally required. The discussion of active corrosion here is, however, quite important, since this type of corrosion can sometimes occur before passivation of the metal takes place, as is shown schematically in Fig. 2 [1]. The following reaction products are to be differentiated:

1. hydrated metal ions
2. complexed soluble metal ions
3. porous protective films of difficulty soluble metal salts

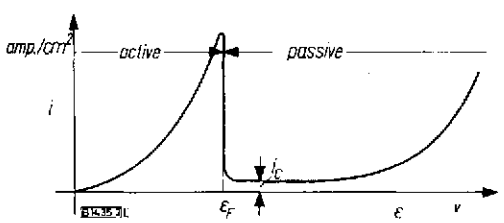


Fig. 2. Schematic representation of the characteristic dependence of the corrosion current density i_c in the active and passive states on the potential (ε_F = Flade potential)

From thermodynamic considerations, active corrosion can occur only when the electrode potential is more positive than the equilibrium potential ε_0. This latter value can be determined with the aid of the Nernst

$$\varepsilon_0 = E_0 + (RT/zF) \cdot \ln a_{Me^{z+}}$$

equation from the concentration c_{Me} (more accurately, the activity $a_{Me^{z+}} \approx c_{Me^{z+}}$). The difference between the electrode potential, $\varepsilon(i_c)$ and the equilibrium potential ε_0 is the overvoltage

$$\eta(i_c) = \varepsilon(i_c) - \varepsilon_0.$$

This overvoltage is composed of charge-transfer, diffusion, reaction, and crystallization overvoltages. Even when the charge-transfer, reaction, and crystallization overvoltages are very small, there still remains the residual diffusion overvoltage η_d, which is connected with the accumulation of metal ions formed at the metal surface. This minimum overvoltage has a corresponding maximum corrosion current density, $i_{c(max)}$ at a given potential. As a result of the corrosion, the accumulation of metal ions becomes so high that it leads to formation of a concentration gradient sufficiently large to permit the diffusion of surface metal ions into solution through the diffusion film of thickness δ.

The concentration intensification in the electrolyte adjacent to the surface can be inferred from Fig. 3. According to Fick's Law of Diffusion, the quantity diffusing is $D(c-\bar{c})/\delta$ mole/cm²·sec., where D is the diffusion coefficient, δ is the diffusion layer thickness, $\bar{c}$ is the metal ion concentration in the bulk of the solution, and c is the concentration of metal ions immediately adjacent to the surface. This quantity is equal to the quantity dissolved according to Faraday's law, i/zF mole/cm²·sec., where z is the valence and F is the Faraday constant; thus:

$$\frac{i}{zF} = (c-\bar{c}) \cdot \frac{D}{\delta}.$$

Hence the concentration of metal ions at the surface becomes

$$c = \bar{c} + \frac{\delta}{zF \cdot D} \cdot i \ (\text{mole/cm}^3)$$

When substituted into the Nernst expression (in units of mole/liter), this concentration gives

$$(1) \quad \varepsilon = E_0 + \frac{RT}{zF} \cdot \ln \left(\bar{c} + \frac{\delta \cdot 10^3}{zF \cdot D} \cdot i \right)$$

where i is the aforementioned maximum corrosion current density in amp/cm². For a given potential ε, the current density i is greater, the smaller $\bar{c}$. When $\bar{c} = 0$, i attains its maximum value, $i_{c(max)}$, and Eq. 1 becomes

$$(2) \quad \varepsilon = E_0 + \frac{0.059}{z} \cdot \log (a \cdot i_{c\,(max)})$$

$$\text{where } a = \frac{\delta \cdot 10^3}{zF \cdot D}$$

Since the values of δ, z, and D in the expression for a in Eq. 2 vary only over a very restricted range in the most diverse cases, the value of $a = 10^3 \times \delta/zFD$ is also limited to a very restricted range. For $1\times10^{-3} < \delta < 5\times10^{-2}$ cm (vigorous agitation on the left of the inequality, natural convection without stirring on the right) and with $0.5\times10^{-5} < D < 3\times10^{-5}$ cm²/sec, the value of a can fall between 1/3 z and 100/z.

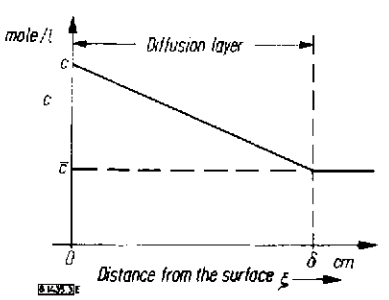


Fig. 3. Diffusion through a stationary (Nernst) diffusion layer of thickness δ

In Fig. 4, Eq. 2 is plotted within the given limits of a and for valences of 1, 2 and 3. The corrosion current density i_c can also be expressed as an erosion rate, *e.g.*, in mm per year. At an average equivalent volume of metal of 5 cm³ per equivalent, a current density of 6.5 μamp/cm² corresponds to a very low erosion rate, *viz.* 0.1 mm per year. From Fig. 4 it can be seen that this erosion

[1] Cf. *K. J. Vetter*: Elektrochemische Kinetik. Springer, Berlin/Göttingen/Heidelberg 1961, p. 603.

rate is certainly not exceeded so long as the electrode potential remains more negative than the standard electrode potential of the metal by 300, 200, or 100 mv for z = 1, 2, and 3, respectively. It is assumed hereby that the corrosion product is a soluble metal ion not bound in a complex. At low concentrations in the electrolyte of the order of 10^{-5} to 10^{-3} mole/liter this corrosion would even be completely repressed, according to Eq. 1.

For the second case, where complexed soluble metal ions are formed, *e.g.*

$$Pt + 4\,Cl^- \rightarrow PtCl_4^{-2} + 2e^-$$

a very similar expression for the maximum corrosion current density $i_{c(max)}$ as a function of potential can be applied. In this case the soluble complexed metal ion concentrates at the surface of the electrode. The general equation for the corrosion resulting from the electrode reaction is

$$Me + \nu A^{-n} \rightarrow MeA^{+z-\nu n} + ze^-$$

with the dissociation constant for the complex

$$K = \frac{a_{Me^{z+}} \cdot a_A^{\nu A}}{a_K}$$

In place of the standard electrode potential of Eqs. 1 and 2 and Fig. 4, a new expression appears:

$$E^* = E_0 + \frac{RT}{zF} \cdot \ln K - \frac{\nu_A}{z} \cdot \frac{RT}{F} \cdot \ln a_A \qquad (3)$$

where a_A is the activity ($\simeq$ concentration) of the complex-former A^{-n} (in the example, Cl^- ion), ν_A is the number of complex forming ions (here $\nu_A = 4$ Cl^- ions) and z is the number of electrons involved in the over-all electrode reaction (here $z = 2$).

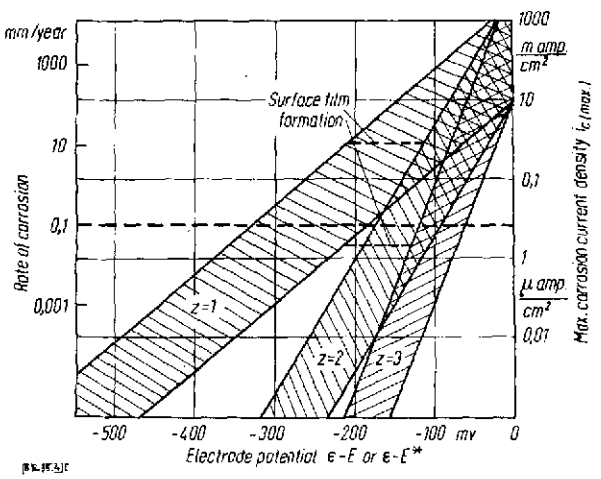


Fig. 4. Maximum active corrosion current density $i_{c(max)}$ as a function of the potential $\varepsilon - E_0$ [difference from standard potential E_0 or E^* (Eq. 3)] on formation of uncomplexed (E_0) or complexed (E^*) metal ions in the presence of pure diffusion overvoltage

Thus, in the presence of a complexing agent, the range of potential in which active corrosion is possible may under certain circumstances be shifted very far in the direction of more negative (less noble) values. This is important for corrosion-free transition from the active to the passive state, as often occurs with noble metals.

The third case, the formation of a porous, difficultly soluble surface film of metal salt, is interesting from the point of view of the industrial problem we are discussing insofar as most metal salts possess either no or only very little electron conductivity and therefore (cf. p. 589) the industrial redox process can occur only in the pores, which are mostly small. For this reason, the anode process is very much impeded. The film acts as an insulator between the metal and the electrolyte. Such a film will be formed above a potential ε^* which can be calculated by the Nernst equation for an electrode of the second kind:

$$(4) \quad \varepsilon^* = E_0 + \frac{RT}{zF} \cdot \ln P - \nu_A \frac{RT}{zF} \cdot \ln a_A$$

where P is the solubility product. An example would be the formation of lead chloride according to the equation

$$Pb + 2\,Cl^- \rightarrow PbCl_2 + 2e^-$$

where a_A is the activity ($\simeq$ concentration of the anions that form the difficultly soluble salt with the metal ions, ν_A is the required number of anions, and z is the number of electrons involved (electrode reaction valence) in the over-all electrode reaction. If the substance forming the porous surface film consists of a complex metal salt, then Eq. 4 becomes somewhat more complicated, since the dissociation constant of the complex and the concentration of the cation must also be included.

Below this potential, the active electrode behaves in the same way as in cases 1 and 2 (soluble metal salt) with regard to the maximum corrosion current density. Above this potential, a limiting current density will often develop, which is equivalent to the rate of dissolution of the surface film. This equivalent current density is equal to the corrosion current density $i_{c(max)}$ (ε^*) at potential ε^*, since even at more positive potentials the solution on the electrolyte side of the surface film is satured. The total surface of the pores adjusts itself in such a way that the average solution rate over the entire electrode surface becomes equivalent to the current density $i_{c(max)}$ (ε^*). A typical example is the coating of iron with a porous film of $FeSO_4 \cdot 7H_2O$ [2]

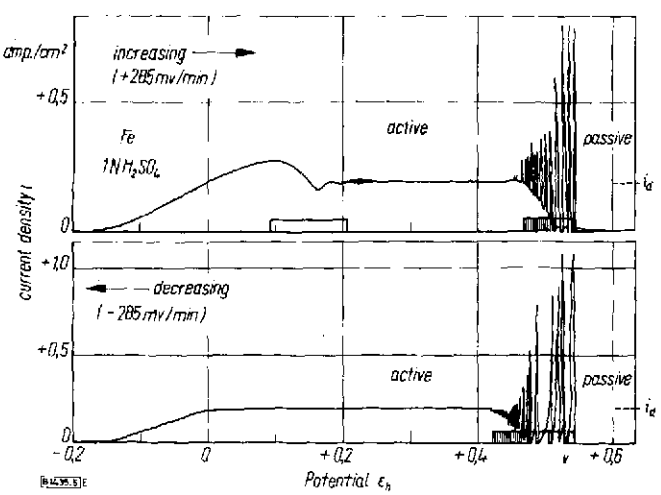


Fig. 5. Curve of current density *vs*, potential for the passivation and activation of iron in 1 *N* H_2SO_4, after *Franck* [3], with increasing and decreasing potential (from *K. J. Vetter* [1])

[2] *U. F. Franck*, Z. Naturforsch. *4a*, 378 (1949).

[3] *U. F. Franck*, Ph. D. Thesis, Universität Göttingen (Germany) 1954.

prior to its anodic passivation in sulfuric acid. Fig. 5 shows the pertinent curve found by *Franck* [3] of the current density *vs.* potential, including limiting current density of active corrosion $i_{c(max)}$ during coating of the surface with porous ferrous sulfate. In Fig. 4 this behavior is presented as a limiting current (dashed line).

Passive Corrosion

An industrially useful anode material should probably exist mainly in the passive state. The electrode is therefore at a potential above the Flade potential [4–7] and is covered with a nonporous protective film [5,8], which is usually an oxide.

For this reason, the electrolyte is unable to attack the metal surface directly. The passive film, however, is dissolved by this electrolyte at a definite rate. If the metal is to remain passive, the passive film must remain intact, *i.e.* a new passive film must be formed electrochemically according to the equation

$$Me + n\,H_2O \rightarrow MeO_n + 2n\,H^+ + 2n\,e^-$$

at the same rate at which the original film dissolves in the electrolyte according to the equation [9]:

$$MeO_n + 2n\,H^+ \rightarrow Me^{2+} + n\,H_2O$$

Adding the two above equations, we get the net corrosion reaction, whose rate can be determined from a

$$Me \rightarrow Me^{2n+} + 2n \cdot e^-$$

current density, *viz.* the corrosion current density i_c (amp/cm²), using Faraday's law. It is exactly equal to that current density with which the passive film must be anodically reformed. Corrosion in the passive state is, therefore, a property of the passive film and the phase boundary between the passive film and the electrolyte, but is not a direct property of the anode material.

The same process can also be represented somewhat differently. It will be recognized from the following phase model, which describes the process at the phase boundary, that the formation of oxide must be connected with a migration either of metal ions to the electrolyte side or of oxygen ions to the metal side of the phase boundary. In the steady state, when oxide is neither being formed nor decomposed, this same number of metal ions are hydrated (solvated) and migrate through the passive film/electrolyte phase boundary into the electrolyte. Thus, this process, depicted by broken arrows in Fig. 6, is the corrosion process. The migration through the passive film is caused by the strong electric field within the film, the magnitude of which lies between 10^6 and 10^7 volts/cm.

The magnitude of this corrosion, *i.e.*, the magnitude of the corrosion current density i_c, depends in general upon the potential, the pH, the nature of the anions (for example Cl^- ions), and the temperature. These variables have very different effects upon different metals. In the following section some examples are discussed.

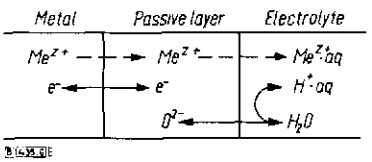


Fig. 6. Phase model for an oxide-coated electrode

The corrosion current density in passive iron is independent of the potential over a wide range of potentials [5,10] and starts to increase only in the potential range of anodic formation of oxygen (see Fig. 7), according to investigations

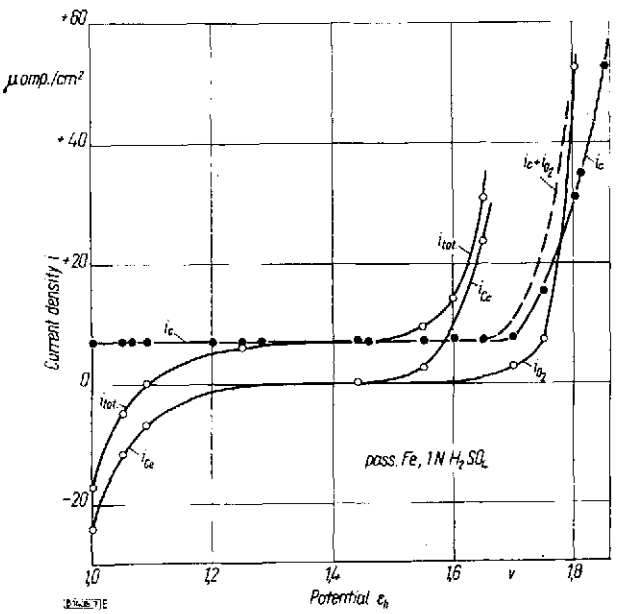


Fig. 7. Passive iron. Steady total current i_{tot}, corrosion current density i_c, partial current density of oxygen evolution, i_{O_2}, and partial current density of the Ce^{4+}/Ce^{3+} redox process, i_{Ce}, as a function of potential ε_h in 1 N H_2SO_4 + 0.0125 M Ce^{4+} + 0.0125 M Ce^{3+} (after *Franck* and *Weil* [10])

of *Frank* and *Weil* [10]. According to *Vetter* [11], here the iron goes directly into solution as Fe^{3+}, while in the active state, it dissolves as Fe^{2+} ion. Corrosion decreases with increasing pH [11].

Passive nickel shows a different behavior. According to *Vetter* and *Arnold* [12,13], at first the corrosion increases with increasing potential, then passes through a maximum and then decreases, as shown in Fig. 8. This decrease in the corrosion is perhaps due to some chemical change in the composition of the passive film. There is no data concerning corrosion at still more positive potentials. It is noteworthy that the corrosion is almost independent of the pH value over a wide potential range.

[4] *F. Flade*, Z. physik. Chem. *76*, 513 (1911).

[5] *K. J. Vetter*, Z. Elektrochem. *55*, 274 (1951).

[6] *K. F. Bonhoeffer* and *K. J. Vetter*, Z. physik. Chem. *196*, 142 (1950).

[7] *K. J. Vetter* in *H. Fischer, K. Hauffe*, and *W. Wiederholt:* Passive Films and Protective Layers. Springer, Berlin/Göttingen/Heidelberg 1956, p. 72.

[8] See reference [7], especially pp. 77–79.

[9] These reactions can also, of course, be more complicated, *e.g.* by the formation of complex ions.

[10] *U. F. Franck* and *K. G. Weil*, Z. Elektrochem. *56*, 814 (1952).

[11] *K. J. Vetter*, Z. Elektrochem. *59*, 67 (1955).

[12] *K. J. Vetter* and *K. Arnold*, Z. Elektrochem. *64*, 244 (1960).

[13] The increase has also been established by *G. Okamoto, H. Kobayashi, M. Nagayama*, and *N. Sato*, Z. Elektrochem. *62*, 775 (1958).

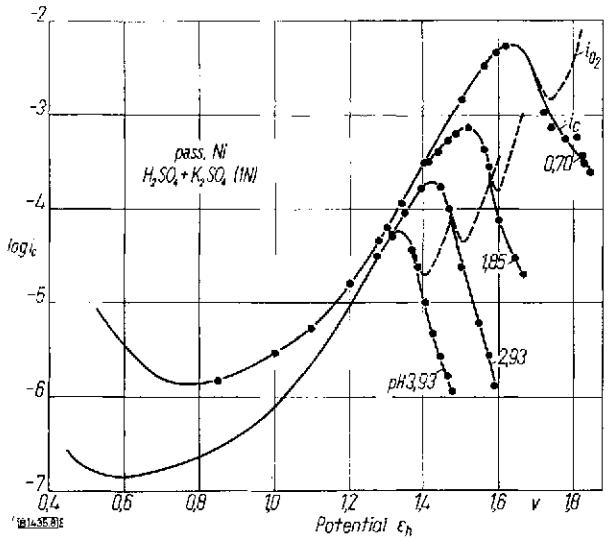


Fig. 8. Corrosion current density i_C (amp/cm²) for passive nickel in $H_2SO_4 + K_2SO_4$ (total concentration 1 N) for various pH values (0.3, 1.85, 2.93, 3.93) [solid lines]. The dashed curve represents an electrode with simultaneous evolution of oxygen (after *Vetter* and *Arnold* [12])

According to *Oliver* [14,15], the behavior of chromium and chromium-iron alloys is still another matter, as shown in Fig. 9. Two clearly distinct regions with markedly different corrosion may be discerned. Below ε_h = 1.2 v, chromium goes into solution as Cr^{3+} ion, while above 1.2 v, it goes into solution as CrO_4^{2-} ion [14,15]. The corrosion mechanism changes, therefore; the corrosion current density depends strongly upon the composition of the alloy.

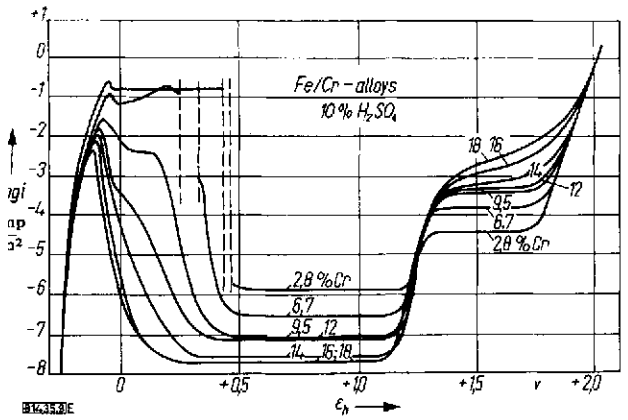


Fig. 9. Static potential current density *vs.* potential curve for various iron-chromium alloys in 10 % H_2SO_4 (*ca.* 2 N) after *Olivier* [14]

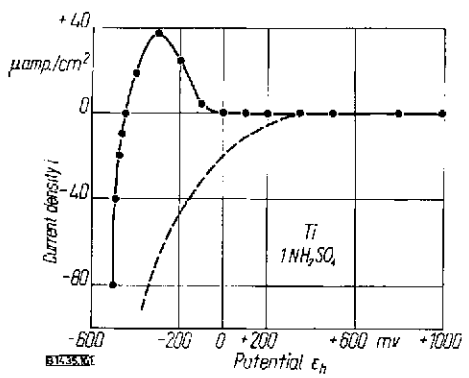


Fig. 10. Current density *vs.* potential curve of titanium in H_2SO_4 at 25 °C; (after *Vetter* and *Oelsner* [16]). Solid line: in stationary states; dashed line: measured rapidly after anodic treatment

[14] *R. Olivier*, Ph. D. Thesis, Leyden (Holland) 1955.

[15] *M. Prazak, V. Prazak*, and *V. Cihal*, Z. Elektrochem. *62*, 739 (1958).

Following passivation, titanium shows no detectable corrosion in acid solution (see Fig. 10) [16] in the absence of a complex-former, such as fluoride ion. In acid solution, aluminum does not show any evidence of corrosion either. In alkaline solution, however, the OH^- ions present bind the Al ion in the form of the AlO_3^{3-} complex, so that the corrosion of the passive film is increased to such an extent that the term "passivity" is practically no longer applicable. However, neither passivated Ti nor passivated Al is useful as an anode material in any case, since the respective films are nonconducting to electrons (cf. p. 589).

In order that the metal be at all in the passive state, its potential must be more positive [5–7] than the Flade potential [4]. At the Flade potential ε_F, the metal passes from the active to the passive state or vice versa. It is

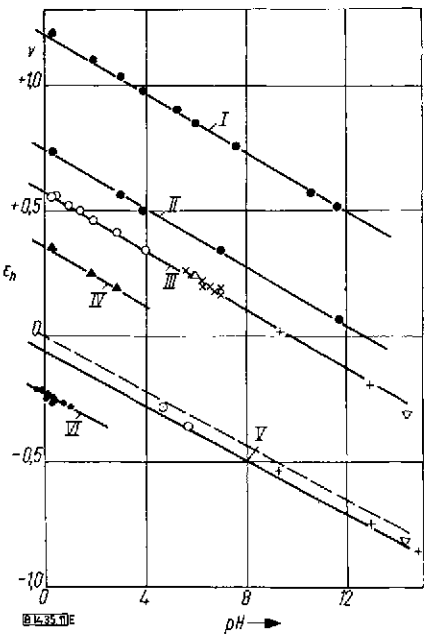


Figure 11. pH-Dependence of the experimental Flade-potential of various metals:
I Gold (−5 μa/cm²) according to *Vetter* and *Berndt* [24]
II Palladium (−20 μa/cm²) according to *Vetter* and *Berndt* [24]
III Iron (o o according to *Franck* [2], X X *Cortledge* [19]
Δ Δ *Weil* and *Bonhoeffer* [17], + + *Heusler, Weil* and *Bonhoeffer* [18]
∇ *Kabanov* et al. [20,21])
IV Nickel (according to *Arnold* and *Vetter* [23])
V Iron (+ + according to *Heusler, Weil* and *Bonhoeffer* [18]
∇ ∇ *Kabanov* et al. [20,21], o o *Vetter* and *Klein* [39])
VI Chromium (according to *Rocha* and *Lennartz* [22])
– · – · – · – hydrogen-electrode (1 atmosphere)

the potential at which the corrosion passes over to the usually small value of passive corrosion, as is shown schematically in Fig. 2 and for iron, chromium, titanium,

[16] *K. J. Vetter* and *G. Oelsner*, unpublished data; *G. Oelsner*, Ph. D. Thesis, Freie Universität, Berlin (Germany) 1961.

[17] *K. G. Weil* and *K. F. Bonhoeffer*, Z. physik. Chem. N.F. *4*, 175 (1955).

[18] *K. Heusler, K. G. Weil*, and *K. F. Bonhoeffer*, Z. physik. Chem., N.F. *15*, 149 (1958).

[19] *G. H. Cartledge* and *R. F. Sympson*, J. physic. Chem. *61*, 973 (1957).

[20] *B. N. Kabanov* and *D. Leykis*, Acta Physicochim. U.S.S.R. *21*, 769 (1946).

[21] *B. B. Lossev* and *B. N. Kabanov*, Zh. Fiz. Khim. *28*, 824, 914 (1954).

[22] *H. J. Rocha* and *G. Lennartz*, Arch. Eisenhüttenwes. *26*, 117 (1955).

[23] *K. Arnold* and *K. J. Vetter*, Z. Elektrochem. *64*, 407 (1960).

[24] *K. J. Vetter* and *D. Berndt*, Z. Elektrochem. *62*, 378 (1958).

palladium, and gold in Figs. 5, 9, 10, 12, and 13, respectively. For the Flade potential, ε_F, the pH dependence of an oxide electrode (second kind) was established for various metals as:

$$\varepsilon_F = E_F - 0.059 \cdot pH \qquad (5)$$

Figure 11 shows this dependence. The standard potential E_F has a characteristic value for each particular metal [25].

For various base metals, such as, Al, Ta, Ti, and Cr, the Flade potential is much more negative than the potential of a hydrogen electrode in the same solution. Thus, a passive film will form here anodically at an electrode in contact with an electrolyte in the absence of current flow with simultaneous equivalent evolution of hydrogen at the cathode and formation of a potential gradient. Thus, it is possible to attain the active states [26] of these metals only under special conditions.

In the case of noble metals, the Flade potential ε_F is also considerably more negative than their standard potentials, so that with increasing potential the metal becomes passive even before active corrosion (Fig. 4) can set in. Since the active maximum of the corrosion current density, such as that shown in Fig. 2, does not appear here, there is little to be seen of passivation of these metals. Observers often fail to consider or are completely unaware of this phenomenon. Actually, at higher potentials, all noble metals are covered with a passive film.

Under certain circumstances, active corrosion-current maxima can be detected in noble metals, although they are quite faint. For palladium, this phenomenon was observed by *Vetter* and *Berndt* [24] in 1 N sulfuric acid (Fig. 12). In more dilute (0.1 N) sulfuric acid, the current peak is no longer ascertainable, since the Flade potential falls by 90 mv, owing to the pH difference of 1.5 units. At very positive potentials, in the range where oxygen begins to be evolved at the anode, an increase in corrosion can be demonstrated in palladium and other noble metals, as well as in many passive base metals.

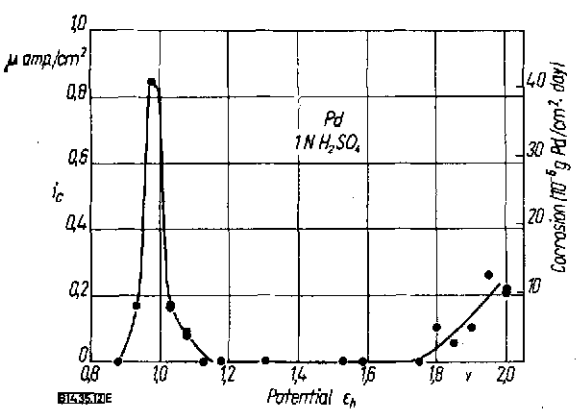


Fig. 12. Corrosion current density, i_C of palladium (determined by analytical chemistry) as a function of electrode potential in 1 N H_2SO_4 at 25 °C (after *Vetter* and *Berndt* [24])

Active corrosion can be greatly intensified by complex formation. An active corrosion-current peak may manifest itself in electrolytes in which soluble complex formation occurs, although no peak appears in electrolytes in which no complex formation takes place. This phenomenon has been observed, for instance, with gold in acid solution. In 1 N sulfuric acid, *Vetter* and *Berndt* [24] were unable to detect an active corrosion current peak, but in hydrochloric acid of similar pH, *Frank* and *Hoppe* [27] found such a strong active corrosion that even a diffusion-limited current density appeared, much like that for iron (Fig. 5, see also Fig. 13). Here active dissolution of complexed gold occurs according to the equation:

$$Au + 4\,Cl^- \rightarrow AuCl_4^{3-} + e^-$$

which is repressed only at the Flade potential owing to formation of a passive film.

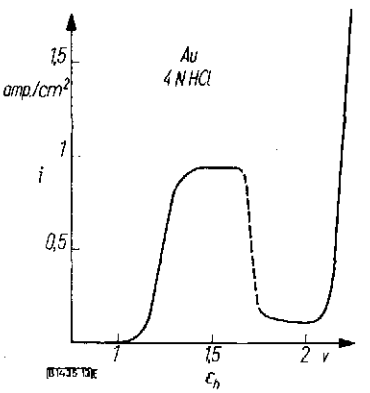


Fig. 13. Anodic current density *vs.* potential curve of gold in 4 N HCl (corrosion with complex formation). After *Franck* and *Hoppe* [27]

The general opinion prevails that in the case of anodic evolution of chlorine, the electrode material is attacked by extremely agressive molecular chlorine. However, this reaction ought rather to be interpreted by considering that, during the evolution of chlorine, the anode material must necessarily be surrounded by a chloride solution and be at a relatively high positive potential. Thus, the complexing effect of the Cl^- ion (as in Fig. 13), in combination with the high potential, is the source of the strong corrosion effect observed during chlorine evolution. Moreover, it is known that in many instances Cl^- ions often increase corrosion and pitting in passive films [5, 28]. Once again, the culprit is Cl^- ion and not elemental chlorine.

Anode Processes

Not only must the anode material be sufficiently stable to corrosion, but the anode processes must also take place with sufficient rapidity. Two quantities determine

[25] Theoretical value, calculated from thermal data for the standard potential of the oxide electrode given by *K. J. Vetter*, reference [1], p. 607. The experimental values often deviate, however, from this value.

[26] *K. J. Vetter* and *G. Oelsner* were able to obtain this active condition on titanium for a brief period.

[27] *U. F. Franck* and *K. Hoppe* in *H. Gerischer*, Angew. Chem. *70*, 285 (1958).

[28] *H. J. Engell* and *N. D. Stolica*, Arch. Eisenhüttenwes. *30*, 239 (1959).

the rate: the electron conductivity of the passive film and the overvoltage at the surface of the passive film.

Electron Conductivity of the Passive Film

The anode processes to be discussed in this connection can only be redox reactions, since a reaction of the type

$$Me \rightleftharpoons Me^{z+} + ze^- \quad \text{(corrosion reaction)}$$

should not be able to take place. Such redox reactions, *e.g.* the anodic evolution of chlorine or oxygen according to the equations:

$$2\,Cl^- \rightarrow Cl_2 + 2e^-$$

and

$$2\,H_2O \dashrightarrow O_2 + 4\,H^+ + 4e^-$$

occur at the phase boundary between the passive film and the electrolyte. Both the starting substances (Cl^-, H_2O) and the end-products (Cl_2, O_2, H^+) of the redox processes are found principally only in the electrolyte (sometimes also partly in the vapor phase above the electrolyte) but not in the passive film or in the metal. The electrons liberated or consumed at the phase boundary of the anode or cathode, respectively, during redox processes finally flow as electric currents in the electrode metal. This means that all the electrons involved in these transfers must penetrate the passive film. This requirement is independent of any particular conception of the transport process or reaction mechanism. The passive film must possess a sufficiently high electrical conductivity; only then can a redox process take place.

With passive iron, these conditions are met, as is shown in Fig. 7 for the Ce^{3+}/Ce^{4+} redox process, the net electrode process being

$$Ce^{3+} \rightleftharpoons Ce^{4+} + e^-$$

The partial current, i_{Ce} of the cerium redox process is determined by chemical analysis. Superposition of this current on the partial corrosion current density i_c, which is also determined by chemical analysis, gives the measured total current density i_{tot}. Here, the redox potential ($i_{Ce} = 0$) has the same value as on platinum. This fact indicates that an electron equilibrium has been established through the film from the metal to the electrolyte.

A sufficient electrical conductivity of the passive film is exhibited by other metals besides the iron discussed above. These include nickel, chromium, the noble metals, and those metals on which oxygen can be evolved anodically [29]. On the other hand, according to investigations of *Guentherschulze* and *Betz* [30] and, later, of *Vermilyea* [31] a potential of some 100 volts can be applied to aluminum, titanium, tantalum, and other metals without evolution of oxygen, since, in the potential range under discussion, the passive films of these metals are nonconducting. The field strength in these films may assume values of 10^6 to 10^7 v/cm. At field strengths of this order, ion migration leading to further film formation is possible [32–34]. Still higher potentials lead to electrical breakdown. Anodic processes at these passive metals are thus not feasible, even though these metals would appear to be eminently suitable because of their high resistence to corrosion. For redox reactions to take place, the electron conductivities of these films would have to be substantially increased. Hence, it is rather surprising that titanium coated with sublimed platinum can find use as an anode material at all as has recently occured. It may be possible that a titanium oxide film (which perhaps partially dissolves the vaporized platinum) has an improved electron conductivity with no change in its good corrosion resistance properties. It may be possible that by doping poorly conducting passive films with certain metals, advances in the development of anode materials can be made.

The degree of insulation against electrons clearly depends upon the potential, since passive metals such as the aluminum, titanium, and tantalum mentioned above, can support cathodic evolution of hydrogen – a redox reaction – at negative potentials, even though the passive film remains intact [35].

Overvoltage at the Passive Film Surface

A redox process, *i.e.* anodic release or cathodic uptake of electrons by the electrolyte, takes place directly at the phase boundary between the passive film and the electrolyte, and is, therefore, a property of the electrolyte side of the passive film. If transport processes of the starting materials and end-products or of preceding or succeeding chemical reactions do not determine the overvoltage and therefore limit the anode process, then a pure charge-transfer barrier exists [36], leading to a charge-transfer overvoltage. The dependence f the current density i on the charge-transfer overvoltage $\eta = \varepsilon - \varepsilon_0$ (ε = electrode potential, ε_0 = equilibrium potential according to the Nernst equation) is described by the following expression [37]:

$$i = i_0 \cdot e^{\eta \alpha F/RT} - e^{\eta(1-\alpha)F/RT} \quad (6)$$

In addition to the transmission factor α (which has a value between 0 and 1, usually 0.5), the overvoltage depends considerably on the exchange current density

[29] In the potential range of from about 1.5 to 2.0 V against a hydrogen electrode (at 1 atm.) in the same solution (the same pH value).

[30] *A. Güntherschulze* and *H. Betz*, Z. Physik *91*, 70 (1934); *92*, 367 (1934).

[31] *D. A. Vermilyea*, Acta metallurgica *1*, 282 (1953); *2*, 476 (1954); J. electrochem. Soc. *102*, 655 (1955); *C. P. Bean, J. C. Fisher*, and *D. A. Vermilyea*, Phys. Rev. *101*, 551 (1956) on tantalum.

[32] *E. J. W. Verwey*, Physica *2*, 1059 (1935).

[33] *N. F. Mott*, Trans. Faraday Soc. *43*, 429 (1947); J. chim. physique *44*, 172 (1947).

[34] *N. Cabrera*, Philos. Mag. *40*, 175 (1949); *N. Cabrera* and *N. F. Mott*, Rep. Progr. Physics *12*, 163 (1949).

[35] Unpublished research by *K. J. Vetter* and *G. Oelsner* [16] confirms this.

[36] *K. J. Vetter*, Z. physik. Chem. *194*, 199 (1950); *194*, 284 (1950), particularly p. 286; Z. Elektrochem. *55*, 121 (1951); *59*, 596 (1955).

[37] Cf. *K. J. Vetter* [1], p. 99 ff.

i_0, whose values can vary widely [38]. For large anodic overvoltages, where $\eta \gg RT/F = 25.6$ mv at 25 °C, Eq. 6 transforms into the Tafel relationship:

$$\eta = -\frac{RT}{aF}\ln i_0 + \frac{RT}{aF}\ln i \qquad (7)$$
$$(\eta = a + b \log i)$$

in which the influence of the exchange current density i_0 is readily apparent.

For one and the same electrode process, this exchange current density i_0 strongly depends on the nature of the electrode material and, therefore, on the passive film covering the electrode. Any alteration made in the properties of this passive film, *e.g.*, by alloying, which corresponds to the doping of semiconducting passive materials, would lead us to expect some alteration in the exchange current and, therefore, in the overvoltage; such an alteration could have great commercial significance. No general rules for achieving this are at present available, however.

Semiconducting Anodes

In place of a passive metal with a nonporous, semiconducting passive film on its surface, the anode material itself may be a semiconductor or coated with a semiconductor film. The same demands are placed upon this material as on passive films. Corrosion and overvoltage should be small and the semiconductor should have sufficiently high electron conductivity. Such a semiconductor electrode would give the same redox potential as platinum.

Magnetite, Fe_3O_4, which is often used as an anode material, possesses these properties to a high degree. The possibilities of developing semiconductor electrodes on the basis of the latest advances in semiconductor physics are obviously far from being exhausted.

[38] Known experimental values range through almost 20 powers of ten.

[39] *K. J. Vetter* and *G. Klein*, Z. physik. Chem. N.F. *31*, 405 (1962).

Graphite Anodes

Graphite has good electron conductivity and, from this point of view, is highly suitable as an anode material. From a thermodynamic point of view, the observed corrosion resistance of graphite is quite unexpected, although, in fact, this property makes graphite extremely popular as an anode material.

Thermodynamically, anodic formation of carbon monoxide and carbon dioxide (or carbon tetrachloride and COCl from chloride solutions) would be expected to occur at much more negative potentials than is actually the case. From the change in free enthalpy ΔG for the cell reaction, (with reference to a hydrogen electrode) and the electrode reaction valence values of n, the following equilibrium potentials are obtained:

1. $C + H_2O \rightarrow CO + 2H^+ + 2e^-$ $\qquad E_0 = +0{,}52$ V
$\varepsilon_h = +0{,}52 + \frac{RT}{2F}\cdot\ln p_{CO} + \frac{RT}{F}\cdot\ln a_{H^+}$

2. $C + 2H_2O \rightarrow CO_2 + 4H^+ + 4e^-$ $\qquad E_0 = +0{,}21$ V
$\varepsilon_h = +0{,}21 + \frac{RT}{4F}\cdot\ln p_{CO_2} + \frac{RT}{F}\cdot\ln a_{H^+}$

3. $C + 4Cl^- \rightarrow CCl_4 + 4e^-$ $\qquad E_0 = +1{,}19$ V
$\varepsilon_h = +1{,}19 - \frac{RT}{F}\cdot\ln a_{Cl^-}$

4. $C + H_2O + Cl^- \rightarrow COCl + 2H^+ + 3e^-$ $\qquad E_0 = +0{,}50$ V
$\varepsilon_h = +0{,}50 + \frac{RT}{3F}\cdot\ln p_{COCl} + \frac{RT}{3F}\cdot\ln\frac{a^2_{H^+}}{a_{Cl^-}}$

By comparison, the reversible potential of the oxygen electrode is

$$\varepsilon_h = +1{,}23 + \frac{RT}{4F}\cdot\ln p_{O_2} + \frac{RT}{F}\cdot\ln a_{H^+}$$

and of the chlorine electrode is

$$\varepsilon_h = +1{,}36 + \frac{RT}{2F}\cdot\ln p_{Cl_2} - \frac{RT}{F}\cdot\ln a_{Cl^-}$$

A theory of the graphite anode must be based upon the kinetics of these possible corrosion reactions. Only elucidation of the kinetics of these electrode reactions will permit us to understand why they are so strongly inhibited. Perhaps measures can be taken to enhance this inhibition and thus further reduce the already small rate of corrosion of graphite anodes.

Received, December 9th, 1961 [B 1435/45 IE]

German version: Chemie-Ing.-Techn. *34*, 362 (1962)

COMMUNICATIONS

Alkaline Earth Dialuminum Octaethyls

By Dr. H. Lehmkuhl and Dipl.-Chem. W. Eisenbach

Max-Planck-Institut für Kohlenforschung
Mülheim-Ruhr (Germany)

In the course of work on complex organoaluminum compounds [1], it was found that aluminum trialkyls, being stronger Lewis acids, displaced alkoxyaluminum dialkyls from complex compounds of the latter with alkali metal alkyls [2]:

$$AlR_3 + M[AlR_3OR'] \rightarrow M[AlR_4] + AlR_2OR' \quad (M = \text{alkali metal})$$

The complex containing OR′ can be obtained in turn from MOR′ and AlR_3. Hence the reaction between alcohol-free alkali alkoxide and 2 moles of aluminum trialkyl constitutes a new, simple way for preparing alkali aluminum tetra-alkyls, *e.g.* according to the equation:

$$2\,Al(C_2H_5)_3 + MOR \rightarrow M[Al(C_2H_5)_4] + Al(C_2H_5)_2OR.$$

The alkoxyaluminum dialkyl formed at the same time can be easily separated from the complex compound either as a consequence of the spontaneous formation of two layers or by distillation *in vacuo*. The process is especially suitable for preparing pure potassium and lithium aluminum tetraethyls. The reaction can also be carried out using calcium, strontium or barium alkoxides. It then yields the alkaline earth dialuminum octaethyls. On the other hand, the course of reaction is different with magnesium alkoxide.

The properties of the new materials are truly remarkable. The calcium and strontium compounds can be smoothly distilled

at low pressures; the barium compound is also volatile, albeit with partial decomposition:

$Ca[Al(C_2H_5)_4]_2$
m.p. = 40 °C; b.p. = 90–95 °C/10^{-3} mm Hg;

$Sr[Al(C_2H_5)_4]_2$
m.p. = 109 °C; b.p. = 122–123 °C/10^{-3} mm Hg

$Ba[Al(C_2H_5)_4]_2$
m.p. = 138 °C; b.p. > 160 °C/10^{-3} mm Hg

Only $Ba[Al(C_2H_5)_4]_2$ has an appreciable electrical conductivity of the order of magnitude of 0.1×10^{-1} mho/cm at 140 °C (*i.e. ca.* $^1/_5$ that of $NaAl(C_2H_5)_4$: 0.55×10^{-1}, or $^1/_{13}$ that of $KAl(C_2H_5)_4$: 1.3×10^{-1} mho/cm.); the calcium ($K < 10^{-6}$) and strontium (K *ca.* 10^{-4}) compounds are almost completely homopolar. Homopolar character bound with volatility has also been established with $LiAl(C_2H_5)_4$ [3, 4] as well as with $CH_3Mg[Al(CH_3)_4]$ [5]. It is surprising that the complex organoaluminum compounds of the essentially more electropositive higher alkaline earth metals agree in their properties not with the complexes of alkali metals in the same periods, but with those of the first members of Groups I and II. Little is known so far about complex organoberyllium aluminum compounds. They appear to be very unstable, if they exist at all.

Of the new materials, the calcium compound is extremely pyrophoric.

Received, June 27th, 1960. Publication withheld until now at the request of the authors. [Z 352/181 IE]

[1] *K. Ziegler, R. Köster, H. Lehmkuhl,* and *K. Reinert,* Liebigs Ann. Chem. *629,* 53 (1960).

[2] *K. Ziegler* and *H. Lehmkuhl,* Belg. Pat. 575 641, German priority, Feb. 13th, 1958.

[3] *E. B. Baker* and *H. H. Sisler,* J. Amer. chem. Soc. *75,* 5193 (1953).

[4] Cf. [5], footnote 6a).

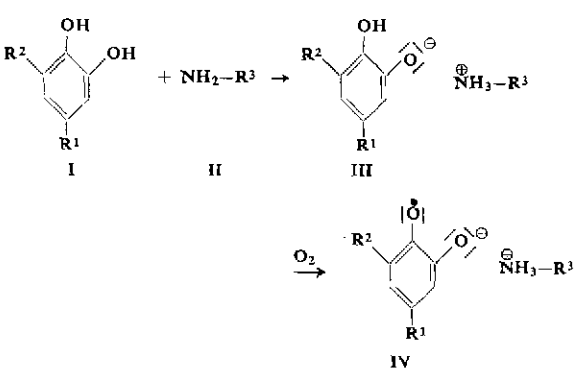
[5] *K. Ziegler* and *E. Holzkamp,* Liebigs Ann. Chem. *605,* 93 (1957).

A New Synthesis of o-Aminophenols [1]

By Dr. K. Ley [*]

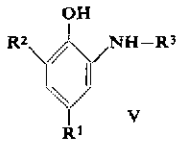
Wissenschaftliches Hauptlaboratorium der Farbenfabriken Bayer AG., Leverkusen-Bayerwerk (Germany)

Catechols containing bulky groups in the 4- and 6-positions form the salts III with primary aliphatic mono- and diamines. By the action of atmospheric oxygen these are transformed into the blue radical-anions IV, which can be recognised in solution (benzene, light petroleum) by paramagnetic electron resonance [1a]:

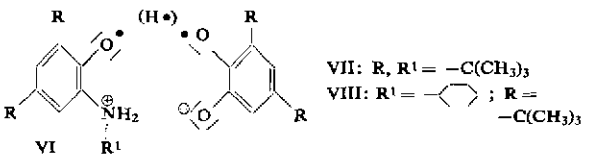


$R^1 = R^2$ = t-alkyl
R^3 = any alkyl or alkylamino group

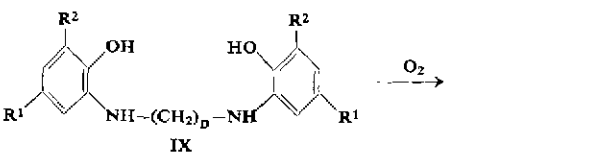
The *o*-aminophenols V [2] are formed from the radicals IV in a redox reaction by exchange of the hydroxyl group by alkylamine even at room temperature. The yields amount to 70–90 % in all cases.



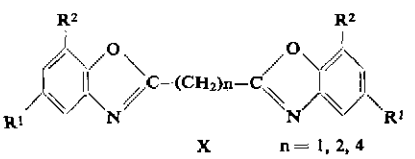
The intermediary radicals VI can be isolated as the catecholates or biradical salts (VII, VIII), in the form of deep blue crystals, by using 4,6-di-t-butylcatechol as phenolic component and t-butylamine or cyclohexylamine as basic reaction partner.



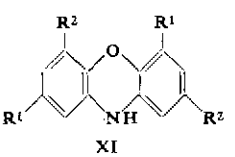
The bis-*o*-aminophenols IX, formed from diamines and I, undergo dehydrogenative cyclisation by the further action of oxygen to give the bisbenzoxazoles X [3]:



n = 3, 4, 6 R^1, R^2 = t-alkyl



By longer action of 2 moles of an aqueous methylamine solution on the catechols I dissolved in benzene, the *o*-aminophenols (unsubstituted on nitrogen) arise *via* the *N*-methyl compounds V. If one assumes quinoneimine ⇌ enamine as an intermediate stage, then the oxidative demethylation is readily explained. The *o*-aminophenols are insoluble in the reaction medium and therefore escape further oxidation. If one uses ammonia as the amine component, *o*-, *o'*-dihydroxydiphenylamines are formed with I, and these can readily be cyclised to phenoxazines XI by warming.



With arylamines or diarylamines [4] (aryl = phenyl, subst. phenyl, naphthyl, subst. naphthyl) the radical exchange reaction does not occur until one converts the catechols I into the anions III by addition of a catalytic amount of a secondary or tertiary, aliphatic amine and thereby makes possible the oxidation to the radical anions IV.

Received, July 13th, 1962 [Z 327/153 IE]

[*] Dedicated to Prof. *Otto Bayer* on his 60th birthday.

[1] 2nd Communication on Radical-anions. 1st Communication: *K. Ley* and *E. Müller,* Angew. Chem. *70,* 469 (1958).

[1a] Measurements by Dr. *Walz.*

[2] DBP 1 104 522 (1962), Farbenfabriken Bayer AG.

[3] DBP 1 115 255 (1962), Farbenfabriken Bayer AG.

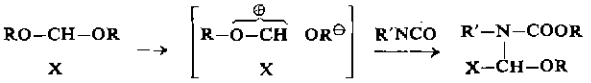
[4] DBP 1 119 297 (1962), Farbenfabriken Bayer AG.

The Reaction of Isocyanates with Ortho-esters and Acetals

By Dr. H. v. Brachel and Dr. R. Merten [*]

Wissenschaftliches Hauptlaboratorium
der Farbenfabriken Bayer AG., Leverkusen (Germany)

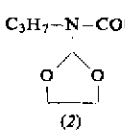
The reactions of isocyanates with ortho-esters or acetals indicate that addition reactions of the isocyanate group are not confined to the transfer of reactive hydrogen atoms [1]. In the presence of Lewis acids (BF_3, $ZnCl_2$, $AlCl_3$), formic acid ortho ethyl ester or formaldehyde dimethylacetal adds to the isocyanate group at 30–70 °C, giving carbamic acid esters (*1a*) or (*1b*) in 70–90 % yields. Carbeniumoxonium ions are probably formed as intermediates.



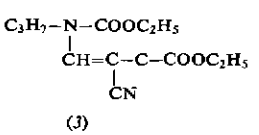
(*1a*): X = OR; R = C_2H_5
(*1b*): X = H; R = CH_3

	X	R	R'	B. P. [°C/mm. Hg]	n_D^{20}
1a)	OC_2H_5	C_2H_5	CH_3	94–96/12–14	1.4202
	OC_2H_5	C_2H_5	n-C_3H_7	108–111/19	1.4224
	OC_2H_5	C_2H_5	C_6H_5	95–96/0.02	1.4917
1b)	H	CH_3	CH_3	53–55/13	1.4246
	H	CH_3	3,4-$Cl_2C_6H_3$–	134–136/0.2	1.5484
	H	CH_3	2,6-$(C_2H_5)_2C_6H_3$–	117–118/0.35	1.5114
	H	CH_3	Cl-CH_2CH_2–	100–102/16	1.4564

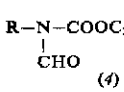
The ortho-ester adducts (*1a*) are dissociated above 150 °C in the aliphatic series and above 100 °C in the aromatic series. The acetal grouping of the adducts (*1a*) can undergo exchange reactions in the presence of non-aqueous acid, *e.g.* with ethylene glycol giving the 1.3-dioxolane (*2*), or it may be condensed with active methylene compounds, *e.g.* with cyanoacetic acid ester to form the unsaturated ester (*3*). In the aliphatic series, *N*-formyl carbamic acid esters (*4*) can be obtained by saponification.



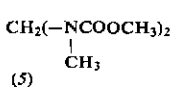
(*2*)
b.p. 131 °C/14 mm. Hg
n_D^{20} = 1.4440



(*3*)
b.p. 126–130 °C/0.03 mm. Hg
n_D^{20} = 1.4970

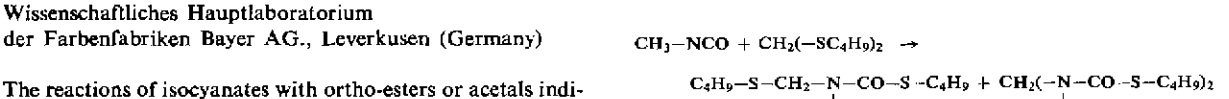


(*4*)
R = CH_3 ; b.p. 72 °C/15 mm. Hg
R = C_3H_7; b.p. 82 °C/15 mm. Hg



(*5*)
b.p. 120 °C/13 mm. Hg
m.p. 40 °C

With increasing quantities of the acidic catalyst the adducts (*1b*) take up further isocyanate, even in the presence of excess formaldehyde dimethylacetal, giving methylenebiscarbamic acid esters like (*5*), which by selection of stoichiometric quantities may be obtained in almost quantitative yield.



(*6*)
b.p. 132–134 °C/0.1 mm. Hg
n_D^{20} = 1.5102

(*7*)
b.p. 155–157 °C/0.1 mm. Hg
n_D^{20} = 1.5172

The addition can be extended to numerous other ortho-esters, acetals [2], α-chloroalkylethers [3], and isocyanates, and also to the analogous sulphur compounds. Thus, the adducts (*6*) and (*7*) are formed from methyl isocyanate and formaldehyde dibutylmercaptal.

Received, August 2nd, 1962 [Z 321/148 IE]

[*] Dedicated to Prof. *Otto Bayer* on his 60th birthday.

[1] See *Houben-Weyl:* Methoden der organischen Chemie. G. Thieme, Stuttgart 1952, vol. 8, p. 130.

[2] German Patent 1072385 (1959), by *R. Merten.*

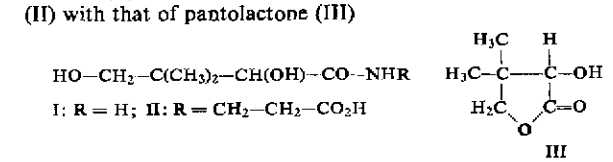
[3] German Patent 1072386 (1959), by *R. Merten.*

Determination of the Conformation of Panthotenic Acid and Pantoylamides by Proton Resonance Spectroscopy

By Doz. Dr. H. Fritz and Dipl.-Chem. W. Löwe

Institut für Organische Chemie
der Universität Frankfurt (Germany)

Comparison of the structures of pantoylamide (α,γ-dihydroxy-β,β-dimethylbutyramide) (I) and panthothenic acid (II) with that of pantolactone (III)



I: R = H; II: R = CH_2–CH_2–CO_2H

III

suggests that the two hydrogen atoms of the methylene groups in the open chain compounds should show a larger degree of equivalence than those in the ring compound owing to their enhanced freedom of rotation. The proton resonance spectra of these three compounds, however, disproved this expectation. In Table 1, the positions of the resonance peaks, the corresponding coupling constants of the various protons,

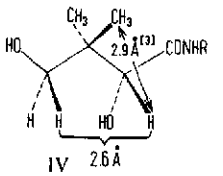
Table 1. 60 Mc Proton resonance spectra of compounds I, II, and III in D_2O. All data in cps. relative to tetramethylsilane = 0 (DOH = 306). Apparatus: Varian A-60.

Type of Proton	Na-Salt of D-(+)-Panthothenic Acid (II)	D-(+)Pantoylamide (I)	D-(−)Pantolactone (III)
O–CH_2– A, B	AB-"Quartet" [1] centred at 228 $\Delta_{A,B}$ = 7.0 $J_{A,B}$ = 11	AB-"Quartet" [1] centred at 230 $\Delta_{A,B}$ = 7.0 $J_{A,B}$ = 11	AB-Multiplet [2] centred at 269 $\Delta_{A,B} \approx 2$ $J_{A,B} \approx 9.6$
H_3C–C–CH_3 c d	c: 71,5; d: 73.5 Δ_{CH_3, CH_3}=2	c: 74.5; d: 76.5 Δ_{CH_3, CH_3}=2	c: 81; d: 91 Δ_{CH_3, CH_3}=10
HO–C(Cl)–H (C, e)	e: 259	e: 262	e: 284
RN(H)– CH_2–CH_2–$CO_2^{\ominus}$ f g	f: Triplet centred at 226 $J_{f,g}$ = 7 g: Triplet centred at 164		

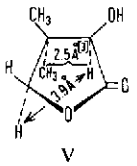
and the values of the chemical shifts of the methylene protons ($\Delta_{A,B}$) and the methyl groups ($\Delta_{CH_3,\ CH_3}$) for each of the substances are summarized.

In the case of pantolactone, $\Delta_{A,B} \approx 2$ cps. $J_{A,B} \approx 9.6$ cps. and $\Delta_{CH_3,\ CH_3} = 10$ cps.; on the other hand, the respective values for both the two open chain compounds I and II are $\Delta_{A,B} = 7.0$ cps., $J_{A,B} = 11$ cps. and $\Delta_{CH_3,\ CH_3} = 2$ cps.

Since the protons of the methylene groups of compounds I and II lead to only a single sharp AB-multiplet, and since the possibility of fast rotation of the hydroxy-methylene groups can practically be ruled out on account of steric hindrance and in view of the higher $\Delta_{A,B}$ values observed for the open chain compounds in comparison with that of the γ-lactone, the results indicate that the open chain compounds exist mainly in the conformation shown in IV.



IV 2.6 Å



V

The two protons of the methylene group in formula IV are nearer to the substituents of the asymmetric C atom than those in the lactone V; this increases the difference in their diamagnetic screening. In accordance with the geometry of conformation IV, in which the distances between the methyl groups and the unequal substituents at the center of asymmetry are larger than in the lactone, a decrease in the value of $\Delta_{CH_3,\ CH_3}$ is observed from 10 cps. in the lactone to 2 cps. in the open-chain compounds. The interatomic distances given were measured on molecular models and are intended to serve only as references for the relative changes in the interatomic distances.

Received, August 28th, 1962. [Z 338/171 IE]

[1] Actually two sharply defined doublets.

[2] Appears as a triplet, since the two middle peaks are not resolved.

[3] Distance between the methyl C and neighboring H.

The Action of Diazonium Halides on Methyl Vinyl Sulphone

By Dr. E. Siegel and Prof. Dr. S. Petersen [*]

Wissenschaftliches Hauptlaboratorium der
Farbenfabriken Bayer AG., Leverkusen (Germany)

Diazonium chlorides react with methyl vinyl sulphone in a type of Meerwein reaction [1] with vigorous evolution of nitrogen to form crystalline compounds containing chlorine and sulfur. The great mobility of the chlorine atom in these reaction products, and also their NMR-spectra [2] indicate a β-chlorethylsulphone structure (cf. [3]).

$$[Ar{-}N_2]^+Cl^- + CH_3{-}SO_2{-}CH{=}CH_2 \xrightarrow[HCl,\ CuCl_2]{H_2O/Acetone} CH_3{-}SO_2{-}\underset{\displaystyle Ar}{\underset{|}{CH}}{-}CH_2Cl + N_2$$

I

The diazo solution from 69 g of *p*-nitraniline (0.5 mole), 300 ml of ice/water, 132 g conc. hydrochloric acid, and 34.5 g of sodium nitrite is added to 55 g of methyl vinyl sulphone (0.52 mole) in 450 ml of acetone. A solution of 20 g of crystalline cuprous chloride in 50 ml of water is then added. The vigorous evolution of nitrogen which sets in at 28 °C (duration 1 h.) is moderated by cooling (28 °–30 °C). After evaporation of the acetone, the crude product (90 g) is recrystallised from methanol (300 ml). Yield: 63 g (48 %); m.p. 121–123 °C. The product Ia has formula I, where Ar = O_2N–C$_6$H$_4$–.

The compounds Ib–Id have been prepared analogous:

	Ar- in I	M.p. [°C]	Yield [%]
Ib		124–125	45
Ic	HOOC–C$_6$H$_4$–	220–221	45
Id	H_2NO_2S–C$_6$H$_4$–	147	35

$$H_3C{-}SO_2{-}\underset{\displaystyle Ar}{\underset{|}{CH}}{-}CH_2{-}Cl \xrightarrow{-HCl} H_3C{-}SO_2{-}\underset{\displaystyle Ar}{\underset{|}{C}}{=}CH_2$$

I II

Elimination of HCl from these compounds (I) gives the vinyl sulphone derivatives II in high yield:

By boiling Ia for forty hours with sodium acetate in aqueous-alcoholic solution, 98 % of IIa (Ar = O_2N–C$_6$H$_4$–), m.p. 197–200 °C is obtained; on boiling Ic for four minutes with 0.2 N sodium hydroxide solution, 1 mole of HCl is eliminated with formation of IIc (Ar = HOOC–C$_6$H$_4$–), yield 80 %, m.p. 287–297 °C.

Received, September 3rd, 1962 [Z 342/174 IE]

[*] Dedicated to Prof. *Otto Bayer* on his 60th birthday.

[1] *H. Meerwein, E. Büchner* and *K.v. Emster*, J. prakt. Chem. *152*, 237 (1939).

[2] Measured and interpreted by *H. Walz*, Ingenieur-Abteilung AP der Farbenfabriken Bayer AG.

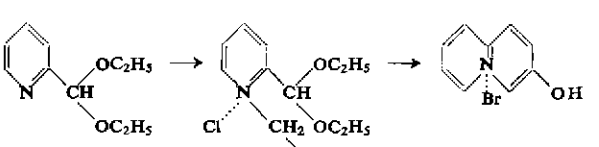
[3] *F. G. Bordwell* and *G. D. Cooper*, J. Amer. chem. Soc. *73*, 5184. (1951).

Synthesis of 3-Hydroxydehydroquinolizinium Bromide

By Dr. E. Schraufstätter [*]

Pharmazeutisch-wissenschaftliche Abteilung
der Farbenfabriken Bayer A.G., Werk Elberfeld (Germany)

During the course of investigations into cholinesterase inhibitors, we discovered a synthesis of a dehydroquinolizinium derivative, which is very simple and which leads to good yields. α-Diethoxymethylpyridine (I) is treated with chloroacetone to give II (m.p. 148 °C, from acetone), which is then cyclized to 3-hydroxydehydroquinolizinium bromide, (III, m.p. 251 °C with decomp., from alcohol) by boiling with hydrobromic acid.



According to its ultraviolet and infrared spectra [1], compound III occurs entirely in the hydroxy-form. The ultraviolet spectrum [maxima at 340 mμ (log ε = 3.92); 330 mμ (log ε = 3.90); 246 mμ (log ε = 4.37); 227 mμ (log ε = 4.39)] is very similar to that of dehydroquinolizinium iodide.

Direct reaction of pyridine-2-aldehyde with chloro- or bromoacetone did not occur.

Received, September 3rd, 1962 [Z 341/173 IE]

[*] Dedicated to Prof. *Otto Bayer* on his 60th birthday.

[1] Thanks are due to Dr. *W. Geiger* for measuring and interpreting the spectra.

Synthesis of 5-Membered Heterocycles from Chloromethanesulfonamides [1]

By Dr. K. Dickoré, Dr. R. Wegler, and Dr. K. Sasse [*]

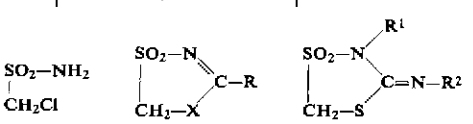
Wissenschaftliches Hauptlaboratorium
der Farbenfabriken Bayer AG., Leverkusen (Germany)

We have found that 5-memhered heterocycles can be made from acylated α-chloroalkanesulfonamides with surprising ease.

Primary sulfonamides react readily with CS_2 and NaOH at room temperature giving sulfonylimino-dithiocarbonates [2]. Applied to chloromethanesulfonamide (I), this reaction is immediately followed by ring closure to give the sodium salt of 5-thio-1,3,4-dithiazoline-3-dioxide (IIa; 75 % yield), from which we obtained derivatives, *e.g.* (IIb–IIg), by alkylation and acylation.

Table 1. 5-Substituted 1,3,4-dithiazoline-3-dioxides

No.	R	M.p. [°C]
IIa	SNa	—
b	SCH_3	158—160
c	SC_4H_9	30—33
d	$SC_{12}H_{25}$	58—60
e	$SCOOCH_3$	105—110 (decomp.)
f	$SCOOC_2H_5$	130—133 (decomp.)
g	$SCOC_6H_5$	165—170 (decomp.)
h	$NHCH_3$	152—156
i	NHC_6H_5	177
j	$NHC_6H_4(p)Cl$	252—255 (decomp.)
k	$NH(CH_2)_2C_6H_5$	83—88
l	$NH(CH_2)_3N(CH_3)_2$	134—137
m	$NH(CH_2)_3N(C_2H_5)_2 \cdot H_2O$	56—58
n	$N(CH_3)_2$	123—125
o	$N(CH_3)C_6H_5$	176
p	$N(CH_3)C_6H_4(p)Cl$	111—113
q		120—123
r		193—195
s	$N(SCCl_3)C_6H_5$	185—187
t	$N(COOCH_3)C_6H_5$	197—199 (decomp.)
u	$N(CSSC_2H_5)CH_3$	155—161



I II: X = S III: X = O IV

Thiols are eliminated from the compounds IIb–IId by reaction with amines. The reaction proceeds especially smoothly with secondary aliphatic amines: the compounds IIq and IIr are obtained from IIb in almost quantitative yields. The products of reaction of isothiocyanates with I also readily undergo cyclization by replacement of the chlorine. Compounds IIh–IIm were prepared in this way (in yields of 60–75 %). The 1,3,4-dithiazoline ring is closed in the presence of base at the temperatures (60–80 °C) required for the formation of sulfonyl thioureas [3].

These new 1,3,4-dithiazoline derivatives are also readily alkylated and acylated in alkaline solution. Proof that the alkylation takes place at the exocyclic nitrogen atom and not at the sulfonamide nitrogen atom is provided by the fact that the same product (IIn) is obtained by alkylation of compound IIh with dimethyl sulfate (82 % yield) or by aminolysis of compound IIb with dimethylamine (60 % yield). The C=N stretching vibrations of compounds IIh–IIr lie in the range 1555–1590 cm^{-1} and those of the acylated derivatives (IIs–IIu) lie between 1520 and 1530 cm^{-1}. These are consistent with the endocyclic position of the double bond in II. For comparison, we prepared the new dithiazoline derivatives IVa ($R^1=R^2=C_6H_5$; m.p. 160–162 °C; 30 % yield) and IVb ($R^1=CH_3$, $R^1=p-ClC_6H_4$; m.p. 124 °C; 45 % yield) from the corresponding chloromethanesulphonamides and isothiocyanates. These compounds can be clearly distinguished from compounds of type II by their exocyclic C=N stretching vibration at 1630 cm^{-1}.

The hitherto unknown 1,3,4-oxathiazoline ring system III can also be readily formed: *e.g.* we obtained compound IIIa from I and phenyl isocyanate. Since the addition of isocyanates onto the sodium salts of sulfonamides according to the method of *Petersen* [3] takes place rapidly at 0–5 °C and the ring-closure to give III only begins at 50 °C, the intermediate *N*-chloromethanesulfonylureas can be isolated. We prepared 1,3,4-oxathiazolines arylated at position 5, *e.g.*

Table 2. 5-Substituted 1,3,4-oxathiazoline-3-dioxides

No.	R	M.p. (°C)
IIIa	C_6H_5NH	152—153 (decomp.)
b	C_6H_5	162—163
c	$o-CH_3-C_6H_4$	130—132
d	$o-Cl-C_6H_4$	132—134
e	$p-O_2N-C_6H_4$	227—230
f		295—310 (decomp.)

IIIb–IIIe, very simply directly from I and aromatic acid chlorides in pyridine. Heterocyclic carbonyl chlorides can readily be made to react with I in an analogous manner to give, for example, compound IIIf, but chloromethanesulfonamides acylated by aliphatic carboxylic acid derivatives are less easily cyclized. The new compounds, particularly ring system III, show interesting reactions with nucleophilic reagents.

Received, September 3rd, 1962 [Z 340/172 IE]

[*] Dedicated to Prof. *Otto Bayer* on his 60th birthday.

[1] The experimental results are recorded in various patent applications.

[2] *R. Gompper* and *W. Hägele*, Angew. Chem. internat Edit. *1*, 55 (1962).

[3] *S. Petersen*, Chem. Ber. *83*, 551 (1950).

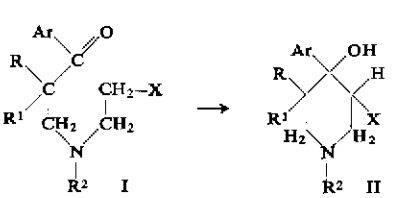
New Derivatives of 4-Hydroxy-4-phenylpiperidine [1]

By Dr. H. Henecka, Dr. G. Aichinger, and Dr. H. W. Schubert [*]

Farbenfabriken Bayer A.G., Wuppertal-Elberfeld (Germany)

As is known, the hydrochlorides of bis-(β-benzoylethyl)-methylamine and similar symmetrical bis-Mannich bases can be cyclised with aqueous sodium hydroxide to give 3-benzoyl-4-hydroxy-4-phenylpiperidines [2].

While attempting to prepare derivatives of 4-hydroxy-4-phenylpiperidine with a carbonyl group in the 3-position, we have now synthesized Mannich bases of general formula I. Although these cannot be cyclised at all in aqueous media, they yielded the desired 4-hydroxy-4-phenylpiperidines (II) in inert solvents by using strongly alkaline condensation reagents, *e.g.* in dry ether or tetrahydrofuran with sodamide or sodium hydride.



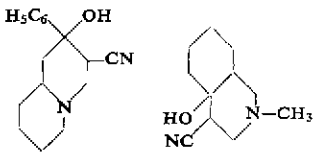
I II

X = CN, $COOR^3$

For the preparation of the Mannich bases (I), we used ketones Ar–CO–CHRR′, *e.g.* ring-substituted or unsubstituted acetophenones, propiophenone and isobutyrophenone, or 1-tetralone and 2-methyl-1-tetralone, in which R is linked to

Ar, for the components with an acidic CH-group, formaldehyde as the aldehyde component, and *N*-alkyl, *N*-aralkyl or *N*-unsubstituted β-aminonitriles (X=CN) or β-aminoesters (X = $COOR^3$) of formula $R^2HN-CH_2CH_2X$ as amine component. When X = $COOR^3$, at least one of the substituents R and R^2 must be an alkyl group, since otherwise 3-aroyl-4-piperidones are formed by intramolecular ester condensation, instead of the 4-hydroxypiperidines desired [3].

This ring closure is not confined strictly to compounds of general formula I. For instance, we were able to prepare III by addition of acrylonitrile onto α-phenacetylpiperidine followed by a cyclization, and obtained IV by using cyclohexanone, formaldehyde, and β-methylaminopropionitrile as starting materials.



(III) (IV)

Received, September 5th, 1962 [Z 339/169 IE]

[*] Dedicated to Prof. *Otto Bayer* on his 60th birthday.

[1] German Patent Applications F. 33529, IVb/12p (March 28th, 1961) and F. 34678, IVd/12p (August 11th, 1961).

[2] *C. Mannich* and *G. Heilner*, Ber. dtsch. chem. Ges. *55*, 356 (1922); *J. T. Plati* and *W. Wenner*, J. org. Chemistry *14*, 543 (1949); *J. T. Plati, R. A. Schmidt*, and *W. Wenner*, J. org. Chemistry *14*, 873 (1949).

[3] *E. van Heyninger*, J. Amer. chem. Soc. *80*, 156 (1958).

Triazidosilanes

By Dr. W. Sundermeyer [*]

Anorganisch-wissenschaftliches Laboratorium der Farbenfabriken Bayer AG, Leverkusen (Germany)

Phenyltriazidosilane (I) has been obtained in quantitative yield by the reaction of phenyltrichlorosilane with trimethylazidosilane.

$$C_6H_5SiCl_3 + 3\ (CH_3)_3SiN_3 \rightarrow \underset{\text{I}}{C_6H_5Si(N_3)_3} + 3\ (CH_3)_3SiCl$$

I is a transparent liquid which boils without decomposition at 62.5–63.5 °C/0.01 mm.

Furthermore, following a procedure described recently [1], methyltrichlorosilane was allowed to react with sodium azide.

$$CH_3SiCl_3 + 3\ NaN_3 \rightarrow \underset{\text{II}}{CH_3Si(N_3)_3},\ \underset{\text{III}}{CH_3Si(N_3)_2Cl},\ \underset{\text{IV}}{CH_3SiN_3Cl_2}$$

Contrary to all previous experience, compounds substituted only partially with azido groups were also obtained. Methylazidodichlorosilane (IV; b.p. 100.5 °C) was isolated, analysed, and its molecular weight determined. II and III were identified from the mass spectrum obtained on examination of the residue remaining after distillation at 200 °C. An attempt to separate II and III (b.p. *ca.* 70 °C/20 mm) by distillation resulted in a shattering explosion which was probably due to enrichment of II. This is the limit of the unexpected stability of the azidosilanes. A warning is therefore given against attempts to isolate II and III under normal conditions.

Received, September 10th, 1962 [Z 345/177 IE]

[*] Dedicated to Prof. *Otto Bayer* on his 60th birthday.

[1] *W. Sundermeyer*, Angew. Chem. Internat. Edit. *1*, 552 (1962).

The Reaction of Dimeric Phosphazenes with Isocyanates. A New Carbodiimide Synthesis

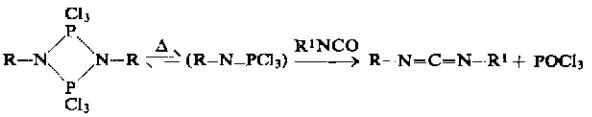
By Dr. H. Ulrich and Dr. A. A. Sayigh

The Carwin Company, North Haven, Connecticut (U.S.A.)

We have found that dimeric phosphazenes, which can be obtained from primary amines and phosphorus chlorides, react readily with polarized double bonds. Since the reactions proceed only at temperatures above 150 °C, dissociation of the dimeric phosphazenes into the monomers prior to reaction is indicated.

On refluxing dimeric *N*-methyltrichlorophosphazene (I) and phenylisocyanate in *o*-dichlorobenzene (175–180 °C), methylphenylcarbodiimide (II) (b.p. 128 °C/4 mm.; yield 51 %) and phosphorus oxychloride are obtained.

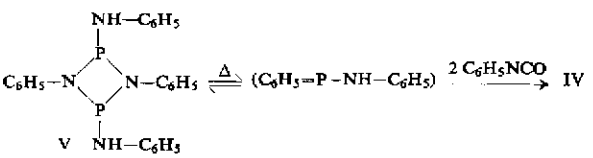
The reaction with isocyanates is not limited to aliphatic phosphazenes. *N*-Phenyltrichlorophosphazene (III) reacts with phenylisocyanate to form diphenylcarbodiimide (IV) (b.p. 119 °C/0.7 mm.; yield 34 %).



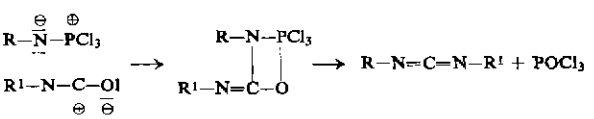
I: R = CH_3 II: R = CH_3; R^1 = C_6H_5
III: R = C_6H_5 IV: R = R^1 = C_6H_5

In a similar fashion, I and III react with carbon disulfide and carbon dioxide to afford isothiocyanates and isocyanates, respectively, as evidenced by infrared studies.

Thermal depolymerization and reaction with isocyanates also proceed with phenylphosphazoanilide (V); thus phenylphosphazoanilide and two moles of phenylisocyanate in refluxing *o*-dichlorobenzene afforded 41 % of IV.



Presumably the reaction proceeds via a four-membered ring intermediate which collapses under the reaction conditions into the final products.



Received, September 11th, 1962 [Z 354/170 IE]

Reactions of *N*-Sulphinyl Derivatives with Carbonyl Compounds

By Prof. Dr.-Ing. G. Kresze and Dipl.-Ing. R. Albrecht

Organisch-Chemisches Institut der Technischen Hochschule München (Germany)

We have found a new reaction of organic *N*-sulphinyl compounds [1]. In a transformation formally analogous to a Wittig reaction, carbonyl oxygen is replaced by the group R–N= or $R-SO_2-N=$ with elimination of SO_2. This reaction is brought about successfully in most cases by simply heating the pure components together, either alone or in a solvent (see Table 1).

$$R-N{=}SO + O{=}CH-R' \rightarrow R-N{=}CH-R' + SO_2$$

The reaction product from formaldehyde ($R=C_7H_7SO_2$, $R'=H$) does not exist in the expected monomeric form, but corresponds in melting point to the compound, probably

Table 1. Reactions leading to azomethines and amidines

R	R'	M.p. [°C]	Yield [%]
C_6H_6	C_6H_5	48	70
C_6H_6	CCl_3	4 (b.p. 136–139/ 10 mm)	40
$C_7H_7SO_2$	C_6H_5	107	71
$C_7H_7SO_2$	$p\text{-}O_2NC_6H_4$	206—207	78
$C_7H_7SO_2$	CCl_3	105—111	80 [*]
$C_7H_7SO_2$	H	166	
$C_7H_7SO_2$	=CH– 	100—102	85
$C_7H_7SO_2$	=CH– 	121—122	92
$C_7H_7SO_2$	$N(CH_3)_2$	135—137	96
$C_7H_7SO_2$	$N(CH_3)C_6H_5$	101	20
$C_6H_5SO_2$	$N(CH_3)_2$	129—130	97
$p\text{-}Cl\cdot C_6H_4SO_2$	C_6H_5	110	

[*] In benzene in the presence of $AlCl_3$

trimeric, prepared by *McMaster* [2]. All the other compounds clearly show (C=N)– absorption in the infrared. For the preparation of sulphonyl derivatives this reaction – in contrast to the direct condensation of sulphonamides and carbonyl compounds [3] – affords higher yields in a much shorter time (3–50 minutes) and is practically free from side reactions. Aliphatic aldehydes give 1,1-bis(arylsulphonamido)-compounds. The C=N bond in *N*-trichlorethylidene-*p*-toluenesulphonamide is so strongly activated that this compound reacts as a dienophile and forms adducts, *e.g.* with dimethylbutadiene ($C_{15}H_{18}Cl_3NO_2S$, m.p. 134–139 °C, 94 % yield) and cyclopentadiene ($C_{14}H_{14}Cl_3NO_2S$, m.p. 133.5 °C, 93 % yield).

Received, September 12th, 1962 [Z 343/175 IE]

[1] Summary, *G. Kresze* et al., Angew. Chem. internat. Edit. *1*, 89 (1962).

[2] *L. McMaster*, J. Amer. chem. Soc. *56*, 204 (1934).

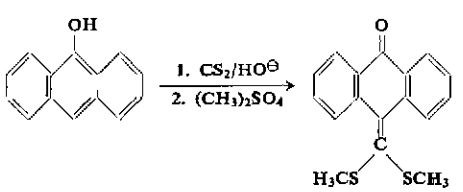
[3] *A. J. Kretov* and *J. A. Abrashanova*, Zh. Obshchey Khimii *27*, (89); 1993 (1957); *J. Lichtenberger*, *J.-P. Fleury* and *B. Barette*, Bull. Soc. chim. France, *1955*, 669; *G. Tosolini*, Chem. Ber. *94*, 2731 (1961).

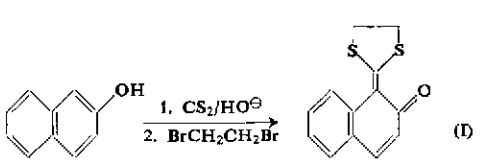
New Ketene Mercaptals and Dithiocarboxonium Salts: ω,ω-Bis(alkylthio)quinonemethides

By Doz. Dr. R. Gompper and Dipl.-Chem. Richard Schmidt

Institut für Organische Chemie und Organisch-chemische Technologie der Technischen Hochschule Stuttgart (Germany)

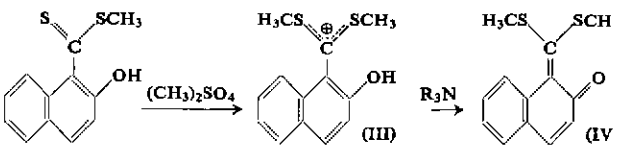
Alkali metal salts of compounds containing acidic C–H groups can be converted with CS_2 into salts of dithiocarboxylic acids, alkylation of which affords ketene mercaptals [1]. We have extended this process to phenols and obtained bis-(alkylthio)quinonemethides. *Inter alia*, dimethyl sulfoxide





(I)

and N,N-dimethylformamide were used as solvents, and concentrated NaOH and KOH as bases. The reaction of CS_2 with phenoxides has already been described [2] (preparation of esters and amides of hydroxydithiobenzoic acid [3]). The type of alkylating agent (dimethyl sulfate, ethyl bromoacetate, ethylene dibromide, ethyl dichloroacetate, dichlorodiphenylmethane, *etc.*) depends on the phenol: in the case of β-naphthol, the use of dimethyl sulfate gives methyl 2-methoxynaphthalene-1-dithiocarboxylate (II). The preparation of 1-bis(methylthio)methylene-1,2-dihydro-2-oxonaphthalene (IV) is accomplished as shown below. The deep-red dithiocarboxonium salt (III), which can be likened to carboxonium



salts [4], is obtained in 78 % yield by heating methyl 2-hydroxynaphthalene-1-dithiocarboxylate with dimethyl sulfate. Treatment with triethylamine in acetonitrile gives compound IV, which is much more reactive than I (reactions with water, alcohol, hydrazine, *etc.*). Esters of alkoxyphenyldithiocarboxylic acids, such as II, can also be converted into dithiocarboxonium salts.

ω,ω-Bis-(alkylthio)quinonemethides, being vinylogues of dithiocarbonic esters, are susceptible to nucleophilic and electrophilic substitution. Hydrazine brings about replacement of the alkylthio groups, or ring-opening in the case of the dithiacylopentane derivatives. Electrophilic reagents (dimethyl sulfate, acetyl chloride) add onto the carbonyl oxygen, forming salts. With halogens, *C*-substitution occurs. In their physical properties, the bis(alkylthio)quinonemethides are similar to the oxonol dyestuffs and to the merocyanines, being yellow to red substances with positive solvatochromism.

Received, September 13th, 1962 [Z 353/185 IE]

[1] *R. Gompper*, Angew. Chem. *73*, 537 (1960); *R. Gompper* and *W. Töpfl*, Chem. Ber., in the press.

[2] See *Houben-Weyl*: Methoden der organischen Chemie. Thieme Verlag, Stuttgart 1955, vol. 9, p. 748.

[3] Personal communication from Dr. *E. Degener*, Farbenfabriken Bayer AG., Leverkusen, Germany.

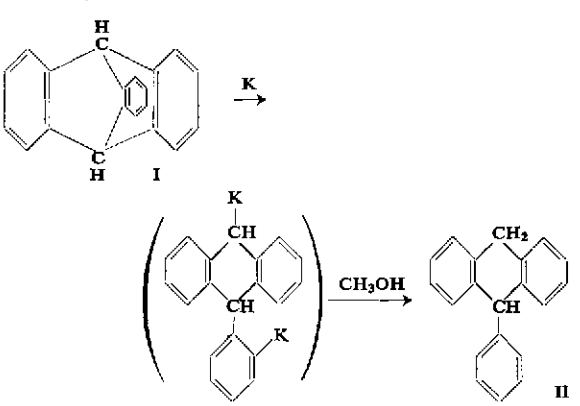
[4] *H. Meerwein* et al., Liebigs Ann. Chem. *632*, 38 (1960).

Cleavage of Arylmethanes by Potassium

By Prof. Dr. W. Theilacker and Dipl.-Chem. E. Möllhoff

Institut für Organische Chemie der Technischen Hochschule Hannover (Germany)

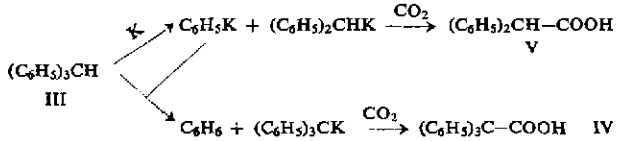
The ring system of triptycene (I) is cleaved by reaction with potassium (in the form of a liquid potassium/sodium alloy) in ether, and 9-phenyl-9,10-dihydroanthracene (II) is obtained by subsequent treatment with methanol [1].



II

This reaction is not brought about by liquid sodium in *n*-dibutyl ether at 110–120 °C. Even though the triptycene ring system displays some ring-strain, this is so small that cleavage of the ring system cannot be understood on these grounds.

We therefore subjected the open analogue, triphenylmethane (III), to the action of potassium in ether and in dioxan and to our surprise, established cleavage here, too, whereas sodium was again without effect. The potassium compounds were treated with carbon dioxide on this occasion, and in this way up to 50 % of diphenylacetic acid (V) was obtained alongside triphenylacetic acid (IV). It is presumed that a cleavage caused by the potassium metal takes place first. On account of its great reactivity, the phenylpotassium formed in this way will immediately metallate compound III, so that the following reaction sequence is probable:



In any case, benzoic acid could not be found among the reaction products.

Diphenylmethane is cleaved more slowly and only to a small extent (about 1 %): the carbonated product very probably contains phenylmalonic acid, because the resulting mixture of acids is odorless at first and acquires the characteristic strong odor of phenylacetic acid only after long standing. It will not be discussed here how the phenylmalonic acid is formed, but in this connection it may be pointed out that phenylmalonic acid is also formed in the reaction of benzylsodium with carbon dioxide [2] Tetraphenylmethane is also cleaved by potassium – actually more rapidly and more fully than III, but the mixture of acids obtained after carbonation has a more complicated composition. However up to 5 % of IV and 13 % of V were obtained from it.

Received, September 17th, 1962 [Z 347/179 IE]

[1] *W. Theilacker* and *U. Berger-Brose*, unpublished work.

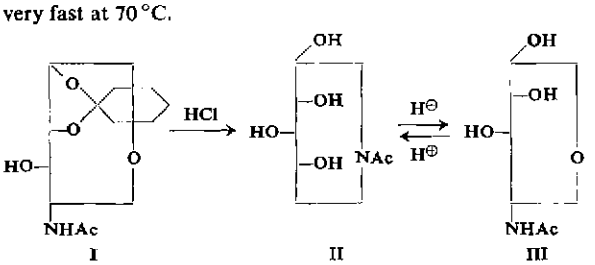
[2] *H. Gilman, H. A. Pacevitz*, and *O. Baine*, J. Amer. chem. Soc. *62*, 1516 (1940).

Preparation of 5-Acetamido-5-deoxy-D-xylopiperidinose

By Dr. H. Paulsen

Institut für Organische Chemie,
Chemisches Staatsinstitut, Universität Hamburg (Germany)

5,6-Diacetamidohexoses exist preferentially in the furanose form. On treatment with acid, 5,6-diaminohexoses, are transformed into 2-aminomethyl-5-hydroxypyridine, with elimination of water [1]. Partial hydrolysis of 5-acetamido-5-deoxy-1,2-*O*-cyclohexylidene-D-xylofuranose (I) leads to a mixture of crystalline 5-acetamido-5-deoxy-D-xylopiperidinose (II; m.p. 154 °C, $[\alpha]_D^{20} = -19.5°$) and a syrup of 5-acetamido-5-deoxy-D-xylofuranose (III; $[\alpha]_D^{20} = +32.5°$) in a ratio of 2:1. Compounds II and III are isolable, are stable in neutral solution, and do not isomerize into one another. In acid solution, the equilibrium II ⇌ III is established starting from either pure II or III, the process being slow at room temperature but very fast at 70 °C.



The bands of the –NH – group present in the infrared spectrum of III are absent in that of II. Four acetylatable hydroxyl groups were detected in the piperidinose II; three were found in the furanose III. A benzylpiperidinoside derivative of II consumed 2 moles of periodate with liberation of 1 mole of formic acid. Thus, a sugar containing nitrogen instead of oxygen in the semi-acetal ring has been prepared for the first time.

Received, September 17th, 1962 [Z 346/178 IE]

[1] *H. Paulsen*, Angew. Chem. internat. Edit. *1*, 454 (1962).

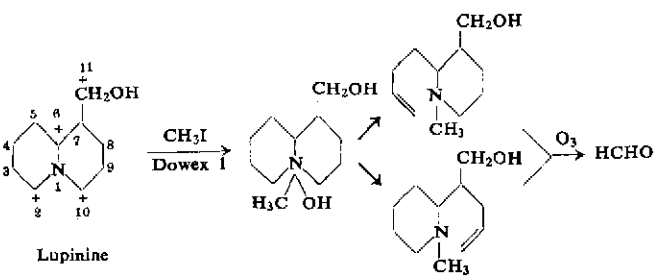
Biosynthesis of Lupinine [1]

By Ing. M. Souček and Doz. Dr. H. R. Schütte

Deutsche Akademie der Wissenschaften zu Berlin
Institut für Biochemie der Pflanzen, Halle/Saale (Germany)
and Institute for Physical Chemistry of the Czechoslovakian Academy of Sciences, Prague (Czechoslovakia)

According to our earlier studies, lupinine can arise from cadaverine or lysine in *Lupinus luteus* [2]. On administering cadaverine-(1,5-^{14}C), to the plants the CH_2OH-group of this alkaloid contained about one-quarter of the specific radioactivity of the whole alkaloid, which would agree with the theory of formation from 2 molecules of cadaverine or lysine [the small crosses in the lupinine formula correspond to the assumed distribution of activity after application of cadaverine-(1,5-^{14}C)].

To verify this theory, lupinine obtained after administration of cadaverine-(1,5-^{14}C) was subjected to exhaustive methylation and a Hofmann degradation; the mixture of bases from the degradation was ozonized and the formaldehyde produced extracted as its dimedone derivative. This formaldehyde corresponds to the C-2 and C-10 of lupinine and should also contain a quarter of the specific radioactivity of the lupinine.



Lupinine

Lupininemethiodide (371 mg) was converted into the base with 10 ml of Dowex 1 (OH^-) and after evaporation, pyrolyzed at 10 mm Hg and with a bath temperature of 200 °C, whereby 163 mg of degradation base distilled over and were then ozonized in 5 ml of acetic acid. The resulting solution was diluted with 50 ml of water and distilled into aqueous dimedone solution, producing 36 mg of formaldimedone. The latter was recrystallized to constant radioactivity, just as the lupininemethoidide had been. The specific radioactivities of the lupininemethiodide and the formaldimedone are summarized in Table 1.

Table 1. Specific radioactivities

Compound	Spec. Activity	Obs.	Theor.
Lupininemethiodide	$1.121 \cdot 10^6$ counts/min/mMol	100 %	100 %
Formaldimedone	$0.289 \cdot 10^6$ counts/min/mMol	25.4 %	25 %

The fact that the C-2 and C-10 each contain a quarter of the radioactivity of the lupinine molecule confirms the theory that in *L. Luteus*, lupinine can arise from two molecules of cadaverine [2].

Received, September 17th, 1962 [Z 351/180 IE]

[1] Part 8 of the series „Zur Biosynthese der Lupinenalkaloide" (The biosynthesis of lupin alkaloids); Part 7: *H. R. Schütte* and *Ch. Schäfer*, Naturwissenschaften *48*, 669 (1961).

[2] *H. R. Schütte*, Arch. Pharmaz. *293*, 1006 (1960).

The Mass Spectroscopic Behaviour of Quadricyclene

By Dr. Z. Dolejšek, Dr. V. Hanuš and Dr. H. Prinzbach

Institute for Physical Chemistry of the Czechoslovakian Academy of Sciences, Prague (Czechoslovakia) and Chemisches Laboratorium der Universität Freiburg/Brsg. (Germany)

When subjected to electron impact ionisation in an ion-source, the behaviour of norbornadiene (I) differs from that of some other C_7H_8 isomers [1, 2] in that acetylene easily splits off from the ion molecule [2a]. The mass spectroscopic behaviour of the quadricyclene (II), a tautomericis omer of (I), is remarkably similar to that of I, in the electron-energy range of 20–75 eV. The following ionisation and appearance potentials were measured using the method of *Waren* [3]. (Benzene, I (C_6H_6) = 9.24 eV, was used to calibrate the energy scale [4].):

I: I (C_7H_8) = 8.60 eV. A($C_7H_7^+$) = 9.75 eV.

II: I (C_7H_8) = 8.70 eV.; 8.85 eV. A($C_7H_7^+$) = 9.56 eV.; 9.75 eV.

The appearance potential A ($C_5H_6^+$) could not be determined; the ion abundance ratios, ($C_5H_6^+$)/($C_5H_5^+$) for compounds I and II however, vary in an identical fashion, even for electron energy values less than 20 eV.



I II

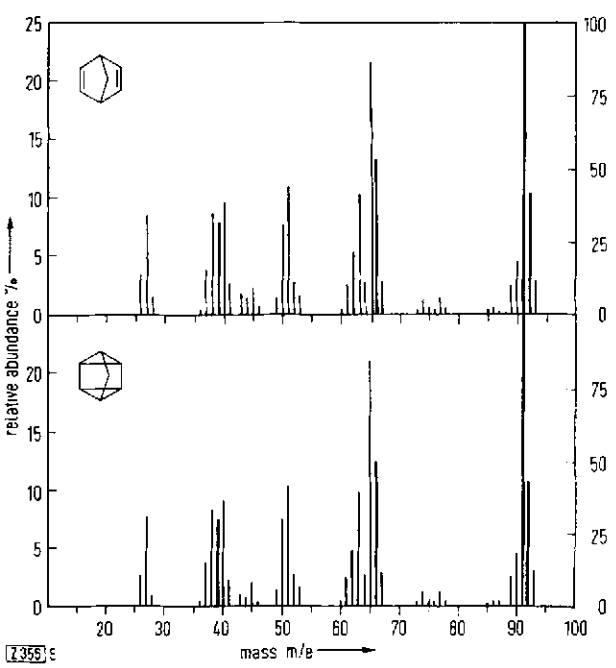


Fig. 1. Schematic representation of the mass spectra
Above: Bicyclo[2,2,1]hepta-2,4-diene
Beneath: Quadricyclene. Electron energy 75 eV.
Left: the scale for the weak, right for the strong lines.

The striking similarity between the mass spectroscopic behaviour of I and II, and in particular the extent of the loss of acetylene (primary back-dissociation of II to I seems impossible under the experimental conditions), suggests that the ion molecules resulting from I and II are in states before dissociation, which are identical with regard to the position of atomic nuclei, excitation states, and frequency distribution of all forms of inner energy. The similarity of the mass spectra and the values of the critical potentials lead to the conclusion that I and II have practically the same heats of formation.

Received, September 21st, 1962 [Z 356/183 IE]

[1] *S. Meyerson, J. D. McCollum*, and *P. N. Rylander*, J. Amer. chem. Soc. *83*, 1401 (1961).

[2] *V. Hanuš* and *Z. Dolejšek*, Kernenergie *3*, 836 (1960).

[2a] *H. Prinzbach* and *J. H. Hartenstein*, Angew. Chem. *74*, 506 (1962).

[3] *J.W. Waren*, Nature (London) *165*, 811 (1950).

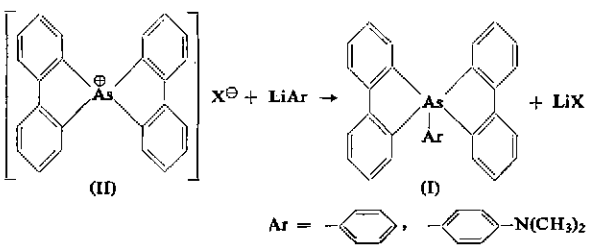
[4] *F. H. Field* and *J. L. Franklin*: Electron Impact Phenomena. Academic Press, New York 1957, p. 266.

Synthesis of As-Bis(diphenylene)-As-arylarsoranes from Spiro-bis(diphenylene)arsonium Salts

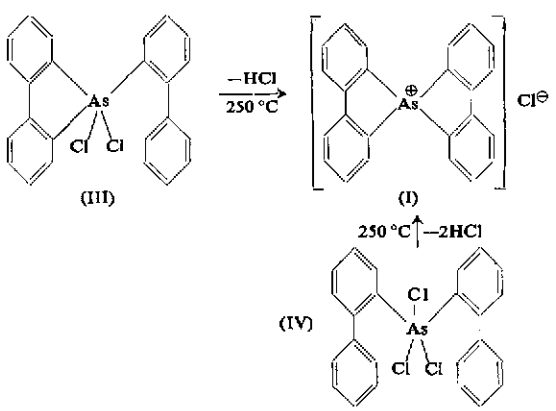
By Prof. Dr. G. Wittig and Dr. D. Hellwinkel

Institut für Organische Chemie der Universität Heidelberg (Germany)

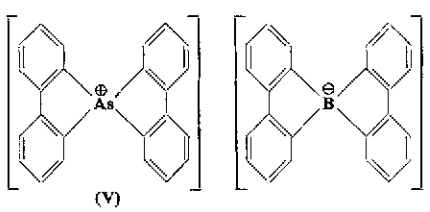
Aryllithium compounds react with spiro-bis(diphenylene)-arsonium salts (II) to give good yields of bis(diphenylene)-arylarsoranes (I), which have been characterized by mixed melting point determination with samples of the same products prepared by another route [1].



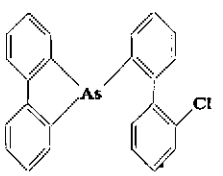
II (X = Cl), m.p. 319 °C is formed in equally good yield by heating diphenylene-*o*-diphenyldichlorarsorane (III), or more simply bis-(*o*-diphenylyl)trichlorarsorane (IV), *in vacuo* at 250 °C, when HCl is eliminated.



The iodide (m.p. 309–311 °C), the tetraphenylborate (m.p. 257.5–259.5 °C) and the bis(diphenylene)borate (V) [2] (m.p. 290–291 °C) have also been prepared.



II rearranges at its melting point into an isomeric compound;



Attempts to prepare spiro-bis(diphenylene)phosphonium and -stibonium salts are in progress with a view to producing the penta-aryl derivatives.

Received, September 21st, 1962 [Z 349/186 IE]

[1] *G. Wittig* and *D. Hellwinkel*, Angew. Chem. internat. Edit. *1*, 53 (1962).

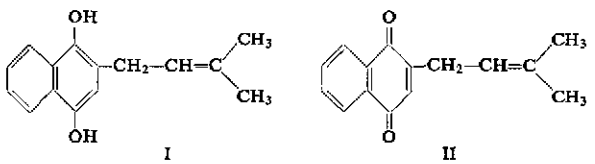
[2] *G. Wittig* and *W. Herwig*, Chem. Ber. *88*, 362 (1955).

A Toxic Quinone from Teakwood

By Prof. Dr. W. Sandermann and
Dipl.-Forsting. M. H. Simatupang

Institut für Holzchemie und Chemische Technologie des Holzes der Bundesforschungsanstalt für Forst- und Holzwirtschaft, Reinbek, Bez. Hamburg (Germany)

Certain varieties of teak cause marked skin irritation and eczema. Investigation of veneers made from such varieties of teak, which had caused skin complaints among many workers in a veneer factory, have now led to the isolation and determination of the constitution of the active principle. Small amounts of golden yellow crystals, which had deposited on the veneers, were purified (m.p. 56–58 °C) by recrystallisation and column chromatography on silica gel. The compound is volatile in steam and has the empirical formula $C_{15}H_{14}O_2$. Its ultraviolet and infrared spectra indicate a naphthaquinone.



I

II

After chemical characterisation, its constitution was clearly ratified by synthesis. The naphthahydroquinone I was obtained by reacting 1,4-naphthahydroquinone and γ,γ-dimethylallyl alcohol together in dioxan with boron trifluoride as catalyst. After oxidation with silver oxide and purification by column chromatography, this yielded a quinone, which, judging by its melting point and mixed melting point determinations, colour reactions, ultraviolet and infrared spectra, was identical with the quinone from teak. Accordingly, the new quinone is γ,γ-dimethylallyl-1,4-naphthaquinone (II).

The toxic quinone can be quickly detected in a cold alcohol extract from teak shavings by the violet-blue colour it develops in the Craven test [1].

Received, September 24th, 1962 [Z 355/182 IE]

[1] *R. Craven*, J. chem. Soc. (London) *1931*, 1605.

Fluorination of Xenon

By Prof. Dr. R. Hoppe, Dr. W. Dähne, Dr. H. Mattauch and Dipl.-Chem. K. Rödder

Anorganisch-Chemisches Institut
der Universität Münster/Westfalen (Germany)

H. H. Claasen et al. [1] have succeeded in preparing XeF_4 by heating a mixture of xenon and fluorine at 400 °C. We too, have been occupied for some time with the fluorination of xenon and have prepared a xenon fluoride differing from that of the American authors. Although our investigations are not yet completed, a brief report on our findings is given. Commercial xenon ("nachgereinigt", *i.e.* extra-purified, as supplied by Linde; 99.9 % Xe, <0.1 % Kr, <0.01 % N_2, <0.001 % O_2) was mixed with carefully purified fluorine (prepared electrolytically) in a $Xe:F_2$ proportion of 1:2 by volume in a sealed quartz vessel and subjected at room temperature to discharges from an induction coil. The electrodes were sealed into quartz fingers which were fused onto and projected into the vessel. After a short interval, a fall in pressure occurred; after several (up to 10) hours, it corresponded at maximum to a 50 % decrease in volume of the original quantity of gas. Simultaneously a colorless crystalline condensate was formed on a cold finger cooled with a solid carbon dioxide/methanol mixture. This primary condensate is strongly "fluorine-active" and on exposure to air has a nauseating characteristically heavy odor; the analytical data show that its overall composition corresponds approximately to the empirical formula XeF_2.

On warming *in vacuo* this condensate sublimes at about 0 °C. Evidently partial decomposition occurs in the process, since only a fraction of the original amount can be subsequently condensed using solid carbon dioxide/methanol; furthermore, elemental xenon was detected. On cooling the bottom of the reaction vessel with solid CO_2 during warming of the primary condensate, well-formed, transparent, single-crystals of millimeter dimensions were formed on the cold finger, which had meantime become clear but whose temperature was now about +10 °C. At room temperature in the absence of atmospheric moisture, these crystals are considerably more stable than those of the primary condensate. The "XeF_2" initially formed is plainly unstable and disproportionates into Xe and a compound containing more fluorine, probably XeF_4. Further investigation is in progress.

Received, October 8th, 1962 [Z 361/188 IE]

[1] *H. H. Claasen*, Chem. and Eng. News, Oct. 1962, p. 39; see also J. Amer. chem. Soc. *84*, 3593 (1962).

Quantitative Gas-chromatographic Separation of all Isomers of n-Octene

By Dr. Elisabeth Bendel, Marianne Kern, Dipl.-Chem. Janssen and Dipl.-Chem. Steffan

Institut für Technische Chemie der Rheinisch-Westfälischen Technischen Hochschule, Aachen (Germany)

In the course of our investigations in the field of the higher olefins, we have achieved an absolutely quantitative separation of all four isomeric n-octenes, including their *cis*- and *trans*-forms by gas-chromatography, using the column combination 8 m β,β′-oxydipropionitrile-silver nitrate [1]/2 m diethyleneglycol-silver nitrate [2] at 42 °C and a helium pressure of 1.36 atm [3]. An apparatus supplied by Research Specialties Co., Richmond, California was used.

n-Octene	Sample Introduced [% by wt.]	Found [% by wt.]
trans-Oct-4-ene	18.0	17.5
trans-Oct-3-ene	9.8	9.1
trans-Oct-2-ene	16.8	17.3
cis-Oct-4-ene	14.1	14.2
Oct-1-ene	18.6	19.7
cis-Oct-3-ene	12.9	12.8
cis-Oct-2-ene	9.8	9.1

Table 1 shows the efficiency of the column arrangement. The seven n-octenes are given in the sequence of their appearance in the chromatogram.

Using a 4 m β,β′-oxydipropionitrile column, we succeeded in separating all the possible *cis-trans*-isomer pairs of the n-undecenes and also in partially separating all the theoretically possible n-undecenes.

Received, October 11th, 1962 [Z 367/192 IE]

[1] Cf., for example, *H. M. Tenney*, Analytic. Chem. *30*, 2 (1958); *H. S. Knight*, Analytic. Chem. *30*, 9 (1958).

[2] Cf. *B. W. Bradford* et al., J. Inst. Petroleum *41*, 80 (1955); *F. van de Craats*, Analyt. chim. Acta *14*, 136 (1956).

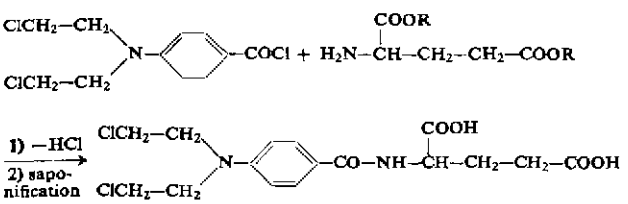
[3] Experimental details will be published elsewhere.

International Cancer Congress in Moscow

July 22nd to 28th, 1962

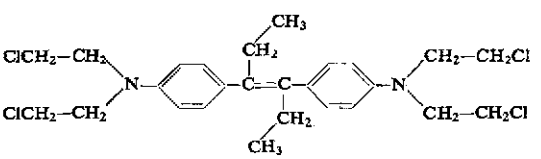
The VIIIth International Cancer Congress in Moscow embraced the whole problem of cancer, beginning with questions of aethiology and prophylaxsis and passing on via the complex of research and therapy to organisational precautions. So abundant was the material that it is difficult to obtain an overall view of it. Here, only that will be mentioned which appears to be of interest in connection with the problem of chemotherapy of malignant diseases.

Substances that have been newly examined in animal experiments and in the clinic are mainly alkylating compounds. Bis-(β-chlorethyl)amino, methanesulphonyloxy, and ethyleneimino residues were still used as active groupings in most cases. An attempt was made to achieve a certain specificity of effect on tumours by incorporating these groupings into molecules that are themselves of importance in biological processes. This was the aim of the synthesis of *p*-[bis-(β-chloroethyl)]aminobenzoylglutamic acid, in which the *N*-mustard grouping is connected to a fragment of folic acid (*S.-C. J. Fu*, Boston, Mass., U.S.A.).

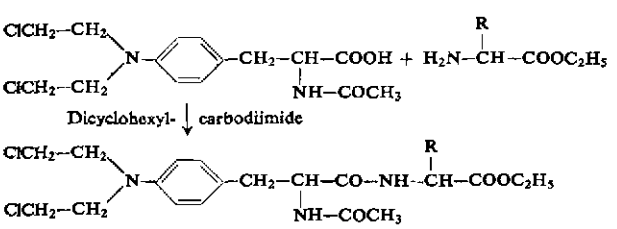


The *m*- and *o*-isomeric compounds were prepared in an analogous fashion. The biological effect on experimental tumours and other microbiological systems is largely restricted to the L-compounds.

The cholesterol ester of *p*-[bis-(β-chloroethyl)]aminophenylacetic acid was tested under the name "Fenesterin." (*S. A. Dyogteva*, Moscow). Owing to its low toxicity and its favourable, in part specific, activity in a series of experimental tumour systems, a clinical examination is intended. By incorporation of bis-(β-chloroethyl)amino groups into molecules that have the effects of sexual hormones (testosterone, stilboestrol, hexoestrol), compounds were obtained which can possibly exert a specific inhibitory effect on tumours in organs controlled by hormones (*A. M. Milcu*, Bucharest, Rumania), *e.g.*

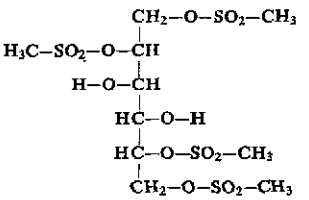


The research team of *L. F. Larionov* (Moscow) has been occupied in determining the structural specificity of tumour inhibition in the sarcolysin peptide series. Various dipeptide esters were prepared in the following manner:

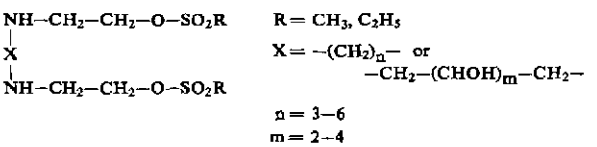


Where phenylalanine was the amino acid component, the L–L-isomer was found to be particularly effective, while the D–D-compound had no effect whatsoever, even in high doses. On the other hand, when valine was attached to the sarcolysin, the activity maximum occurred with the substance with the L–D-configuration. These findings indicate that the action on tumours is not preceded by splitting of the peptide bond.

L. Varga and coworkers (Budapest, Hungary) reported on the continuation of their studies of sugar derivatives with cytostatic activity. The new compounds were mainly methanesulphonic esters of sugar alcohols. Of these, the 1,2,5,6-tetramethanesulphonate of mannitol (TSM) is the most remarkable, being applied clinically on account of its compatibility and anti-tumour activity.

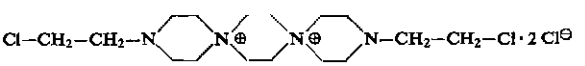


L. Varga replaced the chlorine atoms of previously prepared N-mustard derivatives with methane- or ethane-sulphonyloxy-groups.

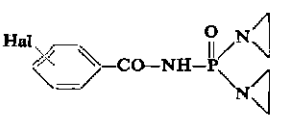


It is striking that most of these compounds show a rather strong tumour-inhibiting activity, while with the corresponding chloroethyl derivatives, this effect is restricted quite narrowly to only a few substances.

J. A. Sorkina (Moscow) reported on investigations with cytostatically active piperazines. "Spiradizin," which has the following structure, had a particularly favourable therapeutic index:

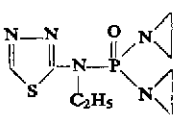


The group of ethyleneimides of phosphoric acid was represented by halogen-substituted derivatives of benzoyldiethylenephosphoramide (benzo-DEPA) (*I. M. Peisaknovich*, Kiev, U.S.S.R.).

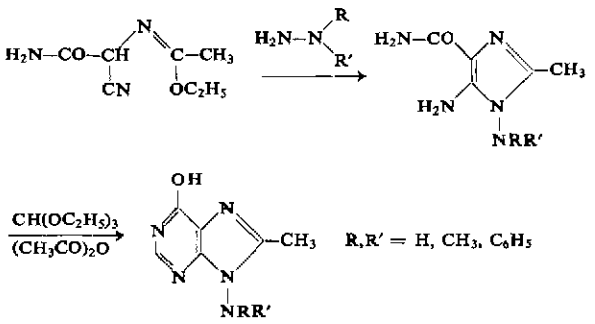


Their tumour-inhibiting properties were examined and compared in several experimental tumour systems.

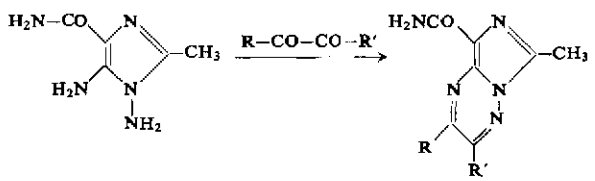
"Thiatriamide" is already being subjected to clinical investigation. This compound is said to surpass preparations previously employed in the treatment of metastatic gastrointestinal tumours as well as metastatic carcinoma of the cervix (*J. C. Bateman*, Washington, U.S.A.).



Antimetabolites that received attention were mainly pyrimidine or purine antagonists. *G. M. Timmis* (London) reported on the synthesis of 9-aminopurines by the following route:

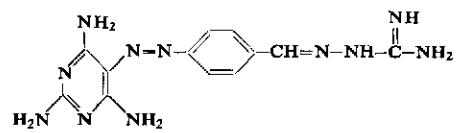


The hydroxyl group of these compounds was subsequently replaced by chlorine, which was in turn exchanged for thio or amino groups. A new ring system, similar to that of the purines, was constructed by means of condensation of 1,5-diamino-4-carboxamidoimidazole, which arose as an intermediate according to the above scheme, with 1,2-diketones (diacetyl, phenanthroquinone):

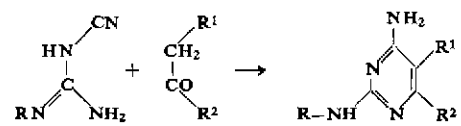


Clinical investigation of these substances is still not carried out.

The presence of amino groups in the 2-, 4-, and 6-positions of the pyrimidine ring is the prerequisite for the appearance of tumour inhibition in the 5-phenylazopyrimidine series. Simultaneously, the benzene nucleus must be substituted in the *p*-position with an electronegative group, *e.g.*, sulphonyl, sulphamyl, phosphonyl (*K. Tanaka*, Osaka, Japan). The guanyl-hydrazone of the 4-(2,4,6-triamino-5-pyrimidinylazo)benzaldehyde showed a particularly favourable effect.

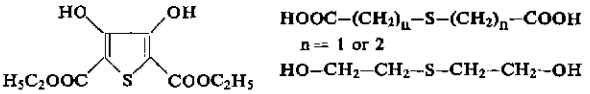


J. Modest (Boston, Mass., U.S.A.) reported the synthesis of 2,4-diaminopyrimidines by condensation of dicyanodiamide with open-chain and cyclic ketones.

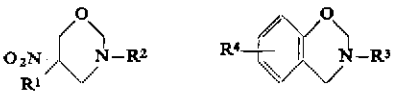


Many of these compounds showed activity in a variety of microbiological systems.

At the VIIth. International Cancer Congress in London in 1958, *M. B. Sahasrabudhe* (Bombay, India) reported that thiophene-2,5-dicarboxylic acid possesses tumour-inhibiting activity. It was assumed that the mechanism of inhibition consisted in an interference with the metabolism of hexosemonophosphate. Meanwhile, a fairly large number of compounds structurally rather closely related to the above substance have been successfully prepared and tested. These include some with remarkable activity and therapeutic breadth (particularly in the case of the ascites form of the Yoshida sarcoma), *e.g.* diethyl 3,4-dihydroxythiophene-2,5-dicarboxylate and open-chain compounds such as thiodiglycolic acid, di(hydroxyethyl) sulphide or di(carboxyethyl) sulphide.



The tetrahydro- and dihydro-1,3-oxazines comprise a further group of substances with tumour inhibiting activity in animal experiments (*J. B. Chylinska*, Breslau, Poland).



Although many compounds have been tested, there was no recognisable relationship between structure and activity.

While screening some 150 acridine derivatives on sarcoma-180, *Z. Ledochowski* (Gdansk, Poland) found only 8 substances with some effect. These all have a dialkylaminoalkyl side chain in the 9-position of the acridine molecule.

While vincaleucoblastin, which has been under discussion for some time, provided the main theme of some lectures in the plant substances group, olivomycin, discovered at the Institute for Antibiotics Research at Moscow, was the main centre of interest in investigations with antibiotics. This substance was isolated from *Actinomyces olivoreticuli*. The growth-inhibiting effect extends in the first instance to rat tumours. It is claimed that favourable results have already been obtained in the clinic as well.

Besides these substances, some of which were new, compounds introduced into cancer therapy some time ago were also the object of numerous investigations, which were designed in the first instance for trying out new testing systems and for elucidating modes of action. With regard to application to patients, it could be seen that attempts were being made to improve the therapeutic yields of existing preparations by means of further development in a methodical fashion. Of importance in this connection were isolated perfusion of tumour-ridden extremities and continuous infusion of cytostatics over lengthy periods.

It is clear from this survey that it has been possible to obtain fresh information in many respects. However, in general the work represents only an extension of known facts. Fresh vistas were not revealed. Chemotherapy is still not in a position to bring about a decisive change in the treatment of cancer. However, the successes that can consistently be achieved with available tools by experienced specialists, in especially favourable instances, justify the hope that this state of affairs is not unalterable.

[VB 638/55 IE]

The Structure and Mode of Action of the Catalyst in the Polymerization of Butadiene with Cobalt Compounds

F. P. van de Kamp, Marl (Germany)

In investigations of the polymerization of butadiene to 1,4-*cis*-polybutadiene with the catalyst system cobalt chloride/ethylaluminum sesquichloride in benzene, it was established that:

The active catalyst is a π-complex of the cobalt with the butadiene. A complex suitable for catalyzing the polymerization is only generated if a Lewis base (water, ether, phosphine, *etc.*) is present in small amounts during the formation of the catalyst. Amines and alcohols are not effective. In the active catalyst, cobalt has a valence of +1, which is stabilized by the Lewis base. In the absence of a Lewis base, a cobalt complex with a valence of −1 is formed. This can be oxidized

to the active complex after addition of a Lewis base. In the presence of relatively large amounts of highly substituted aromatic compounds, *e.g.* mesitylene or hexamethylbenzene, the polymerization is inhibited, the butadiene being displaced from the catalyst complex by the stronger π-electron donor. Since this displacement is an equilibrium reaction, minutest amounts of these stronger π-electron donors have only a retarding effect on the rate of polymerization; π-electron donors also redure the molecular weight of the resulting polymer.

The kinetics of the polymerization of butadiene with the catalyst system Co-(III) acetylacetonate/ethylaluminum sesquichloride were investigated with the aid of adiabatic calorimetry. The rate equation for the polymerization is

$$\frac{d[M]}{dt} = k' \times [M] \times [Co] \times \frac{[M]}{K \times [V] + [M]} \qquad (k'_{45\,^\circ C} = 144.1)$$

The concentration of ethylaluminum sesquichloride does not enter into the rate equation. The fraction on the right side of the equation takes into consideration the partial, reversible inactivation of the catalyst by the benzene solvent. Here [V] is the benzene concentration and K is a constant, the π-electron donor constant, by means of which the tendency of benzene to form a π-complex with cobalt is expressed numerically, taking butadiene as unity. If still other π-electron donors (substituted aromatics, Lewis bases, acetylenes, *etc.*) are present during the polymerization, then additional, similar correction terms must be introduced into the rate equation. By adding small quantities of substituted aromatics to the polymerization mixture, the π-electron donor constants for these compounds were determined from the decrease in the rate of polymerization:

Aromatic	K	Aromatic	K
Benzene	0.0067	Pseudocumene	9.81
Toluene	0.412	Mesitylene	12.18
Butadiene	1.0	Durene	105
p-Xylene	2.27	Isodurene	141
o-Xylene	2.46	Pentamethylbenzene	292
m-Xylene	6.11	Hexamethylbenzene	2798

The rate equation for the catalyst formation was found to be

$$\frac{d\,[Co_K]}{dt} = k_f \times ([Co] - [Co_K]) \times [Al]$$

The butadiene concentration does not enter into the rate equation for catalyst formation. The rate-determining step is the reduction of cobalt from a valence of +2 to +1.

[GDCh-Ortsverband Ruhr, Mülheim/Ruhr (Germany) June 27th, 1962] [VB 599/43 IE]

The Toxic, Inflammatory, and Co-carcinogenic Components of Croton Oil

E. Hecker, Munich (Germany)

Croton oil is a pharmaceutical laxative oil which is obtained from the seeds of the tropical plant *Croton tiglium* L. (Euphorbiaceae). The laxative as well as the toxic and inflammatory or vesicant properties of the oil have long been known and have frequently induced various groups of workers to investigate the chemistry of the oil. It was found [1] that croton oil can cause the development of large tumors from potential tumor cells. This co-carcinogenic action of the oil has acquired considerable importance in cancer research, since its study might provide a clearer understanding of the complicated mechanism of carcinogenesis. The so-called *Two Stage* hypothesis of carcinogenesis based on the results of corresponding investigations is still in dispute since, despite numerous attempts, it has not been possible to isolate the co-carcinogenic component of the oil in a pure state.

[1] *I. Berenblum*, Cancer Res. *1*, 44, 807 (1941).

Using a combination of continuous and discontinuous multiplicative counter current distribution [2] and chromatographic techniques with a new method of assaying inflammatory and co-carcinogenic action, two colourless, amorphous substances A and B were recently [3] separated from croton oil which accounted completely for its toxic, inflammatory and co-carcinogenic properties. Both substances appeared to be chromatographically pure; their R_F values are 0.6 and 0.7; $[\alpha]_D = 47^\circ$ and 46°, respectively. According to their ultraviolet and infrared spectra, they contain free hydroxyl and ester groups and double bonds [4]. When treated with 4-nitroazobenzene-4′-carbonyl chloride [5], substance A produced a deep red crystalline ester [m.p. 86–87 °C, infrared absorption in KBr 2.95 μ (OH); 3.43, 3.51 μ (CH); 5.8–5.85 μ (CO); 6.1–6.15 μ (C=C); λ_{max} (230), 330.5, (345), (460) mμ; ε_{max} in ethanol (15000), 30880, (26800), (634)]. Analyses and molecular weight determinations agreed best with the molecular formula $C_{51}\,H_{64-66}\,O_{12}\,N_3$ [6].

The DL_{50} of both substances was 10 γ/50 g with frogs and the inflammatory level was about 10^{-2} γ/mouse ear. In skin tests, a single dorsal application of 300 γ/mouse of 9,10-dimethyl-1,2-benzantrhacene (DMBA) followed by two treatments per week for 12 weeks with each 0.5 γ of substances A or B produced benignant tumours (mean: 10 or 11/mouse, resp.) in all of the mice. After further 16 weeks without treatment, some of the tumours developed into malignant proliferating, plate-epithelial carcinoma. Sarcoma and leukemia were also observed. Oral administration of DMBA and dorsal application of substance A or B produced epithelial carcinoma and sarcoma in a similar way. Application of 300 γ DMBA alone or application of substance A or B alone did not result in malignant tumours.

The isolation of the co-carcinogens A and B offers a first chance of elucidating the structure of these highly active compounds as well as of testing the two stage hypothesis of carcinogenesis and subjecting it to biochemical analysis.

[Colloquium, Max-Planck-Institut fur Medizinische Forschung, Heidelberg (Germany), June 18th, 1962]

[VB 608/41 IE]

Ions and Radicals from Aromatic Hydrocarbons and Amines

Richard Kuhn, Heidelberg (Germany)

It has proved possible to prepare aza analogues (*F. A. Neugebauer*) of "strongly acidic" hydrocarbons [7]. Like the corresponding hydrocarbons, many of these analogues, *e.g.* IV, yield strongly colored anions in suitable solvents when treated with even dilute aqueous sodium acetate solution. These anions may be oxidized, with formation of free radicals, by treatment with $K_3Fe(CN)_6$ (Electron Paramagnetic Resonance spectra, *K. H. Hausser*). Examples [8]:

I (Biph)C=N–CH(Biph) yellowish, m.p. 199 °C (decomp.) [9]

II (Biph)C=N–$\overset{\ominus}{C}$(Biph) blue

III (Biph)C=N–$\dot{C}$(Biph) olive, forms dimer of m.p. 270 °C (decomp.)

[2] *E. Hecker:* Verteilungsverfahren im Laboratorium. Verlag Chemie, Weinheim/Bergstr. 1955; Z. analyt. Chem. *181*, 284 (1961); Chemiker-Ztg. *86*, 272 (1962).

[3] Reported at a Symposium for Cancer Research, sponsored by the Deutsche Forschungsgemeinschaft, Jan. 2nd–5th, 1962 in Homburg/Saar, Germany.

[4] *J. G. Meyer*, Ph. D. Thesis, University, Munich (1962).

[5] *E. Hecker*, Chem. Ber. *88*, 1666 (1955).

[6] *H. Bresch*, Diploma Thesis, University, Munich (1962).

[7] Definition: *R. Kuhn, H. Fischer, F. A. Neugebauer*, and *H. Fischer*, Liebigs Ann. Chem. *654*, 64 (1962).

[8] (Biph) = 2,2′-biphenylene.

[9] *C. K. Ingold* and *C. L. Wilson*, J. chem. Soc. (London) *1933*, 1493.

The dimer of III is identical with a substance which has been described as tetrafluorenylhydrazine [10] and which should contain four more hydrogen atoms.

IV (Biph)C=CH–NH–CH=C(Biph) orange-yellow, m.p. 320 °C [11]

V (Biph)C=CH–$\underset{\ominus}{\underline{N}}$–CH=C(Biph) red

VI (Biph)C=CH–N=CH–$\dot{C}$(Biph) ↕ (Biph)C=CH–$\dot{N}$–CH=C(Biph) yellow, forms dimer of m.p. 226 °C (decomp.)

If one of the two fluorene residues in VII

VII (Biph)C=CH–CH(Biph)

is replaced by a residue of 1,2;7,8-dibenzofluorene, a colorless hydrocarbon (m.p. 263 °C) results, which yields green anions. The orange isomer (m.p. 251 °C) derived from 3,4;5,6-dibenzofluorene is more strongly acidic and yields blue-red anions. The differences in color and acidity (*D. Rewicki*) were discussed from steric points of view.

[GDCh-Ortsverband Darmstadt (Germany)
July 10th, 1962] [VB 607/42 IE]

End Group Estimation in Polymer Compounds Using Dyes

S. R. Palit, Calcutta (India)

A new technique enables small amounts of organic compounds with functional groups to be detected by colour reactions qualitatively or quantitatively down to amounts of the order of 1 ppm. Either (a) the change in partition coefficient of a dye between two liquid phases is determined when a trace of the compound to be estimated is added to one phase ("dye partition test"), or (b) the change in shade of colour of a solution of a dyestuff in an organic solvent is observed when a salt or a compound with acidic or basic groups is added ("dye interaction test"). Whilst method (a) [12] allows only qualitative estimations, as the compound under investigation may become concentrated in the phase interface, method (b) can be used for quantitative photometric estimations. For example, an aqueous methyl violet solution of pH 7–12 is extracted with benzene. The benzene extract is yellow to brown and reacts with great sensitivity to the smallest amount of an acidic group (*e.g.* –COOH, $-SO_4H$, $-SO_3H$) giving a violet colour. Other dyestuffs, *e.g.* Rhodamine 6 Gx, can similarly be used. Base-sensitive dyes, such as Eosin H and Eosin acid L New, can be employed for the determination of basic groups, *e.g.* amines, at pH 4–5. Examples of applications, especially in macromolecular chemistry, were mentioned, particularly the estimation of end groups for the elucidation of starting, terminal and transfer reactions in polymerisation, the determination of molecular weights, and the estimation of monomer reactivities in copolymerisation.

[Technische Hochschule Stuttgart (Germany) July 17th, 1962]. [VB 625/47 IE]

Recent Contributions to the Chemistry and Biochemistry of some Amino Acids

B. Witkop, Bethesda, Md. (U.S.A.)

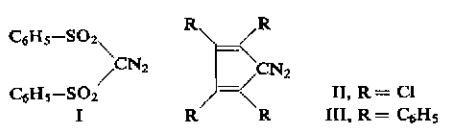
For some time it has been known that hydrolysates of vertebrate and invertebrate collagens show an unidentified peak (Stein and Moore analyzer) in front of hydroxyproline and adjacent to methionine sulfoxides. This peak has now been identified as belonging to a new natural amino acid, *viz.* 3-hydroxyproline which has been isolated and crystallized from acid hydrolysates of mediterranean sponge first by separation of the cyclic imino acids *via* their ether-soluble *N*-nitroso derivatives and separation of the liberated imino acids on columns of IR-120 resin [1]. Out of 64 g of dried sponge there were obtained 62 mg of the crystalline amino acid, $C_5H_9NO_3$, $[\alpha]_D^{20} = -24.4°$. The proof of structure was furnished by the synthesis of the racemic 3-hydroxy-DL-proline by hydroboration of 3,4-dehydro-DL-proline [2] in the following manner: the methyl ester of *N*-carbobenzyloxy-3,4-dehydro-DL-proline [3] was treated with diborane, the resulting alkylborane oxidized with alkaline hydrogen peroxide and the product hydrogenolyzed to a mixture which on automatic amino acid analysis separated into 68% 3-hydroxy-DL-proline, presumably *trans*, 10% 4-hydroxy-DL-proline and a trace of *allo*-4-hydroxy-D-proline. The pure crystalline synthetic 3-hydroxy-DL-proline proved to be sterically homogeneous and was identical with the natural amino acid with regard to mobility in five solvent systems, ion exchange chromatography, high voltage electrophoresis and infrared spectra of the *N*-carbobenzyloxyamino acid methyl esters. D-Amino acid oxidase did not attack the natural amino acid which is, therefore, considered to be *trans*-3-hydroxy-L-proline, whereas the D-isomer in the racemate was quantitatively oxidized by the oxidase, presumably to 1,2-dehydro-3-hydroxyproline. 3-Hydroxy-L-proline has also been identified as a regular constituent of collagen hydrolysates. The diastereoisomeric *cis*-3-hydroxy-DL-proline was synthesized by oxidation of *N*-carbobenzyloxy-3-hydroxy-DL-proline methyl ester with CrO_3 in acetone, reduction with sodium borohydride, hydrolysis of the ester, catalytic decarbobenzyloxylation and separation of the mixture (about 1:1) of diastereoisomeric 3-hydroxy-DL-prolines by chromatographic techniques. Both *cis*- as well as *trans*-3-hydroxy-L-proline appear to be building stones of the peptide antibiotic telomycin [4]. The use of $NaBT_4$ in the reduction of suitable 3- and 4-ketoproline derivatives has permitted the preparation of selectively tritiated 3- and 4-hydroxyprolines which have been used as substrates for the enzymes that effect the incorporation of free into bound hydroxyproline in systems such as chicken embryos as well as *Streptomyces antibioticus*. These studies, carried out in the laboratory of *S. Udenfriend* also used selectively triated proline derivatives for the investigation of the mechanism of hydroxylation of proline to free or bound hydroxyproline.

[Physiologisch-chemisches Institut, Universität Gießen (Germany), July 19th, 1962] [VB 617/52 IE]

A New Procedure for the Determination of the Acidity of Very Strong Acids

F. Klages, K. Bott, and *P. Hegenberg*, Munich (Germany)

In order to investigate the influence of hydrogen bridges on the acidity of acids, the evaluation of acidity according to the rate of decomposition of aliphatic diazo-compounds by acids in ethylene chloride was examined. The diazo-compounds: bis(phenylsulphonyl)diazomethane (I), tetrachlorodiazocyclopentadiene (II), and tetraphenyldiazocyclopentadiene (III), which display varying sensitivities towards acids, were used.



With a sufficient excess of acid, the decomposition reaction is always pseudo-monomolecular and allows the determination

[10] *St. Goldschmidt* et al., Liebigs Ann. Chem. *447*, 197 (1926); *456*, 152 (1927).

[11] *W. Wislicenus* and *K. Russ*, Ber. dtsch. chem. Ges. *43*, 2713 (1910).

[12] *S. R. Palit* et al., Makromolekulare Chem. *36*, 89 (1959); *38*, 96 (1960); J. Polymer Sci. *50*, 45 (1961).

[1] *F. Irreverre, K. Morita, A. V. Robertson*, and *B. Witkop*, Biochem. biophys. Research Commun., in press.

[2] *A. V. Robertson* and *B. Witkop*, J. Amer. chem. Soc. *84*, 1697 (1962).

[3] *N. Izumiya, J. E. Francis, A. V. Robertson*, and *B. Witkop*, J. Amer. chem. Soc. *84*, 1702 (1962).

[4] *F. Irreverre*, unpublished observations.

of a velocity constant which is independent of concentration (k, in Table 1, given in the form of its negative logarithm, pk). This velocity constant is a measure for the acidity of the

Table 1. Acidity Values

	pk(25 °C)≈ pK_α(25 °C)
Chlorosulphonic acid	−11.27
$[R_2OH]^+SbCl_6^-$	−10.50
Perchloric acid	−10.08
Sulphuric acid monomethyl ester	− 7.76
p-Toluenesulphonic acid	− 5.48
$[R_2OH\cdots OR_2]^+SbCl_6^-$	− 4.70
Trifluoroacetic acid	− 2.51
Trichloroacetic acid	− 1.40
Picric acid	+ 0.52
Monochloracetic acid	+ 1.54

acid concerned. Since the ranges of sensitivity of the three diazo-compounds overlap each other and therefore the values of k obtained with them may be related to one another, it was possible to establish a continuous series of acidities over almost 13 pk-units (up to chlorosulphonic acid). On comparison with the "normal" series of acidities obtained from acid-base equilibria, it appeared that the usual pK_a units could be equated with the pk-units determined by us, at least to a first approximation, and that the pk values obtained by the use of (III) at 25 °C are (fortuitously) almost equal numerically to the usual pK_a values in water. From the figures compiled in Table 1, the following observations can be made: 1. R_2OH^+ ions not stabilised by hydrogen bonds have pk values of −10.50 and therefore belong to the strongest acids. 2. The decrease in acidity due to hydrogen bond formation amounts to about 6 pk-units per hydrogen bond, which was to be expected considering that the energy of formation for the hydrogen bonds of strongly acidic substances is about 8 kcal/mole. 3. Strong acids (from *p*-toluenesulphonic acid onwards) which do not tend to form double molecules are essentially stronger in ethylene chloride than in aqueous solution, due to hydration. 4. The extraordinarily high acidity of the R_2OH^+ ion clearly explains the unusually large acylation capacity of its esters, the trialkyloxonium ions.

[GDCh - Ortsverband Freiburg - Südbaden, Freiburg/Brsg. (Germany) July 20th, 1962]. [VB 628/49 IE]

Cleavage of Proteins without Enzymes

B. Witkop, Bethesda, Md. (U.S.A.)

During the last four years several agents have become known that permit a more selective cleavage of peptides and proteins than is possible by enzymatic methods [1]. These novel non-enzymatic cleavage methods are of value in spot-checking and confirming primary sequences. A special test case in this connection has been bovine pancreatic ribonuclease. This enzyme consists of an unbranched chain of 124 amino acids whose secondary and tertiary structure is determined by four disulfide bridges. The cautious reductive opening of these four S—S-bridges in urea solution leads to a complete loss of secondary and tertiary structure which, however, is reconstituted on slow air-oxidation and removal of urea by dialysis, a process which leads to a fully active enzyme indistinguishable from native ribonuclease [2]. It must be concluded that the primary sequence of ribonuclease contains directing groups which help the randomized enzyme in assuming the proper and thermodynamically favored tertiary structure necessary for full enzymatic activity. This historic experiment and similar studies currently conducted in the laboratory of *C. B. Anfinsen* attribute to the primary sequence of certain proteins a novel and far-reaching significance. An interpretation of the directive groups, factors and forces operative in the randomized chain will only be meaningful, if and when the position of each individual amino acid in the primary sequence is known with certainty. Such certainty is difficult to obtain with the conventional methods of sequence determination which have been elaborated into an exacting and complex "book-keeping" or "accounting" procedure in which overlapping peptide sequence must properly add up to a correct total sequence. The "auditing" of such sequences requires non-enzymatic selective cleaving agents which should preferably split peptide bonds that are not attacked by enzymes. Such a cleaving agent is, for example, cyanogen bromide, which selectively and almost quantitatively cleaves the four peptide bonds following the four methionine residues in ribonuclease at room temperature and acidic pH [3]. These cleavages are free of side reactions and lead to three fragments: a core, a chemical tail peptide containing the amino acids 1–13 and free homoserine. If the "*S*-peptide" containing the amino acids 1–20 of ribonuclease is subjected to cleavage by cyanogen bromide, the separation of the products on columns of cyclodextran (Sephadex) led to the same "chemical tail peptide" (*C*-peptide 1–13) and to a new heptapeptide (14–20) whose analysis in conjunction with new results obtained by conventional enzymatic methods [4, 5] necessitated the following correction of the hitherto-accepted sequence:

Old sequence:											NH_2								
	—	Ser	—	Thr	—	Ser	—	Ser	—	Asp	—	His	—	Met	—	Glu	—		
Revised sequence:									NH_2										
	—	Glu	—	His	—	Met	—	Asp	—	Ser	—	Ser	—	Thr	—	Ser	—		
Numbering:	—	11	—	12	—	13	—	14	—	15	—	16	—	17	—	18	—		

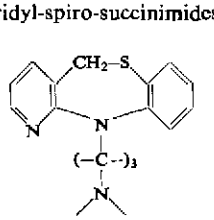
There is reason to believe that the heptapeptide (14–20) which has been carved out of ribonuclease-*S*-peptide with the aid of cyanogen bromide, is associated with the mode of action and the active center of the enzyme. *K. Hofmann* [6] recently succeeded in synthesizing this heptapeptide. Both natural as well as synthetic heptapeptide seem to rearrange or isomerize under the conditions used for characterization on the Stein and Moore analyzer, namely citrate buffer pH < 3.0 and 60 °C. This phenomenon is under active investigation.

[GDCh-Ortsverband Marburg/L. (Germany), July 20th, 1962] [VB 618/53 IE]

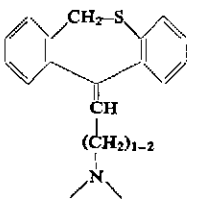
The Influence of Chemical Agents on Mental Illness

E. Jucker, Basel (Switzerland)

There are two basic types of psychopharmacological agents: preparations with psychosedative-depressive action and those with antidepressive-stimulant action. Some classes of compounds can embrace members with both types of action. The investigations of the author and his co-workers [7] led to new thiazepine, thiepine, dibenzocycloheptadiene and dibenzocycloheptatriene derivatives, to derivatives of 1- and 4-azathioxanthene and to the synthesis of the previously unknown piperidyl-spiro-succinimides;



5,11-Dihydrobenzo[*b*]pyrido[2,3-*e*]-1,4-thiazepine derivatives



6,11-Dihydrodibenzo[*b*,*e*]-thiepine derivatives

[1] Cf. *B. Witkop*, Advances Protein Chem. *16*, 221 (1961).

[2] *F. H. White, jr.*, J. biol. Chemistry *235*, 383 (1960).

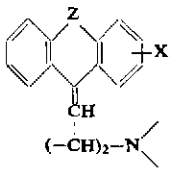
[3] *E. Gross* and *B. Witkop*, J. biol. Chemistry *237*, 1856 (1962).

[4] *D. G. Smyth*, *W. H. Stein*, and *S. Moore*, J. biol. Chemistry *237*, 1845 (1962).

[5] *J.T. Potts*, *A. Berger*, *J. Cooke*, and *C. B. Anfinsen*, J. biol. Chemistry *237*, 1851 (1962).

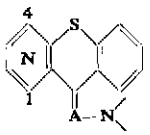
[6] Unpublished results; personal communication.

[7] *A. Ebnöther*, *F. Gadient*, *A. Lindenmann*, *E. Schenker*, *A. Stoll*, and *R. Suess*, Pharmaceutical-chemical Research Laboratories, SANDOZ A.G., Basel (Switzerland).

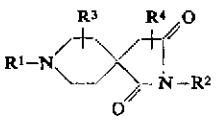


X=H, halogen, alkoxy alkylthio, *etc.*

Z = $-CH_2CH_2-$: Dibenzocycloheptadiene derivatives
Z = $-CH=CH-$: Dibenzocycloheptatriene derivatives

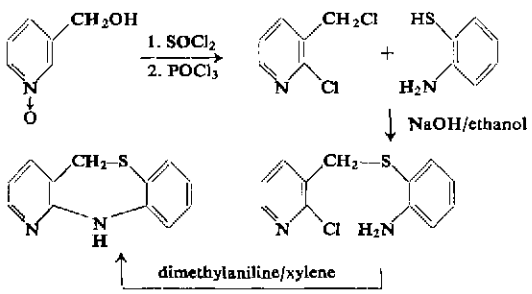


1- and 4-Azathioxanthene derivatives

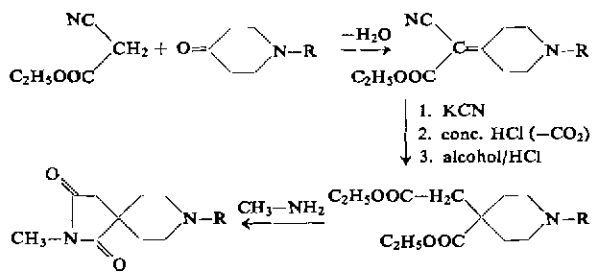


2,8-Diazaspiro[4,5]decane-1,3-diones Piperidyl-spiro-succinimides

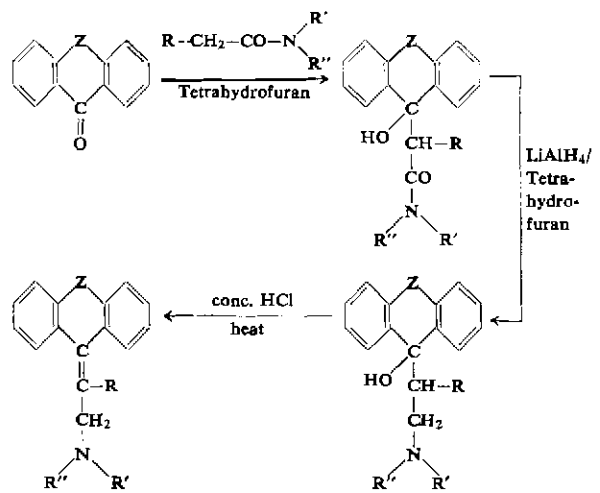
The syntheses of these various classes of compound were illustrated by several examples. Thiazepine derivatives are obtained in the following way:



Piperidyl-spiro-succinimides may be prepared as follows:

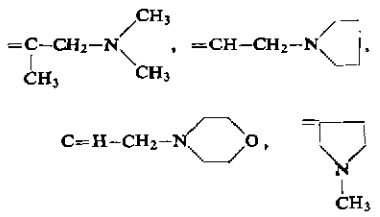


A new procedure was also described for synthesizing from tricyclic compounds, *e.g.* of the dibenzocycloheptadiene type, novel derivatives with a $-C-C-N-$ side-chain; the latter are of particular interest for studying structure-activity relationships:



Z = $-CH_2CH_2-$ or $-CH=CH-$
R = H, alkyl or a heterocyclic ring containing N and R′ or R″
R′ = alkyl or together with N and R or R″ a heterocyclic ring
R″ = as defined under R′.

Examples of the side-chain in the final product:



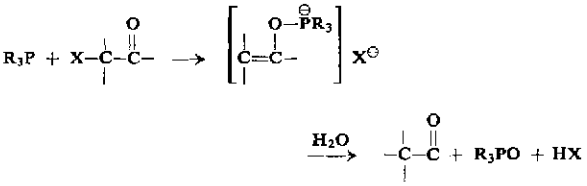
[Colloquium at the Chemical Institute of the University, Mainz (Germany), July 26th, 1962]

[VB 630/50 IE]

Phosphonium Salts and Quasi-phosphonium Salts

Hellmut Hoffmann, Mainz (Germany)

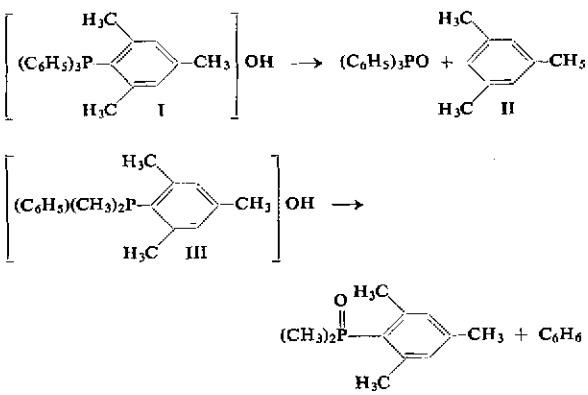
On reaction with tertiary phosphines, α-halogeno-carbonyl compounds can form either C-phosphonium salts or enol-phosphonium salts. Enolphosphonium salts are extremely sensitive to solvolysis. On hydrolysis, phosphine oxides, dehalogenated carbonyl compounds and hydrogen halide are formed:



The formation of the enolphosphonium salts is initiated by nucleophilic attack by the phosphine at the positively polarised halogen. An analogous mechanism can be assumed for the formation of enolphosphates in the Perkow reaction.

Representatives of the following classes of compound also react with tertiary phosphines in the presence of proton donors with the elimination of positive halogen: *o*- and *p*-halogeno-arylamines and -phenols, α-halogeno-phosphonium salts, -phosphine oxides, -sulphones, and -pyridinium salts.

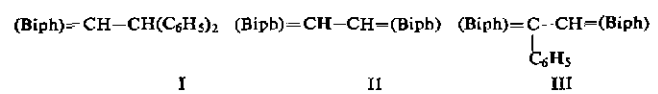
In addition to mesomeric and inductive effects, steric factors may play a part in the alkaline cleavage of *C*-phosphonium salts. This is especially evident in the case of phosphonium salts containing trityl or mesityl residues; thus triphenyl-mesityl phosphonium hydroxide (I) splits off primarily mesitylene (II), whilst with dimethylphenyl-mesityl phosphonium hydroxide (III), in which the steric strain is less, the mesityl residue is held more firmly than the phenyl residue.



[GDCh-Ortsverband Wuppertal-Elberfeld (Germany), August 8th, 1962].

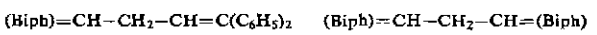
[VB 637/54 IE]

The synthesis of highly acidic hydrocarbons is reported by *Richard Kuhn* et al. The synthesis of the biphenylene derivatives I, II, III, IV, and V is described. These compounds form deep blue or red carbanions with 1 N NaOH in acetone, tetrahydrofuran, or dimethylformamide. Addition of acids

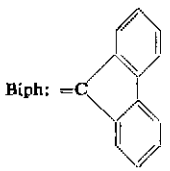


I II III

leads to recovery of the unchanged hydrocarbons but, on addition of phenol, the color remains, showing that the hydrocarbons are more acidic than phenol. Compound V is the most acidic, followed by IV, III, II, and I. The unusual

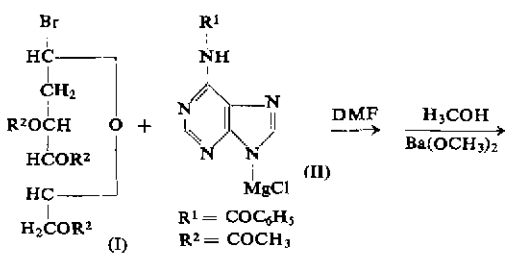


IV V



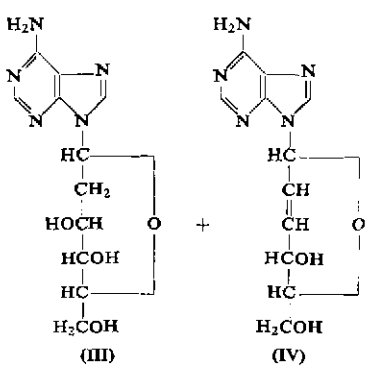
acidity of the hydrocarbons may be due to aromatic portions, becoming planar and to the great number of mesomeric limiting structures possible for the anion. The stability of the anions does not seem to depend on a specific number of π-electrons. The salts can be methylated with methyl iodide, the methyl group being attached to various carbon atoms, depending on the distribution of the negative charge. The anions are oxidised to yellow radicals by $K_3Fe(CN)_6$. / Liebigs Ann. Chem. *654*, 64 (1962) / –Sk. [Rd 297/88 IE]

Unnatural nucleosides with an antileukemic activity were synthetised by *F. Šorm* et al. By reaction of 1-bromo-2-deoxy-3,4,6-tri-*O*-acetyl-D-glucose (I) with II in dimethylformamide and subsequent methanolysis, the anomeric



(I) (II)

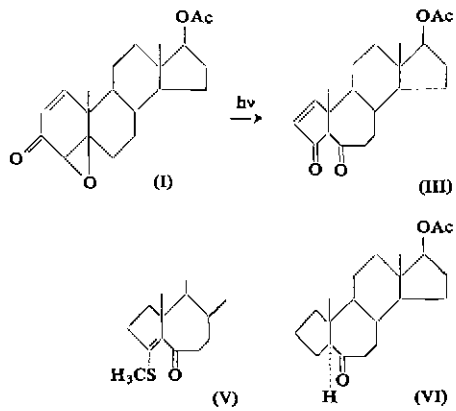
$R^1 = COC_6H_5$
$R^2 = COCH_3$



(III) (IV)

9-(2-deoxy-1-D-glucosyl)adenine compounds III were obtained. Compound IV, which was obtained as a by-product, was found to be active against leukemia in mice. / Experientia *18*, 213 (1962) / –Re. [Rd 290/83 IE]

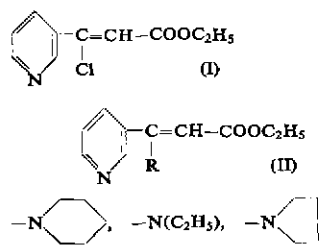
A new photoreaction is the isomerisation of saturated and β,γ-unsaturated 3-oxo-4,5-epoxy-steroids of the androstane series to 10(5 → 4)-*abeo*-steroids with opening of the epoxide ring found by *C. Lehmann, K. Schaffner*, and *O. Jager*. Irradiation with an Hg vapor lamp of a dioxan or ethanol solution of the 4β,5-epoxide I or its 4α-epimer II leads to the isomeric 3,5-dioxo-17β-acetoxy-Δ^1-10(5 → 4)-*abeo*-androstene III (m.p. 171–72 °C, $[\alpha]_D = +98°$, $CHCl_3$; yields about 95 and 60 %, respectively). Under the same conditions, the saturated analogues of the epoxides I and II give rise to the β-diketone IV (m.p. 154–56 °C, $[\alpha]_D = +47°$), which can also be obtained from III by hydrogenation. Spectroscopic



(I) (III) (V) (VI)

data (infrared, NMR) indicate that III and IV are almost completely enolised. The β-dicarbonyl system was characterised by reaction with $FeCl_3$, Cu-complex formation and conversion with hydrazine into the pyrazole derivative. The structure of the compounds, in particular their configuration at C-10, was established by the fact that it was possible to desulfurise the thio-ether V (derived from IV) reductively to give the saturated acetoxy ketone VI, which on hydrolysis gave known 5-oxo-17β-hydroxy-4α-10(5 → 4)-*abeo*-androstane. / Helv. chim. Acta *45*, 1031 (1962) / –Ku.
[Rd 293/84 IE]

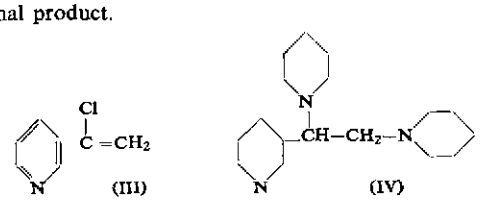
Tertiary enamines of type II were obtained by *K. M. Naef* and *H. Schaltegger* from the chloroacrylic ester I in benzene in 40 to 70 % yield. I was made by chlorination of ethyl nicotinyl acetate with PCl_5 in benzene, giving a *cis: trans* isomer ratio ≈ 1:7. The action of secondary bases on ethyl nicotinyl-acetate yielded the corresponding β-ketoamines.



(I) (II)

R = –N⟨O⟩, –N⟨ ⟩, –N(C₂H₅), –N⟨ ⟩

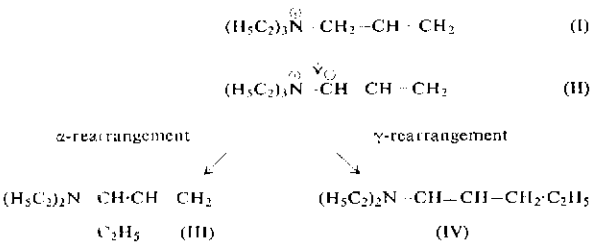
Compound IV was isolated after treatment of III with secondary amines. In contrast, with 2 moles of piperidine, 3-pyridylacetylene gave 1-(3-pyridyl)-2-pipiridino-ethylene as a stable final product.



(III) (IV)

Helv. chim. Acta *45*, 1018 (1962) / –Bs. [Rd 287/89.IE]

The base-catalysed rearrangement of trialkylallylammonium salts has been studied by *H. Hellmann* and *E. N. Scheytt*. On treatment with C_6H_5Li or $NaNH_2$, the triethylallylammonium



ion (I) yields a mixture of the amine III and the eneamine IV, via the mesomeric ylide intermediate II. With phenyllithium in ether or tetrahydrofuran, the ratio of α- to γ-rearrangement is 1:1, with sodamide in xylene, it is 1:2. Under otherwise comparable conditions (in liquid ammonia with $NaNH_2$), the γ-rearrangement was favored by increases in temperature. In no experiment was an amine found which might arise from a *Hofmann* degradation. Rearrangement of tripropylallylammonium bromide in boiling xylene with $NaNH_2$ as the base and subsequent hydrolysis yielded 32 % hexanaldehyde; treatment of tributylallylammonium bromide gave 20 % oenanthaldehyde. / Liebigs Ann. Chem. *654*, 39 (1962) / –Sk.

[Rd 298/90 IE]

BOOK REVIEWS

α-Aminoalkylierung, Darstellung und Eigenschaften der Kondensationsprodukte H-acider Stoffe mit Carbonylverbindungen und Aminen (α-Aminoalkylation: Preparation and Properties of the Condensation Products of Acidic Substances with Carbonyl Compounds and Amines). By *H. Hellmann* and *G. Opitz*. Verlag Chemie, GmbH., Weinheim/Bergstr. 1960. 1st. Ed., XI, 336 pp., 1 fig., 112 tables. Price DM 36.

This book describes the preparation and properties of Mannich bases and similar condensation products of acidic reagents with amines and carbonyl compounds. In Part 1 (222 pp.), after a discussion of the reaction mechanism of aminomethylation reactions, the OH-, SH-, SeOH-, PH- and particularly the CH-acidic compounds that can be aminoalkylated with carbonyl compounds and amines are systematically enumerated. Analogous reactions are compiled in tables giving yields and literature references, so that the reader can rapidly inform himself of the preparative possibilities of various types of reaction.

Part 2 (76 pp.) describes the reactions of Mannich bases and similar aminomethylation products, particularly with nucleophilic reagents. The authors have divided the many possible kinds of reaction into "transaminoalkylation" (transfer of aminoalkyl groups onto nucleophilic reaction components), amine elimination, hydrogenolysis and the various condensation reactions that take place with loss of amine. This part of the book also has a chapter on the reaction mechanisms, while the experimental details are given in a concise but clear and rapidly comprehended form, supplemented by numerous tables.

The extensive factual material is arranged from the preparative point of view. To this the authors have added advice useful for planning and carrying out syntheses, making this book of especial value to the chemist who works in the field of organic synthesis. The literature has been surveyed up to the end of 1958, so that the volume can also be used as a reference book.

The great extent of the literature surveyed (1876 references) has made it difficult to avoid a few inaccuracies [cf. the review by *E. L. Eliel*, J. Amer. chem. Soc. *83*, 4490 (1961)]. Thus, the synthesis of 8-ketospartein, which is described on pp. 210 and 211 has been refuted in Angew. Chem. *65*, 161 (1953).

The book lacks both subject and author index. Whereas the subject index is made largely superfluous by the very comprehensive Table of Contents, the bibliography at the end of the work is no substitute for an author index. One way of correcting this might be to add to each literature reference the number of the page on which it is mentioned in the text. This very well printed (instructively arranged, clear formulae) and produced book should be available to every organic chemist. It will be indispensable to the practical synthetic chemist who has to do with amines and their derivatives.

J. Thesing [NB 903/26 IE]

Fortschritte der Arzneimittelforschung (Advances in Drug Research), edited by *E. Jucker*, Birkhäuser-Verlag, Basel-Stuttgart, 1960/61, Vol. II: 636 pages, numerous tables, cloth bound, price DM 85.–; Vol. III: 563 pages, cloth bound, price DM 90.–.

The two volumes continue the series begun in 1959 of comprehensive reviews [1] of current fields of drug research, the chemical, pharmacological and clinical aspects being dealt with by competent authorities.

In Volume II, the first 79 pages are devoted to new diuretics. *K. H. Beier* and *J. E. Baer* first give an account of the physiology of renal function and its control by endocrinic substances. The following section deals with xanthines and related compounds (pyrimidines, aminouracils, triazines, and guanamines), organomercury compounds, antagonists of nephrotropic hormones (amphenone, spirolactone, and vasopressin antagonists), carbonic anhydrase inhibitors and chlorothiazide and its related compounds. Relationships between structure and activity, sites of attack, mechanisms of activity and clinical uses are considered. Structural formulae of 36 of the most important diuretics are given (487 literature references). – *B. Camerino* and *G. Sala* give a 62-page review of "Anabolic Steroids". They first go into the characteristics of anabolic activity and the possibility of its detection in animal tests.

After touching on the question whether physiological secretion of anabolic steroids occurs, they report on the anabolic action of androgens and on experiments carried out hitherto in attempts to separate anabolic and androgenic activity. The structure and synthesis of relevant testosterone derivatives are discussed (363 references). – *C. J. Cavalito* and *A. P. Gray* give a detailed account (90 pp.) of "The Chemical Nature and Pharmacological Action of Quaternary Ammonium Salts", which are sub-divided into mono-, bis-, and poly-quaternary compounds. Other onium compounds are briefly discussed (518 references). – An appropriate complement to this is a detailed treatment of "Ganglion Blocking Agents", by *K. Nádor* (118 pp.). In addition to methods of pharmacological testing and the potential therapeutic applications, a large number of compounds are considered in 51 detailed tables in which their ranges of activity and constitutional formulae are contrasted. A section, ganglion stimulants, is followed by information on their clinical uses and syntheses (264 references). – In 22 pages, *A. Zerletti* gives a concise account of the occurrence and significance of "Indole Structures in Medicine and Biology". This is a report on the occurrence of indole derivatives in animals and plants. The metabolic products of tryptophan are most important in medicine, for besides 5-hydroxy tryptamine, the endogenous formation of nicotinamide from tryptophan and its significance in causing the pellagra syndrome as a result

[1] Angew. Chem. *72*, 284 (1960).

of tryptophan deficiency in food because of an unbalanced maize diet, are important (69 references). *W. Kunz* deals extensively in 44 pages with new drugs from 29 various fields of symptomatic indication (with structural formulae, 193 references). *A. Pletscher, K. F. Gey* and *P. Zeller* give an exhaustive survey of "Monoamineoxidase Inhibitors"; their chemistry, biochemistry, pharmacology, and clinical uses are considered in equally comprehensive fashion. The literature index containing 1,389 references probably gives a complete survey of the pertinent literature up to 1960.

W. A. Sexton gives an account in 20 pages of "The Structure and Biogenesis of Certain Antibiotics". He shows that one series of antibiotics can be regarded as being built up from acetic acid, whilst others can be regarded as being derived from amino acids. The observation of the occurrence of D-amino acids in antibiotics and the corresponding enzymes in bacteria is noteworthy (95 references). In the last chapter, *D. W. Woolley* draws attention to substances named by him "Antimetabolites", by which he means compounds of similar structure to endocrine substances that can competitively inhibit the latter. Thus, because one can form new classes of physiologically active substances in this way, he speaks of a "revolution in pharmacology". He cites a number of known examples in support of this thesis. (17 references).

In Vol. III, *N. P. Buu-Hoi* describes (66 pp.) pharmacologically interesting fluoro compounds from the groups of antimetabolites, diuretics, narcotics, convulsants, anti-convulsants, relaxants, neuroplegics, steroid compounds, antihistamines, and chemotherapeutic agents. Over 160 structural formulae indicate the great activity of pharmaceutical chemistry in this field (172 references). The connection between "Chemical Constitution and Anthelmintic Activity" in the classes of phenothiazines and piperazine derivatives is discussed by *J. Cymerman Craig* and *M. E. Kate* (54 pp.), who cite 147 literature references in discussing methods of testing; 209 further references are concerned with phenothiazines and 65 with piperazines. The present position of research in the field of 5-hydroxytryptamine and related indole alkylamines is exhaustively surveyed by *V. Erspamer* (213 pp.). No less than 1358 literature references (up to April 1961) are discussed, so that the review gives a complete picture of present knowledge of the physiology, biochemistry, and pharmacology of 5-hydroxytryptamine. In Volume III also, *W. Kunz* gives an account of newly marketed drug preparations in various fields of application. (38 pp., 76 references). *G. B. West* evaluates a large amount of literature (254 papers with titles given) in order to find pharmacological ways of solving the problems of allergies, in which the connection between the liberation of histamine and/or 5-hydroxytryptamine and allergic phenomena is analyzed (42 pp.). Finally, *K. Zepp* and *C. Zepp* discuss (94 pp.) 79 "Anticarcinogenic Antibiotics from Actinomycetes"; they briefly cover the unsatisfactory nature of the existing experimental methods of testing antitumoral activity *in vivo* and *in vitro*. The few (9) preparations hitherto tested clinically or occasionally used have in many cases given a temporary regression of tumours, improvement of general condition or prolongation of life, but have not effected a cure (408 references).

These two volumes of the series fulfil their purpose excellently "... to give the active worker the possibility of orientating himself quickly and thoroughly in a given field and of stimulating him to carry on his inquiries and to set about new lines of research". The thoroughness and effort which the authors have brought to their task is shown by the fact that in the two volumes over 6000 individual references have been critically considered; the contributors and the editor cannot be thanked too much.

The promise of further volumes of the work is very welcome; chemists, pharmacologists and clinical workers will find them equally useful.

The de luxe finish of the volumes is particularly noteworthy.

O. Schaumann [NB 883/24 IE]

Landolt-Börnstein. Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik und Technik. (Numerical Data and Functions in Physics, Chemistry, Astronomy, Geophysics, and Technology). Volume 2. Properties and States of Matter. Part 4. Caloric data. Edited by *K. Schäfer* and *E. Lax*. Springer-Verlag, Berlin/Göttingen/Heidelberg, 1961. 836 pp. DM 438. (about $100.).

The present 4th part of volume II contains mainly caloric data of elements and pure chemical compounds. As to the thermodynamic properties of mixtures and solutions, only those of metallic solutions (alloys) as well as heats of adsorption and neutralisation are included. Tables of heats of mixing, solution, and dilution, specific heats of mixtures and solutions, thermodynamic properties of ions in solution as well as heats of formation of molecular compounds and complexes in solution will be dealt with in a later part. For the first time, all caloric data, in this volume are given in absolute joule, *i.e.* in kj/mole or j/mole/degree.

A review of the development of numerical values of some fundamental constants during the period 1900–1960 (*H. Kienitz*, 14 pp.) is followed by tables of increments for additive calculation of the values for ΔH_f° and ΔG_f° of organic compounds in the gaseous state between 298°K and 1500°K. (*H. Kienitz*, 24 pp.). The main part (*W. Auer, H. Kienitz, K. Schäfer*) starts with an orderly list (140 pp.) of all the substances for which thermodynamic data are published. References to the following tables or to the bibliographic index are given for about 4000 elements and inorganic compounds and about 4500 organic and organometallic compounds. These tables (213 pp.) include the normal values (25°C) for the molecular heat, entropy, enthalpy of formation and free enthalpy of formation under normal conditions, and the phase transformation enthalpies for about 1600 inorganic and about 2300 organic and organometallic substances. These are followed by tables (81 pp.) of the thermodynamic functions at normal pressures as a function of temperature for about 90 substances over the range 0–300°K and for about 170 substances over the range 298–1500°K. Extensive data (94 pp.) on the influence of temperature on the molecular heat C_p at normal pressures are given for about 370 elements and inorganic compounds and for about 230 organic compounds over the range 0–300°K, as well as for about 550 elements and inorganic compounds and for about 200 organic compounds over the range 298–1500°K. Furthermore, 100 diagrams concerning the variation of C_p with temperature are reproduced.

This main part includes an alphabetically arranged annual bibliographic index up to the end of 1959 (119 pp.), comprising about 8000 references, 2700 of these being from the period since 1950.

Further tables and diagrams deal with the influence of pressure on C_p in the case of gases (*H. D. Baehr*, 29 pp.), and the specific heats of gases in the plasma state (*F. Burhorn, R. Wienecke*, 18 pp.), Planck-Einstein and Debye functions (*F. Lösch*, 14 pp.), anharmonicity correction factors, and internal rotation (*K. Schäfer*, 5 pp.). A section by *H. D. Baehr* (18 pp.) is devoted to the Joule-Thomson effect and the isothermal throttling effect. This is followed by a very comprehensive survey of numerical data and diagrams concerning the magneto-caloric effect for 17 paramagnetic salts at very low temperatures (*H. Nelkowski*, 33 pp.). From the field of thermodynamic values for mixed systems, this volume includes thermodynamic data for metallic solutions (*O. Kubaschewski*, 31 pp.), heats of adsorption and wetting (*K. Bratzler*, 7 pp.), and heats of neutralisation of inorganic and organic acids and bases in water and non-aqueous solvents (*A. Neckel*, 18 pp.).

Some detailed recent surveys of caloric data of certain classes of compounds are to be found in the literature, *e.g.* the tables of the National Bureau of Standards, Washington. What was lacking, however, was a volume of tables, covering the entire field of thermodynamic critical data, as comprehensive and up-to-date as this. The publishers and the contributors therefore deserve our gratitude for their painstaking care in

collecting and sorting the factual data, which has grown so considerably in volume in this field. The clear arrangement of the tables and the high quality of print, which render it easy to find the numerical values required, also deserve special mention. The publication of this volume, which has been turned out by the publishers in their customary excellent manner, will tend to enlarge further the circle of users of Landolt-Börnstein.

Friedrich Becker [NB 904/27 IE]

Methoden der organischen Chemie (Methods of Organic Chemistry) (Houben-Weyl), Vol. XIV/1: **Makromolekulare Stoffe** (Macromolecular Substances), edited by *Eugen Müller*. Georg Thieme Verlag, Stuttgart, 1962, 4th edition, lxiv, 1360 pp., 60 figures, 177 tables. Cloth bound, price DM 287.– (about $75.–).

In this "Age of Plastics", particular importance should be attached to volume XIV. While only scant reference was made to macromolecular substances in the 3rd edition, the 4th edition required so vast a volume that it had to be divided into two parts. It is admirable that the enormously extensive material could be incorporated into the handbook at all. The success with which it has been done betrays the initiative of *Otto Bayer* in the reorganization of the complete work.

Polypeptides and polysaccharides are not discussed under the arrangement adopted for volumes XIV/1 and XIV/2. The silicones, too, will only be dealt with in connection with low molecular weight organosilicon compounds. Emphasis is placed on laboratory methods for preparing macromolecular substances and on numerous references to processes of technical importance. Subsequent technological processes such as the spinning of polyamides or the vulcanization of butadiene polymers are not considered.

The present volume XIV/1 begins with nomenclature and terminology (pp. 1–23) in the manner of a textbook. Chemists who do not yet know the meaning of "erythro-diisodaktisch" (erythro-diisotactic), or what a "Pfropfcopolykondensat" (graft co-polycondensate) might be, need only refer to the 8-page table (pp. 16 *et seq.*). The remainder of volume XIV/1, which is the result of the cooperation of twenty-four authors, deals with the preparation of macromolecular substances by polymerization of vinyl and divinyl compounds:

I. General points concerning the polymerization of vinyl and divinyl compounds, and its performance in bulk and in solution (pp. 24–132).

II. General points concerning the polymerization of vinyl and divinyl compounds in heterogeneous phase (emulsion, bead, suspension, and precipitation polymerization, pp. 133 to 560).

III. Special polymerization processes for the most important monomers (pp. 561–1182).

The bibliography, author and subject indexes amount to no less than 177 pages. A good impression is made by the large number of patents included in the author index. Separating the wheat from the chaff is presumably more difficult here than in other sections of chemistry. The fact that a thorough attempt at this has plainly been made is probably among the main advantages of the way the subject has been presented.

It should be noted that much space is also devoted to the preparation of pure monomers and to reaction kinetics. The purification of ethylene, for instance, is discussed in detail before the high pressure, the Phillips, the Standard Oil and the *Ziegler* processes for preparing polyethylene are described.

The volume "Makromolekulare Stoffe" ("Macromolecular Substances") in the Houben-Weyl-Müller series promises to be a special success for the publishers. It will doubtlessly be widely used in industrial laboratories. Its perusal may also be recommended to young chemists whose doctorate thesis involved work in completely different fields and who are about to enter into industry, where interest in developing plastics is becoming increasingly important.

Richard Kuhn [NB 892/23 IE]

Gmelins Handbuch der anorganischen Chemie (Gmelin's Handbook of Inorganic Chemistry). 8th Edition, new and completely revised. Published by the Gmelin-Institut für anorganische Chemie und Grenzgebiete in der Max-Planck-Gesellschaft zur Förderung der Wissenschaften. Begun by *R. J. Meyer* and continued by *Erich Pietsch*. Verlag Chemie, GmbH., Weinheim/Bergstr., Germany.

The following discussion continues the review [1,2] of the recently published Gmelin volumes. The six volumes for the year 1960 are covered.

System No. 29: Strontium. Supplement Volume, 1960, XXX, 306 pages with 39 illustrations, German-English table of contents, English headings and subheadings on the margins of the text, paperbound, DM 195.– ($ 49.–), cloth bound DM 200.– ($ 50.–). Edited by *M. Atterer, H. Balters, K.-C. Buschbeck, Marianne Drössmar-Wolf, H. Golder, A. Hirsch, Erna Hoffmann, G. Huschke, G. Krause, Isa Kubach, H. K. Kugler, Gertrud Pietsch - Wilcke, N. Polutoff, K. Rumpf, Renate Schmieder-Jancke, F. Seuferling, K. Swars, E. Ühlein.*

System No. 30: Barium. Supplement Volume, 1960, XLV, 569 pages with 76 illustrations, German-English table of contents, English headings and subheadings on the margins of the text, paperbound, DM 354.– ($ 88.50), cloth bound DM 359.– ($ 90.–). Edited by the above-mentioned collaborators, and in addition by *H. Gedschold, G. Kirschstein,* and *K. Rehfeld.*

Because of the close chemical relationship between strontium and barium, these two supplementary volumes, which continue the respective main volumes that appeared in 1931 (Sr) and 1932 (Ba), will be treated together. Although they only contain the literature for approximately two decades (Sr: 1931–1949; Ba: 1932–1949), they are, just as is the case for other System Numbers, of considerably larger scope than the corresponding main volumes (Sr: 306 pages with 39 illustrations, in contrast to 239 pages with 26 illustrations; Ba: 569 pages with 76 illustrations, against 390 pages with 31 illustrations).

Twenty-seven percent of the entire text is devoted to the occurrence of the two elements (Sr: 82 pages; Ba: 155 pages). Here, as in many other System Numbers, one has the feeling that in an attempt to attain completeness, there is somewhat too much of a good thing. For example, in the chapter on occurrence in the biosphere, data are found on the barium content of the ashes of *Lithothamnium, Fucus vesiculosus,* and *Equisetum limosum,* of 62 seed samples of *Graminaceae,* of the ash of orange juice, of the air-dried kernels and the shells of Brazil nuts, of the woody part of the sheath membrane of *Bertholletia excelsa,* of the membranes of the ostrich eye (divided into cornea, sclerotic coat, lens, chorioid, retina), of 14 newborn rats, of calf urine, of 56 urinary calculi, of 271 gallstones, *etc., etc.* A poll of the purchasers of the Gmelin Handbook would probably show that the number of readers who are interested in such special details is negligible and insufficient to compensate for the expenditure of time required in recording these details.

On the other hand, the chapter on the technology of strontium and barium and their compounds is considerably shorter (Sr: 5 pages; Ba: 34 pages). Details are given here on the processing of the raw materials celestite and strontianite, and barite and witherite, respectively, as well as on the industrial production of the two alkaline-earth metals and their most important compounds (oxides, hydroxides, peroxides, nitrates, chlorides, chlorates, sulfates, carbonates).

Following on from this is the chapter on elementary strontium and barium (Sr: 59 pages, Ba: 83 pages), in which the preparation on a laboratory scale (including the isolation of isotopes), as well as the physical, electrochemical, chemical, physiological, and analytical properties of the two elements are discussed in the usual way. The summarizing sections on common reactions of strontium and barium ions given here

[1] Angew. Chem. internat. Edit. *1*, 277 (1962).

[2] Angew. Chem. internat. Edit. *1*, 463 (1962).

are especially useful for the inorganic chemist. A separate discussion on the detection and determination of strontium and barium is not given in the present volume, since, on the one hand, the pertinent volumes of the "Handbook of Analytical Chemistry" by *W. Fresenius* and *G. Jander* already contain this material and, on the other hand, a summarizing 154-page section on the detection and determination of calcium, strontium, and barium, surveying the most important literature up to 1959, is contained in Calcium, fascicle B 3 (1961).

The chapters on the alloys and compounds of strontium and barium, which take up approximately one half of the two supplementary volumes (Sr: 160 pages; Ba: 263 pages), discuss, in the case of strontium, the alloy Sr–Ca (1 page) and, in the case of barium, the alloys Ba–Sb, Ba–Bi, Ba–Ca, and Ba–Sr (3 pages). The remaining 159 (Sr) and 260 pages (Ba) are devoted to a consideration of the compounds of the two alkaline-earth metals with the non-metals and metals of System Numbers <29 (Sr) and <30 (Ba), respectively. Naturally, the treatment of the oxides, hydroxides, nitrates, chlorides, bromides, sulfates, and carbonates occupies the main part (more than half) of the space devoted to the compounds of these two elements. In particular, the section on $BaSO_4$ (36 pages) has almost doubled in comparison with the main volume. In view of the significance of barium sulfate as a painter's pigment (permanent white, blanc fixe, lithopone), the methods for obtaining definite particle sizes, the nature and composition of the precipitated sulfate, and the crystallographic properties of the compound are exhaustively treated.

A chapter on the preparation and properties of alkaline-earth oxide cathodes (34 pages) completes the barium volume; this discusses the methods of preparation (laminated cathodes, cathodes formed by vapor deposition, sintered cathodes, storage battery cathodes) and the properties (thermactinic radiation, electrical conductivity, electron-emission, ion-emission) of the alkaline-earth cathodes which are of importance in the manufacture of electron tubes. An evaluation of 334 patents is given and all significant publications on the subject are considered.

In both supplementary volumes the literature is completely surveyed up to the end of 1949. Occasional literature citations indicate the more important recent publications in the fields.

System No. 3: Oxygen. Section 4 (Air. Active Oxygen. Ozone), 1960, XV, 366 pages with 76 illustrations, German-English table of contents, English headings and subheadings on the margins of the text, paperbound DM 223.– ($ 56.–). Edited by *Hildegard Banse, Anna Bohne-Neuber, Margarete Lehl-Thalinger, Gertrud Pietsch-Wilcke, K. Rumpf, F. Seuferling.*

With the issue of the fascicle Oxygen 4, the treatment of the element oxygen now covers no less than 1184 pages with 208 illustrations. While the three previous fascicles (1951 till 1958), deal with historical questions, occurrence (oxygen, ozone, water), technology (industrial preparation of oxygen, ozone, hydrogen peroxide; processing of water), and elementary oxygen (preparation, purification, and properties; reaction with hydrogen), the present fourth fascicle of 366 pages is concerned with air, active oxygen, and ozone. A final fifth fascicle is still forthcoming; this is already in preparation and should appear this year.

The chapter "Air" (157 pages) describes only the physical properties of air (mechanical, thermal, acoustical, optical, magnetic, electrical behavior), since the chemical behavior, except for the reaction with hydrogen (System Number 2) treated in fascicle 3, will be discussed under the heading of respective reaction partners having System Numbers higher than 3 (oxygen), according to the Gmelin "principle of the last place". In this chapter on air the mechanical and thermal properties, important in the liquefaction and fractionation of air, are treated with particular thoroughness (over 80% of the text) and therefore include discussions of phase diagrams, compressibility, the expansion effect (Joule-Thomson effect), coefficients of expansion, temperature-pressure coefficients, critical constants, caloric and thermodynamic data (isotherms, isobars, Mollier diagrams), thermal conductivity, internal friction, diffusion, solubility, and sorption.

The short middle section on "Active Oxygen" (8 pages) deals with the preparation and properties of atomic and excited molecular oxygen. Here the discussion of the afterglow spectrum of oxygen should be particularly singled out.

Far more than half of the fascicle is devoted to the chapter "Ozone" (201 pages). After a historical survey (well worth reading) on errors and misconceptions in our views on ozone (4 pages), an adjoining section on formation and decomposition (113 pages) deals first with the equilibria $3\ O_2 \rightleftarrows 2\ O_3$ and $O_2 + O \rightleftarrows O_3$, then the processes for the formation and decomposition of ozone by heat, by light, by electrical discharges and by the action of corpuscular radiation and finally discusses the electrolytic and chemical formation of ozone. A 9-page section on laboratory methods suitable for the preparation of gaseous, liquid and solid ozone follows, since the usual industrial processes were already dealt with in fascicle 2. The 1-page section on thermodynamic data of formation deals with the thermodynamic quantities involved in the reactions $3\ O \rightarrow O_3$, $O_2 + O \rightarrow O_3$, and $1.5\ O_2 \rightarrow O_3$. In the section on physical properties (29 pages), the discussion of the molecular structure should be singled out. The section on the electrochemical behavior (8 pages) discusses the potentials of ozone electrodes, the section on the chemical behavior (19 pages) deals with the reactions of ozone with elements and compounds. A final section on aqueous and nonaqueous solutions of ozone (18 pages) summarizes the present state of our knowledge of reactions of ozone in solution. The kinetics and mechanisms of the reactions are also discussed here.

The literature is fully treated up to the end of 1949. In cases of literature data which had earlier been considered as valid and then shown to be out-dated by newer work, published since the literature cut-off date (*e.g.*, in the case of the equation-of-state, melting point, molar specific heat, thermodynamic data on ozone), these new data are mentioned in suitable references to the newer literature.

System No. 9: Sulfur. Part B, section 2 (Sulfur Oxyacids), 1960, XXXVIII, 758 pages with 146 illustrations, German-English table of contents, English headings and subheadings on the margins of the text, paperbound DM 466. – ($116.50), cloth bound DM 471.– ($118). Edited by *M. Atterer, Anna Bohne-Neuber, Gertrud Glauner-Breitinger, A. Hirsch, P. Koch, A. Kotowski, G. Krause, A. Kurtenacker, W. Lippert, Anne-Lise Neumann, W. Schröder, Hildegard Wendt.*

Part A of "Sulfur" (Historical, Occurrence, Technology, The Element), with three fascicles (1942–1953; 762 pages with 141 illustrations), has already been completed. The present fascicle Sulfur B 2 (758 pages with 146 illustrations) continues fascicle Sulfur B 1 (Hydrides and Oxides of Sulfur; 372 pages with 45 illustrations), which appeared nine years ago (1953), and describes all sulfur oxyacids known up to the end of 1949. Compounds of sulfur with nitrogen and the halogens, which are still to be considered, will form the principal subject of fascicle Sulfur B 3, which is already in preparation. When the latter fascicle appears, the entire System Number sulfur, which at present already comprises 1892 pages with 332 illustrations, will be completed.

The present fascicle B 2 discusses in the series of sulfur acids with the general formula H_2SO_n the acids H_2SO, H_2SO_2, H_2SO_3, H_2SO_4 and H_2SO_5; in the series of sulfur acids of the general formula $H_2S_2O_n$ the acids $H_2S_2O_2$, $H_2S_2O_3$, $H_2S_2O_4$, $H_2S_2O_5$, $H_2S_2O_6$, $H_2S_2O_7$ and $H_2S_2O_8$; and in the series of sulfur acids of the general formula $H_2S_nO_6$ the acids $H_2S_3O_6$, $H_2S_4O_6$, $H_2S_5O_6$, $H_2S_6O_6$ and $H_2S_{>6}O_6$. The acids of the general formula $H_2S_nO_3$ (sulfanmonosulfonic acids), which were discovered and investigated after the cut-off date for the literature, are not treated. Sulfurous acid H_2SO_3 and the SO_2–H_2O system, sulfuric acid H_2SO_4 and the SO_3–H_2O system, the peroxysulfuric acids H_2SO_5 and $H_2S_2O_8$, the polythionic acids $H_2S_nO_6$ ($n \geq 3$), and thiosulfuric acid $H_2S_2O_3$ are treated with special thoroughness. The space

devoted to their discussion comprises more than 95 % of the toted volume, while the remaining 5 % is allotted to the less important (or, up to this time, less investigated) acids, H_2SO, $H_2S_2O_2$, H_2SO_2, $H_2S_2O_4$ and $H_2S_2O_6$.

The difficulties to be overcome in the editing of the present fascicle were extraordinarily great, since the literature on sulfur oxyacids has become almost impossible to survey. Owing to this impossibility of reviewing the entire field, monographic and critical evaluations of the data are either lacking or are limited to smaller sectors of the field. For example, the description of sulfurous acid alone made it necessary to search through, and to coordinate, the contents of approximately 5000 original publications. One must therefore be grateful to the editors of the volume for undertaking the effort to abstract completely, and for the first time, the vastly accumulating literature on sulfur oxyacids, and to arrange it systematically. From the bulk of the material treated, only a few examples can be singled out in the following paragraphs.

The data on sulfurous acid (302 pages) are divided into a chapter on the acid H_2SO_3 and its ions, HSO_3^-, SO_3^{2-} and $S_2O_5^{2-}$, and a chapter on the system sulfur dioxide-water. The first chapter (217 pages), after some general introductory remarks (3 pages), deals both with the physics (57 pages) and the chemistry (157 pages) of sulfurous acid. In the physics section, details are given on the structure and dimensions of the H_2SO_3 molecule and of the ions HSO_3^-, SO_3^{2-}, and $S_2O_5^{2-}$, as well as on the mechanical, thermal, optical, magnetic and especially the electrochemical properties (potentials, electrical conductivity, polarography) of sulfurous acid. The chemical part deals first with the equilibria existing in aqueous SO_2 solutions ($SO_2 + H_2O \rightleftharpoons H_2SO_3$; $H_2SO_3 \rightleftharpoons HSO_3^- + H^+ \rightleftharpoons SO_3^{2-} + 2\,H^+$; $2\,HSO_3^- \rightleftharpoons S_2O_5^{2-} + H_2O$), as well as with the dissociation constants of the acid and the activity coefficients of the participants in the equilibria. It then discusses the thermal and photochemical decomposition of sulfurous acid and its salts as well as their chemical behavior with non-metals and metals with inorganic and organic compounds. The second chapter, which deals with the SO_2–H_2O system (85 pages), begins, after introductory statements (1 page), with a thorough description of the phase and composition diagrams of the SO_2–H_2O system (42 pages), and then considers the SO_2 hydrates (33 pages), especially SO_2 hexahydrate (as an example of the class of gas hydrates) and the solution of water in liquid sulfur dioxide (9 pages). In the treatment of the SO_2–H_2O system in this part of the fascicle it was necessary to check by re-calculation of the original data and by graphic comparisons the internal agreement between the measurements given in the literature and the agreement of those with the values theoretically derived from phase considerations. The description of the SO_2–H_2O system will be carried still further in the following fascicle B 3, which will deal, in its first part, with the solubility of sulfur dioxide in water and water-containing solvents and with the oxidation of sulfurous acid and sulfites by free oxygen and by ozone. This is a field which could not be accommodated within the frame of the chemical behavior of sulfurous acid treated in fascicle B 2, because of the volume of the literature.

The chapter on sulfuric acid (185 pages) begins with an 18-page section on the SO_3–H_2O system and on SO_3 hydrates, especially the hydrates $SO_3 \cdot H_2O = H_2SO_4$ and $2\,SO_3 \cdot H_2O = H_2S_2O_7$. It then turns to actual sulfuric acid H_2SO_4 and its aqueous solutions (167 pages). In contrast to the case of sulfurous acid, the emphasis is placed here on the physics (104 pages) rather than on the chemistry (63 pages). In the section on physics, both pure sulfuric acid and its aqueous solutions are dealt with, and in each case, both thermodynamic data and questions of structure as well as mechanical, thermal, optical, magnetic, electrical, and electrochemical properties are discussed. In the latter part of the section, material under the headings of "Potentials," "Electrical Conductivity," "Ion Mobility," "Transport Number" and "Electrolysis" takes up a large amount of space. In the introduction, the chemical section reports on the equilibria in sulfuric acid solutions, on the dissociation constants of the acid, and on the activity coefficients of the dissociated components. It then continues with the behavior of sulfuric acid with elements and compounds and closes with descriptions of nonaqueous solutions of sulfuric acid and of solutions of SO_3 in sulfuric acid (fuming sulfuric acid, oleum, pyrosulfuric acid). The preparation of sulfuric acid is not treated, since this has already been thoroughly dealt with in fascicle Sulfur A 2, that is, within the framework of the technology of sulfur and its compounds, which are described there.

From the chapter on the peroxysulfuric acids (55 pages), which deals both with peroxymonosulfuric acid H_2SO_5 (10 pages) and with peroxydisulfuric acid $H_2S_2O_8$ (45 pages), one should single out the sections on the formation and preparation, and the hydrolysis and decomposition of the compound $H_2S_2O_8$, and on the oxidizing action of the two peroxy acids.

The chapter on the polythionic acids $H_2S_nO_6$ (77 pages), begins with introductory remarks on the formation and decomposition, on common reactions and on the Wackenroder's solution (10 pages), and then deals with the specific compounds $H_2S_3O_6$ (13 pages), $H_2S_4O_6$ (19 pages), $H_2S_5O_6$ (13 pages), $H_2S_6O_6$ (4 pages) and $H_2S_{>6}O_6$ (2 pages). The chapter closes with a 16-page section on the detection and determination of polythionic acids (including dithionic acid $H_2S_2O_6$), since the analytical problems encountered here are especially complicated.

Finally, the chapter on thiosulfuric acid (104 pages) is extensive. In this chapter, after introductory sections on the formation and preparation (6 pages) and on the physical (9 pages) and electrochemical properties (4 pages), the chemical behavior (85 pages) of the acid is considered in an especially thorough way. The sections on the composition of the solution, on the decomposition of thiosulfuric acid, on the behavior of the acid with elements and compounds, and on its complex forming properties should be particularly mentioned.

The literature is fully surveyed up to the end of 1949. This early cut-off date for the literature makes itself especially and disturbingly noticeable in this fascicle, since great advances in the area of the sulfur oxyacids have been recorded just in the last ten years, the survey of which is not included here. Thus it proved necessary in a number of cases to at least cite the most important recent literature.

System No. 34: Mercury. Section 1 (Historical. Occurrence. Preparation. Physical Properties), 1960, XVII, 466 pages with 53 illustrations, German-English table of contents, English headings and subheadings on the margins of the text, paperbound DM 283.– ($71.–). Edited by *M. Atterer, Hildegard Banse, Anna Bohne-Neuber, R. Glauner, A. Hirsch, Isa Kubach, A. Kunze, Imberta Leitner, W. Müller, Gertrud Pietsch-Wilcke, N. Polutoff, F. Rex, K. Rumpf, F. Seuferling.*

Fascicle Mercury 1 (466 pages with 53 illustrations) is the first on mercury in the 8th edition of the Gmelin Handbook. Up to this time, the only data available were those in Volume V, 2(Silver,Gold,Mercury) of the 7th edition,which appeared a half-century ago (1914). The contents of the fascicle cover the history, the occurrence, the preparation and the physical properties of the metal. A further fascicle, Mercury 2, will appear in 1962.

The volume begins with an 80-page chapter on the history of mercury, in which, on the basis of 1730 separate references, both the history of the discovery of the element mercury (32 pages) and that of mercury alloys (6 pages) and mercury compounds (39 pages) are dealt with. Among other subjects, the section on the medieval notions that all metals were composed of "sulfur" and "mercury" should be particularly noted.

A further 85 pages are devoted to the occurrence of mercury. The section treats the geochemistry (20 pages), deposits (58 pages), minerals (6 pages) and economic statistics (1 page). From this section of the volume, the data on the discovery of mercury deposits, on the geochemical cycle of mercury, and on the distribution of the deposits in the various continents and countries may be singled out.

A shorter chapter reports on the use of mercury (3 pages) as metal (thermometers, barometers, power stations working on a mercury cycle, Hg-vapor lamps, Hg rectifiers), as amalgam (dentistry, alkali chloride electrolysis, gold and zinc recovery, reducing action), and in the form of compounds such as HgO (underwater paints), HgS (cinnabar), or HgI_2 complexes (thermochroism). Another chapter reports on the deleterious physiological effects (12 pages) induced by mercury and mercury compounds (possibilities of poisoning, symptoms of mercury poisoning, poisonous effect, prophylaxis, therapy), an area which received a new impetus in the thirties from the investigations and experiences of Alfred Stock.

The principal remaining part of the fascicle (286 pages) is devoted to the discussion of elementary mercury. It begins with a chapter (72 pages), which treats chiefly the technology (dressing of Hg ores, preparation of mercury by roasting and by wet processes, recovery of mercury, purification, assay, handling, storage) and the preparation of special forms of mercury (single crystals, films, mirrors, powdered and colloidal mercury, mercury isotopes). The following 214-page chapter on the physical properties of mercury is divided in the usual way into atomic and molecular (19 pages), crystallographic (14 pages), mechanical (45 pages), thermal (46 pages), optical (46 pages), magnetic (5 pages), and electrical properties (39 pages). Here, among other subjects, are found data on the isotopes of mercury, the electronic structure of the atom, the atomic and ionic radii, the atomic and ionic volumes, the atomic weight, the electro-negativity, the Hg_2 molecule and its association in the liquid and gaseous state, the lattice structure of solid and liquid mercury, precision measurements on the liquid density, surface and interfacial tensions, wetting, adhesion, and spreading phenomena, internal friction, diffusion, solubility and sorption, the equation of state, thermal expansion, critical constants, caloric and thermodynamic data, spectral behavior, magnetic susceptibility and electrical conductivity, superconductivity, and the thermoelectric power of mercury. All these data are of special interest in view of the many uses of metallic mercury as a liquid for filling thermometers and manometers, as electrodes for electrolyses, as the standard substance for the definition of the unit of electrical resistance and of the fixed point of the temperature scale, as a source for the generation of ultraviolet light, *etc.*

The literature is fully surveyed up to the end of 1949, and in especially important cases beyond that date. The inorganic chemist will welcome the appearance, at long last, of this first volume on mercury, and will look forward to the appearance of the chemical part (it is to be hoped) in the very near future, which will be even more important to him, just as he is eagerly looking forward to the appearance of the first volume of the element chromium announced for this year.

System No. 20: Lithium. Supplement Volume, 1960, XXXVIII, 525 pages with 73 illustrations, German-English table of contents, English headings and subheadings on the margins of the text, paperbound DM 325.– (\$ 81.50), cloth bound DM 330.– (\$ 82.50). Edited by *M. Atterer, Anna Bohne-Neuber, G. Czack, Marianne Drössmar-Wolf, R. Glauner, A. Hirsch, G. Huschke, Eleonore Kirchberg, Marie-Luise Klaar, H. K. Kugler, H. Lehl, Ellen v. Lindeiner-Schön, W. Müller, Gertrud Pietsch-Wilcke, K. Rehfeld, F. Seuferling, K. Swars, Ursula Trobisch-Raussendorf, Ingrid Wann, Hildegard Wendt.*

The volume (525 pages with 73 illustrations) is a continuation, for the years 1926–1949, of the principal volume "Lithium", which appeared 35 years ago (1927) and was only half as large (254 pages with 13 illustrations) as the present one.

Approximately one fourth of the volume is devoted to the occurrence of lithium (126 pages). Here is documented the growth of lithium chemistry in recent times, which has led to new geochemical investigations and to the opening of new, large deposits. The industrial statistics, according to which the production of lithium minerals rose from 4000 tons in 1925 to more than 100,000 tons in 1958, are very revealing. This growth comes as a consequence of the increasing use of lithium and its compounds in industry: thus, for example, in metallurgy (Li as a constituent of alloys, LiF as a flux), in the glass, enamel and ceramics industries (Li_2CO_3 as an additive to glass and porcelain glazes), in lubricant technology (Li soaps of fatty acids as lubricants for aircraft engines), in storage batteries (LiOH in the Edison and Cd–Ni accumulators), for air drying and cooling (LiCl in air conditioners and cooling systems), and in hydrogenation reactions (LiH as a direct and indirect hydrogenating agent).

The following 16 pages are devoted to the preparation of lithium and the technology of lithium and its compounds. Here the section on the enrichment and isolation of the lithium isotopes ^6Li and ^7Li may be particularly mentioned. This is of interest in view of the use of ^6Li as a means of obtaining tritium, of ^6LiD as a thermonuclear fuel, and of ^7Li as a coolant for reactors.

The chapter on the physical, electrochemical, chemical-physiological and analytical properties of lithium (98 pages) is subdivided in the usual way, and presents a mine of information to the interested reader. The 16-page section on common reactions of the lithium ion may be particularly mentioned.

The chapter on alloys and compounds of lithium, which occupies more than half the volume (285 pages), is the most extensive. The data on alloys (4 pages) are limited to the alloys of lithium (System No. 20) with the metals antimony (System No. 18) and bismuth (System No. 19), since all other alloys are with metals of higher system numbers than 20 and therefore are treated with those. The discussion of lithium compounds (281 pages) includes the compounds of lithium with elements up to System No. 19, that is, with hydrogen, oxygen and nitrogen, with the halogens and chalcogens, with boron, carbon and silicon, and with arsenic, antimony and bismuth. Here the sections on the hydride LiH (14 pages), the hydroxide LiOH (11 pages), the nitrate $LiNO_3$ (21 pages), the halides LiF (22 pages), LiCl (72 pages), LiBr (33 pages), and LiI (26 pages), the sulfate Li_2SO_4 (10 pages), the borohydride $LiBH_4$ (4 pages), and the carbonate Li_2CO_3 (7 pages) are of special interest. Together, these ten compounds occupy over three quartes of the space devoted to lithium compounds. Here are found data on the hydrogenation and condensing action of lithium hydride, the lattice structure of lithium hydroxide, the hydrates and ammoniates of lithium nitrate, the activity coefficients, adducts and optical properties of the lithium halides, the piezoelectric properties of lithium sulfate, the substitution products of lithium borohydride, the hydrolysis equilibria of lithium carbonate, and many more related subjects.

The literature is fully covered up to the end of 1949. Where necessary, especially important publications up to and including 1959 are noted. *E. Wiberg* [NB 857/16 IE]

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Ionic Hydrogenations and Dehydrogenations

BY PROF. DR. H. MEERWEIN, DR. KL. WUNDERLICH, AND DR. K. FR. ZENNER

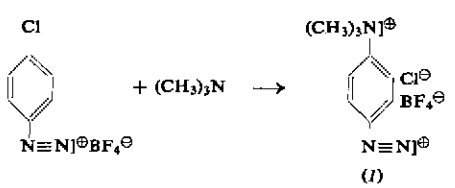
CHEMISCHES INSTITUT DER UNIVERSITÄT MARBURG/LAHN (GERMANY)

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

In acetonitrile, 4-chlorobenzenediazonium fluoroborates readily add onto trimethylamine to give 4-trimethylammoniumbenzenediazonium chloride fluoroborates. These addition products have a pronounced tendency to accept two hydrogen atoms in the form of a hydride ion and a proton from donors such as 1,4-dihydrobenzene, 1,3-dioxolxans, 1,4-dioxan etc. The diazonium group is thereby reduced, and the trimethylammonium group is split off as trimethylammonium fluoroborate and replaced by the chloride ion. In the presence of a trace of copper, the reaction mechanism is changed from an ionic to a free-radical one. In this case, just as in the absence of copper, the diazonium group is reduced, but the trimethylammonium group is retained. Alcohols behave in the same way as the donors of ionic hydrogen cited.

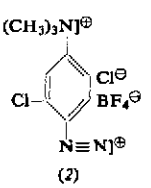
1. Addition of 4-Chlorobenzenediazonium Fluoroborates onto Trimethylamine

In acetonitrile, 4-chlorobenzenediazonium fluorborate readily adds onto trimethylamine to give 4-trimethylammoniumbenzenediazonium chloride fluoroborate *(1)*.

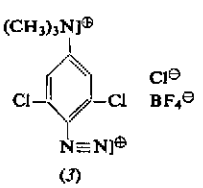


(1)

Similarly, 2,4-dichloro- and 2,4,6-trichlorobenzenediazonium fluoroborates yield the addition products *(2)* and *(3)*.



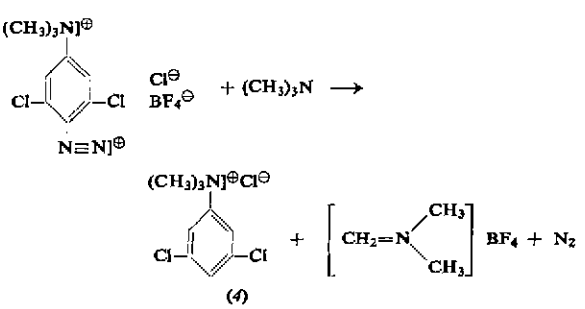
(2)



(3)

The salts form slightly yellowish crystals, which can be stored in a refrigerator for a long time without undergoing alteration. Their stability decreases somewhat as the number of chlorine atoms increases. The yields obtained range from 88 to 96 %. The rate and course of addition can be readily followed by determining the amount of chloride ion formed.

An excess of trimethylamine should be avoided to prevent reduction of the diazonium group [1]. For example, if a solution in acetonitrile of 2,4,6-trichlorobenzenediazonium fluoroborate is added at −35 °C to a solution in acetonitrile of an excess of trimethylamine, trimethyl-3,5-dichlorophenylammonium chloride *(4)* is obtained in 50 % yield:



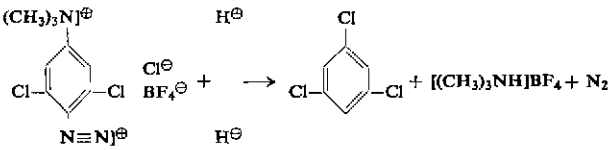
(4)

Recrystallization of the chloride from an aqueous fluoroboric acid solution gives particularly well-formed crystals of fluoroborate, m.p. 220–221.5 °C.

[1] *H. Meerwein* et al., Angew. Chem. *70*, 211 (1958).

2. Ionic Hydrogenation of the Addition Products

The trimethylammoniumbenzenediazonium chloride fluoroborates *(1)*, *(2)*, and *(3)* exhibit a pronounced tendency to accept two hydrogen atoms in the form of a hydride ion and a proton from donors. In this "ionic hydrogenation" [2], the diazonium group is reduced, the trimethylammonium group being split off as trimethylammonium fluoroborate and replaced by chloride ion:



Thus, the chloride ion formed when trimethylamine is added to 4-chlorobenzenediazonium fluoroborates disappears in the course of ionic hydrogenation and reoccupies its original position on the benzene ring.

Most of the experiments described below were carried out with the diazonium salt *(3)*, obtained from 2,4,6-trichlorobenzenediazonium fluoroborate and trimethylamine, since the 1,3,5-trichlorobenzene, which is formed as a result of the ionic hydrogenation, can be isolated very easily and quantitatively.

The following compounds were used as donors of ionic hydrogen: 1,4-dihydrobenzene, 1,4-dihydronaphthalene, various 1,3-dioxolans and 1,4-dioxan. Their ability to donate hydride ions is known [3]. In our case, however, the loss of a hydride ion is followed or accompanied simultaneously by a loss of a proton, resulting in stabilization of the cation initially formed.

The course of reaction is readily understood when 1,4-dihydrobenzene or 1,4-dihydronaphthalene is used. In Table 1, a list is given of the yields of 1,3,5-trichlorobenzene, trimethylammonium fluoroborate and benzene or naphthalene obtained with addition product *(3)*. Benzene was identified and determined quantitatively as 2,4-dinitrobenzene, and naphthalene as its picrate.

Table 1. Ionic hydrogenation of addition compound *(3)* with dihydroaromatic compounds

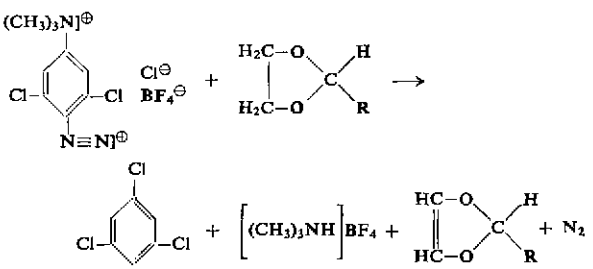
Product	Yields [%] with 1,4-dihydrobenzene	with 1,4-dihydronaphthalene
1,3,5-Trichlorobenzene	49.5	65.6
Trimethylammonium fluoroborate	69.8	73.3
Benzene or naphthalene	52.2	74.6

The ability of 1,3-dioxolans and 1,4-dioxan to act as donors of ionic hydrogen is surprising. Hydrogenations carried out in their presence are smoother than those with dihydroaromatic compounds. The reactions are remarkably accelerated by acetonitrile. When 1,3-dioxolan or 2-methyl-1,3-dioxolan is added to a suspension of 4-trimethylammonium-2,6-dichlorobenzenediazonium chloride fluoroborate *(3)* in acetonitrile, the chloride ions disappear almost completely, while, simultaneously, nitrogen is evolved vigorously. The yields of isolated 1,3,5-trichlorobenzene and trimethylammonium fluoroborate are given in Table 2.

Table 2. Ionic hydrogenations of addition product *(3)* with 1,3-dioxolans

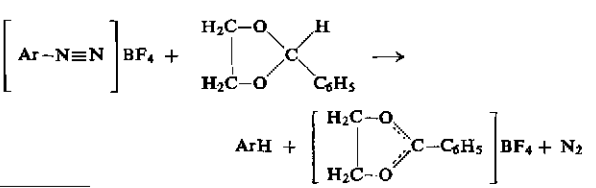
Expt. No.	1,3-Dioxolan	Yield of 1,3,5-trichlorobenzene [%]	Yield of trimethylammonium fluoroborate [%]
1	1,3-Dioxolan	82	84.5
2	2-Methyl-1,3-dioxolan	73.3	71.4
3	2,2-Dimethyl-1,3-dioxolan	70.4	79.7
4	2-Phenyl-1,3-dioxolan	62.5	66.7

So far we have been unable to isolate the 1,3-dioxoles one would expect to obtain according to the following equation:



This is due to the great tendency of these compounds to polymerize [4]. In order to trap the 1,3-dioxole in its nascent state, we carried out an ionic hydrogenation of addition product *(3)* with 2,2-dimethyl-1,3-dioxolan in glacial acetic acid. The yield of 1,3,5-trichlorobenzene was 51.9 % and that of trimethylammonium fluoroborate 89.3% [5]. 4-Acetoxy-2,2-dimethyl-1,3-dioxolan, formed from 2,2-dimethyl-1,3-dioxole but not isolated, was hydrolyzed with cold dilute hydrochloric acid. The resulting glycol aldehyde was identified by converting it into its *p*-nitrophenylosazone of glyoxal (m.p. 307 to 312 °C; yield: 43.8 %). This proves that the ionic hydrogenation and dehydrogenation of addition products *(1)*, *(2)*, and *(3)* with 1,3-dioxolans occur as indicated above.

Some time ago, we were able to show [3] that, in acetonitrile, diazonium fluoroborates are reduced by 1,3-dioxolans, *e.g.* 2-phenyl-1,3-dioxolan, to give ArH compounds and 1,3-dioxolenium fluoroborates:



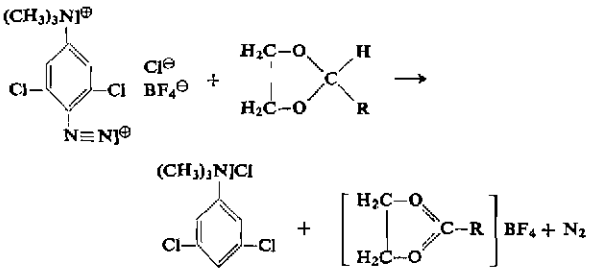
[2] Cf. *H. Meerwein* et al., Liebigs Ann. Chem. *635*, 3 (1960), footnote 4.

[3] *H. Meerwein* et al., Liebigs Ann. Chem. *635*, 1 (1960).

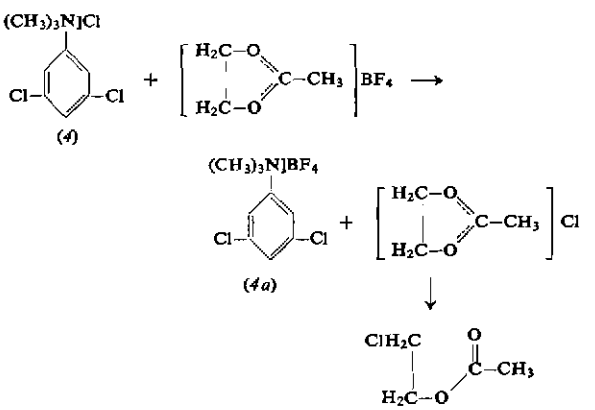
[4] *N. D. Field*, J. Amer. chem. Soc. *83*, 3504 (1961).

[5] The disproportionately high yield of trimethylammonium fluoroborate compared to that of 1,3,5-trichlorobenzene is due to the fact that a part of addition product (*3*) reacts with glacial acetic acid with elimination of the trimethylammonium group, which is activated by the diazonium group. Quaternary ammonium salts of 2,2-dinitroaniline are known to undergo a similar reaction [Brit. Pat. 805761 (1955); National Research Development Corp.; Inventor: *J. H. Wilkinson*; Chem. Abstr. *53*, 8074 (1959)]. In agreement with this, 40% of the ionogenic chlorine remain.

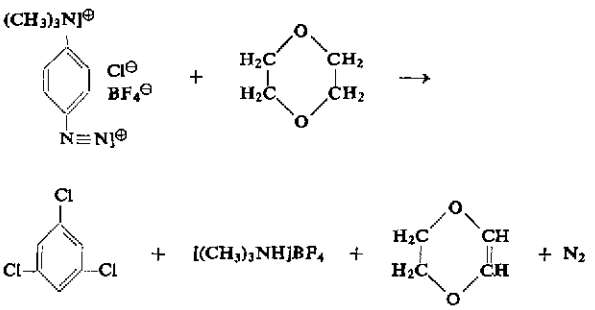
Hence, we initially assumed that the first step in the reaction of 4-trimethylammoniumbenzenediazonium chloride fluoroborates with 1,3-dioxolans occurs similarly, and that the resulting 1,3-dioxolenium fluoroborates are then stabilized by loss of a proton and formation of 1,3-dioxoles:



That this course is not followed is evident from the fact that ionic hydrogenation occurs readily also with 2,2-dimethyl-1,3-dioxolan, which cannot give rise to a 1,3-dioxolenium salt (see experiment 3, Table 2). We were also able to show that, in the reaction of trimethyl-2,5-dichlorophenylammonium chloride *(4)* with 2-methyl-1,3-dioxolenium fluoroborate, the triethylammonium group is not split off, but that a simple exchange of anions takes place:



Ionic hydrogenation of 4-trimethylammonium-2,6-dichlorobenzenediazonium chloride fluoroborate *(3)* with 1,4-dioxan occurs as readily as that with 1,3-dioxolans. The yield of 1,3,5-trichlorobenzene is 68 %, that of trimethylammonium fluoroborate 63 %. Here, too, it has not yet been possible to isolate the dehydro-1,4-dioxan, which should be formed according to the equation:



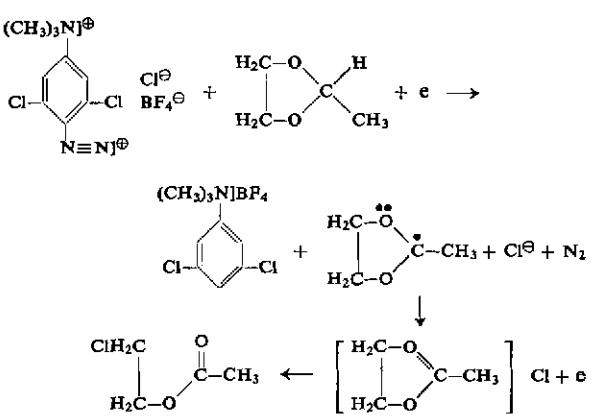
In this case also, as with 2,2-dimethyl-1,3-dioxolan, we carried out a reduction in glacial acetic acid, and isolated the glyoxal-*p*-nitrophenylosazone, m.p. 307 to 309 °C, described above in 23.6 % yield. We were also able to isolate *p*-nitrophenylosazone of glyoxal when the reduction was carried out without acetic acid. However, the yield was low (1.8 %) and the reduction took place only with addition product *(1)*, which is not very reactive and which contains no chlorine on the ring.

3. Free-radical Reduction of the Addition Products

It was possible to prove that, in the reduction of addition products *(1)*, *(2)*, and *(3)* with 1,3-dioxolans, hydrogen is actually transferred in the form of a hydride ion and a proton and not as hydrogen atoms.

As we previously observed during the reduction of diazonium fluoroborates which do not contain a trimethylammonium group with 1,3-dioxolanes, the relatively slow reaction is remarkably accelerated by addition of a small amount of copper bronze. The reduction products, *i.e.* the ArH compound and the 1,3-dioxolenium fluoroborate, remain unaltered [6].

Copper exerts the same effect on the reduction of addition products *(1)*, *(2)*, and *(3)* with 1,3-dioxolans. However, in this case, the result is different. The diazonium group is reduced normally, just as in the absence of copper, but the trimethylammonium group is not split off. When 2-methyl-1,3-dioxolan is allowed to react with 4-trimethylammonium-2,6-dichlorobenzenediazonium chloride fluoroborate *(3)* in the presence of a trace of copper, practically no 1,3,5-trichlorobenzene or trimethylammonium fluoroborate is formed. Instead, a 70.1 % yield of trimethyl-3,5-dichlorophenylammonium fluoroborate *(4a)* and a 75.5 % yield of β-chloroethyl acetate are obtained. The latter is formed by rearrangement of the 2-methyl-1,3-dioxolenium chloride initially formed. The reaction mechanism changes from an ionic to a free-radical one owing to the uptake of an electron released by the copper according to the equation:



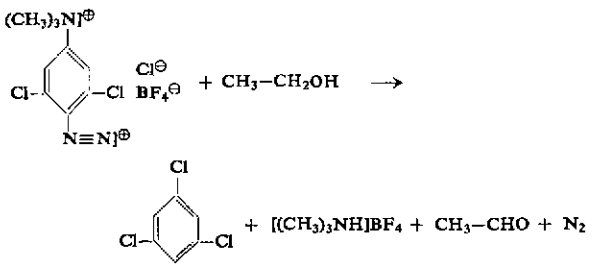
The electron initially taken up by the diazonium ion is again released on conversion of the 2-methyl-1,3-dioxolan radical into the 2-methyl-1,3-dioxolenium ion. In this case, the transfer involves a hydrogen atom and not a hydride ion; subsequent or simultaneous transfer of a proton, which takes place in ionic hydrogenation, does not occur.

[6] See [1], p. 214.

The result of this experiment shows that free-radical reduction takes place much faster than the ionic hydrogenation, so that the latter practically does not take place.

4. Reduction of the Addition Products with Alcohols

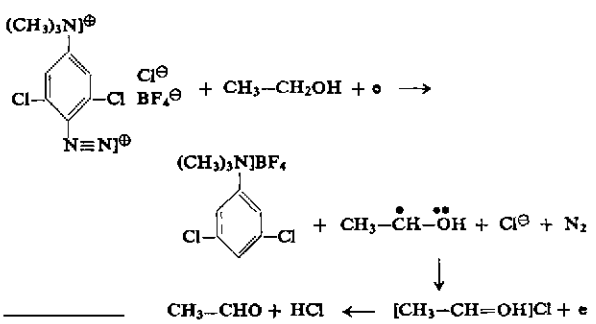
Alcohols, the classical reducing agents for diazonium salts, are also donors of ionic hydrogen. The reaction of 4-trimethylammonium-2,6-dichlorobenzenediazonium chloride fluoroborate *(3)* with ethanol is similar to that with other donors of ionic hydrogen. It is also markedly accelerated by the addition of acetonitrile and takes place exothermically at 30–40 °C. We were able to isolate 93 % of the 1,3,5-trichlorobenzene, 41 % of the trimethylammonium fluoroborate, and 95 % of the acetaldehyde (as its *p*-nitrophenylhydrazone) formed according to the equation:



The chloride ion disappears almost completely.

It has already been demonstrated that the hydride ion undergoing transfer in the reduction of the diazonium salts with alcohols is an α-hydrogen atom by both *Melander* [7] and *Miklukhin* and *Rekasheva* [8] who used tritiated and deuterated ethanol, respectively. The proton undergoing transfer in ionic hydrogenation is the hydrogen atom of the hydroxyl group. This is indicated by the fact that the reaction with methanol is as smooth as that with ethanol.

Here too, the addition of a trace of copper changes the ionic reaction mechanism into a free-radical one. The reaction is so vigorous that cooling is necessary. 1,3,5-Trichlorobenzene and trimethylammonium fluoroborate are formed only in small amounts. Instead, we isolated trimethyl-3,5-dichlorophenylammonium fluoroborate *(4a)* and acetaldehyde in 92.3 % and 95 % yields, respectively. One mole of hydrogen chloride was liberated. Hence, the reaction takes place as follows:



[7] *L. Melander*, Chem. Abstr. *46*, 7534 (1952).

[8] *G. P. Miklukhin* and *A. F. Rekasheva*, Chem. Abstr. *47*, 4855 (1953).

In view of the different opinions which exist with regard to the mechanism of the reduction of diazonium salts with alcohols, it is of interest that it is possible, in this case, to make the reaction occur either by an ionic or a free-radical mechanism.

5. Experimental Procedures

Addition of 2,4,6-trichlorobenzenediazonium fluoroborate onto trimethylamine to give 4-trimethylammonium-2,5-dichlorobenzenediazonium chloride fluoroborate *(3)*:

In a 500-ml flask, fitted with a dropping funnel, stirrer, and a suction tube containing a sealed-in sintered glass filter, 74.5 g (0.252 mole) of 2,4,6-trichlorobenzenediazonium fluoroborate are suspended in 200 ml of acetonitrile and 200 ml of a 1.26 N trimethylamine solution in acetonitrile added dropwise at −18 °C over a period of 4 hours with good agitation. The trimethylamine odor disappears instantly. The solution turns yellow as soon as a few ml have been added, and stays yellow until the end of the addition. Too rapid addition is indicated by the appearance of a brown coloration. Following completion of the addition, the mixture is stirred for 0.5 hr at −18 °C. The yellow product is sucked off with exclusion of moisture, washed with agitation in succession with 200 ml of ice-cold acetonitrile, 200 ml of ice-cold carbon tetrachloride, and two or three times with 200-ml portions of ice-cold methylene chloride, and then sucked dry. Maximum yield: 86.5 g or 96.5 %; slightly yellowish crystals, which decompose at 94–96 °C. The salt is insoluble in all hydroxyl-free organic solvents. It dissolves readily in water and dilute acids, but cannot be recrystallized.

The reactions of 4-chloro- and 2,4-dichlorobenzenediazonium fluoroborates with trimethylamine take place similarly to give addition product *(1)* (yield: 90 %; decomp. 104–108 °C) and *(2)*, respectively (yield: 88 %; decomp. 87–89 °C).

Reaction of addition product *(3)* with 1,3-dioxolan:

In a 300-ml Erlenmeyer flask protected with a calcium chloride tube, 19.2 g of addition product *(3)* are treated with 100 ml of ice-cold 1,3-dioxolan and then stirred at 0 °C with a magnetic stirrer. Nitrogen is evolved slowly; it takes two days for all the diazonium salt to react. The precipitate of trimethylammonium fluoroborate is filtered by suction and the filter cake washed with ether. Yield of nearly pure salt: 6 g. The filtrate give an additional 0.7 g of impurer salt; thus, the total yield is 6.7 g, or 84.5 %.

After removal of the ether from the filtrate, steam-distillation of the residue gave 8.0 g (82 %) of 1,3,5-trichlorobenzene, m.p. 62–63 °C.

Reduction of addition product *(3)* with 2-methyl-1,3-dioxolan in the presence of copper:

Ten grams of addition product *(3)* (28.2 millimoles) are added portionwise, at −40 °C to 35 ml of 2-methyl-1,3-dioxolan, freshly distilled from sodium and containing some copper bronze. When the initially vigorous evolution of nitrogen has subsided, the cooling bath is removed, and more copper added. The addition product does not dissolve but forms a beautifully crystalline reaction product. After 30 minutes, all of the diazonium salt has reacted. The mixture is treated with 100 ml of ether, filtered off by suction, and the filter cake washed with ether. Thus, 6.9 g (83.5 %) of a mixture of 84 % trimethyl-3,5-dichlorophenylammonium fluoroborate (*4a*; m.p. 220–221 °C) and 16 % trimethyl-3,4,5-trichlorophenylammonium fluoroborate (m.p. 294–296 °C) are formed as a result of a Sandmeyer reaction. Separation of the mixture by crystallization from water is difficult. Distillation of ether from the filtrate yields 2.60 g (75.5 %) of β-chloroethylacetate of 95 % purity, as shown by gas chromatography.

Proof of the formation of 2,2-dimethyl-1,3-dioxole in the ionic hydrogenation of addition product *(3)* with 2,2-dimethyl-1,3-dioxolan:

A mixture of 12.5 g of 2,2-dimethyl-1,3-dioxolan and 25 ml of glacial acetic acid is added to 10 grams of addition product *(3)*. The mixture is then stirred and heated to 60 °C. The diazonium salt dissolves, and after 10 minutes, the reaction is completed. After working up as described above, 89.3 % of trimethylammonium fluoroborate and 51.9 % of 1,3,5-trichlorobenzene are obtained.

To demonstrate the presence of the 4-acetoxy-2,2-dimethyl-1,3-dioxolan formed, another reaction mixture on the same scale was treated with 2N hydrochloric acid and 50 ml of water; the mixture was agitated for 3 hours, and the acetone formed removed by vacuum distillation. After filtering off the precipitate of 1,3,5-trichlorobenzene, the filtrate was treated with a solution of 10 g of *p*-nitrophenylhydrazine in 150 ml of 2N hydrochloric acid. The resulting mixture was allowed to stand for 2 days. This yielded 4.06 g (43.8 %) of crude glyoxal-*p*-nitrophenylosazone, which, after recrystallization from pyridine, melted at 307–312 °C.

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Isocyanates of Esters of Some Acids of Phosphorus and Silicon

BY DR. H. HOLTSCHMIDT AND DR. G. OERTEL

WISSENSCHAFTLICHES HAUPTLABORATORIUM DER FARBENFABRIKEN BAYER AG. LEVERKUSEN (GERMANY)

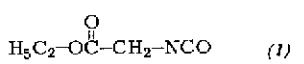
Dedicated to Prof. Dr. Otto Bayer on the occasion of his 60th birthday

Several aminoaryl esters of phosphoric and thiophosphoric acids were prepared by the reaction of phosphorus pentahalides with nitrophenols, followed by catalytic hydrogenation, or by treating aminophenols with phosphorus trihalides and oxidation to pentavalent phosphorus. These amino esters were then converted into isocyanato esters by the action of phosgene. Isocyanates of phosphonates have been synthetized on the same principle, as well as via the Arbusov reaction of halogen-substituted isocyanates with trialkyl phosphites. The reaction of silicon halides or alkylhalogenosilanes with aminophenols yielded aminoaryl esters of silicic acid or its derivatives, which could also be treated with phosgene to convert them into isocyanato esters.

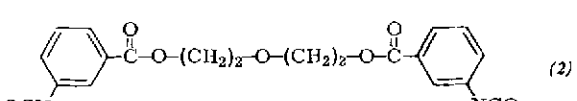
1. Introduction

The preparation of isocyanates bearing an ester group in the molecule was described in 1906 by *Morel* [1], who used phosgenation of the hydrochloride of ethyl aminoethanoate to form ethyl isocyanatoacetate *(1)* as an example. *Siefken* and *Petersen* [2] later prepared isocyanates from esters of other aliphatic and aromatic amino acids, such as ethyl ε-isocyanatohexanoate and *p*-ethoxycarbonylphenyl isocyanate, while *Müller* et al. [3] synthetized higher functional isocyanate esters, *e.g.* the bis-*m*-isocyanatobenzoate of diethylene glycol *(2)*. Isocyanato esters with polymerizable groups, *e.g.* β-isocyanatoethyl acrylate and methacrylate *(3)*, have also become known as the result of recent investigations [4].

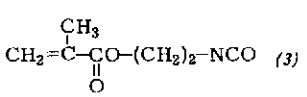
We have been occupied for some time with the preparation of isocyanates of esters of inorganic acids; this work will be discussed in the following.



(1)



(2)



(3)

[1] *A. Morel*, C. r. hebd. Seances Acad. Sci. *143*, 119 (1906).

[2] *A. Siefken* and *S. Petersen*, Liebigs Ann. Chem. *562*, 75 (1949).

A. Isocyanates of Esters of Phosphorus Acids

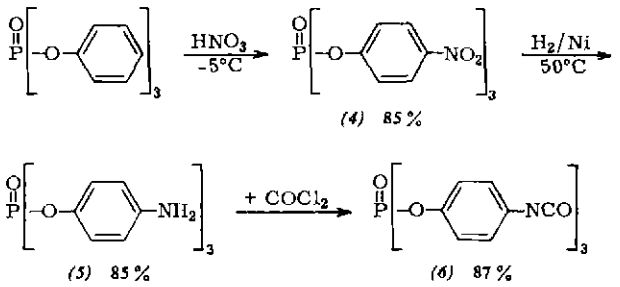
I. Isocyanates of Phosphates and Thiophosphates

Nitration of triphenyl phosphate with concentrated nitric acid yields tris-(*p*-nitrophenyl) phosphate *(4)*, which can easily be hydrogenated with Raney nickel to give

[3] German Pats. 1078115 (Dec. 13th, 1957), 1081667 (April 4th, 1959), and 1085869 (Dec. 16th, 1959); inventors: *E. Müller, O. Bayer, H. Wilms, F. v. Spulak*, and *M. Theis*.

[4] German Pat. 1018050 (April 26th, 1954); inventor: *H. Holtschmidt*.

tris-(*p*-aminophenyl) phosphate *(5)*. Upon treating the latter with phosgene, tris-(*p*-isocyanatophenyl) phosphate *(6)* is obtained.

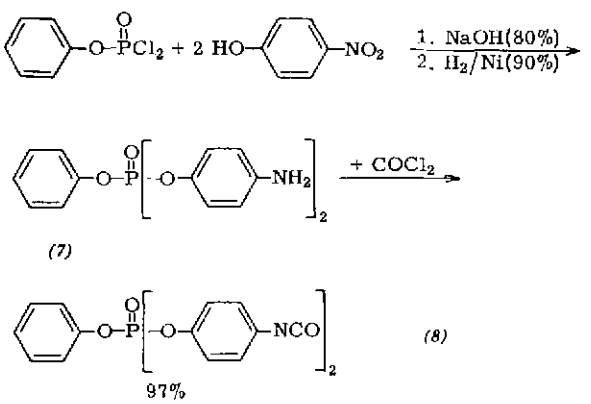


(4) 85 %

(5) 85 % *(6)* 87 %

The ease of hydrogenation [5] of the trinitro compound to the triamine *(5)* is surprising. Amidation or saponification of the ester groups by water formed during hydrogenation does not occur.

The phosgenation [6] of the amine *(5)*, which gives the tri-isocyanate *(6)* in a high yield, indicates the stability of aromatic phosphoric ester bonds toward phosgene and hydrogen chloride, at temperatures up to 150 °C. By analogy, monophenyl-bis-(*p*-aminophenyl) phosphate *(7)* can be converted with phosgene into the diisocyanate *(8)*, without cleavage of the ester bond.

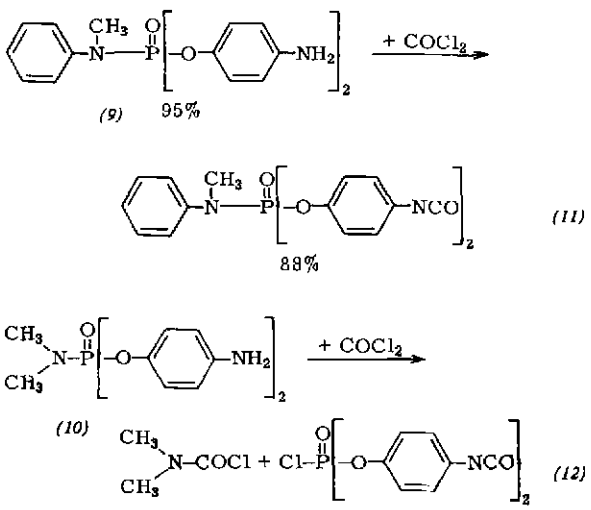


(7)

(8)

97%

Esters of phosphoramidic acid are however not always stable towards phosgene. For example, starting from *N*-methyl-*N*-phenylphosphoramidic dichloride, or from



(9) 95%

(11)

88%

(10)

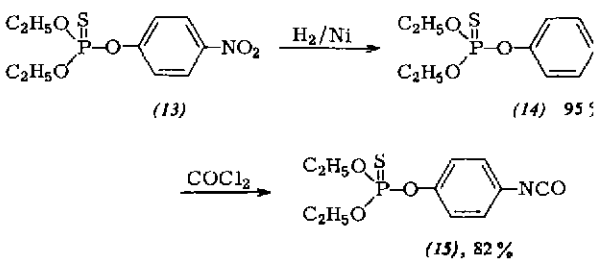
(12)

[5] German Pat. 1085869 (Feb. 1st, 1958); inventors: *H. Holtschmidt* and *H. Wilms*.

[6] Belg. Pat. 575407 (Feb. 6th, 1958); inventor: *H. Holtschmidt*.

N,N-dimethylphosphoramidic dichloride, the phosphoramidic esters *(9)* and *(10)* are obtained in very good yields, following the synthesis principle mentioned above. While the bis-(*p*-aminophenyl)-*N*-methyl-*N*-phenylphosphoramidate *(9)* is easily converted by phosgenation into the expected diisocyanate *(11)*, the *N,N*-dimethyl derivative *(10)* undergoes cleavage under these conditions, resulting in *N,N*-dimethylcarbamyl chloride and the diisocyanate ester derivative of phosphorochloridic acid *(12)*.

The favorable results obtained with the hydrogenation of nitrated phosphoric esters and the phosgenation of amines encouraged us to attempt the corresponding reactions with thiophosphates. Surprisingly, it was found that hydrogenation over Raney nickel of *O,O*-diethyl-*p*-nitrophenyl thiophosphate ("E 605") [7] *(13)* was possible, giving a yield of more than 90 %.

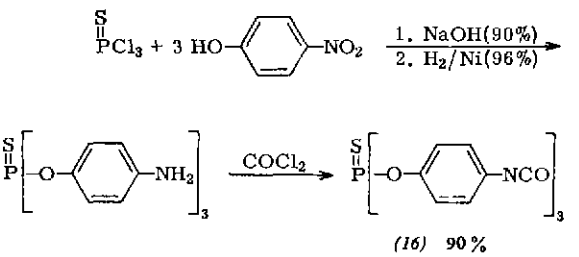


(13) *(14)* 95 %

(15), 82 %

The *O,O*-diethyl-*p*-aminophenyl thiophosphate *(14)* obtained in the hydrogenation reacts easily with phosgene, yielding the isocyanate *(15)*.

The preparation of the tris-(*p*-isocyanatophenyl) thiophosphate *(16)* succeeds particularly well:



(16) 90 %

This triisocyanate is suitable as a glue for rubber adhesive solutions, and has been on the market since 1959 under the name "Desmodur® RF" [8,9]. Compared with tri-(*p*-isocyanatophenyl)methane ("Desmodur R") [9a], besides having equal adhesive strength, it has the advantage of being colorless; "Desmodur R" has an intense violet color, which is a disadvantage in the cementing of light colored, or transparent materials.

During the further course of our attempts to synthetize isocyanates of phosphoric and thiophosphoric esters, we investigated the reaction between phosphorus halides and amino phenols, as well as amino-alcohols. Chlorides of pentavalent phosphorus, *i.e.* phosphorus oxychloride and phosphorus sulfochloride, react with aminophenols,

[7] German Pat. 763153 (Aug. 1st, 1938); inventors: *G. Schrader* and *H. Kükenthal*.

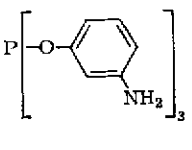
[8] Belg. Pat. 576226 (March 1st, 1958); inventors: *H. Holtschmidt, F. v. Spulak, E. Müller*, and *O. Bayer*.

[9] German Pat. 1092190 (March 22nd, 1958); inventors: *H. Holtschmidt* and *G. Braun*.

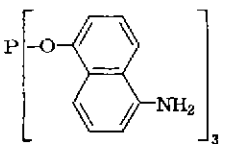
[9a] German Pat. 585902 (March 5th, 1942); inventors: *S. Petersen, H. Kleiner*, and *F. v. Spulak*.

giving nonuniform products which contain aminophenyl ester groupings, as well as hydroxyphenylamido groupings. They therefore show a behaviour similar to carbonyl chlorides, or sulfonyl chlorides.

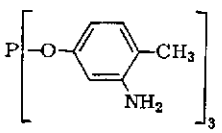
In contrast, the reaction of the trivalent phosphorus halides with aminophenols [10] takes place in an unexpected and uniform manner. For example, the reaction of phosphorus trichloride with *m*-aminophenol in toluene or chlorobenzene gives a nearly quantitative yield of the tris-(*m*-aminophenyl) phosphite hydrochloride, from which the free base *(17)* can be obtained by treatment with dry ammonia gas. The aminoaryl phosphites *(18)* through *(20)* are obtainable in a similar way. Overall yields: *(17)* 95 %, *(18)* 30 %, *(19)* 96 %, and *(20)* 70 %.



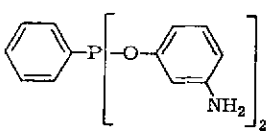
(17)



(18)



(19)



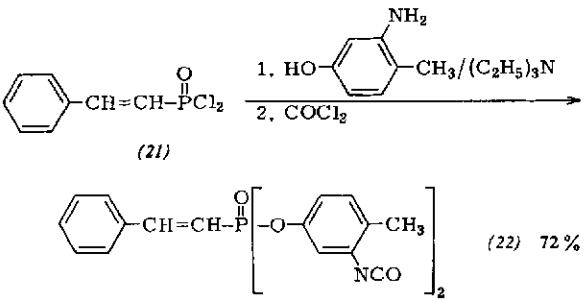
(20)

Direct conversion of these aminoaryl esters into isocyanato esters is not possible, owing to simultaneous cleavage of the ester groups. The aminoaryl phosphites can, however, be converted with oxygen or sulfur into the aminoaryl phosphates or thiophosphates, respectively [11], which, as described above, react readily with phosgene, giving isocyanato esters [*].

II. Isocyanates of Phosphonates

1. *Isocyanates of Phosphonates from Phosphonic Dihalides*

The reactions described in the previous section of nitro- and aminophenols with phosphorus halides permit the preparation of isocyanates of phosphonic and phosphinic esters, when applied to phosphorus halides in which one or two hydrocarbon groupings are linked to the phosphorus. From the vast number of isocyanato esters thus available only the unsaturated isocyanato phosphonate *(22)* will be described. Styrylphosphonic dichloride *(21)*, obtained from styrene and phosphorus pentachloride [12], reacts with 3-amino-4-methylphenol like a trivalent phosphorus halide, although it is a pentavalent phosphorus compound. The aminoaryl ester formed is then easily converted with phosgene into the bis-(3-isocyanato-4-methylphenyl) styrylphosphonate *(22)*, following the usual process [13].



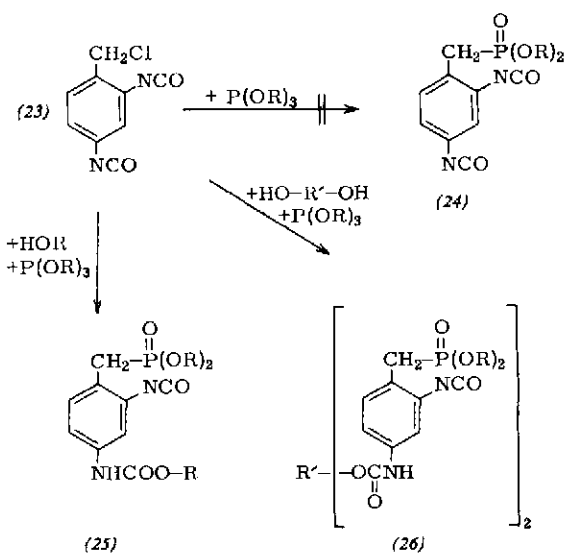
(21)

(22) 72 %

2. *Isocyanates of Phosphonates from α-Halogenoalkylaryl Isocyanates and Trialkyl Phosphites*

Isocyanates containing phosphonic ester groupings were prepared by us in a very simple manner from phosphorus-free polyisocyanates and trialkyl phosphites, by using the Michaelis-Arbusov reaction.

α-Halogenoalkylaryl isocyanates have been easily available since 1953 [14]. We tried to obtain isocyanato phosphonic esters *(24)* for example by reacting 2,4-diisocyanatobenzyl chloride *(23)* with trialkyl phosphites; these attempts failed, however. It could only be ascertained that the Michaelis-Arbusov reaction is possible at approximately 140 °C, whereby alkyl halide is split off. However, a concurrent polymerization of the NCO groups takes place, under the influence of the trialkylphosphite.



(23) *(24)* *(25)* *(26)*

We then found that by simultaneous action of equimolar amounts of trialkyl phosphite and alcohol on the diisocyanatobenzyl chloride *(23)*, the chlorine atom is loosened to such an extent [*] by the basic urethane group originating, that it reacts with the trialkyl phosphite even at room temperature. The reaction under these conditions proceeds without simultaneous polymerization of the NCO groups, yielding phosphorylated monoisocyanates *(25)* with alcohols, and phosphorylated polyisocyanates, *e.g. (26)* with di- or polyols.

[10] German Pat. Appl. F 28 607, IVb/120 (June 4th, 1959); inventors: *G. Oertel* and *H. Holtschmidt*.

[*] Halides of trivalent phosphorus react uniformly with aliphatic amino alcohols, too. However, the conversion of the aminoalkyl phosphites into isocyanates presents difficulties.

[11] German Pat. Appl. F 29 199, IVb/120 (Aug. 18th, 1959); inventors: *G. Oertel* and *H. Holtschmidt*.

[12] *K. N. Anisimov*, Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk *1954*, 796; Chem. Abstr. *49*, 13074 (1955).

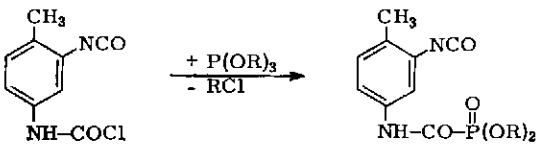
[13] German Pat. Appl. F 30 748, IVb/120 (March 12th, 1960); inventors: *G. Oertel* and *H. Holtschmidt*.

[14] German Pat. 947470 (April 10th, 1953); inventor: *H. Holtschmidt*.

[*] See *H. Holtschmidt*, Angew. Chem. internat. Edit. *1*, 632 (1962).

3. *Isocyanates of Carbamylphosphonates from Isocyanatocarbamyl Chlorides and Trialkyl Phosphites*

Mono- and dialkylcarbamyl chlorides react with trialkyl phosphites even under exceptionally mild conditions, giving carbamylphosphonic esters [15, 16]. This reaction can be applied to isocyanatocarbamyl chlorides: The isocyanatocarbamyl chloride *(27)*, obtained from tolylene-2,4-diisocyanate by the action of equimolar quantities of hydrochloric acid, easily reacts with trialkyl phosphites even at room temperature to yield 3-isocyanato-4-methylphenylcarbamylphosphonic esters *(28)*.

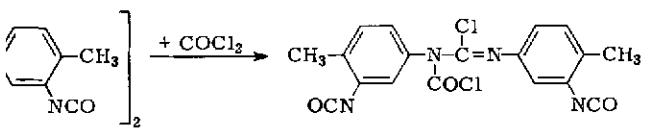


(27) *(28)*

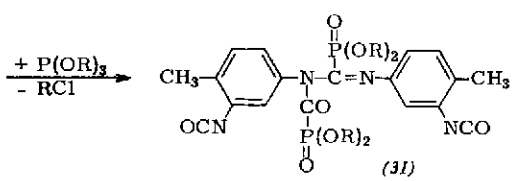
R = CH_3—, $ClCH_2CH_2$—, CH_2=CH—CH_2— *etc.*

4. *Isocyanates of Phosphonates from Trialkyl Phosphites and Chloroformylchloroformamidines containing NCO Groups*

The addition of phosgene onto isocyanates containing carbodiimide groups has become known through the works of *P. Fischer* [17, 18]. The addition products are isocyanates with *N*-chloroformylchloroformamidine groups, and react with trialkyl phosphites even under very mild conditions, giving isocyanato phosphonic esters [19], in the same manner as the isocyanatocarbamyl chlorides described in Section II, 3. The carbodiimide *(29)*, obtained from tolylene-2,4-diisocyanate



(30)

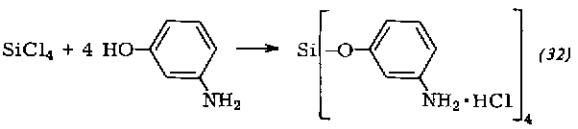


(31)

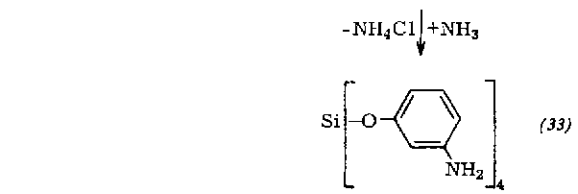
adds on phosgene and forms the *N*-chloroformylchloroformamidine *(30)*, which can be treated with trialkyl phosphites to give isocyanato phosphonic esters *(31)*. The isocyanato phosphonic esters described in the previous Sections II, 2–4 are of interest in the manufacture of fire-resistant polyurethane plastics [20–22].

B. Isocyanates of Esters of Silicic Acid and its Derivatives

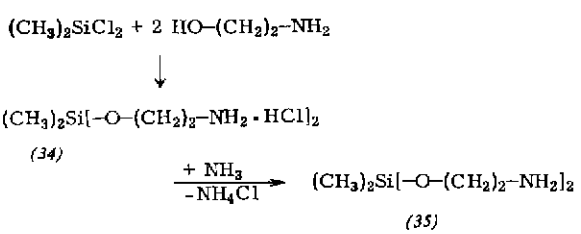
The strange reaction of trivalent phosphorus halides with aminophenols and aminoalcohols has prompted us to react silicon halides with aminohydroxy compounds. In this way, it is in fact possible to prepare aminoaryl and aminoalkyl esters of silicic acid and its derivatives. For example, silicon tetrachloride and *m*-aminophenol react easily to give the hydrochloride of tetra-(*m*-aminophenyl) silicate *(32)*, while the hydrochloride of the silanol etheramine *(34)* is formed from dimethyldichlorosilane and ethanolamine.



(32)

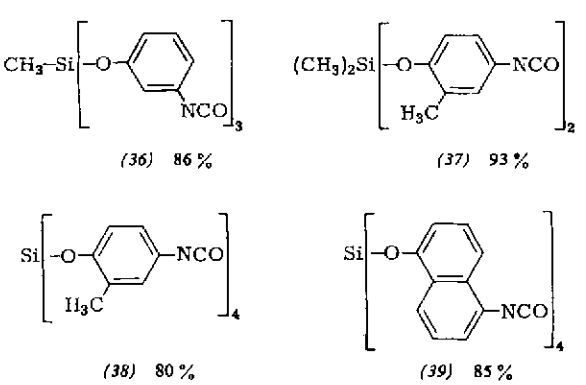


(33)



(34) *(35)*

To isolate the free bases *(33)* and *(35)*, it is generally sufficient to saturate the suspension of the hydrochlorides with gaseous ammonia in an inert solvent, *e.g.* toluene or chlorobenzene. Ammonium chloride precipitates; the free amine can be isolated from the filtrate. The yields are mostly over 90 %.



(36) 86 % *(37)* 93 %

(38) 80 % *(39)* 85 %

[15] *T. Reetz, D. H. Chadwick, E. Hardi,* and *S. Kaufmann,* J. Amer. chem. Soc. *77,* 3813 (1955).

[16] *B. A. Arbusov* and *N. I. Rizpolozhenskii,* Izvest. Akad. Nauk S.S.S.R., otdel. Khim. Nauk *1952,* 847; Chem. Abstr. *47,* 10457h (1953).

[17] German Pat. Appl. F 32 656, IVb/120 (Nov. 30th, 1960); inventor: *P. Fischer.*

[18] German Pat. Appl. F 32 487, IVb/120 (Nov. 5th, 1960); inventor: *P. Fischer.*

[19] German Pat. Appl. F 32 903, IVb/120 (Jan. 5th, 1961); inventors: *G. Oertel, H. Holtschmidt,* and *P. Fischer.*

[20] Belg. Pat. 607480 (Aug. 25th, 1960); inventors: *G. Oertel, H. Holtschmidt, G. Nischk,* and *G. Braun.*

[21] German Pat. Appl. F 32 636, IVb/120 (Nov. 26th, 1960); inventors: *H. Holtschmidt, E. Degener,* and *G. Braun.*

[22] German Pat. Appl. F 34 008, IVb/39b (May 25th, 1961); inventors: *P. Fischer, H. Holtschmidt, G. Oertel,* and *G. Braun.*

These amines react very differently with phosgene. While the silicates or silanol ethers of aliphatic amino-alcohols, such as *(35)*, are completely cleaved, even under extremely mild conditions, the esters or silanol ethers of aminophenols, *e.g. (33)*, can be easily converted into isocyanates, starting with either the hydrochloride or the free base. We have thus been able to obtain the isocyanato esters *(36)* through *(39)* analytically pure without difficulties [23].

Silicones containing aminophenyl terminal groups can be converted into isocyanates in the same manner.

Received May 23rd, 1962 [A 242/59 IE]

[23] German Pat. 1066582 (Oct. 31st, 1958); inventors: *H. Holtschmidt* and *O. Bayer*.

The Preparation of Carbodiimides from Isocyanates

BY DR. W. NEUMANN AND DR. PETER FISCHER

WISSENSCHAFTLICHES HAUPTLABORATORIUM AND ZWISCHENPRODUKTE-ABTEILUNG, FARBENFABRIKEN BAYER A.-G., LEVERKUSEN (GERMANY)

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

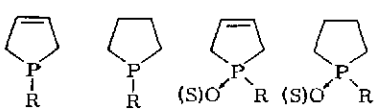
Carbodiimides are formed with simultaneous evolution of CO_2 by the reaction of basic catalysts with sterically hindered isocyanates. Another generally applicable synthesis of carbodiimides involves intermediate formation of cyclic adducts of isocyanates and carbodiimides, which, upon cleavage, exchange the isocyanate and carbodiimide functions. Both processes are suitable for the preparation of polycarbodiimides. Several commercial applications of mono- and polycarbodiimides are pointed out.

Introduction

The formation of carbodiimides [1] on heating isocyanates has been known for a long time [2]. It takes place formally according to the equation:

$$2\ R{-}NCO \rightarrow R{-}N{=}C{=}N{-}R + CO_2.$$

This reaction achieved general and commercial applicability only in recent years when catalysts were found which can greatly accelerate it. Phospholenes *(1)* and phospholanes *(2)* as well as their oxides and sulfides *(3)* and *(4)* [3] provide such a catalytic effect.



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

A few years ago, we found that simple phosphine oxides, such as tributyl-, triphenyl-, tribenzyl-, phenyldibutylphosphine oxide, *etc.*, also react, though less vigorously, with isocyanates to form carbodiimides [4].

[1] Review: *H. G. Khorana*, Chem. Reviews *53*, 145 (1953).

[2] *A. W. Hofmann*, Ber. dtsch. chem. Ges. *18*, 765 (1885); *R. Stolle*, ibid. *41*, 1125 (1908).

[3] *T. W. Campbell* and *J. J. Verbanc*, U.S. Pat. 2853473 (1956/1958); *W. J. Balon*, U.S. Pat. 2853518 (1956/1958). Compounds *(1)* and *(2)* are frequently called phospholines and phospholidines, respectively.

[4] After the conclusion of our work, we found in a conference report [Angew. Chem. *74*, 127 (1962)] the statement that *T. W. Campbell* also observed the catalytic effect of non-cyclic phosphine oxides during the formation of carbodiimides from isocyanates.

1. Carbodiimides from Sterically Hindered Isocyanates

Derivatives of isocyanuric acid [5] are generally formed from isocyanates in exothermic reactions under the influence of strongly alkaline catalysts. Carbodiimides are formed from sterically hindered isocyanates, that is, isocyanates containing bulky groups in positions adjacent to the NCO group, under the influence of these same catalysts [6]. We studied this reaction first on aromatic *o*-alkyl monoisocyanates [7], which were prepared by the reaction of the corresponding amines with phosgene [8]. Effective catalysts for the formation of carbodiimides from such isocyanates are basic compounds usually used for trimerizations such as alcoxides, alkali carbonates, alcoholic sodium or potassium hydroxide, or tertiary amines. Heavy metal salts of carboxylic acids, such as lead octoate, tin(II) octoate, lead and cobalt naphthenates [9], dibutyltin

[5] *A. W. Hofmann*, Ber. dtsch. chem. Ges. *18*, 764 (1885); see also *J. H. Saunders* and *R. J. Slocombe*, Chem. Reviews *43*, 203 (1948).

[6] The process is the subject of patents and patent applications, see *e.g. W. Neumann*, French Pat. 1293252 (1961/1962).

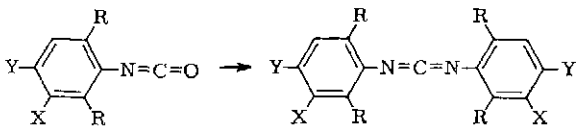
[7] Aromatic *o*-alkylamines are easily accessible by the reaction of olefins with aromatic amines: *R. Stroh* et al., Angew. Chem. *69*, 124 (1957).

[8] We thank Dr. *W. Siefken* (Wissenschaftliches Hauptlaboratorium der Farbenfabriken Bayer AG.) for the preparation of several isocyanates used in this work.

[9] According to a paper published after our patent application, carbodiimides are formed, in addition to derivatives of isocyanuric acid, by the reaction of metal naphthenates and aluminum isopropoxide with 1-naphthylisocyanate and diphenylmethane-4,4'-diisocyanate: *E. Dyer* and *E. E. Read*, J. org. Chemistry *26*, 4677 (1961).

dilaurate, titanium tetrabutylate, iron acetylacetonate, *etc.*, may also be used. The formation of carbodiimide usually begins above 150 °C in the presence of 0.1 to 5 % of the catalyst, and is evidenced by vigorous evolution of CO_2. Since the reaction is endothermic, it can be easily controlled. The carbodiimides listed in Table 1 were prepared in this manner.

Table 1. Carbodiimides prepared from isocyanates by basic catalysis



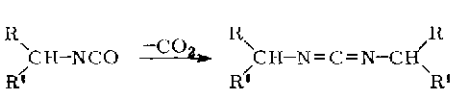
Isocyanate				Carbodiimide		
R	X	Y	B.p. [°C/mm Hg]	Yield [%]	B.p. [°C/mm Hg]	M.p. [°C]
$-CH_3$	—H	—H	90—91/13	80	122—123/0,5	49—50
$-C_2H_5$	—H	—H	111—112/13	80	135—138/0,02	
$-C_2H_5$	—H	$-CH_3$	118—120/11,5	80—90	176—178/0,035	
$-CH(CH_3)_2$	—H	—H	126—127/14	85—95	162—167/0,05	47—49,5
$-CH(CH_3)(C_2H_5)$	—H	—H	140—147/13	85—95	170—180/0,04	
$-C_2H_5$	—Cl	—H	132—134/12	75	166—172/0,03—0,08	
$-CH(CH_3)_2$	$-NO_2$	—H	110—111/0,08 m. p. = 52—57 °C	50		119—122

These substituted diphenylcarbodiimides can be distilled and are soluble in unsubstituted or chlorinated aliphatic and aromatic hydrocarbons, esters, and ethers. They are extremely stable and show no tendency to polymerize [10] as *e.g.* the unsubstituted diphenyl carbodiimide does. The compounds were identified as carbodiimides by elemental analysis, infrared absorption spectra [11], and chemical reactions.

Carbodiimides [12] show a typical absorption band at 4.75 to 4.77 μ; they react with oxalic acid to form ureas, CO, and CO_2 [13].

From aromatic isocyanates containing only one alkyl group in the *ortho*-position, one chiefly obtains mixtures of carbodiimide and more or less large fractions of the corresponding isocyanuric acid derivative.

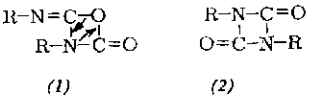
Like the aromatic isocyanates, sterically hindered aliphatic isocyanates also form carbodiimides. The reaction was investigated with several aliphatic isocyanates containing NCO groups attached to secondary carbon atoms:



Benzhydryl isocyanate ($R = R' = C_6H_5$) yields no carbodiimide; only the isocyanuric acid derivative is formed.

Isocyanates containing aliphatic substituents, such as 3-pentyl isocyanate ($R = R' = C_2H_5$) or 1,2,2-trimethylpropyl isocyanate ($R = CH_3$; $R' = t\text{-}C_4H_9$) produce carbodiimides in moderate yields alongside the isocyanuric acid derivatives. From 1-cyclohexylethyl isocyanate ($R = CH_3$; $R' = C_6H_{11}$), the corresponding carbodiimide was obtained in a crude yield of 54 %, and analytically pure in 25 % yield (b.p. 127—135 °C/0.09 mm). Besides isocyanuric acid derivatives, high-molecular products are formed [10]; these are probably polymeric carbodiimides, which originate under the influence of the basic catalysts from the monomeric carbodiimide originally present.

Cyclic dimeric isocyanates are possible intermediates of the formation of carbodiimides. The unsymmetrical structure *(1)* assumed by *Gaylord* and *Snyder* [14] for dimeric isocyanates allows a better interpretation for the formation of carbodiimides than the symmetrical uretidinedione structure *(2)*



(1) *(2)*

first mentioned by *Staudinger* [15] and later confirmed by X-ray diffraction for crystalline dimeric phenyl isocyanate[16].

Since the formation of uretidinediones is inhibited by *ortho*-substituents [17], the reaction in the presence of sufficiently bulky substituents takes place by way of the unsymmetrical unstable structure *(1)*. Carbon dioxide is split off and carbodiimide is formed *via* cyclic electron displacements [18].

On the other hand, *Dyer* and *Read* [9] assume that the formation of carbodiimide takes place by way of an unsymmetrical trimeric isocyanate *(3)*, which was isolated by *Slotta* and *Tschesche* [19] from methyl isocyanate. However,

[10] *H. G. Khorana* [1]: Polymeric carbodiimides are formulated as dimeric or trimeric compounds, in analogy to the uretidinediones and derivatives of isocyanuric acid in the isocyanate series.

[11] We thank Prof. Dr. *M. Pestemer*, Dr. *D. Lauerer*, and Dr. *H. Hoyer* (Wissenschaftliches Hauptlaboratorium und Organisch-analytisches Laboratorium der Farbenfabriken Bayer AG.) for the infrared absorption spectra and their discussion.

[12] *H. G. Khorana* [1].

[13] *F. Zetsche* and *H. Lindlar*, Ber. dtsch. chem. Ges. *71*, 2095 (1938).

[14] *G. Gaylor* and *J. A. Snyder*, Chem. and Ind. *1955*, 145.

[15] *H. Staudinger:* Die Ketene. F. Enke Verlag, Stuttgart 1912, p. 126; see also *H. F. Piepenbrink* in: *Houben-Weyl:* Methoden der organischen Chemie. 4th Edit., G. Thieme Verlag, Stuttgart 1952, vol. 8, p. 220.

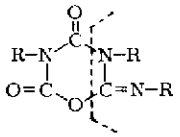
[16] *C. J. Bowen*, J. chem. Soc. (London) *1955*, 2931.

[17] *H. F. Piepenbrink* in: *Houben-Weyl:* Methoden der organischen Chemie. 4th Edit., G. Thieme Verlag, Stuttgart 1952, Vol. 8, p. 220; see also *W. Balon* et al.: Papers presented at the Atlantic City Meeting, September 1956; Symposium on Isocyanate Polymers. Amer. chem. Soc., Div. of Paint, Plastics and Printing Ink Chemistry, vol. 16, p. 69.

[18] For the addition of phenyl isocyanate onto Michler's ketone and onto *p*-nitrosodimethylaniline *Staudinger* assumes a primary addition product in the form of the same four-membered ring as formulated here; the assumption is based on the cleavage products: *H. Staudinger* [15], p. 125.

[19] *K. H. Slotta* and *R. Tschesche*, Ber. dtsch. chem. Ges. *60*, 295 (1927).

Slotta and *Tschesche* did not observe the formation of carbodiimide at elevated temperatures, but only a conversion into symmetrical derivatives of isocyanuric acid.



(3)

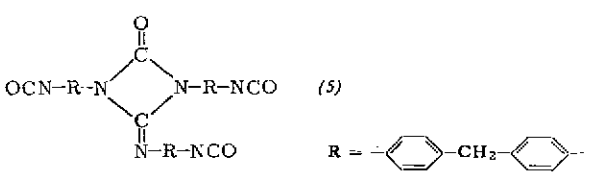
2. Preparation of Polycarbodiimides

The methods for preparing carbodiimides from isocyanates described above may be applied to polyisocyanates. Compounds containing several –N=C=N- groups per molecule, called polycarbodiimides [20] are obtained.

Polycarbodiimides [21] are formed from polyisocyanates by the reaction of *Hofmann* and *Stollé* [2] mentioned above, *i.e.*, by heating. Under suitable reaction conditions, it is possible to prepare polycarbodiimides containing NCO end groups *(4)* from polyisocyanates.

$$OCN-R-N=C=N-(R-N=C=N)_x-R-NCO \qquad (4)$$

These isocyanate groups can combine with carbodiimide groups with ring formation (*cf.* the formation of uretidinedione imines, Section 3). For example, by thermal treatment of diphenylmethane-4,4'-diisocyanate, a carbodiimide with free NCO groups can be obtained which is capable of adding excess diisocyanate to form a branched product *(5)* [22].

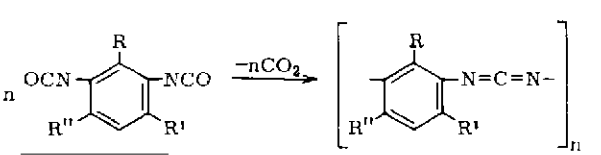


(5)

Polycarbodiimides obtained thermally often contain by-products, such as isocyanurates, *etc.*

Polycarbodiimides are formed from polyisocyanates in the same way as monocarbodiimides are formed from monoisocyanates with phosphorus-containing catalysts. They have been prepared with phospholene oxides [23] and with non-cyclic phosphine oxides in our laboratories.

Especially valuable polycarbodiimides are obtained by the reaction of basic catalysts on sterically hindered polyisocyanates:



[20] Polycarbodiimides must be differentiated from polymeric carbodiimides (see [10]).

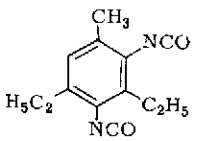
[21] *E. Dyer* and *G. E. Newborn*, J. Amer. chem. Soc. *80*, 5495 (1958).

[22] *P. Fischer* and *E. Meisert*, German Patent 1092007 (1959/1960).

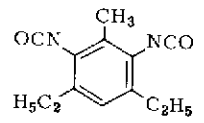
[23] *T. W. Campbell* and *J. J. Verbanc* [3]; *T. W. Campbell*, U.S. Patent 2941966 (1956/1960); *K. C. Smeltz*, U.S. Patent 2941983 (1957/1960); see also *T. W. Campbell*, Angew. Chem. *74*, 127 (1962).

Table 2 shows several isocyanates used in this reaction.

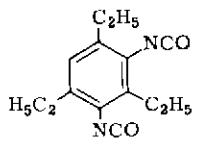
Table 2. Diisocyanates polymerized to polycarbodiimides



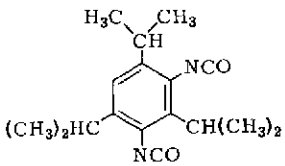
b. p. 108 °C/0,8 mm Hg



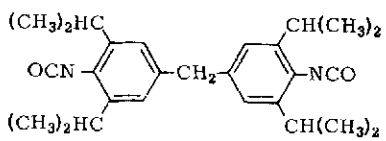
b. p. 109–113 °C/0,6 mm Hg



b. p. 161–171 °C/14 mm Hg



b. p. 144 °C/0,4–0,45 mm Hg



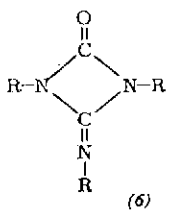
b. p. 187–191 °C/0,1 mm Hg
m. p. 63–67 °C

Since the formation of carbodiimide begins only at elevated temperature, and since the reaction is endothermic, any desired fraction of the NCO groups can be converted into carbodiimide groups by appropriate choice of the reaction time and temperature. Thus, polycarbodiimides of predetermined chain length with NCO end-groups can be prepared, as well as polycarbodiimides which are practically free of NCO groups.

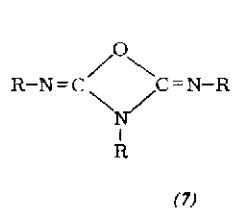
Polycarbodiimides with free NCO groups prepared from sterically hindered diisocyanates have an essentially linear structure, for there are no bands of the ring system *(6)* responsible for branching (see Section 3) in the infrared spectrum of such compounds. Depending on the degree of condensation, such products are soft to brittle resins, and their solubility in organic solvents is dependent on the molecular weight and on the degree of substitution at the benzene rings.

3. Isocyanate-Carbodiimide Exchange Reaction

A few years ago, it was discovered in the laboratories of Farbenfabriken Bayer, Werk Dormagen, and by *E. Schmidt*, Munich, that isocyanates and carbodiimides combine to give well-defined, thermally unstable adducts [24]. Formulae *(6)* and *(7)* have been considered as structures for such compounds.



(6)



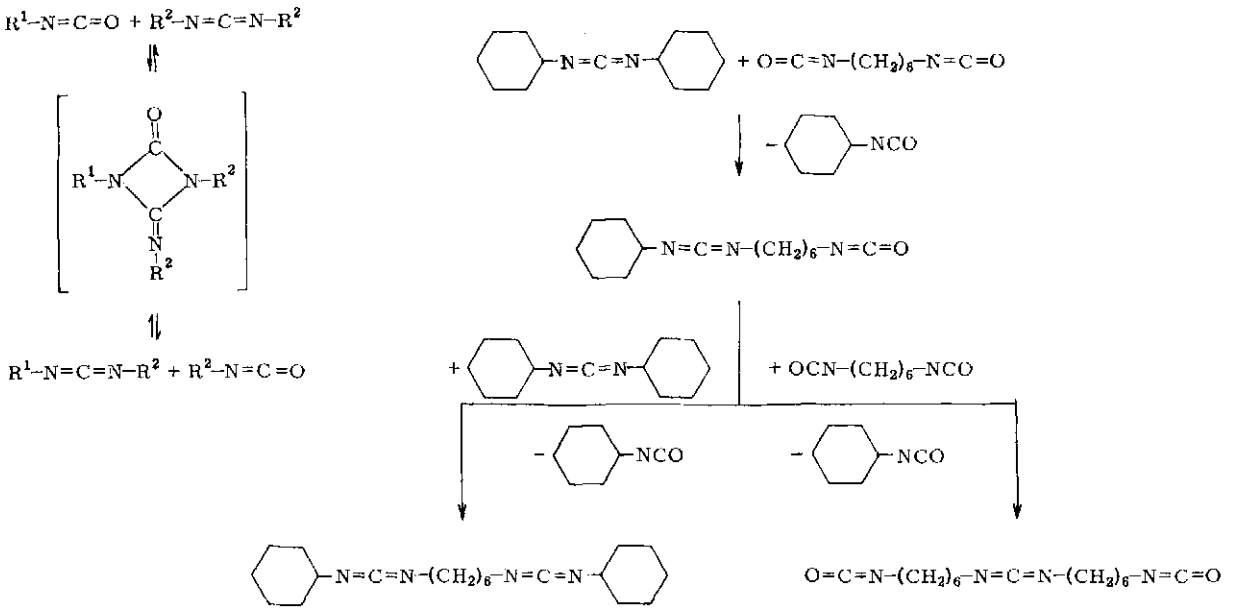
(7)

We prefer Formula *(6)* on the basis of the infrared spectra, which show a characteristic band at 5.7 to 5.8 μ and a second weaker band at 7.2 to 7.5 μ; these compounds are uretidinedione imines [*] (1,3-diazetidine-2,4-dione-4-imine) by analogy to the uretidinediones [15], the dimerization products of aromatic isocyanates [*].

[24] *R. Hofmann*, *E. Schmidt*, *A. Reichle*, and *F. Moosmüller*, German Patent 1012601 (1955/1957).

[*] We propose the shorter term uretoneimines.

The uretidinedione imine prepared from an isocyanate $R^1-N=C=O$ and a carbodiimide $R^2-N=C=N-R^2$ cleaves on heating, not only in the direction of its formation, but also in such a fashion that a new isocyanate $R^2-N=C=O$ and a mixed carbodiimide $R^1-N=C=N-R^2$ are formed:



By removal of $R^2-N=C=O$, the equilibrium is shifted in the direction of the mixed carbodiimide. Table 3 shows several examples of unsymmetrical carbodiimides prepared by this method.

Table 3. Carbodiimides prepared by isocyanate-carbodiimide exchange

Isocyanate	Carbodiimide	Unsym. carbodiimide
1-Naphthyl	Dicyclohexyl	1-Naphthylcyclohexyl b.p. 145–154 °C/0.3 mm Hg
Octadecyl	Dicyclohexyl	Octadecylcyclohexyl b.p. 190–220 °C/1.5 mm Hg
2,6-Diethyl-4-methylphenyl	Diphenyl	Phenyl-2,6-diethyl-4-methylphenyl b.p. 140–150 °C/0.2 mm Hg

By suitable selection of the molar ratios of isocyanate and carbodiimide, both substituents of the original carbodiimide can be replaced, so that another symmetrical carbodiimide is formed (twofold uretidinedione imine formation and cleavage):

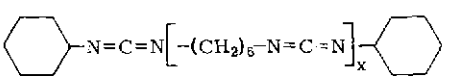
$$R^2-N=C=N-R^2 + 2\ R^1-N=C=O \rightleftharpoons R^1-N=C=N-R^1 + 2\ R^2-N=C=O$$

The only thing that is important is that the isocyanate $R^2-N=C=O$ can be removed from the reaction mixture. Normally the exchange reaction takes place at 80 to 150 °C; more drastic conditions are required for sterically hindered components. Since the reaction is not catalyzed, extraneous materials that might promote side reactions are largely excluded.

The application of the exchange principle to compounds with two or more NCO groups leads again to polycarbodiimides [25].

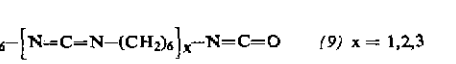
[25] *P. Fischer*, German Patent 1 122 057 (1960/1962).

The idealized reaction mechanism shows that the reaction may be led into either of two directions by proper choice of the ratio of monocarbodiimide to diisocyanate. When an excess of dicyclohexyl carbodiimide is used, *i.e.* $-NCN-:-NCO > 0.5$, polycarbodiimides of variable chain length without isocyanate end groups *(8)* are formed:



(8), x = 1,2,3,...

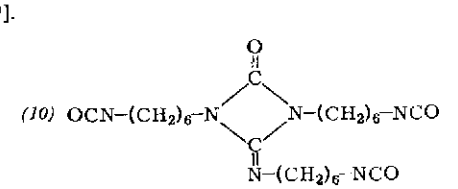
With excess diisocyanate, *i.e.* $-NCN-:-NCO < 0.5$, polycarbodiimides with NCO end groups *(9)* are formed:



(9) x = 1,2,3

Since every compound appearing in the course of the reaction can form uretidinedione imines with its NCN or NCO group, mixtures of compounds of variable chain length are formed in both cases. Products containing both NCO and NCN groups, such as polycarbodiimides of formula *(9)* can form uretidinedione imines, thereby losing their linear structure and forming branches.

Likewise, a branched triisocyanate *(10)* may be formed in the presence of excess diisocyanate by uretidinedione imine formation from a carbodiimide of formula *(9)* with x = 1; a similar triisocyanate is also obtained by elimination of carbon dioxide from diphenylmethane-4,4'-diisocyanate [see Section 2, formula *(5)*].



(10)

The formation of uretidinedione imines, which is an equilibrium reaction, is largely repressed when sterically hindered NCO and NCN groups are involved, or when the equilibrium is frozen on the side of the cleavage products, *i.e.* free NCO and NCN groups.

The exchange reaction is carried out by mixing monocarbodiimide and diisocyanate in the desired ratio and

Table 4. Polycarbodiimides and polyisocyanates prepared by isocyanate-carbodiimide interchange

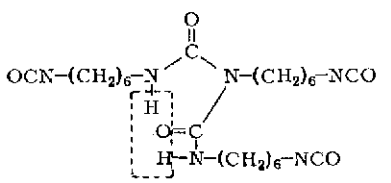
Diisocyanate	Monocarbodiimide	Molar Ratio -NCO:-NCN-	Product
Hexamethylene-1,6-	Diethyl	1:2	Liquid polycarbodiimide 0.8 % oxygen, aver. mol. wt. 340
Hexamethylene-1,6-	Dicyclohexyl	1:2	Polycarbodiimide, 280—360 cP/25 °C 0.6—0.8 % oxygen, aver. mol. wt. 550—650
Dicyclohexylmethane-4,4'-	Dicyclohexyl	1:3	Sirupy polycarbodiimide, 0.5 % oxygen
Toluylene-2,4-/-2,6-	Diphenyl	1:2	Resinous polycarbodiimide, 0.3 % oxygen, mol. wt. 650—700
1-Chlorophenylene-2,4-/-2,6-	Dicyclohexyl	1:2.5	Resinous polycarbodiimide, 0.7 % oxygen, mol. wt. 720
Diphenyldimethylmethane-4,4'-	Diphenyl	1:3.5	Resinous polycarbodiimide, 0.4 % oxygen
Hexamethylene-1,6-	Dicyclohexyl	4:1	Carbodiimide-modified polyisocyanate, 20 % NCO; ca. 1000 cP/25 °C
Toluylene-2,4-/-2,6-	Diphenyl	20:1	Polyisocyanate, 45.1 % NCO; aver. mol. wt. 190
Diphenylmethane-4,4'-	Diphenyl	20:1	Polyisocyanate, 28—35 cP/25 °C 30 % NCO; mol. wt. ca. 320
Diphenyldimethylmethane-4,4'-	Diphenyl	5:1	Polyisocyanate, 22.5 % NCO; m.p. 60—70 °C
Naphthylene-1,5-	Dicyclohexyl	40:1	Polyisocyanate, 37.5 % NCO; mol. wt. ca. 270, m.p. 123—124 °C
1,3,5-Triisopropylphenylene-2,4-	Diphenyl	2:1	Polyisocyanate, 8.5 % NCO; softening point 48—50 °C
3,3',5,5'-Tetraethyldiphenylmethane-4,4'-	Diphenyl	2:1	Resinous polyisocyanate, 5.6 % NCO

heating to 80—160 °C. The monoisocyanate split off is distilled off, under reduced pressure, if necessary. Examples are shown in Table 4.

4. Commercial Applications of Carbodiimides

Of the many possible applications of carbodiimides, we will single out only a few that are of commercial importance.

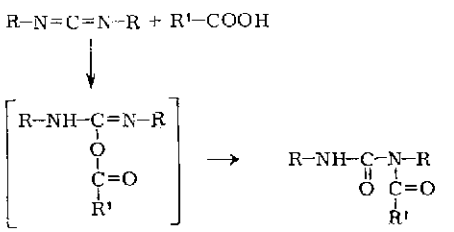
Carbodiimide-modified isocyanates show similarities in structure to biuret resins [26], which are used as lacquer components. The reaction product of structure *(10)* mentioned above which is obtained formally from one mole of dicyclohexylcarbodiimide and three moles of hexamethylenediisocyanate, differs from the biuret resin *(11)* made from three moles of hexamethylenediisocyanate and one mole of water only in that it contains one mole less of water. Thus, the uretidinedione imine *(10)* may be considered as a biuret anhydride.



(11)

Both products do, in fact, show similar properties as lacquer components; they differ only in their flow properties. The biuret resin (of approximately equal molecular weight) is more viscous as a melt or in solution than the uretidinedione imine; this can be explained by the presence of hydrogen bridges.

Carbodiimides are of considerable interest as aging inhibitors against the effects of heat and moisture in polyester/isocyanate plastics [27]. Their mode of protection is based on the property of the NCN group to react preferentially with carboxyl groups to form acylated ureas [1]:



Thus, the carboxyl groups which are formed during the aging of a plastic containing ester groups and which autocatalytically accelerate degradation of the plastic, are thus captured and rendered ineffective. However, the use of such well-known compounds as dicyclohexyl carbodiimide, diisopropyl carbodiimide, *etc.* have never become very important. These compounds did not find broad commercial application because of their volatility, easy extractability from the plastics, and other deficiencies. In contrast, some of the mono- and polycarbodiimides described in this paper, especially from the series of the sterically hindered compounds, have proved to be excellent aging inhibitors for plastics containing ester groups [28]. They are stable and have good compatibility and processability with these same plastics. The polycarbodiimides in particular are practically non-volatile and sparingly extractible. Thus, it has become possible to achieve substantial stability of plastics and elastomers containing ester groups toward humid heat, water, and water vapor, as well as toward aging in open and closed systems.

Received, May 23rd, 1962 [A 239/56 IE]

[26] *K. Wagner*, Angew. Chem. *74*, 799 (1962).

[27] *H. Holtschmidt* et al., German Patent 1005726 (1955/1957).

[28] The use of sterically hindered carbodiimides as aging inhibitors is the subject of patents and patent applications, see *e.g. W. Neumann*, Belg. Pat. 610969 (1961/1962) and 612040 (1961/1962). For details concerning commercial applications, see *W. Neumann*, et al.: Proc. 4th Rubber Technology Conf., London 1962, in the press.

Syntheses Using the Michael Addition of Pyridinium Salts [1]

BY PROF. DR. F. KRÖHNKE AND DR. W. ZECHER
WITH THE COOPERATION OF DIPL.-CHEM. J. CURTZE, DIPL.-CHEM. D. DRECHSLER, DR. K. PFLEGHAR, DIPL.-CHEM. K. E. SCHNALKE, and DIPL.-CHEM. W. WEIS

CHEMISCHES INSTITUT DER UNIVERSITÄT GIESSEN (GERMANY)

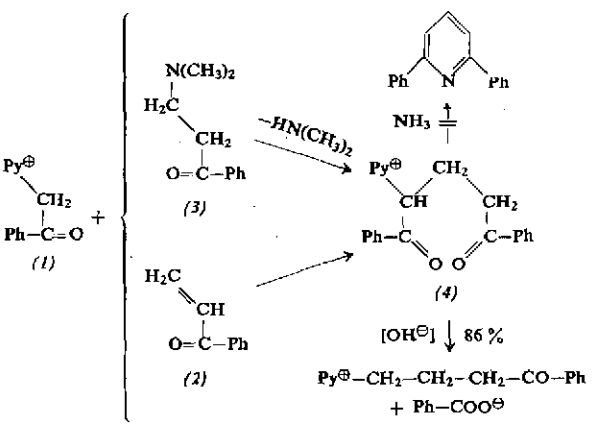
Dedicated with admiration and gratitude to Prof. Dr. Otto Bayer on the occasion of his 60th birthday

By Michael addition of the active methylene groups in pyridinium salts onto suitable acceptor compounds, α-pyridones, substituted pyridines, particularly pyridinecarboxylic acids and pyridylpyridines, including the minor alkaloid of tobacco nicotelline and annelized pyridines, can be prepared by a simple procedure and generally in good yields. From the Michael adducts, polycyclic aromatic hydrocarbons, e.g. substituted fluoranthenes and "bisfluoranthenes" can be prepared; internal Michael addition leads to pyrrolinopyridinium salts. For example, Michael addition of pyridinium salts onto quinones gives phenacyl substituted quinones, from which benzofurans and cinnolines can be readily obtained.

Because of their structure and the manner in which they react, phenacylpyridinium betaines have often been compared to β-diketones [2]. This analogy has also become apparent from the Michael addition of these pyridinium betaines onto the geminal double bonds of phenyl isocyanate [3] and phenyl isothiocyanate [3] or onto quinones [4]. *Heffe*, our coworker at that time, later established that phenacylpyridinium bromide *(1)*, for example, readily adds onto the double bond of diaroylethylenes to give an isolable intermediate capable of splitting off pyridine [5]. Subsequently, *Thesing* and coworkers [6] at Darmstadt and *Kröhnke* and *Zecher* at Giessen were able to carry out abundant syntheses using the Michael addition of pyridinium salts. In view of the analogy between phenacylpyridinium salts and β-diketones, the Michael addition of the former onto quinones was also investigated.

1. Synthesis of α-Pyridones [6]

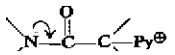
According to *Thesing* and *Müller* [6], *N*-phenacylpyridinium bromide *(1)* readily adds onto α,β-unsaturated carbonyl compounds, *e.g.* vinyl phenyl ketone *(2)*. Mannich bases, *e.g.* ω-dimethylaminopropiophenone *(3)*, which readily give α,β-unsaturated carbonyl compounds, may also be used.



(Here and hereinafter, the anions will be omitted; $Py^{\oplus}$ denotes pyridinium$^{\oplus} = NC_5H_5^{\oplus}$; Ph = C_6H_5).

However, the benzoyl radical, which is already readily split off from *(1)* under alkaline conditions (Schmidt cleavage [7]), is even more labile in alkylated phenacylpyridinium salts such as *(4)* [7]; the rate at which it is hydrolyzed is faster than that of cyclization of *(4)* with ammonia. Thus, *(1)* plus *(2)* or *(1)* plus *(3)* yield only butyrophenone substituted in the ω-position by the pyridinium radical in addition to benzoic acid.

The presence of electron releasing groups next to the carbonyl group retards the Schmidt cleavage [7] or may even prevent it altogether [8], *i.e.* the positive charge on the carbonyl C-atom, which is required for acid hydrolysis, is reduced:



[1] Communication No. II on "Synthesen mit Hilfe von Pyridiniumsalzen" (Syntheses using pyridinium salts). Communication No. I: Angew. Chem. *65*, 605 (1953).

[2] *F. Kröhnke* and *H. Timmler*, Ber. dtsch. chem. Ges. *69*, 615 (1936); *F. Kröhnke* and *W. Heffe*, *ibid. 70*, 867 (1937); *F. Kröhnke* and *H. Kübler*, *ibid. 70*, 539 (1937).

[3] *F. Kröhnke* and *H. Kübler*, Ber. dtsch. chem. Ges. *70*, 538 (1937).

[4] *F. Kröhnke* and *H. Schmeiss*, Ber. dtsch. chem. Ges. *70*, 1729 (1937).

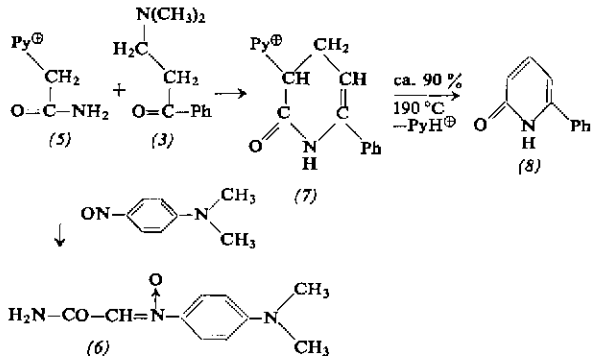
[5] *W. Heffe*, 1952, unpublished data.

[6] *J. Thesing* and *A. Müller*, Angew. Chem. *68*, 338, 577 (1956); Chem. Ber. *90*, 711 (1957).

[7] For information on the Schmidt cleavage, see *F. Kröhnke*, Chem. Ber. *92* (A), CIV (1959).

[8] *F. Kröhnke* and *W. Heffe*, Ber. dtsch. chem. Ges. *70*, 864 (1937).

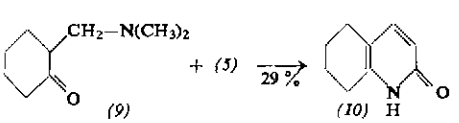
For this reason, *Thesing* and *Müller* [6] used *N*-(aminoformylmethyl)pyridinium chloride *(5)* instead of *(1)*. The same effect which in this case prevents acid hydrolysis, *i.e.* the elimination of carbamic acid, also deactivates the methylene group. However, this group is still sufficiently reactive to undergo a smooth reaction with *p*-nitrosodimethylaniline to give the nitrone of glyoxylic amide *(6)* [9] or to undergo Michael addition, *i.e.* alkylation by the Mannich base *(3)*. In this reaction, dimethylamine is split off, and the intermediate *(7)* is formed, which is not isolated, but instead, is converted into 6-phenyl-2-pyridone *(8)* by heating at 190 °C in formamide.



Preparation of 6-Phenyl-2-pyridone (8) [10]

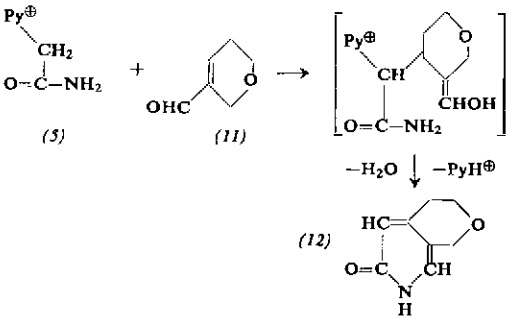
A solution of 1.77 g (0.01 mole) of ω-dimethylaminopropiophenone *(3)* and 1.72 g (0.01 mole) of *N*-(aminoformylmethyl)pyridinium chloride *(5)* in 40 ml of methanol was heated to 65 °C while passing nitrogen through it. After complete evaporation of the solvent, two additional 10 ml portions of methanol were added, and the mixture was again evaporated to dryness. After a total of 3 hrs. 76 % of the dimethylamine was eliminated. The last traces of solvent were removed *in vacuo* at 65 °C. The red resinous residue was heated with 2 ml of glacial acetic acid and 20 ml of formamide at 190 °C for 2 hrs. The formamide solution was cooled and shaken four times with 20 ml portions of chloroform, and the extract dried with sodium sulfate. After evaporation of the chloroform, a small amount of formamide was removed from the residue at 170 °C *in vacuo*. After trituration with water, 0.95 g (55.5 %) of *(8)* was obtained; m.p. of crude material: 170–180 °C; m.p. after crystallization from benzene: 196–197 °C.

Similar results were obtained in the Michael addition of *N*-(aminoformylmethyl)pyridinium chloride *(5)* onto other α,β-unsaturated carbonyl compounds such as cinnamaldehyde (47.3 % yield of 4-phenyl-2-pyridone) or benzalacetophenone (82 % yield of 4,6-diphenyl-2-pyridone). If the Mannich base 2-(dimethylaminomethyl)cyclohexan-1-one *(9)* is used with *(5)*, 5,6,7,8-tetrahydro-2-quinolone *(10)* is obtained.

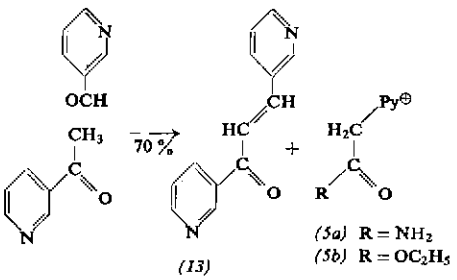


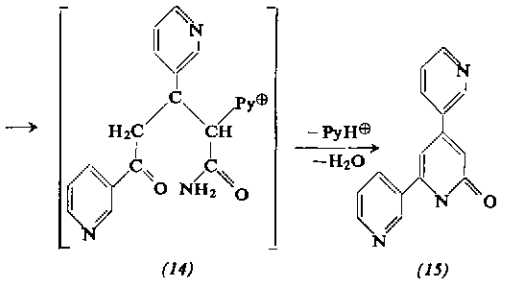
In this case, too, *Thesing* and *Müller* carried out the first step, *i.e.* the Michael addition, by simply heating the reactants together in methanol for 2 hours, and the second step, *i.e.* cyclization to *(10)*, by heating at 200 °C for 2 hrs. in formamide containing 10 % by volume, of glacial acetic acid. In place of *(5)*, salts which are monosubstituted on the amide nitrogen, *e.g.* a derivative of *(5)* containing $-CONHCH_3$ instead of $-CO-NH_2$, may be used.

When 3-formyl-5,6-dihydro-α-pyran *(11)* is used as the α,β-unsaturated carbonyl compound, 3,4-dihydro-1,2-pyrano-[3,4-c]-6-pyridone *(12)* is obtained [11]:



The α-pyridones obtained in this way are useful as pharmaceuticals and intermediates for the synthesis of alkaloids. In particular, using his pyridone synthesis, *Thesing* was able to synthetize nicotelline, a minor tobacco alkaloid [12]; 3-acetylpyridine was condensed with nicotinaldehyde in aqueous alkaline solution to yield the α,β-unsaturated ketone *(13)*:





This was followed by Michael addition of *N*-(aminoformylmethyl)pyridinium bromide *(5a)* onto *(13)* yielding the unisolated adduct *(14)*. In alcohol/acetic acid solution, the latter underwent cyclization to give the pyridone *(15)*. However, considerable losses occur on further conversion of this compound into nicotelline by known methods. In the meantime, a much simpler preparation of this alkaloid in substantially better yields also applying a Michael addition – has been worked out (see below).

In the conversion of the enone *(13)* into "nicotellone" *(15)*, *N*-(ethoxycarbonylmethyl)pyridinium bromide *(5b)* is at least as efficient (yield = 72 %) as the aminoformyl compound *(5a)* [13].

[9] *F. Kröhnke*, Ber. dtsch. chem. Ges. *72*, 532 (1939).

[10] *J. Thesing* and *A. Müller*, Chem. Ber. *90*, 719 (1957); additional examples are to be found therein; also see *W. Zecher* and *F. Kröhnke*, Chem. Ber. *94*, 701 (1961).

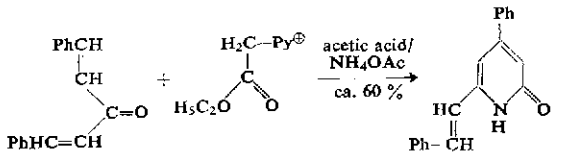
[11] *J. Thesing*, U.S. Patent 2909529; issued on Oct. 20th, 1959; German Patent Application 1092016, from July 19th, 1956/ Nov. 3rd, 1960 (E. Merck AG.).

[12a] *J. Thesing* and *A. Müller*, Angew. Chem. *68*, 577 (1956).

[12b] *J. Thesing* and *A. Müller*, Chem. Ber. *90*, 711 (1957).

[13] *F. Kröhnke* and *K. E. Schnalke*, unpublished data.

Vass [13a] combined this possibility with the method described in the following paragraph:

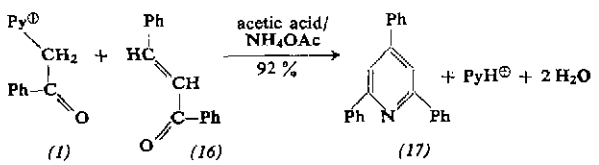


Dibenzylideneacetone — 4-Phenyl-6-styrylpyrid-2-one

2. Synthesis of Substituted Pyridines [15]

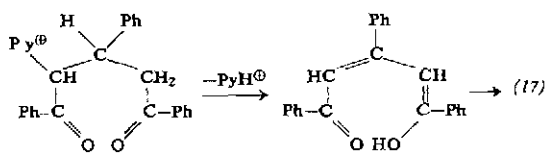
As described in the preceding section, the desired cyclization of the pentane-1,5-dionylpyridinium derivative *(4)* to give a substituted pyridine was prevented by the readiness with which the compound underwent the Schmidt cleavage. However, it had been shown earlier [14] and has recently been confirmed [15b] that the tendency of *N*-phenacylisoquinolinium salts to undergo cleavage with acid by the Schmidt reaction is much less pronounced. In fact, it has been possible to isolate the derivative in the isoquinoline series corresponding to *(4)* [15a]. This compound was found to be very stable toward alkali.

The ring closure with ammonia to substituted pyridines, *e.g.* with *N*-phenacylpyridinium bromide *(1)*, is best carried out in a mixture of glacial acetic acid and ammonium acetate [15a]. This mixture promotes Michael additions of the desired type and does not cause acid cleavage of the adduct *(4)* from phenacylpyridinium bromide *(1)* and the unsaturated ketone. Thus, *(1)* and benzalacetophenone give 2,4,6-triphenylpyridine *(17)* in one step and in about 90 % yield. This appears to be by far the simplest route to this product.



(1) *(16)* *(17)*

Possible intermediates:



Preparation of 2,4,6-Triphenylpyridine (17) [1]

A mixture of 0.84 g (3 millimoles) of phenacylpyridinium bromide *(1)*, 0.63 g (3 millimoles) of benzalacetophenone *(16)*, 3 g of ammonium acetate and 4 ml of glacial acetic acid was refluxed for 1 hour. After addition of water, the precipitate was separated and crystallized from pyridine-methanol. Yield: 0.848 g = 92 %, colorless needles, m.p. 137–139 °C. Replacing *(16)* with 3 millimoles each of benzaldehyde and acetophenone gave a 70 % yield of *(17)*.

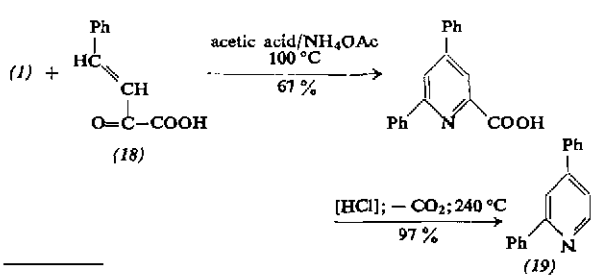
Triphenylpyridine is readily formed from acetophenone and benzaldehyde (Tschitschibabin pyridine synthesis [16a]) on boiling with glacial acetic acid and ammonium acetate [17]. However, the route via pyridinium salts of type *(1)* gives better yields than the Tschitschibabin reaction or other syntheses [16b]. Furthermore, it allows selective introduction of variously substituted phenyl radicals into positions 2, 4, and 6 to be made [1]. For example, the following compounds can be prepared by the procedure described in one step:

Compound	Yield
2,6-diphenyl-4-(*p*-chlorophenyl)pyridine	80 %
2,6-diphenyl-4-(*p*-methoxyphenyl)pyridine	78 %
2,6-diphenyl-(*p*-nitrophenyl)pyridine	85 %
2-(*p*-bromophenyl)-4-(*p*-nitrophenyl)-6-(*p*-methoxyphenyl)-pyridine	79 %

This new synthesis of substituted pyridines appears at a first glance to resemble the improvement of *M. Weiss* [17] of the Tschitschibabin synthesis [16a] but differs from it mainly in the replacement of methyl ketone by the corresponding pyridinium salt. Since the latter is at the next higher oxidation level, dehydrogenation is eliminated. Furthermore, the activation of the methylene group by the pyridinium radical promotes the synthesis. Finally, only symmetrical pyridines can be synthesized by the method of Tschitschibabin, while here one has a free choice of the substituents at C-2, C-4, and C-6.

The pyridine ring can also be substituted with methyl groups or even hydrogen instead of with (substituted) phenyl radicals. Acetonylpyridinium bromide and benzylidene-acetophenone give 2-methyl-4,6-diphenylpyridine, which is isolated as its picrate (yield: 49 %); *(1)* and ethylideneacetophenone form 4-methyl-2,6-diphenylpyridine (78 %); benzylidenedeoxybenzoin reacts with *(1)* to form 2,3,4,6-tetraphenylpyridine (25 %).

2,6-Diphenylpyridine is smoothly obtained in 80 % yield from *(1)* and the Mannich base ω-dimethylaminopropiophenone *(3)*. By contrast, 2,4-diphenylpyridine *(19)* is obtained (as its picrate) from *(1)* and cinnamaldehyde in only 25 % yield. The compound is more readily obtained by reactions of *(1)* with benzylidenepyruvic acid *(18)* to give 4,6-diphenyl-2-picolinic acid, which is decarboxylated [18]:



(18) *(19)*

[13a] *D. Leaver* and *J. D. R. Vass*, unpublished; see *J. D. R. Vass*, Ph.D. Thesis, University of Edinburgh 1962, p. 84 and 153. – We thank the authors for their permission to publish these results.

[14] *F. Kröhnke* and *W. Heffe*, Ber. dtsch. chem. Ges. *70*, 866 (1937).

[15a] *W. Zecher* and *F. Kröhnke*, Chem. Ber. *94*, 690 (1961).

[15b] *F. Kröhnke* and *W. Zecher*, Chem. Ber. *95*, 1128 (1962).

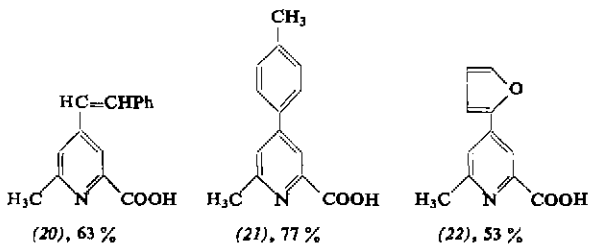
[16a] *R. C. Elderfield*: Heterocyclic Compounds, J. Wiley, New York 1950, vol. I, p. 456.

[16b] See [16a], p. 462.

[17] *M. Weiss*, J. Amer. chem. Soc. *74*, 200 (1952); this article cites further literature references concerning previous applications of the glacial acetic acid/ammonium acetate mixture in synthetic work.

[18] *D. Drechsler*, Diploma Thesis, Universität Giessen, 1962.

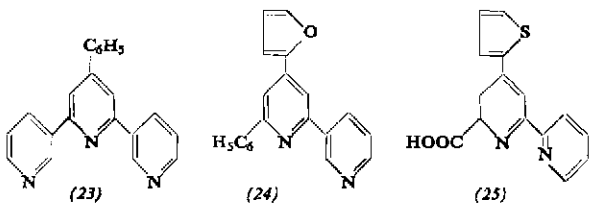
The intermediate, substituted pyridinecarboxylic acids can also be prepared readily [18]. Further examples are represented by formulae *(20)* to *(22)*. In these pyridinecarboxylic acids, the α-substituent is derived from a pyridinium salt analogous in structure to *(1)*, and the γ-substituent from a radical which corresponds to the phenyl group (Ph) in *(18)*. The acids are formed in a one-step reaction [18] analogous to that between *(1)* and *(18)*. However, better yields are obtained when the reaction is run in methanol or water instead of glacial acetic acid.



(20), 63 % *(21)*, 77 % *(22)*, 53 %

(The yields are based on the ammonium salts)

The phenyl ring in the benzylidene group of unsaturated ketone *(16)* can also be substituted readily by a pyridyl, furfuryl, or similar radical. In this manner, substituted di- or tripyridylpyridines, furfurylpyridines, *etc.* can be prepared, often in very good yields [19].



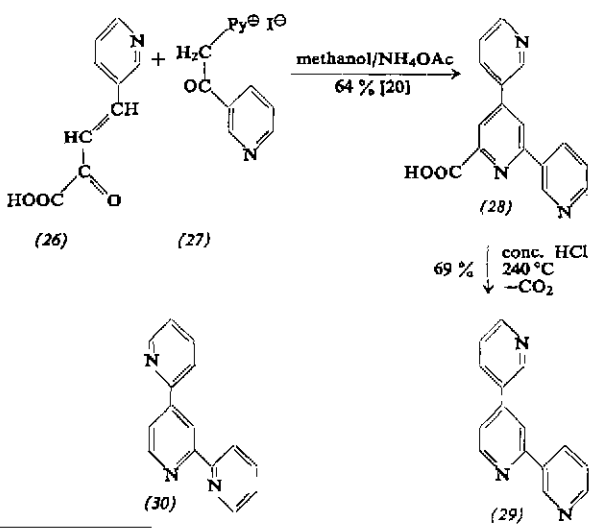
(23) *(24)* *(25)*

2,6-Bis-(3'-pyridyl)-4-phenylpyridine 91 %

2-Phenyl-4-(2'-furfuryl)-6-(3'-pyridyl)pyridine 94 %

2-Carboxy-4-(2'-thienyl)-6-(2'-pyridyl)pyridine 90 %

Of all the dipyridylpyridines theoretically possible, we have synthetized only the minor tobacco alkaloid, nicotelline *(29)*, and "isonicotelline" *(30)* [19].



(26) *(27)* *(28)* *(30)* *(29)*

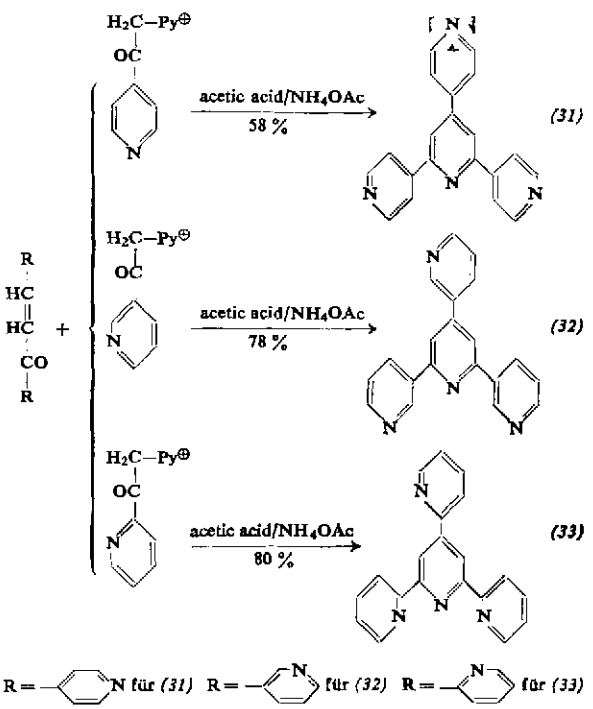
[19] *K. E. Schnalke*, Ph.D. Thesis, Universität Giessen, 1962.

[20] Based on the ammonium salt initially formed.

Nicotellinecarboxylic acid (28): A mixture of 1.77 g (10 millimoles) of 3-picolylidenepyruvic acid *(26)* [21], 3.26 g (10 millimoles) of 3-pyridacylpyridinium iodide *(27)* in 15 ml of methanol, and 8 g of ammonium acetate was refluxed on a water bath for 6 hours. The colorless precipitate of ammonium salt was filtered off by suction and washed with methanol; it was then dissolved in 50 ml of hot 2N nitric acid, and the iodide contaminant precipitated with an excess of silver nitrate solution. The mixture was filtered hot, and the filtrate made alkaline with ammonia. The gelatinous precipitate initially formed became crystalline after warming for some time on a boiling water bath. Yield of ammonium salt: 1.9 g (64 %). The product was sufficiently pure for the decarboxylation step.

Nicotelline (29): A mixture of 1.47 g of the ammonium salt of *(28)* and 4 ml of concd. hydrochloric acid was heated in a sealed tube at 240 °C for 3 hours. The mixture was neutralized with ammonia, and the precipitate obtained extracted three times with 30 ml of boiling water. The precipitate was filtered by suction and once more recrystallized from water. Yield: 0.8 g = 69 %; m.p.: 148 °C. A mixed melting point with nicotelline prepared according to *Thesing* and *Müller* [12b] (yield, based on *(13)*: 10.2 %) showed no depression. The infrared spectra of the two substances (in KBr) were identical in all respects.

It is possible to make the three 2,4,6-tripyridylpyridines *(31)* to *(33)*, for example, in such a way that the N-atoms of the substituent pyridyl radicals are all in the *ortho*-, or the *meta*-, or the *para*-position. Each of the three pyridyl radicals occupied a different position in the starting materials.

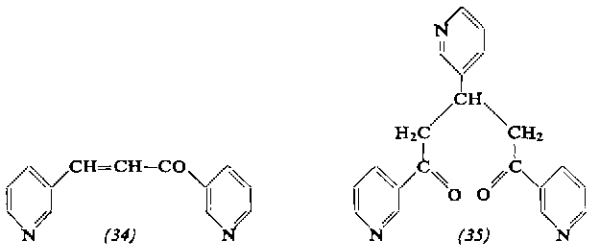


Of the three compounds *(31)* to *(33)*, only one, tripyridylpyridine *(33)*, was previously known. *Frank* and *Riemer* [22] prepared it by treating pyridine-3-aldehyde with 2 moles of 3-acetylpyridine in aqueous ammoniacal solution, in the presence of ammonium acetate at 250 °C in an autoclave. The chalcone *(34)* and the 1,5-diketone *(35)* were intermediate products. After ring closure with ammonia, the

[21] *M. Strell* and *E. Kopp*, Chem. Ber. *91*, 1625 (1958).

[22] *R. L. Frank* and *E. F. Riemer*, J. Amer. chem. Soc. *72*, 4182 (1950).

latter was dehydrogenated by the α,β-unsaturated ketone *(34)* so that one-half of this is lost. The yield was only 32 %.

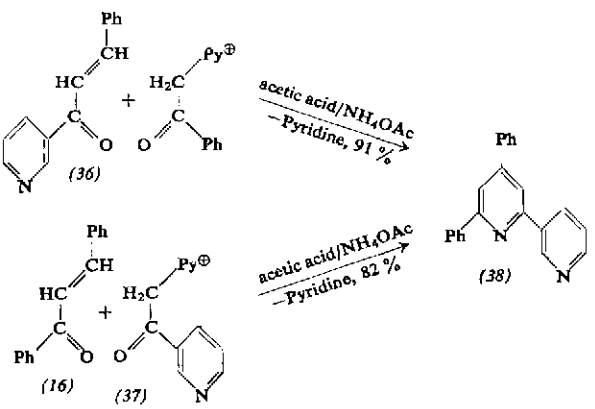


(34) *(35)*

It has not yet been possible to eliminate this inherent disadvantage of the Tschitschibabin synthesis by the use of another dehydrogenation agent.

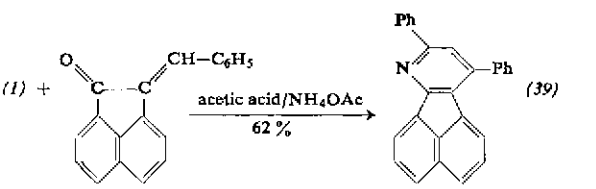
All the other theoretically possible dipyridylpyridine isomers and the twelve possible tripyridylpyridine isomers should be easy to prepare by our process. It need hardly be mentioned that some di- and tripyridylpyridines are of considerable interest in complex chemistry.

It is a characteristic of the synthetic route developed by us that, with compounds containing two identical substituents, the preparation of the same compound can be achieved from different starting materials. For example, 2,4-diphenyl-6-(3'-pyridyl)pyridine *(38)* can be prepared either from benzylidene-3-acetylpyridine *(36)* and phenacylpyridinium bromide *(1)* in 91 % yield, or from benzylideneacetophenone *(16)* and 3-pyridacylpyridinium iodide *(37)* in 82 % yield.



(36) *(38)* *(16)* *(37)*

An example of the smooth synthesis of pyridine derivatives with annelized ring systems is that of the 7-azafluoranthene derivative *(39)*, obtained from *(1)* and benzylideneacenaphthenone:



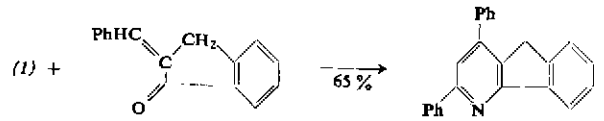
(1) *(39)*

Preparation of 8,10-Diphenyl-7-azafluoranthene (39) [23]

A mixture of 1 39 g (5 millimoles) of *(1)*, 1.28 g (5 millimoles) of benzylideneacenaphthenone, 4 g of ammonium acetate, and 6 ml of glacial acetic acid was allowed to reflux for 2 hours. The precipitate obtained on addition of 30 ml of water was washed with 6 ml of boiling methanol, and the residue dissolved in 5 ml of pyridine. Then, 2 ml of water were added followed by enough methanol to cause clouding. Yield: 1.10 g (62 %); yellow flakes; m.p.: 160–162 °C.

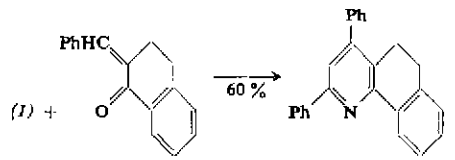
[23] *W. Zecher* and *F. Krohnke*, Chem. Ber. *94*, 698 (1961).

2-Benzylideneindan-1-one and salt *(1)* yield 1,3-diphenyl-4-azafluorene [23]



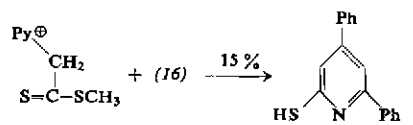
(1) +

On boiling with glacial acetic acid plus ammonium acetate, 2-benzylidenetetralone and *(1)* give 1,3-diphenyl-9,10-dihydro-4-azaphenanthrene [23]:



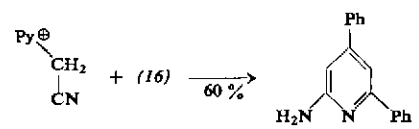
(1) +

As illustrated by the following two examples, it is also possible to vary within wide limits the substituent on the nitrogen atom of the pyridinium salt used as starting material:



(16)

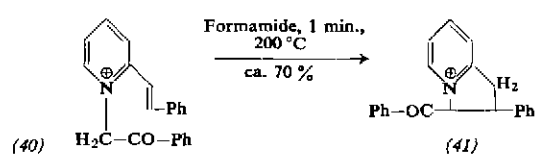
N-(Dithiomethoxycarbonylmethyl)pyridinium iodide — 4,6-Diphenylpyridine-2-thiol [24]



(16)

N-(Cyanomethyl)pyridinium bromide — 4,6-Diphenyl-2-aminopyridine (as its picrate) [23]

Intramolecular Michael addition offers a simple preparative route to condensed heterocycles. Thus, boiling the readily available *N*-phenacyl-2-styrylpyridinium bromide *(40)* [24] in formamide, converts it into the pyrrolino[1,2-a]pyridinium system *(41)*, first synthetized by *Winterfeld* [26], who followed a different route; this system is present in the *Lycoris* alkaloids [27].



(40) *(41)*

Preparation of 2-Phenyl-3-benzoylpyrrolino[1,2-a]-Pyridinium Picrate [*cf. Formula (41)*]

A mixture of 0.475 g (1.25 millimoles) of *N*-phenacyl-2-styrylpyridinium bromide *(40)* [25] and 2 ml of formamide was boiled for 1 minute. After cooling, 5 ml of ethanol and 5 ml of a cold, saturated alcoholic solution of picric acid were added, followed by 15 ml of distilled water. After 12 hours,

[24] *K. Gerlach*, Ph. D. Thesis, Universität Giessen, 1960, p. 37; cited by *W. Zecher* and *F. Krohnke*, Chem. Ber. *94*, 701 (1961).

[25] *W. Weis*, Diploma Thesis, Universität Giessen, 1960.

[26] *K. Winterfeld* and *E. Müller*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *284*, 269 (1951).

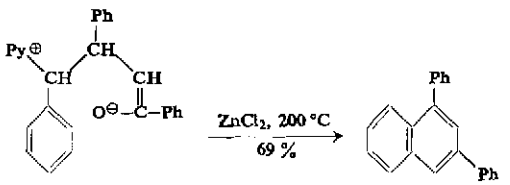
[27] *H. G. Boit:* Ergebnisse der Alkaloidchemie bis 1960. Akademie Verlag, Berlin 1961, p. 431.

0.55 g (84 %) of crude product were filtered off; m.p. after two crystallizations from 20–25 parts of 96 % ethanol in the presence of activated carbon: 146–148 °C.

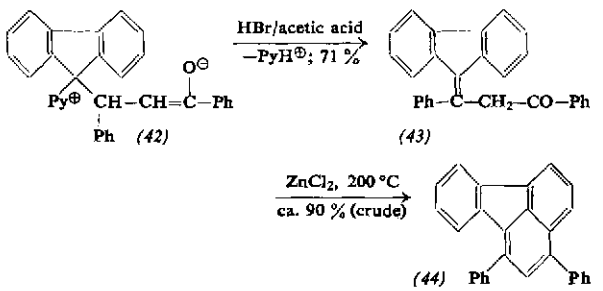
For the synthesis of substituted pyridines from pyridinium salts with active methylene groups in the presence of glacial acetic acid-ammonium acetate other starting materials may also be used, provided that they contain methylene groups of comparable reactivity [29].

3. Synthesis of Polycyclic Aromatic Compounds via Pyridinium Salts

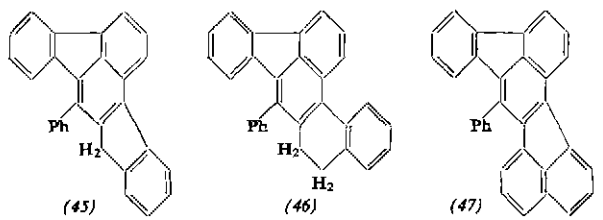
The ability of pyridinium salts with active methylene groups to undergo Michael addition has also made them useful in the synthesis of aromatic ring systems [28]. For example, the addition product from benzylpyridinium bromide and benzalacetophenone can be converted into 1,3-diphenylnaphthalene in one step by heating with zinc chloride. Under standard conditions, fluorenyl-



pyridinium bromide and benzalacetophenone *(16)* react to give the betaine *(42)* in 90 % yield. In the presence of hydrobromic acid/glacial acetic acid, this compound loses pyridine to give 9-(phenylphenacylmethylene)-fluorene *(43)* which undergoes cyclization with zinc chloride at 200 °C to give 2,4-diphenylfluoranthene *(44)*.



The use of benzylideneindanone, benzylidenetetralone, and benzylideneacenaphthenone leads to compounds *(45)* to *(47)*; their ring systems were apparently unknown until now.

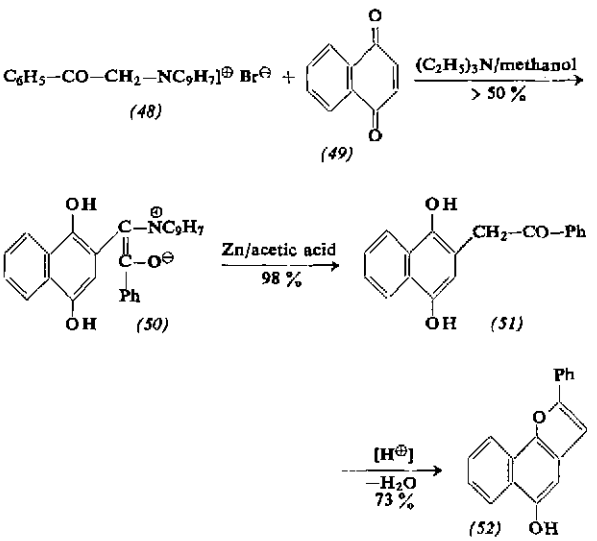


[28] *J. Curtze*, Diploma Thesis and Ph.D. Thesis, Universität Giessen, 1961 and 1963, respectively; further ten examples are to be found therein.

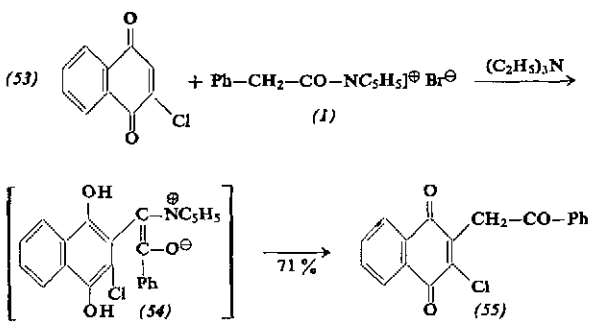
[29] *W. Zecher* and *F. Kröhnke*, Chem. Ber. *94*, 707 (1961).

4. Michael Addition of Cycloimmonium Salts onto Quinones

N-Phenacylcycloimmonium salts [31] also behave like β-keto carboxylic esters in the Michael addition onto quinones [30]. *N*-Phenacylquinolinium bromide *(48)* reacts with 1,4-naphthoquinone *(49)* to give the enol betaine *(50)*, which, in the presence of zinc and glacial acetic acid, is converted into 2-phenacyl-1,4-naphthohydroquinone *(51)*, with elimination of quinoline. On prolonged boiling in glacial acetic acid, compound *(51)* undergoes ring closure to give the substituted benzocoumarine *(52)*.



The reaction of *N*-phenacylpyridinium bromide *(1)* with *e.g.* 2-chloro-1,4-naphthoquinone *(53)* is similar. In this case, however, it was not possible to isolate the enol betaine *(54)* corresponding to *(50)*, since this compound undergoes stabilization via loss of pyridine and formation of a substituted naphthoquinone *(55)*.



With zinc and glacial acetic acid, the latter also gives a benzocoumarine *(56)*; with hydrazine hydrate, it forms the benzocinnoline *(57)*. This reaction has been described by *Clar* [32], *E. Bucnta* et al. [33], and others.

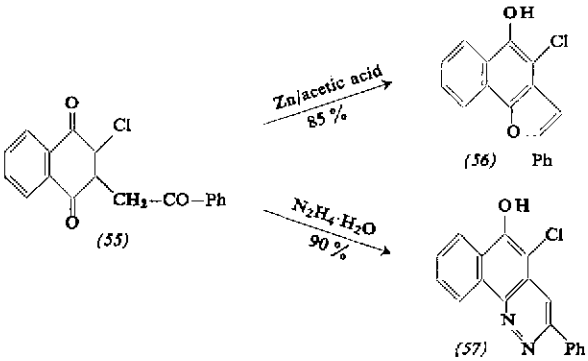
[30] See *H. Henecka:* Chemie der Beta-Carbonyl-Verbindungen. Springer Verlag, Berlin 1950, p. 270.

[31] *F. Kröhnke* and *K. Pfleghar*, unpublished data; *K. Pfleghar*, Ph.D. Thesis, Universität Giessen, 1962.

[32] *E. Clar*, Ber. dtsch. chem. Ges. *62*, 1574 (1929).

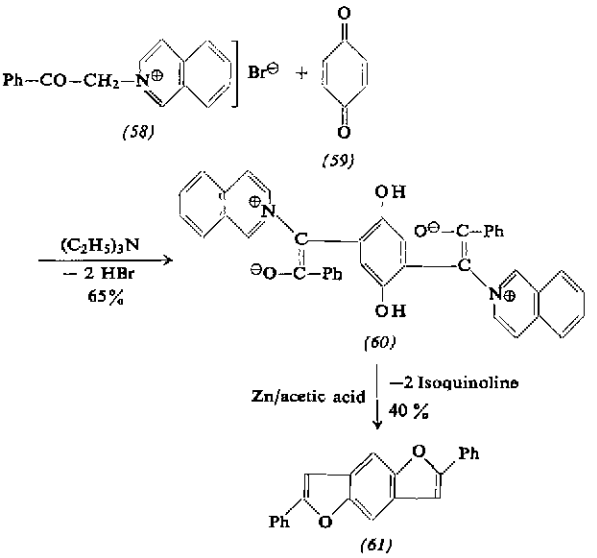
[33] *E. Buchta, M. Klisch, S. Maier*, and *H. Bayer*, Liebigs Ann. Chem. *576*, 7 (1952).

With *p*-benzoquinone *(59)*, *N*-phenacylisoquinolinium bromide *(58)* gives the bis-betaine *(60)*, from which the benzodifuran *(61)* is obtained with zinc-glacial



acetic acid. This compound was recently prepared by *Grinew* et al. [34] from *p*-benzoquinone and 2 moles of ethyl benzoylacetate.

[34] *A. N. Grinew, Pan Bon-Chwar*, and *A. P. Terentjew*, Zhur. Obshchei Khim *27*, 821 (1957).



We wish to thank the Deutsche Forschungsgemeinschaft, the Research Corporation, New York, and Prof. Dr. Otto Bayer for substantial support for this work.

Received, August 3rd, 1962 [A 234/53 IE]

High-temperature Chlorination of Amines and Acylamines

BY DR. H. HOLTSCHMIDT

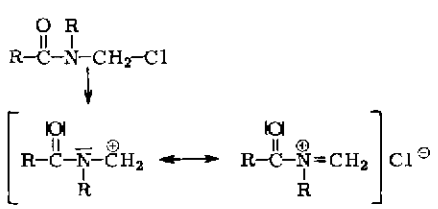
WISSENSCHAFTLICHES HAUPTLABORATORIUM DER FARBENFABRIKEN BAYER AG. LEVERKUSEN (GERMANY)

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

High-temperature chlorination of acyl derivatives of primary and secondary amines and of tertiary aryl and alkyl amines usually yields compounds containing either the imidochloride (monochloromethyleneamino) group $-N=C(Cl)-$ *or the dichloroisocyanide (dichloromethyleneamino) group* $-N=C(Cl)_2$. *In many cases, yields in the range of 80 to 95 % are obtained. Several ring-opening and ring-closing reactions occurring under the conditions of high-temperature chlorination are described.*

Introduction

The halogen atom of *N*-acyl compounds with an α-halogenoalkyl group on the nitrogen (*e.g.* in *N*-chloromethylamides) is very reactive [1]. The formation of a resonance-stabilized *N*-acyl immonium ion promotes release of a halide anion:



[1] *H. Böhme* and *F. Eiden*, German Pat. 1025883 (1955), Farbwerke Hoechst.

In the course of our investigations of isocyanates, the question arose whether the halogen atoms in α-halogeno isocyanates and carbamyl chlorides, and in the urethanes and ureas derived from them, would have equally high reactivity. This led us to search for new methods of synthesis for this group of compounds. Since the primary products of interest were those in which all the α-hydrogens are replaced by chlorine, comparatively high temperatures were used for these preparations, unlike any applied before for halogenations of acylamino compounds.

A. Chlorination of Isocyanates and Carbamyl Chlorides of Primary Amines

Whereas isothiocyanates decompose into SCl_2 and dichloroisocyanides when chlorinated, even at low tem-

peratures [2], the isocyanate group is very stable toward chlorine; consequently, primary amines can be effectively protected during chlorinations by converting the amino group into the isocyanate.

Chlorination of aromatic isocyanates in the cold leads to products of varying degrees of substitution, via carbamyl halides as intermediates [3].

During side-chain chlorination of alkylated aryl isocyanates [4], it was established that NCO groups are stable towards elemental chlorine even at temperatures of 190–200 °C. During chlorination of aliphatic isocyanates, the temperature could in some cases be raised as high as 220–250 °C without resulting in cleavage or polymerization products.

I. α-Halogenoalkyl Isocyanates [5]

α-Halogenated isocyanates behave like acid chlorides. This is observed both in reactions with nucleophilic reagents (*e.g.* ROH, RNH_2, RCOOH and H_2O)[6] and with electrophilic reagents in the presence of Friedel-Crafts catalysts [7]. The spectroscopic behavior of α-halogenated isocyanates also indicates the presence of an *N*-halogenocarbonyl group.

The infrared spectrum of benzyl isocyanate contains an absorption band at 2270 cm^{-1}, which is characteristic of the NCO group. In the spectrum of α-chlorobenzyl isocyanate, this band is weaker, and two new ones appear: *viz.* one at 1635 cm^{-1}, which denotes the presence of a C=N bond, and another at 1770 cm^{-1}, which indicates a chlorocarbonyl group. In the spectrum of α,α-dichlorobenzyl isocyanate, the NCO band disappears completely, but the two new bands are very marked. Many other α-halogenoalkyl isocyanates were found to possess similar spectra.

Alkyl isocyanates with a chlorine atom in the α-position to the NCO group must therefore be in equilibrium with the isomeric alkylidenecarbamyl chloride:

$$RCHCl{-}NCO \rightleftharpoons RCH{=}NCOCl$$

The α-chlorobenzyl isocyanate mentioned above is an example for this phenomenon; it is obtained by chlorinating benzyl isocyanate at 40–60 °C in CCl_4 under the influence of ultraviolet light until the calculated weight increase is achieved.

Alkyl isocyanates which are doubly chlorinated at the α-position exist in many cases practically only as the isomeric α-chloroalkylidenecarbamyl chloride. α,α-Dichlorobenzyl isocyanate may be cited as an example; it is obtained by chlorination of α-chlorobenzyl isocyanate at 150–220 °C.

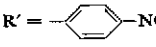
Similarly, it can be shown spectroscopically that perchlorinated methyl isocyanate does not exist as trichloromethyl isocyanate, CCl_3-NCO, but as *N*-chlorocarbonyl dichloroisocyanide, $Cl_2C{=}N{-}COCl$ (b. p. 120 °C/760 mm).

Because of their extraordinarily high reactivity, the alkylidenecarbamyl chlorides are valuable intermediates for numerous syntheses. This will be the subject of a later paper.

II. (α-Halogenoalkyl)aryl Isocyanates

Aryl isocyanates which contain an α-halogenoalkyl group *ortho* or *para* to the NCO group may be regarded as phenylogues of α-halogenoalkyl isocyanates. As indicated by their spectra, they exist exclusively in the isocyanate form. They may be obtained by chlorination of alkyl-substituted aryl isocyanates under the conditions used for side-chain chlorination, *i.e.* with ultraviolet irradiation or free-radical formers such as azo-bis-isobutyronitrile [4]. Like the chlorinated alkyl isocyanates, they exhibit abnormal behavior: when the NCO group is treated with, for instance, alcohol, amines, or water, *i.e.* when the basicity of the nitrogen is enhanced by formation of a urethane or a urea, the resultant increase in the mobility of the halogen atom on the alkyl side-chain is so great that the urethanes or ureas normally expected are often not obtained at all, because of simultaneous side reactions of the halogenoalkyl group (see Table 1).

Table 1. Reaction of (*p*-chloromethyl)phenyl isocyanates with alcohols (ROH)

R′ =  –NCO R″ =  –NH–CO_2R

Starting material	Product
R′–CH_2Cl	R″–CH_2OR + polybenzyl resins
R′–$CHCl_2$	R″–$CH(OR)_2$ [8]
R′–CCl_3	R″–$C(OR)_3$ → R″–COOR [8]

The results summarized in Table 1 are in agreement with the work of *Olivier* [9] on the mobility of the chlorine atom in substituted benzyl chlorides: electron donor groups in the *p*-position enhance the reactivity of the halogen atom, while electrophilic groups have the opposite effect. Thus, *p*-methoxybenzyl chloride is hydrolyzed about 10^4 times as rapidly as benzyl chloride, while *p*-dimethylaminobenzyl chloride is hydrolyzed in water at an immeasurably rapid rate [10]. The ureas and urethanes obtained from (α-halogenoalkyl)aryl isocyanates may be classified as lying between the two compounds.

B. Chlorination of Acyl Derivatives of Secondary Amines

In view of the great reactivity of the isocyanates and their isomers mentioned above, it seemed natural to extend investigations to derivatives of α-halogenated secondary amines, particularly to compounds bearing a chemical similarity to the isocyanates. These include the carbamyl chlorides of secondary amines, which are thermally stable, in contrast to those of primary amines.

[2] *E. Sell* and *G. Zierold*, Ber. dtsch. chem. Ges. *7*, 1228 (1874); *R. S. Bly*, *G. A. Perkins* and *W. L. Lewis*, J. Amer. chem. Soc. *44*, 2896 (1922).

[3] *F. Gumpert*, J. prakt. Chem. *32*, 294 (1885); *E. Tietze* and *S. Petersen*, German Patent Appl. I 77 961 (Aug. 7th, 1944).

[4] *H. Holtschmidt*, German Pat. 947470 (1953) and 1002327 (1953).

[5] *H. Holtschmidt* and *E. Degener*, German Pat. Appl. 1122058 (Aug. 26th, 1960).

[6] *E. Degener*, unpublished results.

[7] *R. Merten*, unpublished results.

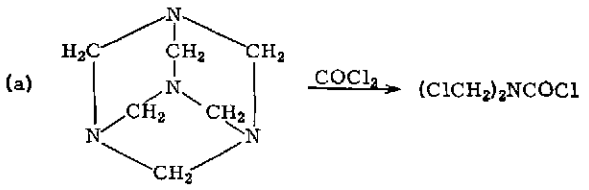
[8] *E. Klauke*, unpublished results.

[9] *S. C. J. Olivier*, Rec. Trav. chim. Pays-Bas *42*, 775 (1923); *49*, 697 (1930).

[10] *J. von Braun*, Ber. dtsch. chem. Ges. *45*, 2992 (1912).

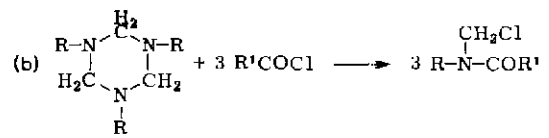
These can be transformed by chlorination into the corresponding α-chloroalkylcarbamyl chlorides. The simplest representatives of this class, *viz.* mono- and bis-(chloromethyl)carbamyl chlorides, were prepared by *E. Stein* [11] by selective chlorination of dimethylcarbamyl chloride.

We have found an additional way of preparing bis-(chloromethyl)carbamyl chloride [12], *viz.* by cleaving hexamethylenetetramine with phosgene under very drastic conditions (200 °C and 150 atm):



140 g of hexamethylenetetramine yield 246 g of bis-(chloromethyl)carbamyl chloride, b.p. 97 °C/15 mm. The remainder consists of a polymeric carbamyl chloride.

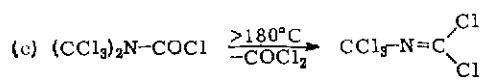
Similarly, but under considerably milder conditions (in part 0 to 10 °C), hexahydrotriazine may be cleaved by phosgene or other acid chlorides [13]:



R' = Cl, aryl, alkyl, *O*-alkyl, *O*-aryl.

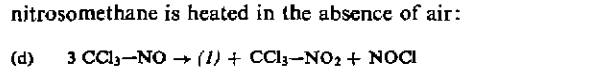
I. High-temperature Chlorination of Carbamyl Chlorides of Secondary Amines

When high-temperature perchlorination of bis(chloromethyl)carbamyl chloride is attempted, the product obtained is surprisingly, not the expected bis(trichloromethyl)carbamyl chloride $(CCl_3)_2N-COCl$; instead, phosgene is evolved, and a compound of empirical formula C_2NCl_5 is obtained in 82 % yield. On the basis of its reactions and infrared spectrum [14], it has been assigned the structure of *N*-trichloromethyl dichloroisocyanide [or *N*-(dichloromethylene)trichloromethylamine]. Its formation may be explained formally by elimination of phosgene from the expected product, which is unstable above 180 °C (cf. also equation f):



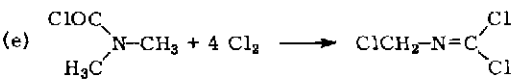
(1) b.p. 57 °C/12 mm

Compound *(1)* had previously been prepared by *Prandtl* and *Sennewald* [15]. It is formed in poor yield when trichloronitrosomethane is heated in the absence of air:



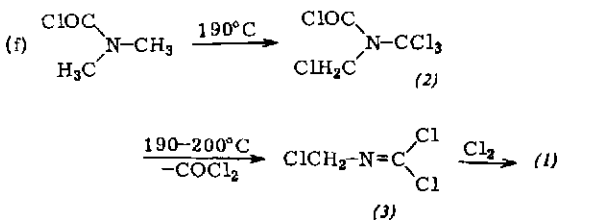
When bis(chloromethyl)carbamyl chloride is chlorinated at 190-210 °C, and care is taken to distill off immediately the *N*-monochloromethyl dichloroisocyanide initially formed, it can be obtained in a yield of 62 % [16]: $CH_2Cl-N=CCl_2$ b.p. 37 °C/12 mm.

Dimethylcarbamyl chloride may also be used as the starting material:



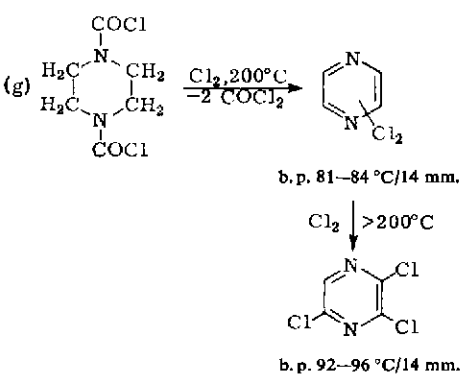


This reaction constitutes evidence against the formation of *N*-trichloromethyl dichloroisocyanide according to equation (c). A reaction pathway that is more consistent with the above observations assumes the formation of the intermediate *(2)*, which loses $COCl_2$ and is converted into *N*-monochloromethyl dichloroisocyanide *(3)*. If the latter is not removed from the reaction mixture, further chlorination yields *N*-trichloromethyl dichloroisocyanide *(1)*:



II. High-temperature Chlorination of Carbamyl Chlorides of Cyclic Secondary Amines

When the nitrogen in a carbamyl chloride forms part of a five- or six-membered ring, chlorination may result in simultaneous aromatization. This is well exemplified by *N,N'*-bis(chlorocarbonyl)piperazine, which may be regarded as dimerized dimethylcarbamyl chloride. Chlorinated pyrazines, which are usually difficult to prepare [17], may be obtained in this manner.



The final hydrogen atom is not displaced by chlorine even at 260 °C.

[11] *E. Stein*, unpublished results.

[12] *H. Holtschmidt* and *K. Wagner*, German Patent Appl. 1132118 (Feb. 1st, 1961).

[13] *H. Kritzler*, *K. Wagner* and *H. Holtschmidt*, German Patent Appl. F 34 670, IV d/120 (Aug. 16th, 1961).

[14] The $-N=CCl_2$ group has two characteristic bands: one between 1650 and 1660 cm^{-1}, and the other at 900 cm^{-1}.

[15] *W. Prandtl* and *K. Sennewald*, Ber. dtsch. chem. Ges. *62*, 1764 (1929).

[16] *H. Holtschmidt*, German Patent Appl. F 33 897, IV b/120 (May 10th, 1961).

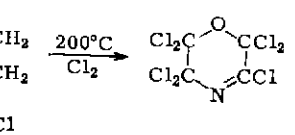
[17] According to U.S. Pat. 2391745 from pyrazine + Cl_2 + steam at 400–500 °C.

Chlorination of N,N'-Bis(chlorocarbonyl)piperazine to Give x,x-Dichloropyrazine

Two moles (422 g) of *N,N'*-bis(chlorocarbonyl)piperazine (prepared by the reaction of phosgene on anhydrous piperazine in xylene, m.p. 158–160 °C) are melted and chlorinated under ultraviolet light at 160–165 °C. The temperature is slowly raised to 190–200 °C. When the evolution of phosgene has ceased, the mixture is fractionated over a column under aspirator vacuum. The yield is 240 g (80 %) of x,x-dichloropyrazine (b.p. 81–84 °C/14 mm) and 20 g (5.5 %) of trichloropyrazine (b.p. 92–96 °C/14 mm). If the chlorination is continued for longer periods of time, the dichloropyrazine is converted into trichloropyrazine.

Owing to the difficulties involved in chlorinating pyridine at C-2, C-4, and C-6 [18], some preparative significance may be attached to the observation that high-temperature chlorination of *N*-chlorocarbonylpiperidine yields pentachloropyridine in addition to lower chlorination products [19]. The same applies to the formation of chloroquinoline and chloroisoquinoline derivatives from *N*-chlorocarbonyltetrahydroquinoline and isoquinoline [19].

Aromatization of six-membered rings cannot be achieved when they contain an ether oxygen in addition to the nitrogen atom. *N*-Chlorocarbonylmorpholine may be cited as an example. It is converted in 64 % yield into a product to which the oxazine derivative formula *(4)* has been ascribed on the basis of analysis and spectral studies.

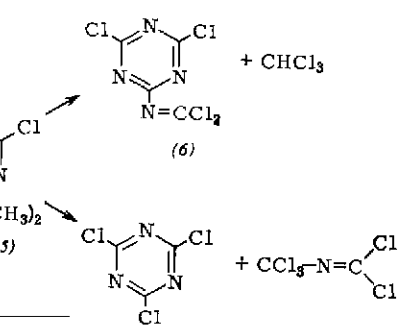
(h) 

(4) b.p. 125–128 °C/12 mm.

III. High-temperature Chlorination of Additional Acyl Compounds of Secondary Amines

A series of *s*-triazine derivatives were used to investigate the question whether substituents other than the chlorocarbonyl group, *e.g.* lower alkyl or acyl radicals, could be split off under the conditions of high-temperature chlorination to form an imidochloride or dichloroisocyanide group.

Two reaction paths may be envisaged for the high-temperature chlorination of 4-dimethylamino-2,6-dichloro-*s*-triazine *(5)*:

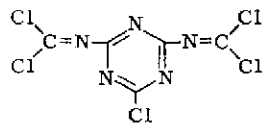
(i) 

[18] *J. P. Wibaut* and *J. R. Nicolai*, Rec. Trav. chim. Pays-Bas *58*, 709 (1939).

[19] *H. Holtschmidt* and *W. Zecher*, German Pat. Appl. F 34 920, IV d/120 (Sept. 13th, 1961).

All four compounds have been found after high-temperature chlorination, but the reaction proceeds mainly in the direction of the upper arrow in equation (i), so that compound *(6)*, 2,6-dichloro-*s*-triazine-4-dichloroisocyanide (b.p. 126 °C/10 mm), so-called "tetrameric cyanogen chloride", is obtained in 72 % yield [20].

Considerably lower yields (45–50 %) are attained in the chlorination of 2,6-bis(dimethylamino)-4-chloro-*s*-triazine to the corresponding 2,6-bis(dichloroisocyanide) derivative *(7)*, which was hitherto unknown.



(7) b.p. 110–112 °C/0.1 mm

Compound *(6)*, cyanuric chloride, trichloromethyl dichloroisocyanide, and chloroform are the by-products of this reaction.

Chlorination of hexamethylmelamine to give the corresponding tris(dichloroisocyanide) has as yet not been satisfactorily achieved.

Volatile acyl residues, *e.g.* the acetyl radical, behave in high-temperature chlorinations in similar fashion to the chlorocarbonyl group: they are eliminated as acetyl chloride or its chlorination products (cf. Section C, I).

C. High-temperature Chlorination of Tertiary Amines

All the starting materials described hitherto were acylation products of amines. A look at the literature dealing with the chlorination of tertiary amines makes it immediately apparent that, in all the investigations, the lowest possible chlorination temperature (as low as −50 to −60 °C) [21] was used. Most authors report cleavage of the carbon-nitrogen bond [22]. In other cases, vigorous decomposition [23] or violent explosions [24] were observed, due either to enrichment of *N*-chloro compounds or to spontaneous alkylation.

Although chlorination of organic compounds is one of the most frequently and thoroughly investigated reactions in organic chemistry, temperature control has never been recognized as an essential factor in this reaction. Whereas chlorination of amines has hitherto always been performed under conditions for an ionic

[20] This "tetrameric cyanogen chloride" is obtained in a yield of a few percent as a by-product in the trimerization of cyanogen chloride to cyanuric chloride (Geigy, Belg. Pat. 599211). Its structure was elucidated by Geigy chemists and independently by *H. Dorlars* and *H. Hoyer*, Farbenfabriken Bayer AG., Leverkusen.

[21] *L. H. Amundsen* and *L. S. Pitts*, J. Amer. chem. Soc. *73*, 1494 (1951); *A. J. Ellis* and *F. G. Soper*, J. chem. Soc. (London) *1954*, 1750; *H. Böhme*, *E. Mundlos* and *E. O. Herboth*, Chem. Ber. *90*, 2003 (1957).

[22] *C. W. Crane*, *M. Forrest*, *O. Stephenson*, and *W. A. Waters*, J. chem. Soc. (London) *1946*, 827; *C. C. Price*, *A. Pohland*, and *B. H. Velzen*, J. org. Chemistry *12*, 308 (1947).

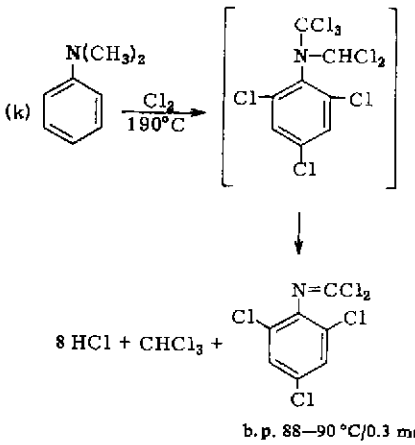
[23] *J. Meisenheimer*, Ber. dtsch. chem. Ges. *46*, 1149 (1913).

[24] *A. J. Ellis* and *F. G. Soper*, J. chem. Soc. (London) *1954*, 1750; *M. Hoehnel*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *237*, 693 (1894).

reaction and initiated by electrophilic attack on the nitrogen, we have chosen conditions for a free-radical chlorination mechanism. Careful attention to temperature control made it possible to isolate, sometimes in high yields, new intermediate products, which therefore have become readily available.

I. Chlorination of Aromatic Tertiary Amines [25]

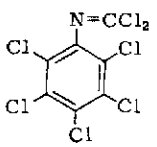
By exercising most careful control of the fixed temperature (see example), dimethylaniline may be converted in 82–87 % yield in to 2,4,6-trichlorophenyl dichloroisocyanide, using high-temperature chlorination in the absence of catalysts:



b.p. 88–90 °C/0.3 mm

The remaining 13–18 % consist of dichlorophenyl dichloroisocyanide (8–12 %), tetrachlorophenyl dichloroisocyanide (2–4 %), a little (< 2 %) pentachlorophenyl dichloroisocyanide, traces of hexachlorobenzene, and resinous distillation residues [26].

If the trichlorophenyl dichloroisocyanide is chlorinated further in the presence of a catalytic quantity (0.5–1 %) of $FeCl_3$, the hydrogen atoms at C-3 and C-5 are quantitatively displaced by chlorine, and pentachlorophenyl dichloroisocyanide is obtained:



b.p. 134–136 °C/0.2 mm
m.p. 73–75 °C

Since the chlorination of dimethylaniline has been known for almost a hundred years [27], and extensive investigations on the subject have been published even very recently [28], it is appropriate to inquire why this simple reaction had not been discovered earlier.

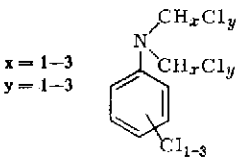
[25] *H. Holtschmidt* and *W. Zecher*, German Pat. Appl. F 34 920, IV d/120 (Sept. 13th, 1961).

[26] We wish to express our thanks to Dr. *Wrabetz* for the analytical investigations of the chlorination products, using high-temperature gas chromatography.

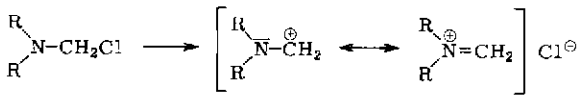
[27] *G. Krell*, Ber. dtsch. chem. Ges. *5*, 878 (1872); *T. Heidelberg*, *ibid. 20*, 150 (1887); *K. Fries* and *H. Glahn*, Liebigs Ann. Chem. *346*, 147 (1906).

[28] *T. H. Chao* and *L. Cipriani*, J. org. Chemistry *26*, 1079 (1961).

The intermediates in the chlorination of dimethylaniline are α-halogenated amines corresponding to the general formula



α-Halogenated amines are extremely reactive compounds [29]. They may be regarded as resonance-stabilized immonium salts; they release a chloride anion with greater facility than *N*-chloromethyl amides, since the basicity of the nitrogen atom is not reduced by acylation.



The intermediates that crop up in every amine chlorination are capable of undergoing a great variety of side reactions, especially at elevated temperatures:

Condensation with hydrogen atoms at the *o*- and *p*-positions of the aryl nucleus,

Reaction with hydrogen atoms of the *N*-alkyl groups,

Quaternization of the nitrogen atom,

Cleavage of carbon-nitrogen bonds similar to a von Braun degradation.

These reactions are all more or less violent above 60 °C and lead to the tarry residues.

To keep yields from dropping practically to zero, it is essential that strict temperature control be maintained in all amine chlorinations. Since the side reactions mentioned above do not make their appearance below 60 °C, the greatest possible number of chlorine atoms should be introduced in the α-position to the nitrogen while the temperature is in this range, if necessary under photolytic conditions. In this manner, a positive charge is induced on the α-C atoms, causing the ensuing cleavage to be favored over the side reactions. Simultaneously, the inductive effect of the chlorine atoms gradually decreases the basicity of the nitrogen, and hence the ability to be quaternized; this effect is parallelled by the replacement of condensable hydrogens by chlorine. All the possibilities for reactions forming resins are therefore eliminated, and the temperature may be raised (at a rate of 10 °C/hour) up to the 190–240 °C necessary for dealkylation.

Example: Chlorination of Dimethylaniline to Give 2,4,6-Trichlorophenyl Dichloroisocyanide and 2,3,4,5,6-Pentachlorophenyl Dichloroisocyanide

a) 732 g (6 moles) of *N*,*N*-dimethylaniline are mixed with 270 g of chloroform. A rapid stream of chlorine is then led into the mixture, which is well cooled in an ice bath. The flow of chlorine is regulated in such a way that the temperature of the reaction mixture is maintained between 50 and 60 °C. The color of the mixture changes from dark green through reddish brown to orange. The temperature is not allowed to exceed 60 °C until the mixture turns light yellow. It is then raised in the course of 4–5 hours to 100–110 °C by removing

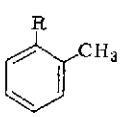
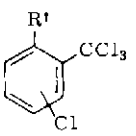
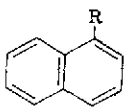
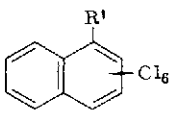
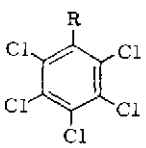
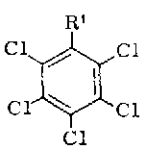
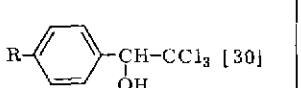
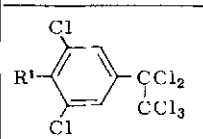
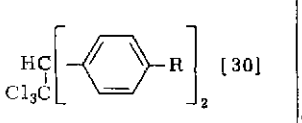
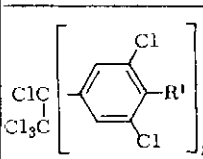
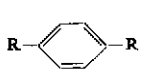
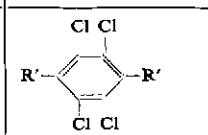
[29] *H. Böhme*, *E. Mundlos*, *O. E. Herboth*, and *W. Lehner*, Chem. Ber. *90*, 2003 (1957).

the coolant, increasing the flow of chlorine, and irradiating with ultraviolet light. Chloroform is completely removed by the stream of chlorine and HCl. The solution is then heated to increase its temperature at a rate of 10–15 °C/hour, the chlorine still being introduced. The elimination of chloroform starts at 190 °C, and may be observed by the appearance of vigorous reflux. The temperature is allowed to rise further until it reaches 200–230 °C, and the chlorination is continued until no more chloroform is evolved (about two hours). The final solution is light to dark yellow (brown or even black color denotes too rapid an increase in temperature and consequently considerably lowered yields). Gross yield: 1890 g, b.p. 107 to 110 °C/0.8 mm. Yield of pure trichlorophenyl dichloroisocyanide: 1360–1450 g.

b) 18 g of anhydrous $FeCl_3$ are added to 1890 g of trichlorophenyl dichloroisocyanide (the raw product of reaction a). The mixture is then chlorinated at 130–150 °C. The reaction is exothermic and the temperature rises to 180–190 °C. When the evolution of heat ceases, the chlorination is continued at 190 °C for further 2–3 hours. The $FeCl_3$ is allowed to settle out at *ca.* 100 °C, and the supernatant is decanted. On further cooling, the liquid solidifies, to a hard crystalline mass. Yield 96–98 %, b.p. 134–136 °C/0.1 mm, m.p. 73–75 °C.

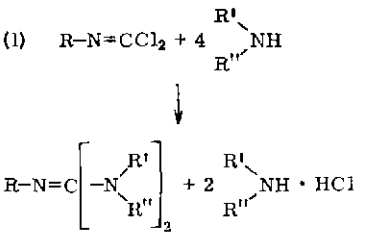
The examples shown in Table 2 illustrate the wide applicability of the reaction.

Table 2. Examples of high-temperature chlorination of aromatic amines. R = $(CH_3)_2N$–, R' = $Cl_2C{=}N$–

Starting material	Product	Yield [%]	b.p. [°C/mm Hg] or m.p. [°C]
		81	130–136/0.05
 [30]		88.3	220/0.3
		75	134–136/0.1 73–75
 [30]		60.6	190/0.6
 [30]		quant.	80–81, product is analytically pure
		85	154–156

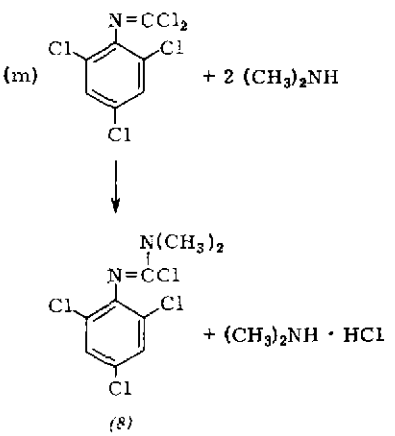
Since the tri- and pentachlorophenyl dichloroisocyanides should become quite inexpensive intermediates in the future [31], it was thought worthwhile to investigate some of their reactions [32]. The following conversion, which leads to a new and interesting starting material for high-temperature chlorination, deserves particular attention.

While dichloroisocyanides usually react with secondary aliphatic amines even in the cold to give guanidine derivatives:



(1) $R{-}N{=}CCl_2 + 4\ HNR'R'' \rightarrow R{-}N{=}C(NR'R'')_2 + 2\ HNR'R'' \cdot HCl$

the reaction of dimethylamine with 2,4,6-trichlorophenyl dichloroisocyanide stops at the chloroformamidine stage when performed in the cold [33] (probably owing to the screening effect of the two chlorine atoms *ortho* to the $-N{=}CCl_2$ group):



(m) + 2 $(CH_3)_2NH$ → (8) + $(CH_3)_2NH \cdot HCl$

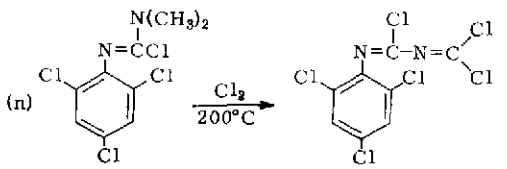
[30] *G. Dankert*, unpublished results.

[31] 1 kg of dimethylaniline yields about 2 kg of trichlorophenyl dichloroisocyanide and 2.8 kg of pentachlorophenyl dichloroisocyanide.

[32] Since the isothiocyanate is obtained in good yield from trichlorophenyl dichloroisocyanide and Na_2S, the reaction may have interesting preparative applications. The classical methods of preparation of isothiocyanate fail with 2,6-disubstituted (halogenated) arylamines because of the slight basicity of the amino group: *E. Kühle*, Belg. Pat. 613 428.

[33] *E. Kühle*, unpublished results.

Compound *(8)* was subjected to further high-temperature chlorination, which resulted in the formation of compound *(9)* with two conjugated carbon-nitrogen double bonds (yield *ca.* 60%).



(8) *(9)* b.p. 136–138 °C/0.1 mm.

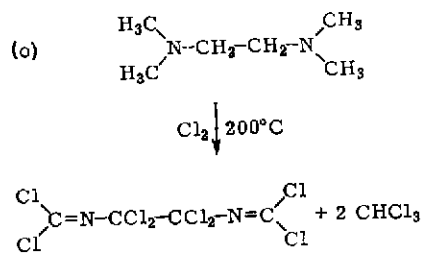
Trichloromethyl dichloroisocyanide, trichlorophenyl dichloroisocyanide, and chloroform were obtained as by-products.

Aryl dichloroisocyanides chlorinated in the ring may of course also be obtained from acylated monomethylanilines such as *N*-methyl-*N*-phenylcarbamyl chloride, *N*-methylacetanilide, *etc.* The acyl residue is split off as the acyl chloride.

II. Chlorination of Aliphatic Tertiary Amines [34]

Chlorination of aliphatic tertiary amines does not proceed as uniformly as in the aromatic series, and the yields are substantially lower. The side reactions of partially chlorinated intermediates, described on p. 636, are even more important than in the aromatic amines. This is understandable, since the transition to the mesomeric immonium structure is easier the higher the basicity of the nitrogen atom. Besides, even chlorination of simple aliphatic hydrocarbons always leads to mixtures of several chlorination products.

The best results so far have been achieved in the high-temperature chlorination of a compound in which all the carbon atoms are in the α-position to the nitrogen, *viz.* tetramethylethylenediamine solution (in trichlorobenzene).



(10) m.p. 166 °C

The yields fluctuate to an extraordinary degree (30 to 71 %) and are even more dependent upon temperature than with aromatic amines. Compound *(10)* is extremely reactive. The chlorine atoms α to the dichloroisocyanide group are more mobile than those in the latter group itself [35].

[34] *H. Holtschmidt* and *W. Zecher*, German Pat. Appl. F 35 319, IV b/120 (Nov. 9th, 1961).

[35] For example, reaction with two moles of Na_2S does not give the isothiocyanate; instead, the four chlorine atoms in the α-position are substituted:

(10) + 2 Na_2S ⟶ $Cl_2C{=}N{-}CS{-}CS{-}N{=}CCl_2$ + 4 NaCl;

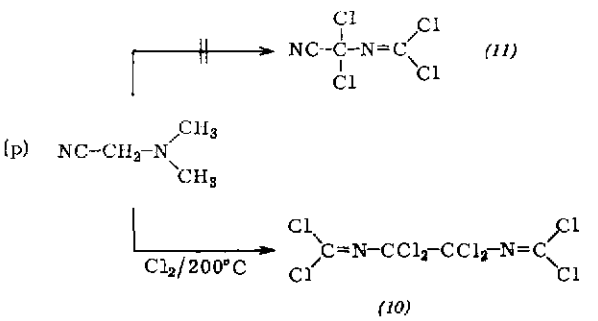
E. Kühle, unpublished results.

Chlorination of Tetramethylethylenediamine to Tetrachloroethane-bis(dichloroisocyanide)

116 g (1 mole) of tetramethylethylenediamine are dissolved in 1000 ml of 1,2,4-trichlorobenzene. A slow stream of chlorine is introduced, and the ensuing, highly exothermic reaction is checked by cooling to keep the mixture at a temperature between 70 and 80 °C. When the evolution of heat has ceased, the chlorination is continued under ultraviolet light and the temperature is raised at the rate of 10–15 °C/hr. When the temperature has reached 190–210 °C, the chlorination is continued for five more hours, after which the chlorine is flushed out with nitrogen. The main portion of the tetrachloroethane-bis(dichloroisocyanide) separates out upon cooling; the remainder is precipitated by further concentration of the solution; m.p. after recrystallization from toluene: 166 °C; white platelets.

Conversion into dichloroisocyanides may be carried out not only with the free aliphatic tertiary amines, but also with their salts, *e.g.* hydrochlorides, or quaternary salts, *e.g.* tetramethylammonium chloride, in trichlorobenzene suspension. However, owing to the heterogeneous character of the reaction mixture, the duration of the reaction is very long, and the yields are only fair. Trichloromethyl dichloroisocyanide has been prepared from both trimethylamine hydrochloride and tetramethylammonium chloride, and 2-chloroethyldimethylamine hydrochloride was converted into pentachloroethyl dichloroisocyanide $CCl_3{-}CCl_2{-}N{=}CCl_2$ (b.p. 120–121 °C/13 mm).

In the chlorination of dimethylaminoacetonitrile, one obtains, unexpectedly, not the dichloroisocyanide *(11)* but compound *(10)*, by splitting off cyanogen chloride and dimerization of the remaining fragment, $-CCl_2{-}N{=}CCl_2$. This compound is identical with the product of chlorination of tetramethylethylenediamine.

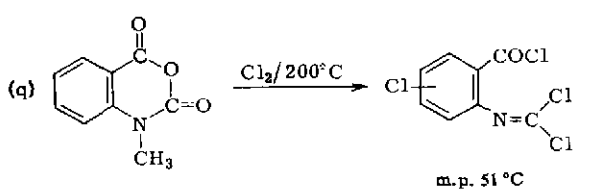


(10)

D. Ring Cleavages and Ring Closures during High-temperature Chlorination of Acylamino Compounds and Tertiary Amines

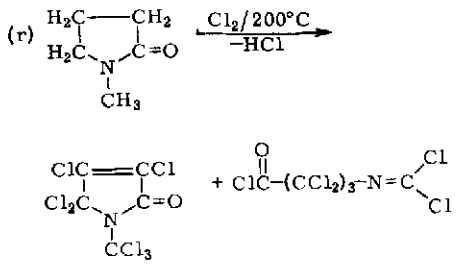
I. Ring Cleavages

When *N*-methylisatic anhydride was subjected to high-temperature chlorination, it was found that ring cleavage had occurred. The yield in this reaction is 42 % [30].



m.p. 51 °C

Aliphatic lactams may be cleaved similarly. For example, *N*-methylpyrrolidone yields 1-chlorocarbonylhexachloropropyl 3-dichloroisocyanide in addition to *N*-trichloromethyltetrachloropyrrolin-2-one [36].

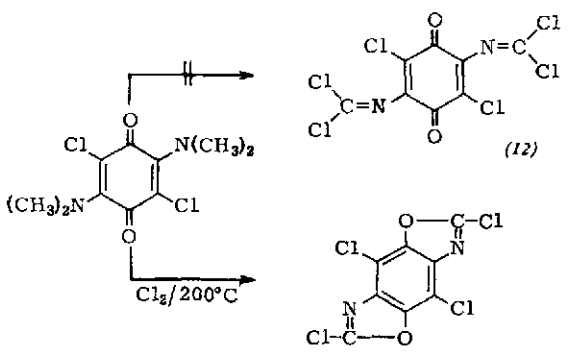


b.p. 188—190 °C/15 mm.
m.p. 98—101 °C

The high-temperature chlorination of hexamethylenetetramine is of interest. Low-temperature halogenation of this compound has long been known [37]. It leads to highly unstable addition products, which contain up to four halogen atoms. Chlorination at high temperature in trichlorobenzene solution causes the ring structure to open, and cyanuric chloride and trichloromethyl dichloroisocyanide are formed. The yields of this reaction are, however, to low for industrial manufacture of cyanuric chloride.

II. Ring Closures

Ring closures have been found to occur in high-temperature chlorination, when the steric conditions are favorable. Chlorination of 2,5-dimethylamino-3,6-dichloro-*p*-benzoquinone is a case in point. The expected product, the bis(dichloroisocyanide) *(12)*, is not obtained; instead, the quinoid system is transformed into a



(13) m.p. 264—267 °C

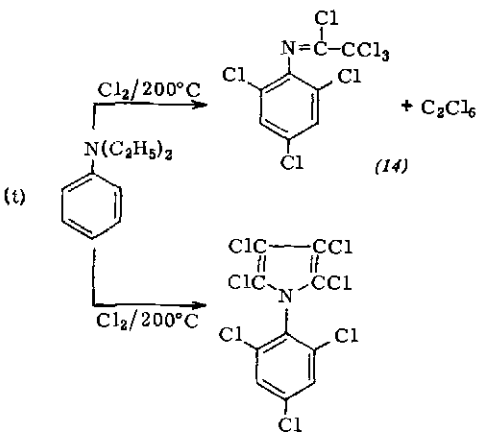
benzenoid system and ring closure occurs at the 1,2- and 4,5-positions, yielding the bis(chloroxazole) *(13)*, together with an unidentified red oil.

[36] *W. Zecher*, unpublished results.

[37] *H. E. L. Horton*, Ber. dtsch. chem. Ges. *21*, 2000 (1888).

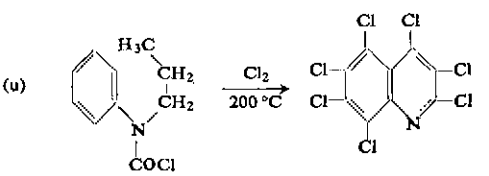
In the high-temperature chlorination of diethylaniline [38], one obtains not only the *N*-trichlorophenyl-trichloromethyl chloroisocyanide *(14)* to be expected from the findings described above (hexachloroethane being eliminated) but, surprisingly, also *N*-(2,4,6-trichlorophenyl)-2,3,4,5-tetrachloropyrrole *(15)*, which is formed by C—C bond formation between the ethyl residues and subsequent ring closure. The yield of this compound is 38 %.

Several instances of C—C bond formation under the conditions of free radical chlorination have been described in the literature [39]. Diethylaniline is a particularly favorable case, owing to the possibility of forming a five-membered ring, followed by aromatization of the latter. For preparative purposes, however, it is preferable to subject *N*-phenylpyrrolidine to high-temperature chlorination. The yield of *(15)* in this reaction amounts to 60—70 %.



(15) m.p. 166 °C

A further example of a ring closure accompanied by simultaneous aromatization is the high-temperature chlorination of *N*-Phenyl-*N*-(n-propyl)carbamylchloride, which leads to the hitherto unknown heptachloroquinoline with a yield of almost 50 % [40]:



m. p. 150—152 °C

Thanks are due to Drs. Dankert, Degener, Kühle, Tarnow, and Zecher for their help in the performance of this work. Furthermore, I am grateful to Prof. Dr. M. Pestemer for numerous spectroscopic examinations.

Received, May 26th, 1962 [A 240/58 IE]

[38] *H. Tarnow, H. Holtschmidt*, and *J. Ugi*, German Pat. Appl. F 37 066, IV d/12 p (June 14th, 1962).

[39] *W. Protzer*, German Pat. Appl. 1116647 (Mar. 6th, 1959) Farbwerke Hoechst.

[40] *H. Tarnow, H. Holtschmidt*, and *O. Bayer*, German patent applied for.

Heterocyclic Azo Dyes by Oxidative Coupling [1]

BY PROF. DR. S. HUNIG [2]
IN COOPERATION WITH DR. H. BALLI, E. BREITHER, DR. F. BRUHNE, DR. H. GEIGER, DR. E. GRIGAT, DR. F. MÜLLER, AND H. QUAST

CHEMISCHES INSTITUT DER UNIVERSITAT MARBURG/LAHN, INSTITUT FÜR ORGANISCHE CHEMIE DER UNIVERSITAT MÜNCHEN, AND CHEMISCHES INSTITUT DER UNIVERSITÄT WÜRZBURG (GERMANY)

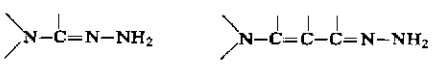
Dedicated to Prof. Dr. O. Bayer on the occasion of his 60th birthday

New findings in the field of oxidative coupling reactions are reported. These involve: extension of this type of reaction to amidrazone systems displaying (vinylogous) tautomerism and to unsymmetrical diarylhydrazines; elucidation of the coupling mechanism for these arylhydrazines and for the amidrazone systems previously described; the properties of some dyes, complexed with heavy metals, and the synthesis of tetraazapentamethine and pentaazapentamethine dyes.

A. Introduction

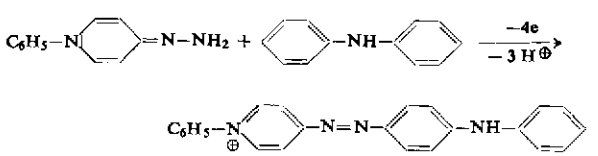
Four years ago, a novel synthesis of azo dyes, some of which were unobtainable and others only indirectly obtainable via conventional azo coupling, was reported under the same title as the present article [3].

The principle upon which this reaction is based represents an extension of the familiar oxidative coupling of *p*-phenylenediamine with aromatic amines, phenols, and reactive methylene compounds, whereby, in a completely general fashion, the *p*-phenylenediamine is replaced by compounds possessing the amidrazone system *(1)* or its vinylogue *(2)*. These compounds capable of undergoing coupling reactions will be designated herein after as "hydrazones".

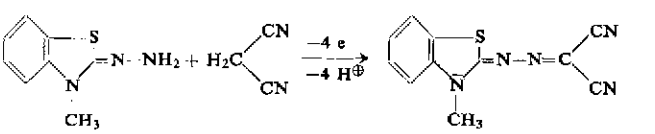


(1) *(2)*

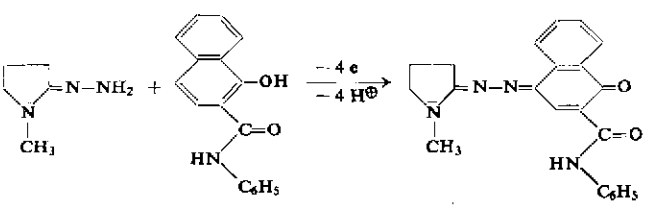
Both the hydrazone and the coupling component can be varied within wide ranges, as demonstrated in the following examples [*]:



λ_{max} = 543 mμ [4]



λ_{max} = 425 mμ [5]

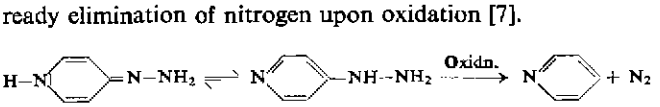


λ_{max} = 500 mμ [6]

Since the appearance of the paper mentioned above, the number of hydrazones suitable for coupling and the number of dyes synthetized with their aid have greatly increased. In the present paper, only those results will be discussed which have led to extensions of the oxidative coupling principle and to an understanding of the course of reaction.

B. Oxidative Coupling with Amidrazones Capable of Tautomerism

As seen in the examples above, the heterocyclic nitrogen atom of the "hydrazones" always carries an alkyl or aryl group to stabilize the hydrazone form. As was stressed previously [3], hydrogen in the same position leads to more extensive isomerization, and hence to ready elimination of nitrogen upon oxidation [7].



[1] XXIII. Communication in this series. XII. Communication, *S. Hünig* and *F. Müller*, Liebigs Ann. Chem. *651*, 89 (1962).

[2] Address: Chemisches Institut der Universität Würzburg, Röntgenring 11, Würzburg, Germany.

[3] *S. Hünig* et al., Angew. Chem. *70*, 215 (1958).

[4] *S. Hünig* and *G. Köbrich*, Liebigs Ann. Chem. *617*, 216 (1958).

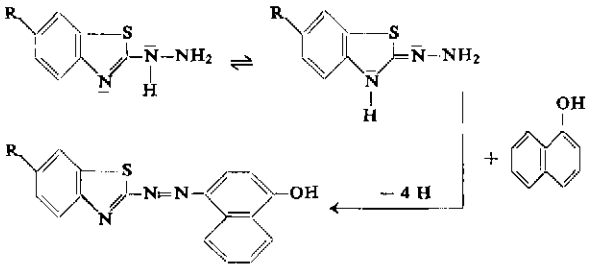
[*] All optical data reported in this paper refer to solutions in methanol, unless stated otherwise.

[5] *S. Hünig* and *K. H. Fritsch*, Liebigs Ann. Chem. *609*, 143 (1957).

[6] *S. Hünig* and *F. Müller*, Liebigs Ann. Chem. *651*, 73 (1962).

[7] *E. Thielepape* and *O. Spreckelsen*, Ber. dtsch. chem. Ges. *55*, 2929 (1922).

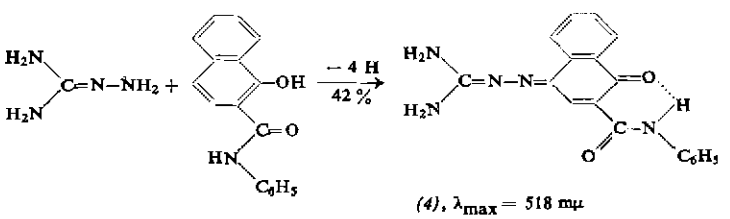
It was to be expected that, on incorporating an amidrazone system into a heterocycle with a lower tendency to aromatize, oxidative coupling would still occur, provided tautomerization is not blocked. This proves true with 2-hydrazinobenzothiazole, 11 % of which is converted into the expected azo dye *(3)* with α-naphthol using potassium ferricyanide at pH 9 [8] [*].



(3) Yields (determined optically)

R = H, 11 %; R = NO_2, 73 %; R = $NHCOCH_3$, 0 %

Substituents on C-6 of the benzothiazole structure that lower the basicity of the heterocyclic nitrogen atom should stabilize the hydrazone form and thereby increase the coupling yield; the reverse should be true of substituents that increase its basicity. Actually, under identical reaction conditions, with 6-nitrohydrazinobenzothiazole the yield of dye increases to 73 %, whereas the 6-acetamino derivative forms no dye at all [8]. With amidrazone compounds without aromatizable rings, coupling of the types capable of tautomerizing was also to be expected. Nevertheless, it was

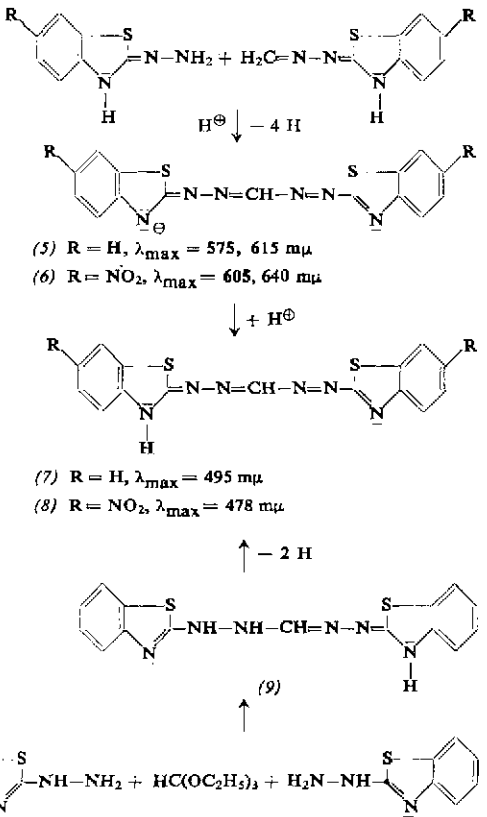


(4), λ_{max} = 518 mμ

surprising that the strongly basic compound aminoguanidine, underwent a smooth reaction, to give the dye *(4)*, which has a long-wave absorption, in striking contrast to the *N*-alkyl and *N*-aryl derivatives [6].

C. Tetraazapentamethine Dyes

On alkaline oxidation of 2-hydrazinobenzothiazole in the presence of traces of formaldehyde, the solution becomes intensely purple; with 6-nitro-2-hydrazinobenzothiazole, a deep blue solution is formed, from which acid precipitates a red dye [8]. This reaction, which has since been discovered independently by *Sawicki*, who developed it into a sensitive test for aliphatic aldehydes [9], leads to the anions *(5)* and *(6)* of the tetraazapentamethine dyes *(7)* and *(8)*.

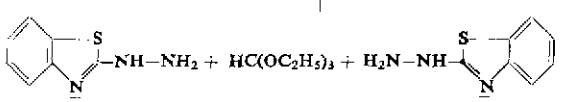


(5) R = H, λ_{max} = 575, 615 mμ

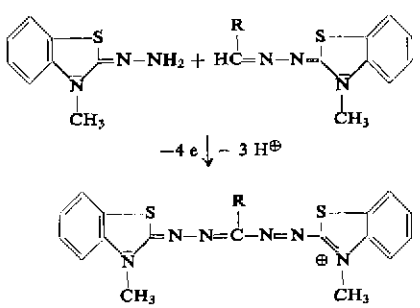
(6) R = NO_2, λ_{max} = 605, 640 mμ

(7) R = H, λ_{max} = 495 mμ

(8) R = NO_2, λ_{max} = 478 mμ



The structure of *(7)* has been proved independently. 2-Hydrazinobenzothiazole condenses with triethyl orthoformate to give the hydrazine *(9)* [*], which can be dehydrogenated easily to yield the dye *(7)* [10]. The reaction of 2-hydrazinobenzothiazoles is thus closely parallel to the formation of cationic tetraazapentamethinecyanines, such as *(10)* [3, 11], which were obtained by *Besthorn* as early as 1910, although he was unable to establish their structures [12].



(10) R = H, λ_{max} = 670, 630 mμ (acetone)

[8] *E. Breither*, Diploma Thesis, Universität Marburg 1957.

[*] The tautomerism of the dye will not be discussed.

[9] *E. Sawicki* and *Th. Hauser*, Analytic. Chem. *32*, 1434 (1960).

[*] The position of the H-atoms in the chain has not been proved.

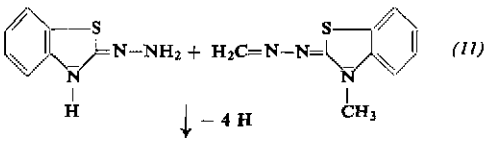
[10] *F. Brühne*, Ph.D. Thesis, Universität Marburg 1960.

[11] *S. Hünig* and *K. H. Fritsch*, Liebigs Ann. Chem. *609*, 172 (1957).

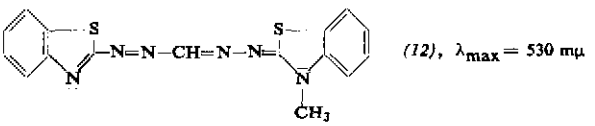
[12] *E. Besthorn*, Ber. dtsch. chem. Ges. *43*, 1519 (1910).

This reaction, too, has recently been expanded by *Sawicki* into an extremely sensitive means of detecting aliphatic aldehydes [13] and even aldehyde-2,4-dinitrophenylhydrazones [14].

It seemed desirable to consider the partially alkylated dyestuff *(12)* for comparison as a connecting link between *(5)* and *(10)*. In this case also, the oxidative coupling follows the scheme:

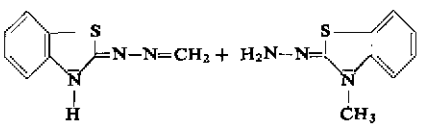


(11)

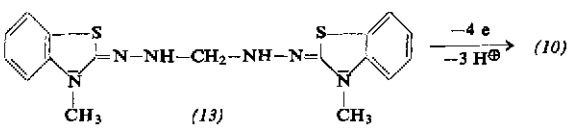


(12), $\lambda_{max} = 530$ mμ

On chromatographic purification, however, both the symmetrical dyes *(5)* and *(10)* appear in addition, hence, a transfer of the formaldehyde residue must have taken place in the solution:



It is thus conceivable that *(12)* is (also) formed *via* the latter two components. The ease of exchange of the aldehyde group raises the question whether the formation of tetraazapentamethinecyanines should be classified as an oxidative coupling at all. For example, *N*-methylbenzothiazol-2-one hydrazone could add onto the formaldehyde derivative *(11)*, to form *(13)*, which then undergoes dehydrogenation.



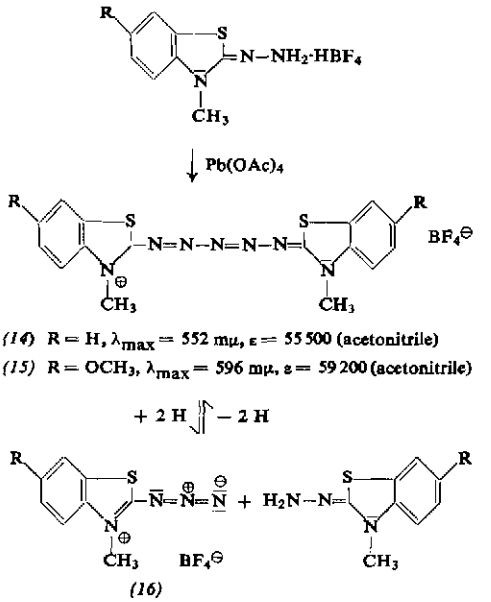
(13)

This path is improbable, since the long-wave extinction of a solution of *(11)* in acetic acid or ethanol is not depressed on addition of *N*-methylbenzothiazol-2-one hydrazone, but, on the contrary, is slightly enhanced [10].

Both the anionic dye *(5)* and the cationic dye *(10)* belong to the fully symmetrical cyanine type. Their longest absorption bands lie in the same region and display high molar extinctions. The absorption maxima [9,11,13], which are dependent on the solvent and the temperature, are probably due to geometric isomerism of the azamethine chain. As is to be expected the absorption maximum undergoes a hypsochromic shift in the transition to the uncharged, unsymmetrical „cyanine base" *(12)*, with simultaneous decrease of the molar extinction.

D. Pentaazapentamethinecyanines

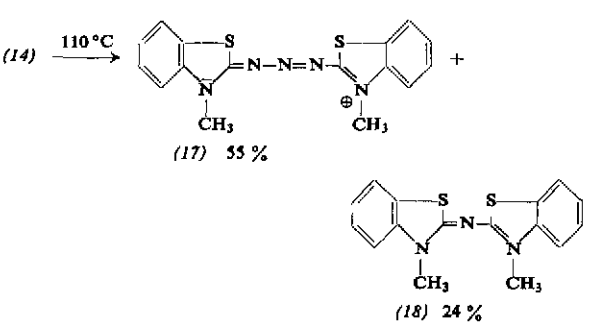
A fugitive purple to blue coloration is observed on oxidation of many hydrazones in the absence of a coupling component: Provided that the formation of tetraazapentamethinecyanines is excluded, this phenomenon may be attributed to the formation of pentaazapentamethinecyanines, which were first isolated as purple dye salts after oxidation of *N*-methylbenzothiazol-2-one hydrazone hydrofluoroborate with lead tetraacetate in weakly acidic methanolic solution [15].



(14) R = H, $\lambda_{max} = 552$ mμ, $\varepsilon = 55\,500$ (acetonitrile)
(15) R = OCH_3, $\lambda_{max} = 596$ mμ, $\varepsilon = 59\,200$ (acetonitrile)

(16)

The structure of these alkali-sensitive dyes, which contain the longest chain of nitrogen atoms with conjugated double bonds so far known, can be derived from their smooth reductive cleavage with $TiCl_3$ in acetonitrile. Two equivalents of reducing agent are consumed, and the dye is decolorized. The two cleavage products, *viz.* the original hydrazone and the azidinium salt *(16)* – a representative of a class of substances discovered by *Balli* [16] – can both be clearly identified. In contrast, the pentaazamethinecyanines are formed by nucleophilic addition of hydrazones onto azidiniun salts, whereby the excess azidinium salt, which is known to be reduced with great ease [16], acts as dehydrogenating agent. This synthesis can be generalized to produce (unsymmetrical) dyes by using other heterocycles [15]. A further proof for the constitution of the new dyes is provided by their thermal decomposition: triazatrimethine- and monoazamonomethinecyanines *(17)* and *(18)* are formed with elimination of nitrogen.



(17) 55 %

(18) 24 %

It is surprising that the oxidative linking of two heterocyclic hydrazone molecules gives a compound containing an azamethine chain with an *odd* number of nitrogen atoms. Perhaps this circumstance is due to the reaction

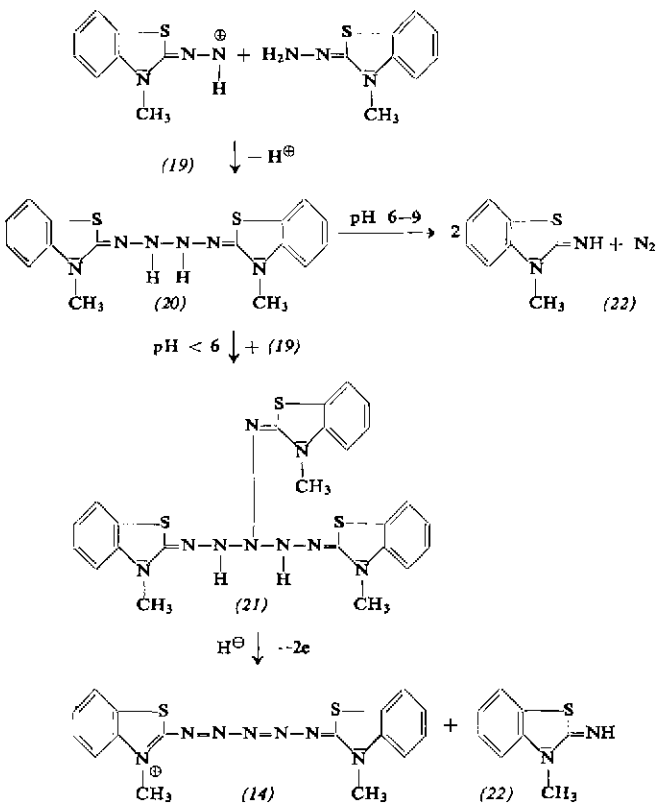
[13] *E. Sawicki, Th. R. Hauser, Th. W. Stanley*, and *W. Elbert*, Analytic. Chem. *33*, 93 (1961).

[14] *E. Sawicki, Th. R. Hauser*, and *F. T. Fox*, Analytica chim. Acta *26*, 229 (1962).

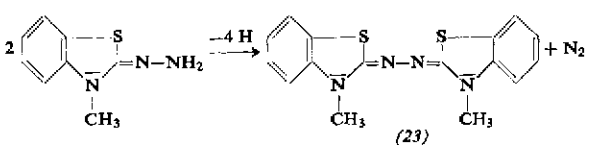
[15] *S. Hünig, H. Balli*, and *H. Quast*, Angew. Chem. *74*, 28 (1962).

[16] *H. Balli*, Angew. Chem. *70*, 442 (1958); Liebigs Ann. Chem. *647*, 11 (1961).

of the active entity of the oxidative coupling (see Section F), *e.g. (19)*, with excess hydrazone as coupling component.



The adduct *(20)* initially formed is again substituted by the electrophile *(19)* in weakly acidic medium to give *(21)*, which, after dehydrogenation and cleavage of *N*-methylbenzothiazol-2-one imine *(22)*, yields the pentaazamethine dye *(14)* [17]. The rupture of an N–N bond in the fashion described is reasonable: at pH 6–9, a solution of *N*-methylbenzothiazol-2-one hydrazone with potassium ferricyanide, evolves only 45–50 % nitrogen [18]. The main product is not the azine *(23)*, expected to be formed according to the equation:



but surprisingly, is the imine *(22)*, along with 10 % of the azine *(23)* [17]. As a result, only 1.2 equivalents of oxidizing agent are consumed.

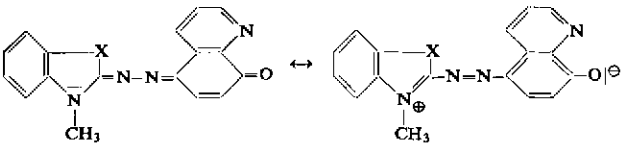
The formation of the imine might be due to an intramolecular redox reaction of the dimer *(20)* – an assumption which remains to be investigated with isotopic nitrogen.

E. Metal Complexes of Diazamerocyanines

As described earlier, assisted by the quinoline nitrogen atom, the diazamerocyanine *(24)* forms deeply colored complex salts with heavy metals in acid solutions [3, 5].

[17] *H. Quast*, Diploma Thesis, Universität Marburg 1961.

[18] *H. Balli*, Ph.D. Thesis, Universität Marburg 1956.



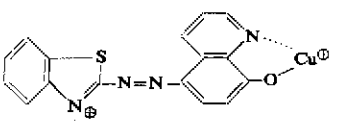
(24): X = >S; *(25)*: X = –CH=CH–; *(26)*: X = >N–CH$_3$

Table 1. Optical data for the dyes *(24)*–*(26)*, and their 1:1 – complexes with heavy metals [19]

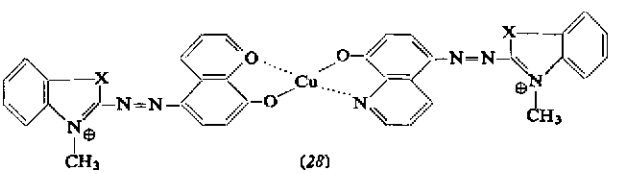
	Free dye		Bathochromic effect due to complex formation			$\Delta\lambda_{max}$ Cu^{2+}-Zn^{2+}
	λ_{max} [*] [mμ]	λ_{max} >C=O [μ]	Zn^{2+} [mμ]	Ni^{2+} [mμ]	Cu^{2+} [mμ]	[mμ]
(24)	495	6.10	56	66	79	23
(25)	520	6.13	47	51	58	11
(26)	525	6.15	27	30	31	4

[*] In methanol.

The investigation was extended to the quinoline derivative *(25)* and the benzimidazole derivative *(26)*, to vary the heterocycle's basicity [19]. The bathochromic effect increases in all cases in the sequence $Zn^{2+} < Ni^{2+} < Cu^{2+}$, which at the same time also corresponds to the general series of increasing complex stability [20]. Ag^+ and Hg^{2+}, as expected, cause only slight color shifts, since these ions necessitate linearly arranged ligands [21], and hence chelation does not result in an energy increase. The Cu^{2+} complexes have been more thoroughly investigated and, according to results obtained by the method of *Job* [22], exist in the case of the weakly basic benzothiazole derivative as the 1:1 complex *(27)*,



(27), λ_{max} = 585 mμ



(28)

X = –CH=CH–, λ_{max} = 600 mμ

X = >N–CH$_3$, λ_{max} = 578 mμ

and in the case of the strongly basic quinoline and benzimidazole derivatives as the 1:2 complex *(28)* [*]. The 1:2 complex formerly assumed [5] in the benzothiazole dye *(24)* can be produced only under special conditions (λ_{max} = 630 mμ) [23]. These complex salts belong to the few types which exist only in the acid range (pH 1 to 7).

[19] *E. Grigat*, Ph.D. Thesis, Universität Marburg 1959.

[20] *H. Irving* and *R. J. P. Williams*, Nature (London) *162*, 746 (1948).

[21] *G. Schwarzenbach*, Experientia Suppl. V (1956).

[22] *P. Job*, Ann. Chimie (*10*) *9*, 118 (1928); (*11*) *6*, 97 (1936); cf. *W. C. Vosburgh*, *A. R. Cooper*, and *R. K. Gould*, J. Amer. chem. Soc. *63*, 437 (1961).

[*] The number of solvent ligands is unknown. The formulae show only one resonance structure.

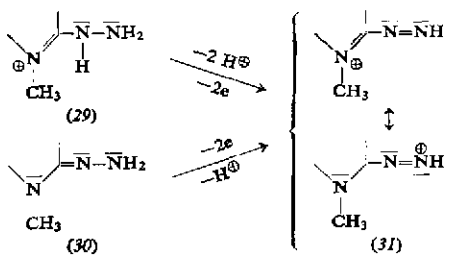
[23] *H. Klamberg*, Personal Communication.

Table 1 shows that, even in the basic state, the length of the C=O bond, and thereby also the negative character of the carbonyl oxygen atom both increase in the series *(24)* through *(26)*. This explains the transition to 1:2 complexes with *(25)* and *(26)*. All three dyes display positive solvatochromism, which means that the nonpolar azino skeleton structure becomes increasingly important [24]. The cyanine-like bond distribution increases with increasing C=O bond length, *i.e.* the excitation energy decreases in the series *(24)* to *(26)* in the color-bound system, which latter can be treated like a disturbed electron gas [25].

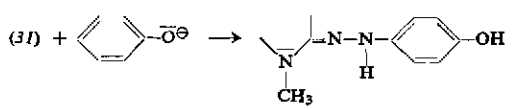
A comparison of the disturbance of the π-electron system caused by complex formation is made possible by using solutions in methanol of the three dyes, which contain metal ions in vast excess. Under these conditions, *(24)*, *(25)*, and *(26)* all form 1:1 complexes, the spectra of which display the bathochromic shifts shown in Table 1. The magnitude of the effect is thus determined by the polarizability of the dye, and not by its polarity. This means that the effect decreases in the sequence *(24)*>*(25)*>*(26)* for all three cations of Table 1. For the same reason, the difference between the bathochromic effects of the strongly active Cu^{2+} ion and the weakly active Zn^{2+} ion decreases in the same sequence.

F. Mechanism of the Reaction

The arguments presented earlier [3] already indicated that the oxidative coupling reaction of the "hydrazones" proceeds analogously to the same reaction with *p*-phenylenediamines [26]. Thereby, two equivalents of oxidizing agent are consumed, and the mesomerism-stabilized oxidation stage *(31)*

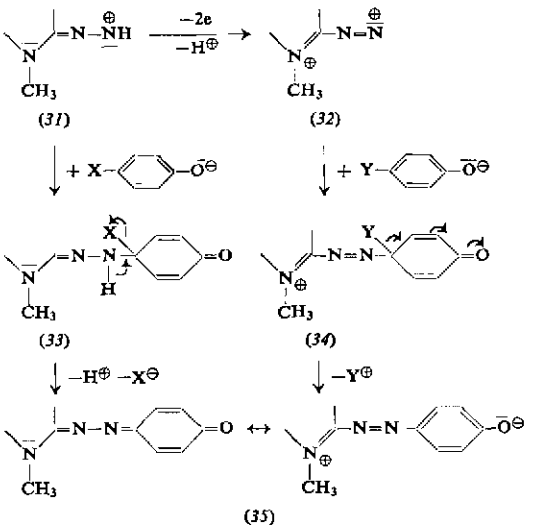


is reached, which then reacts by electrophilic substitution with the coupling components to give the leuco dye, which can be dehydrogenated easily:

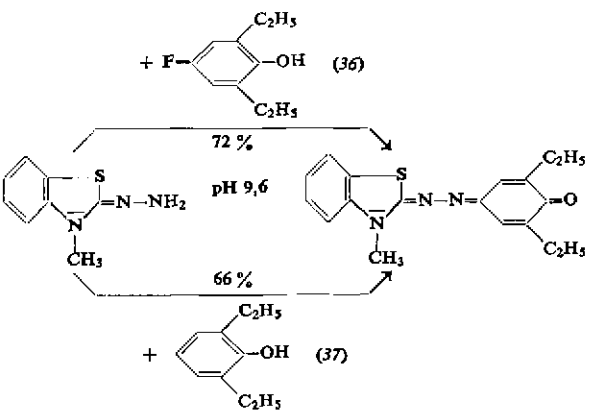


Thus, a total of four equivalents of oxidizing agent are consumed. The pH dependence of the polarographic half wave potential of several hydrazones confirms this concept [27]. The ratio of transferred protons to transferred electrons is 1:1 within the pH range in which the hydrazone is present in the cationic form *(29)*; however, at higher pH, *i.e.* starting from the free hydrazone *(30)*, this ratio becomes 1:2. The dehydrogenation step thus seems to be sufficiently well ratified.

However, the polarogram does not exclude the possibility that the ratio could be 2:4 instead of 1:2, *i.e.* at least a small portion of the hydrazone could be raised to the very high-energy oxidation stage *(32)*, which is doubtlessly an extremely active diazonium coupling ion and which could hence effect the coupling in its entirety. The choice of an appropriate coupling component permits a decision to be made. Oxidation stage *(31)* can also couple with phenols bearing a *para*-substituent X, which is able to undergo anionic cleavage, whereby the dye *(35)* is formed directly, according to the reaction scheme above. Oxidation stage



(32) of the diazonium ion cannot react in this manner. In its case, coupling can only take place by elimination of a *p*-substituent (Y) as a cation. In accordance with this, the 4-fluoro-2,6-diethylphenol *(36)* tested did not couple with *p*-nitrobenzene diazonium salt. In contrast, oxidative coupling yields even more dye than with 2,6-diethylphenol *(37)* [28].



The reaction course by way of the diazonium stage *(32)* is thus eliminated, and the formulation via the "diazenium-stage" *(31)* gains in importance [28].

G. Oxidative Coupling of N,N-Diarylhydrazines

a) The Resulting Dyes

The converse application of the phenylogue principle to the *p*-phenylenediamines and of the vinylogue principle to amidrazones *(1)* leads to hydrazines, which have

[24] Cf., for example, *S. Hünig* and *O. Rosenthal*, Liebigs Ann. Chem. *592*, 161 (1955); *K. Dimroth*, S.-B. Ges. Beförd. ges. Naturwiss. Marburg *76*, issue no. 3, 3 (1953).

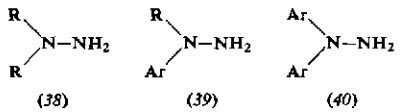
[25] *H. Kuhn*, Z. Elektrochem. angew. physik. Chem. *53*, 165 (1949).

[26] *J. Eggers* and *H. Frieser*, Z. Elektrochem. Ber. Bunsenges. physik. Chem. *60*, 372 (1956); *J. Eggers*, ibid. *60*, 987 (1956); *L. K. J. Tong* and *M. C. Glesmann*, J. Amer. chem. Soc. *78*, 5827 (1956); *79*, 583, 592 (1957).

[27] *S. Hünig* and *H. Balli*, Liebigs Ann. Chem. *628*, 56 (1959).

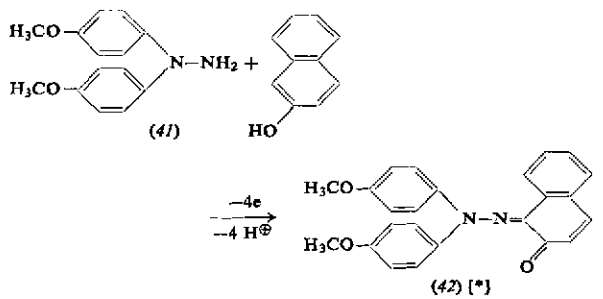
[28] *S. Hünig*, *H. Balli*, *H. Nöther*, and *H. Geiger*, Liebigs Ann. Chem. *628*, 75 (1959).

been subjected to oxidative coupling as dialkylhydrazine *(38)*, alkylarylhydrazines *(39)*, and diarylhydrazines *(40)*.

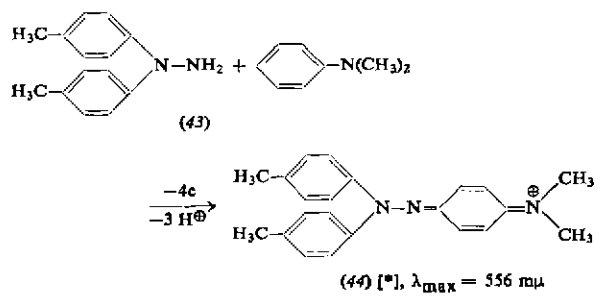


(38) *(39)* *(40)*

Although no coupling products can be isolated with *(38)* and *(39)*, unsymmetrical diarylhydrazines, such as *(41)* and *(43)*, react with both phenols and amines, yielding the expected dyes after the oxidative coupling:



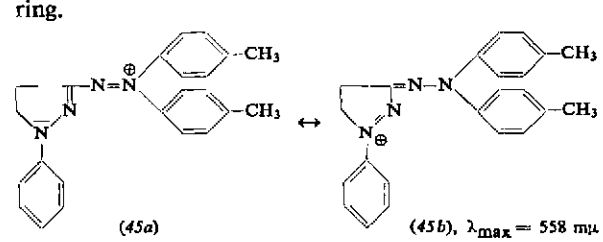
(41) *(42)* [*]



(43) *(44)* [*], λ_{max} = 556 mμ

The phenol dyes, such as *(42)*, are quinone monohydrazones, while the cationic amine dyes are derived from quinone diimmoniumions [29], and are therefore particularly sensitive to hydrolysis.

Even 1-phenyl-Δ^2-pyrazoline, which can be considered as an intramolecular aldehyde hydrazone and which is known to exert coupling activity toward diazonium salts [30], can be linked oxidatively to unsymmetric diarylhydrazines. As can be recognized from the resonance structures *(45a)* and *(45b)*, the dye salt corresponds to an unsymmetrical 1,3-diazatrimethinecyanine dye with terminal heteroatoms which are not part of a ring.

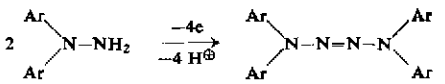


(45a) *(45b)*, λ_{max} = 558 mμ

The oxidative coupling principle has thus been extended to cover a class of compounds that only remotely resemble their classic model, the *p*-phenylenediamines.

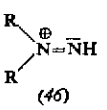
The reaction, which in most features closely follows that of the classic model (see below), requires discussion at this point, although the coupling products shall no longer be considered as azo dyes in the strict sense.

Oxidative coupling of diarylhydrazines gives dyes in yields of 10 to 50 %, since the concurrent coupling between two identical molecules to give tetrazenes [31] sometimes becomes the main reaction.



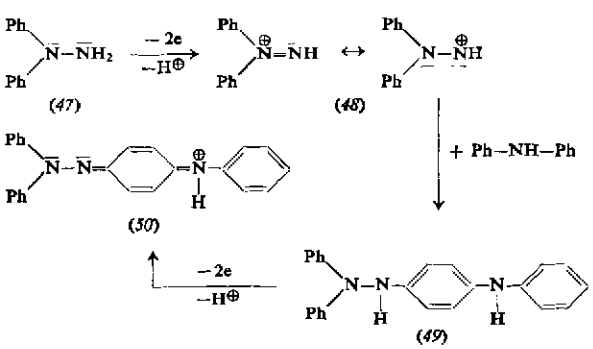
b) Mechanism of Dyestuff Formation

The identification of the dialkyldiazenium ion *(46)*, which originates from oxidation of unsymmetrical dialkylhydrazines in acid solution [32], and the analogy of the oxidative coupling of unsymmetrical diarylhydrazines to that between *p*-phenylenediamines and hydrazones of type *(1)* and *(2)* would also seem to



(46)

indicate the existence of similar intermediate stages here. For example, 1,1-diphenylhydrazine *(47)* should first be dehydrogenated to the mesomeric diazenium ion *(48)*, which would then substitute the coupling component (*e.g.* diphenylamine) electrophilically, and then the leuco dye *(49)* would immediately be dehydrogenated to give the dye cation *(50)*.



(47) *(48)* *(50)* *(49)*

The dye *(50)* was isolated by *Wieland* as early as 1910, after oxidation of *(47)* in acid solution, without an addition of diphenylamine [33]. The reaction course proposed by him after a careful study [34] is, however, different. According to *Wieland*, diphenylhydroxylamine *(51)*, obtained from diphenylhydrazine via an unknown path, reacts with diphenylhydrazine to give

[*] Only one resonance structure is drawn in each case.

[29] *S. Hünig* and *P. Richters*, Chem. *91*, 442 (1958).

[30] *G. F. Duffin* and *J. D. Kendall*, J. chem. Soc. (London) *1954*, 408.

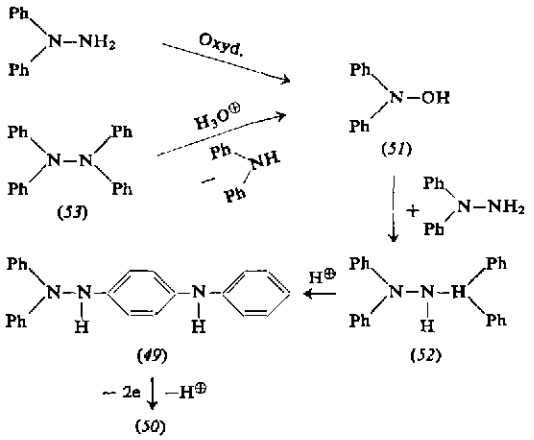
[31] *E. Fischer*, Liebigs Ann. Chem. *190*, 167 (1878).

[32] *W. R. McBride* and *H. W. Kruse*, J. Amer. chem. Soc. *79*, 572 (1957); *W. H. Urry*, *H. W. Kruse*, and *W. R. McBride*, *ibid.* *79*, 6568 (1957); *W. R. McBride* and *E. M. Bens*, *ibid.* *81*, 5546 (1959).

[33] *H. Wieland* and *E. Wecker*, Ber. dtsch. chem. Ges. *43*, 3260 (1910).

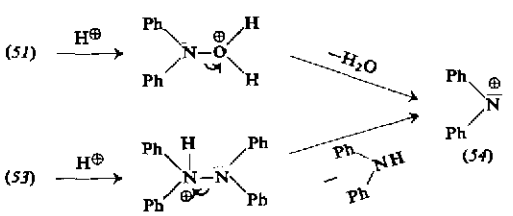
[34] *H. Wieland* and *A. Roseen*, Ber. dtsch. chem. Ges. *45*, 494 (1912).

the hypothetical triazane *(52)*, which is rearranged by acid to the leuco dye *(49)*, and is finally dehydrogenated to yield the red dye salt *(50)*.

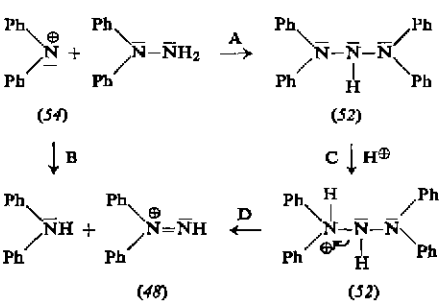


Actually the dye is formed from diphenylhydrazine even in the absence of an oxidizing agent, when diphenylhydroxylamine or tetraphenylhydrazine *(53)* are added [34]. The cleavage by acid of *(53)* into diphenylamine and diphenylhydroxylamine was already known [35].

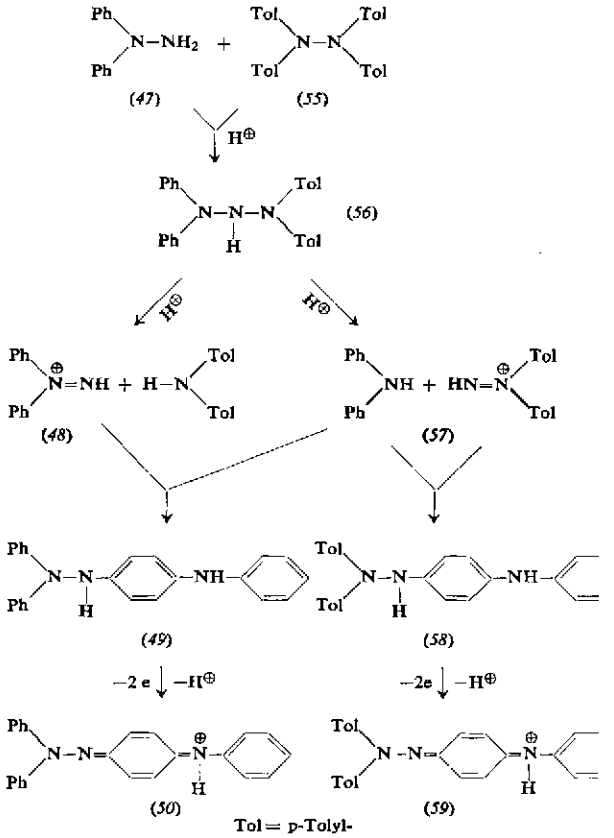
The "enormous reactivity" of diphenylhydroxylamine in acid solution is unquestionably based on the formation of a diarylazenium cation *(54)*, which is familiar from diverse examples [36] and which must also appear as a primary product in the cleavage of tetraarylhydrazines.



The question is therefore to decide whether *(54)* reacts (through A) with diphenylhydrazine to give the symmetrical triazane *(52)* first, or whether it acts (trough B) as a strong dehydrogenating agent and gives rise to the coupling diphenyldiazenium ion *(48)* directly.



Even if the hypothetical triazane *(52)* were to be formed, its proton-catalyzed rearrangement would have to be channelled by way of C to D and lead to the coupling path proposed above. A means of differentiating between paths A and B is furnished by the reaction of tetra-*p*-tolylhydrazine *(55)* and diphenylhydrazine in acid solution [10]:



According to *H. Wieland* the unsymmetrical triazane *(56)* is to be expected in this case. Acid cleavage of *(56)* would produce both the diphenyldiazenium cation *(48)* and the di-*p*-tolyldiazenium cation *(57)*. Thus, a path for the formation of two dye salts would be opened: to *(50)* by way of *(49)*, and to *(59)* by way of *(58)*. However, actually only the diphenyl dye *(50)* is formed [*]. Oxidative formation of dyes therefore is based on the reaction principle of oxidative coupling, which encompasses a surprisingly wide range of applicability. This principle is a variant of electrophilic substitution of aromatic compounds and reactive methylene compounds; the attacking partner is not formed by an acid-base reaction – as for sulfonation or nitration – but instead by dehydrogenation.

I wish to thank the persons named at the heading of this article for their individual contributions to the investigations described above as well as W. Brenninger for his skilled assistance. My special thanks for the generous promotion of this work program are expressed to the Fonds der Chemischen Industrie, and the Deutsche Forschungsgemeinschaft; both institutions also supported some co-workers with stipends. Sincere thanks are also due to the Badische Anilin und Sodafabrik for additional support.

Received, July 30th, 1962 [A 233/57 IE]

[35] *H. Wieland* and *St. Gamberjan*, Ber. dtsch. chem. Ges. *39*, 1501 (1906).

[36] Cf. *K. H. Meyer* and *W. Reppe*, Ber. dtsch. chem. Ges. *54*, 327 (1912).

[*] The joint oxidation of diphenylhydrazine and di-*p*-tolylhydrazine leads, as expected, to a mixture of the dyes *(50)* and *(59)*. The rate of coupling of *(48)* and *(57)* is therefore of the same order of magnitude.

Carbonic Acid Derivatives from Formamides

BY DR. E. KÜHLE

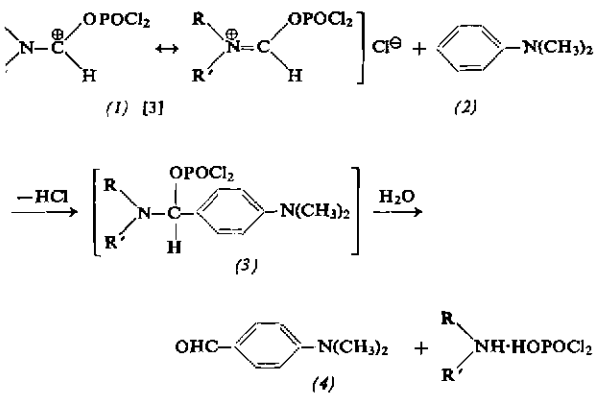
WISSENSCHAFTLICHES HAUPTLABORATORIUM DER FARBENFABRIKEN BAYER AG
LEVERKUSEN (GERMANY)

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

Starting from a few known syntheses employing formamide/acid chloride adducts or the formamide chlorides derived therefrom, new routes leading to aromatic isocyanodichlorides, iminochlorothioformates, and organic thiocyanates are described. The respective reaction mechanisms are briefly discussed.

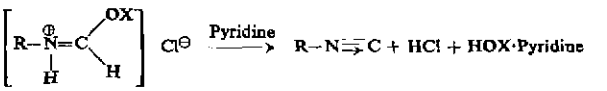
Introduction

Numerous publications have recently appeared concerning the addition products obtained from phosgene, thionyl chloride, phosphorus oxychloride, carbonylic bromides, or *p*-toluenesulfonyl chloride with formamides, particularly dimethylformamide. Some of these investigations revert to the long-known Vilsmeier-Haack reaction [1] between adducts of phosphorus oxychloride onto disubstituted formamides *(1)* [2] and nucleophilic aromatic compounds, *e.g. N,N*-dimethylaniline *(2)*, with formation of a C–C bond. The addition compound *(3)* can be hydrolyzed to 4-dimethylaminobenzaldehyde *(4)*.



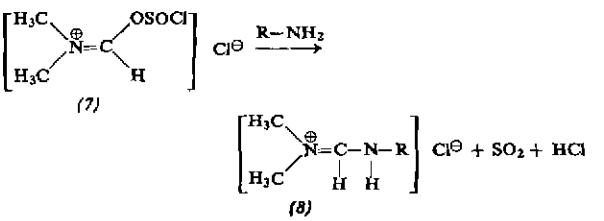
(1) [3] *(2)* *(3)* *(4)*

In the presence of pyridine or potassium t-butoxide, the addition compounds *(5)* obtained from monosubstituted formamides and *p*-toluenesulfonyl chloride [4] or phosphorus oxychloride [5] undergo α-elimination to yield isocyanides *(6)*.



(5) *(6)* X = —$POCl_2$, $ArSO_2$—

Eilingsfeld et al. [6] have reviewed the preparation, properties, and reactions of imidonium chlorides obtained from the primary formamide/acid chloride adducts. The reaction with primary amines [7] which is described in the cited article and which leads to formamidines can be regarded as an introduction to our own investigations. The dimethylformamide/thionyl chloride complex *(7)* reacts with a primary amine to give *N,N*-dimethylformamidinium chloride *(8)*.



(7) *(8)*

The synthesis of formamidines from formamides and thionyl chloride, albeit in the absence of a primary amine, was reported as early as in 1935 by *Warren* and *Wilson* [8]. These authors obtained, for example, very good yields of *N,N'*-diphenylformamidinium chloride *(13)* by treating formanilide with thionyl chloride *(9)*.

In repeating this work, we observed the following. The reaction of 1 mole of formanilide *(9)* with 1 mole of thionyl chloride in carbon tetrachloride at 50–60 °C

[1] *A. Vilsmeier* and *A. Haack*, Ber. dtsch. chem. Ges. *60*, 119 (1927); cf. *O. Bayer* in *Houben-Weyl*: "Methoden der Organischen Chemie" [Methods of Organic Chemistry], 4th edition, Georg Thieme, Stuttgart 1954, vol. 7, pt. 1, p. 29.

[2] Modern formulation according to *H. Bredereck, R. Gompper, K. Klemm*, and *H. Rempfer*, Chem. Ber. *92*, 837 (1959).

[3] Hereinafter, only the immonium form of the mesomeric resonance structures will be given.

[4] *W. R. Hertler* and *E. J. Corey*, J. org. Chemistry *23*, 1221 (1958); cf. *I. Hagedorn* and *H. Tönjes*, Pharmazie *12*, 570 (1957).

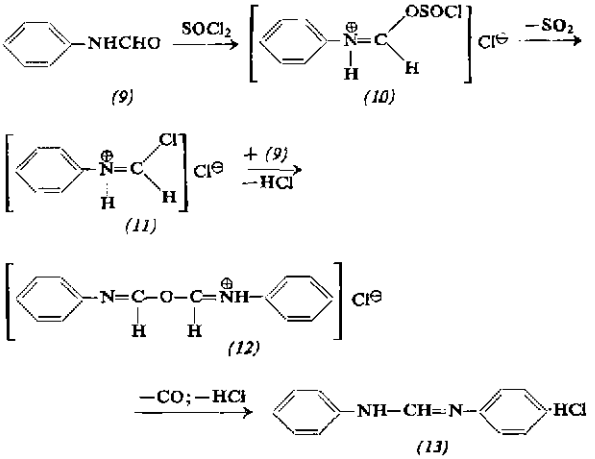
[5] *I. Ugi* and *R. Meyr*, Angew. Chem. *70*, 702 (1958); Chem. Ber. *93*, 239 (1960); cf. *I. Ugi, W. Betz, U. Fetzer*, and *K. Offermann*, Chem. Ber. *94*, 2814 (1961).

[6] *H. Eilingsfeld, M. Seefelder*, and *H. Weidinger*, Angew. Chem. *72*, 836 (1960); further literature references are to be found therein.

[7] Cf. *A. J. Hill* and *J. Rabinowitz*, J. Amer. chem. Soc. *48*, 732 (1926).

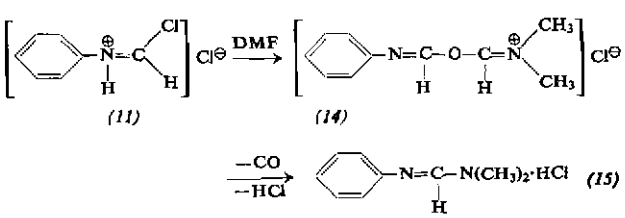
[8] *W. H. Warren* and *F. E. Wilson*, Ber. dtsch. chem. Ges. *68*, 957 (1935).

gave very good yields of *N,N'*-diphenylformamidinium chloride *(13)*; however, the thionyl chloride was not completely consumed. The same yield of *(13)* was obtained even if only 0.5 mole of thionyl chloride was used [9]. The reaction course is illustrated by the following scheme:



As shown, thionyl chloride reacts with formanilide to give the complex *(10)*, which splits off sulfur dioxide even at room temperature to form the imidonium chloride *(11)*. This compound reacts with the excess of formanilide to form the intermediate *(12)*. On heating, this decomposes to yield one mole each of carbon monoxide, hydrogen chloride, and the stable *N,N'*-diphenylformamidinium chloride *(13)*. It has been possible to isolate compound *(12)* [10]. It is relatively stable at room temperature; its infrared spectrum shows bands characteristic of its salt structure at 2700–3300 cm^{-1}, and a band at 1668 cm^{-1}, typical of the N=C double bond.

The observation, that the complex *(10)* or the imidonium chloride *(11)* reacts with another mono- or disubstituted formamide to give unsymmetrical formamidines, lends support to the two-step reaction scheme. For example, at room temperature, *(11)* reacts with dimethyl-formamide to afford mainly *N*-phenyl-*N'*,*N'*-dimethylformamidine *(15)* in addition to small amounts of *N,N'*-diphenylformamidinium chloride and phenyl isocyanide. Distillation of the mixture affords compound *(15)* as the free base.



DMF = dimethylformamide

Subsequently, we used the formamide addition compounds for the synthesis of

I. aromatic isocyanodichlorides,

II. iminochlorothioformates, and

III. organic thiocyanates.

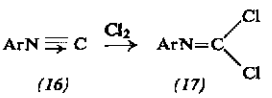
This work is described below.

[9] *H. Bredereck* et al. made similar observations in their study of the preparation of amidines from formamide/phosphorus oxychloride complexes; Chem. Ber. *92*, 837 (1959).

[10] Or, conceivably, an isomeric compound.

I. Aromatic Isocyanodichlorides [*N*-(Dichloromethylene)amines]

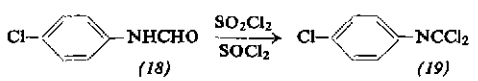
Until now, only two methods [11] have been described for the preparation of aromatic isocyanodichlorides *(17)*: addition of chlorine onto isocyanides *(16)* [12], and chlorination of



aromatic isothiocyanates, with subsequent elimination of sulfur dichloride [13]. The latter method frequently leads to side reactions [14].

The chlorination of formanilide with chlorine and sulfur dichloride in the presence of phosphorus trichloride, phosphorus oxychloride, and thionyl chloride is described in a paper by *Bly* et al. [15]. Whereas, in most runs, ring chlorination affording 2,4-dichloroformanilide was the only reaction observed, chlorination of formanilide in chloroform in the presence of thionyl chloride, gave a mixture of phenyl-, 4-chlorophenyl- and 2,4-dichlorophenyl isocyanodichlorides in addition to 2,4-dichloroformanilide.

Making use of this information, we treated formanilides with thionyl chloride and chlorine or – to ensure accurate charging – with sulfuryl chloride. We established that the reaction takes place more readily in the presence of excess thionyl chloride than, for example, in chloroform. Thus, we obtained *p*-chlorophenyl isocyanodichloride in excellent yield.



Example [16]:

In a 500 ml three-necked flask fitted with a stirrer, a thermometer, a reflux condenser, and a gas outlet tube, 67.5 g (0.5 mole) of sulfuryl chloride is dissolved in 150 ml of thionyl chloride; 77.5 g (0.5 mole) of *N*-(*p*-chlorophenyl)-formamide is added portionwise at 15–20 °C to this mixture, and stirring is continued for several hours at room temperature. The reaction solution is then slowly heated to a temperature of 80 °C hydrogen chloride and sulfur dioxide being liberated. The excess thionyl chloride is recovered by distillation and may be reused. Vacuum distillation of the residue yields 89 g (86%) of *p*-chlorophenyl isocyanodichloride, a light-yellow oil, b.p. 110–113 °C/10 mm.

In agreement with our conception of the course of reaction between formamides and thionyl chloride, in this case, too, *N*-(*p*-chlorophenyl)formamide *(18)* and thionyl chloride, first form a complex *(20)*, which gives rise to the imidonium chloride *(21)*; in the presence of chlorine or sulfuryl chloride, this compound then

[11] Cf. *H. Holtschmidt*, Angew. Chem. Internat. Edit. *1*, 632 (1962).

[12] *J. U. Nef*, Liebigs Ann. Chem. *270*, 267 (1892); *280*, 291 (1894).

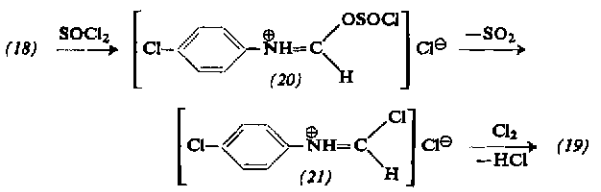
[13] *E. Sell* and *G. Zierold*, Ber. dtsch. chem. Ges. *7*, 1228 (1874).

[14] *G. M. Dyson* and *T. Harrington*, J. chem. Soc. (London) *1942*, 150, 374.

[15] *R. S. Bly*, *G. A. Perkins*, and *W. L. Lewis*, J. Amer. chem. Soc. *44*, 2896 (1922).

[16] German Patent Application 1094737 (May 29th, 1959); Farbenfabriken Bayer AG.; inventor: *E. Kühle*.

undergoes stabilization by elimination of hydrogen chloride forming *p*-chlorophenyl isocyanodichloride *(19)*.



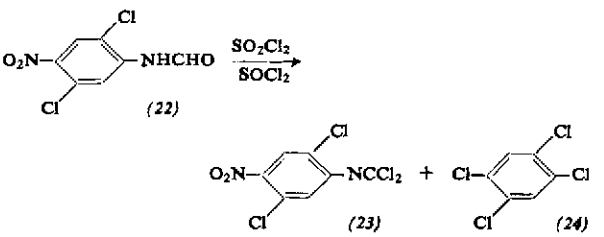
The isocyanodichlorides prepared in this manner are listed in Table 1. The yields are especially good whenever chlorination of the aromatic ring is somewhat hindered by the presence of substitutents (halogen, nitro, carboxyl, aryl radicals, *etc.*). Whereas phenyl isocyanodichloride, for example, can be obtained only in 55–60 % yields, the reaction of formanilide with double the calculated amount of chlorine proceeds quite smoothly. In this case, the reaction product is mainly *p*-chlorophenyl isocyanodichloride; some *o*-chlorophenyl isocyanodichloride is also formed. Substituents capable of reacting with thionyl chloride, *e.g.* carboxyl groups, will do so. Thus, *p*-formylaminobenzoic acid affords the acyl chloride of *p*-carboxyphenyl isocyanodichloride.

Table 1. Isocyanodichlorides [*N*-(dichloromethylene)amines] prepared from formamides

Isocyanodichloride	Temperature [°C]	Yield [%]	B. p. [°C/mm Hg]	M. p. [°C]
Phenyl	10–12	51	94–99/14	
2-Chlorophenyl	10–15	86.7	104–106/10	
2,4-Dichlorophenyl	15–20	85.5	126–132/10	
2,5-Dichlorophenyl	15–20	78.4	128–135/15	
2,3-Dichlorophenyl	15–20	73.5	142–149/14	
3,4-Dichlorophenyl	20–25	80	141–148/13	
3,5-Dichlorophenyl	20–25	53	147–155/13	
2,4,5-Trichlorophenyl	35–40	88	156/14	
2-Methyl-4-chlorophenyl	15–20	96.6	121–123/10	
2-Chloro-6-methylphenyl	35–40	92.5	110–112/11	
2,4-Dichloro-5-methylphenyl	20–25	84	143–146/10	
2-Methoxy-4-chlorophenyl	20–25	37	161–166/11	81
2-Chloro-5-trifluoromethylphenyl	20–25	75	101–102/12	
2-Trifluoromethyl-4-chlorophenyl	15–20	78.3	104–110/10	
2,6-Diethyl-4-methylphenyl	20–25	55.6	151–161/10	
2,6-Diisopropylphenyl	20–25	80.5	104–120/0.4	
4-Fluorophenyl	25–30	71.5	82–87/11	
4-Bromophenyl	20–25	72.5	131–137/12	
2,4-Dibromophenyl	20–25	85.5	161–162/12	
4-Nitrophenyl	60–70	88	127/0.35	78–82
3-Nitrophenyl	20–25	83	120–125/0.5	69
2-Chloro-4-nitrophenyl	55–60	22	131–133/0.1	
4-Chloro-3-nitrophenyl	30–40	79.5	118/0.11	
2-Methyl-5-nitrophenyl	40–50	94	119–120/0.15	59
4-Methyl-3-nitrophenyl	20–25	82.5	166–168/13	
2-Methoxy-5-nitrophenyl	50–60	82.5	140–141/0.17	
4-Methoxycarbonylphenyl	20–25	88.5	157–159/12	96–98
4-(Chloroformyl)-phenyl	55–60	49	152–158/11	50–53
2,5-Dichloro-4-nitrophenyl	40–50	20	136–138/0.15	83
1,4-Phenylene-bis(isocyanodichloride)	45–50	51.7	172–180/14	96–98
Azobenzene-4-isocyanodichloride	50	31 (recryst.)		82–84
Di-(4-chlorophenyl)-ether-2-isocyanodichloride	20–25	81.7	172–180/0.25	46–48
Benzophenone-4-isocyanodichloride	20–25	73.5	170–180/0.2	
Phenylsulfone-2-isocyanodichloride	50–60	39	210/0.3	
Diphenyl-2-isocyanodichloride	20–25	72	172–177/12	
1-Naphthyl isocyanodichloride	20–25	20	183–190/14	

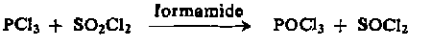
The isocyanodichlorides prepared in this manner are listed in Table 1. The yields are especially good whenever chlorination of the aromatic ring is somewhat hindered by the presence of substitutents (halogen, nitro, carboxyl, aryl radicals, *etc.*). Whereas phenyl isocyanodichloride, for example, can be obtained only in 55–60 % yields, the reaction of formanilide with double the calculated amount of chlorine proceeds quite smoothly. In this case, the reaction product is mainly *p*-chlorophenyl isocyanodichloride; some *o*-chlorophenyl isocyanodichloride is also formed. Substituents capable of reacting with thionyl chloride, *e.g.* carboxyl groups, will do so. Thus, *p*-formylaminobenzoic acid affords the acyl chloride of *p*-carboxyphenyl isocyanodichloride.

If the aromatic ring contains substituents favoring nucleophilic aromatic substitution, the isocyanodichloride grouping may undergo elimination of cyanogen chloride. Thus, the reaction of 2,5-dichloro-4-nitrophenylformanilide *(22)* with thionyl chloride and sulfuryl chloride gives considerable amounts of 1,2,4,5-tetrachlorobenzene *(24)* in addition to the isocyanodichloride *(23)*.

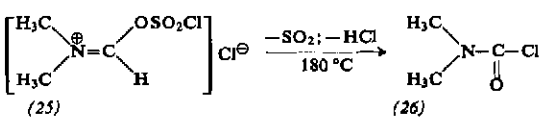


The use of "dehydrating agents" other than thionyl chloride was also investigated. Low yields of isocyanodichlorides resulted when phosgene or oxalyl chloride was employed.

Study of the system phosphorus trichloride/sulfuryl chloride disclosed an interesting fact. When a catalytic amount of a formamide (dimethylformamide, ethylformamide, formanilide) is added to the solution of sulfuryl chloride in phosphorus trichloride, the temperature of the mixture rises instantly to the boiling point [17], and a mixture of phosphorus oxychloride and thionyl chloride is formed.



Further experiments showed that the sulfuryl chloride/formamide complex is responsible for this catalysis. The reaction can be easily controlled by dropwise addition of phosphorus trichloride to sulfuryl chloride containing a small amount of dimethylformamide. The dimethylformamide/sulfuryl chloride complex is a hygroscopic, crystalline compound, m.p. 40–41 °C; on the basis of its infrared spectrum [18], we assign to it the structure *(25)*. It is stable up to 170–180 °C and decomposes above this temperature into sulfur dioxide, hydrogen chloride, and *N,N*-dimethylcarbamyl chloride *(26)*.

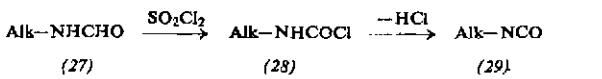


How do formamides of primary aliphatic or cycloaliphatic amines react with thionyl chloride and sulfuryl chloride? If an alkylformamide *(27)* is added

[17] On a larger scale, the reaction becomes explosive.

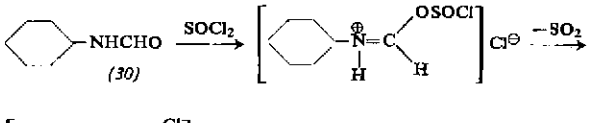
[18] The infrared spectrum is very similar to that of the dimethylformamide/phosphorus oxychloride complex (cf. *H. Bredereck* et al. [9]). Bands appear at 808, 920, 1045, 1155, 1612, and 1725 cm^{-1}.

dropwise to a solution of sulfuryl chloride in thionyl chloride, reaction and dissolution take place as in the case of formanilides. However, the reaction products are different from those formed in the aromatic series. The aliphatic and cycloaliphatic formamides studied so far by us all give isocyanates. This indicates that thionyl chloride does not take part in the reaction but, rather, acts as a solvent. This explains why alkylformamides undergo reaction with chlorine or sulfuryl chloride also in other solvents such as chlorobenzene, or even in the absence of solvent, affording isocyanates *(29)* [19,20], probably via carbamyl chlorides *(28)* as intermediates. For known reasons [21], on distillation, only the methyl and ethyl derivatives of this series may be obtained as carbamyl chlorides.

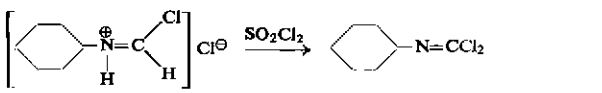


(27) *(28)* *(29)*

Because of their higher basicity, formamides of primary aliphatic amines probably react faster with chlorine or sulfuryl chloride than with thionyl chloride. We were able to confirm this experimentally. We dissolved *N*-cyclohexylformamide *(30)* in an excess of thionyl chloride, and heated the solution for some time at 40 °C to form the imidonium chloride *(31)*. Dropwise addition of sulfuryl chloride then gave cyclohexyl isocyanodichloride *(32)* as the main product in addition to small amounts of cyclohexyl isocyanate and cyclohexyl isothiocyanate.



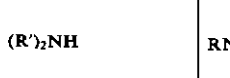
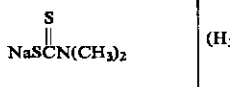
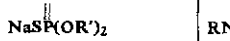
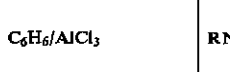
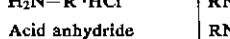
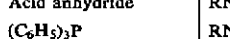
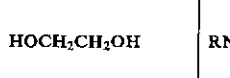
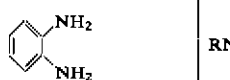
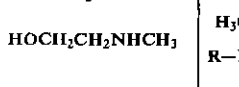
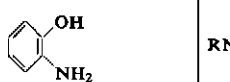
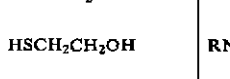
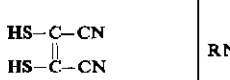
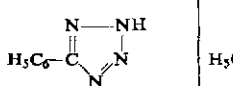
(30)



(31) *(32)*

Being derivatives of carbonic acid, the isocyanodichlorides are closely related to the isocyanates, isothiocyanates, and carbodiimides, as well as to phosgene and thiophosgene. The difunctional character of isocyanodichlorides (iminophosgenes) makes it possible to use them in a great number of reactions leading to open-chain compounds and new ring systems. Some reactions of isocyanodichlorides are illustrated in Table 2.

Table 2. Some reactions of isocyanodichlorides –R–N=CCl_2

Reaction with	Products	Literature ref.
HF		[22]
C_2H_5OH		[13]
$R'NH_2$		[13]
$(R')_2NH$		[13,23,24]
$(R')_3N$		[25]
$R'ONa$		[26, 26a]
$NaSCN(CH_3)_2$		[28]
$NaSP(OR')_2$		[27]
$P(OR')_3$		[27]
$C_6H_6/AlCl_3$		[27a]
Na_2S		[28]
$H_2N–R'·HCl$		[29]
Acid anhydride		
$(C_6H_5)_3P$		[29a]
$HOCH_2CH_2OH$		[30]
		[30a]
$HOCH_2CH_2NHCH_3$		[30a]
		[30a]
$HSCH_2CH_2OH$		[30a]
$HSCH_2COOH$		[30a]
HS–C–CN HS–C–CN		[30a]
		[30b]

[19] Aliphatic and cycloaliphatic isocyanodichlorides are best prepared by action of phosphorus pentachloride on isocyanates; German Patent Application 1126371 (Sept. 17th, 1959), Farbenfabriken Bayer; inventors: *E. Kühle* and *R. Wegler*.

[20] German Patent Application 1090197 (Aug. 19th, 1959), Farbenfabriken Bayer; inventor: *E. Kühle*.

[21] *W. Siefken*, Liebigs Ann. Chem. *562*, 81 (1949).

[22] *K. A. Petrov* and *A. A. Neimysheva*, J. gen. Chem. USSR (English translation) *29*, 2135 (1959).

[23] Austrian Patent 220155 (Aug.15th,1961) Farbenfabriken Bayer, inventors: *E. Kühle* and *L. Eue*.

[24] German Pat. Appl. 1089210 (June 8th, 1959), Farbenfabriken Bayer; inventors: *E. Kühle* und *L. Eue*.

[25] Patent applied for, Farbenfabriken Bayer; inventors: *E. Kühle* and *R. Wegler*.

[26] *F. Lengfeld* and *J. Stieglitz*, Amer. Chem. J. *16*, 70 (1894).

[26a] *W. R. Smith*, Amer. chem. J. *16*, 372 (1894).

[27] Belgian Patent 596090 (Oct. 17th, 1960) Farbenfabriken Bayer; inventors: *H. Malz*, *E. Kühle*, and *O. Bayer*.

[27a] *G. M. Dyson* and *T. Harrington*, J. chem. Soc. (London) *1942*, 150.

[28] Belgian Patent 613428 (Febr. 2nd, 1962) Farbenfabriken Bayer; inventor: *E. Kühle*.

[29] Patent applied for, Farbenfabriken Bayer; inventor: *E. Kühle*.

[29a] Patent applied for, Farbenfabriken Bayer; inventors: *H. Malz* and *E. Kühle*.

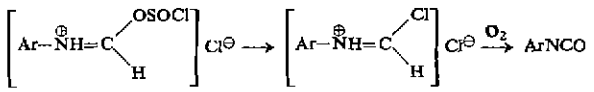
[30] *K. Gulbins* and *K. Hamann*, Angew. Chem. *73*, 434 (1961).

[30a] Patent applied for, Farbenfabriken Bayer; inventors: *B. Anders* and *E. Kühle*.

[30b] *E. Kühle*, unpublished.

II. Iminochlorothioformates [31]

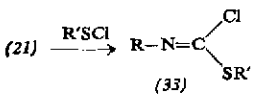
Since the formanilide/thionyl chloride complexes *(20)* and the imidonium chlorides *(21)*, to which they give rise via elimination of sulfur dioxide, react readily with chlorine to give isocyanodichlorides, other reagents were also evaluated. It was hoped that the action of oxygen would lead to aromatic isocyanates.



(20) *(21)*

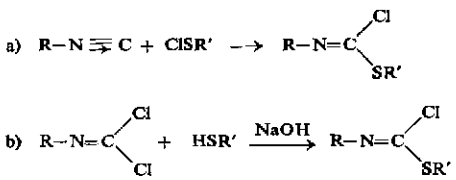
Although we were able to demonstrate the formation of small amounts of isocyanates, in this case, too, isocyanodichlorides are the main reaction products. The oxygen probably oxidizes thionyl chloride to sulfuryl chloride, which then acts as a chlorinating agent.

Better results were obtained when sulfenyl chlorides were used. These react with formamide chloride *(21)* to give iminochlorothioformates *(33)*.



(33)

The structure of compound *(33)* was proved by two independent syntheses:

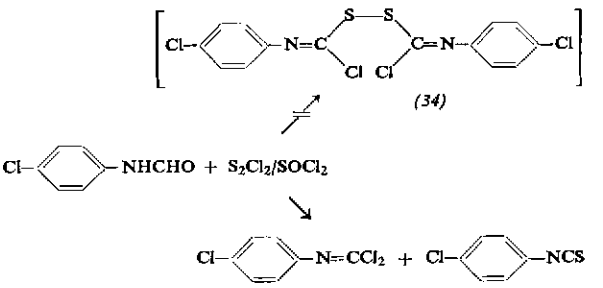


The synthesis of iminochlorothioformates *(33)* by the formamide/thionyl chloride method lends itself to numerous variations. Unlike the preparation of isocyanodichlorides, it is not limited to formamides of aromatic amines, but can readily be extended to aliphatic, cycloaliphatic, and heterocyclic formamides as well as bis-formamides. The choice of sulfenyl chloride is not restricted, either.

Example:

To a solution of 41.0 g of benzenesulfenyl chloride in 200 ml of thionyl chloride is added portionwise, with good stirring, 34.5 g of formanilide; the solution is stirred for about 3 hours at room temperature. Sulfur dioxide and hydrogen chloride are evolved. The excess of thionyl chloride is then distilled off, and the residue fractionated *in vacuo*. This affords 50 g (71%) of phenyl *N*-phenyliminochlorothioformate, b.p. 200–202 °C/16 mm, m.p. 56–58 °C.

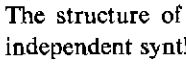
The reaction with S_2Cl_2 was particularly interesting. It was expected that in the reaction with *p*-chloroformanilide, used in a 2:1 molar ratio, the bis-imidochloride *(34)* would be formed. Actually, a mixture of *p*-chlorophenyl isocyanodichloride and *p*-chlorophenyl isothiocyanate, richer in the latter, was obtained [32].



(34)

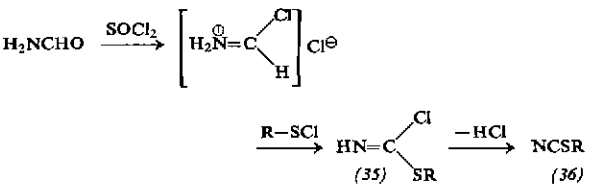
The iminochlorothioformates we have so far prepared are listed in Table 3.

Table 3. Iminochlorothioformates R–N=C(Cl)–SR′ prepared by reacting formamides with thionyl chloride and sulfenyl chlorides

R	R′	Yield [33] [%]	B. p. [°C/mm Hg]	M. p. [°C]
Phenyl	Trichloromethyl	55	183–187/30	
Methyl		46	98–101/21	
Propyl		55	127–128/15	
Phenyl	Pentachlorophenyl	100		124
Methyl		100		116
4-Chlorophenyl		100		134–138
4-Nitrophenyl		95		157–160
2-Chlorophenyl		96		92
2,4-Dichlorophenyl		92		102
		72		270–271
1-Naphthyl		20		266
2-Benzothiazolyl		33		212
Phenyl	Phenyl	71	200–202/16	56–58
Ethyl		21	151–158/30	
4-Chloroformylphenyl		78	186–193/0.2	
3-Nitrophenyl		70	192–194/0.2	
Methyl	2-Benzothiazolyl	53		192–196
Phenyl	Fluorodichloromethyl	79.5	148–150/18	
Methyl		52	64–65/14	
2,4-Dichlorophenyl	4-Nitrophenyl	100		122–124

III. Organic Thiocyanates

It is surprising that, in addition to its use in the particular isothiocyanate synthesis described in section II, the combination of formamides and thionyl chloride also provides a general route leading to thiocyanates. In fact, if in place of a monosubstituted formamide, un-



(35) *(36)*

[31] Belgian Patent 610175 (Nov. 11th, 1961) Farbenfabriken Bayer, inventors: *E. Enders*, *E. Kühle*, and *H. Malz*.

[32] Since we have been successful in converting isocyanodichlorides readily into isothiocyanates, this reaction also provides a new route leading to isothiocyanates.

[33] The yields relate mostly to single experimental runs.

substituted formamide is allowed to react with a solution of sulfenyl chloride in thionyl chloride, at the end of the reaction, the iminochlorothioformate *(35)* again loses hydrogen chloride affording thiocyanate *(36)* [31].

Example:

To a solution of 16 g of pentachlorobenzenesulfenyl chloride in 70 ml of thionyl chloride, 3 g of formamide are added dropwise at 10–15 °C. The solution is agitated for a short time at room temperature, then heated to the boiling point, and the excess thionyl chloride distilled off. The residue consists of 15 g of pentachlorophenyl thiocyanate, m.p. 180–182 °C.

The thiocyanates listed in Table 4 were prepared by this process.

Table 4. Thiocyanates prepared by reacting formamide with thionyl chloride and sulfenyl chlorides

Thiocyanate	B. p. [°C/mm Hg]	M. p. [°C]	Yield [%]
Ethyl-	35–36/10		61 [34]
Chloromethyl-	65–67/11		31 [35]
1,3,3,3-Tetrachloroethyl-	108–110/11		29
Phenyl-	100–103/11		81
4-Chlorophenyl-	131–134/10	36–37	87

I wish to thank Dr. R. Wegler for encouraging our research. I am also indebted to Dr. (Miss) D. Lauerer for recording the spectra and to Dr. H. Herlinger for discussions concerning the reaction mechanisms.

Received, May 23rd, 1962 [A 238/55 IE]

[34] Based on diethyl disulfide.

[35] Based on dimethyl disulfide.

β-Chloroethylphosphonic Dichloride: Its Synthesis and Use

BY DR. F. ROCHLITZ AND DR. H. VILCSEK

FARBWERKE HOECHST AG., FORMERLY MEISTER LUCIUS & BRUNING, FRANKFURT/MAIN (GERMANY)

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Ethylene, phosphorus trichloride, and oxygen react together to give β-chloroethylphosphonic dichloride in good yields. Being a bifunctional acid chloride, this compound undergoes polycondensation reactions with other, at least bifunctional, compounds affording polyesters, polyamides, epoxy resins, etc. β-Chloroethylphosphonic dichloride also may be converted into vinylphosphonic dichloride, thus serving as a starting material for the preparation of vinylphosphonic acid and its derivatives. These undergo both homopolymerization and copolymerization with compounds containing olefinic double bonds. The products are used in the field of synthetic resins, for dressing textiles, and as protective surface coatings.

Introduction

The incorporation of phosphorus atoms into organic polymers yields products which, among other things, are highly resistent to fire or even non-combustible. Polymers containing phosphorus are prepared primarily from compounds where the phosphorus is coordinately tetravalent and especially from phosphonic acids and their derivatives, which can be modified further because of their functional groups. Particularly interesting in this respect is β-chloroethylphosphonic dichloride.

This compound was first prepared by *Kabachnik* and *Rossiyskaya* from β-chloroethylphosphonic esters and PCl_5 [1,2].

Kinnear and *Perren* [3] later described a process starting with ethylene chloride, PCl_3, and $AlCl_3$; their reaction proceeds via an intermediate complex compound which is decomposed by water. The preparation of β-chloroethylphosphonic acid esters by the reaction of 1,2-dichloroethane with trialkyl phosphites or sodium dialkyl phosphites (Arbusov reaction) has long been known [1,4,5]. The bis-(β-chloroethyl) ester can be prepared relatively easily from ethylene oxide and PCl_3: three molecules of ethylene oxide add onto one molecule of PCl_3, forming tris-(β-chloroethyl) phosphites; this compound is then made to undergo an Arbusov rearrangement to the phosphonate at elevated temperature in a high-boiling solvent [1].

[1] *M. I. Kabachnik* and *P. A. Rossiyskaya*, Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1946*, 403; see also *G. M. Kosolapoff:* Organo-phosphorus Compounds. John Wiley & Sons, Inc., New York 1950, p. 73.

[2] *M. I. Kabachnik* and *P. A. Rossiyskaya*, Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1946*, 515.

[3] *A. Kinnear* and *E. A. Perren*, J. chem. Soc. (London) *1952*, 3437; cf. *F. W. Hoffmann, T. C. Simmons*, and *L. J. Glunz*, J. Amer. chem. Soc. *79*, 3570 (1957).

[4] *M. I. Kabachnik* and *P. A. Rossiyskaya*, Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1948*, 95.

[5] *A. H. Foord-Moore* and *J. H. Williams*, J. chem. Soc. (London) *1947*, 1465.

[6] German. Patent 946046 (Jan. 22nd, 1955), Farbwerke Hoechst AG.; inventors: *E. O. Leupold* and *H. Zorn*.

In 1943, *Graf* [7, 8] found a new route leading to phosphonic dichlorides. His synthesis is based on the reaction of aliphatic hydrocarbons with PCl_3 and oxygen. In contrast to sulfochlorination, this reaction also takes place in the dark and in the absence of free-radical formers.

(a) $R{-}H + 2\,PCl_3 + O_2 \rightarrow R{-}P(O)Cl_2 + POCl_3 + HCl$

This reaction was later applied to olefins [9]. In the presence of oxygen, PCl_3 undergoes addition onto the olefinic double bond.

(b) $R{-}CH{=}CH_2 + 2\,PCl_3 + O_2 \rightarrow R{-}\underset{Cl}{CH}{-}CH_2{-}P(O)Cl_2 + POCl_3$

The reaction starts when oxygen is introduced into an olefin/PCl_3 mixture or – in the case of highly volatile olefins – when an olefin/oxygen mixture is passed into PCl_3. Higher olefins in particular, *e.g.* butylene, gave 50 % yields based on the olefin. The reaction of ethylene according to (b), however, gave only very poor yields.

A. Preparation of β-Chloroethylphosphonic Dichloride and its Derivatives

I. β-Chloroethylphosphonic Dichloride

1. Preparation from Ethylene, PCl_3, and Oxygen

If ethylene and oxygen are passed into PCl_3 at room temperature, oxygen is consumed exothermically and $POCl_3$ is formed; the participation of ethylene in the reaction is, however, only minor. Small amounts of chloroethylphosphonic dichloride can be isolated only if the reaction is carried out with great care and on a large scale. Yields of about 2 %, based on the PCl_3 consumed, are obtained.

We were able to obtain acceptable yields of chloroethylphosphonic dichloride by increasing the ethylene concentration in the reaction zone. Measurements of the solubility of ethylene in PCl_3 showed a sharp rise in the ethylene concentration with increasing pressure and decreasing temperature.

a) *Introduction of Oxygen into Solutions of PCl_3 in Liquid Ethylene*

The reaction in liquid ethylene [10] may be conducted either under reflux in a closed vessel, or in an open container. A Dewar flask is suitable for laboratory experiments. Phosphorus trichloride is dissolved in an excess of liquid ethylene, and a thoroughly dispersed, uniform stream of oxygen is passed through the solution. A ratio of 1 mole of PCl_3 to 3–20 moles of ethylene is used. Gases containing oxygen such as air may be employed in place of oxygen, but the yields are then lower.

The reaction starts immediately, with evolution of heat. If a closed vessel is used, the excess ethylene can be recovered and reused without purification. To isolate chloroethylphosphonic dichloride, unreacted starting materials and the phosphorus oxychloride formed in the reaction are removed at normal or reduced pressure, and the residue is distilled *in vacuo*. The yield, based on phosphorus trichloride reacted, is between 38 and 40 %.

b) *Reaction in the Presence of Solvents*

The disadvantage of the process just described is that the reaction must be carried out at −104 °C, the boiling point of ethylene. This is not easy, in view of the exothermic nature of the reaction. Therefore, we attempted to achieve equally good results by operating at higher temperature, in the presence of solvents [11].

Ethylene and oxygen were introduced into a solution at −40 to −70 °C of phosphorus trichloride in a halogenated hydrocarbon, phosphorus oxychloride, or carboxylic ester. When a carboxylic ester is used as solvent, yields are affected by the formation of by-products. Among the halogenated hydrocarbons, methylene chloride, methyl chloride, and ethyl chloride are particularly well suited. In fluorinated hydrocarbons, phosphonylation did not take place at all, and no phosphorus oxychloride formation was observed. Among the carboxylic esters, methyl acetate is particularly useful. Carbon disulfide, benzene, acetonitrile, and ether may also be used. Table 1 shows how the yield depends on the solvent used.

Table 1. Effect of the solvent used on the yield of chloroethylphosphonic dichloride at −65 °C. Ratio of solvent to PCl_3 = 2:1

Solvent	Yield [mole-%]
None	5
Carbon disulfide	5
Ethyl bromide	6
Propyl chloride	6
Methyl acetate	15
Methylene chloride	28
Methyl chloride	30
Ethyl chloride	34

Even in the presence of solvents, the reaction is strongly dependent on the temperature, the yield increasing with decreasing temperature. Best results are obtained at temperatures between −60 and −70 °C. The ethylene: oxygen ratio should be at least 2:1; but it may be varied within a wide range. Thorough dispersion of the gas in the reaction zone is important. The reaction mixture is worked up as described under a). After recovery by distillation, the solvent may be reused.

[7] German. Patent 910649 (Jan. 5th, 1943), Farbwerke Hoechst AG.; inventor: *R. Graf*.

[8] *R. Graf*, Chem. Ber. *85*, 9 (1952).

[9] *L. Z. Soborovskiy, Y. M. Zinov'ev*, and *M. A. Englin*, Dokl. Akad. Nauk SSSR *67*, 293 (1949).

[10] German. Patent 1103922 (June 20th, 1959), Farbwerke Hoechst AG.; inventors: *H. Vilcsek* and *F. Rochlitz*.

[11] German. Patent 1108687 (July 31st, 1959), Farbwerke Hoechst AG.; inventors: *F. Rochlitz* and *H. Vilcsek*.

c) *Reaction under Pressure*

Even in the presence of solvents, the reaction must be conducted at −50 to −70 °C, to achieve optimum yields. In an autoclave, however, a temperature of 20 °C suffices [12]. Ethylene is introduced with agitation into an autoclave containing phosphorus trichloride until a constant pressure of 40 atm is attained. Oxygen is then admitted intermittently through an automatic pressure regulator until the temperature ceases to rise. The autoclave is vented and the reaction mixture worked up by distillation. The yield, based on phosphorus trichloride consumed, is about 40 %.

Continuous feeding of oxygen into the reaction mixture is also possible. In the batch process, the introduction of oxygen must occur in small portions to avoid a violent reaction. In each case, good mixing is required.

2. Properties and Reactions of β-Chloroethylphosphonic Dichloride

β-Chloroethylphosphonic dichloride is a colorless liquid with a pungent odor, and attacks mucous membranes; b.p. 81 °C/5 mm Hg or 120 °C/14 mm Hg; refractive index $n_D^{20} = 1.4980$; density at 20 °C: 1.5448.

The reactions of the chlorine atoms attached to the phosphorus and the reactivity of the chlorine atom at the β-position of the ethyl radical make this an interesting compound. The corresponding acid, its esters, thioesters, and amines can be readily prepared in the presence of bases. The esters react through the chlorine at the β-position with alcohols, thiols, alkali sulfides, and amines, Particularly noteworthy is the elimination of hydrogen chloride to afford vinylphosphonic dichloride.

II. Vinylphosphonic Dichloride

1. Preparation

β-Chloroethylphosphonic dichloride undergoes elimination of hydrogen chloride yielding vinylphosphonic dichloride:

$$ClCH_2CH_2POCl_2 \rightarrow H_2C{=}CHPOCl_2 + HCl$$

This product was first prepared by *Schimmelschmidt* et al. from bis-(β-chloroethyl) vinylphosphonate and phosphorus pentachloride [13, 14]. Elimination of HCl from chloroethylphosphonic dichloride can be accomplished by simply heating [15] or by the action of tertiary amines at room temperature [16].

a) *Elimination of HCl with Tertiary Amines*

β-Chloroethylphosphonic dichloride is dissolved in ether, tetrahydrofuran, dioxan, benzene, toluene, xylene, chlorobenzene, carbon tetrachloride, methyl chloride, nonylnaphthalene, or dodecylbenzene. A stoichiometric amount of a tertiary amine, *e.g.* trimethylamine, triethylamine, tributylamine, dimethylaniline, pyridine, or *N*-methylquinoline, is gradually added to this solution at room temperature. If the boiling point of the solvent used is below that of vinylphosphonic dichloride, the amine hydrochloride is filtered off, the solvent is distilled off, and vinylphosphonic dichloride recovered by distillation *in vacuo*. If the boiling point of the solvent (*e.g.* phenylcyclohexane, dodecylbenzene, or dimethylnaphthalene) is above that of vinylphosphonic dichloride, and the amine hydrochloride is thermally stable, vinylphosphonic dichloride distills over first. The tertiary base is recovered from its hydrochloride by use of a 10–30 % solution of an alkali earth hydroxide or carbonate.

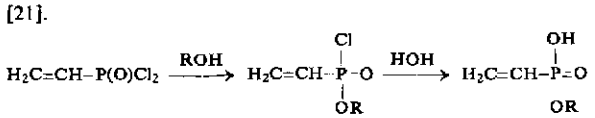
b) *Elimination of HCl by Heating*

β-Chloroethylphosphonic dichloride is heated to 200 to 280 °C in the absence of solvent. After the evolution of hydrogen chloride has subsided, the residue is distilled *in vacuo*. Alternatively, vinylphosphonic dichloride is isolated as fast as it is formed, by distillation through a column of adequate fractionating capacity. Thus, a product of high purity is obtained. In a modification of the process, nitrogen or CO_2 is passed through boiling chloroethylphosphonic dichloride and the vapors are conducted through a heated tube at 240–270 °C. Yield: 85–95 %.

2. Properties and Reactions

Vinylphosphonic dichloride is a colorless liquid with a pungent odor; b.p. 57 °C/5.5 mm Hg; refractive index $n_D^{20} = 1.4818$; density at 20 °C: 1.405. The reaction of vinylphosphonic dichloride with alcohols and phenols gives esters [17]. Some of these can also be prepared by other methods, *e.g.* by elimination of HCl from β-chloroethylphosphonic esters [5, 18, 19] or by elimination of HBr from β-bromoethylphosphonic esters [20]. It is particularly easy to prepare bis-(β-chloroethyl) vinylphosphonate from tris-(β-chloroethyl) phosphite [6].

The reaction of one mole of vinylphosphonic dichloride with one mole of an alcohol yields the alkoxy acid chloride; this reacts further, for example with water, affording monoesters [21].



With amines, first phosphonamidic chlorides, then phosphonic diamides (phosphonamides) are formed.

[12] German. Patent 1123667 (February 16th, 1960), Farbwerke Hoechst AG.; inventors: *C. Heuck*, *F. Rochlitz*, and *H. Vilcsek*.

[13] German. Patent 1020019 (March 14th, 1956), Farbwerke Hoechst AG.; inventors: *K. Schimmelschmidt* and *W. Denk*.

[14] German Patent 1023034 (May 24th, 1956), Farbwerke Hoechst AG.; inventors: *K. Schimmelschmidt* and *W. Denk*.

[15] German Patent Appl. 1138770 (Oct. 21st, 1959), Farbwerke Hoechst AG.; inventors: *F. Rochlitz* and *H. Vilcsek*.

[16] French Patent 1269130 (June 20th, 1960), Farbwerke Hoechst AG.; inventors: *F. Rochlitz* and *H. Vilcsek*.

[17] German Patent 1041045 (July 17th, 1957), Farbwerke Hoechst AG., inventors: *K. Schimmelschmidt* and *W. Denk*.

[18] *G. M. Kosolapoff*, J. Amer. chem. Soc. *70*, 1971 (1948); German Patent 1006414 (Jan. 22nd, 1955), Farbwerke Hoechst AG.; inventors: *E. O. Leupold* and *H. Zorn*.

[19] *E. L. Gefter*, Zhur. Obshchei Khim. *28*, 2500 (1958); *G. S. Kolesnikov*, *E. F. Rodionova* and *L. S. Fedorova*, Vysokomolekulyarnye Soedineniya *1*, No. 3, 367 (1959).

[20] *J. C. Cadogan*, J. chem. Soc. (London) *1957*, 4154.

[21] Belg. Patent 600543 (February 17th, 1961), Farbwerke Hoechst AG.; inventors: *F. Rochlitz* and *H. Vilcsek*.

Vinylphosphonic dichloride reacts nearly quantitatively with water to give vinylphosphonic acid of high purity [22, 23]. This compound (m.p. about 42 °C) crystallizes readily; it is an acid of medium strength (pK = 1.70 and 7.10) with good solubility in water, acetone, ethyl acetate, and the lower alcohols.

Vinylphosphonic esters react at the double bond with alcohols [24], thiols [25], amines [26], and sodium bisulfite [17]. Esters and chlorides of vinylphosphonic acid can be used as dienophiles in Diels-Alder reactions [27,28].

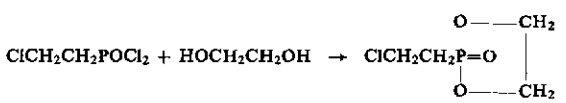
All the vinylphosphonic derivatives cited herein undergo copolymerization with olefins; some are capable of homopolymerization.

B. Use in the Preparation of Synthetic Resins

I. Polycondensations

1. Phosphorus-containing Polyesters

Below 25 °C, β-chloroethylphosphonic dichloride and other phosphonic dichlorides react with glycols to give cyclic esters.



$$ClCH_2CH_2POCl_2 + HOCH_2CH_2OH \rightarrow ClCH_2CH_2P(=O)(-O-CH_2)-O-CH_2$$

The yields can be improved by addition of tertiary amines [29]. Increasing amounts of polymers are formed when the temperature is raised. These polymers are sparingly soluble or insoluble in water [30]. Polyfunctional alcohols, such as glycerol, yield water-soluble or insoluble products, depending on the proportions used. Polymeric phosphorus compounds of this type with free alcoholic hydroxyl groups can be condensed to give polyesters [30].

Since polyester resins are frequently used in the construction and electric industries and in the building of automobile bodies, attempts have been made to reduce their flammability, for example by using halogenated dicarboxylic acids for their synthesis [31], or by addition of antimony compounds [32] or phosphorus compounds [33,34]. Unsaturated phosphonic acid derivatives such as diallyl phosphonate [35] and vinylphosphonic esters [36,37] have also been proposed as monomers imparting fire-resistance.

Partial replacement of dicarboxylic acids in a polyester with β-chloroethylphosphonic dichloride also yields difficultly flammable products [37]. These are prepared by treating polyesters containing an excess of glycol with the phosphonic dichloride, or the latter is first allowed to react with an excess of glycol, and the remaining free hydroxyl groups are then esterified with a dicarboxylic acid. Such phosphorus-containing polyesters may be mixed with styrene and molded. A minimum phosphorus content of 1.5 % is needed for adequate fire resistance. In general, 3–5 % is used. Polyester resins of this structure are self-extinguishing, possess good mechanical properties, and are stable to light.

2. Phosphorus-containing Epoxy Resins

Epoxy resins with free hydroxyl groups also react with β-chloroethylphosphonic dichloride. In this case, however, the epoxide rings are not attacked. The reaction is carried out at 0–20 °C in the presence of tertiary amines [38]. The phosphorus-containing polycondensates are liquids or solids, depending on the starting compound. Common hardening agents convert these materials into cross-linked, insoluble, infusible masses, which possess good mechanical properties and which are hard to burn.

3. Phosphorus-containing Polyamides

Polycondensation of β-chloroethylphosphonic dichloride with polyfunctional amines affords polyphosphonamides. A solution of the phosphonic chloride in an organic solvent immiscible with water, *e.g.* methylene chloride, and an aqueous solution of an alkali are added dropwise to an aqueous solution of the amine. During the reaction, the pH of the aqueous phase should be kept above 7. The resulting product is either an oil or a solid. Naturally, it is also possible to add the amine and sodium hydroxide to the solution of the phosphonic chloride. The reaction generally occurs with all poly-

[22] German Patent 1023033 (April 25th, 1956), Farbwerke Hoechst AG.; inventors: *K. Schimmelschmidt* and *W. Denk*.

[23] Belg. Patent 596622 (Oct. 31st, 1960), Farbwerke Hoechst AG.; inventors: *F. Rochlitz* and *H. Vilcsek*.

[24] U.S. Patent 2535172 (February 25th, 1949), United States Rubber; inventor: *P. O. Tawney*.

[25] U.S. Patent 2535174 (Dec. 26th, 1950), United States Rubber, inventor: *P. O. Tawney*.

[26] U.S. Patent 2570503 (May 11th, 1951), United States Rubber; inventor: *P. O. Tawney*. *A. N. Pudovik*, Dokl. Akad. Nauk SSSR *80*, 65 (1951); *A. N. Pudovik*, Zhur. Obshch. Khim. *23* (85), 263 (1953); *A. N. Pudovik* and *G. M. Denisova*, ibid. *23*, 263 (1953).

[27] *A. N. Pudovik* and *M. G. Imaev*, Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1952*, 916.

[28] German Patent 1044074 (Aug. 1st, 1956), Farbwerke Hoechst AG.; inventors: *H. Krämer*, *G. Messwarb*, and *W. Denk*.

[29] *V. V. Korshak*, *I. A. Gribova*, and *M. A. Andreeva*, Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1957*, 631.

[30] French Patent 1196971 (Nov. 29th, 1957), Farbwerke Hoechst AG., inventors: *W. Starck*, *H. Vilcsek*, *J. Winter*, and *F. Rochlitz*.

[31] U.S. Patent 2783215 (Sept. 10th, 1952), Hooker El. Chem. Corp.; inventor: *P. Robitschek* and *P. Robitschek*, Ind. Engng. Chem. *46*, 1628 (1954).

[32] U.S. Patent 2680105 (Sept. 28th, 1951), Allied Chemical and Dye Corp.; inventor: *T. Baker*.

[33] U.S. Patent 2819247 (June 10th, 1953), American Cyanamide Corp.; inventor: *L. A. Lundberg*, cf. German Patent 1060136 (June 10th, 1954), American Cyanamide Corp.; inventor: *L. A. Lundberg*.

[34] French Patent 1213171 (Nov. 7th, 1958), American Cyanamide Corp.; inventor: *L. A. Lundberg*.

[35] U.S. Patent 2586884 (Oct. 11th, 1947), Victor Chemical; inventor: *A. Fon Toy*, U.S. Patent 2586885 (Oct. 11th, 1947), Victor Chemical; inventor: *A. Fon Toy*; U.S. Patent 2918449 (Jan. 27th, 1955), Victor Chemical; inventor: *A. Fon Toy*; cf. German Patent 1041251 (Dec. 19th, 1955), Victor Chemical; inventor: *A. Fon Toy*.

[36] Brit. Patent 866384 (June 5th, 1958), Monsanto Chem. Corp.

[37] German Patent 1128652 (Dec. 31st, 1956), Farbwerke Hoechst AG.; inventors: *W. Starck*, *H. Vilcsek*, *J. Winter*, and *F. Rochlitz*.

[38] German Patent 1113826 (Feb. 13th, 1958), Farbwerke Hoechst AG.; inventors: *O. Mauz*, *F. Rochlitz*, and *D. Schleede*.

functional amines. The reaction with higher amines, such as hexamethylene diamine, is particularly smooth.

The phosphorus-containing polyamides are either insoluble or only sparingly soluble in most organic solvents. They are somewhat soluble and swell in methanol, ethanol, and butanol. They dissolve readily in acids such as formic or acetic acid and may be reprecipitated from these solutions by neutralization with alkali. They undergo further reactions with aldehydes and isocyanates via the amide hydrogens leading to products with varying degrees of cross-linking. These are no longer capable of swelling; however, they dissolve in acids, such as acetic acid, forming salts.

II. Polymerization Reactions

1. Polymerization of Vinylphosphonic Dichloride

In contrast to other unsaturated phosphonic dichlorides, such as propenylphosphonic dichloride, vinylphosphonic dichloride readily undergoes polymerization. It is capable of both homopolymerization and copolymerization with other compounds containing single or multiple unsaturated bonds [39, 40]. Homo- and copolymerizations occur on heating to above 100 °C; however, it is preferable to use free-radical formers, *e.g.* peroxides or azo compounds, as initiators. Azodiisobutyronitrile is particularly suitable.

The polymers and copolymers, *e.g.* with styrene or methacrylates, are viscous to hard transparent products that fume on exposure to air (hydrogen chloride evolution) and react vigorously with water. The homopolymers dissolve readily in many solvents, *e.g.* acetone and methylene chloride. The copolymers are mostly cross-linked and either partly soluble or altogether insoluble products. Because of their acid chloride structure, these polymers react with alcohols, phenols, thiols, amines, ammonia, or silanols at −20 to 100 °C [41]. Metal oxides, amines, or metal chlorides catalyze the reaction.

2. Polymerization of Vinylphosphonic Acid

Again in contrast to other unsaturated phosphonic acids, vinylphosphonic acid readily undergoes polymerization. Its homopolymerization is readily initiated by heating to 170 °C, by ultraviolet irradiation, or by addition of free-radical formers [42], whereas propenyl- or allylphosphonic acids are capable only of copolymerizing with other monomers.

To facilitate cooling, polymerization in solution is preferred. Water, esters, and alcohols are suitable solvents. Solvents dissolving both monomers and polymers may be used; the polymer must then be recovered by precipitation. However, it is often advantageous to use a solvent, such as ethyl acetate, in which only the monomer dissolves. A nearly quantitative yield of a powder of polyvinylphosphonic acid is thus obtained.

Depending on their degree of polymerization, polyvinylphosphonic acids are viscous liquids or powdery solids soluble in water and alcohols. They are used in protective coatings [43], fireproofing [44], and other applications.

In the presence of common polymerization accelerators, vinylphosphonic acid undergoes copolymerization with vinyl chloride [40] and other monomers [45]. The resulting products improve the dyeability and fire-resistance of textiles and find use as lacquer components.

3. Polymerization of Vinylphosphonic Esters

Vinylphosphonic esters are relatively difficult to polymerize. For example, dimethyl vinylphosphate must be heated under nitrogen for 80 hours at 50 °C in the presence of 2 % benzoyl peroxide to attain a 90 % yield of polymer [46]. The polymerization of the diethyl ester requires nearly 200 hours. Compounds with longer alkyl groups polymerize somewhat faster. The polymer from the bis-(β-chloroethyl) ester is a viscous, transparent liquid [47].

Copolymerization of the esters proceeds much more readily. Suitable comonomers are acrylates, acrylonitrile, methacrylates, styrene [48], vinyl acetate, and others. Polymerization in the aqueous phase is particularly versatile [49]. Copolymerization of dimethyl vinylphosphonates with other monomers yields fireproof plastics; copolymerization of higher esters (*e.g.* isooctyl) of vinylphosphonic acid leads to internally plasticized products.

Received, July 5th, 1962 [A 246/60 IE]

[39] German Patent 1027874 (May 7th, 1956), Farbwerke Hoechst AG.; inventors: *G. Messwarb*, *W. Denk*, and *H. Scherer*; German Patent 1032537 (Sept. 20th, 1956), Farbwerke Hoechst AG.; inventors: *H. Krämer*, *G. Messwarb*, and *W. Denk*.

[40] *E. F. Rodionova* and *G. S. Kolesnikov*, Vysokomolekulyarnye Soedineniya *3*, 459 (1961).

[41] German Patent 1029156 (Sept. 21st, 1956), Farbwerke Hoechst AG.; inventors: *H. Krämer*, *G. Messwarb*, and *W. Denk*.

[42] German Patent 1106963 (Nov. 11th, 1959), Farbwerke Hoechst AG.; inventors: *W. Herbst*, *F. Rochlitz*, and *H. Vilcsek*.

[43] Belg. Patent 597237 (Nov. 18th, 1960), Farbwerke Hoechst AG.; inventors: *W. Herbst*, *F. Rochlitz*, *H. Vilcsek*, and *E. Wagner*.

[44] Belg. Patent 604507 (May 31st, 1960), Farbwerke Hoechst AG.; inventors: *H. Sommer*, *W. Schubert*, *F. Rochlitz*, and *H. Vilcsek*.

[45] German Patent Appl. 1135176 (Jan. 8th, 1960), Farbwerke Hoechst AG.; inventors: *F. Rochlitz*, *H. Vilcsek*, and *G. Koch*.

[46] *G. S. Kolesnikov* and *I. F. Rodionova*, Vysokomolekulyarnye Soedineniya *1*, 641 (1959).

[47] *M. I. Kabachnik*, Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1947*, 233.

[48] *C. L. Arcus* and *G. L. Matthews*, J. chem. Soc. (London) *1956*, 4607; Chem. and Ind. *28*, 890 (1958).

[49] German Patent 1125658 (Aug. 28th, 1959), Farbwerke. Hoechst AG., inventors: *G. Koch*, *M. Lederer*, and *F. Rochlitz*.

Errata

R. BRILL: The Structure of Ice
Angew. Chem. internat.Edit. *1*, 563 (1962)

Figure 1 on page 563 was reproduced from *Zemansky*: Heat and Thermodynamics. McGraw-Hill, New York 1957, p. 205, by permission of the publishers.

On page 567, right column, first line after the equation, read: ν = frequency of *libration* of the water molecules in ice.

O. THUMM and J. BENZ: Reactivity of Dichloro- and Trichloropyrimidyl Dyes and the Sensitivity of Their Dyeings to Hydrolysis
Angew. Chem. internat. Edit. *1*, 568 (1962)

Page 570, Table 1: read IV instead of VI.

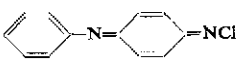
The Formation of Aniline Black-like Compounds from Quinonanil-*N*-chloroimide

By Dr. Helmut Gies

Farbwerke Hoechst AG. vormals Meister Lucius & Brüning
Frankfurt/Main (Germany)

Published on the occasion of the centenary of the founding of Farbwerke Hoechst on January 11th, 1963.

In the pure state, quinonanil-*N*-chloroimide (I) is stable at 20 °C, contrary to data in the literature [1]. When brought

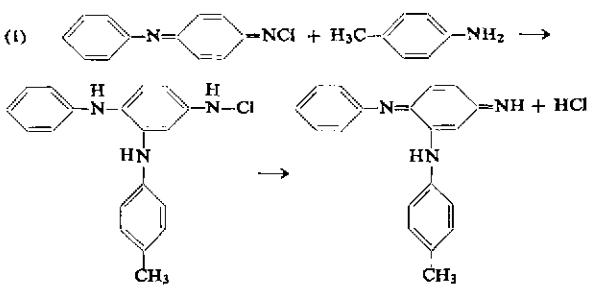


m.p. 74–75 °C

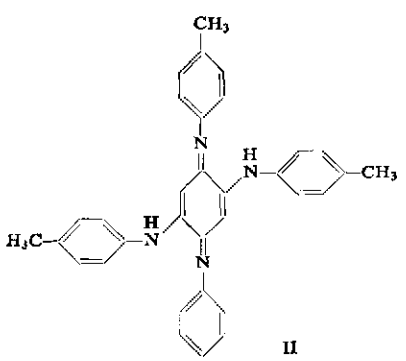
into contact with small amounts of acids, it reacts in solution or in bulk, sometimes very violently, to form aniline black-like compounds. This reaction is also initiated by other compounds which form hydrogen ions during a preliminary reaction with I. These can be divided into two groups.

Group 1: Primary and secondary amines. These compounds probably react with I by 1,4-additions in the manner in which anilidoquinones are formed, *e.g.* in accordance with equation (1).

(1)



The hydrochloric acid liberated reacts with I, forming 1-imido benzoquinone-anil [2]. This polymerizes to aniline black-like compounds by way of emeraldine or azophenine, depending on the hydrogen ion concentration [1,3]. When I was treated with excess *p*-toluidine in alcoholic solution the crystalline, brown compound II was isolated [4].

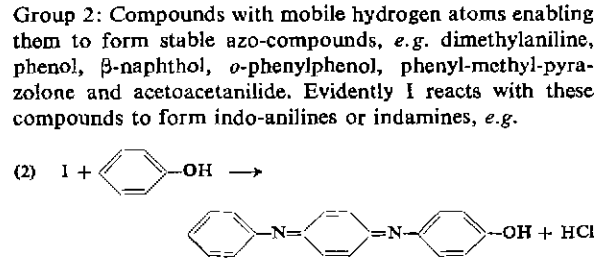


II

There is no formation of azo-compound, as might also have been expected.

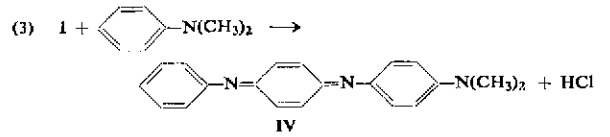
Group 2: Compounds with mobile hydrogen atoms enabling them to form stable azo-compounds, *e.g.* dimethylaniline, phenol, β-naphthol, *o*-phenylphenol, phenyl-methyl-pyrazolone and acetoacetanilide. Evidently I reacts with these compounds to form indo-anilines or indamines, *e.g.*

(2)



III

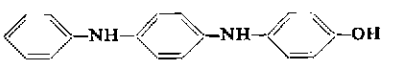
(3)



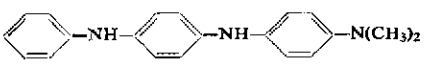
IV

The hydrochloric acid liberated will then act as described in group 1.

An analogous reaction is known with benzoquinone-bis-chloroimide [5]. By using reaction *(1)* with a large excess of phenol or dimethylaniline, the indo-aniline III and the indamine IV were also successfully prepared and then reduced with zinc and glacial acetic acid. The reduction products V and VI were identified by mixed melting points [6] and by analyzing the acylation products.



V



VI

These reactions of I gain in importance by the fact that they can also take place in fibres or films made from plastics. This process is particularly useful with polyester materials. The resultant black colors are characterized by great fastness.

Received, July 4th, 1962 [Z 363/190 IE]

[1] *W. Nover*, Ber. dtsch. chem. Ges. *40*, 288 (1907).

[2] *R. Willstätter* and *E. Mayer*, Ber. dtsch. chem. Ges. *37*, 1495 (1904).

[3] *S. Goldschmidt* and *B. Wurzschmitt*, Ber. dtsch. chem. Ges. *55*, 3224 (1922).

[4] *O. Fischer* and *E. Hepp*, Ber. dtsch. chem. Ges. *20*, 2480 (1887).

[5] *R. Nietzki* and *R. Otto*, Ber. dtsch. chem. Ges. *21*, 1745 (1888).

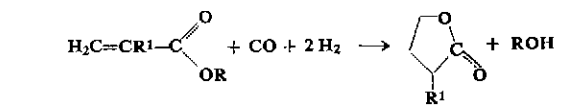
[6] *G. Heller*, Liebigs Ann. Chem. *418*, 272 (1918).

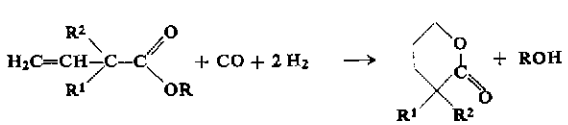
Lactones by Hydroformylation of Unsaturated Carboxylic Esters

By Dr. J. Falbe and Prof. Dr. F. Korte

Shell Grundlagenforschung GmbH.
Schloß Birlinghoven, Siegkreis (Germany)

Aliphatic and alicyclic α,β- and β,γ-unsaturated carboxylic esters react with CO/H_2 in the presence of catalytic amounts of dicobalt octacarbonyl, Raney cobalt, or cobalt salts as catalysts at 200 to 350 °C and 100 to 300 atm to produce saturated mono- and bicyclic lactones in yields of 70–90%. In some instances, it is also possible to use the unsaturated carboxylic acids directly as starting material. Acrylic esters give γ-butyrolactones while δ-valerolactones are obtained from vinyl acetates.

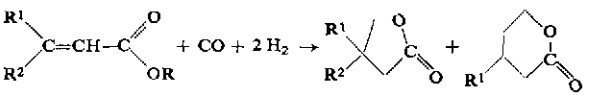




$R = CH_3, C_2H_5$; $R^1 = H, CH_3$; $R^2 = CH_3$

With long-chain carboxylic esters, partial migration of the carbon-carbon double bond takes place under the given

reaction conditions. Thus, both γ-lactones and δ-lactones are obtained from unsaturated, α,β-unsaturated esters: *e.g.* methyl crotonate, gives 72% δ-valerolactone alongside 20% β-methyl-γ-butyrolactone, while with β,β-dimethylacrylic esters, because of complete isomerization, only β-methyl-δ-valerolactone is obtained in 88.5% yield.



$R^1 = H$, $R^2 = CH_3$	20%	72%
$R^1 = R^2 = CH_3$	0%	88.5%

The unsaturated starting materials can be substituted by alkyl, alkylene, ethoxycarbonyl, and other functional groups. Alicyclic unsaturated carboxylic esters, such as cyclohexenyl, cyclopentenyl, and cycloheptenylisobutyric esters, lead to homologues of iridomyrmecin [1].

Surprisingly, it was also possible to convert cinnamates into β-phenyl-γ-butyrolactone in 34% yield by employing stoichiometric amounts of the catalyst, although, according to various authors [2], these esters were not susceptible to hydroformylation reactions, giving hydrogenation products only.

Publication withheld until now at the express wish of the authors. Received, June 13th, 1962 [Z 359/191 IE]

[1] *F. Korte, J. Falbe,* and *A. Zschocke,* Tetrahedron *6,* 201 (1959).

[2] *M. Orchin,* Advances in Catalysis *5,* 385 (1953); *R. Hasek,* Organic Chemical Bulletin, *27* (1955) – published by theResearch Laboratories of the Eastman Company.

β-Dicarbonyl Compounds as Protecting Agents for Amino Groups in Peptides Syntheses [1]

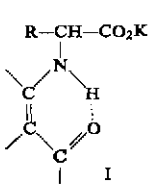
By Prof. Dr. Elisabeth Dane [*], Dr. F. Drees, Dr. P. Konrad and Dr. T. Dockner

Institut für Organische Chemie der Universität München (Germany)

In the presence of methanolic potassium hydroxide, amino acids react with β-dicarbonyl compounds to give the potassium salts of the corresponding azomethines. We have found that, among the potassium salts investigated, those obtained with benzoylacetone, acetylacetone, and ethyl cyclopentan-2-one-1-carboxylate are sufficiently stable to be suitable for use as protecting groups for amino groups in peptide syntheses.

The potassium salts of the β-dicarbonyl-amino acid derivatives can generally be recrystallized from methanol or ethanol, if necessary with the addition of small amounts of water. The yields range from 65 to 95%. In some cases, the protected amino acid derivatives can also be obtained from the corresponding potassium salts.

The azomethines obtained from the dicarbonyl compounds can be assumed to have mainly the enamine conformation (I),



I

stabilized by a hydrogen bond. The infrared spectra of the azomethines obtained from ethyl glycinate and dicarbonyl compounds contain NH-absorption bands. The positions of the NH- and CO-bands of the benzoylacetone and acetylacetone derivatives suggest the existence of especially strong chelation.

In Table 1 some of the peptide esters synthesized using β-dicarbonyl protecting groups are summarized.

These compounds were prepared from the protected potassium salts or amino acids using the dicyclohexylcarbodiimide method. The yields lay between 65 and 87%. The

Table 1

Protected peptidester	M.p. [°C]	Peptide
BA-Gly-Gly-OEt	133—134	Gly-Gly-OH [a]
BA-DL-Ser-Gly-OEt	115—120	
BA-DL-Meth-Gly-OEt	103—106	DL-Meth-Gly-OH [a]
BA-L-Leu-Gly-OEt	105—107	
BA-D-Val-Gly-OEt	97—98	
AC-DL-Ala-Gly-OEt	110	
CP-DL-Ala-Gly-Gly-OEt	123—126	DL-Ala-Gly-Gly-OH [a]
CP-L-Ala-Gly-OEt	138—140	L-Ala-Gly-OH [a, b]
CP-OBz-DL-Ser-Gly-OEt	83—84	OBz-DL-Ser-Gly-OH

Abreviations used for the protecting groups: BA = Benzoylacetone; AC = Acetylacetone; CP = Ethylcyclopentan-2-one-1-carboxylate; Et = C_2H_5.
[a] = chromatographically pure.
[b] $[\alpha]_D^{27} = +49.8°$ (c = 2.6 in water).

cyanomethyl ester method of *R. Schwyzer* [2] also proved to be useful. The cyanomethyl esters were prepared by reacting the potassium salts with chloroacetonitrile.

The protecting groups can be split off by a short treatment with 2N hydrochloric or acetic acid. Saponification of the protected peptide esters with aqueous or methanolic potassium hydroxide gives high yields of the potassium salts of the corresponding peptides.

Received, August 20th, 1962 [Z 344/176 IE]

[*] Dedicated to Prof. *Otto Bayer* on his 60th birthday.

[1] German patent application submitted on April 27th, 1961.

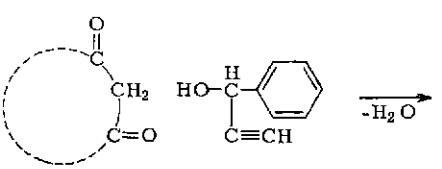
[2] *R. Schwyzer, B. Iselin,* and *M. Feurer,* Helv. chim. Acta *38,* 69 (1955).

A New Synthesis of Condensed Furan Derivatives

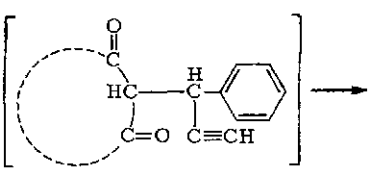
By Dr. J. Reisch [1]

Institut für Pharmazie und Lebensmittelchemie der Universität Münster (Germany)

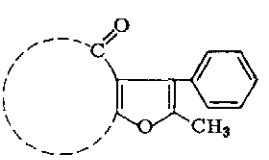
The preparation of condensed furan derivatives from α-alkynyl-β-dicarbonyl compounds has recently been described [2]. Furans are also accessible by the interaction of 1-phenyl-2-propynol and cyclic β-dicarbonyl compounds (I) in the presence of concentrated sulfuric acid or boron trifluoride in glacial acetic acid at 100 °C for 30 min. The intermediates (II) cyclize to III.



I



II



III

Thus, barbituric acid affords 5,6-(2′-methyl-3′-phenylfurano)-uracil, m.p. 268 °C (decomp.) in 75% yield. Similarly, indane-1,3-dione yields 1,2-(2′-methyl-3′-phenylfurano)oxoindene (85%; m.p. 147–148 °C), 4-hydroxycoumarin yields 3,4-(2′-methyl-3′-phenylfurano)coumarin (65%; m.p. 199 °C), and 4-hydroxycarbostyril yields 3,4-(2′-methyl-3′-phenylfurano)-carbostyril (60%; m.p. 264 °C).

Received, September 10th, 1962 [Z 357/184 IE]

[1] Part IV of the series "Furans and Pyrans" by *K. E. Schulte, J. Reisch* et al.

[2] Parts I and II: *K. E. Schulte, J. Reisch*, and *A. Mock*, Arch. Pharmaz. *295*, 627, 645 (1962); Part III: *K. E. Schulte, J. Reisch*, and *K. H. Kauder, ibid.*, in press.

Preparation of Solutions of Anhydrous Perchloric Acid in Halogenated Hydrocarbons and of Perchloric Acid Monohydrate

By Prof. Dr. F. Klages and P. Hegenberg

Institut für Organische Chemie
der Universität München (Germany)

The preparation of solutions of anhydrous perchloric acid in organic solvents was hitherto very laborious and often also dangerous, since pure perchloric acid explodes very easily [1]. By extracting a mixture of oleum and 70% perchloric acid with methylene or ethylene chloride, fairly concentrated perchloric acid solutions are readily obtained (ground glass joints must not be greased). For example, up to 90% of the perchloric acid can be extracted with methylene chloride from a mixture of one part by volume of 70% perchloric acid and four parts by volume of 25% fuming sulfuric acid. The solutions contain up to 0.3 g of $HClO_4$ per cm^3 according to the quantity of solvent used and fume strongly in air. In the mixture proportions specified, they are almost free of sulfuric acid (molar ratio $H_2SO_4/HClO_4 = 0.004:1$) and are absolutely dry, since traces of water immediately precipitate insoluble perchloric acid monohydrate. A fairly pure monohydrate (m.p. 48–49 °C) can be produced by passing in moist air, if no more than 50% of the perchloric acid contained in the solution is allowed to be converted. Otherwise, there is the danger of aggregation of the monohydrate precipitate.

Received, October 1st, 1962 [Z 360/193]

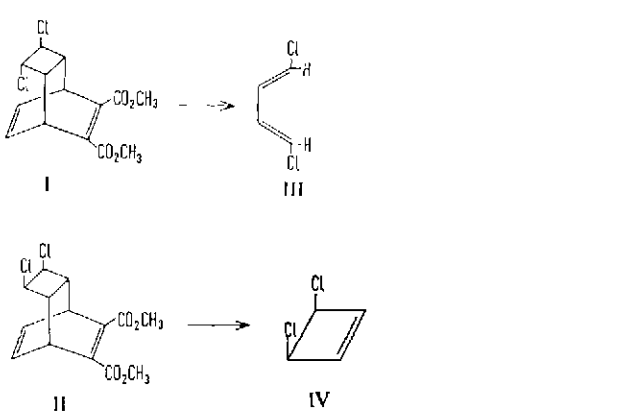
[1] *M. Gomberg*, J. Amer. chem. Soc. *45*, 418 (1923).

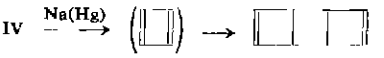
The Dimer of Cyclobutadiene

By Prof. Dr. C. D. Nenitzescu, Dr. Margarete Avram, Elise Marica, I. G. Dinulescu, and G. Mateescu

Chemical Institute of the Academy of the R. P. R.
Bucharest (Rumania)

The Diels-Alder reaction between cyclooctatetraene dichloride and dimethyl acetylenedicarboxylate gives, besides the adduct I (m.p. 126 °C) [1], a second compound II (m.p. 91 °C), which is isomeric with I, probably on account of geometric isomerism of the chlorine atoms: this assumption is supported by the infrared spectra of the two compounds. In addition to methyl phthalate, thermal cleavage of I affords mainly the solid *trans,trans*-1,4-dichlorobutadiene (III; m.p. 37–38 °C) obtained by *Criegee* [2]. Thermal decomposition of compound II gives a liquid (b.p. 34 °C/2 mm Hg), which yields *meso*-dichlorosuccinic acid on ozonolysis and therefore is *cis*-1,2-dichlorocyclobutene (IV). On shaking a solution in ether of IV with 1% sodium amalgam at room temperature, the dimer (C_8H_8) of cyclobutadiene was obtained in *ca.* 30% yield and was identified by its infrared spectrum [3], by elementary analysis, and by the infrared spectrum [5] of its silver nitrate complex $C_4H_4 \cdot AgNO_3$ [4]. Treatment of the solid 1,4-dichlorobutadiene with sodium amalgam under the same conditions left most of it in an unchanged state.





Received, October 1st, 1962 [Z 358/187 IE]

[1] *W. Reppe, O. Schlichting, K. Klager*, and *T. Toepel*, Liebigs Ann. Chem. *560*, 1 (1948).

[2] *R. Criegee, W. Hörauf*, and *W. D. Schellenberg*, Chem. Ber. *86*, 126 (1953).

[3] *M. Avram, G. Mateescu, I. G. Dinulescu, E. Marica*, and *C. D. Nenitzescu*, Tetrahedron Letters *1961*, No. 1, 21.

[4] *M. Avram, E. Marica*, and *C. D. Nenitzescu*, Chem. Ber. *92*, 1088 (1959).

[5] *H. P. Fritz, J. F. W. McOmie*, and *N. Sheppard*, Tetrahedron Letters *1960*, No. 26, 35.

Redox Resins Based on Vinyl-9,10-anthraquinones

By Prof. Dr. G. Manecke and Dipl.-Chem. W. Storck

Fritz-Haber-Institut der Max-Planck-Gesellschaft
Berlin-Dahlem (Germany)

We have succeeded in obtaining cross-linked polymers of 2-vinyl-9,10-anthraquinone (I) and styrene with divinylbenzene as cross-linking agent in practically quantitative yield by thermal copolymerisation in dimethyl sulfoxide. After sulfochlorination and subsequent saponification, these give insoluble redox resins which show only limited swelling in water. (I) has been prepared by pyrolysis of 2-(α-acetoxyethyl)anthraquinone [1]; it is also obtainable by another way [2,3]. Use of dimethyl sulfoxide as solvent permits variation of the monomer ratio within wide limits. Addition of n-butylacetate gives polymers with a micropore structure. 2-Vinylanthraquinone can be replaced by 1-vinylanthraquinone [4] but this copolymerises less readily so that the redox capacities attainable lie appreciably lower. These new redox resins are stable over the entire pH range and possess a very low redox potential. They can be reduced easily in alkaline medium with sodium dithionite or sodium borohydride. Oxidation is possible with compounds of redox potential

No.	Mole ratio of I to sum of comonomers	Mole-% cross-linking agent	Exchange capacity [*] [meq./g]	Redox capacity [**] [meq./g]
1	1:10 micropore	12.5	4.375	1.24
2	1:10	12.5	4.491	1.00
3	1:3	6.0	3.563	2.57
4	1:2	6.0	3.080	3.23
5	1:1	8.0	2.021	4.75
6	1:1	6.0	2.042	4.33
7	1:1	4.0	2.084	4.13

[*] Neutral salt splitting of oxidized form determined with 2 N KCl solution.

[**] Determined by oxidation with 0.05 M Fe^{3+} in 2 N H_2SO_4 [5].

below 0.7 V. Stronger oxidizing agents in the usual analytical concentrations slowly attack the resins on prolonged exposure. The Table shows the characteristics of the resins after four oxidation-reduction cycles.

Resins 1 and 2 both have a redox potential of $E_0 = 175 \pm 1$ mV. Oxidative titration was carried out with Ce^{4+} in 0.1 N sulfuric acid in the presence of 1 % anthraquinone-2-sulfonic acid. The index potentials are 14 mV. The titration curve corresponds to a reversible bivalent redox system.

Received, October 8th, 1962 [Z 362/189 IE]

[1] *G. Manecke* and *W. Storck*, Chem. Ber. *94*, 3239 (1961).

[2] *A. Étienne, G. Izoret*, and *F. Moritz*, C. R. hebd. Séances Acad. Sci. *249*, 708 (1959).

[3] *M. Fernandez-Refojo, Yue-Liang Pan, K. A. Kuhn, and H. G. Cassidy*, J. org. Chemistry *25*, 416 (1960).

[4] *L. W. Butz, E. W. J. Butz*, and *A. M. Gaddis*, J. org. Chemistry *5*, 171 (1940).

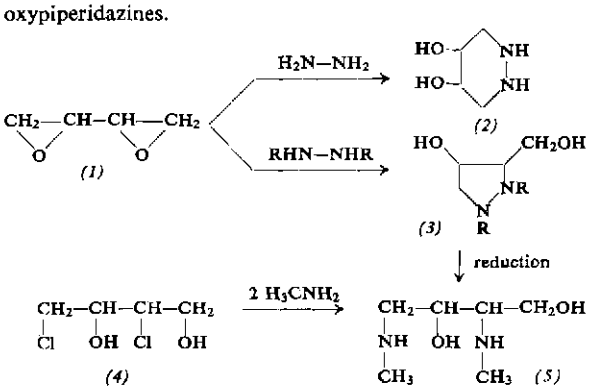
[5] *G. Manecke*, Z. Electrochem., Ber. Bunsenges. physik. Chem. *57*, 189 (1953).

Ring-closure Reaction of Butadiene Dioxide with Hydrazines to Give New Pyrazolidine and Piperidazine Derivatives

By Dr. R. Gabler and Dr. H. R. Meyer

Forschungslaboratorium der Dewey & Almy AG., Zürich (Switzerland)

Earlier work has shown that butadiene dioxide *(1)* adds onto compounds with active hydrogen atoms, *e.g.* primary or secondary amines, exclusively in 1,4-position. It therefore appeared possible that addition of hydrazine or substituted hydrazines onto butadiene dioxide would yield 4,5-dihydroxypiperidazines.



(1) *(2)* *(3)* *(4)* *(5)*

With hydrazine itself in aqueous solution at 20 °C, 4,5-dihydroxypiperidazine was in fact obtained and identified by reductive ring cleavage to give 1,4-diaminobutane-2,3-diol. Starting from (±)-butadiene dioxide, *trans*-4,5-dihydroxypiperidazine *(2)* is formed (m.p. 233 °C, decomp.), while the *meso*-compound gives rise to the *cis*-isomer.

Unexpectedly, the addition of *sym*-dimethylhydrazine onto (±)-butadiene dioxide led to a 1:1-adduct not identical with the compound obtained by *N,N'*-methylation of *(2)* with formaldehyde. Investigation of the structure showed that 1,3-addition had taken place here, giving the pyrazolidine derivative *(3)*, R = CH_3, in 80 % yield. The 5-membered ring structure of *(3)* was indicated by reductive opening of the ring to give *(5)*, m.p. 110 °C, which proved to be identical with the reaction product obtainable from 1,3-dichlorobutane-2,4-diol *(4)* and methylamine.

N,N'-Diethylhydrazine and hydrazobenzene also form 1:1-adducts with *meso*- or (±)-butadiene dioxide in yields of 70–80 %, so that a general and preparatively interesting ring closure reaction seems to occur. Determination of the constitution of the last two adducts has not yet been completed, but there are many indications that they also have 5-membered ring (pyrazolidine) structures.

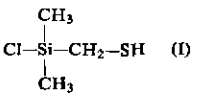
Received, October 8th, 1962 [Z 370/199 IE]

Reactive Silyl-substituted Alkyl Sulfanes

By Dr. M. Wieber and Prof. Dr. M. Schmidt

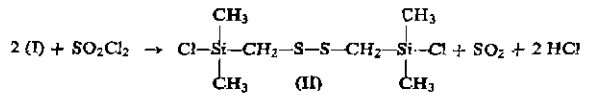
Institut für Anorganische Chemie der Universität Marburg/Lahn (Germany)

On cleavage with dry hydrogen chloride, 1,1,4,4-tetramethyl-1,4-disila-2,5-disulfacyclohexane [1] gives quantitatively 2 moles of dimethylchlorosilylmethylthiol (I), a highly reactive organofunctional chlorosilane.



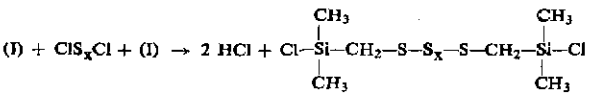
(I)

It is oxidised by sulfuryl chloride to the disulfide (II) according to the equation:

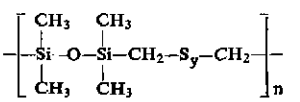


(II)

Condensation with chlorosulfanes leads to higher sulfane derivatives:



Compound II and its higher homologues are colorless liquids (yellow at increased sulfur content); only II can be distilled without decomposition (b.p. 140 °C/1 mm). The new sulfane derivatives react with many other compounds because of the labile nature of the silicon-halogen bond. Thus, hydrolysis results in the formation of sulfur chains of definite composition joined by disiloxane bridges:



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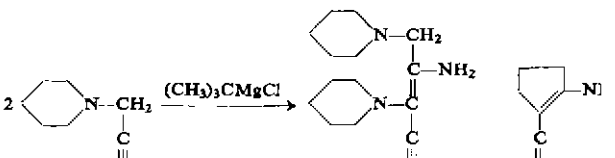
[1] *M. Schmidt* and *M. Wieber*, Inorg. Chem., *1*, 909 (1962).

Dimerisation of Piperidinoacetonitrile under the Influence of a Grignard Reagent

By Prof. Dr. H. Thies, Priv.-Doz. Dr. H. Schonenberger, and K. Qasba

Institut für Pharmazie und Lebensmittelchemie der Universität München (Germany)

Reaction of piperidinoacetonitrile *(1)* with t-butylmagnesium chloride unexpectedly gave rise to a hitherto unknown compound, 3-amino-2,4-dipiperidinocrotonitrile *(2)*, an oil which distils without decomposition *in vacuo*, b.p. 169 °C/0.3 mm Hg and which crystallizes in the cold to form colorless rhombic platelets (m.p. 86–87 °C) when crystallized from isopropanol (yield 71 %). Compound *(2)* is formed from *(1)* by dimerization, the C-atom of the C≡N group of one molecule becoming linked to the α-C-atom of the second molecule.



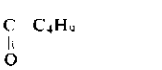
(1) *(2)* *(3)*

Its constitution is indicated by its infrared spectrum, its behaviour with nitrous acid, and its synthesis by the method of *Thompson* [1].

The infrared spectrum shows two typical NH_2 vibrational bands at 3495 and 3380 cm^{-1} and a C=C vibrational band at 1641 cm^{-1}, which are not in the spectrum of the starting material, and the C≡N band at 2186 cm^{-1} is about 50 cm^{-1} lower than that in the starting material owing to conjugation of the C≡N group with the C=C group. The substance evolves 1.04 mole N_2 with HNO_2, in agreement with formula *(2)*, which contains a primary amino group.

Adipodinitrile gave 2-amino-1-cyanocyclopent-1-ene by the method of *Thompson* [1] using sodium t-butoxide as condensing agent. In the same manner, *(2)* can also be obtained from piperidinoacetonitrile. This confirms that *(2)* contains the same enaminonitrile grouping N–C=C–C–NH_2 as does 2-amino-1-cyanocyclopent-1-ene *(3)*.

This new course of reaction seems to be of general importance. It can be attributed to the bulky nature of the organic component in t-butylmagnesium chloride, for n-butylmagnesium chloride and piperidinoacetonitrile do not yield the dimer, the Grignard reagent adding on normally to give n-butyl piperidinomethylketone in 64 % yield.



Received, October 8th, 1962 [Z 382/205 IE]

[1] *Q. E. Thompson*, J. Amer. chem. Soc. *80*, 5485 (1958).

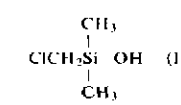
Condensation Reactions with Monochlorinated Trimethylsilanol

By Dr. M. Wieber and Prof. Dr. M. Schmidt

Institut für Anorganische Chemie
der Universität Marburg/Lahn (Germany)

Mixtures of chloromethyl-methylpolysiloxanes have already been prepared by equilibrating cyclic dimethylpolysiloxanes with chloromethyldimethylchlorosilane [1].

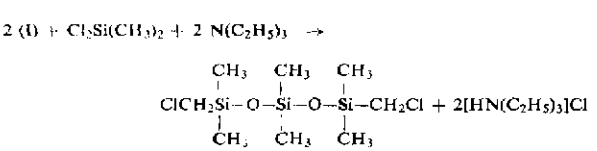
The availability of chloromethyldimethylsilanol (I) – synthetized by hydrolysis of 1,3-bischloromethyltetramethyl-



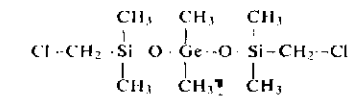
(m.p. –6 °C; b.p. 47 °C/5 mm; $n_D^{20} = 1.4402$; $d_{20}^4 = 1.071$)

disilazane which has recently been prepared [2] – enabled us to prepare definite members of this series in quantitative yields.

Thus, compound I reacts with dimethyldichlorosilane in ether in the presence of stoichiometric quantities of triethylamine to form 1,5-bischloromethyl-hexamethyltrisiloxane (b.p. 109 °C/10 mm, $n_D^{20} = 1.4304$, $d_{20}^4 = 1.023$).



Chlorosiloxanes form higher homologues correspondingly. Compound I reacts in the same manner with dimethyldichlorogermane, giving germanosiloxane.



(b.p. 95–98 °C/2 mm., $n_D^{20} = 1.4495$)

The use of dimethyldichlorostannane does not lead to the corresponding stannosiloxane but to condensation of I to 1,3-bischloromethyl-tetramethyldisiloxane.

Received October 8th, 1962 [Z 366/195 IE]

[1] *J. L. Speier*, J. Amer. chem. Soc. *71*, 273 (1949).

[2] *M. Schmidt* and *M. Wieber*, Inorg. Chem., *1*, 909 (1962).

Introduction of Cystine Bridges into Collagen [*]

By Dr. F. Schade and Prof. Dr. H. Zahn

Deutsches Wollforschungsinstitut
an der Technischen Hochschule Aachen (Germany)

Nitrophenyl esters are generally suitable for introducing mono- and poly-functional carboxylic acids into proteins such as insulin, wool keratin, silk fibroin, and collagen [1]. We have been able to build authentic cystine bridges into tendon collagen by treating it with the bis-(*o*-nitrophenyl ester) of bis(carbobenzyloxy)cystine, to the extent of 5.5 % or 11 millimoles of disulfide groups per gram of collagen. A bifunctional reaction of the bis(nitrophenyl ester) is indicated by the raising of the transition temperature (shrinking temperature) from 64 °C (control experiment) to 69 °C, and by the clear relationship between the transition temperature and the number of disulfide groups during reduction and re-oxidation: reduction with thioglycolic acid splits the disulfide links and lowers the transition temperature, while re-oxidation with air raises both the disulfide content and the transition temperature. Irreversible destruction of the disulfide groups by oxidation with performic acid lowered the transition temperature. This lends support to the cross-linking theory of tanning [2].

Experimental: 1 g of tendon collagen [3] was treated with a solution of 0.5 g of the bis-(*o*-nitrophenyl ester) of bis-(carbobenzyloxy)cystine (made from bis(carbobenzyloxy)-cystine and *o*-nitrophenol with dicyclohexyl carbodiimide, m.p. 125–126 °C) in 200 ml of dimethylformamide and 40 ml of water for 100 hours at 20 °C. The product was washed with dimethylformamide. Excess bis(nitrophenyl ester) and salt-like derivatives were removed by extraction at room temperature with ether for 60 hours and with 0.1 N ammonia for 24 hours. The disulfide content was estimated by the method of *Zahn* and *Traumann* [4]. The disulfide bonds were reduced with 1 N thioglycolic acid (distilled) adjusted to pH 9.2 with ammonia for 4 hours at 20 °C. Thiol group analysis was carried out according to *Zahn, Gerthsen*, and *Meichelbeck* [5]; performic acid oxidation of disulfide groups was performed by the method of *Thompson* [6]; shrinkage temperature estimations were made according to *Zahn* and *Wegerle* [7].

Received, October 15th, 1962 [Z 372/200 IE]

[*] Communication No. 6 on collagen; communication No. 5: *H. Zahn, F. Growitz*, and *G. C. von Heyl*, Kolloid-Z. *180*, 26 (1962).

[1] *F. Schade*, Ph. D. thesis, Aachen 1962; reported briefly by *Kl. Ziegler* at the Informal Discussion on Fibrous Proteins and Related Peptides of the Faraday Society on May 29th, 1962 in Maidenhead, England.

[2] See *K. H. Gustavson:* The Chemistry and Reactivity of Collagen. Academic Press, New York 1956; *W. Grassman*, Das Leder *12*, 165 (1961).

[3] Kindly supplied by the firm C. Freudenberg, Weinheim/Bergstr., Germany.

[4] *H. Zahn* and *K. Traumann*, Melliand Textilber. *35*, 1069 (1954).

[5] *H. Zahn, T. Gerthsen*, and *H. Meichelbeck*, Melliand Textilber. *43*, 1179 (1962).

[6] *E. O. P. Thompson*, Aust. J. biol. Sci. *12*, 282, 490 (1959).

[7] *H. Zahn* and *D. Wegerle*, Kolloid-Z. *172*, 30 (1960).

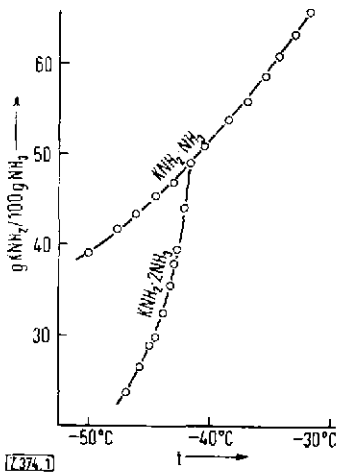
The System Potassium Amide/Ammonia

By Prof. Dr. P. W. Schenk and cand. chem. H. Tulhoff

Institut für Anorganische Chemie
der Freien Universität Berlin (Germany)

Only few data are available on the solubilities of alkali metal amides in liquid ammonia. According to *Kraus* [1], KNH_2 is more soluble than $NaNH_2$, and *Franklin* [2] reports that a saturated solution of KNH_2 at –33.5 °C contains 45 g of

KNH_2 in 100 cm^3 solution. *Hunt* and *Boncyk* [3] found the solubility of KNH_2 at +25 °C to be 3.6 g in 100 g of NH_3. We have developed an apparatus for measuring solubilities in liquefied gases, which will be described elsewhere and which enables us to investigate not only the solubility diagram over a wide range of temperature but also any precipitates formed with only a single initial weighing. For the system KNH_2/NH_3, we found the stable precipitate below −42 °C to be $KNH_2 \cdot 2\,NH_3$, in agreement with *Juza* and *Mehne* [4]. Above this temperature, we obtained $KNH_2 \cdot NH_3$ as cubic crystals of about 3 mm diameter. On slight supercooling below −42 °C, the monoammoniate, which is metastable under these conditions, is formed instead of the platelet-shaped crystals of the diammoniate; it proved possible to measure the solubility of the former. At approximately −50 °C, the system then undergoes a transition with copious separation of the stable diammoniate. The diagram and some numerical results illustrate the different solubilities and show that *Franklin*'s value is in good agreement with our findings. All values are quoted in g of KNH_2 per 100 g of NH_3.



T [°C]	KNH_2/NH_3	$KNH_2 \cdot 2\,NH_3$
−32.4	65.8	
−39.1	54.0	
−42.2	49.2	
−42.5		44.3
−43.5	46.9	
−44.1		32.5
−45.2	45.5	28.9
−46.5	43.4	
−47.1		23.6
−50.5	39.1	

Received, October 15th, 1962 [Z 374/196 IE]

[1] *C. A. Kraus*, J. Amer. chem. Soc. *30*, 1336 (1908).
[2] *E. C. Franklin*, Z. Physik. Chem. *69*, 290 (1909).
[3] *H. Hunt* and *L. Boncyk*, J. Amer. chem. Soc. *55*, 3529 (1933).
[4] *R. Juza* and *A. Mehne*, Z. Anorg. allg. Chem. *299*, 41 (1959).

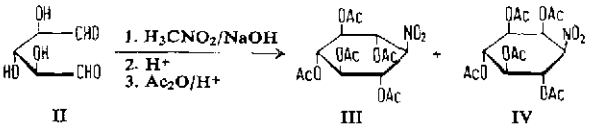
On the Synthesis of myo-Inositol from Glucose

Condensation of Nitromethane with Dialdehydes (II) [1]

By Dr. F. W. Lichtenthaler

Institut für Organische Chemie
der Technischen Hochschule Darmstadt (Germany)

On application of the dialdehyde/nitromethane cyclization [1,2] to *xylo*-trihydroxyglutardialdehyde (II) [3], prepared from 1,2-isopropylidene-α-D-glucofuranose (I) [4], a mixture of *scyllo*- and *myo*-1-deoxynitroinositol is obtained alongside traces of the *muco*-3-isomer upon condensation with barium hydroxide. With sodium hydroxide, II cyclizes exclusively to give a mixture of the *scyllo*- and *myo*-1-compounds, which can be separated easily via the pentaacetates III (20 % yield, based on I) and IV [5]. Since III can be converted into *myo*-inositol in 55 % yield [6], 2-^{14}C-*myo*-inositol, which is required for biochemical studies, can be prepared from I by cyclization with ^{14}C-nitromethane in an overall yield of 10.6 %.



II III IV

Sirupy 1,2-isopropylidene-*xylo*-trihydroxyglutardialdehyde, obtained by periodation [7] of 120 g of I, was dissolved in 800 ml of 0.1 N H_2SO_4 and kept at 100 °C for one hour. The hot solution was adjusted to pH 5 by addition of powdered $Ba(OH)_2$, filtered with charcoal, and adjusted to pH 10–11 with 1 N NaOH after addition of 10 ml of nitrometbane. After 10 hours at room temperature, the solution was neutralized with Amberlite IR-120 (H^+-form) and evaporated to dryness *in vacuo*. The resulting residue was extracted with dioxan in a Soxhlet-apparatus for 12 hours, the content of the thimble being pulverized after 6 hours. The dioxan was evaporated off *in vacuo*, and the remaining crystalline mass was dissolved in a mixture of 200 ml of acetic anhydride and 10 ml of conc. H_2SO_4 by heating to 60 °C for 3 minutes. On cooling, a precipitate formed, which was filtered with suction and recrystallized from a little dioxan; yield: 41.3 g of III (18.1 %, based on I); m.p. 254–256 °C (lit. [8]: 254–256 °C). The mother-liquor remaining after isolation of III was stirred into ice-water, and the resulting precipitate was recrystallized from ethanol, giving 6.15 g of IV (2.7 %, based on I); m.p. 173–176 °C (lit. [8]: 174–176 °C). The yield of III can be raised to 20 % by repeated conversion of IV into III through the following steps: deacetylation of IV [8], isomerization of the 1-deoxy-1-nitro-*myo*-inositol formed with NaOH to a mixture of the *scyllo*- and *myo*-1-isomers, and reacetylation (yield: 31 %).

Received, October 18th, 1962 [Z 381/197 IE]

[1] 1st Communication: *F. W. Lichtenthaler*, Chem. Ber. *96*, in the press.
[2] *H. H. Baer* and *H. O. L. Fischer*, J. Amer. chem. Soc. *81*, 5184 (1959); *82*, 3709 (1960); *H. H. Baer*, Chem. Ber. *93*, 2865 (1960); J. Amer. chem. Soc. *83*, 1882 (1961); *84*, 83 (1962); *A. C. Richardson* and *H. O. L. Fischer*, ibid. *83*, 1132 (1961); *A. C. Richardson*, J. chem. Soc. (London) *1962*, 2499, 2758; *F. W. Lichtenthaler* and *H. O. L. Fischer*, J. Amer. chem. Soc. *83*, 2005 (1961).
[3] In solution, II presumably has a cyclic hemialdal structure: *R. D. Guthrie*, Adv. Carbohydrate Chem. *16*, 105 (1961).
[4] *K. Iwadare*, Bull. chem. Soc. Japan *16*, 40 (1941); Chem. Zbl. *1942*, I, 1753.
[5] Starting from I, *J. M. Grosheintz* and *H. O. L. Fischer*, J. Amer. chem. Soc. *70*, 1476, 1479 (1961), obtained similar mixtures by stepwise condensation with nitromethane (see also [8]).
[6] *G. J. Drummond, J. N. Aronson*, and *L. Anderson*, J. org. Chemistry *26*, 1601 (1961); *T. Posternak, W. H. Schopfer* and *R. Huguenin*, Helv. chim. Acta *40*, 1875 (1957).
[7] *R. Schaffer* and *H. S. Isbell*, J. Res. nat. Bur. Standards *56*, 191 (1956).
[8] *F. W. Lichtenthaler*, Chem. Ber. *94*, 3071 (1961).

Synthesis of Oxazole

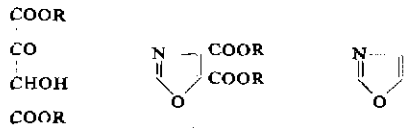
By Prof. Dr. H. Bredereck and R. Bangert

Institut für Organische Chemie und Organisch-chemische Technologie der Technischen Hochschule Stuttgart (Germany)

Oxazole was first prepared by *J. W. Cornforth* and *R. H. Cornforth* [1]. We now report briefly on a relatively simple synthesis.

On heating with formamide at 100–120 °C, hydroxyketosuccinic ester *(1)* and its isomeric enediols [2] afford 4,5-

di(alkoxycarbonyl)oxazoles *(2)* in 60–70 % yield. These esters are hydrolyzed by aqueous barium hydroxide at 50–70 °C or by ether/ethanolic sodium hydroxide at room-temperature to yield the barium or disodium salt of the



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

oxazole-4,5-dicarboxylic acid. By heating the anhydrous salts in quinoline with equimolar amounts of quinoline sulfate in the presence of cupric oxide or copper powder as catalyst, we obtained oxazole *(3)* in 50–70 % yield directly, without isolating the relatively labile oxazole-4,5-dicarboxylic acid.

Received, October 24th, 1962 [Z 371/202 IE]

[1] *J. W. Cornforth* and *R. H. Cornforth*, J. chem. Soc. (London) *1947*, 96.

[2] *E. F. Hartree*, J. Amer. chem. Soc. *75*, 6245 (1953).

Lithium Aluminum Tetrakis(diethylphosphide)

By Prof. Dr. G. Fritz [1] and Dipl.-Chem. G. Trenczek

Anorganisch-chemisches Institut
der Universität Münster (Germany)

With 1 mole of $LiP(C_2H_5)_2$ *(1)*, $AlCl_3$ forms the crystalline trimer $[Cl_2Al{-}P(C_2H_5)_2]_3$ [2]; however, with 3 moles of *(1)*, it gives a viscous substance *(2)* having an Al:P ratio of 1:3. With 4 moles of *(1)*, $AlCl_3$ reacts in ether at room temperature according to the equation:

$$AlCl_3 + 4\ LiP(C_2H_5)_2 \rightarrow LiAl[P(C_2H_5)_2]_4 + 3\ LiCl.$$
$$\text{(1)} \qquad \text{(3)}$$

On concentrating the ether solution, colorless, well-formed crystals of lithium aluminum tetrakis(diethylphosphide) *(3)* result; these are recrystallised from diethyl ether/pentane, m.p. 224–226 °C (in a sealed tube); yield 71 %. Compound *(3)* is also formed from the viscous product *(2)* with a further mole of *(1)*. It is spontaneously inflammable in the atmosphere, stable in nitrogen, very soluble in ether, and insoluble in benzene and pentane. The X-ray diagram of *(3)* is clearly distinguishable from that of $LiP(C_2H_5)_2$.

Received, October 26th, 1962 [Z 376/201 IE]

[1] New address: Institut für Anorganische und Analytische Chemie, Universität Gießen, Germany.

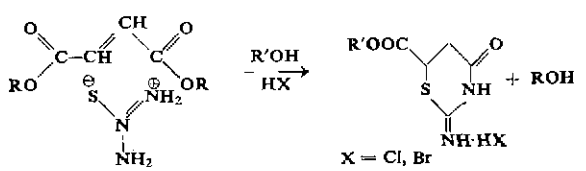
[2] *G. Fritz* and *G. Trenczek*, Z. anorg. allg. Chem. *313*, 236 (1961).

A Simple Synthesis of 2-Imino-4-oxo-3,5H-1,3-thiazine-6-carboxylic Esters

By Dr. R. Zimmermann

Abteilung Allgemeine Organica, Chemische Werke Albert, Wiesbaden-Biebrich (Germany)

According to *Behringer* and *Zillikens* [1], in alcoholic solution, α,β-unsaturated monocarboxylic esters and isothiourea hydrochloride [2] yield open-chain isothiuronium salts.



X = Cl, Br

It has now been found that interaction of α,β-unsaturated dicarboxylic acids, their anhydrides or esters with thiourea in a methanolic solution saturated with hydrogen chloride or hydrogen bromide results in ring-closure and formation of 2-imino-4-oxo-3,5*H*-1,3-thiazine-6-carboxylic esters.

In the above scheme, R is preferably CH_3 or C_2H_5, while R′ may be, for example, CH_3, C_2H_5, n-C_4H_9, $(CH_3)_2CH$, $CH_3(CH_2)_{10}CH_2$, or C_6H_{11}. When R and R′ are unlike, transesterification occurs.

R′	X	Crystallised from	M.p. [°C]	Yield [%]
CH_3–	Cl	isopropanol/ ethanol 1:1	178 (decomp.)	89
C_2H_5–	Cl	ethanol	180–181 (decomp.)	59
n-C_3H_7–	Cl	n-propanol	165–167 (decomp.)	79.2
$(CH_3)_2CH$–	Cl	isopropanol/ pet. ether 1:1	199–200 (decomp.)	70.5
n-C_4H_9–	Cl	acetone/ pet. ether 1:1	148–149 (decomp.)	75
$CH_3(CH_2)_{10}CH_2$–	Cl	acetone	150 (decomp.)	54
	Cl	acetone/ pet. ether 1:1	197–198 (decomp.)	62

The compounds cited in the Table are convertible, irrespective of the substituent R′, into 2-imino-4-oxo-3,5*H*-1,3-thiazine-6-carboxylic acid, m.p. 244–245 °C, using 5 N hydrochloric acid at 80 °C. With methanolic ammonia, the thiazine derivatives yield the corresponding 6-carbonamide (m.p. 222 °C). A patent covering this method is pending.

Received, October 28th, 1962 [Z 375/198 IE]

[1] *H. Behringer* and *P. Zillikens*, Liebigs Ann. Chem. *574*, 140 (1951).

[2] *A. Hantsch*, Liebigs Ann. Chem. *296*, 94 (1897).

Preparation of Aminoarsines by Transamination

By Dr. H. J. Vetter and Priv.-Doz. Dr. H. Nöth

Institut für Anorganische Chemie
der Universität München (Germany)

The $(H_3C)_2N$ - ligands in tris(dimethylamino)arsine, $As[N(CH_3)_2]_3$ *(1)* [1], can be successively substituted by reaction with substances possessing N–H bonds. Compounds of the type X–NH_2 react with *(1)* as follows:

$$2\ As[N(CH_3)_2]_3 + 2\ H_2NX \rightarrow \begin{matrix}(H_3C)_2N{-}As{-}N{-}X \\ \quad\quad\quad\quad | \\ \quad\quad\quad X{-}N \quad As{-}N(CH_3)_2\end{matrix} + 4\ (H_3C)_2NH.$$

X	M.p. [°C]	B.p. [°C]	Mol. wt. calc. dimer	Mol. wt. found
n-C_4H_9	–	undist. oil	380.2	385
C_6H_5	163–165	110 subl. *in vacuo*	420.2	415
C_6H_5CO	213–215	165 subl. *in vacuo*	476.2	–
$N(CH_3)_2$	–	106/2 mm.Hg	354.1	356

The dimethylaminoarsenimides, which were also characterized by infrared spectroscopy, possess no As=N double bonds and dissolve in benzene as the dimer, indicating an As–N four-membered ring structure.

The transamination with excess of monoalkylamines leads to the formation of a tetraarsenic hexakis(alkylimide), $As_4(NR)_6$ (R = CH_3, C_4H_9):

$$4\ As[N(CH_3)_2]_3 + 6\ RNH_2 \rightarrow As_4(NR)_6 + 12\ (H_3C)_2NH.$$

On heating strongly, $[(H_3C)_2NAsNC_4H_9]_2$ disproportionates into *(1)* and tetraarsenic hexakis-(n-butylimide)

$$3\ [(H_3C)_2NAsNC_4H_9]_2 \rightarrow 2\ As[N(CH_3)_2]_3 + As_4(NC_4H_9)_6$$

which can also be synthetized by butylaminolysis of arsenic trichloride in benzene.

$$4\ AsCl_3 + 14\ C_4H_9NH_2 \rightarrow As_4(NC_4H_9)_6 + 12\ C_4H_9NH_2{\cdot}HCl$$

This compound, which is sensitive to air, is a yellowish oil, b.p. 195–200 °C *in vacuo*, $n_D^{22} = 1.5379$, is a homologue of $As_4(NCH_3)_6$ [2], and has a urotropine-type structure.

Received, October 29th, 1962 [Z 379/203 IE]

[1] *G. Kamai* and *Z. L. Khisamova*, Doklady Akad. Nauk SSSR *105*, 489 (1955).

[2] *H. Nöth* and *H. J. Vetter*, Naturwissenschaften *48*, 553 (1961).

1,1-Bis(trimethylsilyl)tetrazadiene [1]

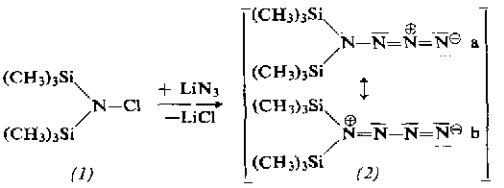
By Dr. Nils Wiberg and cand. chem. A. Gieren

Institut für Anorganische Chemie
der Universität München (Germany)

Treatment of 2-chloro-1,1,1,3,3,3-hexamethyldisilazane, $[(CH_3)_3Si]_2N{-}Cl$ *(1)*, with excess lithium azide in tetrahydrofuran at room temperature for two days leads almost quantitatively (based on the quantity of lithium chloride formed) to 1,1-bis(trimethylsilyl)tetrazadiene (or 2-azido-1,1,1,3,3,3-hexamethyldisilazane) *(2)*, a colorless liquid of b.p. 40–42 °C/11 mm Hg.

Compound *(1)* can easily be prepared by chlorination of the *N*-sodium salt of hexamethyldisilazane in ether at −50 °C. It is a yellow-green, photosensitive, mobile liquid (b.p. 41–43 °C/11 mm) decomposing slowly at 100 °C.

The structure proposed for *(2)* is rendered probable by the method of its synthesis and by its infrared spectrum (ν N=N=N : 2130 cm^{-1}, 1290 cm^{-1}; ν_{as} N−N=N :? 1260



cm^{-1}). Compound *(2)* is relatively stable thermally, decomposing slowly with evolution of nitrogen only above 150 °C [3]. The factors responsible for its surprising stability appear to be the possibility of mesomerism *(2a)* ↔ *(2b)* [2] as well as the presence of silyl groups; the importance of the latter factor may be seen from comparison with the compounds ON_4 and $(CH_3)_2N_4$ [3]. The stabilizing influence of silyl groups on unsaturated nitrogen chains has already been observed with silyl azides [1].

Received, October 29th, 1962 [Z 380/204 IE]

[1] Contributions to the Chemistry of Silicon: 3rd Communication. – 2nd Communication: Angew. Chem. internat. Edit. *1*, 551 (1962).

[2] The formula shows only two of the many possible mesomeric structures.

[3] The tetrazadienes ON_4 [*H. W. Lucien*, J. Amer. chem. Soc. *80*, 4458 (1958)] and $(CH_3)_2N_4$ [*H. Bock* and *K. Kompa*, Angew. Chem. internat. Edit. *1*, 264 (1962)] have similar structures but are less stable.

CONFERENCE REPORTS

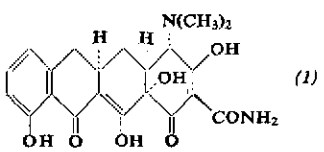
Second International Symposium on the Chemistry of Natural Products

This symposium – excellently organized in every respect – took place from August 27th through September 2nd in Prague. It was arranged by the Czechoslovakian Academy of Sciences, the Czechoslovakian Chemical Society, and the International Union for Pure and Applied Chemistry. The main theme was the chemistry of steroids, terpenes, and alkaloids.

From the Proceedings:

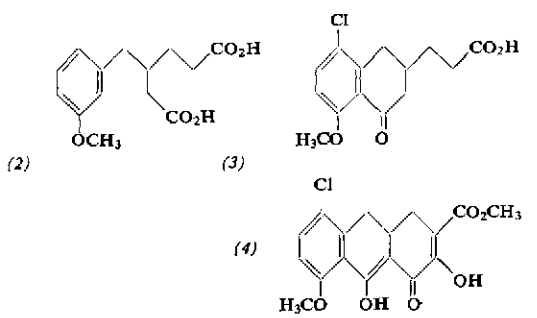
Plenary Sessions

R. B. Woodward (U.S.A.) reported on the total synthesis of (±)-6-demethyl-6-deoxytetracycline *(1)*. The synthesis starts

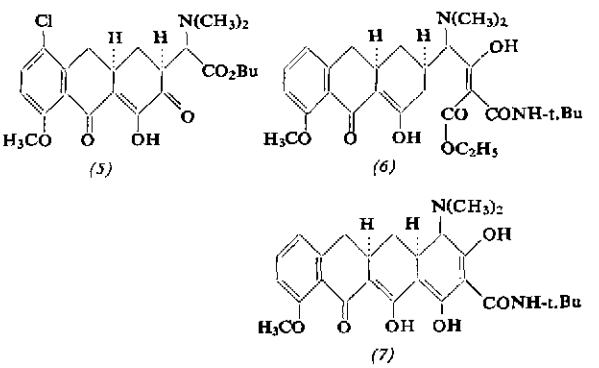


(1)

from methyl *o*-methoxybenzoate and proceeds in four steps to the dicarboxylic acid *(2)*. After chlorination of the aromatic ring with Cl_2/acetic acid at 15 °C, ring C may be closed with liquid HF at 15 °C to give *(3)*. Heating the methyl ester of *(3)* with dimethyl oxalate and sodium methoxide yields *(4)*; the latter is decarboxylated and then heated with n-butyl glyoxylate in toluene for 1 hour in the presence of magnesium methoxide. The condensation product



obtained is treated with dimethylamine at −10 °C, giving *(5)*, which loses its methylamino group readily. In order to stabilize this compound, the carbonyl group of ring B has to be reduced with $NaBH_4$ at −70 °C.

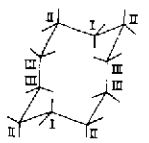


Five further steps lead to *(6)*. When this compound is heated with NaH/dimethylformamide and a trace of methanol at

120 °C for 7 minutes, ring A closes to give *(7)*. This compound differs from the required product owing to the "false" orientation of the amino-group on the A ring and the lack of an HO-group at the A–B ring junction.

After removal of the t-butyl group, the HO-group is introduced by treatment with $CeCl_3/O_2$ in methanol/dimethylformamide at pH 5. As the dimethylamino group blocks the front side of the molecule, the oxidizing agent attacks from behind and the HO-group thus assumes the sterically "correct" position. Finally, the dimethylamino group is isomerized by heating with $CaCl_2$ in butanol/water for three hours at pH 8.5. The ultraviolet spectrum and paper chromatographic properties of the product correspond with those of the natural material; since it is a racemate, its antibiotic activity is half as great as that of the natural product.

V. Prelog (Switzerland) reported on the conformation of carbon rings of medium size. X-ray structural analyses, particularly those of *Dunitz* et al. [1], have shown that one of the many possible conformations of cyclodecane is particularly stable. It can be represented by the formula *(8)*.



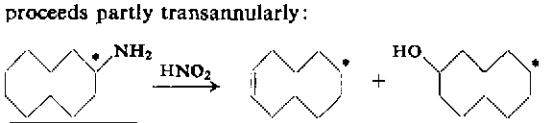
(8)

Three types of conformation (I–III) may be recognised at the carbon atoms [2]. Six hydrogen atoms are inside the ring (intra-annular), the remaining fourteen are outside the ring (extra-annular). The distance between the intra-annular hydrogen atoms is calculated to be only 1.8 to 2.2 Å. It follows that none of these hydrogen atoms can be replaced by a larger substituent without the conformation of the molecule being forced to alter. There are four different extra-annular positions which seem to differ energetically only to a slight extent and which seem to be in equilibrium with each other.

However, of the three positions of different conformation which might be the site of a trigonal carbon atom, two are energetically favored: if a carbon atom of type I or III becomes trigonal, one of the intra-annular hydrogen atoms disappears, and with it two of the total of six transannular interactions. The energy gain at a carbon atom of type III is particularly great, since one of the transannular repulsions removed in this case corresponds to a particularly small H–H distance. A number of chemical peculiarities of monosubstituted cyclodecanes may be explained on the basis of this simple concept in a qualitative and sometimes even a semi-quantitative manner: these include the rate of acetolysis of cyclodecyl-*p*-toluene sulfonate (536 times as fast as that of the cyclohexyl compound), the dissociation constant of cyclodecanone cyanhydrin (2000 times greater than that of the cyclohexanone derivative) and the difference in rate of oxidation of the stereoisomeric cyclodecane-1,2-diols with lead tetraacetate.

One conformation of the cyclononane carbon ring is also energetically favorable. It consists of six carbon atoms of type I, three atoms of type II, with six intra-annular and twelve extra-annular hydrogen atoms. It has considerable similarity to the stable configuration of cyclodecane, accounting for the similarity in chemical behavior of their derivatives.

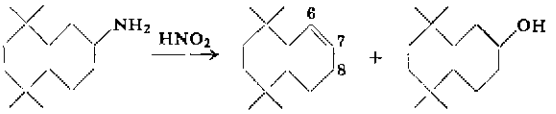
A colloquium on medium-sized rings followed this lecture. *J. Sicher* et al. (Czechoslovakia) described experiments, in which the favored conformation of cyclodecane was stabilized by the introduction of four *gem*-methyl groups: a pair of methyl groups can only be extra-annular at a carbon atom of type II. Although the reaction of cyclodecylamine with nitrous acid proceeds partly transannularly:



[1] *J. D. Dunitz* and *V. Prelog*, Angew. Chem. *72*, 896 (1960).

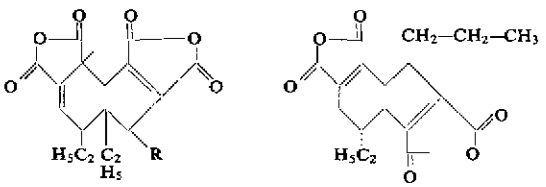
[2] For definition, see [1], page 900.

that of 1,1,4,4-tetramethyl-7-aminocyclodecane cannot:



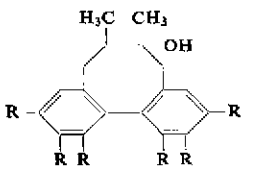
The formation of only the Δ^6-compound without an accompanying Δ^7-derivative may be attributed to the fact that the 6,7-bond is already cisoid in the stable conformation of cyclodecane, so that a *cis*-Δ^6-double bond can be formed with the smallest alteration of configuration. These experiments afford chemical confirmation of the Dunitz model of cyclodecane.

Natural products with a nine-membered ring were discussed by *D. H. R. Barton* (England) in a further plenary session lecture [3]. He and his co-workers have elucidated the structure of glauconic acid *(9)*, glaucanic acid *(10)*, and byssochlamyic acid *(11)*. All three compounds are metabolites of *Penicillium purpurogenum* and have been known for some time. Despite their names, they are not acids but anhydrides



(9) R = OH
(10) R = H
(11)

Natural products with an eight-membered ring were isolated by *O. S. Chizkov* et al. (U.S.S.R.) from *Schizandra chinensis*, *viz.* various dibenzo[1,2:3,4]cycloocta-1,3-dienes with different substituents. Schizandrin, for example, has the formula *(12)*.

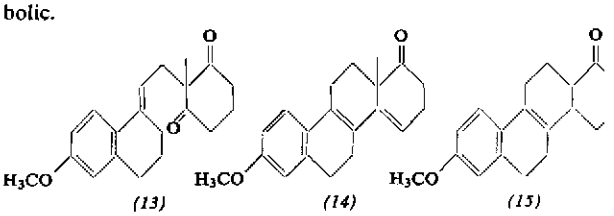


(12) R = OCH_3

Steroids

Syntheses and Structural Determinations

D-Homosteroids were synthetized by *S. N. Ananchenko* et al. (U.S.S.R.) from 6-methoxytetralone by treatment with vinylmagnesium bromide. Reaction of the resulting vinyl carbinol with methyldihydroresorcinol led to the tricyclic diketone *(13)*. The C ring was closed by treatment with acid to give *(14)*. Reduction of the carbonyl group, hydrogenation, Birch-reduction, and hydrolysis yielded 19-nor-D-homo-testosterone. Hydrogenation of *(14)* yielded *(15)*, which gave 17α-alkyl derivatives of 19-nor-D-homo-testosterone with lithium acetylide and ethylmagnesium or methylmagnesium bromide and further treatment. These derivatives are anabolic.



(13) *(14)* *(15)*

Diginigenin, the aglycone of diginin and of digitalonin, has been known for 20 years, but its structure had never been established. On the basis of its ultraviolet, infrared, and

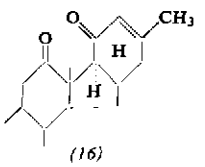
[3] See Experientia *18*, 345, 352 (1962).

nuclear magnetic resonance spectra, its optical rotation, and mass spectroscopic investigations, *C. W. Shoppee* et al. (Australia) succeeded in identifying the compound as 3β-hydroxy-12α,20α-epoxy-Δ⁵-pregnene-11,15-dione.

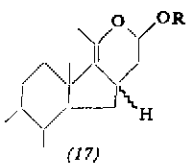
Of the two possible anhydro-derivatives of strophanthidine, the Δ⁵-anhydro-compound was known. *N. K. Abubakirov* et al. (U.S.S.R.) have now made Δ¹⁴-anhydrostrophanthidine by treatment of strophanthidine with thionyl chloride. This gave 3,5-sulfoxy-Δ¹⁴-anhydrostrophanthidine, which was hydrolyzed to give the free compound. The product is identical with diffigenin isolated from seeds of *Erysimum diffusum*.

Reactions

When heated together in the presence of aqueous KOH, acetone and Δ¹⁶-12,20-diketosteroids yield compounds of type *(16)* [*M. E. Wall* et al. (U.S.A.)].



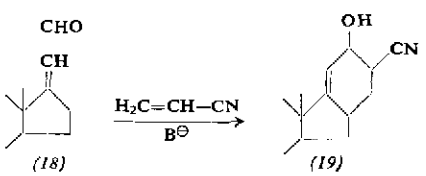
(16)



(17)

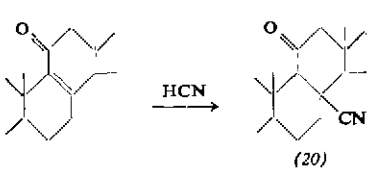
With alkylvinyl ethers, Δ¹⁶-20-ketosteroids give dihydropyran derivatives *(17)*, further treatment of which allows the introduction of side-chains [*J. E. Pike* (U.S.A.)].

C. R. Engel and *J. Lessard* (Canada) found that cyanoethylation of α,β-unsaturated aldehydes with acrylonitrile in the presence of a base can also lead to cyclic allyl alcohols with a six-membered ring *(19)*. An example of this is the cyanoethylation of 3β-acetoxy-5α-Δ¹⁷⁽²⁰⁾-pregnen-21-al.



(18) *(19)*

8β-Substituted steroids were obtained by *W. Nagata* et al. (Japan). For example, the reaction of 3β-acetoxy-Δ⁸,²²-ergostadien-11-one with HCN and $Al(C_2H_5)_3$ at room temperature yielded the compound *(20)* in 70% yield. The reaction is also applicable to other Δ⁸-11-ketosteroids.



(20)

Three types of reaction are possible when steroids are heated with Raney nickel in *p*-cymene:

a) conversion of 3α- or 3β-hydroxysteroids into 3-ketosteroids,
b) saturation of a 5,6-double bond,
c) transformation of A/B-*cis*-steroids to A/B-*trans*-steroids.

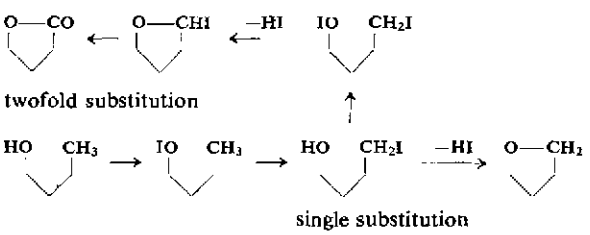
If the catalyst is used in great excess, all three reactions may proceed together [*R. N. Chakravarti* et al. (India)].

17-Amino-20-ketosteroids have been prepared by *F. Winternitz* and *C. R. Engel* (Canada) from 17α-acetyl-16β,17β-epoxysteroids and an azide in aqueous alcoholic solution. A 16β-hydroxy-17α-azide is obtained, which can readily be reduced to the amine with Pt/H_2. Tosylation furnishes the 16β-tosyloxy-17α-azide, which can be reduced likewise to the amine and also allows removal of the 16-hydroxyl-group.

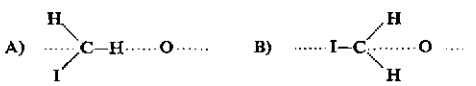
The selenium compounds often formed from Δ⁴-3-ketosteroids on dehydrogenation with SeO_2 were converted by *M. Kocor* et al. (Poland) into the free Δ¹,⁴-3-ketones with ammonium sulfide in alcohol, raising the yields of dehydrogenation to 80%. The procedure could not be applied to 17- and 20-ketones. It is however also useful in raising the yields of Δ¹,⁴,⁶-3-ketones made with SeO_2 from Δ⁴,⁶-3-ketones.

Selective acylation of a 21-hydroxyl group in the presence of an 11-hydroxyl group was achieved by *G. Langbein* (Germany) with an acid anhydride in presence of a cation of group Ia or IIa of the periodic table. The 21-acetate, 21-phenylacetate and 21-succinate of 11α,17α,21-trihydroxy-Δ⁴-pregnen-3,20-dione can be prepared quantitatively in this manner.

Substitution of unactivated methyl groups in a geometrically favourable γ-position to a hydroxyl group can be achieved by reaction with iodine and lead tetraacetate under strong irradiation with visible light. The following reactions take place via radical intermediates:



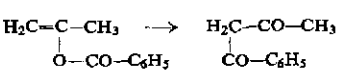
K. Heusler et al. (Switzerland) have investigated the stereochemistry of this reaction. In steroids, a 1,3-diaxial relationship, which is particularly suitable for these reactions, exists between the methyl group in position 18 or 19 and the following hydroxyl groups: 20, 11β, 8β, or 6β, 4β, 2β, respectively. It depends upon the orientation of the ICH_2 group relative to the hydroxyl group whether the product of single or twofold substitution is obtained.



twofold substitution single substitution

Case A applies with a 20- or 4β-hydroxyl group, while B occurs with a 6β-hydroxyl group as long as there is no substituent at C-11. If a substituent is introduced at C-11, the iodomethyl group is twisted so far that products from both single and twofold substitution with the 6β-hydroxyl group are formed. With a 2β- or 11β-hydroxyl group, the situation is not quite so simple: 2β-hydroxysteroids give products of twofold substitution in over 60% yield. In 11β-hydroxysteroids, a reaction may take place with both the 18- and 19-methyl groups. In both cases, products of single and twofold substitution are formed together.

If enol benzoates are irradiated in cyclohexane with light from a mercury vapor lamp (2300 Å) benzoyl ketones are formed:



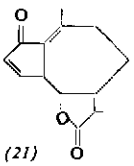
Y. Mazur et al. (Israel) found that the same reaction held good for enol-esters of steroids: Δ²-cholestenyl-3-benzoate gave 2-benzoylcholestan-3-one; 3-acetoxy-17-benzoyloxy-Δ¹⁶-androstene gave the 16-benzoyl-17-ketone; and 3,17-diacetoxy-Δ³,⁵-androstadiene gave the 4-acetyl-3-ketone. This compound is also formed in the presence of a methyl group at C-4.

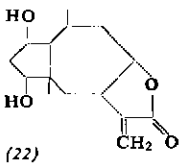
3-Deoxy analogues of steroid hormones were discussed by *F. A. Kincl* et al. (Mexico). With 3β-fluoro-Δ³,⁵-3β-chloro-Δ⁵- and Δ²,⁵-3-deoxy-17α-acetoxyprogesterone it was showin

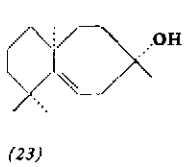
that an oxygen function at C-3 is not necessary for progestational activity. Some of these derivatives are more active than 17α-acetoxyprogesterone.

Terpenes

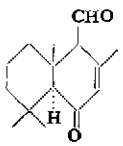
The structures of three sesquiterpenes with seven-membered rings have recently been elucidated: achilline *(21)* from *Achillea lanulosa*, pulchelline *(22)* and widdrole *(23)* from conifers of the order *Cupressales* [*E. H. White* et al. (U.S.A.); *W. Herz* et al. (U.S.A.); *C. Enzell* et al. (Sweden)].


(21)

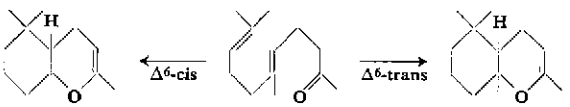

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(23)

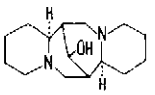
Tadeonal *(24)* has been found to be one of the sharp tasting compounds in *Polygonum hydropiper* [*M. Kotake* et al. (Japan)].


(24)

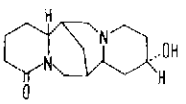
V. F. Kucherov et al. (U.S.S.R.) investigated the cyclisation with sulfuric acid in a nitroparaffin of geranylacetone to 2,5,5,9-tetramethylhexahydrochromene. They found that the reaction is stereospecific (see formula) and that the bicyclic compound is formed in one step from geranylacetone.

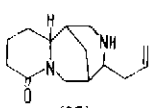


6-Hydroxy-3-tropyloxytropane has been found in the leaves of *Datura ferox* by *A. Romeike* (Germany). The compound was synthetized by *G. Fodor* et al. (Hungary). It is a biological intermediate in the formation of hyoscine from hyoscyamine. New lupin alkaloids were discussed by *S. J. Goldberg* et al. (U.S.A.) and *M. Wiewiórowski* et al. (Poland). 8-Hydroxyspartalupin *(25)* is a minor alkaloid in *Lupinus sericus*. The compound is perhaps the biological precursor of spartalupin, which occurs in the same plant.


(25)

(+)-13-Hydroxylupanin *(26)* occurs as an ester with cinnamic acid in *Lupinus angustifolius*. Attempts to make the compound from angustifolin *(27)* and formaldehyde in the presence of cinnamic acid led to the epimer of the naturally occurring ester. However, in the plant, *(27)* appears to be the precursor of *(26)*, as production of the cinnamic ester rises when lupins are infused with *(27)*.


(26)


(27)

I. V. Terent'eva et al. (U.S.S.R.) have isolated seven alkaloids from *Carex brevicollis*, the major constituent (90 %) being brevicolline, $C_{17}H_{19}N_3$. It has the structure of a methyl-*N*-methylpyrrolidine-β-carboline substituted in the pyridine ring. Its ganglion-blocking action is the most interesting of its pharmacological properties. [VB 644/56 IE]

SELECTED ABSTRACTS

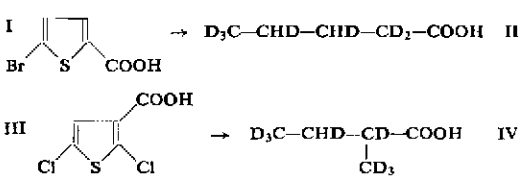
The reactivity of bis(halogenomethyl)zinc compounds is the subject of a report by *G. Wittig* and *F. Wingler*. Bis(chloromethyl)zinc (I), prepared from diazomethane and zinc chloride in ether, reacts with iodine at −80 °C, the zinc-carbon bond being split to form zinc iodide and chloroiodomethane. Methylene iodide can also be isolated. Evidently, compound I reacts with zinc iodide to give bis(iodomethyl)zinc (II) as an intermediate, from which methylene iodide is then formed by the action of iodine.

$ClCH_2ZnCH_2Cl$ ICH_2ZnCH_2I

I II

I and II have proved to be effective reagents for bringing about the formation of cyclopropane rings. For example, a 72 % yield of norcarane is obtained if a 0.5 M solution of I in ether is boiled for 5 hours with cyclohexene. A concentrated solution of II in ether leads to norcarane in 73 % yield when heated with cyclohexene for only 2 hours. With cyclopentene one obtains bicyclo[3,1,0]hexane. / Liebigs Ann. Chem. *656*, 18 (1962) / −Sk. [Rd 343/106 IE]

A method for introducing CD_3 and CT_3 groups conveniently into organic acids is described by *N. Van Bac*, *N. P. Buu-Hoi*, and *N. Dat Xuong*. Halogenated derivatives of heterocyclic compounds containing sulfur are freed from sulfur in deuterium or tritium oxide solution with Raney nickel in the presence of sodium methoxide. Thus II was obtained from I in 70–80 % yield and IV from III in 91 % yield. Thionaphthene derivatives were converted into di(deuteromethyl) compounds by the same method; tri(deuteromethyl) compounds may be obtained, too, by introducing a halogen into



the original compound./Bull. Soc. Chim. France *1962*, 1077 / −Bs. [Rd 311/98 IE]

True alkaline hydrolysis of a monoalkyl phosphate with rupture of the P–O link has been demonstrated by *E. Cherbuliez*, *H. Dahn*, *H. Moll*, *H. Probst*, and *J. Rabinowitz* with propargyl phosphate (I) which was hydrolysed in the presence of $H_2{}^{18}O$ in N NaOH at 100 °C.

$HC{\equiv}C{-}CH_2{-}OPO_3H_2$ (I)

The phosphate formed contained ^{18}O. Other alkyl phosphates studied proved rather stable to alkali, or else if the neighbouring hydrogen atoms are activated exhibited α,β-elimination which is normally more rapid than hydrolysis. This method may be of general utility in distinguishing between α,β-elimination and true hydrolysis in the alkaline hydrolysis of monoalkyl phosphates. / Helv. chim. Acta *45*, 1075 (1962) / −Bs. [Rd 299/91 IE]

The C-acylation of phosphine-alkylenes and a new route to ketones are described by *H. J. Bestman* and *B. Arnason*. Phosphine-alkylenes (I) react with acyl chlorides, thiocarbonic acid-*S*-ethyl ester or acid esters, giving acylated phosphonium salts (II) which rapidly lose a proton to a second molecule of (I).

$$\underset{(I)}{R{-}CH{=}P(C_6H_5)_3} + R'{-}CO{-}X \rightarrow \underset{(II)}{[R'{-}CO{-}\overset{R}{\overset{|}{C}}H{-}\overset{\oplus}{P}(C_6H_5)_2]\,X^{\ominus}}$$

$$\xrightarrow{R{-}CH{=}P(C_6H_5)_3} R'{-}CO{-}\overset{R}{\overset{|}{C}}{=}P(C_6H_5)_3 + [R{-}CH_2\overset{\oplus}{P}(C_6H_5)_3]\,X^{\ominus}$$

(III)

X = −Cl, $-SC_2H_5$, in certain cases −OR.

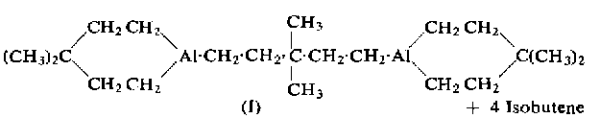
The triphenylphosphine-acylmethylenes (III) which are produced may be hydrolysed by alkali in aqueous alcoholic solution to ketones (IV) and triphenylphosphine oxide.

$$(III) + H_2O \xrightarrow{\ominus OH} \underset{(IV)}{R'{-}CO{-}CH_2R} + OP(C_6H_5)_3$$

They may also be split by Zn-acetic acid or electrolysis to ketones (and triphenylphosphine). The Wittig reaction is undergone slowly by the compounds when reacted with aldehydes in absolute benzene. / Chem. Ber. *95*, 1513 (1962) / −Sk. [Rd 303/95 IE]

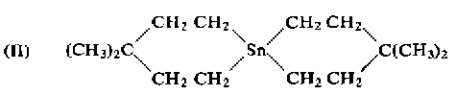
A synthesis of metalheterocyclics is described by *R. Polster*. Interaction of di-isobutene-aluminum hydride and 3,3-dimethylpenta-1,4-diene at 160 °C yields the heterocyclic alumino-organic compound I.

$$2\,(isoC_4H_9)_2AlH + 3\,CH_2{=}CH{-}\overset{CH_3}{\overset{|}{C}}{-}CH{=}CH_2 \rightarrow$$



(I) + 4 Isobutene

(II)



Compound I may be distilled *in vacuo*; in its solid state, the compound resembles a high polymer. It may be presumed that association leading to structures of high molecular weight occurs by electron deficiency bonding. I is an excellent alkylenating agent, affording, for example, 68 % yields of bis-(3,3-dimethylpentamethylene)tin (II) on reacting with stannic chloride. / Liebigs Ann. Chem. *654*, 20 (1962). / −Sk. [Rd 294/85 IE]

An interesting synthesis of block copolymers has been worked out by Russian chemists. An aromatic diazonium salt in the presence of a reducing agent serves as initiator. The diazonium salt also contains an amino-group or a substituent which can be converted into $-NH_2$, *e.g.* $-NO_2$:

$$O_2N{-}C_6H_4{-}N_2Cl + Fe^{2+} + n\,A \rightarrow O_2N{-}C_6H_4{-}(A)_n + Fe^{3+} + Cl^- + N_2$$

(A = monomer unit). The resultant block polymer has a nitrophenyl group at one end, which may be reduced to an anilino group, which is then diazotized. The polymeric diazonium salt is used as initiator for the polymerization of second monomer B; a block copolymer is formed:

$$ClN_2{-}C_6H_4{-}(A)_n + Fe^{2+} + mB \rightarrow$$
$$-(B)_m{-}C_6H_4{-}(A)_n + Fe^{3+} + Cl^- + N_2$$

The polymerization can be carried out in aqueous solution or emulsion, or in organic solvents. The values of n and m may be controlled by a change in reaction conditions or by addition of chain growth regulators. *Yu. G. Kryazhev* and *Z. A. Rogovin*, Vysokomolekulyarnyye soyedineniya *4*, 783 (1962) / −Ko. [Rd 341/104 IE]

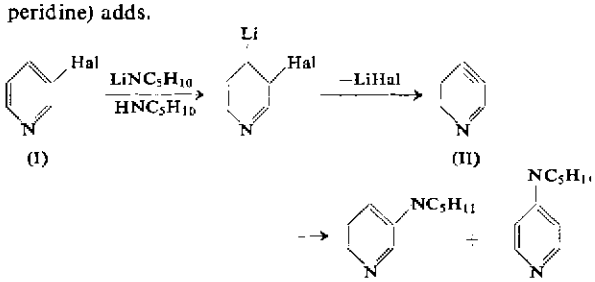
Polyethylene was obtained by *Y. Takami* using a reaction product from equimolecular quantities of $TiCl_4$ and SnR_4 ($R = C_2H_5$ was optimal) at 21–22 °C (15 min., without solvent). Addition of 0.005 mole of $C_2H_5AlBr_2$ or $AlCl_3$ per 0.01 mole of the Ti–Sn catalyst raised the catalytic activity considerably, while small quantities of $SnCl_4$, dioxan or benzophenone quenched it. CCl_4 or $SiCl_4$ are almost without effect. The reaction between SnR_4 and $TiCl_4$ seems to be:

$$R_4Sn + TiCl_4 \rightarrow R_3SnCl + RTiCl_3$$
$$RTiCl_3 \rightarrow R\cdot + TiCl_3.$$

The reactivity with $TiCl_4$ falls in the sequence $CH_2{=}CH > C_6H_5 > CH_3 > C_2H_5 > n\text{-}C_3H_7 > n\text{-}C_4H_9 > i\text{-}C_3H_7$. / Repts. Govt. chem. ind. Res. Inst. Tokyo (Tokyo Kogyo Shikensho Hokoku) *57*, 213 (1962) / −St. [Rd 305/97 IE]

Good yields of the difficultly accessible monoalkylidene- and monoarylidene ketones were obtained by *L. Birkofer*, *S. M. Kim*, and *H. D. Engels* using aldehyde addition to enamines; *e.g.* *N*-(Δ^1-cyclopentenyl)morpholine (I) and benzaldehyde gave 84 % 2-benzylidene-cyclopentanone. The intermediate *N*-(2-benzylidene-Δ^5-cyclopentenyl)morpholine in this transformation can be isolated. Formaldehyde with (I), gives bis-(2-oxocyclopentyl)methane (II), not 2-methylene-cyclopentenone (III) as expected. The latter apparently occurs only as an intermediate and quickly reacts with a further molecule of (I) to be converted to (II). Some of the alkylidene- and arylidenecyclanones formed react like (III) with a further molecule of I, *e.g.* α,α-bis-(2-oxocyclopentyl)ethane is formed from ethylidenecyclopentanone and (I). / Chem. Ber. *95*, 1495 (1962) / −Bi. [Rd 304/96 IE]

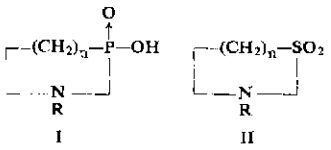
Nucleophilic substitution reactions in halogenated pyridines are the subject of a report by *C. Kaufmann* and *F.-P. Boettcher*. Treatment with lithium piperidide in piperidine-ether of 3-chloro- or 3-bromopyridine (I) gives 3- and 4-piperidinopyridine in the ratio 48:52. Both conversions may go *via* 3,4-dehydropyridine (II), to which lithium piperidide (or piperidine) adds.



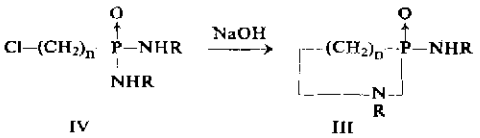
2,3-Dehydropyridine is apparently not formed, although the hydrogen atom at C-2 is more acidic than that at C-4. In the case of 3-fluoropyridine, the ratio of isomers is 96:4, which may be explained as a substitution *via* an addition-elimination reaction. The conversions of 4- and 2-halopyridines with lithium piperidide are largely or completely in accord with the additive mechanism of nucleophilic substitution. / Chem. Ber. *95*, 1528 (1962) / −Sk. [Rd 302/94 IE]

The synthesis of malonyl-CoA, an intermediate of fatty acid biosynthesis, was achieved by *H. Eggerer* and *F. Lynen*. They caused *S*-malonyl-*N*-caprylcysteamine to react in aqueous $KHCO_3$ solution with coenzyme A. An equilibrium is obtained that is displaced entirely in favour of malonyl-CoA by using a 4- to 5-fold excess of malonylcaprylcysteamine and continuous extraction of the *N*-caprylcysteamine with ether. The yield of malonyl-CoA calculated on the quantity of coenzyme A employed is 100 %. Unreacted malonylcaprylcysteamine is regained by extracting it with ether after acidification of the reaction mixture with Dowex 50 (H^+ form). The reagent is obtained by the reaction of malonyl chloride with *N*-caprylcysteamine. It crystallizes in colorless needles (m.p. 70–71 °C, $\lambda_{max} = 236\ m\mu$) and may be kept indefinitely. / Biochem. Z. *353*, 540 (1962) / −Hg. [Rd 317/103 IE]

The term "phostamic acids" is applied by *B. Helferich* and *U. Curtius* to a new class of compounds of general formula I. The term was chosen by analogy with the term sultams for



I II

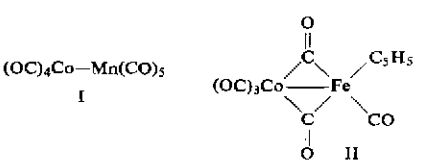


IV III

compounds of structure II. Amides of the phostamic acids (III, n = 3 or 4) are obtained from ω-halogenoalkane-1-phosphonic diamides (IV) by boiling with caustic soda in methanol. The yields lie between 33 and 75%. The phostamic amides are slightly hydrolyzed by acids even at room temperature. Attempts to obtain free phostamic acids from ω-haloalkane-1-phosphonic amides have not yet succeeded, evidently on account of the excessive sensitivity of the free acids to alkali. / Liebigs Ann. Chem. *655*, 59 (1962) / –Hg. [Rd 316/102 IE]

Simultaneous oxidation and esterification of *p*-xylene to give dimethyl terephthalate (I) is reported by *U. Maffezzoni* and *E. Alneri*. A mixture of methanol and air in a ratio of 1:1 by volume is allowed to react with *p*-xylene in a steel autoclave at a temperature of about 200 °C and 10–15 atm pressure. Cobalt salts (about 1–2 g per kg reaction mixture) act as catalysts. Under these conditions, methanol is fairly stable to oxygen, so that the yield of I is 95%, calculated on the xylene or 60–70% calculated on the methanol. Formaldehyde, formic acid, carbon monoxide, methyl formate, and dimethoxymethane are formed as easily separable by-products. The new process, which may be operated either continuously or batchwise, has considerable importance in view of the rapid development of poly(ethylene terephthalates), because production can be increased and investment and operational costs reduced in comparison to the current two-stage processes. / Chim. e l'Ind. *44*, 631 (1962) / –Pf. [Rd 314/101 IE]

Mixed metal carbonyls are described by *K. K. Joshi* and *P. L. Pauson*. Sodium cobalt tetracarbonyl reacts with bromomanganese pentacarbonyl in tetrahydrofuran at room temperature to give cobalt manganese nonacarbonyl (I), which forms orange-red needles, m.p. 45–46 °C.



I II

Under the same conditions, sodium cobalt tetracarbonyl interacts with cyclopentadienyliron dicarbonyl iodide to yield cyclopentadienyliron cobalt hexacarbonyl (II) as reddish black crystals, m.p. 52–53 °C. / Z. Naturforsch. *17b*, 565 (1962) / –Ko. [Rd 342/105 IE]

The Hofmann degradation of tritium-labelled quaternary ammonium salts has been studied by *F. Weygand, H. Daniel*, and *H. Simon*. Decomposition of trimethyl-ethyl(2T)-ammonium hydroxide (I), in vacuum at 40 °C or in glycol at 180 °C or with superheated steam, gave non-radioactive trimethylamine, indicating exclusively β-elimination.

$$\underset{\text{(I)}}{[(CH_3)_3N{-}CH_2{-}CH_2T]^{\oplus}\ OH^{\ominus}} \rightarrow (CH_3)_3N + CH_2{=}CHT + HOT + HOH$$

Trimethyl-ethyl(2T)-ammonium iodide (II) and trimethyl-(T)-ethyl-ammonium iodide (III) were subjected to the modified Hofmann degradation with phenyl-lithium (2 moles) in ether.

$$\underset{\text{(II)}}{[(CH_3)_3N{-}CH_2{-}CH_2T]^{\oplus}\ I^{\ominus}},\quad \underset{\substack{|\\ CH_2T}}{[(CH_3)_2N{-}CH_2{-}CH_3]^{\oplus}\ I^{\ominus}}\ \text{(III)}$$

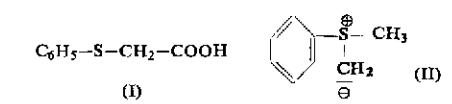
Compound (II) gave trimethylamine containing *ca.* 80% of the possible tritium activity; it follows from this that the primary reaction is the splitting-off of a proton from a methyl group and that the degradation is accomplished by α,β-elimination.

$$\text{(II)} + C_6H_5Li \xrightarrow{-C_6H_6} (CH_3)_2\overset{\oplus}{N}{-}\underset{\substack{|\\ \ominus}}{CH_2}{-}CH_2T \rightarrow (CH_3)_2N + \underset{\substack{|\\ CH_2T}}{CH_2}{=}CH_2$$

$$(CH_3)_3N + CH_2{=}CHT$$

The olefin contains relatively little tritium, indicating a strikingly small isotope effect. The homologous trimethyl-n-propyl(2T)-ammonium iodide shows the same behaviour on treatment with phenyl-lithium, and (III) yielded unlabelled ethylene. / Liebigs Ann. Chem. *654*, 111 (1962) / –Sk. [Rd 301/93 IE]

The reaction of dehydrobenzene with thio-ethers has been studied by *V. Franzen, H.-I. Joschek*, and *C. Mertz*. Dehydrobenzene (obtained from *o*-chlorobromobenzene and butyl-lithium) reacts with dimethyl sulphide to yield on carboxylation *S*-phenyl-thioglycollic acid (I), providing excess butyl-lithium is used. With one equivalent of butyl-lithium, methylphenyl sulphide (75%) and polymethylene are formed. It seems that the intermediate ylide (II) is stabilised by butyl-lithium.



(I) (II)

The polymethylene is not formed from free methylene; CH_2 could not be trapped in an interception reaction. With dietbyl sulphide, dehydrobenzene (III) yields ethylene and phenyl ethyl sulphide; however, in the presence of an organometallic base the reaction of (III) with diphenyl sulphide does not yield an ylide. Instead the organometallic base is added onto (III). Conversely, from triphenylsulphonium bromide and

$$^{\oplus}S(C_6H_5)_3 \xrightarrow{C_4H_9Li} \text{(III)} + (C_6H_5)_2S$$

butyl-lithium dehydrobenzene and diphenyl sulphide are formed. / Liebigs Ann. Chem. *654*, 82 (1962) / –Sk. [Rd 300/92 IE]

BOOK REVIEWS

Lexikon alchemistisch-pharmazeutischer Symbole (Dictionary of Alchemical-Pharmaceutical Symbols), by *W. Schneider*. Verlag Chemie GmbH., Weinheim/Bergstr. 1962. 1st Ed., 140 pp. Price DM 14.– (about $3.75).

The depths of alchemy are particularly illustrated by the fact that for some years alchemical lore has been studied not only by chemical historians, but also by psychologists.

It is exceptionally attractive for the historian to compare the tenets of alchemy with modern chemical dogma founded on rational scientific reasoning. He is concerned with the problem, which alchemical conceptions and what part of the fund of alchemical knowledge have influenced the development of modern natural science.

For the psychologist, alchemy is a treasure trove of symbols that express subconscious mental events. Because of this,

some notable investigators see in alchemical lore a forerunner of psychology.

The liberal use of symbols is a characteristic of alchemical literature. One encounters not only symbols used as a shorthand notation for substances or simple processes such as distillation or sublimation, but also drawn or written symbolic pictures of whole reaction schemes for chemical conversions, used as a veil to be penetrated only by the initiate.

The study of alchemical literature is made more difficult by the use of these symbols in a confusing profusion and variety of form. *Wolfgang Schneider*'s "Dictionary of Alchemical-Pharmaceutical Symbols" is a valuable guide through this labyrinth of prodigality and ambiguity. In this reproduction of symbols from a work that appeared in Ulm in 1755 entitled "Medizinisch-Chymisch- und Alchemistisches Oraculum", enlarged by a compilation of the most frequently used abbreviations and signs and by a valuable bibliography, the modern initiate into alchemy is offered a tool wherewith to acquaint himself with this very interesting historical cultural material. The use of the "Lexikon" is facilitated by a comprehensive index.

G. Huber and *K. Menzi*, Basel (Switzerland) [NB 893/25 IE]

Gmelins Handbuch der anorganischen Chemie (Gmelin's Handbook of Inorganic Chemistry). 8th Edition, new and completely revised. Published by the Gmelin Institute for Inorganic Chemistry and Allied Fields in the Max Planck Society for the Advancement of Science. Initiated by *R. J. Meyer*, continued by *Erich Pietsch*. Verlag Chemie GmbH., Weinheim/Bergstraße (Germany).

This is the last article in a series of reviews of the newly published Gmelin Supplements, which began in Angew. Chem. internat. Edit. *1*, 277 (1962) and was continued in Angew. Chem. internat. Edit. *1*, 463 and 609 (1962). It is a review of the three volumes published in 1961.

System No. 60: Copper, Part B, fascicle 2 (Copper-boron to copper-bismuth compounds), 1961, XLI, 352 pages with 38 figures, German-English table of contents, English headings and subheadings on the margins of the text. Clothbound [*] DM 231.—. By *Olga Angern, M. Atterer, H. Balters, K.-C. Buschbeck, R. Gagarin, Emma Haller, Erna Hoffmann, K. Holzapfel, Ellen v. Lindeiner-Schön, P. Stiess*, and *K. Swars*.

This fascicle Copper B 2 (352 pages with 38 figures) is a continuation of fascicle Copper B 1, which was published three years earlier (1958) and has already been reviewed in this journal [Angew. Chem. internat. Edit. 74, 278 (1962)]. It covers the compounds of copper with the elements boron, carbon, silicon, phosphorus, arsenic, antimony, and bismuth.

The bulk of this fascicle (more than 70 % of the text) is covered by the compounds of copper with carbon (252 pages). The chapter begins with a section on copper acetylides (17 pages) and proceeds, after a brief discussion of the alleged existence of a copper carbonyl (1 page), to the copper carbonates (16 pages); the basic copper(II) carbonates $2CuCO_3 \cdot Cu(OH)_2$ (azurite) and $CuCO_3 \cdot Cu(OH)_2$ (malachite) are discussed in detail. The following large chapter on the copper salts of organic acids (185 pages) includes the salts of aliphatic and aromatic mono-, di-, and polycarboxylic acids, unsaturated carboxylic acids, hydroxy-, oxo-, nitro-, halo-, and cyanocarboxylic acids, picric acid, as well as aliphatic and aromatic sulfinic and sulfonic acids. This selection of organic salts is much more extensive than that in other volumes of the Gmelin Handbook, and is justified by the special importance of many organic copper salts. The selections were not only based on the importance of these compounds, but also made to emphasize relationships. Inner complexes of copper, as opposed to cationic and anionic copper complexes, are not discussed in this chapter. Their description is to be included in the final fascicle of Part B of Copper. For the sake of coherence, the salts of acidocuprate ions, *i.e.* anionic copper complexes, are discussed here, in deviation from the Gmelin Principle of the Last Place, according to which they would have been discussed in the following Copper fascicle, under the heading of the respective metal. This is useful for example in the case of copper tartrates and Fehling's solution (23 pages), since the complex anions play the primary part and the cations have only a secondary role in the tartratocuprate ions which appear in the sediment of Fehling's solution. The cyanides, cyanates, thiocyanates, and related compounds of copper (33 pages) conclude this chapter. While the acidocuprate ions are discussed here as in the previous case, the corresponding metal salts will be covered in the subsequent Copper fascicle B 3 under the respective metals, just as in the case of the anionic copper carbonate complexes.

The sections on the compounds of copper with boron (7 pages), silicon (21 pages), phosphorus (29 pages), arsenic (34 pages), antimony (6 pages), and bismuth (3 pages) take up much less space (100 pages in total) than the copper-carbon compounds. Worth mentioning are the discussions of Cu-B alloys and copper borates, Cu-Si alloys and copper silicates, Cu-P alloys, copper phosphides, and copper phosphates, Cu-As alloys, copper arsenites, arsenates, antimonates, and bismuthites. The section (24 pages) on copper arsenite ("Scheele's Green") and copper arsenate (pest control, plant protection, "Schweinfurt Green") of this part of the volume should be of special interest.

The bibliography is complete to the end of 1949 and is selectively quoted to 1958 in special cases. If anything must be criticized about this volume, it is the often quite unclear typographical arrangement of the German-English index of 41 pages. For example, it requires some effort to find where the section on copper salts of aliphatic monocarboxylic acids ends and the section on copper salts of di- and polycarboxylic acids begins. Captions such as these, which appear as primary headings in the text, are reproduced in the index in the same type face as the individual compounds and thus lack prominence. The same applies to the indexes of other Gmelin fascicles. For example, in the index of the volume on calcium, discussed below, secondary captions are in many cases bolder than primary captions. Thus, for example, the sections "The System $CaO-P_2O_5$" and "The System $CaO-P_2O_5-H_2O$" appear in their typographical arrangement as if they were subheadings of "Calcium Hypophosphate," although in actuality they begin a new chapter on calcium phosphates. Better care should have been taken in this respect to facilitate the use of the index.

System No. 28: Calcium. Part B, fascicle 3 (conclusion of calcium compounds), 1961, LXII, 912 pages with 133 figures. German-English table of contents, English headings and subheadings on the margins of the text. Clothbound DM 568.—. By *B. Apel, M. Atterer, Marianne Drössmar-Wolf, H. Gedschold, Erna Hoffmann, G. Kirschstein, P. Koch, H. K. Kugler, A. Kunze, H. Lehl, J. Nägler, L. Roth, L. Thaler, Ursula Trobisch-Raussendorf*, and *Hildegard Wendt*.

The system number Calcium is concluded with this 912-page fascicle Calcium B 3, which continues fascicle Calcium B 2 (compounds up to dithionite) published four years previously (1957). *In toto*, it comprises 2056 pages with 236 figures in two parts (A: Historical. Sources. The Element and Its Alloys. 488 pages, 29 figures. B: Compounds of Calcium 1568 pages, 207 figures).

This volume contains the calcium-sulfur compounds not already taken up in fascicle B 2 as well as the compounds of calcium (System No. 28) with the elements following sulfur and having the system numbers 10 through 27 (selenium, tellurium, boron, carbon, silicon, phosphorus, arsenic, antimony, bismuth, alkali metals including ammonium, beryllium, magnesium). The technology of all the respective calcium compounds discussed is omitted, since this has already been covered in fascicle Calcium B 1. In view of the great volume of the material, this review must be limited to the discussion of a few examples.

[*] The Gmelin volumes after this fascicle are not available in paperbound form.

The chapter on compounds of calcium with sulfur (142 pages) begins with a three-page survey of the kinetics and statics of the system Ca—S—O. The chapter is primarily devoted to a discussion of calcium sulfite (15 pages) and calcium sulfate (111 pages), the remaining 13 pages treating the less important calcium-sulfur compounds such as calcium thiosulfate (8 pages) and calcium dithionate (2 pages). The section on calcium sulfite $CaSO_3$ — including calcium acid sulfite $Ca(HSO_3)_2$, which is of technical importance in the digestion of wood ("sulfite pulp") — covers the preparation and properties of the compound and, in particular, the systems $CaSO_3$—H_2O (calcium sulfite hydrates) and CaO—SO_2—H_2O (sedimentation, temperatures of crystallization, vapor pressures, conductivity, solution equilibria). The much larger chapter on calcium sulfate deals with the anhydrous compound $CaSO_4$ (anhydrite) and with the hydrates $CaSO_4 \cdot 2H_2O$ (gypsum) and $CaSO_4 \cdot 1/2\ H_2O$ (plaster of Paris). It begins with four pages of data on the system CaO—SO_3 (solid phases, melt equilibria, vapor and dissociation pressures, dissociation rates, thermodynamic data) and then turns to a description of the preparation and the properties of anhydrous calcium sulfate (46 pages), the crystal structures of the three $CaSO_4$ modifications ($CaSO_4$ I: high temperature modification; $CaSO_4$ II: insoluble anhydrite; $CaSO_4$ III: soluble anhydrite). It also treats the optical behavior of $CaSO_4$ crystals and the system $CaSO_4$—H_2O (invariant and univariant equilibria, vapor pressures, thermodynamic data).

This last part of the section is a means of transition to the hydrates of calcium sulfate. In the section on gypsum (18 pages), its crystallographic and optical properties and behavior during dehydration (calcination, formation of stucco and flooring plaster) are considered. This then leads to a discussion of the hemihydrate $CaSO_4 \cdot 1/2\ H_2O$ (16 pages), important as a structural and specialty plaster; in particular, the reaction of plaster with water ("setting") and the related thermodynamic data are covered. The description of calcium sulfate is concluded by sections on special forms of calcium sulfate (1 page), on the properties of aqueous calcium sulfate solutions (20 pages), on organic adducts of calcium sulfate (1 page), on the system $CaSO_4$—H_2SO_4—H_2O and the corresponding calcium hydrogen sulfates (2 pages) and on double-salt systems of calcium sulfate (3 pages).

The chapter on compounds of calcium with the elements of the 6th main group of the periodic system is completed with discussions on calcium-selenium (3 pages) and calcium-tellurium compounds (2 pages) analogous to the calcium sulfur compounds.

The section on compounds of calcium with boron (17 pages) includes calcium boride CaB_6 (3 pages) and calcium borates and their derivatives (14 pages); among the latter, the system CaO—B_2O_3, corresponding to the anhydrous calcium borates, as well as the system CaO—B_2O_3—H_2O, corresponding to calcium borate hydrates, are discussed.

This is followed by the compounds of calcium and carbon, which fill almost 25 % (209 pages) of this volume. First, the industrially important calcium carbide CaC_2 is discussed (30 pages); its technology was covered in detail in fascicle B 1 and this volume gives details of its laboratory preparation, the lattice structures of the four CaC_2 modifications, the chemical behavior of CaC_2 toward elements and compounds (especially water), and data on the system CaC_2—CaO. The subsequent discussion on calcium carbonate $CaCO_3$ (106 pages) begins with an 11-page section on the system CaO-CO_2 (solid phases, kinetics, equilibria), and then proceeds to the production of $CaCO_3$ (17 pages). The various modifications (calcite, aragonite, vaterite) as well as special forms (suspensions, sols, gels) are given consideration. So far as the section on physical properties (42 pages) is concerned, the discussions of mutual transformations and the lattice structures of the three $CaCO_3$ modifications and of the birefringence of $CaCO_3$ crystals deserve mention; the data on the equilibria in the systems $CaCO_3$—H_2O ($CaCO_3$ hydrates) and $CaCO_3$—CO_2—H_2O (acid calcium carbonate) in the section on chemical behavior (36 pages) are also noteworthy. The balance (73 pages) of the chapter on calcium-carbon compounds contains among other things a discussion of calcium cyanide (5 pages), calcium cyanamide (10 pages), calcium thiocyanate (4 pages), calcium formate (6 pages), calcium acetate (10 pages), calcium oxalate (14 pages), calcium tartrate (8 pages), and calcium saccharate (9 pages).

After introductory remarks on the system Ca—Si (1 page), the chapter on compounds of calcium with silicon (86 pages) concerns itself with the three calcium silicides Ca_2Si, $CaSi$, and $CaSi_2$ (5 pages), followed by the calcium silicates (63 pages), and their derivatives (17 pages). The section on the calcium silicates includes both the anhydrous (system CaO—SiO_2; the individual members $3CaO \cdot SiO_2$, $2CaO \cdot SiO_2$, $3CaO \cdot 2SiO_2$, $CaO \cdot SiO_2$) and the hydrated compounds (system CaO—SiO_2—H_2O; the individual members $3CaO \cdot SiO_2 \cdot xH_2O$, $2CaO \cdot SiO_2 \cdot xH_2O$, $3CaO \cdot 2SiO_2 \cdot xH_2O$, $CaO \cdot SiO_2 \cdot xH_2O$, and others), which are of importance for the understanding of the processes occurring during the formation and the setting of cement.

The chapter on the compounds of calcium with phosphorus (108 pages) should also elicit great interest. After introductory remarks on calcium phosphide, hypophosphite, phosphite, and hypophosphate (7 pages) it treats primarily the calcium phosphates and their derivatives 101 pages). First, the systems CaO—P_2O_5 and CaO—P_2O_5—H_2O are discussed; then individual members such as hilgenstockite $Ca_3(PO_4)_2 \cdot CaO$, bydroxyapatite $3Ca_3(PO_4)_2 \cdot Ca(OH)_2$, fluoroapatite $3Ca_3(PO_4)_2 \cdot CaF_2$, chloroapatite $Ca_3(PO_4)_2 \cdot CaCl_2$, sulfate apatite $Ca_3(PO_4)_2 \cdot CaSO_4$, and carbonate apatite $Ca_3(PO_4)_2 \cdot CaCO_3$, the tertiary, secondary, and primary calcium phosphates $Ca_3(PO_4)_2$, $CaHPO_4$, and $Ca(H_2PO_4)_2$, the silicocarnotite $Ca_3(PO_4)_2 \cdot Ca_2SiO_4$ (Thomas flour) and other silicophosphates are treated. A discussion of the calcium polyphosphates $Ca_{n+2}(P_nO_{3n+1})_2$ and calcium metaphosphates $Ca_n(PO_3)_{2n}$, an area of special interest to the fertilizer industry, concludes, this chapter.

The compounds of calcium with arsenic (15 pages), with antimony (3 pages), and with bismuth (1 page), which are analogous to the calcium-phosphorus compounds, complete the discussions of the compounds of calcium with the elements of the 5th main group of the periodic system.

In the 141-page chapter on the compounds of calcium with the alkali metals Li, Na, K, Rb, and Cs (98 pages) and with the alkaline earth metals Be and Mg (43 pages), innumerable systems of compounds are cited. Among others, the silicate systems CaO—K_2O—SiO_2 and CaO—Na_2O—SiO_2 which are typical of glass melts (alkali-lime glasses), the carbonate systems CaO—MgO—CO_2 and CaO—MgO—CO_2—H_2O which are important in dolomites, and the silicate system CaO—MgO-SiO_2 which is basic for the understanding of the formation of magnesium calcium silicate. Data on calcium ammonium and calcium hydrazinium compounds are also included in the chapter on alkali metals.

The volume is concluded by a 31-page chapter on general reactions of the calcium ion and a 154-page chapter on the identification and determination of calcium (75 pages), strontium (36 pages), and barium (43 pages). This portion provides a valuable survey of the behavior of the calcium ion toward inorganic and organic compounds and in ion-exchange reactions, as well as analytical reactions suitable for the identification, the determination, and the separation of calcium and its elemental homologues strontium and barium. The sections on special methods for the determination of the elements in specific materials should be of interest in view of the wide occurrence and importance of the alkaline earth metals.

All in all, fascicle Calcium B 3 is a Gmelin volume which deserves admiration because of its completeness and careful organization. The bibliography is complete to the end of 1949. The subsequent literature beginning with 1950 is added to individual chapters as supplements, in general without complete evaluation of its contents. Only in sections where the development since 1950 has been especially marked, has the text itself been adjusted to accommodate the new material.

System No. 58: Cobalt. Supplementary volume to Part A, 1961, LXXII, 886 pages with 188 figures. German-English table of contents, English headings and subheadings on the margins of the text. Clothbound DM 556 — By *H. Balters, Anna Bohne-Neuber, K.-C. Buschbeck, G. Czack, H. Feicht, R. Gagarin, R. Glauner, H. Golder, G. Huschke, Isa Kubach, H. K. Kugler, H. Lehl, Margarete Lehl-Thalinger, W. Müller, Josef Nägler, Gertrud Pietsch-Wilcke, F. Plessmann, N. Polutoff, G. Rinck, K. Rumpf, Edith Schleitzer-Steinkopf,* and *Ursula Venzke-Sante.*

This supplementary volume of 886 pages continues Part A of Cobalt (Historical. Occurrence. The Element and Its Compounds. 502 pages with 33 figures), which was concluded with two fascicles thirty years ago (1930/31); the present volume covers the years 1932 to 1949. The corresponding supplementary volume to Part B (ammines of cobalt) will be published this year.

The volume begins with a 32-page historical review which covers, for example, more recent studies on the origin and meaning of the word cobalt, the history of the use of cobalt minerals as pigments for glass and enamels in and outside of Europe, and the history of the discovery of metallic cohalt and of cobalt compounds.

The following 150-page chapter covering the occurrenc of cobalt deals first with its extraterrestrial occurrence (13 pages) in the sun, the planets, in the atmosphere of slárs, and as well as a fixed component of the metal, sulfide, and silicate phases of meteorites. It then proceeds to the geochemistry of cobalt (83 pages), the crystallochemical theories as well as the occurrence of cobalt in the lithosphere (magmatic and sedimentary deposits), in the hydrosphere (sea water, ground water, springs rivers, inland lakes, mineral waters), and in the biosphere (concentration, type of occurrence, absorption, migration, physiological significance). The chapter concludes with a 42-page topographical survey (economic statistics, European and non-European deposits) and a 12-page tabulation of the most important cobalt minerals.

The 27-page chapter on the technology of cobalt and its compounds covers the processing of cobalt ores, the beneficiation of the ores and the processing of intermediate products (pyrometallurgical and wet metallurgical processes), the production of metallic cobalt (chemical and electrolytic processes), the preparation of cobalt oxides and of cobalt(III) fluoride, and the use of cobalt and its compounds

There are 167 pages devoted to the element cobalt. The chapter starts with the formation and preparation of cobalt in the laboratory (5 pages), especially the preparation of special forms (powder, pyrophoric metal, sponge cobalt, mirrors and films, single crystals, sols), and the synthesis and isolation of isotopes of elemental cobalt. It then proceeds to a 2-page review of the physiological hazards of cobalt (skin diseases, toxic effects) and follows this with the description of the physical properties (74 pages), especially its spectral behavior. The electrochemical properties of cobalt are described in 53 pages. The latter section discusses in detail the potentials of cobalt toward several electrodes and the behavior of cobalt at the dropping mercury electrode, the overvoltage of hydrogen and oxygen on cohalt, the cathodic and anodic behavior of cobalt, as well as the processes during the electrolytic deposition of cobalt from various solutions. The chapter concludes with a 33-page section about the chemical behavior of cobalt toward elements and compounds and about the general reactions of the cohalt ion (hydration, ion activity, behavior toward inorganic and organic compounds, oxidation of Co^{2+}, reduction of Co^{3+}, exchange reactions between divalent and trivalent cobalt, color changes in cohalt salt solutions, behavior of the cobalt ion in ion exchangers, identification and determination of cobalt).

The alloys of cobalt are discussed in 95 pages; the alloy systems of cobalt (System No. 58) with the metals of systems numbers 18 (antimony) to 57 (nickel) are discussed. Special attention is given to the alloys of cobalt with antimony, zinc, titanium, tin, chromium, molybdenum, tungsten, and nickel. Altogether, these alloys occupy more than 3/4 (74 pages) of the chapter on this subject. In accordance with the importance of cobalt-tungsten alloys as hard metals and their relatively high acid resistance, an extensive bibliography on Co-W alloys has been added to the section on cobalt-tungsten.

The bulk of the volume (almost one half) is devoted to a 416-page discussion of the compounds of cobalt with the elements having system numbers lower than 58 (Co). Especially detailed information is given here on the oxides and hydroxides (36 pages), the fluorides CoF_2 and CoF_3 (10 pages), the chlorides $CoCl_2$ and $CoCl_3$ (47 pages), the bromide $CoBr_2$ (10 pages), the sulfides (21 pages), the sulfate $CoSO_4$ (26 pages), the carbonyls and their derivatives (24 pages), the cobalt salts of several organic acids including their cationic and anionic complexes (10 pages), the cyanides and their complexes (7 pages), the cobalt silicides and silicates (8 pages), the arsenides (11 pages), as well as the double oxides, double salts, and complex compounds of cobalt with the alkali metals including ammonium (79 pages), the alkaline earth metals (13 pages), the metals of the zinc group (14 pages), and with nickel (7 pages). The description of these groups requires more than 3/4 (322 pages) of the space devoted to compounds of cobalt. From the variety of material, the following examples are selected at random: The description of the system Co–O, the oxidation stages CoO, Co_3O_4 Co_2O_3, the lattice structures of the two modifications of $Co(OH)_2$ and the oxidation of $Co(OH)_2$ to $Co(OH)_3$, the preparation and fluorinating action of cobalt(III) fluoride CoF_3, the dehydration of the hydrates of cobalt(II) chloride and the nonaqueous solutions of cobalt(II) bromide $CoBr_2$, the system Co—S and its numerous solid phases, the paramagnetism of cobalt(II) sulfate $CoSO_4 \cdot 7H_2O$, the structure of the cobalt carbonyls $[Co(CO)_4]_2$ and $[Co(CO)_3]_4$, the properties of cobalt carbonyl hydride $HCo(CO)_4$, the tetracarbonyl cobaltates $Co(CO)_4$ and the substitution products of the cobalt carbonyls, the separation of the enantiomorphs, the assignment of configurations, the optical rotation and the racemization of the trioxalato cobaltate(III) ion $Co(C_2O_4)_3^{3-}$, the cyano complexes of mono-, di-, and trivalent cobalt, the use of cobalt silicate as a pigment for glass and porcelain, the system Co—As and the numerous cobalt arsenides, the ammonium salts of acido-cobaltate(II) and of acido-cobaltate(III) ion, the zinc cobalt oxide $(Co,Zn)O_2$ ("Rinman's Green") and systems of cobalt salts with salts of other metals (also in the presence of solvents) including the description of complex compounds occurring in these systems.

The literature published up to the end of 1949 is surveyed in its entirety; however, but only selected literature from the years 1950 to 1960 is presented, and then generally without thorough evaluation of the contents except where areas of unusual development since 1950 are concerned.

E. Wiberg [NB 859/13 IE]

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