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SEMINAR TOPICS

CHEMISTRY 435 II SEMESTER 1957-58

SEMINAR TOPICS

THE CHEMISTRY OF THE CYANOCARBONS

Reported by William A. Hills February 6, 1958

INTRODUCTION

Compounds containing carbon atoms substituted by a large number of cyano groups (cyanocarbons) have been known in the literature for a long time. However, not until the work of Cairns, Middleton (1) et al., had any systematic investigations of these compounds been made. Prior to that time, the cyanocarbons were not even recognized as a distinct group and as a result remained almost unnoticed.

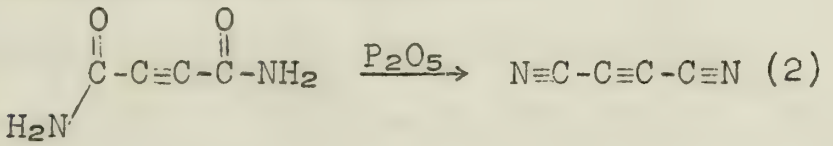
The cyanocarbons represent a group of very reactive compounds, which not only provide routes to rather difficultly accessible compounds, but in themselves provide a series of unusual molecules.

In this seminar the preparations, reactions, and properties of the cyanocarbons will be discussed.

GENERAL PREPARATIVE METHODS

The preparations of the cyanocarbons are illustrative of a variety of rather simple preparative methods and represent nothing new or startling from a synthetic point of view. Far more interesting are the reactions of some of these compounds and their derivatives. Nevertheless, a few illustrations of the preparations of simple cyanocarbons are outlined below.

A. Dehydration of Polyamides.

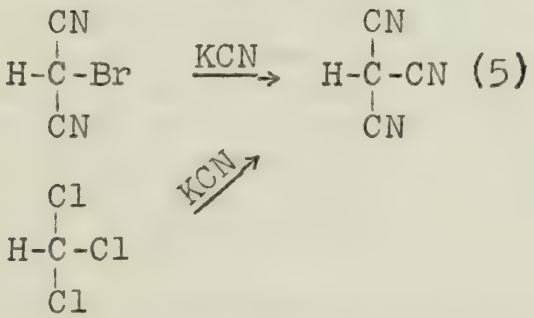


$$H_2N\text{-}C(=O)\text{-}C{\equiv}C\text{-}C(=O)\text{-}NH_2 \xrightarrow{P_2O_5} N{\equiv}C\text{-}C{\equiv}C\text{-}C{\equiv}N \quad (2)$$

B. Oxidative Coupling of Cyanoacetylenes.

$$N{\equiv}C\text{-}C{\equiv}CCu \xrightarrow{K_3Fe(CN)_6} N{\equiv}C\text{-}(C{\equiv}C)_2\text{-}C{\equiv}N \quad (2,3,4)$$

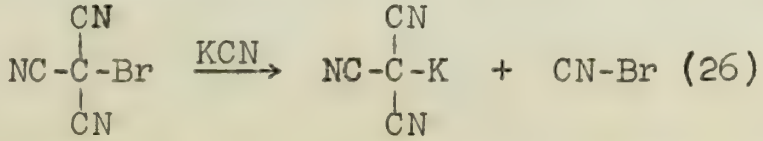
C. Displacement of Halogens by Potassium Cyanide.



$$\begin{array}{l} \mathrm{CN} \\ \mathrm{H\text{-}C\text{-}Br} \\ \mathrm{CN} \end{array} \xrightarrow{KCN} \begin{array}{l} \mathrm{CN} \\ \mathrm{H\text{-}C\text{-}CN} \\ \mathrm{CN} \end{array} \quad (5)$$

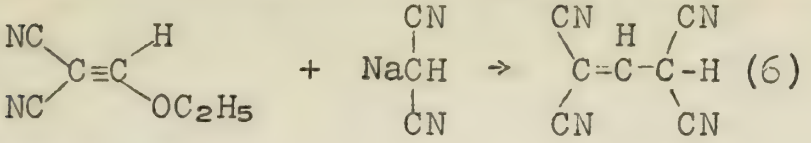
$$\begin{array}{l} \mathrm{Cl} \\ \mathrm{H\text{-}C\text{-}Cl} \\ \mathrm{Cl} \end{array} \xrightarrow{KCN}$$

It is interesting to note that attempts to prepare tetracyanomethane in an analogous manner gave the following:



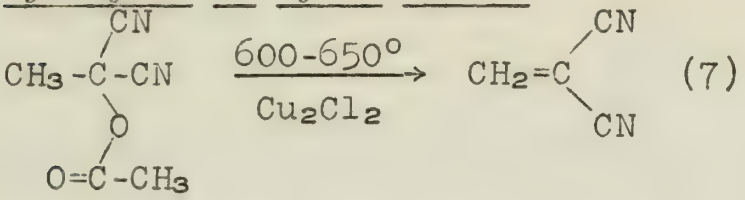
$$\begin{array}{l} \mathrm{CN} \\ \mathrm{NC\text{-}C\text{-}Br} \\ \mathrm{CN} \end{array} \xrightarrow{KCN} \begin{array}{l} \mathrm{CN} \\ \mathrm{NC\text{-}C\text{-}K} \\ \mathrm{CN} \end{array} + \mathrm{CN\text{-}Br} \quad (26)$$

D. Displacement Reactions Involving Cyano-Ethers.



(6)

E. Pyrolysis of Cyano-Esters.



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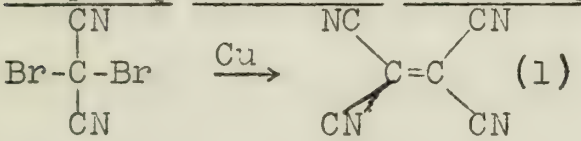
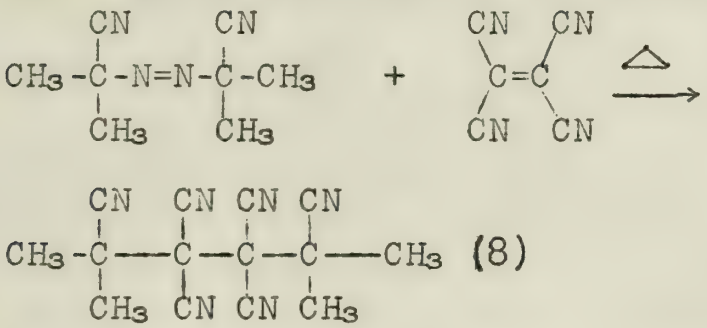
F. Coupling Reactions Involving Dibromomalonitrile.



(1)

G. Free Radical Addition to Unsaturated Cyanocarbons.



(8)

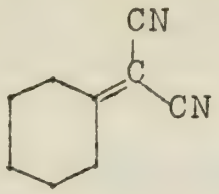
REACTIONS AND PROPERTIES OF THE CYANOCARBONS

Perhaps, of all the simple cyanocarbons prepared tetracyanoethylene (abbreviated TCNE), I, is the most versatile. It provides a route to a number of more highly substituted cyanocarbons and to a number of useful intermediates. Some of the reactions of TCNE have been outlined by Cairns (9). However, since a tremendous part of the knowledge of the Chemistry of the cyanocarbons stems from the study of TCNE, a discussion of the reactions and properties of these compounds in terms of TCNE is desirable. However, this is not intended to imply that the reactions of TCNE and its derivatives are completely general since no thorough studies of the chemistry of other cyanocarbons have been made. Many of the compounds were merely synthesized for other purposes and no attempts were made to study their chemistry in detail. For example, the cyanoacetylenes cited previously were used only in the study of production of ultra-high temperatures by their reactions with oxygen or ozone (2).

Tetracyanoethylene, I, has been synthesized from malonitrile by a number of methods. The most satisfactory is the dimerization of dibromomalonitrile (1) in benzene catalyzed by copper powder. This reaction probably involves the formation of an intermediate dicyanocarbene which, in the absence of another reactive species, reacts with itself. Evidence for this conclusion was obtained by repeating the reaction in cyclohexene, a carbene acceptor. A thick oil was obtained. Its infrared spectrum is consistent with 7,7-dicyanobicyclo[4.1.0]-heptane, II. However, upon distilling this material

only cyclohexylidenemalonitrile, III, was obtained. The latter (27) is known. It seems safe to conclude that III formed from the thermal rearrangement of II.

II



III

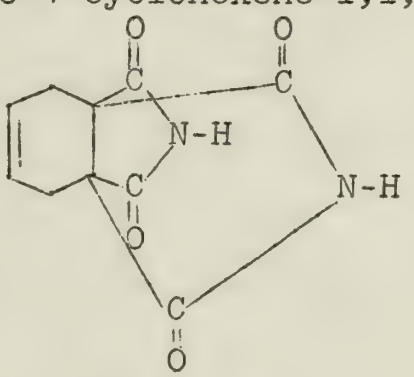
Tetracyanoethylene is a colorless crystalline solid which sublimes readily at temperatures above 120° at atomospheric pressures. Its high stability to heat is shown by its ability to sublime unchanged at a pressure of 2.7 mm. through a tube containing carborundum chips heated to 600°.

Addition Reactions of Tetracyanoethylene

Addition reactions involving the double bond of TCNE occur with several types of reagents, including dienes, ketones, and hydrogen (8). Tetracyanoethylene is an unusually reactive dienophile reacting at room temperature with butadiene, anthracene, β-vinylnaphthalene and other 1,3-dienes to give tetracyanocyclohexenes, IV. The ease of reaction of TCNE is even more striking when one considers that acrylonitrile requires several days to react with butadiene (10) while fumaronitrile (11) requires even more forcing conditions of both time and temperature to give only fair yields of the Diels-Alder adduct.

IV

The structure of IV was proven by its conversion to 4-cyclohexene-1,2-dicarboxylic acid, V, and to 4-cyclohexene-1,1,2,2-tetracarboxylic diimide, VI, (8).



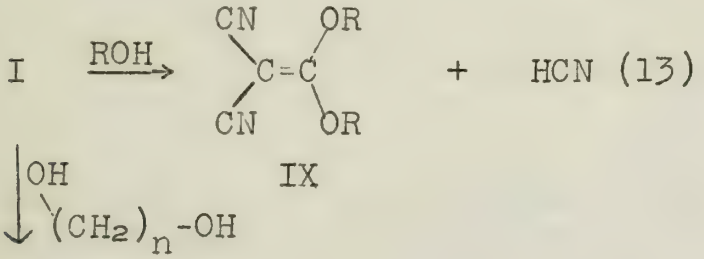
VI

The high dienophilic activity of TCNE, I, may be attributed in part to the tremendous activating influence of four cyano groups. Middleton (8) states that the high dienophilic activity may also be due to the ability of TCNE to form strong π-complexes (12) with various nuclei. π-Complex formation is detected in most of the Diels-Alder reactions involving TCNE. However, since no evidence is available to show that π-complex formation is involved in the rate determining step of these reactions, this explanation must be taken with cautic

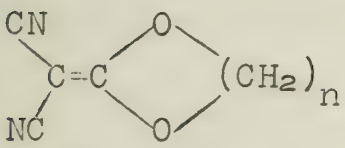
Tetracyanoethylene also reacts with ketones containing α-hydroge to form β,β,γ,γ-tetracyanoketones, [redacted] (8). These reactions are catalyzed by boron trifluoride or "molecular silver". The double bond in TCNE is easily reduced by catalytic hydrogenation, hydrogen sulfide, mercaptans, and hydroiodic acid forming Tetracyanoethane, VIII (8).

NUCLEOPHILIC DISPLACEMENT REACTIONS OF CYANOCARBONS

Tetracyanoethylene, I, is attacked by nucleophilic reagents with the replacement of one or two cyano groups attached to the same carbon atom. In the presence of urea, alcohols and glycols displace two cyano groups to form dicyanoketene acetals, IX, and dicyanoketene cyclic acetals, X, respectively.



R=CH_3-;C_2H_5-

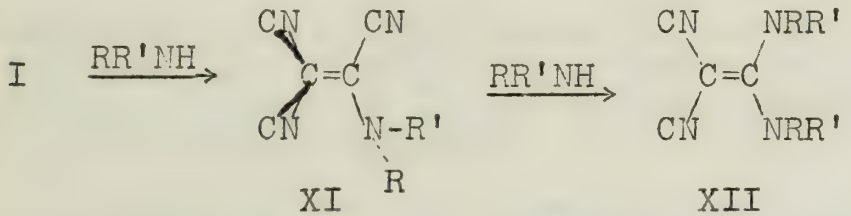


X

n = 2,3

Attempts to displace only one cyano group with an alkoxy group failed

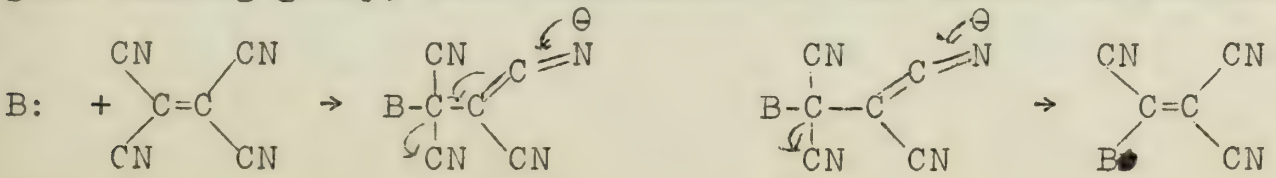
On the other hand, TCNE reacts with primary and secondary aliphatic amines and with most primary and some secondary aromatic amines in a stepwise manner to form tricyano vinylamines, XI, and 1,1-diamino-2,2-dicyanoethylene, XII (25).



XI XII

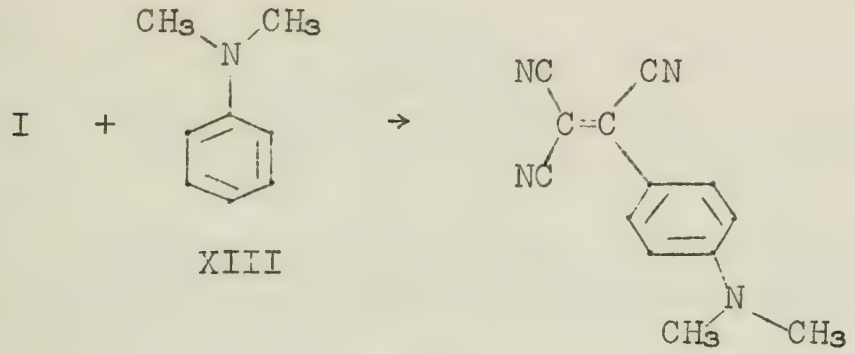
The assignment of these structures are based on chemical analysis and on spectral data (25).

The reaction of TCNE may be rationalized in the following manner The first step involves Michael-Addition of the nucleophile to the double bond. This is followed by elimination of a cyano group (a good leaving group) with reformation of the carbon-carbon double bond



In an analogous manner, the alkoxy group may be displaced from dicyanoketene acetals by nucleophiles such as amines. The reactions of these ketene acetals will be discussed later.

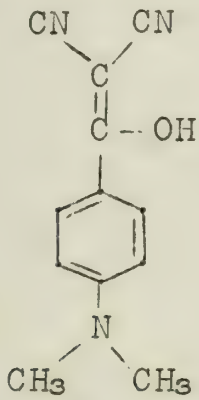
Tertiary and some secondary aromatic amines undergo C-alkylation with TCNE. Thus N,N-dimethylaniline, XIII, gives 4-tricyanovinyl-N,N-dimethylaniline, XIV (25).



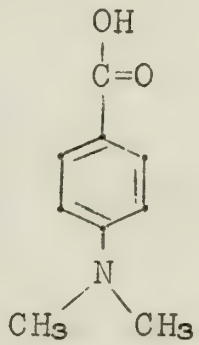
XIII

XIV

The structure of XIV was assigned on basis of its spectrum and its stepwise conversion to 4(1-hydroxy-2,2-dicyanovinyl)N,N-dimethylaniline, XV, by basic hydrolysis and by the conversion of XV to 4-dimethylaminobenzoic acid, XVI, by acid hydrolysis.



XV

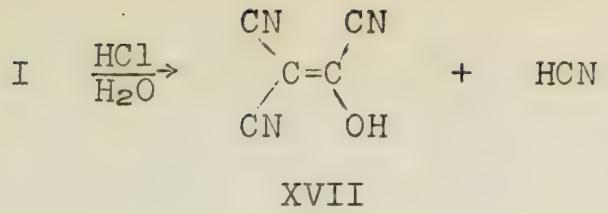


XVI

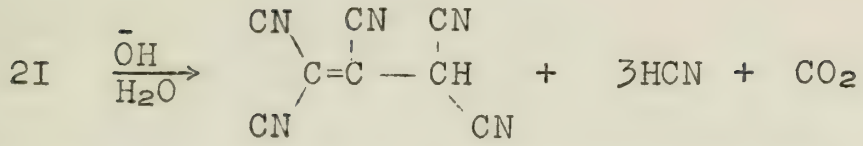
Compound XV is a strong acid (Pka = 2.3). Its infrared spectrum suggests that it exists as a zwitterion (25). Compounds with structures analogous to XIV are highly colored and are used as dyes for hydrophobic materials.

Tetracyanoethylene, I, undergoes acid catalyzed hydrolysis with the replacement of one cyano group to form tricyanovinyl alcohol, XVII (25). This alcohol is acidic and forms very stable salts.

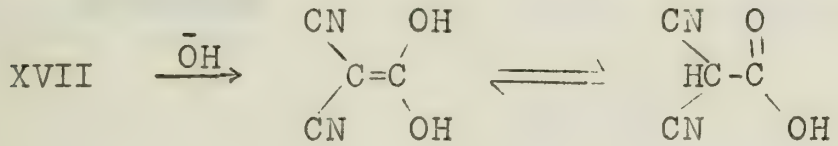
Base catalyzed hydrolysis of TCNE takes a surprisingly different course, forming 1,1,2,3,3-pentacyanopropane, XVIII (14).

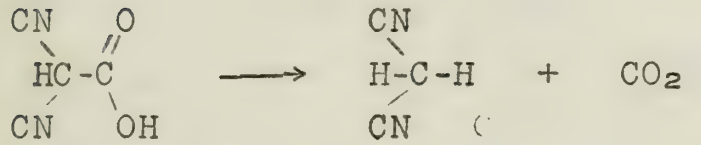


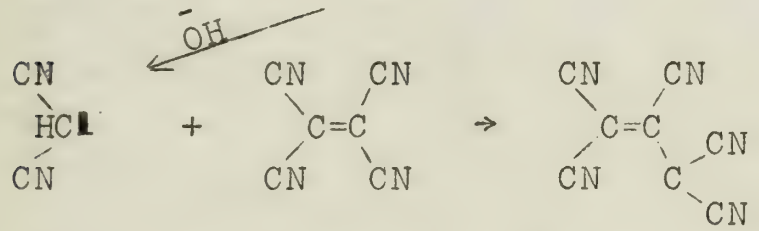
XVII



At first it was thought that XVII was an intermediate in the formation of XVIII. The following mechanism was proposed.

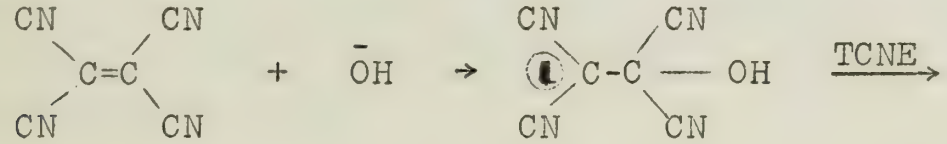




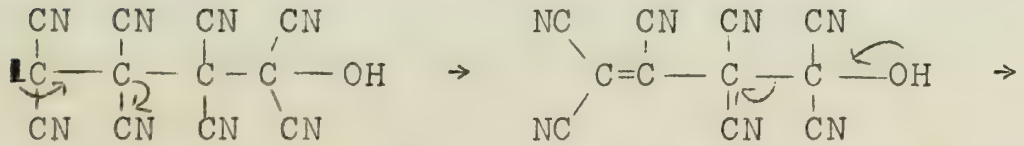


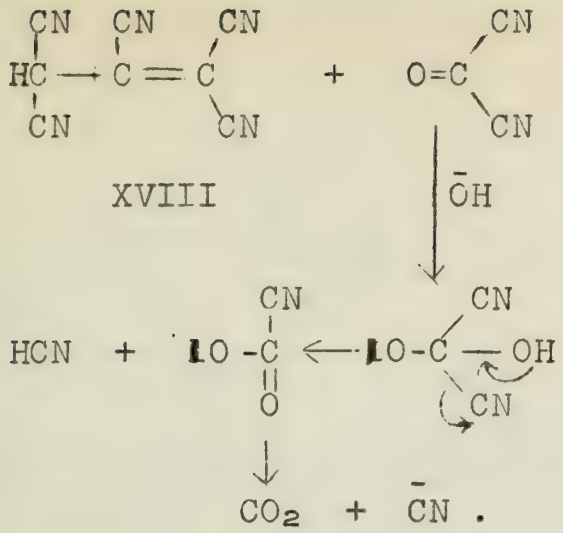
However, this mechanism appears to be unlikely, for attempts to prepare XVIII by basic hydrolysis of TCNE and XVII gave only the amount of XVIII that would be expected from TCNE. Tricyanovinyl alcohol was recovered unchanged. Tricyanovinyl alcohol and malonitrile also gave unchanged material.

In light of this evidence Middleton (14) proposed the following mechanism.



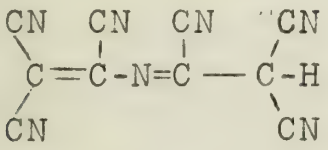
I



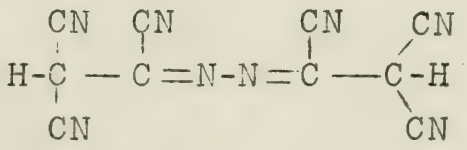


XVIII

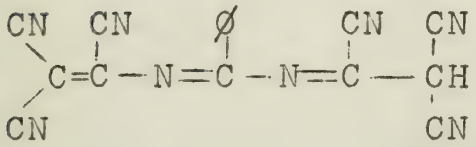
Ammonia, XIX, hydrazine, XX, and benzamidine, XXI, also react readily with TCNE (14). Structures of the adducts formed are given below.



XIX



XX

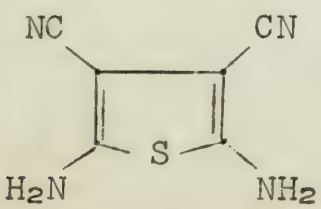


XXI

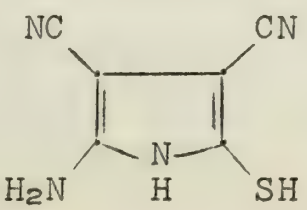
As would the expected XVIII, XIX, XX, and XXI are acids, since the anions formed from the loss of a proton would be highly stabilized by resonance. PKa's for these acids are in the range of 2-3 (14).

ADDITION REACTIONS INVOLVING THE CYANO GROUPS

Tetracyanoethane, VII, readily undergoes reactions involving the triple bands of the cyano groups on adjacent carbon atoms. For example, VII, in presence of a basic catalyst, adds hydrogen sulfide to form 2,5-diamino-3,4-dicyanothiophene, XXII. The latter rearrange to 2-amino-3,4-dicyano-5-mercaptopyrrole, XXIII, on treatment with sodium hydroxide (15).

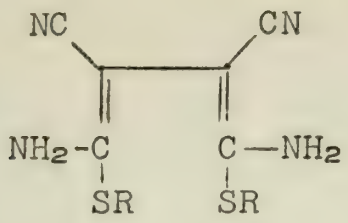


XXII



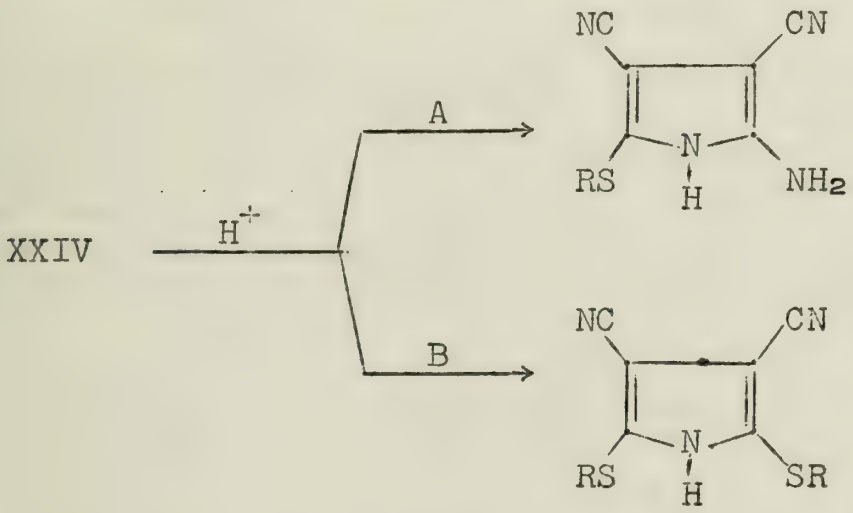
XXIII

Mercaptans react in an analogous manner to give straight chain analogs of XXII.



XXIV

Compounds of type XXIV also undergo cyclization to form substituted pyrroles. However, the reaction may proceed with the elimination of either mercaptan or ammonia (15).



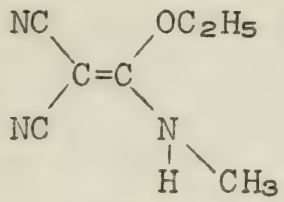
While no thorough study of the factors which determine the course of the reaction has been made, the following observations were reported. When R is phenyl, course A is taken; however, when R is methyl or ethyl, course B is taken. Furthermore, when R is hydroxy ethyl, $-CH_2-CH_2-OH$, the reaction may be made to take either course A or B. When dilute hydrochloric acid is used course A is followed and when cold concentrated hydrochloric acid is used, course B is followed. The latter reaction is the only case where conditions were found which would preferentially produce either pyrrole.

Tetracyanoethane also adds hydrogen bromide and sulfurous acid to form 2-amino-5-bromo-3,4-dicyanopyrroles, XXV, and 5-amino-3,4-dicyanopyrrole-2-sulfonic acid, XXVI, (15), respectively. The structures of these heterocycles were deduced from chemical analysis and from a study of their spectra (infrared and ultraviolet).

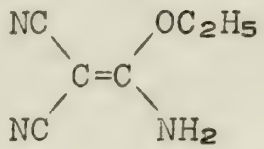
PROPERTIES AND REACTION OF DICYANOKETENE ACETALS

All the dicyanoketene acetals synthesized by Middleton (13) are white crystalline solids with melting points ranging between 51° and 161°. Dimethyl and diethyl dicyanoketene acetal, IX, are unstable at temperatures slightly above their melting points. However, the cyclic ketene acetals, X, are stable at temperatues up to 200°. These compounds are inert to water and alcohols, even in the presence of an acid catalyst.

Like tetracyanoethylene, I, dicyanoketene acetals react with nucleophilic reagents. However, in the case of the ketene acetals, the alkoxy groups are displaced instead of the cyano groups. For example, diethyl dicyanoketene acetal, IX, reacts with methyl amine and ammonia to form 1-methylamino-1-ethoxy-2,2-dicyanoethylene, XXVII, and 1-amino-1-ethoxyl-2,2-dicyanoethylene, XXVIII, respectively. These structures are consistent with the infrared spectra and the chemical analysis of the compounds.

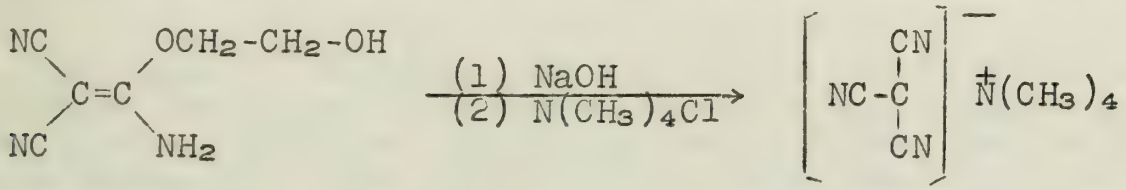


XXVII



XXVIII

These compounds are high melting solids which are stable to heat and water. They behave as weak acids and can be recovered unchanged by acidification of solutions of their salts with mineral acids. Upon boiling these vinyl amine derivatives in aqueous sodium hydroxide an unusual reaction occurs. Cyanoform, XXIX, (25) isolated as the tetramethylammonium salt, is produced when 1-amino-1-(2-hydroxyethoxy)-2,2-dicyanoethylene, XXX, is treated with boiling sodium hydroxide.



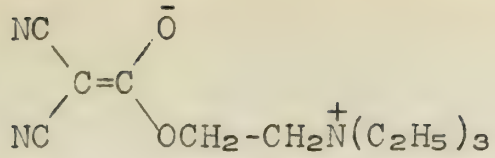
XXIX XXX

+

$HO-CH_2-CH_2-OH$

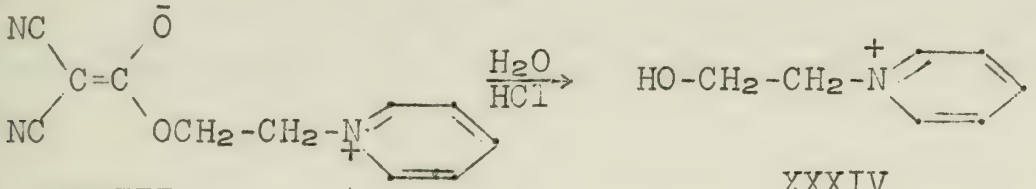
Thus the elements of ethylene glycol were removed and a new cyano group generated under conditions which usually hydrolyze cyano groups. This reaction may be partially rationalized by the fact that the cyano form anion is highly stabilized by resonance. Since the reaction of amines with dicyanoketene acetals is a stepwise process, it is possible to prepare 1,1-diamino-2,2-dicyanoethylenes which contain different substituents on the amino groups. In this manner 1-amino-1-methylamino-2,2-dicyanoethylene, XXXI, (13) was prepared.

Dicyanoketene acetals can act as alkylating agents similar to alkyl sulfates. The products of the reactions of tertiary amines with dialkyl dicyanoketene acetal are usually oils, but the reactions with dicyanoketene cyclic acetals are stable crystalline solids. These compounds are inner salts, so called "mesoionic compounds" (13). A typical example of such compounds is 2,2-dycyano-2-[2-(triethyl-ammonio)ethoxy] ethenolate, XXXII, (13).



XXXII

Similar adducts are formed from the reaction of dicyanoketene cyclic acetals with alkyl sulfides, thioureas, thioamides, and thiosemicarbazides. The structures of these compounds were assigned on the basis of their infrared spectra and the product obtained from their hydrolysis. The hydrolysis of a typical salt, pyridinium dicyanoketene ethylene acetal adduct, XXXIII, gives 1-(2-hydroxyethyl) pyridinium chloride, XXXIV (13).

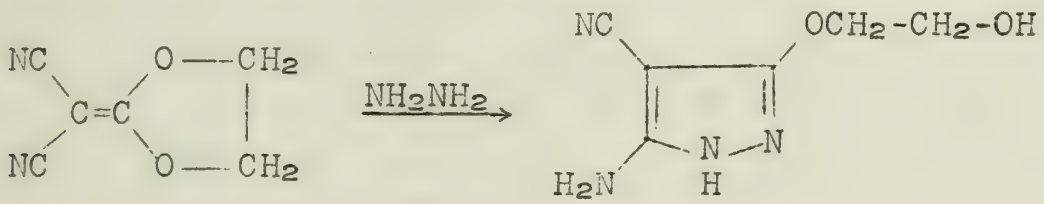


XXXIII XXXIV

Mesoionic compounds are stable, relatively high melting solids. Most of them are soluble in hot water and insoluble in most organic solvents.

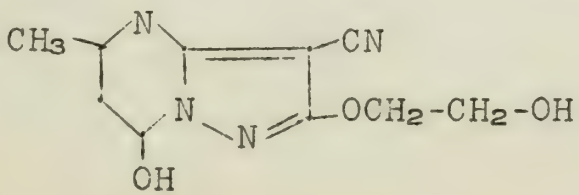
The value of dicyanoketene acetals as synthetic intermediates is further demonstrated by their reactionswith a number of nitrogen bases such as hydrazine, hydroxylamine, and amidines to form heterocyclic molecules. Just as with TCNE these reactions involve displacement of alkoxy groupsfollowed by addition to the triple bond of the cyano group. Substituted pyrazoles,isoxazoles and pyrimidines are obtained.

Hydrazine reacts with 2,2-dicyano-1,1-ethylene-dioxyethylene, X, to form 5-amino-4-cyano-3,2-hydroxyethoxy pyrazole, XXXV (16).



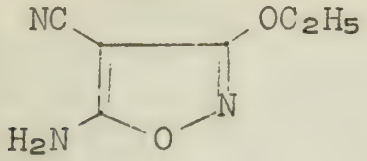
XXXV

Compound XXXV (16) reacts with ethyl acetoacetate to give a substituted pyrozolopyrimidine, XXXVI.

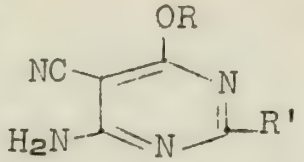


XXXVI

In a similar manner 5-amino-3-ethoxy-4-cyanoisoxazole, XXXVII, was prepared by the reaction of hydroxylamine with diethyl dicyanoketene acetal, IX; and substituted pyrimides, XXXVIII, were prepared by the reaction of the dicyanoketene acetals with amidines.



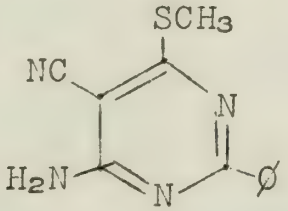
XXXVII



XXXVIII

R' = CH_3-, Ø, NH_2

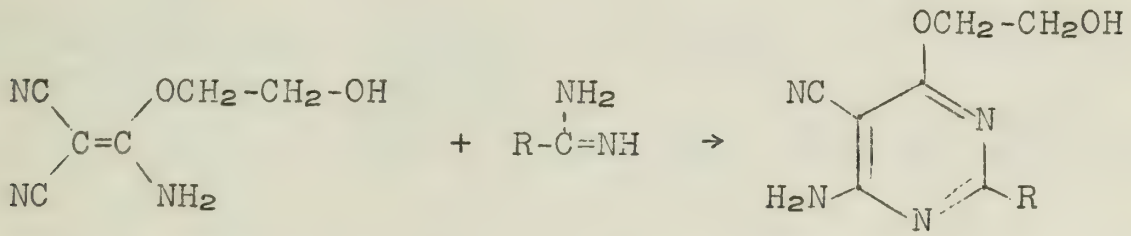
The sulfur analog of dicyanoketene acetal reacts with amidines in a similar manner. Thus 2,2-dicyano-1,1-dimethylthioethylene reacts with phenylamidine to form 5-cyano-6-methylmercapto-2-phenylpyridine, XXXIX.



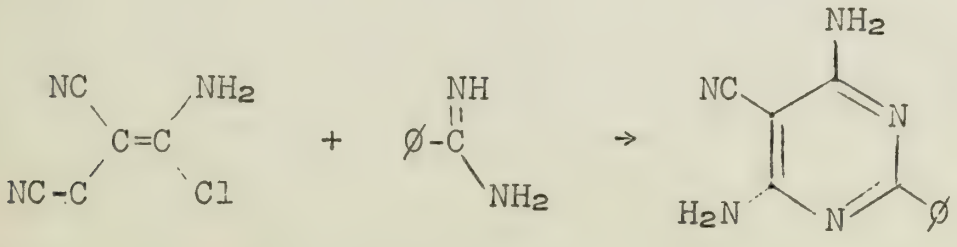
XXXIX

The structures of the above heterocycles were assigned on the basis of functional group analysis, chemical analysis and from infrared and ultraviolet spectra (16).

It is surprising that attempts to synthesize pyrimidines with a 6-amino-1-(2-hydroxyethoxy)-2,2-dicyanethylene gave only the 6-(2-hydroxyethoxy) pyrimidine, XXXX, (16).



However, a 6-aminopyridine, XXXXI, was prepared by the reaction of 1-amino-1-chloro-2,2-dicyanoethylene and benzamidine (16).



XXXXI

BIBLIOGRAPHY

1. T.L. Cairns, R.A. Carboni, W.J. Middleton, D.D. Coffman, et al., J. Am. Chem. Soc. 80, (1958).
2. A.J. Saggiomo, J. Org. Chem., 22, 1171 (1957).
3. F.J. Brockman, Can. J. Chem., 33, 507 (1955).
4. C. Moureau and J. Bongrand, Compte rend., 170, 1025 (1928).
5. E. Cox and A. Fontaine, Bull. soc. chim. France, 948 (1954).
6. Y. Urushibana, Bull. Chem. Soc. Japan, 2, 278 (1927).
7. A.E. Ardis, U.S. Patent 2,476,270; C.A., 43, 9079 (1949).
8. W.J. Middleton, R.E. Heckert, E.L. Little and C.G. Krespan, J. Am. Chem. Soc., 80, (1958).
9. T.L. Cairns, University of Illinois Lecture, May 8, 1957.
10. W.D. Wolfe, U.S. Patent 2,217,632 (1940).
11. K. Ziegler, G. Schenck, et al., Ann., 551, 1 (1942).
12. R.E. Merrifield and W.D. Phillips, J. Am. Chem. Soc., 80, (1958).
13. W.J. Middleton and V.A. Engelhardt, J. Am. Chem. Soc., 80, (1958).
14. W.J. Middleton, E.L. Little, D.P. Coffmann, and V.A. Engelhardt, J. Am. Chem. Soc., 80, (1958).
15. W.J. Middleton, V.A. Engelhardt, and B.S. Fisher, J. Am. Chem. Soc., 80, (1958).
16. W.J. Middleton, and V.A. Engelhardt, J. Am. Chem. Soc., 80, (1958).
17. E.L. Little, Jr., W.J. Middleton, D.D. Coffmann, V.A. Engelhardt, and G.N. Sausen, 80, (1958).
18. M. Strell et al., Ann., 587, 177 (1954).
19. Y. Urushibara and M. Takebayashi, Bull. Chem. Soc. Japan, 11, 557 (1956).
20. D.W. Woodward, U.S. Patent 2,499,441 (1950).
21. G.N. Sausen, V.A. Engelhardt and W.J. Middleton, D.D. Coffman, and H.F. Moyer, J. Am. Chem. Soc., 80, (1958).
22. C.E. Looney and J.R. Downing, J. Am. Chem. Soc., 80, (1958).
23. R.A. Carboni, D.D. Coffman and E.G. Howard, J. Am. Chem. Soc., 80, (1958).
24. K. Alder and H.F. Rickert, U.S. Patent 2,264,354 (1941).
25. B.C. McKusick, R.E. Heckert, T.L. Cairns, D.D. Coffman and H.F. Mower, 80, (1958).
26. L. Birchenbach and Karl Huttner, Ber., 62, 153 (1929).
27. A.C. Cope and K.E. Hoyle, J. Am. Chem. Soc., 63, 733 (1941).

NUCLEOPHILIC SUBSTITUTION ON SILICON

Reported by D. E. Frankhouser February 13, 1958

INTRODUCTION

Any discussion of the chemistry of organosilicon compounds is difficult without reference to the chemistry of analogous carbon compounds. With silicon immediately beneath carbon in the periodic table, it is certainly reasonable to assume that the reactions of organosilicon compounds should be similar to those of carbon compounds. Indeed, when the first organosilicon compound was synthesized, it was thought that this would open the door to a whole new branch of chemistry in which silicon would take the place of carbon Subsequent research in the field of organosilicon chemistry was directed primarily toward showing the similarities in the two branche of chemistry. Kipping, who did much of the fundamental work in thi field around 1900, had this purpose in mind when he succeeded in demonstrating the tetrahedral bonding to silicon by showing optical activity in compounds having four different groups attached to sili con. At the end of 44 years of work, Kipping was sadly forced to conclude that the field of organosilicon chemistry did not match the field of carbon chemistry, and, in fact, the differences between the two fields were greater than the similarities. This feature is brought out clearly by the fact that no organosilicon compound has ever been found in nature.

In comparing silicon to carbon we find that both elements have a normal covalency of four and have normal tetrahedral bonding. Under favorable conditions, however, silicon can have a coordination number greater than four. Silicon is less electronegative (more metallic) than carbon and is also larger and heavier (1).

One of the most common reactionsof organic chemistry is nucleo philic substitution at a saturated carbon atom.

$$Y\text{:} + R_3C\text{-}X \longrightarrow Y\text{-}CR_3 + X^-$$

An analogous reaction also occurs with silicon.

$$Y\text{:} + R_3Si\text{-}X \longrightarrow Y\text{-}SiR_3 + X^-$$

This seminar will deal with reactions of this general type. Examples of nucleophilic substitution on silicon will be given along with a discussion of the mechanism of substitution. Syntheses of organosilicon compounds mentioned as examples will not be discussed since such a discussion would constitute a seminar in itself. No attempt will be made to cover the entire field of nucleophilic substitution at silicon, and certain reaction types, such as acid catalyzed reactions and polymerization, will not be considered.

I. DISPLACEMENT OF HALIDES

In carbon chemistry the simplest and most studied example of nucleophilic substitution is the solvolysis of alkyl or aryl halides. That the reaction can proceed by two limiting mechanisms has been shown experimentally many times over, and Ingold's distinction between S_N1 and S_N2 mechanisms is familiar to all.

Probably the simplest example of nucleophilic substitution on silicon is also the solvolysis of triorganosilyl halides, which undergo the same general types of substitution reactions as carbon compounds.

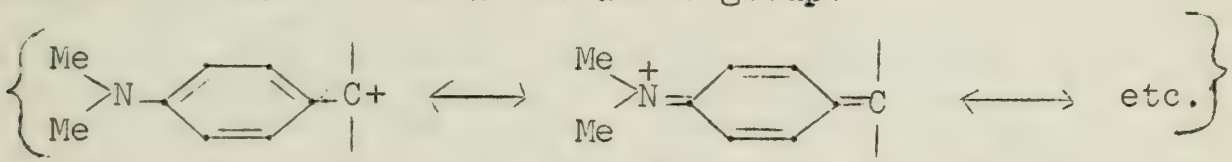
By analogy to carbon compounds, triorganosilyl halides should undergo solvolysis by either S_N1, S_N2, or by both. Since silicon is more metallic than carbon, it might be expected to form a positive ion even more readily than carbon. Thus, a silyl halide should ionize quite readily under S_N1 conditions to form a siliconium ion intermediate.

There is quite good evidence, however, that siliconium ions are not readily formed. Cryoscopic and conductivity measurements with several silanols in sulfuric acid have shown that siliconium ions are not formed to any great extent (2). Conductivity measurements of triphenylsilyl chloride in liquid sulfur dioxide also show no evidence of siliconium ions in that solvent (3).

No organosilicon compound which contains a silicon-carbon double bond has ever been found, and there is no evidence that such a linkage exists. This property is not peculiar to silicon but is shared by most elements outside row one. The reason for the non-existence of the siliconium ion might be that the positive charge on silicon cannot be distributed by resonance interaction with substituent groups, as with carbonium ion. This charge distribution would require large contributions to the resonance hybrid from structures involving double bonds between silicon and carbon. It is possible that such contributions to the resonance hybrid are small and that the siliconium ion is so unstable that it cannot be detected.

Siliconium ions are favored in some instances because, by going to the planar carbonium ion, there is relief of steric strain. The silicon atom is 50% larger than carbon, however, and its tetrahedral configuration should be less sensitive to steric strain. Consequently, relief of steric strain should not be as important (1).

The ultraviolet maxima of tri-(p-dimethylaminophenyl)-carbinol shift markedly to longer wavelengths in acid solution. This is because a very stable carbonium ion is formed, stabilized by resonance interaction with the amine group.



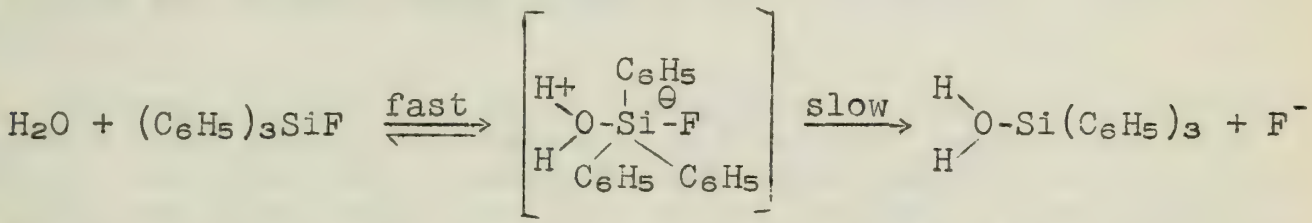
The analogous silicon compound, tri-(p-dimethylaminophenyl)-silanol, showed no absorption shift in acid solution, which seemed to indicate that a siliconium ion is not formed (4).

Thus, it seems that nucleophilic substitution reactions on silicon should not take place by ionization to form siliconium ions (S_N1). This theory is supported very well by kinetic studies. Triphenylsilyl fluoride solvolyzes 10^7 times faster in the presence of hydroxyl ion than in 50% acetone-water, whereas triphenylmethyl fluoride reacts at the same rate regardless of pH (5). Introduction of phenyl groups into silyl halides decreases the rate of hydrolysis,

in contrast to the great enhancement of rate by substitution into methyl halides. Under conditions favorable to the S_N1 mechanism, introduction of alkyl substituents into a silyl halide, which should enhance solvolysis rate, causes a decrease in reaction rate (1). In all the cases of nucleophilic substitution on silicon studied, the reaction was first order in nucleophilic agent. Kinetic studies showing the relationship between para and meta substitution on reaction rate, show that electron donating groups decrease reaction rate and that the reactions have a positive Hammett rho.

If an S_N1 mechanism is ruled out, it remains only to determine whether nucleophilic displacement on silicon occurs by the conventional S_N2 mechanism or by a different mechanism unique to silicon. At the present time there is disagreement over this point.

The first kinetic study of the hydrolysis of a triorganosilyl halide was done by Swain, Esteve, and Jones, in 1946 (5). By use of triphenylsilyl fluoride (trisyl fluoride) and triphenylmethyl chloride for comparison, it was found that introduction of three p-methyl groups into trisyl fluoride decreased the rate of hydrolysis in 50% acetone-water by a factor of about 5. This indicated that in the transition state silicon was less positive than in the ground state. This fact could only be explained, according to Swain, by postulating a pentacovalent silicon intermediate. Silicon, possessing vacant orbitals, can expand its valence shell to more than eight, and stable silicon compounds with a coordination number greater than four are known.



The possibility that the first step is slow and the other fast was ruled out because triphenyl chloride reacted faster than the corresponding fluoride. If step one were rate-determining, the fluoride, being more electronegative, should have reacted faster by giving a more electrophilic silicon atom. The positive salt and solvent effects were consistent with the mechanism because there is greater charge separation in the transition state.

For many years nucleophilic displacements were interpreted on the basis of this evidence. Subsequent work (to be cited later) lends support to this theory, but there has never been any clear evidence for the existence of an intermediate in the reaction. At present the evidence for this mechanism remains inconclusive.

A simpler explanation is that the mechanism is a modified S_N2 mechanism in which bond making predominates over bond breaking. The electron requirements of the S_N2 mechanism are not completely understood; in some cases S_N2 reaction is aided by electron supply, while in other cases it is aided by electron withdrawal. In certain cases, both types of groups may increase reaction rate. Therefore the S_N2 mechanism cannot arbitrarily be ruled out because increased electron supply lowers the reaction rate.

Table I shows the results of the reaction of triisopropylsilylchloride with methanol and water in inert solvents (6).

TABLE I

i-Pr_3SiCl (M)	MeOH (vol %) (in $MeNO_2$ - MeOH)	Et_4NX X	Et_4NX (M)	10^4 k_1 ($sec.^{-1}$)	i-Pr_3SiCl (M)	ROH (vol %) (in dioxane)	Et_4NCl (M)	10^4 k_1 ($sec.^{-1}$)
0.03	5	-	-	1.65	0.01-0.02	MeOH (10)	-	0.04
0.03	10	-	-	7.6	0.03	MeOH (10)	0.01	0.46
0.03	10	Cl	0.01	10.5	0.03	MeOH (22.5)	-	1.6
0.03	10	ClO_4	0.01	9.0	0.01	H_2O (2)	-	2.9
0.03	15	-	-	18.7	0.03	H_2O (3)	-	16.0
					0.03	H_2O (4)	-	51
					0.01	H_2O (4.5)	-	90

The table shows that the reaction is more strongly facilitated by the more polar solvent, (nitromethane). Salt effects are positive and more marked in dioxane. The results in dioxane clearly show the greater reactivity of water than of methanol. The first order rate constant changes more rapidly than the concentration of the nucleophilic reagent; this could be a result of a higher order with respect to the nucleophile or a medium effect.

The rate of alcoholysis of triisopropylsilylchloride varied greatly with the alcohol used; relative rates were MeOH 1; EtOH 10^{-1}; i-PrOH 10^{-4}.

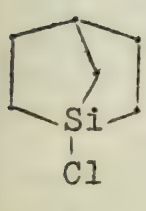
In isopropylalcohol (which is unreactive) a linear relationship between the first order rate constant and initial concentration of nucleophile was observed. A second order rate constant was obtained by dividing the first order constant by the initial concentration of the nucleophilic agent. These second order constants did not vary significantly, thus showing that the reaction is first order with respect to nucleophilic reagent (either methanol or water). Salt effects were small and positive.

The solvolysis rate of trisubstituted silyl chlorides (R_3SiCl) was dependent upon the group substituted in R (7). For the compounds studied, the rate decreased in the order

phenyl > isopropyl > cyclohexyl > 1-naphthyl.

The halogen-exchange reaction between triorganosilylchloride and labelled chloride ion was fast and followed second order kinetics (7).

Recently a chloride substituted bridgehead silicon compound (I) was synthesized. In marked contrast to the carbon analog, this compound was rapidly hydrolyzed by moist air (8).



I

The simplest mechanism to account for the experimental facts would be a nucleophilic displacement in which halide is displaced in a one-step process by the hydroxylic solvent. The reactivity of compound I seems to indicate that rearward attack may not be involved, and that in this respect, displacements on silicon are not strictly analogous to S_N2 displacements on carbon.

II. DISPLACEMENT OF HYDROGEN

A very interesting reaction, which has no strict analogy in carbon chemistry, is the alkaline cleavage of the silicon-hydrogen bond of triorganosilanes to liberate hydrogen gas (9,10). The increased reactivity of the silicon-hydrogen bond is most likely caused by its much greater polarity.

$$R_3Si\text{-}H + Y^- + S\text{-}H \longrightarrow R_3Si\text{-}Y + S^- + H_2$$

$Y = OH^-, RO^-, NH_2^-$ S-H = solvent = HOH, HOR, liq. NH_3

Careful analysis of the evolved gas showed it to be hydrogen (9). That each molecule of hydrogen obtained by hydrolysis of silanes contained one atom of hydrogen from the silane and one atom of hydrogen from solvent was established by isotopic labeling (11). Identical results were obtained when the hydrolysis was run either with deuterated silane in normal solvent or with deuterated solvent and normal silane. Isotopic analysis showed it to be predominantly H-D. This indicated that a hydride ion is split off from the silane. The hydride ion accepts a proton from solvent to form hydrogen gas in much the same manner that sodium hydride liberates hydrogen in ethanol.

The first kinetic study was made by F. Price (9) in 1947. By use of diethylmethylsilane in aqueous ethanolic potassium hydroxide, the rate was followed by measuring the amount of hydrogen evolved. The reaction was first order in silane, since the half-time remained constant at constant hydroxyl concentration, regardless of the initial silane concentration. The first order constant changed linearly with initial hydroxyl concentration, and a second order constant was obtained by dividing the first order constant by the initial hydroxyl concentration. The second order constant obtained did not vary significantly. Therefore, a rate expression was formulated by Price as

$$-\frac{d(\text{silane})}{dt} = k_2(\text{silane})(OH^-).$$

Recent work has shown that, when hydroxide is added to ethanol containing a small amount of water, a large fraction of the total base present is in the form of ethoxide ion (12). Thus, both ethoxide and hydroxide may act as nucleophiles, and both a silanol and a silicon ether should be formed. By hydrolyzing silanes in ethanol labeled with tritium on the methylene carbon, a significant fraction of the products obtained contained labeled ethoxysilanes (11). Therefore Price's rate expression was not completely accurate, since it should have included both hydroxide and ethoxide ion concentrations. A linear relationship between hydroxyl concentration and rate constant was observed, because the ethoxide concentration was proportional to the hydroxyl concentration. However, the important result was that the reaction was first order in nucleophilic agent, which suggested an S_N2 mechanism.

Since the reaction was overall second order, Price reasoned by analogy to the S_N2 mechanism that steric effects might be involved. To test this hypothesis the second order rate constant was determined for a series of trialkylsilanes (9). The rates showed a general, but small, trend with change in structures, as shown in Table II:

TABLE II

	34.4° k_2(min.$^{-1}$ mole^{-1} l.)	4.47°
diethylmethyl	0.157	0.329
triethyl	0.093	0.219
dimethyl propyl	0.364	0.779
dipropylmethyl	0.106	0.241
tripropyl	0.0409	0.096

These rate constants show the same general variation in magnitude with structure as found in carbon chemistry in compounds undergoing nucleophilic attack by the S_N2 mechanism.

In another more recent study (13) the effect of structure on reactivity has been borne out even more strikingly. The rate constants for hydrolysis of triorganosilanes in 94.5% ethanol with 1.12 M sodium hydroxide are given in Table III:

TABLE III

R	Ethyl	n-propyl	n-butyl	i-butyl	i-propyl
k_1 (min.$^{-1}$) 34.9°	0.0633	0.0253	0.0174	0.00261	0.00139
k_1 (min.$^{-1}$) 23.3°	0.226	0.00855	0.00587	0.00852	0.00431
E* kcal./mole	15.9	16.8	16.8	9.7	10.0
log A	10.1	10.3	10.2	9.7	10.0
Relative Rates (34.9°)	100	40	27	4.1	2.2

The order of decreasing activity is either that of increasing electron release in the radical, which is known to lead to a fall in rate, or that of steric hindrance to reaction.

The closely related hydrolysis of triarylsilanes (14) gave very interesting results. By determining the effect of various meta- and para-substitutents on the rate of hydrolysis of these silanes, some indication of the electrical interaction involved should become apparent. A very convenient method for doing this involves the Hammett relationship. With substituents, p-Cl, H, m-CH_3, p-CH_3, m-$N(CH_3)_2$, p-OCH_3, and p-$N(CH_3)_2$ the rates followed the Hammett equation with a rho of $\pm$ 3.09, indicating a negative charge in the transition state at the reaction site.

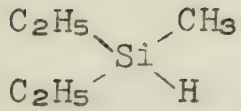
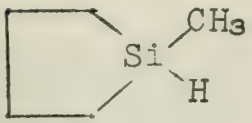
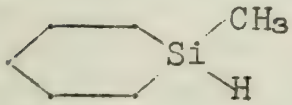
A hydride ion, being very reactive, should not have a long existence. Since hydride ion interacts with solvent by accepting a proton, there is a question of whether or not this reaction with solvent occurs in the rate determining step. There is some evidence that solvent interactions occur in the transition state (11). The isotope effect, when tritium was substituted for hydrogen in triphenylsilane, increased upon changing from piperidine-water solvent to ethanol-water-potassium hydroxide solvent. Also, tripropylsilane reacted faster in normal aqueous ethanolic potassium hydroxide than in an otherwise identical deuterated solvent. The transition state for the alkaline hydrolysis might be formulated as

$$\left[R_3Si(OH)\cdots H\cdots H\cdots S \right]^-$$

where the dotted lines represent bonds in various stages of breaking and forming. The observed effects were small, however, and more work is needed to elucidate the role of solvent.

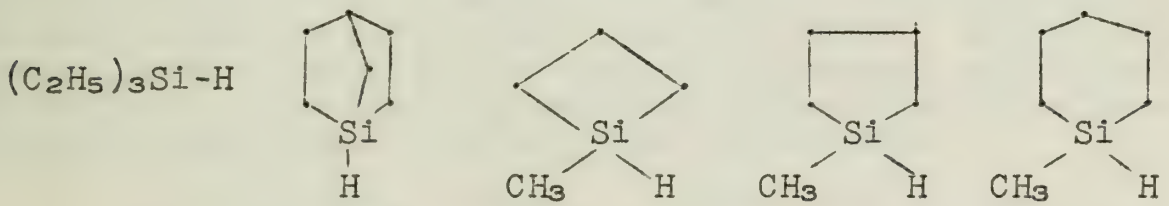
The effect of ring size on reactivity (15) of some silanes is shown in Table IV.

TABLE IV

		(in aqueos ethanol) OH^- (M)	k_1(min.$^{-1}$) 25°	35°
II.		1.85	0.0649	0.151
		0.256	0.0263	0.0621
III.		0.256	0.345	
IV.		1.85	0.0117	0.0326
		0.256		0.00913

The data show that II reacts more slowly than III by a factor of about 13, while IV reacts more slowly than II by a factor of about 6. The seven membered ring compound was impure, but qualitative experiments showed it reacts faster than II but slower than III. These results are in accord with the I-strain theory (16), assuming silanes react to form a five-coordinated transition state.

Recent work (17) has shown some very interesting results concerning the stereochemistry of substitution at a silicon atom. The relative rates of hydrolysis of silanes with hydroxyl ion in 95% ethanol are:

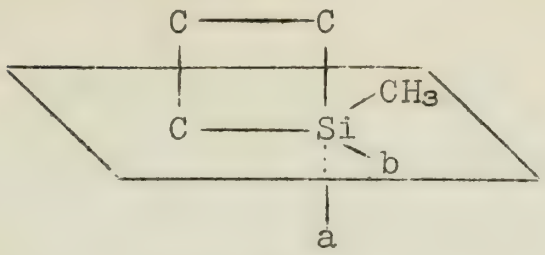


1 10^3 10^4-10^5 10 10-^{1}

The very great rate for the bridgehead compound compared with that for the open chain compound is completely different from that of carbon chemistry.

These results were explained according to a preliminary hypothesis advanced by Sommers (8). A silane and the attacking reagent form an addition complex whose geometry approaches that of a trigonal bipyramid with dsp^3 bonding. However, the entering and leaving groups need not occupy the apices of the pyramid. Instead of an angle of near 180°, the entering group may form an angle of near 90° with the group displaced and the central silicon atom. Thus, in the reaction with hydroxide the geometry of the Si(5) addition complex would approximate one of two idealized structures:

(1) a = H, b = OH
(2) a = OH, b = H



An S_N2 displacement is not precluded since the transition state in the silicon reaction may have a different geometry than in the carbon reaction.

Before leaving Si-H bond cleavage, another reaction, which has no analogy in carbon chemistry, should be mentioned. Triorganosilanes and silver perchlorate react in toluene with precipitation of silver and evolution of hydrogen (18). After treating the reaction mixture with dilute alkali, silanols and their derivatives are obtained in 90% yield. The rate was second order with respect to silver perchlorate. A mechanism involving nucleophilic attack by perchlorate on silicon and electrophilic attack by silver ion on hydrogen was proposed.

The reaction is sensitive to stereochemical changes as shown by the relative rates:

Et_3SiH	n-Pr_3SiH	n-Bu_3SiH	i-Bu_3SiH	i-Pr_3SiH
1	0.5	0.35	0.013	0.001

III. DISPLACEMENT OF CARBANIONS

Silicon-carbon bonds are considerably more reactive than carbon-carbon bonds toward a number of reagents, especially alkali. Alkylsilanes are quite stable toward alkali. Substitution of halogen, however, leads to less stable compounds, which are more easily hydrolyzed. For example, trichloromethyltrichlorosilane is hydrolyzed rapidly with water at room temperature.

$$Cl_3C\text{-}SiCl_3 + HOH \longrightarrow Cl_3CH + SiO_2 + HCl$$

But hexachloroethane is not even cleaved by alcoholic potassium hydroxide at 100°. Lower chlorinated products of methyltrichlorosilane require alkaline conditions (1).

Substituents which tend to increase the polarity of the silicon-carbon bond have a large effect on the stability of the bond. The requirements of substitution of halogen and oxygen on silicon and carbon have been shown by Krieble and Elliot (19). These can be best summarized by using a generalized formula of the type

$$X_3C\text{-}AY_3$$

where A is either a carbon or silicon atom.

When A = carbon, cleavage occurs only when all the X atoms are halogen and at least two valences of A are oxygen. The familiar haloform reaction illustrates this.

$$Br_3C\text{-}\overset{O}{\overset{\|}{C}}R + OH^- \longrightarrow Br_3CH + HO\overset{O}{\overset{\|}{C}}R$$

With less halogen substitution in X, hydrolysis of the C-X bond becomes competitive.

When A = silicon, cleavage of the silicon-carbon bond competes successfully with hydrolysis even when only one X is halogen and one Y is oxygen, proceeding under moderate conditions. A trend toward greater ease of cleavage is evident as halogen substitution is increased.

Cleavage of the silicon-carbon bond is brought about by initial nucleophilic attack on silicon with displacement of the leaving group as an anion, which immediately acquires a proton from the solvent.

$$HO^- + \text{-}\overset{|}{\underset{|}{Si}}\text{-}\overset{|}{\underset{|}{C}}\text{-} \longrightarrow HO\text{-}\overset{|}{\underset{|}{Si}}\text{-} + {}^-\overset{|}{\underset{|}{C}}\text{-}$$

$${}^-\overset{|}{\underset{|}{C}}\text{-} + HS \longrightarrow H\text{-}\overset{|}{\underset{|}{C}}\text{-} + S^-$$

Cleavage of tetraorganosilanes of the type R_3SiCH_2X occurs rather easily if X is an electron withdrawing group. The following reactions are illustrative:

$$R_3SiCH_2SO_2Cl + OH^- \longrightarrow R_3SiOH + CH_3SO_2Cl \qquad (20)$$

$$R_3SiCH_2\overset{O}{\overset{\|}{C}}Y + OH^- \longrightarrow R_3SiOH + CH_3\overset{O}{\overset{\|}{C}}Y \qquad (21)$$

Y = OH, OR, alkyl.

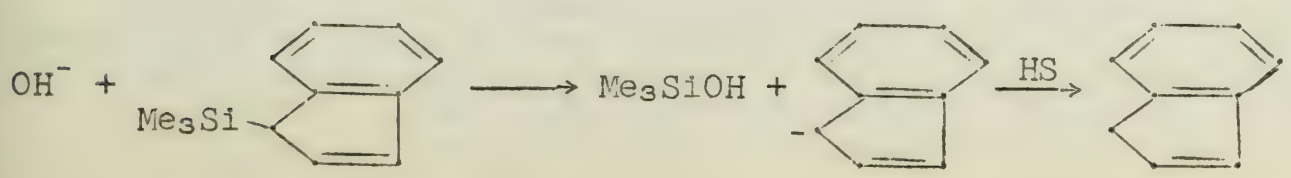
The mechanism of the reaction is formulated (21) as:

$$HO^- \rightarrow \overset{|}{\underset{|}{Si}}\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}Y \longrightarrow HO\text{-}\overset{|}{\underset{|}{Si}} + CH_2{=}\overset{O^-}{\overset{|}{C}}\text{-}Y$$

$$CH_2{=}\overset{O^-}{\overset{|}{C}}\text{-}Y \xrightarrow{HS} CH_2{=}\overset{OH}{\overset{|}{C}}\text{-}Y \longrightarrow CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}Y$$

When the silicon-carbon bond is at an allyl position, cleavage readily occurs because the negative charge on carbon in the transition state is distributed by resonance. The cleavage can be accomplished with methanolic potassium hydroxide.

$$(CH_3)_3Si\text{-}CH_2\text{-}CH{=}CH_2 + OH^- \xrightarrow{MeOH} (CH_3)_3SiOH + CH_3\text{-}CH{=}CH_2 + CH_3O^- \qquad (22)$$



(23)

Aryl groups substituted on the alpha-carbon should enhance cleavage by electron withdrawal. The electron attracting properties of a group may be evaluated by a comparison of the acidity of the corresponding hydrocarbons, the more electron attracting group being the strongest acid.

$$R\text{-}H \rightleftharpoons R^- + H^+$$

A partial series listed according to decreasing acid strength is as follows:

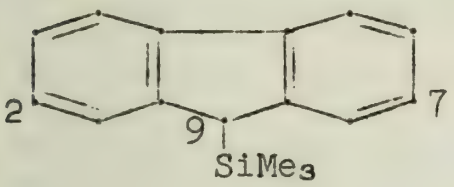
(indene ≈ fluorene) > triphenyl methane > diphenyl methane > toluene > benzene > alkanes.

The ease of hydrolysis of aryl substituted silanes was shown by Gilman (24) to correspond closely to acid strength.

$$RSi(Me)_3$$

R = (phenylethynyl ≈ 1-indenyl ≈ 9-fluorenyl) > triphenylmethyl > benzhydryl > benzyl > α-naphthyl > phenyl > 2-phenylethyl > hexyl.

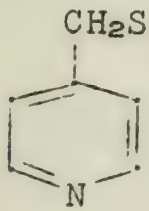
When the silicon is bonded to a reactive methylene position, cleavage is facilitated because the usual polarity, $\overset{\delta+}{Si}\text{-}\overset{\delta-}{C}$, is enhanced with consequent increase in bond reactivity. The 9-position in fluorene is such a position, and hydrolysis of 9-fluorenyltrimethylsilane, V, was investigated to determine the effects of substitution on reactivity (25).



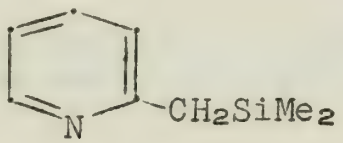
V

Cleavage was clearly facilitated by electron-withdrawing substituents at the 9-position and at the 2 and 7 positions. Both the 2,9-dibromo- and 9-bromo-2-nitro- compounds were completely cleaved by boiling aqueous ethanol in one, and in one and one-half hours, respectively, while 2,7,9-tribromo-9-trimethylsilyl fluorene was completely cleaved with aqueous acetone at room temperature in one-half hour.

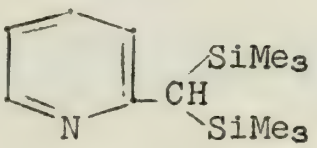
The silicon-carbon bond of trimethylsilyl substituted picolines should be reactive since the α-hydrogen atoms of the picolines are acidic.



VI



VII



VIII

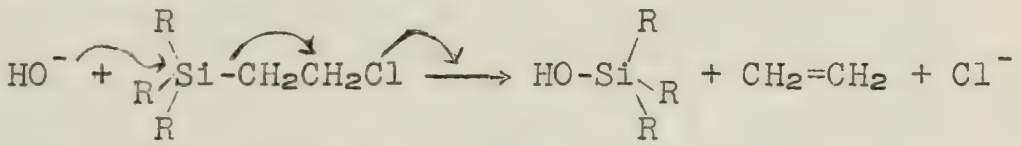
Cleavage by boiling aqueous ethanol and by alcoholic potassium hydroxide both gave the same order of reactivity, VI > VII > VIII. For example, with base VI was cleaved completely in one-quarter hour, VII in eight hours, and VIII only very slowly. The lower reactivity of VIII is due to steric hindrance to solvation and to electron release from silicon (26).

In certain cases silicon-carbon cleavage is accompanied by β-elimination (27).

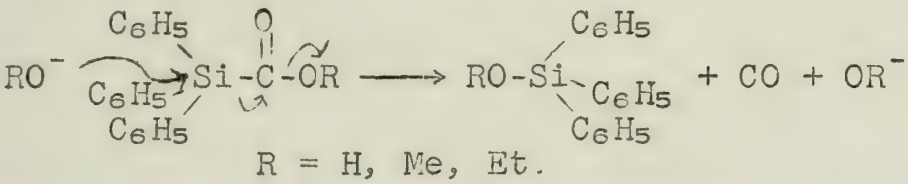
$$ClCH_2CH_2SiR_3 + OH^- \xrightarrow{ROH} SiR_3OH + CH_2{=}CH_2 + Cl^-$$

$$CH_3\text{-}\underset{Cl}{CH}\text{-}CH_2SiR_3 + OH^- \xrightarrow{ROH} SiR_3OH + CH_3\text{-}CH{=}CH_2 + Cl^-$$

The mechanism can be formulated as being initiated by nucleophilic attack on silicon, resulting in electron transfer to give β-elimination.

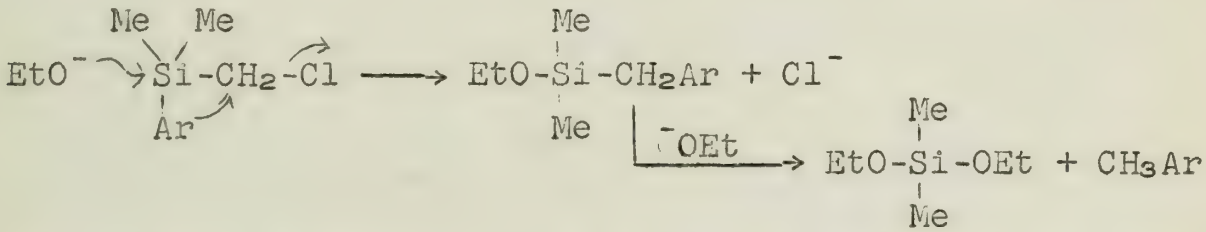


A somewhat similar reaction occurs when triphenylsilanecarboxylic acid and its esters are treated with catalytic amounts of base (28). Complete decomposition of the acid or ester results with evolution of carbon monoxide and formation of triphenylsilanol. A possible mechanism is as follows:

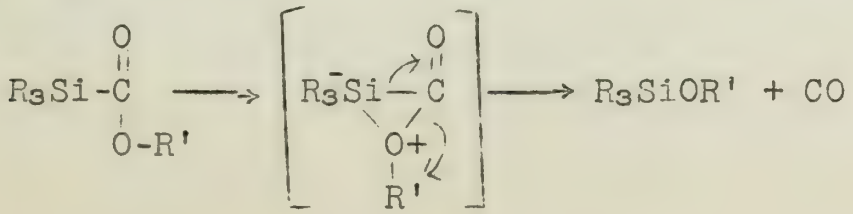


R = H, Me, Et.

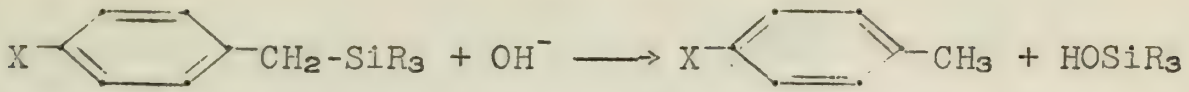
An interesting rearrangement occurs when compounds of the type $Ar\text{-}\underset{Me}{\overset{Me}{Si}}\text{-}CH_2Cl$ are treated with sodium ethoxide in ethanol (29). Toluene derivatives are isolated, being formed by 1,2-migration of the aryl group from silicon to carbon, followed by cleavage of the silicon-benzyl bond. A possible mechanism involved initial nucleophilic attack of ethoxide on silicon with simultaneous phenyl migration and chloride separation.



The thermal decomposition of silane carboxylates can also be included here since the mechanism may involve internal displacement on silicon (30).



Kinetic data are available only for the alkaline cleavage of benzyltrimethylsilanes (31).



The reaction was followed spectrophotometrically and was first order in both silane and alkali concentration. Cleavage is very cl clearly facilitated by electron withdrawal in X. The substituent effect of X on rate agrees markedly with the Hammett sigma values of X. Plotting k_2 against sigma gives a straight line with slope + 4.88 (rho) provided the sigma* value for p-nitro group is used. This high rho value shows the high sensitivity of this reaction to polar influences. Electron withdrawal in X facilitates the reaction by increasing the ease of separation of the benzyl group with the electrons of the Si-C bond.

Benzyltriphenylsilane is cleaved more readily than benzyltritolylsilane so that electron release to silicon hinders cleavage. This is consistent with the mechanism of nucleophilic attack on silicon discussed earlier.

BIBLIOGRAPHY

1. H. Gilman and G. E. Dunn, Chem. Rev., 52, 77 (1953).
2. Flowers, Gillespie, and Robinson, private communication to C. Eaborn, J. Chem. Soc., 3671 (1957).
3. E. D. Hughes, Quart. Revs., 5, 267 (1951).
4. H. Gilman and G. E. Dunn, J. Am. Chem. Soc., 72, 2178 (1950).
5. C. G. Swain, R. H. Esteve, and R. H. Jones, J. Am. Chem. Soc., 71, 965 (1948).
6. A. D. Allen, J. C. Charleton, C. Eaborn, and G. Modena, J. Chem. Soc., 3668 (1957).
7. A. D. Allen and G. Modena, J. Chem. Soc., 3671 (1957).
8. L. H. Sommer and O. F. Bennett, J. Am. Chem. Soc., 79, 1009 (1957).
9. F. Price, J. Am. Chem. Soc., 69, 2600 (1947).
10. B. N. Dolgov, N. P. Kharitnov and M. G. Voronskov, Zhur. Obschei. Khim., 24, 678 (1954).
11. L. Kaplan and K. E. Wilzbach, J. Am. Chem. Soc., 77, 1297 (1955).
12. J. W. Baber and A. J. Neale, Nature, 172, 583 (1953). E. F. Caldin and G. Long, Nature, 172, 583 (1953).
13. C. Eaborn and J. Jeffries, J. Chem. Soc., 4023 (1955).
14. H. Gilman and G. E. Dunn, J. Am. Chem. Soc., 73, 3404 (1951).
15. R. West, J. Am. Chem. Soc., 76, 6015 (1954).
16. M. S. Newman, "Steric Effects in Organic Chemistry," Wiley, New York, 1956, p. 121.
17. L. H. Sommer, O. R. Bennett, P. G. Campbell, D. R. Weyenberg, Abstracts of Papers, 132nd Meeting of American Chemical Society, New York, Sept., 1957, p. 56P.
18. C. Eaborn, J. Chem. Soc., 2517 (1955).
19. R. H. Krieble and J. R. Elliott, J. Am. Chem. Soc., 68, 2291 (1946).
20. G. D. Cooper, J. Org. Chem., 21, 1214 (1956).
21. J. R. Gold, L. H. Sommer and F. C. Whitmore, J. Am. Chem. Soc., 20, 2874 (1948).
22. L. H. Sommer, L. J. Tyler and F. C. Whitmore, J. Am. Chem. Soc., 70, 2872 (1948).
23. L. H. Sommer and L. J. Marans, J. Am. Chem. Soc., 73, 5135 (1951).
24. H. Gilman, A. G. Brooks and L. S. Miller, J. Am. Chem. Soc., 75, 4531 (1953).
25. C. Eaborn and R. A. Shaw, J. Chem. Soc., 1420 (1955).
26. C. Eaborn and R. A. Sauer, J. Chem. Soc., 3306 (1955).
27. L. H. Sommer, P. L. Bailey and F. C. Whitmore, J. Am. Chem. Soc., 70, 2869 (1948).
28. A. G. Brook and H. Gilman, J. Am. Chem. Soc., 77, 2322 (1955).
29. C. Eaborn and J. Jeffries, J. Chem. Soc., 137 (1957).
30. A. G. Brooks and R. J. Mauvis, J. Am. Chem. Soc., 79, 971 (1957).
31. C. Eaborn and S. H. Parker, J. Chem. Soc., 126 (1955).

THE OXIDATION OF ORGANIC SULFIDES TO SULFOXIDES

Reported by G. F. Fanta February 17, 1958

INTRODUCTION

The sulfoxides are a class of compounds having the general formula: R_2SO, where the oxygen is bonded to the sulfur atom by a bond which is accepted by most workers as being semipolar. On examination of the literature, one will find a great variety of preparative methods for the oxidation of sulfides to sulfoxides. A considerable amount of mechanistic work has also been done on these reactions. This seminar will primarily be concerned with the mechanisms of these oxidations. However, some of the synthetic methods for the preparation of sulfoxides from sulfides will be briefly reviewed.

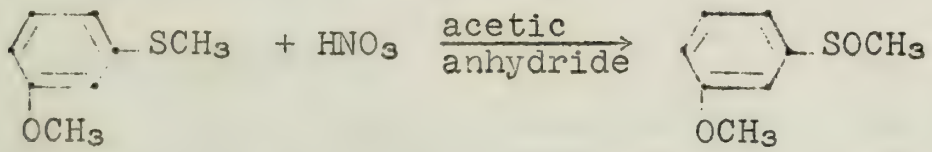
METHODS OF PREPARATION

One of the most widely used reagents for oxidizing sulfides to sulfoxides is 30 per cent hydrogen peroxide in either acetone or acetic acid. Long chain sulfoxides have been obtained from the corresponding sulfides in yields of about 75 per cent by this procedure (1).

$$C_{16}H_{34}SCH_3 + H_2O_2(30\%) \longrightarrow C_{16}H_{34}SOCH_3$$

However, not all sulfides will produce sulfoxides in good yield by this method, for in many instances the product is badly contaminated with sulfone and difficult to purify.

Nitric acid oxidations of sulfides have sometimes been found to produce sulfoxides free of sulfones where other methods failed.



(2)

Bordwell suggests that the failure of the oxidation to go past the sulfoxide stage may be due to the formation of a sulfonium salt which would be resistant to oxidation (2).

$$ArSCH_3 + 3HONO_2 \longrightarrow [ArS(OH)CH_3]^+ \overset{-}{O}NO_2 + 2NO_2 + H_2O$$

Since sulfoxides are weak bases, they probably exist to a great extent as sulfonium salts in the presence of strong acids (2).

Peroxy acids have frequently been used as oxidizing agents. The following equations will serve as examples:

[illegible]

... will produce sulfoxides ... [illegible]

[illegible]

... sulfoxides are weak bases, they primarily ... [illegible]

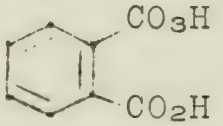
Peroxy acids are frequently ... [illegible]

... following equations will serve to illustrate: [illegible]

+ $C_6H_5CO_3H$(2 mol.) ⟶

(3)

$(CH_3)_2NCH_2CH_2CH_2SCH_3 + CH_3CO_3H$ (1 mole) ⟶ $(CH_3)_2NCH_2CH_2CH_2SOCH_3$ (4)

$(C_6H_5CH_2)_2S$ + 

(1 mole) ⟶ $(C_6H_5CH_2)_2SO$ (5)

Some mechanistic studies involving oxidations by perbenzoic and substituted perbenzoic acids will be presented later in the seminar

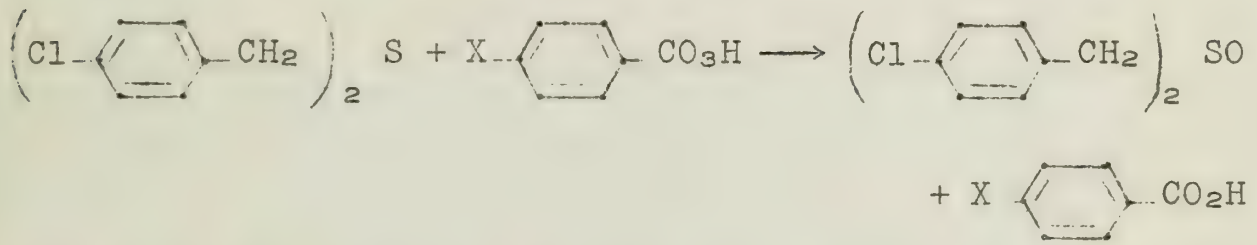
Edwards and Stenlake have shown that both chromic acid in pyridine and manganese dioxide in petroleum ether are suitable for sulfoxide preparation (10). Sodium hypochlorite (Clorox) (6,7), liquid dinitrogen tetroxide (8) and iodosobenzene (9) have also been shown to be valuable. The chromic acid-pyridine combination was found to oxidize di-n-butyl sulfide to the sulfoxide in 49 per cent yield without a trace of sulfone, while the same sulfide produced sulfoxide in 71 per cent yield when reacted with manganese dioxide in petroleum ether. Dibenzoyl and diacetyl peroxides have also been shown to oxidize sulfides to sulfoxides (22).

Both organic hydroperoxides and oxygen itself may be employed as oxidizing agents. Since a considerable amount of mechanistic work has been done on these reactions, they, along with the perbenzoic acid oxidations, will constitute the remainder of this seminar

MECHANISTIC STUDIES

Peracid Oxidations

In 1953, Overberger and Cummins studied the mechanism of the oxidation of p,p'-dichlorodibenzyl sulfide by perbenzoic and para-substituted perbenzoic acids (11).



Rate data were obtained for perbenzoic and para-methoxyperbenzoic acid in toluene and also for perbenzoic, p-methoxy-, p-methyl-, p-chloro- and p-nitroperbenzoic acid in isopropyl alcohol. In all cases studied, the reactions were overall second order.

The effect of added benzoic acid on the oxidation rate was measured at -20, -30 and -40 degrees for peroxybenzoic acid in isopropyl alcohol. At these temperatures, a benzoic acid concentra-

tion of .01M. did not change the rate constant, and the second order rate law continued to be accurately obeyed (11). This served to prove that any benzoic acid formed as a reaction product did not catalyze the reaction. A change in solvent, however, exerted a measurable effect. In toluene the rate constants of perbenzoic and p-methoxyperbenzoic acids were greater, and both the activation energies and entropies of activation were less than when the reaction was run in isopropyl alcohol. Also, the oxidation rates increased with increasing election attracting power of the para substituent. The following data were obtained using perbenzoic acid:

Solvent	Temp.	k ($l.mole^{-1}sec^{-1}$)	E_a ($kcal.mole^{-1}$)	$S^{\ddagger}$ (-35°)
Toluene	-45	4.17 ± 0.21	5.2 ± 0.3	-34.3 ± 2.7
i-propyl alcohol	-20	0.82 ± 0.04	9.6 ± 0.5	-22.3 ± 1.7

A plot of log k/k_o vs. the Hammett σ values gave a straight line with a ρ value of +1.05.

The rate of oxidation of p,p'-dichlorodibenzyl sulfide by perbenzoic acid in isopropyl alcohol containing magnesium perchlorate at a concentration of .01M. was measured at -20 degrees. The added salt did not change the rate beyond experimental error. This agrees with the evidence supporting a second order reaction, for the absence of a salt effect rules out any first order reaction involving the ionization of the peracid as the rate determining step. Therefore, on the basis of the evidence given above, the following mechanism was postulated:

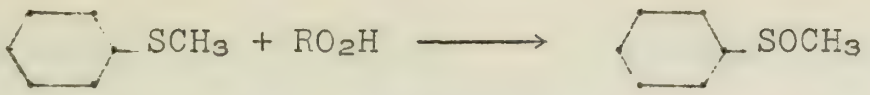
Transition state ($\ddagger$)

The fact that the oxidations proceed faster in toluene than in isopropyl alcohol with lowered energies and entropies of activation suggests, as does the absence of a salt effect, that ions are not formed in the rate determining step. In a non-hydroxylic solvent with a low dielectric constant such as toluene, it is likely that the peracid is in the cyclic form; while in isopropyl alcohol, the peracid may be strongly solvated thus hindering internal hydrogen bonding. The absence of both a salt effect and catalysis by benzoic acid are consistent with the cyclic structure for the transition state.

Oxidation with Hydroperoxides in the Absence of Oxygen

Bateman and Hargrave have studied the interaction of cyclohexyl methyl sulfide with t-butyl and 2-cyclohexenyl hydroperoxide

in alcohol solvents (12). The general reaction studied was as follows:



(R equals $(CH_3)_3C$- and )

The reactions were followed by the disappearance of hydroperoxide and the formation of sulfoxide, methods having been developed which allow these groups to be estimated in the presence of both sulfides and alcohols (13). Control experiments in the absence of sulfide showed that the decomposition of the hydroperoxide alone was negligible under the reaction conditions.

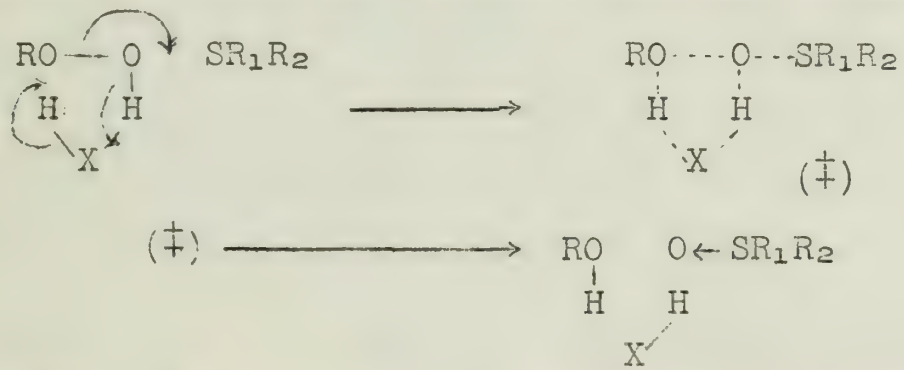
Using either t-butyl or 2-cyclohexenyl hydroperoxide in methanol, n-butanol, t-butanol or ethylene glycol, it was found tha the stoichiometry was accurately defined by the following equation:

$$ROOH + R_1R_2S \longrightarrow ROH + R_1R_2SO$$

Sulfoxide was produced in about 95 percent yield, and there was no further oxidation to the sulfone. Furthermore, when cyclohexyl methyl sulfoxide was added initially at a concentration equivalent to that of hydroperoxide, the reaction was essentially unaffected. The authors also reported an insensitivity to free-radical inhibitors and the presence or absence of air.

The reaction was found to be first order in both hydroperoxide and sulfide, and the overall reaction closely followed a second order plot. The effect of neutral salts (magnesium perchlorate in methanol and potassium acetate in acetic acid) was negligible. Entropies of activation ranging from -29 to -35 were observed.

As a result of the evidence presented above, Bateman and Hargrave suggested the following possible mechanisms (12):

I. 

Here, HX represents a molecule of solvent.

II. $$ROOH + HX \rightleftharpoons ROOH_2^+ + X^-$$

$$ROOH_2^+ + R_1R_2S \longrightarrow ROH + R_1R_2SOH^+$$

$$R_1R_2SOH^+ + X^- \rightleftharpoons R_1R_2SO + HX$$

A more acidic solvent was found to increase the rate of reaction, for the rates in the different alcohols varied as their acidities.

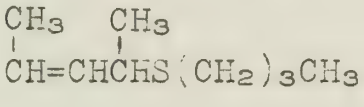
Solvent	10^5 k_2 *	Acidities Relative to Isopropano
t-butanol	1.43	0.3
n-butanol	17.1	1.0
methanol	22	6.7
ethylene glycol	230	72

* mole^{-1} l. sec.$^{-1}$; t-butyl hydroperoxide (50 degrees).

Furthermore, the addition of acetic and trichloroacetic acid to the alcohol solvents also progressively increased the rate, the rate constant in acetic acid being about one tenth that in trichloroacetic acid. This, however, did not serve to distinguish between mechanisms I and II. The most convincing piece of evidence in favor of I was the negligible salt effect. The fact that the system t-butyl hydroperoxide - cyclohexyl methyl sulfide - acetic acid at 20 degrees was completely insensitive to the addition of potassium acetate makes mechanism II highly improbable.

Similarly, Hargrave determined the behavior of 2-cyclohexenyl methyl (III) and 1,3-dimethylallyl n-butyl sulfide (IV) with 2-cyclohexenyl and t-butyl hydroperoxides in alcohol solvents (17).

III



IV

In both methanol and t-butanol, sulfoxide yields were quantitative, reaction rates were unaffected by air or free radical inhibitors, and the reactions were accurately first order with respect to both sulfide and hydroperoxide.

Bateman and Hargrave next studied the interaction of cyclohexyl methyl sulfide with hydroperoxides in hydrocarbon solvents (15). Cyclohexenyl and t-butyl hydroperoxides were used, and the solvents employed were benzene, cyclohexane and cyclohexene. These reactions were similar to those run in alcohol in that the sulfoxide yield was quantitative under all conditions studied.

The following initial reaction orders were observed (15):

System	Solvent	Reaction Orders (50°) Hydroperoxide	Sulfide	10^3 X rate*
Sulfide - 2-cyclohexenyl hydroperoxide (system 1)	Benzene	2.0	1.0	5.6
	Cyclohexane	2.0	0.9	6.7
Sulfide - t-butyl hydroperoxide (system 2)	Benzene	2.0	0.7	0.40
	Cyclohexane	2.0	0.4	1.20
	Cyclohexene	2.0	0.4	0.64

*mole l^{-1} sec^{-1}; for 1.0M reactants at 50 degrees.

The sulfoxide produced was found to retard the reactions of both systems. In system 1 the addition initially of sulfoxide in a concentration of .05M approximately doubled the half life.

System 1 was insensitive to the addition of free radical inhibitors whereas system 2 was retarded by about 5 per cent. However, it was found that in the presence of inhibitors, about 2 per cent more hydroperoxide reacted than sulfoxide produced. This points to an interaction between hydroperoxide and inhibitor rather than the inhibition of reaction chains. In both systems the rates of reaction were increased by the addition of acetic acid. When the acid catalyzed reaction predominated, the reaction orders of sulfide and hydroperoxide became unity; while the order with respect to acetic acid became 0.6. Since acetic acid in the concentrations used (0.002 to 0.04M) exists mainly as the dimer in hydrocarbon solvents (23), a reaction order of 0.6 is not surprising. A reaction which is first order in monomer will appear to be one half order, since the dimer is the species being measured.

On the basis of the above data, Bateman and Hargrave postulated the following mechanism for the reaction in hydrocarbon solvents (15):

As can be seen, this mechanism is similar to the one presented earlier for hydroxylic solvents. However, since the hydrocarbon solvent cannot assume the role of HX, the hydroperoxide will do so thus causing the rate to be second order in hydroperoxide. The addition of acetic acid catalyzes the reaction by performing the function of HX more efficiently than hydroperoxide thereby reducing the hydroperoxide order from 2 to 1.

The different retarding effects by sulfoxides in alcohols and hydrocarbons (i.e. no retardation in alcohols and noticeable retardation in hydrocarbons) were explained as being due to bonding of the weakly basic sulfoxide to the hydroperoxide. In hydrocarbons, where there is nothing else for the sulfoxide to bond with, it will bond with the hydroperoxide thus competing with the sulfide - hydroperoxide association necessary for reaction (15). As support for this theory, it was found that other organic bases such as pyridine and dimethylaniline will also retard this reaction (15). Furthermore, it has been shown by the use of radioactive sulfur that sulfoxide retardation is not due to reversibility of oxygen transfer (16).

The above mechanistic picture was considered in a more quantitative manner as follows (15):

$2RO_2H \rightleftharpoons (RO_2H)_2$ equilib. constant K_2

$(RO_2H)_2 + R_1R_2S \longrightarrow R_1R_2SO + ROH + RO_2H$ rate constant k_A

$RO_2H + R_1R_2SO \rightleftharpoons (RO_2H \cdot OSR_1R_2)$ equilib. constant K_3

Let x equal total measured concentration of hydroperoxide and c equal total measured concentration of sulfoxide. Then, if $[RO_2H] >> [(RO_2H)_2]$,

$$x = [RO_2H] + [RO_2H \cdot OSR_1R_2]$$

$$c = [R_1R_2SO] + [RO_2H \cdot OSR_1R_2]$$

Initial rate in the absence of added sulfoxide = $K_2k_A [R_1R_2S] x_0^2$ where x_0 equals the initial concentration of RO_2H. From this, K_2k_A was calculated.

$$[RO_2H]^2 = \frac{r}{K_2k_A[R_1R_2S]}$$

Thus if the rate, r, at any stage of the reaction is known, RO_2H may be determined. K_3 was then calculated from the following equation:

$$K_3 = \frac{[RO_2H \cdot OSR_1R_2]}{[RO_2H][R_1R_2SO]} = \frac{x - [RO_2H]}{[RO_2H]\{c-x + [RO_2H]\}}$$

For system 1 in benzene at 50 degrees, K_3 had a value of 15 ± 3 l. $mole^{-1}$. This agreed with the value of 16.1 l. $mole^{-1}$ deduced from a spectroscopic study of the association of cyclohexenyl hydroperoxide with cyclohexyl methyl sulfide. Knowing K_3 and k_AK_2, the course of the reactions of system 1 in both the presence and absence of initially added sulfoxide was calculated. The agreement with experimental observations was within experimental error.

It was suggested that in system 2 the orders of 0.7, 0.4 and 0.4 with respect to sulfide and 2.0 with respect to hydroperoxide were due to participation of the solvent in the reaction (15). However, no satisfactory description of this participation was given. Also, the authors could give no definite answer as to why system 2 behaved in this manner and not system 1.

Oxidation with Hydroperoxides in the Presence of Oxygen

The reactions of cyclohexyl methyl sulfide with hydroperoxides in the presence of oxygen were studied by Bateman and Hargrave (15). Benzene, cyclohexane and cyclohexene were used as solvents. The cyclohexyl methyl sulfide - 2-cyclohexenyl hydroperoxide system (system 1) was insensitive to oxygen; however, oxygen exerted a measurable effect on the cyclohexyl methyl sulfide - t-butyl hydroperoxide system (system 2). In the presence of air the rate was increased about tenfold in benzene and threefold in cyclohexane. The rate in cyclohexene was unaffected by oxygen, although peroxidation of the solvent was detected. In system 2 it was found that oxygen catalysis was completely eliminated by the addition of 2,6-di-t-butyl-p-cresol. This suggests that catalysis involves oxy or peroxy radicals in a chain reaction (15). Oxygen catalysis could also be eliminated by the addition of acetic acid.

Since all evidence seemed to point to a chain mechanism involving peroxy radicals, Bateman and Hargrave proposed the following for the propagation steps (15):

$(CH_3)_3CO_2\cdot + R_1R_2S \longrightarrow R_1R_2SO + (CH_3)_3CO\cdot$

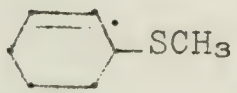
$(CH_3)_3CO\cdot + (CH_3)_3CO_2H \longrightarrow (CH_3)_3COH + (CH_3)_3CO_2\cdot$

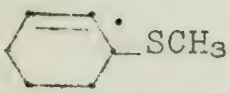
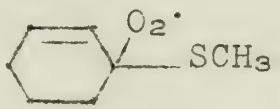
R_1 equals  ; R_2 equals $-CH_3$

However, no satisfactory initiation or termination steps were suggested which would make the above mechanism fit the experimentally observed kinetics (orders of 1.4 with respect to hydroperoxide and 0.9 with respect to sulfide). The slowing down of the rate in various solvents was taken to indicate that solvents such as cyclohexene were reacting so readily with the propagating radicals that a competitive reaction path was being introduced (15).

Hargrave next studied the reactions of 2-cyclohexenyl methyl and 1,3-dimethylallyl n-butyl sulfide with 2-cyclohexenyl and t-butyl hydroperoxides in benzene (17). When reacted with 2-cyclohexenyl hydroperoxide in benzene solution, cyclohexenyl methyl sulfide reacted in a manner similar to that of the saturated analogue discussed previously (15); therefore, the mechanism here is probably identical to that proposed for saturated cases in hydrocarbon solvents (i.e. first order in sulfide and second order in hydroperoxide). However, when 2-cyclohexenyl hydroperoxide was replaced by t-butyl hydroperoxide, non quantitative yields of sulfoxide were produced; and the reaction was not catalyzed by oxygen. This is in sharp contrast with the findings reported for cyclohexyl methyl sulfide where reaction with t-butyl hydroperoxide gave quantitative yields, and a definite oxygen catalysis was observed (15).

To explain this lack of oxygen catalysis, Hargrave postulated that the unsaturated sulfide acts like cyclohexene and inhibits its own catalytic oxidation. The partial mechanism suggested for this inhibition is as follows (17):

$(CH_3)_3CO_2\cdot +$  $\longrightarrow$ 

 $+ O_2 \longrightarrow$ 

Support for this theory was obtained from the fact that unsaturated sulfides inhibit oxygen catalysis of the hydroperoxide - cyclohexyl methyl sulfide reaction in benzene in a manner similar to cyclohexene and the phenolic inhibitors. 1,3-dimethylallyl n-butyl sulfide also produced non quantitative yields of sulfoxide, but its reaction with t-butyl hydroperoxide in benzene was subject to oxygen catalysis.

In order to explain the non quantitative sulfoxide yields, kinetic studies were undertaken on 1,3-dimethylallyl n-butyl sulfide in the absence of oxygen. Since it had been shown (18) that only a 5 per cent yield of sulfoxide and almost quantitative cleavage to di-n-butyl disulfide had resulted from reaction with t-butyl hydroperoxide, this seemed like a promising example to investigate.

The kinetic studies yielded the following results (17):

(1) The interaction was autocatalytic as measured by the disappearance of hydroperoxide. This result favors a mechanism where the product reacts further in a secondary reaction.
(2) The concentration of sulfoxide formed passes through a maximum which has been shown not to result from thermal instability of the sulfoxide.
(3) The sulfoxide yield was quantitative at the beginning of the reaction. Therefore, the low final yield must be due to its disappearance at a later stage in the reaction.
(4) The initial addition of unsaturated sulfoxide increased the rate of reaction. This is in sharp contrast to the reactions of saturated sulfides where the presence of sulfoxide reduces the rate, and the sulfoxide does not disappear in the course of the reaction.
(5) The presence of hydrogen bonding solvents (i.e. methanol and t-butanol) completely eliminated the reaction leading to non-sulfoxide products. This suggests that the reaction involves a hydrogen-bonded complex between sulfoxide and hydroperoxide. Complexes such as this are readily formed in solvents such as benzene but not in hydroxylic solvents, since the sulfoxide will then prefer to bond with solvent molecules rather than hydroperoxide.

From the above observations, Hargrave postulated a reaction occurring in two steps, the first producing sulfoxide in quantitative yield and the second leading to its disappearance (17). The mechanism for step 1 is probably identical to that proposed for the oxidation of saturated sulfides in hydrocarbon solvents (15). The details of step 2, however, still are not clear; although it was determined that hydroperoxide, sulfoxide and sulfide all had to be present for autocatalysis to occur (17). The products isolated from the reaction of one mole of 1,3-dimethylallyl n-butyl sulfide with one mole of t-butyl hydroperoxide were; 0.04 mole sulfoxide, 0.5 mole di-n-butyl disulfide, 0.25 mole water, 0.70 mole t-butanol and 0.5 mole unidentified material (18).

Oxidation by Oxygen

In 1955 Bateman and Cunneen undertook a study of the reactions of a number of allyl and substituted allyl sulfides with oxygen (19). In these reactions sulfoxides were produced in yields ranging from 5 to over 50 per cent. The authors found, however, that a strong retardation occurred at an early stage in the reaction and that the reaction often stopped after only a small amount of oxygen had been absorbed. Since a mild form of inhibition is common for autooxidations and is generally associated with the decomposition of a primary product to yield inhibitory substances, the authors reasoned that a similar reaction sequence was operating here.

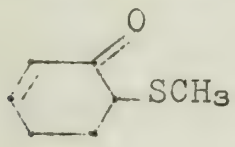
The structure of the sulfide was found to have a pronounced effect on reactivity. Allyl n-butyl sulfide and diallyl sulfide reacted slowly with oxygen at 75 degrees; however, both the rate and the extent of absorption could be increased by the substitution of either a methyl or a phenyl group into the allyl unit. Large changes in reactivity were also achieved through variations in the saturated component of the allyl alkyl sulfide.

In experiments involving n-butyl cinnamyl sulfide it was found that the reaction could be promoted by a number of oxidation catalysts such as α,α'-azoisobutyronitrile; irradiation with a mercury vapor lamp also increased the rate of oxygen uptake and reduced inhibition. Benzoyl peroxide, t-butyl hydroperoxide, and 2-cyclohexenylhydroperoxide, however, did not aid the reaction (19). The autooxidation of n-butyl cinnamyl sulfide was strongly retarded by amine and phenolic types of oxidation inhibitors (e.g. quinol and phenyl-β-naphthylamine) but the major oxidation products (n-butyl cinnamyl sulfoxide, cinnamaldehyde, dibutyl disulfide and water) exerted little inhibiting effect (19).

In a later study, Bateman and Shipley attempted to isolate the products causing the autoinhibition of the oxidation of allylic sulfides (20). The compound chosen for this study was 2-cyclohexenyl methyl sulfide. This compound, when reacted with oxygen at 55 degrees, absorbed 0.3 moles of oxygen per mole of sulfide and yielded the following mixture of products:

Compound:	H_2O				Mixture of keto sulfides
Percent of O_2 absorbed:	25	23	10	8	22

In addition to these compounds, dimethyl disulfide and some unreacted starting material were also isolated. By an independent synthesis, the keto sulfide mixture was shown to be composed mainly of 6-methylthio-2-cyclohexenone (I).



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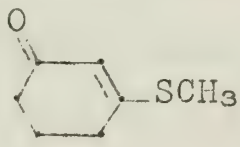
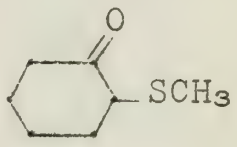


II



III

Of the oxidation products, only (I) had an effect on oxygen uptake sufficient to account for all the autoinhibition. Compound (II), which was synthesized for comparison purposes, was quite similar in this respect. The fact that (III) was inactive shows the importance of conjugation in determining inhibitory powers.

Due to the complexity of the reaction, no satisfactory mechanism was given which would account for the formation of all products isolated.

BIBLIOGRAPHY

1. D. Jerchel, L. Dippelhofer and D. Renner, Chem. Ber., 87, 947 (1954).

2. F. G. Bordwell and P. J. Boutan, J. Am. Chem. Soc., 79, 717 (1957).

3. G. Leandri and M. Palloti, Boll. sci. Fac. Chim. ind. Bologna, 14, 54 (1956).

4. F. K. Kirchner, A. E. Soria and C. J. Cavallito, J. Am. Chem. Soc., 77, 4599 (1955).

5. H. Bohme, Ber., 70B, 379 (1937).

6. C. C. Price and R. G. Gillis, J. Am. Chem. Soc., 75, 4750 (1953)

7. H. Ufer, U.S. Patent 2,163,180, June 20, 1939.

8. C. C. Addison and J. C. Sheldon, J. Chem. Soc., 2705 (1956).

9. A. H. Ford-Moore, J. Chem. Soc., 2126 (1949).

10. D. Edwards and J. B. Stenlake, J. Chem. Soc., 3272 (1954).

11. C. G. Overberger and R. W. Cummins, J. Am. Chem. Soc., 75, 4250 (1953).

12. L. Bateman and K. R. Hargrave, Proc. Royal Soc., 224, 389 (1954)

13. D. Barnard and K. R. Hargrave, Analyt. Chim. Acta, 6, 23 (1952).

14. D. Barnard, J. M. Fabian and H. P. Koch, J. Chem. Soc., 2442 (1949).

15. L. Bateman and K. R. Hargrave, Proc. Royal Soc., 224, 399 (1954)

16. G. Ayrey, D. Barnard and C. G. Moore, J. Chem. Soc., 3179 (1953)

17. K. R. Hargrave, Proc. Royal Soc., 235, 55 (1956).

18. D. Barnard, J. Chem. Soc., 489 (1956).

19. L. Bateman and J. I. Cunneen, J. Chem. Soc., 1596 (1955).

20. L. Bateman and F. W. Shipley, J. Chem. Soc., 1996 (1955).

21. W. van B. Robertson, J. L. Hartwell and S. Kornberg, J. Am. Chem Soc., 66, 1894 (1944).

22. L. Horner and E. Jurgens, Ann., 602, 135 (1957).

23. H. A. Pohl, M. E. Hobbs and P. M. Gross, J. Chem. Phys., 9, 408 (1941).

THE ACTINOMYCINS

Reported by R. Berger February 20, 1958

INTRODUCTION

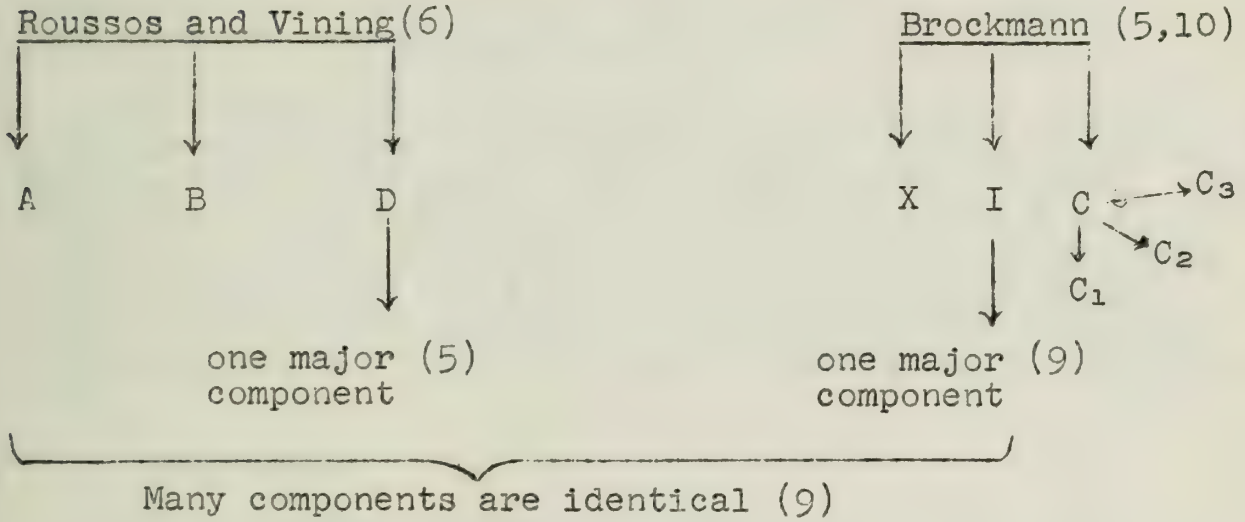
The actinomycins are bright red antibiotics, which were first reported under the singular term actinomycin in 1942 by Waksman and Tishler (1) who isolated it from cultures of Streptomyces antibioticus. Preparations giving reasonable quantities for chemical investigations have been described in the literature (2,3). Besides strong antibiotic properties, high toxicity and cytostatic activity are exhibited (4).

THE DIFFERENT ACTINOMYCINS

During the course of more comprehensive investigations it was found that more than one actinomycin exists. The isolation from various actinomycete strains by paper chromatography and countercurrent extraction is indicated in the following scheme (5,6,7,8,9):

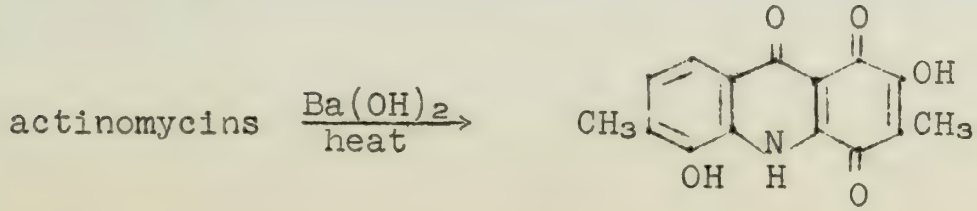
2066 Actinomycete Strains Examined.
21 Strains Produce Actinomycins (5,10):

classified by

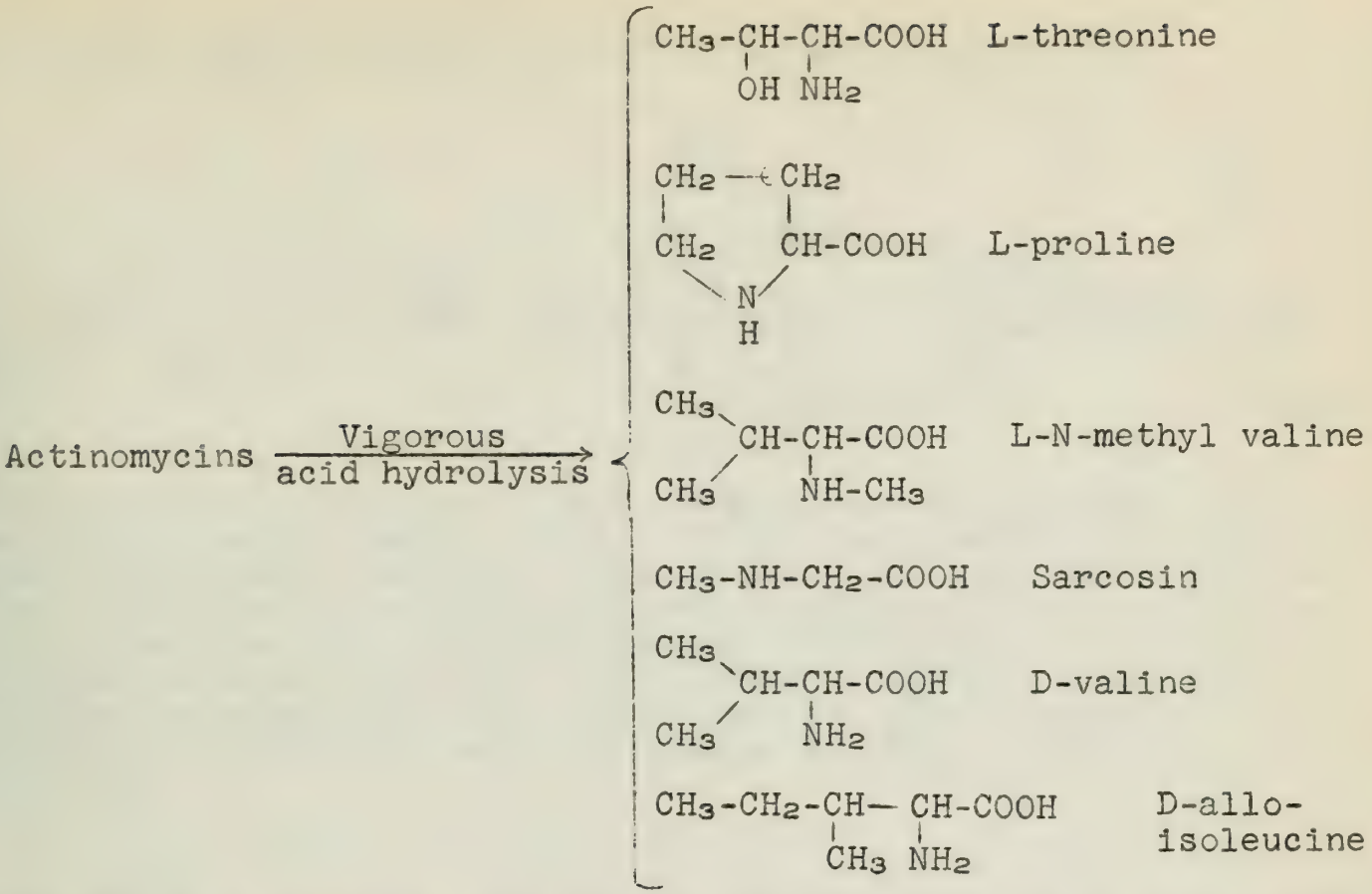


COMMON FEATURES

Two main features characterize all known actinomycins: treatment of the original substance with barium hydroxide yields a common chromophore and hydrolysis with acid a number of different amino acids (11).



actinomycinol (Johnson)
or despeptidoactinomycin (Brockmann)



Other reaction products are tar and ammonia. The amino acids were identified by paper chromatography (3,12,13).

Molecular weight determinations based upon quantitative hydrogenation gave 1200± 25 for actinomycin C (3,12) and 1240± 20 for actinomycin B (14) making use of their quinoid nature. Potentiometric titration showed values of 1325 and 1342 for actinomycin C (15) and a redox titration against chromous acetate gave 1296± 35 for actinomycin C_2 and 1307± 35 for actinomycin C_3 (16). These figures are in good agreement with the molecular formula. $C_{64}H_{90}O_{16}N_{12}$ (MW = 1283) eventually established for actinomycin C_3 (17).

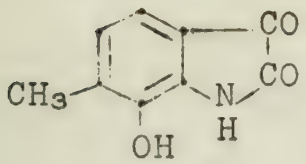
THE CHROMOPHORE

The infrared spectrum of actinomycin B as a mull in Nujol shows bands in the carbonyl region at 1754, 1667 and 1637 $cm.^{-1}$ which are consistent with ester or lactone, quinone and amide-type carbonyl groups respectively (18). The ultra-violet absorption spectrum of an alcoholic solution of actinomycin B indicates maxima at 240-242 and 441-445 mμ inconsistent with a usual quinone type of structure (19).

Johnson at Nottingham carried out an elegant and conclusive degradation (20):

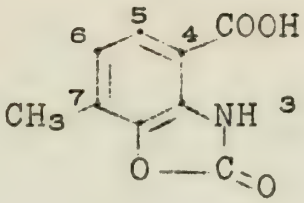
Actinomycin $\xrightarrow[NaOH]{H_2O_2}$ colorless peptide-containing substance

$\downarrow$ HCl



III

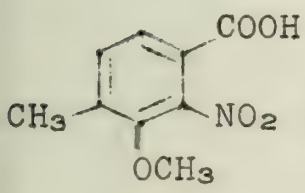
$\xrightarrow[NaOH]{H_2O_2}$



II

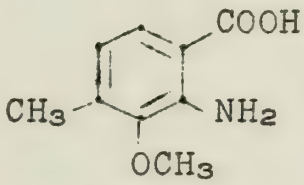
7-methyl benzoxazolone-4-carboxylic acid (19).

Confirmation of structure II was accomplished by synthesis from 7-hydroxy-6-methyl isatin (III). In this way one hydroxyl and one methyl group were located in actinomycinol (I) suggesting that the other hydroxyl- and methyl group were constituents in the quinone ring. The structure for actinomycinol (I) was deduced from spectral analogies with 2,3- and 3,2-hydroxy-methoxy-N-methyl-acridone-quinones (21). Final confirmation of the actinomycinol structure (I) was provided by Brockmann's total synthesis as shown (22).



XII

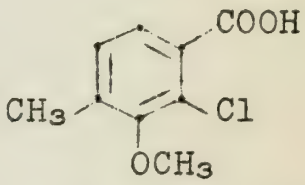
$\xrightarrow{\text{catalytic hydrogenation}}$



81%

XIII

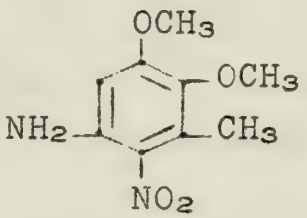
$\xrightarrow[[CuCl]]{HNO_2,\ HCl}$



45%

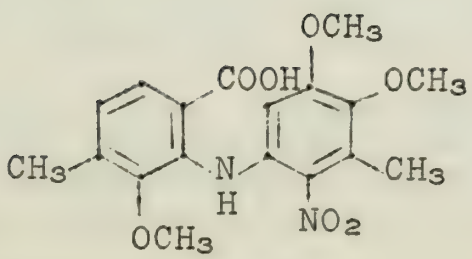
XIV

1.)



2.) K_2CO_3, Cu, CuCl
2 1/2 hrs. at 150°
in isoamylalcohol

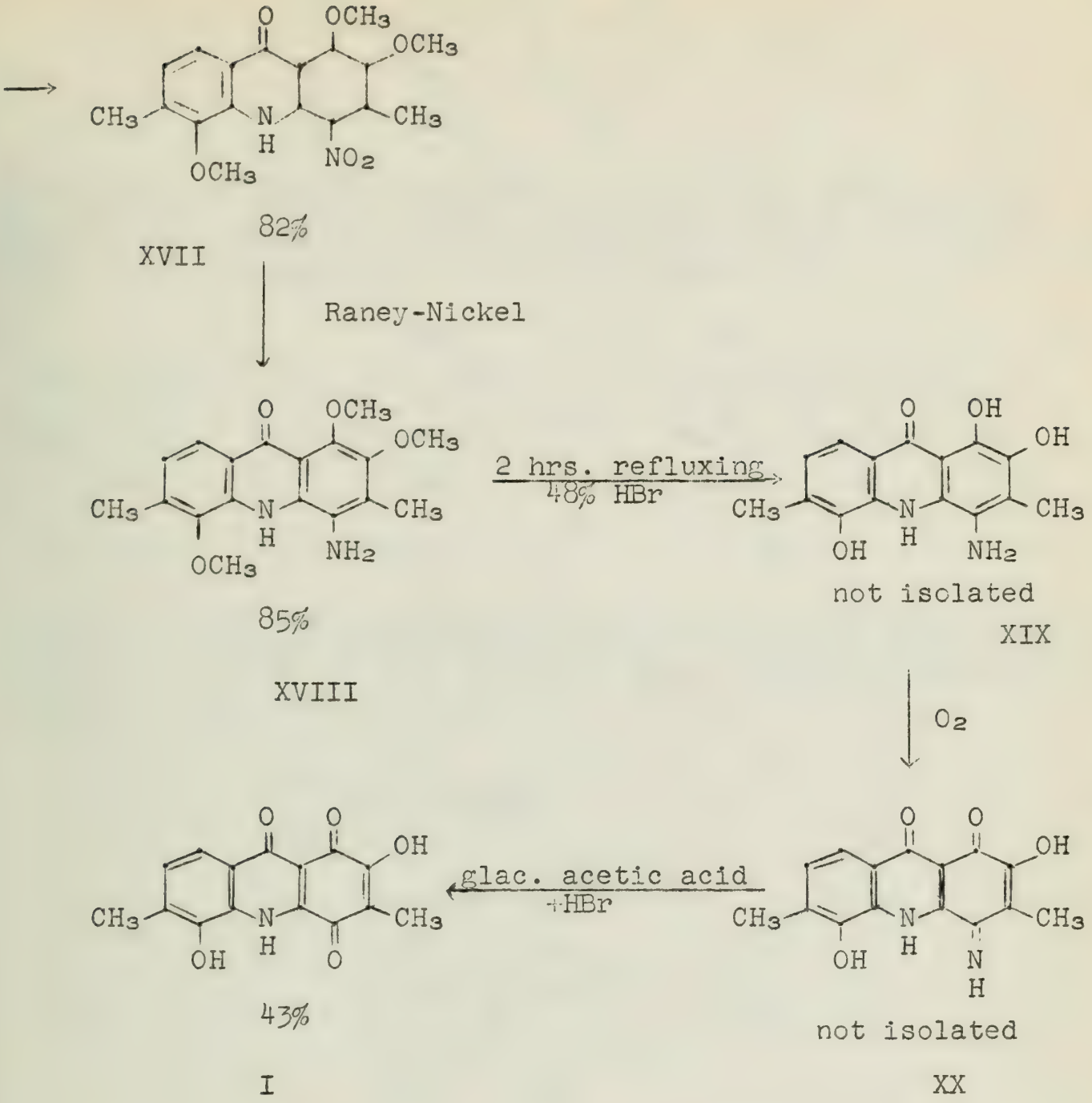
3.) H^+



28%

XVI

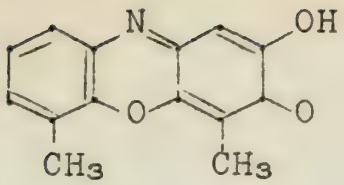
$\xrightarrow[\text{in glac. acetic acid}]{\text{15\% polyphosphoric acid}}$



Infrared and ultra-violet absorption spectra were identical for the synthetically prepared compound and the natural actinomycinol (I). Treatment of (I) with a mixture of acetic anhydride and perchloric acid yielded the diacetate which when mixed with the diacetate of the natural compound did not depress the melting point.

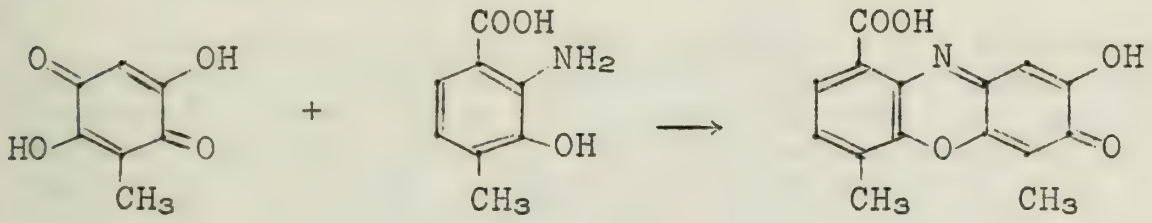
Spectral evidence between the actinomycinol structure (I) and actinomycin did not, however, conform. This led to the belief that extensive rearrangements had occurred when the actinomycin was treated with barium hydroxide to yield actinomycinol (14).

Hydrolysis of actinomycin C for prolonged periods with warm 20% hydrochloric acid had given the first clues to the precise nature of the unrearranged actinomycin chromophore after these two compounds had been isolated: 2,5-dihydroxy-3-methylbenzoquinone (IV) and orange-colored 2-hydroxy-4,6-dimethylphenoxazin-3-one (V). The position of the methyl groups was confirmed by synthesis (23).



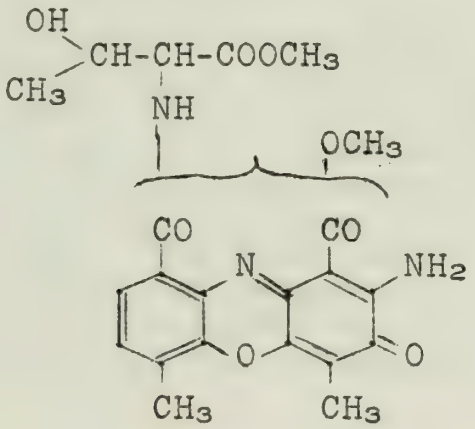
V

Rather mild methanolic acid hydrolysis produced orange colored actinocinin (24) which proved to have structure VI. This was verified by synthesis (23) from 3-hydroxy-4-methyl anthranilic acid (VII) and 2,5-dihydroxy-3-methyl benzoquinone (IV).



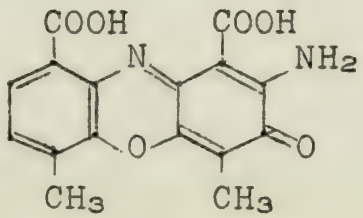
IV VII VI

A by-product of the preparation of actinocinin (VI) from actinomycin was a dimethyl ester (VIII), which on further hydrolysis and examination of the product for amino acids showed the presence of threonine only (25).



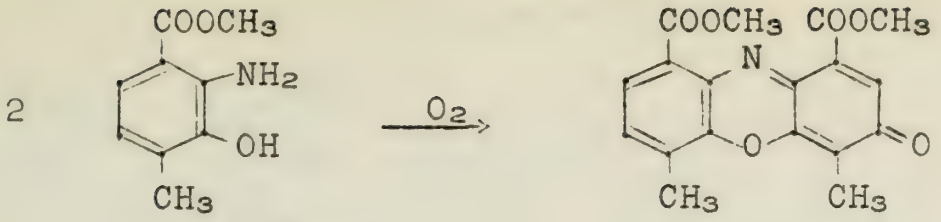
VIII

The similarity of the ultraviolet and visible absorption spectra of all the above phenoxazones to those of actinomycin strongly suggested that actinomycin was a peptide derived from 2-amino-4,6-dimethyl-3-oxophenoxazine-1,9-dicarboxylic acid (actinocin IX)(25).



IX

The dimethylester (XI) was synthesized by oxidative self-condensation of methyl-3-hydroxy-4-methylanthranilate (X)(26).



X XI

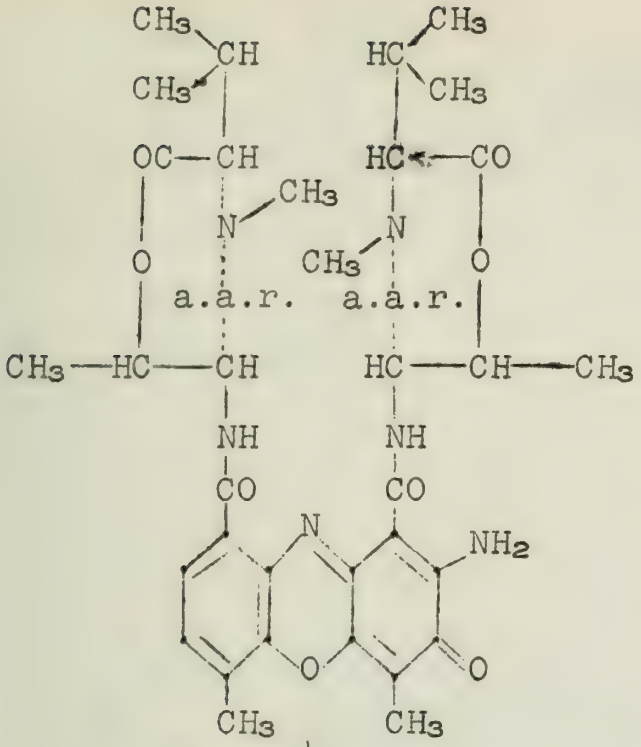
THE PEPTIDE STRUCTURE

The absence of any free aliphatic amino or carboxyl groups in actinomycin led to the supposition that the amino acids are arranged in the form of a peptide and that this peptide is cyclic. The band at 1754 cm.$^{-1}$ in the infrared spectrum of actinomycin supported this view since it is representative of a lactone grouping (28). The molecular weight of approximately 1280 suggests that nine or ten amino acid residues are contained in actinomycin. One arrives at this figure by simply computing:

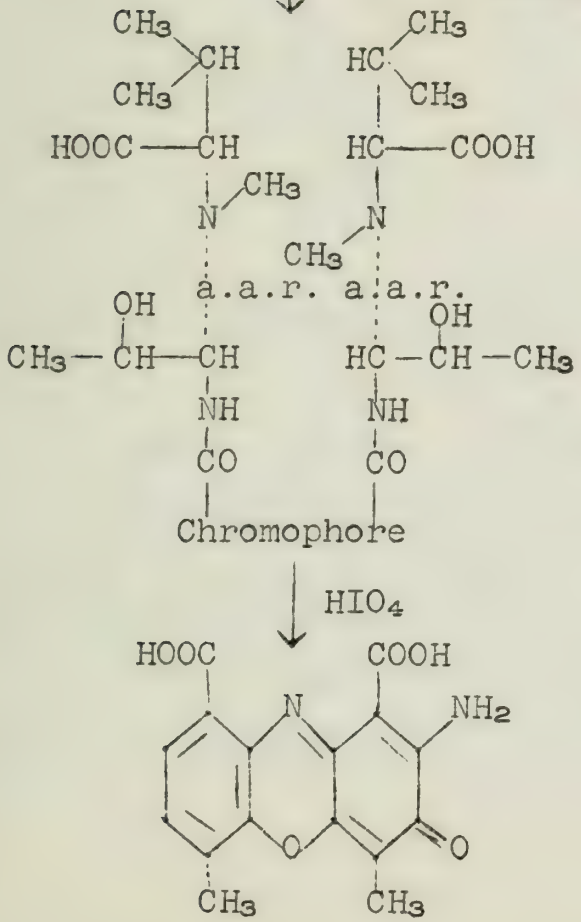
$$\text{no. of a.a.residues} = \frac{\text{MW of actinomycin -- MW of chromophore}}{\text{average weight of a.a.residues}} \quad (27)$$

Potentiometric titration had indicated two ester groups, revealing that the peptide might be arranged in two lactonized rings. As mentioned before threonine was found to be the amino acid bound next to the chromophore. Mild alkaline treatment of actinomycin gave a dicarboxylic acid, actinomycinnic acid (XXI) (29), a peptide of actinocin (XXII). Unlike actinomycin itself when this acid was oxidized by periodic acid, subsequent acid hydrolysis gave no threonine. This may be interpreted as an oxidation of a threonyl peptide containing free hydroxyl groups which are lactonized in actinomycin itself. The free carboxyl groups of actinomycinnic acid (XXI) were shown to be associated with N-methyl valine by a Dakin-West degradation to destroy the terminal amino acid. The degradation so far may be represented as 30.

Actionomycin I



0.1 N methanolic NaOH; 4 hrs. at 40°.

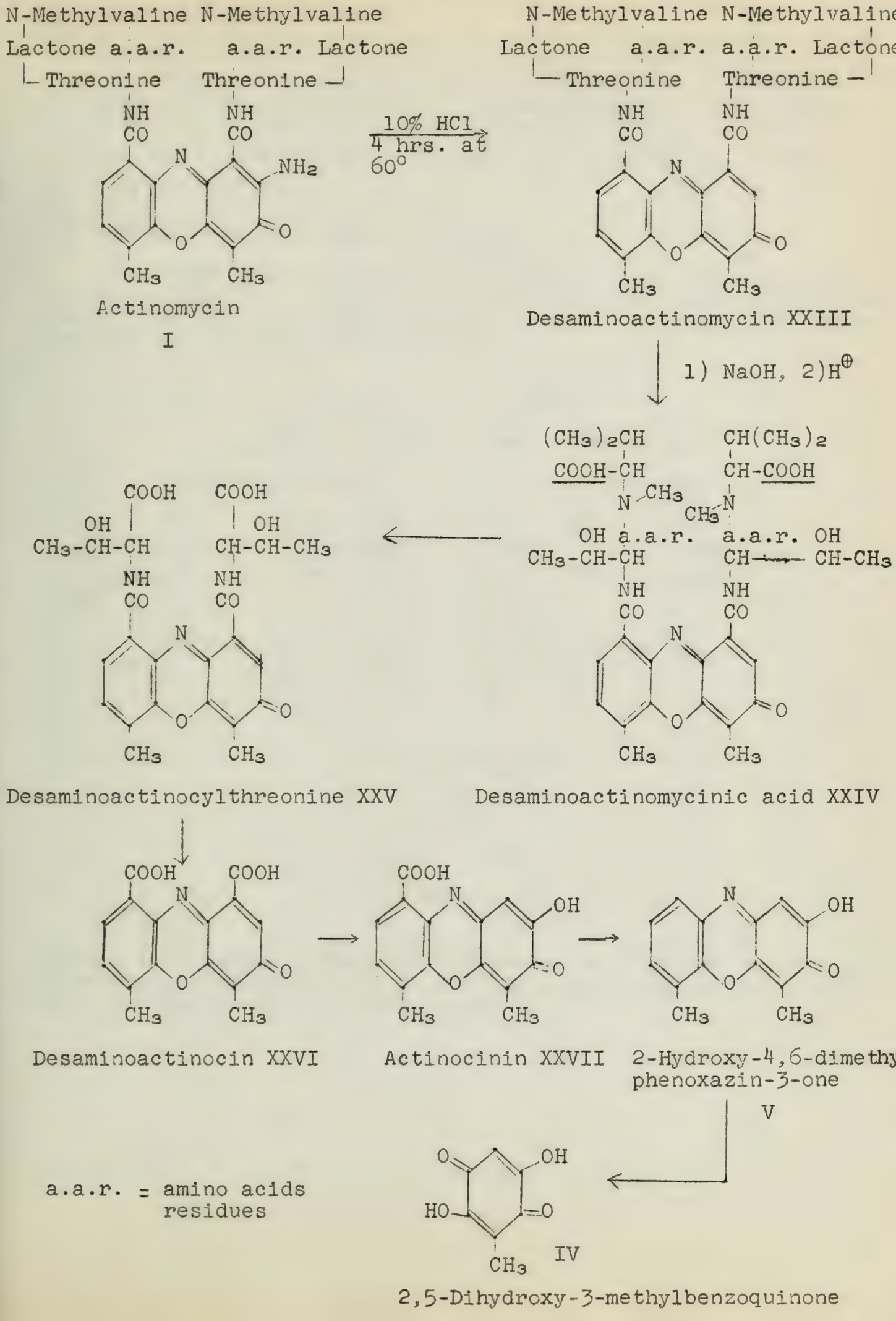


Actinomycinnic acid
XXI

HIO_4

Actinocin
XXII

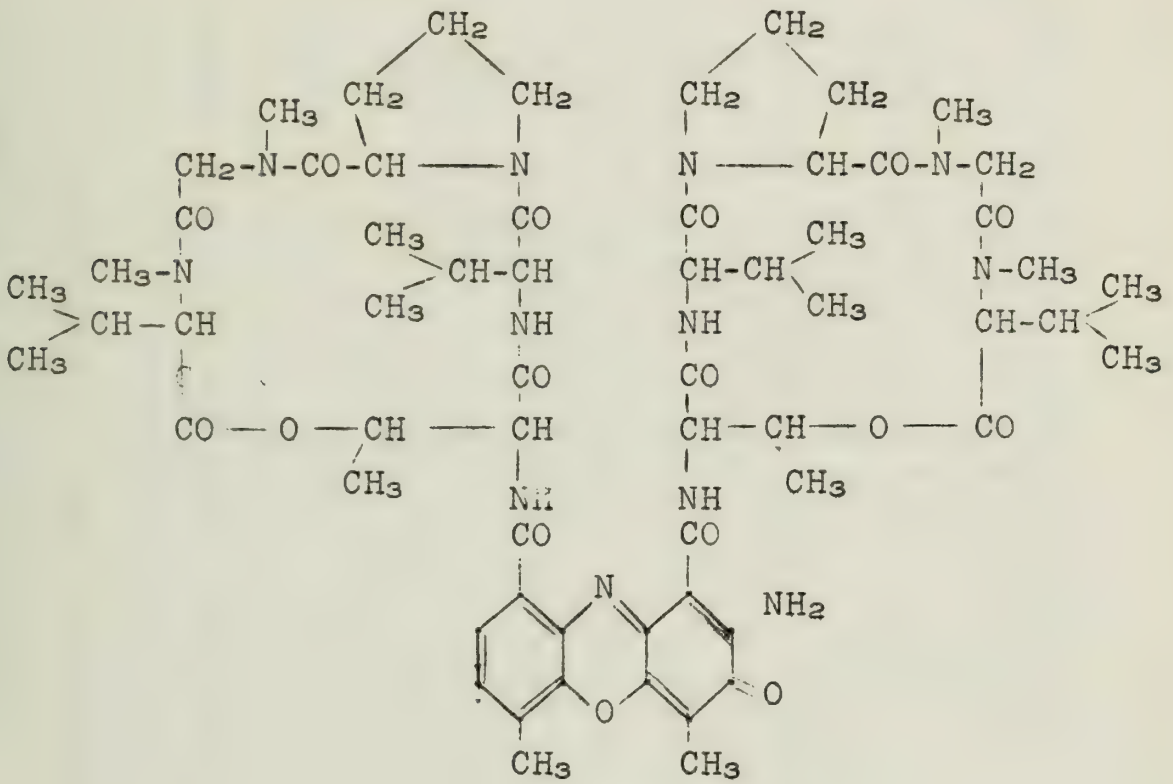
a.a.r. = Amino Acid Residues.


N-Methylvaline N-Methylvaline
Lactone a.a.r. a.a.r. Lactone
Threonine Threonine
10% HCl
4 hrs. at 60°
Actinomycin
I
Desaminoactinomycin XXIII
1) NaOH, 2) H⊕
a.a.r.
Desaminoactinocylthreonine XXV
Desaminoactinomycinic acid XXIV
Desaminoactinocin XXVI
Actinocinin XXVII
2-Hydroxy-4,6-dimethyl-phenoxazin-3-one
V
a.a.r. = amino acids residues
2,5-Dihydroxy-3-methylbenzoquinone
IV

The precise arrangement of the amino acids in the peptide chains was determined by the isolation of certain dipeptide derivatives from the action of hydrazine on actinomycin (31). Evidence was thus obtained for the N-methylvaline-sarcosine linkage in the actinomycins C_2 and C_3 and I_I; for the L-proline-D-valine linkage in actinomycin I_I and the L-proline and D-alloisoleucine linkage in actinomycin C_3 (32).

THE STRUCTURE OF ACTINOMYCINS C_3 AND D

All these investigations led finally to the total structure for actinomycin C_3 (32). Recently the structure for actinomycin D was elucidated, which is identical with that of C_3 except that valine replaces the D-alloisoleucine (33).



Actinomycin C_3

Johnson (27) suggests that the difference between the various kinds of actinomycins is confined to the amino acid composition, which has been determined in several cases (6,8).

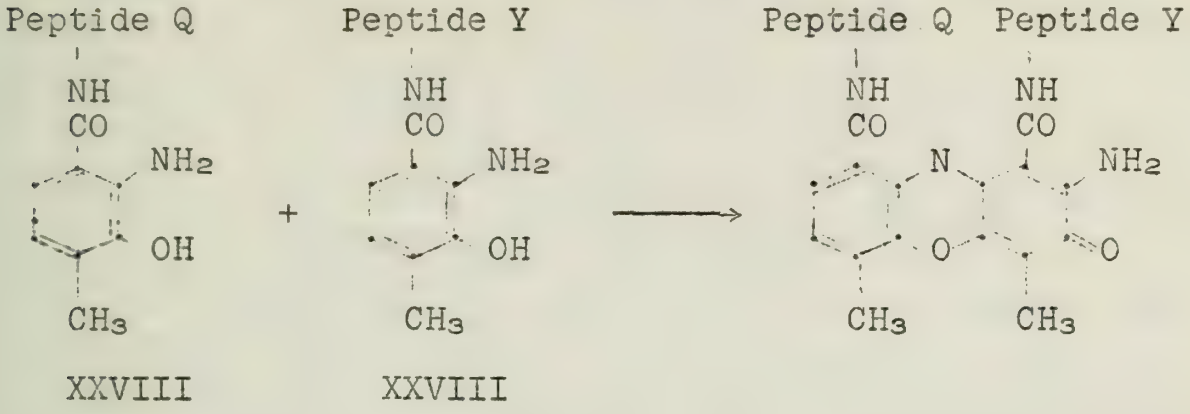
AMINO-ACID ANALYSES OF ACTINOMYCIN

(Expressed as moles of amino-acid per mole of actinomycin and a molecular weight of 1200.)

Actinomycin	Complex of origin	Threonine	Sarcosine	Proline	Valine	N-Methylvaline	alloiso Leucine
I	A	1.3	1.9	1.0	2.0	2.0	0
I	B	1.3	1.8	1.1	1.9	1.9	0
IV	A	1.2	2.0	2.1	2.0	2.0	0
IV	B	1.2	1.9	2.2	1.9	2.0	0
IV	D	1.2	2.0	2.1	2.1	2.1	0
V	A	1.1	1.9	1.0	1.9	1.9	0
V	B	1.0	2.0	1.1	2.0	2.1	0
1	C	0.9	1.5	1.7	1.9	1.7	0
2	C	1.4	1.4	1.9	0.9	1.9	0.9
3	C	1.2	1.4	2.1	0	2.0	2.0

THE BIOSYNTHESIS

It is suggested (34) that the molecule of actinomycin is built up by the oxidative condensation of two molecules of the 3-hydroxy-4-methylanthranilic peptide XXVIII. Unsymmetrical condensations could give rise to the various kinds of actinomycins observed.



XXVIII XXVIII

BIBLIOGRAPHY

1. Waksman and Tishler, J. Biol. Chem., 142, 519 (1942).
2. Fischer, Charney and Bolhofer, Antibiotics and Chemotherapy, 1, 1, 571 (1951).
3. Brockmann, Grubhofer, Kass and Kalbe, Chem. Ber., 84, 260 (1951).
4. Waksman, Antibiotics and Chemotherapy, 4, 502 (1954).
5. Brockmann and Gröne, Naturwissenschaften, 41, 65 (1954); idem, Chem. Ber., 87, 1036 (1954).
6. Roussos and Vining, J. Chem. Soc., 2469 (1956).
7. Brockmann and Pfennig, Naturwissenschaften, 39, 429 (1952); idem, Z. physiol. Chem., 292, 77 (1953).
8. Brockmann and Gröne, Naturwissenschaften, 40, 222, 224 (1953).
9. Vining and Waksman, Science, 120, 389 (1954).
10. Brockmann, Angew. Chem., 66, 1 (1954).
11. A. W. Johnson, Special Publication No. 5, London: The Chemical Society, 1956, p. 82.
12. Brockmann and Grubhofer, Naturwissenschaften, 37, 494 (1950).
13. Dalgliesh, Johnson, Todd and Vining, J. Chem. Soc., 2946 (1950).
14. Johnson, Todd and Vining, J. Chem. Soc., 2672 (1952).
15. Brockmann and Meyer, Chem. Ber., 86, 1514 (1953).
16. Brockmann and Vohwinkel, Angew. Chem., 67, 619 (1955).
17. Brockmann and Franck, ibid., 68, 70 (1956).
18. See ref. 11, p. 87.
19. Angyal, Bullock, Hanger and Johnson, Chem. and Ind., 1295, (1955).
20. See ref. 11, pp. 88-89.
21. Crow and Price, Austral. J. Sci. Res., 2, 283 (1949).
22. Brockmann and Muxfeldt, Angew. Chem., 67, 618 (1955);
23. idem, ibid., 68, 67 (1956).
24. Brockmann and Gröne, ibid., p. 66.
25. See ref. 11, pp. 90-91.
26. Brockmann and Muxfeldt, Angew. Chem., 68, 69 (1956).
27. See ref. 11, p. 85.
28. Brockmann and Franck, Naturwissenschaften, 41, 451 (1954); idem, Chem. Ber., 87, 1767 (1954).
29. idem, Angew. Chem., 68, 68 (1956).
30. See ref. 11, pp. 91-93.
31. Brockmann, Bohnsack and Süling, Angew. Chem. 68, 66 (1956).
32. Brockmann, Bohnsack, Franck, Gröne, Muxfeldt and Süling, ibid., p. 70.
33. Bullock and Johnson, J. Chem. Soc., 3280 (1957).
34. See ref. 11, p. 94-95.
35. See ref. 11, p. 86.

OXIDATIVE DEGRADATIONS OF SACCHARIDES

Reported by T. W. Milligan February 27, 1958

Oxidative methods are of general application for the degradation of saccharides and other glycol-containing compounds, lead tetraacetate and periodate salts being the usual reagents. Various aspects of these topics have been reviewed elsewhere (1,2,3, 4,5). This seminar will present a resumé of some recent applications of these oxidation methods to preparative and structural problems in saccharide chemistry.

INTRODUCTION

Glycol cleavage reagents - i.e., lead tetraacetate and periodate salts - are more or less specific for the oxidation of cis oriented glycols. The more nearly the alpha hydroxyl groups approach a true cis configuration, the faster the rate of oxidation (5). This fact has been utilized in previous degradations of saccharides and glycosides, but variation in reaction conditions has produced some ambiguity in the interpretation of results. The method has been eminently successful in its application to the elucidation of the configuration of methyl glycosides (6,7).

Recently Perlin and other Canadian chemists have utilized these methods to degrade selectively saccharides of many types and have established a pattern of oxidation behavior correlated with the stereochemical structure of the sugar. By a series of alternating oxidations and reductions they have also successfully degraded oligosaccharides to glycosyl - substituted glycerols, thus establishing a direct chemical method for investigating the α or β configuration of the glycoside link. These subjects form the nucleus of this report.

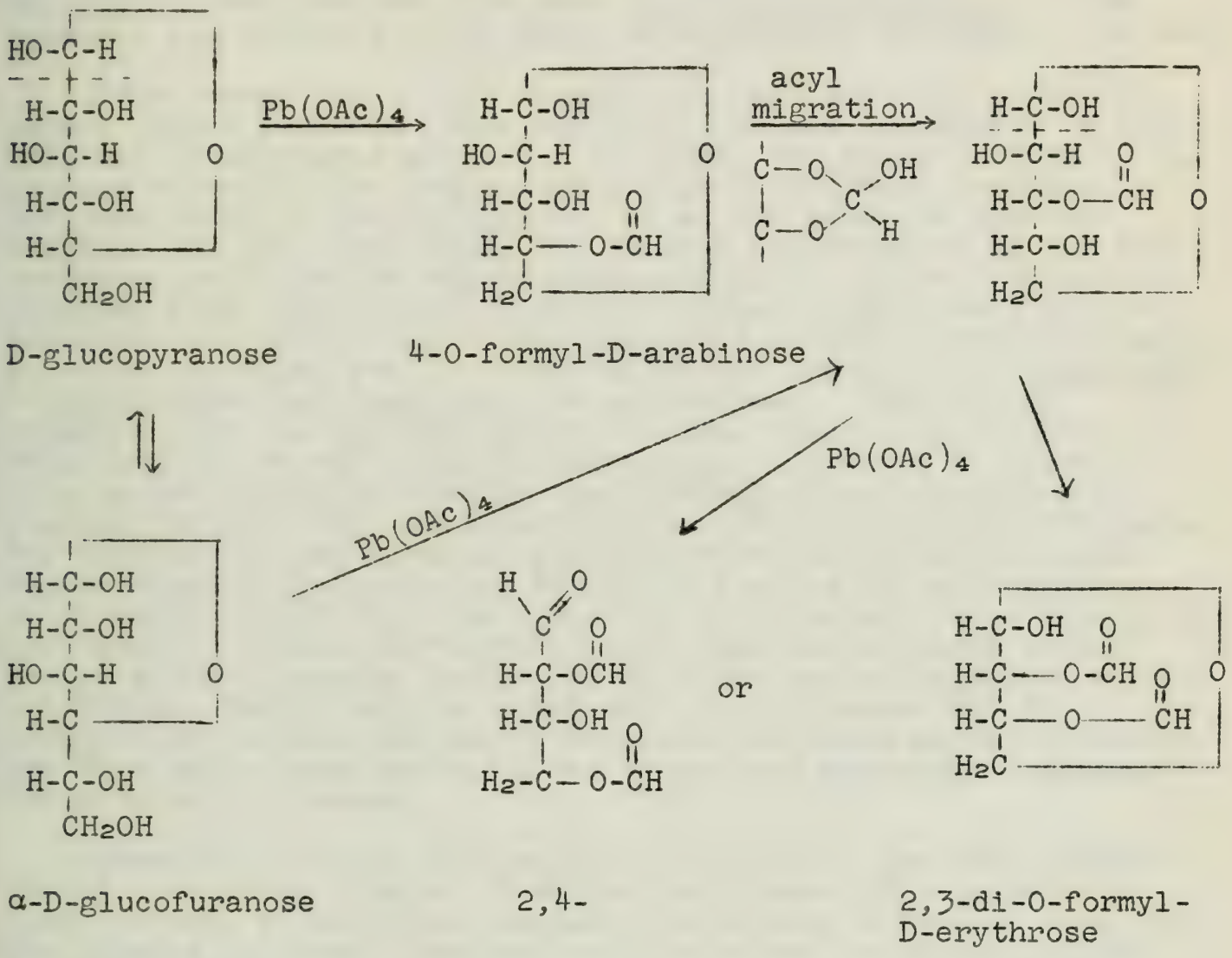
MONOSACCHARIDES

Previous reports of the tetraacetate oxidation of D - glucose state that three (8), two (9) or five (10) moles of oxidant were consumed by the sugar. These divergent results were probably due to differing conditions.

In 1954 Perlin reported the first of a series of oxidations of simple aldoses and ketoses using 2 moles of $Pb(OAc)_4$ (11,12,13). The products were the corresponding diformate esters of the sugars with two less carbon atoms, although an excess of the oxidant caused further degradation. This work has been summarized in a recent paper (14). It was observed that D-glucose absorbed 2 moles of tetraacetate in 3 minutes, after which the reaction became very slow. The rate of this reaction is very rapid compared to that of aliphatic glycols or glycosides. The product was a sirup exhibiting strong reducing properties and strong infrared bands at 1725 $cm.^{-1}$ and 1170 $cm.^{-1}$. It liberated 2 moles of formic acid on hydrolysis, furnishing D-erythrose in 90% yield and was thus characterized as a diformate ester of D-erythrose. The position of the formate groups was not established, partly because of the instability of the formate, which released formic acid upon dissolution in water and underwent hydrogenolysis when hydrogenation was attempted at room temperature with PtO_2. Perlin reasoned that one of the formate groups was probably at the 2-position of the

tetrose because the compound is only very slowly oxidized by tetraacetate.

Two alternative reaction paths were proposed as possibilities for this oxidation of glucose, one involving cleavage of the (normal) pyranose form of the glucose followed by acyl migration and further oxidation, the other involving preferential oxidation of the furanose form directly to the intermediate monoformate:



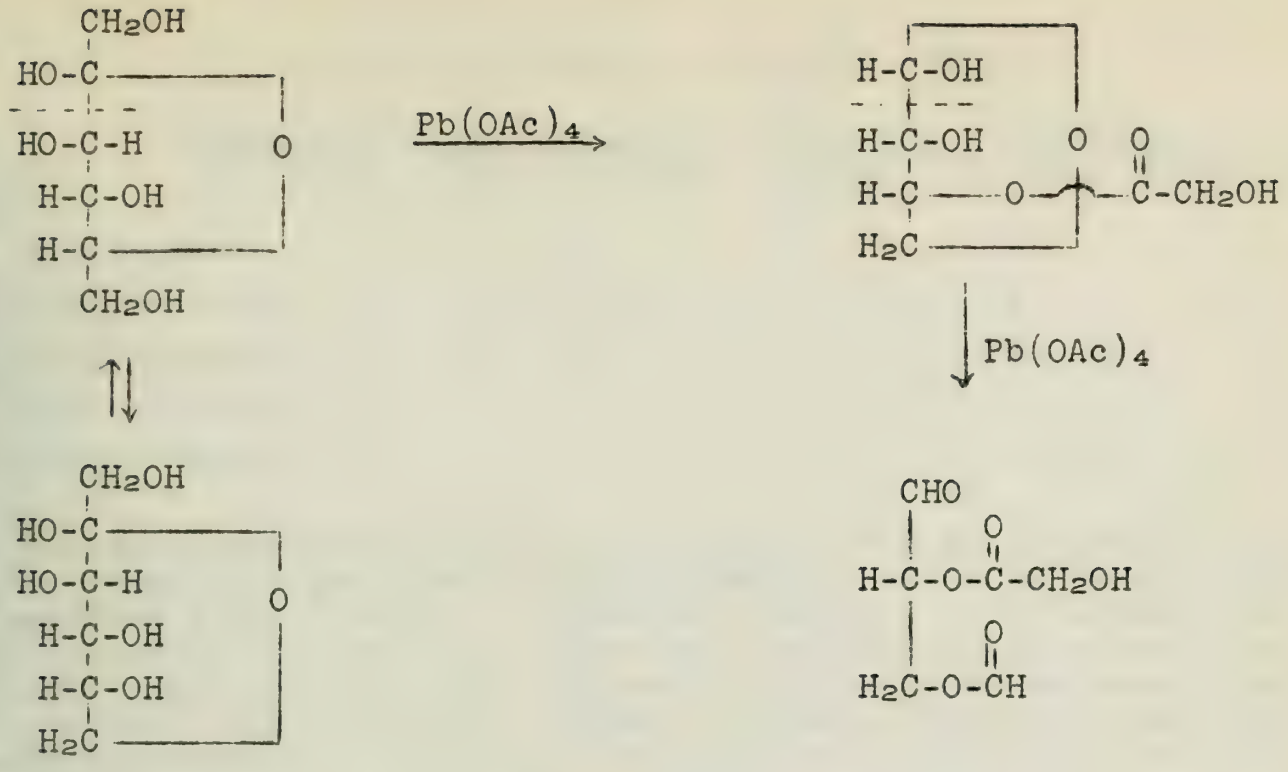
Several known instances of acyl migration (15) provide precedence for the first route, but these cases have not involved migration of formyl groups. Perlin suggested that the great speed of the reaction as compared with the rate for glycols or glycosides could be accommodated by an ionic mechanism rather than the radical mechanisms recently proposed for glycols (16,17) since the hemiacetal α-glycol would be expected to be the prime site of carbonium ion formation; this would be in accord with Criegee's original proposal (8) that the cyclic forms of the sugars were oxidized preferentially by tetraacetate.

The possibility that the furanoid ring form of the sugar is oxidized preferentially finds support in the fact that the furanose ring is nearly planar and the hemiacetal α-glycol is more nearly able to assume a true cis (0°) position. Thus, 2,3-dihydroxytetrahydrofuran may be titrated with $Pb(OAc)_4$ even in the presence of

ethylene glycol or methyl glycopyranosides containing "cis" glycols (18). Reducing sugars, however, interfere with this titration, presumably because they can form furanose rings of their own. These glycol-cleavage reactions demonstrate second order kinetics (19,20), and therefore a rather high concentration of the furanoid form would be necessary to explain the rapid rate. The position of the pyranose/furanose equilibrium of glucose under these conditions is not known, but Perlin was not able to measure the rate of mutarotation when α or β-D glucose was dissolved in acetic acid, leading him to conclude that the very rapid interconversion of the pyranose and furanose forms might be sufficient to explain the rate.

From Reeves' data (18) it might be inferred that reducing sugars (where furanoid forms are possible) are titratable in the presence of aliphatic glycols. If, then, the furanose form is the species attacked, the hemiacetal α-glycol should be oxidized preferentially to the 5,6-glycol, in accord with the observed results. On the other hand, the absence of oxidation at the 5,6-position could also be explained by oxidation of the ordinary pyranose form, since the 1,5-oxygen bridge would protect the 5-position. In an attempt to differentiate between these two possible modes of reaction, Perlin investigated the oxidation of D-glycero -D- guloheptose and D-erythro -D- galaoctose. Even in the pyranose form the heptose contains a free terminal 6,7-glycol group and the octose a 6,7,8-triol group. Thus, if a pyranose ring is the factor preventing the terminal glycol oxidation in glucose (by blocking the 5-position) it would not prevent it here, and cleavage of the terminal glycol groups should occur. Both sugars behaved like glucose, absorbing 2 moles of oxidant in a rapid reaction and yielding arabinose and glucose, respectively, in high yield. It was therefore evident that the terminal glycol groups did not require protection by a hemiacetal bridge to escape oxidation. Perlin made no claim that this evidence had unequivocally established one or the other of these paths, however, and this writer must agree, since no attempt was made to disprove the alternative scheme.

Other aldoses and ketoses were oxidized in the same general manner, absorbing 2 moles of oxidant and producing sugars of a lower series, although overoxidation did occur with some compounds. The ketoses produced formate-glycolate esters as opposed to the diformates from aldose sugars.



The reaction scheme proposed to account for the hexose → tetrose diformate conversion involved a pentose monoformate as an intermediate, implying that the reaction of a hexose with less than two moles of lead tetraacetate might produce pentose. This supposition was supported by the isolation of D-lyxose in 35% yield from D-galactose using 1 mole of oxidant, and similar yields of pentoses from other hexoses.

The results of these investigations, while not allowing a complete mechanistic description of these saccharide degradations, do provide a workable postulate for a reaction scheme which has proved valuable in the work described below, and do furnish a relatively simple means for the stepwise chain degradation of common sugars to some rarer ones.

DISACCHARIDES

A. CATALYZED OXIDATIONS

Perlin's observations on the utility of potassium acetate as a catalyst in the tetraacetate oxidation of formic acid to carbon dioxide (21) led him to inspect the behavior of reducing sugars under these (catalyzed) conditions (22,23). The results are summarized in table I.

TABLE I

CATALYZED OXIDATION OF DISACCHARIDES

Type	Oxidant Consumed (Moles) Total	Reducing End	Oxidation Products Pentose	Tetrose	Formaldehyde
1,3-aldohexose	-	1	1	0	-
1,4-aldohexose	4	2	0	1	0
1,6-aldohexose	6	3	-	-	-
1,4-ketohexose	3	1	0	1	-
1,2-aldohexose	5	-	-	-	1

1,6-Aldohexopyranose sugars are degraded to a much greater extent than other linkage types, yielding about 5 moles of formic acid and consuming about 6 moles of oxidant, 3 moles by the reducing end. By contrast, 1,3- and 1,4- disaccharides yield only about 1 mole of formic acid, most of which appears to arise from the non-reducing end units. The latter two linkage types are distinguished from each other however, since the reducing end of the 1,3- linked sugars absorbs only one mole of oxidant to yield a pentose formate, while that of the 1,4- compounds is further oxidized to give a tetrose diformate. These data are paralled by results obtained from the related 3,4, and 6-O-methyl D-glucoses, after allowing for the absence of an oxidizable non-reducing saccharide end unit.

Only two compounds, 4-O-β-D-mannopyranosyl-D-glucose and 4-O-β-D-mannopyranosyl-D-mannose, gave anomalous results. The reducing ends of other 1,4- reducing disaccharides absorbed the expected 2 moles of oxidant. These two sugars had a total absorption of about 4 moles of oxidant; after the usual allowance for the oxidation of the non-reducing end, it appeared that the reducing end unit in these two compounds had used up only one mole of oxidant. The product, however, was the normal tetrose, and all other evidence indicated the 1,4- link to be correctly assigned. Since previous work (6,7) indicated the oxidation rate of glycosides to be independent of the α or β-configuration, it would seem that the non-reducing mannopyranoside units here are not being oxidized to the usual extent, leading Perlin to suggest an unusual ring conformation in the β-mannopyranose units as a possible explanation.

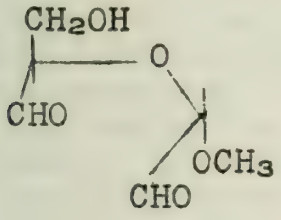
The 1,4-ketohexose disaccharides studied yielded one mole of formic acid and required 3 moles of lead tetraacetate. These data are consistent with the aldose results, assuming glycolate esters instead of formate esters are the products, as previously noted for monoketoses (14).

Since the oxidation behavior which characterizes a given linkage position is determined mainly by the reducing end, these reactions should also be useful for determination of glycosidic links in aldobiuronic acids, in which the non-reducing end-units are easily overoxidized by glycol cleavage reagents owing to the formation of an intermediate active methylene group (23a). Thus, the oxidation of 6-O-β-D-glucuronopyranosyl-D-galactose resembles at the outset that of the 1,6- hexose disaccharides, despite an eventual pronounced overoxidation. The oxidation of 4-O-(4-O-methyl-D-glucuronopyranosyl)-D-galactose, in which the non-reducing

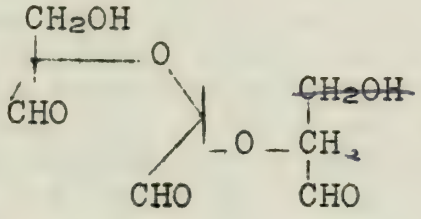
end-unit is protected against overoxidation by the 4-O-methyl group, absorbs 3 moles of oxidant, corresponding to the expected tetrose diformate (threose isolated after hydrolysis) at the reducing end, and cleavage of the 2,3-glycol group in the non-reducing end. Perlin suggested, however, that these overoxidation problems could be overcome by use of the non-catalyzed oxidations described below.

B. NON-CATALYZED OXIDATIONS

A classic application of glycol-cleavage reactions to carbohydrate chemistry is found in the early work on the configuration of the methyl glycosides (6,7). In the D-series all methyl α-hexopyranosides, through cleavage of the 2,3,4-triol group give the same dialdehyde I, with a large positive specific rotation; the β-glycopyranosides give the anomeric compound with a large negative rotation. Thus by reducing the total number of asymmetric centers the contribution of the glycosidic center to the total rotation is made relatively large. Perlin has essentially extended these concepts to compounds in which the glycosidic residue is another saccharide unit (23,24).



I



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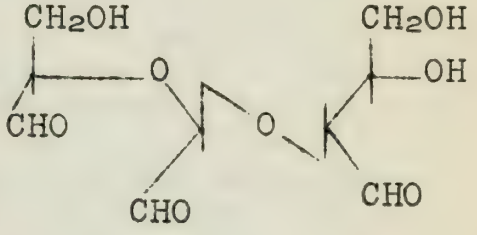

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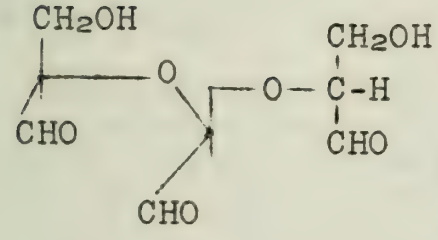

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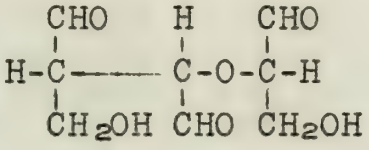
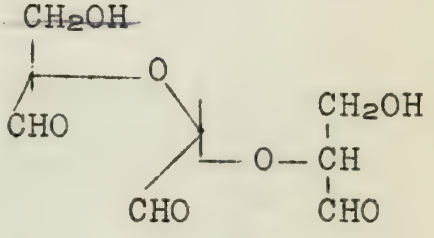


V



VI

For example, D-aldohexose disaccharides with 1,6-links are degraded to the trialdehyde II, in which the reducing end unit has been converted to glycolic aldehyde, and the glycosidic residue yields a dialdehyde of the type derived from simple glycosides. A 1,4-hexose disaccharide (i.e., cellobiose) should be converted to III, in which the D-erythrose unit from the reducing end is linked through the 2-position to a dialdehyde via a β- link. Maltose should give a compound differing only in the α-configuration of the glycosidic bond.

The results with 1,6- and 1,4-disaccharides agree well with these predictions as shown below.

TABLE II

OXIDATION BEHAVIOR OF DISACCHARIDES

Disaccharide	$[\alpha]_D$ Disaccharide	Oxidation Procedure	$[\alpha]_D$ Oxidized Disaccharide
Isomaltose(1,6 α)	+98°	Periodate	+85°
Mannobiose(1,6α)	+50°	"	+88°
Gentiobiose(1,6β)	+8°	"	-109°
Cellobiose(1,4β)	+34°	Tetraacetate	-80°
Lactose(1,4β)	+55°	"	-78°
Glucosido-erythritol(1,2-β)	-17°	Periodate	0°
Glucosido-fructose (1,5-α)	-8°	"	+36°

Thus the specific rotations of the oxidation products of α- and β-1,6-disaccharides differ, and two 1,6-α-compounds give a product with about the same rotation. Three β-1,4-disaccharides gave products having specific rotations all negative and of the same magnitude. These examples with known disaccharides served to delineate the method; its utility may be illustrated by the oxidation of 4-O-D-mannopyranosyl-D-mannose, previously assigned a β-configuration on the basis of a small negative equilibrium rotation ($[\alpha]_D = -2°$) and lack of attack by an α-mannosidase (25). After oxidation the product had $[\alpha]_D = -84°$, definitely indicating the β-configuration.

This method suffers in that it is not applicable to 1,2-(or 1,5)-disaccharides. Saccharides containing 1,2-links are overoxidized by glycol cleavage reagents with the liberation of formaldehyde. This problem can be overcome by prior reduction of the sugar to a polyol, but then the product would be of type V. Three compounds of this type were oxidized, but the specific rotations of the products were essentially 0°. A possible explanation lies in the fact that V is symmetrical and the contribution of the D- and L-glyceraldehyde units cancel. In this case, two D- or two L-groups should give an optically active product; the oxidation of 5-O-D-glucopyranosyl-D-fructose affords a product with $[\alpha]_D = +36°$, but this bears no relation to the original configuration, since the glycosidic center of the product is not then asymmetric. This problem has been overcome by use of the techniques described in section C.

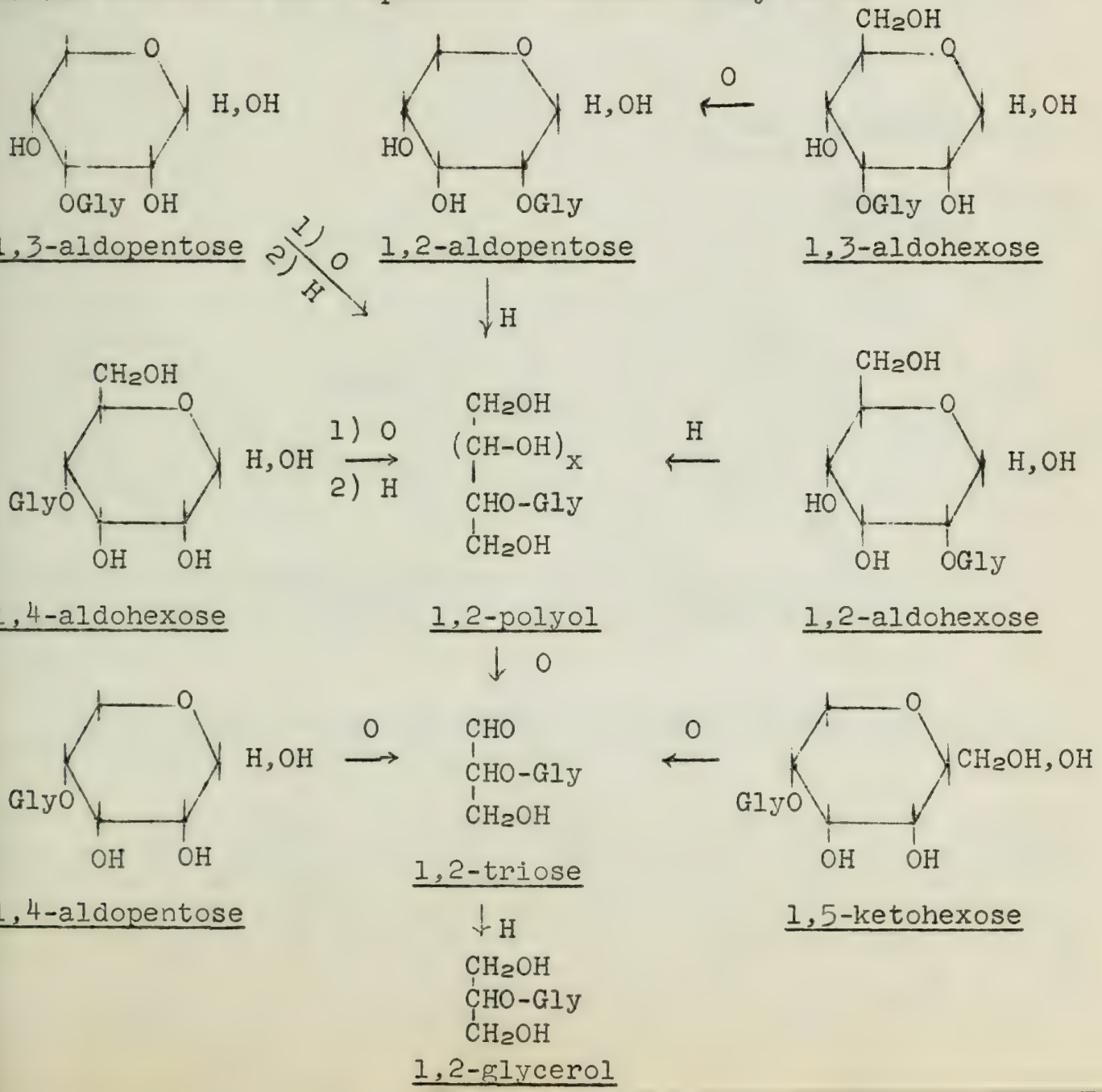
A pentopyranose disaccharide with a 1,4-link should also yield a product containing a glyceraldehyde substituent (VI), which, however, is stereoisomeric with the products (II ~~or IV~~) from 1,6-hexose disaccharides. In this same manner it should be possible to develop methods for the determination of linkage configuration in disaccharides of other types.

C. DEGRADATIONS TO GLYCOSYL-SUBSTITUTED GLYCEROLS

The difficulties encountered in applying direct oxidation procedures to 1,2-reducing disaccharides were noted above. The development of a method for examination of the structures of disaccharides with more general applicability will be described here (26,27).

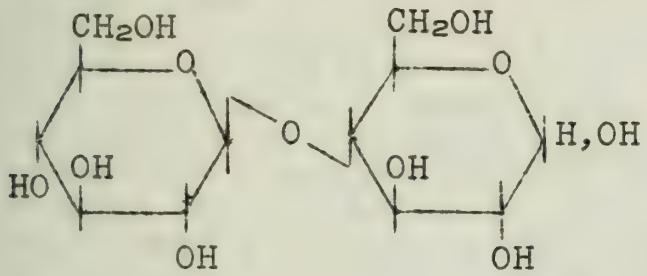
The object of this approach is to degrade selectively the reducing end-unit so as to eliminate asymmetry other than that due to the non-reducing end of the molecule. From the previously described work it is obviously possible to utilize lead tetraacetate for selective oxidation of the reducing end-unit at the α-hemiacetal glycol; the reduction of the intermediate tetrose unit with sodium borohydride furnished a tetritol. Hockett had previously noted the much faster oxidation rates of polyols relative to glycosides (28,29), and the tetritol was accordingly oxidized selectively to a glyceraldehyde residue while the glycoside link remained undisturbed. A final reduction produced the appropriate 2-substituted glycerol whose specific rotation was direct evidence for the nature of the glycosidic link in the original sugar.

The results of a number of these investigations on sugars of varied structure are represented schematically below:

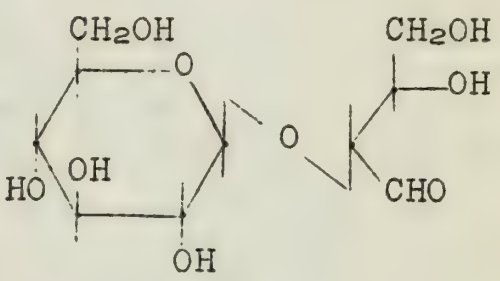


In the course of these experiments, the 2-O-glycosyl-glycerols necessary for use as reference compounds for a whole series of disaccharides have been produced, included those for which the non-reducing end-units are D-glucose, D-galactose, D-mannose, L-arabinose, and D-xylose. A determination of the configuration of a new disaccharide in which the non-reducing residue is included above then simply involves the performance of the necessary alternating oxidation and reduction reactions and a comparison of the specific rotation of the product with that of the standard compounds. The experimental procedures involved are simple and require only small amounts of starting material, an important consideration when dealing with many of the rarer compounds isolated from natural sources.

As an example, consider the production of 2-O-β-D-glucopyranosyl-glycerol from cellobiose.



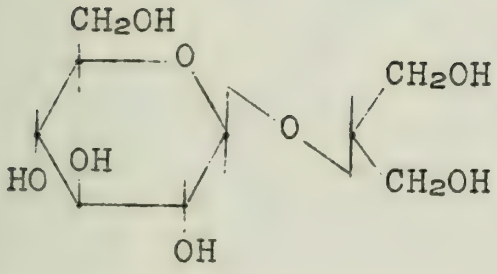
2 moles $Pb(OAc)_4$



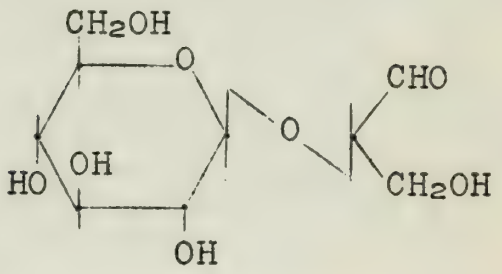
2-O-β-D-glucopyranosyl-D-erythrose

↓ $NaBH_4$, reduce to tetritol

↓ 1 mole $Pb(OAc)_4$



$NaBH_4$



2-O-β-D-glucopyranosyl-glycerol

$[\alpha]_D = -30^\circ$

2-O-β-D-glucopyranosyl-L-glyceraldehyde

By the same series of reactions maltose gives 2-O-α-D-glucopyranosyl-glycerol with $[\alpha]_D = +121^\circ$.

For most of the compounds studied the assignment of configuration had previously been made on the basis of equilibrium rotation values as an extension of Hudson's rules (30), but the validity of this method had not been established, chiefly because the rotatory contribution of the reducing end-unit in the equilibrium mixture is not easily assessed. The general good agreement of the results found here with the previous assignments provides support for the correctness of the polarimetric method in addition to offering better characterization by direct chemical evidence.

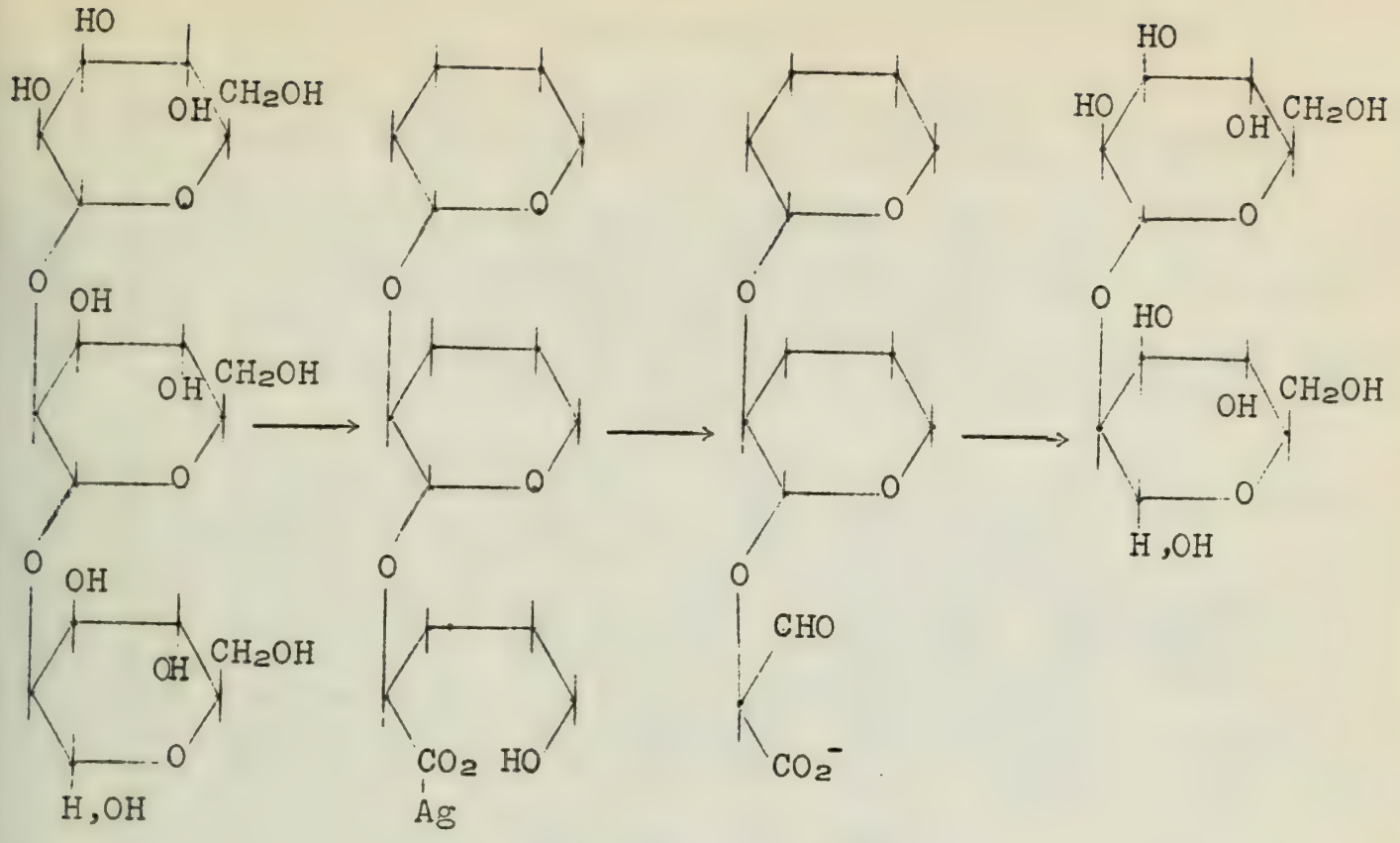
TRISACCHARIDES

The application of these oxidative degradations to more complex oligosaccharides may be illustrated with the selective oxidation of O-α-D-mannopyranosyl-(1→2)-O-α-D-mannopyranosyl-(1→2)-D-mannose, a trisaccharide isolated from the acetolysis of a yeast slime polysaccharide (31). Methylation of the trisaccharide followed by hydrolysis afforded two moles of 3,4,6-tri-O-methyl-D-mannose and one mole of 2,3,4,6-tetra-O-methyl-D-mannose, proving the glycosidic link to be of the 1,2-type. The trisaccharide consumed $Pb(OAc)_4$ very slowly in glacial acetic acid; in aqueous acetic acid and in the presence of potassium acetate the sugar yielded one mole of formaldehyde, confirming the 1,2-nature of the glycoside bonds.

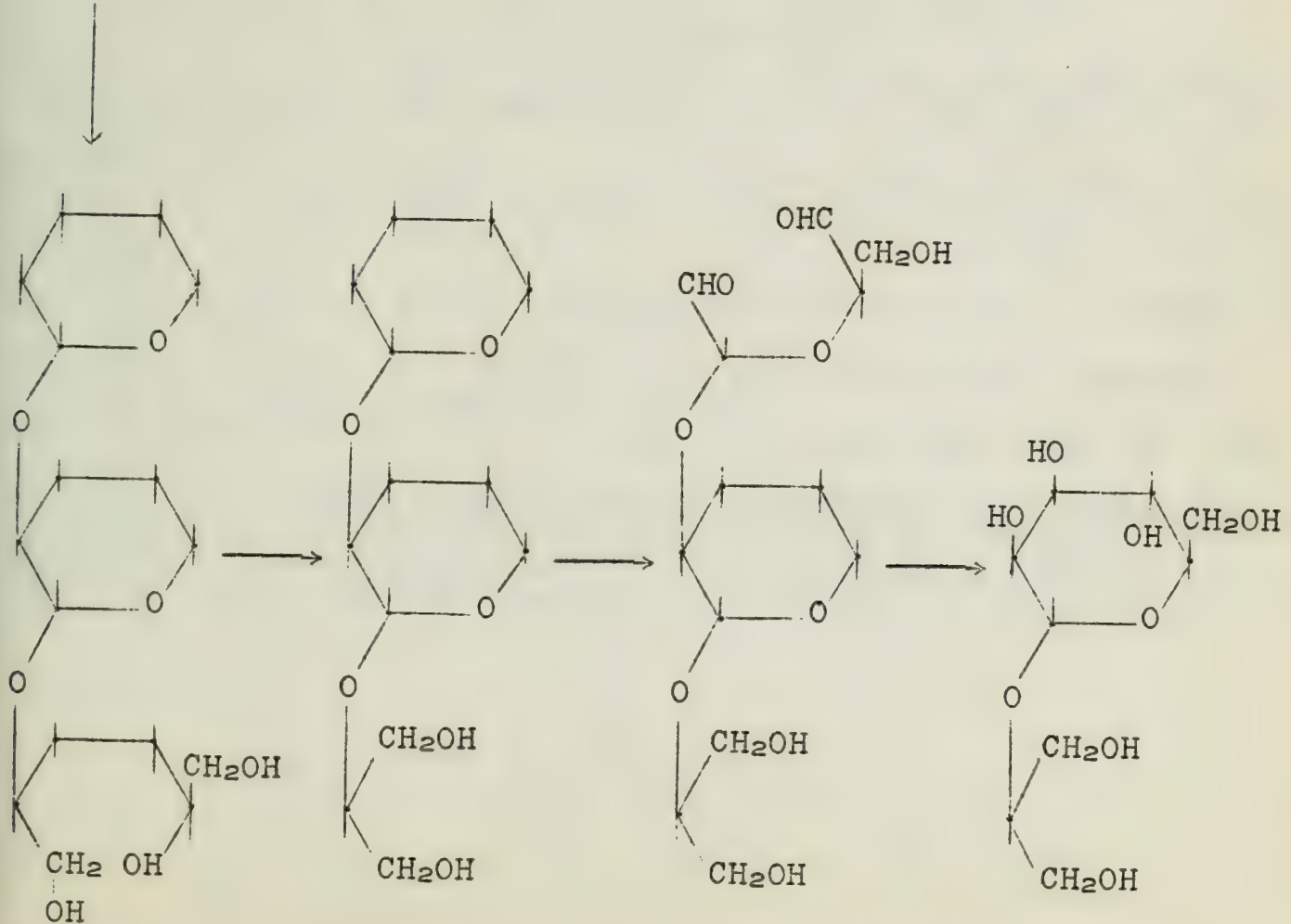
To determine the configuration of each link the trisaccharide was degraded into two different disaccharides, each containing one of the links intact. Preferential removal of the non-reducing end-unit was accomplished by a series of reactions including borohydride reduction of the mannotriose VII to the mannotriitol VIII, which was then oxidized with three moles of tetraacetate and again reduced with borohydride to the mannobiosyl-glycerol IX. Oxidation of this compound then proceeded selectively at the "far" end of the molecule to give the dialdehyde X. Treatment of X with phenylhydrazine acetate cleaved the glycosidic bond adjacent to the dialdehyde end-unit to produce 2-O-α-D-mannopyranosylglycerol, one of the "standard" substituted glycerols previously prepared. Thus the first glycosidic link has the α-configuration.

The nature of the other glycosidic link was determined by degradation of the trisaccharide to the known 2-O-α-D-mannopyranosyl-D-mannose. Oxidation of the trisaccharide with bromine water produced mannobiosyl-mannonic acid, isolated as the silver salt XII. The silver salt was further oxidized by 3 moles of lead tetraacetate, presumably to a salt of a mannobiosyl-triuronic acid XIII. Treatment of the latter with hot dilute acetic acid removed the tartronic semialdehyde residue, affording 2-O-α-D-mannopyranosyl-D-mannose. From these data the configuration of the link between the central unit and the non-reducing end could be assigned as alpha; since both 1,2-links in the trisaccharide had the α-configuration, the 1,2-links in the original polysaccharide are predominantly, if not entirely of this nature.

Modifications of these methods have also been applied to raffinose and stachyose (32).



VII XII XIII XIV



VIII IX X XI

BIBLIOGRAPHY

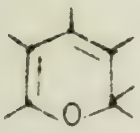
1. E.C. Jackson, Org. Reactions 2, 341 (1944).
2. R. Criegee, Newer Methods of Prep. Org. Chem., 1, New York (1948).
3. J. Kleiman, Univ. of Illinois Seminar, Dec. 17, 1956.
4. J.M. Bobbitt, Adv. in Carb. Chem. 11, 1 (1956).
5. H. H. Wasserman, in Steric Effects in Org. Chem., edited by M.S. Newman, pp. 378-387, New York (1956).
6. E.L. Jackson and C.S. Hudson, J. Am. Chem. Soc. 59, 994 (1937).
7. W.S. McClenahan and R.C. Hockett, J. Am. Chem. Soc. 60, 2061 (1938).
8. R. Criegee, Ann. 495, 211 (1932).
9. R.C. Hockett and M. Zief, J. Am. Chem. Soc. 72, 2130 (1950).
10. S. Abraham, J. Am. Chem. Soc. 72, 4050 (1950).
11. A.S. Perlin, J. Am. Chem. Soc. 76, 2595 (1954).
12. A.S. Perlin and C. Brice, Can. J. Chem. 33, 1216 (1955).
13. A.S. Perlin and C. Brice, Can. J. Chem. 34, 85 (1956).
14. A.S. Perlin and C. Brice, Can. J. Chem. 34, 541 (1956).
15. J.M. Sugihara, Adv. in Carb. Chem. 8, 1 (1953).
16. J.P. Cordner and K. H. Pausacker, J. Chem. Soc. 102 (1953).
17. M.S. Kharasch, H. N. Friedlander and W.H. Urry, J. Org. Chem. 14, 91 (1949).
18. R.E. Reeves, Anal. Chem. 21, 751 (1949).
19. R. Criegee and E. Buchner, Ber. 73, 563 (1940).
20. C.C. Price and M. Knell, J. Am. Chem. Soc. 64, 552 (1942).
21. A.S. Perlin, J. Am. Chem. Soc. 76, 5505 (1954).
22. A.S. Perlin, Anal. Chem. 27, 396 (1955).
23. A.J. Charlson and A.S. Perlin, Can. J. Chem. 34, 1200 (1956).
23a. C.F. Huebner, S.R. Ames and E.C. Bubl, J. Am. Chem. Soc. 68, 1621 (1946).
24. A.J. Charlson and A.S. Perlin, Can. J. Chem. 34, 1804 (1956).
25. R.L. Whistler and J.Z. Stein, J. Am. Chem. Soc. 73, 4187 (1951).
26. A.J. Charlson, P.A.J. Gorin and A.S. Perlin, Can. J. Chem. 34, 1811 (1956).
27. A.J. Charlson, P.A.J. Gorin and A.S. Perlin, Can. J. Chem. 35, 365 (1957).
28. R.C. Hockett, M.T. Dienes, H.G. Fletcher and H.E. Ramsden, J. Am. Chem. Soc. 66, 467 (1944).
29. R.C. Hockett and W.C. McClenahan, J. Am. Chem. Soc. 61, 1667 (1939).
30. See W.W. Pigman and R.M. Goepp, Chemistry of the Carbohydrates, New York (1948) for a discussion of Hudson's Rules.
31. P.A.J. Gorin and A.S. Perlin, Can. J. Chem. 35, 262 (1957).
32. A.K. Mitra and A.S. Perlin, Can. J. Chem. 35, 1079 (1957).

PYRYLIUM SALTS

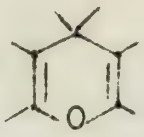
Reported by R. W. Bush March 6, 1958

INTRODUCTION

Related to the pyrans, I and II, are the heterocyclic cations, III, which comprise the pyrylium salts. The pyrylium structure is of theoretical interest because it is isosteric with benzene and



I, α-pyran

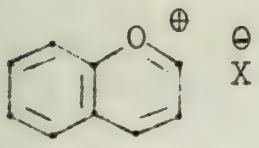


II, γ-pyran

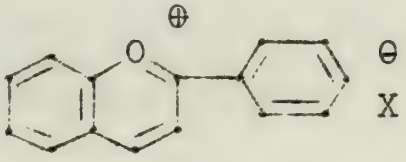
III, pyrylium cation

pyridine. A pyrylium salt which contains substituents capable of extensive resonance hybridization, for example aromatic groups, is typically highly colored. In the literature pyrylium compounds are occasionally called pyroxonium compounds or are named as derivatives of the parent pyrone.

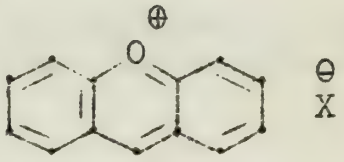
The fusion of a benzene ring with a pyrylium cation gives an especially stable structure. The preparation and reactions of these benzopyrylium (chromylium) compounds, IV, have been extensively investigated (1,2). The 2-phenylbenzopyrylium (flavylium) salts, V, are of special interest because of their relation to the flavones, and because they are the chromophores of the plant pigments, the anthocyanins (2,3,4,5). Dibenzopyrylium (xanthylium) salts, VI, are also well-known (6).



IV



V



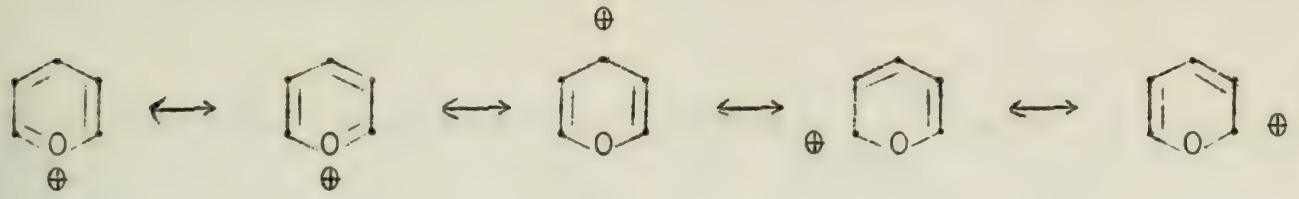
VI

The subject of this report is the preparation and reactions of the monocyclic pyrylium system. Special emphasis has been placed on the more recent literature. Additional references to the extensive research on pyrylium salts done prior to 1940 may be found in references 7,8,9 and 10.

I. STRUCTURE

The structure of pyrylium compounds has been a subject of controversy since they were first prepared (11,12). Explanations in terms of pyrone addition compounds were considered until conductivity measurements established that the compounds were true salts (13). The oxonium structure, VII a, was postulated in analogy to the known oxonium cations R_3O^+. But since pyrylium salts react readily at the 2- and 4-positions, the carbonium formulations, VII c,d, and e, have often been preferred (1,7c). In

light of modern resonance theory, the pyrylium cation is best represented as a resonance hybrid in which all the structures VII a-e contribute (4,5).



a b c d e

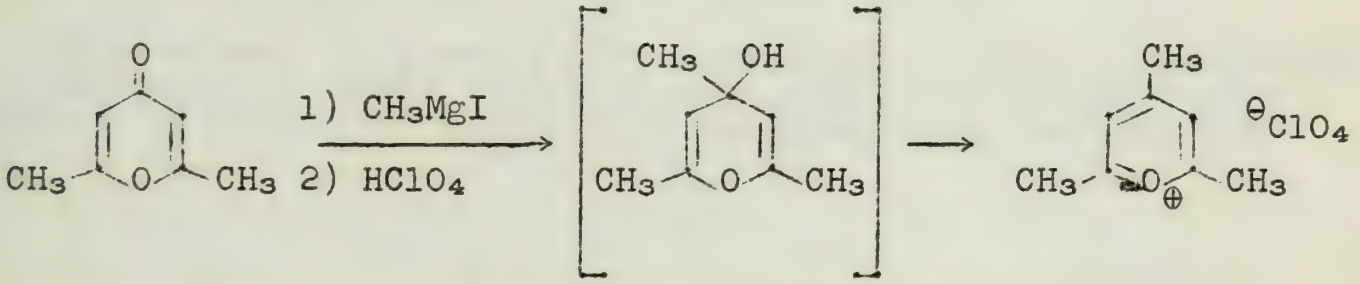
VII

Spectroscopic evidence for a relatively larger contribution by the carbonium structures has been presented (14). A comparison of the effect of introducing auxochromic 2- and 4-substituents into pyrylium salts and into pyridinium salts showed that an appreciably greater bathochromic shift in the ultraviolet maximum occurs in the case of pyrylium salts. This observation was taken to imply a relatively greater electron deficit at the 2 and 4 carbons of the pyrylium salts than of the pyridinium salts. The electrons of nitrogen apparently can be more easily shared than those of oxygen. Therefore, the C-N bond of the pyridinium salts has more double-bond character than does the C-O bond in pyrylium salts. The high reactivity of pyrylium compounds, e.g. in hydrolysis and in permanganate oxidation, attests to the resultant lack of aromatic character.

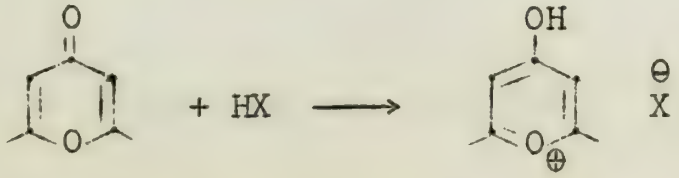
II. PREPARATION

A. Addition to Pyrones.

An early formation of pyrylium salts was accomplished by the action of Grignard reagents upon γ-pyrones (12). The intermediate was assumed to be an unstable pyranol:

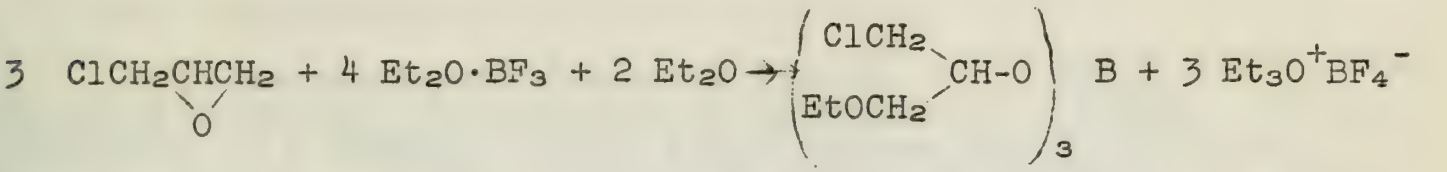


Many addition compounds of γ-pyrones with acids undoubtedly possess the pyrylium structure (10), and represent the first pyrylium salts known (9,11,15):



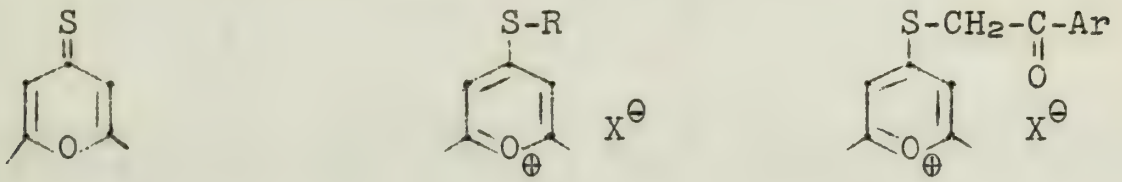
Similarly, dimethyl sulfate reacts with pyrones to form 4-methoxy-pyrylium salts (16).

Electrophilic reagents have also been employed to prepare 4-alkoxypyrylium salts from pyrones. One reagent used with success is triethyloxonium fluoborate $Et_3O^+ BF_4^-$, prepared by reaction of boron trifluoride etherate upon epichlorohydrin in ether solution (17):



Reaction of triethyloxonium fluoborate with 2,6-dimethylpyrone for 3 days at room temperature afforded 2,6-dimethyl-4-ethoxypyrylium fluoborate. A similar reagent, acetyl fluoborate, $CH_3CO^+ BF_4^-$, is prepared by treatment of acetyl fluoride with boron trifluoride (18). Acetyl fluoborate reacts with 2,6-dimethylpyrone at -30° in chloroform to yield 65% 2,6-dimethyl-4-acetoxypyrylium fluoborate.

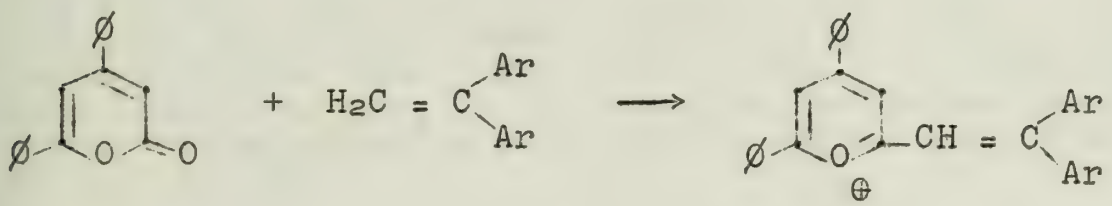
Somewhat less powerful reagents have been found to convert 4-thiopyrones, VIII, to mercaptopyrylium salts, IX, in yields of 80-100% (19). Effective alkylating agents include several alkyl

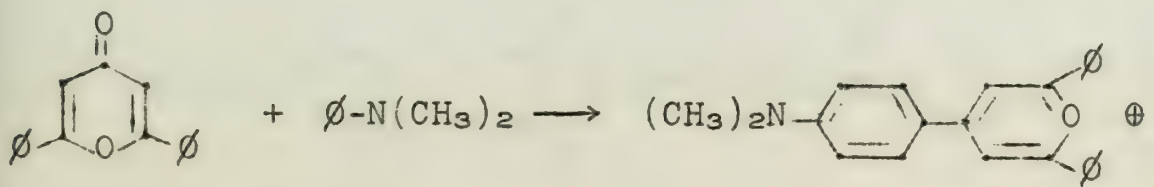


VIII IX X

iodides (e.g., methyl, methylene, benzyl, allyl) and α-bromo-acetophenones. Chlorides generally gave poor results. Kinetic studies (20) showed that the rate of formation of the pyrylium salt, X, was favored by electron withdrawing ring substituents on α-bromoacetophenone. The rate constants decrease in the following order: p-NO_2, m-NO_2, m-Br, p-Ø, H, p-CH_3, p-CH_3O.

Both α- and γ- pyrones have been converted into pyrylium salts by addition to aromatic amines or to 1,1-diarylethylenes in the presence of phosphorus oxychloride and phosphorus pentachloride (21):



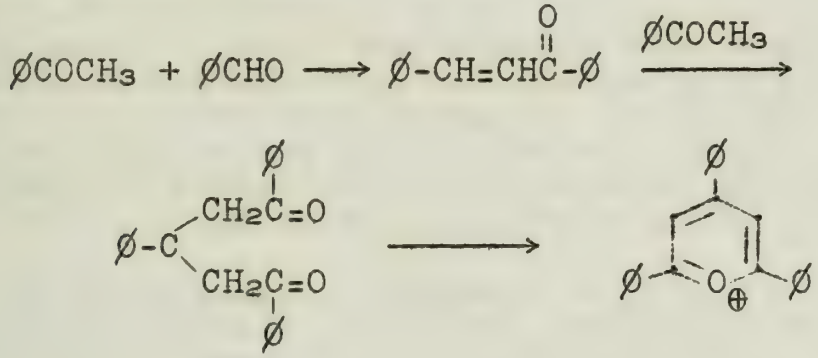


No yields were reported.

Although pyrylium salts may thus be readily prepared by the addition of various reagents to pyrones, the method suffers as a general synthetic technique because of the difficulty in preparing the required substituted pyrones.

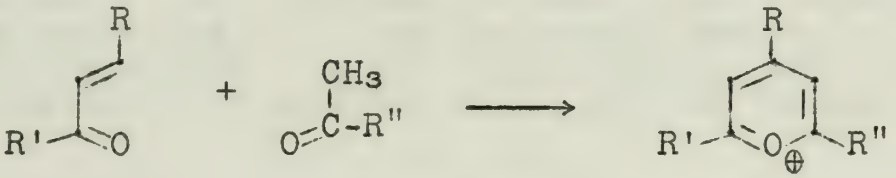
B. Condensation of Carbonyl Compounds.

Pyrylium compounds containing desired substituents are prepared by acid catalyzed condensations of aldehydes and ketones. Acetic anhydride is a common solvent, and oxidizing agents which have been used include $FeCl_3$, $FeCl_3 \cdot 6H_2O$, $SbCl_5$, PCl_5 (7d). Two molecules of acetophenone condense with one of benzaldehyde in the presence of ferric chloride to form triphenylpyrylium chloroferrate (7a):

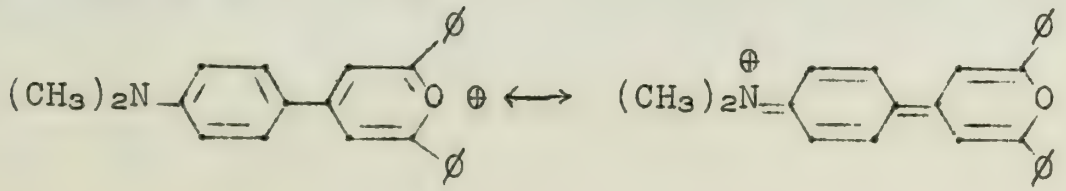


The reaction sequence is suggested by the fact that the pyrylium compound is also afforded directly from a mixture of benzalacetophenone and acetophenone, or from benzal-diacetophenone.

Condensation of substituted benzalacetophenones with substituted acetophenone has been the most generally used synthesis of pyrylium salts:

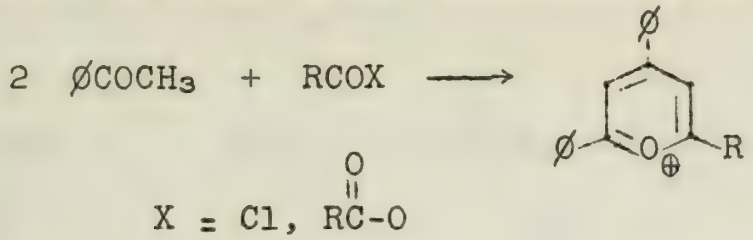


Yields are on the order of 30% (7d). More recently this condensation to pyrylium salts has been effected simply by treatment of the appropriate carbonyl compounds with sulfuric acid (14,21). Among the R groups which have been employed are C_6H_5, $C_6H_4N(CH_3)_2$ and $C_6H_4OCH_3$, because of their auxochromic effect in producing intensely colored dyes. The 2,6-diphenyl-4-(p-dimethylaminophenyl)pyrylium ion, XI, for example, possesses an extended chromophoric system allowing both quinoid and benzenoid resonance structures (22):



XI

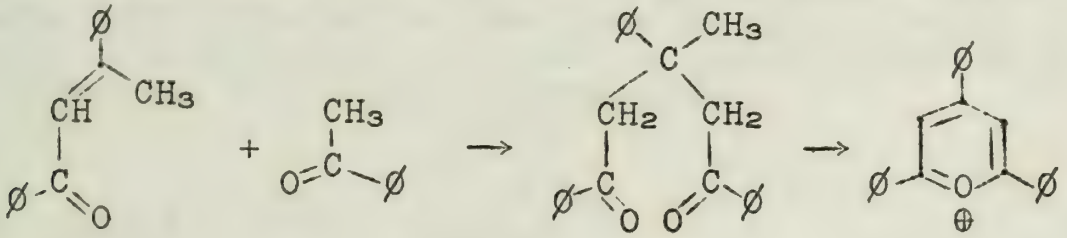
In the absence of an aldehyde or unsaturated ketone, acetophenone can undergo condensation with acid anhydrides or with acyl chlorides to yield alkyl-substituted pyrylium salts (7a,7e,23,24):



It has been postulated that two molecules of acetophenone initially condense to dypnone, since the same product results if dypnone is used in place of acetophenone (23). However, it has also been shown that acetophenone reacts with acetic anhydride to form benzoylacetone, which can subsequently condense with another molecule of acetophenone to form the pyrylium salt (7e). The substituents have been varied by use of various aryl methyl ketones with acid anhydrides in the presence of sulfuric acid (25). When, for example, acetic anhydride is used, the effective condensing agent is believed to be sulfoacetic acid, $HOSO_2CH_2COOH$.

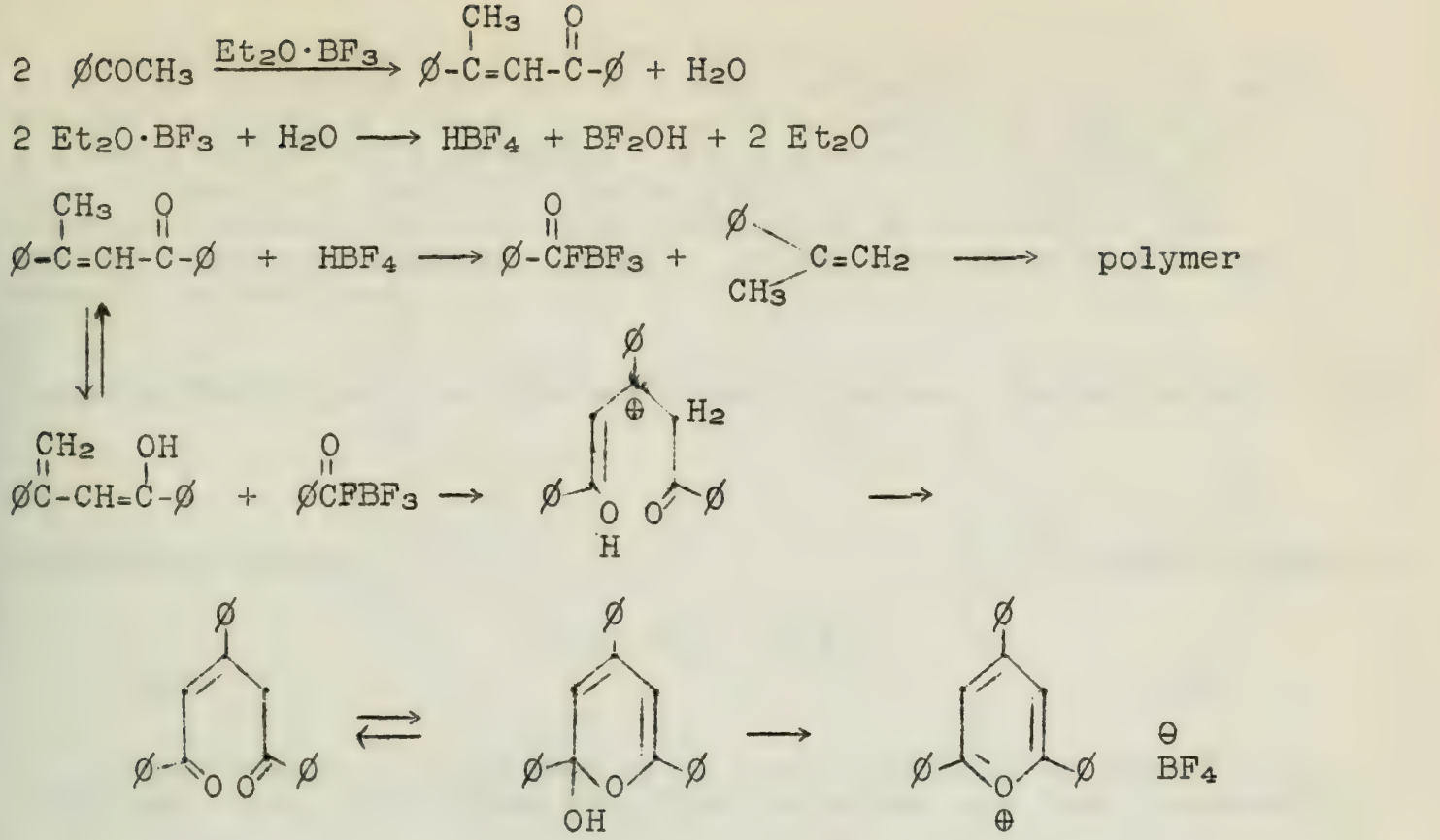
In the attempted synthesis of 1,3,5-triphenylbenzene by condensation of acetophenones, small amounts of highly colored by-products have been observed which proved to be triphenylpyrylium salts (26,27,28). For example, use of BF_3 as a condensing catalyst has converted acetophenone into 2,4,6-triphenylpyrylium fluoborate (29,30) in about 20% yields. (The addition of benzalacetophenone or of benzaldehyde increased the yield of pyrylium compound to 65%.) The stoichiometry of this condensation requires the loss of one molecule of methane or equivalent one-carbon unit; however, no gas was observed to be evolved.

The mechanism of this condensation was finally elucidated by Elderfield. He concluded (31) that the energy gained by formation of the hybridized pyrylium ring was significantly less than the activation energy required to break a C-C bond as in the sequence:



$+ H_2O + CH_4$

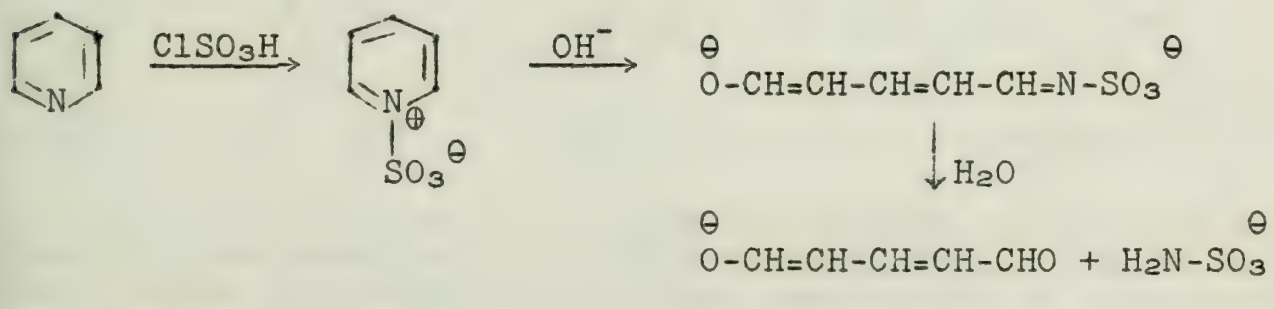
The essential step of the mechanism suggested by Elderfield involves cleavage of dypnone into α-methylstyrene and benzoyl fluoride (32):



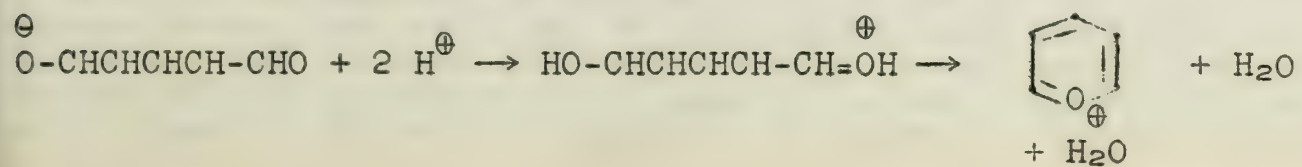
Evidence for this scheme is afforded by the isolation of benzoic acid and of dypnone from the hydrolyzed reaction mixture. Furthermore, an independent reaction of dypnone with $BF_3 \cdot OEt_2$ affords the pyrylium salt, thereby indicating that a third molecule of acetophenone is not required. Finally, the reaction of dypnone with $\emptyset COFBF_3$ also yields the pyrylium compound.

C. Unsubstituted Pyrylium Compounds.

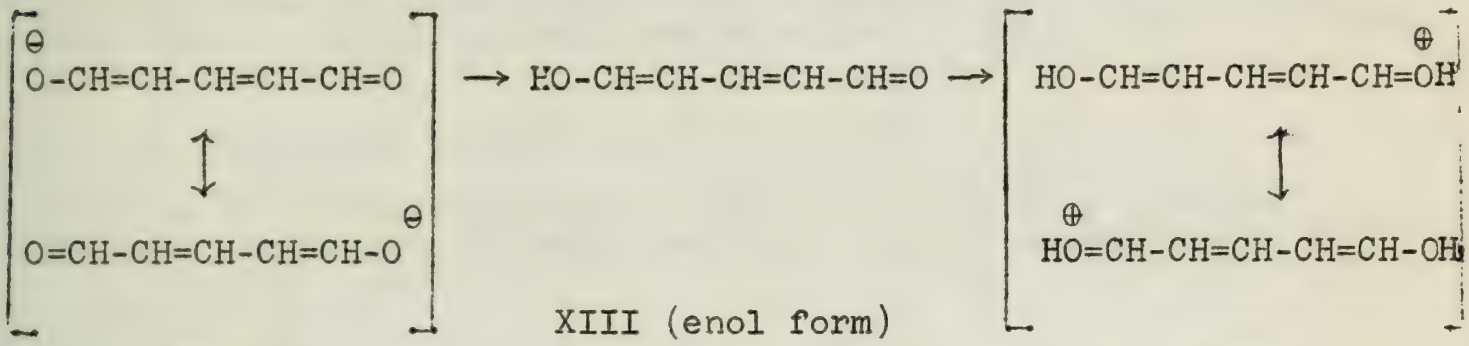
The methods of addition and condensation are applicable only to the preparation of substituted pyrylium salts, and not until recently has an unsubstituted pyrylium compound $C_5H_5O^+X^-$ been prepared (33). The method involves the ring opening of pyridinium sulfonic acid under the influence of sodium hydroxide to form the sodium enolate of glutaconaldehyde (34):



When this enolate was subsequently treated with perchloric acid, an intermediate chain oxonium ion resulted, which underwent ring closure to the pyrylium salt:



The acidification (in ether solution) was done at -20 to -50° to avoid the polymerization of glutaconaldehyde. Yields were raised from 25% to 75-85% if the acid was added as rapidly as possible rather than dropwise. The explanation for this behavior lies in the fact that both the enolate, XII, and the chain oxonium intermediate, XIV, are stabilized by resonance. The neutral glutaconaldehyde, XIII, is not resonance stabilized and readily polymerizes.



XII XIII (enol form) XIV

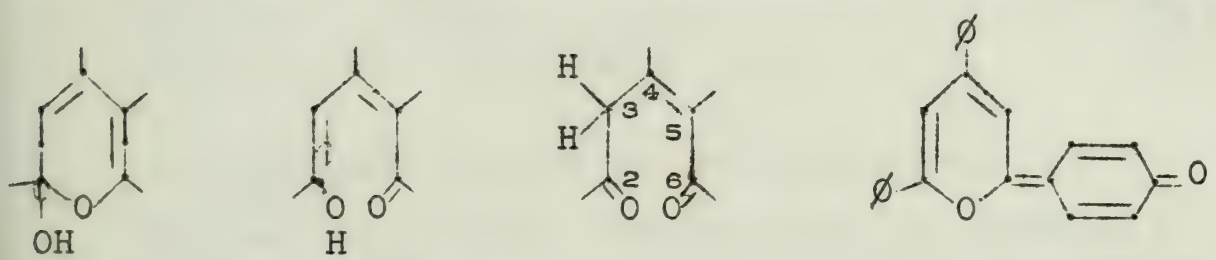
Application of this method to the conversion of substituted pyridines into substituted pyrylium salts has not been successful.

III. REACTIONS OF PYRYLIUM SALTS

The pyrylium salts are highly reactive compounds. Although stable in acid, they readily react with nucleophilic agents. Such reactions include formation of pseudo bases, formation of addition compounds, replacement of ring substituents, and even replacement of the heterocyclic oxygen.

A. Reactions with Aqueous Base.

Treatment of 2,4,6-triphenylpyrylium perchlorate with hydroxide ion affords a colorless pseudo base, generally written as XV or XVI. Dilthey reported the isolation of two discrete forms



XV XVI XVII XVIII

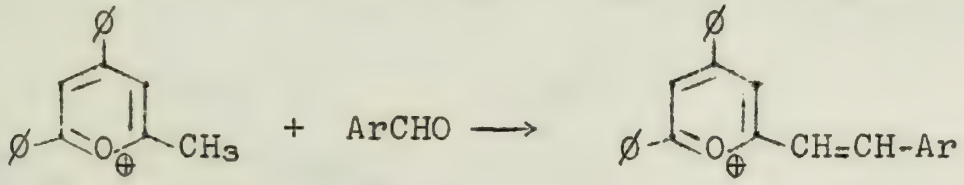
of the pseudo base of 2,4,5,6-tetraphenylpyrylium ion and suggested that they represented enol, XVI, and keto, XVII, desmotropes (7b). More recent investigators (35) have been unable to detect more than one form of triphenylpyrylium pseudo base and give spectral evidence to support structure XVII. Although the ultraviolet spectra of XV and XVI are not predictable due to absence of model compounds, XVII would be expected to show absorption due to two insulated chromophores, one identical to acetophenone and one to benzalacetophenone. The observed absorption maxima of the pseudo base at 247 mμ and 298 mμ coincided nearly exactly in wavelength and intensity with those of the model compounds. Furthermore, replacement of

the 2-phenyl group by p-anisyl caused a bathochromic effect only upon the absorption corresponding to acetophenone. Similar replacement of the 4-phenyl group affected only the absorption corresponding to benzalacetophenone. The infrared spectrum shows no hydroxyl band. A doublet at 1680-1670 cm.$^{-1}$ implies at least one conjugated carbonyl group.

A pyrylium salt possessing a 2- or 4-(p-hydroxyphenyl) substituent does not immediately yield a pseudo base when treated with alkali. It first loses one molecule of acid to form a stable quinoid dye, XVIII (7f).

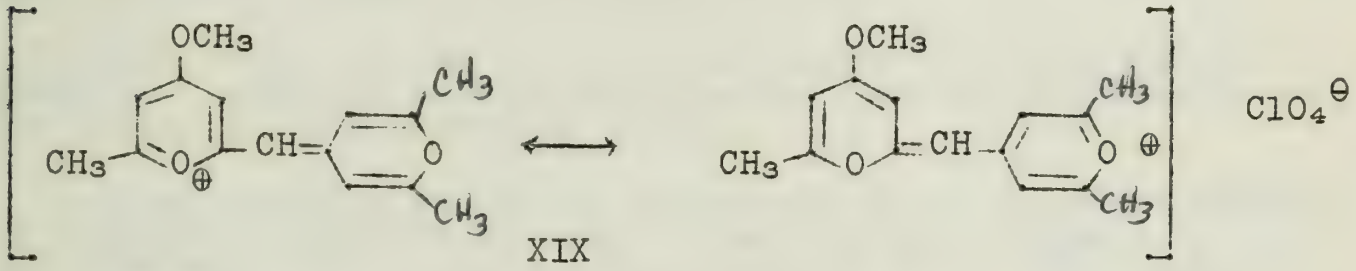
B. Additions Involving α- or γ-Methyl Groups.

The 2- or 4-methylpyrylium salts condense with aromatic carbonyl compounds to form 2- or 4-styrylpyrylium salts (7e,36,37):



The styrylpyrylium salts possess extended chromophoric systems and are listed in the patent literature as useful dyes (38,39,40).

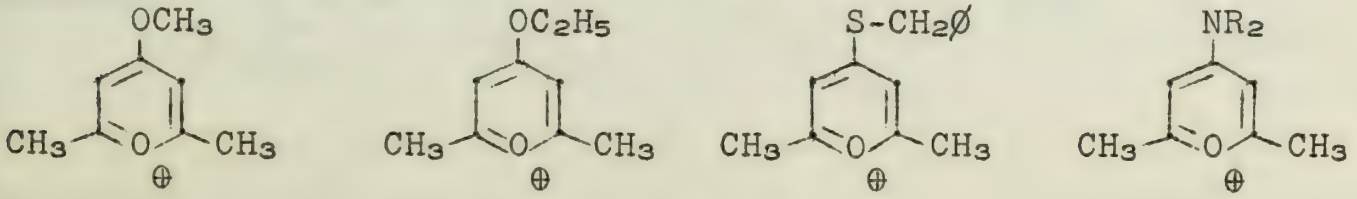
Apparently a competing reaction is the self-condensation of 4-alkoxypyrylium salts (41). Heating 2,6-dimethyl-4-methoxypyrylium perchlorate with sodium acetate in methanol yielded a red dyestuff perchlorate, the properties of which were in accord with structure XIX.



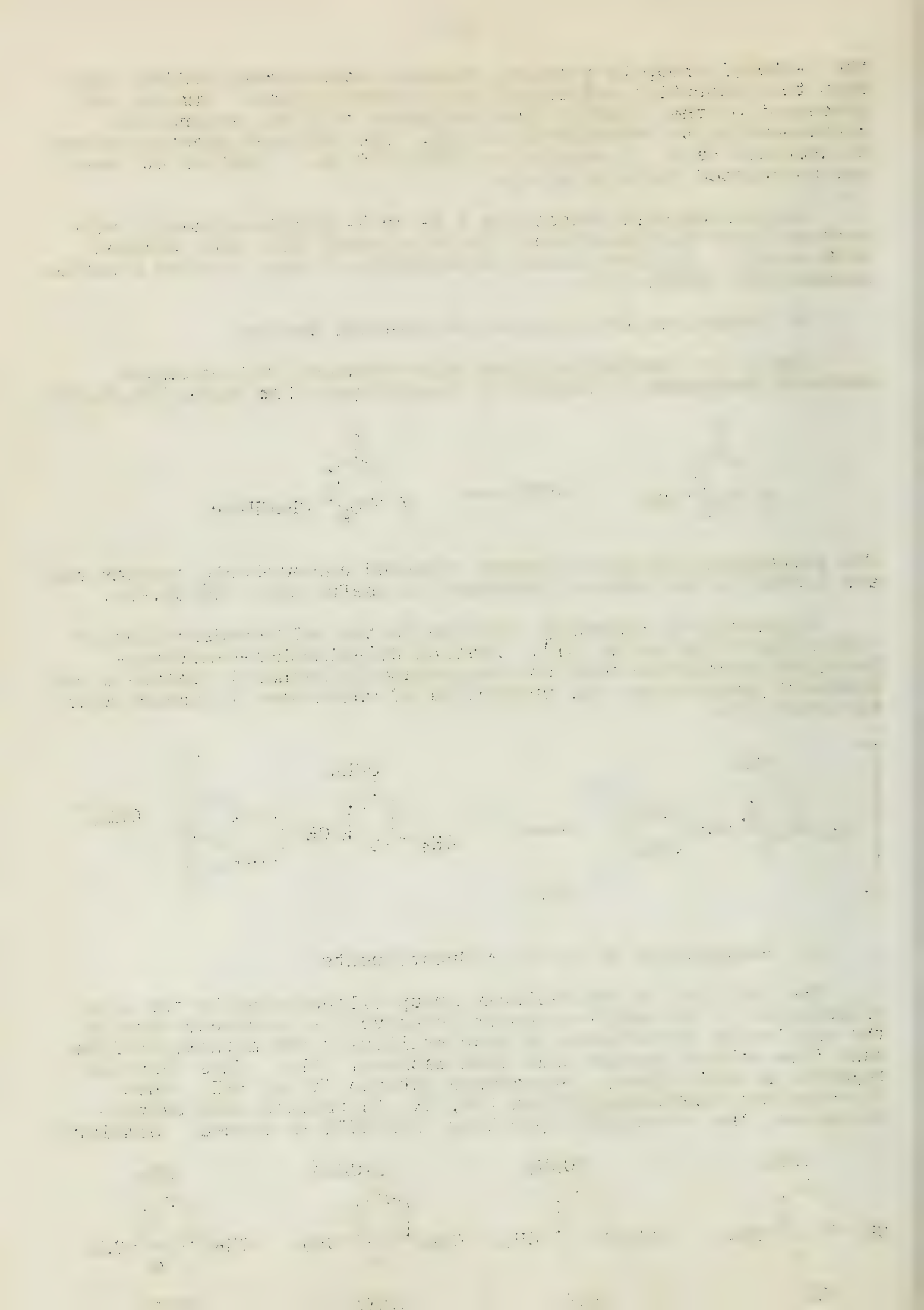
XIX

C. Replacement of α- or γ-Substituents.

The lability of the 4-alkoxy group (illustrated by the loss of methanol in the self-condensation above) is evidenced also by the difficulty encountered in recrystallizing the methoxypyrylium salt from ethanol rather than from methanol (41). This behavior suggests a ready alkoxy interchange between XX and XXI. When 2,6-dimethyl-4-methoxypyrylium ion, XX, is treated with benzylmercaptan, the 4-benzylthiopyrylium ion XXII is formed. Similarly,



XX XXI XXII XXIII

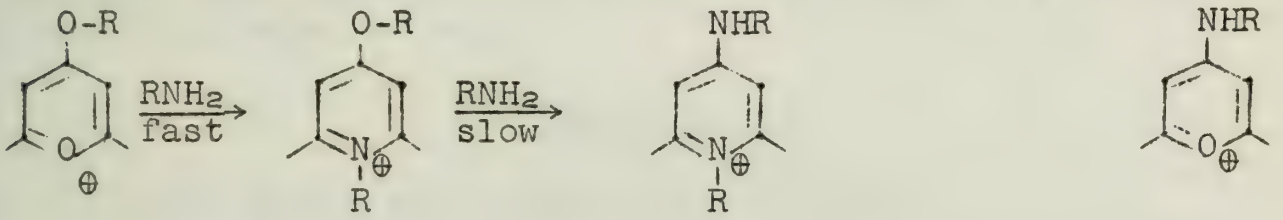


easy replacement is effected by secondary amines to form the ion XXIII (41,42).

D. Replacement of Heterocyclic Oxygen.

The reaction of pyrylium salts with primary amines occupies a significant portion of the studies on pyrylium salts. When treated with ammonia, pyrylium salts are converted into pyridine derivatives; when treated with primary amines, pyridinium salts are formed (12). These pyridine and pyridinium compounds are useful derivatives in characterization of new pyrylium salts.

In addition to replacement of the heterocyclic oxygen, a second molecule of a primary amine may replace a 4-alkoxy or 4-mercapto group. The formation of both XXIV and XXV when the reaction is not run to completion, plus the successful independent conversion of XXIV to XXV, supports the following reaction sequence (42):

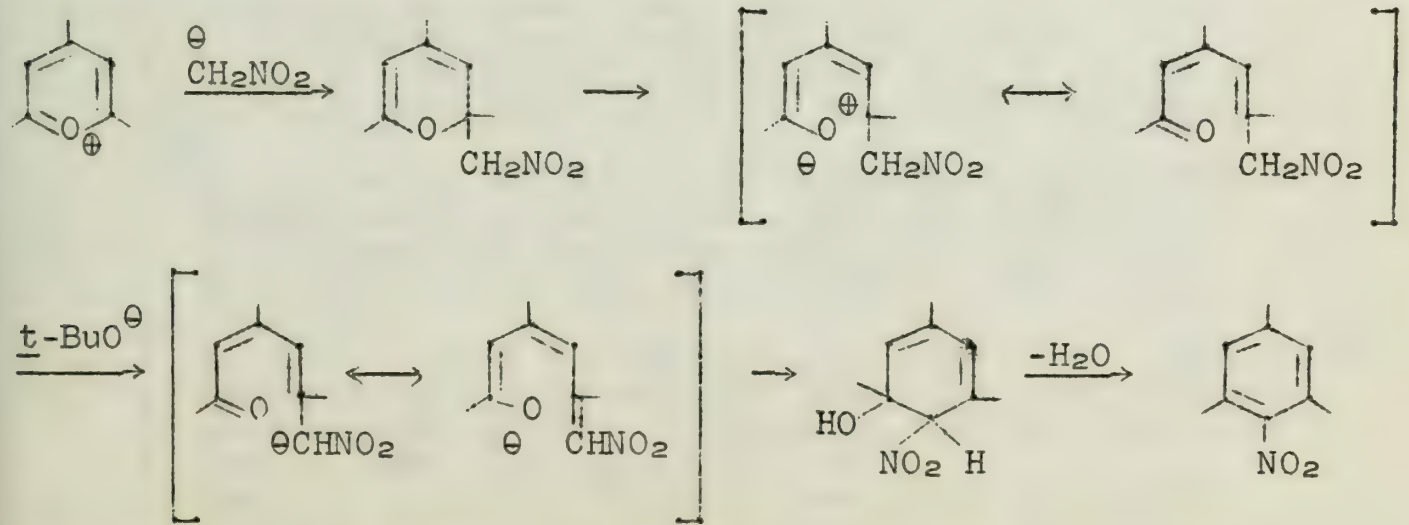


XXIV XXV XXVI

The earlier investigators (41) reported that they were unable to induce the methoxypyridinium ion, XXIV, to undergo replacement at the 4 position. They therefore supposed that formation of XXV must proceed through an intermediate XXVI.

Replacement of the heterocyclic oxygen by sulfur is also possible. Pyrylium salts are converted into thiapyrylium salts by the action of sodium sulfide (43).

Of significant synthetic importance is the recent preparation of complex substituted benzene derivatives by treatment of pyrylium salts with alkaline nitromethane (44). The suggested



mechanism for the reaction involves an initial nucleophilic attack at one of the α-carbons (45).

Yields of 80-95% were realized. The reaction has synthetic value in that aromatic compounds containing desired substituents may be prepared. Thus far the reaction has been utilized for the following substituents: CH_3, C_6H_5, $C(CH_3)_3$, p-$C_6H_4CH_3$, p-C_6H_4Cl, p-C_6H_4Br, p-$C_6H_4OCH_3$. The nitro group can be readily reduced and diazotized, thereby allowing substitution of a variety of functional groups. An additional merit of the reaction of nitromethane with pyrylium compounds is that it yields a single definite product, in contrast to the nitration of the corresponding hydrocarbon. The method is therefore useful in structure determinations.

Substitution of the oxonium oxygen by carbon has been extended to include several other active methylene compounds: acetylacetone, acetoacetic ester, cyanoacetic ester, malonic ester, and malononitrile (46). The products from reaction of 2,4,6-triphenylpyrylium fluoborate with the first three of these reagents are, respectively, 2,4,6-triphenylacetophenone, ethyl 2,4,6-triphenylbenzoate, and 2,4,6-triphenylbenzonitrile. Malononitrile and malonic ester both yielded ketones the structures of which have not been fully elucidated.

BIBLIOGRAPHY

1. D. W. Hill, Chem. Revs., 19, 27 (1936).
2. S. Wawzonek in "Heterocyclic Compounds" Vol. II, ed. R. C. Elderfield, John Wiley and Sons, Inc., New York, 1951, p. 277.
3. K. P. Link in "Organic Chemistry" Vol. II, ed. H. Gilman, John Wiley and Sons, Inc., New York, 2nd edition, 1943, p. 1315.
4. R. L. Shriner, Record of Chem. Progr. (Kresge-Hooker Sci. Lib.) 11, 121 (1950).
5. R. L. Shriner in "The Roger Adams Symposium", John Wiley and Sons, Inc., New York, 1955, p. 103.
6. S. Wawzonek in "Heterocyclic Compounds" Vol. II, ed. R. C. Elderfield, John Wiley and Sons, Inc., New York, 1951, p. 468.
7. W. Dilthey et al., (a) J. prakt. Chem., [2] 94, 53 (1916); (b) Ber., 52, 2040 (1919); (c) Ber., 53, 261 (1920); (d) J. prakt. Chem., [2] 101, 177 (1921); (e) Ber., 57, 1653 (1924); (f) J. prakt. Chem., [2] 111, 153 (1925); (g) ibid., [2] 114, 153 (1926).
8. O. Diels and K. Alder, Ber., 60, 716 (1927).
9. L. F. Cavalieri, Chem. Revs., 41, 559 (1947).
10. J. Fried in "Heterocyclic Compounds" Vol. I, ed. R. C. Elderfield, John Wiley and Sons, Inc., New York, 1950, p. 344, 370.
11. J. N. Collie and T. Tickle, J. Chem. Soc., 75, 710 (1899).
12. A. Baeyer and J. Piccard, Ann., 384, 208 (1911).
13. H. N. K. Rördam, J. Am. Chem. Soc., 37, 557 (1915).
14. R. Wizinger, S. Losinger, and P. Ulrich, Helv. Chim. Acta, 39, 5 (1956).
15. C. S. Gibson and J. L. Simonsen, J. Chem. Soc., 2307 (1928).
16. F. Kehrmann and A. Duttenhöfer, Ber., 39, 1299 (1906).
17. H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, and E. Pfeil, J. prakt. Chem., [2] 147, 257 (1937).
18. F. Seel, Z. anorg. u. allgem. Chem., 250, 331 (1943).
19. L. C. King, F. J. Ozog, and J. Moffat, J. Am. Chem. Soc., 73, 300 (1951).
20. F. J. Ozog, V. Comte, and L. C. King, J. Am. Chem. Soc., 74, 6225 (1952).

21. R. Wizinger, A. Grüne, and E. Jacobi, Helv. Chim. Acta, 39, 1 (1956).
22. A. Treibs and J. Bader, Ber., 90, 789 (1957).
23. P. P. Hopf and R. J. W. LeFèvre, J. Chem. Soc., 1989 (1938).
24. R. J. W. LeFèvre and J. Pearson, J. Chem. Soc., 1197 (1933).
25. W. Schneider et al., Ber. 54, 1484, 2285 (1921); ibid., 55, 2775 (1922); ibid., 74B, 1252 (1941); Ann., 432, 297 (1923).
26. T. L. Davis and C. B. Armstrong, J. Am. Chem. Soc., 57, 1583 (1935).
27. R. J. W. LeFèvre, J. Chem. Soc., 1467 (1938).
28. R. E. Lyle, E. J. DeWitt, N. M. Nichols, and W. Cleland, J. Am. Chem. Soc., 75, 5959 (1953).
29. W. C. Dovey and R. Robinson, J. Chem. Soc., 1389 (1935).
30. R. Lombard and J. P. Stéphan, Compt. rend., 237, 333 (1953).
31. R. C. Elderfield and T. P. King, J. Am. Chem. Soc., 76, 5439 (1954).
32. R. C. Elderfield and T. P. King, J. Am. Chem. Soc., 76, 5437 (1954).
33. F. Klages and H. Träger, Ber., 86, 1327 (1953).
34. P. Baumgarten, Ber., 57, 1622 (1924); ibid., 59, 1166 (1926).
35. J. A. Berson, J. Am. Chem. Soc., 74, 358 (1952).
36. H. Brockmann, H. Junge, and R. Mühlmann, Ber., 77B, 529 (1944).
37. R. Wizinger and K. Wagner, Helv. Chim. Acta, 34, 2290 (1951).
38. Soc. pour l'ind. chim. à Bâle, Swiss Patent 221,930, Sept. 16, 1942; Chem. Abs., 43, 1988d (1949).
39. I. G. Farbenind. A.-G., German Patent 734,920, Apr. 1, 1943; Chem. Abs., 38, 1647^{6} (1944).
40. T. R. Thompson, U.S. Patent 2,461,484, Feb. 8, 1949; Chem. Abs., 43, 6100a (1949).
41. R. M. Anker and A. H. Cook, J. Chem. Soc., 117 (1946).
42. L. C. King and F. J. Ozog, J. Org. Chem., 20, 448 (1955).
43. R. Wizinger and P. Ulrich, Helv. Chim. Acta, 39, 207 (1956).
44. K. Dimroth et al., Angew. Chem., 68, 519 (1956); Ber., 90, 1634 (1957).
45. K. Dimroth, G. Neubauer, H. Möllenkamp, and G. Oosterloo, Ber., 90, 1668 (1957).
46. K. Dimroth and G. Neubauer, Angew. Chem., 69, 95, 720 (1957).

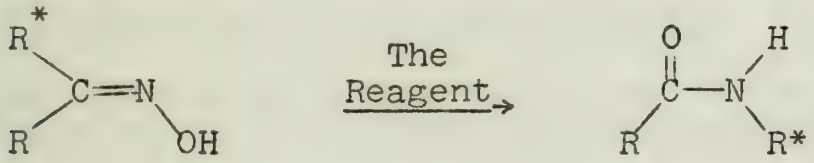
SOME ASPECTS OF THE BECKMANN REARRANGEMENT

Reported by Wayne Carpenter March 10, 1958

INTRODUCTION

Since its discovery in 1886 (1), the Beckmann rearrangement has found wide application and interest in organic chemistry. Consequently, it has been the subject of frequent review (2,3,5). In view of the extensive literature on the subject, this report will not describe any of the synthetic applications of the reaction, but will be limited mainly to a discussion of the mechanism of the catalysis and migration steps.

The Beckmann rearrangement in its most general form is the conversion of a ketoxime to an amide by use of any one of several reagents: PCl_5, H_2SO_4, HCl, $SbCl_5$, BF_3, $AlCl_3$, $\emptyset SO_2Cl$, AcCl, polyphosphoric acid, and others.



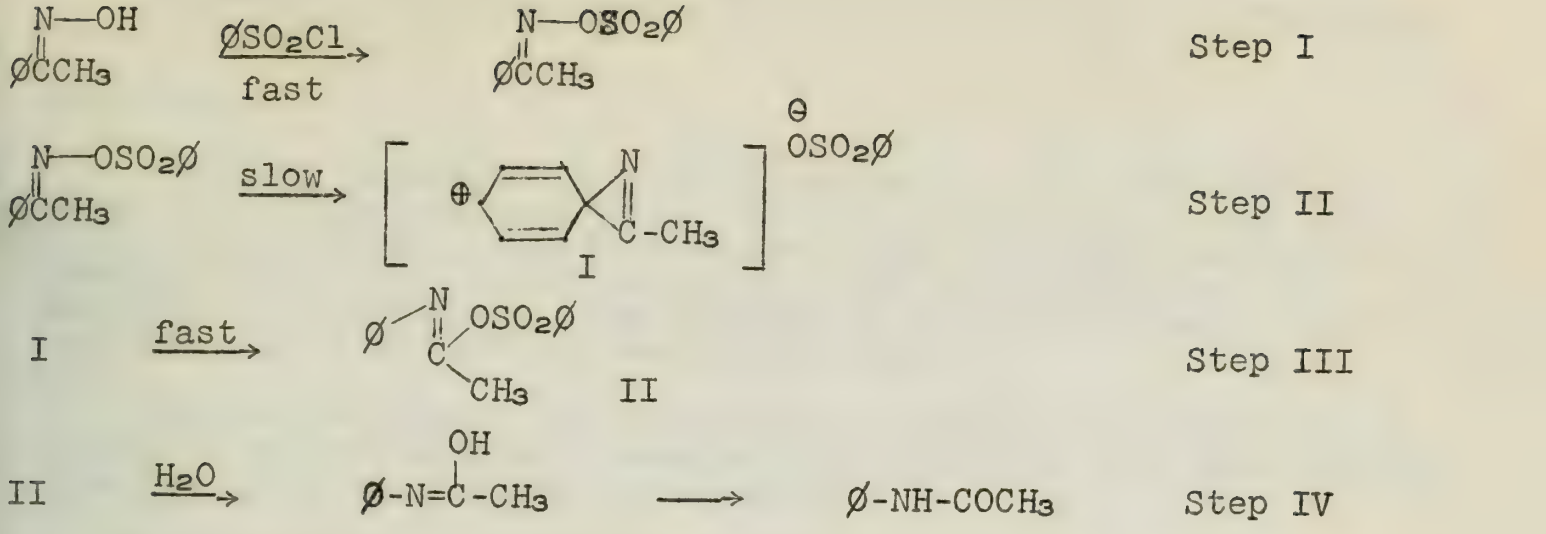
Meisenheimer showed that the group which is anti to the oxime hydroxyl group is the one which migrates to the nitrogen atom. His proof rested on the determination of the structures of the amides formed by the rearrangement of oximes whose syn- or anti-configuration had been determined by several independent methods (6). A complete summary of these methods has been given by Blatt (2). syn-Migration has apparently occurred in a few instances, but may be attributed to isomerization of the oxime before rearrangement (7). The isomerization and relative stabilities of syn- and anti-oximes will not be discussed in this report, but are discussed by Donaruma and Heldt (5) and by Brown and von Gulick (7,8).

The Beckmann rearrangement has long been believed to be an intramolecular process. Kenyon and coworkers (9,10), have shown that the migrating group is transferred with retention of configuration, as shown by a study of the optical activities of the products. This fact hardly permits any other than an intramolecular mechanism.

MECHANISM

The study of the mechanism of the Beckmann rearrangement is complicated by the fact that so many different types of acidic reagents will bring about the change. It was early recognized by Beckmann himself that different reagents might cause the rearrangement by different mechanisms. This proposal has later been verified, at least in part.

The present concept of the mechanism may be illustrated by the rearrangement of acetophenone oxime by benzenesulfonyl chloride.



The reaction may be broken down into four steps as indicated. Steps I and II will be discussed in detail.

Step I - Formation of the Leaving Group

The leaving group may be defined as the group which leaves the nitrogen atom in the process of rearrangement.

By ester formation -

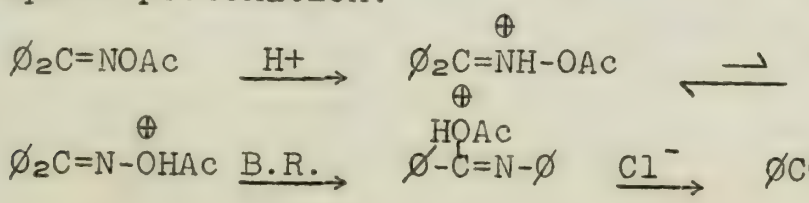
A large group of reagents which catalyze the Beckmann rearrangement react with oximes to produce esters which are potentially capable of ionization. This group includes the acid halides, $POCl_3$, PCl_5, H_2SO_4, and polyphosphoric acid.

Kuhara (2,3) caused benzophenone oxime to rearrange in the presence of acetyl chloride, chloroacetyl chloride, and benzenesulfonyl chloride. (See Table I) It was found that the rate of rearrangement was related to the electronegativity of the acyl group, i.e., the rate was a function of the tendency of the leaving group to ionize.

Table I (Percent Rearrangement)

Time (Min)	AcCl	$ClCH_2COCl$	ϕSO_2Cl
10	0	61.0	93
60	26.9	70.7	--
120	43.9	76.9	--

Benzophenone oxime O-benzenesulfonate was prepared and was found to rearrange upon melting, heating in a solvent, or simply upon standing in air at room temperature. The rearrangement could even be effected in pyridine. The corresponding acetate ester, however, would not rearrange unless HCl were present. Furthermore, the molar quantity of benzophenone oxime acetate rearranged was equal to the molar quantity of HCl added. This result can be explained on the assumption that the acetate group of the ester must be protonated in order to make it a good leaving group. The benzenesulfonate moiety is a good enough leaving group so as not to require protonation.



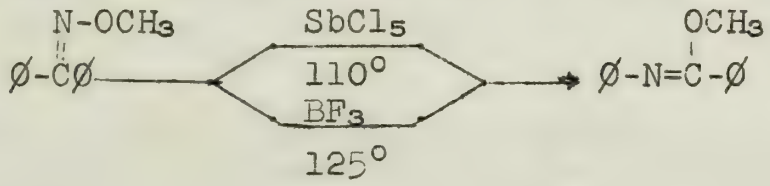
Sulfate esters have also been prepared and found to rearrange upon heating (11,12).

From Ethers -

Ordinary oxime ethers do not possess a good enough leaving group to undergo rearrangement. However, it was found that the 2,4,6-trinitrophenyl ethers of oximes would rearrange readily upon heating (13). The picrate anion is quite stable and makes an excellent leaving group. The product of the rearrangement is the N-picryl derivative of the rearranged amide.

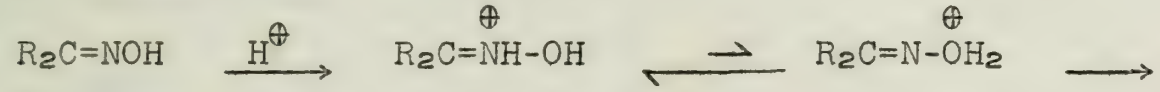
The picryl ethers are often used in studying the kinetics of the Beckmann rearrangement because they rearrange with a minimum of side reactions and require no catalyst.

Methyl ethers of oximes can be made to rearrange if strong Lewis acid catalysts such as $SbCl_5$ (14) or BF_3 (8) are used.



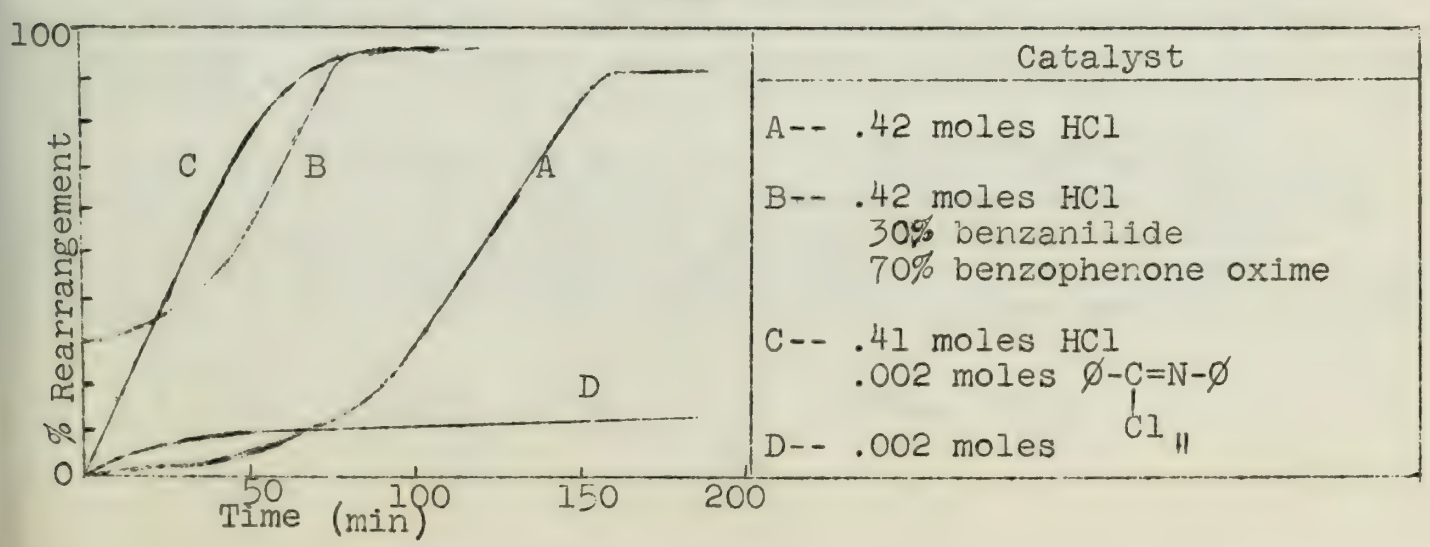
By Protonation -

Still another way of forming a leaving group is by protonation of the oxime. Although most of the oxime is probably protonated on the nitrogen atom, a small amount of the oxonium salt should be present in equilibrium with the immonium salt. All strong acids are thought to be able to catalyze the rearrangement in aqueous solution by this method (15).



Although HCl may catalyze the rearrangement by protonation, a different mechanism is envisaged for the formation of the leaving group when HCl is the catalyst (16,17). Chapman studied the HCl-catalyzed rearrangement of benzophenone oxime.

TABLE II



When benzophenone oxime was rearranged in the presence of HCl alone, an initial period of slow conversion was followed by a period of more rapid conversion (A). When a mixture of 30% benzanilide and 70% benzophenone oxime was used instead of the pure oxime, the length of the initial slow period was decreased (B). When N-phenylbenzimidoyl chloride (ϕ-C(Cl)=N-ϕ) was added in trace amounts, the initial slow period was eliminated entirely (C). When trace amounts of N-phenylbenzimidoyl chloride were used in the absence of HCl, only a 10% conversion was realized (D).

The explanation of the above data is that N-phenylbenzimidoyl chloride is an intermediate and also a catalyst. It can be produced by the slow rearrangement of the protonated oxime or by reaction of HCl with the rearranged amide.

$$\underset{\text{III}}{\phi_2C{=}N\overset{\oplus}{O}H_2} \xrightarrow[-H_2O]{Cl^-} \underset{\text{IV}}{\phi\text{-}C(Cl){=}N\text{-}\phi} \xleftarrow[-H_2O]{HCl} \phi CO\text{-}NH\phi$$

Once formed, it acts like an acid chloride and esterifies more of the oxime to produce an ester which, when protonated, can rearrange to produce a bis(N-phenylbenzimidoyl) ether. This ether can then be cleaved by HCl to produce one molecule of N-phenylbenzimidoyl chloride and one of benzanilide.

$$\text{III} \xrightarrow{\text{IV}} \underset{\text{V}}{\phi_2C{=}N\text{-}O\text{-}C(N\text{-}\phi)\text{-}\phi}$$

$$\text{V} \xrightarrow{H^\oplus} \xrightarrow{\text{B.R.}} \underset{\text{VI}}{\phi\text{-}C(N\text{-}\phi)\text{-}O\text{-}C(N\text{-}\phi)\text{-}\phi}$$

$$\text{VI} \xrightarrow{HCl} \phi\text{-}C(N\text{-}\phi)\text{-}Cl + O{=}C(HN\text{-}\phi)\text{-}\phi$$

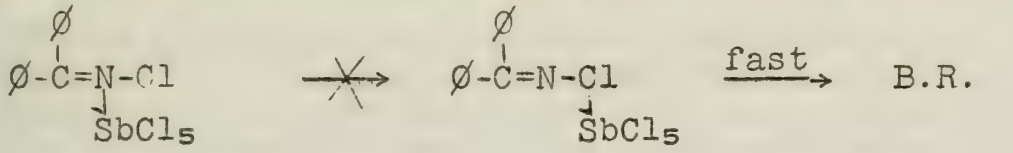
Stephen and Staskun (17) showed that nearly equimolar amounts of N-phenylbenzimidoyl chloride and benzanilide are produced by the rearrangement of benzophenone oxime under anhydrous conditions.

It is interesting to note that chlorimines, which have been shown not to be Beckmann intermediates (18) on the basis of their unreactivity, can be induced to rearrange by the use of a sufficiently strong Lewis acid such as $SbCl_5$ (19).

With the different reagents which catalyze the Beckamnn rearrangement it is possible that different rate-controlling steps may be involved. For example the rate-controlling step in the rearrangement of acetophenone oxime by BF_3 is thought to be the conversion of the more stable immonium salt to the oxonium salt (8).

$$\phi\text{-}C(CH_3){=}N\text{-}OH \rightarrow BF_3 \xrightarrow[140\text{-}150^\circ]{\text{Slow}} \phi\text{-}C(CH_3){=}N\text{-}OH \rightarrow BF_3 \xrightarrow{\text{fast}} \text{B.R.}$$

The conversion of the $SbCl_5$-immonium salt of the chlorimine of benzophenone to the corresponding chloronium salt might be considered as an example of the extreme case of this type of rate-controlling step, since the conversion is so slow that it does not proceed at all. However, the chloronium salt (prepared by a different method) undergoes rearrangement quite readily (14).



A second possible type of rate-controlling step is ester formation. Pearson (11) synthesized the sulfate ester of acetophenone oxime and found it to be very unstable. It rearranges with nearly explosive violence when heated. He reasoned that the rearrangement of such an unstable compound could hardly be the rate-controlling step. If, indeed, the sulfate ester were an intermediate for the rearrangement in sulfuric acid, it would be conceivable that the rate-determining step is the formation of the ester. However, the results of Ogata (20), who determined the dependence of the rate of rearrangement of cyclohexanone oxime in sulfuric acid on the acidity functions (H_o and J_o), would seem to indicate that the species which takes part in the rate-controlling step is a cation formed by the dehydration of the protonated oxime. Such an intermediate, however, is not possible in view of the infallible "trans-migration" principle. The rearrangement in sulfuric acid is very complicated at best and will require further study before final assignment of the rate-controlling step can be made.

Step II - Formation of the Bridged Cation

A third type of rate-determining step to be considered is the simultaneous ionization of the leaving group and transfer of the migrating group.

Chapman (15) has shown that the rate of rearrangement of benzophenone oxime-O-picryl ether is greater in polar solvents than in nonpolar solvents, but it is first order in all solvents. Electron-donating substituents on the migrating phenyl group increase the rate and electron-withdrawing substituents decrease it (21). These two facts indicate that the rate-controlling step involves ionization of the picrate moiety with some nucleophilic "push" by the migrating group.

Pearson (22) made a study of the correlation between log(k) for a series of para-substituted acetophenone oximes and the corresponding sigma values and found that the Hammett relationship was obeyed for all the compounds tested except for the p-t-butyl-, p-chloro-, and p-methoxy-acetophenone oximes. The latter two had log(k) values greater than expected from the Hammett relationship and the p-t-butyl group had a log(k) value less than expected. The higher values than expected for p-Cl and p-OCH_3 were attributed to unusual resonance stabilization of the transition state. The value for p-t-butyl was attributed to a "bulk effect" of the t-butyl group.

The transition state was postulated to be as follows:

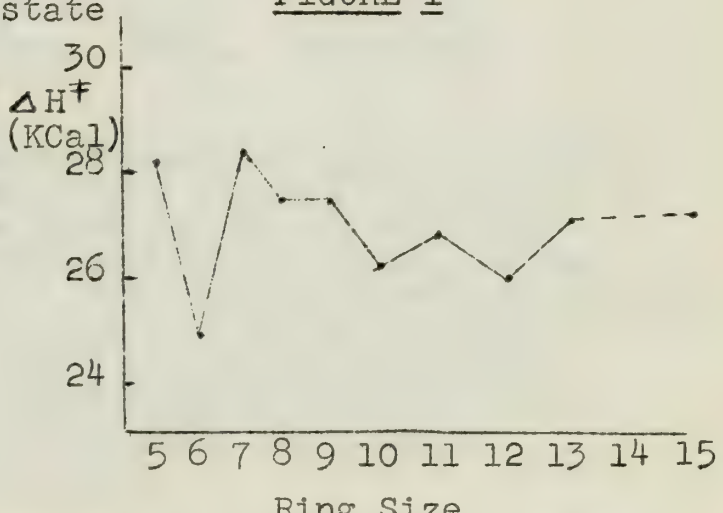
If the p-t-butyl group causes a decrease in the expected rate by virtue of its bulkiness, the same effect should be obtained by 3,4,5-trimethylacetophenone oxime. It was indeed found that 3,4,5-trimethylacetophenone oxime rearranged more slowly than would be predicted from the sigma values of the methyl groups (23). The "bulk effect" of the p-t-butyl and 3,4,5-trimethyl groups has not yet been explained.

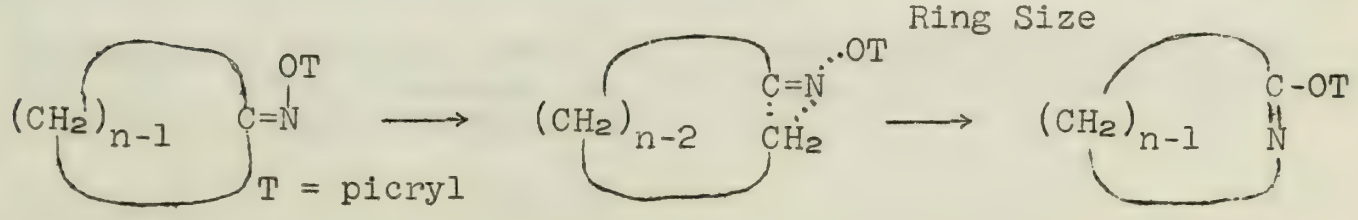
It was found that acetophenone oximes in which the oxime group is flanked by an ortho-substituent rearrange much faster than those in which the substituent is in the para-position (24,25,26). It was shown by u.v. spectroscopy that the C=N bond in ortho-substituted acetophenone oximes has much less resonance interaction with the phenyl group. These facts are further evidence for Pearson's theory of the transition state. The lowered resonance interaction in the ortho-substituted acetophenone oximes causes them to be at a higher energy level, thus facilitating the formation of the transition state. Since the oxime group is crowded out of the plane of the ring, it is in a more geometrically favored position to form the transition state (26).

The most recent work is that of Huisgen. In his kinetic studies he chose to make use of the oxime picryl ethers, since the acid catalyzed Beckmann rearrangement is beset with many uncertainties as to the rate-controlling step and the exact nature of the intermediates. Huisgen (27) determined the rate constants and enthalpies of activation for the rearrangement of cyclanone oxime picryl ethers and found that log (k) as well as $\triangle H^{\ddagger}$ alternated with increasing ring size. See Figure I.

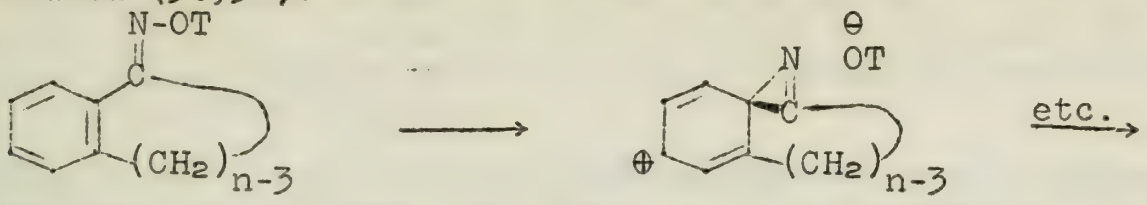
He reasoned that in the transition state an endocyclic double bond is being formed and that even-membered rings prefer endocyclic double bonds and odd-membered rings prefer exocyclic double bonds, a fact which has been shown for the 2-carbalkoxycyclanone (28) and lactam (29) ring systems.

FIGURE I





When the 1,2-benzocyclen-3-one anti-oxime picryl ethers were caused to rearrange, a striking dependence of the rate on ring size was noticed (30,31).



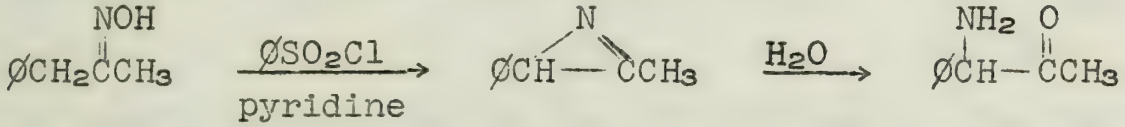
For the syn-oxime picryl ethers much less dependence on ring size was noticed; see Table III.

These results can be explained on the assumption that a bridged cation is formed by an electrophilic attack on the phenyl ring by the electron-deficient nitrogen atom. The three-membered ring formed in the transition state is not coplanar with the phenyl ring. Molecular models of the bridged cation (considered to approximate the transition state) show that the polymethylene sidechain is not long enough to allow the transition state to form when n equals 5 or 6. Only when n equals 8 is the transition state relatively strain-free. The difference in rates between the syn- and anti- oximes (n=7,8) points out the superior migration tendency of the phenyl group over alkyl groups.

TABLE III

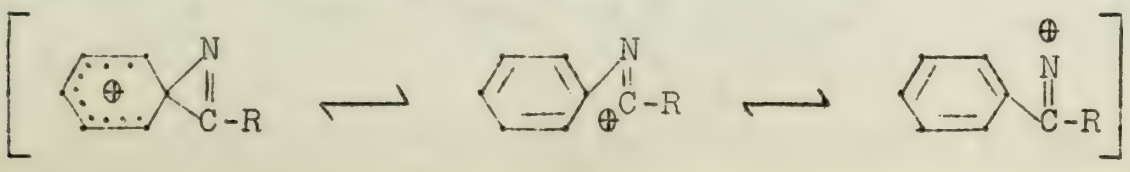
n	Relative Rate
5 (anti)	nil
6 "	.02
7 "	1865
8 "	429,000
7 (syn)	6.43
8 "	2.96

That the bridged cation is a true intermediate similar to Cram's phenonium ion has been proposed by Huisgen (32), who gives the following arguments: 1) Although a three-membered ring containing a double bond is a strained structure, it has been isolated as an intermediate in the Neber rearrangement (33,34), which may be looked upon as a Beckmann rearrangement gone awry.



2) The values of log(k) for the rearrangement of para-substituted acetophenone oxime picryl ethers were found with few exceptions to obey the Hammett relationship. The value of rho was calculated to be -4.1. This value falls well within the limits of rho values for electrophilic aromatic substitution. These limits have been assigned by Brown (35) as -3 to -10. 3) The few values of log(k) which gave a positive deviation from the Hammett plot were those of substituents which are capable of stabilizing a positive charge by resonance. This type of deviation is characteristic of electrophilic ring substitution.

Huisgen next measured the effect of the nonmigrating group on the rate (36). If one assumes the transition state to be a resonance hybrid of the following structures,



it follows that electron-repelling groups in the nonmigrating moiety will stabilize the transition state. The rates of rearrangement of various acylophenone oxime picryl ethers were found to decrease in the following order according to the nonmigrating alkyl group, R: isopropyl $\gg$ ethyl, n-propyl $>$ benzyl $>$ methyl $\gg$ chloromethyl. The rates obtained are in harmony with the relative electron-repelling effects of the various alkyl groups.

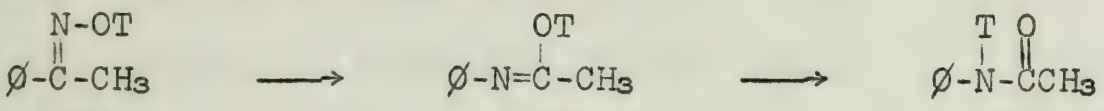
For alkyl group migration (~~in contrast to phenyl migration~~) it has not been established that there is a three-membered ring intermediate. Perhaps alkyl group migration does not involve a well defined intermediate, but takes place in a single step. Since the relative migration tendencies of alkyl groups are in the order of t-butyl $>$ isopropyl $>$ ethyl $>$ methyl (36,37), it might be concluded that there is some degree of positive charge on the alkyl group as it migrates. However, one cannot exclude the possibility of steric acceleration, since the relative rates of migration are in the same order as the bulkiness of the groups.

Step III - Formation of the imide intermediate.

It has long been established that the Beckmann rearrangement proceeds through an imide intermediate. The evidence for the imide intermediate is based on the actual isolation of imides and derivatives of imides from the Beckmann rearrangement (38,39,40,41). They will not be further discussed here.

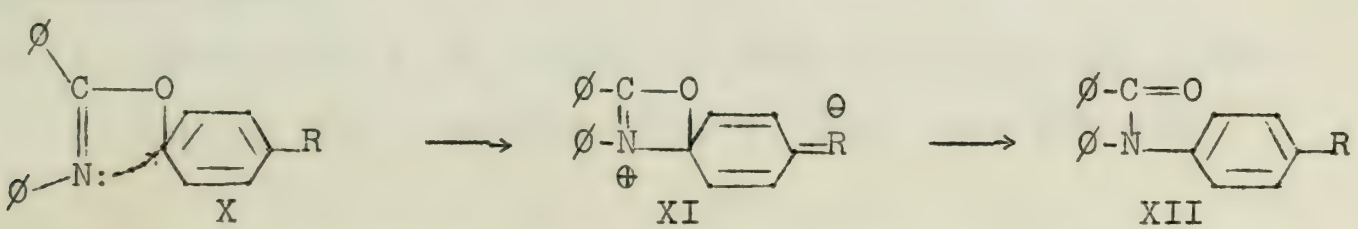
Step IV - Rearrangement of the imide to the amide.

In the preparative applications of the Beckmann rearrangement the imide intermediate is usually hydrolyzed and isomerized to the amide directly, but the imidoyl picrates (VIII), formed by rearrangement of oxime picryl ethers (VII), undergo further rearrangement to the corresponding N-picryl amides (IX).



VII VIII IX

An analogous reaction to step IV (above) is the thermal rearrangement of N-phenylbenzimidoyl phenyl ethers (X, analogous to VIII) to N, N-diphenyl benzamides (XII, analogous to IX) (42). This reaction was found to be first order. Rate studies indicated that electron-withdrawing substituents on the migrating phenyl group increase the rate of rearrangement in accordance with the Hammett equation, where rho equals + 1.75 (4). The function of the electron-withdrawing group is, therefore, to stabilize a negative charge generated in the transition state. Wiberg (4) has proposed a mechanism involving nucleophilic attack of the basic imine nitrogen atom on the migrating phenyl group to produce a four-membered cyclic intermediate (XI).



X XI XII

By analogy this mechanism may be considered as the one involved in the conversion of VIII to IX.

BIBLIOGRAPHY

1. E. Beckmann, Ber., 20, 1507, 2580 (1887).

2. A. H. Blatt, Chem. Rev., 12, 215 (1933).

3. B. Jones, Chem. Rev., 35, 335 (1944).

4. K. B. Wiberg and B. I. Rowland, J. Am. Chem. Soc., 77, 2205 (1955).

5. I. G. Donaruma and W. Z. Heldt, "The Beckmann Rearrangement", a chapter to be published in Organic Reactions.

6. J. Meisenheimer et al., Ann., 446, 205 (1925), plus references cited therein.

7. R. F. Brown, N. M. vanGulick, and G. H. Schmidt, J. Am. Chem. Soc., 77, 1094 (1955).

8. C. Hauser and D. Hoffenburg, J. Org. Chem., 20, 1482, 1491 (1955).

9. J. Kenyon and D. P. Young, J. Chem. Soc., (1941) 263.

10. A. Campbell and J. Kenyon, J. Chem. Soc., (1946) 25.

11. D. E. Pearson and F. Ball, J. Org. Chem., 14, 118 (1949).

12. P. Smith, J. Am. Chem. Soc., 70, 323 (1948).

13. A. W. Chapman and C. C. Howis, J. Chem. Soc., (1933) 806.

14. W. Theilacker, I. Gerstenkom, F. Grunner, Ann., 563, 104 (1949).

15. A. W. Chapman, J. Chem. Soc., (1934) 1550.

16. A. W. Chapman, J. Chem. Soc., (1935) 1223.

17. H. Stephen and B. Staskun, J. Chem. Soc., (1956) 980.

18. J. Stieglitz and P. Peterson, Ber., 43, 782 (1910); P. Peterson, Am. Chem. J., 46, 325 (1911).

19. W. Theilacker and H. Mohl, Ann., 563, 99 (1949).

20. Y. Ogata, M. Okano and K. Matsumoto, J. Am. Chem. Soc., 77, 4643 (1955).

21. A. W. Chapman and F. Fidler, J. Chem. Soc., (1936) 448.

22. D. E. Pearson, J. F. Baxter, and J. C. Martin, J. Org. Chem., 17, 1511 (1952).

23. D. E. Pearson and J. D. Bruton, J. Org. Chem., 19, 957 (1954).

24. D. E. Pearson and W. E. Cole, J. Org. Chem., 20, 488 (1955).

25. D. E. Pearson and F. Greer, J. Am. Chem. Soc., 77, 6649 (1949).

26. D. E. Pearson and E. Watts, J. Org. Chem., 20, 494 (1955).

27. R. Huisgen, I. Ugi, M. T. Assemi and J. Witte, Ann., 602, 127 (1957).

28. G. Schwarzenbach, M. Zimmermann and V. Prelog, Helv. Chim. Acta, 34, 1954 (1951).

29. Doctoral Thesis, H. Brade, Univ. München, (1953).

30. R. Huisgen, I. Ugi, H. Brade and E. Rauenbusch, Ann., 586, 30 (1954).

31. R. Huisgen, J. Witte, I. Ugi, Ber., 90, 1844 (1957).

32. R. Huisgen, J. Witte, H. Walz and W. Jira, Ann., 604, 191 (1957).

33. P. Neber and G. Huh, Ann., 515, 283 (1935).

34. D. Cram and C. Hauser, J. Am. Chem. Soc., 75, 33 (1953).

35. H. C. Brown, C. W. McGary and Y. Okamoto, J. Am. Chem. Soc., 77, 3037 (1955).

36. R. Huisgen, J. Witte and W. Jira, Ber., 90, 1850 (1957).

37. P. T. Scott, D. E. Pearson and L. J. Bircher, J. Org. Chem., 19, 1815 (1954).

38. P. Oxley and W. F. Short, J. Chem. Soc., (1948) 1514.

39. G. Coleman and R. Pyle, J. Am. Chem. Soc., 68, 2007 (1946).

40. Csöros, Zech. and Zech., Acta Chim. Sci. Hung., 1, 83 (1951).

41. F. Atherton and A. Morrison, Chem. and Ind., (1955) 1183.

42. A. W. Chapman, J. Chem. Soc., (1927) 1743.

FREE RADICALS IN GLASS

Reported by J. R. Hanley, Jr. February 24, 1958

INTRODUCTION

The majority of odd electron molecules either cannot exist under conditions of thermodynamic equilibrium except at concentrations too small to measure or can exist at measurable concentrations in equilibrium only under conditions of temperature or pressure which do not readily lend themselves to investigation. Under normal conditions, the rate of establishment of equilibrium is so rapid that the average lifetime of a species at concentrations high enough to be observed directly rarely exceeds a few milliseconds and may be much less (1). As the methods of production and detection of free radicals in both the liquid and vapor phases have been covered quite extensively by several authors (2-13), it will be the intent of this seminar to deal mainly with the production, detection and study of some free radicals trapped in rigid hydrocarbon solvents at liquid nitrogen and liquid helium temperatures and to outline some of the apparatus and procedures necessary to accomplish this. Mention, however, will also be made of a fairly recent method which involves the condensation of free radicals in the gaseous state directly on a cold finger at liquid nitrogen or liquid helium temperatures, and which is finding increasing application to the study of the less stable free radicals.

EARLY WORK

Free radicals may be formed in many different ways among which are: thermal decomposition, electrical discharge and photochemical dissociation; however, for the purpose of formation of free radicals in solid hydrocarbon media it will be subsequently pointed out that photochemical dissociation is the only suitable method.

Thermal decomposition and electrical discharge methods are employed, though, in the case of the free radical condensations mentioned above.

Due to the short lifetime of radicals in suitable concentrations for direct observation, special rapid recording techniques had to be developed in order to make these observations possible.

In 1949, Norrish and Porter (15) realized the inadequacy of experimental techniques which would enable the extension of investigation of free radicals to intensities of light higher than those provided by the sun and high pressure mercury vapor camps (2000-5000 Å), which were the only devices available at the time. Taking note of the observation that photochemical reactions are not much altered in their course by changes of light intensity, they adapted a gas-discharge lamp used in photography to the purpose of initiating photochemical decompositions, employing quartz tubes and tungsten electrodes. This technique was also independently introduced by Davidson and co-workers in 1951 (10).

This method of flash photolysis has found extensive application in both liquids and gases (9, 11, 12, 14); however, the necessity for rapid recording reduces the sensitivity of the measurement, and

the number of physical parameters which can be measured in this manner is limited. The difficulties encountered in applying infra-red spectroscopy and similar techniques to free radicals, together with some applications of these techniques have been recently reviewed by Porter (16), Potts (17), and Sinsheimer (18).

It was noted clearly that a great advantage would be gained if one were able to prepare free radicals and similar reactive molecules under conditions such that their lifetime was extended to a period of sufficient length to enable any physical property to be measured by conventional methods without recourse to rapid recording (i.e., extend the lifetime of theparticle to a period of minutes rather than milliseconds). The short lifetime of free radicals is generally the consequence of collision quenching (19) which involves one of two classes of rapid reaction:

a) Recombination with a second radical usually with nearly unit collision efficiency.

b) Rapid reaction with other molecules, especially when the molecules are in high concentration, such as when they form the solvent.

The reaction with other molecules could be reduced by a proper choice of the solvent employed, as this reaction is usually accompanied by a considerable activation energy (one can usually find a solvent whose energy of activation for reaction with a particular radical is of the order of a few kilocalories or greater). Working at low temperatures could also reduce this reaction to a negligible amount (1). Recombination (reaction "a") may have a zero or even negative temperature coefficient and, therefore, recombination could, in theory, occur with high collision efficiency at all temperatures (19). We can only inhibit the reaction by use of a viscous medium in which we can separate the radical formed from its neighbor and in which its diffusion would be very slow. Such a medium is a hard hydrocarbon glass. It has been common experience that molecules imbedded in such a glass retain their spatial position for a very long period (1, 17).

SOLVENTS APPLICABLE TO LOW TEMPERATURE FREE RADICAL STUDIES

Two methods of approach are available for the production of a solution of free radicals trapped in rigid media (1). They are:

a) trap the radicals by rapid freezing after preparation, or

b) produce the radicals "in situ" from the parent substance already dissolved in a rigid medium at low temperatures.

In view of the fact that the lifetime of many intermediates is very short, approach "a" entails considerable experimental difficulties; thus, approach "b" is the one employed by the majority of the workers in the field. It is quite evident that if we are to use rigid solvents in our studies, thermal methods cannot be employed nor can an electrical discharge of desired magnitude be passed through the rigid solution; we must, therefore, use radiation of some kind.

Photolysis methods have proven to be applicable if dissociation occurs as readily in rigid media as in fluid solvents or gases. No evidence showing failure of photolysis in solid media, when photolysis occurs in liquid or gaseous media has been found by this author.

According to Potts (17), the solvents used for rigid media must be transparent over a reasonable portion of the spectrum under investigation (u.v., visible or I.R.), must form a stable glass upon cooling with liquid nitrogen and the glass formed must remain rigid during irradiation.

A number of pure hydrocarbons form glasses at 77°K., but they tend to crack or crystallize more readily than mixtures. Norman and Porter (1) report the use of pure isopentane and pure 3-methylpentane but claim isopentane will still flow slowly at 77°K. under manual pressures and that most attempts to use it for radical trapping have been unsuccessful.

Norman and Porter (1) claim that 3-methylpentane is quite satisfactory except under intense illumination, when it softens. However, Potts (17) points out that this hydrocarbon is limited by the fact that it sets at a temperature above 77°K. and contracts with further cooling, giving a very deep meniscus or cracks in the hydrocarbon glass.

When substances other than hydrocarbons can be used, a mixture of isopentane, ether and ethanol (E.P.A.) is found to be most satisfactory (1). Some of the hydrocarbon mixtures found to be useful are listed in Table I.

Table I

Hydrocarbon Mixtures Suitable for Glasses (1, 17, 21)

(a) 3-methylpentane-isopentane (3 MeP.P) (3:2), (1:6)*

(b) isopentane-methylcyclohexane (P.MeH) (3:2), (6:1), (1:4)

*This ratio is reported to be superior in all respects to all other glasses (17).

The transmission properties of some of the spectrographic solvents are listed in Table II.

TABLE II

Transmission Properties of Some Spectrographic Solvents

Compound	Transmission Limit at Room Temperature 1-cm Path	0.14 mm Path	Transmission Limit of cm path of glasses at 77°K.	
Ethanol (22)	ca.2100 Å	1890 Å	2 parts Ethanol, 5 parts Isopentane, 5 parts Ether	ca.2200 Å (17)
Ether (22)	2130	1980		
Isopentane (24)	1770	1720		
Water (22)	1870	1785		
n-Heptane (24)	1950	1720		
n-Perfluoro-octane (23)	ca.1800	1580		
3-Methyl Pentane (24)	1950	1720	1 part 3-Methylpentane, 6 parts Isopentane	1670 (17)
Methylcyclo-hexane (24)	2100	1780	6 parts Isopentane, 1 part Methylcyclo-hexane	1700 (17)

APPARATUS

The design of apparatus for studies at low temperatures is of great importance. Low temperature cells which permit spectral absorption and emission measurements as well as high energy irradiation of the materials held at liquid nitrogen or liquid helium temperatures are described by several workers in the field (1, 17, 25, 26). In general, the apparatus consists of a suitable cell fitted closely between two inner windows of a Dewar flask constructed of such a material that the desired radiation may pass through. The cell employed should be removable from the Dewar flask without emptying the liquid refrigerant as this not only permits rapid transfer to a bath at another temperature (to observe phenomena which are detectable at a higher temperature), but also protects the more valuable Dewar flask in case the cell is broken by expansion of the solvent on warming (a not too infrequent occurrence, according to Norman and Porter (1)).

APPLICATIONS

A considerable amount of attention has been devoted to the optical behavior of a great number of molecules dissolved in rigid glasses at low temperatures. These observations have been mainly a study of fluorescence and phosphorescence. However, a notable exception is the investigation of Lewis and Lipkin (27) on the primary photochemical processes of some aromatic molecules and dyestuffs in rigid media. They report evidence for photo-ionization as well as dissociation into radicals and were able to observe the spectra of labile substances for a long time after irradiation.

These observations were limited, however, to relatively stable radicals such as the triphenylmethyl and diphenylamino radicals.

Norman and Porter (28), on repeating this work, reasoned that if the radiation used was of a frequency greater than that required for dissociation, the excess energy of the quantum absorbed must be dissipated as heat. This excess energy in a typical case, such as the photolysis of ethyl iodide using radiation of 2537 Å, will amount to over 50 kcal/mole (1). Since a temperature rise of 10°C is sufficient to produce noticeable softening of the hydrocarbon glass, each quantum absorbed by a molecule of ethyl iodide should result in a lowering of the viscosity of several hundred of the surrounding solvent molecules which would be sufficient to enable the radicals formed to diffuse apart. The heat would, of course, be rapidly conducted away and the glass would again become rigid consequently trapping the radicals. An apparant objection to this postulate would be the primary recombination effect of Franck and Rabinowitch (20) which was previously mentioned and which might be expected to operate very efficiently in glassy solvents; however, no serious limitations due to this effect have been noted (1).

A. CARBON DISULFIDE

In the gas phase, carbon disulfide undergoes photochemical decomposition according to the following equation:

$$C\,S_2 \xrightarrow{h\nu} \cdot C\,S + S\cdot$$

The spectra of CS· and S_2 have been detected after photolysis (9). The CS· radical eventually disappears by a wall reaction having a half-life which may be as long as several minutes. This radical has never been detected during irradiation of a hydrocarbon solution of carbon disulfide at 20°C, although decomposition and the separation of a yellow solid has been reported (29). After several minutes irradiation in a rigid glass solution (3 MeP.P) at 77°K, the first four bands of the $\nu = 0$ progression of "CS" appear at a very high intensity and can be observed for many hours (28). On warming the glass, the spectra disappears instantly. The absorption spectra of this solution observed at 195°K after photolysis at 77°K, showed no trace of absorption by "CS". At no time was the spectrum of molecular sulfur (S_2) observed, which is logical as sulfur atoms are not able to recombine in the rigid media and as the glass becomes fluid, the polymerization of sulfur molecules can very rapidly occur.

B. CHLORINE DIOXIDE

Upon irradiation, the chlorine dioxide spectrum, mainly diffuse in glassy solvents is rapidly destroyed and replaced by a second diffuse spectrum, the position of which agrees exactly with that reported for the "ClO·" radical (maximum intensity 2700 Å) (14). This lends support to the postulate that the photochemical dissociation in rigid media is the same as that reported by Lipscomb (13) for the gas phase reaction.

$$ClO_2 = ClO\cdot + O\cdot$$
$$O\cdot + ClO_2 = ClO_3 \text{ (1\% formed)}$$
$$O\cdot + ClO\cdot = ClO_2$$
$$O\cdot + O\cdot + M = O_2 + M$$
$$2\,ClO\cdot = Cl_2 + O_2$$

The lifetime of the "ClO" radical is reported to be a few milliseconds (13).

The irradiation of iodine, resulting in the disappearance of the molecular spectrum (1, 28), has been reported as well as that of other inorganic molecules. However, the procedures employed are similar to those outlined above and therefore, will not be considered here.

C. ETHANOL

Irradiation with ultraviolet light of a variety of unstated photochemically active compounds dissolved in rigid glasses immersed in liquid nitrogen and containing ethanol as a major component produces an intense violet coloration which is lost as soon as the glass softens. Symons and Townsend (30) postulate that this violet coloration is due to a free radical formed from ethanol by the abstraction of a hydrogen atom. In support of this postulate, they note than the violet glasses are always paramagnetic, the paramagnetism being lost together with the color on softening of the glass (31), and the absorption due to the violet color is the same regardless of the photoactive substance employed.

The spectra of the glasses measured in the visible and ultraviolet region show that the violet color is caused by a species having a peak at about 517 mμ. When hydrogen peroxide (10^{-2}M) was photolyzed in ethanol, this was the only new absorption band observed in the 240 to 1000 mμ region (30). In particular no band or shoulder appeared near 300 mμ, thus indicating no build-up in the concentration of free hydroxyl radicals which are known to absorb strongly in this region. A "cage" back reaction of hydroxyl radicals to give water and oxygen atoms cannot account for the violet band observed.

The reaction: $HO\cdot + H_2O_2 = H_2O + HO_2\cdot$ is improbable in dilute solutions. Glasses containing only water and hydrogen peroxide (40%) became strongly paramagnetic after prolonged irradiation; under these conditions, the $HO_2\cdot$ radical could be formed but the glass remained colorless. A summary of the results of photolysis in several solvents appears as Table III.

TABLE III

Colors Produced on Photolysis of Several Solvents

Compound Photolyzed	Solvent	Color
None	EtOH	None
H_2O_2	EtOH	Violet
H_2O_2	H_3PO_4	None
H_2O_2	H_2O - H_2O_2	None
ClO_2	EtOH	Violet
ClO_2	Mixed Hydrocarbons	None

It may be concluded from the above observations that the violet color observed is due to a radical produced by a secondary reaction with the ethanol portion of the solvent. The radical produced may be one of the following:

$\cdot CH_2CH_2OH$	$CH_3CH_2O\cdot$	$CH_3\dot{C}HOH$
I	II	III

Radical I may be rejected as simple alkyl radicals do not absorb in the visible or near ultraviolet region. As the irradiation of di-t-butylperoxide in ethanol does not result in any coloration, although the glass does become paramagnetic, ethanol is not attacked and the paramagnetism was attributed to t-butoxy radicals in solution which are therefore presumed to be colorless. Since the replacement of a hydrogen atoms by a methyl group is unlikely to result in a large displacement of the absorption band, it was concluded that radical II is also colorless. In view of the possibility that the dissociation of t-butoxy radicals into methyl radicals and acetone might occur in glasses at low temperatures, this conclusion is somewhat tenuous.

Because of the resemblence of radical III to the $HO_2\cdot$ radical (32), it may be expected to undergo a permitted low-energy transition (33) and is, therefore, probably the trapped violet radical. This conclusion is claimed to be supported by the results obtained from paramagnetic resonance studies which were not discussed further.

It appears therefore that despite the low temperature employed, highly reactive radicals formed in a glass are able to react with the surrounding medium to form new radicals which are in turn trapped.

D. BENZENE

An interesting case involving free radical formation in rigid media is that of the photochemical decomposition of benzene reported by Gibson, Blake and Kalm (34), and later by Norman and Porter (1).

Nauman (35) found that when a sample of benzene in E.P.A. (5:5:2) was exposed to ultraviolet light at 77°K for a period of one hour or longer, one could notice a decrease in the intensity of phosphorescence with time. When the sample was brought to room temperature, refrozen and again irradiated, the return of phosphoresence was not quite to the total phosphoresence observed initially. It was concluded that some of the benzene was being converted into another compound and that the reaction occurring was irreversible (34). In order to explain this change in phosphorescence, it was postulated that the photochemical reaction produced a region of nearly opaque material on the surface of the sample container and, therefore, prevented any further excitation of the benzene molecules in the solution by the ultraviolet radiation. On melting, the new substance formed was distributed throughout the bulk of the solution and the intensity of the phosphorescence observed returned to almost its original value, the small difference

being attributed to the shielding effect of the dispersed decomposition product.

The experiment was repeated, the solution being exposed to irradiation until the intensity of phosphoresence observed dropped quite noticeably and the sample then kept at liquid nitrogen temperature for 1-1/4 hours without further irradiation. At the end of this time, the sample was exposed to ultraviolet light just long enough to measure the phosphorescent intensity; it was found the intensity had not changed during this time. Comparison of the ultraviolet absorption spectra of the solution before and after exposure showed that a definite change had occurred, since the extinction coefficient had increased enormously and the structure of the spectrum had changed completely. The investigation of benzene solutions in other hydrocarbon glasses produced similar changes in absorption. Some of the intensity maxima measured in rigid glass solutions are given in Table IV.

TABLE IV

Absorption Maxima of Benzene Solutions (1)

Isopentane glass	2781 Å, 2672 Å, 2559 Å
E.P.A. glass	2766 Å, 2659 Å, 2552 Å

No spectral changes are reported in these areas in the case of ultraviolet irradiation or flash photolysis of benzene in the vapor or liquid phases or in hydrocarbon solutions at normal temperatures even at the shortest times which could be studied (1, 34). Irradiation of the solvents at room temperature and at liquid nitrogen temperature gave no change in spectra. Therefore, the observed change could not be attributed to a reaction which was taking place with the solvent alone.

Although the spectrum obtained had some characteristics of the spectra of substituted benzenes, it was found that the extinction coefficient was much too high for any of these compounds, thus ruling out substituted benzenes as possible products. It was next shown that oxygen and water were not responsible for the photochemical reaction taking place.

A larger amount of the photolysis product was prepared for further investigation by repeated irradiation, melting and refreezing of the benzene -isopentane-methylcyclohexane solution. The solution was distilled to half its volume at atmospheric pressure. A spectrum of the distillate is reported to indicate that only benzene and solvent had been distilled from the solution. The distilland was concentrated by distillation until only the new substance (indicated by its absorption at 275 mμ) and solvent remained.

Upon evaporation of the solvent, an oil was obtained. A small amount of this oil on contact with air for three weeks was found to have lost its absorption. A portion of this material was found to absorb bromine immediately, giving an indication of aliphatic,

rather than aromatic, unsaturation.

The investigation of various unsaturated molecules and their respective absorption spectra gave an indication that the compound was possibly a conjugated polyene. A comparison of the spectrum of the compound with those of divinylacetylene and hexatriene showed that the compound had a spectrum closely resembling that of 1,3,5-hexatriene (36). The major discrepancy between the two spectra was that the entire spectrum of 1,3,5-hexatriene is shifted 7.5 mμ away from the visible region compared with that of the decomposition product. The structures of the curves and distances between the maxima were found to be the same and the maximum extinction coefficient was of the same order of magnitude. This may be explained by the observation of Pinckard and others (37) that in conjugated polyenes geometrical isomerism has an effect on the maximum wave length as well as on the maximum extinction coefficient. It is, therefore, reasonable, according to the investigators (34), to assume that the 1,3,5-hexatriene whose spectrum was published by Woods and Schwartzman (36) might be that of the cis-isomer while that observed for the benzene decomposition product is the trans-isomer, which absorbs at higher wave lengths and has a higher extinction coefficient (34). This assumption, however, is not satisfactorily substantiated by the experimental data presented by the authors. They claim that the photolysis product, supposedly 1,3,5-hexatriene (b.p. 78), was recovered in the residue after distilling off the unreacted benzene (b.p. 80) and a part of the solvent. Due to the closeness of the two boiling points, this separation appears to be extremely unlikely. No infra-red absorption data was presented to substantiate the structure of the new compound. The role of the solvent appears to be that of a contributor of hydrogen. Any solvent which is capable of forming a glass at liquid nitrogen temperatures and contains hydrogen seems to be able to cause the reaction to proceed. It was noted that a solution of benzene in perfluoro-2-methylpentane (which forms a good glass if cooled slowly) produced a change in the spectrum on irradiation; however, this spectrum did not resemble the spectra obtained when solvents containing hydrogen were used. The spectra obtained in this case had certain characteristics of biphenyl, which would fit into the observation noted by Krassina (38) and Prilezhaeva (39) in their work on the photochemical decomposition of benzene vapor. However, no evidence was presented to substantiate the presence of biphenyl, the formation of which could be visualized as resulting from the removal of a hydrogen atom from a benzene molecule giving a phenyl radical. This radical could in turn either extract a hydrogen atom from the solvent giving, once again, benzene or combine with another phenyl radical to give biphenyl. This reaction may account for the formation of biphenyl in the vapor state. However, to get biphenyl in the solid state by one of these mechanisms would be highly improbable as the species are held in place in a rigid medium and radical-benzene or radical-radical collision would be quite small compared with radical-solvent collision (40). Thus, it can only be said that in the absence of hydrogen in the solvent, the decomposition proceeds by a different path and results in the formation of a different product.

Irradiation of solutions of naphthalene and anthracene in rigid glasses for comparable times to those used for benzene produced no observable spectral change.

Substituted benzenes, such as halobenzenes, benzonitrile and nitrobenzene, showed only diffuse absorption, which was also present after melting the glass (1).

E. OTHER MOLECULES

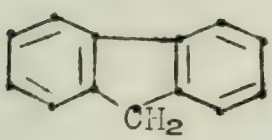
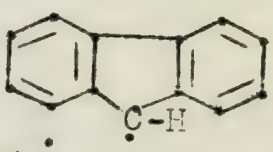
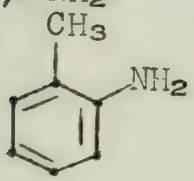
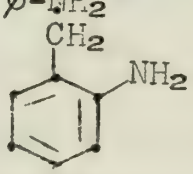
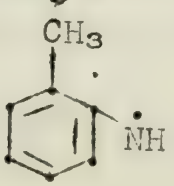
The formation of free radicals in rigid media by photolysis has also been investigated for a number of other molecules such as ethyl iodide (1, 28), aniline (1) and other amines (40, 42), pyrimidines (43), purines (43), toluene (1), and benzyl derivatives (1), to mention a few. Some of the spectra observed and the assignment of the probable radicals produced appear in Table V (1). These assignments were, for the most part, made by comparison with the gas phase spectra of the same molecule. In the case of ortho-toluidine the assignment was based on a comparison of spectral position and band width. The assignment of the probable radicals produced by photolysis of aniline is of some interest. The 3088 Å band was compared with the 3008 Å band found in the photolysis of aniline vapor. The 4288 Å band, appearing in the visible region could hardly belong to the same species as the ultra-violet spectrum, as it was always absent in the gas phase photolysis even when the ultra-violet spectrum was very intense. It is believed that this spectrum is that of the aniline radical cation for the following reasons (1):

(a) Although it is a transient species, the position of absorption is anomalous when compared with the spectra of neutral free radicals such as the benzyl radical and the phenoxy radical.
(b) Lewis and Lipkin (27) demonstrated the occurrence of photo-oxidation processes in E.P.A. glasses by the loss of an electron from triphenylamine and other substances containing an electro-negative atom. (This is discussed in more detail below).
(c) The absence of the spectrum in the gas phase is explained since only when solvation of the ion and electron are possible will the energy required for photoionization (photooxidation) be satisfied.

Lewis and Lipkin (27) noted that a molecule may be dissociated by light into two radicals (photodissociation), into a positive and a negative ion (photoionization) or into a positive ion and an electron (photooxidation). Photooxidation studies in hydro-carbon glasses were reported on several molecules which contained an electronegative atom, such as tetraphenylhydrazine, Wurster's Blue and triphenyl amine. In all cases the substances obtained were identical to those obtained previously by chemical oxidation (44, 45) and were confirmed by similarity of ultraviolet absorption spectra. The authors speculate that the ejected electron becomes attached to a solvent molecule, a group of solvent molecules or to some unique point in the solvent determined by the rigid structure. The electron is believed to be in a potential energy hole of sufficient depth that the large electrostatic field of the ion is unable to dislodge it. Upon raising the temperature, the ejected electron is allowed to recombine with the positive ion and the characteristic color attributed to the ion disappears.

TABLE V

Description of Spectra Observed After Photolysis of Aromatic Substances in Rigid Glasses

Molecule	Solvent	Radical Spectra band Center (Å)	Probable Radical
Ø-CH_3	E.P.A.	3187 3082 3039	Ø-CH_2·
Ø-CH_2Cl	E.P.A.	3182 3082 3047	Ø-CH_2·
Ø-CH_2NH_2	E.P.A.	3186 3078 3043	Ø-CH_2·
Ø-CH_2OH	E.P.A.	3184	Ø-CH_2·
Ø-CH_2CH_3	P.MeH and E.P.A.	3228 (E.P.A.) 3210 (P.MeH) 2902 (E.P.A.) 2896 (P.MeH)	? Ø-$\dot{C}HCH_3$?
	P.MeH	3225 3167 3097 3044	
Ø-CH_2-Ø	P.MeH	3351	Ø-$\dot{C}H$-Ø
Ø-CH_2CH_2-Ø	E.P.A.	3625	Ø-CH_2-$\dot{C}H$-Ø
	P.MeH	3450 3380	
Ø-NH_2 	E.P.A.	3088 4288	Ø-$\dot{N}H$ ⊕ Ø-$\dot{N}H_2$ 
	E.P.A.	3217	
		3119	
Ø-OH	E.P.A.	2870(limit)*	Ø-O·
Ø-OCH_3	E.P.A.	2860(limit)*	Ø-O·

*limit=The long wave length limit of a continuous absorption.

Chlorobenzene, bromobenzene and benzophenone show no change in spectra. Nitrobenzene, benzonitrile and o-chlorotoluene show spectra of stable products only.

The use of hydrocarbon glasses appears to be applicable to a wide range of atoms and free radicals. It seems likely that through a proper choice of solvents and the use of still lower temperatures, any free radical which can be produced by photolysis can be stabilized in this manner and its properties investigated.

OTHER APPLICATIONS

Free radicals have also been produced in the condensed phase without the use of solid hydrocarbon media. This is accomplished by the rapid condensation on a surface cooled by liquid air, nitrogen or helium, of free radicals produced when a gas or vapor is passed through a furnace or subjected to an electrical discharge. By use of this method, free radicals such as the methyl radical (46, 47), dimethylamino radical (47, 48, 49) imine radical (47, 50, 51, 52, 53), HO_2· radical (32) and atomic nitrogen (54, 55, 56), have been isolated.

In view of the reported use of rigid media in conjunction with nuclear reactions (57-61), it is believed this method of maintaining highly reactive species in a rigid state will find extensive application in the near future.

BIBLIOGRAPHY

1. I. Norman and G. Porter, Proc. Roy. Soc. (London), A, 230, 399 (1955).
2. E. W. R. Steacie "Atomic and Free Radical Reactions", 2nd ed., Vol. I and II Reinhold Publishing Corporation, New York, N.Y., (1954).
3. C. Walling "Free Radicals in Solution", John Wiley and Sons, Inc., New York, N.Y., 1957.
4. E. Rabinowitch and W. C. Wood, J. Chem. Phys., 4, 497 (1936).
5. E. Rabinowitch and W. C. Wood, Trans. Faraday Soc., 32, 547 (1936).
6. B. M. Norton, J. Am. Chem. Soc., 56, 2294 (1934).
7. C. H. Bamford, J. Chem. Soc., 17 (1939).
8. J. Zimmerman and R. M. Noyes, J. Chem. Phys., 18, 658 (1950).
9. G. Porter, Proc. Roy. Soc. (London), A, 200, 284 (1950).
10. N. Davidson, R. Marshall, A. E. Larsh, Jr. and T. Corrington, J. Chem. Phys., 19, 1311 (1951).
11. W. H. Hamill and R. H. Schuler, J. Am. Chem. Soc. 73, 3466 (1951).
12. G. Porter and M. W. Windsor, Discussions Faraday Soc., 17, 178 (1954).
13. F. J. Lipscomb, R. G. W. Norrish and G. Porter, Nature, 174, 785 (1954).
14. G. Porter, Discussions Faraday Soc., 9, 60 (1950).
15. R. G. W. Norrish and G. Porter, Nature, 164, 658 (1949).
16. G. Porter, J. phys. radium, 15, 497 (1954).
17. W. J. Potts, Jr., J. Chem. Phys. 21, 191 (1953).
18. R. L. Sinsheimer, J. F. Scott and J. R. Loofbourow, J. Biol. Chem., 187, 299 (1950).

19. M. Kasha, Chem. Revs., 41, 401 (1947).
20. J. Franck and E. Rabinowitch, Trans. Faraday Soc., 30, 120 (1934).
21. G. N. Lewis, T. T. Magel and D. Lipkin, J. Am. Chem. Soc., 62, 2975 (1946).
22. H. B. Klevens and J. R. Platt, J. Am. Chem. Soc., 69, 3005 (1947).
23. H. B. Klevens and J. R. Platt, J. Chem. Phys., 16, 1168 (1948).
24. W. J. Potts, Jr., J. Chem. Phys., 20, 809 (1952).
25. G. N. Lewis and M. Kasha, J. Am. Chem. Soc., 66, 2100 (1944).
26. W. H. Duerig and I. L. Mador, Rev. Sci. Instr., 23, 421 (1952).
27. G. N. Lewis and D. Lipkin, J. Am. Chem. Soc., 64, 2801 (1942).
28. I. Norman and G. Porter, Nature, 174, 508 (1954).
29. G. Porter and M. W. Windsor (quoted by Norman and Porter, Reference 1).
30. M. C. R. Symons and M. Townsend, J. Chem. Phys., 25, 1299 (1956).
31. Gibson, Ingram, Symons and Townsend, To be published (quoted by Symons and Townsend, Reference 30).
32. P. A. Giguère, J. Chem. Phys., 22, 2085 (1954).
33. A. D. Walsh, J. Chem. Soc., 2288 (1953).
34. G. E. Gibson, N. Blake and M. Kalm, J. Chem. Phys. 21, 1000 (1953).
35. R. V. Nauman, Communication quoted by Gibson, Blake and Kalm, Reference 34.
36. G. F. Woods and C. H. Schwartzman, J. Am. Chem. Soc., 70, 3394 (1948).
37. J. H. Pinckard, B. Wille and L. Zechmeister, J. Am. Chem. Soc., 70, 1938 (1948).
38. G. I. Krassina, Acta Physicochim. U.R.S.S., 10, 189 (1939).
39. N. A. Prilezhaeva, Acta Physicochim. U.R.S.S., 10, 193 (1939).
40. P. Debye and J. Edwards, J. Chem. Phys. 20, 236 (1952).
41. H. Linschitz, M. G. Berry and D. Schweitzer, J. Am. Chem. Soc., 76, 5833 (1954).
42. H. Linschitz, J. Rennert and T. M. Korn, J. Am. Chem. Soc., 76, 5839 (1954).
43. R. L. Sinsheimer, J. F. Scott and J. R. Loofbourow, J. Biol. Chem., 187, 313 (1950).
44. L. Michaelis, M. P. Schubert and G. Granick, J. Am. Chem. Soc., 61, 1981 (1939).
45. S. Granick and L. Michaelis, J. Am. Chem. Soc., 62, 2241 (1940).
46. I. L. Mador, J. Chem. Phys., 22, 1617 (1954).
47. H. A. Papazian, J. Chem. Phys., 27, 813 (1957).
48. F. O. Rice and C. J. Grelecki, J. Am. Chem. Soc., 79, 2679 (1957).
49. F. O. Rice and C. J. Grelecki, J. Am. Chem. Soc., 61, 824 (1957).
50. F. O. Rice and G. J. Crelecki, J. Am. Chem. Soc., 79, 1880 (1957).
51. F. O. Rice and M. Freamo; J. Am. Chem. Soc., 73, 5529 (1951); 75, 548 (1953).
52. I. L. Mador and M. C. Williams, J. Chem. Phys., 22, 1627 (1954).
53. D. A. Dows, G. C. Pimentel and E. Whittle, J. Chem. Phys., 23, 1606 (1955).
54. H. P. Broida and J. R. Pellam, Phys. Rev., 95, 845 (1954).
55. A. M. Bass and H. P. Broida, Phys. Rev., 101, 1740 (1956).
56. C. M. Herzfeld and H. P. Bruida, Phys. Rev., 101, 606 (1956).

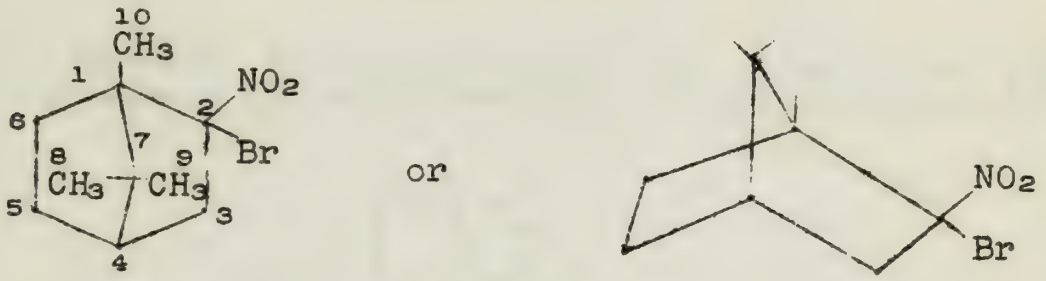
57. L. Friedman and W. F. Libby, J. Chem. Phys., 17, 647 (1949).
58. S. Goldhaber, R. S. H. Chiang and J. E. Willard, J. Am. Chem. Soc., 73, 2271 (1951).
59. F. S. Rowland and W. F. Libby, J. Chem. Phys., 21, 1495 (1953).
60. G. Levey and J. E. Willard, J. Am. Chem. Soc., 74, 6161 (1953).
61. M. Milman, J. Am. Chem. Soc., 79, 5581 (1957).

THE STRUCTURES OF THE ANHYDROBROMONITROCAMPHANES

Reported by R. J. Tuite March 13, 1958

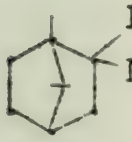
INTRODUCTION

In 1899, Forster (1) synthesized (-)-2-bromo-2-nitrocamphane, I, by the action of KOBr on camphor oxime. In the course of in-



I

vestigating its properties, he found that treatment of I with concentrated sulfuric acid at 0° gave a nearly quantitative yield of a monodehydration product, Anh.-1. The author further noted that dilute mineral acid treatment of Anh.-1 produced a stable isomer Anh.-2. In 1956, van Tamelen and Brenner (2) discovered that treatment of Anh.-2 with concentrated sulfuric acid at room temperature for three days produced still another isomer, Anh.-3. The course of these reactions can be represented as follows:



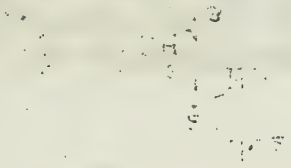
$\xrightarrow[0^\circ]{\text{conc. } H_2SO_4}$ Anh.-1 $\xrightarrow[\text{reflux}]{\text{dil. HCl, EtOH}}$ Anh.-2 $\xrightarrow[\text{R.T.}]{\text{conc. } H_2SO_4,\ 3 \text{ days}}$ Anh.-3

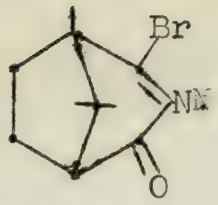
$C_{10}H_{16}NO_2Br$ $C_{10}H_{14}NOBr$ $C_{10}H_{14}NOBr$ $C_{10}H_{14}NOBr$

It is the purpose of this report to review, in a critical way, the literature concerned with the elucidation of the structures of these three isomers. Special emphasis will be given to the recent paper by van Tamelen and Brenner (2), since it is the first recorded work in which modern chemical methods have been applied to the study of these compounds.

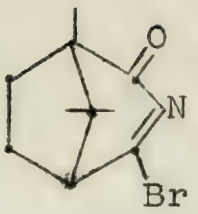
STRUCTURE ELUCIDATION

Historical.--In Forster's subsequent papers (3), he attempted to determine the structures of Anh.-1 and Anh.-2. He found that a similar pair of products was obtained from 2-chloro-2-nitrocamphane, whereas 3-bromo-2-nitrocamphane was indifferent to the reagent. He argued therefore that the 3 position must contain two hydrogen atoms. Since 2-nitrocamphane also gave no reaction, he suggested that the halogen atom was necessary, its function apparently to make the nitro oxygens more labile. From these and other considerations, he decided on the N-acyliminobromide structure II or III for Anh.-1.



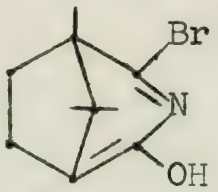


II



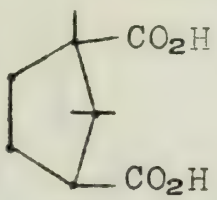
III

Noyes and Ginnings (4) later adopted structure II and postulated that Anh.-2 was merely its enol form, that is the structure IV.

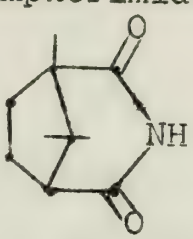


IV

This structural proposal was immediately dismissed by van Tamelen and Brenner, not only because its formation has no suitable analogy, but also because the structure is not in accord with experimental facts. For example, mineral acid treatment of II should give either camphoric acid, V, or camphorimide, VI.



V

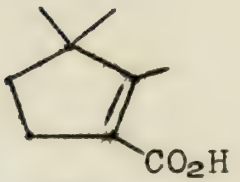


VI

In view of the fact that Anh.-2 is the more stable of the first two isomers, van Tamelen and Brenner chose it for initial investigation.

Properties of Anh.-2.--In addition to dilute HCl treatment, weakly basic reagents like $HONH_2$, $\emptyset NHNH_2$, alcoholic ammonia (3), and also heat alone (2) were shown to isomerize Anh.-1 to Anh.-2. Anh.-2 melts at 240° and is optically inactive. It is stable to bromine, permanganate, and zinc dust in acetic acid (1), and in addition, is virtually transparent in the ultraviolet (2). These facts indicate the absence of unsaturation. It also forms benzoyl and mesylate derivatives and a nitrate ester (3, 2). Infrared peaks at 2.80 μ (3580 $cm.^{-1}$) and at 4.48 μ (2235 $cm.^{-1}$) indicate hydroxyl and nitrile functions respectively. Furthermore, the hydroxyl absorption is absent in the various derivatives.

Forster (3) observed that Anh.-2 was transformed by refluxing dilute aqueous alkali into formic acid and a liquid nitrile of the formula $C_9H_{13}N$. The nitrile, when subjected to basic hydrolysis, yielded an acid which could be isomerized by dilute HCl treatment to isolauronic acid, VII (3).

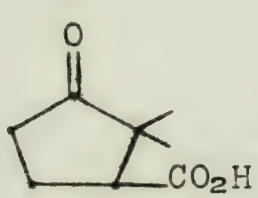
C_8H_{13}-CN $\xrightarrow[5\ \text{days}]{\text{conc. NaOH}}$ C_8H_{13}-CO_2H $\xrightarrow{\text{dil. HCl}}$ 

VII

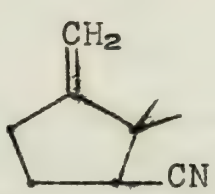
There are various possible structures for the nitrile, since acid treatment not only can result in double bond migration, but also in Wagner-Meerwein 1,2-methyl shifts. The various possibilities are illustrated by the following structures VIII.

VIII

Determination of the correct structure was afforded by ozonolysis of the nitrile (2). The products were formaldehyde and a new nitrile which was hydrolyzed in base to the known 2,2-dimethyl-3-ketocyclopentanecarboxylic acid, IX (5). The C_9 nitrile thus proved to have the structure X.



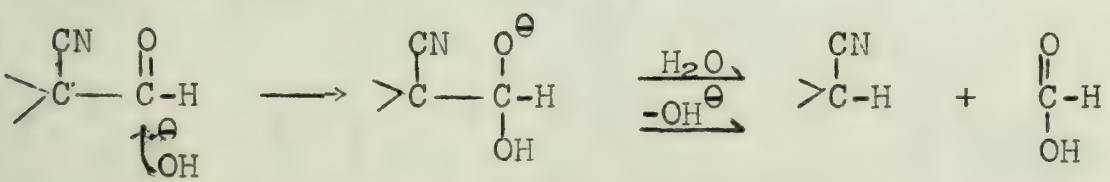
IX



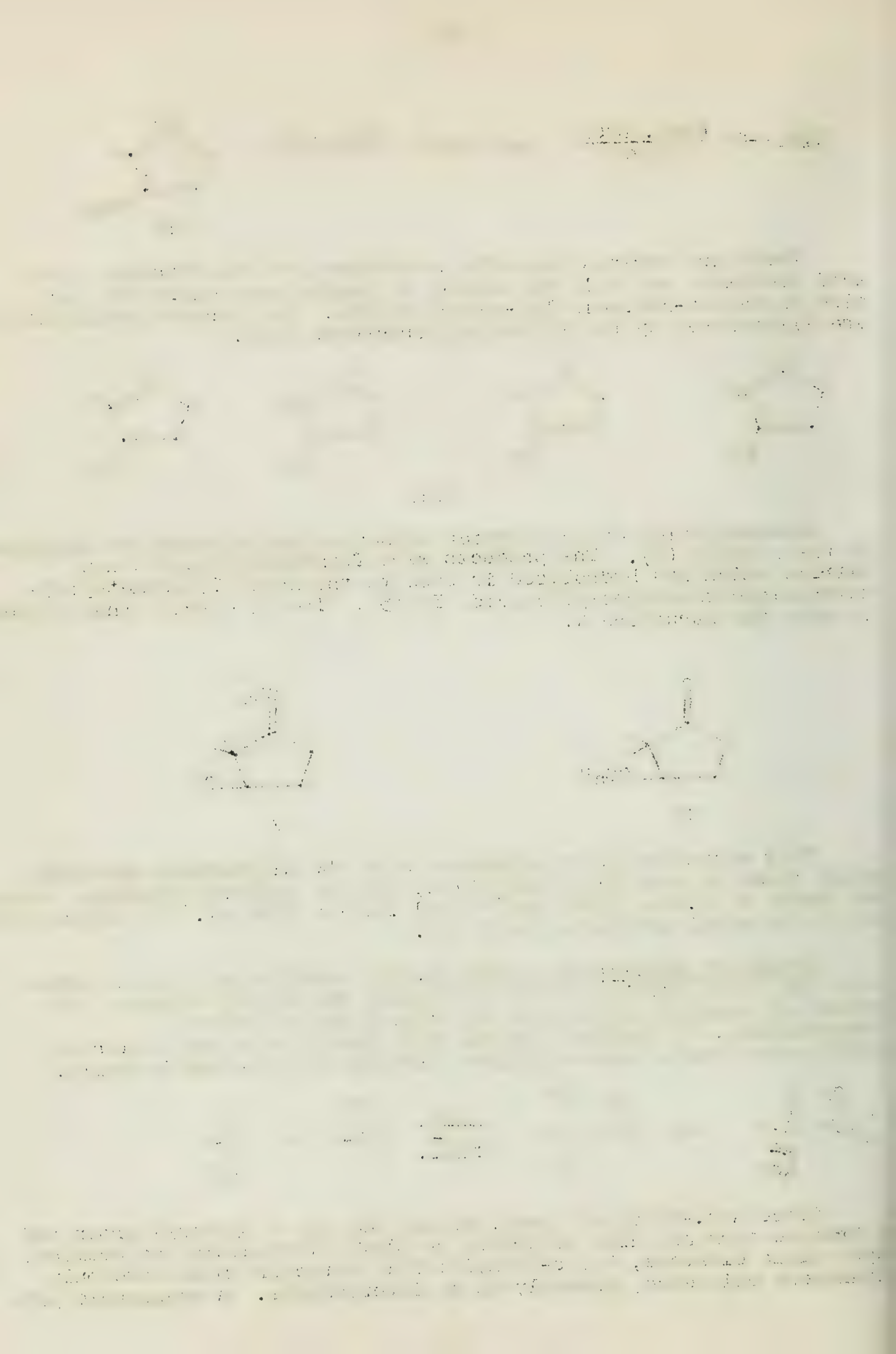
X

This structure is in agreement with the ultraviolet spectrum, which shows no selective absorption, and the infrared spectrum, which has peaks at 6.08μ (1645 cm.$^{-1}$) and 11.27μ (890 cm.$^{-1}$), indicative of the terminal methylene group (2).

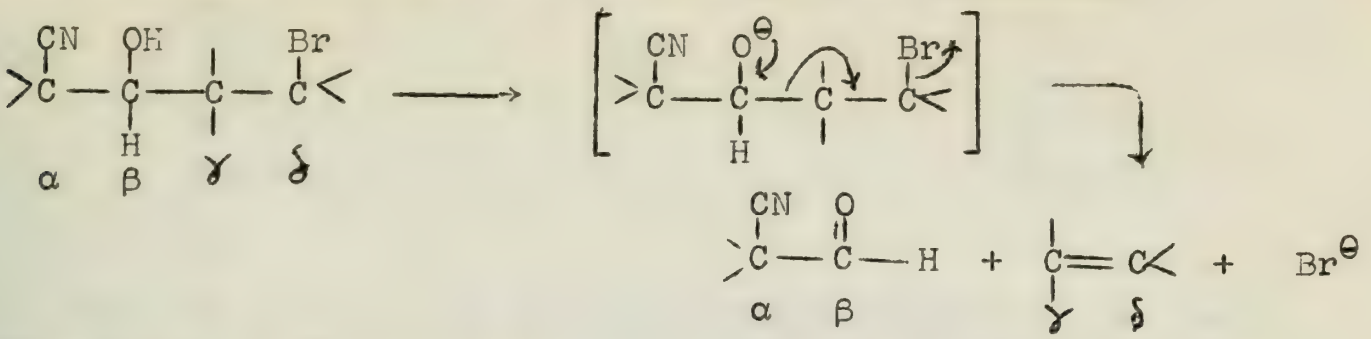
Structure Assignment of Anh.-2.--By correlating this information and incorporating it into a logical mechanistic scheme, the number of possible structures for Anh.-2 can be reduced tremendously. It appears logical that formic acid and a nitrile would arise from a base-catalyzed cleavage of a α-formylnitrile.



Since Anh.-2 has no formyl group, but has a hydroxyl group and a bromine atom and also generates an olefin (containing no bromine) upon basic cleavage, the α-formylnitrile structure must have only transient existence, probably as an intermediate. A reasonable path

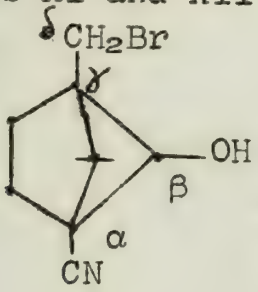


which will explain these changes is a 1,4-elimination attending the base-catalyzed cleavage of a β-hydroxyl-δ-bromonitrile.

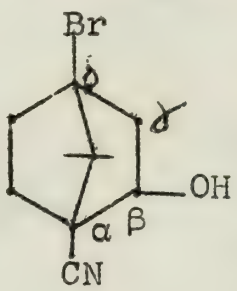


There are many analogies for this reaction (6); e.g., 3-bromo-2,2-dimethylpropanol is converted to isobutylene and formaldehyde by the action of a strong base.

Since a terminal methylene group is produced, either the γ- or the δ-carbon must contain two hydrogen atoms. Correlation of this information with the nitrile structure X suggests the two structures XI and XII for Anh.-2.



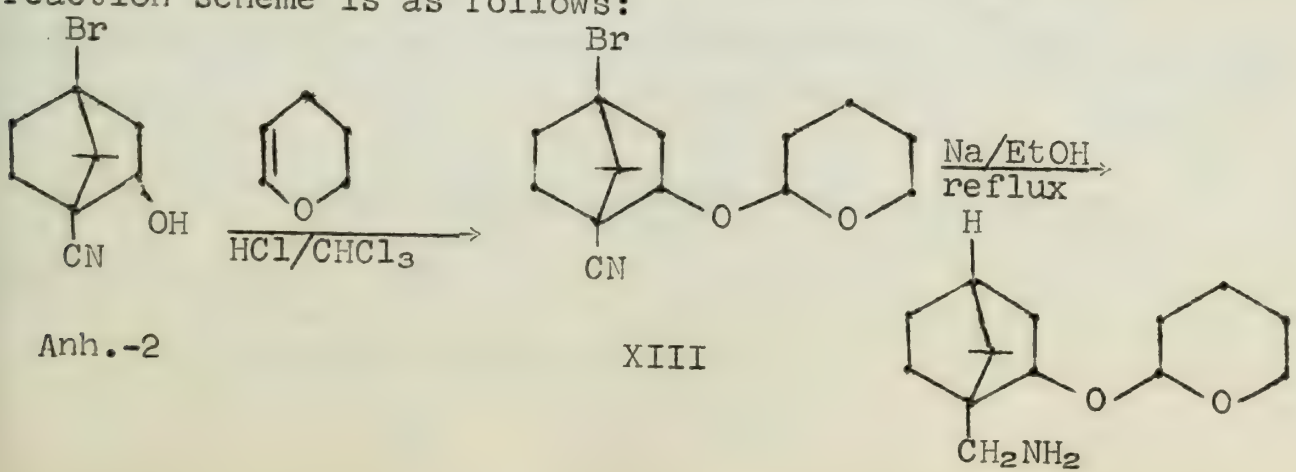
XI



XII

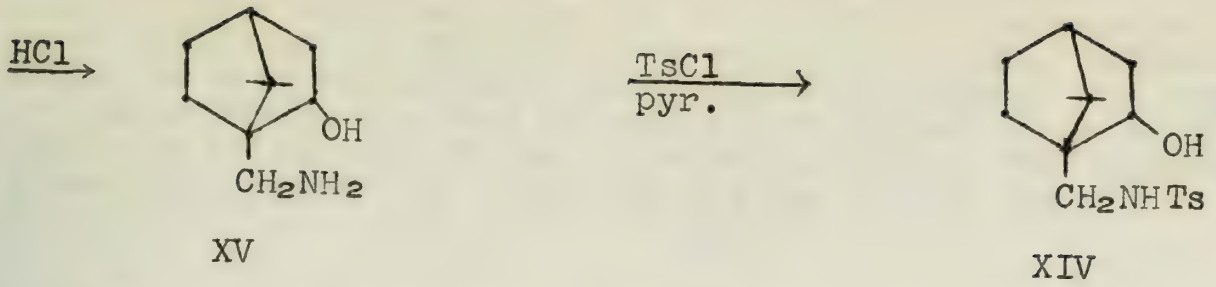
Since Anh.-2 is unaffected by hot $AgNO_3$ treatment (2), it appears that only structure XII (4-bromo-2-hydroxyapocamphane-1-carbonitrile) will accommodate all the chemical evidence presented.

Route to Anh.-2 derivatives via known compounds.--Due to the similarity of Anh.-2 to the camphor carbon-oxygen system, independent confirmation for structure XII is possible. Removal of the bridge-head bromine on Anh.-2 (along with nitrile reduction) can be accomplished by sodium in ethanol treatment, a process already proved successful for this purpose (7). To avoid the elimination reaction, however, the tetrahydropyranyl ether XIII was first made by reaction of Anh.-2 with dihydropyran in the presence of a few drops of HCl. The resulting ether was then reduced by the sodium in ethanol treatment, followed by HCl ether-cleavage. The resulting amine XIV, a green oil, was isolated as the tosylate XV (2). The reaction scheme is as follows:



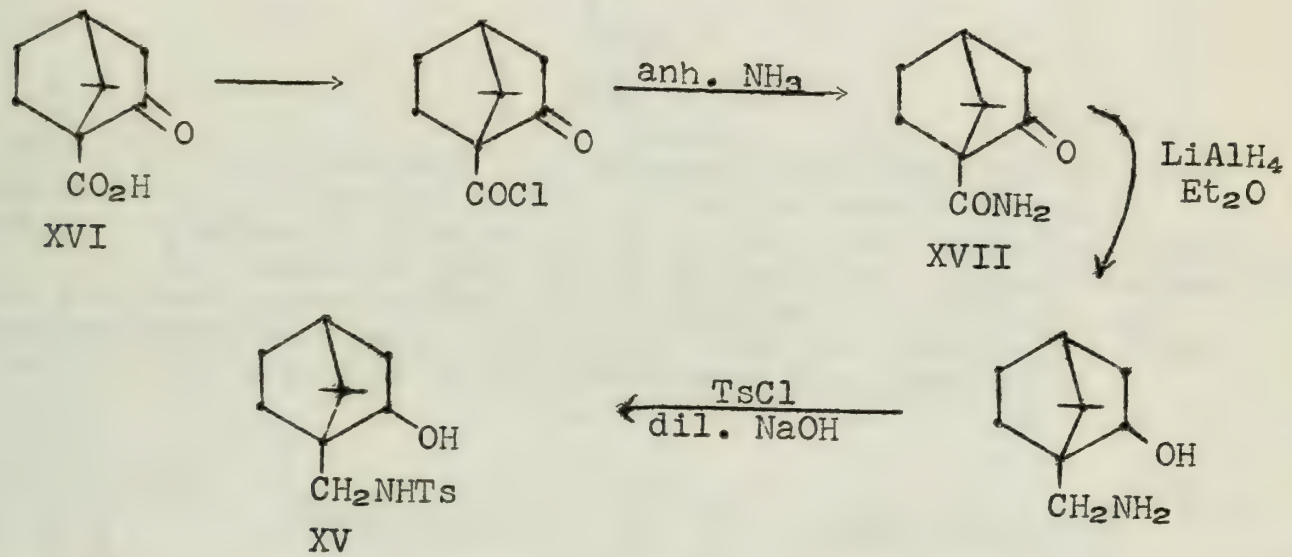
Anh.-2

XIII



XV XIV

The same product was obtained independently from the well-known ketopinic acid, XVI (8), by conversion to ketopinamide, XVII, reduction with $LiAlH_4$, and tosylation to XV (2).

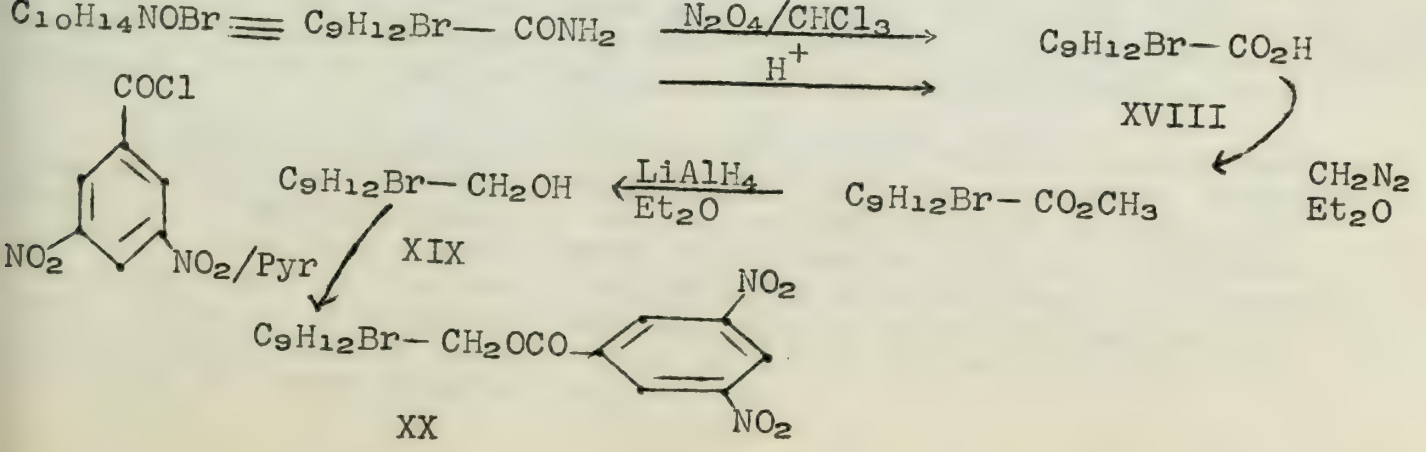


XVI XVII XV

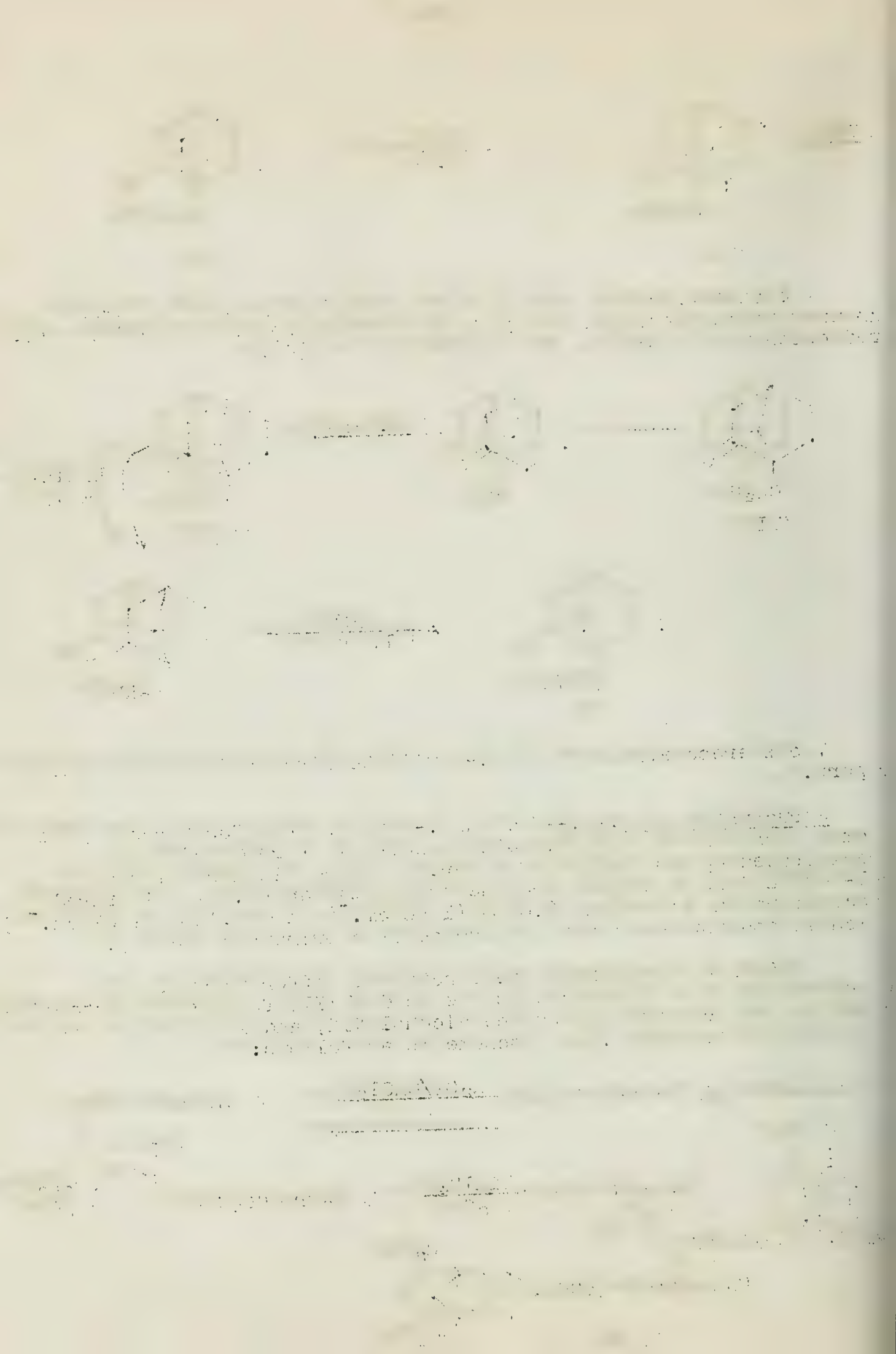
The stereochemistry of Anh.-2 will be discussed later in this report.

Structure of Anh.-3.--When Anh.-2 is treated for three days at room temperature with conc. H_2SO_4, Anh.-3 is formed and is precipitated upon addition of water. This new isomer melts at 201-202° and is stable to bromine and permanganate. Its infrared spectrum has a doublet at 6.08 μ (1650 cm.$^{-1}$) and 6.41 μ (1562 cm.$^{-1}$), which is consistent with the presence of a primary amide (2).

Proof of the primary amide function is afforded by its conversion with nitrous acid to the acid XVIII, followed by esterification and hydrogenolysis to the alcohol XIX, and isolation as the 3,5-dinitrobenzoate XX. The scheme is as follows:



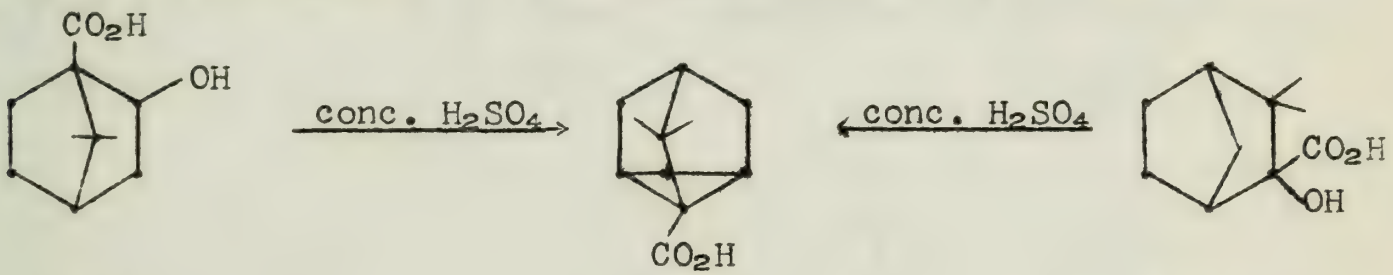
XX



From a consideration of the structure of the starting material Anh.-2, the empirical formula of the parent hydrocarbon can be determined. Upon replacement of the two methyls, the bromine, and the amide functions by hydrogen, the empirical formula becomes C_7H_{10}, which is in agreement with the tricyclene nucleus. An examination of the infrared spectrum reveals a peak around 10 μ (1000 cm.$^{-1}$), which is indicative of the cyclopropane ring. The investigators therefore suggest the structure XXI for Anh.-3 (2).

XXI

Although the structure XXI ~~precludes~~ ignores the possibility of a Wagner-Meerwein 1,2-methyl shift, it is the most reasonable structure, by analogy with suitable models. For example, tricyclenic acid, XXII, is formed in good yield by the conc. H_2SO_4 treatment of either 2-hydroxyapocamphane-1-carboxylic acid, XXIII (9), or α-hydroxycamphenilic acid, XXIV (10). In both cases, the final product is that expected if rearrangement does not occur.



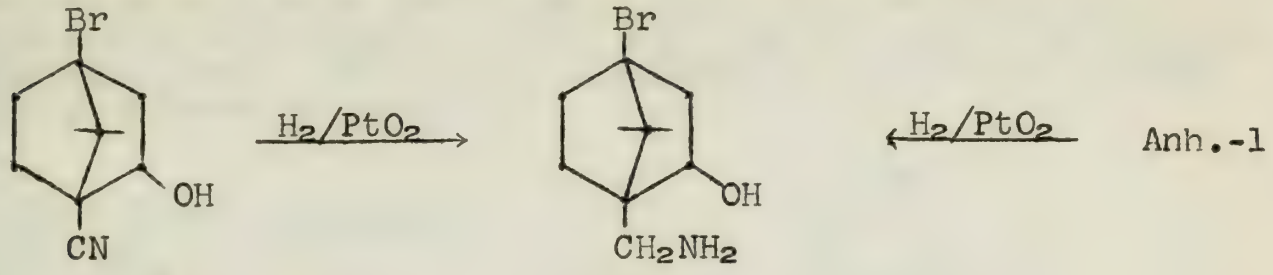
XXIII XXII XXIV

Since the structure XXI is closely related to tricyclenic acid, it seems possible that more positive evidence for that structure could be obtained by conversion of Anh.-3 to this acid or one of its derivatives.

Properties of Anh.-1.--Forster (1) reported that Anh.-1 was stable to cold HNO_3, to hot H_2SO_4, and to bromine in boiling pyridine. It does not melt, but decomposes at 210-220°, rearranging in part to form Anh.-2 (2). Like Anh.-2, Anh.-1 is optically inactive. In the ultraviolet, there is a single band at 225 mμ (ϵ = 2300); the infrared shows no hydroxyl or nitrile function, but a medium peak at 6.40μ (1565 cm.$^{-1}$) is stated by van Tamelen and Brenner (2) to be indicative of a carbon-nitrogen double bond.

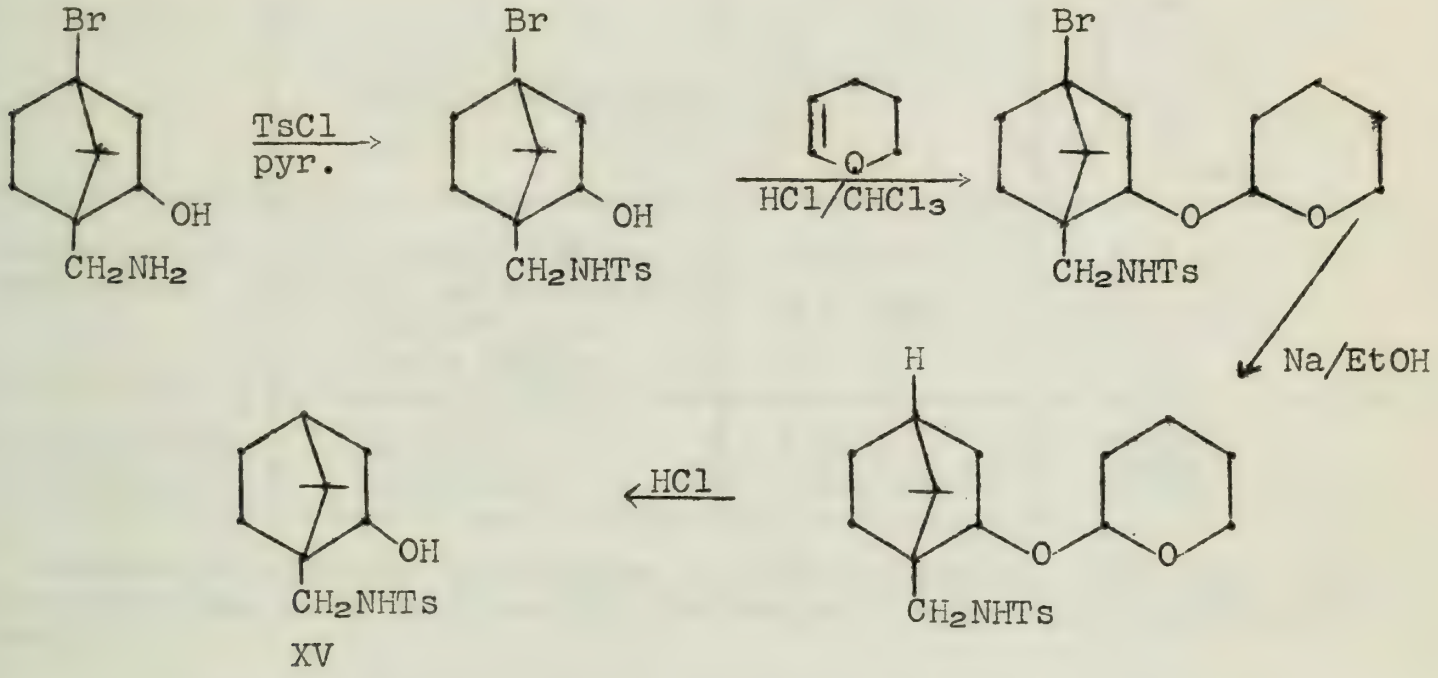
Structure of Anh.-1.--Since Anh.-1 is readily isomerized to Anh.-2, mild conditions were required for its structure determination Catalytic hydrogenation of Anh.-1 in the presence of PtO_2 in sulfuric acid and ethanol gave a tetrahydro-Anh.-1, which was characterized by its tosyl and benzoyl derivatives. In a control run, hydrogen was omitted and Anh.-1 was recovered unchanged. $LiAlH_4$ reduction of Anh.-1 also gave the tetrahydro-Anh.-1 in addition to some dihydro product (2).

Catalytic hydrogenation and $LiAlH_4$ reduction of Anh.-2 also gave the tetrahydro-Anh.-1, which was again characterized by its tosyl and benzoyl derivatives. The amino alcohol structure XXV is the only logical product of hydrogenation of Anh.-2.



Anh.-2 XXV

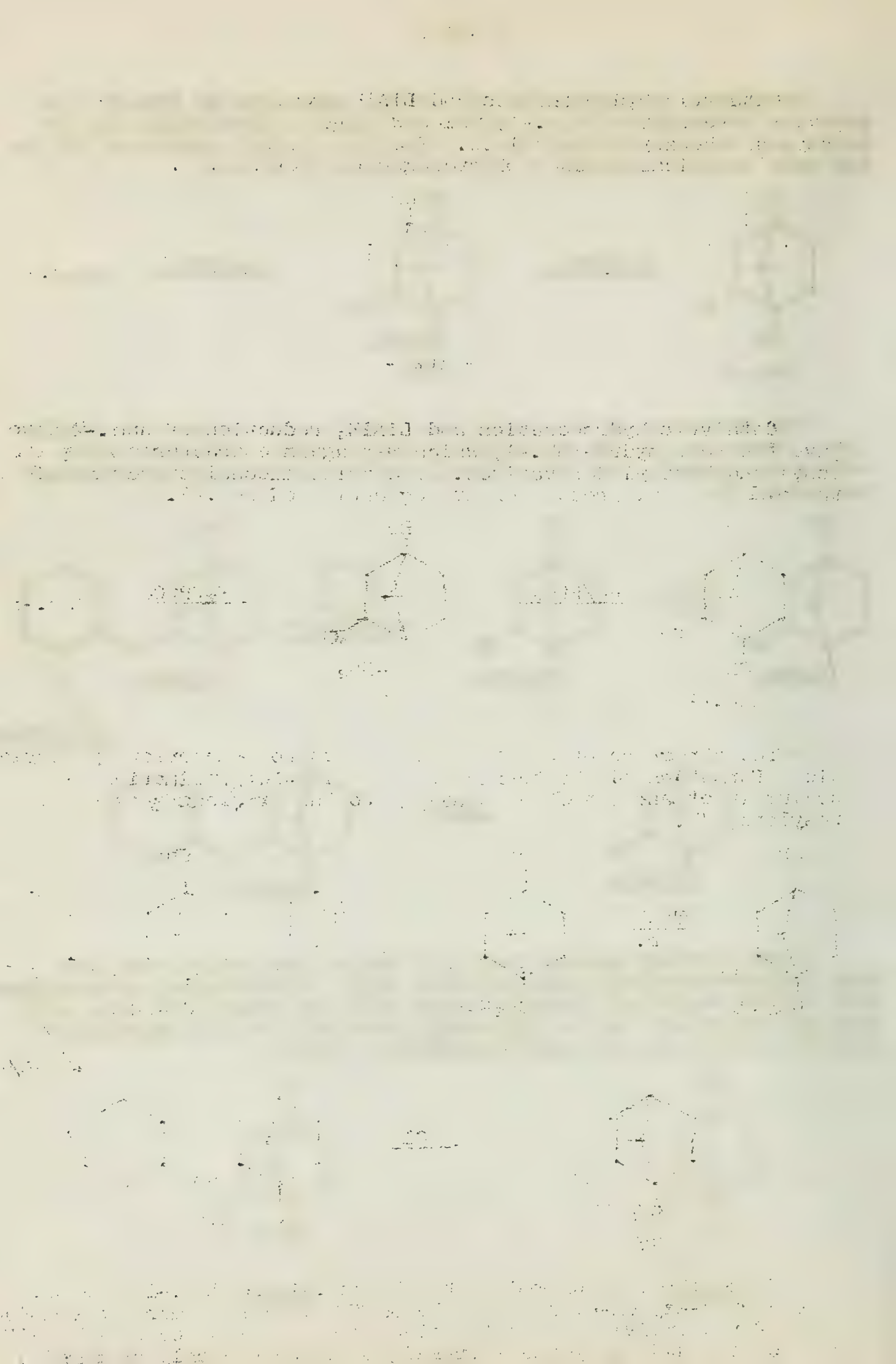
The structure of the amine was shown to be correct by tosylation, formation of the tetrahydropyranyl ether, reduction with sodium in ethanol, and HCl cleavage to the previously synthesized tosylate, XV.



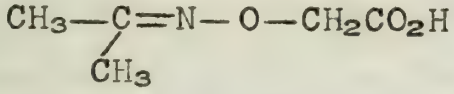
XV

These findings showed that both Anh.-1 and Anh.-2 have the same carbon-oxygen-nitrogen skeleton XXVI. Furthermore, a considera tion of the empirical formula, along with the absence of -NH, -OH, and -CN absorption in the infrared, leads to the only sterically possible structure, the Δ^2-isoxazoline XXVII.

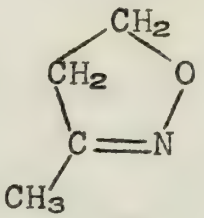
XXVI XXVII



Justification of the Proposed Structure for Anh.-1.--The investigators wished to support their proposed structure for Anh.-1 by comparing its spectral properties with those of model compounds. However, since the literature is lacking in examples of suitably substituted aliphatic $\triangle^2$-isoxazolines, they selected two very simple models acetoxime-O-acetic acid, XXVIII, and 3-methyl-$\triangle^2$-isoxazoline, XXIX. The latter is formed by the action of $HONH_2$ on methyl β-chloroethyl ketone.

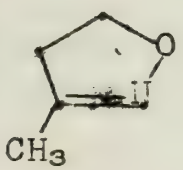
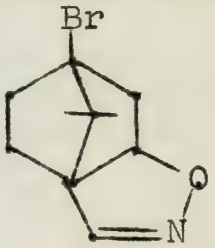


XXVIII



XXIX

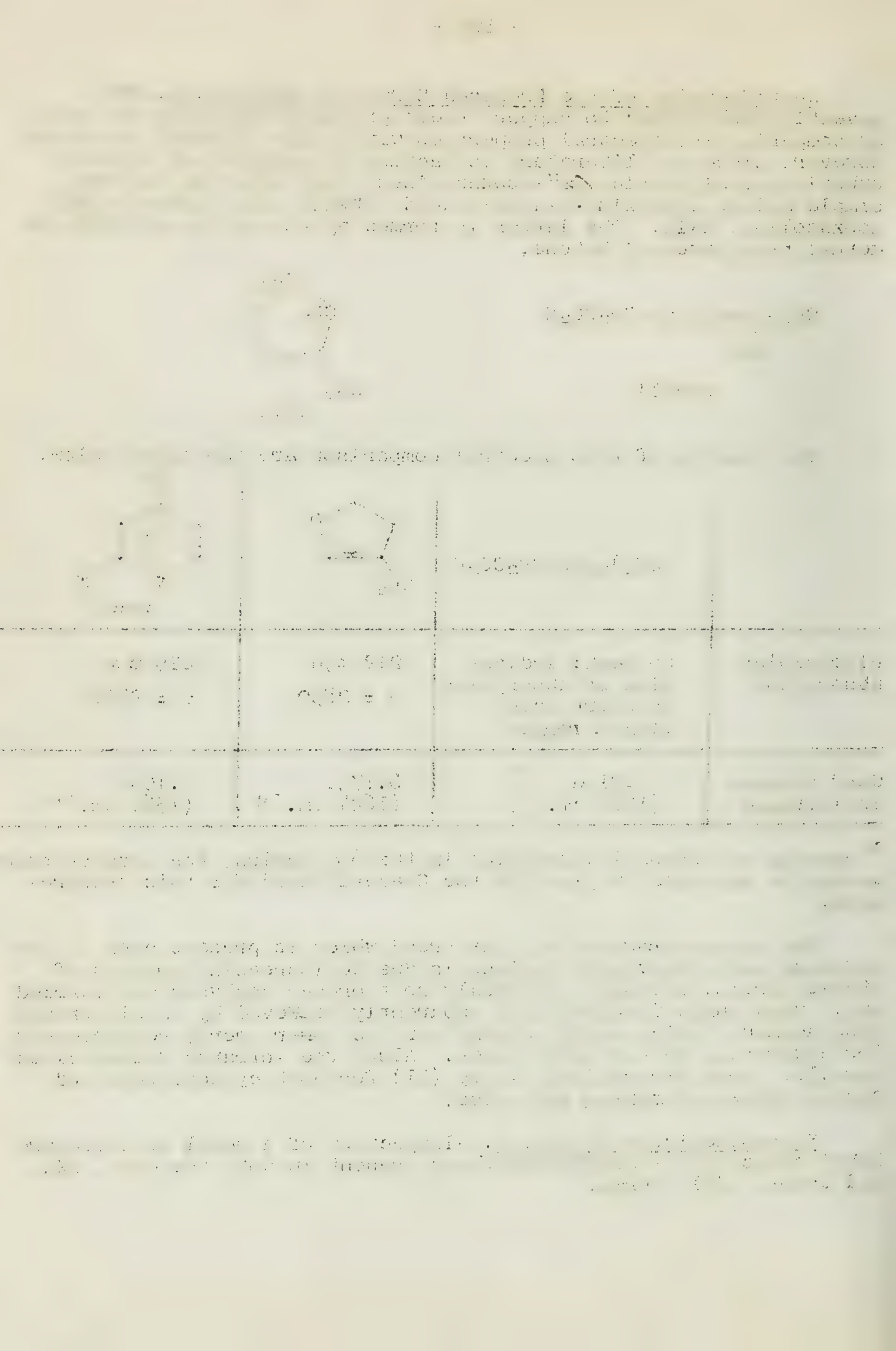
The results of this spectral comparison are tabulated below.

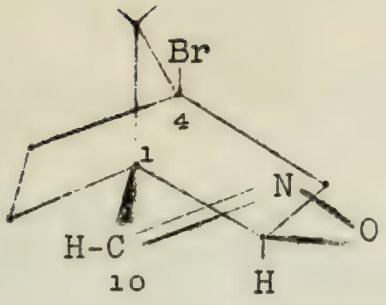
	$(CH_3)_2C{=}NOCH_2CO_2H$		
ultraviolet absorption	no peak; indication of absorption in short wave length region	212 mμ ε = 2830	225 mμ ε = 2300
C=N stretch in infrared	6.01 μ * (1665 cm.$^{-1}$)	6.17 μ (1624 cm.$^{-1}$)	6.40 μ (1564 cm.$^{-1}$)

* Because of carbonyl absorption in the 6 μ region, the unsubstituted acetoxime was used in place of the O-acetic acid for this measurement.

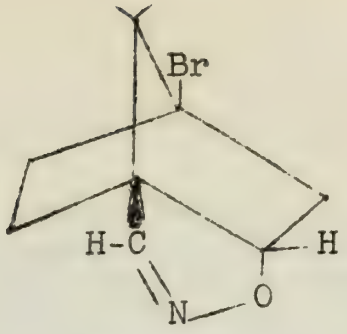
The authors propose that the trend which is present both in the infrared and ultraviolet regions is due to increasing amounts of steric strain, although admittedly no thorough analysis was carried out. Bond angle distortion is apparently relieved by an electronic displacement, which could account for the lower energy requirements for absorption in the ultraviolet. Also, the infrared values cited parallel those reported by Witkop (11) for both cycloalkenes and cyclic imines of medium ring size.

Stereochemistry of Anh.-1.--Inspection of a model of structure XXVII shows that a decided strain is present in both the exo-, XXX, and endo-, XXXI, forms.





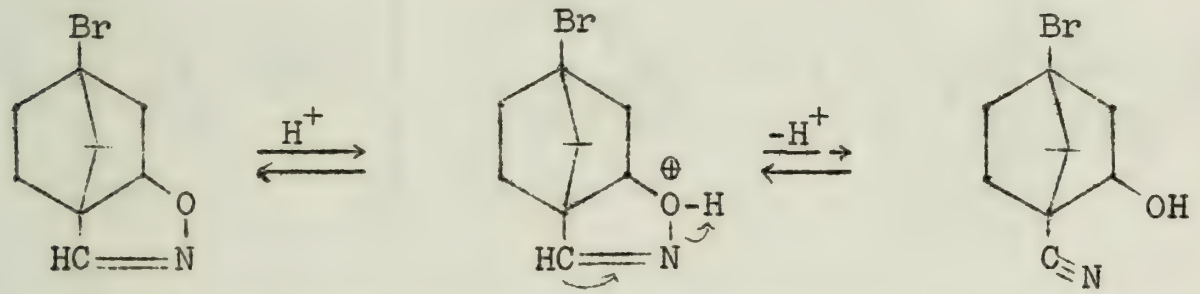
XXX



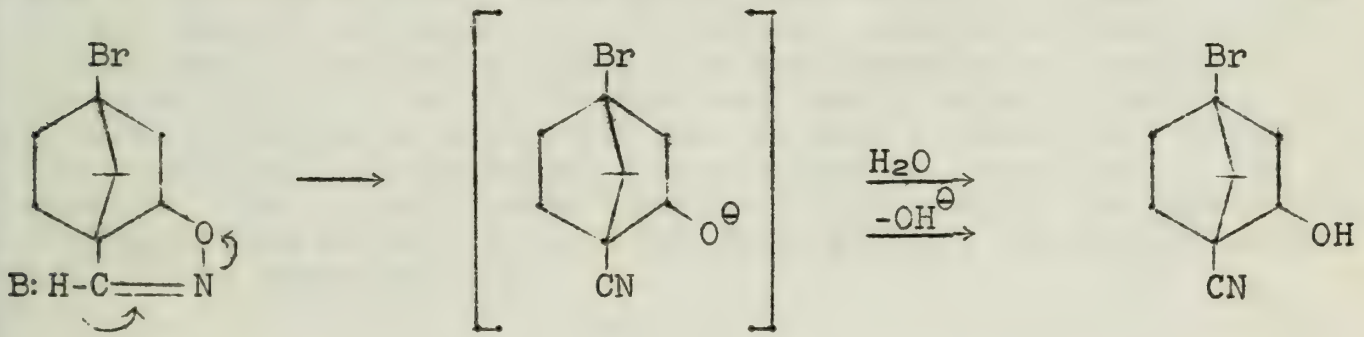
XXXI

However, there is a lack of symmetry in this series due to the presence of the one-carbon bridge. The 10-carbon and the bromine are raised slightly (in the direction of the one-carbon bridge) from the axis through the 1- and 4-carbons. This makes the exo side of the two carbon bridge more accessible than the endo, and therefore, the exo form of Anh.-1 is less strained. Arguing on this basis, van Tamelen and Brenner proposed that Anh.-1 was the exo-Δ^2-isoxazoline XXX (2).

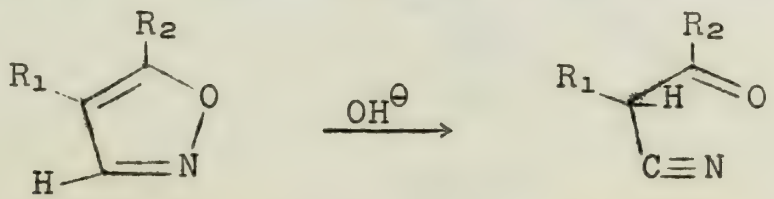
Stereochemistry of Anh.-2.--To obtain information about the configuration of Anh.-2, we must consider the mechanism by which Anh.-1 isomerizes to Anh.-2. A reasonable acid-catalyzed mechanism is:



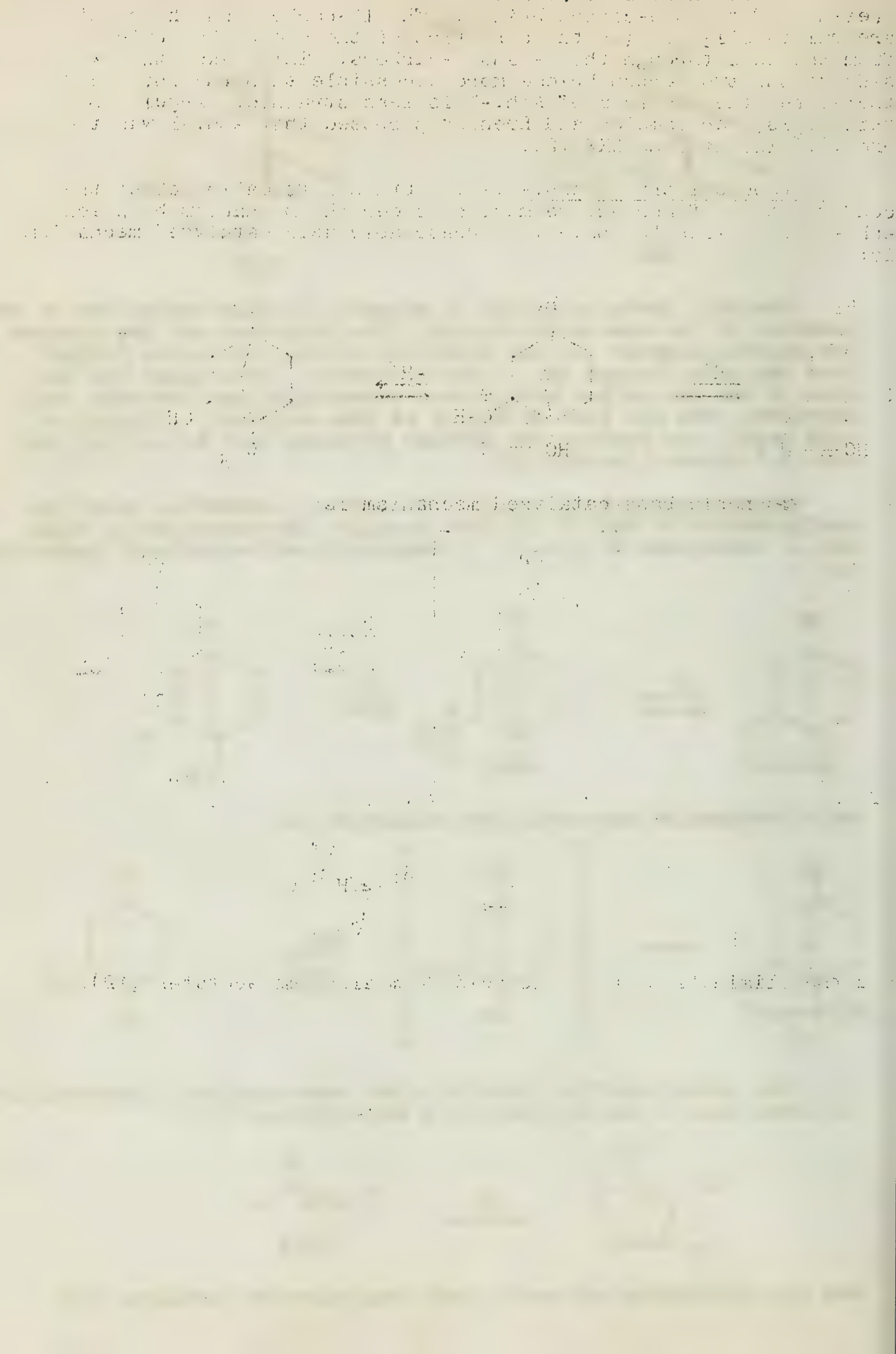
and a reasonable base-catalyzed mechanism is:

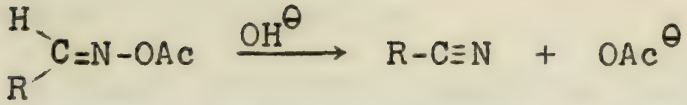


The latter reaction parallels the base-catalyzed isomerization of isoxazoles to the corresponding ketonitriles (12),

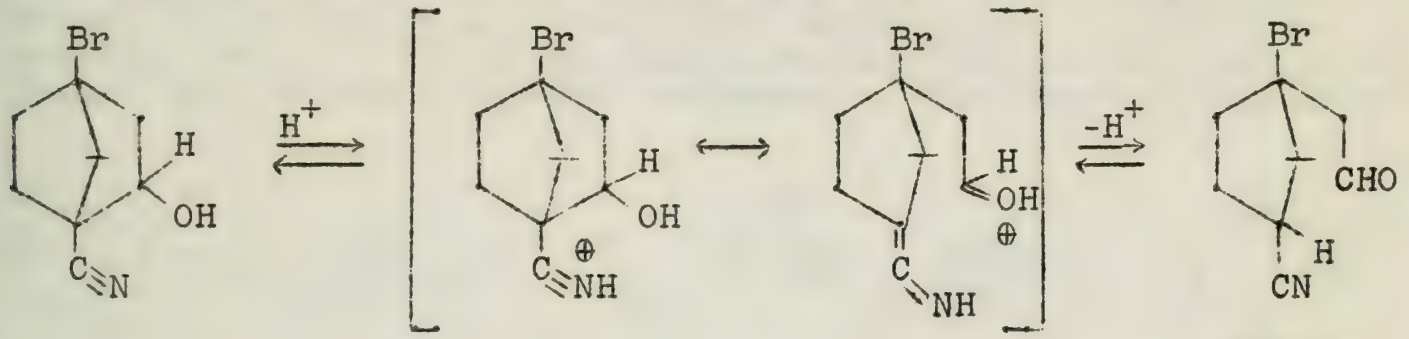


and the elimination of acetic acid from aldoxime acetates (12).

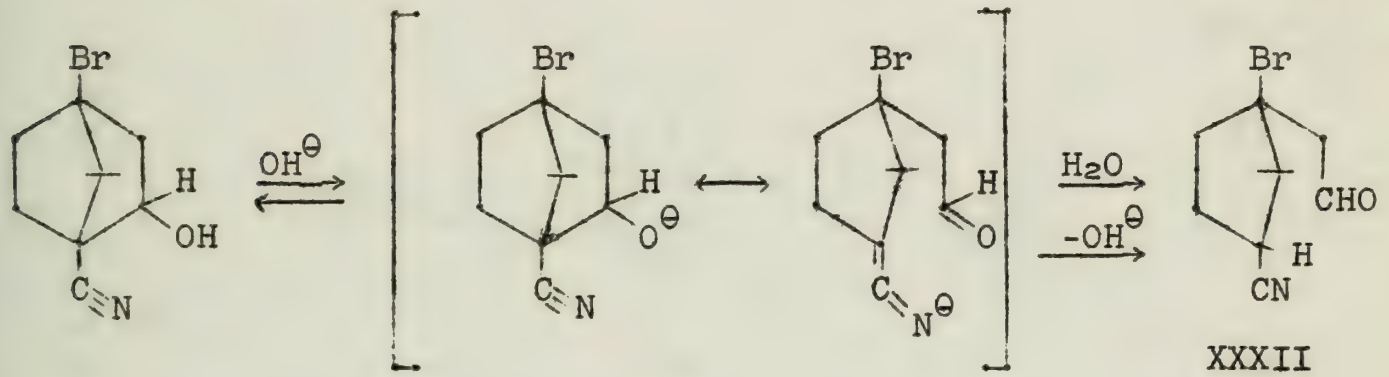




Both possible mechanisms assume no equilibration at the oxygen-containing carbon. However, a closer look at the structure of Anh.-2 reveals the presence of a β-hydroxynitrile moiety which, analogous to the reverse aldol-condensation, has the possibility of existing in equilibrium with the corresponding open chain aldehyde XXXII in either acid or base by the following processes:

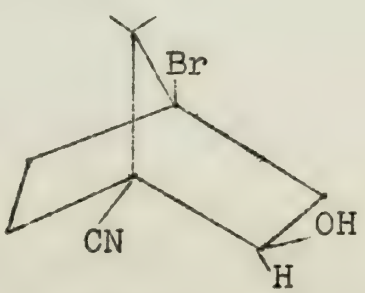


XXXII

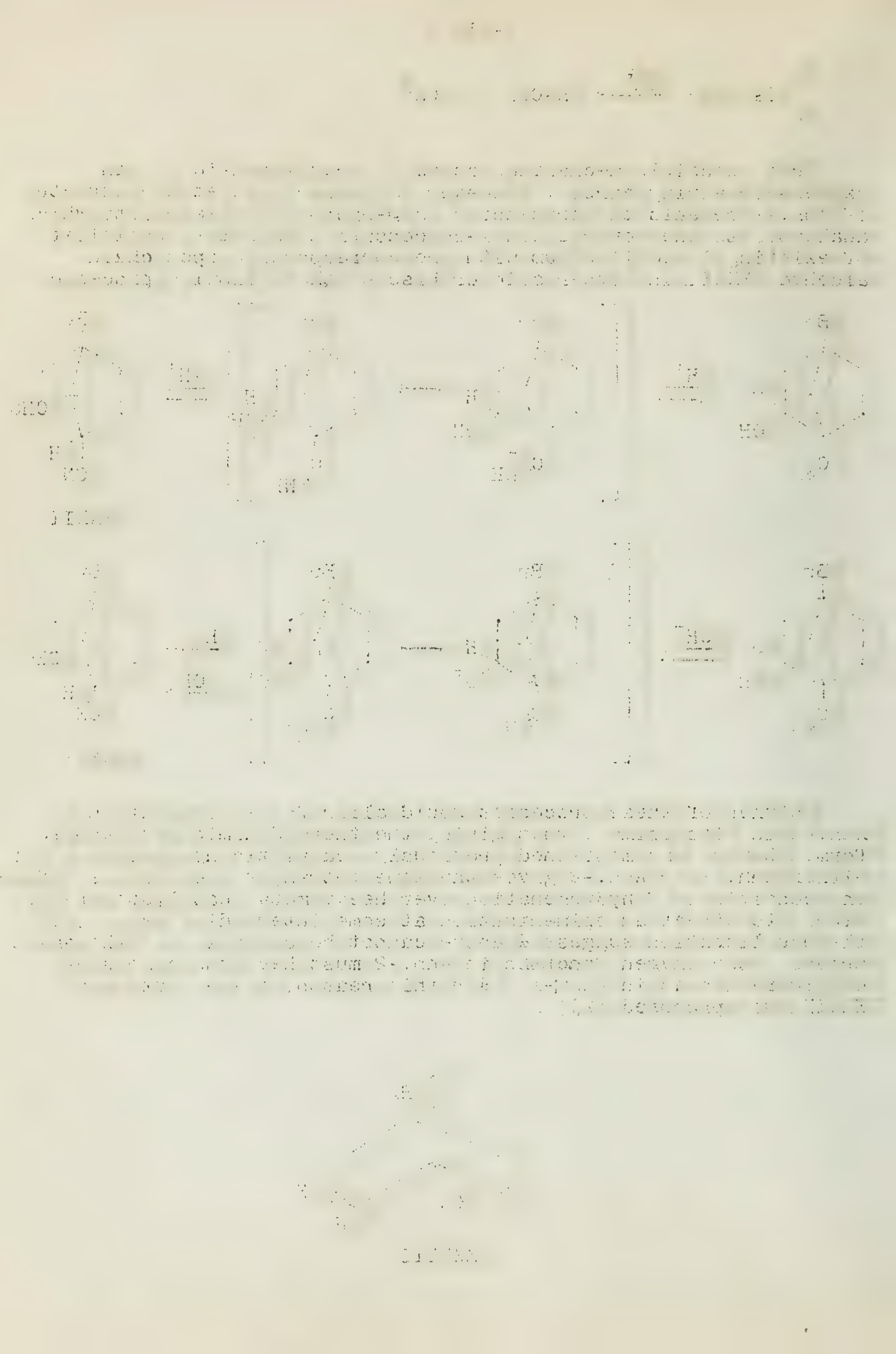


XXXII

Either of these processes would allow for equilibration of Anh.-2 and its epimer, thus giving the thermodynamically favored form. However as mentioned previously, catalytic hydrogenation of either Anh.-1 or Anh.-2 gives the same tetrahydro derivative. Since the conditions of hydrogenation over heavy metal catalysts are not likely to effect an epimerization at some intermediate stage, and the equilibration suggested above cannot be operative on the amine product, the oxygen function in Anh.-2 must have the same steric configuration as in Anh.-1. For this reason, the exo structure XXXIII was proposed (2).

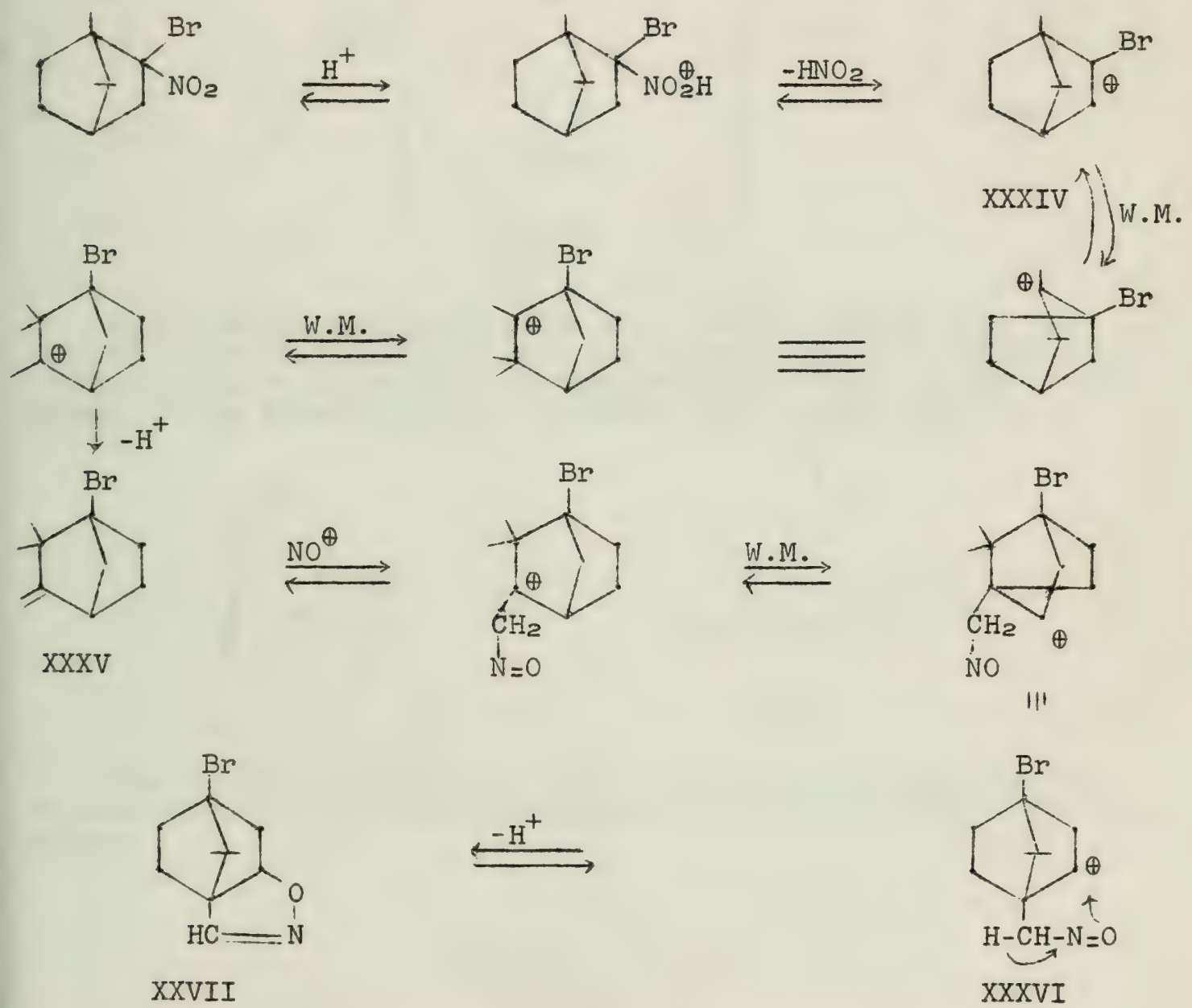


XXXIII



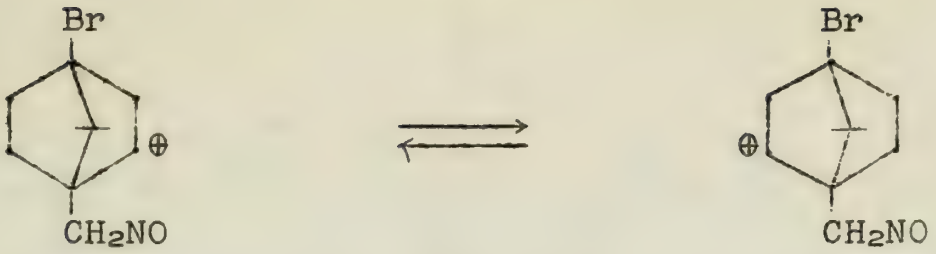
MECHANISM OF DEHYDRATION

Although at first glance the dehydration of bromonitrocamphane, I, appears to involve a random reshuffling of the skeleton, a reasonable mechanism for the process can be written. It involves protonation of the nitro group followed by elimination of the elements of nitrous acid to generate the carbonium ion XXXIV. A pair of Wagner-Meerwein shifts are followed by a deprotonation to form the olefin intermediate XXXV. Nitrosation by a suitable nitrosating agent ($NO^{\oplus}$ is used for simplicity) is followed by 1,2 rearrangement to the nitroso compound XXXVI. At this point the system can undergo ring closure with deprotonation to the final product, Anh.-1. This final step parallels the tautomerization of primary and secondary nitroso compounds to the corresponding oximes.

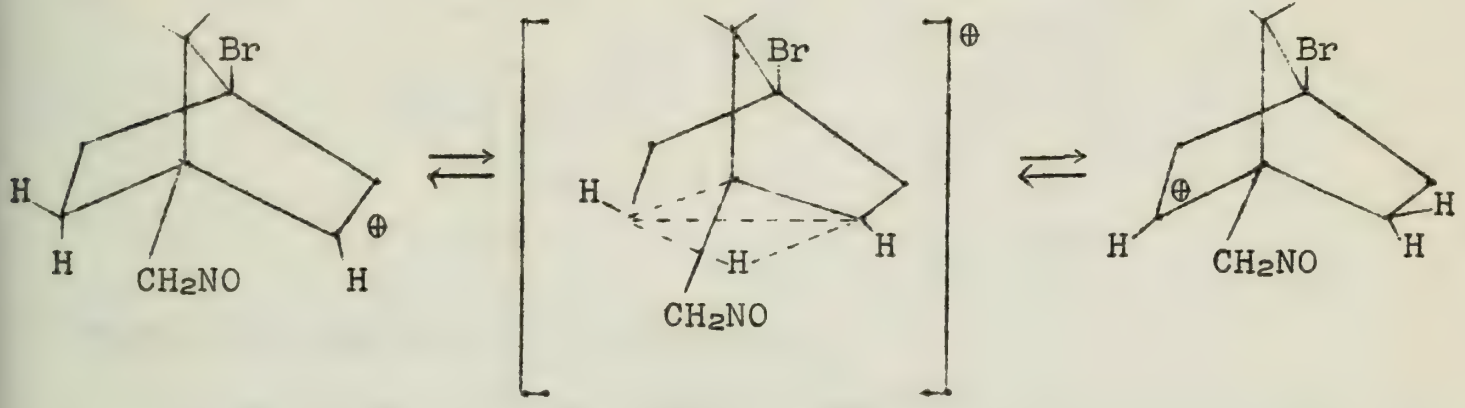


All of these steps have suitable analogies, although the overall change appears to have no known parallel.

Since Anh.-1 and Anh.-2 are both optically inactive as opposed to the highly active bromonitrocamphane, an inversion at some intermediate stage must have occurred. This is best accounted for by 2,6-hydrogen transfer in the nitroso structure XXXVI.

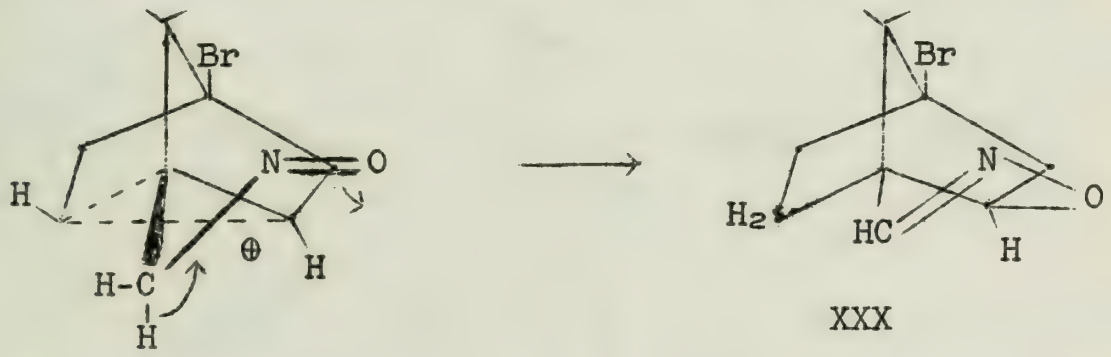


The proposed equilibrium can be explained either by simple enantiomer production, or by way of the Roberts nortricyclonium ion XXXVII (13).



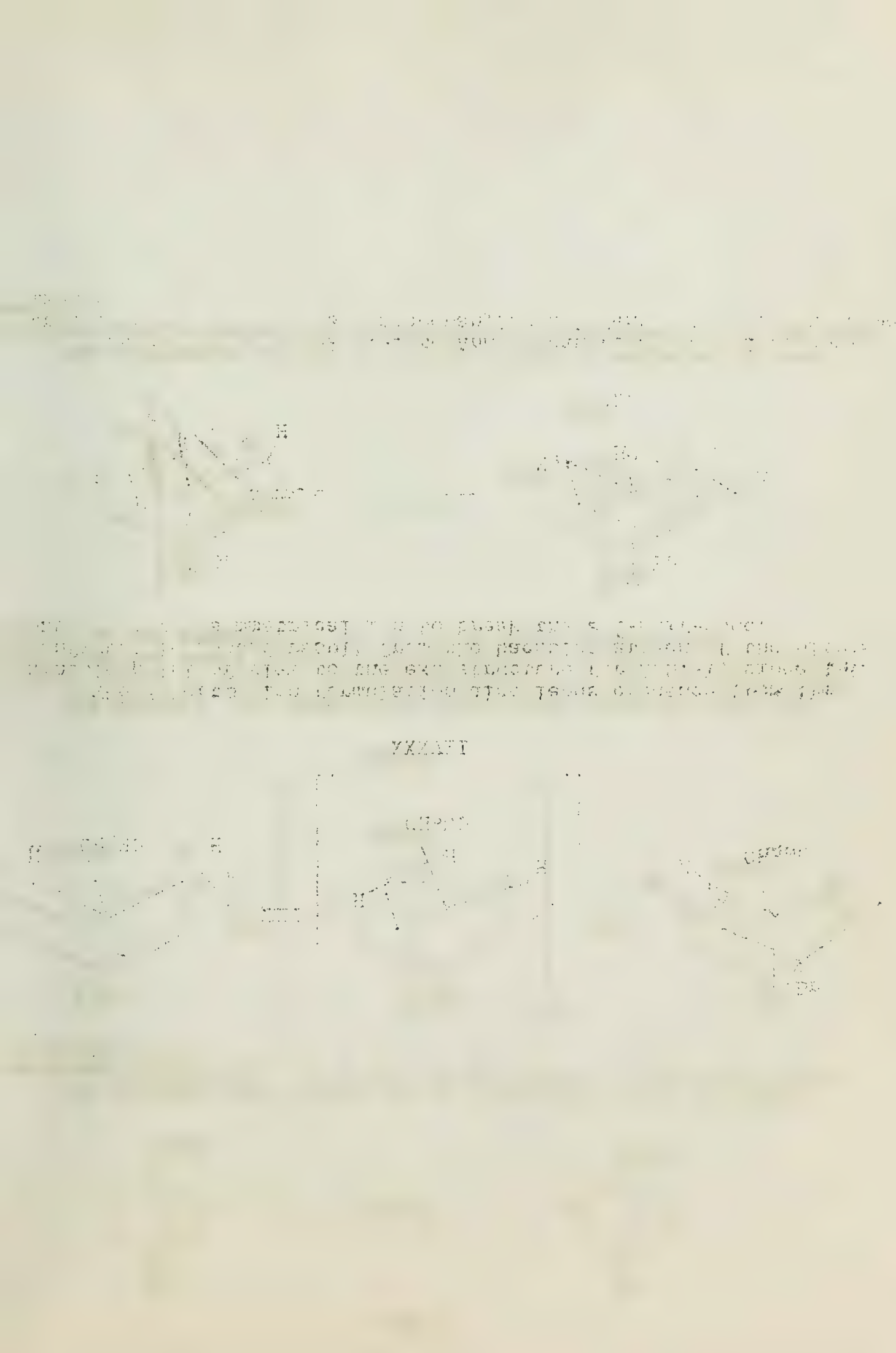
XXXVII

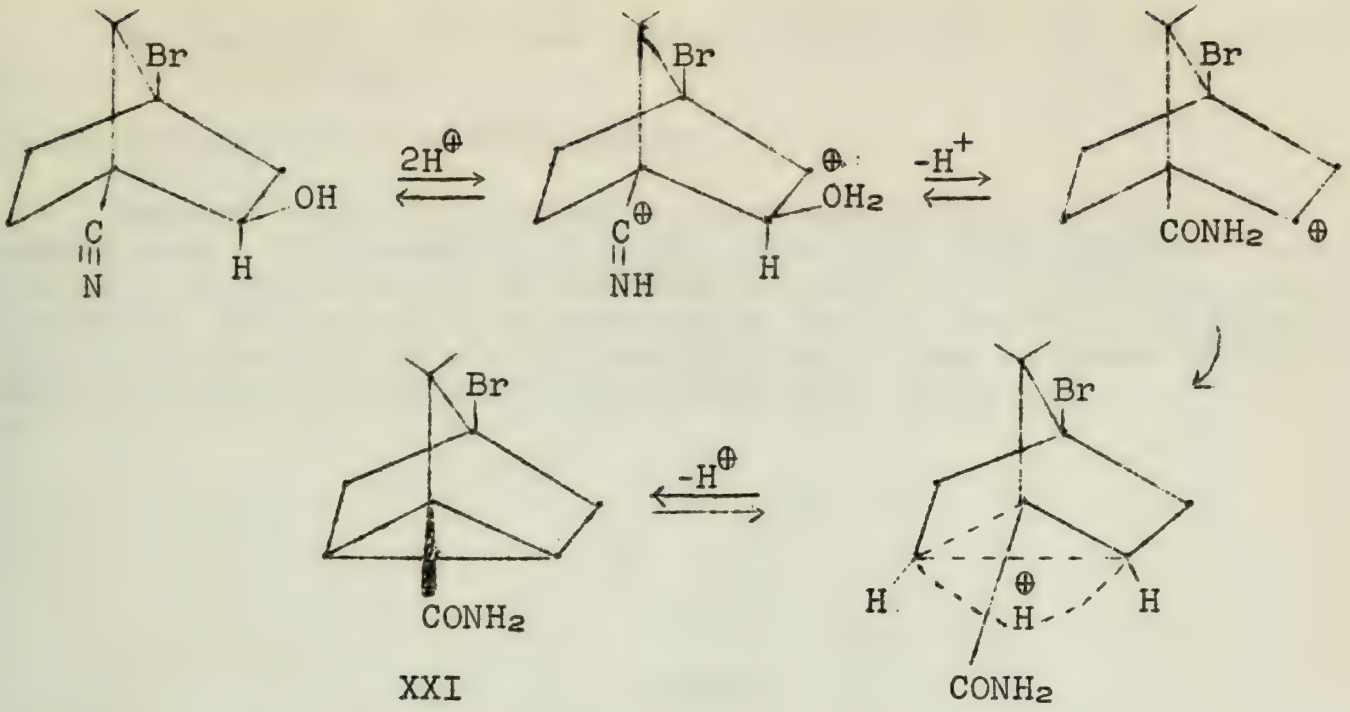
The Roberts ion formulation also lends credence from the kinetic point of view to the exo structure for Anh.-1, since this configuration would result from the backside attack of the nitroso oxygen on the symmetrical ion to break the 2,6-half-bond.



XXX

The conversion of Anh.-2 to Anh.-3 can be explained by controlled nitrile hydrolysis accompanying 2,6-dehydration in the same manner:

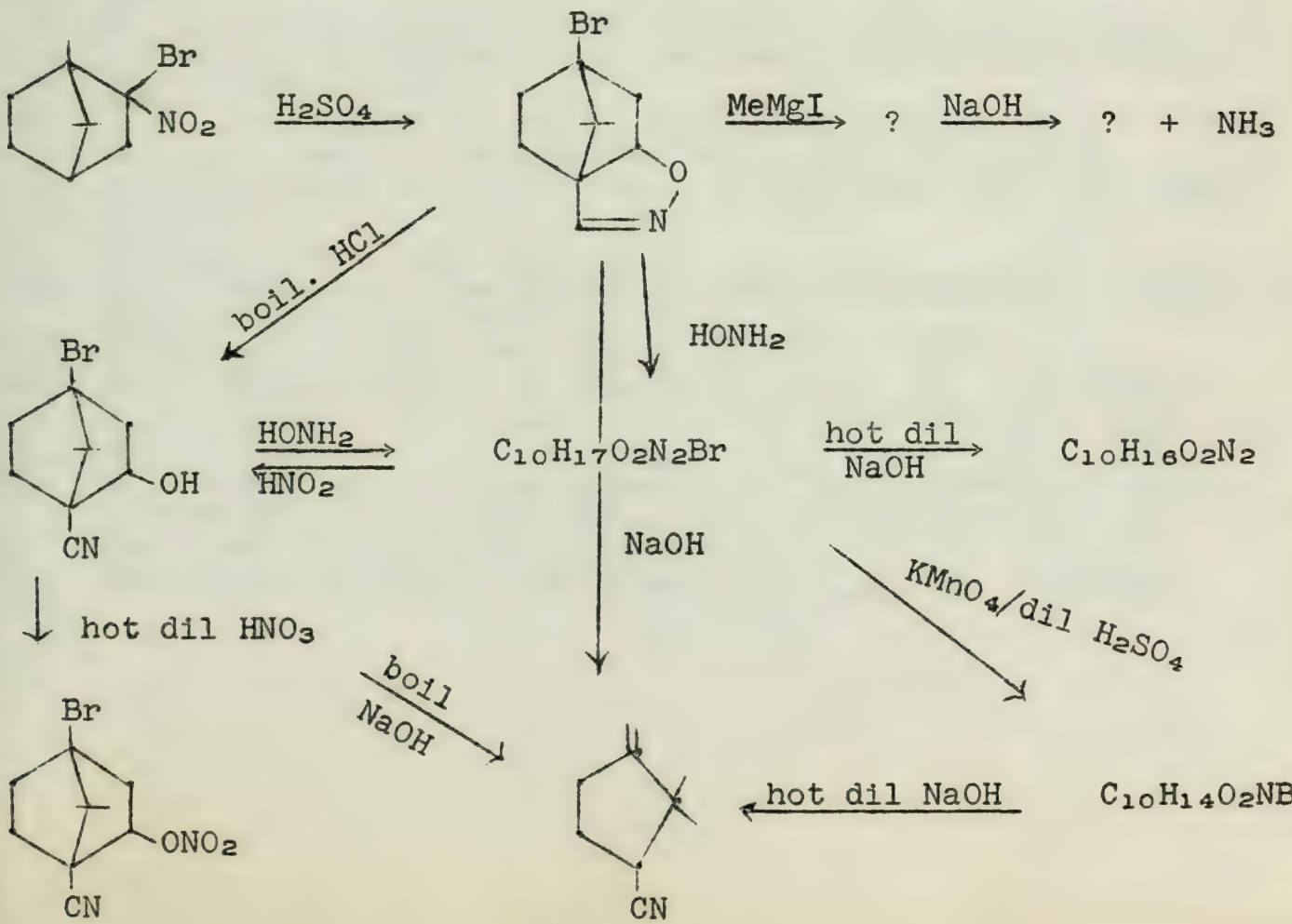




XXI

OTHER REACTIONS OF ANH.-1 AND ANH.-2

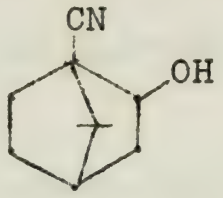
In addition to those reactions mentioned by van Tamelen and Brenner, there are several involving Anh.-1 and Anh.-2 which have been ignored by these investigators. Forster (1,3) and Ginnings (4) had carried out various reactions in attempts to elucidate the structures of these compounds. For the sake of completeness, these reactions are summarized in a brief outline. This outline is a corrected form of that which is in Elsevier's "Encyclopedia of Organic Chemistry" (14).



The empirical formulas indicate compounds whose structures have not been determined.

POSSIBLE EXTENSION OF THIS SERIES

Similar reactions in the terpene series are yet to be investigated. For example, in 1902, Konovalov (15) reported the conversion of camphene by dilute HNO_3 at 100° to an oxidation product $C_{10}H_{15}NO$, but failed to characterize the product. It is possible that this product is the hydroxynitrile in the camphane series, XXXVIII, since it is similar in many ways to Anh.-2.



XXXVIII

BIBLIOGRAPHY

1. M. O. Forster, J. Chem. Soc., 75, 1141 (1899).
2. E. E. van Tamelen and J. E. Brenner, J. Am. Chem. Soc., 79, 3839 (1957).
3. M. O. Forster, J. Chem. Soc., 79, 108 (1901); 79, 653 (1901); M. O. Forster and W. Robertson, ibid., 79, 1003 (1901).
4. P. M. Ginnings with W. A. Noyes, J. Am. Chem. Soc., 44, 2567 (1922); P. M. Ginnings, Ph.D. Thesis, University of Illinois, 1922.
5. W. H. Perkin, Jr., and J. F. Thorpe, J. Chem. Soc., 85, 138 (1904); C. S. Gibson, K. V. Hariharan, and J. L. Simonsen, ibid., 3009 (1927).
6. C. A. Grob and W. Baumann, Helv. Chim. Acta., 38, 594 (1955).
7. G. Komppa and T. Hasselstrom, Ann., 496, 164 (1932).
8. P. D. Bartlett and L. H. Knox, J. Am. Chem. Soc., 61, 3184 (1939).
9. P. Lipp, Ann., 402, 343 (1902).
10. J. L. Simonsen, "The Terpenes," Vol. II, Cambridge University Press, Cambridge, 1932, p. 242.
11. B. Witkop, J. Am. Chem. Soc., 78, 2873 (1956).
12. W. S. Johnson and W. E. Shelberg, ibid., 67, 1745 (1945).
13. J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., ibid., 76, 4501 (1954).
14. E. Josephy and F. Radt, Elsevier's "Encyclopedia of Organic Chemistry", Series III, Vol. 12A, Elsevier Publishing Co., Inc., New York, N. Y., 1948, p. 600.
15. Konovalov, J. Russ. Phys. Chem. Soc., 34, II, 43 (1902).

THE ADDITION OF PHOSPHORUS HALIDES TO MULTIPLE BONDS

Reported by R. T. Hawkins March 17, 1958

I. INTRODUCTION

Because of the increasing importance of phosphonic acids, esters, and amides, the preparations of their precursors, the phosphonyl halides, are of interest to the organic chemist. One of the techniques of phosphonation is the addition of phosphorus halides to unsaturated systems. This report will discuss the addition of phosphorus halides to carbon-carbon and carbon-oxygen multiple bonds. Other related additions and substitutions will be mentioned only briefly.

II. ADDITIONS TO ETHYLENIC AND ACETYLENIC LINKAGES

A. Addition of PCl_5 to olefins

The first documented evidence for the addition of PCl_5 to a double bond dates from 1891 (1). By 1910, Harnist recognized the addition of PCl_5 to olefins (2), and shortly afterward further reports appeared (3, 4, 5). With the researches of Bergmann and Bondi (6, 7, 8), the addition of PCl_5 to acetylenes as well as to olefins was well established.

The usual procedure for conducting the reaction is the following (9). An excess of the unsaturated hydrocarbon is added with cooling to a stirred suspension of finely divided PCl_5 in an inert solvent such as benzene. The adduct, a chloroalkylphosphorus tetrachloride, may be removed by filtration or poured into ice water. Normally no attempt is made to isolate the pure adduct because it and the residual PCl_5 possess similar solubility characteristics. The phosphonic acid is recovered by removal of the benzene solvent from a hydrolyzed reaction mass. Generally the hydrolytic treatment is sufficient to dehydrohalogenate the final product, yielding an unsaturated phosphonic acid.

$$R_2C{=}CH_2 + ClPCl_4 \xrightarrow{\text{cold}} R_2CCl{-}CH_2PCl_4 \xrightarrow[-HCl]{H_2O} R_2C{=}CHPO_3H_2$$

Loss of the elements of hydrogen chloride upon hydrolysis of the adduct is especially facile with aryl-substituted olefins, but alkyl-substituted olefins may tend to retain the carbon-bonded chlorine until treated with caustic (10).

Some limitations of the reaction are known. Obviously, the reaction cannot be used with olefins containing hydroxyl, amino, mercapto, or carboxyl groups (9, 11). The reagent adds in the sense $Cl{-}PCl_4$ to terminal olefins (6). The only known exception to the requirement for a 1,2-olefin is indene, which adds PCl_5 apparently because of its extreme reactivity and its "sterically exposed double bond" (3, 6, 9, 11). However, some ethylenic systems with double bonds not sterically hindered fail to yield phosphonic acids. For example, 1,4-diphenyl-1,3-butadiene and 1-phenyl-1,3-pentadiene do not add PCl_5; and allylbenzene, α-benzylstyrene, and 1,1-diphenyl-1-propene yield no phosphonic acids (7, 11). Other compounds failing to undergo the reaction have been tabulated (11). 1,3-Butadiene,

1-phenyl-1,3-butadiene (in yields up to 88%), and 4-methyl-1,3-pentadiene undergo the reaction (9, 12), probably by 1,2- or 1,4-addition (which would yield the same acids upon hydrolysis). Some evidence for terminal addition is the fact that PCl_5 does not add to the 1,4-disubstituted-1,3-butadienes. Although the phosphorus atom usually appears in the final product attached to the α-carbon atom of the original olefin (hence a 1-phosphonic acid), some patents have claimed 1,2-additions wherein a 2-phosphonic acid may be produced from olefins and 1,3-diolefins (12, 13, 14, 15). Such additions have been disproved for olefins but not for diolefins, except by analogy. Kosolapoff (10) showed that the addition of PCl_5 to 1-butene yielded, upon hydrolysis, 1-butenyl-1-phosphonic acid, not a 2-phosphonic acid as elsewhere claimed (13). Upon reduction, the unsaturated phosphonic acid yielded an acid identical to authentic butyl-1-phosphonic acid. Ozonolysis of the unsaturated phosphonic acid failed to yield any formaldehyde as would be expected from 1-butenyl-2-phosphonic acid.

The results of the addition of PCl_5 to substituted styrenes display the so-called ortho effect (7, 9, 16). While ortho-substituted styrenes bearing bulky groups may still add PCl_5, the yields may also be very low. For example, the presence of an ortho-t-butyl group in styrene compared to an ortho-methyl group resulted in one-sixtieth the yield. The ortho effect is said to be particularly noticeable with 1,1-diarylethylenes.

Chlorine may be passed into a mixture of an olefin and PCl_3 to yield the same products as are obtained when PCl_5 is used; also, some olefin dichloride is obtained (9). The phosphorus halides are said to compete successfully for the olefin, yielding reasonable amounts of organophosphorus products (16). The reaction has not been explored in detail but may entail the in situ preparation of PCl_5.

The intermediate chloroalkylphosphorus tetrachloride is usually converted to a phosphonyl halide with, for example, acetic acid; or transformed directly into an unsaturated phosphonic acid by hydrolysis, an ester by alcoholysis, or an amide by ammonolysis or aminolysis. The yields are greater than 50% in most cases (9). It should be noted that other operations upon the chloroalkylphosphorus tetrachloride have also been explored. For example, PCl_5 was caused to react with diisobutylene to yield an adduct which was dehydrohalogenated in vacuo, and then reduced with phosphorus in the presence of a catalyst (17). The scheme may be represented thus:

$$RCH{=}CH_2 + PCl_5 \longrightarrow RCHClCH_2PCl_4 \xrightarrow[-HCl]{} RCH{=}CHPCl_4$$

$$3\ RCH{=}CHPCl_4 + 2\ P \xrightarrow[NaI]{I_2\ or} 3\ RCH{=}CHPCl_2 + 2\ PCl_3$$

The unsaturated dichlorophosphine was characterized, and it was also shown that phenylphosphorus tetrachloride was reduced by phosphorus in the presence of iodine to phenyldichlorophosphine.

B. Addition of PCl_5 to acetylenes

Bergmann and Bondi found the addition of PCl_5 to acetylenes to be generally applicable and quite comparable to the addition of PCl_5 to

olefins (8). The main difference noted in the acetylene series is that the vinyl-type halogen atom of the final product, $-\underset{Cl}{C}=\underset{H}{C}PO_3H_2$ (I), resists dehydrohalogenation until attacked by hot alcoholic caustic (9). The difference is, of course, consistent with the known chemistry of vinyl halides. It should be mentioned that the same final product (I) can be obtained by the addition of PCl_5 to a β-chloroethylene. In this case, the intermediate $-CCl_2CH_2PCl_4$ (II) readily loses one mole of hydrogen chloride during hydrolysis.

No ortho effect was noted in the acetylene series. This observation is consistent with the linear configuration of the acetylenes. The usual products were obtained from o-chloro- and o-methoxyphenylacetylene, but the p-methoxyphenylacetylene product tended to dephosphonate; and p-nitrophenylacetylene would not undergo the reaction (8). No explanation has been offered; one possibility may be the electron-releasing and electron-withdrawing powers, respectively, of the methoxy and nitro groups. Whereas 3-phenyl-1-propyne and 1-heptyne react normally, 4-phenyl-1-butyne does not yield any phosphonic acid (11). Non-terminal acetylenes fail to undergo the reaction.

C. Reaction of an olefin and PCl_3 in the presence of a catalyst

Normally, PCl_3 is not observed to add to an olefin. However, with suitable catalysts, the halide appears to add in the sense $Cl\text{-}PCl_2$ to those alkyl-substituted olefins which carry an α-hydrogen atom (18, 19, 20, 21).

A mixture of olefin, more than catalytic amounts of acetyl peroxide, and excess PCl_3 as solvent is heated at 85° several hours under an inert atmosphere and slight pressure. The reaction mass may then be cooled, the PCl_3 removed at room temperature under reduced pressure, and the excess olefin and product distilled in vacuo (21). Benzoyl peroxide or ultraviolet irradiation (20) may also be used as catalysts. No yields have been reported.

$$RCH=CH_2 + PCl_3 \xrightarrow[(\text{or } h\nu)]{Ac_2O_2,\ (\text{or } (\text{Ø}CO_2)_2,} RCHClCH_2PCl_2$$

Obviously, the chloroalkyldichlorophosphine may be of interest as such---other preparative routes to $RPCl_2$ are said to be inadequate (19)---or it may be oxidized and solvolyzed to phosphonyl halides or phosphonic acids or derivatives.

Although an ionic mechanism for the reaction has not been completely ruled out (18), a radical mechanism has been postulated by Kharasch (19), based upon the known radical-inducing character of the catalysts used. The reaction scheme may be written as below

(neglecting initiation steps leading to formation of a radical):

$$R\cdot + PCl_3 \longrightarrow RCl + \cdot PCl_2$$

$$\cdot PCl_2 + RCH{=}CH_2 \longrightarrow R\dot{C}HCH_2PCl_2$$

$$R\dot{C}HCH_2PCl_2 + PCl_3 \longrightarrow RCHClCH_2PCl_2 + \cdot PCl_2$$

According to the scheme, polymeric materials could arise as follows, thus accounting for observed higher boiling materials:

$$R\dot{C}HCH_2PCl_2 + RCH{=}CH_2 \longrightarrow R\dot{C}HCH_2CHRCH_2PCl_2$$

$$R\dot{C}HCH_2CHRCH_2PCl_2 + PCl_3 \longrightarrow RCHClCH_2CHRCH_2PCl_2 + \cdot PCl_2$$

$$RCHClCH_2PCl_2 \xrightarrow{RCH=CH_2} RCHClCH_2\text{-}\overset{\displaystyle Cl}{\underset{|}{P}}\text{-}CH_2CHClR \xrightarrow{RCH=CH_2} \text{etc.}$$

Although no direct experimental evidence has been provided to support the entire scheme, the radical addition steps are in good agreement with known radical processes.

It is claimed that the general reaction may be extended in that PCl_3 may be added to acetylenes, and that dihalophosphines of the general formula $RPCl_2$ may be added to olefins (19). Further details and confirmatory evidence have not been provided.

D. Reaction of olefins or acetylenes with PCl_3 or PCl_5 in the presence of oxygen.

In the presence of oxygen, PCl_5 may be caused to add to acetylenic linkages under essentially the same conditions as without oxygen. In the presence of oxygen, however, the chief product is the phosphonyl chloride without the usual solvolytic step (22). Other products are unspecified.

In the presence of oxygen, PCl_3 may be caused to add to acetylenes and olefins; the oxygen is necessary in order for the reaction to proceed (22, 23). The isolated products are $POCl_3$ and the phosphonyl chlorides of the same structures as when PCl_5 is added to olefins or acetylenes.

The passage of oxygen into a mixture of PCl_3 and 1-hexyne maintained at 0-10° yielded a reaction mixture from which, after removal of $POCl_3$, 2-chloro-1-hexenyl-1-phosphonyl dichloride could be isolated. When phenylacetylene was a reactant, the yield was 24%. With acetylene, only a small yield of 2-chloroethenyl-1-phosphonyl dichloride was obtained. Of interest is the addition of PCl_3 to vinylacetylene to produce 2-chloro-1,3-butadienyl-1-phosphonyl dichloride in 15% yield (22):

$$CH_2{=}CHC{\equiv}CH + 2\ PCl_3 \xrightarrow[-20^\circ]{O_2} POCl_3 + CH_2{=}CHCCl{=}CHPOCl_2$$

The preferred site of attack as judged by products isolated is thus the acetylenic linkage. The structure of the product was proved by elemental analyses, molecular weight, molecular refraction, the addition of four bromine atoms, and the absence of any acetylenic hydrogen. However, in view of the known substitution of PCl_3 in the presence of oxygen for an aliphatic hydrogen atom to yield a phosphonyl halide (a reaction to be discussed later) the possibility of substitution rather than addition under certain conditions has been entertained.

III. ADDITIONS TO CARBONYL GROUPS

A. Addition of PCl_3 to carbonyl groups

The addition of trivalent phosphorus halides to aldehydes and ketones has proved to be a general reaction of some utility, yielding (depending upon the reaction conditions and isolation procedures) phosphonyl halides, cyclic anhydro acids or derivatives; unsaturated phosphonyl halides, unsaturated phosphonic acids or derivatives; 1-halophosphonic, 1-hydroxyphosphonic, 3-ketophosphonic, and 2-halo-3-ketophosphonic acids or derivatives (24).

Different reaction conditions and, especially, isolation procedures have been used by various investigators. It is therefore impossible to describe only one way in which the reaction is conducted. The following outlines of experimental procedures are essentially those of Fossek (25-28), Conant (29-40), and Kabachnik (42-53), respectively.

1) At about room temperature, one mole of PCl_3 is dropped into three moles of the carbonyl compound. Sometimes external cooling or gentle warming is required. The resultant adduct, a non-distillable, heat-sensitive oil, is hydrolyzed with caution. The two moles of carbonyl compound liberated are removed, and evaporation of the water phase yields the phosphonic acid. For example, from benzaldehyde, a good yield of α-hydroxybenzylphosphonic acid is obtained.

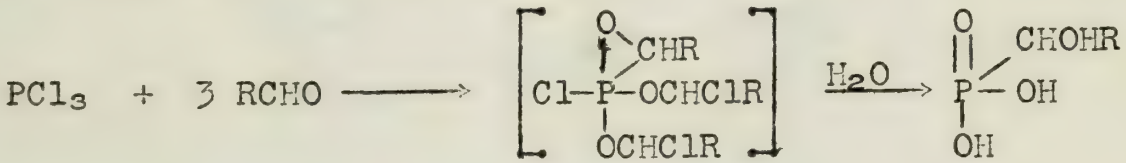
2) Similarly, one mole of PCl_3 is caused to react with only one mole of carbonyl compound in the presence of acetic acid or acetic anhydride as "solvent". Acetyl chloride is evolved and the resultant phosphonyl chloride may be distilled, hydrolyzed to the acid, or converted to esters. For example, from acetophenone there are obtained 1-phenyl-1-hydroxyethyl-1-phosphonic acid and also some styrene-α-phosphonic acid, the latter by loss of the elements of water from the former during the process of isolation.

3) A mixture of one mole of carbonyl compound and about one mole of PCl_3 is heated under pressure to about 200° for several hours. After being cooled, the reaction mixture is degassed by removing hydrogen chloride under reduced pressure. Then the phosphonyl halide can be distilled *in vacuo* or solvolyzed to α-chlorophosphonic acids or derivatives. For example, from paraformaldehyde a 50% yield of chloromethylphosphonyl dichloride is obtained. The corresponding halide can be obtained in yield of over 60% from benzaldehyde.

Although a great deal of work has been done on these reactions, the true mechanisms are not known at present in their entirety (24, 42). The following discussion is intended to outline the

historical development of ideas concerning mechanisms of the reactions and to summarize what are currently believed to be the most probable mechanistic schemes.

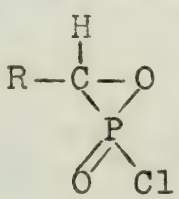
In 1884, Fossek reported the reaction of PCl_3 with excess benzaldehyde to give an adduct which, upon hydrolysis, afforded an 80% yield of α-hydroxybenzylphosphonic acid (25, 26, 27). Fossek and, later, Page (28) recognized the adduct, an unstable oil which could not be isolated in the pure state, to be a chemical entity of the composition $3RCHO.PCl_3$. The oil was observed to react vigorously with water to yield the phosphonic acid, benzaldehyde, and hydrochloric acid. Page proposed for the adduct the following structure, based upon no other supporting evidence:



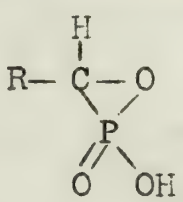
It should be noted that the proposed structure is strikingly similar to some intermediate structures proposed lately (42).

In 1917, Conant began reporting on what was to be a decade of study of the reaction and of a related one, the addition of PCl_3 to α,β-unsaturated ketones (29-40). Conant and his co-workers chose to study the reaction with an approximately one to one mole ratio of carbonyl compound to PCl_3 and with an added component in excess (such as acetic acid, acetic anhydride, or benzoic acid) acting not only as solvent but also as a reactant.

Conant was able to isolate some possible precursors of the hydroxyphosphonic acid. One of these was found when acetic anhydride was used as solvolyzing medium. Conant concluded that the compound, of structure I, probably was the acid chloride of what he called an "anhydro" or "phostonic" acid. Similarly the "anhydro" or "phostonic"

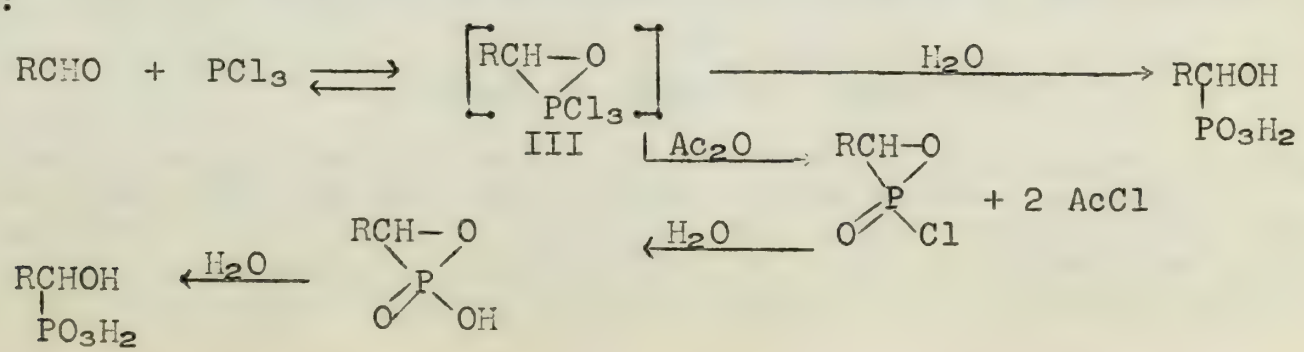


I

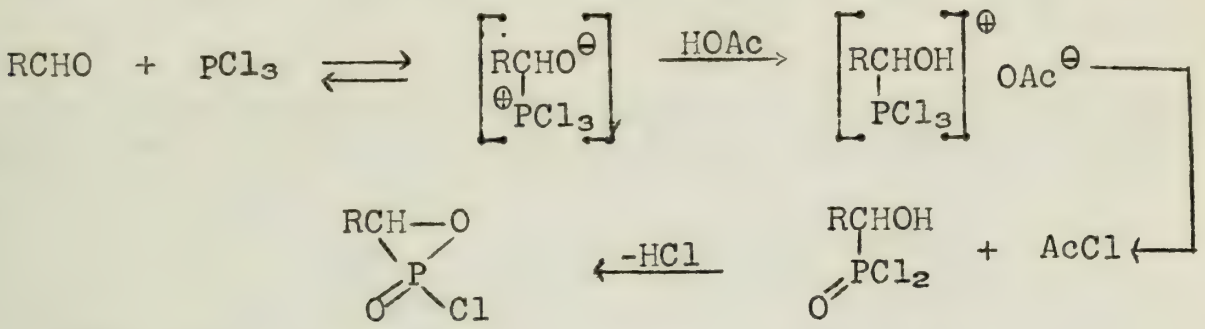


II

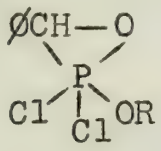
acid isolated from acetic acid solvolyses was concluded to have the structure II. On the basis of these conclusions, Conant proposed the scheme:



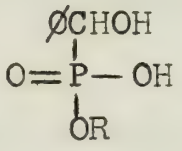
Later, from the results of a kinetic study (39), he was forced to conclude that the adduct III could not be the true intermediate because the apparent rate of formation of the adduct was a least 200 times slower than the course of the preparative reaction. In the absence of further evidence, and dismissing a trimolecular mechanism as being unlikely, Conant modified his proposed scheme as follows:



Conant's original scheme for the addition of a dichlorophosphite, $ROPCl_2$, to benzaldehyde would have called for an adduct of the structure IV which could be hydrolyzed to the hydroxyphosphonate V (observed experimentally).

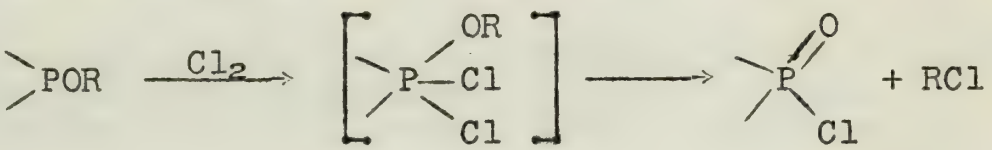


IV



V

However, Todd and his co-workers were able to show from parallel reactions with known phosphites that the adduct IV should lose the elements of alkyl halide and rearrange thus (41):

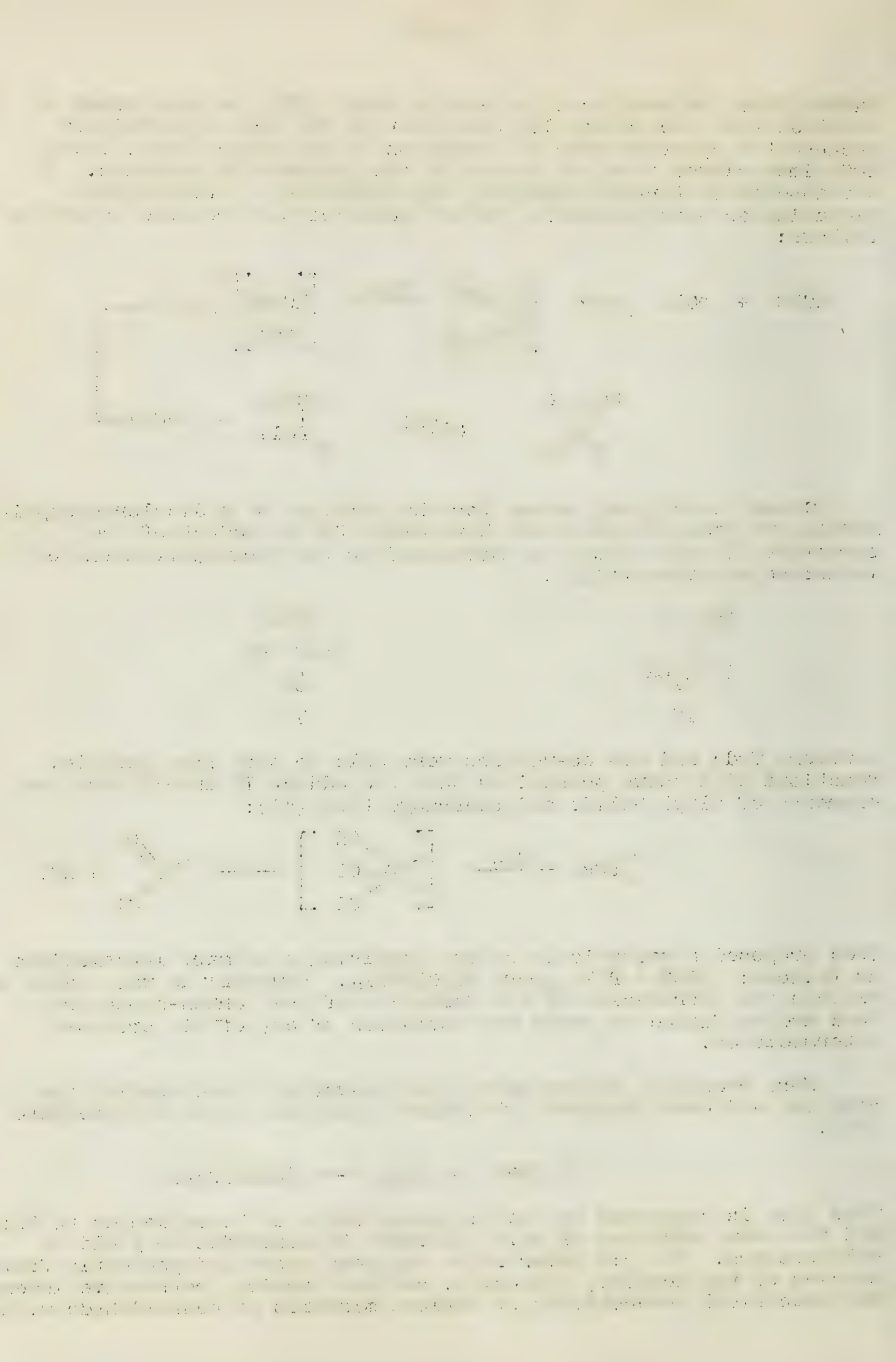


Todd proposed a mechanistic scheme involving a primary intermediate as follows: $RCHO + PCl_3 \rightleftharpoons RCHClOPCl_2$. However, he was unable to explain the intricacies of the formation of the carbon-phosphorus bond and he failed to prove the isolation of any of his proposed intermediates.

More recently, Kabachnik and his co-workers have studied the reaction and have proposed a trivalent phosphite as an intermediate (42):

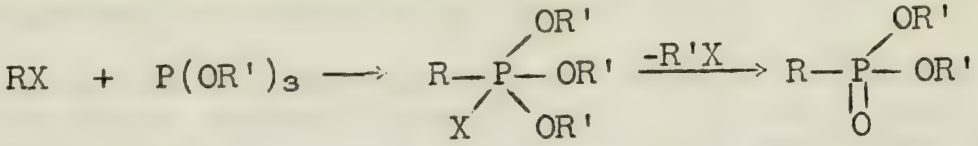
$$3\ \text{ØCHO} + PCl_3 \longrightarrow (\text{ØCHClO})_3P$$

This idea is supported by the 3:1 molar ratio of benzaldehyde to PCl_3 and the known addition of acid chlorides to aldehydes to yield α-chloroesters. The 3:1 molar ratio has been shown independently from studies of the density, viscosity, surface tension, refractive index, and electrical conductivity of various mixtures of benzaldehyde with

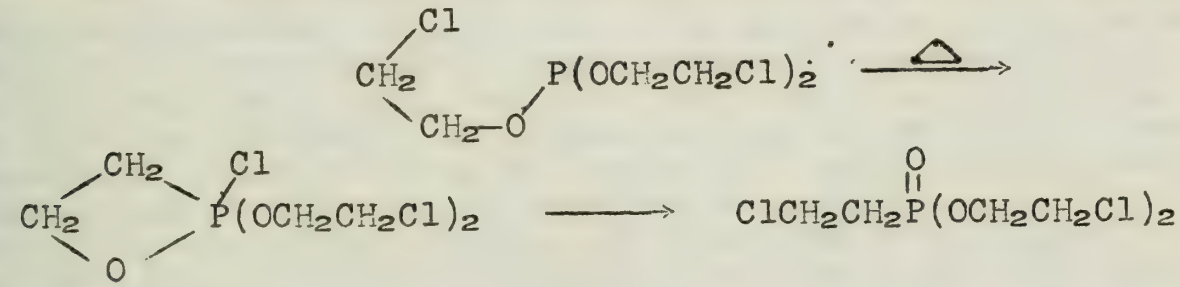


PCl_3 and PBr_3 (46-49).

Kabachnik next pictured an inter- or intramolecular Arbuzov-type rearrangement to yield a phosphonate ester. The usual Arbuzov rearrangement is represented thus:

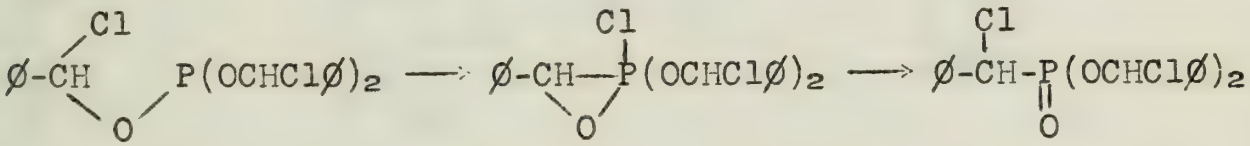


The above rearrangement is comparable to the postulated intramolecular rearrangement of β-chlorophosphites which is represented below (42a):

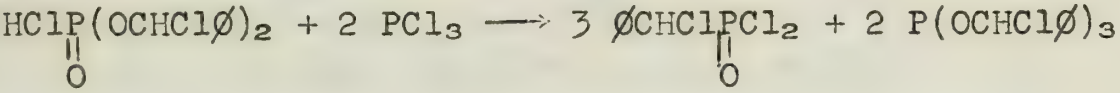


For α-halophosphites the rearrangement is expected to be even more facile. The analogous rearrangement for the present reaction is written thus:

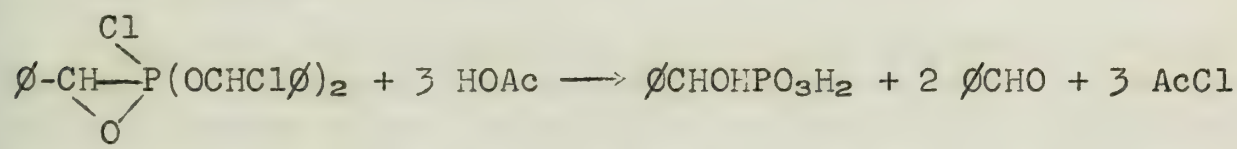
1.



2.



The second equation should explain the completeness of the reaction when less than three moles of benzaldehyde to one of PCl_3 are employed. The following reaction is postulated for acetic acid solvolysis:



While the reaction scheme of Kabachnik is consistent with the experimentally observed facts, still none of the proposed intermediates has been isolated and analyzed.

It should be mentioned that some variations of the addition of PCl_3 to ketones have been reported (53-56). They will not be reviewed here.

B. Addition of PCl_3 to α,β-unsaturated carbonyl groups

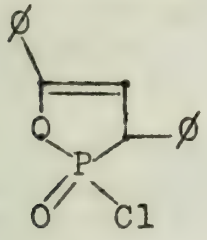
The addition of trivalent phosphorus halides to α,β-unsaturated carbonyl systems has proved to be general (57). The observed net

result is the 1,4-addition of the halide across the conjugated system (29-34, 37, 38).

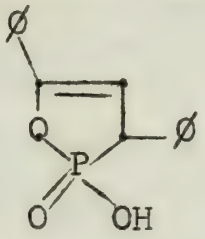
While any of the experimental procedures outlined earlier for the addition of PCl_3 to carbonyl compounds may be employed, the method of Conant has been most used (29-40, 62).

The mechanism of the reaction is as obscure as that of additions to ordinary carbonyl groups (57). It seems reasonable to assume that mechanistically both systems may be analogous (44), but the extent of differences is not yet clearly known.

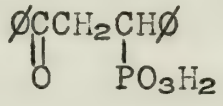
Conant first reported the reaction of PCl_3 with ketones like benzalacetophenone in 1917 (29). He succeeded in isolating and proving the structures of some interesting species which, according to his reaction scheme, would be intermediates. Since he was able to show the existence of structures like I and II (by elemental analyses, uptake of bromine, equivalent weight titrations and hydrolysis to III) and to prove the structure of III (by elemental analyses, equivalent weight, and formation of an oxime), Conant suggested a mechanism analogous to that suggested for addition to unconjugated carbonyls. According to the scheme, the initial adduct



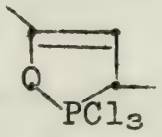
I



II



III

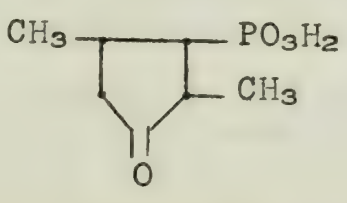


IV

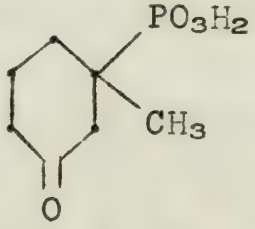
would be IV, but this idea later was abandoned (39).

Conant was able to show that no diphosphonic acids resulted from the reaction of PCl_3 with dibenzalacetone, $\phi CH{=}CHCOCH{=}CH\phi$, and that no 1,6-addition resulted from the reaction of PCl_3 with cinnamylideneacetophenone, $\phi CH{=}CHCH{=}CHCO\phi$ (33). In each case, 1,4-addition was the rule.

According to Conant's original idea, addition of PCl_3 across a cyclic α,β-unsaturated ketone should produce a double bond at a bridged carbon atom. Kabachnik considered this unlikely and succeeded in carrying out the reaction on cyclopentenones and cyclohexenones to produce the following phosphonic acids (44):



about 66% yield



about 40% yield

The reaction is considered to be analogous to that suggested for regular ketones. The Arbuzov-type rearrangement is represented as being not necessarily bicylic since such reactions can proceed intermolecularly.

It should be noted that considerable effort has been expended in reviewing some seemingly anomalous work of Michaelis regarding phosphonation of α,β-unsaturated ketones (57-61). The matter will not be reviewed here.

C. Addition of other phosphorus halides to carbonyl groups

As already mentioned, the addition of trivalent phosphorus halides, $\geq P-X$, to carbonyl groups has proved to be quite general (24, 32, 34, 37, 53, 57, 63). Examples of phospenyl halides that have been used successfully are PCl_3, PBr_3, $RPCl_2$, R_2PCl, $ROPCl_2$, and $(RO)_2PCl$. Obviously, where the phosphorus atom bears substituents other than halide one does not usually obtain acids as final products. Where the reagent is RPX_2 or R_2PX, phosphine oxides result; where the reagent is $ROPX_2$ or $(RO)_2PX$, phosphonate esters result.

The addition of diphenylchlorophosphine has been shown to be slower than the addition of either PCl_3 or phenyldichlorophosphine. The bulk of the reagent thus may be important (63).

It should be noted that PCl_5 normally does not add in the sense discussed here to aldehydes and ketones, or to amides (64-68). The products isolated are chlorides containing no phosphorus.

III. RELATED ADDITIONS AND SUBSTITUTIONS

In addition to the processe s already discussed, two other phosphonation reactions of related nature are known. They will be mentioned briefly in this report for the sake of completeness.

A. Reaction of a hydrocarbon, PCl_3 and oxygen

In 1948, Clayton and Jensen reported a curious reaction whereby the dichlorophosphono radical $-POCl_2$ can be substituted for a hydrogen atom in a paraffinic hydrocarbon (69):

$$-\overset{|}{\underset{|}{C}}-H \;+\; PCl_3 \xrightarrow{O_2} -\overset{|}{\underset{|}{C}}-POCl_2 \;+\; HCl$$

Little is known about the reaction and there is some disagreement among researchers (70, 71).

Typically, the hydrocarbon is dissolved in PCl_3 and blown with oxygen at room temperature or slightly above. The resultant phosphonyl dichloride is then isolated or converted to derivatives. The reaction is non-selective and produces mixtures. The yields are reported to range from 15 to 30%. Any olefins present may also add the PCl_3 as previously discussed (70, 71).

Oxygen oxidizes PCl_3 to $POCl_3$, but that reaction is said to be readily inhibited by any impurities. Furthermore, the addition of $POCl_3$ to a reaction mass of hydrocarbon, PCl_3, and oxygen does not affect the yield. Likewise, added phosphonation products have no effect on yields, which are said to be more or less constant over a temperature range of $\pm 100^{\circ}$. Oxygen, air, and nitrogen dioxide have been used as oxidants (71).

At least 18 catalysts, including light and peroxides, have been investigated; all proved to be ineffective, and several inhibited the reaction entirely. Among the inhibitors were iron, boron trifluoride, iodine, aluminum chloride, and sulfuric acid (70, 71).

A recent paper summarizes the literature pertaining to the reaction and cites eleven references through 1956 (71).

B. Reaction of aromatic compounds with PCl_3 and $AlCl_3$

A variation of the Friedel-Crafts reaction produces dihalophosphines which, in theory, can be converted to phosphonyl halides, phosphonic acids, and derivatives (72, 73). The reaction may be summarized thus:

$$\text{ØH} + PCl_3 \xrightarrow{AlCl_3} \text{ØP}Cl_2 + HCl$$

This reaction, used with a variety of aromatic compounds, has recently been extended to the aliphatic series (74). For further details, see the reviews by Kosolapoff (72).

Finally, mention should be made of a Russian review with 46 references pertaining to the addition of phosphorus halides to organic compounds (75).

BIBLIOGRAPHY

1. J. E. Marsh, M. A. Balliol, and J. A. Gardner, J. Chem. Soc. 59, 648 (1891).
2. K. Harnist, Dissertation, Strassburg, 1910.
3. F. Bulle, Dissertation, Strassburg, 1912.
4. J. Thiele, Chem. Ztg. 36, 657 (1912).
5. a) C. Harnist, Ber. deut. chem. Ges. 63, 2307 (1930).
   b) L. Anschutz, F. Koenig, F. Otto, and H. Walbrecht, Ann. 525, 297 (1936).
6. E. Bergmann and A. Bondi, Ber. deut. chem. Ges. 63, 1158 (1930).
7. E. Bergmann and A. Bondi, ibid. 64, 1455 (1931).
8. E. Bergmann and A. Bondi, ibid. 66, 278, 286 (1933).
9. a) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, New York, N.Y., 1950, pp. 59, 127-128.
   b) G. M. Kosolapoff, Chapter in "Organic Reactions," vol. 6, John Wiley and Sons, New York, N.Y., 1951, pp. 291-3.
10. G. M. Kosolapoff and J. F. McCullough, J. Am. Chem. Soc. 73, 855 (1951).
11. Reference 9b, pp. 291 f.
12. G. B. Bachmann and R. E. Hatton, J. Am. Chem. Soc. 66, 1513 (1941).

13. a) W. H. Woodstock, U. S. Patent 2,495,799. January 1950. Chem. Abstracts 44, 3517 (1950).
b) W. H. Woodstock, U. S. Patent 2,471,472. May 1949. Chem. Abstracts 43, 7499 (1949).
14. G. M. Kosolapoff, U. S. Patent 2,389,576. November 1945. Chem. Abstracts 40, 1536 (1946).
15. G. M. Kosolapoff, U. S. Patent 2,486,657. November 1949. Chem. Abstracts 44, 2009 (1950).
16. G. M. Kosolapoff and W. F. Huber, J. Am. Chem. Soc. 68, 2540 (1946).
17. E. N. Walsh, T. M. Beck, and W. H. Woodstock, J. Am. Chem. Soc. 77, 929 (1955).
18. Reference 9a, pp. 48-49.
19. M. S. Kharasch, E. V. Jensen, and W. H. Urry, J. Am. Chem. Soc. 67, 1864 (1945).
20. M. S. Kharasch, E. V. Jensen, and W. H. Urry, ibid. 68, 154 (1946).
21. M. S. Kharasch, U. S. Patent 2,489,091. November 1949. Chem. Abstracts 44, 2010 (1950).
22. Y. M. Zinov'ev, L. I. Muler, and L. Z. Soborovskii, Zhur. Obschei Khim. 24, 380 (1954). Chem. Abstracts 49, 4503 (1955). In English, J. Gen. Chem. U. S. S. R. 24, 391 (1954).
23. L. Z. Soborovskii, Y. M. Zinov'ev, and M. A. Englin, Doklady Akad. Nauk S. S. S. R. 67, 293 (1949). Chem. Abstracts 44, 1401 (1950).
24. Reference 9a, pp. 130-2; reference 9b, pp. 308-15.
25. W. Fossek, Monats. 5, 121 (1884).
26. W. Fossek, ibid. 5, 627 (1884).
27. W. Fossek, ibid. 7, 20 (1886).
28. H. J. Page, J. Chem. Soc. 101, 423 (1912).
29. J. B. Conant, J. Am. Chem. Soc. 39, 2679 (1917).
30. J. B. Conant and A. A. Cook, ibid. 42, 830 (1920).
31. J. B. Conant and A. D. MacDonald, ibid. 42, 2337 (1920).
32. J. B. Conant and S. M. Pollack, ibid. 43, 1665 (1921).
33. J. B. Conant, A. H. Bump, and H. S. Holt, ibid. 43, 1677 (1921).
34. J. B. Conant, ibid. 43, 1705 (1921).
35. J. B. Conant, A. D. MacDonald, and A. M. Kinney, ibid. 43, 1928 (1921).
36. J. B. Conant, B. B. Coyne, ibid. 44, 2530 (1922).
37. J. B. Conant, J. B. S. Braverman, and R. E. Hussey, ibid. 45, 165 (1923).
38. J. B. Conant, V. H. Wallingford, and S. S. Gandheker, ibid. 45, 762 (1923).
39. J. B. Conant and V. H. Wallingford, ibid. 46, 192 (1924).
40. J. B. Conant and E. L. Jackson, ibid. 46, 1003 (1924).
41. F. R. Atherton, V. M. Clark, and A. R. Todd, Rec. trav. chim. 69, 295 (1950).
42. a) M. I. Kabachnik and E. S. Shepeleva, Izvest. Akad. Nauk S. S. S. R., Otdel Khim. Nauk 1950, 39.
b) M. I. Kabachnik and P. A. Rossiyskaya, ibid. 4, 403 (1946).
43. M. I. Kabachnik and E. S. Shepeleva, Doklady Akad. Nauk S. S. S. R. 75, 219 (1950). Chem. Abstracts 45, 6569 (1951).
44. M. I. Kabachnik and T. Y. Medved, Izvest. Adad. Nauk 1952, 540. In English, Bull. Acad. Sci. U. S. S. R., Div. Chem. Sci. 1952, 517.
45. R. L. McConnell, M. A. McCall, and H. W. Coover, Jr., J. Org. Chem. 22, 462 (1957).

46. N. A. Trifonov and F. F. Faizullin, Uchenye Zapiski Kazan. Gosudarst. Univ. 112, No. 4, 131 (1953); Referat. Zhur., Khim., 1954, No. 14265. Chem. Abstracts 49, 2167 (1955).
47. F. F. Faizullin and N. A. Trifonov, ibid. 112, No. 4, 145 (1953); ibid. No. 14266.
48. F. F. Faizullin and N. A. Trifonov, ibid. 112, No. 4, 145 (1953); ibid. No. 14267.
49. F. F. Faizullin, L. S. Drabkina, and L. I. Ivankina, ibid. 113, No. 8, 51 (1953); ibid. No. 37442.
50. M. I. Kabachnik and T. Y. Medved, Izvest. Akad. Nauk S. S. S. R. Otdel. Khim. Nauk 1950, 635. Chem. Abstracts 45, 8444 (1951).
51. M. I. Kabachnik and E. S. Shepeleva, ibid. 1951, 185. Chem. Abstracts 45, 10191 (1951).
52. M. I. Kabachnik and E. S. Shepeleva, Akad. Nauk S. S. S. R., Inst. Org. Khim., Sintezy Org. Soedinenii, Sbornik 2, 150 (1952). Chem. Abstracts 48, 564 (1954).
53. M. I. Kabachnik and E. S. Shepeleva, Izvest. Akad. Nauk S. S. S. R., Otdel Khim. Nauk 1953, 862. In English, Bull. Acad. Sci. U. S. S. R., Div. Chem. Sci. 1953, 763. Chem. Abstracts 49, 5277 (1955).
54. C. S. Marvel and J. C. Wright, J. Polymer Sci. 8, 495 (1952).
55. R. W. Upson, U. S. Patent 2,599,501. June 1952. Chem. Abstracts 46, 8416 (1952).
56. L. A. Hamilton, U. S. Patent 2,365,466. December 1944. Chem. Abstracts 39, 4619 (1945).
57. Reference 9a, pp. 67-8, 132.
58. A. Michaelis, Ber. deut. chem. Ges. 17, 1273 (1884).
59. A. Michaelis, ibid. 18, 898 (1885).
60. A. Michaelis, ibid. 19, 1009 (1886).
61. L. Anschutz, E. Klein, and G. Cernak, ibid. 77, 726, (1944).
62. L. R. Drake and C. S. Marvel, J. Org. Chem. 2, 387 (1937).
63. Reference 9a, pp. 110-1; reference 9b, pp. 308-15.
64. S. E. Brady and S. P. Massie, Proc. Okla. Acad. Sci. 33, 261 (1952).
65. F. Strauss, Ann. 393, 235 (1912).
66. E. Bergmann and A. Bondi, Ber. deut. chem. Ges. 64, 1462 (1931).
67. G. Coleman and R. Pyle, J. Am. Chem. Soc. 68, 2007 (1946).
68. A. Behal, Bull. soc. chim. (2), 50, 632 (1888).
69. J. O. Clayton and W. L. Jensen, J. Am. Chem. Soc. 70, 3880 (1948).
70. Reference 9a, p. 66.
71. A. F. Isbell and F. T. Wadsworth, J. Am. Chem. Soc. 78, 6042 (1956).
72. Reference 9a, pp. 43-6, 128-9; reference 9b, pp. 297-303.
73. L. D. Freeman and G. O. Doak, Chem. Rev. 57, 499 (1957).
74. Id., 483.
75. M. I. Kabachnik, Uspekhi Khim. 16, 403 (1947). Chem. Abstracts 42, 2576 (1948).

1,2-MIGRATIONS IN FREE RADICAL INTERMEDIATES

Reported by J. R. Rogers March 20, 1958

INTRODUCTION

Although rearrangements involving free radical intermediates have been known for many years, only recently have there been particular efforts made to study such rearrangements. The object of this seminar will be to bring up to date the work concerning only 1,2-migrations which occur in free radical intermediates. This will include 1,2-carbon-to-carbon and 1,2-carbon-to-oxygen migrations. The seminar will be subdivided according to the migrating groups. Rearrangements occurring during Kölbe-type electrolysis reactions will be discussed separately.

ARYL MIGRATION

Wieland (1) in 1911 recognized what is considered to be the first recorded rearrangement of a free radical intermediate. He generated the triphenylmethoxy radical from triphenylmethyl peroxide in boiling xylene and recovered, in seventy-five per cent yield, benzpinacol diphenyl ether (I) which is the dimer of the rearranged intermediate.

$$(C_6H_5)_3COOC(C_6H_5)_3 \longrightarrow 2[(C_6H_5)_3CO\cdot] \longrightarrow 2[(C_6H_5)_2\dot{C}OC_6H_5] \longrightarrow$$

$$(C_6H_5)_2(C_6H_5O)CC(C_6H_5O)(C_6H_5)_2 \quad (I)$$

The same product was obtained by Kharasch and co-workers (2) when they treated triphenylmethyl hydroperoxide with ferrous salts, and they also suggested that rearrangement of the methoxy free radical had occurred.

$$(C_6H_5)_3COOH + Fe^{++} \longrightarrow (C_6H_5)_3CO\cdot + FeOH^{++}$$

$$(C_6H_5)_3CO\cdot \longrightarrow (C_6H_5)_2\dot{C}OC_6H_5$$

$$2(C_6H_5)_2\dot{C}OC_6H_5 \longrightarrow (I)$$

Several systems have been used to study the rearrangement of aryl groups. 1,2-Migrations have been studied in the neophyl (2-methyl-2-phenylpropyl) and related radicals (Table I). And the relative rates of migration of various aryl groups have been investigated by several workers who studied the thermal decomposition of triarylmethyl peroxides and hydroperoxides (Table II). The latter rearrangements involve 1,2-carbon-to-oxygen migrations.

As can be seen from the data in Table I, partial or complete aryl migration occurs only in radicals in which there is considerable crowding on the β-carbon atom. These radicals which rearrange also undergo a change from either a primary or secondary to a more stable tertiary radical. No good evidence for the change from a primary to a secondary radical was reported (Table I; E, F). Also, the reaction conditions under which the radical is formed have

TABLE I

Aryl Migration in the Neophyl and Related Radical Intermediates

Original Compound	Initiator	Initial Radical	Migrating Group	Rearranged Radical	% Rearr.	Ref.
A. $PhMe_2CCH_2Cl$	PhMgBr, $CoCl_2$	$PhMe_2CCH_2\cdot$	Ph	$Me_2\dot{C}CH_2Ph$	50	4
B. $PhMe_2CCH_2CHO$	DTBP*, $\triangle$	$PhMe_2CCH_2\cdot$	Ph	$Me_2\dot{C}CH_2Ph$	50	5
C. (p-Tol)Me_2CCH_2Cl	EtMgBr, $CoCl_2$	(p-Tol)$Me_2CCH_2\cdot$	p-Tol	$Me_2\dot{C}CH_2$(p-Tol)	40	6
D. (p-Tol)Me_2CCH_2CHO	DTBP, $\triangle$	(p-Tol)$Me_2CCH_2\cdot$	p-Tol	$Me_2\dot{C}CH_2$(p-Tol)	48	7
E. (p-MeOPh)$PhCHCH_2CHO$	DTBP, $\triangle$	(p-MeOPh)$PhCHCH_2\cdot$	Ph or p-MeOPh	(p-MeOPh)$\dot{C}HCH_2Ph$, $Ph\dot{C}HCH_2$(pMeOPh)	<15,0	7,8,9
F. (p-MeOPh)$PhCDCH_2CHO$	DTBP, $\triangle$	(p-MeOPh)$PhCDCH_2\cdot$	Ph or p-MeOPh	$Ph\dot{C}DCH_2$(p-MeOPh), (p-MeOPh)$\dot{C}DCH_2Ph$	0	9
G. Ph_2MeCCH_2CHO	DTBP, $\triangle$	$Ph_2MeCCH_2\cdot$	Ph	$PhMe\dot{C}CH_2Ph$	100	8
H. $Ph_3CCHMeCHO$	DTBP, $\triangle$	$Ph_3\dot{C}CHMe$	Ph	$Ph_2\dot{C}CHMePh$	100	8
I. Ph_3CCH_2CHO	DTBP, $\triangle$	$Ph_3CCH_2\cdot$	Ph	$Ph_2\dot{C}CH_2Ph$	100	8
J. (p-NO_2Ph)Ph_2CCH_2CHO	DTBP, $\triangle$	(p-NO_2Ph)$PH_2CCH_2\cdot$	p-NO_2Ph	$Ph_2\dot{C}CH_2$(P-NO_2Ph)	~ 30	9
K. Ph_3CCH_2Ph	NBS, light or perox.	$Ph_3\dot{C}CHPh$	Ph	$Ph_2\dot{C}CHPh_2$	100	10,43

*DTBP = di-t-butyl peroxide

L.(a) $Ph_2MeCCH{=}CH_2$	CH_3COSH, Me_3COOH	$Ph_2MeC\dot{C}HCH_2\text{-}SCOCH_3$	Ph	$PhMe\dot{C}CHPhCH_2\text{-}SCOCH_3$	0	11
(b) $Ph_2MeCCH{=}CH_2$	n-BuSH, Me_3COOH	$Ph_2MeC\dot{C}HCH_2\text{-}SC_4H_9$	Ph	$PhMe\dot{C}CHPhCH_2\text{-}SC_4H_9$	0	11
(c) $Ph_2MeCCH{=}CH_2$	n-PrCHO, Me_3COOH	$Ph_2MeC\dot{C}HCH_2COC_3H_7$	Ph	$PhMe\dot{C}CHPhCH_2COC_3H_7$	100	11

TABLE II

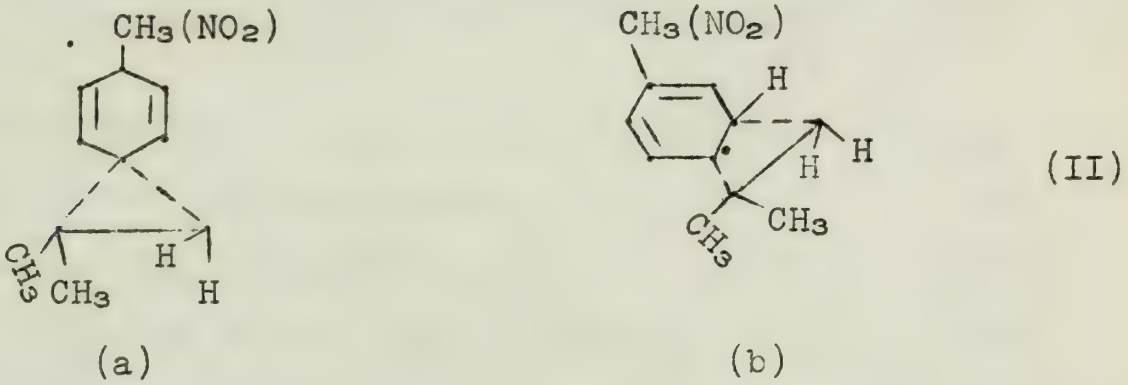
Aryl/Phenyl Migration in Peroxide and Hydroperoxide Systems

Original Compound	Rearranged Radical	Migrating Group	Aryl/Phenyl Migration Ratio	Ref.
A. (p-NO_2Ph)Ph_2COOH	[$Ph_2\dot{C}O$(p-NO_2Ph)]	p-NO_2Ph	8	13
B. (p-NO_2Ph)$Ph_2COOCMe_3$	[$Ph_2\dot{C}O$(p-NO_2Ph)]	p-NO_2Ph	?	2
C. (p-C_6H_5Ph)$Ph_2COOCMe_3$	$Ph_2\dot{C}O$(p-C_6H_5Ph)	p-C_6H_5Ph	6	2
D. [(p-C_6H_5Ph)Ph_2CO-]$_2$	$Ph_2\dot{C}O$(p-C_6H_5Ph)	p-C_6H_5Ph	5.6	12
E. (α-napth)*$Ph_2COOCMe_3$	$Ph_2\dot{C}O$(α-napth)	α-napth	6	2
F. (p-Tol)$Ph_2COOCMe_3$	$Ph_2\dot{C}O$(p-Tol)	p-Tol	1	2
G. [(p-Tol)Ph_2CO-]$_2$	$Ph_2\dot{C}O$(p-Tol)	p-Tol	0.99	12
H. [(p-MeOPh)Ph_2CO-]$_2$	$Ph_2\dot{C}O$(p-MeOPh)	p-MeOPh	0.94	12
I. [(m-Tol)Ph_2CO-]$_2$	$Ph_2\dot{C}O$(m-Tol)	m-Tol	0.87	12
J. [(o-ClPh)Ph_2CO-]$_2$	$Ph_2\dot{C}O$(o-ClPh)	o-ClPh	0.25	12

*α-napth=α-napthyl

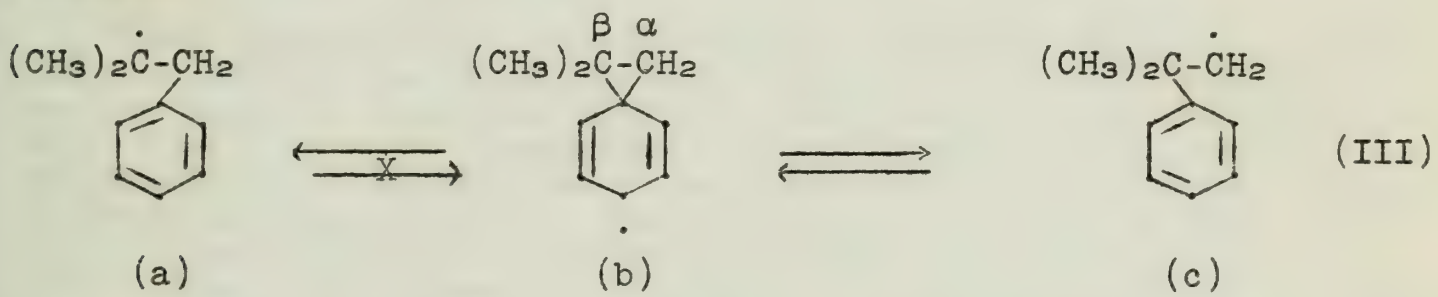
considerable effect on the rearrangement tendency of the intermediate radical. These factors will be discussed in the following paragraphs. For a discussion of the aldehyde decarbonylation reactions which lead to the formation of many of these radicals, see the recent seminar presented by Kleiman (3).

The radical initially formed rearranges by a 1,2-shift of the aryl group through a three-membered cyclic transition state (IIa). In support of this the rearrangement of p-methylneophyl (Table I; C,D) and β,β-dimethyl-β-p-nitrophenylethyl (I) radicals gave rise to products in which the p-methyl and p-nitro groups are retained in the same position. If the transition state were four-membered, these groups would be meta in the rearranged products (IIb).



(a) (b) (II)

Several workers (6,11,14,18) have presented evidence that a stable cyclic intermediate radical such as (IIIb), which could be attacked at either of two positions to yield rearranged or unrearranged product, is not important in aryl migrations. The α,α-dimethyl-β-phenylethyl radical (IIIa) generated by the di-t-butyl peroxide-catalyzed decarbonylation of α,α-dimethyl-β-phenylpropionaldehyde gave only isobutylbenzene (6). Thus equilibrium between (IIIa), the bridged intermediate (IIIb), and the neophyl (IIIc) radicals is not attained under the conditions of this reaction.



(a) (b) (c) (III)

It is possible, however, that (IIIb) existed and reacted more rapidly at α and β than it was converted to (IIIa) (9).

In an investigation of the rearrangement of the neophyl radical generated by the di-t-butyl peroxide-catalyzed decarbonylation of β-phenylisovaleraldehyde with the pure liquid aldehyde (initially 6.4 molar) and with a 1.0 molar solution of the aldehyde in chlorobenzene, Süebold (14) found that the ratio of rearranged to unrearranged product was 1.3 and 4.0, respectively. If the cyclic intermediate radical (IIIb) were formed and would react at either α or β to yield the observed products, t-butylbenzene and isobutylbenzene, the ratio of isobutylbenzene to t-butylbenzene should be

independent of the concentration of hydrogen atom donor. Since this was not the case, it was concluded that the neophyl radical is formed as a discrete intermediate without the aid of bridging involving the phenyl group and that rearrangement and hydrogen abstraction compete as alternative paths for the reaction of this radical.

This mechanism is strengthened by recent results obtained by Weinstock and Lewis (Table I; La,b,c)(11). In their studies on free radical additions to 3,3-diphenyl-1-butene they found that the t-butyl hydroperoxide-catalyzed addition of thiolacetic acid and n-butyl mercaptan proceeds without rearrangement while the addition of n-butyraldehyde goes with rearrangement of the intermediate radical to form 6,7-diphenyl-4-octanone. The course of these additions after initiation is represented as follows (Y· = $CH_3COS\cdot$, n-$C_4H_9S\cdot$, n-$C_3H_7CO\cdot$):

$$CH_3(C_6H_5)_2CCH{=}CH_2 + \cdot Y \rightleftharpoons CH_3(C_6H_5)_2\dot{C}CHCH_2Y \quad (L) \qquad (1)$$

$$L + HY \longrightarrow CH_3(C_6H_5)_2CCH_2CH_2Y + Y\cdot \qquad (2)$$

$$L \longrightarrow CH_3(C_6H_5)\dot{C}CH(C_6H_5)CH_2\,Y \quad (Lr) \qquad (3)$$

$$Lr + HY \longrightarrow CH_3CH(C_6H_5)CH(C_6H_5)CH_2Y + Y\cdot \qquad (4)$$

For the additions of thiolacetic acid and butyl mercaptan reaction 2 must be faster than reaction 3, while for the addition of n-butyraldehyde the opposite must be true. The different courses of these additions are readily explained by considering the relative reactivity of n-butyl mercaptan and n-butyraldehyde toward radicals as indicated by chain transfer constant measurements. In the system styrene-n-butyl mercaptan at 60° this constant is 22 ± 3 (15), and in the system styrene-n-butyraldehyde it is about 5.7×10^{-4} (16); that is, the benzyl-type radical in these systems can abstract a hydrogen atom from n-butyl mercaptan about 40,000 times as readily as it can from n-butyraldehyde.

These results show that the amount of phenyl migration is at least related to the relative rates of reaction 2 of the addition for the three HY compounds studied. They also provide further evidence that a bridged intermediate radical capable of rearranging is not formed simultaneously with the formation of the radical. Other evidence to support this is the observation by Lapporte (18) that in the decarbonylation of β-phenylisovaleraldehyde the amount of rearrangement is decreased when benzyl mercaptan is added. In this reaction and in similar reactions studied by Harris and Waters (19) and Barrett and Waters (20) the addition of small amounts of benzyl mercaptan greatly increases the chain length of the decarbonylation reaction. Decarbonylation of aldehydes using the radical, $(CH_3)_2\dot{C}CO_2CH_3$, produced by the thermal decomposition of dimethyl-α,α'-azoisobutyrate as initiator, was increased from about 5% to 80-90% for α-branched aldehydes and to a lesser extent for n-aldehydes by the addition of as little as 0.5 mole % of mercaptan. For this reaction the following chain sequence was proposed.

$$(CH_3)_2\dot{C}CO_2CH_3 + C_6H_5CH_2SH \longrightarrow (CH_3)_2CHCO_2CH_3 + C_6H_5CH_2S\cdot \qquad (1)$$

$$C_6H_5CH_2S\cdot + RCHO \longrightarrow C_6H_5CH_2SH + RCO\cdot \qquad (2)$$

$$RCO\cdot \longrightarrow R\cdot + CO \qquad (3)$$

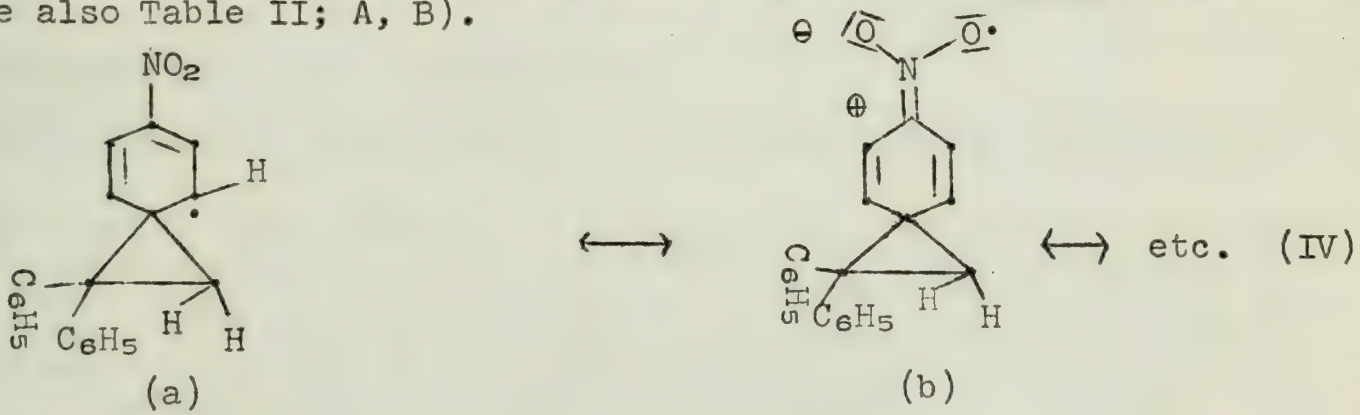
$$R\cdot + C_6H_5CH_2SH \longrightarrow RH + C_6H_5CH_2S\cdot \qquad (4)$$

The greater ease of chain occurrance must be due to the thiyl radical, $C_6H_5CH_2S\cdot$, which can attack a saturated alkphatic aldehyde more readily than do alkyl radicals. Hydrogen transfer through the transition state, which is stabilized by the polar structure,

speeds the reaction. The lifetime of the intermediate neophyl radical would be decreased by a similar reaction so that rearrangement could not occur.

The driving force for aryl migration in the radical initially formed is apparently derived from two sources. The change from a primary or secondary to a more stable tertiary radical is energetically favorable. Also, in radicals which show considerable crowding on the β-carbon atom, the relief of steric strain could provide the driving force for rearrangement (8, 9). Kauer (9), in a comparison of the rearrangement tendencies of the neophyl (Table I; A, B) and β-p-anisyl-β-phenylethyl (Table I; E) radicals, proposed, on the basis of bond dissociation data, that p-anisyl migration in (E) would produce a radical more stable than the one resulting from phenyl migration in the neophyl radical. Thus it appears that crowding on the β-carbon atom of an intermediate radical provides considerable driving force for rearrangement.

The rearrangement of the β-p-nitrophenyl-β,β-diphenylethyl radical (Table I; J) proceeds by preferential migration of the p-nitrophenyl group. But the products of the decarbonylation of the substituted propionaldehyde could not be identified completely, the only identifiable product being 2-p-nitrophenyl-1,1-diphenylethylene. A comparison of the structures of the transition states for phenyl and p-nitrophenyl migration shows that more structures can contribute to the resonance stabilization of the transition state for p-nitrophenyl than for phenyl migration. This increased stabilization no doubt accounts for this group's greater tendency to migrate (see also Table II; A, B).



(IV)

(a) (b)

Structures such as (IVa) are common to both transition states, but increased stabilization is gained by structures like (IVb) for p-nitrophenyl migration.

In a study of the steric requirements of free radical substitution reactions, Meislich and Costanza (10, 43) observed that from the light- or benzoyl peroxide-catalyzed reaction of N-bromosuccinimide with 1,1,1,2-tetraphenylethane rearranged tetraphenylethylene

(46% yield) was recovered as was 48% of the starting material (Table I; K). The normal bromination product, 1,1,1,2-tetraphenyl-2-bromoethane, is not an intermediate for it was found to be stable under the reaction conditions employed. Evidence for the free radical nature of the reaction is as follows: (1) The reaction with NBS does not proceed in the dark. (2) This reaction occurs in the presence of calcium carbonate indicating that hydrogen bromide does not catalyze the reaction. (3) The reaction with NBS and benzoyl peroxide in the dark gave the same product.

$$\rangle N{:}Br \xrightarrow[\text{peroxide}]{h\nu \text{ or}} \rangle N\cdot + Br\cdot \quad (\rangle N{:}Br = \text{NBS}) \qquad (1)$$

$$(C_6H_5)_3CCH_2C_6H_5 + \rangle N\cdot \longrightarrow (C_6H_5)_3\dot{C}CHC_6H_5 + \rangle N{-}H \qquad (2)$$

$$(C_6H_5)_3\dot{C}CHC_6H_5 \longrightarrow (C_6H_5)_2\dot{C}CH(C_6H_5)_2 \qquad (3)$$

$$(C_6H_5)_2\dot{C}CH(C_6H_5)_2 + \rangle N{:}Br \longrightarrow (C_6H_5)_2C{=}C(C_6H_5)_2 + \rangle N\cdot + HBr \qquad (4)$$

$$HBr + \rangle N{:}Br \longrightarrow Br_2 + \rangle N{-}H$$

Step 5 accounts for the recovery of half of the starting material, the formation of bromine in the reaction, and the quantitative yield of succinimide. A similar reaction with 1-phenyl-2,2-dimethyl-propane gave the expected 1-phenyl-1-bromo-2,2-dimethylpropane.

To determine the relative migratory aptitudes of various aryl groups Kharasch and coworkers (2) investigated the thermal decomposition of t-butyl heterotriarylmethyl peroxides (Table II; C, F). These unsymmetrical peroxides were decomposed in cumene at 120-140°; and the reaction may be represented by the following scheme.

$$(Ar)(C_6H_5)_2COOC(CH_3)_3 \xrightarrow{\Delta} (Ar)(C_6H_5)_2CO\cdot + (CH_3)_3CO\cdot \qquad (1)$$

$$(CH_3)_3CO\cdot + C_6H_5CH(CH_3)_2 \longrightarrow (C_6H_5)(CH_3)_2C\cdot + [CH_4 + (CH_3)_2CO, \text{ or } (CH_3)_3COH] \qquad (2)$$

$$(Ar)(C_6H_5)_2CO\cdot \longrightarrow (ArO)(C_6H_5)_2C\cdot \qquad (3)$$

$$(ArO)(C_6H_5)_2C\cdot + (C_6H_5)(CH_3)_2C\cdot \longrightarrow (ArO)(C_6H_5)_2C{-}C(CH_3)_2(C_6H_5) \qquad (4)$$

The final product formed is a 2-methyl-2,3,3-triphenyl-3-aroxypropane or a 2-methyl-2,3-diphenyl-3-aryl-3-phenoxypropane, depending on which group undergoes migration. Treatment of the product with glacial acetic acid in the presence of perchloric acid afforded complete solvolysis to give quantitative yields of phenols which, after identification and quantitative estimation, established the aryl/phenyl migration ratios.

The thermal decomposition of t-butyl triphenylmethyl peroxide was studied in several solvents and, based on the rate of methane evolution, the decomposition is probably first order and is independent of the solvent used (ethylbenzene or cumene). Raley, Rust and Vaughan (17) showed that the decomposition of di-t-butyl peroxide in both the vapor state and in solution is first order, independent of

the solvent used (cumene, t-butylbenzene, and tri-n-butylamine), and involves the same, rate determining dissociation step, cleavage of the oxygen-oxygen bond to form two t-butoxy free radicals. Kharasch thus assumed that decomposition of t-butyl triarylmethyl peroxides also proceeds through an initial breakdown into two free alkoxy radicals. He did not establish the presence of free $(Ar)(C_6H_5)_2CO\cdot$ radicals but did suggest that rearrangement might occur simultaneously with the initial dissociation.

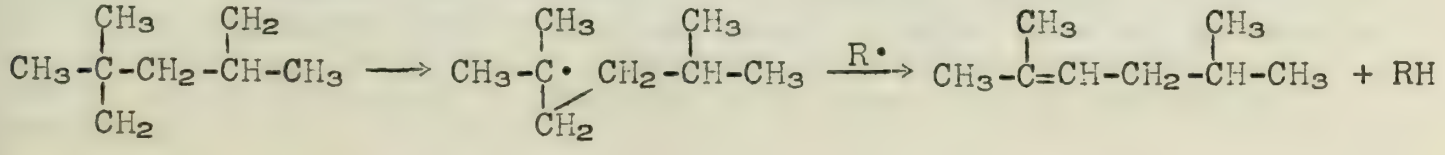
In a similar study, Urry (12) determined aryl/phenyl migration ratios by thermal decomposition of symmetrically substituted peroxides (Table II; D, G-J). The products obtained were ethers analogous to benzpinacol diphenyl ether. Reductive cleavage of these ethers yielded phenol mixtures which were then analyzed.

Bartlett and Cotman (13) recovered phenol, p-nitrophenol, p-nitrobenzophenone, p-nitrophenylcarbinol and biphenyl as thermal decomposition products of p-nitrophenyldiphenylmethyl hydroperoxide (Table II; A) in a sealed tube in benzene at 115-128°. Since acid catalysis of the decomposition of this compound favors phenyl migration, the isolation of p-nitrophenol indicates that this reaction probably involve free radicals. Also, the isolation of biphenyl, a coupling product of solvent radicals, supports the free radical nature of the reaction. Kharasch (2) recovered p-nitrophenol and a mixture of unidentified ketones from the decomposition of (B) in cumene. The course of these reactions is not clear cut, but they undoubtedly involve the initial formation of β-p-nitrophenyl-β,β-diphenylmethoxy radical which undergoes a 1,2-carbon-to-oxygen migration.

ALKYL MIGRATIONS

Free radical rearrangements involving the migration of an alkyl group have been found to occur, but not under moderate conditions. Urry and Nicolaides (6) recovered only 2,2-dimethylbutane and a dimer (probably 3,3,6,6-tetramethyloctane) as unrearranged products of the cobaltous chloride-catalyzed reaction of ethyl magnesium bromide with 1-chloro-2,2-dimethylbutane. Suebold (21) generated the 2,2-dimethylbutyl, cyclohexyl, and cyclopentylmethyl radicals by the di-t-butyl peroxide-catalyzed decarbonylation of their respective carboxaldehydes in the liquid phase at 130 ± 5° and recovered only cyclohexane, methylcyclopentane and 2,2-dimethylbutane, respectively.

In the high temperature (450°) oxidation of 2,2,4-trimethylpentane Rust and Collamer (22) reported that they recovered about one percent of rearranged product as t-amylenes and 2,5-dimethylhexenes. They proposed the following mechanisms by which alkyl 1,2-migrations could occur:



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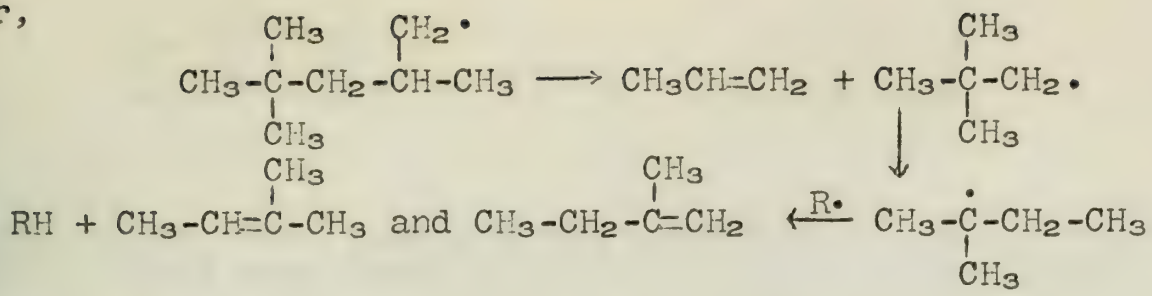


The formation of these rearranged products could also be explained on the basis that methyl and isobutyl radicals attacked isobutene, one of the major products, to produce radicals which appeared to have rearranged. The data found do not support one mechanism or the other.

The first reasonably well substantiated report of alkyl migration in a free radical intermediate was presented by Kharasch and coworkers (23, 24). Vapor phase photochemical bromination of 2,2,4,4-tetramethylpentane occurs readily at 200° in high yield provided the bromine is introduced slowly so that a large excess of hydrocarbon is present at all times. The rearranged product, 2-bromo-2,3,4,4-tetramethylpentane, was obtained in 72% yield; also, an unidentified dibromide, $C_9H_{18}Br_2$, was recovered in 5% yield. The rearranged bromide may have been produced by rearrangement of the di-t-butylmethyl radical, or else di-t-butylmethyl bromide may have been formed first and then rearranged in the presence of hydrogen bromide by an ionic mechanism. When they generated the di-t-butylmethyl radical from the chloride with isopropylmagnesium bromide and cobaltous bromide, they obtained 2,2,4,4-tetramethylpentane and 2,3,4,4-tetramethylpentene-1. These products could have been formed by disproportionation between the rearranged and unrearranged radicals, or by disproportionation of two unrearranged free radicals such that migration and disproportionation occur during collision.

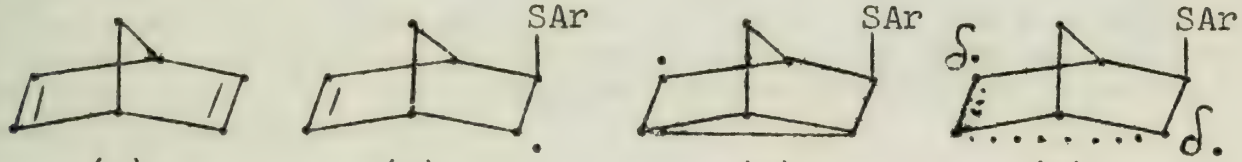
The structure of the rearranged bromide was surmised from several facts: (1) It reacted instantly with silver acetate in 75% ethanol to give 2,3,4,4-tetramethylpentene-1. 2-Chloro-2,3,4,4-tetramethylpentane was shown to react rapidly with alcoholic silver nitrate to yield the same olefin, while di-t-butylmethyl chloride reacted hardly at all under the same conditions. (2) When the bromide was dissolved in anhydrous ether and shaken with the silver salt of 3,5-dinitrobenzoic acid, 2,3,4,4-tetramethylpentene-1, silver bromide, and 2,5-dinitrobenzoic acid were recovered. (3) Ozonolysis of the olefin gave formaldehyde but no acetone. Even with these data the possibility that rearrangement occurred by an ionic mechanism cannot be discounted.

Two examples of what can also be classified as a 1,2-migration of an alkyl group in a free radical intermediate have recently been reported. Roberts and coworkers (25) reacted norbornene (bicyclo [2.2.1]-2-heptene) (Va) with N-bromosuccinimide in boiling carbon-tetrachloride, the reaction catalyzed by benzoyl peroxide, and recovered in 35% yield 3-bromonortricyclene (Vb) as rearranged product.

(a) (b) (V)

Free radical additions of ethyl bromoacetate (26) and p-thiocresol (27) to (Va) were found to proceed without rearrangement. In each case the products resulting from cis-exo addition were formed.

Cristol and coworkers (28) have investigated the addition of thiophenol and p-thiocresol to 2,5-norbornadiene (bicyclo[2.2.1]-2,5-heptadiene) (VIa). The reaction proceeds by a free radical chain mechanism involving intermediates such as (VIb) and (VIc) to yield the observed aryl thioethers, exo-5-norbornen-2-yl and 3-nortricyclyl aryl thioether. That the non-classical mesomeric homoallylic radical (VId) is not an intermediate which can react at



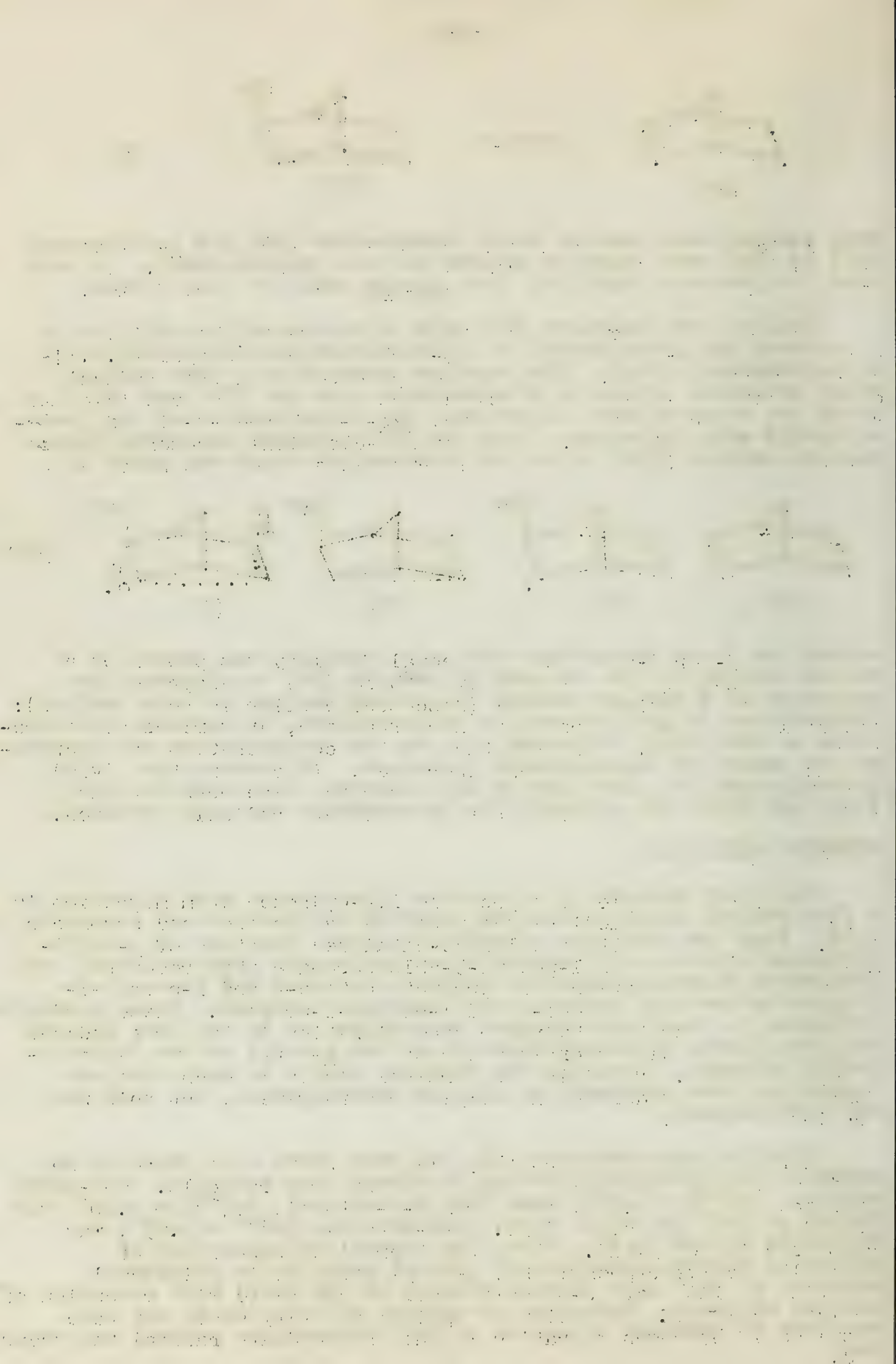
(a) (b) (c) (d) (VI)

either the 3- or 5-position with equal facility was proven by a method similar to the one used by Suebold (14) to disprove the existence of a similar radical (discussed earlier in this seminar): The addition of p-thiocresol to norbornadiene, at various concentrations of the thiol, indicated that as the concentration was decreased the amount of rearrangement increased. This means that (VId) probably does not give rise to the observed thioethers but that (VIb) and (VIc) are actually the intermediate radicals involved.

HYDROGEN MIGRATION

The first example of a possible 1,2-hydrogen atom migration in a free radical intermediate was reported by Kharasch and coworkers (29). From the cobaltous chloride-catalyzed reaction of n-butylmagnesium bromide with 1-phenyl-3-chloropropane they recovered the unexpected disproportionation products butene-2 and 1-phenyl-1-propene rather than butene-1 and 1-phenyl-2-propene. These products indicated to them that hydrogen atom migration in the free radical occurred during disproportionation of two n-butyl or two 3-phenylpropyl radicals. Possibly the terminal olefin in each case was formed and then underwent an allylic rearrangement, but this was not investigated.

Kornblum and coworkers (30, 31) have shown that there is no evidence for hydrogen migration in alkoxy free radicals. d-2-Octyl nitrite, $[\alpha]^{25}D$ + 6.44°, made from d-2-octanol, $[\alpha]^{25}D$ + 9.30°, was heated at 200° for eight days. d-2-Octanol, $[\alpha]^{25}$ + 9.23°, was recovered in 80% yield. Also, the thermal decomposition of optically active α-phenylethyl t-butyl peroxide in thiophenol solution at 125° gave α-phenylethanol in 55% yield with retention of optical activity. Retention of optical activity would not have resulted if hydrogen migration in the intermediate radical had occurred.



1,2-Hydrogen atom migration under extremely energetic conditions has been reported by Friedmann and Libby (32). The effect of recoil from the capture of γ-radiation produced by the (n,γ) reaction on bromine 81 in both normal- and isopropyl bromide was investigated. It was found that irradiation of either bromide gave the same mixture of the two bromides, and the ratio of n-propyl bromide to isopropyl bromide in each case was about 2.4. The free hydrocarbon radicals formed after γ-capture apparently have enough energy to isomerize before recombination with the bromine radical.

HALOGEN MIRATIONS

Urry and coworkers (33, 34, 35) have reported several examples of 1,2-migrations of chlorine atoms in free radical intermediates. The photochemical reactions of diazomethane with polyhalomethanes and α-haloesters to yield polyhaloneopentane derivatives and β-haloesters, respectively, were considered to proceed by a free radical, chain mechanism involving chlorine migration at each step of the chain reaction. The reaction of carbon tetrachloride and diazomethane was very thoroughly studied (35), and the experimental evidence found leaves little doubt about the free radical nature of the reaction. For this reaction, after initiation, the following mechanism was proposed.

$$CCl_3CH_2\cdot \longrightarrow \cdot CCl_2CH_2Cl \qquad (1)$$

$$\cdot CCl_2CH_2Cl + CH_2N_2 \longrightarrow \cdot CH_2CCl_2CH_2Cl + N_2 \qquad (2)$$

$$\cdot CH_2CCl_2CH_2Cl \longrightarrow (CH_2Cl)_2CCl\cdot \text{ , etc.} \qquad (3)$$

$$(CH_2Cl)_3CCH_2\cdot + CCl_4 \longrightarrow C(CH_2Cl)_4 + \cdot CCl_3 \qquad (7)$$

Nesmayanov and coworkers (36, 37) have also reported chlorine migration in free radical intermediates. The addition of bromotrichloromethane and hydrogen bromide to 3,3,3-trichloropropene in the presence of benzoyl peroxide gave 1-bromo-1,1,2,4,4,4-hexachlorobutane and 3-bromo-1,1,2-trichloropropane, respectively, as rearranged products. The radical $Cl_3C\dot{C}HCH_2X$, where X=Br or CCl_3, is formed after initiation and isomerizes to $Cl_2\dot{C}CHClCH_2X$ prior to the chain-propagating step, the transfer of a β-chlorine atom from the radical to a reactant molecule. Homolytic isomerization of 3,3,3-trichloro-2-bromopropene to 1,1,2-trichloro-3-bromopropene occurs on standing for one to two days in the presence of light or when exposed to ultraviolet light for several minutes. Hydroquinone or dimethylaniline inhibits the isomerization.

REARRANGEMENTS DURING ELECTROLYSIS REACTIONS

Walker and Wood (38) in 1906 reported that the electrolysis of sodium β,β-dimethyl glutarate in an aqueous solution produced about 1% of a rearranged product, 2-methyl-1-butene. Hine (39) suggested that this could occur in a trimetylene diradical which he postulated was formed by the loss two electrons and carbon dioxide from the original ion.

Urry (12) reported the observation that rearrangement occurred during the electrolysis of β-phenylisovaleric acid in ethanol, resulting in the formation of isobutylbenzene, 2-methyl-3-phenylpropene, and 1-phenyl-2-methylpropene, which accounted for about 23% of the products formed. Presumably the rearrangement occurred in the neophyl radical which was formed, for about 55% of unrearranged dimer, bineophyl, was also recovered. Breederveld and Kooyman (40) ran a mixed electrolysis of the same acid with an excess of sodium acetate in methanol using a much higher current density than did Urry and recovered only unrearranged products. They proposed that the high current density employed caused a high concentration of free radicals to occur at the anode, thereby providing conditions for radical-radical interaction rather than rearrangement.

Doubt that these rearrangements proceed through a free radical intermediate has been substantiated by work done by Muhs (41, 42). From the electrolysis of 1-methylcyclohexylacetic acid in methanol he recovered as rearranged products 1-methylcycloheptene (11%) and methyl 1-methylcycloheptyl ether (13%). Di-t-butyl peroxide catalyzed decarbonylation of 1-methylcyclohexylacetaldehyde gave only unrearranged product, 1,1-dimethylcyclohexane. Also, since a free radical attack on the solvent would result in the abstraction of a hydrogen atom from carbon rather than oxygen (42), the formation of the ether cannot be explained by this type of reaction. A more reasonable explanation for these rearrangements is that the radicals initially formed may lose carbon dioxide and an electron at the anode to form carbonium ions, for a carbonium ion mechanism can account for the rearranged products found in all of these electrolysis reactions.

BIBLIOGRAPHY

1. H. Wieland, Ber., 44, 2550 (1911).
2. M. S. Kharasch, A. C. Poshkus, A. Fono and W. Nudenberg, J. Org. Chem., 16, 1458 (1951).
3. J. Kleiman, University of Illinois Organic Seminars, II Semester, 1956-57, p. 33.
4. W. H. Urry and M. S. Kharasch, J. Am. Chem. Soc., 66, 1438 (1944).
5. S. Winstein and F. H. Süebold, Jr., ibid., 69, 2916 (1947).
6. W. H. Urry and N. Nicolaides, ibid., 74, 5163 (1952).
7. M. J. Hurwitz, Thesis (Columbia University) 1952; Dissertation Abstracts, 15, 699 (1955).
8. D. Y. Curtin and M. J. Hurwitz, J. Am. Chem. Soc., 74, 5381 (1952).
9. J. C. Kaňer, Thesis (University of Illinois), 1955.
10. H. Meislich and J. Costanza, Abstracts of the 132th Meeting of the American Chemical Society, New York, N.Y., Sept. 8-13, 1957, p. 9-P.
11. J. Weinstock and S. N. Lewis, J. Am. Chem. Soc., 79, 6243 (1957).
12. W. H. Urry, Am. Chem. Soc. Nat'l. Org. Chem. Symposium, 12, 30 (1951).
13. P. D. Bartlett and J. D. Cotman, Jr., J. Am. Chem. Soc., 72, 3095 (1950).
14. F. H. Süebold, Jr., ibid., 75, 2532 (1953).
15. C. Walling, ibid., 70, 2561 (1948).

16. R. A. Gregg and F. R. Mayo, ibid., 75, 3530 (1953).
17. J. H. Raley, F. F. Rust, and W. E. Vaughan, ibid., 70, 1337 (1948).
18. S. Winstein, R. Heck, S. Lapporte and R. Baird, Experientia, 12, 138 (1954).
19. E. F. P. Harris and W. A. Waters, Nature, 170, 212 (1952).
20. K. E. J. Barrett and W. A. Waters, Discussions Faraday Society, 14, 221, 255 (1953).
21. F. H. Suebold, Jr., J. Am. Chem. Soc., 76, 3732 (1954).
22. F. F. Rust and D. O. Collamer, ibid., 76, 1055 (1954).
23. M. S. Kharasch, Y. C. Liu and W. Nudenberg, J. Org. Chem., 19, 1150 (1954).
24. Idem, ibid., 20, 680 (1955).
25. J. D. Roberts, E. R. Trumbull, Jr., W. Bennett and R. Armstrong J. Am. Chem. Soc., 72, 3116 (1950).
26. J. Weinstock, Abstracts of the 128th Meeting of the American Chemical Society, Minneapolis, Minn., Sept. 11-16, 1955, p. 19-O.
27. S. J. Cristol and G. D. Brindell, J. Am. Chem. Soc., 76, 5699 (1954).
28. Idem and J. A. Reeder, ibid., 80, 635 (1958).
29. M. S. Kharasch, F. L. Lambert and W. H. Urry, J. Org. Chem., 10 298 (1945).
30. N. Kornblum and E. P. Oliveto, J. Am. Chem. Soc., 71, 226 (1949).
31. N. Kornblum and H. E. DeLaMare, ibid., 74, 3079 (1952).
32. L. Friedman and W. F. Libby, J. Chem. Phys., 17, 647 (1949).
33. W. H. Urry and J. R. Eiszner, J. Am. Chem. Soc., 74, 5822 (1952).
34. W. H. Urry and J. W. Witt, ibid., 76, 2594 (1954).
35. W. H. Urry, J. R. Eiszner, J. W. Witt, ibid., 79, 918 (1957).
36. N. Nesmeyanov, R. Kh. Freidlina, and L. I. Zakharkin, Quart. Revs., 10, 330 (1956); Dokolady Akad. Nauk S.S.S.R., 81, 199 (1951).
37. N. Nesmeyanov, R. Kh. Freidlina, and V. N. Kost, Tetrahedron, 1, 241 (1957).
38. J. Walker and J. K. Wood, J. Chem. Soc., 89, 598 (1906).
39. J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N.Y., 1956, p. 446.
40. H. Breederveld and E. C. Kooyman, Rec. trav. chim., 76, 297 (1957).
41. M. A. Muhs, Thesis (University of Washington), 1954; Dissertation Abstracts, 14, 765 (1954).
42. C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N.Y., 1957, pp. 479, 522, 580.
43. H. Meislich, private communication.

INFRARED INTENSITIES IN ORGANIC CHEMISTRY

Reported by J. L. Tveten March 24, 1958

Introduction.---The qualitative use of infrared spectroscopy has been a valuable tool for the organic chemist for some time, as has been the use of relative intensities for quantitative analysis; however it is only recently that the photometry of infrared radiation has become precise enough to allow measurements of absolute intensities. This seminar will be concerned with general techniques of intensity measurement, its use in quantitative analysis of organic compounds, and the measurement and applications of absolute intensities. For a more detailed treatment of the theory of infrared spectra reference should be made to the volume on chemical applications of spectroscopy edited by West (1) and to the comprehensive monograph of Herzberg (2).

General Considerations.---The basis of all quantitative work with infrared intensities is the Lambert-Beer law

whereby

$$I = I_o \exp(-Kcx)$$

$$K = \left(\frac{1}{cx}\right)\log_e (I_o/I)$$

In this formula I_o is the energy of the radiation entering the absorbing material and is measured as the energy transmitted by a reference cell containing only solvent. I is the energy transmitted by the absorbing material which is present in the sample at a concentration of c moles per liter in a cell x centimeters in length. The quantity K is known as the absorption coefficient.

For many purposes it is more convenient to use common logarithms and write

$$\epsilon = \left(\frac{1}{cx}\right) \log_{10} (I_o/I)$$

where ϵ is the molecular extinction coefficient. One other term of great importance is the absorbance (A) where

$$A = \epsilon cx = \log_{10} (I_o/I)$$

An important corollary of Beer's law is the law of additivity of absorbance which states that the absorbance A of a mixture is equal to the sum of the absorbances of its components. This means that equal absorbing paths of the same material will always absorb the same fraction of the incident light. This enables the concentration of a component in the mixture to be calculated and is the basis of the standard methods of quantitative analysis which will be covered later in this discussion.

In the measurement of infrared intensities some simple ratio of I and I_o is used. The common functions employed are the following.

Percentage transmission..... $100\ I/I_o$

Absorbance (optical density)... $\log_{10} (I_o/I)$

Of these units the absorbance is preferred in most cases, since for moderate intensities, the absorption plotted on this scale is directly proportional to the concentration of the absorbing material. Both frequency reported in units of wave numbers (ν), measured in reciprocal centimeters ($cm.^{-1}$), and wavelength (λ) measured in microns (μ) have been used as the abcissa in infrared measurements. Of the two, the frequency is preferred for intensity work since it is the unit used for calculation of band areas.

Of greater theoretical importance than the height of absorption peaks in terms of absorbance or molecular extinction coefficients is the integrated absorption intensity. This is the actual area beneath the absorption curve and is a much more reliable criterion for absolute measurements. A great deal of work has been reported on integrated intensities, generally in the gas phase; however it is only quite recently that attempts have been made to correlate the areas with structures of organic compounds.

Error and Reproducibility.---There are numerous possible sources of error in intensity measurements (1,3), and these must necessarily be considered in the evaluation of the data obtained.

Reflection losses of energy in the cells are of considerable importance in accurate work. For a pair of well-matched cells the reflection losses at the outer faces cancel, but losses as the radiation enters and leaves the liquid medium are different since the refractive indices of the solvent and solution are not the same. This difference can generally be considered negligible for dilute solutions but becomes more serious in measurements on pure liquids.

Scattering losses, solvent absorption, stray radiation, non-linearity in the detecting and recording system and many other factors may lead to error in intensity measurements; however these can be greatly reduced with improved instruments and well-matched cells.

In all quantitative work it is assumed that the absorbing material is uniformly distributed in the radiation beam. In solution, of course, this is essentially true, but when working with solids in the form of mulls or films the possibility of nonhomogeneous distribution becomes of great importance. Thus it is best to use solutions for quantitative work whenever possible. When it is necessary to use solids great care must be taken to prepare homogeneous samples.

It has been shown that finite slit width has a large effect on the absorption spectrum and may cause large deviations in the height of the absorption peak (4). This is due to the fact that Beer's law assumes that the incident radiation is strictly monochromatic. Since the exit slit of the monochromator is necessarily of finite width, however, the radiation is not really monochromatic but contains a range of frequencies. This causes the failure of Beer's law and a decrease in the extinction coefficient of a given absorption band accompanied by band broadening.

Russell and Thompson (5) have found that in order to obtain fairly accurate absolute values for the height of a given band, the slit width must be less than one fifth $\Delta\nu_{1/2}$, the band width at one half intensity. Most fairly sharp absorption peaks in the infrared region have a $\Delta\nu_{1/2}$ value of approximately 5 $cm.^{-1}$, necessitating a slit width of less than 1 $cm.^{-1}$. However Russell and Thompson also found that the integrated intensity of a given band is almost independent of slit width in the range generally used. Thus it is possible to obtain better resolution and still measure fairly accurately the absolute intensity.

Temperature effects in infrared analysis have been investigated (6) for several phenols in solvents of very low vapor pressure. It was found that there was a slight shift of bands to lower frequencies with increasing temperature. The magnitude of the shift was about 1 $cm.^{-1}$ for a 50° temperature rise. Accompanying this shift was a decrease in the absorbance. At 25° a temperature increase of 45-50° resulted in a

decrease of 8-15% in the absorbance. Approximately 4% of this decrease was shown to be due to decreased concentration of absorbing material caused by expansion of the solvent; however this does not explain the entire effect.

Brown (7) has made more detailed calculations of this effect and has shown that the lower absorption maximum may be attributed to molecular collisions which change the shape of the absorption curve. This theory does not predict a decrease in integrated intensity with increasing temperature, but as yet very little has been done to substantiate this theory.

Although these temperature effects are important in theoretical work, they are relatively insignificant in organic applications as long as spectra are obtained at normal room temperatures (15-35°).

One of the most important considerations in determining the accuracy of quantitative measurements is the optimum absorbance or transmission. It can be shown (8) that the minimum percentage error is found when the absorbance is 0.43. The function, however, changes slowly enough so that values of absorbance between 0.2 and 0.7 will give quite good accuracy for most applications.

Bowman and Tarpley (9) conducted a study of the reproducibility of infrared intensities over a period of several months. They made accurate measurements on polystyrene films using several types of absorption bands. Using the "base line" methods which will be described later, they found that the absorbance reproducibility when measurements were repeated with the same instrument on the same day was as low as 0.3%. Over a period of weeks the absorbance sometimes varied by as much as 4%. When measurements are being made over a considerable period of time it is essential to adjust the 0 and 100% transmission points to the same position for all measurements.

Using careful technique and adjusting samples so that the absorption is neither very high nor very low, it is generally possible to approach a relative accuracy of 1% in quantitative work. It must be noted, however, that the results obtained are constant only for a given instrument and may not be reproduced on another spectrometer. As will be seen later, integrated intensities are much more reliable in an absolute sense, but they too are partially dependent on the system used.

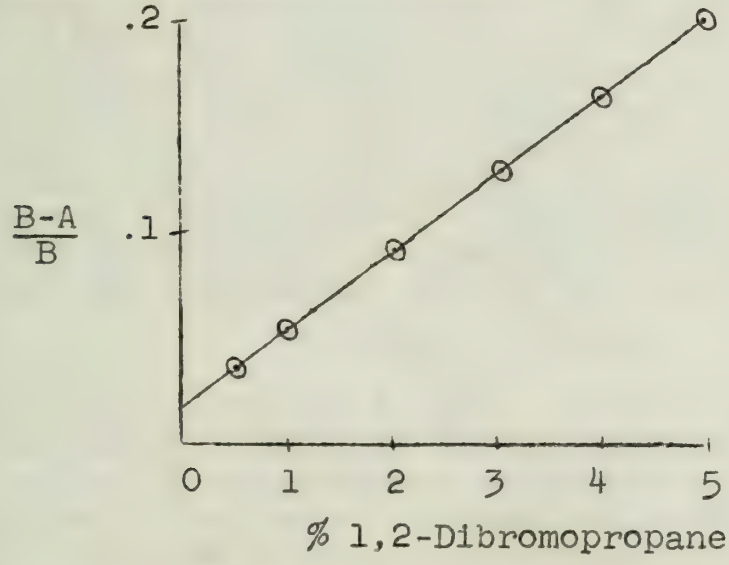
QUANTITATIVE ANALYSIS

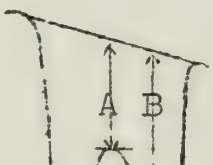
There are several methods available for quantitative analysis depending on the speed and accuracy desired and the kind of sample to be used. For reliable results it is generally necessary to construct a "working curve", and such a curve is used whenever possible. This involves using a series of mixtures of known composition and plotting some function of the absorption against percentage of the material to be determined. When such a procedure is used it is possible to obtain accurate results even when Beer's law fails and the absorbance is not a linear function of concentration. It should be emphasized that such a working curve is characteristic of a specific infrared instrument and should not be used for calculations from spectra obtained on another instrument. The same cells, slit width, scanning speed, etc. must also be used for all measurements.

Base Line (Absorbance) Method.---Perhaps the most widely used method of quantitative analysis with infrared spectra is the base line method devised by Wright (10) which combines both speed and accuracy for a large number of cases. First a complete spectrum is obtained of the compound to be determined, as well as each impurity. For the compound in question a peak is then selected which is characteristic of that component and in which region each of the other components shows relatively little absorption. A small range of frequencies on each side of the band under consideration is then scanned and a suitable base line drawn. In most cases the line may be drawn from the absorption minimum on each side of the peak. Some function of the absorption or transmission, depending on the scale available, is measured for the distance from the base line at the center of the band to the maximum and this is plotted against the concentration of the component. After such a curve has been drawn for a series of mixtures of known composition, the values obtained from unknown mixtures may be applied directly to the curve and the concentration obtained.

A slightly modified base line method was used by Wright for the determination of several halogenated hydrocarbons. An example is the determination of small amounts of 1,2-dibromopropane in 1,3-dibromopropane. Although the spectra of the two compounds are quite similar, there are nevertheless characteristic differences, one of them being the absorption peak at 1372 $cm.^{-1}$. In the 1,3-isomer this peak is a single one, whereas in 1,2-dibromopropane it is split into two peaks. Mixtures of the two isomers show amounts of peak splitting corresponding to concentration.

Figure I shows the base line and measurements made on the spectrum and the working curve constructed for small amounts of 1,2-dibromopropane. Wright found that with this method he could obtain an accuracy of $\pm$ 0.05 per cent (of the total sample) and a concentration as low as 0.3 per cent could be detected.

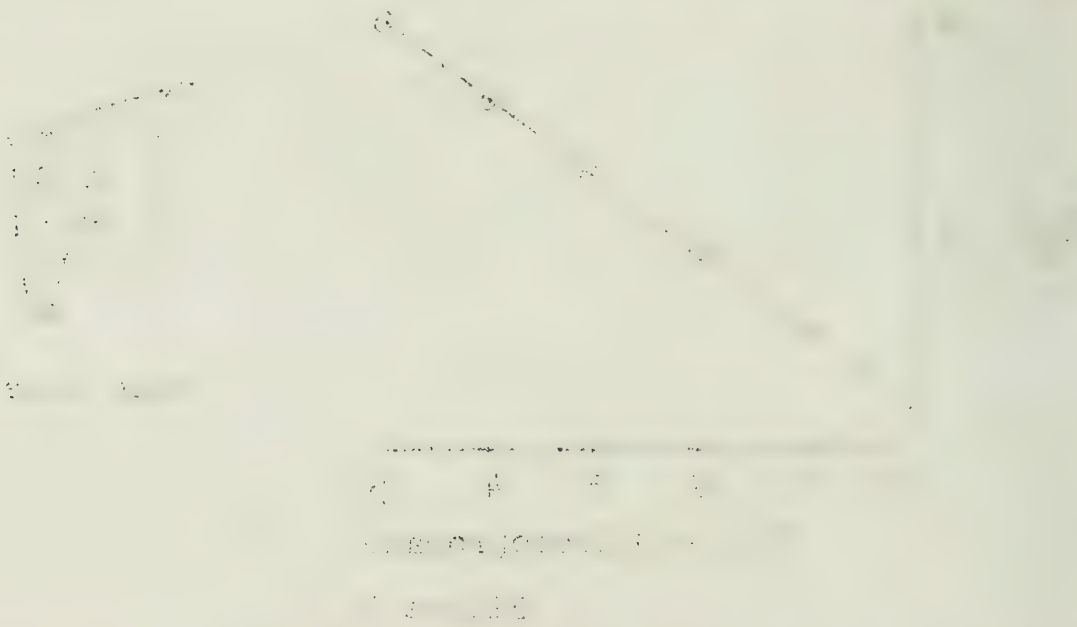




Base Line

Figure I

Similar methods have been used for numerous analysis problems including liquid hydrocarbon mixtures (11), mixtures of phenol, cresols, xylenols and ethyl phenols (12) and many others. Another interesting application is the determination of 1,2-addition in polymers and copolymers of butadiene by Treumann and Wall (13). They found that the absorbance of the peak at 910 $cm.^{-1}$ characteristic of the vinyl group varies with the relative concentration of vinyl segments and is



essentially independent of other structural features such as chain length. Thus by simple absorbance measurements of the characteristic peak, they were able to estimate the number of vinyl groups and hence the relative amount of 1,2-addition.

Sometimes, as in the case of a crude reaction mixture, it is impossible to construct a working curve. In this case a crude base line method may still be used to estimate the concentration of a desired compound. The only procedure available for such a mixture is to obtain a spectrum of the mixture at a known concentration in a suitable solvent and a spectrum of a solution of the pure compound of the same concentration. A peak characteristic of the compound is then selected and base lines drawn for each curve. The absorbances are then obtained and the concentration of the material in the mixture calculated by Beer's law. Accuracy is very difficult to estimate in such cases and is often quite poor since the method does not allow for failure of Beer's law or absorption of unknown impurities in the mixture.

Simultaneous Equations.---Although the base line method of analysis is widely applicable to organic problems, there are times when it lacks sufficient accuracy (because of absorption characteristics of the components of the mixture). When several components are present in the mixture it is often impossible to find bands unique to each component. If other materials present absorb in the same region to any great extent the methods described above fail and it becomes necessary to adopt a more involved procedure.

Daasch (14) has used a method of simultaneous equations to ascertain the relative amounts of five isomers of 1,2,3,4,5,6-hexachlorocyclohexane obtained from the industrial preparation of the compound by chlorination of benzene. Spectra of each of the pure isomers of the hexachlorocyclohexane were obtained at several concentrations in carbon disulfide. For each isomer a peak in the region 700 to 850 $cm.^{-1}$ was selected and the molecular extinction coefficient (ϵ) calculated from the observed absorbance (A) and known concentration (c) and cell length (x). These absorption bands were found to follow Beer's law very closely. The mixture to be analyzed was then placed in the cell, the spectrum obtained, and the absorbance calculated at the frequency characteristic of each isomer. Since the spectra were found to obey Beer's law, the absorbance at any point may be regarded as the sum of the absorbances of the components. Thus

$$A_{obs.} = \epsilon_1 c_1 x_1 + \epsilon_2 c_2 x_2 + \epsilon_3 c_3 x_3 + \ldots$$

where subscripts 1,2,3, etc. refer to each isomer present. For a mixture of n components the absorbance is measured at n frequencies and the set of n simultaneous equations solved for the individual concentrations. When known mixtures were analyzed by this method, it was found that the accuracy obtainable was $\pm$ 0.5% of the total sample.

This method has been applied to multicomponent hydrocarbon mixtures (15), isomeric xylenes and ethylbenzene mixtures (16) and similar mixtures which would otherwise be extremely difficult to analyze. It may generally be relied on for considerable accuracy and its main drawback is the amount of time required for actual experimental work and for calculations. However once the extinction coefficients have been obtained for the components, data for unknowns may be obtained quite easily and the preliminary work need only be done once. Electronic computors when available also are of considerable help, although the

equations may be solved by ordinary methods. A graphical method described by Dewar and Urch (17) has also been devised for the solution of the equations obtained.

Differential Method.---A method has been described by Robinson (18) in which very small amounts of impurities can be determined with considerable accuracy. The mixture to be analyzed is placed in the sample cell either as a solution of known concentration or as a liquid. In the reference cell is placed a solution of identical composition except for the impurity to be determined. When the spectrum is scanned over the desired range, only the absorption due to the impurity is recorded. When this is done, the cells are kept in the same beams but the sample and reference are interchanged. When the frequency range is now scanned a curve that is the inverse of the first is formed. The two curves thus form a closed area the height of which may be measured and correlated directly with concentration. Interchanging the cells not only serves to eliminate errors due to cell mismatch but also doubles the absorption to be read from the graph, thus reducing the relative error. In this method, too, a calibration curve is first constructed with mixtures of known concentrations.

Washburn and Scheske (19) have applied this method to the analysis of trace amounts of ketone in a carbinol with excellent results. Determinations of a reaction intermediate, ethyl chlorovinyl ketone, in β-chlorovinylethinylethylcarbinol were made at ketone concentrations of 0.1 to 1.0% with an accuracy of ± 0.02%. In this case solutions of 25% sample and pure carbinol in chloroform were used in the two cells and the intense carbonyl absorption at 1690 $cm.^{-1}$ was used as the ketone peak.

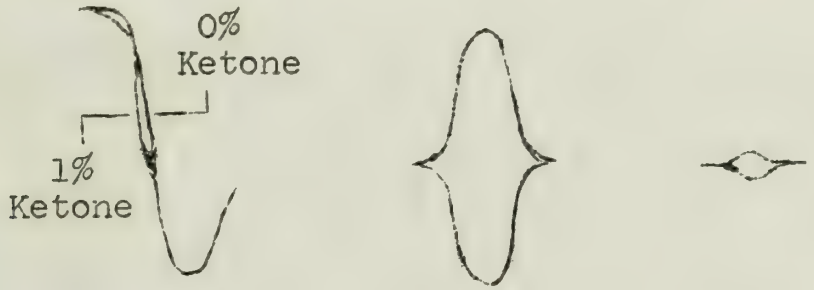


Figure II

Figure II above shows the advantage of the differential method for very small concentrations. In the standard spectrum of the mixture the 1% ketone shows up only as a barely discernible shoulder; while when all other absorption is cancelled out the band becomes very clear.

Derivative Method.---In the measurement of infrared absorption spectra it is difficult to detect low intensity bands which are overlapped by bands of higher intensity. Giese and French (20) have described a method whereby the first derivative of the transmission with respect to wavelength is plotted and have shown its effectiveness with a series of hypothetical curves. An obscured band which may be detected only as a slight shoulder appears as a distinct peak in the derivative plot.

This unique method has been further extended by Collier and Singleton (21) to include actual spectra. By modification of a standard infrared instrument they were able to obtain a plot of the second derivative of the logarithm of the light intensity with respect to time. This derivative quite closely approximates the second derivative of absorbance and is a quantitative function of the absorbing material. Time was used instead of frequency for mechanical reasons, but at constant scanning rate the two are closely related. The mathematics of the curves will not be covered here; however Figure III illustrates the increased resolving power of the successive derivatives for the carbon dioxide doublet at 2330 $cm.^{-1}$.

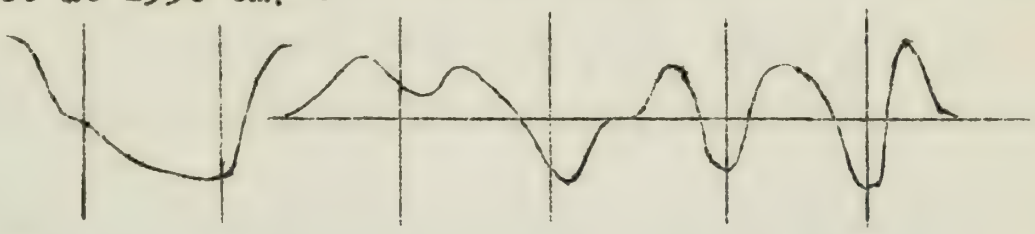


Figure III

It is obvious that such a method can be a powerful tool for both qualitative and quantitative work. Collier and Singleton have applied it to analysis of isomeric cresols with very good results. As yet very little has been done with derivative methods, but their future appears very great.

Special Techniques.---A great many special methods have been devised for the handling of infrared samples and the chemist is by no means limited to liquids, mulls, and organic solutions. Dinsmore and Smith (22) actually obtained excellent results in the quantitative analysis of synthetic rubbers by spreading solutions of the elastomers on salt plates and drying them. In other cases polymers have been pressed into "sandwiches" between sheets of mica, silver chloride or polyethylene and studied in regions transparent to these substances (23). Another common method for small amounts of solids is to mix the solid with powdered potassium bromide and press it into small pellets under high pressure. Such pellets can be made of very constant size and consistency and allow quantitative measurements. By using insoluble materials such as barium fluoride, quartz, sapphire, silver chloride, thallium bromide-iodide, and others for cell construction it is possible to obtain spectra of aqueous solutions of compounds insoluble in organic solvents (24,25). Sometimes it is convenient to include an internal standard in a mixture for quantitative analysis. The standard is mixed with the sample in known concentration and especially when used with solid mulls, provides a band which may be used to determine actual concentration of the sample in the beam. Calcium carbonate (26), potassium thiocyanate (27), and other compounds containing relatively few and sharp bands have been used for such purposes.

Integrated Absorption Intensities.---As was mentioned previously, integrated areas under the absorption curves are of greater theoretical importance than the actual height of the absorption band. Ramsay (28) has studied the factors influencing the shape of the absorption bands and shown that although apparent molecular extinction coefficients may vary by as much as 20% with moderate slit widths, the integrated

intensity differences are only 2-3%. Thus it is possible to obtain a more absolute criterion for absorption than has previously been possible.

The true integrated absorption intensity of a band is defined as

$$\text{Area} = \int K d\nu = \frac{1}{cx} \int \log_e (I_o/I)_\nu \, d\nu$$

where the integral is measured over the limits of the absorption band. In actual use, due to finite slit width, the infrared radiation is not monochromatic and the measured quantity is the apparent integrated intensity

$$\text{Apparent Area} = \frac{1}{cx} \int \log_e (T_o/T)_\nu \, d\nu$$

where T_o and T are the apparent intensities of incident and transmitted radiation.

Ramsay has investigated several methods of obtaining the true integrated intensity of infrared bands of organic compounds, the mathematics of which will not be dealt with here. The first method available is to assume the band has the shape of a Lorentz curve and substitute the quantities read from the spectrum into the integrated Lorentz equation. Since most bands closely approach this idealized shape, the approximation is generally quite good. A second technique, and perhaps the most widely used, is the extrapolation method of Wilson and Wells (29). In this case the apparent integrated intensity is measured directly from the spectrum and plotted against $\log_e (T_o/T)$. In most cases the curve obtained is a straight line of negative slope. The extrapolated value of the apparent area at zero absorption is the true intensity. Other similar techniques have been devised, but these two are the ones generally used in actual applications.

In practice the band area is measured only for a finite frequency range on each side of the band center; however the expression for the area involves integration from $-\infty$ to $+\infty$ if the band is considered to extend indefinitely. Ramsey has worked out a method for calculation of the residual area under the "wings" and these corrections may be applied to the finite values obtained. In general, for most bands of organic compounds, these corrections are of the order of 10%. Brown (30), however, feels that such corrections are ordinarily superfluous, since for a given series of compounds the corrections tend to cancel and the accuracy inherent in the experimental method is no greater than that obtained by assuming this cancellation.

INTENSITY APPLICATIONS

Crystal Structure.---Polarized infrared radiation may often be used to study the orientation of molecules in crystals and polymeric materials. Since infrared absorption is due to a change in dipole moment of the molecule, it is to be expected that radiation in a given direction will have a varying influence on molecules of different orientation. In fact, if a molecule is oriented so the direction of vector dipole change of vibration is in the same direction as the incident beam there will be no absorption. Mann and Thompson (31) have used a beam of polarized radiation in this manner to determine the structure of single crystals and such work is in good accord with X-ray data. Similar methods have been used to study orientation in polymers such as polychlorotrifluroethylene (32) and polyethylene (33). In these cases it was possible to determine the nature of chain orientation after extrusion, rolling, and other orienting processes.

Organic Compounds.---Luther and Czerwony (34) have made a detailed study of the intensity of the C-H deformation bands of normal hydrocarbons and found excellent correlation between the number of methylene groups and the intensity of the band. Both the molecular extinction coefficient and the integrated intensity were found to increase regularily with chain length. Jones (35), in some similar studies, obtained linear plots of extinction coefficient versus methylene units for both the C-H stretching and C-H deformation frequencies.

It is only within the last two years that any great attempt has been made to correlate intensities with the actual chemical structure of the molecule and the electronic environment of the vibrating bond. Brown and Rogers (36) have made a study of the integrated intensity of the O-H stretching band in aliphatic alcohols. The intensity of absorption due to a vibration is proportional to the square of the first derivative of the electric moment with respect to the vibration coordinate, $(\partial u/\partial r)^2$. For the O-H stretch the hydrogen may be considered to be vibrating against the stationary mass of the molecule and the observed intensity due largely to a change in the O-H bond moment by a change in the degree of ionic character in the bond. Since the ionic character of the extended bond will be determined by the electron-donating power of the alkyl groups attached, it should thus be possible to characterize the alcohol by its absorption intensity.

Table I

Alcohol	Observed Area	Corrected Area
Methanol	0.45	0.54
n-Propyl alcohol	.44	.52
sec-Butyl alcohol	.38	.46
t-Butyl alcohol	.34	.39
Cyclopentanol	.44	.50
Cyclohexanol	.38	.44
Benzyl alcohol	.54	.66
Allyl alcohol	.48	.58
Propargyl alcohol	.59	.69
3-Butyn-2-ol	.56	.66
2-Methyl-3-butyne-2-ol	.52	.59
3-Chloro-1-propanol	.63	.74
2,2,2-Trichloroethanol	.76	.92

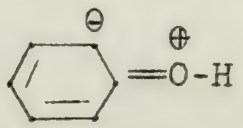
Table I shows the observed intensity and the corrected intensity employing Ramsay's wing corrections for a series of alcohols. The spectra were obtained in dilute carbon tetrachloride solution to eliminate hydrogen bonding. It was estimated that the corrected intensities have a relative accuracy of 0.02 intensity unit. Examination of the data reveals that the O-H intensity is quite sensitive to structural changes; the ratio of highest to lowest intensity in this case being almost 2.5. As expected for the series of simple aliphatic alcohols, the intensity decreases as the electron-donating power of the alkyl group (methyl through t-butyl) increases, and as the polarizability increases. Substitution of methyl groups on the α-carbon atom of propargyl alcohol also decreases the intensity. The difference between cyclopentanol and cyclohexanol is also in agreement with the view that strained ring systems possess a greater electron-withdrawing power than unstrained systems. Substitution of halogen for hydrogen would be expected to increase the intensity to a very large extent and this is readily observed.

Similar work has been done by Brown (37) on the integrated intensities of substituted phenols with similar conclusions.

Table II

Substituent	Observed Intensity	ν_m	σ	pKa
m-Nitro	1.71	3600	0.71	8.35
m-Chloro	1.31	3602	.37	9.02
m-Bromo	1.29	3604	.39	9.11
p-Bromo	1.23	3607	.23	9.34
p-Chloro	1.19	3607	.23	9.38
None	0.99	3610	.00	9.95
p-Methoxy	1.06	3614	-.27	10.20
p-t-Butyl	1.06	3612	-.12	---
3,5-Dimethyl	0.95	3611	-.17	10.17

In this case the intensities were not corrected for wing absorption, but the relative magnitudes are considered correct to within 3%. Decreasing values of the Hammett σ-constant denote greater electron-releasing power, and as might be expected, this decreases the intensity of the O-H band. This is also in accord with the observed pKa values of the phenol. The fact that the O-H group itself interacts with the ring, as shown in structures I and II, is reflected in the higher



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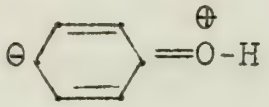


II

intensity values of phenols as compared with aliphatic alcohols.

Russell and Thompson (38) have determined integrated intensities for a large series of amines. Here too there are differences caused by the electrical properties of the molecule as expected. The simple dialkylamines have a very low intensity as compared with the heterocyclic amines and this indicates that $\partial\mu/\partial r$ is much greater in the cyclic compounds. Work by Skinner and Thompson (39) on aliphatic and aromatic nitriles and by Brown (40) on substituted aromatic nitriles has again shown the predicted effect of substituents; however in this case the intensity increases with the electron-donating power of the group since the dipole of the extended bond has the positive charge adjacent to the ring.

Before the advent of integrated intensity work, Cross and Rolfe (41) calculated the extinction coefficients from the spectra of a large number of carbonyl compounds. Although these values may not be depended on in an absolute sense, they nevertheless show that by use of reference compounds a great deal may be determined about the structure of the carbonyl compound from the intensity as well as the frequency of the absorption. Subsequent investigation of a series of steroids (42) indicates that integrated intensities may also be used as a criterion for determination of the carbonyl environment, and is especially useful when there are overlapping bands which make accurate frequency determination impossible.

The field of integrated infrared absorption intensities is still extremely undeveloped; however it is obvious that there is great potential for applications in both synthetic and theoretical organic

chemistry. Among these are calculations of dipole moments (43,44) and the study of hydrogen bonding and molecular association (45-49). There is still need for a great deal of both theoretical and experimental work.

BIBLIOGRAPHY

1. W. West, ed., "Chemical Applications of Spectroscopy", Inter-Science, New York, 1956.
2. G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules", Van Nostrand, New York, 1945.
3. A. E. Martin, Trans. Faraday Soc., 47, 1182 (1951).
4. A. R. Philpotts, W. Thain and P. G. Smith, Anal. Chem., 23, 268 (1951).
5. R. A. Russell and H. W. Thompson, Spectrochim. Acta., 9, 133 (1957).
6. R. H. Hughes, R. J. Martin and N. D. Coggeshall, J. Chem. Phys., 24, 489 (1956).
7. T. L. Brown, ibid., 24, 1281 (1956).
8. R. B. Barnes, U. Liddel and V. Z. Williams, Ind. Eng. Chem., Anal. Ed., 15, 659 (1943).
9. H. M. Bowman and W. B. Tarpley, Appl. Spectroscopy, 7, 57 (1953).
10. N. Wright, Ind. Eng. Chem., Anal. Ed., 13, 1 (1941).
11. J. J. Heigl, M. F. Bell and J. U. White, ibid., 19, 293 (1947).
12. R. A. Friedel, L. Pierce and J. J. McGovern, Anal. Chem., 22, 418 (1950).
13. W. B. Treumann and F. T. Wall, ibid., 21, 1161 (1949).
14. L. W. Daasch, Ind. Eng. Chem., Anal. Ed., 19, 779 (1947).
15. J. W. Kent and J. Y. Beach, ibid., 19, 290 (1947).
16. W. J. Kaye and M. V. Otis, ibid., 20, 1006 (1948).
17. M. J. S. Dewar and D. S. Urch, J. Chem. Soc., 345 (1957).
18. D. Z. Robinson, Anal. Chem., 24, 619 (1952).
19. W. H. Washburn and F. A. Scheske, ibid., 29, 346 (1957).
20. A. T. Giese and C. S. French, Appl. Spectroscopy, 9, 78 (1955).
21. G. L. Collier and F. Singleton, J. Appl. Chem., 6, 495 (1956).
22. H. L. Dinsmore and D. C. Smith, Ind. Eng. Chem., Anal. Ed., 20, 11 (1948).

23. J. D. Sands and G. S. Turner, Anal. Chem., 24, 791 (1952).
24. W. J. Potts, Jr. and N. Wright, ibid., 28, 1255 (1956).
25. H. Sternglanz, Appl. Spectroscopy, 10, 77 (1956).
26. L. E. Kuentzel, Anal. Chem., 27, 301 (1955).
27. S. E. Wiberley, J. W. Sprauge and J. E. Campbell, ibid., 29, 210 (1957).
28. D. A. Ramsay, J. Am. Chem. Soc., 74, 72 (1952).
29. E. B. Wilson, Jr., and A. J. Wells, J. Chem. Phys., 14, 578 (1946).
30. T. L. Brown, Personal communication.
31. J. Mann and H. W. Thompson, Proc. Roy. Soc., A211, 168 (1952).
32. H. Matsuo, J. Polymer Sci., 21, 331 (1956).
33. M. C. Tobin and M. J. Carrano, ibid., 24, 93 (1957).
34. H. Luther and G. Czerwony, Z. Phys. Chem., 6, 286 (1956).
35. R. N. Jones, Spectrochim. Acta., 9, 235 (1957).
36. T. L. Brown and M. T. Rogers, J. Am. Chem. Soc., 79, 577 (1957).
37. T. L. Brown, J. Phys. Chem., 61, 820 (1957).
38. R. A. Russell and H. W. Thompson, J. Chem. Soc., 479 (1955); Proc. Roy. Soc., A234, 318 (1956).
39. M. W. Skinner and H. W. Thompson, J. Chem. Soc., 487 (1955).
40. T. L. Brown, J. Am. Chem. Soc., 80, 794 (1958).
41. L. H. Cross and A. C. Rolfe, Trans. Faraday. Soc., 47, 354 (1951).
42. R. N. Jones, D. A. Ramsay, D. S. Keir and K. Dobriner, J. Am. Chem. Soc., 74, 80 (1952).
43. A. R. H. Cole and H. W. Thompson, Trans. Faraday Soc., 46, 103 (1950).
44. I. M. Mills and H. W. Thompson, Proc. Roy. Soc., A228, 287 (1955).
45. H. Tsubomura, J. Chem. Phys., 24, 927 (1956).
46. J. N. Finch and E. R. Lippincott, ibid., 24, 908 (1956).
47. C. M. Huggins and G. C. Pimentel, J. Phys. Chem., 60, 1615 (1956).
48. R. C. Lord, B. Nolin and H D. Stedham, J. Am. Chem. Soc., 77, 1365 (1955).
49. J. M. Widom, R. J. Philippe and M. E. Hobbs, ibid., 79, 1383 (1957).

THERMAL ADDITION OF DIENOPHILES TO MONOOLEFINS

Reported by W. H. Pittman March 27, 1958

INTRODUCTION

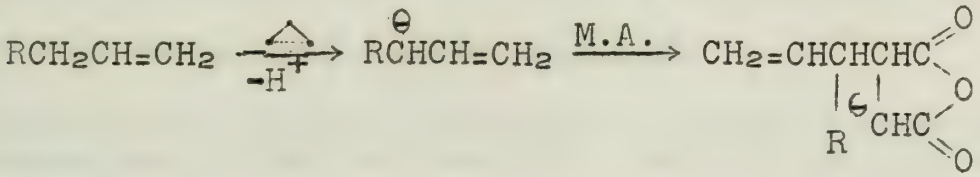
A reaction which is similar in many respects to the well-known Diels-Alder or "diene-synthesis" reaction takes place between dienophiles and monoolefins (or non-conjugated polyolefins) at elevated temperatures. This process (which may be known as the "pseudo-Diels-Alder reaction") is the subject of this report. Both synthetic and mechanistic aspects will be considered.

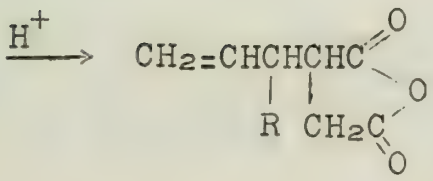
Hultzsch reported in 1939 (1) that maleic anhydride adds to unsaturated terpenes at temperatures in the vicinity of 200° C. Condensation of maleic anhydride with long-chain unsaturated fatty acids (2) and their methyl esters (3) at 150-250° was reported in the early 1940's. However, nothing definite was known about the structures of the adducts until Alder began his investigations into this subject in 1943.

ELUCIDATION OF REACTION COURSE

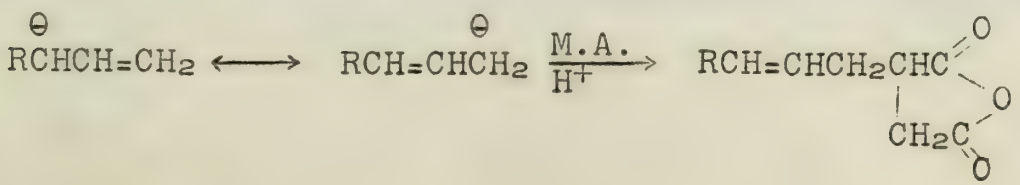
In connection with their work on "diene-synthesis" reactions, Alder and coworkers (4) studied the reaction of maleic anhydride (M.A.) with several monoolefins at 200-250°. They found that maleic anhydride did not react with ethylene under these conditions, but that higher olefins gave well-defined 1:1 adducts. (See Table I.)

On the basis of the products obtained from propylene, isobutylene, cyclopentene, and cyclohexene, Alder postulated (4) that the reaction was one of "allyl substitution" by the M.A. molecule, with previous or simultaneous abstraction of one of the allylic hydrogen atoms. The hydrogen could be removed as a proton, a radical, or a hydride ion; in the event that it left as a proton, the mechanism would be that given below.





The anomalous (or "indirect") addition to allylbenzene and 1,5-hexadiene was at first explained as follows.



Further work, however, showed that the "indirect" reaction occurred in by far the greater number of instances. Also for all compounds of the type shown in Figure 1 for which one of the groups R_1, R_2, R_3, R_4 was different from all the other three, "indirect" substitution was found to occur; in all other cases, the products resulting from the "normal" and the "indirect" reaction were indistinguishable (5). These findings caused Alder to reject his original theory. Instead, he proposed that the reaction passed through a cyclic transition state similar to that suggested for the ordinary "diene-synthesis" reaction (5).

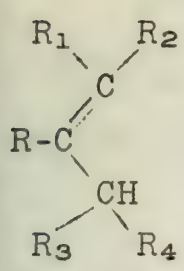
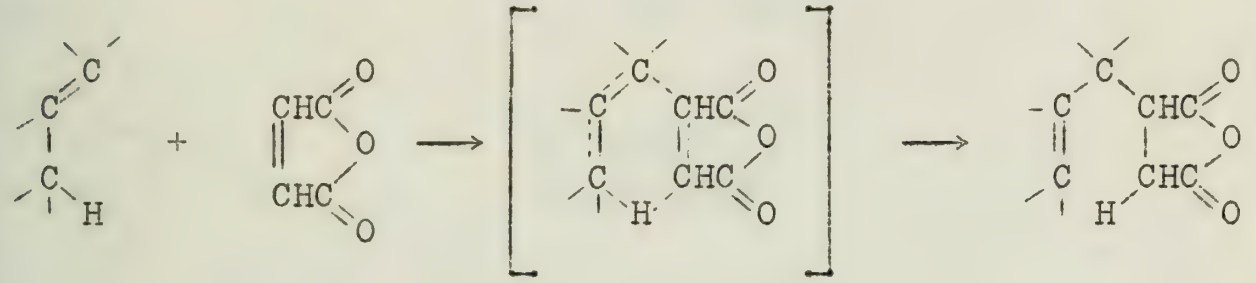


Figure 1



The cyclic transition state approach can be successfully applied to almost all of the olefin-dienophile reactions investigated so far; however, several other mechanisms have since been proposed. These will be discussed later in this report.

In general, the addition of dienophiles to olefins follows these rules (6):

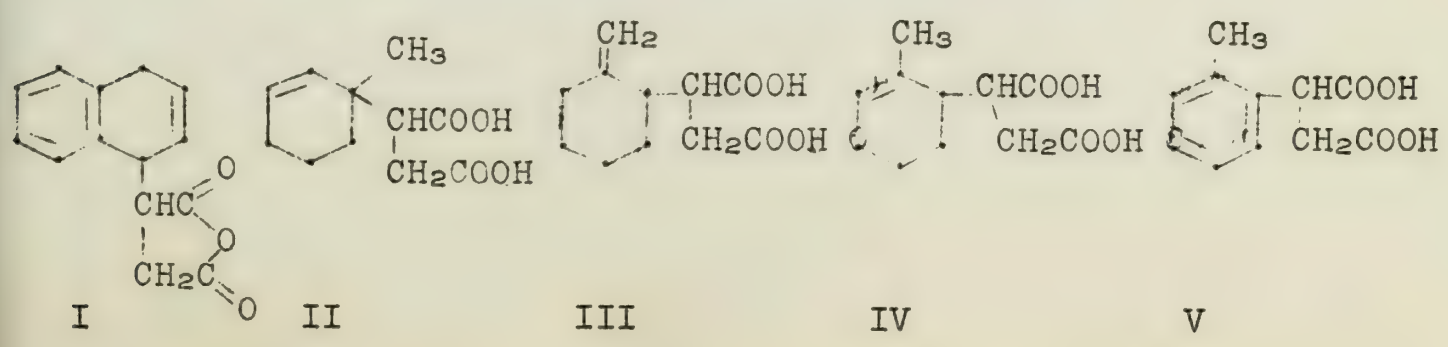
(a) The dienophile adds to the double bond, with simultaneous or subsequent shifting of the double bond away from the dienophile and migration of a hydrogen to the other end of the dienophile.

(b) If the olefin contains a terminal methylene group, dienophile attack takes place entirely at this group. If the double bond is not in a terminal position, a mixture may be formed.

FURTHER REACTIONS WITH MALEIC ANHYDRIDE

The normal addition reactions of maleic anhydride with olefins are summarized in Tables I and II. Several unusual reactions will now be described.

When maleic anhydride is heated with 1,2-dihydronaphthalene at 240°, a 1:1 adduct is obtained (12). The position of the double bond has not yet been determined, but by analogy the product should have the structure I.



I II III IV V

TABLE I

Reaction of Maleic Anhydride with Certain Monoölefins

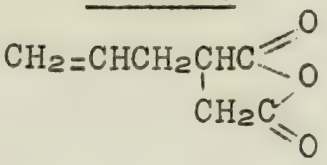
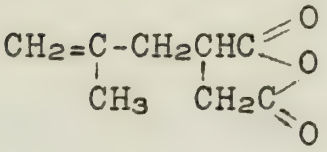
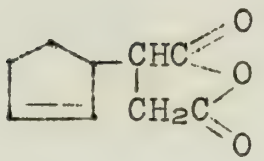
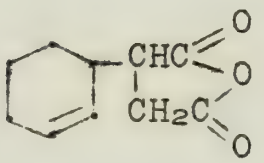
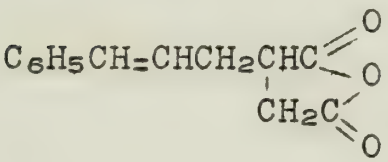
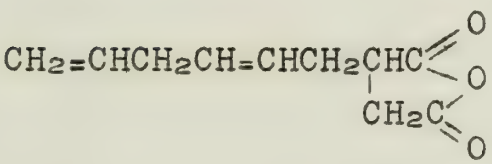
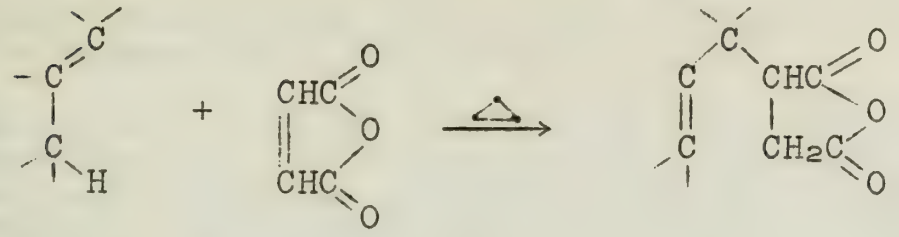
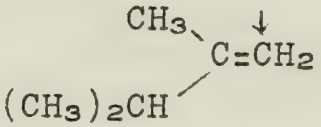
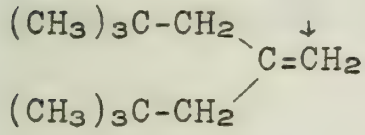
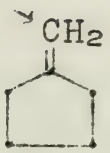
Olefin	Product	Reference
$CH_3CH=CH_2$		4
$(CH_3)_2C=CH_2$		4,7
		4
		4,8
$C_6H_5CH_2CH=CH_2$		4,9
$CH_2=CHCH_2CH_2CH=CH_2$		4

TABLE II

Other Monoölefins Which Form Normal Addition Products with Maleic Anhydride



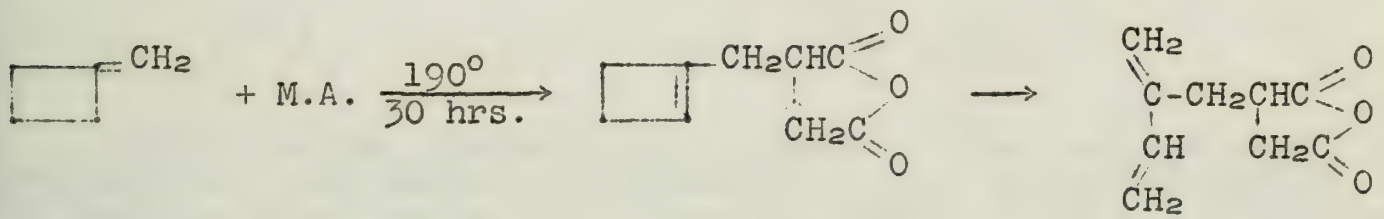
Arrow indicates carbon atom attacked by M.A.

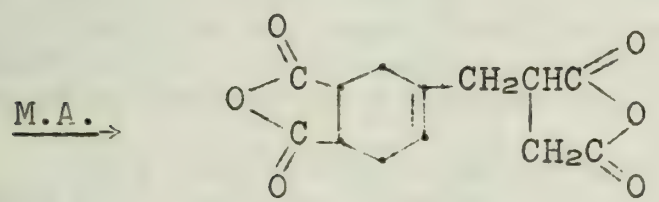
Olefin	Reference	Olefin	Reference
$CH_3CH_2CH{=}\overset{\downarrow}{C}HCH_3$	7		5
	7	$CH_3\overset{\downarrow}{C}H{=}C(CH_3)_2$	5
$CH_3(CH_2)_3CH{=}\overset{\downarrow}{C}H_2$	5		8,10
$C_6H_5CH_2CH_2CH{=}\overset{\downarrow}{C}H_2$	5		11
$C_6H_5CH_2CH{=}\overset{\downarrow}{C}HCH_2CH_3$	5		12,13
$C_6H_5(CH_2)_3CH{=}\overset{\downarrow}{C}H_2$	5	$CH_3OOC(CH_2)_8\overset{\downarrow}{C}H{=}CH_2$	6
$(CH_3)_2C{=}\overset{\downarrow}{C}(CH_3)_2$	5		
$C_6H_5CH_2CH{=}\overset{\downarrow}{C}HCH_3$	5		

1-Methyl-1-cyclohexene could theoretically react with M.A. to give three anhydrides; the structures of the acids resulting from hydrolysis of these products are given above (II, III, IV). It was found (8) that two acids, A and B, were formed depending on whether the addition reaction was run at 175° or 235°. Hydrogenation of A and B, respectively, afforded two acids which were cis-trans isomers. Both A and B gave compound V on dehydrogenation. Furthermore, A could be isomerized to B by heating at 235°.

Ozonolysis of A and B yielded no formaldehyde; thus, structure III was ruled out. Structure II was excluded on the basis of the dehydrogenation results. Hence, both A and B were assigned the structure IV. Since there are two asymmetric carbon atoms in IV, it was concluded that the products are diastereoisomers.

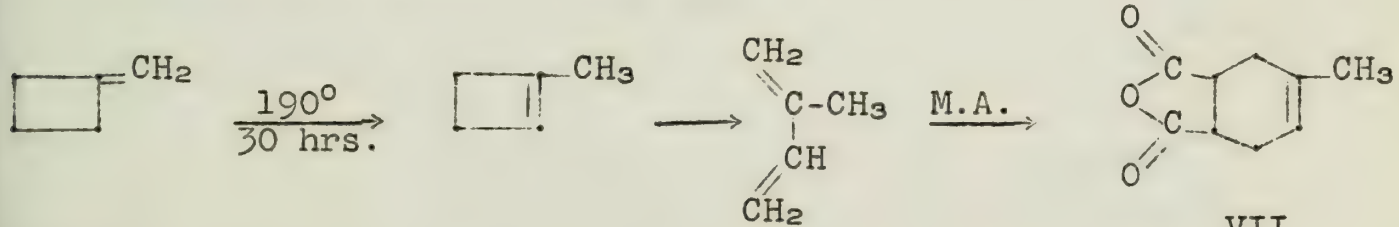
The reaction of M.A. with methylenecyclobutane at 195° yielded two products, one containing a 2:1 and the other a 1:1 molar ratio of M.A. to olefin (14). They were found to be compounds VI and VII, respectively. The principal product (VI) was apparently formed by thermal addition of M.A. to methylenecyclobutane with migration of the double bond into the ring, followed by ring-opening to the isoprene derivative and normal Diels-Alder addition.





VI

The 1:1 addition product (VII) was formed in smaller amounts, apparently by double bond migration followed by ring opening and normal Diels-Alder addition. Reaction of methylenecyclobutane with acrylic acid gave similar results.

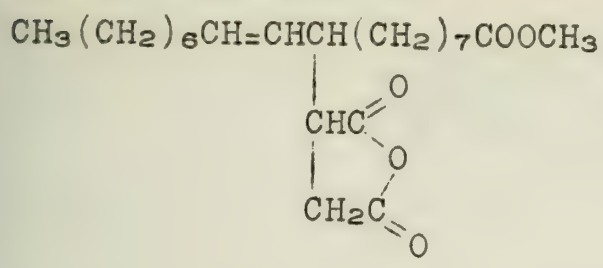


VII

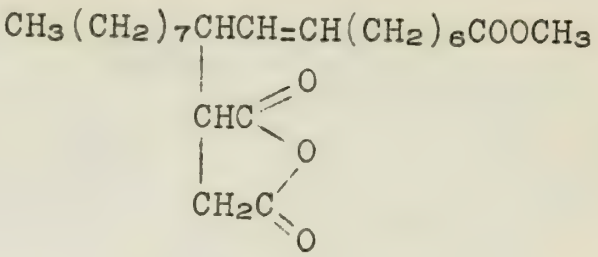
This reaction scheme was given some support when it was found that treatment of methylenecyclobutane with acetic acid under similar conditions afforded α-terpinene and 1-methyl-1-cyclobutyl acetate. It seems probable that the former was formed by isomerization of dipentene, a dimerization product of isoprene.

Two groups of workers have investigated the reaction of M.A. with methyl oleate. Bickford, Fisher, Kyame and Swift found (15)

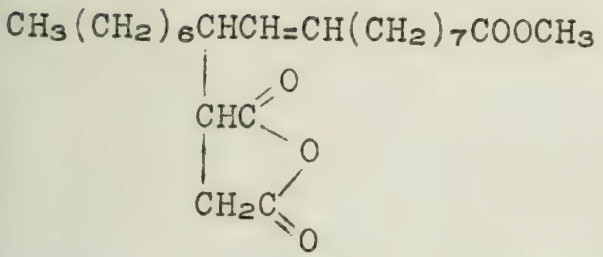
that four products (VIII, IX, X, XI) were formed in approximately equal amounts when the reactants were heated at 220° for two hours. Ross, Gebhart and Gerecht obtained only compounds VIII and IX under similar conditions (6). These results have mechanistic significance and will be discussed again later in this report.



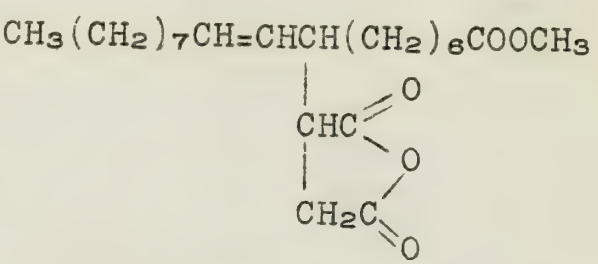
VIII



IX



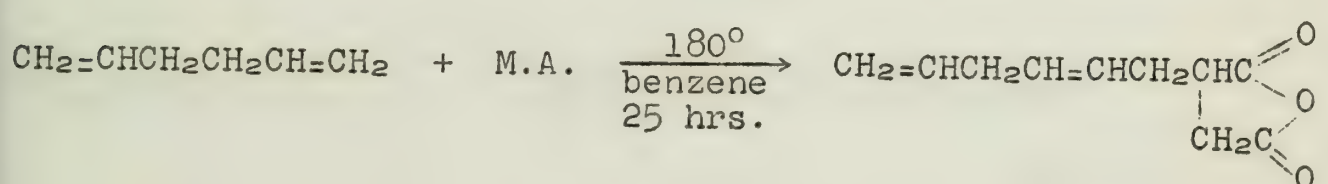
X

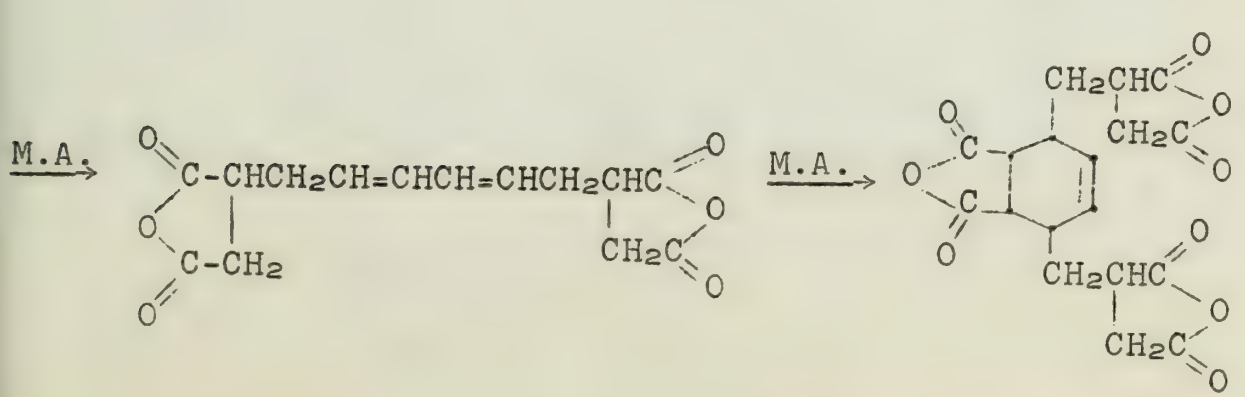


XI

An interesting synthetic application of the olefin-dienophile reaction has been devised by Rondestvedt (9). It is a preparation of γ-phenylallylsuccinic acid from allylbenzene and M.A., and it differs from the work described so far chiefly in the fact that the reaction is carried out in refluxing o-dichlorobenzene rather than in an autoclave or a sealed tube.

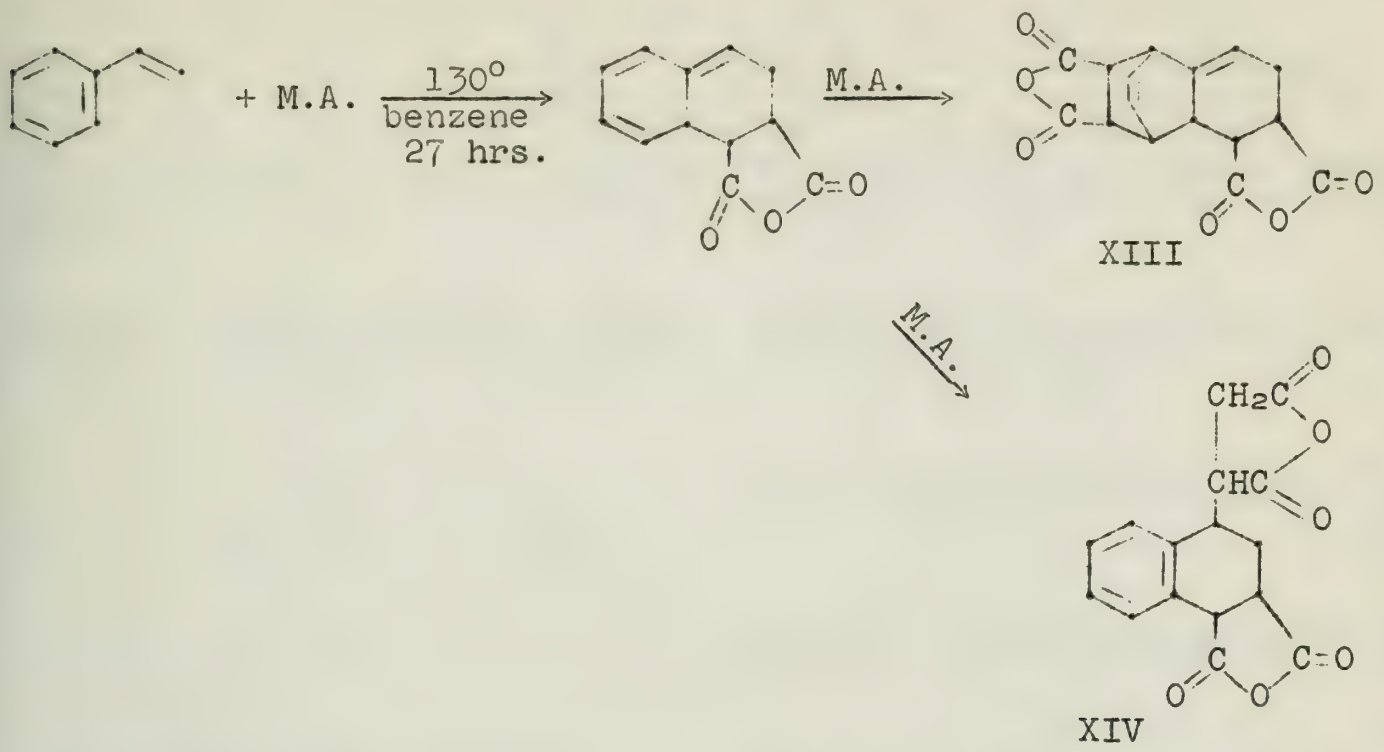
If a polyolefin with suitably located double bonds is reacted with M.A., either "normal" or "pseudo" Diels-Alder reactions may occur, or one may follow the other. For example, when 1,5-hexadiene is heated with an excess of M.A., a 3:1 addition product (XII) is formed (16).



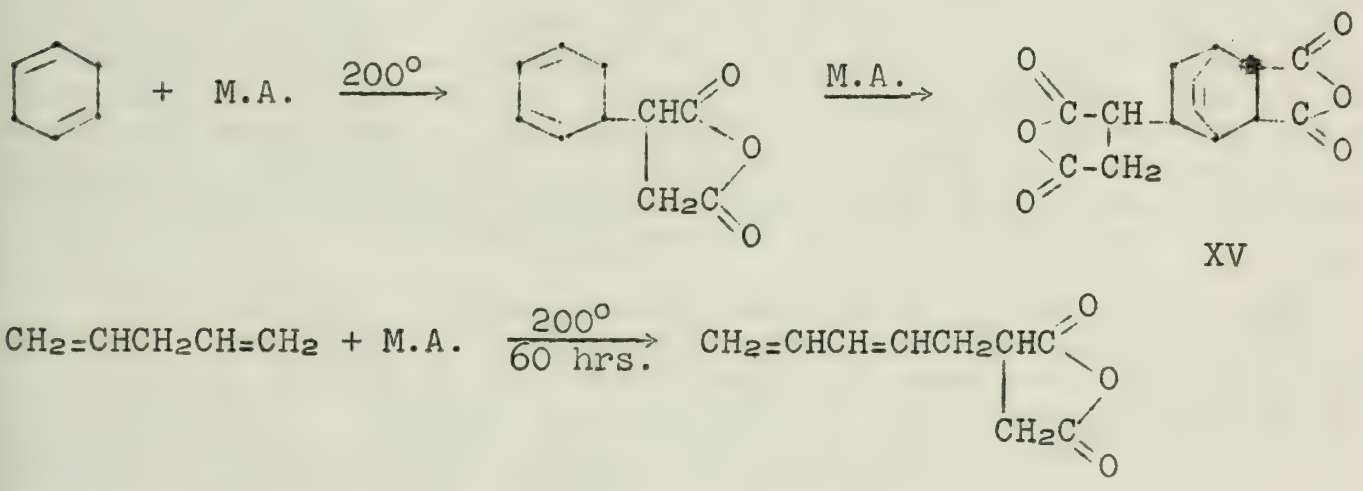


XII

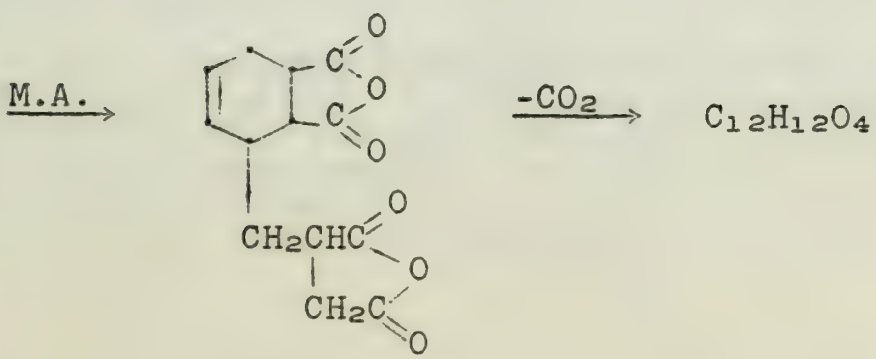
Styrene reacts to form two products, one (XIII) by two "normal" Diels-Alder reactions and the other (XIV) by a "normal" followed by a "pseudo" reaction (17,18).



1,4-Cyclohexadiene yielded a 1:2 adduct (XV) with M.A. 1,4-Pentadiene afforded a keto anhydride, $C_{12}H_{12}O_4$, of unknown structure, which was assumed to be a decarboxylation product of the dianhydride XVI (17).

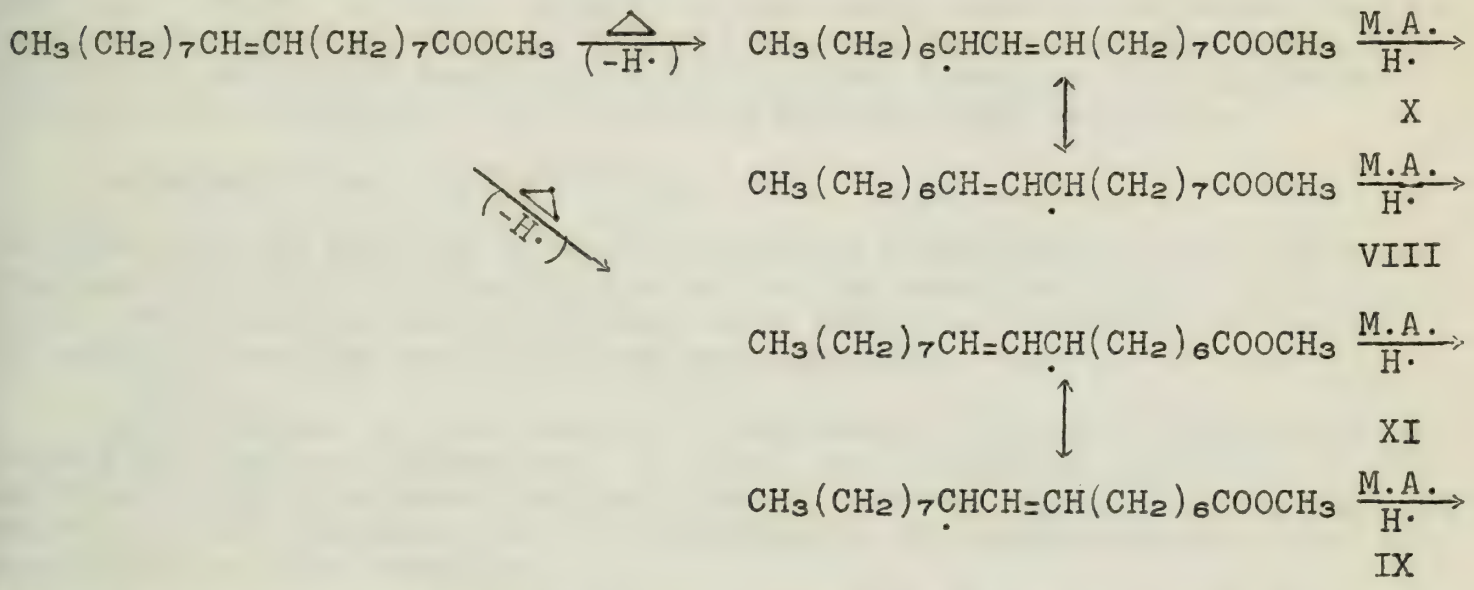


$CH_2{=}CHCH_2CH{=}CH_2$ + M.A. $\xrightarrow[60\ hrs.]{200°}$ $CH_2{=}CHCH{=}CHCH_2CH$



MECHANISM

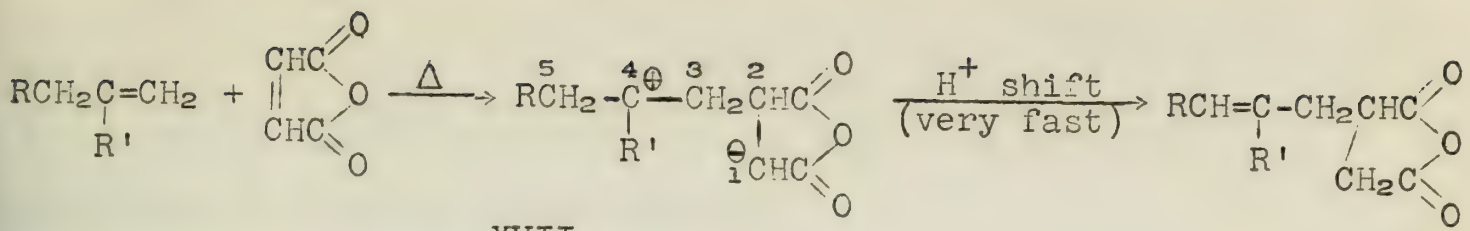
There is still some doubt as to the mechanism of the olefin-dienophile reaction. As mentioned earlier, Ross and associates obtained only compounds VIII and IX from the reaction of M.A. with methyl oleate (6). They postulated a molecular mechanism involving a cyclic transition state similar to that suggested by Alder (5). Bickford and coworkers considered the molecular mechanism insufficient to explain the occurrence of X and XI among the products (15). They therefore suggested the following radical scheme.



A chain mechanism, with the abstraction of a hydrogen radical from another methyl oleate molecule, would also be possible. However, these theories are not basically different from Alder's original one (4), and they do not explain the predominance of compounds of the type exemplified by XII and XIII in most of these reactions. To be sure, anomalous products (with respect to double bond location) have been noted in several instances (14,16,19,20,21), but it has not been established that rearrangement of the olefin takes place during the reaction with the dienophile rather than before or after. Until sufficient controls are run to establish this fact, there is no real evidence for a free radical mechanism.

Koch favored a radical over a molecular mechanism for the thermal isomerization of 3,4-diphenyl-1,5-hexadiene (22) because the product was a mixture of 1,6-diphenyl-1,5-hexadiene and 1,4-diphenyl-1,5-hexadiene. However, the addition of M.A. to olefins gave only one product in an overwhelming number of cases. Koch cited this fact in support of the molecular mechanism.

Arnold and his associates rejected the radical mechanism for the addition of M.A. to methylenecyclopentane (10,11), since mixtures of M.A. and the olefin gave a quantitative yield of polymer when heated with benzoyl peroxide at 80°. They suggested, as an alternative to the molecular mechanism, that a short-lived ionic intermediate (XVII) was possible.



XVII

Rondestvedt and Wark undertook a study of the reaction of allylbenzene with M.A. and substituted maleic anhydrides, in an attempt to decide between the radical and ionic mechanisms. They found (23) that the M.A.-allylbenzene reaction was first order in allylbenzene and first order in M.A. A radical mechanism would be expected to give more complicated results if a chain process were involved; a radical non-chain mechanism should give first-order kinetics in allylbenzene only, corresponding to the following rate-determining step.

$$C_6H_5CH_2CH{=}CH_2 \rightarrow C_6H_5\dot{C}HCH{=}CH_2 + H\cdot$$

The presence or absence of polymerization inhibitors in the reaction mixture made very little difference in the reaction rate. On the other hand, when allylbenzene and M.A. were heated with catalytic amounts of acetyl peroxide, only polymer was obtained.

On the basis of the results cited above, it seems reasonable to reject the radical mechanism, at least until further evidence of its applicability is offered in the form of control tests showing that the reactants and products are not susceptible to rearrangement under the conditions of the reaction.

In their work on the thermal reaction of allylbenzene with substituted maleic anhydrides (24), Rondestvedt, Spliethoff and Filbey found that the reaction rate varied in the order $CH_3 < H < Cl$. In order to determine the relative importance of steric and polar effects on reactivity and orientation, Rondestvedt and Filbey allowed allylbenzene to react with phenylmaleic anhydride and with p-nitrophenylmaleic anhydride (25). The reaction with phenylmaleic anhydride gave a mixture of the two possible products in 43% yield after 14 hours at 250°; the p-nitrophenylmaleic anhydride reaction required only 3 hours at 230° to give the corresponding compounds in 35% yield. The ratio of isomers was about the same for both reactions--2:1 in favor of the less hindered isomer.

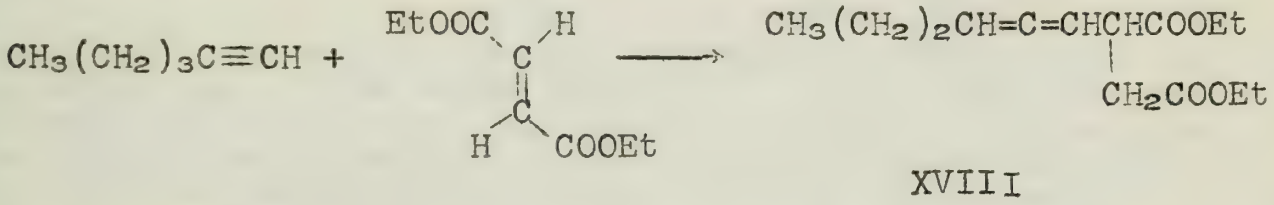
The nearly identical isomer ratio for both reactions indicates that steric effects are predominant in controlling orientation. The results are compatible with the ionic mechanism proposed by Arnold (10). However, an ionic intermediate such as XVII would be expected to yield a mixture of products depending on whether the migrating hydrogen was attached to the carbon in the 3 or 5 position. The fact that such a mixture was not obtained would seem to exclude a carbonium ion intermediate. The fact that t-butylethylene reacts with M.A. to give a product with a rearranged carbon skeleton was cited by Rondestvedt, Spliethoff and Filbey as evidence in favor of a carbonium ion intermediate (24). Since there are no hydrogens on the carbon atom alpha to the double bond in t-butylethylene, some rearrangement must occur if the reaction is to take place. However, this rearrangement might well happen before the reaction rather than as an integral part of it.

Further work is necessary before a final decision can be made between the ionic and molecular mechanisms. A determination of the entropy of activation for the reaction would obviously be a long step in the right direction. However, it appears from what is known so far that the molecular process is the more likely of the two.

REACTIONS OF ALLENES AND ACETYLENES

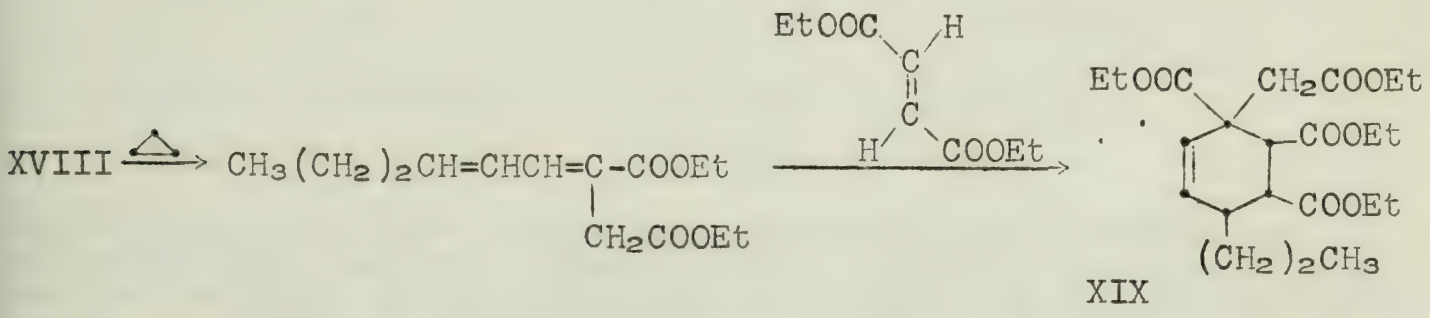
The major products of thermal reactions of M.A. with allenic compounds are cyclobutane derivatives, resulting either from dimerization of the allene (26) or cycloaddition of M.A. to the allene (27). However, several by-products which could have been formed by a pseudo-Diels-Alder reaction have also been identified. For example, the thermal reaction of M.A. with allene afforded propargylsuccinic anhydride as a by-product (26,27). Substituted allenes can react to form several compounds, depending on which carbon atom is attacked and which way the double bond shifts (26).

While allenes sometimes react with dienophiles to form acetylenes, acetylenes normally react to form allenic compounds. Thus, 1-hexyne and diethyl fumarate give the allenic diester, XVIII, when heated in an autoclave at 230° for four hours (21).



XVIII

A second product (XIX), containing two moles of ester to one mole of 1-hexyne, was the major product of the reaction. Although its structure was not investigated, it was thought to be a Diels-Alder adduct resulting from isomerization of XXII to an α,β,γ,δ-unsaturated ester followed by reaction with diethyl fumarate.



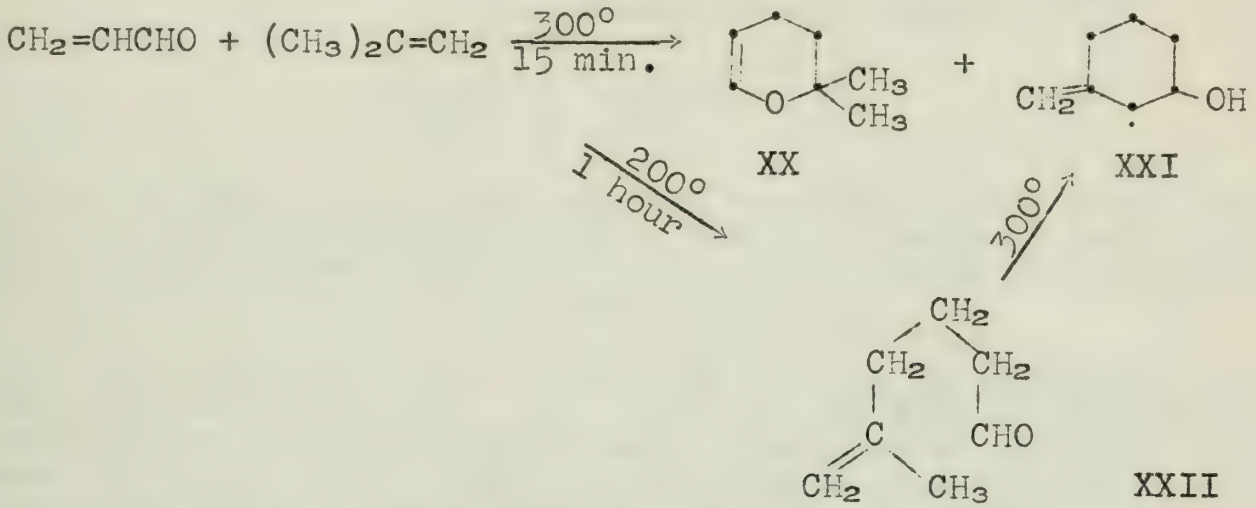
XIX

Alder, Böhne and Müller reported (16) that the reaction of 1-hexyne with M.A. yielded three products. Only two of these were identified; they were found to have structures analogous to XVIII and XIX.

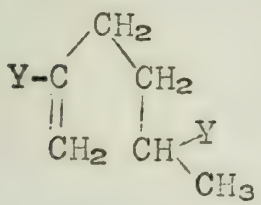
OTHER DIENOPHILES

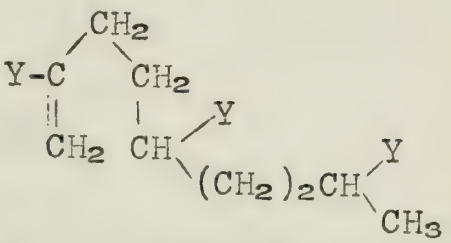
Several other compounds serve as dienophiles in reactions similar to those already described. Alder reported that ethyl azodicarboxylate underwent reactions with tetralin, α-methylstyrene, and allylbenzene to form products analogous to the M.A. adducts (4). Numerous examples of the addition of acrylic compounds to olefins have been published, largely in the patent literature (20,28,29,30,31). The reactions are generally run at 200-300°, with the addition of a small amount of polymerization inhibitor to prevent polymerization of the acrylic compound.

The reaction of isobutylene with acrolein (20) furnishes an interesting example of the effect of reaction conditions on the products formed. When the reaction was run for fifteen minutes at 300°, two principal products were formed: the "normal" Diels-Alder adduct (XX) and the methylenecyclohexanol XXI. The latter was assumed to be formed by cyclization of the expected product, XXII; this was shown to be the case when it was found that XXII was formed if the reaction was carried out at 200° for one hour, and that it was converted to XXI by heating.



Acrylic compounds can be made to dimerize under conditions similar to those used in the above reactions. Indeed, such dimerization often occurs as a nuisance reaction when addition to other olefins is desired (20). Methyl methacrylate and methacrylonitrile afford XXIII and XXIV, respectively, as dimerization products; the trimers XXV and XXVI are among the by-products (32,33,34).





XXIII: Y = $COOCH_3$ XXV: Y = $COOCH_3$

XXIV: Y = CN XXVI: Y = CN

Methacrylonitrile also yields some cis- and trans-1,2-dimethyl-1,2-dicyanocyclobutane (32). These products are to be expected, since similar treatment of acrylonitrile gives cis- and trans-1,2-dicyanocyclobutane (35).

Crawford found that dimethyl α,δ-dimethyl-α,β-dihydromuconate was formed as a by-product in the commercial process for making methyl methacrylate. This process consists in heating acetone cyanohydrin with sulfuric acid and methanol (36,37). Albisetti and coworkers obtained traces of dimethyl α,δ-dimethyl-α,β-dihydromuconate upon acid hydrolysis of XXIV (32), and suggested that double bond migration in the presence of acids accounts for its formation.

Under high temperature and pressure conditions, ethylene can be made to add to activated olefins (19). The 1:1 adducts with mesityl oxide and β-methylcrotononitrile have structures XXVII and XXVIII, respectively. These are not the expected products, but the 2:1 adducts

(XXIX and XXX) are the normal ones. Apparently, double bond migration occurs in the mono-adducts under the strenouous reaction conditions.

$$(CH_3)_2C{=}CHY + CH_2{=}CH_2 \xrightarrow[3000\ atm.]{290^\circ} \left[CH_2{=}\underset{CH_3}{C}{-}\underset{Y}{CH}CH_2CH_3\right] \rightarrow (CH_3)_2C{=}\underset{Y}{C}{-}CH_2CH_3$$

$$\left[CH_2{=}\underset{CH_3}{C}{-}\underset{Y}{CH}CH_2CH_3\right] \xrightarrow{CH_2=CH_2} CH_3CH_2CH_2\underset{CH_3}{C}{=}\underset{Y}{C}{-}CH_2CH_3$$

XXVII: Y = $COCH_3$
XXVIII: Y = CN

XXIX: Y = $COCH_3$
XXX: Y = CN

Ross, Gebhart and Gerecht studied the polymerization of undecylenic acid at high temperatures (38). They were able to isolate the dimethyl ester of 8-eicosene-1,20-dicarboxylic acid in 14% yield as the chief product, along with higher polymers.

Finally, mention should be made of the use of aldehydes and sulfur trioxide as dienophiles. The synthesis of alkenyl alcohols by the reaction of aliphatic olefins with aldehydes at 100-250° has been patented by Ritter (39). Addition of formaldehyde to unsaturated terpenes (40), methylenecyclopentane (11), or methylenecyclohexane (10) affords the corresponding 3,4-unsaturated alcohol.

The addition of sulfur trioxide to methylenecyclopentane (11), methylenecyclohexane (10), or 2-benzyl-1-propene (41) was carried out under much milder conditions than any of the reactions discussed so far. This reaction is run at 0° in dioxane solution; the products are β,γ-unsaturated sulfonic acids.

BIBLIOGRAPHY

1. K. Hultzsch, Ber., 72, 1173 (1939).
2. E. T. Clocker, U. S. Patents 2,188,882-90 (1940); C. A., 34, 3845-46 (1940).
3. W. G. Bickford, P. Krauczunas and D. H. Wheeler, Oil and Soap, 19, 23 (1942).
4. K. Alder, F. Pascher and A. Schmitz, Ber., 76, 27 (1943).
5. K. Alder, H. Sölll and H. Sölll, Ann., 565, 73 (1949).
6. J. Ross, A. I. Gebhart and J. F. Gerecht, J. Am. Chem. Soc., 68, 1373 (1946).
7. K. Alder and H. Sölll, Ann., 565, 57 (1949).
8. K. Alder and A. Schmitz, Ann., 565, 99 (1949).
9. C. S. Rondestvedt, Org. Syn., 31, 85 (1951).
10. R. T. Arnold and J. F. Dowdall, J. Am. Chem. Soc., 70, 2590 (1948).
11. R. T. Arnold, R. W. Amidon and R. M. Dodson, J. Am. Chem. Soc., 72, 2871 (1950).
12. K. Alder and O. Wolff, Ann., 576, 182 (1952).
13. K. Alder, H. Wollweber and W. Spanke, Ann., 595, 38 (1955).
14. K. Alder and H. A. Dortmann, Chem. Ber., 85, 556 (1952).

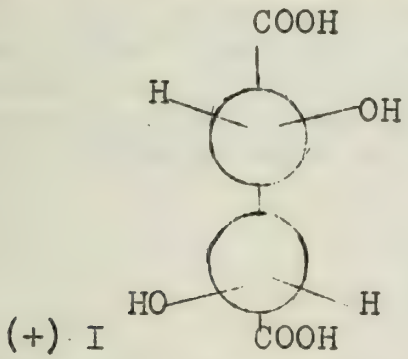
15. W. G. Bickford, G. S. Fisher, L. Kyame and C. E. Swift, J. Am. Oil Chemists' Soc., 25, 254 (1948).
16. K. Alder, H. Böhne and G. Müller, Chem. Ber., 87, 447 (1954).
17. K. Alder and F. Münz, Ann., 565, 126 (1949).
18. K. Alder and R. Schmitz-Josten, Ann., 595, 1 (1955).
19. M. J. Hogsed and R. V. Lindsey, J. Am. Chem. Soc., 76, 2305 (1954).
20. C. J. Albisetti, N. G. Fisher, M. J. Hogsed and R. M. Joyce, J. Am. Chem. Soc., 78, 2637 (1956).
21. M. J. Hogsed and R. V. Lindsey, J. Am. Chem. Soc., 75, 4846 (1953).
22. H. P. Koch, J. Chem. Soc., 1111 (1948).
23. C. S. Rondestvedt and B. H. Wark, J. Org. Chem., 20, 368 (1955).
24. C. S. Rondestvedt, W. L. Spliethoff and A. H. Filbey, Abstracts of ACS Meeting, April, 1951, p. 41M.
25. C. S. Rondestvedt and A. H. Filbey, J. Org. Chem., 19, 548 (1954).
26. K. Alder and O. Ackermann, Chem. Ber., 90, 1697 (1957).
27. W. H. Sharkey, Special Seminar, University of Illinois, February 10, 1958.
28. C. J. Albisetti and N. G. Fisher, U. S. Patent 2,584,527 (1952); C. A., 46, 8674 (1952).
29. C. J. Albisetti and N. G. Fisher, U. S. Patent 2,641,607 (1953); C. A., 48, 4583 (1954).
30. C. J. Albisetti, U. S. Patent 2,628,252 (1953); C. A., 48, 1424 (1954).
31. C. J. Albisetti and M. J. Hogsed, U. S. Patent 2,671,106 (1954); C. A., 49, 2482 (1955).
32. C. J. Albisetti, D. C. England, M. J. Hogsed and R. M. Joyce, J. Am. Chem. Soc., 78, 472 (1956).
33. B. W. Howk, U. S. Patent 2,232,785 (1941); C. A., 35, 3742 (1941).
34. M. J. Hogsed, U. S. Patent 2,566,203 (1951); C. A., 46, 2563 (1952).
35. E. C. Coyner and W. S. Hillman, J. Am. Chem. Soc., 71, 324 (1949).
36. J. W. C. Crawford, J. Soc. Chem. Ind. (London), 66, 155 (1947).
37. J. W. C. Crawford, U. S. Patent 2,244,487 (1941); C. A. 35, 5597 (1941).
38. J. Ross, A. I. Gebhart and J. F. Gerecht, J. Am. Chem. Soc., 67, 1275 (1945).
39. J. J. Ritter, U. S. Patent 2,335,027 (1943); C. A., 38, 2662 (1944).
40. J. P. Bain, J. Am. Chem. Soc., 68, 638 (1946).
41. F. G. Bordwell, C. M. Suter and A. J. Webber, J. Am. Chem. Soc., 67, 827 (1945).

Absolute Configuration of Optically Active Diphenyls

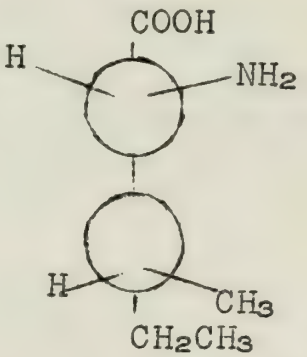
Reported by S. H. Metzger April 7, 1958

INTRODUCTION

Until 1951 when the absolute configuration of (+)-tartaric acid (I) was determined by X-ray diffraction studies (1), there were no reliable means, either chemical or theoretical, for determining the absolute configurations of optically active compounds. Fortunately, the absolute configuration of (+)-I and the absolute configuration of (-)-isoleucine (II), which was also determined by X-ray diffraction methods (2), agreed with the Fischer postulate for the two compounds. Thus was made possible the determination of



(+) I



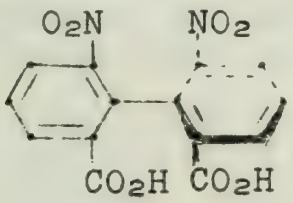
(-) II

the absolute configuration of a large number of compounds which had been, or could be, configurationally correlated to (+)-I or (-)-II, or their respective enantiomers.

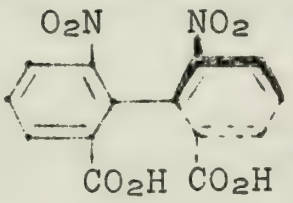
Very recently the determination of absolute configurations has been extended to include ortho-substituted diphenyls and related compounds. This seminar will cover these investigations.

OPTICALLY ACTIVE DIPHENYLS

In 1922, Christie and Kenner (3) reported the separation of 6,6'-dinitro-2,2'-diphenic acid into a pair of enantiomorphs (III and IV). This was the first compound known to owe its optical activity

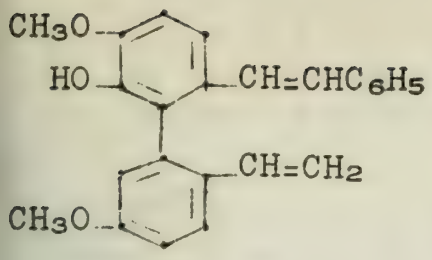


III

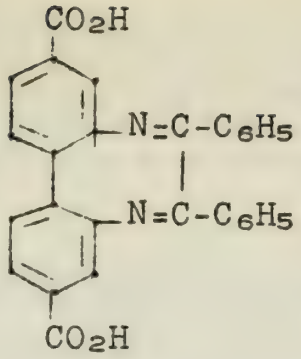


IV

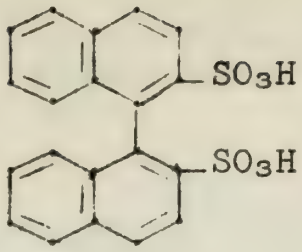
to restricted rotation about a single bond. Since that time numerous other ortho-substituted diphenyls, as well as bridged diphenyls, terphenyls, and other diaryl systems, have been resolved (4,5). Adams and his co-workers have made a major contribution. A few recent examples are given in compounds V-VIII.



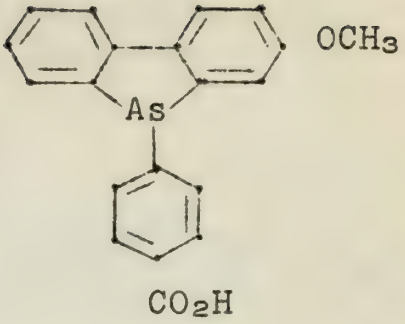
V (6a,6b,6c)



VI (7)

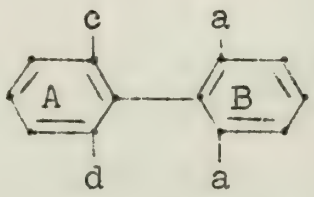


VII (8)



VIII (9)

All the above examples owe their optical activity to two factors: 1) restricted rotation around the pivot bond, 2) neither aryl group (connected to the pivot bond) possesses a plane of symmetry that is perpendicular to the plane of the ring and contains the pivot bond. A diphenyl derivative of the type shown in IX cannot be



IX

resolved since ring B possesses a plane of symmetry.

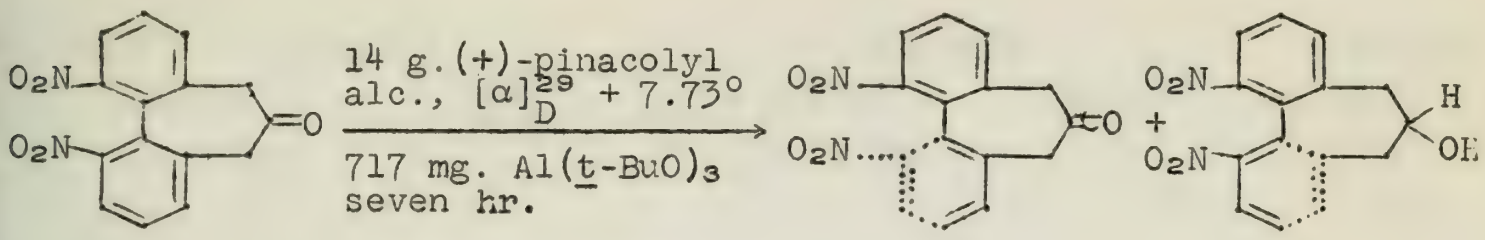
The rates of racemization of diaryl systems are dependent upon the degree of strain in the conformation with the two rings coplanar. For the simple o,o'-diphenyl series the rate may be estimated by comparing the sum of the atomic or group radii of the substituents to the distance (2.90 Å) between the two ortho positions in the planar conformation (5). If the sum of the radii is appreciably less than 2.90 Å, the diphenyl racemizes too rapidly to be resolved; if it is considerably larger than 2.90 Å, the diphenyl should be resolvable at ordinary temperatures. Radii for most of the common substituents have been tabulated (5).

Another quite useful method for estimating the racemization rate of diphenyl derivatives is based on the ultra-violet light absorption. Diphenyl exhibits a K-band near 2500 Å ($\epsilon \sim 15{,}000$) which may be ascribed to the transitions from the homopolar ground state to a dipolar excited state represented as $^{\oplus}Ph\text{-}Ph^{\ominus}$ (10). In non-bridged diphenyl derivatives, any steric hindrance to uniplanarity is reflected in the ultra-violet absorption spectra by a hypsochromic wavelength shift accompanied by a decrease in intensity (11,12).

From the spectral data the angle made by the planes of the two benzene rings may be estimated ($\cos^2\theta = \epsilon/\epsilon_0$) (11).

Finally, fairly accurate calculations of the activation energy for racemization of diphenyl derivatives may be made by the method of Westheimer and Mayer (13). Since Kistiakowsky and Smith (14) have determined that resolvability of a racemic diphenyl is impossible if the activation energy is appreciably less that 20 kcal. [$<$17 kcal. (13)], prior knowledge of the rate of racemization of a particular diphenyl derivative may be obtained.

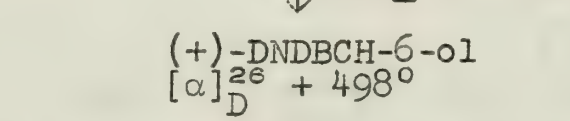
Absolute Configuration Determinations.--Mislow and co-workers (15a,15b) conducted a partially asymmetric reduction of (±)-4',1"-dinitro-1,2,3,4-dibenz-1,3-cycloheptadiene-6-one [(±)-DNDBCH-6-one] (X) by the Meerwein-Ponndorf-Verley method using a large excess of (+)-pinacolyl alcohol for a minimal time.



X
(±)-DNDBCH-6-one
951 mg.

XI
(+)-DNDBCH-6-one
139mg., $[\alpha]_D^{26}$ +136°

XII
(-)-DNDBCH-6-ol
665mg., $[\alpha]_D^{26}$ - 109°



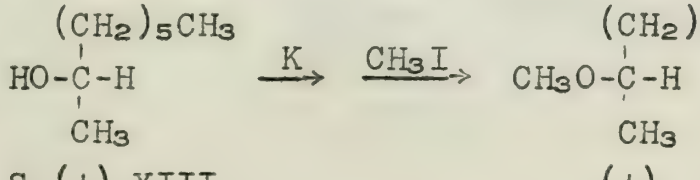
(+)-DNDBCH-6-ol
$[\alpha]_D^{26}$ + 498°

The unreacted ketone and the alcohol were quantitatively separated by chromatography on silica gel, and the (+)-ketone was further reduced as shown. A similar experiment using (+)-2-octanol gave (+)-DNDBCH-6-one, $[\alpha]_D^{26}$ + 52° (reduced to (+)-DNDBCH-6-ol, $[\alpha]_D^{26}$ + 212°) and (-)-DNDBCH-6-ol, $[\alpha]_D^{26}$ - 54°. If the above illustrated reaction is run for 25 hr., only racemic DNDBCH-6-ol is obtained. Likewise, only racemic product is obtained if the reduction is conducted using aluminum isopropoxide in isopropyl alcohol. It was unequivocally concluded (15a,15b) that (+)-DNDBCH-6-one has the absolute configuration XI [S-isomer by the nomenclature of Cahn, Ingold, and Prelog (16)] and that (-)-DNDBCH-6-ol has the absolute configuration XII (R-isomer).

The basis for the configuration assignments rests on a knowledge of the mechanism of Meerwein-Ponndorf-Verley reductions and on a knowledge of the absolute configurations of (+)-pinacolyl alcohol and (+)-2-octanol. It is of particular theoretical interest that the assignments were made possible by relating diphenyl isomers with tartaric acid (I).

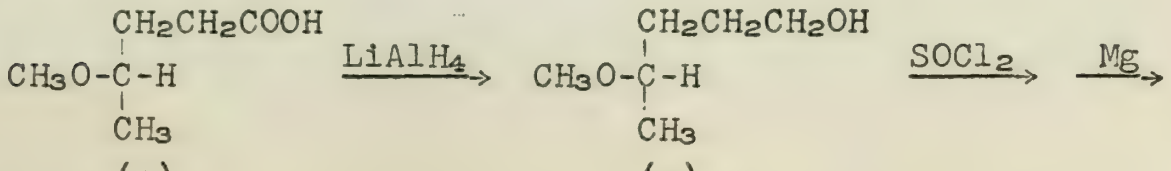
The absolute configuration of (+)-2-octanol (S-configuration) (XIII) has been unequivocally established by chemical correlation to (-)-tartaric acid (XIV).

1. (17)

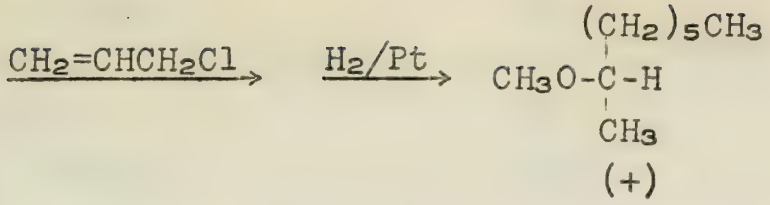


S-(+)-XIII (+)

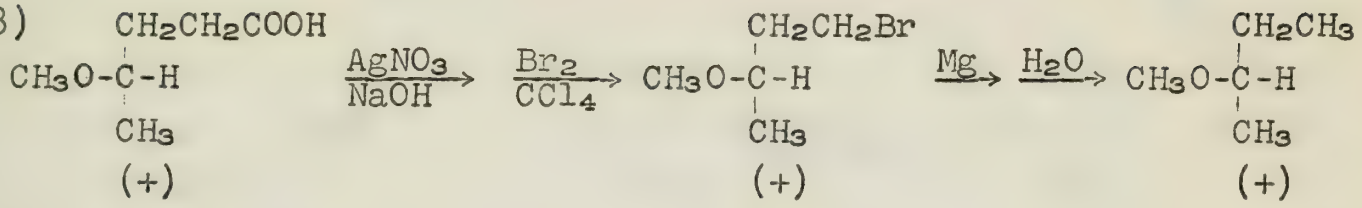
2. (18)



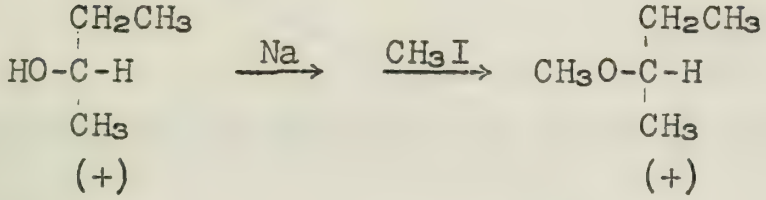
(+) (+)



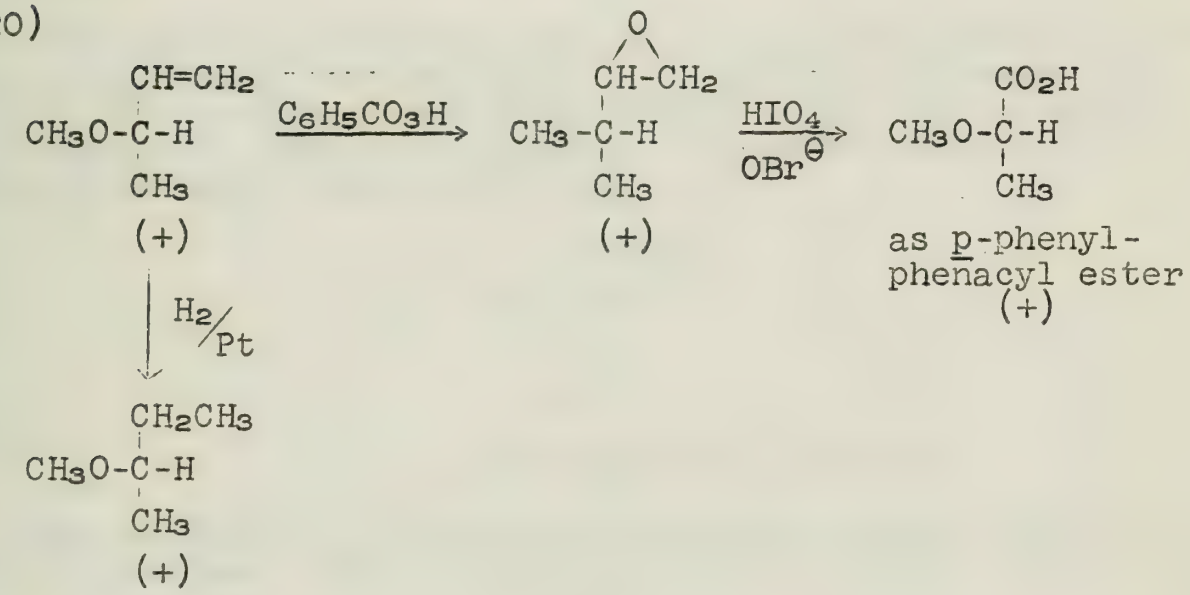
3. (18)



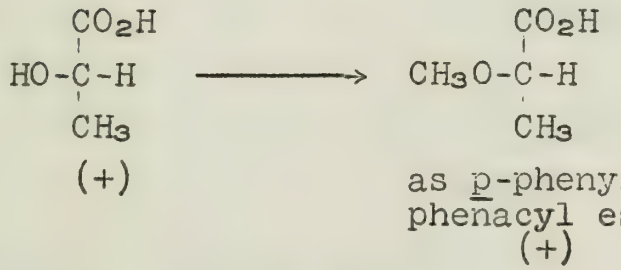
4. (19)



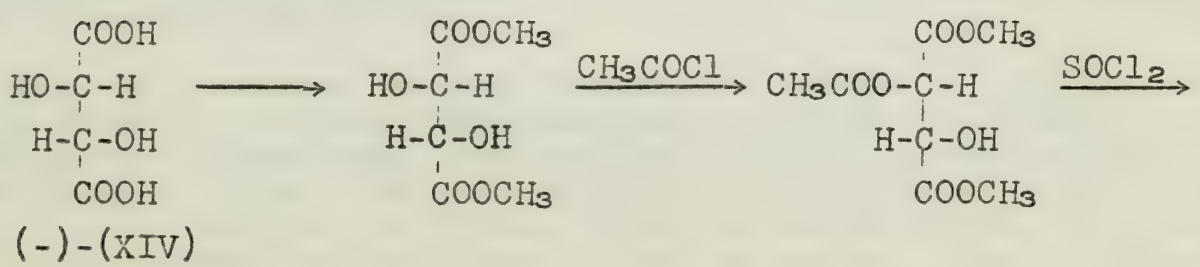
5. (20)

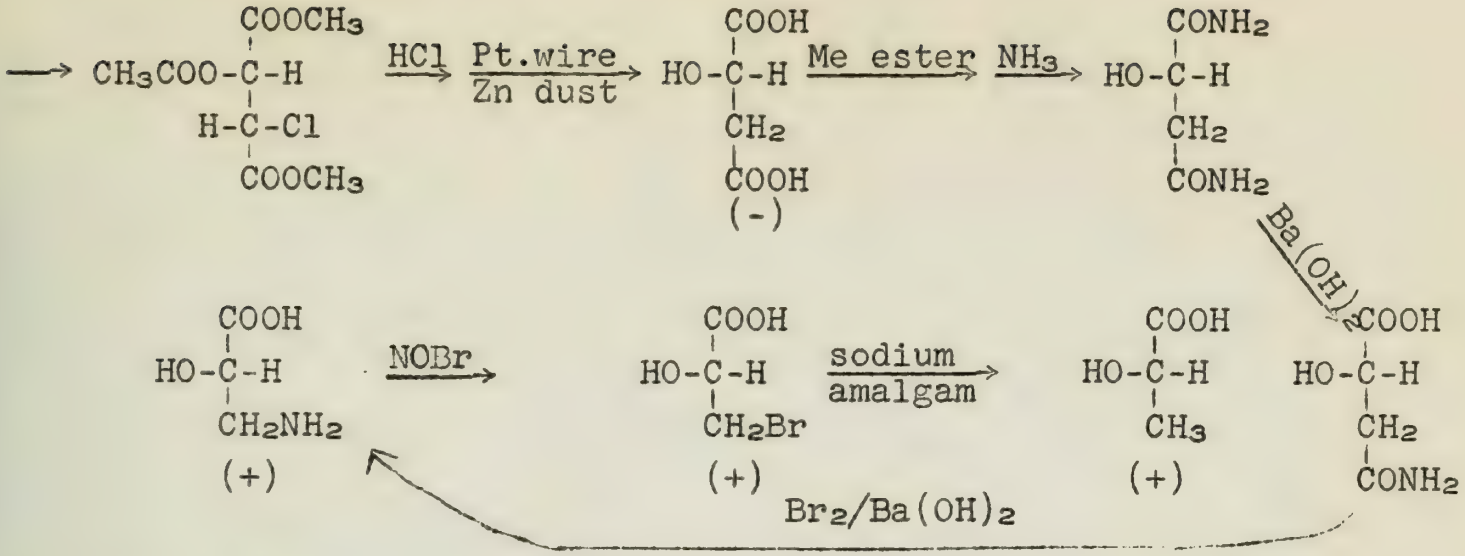


6. (21)



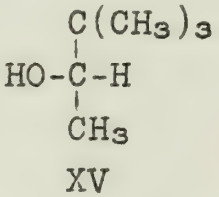
7. (22)





It should be noted that all the signs in numbers 3,5,6, and 7 were reversed from the original literature so as to obtain a smooth transition.

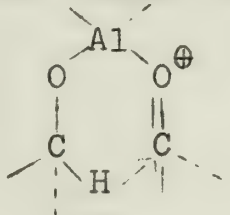
Although (+)-pinacolyl alcohol has not been chemically correlated with either tartaric acid or isoleucine, Stevens (23), by careful application of the Displacement Rule, has correlated it with (+)-2-octanol. The S-configuration (XV) may be assigned to (+)-pinacolyl alcohol with confidence.



XV

S-(+)-pinacolyl alcohol

The mechanism of the Meerwein-Ponndorf-Verley reaction has been well established. The cyclic transition state XVI first postulated

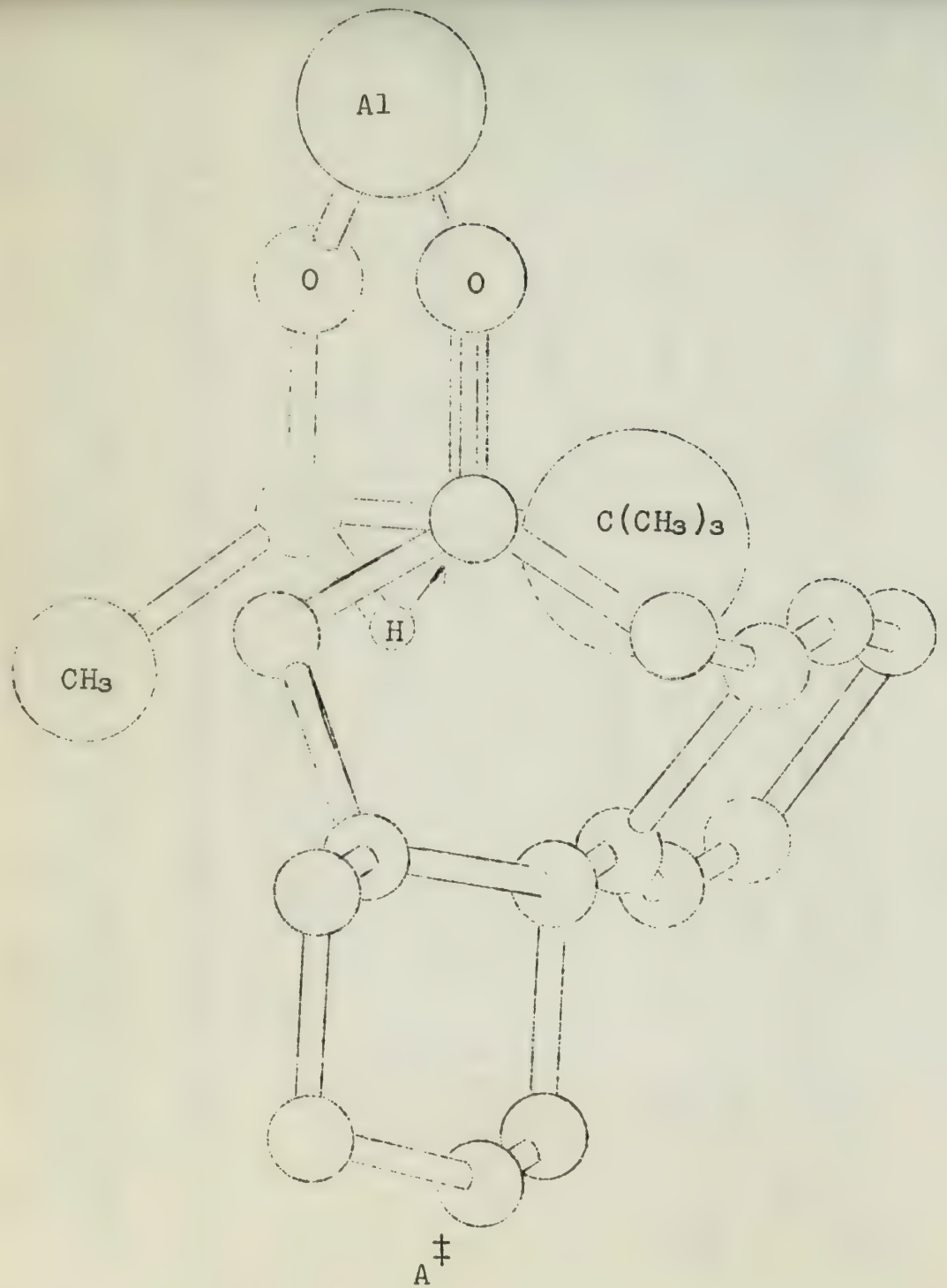


XVI

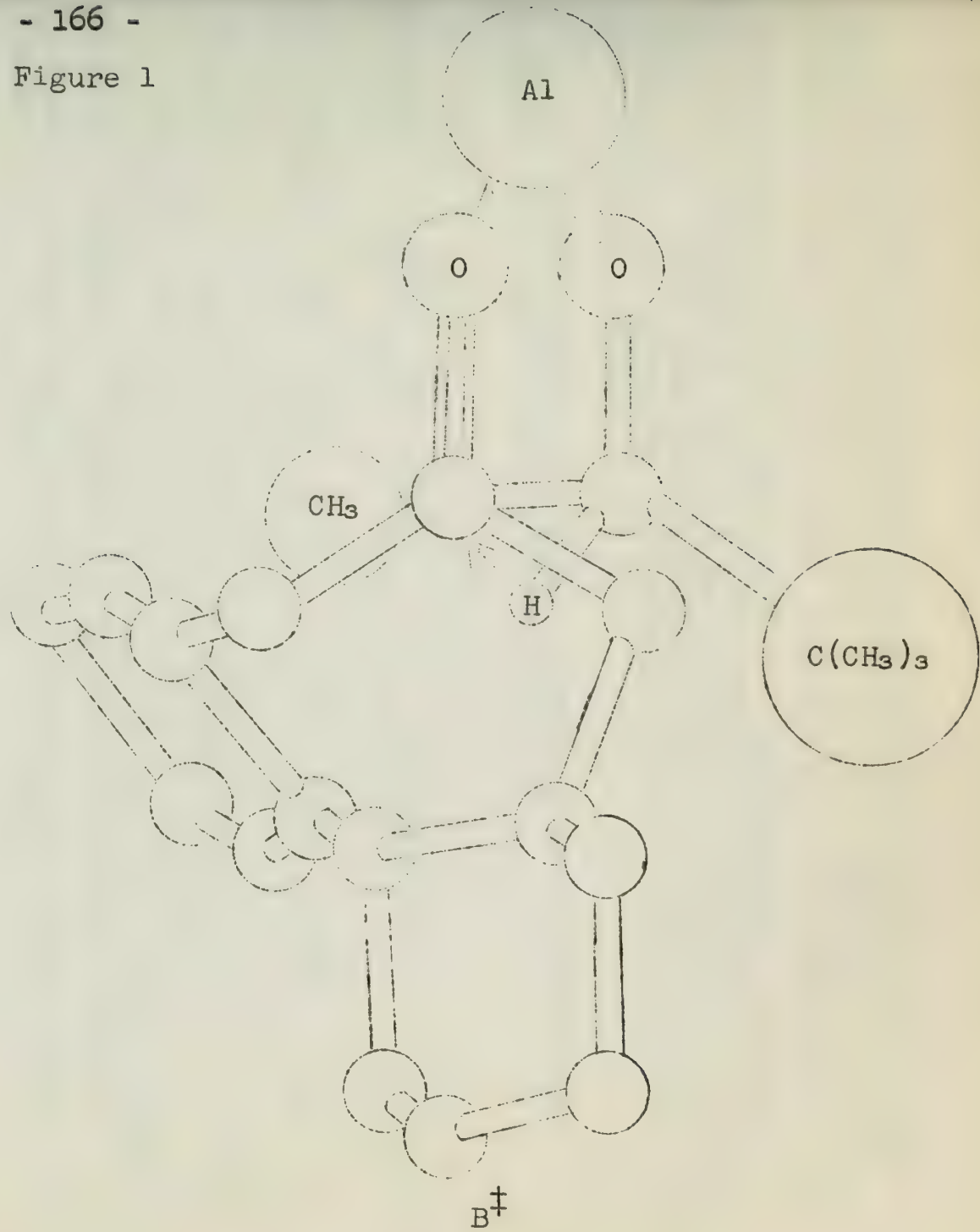
by Woodward, Wendler, and Brutschy (24) has been confirmed by several groups of workers (25,26,27).

Now we may examine the two transition states ($A^{\ddagger}$ and $B^{\ddagger}$, Fig. 1) corresponding to the two enantiomorphic forms of (±)-DNDBCH-6-one (the two nitro groups have been omitted since they add nothing to the analysis). First, two very important points should be made clear: 1. It makes no difference whether the alkoxide attacks from the back (as shown) or the front of the molecule. Steric effects are exactly the same (the two sides are equivalent). 2. It follows from 1. that there is one, and only one reduction product of each isomer of (±)-DNDBCH-6-one. The resulting carbinol carbon is not asymmetric.

Figure 1



A‡



B‡

In $A^{\ddagger}$ there is considerably more steric interference between a t-butyl group and a phenyl then in $B^{\ddagger}$ where there is only compression of a methyl group against a phenyl. Therefore, it may be concluded that $\triangle F_A^{\ddagger}$ is larger than $\triangle F_B^{\ddagger}$. As a consequence, the rate constant for the formation of the carbinol from the ketone isomer corresponding to $B^{\ddagger}$ will be larger than the rate constant for the formation of the carbinol from the ketone isomer corresponding to $A^{\ddagger}$. From this reasoning Mislow and co-workers (15a,15b) concluded that the unreacted (+)-ketone had the absolute configuration of $A^{\ddagger}$ (S-configuration) (XI).

In further support for their argument a more quantitative analysis was made of the reactions (Table I).

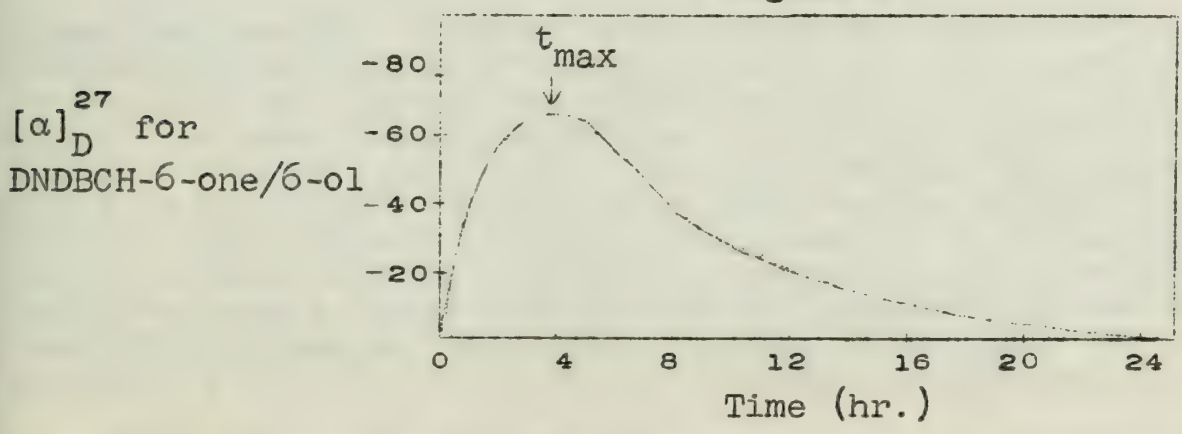
TABLE I

Reducing alcohol	k_R[a] hr.$^{-1}$	k_S[a] hr.$^{-1}$	k_R/k_S	$\triangle\triangle F^{\ddagger}$[b]	t_{max}[c], hr.	W_k[d]	W_A[d]
(+)-Pinacolyl	0.39	0.18	2.2	0.51	3.66	0.624	0.157
(+)-2-Octanol	5.4	3.9	1.4	0.21	0.217	0.239	0.068

[a] k_R and k_S = rate constants for R- and S-isomers. [b] $\triangle\triangle F^{\ddagger}$ (= -RT ln k_S/k_r) is a measure of the efficiency of the reaction. [c] t_{max} is the point where mixture of the ketone and alcohol exhibit maximum specific rotation. [d] W_K and W_A = the optical purity of the recovered (+)-ketone and (-)-alcohol respectively, based on pure (+)-DNDBCH-6-one, $[\alpha]_D$ + 218° and pure (-)-DNDBCH-6-ol, $[\alpha]_D$ -696°.

As would be expected k_R/k_S and $\triangle\triangle F^{\ddagger}$ are greater for (+)-pinacolyl alcohol than for (+)-2-octanol since compression of a t-butyl group against a phenyl is more prohibitive than the compression of a n-hexyl group against a phenyl. The calculated t_{max} (Table I) for (+)-pinacolyl alcohol agrees quite well with the experimental t_{max} (Fig. 2). The t_{max} is of interest because it is at this point that

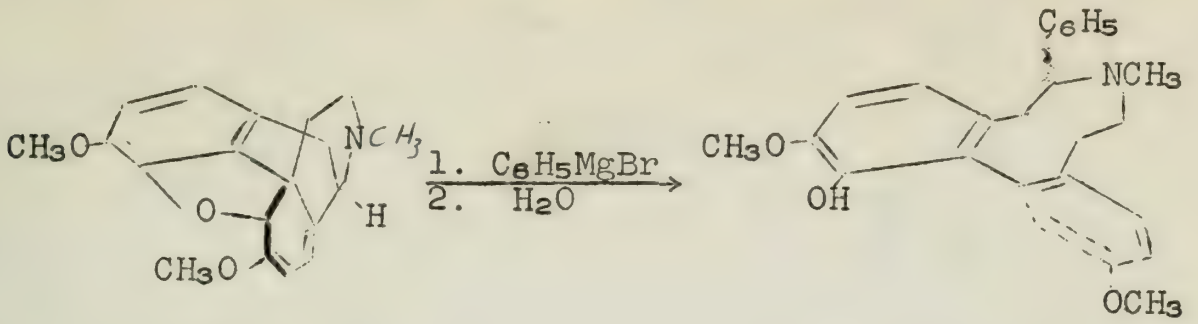
Figure 2



the rate of reaction of the S-enantiomer becomes faster than that of the R-enantiomer.

Concurrent with the work just discussed Berson and Greenbaum (6a,6b,6c) determined the absolute configuration of diphenyl derivatives by an entirely different method. They allowed phenylmagnesium bromide to react with thebaine (XVII) and assigned the

absolute configuration (XVIII) to the (+)-phenyldihydrothebaines obtained (no (-)-products were obtained).

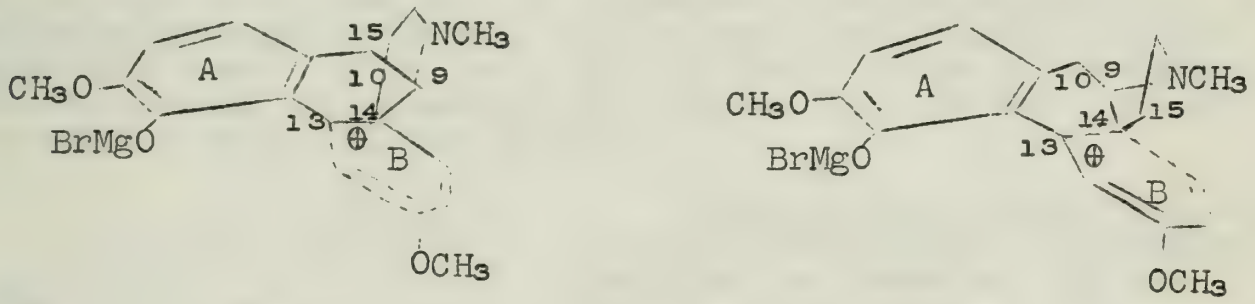


XVII (+)-XVIII

Two products were obtained, a major product called (+)-α-phenyldihydrothebaine and a small amount of the (+)-β-isomer. These two isomers differ only in the configuration of the asymmetric carbon since Hofmann degradation of either isomer gives the same product.

The absolute configuration of thebaine (XVII) is known because it has been correlated with morphine, the absolute configuration of which has been established beyond question by Bentley and Cardwell (28) and by X-ray diffraction studies of Mackay and Hodgkin (29).

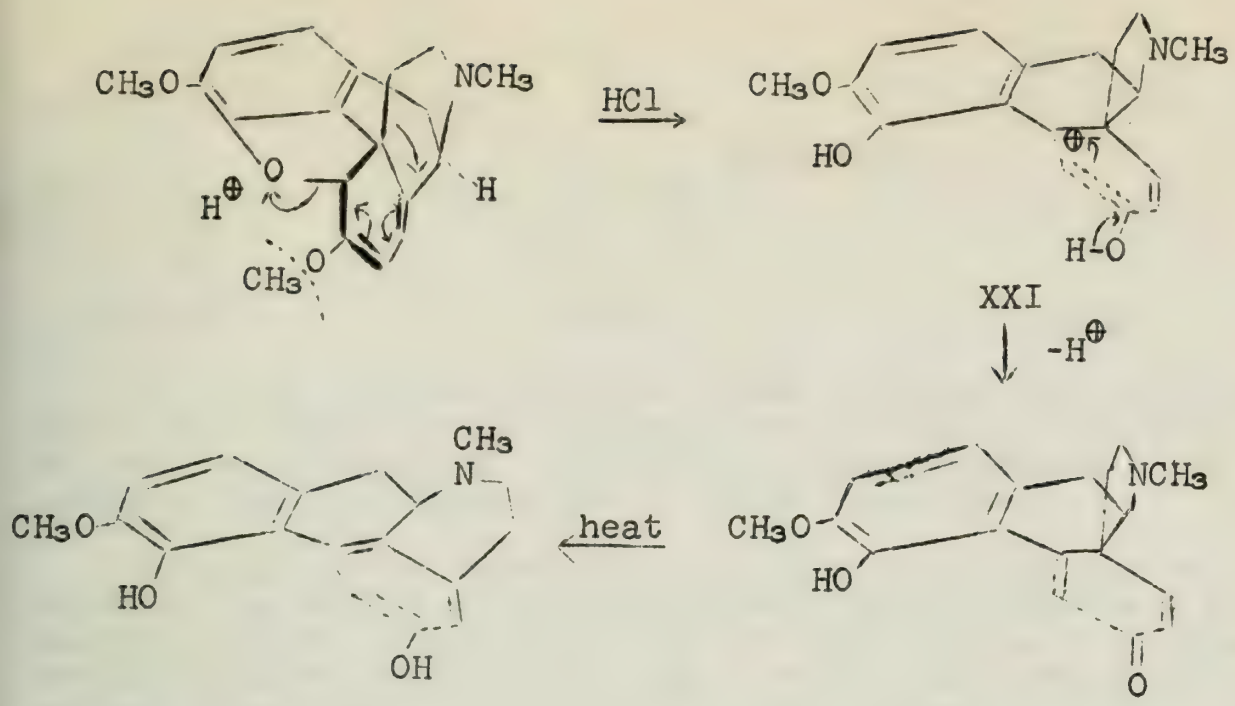
The assignment of the correct configuration for (+)-phenyldihydrothebaine stems from an analysis of the metastable intermediates XIX and XX, or the corresponding transition states.



XIX XX

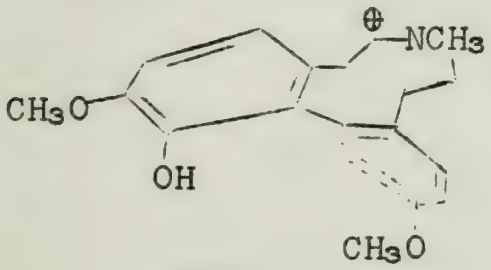
These two possible intermediates arise as a result of C_{13} going from tetrahedral to planar (trigonal) during the migration of C_{15} from C_{13} to C_{14} (XIX and XX are not interchangeable (6c)). In XIX the dihedral angle Θ between the plane defined by C_{15}-C_{14}-C_9 and that defined by C_{14}-C_9-N is close to 0° when the angle between the planes of rings A and B is about 45°. This allows construction of the five-atom ring without angle strain. On the other hand, Θ in XX must be greater than 60°, and this puts an intolerable strain on the five-membered ring and requires severe distortion in the C_9-C_{10} ring. On the basis of this reasoning Berson and Greenbaum (6a,6b,6c) assigned the absolute configuration XVIII to (+)-α-and (+)-β-phenyldihydrothebaine.

The above arguments may be confirmed with molecular models (Fischer-Taylor-Hirschfelder). Intermediate XX cannot be constructed. Furthermore, the mechanism leading to the intermediate XIX has an analogy in the conversion of thebaine to morphothebain (30). Since magnesium bromide (present in solutions of phenylmagnesium bromide) can act as a Lewis acid, it will probably attack in the same way as



the proton. The intermediate XXI is reasonable since XXII can be isolated (XXI need not necessarily be formed from a concerted attack, as shown).

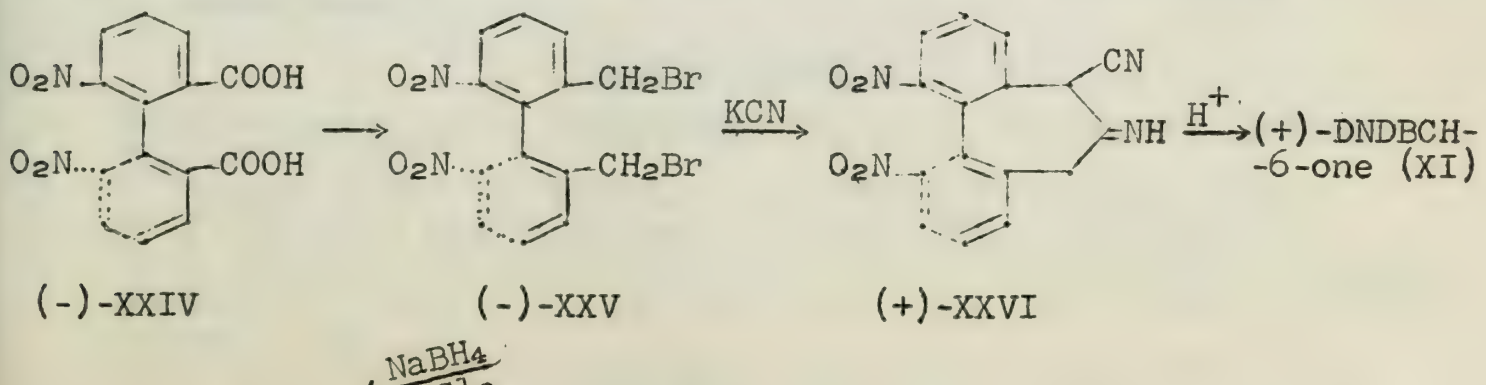
Now intermediate XIX cannot rearrange by tautomeric shift (like XXI) since the methyl group has not been removed from the methoxy group at C_6. Formation of the predominant α-configuration at C_9 in phenyldihydrothebaine (XVIII) can be explained either by a concerted displacement reaction at C_9 in XIX by phenyl anion or by asymmetric induction during the attack of the phenyl anion on the disymmetric intermediate carbonium ion XXIII.

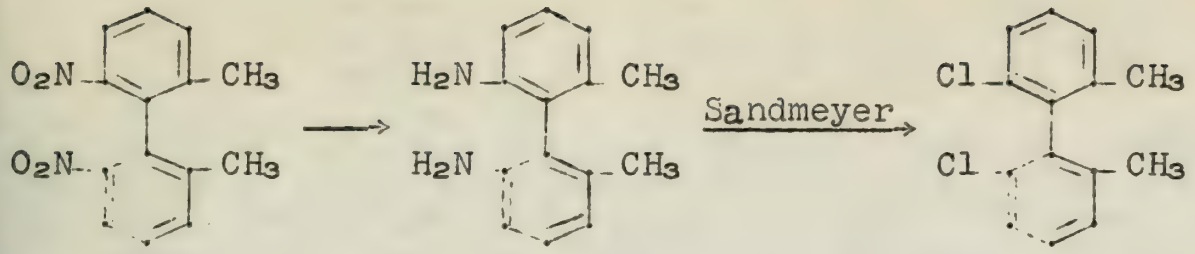


XXIII

Experimental Correlations.--Simple chemical correlations to phenyldihydrothebaine are somewhat limited. Berson and Greenbaum (6b,6c) did relate some non-bridged biphenyls by conducting Hofmann degradations on (+)-phenyldihydrothebaine (XVIII).

Configurational correlations to DNDBCH-6-one are quite extensive (15a, 15b,31,32,33) as can be visualized from its preparation and some selected reactions. All the compounds have the S-configuration.





(-)-XXVII (-)-XXVIII (-)-XXIX

It is of interest that the above absolute configurations of (-)-(XXIV) and -(XXVIII) are in opposition to Kuhn and co-workers (34,35, 36) who, as a result of calculations based on theoretical models, assigned the R-configuration to these enantiomers.

In addition to chemical correlations, Siegel and Mislow (37) extended the method of configurational intercorrelation by thermal analysis (phase diagrams) to include optically active diphenyls. This powerful and reliable method was developed by Timmermans in 1929 (38) and was extended by Fredga (39) to many examples. The first correlations made (37) were (+)-6,6'-dimethyl- to (-)-6,6'-dichloro-, (+)-6,6'-dimethyl- to (-)-6,6'-dinitro-, and (+)-6,6'-dichloro- to (+)-6,6'-dinitro-2,2'-diphenic acid. Thus, the S-configuration could be assigned to the (-)-6,6'-dichloro- and the (+)-6,6'-dimethyl-2,2'-diphenic acid. The method was extended further to include the correlation of (+)-6,6'-dichloro- to (+)-6,6'-dimethyl-2,2'-bis-(hydroxymethyl)-diphenyl. All the correlations were confirmed by chemical correlations. A typical diagram obtained with the diphenic acid series is given in Fig. 3. It can easily be seen that the configurationally opposite enantiomers give a quasi-racemate (arrow, curve A) while the configurationally similar enantiomers form a solid solution (curve B).

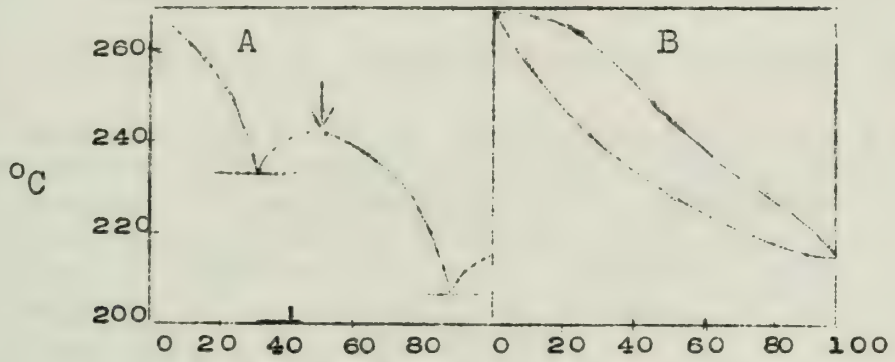


Fig. 3--Phase diagrams of (+)-6,6'-dimethyl-2,2'-diphenic acid vs. (+)- and (-)-6,6'-dichloro-2,2'-diphenic acid (curves A and B, respectively).

BIBLIOGRAPHY

1. J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, Nature, 168, 271 (1951).
2. J. Trommel and J. M. Bijvoet, Acta Cryst., 7, 703 (1954).
3. G. H. Christie and J. Kenner, J. Chem. Soc., 614 (1922).
4. R. L. Shriner, R. Adams, and C. S. Marvel in H. Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, 2nd ed., 1943, Volume I, pp. 343 ff.
5. G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, 2nd Ed., 1949, pp. 202 ff.

6. (a) J. A. Berson, J. Am. Chem. Soc. 78, 4170 (1956);
(b) J. A. Berson, M. A. Greenbaum, ibid., 79, 2340 (1957);
(c) J. A. Berson, M. A. Greenbaum, ibid., 80, 445 (1958).
7. F. Bell, J. Chem. Soc., 1527 (1952).
8. W. L. F. Armarego and E. E. Turner, ibid., 13 (1957).
9. I. G. M. Campbell and R. C. Poller, ibid., 1195 (1956).
10. E. A. Braude and E. S. Waight in Klyne, "Progress in Stereochemistry," Academic Press, Inc., New York 1954, pp. 136 ff.
11. E. A. Braude and W. F. Forbes, J. Chem. Soc., 3776 (1955).
12. G. H. Beaven and D. M. Hall, ibid., 4637 (1956).
13. F. H. Westheimer in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, 1956, pp. 543 ff.
14. G. B. Kistiakowsky and W. R. Smith, J. Am. Chem. Soc., 58, 1043 (1936).
15. (a) K. Mislow and P. Newman, ibid., 79, 1769 (1957);
(b) P. Newman, P. Rutkin and K. Mislow, ibid., 80, 465 (1958).
16. R. S. Cahn, C. K. Ingold, and V. Prelog, Experientia, 12, 81 (1956).
17. J. Kenyon and R. A. McNicol, J. Chem. Soc., 14, (1923).
18. W. von E. Doering and R. W. Young, J. Am. Chem. Soc., 74, 2997 (1952).
19. D. S. Tarbell and M. C. Paulson, ibid., 64, 2842 (1942).
20. K. B. Wiberg, ibid., 74, 3891 (1952).
21. M. L. Wolfrom, R. U. Lemieux, S. M. Olin and D. I. Weisblat, ibid., 71, 4057 (1949).
22. K. Freudenberg, "Stereochemie," Franz Deuticke, Leipzig and Wien, 1932, p. 675.
23. P. G. Stevens, J. Am. Chem. Soc., 55, 4237 (1933).
24. R. B. Woodward, N. L. Wendler, and F. J. Brutschy, ibid., 67, 1425 (1945).
25. L. M. Jackman, A. K. Macbeth and J. A. Mills, J. Chem. Soc., 2641 (1949).
26. W. von E. Doering and R. W. Young, J. Am. Chem. Soc., 72, 631 (1950).
27. E. D. Williams, K. A. Krieger, and A. R. Day, ibid., 75, 2404 (1953).
28. K. W. Bentley and H. M. E. Cardwell, J. Chem. Soc., 3252 (1955).
29. M. Mackay and D. C. Hodgkin, ibid., 3261 (1955).
30. K. W. Bentley, "The Chemistry of the Morphine Alkaloids," The Clarendon Press, Oxford, England, 1954, p. 319.
31. K. Mislow, P. Rutkin, and A. K. Lazarus, ibid., 79, 2974 (1957).
32. F. A. McGinn, A. K. Lazarus, M. Siegel, J. E. Ricci and K. Mislow, ibid., 80, 476 (1958).
33. K. Mislow, Trans. N. Y. Acad. Sci., [2], 19, 298 (1957).
34. W. Kuhn and K. Bein, Z. physik. Chem., 24B, 335 (1934).
35. W. Kuhn and R. Rometsch, Helv. Chim. Acta, 27, 1346 (1944).
36. W. Kuhn, Z. Electrochem., 56, 506 (1952).
37. M. Siegel and K. Mislow, J. Am. Chem. Soc., 80, 473 (1958).
38. J. Timmermans, Rec. trav. chim., 48, 890 (1929).
39. A. Fredge in "The Svedberg," Almgrist and Wiksells Boktryckeri Ab, Uppsala, Sweden, 1944, pp. 261 ff.

METHYL AFFINITIES OF AROMATIC AND OLEFINIC COMPOUNDS

Reported by G. L. DeTommaso April 10, 1958

I. INTRODUCTION

A characteristic reaction of ethylenic compounds is the addition of a free radical to the carbon-carbon double bond, the outstanding example being that of vinyl polymerization.

Sufficient evidence (1-7) has been presented recently indicating that reactions between radicals and aromatic compounds do occur. However, little work has been done (7-16) to place the reactivities of unsaturated compounds on a quantitative basis.

It is the purpose of this seminar report to present additional quantitative work reported as methyl affinities (m.a.) which are the relative (to benzene) rates of addition of methyl radicals to various substrates.

II. GENERAL METHOD

Methyl radicals are generated by the decomposition of acetyl peroxide in an inert solvent as isooctane, the decomposition following the stoichiometric relation $[CH_4 + 2C_2H_6/CO_2] \simeq 1$; in the presence of an aromatic or ethylenic compound, the amount of CH_4 decreases with no change in the amount of CO_2 indicating two competing reactions for methyl radicals (17,18).

(1) $CH_3\cdot + \text{iso-}C_8H_{18} \xrightarrow{k_1} CH_4 + \text{iso-}C_8H_{17}$

(2) $CH_3\cdot + A \xrightarrow{k_2} CH_3A.$

The following relation holds for the reactions:

$$\text{I} \quad k_2/k_1 = \left\{(CH_4/CO_2)_{SH} - (CH_4/CO_2)_A / (CH_4/CO_2)_A\right\} X_{SH}/X_A$$

k_2 and k_1 are the specific rate constants for (2) and (1) respectively; $(CH_4/CO_2)_{SH}$ and $(CH_4/CO_2)_A$ denote the respective quantities measured in solvent only and solvent plus aromatic or olefin; X_{SH} and X_A are the respective molar fractions of solvent and substrate.

In addition to reactions (1) and (2) above, there is a third possible competing reaction (19).

(3) $CH_3\cdot + A \xrightarrow{k_3} CH_4 + A\cdot$

in which case the above expression transforms to:

$$\text{II} \quad \left\{\frac{ACH_3 \text{ formed}}{CH_4 \text{ formed}} \cdot \frac{X_{SH}}{X_A}\right\}^{-1} = \left(\frac{k_2}{k_1}\right)^{-1} + \frac{k_3}{k_2}\left(\frac{X_A}{X_{SH}}\right).$$

A plot of $(k_2/k_1)^{-1}$ vs. X_A/X_{SH} should give a straight line; the intercept equals k_1/k_2 and the slope is k_3/k_2.

III. METHYL AFFINITIES OF AROMATIC COMPOUNDS

The m.a.'s of a series of "normal" aromatic compounds were investigated (17,18,20,21); the results are given in Table I along with the localization energy (β^{-1}) and the number (n) of carbon atoms exhibiting maximum reactivity.

TABLE I

Compound	m.a.	n	β^{-1}	Compound	m.a.	n	β^{-1}
benzene	1	6	2.54	benzpyrene	515	1	1.94
biphenyl	5	4	2.38	anthracene	820	2	2.01
naphthalene	22	4	2.30	naphthacene	9250	4	1.93
phenanthrene	27	4	2.30	pyridine	3	-	-
chrysene	57.5	2	2.24	benzophenone	11	-	-
pyrene	125	4	2.19	quinoline	29	-	-
trans-stilbene	183	2	2.16	isoquinoline	36	-	-
dibenzanthracene	370	2	2.13	acridine	430	-	-
benzanthracene	468	1	2.04	diphenyl ether	2.5	-	-

Reactivity parallels an increase in conjugation, e.g., compare benzene, biphenyl, and diphenyl ether; the m.a. of diphenyl ether is twice that of benzene because of the two unconjugated rings whereas the m.a. of biphenyl is five times that of benzene.

The reactivity of heterocycles such as pyridine and quinoline compared to the corresponding isocyclic compounds is somewhat affected by the hetero atom; however, the effect decreases with increasing size of the molecule.

The data of Magat and Boneme (1,22) indicates that compounds with high m.a.'s are efficient inhibitors, e.g., nitrobenzene (80) and m- and p-dinitrobenzene (500).

The reactivity is dependent on the localization energy of the unsaturated molecule; a linear relation was found between log m.a. and localization energy (23,41).

The m.a.'s of distorted aromatic hydrocarbons were studied. Certain aromatic hydrocarbons, Table II, as the substituted benzo (c) phenanthrenes exemplify the effect of intramolecular crowding on reactivity (24).

TABLE II

Compound	m.a.	Compound	m.a.
unsubstituted	64	6-methyl-	65
2-methyl-	55	1-methyl-	107
3-methyl-	70	1,12-dimethyl-	184
4-methyl-	73	hexahelicene	285
5-methyl-	58.5		

The m.a.'s of the 2-,3-,4-,5-, and 6-methyl- substituted benzo (c) phenanthrenes are approximately equal to that of the parent hydrocarbon. The decided increase in the 1-methyl and 1,12-dimethyl compounds parallels increasing strain and decreasing planarity of the conjugated system. The effect of strain is greatly emphasized by the magnitude of the m.a. of hexahelicene.

The deformation increases the localization of electrons which ordinarily would be delocalized in a planar aromatic molecule and hence leads to a greater availability of electrons.This is substantiated by the linear relationship found between log m.a., maximum free valence, and localization energy.

Szwarc and Leavitt (25) have investigated the effect of twisted and stretched double bonds on the reactivity of poly-arylated double bonds in particular.

TABLE III

Compound	m.a.	Compound	m.a.
bis-diphenylene ethylene	1370	triphenylethylene	85
phenyldiphenylene ethylene	820	tetraphenylethylene	<25
diphenyldiphenylene ethylene	$\sim$15	acenaphthalene	1030

The proximity of the hydrogen atoms on the 1,8,1', and 8' carbon atoms prevents the coplanarity of the bis-diphenylene ethylene molecule which distorts the pi electron system and increases reactivity.

A comparison of triphenyl- and tetraphenylethylene exemplifies the effect of steric hindrance on reactivity.

A comparison of bis-diphenylene ethylene and phenyldiphenylene ethylene indicates two factors affecting reactivity, pi cloud distortion which does not occur in the latter and steric hindrance.

The possible rotation about the carbon-phenyl bond of diphenyldiphenylene ethylene removes any distortion from steric strain; hence the difference in reactivity between bis-diphenylene- and diphenyldiphenylene ethylene. The similar reactivities of diphenyldiphenylene and tetraphenylethylene is attributed to this effect also.

The reactivity increase of a distorted pi cloud is due to a decrease in the overlaop integral, β, which is paralleled by a decrease in the localization energy; this may be expressed in terms of increasing potential energies.

Another factor affecting reactivity, e.g., the difference in the m.a.'s of phenyldiphenylene- and triphenylethylene, is essentially the greater stability of the fluorenyl radical as compared to the diphenylmethyl radical (12,26). Furthermore the interaction between the two phenyl groups in the cis configuration of the latter radical also lowers reactivity since the planarity is affected.

The m.a. of acenaphthalene is very large due to the abnormal length of the 9,10 double bond the effect of which may be interpreted in terms of localization energy and overlap integral.

A study of the quinones is appropriate because of their inhibitory action on chain processes. Rembaum and Szwarc (27) have studied a series of quinones, Table IV.

TABLE IV

Compound	m.a.	Compound	m.a.
p-benzoquinone	1.00	1,4-naphthoquinone	.32
2-methylbenzoquinone	.68	2-methylnaphthoquinone	.22
2,5-dimethylbenzoquinone	.43	2,7-dimethylnaphthoquinone	.27
duroquinone	.052	2,3-dimethylnaphthoquinone	.036
2-methoxybenzoquinone	.52	2,3-dichloronaphthoquinone	.006
2-chlorobenzoquinone	1.71	1,2-naphthoquinone	.225
2,5-dichlorobenzoquinone	2.59	phenanthroquinone	.046
2,6-dichlorobenzoquinone	2.54	2-t-butylanthraquinone	.006
chloranil	.02	anthraquinone	-

The reactivity decreases rapidly along the series p-benzoquinone, 1,4-naphthoquinone, and 1,4-anthraquinone reflecting a decrease in the "olefinic" character of the double bond and the increasing shielding effect of bulky groups.

Substitution of a hydrogen atom by an electron donating group, such as methyl or methoxy, decreases reactivity; and introduction of an electron withdrawing group as chlorine in place of a hydrogen atom increases the reactivity. This will be pursued in the latter part of this report.

There is a relation between redox potentials and m.a.. It is tentatively suggested that the changes in the resonance energy of the system $Q + R\cdot \rightarrow QR\cdot$ parallels the changes in the resonance energy of the system $Q + 2H \rightleftharpoons QH_2$.

The structure of the initial adduct is controversial; however it appears that the carbon-carbon double bond is initially attacked since the presence of bulky groups or atoms decreases the reactivity, e.g., duroquinone, toluquinone, and xyloquinone. Additional evidence cited is the low m.a. of 2,5-di-t-butylbenzoquinone in which the bulky t-butyl groups shield the carbon-carbon double bond but not the carbonyl function.

A linear relation was found between log m.a. vs. log relative addition rate of R· (R· = $\cdot CCl_3$, $PhCOO_2\cdot$, $\sim\sim CH_2\text{-}\dot{C}HPh$, $CH_3\dot{C}H_2$, and $CH_3CH_2\dot{C}H_2$). The slope of the plot, called intrinsic reactivity, may be expressed as

Reactivity of $CH_3\cdot$ = slope x Reactivity of R·

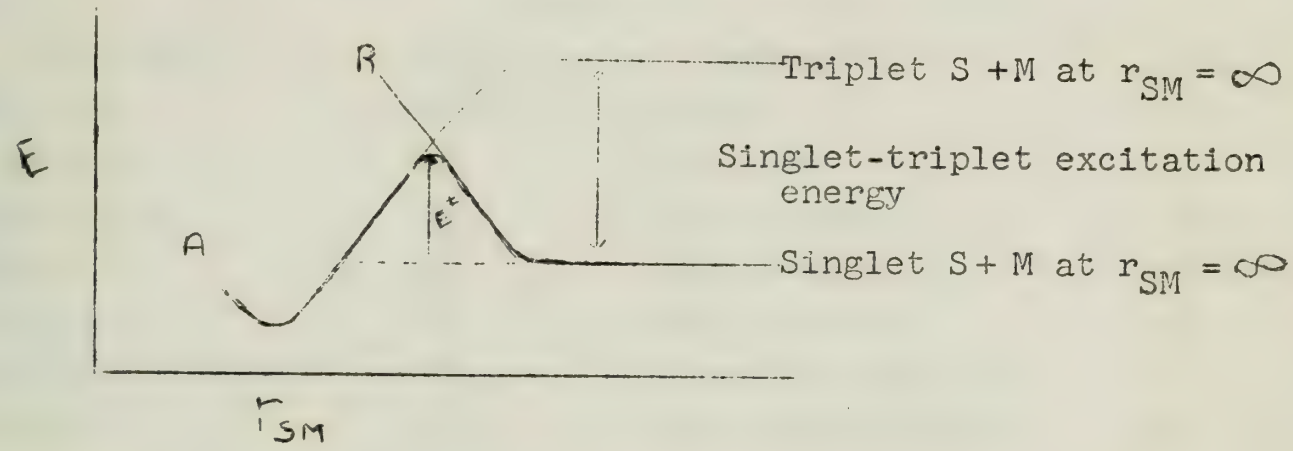
TABLE V

Radical	Slope	Reference
trichloromethyl	1.8	17
perbenzoyl	1.8	17
styryl	2.18	27
ethyl	1	21
n-propyl	1	28
hydrogen atom	<1	29
methyl	-	-

IV. MECHANISM OF ADDITION

A linear relation was found between log m.a.'s, maximum free valences, localization energies, and singlet-triplet excitation energies (23,30).

The progress of the addition reaction may be represented by the following diagram in which the differences in activation energies (and therefore the m.a.'s) are proportional to the singlet-triplet excitation energy.



The course of the reaction follows the heavy line. The repulsion curve (R) which represents the initial stages of the reaction results from coulombic forces between the pi cloud of the substrate, S, and the p-electron cloud of the radical, M. The Morse-like attraction curve results from S, with a localized electron, attracting the radical forming a new carbon-carbon bond. The point of interaction of these two curves represents the transition state.

Assuming the slopes of the curves A and R remain constant for a series of reactions involving the same radical but different substrates; and assuming that the difference in the rates at which a methyl radical will add to two different hydrocarbons is the distance between the plateaus at $r_{SM} = \infty$, then one obtains the expression $\Delta E_{act.} = \alpha \Delta E_{ex}$. The activation energy is determined therefore by the initial state and is little affected by the depth of the Morse curve.

The reactivity of the substituted quinones may now be interpreted utilizing the above diagram. A flatter repulsion curve would result

from electron withdrawing groups attached to the carbon-carbon double bond, and conversely the presence of electron donating groups would cause a sharp rise in curve R. The effect of these would be to change the point of interaction of the two curves thereby affecting the activation energy.

Matsen (31) has shown that log m.a. and electron affinity vary linearly. He proposes that the unpaired electron of the radical initially enters into the lowest unoccupied orbital without bonding to a particular carbon atom. The electron affinity should have the effect of flattening out the repulsion curve leading to a lower activation energy.

A change in the slope of the repulsion curve affects the intrinsic reactivity of a radical (23); since $1/\alpha$ equals the intrinsic reactivity, a flatter repulsion curve results in a greater intrinsic reactivity. This can be seen from the relation $\Delta E_{act} = \alpha \Delta E_{ex}$.

V. METHYL AFFINITIES OF OLEFINS

The increase in reactivity from ethylene (34/statistical factor of 2) to iso-butene (36) parallels the greater stability of the radical formed (19,32,33,34). A calculation of steric factors (29) bears out this increased reactivity.

TABLE VI

Compound	k_2/k_1	Compound	k_2/k_1
ethylene	17(87)*	decene-1	22
propylene	22	hexadecene-1	22
iso-butene	36	trans-butene-2	6.9
butene-1	22	cis-butene-2	3.4
pentene-1	22	vinyl acetate	34
3-methyl-butene-1	22	tetrachloroethylene	<3
heptene-1	22	tetrafluoroethylene	345

* Relative to benzene

The m.a.'s are unaffected by the "tail" length or branching of the "tail" attached to the double bond; the reactivity of the butenes-2 is affected by steric hindrance caused by the methyl group on the carbon to which methyl radical is adding.

The difference in the m.a.'s of C_2H_4, C_2Cl_4 and C_2F_4 (35) is interpreted as due to repulsive forces, very low in C_2F_4, and steric effects, very high in C_2Cl_4.

The two major factors affecting the reactivity of phenylated ethylenes are steric hindrance and radical stability (36); the resonance stabilization affects the activation energy and steric hindrance affects the entropy of activation.

TABLE VII

Compound	m.a.	$\Delta E^{\ddagger}$	Compound	m.a.	$\Delta E^{\ddagger}$
styrene	1630	-3.0	triphenylethylene	85	-3.6
1,1-diphenylethylene	2240	-6.5	tetraphenylethylene	~25	-
trans-stilbene	205	-2.4	α-methylstyrene	1890	-2.5

That increased reactivity parallels greater resonance stabilization is indicated in the series styrene, α-methylstyrene, and 1,1-diphenylethylene; this is attributed to a lower energy of activation.

The shielding of bulky groups manifests itself in the pre-exponential term ($\Delta S^{\ddagger}$) since the activation energy for styrene and stilbene is about the same.

The reluctance of α-methylstyrene to polymerize is attributed to the difficulty of attack of the radical produced.

The m.a.'s for a series of cis and trans olefins were studied (37); the results are given in Table VIII.

TABLE VIII

Compound	k_2/k_1	$\Delta E^{\ddagger}$	A_2/A_1	Compound	k_2/k_1	$\Delta E^{\ddagger}$	A_2/A_1
s-2-butene	3.4	-2	.2	diethyl fumarate	1998(2050)	-7.1	0.4
ans-2-butene	6.9	-2	.4	maleic anhydride	(3880)	-	-
s-di-t-butylethylene	1.9	-	-	chloromaleic anhydride	(5600)	-	-
ans-di-t-butylethylene	.4	-	-	dichloromaleic anhydride	(400)	-	-
s-stilbene	29	-1	5	maleonitrile	(1750)	-	-
ans-stilbene	104.5	-2.4	3	fumaronitrile	(1790)	-	-
ethylmaleate	333(229)	-4.6	.4				

) - run in methyl ethyl ketone.

Although the final product (radical adduct) is the same, the transition state for cis and trans isomers is different due to restricted internal rotation.

The difference between the stilbenes is due to the planarity of the trans in contrast to the non-planarity of the cis isomer. This effect is also demonstrated in the maleate (interference of carboxylic groups distorts the planar configuration) and fumarate esters. In contrast to this, the m.a. of maleic anhydride is high since the ring retains the planar configuration.

Linear ($-C\equiv N$) or spherically symmetrical ($-CH_3$) substituting groups do not effect a difference in reactivity between the isomers, e.g., fumaro- and maleonitrile and the 2-butenes, since the activation energies are about equal for the respective isomers.

It is tentatively suggested that the approach of the methyl radical is along the double bond axis of the olefin since the frequency factors for cis- and trans-stilbene are approximately equal (5 and 3 respectively); if the approach was perpendicular, then A cis $\ll$ A trans. This direction of attack is substantiated by the maleate and fumarate esters; the oxygen atoms of the planar fumarate hinder axial approach whereas axial approach to the non-planar maleate is accessible. The order found was A fumarate $<$ A maleate (.04 and .4 respectively).

M.a.'s have been a useful tool in the elucidation of the ethylene glycol-maleic anhydride polyester (38). The m.a. found for the polyester indicates an isomerization of the maleate to fumarate during polyesterification.

Rajbenbach and Szwarc obtained the following k_2/k_1 values for dienes (39).

TABLE IX

Compound	k_2/k_1	$\Delta E^{\ddagger}$	A_2/A_1	Compound	k_2/k_1	$\Delta E^{\ddagger}$	A_2/A_1
allene	20	-2.6	.41	1,4-diphenyl-butadiene-1,3	378	-	-
butadiene-1,2	17	-1.9	.87	2,5-dimethyl-hexadiene-2,4	21	-	-
butadiene-1,3	2350	-3.0	25	1,1,4,4-tetramethyl-butadiene-1,3	60	-	-
isoprene	2460	-3.9	6.9	hexadiene-1,5	68	-	-
2,3-dimethyl-butadiene-1,3	2230	-	-	2,5-dimethyl-hexadiene-1,5	77	-	-

The reactivity of isolated dienes is twice that of the corresponding olefin. A low frequency factor is responsible for the very low reactivity of cumulated dienes in which attack is probably at the center carbon atom.

The reactivity of conjugated dienes is very high due to a lower activation energy attributed to the resonance energy stabilization which is increased by the hyperconjugation effect of alkyl radicals in the two or three position. However, substituents in the one and four positions exhibit a blocking effect; compare 1,1,4,4-tetramethylbutadiene-1,3, butadiene, and isoprene.

The resonance energy of the allyl radical formed decreases the activation energy of the addition reaction by 2-2.5 kcal./mole.

It has been demonstrated previously that a distorted pi electron system leads to increased reactivity. If an acetylenic linkage is considered as a "compressed" double bond, a decreased reactivity is expected for acetylenic compounds due to the large value of the overlap integral (40). A comparison of the reactivities of the acetylenes and ethylenes bears this out.

TABLE X

Compound	k_2/k_1	A_2/A_1	Compound	k_2/k_1	A_2/A_1
acetylene	29.4	30	diphenylacetylene	12.0	3.4
methylacetylene	10.8	5.0	pentyne-1	8	-
dimethylacetylene	2	-	hexyne-1 (or propyne)	11	-
phenylacetylene	185	60			

The stronger interaction of pi electrons (more negative β) requires a greater activation energy; on the other hand the cylindrical symmetry of a carbon-carbon triple bond leads to a greater entropy of activation (larger A factor).

The rate of addition of a methyl radical to alkyl acetylenes is approximately independent of the length of the alkyl groups. The decreased reactivity of dimethyl- and diphenylacetylene is due to steric hindrance. On the other hand the lower reactivity of hexyne-1 as compared to phenylacetylene reflects the greater resonance stabilization of the radical formed from the latter.

VI. ALKYL AFFINITIES

Ethyl (21) and n-propyl (28) affinities have been measured for a series of aromatic and olefinic compounds.

Results indicate the reactivity of the methyl, ethyl, and n-propyl radicals is the same (intrinsic reactivity is unity); however, the rate of hydrogen abstraction by methyl radicals is greater than that of the other two. This is reflected in the greater bond dissociation energy of methane in comparison to that of ethane and propane.

BIBLIOGRAPHY

1. Magat and Bonême, Compt. rend., 232, 1657 (1951).
2. Stockmeyer and Peebles, J. Am. Chem. Soc., 75, 2279 (1953).
3. Marvel and Anderson, ibid., 75, 4600 (1953).
4. Kooyman and Farenhorst, Trans. Faraday Soc., 49, 58 (1953).
5. Beckwith and Waters, J. Chem. Soc., 1956, 1108.
6. Beckwith and Waters, ibid., 1957, 1665.
7. Goldschmidt and Minsinger, Ber., 87, 956 (1955).
8. Danby and Hinshelwood, Proc. Roy. Soc., A, 179, 169 (1941).
9. Raal and Danby, J. Chem. Soc., 1949, 2222.
10. Roitt and Waters, ibid., 1952, 2695.
11. Dunn and Waters, ibid., 1954, 580.
12. Kice, Abstracts of the 132th Meeting of the American Chemical Society, New York, New York, Sept. 8-13, 1957, p. 9-P.
13. Eliel, ibid., p. 35-P.
14. Eliel, Rabindran and Wilen, J. Org. Chem., 22, 859 (1957).
15. Levy, Steinberg and Szwarc, J. Am. Chem. Soc., 76, 3439 (1954).
16. Levy and Szwarc, ibid., 76, 5981 (1954).
17. Levy and Szwarc, ibid., 77, 1949 (1955).

18. Szwarc, J. Polymer Sci., 16, 367 (1955).
19. Buckeley, Leavitt and Szwarc, J. Am. Chem. Soc., 78, 5557 (1956).
20. Levy and Szwarc, J. Chem. Phys., 22, 1621 (1954).
21. Smid and Szwarc, J. Am. Chem. Soc., 78, 3322 (1956).
22. Magat and Bonême, Disc. Faraday Soc., 10, 266 (1951).
23. Szwarc, J. Phys. Chem., 61, 40 (1957).
24. Levy, Newman and Szwarc, J. Am. Chem. Soc., 77, 4225 (1955).
25. Szwarc and Leavitt, J. Am. Chem. Soc., 78, 3590 (1956).
26. Haszeldine and Steele, J. Chem. Soc., 1953, 1199.
27. Rembaum and Szwarc, J. Am. Chem. Soc., 77, 4468 (1955).
28. Smid and Szwarc, ibid., 79, 1534 (1957).
29. Stepukhovich and Etingof, Doklady Akad. Nauk. S.S.S.R., 99, 815 (1954): C.A., 49, 15392 f (1955).
30. Szwarc, J. Chem. Phys., 23, 204 (1955).
31. Matsen, ibid., 24, 602 (1956).
32. Buckeley, Rembaum and Szwarc, J. Polymer Sci., 24, 135 (1957).
33. Buckeley and Szwarc, Proc. Roy. Soc., 240, 396 (1957).
34. Mandelcorn and Steacie, Canad. J. Chem., 32, 474 (1954).
35. Buckeley and Szwarc, J. Am. Chem. Soc., 78, 5696 (1956).
36. Leavitt, Levy, Szwarc and Stannett, ibid., 77, 5493 (1955).
37. Bader, Buckeley, Leavitt and Szwarc, ibid., 79, 5621 (1957).
38. Leavitt, Stannett and Szwarc, Chem. Ind., ---, 985 (1957).
39. Rajbenbach and Szwarc, J. Am. Chem. Soc., 79, 6343 (1957).
40. Gazith and Szwarc, ibid., 79, 3339 (1957).
41. Coulson, J. Chem. Soc., 1435 (1955).

THE GUERBET REACTION

Reported by William A. Hills March 31, 1958

INTRODUCTION

The direct formation of a higher alcohol from a lower one was first observed by Guerbet (1) in an attempt to reduce an aromatic ester with metallic sodium and alcohol (Bouveault-Blanc method). Guerbet was subsequently able to convert a number of primary alcohols into "dimeric isoalcohols" by heating them to high temperatures in the presence of their alkoxides. In most cases, however, the yields were extremely poor; moreover, the reaction did not always follow the normal course.

Since the work of Guerbet, this reaction has been investigated by a number of workers. This seminar consists of a brief review of the reaction, a discussion of its probable course, and a survey of reactions which may be considered extensions or modification of the classical Guerbet reaction.

A SURVEY OF REACTION

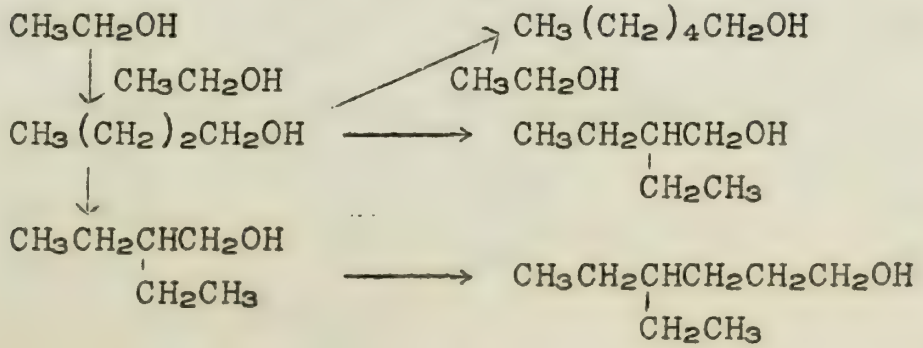
The Guerbet reaction affords a convenient route to alcohols containing a branched chain beta to an alcohol group. The reaction is general for primary and secondary alcohols containing an α-methylene group. A typical example is the conversion of n-butyl alcohol to 2-ethyl-1-hexanol (4,5,6).

$$CH_3CH_2CH_2CH_2OH \xrightarrow{CH_3CH_2CH_2CH_2ONa} CH_3CH_2CH_2CH_2\underset{\displaystyle CH_3CH_2}{\underset{|}{C}}HCH_2OH$$

The reaction is of value not only for the condensation of identical alcohol molecules but also for unlike alcohol molecules. The so-called "mixed" Guerbet reaction occurs with many alcohols. Thus isobutyl alcohol reacts with cyclohexanol to give 2-isobutylcyclohexanol.

In a similar way ethanol and 1-hexanol afford 1-octanol. In "mixed" Guerbet reactions it is necessary for only one of the alcohols to have an α-methylene group.

The Guerbet reaction is complicated by several factors of which the two most important are further condensation of the newly formed alcohol and oxidation of the alcohols to acids. The first factor is illustrated by the condensation of ethanol (6).



The major product is 1-butanol. In each step of the above outline an acid can and often does form from the alcohol. Secondary alcohols yield lower acids, which undoubtedly are derived from oxidative cleavage. As would be expected, the products from mixed Guerbet reactions are even more complicated. Oxidation of the original alcohol to an acid was extensive in the work of Guerbet (1,2,3); the desired product was usually isolated in only 3 to 5% yield.

The importance of the Guerbet synthesis has led to many attempts to minimize the side reactions. The most effective modifications have been the use of dehydrogenation metals as catalysts and the immediate removal of water from the reaction mixture. Such catalysts as nickel, copper-bronze, magnesium chromite, copper-magnesium chromite, and magnesium oxide (7,9,10,11) have been used extensively. With some of the metals or combinations of them weaker bases than the alkoxides could be employed. Farrar (6) has shown that basic reagents such as magnesium oxide, calcium oxide, potassium carbonate, and sodium carbonate in the presence of Raney nickel, copper chromite, or zinc chromite are effective in these conversions. The use of the three catalysts in equal amounts by weight affords the best results. The reaction was also shown to go well when a mixture of sodium hydroxide and boric anhydride was employed with continuous removal of the water as it is formed. In other cases alkaline reacting phosphates (7) proved to be very useful.

Other publications (9,14,10) disclosed that the removal of water in potassium hydroxide catalyzed reactions also improved the yields. In Table 1 are examples of alcohols which have been condensed by use of a nickel catalyst in conjunction with the alkoxide of the alcohol. In Table 2 it is shown that the reaction goes in good yield without the nickel catalyst if the temperature is sufficiently high. In Table 2 are listed examples of "mixed" Guerbet reactions.

TABLE 1

$CH_3(CH_2)CH_2OH$

(0.5 mole Nickel* per mole of alcohol)

n	Temperature at which reaction is run	Percent yield of "dimeric" alcohol	Percent yield of acid derived from starting alc.
2	136-155	75	5
3	155-180	74	3
4	174-204	72	8
5	195-238	66	17
6	205-250	72	20
7	222-276	61	24
8	237-271	70	26
	Reactions without Nickel catalyst		
5	195-254	71	24
6	207-262	70	24
7	224-305	68	30

* Union Oil Product Nickel

TABLE 2

Condensation of benzylalcohol with other alcohols

Alcohol	Temperature	Percent Yield
n-butyl-	143-187°	55
n-hexyl-	177-207	59
n-heptyl-	184-211	58
3-phenylpropyl	225-241	62
Condensation of cyclohexanol with other alcohols		
p-methoxybenzyl-	172-186	61
p-chlorobenzyl-	175-182	47
n-octyl-	175-190	61

COURSE OF THE REACTION

As stated previously the exact stoichiometry of this reaction is unknown because of complications caused by side reactions. The extent of these side reactions varies from one alcohol to another and is also greatly dependent on the conditions under which the process is carried out. In spite of these complications, Guerbet (15) postulated the following equations for the stoichiometry of these reactions.

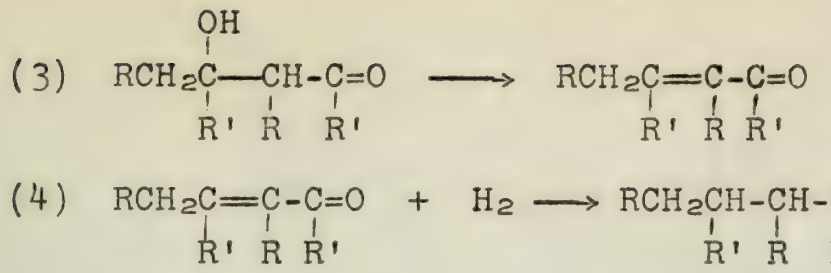
$$C_nH_{2n+1}ONa + 2C_nH_{2n+1}OH \xrightarrow{\Delta} C_{2n}H_{4n+1}OH + C_{n-1}H_{2n-1}COONa + 2H_2$$

$$C_nH_{2n+1}ONa + 2C_mH_{2m+1}OH \xrightarrow{\Delta} C_{m+n}H_{2(m+n)+1}OH + C_{m-1}H_{2m-1}COONa + 2H_2$$

The reaction was interpreted by Guerbet to be the direct alkylation of an alcohol by an alkyl radical. No detailed mechanism was given, however. The scheme of Guerbet was adopted by Weizmann (4,11,16) who thought, however, that the reaction proceeded by the alkylation of an aldehyde by an alkyl radical followed by reduction of the aldehyde to the corresponding alcohol. The possibility of a radical mechanism can be easily discarded, however, since both investigators found that the reaction went more smoothly when air was present. This observation, coupled with the fact that the products formed in these reactions appear to have originated from an aldol-type intermediate, led Bolle (5) to formulate a mechanism which has been successful in accounting for all products usually formed. The mechanism is as follows: (1) dehydrogenation of the alcohol to a carbonyl intermediate, (2) an aldol condensation of the carbonyl intermediate, (3) dehydration of the product from step 2 and (4) hydrogenation of product formed in step 3. This scheme is given below.

(1) $RCH_2\underset{\displaystyle R'}{\underset{|}{C}}HOH \longrightarrow RCH_2\underset{\displaystyle R'}{\underset{|}{C}}{=}O + H_2$

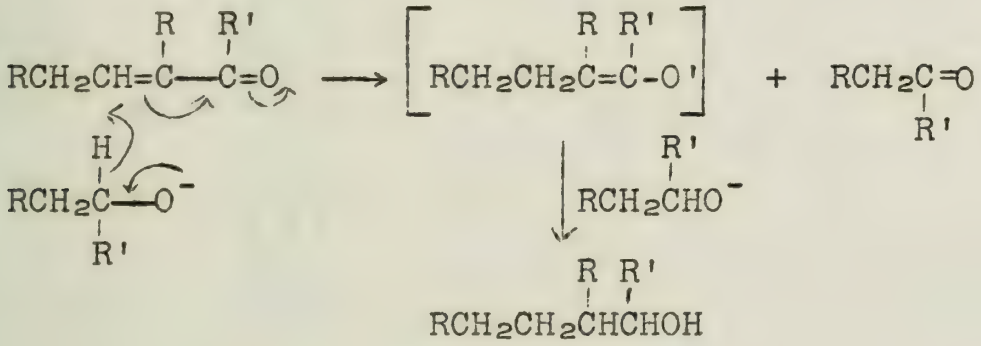
(2) $2RCH_2\underset{\displaystyle R'}{\underset{|}{C}}{=}O \longrightarrow RCH_2\overset{\displaystyle OH}{\overset{|}{\underset{\displaystyle R'}{\underset{|}{C}}}}-\underset{\displaystyle R}{\underset{|}{CH}}-\underset{\displaystyle R'}{\underset{|}{C}}{=}O$



(3) $RCH_2\overset{OH}{\overset{|}{C}}(R')-\overset{R}{\overset{|}{C}}H-\overset{R'}{\overset{|}{C}}=O \longrightarrow RCH_2C(R')=C(R)-C(R')=O$

(4) $RCH_2C(R')=C(R)-C(R')=O + H_2 \longrightarrow RCH_2CH(R')-CH(R)-CHOH(R')$

It is readily seen that the carboxylic acids are formed by the action of hydroxyl ion on the carbonyl intermediate (the Cannizzaro or Dumas-Stas type reaction). It was suggested by Pratt (9) that the reduction in step 4 may occur by a mechanism analogous to that proposed for reduction of carbonyl compounds by aluminum alkoxides (Meerwein-Ponndorf-Verley reaction) (17). This reduction is illustrated below.



$RCH_2CH=C(R)-C(R')=O \longrightarrow [RCH_2CH_2C(R')=C-O'] + RCH_2C(R')=O$

$RCH_2C(H)(R')-O^-$

$[RCH_2CH_2C(R')=C-O'] + RCH_2CH(R')O^- \rightarrow RCH_2CH_2CH(R)CHOH(R')$

It was also shown that if the reaction is interrupted at various stages, carbonyl intermediates corresponding to steps 1 and 3 could be isolated. Furthermore, an intermediate corresponding to step 3 with the α,β-double bond reduced could likewise be isolated (9). Also, the intermediate in step 3 could be reduced to the final alcohol under the reaction conditions.

Step 1 is believed to initiate the reaction, and the bulk of the carbonyl intermediate necessary for the propagation of the process is via the reduction step. Thus the hydrogen liberated in step 1 does not serve to saturate the olefin and carbonyl functions. In support of this it was noted that when $RCH_2\overset{R'}{\overset{|}{C}}=O$ was introduced into the reaction mixture, no induction time was necessary and more than an equivalent amount of product alcohol was formed. When $RCH_2CH_2\overset{R}{\overset{|}{C}}HC(R')=O$ was introduced, the same observations were made.

Perhaps the most convincing evidence for the above reaction scheme is found in the work of Sulzbacher (8) on the condensation of cetyl alcohol. He conducted the reaction in the conventional way with the corresponding alkoxide as the catalyst and also in a modified way with a sodium hydroxide-boric anhydride catalyst. In each procedure the amount of hydrogen given off was measured and the reaction mixture analyzed. The results of these experiments are given in Table 3.

TABLE 3

Experiment	I	II	III
Product isolated from the reaction mixture	Reaction interrupted before completion 0.66 mole cetyl alc.; 0.33 mole alkoxide (%)	Reaction completed 0.66 mole cetyl alc.; 0.33 mole alkoxide (%)	Reaction catalyzed by NaOH-boric anhydride (%)
cetyl alc. recovered	25.5	2.1	20
unsat. alc. C_{32}	40.9	0.8	
sat. alc. C_{32}	9.8	63.7	79
palmitic acid	21.8	30.7	
undetermined biproducts	2.0	2.1	
hydrogen evolved		66	very small amount

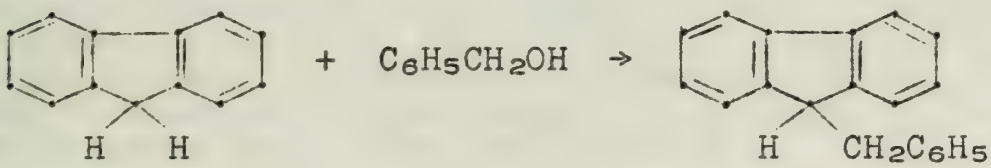
From experiment I it is seen that the hydrogen formed initially escapes before it can saturate the olefin and carbonyl bonds. It is also apparent that only one-half mole of acid per mole of alcohol is formed. This suggests that the acid originates from a Cannizzaro type reaction catalyzed by the aqueous sodium hydroxide (from H_2O + NaOR). The quantity of acid is equivalent to the amount of water given off in the dehydration step. In the modified procedure, experiment III, where the water is removed rapidly either by a thermal process or by reaction with boric anhydride, no acid is formed. This observation also indicates that the first step serves only to initiate the reaction. This discovery seems to raise a doubt as to the order suggested by Pratt (9) for the reduction of the olefin and carbonyl bonds. This order does not affect the general scheme given earlier for the mechanism.

Even though in most cases reductions with alkoxides are specific for the carbonyl group, the analogy is a good one. It will be seen later that, in many reactions closely related to that of Guerbet the reduction of a double bond does occur. Evidence which strongly suggests that such a hydride transfer mechanism is operative has been reported by Pratt (9).

EXTENSION OF THE GUERBET REACTION

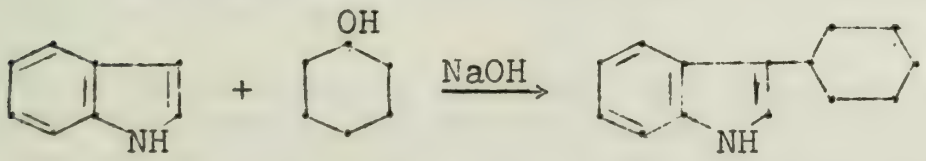
Many examples of alkylations with alcohols under basic conditions are to be found in the literature--transformations closely related to the classical Guerbet reaction. One may think of these condensations as "mixed" Guerbet reactions, in which an alcohol and an amine or an active methylene compound are condensed instead of two alcohols. Examples of such condensations are given below.

$$C_6H_5NH_2 + C_6H_5CH_2OH \xrightarrow{KOH} C_6H_5NHCH_2C_6H_5 + C_6H_5CHO \qquad (18)$$



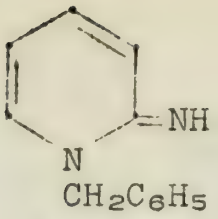
$$+ C_6H_5CH_2OH \rightarrow \qquad (19,25)$$

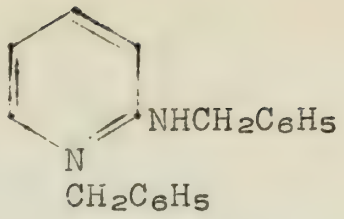
$$C_6H_5COCH_3 + C_6H_5CH_2OH \xrightarrow[C_6H_5CH_2OLi]{} C_6H_5COCH_2CH_2C_6H_5 \qquad (20)$$



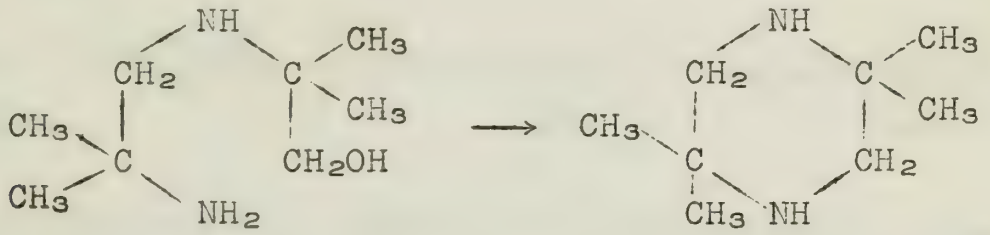
(21)

In certain instances alkylation of amines by this method has proved to have definite advantages over alkylation involving sodium amide and alkyl halides. For example, α-aminopyridine is easily alkylated with benzyl alcohol (22), while with benzyl chloride and sodium amide, the reaction gives the pyridone imine (23,24) instead of N-benzyl-α-aminopyridine.





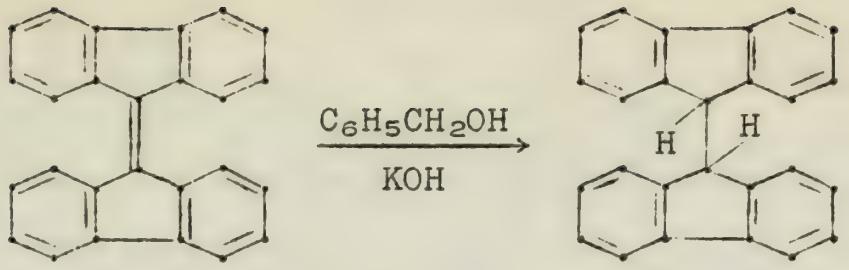
This method of alkylation has also been shown to be useful in cyclization reactions. The following reaction has been reported by Clapp and coworkers (26,27).



Pratt and co-workers (18,21) have shown that these alkylations follow the course described previously for the simple alcohol condensations. In addition, the study of the rates of alkylation of indole and aniline with p-substituted benzyl alcohols gives even stronger evidence for the reduction step of the mechanism. That this step is a slow one and does not involve simple hydrogenation by molecular hydrogen has been demonstrated by Pratt. Electron donating groups on the benzyl alcohol increase the reaction rate. Thus the order of decreasing reaction rate is $(CH_3)_2N- > CH_3O- > CH_3 > H > Cl$. When the same groups are placed in the para-position of aniline, the reaction is retarded. From these facts it can be stated with certainty that a hydride transfer mechanism is operative. It was shown also that a trace of aldehyde was sufficient to initiate the reaction and no dehydrogenation metal was then necessary.

Like other active methylene compounds the picolines are also benzylated under Guerbet conditions. Two benzyl groups may be introduced into 2- and 4-picolines. Quinaldine, however, forms only a monobenzyl derivative. Even 3-picoline can be benzylated, although the yield is rather poor.

The effectiveness of alkoxides as reducing agents, already indicated repeatedly, becomes even more evident when one considers the reaction of quinoline with benzyl alcohol in base. Quinoline is transformed into 1,2,3,4-tetrahydroquinoline, 3-benzyl quinoline, and 3-benzyl-1,2,3,4-tetrahydroquinoline in good yields. These products may be rationalized in the following way: the pyridine ring is partially reduced; the reduction is followed by two concurrent reactions, reduction to 1,2,3,4-tetrahydroquinoline and condensation of dihydroquinoline with benzaldehyde to give 3-benzal-3,4-dihydroquinoline, which isomerizes to 3-benzylquinoline. The latter is then reduced to 3-benzyl-1,2,3,4-tetrahydroquinoline. 3-Methyl- and 3-phenylquinoline (28) are also reduced by the above reagent. In a similar manner fulvene (22) and some of its derivatives are reduced by basic alcoholic solutions.



Another illustration of the reducing action of these reagents is the conversion of α,β-diphenylacrylonitrile to α,β-diphenylpropionic acid (28).

$$C_6H_5CH{=}\underset{\displaystyle C_6H_5}{\overset{|}{C}}CN \xrightarrow[KOH]{C_6H_5CH_2OH} \left[C_6H_5CH_2\text{-}\underset{\displaystyle C_6H_5}{\overset{|}{C}}H\text{-}CN \right] \rightarrow C_6H_5CH_2\underset{\displaystyle C_6H_5}{\overset{|}{C}}HCO_2H$$

An interesting series of alkylations with alcohols, reported by Carroll (29), does not seem to fit into the mechanistic scheme proposed for the normal Guerbet reaction. Thus when linalöol was treated with ethyl acetoacetate and sodium ethoxide, the following conversion took place.

$$R\text{-}\underset{\displaystyle CH_3}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}CH{=}CH_2 + CH_3COCH_2CO_2C_2H_5 \rightarrow R\text{-}\underset{\displaystyle CH_3}{\overset{|}{C}}{=}CHCH_2CH_2COCH_3 + CO_2 + C_2H_5OH$$

[R=$(CH_3)_2C{=}CHCH_2CH_2$-]

On the other hand, phenylvinylcarbinol underwent the following change.

$$C_6H_5\text{-}\underset{\displaystyle OH}{\overset{|}{C}}HCH{=}CH_2 \longrightarrow C_6H_5CH{=}CHCH_2CH_2COCH_3$$

Cinnamyl alcohol reacted in a similar way.

$$C_6H_5CH{=}CHCH_2OH \longrightarrow CH_2{=}CH\text{-}\underset{\displaystyle C_6H_5}{\overset{|}{C}}HCH_2COCH_3$$

BIBLIOGRAPHY

1. M. Guerbet, Compt. rend., 128, 511, 1002 (1899).
2. M. Guerbet, Compt. rend., 132, 207 (1901).
3. M. Guerbet, Bull. soc. chim. France, [4], 3, 560 (1908).
4. C.H. Weizmann, E. Bergmann and M. Sulzbacher, J. Org. Chem., 15, 54 (1950).
5. J. Bolle and L. Bourgeois, Compt. rend., 233, 1466 (1951).
6. M. N. Dvornikoff and M.W. Farrar, J. Org. Chem., 22, 540 (1957).
7. R.E. Miller and G.E. Bennett, U. S. Patent 2,762,847, September 11, 1956.
8. M. Sulzbacher, J. Appl. Chem., 5, 637 (1955).
9. E.F. Pratt and D. Kubler, J. Am. Chem. Soc., 76, 52 (1954).
10. J. Bolle, Compt. rend., 233, 1628 (1951).
11. C. Weizmann, E. Bergmann and L. Haskilberg, Chem. Ind., 56, 587 (1937).
12. M. Sulzbacher, Brit. Patent 655,864, August 1, 1951.
13. M. Sulzbacher, J. Appl. Chem., 5, 637 (1955).
14. C.A. Carter, U. S. Patent 2,457,866, January 4, 1949.
15. H. Machemer, Angew. Chem., 64, 213 (1952).
16. C.H. Weizmann and S.F. Garrard, J. Chem. Soc., 117, 325 (1920).
17. J. Hine, "Physical Organic Chemistry," p. 263, McGraw-Hill Book Company, Inc., New York, 1956.
18. E.F. Pratt and E.G. Frazzer, J. Am. Chem. Soc. 76, 6174 (1954).
19. Y. Sprinzak, J. Am. Chem. Soc., 78, 466 (1956).
20. E.F. Pratt and A.P. Evans, J. Am. Chem. Soc., 78, 4950 (1956).
21. E.F. Pratt and L. W. Botimer, J. Am. Chem. Soc., 79, 5248 (1957).
22. Y. Sprinzak, J. Am. Chem. Soc., 78, 3207 (1956); French patent 1,082,636, January 8, 1953.
23. H.M. Sharp, J. Chem. Soc., 1855 (1939).
24. J.H.Biel, J. Am. Chem. Soc., 71, 1306 (1949).
25. K. L. Schoen and E.I. Becker, J. Am. Chem. Soc., 6030 (1955).
26. L.T. Plante, W.G. Lloyd, E. Schilling and L.B. Clopp, J. Org. Chem., 21, 82 (1952).
27. L.T. Plante and L.B. Clapp, J. Org. Chem., 21, 86 (1956).
28. M. Avramoff and Y. Sprinzak, J. Am. Chem. Soc., 78, 4090 (1956).
29. M.F. Carroll, J. Chem. Soc., 1266 (1940).
30. M.F. Carroll, J. Chem. Soc., 507 (1941).
31. S.M. Linder, E.I. Becker and P.E. Spoerri, J. Am. Chem. Soc., 75, 5972 (1953).
32. J.U. Nef Ann., 318, 137 (1901).
33. J.U. Nef, Ann., 318, 171 (1901).
34. J.W. Conforth, R.H. Conforth and R. Robinson, J. Chem. Soc., 682 (1942).

EFFECTS OF HIGH PRESSURES ON NON-RADICAL REACTIONS

Reported by H. Babad April 21, 1958

INTRODUCTION

The investigation of rates and equilibria as functions of pressure is a tool which promises to shed much light on the nature of the transition state in chemical reactions. The earliest work in this field was carried out by M. W. Perrin and co-workers (1,8) in 1938. Upon investigation of the change in the Arrhenius parameters with pressure ($K = Ae^{-E/RT}$) Perrin discovered three types of behavior. Perrin found that normal S_N2 reactions by anions showed a small increase in rate with a large increase in pressure. Unimolecular decompositions of quaternary ammonium salts were decreased by an increase in pressure, while the reverse reaction, that of the formation of quaternary ammonium salts (so called slow reactions) showed a very large increase in rate as the pressure increased. These reactions are exemplified by the following equations.

(1) $ClCH_2CO_2^- + OH^- \longrightarrow HOCH_2CO_2^- + Cl^-$ (normal S_N2)

(2) $\phi CH_2(\phi)\overset{+}{N}CH_2CH{=}CH_2(CH_3)\ I^- \longrightarrow CH_2{=}CHCH_2I + \phi CH_2(\phi)NCH_3$

(3) $Et_3N + MeI \longrightarrow Et_3\overset{+}{N}Me\ I^-$ (Menschutkin Reaction)

It was not until 15 years later that this phenomenon was again investigated, and some attempt at explanation and generalization was made.

THEORETICAL BACKGROUND

In 1953 Hamann and Buchanan investigated Perrin's reactions (2) and found that they could be generalized and extended to cover most non-radical reactions in organic chemistry by considering the nature of the changes in ionic charge between the starting materials and the transition state. The following table will illustrate this extension of the observations of Perrin (3).

Table I

	Pressure Effect	Reaction Type	$\Delta Z^{\ddagger}$ (Charge)
(I)	Large increase	Menschutkin Reaction Dark Olefin Halogenation Solvolysis Reactions Ionization of Weak electrolytes	increases
(II)	Small increase	Redox Reactions Negative ion substitutions	No change
(III)	decreases	Ammonium Decompositions Urea Formation ($NH_4^+ + NCO^-$)	decreases

The Perrin classification became out-moded and invalid when it was found that there was pressure-caused retardation of a reaction which was a bimolecular reaction. From the above table we see that if there is an increase in the amount of charge (positive $\Delta Z^{\ddagger}$) appearing

between the starting material and the transition state, the reaction is greatly accelerated by pressure. Conversely, charge neutralization or disappearance(negative $\Delta Z^{\ddagger}$)retards the reaction with respect to a pressure increase on tne system. K. J. Laidler and co-workers (4) applied the van't Hoff equation ($d \ln K/dp = -\Delta V/RT$) to reactions run at high pressures and found a correlation between volume changes in the reaction and changes in ionic charge, as discussed in the previous section. Their major assumption was that the rate of any reaction depends only on conditions found in the activated complex, thus enabling one to use the van't Hoff equation for both rate and equilibrium studies. From the preceeding discussion, the problem of the effect of pressure on rates and equilibria reduces to one of understanding the volume changes in the overall reaction or activation process. The effects which must be considered are changes in volume and structure of the molecules reacting (molecular deformation under pressure) and the changes in volume due to packing of the adjacent solvent molecules. For reactions involving polarity changes, the latter effect predominates. Hamann, et al., (2,3) and Burris and Laidler (5) showed that for reactions of widely differing ionic types the volumes of activation ($\Delta V^{\ddagger}$) are primarily determined by the influence of changes in polarity in ($\Delta Z^{\ddagger}$) the reaction system on the surrounding solvent molecules.

This is the so-called electrostriction theory, which in brief states that when ions of the same sign come together, or when two neutral molecules unite to form a polar substance, there will be contraction of the system due to the increased binding of solvent molecules. Conversely, if the electric field is weakened during the reaction by charge distribution, splitting or neutralization, there will be a release of bonded solvent and a consequent expansion of the reaction system. From the van't Hoff equation it can be readily seen that contraction(negative $\Delta V^{\ddagger}$)causes an increase in the reaction rate with pressure, and, conversely, an expansion(positive$\Delta V^{\ddagger}$) will cause a decrease in the reaction rate. Laidler and co-workers have correlated the values for the volumes of activation and reaction with the charge on the complex for a few types of reactions, and their results for monatomic ions and oxy-anions ($SO_4^{=}$, NO_3^{-}) in aqueous solution are discussed below.

The partial molal volume (ml./mole) for monatomic ions was empirically found to be.....

$\bar{V}_+ = 16 + 4.9r^3 - 20|z|$ for monatomic cations

$\bar{V}_- = 4 + 4.9r^3 - 20|z|$ for monatomic anions

$\bar{V}_- = 59 + 0.9R^3 - 20|z|$ for oxy-anions

r = crystallographic radius of ion in $\mathring{A}$

z = change of the ionic species

ΔZ = the change in valence between the product or transition state and the starting material

R = $.25n(r_{1-2} + 1.4)$ where n is number of charge bearing ligands (oxygen in this case) and r_{1-2} is the crystallographic bond distance between the center of the oxygen atom and the center of the central atom. 1.4 is the Van der Waal's radius of oxygen so R^3 term represents the intrinsic volume of the sphere which circumscribes the oxy-anion.

From the preceeding equations one can calculate the changes in volume between the products and starting materials for some reactions, and as the volume of activation ($\Delta V^{\ddagger}$) is somewhere between these two volumes we have a method of approximating some volumes of activation. This gives us a means of comparing the actual charge density on the transition state, as expressed by experimentally obtained values for the volume of activation, with values calculated from Laidler's empirical equations for hypothetical transition states. It should be noticed that there is a linear dependence of volume on the ionic charge of the species involved in the reaction and that the z term in Laidler's equation (electrostriction term) is much larger than the r^3 term (intrinsic volume of the ion). When the total change in charge of a reaction is zero the changes in volume may be expected to be small, reflecting only changes in the ionic radius of the species involved. This is the sort of phenomenon observed when all the particles in a reaction have the same sign. A negative change in charge means that a reaction has been accompanied by charge neutralization, so $\Delta V^{\ddagger}$ is positive and the rate or equilibrium constant decreases. Conversely, for a positive change in charge the rate or equilibrium constant increases. Entropy changes have been empirically related to the square of the change in charge (4).

Comparison of the values of the change in molecular volume for the reaction $Ti^{+} + 2Fe^{+++} = Ti^{++++} + 2Fe^{++}$ shows a 10% difference between the theoretical values and those observed experimentally. $\Delta Z = 0$, and $\Delta V = -8.9$ ml./mole are the values calculated for this reaction.

When neutralization occurs, much larger volume changes occur, as can be seen when we examine the reaction of $HCO_3^- \rightleftharpoons H^+ + CO_3^=$ in which $\Delta V = -27.8$ ml./mole; at 1000 atm. the equilibrium constant increases by a factor of 3.12.

Volumes of Activation

Given the reaction $A^z + B^{z'} \rightleftharpoons (X^{z+z'})^{\ddagger}$, two types of reactions are found.

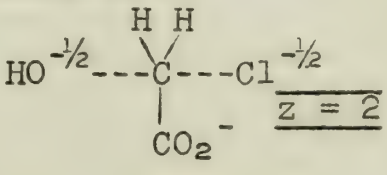
1) The charge change is zero resulting in a small volume change;

Examples:

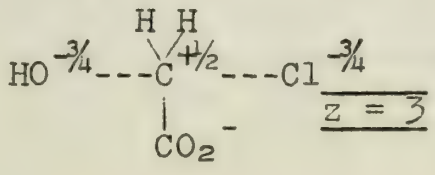
$$ClCH_2CO_2^- + OH^- \longrightarrow HOCH_2CO_2^- + Cl^- \qquad (4)$$

$$BrCH_2CO_2^- + S_2O_3^= \longrightarrow S_2O_3CH_2CO_2^= + Br^- \qquad (4)$$

The volumes of activation at 25°C are -6.1 and -4.8 ml./mole, respectively, and the entropies are -11.6 and -17.0 cal./mole °C, which are in close agreement with the values calculated from the empirical relationships of Laidler. A simple view of these reactions is:-



I.



II.

The fact that $\Delta V^{\ddagger}$ is negative suggests some contribution by a transition state in which the total absolute charge of the complex is some-what greater than -2 and might be something like structure (II) since such a structure would be expected to bind solvent to a greater extent, thus giving a negative $\Delta V^{\ddagger}$.

2) The valency change is either positive or negative resulting in a large volume change, as in reactions where charge is either gained or lost in the transition state.

Examples:

$$Co(NH_3)_5Br^{++} + OH^- \longrightarrow Co(NH_3)_5OH^{++} + Br^-$$

$\Delta V^{\ddagger}$ = +8.4 ml./mole, $\Delta S^{\ddagger}$ = 21.7 cal./mole °C.

$$Et_3N + MeI \longrightarrow Et_3\overset{+}{N}\text{-Me } I^-$$

$\Delta V^{\ddagger}$ = -16.5 ml./mole, $\Delta S^{\ddagger}$ = -32.5 cal./mole °C.

For the first reaction above the positive values for the volume and entropy of activation are due to partial charge neutralization in the transition state.

Temperature Dependence of Volume Changes

The relationship between entropy and pressure $\partial\Delta S^{\ddagger}/\partial p = -\partial\Delta V^{\ddagger}/\partial T$ can be found in any elementary book on thermodynamics, and when data obtained by measuring reaction rates at various temperatures (solving the Arrhenius Equation for the A and E parameters) are used in conjunction with this, it becomes possible to calculate the temperature coefficient of volumes (coefficient of expansion of the transition state) for many reactions. Though no data in the literature have been presented for equilibrium reactions, Fajans and Johnson (6) have presented and discussed temperature coefficients for partial molal volumes of individual ions in aqueous solution and have found that there is a nearly linear relationship between the temperature coefficients and the volume itself. This implies that electrostriction effects play a very important part in connection with ionic volumes. An ion with a large volume tends to be one on which water molecules are loosely bound, and the temperature coefficient of weakly held water will be similar to that of unbound water. However, if water molecules are strongly bound, they will not be as much disturbed by a rise in temperature; in this case there will be low volumes and low temperature coefficients.

This correlation between temperature coefficient and volume cannot be expected to be very close for various reasons. One of these is the fact that a low volume may arise from the strong binding of a small number of water molecules or from the weak binding of many. In the former case there will be a correlation between temperature coefficient and volume, while in the latter the temperature coefficient may be quite high. It will be shown later that there are several cases in which it seems that the activated complex bears a smeared charge which tends to bind a number of solvent molecules in a relatively loose manner.

As far as rates are concerned, there are several reactions for which suitable data are available (Table II). When one plots the entropies of activation for these reactions against pressure, there is a fairly linear dependence of $\Delta S^{\ddagger}$ on pressure. From the slopes of these lines the temperature coefficients of the volumes of activation can be obtained, and these are listed in Table II. Another interesting relationship can be observed if the values of $T\Delta S^{\ddagger}$ obtained at various pressures are plotted against the corresponding energies (heats) of activation; the dependence is found to be linear at high pressures, and surprisingly, the slope is unity. This result means that the influence of pressure on the free energy of activation at high pressures is much less than that on its component parts. In other words, there is an almost complete compensation between changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ as the pressure changes. Such compensation had been noticed before, although not when pressure was a variable (7).

Since such compensation effects are found in equilibrium studies as well as rate studies, it is clear that they are not to be explained in terms of the nature of the collisions during the course of the reaction. The most plausible explanation seems to be in terms of the effects of changes in polarity of the reaction system on the behavior of the neighboring solvent molecules. Factors that tend to increase the binding of solvent molecules during the course of the reaction (or activation process) bring about a decrease in $T\Delta S^{\ddagger}$ and at the same time decrease $\Delta H^{\ddagger}$, and as a rule there seems to be very close compensation between the two factors. As a result solvent effects of this kind frequently escape notice, particularly when reactions are studied at one temperature.

Turning now to consider the values of the temperature coefficients in Table II, we observe that for reactions 1-3 the values for the coefficient are negative and for reactions 6-8 they are positive. Reaction 1-3 are all of the same general type, in that they involve significant increases in polarity as the activated complexes are formed as revealed by negative values for $\Delta V^{\ddagger}$, and $\Delta S^{\ddagger}$. The solvent is more tightly bound in the activated state than in the initial state so it is not difficult to see why the coefficient of expansion for the activated state is less than for the initial state.

Table II TEMPERATURE COEFFICIENTS OF VOLUMES OF ACTIVATION

Reaction	Solvent	t°C.	$\Delta S^{\ddagger}$	$\Delta V^{\ddagger}$	$\partial \Delta V^{\ddagger}/\partial T = \partial \Delta S^{\ddagger}/\partial p$	ref
1) ØN + EtI = ammonium salt	acetone	25.0°	-35.4	-15.8	-.037	(8)
2) t-butyl-Cl = Cl^- + t-butyl carbonium ion	80% EtOH	35.0°	+35.1	-23.0	-.210	(2)
3) $\text{Ø}CCl_3 = \text{Ø}CCl_2^+ + Cl^-$	80% EtOH	35.0°	+35.0	-14.0	-.314	(2)
4) $EtO^- + EtI = EtOEt + I^-$	80% EtOH	35.0°	- 5.7	- 4.1	---	(9)
5) $BrCH_2CO_2CH_3 + S_2O_3^= = S_2O_3CH_2CO_2CH_3^- + Br^-$	80% EtOH	35.0°	- 5.9	+ 3.2	---	(9)
6) $CH_3(C_3H_5)\text{Ø}\overset{+}{N}CH_2\text{Ø}\ Br^- = CH_3(\text{Ø}CH_2)N\text{Ø} + C_3H_5Br$	$CHCl_3$	25.0°	+14.9	+ 3.3	+.032	(1,10)
7) $ClCH_2CO_2^- + OH^- = HOCH_2CO_2^- + Cl^-$	H_2O	25.0°	-11.6	- 6.1	+.008	(1)
8) N:N-dimethyl, o-tolui- dine + MeI = ammonium salt	MeOH	40.0°	-18.7	-26.7	+.031	(4,9)
	acetone	40.0°	-36.0	-10.2	---	(11)

In reactions 4 and 5 we have two reactions in which there is very little ionic charge formation or neutralization when the activated complex is formed, but the values for the volumes of activation have opposite signs. Upon careful examination of these reactions certain structural differences become apparent, the most important being the splitting of the double charge in the thiosulfate reaction with methyl-α-bromoacetate, which would lead to an overall weakening of the electrical field in the activated state and cause release of solvent molecules. In the reaction of ethoxide ion with ethyl iodide, the contribution by the greater ionization of the C-I bond (as compared to the C-Br ionization in methyl-α-bromoacetate) may result in the development of greater total absolute charge in the transition state for this reaction, resulting in a negative $\Delta V^{\ddagger}$ due to increased binding of solvent. In the light of this evidence it is not surprising that the thiosulfate reaction has a positive volume of activation while the volume of activation for the ethyl iodide reaction is negative. More will be said concerning the effects of structural characteristics upon the volumes of activation in a later part of this seminar.

The polarity of the system is decreased in reaction 6 and consequently there is a decrease in the degree of bonding, so there is a higher coefficient of expansion for the activated state than for the initial state.

Some ambiguity arises when one tries to explain reaction 7 in terms of correlations between volumes of activation and temperature coefficients. As was discussed previously, a low volume of activation may arise from the weak binding of a large number of solvent molecules, as would be the case where the charge is smeared over a large area, rather than being concentrated in a small one. It is possible that the transition state in this case resembles structure II as presented earlier in that the absolute charge on the transition state is closer to 3 than to 2 which would have been ordinarily predicted. This is evidence in favor of the hypothesis that even in S_N2 reactions the central carbon atom has somewhat of a carbonium ion nature in the transition state. Owing to the smearing of charge, however, none of the solvent molecules will be bound as strongly in the transition state as in the initial state, and thus the temperature coefficient will be positive.

In reaction 8 we have a case of a sterically hindered amine being used in a Menschutkin reaction in both methanol (4,9) and acetone (11). Weale found no indication that pressures up to 3,000 atm. alleviated steric retardation of the rate of reaction with methyl iodide. It was found that the Arrhenius parameters for this reaction were affected by pressure, in a manner similar to the way these parameters varied for the unhindered Menschutkin reactions. The acceleration of the hindered reaction in acetone was thought to be due to ionic polarization effects, causing electrostriction of the solvent molecules. When the reaction was carried out in methanol, it was found that the trend in $\Delta H^{\ddagger}$ was reversed, becoming more positive. The overall picture at first glance seemed similar for both solvents, namely, that the ortho methyl group screened the solvent molecules. Since there is a charge produced in the transition state, there will be more bonding to solvent in the transition state than in the initial state ($\Delta V^{\ddagger}$ = -26.6 ml./mole). Laidler's (4) explanation of the positive temperature coefficient of the volume of activation for the reaction in methanol solvent was that due to

screening effects the molecules are not as strongly bound in the shielded transition state relative to the initial state as in para substituted compounds. This interpretation gains support from the fact that it has been shown that the entropies of activation for ortho substituted compounds are approximately 5.52 times higher than those for para substituted compounds (13).

S. D. Hamann and W. Straus (12) felt that it would be more profitable to use a bulk model for solvation rather than Laidler's molecular one for predicting the effects of pressure on a reaction in various solvents. These authors felt that the change in trend of $\Delta H^{\ddagger}$ values for the sterically hindered Menschutkin reaction in methanol could be adequately explained and predicted by utilizing the macroscopic theory of solvation in two solvents. On this basis an attempt was made to predict the way $\Delta F^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ might change with pressure and solvent using cesium iodide as a model and allowing for the changes in bulk dielectric constants with temperature and pressure. The solvation functions were taken as the differences in ΔF, ΔH, and ΔS of solution with pressure, which Hamann and Strauss attributed to an increase in the degree of solvation. Their results are listed in Table III below.

Table III

Solvation functions for $Cs^+ I^-$

Solvent	(f)	pressure.... 1	2,000	4,000	6,000	atm.
H_2O	ΔF	0	-1.2	-2.2	-3.1	
	ΔH	0	-0.7	-1.2	-1.3	
	$T\Delta S$	0	+0.5	+1.0	+1.8	
MeOH	ΔF	0	-1.7	-2.9	-4.0	
	ΔH	0	-0.1	-0.3	-0.6	←
	$T\Delta S$	0	+1.6	+2.6	+3.5	
EtOH	ΔF	0	-2.0	-3.4	-4.4	
	ΔH	0	+0.2	+0.1	+0.1	
	$T\Delta S$	0	+2.2	+3.5	+4.5	
acetone	ΔF	0	-2.4	-3.9	-5.0	
	ΔH	0	+1.2	+1.4	+1.4	←
	$T\Delta S$	0	+3.6	+5.3	+6.4	

It will be seen that the trend in ΔH inverts between methanol and acetone although there is little change in the general behavior of ΔF. The results for the Menschutkin reactions showed an increase in this function with pressure in acetone, but a decrease in methanol, while the acceleration ($-\Delta F^{\ddagger}$) should be greater in acetone than in methanol. Weale's work confirmed this (11).

LIQUID PHASE REACTIONS AT HIGH PRESSURES

The usefulness of high pressure work for the investigation of reaction mechanisms can be illustrated by the work of R. T. Harris and K. E. Weale (14), who studied the following isomerizations and molecular rearrangements at several temperatures and pressures up to 5,000 atmospheres.

I. Isomerization of maleic to fumaric acid in aqueous solution as catalyzed by KCNS. $\Delta V^{\ddagger}$ = -5.44 ml./mole

II. Diethyl maleate isomerization to diethyl fumarate in acetone as catalyzed by diethylamine $\Delta V^{\ddagger}$ = -22 to -12 ml./mole

III. Rearrangement of N-chloroacetanilide to ortho- and para-chloroacetanilide as catalyzed by HCl in aqueous solution. $\Delta V^{\ddagger}$ = +7.2 to 1.0 ml./mole

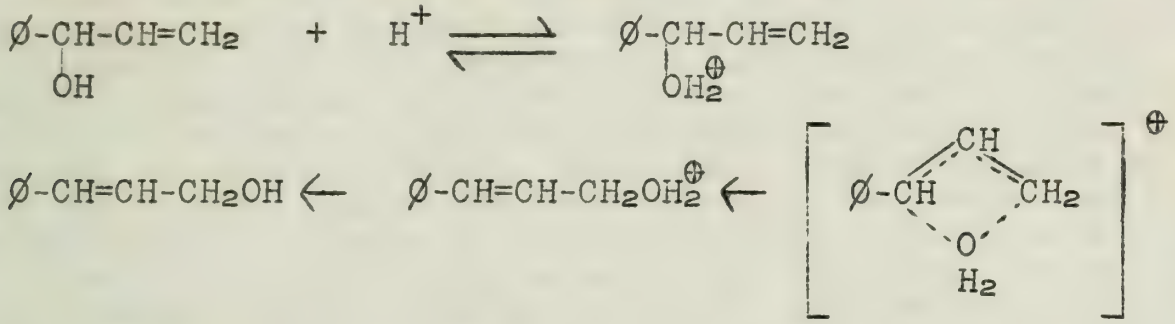
IV. Rearrangement of α-phenallyl alcohol with an HCl catalyst to cinnamyl alcohol in aqueous dioxane. $\Delta V^{\ddagger}$ = -6.0 to 1.0 ml./mole.

Analysis of Data

Reaction (III), the rearrangment of N-chloroacetanilide resembles the reaction of ammonium bromides to give a halide and a tertiary amine in that there is a decrease in polarity as one approaches the transition state. The rate determining step in this rearrangement has been shown to be (15)....

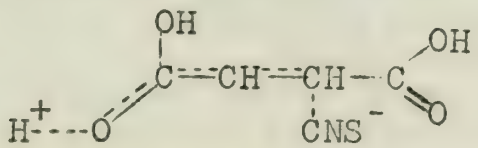
followed by chlorination. In view of this, it is not surprising to find the reaction retarded by pressure even though there is no net gain or loss of charge in the overall reaction.

Reaction (IV) The decomposition of α-phenallyl alcohol doesn't involve the appearance or disappearance of charge according to the mechanism proposed by Braude, et al. (16).



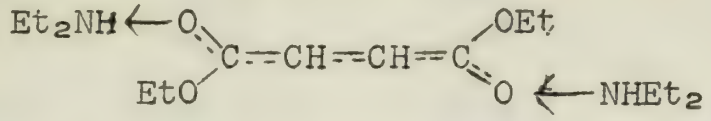
Small changes that appear seem to be due primarily to differences in ionic charge distribution, or in part to an increase in catalyst concentration caused by the compression of the solvent, which was not corrected for.

Reaction (I) The mechanism advanced for the KCNS isomerization of maleic acid by Nozaki and Ogg (17) postulated the addition of a proton to a carbonyl oxygen in the acid molecule and the approach of the CNS anion at a more remote point. The resulting weakening of the double bond enables isomerization to occur.



Protons for the first step are derived from the ionization of other acid molecules, and the change in rate observed is due primarily to the increased proton concentration caused by a pressure induced shift in the ionization constant of the weak acid.

Reaction (II) The other cis-trans isomerization was established to be second order with respect to the amine by Nozaki and Ogg (17) who confirmed the absence of catalysis by tertiary amines. The transition state for this isomerization is postulated as (III) in which molecules of the amine complex the ethyl maleate, causing a weakening of the double bond and subsequent isomerization. This involves the



(III)

appearance of partial or whole ionic charge in the molecule, and in accordance with the electrostriction theory acceleration by pressure should be observed and this acceleration should be greater than for the CNS^- catalyzed isomerization and in the order of the Menschutkin reaction. This is confirmed by the observation of Weale and co-workers (14).

OTHER REACTIONS AT HIGH PRESSURES

Weale and co-workers (11) found that there was no alleviation of steric hindrance at pressures up to 3,000 atmospheres in either the hindered Menschutkin reaction or the reaction of neopentyl chloride with NaOEt in dry EtOH, and the literature contains no examples proving that bond angles were deformed under high pressures to reduce steric hindrance.

S. D. Hamann and D. R. Teplizky (18) have shown that the mechanism proposed for dark olefin halogenation in polar solvents is consistent with data obtained in high pressure studies. The mechanism postulates the slow addition of a positive halide ion to the olefin as the rate determining step, followed by the rapid addition of the anion (19). Since the transition state is more polar than the initial state, the reaction will be accelerated by pressure. The addition of bromine to trans-stilbene in methanol and the addition of iodine to allyl alcohol in both water (in presence of KI) and nitomethane were carried out at 0°C and pressures up to 3,000 atmospheres. After corrections were made for the retardation effects due to the formation of the trihalide ions (X_3^-) during the course of the reaction, the rates were found to have been increased by a factor of 6.5 for the bromination of trans-stilbene and a factor of 9 for the iodination of allyl alcohol at 3,000 atmospheres.

The effects of structure on the Menschutkin reaction were experimentally determined for the reaction of MeI, EtI and EtBr with dimethylaniline. The trend observed upon changing the halogen atom in the alkyl halide is in agreement with the results obtained for the relative rates of solvolysis of ethyl halides in compressed methanol., as shown in Table IV below. These effects are consistent with the electrostriction theory since iodide is a large ion having its charge distributed over a larger area, so there is less solvation energy and thus a smaller pressure effect.

Table IV

Reactivities of Alkyl Halides at High Pressures

Reaction	Solvent	Temperature	$K_{3,000}/K_1$	$K_{15,000}/K_1$
EtCl solvolysis	MeOH	65°C	7.9	136
EtBr solvolysis	MeOH	65°C	5.4	60
EtI solvolysis	MeOH	65°C	4.7	19
Py. + C_4H_9Br	acetone	60°C	8.3	--
Py. + C_4H_9I	acetone	60°C	6.5	--
$(CH_3)_2N\emptyset$ + EtBr	MeOH	25°C	13.7	480
$(CH_3)_2N\emptyset$ + EtI	MeOH	25°C	11.9	420

BIBLIOGRAPHY

1. M. W. Perrin, Trans Faraday Soc., 34, 144 (1938).
2. J. Buchanan and S. D. Hamann, ibid., 49, 1425 (1953).
3. H. G. David and S. D. Hamann, ibid., 50, 1188 (1954).
4. K. J. Laidler, Disc Faraday Soc., 22, 88 (1956).
5. C. T. Burris and K. J. Laidler, Trans Faraday Soc., 51, 1497 (1955).
6. K. Fajans and O. Johnson, J. Am. Chem. Soc., 64, 668 (1942).
7. M. G. Evans and M. Polanyi, Trans Faraday Soc., 32, 1333 (1936).
8. E. W. Fawcett, R. O. Gibson and M. W. Perrin, Proc. Roy. Soc. A, 150, 223 (1935).
9. K. E. Weale, J. Chem. Soc., 2959 (1954).
10. F. J. Stubbs and C. Hinshelwood, ibid., 1180 (1949).
11. K. E. Weale, Disc Faraday Soc., 22, 122 (1956).
12. W. Straus and S. D. Hamann, ibid., 22, 144 (1956).
13. H. M. Papee, W. J. Canaday and K. J. Laidler, Can. J. Chem., 35, (1957).
14. K. E. Weale and R. T. Harris, J. Chem. Soc., 953 (1956).
15. G. Huges and C. K. Ingold, Quart. Rev., 6 34 (1952).
16. E. A. Broude, E. R. H. Jones and E. S. Stern, J. Chem. Soc., 396 (1946).
17. K. Nozaki and R. Ogg Jr., J. Am. Chem. Soc., 63, 2583 (1941).
18. S. D. Hamann and D. R. Teplitzky, Disc. Faraday Soc., 22, 114 (1956).
19. I. Roberts and G. E. Kimball, J. Am. Chem. Soc., 59, 947 (1937).

SOLVOLYSIS IN NON-POLAR SOLVENTS

Reported by J. W. Hausser April 24, 1958

INTRODUCTION

The S_N1 or "limiting" mechanism for nucleophilic substitution involves a rate determining ionization and a subsequent rapid combination with the Nucleophile (1). The S_N2 or "nucleophilic" mechanism is a bimolecular, single-step substitution with attack by the nucleophile and removal of the leaving group occurring simultaneously. It was known that solvolysis reactions in less-polar solvents exhibited a kinetic dependence on the nucleophile of varying orders greater than one (2).

In 1947, C. G. Swain (3) reported a study of the solvolysis of trityl halides by methanol in benzene solution in which the reaction was third order, first order in trityl halide and second order in methanol. This exact third-order dependence led him to propose a single termolecular or "push-pull" mechanism to account for this reaction and for all nucleophilic substitutions. This mechanism requires both a nucleophile (N) and an electrophile (E) in the transition state for the nucleophilic displacement on an alkyl halide (RX). The transition state would look like I.

$$N - - \rightarrow R\text{-}X - - \rightarrow E$$

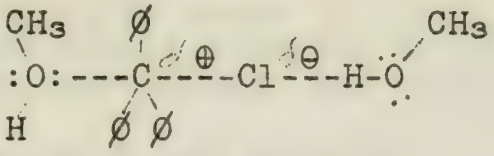
I

Considerable controversy appeared in the literature following Swain's original article. This seminar will be primarily concerned with the work of C. G. Swain and co-workers and C. K. Ingold and co-workers on the solvolysis of trityl halides in benzene solution.

Original Work of Swain on the Methanolysis of Trityl Chloride. Swain (3) chose the solvolysis of trityl chloride by methanol in benzene solution as the starting point for his investigation. The trityl chloride concentration was 0.1 molar, and the methanol concentration was varied in the range of 0.05 to 0.1 molar. A tertiary amine was used to remove the hydrogen chloride as it was formed and render the reaction irreversible. The amines were shown to react only very slowly with the trityl chloride, and they were reported not to affect the rate of solvolysis. At 25° the solvolysis was reported to have a first order dependence on trityl chloride and a second order dependence on methanol.

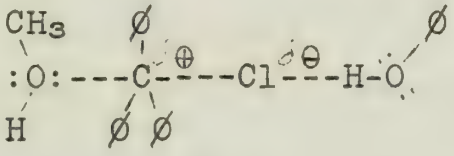
The rate of solvolysis by phenol under the same reaction conditions was 1/50th that of methanol solvolysis, but the reaction was still supposedly third order. An inverse order in amine was explained by the lowering of the effective phenol concentration due to hydrogen bonding. A mixture of phenol and methanol was reported to give a third order rate constant seven times as great as the solvoylsis by methanol alone. The reaction was first order in methanol, phenol and trityl chloride. The initial rapid reaction was methanolysis, and only when the methanol was used up did the phenol act as a nucleophile in the much slower reaction. A rate increase by a factor of twenty was reported when methanol and p-nitrophenol were used. Further study of the reaction indicated that there was no mass-law effect and the salt effect was negligible (4).

Swain interpreted the exact third order kinetics as evidence for the existence of a termolecular mechanism operative in this reaction. The transition state for the methanolysis of trityl chloride would be II.



II

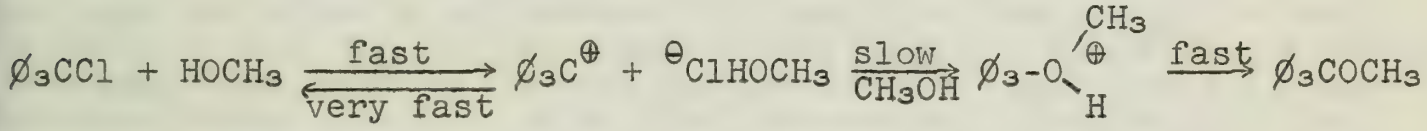
In the mixed methanol and phenol solvolysis, since methanol is the better nucleophile and phenol is the better electrophile, the methanol was supposed to act exclusively as the nucleophile and the phenol to act exclusively as the electrophile. Further, since p-nitrophenol is a stronger electrophile than phenol, the rate increase was to be expected. The transition state for the mixed solvolysis would involve one molecule each of phenol, methanol and trityl chloride (III).



III

A three-bodied collision or two successive two-bodied collisions are indistinguishable by kinetic methods. However, their bearing on mechanism is trivial.

An alternative mechanism that was ruled out by Swain (4) involved a rapid initial ionization of trityl chloride assisted by methanol followed by a rate determining nucleophilic attack by another methanol molecule.



This mechanism was excluded on the basis that there was no salt effect or mass-law effect with added quaternary chlorides and sulfonates.

The solvolysis of trityl chloride would be expected to proceed by an S_N1 mechanism, whereas the reaction of methyl bromide with pyridine would be expected to go by an S_N2 mechanism. For the latter case Swain (5) also reported third order kinetics. From this he concluded that there is only one mechanism operative, and the degree of solvent participation determines the kinetic order.

The application of the Hammett equation to substituent effects indicated that there was a spread of ρ values for nucleophilic displacements (6). A pure S_N1 mechanism should have a large negative ρ-value, whereas a pure S_N2 mechanism should have a zero ρ-value. Since the ρ-values for various nucleophilic displacements cannot be grouped into these categories but are spread out, Swain accepted this as evidence supporting a single termolecular mechanism.

Original Work by Swain on Azide Exchange. Swain (7) looked into the anion exchange of trityl chloride with several quaternary ammonium salts. Radiochloride salts and fluoride salts were reported to exchange with trityl chloride with first-order kinetics, the reaction being first order in trityl chloride and zero order in salt. The kinetic order increased to two on the addition of phenol, first order in trityl chloride and first order in phenol.

The azide exchange was reported to be first order in trityl chloride and first order in azide salt. The addition of phenol increased the order to three, with a first order dependence on phenol.

Experimental Disagreement Between Swain's and Ingold's Work. It appeared as though Swain had found a system that was unique, in that it was exactly third order as compared to the variable orders reported earlier (2). Swain attempted to extend his termolecular mechanism from the non-polar solvent benzene to encompass a large scope of reactions in polar solvents. Ingold (8), who had studied the solvolysis of trityl halides in nitromethane, felt that such an extension was unjustified. In addition, he argued that third-order kinetics would be observed for both S_N1 and S_N2 reactions if there was a large co-solvent effect in the presence of small amounts of reagent. The questioning of Swain's interpretation led Ingold into a study of the solvolysis by methanol in benzene, and he found considerable disagreement between his results and the data Swain had published.

The first objection was to Swain's use of tertiary amines to remove the hydrogen chloride from the reaction. Ingold (9) reported that tertiary amines and, in particular, pyridine react more rapidly with trityl chloride than does methanol. He has not yet presented any evidence to substantiate this. He proposes that the pyridine reacts reversibly with the trityl halide to form a less reactive species and thereby slows down the rate of methanolysis. If the hydrogen chloride is not removed the reaction does not go to completion, so only the initial phase of the reaction could be considered. An attempt was made to correct for catalysis by hydrogen chloride by considering reactions with known amounts of hydrogen chloride present. The validity of Ingold's kinetic treatment will be considered later in addition to the question of the effect of the pyridine on the reaction. Tables I, II, III and IV list the observations of Swain and Ingold on four nucleophilic displacements in non-polar solvents.

It is readily seen that there are large discrepancies between the data of Ingold and Swain. These are largely due to differences in experimental techniques, and we will consider the interpretation of the data independently.

Interpretation of Ingold's Results. To explain the overall first-order reaction of trityl chloride with various nucleophiles, Ingold (10) considered the possibility of an initial rate-determining formation of an ion pair and subsequent rapid steps leading to prouct.

$$\phi_3CCl \xrightarrow{slow} \phi_3C^{\oplus}Cl^{\ominus} \underset{fast}{\overset{X^{\ominus}}{\longrightarrow}} X^{\ominus}\phi_3C^{\oplus}Cl^{\ominus} \begin{array}{l} \xrightarrow{fast} \phi_3CCl \\ \xrightarrow{fast} \phi_3CX \end{array}$$

Table I

Chloride Exchange of Trityl Chloride

$\phi_3CCl + Q^{\oplus}Cl^{36\ominus} \longrightarrow \phi_3CCl^{36} + Q^{\oplus}Cl^{\ominus}$

Reference	Kinetic Order		Rate Constant	$\triangle E^{\ddagger}$	Catalytic Effects		
	ϕ_3CCl	$Q^{\oplus}Cl^{36\ominus}$		$K_{cal/mole}$	Rate Increasing	Rate Decreasing	No Effect
Ingold and co-workers (12)	1	$Q^{\oplus}=(n\text{-}Bu)_4N^{\oplus}$	0.32×10^{-5} Sec^{-1} at 25°	16.0	Phenol Hydroxy Compounds Nitro Compounds	$(n\text{-}Bu)_4N^{\oplus}N_3^{\ominus}$ (forms ϕ_3CN_3)	$(n\text{-}Bu)_4NClO_4$
Swain and co-workers (7)	1	$Q^{\oplus}=(CH_3)_2(C_{18}H_{37})N^{\oplus}$	3.3×10^{-5} Sec^{-1} at 36°	25.0	Phenol (first order) Flouride Salts		

Table II

Azide Exchange of Trityl Chloride

$\phi_3CCl + Q^{\oplus}N_3^{\ominus} \longrightarrow \phi_3CN_3 + Q^{\oplus}Cl^{\ominus}$

Reference	$Q^{\oplus}N_3^{\ominus}$	Kinetic Order		Rate Constant	Catalytic Effects		
		ϕ_3CCl	$Q^{\oplus}N_3^{\ominus}$		Rate Increasing	Rate Decreasing	No Effect
Ingold and co-workers (13)	$(n\text{-}Bu)_4N^{\oplus}N_3^{\ominus}$	1	0	2.5×10^{-5} Sec^{-1} at 30°	Phenol (no specific order) Hydroxyl Compounds	$(n\text{-}Bu)_4N^{\oplus}Cl^{\ominus}$	$(n\text{-}Bu)_4N^{\oplus}ClO_4^{\ominus}$
Swain and co-workers (7)	$(CH_3)_2(C_{18}H_{37})_2N^{\oplus}N_3^{\ominus}$	1	1	3.3×10^{-2} M^{-1} Sec^{-1} at 50° $[Q^{\oplus}X^{\ominus}]=0.03M$	Phenol (first order)		

Table III
Solvolysis of Trityl Chloride by Benzyl Alcohol
$\emptyset_3CCl + \emptyset CH_2OH \longrightarrow \emptyset_3COCH_2\emptyset + HCl$

Reference	Kinetic Order		Rate Constant	Catalytic Effects		
	$\emptyset_3CCl$	$\emptyset CH_2OH$		Rate Increasing	Rate Decreasing	No Effect
Ingold and co-workers (14)	1	Variable	$0.37 \times 10^{-5} Sec^{-1}$ at 30° $[\emptyset CH_2OH]=0.02M$	Phenol Hydroxyl Compounds Nitro Compounds $(n\text{-}Bu)_4N^{\oplus}ClO_4^{\ominus}$	$(n\text{-}Bu)_4N^{\oplus}Cl^{\ominus}$	$(n\text{-}Bu)_4N^{\oplus}Cl^{\ominus} + (nBu)_4N^{\oplus}ClO_4^{\ominus}$ (canceling effect)
Swain and co-workers (7)	1	2	$1.68 \times 10^{-3} M^{-2} Sec^{-1}$	Phenol (causes side reaction forming $\emptyset_3CO\emptyset$)		

Table IV
Solvolysis of Trityl Chloride by Methanol
$\emptyset_3CCl + CH_3OH \longrightarrow \emptyset_3COCH_3 + HCl$

Reference	Kinetic Order		CH_3OH Concentration	Rate Constant	Catalytic Effects		
	$\emptyset_3CCl$	CH_3OH			Rate Increasing	Rate Decreasing	No Effect
Ingold and co-workers (9)	1	0	0.002 to 0.01M	$0.35 \times 10^{-5} Sec^{-1}$	Nitro Compounds Phenol Hydrogen Chloride $(nBu)_4N^{\oplus}ClO_4^{\ominus}$ (one-half order)	$(nBu)_4N^{\oplus}Cl^{\ominus}$	$(n\text{-}Bu)_4N^{\oplus}Cl^{\ominus} + (n\text{-}Bu)N^{\oplus}ClO_4^{\ominus}$ (canceling effect)
		Variable (0to3)	0.01 to 0.5M				
			0.1M	$5.6 \times 10^{-5} Sec^{-1}$			
			0.3M	$136 \times 10^{-5} Sec^{-1}$ All at 25°			
Swain and co-workers (3)	1	2	0.05 to 0.1M	$4.38 \times 10^{-3} M^{-2} Sec^{-1}$ at 25°	Phenol (first order)		Pyridine Hydrochloride
Swain and co-workers	1	1	5×10^{-7} to $10^{-3}M$	$7.5 \times 10^{-5} M^{-1} Sec^{-1}$ at 25°	Phenol (first order)		Pyridine Hydrochloride
		Variable (1to2)	10^{-3} to $5 \times 10^{-2}M$				

In addition to having other shortcomings as pointed out by Swain (11), this mechanism violates the principle of microscopic reversibility. However, in further considerations in this same paper (10), Ingold revises his own mechanism to avoid this difficulty.

The major problem is one of explaining the reported zero order salt dependence since different salts have different rates of reaction. There is an apparent dependence on the nature of the salt and not on the concentration. Ingold proposed a mechanism "on the particular basis that S_N1 substitutions in benzene involve two slow, jointly rate-controlling steps" (10). The mechanism proposed for the salt exchange is the following:

$$RCl \underset{\text{fast}}{\overset{\text{slow}}{\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}}} R^{\oplus}Cl^{\ominus} \underset{\text{fast}}{\overset{\text{fast}}{\underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}}}} \left\{ \begin{matrix} R^{\oplus}Cl^{\ominus} \\ Q^{\oplus}X^{\ominus} \end{matrix} \right\} \underset{\text{slow}}{\overset{\text{slow}}{\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}}}} \left\{ \begin{matrix} R^{\oplus}X^{\ominus} \\ Q^{\oplus}Cl^{\ominus} \end{matrix} \right\} \underset{\text{fast}}{\overset{\text{fast}}{\underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}}}} R^{\oplus}X^{\ominus} \underset{\text{slow}}{\overset{\text{fast}}{\underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}}}} RX$$

The mechanism for alcoholysis is similar.

$$RCl \underset{\text{fast}}{\overset{\text{slow}}{\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}}} R^{\oplus}Cl^{\ominus} \underset{\text{fast}}{\overset{\text{fast}}{\underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}}}} \left\{ \begin{matrix} R^{\oplus}Cl^{\ominus} \\ R'OH \end{matrix} \right\} \underset{\text{slow}}{\overset{\text{slow}}{\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}}}} \left\{ \begin{matrix} R^{\oplus}OR' \\ HCl \end{matrix} \right\} \underset{\text{fast}}{\overset{\text{fast}}{\underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}}}} R^{\oplus}OR' \underset{\text{slow}}{\overset{\text{fast}}{\underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}}}} ROR'$$

Steps one and three are jointly rate-controlling according to Ingold, and step two is a rapid product-determining step. The initial step is a slow dissociation into an ion pair, the second step is a rapid association of dipoles, and the third step is a slow quadrupole rearrangement. Ingold thought that these mechanisms explained the kinetics; however, he did not determine the rate expression from the mechanisms.

The explanation of the various catalytic effects is difficult. The selective catalytic effect of perchlorate salts in the alcoholysis can be explained only in a qualitative way by considering solvation in the transition state. Retardation by chloride salts seems to be inexplainable if the reaction involves only ion pairs.

Besides these apparent difficulties, there is other evidence that makes this mechanism invalid. A steady-state treatment of the mechanism gave a rate expression of the following form:

$$\text{rate} = -\frac{d[RCl]}{dt} =$$

$$\frac{k_1k_2k_3k_4k_5[RCl][Q^{\oplus}X^{\ominus}] - k_{-1}k_{-2}k_{-3}k_{-4}k_{-5}[RX][Q^{\oplus}Cl^{\ominus}]}{k_2k_3k_4k_5[Q^{\oplus}X^{\ominus}] + k_{-1}k_{-3}k_4k_5 + k_{-1}k_{-2}k_4k_5 + k_1k_{-2}k_{-3}k_5 + k_{-1}k_{-2}k_{-3}k_{-4}[Q^{\oplus}Cl^{\ominus}]}$$

If it is assumed that k_1, k_3, k_{-3} and k_{-5} are small and the other rate constants large, and if the initial concentration of products, RX and QCl, is zero, the last term in the numerator and three terms in the denominator may be neglected. This leaves an expression of the form

$$-\frac{d[RCl]}{dt} = \frac{k_1k_2k_3k_4k_5[RCl][Q^{\oplus}X^{\ominus}]}{k_2k_3k_4k_5[Q^{\oplus}X^{\ominus}] + k_{-1}k_{-2}k_4k_5}$$

If the first term in the denominator is dominant, the rate becomes first order in RCl, and there is no possible way of explaining the dependence on the nature of the salt. If the last term in the denominator is dominant, which is more likely the case, the rate is second order, which was not reported. When appropriate activity coefficients are used in the rate expression (11) there is still no reasonable explanation that is compatible with the reported observations. For these reasons this mechanism is ruled out for the interpretation of Ingold's data.

Swain has considered other mechanistic schemes to account for Ingold's data. The possibility exists of having two successively formed intermediates which are both ion pairs, but which have different bonding natures (15). Since the azide exchange is more rapid than the chloride exchange, it is postulated that the azide can react with either intermediate, and the radiochloride can only react with the second intermediate. This fulfills the kinetic requirements.

$$RCl \underset{\text{fast}}{\overset{\text{slow } k_1}{\rightleftarrows}} I \underset{\text{fast}}{\overset{\text{very slow } k_2}{\rightleftarrows}} II \underset{\text{very fast}}{\overset{\text{very fast } Q^{\oplus}Cl^{36\ominus}}{\rightleftarrows}} II' \underset{\text{very slow}}{\overset{\text{fast}}{\rightleftarrows}} I' \underset{\text{slow}}{\overset{\text{fast}}{\rightleftarrows}} RCl^{36}$$

The rate-determining step for this mechanism is the second step. The rate expression would be the following:

$$-\frac{d[RCl]}{dT} = \frac{k_1k_2[RCl]}{k_{-1} + k_{-2}}$$

The mechanism and rate expression for azide exchange may be written as the following:

$$RCl \underset{\text{fast}}{\overset{\text{slow } k_1}{\rightleftarrows}} I \underset{\text{very slow}}{\overset{\text{very fast } Q^{\oplus}N_3^{\ominus}}{\rightleftarrows}} RN_3$$

$$-\frac{d[RCl]}{dT} = k_1[RCl]$$

The complex salt effects and mass-law effect in the anion exchange still remain unexplained. If the data are correct, a more compatible mechanism is still desired.

Differences in Experimental Technique. The experimental techniques of Ingold must be critically examined. Swain (11) points out that a possible source of error in Ingold's procedure lies in the purity of the reagents. The observed zero-order dependence on the nucleophile could be explained by the presence of small traces of water in the reaction medium. The method of analysis was the titration of hydrogen chloride liberated. At low concentrations of the

nucleophile it is possible that the water reacts more rapidly to form the carbinol and liberates hydrogen chloride. If the same amount of "wet" reagent was used in each case, one would observe the solvolysis by water and in this way a zero-order dependence on added nucleophile. This is a possibility; however, there are more serious difficulties present.

The major difficulty in the experimental procedure is caused by the presence of hydrogen chloride. Hydrogen chloride is a very strong electrophile, and it is known that the triple ion $HCl_2^{\ominus}$ is stable in benzene solution (16). Thus the hydrogen chloride present should have a large catalytic effect, and it should reverse the reaction. Ingold was satisfied that he had corrected for these two effects by first, considering only the initial rate of the reaction and second, correcting for the catalysis by considering the rates of reactions with known amounts of hydrogen chloride. Whether or not these corrections make the data valid is questionable. The best way around this situation is to use a tertiary amine to remove the hydrogen chloride as it is formed. Ingold objected to this on the basis that tertiary amine reacted more rapidly than did methanol (9). Since then Swain (11) has shown that there is no reaction between the amine and trityl chloride under the experimental conditions. Equimolar quantities of pyridine and trityl chloride were dissolved in benzene, and the infrared spectrum of the solution was observed over a 24 hour period. There was no change in the spectrum. At the end of this time, a quantitative recovery of trityl chloride was possible. This eliminates the possibility of reaction and lends weight to the experimental work of Swain.

The method of analysis used by Swain in this earlier work was titration for hydrogen chloride. Now he has a much more accurate and reliable method of analysis. Tritium-labeled methanol is used in the solvolysis, and by a tracer technique the amount of unreacted methanol can be determined. Thus, even at very low concentrations there is no question about what is being measured.

The Recent Work of Swain. In his most recent paper (11), Swain has extended the concentration ranges. From this it is obvious that his early data led to a distorted picture of the kinetics. The "exact third-order" kinetics was just a small range in a varying kinetic order. Unlike Ingold's, however, the order varied from second order at low methanol concentrations (first order in both methanol and trityl chloride) to third and higher orders at higher concentrations. There was a range reported between 10^{-3} molar and 5×10^{-7} molar in which the order in methanol was one.

These recent data of Swain are readily interpreted. The first order dependence on methanol and trityl chloride is in agreement with the following mechanism:

$$RCl \underset{k_{-1}}{\overset{k_1}{\underset{\text{fast}}{\overset{\text{slow}}{\rightleftharpoons}}}} R^{\oplus}Cl^{\ominus} \xrightarrow[\text{slow}]{k_2 \ CH_3OH} R\text{-}O(H)(CH_3)^{\oplus} \quad Cl^{\ominus} \xrightarrow[R'_3N]{\text{fast}} ROCH_3 + R'_3NHCl$$

The steady state treatment of this mechanism gives a rate expression of the form

$$-\frac{d[RCl]}{dt} = \frac{k_1 k_2 [RCl][CH_3OH]}{k_{-1} + k_{-2}[CH_3OH]} \cong \frac{k_1 k_2}{k_{-1}} [RCl][CH_3OH]$$

Nucleophilic displacement by salts can be represented by the following mechanism and rate expression:

$$RCl \underset{\text{fast}}{\overset{\text{slow } k_1}{\underset{k_{-1}}{\rightleftharpoons}}} R^{\oplus}Cl^{\ominus} \xrightarrow[\text{very fast}]{Q^{\oplus}X^{\ominus}} R^{\oplus}X^{\ominus} \xrightarrow{\text{fast}} RX$$

$$-\frac{d[RCl]}{dT} = \frac{k_1 k_2 [RCl][Q^{\oplus}X^{\ominus}]}{k_{-1} + k_2[QX]} \cong k_1[RCl]$$

A study of the deuterium isotope effect clarifies the role of methanol in solvolysis at higher concentration. Deuterated methanol would be a much weaker electrophile, but the nucleophilic properties of such a molecule would not be significantly affected. When deuterated methanol is used at concentrations that would normally give a high order dependence in methanol, the order is reduced to approximately one. This means the methanol is acting as an electrophile, catalyzing the solvolysis reaction.

The recent experimental work by Swain (11) is the most reliable and is readily interpreted. The data of Ingold are questionable. The original interpretation by Swain (3) of his early data in terms of a termolecular mechanism is invalidated by this recent work since the order is not exactly third, but increases continuously from ~~d first~~ order. This system may be interpreted as a nucleophilic displacement in which the nucleophile also has a catalytic effect.

BIBLIOGRAPHY

1. E. D. Hughes, Trans. Faraday Soc., 37, 603 (1941).
   E. D. Hughes, J. Chem. Soc., 968 (1946).
   C. K. Ingold, "Structure and Mechanisms in Organic Chemistry", Cornell University Press, Ithica, N. Y., 1953, Chapter VII.
2. P. D. Bartlett and R. W. Nebel, J. Am. Chem. Soc., 62, 1345 (1940).
   N. T. Farinacci and L. P. Hammett, ibid., 59, 2542 (1937).
   D. R. Read and W. Taylor, J. Chem. Soc., 479 (1939).
3. C. G. Swain, J. Am. Chem. Soc., 70, 1119 (1948).
4. C. G. Swain, ibid., 72, 2794 (1950).
5. C. G. Swain and R. W. Eddy, ibid., 70, 2989 (1948).
6. C. G. Swain and W. P. Langsdorf, Jr., ibid., 73, 2813 (1951).
7. C. G. Swain and M. M. Kreevoy, ibid., 77, 1122 (1955).
8. E. G. Gelles, E. D. Hughes and C. K. Ingold, J. Chem. Soc., 2918 (1954).
9. E. D. Hughes, C. K. Ingold, S. F. Mok and Y. Pocker, ibid., 1238 (1957).
10. E. D. Hughes, C. K. Ingold, S. F. Mok, S. Patai and Y. Pocker, ibid., 1265 (1957).
11. C. G. Swain and E. E. Pegnes, J. Am. Chem. Soc., 80, 812 (1958).
12. E. D. Hughes, C. K. Ingold, S. F. Mok, S. Patai and Y. Pocker, J. Chem. Soc., 1220 (1957).
13. E. D. Hughes, C. K. Ingold, S. Patai and Y. Pocker, ibid., 1230 (1957).
14. E. D. Hughes, C. K. Ingold, S. Patai and Y. Pocker, ibid., 1256 (1957).
15. S. Winstein, E. Clippinger, A. Fainberg, R. Heck, and G. C. Robinson, J. Am. Chem. Soc., 78, 328 (1956); ibid., 76, 2597 (1954).
16. E. D. Hughes, C. K. Ingold, S. Patai and Y. Pocker, J. Chem. Soc., 1206 (1957).

THE MECHANISM OF AMINOMETHYLATION REACTIONS

Reported by J. Diekmann April 28, 1958

INTRODUCTION

The reaction between formaldehyde, a nontertiary amine, and an acidic compound is commonly known as the Mannich reaction. A more descriptive name for this type of change is aminomethylation. The synthetic aspects of the chemistry of Mannich bases have been reviewed elsewhere (1). Examples of alkylation with such bases are to be found in the work of Snyder and Hellmann (2,3). Mannich bases may also be intermediates in biogenesis (4). This seminar will review the work done to elucidate the mechanism of aminomethylation reactions.

THEORETICAL CONSIDERATIONS

Aminomethylation can be represented as follows:

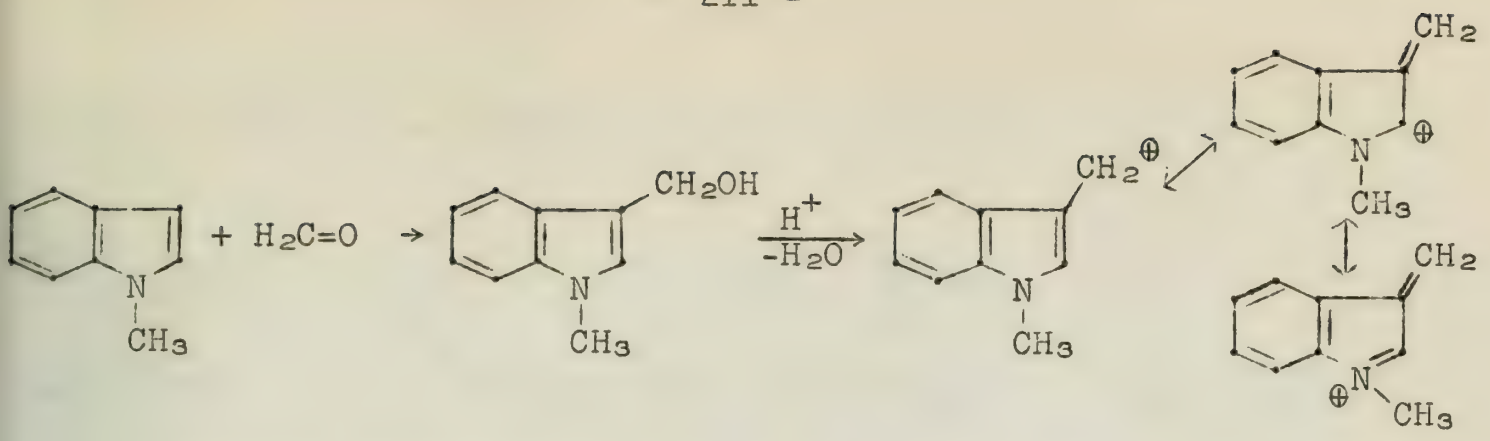
acidic component amine Mannich base

In practice, the amine hydrochloride is frequently used and the Mannich base is then also isolated as the hydrochloride salt.

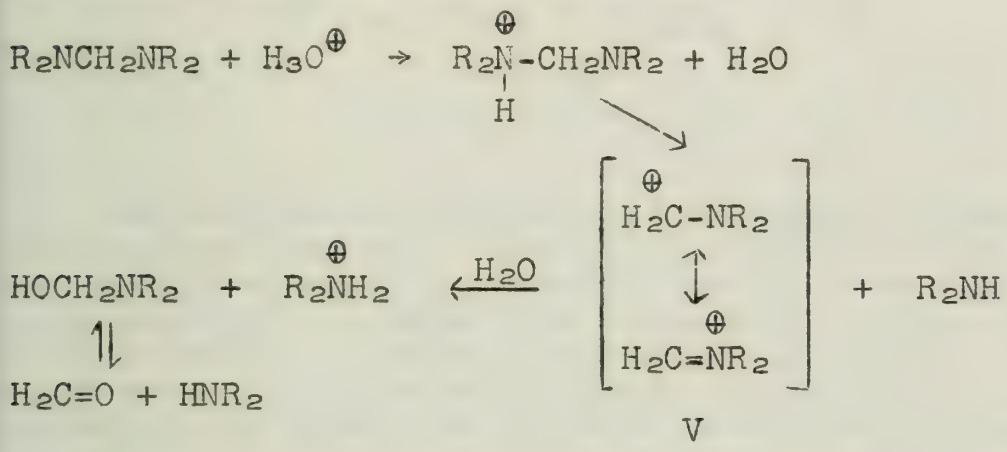
Two nucleophilic compounds, the acidic component Z-H and the amine, compete for the available formaldehyde (electrophile). It is to be expected that the one with the higher nucleophilic potential will react with formaldehyde first. Depending upon the nucleophilicity we would therefore expect either ZCH_2OH or R_2NCH_2OH to be formed. Mannich assumed R_2NCH_2OH to be an intermediate, since he found that the pH of the solution was lowered appreciably when he mixed an amine hydrochloride with formaldehyde and Z-H (5). He never attempted to find out more about the mechanism, however.

The first workers to test this hypothesis were Bodendorf and Koralewski (6). They decided to employ antipyrine and cyclohexanone as acidic components, and dimethylamine and piperidine as amines. By use of the corresponding amine hydrochloride and formaldehyde they obtained good yields. The preformed N-hydroxymethylamines, however, gave decreased yields. Therefore they decided to investigate the alternative intermediate and prepared the methylol derivatives of acetone (I), cyclohexanone (II), phenylacetylene (III), and antipyrine (IV). None of them reacted to give the corresponding Mannich base. By use of the free amine, however, they were able to obtain the Mannich bases from I and II. Since I and II can lose a molecule of water to give an α,β-unsaturated ketone, which easily takes up free amine at room temperature, this would furnish an explanation for the attainment of the Mannich bases from I and II. The authors therefore concluded that neither hydroxymethylamine nor hydroxymethylketones were really intermediates.

It has been shown in the meantime, however, that methylol derivatives of certain acidic components condense with amines to give Mannich bases (7,8,9). This reaction appears favorable when the resulting methylol derivative can form a resonance stabilized cation, which then acts in place of the formaldehyde. 1-Methylindole is a good example (10):



Meanwhile, in experiments with the Mannich reaction, Stewart was able to obtain the desired Mannich bases in good yields by employing either formaldehyde and amine, hydroxymethylamine, alkoxymethylamine or bis-methylene amine (11). The reactions had to be carried out in acid, however. Since acetals are unstable in an acidic medium the following reaction probably occurs:



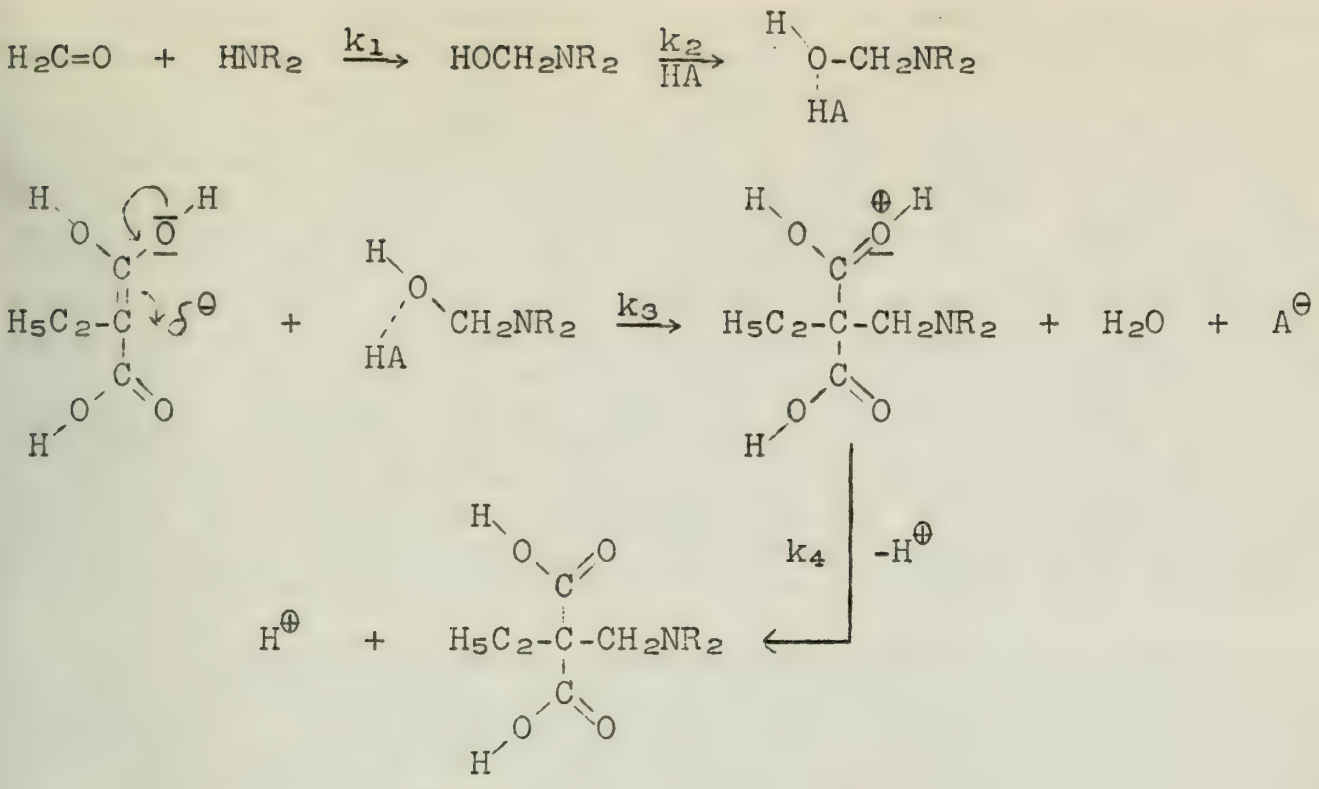
V

The N-hydroxymethylamine and N-alkoxymethylamine can react similarly with acid to give the resonance stabilized carbonium-immonium ion V. This report has been confirmed by several independent workers (12,13,14), and therefore led to the conclusion that ion V is an intermediate in the Mannich reaction, acting as an electrophilic agent on the nucleophilic Z-H, possibly according to an S_E2 mechanism.

This finding was in contrast to Bodendorf's report, who on the basis of decreased yields came out against the formation of hydroxymethylamine, which would be a precursor of the proposed intermediate V. This work was therefore repeated by Hellmann, who was able to show that Bodendorf's products were contaminated with previously undetected byproducts (14). Hellmann considered his results to be consistent with the proposed intermediate V.

THE KINETICS OF THE MANNICH REACTION

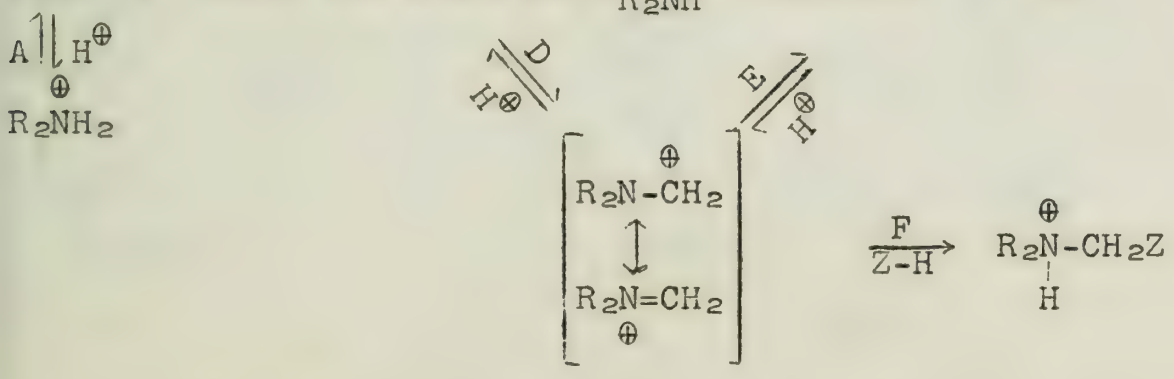
The only workers to study the kinetics of the Mannich reaction so far have been Alexander and Underhill (15). They chose the condensation of ethylmalonic acid with formaldehyde and dimethylamine as an example. Mixing formaldehyde and amine twelve hours before the reaction time and then treating this mixture with ethylmalonic acid in buffer solution, they found that the reaction very accurately obeyed third order kinetics. The rate was pH dependent; the optimum pH was 3.8, while strongly acidic and basic solutions resulted in very slow rates. No third order kinetics were obtained on mixing the three components simultaneously. Ionic strength had no effect upon the rate. Alexander therefore suggested the following mechanism:



He proposed k_3 as the rate determining step, whereby k_1 was faster than the rate controlling step but of the same order of magnitude. He rejected a carbonium ion as attacking species, since the rate expression should then be a proportionate function of the $H_3O^{\oplus}$ concentration. The complicated pH dependence of the reaction did not show such a relationship. Since ethylmalonic acid did not react with formaldehyde under the reaction conditions he was sure that, at least in acid, the formation of hydroxymethylamine was the initial step.

THE pH DEPENDENCE OF THE MANNICH REACTION

In agreement with Alexander, Liebermann and Wagner found an optimum pH value for every Mannich condensation which they investigated (16). In general, the more basic the amine and the more acidic Z-H, the less acid was needed. A rational explanation for such behavior can be seen in the following sequence of equilibria:



V

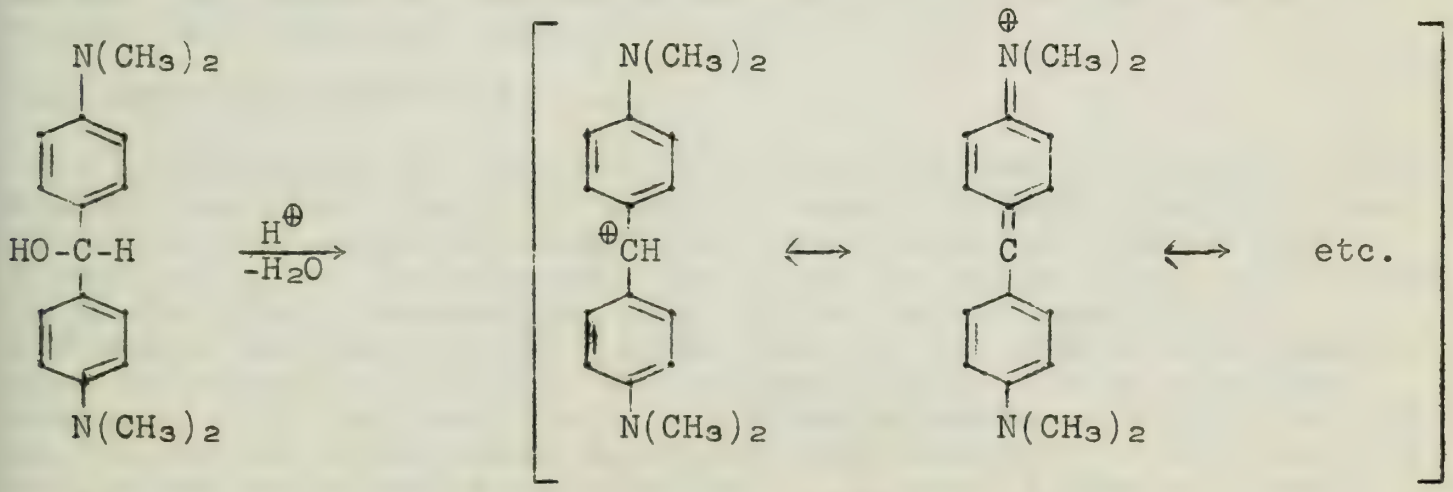
As far as the formation of the hydroxymethylamine is concerned, acid would have a retarding influence on equilibria A and B. In view of the acidic conditions and the small amount of free amine the formation of the bis-methylene amine via equilibrium C appears doubtful; some workers tend to favor it as the predominant precursor to ion V, however (9,16). Acid would be beneficial, on the other hand, in equilibria D and E to give the carbonium ion. These two opposing effects therefore result in an optimum pH. Further support for this explanation lies in the fact that by use of preformed hydroxymethylamine the pH of the reaction medium can be lowered considerably without affecting the yield of the condensation; formaldehyde, amine, and the acidic component at the same pH show virtually no reaction (14). Similarly, dropping hydroxymethylamine into a solution of acid and the acidic component affords a good yield of Mannich base, while slow addition of acid to the hemiacetal and the acidic component mainly results in a neutralization of the amine present through equilibrium B (11). Formation of the Mannich base therefore does not take place.

On the basis of these proposed equilibria the argument for the hydrogen-bonded complex as attacking species in Alexander's rate study are removed, since acid can disturb the formation of the hydroxymethylamine so much that this becomes the rate controlling step. The fact that no third order kinetics were obtained on simultaneous mixing of the three components can be taken as evidence for this hypothesis. The rate study could therefore still be consistent with a carbonium ion as attacking species.

Through rationalization, such a carbonium ion has also been suggested as the common intermediate in acid-induced reactions of methylene-bis-amines, methylene amines, and of formaldehyde and amines (21).

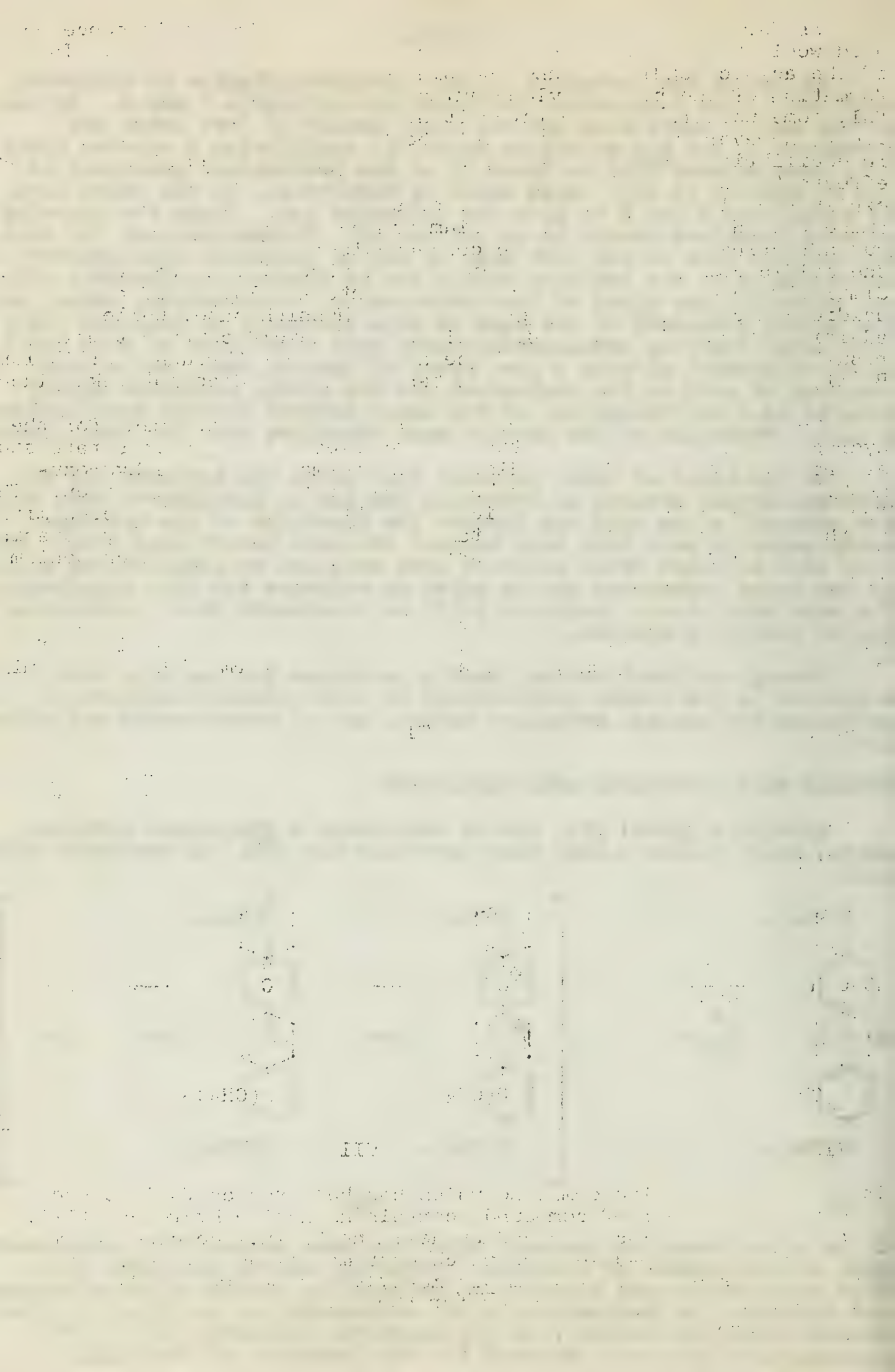
STUDIES WITH VINYLOGOUS AMINOALKYLATION

Michler's hydrol (VI) can be considered a vinylogous carbinolamine, which yields a deep blue carbonium ion (VII) on treatment with acid.

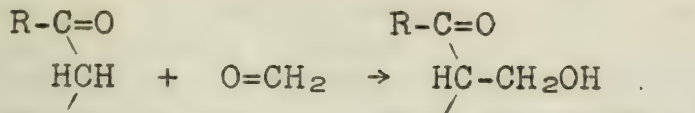


VI VII

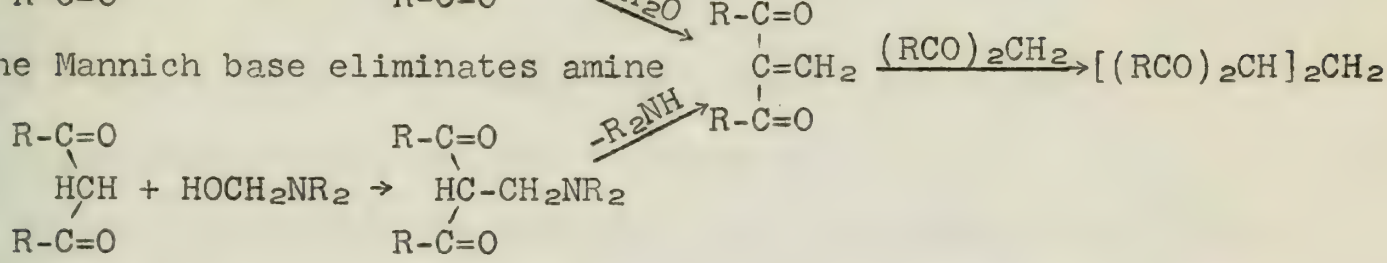
It is a very reactive compound which has been successfully condensed with a large number of compounds containing active hydrogens (17). This condensation was extended by Hellmann to include dibenzoylmethane and dimedone, two β-diketones which customarily do not react to give Mannich bases but rather form bis-methylene compounds (18). Two explanations have been advanced for the formation of these bis-methylene β-diketones.



a) The β-diketone is more nucleophilic than the amine



b) The Mannich base eliminates amine



The facile elimination of amines from Mannich bases having a labile β-hydrogen is quite common. Since the amine component dimethylaniline in VI is very tightly bound one would not expect amine elimination from the resulting Mannich base, which would explain the ability to form such Mannich bases of β-diketones with Michler's hydrol. Reaction sequence (b) therefore seems more probable for the formation of bis-methylene β-diketones in the cases where an aliphatic amine and formaldehyde are used. Further support for this theory can be found in the fact that dibenzoylmethane reacts with formaldehyde only in the presence of amine (19); it has also been found that piperidine catalyzes condensations of aldehydes with methone (20). The Knoevenagel reaction may take a similar course. The apparently anomalous formation of the bis-methylene β-diketones may therefore very well proceed through a Mannich base as an intermediate.

By heating the Mannich base from dimedone and VI at 180°, Hellmann was able to force the elimination of dimethylaniline in poor yield. He failed to identify the remaining fragments positively, however (18).

Indirect evidence for VII as the attacking species was seen in the fact that condensation occurred only when the mixtures of VI and the acidic component were acidified, which afforded a deep blue color. Acetophenone, cyclohexanone, and 2-nitropropane failed to react. No explanation was offered.

THE ACIDIC COMPONENT Z-H

In principle, all nucleophilic compounds are accessible to the Mannich reaction. Short of being an anion Z-H would therefore have to contain an unshared electron pair or a polarized double bond. A combination of the carbonium ion V and the anion Z^- was considered to be the final condensation step in the Mannich reaction by Liebermann and Wagner (16). While this may be true in some cases it does not appear to hold for the condensation of active methylene compounds. In his rate study, Alexander rejected a reaction of Z-H in its anionic form, since increased ionic strength of the reaction medium had no influence upon the rate. If such a dissociation of Z-H took place before reaction in many cases the resulting anion would be more nucleophilic than the amine; thus one should obtain the methylol derivatives of Z-H, which may react further to give the bis-methylene compound of the acidic component. Compounds such as acetophenone, acetone, and antipyrine are ideal for Mannich reactions in an acidic medium. To convert these compounds into their respective anions would require at least an alcoholate as a base.

Further support for this theory comes from the recent work of Hellmann who, upon failing to condense sulfones with either formaldehyde and secondary amines or Michler's hydrol to give Mannich bases, examined various factors involved (22). If dissociation was of predominant effect one would expect the following series of proton-loosening tendency to give decreasing yields:

$$F > NO_2 > SO_2OR > SO_2R > \overset{\oplus}{N}R_3 > CN > CO_2R > CHO > COR$$

This relationship expresses the F effect (23).

If tautomerization was important the following series should hold:

$$CHO > COR > CO_2R > CN > NO_2 > \underbrace{\overset{\oplus}{N}R_3,\ SO_2OR,\ SO_2R,\ F}_{\text{about zero}}$$

This relationship is known as the T effect.

The failure of the sulfones to react therefore shows that the F effect alone is not enough to bring about reaction when the T effect is virtually nil. Ketones with a weak F effect react because the T effect is large. Simple esters do not react because of a smaller T effect which is not offset by an increase in the F effect. Nitriles, despite a larger F effect, do not react because of a small T effect, unless a phenyl group aids with an inductive influence. Nitroalkanes show a very weak T effect, but the large F effect makes them accessible to Mannich condensations.

A reactivity series of active methylene compounds, established by Huenig through coupling reactions, was found to reflect well the behavior of the acid component Z-H in Mannich condensations (24):

$$NO_2 > CHO > COCH_3 > CN > CO_2C_2H_5 > CONH_2 > CO_2H > SO_2CH_3 > SOCH_3 \gg C_6H_5$$

On treatment of resolved o-nitromandelic acid with formaldehyde and piperidine Grillot claimed to have obtained an optically active Mannich base of higher rotation than the acid (25). Since such an observation would rule out the enol form of Z-H as the reacting species, the work was repeated by Meinwald who showed that Grillot did not obtain a Mannich base but rather an acid salt (26). Condensation of d-2-nitrobutane with a rotation of +5.07 with formaldehyde and isopropylamine gave a Mannich base with a rotation of 0.03 ± 0.02 (25).

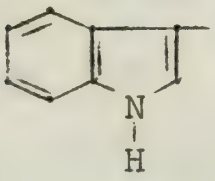
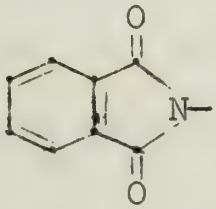
TRANSAMINOMETHYLATION REACTIONS

Mannich bases not possessing a labile β-hydrogen and which cannot form a resonance stabilized cation after cleavage of the amine component--after quaternization of the Mannich base--can exchange their aminomethyl group for a hydrogen atom of the condensation partner (27):

$$CH_3CONC(H)(CO_2CH_3)-CH_2NR_2 + H_2C(CO_2R)_2 \rightarrow H-C(CO_2CH_3)_2-NHCOCH_3 + H-C(CO_2R)_2-CH_2NR_2$$

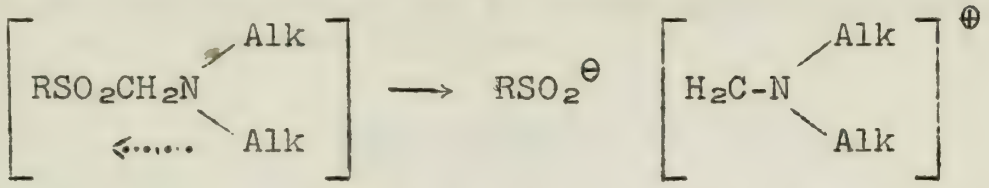
This transaminomethylation, in a general sense, describes the Mannich reaction, whereby a relatively unstable aminomethyl compound is changed to a more stable one. The accompanying table lists aminomethylated compounds in the order of decreasing stability. The N-chloromethylamine is a solid salt with an ionic bond (28). The first covalently bonded compound is hydroxymethylamine, which is a very unstable oil. The stability of the covalent bond then increases, trimethylamine being an extremely stable "Mannich base."

TABLE

Aminomethyl compound from:	
Hydrogen	H-
Methane	CH_3-
Benzene	C_6H_5-
Indole	
Acetonitrile	$NCCH_2$-
Acetophenone	$C_6H_5COCH_2$-
Ethylmalonic acid	$(HO_2C)_2C(H_5C_2)$-
Piperidine	 $-CH_2NR_2$ (covalent bond)
Phthalimide	
Hydrogen Cyanide	NC-
Bisulfite anion	$O_3S^{\ominus}$-
Thiophenol	C_6H_5S-
Methanol	CH_3O-
Water	HO-
Hydrogen Halide	$X^{\ominus}$ $[CH_2NR_2 \leftrightarrow H_2C{=}NR_2^{\oplus}]$ (ionic bond)

stability increases ↑

The failure of sulfinic acids and their methylol derivatives to undergo a Mannich condensation with secondary aliphatic amines can be explained on this basis (7,29). Sulfinic acid anions are between halide and hydroxide ion with regards to their nucleophilicity (30). Evidently the nucleophilicity of the sulfinate ion is not strong enough to form a covalent bond with the carbonium ion V because the electron-pull by the SO_2 group is too strong:



If one of the alkyl groups of the amine is replaced by a phenyl group, however, the corresponding Mannich base can be formed, presumably because the phenyl group can counterbalance the electron withdrawing effect of the SO_2 group. Support for this theory is found in the fact that sulfinic acids can be aminomethylated with piperazine and piperazine derivatives which carry an electron attracting substituent on the nitrogen (29).

The aminomethylation of nucleophilic compounds can therefore be viewed as initially involving the formation of the aminomethyl compound of water which--under acid catalysis--forms the more labile aminomethyl compound of HX, which then reacts to give the Mannich base.

It is possible for Z-H to react without acid if it is sufficiently nucleophilic because of unshared electron pairs, such as alcohols, amines, CN^-, HS^-, and polar Grignards; the more stable aminomethyl compound is always obtained.

$$Z\text{-}H + HOCH_2NR_2 \rightarrow ZCH_2NR_2 + H_2O \qquad (Z = CH_3S\text{-}, CH_3O\text{-}, R_2N\text{-})$$

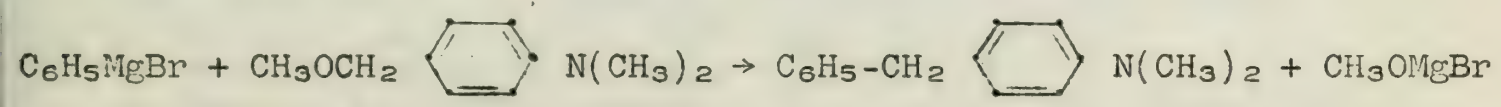
$$SO_3^{\ominus} + HOCH_2NR_2 \rightarrow {}^{\ominus}O_3SCH_2NR_2 + OH^{\ominus}$$

$$NC^{\ominus} + O_3{}^{\ominus}SCH_2NR_2 \rightarrow NCCH_2NR_2 + SO_3^{\ominus}$$

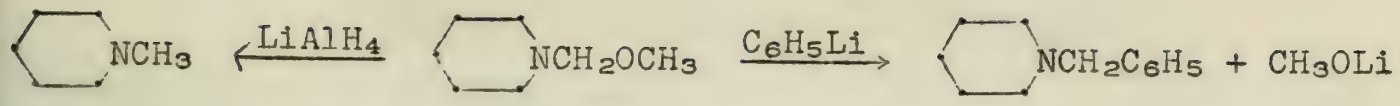
Aminomethylation cannot be effected if Z-H is not nucleophilic at all, such as benzene, methane, or hydrogen. Through suitable substituents the possibility for dissociation into nucleophilic groups has to be created in order to obtain compounds which can be aminomethylated:

$$CH_3MgI + H_5C_2OCH_2NR_2 \rightarrow CH_3CH_2NR_2 + H_5C_2OMgI$$

Vinylogs also react (31):



The cleavage of N-methoxymethylpiperidine by lithium aluminum hydride is noteworthy, since O,O-acetals are not attacked by this reagent (32). Similar cases have been reported (33,34).



While the acid-catalyzed reactions most likely proceed by an S_E2 mechanism, the non-catalyzed reactions probably proceed via an S_N2 mechanism. Steric hindrance has been noted (35,36). The resonance stabilization of the carbonium ion V in the transition state may play an important role in aminomethylations.

BIBLIOGRAPHY

1. F.F. Blicke, "The Mannich Reaction," Organic Reactions, ed. by R. Adams, John Wiley and Sons, Inc., New York, N.Y., 1942, Vol. I, p. 303.
2. H.R. Snyder and E.L. Eliel, J. Am. Chem. Soc., 70, 1703 (1948).
3. H. Hellmann, Angew. Chem., 65, 473 (1953).
4. R. Goutarel, M.-M. Janot, V. Prelog and W.I. Taylor, Helv. Chim. Acta, 33, 150 (1950).
5. C. Mannich, Arch. Pharm., 255, 261 (1917).
6. K. Bodendorf and G. Koralewski, Arch. Pharm., 271, 101 (1933).
7. H. Bredereck and E. Baeder, Ber., 87, 129 (1954).
8. H. G. Johnson, J. Am. Chem. Soc., 68, 12 (1946).
9. G.B. Butler, ibid., 78, 482 (1956).
10. H.R. Snyder and E.L. Eliel, ibid., 70, 4230 (1948).
11. T.D. Stewart and W.E. Bradley, ibid., 54, 4172 (1932).
12. C.M. McLeod and G.M. Robinson, J. Chem. Soc., 119, 1470 (1921).
13. H.-F. Tseou and C.-T. Yang, J. Org. Chem., 4, 123 (1939).
14. H. Hellmann and G. Opitz, Ber., 89, 81 (1956).
15. E.R. Alexander and E.J. Underhill, J. Am. Chem. Soc., 71, 4014 (1949).
16. S.V. Liebermann and E.C. Wagner, J. Org. Chem., 14, 1001 (1949).
17. R. Fosse, Ann. Chim. [8], 18, 400, 503, 531 (1909).
18. H. Hellmann and G. Opitz, Ann., 604, 214 (1957).
19. Wesenberg, Dissertation, Leipzig, 1898, p. 31.
20. R.D. Desai, J. Indian Chem. Soc., 10, 663 (1938).
21. E.C. Wagner, J. Org. Chem., 19, 1862 (1954).
22. H. Hellmann and G. Opitz, Ann., 605, 141 (1957).
23. F. Klages, "Lehrbuch der Organischen Chemie," W. de Gruyter, Berlin 1954, Vol. II, p. 375.
24. S. Huenig and O. Boes, Ann., 579, 28 (1953).
25. G.F. Grillot and R.I. Bashford, J. Am. Chem. Soc., 73, 5598(1951).
26. J. Meinwald and F.B. Hutto, Jr., ibid., 75, 485 (1953).
27. H. Hellmann and G. Opitz, Angew. Chem., 68, 265 (1956).
28. H. Boehme and E. Mundlos, ibid., 68, 224 (1956).
29. H. Hellmann and G. Opitz, Ber., 90, 8 (1957).
30. J.F. Bunnett and R.E. Zahler, Chem. Revs., 49, 273 (1951).
31. F.G. Mann and F.H.C. Stewart, J. Chem. Soc., 1954, 4127.
32. H. Hellmann and G. Opitz, Ber., 90, 15 (1957).
33. S. Bose, J. Indian Chem. Soc., 32, 450 (1955).
34. M. Nomura, K. Yamamoto and R. Oda, J. Chem. Soc. Japan, Ind. Chem. Sect., 57, 219 (1954).
35. S. Winstein, T.L. Jacobs, D. Seymour and G.B. Linden, J. Org. Chem., 11, 215 (1946).
36. H.R. Snyder and J.H. Brewster, J. Am. Chem. Soc., 71, 1061 (1949).

A NEW SYNTHESIS OF 1,4-NAPHTHOQUINONES FROM o-DIACYLBENZENES AND PHTHALIDES

Reported by W. A. DeMeester May 1, 1958

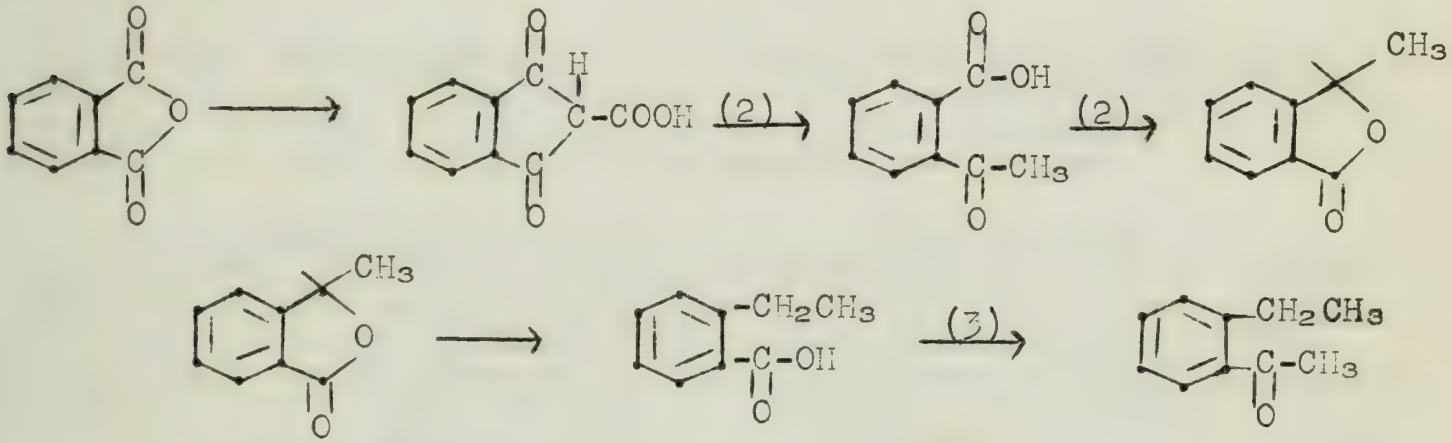
INTRODUCTION

The preparation of o-diacylbenzenes has been carried out in a limited number of ways. In connection with the preparation of phthiocol (2-hydroxy-3-methyl-1,4-naphthoquinone) as well as methoxylated phthiocols, a new synthesis of these materials has been devised by Weygand and his coworkers. The starting materials for the synthesis would logically be the o-diacylbenzenes; a new method for preparation of these diketones from phthalides will also be presented.

It is the purpose of this seminar to survey the methods of preparation of o-diacylbenzenes, 3-methylphthalides, 3-methyl methoxylated phthalides, and their use in the synthesis of substituted 1,4-naphthoquinones.

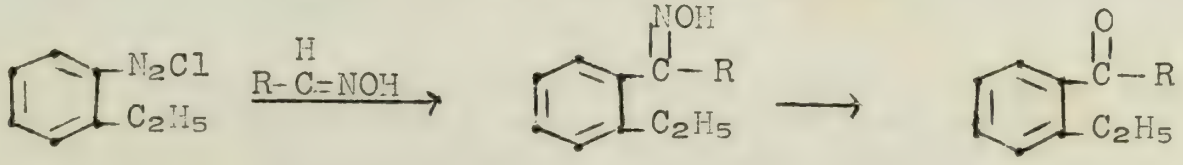
o-DIACYLBENZENES

o-Diacylbenzenes have been prepared from acetophenone derivatives. Usually the most difficult step of the preparation was to obtain the alkylated acetophenone. Phthalic anhydride was used by Riemschneider (1) as a starting material in making o-ethylacetophenone by the following scheme:



The yield of o-ethylacetophenone is 74% based on o-ethylbenzoic acid, according to Winkler (3).

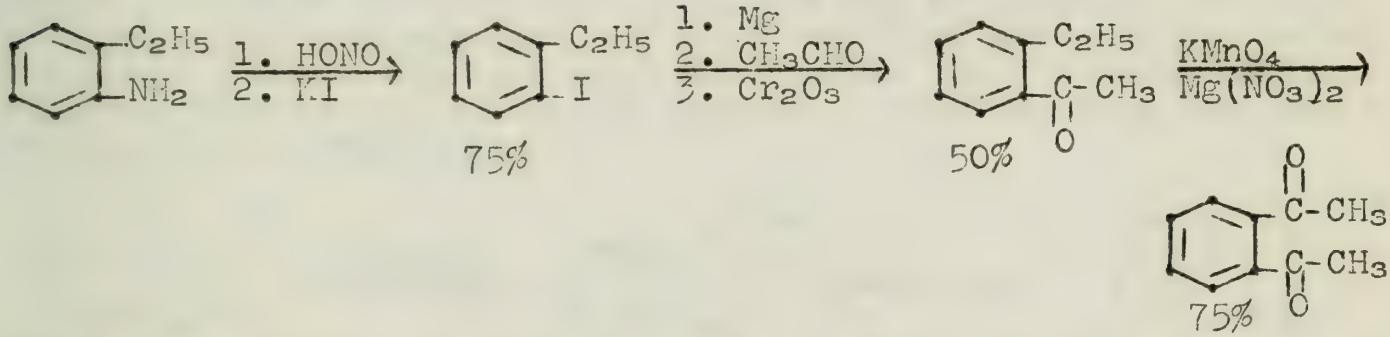
o-Ethylacetophenone has also been prepared through the diazotization of o-aminoethylbenzene and reaction of the diazonium salts with formaldoxime, acetaldoxime or propionaldoxime (4).



The yields which were obtained from this type of reaction depended critically on the conditions, with a pH of 5.5 - 6 as most favorable. Formaldoxime gave higher yields than either of the others. When

acetaldoxime was used, the resulting o-ethylacetophenone was extremely impure and was produced in a very low yield.

Another method for the preparation of o-ethylacetophenone was devised by Weygand and coworkers (5), who nitrated ethylbenzene and converted the o-nitroethylbenzene to o-iodoethylbenzene by way of the diazotized amine. The carbinol, made by condensing the corresponding Grignard reagent with acetaldehyde was oxidized with chromic acid to o-ethylacetophenone. By use of potassium permanganate buffered with magnesium nitrate, the ethyl group was oxidized to the acetyl group, to yield o-diacetylbenzene (25% yield, based on o-aminoethylbenzene).



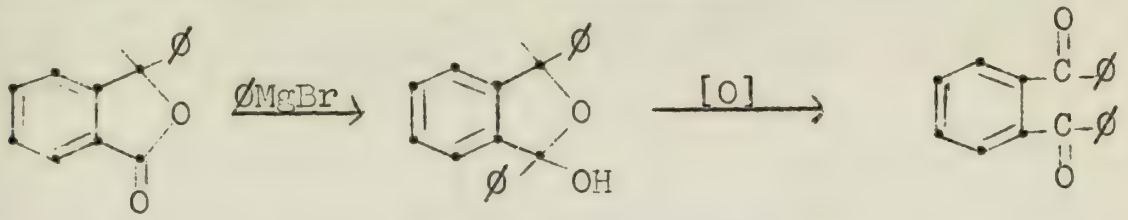
When butyraldehyde was used in place of acetaldehyde, the yield of o-ethylbutyrophenone was much lower than that of the corresponding acetophenone, but the conversion to o-acetylbutyrophenone was satisfactory.

Another method (6) for the preparation of o-diacetylbenzene is the oxidation of o-diethylbenzene with potassium permanganate and magnesium nitrate. Conversion to the o-diacetylbenzene was very low, and an equal amount of o-ethylacetophenone was formed.

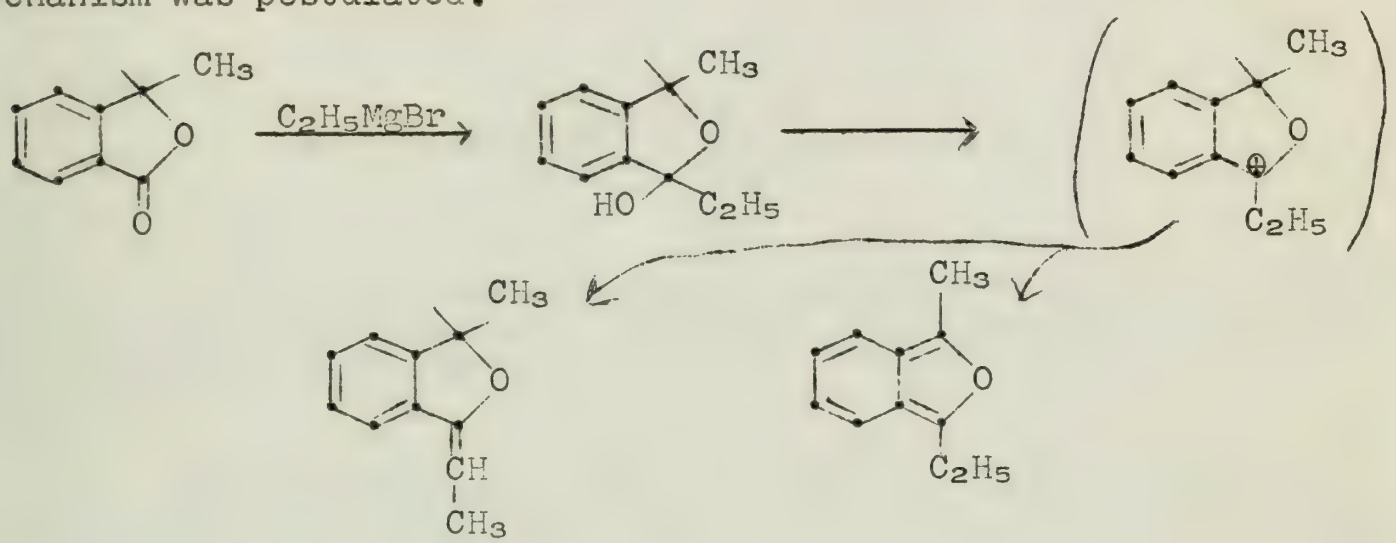
One interesting phenomenon which has been observed by some experimenters (3,5) was that o-diacetylbenzene produced a reddish stain on the skin in about 15 minutes, which later became violet. The stain could not be removed with acids, alkalies, potassium permanganate or sulfurous acid. o-Diacetylbenzene has a sensitivity of color reaction equal to that of ninhydrin, according to Hillmann (7). In water or aqueous alcohol, as was shown by Winkler, it gives a reddish to blue color with glycine, alanine, phenylalanine, aspartic acid, glutamic acid, leucine, isoleucine and histidine, the color intensity decreasing with the different amino acids in the order given. The color test was negative with cysteine but gave a green shade with tryptophane. Synthetic polypeptides and native albumin gave a very positive reaction even in the cold. Glycine can be easily detected in one part in 50,000. Acid intensifies the color; sodium hydroxide destroys it.

An aniline-acetic acid mixture in the hands of Weygand and coworkers (8) served to detect the presence of o-diacylbenzenes in a reaction mixture. The intensity of the color produced in the test has been useful in quantitatively estimating the amount of diketone formed in a reaction. This test has been of particular value in the preparation of o-diacylbenzenes from 3-methylphthalides.

A known method (9) for the preparation of o-dibenzoylbenzene is the reaction of phenylphthalide with phenylmagnesium bromide followed by oxidation of the resulting hemiacetal.



An analogous reaction was realized by Weygand and coworkers (10) in an attempt to prepare o-diacylbenzenes. The condensation product of 3-methylphthalide with ethylmagnesium bromide was subjected to acidic oxidation with sodium dichromate and to alkaline oxidation with potassium permanganate. A color reaction with primary amines indicated that no diketone had been formed. On the basis of the negative results for the diacyl material, the following reaction mechanism was postulated.

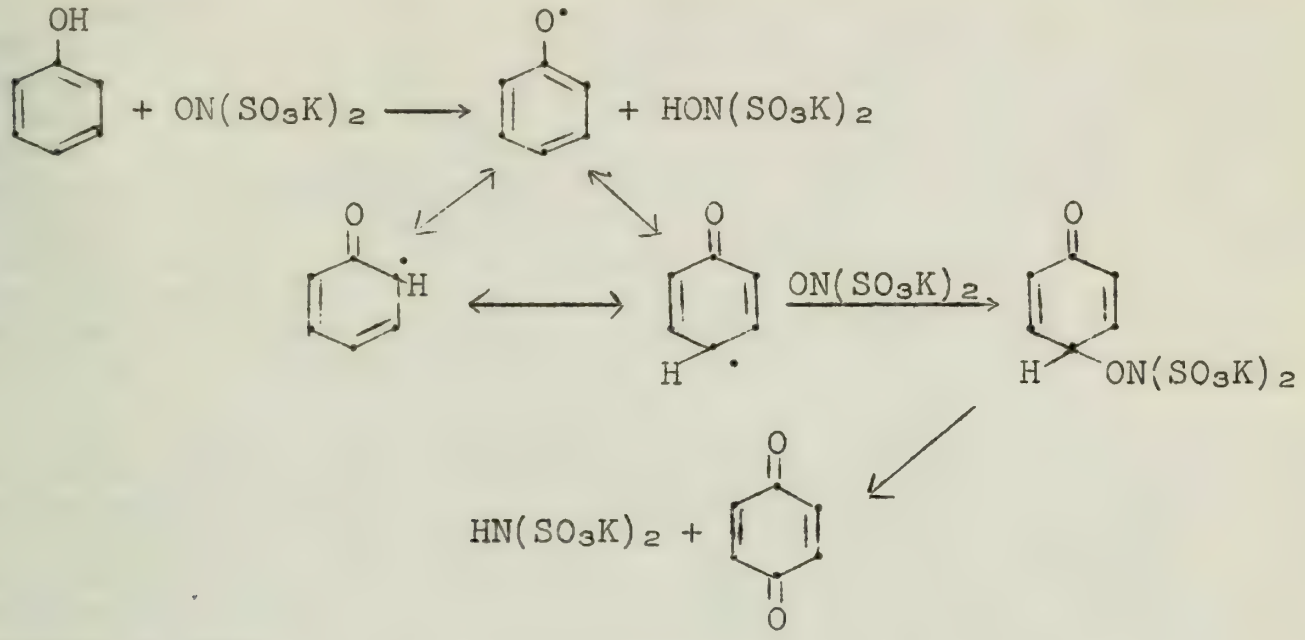


In the preparation of o-dibenzoylbenzene, the isobenzofuran system appears to be energetically more stable than the system just considered. Confirmation of this hypothesis was shown by the avoidance of acidic reaction during hydrolysis. An aqueous solution of magnesium nitrate was used to destroy the Grignard adduct and this was followed by potassium permanganate oxidation in the cold. A strong color reaction with aniline-acetic acid showed the presence of the desired o-diacylbenzene.

This study of 3-methylphthalide was extended to the methoxylated derivatives. 3-Methyl-6,7-dimethoxyphthalide, which was prepared from opianic acid (11), was converted to 2-acetyl-5,6-dimethoxypropiophenone in very good yield, as shown by the color reaction. This result was substantiated by oxidation and ring closure with selenium dioxide to be discussed later.

The tetramethoxyphthalide was also prepared but with extreme difficulty. The first attempts to make this phthalide were carried out with 3-methyl-6,7-dimethoxyphthalide. This compound was nitrated (12) in the 4-position and converted to the hydroxylated phthalide by warming the diazotized amine obtained by reduction of the nitro compound. Conversion of 3-methyl-4-amino-6,7-dimethoxyphthalide or

the 4-hydroxy-6,7-dimethoxyphthalide to the o-quinone by the method of Teuber (13,14) was unsuccessful. Teuber's procedure involves the oxidation of phenols to quinones or naphthols to naphthoquinones by means of potassium nitrosodisulfonate. If the phenol has p-alkyl or -alkoxy substituents, the main product is the 1,2-quinone. The mechanism for the oxidation of an unsubstituted phenol has been postulated to be the following:



3-Methyl-4-iodo-6,7-dimethoxyphthalide was obtained from the diazonium salt by means of the Sandmeyer reaction. The iodo substituent could not be exchanged for a methoxyl group by treatment with potassium methoxide.

In a second attempt to prepare the tetramethoxy phthalide, the 3-methyl-4,5,6-trimethoxyphthalide was used, but this attempt was unsuccessful since the starting material could not be easily synthesized. A preparation of the starting material, by use of 3-trichloromethyl-4,5,6-methoxyphthalide prepared by Alimchandani (15) by reaction of 3,4,5-trimethoxybenzoic acid with chloral hydrate in 90% sulfuric acid, was tried. All the known procedures for the reduction of a trichloromethyl group to a methyl group failed (16,17). In all attempts the dichloromethyl compound resulted.

On the assumption that the tetramethoxy 3-methylphthalide could be prepared from the tetramethoxy phthalide, attempts were made to secure this material. 4,5,6,-Trimethoxyphthalide could be obtained from trimethylgallic acid (18) or possibly from the 3-trichloromethyl-4,5,6-trimethoxyphthalide which could be converted to the acid, then decarboxylated to the trimethoxyphthalide in good yield. The trimethoxy phthalide was then nitrated, and the iodo compound prepared by way of the diazotized amine by means of a Sandmeyer reaction; then treatment with potassium methoxide gave the tetramethoxyphthalide in small yield.

Since the nitration of the trimethoxy phthalide proved so difficult, a method for obtaining the tetramethoxy phthalide from 1,2,3,4-tetramethoxybenzene appeared to be more desirable. One method

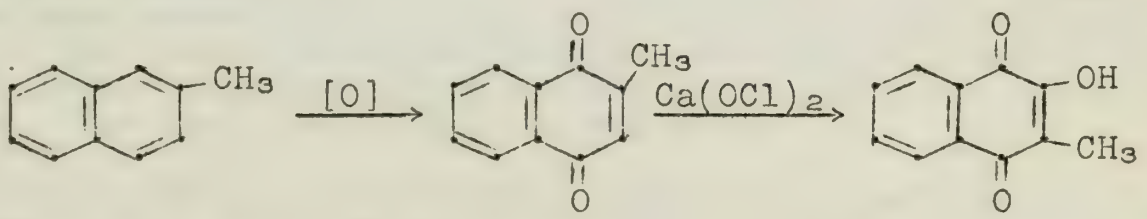
for the preparation of this material used gallacetophenone-3,4-dimethyl ether (19) in the Dakin reaction (hydrogen peroxide in aqueous alkali) to yield 1,2-dimethoxy-3,4-dihydroxybenzene, which was converted to the tetramethoxybenzene with dimethyl sulfate 2-Hydroxy-3,4-dimethoxybenzaldehyde was also used as the starting material in a similar reaction, but the availability of this material is limited.

Another method for the preparation of 1,2,3,4-tetramethoxybenzene was carried out in the following manner: pyrogallol was converted to pyrogallol-4-carboxylic acid, which was transformed to pyrogallol-1,2-dimethyl ether; the ether was oxidized according to the method of Teuber (14), to 2,3-dimethoxy-p-benzoquinone. This benzoquinone was reduced to the hydroquinone, which in turn was methylated to the 1,2,3,4-tetramethoxybenzene in 50% yield, based on the pyrogallol-1,2-dimethyl ether. Two other methods (20,21) have been used to prepare the tetramethoxybenzene from pyrogallol-1,2-dimethyl ether, but neither gave as good a yield. This material has been prepared by Baker as an intermediate in the preparation of parsley and dill apiole.

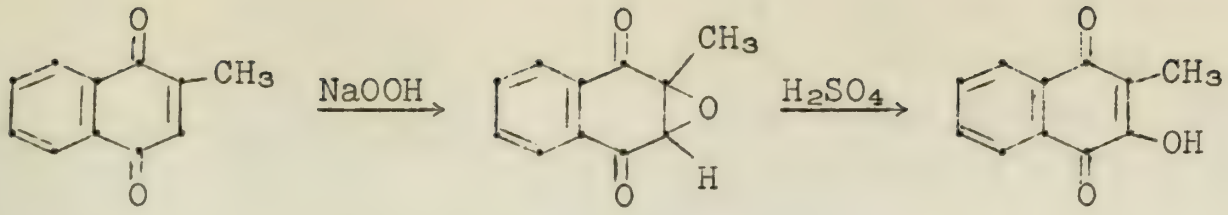
In order to obtain the methoxylated naphthoquinone, 1,2,3,4-tetramethoxybenzene was chloromethylated (67% yield) to 1,2-bis-chloromethyl-3,4,5,6-tetramethoxybenzene. This compound was converted in 95% yield to the diacetate and on to the dialcohol (22). The dialcohol was oxidized directly to 4,5,6,7-tetramethoxyphthalide with sodium dichromate in acetic acid (20% yield, based on the tetramethoxybenzene) and in reaction with active manganese dioxide to 2-hydroxymethyl-3,4,5,6-tetramethoxybenzaldehyde in 65% yield. In order to form 4,5,6,7-tetramethoxyphthalaldehydic acid, the tetramethoxyphthalide was treated with N-bromosuccinimide; the aldehydic acid was obtained in 85% yield. This material was also obtained (in 68% yield) by treating the 3,4,5,6-tetramethoxyphthalalcohol with N-bromosuccinimide in benzene and carbon tetrachloride. Treatment of the aldehyde with methylmagnesium iodide gave 3-methyl-4,6,6,7-tetramethoxyphthalide in 68% yield.

FORMATION OF SUBSTITUTED NAPHTHOQUINONES FROM o-DIACYLBENZENES

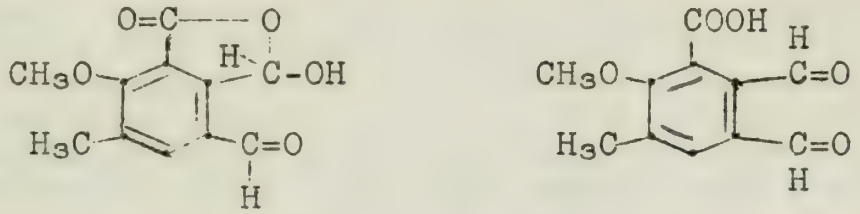
Interest in 1,4-naphthoquinones was stimulated by the announcement that 2-hydroxy-3-methyl-1,4-naphthoquinone (phthiocol) possessed anti-hemorrhagic activity similar to vitamin K (23). Various preparations for this compound had been known; however, they afforded the compound in only low yields. A method proposed by Anderson (24) gave phthiocol in a 57% yield.



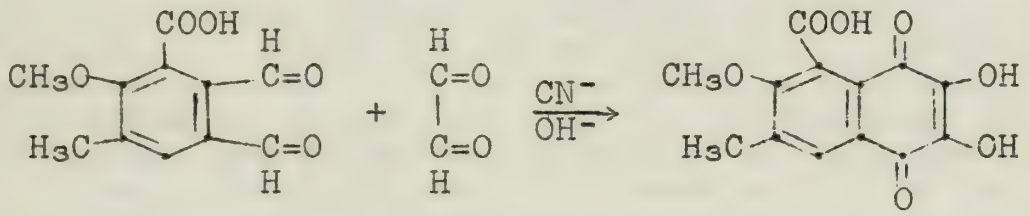
Various series of substituted 1,4-naphthoquinones were prepared and checked for anti-hemorrhagic activity (24,25,26). Fieser (27) prepared phthiocol in the following manner.



In 1952-1954, elucidation of the structure of gladiolic acid was carried out (28,29). This acid was shown to exist in two forms.



Many derivatives of the lactol form had been made, but no simple derivative of the open chain form was prepared until Weygand (30), in 1954, discovered a new synthetic route to isonaphthazarins by the condensation of suitable phthalaldehydes (such as gladiolic acid) with glyoxal in weakly alkaline solution in the presence of cyanide ion.

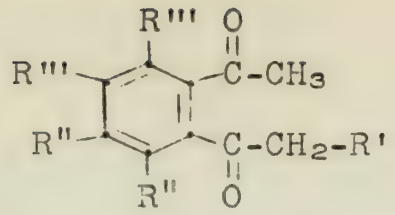


The yield of 2,3-dihydroxy-6-methoxy-7-methyl-1,4-naphthoquinone-5-carboxylic acid was 35%.

Weygand and his coworkers (8) also observed that the condensation does not take place with methyl- or phenylglyoxal. Thus, this synthesis is not suitable for the β-substituted alkyl hydroxynaphthoquinones.

It was also noted that the reaction of o-diacetylbenzene in warm 2-propanol containing selenium dioxide, became red; a small amount of 2-hydroxy-1,4-naphthoquinone was isolated. A small quantity of dinaphthoquinone was also obtained but not investigated. Since the ring closure to 2-hydroxy-1,4-naphthoquinone could be carried out smoothly, longer chain acyl groups were investigated. o-Acetylpropiophenone was converted to phthiocol in good yield. Also, o-acetylbutyrophenone was converted to 2-hydroxy-3-ethyl-1,4-naphthoquinone in 40% yield. The nonhydroxylated compound was also obtained in small quantity. A smooth reaction with 3,4-dimethoxy substituted o-acetylpropiophenone under the same conditions occurred.

These results led to preparation of more highly methoxylated 1,4-naphthoquinones (10). The purity of the diketone appears to be a deciding factor in determining the yield obtained from the oxidative ring closure of o-diacylbenzenes to 1,4-naphthoquinones. The o-diacetylbenzene and the o-acetylbutyrophenone have been obtained as pure compounds while those derived from the 3-methyl phthalides have not. The percentage of diketone present in the product appears to decrease in the following order.



R' = CH_3; R", R'" = H
R' = CH_3; R" = OCH_3; R'" = H
R' = CH_3; R", R'" = OCH_3
R' = C_2H_5; R", R'" = OCH_3

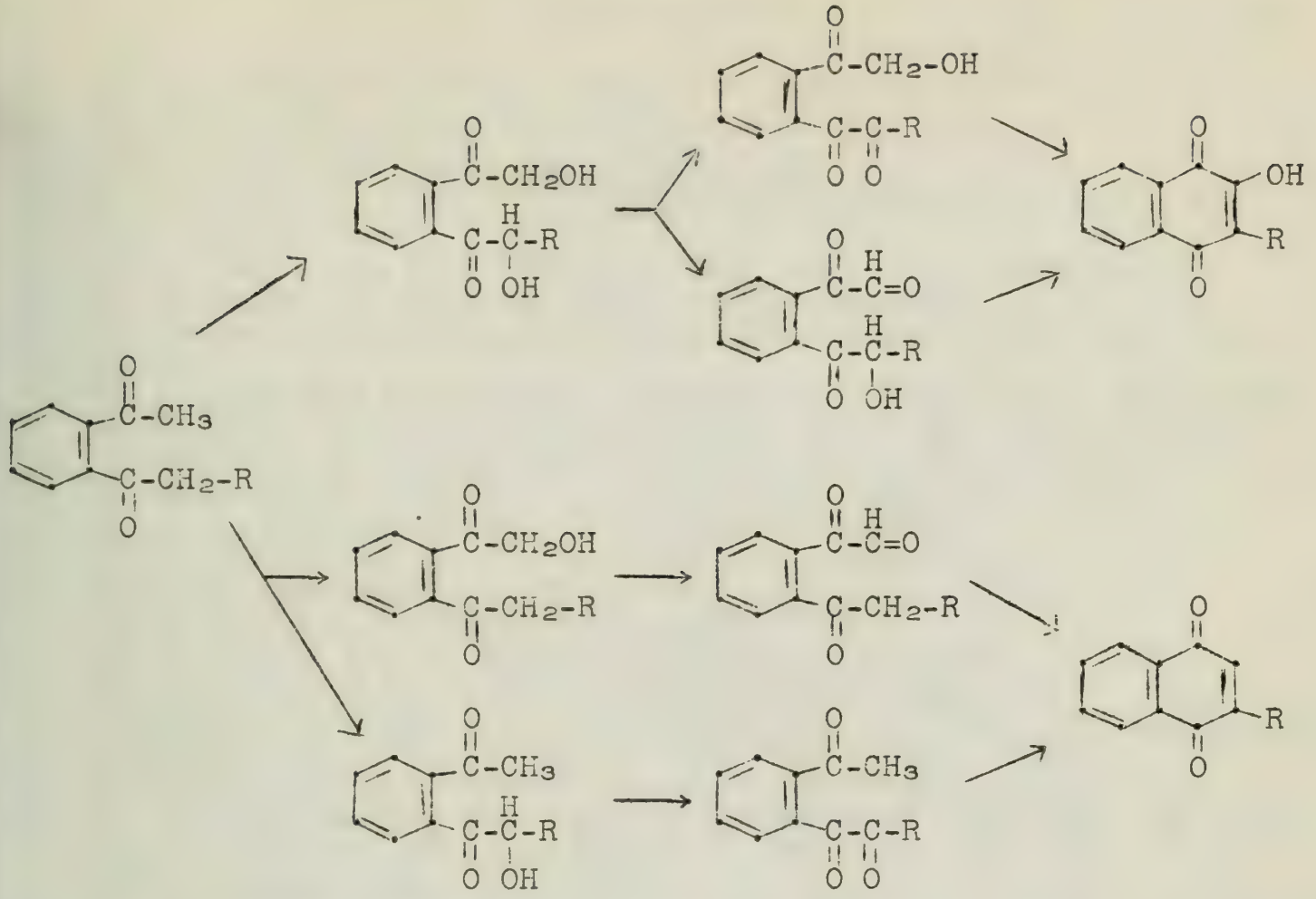
The amount of diketone was indicated in each case by the aniline-acetic acid color test.

The treatment of 3-methylphthalide with ethylmagnesium bromide and then oxidative ring closure to 2-hydroxy-3-methyl-1,4-naphthoquinone gave this desired product in 10% yield along with a small amount of the nonhydroxylated product. When the nonhydroxylated product was retreated with selenium dioxide in 2-propanol to determine if hydroxylation could take place under these conditions, 2-methyl-1,4-naphthoquinone was recovered.

3-Methyl-4,5,6,7-tetramethoxyphthalide gave only a small quantity of impure diketone when either the ethyl- or the propyl Grignard reagent was used. Although no crystalline products were obtained from the selenium dioxide ring closure, extraction of the reaction mixture with sodium carbonate solution produced a red color. Reextraction and chromatography on alumina produced a yellow oil which showed UV absorption maxima at 260 and 297-298 mμ. This solubility in alkali is accompanied by color intensification. Vitamin K and 2,3-dimethoxy-1,4-naphthoquinone have absorption maxima at 260 and also produce an intense red color when dissolved in alkaline solution; accordingly, the authors assumed the presence of both the 2-hydroxy-3-methyl-(or ethyl) 5,6,7,8-tetramethoxy-1,4-naphthoquinone. The presence of the nonhydroxylated species was not determined.

POSSIBLE REACTION MECHANISM

In the oxidative ring closure of o-diacylbenzenes to the 2-hydroxy-1,4-naphthoquinones, it was at first assumed that the nonhydroxylated naphthoquinones were intermediates. This is not the case, however, since hydroxylation does not take place under the selenium dioxide reaction conditions. The following mechanism has been proposed.



The selenium dioxide first oxidizes an active $-CH_2-$ or $-CH_3$ group to an alcohol, which then can be dehydrogenated to either an aldehyde or a ketone. The o-diacylbenzenes, according to the theory, can be oxidized at both of the active positions to form a diketol. At this point, either of the alcoholic groupings can be oxidized to the corresponding aldehyde or ketone, which in turn is converted to the energetically more stable ring structure. In postulating a mechanism for the formation of the nonhydroxylated material, it is assumed that only one of the acyl groups is oxidized.

BIBLIOGRAPHY

1. R. Riemschneider, Gazz. chim. ital., 77, 607 (1947).
2. G. Giebe, Ber., 29, 2533 (1896).
3. W. Winkler, Ber., 81, 256 (1948).
4. W. F. Beech, J. Chem. Soc., 1954, 1297.
5. F. Weygand, H. Weber, E. Maekawa and G. Eberhardt, Ber., 89, 1994 (1956).
6. W. E. Truce and P. T. Mori, J. Org. Chem., 18, 1655 (1953).
7. G. Hillmann, Z. physiol. Chem., 277, 222 (1943).
8. F. Weygand, H. Weber and G. Eberhardt, Angew. Chem., 66, 680 (1954).
9. W. Schlenk and E. Bergmann, Liebigs Ann. Chem., 463, 162 (1928).
10. F. Weygand, H. Weber and E. Maekawa, Ber., 90, 1879 (1957).
11. H. Simonis, E. Marben and E. Mermod, Ber., 38, 3981 (1905).
12. E. Hope and R. Robinson, J. Chem. Soc., 105, 2103 (1914).
13. H. J. Teuber and W. Rau, Ber., 86, 1036 (1953).
14. H. J. Teuber and G. Staiger, Ber., 88, 802 (1955).
15. R. L. Alimchandani, J. Chem. Soc., 125, 539 (1924).
16. W. B. Whalley, J. Chem. Soc., 1951, 3229.
17. C. Grundmann and G. Weisse, Ber., 84, 684 (1951).
18. F. E. King and T. J. King, J. Chem. Soc., 1942, 726.
19. W. Baker, E. Jukes and C. Subrahmanyam, J. Chem. Soc., 1934, 1681.
20. W. Baker and H. A. Smith, J. Chem. Soc., 1931, 2542.
21. W. Baker and R. I. Savage, J. Chem. Soc., 1938, 1602.
22. F. Weygand, K. Vogelbach and K. Zimmermann, Ber., 80, 391 (1947).
23. H. J. Almquist and A. A. Klose, J. Am. Chem. Soc., 61, 1611 (1939); ibid., 61, 1923 (1939).
24. S. Ansbacher and E. Fernholz, J. Am. Chem. Soc., 61, 1924 (1939).
25. L. F. Fieser, et al., J. Am. Chem. Soc., 61, 1925 (1939).
26. L. F. Fieser, et al., J. Am. Chem. Soc., 61, 1926 (1939).
27. L. F. Fieser, J. Biol. Chem., 133, 391 (1940).
28. H. Raistruk and D. J. Ross, Biochem. J., 50, 635 (1952).
29. J. J. Brown and G. T. Newbold, Chem. and Ind., 1953, 1151.
30. F. Weygand, H. Weber and J. F. Grove, Chem. and Ind., 1954, 106.

POLYMERIZATION OF OLEFINS BY ZIEGLER CATALYSTS

Reported by E. J. Gall May 5, 1958

I. Historical

As early as 1930, Friedrich and Marvel (1) had reported that lithium alkyls may cause the polymerization of ethylene to non-gaseous products. In 1941, Ellis (2), in a duPont patent, described the polymerization of olefins by the use of lithium alkyls and a hydrogenating contact catalyst, such as reduced nickel on kieselguhr. In 1943, Max Fischer (3), had succeeded in polymerizing ethylene by the action of aluminum chloride in the presence of titanium tetrachloride and a small amount of aluminum powder. The products obtained were lubricating oils along with a small amount of insoluble solid white mass, which was considered an unfortunate by-product. By 1949, Ziegler had shown that α-olefins could add to metal hydrides or aluminum trialkyls, such as aluminum triethyl to form higher olefins (4,5). He proposed the following process for the polymerization:

$$Al(C_2H_5)_3 + C_2H_4 \xrightarrow{100^\circ} Al\begin{matrix}\diagup CH_2CH_2C_2H_5\\ -C_2H_5\\ \diagdown C_2H_5\end{matrix} \longrightarrow \qquad (1)$$

$$Al\begin{matrix}\diagup (C_2H_4)_l C_2H_5\\ -(C_2H_4)_m C_2H_5\\ \diagdown (C_2H_4)_n C_2H_5\end{matrix} \longrightarrow AlH_3 + CH_2{=}CH(C_2H_4)_{\substack{l-1\\ m-1\\ n-1}}C_2H_5$$

Ziegler reasoned that this stepwise organo-metallic synthesis should lead to high molecular weight polyethylene, but, in actual practice this was not the case. To explain the lack of high molecular weight polymer, he proposed (5) that the growing chain was destroyed by a "displacement" reaction characteristic of aluminum alkyls and ethylene at high temperatures (>100°):

$$H(C_2H_4)_{n-1}CH_2CH_2\text{-al} + C_2H_4 \longrightarrow H(C_2H_4)_{n-1}CH{=}CH_2 + CH_3CH_2al \qquad (2)$$
$$al = 1/3\ Al$$

In the course of their investigation of this polymerization process, Ziegler and his co-workers accidentally discovered that certain metals, such as nickel or cobalt, were very effective in catalyzing the above displacement reaction (6,7). Further experiments aimed at elucidating the effect of various other metal co-catalysts on the ethylene polymerization led to the discovery of "The Muhlheim Normal Pressure Polyethylene Process", in which aluminum triethyl is combined with titanium tetrachloride at one atmosphere to produce a catalyst which is very effective for the polymerization of ethylene to high molecular weights (8).

These experiments of Ziegler and his co-workers, with their claim of having produced polyethylene of molecular weight as high as 3,000,000 at low temperature and normal pressures, aroused a great deal of interest in polymer chemists everywhere. Natta, in Italy, began his intensive investigation of the new process, and prepared a number of polymers from α-olefins other than ethylene by the use of what he first called the "Ziegler catalyst" (9,10). Natta was the first to recognize the fundamental importance of Ziegler's discovery and his group has contributed the most toward a greater understanding of the new polymers and polymerization procedures (11).

At about the same time that Ziegler was carrying out his experiments various other workers were also developing new solid catalysts for the polymerization of olefins. Several patents issued to Standard Oil of Indiana (12) described the use of preformed solid catalysts, such as molybdena on alumina. The Phillips Petroleum Company, in a Belgian patent (13), described the use of chromium oxide on a silica-alumina support as a polymerization catalyst. The polymers obtained by the use of these metal oxide catalysts are similar to those obtained by Ziegler; this seminar, however, will consider in detail only the "Ziegler-type catalysts".

II. The Ziegler Catalyst

Since Ziegler's initial work with aluminum triethyl and titanium tetrachloride, a number of catalyst systems of the same type have been investigated. These catalyst types can be classified as complex metal alkyls and hydrides. Metal hydrides alone, without a "co-catalyst", as used by Ziegler (4), are not effective catalysts since at best only low molecular weight polymers are obtained. The metal alkyls, such as aluminum and beryllium alkyls, either alone or with nickel, cobalt, or platinum co-catalysts added, are also not effective (7). The most effective co-catalysts, when used with aluminum alkyls, are the salts of the metals zirconium and titanium (8). In general, the salts of any of the metals of the fourth, fifth, and sixth groups of the periodic system, including thorium and uranium, areeffective as co-catalysts (8,14). These co-catalyst salts are used together with organometallic compounds of group II and III metals.

In addition to the forementioned catalysts, Ziegler has also claimed hydrides or certain organo compounds of aluminum or the next two higher members of the same group in the periodic system, or beryllium in the next preceding group, as expecially effective catalysts (15).

Natta (17) has reported the use of catalysts essentially the same as those described by Ziegler. He has shown that a better crystallinity of polymer can be obtained with diethylaluminum chloride and titanium trichloride than with aluminum triethyl and titanium tetrachloride (18). He has reported the isolation of a crystallizable organometallic complex containing titanium and aluminum, having the empirical formula $(C_5H_5)_2TiCl_2Al(C_2H_5)_2$ (19). This blue crystalline compound was prepared by treating bis-(cyclopentadienyl)-titanium dichloride with aluminum triethyl in n-heptane at 70°. The complex was active for the polymerization of ethylene, although not as active as the catalyst prepared from $TiCl_4$ and aluminum triethyl. This is perhaps the only catalyst of this type which has been isolated in a crystalline state. Breslow and Newburg (20) have isolated a similar complex from the reaction of bis-(cyclopentadienyl)-titanium dichloride with two moles of diethylaluminum chloride in n-heptane. They report their crystallized compound to be a complex of $(C_5H_5)_2Ti(III)Cl$ with aluminum sesquichloride, $(C_5H_5)_2TiCl \cdot 1/2(C_2H_5)_2AlCl \cdot 1/2C_2H_5AlCl_2$. This blue complex is a very poor catalyst for the polymerization of ethylene, unless the ethylene contains a trace of oxygen, in which case this catalyst was shown to be fully as active as the usual Ziegler type. The oxygen here seems to be functioning in such a way so as to form a tetravalent titanium compound, and their conclusion was that this soluble catalyst system (the polymerizations were run in toluene, in which the complex is soluble) depends for its catalytic activity on the presence of at least some tetravalent titanium.

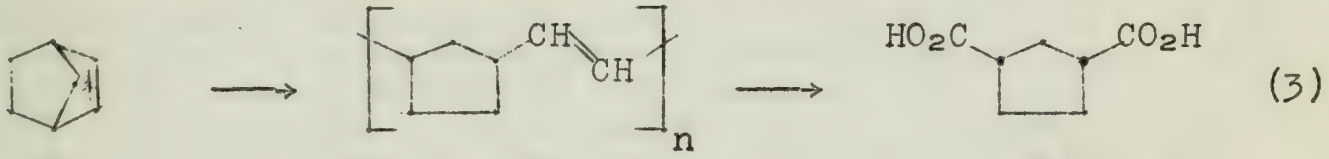
The most generally used catalyst of the Ziegler type has been the combination of aluminum trialkyl and titanium tetrachloride. In order for the catalyst to be effective at least the metal salt as "co-catalyst" must be present along with some reducing agent (22).

III. Olefin Types

In addition to ethylene, which was the first olefin to which the Ziegler polymerization process was applied, a number of other monoolefins have been polymerized by this process. As a general rule, the monoolefin must be an α-olefin with no branching closer than the 3 or 4-position to the double bond (8). Some examples of these olefin types, whose polymerization by Ziegler catalysis has been reported are propylene (17), butene-1 (9), 3-methyl-1-butene and pentene (22). The branched olefins 4-methyl-1-pentene, 4-methyl-1-hexene, and 5-methyl-1-hexene have also been polymerized by this procedure (23).

Styrene, which might be classed as an exception to the rule stated above, readily undergoes polymerization to a high molecular weight crystalline polymer (9,24). The long-chain α-olefins dodecene and octadecene have been polymerized in good conversion to high molecular weight polymers (25).

A novel example is the polymerization of bicyclo-(2,2,1)-hept-2-ene (26). (I) Either a rigid or a flexible polymer was obtained, depending on the catalyst used (27). Infra-red studies showed that the two types of polymers possessed different structural characteristics. It was proposed that the flexible polymer contained the structural unit II. This structure was shown by its oxidation to cis-cyclopentane-1,3-dicarboxylic acid (III).



(3)

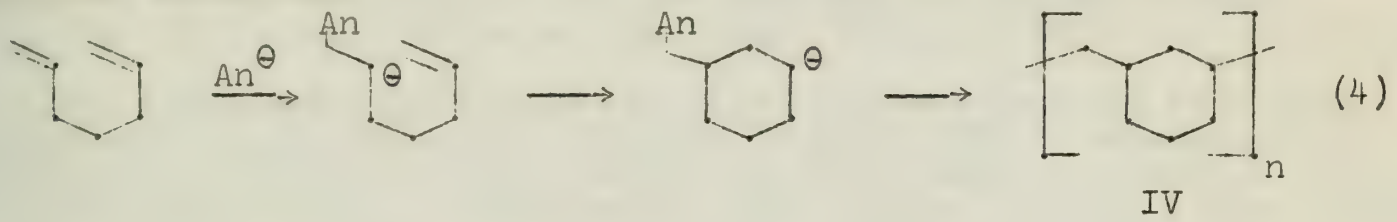
I II III

When functional groups, which are capable of destroying the catalyst, such as carbonyl groups, groups containing nitrogen, sulfur, phosphorus, etc., easily reducible groups or active halogens and hydrogens, are present in the olefin, polymerization is not possible (22).

Conjugated diolefins have been polymerized by means of the various catalyst systems previously described. Goodyear has obtained a "synthetic natural rubber" from isoprene by the use of aluminum triethyl and an unspecified co-catalyst (28). The polymer is nearly all cis-1,4-polyisoprene, a structure almost identical with that of natural rubber. Horne and co-workers have reported the polymerization of isoprene to either an all cis-1,4 or an all trans-1,4-polymer at will by the use of Ziegler-type catalysts (29). The polymerization of various other substituted conjugated diolefins, such as 2,3-dimethyl-1,3-butadiene, chloroprene, 2,3-dimethyl-1,3-pentadiene and 2-phenylbutadiene, has been reported (30). The geometry of the polymers obtained depends largely on the kind of catalyst used. Cyclohexadiene has been polymerized by the Ziegler process to 92% conversion (31).

The polymerization of a series of non-conjugated diolefins has been reported (22), in which the polymerization reaction takes place

with only one of the double bonds. A group of interesting polymerization reactions effected by the Ziegler catalyst are those of the non-conjugated dienes 1,6-heptadiene, 1,5-hexadiene and 2,5-dimethyl-1,5-hexadiene (32). The products obtained in these polymerizations were soluble polymers of high molecular weight and high melting point. The polymer from 1,6-heptadiene, readily soluble in benzene, could be dehydrogenated to a polymer which showed aromatic and meta substitution in the infra-red and ultra-violet absorption spectra. To explain this behavior a cyclic recurring unit (IV) was proposed as the main structural feature of the polymer, and the formation of the polymer has been explained by an alternating intermolecular-intramolecular mechanism.



(4)

IV

IV. Stereochemistry of the Polymers

The Ziegler process for the polymerization of ethylene to polyethylene yields a polymer which is highly crystalline, since the chain is linear with little chain branching (7,14). In general, the polymers, both high and low molecular weight, obtained by means of the Ziegler process exhibit a high degree of crystallinity along with a high melting point and other properties quite different from the corresponding "amorphous" polyhydrocarbons having intrinsic viscosities of the same order of magnitude (10). Natta has investigated extensively the structures of the stereospecific polymers of α-olefins by means of x-ray and electron diffraction (24). He has made a distinction among three general stereoisomeric types, which he calls isotactic, syndiotactic, and atactic (33). When a monomor CH_2=CHR is polymerized to give a polymer chain -CH_2-CHR-, there is the possibility that the tertiary carbon atoms have the same steric configuration with respect to the other tertiary carbon atoms (11,33). If the zig-zag chain backbone is visualized as lying all in a plane, then the relative positions of the R-groups on the alternate tertiary carbon atoms will determine the type of isomerism. If all the R-groups are situated on the same side of the plane, either above or below, the tertiary carbon atoms all have the same steric configuration and the polymer is said to have an isotactic structure. If, however, the R-groups are located alternately above and below the plane, i.e., every other tertiary carbon atom has an identical configuration, the polymer is said to have a syndiotactic structure. A polymer structure, in which the R-groups are arranged completely at random and there is no regularity in the configuration of the tertiary carbon atoms, is said to be atactic. The configurations of all the tertiary carbons will be completely identical actually only in infinitely long chain polymers, and, although the polymers possess asymmetric carbon atoms, optical activity is not observed because of internal compensation.

Natta lists the following requirements for a stereospecific polymerization process (33):

1) The polymerization must occur always in a head to tail fashion

2) The polymerization must occur without chain branching due either to chain transfer processes or through copolymerization of the monomers with their low molecular weight polymers

3) The polymerization must occur in a manner so that the monomer units assume steric configurations corresponding to a determined order of absorption on the catalyst surface.

The x-ray studies on various isotactic polymers, such as polypropylene, poly-1-butene, and poly-1-pentene, have shown the identity period to be 6.5 to 6.7A° (34,35). According to Natta, this identity period corresponds to three monomeric units (-CH_2-CHR-). The calculated value for this identity period is 7.62A°, if a planar and fully extended paraffinic chain corresponding to three monomeric units is considered (10). The difference in the two values is explained by the assumption that the crystalline polymer assumes a helical configuration due to the steric requirements of the R-groups.

The sterochemistry of the polymers obtained from the conjugated diolefin, butadiene, has been studied by Natta (35). Butadiene can polymerize in different ways yielding either linear or branched chains or even, under certain conditions bridged chains. In the linear chain of the polymers of diolefins there can be found three types of concatenation: (1-4)-trans, (1-4)-cis, and (1-2). Natural polyisoprene exhibits the (1-4)-trans concatenation as seen in guttapercha, and the (1-4)-cis type in natural rubber. Natta was able to produce polymers from butadiene which contained almost exclusively the (1-2) concatenation. This (1-2) poly-butadiene was the first example of a syndiotactic polymer, and was also the first polymer of a diolefin to contain exclusively the (1-2) structure. He has also obtained, by the use of heterogeneous catalysts, crystalline polymers of butadiene of the (1-4)-trans type. In contrast to the isotactic polymers, these syndiotactic polybutadienes have an almost planar principal chain with an identity period of about 5.14A°, corresponding to two monomer units.

V. Mechanism of Polymerization

The elucidation of the mechanisms of vinyl-type polymerizations at solid surfaces and by complex catalysts has always been a formidable theoretical problem (36). The solution to the mechanistic problem in the case of polymerization by Ziegler catalysts has been difficult for two reasons: the composition of the active catalyst is not exactly known, and, since the reaction takes place in a heterogeneous system, the rate of reaction is dependent on the surface or degree of dispersion of the catalyst (22).

The mechanism which Ziegler postulated for the polymerization has been discussed previously - equations (1) and (2). Robinson (37) has proposed a similar mechanism. Natta (33,34) has suggested an anionic mechanism, which is analogous to that of Ziegler, except that Natta takes into account the important effect of the catalyst surface. He has ruled out both a free radical and a cationic mechanism on the basis of the requirements he feels necessary for stereospecific polymerization (see Section IV). Since free radical polymerizations are in general not stereoselective, and cationic polymerizations frequently proceed by chain transfer, neither would be expected to lead to stereospecific polymers. Natta believes the true catalyst to be a surface complex compound of aluminum alkyl with a titanium compound, and that the propagation step consists of the insertion of a monomer molecule between the positively charged ion of the catalytic complex and the negatively charged methylene end group of the growing polymer chain. He has observed that groups originally bound to aluminum are later found as end groups on the

polymer (33), and has concluded that the polymerization process depends upon the formation of a positive aluminum atom, formed by the breaking of an aluminum-carbon bond. Natta and co-workers (42) have studied the kinetics of the polymerization of propylene with catalysts based on $TiCl_3$ and AlR_3, and have reported a first-order dependence of rate on propylene and $TiCl_3$ concentration.

A group of duPont workers has also reported kinetic data on polymerization by Ziegler catalysts (41). Their data on the polymerization of ethylene agree closely with that reported by Natta in that they observed that, over a pressure range of 1-1.5 atmospheres, and at a given temperature, rates were proportional to the concentration of ethylene and the concentration of $TiCl_4$ in the active catalyst. They further reported that catalytic activity was also dependent upon the nature of the alkylating agent (lithium or aluminum alkyl), the alkylating agent-to-titanium tetrachloride mole ratio, which determines the valence state of the titanium, and temperature.

To relate catalytic activity to the average valence state of titanium, these workers investigated catalysts prepared from $TiCl_4$ and $Al(C_2H_5)_3$. One of the reactions possible between organometallics and $TiCl_4$ is reduction of the latter. When $Al(C_2H_5)_3$ is allowed to interact with $TiCl_4$, the organotitanium compounds formed initially would release ethyl radicals to form ethane. If it is assumed that each mole of ethane released in this reaction corresponds to a reduction of one in the valence state of one mole of titanium, then it is possible to calculate the average valence state of titanium from quantitative off-gas measurements in this catalyst system. When these measurements were made on the reaction of $TiCl_4$ with $Al(C_2H_5)_3$ in boiling cyclohexane, it was observed that the average valence state of titanium decreased gradually as the alkylaluminum-to-titanium halide ratio was increased. When these results were combined with data which showed that catalyst activity was strongly related to catalyst composition, a relationship between catalyst activity and average valence state was obtained which suggested that maximum activity is associated with titanium in an average valence state of two.

On the basis of their data the duPont workers propose the following as the propagation reaction (assuming RTiCl to be the active catalyst):

$$ClTi(C_2H_4)_nR + C_2H_4 \xrightarrow{k_p} ClTi(C_2H_4)_nR \xrightarrow{\text{fast}} ClTi(C_2H_4)_{n+1}R \qquad (5)$$

The coordination of ethylene with the active catalyst is regarded as the rate-determining step, and leads to the differential rate equation

$$R_p = k_p[E][C] \qquad (6)$$

where R_p is the polymerization rate, [E] is the concentration of ethylene, k_p is the propagation constant, and [C] is the concentration of active catalyst. It is difficult to apply equation (6) to polymerization over an extended period of time unless the polymer remains in solution, because insoluble polymer will cause occlusion of catalyst sites, and the effective catalyst concentration, C, will

decrease. When the polymer remains in solution, equation (6) predicts that the rate of polymerication will remain constant with time, and will be proportional to both ethylene and $TiCl_4$ concentrations. By using the volume of gas polymerized after two hours at 100° as their measure of catalytic activity, these workers found experimentally that the second-order dependence predicted was obeyed even when the polymer was partially insoluble.

In a more recent paper, McGowan and Ford (43) have reported kinetic data on the polymerization of ethylene at 30° which indicated that the rates of polymerization were proportional to the $TiCl_4$ concentration and to the squares of the ethylene pressures. These results seem to invalidate the conclusions reached by the duPont workers described above. A close examination of the two sets of data, however, shows that a direct comparison of the two cannot be made. Whereas the duPont workers followed the rates of polymerizations for two hours and longer, and used the volume of gas polymerized after two hours as a measure of catalyst activity, McGowan and Ford limited their observations to polymerization times of 30 minutes. The duPont workers have stated that initial rates could not be used because they are less reproducible than the volume of gas polymerized after a given time interval. Fig. 1 shows a typical polymerization curve obtained by the duPont workers. It is seen that the initial portion of this curve is rather complex.

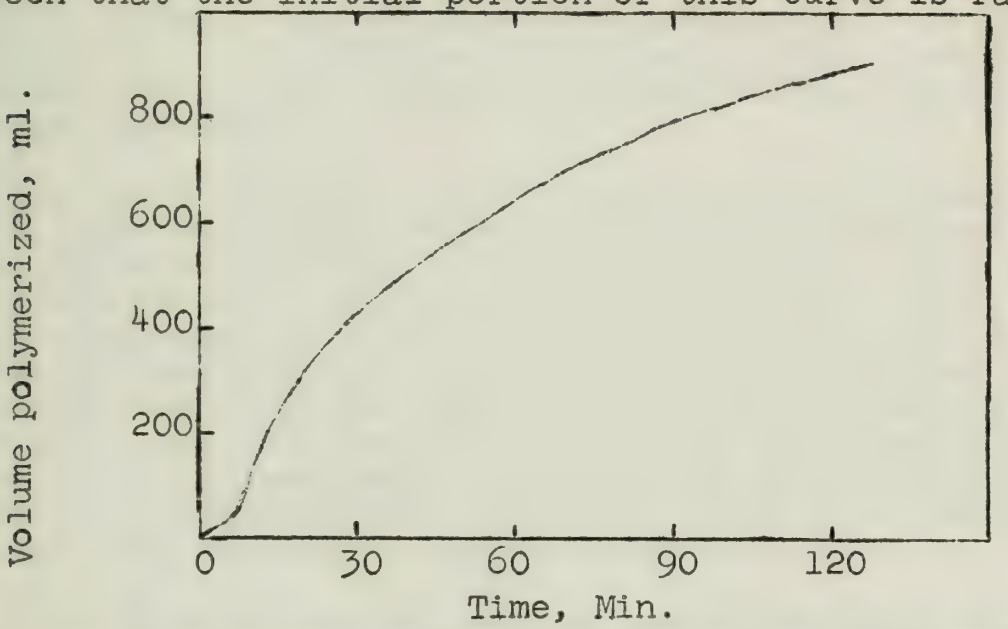


Fig. 1 - Typical polymerization with a $TiCl_4$-AlR_3 catalyst at 100°; 49 micromoles of $TiCl_4$ and 180 micromoles of AlR_3 in 100 ml. of Decalin.

By limiting their measurements to the first 30 minutes of the polymerization reaction, it is entirely conceivable that McGowan and Ford were observing the operation of a mechanism quite different from that observed by the duPont workers. If the composition or nature of the active catalyst is changing during this period, and these changes involve monomer molecules, then second-order kinetics with respect to ethylene can be understood on the basis of the following equilibria:

$$R\text{-}\overset{|}{Ti} + CH_2{=}CH_2 \rightleftharpoons [R\text{-}\overset{|}{Ti}^{\oplus}]\,[\overset{\ominus}{CH_2}\text{-}\dot{C}H_2] \qquad (7)$$

$$[R\text{-}\overset{|}{Ti}^{\oplus}]\,[\overset{\ominus}{CH_2}\text{-}\dot{C}H_2] + CH_2{=}CH_2 \rightleftharpoons R^{\oplus}\,[\overset{|}{Ti}^{\oplus}]\,[\overset{\ominus}{CH_2}\text{-}\dot{C}H_2]_2 \qquad (8)$$

If these two equilibria are quickly established and the conversion of $TiCl_4$ into the alkyl titanium derivative is rapid and complete

with an excess of metal alkyl present, then the overall rate of the polymerization will be proportional to the $TiCl_4$ concentration and to the square of the ethylene pressure.

None of the work described above has yielded sufficient information regarding the exact nature of the active catalyst species. Friedlander and Oita (39) have carried out studies aimed at understanding the role played by organometallics in the polymerization of ethylene, and have concluded that the interaction of lithium and aluminum alkyls with $TiCl_4$ resulted in the formation of titanium alkyls. These workers allowed $TiCl_4$ to interact with metal alkyls in small amounts of purified solvent. After 10 minutes of interaction, samples of the total material were withdrawn for qualitative tests to determine the type of organometallic compound formed at various component ratios. Aliquot samples of total material were also hydrolyzed to determine the amount of $TiCl_4$ reduced and the valence state of the reduced material. The two qualitative tests used for determining the type of organometallic compounds present were Michler's ketone test, which reveals any organometallic capable of reacting with the carbonyl group of the ketone (44), and the Gilman-Swiss test (45), which is specific for lithium alkyls. To determine the amount of trivalent titanium present, the hydrolyzed reaction products were titrated with iron (III) in the presence of ammonium thiocyanate as indicator. In the hydrolysis of the reaction product, any divalent titanium present is oxidized to the trivalent form and hydrogen is evolved. Hence, any divalent titanium present was determined by collecting and measuring the hydrogen released.

The tests described above showed that the catalyst precipitates formed from interaction of both lithium and aluminum alkyls and $TiCl_4$ contained primarily trivalent titanium. Some reduction beyond the trivalent state was observed; the authors claim, however, that this further reduction was minor. On the basis of these experiments, it was concluded that the active catalyst is either a complex between the metal alkyl and the titanium halide or is an alkyltitanium compound. When lithium alkyls are used, the complexes involve both trivalent and tetravalent titanium, and their presence depends on the ratio of alkyllithium and $TiCl_4$. When aluminum alkyls are used, the complexes or alkyls involve trivalent titanium.

Further experimental work is needed in order to reconcile these findings with the conclusions of the duPont workers that maximum catalyst activity is associated with titanium in an average valence state of two. It can reasonably be concluded, however, that the active catalyst certainly involves titanium in a reduced valence state.

BIBLIOGRAPHY

1. M. E. P. Friedrich and C. S. Marvel, J. Am. Chem. Soc., 52, 376 (1930).
2. L. M. Ellis, U. S. Patent 2,212,155 (1941); Chem. Abstr. 35, 464 (1941).
3. M. Fischer, German Patent 874,215 (1953); Chem. Abstr. 51, 10124 (1957).
4. K. Ziegler and H. G. Gellert, Brennstoff Chem., 33, 193 (1952).
5. K. Ziegler, Petroleum Refiner, 34, No. 8, 111 (1955).
6. K. Ziegler, H. G. Gellert, E. Holzkamp and G. Wilke, Brennstoff Chem., 35, 321 (1954).
7. K. Ziegler, E. Holzkamp, H. Breil and H. Martin, Angew. Chem., 67, 426 (1955).
8. K. Ziegler, et al, ibid., 541 (1955).
9. G. Natta, J. Poly. Sci., 16, 143 (1955).
10. G. Natta, et al, J. Am. Chem. Soc., 77, 1708 (1955).
11. A. V. Tobolsky, American Scientist, 45, 34 (1957).
12. U. S. Patent 2,692,257 (1954); U. S. Patent 2,691,647 (1954); U. S. Patent 2,692,261 (1954).
13. Phillips Petroleum Company, Belgian Patent, 530,617 (1955).
14. S. L. Aggarwal and O. J. Sweeting, Chem. Rev., 57, 665 (1957).
15. K. Ziegler and H. G. Gellert, U. S. Patent 2,699,457 (1955).
16. K. Ziegler and H. Martin, Makromoleculare Chem., 19, 186 (1956).
17. G. Natta, P. Corradini and I. W. Bassi, Makromol. Chem., 21, 240 (1956).
18. J. K. Stille, Univ. of Illinois Ph.D. Thesis, 1957, p. 65.
19. G. Natta, P. Pino, G. Mazzanti, U. Giannini, J. Am. Chem. Soc., 79, 2975 (1957).
20. D. S. Breslow and N. R. Newburg, J. Am. Chem. Soc., 79, 5072 (1957).
21. H. N. Friedlander and K. Oita, Ind. Eng. Chem., 49, 1885 (1957).
22. J. K. Stille, Chem. Rev., in press.
23. G. Natta, Chim. e ind. (Milan), 38, 751 (1956).
24. G. Natta and P. Corradini, Makromoleculare Chem., 16, 77 (1955).
25. C. S. Marvel and J. R. Rogers, unpublished results.
26. A. W. Anderson and N. G. Merckling, U. S. Patent 2,721,189 (1955).
27. W. L. Truett, D. L. Johnson, and J. M. Robinson, Abstr. Am. Chem. Soc. Meeting, Atlantic City, N. J., 16-21 Sept., 15s (1956).
28. Chem. Eng. News., 33, 4518 (1955).
29. S. E. Horne, et al, Ind. Eng. Chem., 48, 784 (1956).
30. Goodrich-Gulf Chemicals, Inc., Belgian patent 543,292 (1955).
31. C. S. Marvel and G. W. Hartzell, unpublished results.
32. C. S. Marvel and J. K. Stille, J. Am. Chem. Soc., 80, 1740(1958).
33. G. Natta, Angew. Chem., 68, 393 (1956).
34. G. Natta, P. Pino, G. Mazzanti and P. Corradini, ibid.,67, 430 (1955).
35. G. Natta, Chim. e ind. (Milan), 37, 888 (1955).
36. F. Eirich and H. Mark, J. Colloid Sci., 11, 748 (1956).
37. R. Robinson, Chem. Age (London), 74, 997 (1956).
38. F. J. Welch, B. R. Thompson, F. E. Bailey, and S. Gates, Abstr. Am. Chem. Soc. Meeting, Atlantic City, N. J., 16-21 Sept., 13s (1956).
39. H. N. Friedlander and K. Oita, Ind. Eng. Chem., 49, 1885 (1957).
40. M. S. Kharasch, D. W. Lewis and W. B. Reynolds, J. Am. Chem. Soc., 65, 493, 498 (1943).
41. D. B. Ludlum, A. W. Anderson and C. E. Ashby, J. Am. Chem. Soc., 80, 1380 (1958).
42. G. Natta, I. Pasquon, and E. Giachetti, Angew. Chem., 69, 213 (1957).

43. J. C. McGowan and B. M. Ford, J. Chem. Soc., 1149 (1958).
44. H. Gilman, F. Schultze, J. Am. Chem. Soc., 47, 2002 (1925).
45. H. Gilman, J. Swiss, ibid., 62, 1847 (1940).

SUBSTITUTION AND MIGRATION IN THE AZULENE SERIES

Reported by James F. Dunphy May 8, 1958

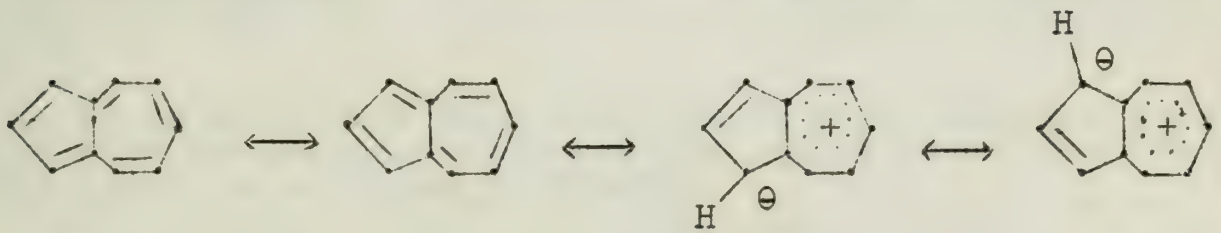
INTRODUCTION

Azulene (I) is the parent substance of a group of coloring matters obtained from certain essential oils by dehydrogenation. Though these materials were known for many years, it was not until 1936 that the structure (I) was proposed and proved by synthesis (1). Since then numerous synthetic methods have been developed and these are the subject of recent reviews (2,3). A recent M.I.T. seminar summarizes the synthetic aspect of azulene chemistry (4). The present seminar will be concerned with the reactions of azulene which involve substitution or migration on the azulene nucleus; syntheses of azulenes will not be discussed except where they bear on these subjects.

I

THEORETICAL CONSIDERATIONS

The question of the aromatic character of azulene cannot yet be considered settled. It has long been observed (10) that: 1) azulenes react vigorously with bromine and nitrosyl chloride, yielding no well-defined products; 2) oxidative decomposition occurs when azulene is treated with nitric acid or potassium permanganate; 3) azulene is readily hydrogenated in the presence of catalysts. Thus, Pommer, as recently as 1950, asserts that azulene has no aromatic properties and that it should be considered merely as a cyclic polyolefin (5). Measurements of the heats of combustion of substituted azulenes, and of their naphthalene isomers, indicate that azulene has a resonance energy of ca. 46 kcals/mole (6). Brown has calculated the energies required to polarize the azulene molecule in a manner appropriate for electrophilic, nucleophilic and radical substitution (7). He predicted that electrophilic substitution would occur at the 1-position, while nucleophiles and radicals would attack the 4-position. He pointed out that calculations of the electron density at the various positions led to the same predictions. On the basis of Brown's calculations, as well as measurements of the dipole moment of azulene (8) and of its remarkable basicity (9), it has been suggested that azulene is best represented as a resonance hybrid of two types of structures (II) (10). Anderson has invoked the 4n+2 rule to



IIA IIB IIC IID

account for the observed resonance stability of azulene, which has a ring of 10 π-electrons in the perimeter of the molecule. In the case of the structures C and D, it is postulated that stabilization is due to 6 π-electrons resonating among 7 π-orbitals. This concept had been advanced earlier to explain the unusual properties of tropone (11,12).

DIAZONIUM SUBSTITUTION

It has been shown that azulene readily adds a proton to form an azulenium ion. This acid-base reaction can be considered the simplest electrophilic substitution of azulene. However, a detailed discussion of this reaction is beyond the scope of this seminar; most of this work has been done by Plattner and Heilbronner of Zurich and leading references may be found in the bibliography (13,9).

The first studies of the electrophilic substitution of azulene were without issue, due to the fact that the methods employed were far too vigorous, and usually led to decomposition (14).

Coupling of diazonium salts with aromatic systems is one of the mildest of electrophilic reactions and it is therefore not surprising that it was the first to be studied in detail. Plattner (14) had stated that the 1,3,4,6, or 8-positions should be preferred, while Brown, as has been stated, claimed that the 1-position is by far the most susceptible to electrophilic attack. A detailed study of the behavior of various substituted bi- and polycyclic azulenes toward diazonium salts was undertaken (15). It was found at the outset that it was impossible to isolate the aminoazulenes formed by reductive cleavage of the resulting diazo compounds. With this avenue of attack apparently closed, Treibs undertook what he referred to as an "elimination experiment"; he reasoned that if coupling were possible only at specific positions of the azulene nucleus, then if one of those positions is open the coupling reaction will occur, but if all of the susceptible positions are occupied then no coupling will occur. Twenty three azulenes of known structure were treated with phenyldiazonium chloride. Those which produced an immediate color change were considered to have coupled with the reagent, while those which showed no color change were considered to have been unaffected by the reagent. A representative selection of the compounds used are gathered in Table I, with the results of this qualitative test.

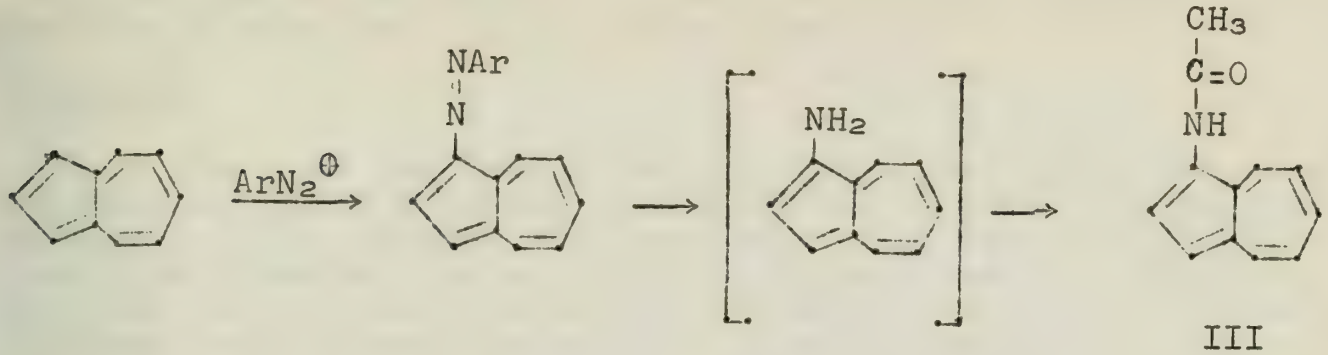
TABLE I

Positive	Negative
Azulene	1,3-dimethylazulene
1,4-dimethyl-7-isopropylazulene	1,3-dimethylazulene carboxylate
2,4-dimethyl-7-isopropylazulene	1,2,3-trimethylazulene
5,8-dimethylazulene	3-methyl-1,2-benzazulene
1,2-benzazulene	3-methyl-1,2-benzazulene

It is clear that those azulenes in which both the 1 and 3-positions are occupied do not couple, while those in which either or both positions are open, do couple.

When azulene is treated with a benzenediazonium salt under conditions similar to those described for the radical arylation of quinones (16), an azuleneazobenzene is formed rather than the expected phenylazulene (10). Reductive cleavage of the diazo compound followed by immediate acetylation of the unstable amine gave 48% of N-acetyl-1-azulylamine (III), thus establishing the position of attack of the benzenediazonium moiety as the 1-position. By this technique Anderson has succeeded in "trapping" the elusive aminoazulene, permitting precise chemical characterization of the product.

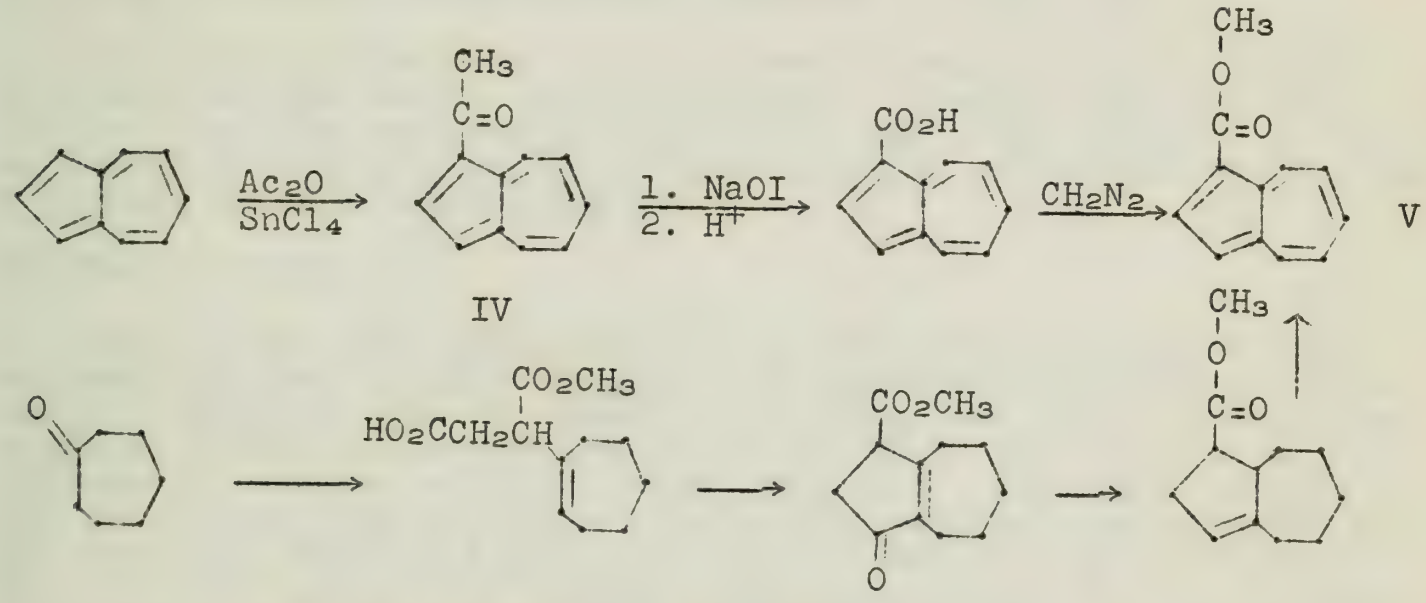
Because of the apparent 1-substitution it was supposed that an electrophilic reaction had occurred, but recent work indicates that the 1-position may be involved in radical reactions (28).



III

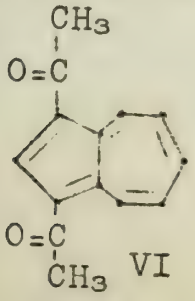
FRIEDEL-CRAFTS REACTION

The first unequivocal chemical evidence that azulene undergoes electrophilic substitution in the 1-position was obtained in 1953 by Anderson (10). When azulene is treated with a slight excess of stannic chloride in a large excess (22:1) of acetic anhydride, 57% of a slightly unstable lavender oil was obtained, plus 11% of a red crystalline material. The oil yielded stable derivatives with trinitrobenzene (TNB) and the common carbonyl reagents. Carbon-hydrogen analysis of these derivatives agreed with the values calculated for an acetylazulene (IV). The location of the acetyl group was shown by conversion to methyl azuloate (V). This was identical with methyl azuloate prepared by an independent unequivocal route from cycloheptanone (17).



IV V

When azulene is treated with aluminum chloride and a 2:1 excess of acetic anhydride there was obtained in good yield red needles which were identical with the red needles obtained as a side-product in the stannic chloride reaction. Analysis agreed with the values calculated for diacetylazulene and it was assumed to be the 1,3-isomer (VI). Acetylation of 1-acetylazulene under conditions similar to those used for acetylation of azulene gave none of the disubstituted product. However, acetylation of both azulene and 1-acetylazulene with acetyl chloride and stannic chloride in refluxing carbon tetrachloride gave 85% of the



VI

diacetylazulene in each case. Though the structure of the monoacetylazulene was now firmly established, it still remained to prove the structure of diacetylazulene. The structure VI was assigned as most probable for the reason that reaction of diacetylazulene with hypobromite gives the known 1,3-dibromoazulene (18). It had been observed that 1-acetylazulene reacts with hypochlorite in similar fashion to give the 1,3-dichloroazulene (10).

NITRATION

It has long been known that, upon treatment with nitric acid, azulene undergoes oxidative decomposition to yield yellow amorphous materials (19). Indeed, this was one of the reactions which for a long time obscured the recognition of the aromatic character of azulene. It has been found recently that nitro groups can be introduced into the azulene nucleus if sufficiently mild conditions are used. Of several procedures studied one has been found to be particularly effective: reaction of azulene with an equivalent of cupric nitrate in acetic anhydride gave 63% of a red crystalline mononitroazulene (10). It has been postulated (20) that nitrations carried out in this manner proceed by the intermediate acetyl nitrate

$$(CH_3CO)_2O + NO_3^- \longrightarrow CH_3CO_2NO_2 + CH_3CO_2^-$$

Reductive acetylation of nitroazulene with zinc dust and acetic acid gave 90% of N-acetyl-1-azulylamine (III). Beckmann rearrangement of the oxime of 1-acetylazulene resulted in the same product. By these reactions the orientation of azulene nitration has been established as attack at the 1-position. The same reaction has been carried out using tetranitromethane as nitrating agent; the yield of 1-nitroazulene from this reaction is 81% (18).

No dinitroazulene was obtained when cupric nitrate or tetranitromethane was used to nitrate azulene. However, the dinitroazulene could be prepared in fair yield from 1-nitroazulene by treatment with nitric acid in acetic anhydride for one minute at 0°C. and 5 minutes at room temperature (18).

PLATTNER's RULES

One of the most characteristic of the physical properties of azulenes is their absorption spectrum, particularly in the visible region. Plattner was the first to recognize the additivity of the spectral shifts in the visible range caused by alkyl groups on the different positions of the azulene ring (21). His correlations of the spectra of a large number of alkylated azulenes have become known as Plattner's Rules and have been indispensable in the identification of many natural and synthetic alkylazulenes. In their simplest form Plattner's Rules state that alkyl substituents in the odd-numbered positions of the azulene nucleus produce a bathochromic shift (i.e. to longer wavelengths), while those in even-numbered positions produce a hypsochromic shift (i.e. to shorter wavelengths). Plattner found that these effects were independent of the nature of

TABLE II

Average Shifts of Principal Peak Caused by Group at the 1(=3) Position

Group	$\Delta\lambda$ max.
$-COCH_3$	-43
$-CO_2CH_3$	-36
$-NO_2$	-40
$-NHCOCH_3$	+41

the alkyl substituent and were more pronounced if the group were on the 5-membered ring. Since the position of the maxima in the visible region is affected by changes in the solvent, careful attention should be given to the solvent by anyone who makes use of these correlations. The effect of substituents other than alkyl has been studied. In the accompanying tables are gathered data obtained by Anderson from a study of the various 1- and 1,3-substituted azulenes which he has prepared (18).

TABLE III

Absorption Maxima of 1,3-Disubstituted Azulenes

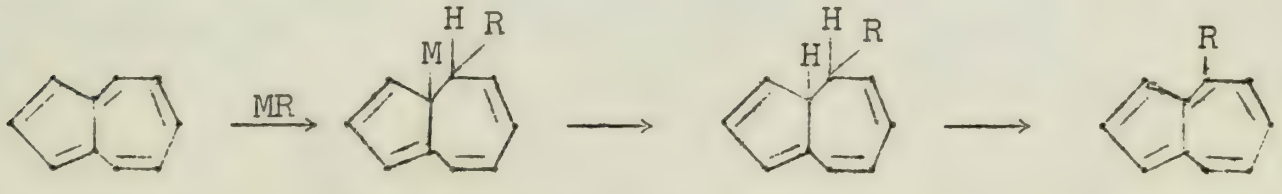
Groups	λ max.(calcd.)	λ max.(obs.)
$-COCH_3$, $-COCH_3$	492	498
$-CO_2CH_3$, $-CO_2CH_3$	506	511
$-COCH_3$, CO_2CH_3	499	498
$-CO_2CH_3$, $-NO_2$	502	503
$-CO_2CH_3$, $-NHCOCH_3$	583	583
$-COCH_3$, $-NHCOCH_3$	576	575
$-NHCOCH_3$, $-NHCOCH_3$	660	653
$-NO_2$, $-NO_2$	498	488

The calculated values were obtained by addition of the appropriate value in Table II to the observed value for azulene (λ max. 578).

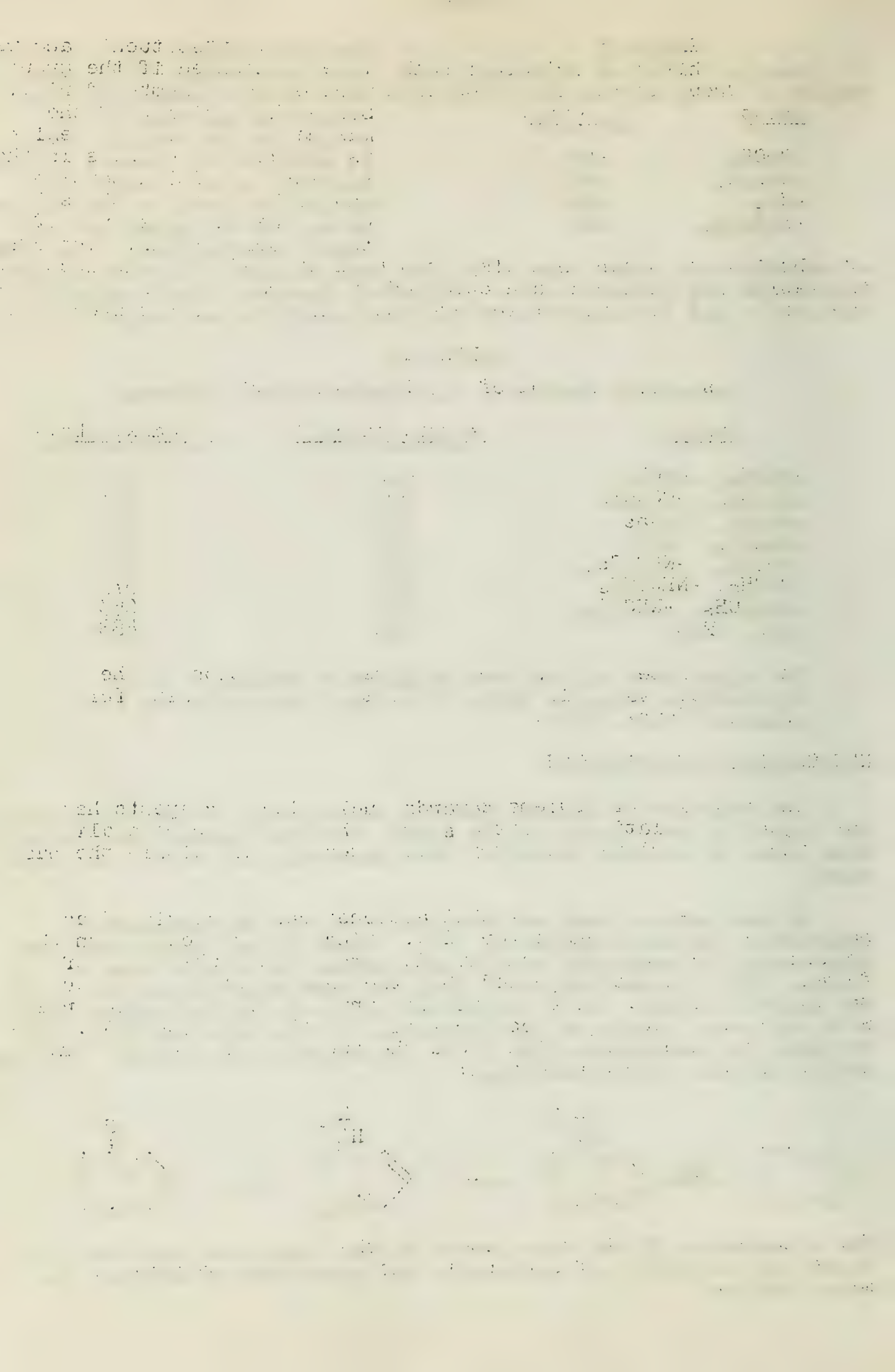
NUCLEOPHILIC SUBSTITUTION

The behavior of azulene towards nucleophilic reagents has been the object of relatively little study; the first papers dealing with this phase of azulene chemistry have appeared only within the past year.

It has been pointed out that azulenes can be considerd as possessing fulvenoid character (22). Since it had been shown that organometallic compounds readily add across the double bond of fulvene (23), it was suggested that the same reaction may occur in the azulene series. Metal alkyls and aryls do in fact react readily with azulenes, causing a decolorization of the solution (24). Hydrolysis and dehydrogenation yield the substituted azulene. The reaction has been formulated thus:

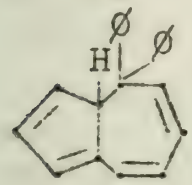


The orientation of the substituent in the 4-position has been confirmed by conversion of azulene to the known 4-methylazulene via methyllithium.



Alkali metal alkyls and aryls, as well as complexes of alkali alkyls and aluminum trialkyls are effective alkylating agents, but Grignard reagents, magnesium dialkyls and aluminum trialkyls are ineffective.

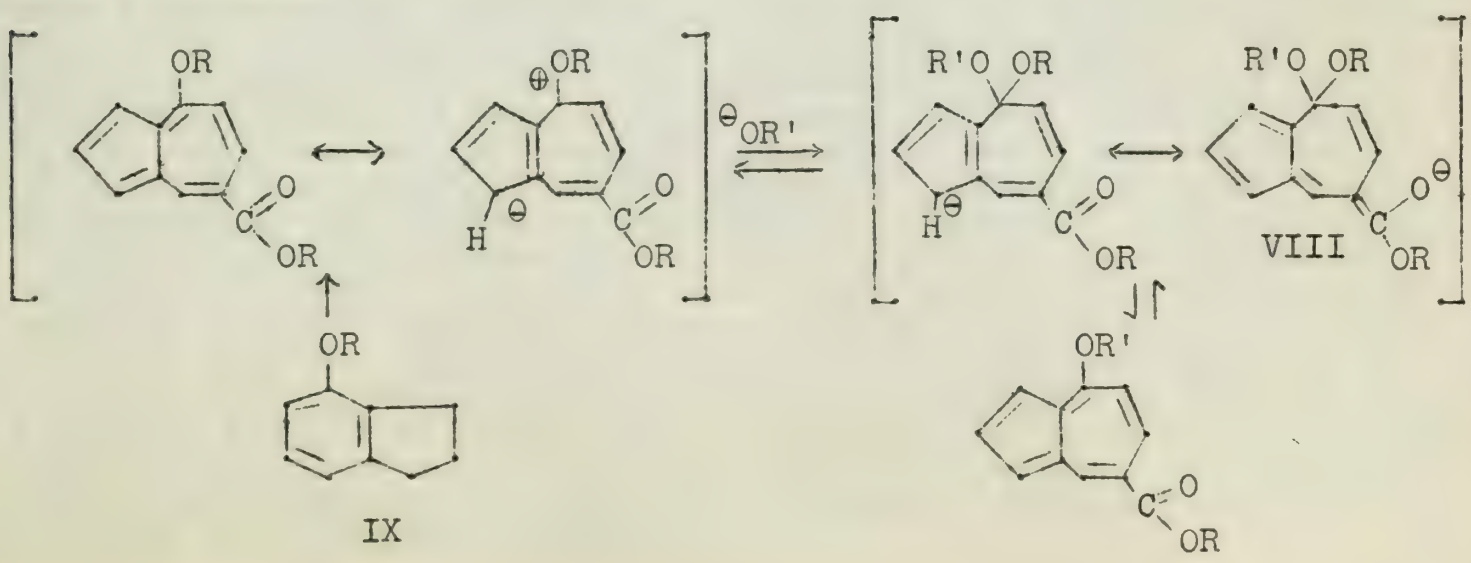
Azulenes which are already substituted in the 4-position lead to 4,8-disubstituted azulenes, but the latter do not react further. This preference for substitution of the anionic organic moiety at the 4- or 8-position is advanced as confirmation of the prediction of nucleophilic attack at the 4-position, as well as of the aromatic character of azulenes. Apparently, the failure of the reagent to attack other positions of the 7-membered ring is taken as evidence for the latter remark. When 4,8-diphenylazulene is treated with a mole of phenyllithium, the color of the solution is discharged, but hydrolysis and dehydrogenation lead to quantitative recovery of the starting material. A structure such as VII could not be dehydrogenated to an azulene.



VII

When 1-isopropylazulene is treated with methyllithium, hydrolyzed and dehydrogenated, an uncharacterized isopropylmethylazulene is obtained which, upon reaction with another mole of reagent yields vetivazulene. Since at no time did the temperature rise above that of boiling ether, this migration occurs under extremely mild conditions. The problem of at what stage of the reaction the migration occurs is being studied.

A nucleophilic substitution reaction has recently been shown to occur at the 4-position when ethyl 4-methoxyazulene-6-carboxylate is hydrolyzed in ethanolic KOH (25). An ether interchange reaction occurs and 4-ethoxy-6-azulene carboxylic acid is formed. Neither ethyl 5-methoxyazulene-6-carboxylate nor 4-methoxyazulene undergoes such a reaction. To account for the apparent necessity of the carbethoxy group in this reaction the authors have proposed a mechanism in which resonance structures such as VIII contribute to the stability of the intermediate. However, an inspection of this mechanism reveals that while a carbethoxy group at the 5- or 7-position might behave in this way, it is impossible to write such a structure for the 6-isomer. The ether interchange reactions were carried out on a compound which the authors had established as the 6-carboxylate by a study of the visible absorption spectra of the three esters obtained when 4-methoxyindane (IX) was treated with diazoacetic ester.



IX

VIII

Reaction of azulene with methoxide ion leads to degradation of the azulene nucleus. Sodamide reacts with azulene to give a red material whose solutions are stable for a few hours, but which deteriorates rapidly in the solid state. The visible spectrum of the freshly prepared solution shows a hypsochromic shift of 75 mu. This is consistent with 4- or 6-substitution; the former is likely but not certain (25). In this connection it should be pointed out that Anderson, while investigating an improved synthesis of azulene via 4-ketoöctahydroazulene (26), observed an extremely unstable red oil, which gave a color change with dilute ferric chloride solution and reacted with benzoyl chloride. He assumed that it was 4-hydroxyazulene. Thus it seems that placing electropositive groups such as -OH and $-NH_2$ on the 7-membered ring produces extremely unstable compounds.

Attempts to prepare alcohols from 3-formyl and 3-acetylguaiazulene by means of Grignard reagents or lithium aluminum hydride have failed (27). This may be due to attack of the azulene nucleus by these nucleophilic reagents, but no products were isolated.

RADICAL SUBSTITUTION

Anderson has recently published a preliminary communication in which he describes the reactions of azulene with several radical producing substances (28). He reports that only 1-substituted azulenes are isolated. This is in agreement with the work of Arnold (29), who obtained 1-phenylazulene by treating azulene with N-nitrosoacetanilide. On the basis of these results doubt may be cast on the ionic mechanism proposed for the reaction of azulene with benzenediazonium chloride (10).

MIGRATIONS ON THE AZULENE NUCLEUS

Migration of alkyl substituents from the 1- to the 2-position of azulenes has been observed from time to time (2). Further examples of this type of migration have been discovered recently and some insight has been gained into their nature and causes.

While attempting to prepare 1-phenylazulene from 1-phenylindane by dehydrogenation of the ring-expanded intermediate over palladium-charcoal, it was observed that considerable quantities of an isomeric phenylazulene was obtained (30). The two isomers differed in their adsorption on alumina and were easily separated chromatographically. An examination of the visible spectra of these materials indicated that 1-phenylazulene was formed as expected, but that partial migration of the phenyl group had occurred and that 2-phenylazulene was formed in small quantities. The spectrum of 1-phenylazulene was practically identical with that of 1-methylazulene, whereas the 2-isomer exhibited the pronounced hypsochromic shift characteristic of alkyl groups in even-numbered positions. The identity of the 1-phenylazulene was further established by independent synthesis from 8-phenylbicyclo[5.3.0.]decadiene, using sulfur as dehydrogenation catalyst at 200°C. Under these conditions migration does not occur. Evidence that the migration occurred during or after the dehydrogenation step (as opposed to rearrangement of some intermediate in the synthesis of the starting material) was obtained by heating authentic samples of pure 1- and 2-phenylazulene in an evacuated tube under a variety of conditions, extracting the residues with benzene and chromatographing the solutions obtained. Results of this experiment are recorded in Table IV:

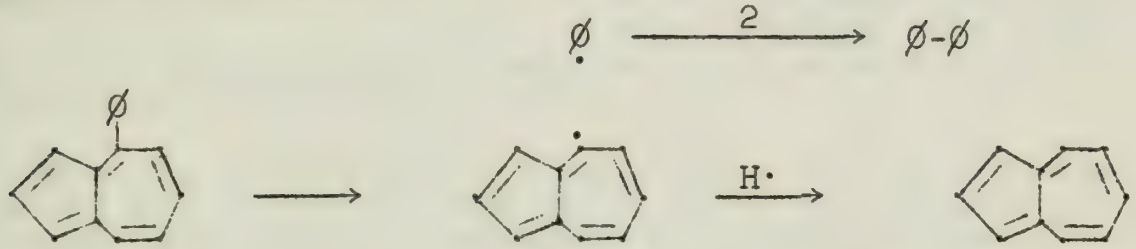
Table IV. Isomerization of Phenylazulenes

Isomer	Amount	Temp.°C	Time	1-phenyl	2-phenyl
2-phenyl	2 mg.	350	30 min.	*	1.8 mg.
1-phenyl	10 mg.	350	30 min.	*	*
1-phenyl	35 mg.	310-320	30 min.	9.0 mg.	2.2 mg.
1-phenyl	35 mg.	290-300	30 min.	31.0 mg.	---

*The isomer was visible on the column but was not present in sufficient quantity to work up.

It is clear that migration can occur in either direction, but the 1⟶ 2 shift predominates.

The only example of migration known to occur from one position of the 7-membered ring to another position on the same ring also involves the phenyl group (31). When 2-phenylbicyclo[5.3.0.]decene is dehydrogenated over sulfur, the expected 4-phenylazulene is obtained with no complications. When the dehydrogenation is carried out over palladium-charcoal at 390-400°C., followed by recovery of the azulene fraction with 85% H_3PO_4 and chromatographing of a petroleum ether solution, four different colored zones are observed. One of these zones was shown to contain azulene and biphenyl. The remaining three azulenes were characterized as 4-, 5-, and 6-phenylazulene. The 4- and 5-isomers were identical with samples prepared via S-dehydrogenation, but the 6-phenylazulene has not been established with certainty. The occurrence of azulene and biphenyl was quite unexpected and the following mechanism has been advanced to explain their formation:



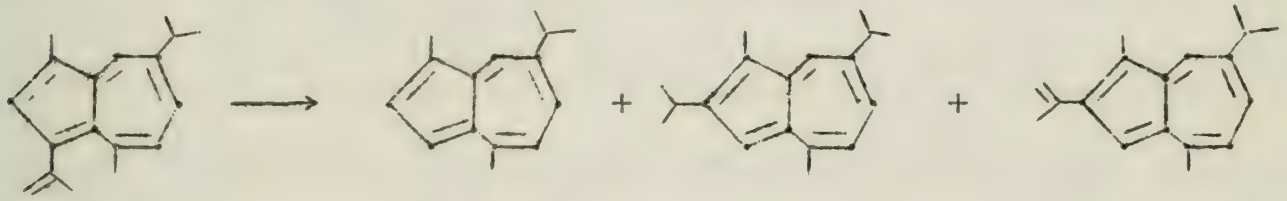
Two azulyl radicals could conceivably couple to form biazulyl. However, all attempts to prepare biazulyl from dihydrindene resulted in the formation of azulene, pointing to the instability of the biazulyl under these conditions (32). Pommer assumes that the azulyl radical abstracts a hydrogen atom from the palladium-charcoal catalyst. The proposed mechanism seems to be the only way to account for the formation of biphenyl, which is quite stable at the temperatures employed.

The behavior of the 3-phenylbicyclo[5.3.0.]decene under these conditions is in marked contrast to that just described for the 2-isomer. 5-phenylazulene is recovered exclusively. The explanation may lie in the fact that the 5-azulyl radical is much less stable than the 4-azulyl radical.

That steric hindrance may be a factor in azulene migrations has been suggested (31,33). A comparison of the UV spectra of the phenylazulenes lends support to this suggestion (31). When compared with the spectra of 2- and 5-phenylazulene (supposedly unhindered), the spectra of 1- and 4-phenylazulene exhibit a definite decrease of the molar extinction as well as a shift of the absorption

maxima to shorter wavelengths, both of which point to the possibility of steric inhibition of resonance, arising from deviations of the 1- and 4-phenyl groups from coplanarity (34).

The migration of an isopropyl group from the 3-position of guaiazulene has been observed (35). Guaiazulene (X) was treated with acetyl chloride and aluminum chloride; the 3-acetylguaiazulene obtained was converted to the 3-isopropenyl derivative (XI) via dehydration of the tertiary alcohol which resulted when the acetyl derivative was treated with CH_3MgI. Dehydrogenation of the 3-isopropenylguaiazulene over palladium-charcoal produced a mixture of azulenes which were separated via their TNB complexes. An examination of the visible spectra of these compounds confirmed their structures to be those indicated:



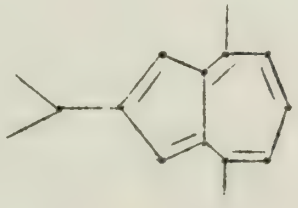
XI X XII XIII

Table V

Compound	λ max.(pet. ether)
guaiazulene(X)	604
2-isopropyl(XII)	588
2-isopropenyl(XIII)	582
3-isopropenyl(XI)	620

Thus, the new alkyl group of XI must be in an odd-numbered position while those of XII and XIII must be in an even-numbered position. Compound XIII was shown to be identical with the rearranged product obtained by dehydrogenation of the tertiary alcohol prepared by reacting α-kessyl ketone with isopropyl magnesium iodide. The migration described here is another example in which the reaction conditions are quite mild.

Herz has isolated vetivazulene from the dehydrogenation of 1-isopropyl-4,7-dimethylindane (36). However, the fact that the trimethyl analogue is dehydrogenated without migration, is in contrast to Pommer's steric hindrance picture.



Vetivazulene

BIBLIOGRAPHY

1. A. St. Pfau and Pl. A. Plattner, Helv. Chim. Acta, 19, 858 (1936).
2. M. Gordon, Chem. Revs., 50, 168 (1952).
3. W. Treibs, W. Kirchoff and W. Ziegenbein, Fortschr. chem. Forsch., 3, 334 (1955).
4. H. L. Burkard, M.I.T. Seminar, March 20, 1957.
5. H. Pommer, Angew. Chem., 62, 281 (1950).
6. E. Heilbronner and K. Wieland, Helv. Chim. Acta, 30, 947 (1947).
7. R. D. Brown, Trans. Faraday Soc., 44, 984 (1948).
8. G. W. Wheland and D. E. Mann, J. Chem. Phys., 17, 264 (1949).
9. Pl. A. Plattner, E. Heilbronner and S. Weber, Helv. Chim. Acta, 35, 1036 (1952).
10. A. G. Anderson, Jr., J. A. Nelson and J. J. Tazuma, J. Am. Chem. Soc., 75, 4980 (1953).
11. H. J. Dauben and H. J. Ringold, J. Am. Chem. Soc., 73, 876 (1951).
12. W. von E. Doering and F. L. Dietert, J. Am. Chem. Soc., 73, 876 (1951).
13. E. Heilbronner and M. Simonetta, Helv. Chim. Acta, 35, 1049 (1952).
14. Pl. A. Plattner, Angew. Chem., 62, 513 (1950).
15. W. Treibs and W. Ziegenbein, Ann., 586, 194 (1954).
16. D. E. Kvalnes, J. Am. Chem. Soc., 56, 2478 (1934).
17. A. G. Anderson, Jr. and J. J. Tazuma, J. Am. Chem. Soc., 75, 4979 (1953).
18. A. G. Anderson, Jr., R. Scotoni, Jr., E. J. Cowles and C. G. Fritz, J. Org. Chem., 22, 1193 (1957).
19. A. E. Sherndal, J. Am. Chem. Soc., 37, 167 (1915).
20. G. Bacharach, J. Am. Chem. Soc., 49, 1522 (1927).
21. Pl. A. Plattner, Helv. Chim. Acta, 24, 283E (1941).
22. K. Hafner and H. Weldes, Angew. Chem., 67, 302 (1955).
23. K. Ziegler and W. Schäfer, Ann., 511, 107 (1934).
24. K. Hafner and H. Weldes, Ann., 606, 90 (1957).
25. D. H. Reid, W. H. Stafford and J. P. Ward, J. Chem. Soc., 1100 (1958).
26. A. G. Anderson, Jr. and J. A. Nelson, J. Am. Chem. Soc., 73, 232 (1951).
27. D. H. Reid, W. H. Stafford and W. L. Stafford, J. Chem. Soc., 1118 (1958).
28. A. G. Anderson, Jr., and G. M-C. Chang, J. Org. Chem., 23, 151 (1958).
29. H. Arnold and K. Pahls, Ber., 89, 121 (1956).
30. Pl. A. Plattner, A. Furst, M. Gordon and K. Zimmerman, Helv. Chim. Acta, 33, 1910 (1950).
31. H. Pommer, Arch. Pharm., 291, 23 (1958).
32. W. Treibs and H. Froitsheim, Ann., 564, 43 (1949).
33. W. Herz and B. E. Cleare, J. Am. Chem. Soc., 77, 2318 (1955).
34. A. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy in Organic Chemistry", Edward Arnold Ltd., London, 1954, p. 232.
35. T. Ukita, H. Watanabe and M. Miyazaki, J. Am. Chem. Soc., 76, 4584 (1954).
36. W. Herz, J. Am. Chem. Soc., 75, 73 (1953).

ANOMALOUS REACTIONS OF ARYLMETHYL GRIGNARD REAGENTS

Reported by W. C. Rife May 12, 1958

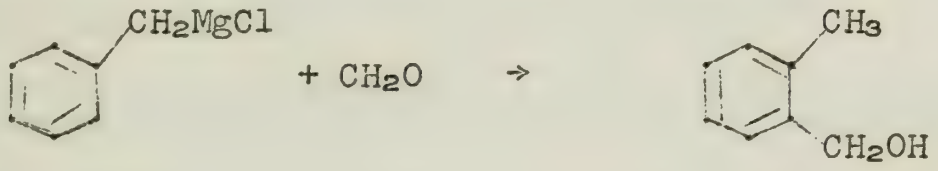
INTRODUCTION

Because of their utility, increased by the availability of chloromethylation products, a review of the reactions of arylmethyl Grignard reagents in which unexpected substitution occurs seems desirable. In addition, the use of these unusual reactions as synthetic steps has shown some promise, although the cases characterized by high yields have been few. These reactions have been utilized in studies on allylic Grignard reagents and in investigations on aromatic character; they have also contributed to an understanding of similar reactions of arylmethyllithium compounds.

GENERAL CONSIDERATIONS

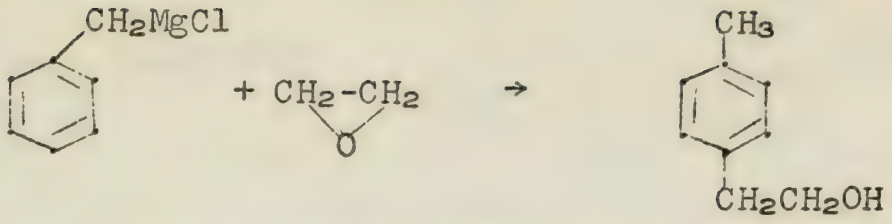
(Note: In the following equations indicating Grignard reactions, two steps have been omitted for present purposes and should be assumed present in each case. These are: (1) the formation of the Grignard reagent from the corresponding halide and (2) the hydrolysis of the carbonyl-halomagnesium complex to yield product.)

Since Tiffeneau and Delange first discovered the formation of o-tolylcarbinol (I) from benzylmagnesium chloride and formaldehyde (1) many similar reactions have been cited.



(I)

Benzylmagnesium halides have been shown to react in the anomalous manner with formaldehyde (1,9,11,12,17,23), ethylene oxide (4,8,9), chloromethyl ethers (7,9), acetyl chloride (8,9,17), benzoyl chloride (9), methyl chloroformate (9), ethyl chloroformate (8,9), ethyl formate (8,9), acetic anhydride (9), and chloroacetic anhydride (9), yielding o-substituted toluene derivatives; several of these reagents yielded the corresponding p-compounds as well. Other Grignard reagents which have been shown to give anomalous substitution products have been derived from o-methylbenzyl bromide (15), m-methylbenzyl bromide (18), p-methylbenzyl bromide (15), o-chlorobenzyl chloride (9), 2,6-dichlorobenzyl chloride (9,17), α-naphthylmethyl chloride (4,6), 3-furylymethyl chloride (20), 2-thenylmethyl chloride (21,22), 3-thenylmethyl bromide (16), 2-thianaphthenylmethyl chloride (25), and 3-thianaphthylmethyl chloride (26). The products of these anomalous reactions are commonly compounds in which substitution has taken place o- to the point of attachment of the aryl group to the methyl Grignard segment. In some reactions, however, p-substitution has been observed, and in at least one reaction the substitution is exclusively p- (4,8).



In most, but not all reactions some of the normal product is also found to be present. Di-substitution (normal and o-) has been reported also, and will be discussed later.

The usual Grignard procedure has been used invariably in the preparation of these compounds, except that in some reactions reverse addition (i.e., addition of the Grignard reagent to the carbonyl compound) has been found to favor the abnormal product. Identification of the products, where these are not known compounds, has usually rested on molecular weight determination, elemental analysis, and permanganate oxidation; a carboxyl group appears at each point of substitution in the oxidized product, revealing the site of reaction.

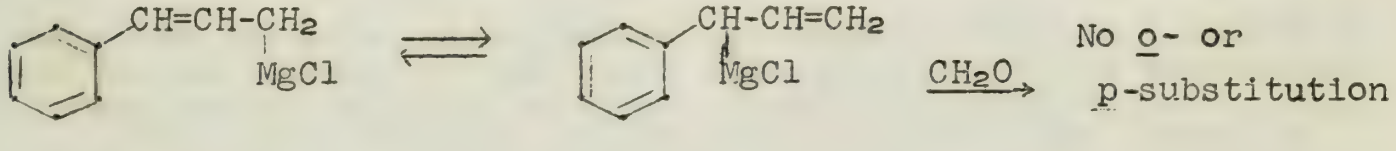
For example, the product of the reaction performed by Tiffeneau and Delange, o-tolylcarbinol, is oxidized by this procedure to phthalic acid, whereas, if normal substitution had occurred, only benzoic acid would be expected.

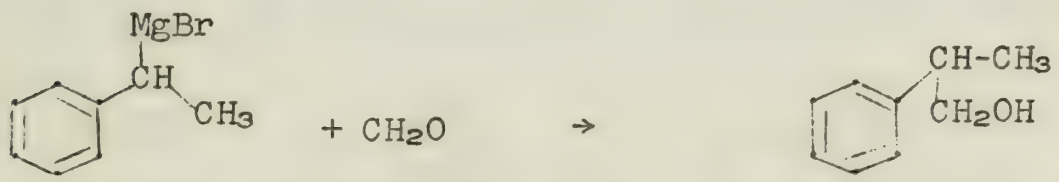
Independent syntheses of reaction products has been utilized also and in recent work, spectroscopic evidence has been cited.

STRUCTURAL REQUIREMENTS OF THE GRIGNARD REAGENT

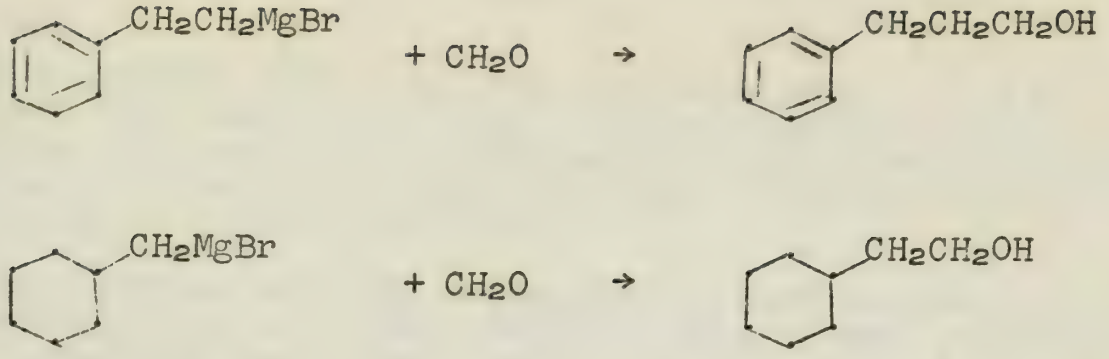
The structural requirements of the Grignard reagent which will allow o- or p-substitution are observed to be the following:

The halomagnesium group must be attached to a methylene carbon atom. The following Grignard reagents do not react under conditions either of normal or reverse addition (3,15).





The methylene carbon atom must be attached directly to an aromatic nucleus. (Allylic Grignard reagents, such as cinnamylmagnesium chloride, shown above, also give unexpected substitution but these will not be considered further here). The following reactions illustrate these limitations (8).



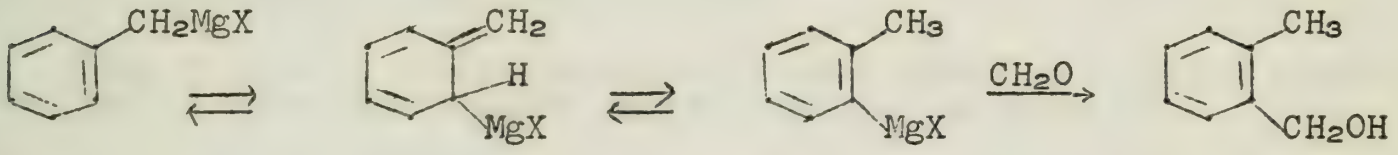
In all cases substitution occurs at o- or p-positions which are not already substituted in the Grignard reagent.

Some limitations may also be placed on the compound with which the Grignard reagent reacts. With two exceptions the attack is at a carbon-oxygen double bond.

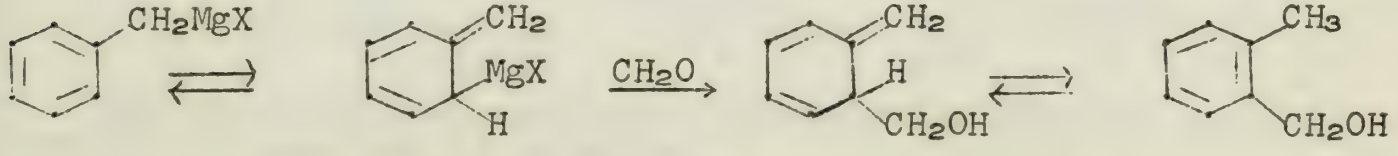
With benzyl, substituted benzyl, and α-naphthylmethylmagnesium halides, ketones and esters of acids other than formic do not react in the abnormal manner. The reactive compounds fall under the following headings: diethyl sulfate (28), carbon dioxide (18), acid chlorides, acid anhydrides, derivatives of formaldehyde (including $R\text{-}OCH_2\text{-}X$), formic esters, and aromatic and aliphatic aldehydes (9,10, 13). Grignard reagents in which the aryl group is heterocyclic add ethyl benzoate to this list (25).

MECHANISM

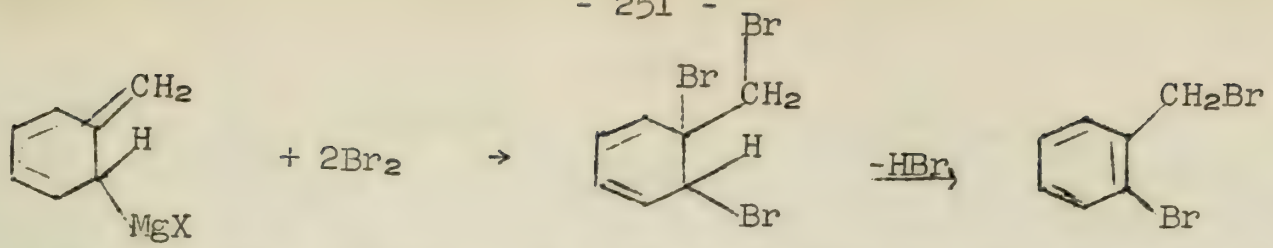
Gilman first suggested a rearrangement of the Grignard reagent prior to reaction, a scheme involving a double 1,3-shift (3).



If this were the case, o-tolylmagnesium bromide would be expected to yield, by the reversal of the above equilibria, products corresponding to the benzyl Grignard reagent. Despite repeated efforts, none has ever been found (9,17). Gilman later modified this scheme to one in which the second 1,3-shift was postponed until the hydrolysis of the product-magnesium halide complex (8).

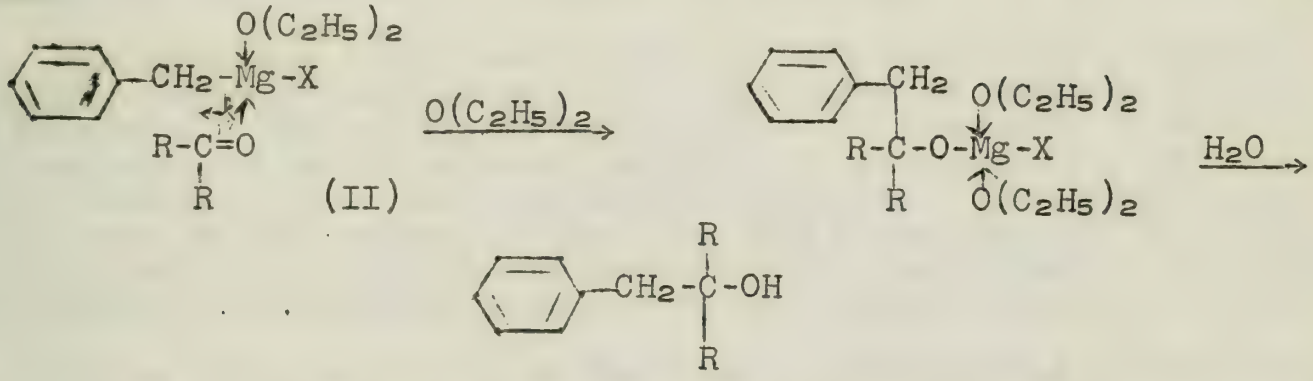


The rearranged form of the Grignard reagent should be susceptible to bromination to yield o-bromobenzyl bromide:



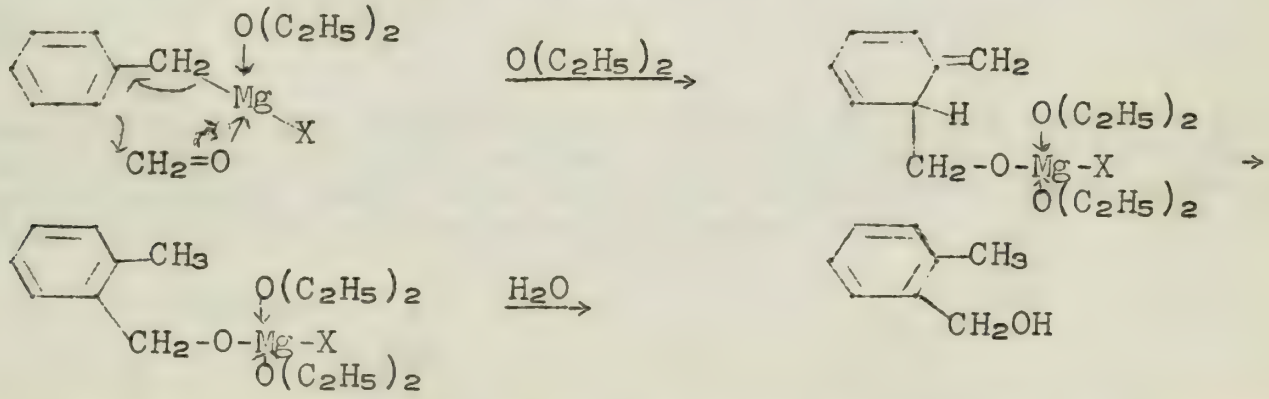
Only benzyl bromide, resulting from the unrearranged form of the Grignard reagent, has been found (8,9). Gilman suggested in this respect, however, that fast reaction of bromine with the normal form of the benzylmagnesium bromide and rapid shifting of all the above equilibria to the left would account for this..

The most widely accepted mechanism has been suggested by Johnson (13,29) and modified by Siegel (14,23). This scheme has been tied in with the "transient chelation" theory. The normal course of reaction of benzyl Grignard reagents followed, for example, when ketones are used as the carbonyl compound, is represented in the following equations.



An unshared electron pair of the carbonyl oxygen atom coordinates with the magnesium of the Grignard reagent to yield complex II. This coordination promotes the formation of increased negative charge on the methylene group at the expense of the carbon-magnesium bond, and increases the polarity of the carbonyl group. Bonding then occurs between the electron-deficient carbonyl carbon atom and the electron-rich methylene carbon atom. The magnesium atom bonds to the carbonyl oxygen atom and also coordinates with an additional molecule of solvent. Hydrolysis yields the product.

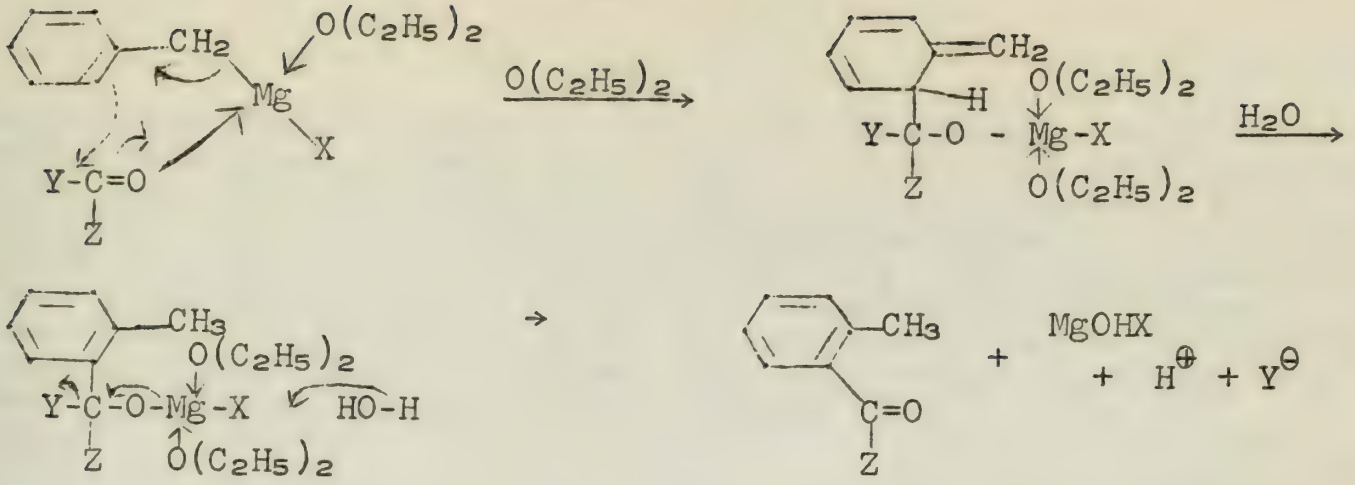
The formation of the abnormal product when the Grignard reagent is treated with formaldehyde may be pictured as follows:



The mechanism when acid chlorides, acid anhydrides, and chloroformates are used may be shown as:

Z is alkyl, aryl, or alkoxide

Y is halogen or RCO_2^-

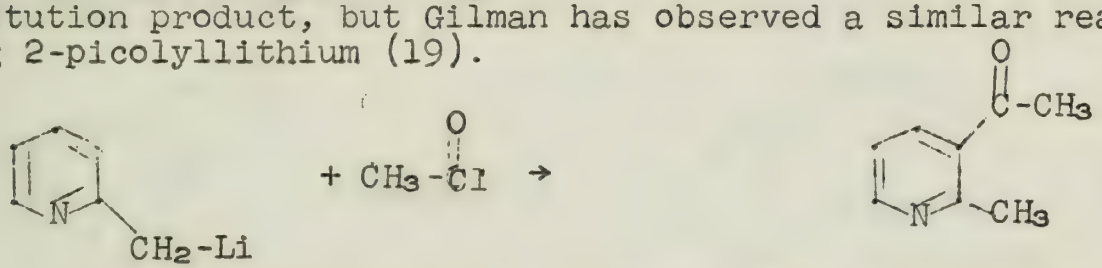


The anomalous reactions involving chloromethyl ethers and carbon dioxide may be treated by a suitable modification of the above schemes.

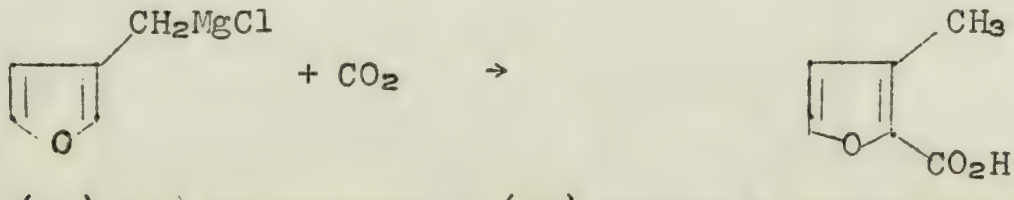
The empirical requirements for certain structural features in the Grignard reagent noted above may be discussed in relation to this type of mechanism. The effect of substitution on the carbon atom to which the magnesium atom is attached would be to increase the intrinsic negative charge at this point by hyperconjugation. This might cause attraction of the carbonyl carbon to this site prior to reaction, favoring formation of the normal product. The requirements for direct attachment of the methyl Grignard to an aromatic ring are obvious.

Since the aromaticity of the ring is interrupted in the course of the abnormal reaction, the abnormal product should be favored by rings having low resonance energy. This has been verified by Johnson, who has shown that the following order corresponds both to increasing resonance energy of the ring and to decreasing tendency of the methyl Grignard reagent to undergo o-substitution: (22) 3-furfuryl, 2-thenyl, benzyl, 2-picolyl.

Picolyl Grignard reagents, in fact, do not give the abnormal substitution product, but Gilman has observed a similar reaction involving 2-picolyllithium (19).

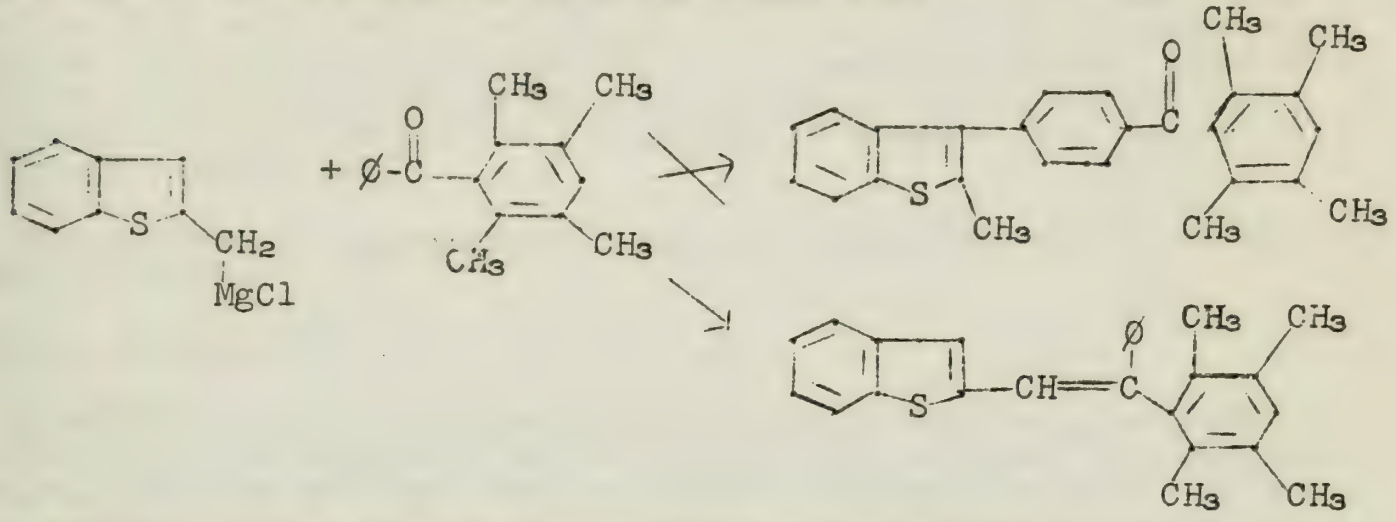


According to the above series, furfuryl Grignard reagents are the most reactive. In this respect it is interesting to note that the following reaction, which does not occur at all with benzylmagnesium chloride, yields 90% of the abnormal product (20).



Thenyl- (11) and thianaphthyl- (25) methyl Grignard reagents have been investigated by Gaertner and are found to give unusually good yields of the abnormal product. The Grignard reagent from 2-chloromethylthianaphthene is so favorable to abnormal substitution that the only carbonyl compound with which normal reaction has been shown to occur is benzoyldurene. This reaction is of interest in a second respect.

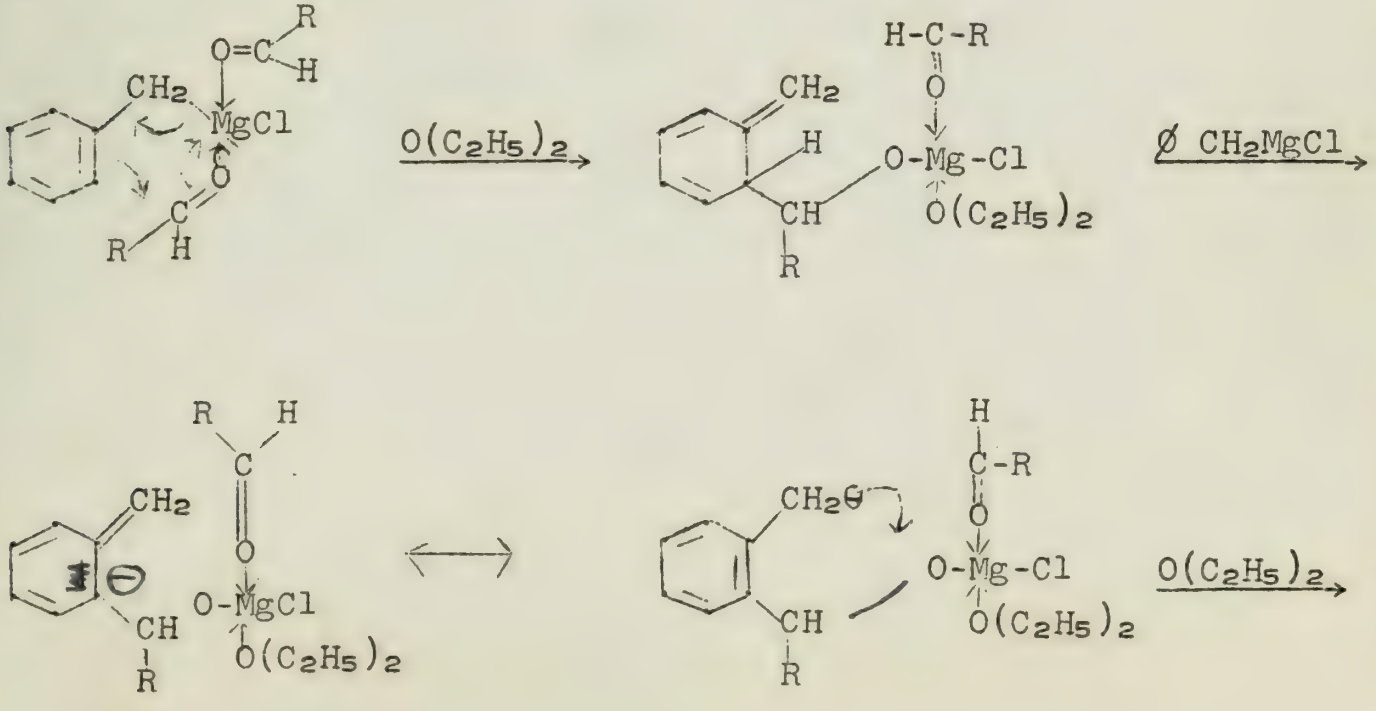
Benzoyldurene has been shown to react with benzylmagnesium chloride to yield only p-benzylphenyl duryl ketone, the product resulting from 1,6-addition. This reaction course was attributed to steric hindrance (30). The reaction with 2-thianaphthylmethylmagnesium chloride would be expected, on this basis, to lead to p-3-(2-methylthianaphthyl)-phenyl duryl ketone (III), the product corresponding to abnormal 1,6-addition. The sole product of the reaction proved to be 1-phenyl-1-duryl-2-(2-thianaphthyl)ethylene (IV), the product resulting from normal 1,2-addition followed by dehydration (25).

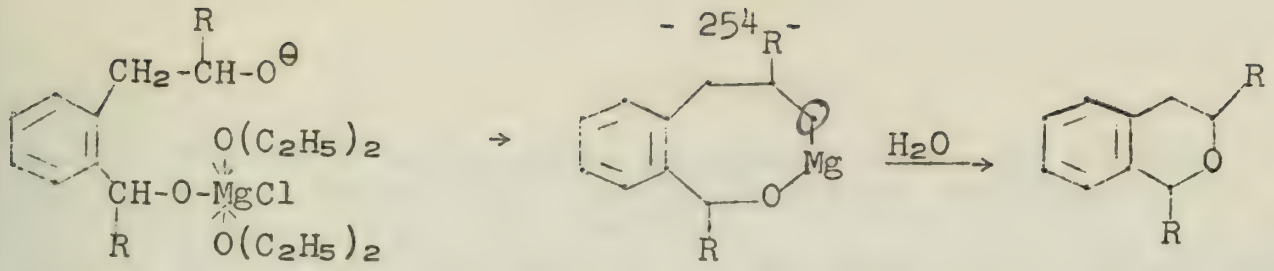


The Grignard reagent from 3-chloromethylthianaphthene reacts similarly (26).

DI-ADDITION REACTIONS

With aldehydes other than formaldehyde, di-addition products may be obtained. Increasing the proportion of the aldehyde favors these abnormal products. These facts have led Siegel to propose the following mechanism (14,23).



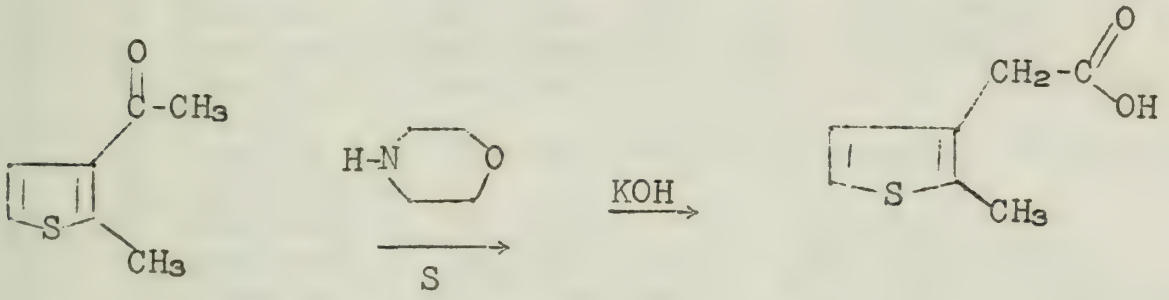


It is proposed in support of this mechanism that when the magnesium is coordinated by two carbonyl oxygen atoms there is an increased ease of formation of a relatively free benzyl carbanion, which can more readily yield the resonance form bearing the o-negative charge. Reactions utilizing tritium-substituted Grignard reagents have supported the above step in which the active o-hydrogen is removed by a second mole of Grignard reagent (27).

The observed p-rearrangements have not been treated in any of the mechanistic schemes.

SYNTHETIC APPLICATIONS

In addition to those cases in which the product of the abnormal reaction or its permanganate oxidation product is itself the desired compound, some use has been made of these reactions in synthetic work. Newman has used the reaction of Tiffeneau and Delange in a step in the synthesis of 4,5-dimethylchrysene (11), and Gaertner has utilized an abnormal substitution product in the Willgerodt-Kindler reaction to yield 3-(2-methylthenyl) acetic acid (21).



BIBLIOGRAPHY

1. M. Tiffeneau and R. Delange, Compt. rend. 137, 573(1903)
2. A. Garcia-Banus and L. Medrano, Anales soc. espan. fis. quim. 21, 436(1923). C.A. 18, 2144(1924)
3. H. Gilman and S.A. Harris, J. Am. Chem. Soc., 49, 1825(1927)
4. H. Gilman, J.E. Kirby, R. Fothergill, and S.A. Harris, Proc. Iowa Acad. Sci. 34, 221(1927). C.A. 22, 4504(1928)
5. A. Garcia-Banus, Anales soc. espan. fis. quim. 26, 372(1928). C.A. 23, 2178(1929)
6. H. Gilman and J.E. Kirby, J. Am. Chem. Soc., 51, 3475(1929)
7. A.C. Bottomley, A. Lapworth, and A. Walton, J. Chem. Soc., 2215(1930)
8. H. Gilman and J.E. Kirby, J. Am. Chem. Soc., 54, 345(1932)
9. P.R. Austin and J.R. Johnson, J. Am. Chem. Soc., 54, 647(1932)
10. J.R. Johnson, J. Am. Chem. Soc., 55, 3029(1938)
11. M.S. Newman, J. Am. Chem. Soc., 62, 2295(1940)
12. F.C. Whitmore and T.K. Sloat, J. Am. Chem. Soc., 64, 2968(1942)
13. J.R. Johnson in Gilman "Organic Chemistry", Wiley, 2nd ed., 1943, Vol. II, p. 1879
14. W.G. Young and S. Siegel, J. Am. Chem. Soc., 66, 354(1944)
15. M. Mousseron and N. Du, Bull. soc. chim. (5) 15, 91(1948)
16. E. Campaigne and W.M. LeSeur, J. Am. Chem. Soc., 70, 1555(1948)
17. G.W. Wheland, "Advanced Organic Chemistry", John Wiley and Sons, Inc., New York. 2nd Edition, Copyright 1949, p. 543
18. C. Moser and H.W. Sause, J. Org. Chem., 15, 631(1950)
19. H. Gilman, Rec. trav. chim. 69, 428(1950)
20. E. Sherman and E.D. Amstutz, J. Am. Chem. Soc. 72, 2195(1950)
21. R. Gaertner, J.Am. Chem. Soc. 72, 4326(1950)
22. R. Gaertner, J.Am. Chem. Soc. 73, 3934(1951)
23. S. Siegel, M. Boyer and R.R. Jay, J. Am. Chem. Soc., 73, 3237(1951)
24. S. Siegel, S.K. Coburn, and D.R. Levering, J. Am. Chem. Soc., 73, 3163(1951)
25. R. Gaertner, J. Am. Chem. Soc., 74, 766(1952)
26. R. Gaertner, J. Am. Chem. Soc., 74, 2185(1952)
27. M.S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, Inc, New York, N.Y., 1954, p. 1133
28. R.L. Shriner and J.G. Burtle, J. Am. Chem. Soc., 69, 2059(1947)
29. J.R. Johnson, J. Am. Chem. Soc., 55, 3029(1933)
39. R.C. Fuson and B.C. McKusick, J. Am. Chem. Soc., 65, 60(1943)

ACRIDIZINIUM ION SALTS

Reported by R. L. Harris May 15, 1958

INTRODUCTION:

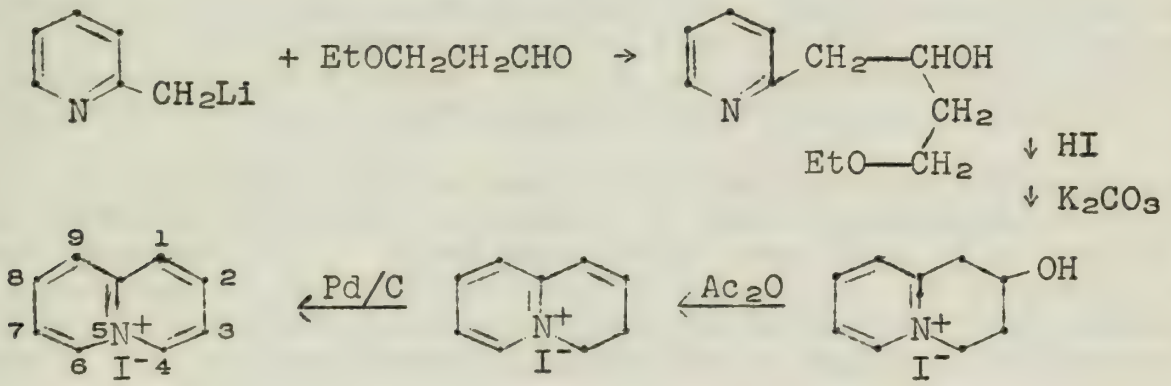
This seminar will include the structure, synthesis, and reactions of the simple acridizinium ions. The chemistry of quinolizinium ions will be discussed only to allow comparison with the acridizinium system; the chemistry of the complex alkaloids containing the acridizinium nucleus will not be covered.

The acridizinium ion (I), or benzo[b]quinolizinium ion, represents the nitrogen analog of anthracene in which the nitrogen atom occurs at a bridgehead position. The synthesis of the first simple acridizinium ion was reported by Bradsher and Beavers (1) in 1954. This nucleus previously had been known to occur in certain alkaloids, though not usually as the fully aromatic system. Examples of such alkaloids are: the Berberine alkaloids (2,3), sempervirine (4,5,6), coralydin (7), and cryptopleurine (8). Little was known regarding the chemistry of this ion previous to this time, all available information having been gained from the study of the alkaloids containing this nucleus.

The acridizinium ion is the linear benzolog of the quinolizinium ion (II), synthesis of which was reported by Boekelheide and Gall (9) in 1954. The quinolizinium nucleus is contained in a number of alkaloids in addition to those listed above (9,10,11).

SYNTHESIS AND STRUCTURE:

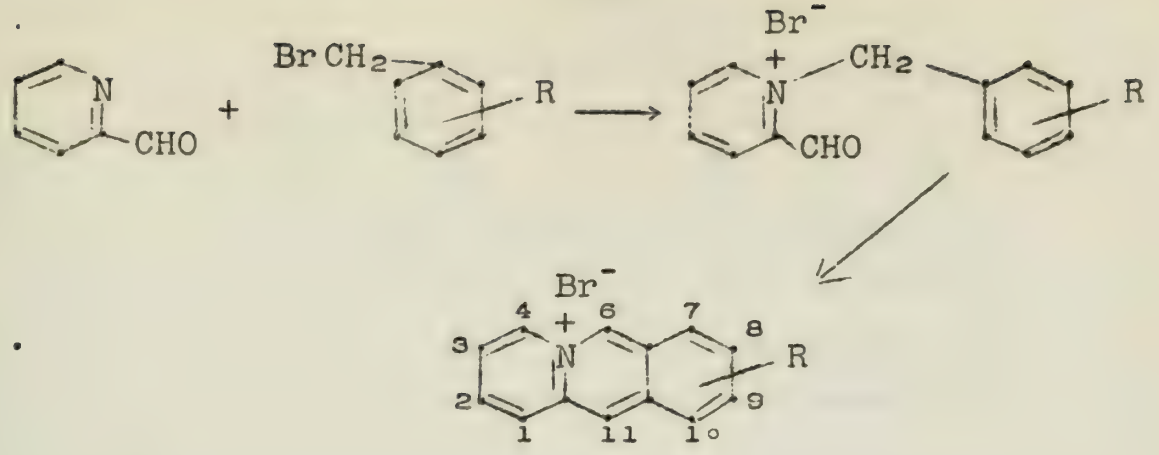
Since the method of synthesis of the acridizinium derivatives is not an extension of the synthesis of quinolizinium compounds, both methods will be illustrated. The quinolizinium synthesis of Boekelheide and Gall is shown first, being the simpler system.



II

An extension of this synthesis has been used by Richards and Stevens to prepare substituted quinolizinium derivatives (12).

The method of Bradsher and co-workers is that of cyclodehydration, which had been employed previously for various syntheses of many compounds, especially phenathrene derivatives (13). The general outline is as follows:



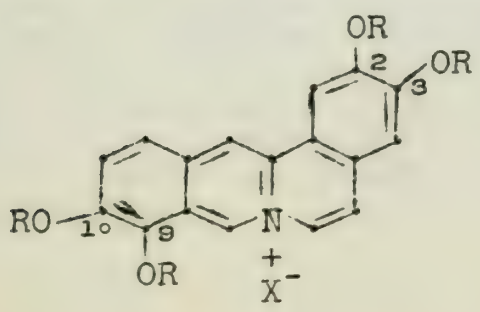
I

The general method of synthesis involves treatment of pyridine-2-aldehyde with the appropriate benzyl halide, this mixture being allowed to stand at room temperature for periods up to three weeks until quaternization occurs. The product at this point usually resembles a dark glass. The crude material is then heated under reflux in 48-percent hydrobromic acid and in an atmosphere of nitrogen for varying periods of time to effect cyclization. The reaction mixture is then evaporated under reduced pressure; a solution of the product in hot water is decolorized, and the salt is crystallized in an ice bath. Yields range from 37 to 75 percent.

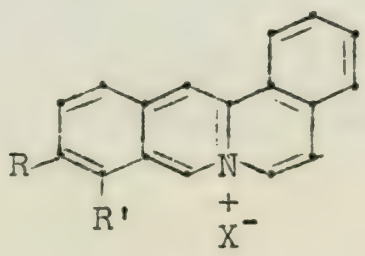
The compounds produced are highly colored and generally fluorescent in ethanol solution. The ultraviolet spectrum indicates a high degree of conjugation; the absorption extends further into the visible region than that of anthracene.

By this general method, a number of substituted acridizinium ions have been synthesized. These are: 7-methylacridzinium bromide (14), 9-methylacridizinium bromide (14), benzo[h]acridizinium bromide (15), benzo[j]acridizinium bromide (15), dibenzo[h,j]acridizinium bromide (15), 8-methoxyacridiznium chloride (16), 8-hydroxyacridizinium bromide (16), 7,8-dimethoxyacridizinium perchlorate (16), 8,9-methylenedioxyacridizinium bromide (16), and 7,8-methylenedioxyacridizinium bromide (16).

In addition, by the use of 1-isoquinoline aldehyde rather than the pyridine aldehyde, a number of benzo[a]acridizinium ions had been prepared (2). These compounds were made in an effort to relate them to the protoberberine alkaloids. The general structure (III) of these alkaloids is illustrated below. The table illustrates the various benzo[a]acridizinium salts (IV) prepared (2):



III



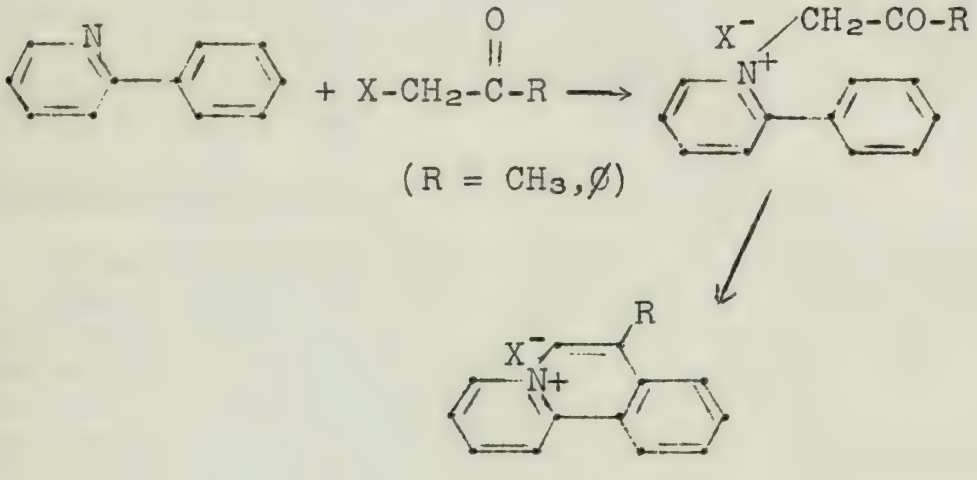
IV

TABLE I

Benzo[a]acridizinium Salts (IV)

R	R'	R	R'
H	H	CH_3O	CH_3O
CH_3O	H	$-O-CH_2-O-$	

It might also be mentioned at this point that a similar synthesis illustrated below makes possible the preparation of benzo[a]quinolizinium salts (V), which are closely related to the benzo[b]quinolizinium or acridizinium salts (17,18).



V

In this synthesis, the carbonyl group involved in cyclization is part of the halide used in quaternization rather than the heterocyclic compound.

Generally, the synthesis of the acridizinium salts involves more strenuous conditions than those necessary for the analogous carbocyclic compounds, due to the inactivating effect of the nitrogen in the ring during the cyclization step of the synthesis. It was necessary in one instance to convert from the iodide salt to the chloride, since the iodide was oxidized to iodine under the vigorous reaction conditions (17). It was also found that steric factors have some influence, since it was not found possible to cyclize 1-phenyl-2-acetonylisoquinolinium bromide or N-acetonyl-6-phenylanthridinium bromide even by the use of concentrated sulfuric acid (15). This was believed to be caused by the interference of the hydrogen atoms attached to the two ortho-positions of the phenyl group with that at the 8-position of the isoquinoline ring, which would impede the attainment of the coplanarity necessary for cyclization.

Presence of alkoxyl groups ortho or para to the position at which cyclization occurs was found to facilitate the ring closure. These effects were noted during the synthesis of the methoxy acridizinium salts. Cyclization was realized in high yield with these salts in as little as fifteen minutes, as compared with 20 to 50 hours with alkyl substituted compounds (16).

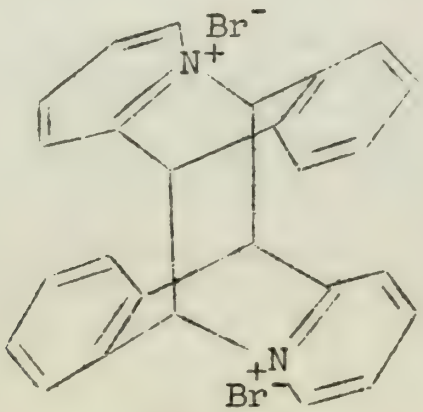
One example of ether cleavage was observed in synthesis of the methoxy acridizinium salts. This occurred only with a monomethoxybenzyl halide, while dimethoxy- and methylenedioxybenzyl halides underwent reaction in the normal manner with hydrobromic acid without ether cleavage. By the use of hydrochloric acid as the agent, cyclization without cleavage could be obtained. Again, treatment of the monomethoxyacridizinium salt with hydrobromic acid after formation by the use of hydrochloric acid resulted in ether cleavage, which occurred in three minutes.

The structure of the acridizinium salts has been shown in two ways. Acridizinium bromide produces phthalic acid when oxidized with potassium permanganate (14). In catalytic hydrogenation four moles of hydrogen were absorbed, to give the hydrobromide of benzo[c] azabicyclo[4.4.0]decane, the picrate of which was compared with an authentic sample (19).

PHOTODIMERIZATION OF ACRIDIZINIUM BROMIDE:

Since the acridizinium salts are nitrogen analogs of the anthracene system, it might be expected that certain types of reactions might occur with both compounds. This analogy cannot be carried far, of course, since the presence of the heterocyclic nitrogen atom has a considerable influence on the properties of the compounds. It has been found, however, that acridizinium bromide will indeed undergo a photodimerization reaction similar to that which takes place with anthracene (20).

When acridizinium bromide monohydrate was exposed to irradiation by sunlight or from a sun lamp, it was converted to a higher melting, less soluble compound (VI) lacking the yellow color or fluorescence characteristic of the starting material. The ultraviolet spectrum of the irradiated product indicated that the conjugation characteristic of the acridizinium system was no longer present. Photooxidation was ruled out since there was no increase in weight during irradiation, and analysis indicated that the product had the same elemental composition as the starting material.



VI

The product was shown to be a salt and, when heated to 100° with 6 N nitric acid, was converted to the nitrate salt. Catalytic reduction of the irradiated products with platinum oxide produced a salt of benzo[c]azabicyclo[4.4.0]decane, mentioned earlier in the abstract as the reduction product obtained from acridizinium bromide under similar conditions.

Since anthracene derivatives undergo photodimerization under conditions similar to the above (21), it was thought probable that an analogous reaction had taken place with the acridizinium salt. The photodimerization of anthracene is known to be reversible in solution, and a similar effect was noted for the acridizinium product. After standing for ten days, an ethanol solution of the irradiated product showed a faint fluorescence, and when subjected to spectroscopic examination, was found to exhibit absorption characteristic of the acridizinium ion, though of much lower intensity due to the lower concentration. It was then found that refluxing the irradiation product (VI) for eighteen hours in 95-percent ethanol produced acridizinium bromide in 82-percent yield (20). The crystalline irradiation product underwent no change when heated for 24 hours at 75 degrees. Boiling point elevation measurements in absolute ethanol also indicated that the product had a molecular weight of twice that of acridizinium bromide. An increase in boiling point during the measurements indicated once again that dissociation of the dimer was taking place.

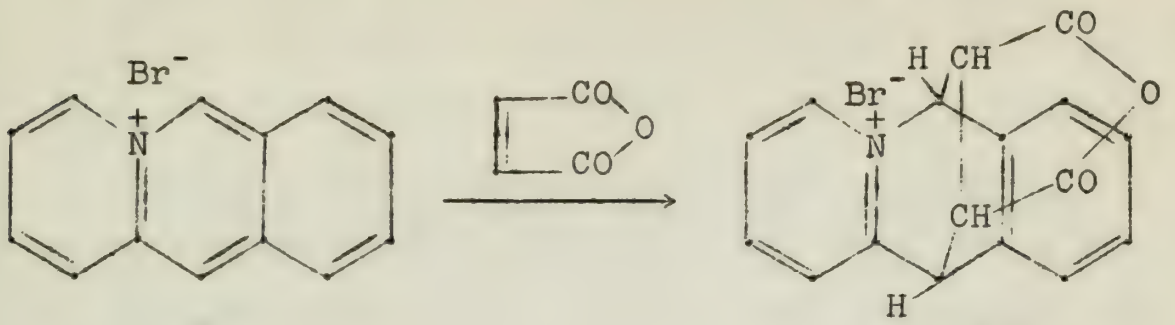
Since the acridizinium ion is unsymmetrical, several isomeric forms of the meso-connected ion are possible. Structure VI was believed to be the most likely in that it permitted maximum separation of like charges. It is possible that an X-ray crystallographic analysis of the dimer will become available which should indicate more about the structure of the compound.

DIELS-ALDER REACTIONS OF ACRIDIZINIUM BROMIDE:

A second reaction in which acridizinium bromide reacts in a manner analogous to anthracene is the Diels-Alder reaction. This is a somewhat unusual case considering the reactions of other nitrogen compounds in the Diels-Alder reaction. It has been shown in almost every condensation studied, concerning reaction of heterocyclic dienes which contain nitrogen as a member of the ring, that abnormal diene reactions occur (22). The Diels-Alder reaction of acridizinium bromide appears to be the first instance in which the diene is a quaternary salt, and also one of the few heterocyclic nitrogen dienes undergoing a normal diene reaction.

As examples of compounds that do not give adducts with maleic anhydride, the following may be mentioned: 2,4-dimethylbenzo[h] quinoline (23), 1,2,3,4-dibenzophenazine (24), and the azine of indanthrone (25). Examples exhibiting abnormal products are: pyrroles (22), dehydroindigo (26), anthranil (27), and 2,3-dimethylquinoxaline (27). The only other example of normal reaction is that of 2,4,10-trimethylbenzo[g]quinoline, which yields a normal adduct with maleic anhydride (23). The nitrogen atom in this base, however, is not a part of the ring directly involved in adduct formation.

The reaction between acridizinium bromide and maleic anhydride is believed to yield the product (VII) shown (28):



I VII

When I is heated with maleic anhydride on a steam bath, a colorless non-fluorescent salt is formed. The infrared spectrum exhibits the characteristic anhydride double absorption in the carbonyl region and the ultraviolet spectrum resembles that of the photodimer previously discussed.

Opening of the anhydride ring with dilute perchloric acid yielded what is proposed to be the cis-dicarboxylic acid salt. Treatment of this salt with hydrogen and platinum oxide yielded a product in which the double bonds of the heterocyclic ring were reduced. When ethyl fumarate or ethyl maleate served as the dienophiles, the same product was obtained in both cases. This compound was believed to be the trans-diethyl ester and its formation was explained by the assumption that isomerization of maleate to fumarate ester had taken place before reaction with the diene.

By esterification of the cis-dicarboxylic acid obtained from the maleic anhydride adduct, an isomeric diethyl ester of the above acid was obtained, indicating further that the product of fumarate or maleate reaction was the trans-ester. Methyl maleate gave a dimethyl ester which was isomeric with that formed by direct esterification of the cis-diacid with methanol. Since the quaternary ammonium ion is unstable in the presence of bases, it was not found possible to carry out an isomerization of the cis-ester to the trans-form by alkoxide ion.

Because of the unsymmetrical nature of the acridizinium ion, two adducts with maleic anhydride should be possible, with the anhydride ring inclined toward the benzenoid ring in one and in the direction of the pyridinium ion in the other. The course of the reaction in this respect was not established, so the exact stereochemical structural formulas of the products are not known.

Acridizinium bromide also gives a mixture of products with acrylonitrile, which is to be expected because of unsymmetrical nature of both the diene and dienophile. One pure product was isolated, but which isomer it may have been was not determined. It was also found that acridizinium bromide did not yield an adduct with quinone.

BIBLIOGRAPHY

1. C. K. Bradsher and L. E. Beavers, Chem. and Ind., 1954, 1394.
2. C. K. Bradsher and J. H. Jones, J. Org. Chem., 23, 430 (1958).
3. E. Späth and E. Kruta, Monatsh., 50, 341 (1928).
4. R. B. Woodward and B. Witkop, J. Am. Chem. Soc., 71, 379 (1949).
5. R. B. Woodward and W. McLamore, J. Am. Chem. Soc., 71, 379 (1949).
6. R. Schwyzer, Helv. Chim. Acta, 35, 867 (1952).
7. W. Schneider and O. Bögen, Ber., 54B, 2021 (1921).
8. C. K. Bradsher and H. Berger, J. Am. Chem. Soc., 80, 930 (1958).
9. V. Boekelheide and W. G. Gall, J. Am. Chem. Soc., 76, 1832 (1954).
10. O. Diels and K. Alder, Ann., 505, 103 (1933).
11. S. Sugasawa and K. Kakemi, Ber., 71B, 1860 (1938).
12. A. Richards and T. S. Stevens, Chem. and Ind., 1954, 905.
13. C. K. Bradsher, Chem. Revs., 38, 447 (1946).
14. C. K. Bradsher and L. E. Beavers, J. Am. Chem. Soc., 77, 4812 (1955).
15. C. K. Bradsher and L. E. Beavers, J. Am. Chem. Soc., 78, 2459 (1956).
16. C. K. Bradsher and J. H. Jones, J. Am. Chem. Soc., 79, 6033 (1957).
17. C. K. Bradsher and L. E. Beavers, J. Am. Chem. Soc., 77, 453 (1955).
18. C. K. Bradsher and L. E. Beavers, Abstracts of Papers Presented Before the Division of Organic Chemistry of the American Chemical Society, New York, N.Y., Sept. 12-17, 1954, pp. 45-O.
19. N. J. Leonard, S. Swann, Jr., and G. Fuller, J. Am. Chem. Soc., 76, 3193 (1954).
20. C. K. Bradsher, L. E. Beavers, and J. H. Jones, J. Org. Chem., 22, 1740 (1957).
21. F. D. Greene, S. L. Misrock, and J. R. Wolfe, Jr., J. Am. Chem. Soc., 77, 3852 (1955).
22. J. A. Norton, Chem. Revs., 31, 319 (1942).
23. W. S. Johnson and F. T. Mathews, J. Am. Chem. Soc., 66, 210 (1944).
24. M. C. Kloetzel, "Organic Reactions," Vol. IV., John Wiley and Sons, Inc., N.Y., N.Y., 1948, pp. 1.
25. E. deBarry Barnett, W. F. Goodway, A. G. Higgins, and C. A. Lawrence, J. Chem. Soc., 1934, 1224.
26. R. Pummerer and H. Fiesselmann, Ann., 544, 206 (1940).
27. A. Schönberg and A. Mostafa, J. Chem. Soc., 1943, 654.
28. C. K. Bradsher and T. W. G. Solomons, J. Am. Chem. Soc., 80, 933 (1958).
29. R. S. Barrows and H. G. Lindwall, J. Am. Chem. Soc., 64, 2430 (1942).

NUCLEOPHILIC AROMATIC DISPLACEMENTS

Reported by H. Gruen April 18, 1958

INTRODUCTION

The field of aromatic nucleophilic reactions has received much less attention than the corresponding one of electrophilic substitutions. The reasons for this are varied, one important one being the relative difficulty in carrying out substitution reactions in non-activated systems and in displacing hydrogen as hydride ion, although this may be shown to be quite facile in more complex systems.

The mechanism picture shows much of the ambiguity encountered in aliphatic nucleophilic substitution, and it is only recently that a more critical approach with regard to the details of possible reaction paths has been initiated. The general review by Bunnett and Zahler (1) is an eminently useful one, and since then an M.I.T. seminar (2) has dealt with this topic.

MECHANISM

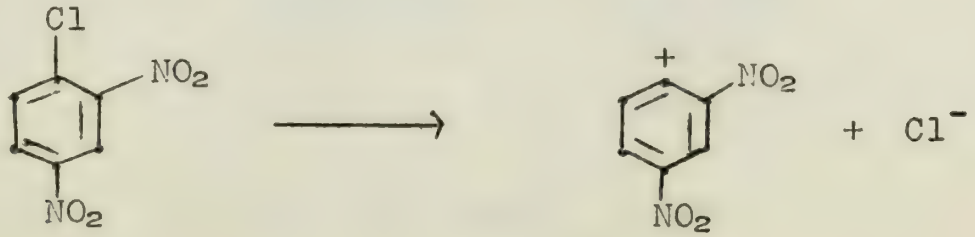
The mechanistic picture is best analyzed in terms of possible limiting structures of the transition state.

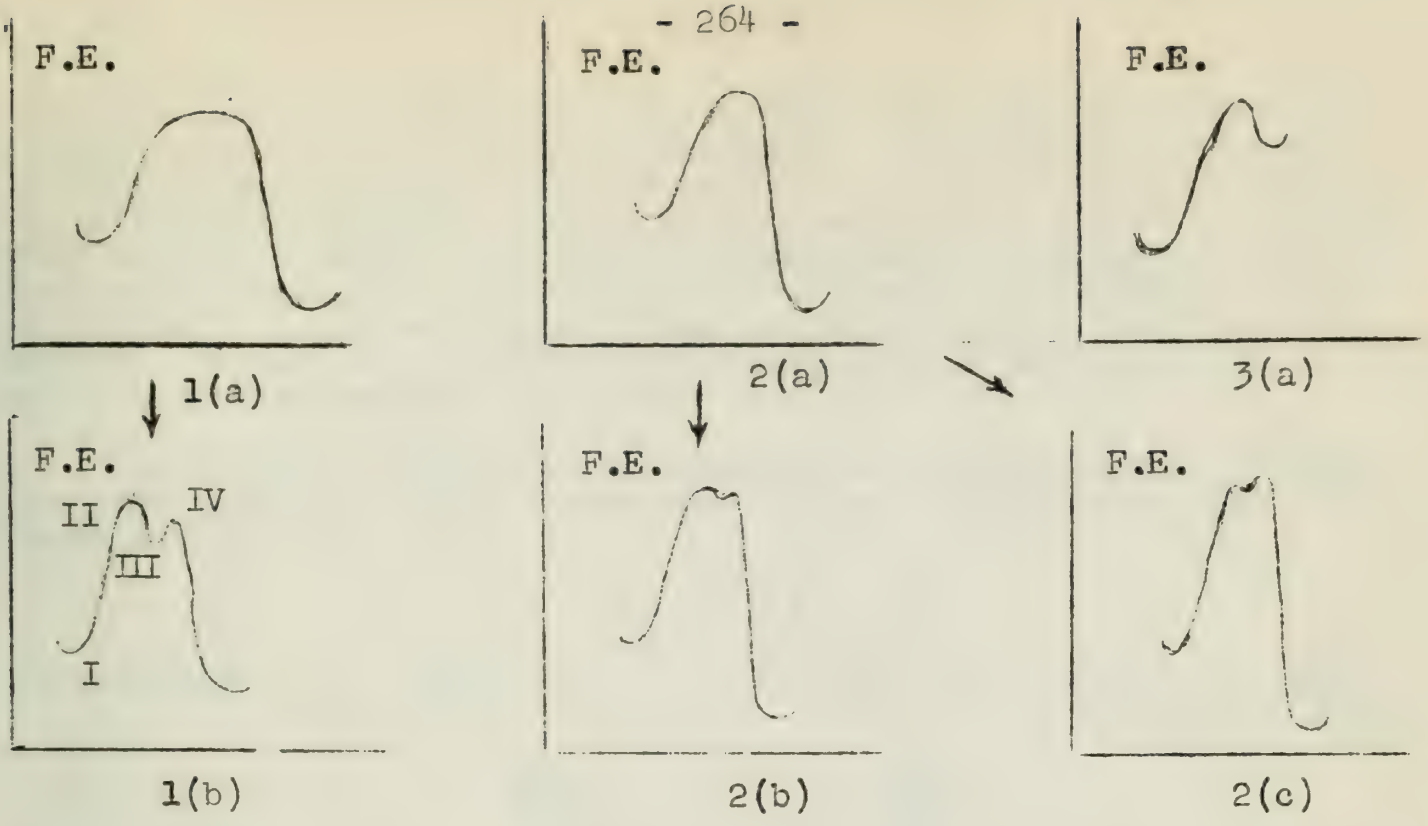
1) in which essentially only bond-making has occurred;
2) in which nearly equal bond-making and bond-breaking have taken place;
3) in which bond-breaking only has occurred significantly;
4) the addition - elimination mechanism.

Only the first two will be considered in the present discussion; the third represents the mode of decomposition of most aromatic diazonium compounds, and the fourth leads to formation of a neutral "benzyne" intermediate which then adds the nucleophile.

The extreme structure of the transition state for mechanism 1) would be almost quinonoid in character for which there is no adequate analogy in aliphatic nucleophilic displacement. Mechanism 2) resembles the "N" mechanism in aliphatic substitution at a saturated carbon atom and 3), the "LIM" or S_n1 mechanism.

It may be demonstrated that essentially all nucleophilic reactions studied may be fitted into the range between mechanisms 1) and 2). The existence of an intermediate is expected to be more significant in case 1) than in case 2) while the limiting case 3) has never been observed with leaving groups other than the nitrogen molecule; it would involve ionization as shown.





The relative displacement rates for leaving groups in the aliphatic series are indicated in the next table (4).

$$C_2H_5X + C_2H_5O^- \longrightarrow (C_2H_5)_2O + X^-$$

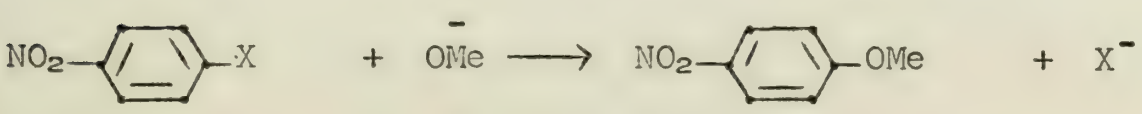
Table I

Replaced group (X)		k_X / k_{Br}
F	(C_4H_9X)	1.4×10^{-4}
Cl		2.4×10^{-2}
Br		1
I		1.9
$^+S(CH_3)_2$	(CH_3X)	1
$OSO_2\emptyset$		5.8

Among the halogens, the order parallels the decrease in bond strength.

The general order of replacement of X in 4-nitro-X benzenes by methoxide in methanol is indicated in table II below (3).

Replaced Group	Relative Rate	Ea/cals.	log pz
Cl	0	24,050	11.2
F	7.0×10^2	21,200	11.75
NO_2	2.9×10^2	22,400	12.65
$^+NMe_3$	7.48×10^3	20,000	11.8
$^+SMe_2$	1.8×10^5	24,550	16.85



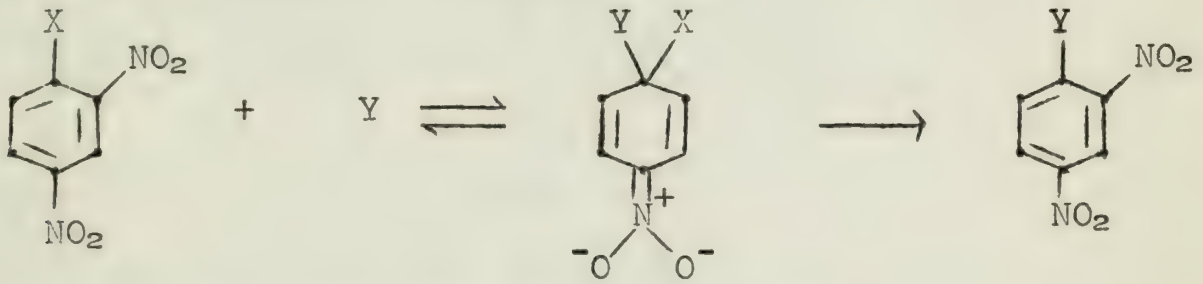
The order indicated particularly in table III parallels electronegativities rather than bond strengths. The ease of displacement by MeO^- in methanol is found to be $ArX^+ > ArX > ArX^-$, and the specific order for Ar-halogens F> Cl> Br> I. The order of replacement in the aromatic case is best represented by mechanism 1) with bond-making predominating. Mechanism 1) may be considered to be operative in an attack by a strong nucleophile in a good solvating medium. Mechanism 2) could be expected with a fair nucleophile in a solvent of intermediate solvating ability.

The study of condensation rates of 1-substituted 2,4-dinitrobenzenes with piperidine in methanol shows the pattern attributed to mechanism 1).

Table III

Substituent	Rate coeff.	Rel. rate	$\triangle E$ k cal/mole	$\triangle S$ cal/degr.
F	90	3300		
NO_2	24.2	890		
$OSO_2C_6H_4CH_3$	2.72	100		
$SO\emptyset$	0.129	4.7	10.8	-33.3
Br	0.118	4.3	11.8	-29.5
Cl	0.117	4.3	11.6	-30.2
$SO_2\emptyset$	0.086	3.2	12.0	-29.3
$^-OC_6H_4NO_2$	0.081	3.0	10.5	-35.3
I	0.027	1.0	12.0	-31.7

Displacement by substituted anilines on 2,4-dinitronaphthalenes and 2,4-dinitrochlorobenzene have ρ-values of -3.96 and -3.19 respectively (6) indicating a significant development in charge on the nitrogen atom and hence bond formation between the nitrogen atom and the aromatic ring. Bunnett (1) had previously advocated a two-step mechanism involving an intermediate.

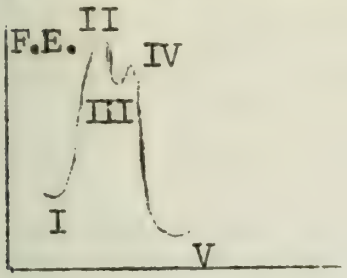


Significant also are the results by Chapman, Parker and Soames (7).

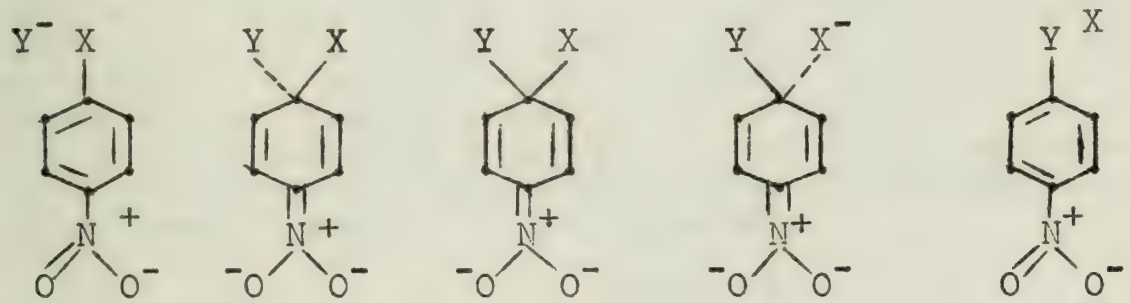
Table IV

	React. piperidine in EtOH			React. piperidine in benzene			React. OEt in EtOH		
Nitrobenzene	$\log_{10}A$	E	k	$\log_{10}A$	E	k	$\log_{10}A$	E	k
derivative		kcal/mole	$10^5(90^\circ)$		kcal/mole	$10^5(90^\circ)$		kcal/mole	$10^5(90^\circ)$
o-fluoro	7.0	14.8	1230				11.7	20.1	4×10^4
o-chloro	6.4	18.1	2.3	3.8	13.4	5.4	10.0	22.4	39.7
o-bromo	6.8	18.3	5.6	4.6	14.1	13.9			
o-iodo	6.9	19.2	2.3	5.0	15.3	6.2			
p-fluoro	5.3	13.2	225				10.7	19.0	2.2×10^4
p-chloro	5.3	17.1	1.1	2.3			9.0	20.1	96.3
p-bromo	5.2	16.8	1.4	3.6(2.6)	15.5(13.6)	.2(.26)	9.2	20.3	83.8
p-iodo	5.5	18	.4	5.8	19.5	.12			

They indicate that rates with fluorine are strikingly faster under all conditions examined, that in the reaction of piperidine in benzene, the rates for Cl, Br, I are quite similar, and that the reaction always takes place faster with the ortho substituted derivative. The situations described may be represented by an energy profile as shown.



A dipolar quinonoid intermediate is thought to exist along the reaction co-ordinate. If the loss of X^- is facile the energy level of IV will be lower than that of II as shown.

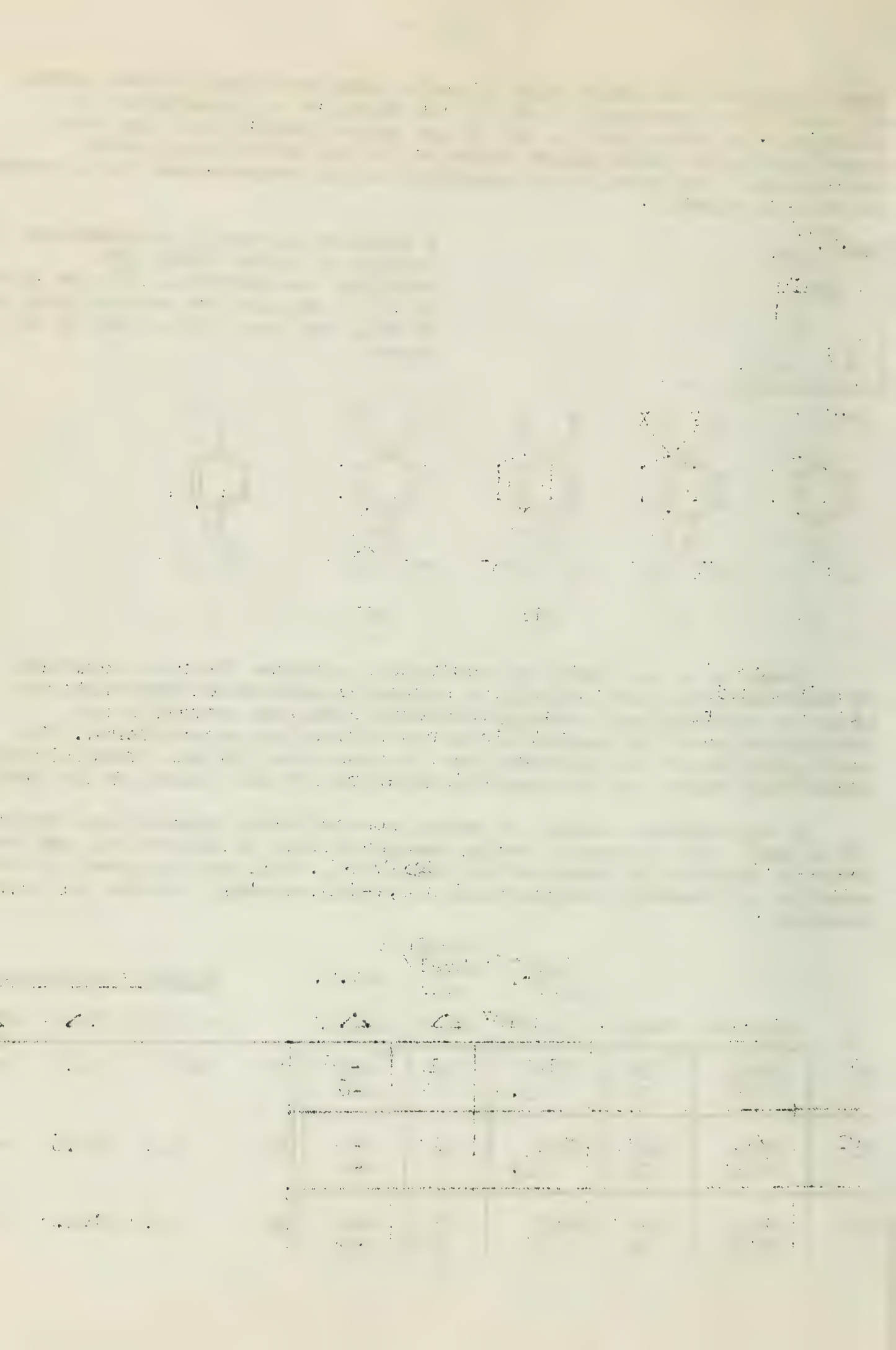


There is a good deal of convincing evidence for the existence of intermediates particularly in strongly activated substrates, but since no satisfactory isotopic exchange data are available no conclusive proof is available for the situations considered. The configuration of the intermediate is such that it may resemble both transition states or the starting material if its formation is fast.

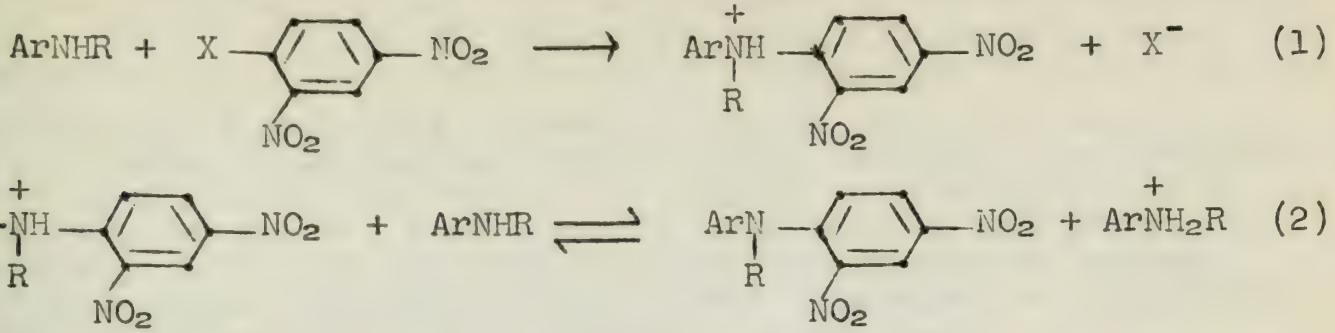
By appropriate design of reaction conditions Hammond and Parks (8) showed that aliphatic N-type mechanism may be approached and the order of reactivity inverted to Br > Cl > F. This was achieved in the reaction of N-methyl aniline with 2,4-dinitrophenyl halides in nitro benzene.

Table V

	Solvent	Temp.	$l\ mol^{-1}\ sec^{-1}$ $k \times 10^7$	kcal/mol ΔH	e.u. ΔS		aniline in ethanol $k \times 10^4$	ΔH	ΔS
F	ϕNO_2	120	182	10	-56	F	168	5.8	-49
	EtOH	50	4.5	7	-68				
Cl	ϕNO_2	120	2750	12	-48	Cl	2.7	10.6	-43
	EtOH	50	6.2	7	-62				
Br	ϕNO_2	120	8450	11	-44	Br	4.05	10.6	-42
	EtOH	50	51	8	-50				



Hammond describes displacement on activated aryl halides by "neutral" nucleophiles as shown, in which (1) is rate determining. There may



(1)

(2)

be two steps involved; if so the second bond-breaking one is slow. No evidence for existence of an intermediate here is available. The displaceability of fluorine is probably due to a lower heat of activation not completely compensated for by large negative entropies. It has also been suggested that this was due to the large heat and negative entropy of solvation of the fluoride ion. The reaction rates of a group of substituted benzoates with 2,4-dinitrochlorobenzene was investigated by the same workers and significant Hammett ρ values obtained.

Table VI

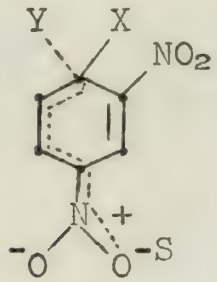
Halo compound	potassium benzoate	Temp.	$k \times 10^{-6}$ $l.mol^{-1}sec^{-1}$	ρ
dinitrochlorobenzene	p-methoxy	93	47.6	-.20
	unsubstituted	93	41.7	
	p-nitro	93	22.8	
methyliodide	p-methoxy	25.5	14.7	-.12
	unsubstituted	25.5	14.5	
	p-nitro	25.5	9.47	

The above ρ values compare with a value of 1.5 for the ionization of benzoic acid in the same medium. The lack of sensitivity to substituent effects suggests that little bond formation has occurred in the transition state. The situations described here resemble energy diagram 2a with extensive bond breaking in the transition state.

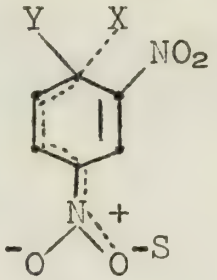
Notwithstanding Hammond's (8) criticism of the interpretation of Melander's (9) kinetic isotope work in aromatic electrophilic substitution, more decisive kinetic studies by Zollinger (10) coupled with isotope and base catalysis measurements have established the existence of a quinonoid intermediate for diazo-coupling reactions. Iodide isotope exchanges with o- and p-iodonitrobenzene (11) and iodobenzene in a two-phase system have been carried out (12). The data obtained from these investigations are not adequate yet for elucidation of the details of the mechanism involved.

The extent of C-X bond breaking in the rate-determining step has been suggested as a criterion for the mechanism. If the C-X bond remains intact and if steric requirements for several different X's are similar, the rates for different X-elements should be very similar for a single attacking nucleophile for an element effect to have

meaning as a criterion of mechanism; the absence of compensating factors must be insured. Table III shows that six groups representing five different elements react at essentially the same rate hence C-X bond breaking has made little progress in the rate determing step. $\triangle E^{\ddagger}$ and $\triangle S^{\ddagger}$ valves are very similar and suggest the same mechanism. These results are not compatible with an S_N2 type mechanism at a saturated aliphatic carbon. The situation is probably adequately represented by energy plot 1(b). The alternate one-step mechanism 1(a) may be considered to involve concerted completion of the C-Y bond formation and partial rupture of the C-X bond. It is not considered likely for reasons of analogy. Positions along the reaction coordinates indicated as structures labelled III and IV represent transition states.



III

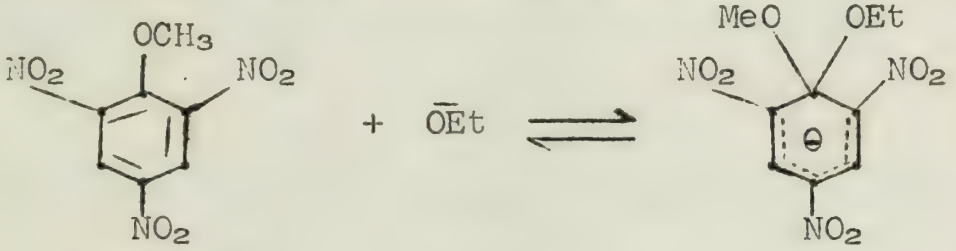


IV

It seems reasonable that all of the available evidence will permit the various reactions to be accommodated by a mechanistic spectrum which ranges from 1(a) to 2(c) [see energy profiles] and tapering off towards 3 which may not have been closely approached as yet.

INTERMEDIATES IN NUCLEOPHILIC DISPLACEMENT

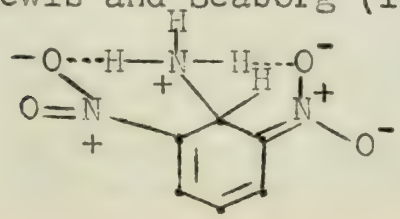
Addition complexes of di- and trinitrobenzenes capable of being intermediates have been described in the chemical literature.



I II

II was isolated by Meisenheimer (13) and well characterized by Hammick and Foster (14) by infrared and ultraviolet analysis; the corresponding adduct of I and isopentyl oxide has also been described.

Aliphatic amines form highly colored adducts with polynitroaromatic hydrocarbons with the structures indicated assigned by Lewis and Seaborg (15).



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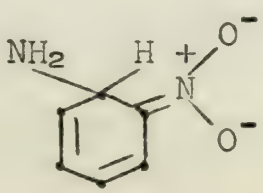
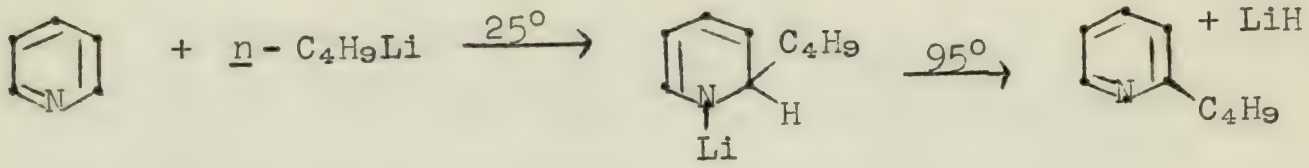


IV

Solutions of m-dinitrobenzene in liquid ammonia are deep purple and good conductors; Farr, Boyd and Wheland (16) concluded from a study of the electrolysis products that the solution contained IV. A good example of the formation of an adduct is the reaction of n-butyl lithium with pyridine studied by Ziegler and Zeiser (17).



NUCLEOPHILICITY OF THE ATTACKING BASE

For comparable series of displacements at an aromatic carbon atom data are limited. Recently, Bevan & Hirst (18) attempted to set up a meaningful scale as indicated in the Table VIa.

Table VIa

p-fluoronitrobenzene

X	$^-$OMe	Sϕ^-	O$^-\phi$	ϕNH_2
k_2 l.sec^{-1}mol^{-1}	1.8×10^{-4}	1.7×10^{-4}	10^{-6}	1.56×10^{-8}
log B	11.0	10.7		2.11
E kcal/mol	20.1	19.8		13.5

picryl chloride

X	ϕNH_2	m-$NO_2.C_6H_4NH_2$	Cl^-	MeOH
k_2 l.sec^{-1}mol^{-1}	6.77	2.27×10^{-3}	7.4×10^{-6}	7.5×10^{-9}
log B	5.6	5.34	11.5	6.64
E kcal/mol	7.86	10.9	22.7	18.1

Table VIb

for reaction of p-fluoronitrobenzene with X in methanol

X	OMe^-	Sϕ^-	O$^-\phi$	ϕNH_2
k_2 l.sec^{-1}mol^{-1}	1.8×10^{-4}	1.68×10^{-4}	10^{-6}	1.56×10^{-8}
X	m-$NO_2C_6H_4NH_2$	Cl^-	MeOH	
k_2 l.sec^{-1}mol^{-1}	5.23×10^{-12}	1.71×10^{-14}	1.74×10^{-17}	

Data in Table VIb are obtained on the assumption that relative values for both substrates are preserved for other nucleophiles X; the last three values are probably only approximate.

A tentative order for displacement on 1-chloro-2,4-dinitrobenzene had previously been compiled by Bunnett (1).

$SO_3^=$ > OEt^- > OMe^- > piperidine > O$^-\phi$ > NH_3 > LiI > ϕNH_2 > LiBr
[Solvents - methanol, ethanol and ethylene glycol]

However, conditions used were not standardized, and the sequence is subject to change. It is interesting to compare this with Swain's order of nucleophilicity in the methyl bromide-water system.

$SO_3^{=} > SH^- > CN^- > I > SCN > \emptyset NH_2 > OH^- >$ thiourea $> N_3^- > Br >$  $> Cl^-$

A striking feature in Bevan's scale is the close order of $\bar{O}Me$ and $\bar{S}\emptyset$ in contrast to the expected ratio of $\frac{\bar{S}\emptyset}{\bar{O}Me} \sim 10^{+3}$. The equilibrium $\emptyset SH + MeO^- \rightleftharpoons \emptyset S^- + MeOH$ lies well to the right (22).

It appears that in the situation described both $\equiv C-O^-$ and $C-S^-$ must approach closely to the tetrahedral bond distance; the latter looses the advantage of forming partial bonds at greater internuclear distance; this leads to a relative levelling of the reactivities of the ions. Results of the above tables show that within a narrow reactivity range a detailed examination of the nature of the transition state is required.

SUMMARY

While the mechanistic frame work of aromatic nucleophilic displacements is now available, little is known about the details of the reactions involved. It was determined only quite recently (19) that for displacements by a primary and secondary aliphatic amine on activated halides the rate expression is not a simple second-order one but also contains a third-order term suggesting significant base catalysis. The data used in the discussion of the "element" effect imply that there may be a "merged" addition-substitution effect involving some bonding between the attacking and leaving group. Judicious isotope experiments combined with examination of the extent of base catalysis should provide a more detailed picture of the path of the displacements mentioned.

BIBLIOGRAPHY

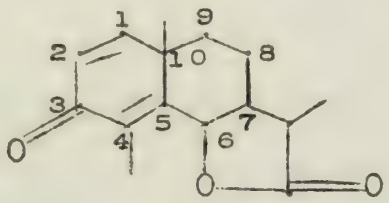
1. J. F. Bunnett and R. Zahler, Chem. Revs., 49, 273 (1951). Since this seminar was presented another review has appeared - J. F. Bunnett, Quart. Rev., 12, (1958).
2. L. A. Kaminski, M.I.T. Seminar, 336 (1957).
3. (a) B. A. Bolto and J. Miller, Austral. J. Chem., 9, 75 (1956) (b) J. Miller, Rev. Pure and Appl. Chem., 1, 171 (1951).
4. A. Streitwieser, Chem. Revs., 56, 572 (1956).
5. J. F. Bunnett, E. W. Garbish and K. M. Pruitt, J. Am. Chem. Soc., 79, 385 (1957).
6. L. P. Hammett, Physical Organic Chemistry, McGraw-Hill Book Co., New York, 1940, p. 189.
7. N. B. Chapman, R. E. Parker and P. W. Soanes, J. Chem. Soc., 2109 (1954).
8. G. S. Hammond and L. R. Parks, J. Am. Chem. Soc., 77, 340 (1955); 77, 2905 (1955); 77, 334 (1955).
9. L. Melander, Arkiv Kemi., 2, 213 (1950).
10. Hch. Zollinger, Helv. Chim. Ada., 38, 1957 (1955).
11. A. M. Kristjanson and C. A. Winkler, Can J. Chem., 29, 154 (1951).
12. P. J. Mano and W. H. Johnston, J. Am. Chem. Soc., 79, 807-811 (1957).
13. J. Meisenheimer, Ann, 323, 205 (1902).
14. D. Ll. Hammick and R. Foster, J. Chem. Soc., 2153 (1941).
15. G. N. Lewis and G. T. Seaborg, J. Am. Chem. Soc., 62, 2122 (1940).
16. J. D. Farr, C. C. Bard and G. W. Wheland, J. Am. Chem. Soc., 71, 2013, 1949.
17. K. Ziegler and H. Zeiser, Ber., 63, 1847 (1930).
18. C. W. L. Bevan and J. Hirst, J. Chem. Soc., 254 (1956).
19. S. D. Ross and M. Finkelstein, J. Am. Chem. Soc., 79, 6547 (1957).

PHOTOCHEMICAL REACTIONS OF DIENONES

Reported by W. B. Chipman May 22, 1958

I. INTRODUCTION

This seminar will deal with a series of photochemical reactions--apparently quite general--of alicyclic dienones (1), concentrating on those of santonin, since this compound has been the object of the major effort to date. Santonin (2) provided the first established example of the dienone-phenol rearrangement, and the proper interpretation of this reaction helped Clemo, Haworth and Walton to establish its structure (I) (3).

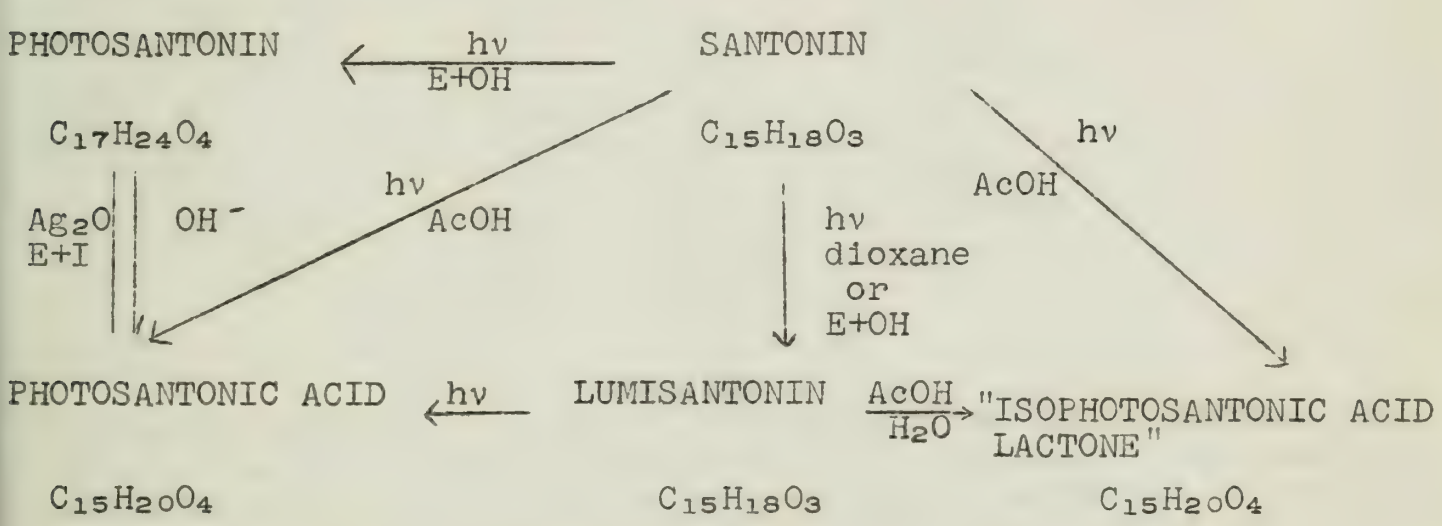


(I)

Recently Woodward and his co-workers have established the nature of the major ionic rearrangements of santonin (4).

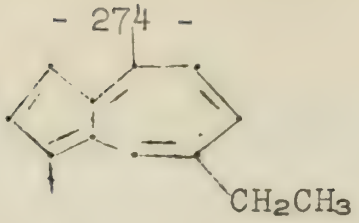
The photochemistry of santonin was extensively investigated by a number of early Italian workers, but the nature of some of the rearrangements involved has resisted explanation until the present time, (2). A summary of the major photochemical reactions of santonin is given in Chart 1.

CHART 1



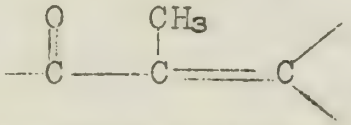
II: "ISOPHOTOSANTONIC ACID LACTONE"

Irradiation of santonin in aqueous acetic acid has long been known to produce "isophotosantonic acid lactone" ($C_{15}H_{20}O_4$) (2). Barton, de Mayo and Shafiq have recently established the structure of this compound (5a). The basic carbon skeleton was shown to be a trisubstituted perhydroazulene since acid catalyzed hydrogenation afforded a mixture of alcohols which was dehydrogenated to the known chamazulene (II).

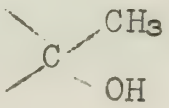


(II)

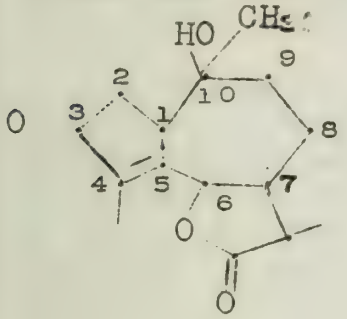
Previous work had shown the presence of one tertiary hydroxyl, one lactone and an α,β-unsaturated ketone in a cyclopentanone ring. Ozonation afforded acetic acid and a dilactone ($C_{13}H_{16}O_5$) which possessed a non-conjugated ketone. The above result was assumed to imply the system



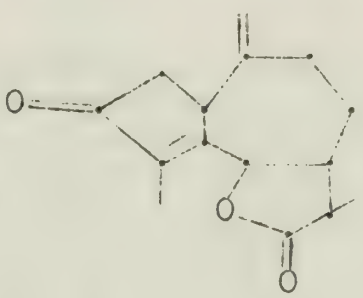
which on ozonation would generate acetic acid, a non-conjugated [illegible] ketone and a carboxylic acid which could lactonize with the original hydroxyl. Treatment of "isophotosantonic acid lactone" with pyridine-thionyl chloride yielded an anhydro compound which contained an exo-methylene group. (i.r. max. 905 cm^{-1}) Hence the parent compound must contain the system



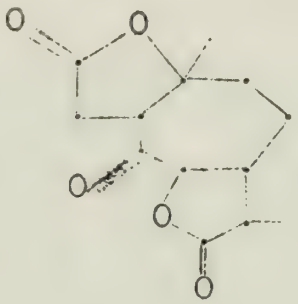
and since the ultraviolet spectra of both the parent compound and the anhydro compound are identical, the methylene grouping of the anhydro compound cannot be conjugated with the α,β-unsaturated ketone. Based on the above evidence and the structure of santonin, structure III may be written for "isophotosantonic acid lactone". The anhydro compound may then be formulated as IV and the ozonation product as V.



III

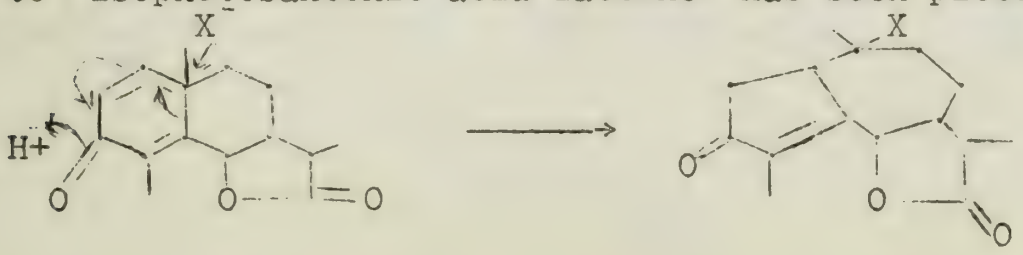


IV



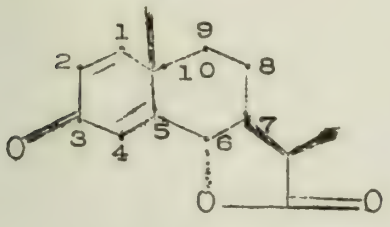
V

Confirmation of the structure III was obtained by comparison of "isophotosantonic acid lactone" and its acetate with the previously known compounds (5b). The course of the rearrangement of santonin to "isophotosantonic acid lactone" has been pictured as follows (5a),

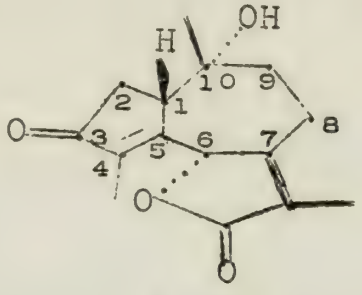


where X is hydroxyl or acetate ion, although evidence to be presented below indicates that it is probably much more complicated.

The stereochemistry of santonin has been established to be as shown in VI (6). The asymmetric centers at C-6 and C-7 are not affected during the photochemical rearrangement; the same stereochemistry is to be expected in "isophotosantonic acid lactone". On the basis of rotary dispersion studies Djerassi and his co-workers



VI



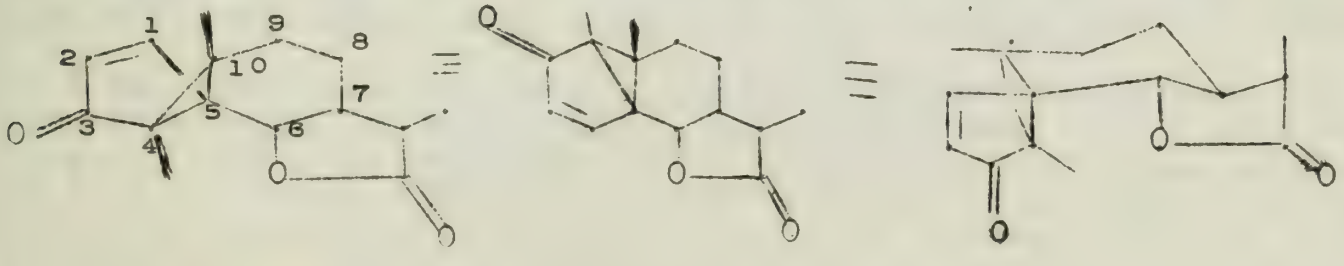
VII

have assigned the configuration at C-1 of the photoproduct as that with the hydrogen β-oriented (7). The configuration at C-10 has been assigned as β-CH_3 on the basis of elimination evidence and also on the basis of the preferred conformation for the 7-membered ring. The stereochemistry of "isophotosantonic acid lactone" is summarized in VII.

This type of rearrangement is apparently quite general. Barton and his co-workers have reported the following conversions where the stereochemistry of the photoproduct is based in each case on analogy with the santonin series: prednisone acetate, atremisan acetate, 6 epi-α-santonin, 6 epi-β-santonin and β-santonin.

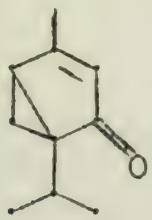
III. LUMISANTONIN

Irradiation of santonin in ethanol or dioxane for a controlled period of time affords the isomeric lumisantonin ($C_{15}H_{18}O_3$) whose existence was unknown to earlier workers, (8,9). The importance of this compound to an understanding of the photochemistry of santonin is shown by the fact that on treatment with aqueous acetic acid in the dark it hydrates and rearranges to give "isophotosantonic acid lactone" (III) and also by the fact that on further irradiation in dioxane it is converted to photosantonic acid (the second product isolated in addition to "isophotosantonic acid lactone" from the acetic acid irradiation of santonin). Arigoni, Bosshard, Bruderer, Buchi, Jeger and Krebaum have assigned the structure VIII to

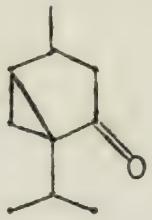


VIII

lumisantonin on the following grounds (9). Hydrogenation of lumisantonin over palladized charcoal affords dihydrolumisanton (1 mole uptake), which gives a negative tetranitromethane test and is inert to ozone. The infrared and ultraviolet spectra of lumisantonin indicate the presence of a γ-lactone (i.r. max. 1772 cm^{-1}) and an α-β-unsaturated ketone in a 5-membered ring (i.r. max. 1708 cm^{-1} ; u.v. max. 238 mu, log ε 3.7). In addition, the infrared and ultraviolet spectra of lumisantonin and dihydrolumisantonin are very similar to those of umbellone (IX) and dihydroumbellone (X), respectively.

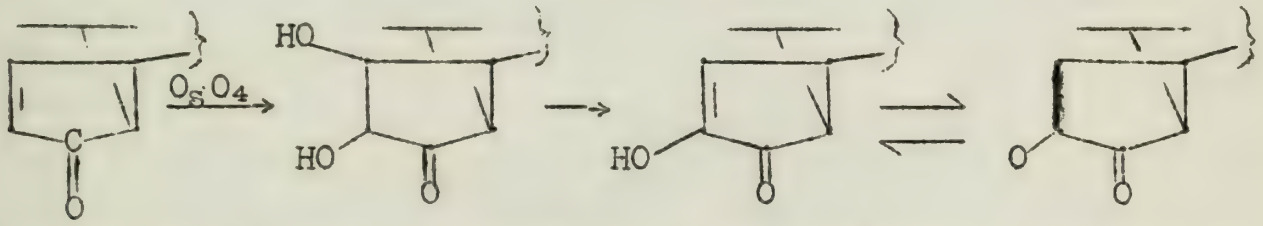


IX



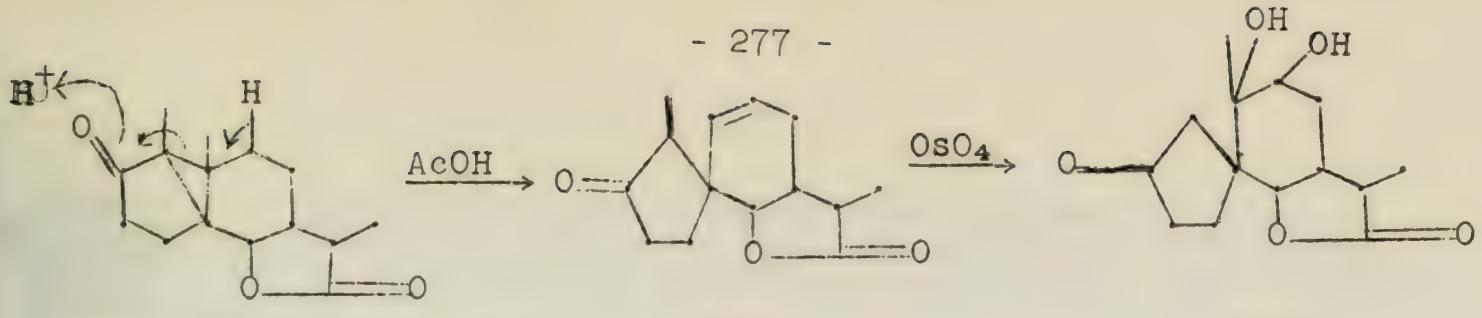
X

Further evidence for the proposed structure includes the following: Pyrolysis of lumisantonin (200°) affords an isomeric ketolactone, pyrolumisantonin, which has two double bonds (two moles hydrogen uptake over palladized charcoal). The presence of the original double bond is apparently necessary for the isomerization since dihydrolumisantonin is unaffected under the same conditions. Spectral evidence indicates that the ketone of pyrolumisantonin is in a 5-membered ring (i.r. max. 1705 cm^{-1}) and is conjugated with only one of the two double bonds (u.v. max. 220 mu, log ε 4.07). The pyrolysis of lumisantonin is interpreted as the pyrolytic cleavage of a cyclopropane ring resulting in the formation of a double bond. Infrared evidence indicates that both of the carbon atoms of the cyclopropane ring which are β to the caraonyl (C-5 and C-10) bear at least one substituent (i.r. max. 2950 - 3035 cm^{-1}). Osmium tetroxide oxidation of lumisantonin affords a glycol which loses water to form an α-diketone (u.v. max. 260 mu, log ε 4.09). This establishes the presence of a hydrogen atom at C-2.

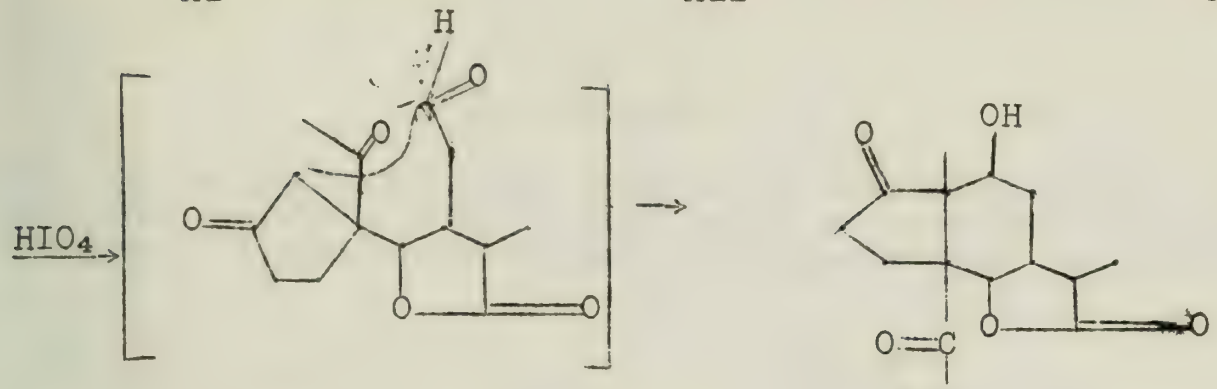


The presence of a cyclopentenone ring in lumisantonin was confirmed by ozonization to an acid, $C_{14}H_{18}O_5$, (loss of one carbon atom) which on reduction with sodium borohydride in methanol afforded a saturated dilactone, $C_{14}H_{18}O_4$. The presence of a sharp infrared band at 1765 cm^{-1} indicates that both lactones are 5-membered, and hence that the ring which was oxidatively cleaved in lumisantonin must be 5-membered.

The acid catalized isomerization of dihydrolumisantonin (XI) affords a bicyclic, singly unsaturated ketolactone, isodihydrolumisantonin (XII), in which the ketone is present in a saturated 5-membered ring (i.r. max. 1745 cm^{-1}). The formation of a double bond under such mild conditions is taken as additional evidence for the cyclopropane ring. Osmium tetroxide oxidation of isodihydrolumisantonin affords a glycol (XIII), $C_{15}H_{22}O_5$, which on treatment with periodic acid yields not the expected tricarbonyl-lactone, but a diketo-hydroxy lactone (XIV) (i.r. max. 3400, 1780, 1740, 1686 cm^{-1}). The formation of XIV may be explained by an intramolecular aldol condensation.

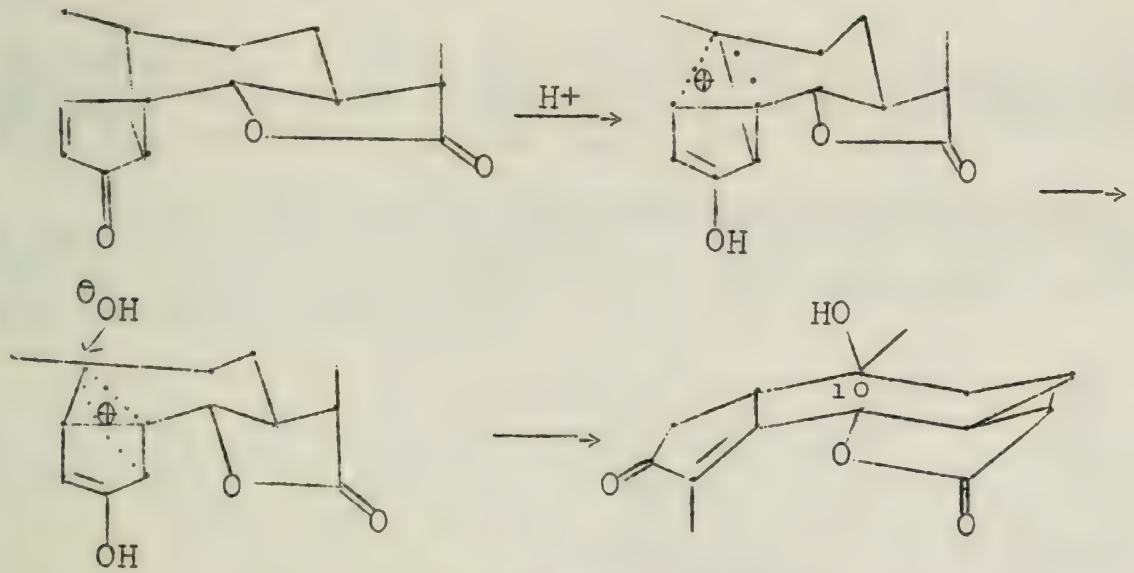


XI XII XIII

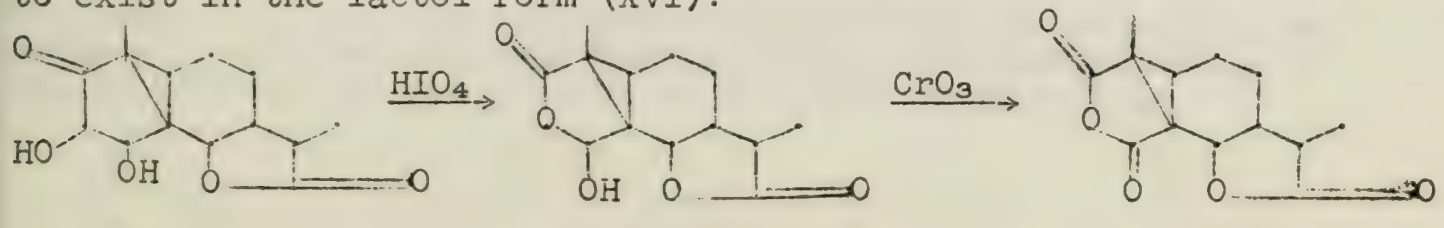


XIV

The formation of "isophotosantonic acid lactone" from lumisantonin may then be pictured as follows, where the stereochemistry of lumisantonin follows from the established stereochemistry of "isophotosantonic acid lactone" (inversion at C-10).

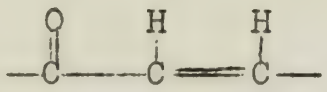


Barton, deMayo and Shafiq agree on the structure of lumisantonin (1,10). Infrared and Kuhn-Roth determinations indicate the presence of three C-methyl groups. The osmium tetroxide oxidation of lumisantonin afforded a glycol, formulated as XV, which reacted with two moles of periodic acid yielding a C_{14} - aldehydo acid which was shown to exist in the lactol form (XVI).

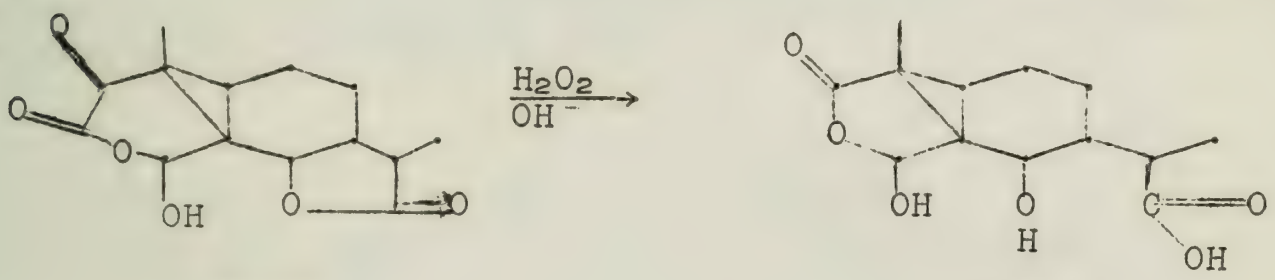


XV XVI XVII

Chromic acid oxidation of the aldehydo acid consumed 1 equivalent of CrO_3 and afforded an anhydride (i.r. max. 1830 cm^{-1}) formulated as XVII. These reactions are sufficient to establish the presence of the grouping



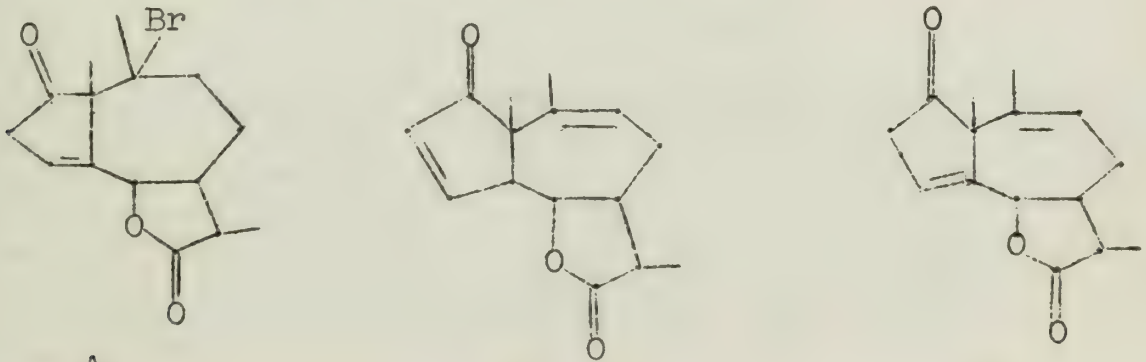
and the isolation of formic acid as an ozonation product of lumisantonin, together with a small amount of product formulated as XVIII or its open chain derivative, support this formulation.



XVIII XIX

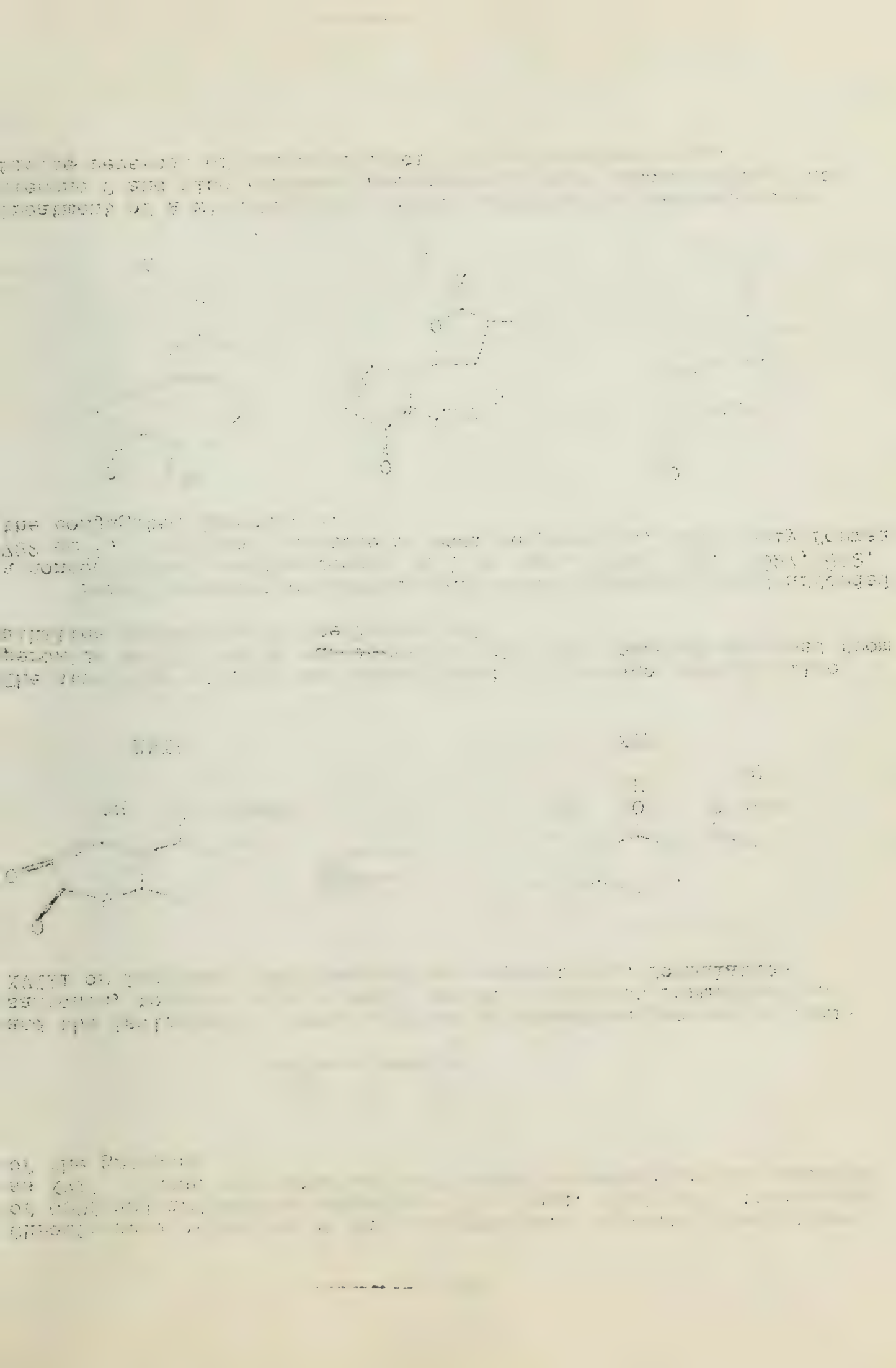
The structure of XVIII was established by cleavage with alkaline peroxide to XIX, which was identical with the compound obtained from alkaline hydrolysis of the lactol XVI.

Brief treatment of lumisantonin with hydrobromic acid afforded a nonconjugated cyclopentenone, A (i.r. max. 1792, 1752, 1627, 802, 722 cm^{-1}), which was unstable at room temperature, and slowly formed the conjugated dienone, B.



A B C

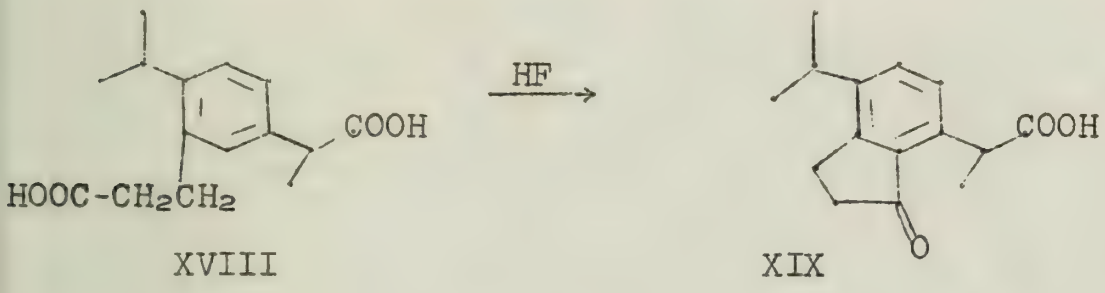
Treatment of A with boiling pyridine afforded the nonconjugated dienone C and also reformed lumisantonin, thus demonstrating the facile reversal of the opening of the cyclopropane ring.



IV. PHOTOSANTONIC ACID

A second product resulting from the irradiation of santonin in acetic acid is the lactonic acid, photosantonic acid $C_{15}H_{20}O_4$). Irradiation of lumisantonin in dioxane also affords this compound, while irradiation of lumisantonin in ethanol affords the ethyl ester of photosantonic acid, photosantonin, which has long been known as the product of the irradiation of santonin in ethanolic solution (2). The structure of photosantonic acid is the subject of a recent controversy.

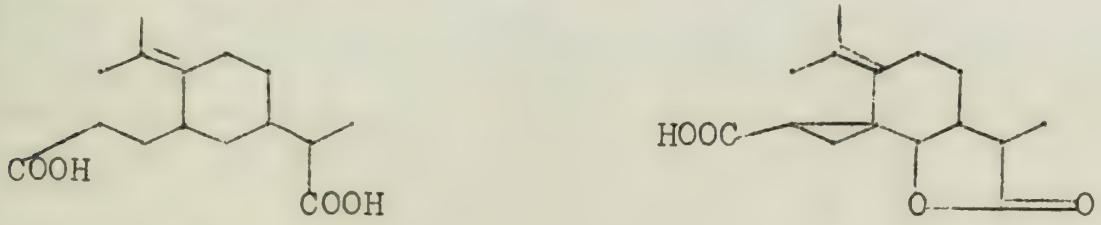
Treatment of photosantonic acid with hydrochloric acid affords a mixture of active and racemic dehydrophotosantonic acids ($C_{15}H_{20}O_4$). These acids are formulated as XVIII, since acid catalyzed cyclodehydration yields the indanone, XIX.



XVIII XIX

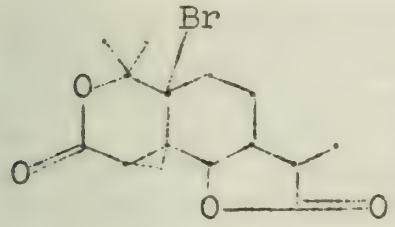
XX XXI

Chromium trioxide oxidation of the dehydroacids affords the known canabinolactonic acid, XX. Stepwise, decarboxylation of the dehydroacids yields the hydrocarbon, XXI, of well-established structure. Based on the above evidence, the structure of santonin, and the knowledge that photosantonic acid is an γ-lactonic carboxylic acid (i.r.) containing an isopropylidine group (acetone as an ozonation product) the basic carbon skeleton of photosantonic acid may be tentatively represented as XXIV.

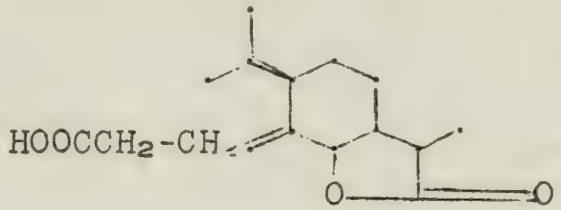


XXII XXIII

Barton has proposed XXIII as the structure of photosantonic acid on the following grounds (11). The formula for photosantonic acid ($C_{15}H_{20}O_4$) is such that it implies either a second double bond or a second carbocyclic ring. Oxidation studies and tests with the conventional double bond reagents indicate the presence of only one double bond. Bromination of photosantonic acid affords a monobromodilactone in which the new ring is a γ-lactone (i.r. max. 1730 cm^{-1}). The bromination product, which is formulated as XXIV, does not react with ozone or tetranitrimethane and is converted to the original acid on debromination with zinc and acetic acid.



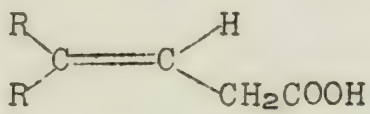
XXIV



XXV

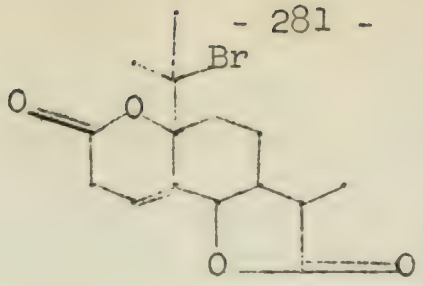
The formation of dehydrophotosantonic acid, XVIII, as a degradation product resulting from hydrochloric acid treatment of photosantonic acid is consistent with the known facile cleavage of cyclopropane groups conjugated with a carbonyl. The formation of the indanone, XIX, from dehydrophotosantonic acid requires that the carboxyl group of photosantonic acid be in a position γ to the cyclohexane ring. The relationship of the carboxyl group to the double bond of the isopropylidene group (vide supra) requires that the carboxyl group be β to the cyclohexane ring. The apparent dichotomy may be explained by the assumption of the cyclopropane group. The ultraviolet absorption spectra of photosantonic acid (end absorption: 210 mμ, log ε 3.57) is consistent with the known fact that the cyclopropane group can extend a previously existing chain of conjugation, but does not itself exhibit a maximum above 210 mu, even when it is in conjugation with a double bond (12).

A second structure, XXV, has been proposed for photosantonic acid by van Tamelen (13). This formulation is based on nuclear magnetic resonance data for methyl photosantoate which shows signals which are attributed to the system XXVI. While ozonization affords



XXVI

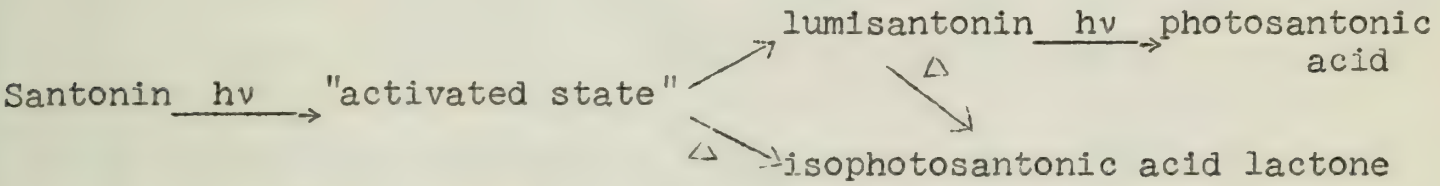
acetone, ozonization follwed by zinc dust reduction of the ozonide affords acetaldehyde; ozonization with an oxidative work-up affords malonic acid. The same products have been reported from a similar ozonolysis of 4-methyl-3-pentenoic acid (XXVI, R=CH_3), (14). The absence of the expected ultraviolet absorption for a 1,3-dienoid is attributed to steric hinderance around the heavily substituted diene resulting in out-of-plane distortion. The pronounced lack of reactivity of the trisubstituted double bond is similarly attributed to steric hinderance. The formulation which is implied for the monobromodilactone of Barton is then XXVII.



XXVII

The formation of dehydrophotosantonic acid, and its subsequent cyclization to the indanone, XIX, are consistent with this formulation.

Irradiation of santonin in hot aqueous acetic acid gives "isophotosantonic acid lactone" while irradiation in cold aqueous acetic acid gives equal amounts of this compound and photosantonic acid. Irradiation of lumisantonin yields "isophotosantonic acid lactone" but lumisantonin is stable in cold aqueous acetic acid. Irradiation of lumisantonin in the cold gives photosantonic acid, but no lactone.



The above facts have led Barton to postulate the existence of an "activated state" which may collapse to lumisantonin or the lactone, depending on the conditions of the experiment. Lumisantonin may then undergo photochemical transformation to photosantonic acid or thermal transformation to the lactone.

1. D.H.R. Barton, Proc. Chem. Soc., 61(1958).

2. J. Simonsen and D.H.R. Barton, "The Terpenes", University Press, Cambridge, England, 1952, Vol. III, Chap. V.

3. G. Clemo, R. Haworth and E. Walton, J. Chem. Soc., 2368(1929).

4. R.B. Woodward, F. Brutschy and H. Baker, J. Am. Chem. Soc., 70, 4216 (1948). R.B. Woodward and E. Kovach, ibid, 72, 1009 (1950).

5. (a) D.H.R. Barton, P. deMayo, and M. Shafiq, J. Chem. Soc., 929 (1957).
(b) S. Cannizzaro and T. Fabris, Ber., 19, 2261 (1866).

6. M. Sumi, Pharm. Bull., (Japap), 4, 158 (1956).
E.J Corey, J. Am. Chem. Soc., 77, 1044 (1955).
R.B. Woodward and P Yates, Chem. and Ind., 1319 (1954).

7. C. Djerassi, J. Osiecki and W. Herz, J. Org. Chem., 22, 1361(1957).

8. W. Cocker, K. Crowley, J. Edward, T. McMurry and E. Stuart, J. Chem. Soc., 3416 (1957).

9. D. Arigoni, H. Bosshard, H. Bruderer, G. Buchi, O. Jeger and L. Krebaum, H.C.A., 40, 1733 (1957).

10. D.H.R. Barton, P. deMayo and M. Shafiq, Proc. Chem. Soc., 205 (1957). J. Chem. Soc., 140 (1958).

11. D.H.R. Barton, P. DeMayo and M. Shafiq, Proc. Chem. Soc. 345(1957).

12. R.H. Eastman, J. Am. Chem. Soc., 76, 4115 (1954).

13. E.E. van Tamelen, S.H. Levin, G. Brenner, J. Wolinsky and P. Aldrich, J. Am. Chem. Soc., 80, 501 (1958).

14. A.A. Goldman and R.P. Linstead, J. Chem. Soc., 2354 (1928).

α-FLUORO ETHERS

Reported by J. L. Fedrick May 26, 1958

INTRODUCTION

The synthetic use of the α-halo ether functional group has been studied extensively (1), but because of the limited number of reactions this group undergoes, its use has been infrequent. α-Halo ethers, readily prepared by a variety of methods, lie between acyl halides and simple alkyl halides in stability and undergo nucleophilic displacement of halide. Dehydrohalogenation to vinyl ethers, hydrolysis, halide exchange and thermal decomposition are also characteristic of these compounds. The preparation and properties of α-fluoro ethers have not been reviewed previously.

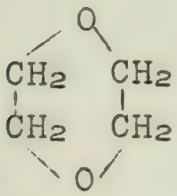
PREPARATION

Electrochemical

The most stable and the most widely utilized members of this series are the perfluoro ethers. Their usage as solvents, refrigerants, fire-extinguisher fluids, dielectrics and lubricants has achieved industrial importance. A one-step synthesis of these compounds from the corresponding alkyl ethers is accomplished by electrolysis in liquid hydrofluoric acid (2). Diethyl ether, like most ethers, undergoes simple perfluorination, but other ethers,

$$CH_3\text{-}O\text{-}CH_3 + 6\ HF \xrightarrow[\text{electrolysis}]{0^\circ,\ 760\ mm} CF_3\text{-}O\text{-}CF_3 + 6H_2$$

such as dioxane (I), undergo simultaneous chain cleavage, yielding open chain compounds (II).



$$+\ 10\ HF \longrightarrow CF_3\text{-}O\text{-}CF_2CF_2\text{-}O\text{-}CF_3 + 9\ H_2$$

I II

A characteristic property of these solvents is illustrated by their inability to dissolve strong Lewis acids. This is only another manifestation of the strong inductive effect of the fluorine atom which renders the ether oxygen atom void of all basic properties. It will be shown later that few if any reactions of fluoro ethers involve ~~nucleo~~electrophilic attack on oxygen.

The Fowler Process

The Fowler process, a second industrial method, utilizes powdered cobalt trifluoride as a fluorinating agent (3). Cobalt trifluoride is first prepared by passage of fluorine gas over well-stirred solid cobalt (II) fluoride in a column at 250°. Excess

$$CoF_2 + F_2 \xrightarrow{250^\circ} 2\ CoF_3$$

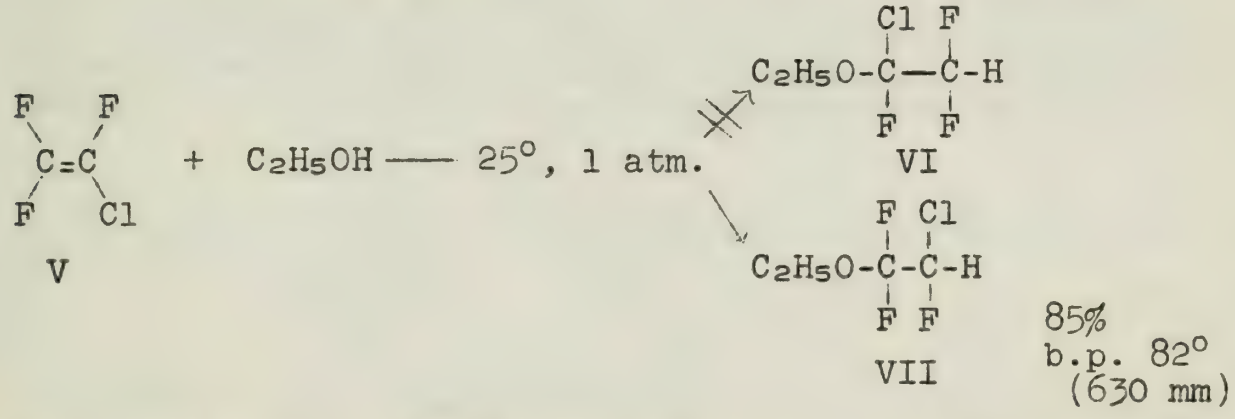
fluorine gas is removed by subsequent flushing with an inert gas. Fluorination is conducted next by passing the vaporized alkyl ether through the gradiently heated column. It was found that during the initial step of the substitution reaction, when relatively few fluorine atoms are in the molecule, that temperatures just above the boiling point of the starting material were desirable. As the degree of fluorination increases, substitution becomes increasingly more difficult and therefore higher temperatures are required to complete the process. In order to achieve complete fluorination the column must be gradiently heated from just above the boiling point of the starting material to a final temperature of 350°. Perfluorodicyclohexyl ether (IV) is produced in this manner in a yield of 15% for each fluorinating cycle of diphenyl ether (III). Regeneration of

$$\underset{\text{III}}{C_6H_5\text{-}O\text{-}C_6H_5} + CoF_3 \longrightarrow CoF_2 + \underset{\text{IV}}{C_6F_{11}\text{-}O\text{-}C_6F_{11}} \quad 15\%$$

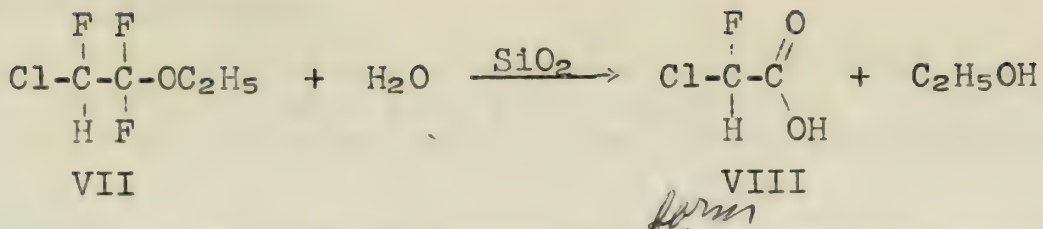
the catalyst is accomplished by removal of the hydrocarbon and repetition of step one. Although cobalt trifluoride has been the most widely used fluorinating agent in the Fowler process, manganese trifluoride and cerium tetrafluoride have been found to be better halogenating agents for higher boiling hydrocarbons (4).

Olefinic Addition

α,α-Difluoroethers are most commonly prepared by the base-catalyzed addition of alcohols or phenols to polyfluoroethylenes (5,6,7,8,9). Yields of seventy to eighty per cent are readily obtained by bubbling the olefin into a solution of the desired alcohol or phenol saturated with potassium hydroxide. It is apparent that if the olefin is unsymmetrical the addition may proceed by two different routes. When chlorotrifluoroethylene (V) is condensed with ethanol, either the 1-chloro-1-fluoroether (VI) or the 1,1-difluoro-



ether (VII) may be formed (10); however, only the α,α-difluoroether was isolated. Furthermore structure VI is not consistent with the stability of the ether (8). An α-choloroether of this type would permit elimination of hydrochloric acid quite easily with the formation of trifluorovinyl ether, $C_2H_5\text{-}O\text{-}CF{=}CF_2$. Such a compound was not isolated. That the thermodynamically more stable product (VII) was formed has been established by hydrolysis of the product over silica to chlorofluoroacetic acid (VIII).



VII VIII

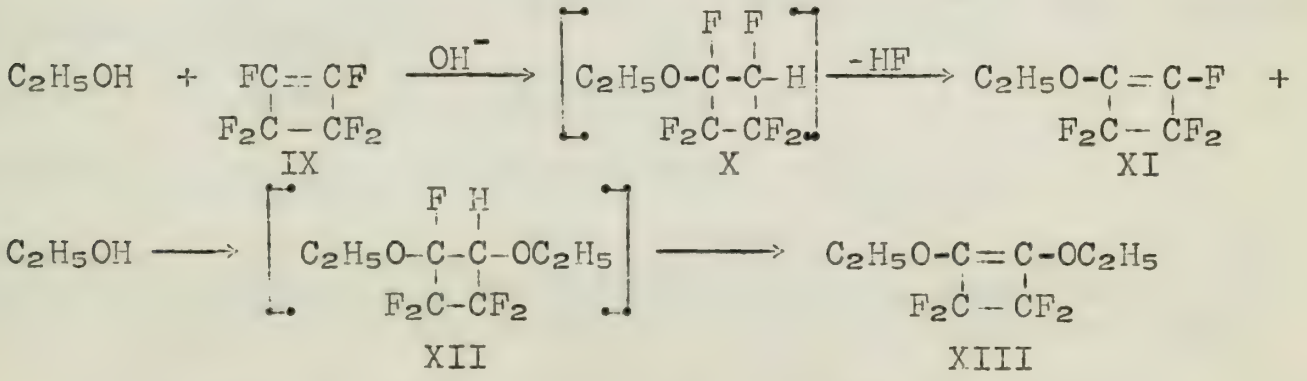
In every example of alcohol addition to chlorotrifluorethyl, 1,1-dichloro-2,2-difluoroethyl, and 1-chloro-2,2-difluoroethyl ethyl ethers only the α,α-difluoroethers can be isolated (5).

The effect of variations in the basicity of alcohol was also studied (5). Methyl, ethyl, isopropyl and t-butyl alcohols were added to each of the above olefins. Although relatively wide variations in conditions were employed during the addition reactions, no products were identified that could have resulted from addition except as postulated. The addition in each case leads to saturated ethers as the principal product with the exception of t-butyl alcohol.

That the reaction is spontaneous is shown by the free energy change for the addition of ethyl alcohol to chlorotrifluoroethylene. This change is plus 2.6 kcal. and becomes zero at 200°K. Although the reaction proceeds smoothly at room temperature and atmospheric pressure the equilibrium would be favored by low temperature and high pressure (8).

In a similar fashion phenols have been added to α,α-difluoroethylenes in the presence of base (9). It was found that with chlorotrifluoroethylene the best yield was obtained at 40°; addition at lower temperature resulted in lower yields, and at 0° no ether was formed. Maximum yield of phenolic addition to unsym-dichlorodifluoroethylene was obtained at 10°. In this reaction higher temperatures leads to the formation of dichlorofluorovinyl ether.

Isolation of saturated ethers from the condensation of alcohols with haloölefins is not always possible (7). In an attempted preparation of ethoxyhexafluorocyclobutane (X) from the cyclobutene IX only an olefin, ethoxypentafluorocyclobutene (XI), was isolated.



IX X XI

XII XIII

Apparently elimination of hydrogen fluoride from the intermediate is spontaneous at room temperature. Since hydrofluoric acid neutralizes the basic catalyst, diaddition of ethanol is prevented. On the other hand, if excess base is employed 1,2-diethoxytetrafluorocyclobutene (XIII) is isolated as the major product.

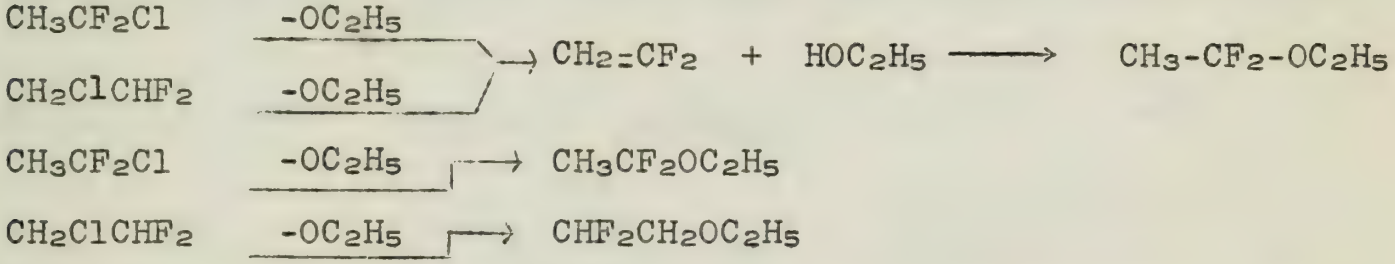
Saturated Fluoroethanes

α,α-Difluoroethers are readily prepared by treating 1,2,2-trichloro-1,1-difluoroethane with aryl oxides (11). It was originally believed that the chlorine atom of the $-CF_2Cl$ group possessed

unusual activity since it was apparently the point of attack by the aryl oxide in a Williamson type reaction. It has also been suggested that the phenoxide ion might remove a proton forming an olefin by an E_2 elimination. The olefin in turn could combine with a molecule of phenol to form an aryl ether (12). In the present example it is impossible to draw any conclusion concerning the mechanism by which

the fluoroethers are formed since both the displacement and the olefin addition mechanism yield the same product. However by judicious choice of starting materials the two routes can be made to give different results and the predominance of one mechanism over the other determined by the nature of the products.

A study of the reactions of the isomeric chloro-1,1-difluoroethanes with sodium ethoxide in ethanol would indicate the course of the reaction. If the formation of the fluoroether proceeds by elimination and subsequent addition of the alcohol, both ethanes will give the same fluoroether; if the reaction is a simple displacement of the chlorine atom by the ethoxide ion, two different

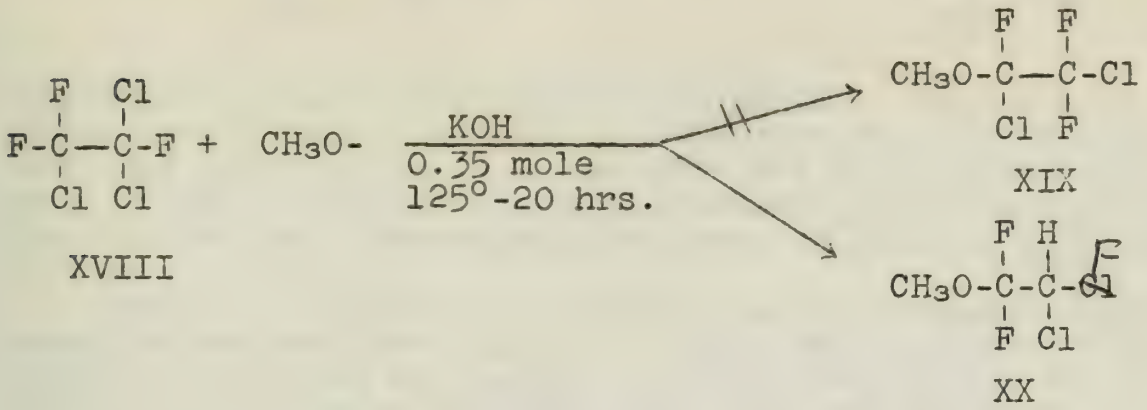


products will be obtained. It has now been found that both difluorochloroethanes give the same end product, ethyl acetate--a hydrolysis product of the expected 1-ethoxy-1,1-difluoroethane.

In a number of cases, α,α-difluoroethers are reactive and this property seems to be associated with the atoms on the adjacent carbon atom. For example, while perfluorodibutyl ether is inert under a variety of conditions, 1-ethoxy-1,1,2,2-tetrafluoroethane is readily converted to ethyl difluoroacetate by treatment with sulfuric acid.

If 1,1,2-trichloro-1,2,2-trifluoroethane (XVIII) is treated with an alkoxide, an S_N2 displacement should take place since there are no

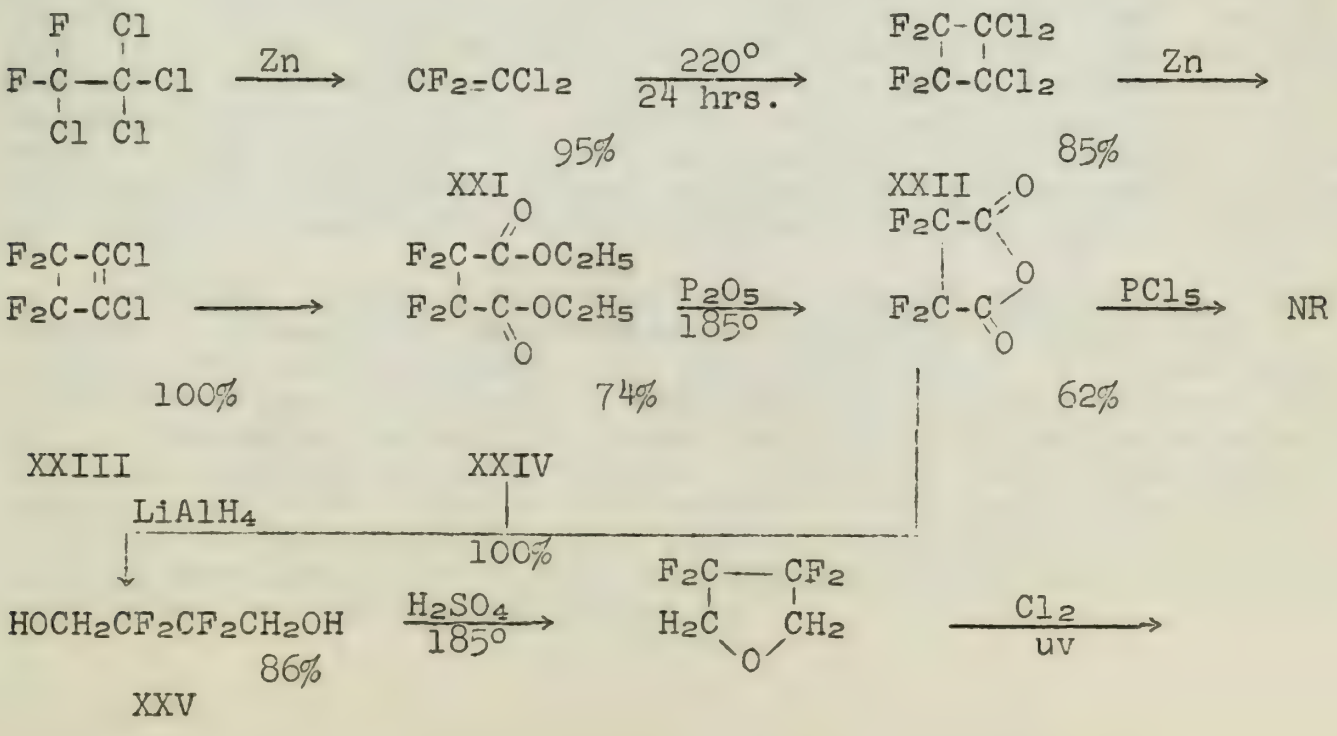
β-hydrogen atoms, and therefore elimination of hydrogen halide is impossible. The expected product of the Williamson synthesis (XIX)

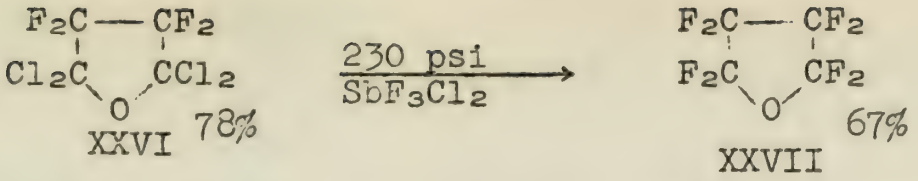


did not form but rather a tetrahalo derivative (XX) (13). In this example as well as in the reaction of unsym-trichlorotrifluoroethylene (XVIII) with sodium phenoxide (11) the tetrahalo ether (XX) is the product of addition of CH_3O^- to the olefin, but here the olefin must be formed by a dechlorofluorination reaction. This unusual reaction sequence and the fact that perfluoromethyl ether is extremely stable (14) indicate that S_N2 displacement of fluorine in α-fluoro ethers proceeds with difficulty.

Halide Exchange

Halide exchange with the easily prepared α-chloro ethers provides a convenient route to α-fluoro compounds (15). α,α-Dichloroethers may be fluorinated by refluxing them with antimony trifluoride for several hours, after which the mixture is washed with water, dried and fractionated. This method has also been employed in the preparation of perfluorotetrahydrofuran (16). The initial step of the reaction is dimerization of 1,1-dichloro-2,2-difluoroethylene (XXI) to a cyclobutane derivative (XXII). This in turn was dechlorinated to a cyclobutene (XXIII) which was oxidized to diethyl perfluorosuccinate (XXIV). This ester was saponified and the acid



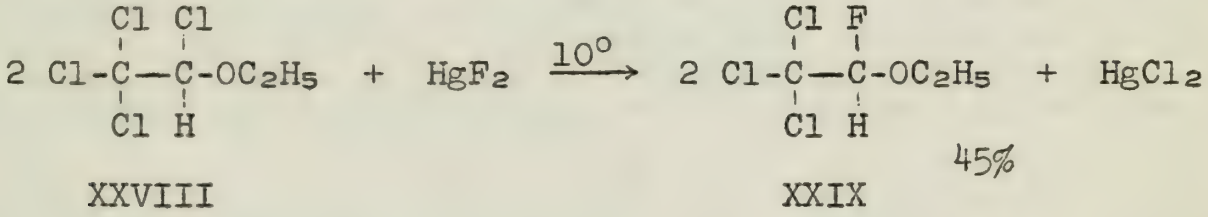


XXVI 78%

XXVII 67%

converted to the corresponding anhydride. When chlorination of the anhydride failed, the perfluoro diester was reduced to a diol (XXV); this was cyclized to an ether that was chlorinated (XXVI). Treatment of the tetrachloride with antimony chlorotrifluoride produced the desired perfluorotetrahydrofuran (XXVII) in good yield (16).

While information on polyfluoroethers is abundant, data on monofluoroethers are scarce. It has been found that monofluoroethers (XXIX) can be prepared readily from their chloro analogs (XXVIII) by halogen exchange with mercuric fluoride (17). The exchange reaction is favored by high temperature but so are the un-

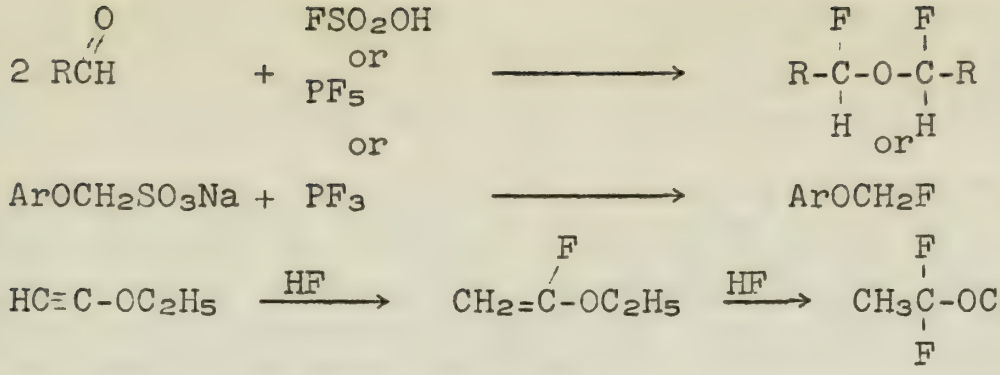


XXVIII XXIX 45%

desirable side reactions, elimination of hydrogen halide and polymerization. These side reactions could be avoided only with compounds in which hydrohalide was not readily lost as with $CCl_3CHClOR$, CH_2ClOR and $CHCl_2CClHOR$. Fluoro compounds could not be prepared from α-chloro diethyl ether or from α,α-dichlorodiethyl ether by this method. Mercuric fluoride was added to these compounds at 0°, but on coming to room temperature the reaction mixture polymerized. Since acids initiate polymerization this side reaction might be prevented by adding silica gel to the cold reaction mixture.

The efficiency of other catalysts in exchange reactions was found to decrease in the following order $HgF_2 > TlF > AgF > KF$ while Al_2F_6, $CrF_3 \cdot 3 \cdot 5H_2O$ and fluorosulfonic acid did not act as exchange agents. With the better reagents yields of fluoroethers varied from 15 to 40%. The presence of free hydrochloric acid decreased the yield of fluoroether. Hydrochloric acid is a product of the decomposition of the α-chloroethers and is always present after these ethers have been allowed to stand for a short period of time. Stirring the freshly distilled chloroether with active silica gel and using it immediately affords higher yields of α-fluoroethers.

Attempts to prepare α-fluoroethers by the addition of formaldehyde to ethanol in the presence of potassium fluoride and hydrochloric acid produced only the chloroether. A better procedure might be to use hydrofluoric acid directly, but this was not tried (17). Analogous methods to those for preparing α-chloroethers have not been applied to α-fluoroethers because of the inconvenience in handling hydrogen fluoride and because of the lack of available fluorine-containing reagents. Addition of hydrofluoric acid to vinyl ethers and other potential reactions which have not been investigated are illustrated below.



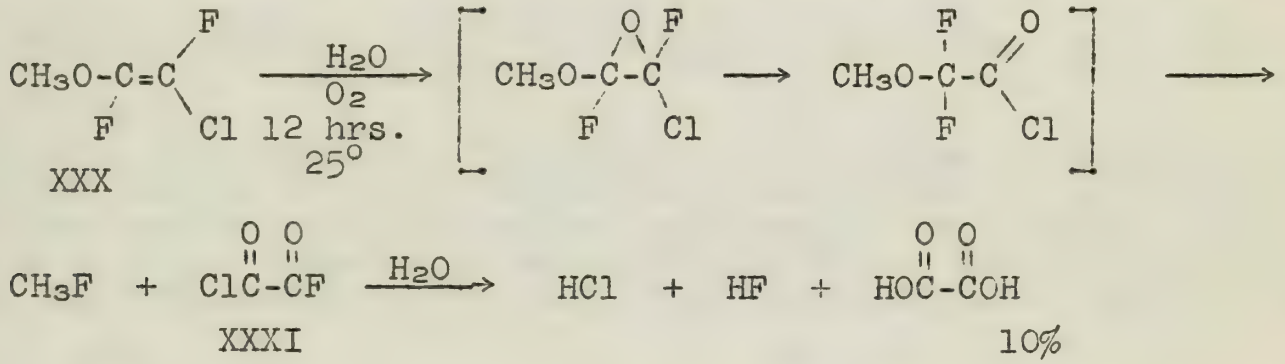
(1)

(18,19)

REACTIONS

Oxidation

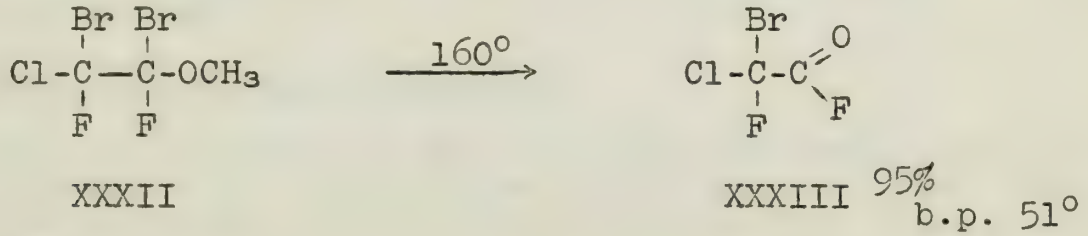
The α-fluoroethers are rather inert and experience only a limited number of reactions. They are easily converted to vinyl ethers by loss of hydrogen fluoride and undergo reactions characteristic of these olefins. In addition to polymerization and addition vinyl ethers readily suffer oxidation. 1-Methoxy-1,2-difluoro-2-chloroethylene (XXX) is autoxidized on standing to a mixed oxalyl



halide (XXXI); an epoxide has been postulated as the intermediate. The acid halide was characterized by hydrolysis to hydrochloric, hydrofluoric and oxalic acid (13).

Pyrolysis

Thermal instability is illustrated by the pyrolysis of 1,2-dibromo-2-chloro-1,2-difluoroethyl methyl ether (XXXII) to the novel



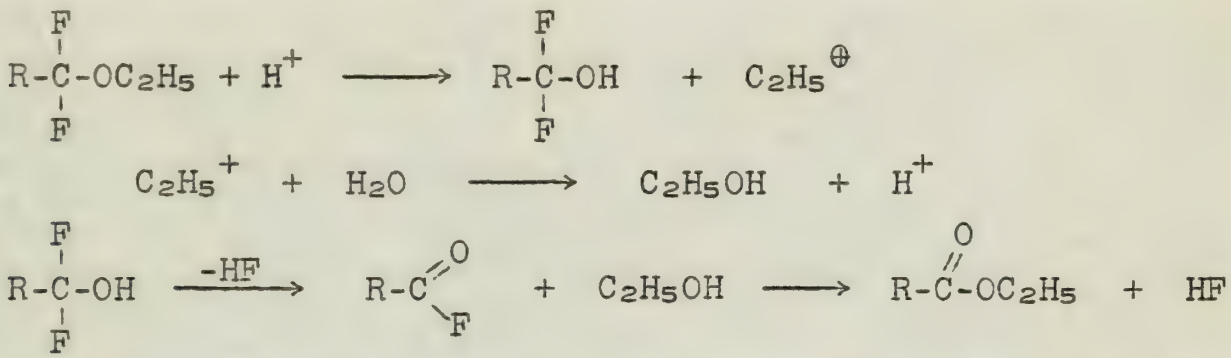
acid halide, bromochlorofluoroacetyl fluoride (XXXIII), which was further characterized by hydrolysis and ammonolysis (13).

Solvolysis

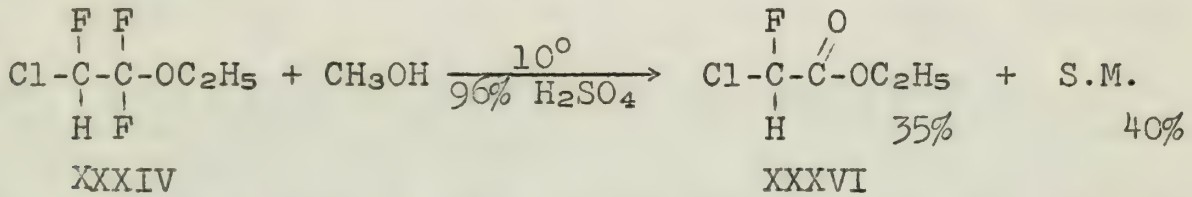
Orthoester formation has been demonstrated as characteristic of α,α-dihaloethers. Refluxing ethanol and sodium methoxide under

forcing conditions converts 1,1,2-trifluorochloroethyl ethyl ether (XXXIV) into the corresponding ortho ester. Hydrolysis with sulfuric acid converts the product to ethyl chlorofluoroacetate (XXXVI), thus proving that the compound was the ortho ester (5).

The ease of hydrolysis of 1,1,2-trifluorochloroethyl ether (XXXIV) and similar ethers is surprising since most α,α-difluoroethers are unreactive. Good yields of the hydrolysis product are obtained at low temperature, since heat favors polymerization reactions, with concentrated sulfuric acid. During the process etching of the glass apparatus was observed; therefore, hydrogen fluoride elimination must have taken place (20). If the reaction occurs as suggested by Hammett for nonfluorinated ethers, then the ether oxygen atom must be protonated initially. This ion cleaves into a molecule of alcohol and a carbonium ion, which in turn reacts to



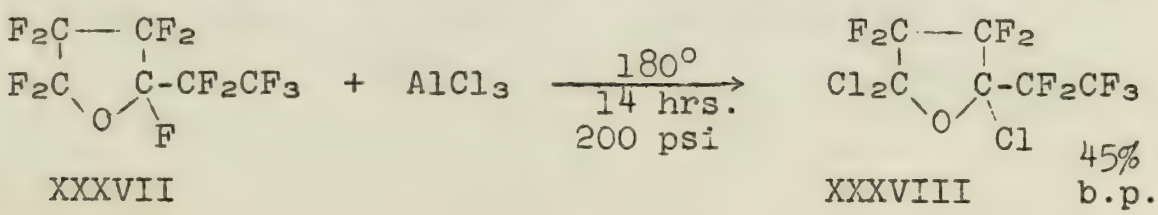
produce a second alcohol. Elimination of hydrogen fluoride followed by solvolysis of the acyl halide could account for the products. To test this mechanism 1,1,2-trifluorochloroethyl ethyl ether (XXXIV) was solvolyzed in methanol; however, none of the expected methyl ester was obtained but only ethyl chlorofluoroacetate (XXXVI). This



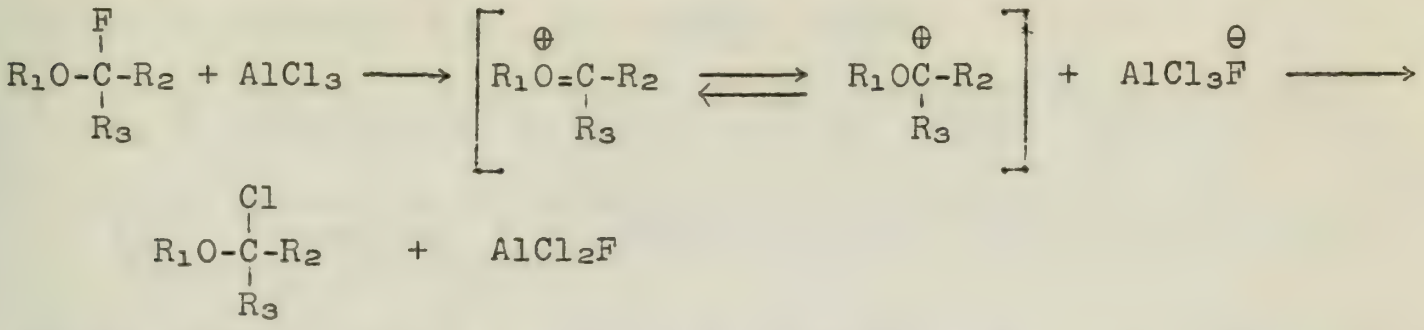
demonstrates that hydrolysis does not involve cleavage of the ethoxyl group (20) but proceeds by E2 elimination of hydrogen fluoride and addition to the vinyl ether. This is reasonable since protonation of the ether oxygen atom is highly unlikely because of its low electron density.

Reactions with Aluminum Chloride

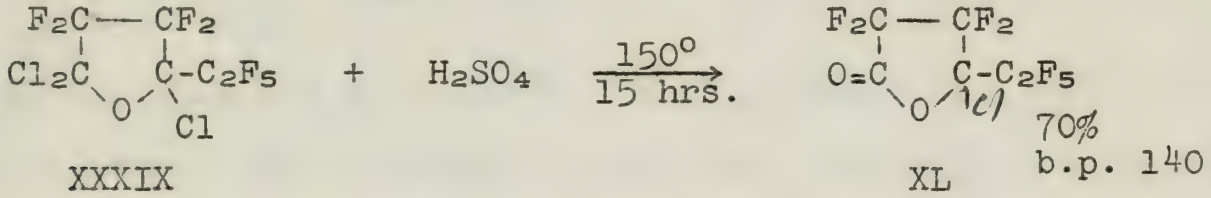
The only reaction so far reported for perfluoroethers, which do not permit E 2 elimination to the corresponding olefin, is that of halide exchange with aluminum chloride (21). Perfluoro-α-ethyltetrahydrofuran (XXXVII) exchanges fluorine for chlorine atoms under forcing conditions to produce the stable trichloride (XXXVIII). Apparently the mono and dichloroether intermediates are more reactive



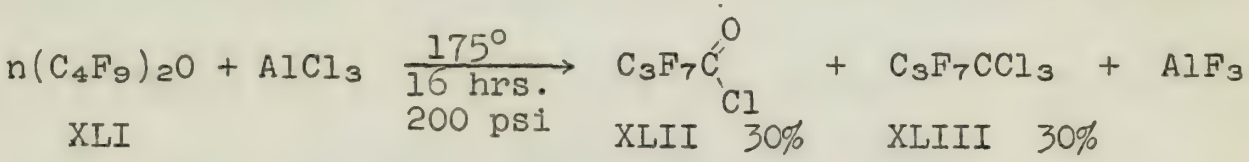
than the perfluoroether since they could not be isolated. The proposed mechanism for this exchange does not involve either an olefin intermediate or cleavage of the ether linkage. Aluminum chloride first coordinates with one of the α-fluoro atoms and then



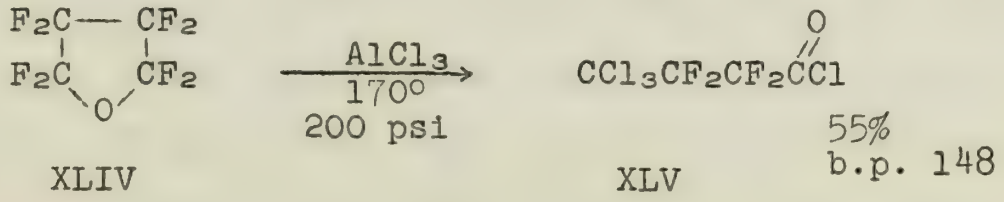
removes it as part of a complex ion. The residual carbonium-oxonium ion later captures a chlorine atom from the aluminum chlorofluoride complex to complete the exchange. The low reactivity of the perfluoroethers may be accounted for by this mechanism as R_2 and R_3 are powerful electron attracting fluorine atoms or perfluoroalkyl groups which decrease the ease of formation of the positive ion. Similarly this argument implies that the α,ά,ά-trichloroperfluoroethers should be more reactive towards strongly acidic reagents than are the perfluoroethers themselves. This is illustrated by the slow solvolysis of the trichloride (XXXIX) in hot fuming sulfuric acid to a lactone (XL), while the perfluoroethers are inert toward the same



reagent. When α,α,ά,ά-tetrafluoroethers were similarly treated a quite different result was obtained (22). Exchange halogenation of perfluorodi-n-butyl ether (XLI) cleaved the ether to an acid halide (XLIII). Although the trichloroethers are stable under the reaction conditions it is known that α,α,ά,ά-tetrachloroethers cleave spontaneously to acid halides and trichloroalkyls under these conditions. An extension of this study to perfluorotetrahydropyran



and perfluorotetrahydrofuran proceeded in a similar manner with ring cleavage to form the ω-trichloromethylperfluoroacyl chloride (XLV) (23).



BIBLIOGRAPHY

1. L. Summers, Chem. Rev., 55, 301 (1955).

2. J. H. Simmons, C.A., 44, P-5236b (1950).

3. W. B. Burford, R. D. Howler, J. M. Hamilton, H. C. Anderson, C. E. Weber and R. G. Sweet, Ind. Eng. Chem., 39, 319 (1947).

4. R. D. Gowler, H. C. Anderson, J. H. Hamilton, Jr., W. B. Burford III, A. Spadetti, S. B. Bitterlich and I. Litant, Ind. Eng. Chem., 39, 343 (1948).

5. P. Tarrant and H. C. Brown, J. Am. Chem. Soc., 73, 1781 (1951).

6. W. T. Miller, E. W. Fager and P. H. Griswold, J. Am. Chem. Soc., 70, 431 (1948).

7. J. T. Barr, H. E. Rapp, R. L. Pruett, J. D. Gibson and R. H. Lafferty, J. Am. Chem. Soc., 72, 4480 (1950).

8. J. D. Park, J. Am. Chem. Soc., 70, 1550 (1948).

9. P. Tarrant and H. C. Brown, J. Am. Chem. Soc., 73, 5831 (1951).

10. J. D. Park, E. Halpern and J. R. Lacher, J. Am. Chem. Soc., 74, 4104 (1952).

11. E. T. McBee and R. O. Bolt, Ind. Eng. Chem., 39, 412 (1947).

12. P. Tarrant and J. Young, J. Am. Chem. Soc., 75, 932 (1953).

13. R. S. Corley, J. Lal and M. W. Kane, J. Am. Chem. Soc., 78, 3489 (1956).

14. R. G. Jones, J. Am. Chem. Soc., 70, 143 (1948).

15. H. S. Booth, C.A., 31, P-1037 (1937).

16. A. L. Henne and S. B. Richter, J. Am. Chem. Soc., 74, 5420 (1952).

17. C. T. Mason and C. C. Allain, J. Am. Chem. Soc., 78, 1682 (1956).

18. J. F. Arens, Rec. trav. chem., 74, 271 (1955).

19. L. Heslinga, G. J. Katerberg and J. H. Arens, Rec. trav. chem., 76, 968 (1957).

20. J. A. Young, P. Tarrant, J. Am. Chem. Soc., 71, 2432 (1949).

21. G. V. D. Tiers, J. Am. Chem. Soc., 77, 4837 (1955).

22. G. V. D. Tiers, J. Am. Chem. Soc., 77, 6703 (1955).

23. G. V. D. Tiers, J. Am. Chem. Soc., 77, 6705 (1955).

NEURAMINIC AND SIALIC ACIDS

Reported by J. F. Porter May 19, 1958

The chain of events which led to the recognition of neuraminic and sialic acids as chemical entities began with a study of the lipids found in horse kidney tissue (1,2,3). A lipid fraction was isolated which was water soluble and formed a viscous solution in concentrations of about two per cent. It developed an unusual red color when heated with orcinol and hydrochloric acid. A similar material was found in bovine brain and spleen tissue (4).

A class of lipids known as gangliosides can be isolated from the brains of men suffering from Nieman-Picks disease (5,6,7,8). The disease produces large deposits of fatty material in the brain, liver, and spleen (9). Like the lipids from horse kidney tissue, the gangliosides produced a red color when heated with orcinol and hydrochloric acid. They formed charcoal when treated with dilute solutions of mineral acids, and gave a positive Ehrlich test. The Ehrlich test involves treatment of the material with alkali and the subsequent addition of a mixture of p-dimethylaminobenzaldehyde and hydrochloric acid (10). A red color is produced by N-acetyl galactosamine and pyrrole. The gangliosides produced the usual color without the customary alkali pretreatment.

The nature of the reactions which occur during the Ehrlich test is not known. Their study is complicated by the fact that the action of alkali on simple sugars produces a wide variety of rearrangements (11). It seems possible that the hexosamines for which the test is primarily used first form a heterocyclic ring before undergoing further reaction. The gangliosides are found to a much lesser extent in normal brain tissue (12).

A low-molecular weight compound could be split from the gangliosides by heating them in a sealed bomb with methanolic hydrogen chloride (13,14,18). The compound gave a positive ninhydrin test and was given the name neuraminic acid.

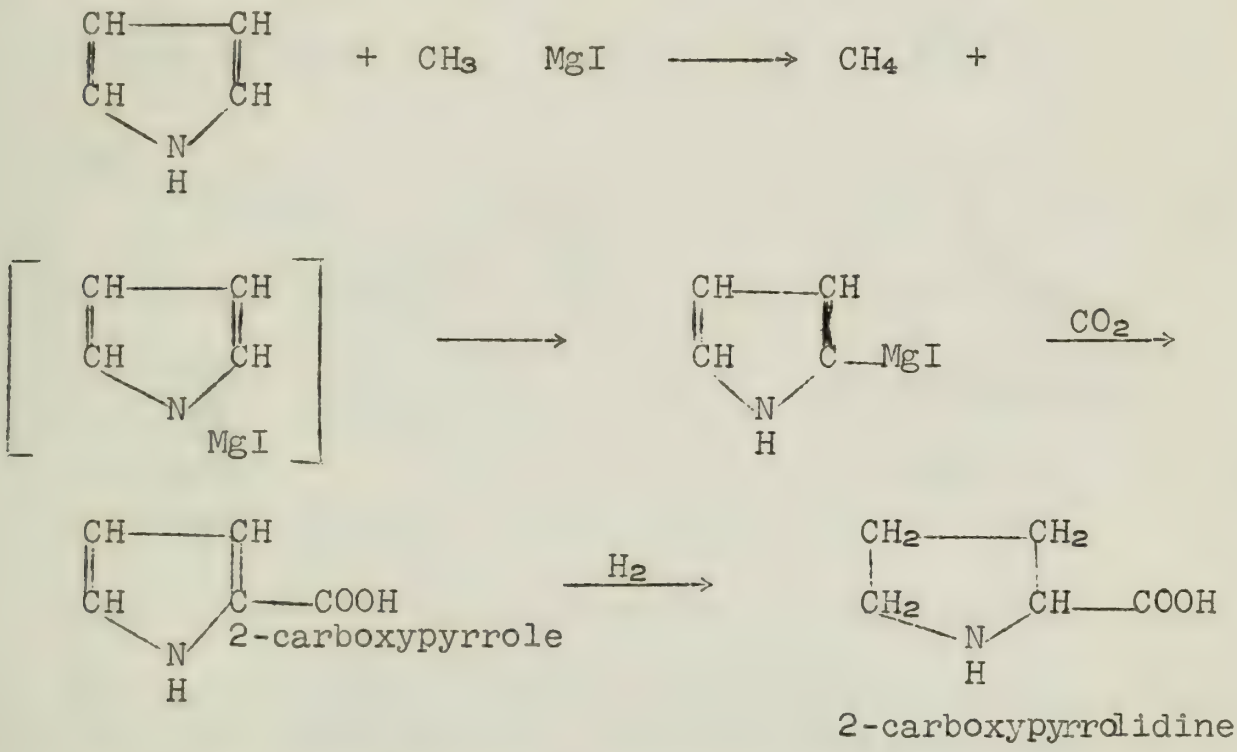
Another similar substance was isolated during an investigation of the carbohydrate moities of the glycoproteins (proteins containing a carbohydrate prosthetic group) of bovine submaxillary glands (15). A crystalline solid was isolated which gave positive orcinol and Ehrlich tests and formed charcoal when heated with mineral acids. It was later named sialic acid (16).

Sialic acid was rather unstable and decomposed quickly on standing (17). A stable methoxy derivative of sialic acid could be formed by heating the acid with methanolic hydrogen chloride (19).

Still another similar substance was found during a study of the effect of hemagglutination by influenza virus. The effect is produced by treatment of a suspension of red blood cells from an animal immunized against a virus strain with a suspension of the virus. A clumping and flocculation of the cells is produced. It was found that certain mucoproteins act as inhibitors for this effect (20). The

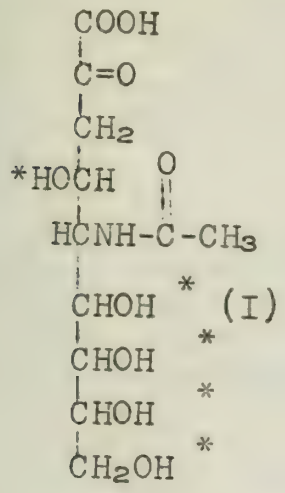
inhibitory power is lost if the protein is pretreated with the virus. During an attempt to characterize the products of the reaction between the mucoprotein and influenza virus it was found that a water-soluble dialyzable substance was split from the mucoprotein. Like the neuraminic acid it gave a positive Ehrlich test without alkali pretreatment, produced charcoal on treatment with mineral acids, and contained nitrogen. The presence of a keto group was shown by the Seliwanoff test, and of a free reducing group by the ability to reduce ferricyanide ion (21). In the earlier reports this compound was referred to as the "split product".

The fact that neuraminic acid, sialic acid, and the split product all gave a positive Ehrlich test without alkaline treatment made it seem possible that the substances were pyrrole derivatives. An alkaline hydrolysate of beef submaxillary gland mucoprotein was found to contain 2-carboxypyrrole (22). The product was compared with a synthetic sample of 2-carboxypyrrole, and the two substances proved to be identical in their R_f values in several solvents and ultra-violet absorbtion spectrum (23). The preparation of the synthetic material is outlined below (24):

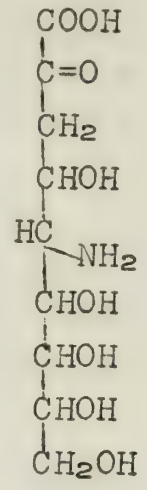


The derivative formed by hydrogenation of the natural product was identical with an authentic sample of 2-carboxypyrrollidine. The possibility that 2-carboxypyrrole was present in the natural material was excluded by an examination of the ultra-violet absorbtion spectrum of the material before hydrolysis. Contrary to the results expected by the investigators, no absorbtion peak was found near 256 mu, a point at which 2-carboxypyrrole absorbs intensely. Treatment of the split product with 0.1 N. sodium carbonate for ten minutes at 100°C. also produced 2-carboxypyrrole.

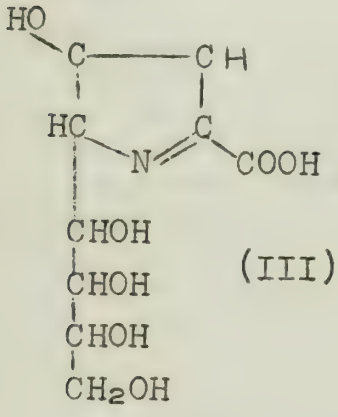
It seemed probable that the natural products contained an amino acid which on treatment with very mild alkali would form 2-carboxypyrrole. Treatment of 2-carboxypyrrolidine (proline), 4-hydroxy-2-carboxypyrrolidine, and N-acetylglucosamine with 0.1 N. sodium carbonate did not cause this transformation. It was postulated that the structure of the natural product might be that of compound (I) below and the following reaction scheme was proposed for the formation of 2-carboxypyrrole from sialic acid (25):



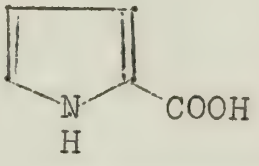
natural product



(II)



(III)



2-carboxypyrrole

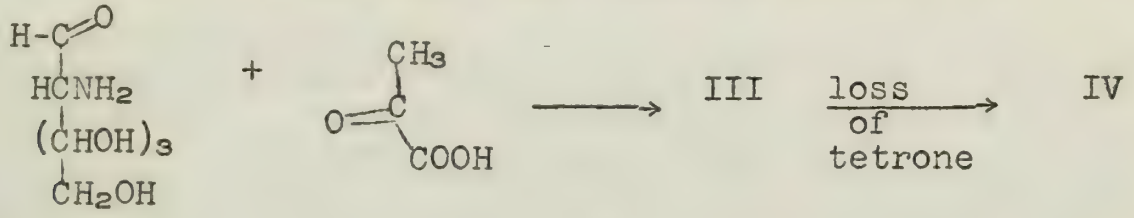
(IV)

One of the H's is replaced by an acetyl group

The proposal that a hexosamine might be built into the molecule was advanced, retracted, and later advanced again. It was first assumed that the sugar was split out under the conditions of the Ehrlich test. Attempts were made to test this assumption by a spectrophotometric comparison of the color produced in the Ehrlich reaction by N-acetylgalactosamine, the split product, and sialic acid, (20). The proposal was later believed to be wrong, however, after it was demonstrated that no hexosamine was liberated from the natural products upon acid hydrolysis, (16,26). It was assumed that the hexosamine was attached to the rest of the molecule by a glycosidic linkage, which should be easily hydrolysed.

The formula shown by structure (I) contains a hexosamine residue bound by an aldol linkage to the rest of the molecule. The structure is consistent with the following observations (27): Sialic acid prepared from bovine submaxillary mucin contains an N-acetyl group, an O-acetyl group, and five hydroxyl groups. Periodate splits off one primary alcohol group from the molecule. On treatment with concentrated sulfuric acid carbon monoxide was liberated, probably indicating an α-hydroxy or keto group. The reduction of sialic acid with sodium borohydride and subsequent treatment of the products with dilute hydrochloric acid at 100°C. produced no reducing substance. This excludes the presence of a glycosidic linkage in the molecule.

Evidence for the existence of the reaction (III)→(IV) was provided by condensing glucosamine with pyruvic acid in an alkaline medium. The two compounds would be expected to undergo a Knorr reaction under these conditions to form (III). It was possible to isolate 2-carboxypyrrole form the reaction mixture (28).



The formation of charcoal from compounds similar to neuraminic acid on treatment with mineral acid may be explained by a decarboxylation and deacetylation of the structure shown in formula (I) to form a 2-desoxy-4-amino-octose. It is well known that 2-desoxy sugars are extremely sensitive to treatment with mineral acids (30, 31). The compounds similar to neuraminic acid so far discussed bear a close chemical relationship to each other. Bovine sialic acid contains two acetyl groups, the split product one, and neuraminic acid none (32). That the sialic acid from bovine submaxillary glands was a derivative of neuraminic acid was shown by treating the former substance with methanolic hydrogen chloride in a sealed bomb at 105°C. The product was identified as neuraminic acid.

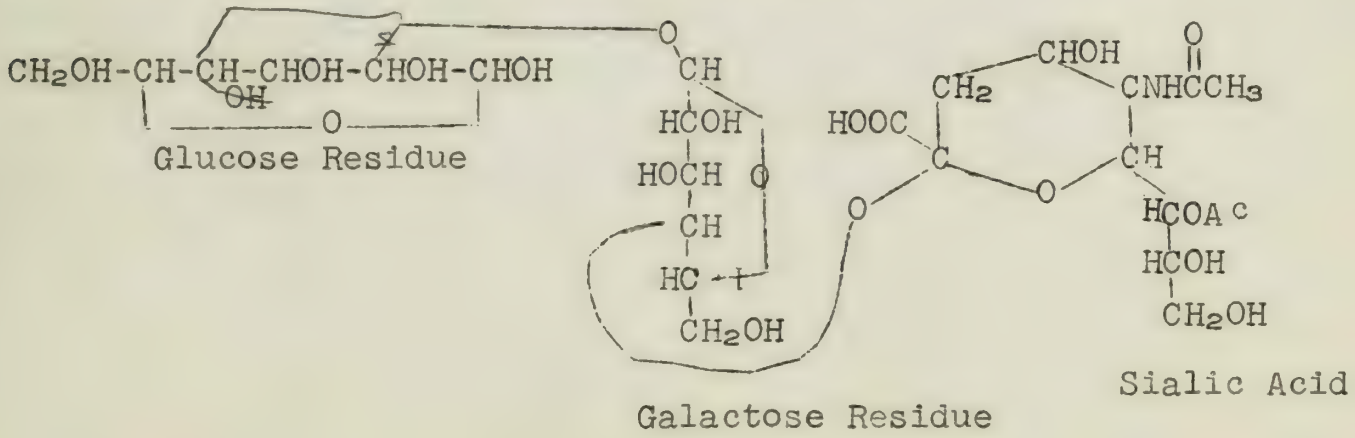
It was at first believed that the hexose structure built into sialic acid was D-glucosamine. The split product can be transformed into N-acetylglucosamine, carbon dioxide, and an unidentified two-carbon fragment by treatment with pyridine and nickel acetate (28). Chemical degradation of bovine sialic acid gives several products, one of which is N-acetylglucosamine (33). A compound identical to the split product was synthesized in low yields by leaving a mixture of N-acetylglucosamine and oxalacetic acid at pH 10-11 for three days (34,35). Sialic acid may be split to pyruvic acid and N-acetylglucosamine by extracts of Vibrio cholerae (36). An enzyme from Clostridium Perfringens was found, however, which cleaved the split product to pyruvic acid and N-acetyl-D-mannosamine (37). The enzyme would catalyze the formation of the split product from pyruvic acid and N-acetyl-D-mannosamine, but not from the glucosamine or galactosamine derivatives. It was recently found that N-acetyl-D-glucosamine may be isomerized to N-acetyl-D-mannosamine under the conditions used in the preparation of the split product from N-acetylglucosamine and oxalacetic acid.

Natural products similar to neuraminic acid have been found in a dozen or more types of animal tissue. In many cases the substance was identified by the formation of a red color in the orcinol test, with no attempt made to determine structure (38-59). Sialic acid preparations from horse and pig submaxillary glands differ from the bovine product in their X-ray diffraction patterns (27). The difference may be due to differences in the acyl groups bound to the molecule (60, 61). The three authors who have done by far the greater part of the work in the field, G. Blix, A. Gottschalk, and E. Klenk, have recently published a joint paper which summarizes the nomenclature they have agreed upon (62). The unsubstituted parent compound shown below is designated neuraminic acid.

$$HOCH_2\text{-}(CHOH)_3\text{-}CHNH\text{-}CHOH\text{-}CH_2\text{-}C(=O)\text{-}COOH$$

In the future, "sialic acid" will be used as a group name for acetylated derivatives of neuraminic acid. An acid previously named haematinic acid isolated from horse blood cells (29,63,64) proved to be identical with methoxyneuraminic acid (65). Two other acids, probably quite similar to if not identical with N-acetylneuraminic acid have been reported. Gynaminic acid was prepared from human milk during an attempt to isolate a growth-promoting factor for a bacteria, lactobacillus bifidus. It was at first believed to differ from N-acetylneuraminic acid because of an ambiguous elemental analysis and acetyl determination. The substance was found later to be chromatographically inhomogeneous. The infrared absorbtion spectrum and elemental analysis of a pure preparation of the material made it appear to be identical with N-acetylneuraminic acid (67). Although purified gynaminic acid preparations have no activity as growth factors for the bacteria they are isolated from the saccharide fractions having the highest activity.

A similar substance, isolated from cow's milk as a crystalline derivative, was called lactiminic acid (68,69). It has the same empirical formula as N-acetylneuraminic acid. From rat mammary gland tissue was isolated (70) a "neuraminlactose", which on mild acid treatment gave N-acetylneuraminic acid and lactose. The structure proposed for this compound is shown below (67).



Both neuraminic acid and its N-acetyl derivative have strong reducing power. A two per cent solution of bovine submaxillary mucin, however, does not reduce the weakly basic Benedict's reagent. Reduction takes place when the more strongly basic Fehling's reagent is used. This finding indicated a masking of the reducing group by an alkali sensitive glycosidic link. The pretreatment of the mucin with a viral enzyme increased its reducing power greatly. The low non-amino sugar content and high galactosamine content of the mucin (71,72) suggested galactosamine was a partner in the bond, a suggestion that was upheld by a chromatographic examination of the barium hydroxide hydrolysate of the mucin (73). Neuraminic acid, a spot found when N-acetylgalactosamine was subjected to the same conditions, and an unknown compound were found on the chromatogram. Treatment of the unknown with a culture of influenza virus liberated neuraminic acid. Heating of the unknown with barium hydroxide at 100°C. for six hours gave 2-carboxypyrrole and a compound found to be produced from N-acetylglucosamine under the same conditions.

Neuraminlactose was treated with a culture of influenza virus, and the sialic acid present was liberated. The original material is thought to contain sialic acid joined to a galactose moiety by an O-glycosidic linkage. If the influenza virus enzyme is fairly specific and will act only on O-glycosidic linkages the sialic acid may be joined by such a linkage in all influenza-virus-inhibitory mucoproteins.

A high-molecular-weight substance similar to sialic acid has been found in cultures of Escherichia coli and has been named colominic acid, (74). Work has been done on the linkage of neuraminic derivatives in the gangliosides (25). Because of the wide occurence of neuraminic acid derivatives in animal tissue it has been postulated that they may serve as virus antagonists. No quantitative relationship was found, however, between the concentration of sialic acid and in a mucin sample (as measured (76,77) by the depth of color in the orcinol test) and its virus inhibitory activity (78). The biological role of the neuraminic acid derivatives is not known.

BIBLIOGRAPHY

1. K. Landsteiner and P.A. Levene, Proc. Soc. Exptl. Biol. Med., 23, 343 (1926).
2. K. Landsteiner and P.A. Levene, J. Biol. Chem., 75, 607 (1927).
3. K Landsteiner and P.A. Levene, Proc. Soc. Exptl. Biol. Med., 24, 693 (1927)
4. E. Walz, Z. physiol. Chem. Hoppe-Seyler's, 210, 66 (1927).
5. E. Klenk, Z. physiol. Chem. Hoppe-Seyler's, 235, 24 (1935).
6. E. Klenk, Z. physiol. Chem. Hoppe-Seyler's, 262, 128 (1939).
7. E. Klenk, Z. physiol. Chem. Hoppe-Seyler's, 267, 128 (1940).
8. E. Klenk, Z. physiol. Chem. Hoppe-Seyler's, 282, 84 (1947).
9. E. Klenk, Z. physiol. Chem. Hoppe-Seyler's, 229, 151 (1934).
10. W.W. Pigman and R.M. Goepp, Jr., "Chemistry of the Carbohydrates Academic Press, Inc., New York, 1948, p. 418.
11. M.L. Wolfram, J. Am. Chem. Soc., 77, 3318 (1955).
12. G. Blix, Skand. Arch. Physiol., 80, 46 (1938).
13. E.Klenk, Z. physiol. Chem. Hoppe-Seyler's, 268, 50 (1941).
14. E. Klenk, Z. physiol. Chem. Hoppe-Seyler's, 288, 216 (1951).
15. G. Blix, Z. physiol. Chem. Hoppe-Seyler's, 240, 43 (1936).
16. G. Blix and L. Svennerholm, Acta. Chem. Scand., 6, 358 (1956).
17. E. Klenk, Angew. Chem. 68, 349 (1956).
18. E. Klenk, Z. physiol. Chem. Hoppe-Seyler's, 292, 241 (1953).
19. E. Klenk and K. Lauenstein, Z. physiol. Chem. Hoppe-Seyler's, 291, 147 (1952).
20. A. Gottschalk and P.E. Lind,Nature, 164, 232 (1949).
21. A. Gottschalk, Nature, 167, 845 (1951).
22. A. Gottschalk, Nature, 172, 808 (1953).
23. A. Gottschalk, Nature, 174, 653 (1954).
24. B. Oddo, Gazz. chem. ital., 39, 649 (1909).
25. A. Gottschalk, Nature, 176, 881 (1955).
26. E. Klenk, Z. physiol. Chem. Hoppe-Seyler's, 301, 235 (1955).
27. G. Blix, E. Lindberg, and L.Odin, Nature, 175, 340 (1955).
28. A. Gottschalk, Arch. Biochem. and Biophys., 69, 37 (1957).
29. T. Yamakawa and S. Suzuki, J. Biochem. Tokyo, 38, 199 (1951).
30. A. Gottschalk, Australian J. Sci., 18, 178 (1956).
31. A. Gottschalk, Yale J. Biol. Med., 28, 525 (1956).
32. E. Klenk and H. Faillard, Z. physiol. Chem. Hoppe-Seyler's, 298, 230 (1954).
33. R. Kuhn and R. Brosmer, Chem. Ber., 89, 158 (1956).
34. J.W. Cornforth, M.E. Davies, and A. Gottschalk, Proc. Chem. Soc., 1957, 25.
35. J.W. Cornforth, Biochem. J., 68, 57 (1958).
36. R. Heimer and K. Meyer, Proc. Natl. Acad. Sci. U.S., 42, 728 (1956).
37. S. Roseman, J. Am. Chem. Soc., 80, 498 (1958).
38. E. Klenk and F. Rennkamp, Z. physiol. Chem. Hoppe-Seyler's, 273, 253 (1942).
39. K. Schuwirth, Z. physiol. Chem. Hoppe-Seyler's, 278, 1 (1943).
40. T. Yamakawa and S. Suzuki, J. Biochem. Tokyo, 43, 63 (1956).
41. J. Folch, S. Arsove, and J.A. Meath, J. Biol. Chem. 191, 819 (1951).
42. E. Klenk, Z. physiol. Chem. Hoppe-Seyler's, 275, 164 (1953).
43. E. Klenk, Z. physiol. Chem. Hoppe-Seyler's, 303, 78 (1956).

44. E. Klenk and K. Lavenstein, Z. physiol. Chem., Hoppe-Seyler's, 291, 249 (1952).
45. T. Yamakawa and S. Suzuki, J. Biochem. Tokyo, 40, 611 (1953).
46. E. Klenk and K. Lavenstein, Z. physiol. Chem. Hoppe-Seyler's, 295, 164 (1953).
47. L.I. Woolf, Biochem. J., 56, XVI (1954).
48. L. Svennerholm, Acta. Chem. Scand. 10, 1048 (1956).
49. J. Hoover, G.A. Braun, and P. Gyorgi, Arch. Biochem. and Biophys., 47, 216 (1953).
50. L Odin, Acta Chem. Scand., 9, 1235 (1955).
51. P.B. Diezel, Naturwissenschaften, 42, 487 (1955).
52. E. Klenk and H. Faillard, Z. physiol. chem. Hoppe-Seyler's, 299, 191 (1955).
53. L. Odin, Acta Chem. Scand., 9, 714 (1955).
54. L. Odin, Acta Chem. Scand., 9, 862 (1955).
55. P Bohm and L. Baumeister, Z. physiol. Chem. Hoppe-Seyler's, 305, 42 (1956).
56. L.L Uzmann and M.K. Rumley, Proc. Soc. Exptl. Biol. Med., 93, 497 (1956).
57. A. Martinson and L. Svennerholm, Biochem. et Biophys. Acta, 23, 652 (1957).
58. G. Springer, Naturwissenschaften, 42, 37 (1955).
59. L. Svennerholm, Acta Chem. Scand. 9, 1033 (1955).
60. E. Klenk and G. Uhlenbruch, Z. physiol. Chem. Hoppe-Seyler's, 303, 266 (1957).
61. P.I. Werner and G. Blix, Bull. soc. chim. Belge, 65, 202 (1956).
62. G. Blix, A. Gottschalk, and E. Klenk, Nature, 179, 1088 (1957).
63. T. Yamakawa and S. Suzuki, J. Biochem. Tokyo, 38, 199 (1951).
64. T. Yamakawa and S. Suzuki, J. Biochem, Tokyo, 40, 7 (1953).
65. E. Klenk and H Wolter, Z. physiol. Chem., 291, 259 (1952).
66. F. Zilliken, G.A. Braun, and P. Gyorgi, Arch. Biochem. and Biophys, 54, 564 (1955).
67. F Zilliken, G. Braun, and P. Gyorgi, Arch. Biochem. and Biophys., 63, 394 (1956).
68. R. Kuhn and R. Brosmer, Chem. Ber., 87, 123 (1954).
69. R. Kuhn and R. Brosmer, Angew, Chem., 69, 514 (1957).
70. A. Gottschalk, Biochim. et Biophys. Acta, 23, 645 (1957).
71. A. Gottschalk, Biochim. et Biophys. Acta, 20, 560 (1956).
72. A. Gottschalk and G. Ada, Biochem. J. 62, 681 (1956).
73. A. Gottschalk, Biochim. et Biophys. Acta, 24, 649 (1957).
74. G.T. Barry and W.F. Goebel, Nature, 178, 207 (1957).
75. S. Bogoch, Nature, 180, 197 (1957).
76. E. Klenk and H. Langerbeins, Z. physiol. Chem. Hoppe-Seyler's, 270, 185 (1941).
77. L. Svennerholm, Biochim. et Biophys. Acta, 24, 604 (1957).