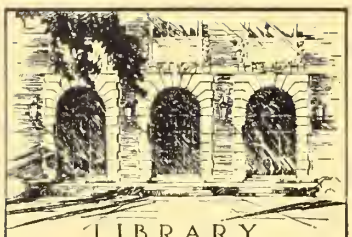
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RING ENLARGEMENT REACTIONS WITH DIAZOALKANES

Reported by T. H. Shepherd February 11, 1957

Introduction

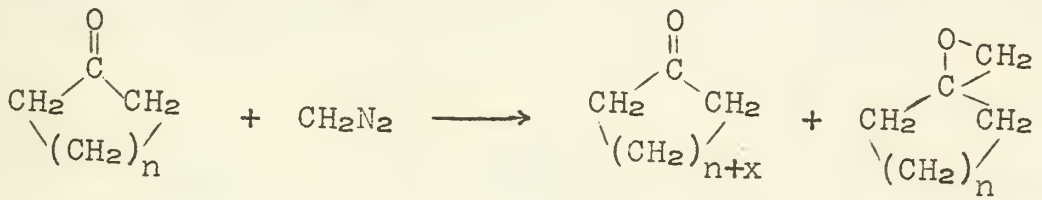
Diazoalkanes are among the most versatile reagents in organic chemistry. They can react as nucleophilic agents, electrophilic agents, radical sources, and as carbene sources. However only the first and last of these possibilities are important with regard to ring enlargement reactions.

Carbonyl compounds react with diazoalkanes to form a variety of products. Aldehydes yield the homologous methyl ketones in most cases, along with the epoxide. Alicyclic ketones react to give a preponderance of the epoxide except with the most simple ketones where appreciable yields of homologous ketones are obtained. Carbocyclic ketones yield both ring-enlarged products and the epoxide. Aromatic nuclei also are attacked by diazoalkanes under certain conditions to give ring-enlarged products. The remainder of the seminar is concerned with the latter two reactions.

Ring enlargement, for the purposes of this seminar is defined as the insertion of a R_2C moiety between two adjacent atoms in a ring. Thus the action of diazoalkanes on carbon-carbon unsaturation to form pyrazoline derivatives (1, 2), is not included.

RING ENLARGEMENT OF CYCLOALKANONES

Ketene and carbocyclic ketones react with diazomethane according to the following scheme:



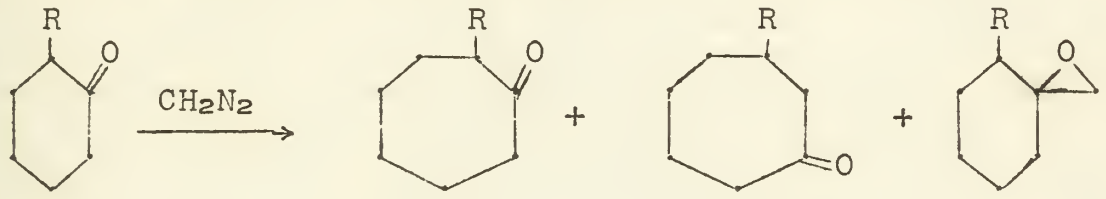
The products of the reaction of diazomethane with common cyclic ketones, and typical yields, are listed in the following table (3):

Ketone	Products (yield)	Solvent
Ketene	Cyclobutanone (60)	Ether
Cyclopentanone	Cycloheptanone (50)	Ether-MeOH
	Cyclohexanone (8) (some cycloöctanone)	
Cyclohexanone	Cycloheptanone (60), epoxide (15) Some cycloöctanone	Ether-MeOH
Cycloheptanone	Cycloöctanone (45), epoxide (20)	Methanol

(Cont.)

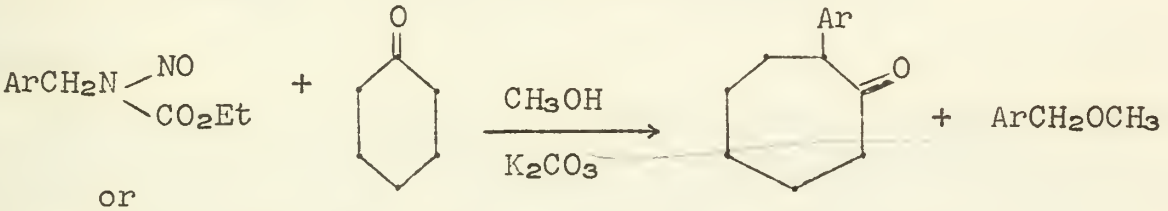
Ketone	Products (Yield)	Solvent
Cycloöctanone	Cyclononanone (22)	Methanol
Cyclononanone	Cyclodecanone (44)	Methanol

Substituted carbocyclic ketones upon reaction with diazoalkanes give rise to isomeric products as shown below (4).



R=Cl	24%	76%	
$R=C_6H_5$	40%	10%	21%

Two general procedures for carrying out diazoalkane ring enlargements of cycloalkanones are the ex situ method, in which a solution of the diazoalkane is added to the ketone, and the in situ method, in which the diazoalkane is generated in the presence of the ketone. N-nitrosoalkylurethans are most commonly used in the latter method since only a catalytic amount of base decomposes them to the diazoalkane. In many cases, the in situ method gives better results for more unreactive carbonyl compounds (3), however recent studies indicate that reaction of the solvent with the nitrosourethan leads to serious side reactions (5). Cyclohexanone was treated with various substituted benzyl-N-nitrosourethans, and aryldiazomethanes (6) bearing the same substituents.



or

$ArCHN_2$ (no K_2CO_3) (no ether produced from $ArCHN_2$)

Aryl Group	Yield of 2-Arylcycloheptanone		Yield of Ether from Urethane
	from $ArCH_2N(NO)CO_2Et$	from $ArCHN_2$	
Phenyl	41%	34%	29%
2-Methoxyphenyl	29%	47%	50%
3-Methoxyphenyl	41%	32%	32%
4-Methoxyphenyl	7%	29%	64%
2,3-Dimethoxyphenyl		45%	

(Table cont.)

2,4-dimethoxyphenyl		25%	
3,4-dimethoxyphenyl		40%	
2,3,4-trimethoxyphenyl	0%	33%	72%
3,4,5-trimethoxyphenyl		39%	

The ex situ method is the more general of the two procedures since the in situ failed completely in some instances, and produced low yields in others. The following scheme has been proposed for the decomposition of ethyl-N-nitrosobenzylcarbamates (5), based on the observatinns that the evolution of nitrogen occurs in two phases during the reaction, and the volume of nitrogen evolved in the second phase roughly corresponds to the yield of 2-aryl-cycloheptanone. The yield of ether is greater when the aryl groups have substituents which stabilize benzyl carbonuim ions; the carbamates are unreactive in methanol solution, but decompose upon the addition of K_2CO_3; and the potassium salt of I is isolable when the urethan is treated with concentrated KOH at low temperatures (7). The salt shows a strong tendency to undergo solvolysis and treatment with water or ethanol induces the formation of phenyldiazomethane and benzyl alcohol or ethyl benzyl ether.

1. $ArCH_2N(N{=}O)(CO_2Et) + CH_2O^{\ominus} \longrightarrow \underset{I}{ArCH_2N{=}NO^{\ominus}} + MeOCO_2Et$

2. $ArCH_2N{=}NO^{\ominus} + CH_3OH \longrightarrow ArCH_2N{=}NOH + CH_3O^{\ominus}$

3a. $ArCH_2N{=}NOH + CH_3O^{\ominus} \longrightarrow ArC^{\ominus}HN{=}NOH + MeOH$
$ArC^{\ominus}HN{=}NOH \longrightarrow OH^{\ominus} + ArCHN_2$

3b. $ArCH_2N{=}NOH \rightleftharpoons ArCH_2^{\oplus} + [N_2OH]^{\ominus} \longrightarrow OH^{\ominus} + N_2$

$ArCH_2^{\oplus} + CH_3OH \longrightarrow ArCH_2OCH_3 + H^{\oplus}$

MECHANISM

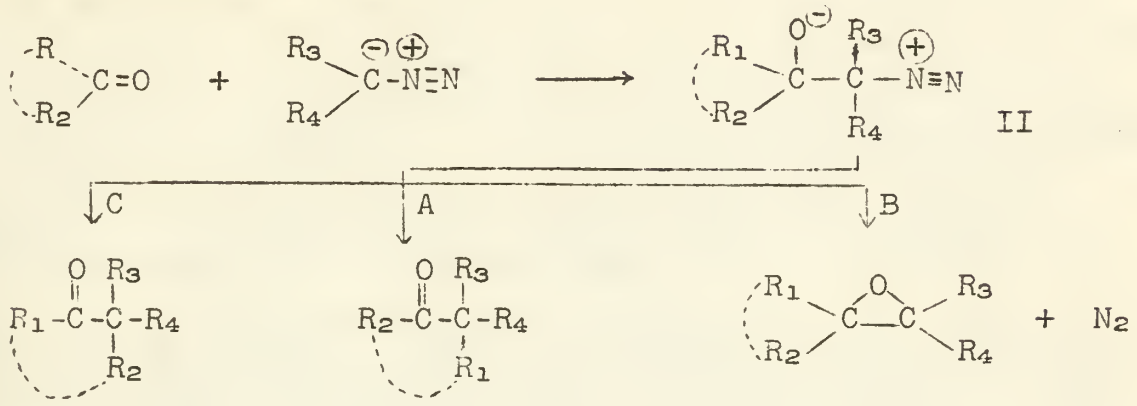
The reaction of diazoalkanes with carbonyl compounds has been interpreted as a nucleophilic attack of the diazoalkane on the carbonyl carbon to give a diazonium betaine addition compound II which decomposes by path A, B, or C (3). Similar intermediates have been postulated in the reaction of β-amino alcohols with nitrous acid (8), and in the oxidation of olefins with nitrous oxide (9), although, different products are formed in these two cases.

$R_2C(OH)\text{-}CH_2NH_2 + HONO \xrightarrow{HOAC} R_2C(OH)\text{-}CH_2N_2^{\oplus}$

$R_2C{=}CH_2 + N_2O \xrightarrow[200\ atm.]{250^{\circ}} R_2C(O^{\ominus})\text{-}CH_2N_2^{\oplus}$

Chloral forms an addition compound with diazomethane that is stable in solution, and evolves nitrogen only upon evaporation of the

ether solvent (10). It is thought that the displacement of nitrogen is a concerted process (11).



This mechanism is supported by the following observations. Hydroxylic solvents and lithium chloride catalyze the reaction. For example, acetone is unreactive toward diazomethane in ether solution, but reacts readily when 10-15% water is added (10, 12), and cyclohexanone reacts only slowly with diazomethane in ether solution, but rapidly in alcoholic solution (11, 13). This catalysis suggests that the reaction proceeds through a transition state in which there is charge separation. Rate studies of reactions between various ketones and diazomethane indicate that the overall reaction is second order (14). The reaction proceeds at the same rate in water (in which $[H^+] = 10^{-7}$) as in 0.1N NaOH ($[H^+] = 10^{-13}$) showing that there is no catalysis by $[H^+]$ ions, at least at very low $[H^+]$ concentrations (12, 14). Steric, electronic and solvent effects play an important role in determining the path followed in the stabilization of the intermediate II.

STERIC EFFECTS

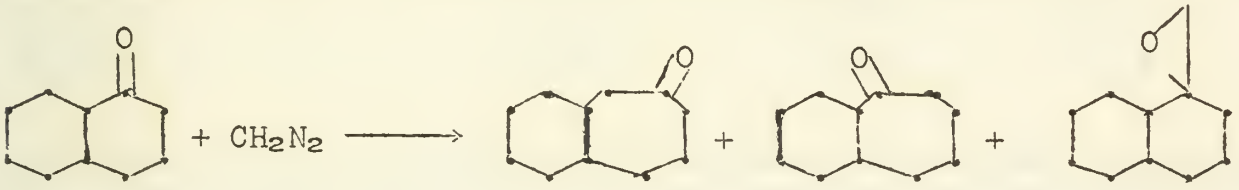
Steric factors can influence the course of the reaction at two points; (a) in the initial attack of the nucleophile on the carbonyl group, and (b) in the subsequent rearrangement of the intermediate. The following table shows the amount of ketone and epoxide from several methyl alkyl ketones (3). The decrease in rate of reaction as the alkyl groups become larger probably is an example of the first effect. The increase in amount of oxide formed exemplifies the second effect.

Starting ketone	Product		Relative Rate
	Ketone	Oxide	
CH_3COCH_3	38%	33.5%	1.0
$CH_3COCH_2CH_3$	32%	40%	0.4
$CH_3COCH_2CH_2CH_3$	18%	55%	0.15
$CH_3COCH(CH_3)_2$			0.095
$CH_3CO(CH_2)_8CH_3$	0	100%	

These effects have been studied less extensively in cycloalkanones, however in many cases, ring enlargements of 2-substituted cyclohexanones proceed in lower yield than those involving cyclohexanones lacking 2-substituents. Cyclohexanone yields cycloheptanone in 60-65% yield (15), methylcycloheptanones are obtained in 37% yield from 2-methylcyclohexanone (13), and 2-cyclohexylcyclohexanone gives rise to ring enlarged ketones in only 4-5% yield (16), although phenylcycloheptanones are obtained in 50% yield from 2-phenylcyclohexanone (4) in which steric factors should be operating to about the same extent as in the cyclohexyl case.

The ratio of carbonyl product to epoxide, and the ratio of isomeric carbonyl products formed from unsymmetrically substituted cycloalkanones may be determined in part by steric factors. For example, the ratio of ketone to epoxide is about 4:1 in the ring enlargement of cyclohexanone, but is more near to 1:1 with 3,5,5 trimethyl cyclohexanone. Also, the two isomeric trimethylcycloheptanones are not formed in equal amounts (17). However, electronic effects may exert an influence in all the above examples.

In order to avoid electronic effects, Gutsche and Peters (18) studied the ring enlargement of cis and trans α-decalone.

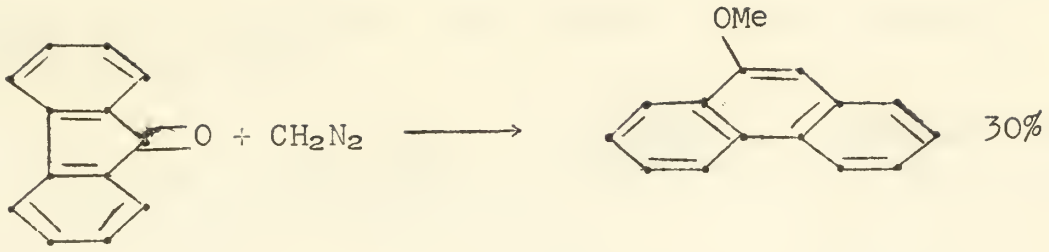


cis	46%	54%	3%
trans	50%	9%	41%

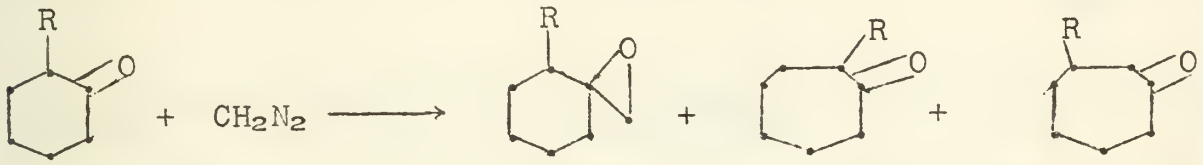
The products of the reaction were determined quantitatively by I.R. spectra (accurate to ± 5%). Slightly more starting material was recovered from the cis ketone than from the trans (yields are adjusted on that basis). This evidence shows that the diazomethane-carbonyl reaction is quite susceptible to steric influences, not only with respect to rate, but also the course of reaction.

ELECTRONIC EFFECTS

It has been previously noted that acetone is unreactive toward diazomethane in ether solution (10), however chloroacetone and trichloroacetone react readily under the same conditions (3). The reaction of α-tetralone with diazomethane proceeds only slowly to give a product in poor yield which is thought to be β-benzosuberone (19) whereas fluorenone reacts readily with an excess of diazomethane to give 9-methoxyphenanthrene (20).



However, benzophenone is unreactive toward diazomethane (3). The ring enlargement of 2-(p-substituted-phenyl)-cyclohexanones has also been studies by Gutsche and coworkers (21). The results are as follows:

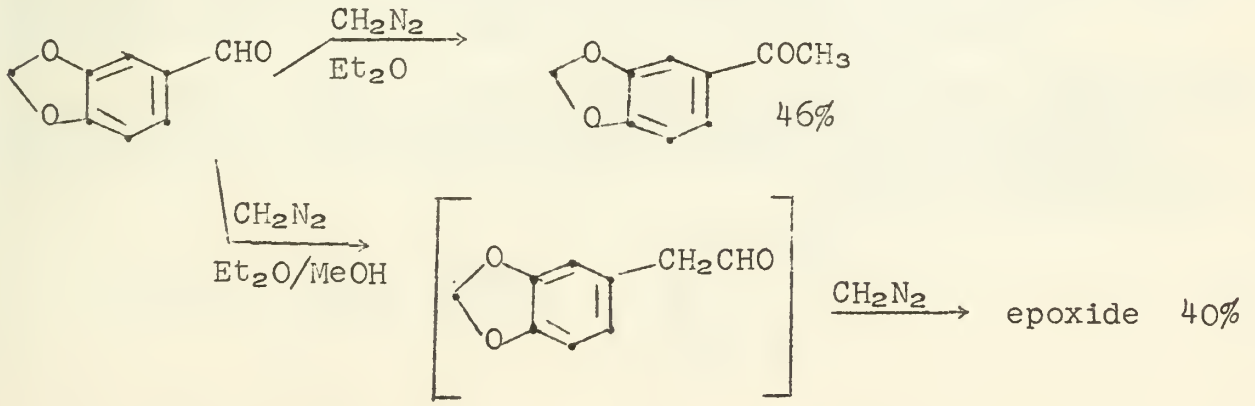


R Group	Oxide	α-7 ketone	β-7 ketone	α/β ratio
C_6H_5	22.5%	63.0%	14.5%	4.3
$CH_3C_6H_4$	20.0%	58.0%	22.0%	2.8
$CH_3OC_6H_4$	15.5%	62.0%	22.5%	2.8
$Cl\text{-}C_6H_4$	27.5%	50.0%	22.5%	2.2

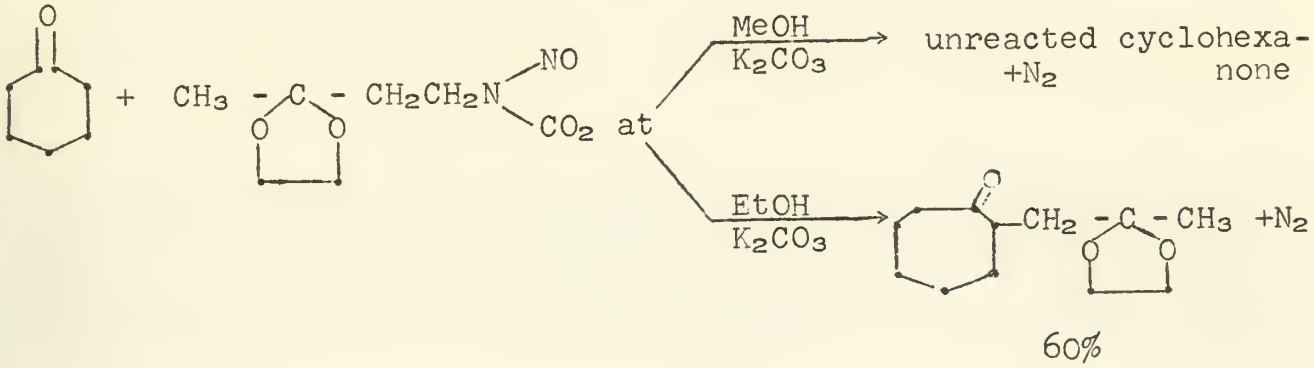
It appears that both steric and electronic factors must be considered in this instance, however the α/β ratio which is dependent on the migratory preferences of the groups adjacent to the carbonyl may be controlled by electronic effects although in the p-chloro and P-methoxy case little difference is noted. Migratory preferences may be strongly influenced by both the solvent and the diazoalkane employed, but in general, the group migrating preferentially is the one most able to contribute electrons (3).

SOLVENT EFFECTS

Piperonal reacts with diazomethane in the presence of methanol to give a product obtained by aryl migration, whereas in the absence of methanol, hydrogen migration to give the ketone occurs (22, 36). Thus this indicates that methanol promotes



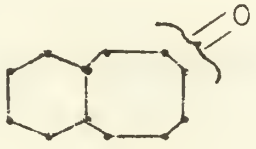
aryl migration. A different type solvent effect is found in the following example (23).



The failure of the reaction in methanol is due to the preferential reaction of the solvent with the urethan.

BIS-HOMOLOGATION

When trans-α-decalone is treated with an excess of diazomethane, the cyclooctanone derivative III is produced. However, neither of the cycloheptanone derivatives from trans-α-decalone form III upon treatment with diazomethane. Thus the question of a different intermediate species is raised (18).

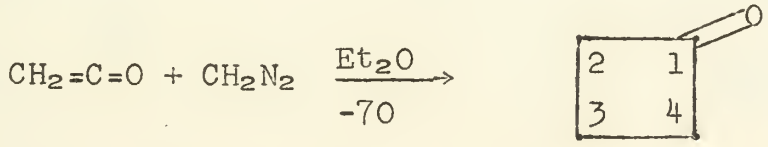


III

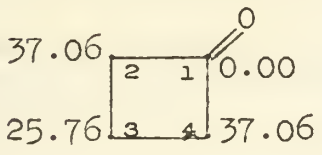
A similar situation exists in the preparation of cyclobutanone from ketene and diazomethane. The question of whether the reaction proceeds through a cyclopropanone intermediate is one of long standing. If the reaction is carried out in the presence of alcohol or water, cyclopropanone hemiacetal or hydrate is isolated, however later workers have questioned the cyclopropane intermediate on the grounds that it is unlikely that cyclopropanone would react smoothly with diazomethane in ether at -70° when cyclobutanone is stable under the same conditions. Although this objection isn't valid, since cyclopropanone is much less stable than cyclobutanone.

A recent study in which ketene was treated with diazomethane-C^{14} indicates that an intermediate possessing the symmetry properties of cyclopropanone is involved in the reaction (24).

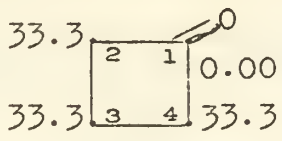
Subsequent degradation



and analysis showed the following distribution of radioactivity IV. If a trigonally symmetrical intermediate were involved, the



IV



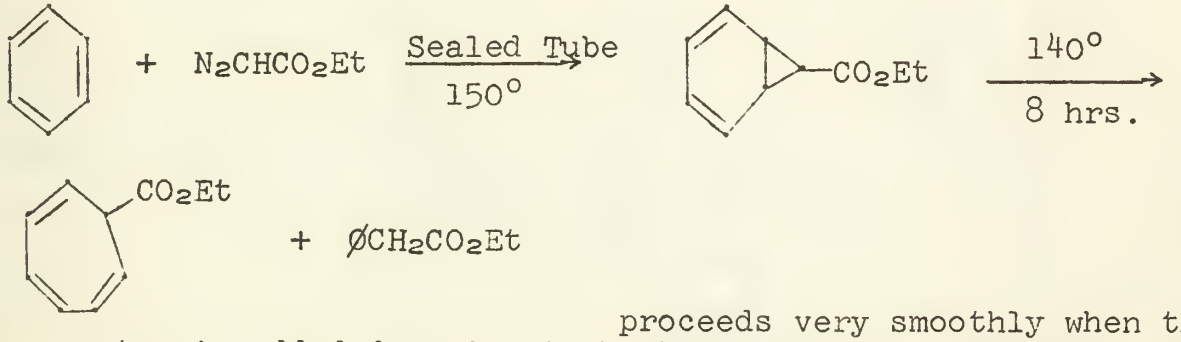
V

C^{14} distribution would be as that in V. The predicted activity distribution for the cyclopropanone intermediate is 37.5, 25.00, and 37.5. Thus the cyclopropanone type intermediate is strongly indicated. A similar intermediate is postulated in the synthesis of N-phenyl-β-lactom from phenylisocyanate and diazomethane (25).

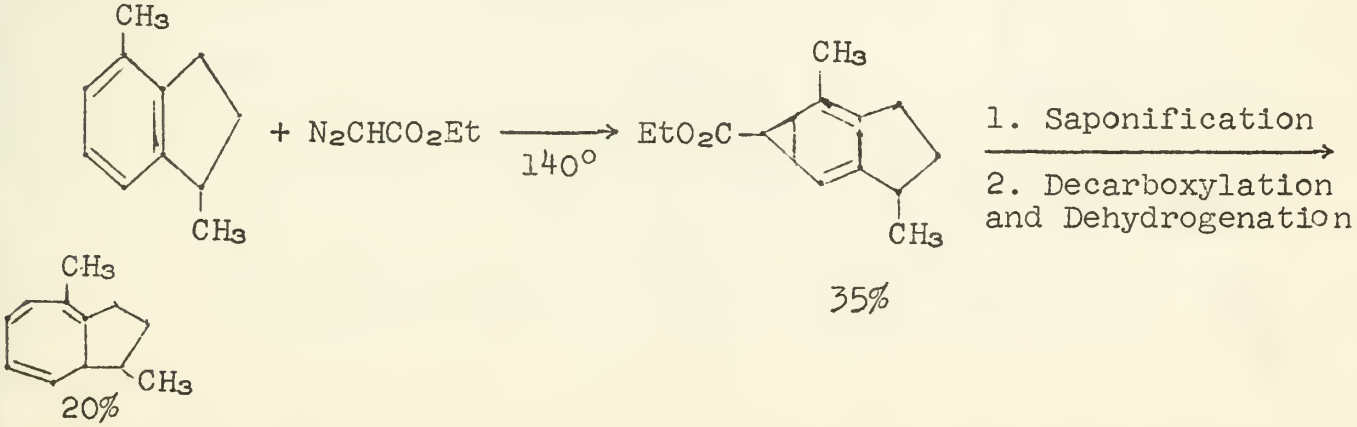
$$\text{Ø-N=C=O} + 2\text{CH}_2\text{N}_2 \xrightarrow[\text{Et}_2\text{O}]{0^\circ} \text{Ø-N}\!\!<\!\!\begin{matrix}\text{CH}_2\text{-CH}_2\\ \\ \text{C=O}\end{matrix} \quad 20\%$$

RING ENLARGEMENTS INVOLVING DIAZOALKANES AS CARBENE SOURCES

Ring enlargements involving what are thought to be carbenes have been studied less extensively than those proceeding via nucleophilic attack of the diazoalkane. The Buchner synthesis (26), in which an aromatic compound is treated with diazoacetic ester is thought to proceed through a carbene intermediate (27). The discovery that the reaction

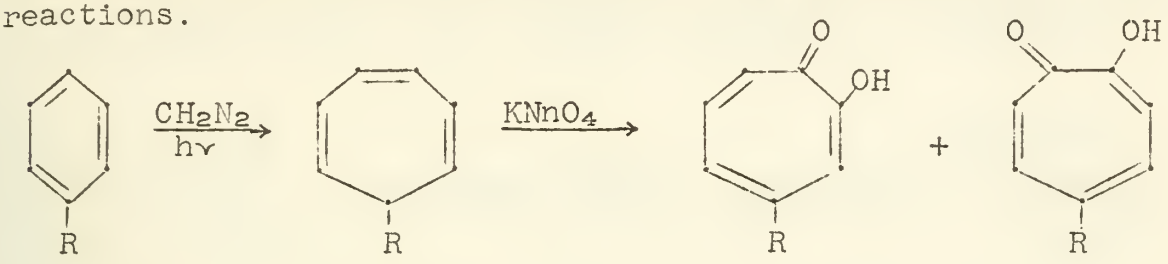


proceeds very smoothly when the diazo-ester is added dropwise to boiling benzene containing a fine suspension of copper bronze (28) supports the carbene thesis since there is other evidence (29) that copper catalyzes formation of carbenes from diazoalkanes. Other examples of the Büchner reaction are the preparation of substituted azulenes (30, 31).



Other azulene syntheses have been effected by the photochemical decomposition of diazomethane in the presence of aromatic compounds (32).

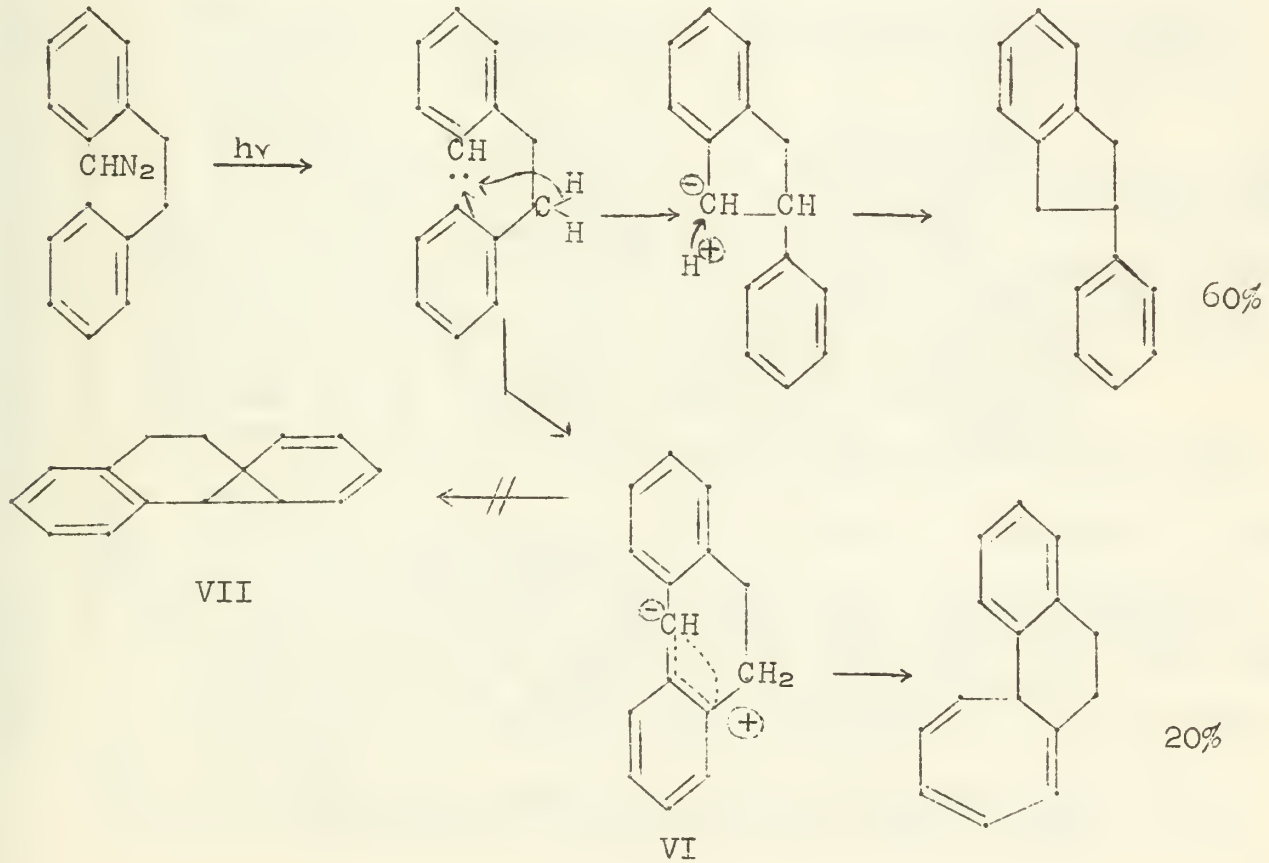
Doering and Knox (33) prepared some substituted tropilidenes which were oxidized to the tropolones by the following sequence of reactions.



ca 16%

The decomposition of diazoalkanes to nitrogen and carbenes can be accomplished by use of heat, light, and certain metal catalysts such as copper (29). Carbenes will attack any electron source, the only selectivity seemingly practiced is dependent on the availability of electrons, e.g., a carbene will react more rapidly with an unsaturated bond or Lewis base than with a single bond (21). In the following example, π electrons are attacked by the carbene, and in the last example, the attack occurs on p electrons.

Ring enlargement is obtained when 2-(β-phenylethyl)-phenyldiazomethane is irradiated in petroleum ether (34). The following mechanism has been proposed (21).

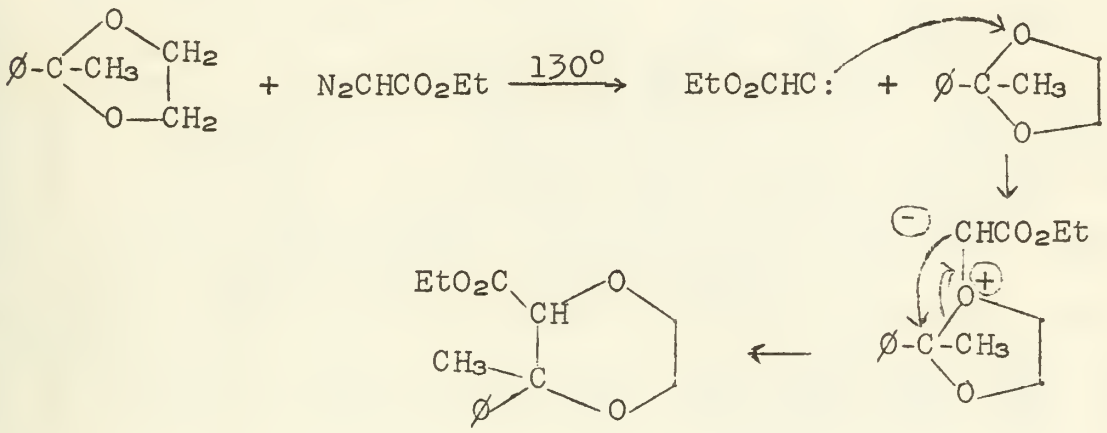


VII

VI

None of VII was found among the products, so the existence of a cyclopropane ring in VI is doubted.

G. Gutsche and Hillman found that the heterocyclic ring is enlarged upon treatment of 2-phenyl-2-methyl-1,3-dioxolane with diazoacetic ester (35). The following mechanism is proposed.



α + β

BIBLIOGRAPHY

1. A. Burger and W. L. Yost, J. Am. Chem. Soc., 70, 2198 (1948).
2. N. L. Drake and T. R. Sweeney, J. Org. Chem., 11, 67 (1946).
3. C. D. Gutsche, in "Organic Reactions" Vol. VIII, Wiley, New York (1954).
4. C. D. Gutsche, J. Am. Chem. Soc., 71, 3513 (1949).
5. C. D. Gutsche and H. E. Johnson, J. Am. Chem.Soc., 77, 109 (1955).
6. C. D. Gutsche and E. F. Jason, J. Am. Chem. Soc., 78, 1184 (1956).
7. A. Hantsch and M. Lehman, Ber., 35, 897 (1902).
8. A. McKenzie and A. C. Richardson, J. Chem. Soc., 123, 79 (1923).
9. F. S. Bridson-Jones, et. al., J. Chem. Soc., 1951, 2999.
10. H. Meerwein, T. Bersin, and W. Burneleit, Ber., 62, 999 (1929).
11. R. Robinson and L. H. Smith, J. Chem.Soc., 1937, 371.
12. H. Meerwein and W. Burneleit, Ber., 61, 1840 (1928).
13. D. W. Adamson and J. Kenner, J. Chem. Soc., 1939, 181.
14. P. Pohls, Inaug. Diss., University of Marburg, Marburg (1934). (See Ref. 3).
15. E. P. Kohler, M. Tishler, H. Potter, and H. T. Thompson, J. Am. Chem. Soc., 61, 1057 (1939).
16. M. Mousseron and G. Manon, Bull. Chim. Soc. France, 1949, 392.
17. M Stoll and W. Scherrer, Helv. Chim. Acta, 23, 941 (1940).
18. C. D. Gutsche and H. H. Peter, J. Am. Chem. Soc., 77, 5971 (1955)
19. R. B. Thompson, J. Am. Chem. Soc., 66, 156 (1944).
20. R. F. Schultz, E. D. Schultz, and J. Cochran, J. Am.Chem. Soc., 62, 2902 (1940).
21. C. D. Gutsche, "The Chemistry of High Nitrogen Compounds", Symposium Proceedings, Duke University, March (1956). P. 76.

22. E. Mosettig, Ber., 61, 1391, (1928).
23. A. M. Islam and R. A. Raphael, J. Chem. Soc., 1955, 3151.
24. D. A. Semenow, E. F. Cox, and J. D. Roberts, J. Am. Chem. Soc., 78, 3221 (1956).
25. E. Buchner, et. al., Ber., 18, 2337 (1885); 34, 982 (1901); 36, 3502 (1903); 37, 931 (1904).
26. J. C. Sheehan and P. T. Izzo, J. Am. Chem. Soc., 70, 1985, (1948)
27. A. Dyakonov, J. Gen. Chem. USSR, 19A, 173 (1949).
28. A. Loose, J. pract. Chem., (2) 79, 509 (1909).
29. W. R. Richardson, Ill. Seminar Abst., Oct. 4, 1956.
30. P. A. Plattner and J. Wyss, Helv. Chim. Acta., 23, 907 (1940).
31. A. S. Pfau and P. A. Plattner, Helv. Chim. Acta., 22, 202 (1939).
32. W. Treibs and M. Quarg, Angew Chem., 67, 76 (1955).
33. W. von E. Doering and L. H. Knox, J. Am. Chem. Soc., 72, 2305 (1950); 73, 828 (1951); 75, 297 (1953).
34. C. D. Gutsche and H. E. Johnson, J. Am. Chem. Soc., 77, 5933 (1955).
35. C. D. Gutsche and M. Hillman, J Am. Chem. Soc., 76, 2236 (1954).
36. F. Arndt, J. Amende and W. Ender, Monatsh. Chem., 59, 202 (1932).

PHOTOSENSITIZED ORGANIC REACTIONS

Reported by Robert A. Mooney February 25, 1957

INTRODUCTION

Several light catalyzed reactions are accelerated by or require the presence of a substance called a photosensitizer. The most familiar instance of photosensitization is the action of chlorophyll in permitting carbon dioxide and water to react in sunlight to produce carbohydrates in plants. This reaction is remarkable in that it requires 112 kcal. per mole of carbon dioxide, yet red

$$CO_2 + H_2O \xrightarrow[h\nu]{\text{chlorophyll}} 1/6\ (C_6H_{12}O_6) + O_2$$

light (λ7500 Å) corresponding to 38 kcal. is sufficient to bring it about (14).

Photosensitized processes can be conveniently divided into two types. The first includes those reactions of organic molecules which are brought about in the absence of oxygen by excited atoms such as mercury, cadmium, zinc or noble gas atoms. Detailed investigations into the mechanisms of such reactions are frequently rendered difficult by the large number of products obtained and by the fact that the reactions must be run in the gas phase and therefore on very small quantities. The photochemist here must resort to mass spectrometric and spectrophotometric techniques for product analysis, and the reactions have little value in application to organic synthesis. Their value rests on the information they give concerning molecular structure and theory.

A second type of photosensitized process includes reactions of organic molecules with molecular oxygen brought about by irradiation with light in the presence of molecular photosensitizers, often dyes. In contrast to the former type, sensitized photooxidations frequently give excellent yields and can be run on a preparative scale.

This review will include a brief account of the theory of photosensitization with some examples of each of the types described above.

THEORY (46)

In order that a photochemical reaction may occur, two conditions must be fulfilled:

(a) The magnitude of the quantum of the incident light must be large enough. The energy per mole associated with a quantum is given by the relation $E = \frac{Nhc}{\lambda}$

where N is Avogadro's number
h is Planck's constant
c is the velocity of light
λ is the wavelength

(b) The light must be absorbed (Grotthuss - Draper Law).

In many cases substances have dissociation energies corresponding to wavelengths in a convenient region of the spectrum, but are transparent down to the Schumann region (ca. 1300 Å), where photochemical experiments are difficult to carry out. For example, molecular hydrogen has a dissociation energy of 103 kcal. corresponding to radiation with wavelength 2775 Å, but the continuum in its absorption spectrum does not begin until 849 Å.

However, if a substance is added to hydrogen which can absorb below 2775 Å and which can transfer efficiently the absorbed energy to a hydrogen molecule, a photosensitized dissociation of H_2 may take place. An example of such a substance is mercury vapor. The mercury atom is $^1S_0$ in its ground state, but when irradiated with light of wavelength 2537 Å, it is raised to an excited level, the $^3P_1$ state. The energy involved in this transition is 112 kcal. per mole. The excited atom can return to the ground state by either of two processes:

(1) It can lose its energy by reëmitting the light of λ 2537 Å (fluorescence).
(2) It can give up its energy to another atom or molecule by collision (quenching).

The latter process is the one on which the sensitized photochemical reaction is based. The 112 kcal. available is greater than the activation energy of almost any chemical reaction. The actual mechanism of quenching is still an unsolved problem.

A more detailed treatment of the theory of photosensitization can be found in references (6,19,25,26,30).

PHOTOSENSITIZATION BY EXCITED ATOMS

In general, the primary reaction between a $Hg(^3P_1)$ atom and a straight chain hydrocarbon is the cleavage of a carbon-hydrogen bond. This can be represented by the equations:

$$Hg\ (^1S_0) + h\nu \longrightarrow Hg\ (^3P_1)$$

$$Hg\ (^3P_1) + R\text{-}H \longrightarrow R^{\cdot} + H^{\cdot} + Hg\ (^1S_0)$$

An example is the decomposition of n-butane (7):

$$n\text{-}C_4H_{10} + Hg\ (^3P_1) \longrightarrow C_4H_9\cdot + H\cdot + Hg\ (^1S_0)$$

An alternative scheme which postulates the formation of a HgH molecule has now been discarded on the basis of theoretical work by Laidler (21) and by the failure to detect the HgH species spectroscopically in reactions of this type. The major products of the above reaction resulting from decomposition of the butyl radical are hydrogen, ethane, ethylene and propylene.

The reactions between excited atoms and ethylenic systems has been studied by a number of workers (2,8,9,16,20,47). The nature of the products appears to depend on the temperature, pressure, sensitizer, duration of radiation and concentration of reactants. Some of the products which have been reported are given in the following equations:

$$CH_2{=}CH_2 + Hg\ (^3P_1) \longrightarrow C_2H_2 + H_2 + \text{polymers} \quad (8)$$

$$CH_2{=}CH_2 + Zn\ (^1P_1) \longrightarrow \text{polyethylenes} \quad (16)$$

$$CH_2{=}CH_2 + Cd\ (^1P_1) \longrightarrow \text{butene, hexene and higher olefins} \quad (45)$$

$$CH_2{=}CHCl + Hg\ (^1P_1) \longrightarrow \text{polyvinyl chloride} \quad (20)$$

Other work on photosensitized polymerizations is reported in references (11, 27, 31, 48, 49).

Atkinson (2) has reported some interesting work on the $Hg(^3P_1)$ photosensitized reaction of tetrafluoroethylene. Almost all of the volatile product obtained at low conversion was analyzed as hexafluorocyclopropane. The evidence given in support of this structural assignment was a molecular weight determination from vapor density measurements, a determination of the melting point of the compound which differed appreciably from that of hexafluoropropylene, and the fact that the compound did not react with bromine. The main product of the reaction was a white polymer, polytetrafluoroethylene. If these are the products, one can consider

$$CF_2 = CF_2 \xrightarrow[h\nu]{Hg} \text{(cyclopropane: } F_2, F_2, F_2\text{)} + (-CF_2-)n$$

the following mechanism:

$$CF_2 = CF_2 + Hg(^3P_1) \longrightarrow C_2F_4^* + Hg\ (^1S_0)$$

$$C_2F_4^* \longrightarrow 2\ CF_2 \text{ (singlet or triplet)}$$

$$C_2F_4 + CF_2 \longrightarrow \underbrace{CF_2\text{-}CF_2\text{-}CF_2}$$

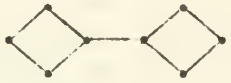
$$C_2F_4^* + C_2F_4 \longrightarrow C_4F_8, \text{ etc.}$$

There is a marked difference between the mechanism proposed for the photochemical reaction of C_2F_4 and that proposed for C_2H_4. With the latter, there is no dissociation of the carbon-carbon double bond. Unless deactivated by collision, the excited ethylene molecule dissociates into acetylene and hydrogen. The reason for the difference in mechanism is given to be the smaller carbon-carbon bond energy in tetrafluoroethylene and the stabilization of the difluorocarbene molecule by delocalization effects of the

fluorine atoms.

The cyclic hydrocarbons from C_3 to C_6 form an interesting series with regard to their reactions with $Hg(^3P_1)$ atoms. The major products of the photosensitized reactions are summarized below. The stability of the cyclopentane and cyclohexane rings is indicated by the fact that no open chain products were detected in

Cyclopropane $\xrightarrow{Hg,\ h\nu}$ linear polymer (15)

Cyclobutane $\longrightarrow$ H_2 + $\underline{n}$-C_4H_9—  +  (18)

Cyclopentane $\longrightarrow$ H_2 +  +  (4)

Cyclohexane $\longrightarrow$ H_2 +  +  (3)

the reaction mixtures with these compounds.

The mercury photosensitized reaction of cyclooctatetraene has been reported by Yamazaki and Shida (51) to give benzene, hydrogen, styrene and polymers.

Benzene and toluene appear to be very stable to Hg ($^3P_1$) atoms at room temperature (42, 43). Steacie (42) obtained biphenyl as the major product in the Hg ($^3P_1$) sensitized photolysis of benzene at 400°. Some low molecular weight hydrocarbons were also obtained which indicated rupture of the aromatic nucleus. Darwent (43) has photolyzed toluene in the presence of mercury vapor at 295° and reports hydrogen, methane and ethane as the major gaseous products.

Phibbs and Darwent (29) obtained ethylene glycol from the mercury sensitized reaction of methanol. The reaction appears to be:

$$Hg\ (^3P_1) + CH_3OH \longrightarrow .CH_2OH + H. + Hg\ (^1S_0)$$

$$2\ .CH_2OH \longrightarrow HOCH_2CH_2OH$$

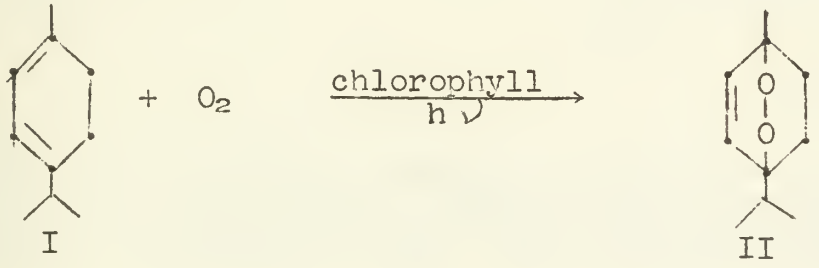
The transition $Na(^2P) \longrightarrow Na(^2S)$ involves an energy of 48.3 kcal., while the highest activation energy reported for the thermal cis-trans isomerization of ethylene derivatives is about 46 kcal. It would therefore seem reasonable to expect that irradiation of a

cis- substituted ethylene molecule with the 5890 Å resonance line of sodium in the presence of sodium vapor would lead to isomerization. However, Smith (44) was unable to detect an appreciable amount of isomerized cis-butene-2 in such a reaction. One explanation given is that although butene-2 is an effective quencher of sodium atoms in the ^2P state, a rapid flow of energy away from the site of reception, presumably the double bond, prevents the isomerization from taking place.

PHOTOSENSITIZED OXIDATIONS

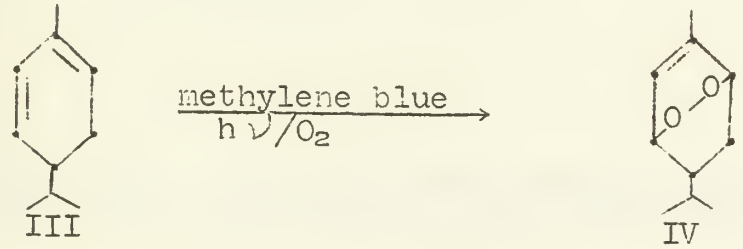
Some organic dyes are similar to mercury atoms in their ability to sensitize photochemical reactions, but knowledge of the processes involved is even more obscure in the case of dye sensitization. The work of G. N. Lewis (23), Lewis, Calvin and Kasha (24), and Oster and Adelman (1, 28) indicates that excited dye molecules are in the triplet state. The oxygen molecule is generally pictured as forming a complex with the sensitizer, which reacts with the accepting molecule. The most frequently used dyes are eosin, methylene blue, chlorophyll and fluorescein, although many others have been found to be effective.

Conjugated dienes appear to give Diels-Alder type adducts, although in some cases the peroxides formed cannot be isolated. Schenck and Ziegler (32, 37) synthesized from α-terpinene I the naturally occurring substance, ascaridole II, in 29% yield by the following reaction:



I II

Similarly, α-phellandrene III gave a transannular peroxide IV in 52% yield (37):

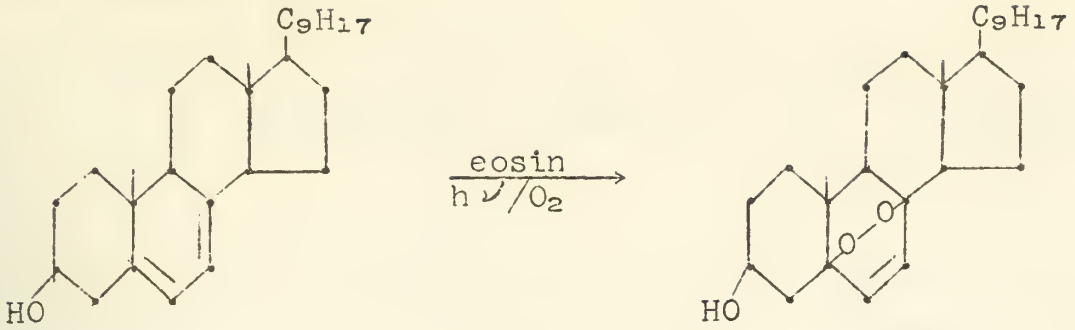


III IV

The peroxides obtained above, as well as those from α-pyronene and β-pyronene, are all stable and isolable.

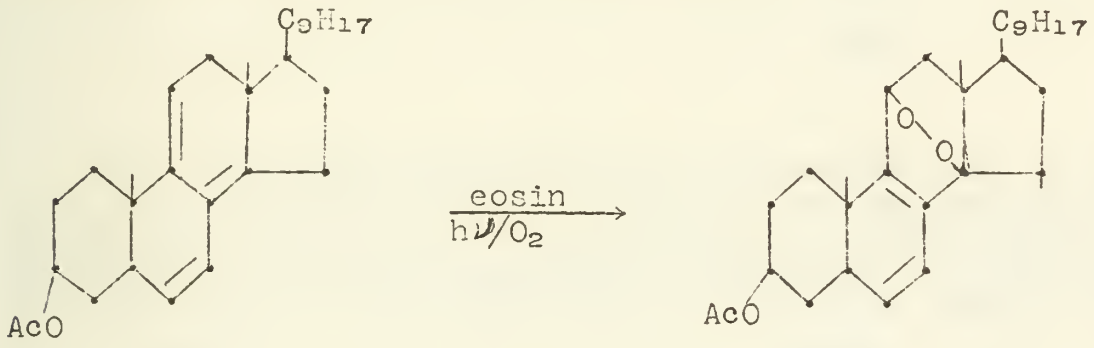
The discovery of the first transannular steroid peroxide was a result of the early work on vitamin D (5). In attempting to convert ergosterol V into vitamin D by solar irradiation in the presence of eosin and oxygen, Windaus (50) obtained a photoperoxide

of structure VI.



V VI

Other steroids have been found to react in a similar manner. A recent paper (22) reports the use of a sensitized photooxidation in preparing intermediates for corticosteroid syntheses. The α-peroxide VII was formed in 64% yield.

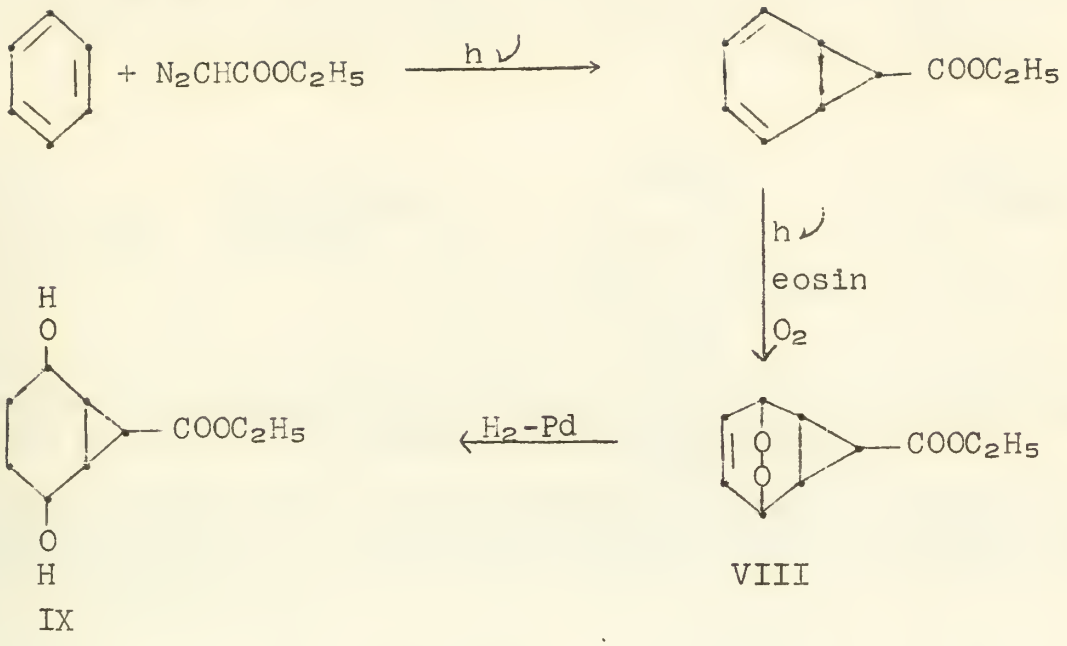


VII

The endoperoxide of 1,3-cyclohexadiene has been isolated and is stable up to 100° (35). Although much less stable, the corresponding cyclopentadiene endoperoxide was isolated by careful distillation in vacuo at -30°. The endoperoxide decomposes

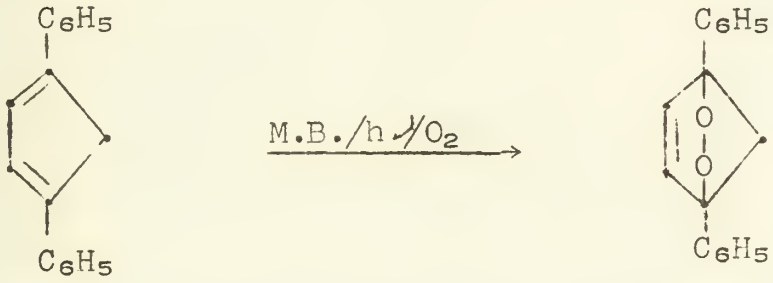
violently at 0°. The light source used in the oxidation was a sodium vapor lamp. Reduction of the endoperoxide with thiourea yielded cis-1,3- dihydroxycyclopentene-4 in an overall yield of 50% (41).

Endoperoxides have found application in syntheses in the norcaradiene series (34). The transannular peroxide VIII was obtained in 90% yield. Catalytic hydrogenation produced the glycol IX.



IX VIII

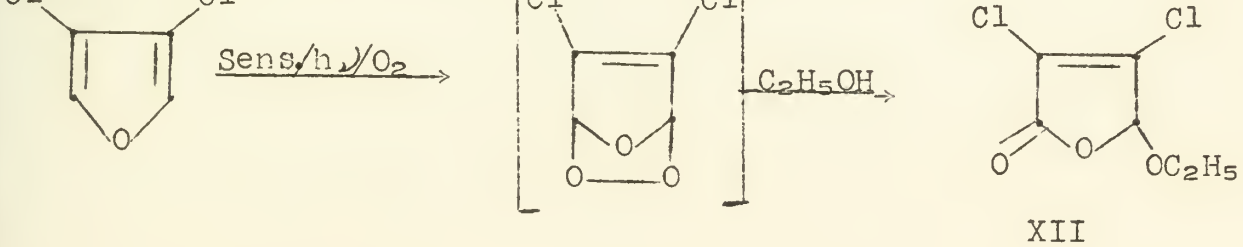
Some substances can act both as sensitizers and as oxygen acceptors in a photooxidation reaction. An example is 1,4-diphenyl-cyclopentadiene-(1,3) X. In the presence of this substance, α-terpinene can be photooxidized to ascaridole. In the presence of methylene blue, on the other hand, X become the acceptor and is



X XI

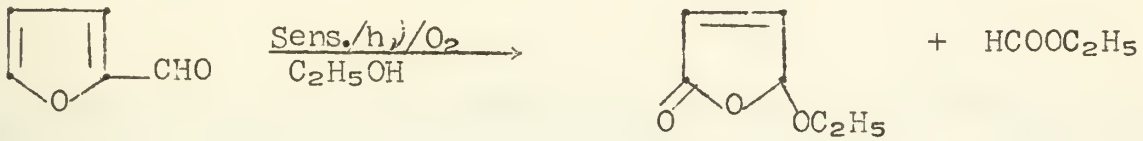
converted to the peroxide XI in 37% yield (40).

A new route has been found to pseudoesters by conducting the photosensitized oxidations of furans in alcohols. For example, 3,4-dichlorofuran on photooxidation in ethanol yields the pseudoethylester of mucochloric acid XII (35).



XII

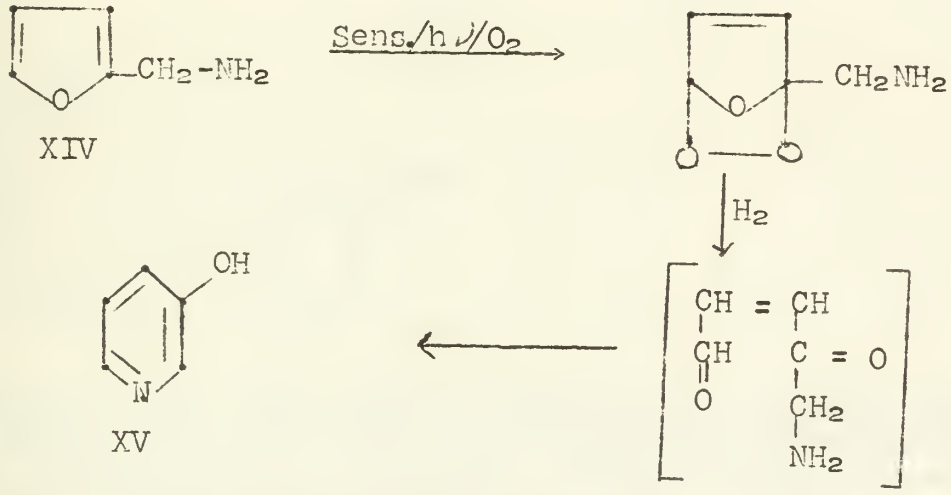
A similar treatment of furfural produced the previously unknown pseudoethylester of malealdehydic acid XIII in 74% yield (38). Ethyl formate was another product of the reaction. Schenck



XIII

synthesized the corresponding methyl, n-propyl and n-butyl pseudo-esters in yields of 46%, 48% and 13%, respectively.

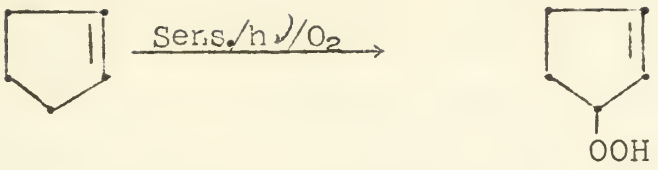
Furfurylamine XIV on sensitized photooxidation followed by hydrogenation yielded 3-hydroxypyridine XV (35). No yield was given for this reaction.



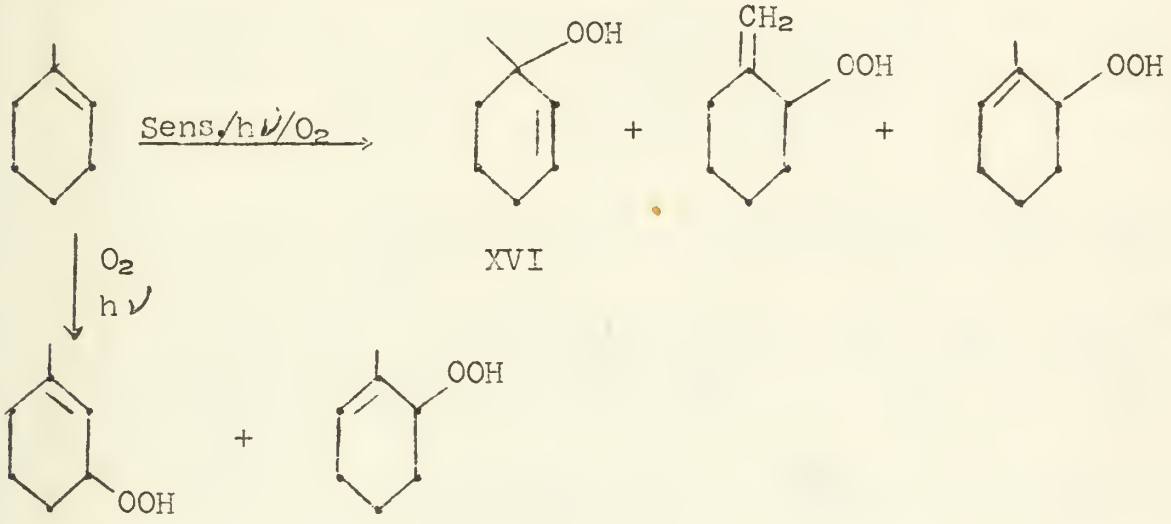
XIV

XV

Photosensitized oxidations of organic molecules containing an isolated double bond lead to the formation of hydroperoxides. Cyclopentene, for example, gives the Δ^2- cyclopentene hydroperoxide both with and without the use of a dye sensitizer (35). Schenck states, however, that better yields are often obtained in reactions of this type if a sensitizer is present.



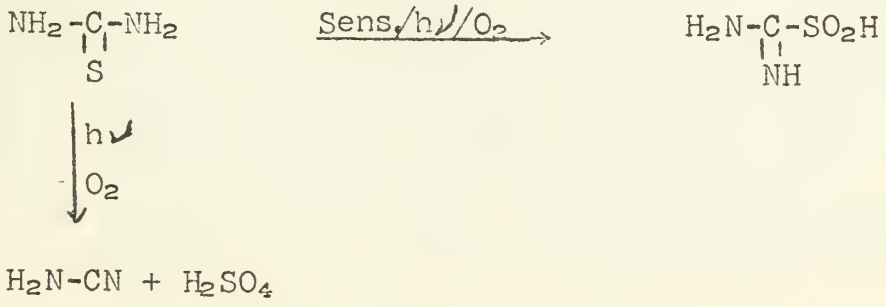
Farmer (12, 13) has shown that the attack of oxygen in the unsensitized reaction is at the allylic carbon atom. The work of Schenck (33, 35), however, indicates that in the presence of a sensitizer such as eosin, initial attack is at the position of unsaturation followed by a shift of the double bond. The following reactions of 1-methylcyclohexene illustrate this feature:



XVI

The products were identified by reduction to the saturated alcohols. About 45% of the product in the photosensitized reaction corresponded to the tertiary hydroperoxide XVI. Only secondary peroxides were obtained from the unsensitized reaction.

Thiourea on photoöxidation in the presence of protoporphyrin has been found to give amino-imino-methane-sulfinic acid. In the absence of sensitizers the products are cyanamide and sulfuric acid (36).



BIBLIOGRAPHY

1. A. H. Adelman and G. Oster, J. Am. Chem. Soc. 78, 3977 (1956).
2. B. Atkinson, J. Chem. Soc. 2684 (1952).
3. P. W. Beck, D. V. Kniebes and H. E. Gunning, J. Chem. Phys. 22, 672 (1954).
4. P. W. Beck, D. V. Kniebes and H. E. Gunning, ibid., 22, 678 (1954).
5. W. Bergmann and M. J. McLean, Chem. Revs. 28, 367 (1941).
6. A. Berthoud, Trans. Faraday Soc. 21, 554 (1926).
7. S. Bywater and E. W. R. Steacie, J. Chem. Phys. 19, 172 (1951).
8. A. B. Callear and R. J. Cvetanovic, ibid., 24, 873 (1956).
9. B. deB. Darwent, ibid. 20, 1673 (1952).
10. C. Ellis and A. Wells, "The Chemical Action of Ultraviolet Rays," Reinhold Publishing Corp., New York, 1941.
11. M. G. Evans, M. Santappa and N. Uri, J. Polymer Sci. 7, 243 (1951).
12. E. H. Farmer and A. Sundralingam, J. Chem. Soc. 121 (1942).
13. E. H. Farmer and D. A. Sutton, ibid., 10 (1946).
14. S. Glasstone, "Textbook of Physical Chemistry," D. Van Nostrand Company, Inc., New York, 1946, pp. 1180 ff.
15. H. E. Gunning and E. W. R. Steacie, J. Chem. Phys. 17., 351 (1949).
16. H. Habeeb, D. J. LeRoy and E. W. R. Steacie, ibid. 10, 261 (1942).
17. R. Hill and C. P. Whittingham, "Photosynthesis," John Wiley and Sons, New York, 1955.
18. D. L. Kantro and H. E. Gunning, J. Chem. Phys. 21, 1797 (1953).
19. G. B. Kistiakowsky, "Photochemical Processes," The Chemical Catalog Company, Inc., New York, 1928.
20. M. Koizumi, K. Nakatsuka and S. Kato, Bull Chem. Soc. Japan, 27, 185 (1954).
21. K. J. Laidler, J. Chem. Phys. 10, 43 (1942).
22. G. D. Laubach, E. C. Schreiber, E. J. Agnello, K. J. Brunings, J. Am. Chem. Soc. 78, 4746 (1956).
23. G. N. Lewis and M. Kasha, ibid. 66, 2100 (1944).
24. G. N. Lewis, M. Calvin and M. Kasha, J. Chem. Phys. 17, 804 (1949).
25. R. Livingston, J. Chem. Edu. 11, 400 (1934).
26. W. A. Noyes, Jr. and P. A. Leighton, "Photochemistry of Gases," Reinhold Publishing Corp., New York, 1941.
27. G. Oster, Nature 173, 300 (1954).
28. G. Oster, and A. H. Adelman, J. Am. Chem. Soc. 78, 913 (1956).
29. M. K. Phibbs and B. deB. Darwent, J. Chem. Phys. 18, 495 (1950).
30. P. Pringsheim, "Fluorescence and Phosphorescence," Interscience Publishers, Inc., New York, 1949.
31. R. Pummerer and H. Kehlen, Ber. 66, 1107 (1933).
32. G. O. Schenck and K. Ziegler, Naturwiss. 32, 157 (1944).
33. G. O. Schenck, Z. Elektrochem. 55, 505 (1951).
34. G. O. Schenck and H. Ziegler, Naturwiss. 38, 356 (1951).
35. G. O. Schenck, Angew. Chem. 64, 12 (1952).
36. G. O. Schenck and H. Wirth, Naturwiss. 40, 141 (1953).
37. G. O. Schenck, K. C. Kinkel, H. J. Mertens, Ann. 584, 125 (1953).
38. G. O. Schenck, Ann. 584, 156 (1953).

39. G. O. Schenck, H. Eggert, and W. Denk, Ann. 584, 177 (1953).
40. G. O. Schenck, W. Müller and H. Ffennig, Naturwiss. 41, 374 (1954).
41. G. O. Schenck and D. E. Dunlap, Angew. Chem. 68, 248 (1956).
42. E. J. Y. Scott and E. W. R. Steacie, Can. J. Chem. 29, 233 (1951).
43. A. H. Sehon and B. deB. Darwent, J. Chem. Phys. 23, 822 (1955).
44. W. Mac F. Smith, ibid., 20, 1808 (1952).
45. E. W. R. Steacie and D. J. LeRoy, ibid., 10, 22 (1942).
46. E. W. R. Steacie, "Atomic and Free Radical Reactions," Reinhold Publishing Corp., New York, 1946.
47. H. S. Taylor and H. J. Emeleus, J. Am. Chem. Soc. 52, 2150 (1930).
48. N. Uri, ibid., 74, 5808 (1952).
49. R. B. Whyte and H. W. Melville, J. Soc. Dyers Colourists 65, 703 (1949).
50. A. Windaus and H. Brunken, Ann. 460, 225 (1928).
51. H. Yamazaki and S. Shida, J. Chem. Phys. 24, 1278 (1956).

Carbonyl-forming Elimination Reactions

Reported by R. R. Fraser March 4, 1957

The reactions covered in this seminar may be represented by the following general expression:

$$R\text{-}\underset{H}{\overset{R^1}{C}}\text{-}OX \longrightarrow R\text{-}\overset{R^1}{C}{=}O + H^+ + X^- \quad (R \text{ and } R^1{=}H, \text{ alkyl or aryl}).$$

Thus, other carbonyl-forming eliminations of the type $R\text{-}\underset{X}{\overset{R^1}{C}}\text{-}OH \longrightarrow R\text{-}\overset{R^1}{C}{=}O + HX$, such as the reverse aldol condensation and cyanohydrin hydrolysis, will not be covered by this presentation.

CHROMATE ESTERS

The oxidation of secondary alcohols using chromic acid in sulfuric acid is a useful method for the preparation of ketones. The mechanism of this reaction has been thoroughly investigated by Westheimer using isopropyl alcohol (1). He has found the rate to be first order in alcohol, first order in acid chromate ion ($HCrO_4^-$), and either first or second order in hydrogen ion depending on the pH (2). With deuterium in the 2-position of isopropanol, the rate of oxidation was decreased to one-sixth of the rate of unsubstituted alcohol (3). He also found that manganous ion inhibited the rate of oxidation by 50% (4). He concluded that acid chromate ion is the active agent in the oxidation. Since this ion had no effect on Mn^{++} under the reaction conditions, he proposed Cr^{+4} to be the intermediate responsible for the reaction with Mn^{++}. The isotope effect shows that the C-D bond is being broken in the rate-determining step. He outlined the following mechanism to accommodate these facts:

$$HCrO_4^- + H^+ + CH_3CHOHCH_3 \rightleftharpoons (CH_3)_2\text{-}CHOCrO_3H + H_2O$$

$$H_2O + (CH_3)_2\text{-}CH\text{-}OCrO_3H \longrightarrow H_3O^+ + (CH_3)_2\text{-}C{=}O + HCrO_3^-$$

Because of the large number of ionic species of chromium there are four possible paths for the remaining steps of the reaction. The most likely of these is given below:

$$CH_3CHOHCH_3 + Cr^{IV} \longrightarrow Cr^{II} + (CH_3)_2C{=}O$$

$$Cr^{VI} + Cr^{II} \longrightarrow Cr^{III} + Cr^{V}$$

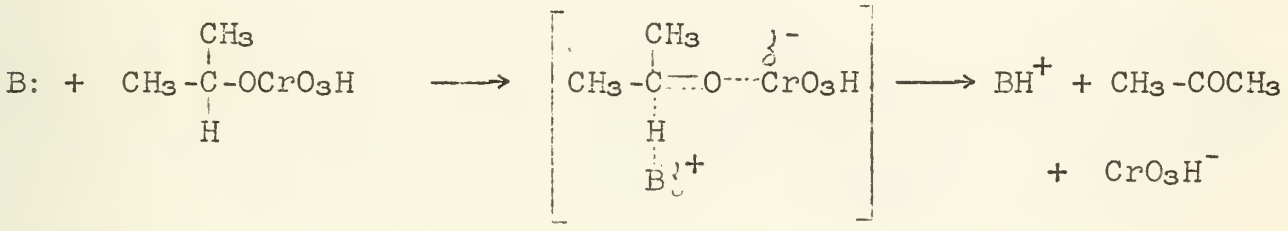
$$Cr^{V} + CH_3COHCH_3 \longrightarrow Cr^{III} + (CH_3)_2C{=}O$$

The Mn^{II} can interfere by reacting with Cr^{IV}.

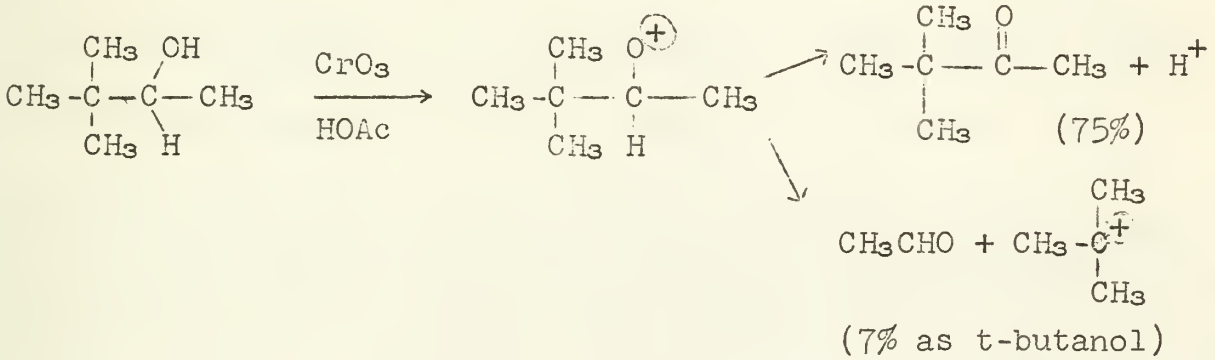
$$Mn^{II} + Cr^{IV} \longrightarrow Mn^{III} + Cr^{III}$$

$$2Mn^{III} + 2H_2O \longrightarrow MnO_2 + Mn^{II} + 4H^+$$

In support of his mechanism he has shown that isopropyl alcohol forms a neutral di-ester, $RCCrO_2OR$, with chromic acid (6). Although the ester was too unstable for isolation, it was stable enough in dry benzene to be analysed. The analysis showed two moles of alcohol present per mole of chromium. The compound was insoluble in sodium carbonate solution, an indication of its neutrality, and it was found to undergo oxidation or hydrolysis. The oxidation was catalysed by pyridine, even in acid medium (5). Water also acted as a base catalysing the reaction. This evidence along with the isotope effect led Westheimer to the following formulation of the ester decomposition:

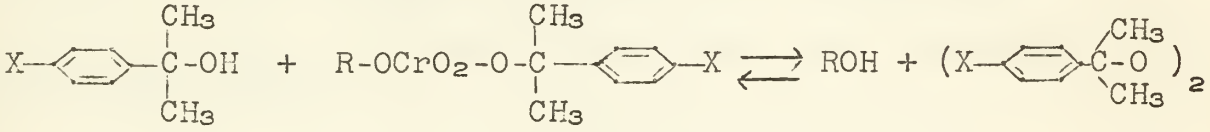


Mosher and Whitmore, in an investigation of the oxidation of methyl-t-butylcarbinol with chromic acid, found that a mixture of t-butyl alcohol and methyl t-butyl ketone resulted (7). To account for the products they proposed a reaction sequence involving initial loss of a hydride ion followed by expulsion of a proton or other positively charged species.



Westheimer's deuterium studies proved this mechanism invalid for his isopropanol oxidation although he pointed out that it might be operative in the latter steps of his reaction scheme as they are not rate-determining. In order to obtain information on this point, Kaplan has studied the rate of oxidation of 2-tritioisopropyl alcohol in $HClO_4$ (8). The determined value for the isotope effect lay in between the theoretical values for the two mechanisms. He offered, as a possible explanation, simultaneous reaction by both paths although he admitted to other interpretations of his results as well.

Kwart and Francis have studied the oxidation of a series of p-substituted phenylmethylcarbinols (9). The values of ρ in each of three solvents were negative. Assuming that C-H bond breaking leads CrO_3H^- elimination, it would be expected that electron-withdrawing ($+\sigma$) para-substituents would aid the reaction by stabilization of a partial negative charge induced on carbon. Thus ρ should be positive. In order to explain his results Kwart proposed that the esterification reaction has a large negative ρ value which overwhelms the smaller positive ρ for the base-catalysed ester decomposition: i.e. $\rho_{obs.} = \rho_{esterification} + \rho_{decomposition}$. Assuming for ρ_{ester} a value of -0.94, which was found to be the value for the ester interchange reaction,



CrO_2, the value of $\rho_{decomposition}$ would be +0.57 since $\rho_{obs.}$ was -0.37. The values he obtained, however, have alternative possible explanations. If the transition states have an appreciable amount of double-bond character they will resemble the product ketones in their stability. If this is the case, the methoxyl group would be expected to stabilize the transition state and the nitro group to destabilize the transition state as is indicated by the negative ρ values.

NITRATE ESTERS

Most of the work on the mechanism of decomposition of nitrate esters has been done by Baker in England. He points out that three reaction paths are available for the reaction of nitrate esters (10).

a) $R\text{-}CH_2\text{-}CH_2ONO_2 + X^- \longrightarrow RCH_2\text{-}CH_2\text{-}X + NO_3^-$ (S_n)

b) $R\text{-}CH_2\text{-}CH_2ONO_2 + X^- \longrightarrow RCH{=}CH_2 + HX + NO_3^-$ (E)

c) $R\text{-}CH_2\text{-}CH_2ONO_2 + X^- \longrightarrow RCH_2CHO + HX + NO_2^-$ (E_{co})

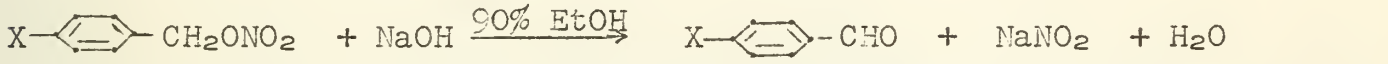
In the alkyl series very little carbonyl-forming elimination occurs (11). When the benzyl nitrate esters are treated with sodiumphenoxide in alcohol, 10% of the reaction is elimination. A plot of the logarithm of the reaction rate vs. pK_b for four substituted phenoxides gave a straight line plot in agreement with the Brönsted Catalysis Law (12). Baker has also shown that as the solution becomes neutral, elimination ceases. Water is evidently too weak a base to promote this reaction.

In an earlier paper Hammett had reported that hydroquinone had suppressed the elimination to form benzaldehyde (13). Baker also noted the effect and explained it on the basis of ion exchange. The hydroquinone by proton exchange with hydroxyl gives a weaker base.

$H_2Q + OH^- \longrightarrow H_2O + HQ^-$ The conjugate base of hydroquinone is too weak to promote the decomposition and so the reaction is inhibited.

In the same paper, Hammett reports the formation of benzaldehyde in acidic aqueous dioxane. Baker verified the finding and also tested the stability of the ester in acidic alcohol. In this medium no trace of a carbonyl-forming reaction was found (14). Both authors believe the production of benzaldehyde in dioxane to be a peroxide-catalysed reaction.

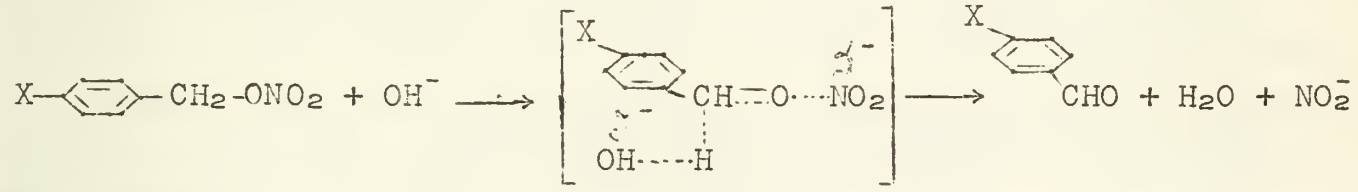
From a study of the elimination reaction for several para-substituted benzyl nitrate esters, Baker has obtained much information (15). For the reaction



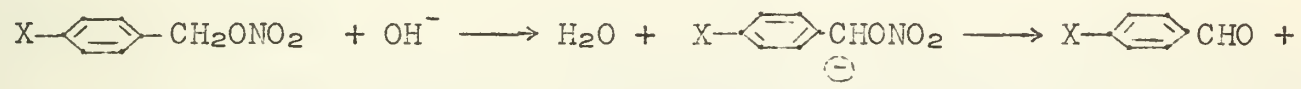
the rate constants which were found to be second order constants are as listed in the table below:

Substituent	p-NO_2	m-NO_2	p-Br	p-CH_3	H	p-OCH_3
Rate ($mole^{-1}$ l sec^{-1})	10^5	4560	85.2	2.9	9.2	1.91
Temperature	10	20	20	20	20	20

It can be seen that the p-nitro group has a tremendous accelerating effect on the reaction. It increases the rate by delocalization of the partial negative charge formed on carbon in the transition state both by its resonance and inductive capabilities.
The effects of the other substituents are all as expected from consideration of their inductive and resonance capabilities. These additional results for the second order base-catalysed reaction make the following mechanism likely:



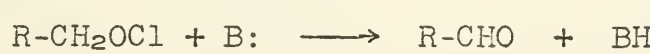
Baker admits the alternative two-step mechanism,



NO_2^-, is possible although unlikely. The settlement of this possibility by deuterium exchange studies has not yet been achieved.

ALKYL HYPOCHLORITES

Alkyl hypochlorites have been prepared readily by Fort and Denivelle (16) from hypochlorous acid and alcohol in $CFCl_3$ (Freon 11). These authors report the decomposition of these esters with tertiary amines to the corresponding aldehydes. It is very likely that the same mechanism is operative here as in the above case of nitrate esters.



Most of the hypochlorites are extremely unstable in neutral media, eliminating HCl spontaneously.

PERSULFATE ESTERS

Levitt has recently examined the oxidation of isopropanol by potassium persulfate (17). He proposed a mechanism from which he was able to derive the observed rate equation.

$$^{-}O_3SOOSO_3^{\ominus} \rightleftharpoons {}^{-}O_3SO^{-} + {}^{+}OSO_3^{-}$$

$$R_2CHOH + {}^{+}OSO_3^{-} \rightleftharpoons R_2\text{-}\overset{+}{C}H\text{-}O\text{-}OSO_3^{-}$$

$$R_2\overset{+}{C}HO\text{-}OSO_3^{-} \longrightarrow H^{+} + [R_2CHOOSO_3^{-}] \longrightarrow R_2C{=}O + H^{+} + SO_4^{=}$$

Noting the similarity of this to other decompositions involving esters of inorganic acids he made some general observations correlating the reactions."

"1. The oxidizing agent is usually positive (e.g. NO_2^{+}, Cl^{+}, ${}^{+}OSO_3^{-}$, CrO_3H^{+}).

2. Attack occurs at the oxygen atom resulting in the expulsion of a proton.

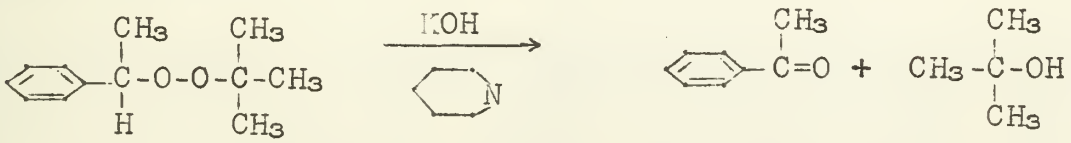
3. Oxidant moves off as anion with simultaneous loss of a proton.

The intermediate ester formed may be quite stable if no proton is available for expulsion. For example, t-butyl hypochlorite is a relatively stable hypochlorite since it has no alpha hydrogen atoms."

Levitt's postulation of CrO_3H^{+} as the attacking species is made purely from analogy. It is likely that the concentration of this species will be too small to enter into the reaction to any appreciable extent.

DIALKYL PEROXIDES

Kornblum has found that unsymmetrical or symmetrical hydroperoxides are unstable in basic media, in which they decompose into ketone or aldehyde and alcohol (19). When t-butyl-α-phenethyl peroxide is treated with KOH the products are acetophenone (80%) and t-butanol (25%).

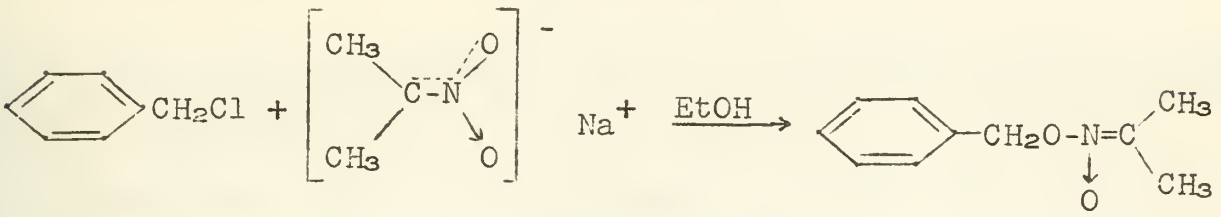


As in the case of the hypochlorite di-t-butyl peroxide is stable to alkali (20).

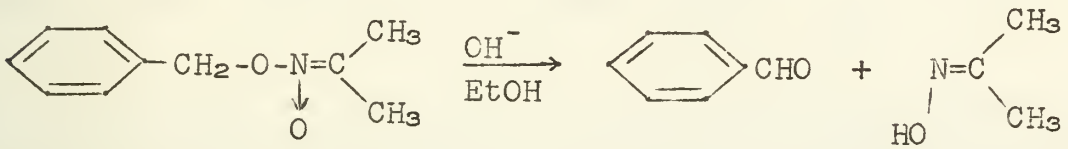
NITRONIC ACID ESTERS

The product from the reaction of the sodium salt of a nitroparaffin

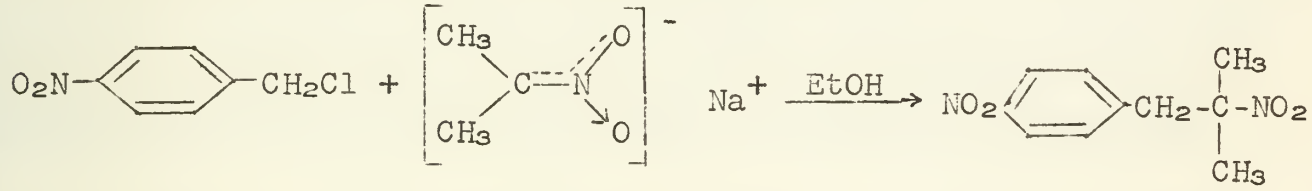
with an alkyl halide is normally the O-alkylation product, a nitronic acid ester. 2-Nitropropane sodium salt reacts with benzyl chloride in this manner giving presumably benzyl 2-propanenitronate as an intermediate (21).



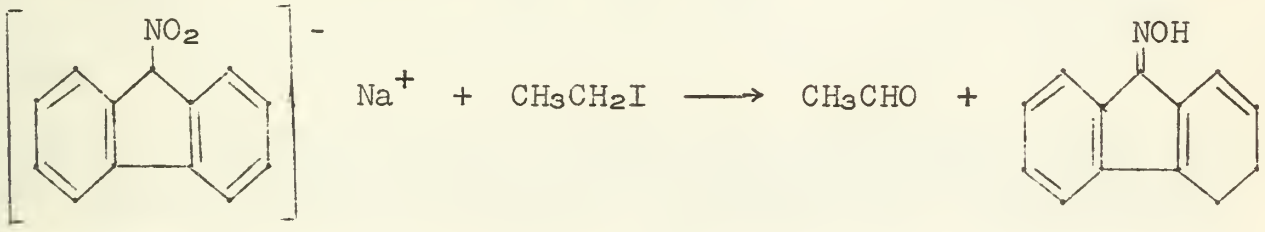
This ester is unstable under the reaction conditions breaking down into benzaldehyde and acetone oxime. The yield of benzaldehyde is 73%.



The reaction has been investigated by Hass and Bender and found to be a good method for the conversion of substituted benzyl halides into the corresponding benzaldehydes (21). It appears to be equivalent to the Sommelet method in yields and practicality but fails for p-nitro, o-nitro, and 2,4-dinitrobenzaldehydes, which give the C-alkylation product, a tertiary nitroparaffin (22).

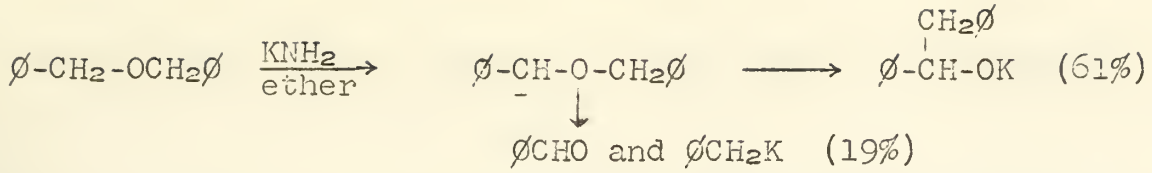


The reaction is not limited to benzyl halides. Methyl and ethyl iodide are converted to aldehydes by 9-nitrofluorene with concomitant production of fluorenone oxime (23).



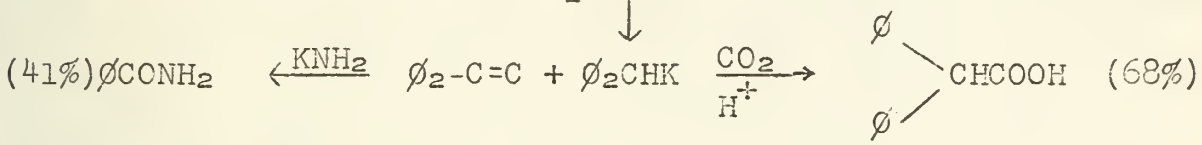
BENZYL ETHERS

The products of the reaction of benzyl ethers with base vary with the base employed. Although dibenzyl ether gave only rearranged benzylphenylcarbinol when treated with phenyllithium (24), Hauser has isolated benzaldehyde and toluene in addition to the rearranged alcohol from the reaction of dibenzyl ether and potassium amide (25).



He has shown that the carbinol is not an intermediate in the production of benzaldehyde since it gave no aldehyde when subjected to the reaction conditions.

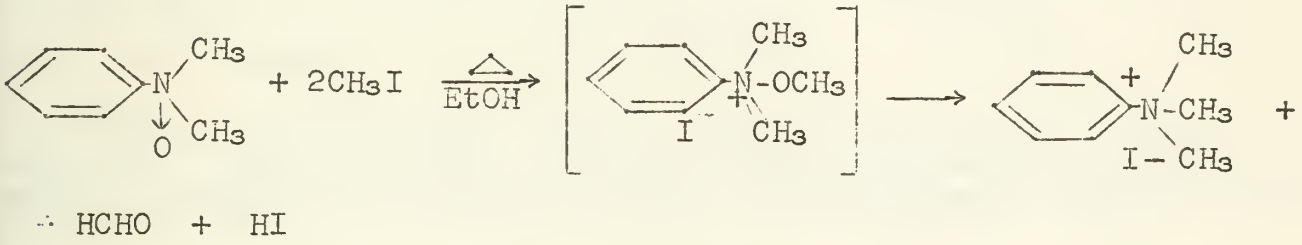
Dibenzhydryl ether gave elimination products only.



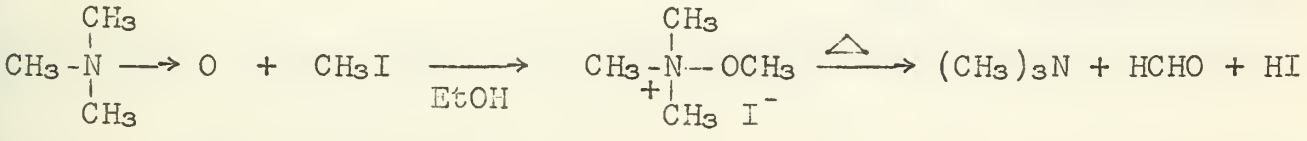
The benzophenone was converted to benzamide by the potassium amide. Potassium diphenylmethide was converted by carbonation of the reaction mixture into diphenylacetic acid. In this reaction, the possibility that the carbinol is an intermediate was not eliminated.

AMINE OXIDES

In 1899, two separate investigators disclosed a carbonyl-forming elimination reaction involving amine oxides (26, 27). It was found that both dimethylaniline oxide and trimethylamine oxide gave, upon heating with methyl iodide, formaldehyde and a quaternary iodide. Bamberger proposed the following reaction sequence to explain his results (26).



Dunstan and Goulding actually isolated an intermediate of the type postulated by Bamberger by running the reaction at room temperature (27). Subsequent heating produced formaldehyde and trimethylamine.

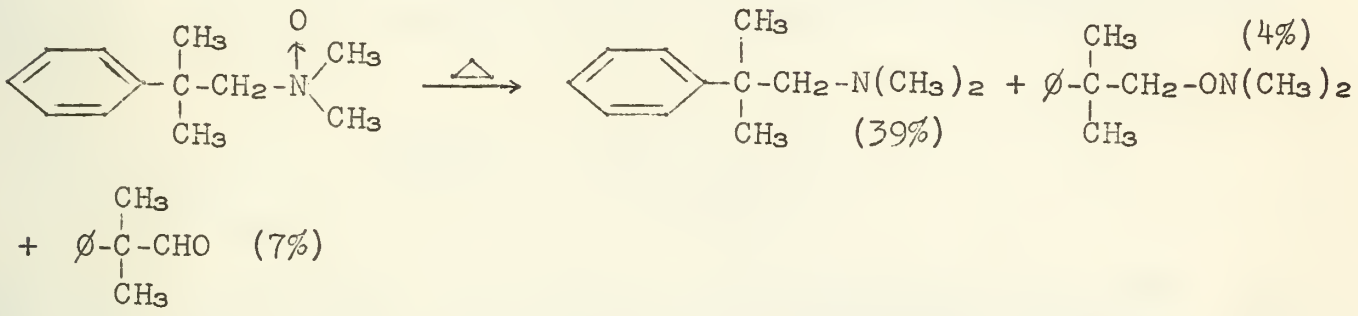


When benzyl chloride was used in place of methyl iodide the carbonyl compound formed was benzaldehyde (27).

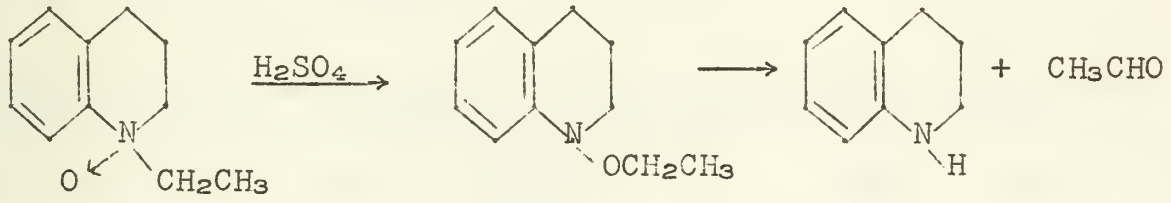
The isolable intermediate in the methyl iodide reaction gave formaldehyde and dimethylamine when heated with hydrogen iodide. The acid decomposition was thought to follow a different path.

$$(CH_3)_3\overset{+}{N}\text{-}OCH_3\ I^- \xrightarrow[\triangle]{HI} (CH_3)_3NO + CH_3I \longrightarrow HCHO + (CH_3)_2NH.HI$$

This type of decomposition has recently been investigated by Cope (28). In examining the scope of the pyrolysis of amine oxides, he studied the following reaction:



The amine is unable to form olefine since it has no beta hydrogen atoms. However it rearranges to the trisubstituted hydroxylamine which undergoes the carbonyl-forming elimination reaction. Cope point out the similarity in behavior of N-ethyltetrahydroquinoline when treated with sulfuric acid. This oxide is converted to tetrahydroquinoline and acetaldehyde, probably through the hydroxylamine intermediate (29).



When a tertiary amine oxide is treated with sulfur dioxide, an addition compound results. This compound decomposes in aqueous acid to aldehyde and secondary amine. Trimethylamine oxide serves as an example (30).

$$(CH_3)_3N \longrightarrow O + SO_2 \xrightarrow{EtOH} (CH_3)_3\text{-}\overset{+}{N}\text{-}OSO_2^- \xrightarrow[H_2O]{H^+} [(CH_3)_2\overset{+}{N}{=}CH_2 + HSO_3^-]$$

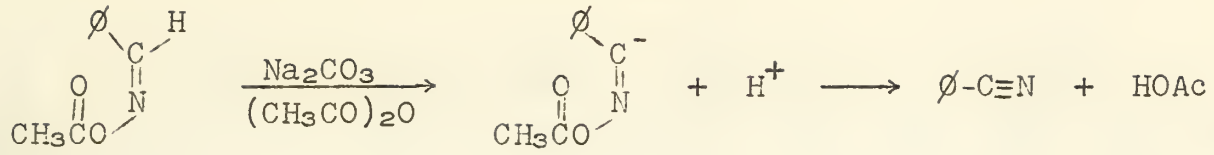
$$\downarrow$$

$$HCHO + (CH_3)_2NH{\cdot}H_2SO_3$$

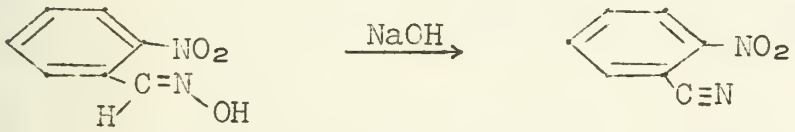
The reaction offers a means of converting tertiary amines to secondary amines in 50% yield.

NITRILE-FORMING ELIMINATIONS

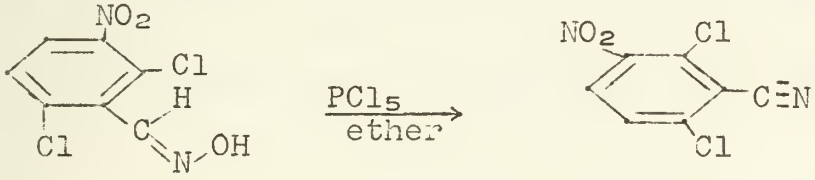
Aryl β-oximes react with base to produce nitriles in a manner analogous to their oxygen counterparts. Brady has made an extensive study of the reaction and has formulated it as shown below (31, 32):



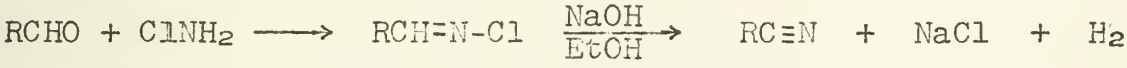
The decomposition occurs with the β isomer only. Brady feels that th stability of the α-isomer is due to hydrogen bonding which decreases the acidity of the hydrogen atom attacked by base. It is likely that the increased energy requirements for a cis-elimination are at least of equal importance. The free oximes are stable to alkali, probably since OH^- is a poor leaving group. A notable exception is o-nitrobenzaldoxime.(33).



On the other hand the free oximes are unstable to acids. The Beckmann rearrangement of aldoximes often produces nitriles in additio to the normal rearranged products (36). In many cases, with strong acids, nitriles are formed almost exclusively (35, 37). The conversion of 2,6-dichloro-3-nitrobenzaldoxime into the corresponding nitrile in 90% yield serves as an example.



The conversion of an aldehyde to a nitrile proceeds through the chlorimine which is decomposed by base (34).



The overall yield for the reaction is 75%.

BIBLIOGRAPHY

1. F. H. Westheimer, Chem. Revs., 45, 419 (1949).
2. F. H. Westheimer, J. Chem. Phys., 11, 506 (1943).
3. F. H. Westheimer and N. Nicolaides, J. Am. Chem. Soc., 71, 25 (1949).
4. W. Watanabe and F. H. Westheimer, J. Chem. Phys., 17, 61 (1949).
5. A. Leo and F. H. Westheimer, J. Am. Chem. Soc., 74, 4383 (1952).
6. F. H. Westheimer, M. Cohen and F. Holloway, J. Am. Chem. Soc., 73, 25 (1951).
7. W. A. Mosher and F. C. Whitmore, J. Am. Chem. Soc., 70, 2544 (1948
8. L. Kaplan, J. Am. Chem. Soc., 77, 5469 (1955).
9. H. Kwart and P. S. Francis, J. Am. Chem. Soc., 77, 4907 (1955).
10. J. W. Baker and D. M. Easty, Nature, 166, 156 (1950).
11. J. W. Baker and D. M. Easty, J. Chem. Soc., 1193 (1952).
12. J. W. Baker and A. J. Neale, J. Chem. Soc., 3225 (1954).
13. L. P. Hammett and G. R. Lucas, J. Am. Chem. Soc., 64, 1928 (1942).

14. J W. Baker and A. J. Neale, J. Chem. Soc., 609 (1955).
15. J. W. Baker and T. G. Heggs, J. Chem. Soc., 616 (1955).
16. R. Fort and L. Denivelle, Bull. Soc. Chim. Fr., 1109 (1954).
17. L. S. Levitt and E. R. Malinowski, J. Am. Chem. Soc., 77, 4519 (1935).
18. F. D. Chattaway and O. G. Backeberg, J. Chem. Soc., 2999 (1923).
19. N. Kornblum and H. E. DeLaMare, J. Am. Chem. Soc., 73, 880 (1951)
20. N. A. Milas and D. M. Surgenor, J. Am. Chem. Soc., 68, 205 (1946).
21. H. B. Hass and M. L. Bender. J. Am. Chem. Soc., 71, 1767 (1949).
22. L. Wiesler and R. W. Helmkamp, J. Am. Chem. Soc., 67, 1167 (1945).
23. E. Ninitzescu and L. Isaceacu, Ber., 63, 2484 (1930).
24. G. Wittig and L. Lohman, Ann., 550, 260 (1942).
25. C. R. Hauser and S. W. Kantor, J. Am. Chem. Soc., 73, 1437 (1951).
26. W. R. Dunstan and E. Goulding, J. Chem. Soc., 1004 (1899).
27. E. Bamberger and F. Tschirner, Ber., 32, 1886 (1899).
28. A. C. Cope, T. T. Foster and P. H. Towles, J. Am. Chem. Soc., 71, 3930 (1949).
29. J. Mesenheimer, Ber., 52, 1667 (1919).
30. H. Z. Lecher and W. B. Hardy, J. Am. Chem. Soc., 70, 3789 (1948).
31. M. Berger and O. L. Brady, J. Chem. Soc., 1221 (1950).
32. O. L. Brady and S. Jarrett, J. Chem. Soc., 1227 (1950).
33. A. Reissert, Ber., 41, 3815 (1908).
34. C. R. Hauser and J. W. Le Maistre, J. Am. Chem. Soc., 57, 1056 (1935).
35. C. M. Luxmore, J. Chem. Soc., 69, 190 (1896).
36. S. Yamaguchi, Bull. Soc. Chem. Japan, I, 35 (1926), C.A., 21, 75. (1927).
37. J. Mesenheimer and W. Theilacker, Ann., 495, 249 (1932).

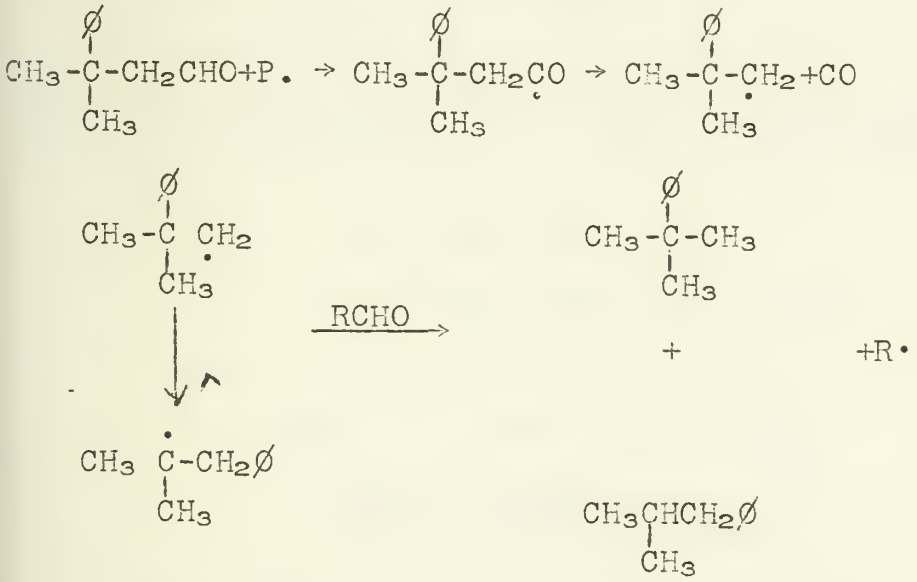
DECARBONYLATION REACTIONS

Reported by Joseph Kleiman March 11, 1957

A decarbonylation reaction may be defined as a reaction in which a molecule loses the grouping C=O, usually as carbon monoxide, but sometimes as carbon dioxide. One of the earliest examples is the formation of carbon monoxide from formic acid on treatment with concentrated sulfuric acid (1). Compounds which can be decarbonylated are aldehydes, ketones, α-diketones, triketones, oxalyl esters, acids, α-ketoacids, carbonates (2), acid chlorides, and α-hydroxycidids. Decarbonylations may be carried out by heat, ionic catalysis, free radical catalysis, and photolysis. This seminar will deal mainly with the mechanisms for these reactions. Photolysis reactions will not be covered.

FREE RADICAL DECARBONYLATIONS

Aside from photolysis reactions, the research in free radical decarbonylations is realtively recent. Winstein and Seubold (3) found that if β-phenylisovaleraldehyde was treated with a free radical initiator, a one to one mixture of isobutyl and t-butyl benzene was obtained plus an equivalent amount of carbon monoxide. They proposed the following mechanism:

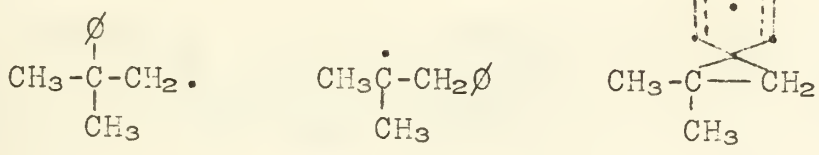


Further evidence for a free radical mechanism was provided by the reaction in carbon tetrachloride at lower temperatures from which the corresponding acid chloride was isolated.

$$RCO + CCl_4 \rightarrow RCOCl + Cl_3C\cdot$$

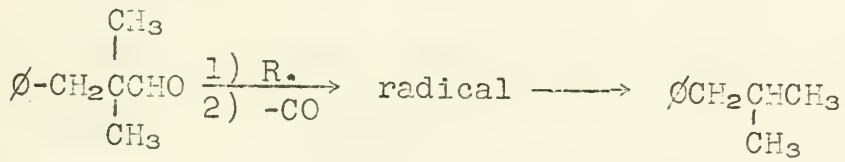
$$Cl_3C\cdot + RCHO \rightarrow Cl_3CH + RC\dot{O}$$

Seubold (4) and Urry and Nicolaides (5) both showed that at least two radicals are intermediate in the decarbonylation of β-phenylisovaleraldehyde.



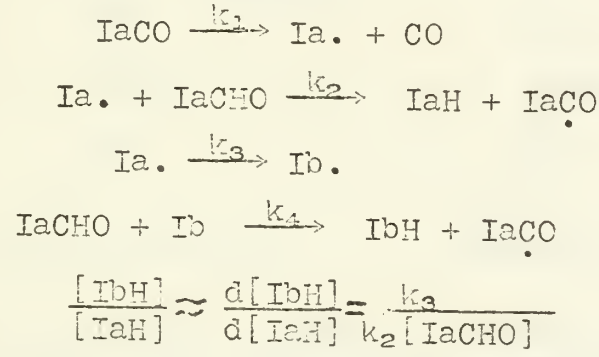
Ia Ib Ic

It was found (5) that 3-phenyl-2,2-dimethylpropionaldehyde, II, did not give any rearranged product, which indicated that the radical formed might exist as Ib or Ic or both if Ic reacted only at the tertiary carbon.

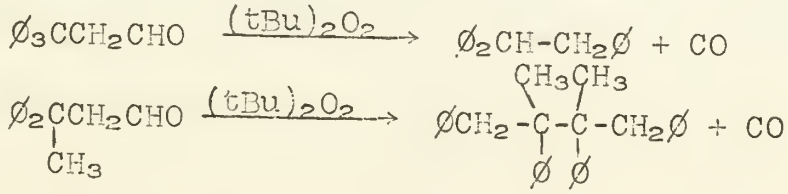


II

Seubold pointed out that in the decarbonylation of β-phenylisovaleraldehyde, at least two radicals must exist to explain the fact that the ratio isobutylbenzene (IbH)/t-butylbenzene (IaH) increases from 1.3 to 4.0 as the aldehyde concentration decreases. This can be explained by the following mechanism:



Curtin and Hurwitz (6) studied the decarbonylation of various phenyl-substituted aldehydes. β,β,β-triphenylpropionaldehyde and β,β-diphenylbutyraldehyde were found to rearrange completely.



Barret and Waters investigated the decarbonylation of aldehydes by dimethyl α,α'-azobutyrate (III) (7,8) and found that the chain length was increased by thiols.

$$(CH_3)_2\underset{\underset{CO_2CH_3}{|}}{C} - N = N - \underset{\underset{CO_2CH_3}{|}}{C}(CH_3)_2 \longrightarrow N_2 + 2(CH_3)_2\underset{\underset{CO_2CH_3}{|}}{C}\cdot$$

III IV

$$IV + \emptyset CH_2SH \longrightarrow (CH_3)_2\underset{\underset{CO_2CH_3}{|}}{CH} + \emptyset CH_2S\cdot$$

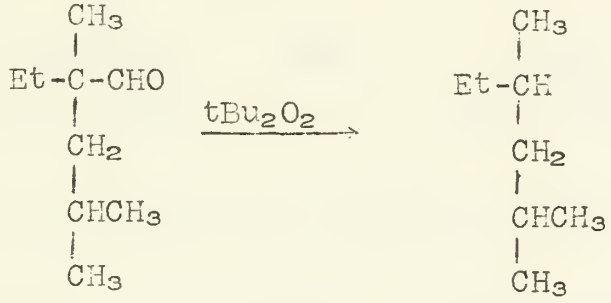
$$\emptyset CH_2S\cdot + RCHO \longrightarrow \emptyset CH_2SH + RCO\cdot$$

$$RCO\cdot \longrightarrow R\cdot + CO$$

$$R\cdot + \emptyset CH_2SH \longrightarrow RH + \emptyset CH_2S\cdot$$

$$2\emptyset CH_2S\cdot \longrightarrow (\emptyset CH_2S)_2$$

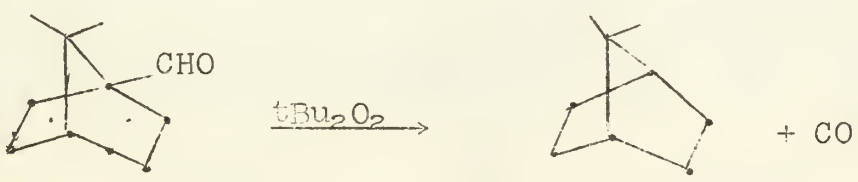
The work of Doering and co-workers (9) provided further evidence on the nature of the reactions. They found that optically active 2,4-dimethyl-2-ethylpentanal (V) gave inactive 2,4-dimethyl-hexane (VI). They also found that apocamphane-1-carboxaldehyde



V optically active

VI inactive

(VII) reacted normally to give apocamphane, which indicated that there is no particular inhibition to formation of a bridgehead free radical.

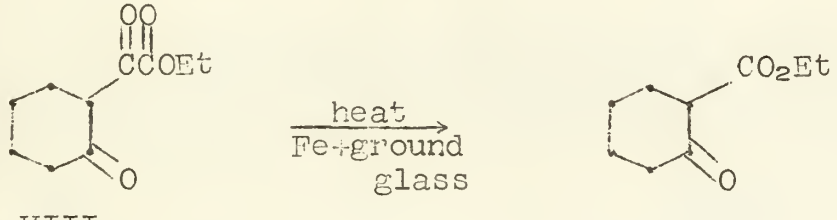


VII

Van Heyningen discovered that certain esters lost carbon monoxide under the conditions of the acyloin condensation, which provided evidence for a free radical mechanism in that reaction (10-12).

DECARBONYLATIONS OF UNKNOWN MECHANISM

An interesting reaction for which the mechanism is unknown is the decarbonylation of VIII (13).

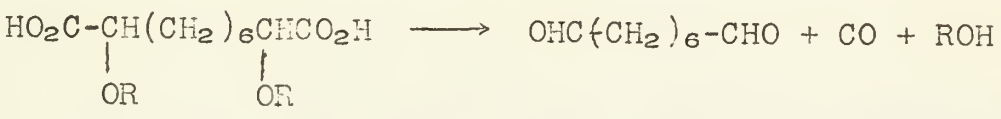


VIII

Compounds of type X-CCCHY, where X=CHCOR' or OR'; R=H, alkyl, or aryl; and Y is an electron attracting group, can generally be decarbonylated (14).

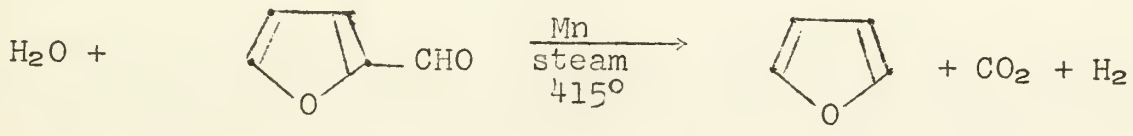
Compounds of the above type can be used in synthesis of substituted malonic esters (15-17). An example is the formation of phenoxymalonic ester.

Hydroxy acids can be decarbonylated to aldehydes (18).



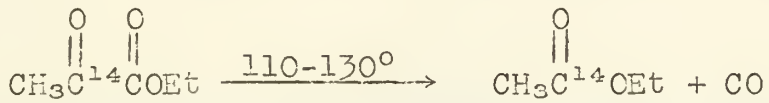
R=H or Ac

The conversion of furfural to furan is accomplished by heating at a temperature of 415° in the presence of Mn, Fe, Co, Ni, or Zn chromite, and a large excess of steam (19). In the presence of steam, carbon dioxide and hydrogen are given off. Under anhydrous conditions carbon monoxide is formed.

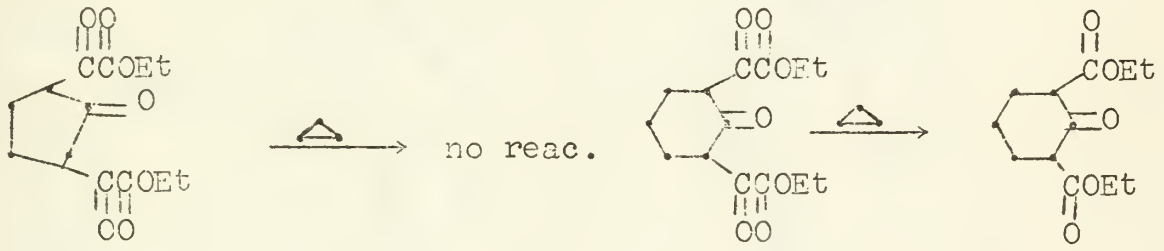


The decarbonylation in the presence of steam is a second order reaction in furfural (19).

Calvin and Lemmon studied the decarbonylation of labeled pyruvic acid and found that the ester carbonyl is lost (20).

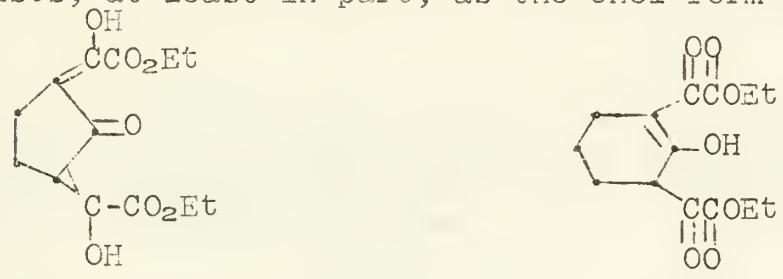


Mayer (16) investigated the reactions of certain cyclic keto-esters. He found that the ester, IX, would not decarbonylate under extreme conditions although the corresponding six ring compound, X, decarbonylates easily (21).



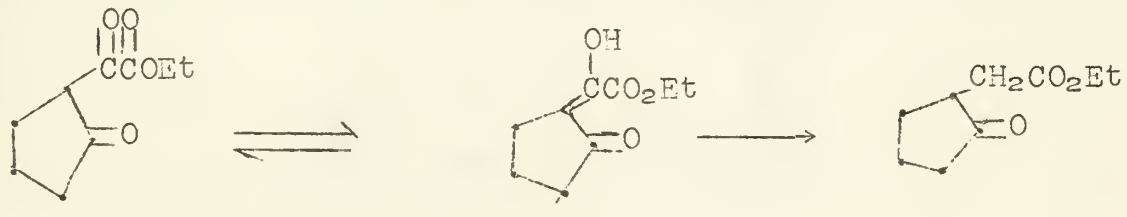
IX X

He postulated that IX exists primarily in the enol form XI, while X exists, at least in part, as the enol form XII.



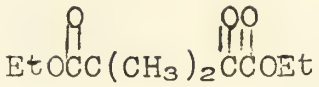
XI XII

Hydrogenation of XIII provides evidence for the enol form XI in that it proceeds under conditions that do not reduce the ring carbonyl.



XIII

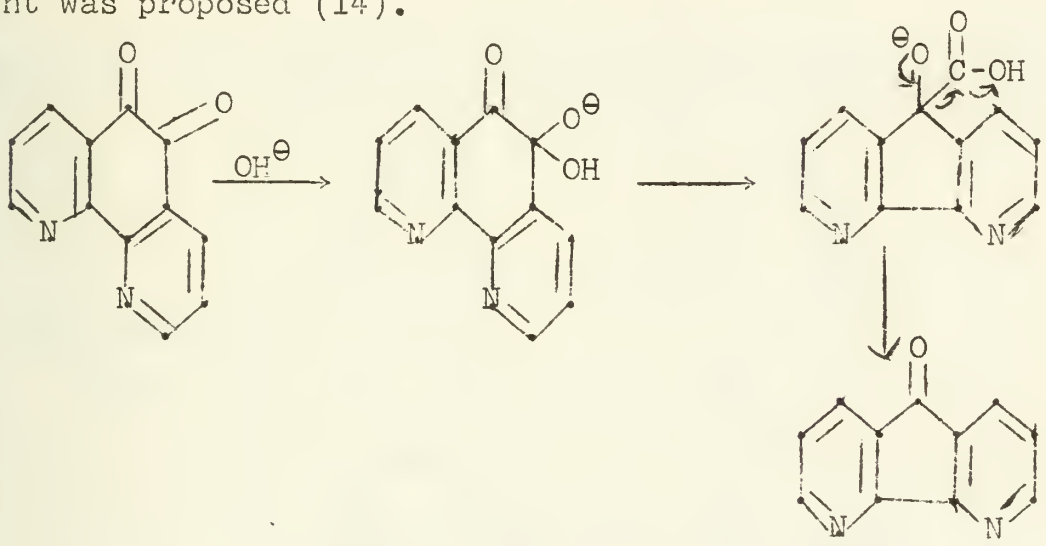
He suggested that XI and XIII can not be decarbonylated since they exist primarily as the enols. However, Wislicenus (16) observed that XIV could not be decarbonylated at about 200°, which suggests that enolization may be an important step in the mechanism.



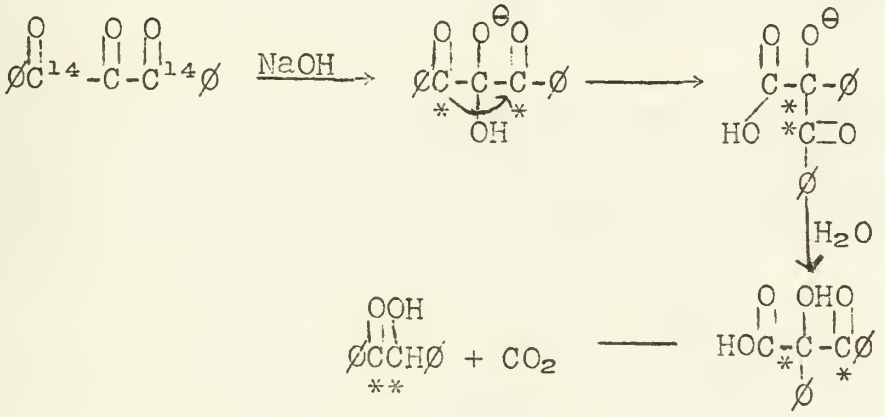
XVI

IONIC REACTIONS

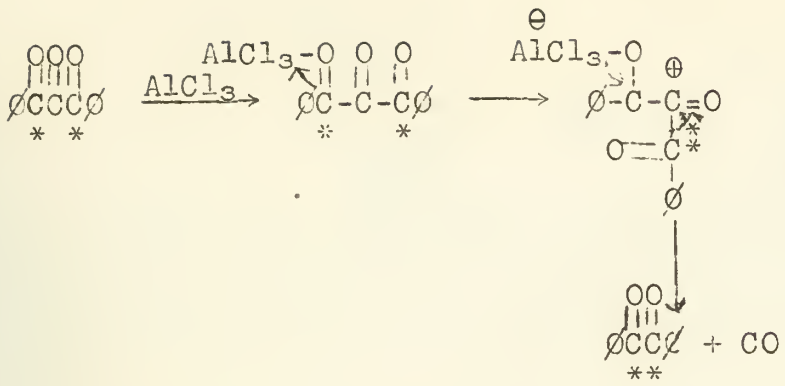
Decarbonylations can be catalyzed by both acidic and basic reagents. The decarbonylation of XV is catalyzed by dilute sodium hydroxide (22). A mechanism similar to the benzilic acid rearrangement was proposed (14).



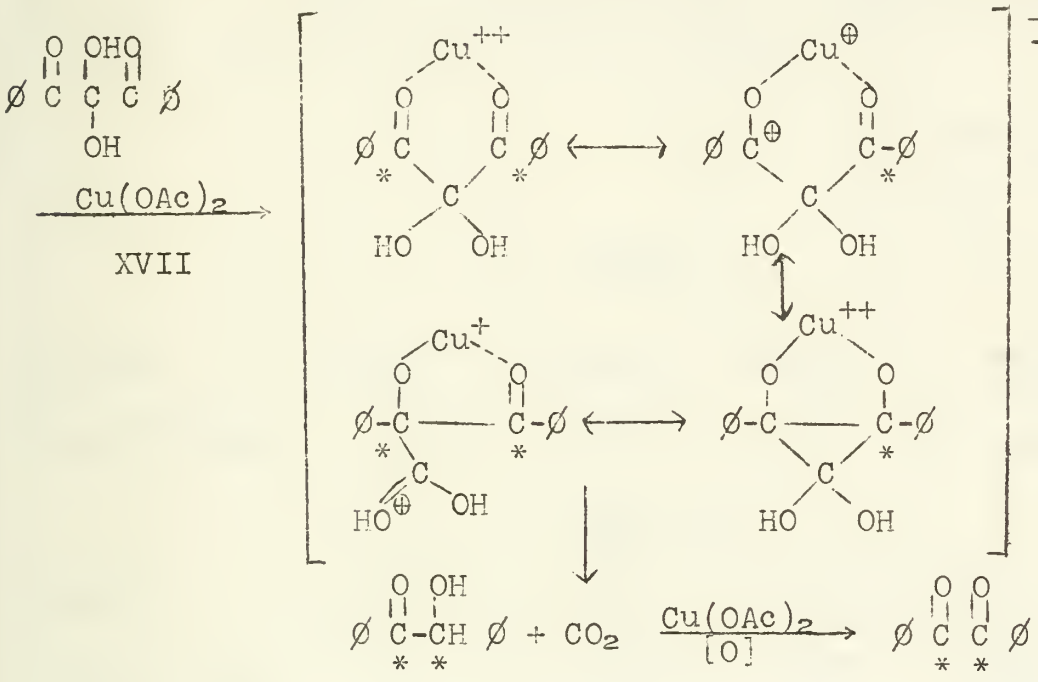
Roberts and coworkers have studies the decarbonylation of diphenyl triketone, XVI, under a variety of conditions by use of carbon 14 (23). They postulated the following mechanism for the sodium hydroxide catalyzed reaction.



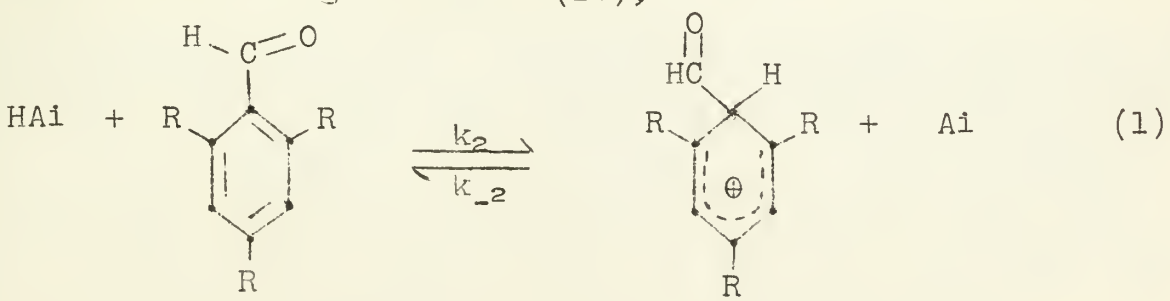
The decarbonylation is also catalyzed by aluminum chloride.

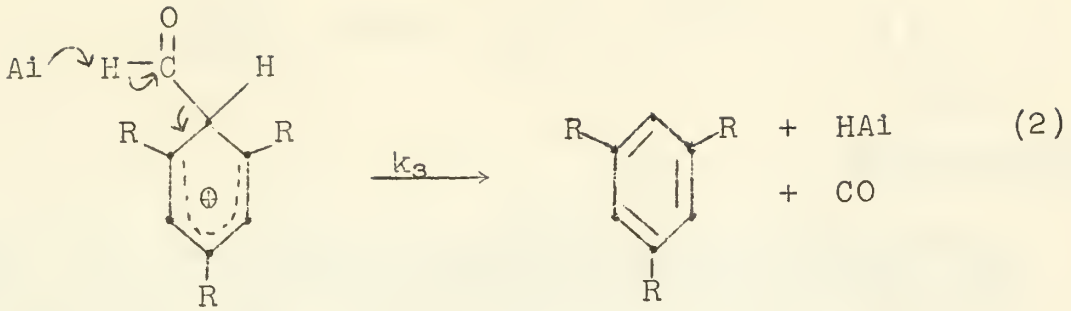


The cupric acetate catalyzed decarbonylation probably proceeds by a similar mechanism. In solution, the triketone exists as the hydrate, XVII, and this possibly loses carbon dioxide as follows:



Schubert and coworkers (24, 25) have studied the acid-catalyzed decarbonylation of mesitaldehyde. The reaction was first order in aldehyde concentration and undetermined order in acid ($H_3O^{\oplus}$, H_2SO_4, $H_3SO_4^{\oplus}$). It did not follow the Hammett acidity function. They proposed the following mechanism (24);





(2)

Ai=H_2O,$HSO_4^{\ominus}$,H_2SO_4 in very conc. solution.

Further studies with deuteromesitaldehyde and deuterosulfuric acid are consistent with the above mechanism provided that the rate constants k_2, k_{-2}, and k_3 vary at different acid concentrations. The ratio of rates of decarbonylation of ArCHO and ArCDO are given in table I (25) and the ratio of rates in sulfuric acid and deuterosulfuric acid are given in table II (25).

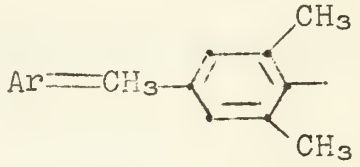


TABLE I

% H_2SO_4	100.4	96.31	85.21	59.88
k_{ArCHO}/k_{ArCDO}	1.8	2.8	2.8	1.8

TABLE II

Acid %	99.5	96	85	70	65	59
$k_{H_2SO_4}/k_{D_2SO_4}$	2.4	2.1	1.5	0.85	0.72	0.56

The acid catalyzed decarbonylations of acids and acid derivatives have been observed or studies by many workers (26-47). Acids which can form relatively stable carbonium ions by loss of C=O exhibit this behavior.

Elliott and Hammick (26) studied the acid catalyzed decarbonylation of benzoylformic acid. The reaction was found to be inhibited by the addition of bases (H_2O, K_2SO_4) indicating that some acidic or positive species essential to the reaction was being destroyed. A plot of log k against Ho gave a slope of -2.1 which indicated a di-protonated transition state. They proposed two mechanisms. Banholzer and Schmid investigated the same reaction using carboxyl-labeled carbon (27). They were able to show that the carbon monoxide contained all the radioactivity in support of mechanism (1) or its equivalent, proposed by Elliott and Hammick (26).

$$\phi\,C_2O_3H_3^{\oplus\,\oplus} \xrightarrow{\text{slow}} H_3O^{\oplus} + \phi\,\overset{O}{\overset{\|}{C}}\,\overset{O}{\overset{\|}{C}}{}^{\oplus} \longrightarrow \phi\,CO + CO$$

$$\downarrow HSO_4^{\ominus}$$

$$\phi COOSO_3H \rightarrow \phi CO_2H_2^{\oplus}$$

Ditmar (28) investigated the decarbonylation of triphenylacetic acid by acid and his data were interpreted by Taft and Deno (29) who found that a plot of log k vs. $J_o = H_o + \log a_{H_2O}$ gave a slope of -1, which is consistent with the following mechanism:

$$\phi_3C\text{-}COOH + H^{\oplus} \rightleftharpoons H_2O + \phi_3C\text{-}\overset{\oplus}{C}O \quad \text{equilibrium}$$

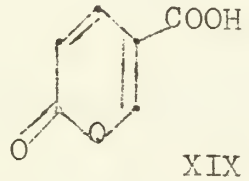
$$\phi_3C\text{-}\overset{\oplus}{C}O \longrightarrow \phi_3C^{\oplus} + CO \quad \text{rate determining}$$

Ditmar (30) and Whitford (31) investigated the decarbonylation of malic acid, XVIII, to give eventually XIX.

$$HOOCCH_2CHOHCOOH \xrightarrow{k} CO + H_2O + HOOCCH_2CHO$$

XVIII

$$2\ CHOCH_2COOH \longrightarrow$$



XIX

Whitford's data show that $-(\log k_{50^\circ} + Ho) = 10.48 \pm .04$ for 99.2 to 96.6% sulfuric acid and $-(\log k_{30^\circ} + Ho) = 11.54 \pm .08$ for 99.5 to 97.5% sulfuric acid. The correlation with C_o and J_o is poor, assuming that in these concentration ranges $C_o - J_o = 4.92$ (48). This is consistent with the following mechanism:

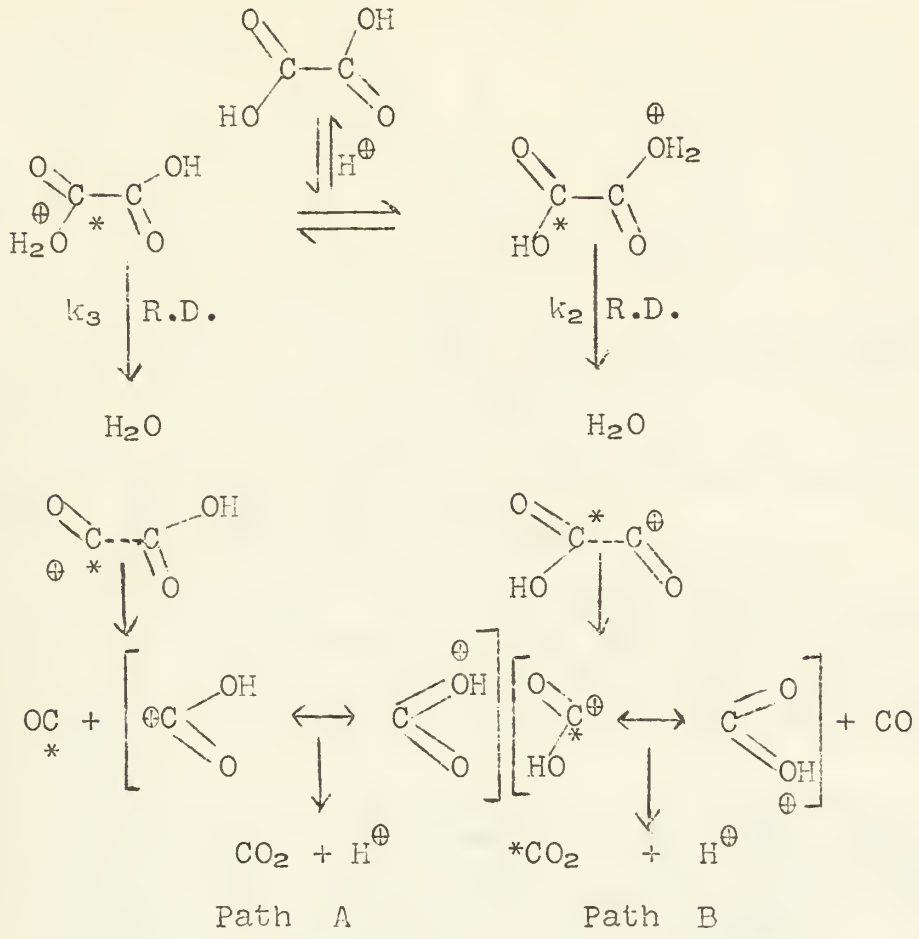
$$HOOCCH_2\overset{OH}{\overset{|}{C}}HCOOH \xrightarrow{H^{\oplus}} HOOCCH_2\overset{OH}{\overset{|}{C}}HCOOH_2^{\oplus} \xrightarrow[\text{step}]{\text{rate det'g}} HOOCCH_2\overset{OHO}{\overset{|\ \ \|}{C}}H^{\oplus} + H_2O$$

$$\downarrow \text{fast} -CO$$

$$HOOCCH_2\overset{OH}{\overset{|}{C}}H^{\oplus}$$

The acid-catalyzed decomposition of oxalic acid has been investigated by studying the isotope effect in carbon 13 labeled oxalic acid (32, 33). It was found that the carbon dioxide was enriched in carbon 13 and that oxalic acid containing only carbon

12 reacted faster. The following mechanism fits the data (33):



Path B is most likely since carbon dioxide is enriched in carbon 13.

Rothstein and coworkers (38-42, 45-47) made a most detailed study of the decomposition of pivaloyl chloride by aluminum chloride. The reaction was found to be first order in acid chloride and $k_{obs} = 0.4928\ [AlCl_3]^2 + 0.025\ [AlCl_3] - 0.00037$. The following mechanism is in accord with the data (47):

$$2AlCl_3 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Al_2Cl_6$$

$$AlCl_3 + RCOCl \xrightarrow{k_3} RCOAlCl_4^{\ominus}_{\oplus}$$

$$Al_2Cl_6 + RCOCl \xrightarrow{k_3'} RCOAlCl_4^{\ominus}_{\oplus} + AlCl_3$$

alternative slow steps

$$RCOAlCl_4^{\ominus}_{\oplus} \xrightarrow{k_5} \text{products}$$

In this scheme, $k_3 = 0.025$ liter/moles sec and $k_1k_3'/k_2 = 0.4928$ liters ^{2}/moles ^{2}sec. The reaction product is t-butyl benzene if the reaction is run in benzene.

BIBLIOGRAPHY

1. Doebereiner, Schweiger-Meinecke's J. Chem. Phys., 32, 345 (1821).
2. S. T. Bowden and T. John, J. Chem. Soc., 213 (1940).
3. S. Winstein and F. Seubold, J. Am. Chem. Soc., 69, 2916 (1947).
4. F. H. Seubold, J. Am. Chem. Soc., 75, 2532 (1953).
5. W. H. Urry and N. Nicolaides, J. Am. Chem. Soc., 74, 5163 (1952).
6. D. Y. Curtin and M. J. Hurwitz, J. Am. Chem. Soc., 74, 5381 (1952)
7. K. E. J. Barret and W. A. Waters, Dis. Far. Soc., 14, 221 (1953).
8. E. F. P. Harris and W. A. Waters, J. Chem. Soc., 3108 (1952).
9. W. v. E. Doering, M. Farber, M. Sprecher, and K. B. Wiberg, J. Am. Chem. Soc., 74, 3000 (1952).
10. E. Van Heyningen, J. Am. Chem. Soc., 74, 4861 (1952).
11. E. Van Heyningen, J. Am. Chem. Soc., 77, 4016 (1955).
12. G. Hartzell, U. of Ill. Seminar Abstract, 1st Sem., 1956-1957.
13. Org. Syn., Coll. Vol. II, p. 531.
14. P. H Gore and G. K. Hughes, J. Am. Chem. Soc., 72, 5770 (1950).
15. E. H. Huntress and R. T. Olsen, J. Am. Chem. Soc., 70, 2856 (1948).
16. R. Mayer, Ber., 88, 1859 (1955).
17. W. Wislicenus, Ber., 28, 811 (1895).
18. H. R. LeSueur, J. Chem. Soc., 91, 1365 (1907).
19. J. Vandor, Acta Chim. Acad. Sci. Hung., 3, 169 (1953).
20. M. Calvin and R. M. Lemmon, J. Am. Chem. Soc., 69, 1232 (1947).
21. G. A. R. Kon and D. L. Nandi, J. Chem. Soc., 1628 (1933).
22. G. E. Inglett and G. F. Smith, J. Am. Chem. Soc., 72, 842 (1950).
23. J. D. Roberts, D. R. Smith, and C. C. Lee, J. Am. Chem. Soc., 73, 618 (1951).
24. W. M. Schubert,and R. E. Zahler, J. Am. Chem. Soc., 76, 1 (1954).
25. W. M. Schubert and K. H. Burkett, J. Am. Chem. Soc., 78, 64 (1956).
26. W. W. Elliott and D. Ll. Hammick, J. Chem. Soc., 3402 (1951).
27. K. Banholzer and H. Schmid, Helv. Chim. Acta, 39, 548 (1956).
28. H. R. Dittmar, J. Phys. Chem., 33, 533 (1929).
29. N. C. Deno and R. W. Taft, J. Am. Chem. Soc., 76, 244 (1954).
30. H. R. Dittmar, J. Am. Chem. Soc., 52, 2747 (1930).
31. E. L. Whitford, J. Am. Chem. Soc., 47, 953 (1925).
32. J. G. Lindsay, D. E. McElcheran, and H. G. Thode, J. Chem. Phys., 17, 589 (1949).
33. A. Fry and M. Calvin, J. Phys. Chem., 56, 897 (1952).
34. C. S. Schuerch, Jr. and E. H. Huntress, J. Am. Chem. Soc., 71, 2233 (1949).
35. C. S. Schuerch, Jr. and E. H. Huntress, J. Am. Chem. Soc., 71, 2238 (1949).
36. S. Archer and M. Jackman, Chem. and Ind., 784 (1954).
37. D. E. Pearson, J. Am. Chem. Soc., 72, 4169 (1950).
38. E. Rothstein and M. A. Saboor, J. Chem. Soc., 425 (1943).
39. E. Rothstein and R. W. Saville, J. Chem. Soc., 1946 (1949).
40. E. Rothstein and R. W. Saville, J. Chem. Soc., 1950 (1949).
41. E. Rothstein and R. W. Saville, J. Chem. Soc., 1954 (1949).
42. E. Rothstein and R. W. Saville, J. Chem. Soc., 1961 (1949).
43. J. V. Braun and K. Wirz, Ber., 60, 102 (1927).
44. J. V. Braun, G. Blessing, and R. S. Cahn, Ber., 57, 908 (1924).
45. E. Rothstein, Chem. and Ind., 403 (1954).
46. M. E. Grundy, W. Hsu, and E. Rothstein, J. Chem. Soc., 4136 (1952).
47. M. E. Grundy, E. Rothstein, and W. Hsu, J. Chem. Soc., 4561 (1956).
48. N. C. Deno, J. J. Jaruzelski, and A. Schrieshiem, J. Am. Chem. Soc. 77, 3044 (1955).

RADICAL HALOGENATION

Reported by M. M. Martin March 18, 1957

A. Introduction.

The photohalogenation of paraffinic compounds has been a favorite subject of study ever since its discovery early in the history of organic chemistry. However, work on the mechanism of this important reaction was not undertaken until the late 1930's, and has extended to the present day. It is the purpose of this seminar to present the more recent studies on the mechanism of radical halogenation. The synthetic applicability and commercial importance of the reaction will not be emphasized, but several lead references appear in the bibliography (1-5). The material to be covered includes halogenation by molecular halogen and sulfuryl chloride, but will not include a discussion of the use of N-bromosuccinimide. The first part of the seminar will deal with the theoretical aspects of the mechanism, while the second part will deal with the orienting influences observed and will discuss them in terms of the mechanism proposed.

B. Mechanism.

Although aliphatic halogenation had been known since the turn of the century, there were no significant advances in the elucidation of the mechanism until Kharasch's work in the late 1930's (6-11). In his work, Kharasch demonstrated that halogenation of aliphatic hydrocarbons proceeded by a free radical chain mechanism. It was recognized that two possible reaction sequences existed, one involving the abstraction of a hydrogen atom by the atomic halogen to form an alkyl radical which then attacks a halogen molecule (scheme A), the other involving a direct substitution and a Walden inversion. (scheme B).

Scheme A

$$X_2 \longrightarrow 2X\cdot \quad (1A)$$

$$R\text{-}H + X\cdot \underset{\text{det.}}{\overset{\text{rate}}{\rightleftharpoons}} R\cdot + H\text{-}X \quad (2A)$$

$$R\cdot + X_2 \longrightarrow R\text{-}X + X\cdot \quad (3A)$$

Scheme B

$$X_2 \rightleftharpoons 2X\cdot \quad (1B)$$

$$R\text{-}H + X\cdot \longrightarrow R\text{-}X + H\cdot \quad (2B)$$

$$H\cdot + X_2 \longrightarrow H\text{-}X + X\cdot \quad (3B)$$

These two possible sequences follow the same kinetic law. It may be stated that at present, evidence indicates that scheme A is the one more frequently followed, but there are a few instances in which scheme B remains a possibility.

Calculations (12) based on activation energies favor scheme A. It is calculated that for the chlorination of methane, the energy of activation of step 2A would be approximately 15 kcal/mole, while for step 2B it would be closer to 30 kcal/mole. There is also experimental evidence favoring scheme A. The chlorination of primary active amyl chloride was found to give an optically inactive product when chlorinated with molecular chlorine or sulfuryl chloride (13). This was taken as evidence in favor of an optically inactive free radical

$$ClCH_2\text{-}\underset{\underset{H}{|}}{\overset{\overset{CH_3}{|}}{C}}\text{-}CH_2CH_3 \;(+) \xrightarrow{[Cl\cdot]} ClCH_2\text{-}\underset{\underset{Cl}{|}}{\overset{\overset{CH_3}{|}}{C}}\text{-}CH_2CH_3 \;d,l$$

intermediate, since a Walden inversion would result in an active product. Unfortunately however, the authors did not establish conclusively that racemization of an active product did not occur under experimental conditions. In earlier work, Yuster and Reyerson (14) failed to find evidence for direct replacement during the chlorination of propane. The presence of alkyl free radicals was demonstrated by the isolation of products formed from coupling. Furthermore, they failed to detect any hydrogen, which would be produced by a direct replacement.

The statement that replacement of a hydrogen by a halogen proceeds by abstraction of the hydrogen to give the alkyl free radical seems fairly well substantiated. However, Gorin, Kauzman, Walter, and Eyring (12) point out that in a reaction involving the free radical replacement of one halogen atom by another, theoretical calculations are unable to rule out the possibility that scheme B is operative. Since the C-X bond is considerably weaker than the C-H bond, it would be predicted that the activation energy of step 2B would be considerably less than that calculated for methane.

Several examples of such halogen exchange have been investigated. Davidson and Sullivan (15, 16) clearly demonstrated that scheme A is operative in the vapor phase exchange of radioactive bromine between trichlorobromomethane and bromine. They found that if the

$$CCl_3Br + Br^{*} \overset{420\text{-}445^{\circ}}{\rightleftharpoons} CCl_3Br^{*} + Br$$

reaction were carried out in the presence of HBr, chloroform was produced at a rate comparable to the rate of exchange. This is compelling evidence for the existence of trichloromethyl radicals. The reaction sequence appears below:

$$CCl_3Br + Br^{*} \longrightarrow CCl_3\cdot + Br\text{-}Br^{*}$$
$$CCl_3\cdot + Br_2^{*} \longrightarrow CCl_3Br^{*} + Br^{*}$$
$$CCl_3\cdot + HBr \longrightarrow CCl_3H + Br$$

If an inversion mechanism were to occur at all, it would be expected to occur in the radical exchange of iodine, since the

$$R_1R_2R_3CI + I^{*} \rightleftharpoons R_1R_2R_3CI^{*} + I$$

weakness of the C-I bond would lower the activation energy of step 2B to a value below 20 kcal/mole (12). Indeed, the first data which supported the inversion mechanism concerned the vapor phase racemization of sec-butyl iodide by iodine formed by the decomposition of the butyl iodide at 240-280° (17). These data are suggestive, but by no means conclusive, because of heterogeneous effects and an overly complex system. Recently, however, Herrmann and Noyes (18) have

redirected attention to this reaction and studied the racemization of sec-butyl iodide by labelled iodine atoms in hexachlorobutadiene solution. They compared the rate of racemization of active sec-butyl iodide with the rate of exchange of iodine. If the reaction proceeds by the abstraction mechanism, scheme A, then for every atom of labelled iodine incorporated into butyl iodide, one molecule of active material would be racemized, i.e. the ratio of the rate of racemization to the rate of exchange would be 1.00. On the other hand, if a Walden inversion occurs, two molecules of butyl iodide would be racemized for every atom of labelled iodine incorporated, i.e. the ratio of the rate of racemization to the rate of exchange would be 2.00. In fifteen runs, over varied concentrations of iodine and butyl iodide, this

ratio had an average value of 1.54. A statistical treatment established that within ninety-nine per cent confidence limits, the true value was between 1.32 and 1.80. At any rate, its value was greater than unity, indication that some Walden inversion had occurred.

There are three other radical mechanisms which would give similar results, two of which are readily ruled out. The possibility of spontaneous racemization, i.e. decomposition of butyl iodide into a butyl radical and an iodine atom, followed by recombination of the same species, which would increase the rate of racemization with respect to exchange, is ruled out by the independence of the ratio on iodine concentration. Such spontaneous racemization would decrease with increasing iodine concentration. The possibility that racemization occurred by extraction of the iodine atom from butyl iodide by a butyl radical, which also would increase the rate of racemization with respect to exchange, is ruled out by the independence of the ratio on butyl iodide concentration. If such a mechanism occurred, the ratio would increase with increasing butyl iodide concentration. Another possibility which their data do not rule out is the abstraction of iodine from butyl iodide by an iodine atom, followed by immediate recombination of the radical with the iodine molecule formed at its genesis, scheme C. If it is assumed that the butyl radical combines

Scheme C

$$d\text{BuI} + I^* \longrightarrow [d,l\ \text{Bu}\cdot\ I\text{-}I^*]$$

$$[d,l\text{Bu}\cdot\ I\text{-}I^*] \longrightarrow 1/2\ d,l\text{BuI} + 1/2\ d,l\text{BuI}^* + 1/2\ I + 1/2\ I^*$$

with equal probability with either atom of the iodine molecule, the ratio of the rates of racemization to exchange would be 2.00. This possibility cannot be ruled out in a solution process.

This paper presents the strongest evidence to date in favor of a Walden inversion mechanism. However, it is not conclusive. Scheme C is eminently plausible in a solution reaction. Furthermore, the authors did not exclude the possibility that the process was going through an ionic mechanism. Obviously if iodide ions were involved the observed results would be obtained. If the reaction could be studied in the vapor phase without the heterogeneous effects which plagued Ogg and Polanyi (17), and the ratio of racemization to exchange were still greater than unity, then the argument would be much more convincing.

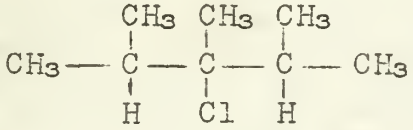
C. The nature of the transition state.

Before undertaking a discussion of the orienting influences observed in the halogenation of saturated compounds, it is advantageous to compare the processes of chlorination, bromination, and iodination. Schumacher (19) observed that chlorination is very exothermic, bromination is mildly endothermic, and iodination very endothermic. According to Hammond's principle (20), which states that for a fast exothermic process the transition state more closely resembles the reactants, and for an endothermic process the transition state resembles products, it would be predicted that the energy of activation would be greatest for iodination and least for chlorination. Likewise, the reverse of the abstraction step, i.e. recombination of the alkyl radical with the hydrogen halide, should occur most readily with hydrogen iodide and least readily with hydrogen chloride. Indeed, all of these predictions are verified. It is found that hydrogen bromide and hydrogen iodide inhibit halogenation while hydrogen chloride has no effect. In fact, iodination has no synthetic utility.

It is interesting to speculate on the nature of the transition state leading to an alkyl free radical. From the preceding discussion it is clear that there will be significant differences between the transition states for each of the halogenation processes. All evidence leads to the conclusion that in chlorination reactions, very little bond breaking has taken place. Brown and Russell (21) found isotope effects of about 2.0 in the chlorination of isobutane deuterated at the tertiary carbon at -15°C, and in the chlorination of toluene deuterated in the methyl side chain at 80°C. These observations indicate very little bond breaking at the transition state (22).

Activation energy calculations also lead to the conclusion that bond breaking has not proceeded to the extent of more than ten or twenty per cent. The difference in activation energy of a primary and a tertiary C-H bond has been calculated to lie between 0.6 kcal/mole and 1.7 kcal/mole (3,23-25), although the difference in bond dissociation energy is 7 kcal/mole (26).

Further evidence in support of this hypothesis is presented by Russell and Brown (24), who found that the reactivity of a tertiary hydrogen is not affected by bulky groups. Thus, while diisopropylmethylcarbinyl chloride (I) solvolyzes considerably faster than t-butyldimethylcarbinyl chloride (II), there is no difference in the



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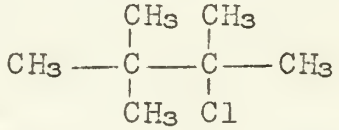

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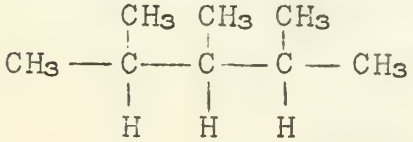

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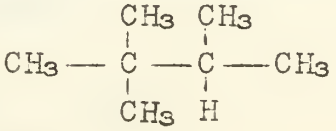


IV

rates of halogenation of the corresponding hydrocarbons, 2,3,4-trimethylpentane (III) and triptane (IV). Furthermore, it is found that the attack of the two different types of tertiary hydrogens of 2,3,4-trimethylpentane is statistical (27), whereas the corresponding chlorides solvolyze at appreciably different rates. Presumably, the effect of bulky groups in the solvolysis of tertiary chlorides is to be attributed to the relief of steric strain in the transition state, which closely resembles a free carbonium ion. Thus it would appear that in free radical chlorination there is no release of steric strain in the transition state, which implies that either free radicals are not planar or that in the transition state very little bond breaking has occurred. The latter explanation seems the more reasonable.

When the bromination process is considered, however, it becomes clear that bond breaking has proceeded to a greater extent than in chlorination, as would be predicted on the basis of Hammond's principle. Russell and Brown (23) studied the competitive halogenation of toluene and cyclohexane, and found that in photobromination, toluene reacts sixty times as fast as cyclohexane at 80°, while in photochlorination, cyclohexane reacts 11.2 times as fast as toluene, and in sulfuryl chloride chlorination, cyclohexane reacts 13.1 times as fast as toluene. This means that during photobromination, a toluene hydrogen is 240 times as reactive as a cyclohexane hydrogen, but in photochlorination the order of reactivity is reversed, and a cyclohexane hydrogen is 2.8 times as reactive as a toluene hydrogen.

These apparently anomolous results are readily explicable on the basis of differences in the transition state. If it is assumed that bond breaking has occurred to a significant extent, then the stability of the incipient free radical will be an important factor in determining the point of attack. On the other hand, if very little bond breaking has occurred then radical stability will be of negligible importance, and electron availability will be the determining factor. Thus during photobromination, stabilization of the incipient benzyl free radical through resonance with the aromatic ring lowers the activation energy and causes toluene to be more reactive than cyclohexane. However, in photochlorination, the inductive effect of the phenyl group reduces the electron density in the C-H bonds of the methyl group in toluene, resulting in a decreased activity relative to cyclohexane. Manifestations of this important difference between bromination and chlorination are observed in the halogenation of many polar substitute aliphatic compounds.

It is also noteworthy that sulfuryl chloride is more selective in its attack than molecular chlorine. In the chlorination of triptane (IV) at 80°, the tertiary hydrogen is 3.2 times as reactive as a primary hydrogen when free chlorine is the chlorinating agent, but 7.3 times as reactive when sulfuryl chloride is used (24). These results indicate that the hydrogen abstracting radical differs for the two reagents, and that sulfuryl chloride is not just a source of atomic chlorine as early investigators had assumed (7, 29, 30). Russell and Brown (24) propose the following mechanism for propagation.

(1) $R\cdot + SO_2Cl_2 \longrightarrow R\text{-}Cl + SO_2Cl\cdot$

(2) $SO_2Cl\cdot \rightleftharpoons SO_2 + Cl\cdot$

(3) $R\text{-}H + SO_2Cl\cdot \longrightarrow R\cdot + SO_2 + HCl$

(4) $R\text{-}H + Cl\cdot \longrightarrow R\cdot + H\text{-}Cl$

The relative occurrence of steps (3) and (4) depends upon the reactivity of the substrate and the sulfur dioxide concentration. Since $SO_2Cl\cdot$ is less reactive than atomic chlorine, a reactive substrate should favor step (3), while an unreactive substrate should favor step (4).

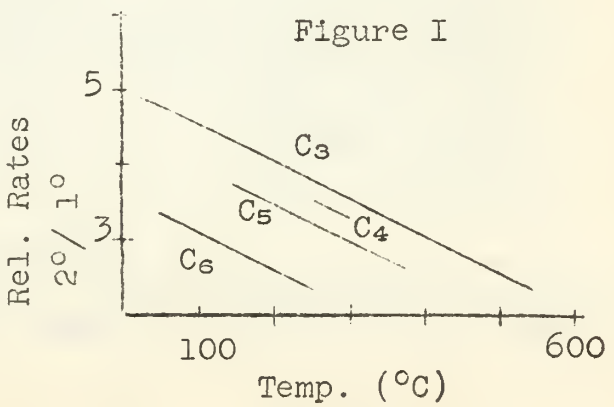
D. Orienting influences.

1. Hydrocarbons. It was recognized very early in the study of halogenation that a tertiary hydrogen is replaced more readily than a secondary hydrogen, which in turn is more reactive than a primary hydrogen. Extensive work has been carried out to determine the relative reactivities of the different kinds of hydrogen. For example, it was found that for liquid phase chlorination at 25°, the relative rates of reaction are primary/secondary/tertiary equals 1.0/3.3/4.4 (31). This ratio approaches 1.0/1.0/1.0 as the temperature is raised. A lower temperature is required to obtain a statistical ratio in the liquid phase than in the vapor phase. This results from the fact that for vapor phase substitution to be random, every collision must be effective, while in solution, a solvent cage holds the atomic chlorine at the reaction site long enough for several collisions to occur. Liquid phase bromination of hydrocarbons which contain only primary hydrogens in addition to a tertiary hydrogen gives good yields of tertiary bromides, but if there are additional secondary or tertiary hydrogens at adjacent positions, dibromides are formed (32). The formation of dihalides can be minimized by using a large hydrocarbon to halogen ratio.

The observed order of reactivity of hydrogen atoms in bromination is usually explained on the basis of radical stability. The more substituted the carbon on which the radical resides, the greater the stabilization by radical hyperconjugation (33, 34) and the greater the release of steric strain in going to the planar intermediate. However, as was pointed out previously, the relative ease of replacement of the various kinds of hydrogens by chlorine does not depend greatly upon the stability of the radical formed, but rather on the availability of electrons in the given C-H bond. Thus the more readily a carbon is able to compensate for the loss of electronic charge to the attacking chlorine atom, the more readily it will surrender a C-H bond electron. Clearly a C-C bond will be a better charge reservoir than a C-H bond, because of the greater longitudinal polarizability of the former. A primary carbon has only one C-C bond through which to partially compensate for its charge deficit, while a secondary carbon has two, and a tertiary carbon, three. This so-called "reservoir effect" provides a satisfactory explanation of hydrogen reactivity in chlorination (35).

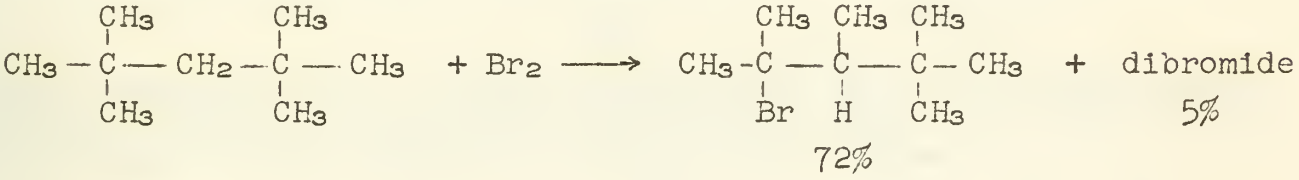
However, as the length of the hydrocarbon chain increases, the ratio of reactivity of secondary to primary hydrogen decreases, as is illustrated in Figure I (36). Several Russian papers report greater reactivity for the primary hydrogens than secondary for normal hexane, heptane, and dodecane during vapor phase chlorination, but their definition of reactivity is not clear (37, 38).

Figure I



It has been suggested that this is a result of coiling of the hydrocarbon chain which causes some of the methylene groups in the middle of the chain to be shielded from attack (36, 39-43).

There is only one substantiated report of a rearrangement of a carbon skeleton during radical halogenation (44, 45).



2. Alkyl halides. The halogen substituent has a marked effect on the electron availability in the various C-H bonds of an alkyl halide. Smith, Ree, Magee, and Eyring (46) have developed a semi-empirical method of calculating the charge distribution in polar substituted aliphatic compounds, and have correlated charge distribution with electron availability. They assume that during the chlorination of an alkyl halide, the incomplete H-Cl bond formed in the transition state with the attacking chlorine atom has removed about as much charge from the carbon atom concerned as a chlorine atom would remove if attached directly to the carbon. This is consistent with the assumption of limited bond breaking in the transition state (35). Thus, the charge actually removed by a chlorine substituent in a position may be used as a measure of the electron availability at that position. The more charge a substituent is found to remove, the greater must be the availability of the electrons in the bonds surrounding the given carbon. Thus, in the case of the chlorination of 1-chlorobutane, it is necessary only to calculate the charge residing on the second chlorine of each of the compounds $CH_3(CH_2)_2CHCl_2$, $CH_3CH_2CHClCH_2Cl$, $CH_3CHClCH_2CH_2Cl$ and $Cl(CH_2)_4Cl$. Chlorination will be favored at that carbon from which the greatest amount of charge can be removed. The results for 1-chlorobutane, 1,1-dichlorobutane, and 1,1,1-trichlorobutane appear in Table I. A good parallel is observed between electron availability and per cent substitution (35, 47).

TABLE I

	Carbon Atom				
Cpd	4	3	2	1	
4 3 2 1 C-C-C-C-Cl	-1.056	-1.129	-1.024	-0.799	Charge removed
	24	47	22	7	Per cent Subst.
C-C-C-CCl_2	-1.051	-1.071	-0.966	-0.618	Charge removed
	37	48	13	2	Per cent subst.
C-C-C-CCl_3	-1.043	-1.058	-0.925	-	Charge removed
	48	49	3	-	Per cent subst.

The reservoir effect is the same for positions 2 and 3, but there is more substitution at position 3 because of the inductive effect of the chlorine on carbon 1. In the trichloro compound, position 3 has been

deactivated to the extent that it and carbon 4, a primary carbon, are equally susceptible to attack.

As would be expected, fluorine substituents deactivate nearby positions to a greater extent than chlorine toward chlorination (48).

$$CH_3CH_2CH_2CF_3 \xrightarrow{Cl_2} \underset{45\%}{CH_3\overset{Cl}{\overset{|}{C}}HCH_2CF_3} + \underset{55\%}{\overset{Cl}{\overset{|}{C}}H_2CH_2CH_2CF_3}$$

Halogen substituents do not deactivate nearby positions toward bromination to as marked a degree as toward chlorination (49). This can be attributed to the difference in transition states.

$$CH_3CH_2CH_2CH_2Cl \xrightarrow{Br_2} \underset{23\%}{CH_3CH_2CH_2\overset{Br}{\overset{|}{C}}HCl} + \underset{23\%}{CH_3CH_2\overset{Br}{\overset{|}{C}}HCH_2Cl} + \underset{46\%}{CH_3\overset{Br}{\overset{|}{C}}HCH_2CH_2Cl}$$

3. Acid derivatives. The orienting effects of the carbonyl group have also been studied extensively (47, 50, 51). Although there is disagreement as to the exact magnitude of this effect, it is evident that the carbonyl group deactivates the alpha position of an acid derivative toward chlorination. This is a result of the reduced

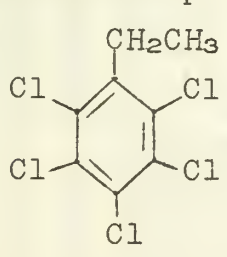
$$CH_3CH_2CH_2CO_2H \xrightarrow{Cl_2} \underset{30\text{-}45\%}{C} - \underset{45\text{-}65\%}{C} - \underset{5\text{-}10\%}{C} - CO_2H$$

electron availability around the carbons in the vicinity of a carbonyl group. Bromination has received less attention.

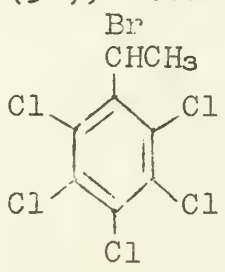
Chlorination of the alcohol portion of acetate esters has also been investigated (47, 50). The results indicate that the acetate group is a strong deactivator of nearby positions.

$$CH_3\text{-}CO_2CH_2CH_2CH_3 \xrightarrow{Cl_2} \underset{\substack{0\text{-}25\% \quad 46\text{-}69\% \quad 29\text{-}31\%}}{CH_3CO_2\text{-}C - C - C}$$

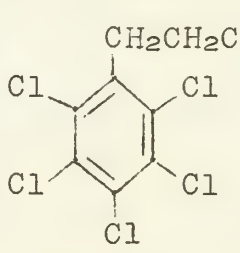
4. Alkyl benzenes. The results obtained from the side chain halogenation of alkyl benzenes are not as readily explained as those from other polar substituted aliphatic compounds. Photobromination of 2,3,4,5,6-pentachloroethylbenzene (V) gives exclusively the alpha substituted product (VI) (52), while photochlorination or sulfuryl



V.

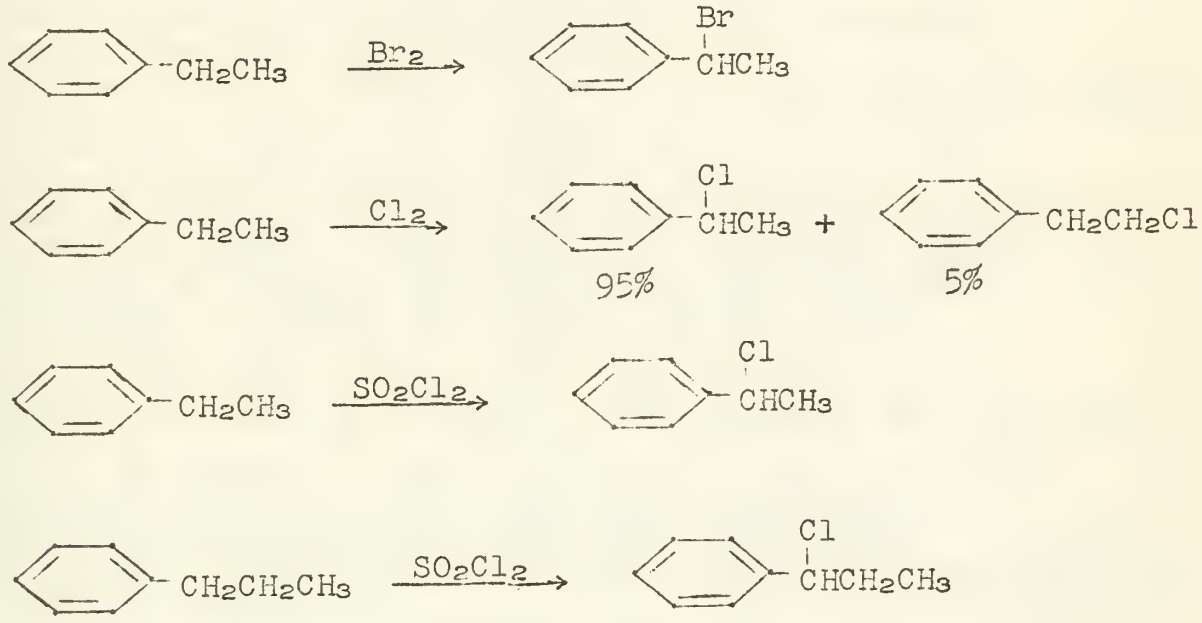


VI



VII

chloride chlorination gives mainly the beta substituted product (53). It is also found that the ratio of beta chlorination to alpha chlorination increases as the temperature increases (54). At 70-75°, the ratio of beta:alpha is 1.6:1.0 and at 180° almost 4.6:1.0. These results are not inconsistent with the transition state postulate, but discrepancies arise when unsubstituted alkyl benzenes, such as ethylbenzene or n-propylbenzene, are considered, in which it is found that the alpha position is favored in chlorination (47, 55, 56). On the



basis of electron availability, it would be predicted that attack at a position removed from the phenyl ring would be favored in chlorination. Russell and Brown (47) have alluded to a possible explanation. They suggest that the attacking species is not the same during chlor nation of a completely aliphatic compound and one possessing an arom tic function. Since a chlorine atom is an electronegative species, it is conceivable that it would form a π-complex with an aromatic structure, and that this complex would serve as the actual attacking species. Since this would imply the participation of a transition state, differing from that for the chlorination of completely alipha tic compounds, the two processes would not be expected to obey the same rules.

BIBLIOGRAPHY

1. E. McBee, C. Roberts, Ind. and Eng. Chem., 47, 1876 (1955).
2. E. McBee, O. Pierce, Ind. and Eng. Chem., 46, 1835 (1954).
3. H. Hass, E. McBee, F. Weber, Ind. and Eng. Chem., 28, 333 (1936).
4. H. De La Mare, W. Vaughan, J. Chem. Ed., 34, 15 (1957).
5. Brooks, Kurtz, Boord, Schmerling, The Chemistry of Petroleum Hydrocarbons, Vol. 3, pp. 59-71, New York, 1955.
6. M. Kharasch, P. White, F. Mayo, J. Org. Chem., 3, 33 (1938).
7. M. Kharasch, H. Brown, J. Am. Chem. Soc., 61, 2142 (1939).
8. M. Kharasch, W. Hered, F. Mayo, J. Org. Chem., 6, 818 (1941).
9. M. Kharasch, M. Berkman, J. Org. Chem., 6, 810 (1941).
10. M. Kharasch, M. Berkman, J. Org. Chem., 6, 814 (1941).
11. M. Kharasch, L. Hobbs, J. Org. Chem., 6, 705 (1941).

12. E. Gorin, W. Kauzman, J. Walter, H. Eyring, J. Chem. Phys, 7, 633, (1936).
13. H. Brown, M. Kharasch, T. Caro, J. Am. Chem. Soc., 62, 3435 (1940).
14. S. Yuster, H. Reyerson, J. Phys. Chem., 39, 859 (1935).
15. N. Davidson, J. Sullivan, J. Chem. Phys., 17, 176 (1949).
16. N. Davidson, J. Sullivan, J. Chem. Phys., 17, 143 (1949).
17. R. Ogg, M. Polanyi, Trans, Faraday Soc., 31, 482 (1935).
18. R. Herrmann, R. Noyes, J. Am. Chem. Soc., 78, 5764 (1956).
19. H. Schumacher, Angew. Chem., 53, 501 (1940).
20. G. Hammond, J. Am. Chem. Soc., 77, 334 (1956).
21. H. Brown, G. Russell, J. Am. Chem. Soc., 74, 3995 (1952).
22. K. Wiberg, Chem. Rev., 55, 713 (1955).
23. H. Hass, E. McBee, P. Weber, Ind. and Eng. Chem., 27, 1190 (1935).
24. G. Russell, H. Brown, J. Am. Chem. Soc., 77, 4031 (1955).
25. H. Steiner, H. Watson, Disc. Faraday Soc., 2, 88 (1947).
26. A. Trotman-Dickerson, Quart. Rev., 7, 198 (1953).
27. H. Brown, R. Fletcher, J. Am. Chem. Soc., 73, 1317 (1951).
28. G. Russell, H. Brown, J. Am. Chem. Soc., 77, 4578 (1955).
29. M. Kharasch, H. Brown, J. Am. Chem. Soc., 62, 925 (1940).
30. H. Schumacher, J. Stauff, Die Chemie, 55, 341 (1942).
31. A. Ash, H. Brown, Rec. Chem. Progr., 9, 81 (1948).
32. G. Russell, H. Brown, J. Am. Chem. Soc., 77, 4025 (1955).
33. E. Baughan, M. Evans, M. Polanyi, Trans, Faraday Soc., 37, 377 (1941).
34. E. Butler, M. Polanyi, Trans. Faraday Soc., 39, 19 (1943).
35. H. Eyring, R. Smith, J. Phys. Chem., 56, 972 (1952).
36. G. Chambers, R. Ubbelohde, J. Chem. Soc., 1955, 285.
37. R. Galanina, A. Nekrasova, Ukrain. Khim. Zhur., 21, 222 (1955). CA, 50, 9276 f (1956).
38. R. Galanina, A. Nekrasova, Doklady Akad. Nauk S.S.S.R., 108, 251 (1956). CA, 50, 14502C (1956).
39. J. McCoubrey, J. McCrea, A. Ubbelohde, J. Chem. Soc., 1951, 1961.
40. G. Cummings, A. Ubbelohde, J. Chem. Soc., 1953, 3751.
41. A. Ubbelohde, J. McCoubrey, Disc. Faraday Soc., 10, 94 (1951).
42. G. Cummings, J. McCoubrey, A Ubbelohde, J. Chem. Soc., 1952, 2725.
43. A. Ubbelohde, J. Woodward, Trans. Faraday Soc., 48, 113 (1952).
44. M. Kharasch, Y. Liu, W. Nudenberg, J. Org. Chem. 19, 1150 (1954).
45. M. Kharasch, Y. Liu, W. Nudenberg, J. Org. Chem., 20, 680 (1955).
46. R. Smith, T. Ree, J. Magee, H. Eyring, J. Am. Chem. Soc., 73, 2263 (1951).
47. H. Brown, A. Ash, J. Am. Chem. Soc., 77, 4019 (1955).
48. A. Henne, J. Hinkamp, J. Am. Chem. Soc., 67, 119 (1945).
49. M. Kharasch, W. Zimmt, W. Nudenberg, J. Org. Chem., 20, 1430 (1955).
50. A. Bruylants, M. Tits, R. Dauby, Bull. Soc. Chim. Belges, 58, 310 (1948).
51. A. Bruylants, M. Tits, R. Gauther, Bull Soc. Chim. Belges, 61, 366 (1952).
52. S. Ross, M. Markarian, M. Nazzewski, J. Am. Chem. Soc., 69, 2469 (1947).
53. S. Ross, M. Markarian, M. Nazzewski, J. Am. Chem. Soc., 69, 1914 (1947).
54. S. Ross, M. Markarian, M. Nazzewski, J. Am. Chem. Soc., 71, 396 (1949).
55. R. Dieck, J. Jungers, Bull Soc. Chim. Belges, 60, 377 (1951).
56. D. Benouy, J. Jungers, Bull. Soc. Chim. Belges, 65, 769 (1956).

THE PYROLYSIS OF CARBOXYLIC ESTERS

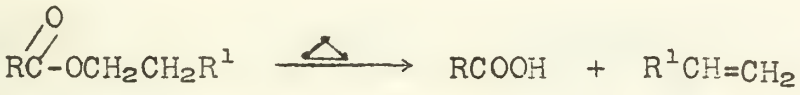
Reported by William Garrison March 25, 1957

INTRODUCTION

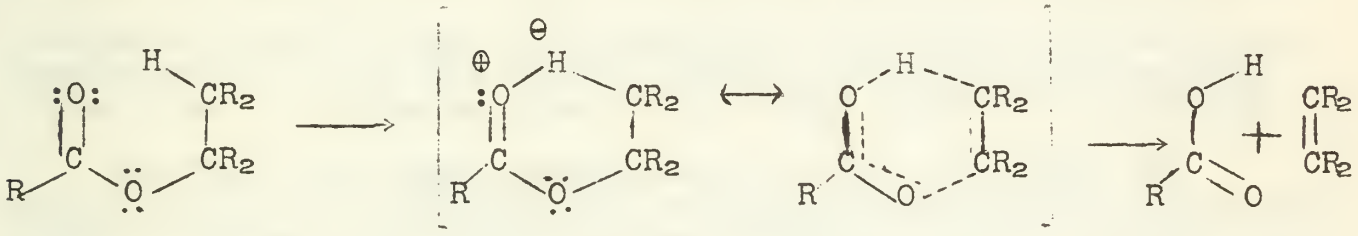
The subject of ester pyrolysis is quite old, and earlier work in this field has been treated in an ACS monograph by Hurd (1), which covers the literature reported through 1928. This report will be concerned chiefly with work done since that time. Work done on closely related reactions, such as thermal decomposition of xanthates, halides, and amine oxides will not be covered.

MECHANISM

The nature of the decomposition depends upon the presence or absence of at least one hydrogen on the beta carbon of the alkyl group. The greater interest lies in the pyrolysis of those esters having a hydrogen atom so placed. These decompose into the acid and an olefin:

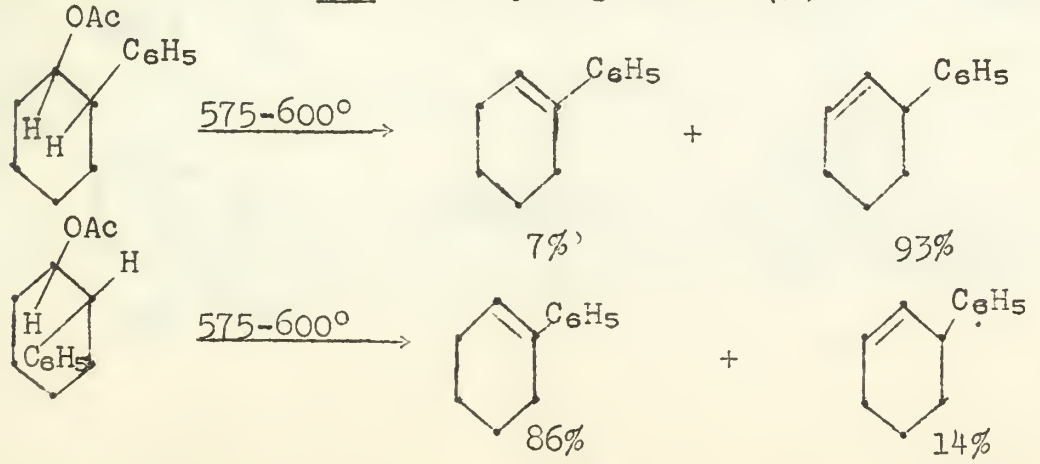


The mechanism now accepted for this process is that proposed by Hurd and Blunk in 1938 (2), who applied the recently developed concept of hydrogen bonding to a cyclic hydrogen bridge mechanism:



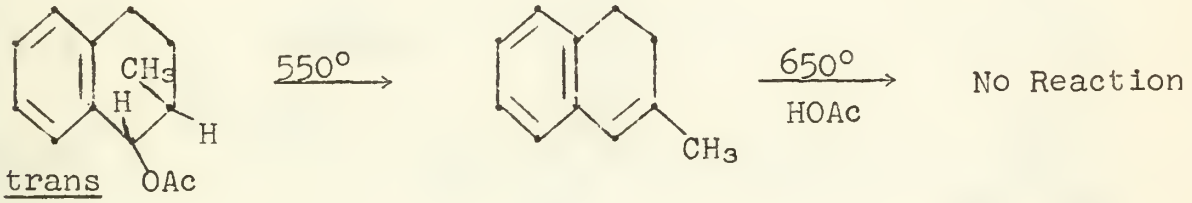
If the reaction does proceed through such a cyclic transition state, then *cis* elimination should predominate. There are many examples of this:

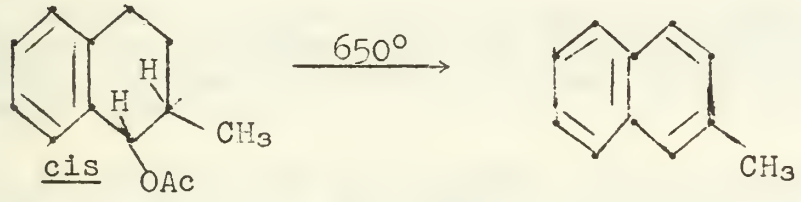
1. The pyrolysis of the *cis* and *trans* isomers of 2-phenylcyclohexyl acetate yielded the following products, with preferential elimination of the *cis* beta hydrogen atom (3):



Similar results are obtained by pyrolysis of the corresponding xanthates.

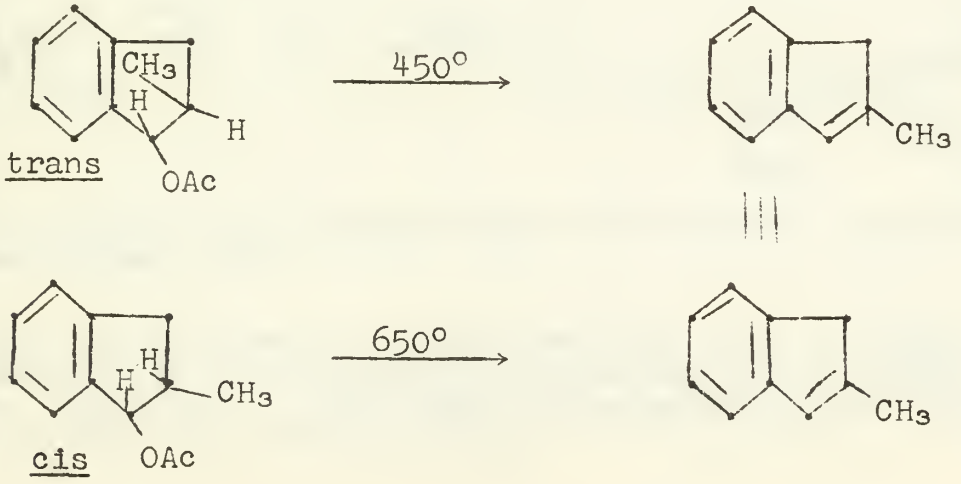
2. Studies on the pyrolytic decomposition of cis and trans 2-methyl-1-tetralyl acetates showed that the cis form was considerably more stable. The trans form could be completely decomposed at 550°, while a temperature of 650° was necessary to effect decomposition of the cis form (4):

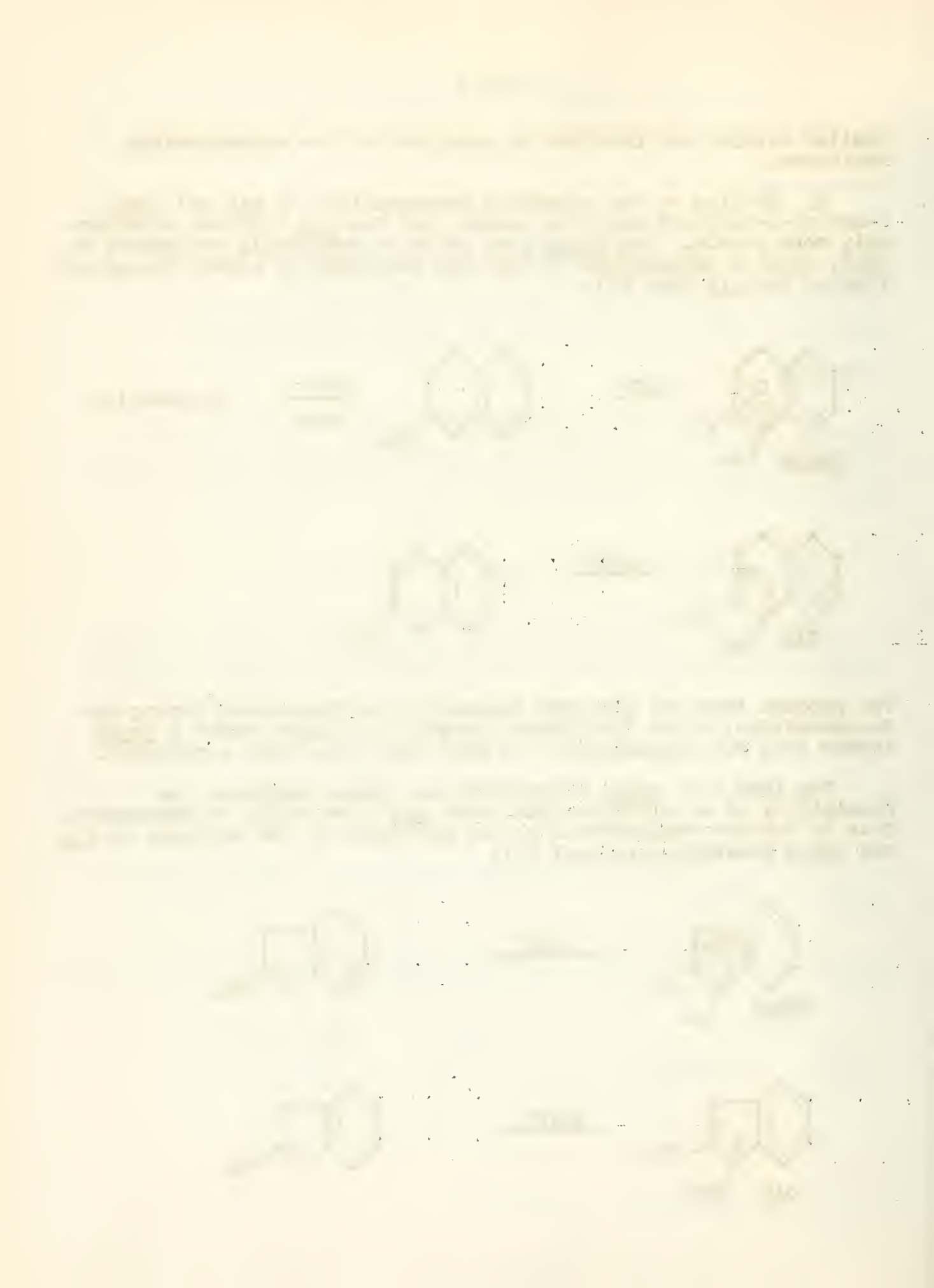




The product from the cis form apparently dehydrogenated during the decomposition, since the dihydro tetralin produced from the trans isomer does not dehydrogenate at 650° under identical conditions.

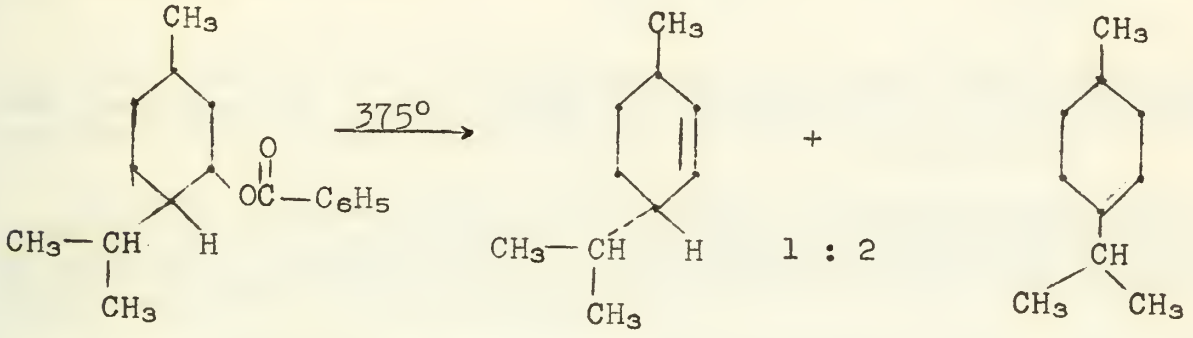
The fact that trans elimination can occur indicates the possibility of an alternate path when cis elimination is impossible. This is further demonstrated by the pyrolysis of the acetates of cis and trans 2-methyl-1-indanol (5):





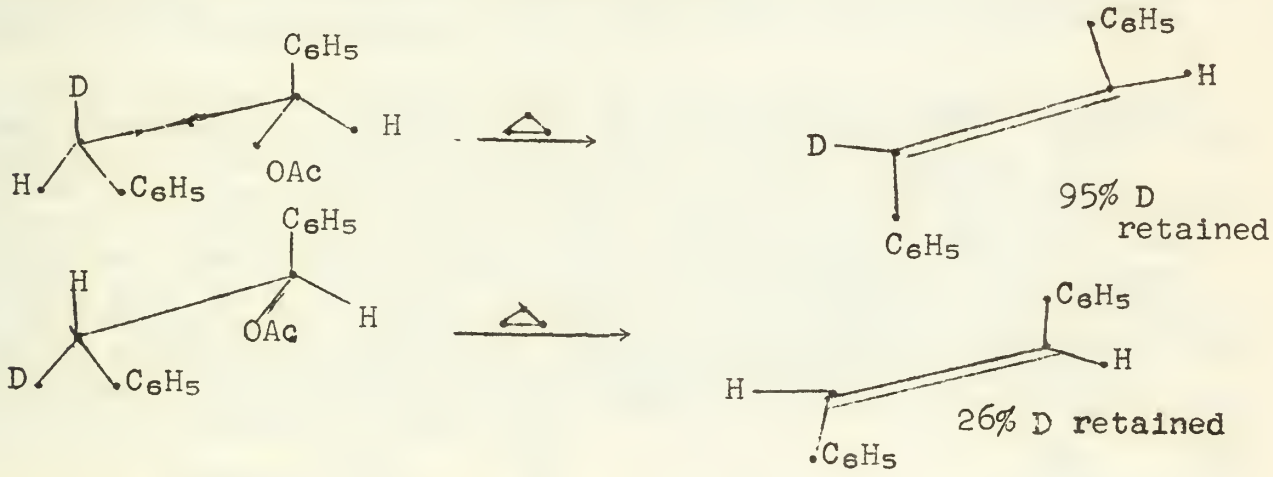
The trans isomer can be pyrolyzed at 450°, while a temperature of 650° is necessary for the pyrolysis of the cis isomer. Both isomers yield 2-methyl indene, and so a trans elimination has occurred in the cis isomer.

3. Barton and coworkers have studied the pyrolysis of (-)-menthyl benzoate (6):



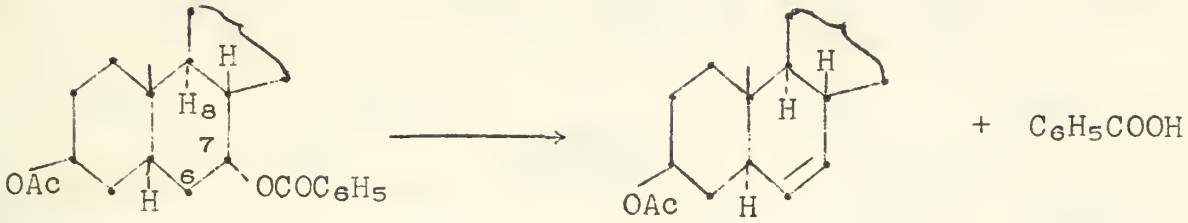
The formation of the latter product indicates occurrance of a cis elimination, provided that the first product cannot isomerize to the second. Similar products have been obtained by the pyrolysis of (-)-menthyl acetate.

4. Curtin and Kellom have shown preferential cis elimination in the pyrolysis of the erythro and threo forms of 2-deutero-1,2-diphenylethyl acetate. The following results were obtained by analysis of the products for deuterium:



Similar results were obtained with the benzoate and 2,4,6 triethyl benzoate esters (8).

The cis elimination concept has been used to assign the configuration at the 7-position in steroids of the allocholane series. Pyrolysis of one epimer of 3-β-acetoxycholest-7-yl benzoate gives cholest-6-en-3-β-yl acetate:



Pyrolysis of the other epimer yieldscholest-7-en-3-β-yl acetate, and therefore the former epimer was assigned the 7-α configuration, and the latter epimer was assigned the 7-β configuration.

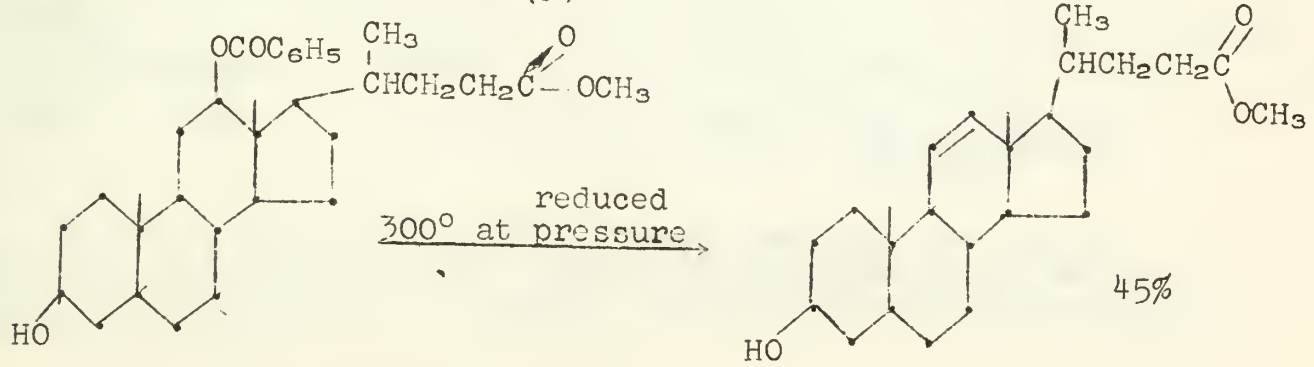
Kinetic studies showed the reaction to be homogeneous and unimolecular. It exhibited no induction period and was unaffected by addition of large amounts of free-radical inhibitors such as propylene oxide or nitric oxide (6).

The absence of free radicals has also been shown by Blades, who studied the pyrolysis of ethyl and isopropyl formates in toluene. If free radicals were present then one might expect the following reactions to occur:

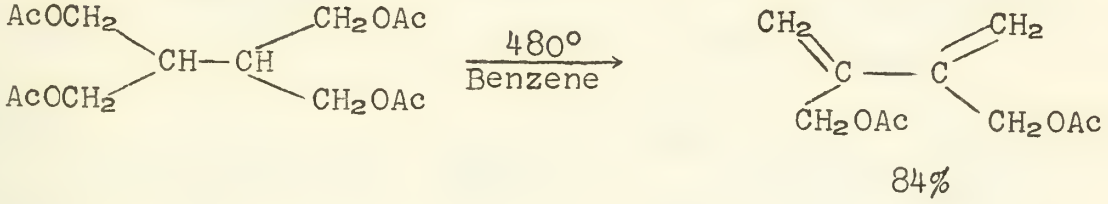
$$R\cdot + C_6H_5CH_3 \longrightarrow RH\cdot + C_6H_5CH_2\cdot \longrightarrow C_6H_5CH_2CH_2C_6H_5$$

Since no bibenzyl was found in the products, even when the pyrolysis was run at 650°, it was concluded that no significant amount of free radicals was formed (7).

In the case of esters which do not possess a beta hydrogen atom, decomposition usually does not occur below 650°. Above this temperature free radical decomposition occurs, yielding many products. These reactions are generally of little importance and will not be discussed further here. However, the fact that these esters are stable under conditions which decompose other esters affords some good synthetic methods. For example, a synthesis of 3-(α)-hydroxyl-Δ^{9,11}-chlolenic acid, an intermediate in the preparation of dehydrocorticosterone, involves pyrolysis of an ester containing a beta hydrogen atom, leaving a more stable methyl ester on the same molecule intact (9):



A synthesis of 2,3-di (acetoxymethyl) butadiene depends on partial pyrolysis; the product formed is stable since it contains no beta hydrogens in the alcohol portion of the ester (17):



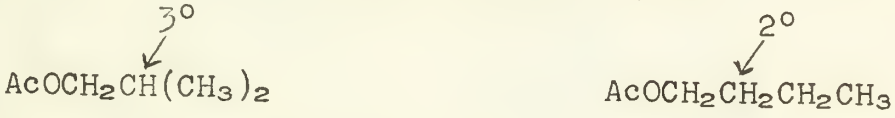
84%

CONDITIONS FOR DECOMPOSITION

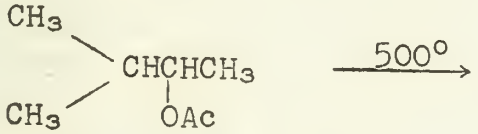
Esters of tertiary alcohols usually decompose at 300°, and those of secondary alcohols at 450° on clean glass. However, primary esters do not decompose even at 500° on clean glass. At 625°, decomposition and disproportionation take place, together with carbon deposition on the glass surface. Then, on lowering the temperature to 500°, the expected alkene formation occurs. The presence of small amounts of free acid in the ester also catalyzes the decomposition, probably by promoting carbon formation. It has also been observed that carbonized glass loses its activity after several months of storage (10).

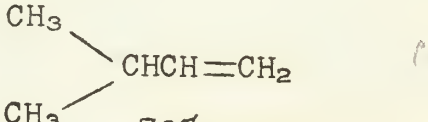
DIRECTION OF ELIMINATION

In the decomposition of esters of secondary alcohols where there are two possible reaction products, the ratio in which the two alkenes are formed will depend on the relative strength with which each hydrogen atom is bound. In ease of splitting off the hydrogen atom: $1^{\circ} > 2^{\circ} > 3^{\circ}$. For example isobutyl acetate requires a higher temperature than n-butyl acetate (10):



Bailey and King have observed similiar effects, stating that the dehydroacetoxylation proceeds in a highly selective fashion, to give a single olefin by the Hofmann rule (11):



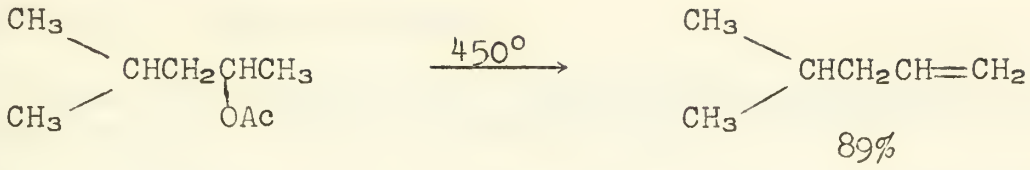


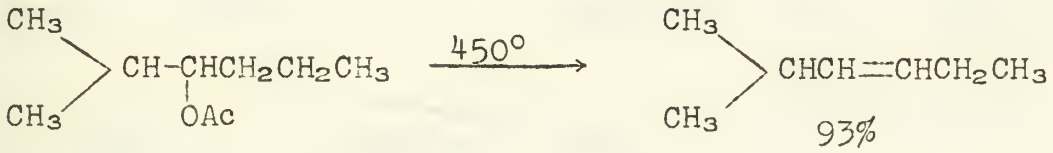
70% conversion
89% yield

(11 JACS 81, 643 (1959))

Isomerically pure 3-methyl-1-butene was also made by the pyrolysis of isoamyl acetate, and its IR spectrum was shown to be identical with that of the product obtained from methylisopropyl-carbinyl acetate.

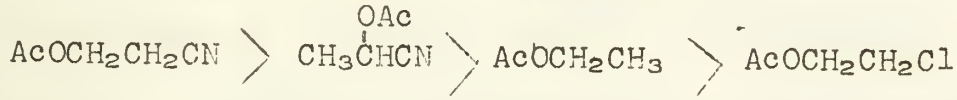
Likewise:



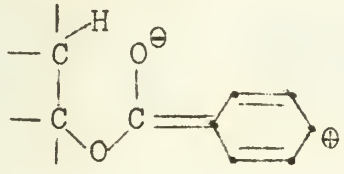


Yields reported are corrected for recovery of starting material, since conditions were adjusted so that only 70% of the material would be pyrolyzed, in order to eliminate charring. Note that Hofmann elimination occurs.

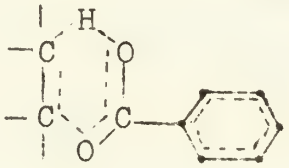
It appears that electron releasing groups in the beta position stabilize the alkoxy group, while electron withdrawing groups weaken it, increasing the ease of pyrolysis. This effect is shown by the cyano group. In ease of pyrolysis (14):



It has been observed that benzoate esters are less stable than the corresponding acetates. This has been attributed to resonance structures of the type (I) which increase the nucleophilic character of the oxygen, as well as stabilization of the cyclic transition state by resonance with the conjugated phenyl ring as in (II) (15):



I



II

Smith and Wetzel have related molecular size and structure to the ease of pyrolysis of esters. The relationships follow a zig-zag pattern, but it can be concluded that ease of pyrolysis increases with increasing molecular size, increasing ionization constant of the acid, and decreasing wave number for the O-C stretching band in the infrared region (12).

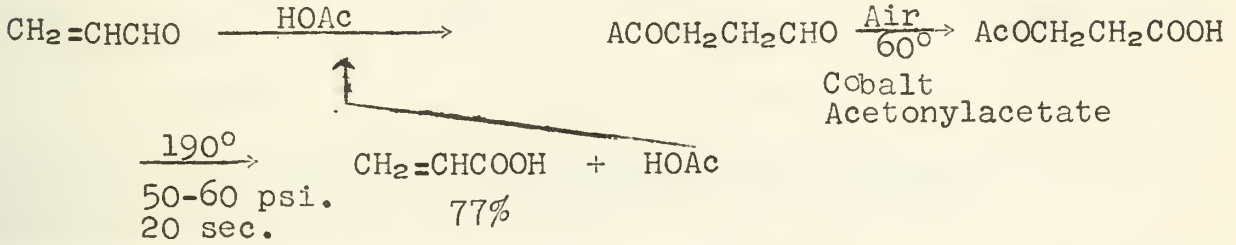
APPLICATIONS TO SYNTHESIS

Because of the specificity and simplicity of the reaction, as well as the high yields obtainable, the pyrolysis of esters containing at least one beta hydrogen atom has become a valuable synthetic tool. Its commercial applicability is demonstrated by the fact that over half of the work reported has been patented.

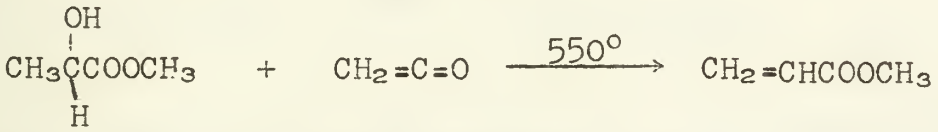
The method finds particular value in the preparation of polymerizable dienes and acrylates.

PREPARATION OF ACRYLIC MONOMERS

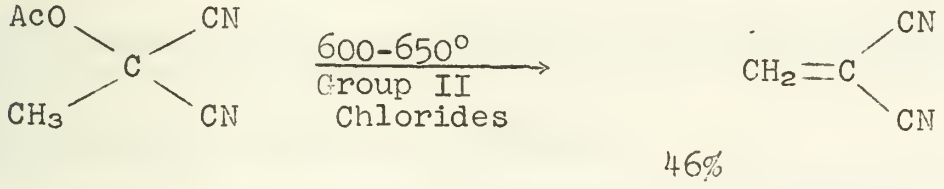
A Shell Oil Company patent describes the production of acrylic acid from acrolein as the starting material (18):



Acrylic acid may be made on a laboratory scale by the pyrolysis of ethyl acrylate, and acrylic esters may be produced from the appropriate acetylated lactic acid esters (19-24). An example of this is the preparation of methyl acrylate by the pyrolysis of the acetylated material formed *in situ*:

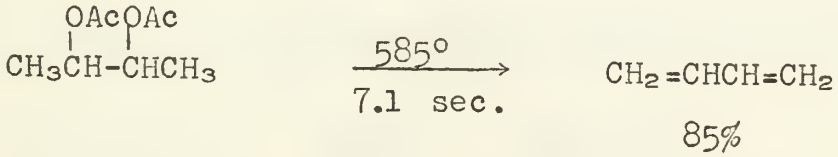


Yields as high as 98% have been reported. In addition, methacrylates may be prepared by the pyrolysis of the corresponding acetoxy isobutyric esters (25, 26), and methacrylonitrile may be produced by pyrolysis of acetone cyanohydrin (25, 27). 1,1 dicyanoethylene has also been made in an analogous fashion (28, 29):



BUTADIENES

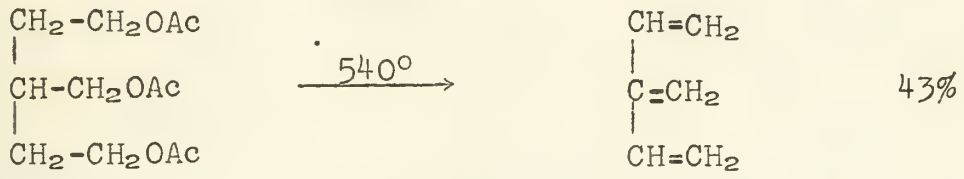
Butadiene may be produced by the pyrolysis of 2,3-butylene glycol diacetate, available from the fermentation of carbohydrate materials (30, 31):



In a similar manner, substituted butadienes have been made from the substituted diacetates (32-36). A 1,4 glycol diacetate will give the

same diene as the corresponding 2,3 diacetate. The preparation of cyanobutadienes has also been reported (37-39).

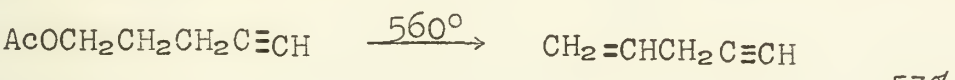
Bailey and Economy have reported the synthesis of 2-vinyl butadiene by pyrolysis of a triacetate synthesized from aconitic acid (40):



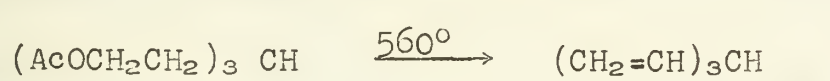
Blomquist and Verdol have prepared the same compound by the pyrolysis of 3-methylene-1,5-pentanediol diacetate (41).

OTHER UNSATURATED ALIPHATIC HYDROCARBONS

Allylacetylene may be prepared by pyrolyzing the acetate of 5-pentynol (42):



Trivinylmethane has been prepared in low yields from the triacetate of tris(β-hydroxyethyl)methane (46):

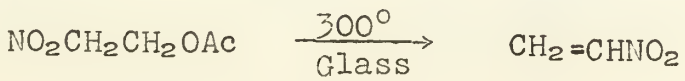


This compound cannot be produced by dehydrohalogenation of the corresponding bromide.

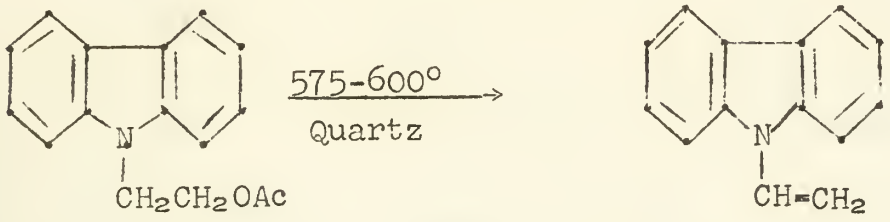
MISCELLANEOUS OLEFINIC COMPOUNDS

Allyl acetate may be produced from propylene glycol diacetate (48):

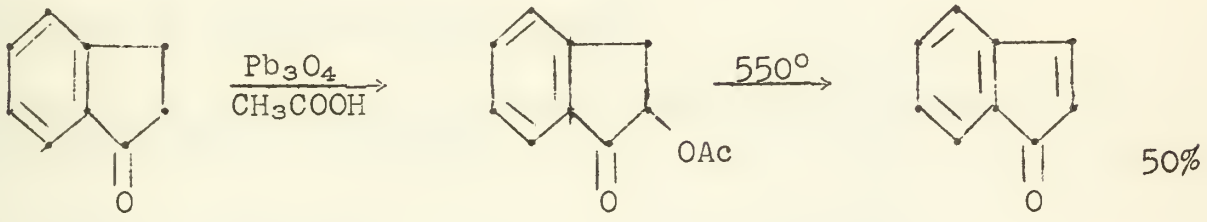
Nitro olefins are formed in good yields by pyrolysis of the appropriate acetate (49):



N-vinyl carbazole monomer is made by acetate pyrolysis. The product is easily polymerized by Lewis acid catalysts (43):

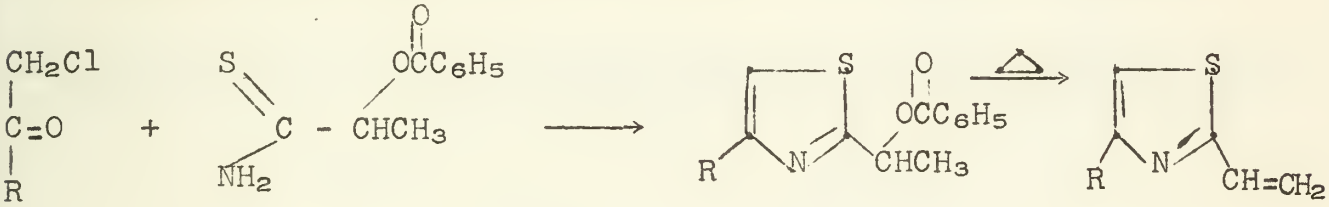


Marvel and Hinman have reported the conversion of indanone to indone (44):



The product is collected over trinitrobenzene to avoid polymerization.

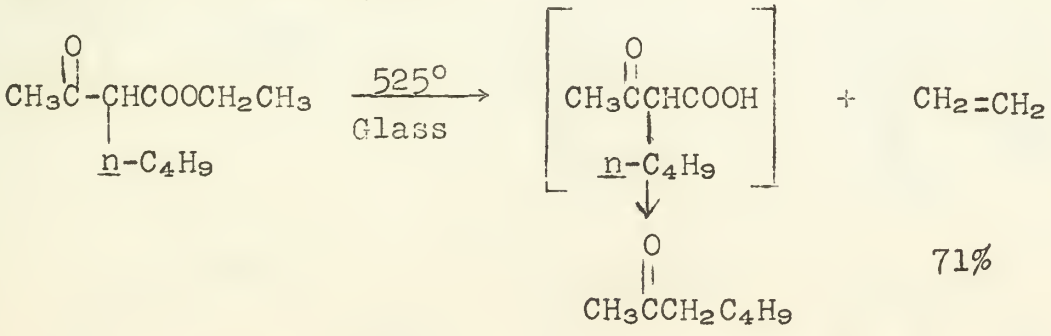
Benzoate pyrolysis affords a method for the preparation of 2-vinyl thiazoles (45):



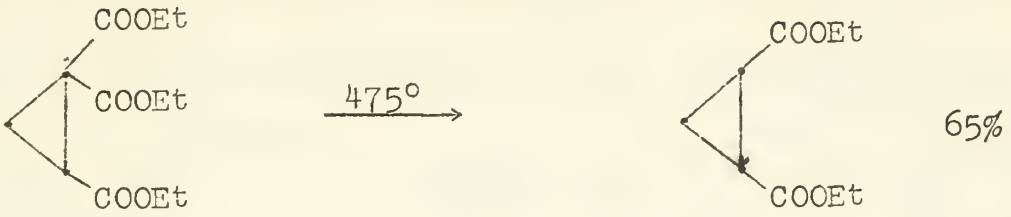
40 - 70%

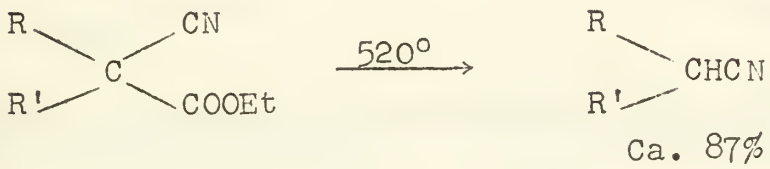
PYROLYSIS OF ACETOACETIC, CYANOACETIC, AND MALONIC ESTERS

Pyrolysis can take the place of hydrolysis in the case of substituted acetoacetic esters, resulting in a considerabl saving of time and material (50):



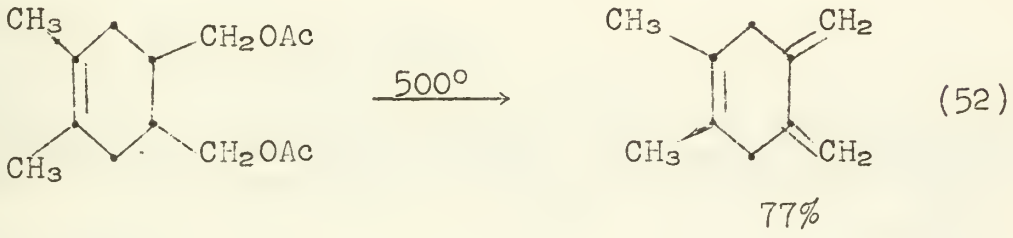
Substituted malonic and cyanoacetic esters may be pyrolyzed to yield an ester or nitrile directly (51):





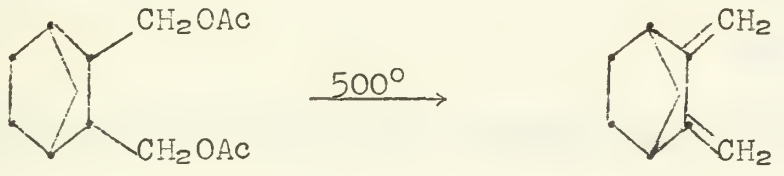
PREPARATION OF STRAINED CYCLIC DIENES

Bailey has reported that highly strained dienes may be prepared by pyrolytic methods:

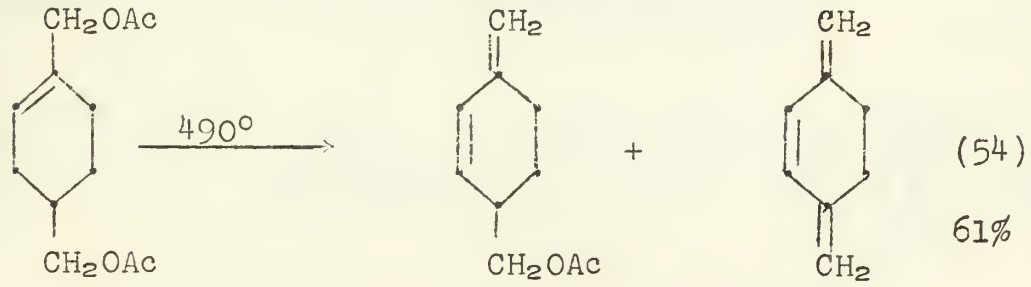


(52)

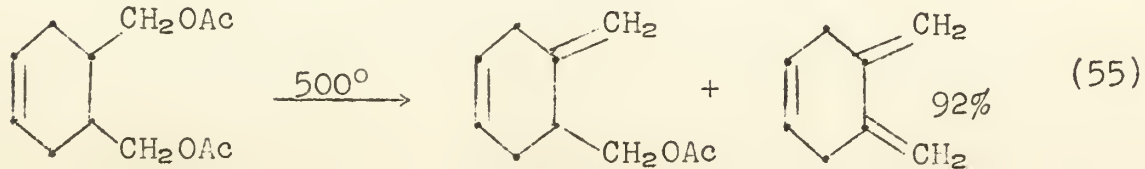
This material is stable under the conditions of the pyrolysis, but can be aromatized to durene by treatment with palladium on carbon.



(53)



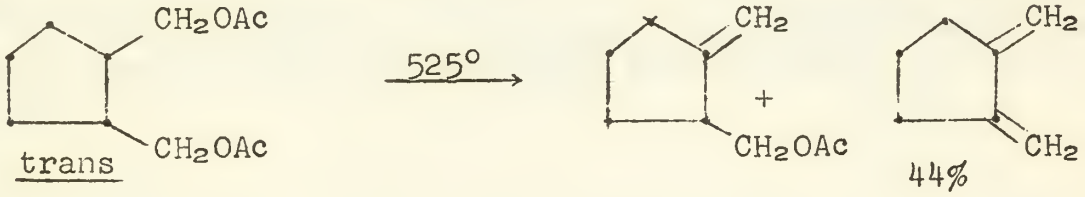
(54)



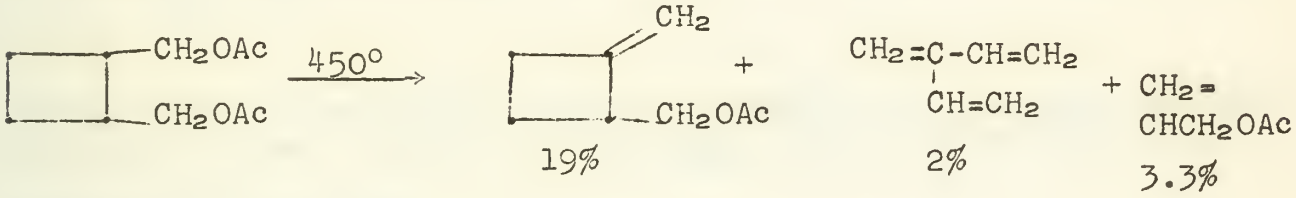
(55)

One drop of concentrated HCl will cause an immediate isomerization of 4,5 dimethylene cyclohexene to o-xylene and a polymer.

1,2 dimethylenecyclopentane has also been prepared (56):

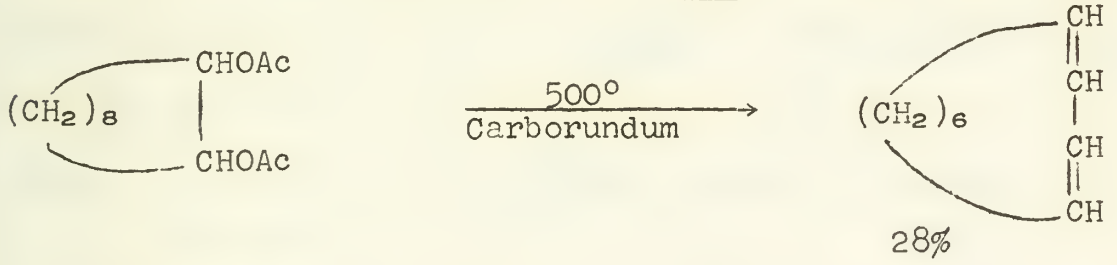


An attempt to prepare 1,2 dimethylene cyclobutane resulted in the cleavage of the ring (57):



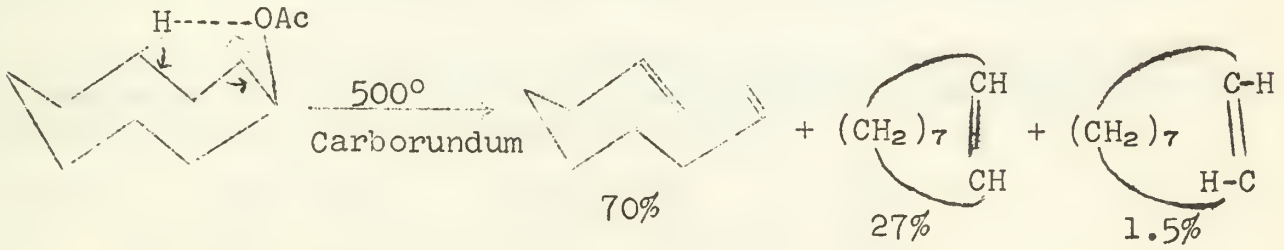
PYROLYSIS OF MEDIUM RING ESTERS

Blomquist and coworkers have studied the pyrolysis of 8-9- and 10-membered cycloalkyl acetates. Cis-cis cyclodecadiene is obtained from the pyrolysis of the cis 1,2 diacetate (13):



Spectroscopic data showed this compound to be a rigid, unconjugated system.

Cyclononyl acetate decomposes at 500° to give a good yield of 1,8-nonadiene along with the cyclononenes (47):

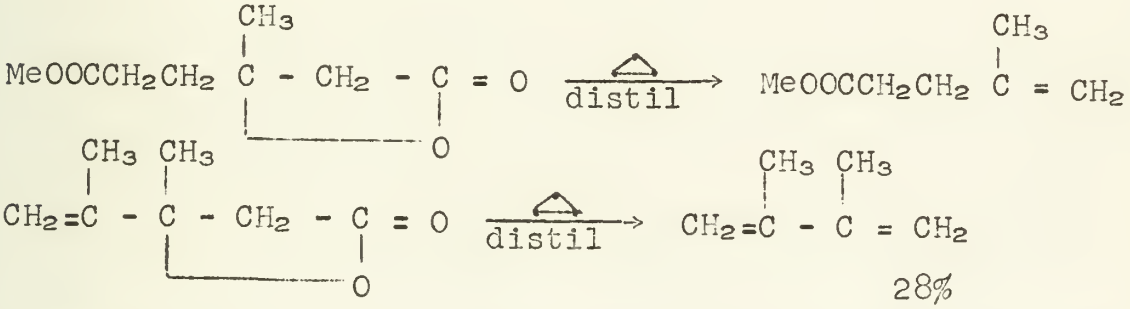


This may be accounted for by assuming a transannular 1,4 elimination of acetic acid. However, it has been found that trans cyclononene is converted at 500° to 1,8-nonadiene (85%) and cis cyclononene (15%). This points to another possible mechanism involving 1,2-elimination of acetic acid from the quasi-equatorial form of cyclononyl acetate to form trans cyclononene, which then undergoes a transannular intramolecular rearrangement to form the diene (63):

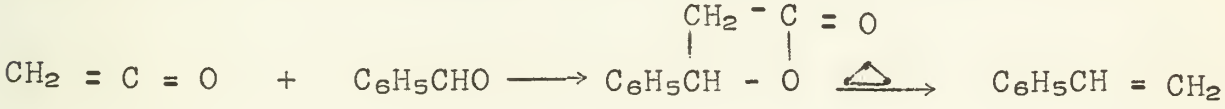
Cycloöctyl and cyclodecyl acetates decompose in a similar manner, although the main product is the trans cyclic olefin (63, 64).

PYROLYSIS OF LACTONES

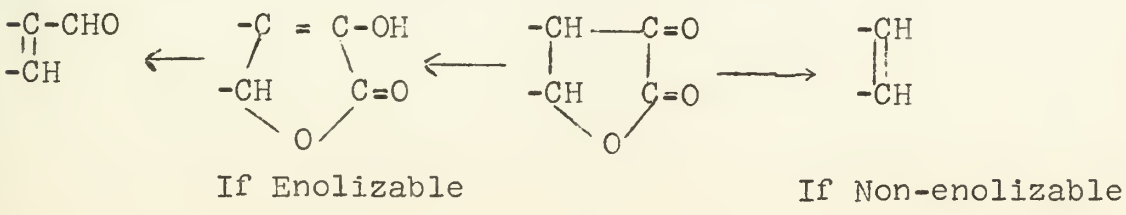
β-lactones decarboxylate when distilled at atmospheric pressure, forming olefins (58, 59):



Benzaldehyde may be converted to styrene in good yields by pyrolysis of the β-lactone which it forms with ketene (60):



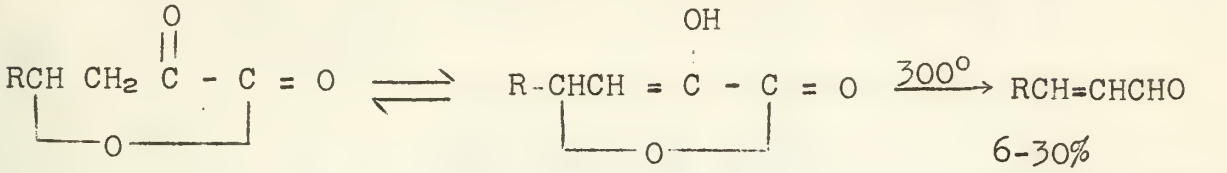
Schinz and coworkers have studied the pyrolysis of α-keto-γ-lactones, and have found that the products formed depend on the enolizability of the keto group (61, 62):

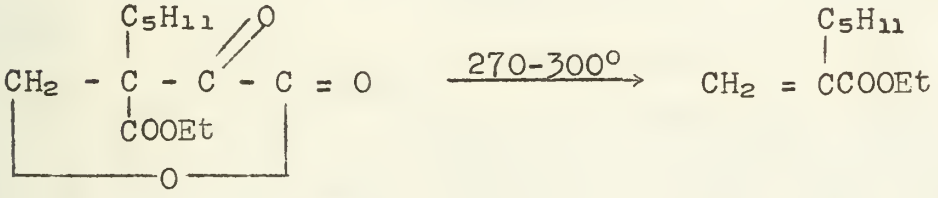


If Enolizable

If Non-enolizable

An enolizable α-keto-γ-lactone yields an unsaturated aldehyde, while one which is non-enolizable yields an olefin:





1. C. D. Hurd, "The Pyrolysis of Carbon Compounds," The Chemical Catalog Co., Inc., N. Y., 1929. pp. 524-565.
2. C. D. Hurd and F. H. Blunck, J. Am. Chem. Soc., 60, 2419 (1938).
3. E. R. Alexander and A. Mudrak, J. Am. Chem. Soc., 72, 1810 (1950).
4. ibid., 72, 3194 (1950).
5. ibid., 73, 59 (1951).
6. D. H. R. Barton, A. J. Head, and R. J. Williams, J. Chem. Soc., 1715 (1953).
7. A. T. Blades, Can. J. Chem., 32, 366 (1954).
8. D. Y. Curtin and D. B. Kellom, J. Am. Chem. Soc., 75, 6011 (1953).
9. B. F. McKenzie, W. F. McGuckin, and E. C. Kendall, J. Biol. Chem., 162, 555 (1946).
10. J. P. W. Houtman, J. van Steenis, and P. M. Heertjes, Rec. trav. chim., 65, 781 (1946).
11. W. J. Bailey and C. King, J. Am. Chem. Soc., 77, 75 (1955).
12. G. G. Smith and W. H. Wetzel, J. Am. Chem. Soc., 79, 875 (1957).
13. A. T. Blomquist and A. Goldstein, J. Am. Chem. Soc., 77, 998 (1955).
14. R. Burns, D. T. Jones, and P. D. Ritchie, J. Chem. Soc., 400 (1935).
15. G. L. O'Conner and R. R. Nace, J. Am. Chem. Soc., 75, 2118 (1953).
16. D. H. R. Barton and W. J. Rosenfelder, J. Chem. Soc., 2459 (1949).
17. W. J. Bailey and W. R. Sorenson, J. Am. Chem. Soc., 78, 2287(1956).
18. S. A. Ballard and B. P. Geyer, U. S. Patent 2,459,677; C.A. 43, 3026 (1949).
19. W. P. Ratchford, C. E. Rehberg, and C. H. Fisher, J. Am. Chem. Soc., 66, 1864 (1944).
20. W. P. Ratchford, Organic Syntheses 29, 2 (1949); Coll. Vol. III, p. 30.
21. L. T. Smith, C. H. Fisher, W. P. Ratchford, and M. L. Fein, Ind. Eng. Chem., 34, 473 (1942).
22. H. J. Hasemeyer, Jr., U. S. Patent 2,417,748; C. A. 41, 3478 (1947).
23. S. M. Weisberg and E. G. Stimpson, U. S. Patent 2,442,716; C. A. 42, 7787 (1948).
24. W. P. Ratchford and C. H. Fisher, U. S. Patent 2,408,177; C. A. 41, 773 (1947).
25. R. Burns, D. T. Jones, and P. D. Ritchie, J. Chem. Soc., 714 (1935).
26. W. J. Bailey and F. E. Naylor, Abstr. 128th. Meeting ACS, Sept. 1955, p. 2-S.
27. A. Y. Yakubovich, V. A. Rudenko, and E. N. Merkulova, Zhur. Priklad. Khim., 21, 151 (1948).; C.A. 43, 564 (1948).
28. A. E. Ardis, U. S. Patent 2,476,270; C.A. 43, 9079 (1949).
29. ibid.,2,665,298; C. A. 48, 4883 (1954).
30. S. A. Morell, H. H. Geller, and E. C. Lathrop, Ind. Eng. Chem., 37, 877 (1945).
31. N. Shlechter, D. F. Othmer, and R. Brand, ibid., 37, 905 (1945).
32. C. S. Marvel, R. L. Meyers, and D. H. Sanders, J. Am. Chem. Soc., 70, 1694 (1948).
33. C. S. Marvel and J. L. R. Williams, J. Am. Chem. Soc., 70, 3842 (1948).
34. R. L. Frank, R. D. Emmick, and R. S. Johnson, J. Am. Chem. Soc., 69, 2313 (1947).
35. C. G. Overberger, A. Fischman, C. W. Roberts, L. H. Arond, and J. Lal, J. Am. Chem. Soc., 73, 2540 (1951).
36. H. S. Davis, U. S. Patent 2,375,086; C. A. 40, 586 (1946).
37. H. Gudgeon, R. Hill, and E. Isaacs, J. Chem. Soc., 1926 (1951).

38. V. L. Hansley, U. S. Patent 2,452,460; C. A. 43, 2220 (1949).
39. E. J. Prill, U. S. Patent 2,446,167; C. A. 42, 8820 (1948).
40. W. J. Bailey and J. Economy, J. Am. Chem. Soc. 77, 1133 (1955).
41. A. T. Blomquist and J. A. Verdol, J. Am. Chem. Soc. 77, 81 (1955).
42. R. Paul and S. Tchelitcheff, Compt. Rend. 233, 1116-17 (1951).
43. British Thomson-Houston Co., Ltd., British Patent 620, 733; C. A. 43, 6669 (1949).
44. C. S. Marvel and C. W. Hinman, J. Am. Chem. Soc., 76, 5435 (1954).
45. D. L. Schoene, J. Am. Chem. Soc., 73, 1970 (1951).
46. R. Paul and S. Tchelitcheff, Compt. Rend. 232, 1939 (1951).
47. A. T. Blomquist and P. R. Taussig, J. Am. Chem. Soc., 77, 6399 (1955).
48. P. E. Burchfield, U. S. Patent 2,485,694; C. A. 44, 2007 (1950).
49. Visking Corp., British Patent 593, 109; C. A. 44, 653 (1950).
50. W. J. Bailey and J. J. Daly, Abstr. 124th. Meeting ACS, Sept. 1953, p. 39-O.
51. W. J. Bailey and J. J. Daly, Abstr. 126th. Meeting ACS, Sept. 1954, p. 11-O.
52. W. J. Bailey, J. Rosenberg, and L. J. Young, J. Am. Chem. Soc., 77, 1163 (1955).
53. W. J. Bailey and W. B. Lawson, J. Am. Chem. Soc., 77, 1606 (1955).
54. W. J. Bailey and R. Barclay, Jr., Abstr. 130th. Meeting ACS, Sept. 1956, p. 6-O.
55. W. J. Bailey and J. Rosenberg, J. Am. Chem. Soc., 77, 73 (1955).
56. W. J. Bailey and W. R. Sorenson, J. Am. Chem. Soc., 76, 5421 (1954).
57. W. J. Bailey, C. H. Cunov, and L. Nicholas, J. Am. Chem. Soc., 77, 2787 (1955).
58. J. R. Caldwell, U. S. Patent 2,585,223; C. A. 46, 8672 (1952).
59. H. J. Hagemeyer, Jr., U. S. Patent 2,478,388; C. A. 44, 1133 (1950).
60. R. C. Fuson, "Advanced Organic Chemistry," Wiley, N. Y., 1950. p. 393.
61. H. Schinz and A. Rossi, Helv. Chim. Acta, 31, 1953 (1948).
62. M. Hinder, H. Schinz, and C. F. Seidel, Helv. Chim. Acta, 30, 1495 (1947).
63. A. T. Blomquist and P. R. Taussig, Abstr. 131st. Meeting ACS, April 1957, p. 2-O.
64. A. T. Blomquist and A. Goldstein, J. Am. Chem. Soc., 77, 1001 (1955).

SYNTHESIS OF NITROPARAFFINS

Reported by Donald J. Casey April 1, 1957

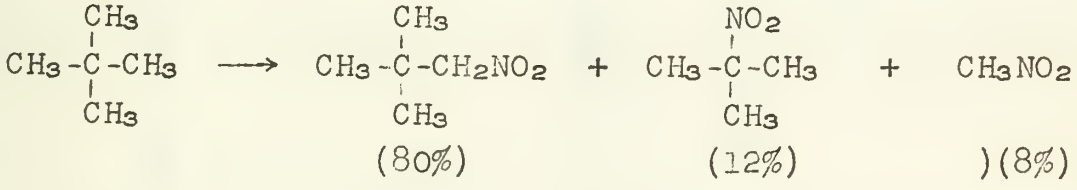
Introduction

The object of this seminar is to survey the most common and generally useful procedures for the synthesis of nitro paraffins and cycloparaffins. Due to the extensive literature available on the liquid and vapor phase nitration of hydrocarbons, the coverage of these techniques will be very limited.

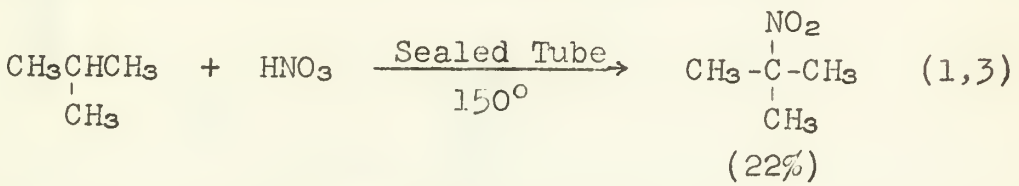
From Hydrocarbons

(a) Vapor Phase

The vapor phase nitration of hydrocarbons using nitric acid or nitrogen tetroxide has received considerable attention since the 1930's from Hass and coworkers and more recently from Bachman, et al. The results obtained by Hass in the nitration of the lower paraffins using a flow apparatus at 420°C. and a hydrocarbon: nitric acid ratio of 2:1 are shown in Table I. (See following sheet). At the temperatures employed, the reaction produces all the mononitro derivatives possible by cleavage of any C-H or C-C bond as is illustrated in the nitration of neopentane at 410°C. with a contact time of 1.5 sec. for a total yield of 28-36% based on the hydrocarbon (2).



An indication of the relative ease of replacement of hydrogens ($3^\circ > 2^\circ > 1^\circ$) is given by the nitration of isobutane.



But at 420°C. the product composition changes to that outlined in Table I illustrating the decrease in selectivity of attack at higher temperatures. Polynitro paraffins are not usually formed unless paraffins of rather high molecular weight are used (4).

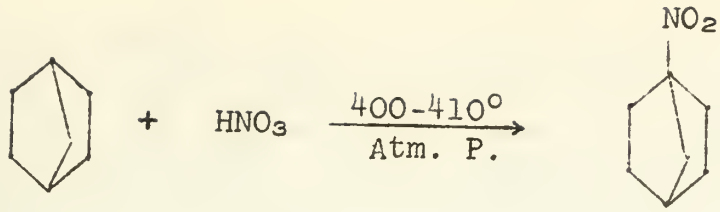
The technique has been applied to cycloparaffins with moderate success as shown by:

Table I (1)

Vapor Phase Nitration - Contact Time: 2 sec.

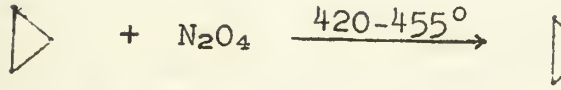
Hydrocarbon	Ace tone	Nitro Methane	Nitro Ethane	1-Nitro Propane	2-Nitro Propane	1-Nitro Butane	2-Nitro Butane	1-Nitro i-Butane	2-Nitro i-Butane	Yield*
Ethane		10-20	80-90							9
Propane		9	26 (?)	32	33					21
Butane		6	12	5		27	50			28
Isobutane	5	3			20			65	7	25

* Yield per pass based on HNO_3 consumed



Yield, about 50% of the nitrated product

(5)



(6)

(15%)

Bachman and coworkers have suggested a radical mechanism for vapor phase nitration with nitric acid as follows (7):

$$HNO_3 \longrightarrow HO\cdot + \cdot NO_2$$
$$RH + HO\cdot \longrightarrow R\cdot + HOH$$
$$R\cdot + \cdot NO_2 \longrightarrow RNO_2$$

In support of the suggestion that it is a radical reaction they note: (1) The extent of nitration is increased by small amounts of O_2 or Cl_2, (2) Radical inhibitors (reactor surface, excess oxygen or chlorine, nitric oxide, etc.) decrease the extent of nitration, (3) Ionic catalysts do not catalyze vapor phase nitration (7, 8, 9). Additional evidence is offered by the production of small amounts of olefins in the reactions (9, 10) and the formation of nitroethane from tetraethyl lead (10). It is believed a similar mechanism is operative in nitrations with nitrogen tetroxide (9). The effect of a small amount of oxygen may be similar to that suggested by Walsh (11) for the vapor phase oxidation of hydrocarbons in that it increases the rate of formation of alkyl radicals (7). This may involve in part:

$$(CH_3)_2CH_2 + O_2 \longrightarrow (CH_3)_2CHOOH$$
$$\longrightarrow (CH_3)_2CHO\cdot + \cdot OH$$
$$\downarrow$$
$$CH_3\cdot + CH_3CHO$$
$$(CH_3)_2CHO\cdot + (CH_3)_2CH_2 \longrightarrow (CH_3)_2CHOH + (CH_3)_2CH\cdot$$

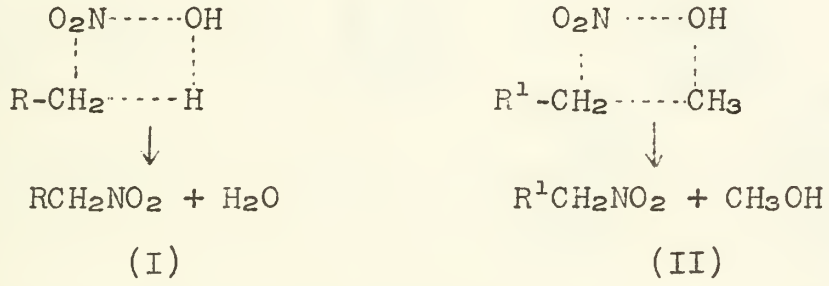
The formation of alkyl nitrites is in accord with the radical mechanism but at the reaction temperature they decompose, possibly by:

$$CH_3CH_2ONO \longrightarrow CH_3CH_2O\cdot + NO$$
$$CH_3CH_2O\cdot \longrightarrow HCHO + CH_3\cdot \qquad (7, 8, 12)$$
$$CH_3\cdot + CH_3CH_2ONO \longrightarrow CH_4 + CH_3\dot{C}HONO$$
$$CH_3\dot{C}HONO \longrightarrow CH_3CHO + NO$$

This would help to explain the production of lower nitro compounds and

various aldehydes, and is consistent with the work of McCleary and Degering (10) who showed that the lower nitroparaffins can not result from the known decarboxylation of α-nitrocarboxylic acids as had originally been suggested by Hass (1). There are two possible sources of α-nitrocarboxylic acids in vapor phase nitration: (1) Direct nitration of fatty acids, or (2) Oxidation of nitro compounds. McCleary and Degering found that no nitroparaffins were produced when lower aliphatic acids were subjected to nitration conditions, nor were lower nitroparaffins produced when nitroethane, 1-nitro-propane, 2-nitro-propane, etc., were passed through a nitration reactor. They concluded from this that α-nitro acids could not be intermediates in the formation of lower nitro compounds since reactions leading to their formation do not occur under vapor phase conditions.

A suggestion by Hass (3) that the nitration reaction and production of lower nitro compounds could be explained by a four center mechanism such as:



has recently been examined by Hass and Shechter who showed that cyclopropane yielded only nitrocyclopropane and not 3-nitro-1-propanol as would have been predicted by (II).(6). On the basis of this evidence, it can be concluded that (II) does not play an important part in alkyl replacement in the vapor phase.

(b) Liquid Phase

Liquid phase nitration has been extensively reviewed, and there appear to be no recent developments (3, 13, 14, 15). The procedure has been shown to be useful for the preparation of polynitro compounds (3, 15).

From Olefins

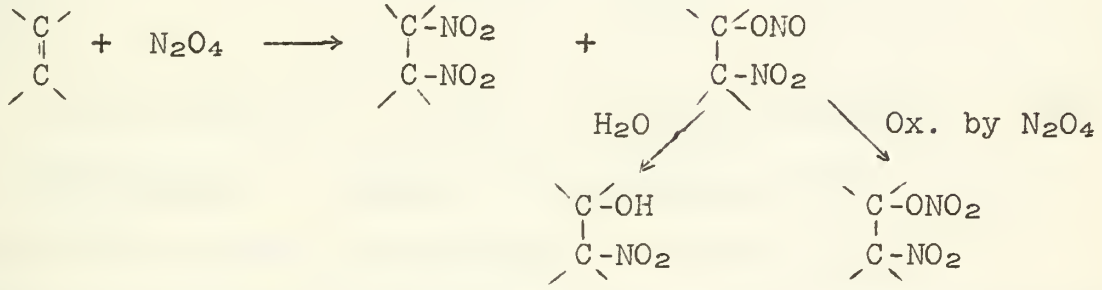
(a) Addition of Nitrogen Tetroxide to Olefins

It has been found that the reaction of an olefin with nitrogen tetroxide at approximately 0° results in good total yields (65-85 %) of dinitro compound, nitro alcohol, and nitro nitrate. The use of solvents such as ether and dioxane moderates the oxidizing action of N_2O_4, apparently through molecular association with the tetroxide (13, 16). A few of the dinitro compounds obtained are listed in Table II.

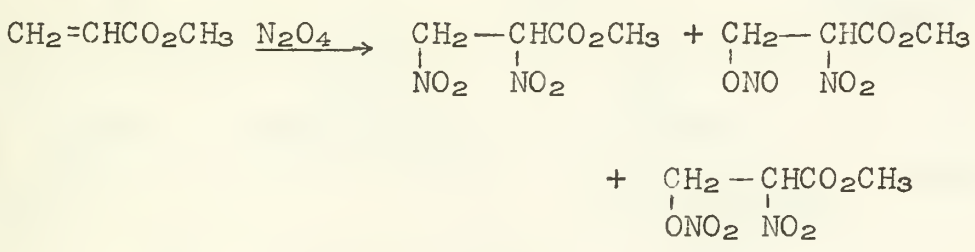
Table II

Olefin	Product	Yield-%	Reference
Ethylene	1,2-Dinitroethane		16,20
Propylene	1,2-Dinitropropane		16,17
1-Butylene	1,2-Dinitrobutane	39	16,18
2-Butylene	2,3-Dinitrobutane	30	18
Isobutylene	1,2-Dinitroisobutane	35-42	16,18
		12	21
2,3-Dimethyl-2-butene	2,3-Dinitro-2,3-dimethyl butane	19-22	22
Cyclohexene	1,2-Dinitrocyclohexane	30-42%	19

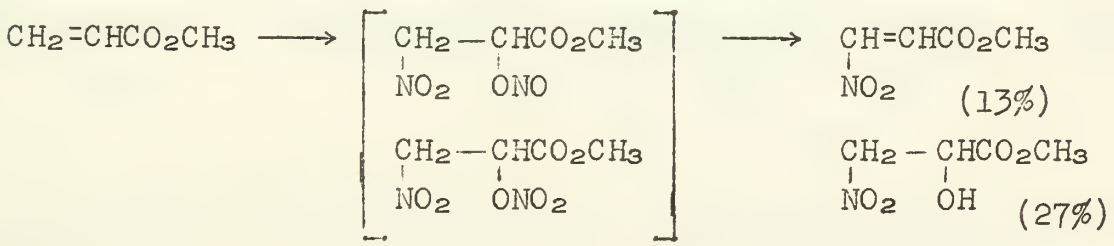
Levy and Scaife explain the products of these reactions by the following scheme (16):



It has been noted that in the formation of nitro-nitrites from unsymmetrical olefins the nitro group attaches to the carbon with the greater number of hydrogens. This has been interpreted by Levy, et.al., to mean an electrophilic attack with $^{\oplus}NO_2$ or a source of $^{\oplus}NO_2$ adding first to form a C-N bond and nitrite adding to form a C-N or C-O bond (13, 16). Shechter and Conrad have investigated the mechanism of this reaction in the addition of N_2O_4 to methyl acrylate (23). They point out that attack by $^{\oplus}NO_2$ would be expected to give:



At 0°C. in ether they found:



They did not isolate any compound with an α-nitro group, so it is doubtful whether in this case the reaction proceeds by an electrophilic attack. On the basis of the orientation of addition, the extensive polymerization during the reaction, and the paramagnetism of N_2O_4 complex solutions (indicating the presence of NO_2), Shechter and Conrad suggest that the reaction proceeds "by a homolytic process in which initial attack by NO_2 at the terminal position occurs exclusively with C-N attachment" (23).

(b) Addition of Nitroparaffins to Nitroölefins

A considerable number of procedures have been devised for the preparation of nitroölefins; the most useful techniques include the following:

$$\underset{\text{NO}_2}{\overset{\text{OCOCH}_3}{\text{RCH-CR}_2}} + \text{Na}_2\text{CO}_3 \xrightarrow[\text{reflux}]{\text{C}_6\text{H}_6} \underset{\text{NO}_2}{\text{RC=CR}_2} \qquad (3)$$

$$(CH_3)_2(C_2H_5)COH + HNO_3 \longrightarrow (CH_3)_2C=C(NO_2)CH_3 \qquad (60)$$

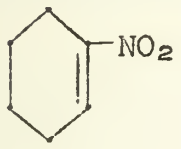
$$HOCH_2CH_2NO_2 + NaHSO_4 \longrightarrow CH_2=CHNO_2 \qquad (61)$$

Additional procedures are mentioned in (3 and 13).

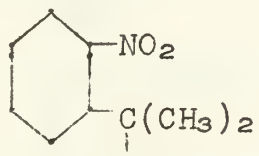
The addition of a 1° or 2° nitro compound to α-nitroölefins provides a useful route to 1,3-dinitroparaffins. The procedures involve the reaction of the nitroölefin with a nitroparaffin in ethanolic sodium ethoxide.

$$\underset{\text{NO}_2}{\text{CH}_3\text{CH=C-CH}_3} + (CH_3)_2CHNO_2 \xrightarrow[\text{EtOH}]{\text{NaOEt}} \underset{\text{NO}_2}{\overset{\text{CH}_3}{(CH_3)_2\text{-C-CH}}}\text{-}\underset{\text{NO}_2}{\text{CHCH}_3} \qquad (24)$$

(47%)



$$+ (CH_3)_2CHNO_2 \longrightarrow$$



(24)

(16%)

$$\underset{\text{NO}_2}{\text{CH}_3\text{CH}_2\text{C=CH}_2} + (CH_3)_2CHNO_2 \longrightarrow \underset{\text{NO}_2}{\text{CH}_3\text{CH}_2\text{CH}}\cdot\text{CH}_2\text{-}\underset{\text{NO}_2}{\text{C}}(CH_3)_2 \qquad (25)$$

(≈ 90%)

Bachman and Atwood have reported that a similar reaction occurs in the condensation of a 1° nitroparaffin with formaldehyde in the

presence of a secondary amine.

$$CH_3CH_2NO_2 + CH_2O + (CH_3)_2NH \longrightarrow (CH_3CHNO_2)_2CH_2$$
$$n\text{-}C_6H_{13}CH_2NO_2 + CH_2O + (CH_3)_2NH \longrightarrow (n\text{-}C_6H_{13}CHNO_2)_2CH_2 \qquad (26)$$

These workers assume the reaction proceeds through an intermediate Mannich type base, $RCH(NO_2)CH_2NR_2$, which eliminates a secondary amine to form an α-nitroölefin. As evidence for this they point out the failure of 2° nitroparaffins to yield 1,3-dinitro compounds in this reaction, presumably due to their inability to form a nitroölefin intermediate. Similar results with ketones have been recorded by Fraser and Kon (27), and by Heim (28). Analogous results have been found in the alkylation of salts of nitroparaffins with Mannich bases. Snyder and Hamlin have suggested that the Mannich bases employed may serve as sources of unsaturated compounds and the alkylations are actually Michael type condensations (55). As evidence for this they have reported the inertness of amines such as $(CH_3)_2C(NO_2)CH_2N(CH_3)_2$ which can not eliminate a 2° amine to form a nitroölefin, whereas compounds of the type $CH_3CH_2CH(NO_2)CH_2NR_2$ can be used as alkylating agents.

$$CH_3CH_2\underset{\displaystyle NO_2}{\underset{|}{C}}HCH_2N(CH_3)_2 + (CH_3)_2CHNO_2 \xrightarrow[120^\circ]{NaOH} CH_3CH_2\underset{\displaystyle NO_2}{\underset{|}{C}}HCH_2\underset{\displaystyle NO_2}{\underset{|}{C}}(CH_3)_2 \quad (55\%)$$

(c) Addition of Organo Metallic Compounds to Nitroölefins

Varying yields of nitroparaffins have been obtained by the reaction of an α-nitroölefin with a Grignard or an alkyl zinc halide (29, 30). The procedure is complicated by the polymerization of the nitroölefin and the addition of excess Grignard reagent to the complex formed by the nitroölefin and one mole of Grignard reagent.

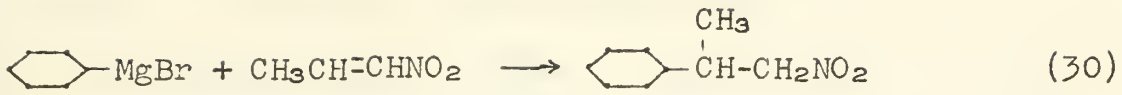
$$(CH_3)_2C{=}CHN\begin{matrix}=O\\ \searrow O\end{matrix} \xrightarrow[<10^\circ]{EtMgBr} (CH_3)_2\underset{\displaystyle C_2H_5}{\underset{|}{C}}\text{-}CH{=}N\begin{matrix}\swarrow OMgBr\\ \searrow O\end{matrix} \xrightarrow{H_2O} CH_3\text{-}\underset{\displaystyle C_2H_5}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}\text{-}CH_2NO_2 \quad (60\%)$$

$$\Big|\ x\text{'s } EtMgBr$$

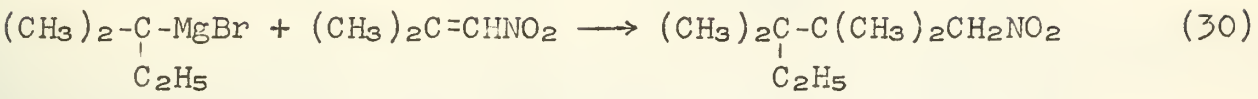
$$(CH_3)_2\underset{\displaystyle C_2H_5}{\underset{|}{C}}\text{---}\underset{\displaystyle C_2H_5}{\underset{|}{CH}}\text{-}N(OMgBr) \xrightarrow{H_2O}$$

$$(CH_3)_2\underset{\displaystyle C_2H_5}{\underset{|}{C}}\text{---}\underset{\displaystyle C_2H_5}{\underset{|}{C}}{=}NOH \qquad (30)$$

Among the more interesting nitro compounds obtainable by this method are the following:



(30)



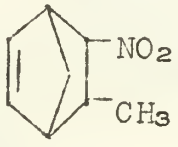
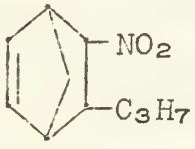
(30)

(d) Diels-Alder Procedures

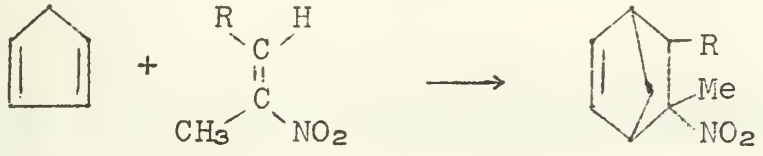
Cyclopentadiene has been found to undergo Diels Alder reactions with a number of nitroölefins to yield 2° nitrocompounds.

Table III

Diels Alder Adducts of Cyclopentadiene

Olefin	Product	Yield-%	Reference
$CH_2=CHNO_2$		61 67	31 32
$CH_3CH=CHNO_2$		59 55	33 34
$CH_3CH_2CH_2CH=CHNO_2$		72	34

Noland and Bambury reported the preparation of two 3° nitro compounds by Diels Alder reactions with cyclopentadiene.



R=H, 27%
Me, 41%

(35)

Butadiene, methylbutadiene, and 2,3-dimethylbutadiene have also been added to 1-nitro-1-pentene (34). A few additional examples are listed in reference 36.

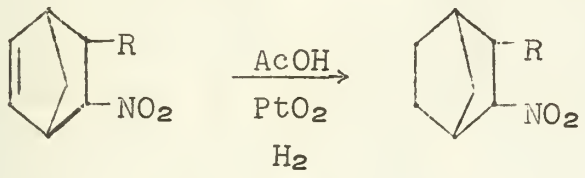
(e) Reduction of Nitroölefins

Conjugated and non-conjugated nitroölefins have been successfully reduced to nitroalkanes by catalytic and hydride procedures. De Mauny has reported excellent yields in the catalytic reduction of

a number of conjugated nitroölefins such as:

$$CH_3(CH_2)_5CH{=}CHNO_2 \xrightarrow[R.T.]{\overset{PtO_2}{H_2}} CH_3(CH_2)_7NO_2 \quad (>80\%) \qquad (37)$$

The non-conjugated nitroölefins resulting from Diels Alder reactions of nitroalkenes have been reduced by similar procedures.



R= H
Me, 90%
C_3H_7, 90% (34)

A recent reduction procedure for conjugated nitroölefins involves the addition of ether solutions of the nitroalkene to ether-tetrahydrofuran suspensions of excess $NaBH(OCH_3)_3$, $LiBH_4$, $NaBH_4$, or $LiAlH_4$ at -70 to 0° C. The reaction is complicated by the Michael addition of the initial reduction products to the nitroölefin to yield 1,3-dinitro compounds or higher polynitroalkanes (38). It was found that the non-conjugated nitroalkene, 1-(nitromethyl)-cyclopentene, could not be reduced by this technique.

Table IV (38)

Reduction of Nitroölefins With $NaBH(OCH_3)_3$

Nitroölefin	T°C	Products
$CH_3CH{=}CHNO_2$	-70	$C_3H_7NO_2$, 82%; $C_2H_5CH(NO_2)CH(CH_3)CH_2NO_2$, 11%
$CH_3CH{=}C(NO_2)CH_3$	-70	$C_2H_5CH(NO_2)CH_3$, 63%; $C_2H_5C(CH_3)(NO_2)CH(CH_3)CH(NO_2)CH_3$, 11%
$(CH_3)_2C{=}CHNO_2$	-3	$(CH_3)_2CHCH_2NO_2$, 59%
$C_3H_7C(NO_2){=}CHC_2H_5$	0	$C_3H_7CH(NO_2)C_3H_7$, 55%

From Oximes

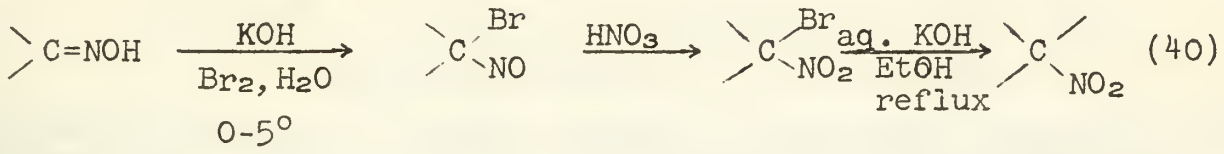
In 1896, Born reported the preparation of dinitro compounds from oximes by the action of N_2O_4 on the oxime followed by oxidation with chromic acid (39).

$$R\text{-}\underset{\underset{NOH}{\|}}{C}\text{-}R^1 \xrightarrow[Et_2O]{N_2O_4} R\text{-}\underset{\underset{NO_2}{|}}{\overset{\overset{NO}{|}}{C}}\text{-}R' \xrightarrow[H_2CrO_4]{AcOH} R\text{-}C(NO_2)_2R'$$

40°

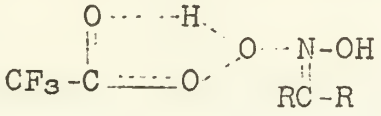
R = Me, R' = Pr
R = Pr, R' = Pr
R = Et, R' = Et
} Low Yields

A number of procedures for the preparation of mono-nitro compounds from oximes have been reported by Iffland. The earliest of these involved the series of reactions:



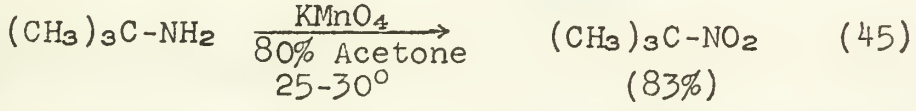
(40)

Using this technique, the oximes of cyclobutanone, cyclopentanone, and cyclohexanone were converted to nitro compounds in overall yields of 3%, 13%, and 13%. A modification of the procedure employing N-Bromosuccinimide as the brominating agent and $NaBH_4$ for the final reduction raised the yields for the same ketoximes to 15-33%, 60-76%, and 80%.respectively (41, 42). Emmons and Pagano have obtained 50-80% yields of nitro compounds in a one step oxidation of the ketoxime with peroxytrifluoroacetic acid in acetonitrile (43). They assume the reaction proceeds through a cyclic transition state such as:



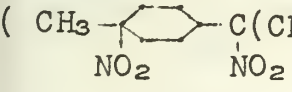
From Amines

The possibility of oxidizing 1° amines to nitro compounds was illustrated in 1902 by Bamberger, who converted methyl and ethyl amines to the corresponding nitroparaffins with Caro's acid (44). Kornblum and Clutter have recently applied the idea to the synthesis of nitro compounds from tertiary carbinamines, $RR'R''CNH_2$.



(45)

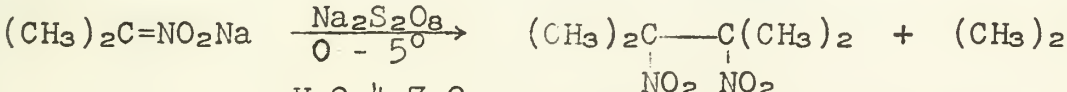
The reaction has been used to obtain 1-nitro-1-methyl-cyclopentane, 1-nitro-1-methyl-cyclohexane, and 1,8-dinitro-p-methane,



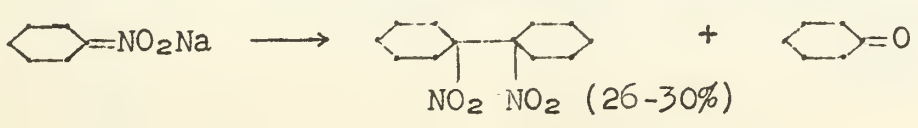
in 70-80% yields (45, 46).

Oxidative Dimerization

The oxidation of alkaline solutions of 2° nitro compounds with sodium persulfate, hydrogen peroxide, ferricyanides, etc. results in the formation of 1,2-dinitroalkanes and ketones.



(47)



Shechter and Kaplan have suggested that the oxidation of 2° alkane nitronates with anionic oxidants proceeds through the transfer of one electron and involves nitroalkyl radicals as intermediates.

$$RRC{=}NO_2^{\ominus} + \text{Oxidant} \longrightarrow RR\dot{C}\text{-}NO_2 + Ox^{\ominus} \qquad (47)$$

$$RRC(NO_2)C(NO_2)RR \leftarrow \quad \rightarrow RRC{=}O + NO$$

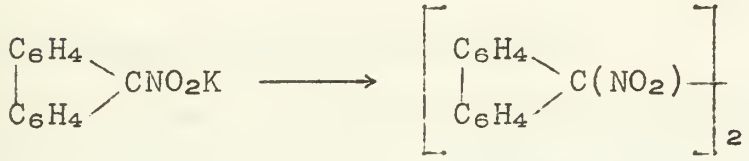
In a reaction which is formally similar to the Kolbe synthesis, the electrolysis of the salts of 1° of 2° nitroparaffins has also been shown to produce vicinal dinitro compounds. The discharge of the anion at the anode presumably yields a radical which, as in the example above, can either dimerize or decompose to a ketone (48, 49, 50).

$$(CH_3)_2CNO_2Na \xrightarrow[aqNaOH]{\text{Electrolysis}} \left[(CH_3)_2\text{-}C(NO_2)\text{—}\right]_2 \qquad (48)$$

(15%)

$$CH_3CH_2CHNO_2Na \longrightarrow \left[CH_3CH_2CH(NO_2)\text{—}\right]_2 \qquad (49)$$

(25-30%)

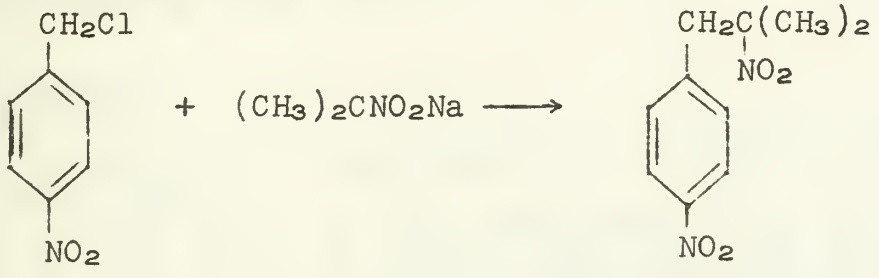


(50)

(71%)

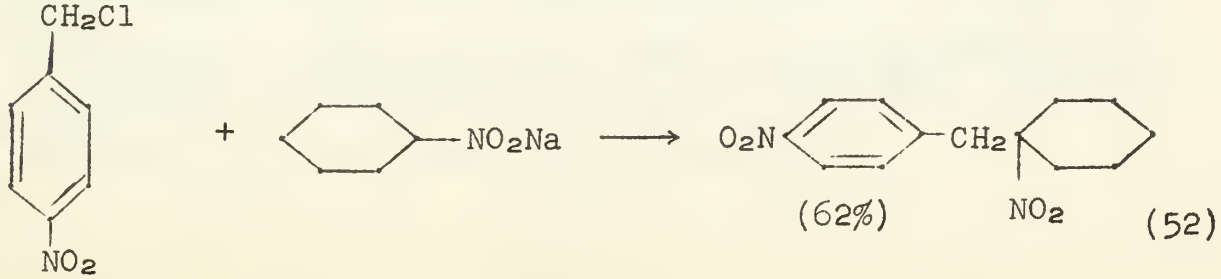
By Alkylation Reactions

In a limited number of cases, the reaction of a silver or alkali metal salt of a nitroparaffin with an alkyl halide will lead to the formation of a substituted nitroparaffin. Among the few known examples are the following:



(51)

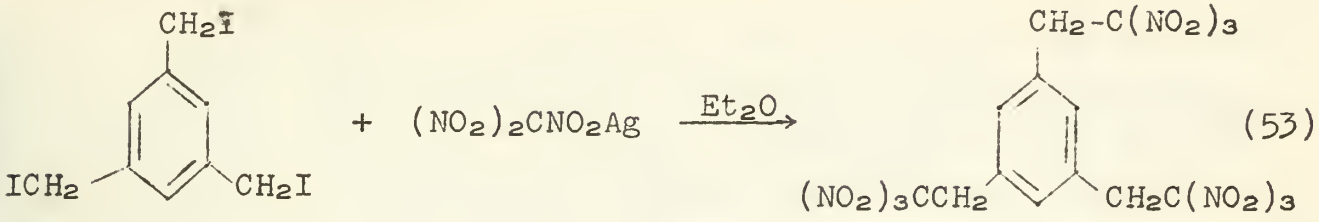
(83%)



(52)

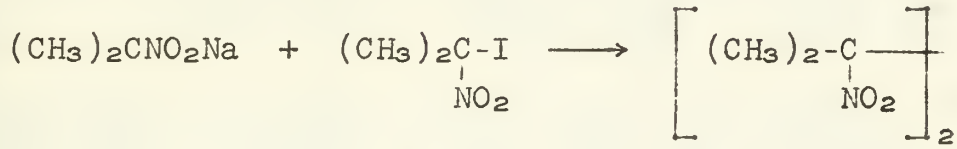
(62%)

Reich and coworkers used this procedure in the synthesis of derivatives of trinitromethane.

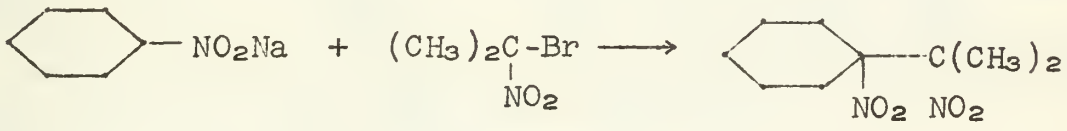


(53)

Vicinal dinitro paraffins can be formed by an analogous procedure developed by Seigle and Hass (54).



(43%)



(19%)

Reaction of Alkyl Halides With Nitrite

Perhaps the most familiar laboratory preparation of nitroparaffins is the reaction of an alkyl halide with silver nitrite. With this procedure, 1° nitro compounds can be snythesized in yields of 73-83%, but with 2° halides the yields drop to around 15-25%, and with 3° halides the yields are from 0 to 5% (56, 57). It has also been found that branching on the carbon α to the carbon bearing the halogen reduces the yield of nitroparaffin (58). Somewhat better yields of 2° nitroparaffins have been obtained using KNO_2 or $NaNO_2$ in dimethylformamide (56). A discussion of the applicability and mechanisms of these reactions is to be found in a previous Illinois Organic Seminar (59).

BIBLIOGRAPHY

1. H. B. Hass, E. B. Hodge and B. M. Vanderbilt, Ind. Eng. Chem., 28, 339 (1936).
2. A. P. Howe and H. B. Hass, Ind. Eng. Chem., 38, 251 (1946).
3. H. B. Hass and E. F. Riley, Chem. Rev., 32, 373 (1943).
4. H. B. Hass, Ind. Eng. Chem., 35, 1146 (1943).
5. R. T. Blickenstaff and H. B. Hass, J. Am. Chem. Soc., 68, 1431 (1946).
6. H. B. Hass and H. Shechter, J. Am. Chem. Soc., 75, 1382 (1953).
7. G. B. Bachman, L. M. Addison, et. al., J. Org. Chem., 17, 906 (1952).
8. H. B. Hass, Ind. Eng. Chem., 41, 2266 (1949).

9. G. B. Bachman, et.al., J. Org. Chem., 17, 914, 928, 935, 942 (1952) ibid., 19, 312 (1954).
10. R. F. McCleary and E. F. Degering, Ind. Eng. Chem., 30, 64 (1938).
11. A. D. Walsh, Trans. Faraday Soc., 42, 269 (1946).
12. C. E. Boord, "Third Symposium on Combustion, Flame and Explosion Phenomena", William and Wilkins Co., Baltimore, 1949, p. 416.
13. N. Levy and J. D. Rose, Quart. Rev., 358 (1947).
14. B. T. Brooks, "Chemistry of Petroleum Hydrocarbons", Vol. 3, Reinhold, New York, 1955, p. 85.
15. Carleton Ellis, "The Chemistry of Petroleum Derivatives", Chemical Catalog Co., New York, 1934, p. 1039.
16. N. Levy and C. W. Scaife, J. Chem. Soc., 1946, 1093, 1096.
17. N. Levy and C. W. Scaife, J. Chem. Soc., 1946, 1100.
18. N. Levy, C. W. Scaife, and A. Wilder Smith, J. Chem. Soc., 1948, 52.
19. N. Levy, C. W. Scaife, and A. Wilder Smith, J. Chem. Soc., 1949, 2627.
20. A. E. W. Smith, U. S. Pat., 2,384,048, (C.A., 40, 347 (1946).).
21. A. Michael and G. Carlson, J. Org. Chem., 5, 1 (1940).
22. A. Michael and G. Carlson, J. Org. Chem., 5, 14 (1940).
23. H. Shechter and F. Conrad, J. Am. Chem. Soc., 75, 5610 (1953).
24. A. Lambert and H. A. Piggott, J. Chem. Soc., 1947, 1489.
25. C. T. Bahner and H. T. Kite, J. Am. Chem. Soc., 71, 3597 (1949).
26. G. B. Bachman and M. T. Atwood, J. Am. Chem. Soc., 78, 484 (1956).
27. H. Fraser and G. Kon, J. Chem. Soc. 1934, 604.
28. F. Heim, Ber., 44, 2016 (1911).
29. G. Buckley, J. Chem. Soc., 1947, 1494.
30. G. Buckley and E. Ellery, J. Chem. Soc., 1947, 1497.
31. J. D. Roberts, C. C. Lee, and W. H. Saunders, J. Am. Chem. Soc., 76, 4501 (1954).
32. W. C. Wildman and C. H. Hemminger, J. Org. Chem., 17, 1641 (1952).
33. E. E. Van Tamelen and R. J. Thiede, J. Am. Chem. Soc., 74, 2615 (1952).
34. K. Alder, H. F. Rickert, and E. Windemuth, Ber., 71, 2451 (1938).
35. W. E. Noland and R. E. Bambury, J. Am. Chem. Soc., 77, 6386 (1955).
36. J. A. Norton, Chem. Rev., 31, 319 (1942).
37. H. Cerf de Mauny, Bull. soc. chim. France, 7, [5], 133 (1940).
38. H. Shechter, D. E. Ley and E. B. Roberson, J. Am. Chem. Soc., 78, 4984 (1956).
39. G. Born, Ber., 29, 90 (1896).
40. D. C. Iffland, G. Criner, et.al., J. Am. Chem. Soc., 75, 4044 (1953).
41. D. C. Iffland and G. Criner, J. Am. Chem. Soc., 75, 4047 (1953).
42. D. C. Iffland and Teh Fu Yen, J. Am. Chem. Soc., 76, 4083 (1954).
43. W. D. Emmons and A. S. Pagano, J. Am. Chem. Soc., 77, 4557 (1955).
44. E. Bamberger, Ber., 35, 4293, 4299 (1902).
45. N. Kornblum and R. Clutter, J. Am. Chem. Soc., 76, 4494 (1954).
46. N. Kornblum, R. Clutter, and W. Jones, J. Am. Chem. Soc., 78, 4003 (1956).
47. H. Shechter and R. B. Kaplan, J. Am. Chem. Soc., 75, 3980 (1953).
48. R. Pearson and W. Evans, Trans. Electrochem. Soc., 84, 173 (1943).
49. C. T. Bahner, U. S. Pat. 2,485,803, (C.A., 44, 2876b (1950)).
50. C. D. Nenitzescu and D. Isacescu, Ber., 63, 2484 (1930). ibid., 62, 2669 (1929).
51. H. B. Hass and M. L. Bender, J. Am. Chem. Soc., 71, 1767 (1949).

52. H. B. Hass, E. J. Berry, and M. L. Bender, J. Am. Chem. Soc., 71, 2290 (1949).
53. W. S. Reich, G. G. Rose, and W. Wilson, J. Chem. Soc., 1947, 1234.
54. L. W. Seigle and H. B. Hass, J. Org. Chem., 5, 100 (1940).
55. H. R. Snyder and W. E. Hamlin, J. Am. Chem. Soc., 72, 5082 (1950).
56. N. Kornblum. H. O. Larson, and R. K. Blackwood, J. Am. Chem. Soc., 78, 1497 (1956).
57. N. Kornblum, R. A. Smiley, et.al., J. Am. Chem. Soc., 77, 5528 (1955).
58. N. Kornblum, B. Taub, and H. E. Ungnade, J. Am. Chem. Soc., 76, 3209 (1954).
59. R. Scherrer, Illinois Org. Seminars, 1955-56, p.7.
60. L. Haitinger, Monatsh., 2, 290 (1881).
61. H. Wieland and E. Sakellarios, Ber., 52, 898 (1919).

THE STRUCTURE OF MAGNAMYCIN

Reported by W. Kenneth Musker April 8, 1957

In recent years there has been an extensive search for antibiotics which have useful activity toward pathogenic microörganisms. This search has led to the isolation of a group of metabolic products which may be extracted from different types of streptomyces. Magnamycin (the Chas. Pfizer and Co. trademark for the antibiotic carbomycin) is a new antibiotic of this type formed by strains of the microörganism Streptomyces halstedii. It was also isolated from the fermentation broths of a soil actinomycete, labeled M-4209 by Dutcher (3).

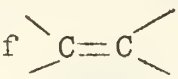
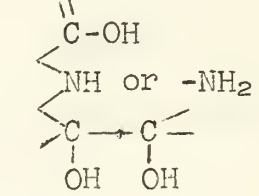
This seminar will discuss only the structure and some recent work on the stereochemistry of magnamycin and magnamycin B, a naturally occurring companion of magnamycin (6). The biogenesis of magnamycin was discussed by Woodward (1).

INTRODUCTION

Since magnamycin is a large molecule neither molecular weight determinations nor elemental analysis may accurately specify the molecular formula of this antibiotic. The best approximation of the molecular formula that could be made before a complete structure determination was finished was $C_{40-42}H_{67-71}NO_{16}$. The correct molecular formula was finally determined to be $C_{42}H_{67}O_{16}N$.

Listed below are the preliminary physical and chemical data accumulated for magnamycin and the conclusions permissable at each stage.

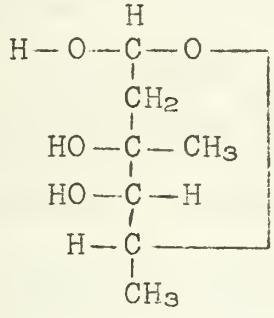
Data	Conclusion
pKa' 7.0 (3)	Amine grouping (Neighborhood of hydroxy or similar groupings.)
Optical activity (2)	Asymmetry
λ max 238 mμ (ϵ15,900) (1)	$-C{=}C-\overset{O}{\overset{\|}{C}}-$ (further enhanced)
Zeisels methoxyl determination (3)	$1CH_3O-$
Kuhn-Roth determination (8)	$6CH_3C-$
OH $\rightarrow$ $(CH_3)_2NH$ (3)	$-N(CH_3)_2$
H $\rightarrow$ CH_3COOH	$-OCOCH_3$
$(CH_3)_2CHCH_2COOH$	$-OCOCH_2CH(CH_3)_2$
$H^+ \rightarrow$ $(C_7H_{13}O_4)-\overset{O}{\overset{\|}{C}}CH_2CH(CH_3)_2$ (3)	$-OCOCH_2CH(CH_3)_2$
$C_{29-30}H_{47-49}NO_{12}$	possible similarity to erythromycin.

Data (cont.)	Conclusion (cont.)
$2H_2$ → compound devoid of λ max Pd-C 238 mμ (3)	Destruction of conjugated system
Qualitative Tests (5)	Presence of  -CHO -CO-
	Absence of 
Acetylation (mild)→diacetate (strenuous)→tetraacetate	2 OH groups ?

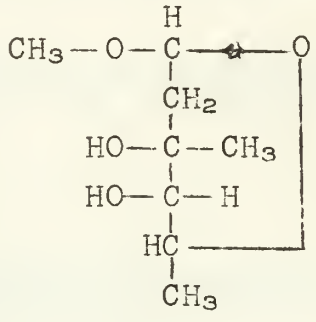
Magnamycin B is very similar to magnamycin; however, the λ max (278 mμ , ε 25000) indicated an α,β, ϒ, δ— unsaturated system.

MYCAROSE, A DESOXY SUGAR (5)

Methanolysis of magnamycin yielded a base with formula $C_{29\text{-}30}H_{47\text{-}49}NO_{12}$ and a neutral substance ($C_{12}H_{24}O_5$) which was found to be the isovaleryl ester of methyl mycaroside (II), the structure of which was proven by the sequence outlined below.



I. MYCAROSE

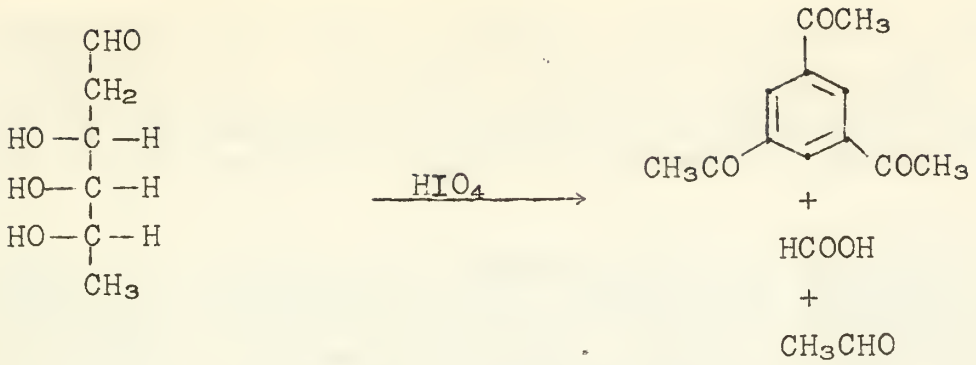


II

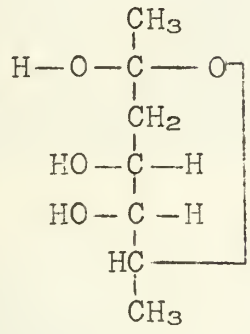
Alkaline hydrolysis of the methanolysis product yielded isovaleric acid and a mixture of anomeric methyl mycarosides (II). Acid hydrolysis of methyl mycaroside gave mycarose (I).

Mycarose reduced hot Fehling's solution, contained two C-methyl groups and three active hydrogens. It exhibited only end absorption in the ultraviolet.

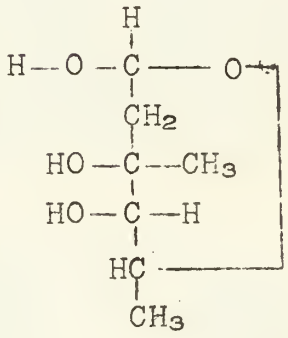
Periodic acid oxidation gave three products: 1 mole of acetaldehyde, 1 mole of formic acid, and a small amount of 1,3,5 triacetyl benzene (9).



Using this information the structure of mycarose may be formulated as I or III.



III



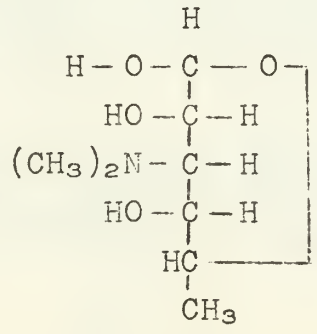
I

Structure III was discarded since a lactone was formed by hypobromite oxidation of mycarose.

It was shown that the isovaleryl ester of methyl mycaroside is not oxidized by periodic acid; therefore, the isovaleryl residue must be attached at position 4.

MYCAMINOSE, AN AMINO SUGAR (7)

Vigorous acid hydrolysis of magnamycin (or magnamycin B) yielded two sugars, mycarose I and mycaminose IV.



IV

Mycaminose was found to possess a dimethylamino group and a C-methyl group (7). It reduced Fehling's solution, lost dimethylamine slowly in base, and gave a positive iodoform test (slowly). Methylation with methanol and hydrogen chloride gave a derivative which no longer reduced Fehling's solution or liberated dimethylamine.

Mycaminose reacted with periodic acid to form formic acid and a C_7 sugar, the properties of which were quite similar to mycaminose. Hydrogenation gave an alcohol only under vigorous conditions. Further oxidation proceeded much more slowly, as would be expected for the cleavage of $CHOH-CHN(CH_3)_2$ (10, 15). Mycaminose eventually consumed 4 moles of periodic acid.

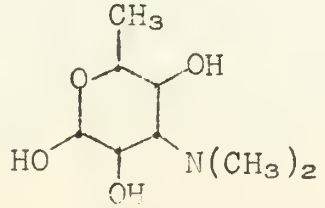
Since mycaminose liberated formic acid and a dimethylaminopentose with periodic acid and showed an acetal linkage by the qualitative analysis, it had to have a terminal -CHOH-CHO group common to C_1 and C_2 of formulas V and VI. The formation of iodoform with potassium hypoiodite and acetaldehyde with periodate indicated the presence of a $CHOH-CH_3$ group at C_5 and C_6.

	1 CHO	1 CHO	
CHO	2 CHOH	2 CHOH	CHO
$CHN(CH_3)_2$	3 $CHN(CH_3)_2$	3 CHOH	CHOH
CHOH	4 CHOH	4 $CHN(CH_3)_2$	$CHN(CH_3)_2$
CHOH	5 CHOH	5 CHOH	CHOH
CH_3	6 CH_3	6 CH_3	CH_3
Va	V	VI	VIa

Mycaminose may have the structure V or VI and the corresponding seven carbon sugar Va or VIa. It is known, however, that β-aminocarbonyl compounds are unstable to alkali. Therefore, if mycaminose has structure V, it should lose dimethylamine more rapidly than its derived pentose. If it has a δ-aminoaldehyde structure (VI), the pentose should lose dimethylamine more rapidly than mycaminose. Methyl mycaminoside did not liberate dimethylamine when treated with alkali since the proton removal necessary for β-elimination will not occur. Therefore, it can be shown that mycaminose has structure V.

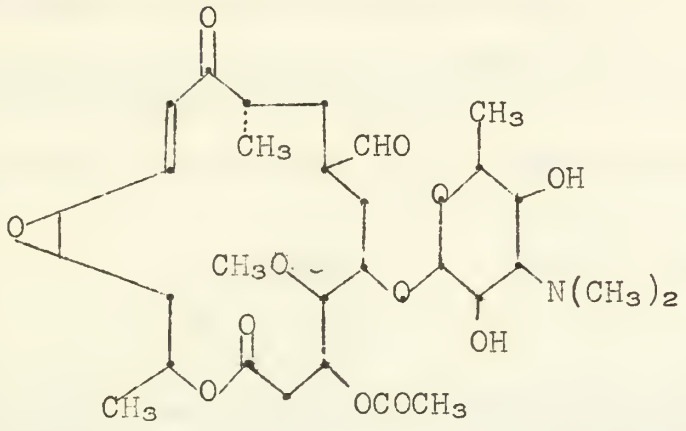
The pyranose ring structure in VII was deduced by analogy to the aminosugar desosamine obtained from erythromycin (10). Desosamine differs from mycaminose only in the lack of a hydroxyl group at position 4, which renders it unable to form a furanose ring.

VII



CARIMBOSE

The products of the methanolysis of magnamycin were mycarose and a crystalline base, carimbose (VIII).

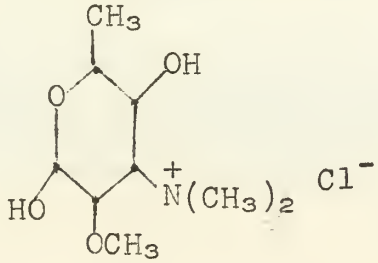


VIII

Mycaminose was obtained from carimbose only after vigorous acid hydrolysis. During this hydrolysis the real nucleus of carimbose was completely destroyed. This acid instability of the carimbose nucleus made the isolation of higher order derivatives of magnamycin and carimbose impossible. First it will be shown how mycaminose and mycarose are combined in the molecule and subsequently how the structure of the entire magnamycin molecule was determined.

THE COMBINATION OF MYCAMINOSE AND MYCAROSE (1)

Carimbose is a stronger base (pKa'-8.3) than mycaminose (pKa=7.0). This fact suggests that one hydroxyl group near the amine function carries the acetal group of the mycarose unit since the acetal group is electron-withdrawing and would tend to reduce the basicity. The same conclusion is reached by considering the effects of acetylation on the basicity of magnamycin and carimbose. Acetylation of magnamycin lowered the pKa' from 7.0 to 6.0., while the acetylation of carimbose lowered the pKa' from 8.3 to 5.4. This is reconcilable also by the presence of one hydroxyl group in the vicinity of the amine in magnamycin, with two such groups near the amine function in carimbose. In order to establish which of the two hydroxyl groups is connected to the mycarose unit, magnamycin was completely reduced and methylated with Ag_2O and CH_3I in DMF. When the methylated material was hydrolyzed, O-methylmycaminose methochloride (IX) was obtained.



IX

This structure was identified since acetaldehyde was one of the products of periodate oxidation. Therefore the mycarose entity must be joined at C -4.

THE STRUCTURE OF THE MAGNAMYCIN NUCLEUS (1)

In the light of previous evidence magnamycin can now be formulated as $C_{22}H_{31}O_8$-O- sugars.

The functions of the eight oxygen atoms may be formulated as follows.

1, 2 and 3. CH_3-O- and $CH_3\overset{O}{\overset{\|}{C}}O$-

4. CHO

The fact that magnamycin formed an oxime, a semicarbazone, a dimethyl acetal, and shows an infrared maximum at 2700 cm^{-1} indicated that an aldehyde group may be present

5 and 6. $\overset{O}{\diagdown\diagup}C-C-CH=CH-\overset{O}{\overset{\|}{C}}-$

The ultraviolet spectrum of magnamycin is characteristic of an α, β unsaturated carbonyl system. The intense absorption disappeared after catalytic reduction of the double bond or $NaBH_4$ reduction of the ketone. When magnamycin was treated with potassium iodide in glacial acetic acid, iodine was evolved and a new ultraviolet absorption maximum at 278 mμ was observed. This band is indicative of an α, β, γ, δ- unsaturated carbonyl system (X).

$$\diagdown C=C-C=C-\overset{O}{\overset{\|}{C}}-$$

X

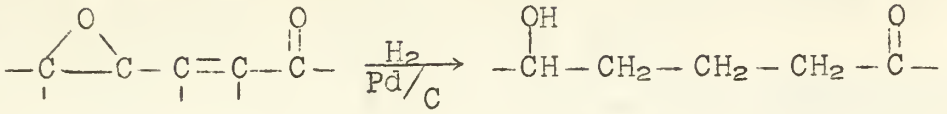
This reaction product differed from magnamycin in stoichiometry by only one oxygen atom and was identical with magnamycin B. The presence of the ethylene oxide group was shown by the fact that nitric acid oxidation of magnamycin gave ethylene oxide-<u>cis</u>-dicarboxylic acid (XI).

$$HOOC-\underset{H}{C}-\overset{O}{\diagup\diagdown}-\underset{H}{C}-COOH$$

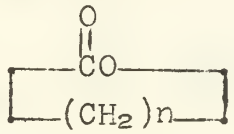
XI

This is the first known case of an epoxide group in an antibiotic. Hydrogenation of magnamycin and carimbose converted both of these substances into their tetrahydro derivatives, and all attempts to isolate an intermediate product failed. This catalytic

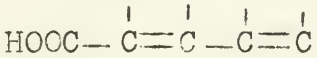
hydrogenation can be shown to proceed in the following way.



Later it was found that tetrahydrocarimbose formed a triacetate while carimbose formed only a diacetate.

7 and 8 

If the tetrahydro derivative was further reduced by hydrogen over platinum in glacial acetic acid, the aldehyde was reduced and the corresponding hexahydro compound was obtained. Further reduction with $NaBH_4$ yielded an octahydro compound which liberated dimethylamine on treatment with strong base. A new ultraviolet band was observed at 265 mμ which is shifted to longer wave lengths by increased pH. This shift indicates the presence of an α, β, γ, δ- unsaturated acid system XII

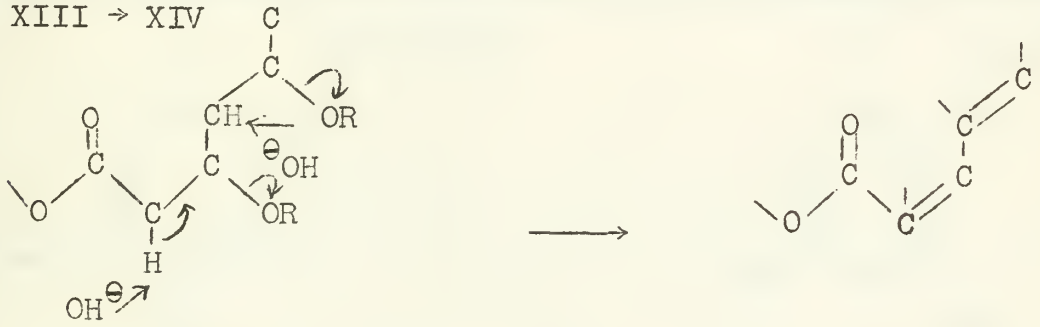


XII

The only way an acid of this type could have resulted is from the cleavage of a lactone ring.

In order to allow base-catalyzed removal of a neighboring proton which in turn leads to the formation of a conjugated double bond system and ultimately leads to the elimination of dimethylamine, the following conditions must be observed.

XIII → XIV

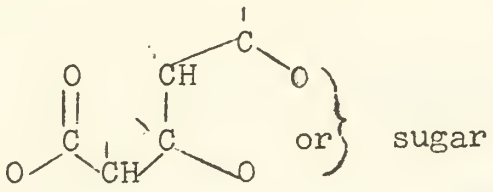


XIII XIV

The substance which was obtained by the reduction of octahydro magnamycin by $LiAlH_4$ was completely stable to base. On the basis of the preceeding discussion, it should be pointed out that it is

necessary to place two of the oxygen functions at positions 3 and 5 in relation to the carbonyl group. Since dimethylamine is eliminated, the glycoside entity should be placed at one of these positions and the acetate group at the other.

At this point we may write the fragmentary partial structure XV.



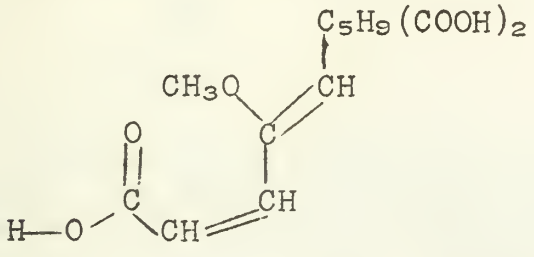
XV

When magnamycin, magnamycin B and the corresponding carimboses were oxidized by periodic acid after treatment with cold, dilute $KMnO_4$ and then submitted to treatment with strong base, a methoxy acid ($C_{13}H_{18}O_7$) was obtained. The ultraviolet spectrum was characteristic of an α, β, γ, δ-unsaturated acid system. (265 mμ ε max 25,900)

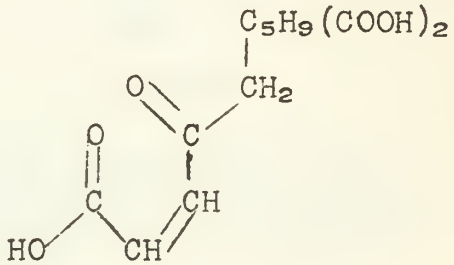
Treatment of the methoxy acid with dilute acid converted it into a new acid ($C_{12}H_{16}O_7$), the spectra and chemical properties of which indicated the presence of an α β-unsaturated acid system. (222 mμ, ε 1200)

The C_{13} acid was converted into a saturated tribasic C_8 acid by ozonization followed by oxidation with peroxide. The same C_8 acid was formed from the C_{12} acid by boiling nitric acid. A C_9 tricarboxylic acid was formed from the C_{12} acid by oxidation with permanganate and periodate.

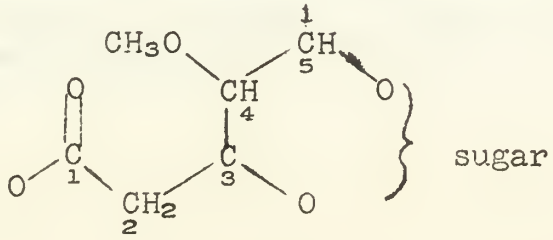
Now the C_{13} and C_{12} acids can be written as XVI and XVII, and the partial structure of magnamycin can be expanded to XVIII.



XVI

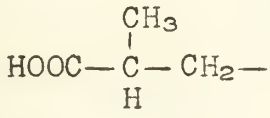


XVII



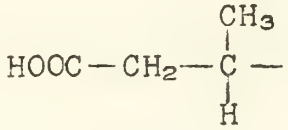
XVIII

The elimination of the oxygen atoms at C3 and C5 proceeds exactly as before (XIII). A small amount of L-(-) methylsuccinic acid is formed along with the C_8 acid upon nitric acid oxidation of the C_{12} acid XVII. This evidence shows the presence of the structural elements XIX and XX in the C_8 acid, the structure of which can be written as XXI or XXII.

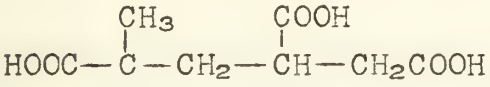


XIX

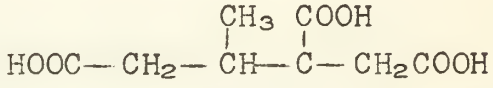
or



XX



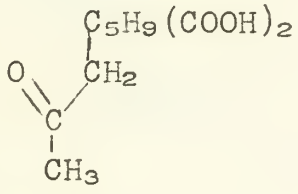
XXI



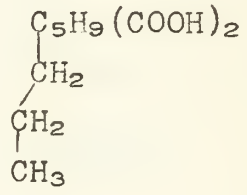
XXII

The correctness of structure XXI was determined on the basis of its preparation by a reaction between ethyl itaconate and methyl malonic ester.

The carboxylic acid which results from the cleavage of the α,β-unsaturated system of the C_{13} acid (XVI) was found by causing the C_{12} acid to react with potassium hydroxide. The resultant CH_3CO- system (XXIII) gave a positive iodoform test with hypoiodite and the acid formed was exactly the same as the one formed by direct permangante and periodate oxidation of the C_{12} acid.



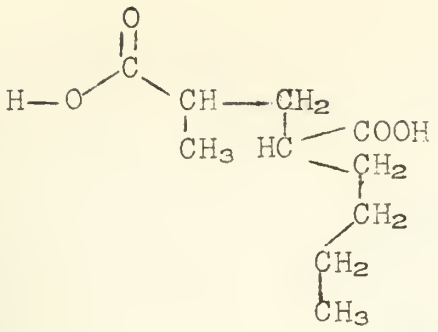
XXIII



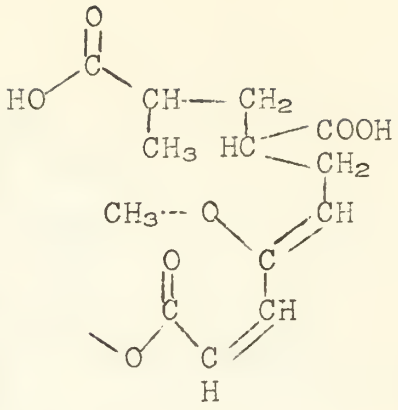
XXIV

Wolff-Kishner reduction of XXIII gave a dicarboxylic acid (XXIV). The dicarboxylic acid was identical with an α, α'-disubstituted glutaric acid which could be converted into a normal glutaric anhydride under vigorous conditions.

The dibasic acid can be written as XXV and the C_{13} acid (XVI) can now be expanded to XXVI.

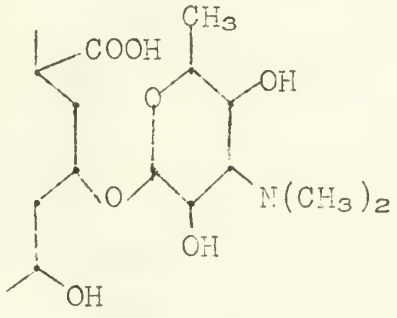


XXV



XXVI

The carbonyl group which is associated with the aldehyde can be found by first converting carimbose into its dimethyl acetal and reducing the entire molecule with $LiAlH_4$. If the acetal is hydrolyzed and then oxidized by peroxide, an acid (XXVII) is formed which shows amphoteric properties, but will not form a 5- membered lactone.

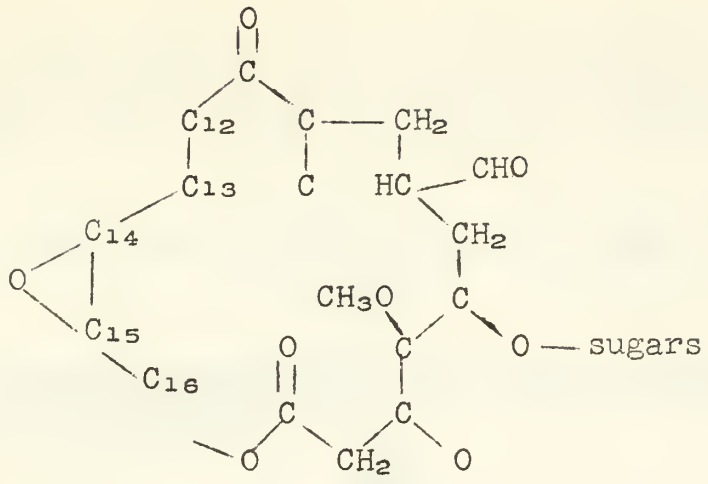


XXVII

XXVIII

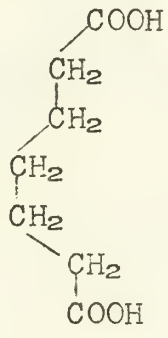
When XXVII was subjected to strong hydrolysis to remove the mycaminose unit a 5-membered lactone was formed (XXVIII).

These results show that the aldehyde must be placed at C-7, the glycoside portion at C-5, and the acetyl group at C-3. (see XIII). The partial structure of magnamycin can be written as XXIX.

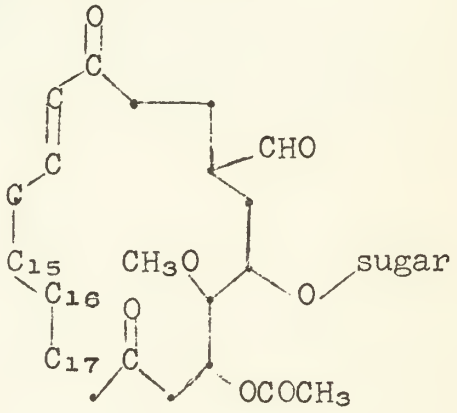


XXIX

When tetrahydro magnamycin B was oxidized with boiling nitric acid, pimelic acid (XXX) was one of the products. This showed that magnamycin B possesses a fragment of five methylene groups, and the structure of magnamycin B may be formulated as XXXI.



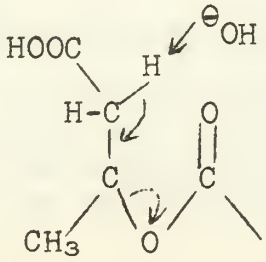
XXX



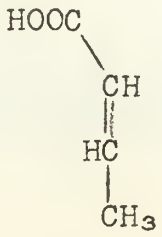
XXXI

Nitric acid oxidation of tetrahydro magnamycin yielded glutaric acid, showing that cleavage occurred at C-15.

These results showed that carbon atom 17 may be attached to the oxygen atom of the lactone ring. In addition, it was found that crotonic acid (XXXIII) was formed during the oxidation of both magnamycin and magnamycin B. The first oxidation product XXXII underwent β-elimination of the acyloxy group to form crotonic acid.



XXXII



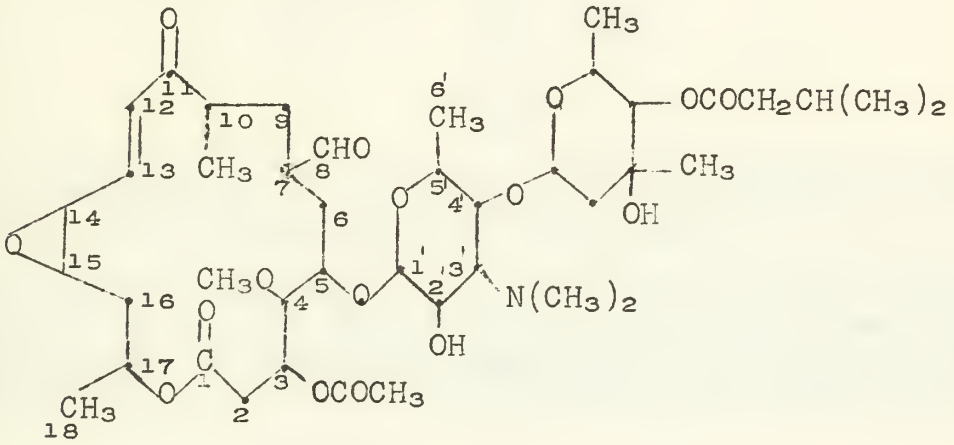
XXXIII

In order to confirm the system of seven methylene groups, tetrahydromagnamycin B was converted to its enol acetate and ozonized. Treatment with potassium iodide was followed by reduction with zinc and acetic acid. The product obtained was n-caprylic acid (XXXIV).

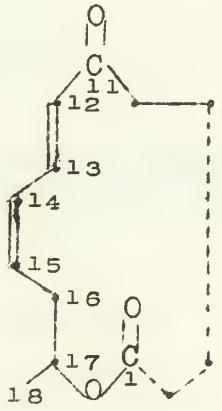
$$CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-COOH$$

XXXIV

The final structure of magnamycin can now be formulated as XXXV and magnamycin B as XXXVa



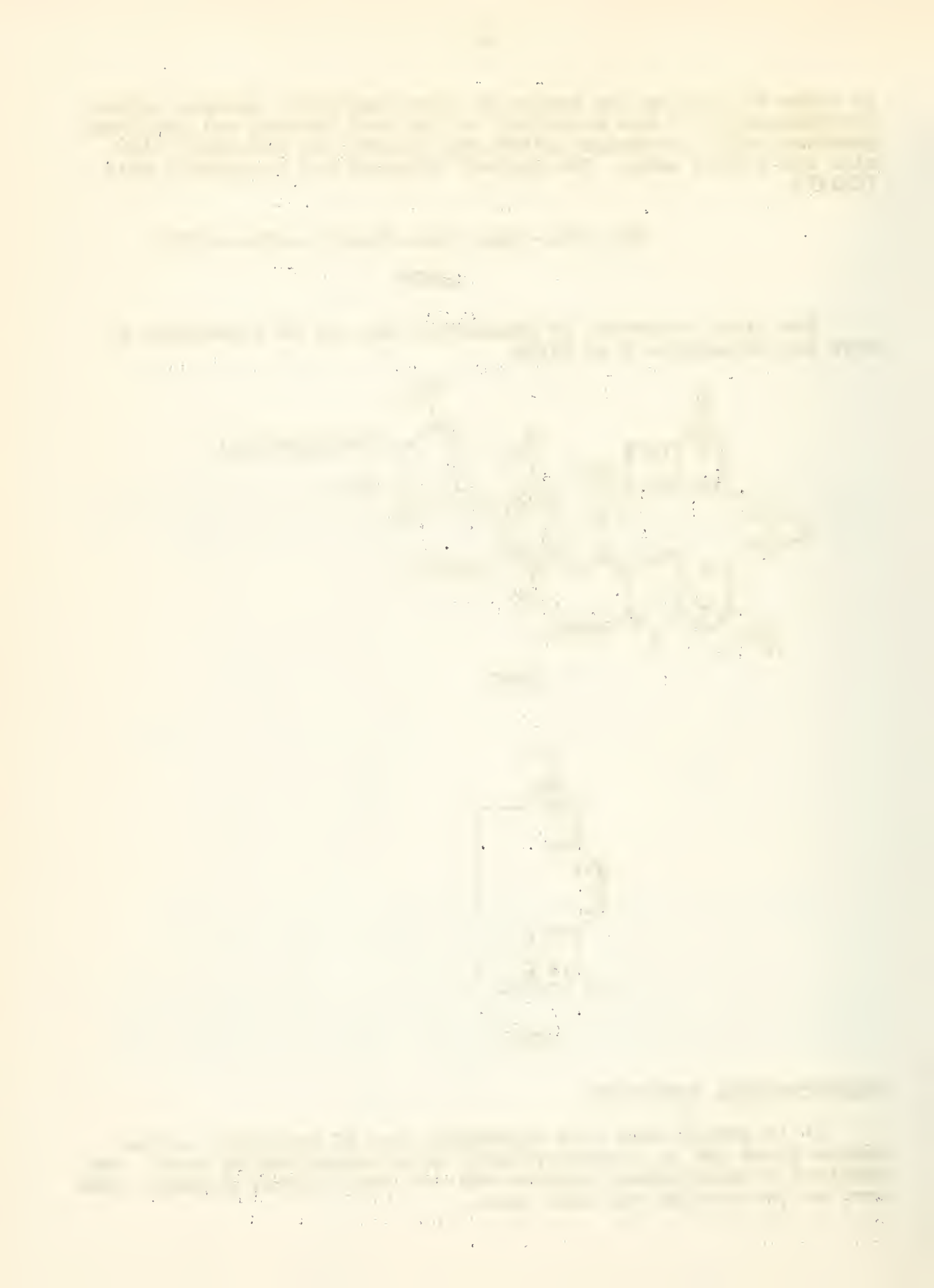
XXXV



XXXVa

STEREOCHEMICAL STRUCTURE

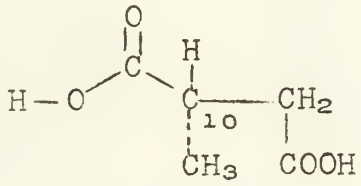
It is easily seen that magnamycin has 17 optically active carbon atoms and an unsymmetrically substituted double bond. The complete stereochemical problem has not been solved; however, some work on the problem has been done.



The presence of an infrared band at 920 cm^{-1} which disappeared upon saturation of the double bond showed that the substituents on the double bond are in trans position.

The isolation of ethylene oxide-cis-dicarboxylic acid (XI) showed that the hydrogens are in cis-position on the epoxide ring.

The isolation of L-(-) methylsuccinic acid from the nitric acid oxidation of magnamycin showed that the configuration may be written as XXXVI.



XXXVI

The configurations in magnamycin as formulated in XXXVI are all relative to this configuration at C-10.

The steric arrangement of all the atoms in the mycaminose ring aside from that at C-5' can be derived by means of an exhaustive treatment of the basicity relations between magnamycin and its various derivatives. The known data are summarized below.

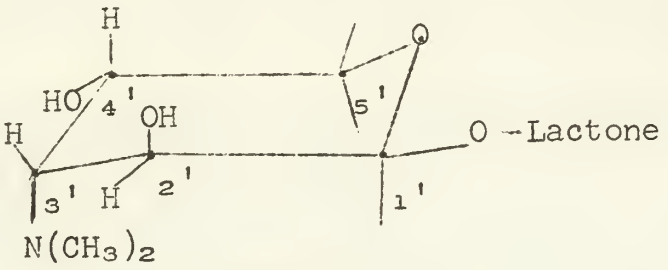
	pKa'
Magnamycin	7.0
Acetyl Magnamycin	6.0
Carimbose	8.3
Diacetyl Carimbose	5.4

An arrangement of the figures shows that the effect upon the basic nitrogen atom by acylation of one of the hydroxyl groups is much greater than the other.

C-2'- OH ⟶ C-2'-OAc	$\triangle$pKa = -1.0
C-4'- OH ⟶ C-4'-OAc	$\triangle$pKa = -1.9
C-4'- OH ⟶ C-4'-O Mycarose	$\triangle$pKa = -1.3

The basicity of the amine group was reduced more by the weak electron attracting mycarose unit at C_4' than by the stronger acetyl group at C2'. These observations show that the oxygen atom at C-4' lies nearer to the dimethylamino group than the one at C-2'.

The dimethylamino group must be placed in an axial position since it would be equidistant from both C-4' and C-2' if it were equatorial. The large lactone nucleus must be placed in an equatorial position. If the oxygen atom at C-4' were attached in a position cis to the dimethylamine group, and the oxygen atom at C-2' in a position trans the structure may be shown as XXXVII.



XXXVII

As additional evidence for the stereochemistry of the group at C-4' it was found that carimbose was converted into an amine oxide by potassium periodate while magnamycin was unaffected under the same conditions. The reaction must involve a pseudo cyclic mechanism with the hydroxyl group at C-4', since the hydroxyl group at C-2' is too far removed from the amine to assist in this reaction. The formation of a similar amine oxide with periodate was reported (10) by E. H. Flynn and coworkers in their investigation of erythromycin.

BIBLIOGRAPHY

1. R. B. Woodward, Angew. Chem, 68, 50 (1957).
2. F. W. Tanner, A. R. English, T. M. Lees, and J. B. Poutien, Antibiotics and Chemotherapy, 2, 441 (1952).
3. J. D. Dutcher, J. Vandeputte, S. Fox and L. J. Heuser, Antibiotics and Chemotherapy, 3, 910 (1953).
4. R. L. Wagner, F. A. Hochstein, Kotaro Murai, N. Messina and P. P. Regna, J. Am. Chem. Soc., 75, 4684 (1953).
5. P. P. Regna, F. A. Hochstein, R. L. Wagner, Jr., R. B. Woodward, J. Am. Chem. Soc., 75, 4625 (1953).
6. F. A. Hochstein and Kotaro Murai, J. Am. Chem. Soc., 76, 5080 (1954).
7. F. A. Hochstein and P. P. Regna, J. Am. Chem. Soc., 77, 3353 (1955
8. R. Corbaz, L. Ettlinger, E. Gavmann, W. Keller-Schierlein, L. Niepp, V. Prelog, P. Reusser, and H. Zahner, Helv. Chim. Acta, 38, 1202 (1955).
9. L. Claisen and N. Stylos, Ber., 21, 1145 (1888).
10. E. H. Flynn, M. V. Sigal, P. F. Wiley, and Koert Gerzon, J. Am. Chem. Soc., 76, 3121 (1954).
11. A. G. Gillam and E. S. Stern, Electronic Absorption Spectroscopy, Edward Arnold Ltd., London 1954, pp. 62-8.
12. R. B. Woodward, J. Am. Chem. Soc., 63, 1123 (1941).
13. A. E. Gillam and L. K. Evans, J. Chem. Soc., 1943, 565.
14. M. T. Rogers, J. Am. Chem. Soc., 69, 2544 (1947).
15. Organic Reactions, Vol. II, ed. Roger Adams, John Wiley and Sons Inc., New York p. 343.

STRUCTURES AND CONFIGURATIONS OF SOME TETRACYCLIC TRITERPENES

Reported by Peter Woo April 15, 1957

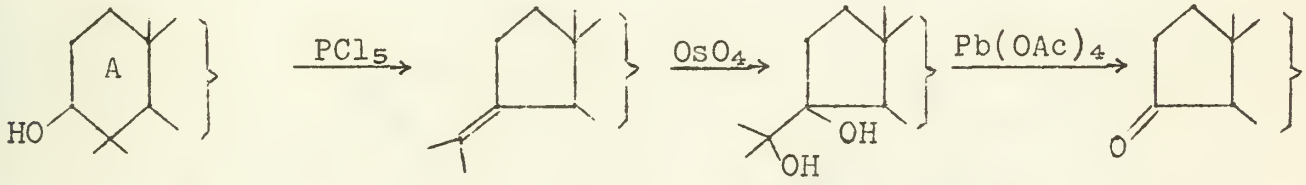
Tetracyclic triterpenes are widely distributed in nature. They occur in higher plants, fungi, and in animal sources. Intensive investigation of this group of compounds was begun about six years ago, resulting in the elucidation of more than twenty structures, the formulas of some of which are listed on page 98 and page 99.

With the exception of onocerin IX, the tetracyclic triterpenes can be divided into the lanosterol I and euphol III subgroups, based on their stereochemistry at the C/D ring junction. It is impossible to deal here with everyone of these compounds. However, these compounds undergo many similar reactions, and in the structural and configurational determinations members in each subgroup could often be related to each other by formation of identical derivatives. Therefore, among the works done before 1955, only one representative from each subgroup, lanosterol and euphol, will be treated in this seminar. The rest of the seminar will be a brief review of the more recent work. There are two detail review articles on the work done before 1955. (1, 2) The biogenesis (3, 4) of these terpenes will also not be treated here.

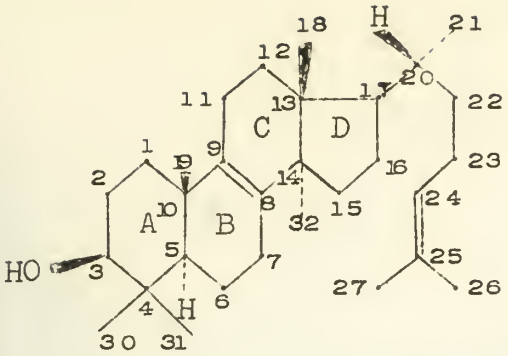
LANOSTEROL

Lanosterol I, $C_{30}H_{50}O$, is obtained from sheep wool-wax, which contains 10% of lanosterol-dihydrolanosterol mixture. Early work (5, 6) found the presence of one secondary hydroxyl group, two double bonds, only one of which could be hydrogenated. There is an isopropylidene group, because oxidative fission gave acetone. Selenium dehydrogenation gave mainly 1,2,8-trimethylphenanthrene XVIII (6). This reaction was subsequently found to be typical of the tetracyclic group. The pentacyclic group gives picene and naphthalene derivatives on selenium dehydrogenation.

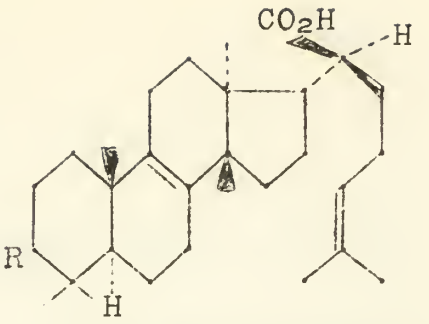
Ruzicka (7) found that the hydroxyl group is situated in a terminal ring and adjacent to a carbon carrying a gem-dimethyl group by the following reactions, which had been previously applied to the pentacyclic triterpenes.



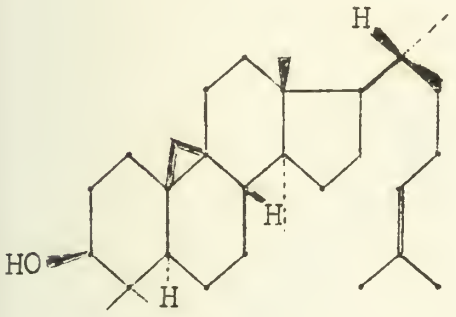
This reaction sequence was also employed for other tetracyclic triterpenes. It is now known that the ring contraction requires a equatorial hydroxyl group, while and axial hydroxyl group would lead to a cyclohexene derivative, because the geometric condition of "four centers in a plane" is necessary for facile elimination (8).



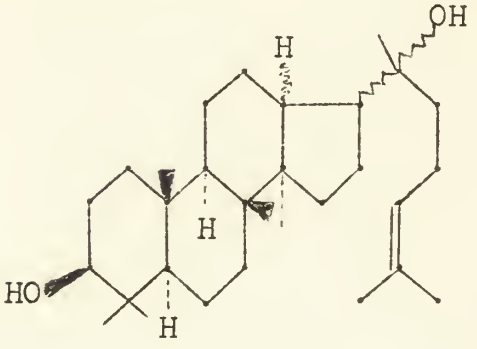
I. lanosterol



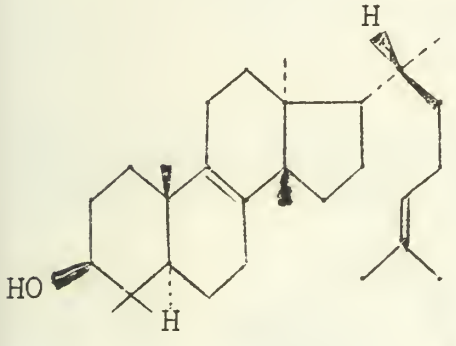
R=O elemonic acid
R=β-OH epielemolic acid
R=α-OH elemolic acid



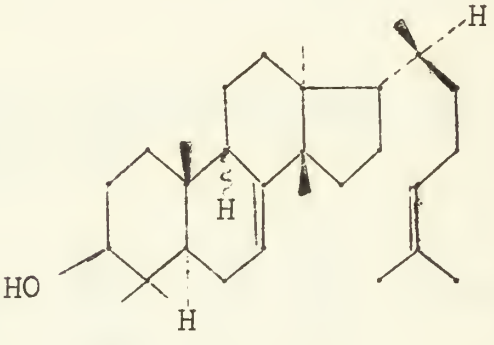
II. cycloartenol



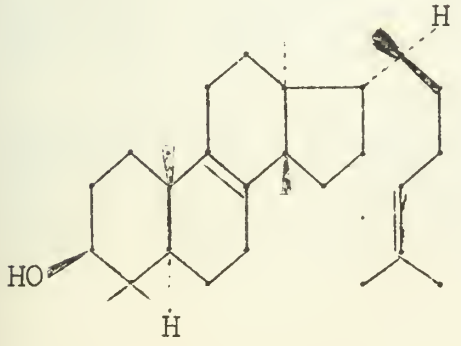
VI. dammarendiol



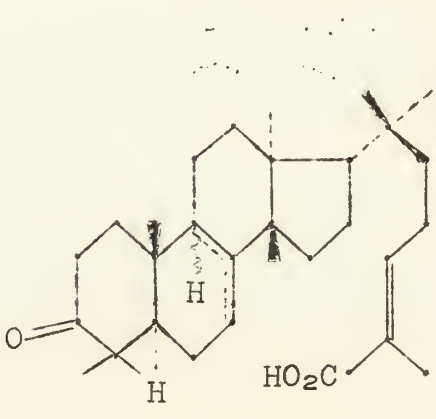
III. euphol



VII. butyrospermol

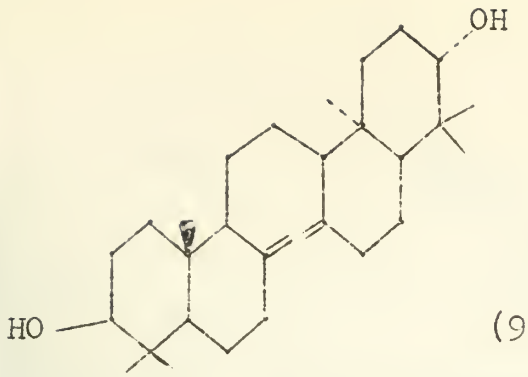


IV. tirucallol



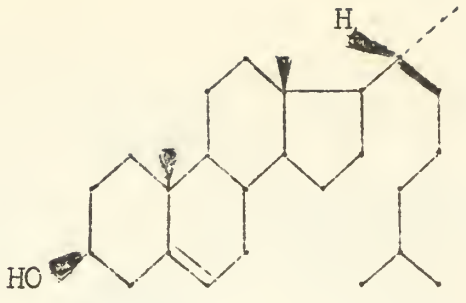
VIII a masticadienonic acid Δ^{7}

VIII b isomasticadienonic acid Δ^{8}



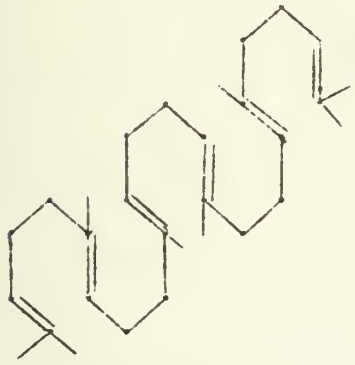
(9)

IX. α-onoceradienediol



(10)

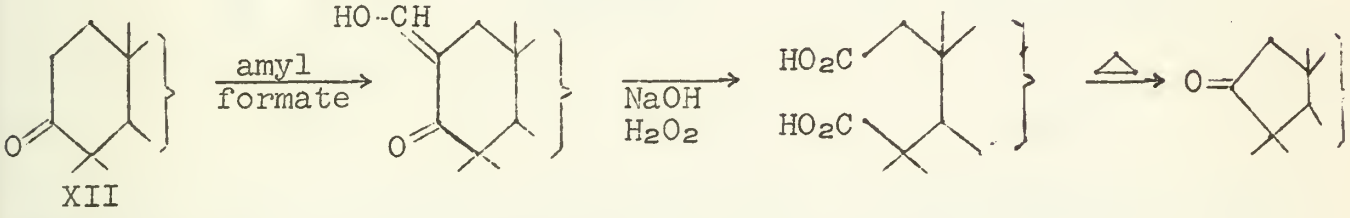
XI. cholesterol
(steroid)



(11)

X squalene
(acyclic triterpene)

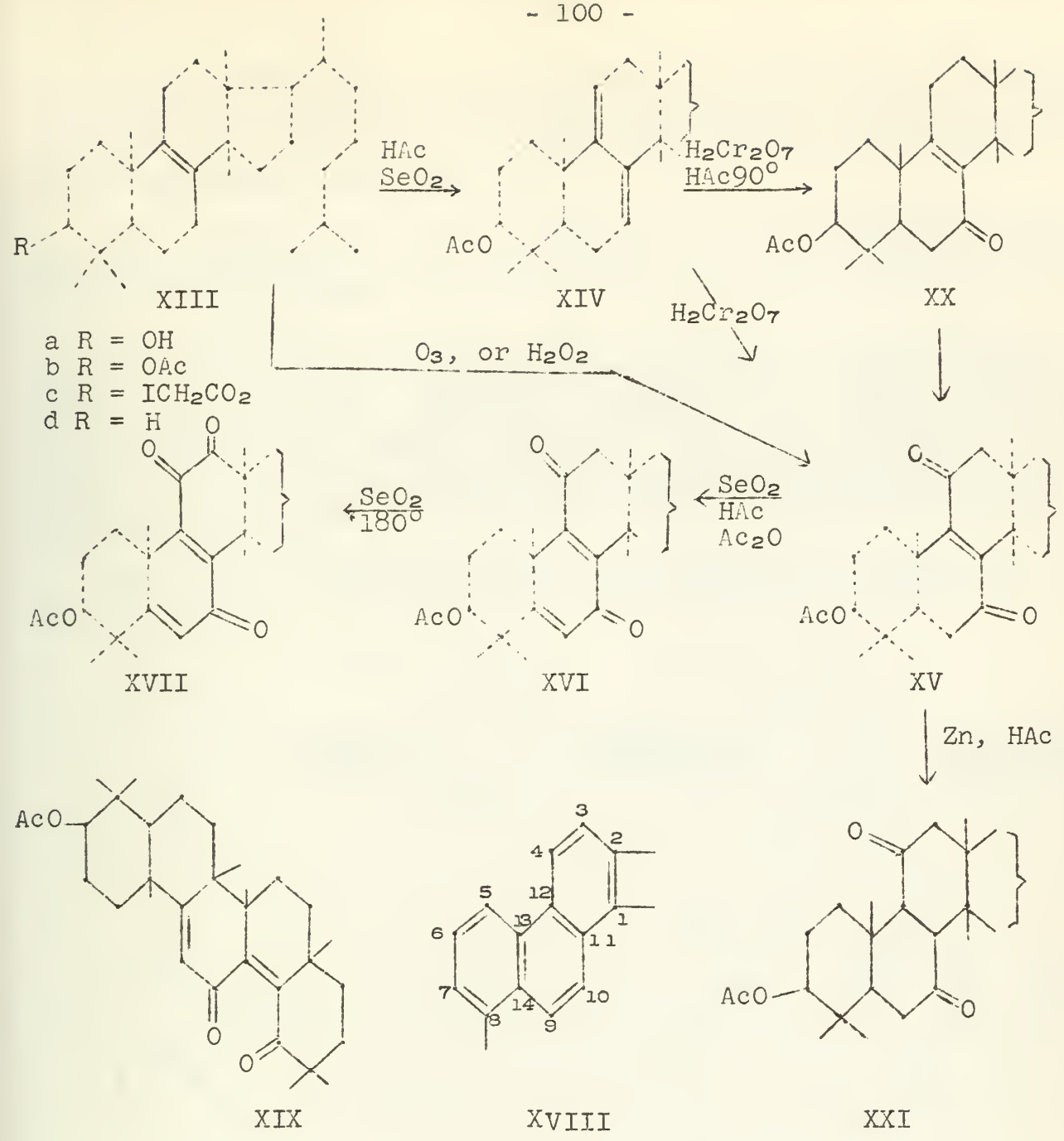
The hydroxyl group is also adjacent to a methylene group, for lanostenone XII condenses with amyl formate (6).



XII

Based on the above evidence and the spectroscopic and chemical studies of a series of oxidation products (XIII to XVII), Ruzicka correctly deduced the structure of ring A, B, C, and the location of the inert double bond in dihydrolanosterol (12).

The absence of infrared absorption for double bond in dihydrolanosterol XIII a indicates that it is tetrasubstituted. Oxidation of XIII to XIV involves an allylic shift. Compound XIV had λmax. 243 mμ, log e 4.2, typical of a conjugated diene distributed over two rings. Infrared has δ-(CH)-frequency of grouping -CH:C< at 814 cm.$^{-1}$



and weak ν(C=C) frequency at 1602 cm.$^{-1}$. It is therefore a butadiene grouping with at least one -CH:C< group.

The yellow diketone XV is a typical oxidation product of the tetracyclic but not pentacyclic triterpenes; λ max 275 mμ, log e 3.94 indicates a ene-1,4-dione grouping. There are no infrared bands assignable to the double bond. Therefore, it was concluded that the molecule contains a central-symmetric system.

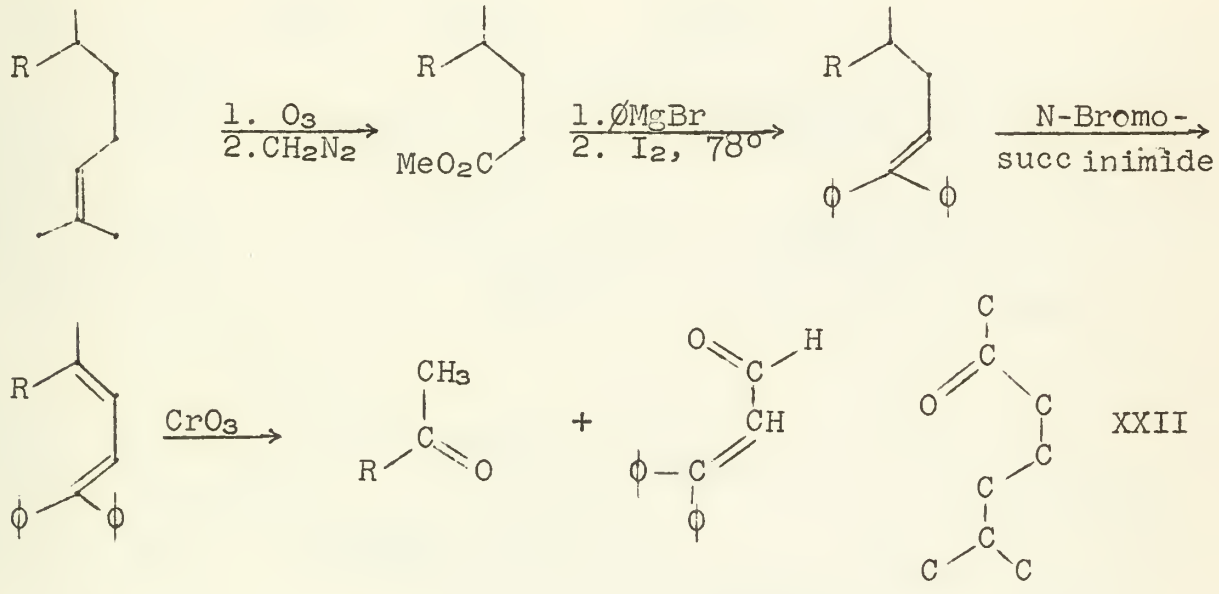
Acetoxy-lanostadiene dione XVI has λmax 275 mμ, log e 4.2. The two ketone groups are not at spatial proximity, because the compound does not form a pyridazine derivative with hydrazine. Although a diketo pentacyclic triterpene, $\Delta^{10,11,13,(18)}$-2-acetoxy-12, 19-dioxo-oleadiene (XIX) has similar ultraviolet spectrum, λmax 280 mμ, log e 4.1, it readily reacts with hydrazine.

Diene-trione XVII is an α-diketone, since it forms a dicarboxylic acid on oxidative fission with alkalinic hydrogen peronide. (Later, compound XV was reduced to the saturated diketone XXI. One of the carbonyl groups was unreactive (13). Compound XX was obtained in milder oxidation conditions (14)).

The partial structures of rings A, B, and C of lanosterol were therefore postulated. The methyl group at C_{10} was assumed by analogy with other triterpenes.

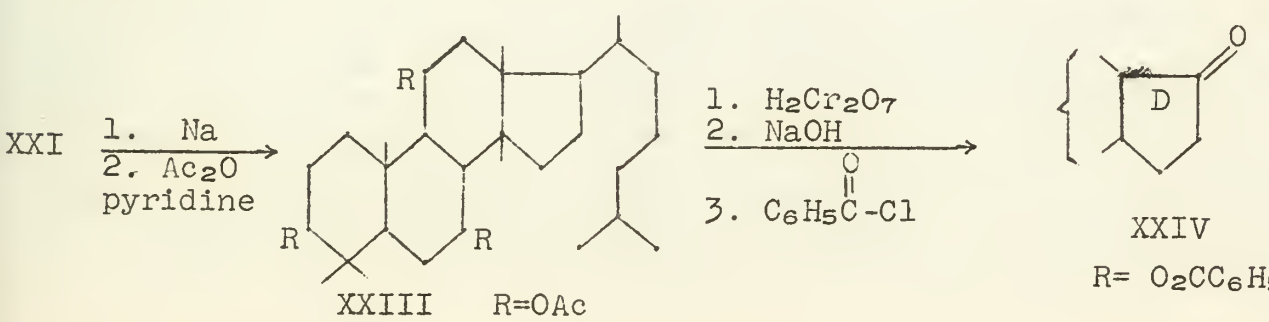
The conclusions of Ruzicka were confirmed by McGhie (15) and Barton (16). Barton also showed the presence of angular methyl groups at C_{14} and C_{13}. Lanostenyl acetate, XIII b, when treated with acid, isomerises to the Δ^7-isomer. However, in steroids the double bond migrates to the $\Delta^{8(14)}$- position. Thus the 14-position is possibly blocked by an angular methyl group. The dehydrogenation evidence (16, 17) and the failure to introduce more double bonds into XVII confirmed this.

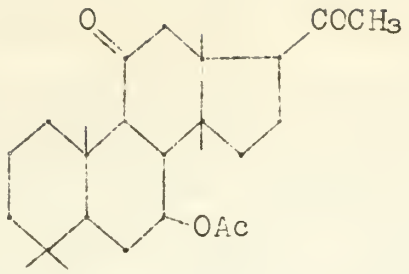
Degredation reactions showed the presence of an isooctenyl side chain (17, 18).



Barton and co-workers also isolated a small yield of 6-methyl (19) heptane-2-one, XXII, by vigorous oxidation of lanostenyl acetate, XIII

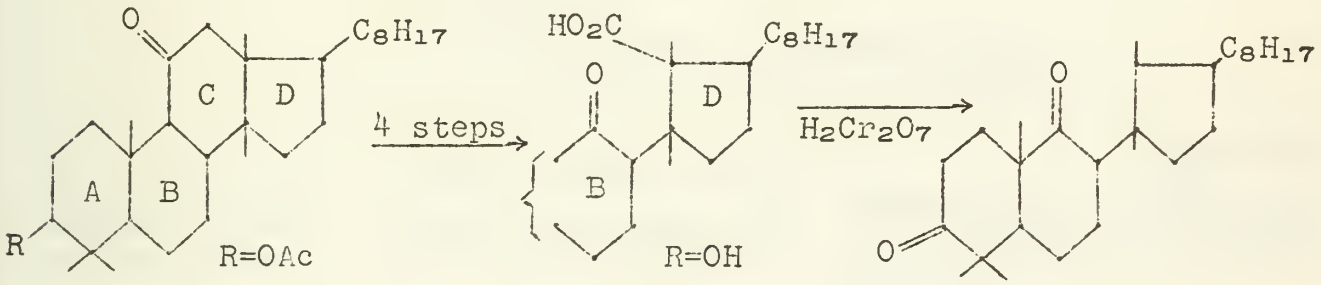
Barton (20) found that ring D is five-member by showing that the ring D ketone XXIV has infrared absorption at 1747 cm.$^{-1}$. This ketone was obtained as follows:



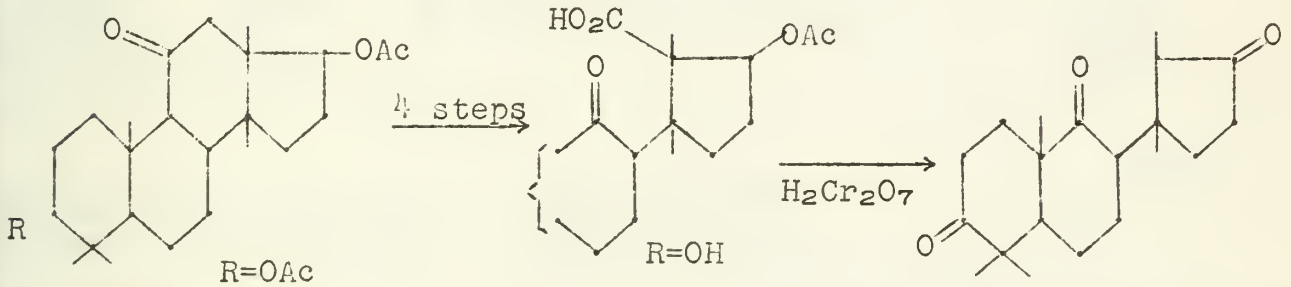


XXV

Ruzicka (21) had previously arrived at the same conclusion by infrared study of XXV. Later he also determined the location of the side chain (22, 23); 11-oxolanostanyl acetate XXVI was converted to the nor-keto carboxylic acid XXVIII, which was found to be stable. The same reaction sequence carried out on the diacetoxy ketone XXIX, however, gave the triketone XXXI. No keto acid could be isolated. The ease of decarboxylation indicates the presence of a β-keto acid intermediate. The keto group is therefore at C_{17}.



XXVI XXVII XXVIII



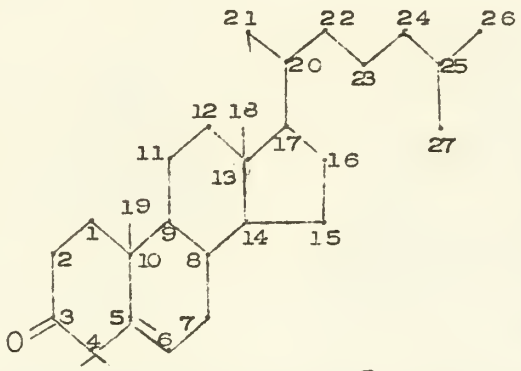
XXIX XXX XXXI

X-ray diffraction (24) of lanostenyl iodoacetate, XIII c, provided a detail structural and stereochemical description of the molecule. In addition to confirming the tetradecahydrocyclopentanophenanthrene ring system, the Δ^8-position of the inert double bond, the C-3 gem-dimethyl group, it showed the location of the side chain without ambiguity and established the configuration of the molecule. Rings A and B and C and D are trans-fused. The C_{10} and C_{13} methyls and C_3 hydroxyl are β-oriented; the C_{14} methyl, α-oriented. Biological method, (25) molecular rotational differences, (26) conformation

analysis (22, 27), and asymetric (27a) synthesis all provided additional support to this configuration.

The conversion of cholesterol XI, the configuration and structure of whichwere known, to naturally occurring dihydrolanosterol, not only represented the first total synthesis of a tetracyclic triterpene, but also provided rigorous chemicalconformation in structural and stereochemical relationship between the lanostane group and steroids (28). C_4 gem—dimethyl and C_{14} methyl groups were introduced to Δ^4 or Δ^5-cholestenone-3 to convert it to the tetracyclic triterpene as follows:

Δ^4 or Δ^5-cholestenone-3 $\xrightarrow[\text{tBuOK}]{\text{tBuOH}}$ (MeI)



$\xrightarrow[\text{4. collidine}]{\text{1. LiAlH}_4\text{ 2. acetylation 3. CCl}_4\text{, N-Br succinimide}}$

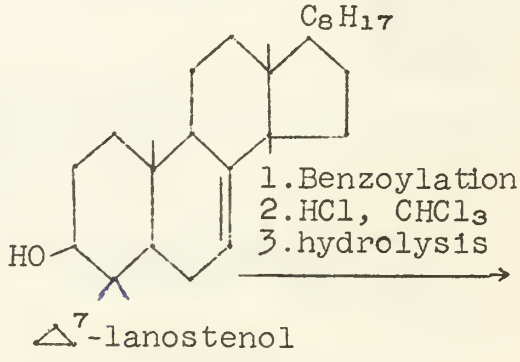
4,4-dimethyl-Δ^5-cholestenone-3

3β-acetony-4,4-dimethyl-$\Delta^{5,7}$-cholestadiene $\xrightarrow[\text{2. anhy. NH}_3\text{,MeOH,-60°}]{\text{1. HCl in CHCl}_3\text{, -40°}}$ 3β-acetoxy-4,4-dimethyl $\Delta^{7,14}$-cholestadiene $\xrightarrow[\text{2. EtOH,KOH}]{\text{1.perphthalic acid}}$

3,7,15 trihydrony $\Delta^{8(14)}$ Cholestene $\xrightarrow[\text{EtOH}]{\text{HCl}}$ 3β-hydroxy-4,4-dimethyl-15-keto $\Delta^{8(14)}$ cholestene $\xrightarrow[\text{CH}_3\text{I}]{\text{tBuOH, tBuOK}}$

3β-hydroxy-4,4-dimethyl-15-keto Δ^7 cholestene $\xrightarrow[\text{reduction}]{\text{1.benzoylation 2.Wolf-Kishner}}$

lanostenol (dihydrolanosterol) XIIIa



$\xrightarrow[\text{2.HCl, CHCl}_3\text{ 3.hydrolysis}]{\text{1.Benzoylation}}$

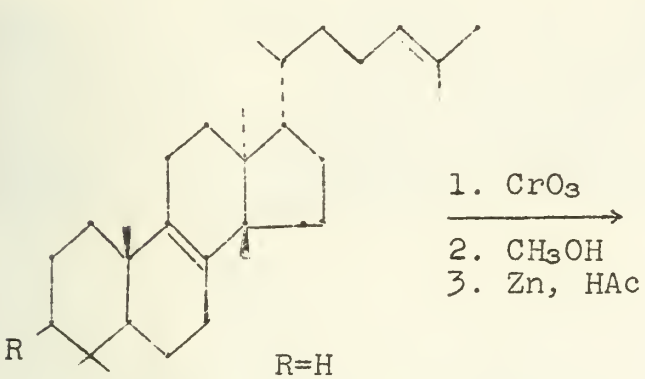
Δ^7-lanostenol

EUPHOL

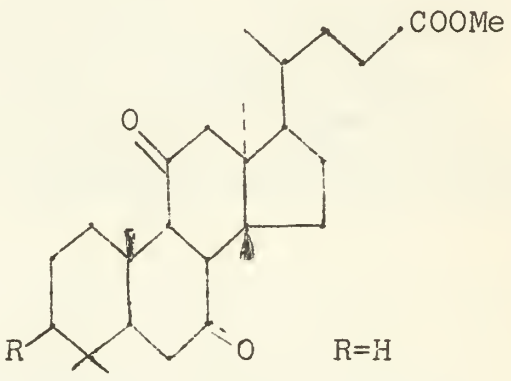
Euphol III is in many ways similar to lanosterol I. Early works (29) showed that it is a tetracyclic alcohol, $C_{30}H_{50}O$, containing two double bonds, one of which can be hydrogenated and is present in an

isopropylidene side chain. Selenium dehydrogenation yielded 1,2,8-trimethylphenanthrene XVIII as the sole product.

The presence of an isooctenyl side chain was demonstrated by oxidizing euphene XXXII to a diketo-trisnor-acid XXXIII. Then identical degredation reaction series as used for lanosterol were carried out (30).

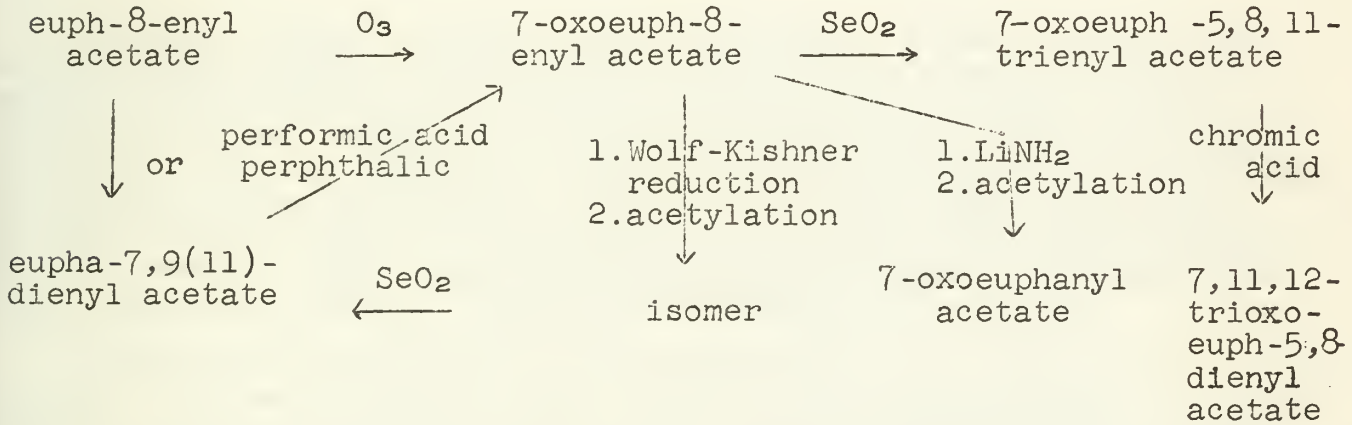


XXXII

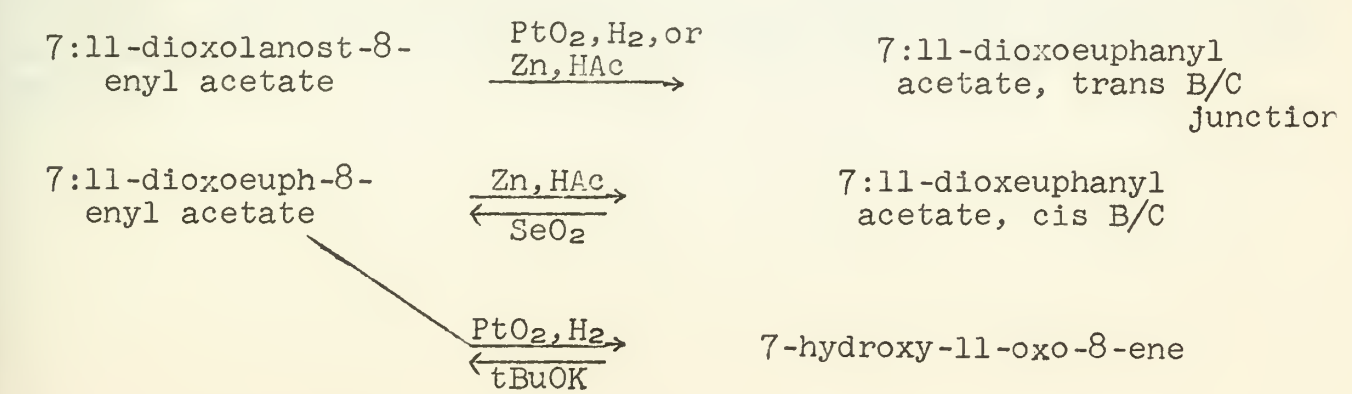


XXXIII

Euphol also undergoes the ring contraction reaction with phosphorous pentachloride. Oxidation (31) and reduction reactions parallel to those of lanosterol have been carried out on ring B and ring C, summarized as follows (32, 33).

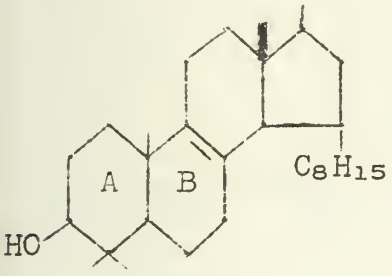


However, some reactions proceed in contrast to those in the lanostane series (32). For example,

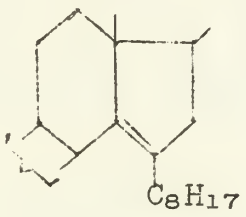


Another important difference is in their behaviors in acid-catalyzed rearrangement. While the tetrasubstituted double bond of lanost-8-enyl acetate XIIIa migrates to the trisubstituted position of lanost-7-enyl acetate, euph-8-enyl acetate rearranges to isoeuphenyl acetate, in which the double bond was found to be tetrasubstituted and exocyclic to one ring, both by ultraviolet absorption and chemical data (31,33)

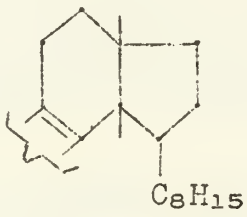
Jeger (31) postulated the structure XXXIV for euphol and XXXV for isoeuphol because isoeuphenyl acetate was oxidized to a diketone by ozonolysis or by treatment with osmium tetroxide followed by lead tetraacetate. The diketone formed a dioxime and gave a negative haloform test. However, structure XXXIV would not be expected to give 1,2,8-trimethylphenanthrene on dehydrogenation. Later, based on biogenetical consideration, Ruzicka (34) suggested XXXVI and XXXVII as euphol and isoeuphenol.



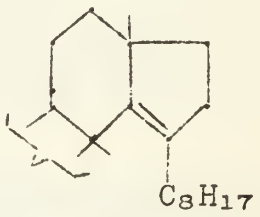
XXXIV



XXXV



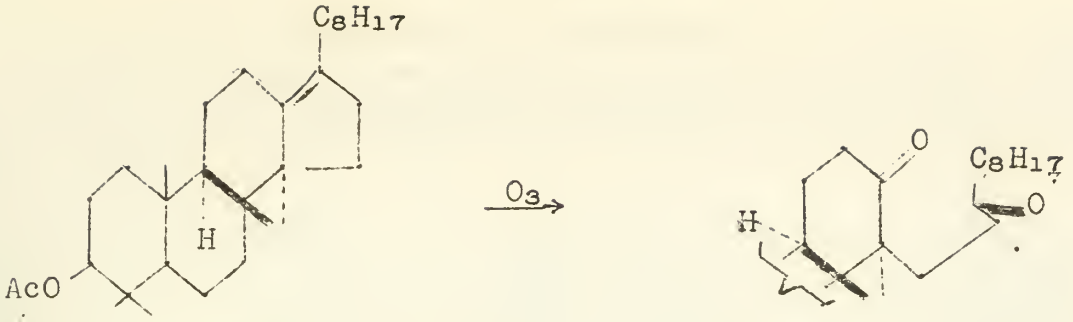
XXXVI



XXXVII

However, these structures were disproved in the light of new evidence given below. Barton (32) inferred the size of ring D from quantitative comparison of infrared absorption of euphene and lanostene XIIId. Measured at the same concentration the curves are identical near the 1380 $cm.^{-1}$ region, corresponding to the -CH bending of methyl groups. Therefore, they have the same number of methyl groups, namely, eight. After allowing for the carbon atoms in ring A, B, C and the side chain, only three carbons are left unaccounted for. Therefore, ring D cannot be more than five-membered.

Barton (32) proposed the structure XXXVIII as isoeuphenyl acetate because this was compatible with the following observations. Dehydrogenation of isoeuphadiene gives 1,2,5-trimethyl naphthalene instead of 1,2,8-trimethylphenanthrene XVIII, strongly indicating the migration of a methyl group in the rearrangement. The diketone mentioned above, obtained by ozonolysis of isoeuphadienyl acetate, took up five moles of bromine, and quantitative infrared data showed the presence of two $-CH_2-\overset{\displaystyle O}{\overset{\|}{C}}=O$ groups. Ruzicka's structure would not undergo these reactions.

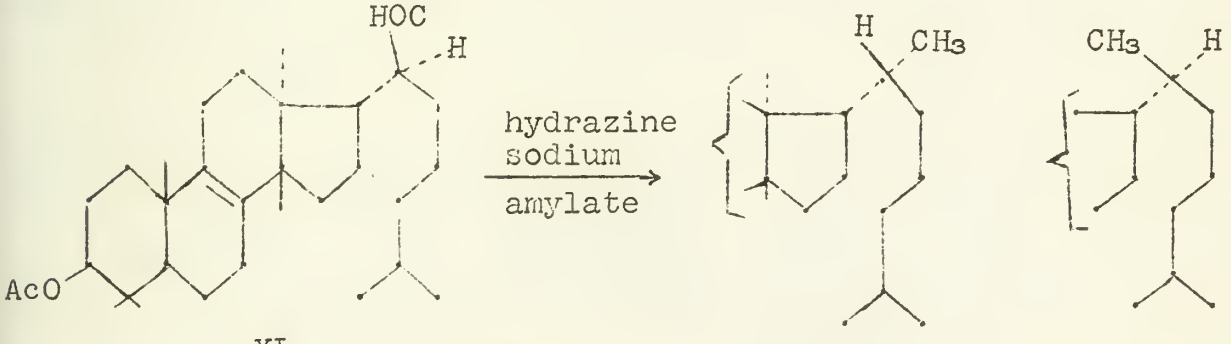


XXXVIII XXXIX

Barton suggested that euphol is 13:iso:14:iso:17 iso (?) lanosterol, and postulated the rearrangement as involving a concerted double methyl migration, each being a Wagner-Meerwein shift. The stereochemistry of the C-methyl groups at $C_{(13)}$ and $C_{(14)}$, as assigned, would force rings B and C to assume the unfavorable conformation of two helf-boats. This steric strain, after the addition of a proton at $C_{(9)}$ from the α side of the molecule, provides a "conformational driving force", causing the migration of methyl groups to give the favorable all-chair, trans-anti-trans-anti arrangement of isoeuphenol. The two methyl groups must be trans to each other if the migrations are to be concerted.

In support for the assignment of XXXVIII for the structure of isoeuphenyl acetate, Jeger and Ruzicka (35) showed that a methylene group in a six member ring is adjacent to the double bond of isoeuphenyl acetate by spectroscopic studies of its t-butyl-chromate oxidation products.

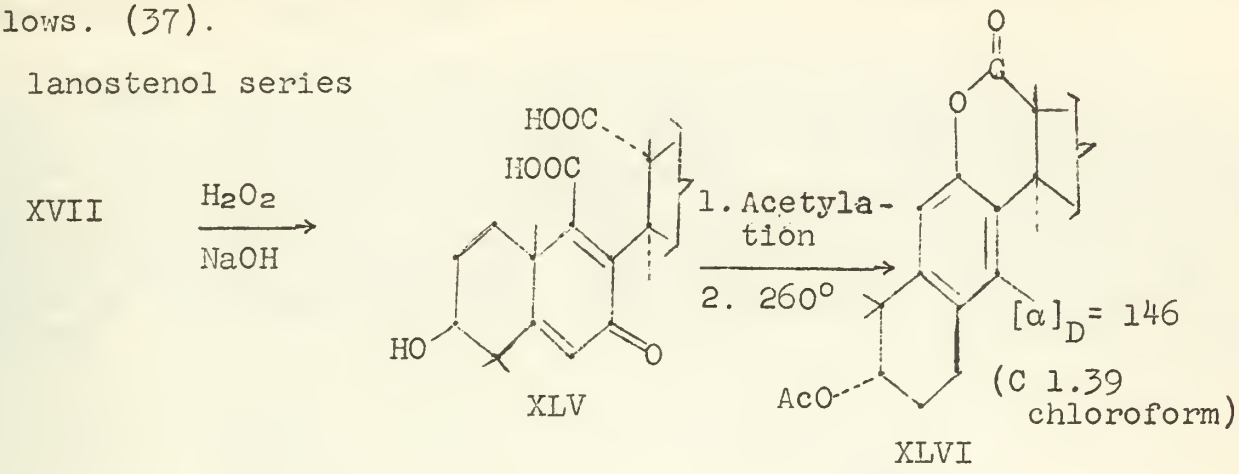
The stereochemistry at C_{17} may be inferred from indirect evidence. It has been found that tirucallol IV euphol III and elemonic acid V are interrelated. Elemonic acid has been converted to tirucallol by a series of reactions in which no inversion at the carbon centers is expected to take place (36). Also the acetate of epielemolic aldehyde XL has been reduced to tirucallenol XLII and a smal amount of euphenol XLI which must have originated from partial inversion at $C_{(20)}$ (36). Thus euphol and tirucallol have different configurations at C_{20} but the same configuration at C_{17}.



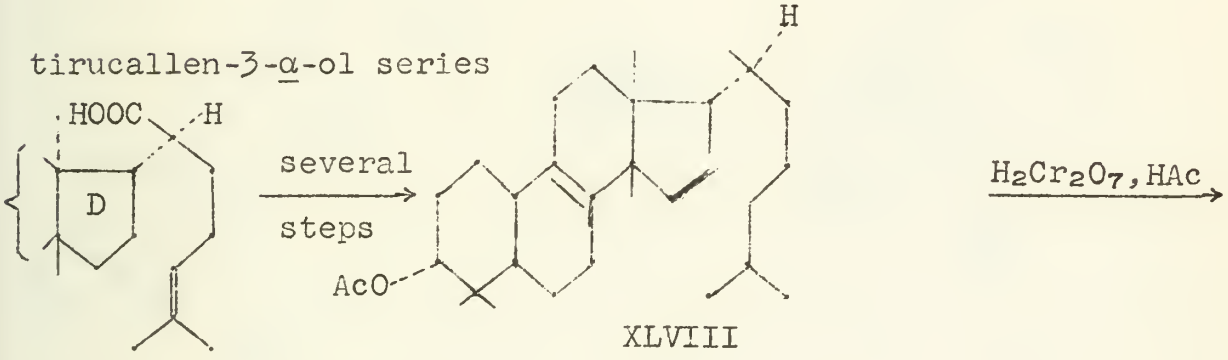
XL XLI XLII

It was later found that the configuration of $C_{(13),(14),(17),(20)}$ of tirucallol is the morror image of that in lanosterol. Therefore, euphol has a $C_{(17)}$ configuration opposite to that of lanosterol, too. The correlation of lanosterol and tirucallol was carried out as follows. (37).

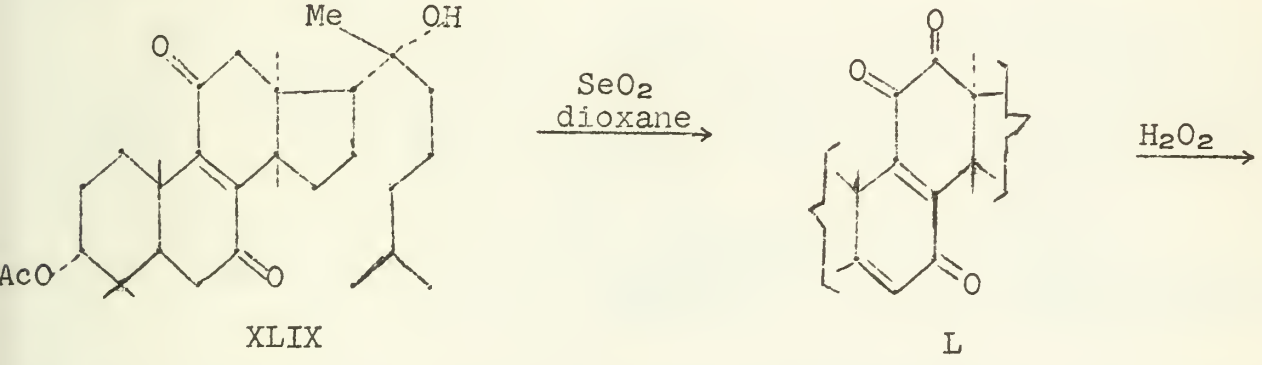
lanostenol series

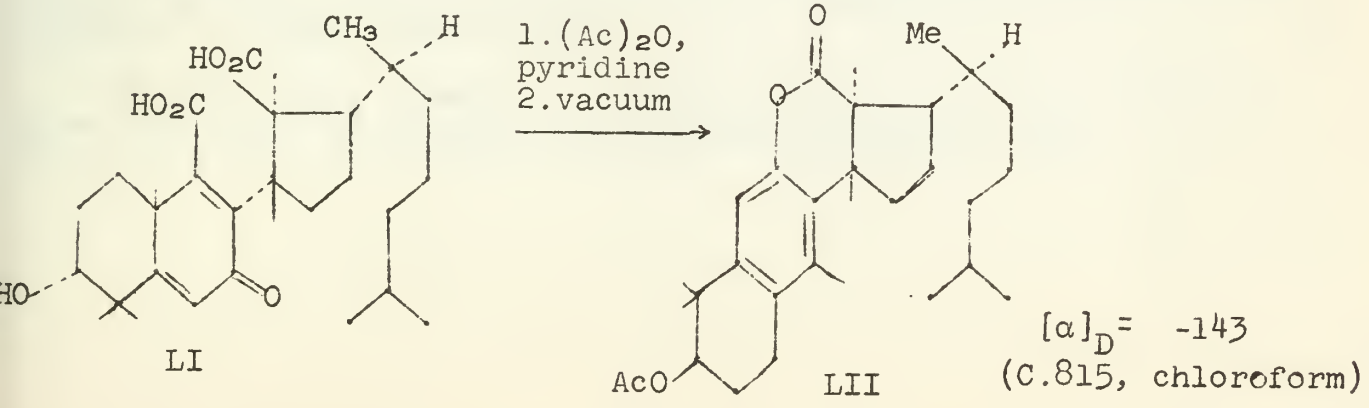


tirucallen-3-α-ol series



elemolic acid V

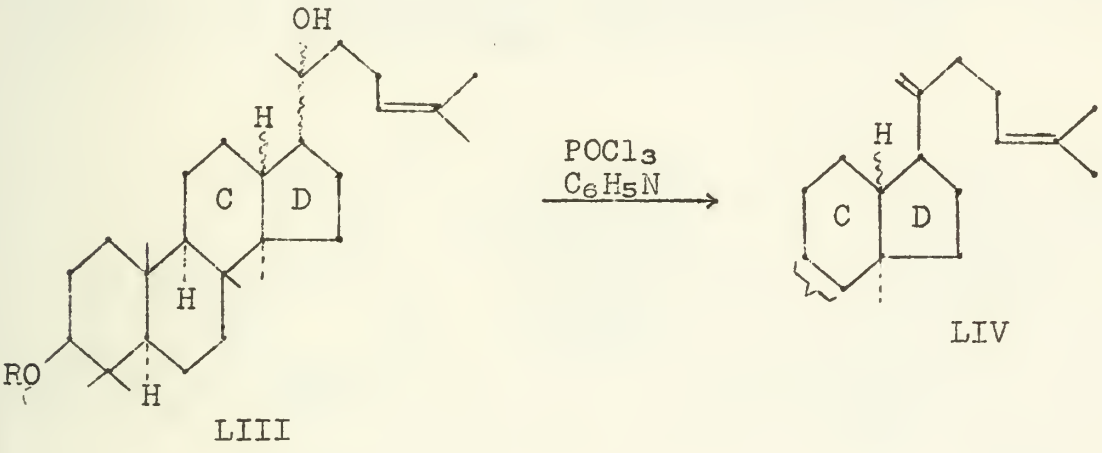


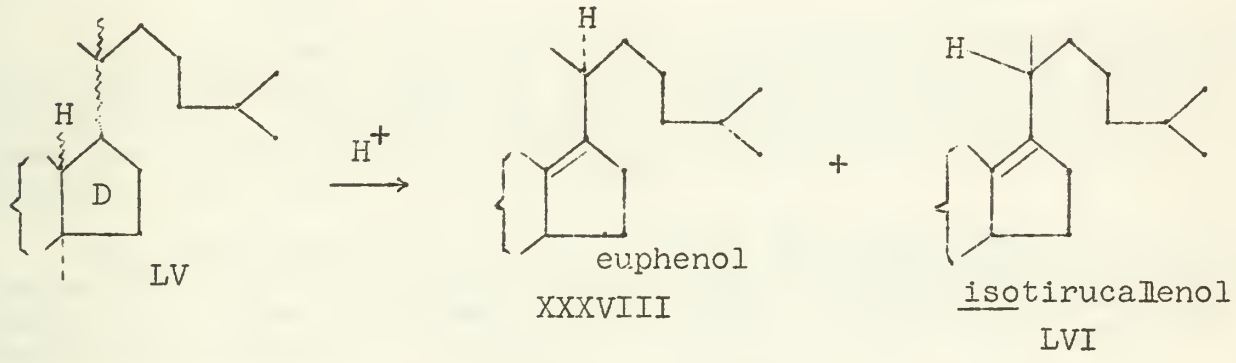


Compound XLVI and LII were shown to be entiomorphic by their identical infrared spectrums and melting points (115-116°C), and equa but opposite specific rotations.

Dammarendiol I and II (38)

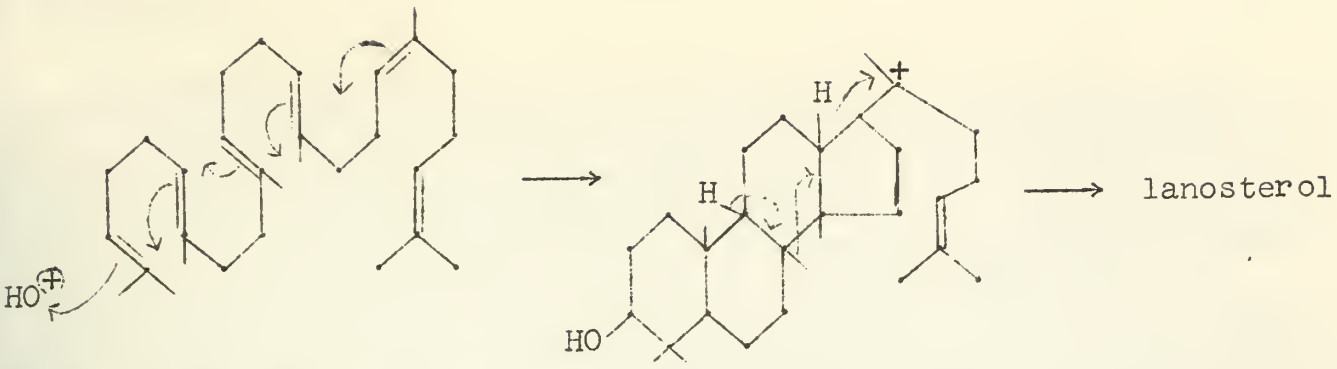
The main constitutional features of Dammarenediol I and II (LIII, R=OH) has been elucidated. Both can be dehydrated to a compound (LIV) containing a vinylidene group. Acid-catalyzed dehydration of the dihydro-derivative of diammarenediol II monoacetate (LV R=OAc) yields isotirucallenyl acetate (LVI) and isoeuphenyl acetate (XXXVIII) This established the main carbon skeleton and the location of the tertiary hydroxyl group at C_{20}. The isomer I and II give the same ketone on oxidation; therefore, they differ only in the configuration at $C_{(20)}$.





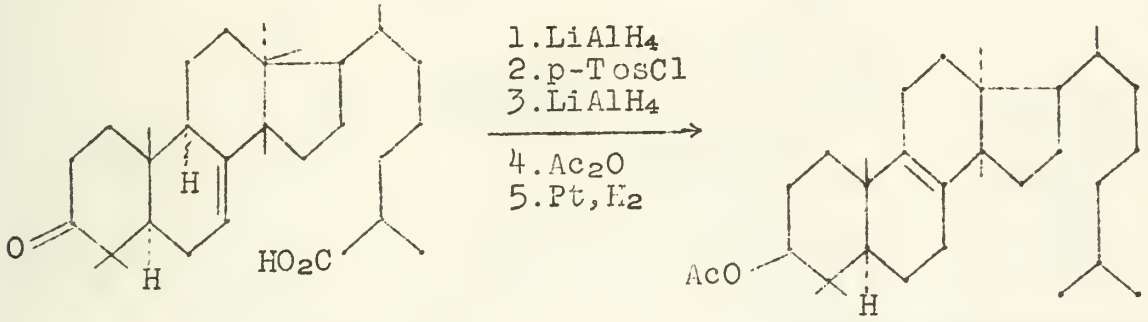
These compounds are of special interst in connection with the biogenesis of the tetracyclic triterpenes, pentacyclic triterpenes, and steroids starting from squalene.

The following scheme represents the cyclization of squalene to give lanosterol as proposed by Woodward and Bloch. (4).



MASTICADIENONIC ACID (39)

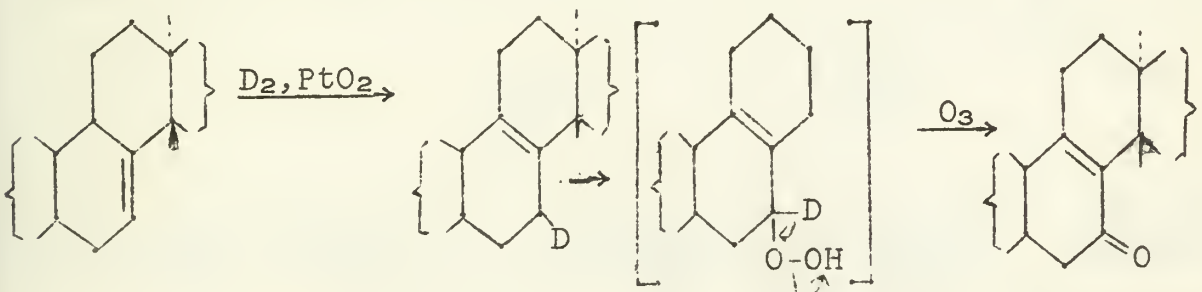
The constitution and stereochemistry of masticadienonic acid, $C_{30}H_{46}O_3$, VIII a, were elucidated recently. The nature of the carbon skelton and the position of the ketone grouping were established by conversion of masticadienonic acid to tirucallenol acetate LVIII, the structure of which had been established.



LVII LVIII

The structure of the side chain was deduced from spectroscopic data and ozonolysis reaction, which produced acetic acid as one of the products. The stability of the ethylenic double bond in the side chain toward drastic isomerization condition showed that it probably has a trans configuration.

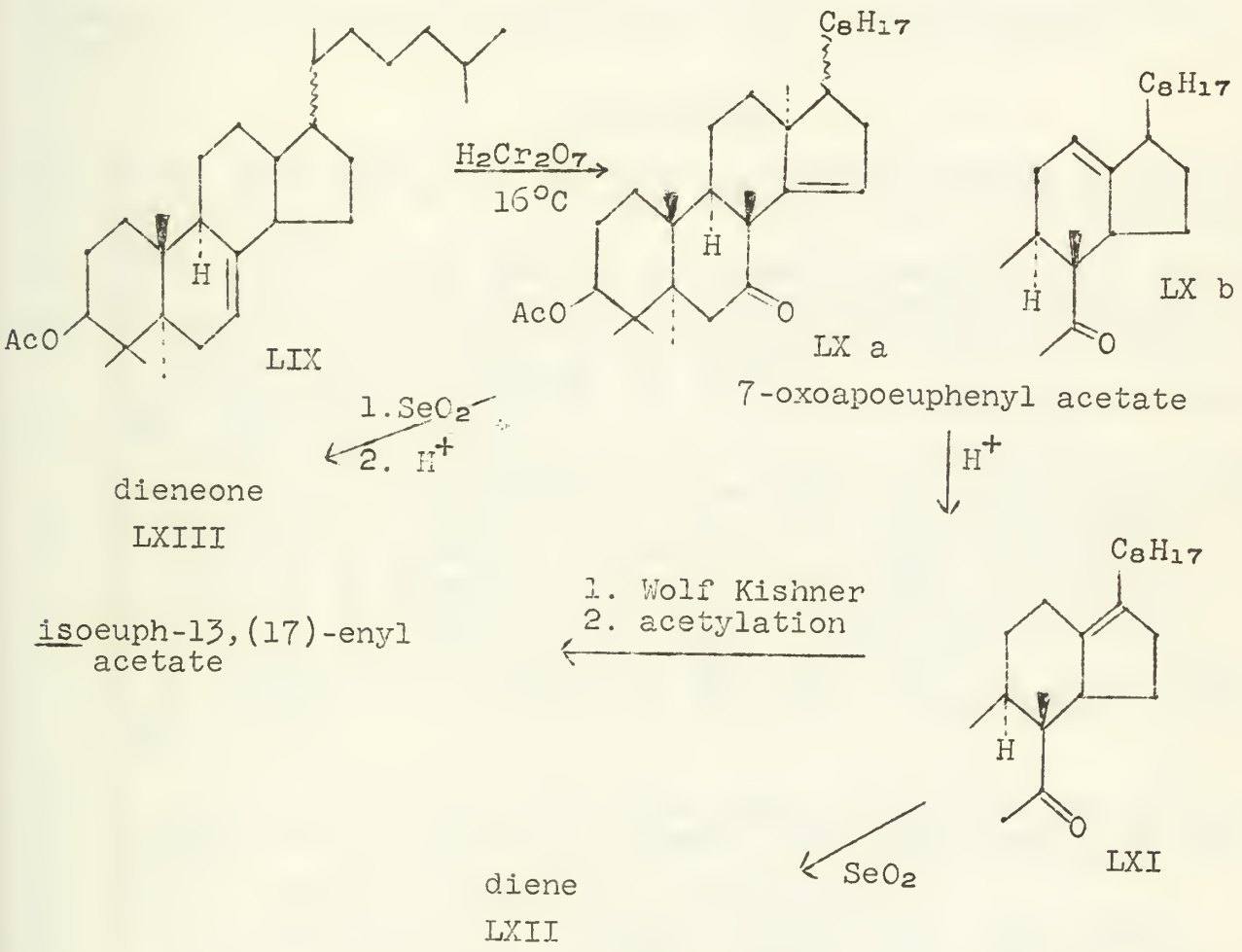
The position of the nuclear double bond was shown to be Δ^{7} rather than $\Delta^{9(11)}$ on the basis of the following reactions, in which the final product contained no deuterium. A $\Delta^{9(11)}$ double bond would have resulted in deuterium retention in the final product.



no deuterium retentio

BUTYROSPERMOL

Butyrospermol VII has been isolated from shea-nut fat. When dihydrobutyrospermol is treated with strong acid, dihydro isobutyrospermol results, which is identical with dihydro-euphol (40). Much of the structure is therefore established. Jones (41) and Laurie (42) both proposed the structure VII of butyrospermol, with the nuclear double bond at $C_{(7)}$. Jones favored a β-$C_{(19)}$ configuration because of the similarity between the molecular rotation differences of butyrospermol and cycloartenol, which has a β-Ca substituent. Laurie, however, favored an α-$C_{(9)}$ configuration by the reactions indicated below. Oxidation of LIX to LX is believed to involve a simultaneous oxidation and methyl migration, the product, 7-oxo-apoeuphenyl acetate, has either structure LXa or LXb. It can be isomerized to an isoeupha-13(17)-enyl acetate derivative. Compound LXII is a conjugated diene, which is not conjugated to the ketone group. Compound LXIII has an isolated double bond and an α,β-unsaturated carbonyl group. The

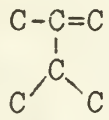


workers reason that the reactions proceed as indicated. Therefore the $C_{(9)}$ hydrogen maintains its configuration throughout. Therefore the configuration at $C_{(9)}$ is same as that in isoeuphol.

ISOMASTICADIENOLIC ACID (43)

Isolated from the acid fraction of gum mastic, isomasticadienolic acid differs from masticadienonic acid in the position of one ethylenic linkage. The structure Xb proposed was confirmed by the fact that when masticadienolic acid is treated with mild acid, the isomasticadienolic acid is formed.

CYCLOEUCALENOL (44)

This is a non-hydric secondary alcohol, apparently $C_{31}H_{52}O$. One ethylenic double bond is present in a side chain terminated by grouping  . The presence of a cyclopropane ring is indicated by IR at 3050 and action of hydrochloric acid. Oxidation of the acid isomerization product gives a diketone containing the transoid system -CO-C=C-CO- but is different from 7:11-dioxolanost-8-enyl acetate.

BIBLIOGRAPHY

1. R. M. Gascoigne, J. J. H. Simes, Quarterly Reviews 9, 328(1955).
2. E. R. H. Jones, T. G. Halsall, Fortschr. chem. org. Naturstoff 12, 44(1955).
3. N. A. Lebel, M.I.T. Seminar in Organic Chemistry, Feb. 29, 1956
   W. S. Saari, M.I.T. Seminar in Organic Chemistry, Sept. 24, 1954
4. R. Tschesche, Fortschr Chem. org Natursfoff 12, 131 (1955).
   L. Ruzicka, Experientia 9, 357 (1953).
   A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, Helv. Chim. Acta. 38, 1890 (1955).
   G. Clemo, Perfumery Essent. Oil Record, 435 (1953).
   G. Stork, A. W. Burgstahler, J. Am. Chem. Soc., 77, 5068 (1955).
   R. Woodward, K. Block, J. Am. Chem. Soc. 75, 2023 (1953).
5. H. Wieland, H. Pasedach, A. Ballauf, Ann 529, 68 (1937).
   H. Wieland, W. Benend, Z. physiol. Chem. 274, 215 (1942).
   A. Windaus, R. Tschesche, Z. physiol Chem. 190, 51 (1930).
   H. Schulze, Z. physiol. Chem. 238, 35 (1936).
   R. E. Marker, E. L. Wittle, J. Am. Chem. Soc. 59, 2289 (1937).
   R. E. Marker, E. L. Wittle, L. M. Mixon, J. Am. Chem. Soc. 59, 1368 (1937).
6. L. Ruzicka, Ed. Rey, A. C. Muhr, Helv. Chim Acta. 27, 472 (1944).
7. L. Ruzicka, M. Montavon, O. Jeger, Helv. Chim. Acta. 31, 818 (1948).
8. D. H. R. Barton, J.Chem. Soc., 1027 (1953).
9. D. H. R. Barton, K. H. Overton, J. Chem. Soc. 1955, 2639.
10. B. Rimker, D. Arigoni, O. Jeger, Helv. Chim. Acta. 37, 546 (1954).
    R. B. Woodward, Franz Sondheimer, D. Taub, J. Am. Chem. Soc., 73, 3548 (1951).
    J. W. Cornforth, I. Youhotsky, G. Popjak, Nature 173, 536 (1954).
11. P. Karrer, A. Helfenstein, Helv. Chim. Acta. (1931).
12. W. Voser, M. Montavon, Hs. H. Günthard, O. Jeger, L. Ruzicka, Helv. Chim Acta. 33, 1893 (1950).
13. M. V. Mijovic, W. Voser, H. Heusser, O. Jeger, Helv. Chim. Acta, 35, 964 (1952).

14. J. F. McGhie, M. K. Pradhan, W. A. Ross, J. Chem. Soc. 1953, 305.
15. J. F. Cavalla, J. F. McGhie, M. K. Pradhan, J. Chem. Soc. 1951, 3142.
16. D. H. R. Barton, J. S. Fawcett, B. R. Thomas, J. Chem. Soc., 1951, 3147.
17. W. Voser, M. V. Mijović, O. Jeger, L. Ruzicka, Helv. Chim. Acta. 34, 1585 (1951).
18. J. F. McGhie, M. K. Pradhan, J. F. Cavalla, S. A. Knight, Chem. and Ind. 1951, 1165.
19. C. S. Barnes, D. H. R. Barton, J. S. Fawcett, S. K. Knight, J. F. McGhie, M. K. Pradhan, B. R. Thomas, Chem. and Ind. 1951, 1067.
20. C. S. Barnes, D. H. R. Barton, A. R. H. Cole, J. S. Fawcett, B. R. Thomas, Chem. and Ind. 1952, 426; J. Chem. Soc., 1953, 571.
21. W. Voser, Hs. H. Günthard, O. Jeger, L. Ruzicka, Helv. Chim. Acta. 35, 66 (1952); W. Voser, O. Jeger, L. Ruzicka, ibid., 503.
22. W. Voser, M. V. Mijović, H. Heusser, O. Jeger, L. Ruzicka, Helv. Chim. Acta. 35, 2414 (1952).
23. W. Voser, Hs. H. Günthard, H. Heusser, O. Jeger, L. Ruzicka, Helv. Chim. Acta, 35, 2065 (1952).
24. R. G. Curtis, J. Fridrichsons, A. Mathieson, Nature 170, 321 (1952); J. Fridrichsons, A. Mathieson, J. Chem. Soc. 1953, 2159.
25. E. Kyburz, B. Riniker, H. R. Schenk, H. Heusser, O. Jeger, Helv. Chim. Acta. 36, 1891 (1953).
26. W. Klyne, J. Chem. Soc. 1952, 2916.
27. C. Barnes, D. H. R. Barton, J. S. Fawcett, B. R. Thomas, J. Chem. Soc. 1953, 576.
27a. W. G. Dauben, D. F. Dickel, O. Jeger, V. Preglog, Helv. Chim Acta., 36, 325 (1953).
28. R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, R. B. Kelley, J. Am. Chem. Soc., 76, 2852 (1954); Chem. and Ind. 1954, 605.
29. G. T. Newbold, F. S. Spring, J. Chem. Soc., 1944, 249.
J. B. Barbour, F. L. Warren, Chem. and Ind., 295 (1952); J. Chem. Soc., 1951, 2540.
O. Jeger, Hs. K. Krüsi, Helv. Chim. Acta., 30, 2045 (1947).
M. Roth, O. Jeger, Helv. Chim. Acta. 32, 1620 (1949).
G. Dupont, R. Dulous, M. Vilkas, Bull. Soc. chim. France, 16, 809 (1949).
M. Vilkas, Bull. Soc. Chim France, 17, 582 (1950); Ann. Chim. 6, 325 (1951).
30. K. Christian, O. Jeger, L. Ruzicka, Helv. Chim. Acta., 34, 1675 (1951).
31. K. Christian, M. Dünnenberger, C. Roth, H. Heusser, O. Jeger, Helv. Chim. Acta, 35, 1756 (1952).
32. D. H. R. Barton, J. F. McGhie, M. K. Pradhan, S. A. Knight, J. Chem. Soc. 1955, 876; Chem. and Ind. 1954, 1325.
33. M. C. Dawson, T. G. Halsall, R. E. H. Swayne, J. Chem. Soc. 1953, 590.
34. L. Ruzicka, Experientia 9, 357 (1953).
35. D. Arigoni, R. Viterlo, M. Dünnenberger, O. Jeger, L. Ruzicka, Helv. Chim. Acta. 37, 2306 (1954).
36. D. Arigoni, H. Wyler, O. Jeger, Helv. Chim Acta. 37, 1553 (1954).
D. Arigoni, O. Jeger, L. Ruzicka, ibid., 38, 222 (1955).
37. E. Ménard, H. Wyler, A. Hilstand, D. Arigoni, O. Jeger, L. Ruzicka, Helv. Chim. Acta. 38, 1517 (1955).
38. J. S. Mills, J. Chem. Soc., 1956, 2196.

39. D. H. R. Barton, E. Seone, J. Chem. Soc., 4150 (1956).
40. M. C. Dawson, T. G. Halsall, E. R. H. Jones, G. D. Meakins, P. C. Phillips, Chem. and Ind., 1955, 918.
M. C. Dawson, T. G. Halsall, E. R. H. Jones, P. A. Robins, J. Chem. Soc., 1953, 586.
D. S. Irvine, Lowrie, McNab, Spring, Chem. and Ind., 1955, 626.
41. M. C. Dawson, T. G. Halsall, E. R. H. Jones, G. D. Meakins, P. C. Phillips, J. Chem. Soc. 1956, 3172.
42. W. Lowrie, W. Hamilton, F. S. Spring, H.S. Watson, J. Chem. Soc., 1956, 3272.
43. E. Seoane, J. Chem. Soc., 1956, 4158.
44. J. S. G. Cox, F. E. King, T. J. King, J. Chem. Soc., 1956, 1384.

REACTIONS OF DIAZOKETONES AND DIAZOACETIC ESTER

Reported by J. D. Albright April 22, 1957

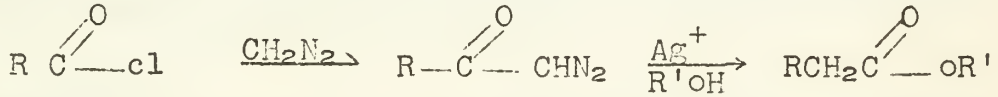
INTRODUCTION

Aliphatic diazo compounds are quite useful reagents which have found many applications in the synthesis of organic molecules. These reagents can act as nucleophiles, electrophiles and can yield carbene intermediates under the proper experimental conditions.

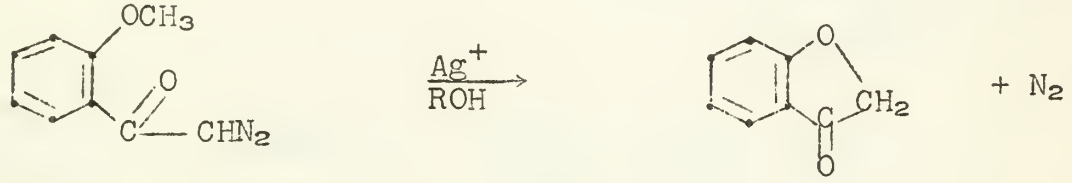
REARRANGEMENT OF DIAZOKETONES

The rearrangement of diazoketones was first observed in 1902 by Wolff who isolated benzyl methyl ketone from benzoyl acetyl diazomethane (1). That ketenes were intermediates was shown by the production of diphenyl ketene in the rearrangement of azibenzil (2, 3). The reactions of diazoketones up through 1942 have been reviewed by Bachmann and Struve (4).

Diazoketones are produced by the reaction of diazomethane on acid chlorides (4). The rearrangement of the diazoketone produced is catalysed by colloidal silver, platinum, copper and silver salts. Acids, esters, or amides, containing one more carbon atom that the original acid, are formed in the presence of water, alcohols or amines, respectively.



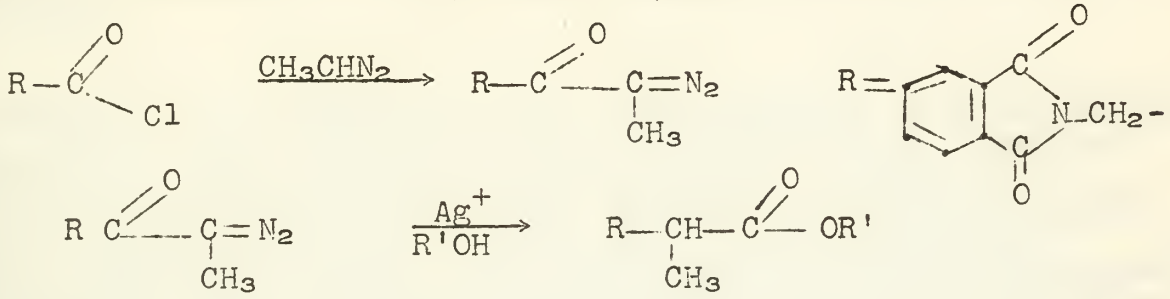
With the o-hydroxy and o-methoxy aromatic diazoketones, cyclic ethers were produced (5). For example, the diazoketone from o-methoxybenzoic could not be rearranged (6, 7).



A modified procedure for the rearrangement of diazoketones was developed by Newman (8). The catalytic reagent effecting the rearrangement was a solution of silver benzoate in triethyl amine. An α-hydrogen atom in the diazoketone was necessary, since α-diazopropiophenone did not rearrange. Methyl p-methoxyphenylacetate, methyl hydrocinnamate, and t-butyl p-nitrophenylacetate were prepared in 84, 70, and 57 per cent yield, respectively.

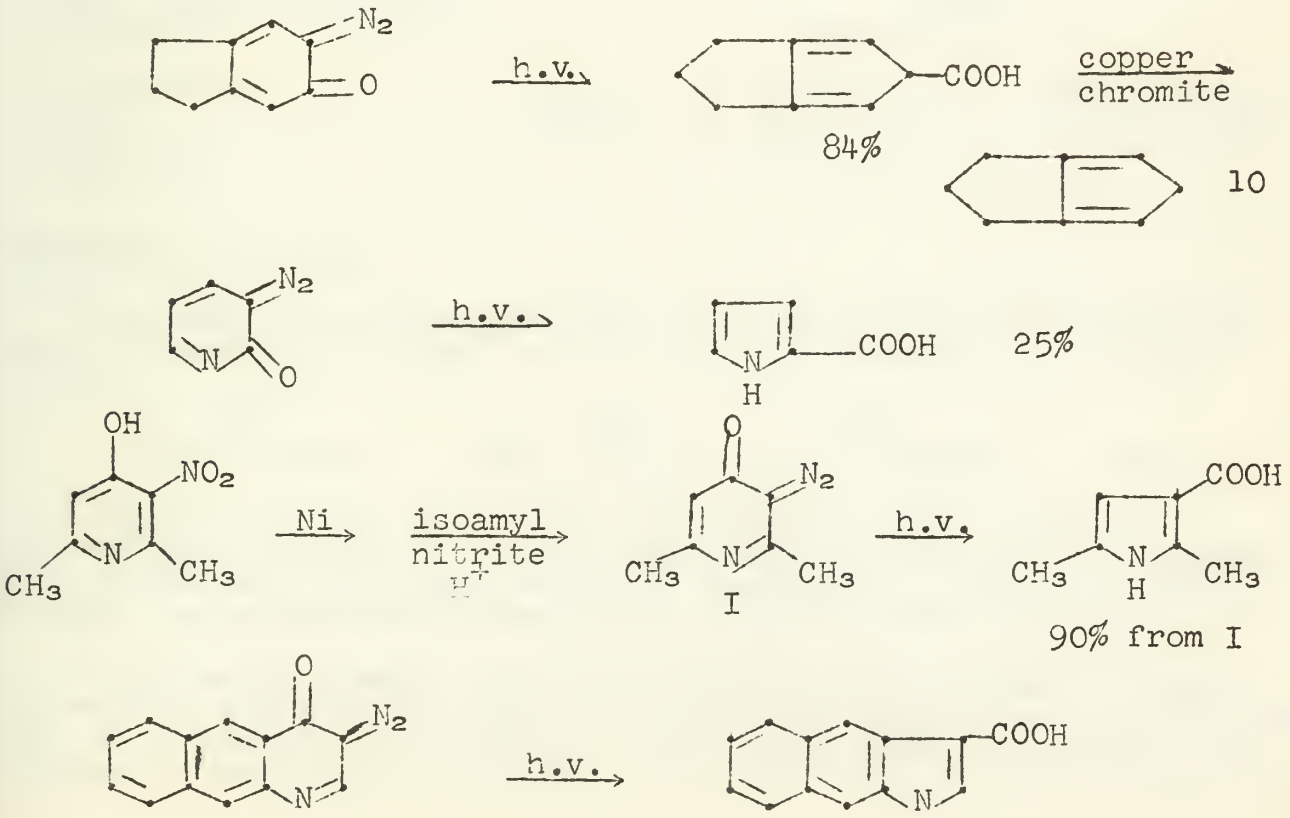
The use of higher diazohydrocarbons in the Arndt-Eistert synthesis has been described (9). Diazoethane and diazopropane were prepared from the N-nitroso-N-alkylurethans by decomposition in a solution of potassium hydroxide and n-propyl alcohol. The diazoketones could not be rearranged under the usual experimental conditions (i.e. with silver oxide or silver nitrate in methanol). Good yields

were obtained by heating the diazoketones to 180-190° in the presence of benzyl alcohol and dimethylaniline. A recent example is the formation of α-methyl-β-alanine and hydrotropic acid from glycine and benzoic acid, respectively (10).



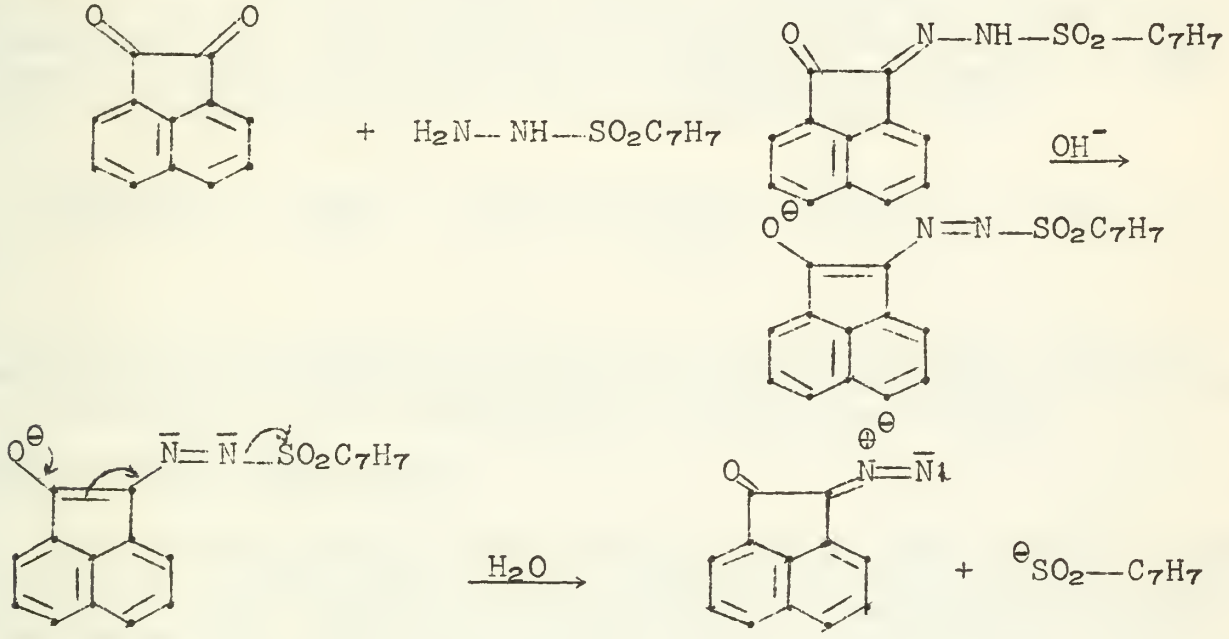
A variation of the Wolff rearrangement is the photochemical decomposition of diazoketones (11, 12).

Diazoketones rearrange in light to yield ring-contraction products (13-16). The diazoketones were dissolved in aqueous acetic acid and irradiated for 2-12 hours. By extraction of the reaction mixture with sodium carbonate followed by neutralization with sulfuric acid, good yields of the corresponding acids were observed. The acids obtained could be decarboxylated in suitable solvents to the aromatic hydrocarbons. Compounds of the following types have been prepared by the photochemical decomposition of diazoketones: (1) indenes with substitution in the aromatic ring; (2) cyclopentadiene derivatives; (3) substituted indoles and derivatives of pyrrole; (4) bicyclooctadiene and derivatives.



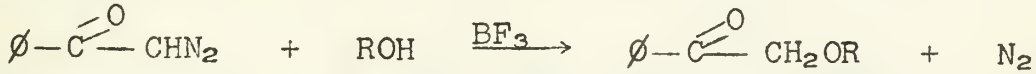
There is no standard procedure for preparing cyclic diazoketones but most of the compounds were prepared from the hydroxy nitro compounds by reduction with Raney nickel to give the amino compound. Treatment of the amino compound with isoamyl nitrite yielded the diazoketone.

Recently a few diazoketones have been prepared from α-diketones (17). The mercuric oxidation of the monohydrazones of benzil and camphorquinone gave satisfactory yields of the α-diazoketones. Difficulties were encountered in the preparation of the monohydrazones of other α-diketones. However, with one equivalent of toluene-p-sulphonylhydrazine, the monotoluene-p-sulphonylhydrazones of α-diketones, were obtained in good yields. The sodium salts of the hydrazones could be readily decomposed in water to yield the α-diazoketones.



REACTION WITH ACIDS

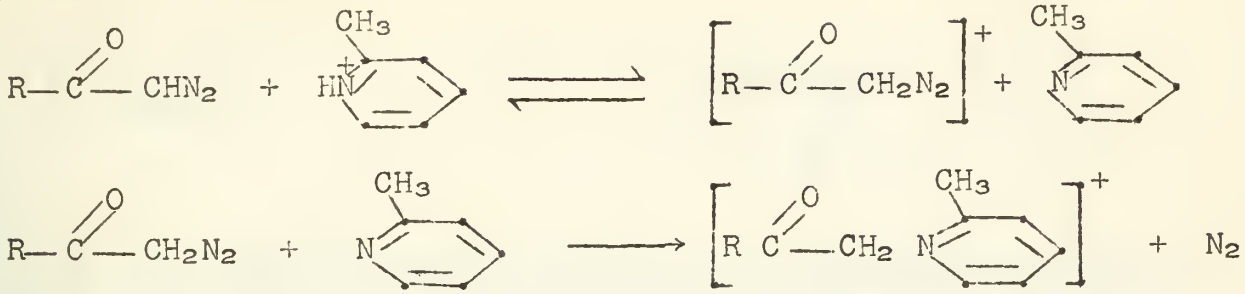
Acid-catalysed decomposition of diazoketones by non-protonic acids in methanol yielded the unrearranged methyl ethers (18).



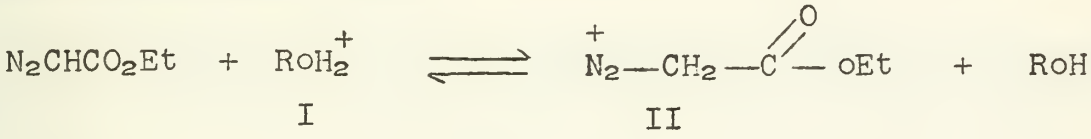
Copper has also been used to effect the above reaction, although in lower yields (19). The reaction seems to be a general one, as indicated by preparation of α-methoxy-, α-ethoxy-, α-t-butoxy-, α-1-hexoxy-acetophenone in yields of 40-70 per cent.

Diazoketones react with perchlorate salts of amines to give quaternary salts (20). Salts of 2-picoline, quinoline, isoquinoline have been prepared in 30-60 per cent yields either by warming the mixture of amine salt and diazoketone on a steam bath or by heating

an alcoholic mixture of the reactants. The reaction probably proceeds as follows:



The results of kinetic studies on the decomposition of diazoacetic ester and diazoketones support this mechanism (21-24). In the reaction of ethyl diazoacetate with ethanol and acetic acid deuterated ethyl ethoxyacetate was formed in the presence of deuterated ethanol, with the extent of deuteration depending on the ratio of deuterated ethanol to ethyl diazoacetate (24).

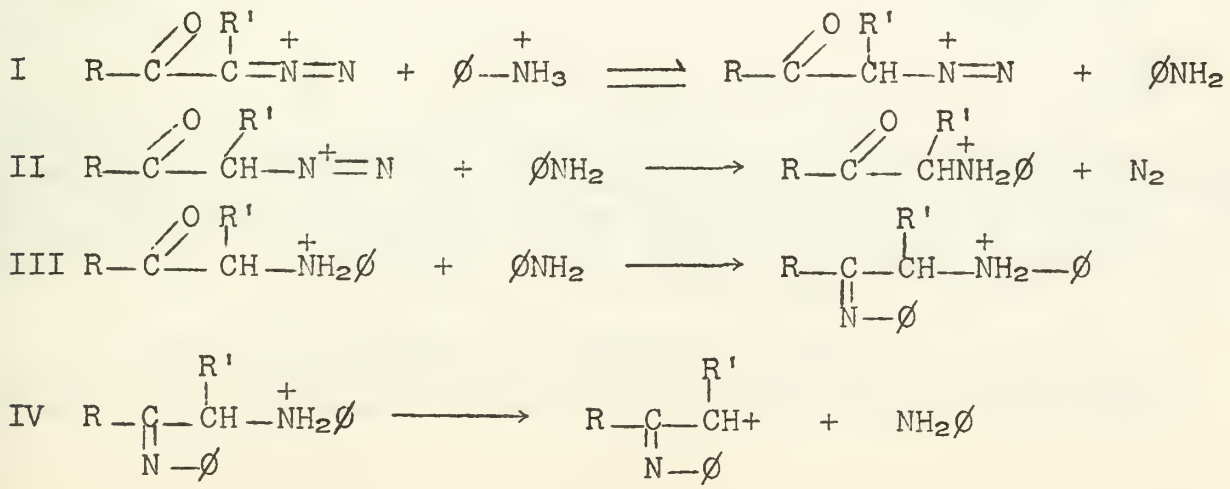


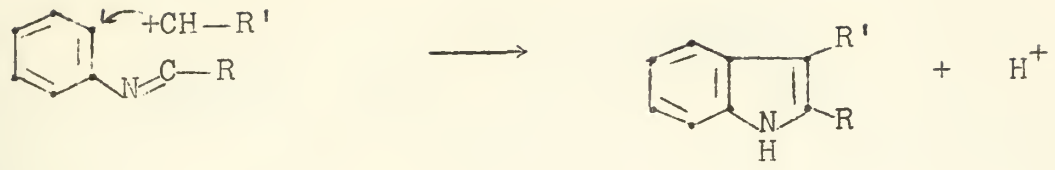
If II were not in equilibrium only one deuterium atom should be present in each molecule of ethyl ethoxyacetate formed, irrespective of the ratio of ethyl diazoacetate to deuterated ethanol.

INDOLES FROM DIAZOKETONES

The decomposition of aryl diazoketones at 180° in the presence of salts of aniline led to 2-aryl substituted indoles (25). Since haloketones when heated with aniline yield 2-substituted indoles, experiments were carried out to show that the products obtained did not originate from chloroketones in the diazoketones used. The use of salts of N-alkylanilines produced 1-alkyl-3-arylindoles as the major products. By the use of diazoethyl ketones 2-aryl-3-alkylindoles were produced.

PROPOSED MECHANISM

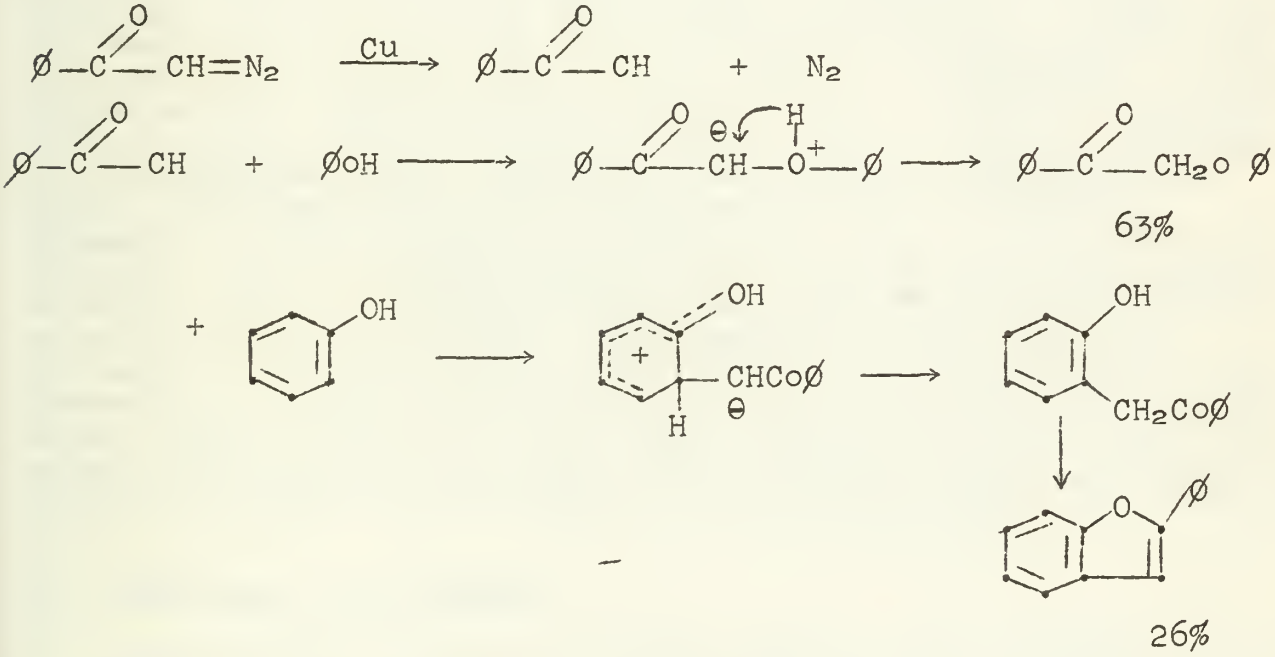


V 

In the first step of the reaction the diazoketone removes a proton from the anilinium salt to form an α-diazonium ketone. Nucleophilic attack by aniline then leads to the salt of an α-anilino ketone. Step III in the mechanism is supported by the fact that the quaternary salts of diazoketones prepared by King and Miller (20) could be converted to indoles by heating with anilinium salts. N-Phenacyl-4-picolininum bromide yielded 2-phenylindole in 69 per cent yield.

CARBENE INTERMEDIATES (26).

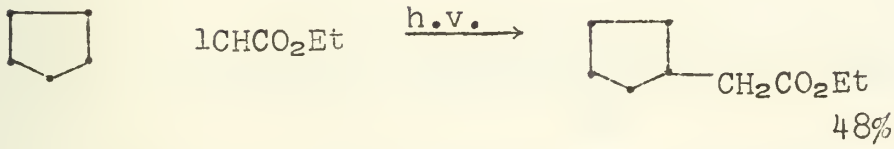
The decomposition of α-diazoketones by copper in the presence of phenol, thiophenol, aniline, and piperidine has been investigated (19).



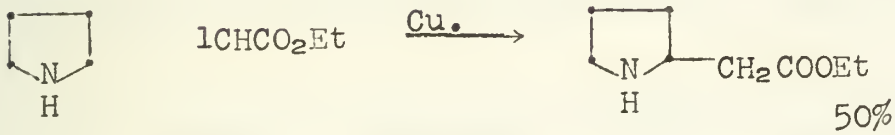
The action of copper may be to share its valence electrons with the intermediate carbene, thus completing the octet of the methine carbon atom. The carbene-copper complex may then be attacked by an unshared pair of electrons on the oxygen, nitrogen or sulfur atom, followed by a proton shift to yield the observed product.

The carbethoxycarbene intermediate produced by loss of nitrogen from diazoacetate can attack saturated hydrocarbons or aromatic hydrocarbons to yield substitution products (27, 28).

(28)



(28)

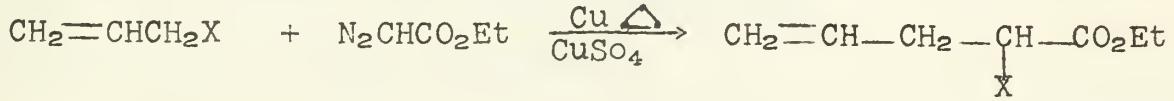


(27)

When a copper catalyst is present the diazoacetic ester intermediate does not attack saturated hydrocarbons. Perhaps the copper complexes with the carbene intermediate decreasing its reactivity. No reactions have been observed in which the carbene attacks the electrons of a carbon-carbon single bond of a hydrocarbon. Pentane yields methyl 3-methylhexanoate (42 per cent), methyl heptanoate (38 per cent), methyl 3-ethylpentanoate (25 per cent). The ratio of the products formed indicates that secondary hydrogens are about 1.62 times as reactive as primary ones. In order to determine whether tertiary hydrogen atoms would react faster than secondary ones, 2,3-dimethylbutane was reacted with methyl diazoacetate. Methyl 4,5-dimethylhexanoate and 3,3,4-trimethyl pentanoate (structure not proven) were produced in 76.5 and 23.5 per cent of the total yield. Provided no discrimination existed between the primary and secondary hydrogens the statistical ratio would have been 85.7 to 14.3. Tertiary hydrogen atoms, therefore, appear to be 1.84 times as reactive as primary ones. Although not conclusively proven the order of reactivity appears to be $3^{\circ} > 2^{\circ} > 1^{\circ}$.

(1) REACTIONS WITH HALIDES

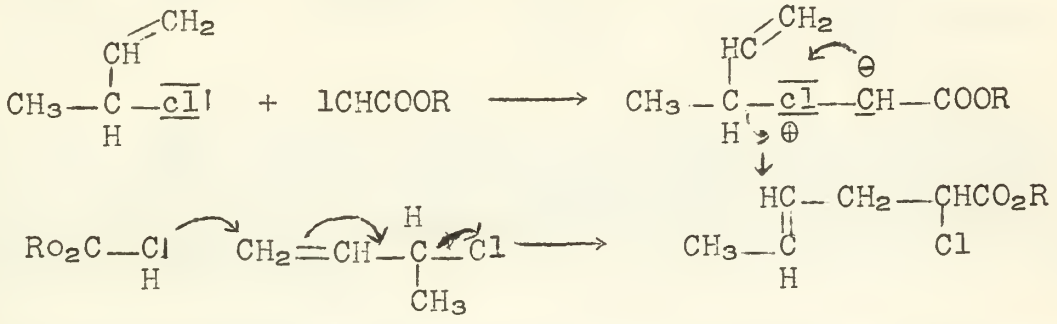
Allyl halides react with diazoacetate in the presence of copper catalyst in the following manner (29).



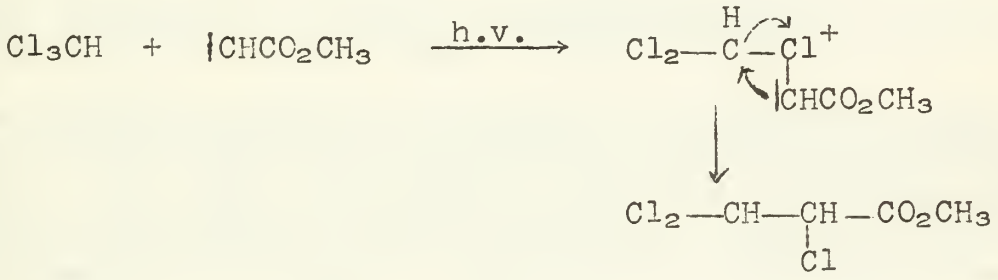
X= Cl, Br, I

Yield= 20, 80, 70

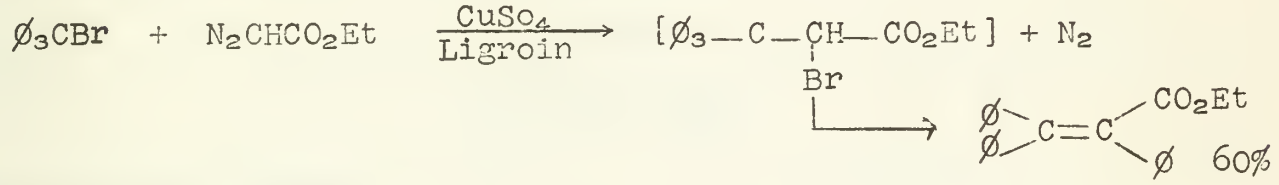
The mechanism of this reaction was studied by Phillips (30). The reaction of 3-chlorobutene-1 and allylidene chloride produced mainly rearranged products, thus supporting an SN2' or cyclic mechanism similar to Claisen rearrangement of ally ethers of phenols.



A similar mechanism explains the formation of methyl α, β, β-trichloropropionate when diazoacetate in chloroform is decomposed by light (31).



The reaction with halides has been extended to include aralykyl halogen derivatives (32, 33).



It has been reported that triphenylbromomethane yielded 1,1,2-triphenylbutene-1 (78 per cent) and 2,3-diphenylindenone (4,5 per cent) in the absence of solvent at 160-165°. However, no structure proof for the two compounds was given (32). In the presence of anhydrous copper sulfate (no solvent) diphenylbromomethane produced α-phenyl-β-bromo-hydrocinnamate, but only tars were obtained with benzyl bromide. With solvent a 24 per cent yield of ethyl α-chloro-cinnamate was obtained from benzalbromide (33).

(2) REACTIONS WITH ETHERS AND ALCOHOLS

The reactions of ethyl diazoacetate with ethers and alcohols are best interpreted as attacks of the carbene intermediates on the electrons of the oxygen atoms. The reaction of ethyl diazoacetate with methylenedioxybenzene probably proceeds by attack of the carbethoxycarbene on the oxygen of the ether, leading to ring

expansion in this case (34).

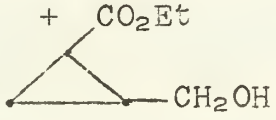
Aliphatic ethers are also attacked at the oxygen atom, resulting in cleavage of the ether linkage. The reaction with 1-butoxybutane gives a 10 per cent yield of ethyl butoxyacetate while methoxyheptane yields 30 per cent of methoxyacetic ester plus 45 per cent of heptoxyacetic ester (35).

$$CH_3—O—C_7H_{15} \xrightarrow[N_2CHCO_2Et]{140^\circ} CH_3O—CH_2CO_2Et \;(30\%) + C_7H_{15}—O—CH_2CO_2Et \;(45\%)$$

In the preparation of the seven-membered system from methoxybenzenes, phenoxyacetic acids were produced (34-36).

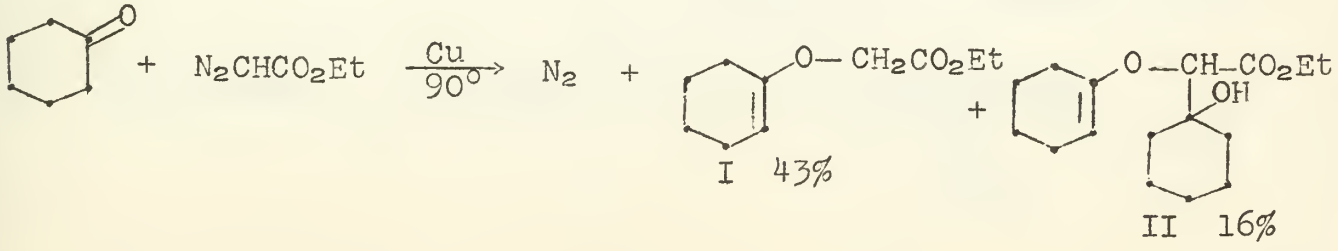
In an attempt to prepare a cyclopropane derivative, allyl alcohol and diazoacetate in the presence of copper were allowed to react (37). A 52.5 per cent yield of the ethyl α-allyloxyacetate and a 7.2 per cent yield of the ethyl ester of trans-2-hydroxymethylcyclopropane-1-carboxylic acid were obtained, showing the main reaction to be that of attack at oxygen of the hydroxyl rather than the double bond.

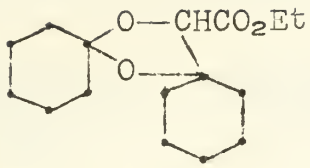
$$CH_2{=}CH—CH_2OH \xrightarrow{Cu} CH_2{=}CHCH_2OCH_2CO_2Et + N_2$$



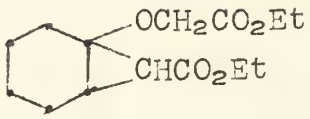
REACTIONS WITH KETONES

The products obtained with cyclohexanone and acetone have been thoroughly investigated (38). Cyclohexanone and acetone did not react with ethyl diazoacetate below 120° in the absence of catalysis. The only apparent effect of the catalyst was to lower the reaction temperature. Copper was the most effective catalyst; however, Pt, Pd, Raney Ni, Ag_2O and $AgNO_3$ could also be used.





III 4%

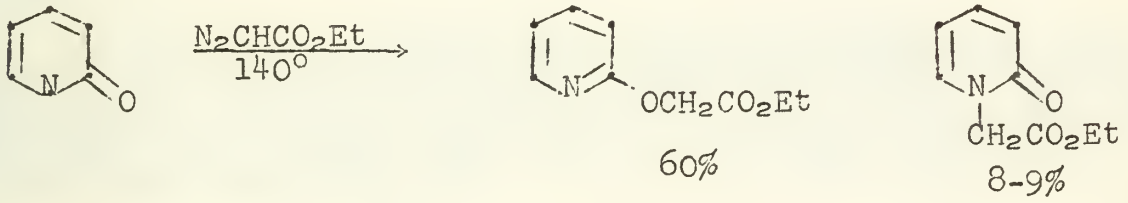


IV 1%

Product II, the 1:2 adduct, was shown to rearrange to III at high temperatures, and IV could be produced from the addition of ethyl diazoacetate to the 1:1 adduct.

The products obtained from acetone and ethyl diazoacetate showed that acetone acts like cyclohexanone.

Benzosuberone and pyridone also yield 1:1 adducts with ethyl diazoacetate in about 50 per cent yields (39, 40).



60%

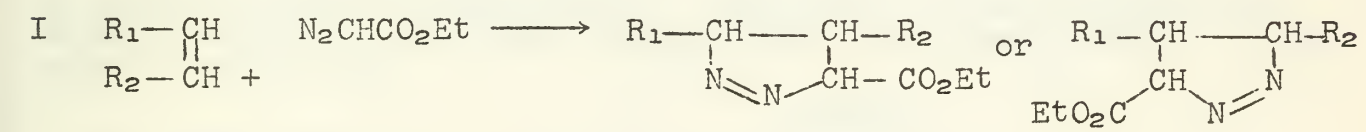
8-9%

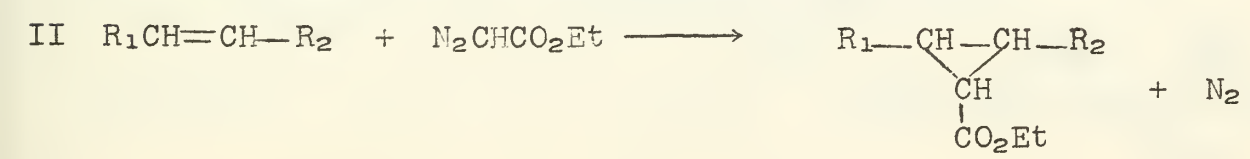
ADDITION TO ETHYLENIC COMPOUNDS

(1) Formation of cyclopropane derivatives.

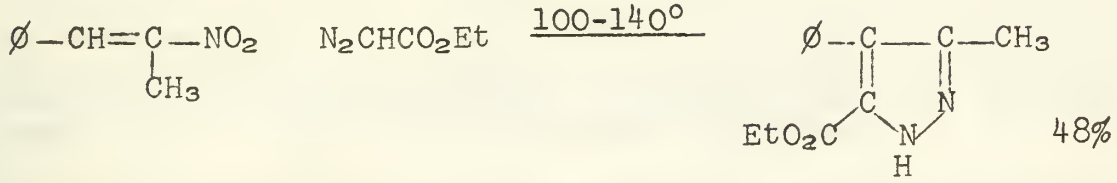
The formation of cyclopropane derivatives in the reaction of alkenes can be illustrated by the formation of 2-phenylcyclopropane-1-carboxylic ester from styrene (41, 42).

Aliphatic diazo compounds can react with ethylenes in two ways: either directly, forming pyrazolines, or by loss of nitrogen followed by combination to form cyclopropane derivatives (43-45). Usually the pyrazoline derivative can be decomposed to a cyclopropane derivative.

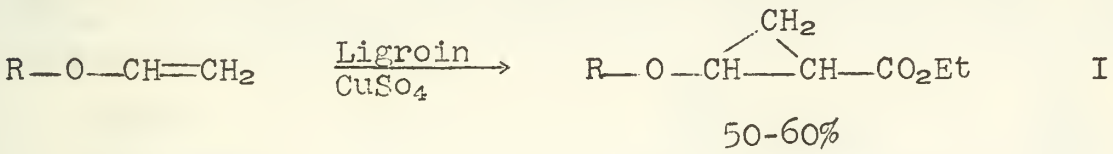




An interesting example of the first reaction is the formation of pyrazoles from nitroolefins (46).



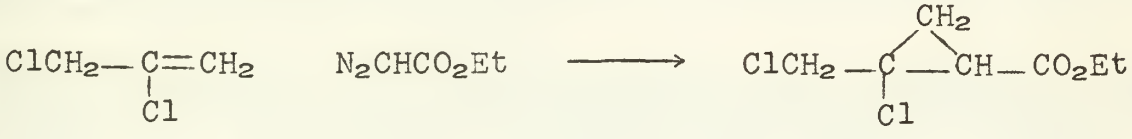
With vinyl ethyl ether and vinyl butyl ether the expected cyclopropane derivatives were obtained in good yields (47, 48).



Attempts to prepare the unknown 2-hydroxycyclopropane-1-carboxylic acid through hydrolysis of I led to cleavage of the cyclopropane ring (49).

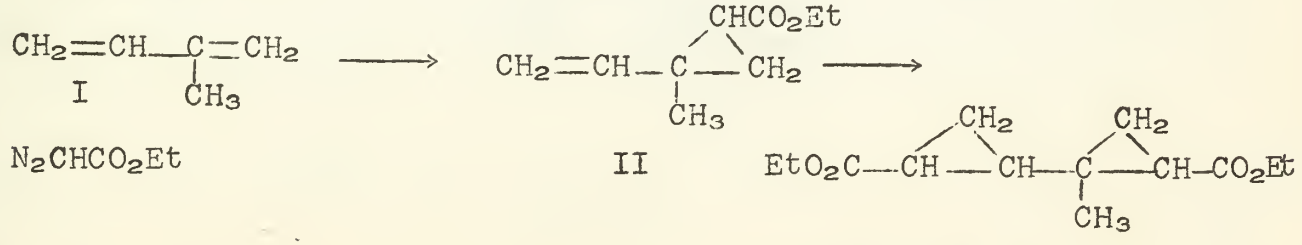
Allyl acetate yielded ethyl 2-acetoxycyclopropane-1-carboxylate, while 2-bromoallyl acetate gave only polymers. Oxidation of the product obtained from allyl acetate gave a 7 per cent yield of the cis and a 84.6 per cent yield of the trans cyclopropane dicarboxylic acid (50, 51).

2,3-Dibromopropene in the presence of copper sulfate yielded the ethyl ester of α, γ -dibromoallylacetic acid (55 per cent) (52). The reaction proceeded in a manner similar to that of allyl halides. However, with 2,3 dichloropropene, a mixture of cis and trans ethyl 2-chloro, 2-chloromethylcyclopropane-1-carboxylate was obtained as the major product (53).



No reaction occurred with 1,3-dichloropropene.

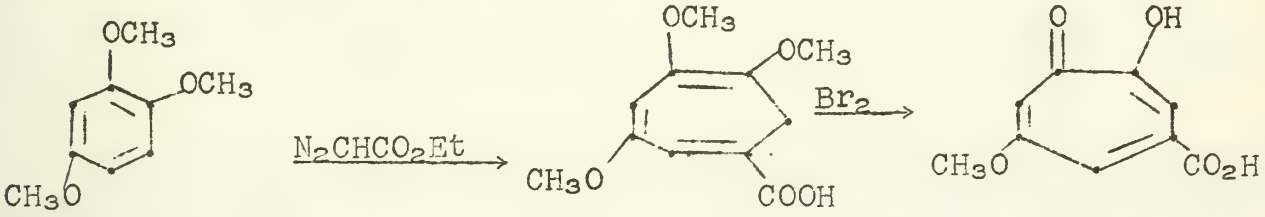
Isoprene yielded a 35.8 per cent yield of ethyl 2-methyl-2-vinylcyclopropane-1-carboxylate. Treatment of this compound with ethyl diazoacetate produced 2-methyl-2,2'-bicyclopropane-1,1'-dicarboxylic ester (54).



(2) Reaction with Aromatic Compounds

The addition products of diazoacetate and benzene have been known for a long time (55). Only recently, however, have the structures of the four acids isolated by Buchner been correctly determined (56, 57). The structures were determined from NMR date and from the products obtained in the pyrolysis of the Diels-Alder adducts with dimethylacetylene disarboxylate (57). All four acids were shown to have cycloheptatriene structures.

Another example of ring expansion giving seven-membered rings is the synthesis of azulenes (58-60). Many substituted azulenes have been prepared from indanes and diazoacetic ester. Diazoacetic ester also reacts with trimethoxybenzenes to give cycloheptatriene compounds (35, 61-63).

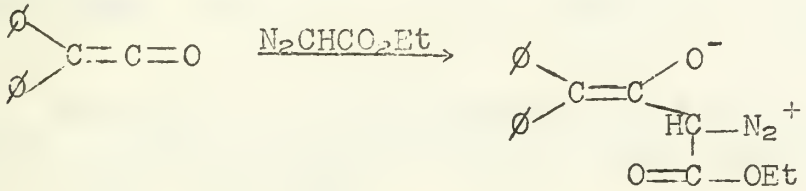


A cyclopropane adduct is formed with phenanthrene (64), anthracene (65), and cyclooctatetraene (66, 67), the most active double bond being attacked in each case.

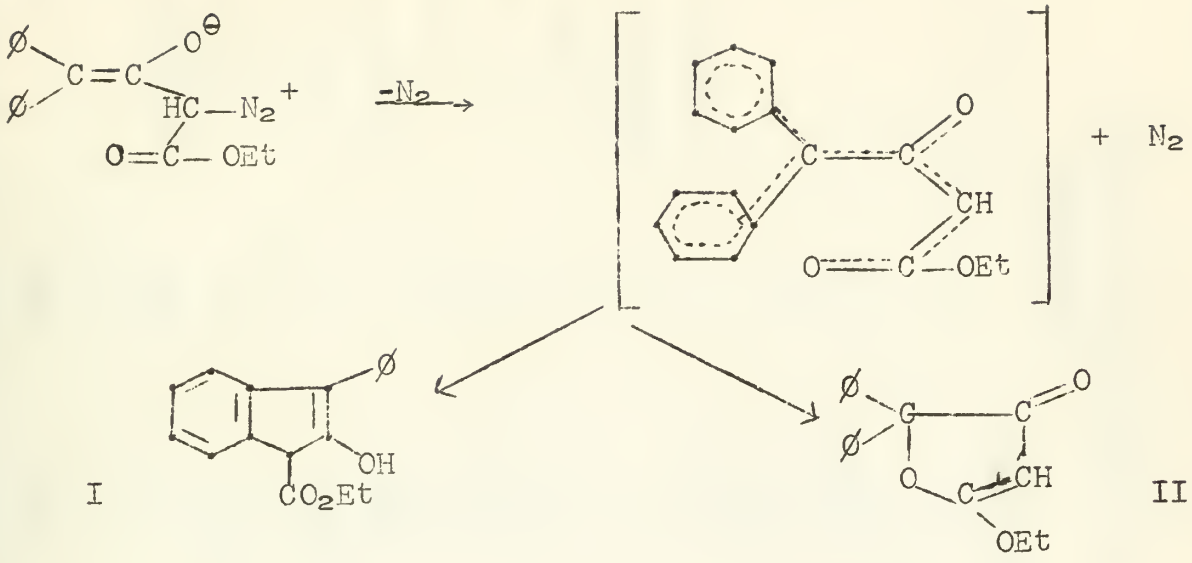
MISCELLANEOUS REACTIONS

The products formed with diphenylketene and dimethylketene have recently been reinvestigated (68). No cyclopropane derivative was obtained with diphenylketene as had been proposed earlier (69). The two products obtained from diphenyl ketene were identified as ethyl 2-hydroxy-3-phenylindene-1-carboxylate (I) and a ketene acetal (II). Dimethylketene yielded ethyl β,β-dimethylacrylate and the enol ether of α,α-dimethylsuccinic anhydride.

Ethyl diazoacetic ester probably reacts as a nucleophile toward both diphenyl and dimethylketene to give a diazonium betaine. Loss of nitrogen from the betaine of diphenylketene yields a complex Zwitterion which can collapse in either of two ways to yield the products observed.

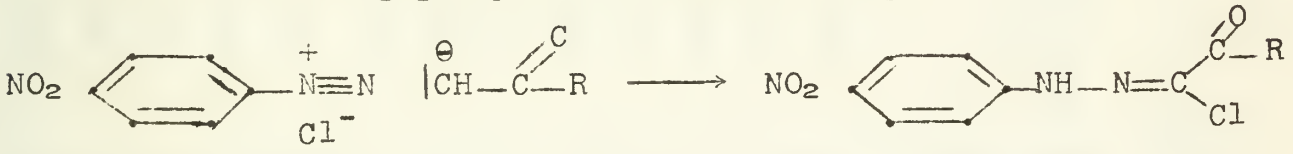


III



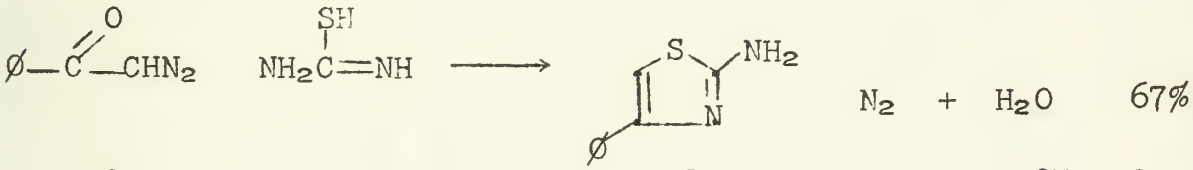
I II

The reaction of aromatic diazonium salts with diazoketones and diazoacetic ester led to azo coupling products (70). Good yields were obtained only with aromatic diazonium salts having an electron-withdrawing group in the benzene ring.



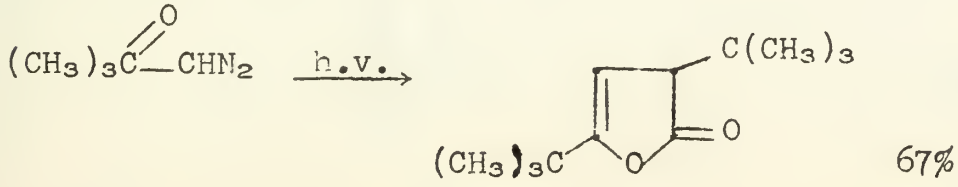
R=Ø; CH_3; OC_2H_5 79%

Diazoketones react with thiourea and thioamide derivatives to give substituted thiazoles (71) and with sulfenyl chlorides to give the corresponding α-chloro compounds which when hydrolysed yield α-hydroxy acids (72).



N_2 + H_2O 67%

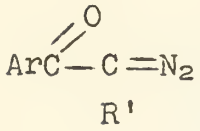
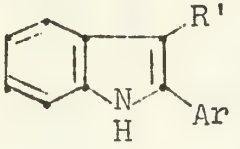
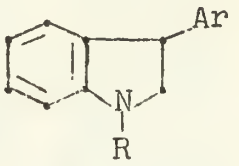
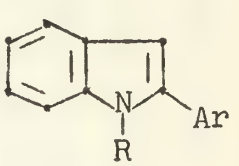
Photolysis of diazomethyl t-butyl ketone yielded α, γ-di-t-butyl-$\Delta^{\beta,\gamma}$-butenolide; however, the reaction does not appear to be a general one (73).



67%

TABLE I

Indoles Obtained from the Reaction of Diazoketones with Anilinium Salts

Reactants				Products		
		∅—NH—R	Anilinium Salt			
Ar	R'	R		Yield		
phenyl	H	H	HBr	67		
p-chlorophenyl	H	H	BF_3	79-80		
p-methoxyphenyl	H	H	BF_3	61-65		
p-nitrophenyl	H	H	BF_3	3		
p-tolyl	H	H	BF_3	77		
2-naphthyl	H	H	BF_3	83		
p-chlorophenyl	H	CH_3	BF_3	7-8	39-40	12-18
p-chlorophenyl	H	C_2H_5	BF_3	1	55	0.3-0.5
p-biphenylyl	H	C_2H_5	BF_3	2	64	. 4
p-chlorophenyl	CH_3	H	BF_3	42		
phenyl	CH_3	H	HBr	32		
p-tolyl	CH_3	H	HBr	50		
p-biphenylyl	CH_3	H	HBr	55		

BIBLIOGRAPHY

1. L. Wolff, Ann., 325, 129 (1902).
2. G. Schroeter, Ber., 42, 2336 (1909).
3. H. Staudinger and H. Hirzel, Ber., 49, 2522 (1916).
4. W. E. Bachmann and W. S. Struve, Organic Reactions, Vol. I, p. 38 (1942).
5. B. Eistert, Neuere Methoden Der Praparativen Organischen Chemie. p. 382 (1943).
6. H. Kizikalla and B. Eistert, J. Prakt. Chem., 143, 50 (1935).
7. P. Pfeiffer and E. Enders, Ber., 84, 247 (1951).
8. M. S. Newman and P. F. Beal III, J. Am. Chem. Soc., 72, 5163 (1950).
9. A. L. Wilds and A. L. Meader, Jr., J. Org. Chem., 13, 763-769 (1948).
10. K. Balenovie and I. Jambresic, Chem. and Ind., 1673 (1955).
11. L. Horner, E. Spietschka and A. Gross., Ann., 573, 17 [1951].
12. L. Horner and E. Spietschka, Ber., 85, 225-228 (1952).
13. O. Süs, Ann., 556, 65-70 (1944).
14. O. Süs and K. Möller, Ann., 593, 91-126 (1955).
15. O. Süs, M. Glas, K. Möller and H. D. Eberhart, Ann., 583, 150-160 (1953).
16. O. Süs, Ann., 579, 133-158 (1953).
17. M. P. Cava and R. L. Litle, Chem. and Ind., 367 (1957).
18. M. S. Newman, and P. F. Beal III, J. Am. Chem. Soc., 72, 5161 (1950).
19. P. Yates, J. Am. Chem. Soc., 74, 5376-81 (1952).
20. L. C. King and F. M. Miller, J. Am. Chem. Soc., 70, 4154 (1948).
21. J. N. Broensted and R. P. Bell, J. Am. Chem. Soc., 53, 2478 (1931).
22. J. E. Lane and R. L. Feller, J. Am. Chem. Soc., 73, 4234 (1951).
23. C. E. McCauley and C. V. King, J. Am. Chem. Soc., 74, 6221-6225 (1952).
24. J. D. Roberts, C. M. Regan, and I. Allen, J. Am. Chem. Soc., 74, 3679-3683 (1952).
25. C. E. Blades and A. L. Wilds, J. Org. Chem., 21, 1013-1021 (1956).
26. W. R. Richardson, Ill. Seminar Abst. Oct. 4, 1956.
27. W. Kutscher and O. Klamerth, Z. Phys. Chem., 289, 229 (1952).
28. W. E. Doering and L. H. Knox, J. Am. Chem. Soc., 78, 4947 (1956).
29. I. A. Dyakonov and N. B. Vinogradova, J. Gen. Chem. U.S.S.R, 21, 851-60 (1951); 22, 1349-55 (1952); 23, 66-71 (1953).
30. D. D. Phillips, J. Am. Chem. Soc., 76, 5385-5388 (1954).
31. W. H. Urry and J. W. Wilt, J. Am. Chem. Soc., 76, 2594 (1954).
32. I. A. Dyakonov and N. B. Vinogradova, J. Gen. Chem. U.S.S.R., 23, 255-61 (1953).
33. R. Huisgen, Angew. Chem., 67, 452 (1955).
34. A. W. Johnson, A. Langeman and J. Murray, J. Chem. Soc., 2136-3140 (1953).
35. G. B. R. DeGraaff, J. H. Dijck-Rothuis and G. V. Kolk, Rec. Trav. Chim., 74, 143-154 (1955).
36. J. R. Barthels-Keith, A. W. Johnson and A. Langemann, J. Chem. Soc., 4461 (1952).
37. I. A. Dyakonov and N. D. Pirogova, J. Gen. Chem. U.S.S.R., 21, 2201-2207 (1951).

38. M. S. Kharasch, T. Rudy, W. Nudenberg and G. Büchi, J. Org. Chem., 18, 1030-1040 (1953).
39. G. D. Gutsche and M. Hillman, J. Am. Chem. Soc., 76, 2236-2240 (1954).
40. J. Maas, G. B. R. DeGraaff and H. J. Den Hertog, Rec. Trav. Chim., 74, 175 (1955).
41. A. Burger and W. L. Yost, J. Am. Chem. Soc., 70, 2198 1948.
42. H. L. DeWaal and G. W. Perold, Ber., 85, 574 (1952).
43. E. P. Kahler and L. L. Steele, J. Am. Chem. Soc., 41, 1093-1105 (1919).
44. I. A. Dyakonov, J. Gen. Chem., U.S.S.R., 19, a173-a183 (1949).
45. J. A. Moore, J. Org. Chem., 20, 1607-1612 (1955).
46. W. E. Parham and J. L. Bleasdale, J. Am. Chem. Soc., 72, 3843-3846 (1950).
47. I. A. Dyakonov and N. A. Lugovtsova, J. Gen. Chem., U.S.S.R., 21, 921-931 (1951).
48. I. A. Dyakonov, J. Gen. Chem. U.S.S.R., 19, a355-a369 (1949); 20, 2385-2396 (1950).
49. I. A. Dyakonov and N. A. Lugovtsova, J. Gen. Chem. U.S.S.R., 20, 2109-2118 (1950).
50. I. A. Dyakonov and O. V. Guseva, J. Gen. Chem. U.S.S.R., 22, 1399-1405 (1952).
51. I. A. Dyakonov and N. B. Vinogradova, J. Gen. Chem. U.S.S.R., 22, 1393 (1952).
52. I. A. Dyakonov and T. V. Domareva, J. Gen. Chem. U.S.S.R., 25, 899-903 (1955).
53. I. A. Dyakonov and T. V. Domareva, Zhiv. Obshchei. Khim., 25, 1486-93 (1955); C.A. 50 4795h.
54. I. A. Dyakonov and V. F. Myynikova, Sbornik Statei Obshchei Khim, 489-97 (1953); C.A. 49, 833b.
55. E. Buchner, Ber, 30, 632 (1897).
56. G. Grundmann and G. Ottmann, Ann., 582, 163 (1953).
57. W. E. Doering, G. Laber, R. Vonderwahl, N. E. Chamberlain, and R. B. Williams, J. Am. Chem. Soc., 78, 5448 (1956).
58. P. A. Plattner, A. Fürst, A. Müller and H. R. Somerville, Helv. Chem. Acta., 34, 971-981 (1951).
59. H. Arnold and W. Spielmann, Ber., 83, 28-34 (1950).
60. M. Gordon, Chem. Rev., 50, 127 (1952).
61. J. R. Bartels-Keith and A. W. Johnson, Chem. and Ind. 677 (1950).
62. R. B. Johns, A. W. Johnson and J. Murry, J. Chem. Soc., 198-202 (1954).
63. A. W. Johnson, J. Chem. Soc., 1333 (1954).
64. N. L. Drake and T. R. Sweeny, J. Org. Chem., 11, 67-73 (1946).
65. G. N. Badger, J. W. Cook and A. R. Gigg, J. Chem. Soc., 3456-3459 (1951).
66. S. Akigoshi and T. Matsuda, J. Am. Chem. Soc., 77, 2476 (1955).
67. D. D. Phillips, J. Am. Chem. Soc., 77, 5179 (1955).
68. A. S. Kende, Chem. and Ind., 1053-1054 (1956).
69. H. Staudinger and T. Reber, Helv. Chem. Acta, 4, 3 (1921).
70. R. Huisgen and H. J. Koch, Ann., 591, 200 (1955).
71. L. C. King and F. M. Miller, J. Am. Chem. Soc., 71, 367-8 (1949).
72. F. Weygand and H. J. Bestman, Ber., 88, 1988-1991 (1955); 89, 1912-1913 (1956).
73. K. B. Wiberg and T. W. Hutton, J. Am. Chem. Soc., 76, 5367-71 (1954).

ACID-CATALYZED REARRANGEMENTS WITH HYDRAZOIC ACID

Reported by Theodore C. Miller April 29, 1957

INTRODUCTION

One of the several rearrangements (1, 2) involving a 1,2-shift of a carbon atom to an electron-deficient nitrogen atom is the Schmidt reaction. Since the appearance of a review in 1946 (3) there have been numerous papers dealing both with further synthetic applications of the reaction and with elucidation of its mechanism. This report will be divided into three sections -- the reactions of carboxylic acids, the reactions of alcohols and olefins, and the reactions of ketones and aldehydes. The discussion will deal chiefly with the mechanism of these reactions, insofar as it has been determined.

The reaction of carboxylic acids with hydrazoic acid in the presence of a strong acid catalyst is known as the Schmidt reaction. It differs from the Curtius reaction of acyl azides in that the azide is formed in situ and that its decomposition is accelerated by the acid present. Strong acids also catalyze the reactions of hydrazoic acid with alcohols, olefins, ketones, and aldehydes. These are also sometimes referred to as the Schmidt reaction. The synthetic usefulness of these reactions is summarized in the following equations.

$$RCOOH + HN_3 \longrightarrow RNH_2$$

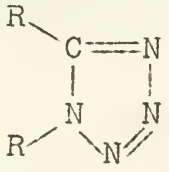
$$R_3COH + HN_3 \longrightarrow RCOR + RNH_2$$

$$R_2C{=}CH_2 + HN_3 \longrightarrow RCOCH_3 + RNH_2$$

$$RCOR + HN_3 \longrightarrow RCONHR$$

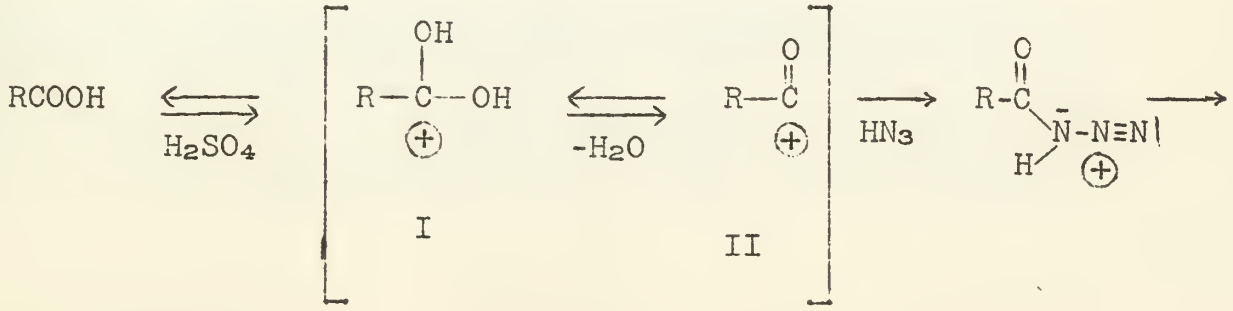
$$RCHO + HN_3 \longrightarrow RCN \text{ and } HCONHR$$

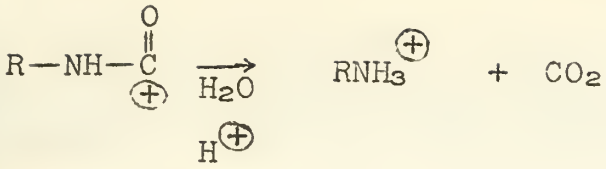
$$RCOR + HN_3 \text{ (excess)} \longrightarrow$$



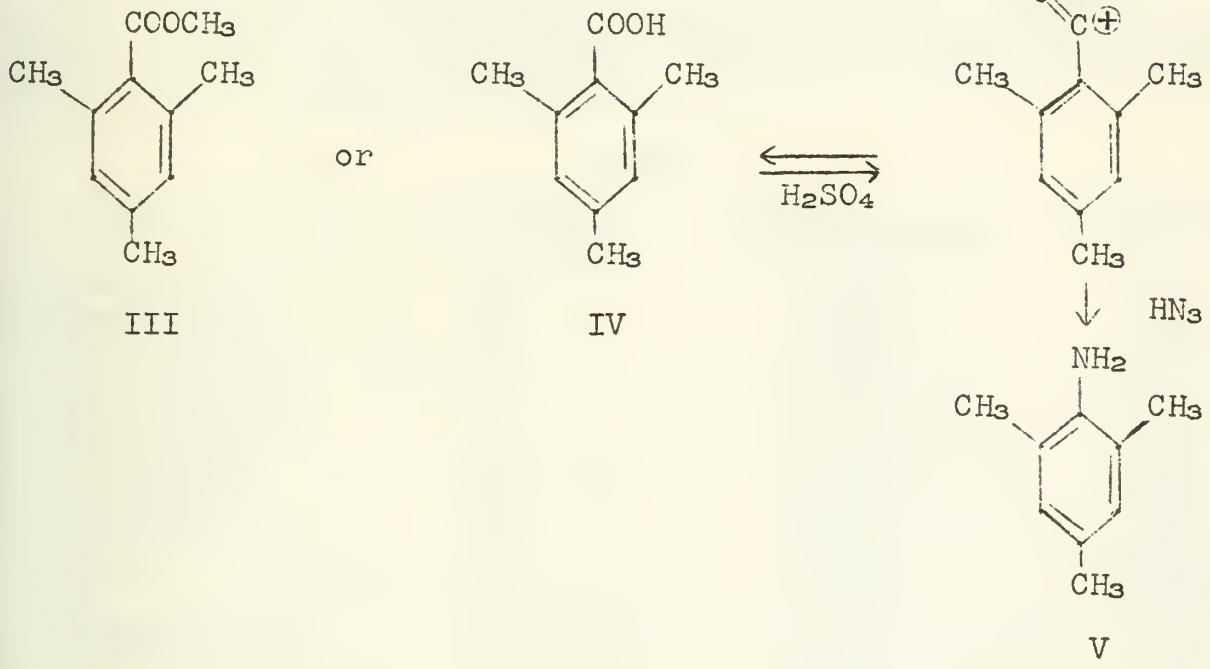
CARBOXYLIC ACIDS

Newman and Gildenhorn (4) studied the reaction of several aryl carboxylic acids and proposed what is still the accepted mechanism.

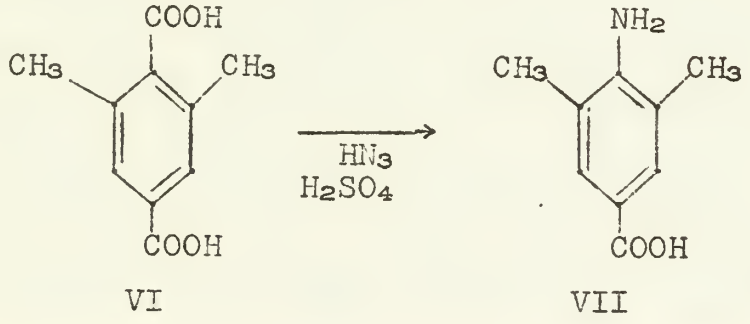




Both methyl mesitoate (III) and mesitoic acid (IV) gave good yields of mesidine (V) at 0° in concentrated sulfuric acid.



Benzoic acid required temperatures of 35-50° for reaction. The species which reacts with hydrazoic acid may be either I or II. The higher temperature may be required 1) to increase the rate of reaction of the dihydroxycarbonium ion (I) with hydrazoic acid or 2) to shift the equilibrium toward oxocarbonium ion (II). 2,6-Dimethylterephthalic acid (VI) formed 3,5-dimethyl-4-amino-benzoic acid (VII) exclusively.



It has been demonstrated (5) that the conversion of (+)-α-phenylpropionic acid with hydrazoic acid to (-)-α-phenylethyl amine proceeds with 99.6% retention of optical purity. Studies on the appropriate derivatives of (+)-α-phenylpropionic acid indicate that the Lossen reaction of the hydroxamic acid (5), the Beckmann rearrangement of (+)-α-phenylethyl methyl ketone (5), the Hofmann

rearrangement of the amide (6), and the Curtius reaction of the azide (7) occur with essentially complete retention of optical purity. It has also been shown that the configuration at the migrating center is retained in these five related reactions (5, 8, 9).

Briggs and Lyttleton (10) studied the Schmidt reaction of fourteen substituted benzoic acids, most of them in the meta series. A trichloroethylene solution of the acid was stirred rapidly at 40° with a one-tenth molar quantity of hydrazoic acid and an excess of concentrated sulfuric acid. The rate of nitrogen evolution was measured. The data are summarized in Table 1.

TABLE 1

Acid	$t_{1/2}$ (min.)	$\log(t^{\circ}_{1/2}/t_{1/2})$	Hammett σ (11)
m-chlorobenzoic	12	-0.602	0.373
m-bromobenzoic	10	-0.478	0.391
m-iodobenzoic	15	-0.699	0.352
m-hydroxybenzoic	5	-0.400	0.014(12)
m-methoxybenzoic	4	-0.124	0.115
m-ethoxybenzoic	4	-0.124	0.15
m-nitrobenzoic	100	-1.478	0.710
m-cyanobenzoic	18	-0.778	0.678
isophthalic	17	-0.752	0.355
m-toluic	2	0.176	-0.110(13)
benzoic	3	0.000	0.000
o-methoxybenzoic	5	-----	-----
p-methoxybenzoic	1 1/2	0.301	-0.268
o-nitrobenzoic	2	-----	-----
p-nitrobenzoic	120	-1.602	0.778

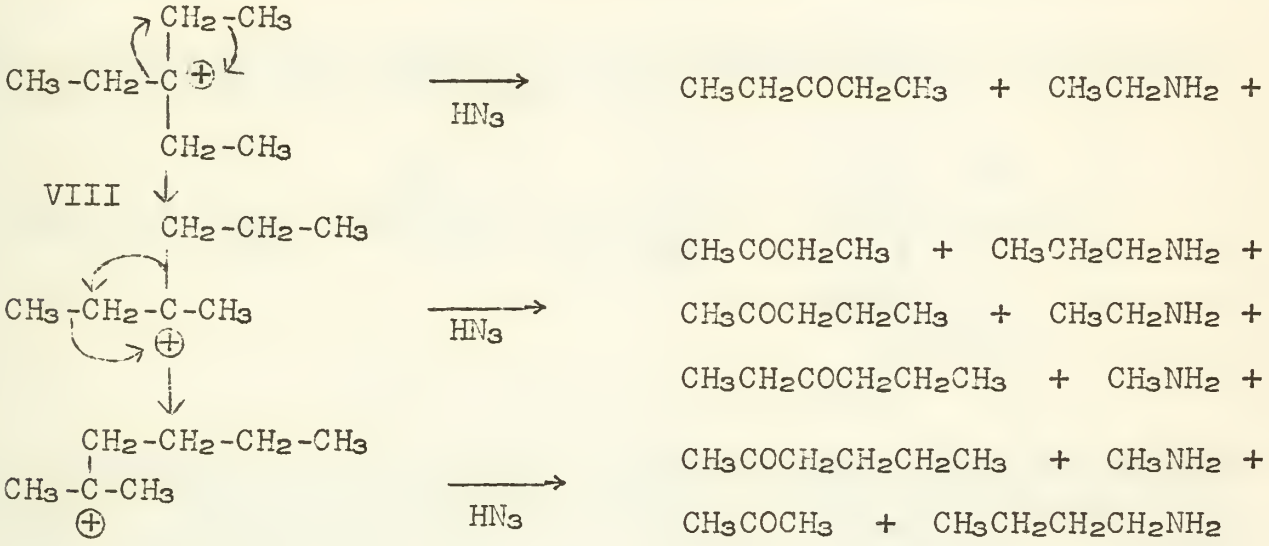
The symbol $t_{1/2}$ refers to the time of half-reaction; $t^{\circ}_{1/2}$ refers to the time of half-reaction of benzoic acid. Since $t_{1/2}$ is inversely proportional to the specific rate constant k and since in this work, the initial concentration of each of the acids was the same, $\log(t^{\circ}_{1/2}/t_{1/2})$ is equal to $\log(k/k_{\circ})$, where $k_{\circ}$ refers to benzoic acid. If a plot is prepared with $\log(t^{\circ}_{1/2}/t_{1/2})$ along the ordinate and σ along the abscissa, a straight line with considerable scatter results. (Figure 1, p.135). The line was estimated roughly, but it passes through the origin and yields a value of ρ of about -2, indicating that the rate-determining step is favored by electron-donating substituents. Whether the rate-determining step is the loss of a molecule of nitrogen, migration of the aryl group, or a concerted process involving both has not been demonstrated.

The substituent effects can also be discussed qualitatively. The measured rates of decomposition are roughly in the inverse order of the dissociation constants of the corresponding acids.

The latter are in the order (meta series only): $NO_2 > COOH > CN > Br > Cl > I > OH > CH_3O > C_2H_5O > H > CH_3$, while the rates of decomposition are in the order (meta series only): $CH_3 > H > C_2H_5O$, $CH_3O > OH > Br > Cl > I > COOH > CN > NO_2$. The large accelerating effect of

the o-nitro substituent was attributed to the participation of the non-bonding electrons of an oxygen atom of the nitro group in the departure of the nitrogen molecule. Considering the fact that the reaction is a heterogeneous one, the correlations seem quite good.

Acetic acid and isobutyric acid react normally when treated with hydrazoic acid in the presence of a large excess of sulfuric acid (14), while trimethyl- and triethylacetic acids react abnormally, giving cleavage products (15). Triethylacetic acid gave a 12.3% yield of carbon dioxide and a 24.9% yield of carbon monoxide, the latter presumably arising by decarbonylation of the oxocarbonium ion. Rearrangement products of the resulting carbonium ion (VIII) were observed.



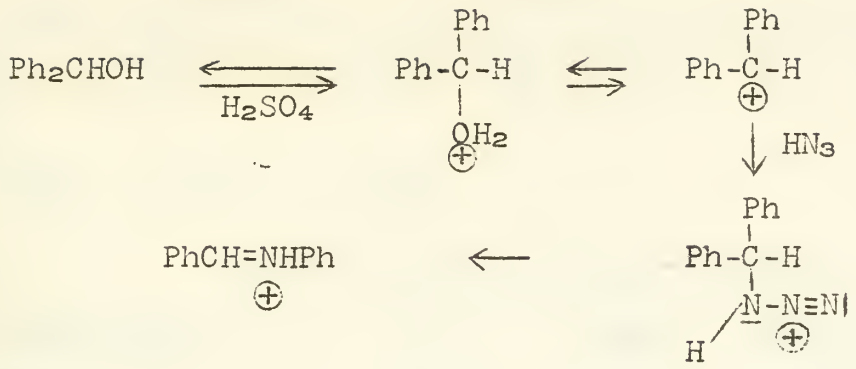
ALCOHOLS AND OLEFINS

Gratifying results have been obtained in the reactions of alcohols and olefins. When a secondary alcohol is treated with hydrazoic acid in the presence of a strong acid catalyst, the intermediate is a Schiff's base (IX), which on hydrolysis gives an aldehyde and an amine. The anil (X) from a 1,1-disubstituted ethylene gives a ketone and an amine on hydrolysis. Current studies have been made using diaryl carbinols and 1,1-diaryl-ethylenes.

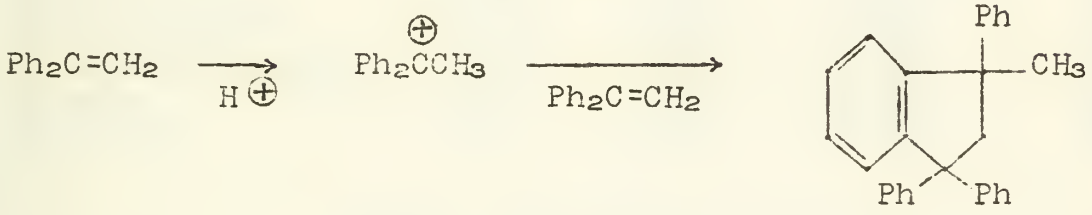
$$R_2CHOH \xrightarrow[HN_3]{H_2SO_4} \underset{IX}{RCH{=}NR} \xrightarrow{H_2O} RCHO + RNH_2$$

$$R_2C{=}CH_2 \xrightarrow[HN_3]{H_2SO_4} \underset{X}{RC(CH_3){=}NR} \xrightarrow{H_2O} RCOCH_3 + RNH_2$$

The mechanism for the reaction of the two types of compounds is similar and is illustrated below for benzhydrol.



A side reaction in the treatment of 1,1-diphenylethylene with hydrazoic acid produced XI in 26% yield (16).



XI

An important advance was made by Ege and Sherk (17), who treated 1,1-diphenylethanol with hydrazoic acid in trichloroacetic acid and isolated 1,1-diphenylethyl azide -- a stable, non-explosive compound. They found that trifluoroacetic acid caused slow evolution of nitrogen at room temperature, while ethanesulfonic and sulfuric acids caused rapid evolution. It was concluded that the acid catalyst plays a dual role in: 1) formation of the conjugate acid of the azide and 2) its decomposition.

Studies on the migration ratios in the rearrangements of 1-phenyl-1-arylethylenes, where the aryl group is substituted in the meta- or para-position, have been made (17, 18, 19). McEwen and Mehta (18) found equation 1 to be applicable; the migration ratio is defined in equation 2.

(1) $\log M = -2.11\sigma + 0.293$

(2) $M = \dfrac{\%\text{ migration of m- or p-phenyl}}{\%\text{ migration of phenyl}}$

The non-zero intercept is attributed to a systematic error in the experimental data. The data obtained by the several authors are summarized in Table 2 and plotted in Figure 2 (p. 135). Tietz and McEwen (20) studied the migration ratios of several meta- and para-substituted benzhydrols. The corresponding benzhydryl azides were

prepared and rearranged. The aldehyde mixture was oxidized with silver oxide and the resulting acid mixture was analyzed. An accuracy of ±10% is claimed for the individual values of M. Equation 3 fits the curve pictured in Figure 2, the data for which are tabulated in Table 3.

(3) $\log M = -2.03\sigma + 0.237$

TABLE 2: 1-Phenyl-1-arylethylenes

Aryl group	M	logM	Hammett σ (11)	Reference
phenyl	1.00	0.00	0.000	--
p-chlorophenyl	0.62	-0.21	0.227	26
p-ethylphenyl	4.53	0.65	-0.151	27
m-tolyl	2.36	0.37	-0.110(13)	27
p-fluorophenyl	1.76	0.24	0.062	27
p-bromophenyl	0.54	-0.27	0.232	27
3,4-dimethylphenyl	5.42	0.73	-0.229	27
p-tolyl	3.44	0.47	-0.170	28
p-anisyl	6.4	0.77	-0.268	28

TABLE 3: Phenylarylcarbinols

Aryl group	M	logM	Hammett σ
m-chlorophenyl	0.27	-0.57	0.373
p-bromophenyl	0.58	-0.24	0.232
p-chlorophenyl	0.67	-0.18	0.227
p-tolyl	3.44	0.54	-0.170
p-anisyl	6.50	0.81	-0.268

Recent work by Arcus and coworkers (21, 22) indicates that the effects of 2- and 3-substituents in fluorenols can be correlated by an adaptation of the Hammett relationship. When fluorenol is treated with hydrazoic acid, the product obtained is phenanthridine (XII) (23).

XII

The 9-alkyl- and 9-arylfluorenols give 9-alkyl- or 9-arylphenanthridines (22, 24). The data gathered by Arcus and Coombs (22) for the 2- and 3-substituted fluorenols (XIII) are given in Table 4.

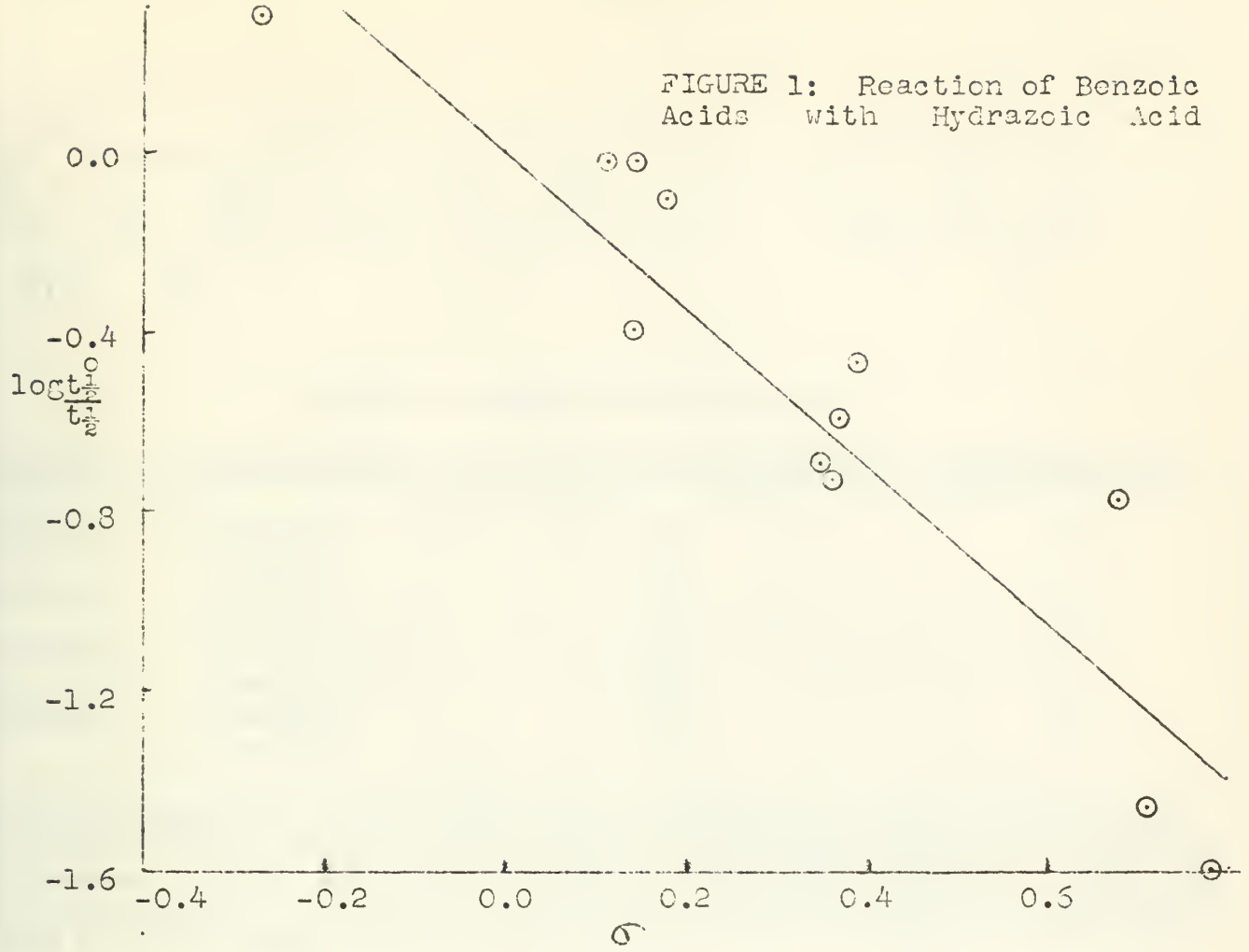


FIGURE 1: Reaction of Benzoic Acids with Hydrazoic Acid

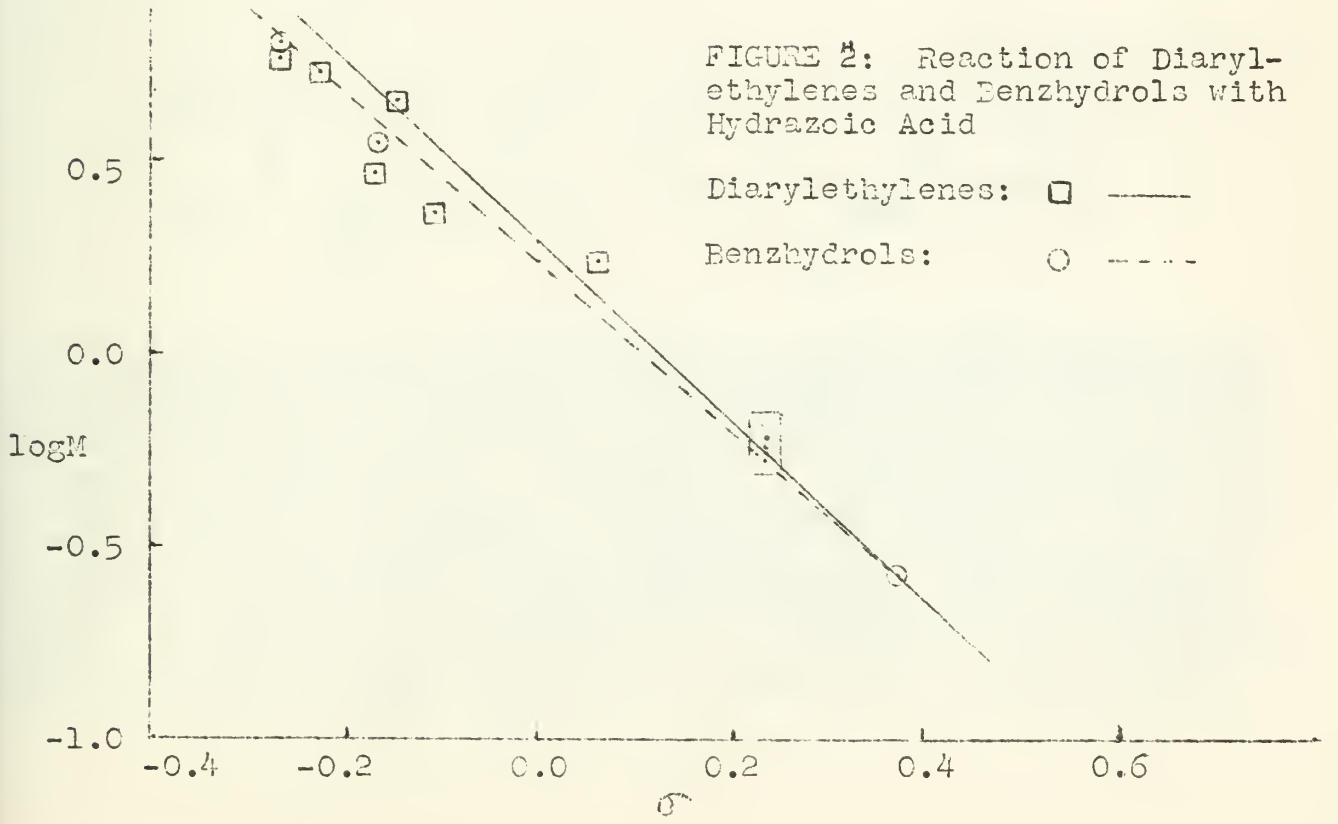


FIGURE 2: Reaction of Diarylethylenes and Benzhydrols with Hydrazoic Acid

Diarylethylenes: □ ——

Benzhydrols: ○ - - - -

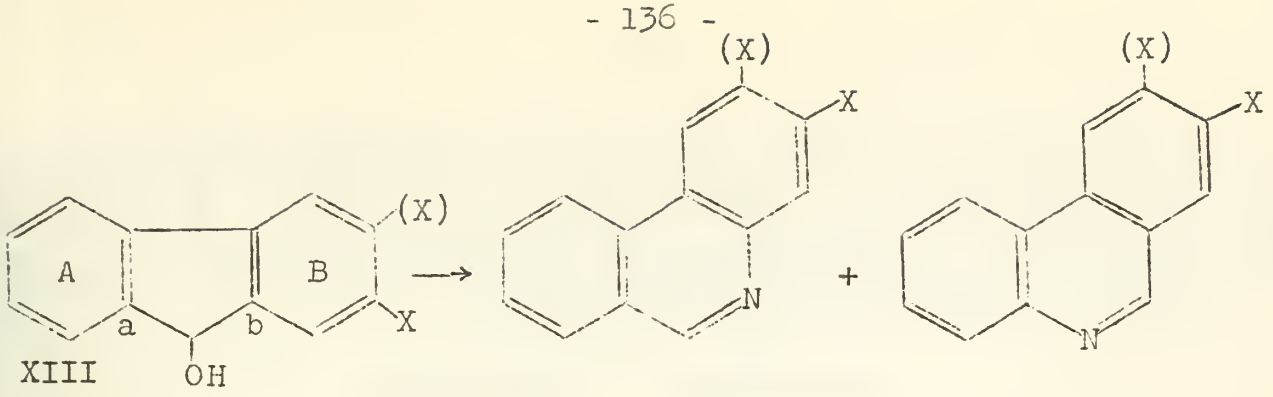
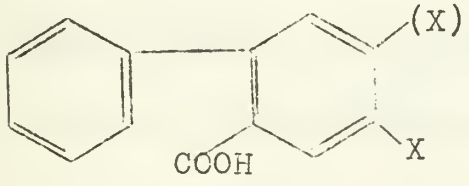


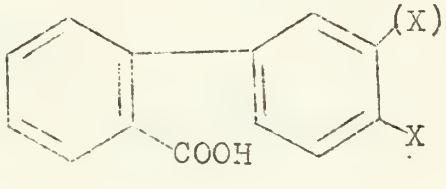
TABLE 4: Substituted Fluorenols

Fluorenol	Phenanthridine	% of total phenanthridine	Migrating ring
2-nitro	2-nitro	3	B
	7-nitro	97	A
3-nitro	3-nitro	6	B
	6-nitro	94	A
2-methoxy	2-methoxy	32	B
	7-methoxy	68	A
2-methyl	2-methyl	53	B
	7-methyl	47	A

Using an empirical relationship for estimating the pK's of the acids XIV and XV, these authors (21) obtained a straight line plot when the difference in pK's was plotted against the product ratios. A qualitative discussion in terms of the electron-availability at carbon atoms a and b can be made.



XIV



XV

It is clear that the rate-determining step in the decomposition of the azides derived from alcohols and olefins is also enhanced by electron-donating substituents in the migrating ring. On the other hand, the diazonium ions from the 2,2-diarylethyl-amines (25) and the 1,1-diaryl-2-aminoethanols manifest little participation by the aryl group in the expulsion of the nitrogen molecule. Thus, when the leaving nitrogen molecule is attached to a nitrogen atom, as in the azides, the expulsion becomes more difficult. But the nitrogen molecule is a better leaving group than bromide ion in the Hofmann reaction of substituted benzamides (ρ = -2.58) (27) and better than benzoate ion in the Lossen reaction of substituted benzoylbenzhydroxamic acids (ρ = -2.51) (28).

An elegant study by Gudmundsen and McEwen (29) has revealed the timing of the rearrangement of benzhydrols and 1,1-diarylethylenes. By measuring the rate of nitrogen evolution of acetic acid solutions of the azides, using sulfuric acid as the catalyst, it was found that the rate of decomposition obeys a second-order rate law (Equation 4). Equation 5 defines the acidity function h_o. (Reference 1, p. 59).

$$(4) \quad -d(\text{azide})/dt = k_2(\text{azide})h_o$$

$$(5) \quad h_o = a_H \gamma_A / \gamma_{AH^{\oplus}}$$

The following argument was advanced to prove that the loss of the nitrogen molecule is not synchronous with migration but precedes it. Consider the phenylarylcarbinyl azide.

k_2 = specific rate constant for nitrogen evolution
k_P = specific rate constant for phenyl migration
k_A = specific rate constant for aryl migration

If it is assumed that nitrogen evolution is synchronous with migration and that nitrogen and the isomeric Schiff's bases are the only products formed, it follows that:

$$d(N_2)/dt = k_2(\text{azide})h_o$$

$$d(ArCH{=}\overset{\oplus}{N}HPh)/dt = k_P(\text{azide})h_o$$

$$d(PhCH{=}\overset{\oplus}{N}HAr)/dt = k_A(\text{azide})h_o$$

$$d(N_2)/dt = d(ArCH{=}\overset{\oplus}{N}HPh)/dt + d(PhCH{=}\overset{\oplus}{N}HAr)/dt$$

$$k_2 = k_P + k_A$$

$k_A/k_P = M$, where M has the same meaning as before.

$$k_2 = k_P(1 + M)$$

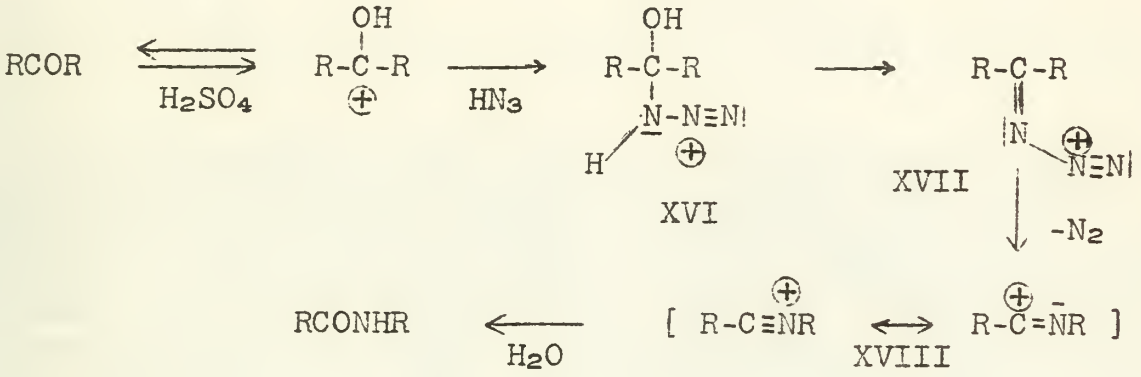
$$\log(k_2/k_2^o) = \log(k_P/k_2^o) + \log(1 + M)$$

k_2^o = specific rate constant for unsubstituted azide

If the assumption which was made is correct, a plot of $\log(k_2/k_2^o)$ versus $\log(1 + M)$ should give a straight line with a slope of one. The line actually obtained has a slope of nearly two, proving that the assumption was incorrect and that the loss of the nitrogen molecule precedes migration.

KETONES AND ALDEHYDES

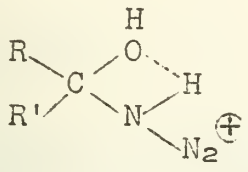
Fewer quantitative correlations have been made to elucidate the mechanism of the reactions of ketones and aldehydes. However, they have been more useful synthetically than the reactions of acids, alcohols, and olefins. The mechanism proposed by Smith (30) is similar to the mechanisms discussed above.



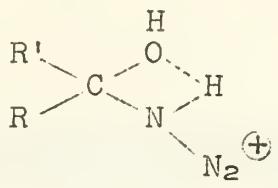
The order of reactivity of ketones -- dialkyl > alkylaryl > diaryl -- is the same as the order of their basicities. In the dialkyl ketone series the more substituted alkyl group migrates preferentially. This has been demonstrated recently for the reaction of 2-alkylcyclopentanones and 2-alkylcyclohexanones (31) and for the reaction of several piperidones (32, 33). The percentage migration of the methyl group of acetophenone is 5% while the isopropyl group of phenyl isopropyl ketone migrated to the extent of 49% (34). However, only a small percentage of migration of the cyclopropyl group occurred in the reaction of three cyclopropyl aryl ketones (35). With toluene as the diluent and sulfuric acid as the catalyst, the reaction of methyl t-butyl ketone with hydrazoic acid gave a 72% yield of t-butyltoluenes (90% para and 10% meta) (36). Presumably, t-butylcarbonium ion is eliminated from the intermediate corresponding to XVII.

There has been some controversy concerning whether it is the intermediate XVI or XVII which rearranges. Smith (30) suggested that the bulkier group should migrate in a manner analogous to the Beckmann rearrangement of ketoximes, since XVII would be expected to exist in the syn and anti forms. This argument applies for the dialkyl ketones, but numerous exceptions have been observed in the diaryl ketones. Dice and Smith (37) prepared a series of amino-phenanthrenes from benzoylphenanthrenes. Several cases where the phenyl group migrates to a greater extent than would be expected have occurred in the ortho-substituted benzophenones and related compounds (38-41). It has been pointed out that if the interconversion of the syn and anti forms of XVII is rapid compared with the rate of migration, electrical effects instead of the bulk effect could operate (40). Fluorenone was treated with hydrazoic acid and sulfuric acid under anhydrous conditions and the reaction mixture was then treated with

anhydrous methanol instead of water (21). When only phenanthridone and not 9-methoxyphenanthridine was obtained, Arcus and Coombs proposed the isomeric hydrogen-bonded intermediates XIX and XX, in which rearrangement would occur by migration of the group trans to the leaving nitrogen molecule.

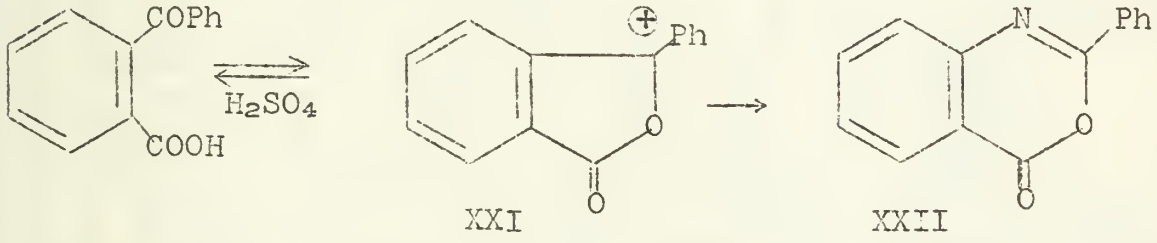


XIX



XX

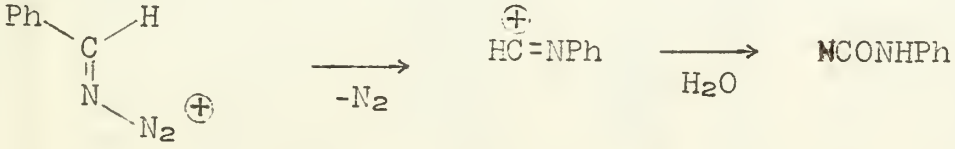
o-Phenylbenzophenone and o-acyl- or o-aroylbenzoic acids give cyclization products when treated with hydrazoic acid (42-44). 9-Phenylphenanthridine was obtained in 89% yield from the former when sulfuric acid was used as the catalyst (41). Under non-hydrolyzing conditions 2-phenyl-6-oxo-4,5-benz-1,3-oxazine (XXII) was obtained in excellent yield from o-benzoylbenzoic acid (43). Alkylidenephthalides also gave oxazines with hydrazoic acid, probably through an intermediate corresponding to XXI. N-Benzoylanthranilic acid was obtained in nearly quantitative yield from XXII when it was subjected to the normal hydrolyzing conditions, in the absence of hydrazoic acid, indicating that the oxazine is probably an intermediate in amide formation.



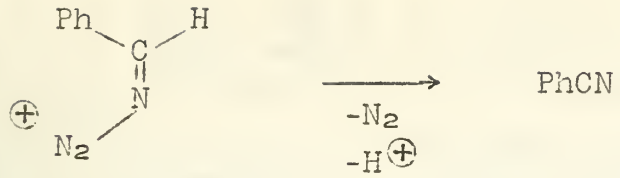
XXI XXII

Bulk effects should be negligible in the para-substituted benzophenones and in the 2- and 3-substituted fluorenones. However, attempts to correlate migration ratios with the Hammett values using these compounds have failed (34, 21).

In the reaction of benzaldehyde with hydrazoic acid it was suggested that formanilide arises by migration of the phenyl group trans to the leaving nitrogen molecule in the anti-form (XXIII) of the intermediate, while benzonitrile arises from a trans elimination in the syn-form (XXIV) (45).

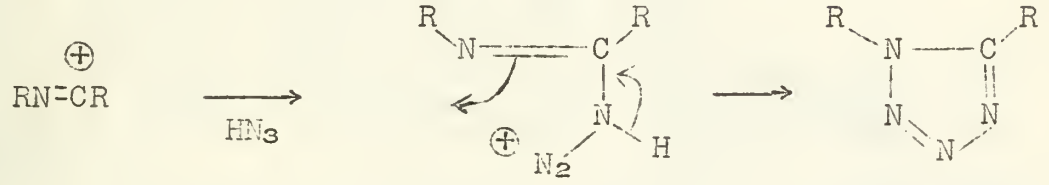


XXIII



XXIV

Since tetrazoles are the products when an excess of hydrazoic is employed, it seems likely that XVIII attacks a hydrazoic acid. molecule (30).



BIBLIOGRAPHY

1. J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, 1956, p. 317.
2. C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell, Ithaca, 1953, p. 494.
3. H. Wolff, "Organic Reactions," Wiley, New York, 1946, Vol.III, p.307.
4. M. S. Newman and H. L. Gildenhorn, J. Am. Chem. Soc., 70, 317 (1948)
5. A. Campbell and J. Kenyon, J. Chem. Soc., 25 (1946).
6. C. L. Arcus and J. Kenyon, J. Chem. Soc., 916 (1939).
7. J. Kenyon and D. P. Young, J. Chem. Soc., 263 (1941).
8. J. Kenyon, H. Phillips, and V.P. Pittmann, J. Chem. Soc., 1072(1935)
9. J. v. Braun and E. Friehmelt, Ber., 66, 684 (1933).
10. L. H. Briggs and J. W. Lyttleton, J. Chem. Soc., 421 (1943).
11. L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 188.
12. J. D. Roberts and W. T. Moreland, J. Am. Chem. Soc., 75, 2267 (1953).
13. C. C. Price and D. C. Lincoln, J. Am. Chem. Soc., 73, 5836 (1951).
14. C. Schuerch and E. H. Huntress, J. Am. Chem. Soc., 71, 2233 (1949).
15. C. Schuerch and E. H. Huntress, J. Am. Chem. Soc., 71, 2238 (1949).
16. W. E. McEwen, M. Gilliland, and B. I. Sparr, J. Am. Chem. Soc., 72, 3212 (1950).
17. S. N. Ege and K. W. Sherk, J. Am. Chem. Soc., 75, 354 (1953).
18. W. E. McEwen and N. B. Mehta, J. Am. Chem. Soc., 74, 526 (1954).
19. D. R. Nielsen and W. E. McEwen, J. Am. Chem. Soc., 76, 4042 (1954).
20. R. F. Tietz and W. E. McEwen, J. Am. Chem. Soc., 77, 4007 (1955).
21. C. L. Arcus and M. M. Coombs, J. Chem. Soc., 1498 (1956).
22. C. L. Arcus and M. M. Coombs, J. Chem. Soc., 4319 (1954).
23. C. L. Arcus and R. J. Mesley, J. Chem. Soc., 178 (1953).
24. C. L. Arcus and E. A. Lucken, J. Chem. Soc., 1634 (1955).
25. L. S. Ciereszko and J. G. Burr, J. Am. Chem. Soc., 74, 5431 (1952).

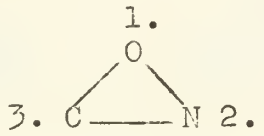
26. D. Y. Curtin and M. C. Crew, J. Am. Chem. Soc., 76, 3719 (1954).
27. C. R. Hauser and N. B. Renfrow, J. Am. Chem. Soc., 59, 121 (1937).
28. R. D. Bright and C. R. Hauser, J. Am. Chem. Soc., 61, 618 (1939).
29. C. H. Gudmundsen and W. E. McEwen, J. Am. Chem. Soc., 79, 329 (1957).
30. P. A. S. Smith, J. Am. Chem. Soc., 70, 320 (1948).
31. H. Shechter and J. C. Kirk, J. Am. Chem. Soc., 73, 3087 (1951).
32. S. C. Dickerman, J. Org. Chem., 14, 530 (1949).
33. S. C. Dickerman and E. J. Moriconi, J. Org. Chem., 20, 206 (1955).
34. P. A. S. Smith and J. P. Horwitz, J. Am. Chem. Soc., 72, 3718, (1950).
35. S. C. Bunce and J. B. Cloke, J. Am. Chem. Soc., 76, 2244 (1954).
36. H. D. Zook and S. C. Paviak, J. Am. Chem. Soc., 77, 2501 (1955).
37. J. R. Dice and P. A. S. Smith, J. Org. Chem., 14, 179 (1948).
38. V. A. Petrow, J. Chem. Soc., 200 (1946).
39. V. A. Petrow, J. Chem. Soc., 888 (1946).
40. R. D. Westland and W. E. McEwen, J. Am. Chem. Soc., 74, 6141 (1952)
41. P. A. S. Smith, J. Am. Chem. Soc., 76, 431 (1954).
42. G. M. Badger, R. T. Howard, and A. Simons, J. Chem. Soc., 2849 (1952).
43. C. L. Arcus and M. M. Coombs, J. Chem. Soc., 3698 (1953).
44. C. L. Arcus and R. E. Marks, J. Chem. Soc., 1627 (1956).
45. W. E. McEwen, W. E. Conrad, and C. A. Yanderwerf, J. Am. Chem. Soc. 74, 1168 (1952).

OXAZIRANES

Reported by J. P. Collman May 6, 1957

INTRODUCTION

In 1956 Emmons (1) reported a new heterocycle in which carbon, oxygen, and nitrogen are joined in a three-membered ring. These reactive compounds are called oxaziranes. Such a ring system had been postulated in the older literature but had always been discredited in the light of further evidence (2). The numbering of the oxazirane ring system is:



PREPARATION

The preparation of these compounds is an excellent illustration of the use of analogy in organic synthesis. Peracetic acid reacts rapidly with acid stable imines at low temperatures to form oxaziranes in yields ranging from 50 to 80 per cent. This reaction is, of course, analogous to the preparation of oxirane compounds by the action of peracids on olefins.

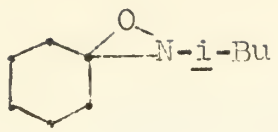
The reaction is limited by the inherent stability of the particular oxazirane and by its stability in the acidic reaction medium.

Oxaziranes can also be prepared from 1,3,5-trialkylperhydro-s-triazines. Table I lists some of the oxaziranes prepared by Emmons (3). The liquid compounds were purified by vacuum distillation below 100°. Above this temperature many of the oxaziranes undergo spontaneous decomposition.

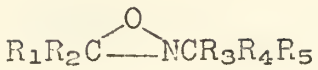
The reaction of imines with peracids is described in British Patent 743,940, January 25, 1956 (4). The same three-membered heterocyclic ring system is postulated for the products, which are said to contain the "isonitrone" group. The chemical properties and analyses of these compounds are not mentioned in the abstract of this work. Eighteen compounds are reported. Their structures are listed in Table II.

STABILITIES

The stabilities of oxaziranes follow certain trends. All trialkyl oxaziranes investigated are stable with the exception of 2-isobutyl-3,3-pentamethyleneoxazirane (A). All 2-t-alkyloxaziranes (B) are relatively stable.

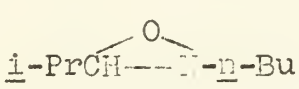


(A)

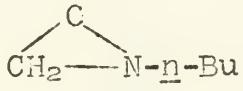


(B)

2,3-Dialkyloxaziranes not having a 2-t-alkyl substituent are unstable and slowly decompose. For example, the active oxygen assay of 2-n-butyl-3-isopropyloxazirane (C) dropped from 95% to 2% upon standing two months at room temperature. 2-n-Alkyloxaziranes are even less stable. Thus 2-n-butyloxazirane (D) lost 37% of its active oxygen in three days and was completely decomposed after eight days.



(C)



(D)

Emmons (3) reports that oxaziranes containing a 2-phenyl or 2-benzyl group could not be isolated. Although 2-n-alkyl-3-(p-nitrophenyl)-oxaziranes were easily prepared, the oxaziranes having an unsubstituted 3-phenyl substituent could not be prepared unless the 2-alkyl group was tertiary. These observations disagree with the British work (4).

SURVEY OF OXAZIRANE REACTIONS

The highly strained oxazirane ring system undergoes a variety of reactions. The course of a given reaction usually varies widely with the substituent on the oxazirane ring.

Oxaziranes undergo many reactions that are typical of active oxygen compounds. Thus, aryl Grignard reagents react with oxaziranes to form phenols (5). Tertiary amines are converted to N-oxides in high yields. Ferrous ions undergo one-electron transfer reactions with oxaziranes. Oxaziranes may be analyzed by iodometric titrations.

Vapor-phase pyrolysis of oxaziranes yields a variety of products including amides, nitrones, and amines. Liquid phase thermal rearrangement yields amides, nitrones, and ketones.

Aqueous acid hydrolysis may be used to produce t-hydroxylamines, aldehydes, ketones, and amines. Certain oxaziranes undergo basic hydrolysis.

STRUCTURE PROOF

The following evidence clearly establishes the structure of the oxazirane ring. These compounds have the same molecular formulae as the corresponding nitrones. Oxaziranes are all active oxygen

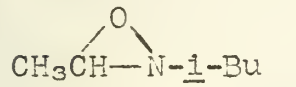
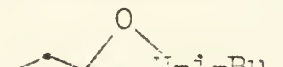
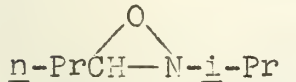
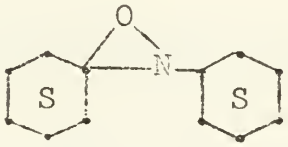
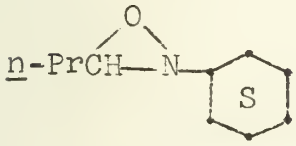
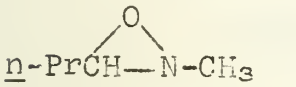
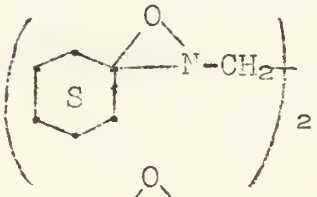
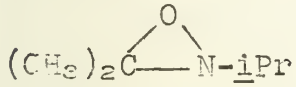
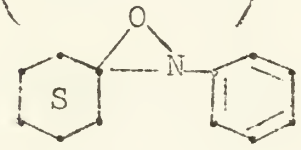
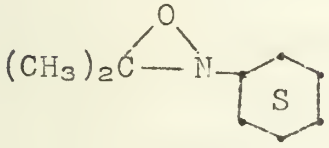
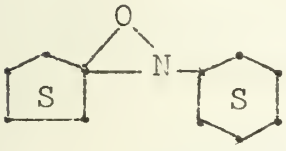
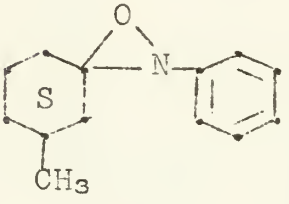
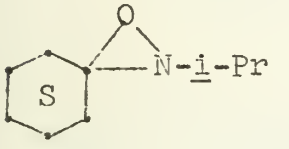
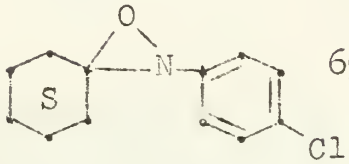
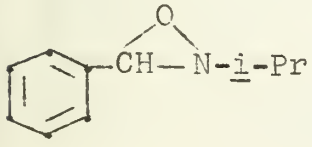
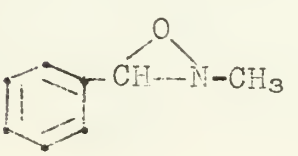
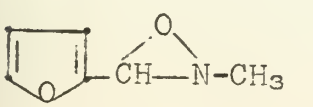
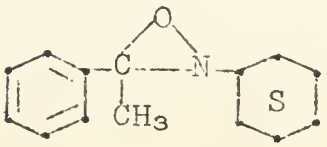
TABLE I

Oxaziranes Prepared by Emmons, $RR'C\overset{O}{\diagdown\diagup}NR''$

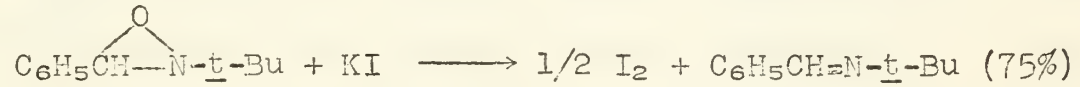
R	R'	R''	Yield,%	B.p. °C	mm.
H	H	t-Bu	46	52-4	75
H	H	t-Oct	69	64-6	6
C_6H_5	H	t-Bu	71	61-3	0.3
C_6H_5	H	t-Oct	67		
p-$O_2NC_6H_4$	H	i-Pr	60	46-8	(m.p.)
p-$O_2NC_6H_4$	H	Et	97	34-5	(m.p.)
p-$O_2NC_6H_4$	H	t-Bu	78	65-6	(m.p.)
i-Pr	H	t-Bu	71	68-70	39
i-Pr	H	n-Bu	65	56-8	10
n-BuCH(Et)	H	n-Bu	83		
i-Pr	H	$C_6H_5CH(CH_3)$	80		
i-Bu	Me	n-Pr	73	61	8
p-$O_2NC_6H_4$	H	t-Oct	66	54-6	(m.p.)
Me	i-Pr	n-Pr	64	60	15
n-Bu	H	H	74	43	20
i-Pr	H	t-Oct	78		
Me	Et	Allyl	49	51	6
Et	Et	Et	56	54	19
Me	Me	n-Hex	14	58	3
i-Pr	H	i-Bu	50	53	12
Et	Et	$C_6H_5CH(CH_3)$	91		
α-Pyridyl	H	t-Bu	75	68-70	0.4

TABLE II

Oxaziranes Reported in British Patent 743,940, Jan. 25, 1956

Structure	B.P. °C.	mm.	Structure	B.P. °C.	mm.
	40-42	32		55-57	0.6
	43-45	13		90-92	0.3
	78-80	0.8			
	42-44	32		106-7	(M.P.)
	58-59	10		75	(M.P.)
	72				
	74-6	0.4		65-66	(M.P.)
	72-4	8		69-70	(M.P.)
	65-67	0.9		70	2.5
	44-46	0.6		118-20	0.8

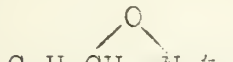
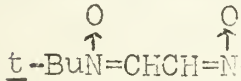
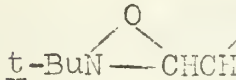
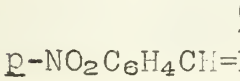
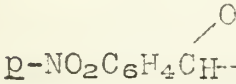
compounds, whereas the corresponding nitrones do not show active oxygen reactions. This is illustrated by the reaction of 2-t-butyl-3-phenyloxazirane with potassium iodide in aqueous acetic acid to produce a 75% yield of N-benzylidine-t-butylamine. Oxidation of the iodide is quantitative in this reaction. Except for some hydrolysis, the isomeric nitrone did not react under these conditions.



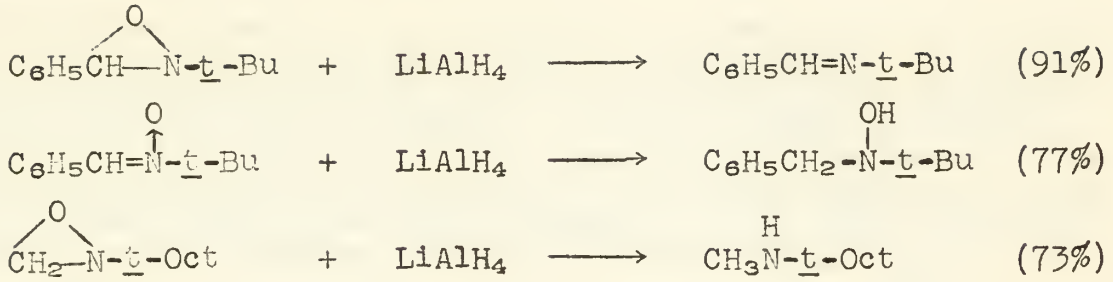
The oxazirane ring shows no absorption in the ultraviolet region, whereas the nitrones absorb strongly in this region. This is illustrated in Table III.

Table III

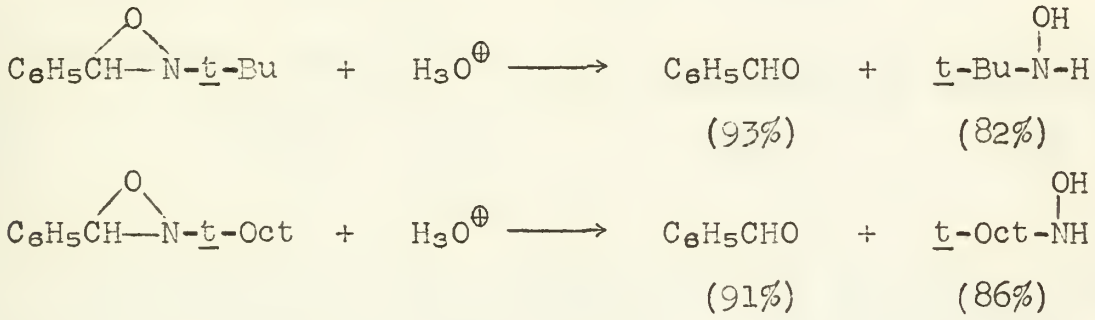
Ultraviolet Spectra of Oxaziranes and Isomeric Nitrones

Compounds	λ max. mμ	ε max.
	295	16,700
	249	930
	336	20,800
	none	
	252; 362	11,400; 15,800
	268	11,900

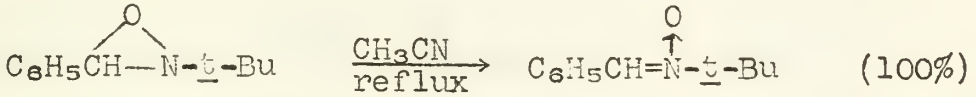
Reduction of 2-t-butyl-3-phenyloxazirane with lithium aluminum hydride produced N-benzylidine-t-butylamine in 91% yield. The isomeric nitrone was reduced to the N-benzyl-N-t-butylhydroxylamine in 77% yield. Lithium aluminum hydride reduction of 2-t-octyloxazirane produced a 73% yield of N-methyl-t-octylamine. These reactions establish the skeletal arrangement of these oxaziranes and illustrate another difference in the chemical behavior of an oxazirane and its isomeric nitrone.



Acid hydrolysis of 2-t-butyl-3-phenyloxazirane produced a 93% yield of benzaldehyde and an 82% yield of β-t-butylhydroxylamine. The corresponding nitrone, N-t-butylbenzaldoxime, formed a salt under these conditions (presumably undergoing slow hydrolysis). This nitrone is a solid, whereas the oxazirane is a liquid. Parallel reactions were observed in the case of 2-t-octyl-3-phenyloxazirane and its isomeric nitrone.



Since the oxazirane structure is an electronic tautomer of the nitrone structure, it might be expected that under the proper conditions an oxazirane could isomerize to the more stable nitrone. This has been shown to be the case with 2-t-butyl-3-phenyloxazirane. This compound was quantitatively converted to the isomeric N-t-butylbenzaldoxime upon refluxing three days in acetonitrile.

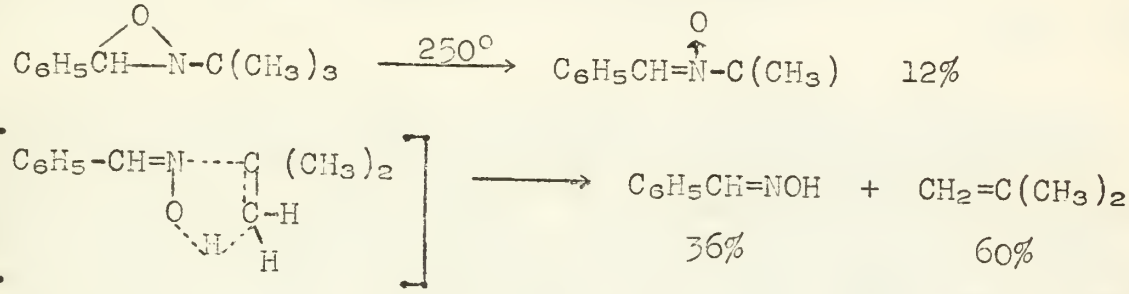


The final establishment of the oxazirane structure required the proof of an asymmetric center in oxaziranes that are unsymmetrically substituted in the three position. The partial resolution of 2-n-propyl-3-methyl-3-isobutyloxazirane provided the evidence for this requirement. This resolution (α_d^{22} -3.94°) was accomplished by a clever use of stereochemical control. An excess of this oxazirane was refluxed in methylene chloride with brucine. The tertiary, optically-active amine was quantitatively converted to its insoluble N-oxide. The remaining oxazirane showed optical activity. This method failed to resolve 2-t-butyl-3-phenyloxazirane.

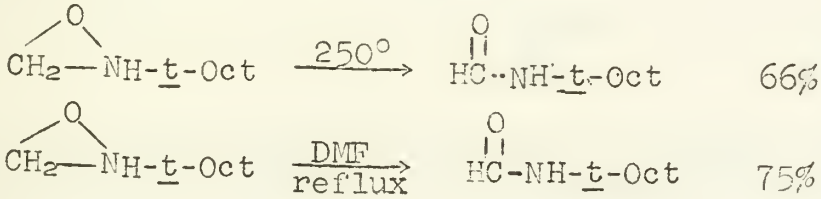
THERMAL DECOMPOSITION OF OXAZIRANES

Liquid-phase conversion of oxaziranes to the isomeric nitrones appears to be a general reaction of 3-phenyloxaziranes. The most carefully studied example of this is the above-mentioned isomerization of 2-t-butyl-3-phenyloxazirane. A kinetic study (6) showed that this reaction is first order and goes to 100% completion. The energy of activation was found to be +27 Kcal/mole, and the entropy of activation was found to be +60 e.u./mole. This large, positive entropy reflects the strained nature of the oxazirane ring.

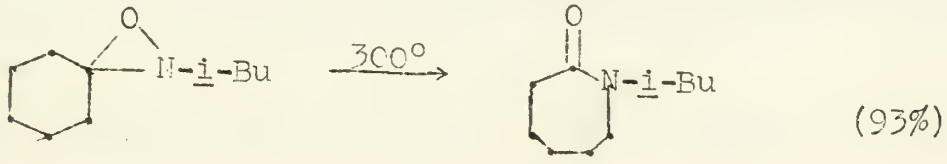
The 2-t-butyl-3-phenyloxazirane reacts in a similar manner when pyrolyzed in the vapor state. Pyrolysis of this compound at 250° produced 12% of the nitrone, 60% isobutylene, and 36% benzaldoxime. The last two products appear to result from a cyclic elimination path, similar to the Cope elimination of amine oxides (7). Such a β-elimination has never been reported for nitrones.



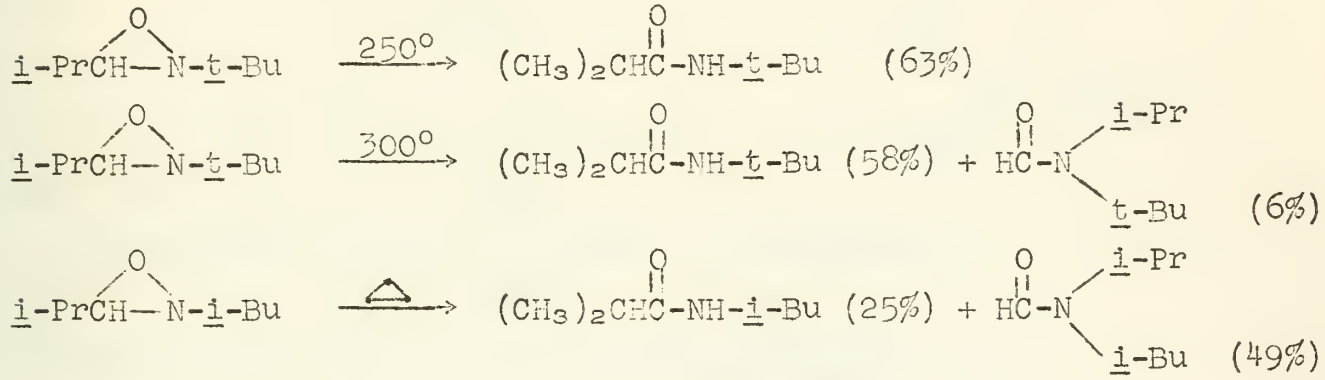
The alkyloxaziranes react differently from the 3-phenyloxaziranes. When subjected to vapor-phase pyrolysis at 250-300°, alkyloxaziranes rearrange to form amides. These rearrangements involve the migration of a hydrogen or alkyl group from the carbon to the nitrogen of the oxazirane ring. Thus at 250° 2-t-octyloxazirane is converted to t-octylformamide in 66% yield. This reaction also occurs in solution at lower temperatures. Refluxing this oxazirane in dimethylformamide produced a 75% yield of the t-octylformamide.



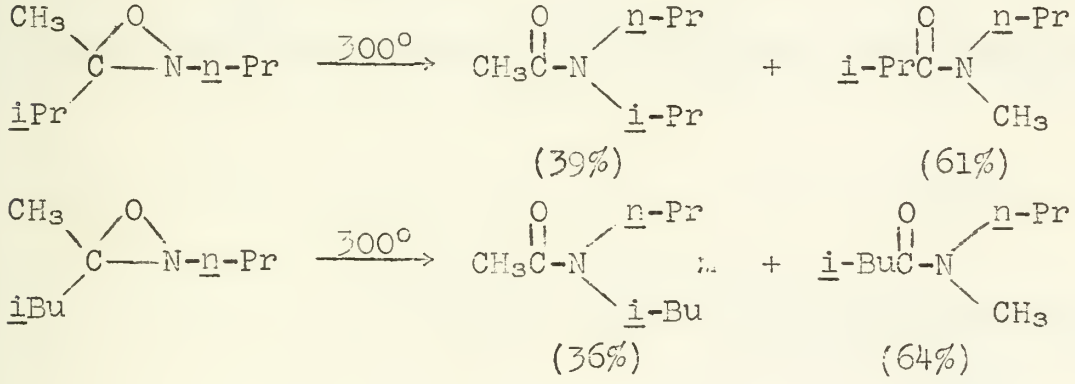
N-Isobutylcaprolactam is produced in 93% yield by vapor-phase pyrolysis of 2-isobutyl-3,3-pentamethyleneoxazirane.



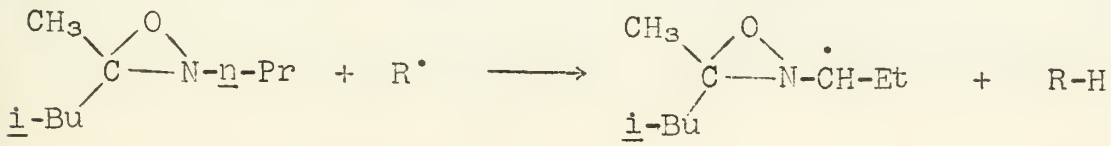
The course of these pyrolysis reactions was found to be dependent on the temperature. Thus, at 250° 2-t-butyl-3-isopropyl-oxazirane was converted into t-butylisobutyramide in (63%). Reaction at 300° produced 58% t-butylisobutyramide and 6% N-t-butyl-N-isopropylformamide. When the 2-t-butyl group was replaced by the slightly less bulky isobutyl group, the isopropyl group showed a two-to-one migratory preference over hydrogen.

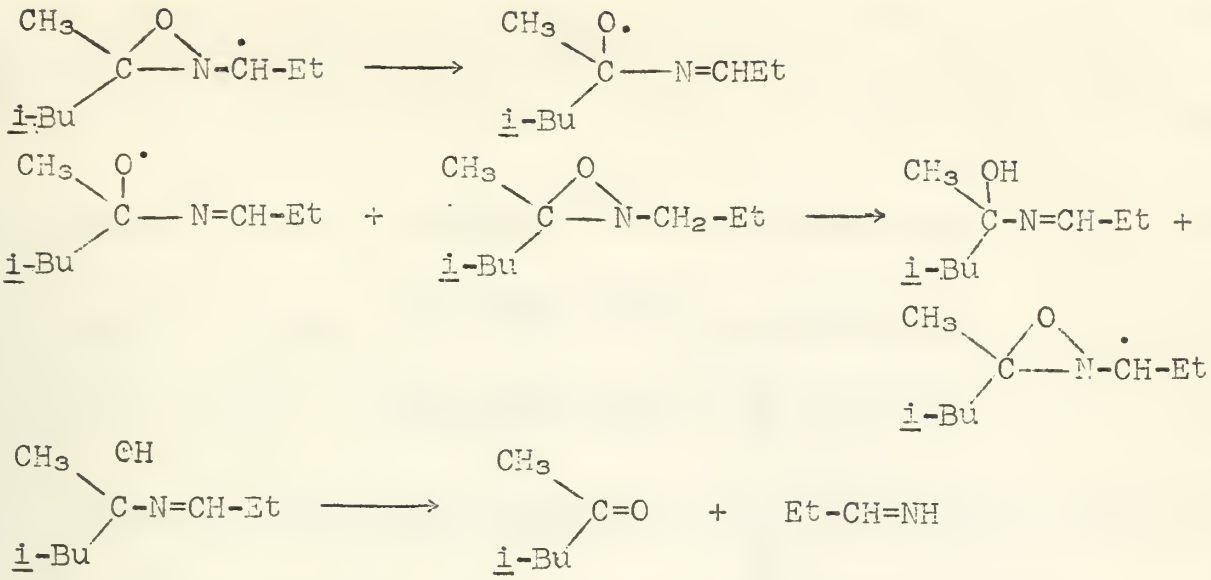


The pyrolysis of trialkyloxaziranes produces a mixture of N-disubstituted amides. Thus, 2-n-propyl-3-methyl-3-isopropyl-oxazirane reacted to form N-isopropyl-N-n-propylacetamide and N-n-propyl-N-methylisobutyramide. In a similar manner 2-n-propyl-3-methyl-3-isobutyramide produced a mixture of the two possible isomeric amides. Again the methyl group showed a migratory preference over the secondary alkyl group. The yields given below are based on 100% mixed amides. The total conversion is about 65%.



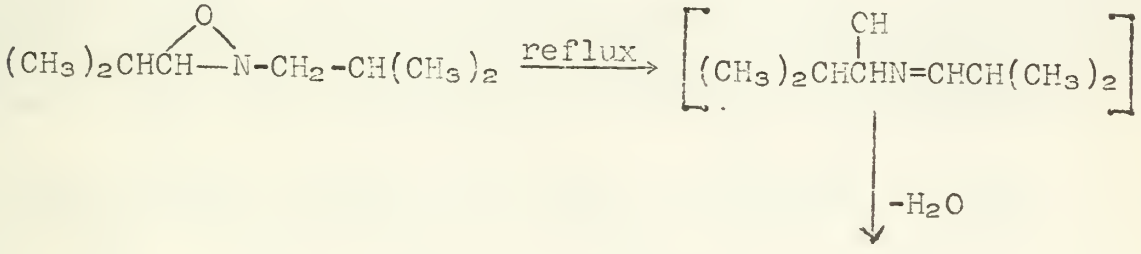
2-n-Propyl-3-methyl-3-isobutyl oxazirane was heated to reflux at atmospheric pressure. The temperature dropped from 168° to 128° over a period of two hours. The resulting oil yielded methyl isobutyl ketone (92%), ammonia (32%), oxazirane (2%), mixed amides (4%), and an acid-soluble tar. This tar is believed to be a condensation product of propionaldimine. The following reaction scheme was postulated to explain these results. R· is an unknown initiator.





$$Et\text{-}CH{=}NH \longrightarrow NH_3 + \text{aldol-like polymer}$$

It is of interest that in the case of 2-isobutyl-3-isopropyl-oxazirane a similar autodecomposition reaction produced an olefinic imine (E) which could have come from an alpha-hydroxy imine such as the one predicted in the above reaction scheme. Such a diene structure could lead to the acid-soluble polymer found in the reaction of 2-n-propyl-3-methyl-3-isobutyloxazirane.

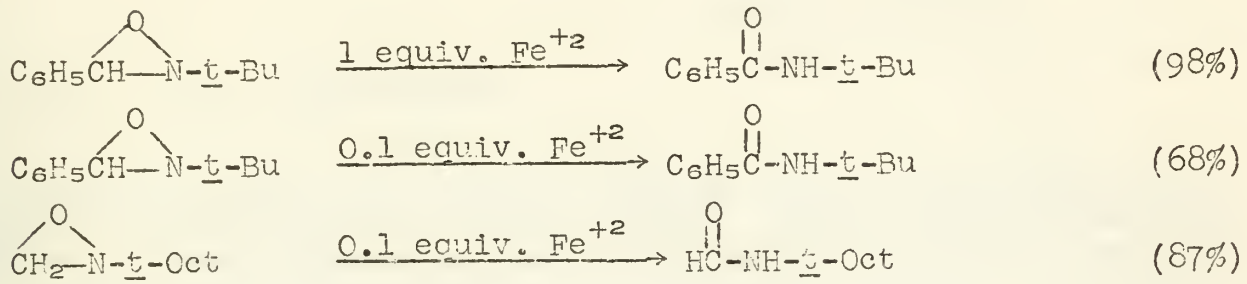


(E) $(CH_3)_2C{=}CH\text{-}N{=}CHCH(CH_3)_2$ (32%)

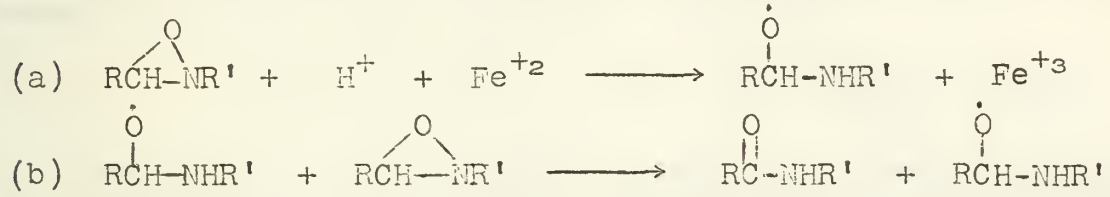
REACTION OF OXAZIRANES WITH FERROUS ION

Oxaziranes undergo one-electron transfer reactions with ferrous salts. Available experimental evidence strongly suggests that these are chain processes analogous to reactions of peroxides with ferrous ions. 2-t-Alkyloxaziranes and 2-t-alkyl-3-phenyloxaziranes produced high yields of the corresponding amides when treated with an aqueous solution of ferrous ammonium sulfate. For example, 2-t-butyl-3-phenyloxazirane is converted into t-butylbenzamide in 98% yield by reaction with one equivalent of ferrous ammonium sulfate. Evidence for the chain

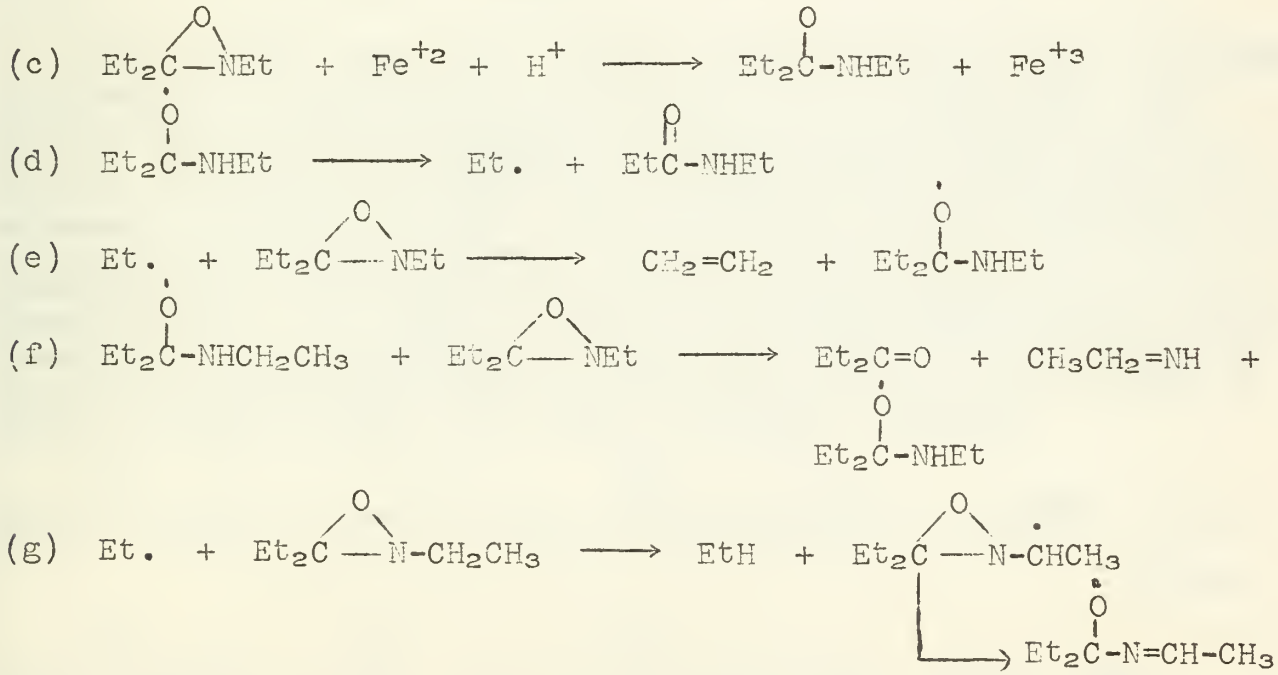
nature of this reaction is given by the fact that one-tenth equivalent of ferrous ion produced 68% of the amide. The similar reaction of 2-t-octyloxazirane further illustrates this method. The scope of this general reaction has not been extensively investigated.



Emmons proposed the following mechanism to explain these results:



The above reaction scheme requires the exchange of hydrogen from the oxygen-bearing carbon atom to the newly formed radical. When this hydrogen atom is replaced by an alkyl group, such a reaction scheme is not possible. This is exemplified by the behavior of trialkyloxaziranes in the presence of ferrous ion. For example, triethyloxazirane reacts with twenty mole per cent ferrous ammonium sulfate to produce diethyl ketone (55%), N-ethylpropionamide (25%), ammonia (59%), and a mixture of butane, ethane, and ethylene. The following mechanism was proposed to explain these results:



(h) $Et_2\dot{C}(O)-N=CH-CH_3 + Et_2C(O)-NEt \longrightarrow Et_2C(OH)-N=CHCH_3 + Et_2\dot{C}(O)-N=CH-CH_3$

$Et_2C(OH)-N=CHCH_3 \longrightarrow Et_2CO + HN=CHCH_3$

(i) $2Et. \longrightarrow CH_3CH_2CH_2CH_3$

Twenty mole per cent ferrous chloride reacted with triethyloxazirane to give a similar set of products. Ethane and ethylene were obtained in lower yields, however, and were replaced by a "considerable" amount of ethyl chloride. This behavior supports the presence of ethyl radicals which could react with ferric ions to form ethyl chloride. A study of the ferric ion concentrations of the two reaction mixtures might elucidate this point.

$$Et. + Cl^- + Fe^{+3} \longrightarrow EtCl + Fe^{+2}$$

Ferrous ion reacted with 2-(α-phenylethyl)-3,3-diethyloxazirane to produce N(α-phenylethyl)propionamide (81%), ammonia (2%), and a mixture of butane, ethane, and ethylene. Again the use of ferrous chloride resulted in a substantial amount of ethyl chloride. Although a trace of acetophenone was isolated, no diethyl ketone was found in the reaction mixture. Evidently reactions such as (f), (g), and (h) are not important here.

$$Et_2C(O)-N(C_6H_5)-CHCH_3 \xrightarrow{Fe^{+2}} EtC(=O)-NH-C(C_6H_5)HCH_3 + NH_3 + C_4H_{10} + C_2H_6 + C_2H_4$$

81% 2%

Under these conditions, dialkyl oxaziranes were found to undergo alkyl-radical fragmentation reactions to form formamides. Thus, 2-isobutyl-3-isopropyloxaziraine reacted with ferrous ammonium sulfate to form N-isobutylformamide (83%), ammonia (6%), and equal amounts of propane and propylene. 2-t-Butyl-3-isopropyloxazirane underwent the same reaction. These reactions can be explained by the preceding free radical scheme. It is interesting to note that carbon-hydrogen bond breaking is preferred over carbon-carbon bond breaking only in the case of the 2-t-butyl-3-phenyloxazirane. This observation is in agreement with work reported by Kharasch (8) who observed preferred rupture of carbon-carbon bonds over breaking of carbon-hydrogen bonds in the case of alkoxyl radicals.

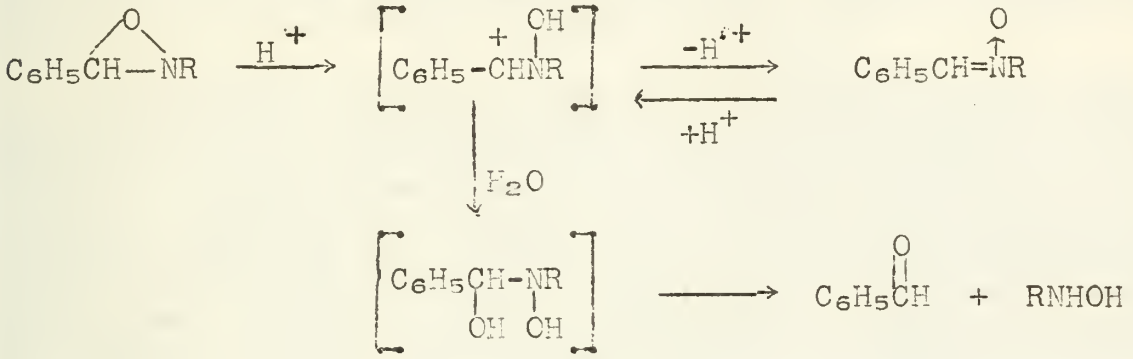
$$i\text{-}PrCH(O)-N-i\text{-}Bu + Fe^{+2} \longrightarrow HC(=O)-NH-i\text{-}Bu(83\%) + NH_3(6\%) + C_3H_8 + C_3H_6$$

$$i\text{-}PrCH(O)-N-t\text{-}Bu + Fe^{+2} \longrightarrow HC(=O)-NH-t\text{-}Bu(82\%) + C_3H_8 + C_3H_6$$

REACTIONS OF OXAZIRANES WITH ACIDS

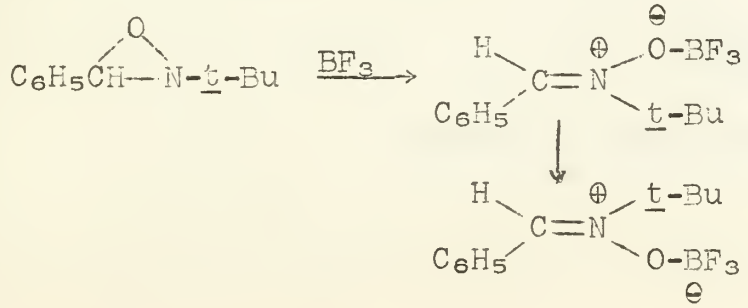
Aqueous acid hydrolysis of 2-t-alkyl-3-phenyloxaziranes produces high yields of benzaldehyde and the t-alkylhydroxylamine. This reaction has been utilized as a synthetic route to t-nitrosoalkanes. These nitroso compounds are produced in high yield by the action of alkaline hypobromite on the corresponding t-alkylhydroxylamine.

The course of the acid hydrolysis appears to go through an unstable carbonium ion which acts like the salt of a nitrone and reacts with water to form benzaldehyde and a hydroxylamine. The isomeric nitrones were hydrolyzed rapidly under these conditions.



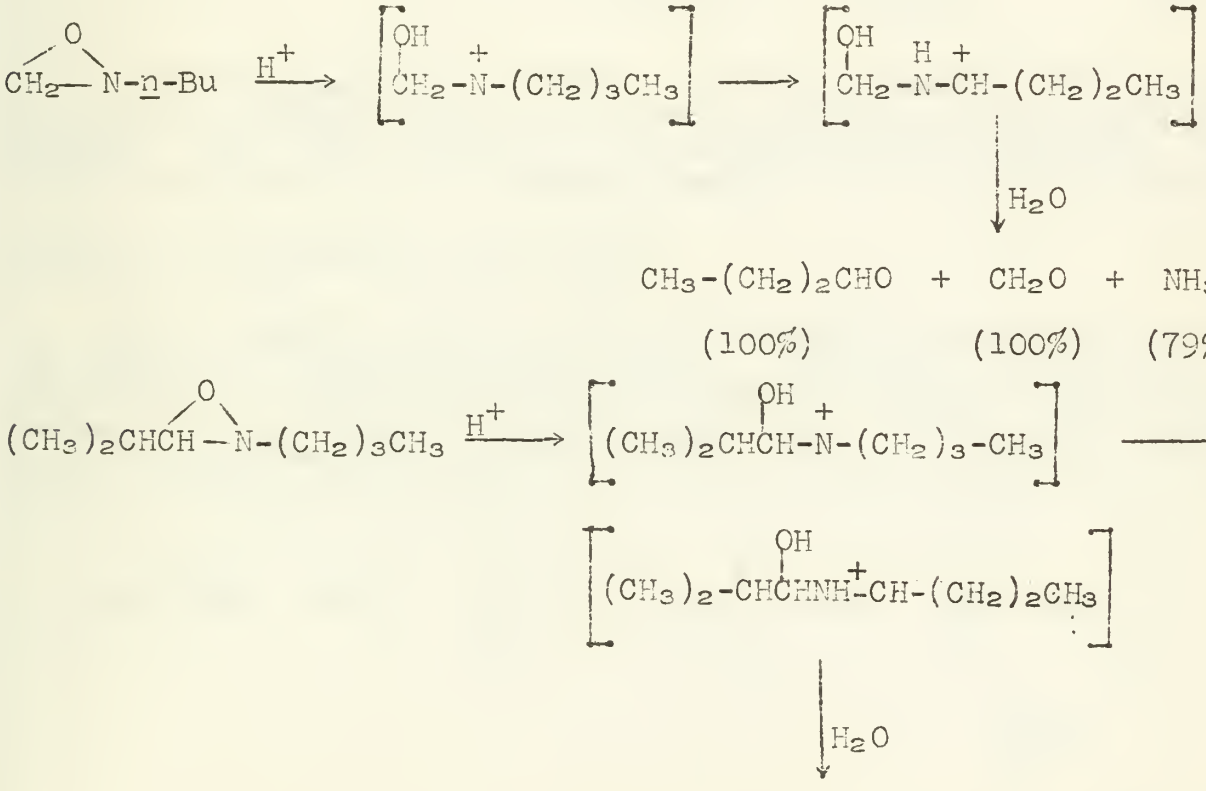
This mechanism appears reasonable in light of the fact that 2-t-butyl-3-phenyloxazirane reacts with methanesulfonic acid to form a hydroscopic salt which does not contain active oxygen but gives the isomeric nitrone upon hydrolysis. The structure of this salt was not investigated further.

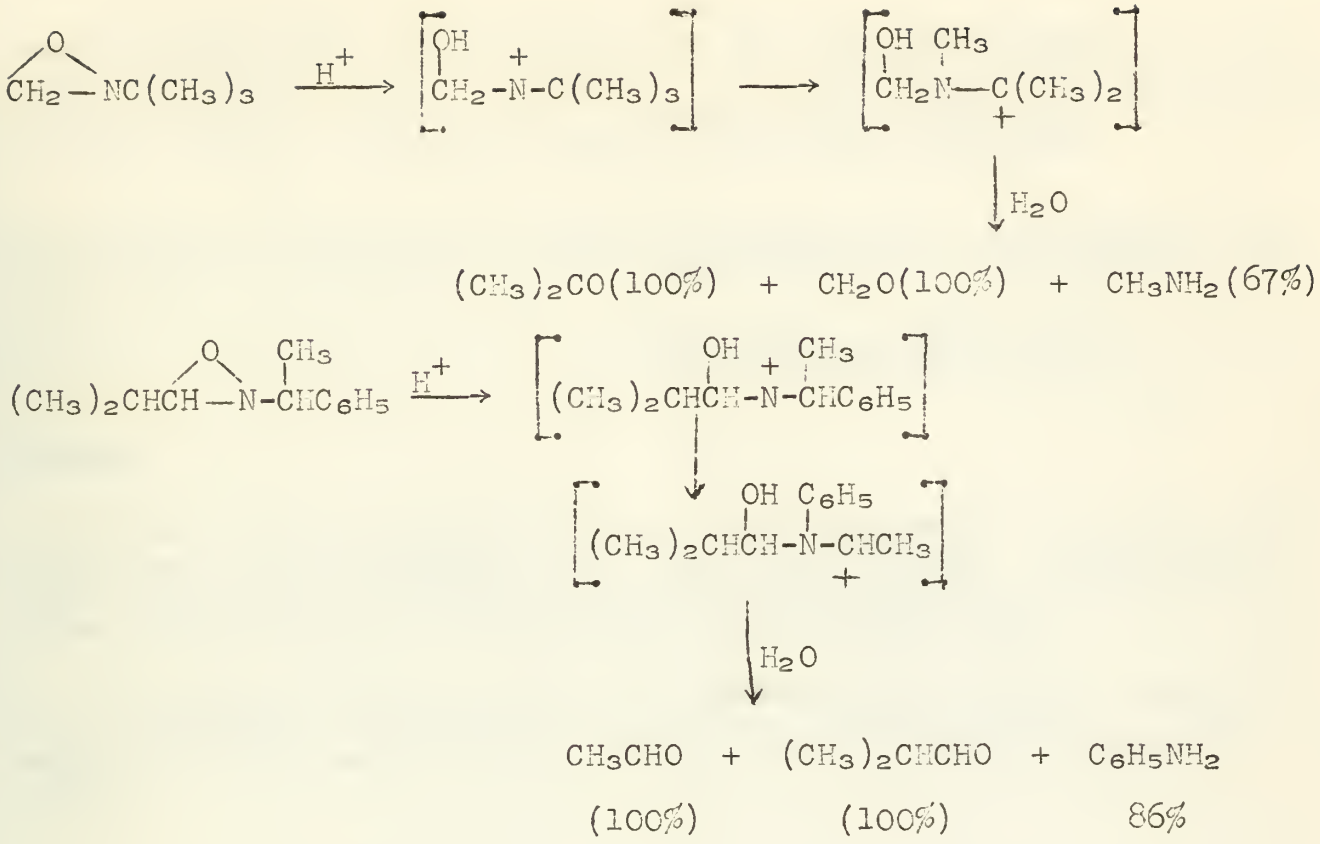
The reaction of boron trifluoride with 2-t-butyl-3-phenyloxaziranes in anhydrous benzene gives further evidence for the initial formation of a nitrone salt. This Lewis acid slowly reacted with 2-t-butyl-3-phenyloxazirane to form a crystalline salt the composition of which corresponded to one mole of boron trifluoride per mole of oxazirane. This salt melted at 65-68° and did not contain active oxygen. When allowed to stand, it slowly isomerized to another salt melting at 135-137° but having the same composition. The infrared spectra of the two salts differed in the fingerprint region. The more stable salt was shown to be identical with the boron trifluoride salt of the isomeric nitrone, N-t-butylbenzaldoxime. The unstable salt is thought to be the hitherto unknown cis nitrone and, if this is the case, the stable salt probably has the trans configuration.



The ultraviolet absorption of dilute methylene chloride solutions of the two salts was illuminating. The unstable salt showed a λmax. 294 mμ, εmax. 8600; whereas, the stable salt showed an absorption at 300 mμ, εmax. 19,300. Upon standing 24 hours the unstable form completely isomerized to the stable form. Since the spectrum of N-t-butylbenzaldoxime was shown to be the same as the spectrum of the stable salt, these salts are probably completely dissociated at these low concentrations (10^{-5} molar). To elucidate this point, the spectra of the salts were then determined in the presence of 10^{-2} molar boron trifluoride etherate. This time each salt showed a λmax. at 280 mμ, the unstable salt having an εmax. at 10,300, while the stable salt had an εmax. of 28,000. Again the unstable salt isomerized in 24 hours. These spectra were undoubtedly those of the undissociated salts.

2-Alkyloxaziranes not containing a 3-phenyl group react in a different manner. Aqueous acid appears to open these oxaziranes in the opposite direction producing a reactive intermediate bearing a positive nitrogen atom. These intermediates then rearrange and undergo hydrolysis to form an amine and two carbonyl compounds. The carbonyl products were trapped as the 2,4-dinitrophenylhydrazones, which were analyzed by paper chromatography. The bulk reaction mixture was separated into its components by column chromatography. The amines produced were isolated as the thiourea or N-phenylthiourea derivatives. The following reactions were examined:

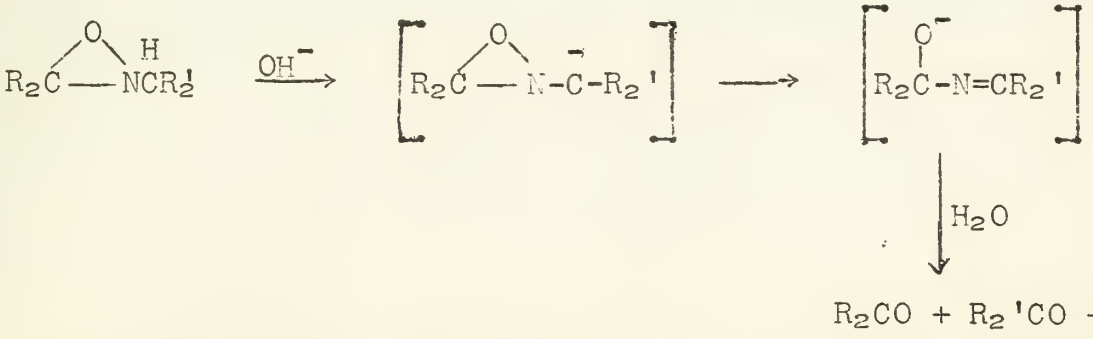




2-t-Octyloxazirane reacted in a complex manner with aqueous methanolic sulfuric acid. No attempt was made to trap any carbonyl groups. Only trace amounts of t-nitrooctane were isolated. Boron trifluoride etherate in anhydrous benzene gave the same result.

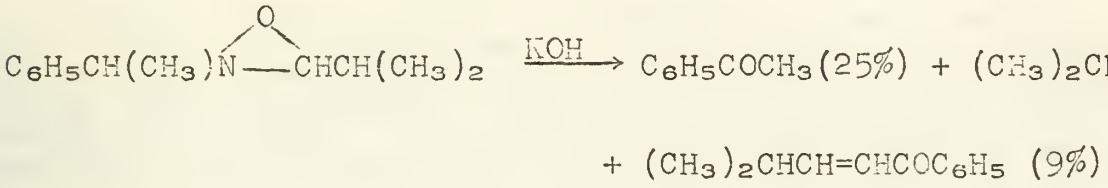
REACTION OF OXAZIRANES WITH BASES

Basic reagents have no effect on 2-t-alkyloxaziranes or indeed in general on the ring system itself. α-Hydrogen atoms on the 2-alkyl groups appear to be easily removed by bases. Oxaziranes containing this type of hydrogen atom react rapidly with hydroxyl ion in alcohol-water. These reactions produce a mixture of two carbonyl compounds and ammonia.



The quantitative nature of this reaction permitted its use to assay the nitrogen content of these oxaziranes by analysis of the

ammonia liberated. The isolation of the carbonyl products of this basic hydrolysis proved difficult. The complete reaction mixture was examined for the reaction of 2-(α-phenylethyl)-3-isopropyloxazirane with an ethylene glycol solution of potassium hydroxide.



$$C_6H_5CH(CH_3)N\!-\!CHCH(CH_3)_2 \xrightarrow{KOH} C_6H_5COCH_3(25\%) + (CH_3)_2CHCHO\ (57\%)$$

$$+\ (CH_3)_2CHCH{=}CHCOC_6H_5\ (9\%)$$

SUMMARY

A new, reactive heterocycle has been discovered, its structure established, and a number of its reactions studied. Perhaps the best appraisal of this work was given by a chemist who stated that a new and reactive functional group has been discovered.

The author wishes to thank Dr. Emmons for a private communication essentially encompassing the whole of this seminar. It is hoped that the oxaziranes will provide new and useful synthetic routes.

BIBLIOGRAPHY

1. W. D. Emmons, J. Am. Chem. Soc., 78, 6208 (1956).
2. L. I. Smith, Chem. Rev., 23, 223 (1936).
3. W. D. Emmons, private communication.
4. British Patent 743,940, January 25, 1956; C. A. 51, 3656.
5. W. D. Emmons, Abstr. Am. Chem. Soc. Meeting, Miami, Florida, April 7 - 12, 1957, p. 77-O.
6. M. F. Hawthorne and R. D. Strahm, J. Org. Chem., In Press.
7. A. C. Cope and A. C. Haven, J. Am. Chem. Soc., 72, 4896 (1950).
8. M. S. Kharasch, A. Fono, and W. Nudenberg, J. Org. Chem., 15, 763 (1950).

AROMATIC MERCURATION; SOME THEORETICAL APPLICATIONS

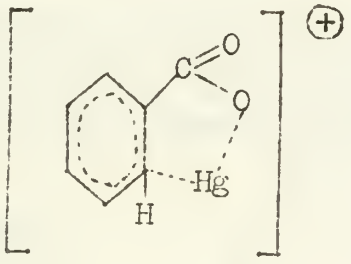
Reported by S. W. Blum

May 13, 1957

Aromatic mercuration is considered as an electrophilic aromatic substitution (1), though some of the results have been anomalous, such as high percentages of meta isomer from toluene, low percentages of meta from nitrobenzene, and almost exclusive ortho mercuration of benzoic acid (2, 30). This seminar will deal with some of the recent experiments which serve both to explain these anomalies and to provide data for a general theory of electrophilic aromatic substitution.

METHODS

Mercuration can be conducted in a number of ways. Klapproth and Westheimer (3) used $Hg(ClO_4)_2$ in aqueous acid solution with $HClO_4$ as catalyst, and obtained results typical of electrophilic substitution; toluene gave 27% ortho, 6% meta, and 67% para, while nitrobenzene gave 11% of ortho and para combined and 89% meta. Their results indicate that an ionizing solvent (such as 40-60% aqueous $HClO_4$) leads to results normal for electrophilic substitution; they postulated a transition state consisting of one molecule of the aromatic, one of Hg^{++}, and one of anion (such as ClO_4^-). Thus the mercuration reaction appears to be ionic in nature and it requires an ionizing (or polar) solvent. In a non-polar solvent (toluene) mercuration is much more random. A cyclic transition state might account for the observed ortho mercuration of benzoic acid.



Mercuration using $Hg(OAc)_2$ in glacial acetic acid solvent with $HClO_4$ as catalyst, the method employed by Brown and McGary (4, 5, 6), also gives typical electrophilic results. Brown and McGary's method (4) uses an aromatic/mercuric acetate ratio of from 5/1 to 20/1; best results are obtained at the higher ratios. The aryl mercuric acetates produced were converted to aryl mercuric bromides with NaBr, and then caused to react with bromine in carbon disulfide to give aryl bromides; these were analyzed by infrared. A process method very similar to this gives yields of the aryl mercuric compounds of 80-98% (7).

EXPERIMENTAL RESULTS

Under Brown and McGary's conditions toluene gives (in a short-time reaction) 21.0 ± .5% ortho, 9.5 ± .5% meta, and 69.5 ± 1.0% para substitution. The relative rates of mercuration of toluene and benzene are:

Competitive Mercuration

Time	o	m	p	T/B Relative Rate
1 hr.	21.8	10.3	67.9	7.5
6 hrs.	22.1	10.7	67.2	7.6
1 day	25.1	11.1	62.8	7.4
4 days	34.4	14.6	51.0	5.9

These results suggest that the reaction is a reversible one, somewhat similar to sulfonation, with the para position most susceptible to protolytic attack; reversibility has been demonstrated with HNO_3 as solvent (8, 9).

The amount of catalyst ($HClO_4$) also has a large effect on the rate of mercuration (5,9); the rate law, as found by Westheimer and coworkers (9), was

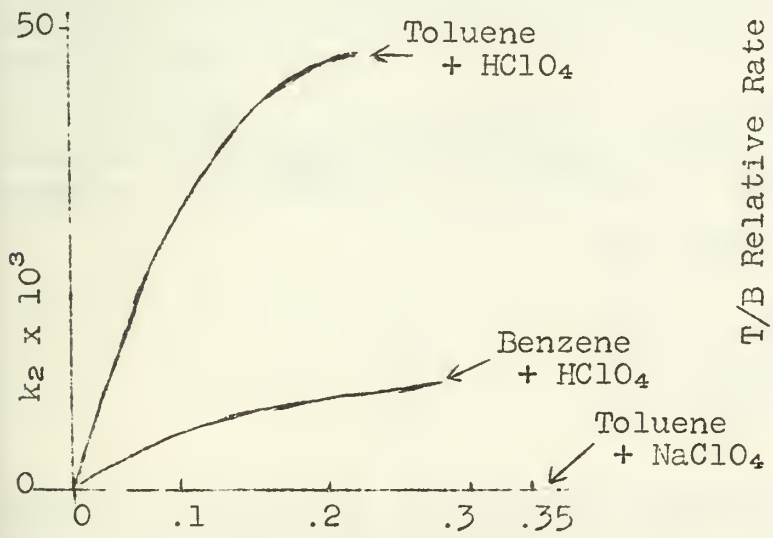
$$v = k_{obs} (C_6H_6) (Hg^{++}) = k_o (C_6H_6) (Hg^{++}) + k_{3A} (C_6H_6) (Hg^{++}) (A^-)$$

k_{obs} = observed bimolecular rate constant

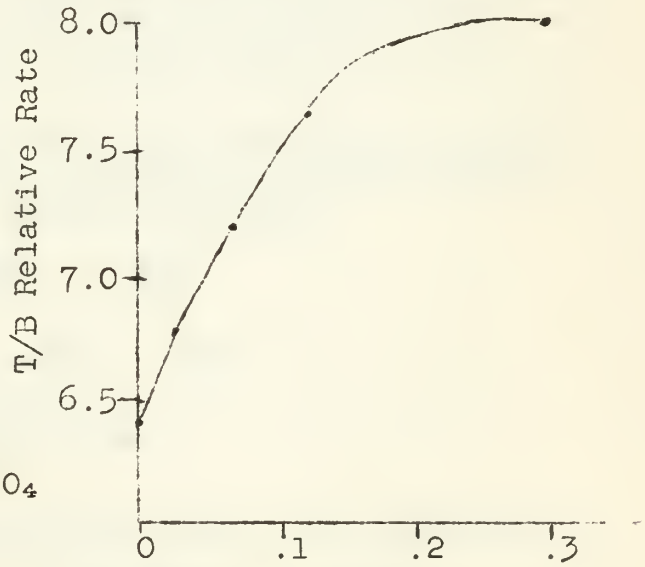
k_o = rate constant extrapolated to zero salt concentration

k_{3A} = termolecular rate constant for the particular anion.

The observed rate of mercuration increases directly with increasing catalyst concentration until a 1/1 ratio of $HClO_4/HgCOAc)_2$ is reached, and then the effect falls off; this is illustrated in Graph I, while Graph II shows the change in the toluene/benzene reactivity ratio with catalyst concentration.



Graph I



Graph II

Catalyst concentration also affects the isomer distribution, as illustrated in the following table:

Mercuration of Toluene

	Catalyzed Reaction			Uncatalyzed Reaction		
Temp.	o	m	p	o	m	p
25°C	21.0	9.5	69.5			
50	20.0	11.5	68.5	30.7	13.2	56.1
70				32.0	14.5	53.5
75	18.3	12.6	69.1			
90				32.5	15.7	51.8

These results (Graph II and the preceding table) definitely suggest that catalysts can alter both the reactivity ratio and the isomer distribution in electrophilic aromatic substitution.

THEORETICAL APPLICATIONS

First let us consider the polymethylbenzene series of compounds. Condon (10) has shown that in halogenation the relative reactivities of these compounds can be calculated from data obtained with toluene; his calculated values are within a two-fold range of the experimental data. Brown and McGary (6) have applied this type of calculation to the mercuration reaction, obtaining agreement within a 12% mean deviation; by refinement of the partial rate factors involved this was lowered to a 6% mean deviation. The method (10) involves finding the partial rate factor for each position of toluene; then the partial rate factor for a position in another compound is the product of the corresponding toluene partial rate factors; the rate relative to benzene is 1/6 of the sum of the partial relative rates for all available positions.

For example, in chlorination the T/B ratio is 345, and the products are 58% ortho and 42% para. Then relative to one position in benzene, the rate is 6 x 345 = 2070. Then for toluene,

$$p_f = .42 \times 2070 = 870$$

$$o_f = .58/2 \times 2070 = 600$$

$$m_p = \text{approximated as } 5$$

Applied to p-xylene, the rate at any position is $p_f \times m_f = 600 \times 5 = 3000$, and the p-xylene/benzene ratio $= \frac{4 \times 3000}{6} = 2000.$

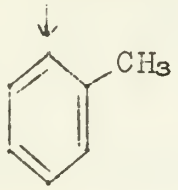
Using this method, Brown and McGary obtained the following results (6):

Relative Reactivities (to Benzene) on Mercuration

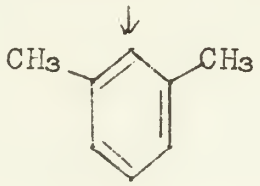
Compound	Exp.	Calc.I	Calc.II	Calc.III
benzene	1.0	1.0	1.0	1.0
toluene	5.0	5.0	5.3	5.28
o-xylene	16.0	14.1	16.0	14.7
m-xylene	34.5	30.0	34.5	35.0
p-xylene	8.2	6.1	8.2	7.2
hemimellitene	68	62	78	71.5
pseudocumene	49	35.3	48.2	41.4
mesitylene	209	178	235	194
prehnitene	126	101	147	121
isodurene	257	235	353	255
durene	30.0	27.8	50.6	30.4
pentamethylbenzene	224	233	388	255

For I, $p_f = 16.8$, $m_f = 1.98$, $o_f = 4.61$
II, $p_f = 15.8$, $m_f = 2.26$, $o_f = 5.45$
III, $p_f = 16.8$, $m_f = 1.98$, $o_f = 5.45$ (single ortho), $o_f = 4.8$ (double ortho).

The first set of calculated values, based on toluene, shows a mean deviation of 12%, but Brown and McGary (6) consider the values to be too low; the second set, calculated from the xylenes, is far too high for the compounds with three or more methyls. For the factors derived from toluene, the o_f factor does not fit all the situations; the steric effect of a compound like II should not be merely twice that of I, since steric effects increase very rapidly with increasing



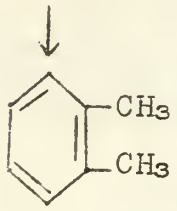
I



II

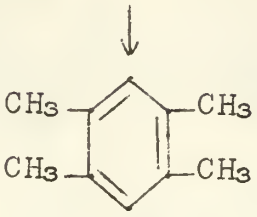
steric requirements. Using the factors refined according to this consideration (set III, derived from appropriate compounds) the calculated values show a 6% mean deviation from experimental data. A more complete treatment would also take into account the buttressing

effect, as indicated in compounds III and IV, but this has not yet been done.



buttressed
single ortho

III



buttressed
double ortho

IV

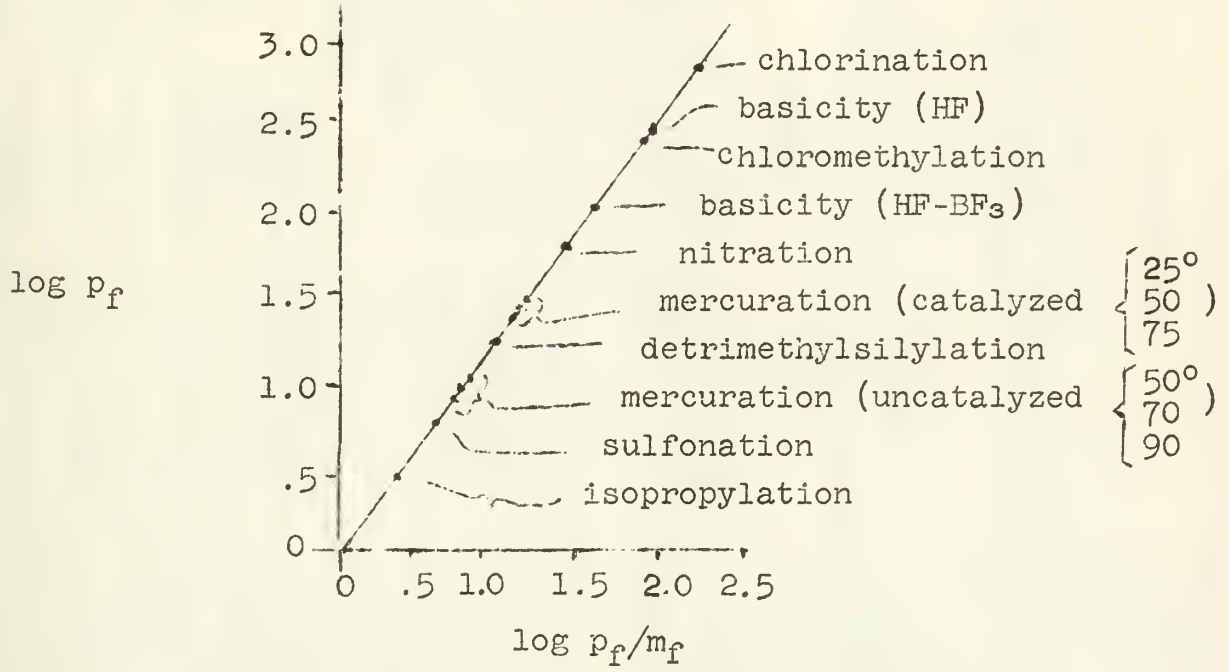
The next theoretical application of the mercuration reaction concerns the alkylbenzene series. The experimental results are as follows:

Compound	Relative Rate of Mercuration, C_6H_5R/C_6H_6
benzene	1.0
toluene	5.0
ethylbenzene	4.2
isopropylbenzene	3.9
t-butylbenzene	3.2

Toluene has been reported (11) to react five times as fast as t-butylbenzene in bromination, but the effect is much less in nitration (12), isopropylation (13), and mercuration. Since the t-butyl group has large steric requirements (toluene on nitration gives 58.5% ortho, t-butylbenzene gives only 15.8% ortho (14)), and the mercuration reaction also seems to have a large steric effect (toluene in uncatalyzed mercuration gives 31% ortho), an assumption that no ortho-isomer is produced with t-butylbenzene would account for a 31% rate decrease; the observed decrease is 36%. A change from methyl to t-butyl produces minor changes in rate at positions other than ortho during nitration, isopropylation, and mercuration, but in bromination this change results in large rate changes. Bromination is highly selective, so that the C-Br bond in the transition state must require a large electronic contribution from the ring; in the less selective reactions (using species with a large amount of ionic character) no large electronic contribution are required, so various "electron-affects" are of much less importance (15). Recent work by Swain, et al. (16) shows that the effect of substituting D for H in the CH_3- of toluene during mercuration, nitration, and bromination gives rise to a secondary isotope effect of 1.00 $\pm$ .03 per D atom, so that the effects are 3% per D atom or less.

The third theoretical application of the mercuration reaction is found in a correlation (4, 15) of the "activity" of a substituting species with relative reactivities and isomer distribution. For example, a highly active species should give a low T/B ratio and a large amount of meta isomer; this means that the species is not

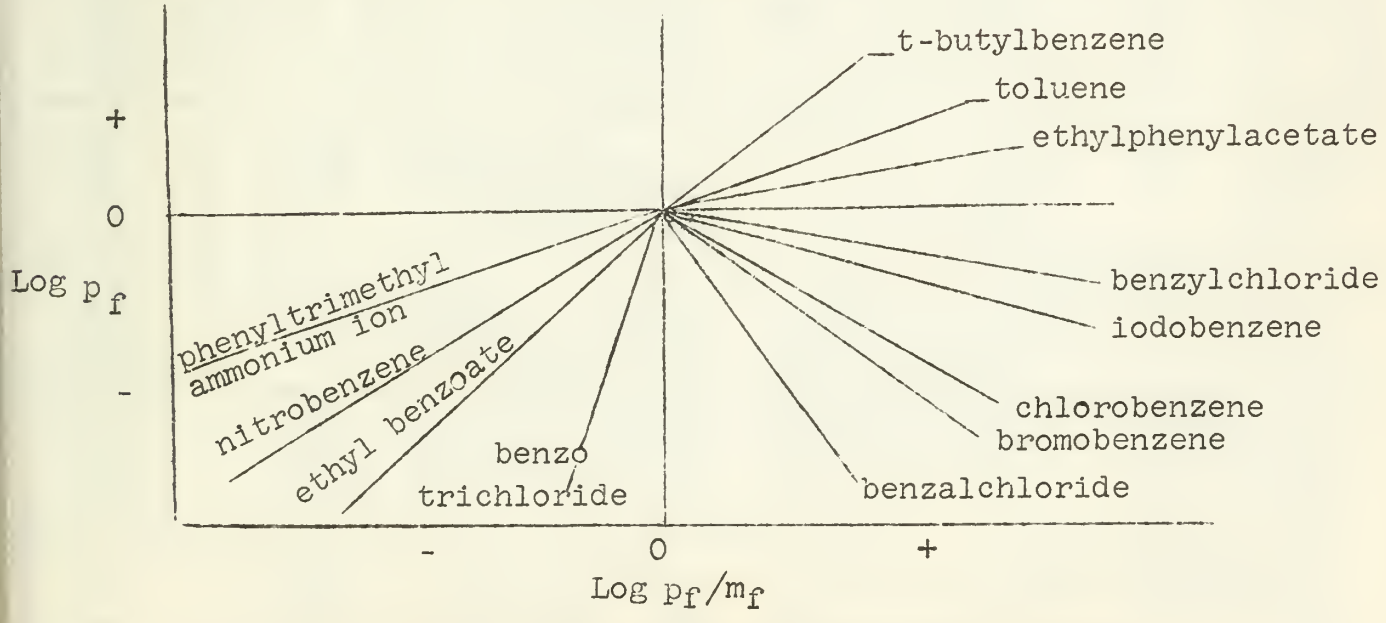
selective between benzene and toluene or between para and meta positions. An example is isopropylation using propylene and $AlCl_3$; the T/B ratio is 2.1 and 28% meta isomer is formed (13). This correlation of "activity" and selectivity is expressed in a simple linear function by plotting log p_f versus log p_f/m_f; the data from the mercuration reaction, both catalyzed and uncatalyzed, and at different temperatures, agree very well with this linear correlation, as shown in Graph III (the data for this graph are found on page 163 of the abstract.



Activity - Selectivity Correlation for Toluene

Graph III

Graph III is for the toluene case; in Graph IV is shown the extension of the correlation between "activity" and selectivity as proposed by Brown and McGary (4).



Proposed Extension of the Correlation Theory

Graph IV

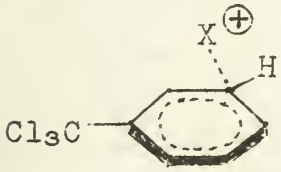
Data and References for Graph III and Graph IV

Reaction	Conditions	Isomer Distribution			C_6H_5R/C_6H_6	Partial Rate Factor			Ref.
		o	m	P		of	mf	Pf	
Chlorination	C_7H_8 Cl_2 in HOAc at 24°					611	5.3	887	10
Chloromethylation	C_7H_8 CH_2O in HOAc at 60° + HCl + $ZnCl_2$	34.7	1.3	64.0	112	117	4.37	430	15
Basicity	C_7H_8 HF at 20°					145	3.6	414	18
	C_7H_8 HF-BF_3					103	3.1	145	19
Nitration	C_7H_8 HNO_3 in 90% HOAc at 45°	56.5	3.5	40.0	24.5	42	2.5	58	12
Mercuration	C_7H_8 $Hg(OAc)_2$ in HOAc + $HClO_4$ 25°	21.0	9.5	69.5	7.9	4.98	2.25	32.9	4
	C_7H_8 $Hg(OAc)_2$ in HOAc + $HClO_4$ 50°	20.0	11.5	68.5	7.0	4.20	2.41	28.8	4
	C_7H_8 $Hg(OAc)_2$ in HOAc + $HClO_4$ 75°	18.3	12.6	69.1	5.9	3.24	2.23	24.5	4
Detrimethylsilylation	$ArSi(CH_3)_3$ + pTSA in HOAc at 25°					17.5	2.0	16.5	20
Sulfonation	$MeSO_2Cl$ + $AlCl_3$ at 100°	49	15	36		5.44	1.67	7.99	21
	pBr $C_6H_4SO_2Cl$ + $AlCl_3$ at 30°				3.7				22
Isopropylation	C_7H_8 C_3H_8 + $AlCl_3$ in $MeNO_2$ at 40°	37.6	28.5	33.9	2.1	2.37	1.80	4.27	13
Nitration of Miscellaneous compounds	$C_6H_5C(CH_3)_3$ HNO_3, HOAc at 45°	12.0	8.5	79.5	15.7	5.5	4.0	75	12
	$C_6H_5CH_2Cl$ HNO_3, Ac_2O at 25°	32.0	15.5	52.5	0.302	.29	.14	0.951	23
	$C_6H_5CH_2COOEt$ " " "	42.0	10.6	47.4	3.66	4.62	1.16	10.41	23
	C_6H_5COOEt " " "	24.1	72.0	4.0	.00367	.0026	.0079	.0009	24
	C_6H_5Br $AcONO_2$ CH_3NO_2 at 25°	29.6	0.9	69.5	:0312	.0277	.00084	.13	25,26
	C_6H_5Br HNO_3 " "	36.5	1.2	62.4					25
	C_6H_5Br $AcONO_2$ " "				.0276	.0303	.0010	.1033	26
	C_6H_5I " " "	38.3	1.8	59.7	0.22	.253	.0119	.789	25
	$C_6H_5CHCl_2$ HNO_3, Ac_2O at 20-30°	23.3	33.8	42.9					27
	$C_6H_5CCl_3$ " " "	6.8	64.5	28.7					27
	$C_6H_5NO_2$ HNO_3, 0°	6.4	93.3	0.3					28
Phenylation	Ø-Ø + benzoyl peroxide at 80°	48.5	23.0	28.5	4.0	2.9	1.4	3.4	29

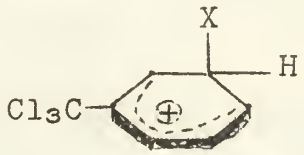
To go into a particular example, for benzotrichloride ($C_6H_5CCl_3$) the P/m ratio will vary little with the activity of the substituting species, while the benzotrichloride/benzene ratio will be quite sensitive to "activity". This may be clearer on looking at some possible transition states (17).

Va

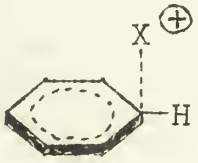
Vb



VIa



VIb



VIIa

VIIb

The transition states may be represented as somewhere between (a) and (b) in each case. With an "active" substituting species, which does not require much charge contribution from the ring, Va and VIa will be formed about as easily relative to VIIa. With a less "active" species, which does require much charge contribution from the ring, Vb and VIb will not be as easily formed as VIIb, so that log p_f will depend on the "activity" of the substituting species. The P/m ratio will not be very sensitive to "activity" because Va and VIa (or Vb and VIb) would have approximately equal stabilities regardless of the "activity" of an attacking species.

This linear relationship between selectivity and isomer distribution was also proposed as able to be modified by catalytic agents (15); this has been shown to be the case in the mercuration reaction. In another experiment, bromination of toluene was conducted with $AlBr_3$ as catalyst and 30% meta (20% ortho, 50% para) substitution was obtained (5); the normal iodine-catalyzed bromination is, on the contrary, highly selective (T/B ratio about 470, almost no meta formed), so that catalysts can change the activity of an attacking species.

BIBLIOGRAPHY

1. C. K. Ingold, Structure and Mechanism in Organic Chemistry, (Cornell, 1953) 304.
2. F. C. Whitmore, Organic Compounds of Mercury, (ACS Monograph No. 3, The Chemical Catalog Co.Inc., 1921) 34.
3. W. J Klapproth and F. H. Westheimer, J. Am. Chem. Soc., 72, 4461 (1950).
4. H. C. Brown and C. W. McGary, Jr., J. Am. Chem. Soc., 77, 2300 (1955)
5. Ibid., 2306.
6. Ibid., 2310.
7. A. J. Barduhn and K. A. Kobe, Ind. Eng. Chem., 38, 247 (1946).
8. F. H. Westheimer, E. Segel, and R. M. Schramm, J. Am. Chem. Soc., 69, 773 (1947).
9. R. M Schramm, W. Klapproth, and F. H. Westheimer, J. Phys. and Colloid Chem., 55, 843 (1951).
10. F. E. Condon, J. Am. Chem. Soc., 70, 1963 (1948).
11. E. Berliner and F. Berliner, J. Am. Chem. Soc., 71, 1195 (1949).
12. H. Cohn, et al., Nature, 169, 291 (1952).
13. F. E. Condon, J. Am. Chem. Soc., 70, 2265 (1948).
14. H. C. Brown and . H. Bonner, J. Am. Chem. Soc., 76, 605 (1954).
15. H. C Borwn and K. L. Nelson, J. Am. Chem. Soc., 75, 6292 (1953).
16. C. G. Swain, T. E. C. Knee, and A. J. Kresge, J. Am. Chem. Soc., 79, 505 (1957).
17. E. J Corey and C. K. Sauers, J. Am. Chem. Soc., 79, 249 (1957).
18. M. Kilpatrick and F. E. Luborsky, J. Am. Chem. Soc., 75, 577 (1953).
19. F. E. Condon, J. Am. Chem. Soc., 74, 2528 (1952).
20. Unpublished data; see (4).
21. W. E. Truce and C. W. Vriesen, J. Am. Chem. Soc., 75, 5023 (1953).
22. S. C. J. Olivier, Rec. trav. chim., 33, 163 (1914).
23. C. K. Ingold and F. R. Shaw, J. Chem. Soc., 575 (1949).
24. C. K. Ingold and M. S. Smith, J. Chem. Soc., 905 (1938).
25. J. D. Roberts, et al., J. Am. Chem. Soc., 76, 4525 (1954).
26. M. J. Bird and C. K. Ingold, J. Chem. Soc., 918 (1938).
27. A. F. Holleman, J. Vermeulen, and W. J. deMoog, Rec. trav. chim., 33, 1 (1914).
28. A. F. Holleman and B. R. deBrugs, Rec. trav. chim., 19, 79 (1900).
29. J. I. G. Cadogan, D. H. Hey and G. H. Williams, J. Chem. Soc., 794 (1954).
30. Y. Ogata and M. Tsuchida, J. Org. Chem., 20, 1637, 1644 (1955).

2-AMINOHEXOSES

Reported by Alexander Argoudelis May 20, 1957

I. INTRODUCTION

In 1878 "glucosamine" the first aminosugar to be isolated was obtained by Ledderhose.

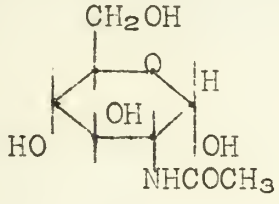
The wide distribution of the aminosugars in nature has been revealed during the past eight decades until today they are recognized to be the structural components of a broad general group of substances, the mucopolysaccharides and mucoproteins (1).

The field of the aminosugar chemistry has expanded enormously in recent years since scarcely a field of biological activity can be found in which aminosugars or mucosubstances are not involved. These substances play significant parts for instance in processes of immunity and fertility, in the regulation of blood clotting and in some antibiotic activities. Substances containing aminosugars are also extensively implicated in pathological conditions such as rheumatic diseases and virus infections (2, 3).

This seminar will review part of the chemistry of 2-amino-hexoses: the distribution of these aminosugars in nature, their isolation their synthesis and some of the chemical properties related to structural studies.

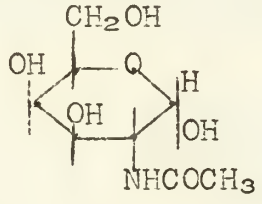
II. DISTRIBUTION IN NATURE

The most important aminosugars which occur in nature are D-glucosamine and D-galactosamine. Both are found almost as N-acetyl compounds (I, II) which seldom occur free but always as components of high molecular weight substances (3).



I

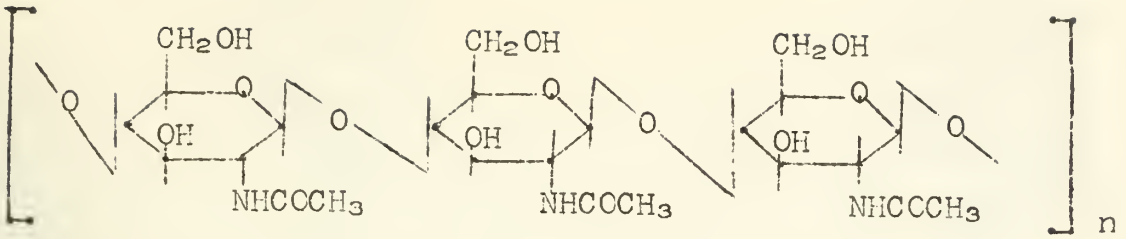
N-acetyl-glucosamine



II

N-acetyl-galactosamine

Chitin (III) the high molecular weight substance which has been found in the armor of lobsters and insects is composed exclusively from N-acetyl-D-glucosamine units which are bound together in a 1-4 β glycosidic linkage (2)



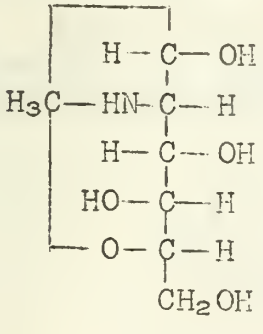
III

Besides chitin, which constitutes an important skeletal substance of invertebrate species, many natural products in which aminosugars are components show a variety of functions which are important not only in physiological processes butalsoin pathology. The mucopolysaccharides and mucoproteins, which constitute most of the slime compounds of the animal body, belong to this class.

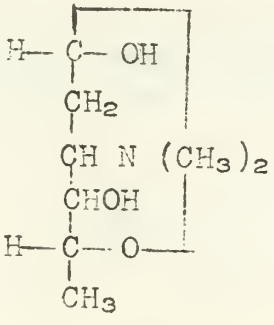
Mucopolysaccharides are found in the lens of the eye and in the synovial fluid of the joints in high concentration. They are involved in the construction of blood vessels, in the regulation of clotting ability of the blood, and in the formation of red blood cells.

While glucose possesses the same relative importance in both plant and animal cells, the compounds composed of aminosugars are much less important in higher plants than in higher animals. For that reason the chemistry of aminosugars is of special importance to animal and human physiology (3).

In the microorganisms nature has experimented with synthetic abilities. So one sees in the area of antibiotics strange molecules which are not found in higher plants and animals. N-methyl-L-glucosamine (IV) is found in the streptomycin molecule (4), desosamine (V) Rhodosamine, and mycaminose (VI) in macrolide antibiotics (5) 3-deoxy-3-aminoribose (VII) in puromycin (6) and D-gulosamine (VIII) in streptothricin (7).



IV



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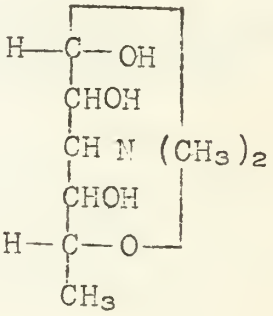

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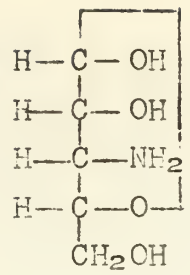
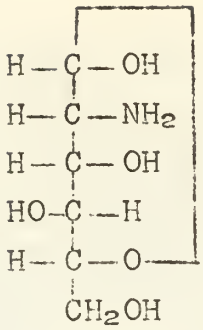


VII



VIII

Finally, aminosugars play an important part in many fields of immuno-chemistry, where, for example, they are involved in the structure of the influenza-virous.

III. ISOLATION AND STABILITY STUDIES

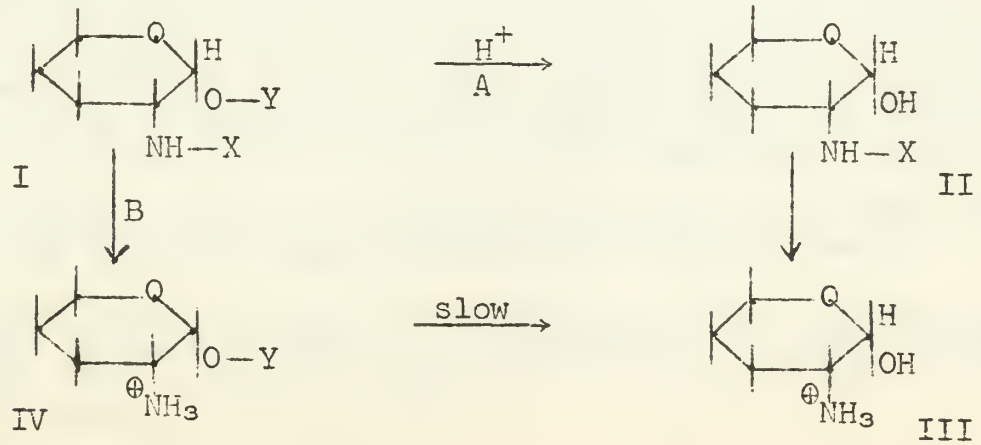
The naturally occurring 2-aminohexoses glucosamine and galactosamine have been isolated by enzymatic or acidic degradation of the natural products in which they occur.

In general acidic hydrolysis proceeds with difficulty, stable disaccharides frequently being produced. Strong mineral acids in high concentrations are usually used. For example chitin (8) yields glucosamine hydrochloride and acetic acid on hydrolysis with 10 N hydrochloric acid at 100°. Acidic hydrolysis under these drastic conditions is attended by destruction of some of the aminosugar. In connection with that Folkes et.al. (9) found that glucosamine autoclaved with 3N hydrochloric acid for 5 hours at 15 lb. pressure and 87°C lost 20 per cent of the nitrogen as ammonia.

The fact of the stability of the glycosidic bond in aminopolysaccharides led to extensive study of its nature.

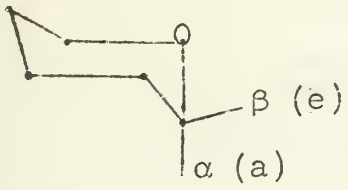
Moggidge and Neuberger (10) studying the hydrolysis of methyl N-acetyl-a-glucosaminide, concluded that in glycosidically linked glucosamine the rate of acidic hydrolysis is in part regulated by the nature and stability of the N-substituent and partly by the configuration of the glycoside.

Foster (11), also, studied the problem of hydrolysis of glucosaminides and noted the following scheme for the hydrolysis of glycosidic derivatives of glucosamine.

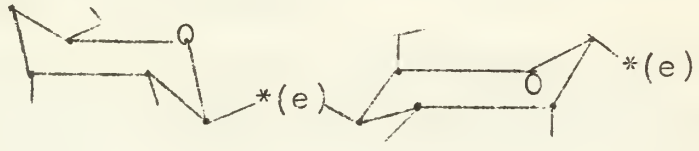


Cleavage of the glycosidic substituent Y may occur first to give the intermediate (II) which is further hydrolyzed to yield the free aminosugar (III) [Path A]. On the other hand initial hydrolysis of the N- substituent X will yield the 2-amino-2-deoxy-D-glycoside derivative (IV) [Path B]. The derivative IV is strongly resistant to further acidic hydrolysis since the positive charge acquired by the amino group in the reaction medium electrostatically shields the neighboring glycosidic substituent from attack by protons. The extent to which paths A and B are favored depends on the nature of X and Y and on the configuration of the glycosidic center. Thus when X is SO_3H and Y is alkyl the main pathway of hydrolysis is B (heparin), while when X is acetyl and Y is alkyl the main pathway is A (Yaluronic acid).

Furthermore, Foster and Overend (11) studied the effect of the configuration at the glycosidic center on the rate of hydrolysis. In general β-glycopyranosides are hydrolyzed more rapidly than the α-anomers since in most cases the preferred conformations of the α anomers have the glycosidic substituent in an axial position (V) which results in shielding it from protonation by substituents in the pyran ring and by the ring itself. The D-gulopyranosides are an exception but this is attributed to conformation differences between the gulosides and other glycosides. In the case of gulopyranosides the glycosidic bond is probably equatorial in the preferred conformations of both α and β-gulosides (VI) (12).



V



VI

β-gulopyranoside α-gulopyranoside

The aminosugars present in acidic hydrolysates are determined by comparison with known aminosugars using paper chromatography or paper electrophoresis.

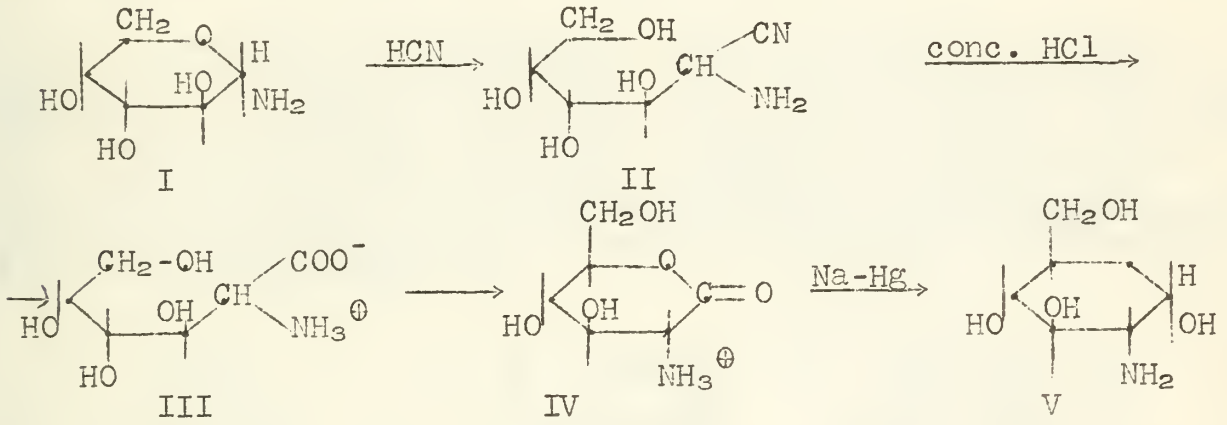
Separation of aminosugar mixtures by electrophoresis on paper treated with borate buffer has recently been described. High voltages (~500 V) applied across the paper strips cause a differential migration of the borate-sugar complexes (13, 14, 15). Glucosamine itself is incapable of forming a complex with the metaborate ion (16) since the requisite (cis) glycol grouping is absent. Glucosamine is thus distinguished from many other sugars by its zero ionophoresis at pH 8.6. On the other hand galactosamine is able to form a complex with the metaborate ion due to the cis glycol grouping at C-3, C-4 and so may be separated from glucosamine.

Ion exchange resins and starch, cellulose, and silica gel columns have also been used extensively in recent years.

A great number of papers have been published recently dealing with modern techniques used in the separation and identification of aminosugars (3). However a detailed discussion of this subject is beyond the scope of this seminar.

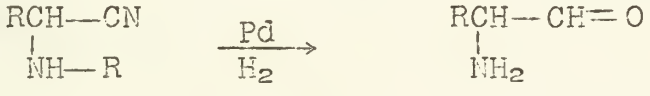
IV. SYNTHESIS OF 2-AMINOHEXOSES

The first synthesis of an aminosugar by Fischer and Leuchs (17), involved the addition of hydrogen cyanide to arabinosylamine (I) and hydrolysis of the resulting nitrile (II) to 2-aminohexonic acid (III). This compound was transformed to lactone (IV) by further treatment with hydrochloric acid. The lactone yielded the aminosugar, D-glucosamine (V), which was isolated as the urethane, upon treatment with sodium amalgam in strongly acidic medium. The yield amounted to 1.5%.



Using this method P. Levene (18) synthesized D-galactosamine and K. Folkers (19) N-methyl-L-glucosamine.

Kuhn (20) has recently found that the aminonitriles, which can be easily obtained from aldoses, primary amines, and hydrogen cyanide can be very easily transformed to the corresponding aminosugars by catalytic hydrogenation in dilute acid solution (21).



The yields obtained by this method are shown in table I (20).

Table I

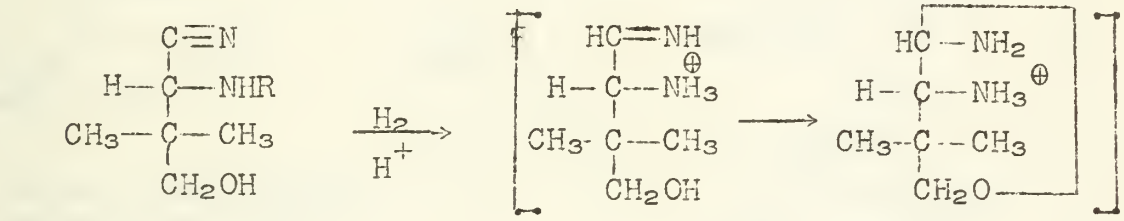
Aminosugar	Starting Sugar	Amine	Yield
Glucosamine	Arabinose	NH_3	71
		Benzylamine	75
		Aniline	68
		p.toluidine	71
L-Mannosamine	L-Arabinose	Benzylamine	71
D-galactosamine	D-Lyxose	NH_3	70
		Aniline	35
D-galaheptosamine	D-galactose	Benzylamine	60
N-AC-lactosamin	3-β-D-galact.		
	Darabinose	benzylamine	42
		Aniline	42
N-methyl-L-glucosamine	Larabinose	Methylamine	75

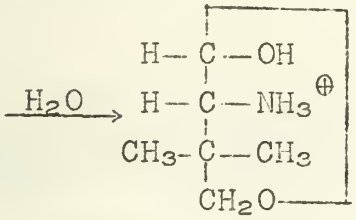
With N-methyl-L-glucosamine, the hydrolysis product of streptomycin, the yield (75% of theory) is about 100 times greater than by the method of Fischer (20).

Another advantage of this method is that it avoids concentrated hydrochloric acid. Therefore it is possible to preserve glycosidic bonds and to prepare compounds like N-acetyl-lactosamine (22).

The catalytic hydrogenation of nitriles to aldehydes is in general possible in the presence of substances like phenylhydrazine and semicarbazide which trap the aldehyde step (23).

In the sugars and aminosugars, however, there is no need of addition of "trapping" substances. Aminosugars do not occur as the aldehydes but as hemiacetals which take up more hydrogen only under very drastic conditions. Kuhn (20) showed that the γ as well as the δ-hydroxy nitriles are easily transformed to the γ- or δ-hydroxy aldehydes. The mechanism of the reaction suggested by Kuhn is illustrated below in the synthesis of α-amino-ββ-dimethyl-γ-hydroxybutylaldehyde (I)





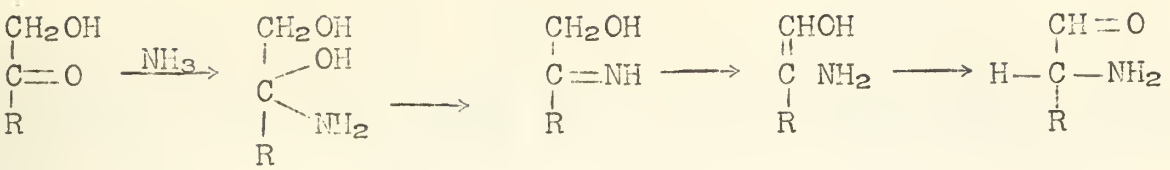
I

R=H, Ar, $ArCH_2$, Alkyl

Furthermore, Kuhn (21) found that amino-, benzylamino- and arylamino-nitriles take up one, two, and three moles of hydrogen respectively. This is explained by the formation of toluene in the case of the benzylamino and cyclohexanone in the case of arylamino-nitriles.

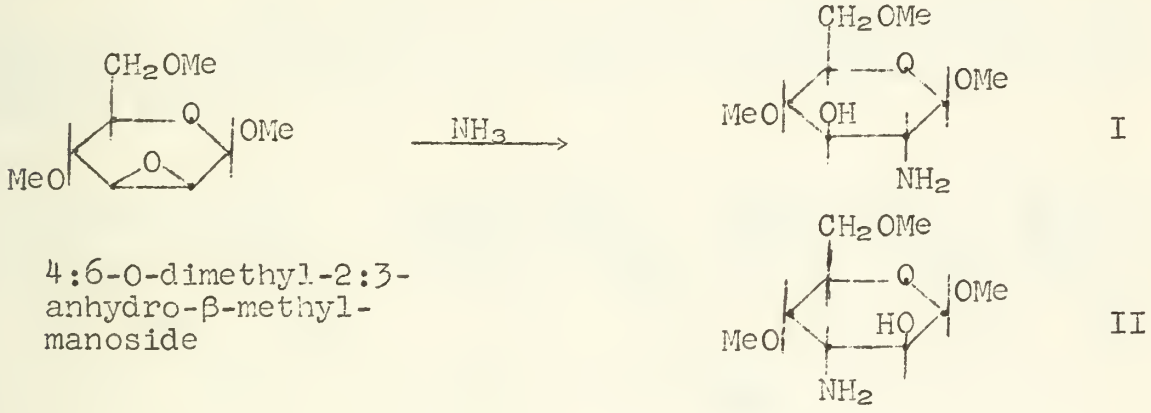
2-Amino-2-deoxy-D-gulose, a recently discovered degradation product of streptothricin, was prepared by Kuhn (24) from D-xylose by the catalytic hydrogenation of the corresponding phenylamino-nitrile.

Heyns (25) and coworkers achieved the synthesis of glucosamine by treatment of fructose with ammonium chloride in liquid ammonia. The following sequence of reactions was suggested.



The formation of 2-aminohexoses by scission of sugar epoxides is of general application but usually results in the formation of two isomers. Considerable interest has centered about the problem of the usually unequal proportions of the products formed by scission of epoxides.

In a synthesis of glucosamine by Haworth (26) the glucosamine derivative (I) was obtained in less than 10 per cent yield and was accompanied by 90 per cent of the 3-aminoaltrose compound (II)



4:6-O-dimethyl-2:3-anhydro-β-methyl-manoside

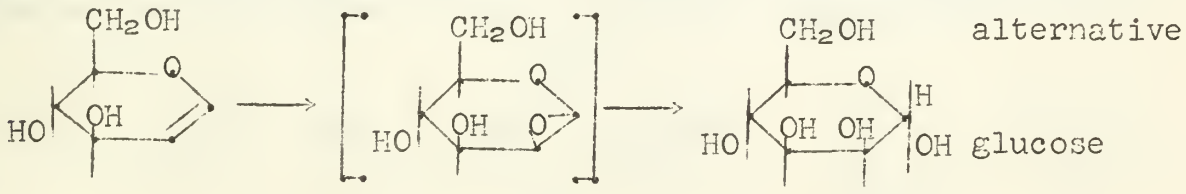
I

II

The distribution of products has been studied with reagents other than ammonia e.g. halogen acids and sodium methoxide on both sugar and steroid epoxides (dicyclic systems).

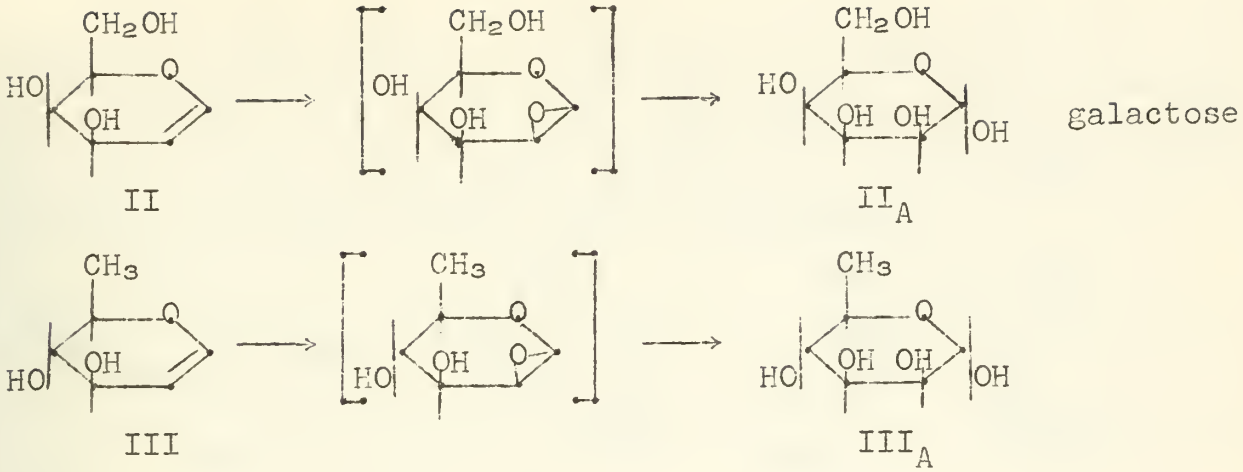
Fürst and Plattner (27) have shown that the scission of the epoxide ring in steroids leads to the formation of compounds in which the newly introduced groups are in the axial conformation.

Bose and his colleagues (28) in an attempt to extend this rule to anhydrosugars of the ethylene type, pointed out that the reaction of perbenzoic acid on the unsaturated compounds glucal (I) galactal (II) and rhamnal (III) almost certainly involves 1:2 anhydro intermediates and that mannose (I_A) talose (II_A) and rhamnose (III_A) are the principal products respectively

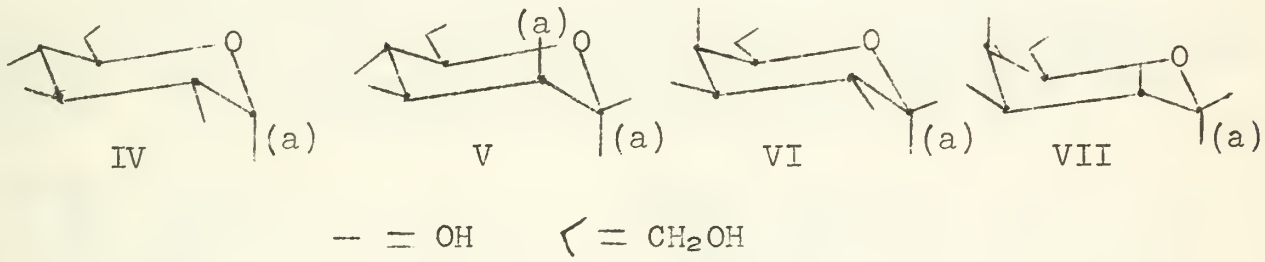


I

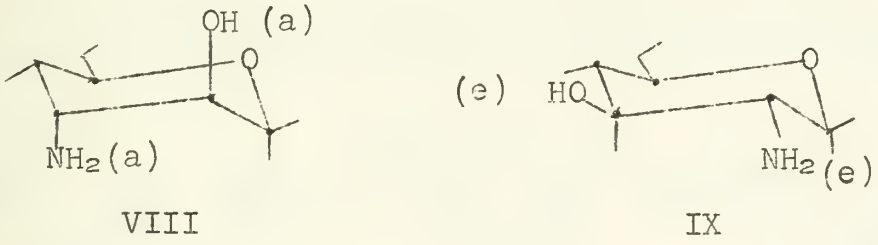
I_A



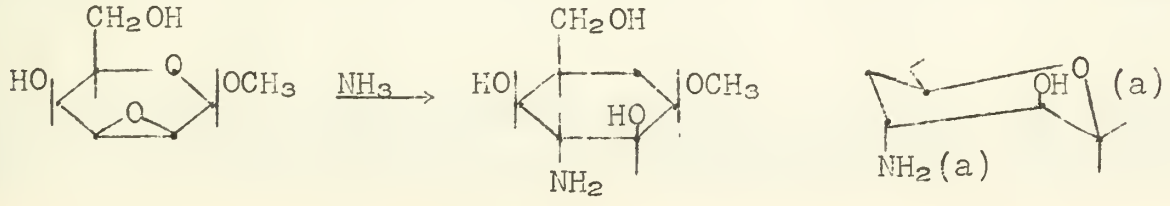
In all these products the incoming hydroxyl groups have taken up axial conformation as it seems by inspection of the preferred conformations of glucose (IV) mannose (V) galactose (VI) and talose (VII)



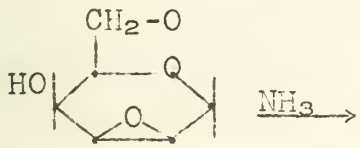
The large amount of the aminoaltroside formed simultaneously in the synthesis of glucosamine is therefore ascribed to the axial conformation taken up by the entering group in the former (VIII) and to an equatorial of these in the latter case (IX).

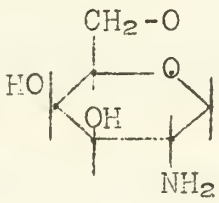


In the chemical synthesis of galactosamine treatment of methyl β-2:3-anhydro-taloside (X) with ammonia, the sole product was methyl 3-amino-3-deoxy-β-idoside (XI) as would be expected (29, 30).

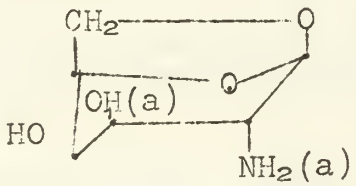


On the other hand the formation of galactose derivatives (XIII) instead of idose derivatives from 2:3-1:6 dianhydro-β-talose (XII) by the action of ammonia or sodium methoxide is not in contradiction with the Fürst and Plattner rule. The geometry of the 1:6 anhydro ring demands that the methylene group in C-6 and the oxygen at C-1 be axial, therefore making the substituents at positions 2 and 3 of 1:6-anhydrogalactone (XIII) axial in conformation.





XII

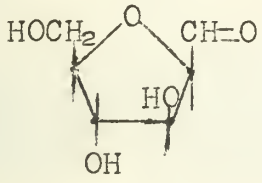


XIII

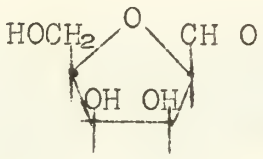
V. DEAMINATION

Action of nitrous acid

2-Aminohexoses are quantitatively deaminated by the action of nitrous acid with the production of a reducing sugar derivative and Nitrogen. From glucosamine and galactosamine there are obtained "chitose" (I) and "chondrose" (II) respectively (31, 32).

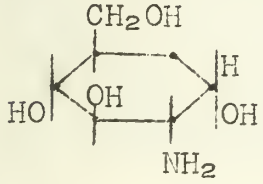


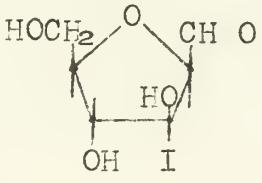
I

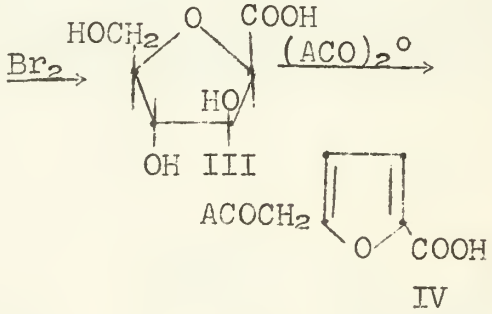


II

Chitose was characterized by oxidation to chitonic acid (III) which on treatment with acetic anhydride gave 6-acetoxymethylfuroic acid (IV) (33).

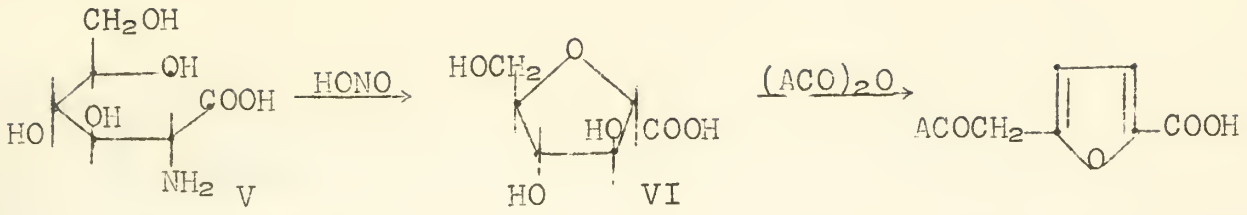






IV

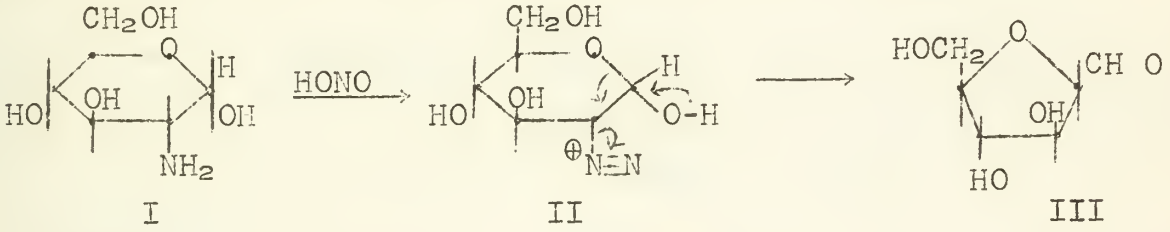
Deamination of glucosaminic acid (V) by nitrous acid leads to chitaric acid (VI) different from chitonic acid which by treatment with acetic anhydride gave also 6-acetoxymethylfuroic acid (31).



Both chitonic and chitaric acids were shown to be 2:5 anhydrohexonic acids. Furthermore chitaric acid was shown to be 2:5-anhydro-D-gluconic acid and chitonic acid, 2:5-anhydro-D-mannonic acid. From this it follows that deamination of glucosamine proceeds with a configurational change at C-2 giving chitose, 2:5-anhydromannose.

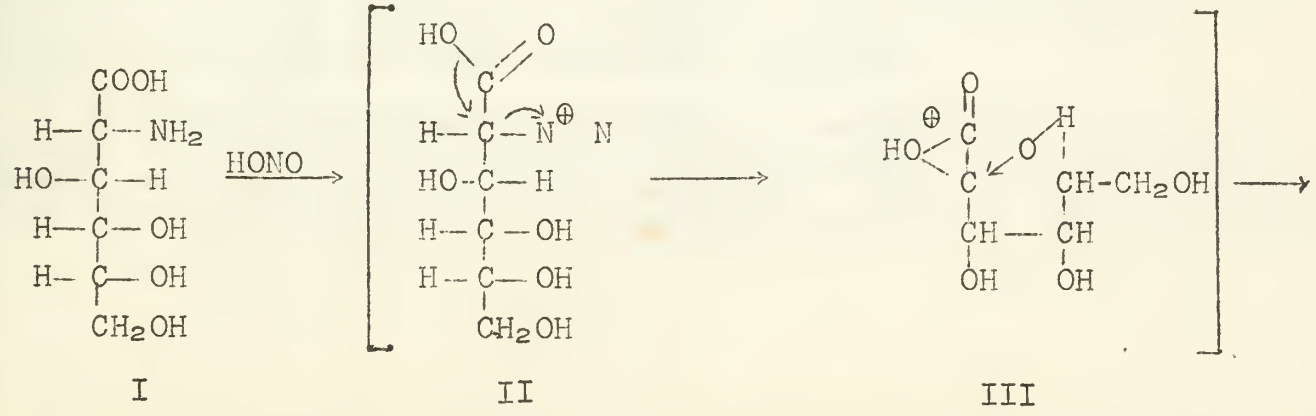
Levene and La Forge in 1915 established that a Waldey inversion occurred in the formation of chitose and suggested a mechanism (34).

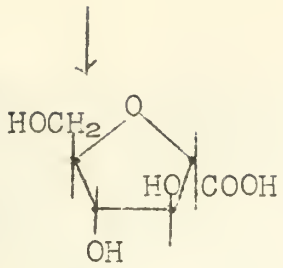
Recently Peat (35) suggested that the oxygen which originally formed part of the pyranoze ring acts as the displacing group with concomitant Walden inversion and anhydro-ring closure.



The trans arrangement of the C-4 hydroxyl group and the aldehyde group on C_1 in (III) makes the establishment of a furanose ring sterically unlikely and consequently 2:5 anhydro-D-mannose (chitose) probably exists as an aldehyde sugar.

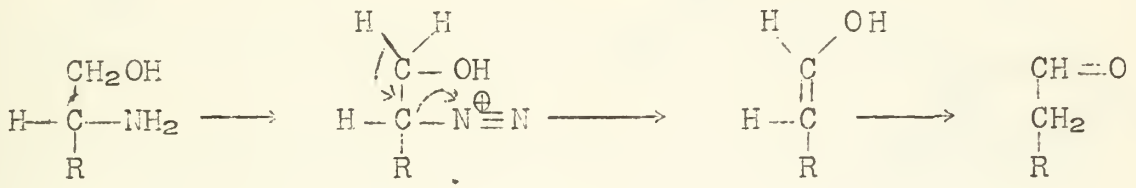
Foster (36) relates the deamination of D-glucosaminic (I) and galactosaminic acids to that of alanine which is known to undergo deamination with retention of configuration (37). Thus as nitrogen is released from the diazonium ion intermediate (II) derived from (I), participation of the adjacent carboxyl group gives the intermediate (III) with inversion of configuration at C-2. Further attack at C-2 by the C-5 hydroxyl-group in (III), which must be more available stereochemically than other hydroxyl groups, or solvent molecules, leads to a second Walden inversion with the formation of 2:5-anhydro-D-gluconic acid (IV).



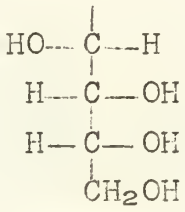


IV

Deamination of D-glucosaminol with nitrous acid affords 2-deoxy-D-glucose. The following mechanism was proposed by Foster (36).



where R =



VI. OXIDATION

2-Aminohexoses react with a large number of oxidizing agents and the type of reactions involved fall into the following broad classes.

1. Oxidation of the reducing group to yield the corresponding 2-aminohexonic acids.

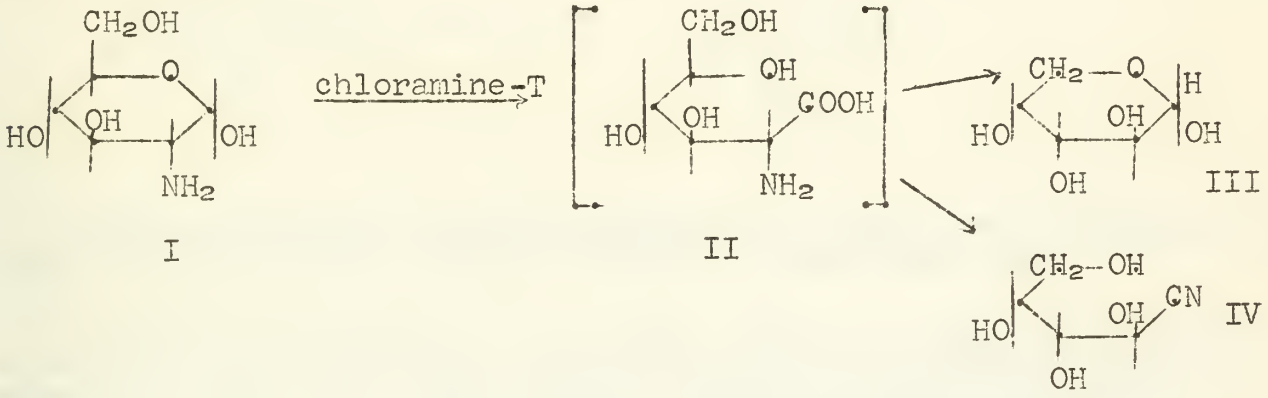
2. Simultaneous oxidation of the reducing and the amino group and

3. Cleavage of carbon-carbon linkages of the sugar ring.

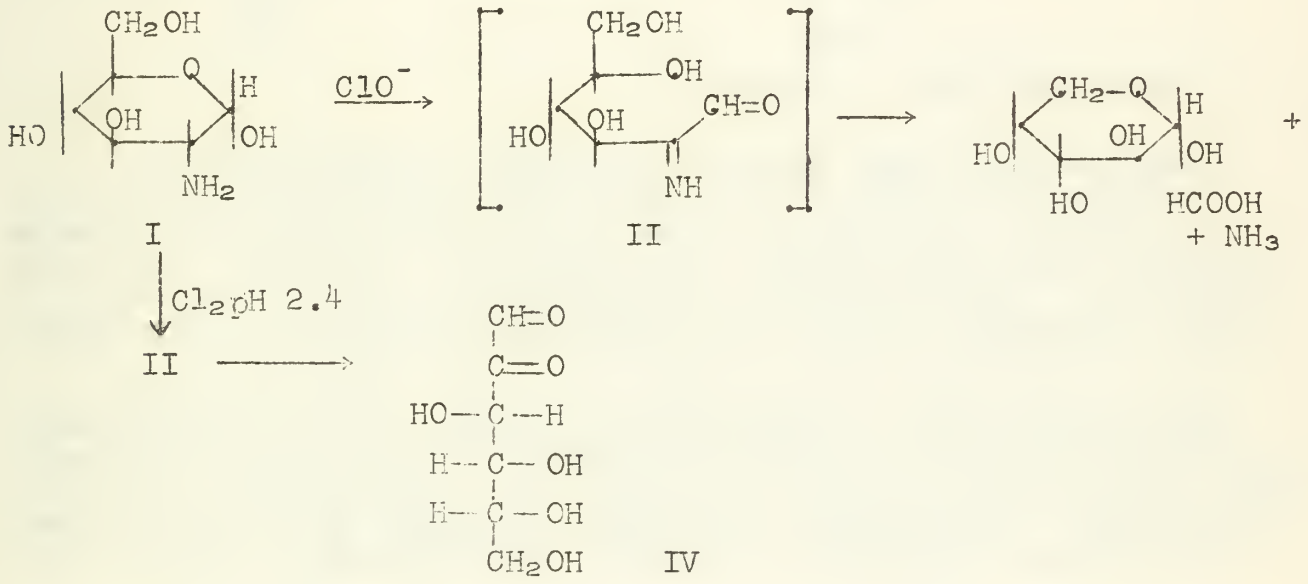
Oxidation of the first type occurs when glucosamine and galactosamine or their salts react with bromine water (31, 41) mercuric oxide (42) or with oxygen in the presence of platinum catalyst (43). It seems that the amino group is involved since N-acetyl-glucosamine is not oxidized under identical conditions.

Oxidative deamination constitutes the second type of oxidation. Herbst (44) studied the oxidation of glucosamine (I) by chloramine T. D-arabinose (III) and D-arabinonitrile (IV) were the chief products when two molar proportions of chloramine-T were used. Newberger (45)

found the course of the reaction of glucosamine with the naphthalene analogue of chloramine-T to be pH dependent. Since one more mole of these oxidants is required to oxidize glucosamine than the a-aminoacids it is assumed that glucosaminic acid (II) is an intermediate product.



However in a similar reaction, glucosamine is oxidized by one equivalent of alkaline hypochlorite. In addition to arabinose (III) formic acid and ammonia are formed. No carbon dioxide is produced as would be expected if a carboxylic acid is found as intermediate. The course of the reaction appears to be as follows (46).



D-glucosone (IV) is formed in the oxidation of glucosamine by chlorine at pH 2.4 in addition to D-arabinose resulting from hydrolysis of the intermediate imino-sugar (II) of the above scheme (47).

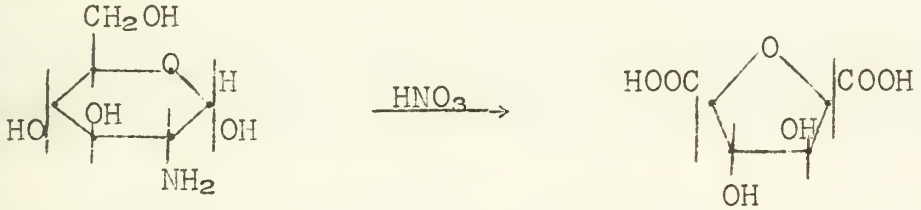
Solutions of hypoiodites eliminate partially the nitrogen with the formation of arabinonitrile and evolution of carbon dioxide. From the amount of oxidizing agent consumed it is assumed that

2-Imino-D-gluconic acid is formed intermediately (V) this compound being readily decarboxylated to give D-arabonitrile (VI) (48).

V VI

Both glucosamine and glucosaminic acid react with ninhydrin in the same way as a-aminoacids, to yield D-arabinose (49).

Nitric acid eliminates the amino group of 2-aminohexoses and oxidizes the molecule at C_1-C_6 giving among the products anhydro-saccharic acids. The same product results from the oxidation of glucosamine or chitin under the same conditions (50, 51, 52).



2:5-anhydro-D-mannaric acid.

Periodate oxidation (Oxidation of the third type) has been widely employed in the study of the constitution of aminopoly-saccharides, particularly in attempts to decide the position of glycosidic linkages. The amino group (primary-secondary) behaves in a similar manner but slower than a hydroxyl group, the adjacent carbon-carbon linkages being cleaved and ammonia liberated (53).

Although Nicolet and Shinn (53) observed that 1,2-tertiary aminoalcohols are not oxidized by periodate at room temperature, Clark (5), Brockman (54) and Folker et al (3) working independently, isolated crotonaldehyde (as the DNP derivative), dimethylamine and formic acid in the periodate oxidation of desosamine the degradation product of erythromycin, picromycin and other antibiotics.

The course of the periodate oxidation may be followed by estimation of the liberated ammonia, by dissapearance of oxidizing agents, or by determination of the rate of formation of oxidation products

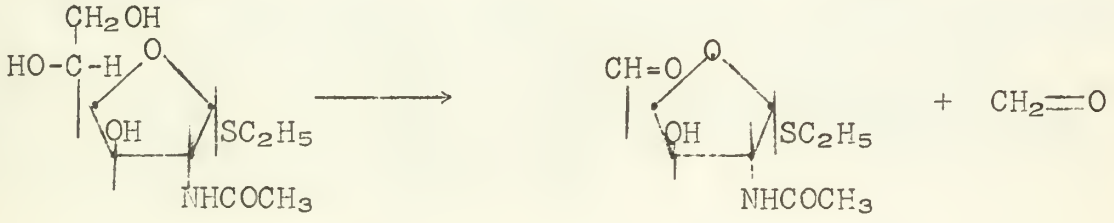
(aldehydes or formic acid).

N-acetyl-glucosamine is oxidized less rapidly than salts of the aminosugar. It is reported that at 5° (pH 4.5) 4.7 moles of metaperiodate (theoretical amount 5 moles) are consumed with the generation of 2.4 moles of HCOOH (Theor. 5 moles) and no ammonia (55). Other investigators (56) have arrived at different conclusions. Similar lack of unanimity exists in regard to reports of the periodate oxidation of methyl N-acetyl-glucosaminides and of methyl a-glucosaminides hydrochloride (2).

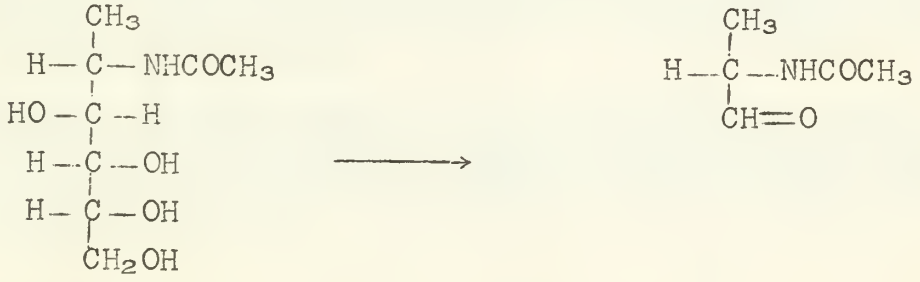
It is reported (57) that N-methyl-glucosaminides are resistant to oxidation by sodium metaperiodate. When however, excess of the oxidizing agent is used the reaction is similar to that of the N-acetylated aminosugar. This effect is probably due to the enhancement of ionic properties arising from N-alkylation and to the removal of periodate ions in salt formation with the secondary amine.

Lead tetraacetate has somewhat more limited applications than sodium and potassium metaperiodate. The reagent distinguishes in rate of oxidation between cis and trans form of glycols and α-aminoalcohols.

Lead tetraacetate have been used successfully in the degradation of furanosides. The terminal glycol group is readily oxidized by one mole of the reagent producing one mole of formaldehyde (58, 59).



The N-acetylamino center appears to be stable to this reagent. Further demonstration of this is given in the oxidation of acyclic derivatives of glucosamine i.e. 2-acetamido-1:2-dideoxy D-sorbitol (60).



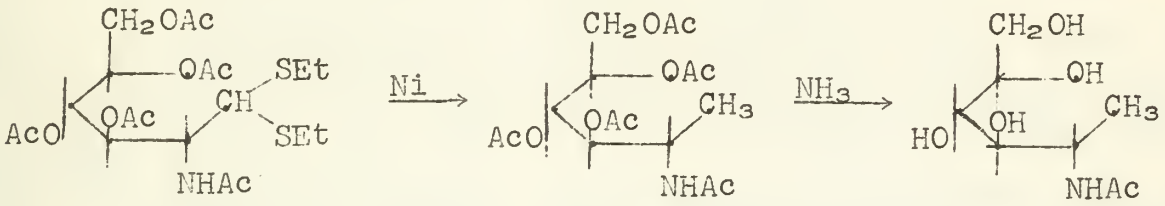
VII REDUCTION

Glucosamine as the base is catalytically reduced to D-glucosaminol by hydrogenation under pressure at 90°-100° using a Nickel catalyst (61).

Hydrogenation of glucosamine as the base in the presence of Adams platinum catalyst leads to a Cannizaro type of reaction in which D-glucosaminic acid and D-glucosaminol are formed in equal proportions (61).

Reduction of salts of the N-acetyl-compound gives only D-glucosaminol and its N-acetyl derivative respectively.

1-Deoxy derivatives of glucosamine have been prepared by reductive desulphurization (59, 62).



Reduction of glucosaminol hydrochloride with hydroiodic acid does not lead to the production of 2-aminohexane but to a compound $C_6H_{13}ON$ (as a monohydrochloride) corresponding to 2-aminohexene oxide (63).

VIII ACTION OF ALKALINE REAGENTS

2-Aminosugars undergo a series of complex changes in aqueous alkaline media. Cold dilute alkali liberates the free amino-bases which appear to be very reactive compound, dimerize to give pyrazine derivatives and undergo oxidation and deamination in the presence of oxygen. The rate of deamination increase with the temperature and the PH. Between PH 10 and 11 the liberation of NH_3 is approximately quantitative (2).

Glycosides with the amino-group unsubstituted are deaminated by alkali media much less readily than the aminosugar itself (10).

Epimerization has not been demonstrated in the action of alkalis on the 2-aminosugars, though epimeric changes are observed with the related 2-aminohexonic acids (67) for example 2-amino-2-deoxy-D-mannonic acid is obtained by the epimerization of glucosaminic acid on treating in pyridine.

Degradation of aminosugars is promoted also by organic bases, such as collidine and leutidine. This is particularly significant in view of the use of the basic substances as solvents in chromatographic procedures (65).

BIBLIOGRAPHY

1. A. B. Foster and M. Stacey, Advanc. Carbohyd. Chem., 7, 247 (1952).
2. P. W. Kent, and M. W. Whitehouse "Biochemistry of the Amino-sugars" Butterworths Scientific Publications, London, 1955.
3. R. Kuhn, Angew. Chem., 69, 23 (1957).
4. F. A. Kuehl, E. H. Flynn, F. W. Holly, R. Mozingo, and K. Folkers, J. Am. Chem. Soc., 69, 1847 (1947).
5. R. K. Clark, Antibiotics and Chemotherapy 3, 663 (1953).
6. C. W. Waller, J. Am. Chem. Soc., 75, 2025 (1953).
7. E. E. van Tamelen, J. R. Dyer, H. E. Carter, J. V. Pierce, and E. E. Daniels, J. Am. Chem. Soc., 78, 4817 (1956).
8. E. R. Purchase and C. E. Braun, Org. Syntheses 26, 36 (1946).
9. B. F. Folkes, R. A. Grant and J. K. N. Jones, J. Chem. Soc., 1950, 2136.
10. R. C. G. Moggridge and A. Newberger, J. Chem. Soc., 1938, 745.
11. A. B. Foster, D. Horton, and M. Stacey, J. Chem. Soc., 1957, 51.
12. Grant White, University of Illinois Organic Seminar, July 6, 1956.
13. R. Consden and W. M. Stanier, Nature, 169, 783 (1952).
14. R. Consden and W. M. Stanier, Biochem. J., 51, 19 (1952).
15. L. Jaenicke, Naturwissenschatten, 39, 86, (1952).
16. J. Boeseken, Advanc. Carbohyd. Chem., 4, 189 (1948).
17. E. Fischer and H. Leuchs, Ber., 53, 509 (1903).
18. P. A. Levene, J. Biol. Chem., 26, 155 (1916).
19. F. A. Kuehl, E. H. Flynn, F. W. Holly, R. Mozingo and K. Folkers J. Am. Chem. Soc., 69, 3032 (1947).
20. R. Kuhn, Angew. Chem. 69, 23 (1957).
21. R. Kuhn, and W. Kirschenlohr, Angew. Chem. 67, 786 (1955).
22. R. Kuhn and W. Kirschenlohr, Ann. 600, 135 (1956).
23. H. Plieninger and G. Werst Angew. Chem. 67, 156 (1955).
24. R. Kuhn Angew. Chem. 69, 60 (1957).
25. K. Heyns and K. H. Meinecke, Chem. Ber. 86, 1453 (1953).
26. N. W. Haworth, W. H. G. Lake and S. Peat, J. Chem. Soc. 1939, 271.
27. A. Fürst, and P. A. Plattner, 13th. Int. Congr. Chem. 1951, 409.
28. A. K. Bose, D. K. R. Chaudhuri, and A. K. Bhattacharya, Chem. and Ind. 1953, 869.
29. S. P. James, F. Smith, M. Stacey, and L. F. Wiggins, Nature Lond. 156, 308 (1945).
30. S. P. James, F. Smith, M. Stacey and L. F. Wiggins, J. Chem. Soc., 1946, 625.
31. E. Fischer, and F. Tieman, Ber. 27, 138 (1894).
32. P. A. Levene, J. Biol. Chem. 31, 609 (1917).
33. E. Fischer, and E. Andrease, Ber. 36, 2587 (1903).
34. P. A. Levene, and F. B. LaForge, J. Biol. Chem. 21, 345, 351 (1915).
35. S. Peat, Advanc. Carbohyd. Chem. 2, 63 (1946).
36. A. B. Foster, Chem. and Ind., 1955, 627.
37. K. C. Ingold, Nature, 166, 178 (1950).
38. J. C. Irvine and A. Hynd, J. Chem. Soc., 1914, 698.
39. P. W. Kent and M. W. Whitehouse, "Biochemistry of the Amino-sugars" Butterworths Scientific Publications, London, 1955 p. 215.

40. L. F. Wiggins, Nature, 157, 300 (1946).
41. G. Newberg and H. Wolf, Ber., 34, 3840 (1901).
42. H. Pringsheim, Ber. 48, 680 (1915).
43. J. Heyns and W. Kogh, Chem. Ber. 86, 110 (1953).
44. R. M. Herbst, J. Biol. Chem. 119, 35 (1937).
45. A. Newberger, J. Chem. Soc., 1940, 29.
46. Y. Matsushima, Bull. Chem. Soc., Japan 24, 17 (1951).
47. Y. Matsushima,Chem. Abstr. 46, 7052 (1952).
48. C. Dumazert and H. Lehr, Trav. Soc. Chim. Biol. 24, 1047 (1942).
49. S. Gardel, F. Heijkensjold, and A. Rochnorlund, Acta Chem. Scand. 4, 970 (1950).
50. M. Sumiki, Chem. Abstr. 43, 578 (1949).
51. M. Sumiki, Chem. Abstr. 44, 7773 (1950).
52. F. Tieman, Ber. 27, 118 (1894).
53. H. B. Nicolet and L. A. Shinn, J. Am. Chem. Soc., 61, 1615 (1939).
54. H. Brockman, H. B. König and R. Oster, Chem. Ber. 87, 856 (1954); R. K. Clark, Antibiotics and Chemotherapy 3, 663 (1953).
55. R. Jeanloz., J. Am. Chem. Soc., 76, 555 (1954).
56. H. D. Brown, Biochim. Biophys. Acta 7, 487, (1951).
57. R. Jeanloz, and E. Forchielli, J. Biol. Chem. 188, 361 (1951).
58. P. W. Kent, Research Lond. 3, 427 (1950).
59. L. M. Wolfrom, R. V. Lemieux and S. M. Olin, J. Am. Chem. Soc., 71, 2870 (1949).
60. L. M. Wolfrom, M. S. Olin and W. J. Polglase, J. Am. Chem. Soc., 72, 1724 (1950).
61. P. A. Levene and C. C. Christman, J. Biol. Chem. 120, 575 (1937).
62. L. M. Wolfrom and J. V. Karabinos, J. Am. Chem. Soc., 66, 909 (1944).
63. P. A. Levene and C. C. Christman, J. Biol. Chem. 123, 77 (1938).
64. P. A. Levene, J. Biol. Chem. 39, 69 (1919).
65. D. Aminoff and W. T. J. Morgan, Biochem. J. 48, 74 (1951).

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