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D

SEMINAR TOPICS

I Semester 1937-38

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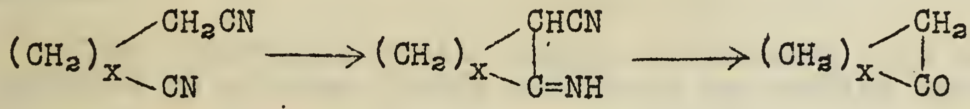
MANY-MEMBERED RINGS

Ziegler and associates, University of Halle

A quantitative study of the ease of formation of many-membered rings by comparison of the yields in each instance under carefully controlled conditions has been made. Experiments covering rings from 5 to 33 members have been completed using the dinitrile synthesis shown below.



The dinitriles of larger molecular weight were prepared by the following series of reactions and explicit directions furnished.

$HOOC-(CH_2)_n-COOR \longrightarrow ROOC-(CH_2)_{2n}-COOR \longrightarrow HOCH_2-(CH_2)_{2n}-CH_2OH$

$\longrightarrow BrCH_2-(CH_2)_{2n}-CH_2Br \longrightarrow$ malonic ester syn. $\longrightarrow$ acid

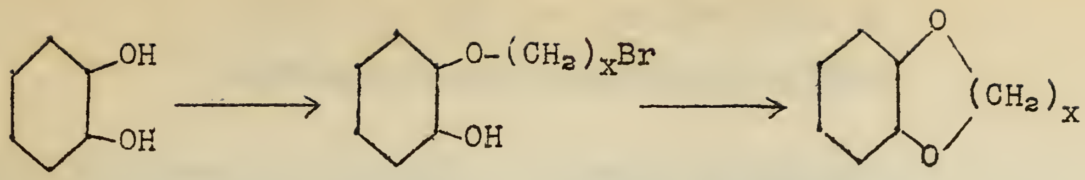
$\longrightarrow$ amide $\longrightarrow$ nitrile

The cyclization was carried out by the dilution method, e. g., 0.1 mole of dinitrile was added over a period of 72 hours to 1.5 liters of 0.67 N ether solution of sodium alkyl aniline (containing 25 per cent excess of alkyl aniline) boiling under reflux.

The 9-13 membered rings were obtained in only an extremely small yield which is explained by the crowding or packing effect to be expected in such molecules. From the 12 ring to the 33, the yields increased rapidly in zig-zag form for odd and even numbers till a maximum yield at the 20 ring was reached (about 85 per cent yield). There was then a drop culminating at the 26 ring (60 per cent yield), followed by another increase and decrease. A similar phenomenon was observed in melting points--irregularity until the 12 ring, a dip and gradual increase to the 19 ring, a falling off to the 24 and 25 ring and subsequent increase. The authors believe some periodicity may be expected at the 24-26 range less marked than in the C_9-C_{13} range.

Experiments were performed to produce ketones from $CN(CH_2)_4-O-(CH_2)_4CN$ and $CN-(CH_2)_4-O-(CH_2)_2-O-(CH_2)_4-CN$. The ten ring and thirteen ring molecules, respectively, were formed in 5 per cent and 70 per cent yields indicating that oxygen released the crowding effect.

Extensive work was also done on cyclic ethers of pyrocatechi resorcinol, hydroquinone and dihydroxy naphthalenes shown below.

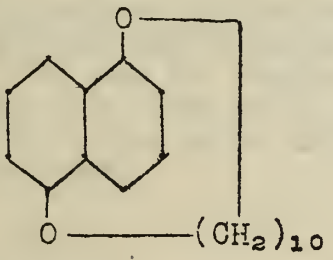


The cyclization was carried out (a) by allowing equimolar concentrated solution of sodium ethylate and bromoalkyl ether into a large volume of solvent over a long period of time or, (b) by adding slowly the bromoalkyl ether to a large volume of hot solvent (amyl alcohol) containing anhydrous potassium carbonate.

From resorcinol cyclic ethers containing 6-14 members indicated no minimum yields and hence no packing effect.

From hydroquinone the following yields were obtained; with decamethylene bromide 79 per cent, octamethylene 18 per cent, heptamethylene or hexamethylene 0 per cent.

The 1,5-dihydroxnaphthalene and decamethylene bromide gave 61 per cent yield, the 2,6-dihydroxy with the same bromide 22 per cent. These cyclic compounds



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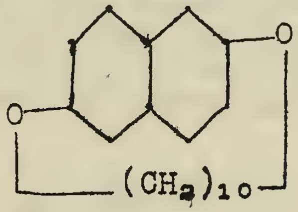

are interesting in that they should be capable of existing in optically active form providing the naphthalene nucleus cannot rotate in and out of the large ring.

The odor of the various ethers from pyrocatechin and hydroquinone compared with the odor reported for certain many-membered ethers, lactones, anhydrides, etc., led the authors to conclude that many-membered ring regardless of chemical constituents will give these results; 15-17 members--musk odor; 14 members--cedar odor, 12 members--camphor odor. The benzene ring apparently has no effect.

Cyclization of p,p-dihydroxydiphenyl methane and p,p-dihydroxydiphenyl ether was accomplished. It was shown that in general a chain about 2 Å longer than that calculated gave the best yields. The diphenyl ether derivative formed in yields which indicated the oxygen valence angle might be larger than tetrahedral.

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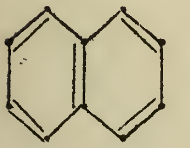
Reported by Roger Adams
September 22, 1937.

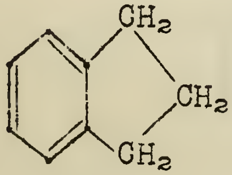
RECENT EVIDENCE ON THE STRUCTURE OF NAPHTHALENE—THE MILLS-NIXON EFFECT

Fieser and Lathrop -- Harvard University.
Baker and Carruthers -- Oxford University.
McLeish and Campbell -- University of Edinburgh.
Kistiakowsky et al -- Harvard University.

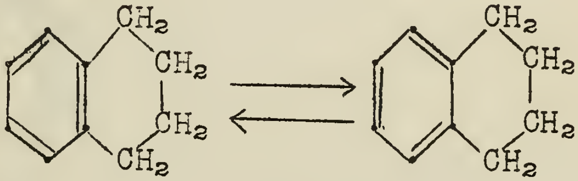
From the earlier work of Fieser and Lathrop and others the structure of naphthalene, hydrindene, and tetralin seem to be I, II and III, respectively.



I.

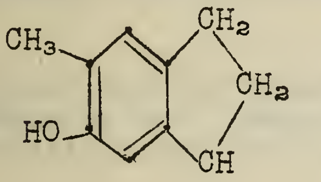


II.

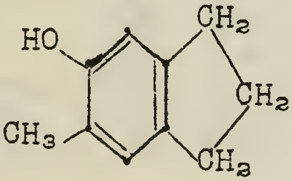


III.

Recent findings throw some doubt on the validity of these formulas. Fieser and Lathrop have shown that 5-methyl-6-hydroxyhydrindene (IV) can be coupled, indicating that the compound does exist in the form of V. This, according to the Mills-Nixon theory, would be the more highly strained and hence more improbable structure.

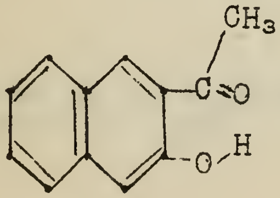


IV.

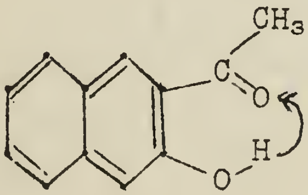


V.

Baker and Carruthers have made a study of the chelation of *ortho*-acetylnaphthols. They discovered that 2-acetonaphthol-3 (VI) is chelated, indicating that the bonds of the naphthalene may shift to the asymmetric form (VII).



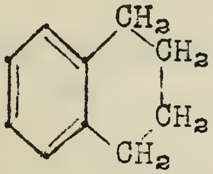
VI.



VII.

Experiments of a similar type with hydrindene compounds showed that the bond structure was not fixed.

From a study of the rates of hydrolysis of 2-bromo-3-nitronaphthalene as compared with 1-bromo-2-nitronaphthalene and other compounds McLeish and Campbell have concluded that the C_2-C_3 bond differs from the C_1-C_2 bond. Application of the same methods to the study of the hydrindene problem showed that hydrindene exists largely in the form predicted by Mills and Nixon (II). The reaction of the nitro-bromotetralins indicates the formula VIII for the hydrocarbon.



VIII.

Finally Kistiakowsky and others have concluded from a study of the heats of hydrogenation of tetralin and hydrindene that there is probably no such thing as the Mills-Nixon effect.

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58, 2050 (1936)
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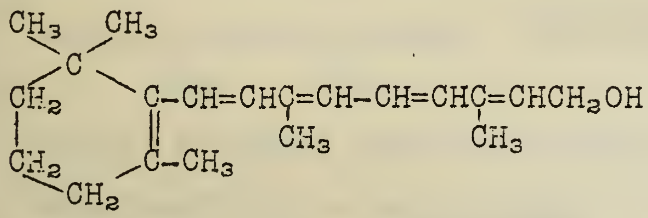
Reported by C. K. Bradsher
September 29, 1937

THE SYNTHESIS OF VITAMIN A

Karrer -- University, Zurich.
Kuhn -- Kaiser Wilhelm Institute, Heidelberg.

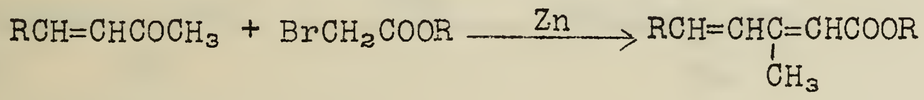
The existence of a fat-soluble factor necessary for growth was first demonstrated in 1913 by workers at Yale and Wisconsin. Further studies by many workers showed that two fat-soluble vitamins must be distinguished, A, which promotes growth, and D, the antirachitic vitamin. Vitamin A was first isolated in nearly pure form from fish-liver oils by Karrer and Heilbronn independently, and Karrer assigned it the following structure, based on degradation and hydrogenation experiments:



He later synthesized the saturated alcohol corresponding to this structure and showed it to be identical with the perhydro vitamin obtained by complete reduction of the natural product.

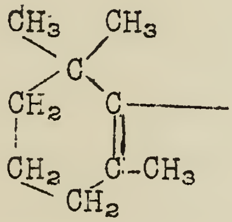
Some of the important synthetic work, which has been extensive, is indicated by the following compounds:

(Karrer)

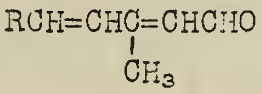


$$\mathrm{RCH{=}CHCOCH_3 + BrCH_2COOR \xrightarrow{Zn} RCH{=}CH\underset{\displaystyle CH_3}{C}{=}CHCOOR}$$

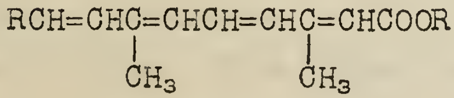
where R=



Heilbronn has prepared substances given the following structure:



$$\mathrm{RCH{=}CH\underset{\displaystyle CH_3}{C}{=}CHCHO}$$

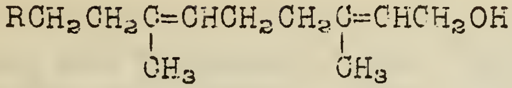


$$\mathrm{RCH{=}CH\underset{\displaystyle CH_3}{C}{=}CHCH{=}CH\underset{\displaystyle CH_3}{C}{=}CHCOOR}$$

Gould and Thompson prepared, among other compounds,

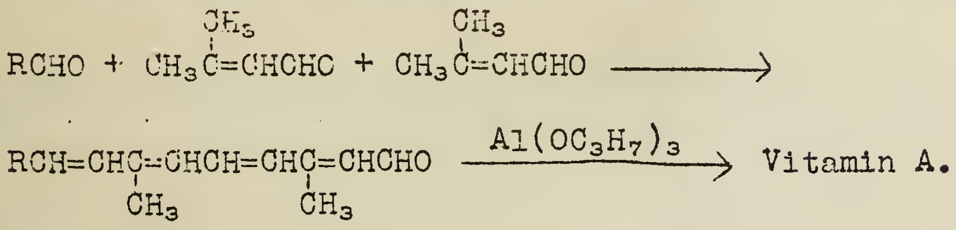
$$\mathrm{RCH{=}CH\underset{\displaystyle CH_3}{C}{=}CHCH_2CH_2COCH_3}$$

and Ruzicka made the tetrahydro vitamin:



$$RCH_2CH_2\underset{CH_3}{C}=CHCH_2CH_2\underset{CH_3}{C}=CHCH_2OH$$

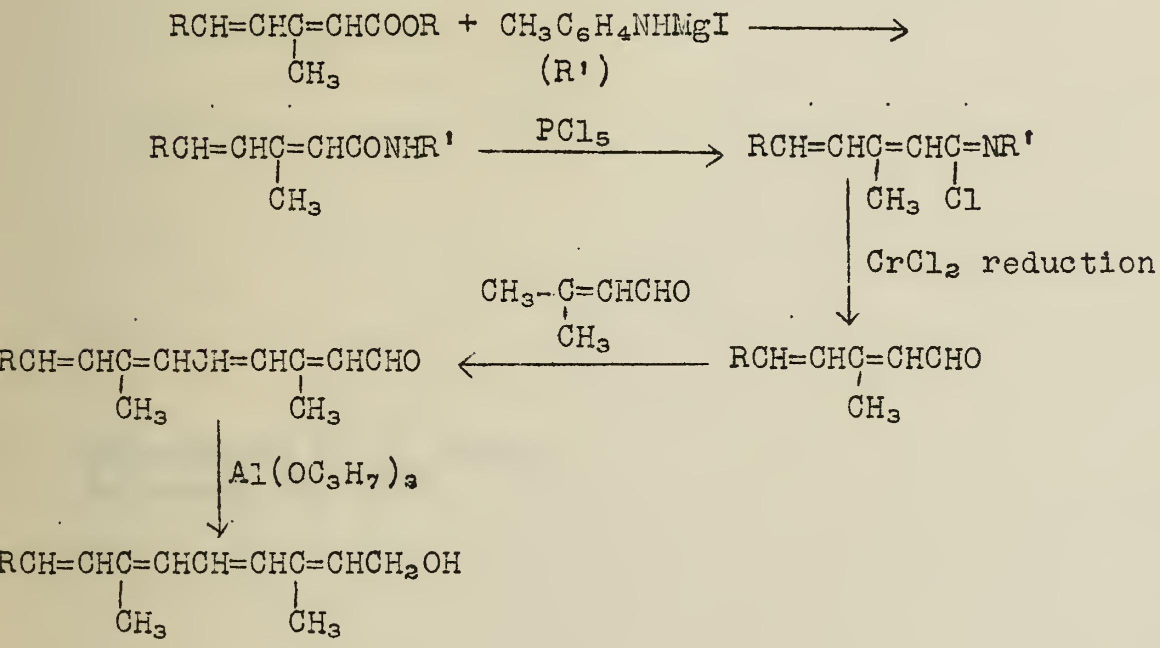
The following reactions were carried out in this laboratory by Dr. Fuson and Dr. Christ:



$$RCHO + CH_3\overset{CH_3}{C}=CHCHO + CH_3\overset{CH_3}{C}=CHCHO \longrightarrow$$

$$RCH=CH\underset{CH_3}{C}=CHCH=CH\underset{CH_3}{C}=CHCHO \xrightarrow{Al(OC_3H_7)_3} \text{Vitamin A.}$$

Kuhn's recently reported synthesis follows:



$$RCH=CH\underset{CH_3}{C}=CHCOOR + \underset{(R')}{CH_3C_6H_4NHMgI} \longrightarrow$$

$$RCH=CH\underset{CH_3}{C}=CHCONHR' \xrightarrow{PCl_5} RCH=CH\underset{CH_3}{C}=CH\underset{Cl}{C}=NR'$$

$$\xrightarrow{CrCl_2 \text{ reduction}} RCH=CH\underset{CH_3}{C}=CHCHO \xrightarrow{CH_3-\underset{CH_3}{C}=CHCHO} RCH=CH\underset{CH_3}{C}=CHCH=CH\underset{CH_3}{C}=CHCHO$$

$$\xrightarrow{Al(OC_3H_7)_3} RCH=CH\underset{CH_3}{C}=CHCH=CH\underset{CH_3}{C}=CHCH_2OH$$

Vitamin A.

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Isolation and proof of structure.

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Reported by D. S. Tarbell
September 29, 1937.

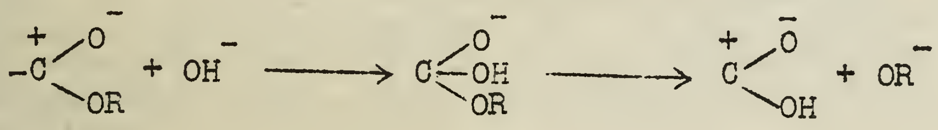
STERIC HINDRANCE: ESTERIFICATION OF SUBSTITUTED ACETIC ACIDS

von Braun -- Heidelberg (formerly Frankfort a. M.)
Ingold -- University College -- London.

The studies started by v. Braun on steric hindrance in 1913 have in recent years been extended to acetic acids with branched-chain substituents.

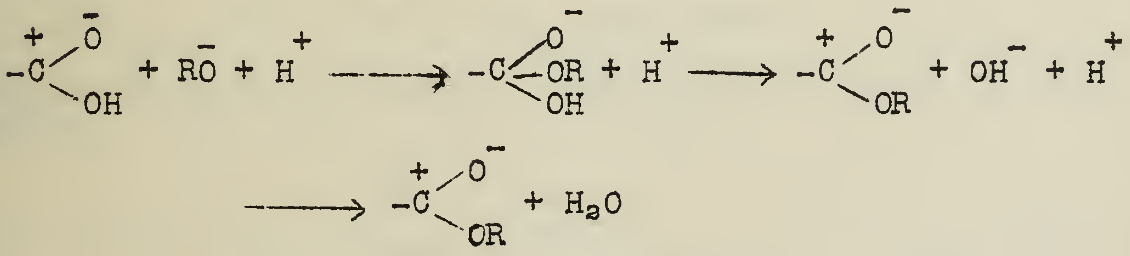
Ingold[1] has discussed the esterification of acids and the saponification of esters from the electronic standpoint; modern views indicate the following courses for these reactions:

(a)

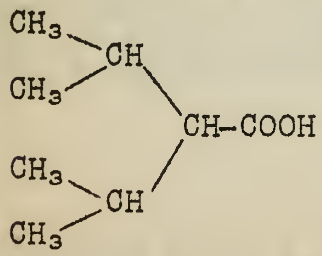


$$OR^- + H_2O \longrightarrow ROH + OH^-$$

(b)



As the primary addition of $\bar{OR}$ or $\bar{OH}$ to the + carbon atom of the carbonyl group is made more difficult, either by purely steric effects or by some influence which alters the + character of the carbon atom, so will saponification or esterification be more difficult. It is known that hydrocarbon residues, such as $-CH_3$, are "electron-repelling" groups, and it is known also that trimethylacetic acid is rather difficultly esterified, while trichloroacetic acid, which carries three chlorine atoms in the same position, is much more easily esterified. The presence of a number of hydrocarbon residues at a greater distance from the carboxy group should influence the saponification and esterification, but due to the spatial removal of the groups, through electrochemical effects only.



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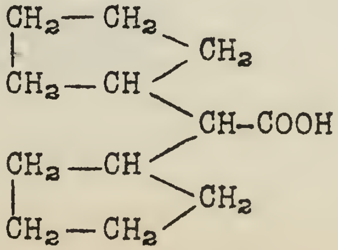
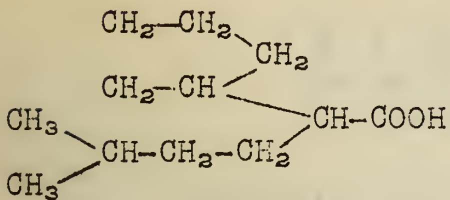


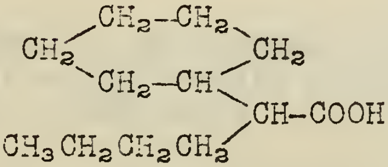
(A)

were prepared[2] and were extremely difficult to esterify.

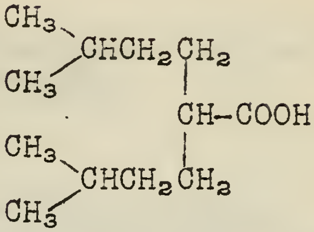
Further studies[3] on the following acids



(B)



(C)

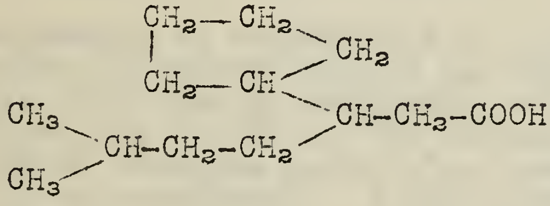


(D)

showed that acids and esters (B) and (C) were more difficult to esterify and saponify than (D). In the table, (I) is per cent esterification, (II) is per cent saponification of the corresponding esters, under an arbitrary, but uniform, set of conditions:

Acid	A	B	C	D	E
I.	0	80	60	100	100
II.	0	59	41	100	100

(E) was prepared through the reduction of the ester of (B), and is



(E)

These results indicate clearly that there is more to "steric hindrance" in many cases than purely mechanical blocking effects, and that the electrochemical nature, as well as the size, of interfering groups must be considered in order to arrive at a complete explanation of steric effects.

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1. Ingold, J. Chem. Soc., 1932, 756.
2. v. Braun and Fischer, Ber., 66, 101 (1933).
3. v. Braun and Kurtz, Ber., 70, 1224 (1937).

Reported by T. A. Geissman
October 6, 1937.

THE ISOMERIZATION OF 2,3-DIMETHYLASCORBIC ACID

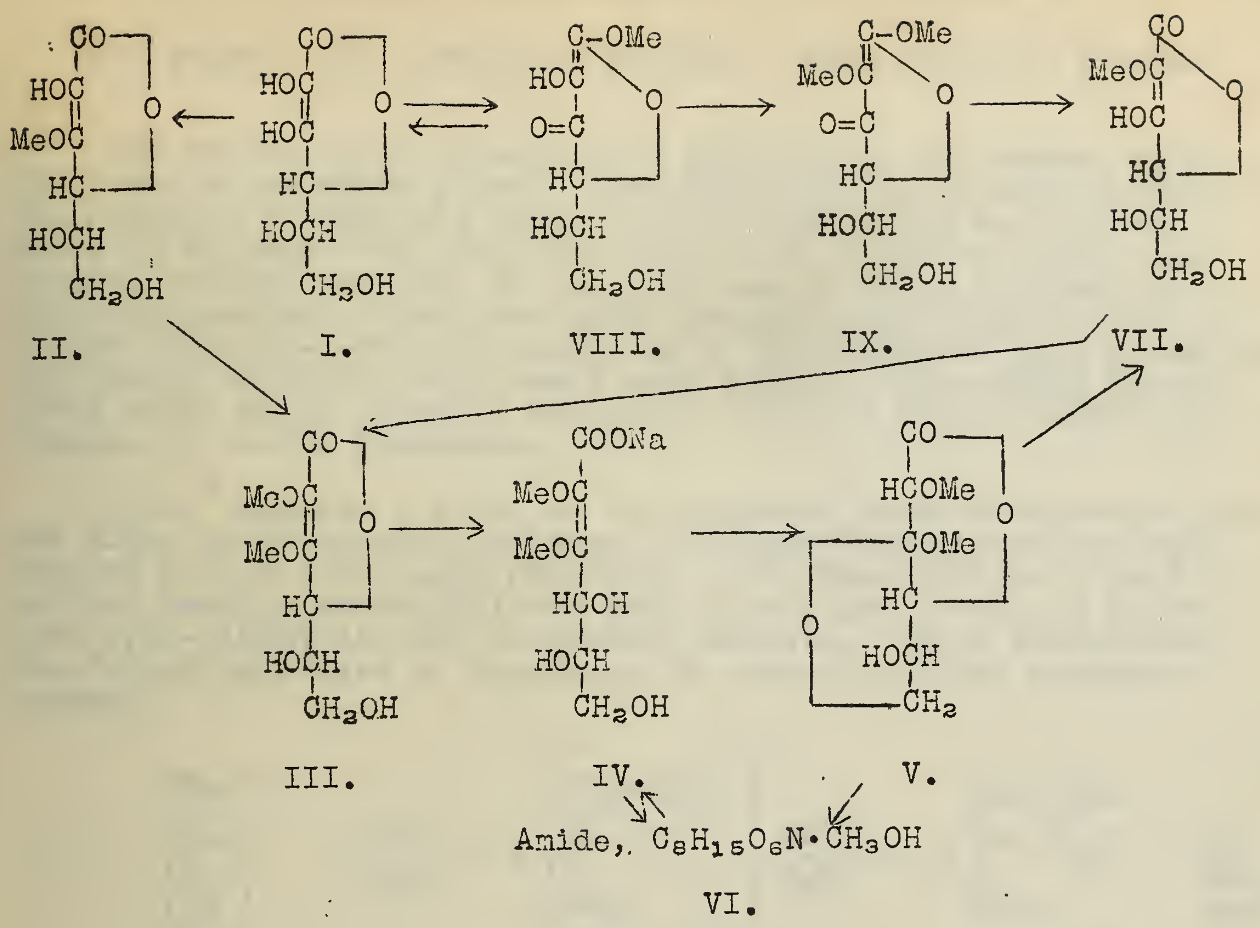
W. N. Haworth -- University of Birmingham (England)
E. L. Hirst -- University of Birmingham
F. Micheel -- Göttingen

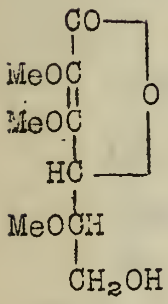
Ascorbic acid (I), 3-methylascorbic acid (II), 2,3-dimethylascorbic acid (III), and 2,3,5,6-tetramethylascorbic acid all have the normal ascorbic acid ring system. When 2,3-dimethylascorbic acid is reacted with alkali and the resulting open chain compound (IV) is acidified with mineral acid, the nature of the resulting product has been uncertain. The present work deals with this product.

Haworth, Hirst, et al, have shown that from this product it is possible to regenerate 2,3-dimethylascorbic acid. The work of Micheel has shown that this direct regeneration of 2,3-dimethylascorbic acid is not the usual course of the reaction, but a structural isomer of this compound is generally formed. He suggested formulas XI and V, but preferred formula XI. The formation of the isomeric compound, isodimethylascorbic acid is dependent upon a free hydroxyl at carbon number 6 since 6-trityl-2,3-dimethylascorbic acid will not undergo isomerization. The formation of III from IV appears to depend on catalysis and occurs only under drastic conditions.

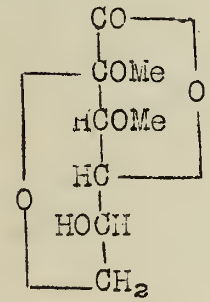
The iso-compound is converted into VI in almost quantitative yields, while III gives only 25 per cent yields under the same conditions. The ease of hydrolysis of this amide indicates that the structure may be VIb or VIc instead of VIa which would be expected. These formulas would also account for the resistance of VI to ozonolysis. Sodium hydroxide converts VI into IV. Hydrogen chloride in methyl alcohol converts V into VII, different from II and converted by diazomethane into III. Therefore, VII is 2-methylascorbic acid. The compound previously reported as 2(?)-methylascorbic acid by Haworth and Hirst, therefore, appears to be a 1-methyl derivative of one of the tautomeric forms of ascorbic acid (VIII), which is converted to IX by methylation and this to VII by water.

The various reactions are summarized in the following scheme. Besides those indicated the conversion of 2,3,5-trimethylascorbic acid (X) has been carried through the cycle (III) ⟶ (IV) ⟶ (V) ⟶ (VI) and (V) ⟶ (VII) ⟶ (III), the product being in each case the 5-methyl derivative of the compound shown.

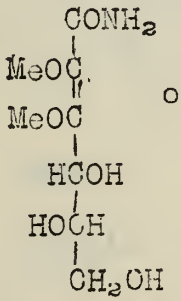




X.

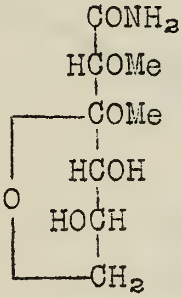


XI.



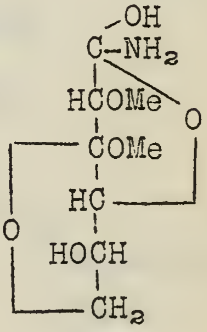
VIa.

or



VIb.

or



VIc.

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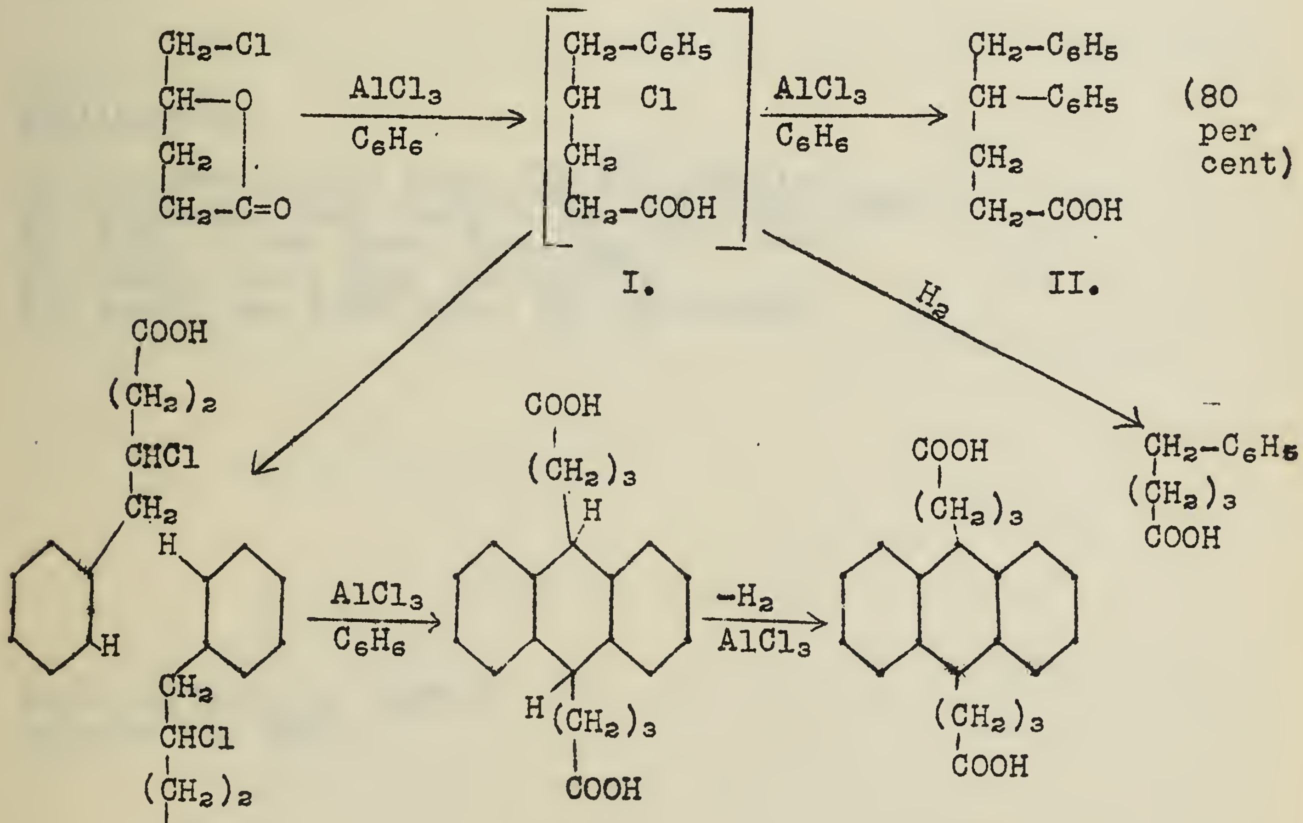
Reported by R. Mozingo
October 6, 1937.

THE FRIEDEL AND CRAFTS REACTIONS WITH LACTONES.

Hans Beyer - The Chemical Institute - University of Berlin.

The reactions of ethers, acid anhydrides, and esters with $AlCl_3$ and an aromatic solvent have been studied in some detail.[1] The reaction of lactones under similar conditions was investigated by Eijkmann[2] in 1904, who found that γ-valerolactone and benzene reacted together in the presence of $AlCl_3$ to form only γ-phenyl-n-valeric acid, and later from α-angelicalactone he obtained diphenyl-n-valeric acid. King[3] has reported that phthalide and phenyl phthalide will react with $AlCl_3$ to form ortho substituted acids while diphenyl phthalide will not react, supposedly because of steric hindrance.

Beyer[4] reports a study of the reaction between chlorolactones and $AlCl_3$ in an aromatic solvent. δ-Chloro-γ-valerolactone with benzene yields three main products: δ-γ-diphenylvaleric acid (80 per cent), δ-phenylvaleric acid (15-20 per cent) and anthracene 9,10-dibutyric acid in smaller amounts. Beyer postulated the following series of reactions to account for the products formed:



I. II. III. IV.

Compound IV was proved by oxidation to succinic acid and anthraquinone using ozone. The formation of III from two moles of the hypothetical I was assumed to take place by the removal of

HCl followed by wandering of a hydrogen from the δ to the γ carbon atom and then ring closure. The dehydrogenation of III to IV is analogous to reactions reported by Scholl and Seer.[5]

The compound IV showed a strong violet fluorescence in ultra violet light which was not present in the corresponding tetrahydro derivative. IV would add maleic anhydride, apparently across the 9,10 positions since the resulting addition product would not hydrogenate and showed no fluorescence in ultra violet light.

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1. Calloway, Chem. Rev., 17, 327 (1935).
2. Eijkmann, Chem. Zentr., 75, (1) 1416 (1904).
3. King, J. Am. Chem. Soc., 49, 562 (1927).
4. Beyer, Ber., 70B, 1101 (1937).
5. Scholl and Seer, Ber., 55, 330 (1922).

Reported by T. L. Cairns
October 13, 1937.

THE DISSOCIATION OF HEXAVINYLETHANE DERIVATIVES

Wittig -- Technische Hochschule, Braunschweig.
Ziegler -- University of Halle.

The observation by Wittig and Obermann[1] in 1935 that tetra-(diphenylvinyl)ethane existed in boiling xylene as the free radical led Wittig to investigate the effect of vinyl groups on hexa-substituted ethanes.

In the present paper he reports the preparation of the series:

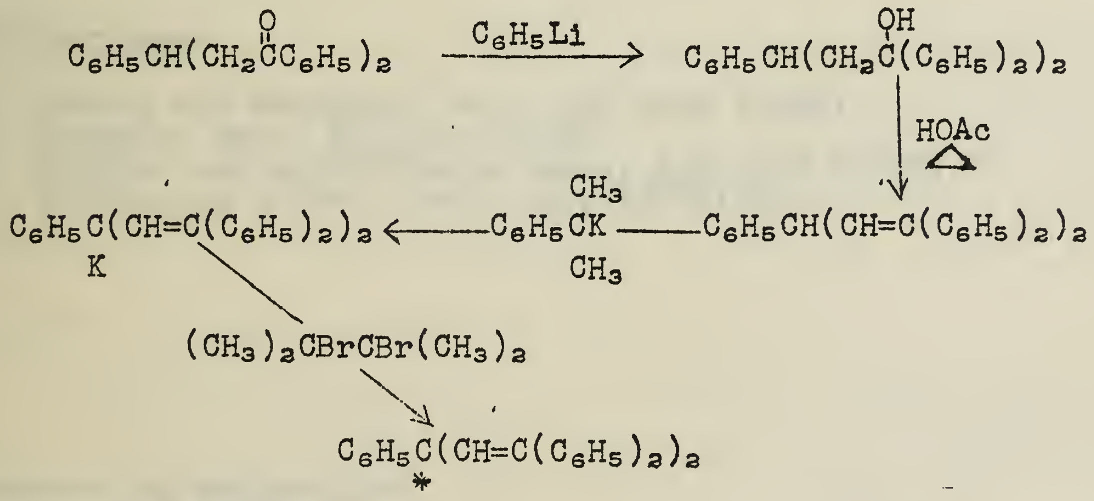
$$(C_6H_5)_2\overset{*}{C}CH{=}C(C_6H_5)_2 \quad ; \quad C_6H_5\overset{*}{C}(CH{=}C(C_6H_5)_2)_2 \text{ and}$$

$$((C_6H_5)_2C{=}CH)_3C*$$

The general method of synthesis was:

$$RR'R''CH \longrightarrow RR'R''CK \longrightarrow RR'R''{-}{-}R''R'R$$

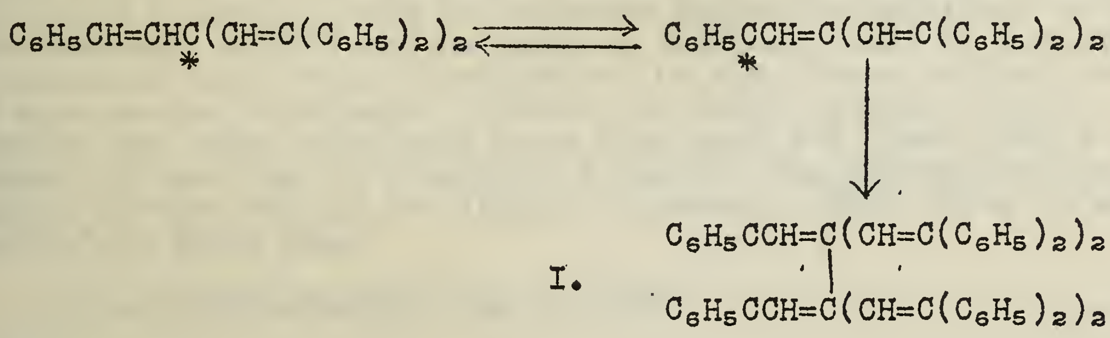
In particular he prepared phenyl-di(β,β-diphenylvinyl)methyl by the following series of reactions:



Ziegler[2] had already reported that diphenyl(β,β-diphenylvinyl)methyl existed in the monomeric form to the extent of eighty per cent. Since under corresponding conditions triphenylmethyl is only about four per cent dissociated, this would indicate that the diphenylvinyl group has a greater effect than the phenyl group in weakening the ethane bond. That it is also more effective than the biphenyl group is shown by the failure of tetra-biphenylethane to demonstrate any sign of dissociation.

Wittig reports that both phenyl-di(β,β-diphenylvinyl)methyl and tri(β,β-diphenylvinyl) methyl are completely dissociated at room temperature, in solution as well as in the solid state.

Wittig next attempted to prepare styryl-di(β,β-diphenylvinyl)methyl by a similar series of reactions. Instead of the expected free radical he obtained a stable dimer which he believes has formula I:



$$C_6H_5CH{=}CH\underset{*}{C}(CH{=}C(C_6H_5)_2)_2 \rightleftarrows C_6H_5\underset{*}{C}CH{=}C(CH{=}C(C_6H_5)_2)_2$$

$$\downarrow$$

$$\text{I.}\quad \begin{array}{l} C_6H_5CCH{=}C(CH{=}C(C_6H_5)_2)_2 \\ \qquad\qquad\quad | \\ C_6H_5CCH{=}C(CH{=}C(C_6H_5)_2)_2 \end{array}$$

Bibliography:

1. Wittig and Obermann, Ber., 68, 2214 (1935).
2. Ziegler, Ann., 434, 34 (1923).
3. Ziegler and Luttringhaus, Ann., 504, 200 (1933).
4. Wittig and Kosach, Ann., 530, 167 (1937).

Reported by Max Mueller
October 13, 1937.

Catalytic Dehydrogenation of Cyclic Compounds.

Linstead, --- University of London
Ruzicka, --- Zürich
Zelinsky, --- Moscow.

The velocity and course of dehydrogenation of cyclic compounds depend to a considerable extent upon the catalyst used. Platinised charcoal, made by reducing hydrochloroplatinic acid with hydrogen at 135° and palladised charcoal, made by reduction of palladium salts with formaldehyde in alkaline solution, are the most active catalysts. Nickel, rhenium, osmium, copper chromite and other catalysts have been used but these lead to rupture of the ring in a number of cases. The dehydrogenation is usually carried out in the liquid or gaseous state using an atmosphere of an inert gas.

The dehydrogenation may proceed:

I. Normally.

The normal dehydrogenation proceeds for most completely hydrogenated aromatic compounds at lower temperatures than are required for selenium and sulfur dehydrogenations.

Fully saturated six membered mono- or poly-carbocyclic compounds dehydrogenate readily unless they contain a quarternary carbon atom, e.g., cyclohexane, tetralin, decalin, 5-octahydrophenanthrene, 5-octahydroanthracene, etc. readily give their aromatic counterparts. There is no evidence for migration of alkyl groups except in cases where a neighboring group (as hydroxyl) is eliminated. Unsaturated side-chains are reduced in the usual manner.

II. With Disproportionation of Hydrogen.

Partially reduced aromatic derivatives undergo disproportionation of hydrogen, forming mixtures of aromatic and completely saturated alicyclic compounds, e.g., cyclohexene or cyclohexadiene yield cyclohexane and benzene, methyl cyclohexene yields toluene and methyl cyclohexane, octalins give tetralins and decalins. 1- and 2-methyloctalins behave similarly.

III. Abnormally.

Substances containing a quarternary carbon are very difficult to dehydrogenate. 1,1-dimethylcyclohexane does not dehydrogenate. Compounds containing an angular methyl group undergo dehydrogenation. The fate of the methyl group depending upon the catalyst. With platinum and palladium as prepared above the methyl is eliminated. Platinum prepared by Loew's Method caused the methyl to migrate to the <u>alpha</u> position. 9-Methyl-octalin or -decalin gives excellent

yields of the aromatic counterpart for both the migration and elimination.

Cyclopropane and cyclobutane rings are opened, forming unsaturated compounds. Simple cyclopentane rings are unaffected by metallic catalysts. Cycloheptane and cyclooctane yield toluene and p-xylene respectively.

Oxygen-containing groups are prone to be eliminated but some, such as ketonic and alcoholic, may be preserved with the formation of a phenol, Methoxyl groups on aromatic rings are not removed. Angular carboxyl groups are eliminated.

Heterocyclic compounds show a great variation in their behavior during dehydrogenation, e.g., piperidine yields pyridine, thiophane gives hydrogen sulfide along with saturated and unsaturated compounds.

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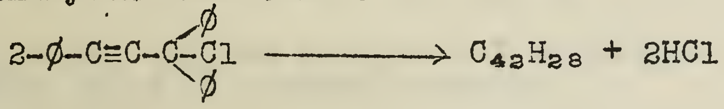
ibid 18, 611 (1935)
ibid 19, 370 (1936).
Ann. Reports. 33, 305 (1936)
Linstead, et al., J. Chem. Soc., 1937, 1146.

Reported by Dudley B. Glass
October 20, 1937.

RUBRENE--IDENTIFICATION AND SYNTHESIS

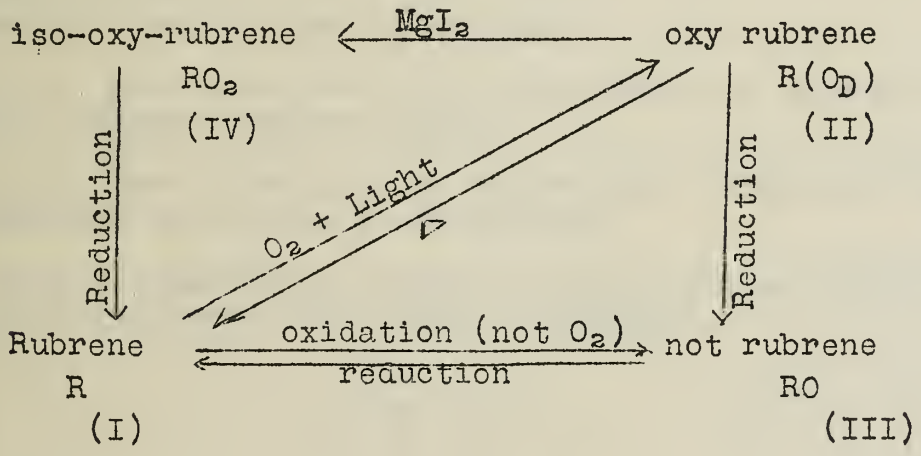
Ch. Dufraisse (College of France), Bull. Soc. Chim., (5), 3, 1847 (1936).
Ch. Dufraisse and R. Harclois, Bull. Soc. Chim., (5), 3, 1847 (1936).
Ch. Dufraisse and L. Velbez, Bull. Soc. Chim., (5), 3, 1904 (1936).
C. F. H. Allen and Lucius Gilman (McGill University), J. Am. Chem. Soc., 58, 937 (1936).

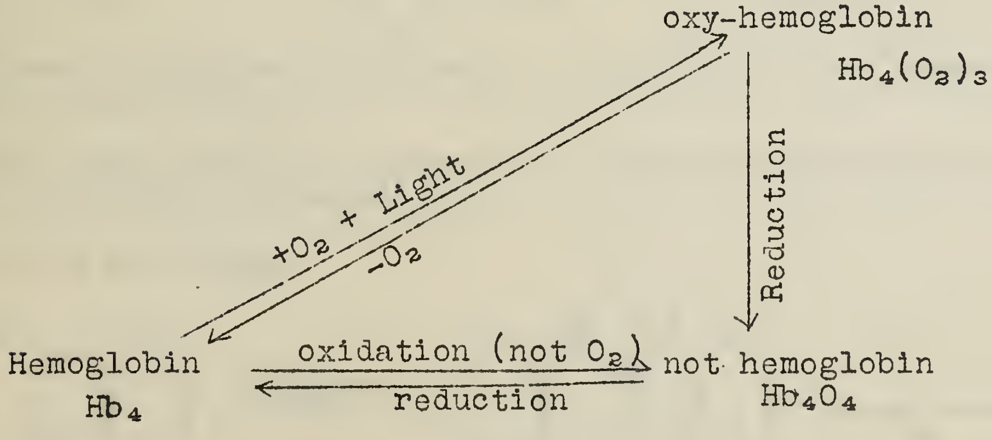
Rubrene, a red hydrocarbon of molecular formula $C_{42}H_{28}$, was first obtained by Mourou in 1928 by the pyrolysis of diphenylphenylethinylchloromethane.



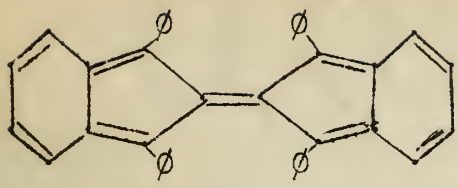
$$2\text{-}\phi\text{-}C{\equiv}C\text{-}C(\phi)_2\text{-}Cl \longrightarrow C_{42}H_{28} + 2HCl$$

Since its first appearance, rubrene has attracted much attention by reason of its photo-oxidative properties. The similarity in photo-oxidation of rubrene and hemoglobin is shown by the following schemes.

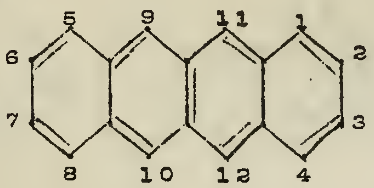




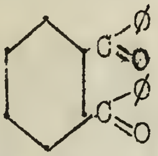
The first structure proposed contained the Bifulvene nucleus,



based on the formation of *o*-dibenzoyl benzene from rubrene by oxidation. The diindenyl structure does not explain the following facts and has now been discarded in favor of the naphthacene nucleus.



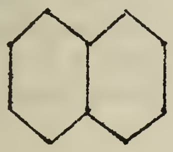
1. No one has synthesized rubrene or a rubrene derivative using the indenyl nucleus.

2. The yield of  is not as large as would be expected from an indone structure.

3. Mild oxidation does not cleave the molecule and leave the indenyl nucleus intact.

4. Upon hydrogenation the central ethylenic bond is not saturated as readily as predicted.

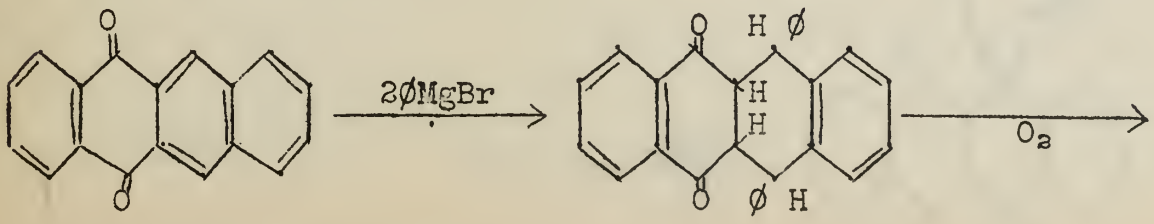
From a comparative study of colors, photo-oxidation, and absorption spectra of the benzene homologs

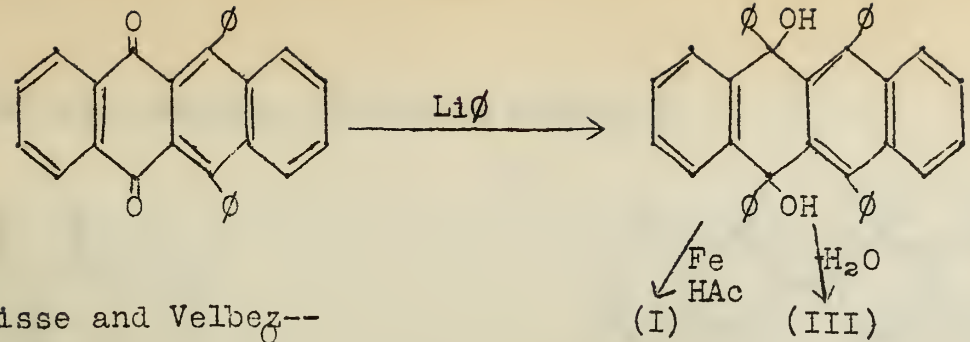


and rubrene, Dufraisse found many indications of the naphthacene nucleus in the rubenes.

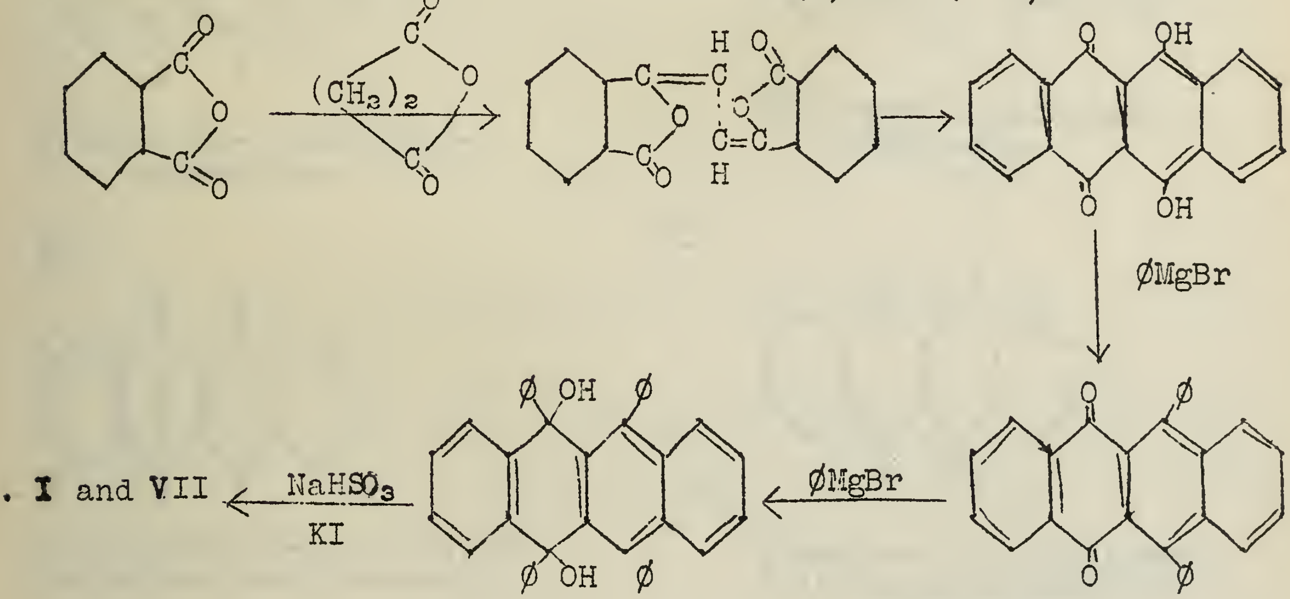
The naphthacenic structure for rubrene has been proved by the two following syntheses:

Allen and Gilman--



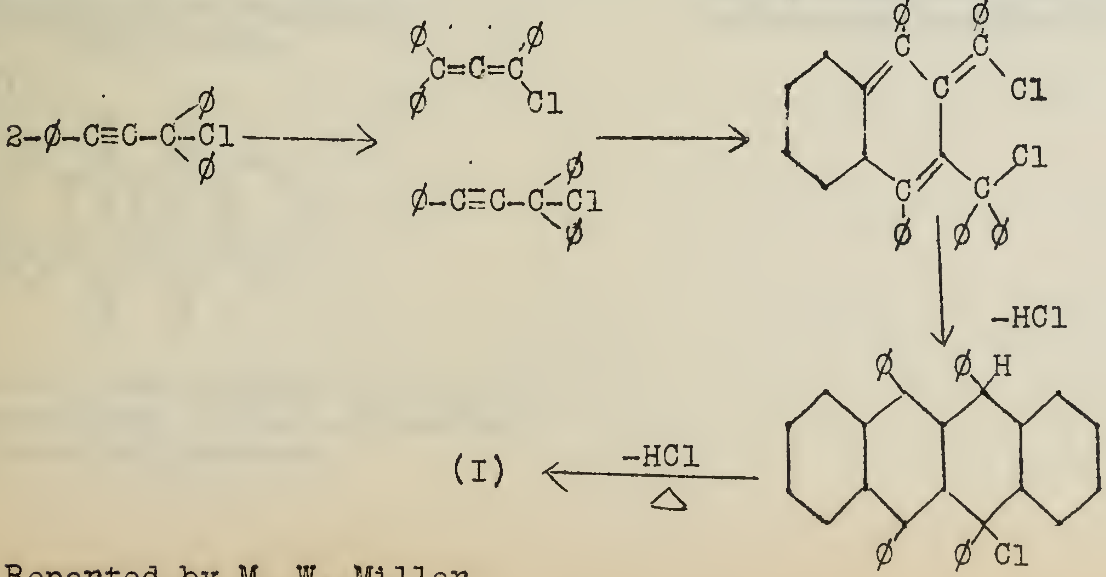


Dufraisse and Velbez--



The tetraphenyl naphthacene obtained in each case was identical with rubrene obtained by the pyrolysis of diphenylphenylethinylchloromethane.

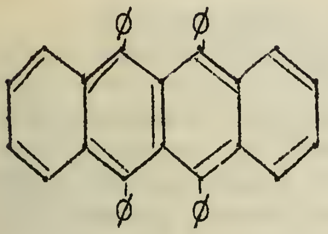
The most plausible mechanism for the formation of rubrene from the acetylenic compound is set forth by Allen and Gilman. It embodies first a Meyer-Schuster shift in the acetylenic compound, then a diene synthesis followed by loss of HCl. If the dimerization of diphenylphenylethinylchloromethane is carried out in quinoline the intermediate (VI) is obtained, giving partial proof of the following mechanism.



Reported by M. W. Miller
October 20, 1937.

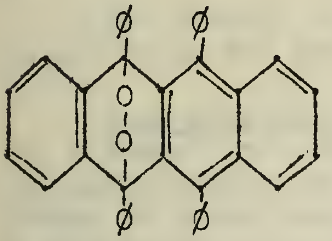
Formulas for compounds listed in abstract:

I.



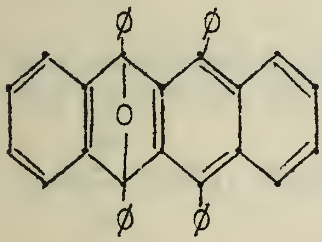
9,10,11,12-tetraphenylnaphthacene.

II.



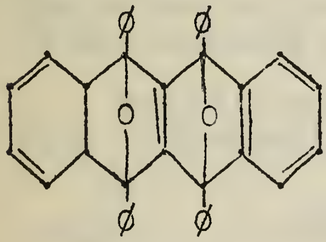
9-10 peroxide-9,10-,11,12-tetraphenylnaphthacene.

III.



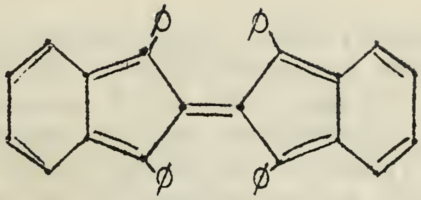
9-10-epoxy-9,10-dihydro 9 ,10,11,12-tetraphenylnaphthacene.

IV.



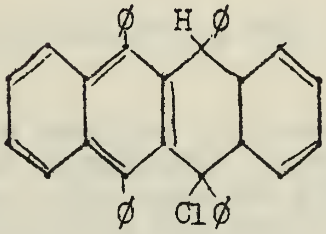
9-10,11-12-biepoxy 9,10,11,12-tetrahydro 9,10,11,12-tetraphenylnaphthacene.

V.



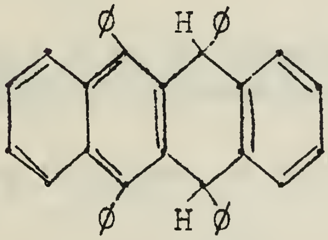
Willemart's bifulvene structure.

VI.



12-chloro-11,12-dihydro-9,10,11,12-tetraphenylnaphthacene.

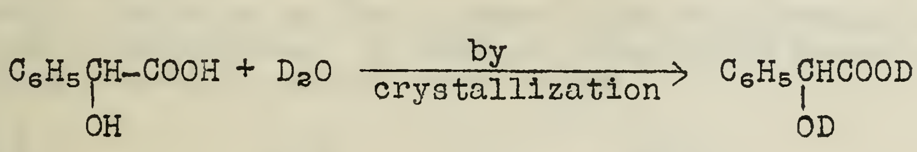
VII.



11,12-dihydro-9,10,11,12-tetraphenylnaphthacene.

USE OF DEUTERIUM IN THE STUDY OF RACEMIZATION

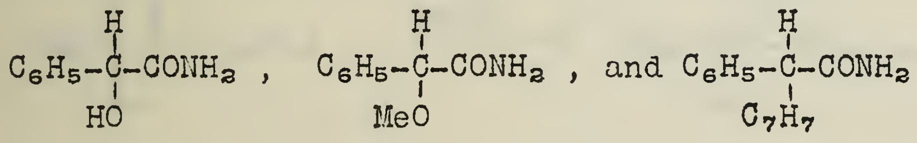
<u>Replacement of active hydrogen by deuterium</u>.--The readiness with which hydrogen may be replaced by deuterium depends upon the activity of the hydrogen atom, varying from the almost instantaneous replacement of ionic hydrogen to the extremely slow replacement of inactive hydrogen in the presence of catalyst. The replacement of active hydrogen may be illustrated by the following equation:



$$C_6H_5\underset{OH}{CH}-COOH + D_2O \xrightarrow[\text{crystallization}]{\text{by}} C_6H_5\underset{OD}{CH}COOD$$

The amount of hydrogen replaced by deuterium may be determined from the gain in weight.

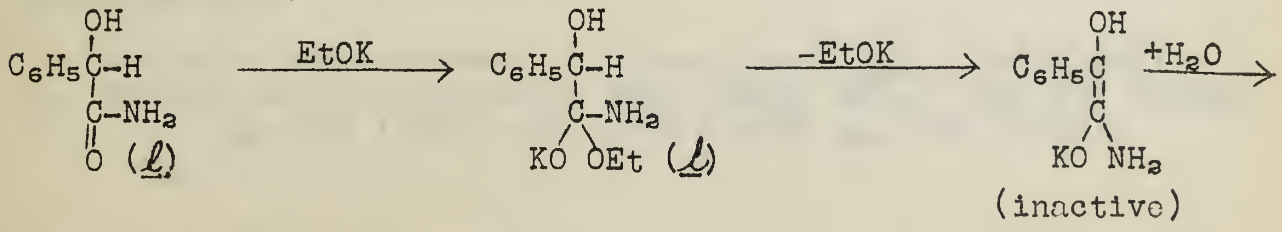
<u>Racemization study</u>.--McKenzie has studied the racemization of a number of compounds containing an asymmetric carbon atom in the α-position to an enolizable group. The rate at which a compound of this type is racemized depends upon the mobility of the α-hydrogen atom. For example, the following compounds,



$$C_6H_5-\overset{H}{\underset{HO}{C}}-CONH_2\ ,\quad C_6H_5-\overset{H}{\underset{MeO}{C}}-CONH_2\ ,\ \text{and}\ C_6H_5-\overset{H}{\underset{C_7H_7}{C}}-CONH_2$$

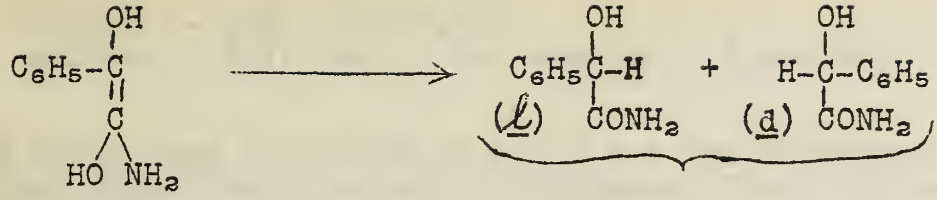
are arranged in the order of increasing rate of racemization in the presence of traces of alkali. *l*-Atrolacticamide, $C_6H_5\overset{Me}{\underset{OH}{C}}-CONH_2$, containing a methyl group in place of the migrational hydrogen atom shows no tendency to racemize. *l*-β-Hydroxy-β-phenylpropionamide, $C_6H_5-\underset{OH}{CH}CH_2-CONH_2$, does not racemize showing the effect of the removal of the active carbon from the α-position to the carbonyl group.

McKenzie proposed the following mechanism for the racemization of *l*-mandelamide:



$$C_6H_5\overset{OH}{\underset{\underset{\underset{O}{\|}}{C-NH_2}}{C}}-H\ (l) \xrightarrow{EtOK} C_6H_5\overset{OH}{\underset{\underset{KO\ \ OEt}{C-NH_2}}{C}}-H\ (l) \xrightarrow{-EtOK} C_6H_5\overset{OH}{\underset{\underset{KO\ \ NH_2}{\overset{\|}{C}}}{C}} \xrightarrow{+H_2O}$$

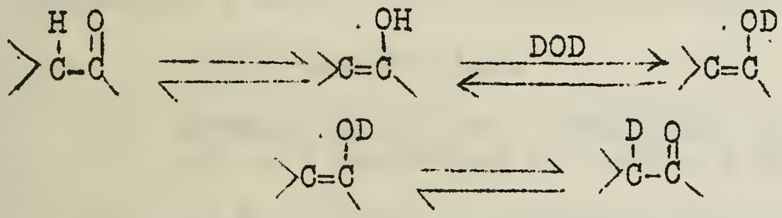
(inactive)



$$C_6H_5-\overset{OH}{C}=\underset{HO\quad NH_2}{C} \longrightarrow \underbrace{(l)\ C_6H_5\overset{OH}{\underset{CONH_2}{C}}-H + (d)\ H-\overset{OH}{\underset{CONH_2}{C}}-C_6H_5}$$

(inactive) (inactive)

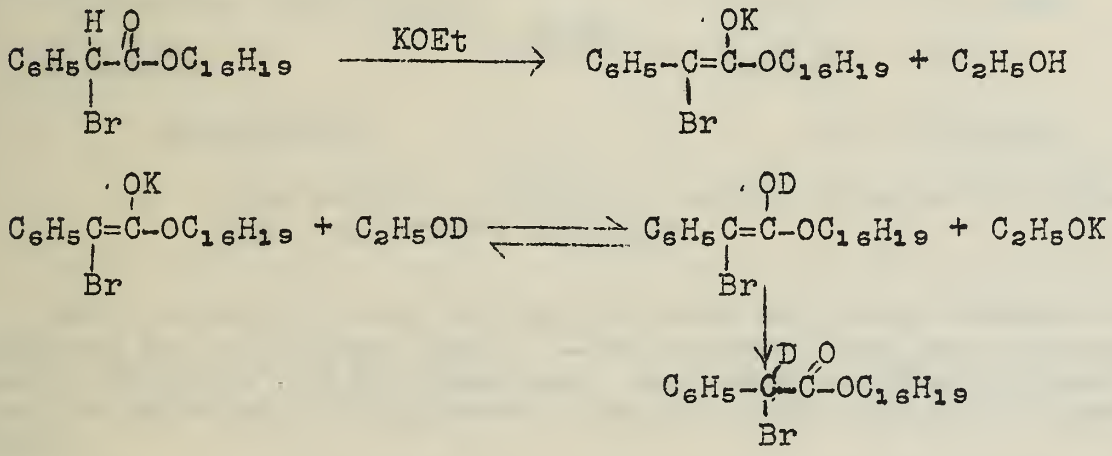
Erlenmeyer has introduced the use of deuterium to give experimental evidence on the interrelationship between enolization and racemization. If such an interrelationship exists the following reactions should take place:



$$>\overset{H}{C}-\overset{O}{\overset{\|}{C}}\diagdown \rightleftharpoons >C=\overset{OH}{C}\diagdown \xrightleftharpoons{DOD} >C=\overset{OD}{C}\diagdown$$

$$>C=\overset{OD}{C}\diagdown \rightleftharpoons >\overset{D}{C}-\overset{O}{\overset{\|}{C}}\diagdown$$

l-Menthyl-d-phenylbromoacetate was dissolved in C_2H_5OD and subjected to racemization using KOEt as catalyst.



$$C_6H_5\overset{H}{\underset{Br}{C}}-\overset{O}{\overset{\|}{C}}-OC_{16}H_{19} \xrightarrow{KOEt} C_6H_5-\underset{Br}{C}=\overset{OK}{C}-OC_{16}H_{19} + C_2H_5OH$$

$$C_6H_5\underset{Br}{C}=\overset{OK}{C}-OC_{16}H_{19} + C_2H_5OD \rightleftharpoons C_6H_5\underset{Br}{C}=\overset{OD}{C}-OC_{16}H_{19} + C_2H_5OK$$

$$\downarrow$$

$$C_6H_5-\overset{D}{\underset{Br}{C}}-\overset{O}{\overset{\|}{C}}-OC_{16}H_{19}$$

Racemization was completed in about one hour. The resulting compound contained one atom of deuterium per molecule, which would seem to support the theory that racemization in the presence of alkali takes place through the enol form.

Bibliography:

1. McKenzie and coworkers, J. Chem. Soc., 121, 1348 (1922).
2. Erlenmeyer and coworkers, Helv. Chim. Acta., 19, 543 (1936); 19, 129 (1936); 19, 1053 (1936); 20, 367 (1937).

Reported by S. O. Greenlee
October 27, 1937.

MECHANISM OF THE ACETOACETIC ESTER CONDENSATION

Hauser -- Duke University
McElvain, Spielman -- University of Wisconsin

Many mechanisms have been proposed for the acetoacetic ester condensation since its discovery by Claisen. The experimental facts to be explained have been:

1. Sodium ethylate, and not sodium is the condensing agent.

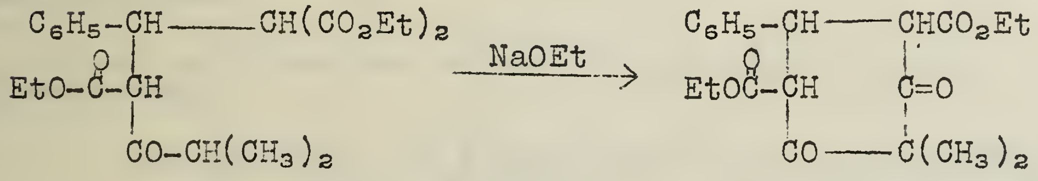
2. The overall reaction

$$2CH_3COOEt + NaOEt \rightleftharpoons [CH_3COCHCOOEt]^-Na^+ + 2EtOH$$

is an equilibrium.

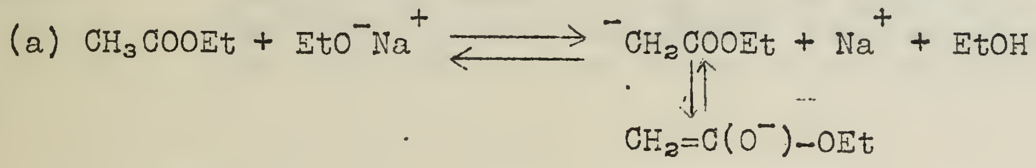
3. Esters of the type CHR_2COOEt (R is an alkyl group) are not condensed by sodium ethylate, though,

4. If R is C_6H_5O- or C_2H_5O-, condensation apparently occurs, and the cyclization

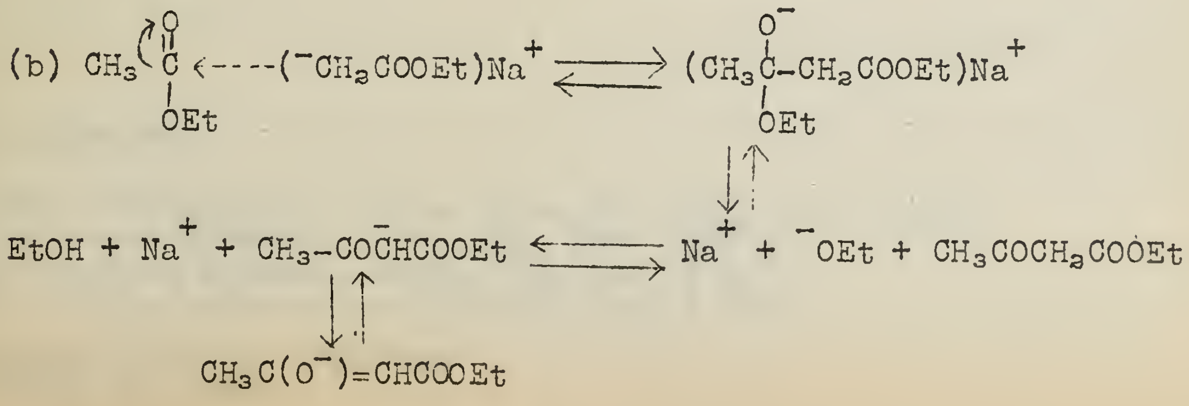


goes readily, though no carbon atom carries more than one active hydrogen.

Until recently, none of the proposed mechanism satisfactorily accounted for all these facts. Now, however, new data obtained by Hauser, McElvain and Spielman have enabled the former to postulate a mechanism which is consistent with the facts and with modern theory.



$$\text{(a)}\ CH_3COOEt + EtO^-Na^+ \rightleftharpoons {}^-CH_2COOEt + Na^+ + EtOH$$
$$\updownarrow$$
$$CH_2=C(O^-)-OEt$$



$$\text{(b)}\ CH_3\underset{OEt}{\overset{O}{\overset{\|}{C}}} \leftarrow ({}^-CH_2COOEt)Na^+ \rightleftharpoons (CH_3\underset{OEt}{\overset{O^-}{C}}-CH_2COOEt)Na^+$$
$$\updownarrow$$
$$EtOH + Na^+ + CH_3-CO\overset{-}{C}HCOOEt \leftrightharpoons Na^+ + {}^-OEt + CH_3COCH_2COOEt$$
$$\updownarrow$$
$$CH_3C(O^-)=CHCOOEt$$

The ester, in (a) loses a proton to the EtO^- ion, forming the ester enol. The C unsaturated form of the enol, in (b), donates a pair of electrons to the carbonyl carbon atom of another ester molecule to form the enol shown. This enol then loses an ethylate ion, forming ethylacetoacetate, which in turn is carried over to the enol form by the ethylate ion.

Since ethyl acetate is a weaker acid than alcohol, the equilibrium in the first step is on the side of the free ester. Acetoacetic ester, however, is a strong enough acid so that in the presence of EtO^-, the overall equilibrium is shifted toward the keto-ester enolate.

On the basis of this mechanism, the failure of $R_2CHCOOEt$ to condense is readily explained. Ingold's work has shown that alkyl groups tend to repel electrons, and this effect would so reduce the acidity of the ester, and of the keto ester $CHR_2-CO-CR_2COOEt$ that little or no enolate would form, and the equilibrium would be far to the side of the free ester. The ester cited in (4) above, however, should all be sufficiently acidic to condense. This mechanism would also predict that esters of the types R_2CH-CH_2COOEt and R_3CCH_2COOEt should not condense in the presence of sodium ethylate, though both of these, as well as $R_2CHCOOEt$ should be condensable by a stronger base than EtONa.

Recent articles have supported this theory by the following data:

1. McElvain has found that neither $(CH_3)_2CHCH_2COOEt$ nor $(CH_3)_3C-CH_2COOEt$ is condensable by sodium ethylate.

2. By the use of sodium triphenylmethyl (a strong base), Hauser has formed ethyl isobutyryl-isobutyrate from ethyl isobutyrate.

3. Spielman, by the use of mesitylene Grignard (a very strong base), has obtained fair yields of keto-esters from esters of the types $R_2CHCOOEt$, R_2CHCH_2COOEt and R_3CCH_2COOEt, and has shown that the keto-esters form little or no enolate.

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Reported by C. L. Levesque
October 27, 1937.

SULFONES FROM BUTADIENES

Backer -- Groniugue
Eigenberger -- Prague

Sulfur dioxide adds 1,4 to butadienes under controlled conditions to yield monomeric cyclic sulfones of the type I.

Eigenberger established this structure by a special saponification of the dibromide of the isoprene sulfone to an alpha-hydroxy carbonyl compound.

Bulky 3,4 substituents hinder bromination and hydrogenation.

Addition of halogens in acetic acid solution form acetoxy halides (as II), analogously to the formation of β-chloroethyl acetate from ethylene. This is attributed to the addition of acetyl hypochlorite.

The diol (IV) obtained from aqueous hydrolysis of the dibromide (III) is stereoisomeric with that obtained by permanganate oxidation of the original sulfone.

Backer's ozonization of 3,4-dimethyl-3-thiacyclopentene-1,1-dioxide to a cyclic ether (V) through the intermediate of a diketone (VI) confirmed the position of the double bond in the ring.

III treated with dilute aqueous alkali yields a sulfone with two double bonds (VII or VIII). Ozonization yields formic acid and a white ketone (IX), suggesting VIII as the correct formula. VIII adds but one molecule of bromine, presumably at the active methylene. The ketone also exists in a yellow enol form (X).

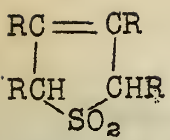
Keto-isocarboxylic acids (XI) are obtained on ozonization of sulfones of monosubstituted butadienes. These oxidize two moles of HI; they irreversibly rearrange to ordinary carboxylic acids.

The monoalkylated butadiene sulfones isomerize on irradiation of their alkaline solutions to compounds of the type XII, the structure being proved by ozonization to isocarboxylic acids (XIII) or sulfonic acids (XIV). Backer interprets the isomerization as occurring through intermediate addition of water and subsequent preferential splitting out of water involving the hydrogen on the carbon alpha to the sulfone group.

Hydrogenation studies indicated the relative activities of olefinic linkages at different parts of the sulfone molecule.

Sulfur dichloride adds to substituted butadienes producing substances of the type XV. Better yields from heavier butadienes is hypothesized by Backer as being a result of the formation, by the voluminous groups, of a curved diene structure.

3-Chloroisoprene forms a sulfone (XVI) with an active halogen which reacts with mercaptides to form sulfides (XVII) and with K_2S to form XVIII. Both XVII and XVIII form the corresponding sulfones on H_2O_2 oxidation.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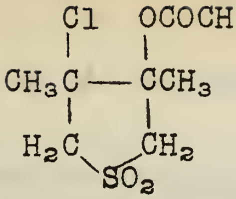
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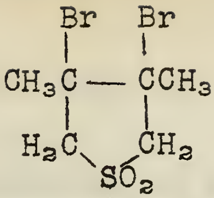
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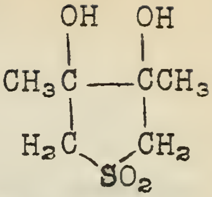
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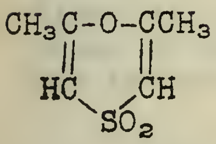
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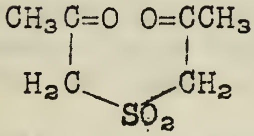
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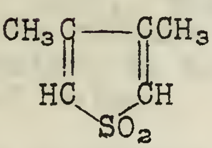
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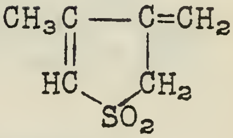
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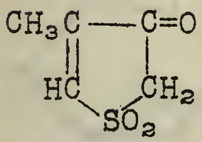
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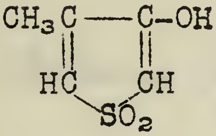
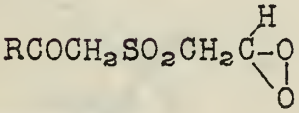

X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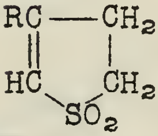
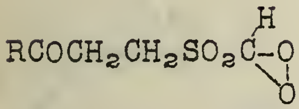
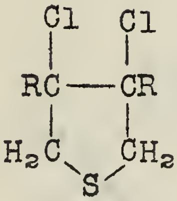

XII


XIII

$RCOCH_2CH_2SO_3H$

XIV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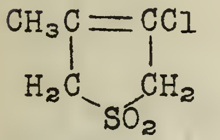
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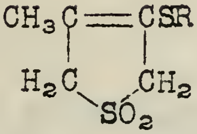
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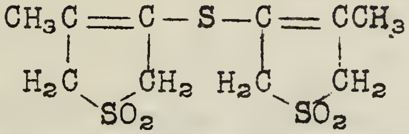
XVIII

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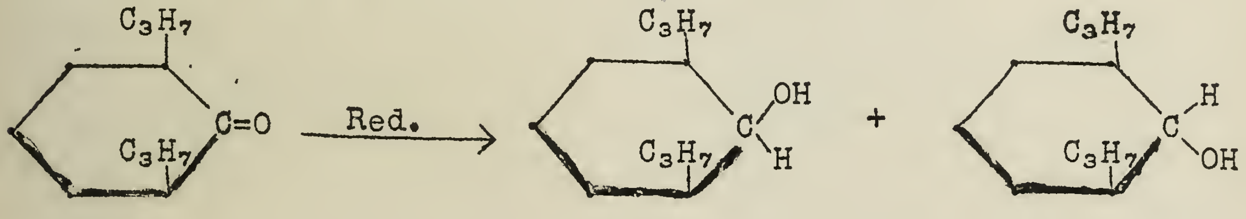
Reported by W. W. Williams
November 3, 1937.

A STUDY OF THE DI-ORTHO-PROPYLCYCLOHEXANOLS

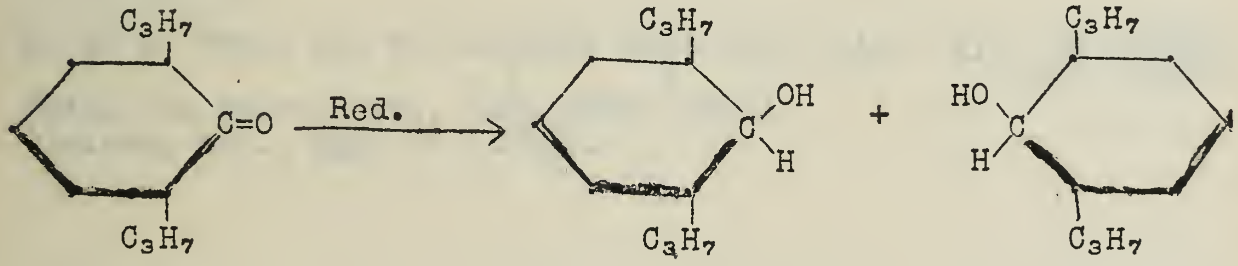
M. M. G. Vavon and P. Anziani

Hydrogenation of di-ortho-propylphenol in acetic acid medium, using a platinum black catalyst, produces an alcohol which after purification melts at 25-26°. Chromic oxidation of this alcohol to the ketone, followed by reduction with sodium and alcohol produced another alcohol melting at 113°. The esters of the first alcohol are much more difficult to form and saponify than those of the second. Both the alcohols, m. p. 25-26° and 113°, may be oxidized to the same original ketone.

Using these data it is possible to select the probable formula for each of these alcohols.



1. 3. 4.



2. 5. 6.

As 5 and 6 are mirror images only a single racemic alcohol is possible in which the propyl groups are on opposite sides of the ring. Therefore, the two alcohols formed in this experiment must correspond to formulas 3 and 4; the one formed by catalytic hydrogenation was assumed to be the dipropyl-cis-cis-cyclohexanol-cis (3) because this would be more difficult to esterify than 4. Due to a plane of symmetry through ketone 1 and alcohols 3 and 4, these compounds cannot be resolved. If one of the alcohols was 5, ketone (2) would presumably be obtained on oxidation.

The sodium derivative of the alcohol-cis (3) heated at 200° isomerizes to the sodium derivative of the alcohol-trans (4). This isomerization has been found to be general in a variety of compounds of certain cyclic types, both for the mono- and disubstituted cyclanols. Several mechanisms have been offered for this isomerization:

1. An inversion of the carbon atom carrying the alkyl radical.

2. An inversion of the carbon atom carrying the hydroxyl group.

In the case of the monosubstituted alcohols, inversion of either carbon atom would lead to the same result. However, in the case of the dipropylcyclohexanol, inversion must take place on the carbon atom carrying the -OH group since oxidation reconverts the alcohols to the original ketone.

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" " " " " " " " " " 1080 (1937).
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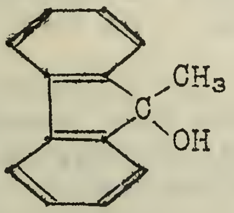
Reported by H. G. Cooke
November 3, 1937.

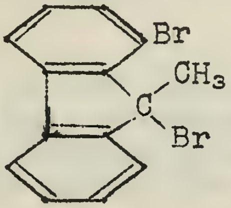
SOME REACTIONS OF BIPHENYLENEETHYLENE

Wieland — Munich

Biphenyleneethylene was reported to be formed in small amounts by Manchot (1904), on heating dibiphenylenethiopinacol at 300° or at lower temperatures with copper or lead oxide. Sieglitz and Jāssoy (1922) found that small amounts were formed when (fluorenyl-9-methyl) urethane, $(C_6H_4)_2CH{-}CH_2NHCO_2Et$, was heated with CaO in a hydrogen atmosphere. Wieland (1922) obtained much better yields by heating 9-methylfluorenol (I) with $AlPO_4$ in a vacuum; he improved his method by heating 9,9-methylchlorofluorene at 80°.

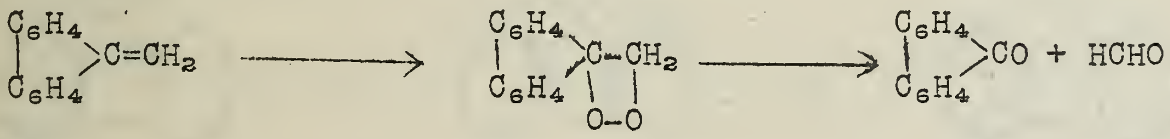


I



II

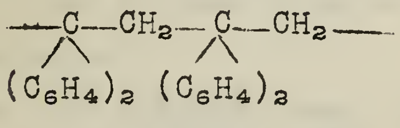
Biphenyleneethylene rapidly polymerizes, and the polymerization is catalytically increased by the presence of oxygen. Higher peroxides, fluorenone, and formaldehyde are always found in the polymerized product, if air was accessible. The mechanism is probably:



$$\begin{array}{l}C_6H_4\\ |\\ C_6H_4\end{array}\!\!>C{=}CH_2 \longrightarrow \begin{array}{l}C_6H_4\\ |\\ C_6H_4\end{array}\!\!>\begin{array}{c}C{-}CH_2\\ |\quad\;\; |\\ O{-}O\end{array} \longrightarrow \begin{array}{l}C_6H_4\\ |\\ C_6H_4\end{array}\!\!>CO + HCHO$$

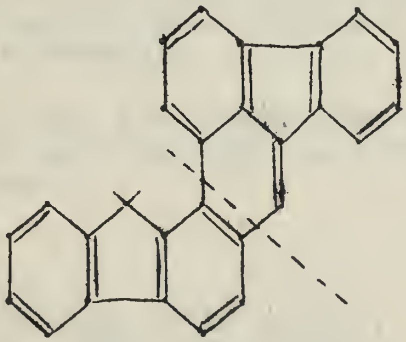
The autoxidation can be inhibited by pyrogallol, and in turn the rate of polymerization is greatly decreased.

The products of polymerization are complex. In addition to a resinous material to which the usual chain formula (III) has been assigned, a distillation gives a hydrocarbon $C_{27}H_{16}$ (IV).



$$-\underset{(C_6H_4)_2}{C}-CH_2-\underset{(C_6H_4)_2}{C}-CH_2-$$

III



IV

The dotted line indicates how this compound can be formed through dehydrogenating polymerization condensation between fluorene and biphenyleneethylene.

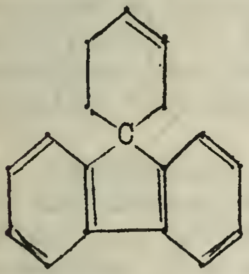
Biphenyleneethylene reacts with bromine to form 8,9-dibromo-9-methylfluorene (II). The hydrocarbon is regenerated on heating with zinc and alcohol. Biphenyleneethylene dibromide is prepared by reacting 9-methylchlorofluorene with bromine. This forms ω-bromobiphenyleneethylene with sodium acetate in acetic acid. With dimethylaniline, diphenyleneethylene dibromide condenses to form dibiphenylenebutadiene.

Catalytic hydrogenation of biphenyleneethylene with platinum oxide gives 2,3-dibiphenylenebutane.

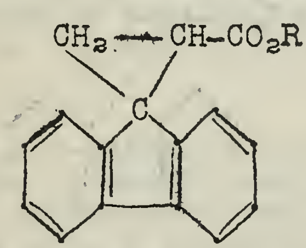
Biphenyleneethylene reacts with sodium to give a red colored sodium compound, which on decomposition with water gives 1,4-dibiphenylenebutane. Some 1,3-dibiphenylenebutane is formed when moist ether is used as a solvent.

On treating the sodium compounds of both the precoursers of the above butanes with carbon dioxide and then decomposing with water, α,α'-dibiphenyleneadipic acid and α,γ-dibiphenylenevaleric acid are obtained. Decarboxylation of the acids yields the 1,4- and 1,3-dibiphenylenebutanes, respectively.

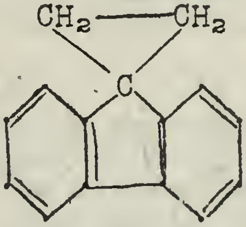
Biphenyleneethylene reacts with butadiene in a diene synthesis to give the spirane, biphenylenecyclohexene (V).



V



VI



VII

Diazoacetic ester and diazomethane give the expected compounds with biphenyleneethylene (VI and VII respectively). The decarboxylation of the free acid to the hydrocarbon was not possible.

An ether solution of the olefine treated with NO_2 gives α,β-dinitrobiphenyleneethane. This can be converted to ω-nitrobiphenyleneethylene on heating with alcoholic ammonia.

The coloration of biphenyleneethylene and its compounds, together with its great reactivity, relates it more closely to a ring-substituted fulvene than to diphenylethylene.

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457, 249 (1927);
530, 274 (1937).

Reported by J. W. Corse
November 10, 1937.

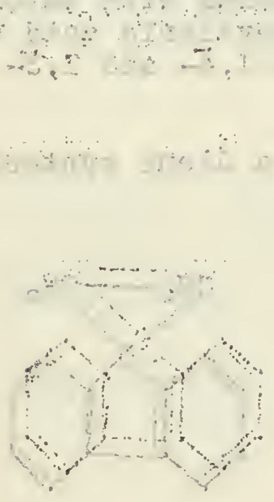
Biphenylenediazomethane reacts with [illegible] to form [illegible] methylfluorene (III). The hydrazone [illegible] in [illegible] with zinc and alcohol. [illegible] is [illegible] by reacting [illegible] with [illegible]. This [illegible] diphenylene-phenylmethane [illegible] with aniline [illegible] in acetic acid. With dimethylaniline, [illegible] to form [illegible].

Catalytic hydrogenation of [illegible] with [illegible] gives [illegible].

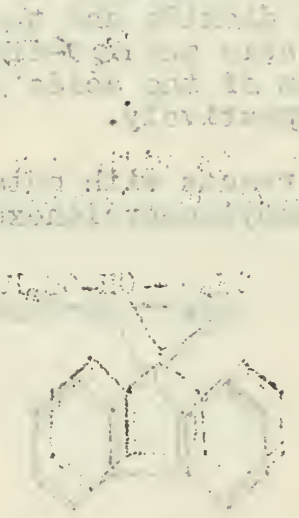
Biphenylene [illegible] reacts with aniline to give a [illegible] compound, which [illegible] with water gives [illegible]. [illegible] is formed when ether is used as a solvent.

On heating the [illegible] compounds of [illegible] with the [illegible] benzene with [illegible] and [illegible] obtained. Decarboxylation of the acids [illegible] the 1,2- and 1,3-[illegible], respectively.

Biphenylene [illegible] reacts with [illegible] in a [illegible] to give the [illegible] (V).



III



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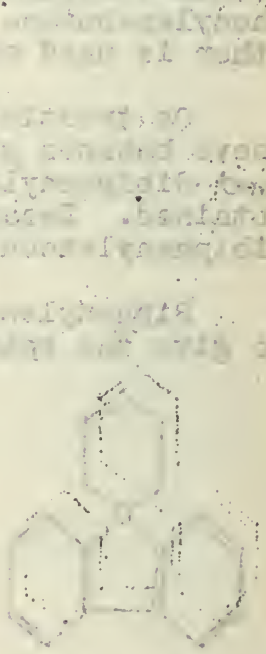

V

[illegible] with [illegible] gives [illegible] (IV) [illegible].

An [illegible] solution of the [illegible] with [illegible].

The [illegible] of [illegible] and the [illegible].

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Wieland et al., [illegible]

Reported by [illegible]
November [illegible]

THE ALLYLIC REARRANGEMENT-ALLYLIDENE DIACETATE

A. Kirrmann
C. Prévost

It has been known for some time that many compounds containing a double bond could undergo a 1,3 or allylic rearrangement. Compounds of the type $XYCH{-}CH{=}CH_2$ on heat treatment rearranging as follows:

$$XYCH{-}CH{=}CH_2 \longrightarrow X{-}CH{=}CH{-}CH_2Y$$

A B

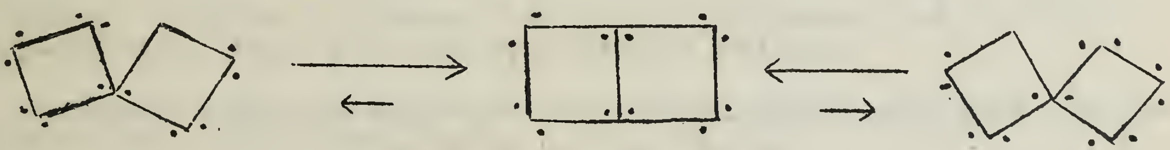
Also in reactions of the double decomposition type rearrangements occur.

$$CH_2{=}CH{-}CHRX + AY \longrightarrow YCH_2{-}CH{=}CHR + AX$$

Usually B is the more stable form and gives normal products on reaction, while A gives the rearranged product.

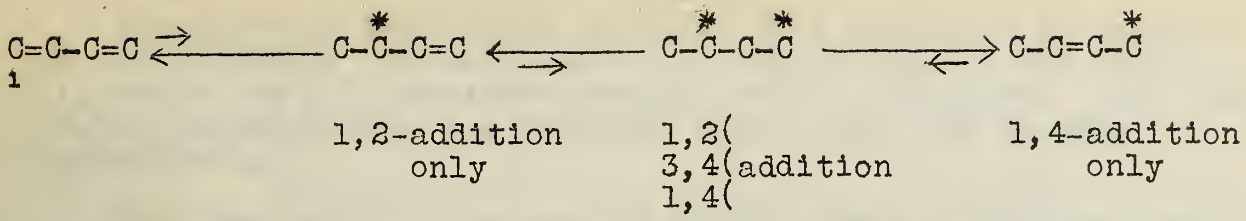
Addition to a conjugated system was postulated by Gillet as occurring through the mechanism of a 1,2-addition and a 1,3-shift as opposed to Thiele's idea of residual affinities. In such an addition the negativity of the adding group is a prime factor in causing the shift.

Carothers explained 1,4-addition electronically on the basis of the Lewis octet theory. A double bond should exist in a nonpolar and an active form in dynamic equilibrium. The active form consists of a carbon atom with 8 electrons in its outer shell and one with 6 outer electrons. The amount of active form is never great, and the extent of dissociation depends on the effective nuclear charge of the substituent groups. The equilibrium may be portrayed as follows:



Although both the dynamic forms can exist in a carbon-carbon double bond, that atom which contains substituent groups having the highest effective nuclear charge will retain the extra electron.

In the case of a conjugated system $\underset{1}{C}{=}\underset{2}{C}{-}\underset{3}{C}{=}\underset{4}{C}$, C_1 having substituent groups with higher effective nuclear charges than the other carbon atoms, the equilibria existing can be shown thus:



$$C{=}C{-}C{=}C \rightleftarrows C{-}\overset{*}{C}{-}C{=}C \leftrightarrows C{-}\overset{*}{C}{-}C{-}\overset{*}{C} \rightleftarrows C{-}C{=}C{-}\overset{*}{C}$$

1,2-addition only

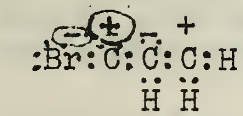
1,2(3,4(addition 1,4(

1,4-addition only

The *C atoms indicate carbon atoms with 6 electrons. From the effective nuclear charges of substituents it is possible to predict which type of addition will take place.

Prévost and Kirrmann and their work on ionic reactions consider allylic rearrangements as occurring according to the following scheme:

1. In a molecule of the type $BrCH_2-CH=CH_2$, if Br tends to ionize, say in the presence of some reagent, it will do so as an anion leaving the carbon to which it is attached positive and the double bond will open to give the multipolar ion, where the circles indicate tendencies.



2. In a compound such as $CH_3-CHOH-CH=CH_2$ when treated with PBr_3 the OH ionizes to give the tripolar ion

$CH_3-\overset{+}{C}H-\overset{-}{C}H-\overset{+}{C}H_2$ + $O\overset{-}{H}$ and $B\overset{-}{r}$ can add to either of the positive carbon atoms to give the "synionic isomers"

$CH_3-CHBr-CH=CH_2$ and $CH_3-CH=CH-CH_2Br$

Compounds such as $CH_3-CHOH-CH=CH_2$ and $CH_3-CH=CH-CH_2Br$ are called "synionic derivatives."

Kirrmann and Rambaud have shown that there is an equilibrium between the synionic forms, as for example the equilibrium of $CH_2=CH-CHCl_2$ and $ClCH_2-CH=CHCl$ at 175°.

Raman spectrum evidence obtained by Kirrmann and also by Gredy indicates that such an equilibrium exists.

Kirrmann explains the case when only normal products are obtained or when they predominate on two bases.

1. The double bond has not been activated.
2. The double bond has been activated but the normal structure is more stable.

It has been proposed to explain the isomerism of 1,1-dibromopropene-2 and 1,3-dibromopropene-1 by the mechanism of addition and subsequent loss of HBr since HBr is an active catalyst in the isomerization.

$$CH_2=CH-CHBr_2 \xrightarrow{+HBr} CH_2Br-CH_2-CHBr_2 \xrightarrow{-HBr} CH_2Br-CH=CHBr$$

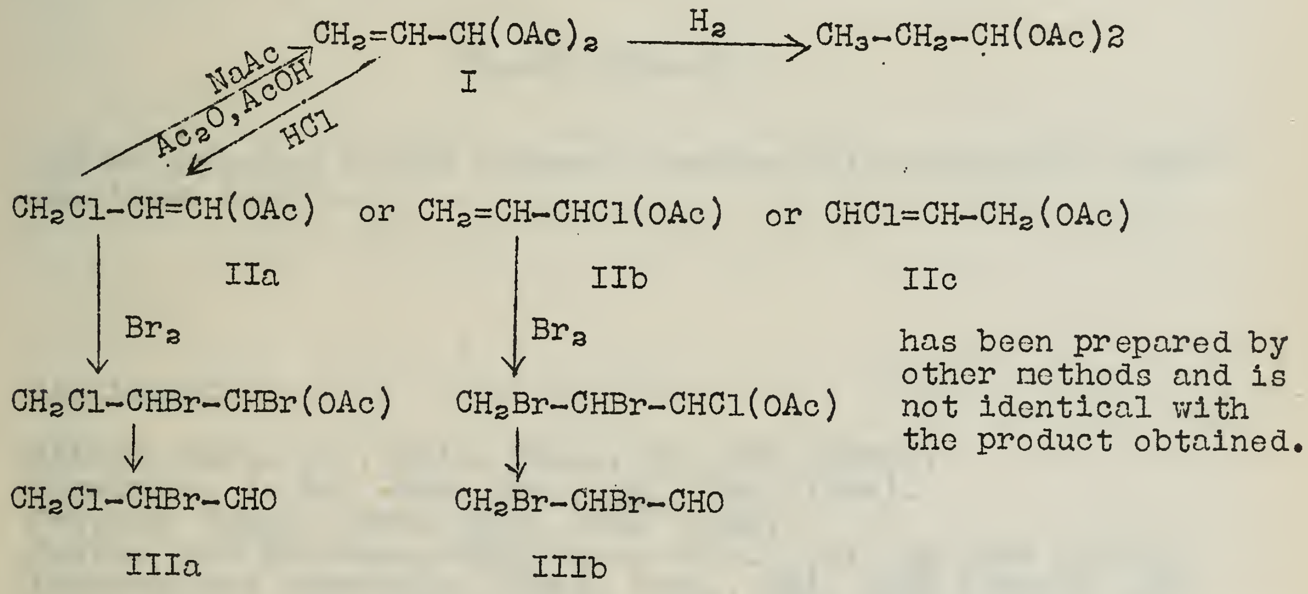
Kirrmann and Renn tried to check this mechanism by preparing the intermediate. It was possible to add a mole of HBr with difficulty but 1,1,3-tribromopropane was not obtained. Its isomer 1,2,3-tribromopropane was obtained which loses HBr to give $CH_2Br-CBr=CH_2$.

They were able to prepare $CH_2Br-CH_2-CHBr_2$ by another set of reactions. However, this loses HBr with great difficulty to give $CH_2=CH-CHBr_2$. Hence, the proposed mechanism failed in its main assumption.

The latest work on this field by Kirrmann has been on the compound allylidene diacetate. From previous work on allylidine dibromide and dichloride it was expected that the diacetate would rearrange on heating.

$$CH_2=CH-CH(OCOCH_3)_2(I) \longrightarrow CH_2(OCOCH_3)-CH=CH(OCOCH_3)$$

However, such a reaction did not take place, and catalytic hydrogenation of the heat treated diacetate gave propylidine diacetate. Treatment of I with HCl replaced one of the acetates by a Cl to give II which on treatment with sodium acetate in a mixture of glacial acetic acid and acetic anhydride gave I again.



has been prepared by other methods and is not identical with the product obtained.

II is shown to have the rearranged formula (IIb), since bromination followed by vacuum distillation gives an aldehyde containing one bromine and one chlorine, hence IIIa and not IIIb. The extreme mobility of the Cl in II also indicates the structure assigned.

Kirrmann proposes a mechanism based on the synionic theory.

$$\begin{tikzcd} CH_2=CH-CH(OAc)_2 \arrow[r, "HCl"] & CH_2=CH-CHCl(OAc) \arrow[d, "\text{HCl as catalyst}"] \\ & CH_2Cl-CH=CH(OAc) \end{tikzcd}$$

First a replacement reaction, then the shift occurring as in

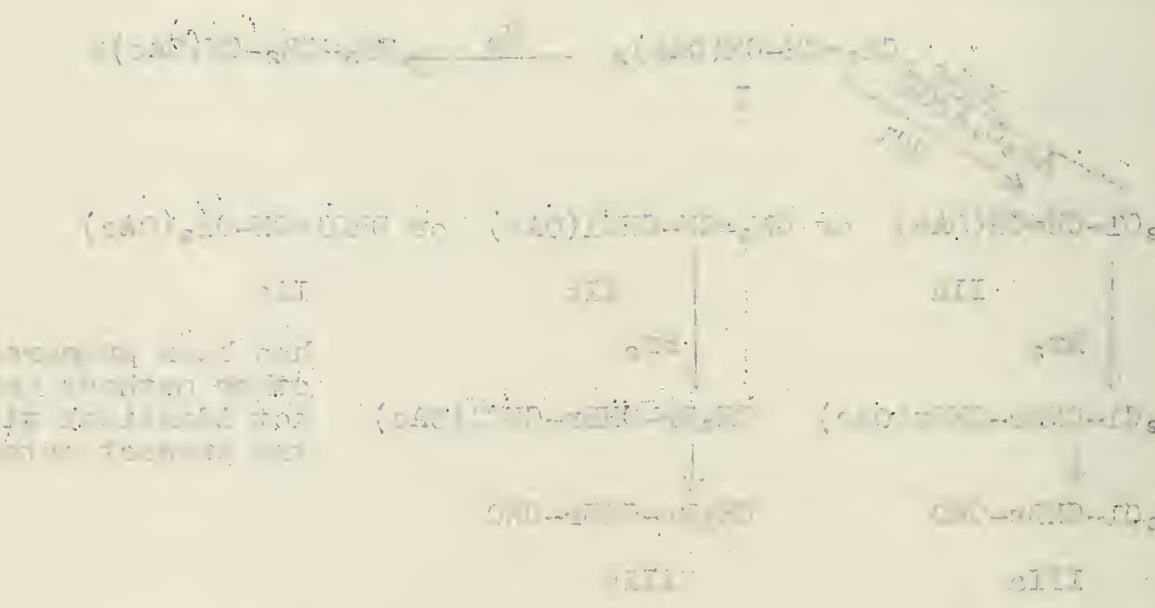
Hirschmann and Dorr tried to check this mechanism by preparing the intermediate. It was possible to get a yield of any with difficulty, but 1,1,3-tribromopropane was not obtained. The isomer 1,2,3-tribromopropane was obtained which loses HBr to give $CH_2Br\text{-}CBr{=}CH_2$.

They were able to prepare $CH_2Br\text{-}CH_2\text{-}CHBr_2$ by another set of reactions. However, this loses HBr only with difficulty to give $CH_2Br\text{-}CH{=}CHBr$. Hence, the proposed mechanism failed in its main assumption.

The latest work on this field Hirschmann has done on the compound allylidene diacetate. From previous work on allylidene dibromide and dichloride it was expected that the diacetate would rearrange on heating.

$$CH_2{=}CH\text{-}CH(OCOCH_3)_2\,(I) \longrightarrow CH_2(OCOCH_3)\text{-}CH{=}CH(OCOCH_3)$$

However, such a reaction did not take place, and catalytic hydrogenation of the heat treated diacetate gave n-propylidene diacetate. Treatment of I with HCl replaced one of the acetate groups by Cl to give II which on treatment with sodium acetate in a mixture of glacial acetic acid and acetic anhydride gave I again.


$CH_2{=}CH\text{-}CH(OAc)_2 \xrightarrow{HCl} CH_2{=}CH\text{-}CH(OAc)Cl$

I

$CH_2Cl\text{-}CH{=}CH(OAc)$ or $CH_3\text{-}CH{=}CCl(OAc)$ or $CHCl{=}CH\text{-}CH_2(OAc)$

IIa IIb IIc

has been prepared by other methods and is not identical with the product obtained.

Br_2 Br_2

$CH_2Cl\text{-}CHBr\text{-}CHBr(OAc)$ $CH_3\text{-}CHBr\text{-}CClBr(OAc)$

$CH_2Cl\text{-}CHBr\text{-}CHO$ $CH_3\text{-}CHBr\text{-}COCl$

IIIa IIIb

II is shown to have the unsymmetrical formula (IIa), since bromination followed by vacuum distillation gives an aldehyde containing one bromine and one chlorine, hence IIIa and not IIIb. The extreme mobility of the Cl in II also indicates the structure assigned.

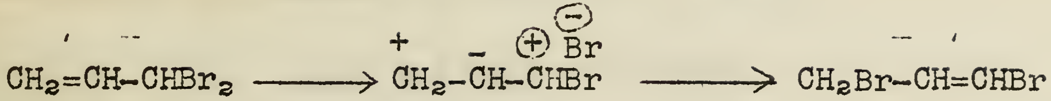
Hirschmann proposed a mechanism based on the synthetic theory.

$$CH_2{=}CH\text{-}CH(OAc)_2 \xrightarrow{HCl} CH_2{=}CH\text{-}CH^{+}(OAc)$$

HCl or acetyl

$CH_2Cl\text{-}CH{=}CH(OAc)$

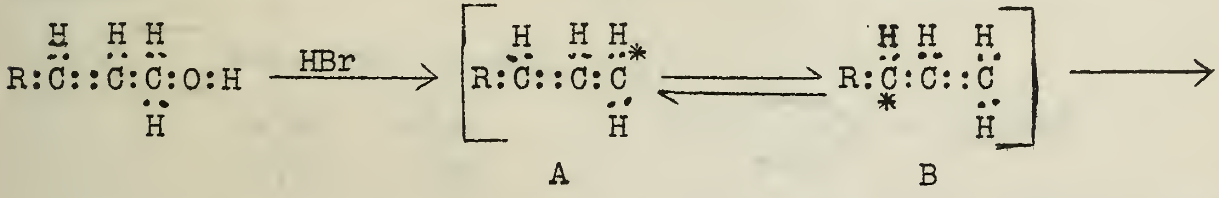
First a rearrangement reaction, then the [illegible] occurs as in allylidene dibromide.



$$\mathrm{CH_2{=}CH{-}CHBr_2} \longrightarrow \overset{+}{\mathrm{CH_2}}{-}\overset{-}{\mathrm{CH}}{-}\overset{\oplus\ \overset{\ominus}{\mathrm{Br}}}{\mathrm{CHBr}} \longrightarrow \mathrm{CH_2Br{-}CH{=}CHBr}$$

The stable allylidene diacetate is the only example of the type $CH_2{=}CH{-}CHY_2$ which is more stable than the rearranged form indicating a distinct difference in reaction between it and the dihalogens.

An electronic picture of the 1,3-shift has been given as follows:



$CH_3{-}CH{=}CH{-}CH_2Br$

+

$CH_2{=}CH{-}CHBr{-}CH_3$

The Br attaches to the starred electronically-deficient carbon in either A or B.

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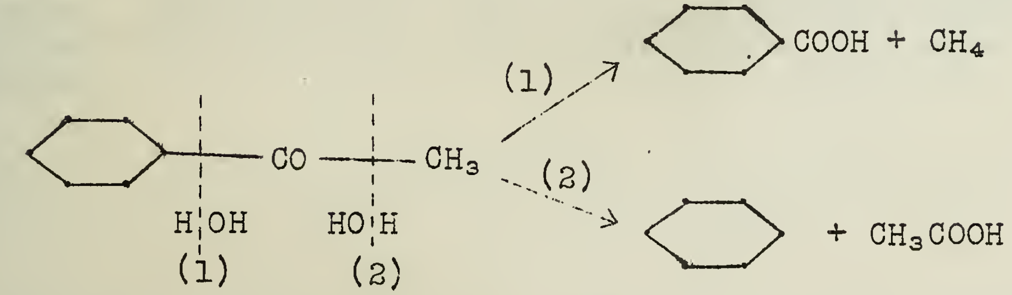
Kirrmann and coworkers, Compt. rend., 194, 1168 (1932); 199, 1228 (1934); 202, 1934 (1936); Bull. soc. chim., (5), 1, 860 (1934); (5), 4, 502 (1937); (5), 2, 2143 (1935).

Reported by E. Ginsberg
November 10, 1937.

CLEAVAGE OF KETONES BY ALKALI

Lock and Bock -- Vienna

Alkyl aryl ketones can be cleaved in two ways; for example:



Earlier workers stated that cleavage (1) of the carbon chain of carbonyl compounds under the influence of alkali is due to the coordination of the carbonyl atom with hydroxyls. It is assumed that the polarity of the bond between the carbonyl atom and the <u>alpha</u> carbon is thus enhanced permitting a splitting of the linkage.

Fuson and other workers found that substitution of halogen in the side chain greatly facilitated cleavage according to (1). Also these workers observed that certain trihalo-methyl ketones whose carbonyl groups do not undergo addition reactions were stable to alkali, thus supporting the assumption that cleavage according to (1) is dependent on an addition reaction of the carbonyl group.

Recently a study has been made of the influence which chlorine atoms on the benzene nucleus exert on the cleavage by alkali. The 3-chloro, 2,4-, 3,5-, and 2,6-dichloro, the 2,3,6- and 2,4,7-trichloro and 2,3,4,5,6-pentachloroacetophenones were investigated.

The results have proved that the generalization that ketones without typical oxo-reactivity are not cleaved at all or only with great difficulty by alkali holds only for those with halogen on the side chain. In the nucleus substituted compounds on the contrary only those are easily cleaved in which both <u>o</u>-positions are substituted and which, therefore, form no oxo-derivatives. In the acetophenones substituted in the side chain the cleavage proceeds according to (1) and in the nucleus substituted compounds according to (2). As the former cleavage is much more rapid than the latter, acetophenone highly halogenated both in the side chain and in the nucleus, such as 2,4,6-$Br_3C_6H_2COCBr_3$ decomposes only according to (1). This work has also shown that when there is at least one free <u>o</u>-position, cleavage, if it occurs at all, takes place according to (1).

The cleavages were effected by heating the ketones with fifty per cent KOH for twenty-four hours at 150° in a nickel tube provided with a reflux condenser, diluting the contents with water, extracting with ether, acidifying with phosphoric acid, distilling with steam, and titrating with potassium hydroxide.

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Reported by R. M. Haskins
November 17, 1937.

THE PREPARATION OF LONG CHAIN POLYMETHYLENE DIHALIDES

Julius v. Braun -- Heidelberg (formerly Frankfort a. M.)
K. Ziegler -- University of Halle

High molecular weight dihalogen compounds of the type XRX (where R is a long aliphatic chain) are in general prepared in two ways: (1) Synthesis of long chain dicarboxylic acids $HO_2CR'CO_2H$ and their reduction to the glycols which are readily converted into the halides. The dicarboxylic acids themselves are prepared from lower dihalides through the nitriles or through the malonic ester synthesis. (2) The acids $HO_2CR''CO_2H$ are converted into the acid ester $HO_2CR''CO_2Et$ which on electrolysis gives the homologs $HO_2CR''R''CO_2H$. These methods involve many repetitions of the process for higher members.

In 1910 v. Braun suggested another method which embodies the following conversions:

$$Br(CH_2)_nBr \longrightarrow PhO(CH_2)_nBr \xrightarrow{Na} PhO(CH_2)_{2n}OPh \xrightarrow{HBr} Br(CH_2)_{2n}Br$$

As n becomes larger (>10-12) in these compounds the di-ether resists cleavage.

v. Braun has recently continued this work investigating the possibility of using aliphatic ethers of type $RO(CH_2)_{2n}OR$. Here, however, the boiling points of the intermediate $RO(CH_2)_nBr$ and the starting material $Br(CH_2)_nBr$ were so close that the product of the Wurtz reaction could not be obtained sufficiently pure. The difficulty was overcome by the use of the following conversions.

$$Br(CH_2)_nBr \longrightarrow PhO(CH_2)_nBr \xrightarrow{Na} PhO(CH_2)_{2n}OPh \xrightarrow[Ni]{H_2}$$

$$\begin{tikzcd} C_6H_{11}O(CH_2)_{2n}OC_6H_{11} \arrow[d, "HBr"] \\ Br(CH_2)_{2n}Br \end{tikzcd}$$

Ziegler in a recent publication describes another solution to the problem of increasing the ease of splitting the diaryl ethers. They found that using ethers of the type

$$p\text{-}MeO\text{-}C_6H_4\text{-}O\text{-}(CH_2)_nO\text{-}C_6H_4OMe$$

the split is accomplished smoothly on several hours' boiling with HI. Guiacol can also be used instead of hydroquinone monomethyl

ether and at the present time the possibility of using resorcinol monomethyl ether and other substituted phenols is being studied.

In both the foregoing methods the preparation of $ArO(CH_2)_nX$ presents some difficulty as the use of $Br(CH_2)_nBr$ in large excess is not desirable because of the difficulty of obtaining this reagent. While v. Braun obtains reasonable yields (85 per cent) by using a ratio of 1.5 mol PhONa to 1 mol dihalide and recovering the unreacted dihalide and again reacting it with the phenoxide, Ziegler has worked out a method based upon solubility differences of reactants and product in the solvent used in the reaction. In this way he obtains the ω-halo alkyl ether in 80-90 per cent yields in a single step from equivalent amounts of reactants.

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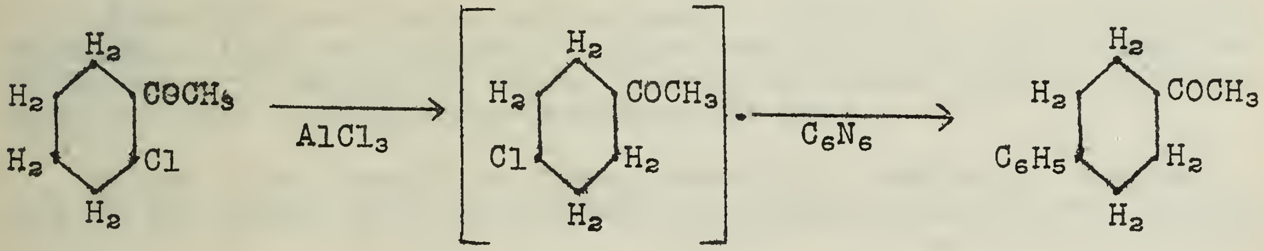
Reported by Wm. R. Dial
November 17, 1937

KETONE MIGRATION WITH ALUMINUM CHLORIDE

C. D. Nenitzescu, University of Bucharest

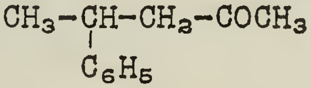
Beta-chlorinated ketones may be obtained by the addition of acid chlorides to olefins in the presence of $AlCl_3$. Replacement of the halogen by a phenyl group resulted in an isomer of the expected ketone whose properties did not agree with those of the compound expected. 1-Chloro-2-acetylcyclohexane was treated with benzene and $AlCl_3$. The product obtained was not 1-phenyl-2-acetylcyclohexane and oxidation of it produced an acid which was not 2-phenyl-cyclohexane carboxylic acid, but had the same melting point as one of the stereoisomers of 4-phenyl-cyclohexane carboxylic acid. The 4-position of the phenyl group was proved by Clemmenson reduction of the ketone, dehydrogenation of the hydrocarbon over Pt-black, and oxidation of the ethyl biphenyl to the acid, which was identical with p-phenylbenzoic acid. It was, therefore, assumed that the following migration occurred:



In the cyclopentane series 2-chloro-acetylcyclopentane, under similar treatment, gave 3-phenyl-acetylcyclopentane. The product was oxidized to the corresponding acid, $C_6H_5\text{-}C_5H_8\text{-}COOH$, whose structure was proved by synthesis.

In the open-chain series the reaction with ethylene offers no chance for rearrangement. Propylene might react in either of two ways:

$$CH_3\text{-}CH{=}CH_2 + CH_3\text{-}COCl \xrightarrow[AlCl_3]{} \left[CH_3\text{-}CHCl\text{-}CH_2\text{-}COCH_3\right] \xrightarrow[C_6H_6]{}$$



$$CH_3\text{-}\underset{C_6H_5}{CH}\text{-}CH_2\text{-}COCH_3 \qquad \text{II.}$$

$$\text{or} \quad \left[CH_3\text{-}CHCl\text{-}CH_2\text{-}COCH_3 \longrightarrow CH_2Cl\text{-}CH_2\text{-}CH_2\text{-}COCH_3\right] \xrightarrow[C_6H_6]{}$$

$$C_6H_5\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}COCH_3 \qquad \text{III.}$$

The ketone obtained was oxidized to β-phenylbutyric acid, corresponding to reaction II. Also 2-butylene reacted to give a ketone which on oxidation produced α,β-dimethylhydrocinnamic acid. Similarly isobutylene resulted in β,β-dimethylhydrocinnamic acid. In each of these cases any shift would have to be to a terminal methyl group. However, 1-butylene under similar treatment resulted in 5-phenyl-2-hexanone.

[illegible]

[illegible]

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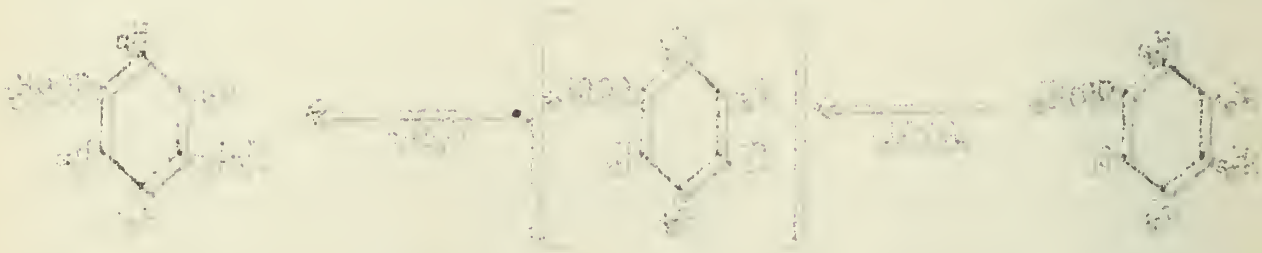

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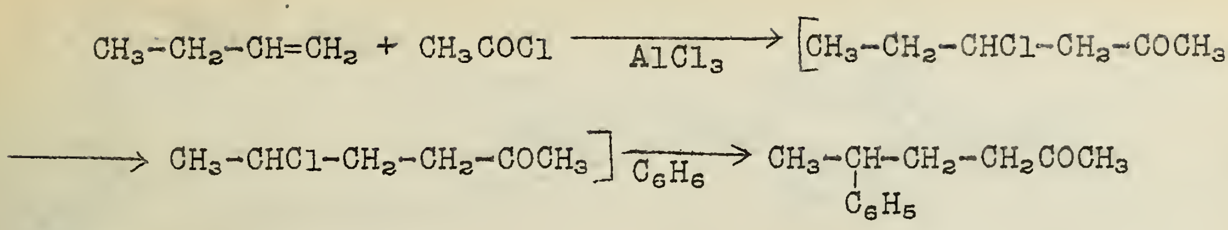


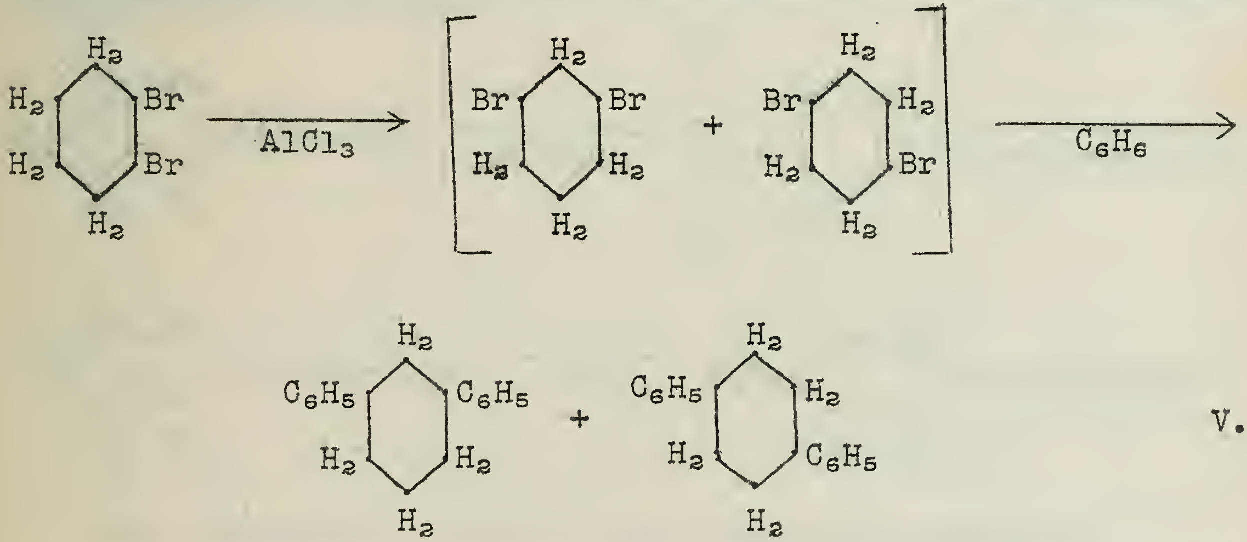
$$\mathrm{CH_3{-}CH_2{-}CH{=}CH_2 + CH_3COCl \xrightarrow[AlCl_3]{} \Big[CH_3{-}CH_2{-}CHCl{-}CH_2{-}COCH_3 \longrightarrow CH_3{-}CHCl{-}CH_2{-}CH_2{-}COCH_3\Big] \xrightarrow[C_6H_6]{} CH_3{-}\underset{\displaystyle C_6H_5}{\underset{|}{C}H}{-}CH_2{-}CH_2COCH_3}$$

IV.

For longer chains the method above gave poor yields, as the amount of byproducts increased. To avoid this, α,β-unsaturated ketones were treated with benzene and $AlCl_3$. The same β-chloroketones should be formed as intermediates as in the first method. Ethylidene acetone gave the same ketone as propylene and acetyl chloride. With propylidene acetone a migration occurred, resulting in the same ketone as that from 1-butylene. Butylidene acetone formed 6-phenyl-2-heptanone. The constitution of these compounds was proved by synthesis.

Also α,β-unsaturated acids behave similarly. 1,2-cyclohexene carboxylic acid reacted with benzene and $AlCl_3$ to give 1-phenylcyclohexane-4 carboxylic acid. 1,2-cyclopentene carboxylic acid gave 1-phenyl cyclopentane-3-carboxylic acid.

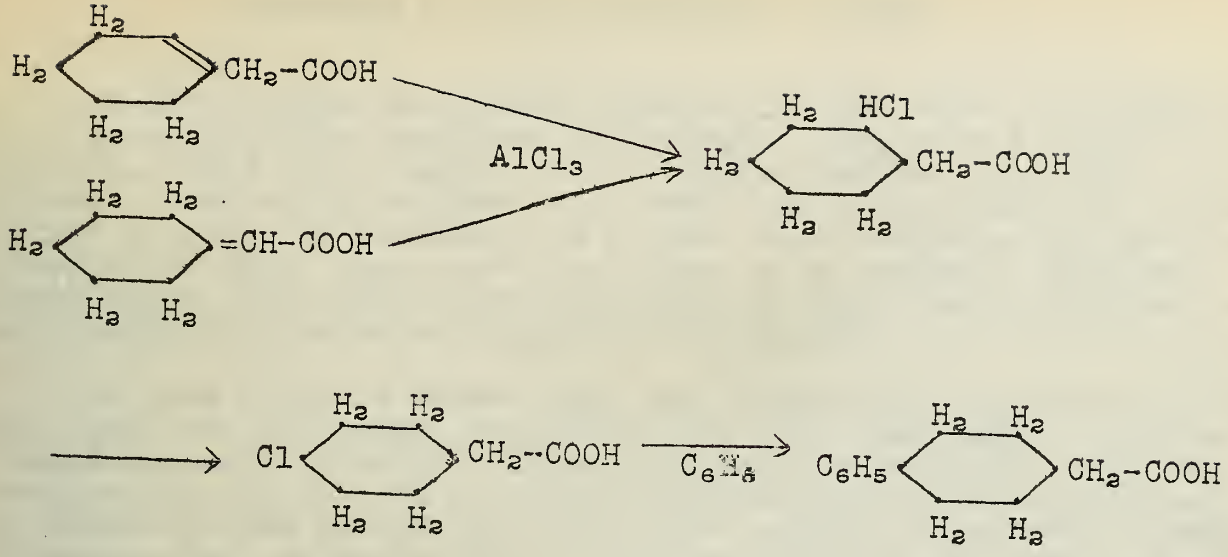
Other electronegative groups should be similarly repelled, and it was found that 1,2-dibromocyclohexane produced two isomers.



V.

Selenium dehydrogenation produced terphenyl and *m*-diphenylbenzene. The migration was not quantitative, as with oxygen. No *ortho*-diphenylbenzene was found.

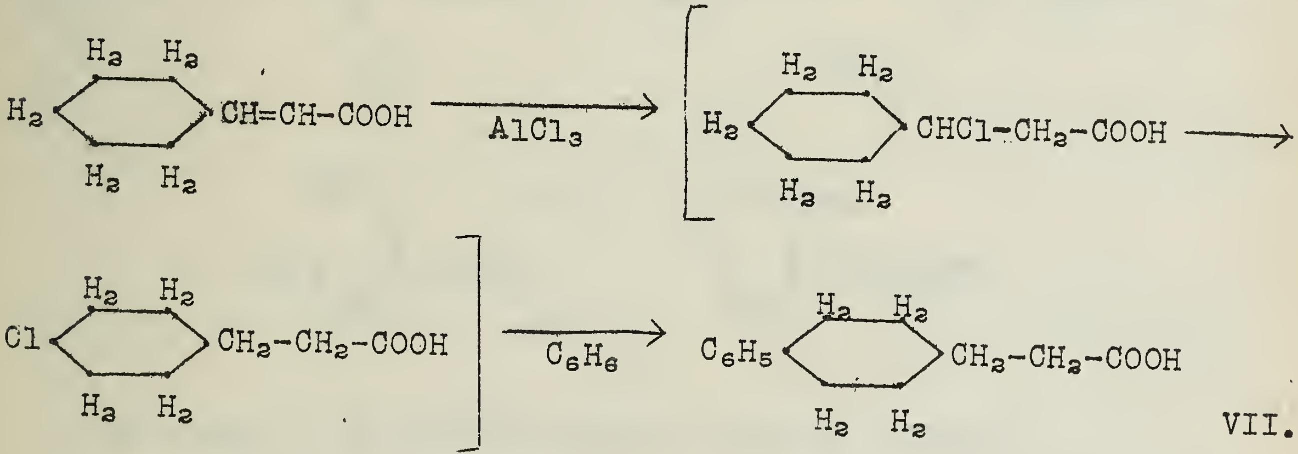
The next step was the investigation of the effect of a carboxyl group on the side-chain of a cyclohexane ring. Cyclohexylidene and cyclohexenyl acetic acid were prepared and with benzene and $AlCl_3$ both gave the same phenylcyclohexyl carboxylic acid.



VI.

The structure was proved by degradation of the ester with C_6H_5MgBr to the tertiary alcohol, oxidation with H_2CrO_4 to the next lower carboxylic acid, which was identical with 4-phenylcyclohexane carboxylic acid.

Cyclohexylacrylic acid produced with benzene and $AlCl_3$ phenyl cyclohexylpropionic acid.



VII.

The structure of this acid was proved by synthesis.

It appears that under the influence of $AlCl_3$ a migration of the halogen atoms in halogenated ketones or acids in both ring and chain forms occurs, with the phenyl group replacing the halogen in the position farthest removed from the carbonyl or carboxyl group. The shift does not take place to the terminal methyl group. Less electronegative groups exert less repulsion.

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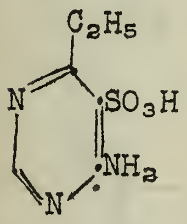
Reported by L. H. Dunlap
November 24, 1937.

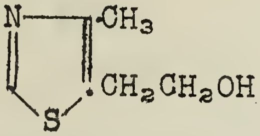
SYNTHESES OF THE ANTINEURITIC VITAMIN

In 1926 Jansen and Donath reported the isolation of Vitamin B_1 in crystalline form from rice polishings. They gave it the formula $C_6H_{10}ON_2$ based upon analysis of the hydrochloride. In 1932, Windaus obtained the vitamin from yeast and discovered that it contained sulfur. He proposed the formula $C_{12}H_{18}ON_4SCl_2$ for the hydrochloride which later work has shown to be correct. Windaus later found that nitric acid treatment of the vitamin produced two acid oxidation products, $C_5H_6O_2N_2$ and $C_5H_5O_3NS$.

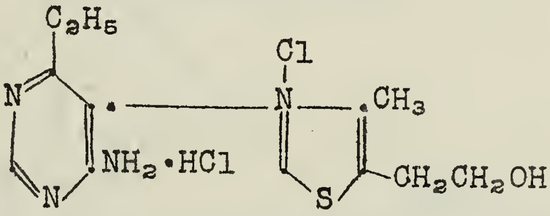
In 1934 Williams showed that the vitamin is cleaved by sulfurous acid into two parts, one acidic and the other basic. He believed the acid to be an ethylaminopyrimidine sulfonic acid, and assigned it the formula I. In connection with evidence obtained by Clarke he was able to show that the base is undoubtedly 4-methyl-5-hydroxyethyl thiazole (II). Williams proposed the structure III for the vitamin but in view of later evidence modified it to IV. The correctness of this latter structure has been proved by synthesis, by Williams and also by two other groups of workers.



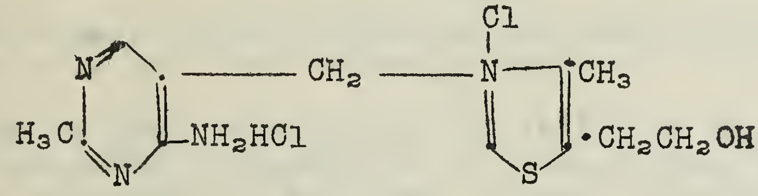
I.



II.



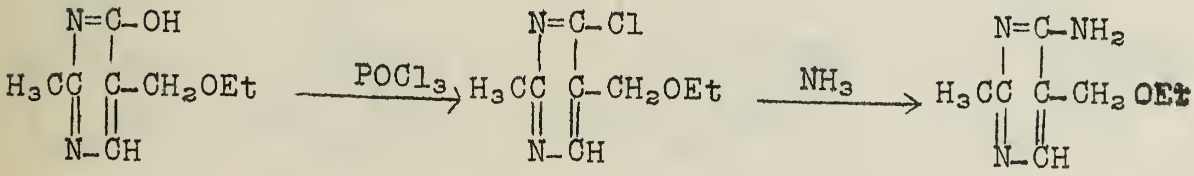
III.



IV.

The steps in Williams' synthesis are as follows:

$$\underset{V.}{EtOCOCH_2CH_2OEt} \xrightarrow{HCOOEt} \underset{VI.}{EtOCOCH_2CH_2OEt} \xrightarrow{NH_2-C(CH_3)=NH}$$



VII. VIII. IX.

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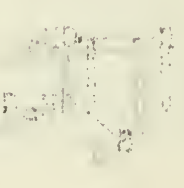

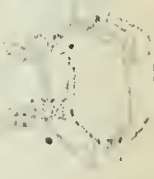

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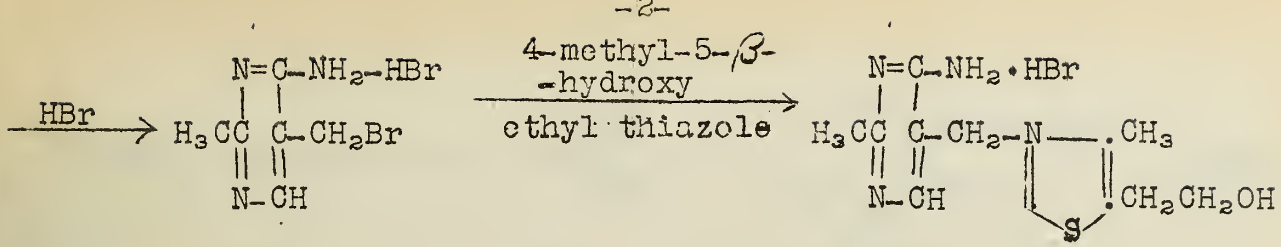
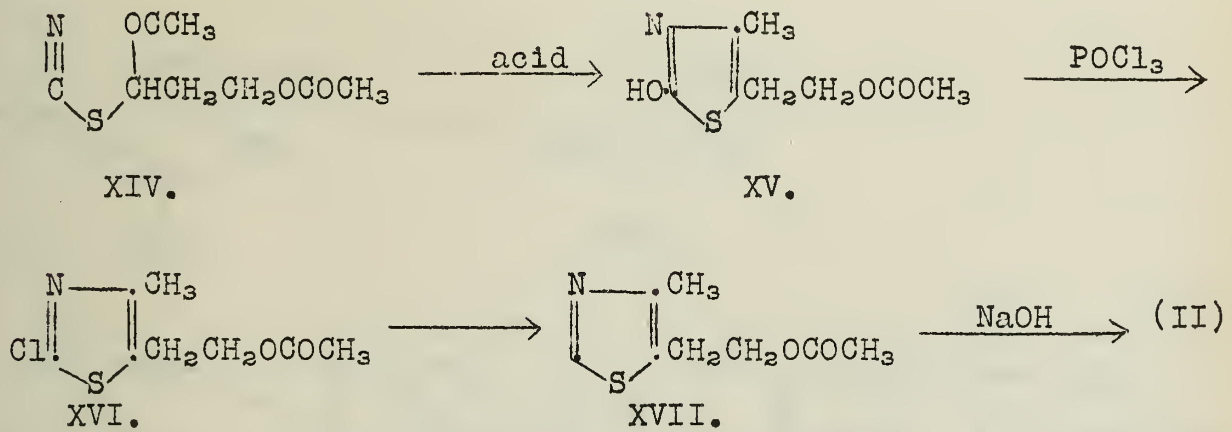


X. XI.

Andersag and Westphal have recently reported a synthesis which they began early in 1935. The thiazole part of the molecule was synthesized according to the following scheme:

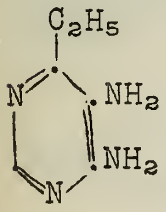
$$CH_3COCH_2CH_2CH_2OCOCH_3 \xrightarrow{Br_2} CH_3COCHBrCH_2CH_2OCOCH_3 \longrightarrow$$

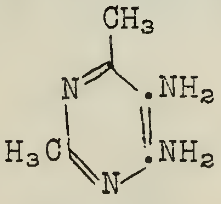
XII. XIII.

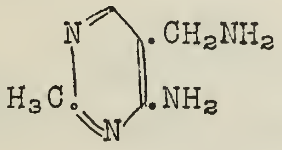


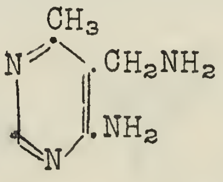
The properties of the synthetic base were found to be identical with those of the basic cleavage product.

By means of acid permanganate oxidation of the vitamin, Windaus had obtained a diamine of the composition $C_6H_{10}N_4$, which according to the original Williams' vitamin formula (III) should be ethyl-diaminopyrimidine (XVIII). Windaus, however, suggested formula XIX for the diamine. Compounds XVIII and XIX were both synthesized but neither found to correspond to the oxidation product. Andersag and Westphal then prepared compounds XX and XXI. XX proved to be identical with the oxidation product and furthermore could be converted into a compound (XXVII) which upon heating with the thiazole and derivative (II) gave the vitamin.

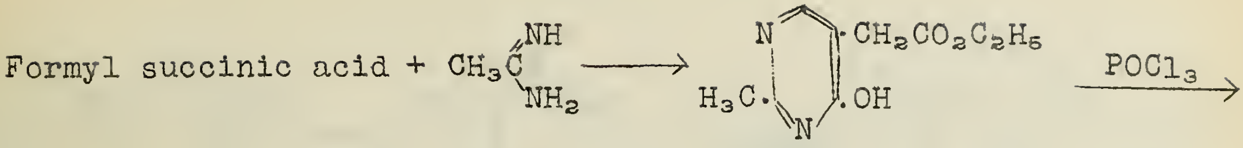

XVIII


XIX

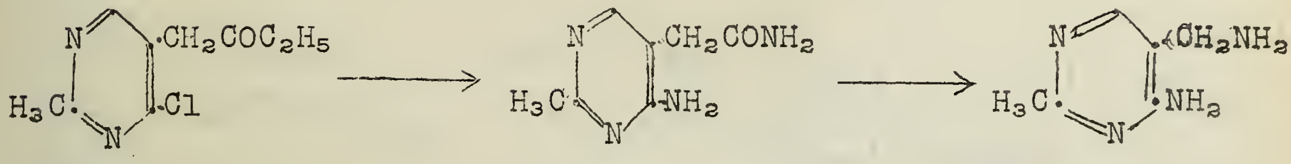

XX


XXI

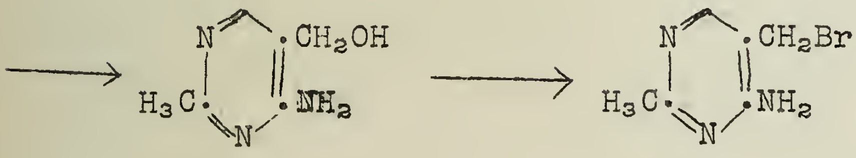
The steps in this procedure including the synthesis of XX are:



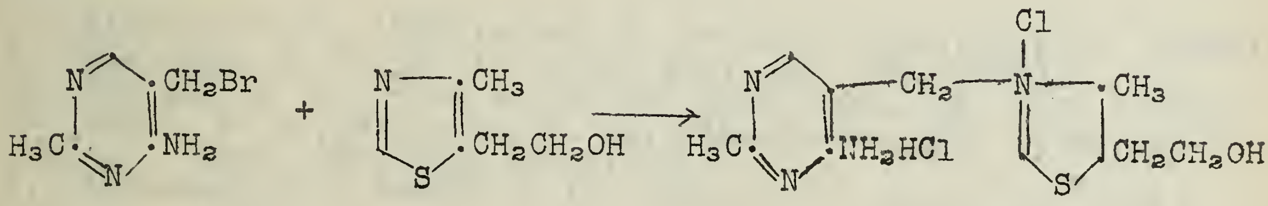
XXII. XXIII.



XXIV. XXV. XX.



XXVI. XXVII.

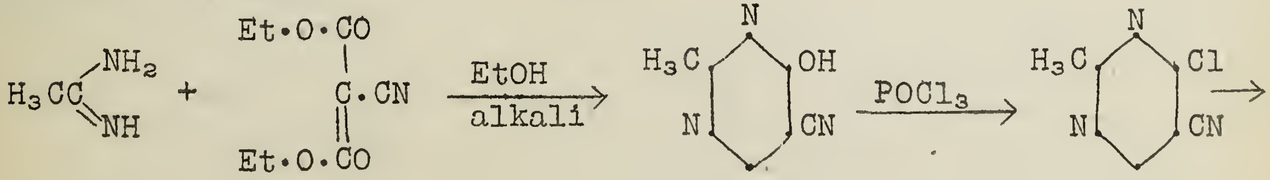


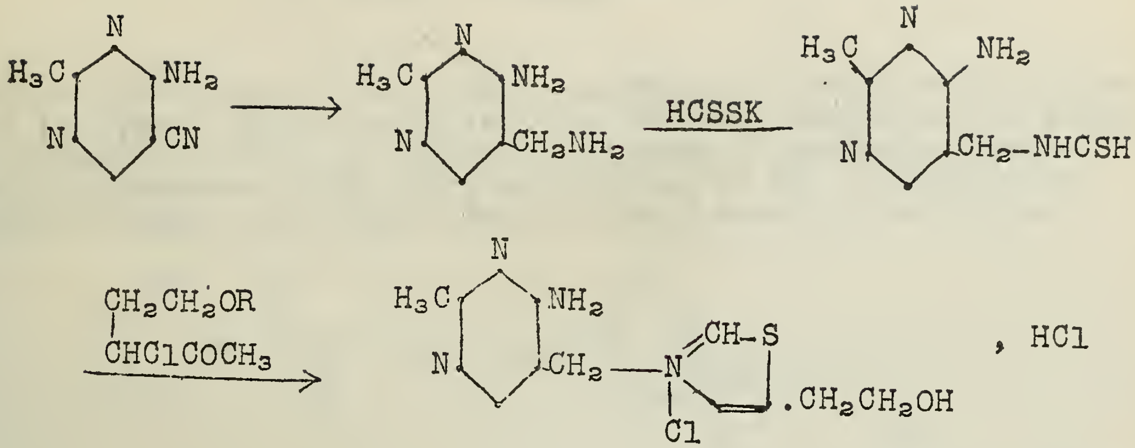
IV.

The synthetic hydrochloride melts at 252° C. and is, in its chemical, physical and physiological properties identical with the natural product.

Andersagg and Westphal have also synthesized an isomer of Vitamin B_1 by a similar procedure to that outlined above, using XXI as an intermediate.

Todd and Bergel have recently reported an independent synthesis of Vitamin B_1 (aneurin) carried out by the following scheme:





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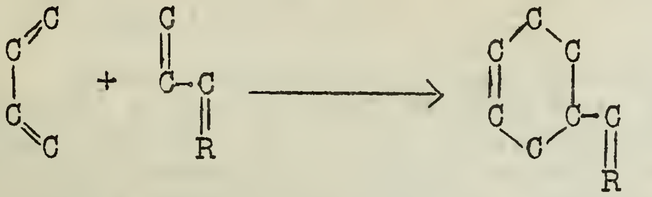
Reported by A. J. Johanson
November 24, 1937.

STERIC PROGRESS OF THE DIENE SYNTHESIS

K. Alder –– Leverkusen
G. Stein –– Oppau

According to the Diels Alder reaction, compounds with a conjugated system of double bonds add to "active" ethylenic or acetylenic linkages in the 1,4-position, forming a partially hydrogenated six-membered ring. The activation of the ethylenic or acetylenic linkage can result from an α,β-unsaturated group.

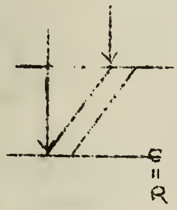


I.

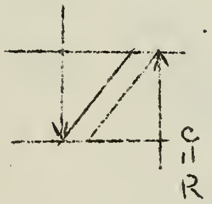
In the study of the course of the cyclopentadiene polymerization a decided steric selectivity was noticed and studied.

Three questions arise in connection with the investigation:

I. Will the diene add cis or trans or will both occur simultaneously?

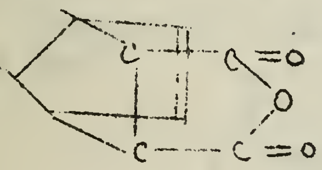


or



II. III.

II. Will the diene add to the side of the double bond to which the activating group (such as the anhydride linkage in maleic anhydride) is attached (IV) or to the opposite side (V)?



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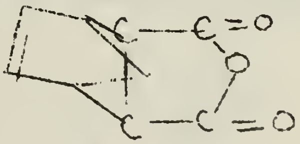


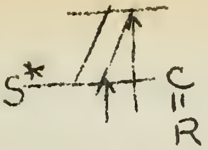
Endo
IV.

Exo
V.

III. The third question is encountered only when the molecule to which the double bond adds contains an asymmetric carbon atom (S^*). Will the diene add right over (VI) or right under (VII) the asymmetric center?

VI.

or



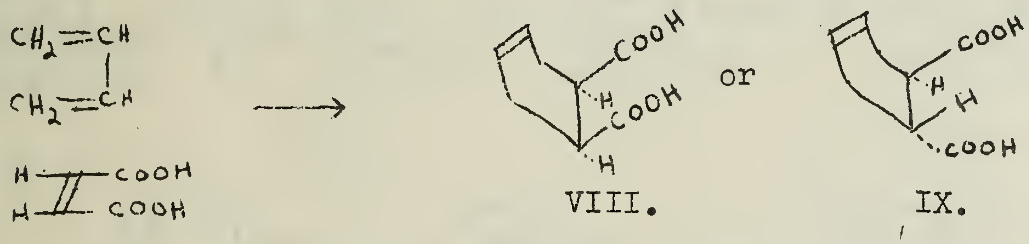
VII.

It is necessary to know the answers to I and II before the third question can be explained.

I. The cis-Principle.

From a mechanical viewpoint the addition of simple reagents to a double bond demands pure cis-addition. This has been found, however, to be the exception rather than the rule. One example is the formation of meso-tartaric acid by the oxidation of maleic acid with permanganate. Rather, experiment has shown that in most cases both additions take place, and, in a few cases, pure trans-addition occurs. The course of the addition then depends upon the nature of the compound and reagent and cannot be predicted. However, such incongruity is not the rule in diene syntheses as shown by the following examples:

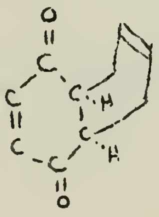
Example 1:



VIII. IX.

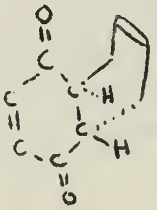
The cis-acid (VI) is isolated from the reaction. This is proved by the fact that after hydrogenation the cis-hexahydrophthalic acid is obtained. The trans-compound (IX), (if it had been obtained), did not rearrange during hydrogenation, because from the rearranged butadiene maleic acid (VIII ⟶ IX) the trans-hexahydrophthalic acid was obtained after hydrogenation.

Example 2: The addition of butadiene to quinone again goes cis:



X.

or



XI.

The cis-acid (X) is obtained and can be degradated to the cis-tetrahydrophthalic acid by mild oxidation. The cis-compound (X) can also be rearranged to the trans (XI) and by a

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

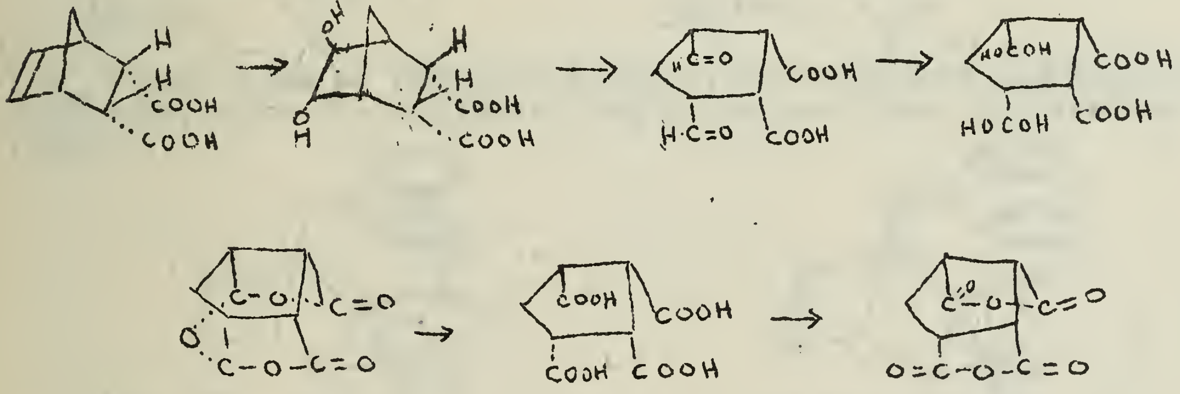
[illegible]

similar process oxidized to the trans-hexahydrophthalic acid.

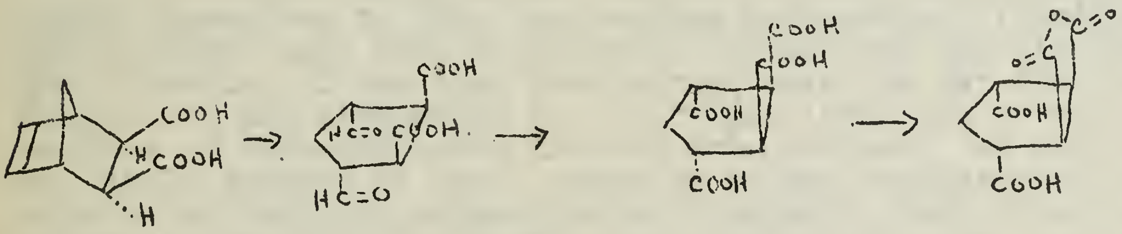
Example 3: The addition of cyclopentadiene to maleic acid has been proven to lead to a cis-configuration (XII) while to fumaric acid a trans-configuration results.

Pure cis addition, therefore, is the rule in diene synthesis.

II. Will the diene add on the side of the activating group or on the other side? Examination of models IV and V show that the CH_2 bridge in cyclopentadiene when added to maleic acid has made it possible for two forms to exist. Only the endo cis-form (IV) is isolated in the addition reaction. The geometric structure of such a molecule indicates the orientation of the two components into parallel planes. The selectivity indicates that an attractive or repulsive force exists between parts of each molecule such as, in this instance, the force between the double bond of the diene residue and the anhydride residue of maleic anhydride (see IV and V). The proof of the endo cis-addition is as follows:



The oxidation of the trans- (exo) form (V), which is obtained by rearrangement of the endo (IV) follows a different course:



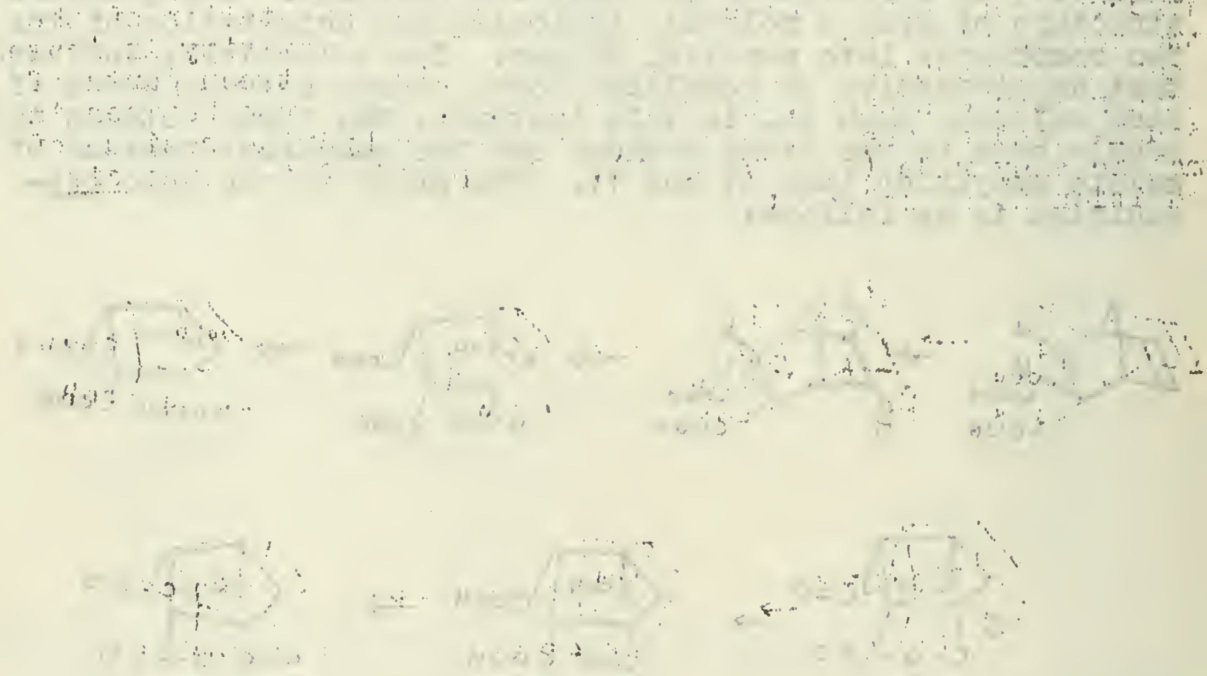
The final product will form only a mono-anhydride as would be expected from an exo compound.

similar process described in the [illegible]

Example 3: The addition of [illegible] with [illegible] (XXII) [illegible]

[illegible] addition, [illegible], in the [illegible]

[illegible]

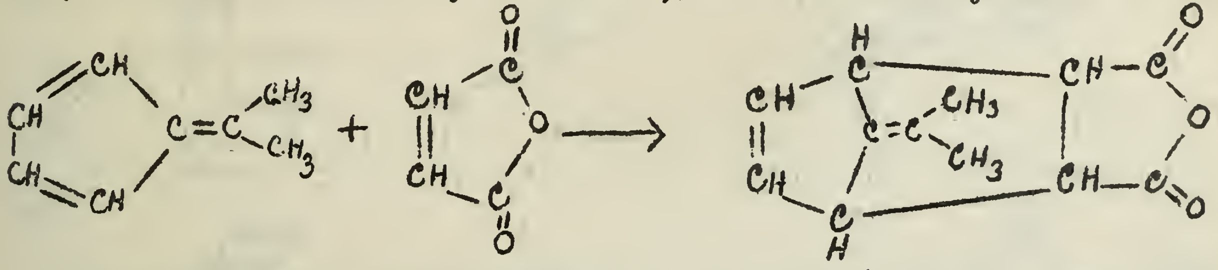


[illegible]

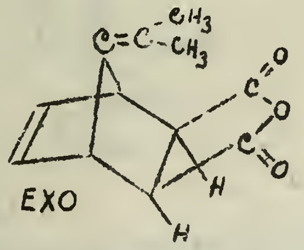
[illegible]

There is definitely some limit to the general orientation scheme just described in answer to question II. The dimerization of cyclopentadiene shows strong selectivity at room temperature, but no selectivity at 150°C. Other diene syntheses may be expected to show the same results.

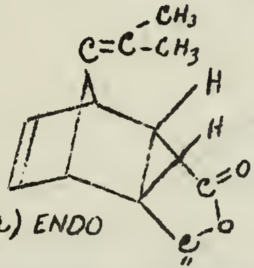
Also, if one component has an additional conjugated double bond, such as is shown by a fulvene, the selectivity is altered.



Approximately equal mixtures of isomers (a), the endo form, and (b), the exo form are obtained.

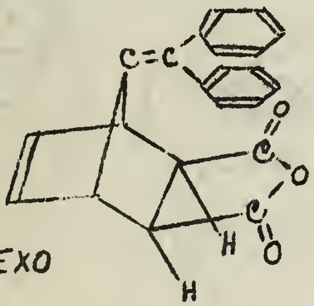


(b) EXO

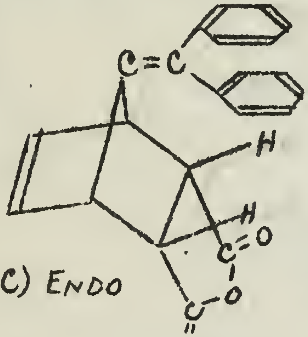


(a) ENDO

In the case of diphenyl fulvene, the relative aggregation of double bonds in the products favors the exo form (d) over the endo form (c).



(d) EXO



(C) ENDO

Experimentally the yield was close to 100 per cent exo form.

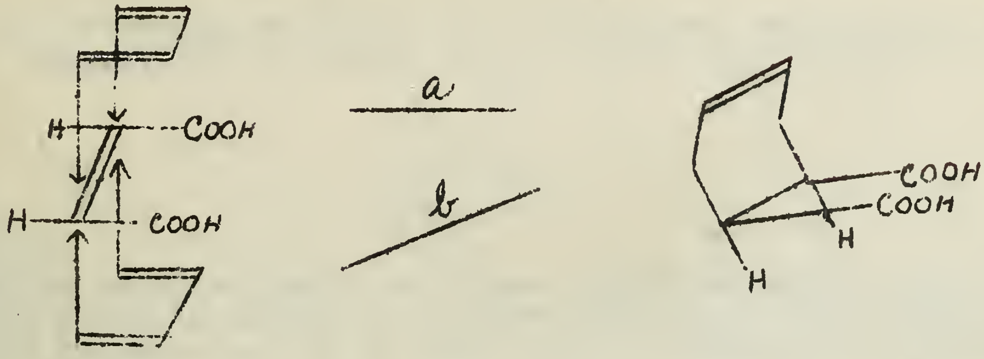
On the other hand, maleic anhydride and cyclopentadiene orient themselves to give the maximum aggregation of double bonds such that the endo form is produced rather than the exo form. This formation of the endo form rather than the exo form may be affected by the difference in electrical intensity between the residues of the components in both orientations. By addition of the dipole moments of each component in the product, the force between the residual components is obtained. This force proved larger in the case of the endo orientation than for the exo orientation.

III. Diene synthesis and asymmetric synthesis.

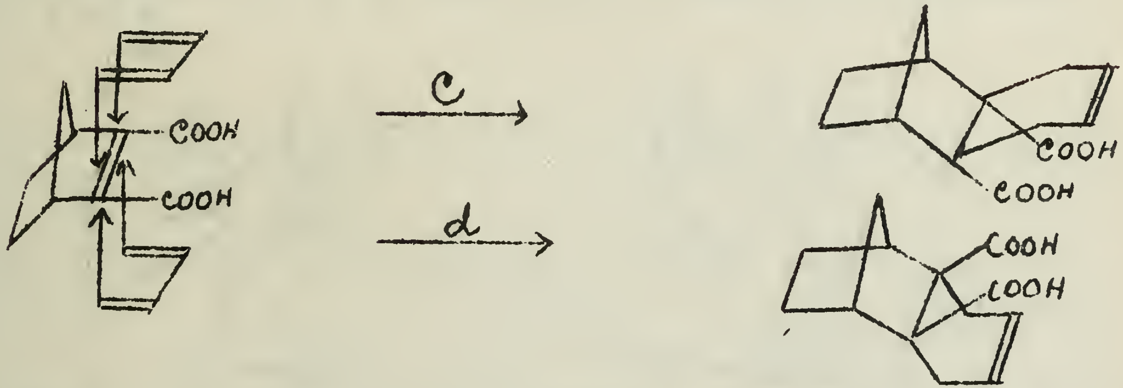
Compare reactions I and II below, representing butadiene and maleic anhydride (I) and the bicycloheptene system (which contains an asymmetric center) and butadiene (II). In I,

merely one product is formed upon application of the cis-principle, while in II, C is the favored process.

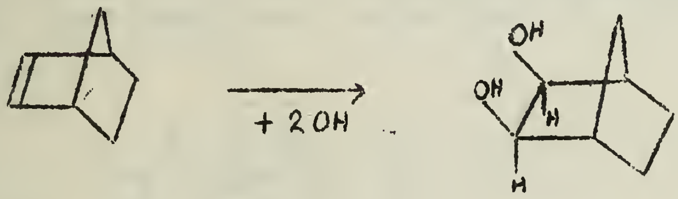
I



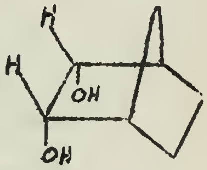
II



Analogies to reaction II have been found. The possibility of one form over the other form in simple compounds has been demonstrated.



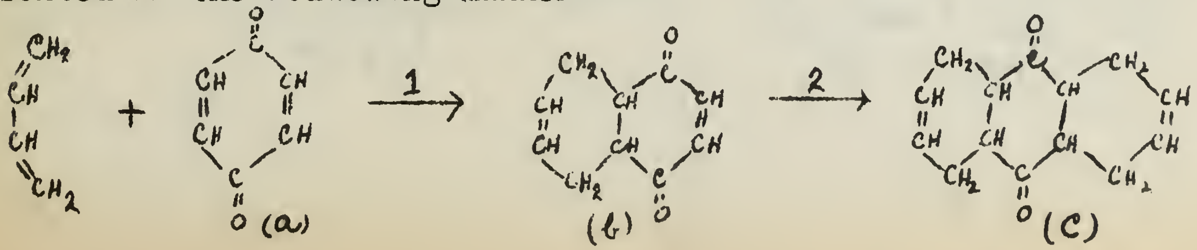
and not



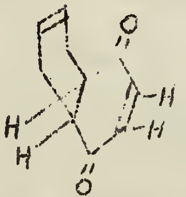
When *l*-bornyl fumaric acid ester is oxidized and then hydrolyzed, an asymmetric synthesis occurs with the formation of tartaric acid in which a slight excess of one active form is produced. The difference in velocity should be more marked when the asymmetric group is immediately adjacent to the double bond.

Addition to quinones.

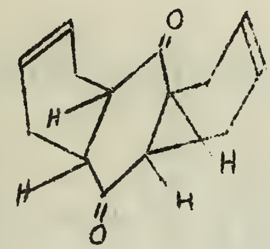
The general addition of butadiene to quinone may be represented in the following manner:



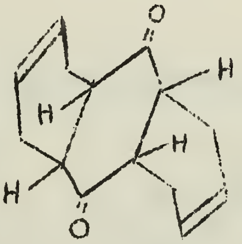
From this cis-principle and the general orientation scheme due to aggregation of double bonds, (b) is represented as



The second addition has been showed experimentally to give one compound which is either A or B and not one of the other three possible isomers C, D or E, which can be formed by rearrangement of A or B.



(A) an-cis

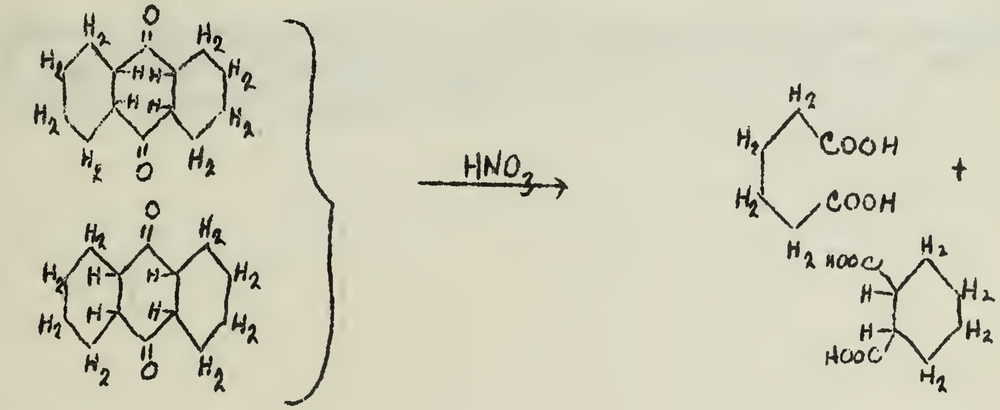


(B) an-trans

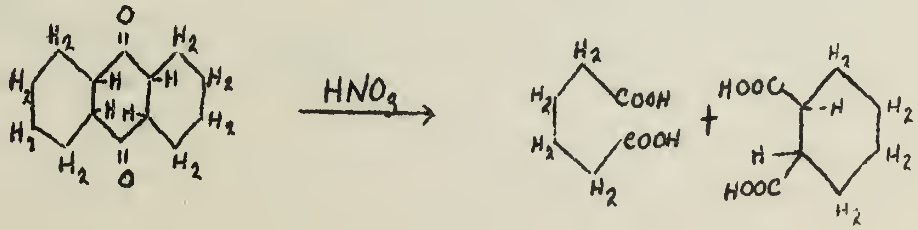
By hydrogenation to the dodecahydroanthraquinone of all five isomers, and subsequent oxidation, A^1 and B^1 may be distinguished from C^1, D^1 and E^1.

A^1 (an-cis)

B^1 (an trans)

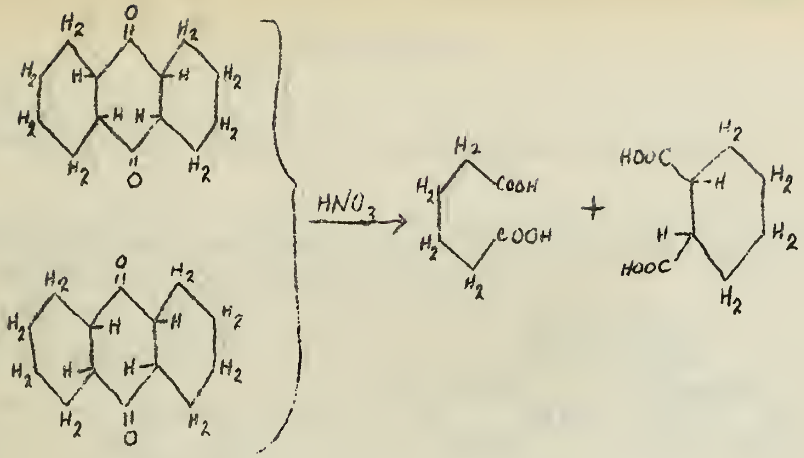


C^1 (cis-trans)

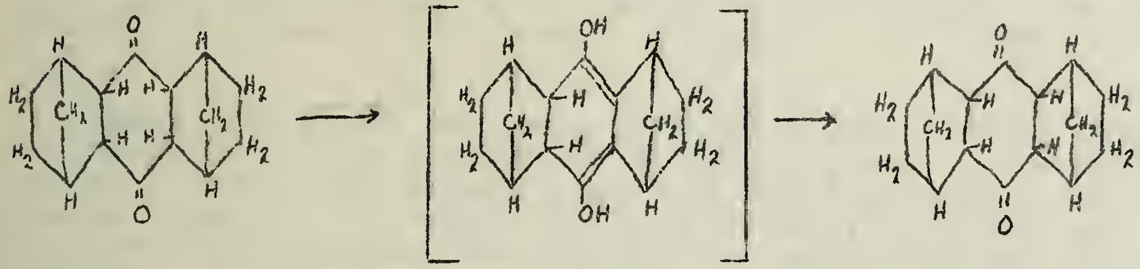


D^1
(*trans*-*trans*)

E^1
(*trans*-*trans*)



By analogy to the rearrangement of the dicyclopentadiene quinones



(an-*cis*)

(an-*trans*)

which was proven experimentally, it was deduced that the an-*cis* compound (A^1) of dodecahydroanthraquinone is first formed and then rearranged to the an-*trans* (B^1).

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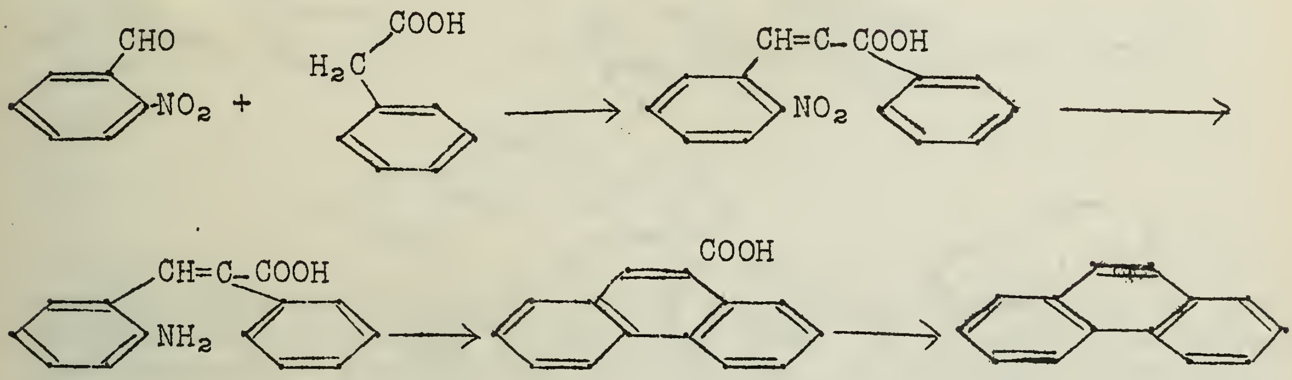
Angew. Chemie., *50*, 510 (1937).

Reported by D. E. Pearson
J. W. Robinson
December 1, 1937.

STEREOISOMERISM OF THE PHENANTHRENE SYNTHESIS OF PSCHORR

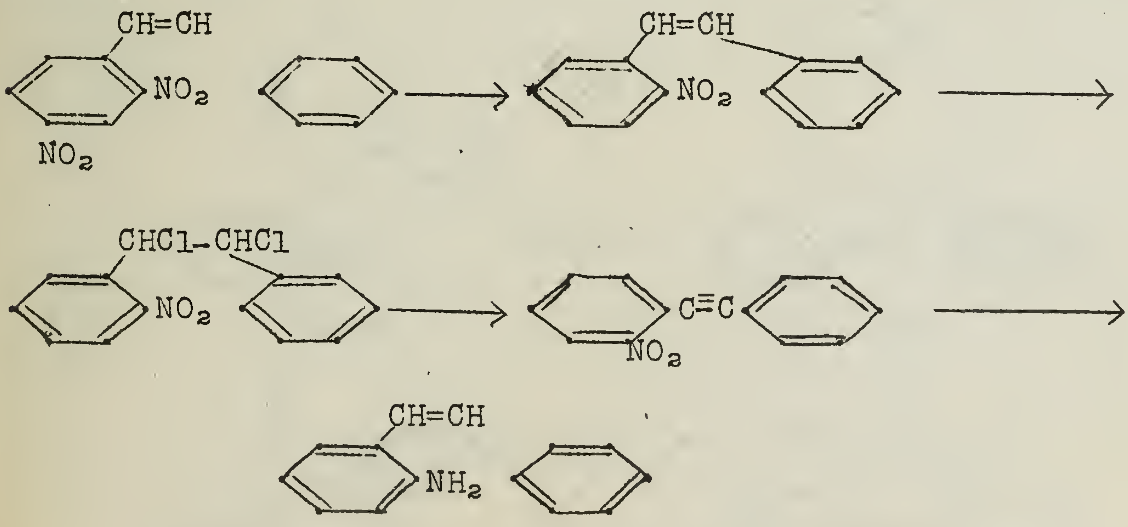
Ruggli and Staub -- University of Basel

In 1896 Pschorr[1] proposed the following synthesis of phenanthrene and certain of its derivatives.



Ruggli and Staub[2] indicate that the carboxyl group performs two functions. It activates the methylene group so the condensation will occur, for toluene itself will not condense. Due to its greater negativity it repels the o-nitrophenyl group of the aldehyde into the trans-position so the two aryl groups are in the cis-position. Bakunin[3] had reported that condensations of this type produce a cis-product predominantly. This explains why Sacks and Hilpert[4] could not obtain phenanthrene from o-amino stilbene (trans).

Ring closure with trans-o-amino stilbene was unsuccessful but the cis-form underwent ring closure yielding 34 per cent phenanthrene. The latter compound was prepared as follows.



The amine was impure with o-amino dibenzyl and traces of trans-o-amino stilbene were produced in small amounts during distillation.

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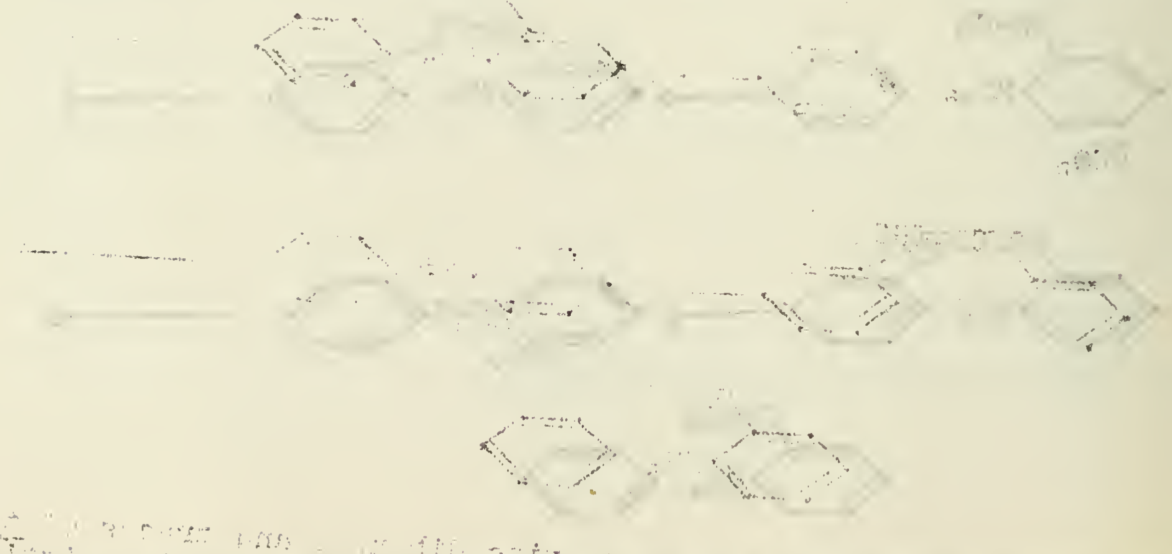
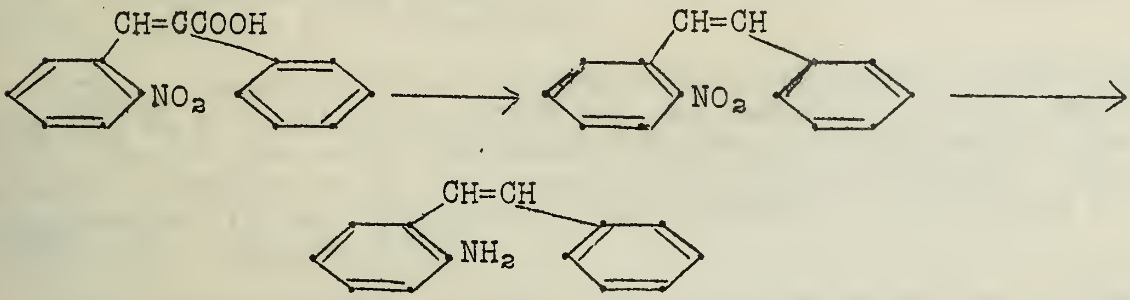


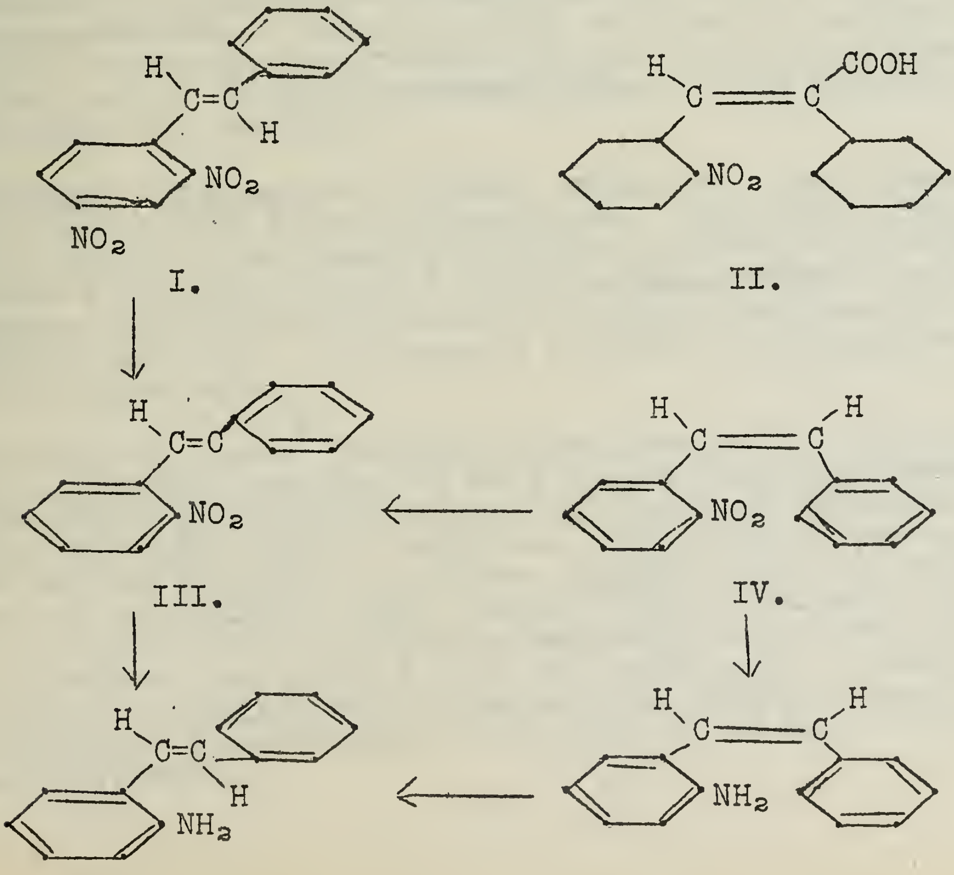
[illegible]

Stilbene (*trans*) would not lead to the formation of phenanthrene with $AlCl_3$ in a Friedel and Crafts reaction according to Ruzicka and Hösli.[5] With dibenzyl tarry products were produced although it would be expected to yield 9,10-dihydro phenanthrene due to free rotation.

The *cis*-*o*-amino stilbene was prepared as follows:[6]



No *trans*-form was produced in this preparation because it is difficult to convert the *cis* to the *trans* form. To convert this product to phenanthrene the reaction was carried out in three ways: (1) Diazotization in aqueous solution followed by treatment with copper powder (yield 61 per cent),[2] diazotization with amyl nitrite in alcoholic solution followed by treatment with copper powder or (3) with NaH_2PO_2 solution, (yield 64 per cent and 80 per cent respectively). Thus the synthesis could be carried out with carboxyl-free substances. The properties of the *cis* and *trans*-*o*-nitro and *o*-amino stilbenes were also studied.



I. II. III. IV. V. VI.

Cis-o-nitro stilbene (IV) could be converted to the *trans*-form (III) by heating it in nitrobenzene to which small amounts of iodine had been added. Neither iodine in other solvents nor nitrobenzene itself produced appreciable changes. The *trans*-nitro compound is best prepared, therefore, from the *trans*-2,4-dinitro compound (I) by reduction.

Cis-o-amino stilbene (III) was best converted to the *trans*-form (V) by refluxing in quinoline for two and one-half hours at 250°. Twenty per cent conversion occurred. This conversion is never so complete as in the case of the nitro compound. The *trans*-amine (V) is, therefore, best prepared by reduction of the *trans*-nitro compound (III).

The *trans*-amine was used in the Pschorr reaction. Diazotization in aqueous solution and treatment with copper powder led to the formation of much tar, *o*-hydroxy stilbene and traces of benzaldehyde. Diazotization in alcoholic solution and treatment with copper powder led to the formation of 65 per cent stilbene. Diazotization in alcoholic solution and treatment with NaH_2PO_2 led to the production of 45 per cent stilbene and tar.

O-Amino-dibenzyl was also used in the Pschorr reaction. Positive results were expected due to free rotation. Diazotization in aqueous solution and treatment with copper powder led to the formation of *o*-hydroxy-dibenzyl, dibenzyl and traces of 9,10-dihydrophenanthrene.. Diazotization in alcoholic solution and addition of copper powder produced 30 per cent *o*-hydroxy-dibenzyl and 35 per cent 9,10-dihydrophenanthrene.. With NaH_2PO_2 47 per cent dibenzyl was obtained.

Summary.—*Cis-o*-amino stilbene undergoes ring closure in the Pschorr reaction and forms phenanthrene. In *o*-amino dibenzyl, the amino group is replaced by hydrogen without ring closure but in alcoholic solution some 9,10-dihydrophenanthrene is produced. In *trans-o*-amino stilbene the amino group is replaced by hydrogen in *alcoholic* solution. In aqueous solution the amino group is replaced by hydroxyl.

Ruzicka and Hösli[5] obtained phenanthrene from dibenzyl in a Friedel and Crafts reaction by ring closure and simultaneous dehydrogenation. Phenanthraquinone has also been obtained from benzil[7] in the same type of reaction. These reactions are dependent on free rotation. Stilbene (*trans*) does not undergo ring closure but isostilbene (*cis*) yields a tarry product. However, Biltz[8] obtained 9,10-diphenylphenanthrene from tetraphenyl ethylene because the product does not polymerize. Isostilbene is best prepared from α-phenyl-cinnamic acid prepared from phenyl acetic acid and benzaldehyde with yields of 80 per cent followed by decarboxylation.

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[illegible]

[illegible]

[illegible]

[illegible]

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   ibid , 27, (II), 41 (1897).
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Reported by F. J. Sprules
December 8, 1937.

THE LICHEN COMPOUNDS; BONINIC ACID

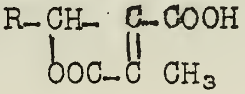
Asahina, University of Tokyo

From lichens, a fungus which lives symbiotically with an algae, food and dyes have been obtained, especially in northern countries. About 200 different compounds have been isolated from lichens, while definite structures have been assigned to less than half of this number.

The lichen is dried and extracted by organic solvents. From the extracts and residues have been obtained compounds which belong to different classes.

(1) Carbohydrates.--Lichenin (a "reserve cellulose" composed of approximately 60 units of d-glucose, according to recent viscosity measurements by Staudinger), isolichenin, and also sugar alcohols (mannitol, erythritol, etc.).

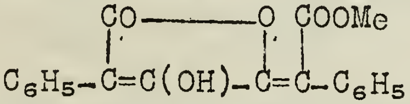
(2) Aliphatic acids of the type.--



$$\begin{array}{lll} \mathrm{R{-}CH{-}} & \mathrm{C{-}COOH} & \\ \quad | & \ \ \| & \\ \mathrm{OOC{-}} & \mathrm{C} & \mathrm{CH_3} \end{array}$$

e.g., when R is $C_{13}H_{27}$, Lichesteric acid.

(3) Pulvinic acid type.--

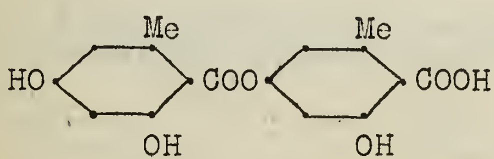


$$\begin{array}{lllll} & \mathrm{CO} & \text{———} & \mathrm{O} & \mathrm{COOMe} \\ & | & & | & | \\ \mathrm{C_6H_5{-}} & \mathrm{C{=}} & \mathrm{C(OH){-}} & \mathrm{C{=}} & \mathrm{C{-}C_6H_5} \end{array}$$

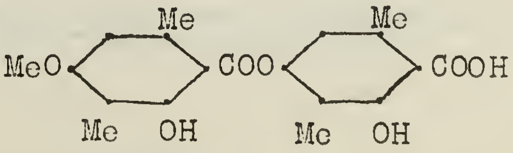
(4) Cumarones, thiophaninic acids and anthraquinone derivatives have been reported.

(5) Depsides and depsidones were first isolated from lichens and were named by Fischer on their formal relationship to peptides. These are the most important type of lichen acids. About 33 crystalline acids of this type have been given definite structural formulas.

Depsides are compounds produced by the linking of the carboxy group of a phenolic acid to the phenolic group of a similar acid. Most of the lichen depsides are derivatives of carboxy acids of orcinol (5-methyl resorcinol) or β-orcinol (2,5-dimethyl resorcinol). Two orsellinic acids linked in the p-position is Lecanoric acid (A), a (di) depside. Three acids linked similarly is a tridepside (e.g., Gyrophoric acid). Barbatic acid (B) is a depside of β-orsellinic acid.



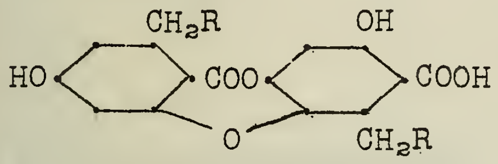
A.



B.

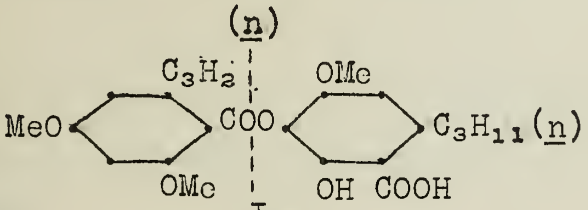
Depsides split with alkali and certain enzymes. Concentrated sulfuric acid has been shown recently to be a quantitative hydrolytic agent. The occurrence of tridepsides and m-depsides is rather rare.

Depsidones are essentially depsides with an O-ether linkage between the two aromatic nuclei. Because of this linkage, they do not hydrolyze.



when R is COC_5H_{11}(n), Alectoronic acid

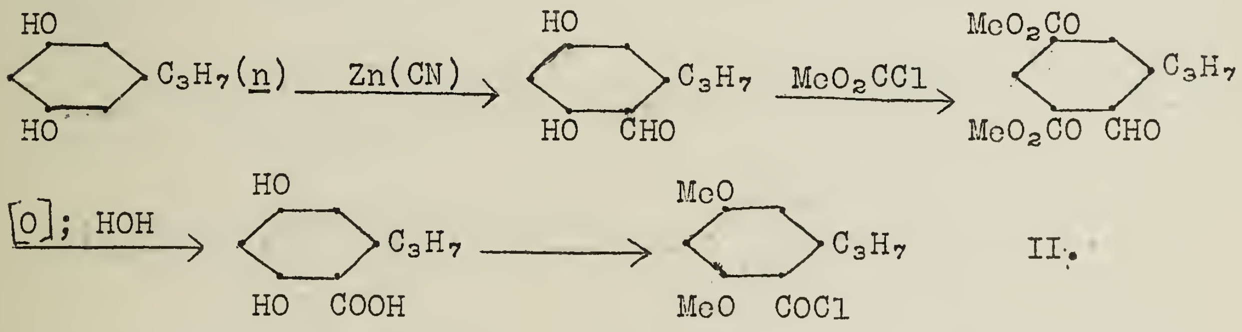
A new depside, boninic acid ($C_{25}H_{32}O_8$) has been recently found in a lichen and synthesized by Asahina. This will be taken as an illustration of the methods employed in the synthesis of these compounds. On the basis of the similarity of derivatives to certain previously known depsides and analytical data, it was given the formula



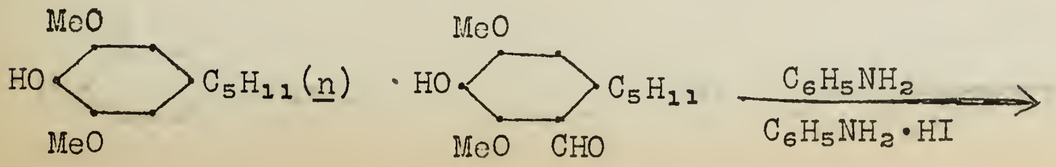
I.

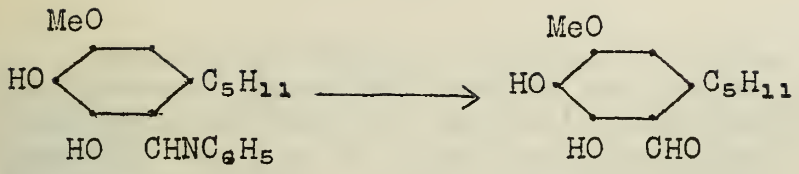
Hydrolysis of bonninic acid by concentrated sulfuric gave the two units as indicated by the dotted line in the formula. Synthesis of the acid consisted essentially of coupling derivatives of the two units.

The synthesis of the divaricatinoyl chloride (II) can be diagrammatically represented in the following manner:



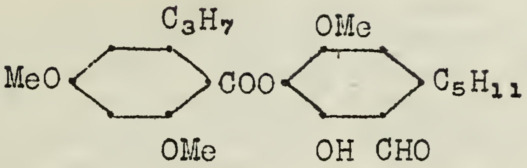
From gallic acid, the n-amyl side-chain was attached by Sonn's method. The pyrogallol portion was then prepared.





III.

II + III → Boninaldehyde



Carbethoxylate, oxidize, and decarbethoxylate → boninic acid I.

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Reported by A. G. Sharp
December 8, 1937.

A GENERAL METHOD OF CARBONYL REDUCTION

H. Lund

Reductions catalyzed by metal alcoholates have been studied by Meerwein, Ponndorf, Verley and others. In the above cases the reduction has been for specific substances. Recently H. Lund has reported the use of aluminum isopropylate as a general reagent for the reduction of the carbonyl group.

Metallic alcoholates have the advantage over other reducing agents in that they attack only the >C=O group (perhaps the nitroso group) and have no effect on the ethylene bonds, α-hydrogen atoms, or nitro groups. A great many metallic alcoholates have been found which promote the reduction but the aluminum and magnesium alcoholates appear to be most effective. This is probably due to the solubility of their salts.

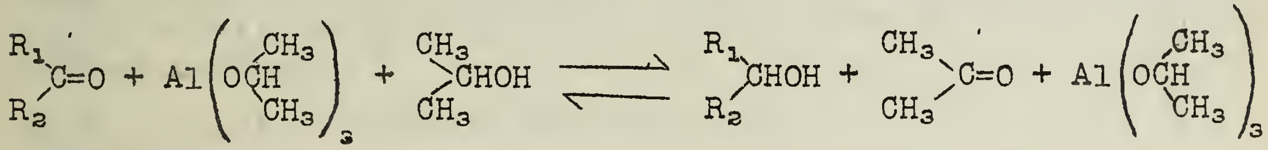
Several mechanisms have been proposed. The one supported by the most evidence (Meerwein, 1936) is represented as follows.

$$\mathrm{RCHO} + \mathrm{Al(OEt)_3} \longrightarrow \mathrm{RCHO\cdot\cdot\cdot\cdot\cdot Al(OEt)_3}$$

$$\mathrm{RCHO\cdot\cdot\cdot\cdot\cdot Al(OEt)_3} \longrightarrow \mathrm{RCH_2OAl(OEt)_2} + \mathrm{CH_3CHO}$$

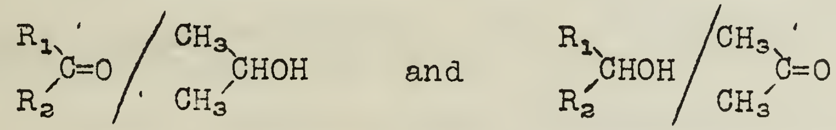
$$\mathrm{RCH_2OAl(OET)_2} + \mathrm{EtOH} \longrightarrow \mathrm{RCH_2OH} + \mathrm{Al(OEt)_3}$$

Ponndorf, Young and coworkers, and Lund have found that aluminum alcoholates of secondary alcohols are better reducing catalysts than those of primary alcohols, especially on aldehydes which are hard to reduce and ketones. The overall reaction for aluminum isopropylate is as follows.



$$\mathrm{R_1R_2C{=}O} + \mathrm{Al\left(OCH(CH_3)_2\right)_3} + \mathrm{(CH_3)_2CHOH} \rightleftharpoons \mathrm{R_1R_2CHOH} + \mathrm{(CH_3)_2C{=}O} + \mathrm{Al\left(OCH(CH_3)_2\right)_3}$$

It is readily seen that the reaction is reversible, and the extent to which the reaction goes to completion depends upon the oxidation potential of the



$$\mathrm{R_1R_2C{=}O} \,/\, \mathrm{(CH_3)_2CHOH} \quad \text{and} \quad \mathrm{R_1R_2CHOH} \,/\, \mathrm{(CH_3)_2C{=}O}$$

In using secondary alcoholates the ratio is approximately 1:1. Young and coworkers report the following on the comparison of aluminum isopropylate, and aluminum ethylate.

		Ethylate	Isopropylate
Butyraldehyde	→ Butyl alcohol	6 per cent	30 per cent
Crotonaldehyde	→ Crotonyl alcohol	28 " "	55 " "

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Lund has used aluminum isopropylate on a long series of aldehydes and ketones.

	Per cent
diethyl ketone to corresponding alcohol	60
di-n-propyl ketone	92
cyclohexanone	95
methyl cyclohexanone	90-95
α-decalone	95
menthone	90
camphor (long time)	100
estrinbenzoate	75
acetophenone	93
dibenzophenone	100
α-naphthyl methyl ketone	95
β-naphthyl methyl ketone	90
fluoronone	89
xanthone	90
benzoin	90

Qualitative reduction was observed for pinacolin, alloxan, diacetone alcohol, dimethylaminobenzophenone, mexoxal ester, and others.

Preparation of the aluminum isopropylate.--Heat to boiling the aluminum and isopropyl alcohol and .2 gram $HgCl_2$, control the evolution of the H_2 by cooling and let stand overnight at 70°.

The reduction.--The acetone is removed as it is formed, thereby causing a complete reaction. This process works well for all ketones and aldehydes except those ketones having strong tendency to enolize, and phenolic ketones and ketonic acids whose aluminum salts are insoluble in isopropyl alcohol. The phenolic ketones may be readily reduced by first changing them to the corresponding methoxy compound.

Nitro ketones.--Reduction runs smoothly

m-nitro acetophenone ⟶ 76 per cent
p-nitro acetophenone reduces easily but recrystallization of product very different.

Unsaturated ketones.--Reduction easy. Isolation of carbinol quite difficult on some due to the ready formation of ethers.

α-Halogen ketones, quickly reduced but carbinols are unstable in air.

phenacyl bromide ⟶ 77 per cent
bromal ⟶ 76 per cent

Reversibility.--Oppenauer reports the dehydrogenation of sterols by the use of $Al(OC(CH_3)_3)_3$. He refluxed the alcoholates and sterol in boiling acetone and benzene solution for several hours. The tertiary butyrate serves only as a carrier for the aluminum,

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the equilibrium being as follows:

Chlorosterol + acetone $\rightleftharpoons$ chlorosterone + isopropyl alcohol

chlorosterol	→	chlorestenone	94 per cent
ergosterol	→	ergostatrienone	60 per cent
dehydroandrosterone	→	androstendione	83 per cent
pregnenolone	→	progesterone	60 per cent

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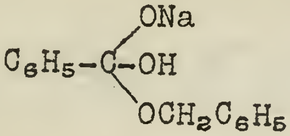
Reported by C. H. McKeever
December 15, 1937.

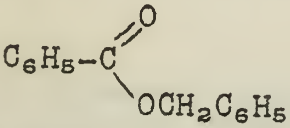
CANNIZZARO REACTION

Tischenko -- University of St. Petersburg
Kharasch and Foy, George Herbert Jones Chemical
Laboratory, Chicago
Davidson and Bogert -- Columbia and Booklyn Colleges
Delepine and Horeau -- Ecole Superieure de Pharmacie
de Paris

Several mechanisms have been suggested for the Cannizzaro reaction. Claisen has suggested an addition compound,



as an intermediate in the Cannizzaro reaction. Tischenko suggested the formation of an ester,



as the intermediate step in the Cannizzaro reaction. He was able to prepare several esters using sodium ethoxide and aluminum ethoxide as catalysts.

Willstater and Haber suggested that the Cannizzaro reaction had a chain mechanism catalyzed by heavy metal ions. Kharasch and Foy have shown this was due to peroxides and that the Cannizzaro reaction did not take place in the absence of peroxides even if ferric ions were present.

Davidson and Bogert have shown that a crossed Cannizzaro reaction occurs when an aromatic aldehyde is treated with formaldehyde. The aromatic alcohol and formic acid are formed almost exclusively. This has been successfully used in the preparation of anisyl, piperonyl and veratryl alcohols.

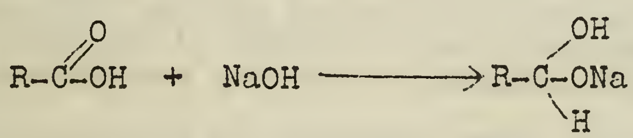
Delepine and Horeau have found that the Cannizzaro reaction will take place in the presence of Raney nickel in a half normal sodium hydroxide solution at ordinary temperatures. Within an hour the reaction was almost complete in the presence of nickel, while in the presence of alkalies alone it was only fifty per cent complete in thirty hours. The following reactions were obtained:

formaldehyde ⟶ methyl alcohol + formic acid
butyraldehyde ⟶ *n*-butyl alcohol + butyric acid
benzaldehyde ⟶ benzyl alcohol + benzoic acid
galactose ⟶ dulcitol + galactonic acid
glucose ⟶ sorbitol + gluconic acid
arabinose ⟶ arabitol + arabonic acid

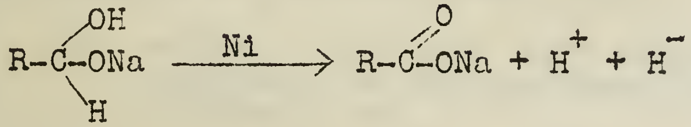
Usually when aldohexoses are treated with alkalies the solution yellows. Lobry de Bruyn and A. von Ekenstein have shown that the aldohexoses are converted into isomeric aldoses and ketoses.

When treated as above with a catalyst the solution of these aldoses remained colorless and no isomerization was observed.

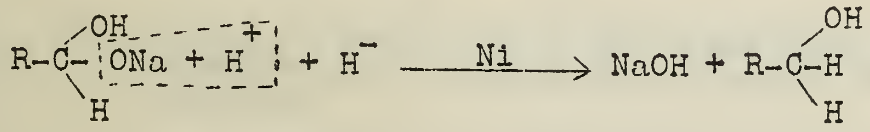
The authors have suggested the following mechanism when nickel is used:

(1) 

$$\mathrm{R{-}\overset{O}{\overset{/\!/}{C}}{-}OH + NaOH \longrightarrow R{-}\underset{H}{\overset{OH}{C}}{-}ONa}$$

(2) 

$$\mathrm{R{-}\underset{H}{\overset{OH}{C}}{-}ONa \xrightarrow{Ni} R{-}\overset{O}{\overset{/\!/}{C}}{-}ONa + H^+ + H^-}$$

(3) 

$$\mathrm{R{-}\underset{H}{\overset{OH}{C}}{-}\boxed{ONa + H^+} + H^- \xrightarrow{Ni} NaOH + R{-}\underset{H}{\overset{OH}{C}}{-}H}$$

If platinum is used in place of nickel the hydrogen is freed so rapidly that instead of reducing another molecule of aldehyde the following reaction occurs:

(4) $\mathrm{H^+ + H^- \longrightarrow H_2}$

If a substance that is more easily reduced than the aldehyde is added to the mixture of platinum, sodium hydroxide and aldehyde the added substance will be reduced. In this way crotonic acid, cinnamic acid and acetonitrile were reduced to butyric acid, phenyl propionic acid and ethylamine, respectively.

In support of the above theory Müller has shown that on electrolyzing an alkaline formaldehyde solution equal amounts of hydrogen were formed at the anode and cathode.

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Reported by Gerald F. Grillot
December 15, 1937.

HYDROGENATION OF QUATERNARY AMMONIUM COMPOUNDS

Herman Emde) _ Pharmaceutical-Chemical Institute of
Herbert Kull) the University of Königsburg, Prussia.

Emde and Kull have investigated the effect of structure upon the stability of the carbon-nitrogen bond. This is a summary of their findings in regard to the hydrogenation of certain exhaustively methylated quaternary ammonium compounds.

Two methods of reduction were used:

A. Action of five per cent sodium amalgam on aqueous solutions of the quaternary salts (chlorides or iodides), and

B. Catalytic reduction of the quaternary salt with hydrogen under atmospheric pressure using as catalysts

  I. Pd-$BaSO_4$ in glacial acetic acid buffered with sodium acetate,
  II. Pd-$BaSO_4$ in aqueous solution,
  III. PtO_2-Pt in glacial acetic acid buffered with sodium acetate,
  IV. PtO_2-Pt in aqueous solution.

The possible degradation reactions in method "A" are several in number:

(1) The quaternary salt may undergo a Hofmann degradation if this is possible under the mild conditions.
(2) A carbon-nitrogen bond may be hydrogenated.
(3) The quaternary compound may be inert.

With method "B", these possibilities exist:

(1) A carbon-nitrogen bond may be hydrogenated.
(2) A benzene nucleus or other point of unsaturation may be hydrogenated.
(3) Both 1 and 2 may occur, either simultaneously or sequentially.
(4) The quaternary compound may be inert.

The results obtained are summarized below. In most cases, homologs and analogs behave similarly. In all cases the groups on the nitrogen except those indicated are methyl. Only the <u>primary</u> reaction products are given; secondary hydrogenations take place normally.

1. Quaternary allyl salts were inert to sodium amalgam, but split with PtO_2-Pt in glacial acetic acid or in water to propylene and NMe_3:

$$CH_2{=}CHCH_2NMe_3I \xrightarrow{H_2} CH_2{=}CHCH_3 + NMe_3HI$$

2. Quaternary aniline salts were inert to sodium amalgam, but in the presence of PtO_2-Pt split to benzene and NMe_3:

$$C_6H_5NMe_3I \xrightarrow{H_2} C_6H_6 + NMe_3HI$$

Certain substituted aniline derivatives, however, easily hyhydrogenated with sodium amalgam to NMe_3 and the corresponding hydrocarbon.

3. Quaternary benzyl salts hydrogenated both with sodium amalgam and in the presence of PtO_2-Pt to toluene and NMe_3:

$$C_6H_5CH_2NMe_3Cl \xrightarrow{H_2} C_6H_5CH_3 + NMe_3HCl$$

4. Quaternary phenylethyl salts were inert in the presence of both Pd-$BaSO_4$ and PtO_2-Pt. Treatment with sodium amalgam, however, resulted in a Hofmann degradation to styrene:

$$C_6H_5CH_2CH_2NMe_3Cl \xrightarrow[(NaHg)]{NaOH} C_6H_5CH{:}CH_2 + NMe_3 + H_2O + NaCl$$

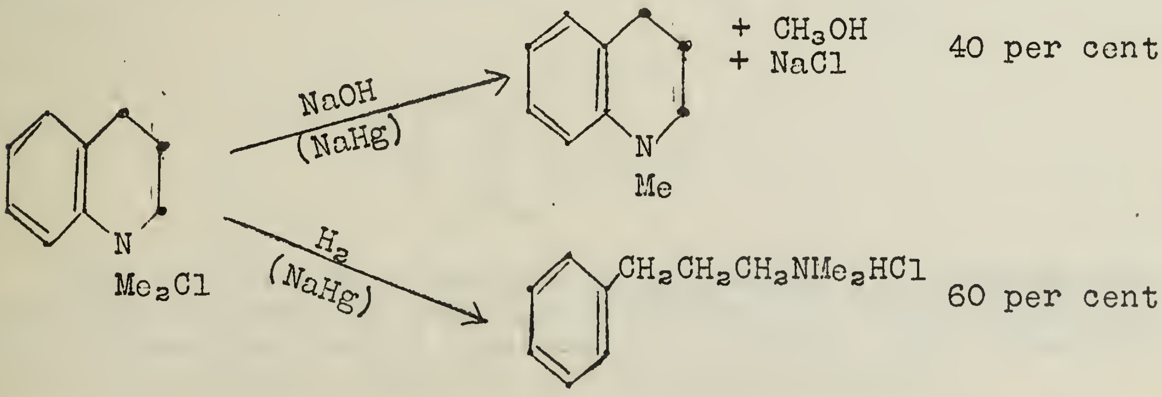
5. Quaternary phenylpropyl (and higher alkyl) salts were inert both to sodium amalgam and to catalytic hydrogenation.

6. Quaternary cinnamyl salts hydrogenated both with sodium amalgam and in the presence of Pd and Pt catalysts to α-phenyl propylene and NMe_3:

$$C_6H_5CH{:}CH_2CH_2NMe_3Cl \xrightarrow{H_2} C_6H_5CH{:}CH_2CH_3 + NMe_3HCl$$

7. Quaternary piperidinium salts were inert both to the action of sodium amalgam and to catalytic hydrogenation.

8. Quaternary tetrahydroquinolinium salts with sodium amalgam underwent both a Hofmann degradation to cairoline and a hydrogenation to phenylpropyldimethylamine:



Certain substituents caused one or the other reaction to predominate to the exclusion of the other. In the presence of PtO_2-Pt only the hydrogenation reaction took place.

[illegible] Quaternary [illegible]

[illegible]

[illegible]

[illegible] Quaternary [illegible] in the presence of [illegible]

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[illegible] Quaternary [illegible] in the presence of [illegible]

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[illegible] Quaternary [illegible]

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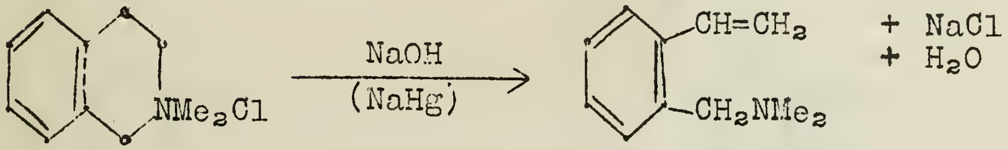
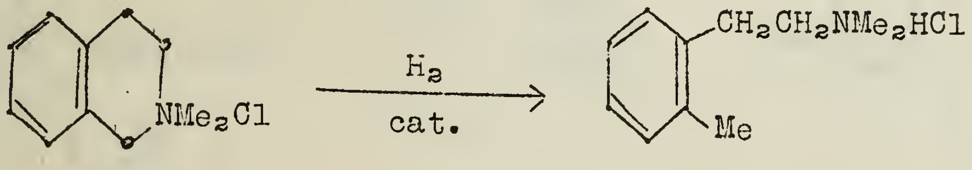
9. Quaternary tetrahydroisoquinolinium salts with sodium amalgam underwent a Hofmann degradation to o-vinylbenzyldimethylamine:



With both Pd and Pt catalysts, a remarkable cleavage of the ring between the 1-2 positions resulted:

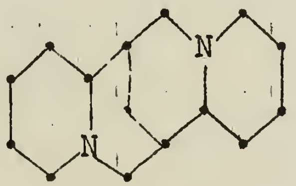


Quaternary tetrahydroisoquinolinium salts carrying a benzyl group on the number one carbon atom underwent this 1-2 cleavage with both sodium amalgam and catalytic hydrogenation.

10. Quaternary salts of certain bicyclo nitrogen compounds cleaved to form monocyclic ten-membered nitrogen rings; (for an example, see the case of corydaline, below).

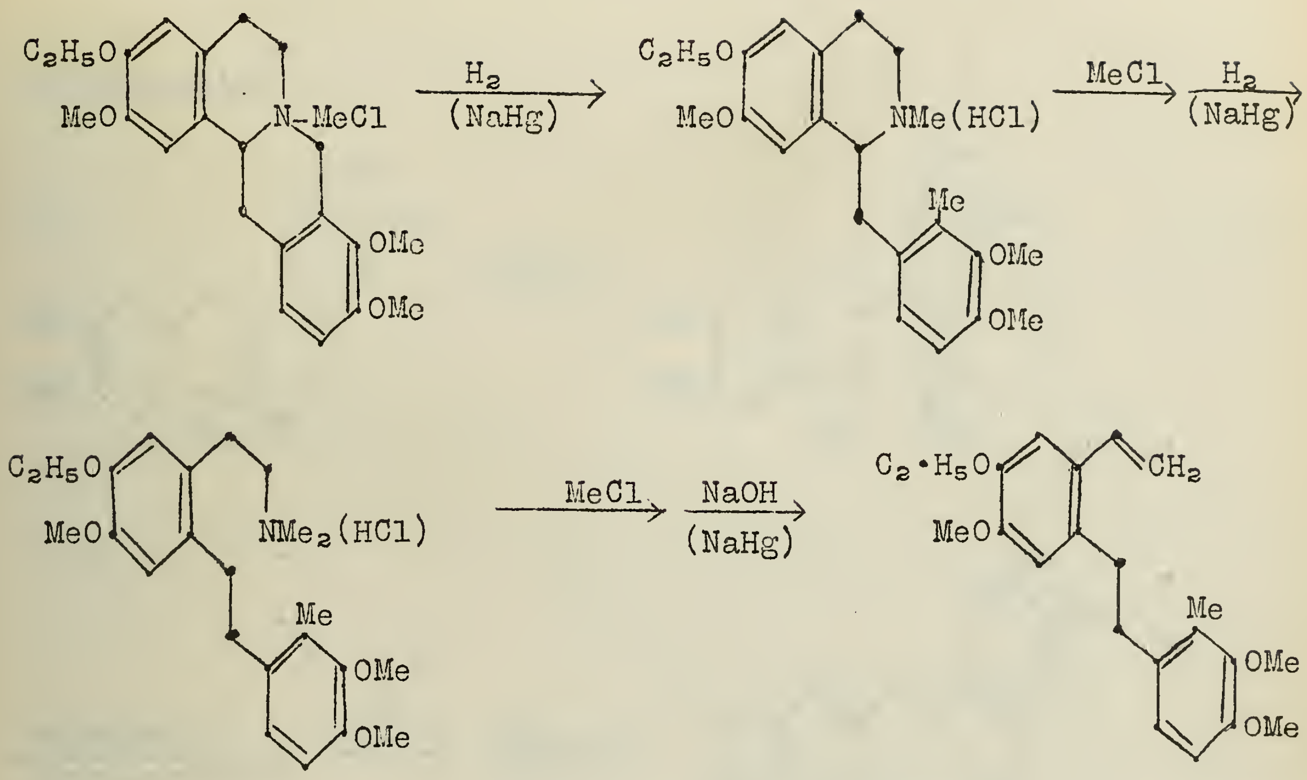
11. Certain alkaloids behave as derivatives of some one of the types outlined above. (For examples, see below).

12. Alkaloids so constituted that through degradation no phenyl group can stand α- or β- to the nitrogen atom are inert to sodium amalgam. For example, sparteine:

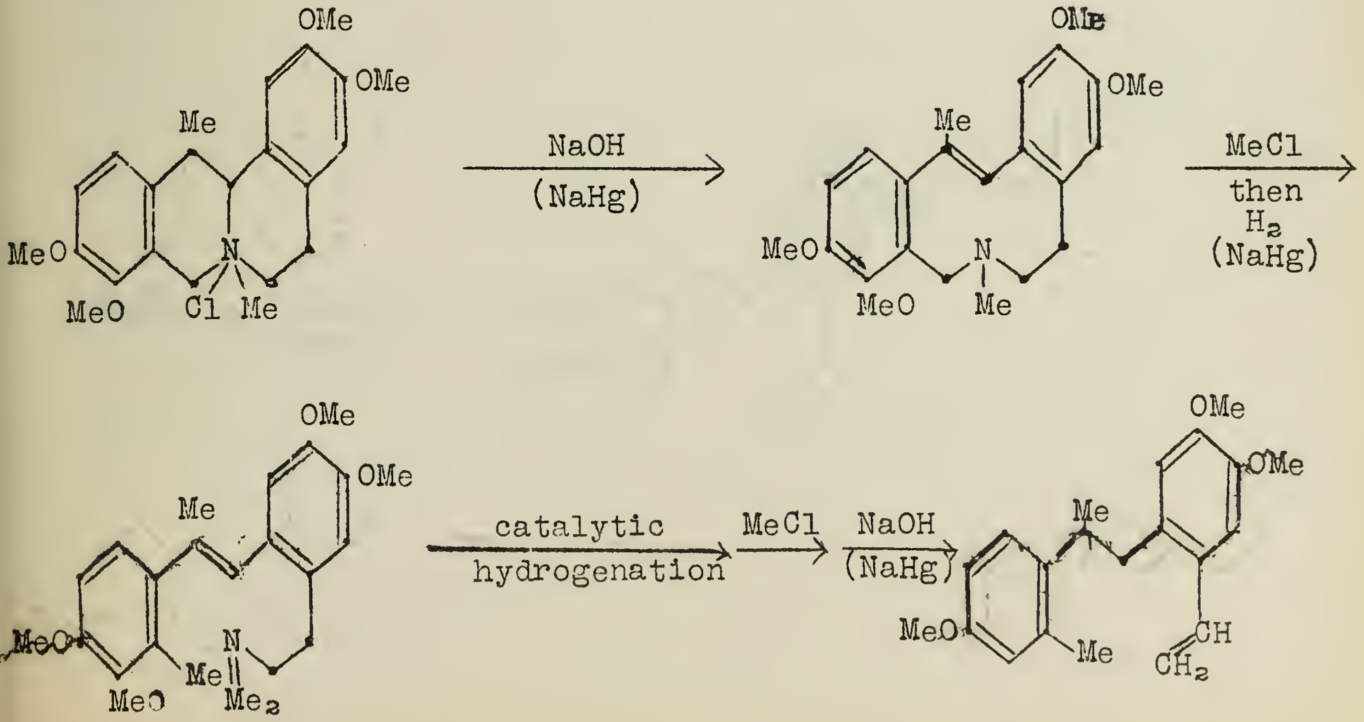


Ende and Kull have applied these methods to the degradation of alkaloids. Because of the mild conditions, no rearrangements occur, and nitrogen-free carbon residues are obtained. The degradation schemes for several alkaloids are presented below.

Jatrorrhizine



Corydaline



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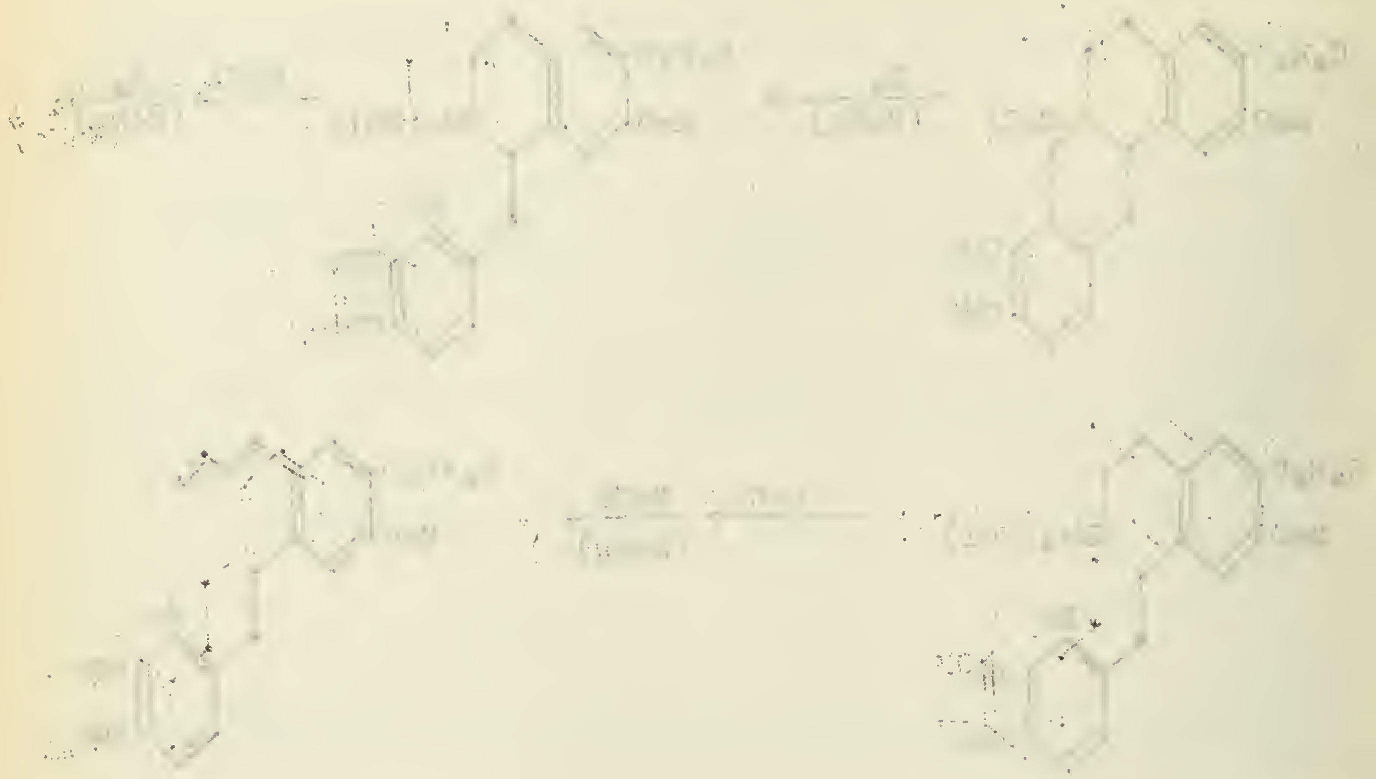

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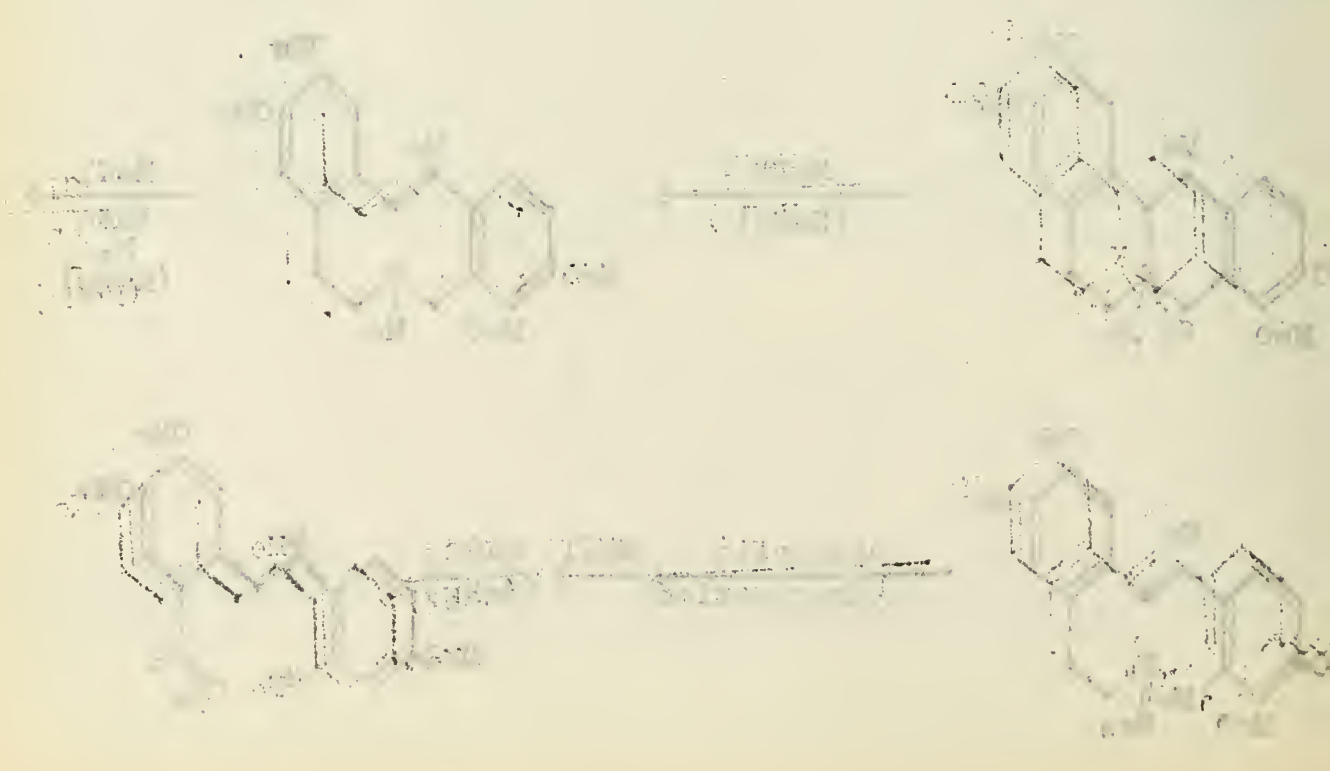
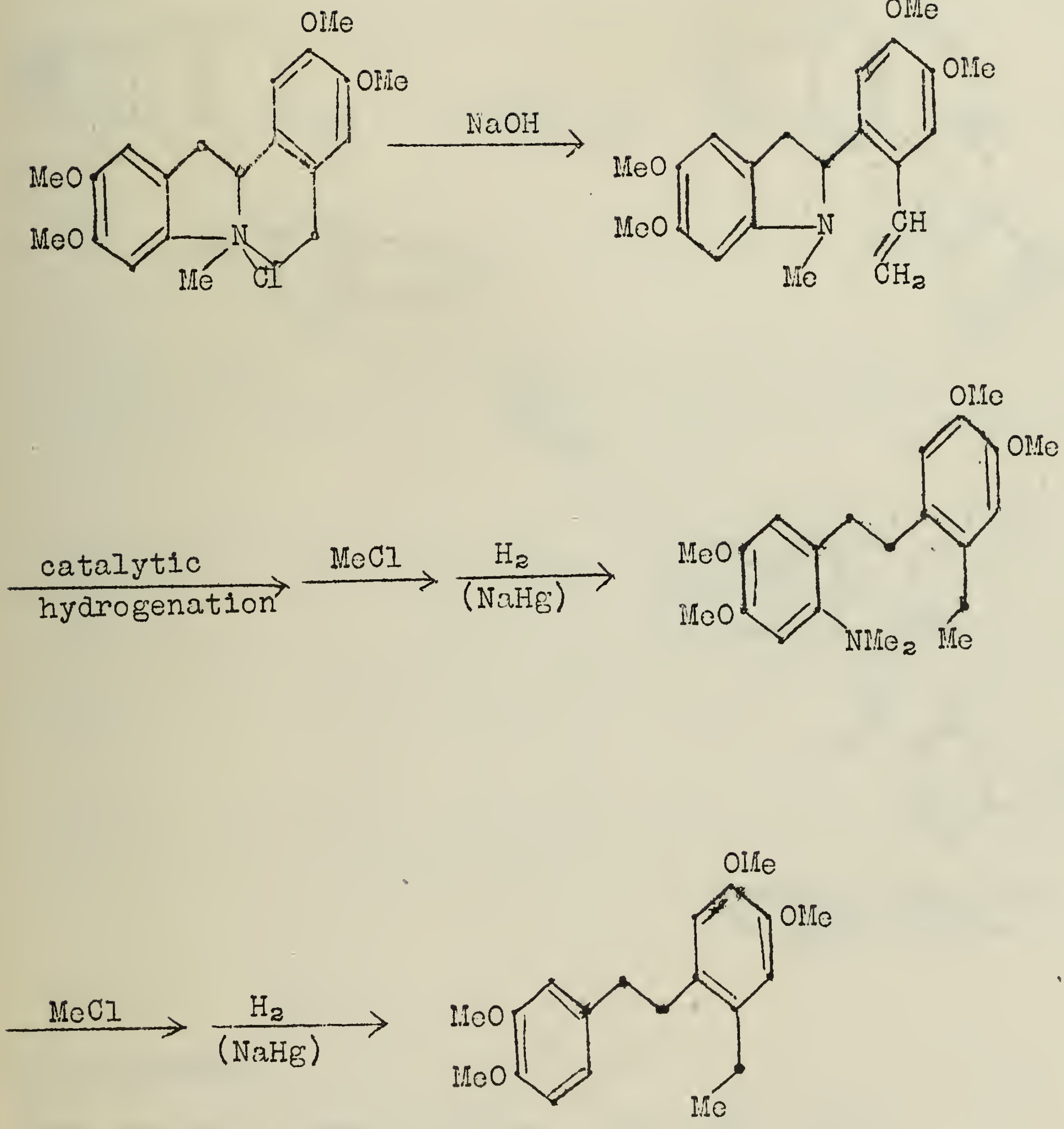


Laudanolosine



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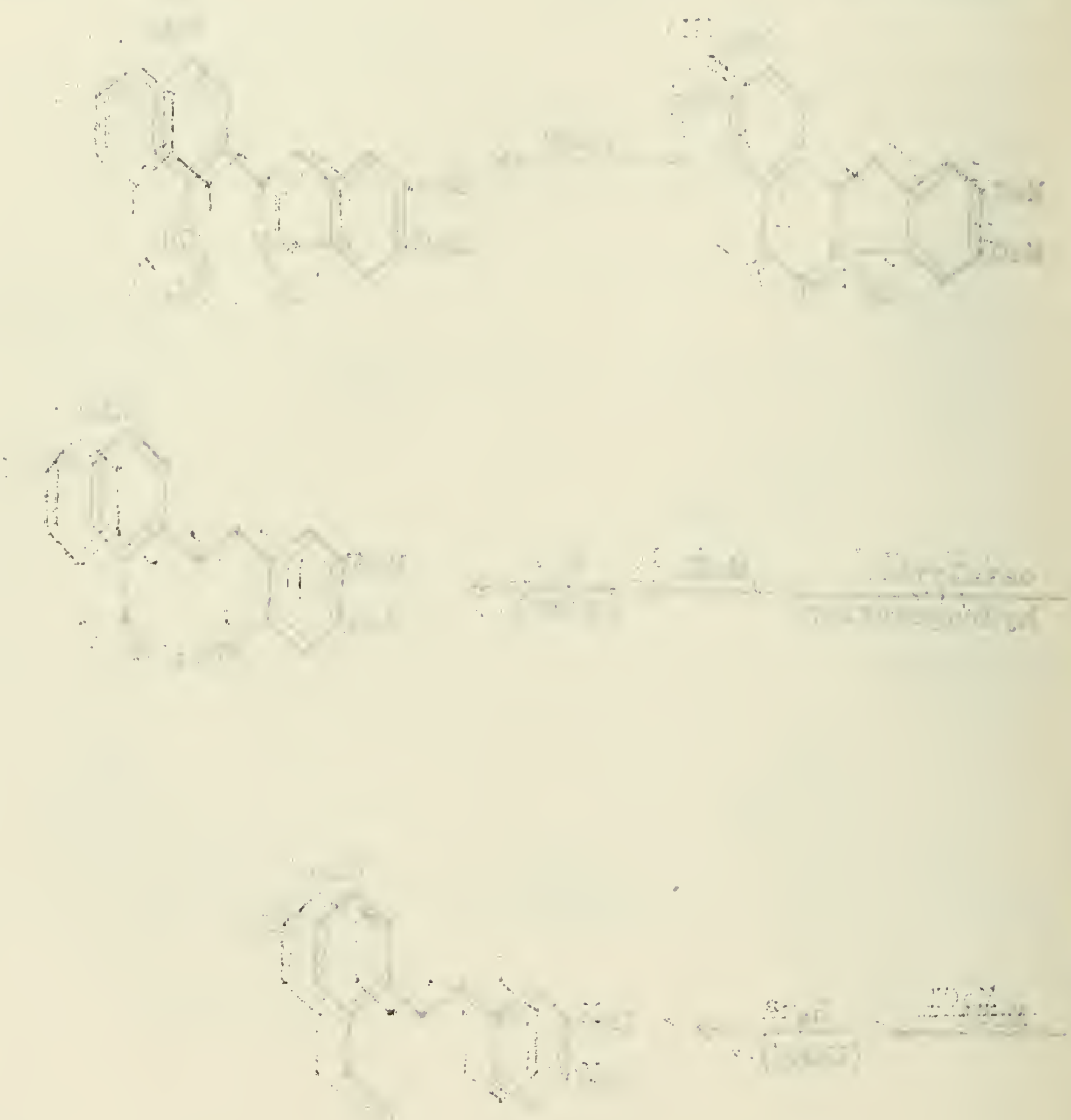
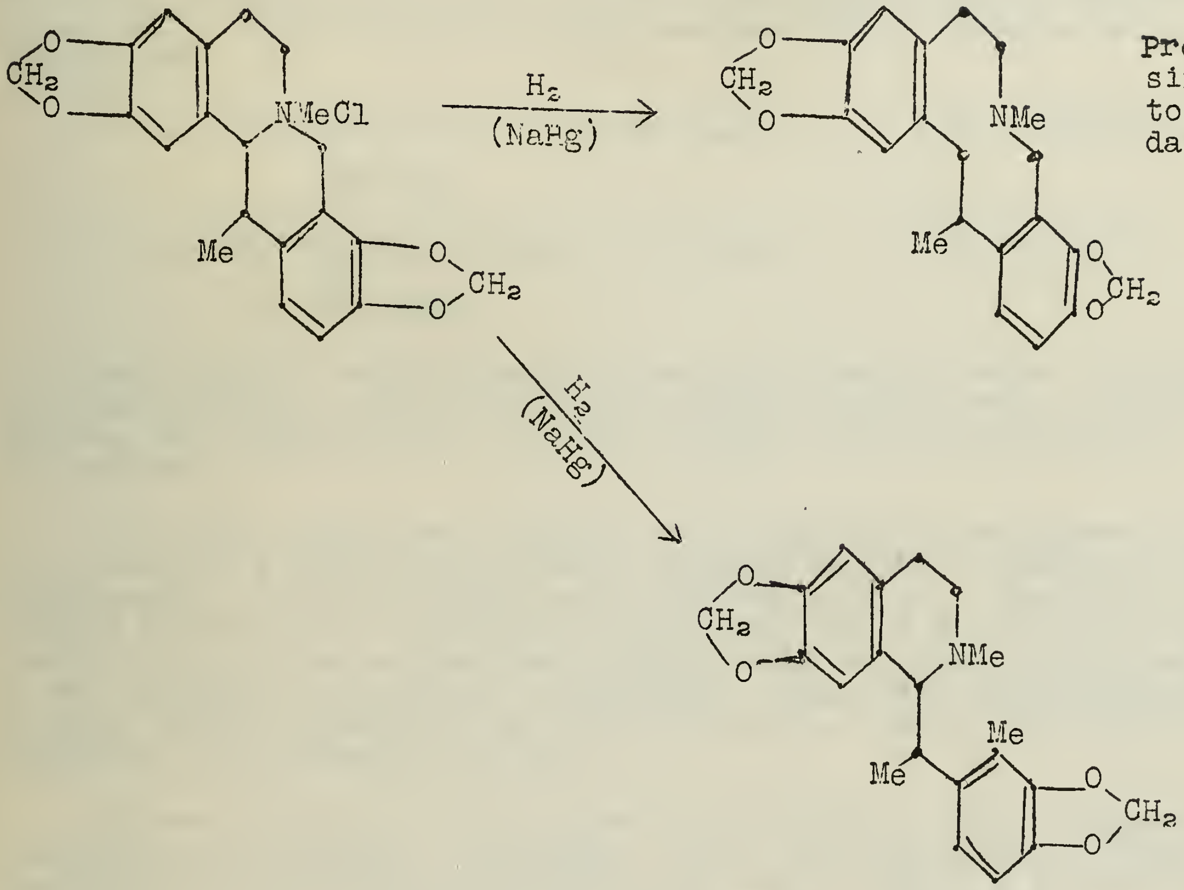


Corycavine, unusual because it splits two ways:



Proceeds similarly to corydaline

Proceeds similarly to jatrorrhizine

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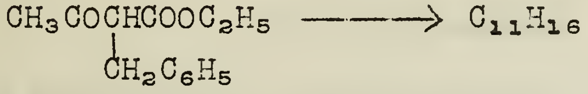
Emde and Kull, Arch. d. Pharm., 274, 173 (1936).

Reported by L. J. Dankert
December 22, 1937.

THE TAFEL REARRANGEMENT

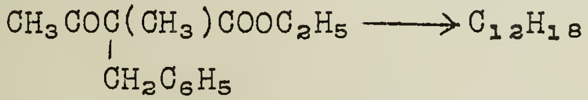
Julius Tafel -- Chemical Institute, University of Würzburg
Hans Stenzl -- Anstalt für anorganische Chemie, Basel
Fr. Fichter -- Anstalt für anorganische Chemie, Basel

From 1900 to 1912, Tafel worked on the electrolytic reduction of organic compounds in alcohol-sulfuric solution, using a lead cathode. During the course of his investigations, he reduced α-benzyl acetoacetic ester (I), and α,α-methyl benzyl acetoacetic ester (II), and obtained the hydrocarbons whose formulas are indicated.

I. 

$$CH_3CO\underset{CH_2C_6H_5}{\underset{|}{C}}HCOOC_2H_5 \longrightarrow C_{11}H_{16}$$

B.P. 203-204°C.

II. 

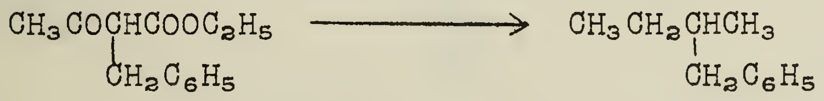
$$CH_3CO\underset{CH_2C_6H_5}{\underset{|}{C}}(CH_3)COOC_2H_5 \longrightarrow C_{12}H_{18}$$

B.P. 214.5°C.

Although certain substituted benzene hydrocarbons were eliminated as possibilities for I and II by reason of differences in boiling points, the compositions of I and II were not satisfactorily determined.

In 1934, Stenzl and Fichter reduced α-benzyl acetoacetic ester, and obtained a hydrocarbon which corresponded identically to the hydrocarbon (I) which Tafel had prepared earlier. They did not employ electrolytic reduction, but simply added a powdered lead-sodium alloy to an alcoholic-sulfuric acid solution of the ester. I was obtained in a 28 per cent yield. They then prepared n-amyl benzene by the reduction of n-valerophenone, and found that it was identical in properties with I.

It was realized by these two investigators that, inasmuch as reduction of α-benzyl acetoacetic ester did not yield a benzene derivative containing a branched side chain (III), a rearrangement must have occurred during the course of the reduction.

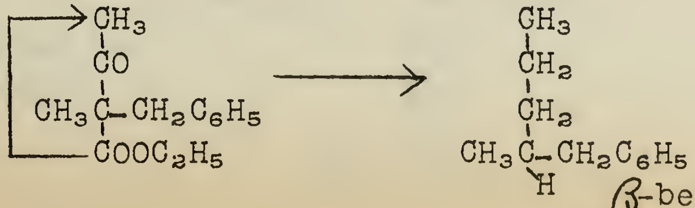


$$CH_3CO\underset{CH_2C_6H_5}{\underset{|}{C}}HCOOC_2H_5 \longrightarrow CH_3CH_2\underset{CH_2C_6H_5}{\underset{|}{C}}HCH_3$$

(III)

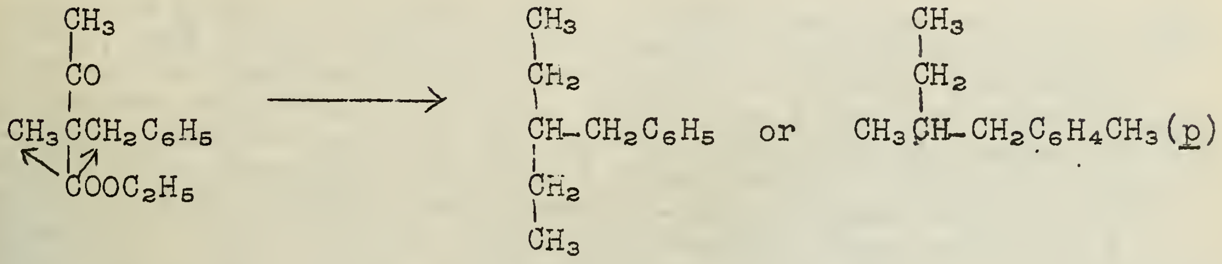
They studied the reduction of α,α-methyl benzyl acetoacetic ester, and obtained the hydrocarbon (II), which also corresponded identically to the hydrocarbon obtained by Tafel under similar conditions, and proposed five mechanisms for the rearrangement.

(a) Wandering of the methyl group, newly formed from the carboxyl group on reduction, to the γ-position of the aceto-acetic ester.



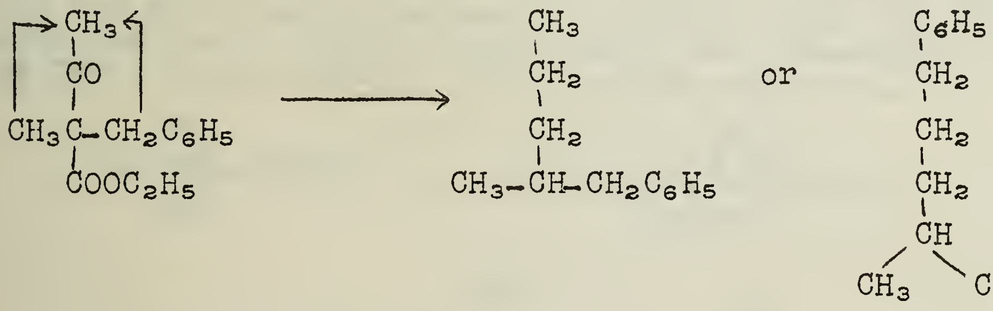
β-benzyl pentane

(b) Wandering of the newly formed methyl group to one of the alkyl or aralkyl groups on the α-carbon.



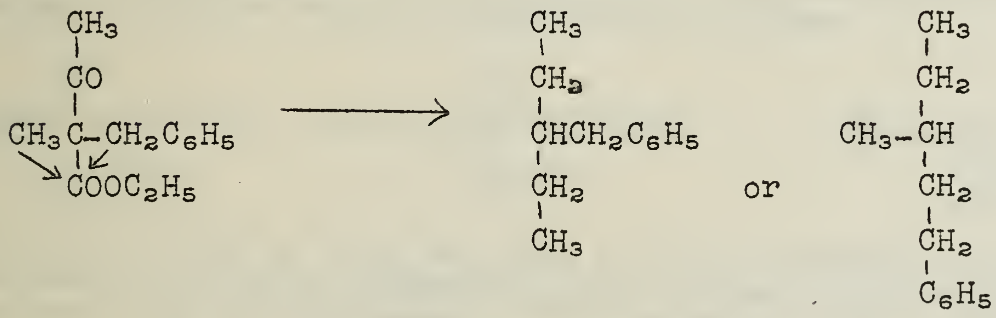
γ-benzyl pentane

(c) Wandering of a substituent on the α-carbon to the γ-position.



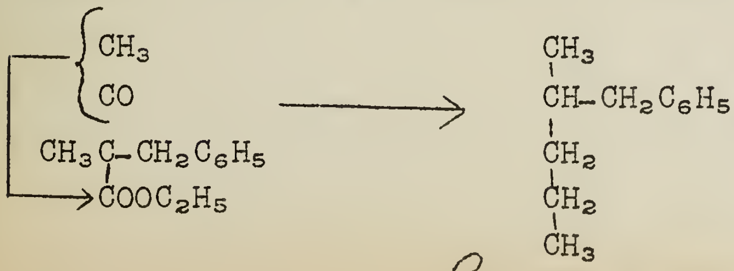
β-benzyl pentane   isohexyl benzene

(d) Wandering of a substituent on the α-carbon to the newly formed methyl group.



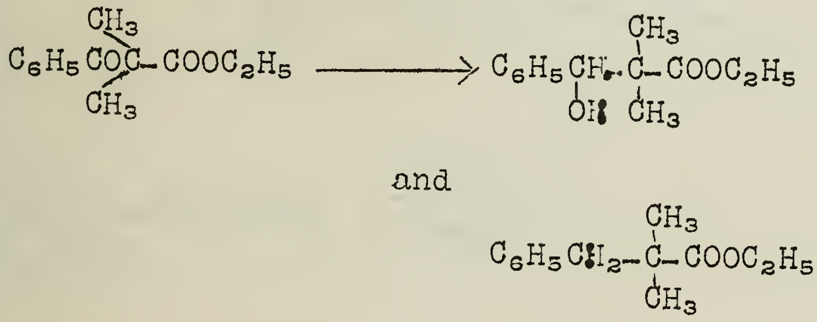
γ-benzyl pentane   γ-methyl amyl benzene

(e) Wandering of the acetyl group to the reduced carboxyl group, followed by reduction of the carbonyl group.



β-benzyl pentane

Mechanism b did not occur, since γ-benzyl pentane boils at 216.5-217°C., and in the reduction of α-benzyl acetoacetic ester, the hydrocarbon isolated did not consist of a benzene derivative having two substituent groups. Mechanism c did not occur, since β-benzyl pentane boils at 203-207°C., and isohexyl benzene boils at 216.4°C. Mechanism d did not occur, since γ-benzyl pentane boils at 216.5-217°C., and γ-methyl-n-amyl benzene boils at 219-220°C. The only two remaining possibilities were a and e. Since the wandering of a methyl group at the moment of its formation from an α-carbon to a γ-carbon has no analogy, it was assumed that e afforded the best explanation of the rearrangement. This mechanism was also supported by the fact that α,α-dimethyl-benzoyl acetic ester on reduction yielded no rearranged products, but instead yielded α,α-dimethyl-β,β-hydroxyphenyl propionic ester (IV) and α,α-dimethyl-β-phenyl propionic acid (V). Thus they concluded that a labile acetyl group was necessary, in order that the Tafel rearrangement occurs during reduction.



$$C_6H_5CO\underset{CH_3}{\overset{CH_3}{C}}-COOC_2H_5 \longrightarrow C_6H_5\underset{OH}{CH}-\underset{CH_3}{\overset{CH_3}{C}}-COOC_2H_5 \quad (IV)$$

and

$$C_6H_5CH_2-\underset{CH_3}{\overset{CH_3}{C}}-COOC_2H_5 \quad (V)$$

The rearrangement of α,α-methyl benzyl acetoacetic ester during reduction was now explained as follows:

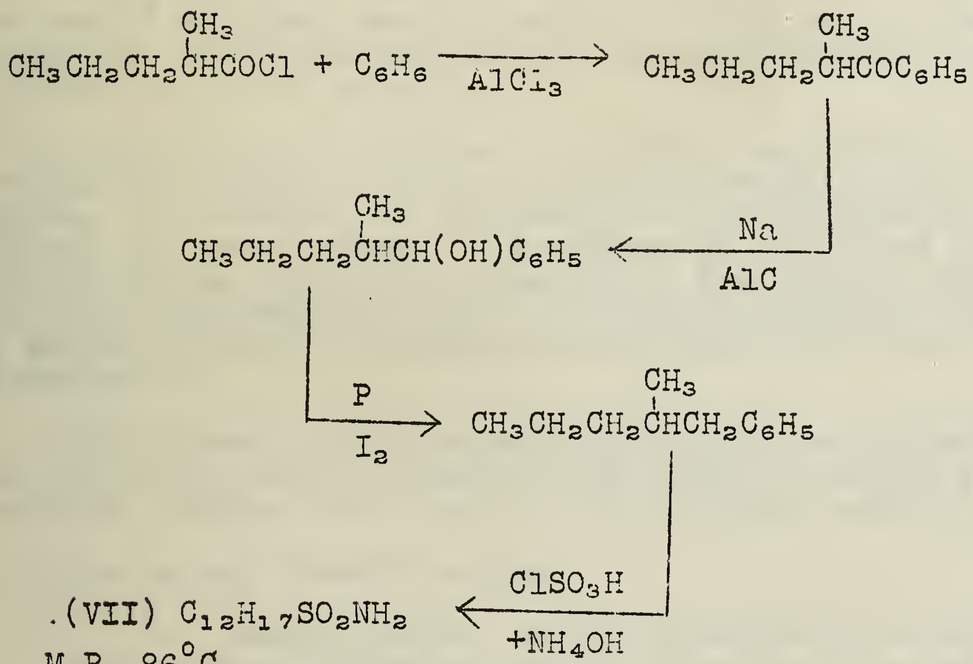
$$CH_3CO\underset{CH_2C_6H_5}{\overset{CH_3}{C}}-COOC_2H_5 \longrightarrow \underset{CH_2C_6H_5}{\overset{CH_3}{CH}}-CH_2CH_2CH_3$$

β-benzyl pentane
(II)
B.P. 214°C.

The sulfonamide of this compound (VI) was prepared ($C_{12}H_{17}SO_2NH_2$) and melted at 86°C. β-Methyl-n-amyl benzene was prepared as follows, and its sulfonamide (VII) melted at 86°C. Mixed melting points of VI and VII showed no depression.

$$\text{(II)}\quad C_{12}H_{18} \xrightarrow{ClSO_3H} C_{12}H_{17}SO_2Cl \xrightarrow{NH_4OH} C_{12}H_{17}SO_2NH_2\ \text{(VI)}$$

M.P. 86°C.



$$CH_3CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCOCl + C_6H_6 \xrightarrow[AlCl_3]{} CH_3CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCOC_6H_5$$

$$CH_3CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCOC_6H_5 \xrightarrow[AlC]{Na} CH_3CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH(OH)C_6H_5$$

$$CH_3CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH(OH)C_6H_5 \xrightarrow[I_2]{P} CH_3CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_2C_6H_5$$

$$CH_3CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_2C_6H_5 \xrightarrow[+NH_4OH]{ClSO_3H} \text{(VII)}\ C_{12}H_{17}SO_2NH_2$$

M.P. 86°C.

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Tafel, Ber., 33, 2209 (1900); 40, 3313 (1907); 45, 437 (1912).
Stenzl and Fichter, Helv. Chim. Acta, 17, 669 (1934); 19, 392 (1936); 20, 846 (1937).

Reported by C. F. Segal
December 22, 1937.

STERIC ORIENTATION IN SUBSTITUTION REACTIONS

Ingold and Hughes, University College, London
Olson, California (Berkeley)
Hammett, Columbia

A common starting point for most of the theories attempting to summarize and generalize the empirical observations of organic chemistry has been the hypotheses 1) that it is possible to assign to each functional group a certain effect and 2) that rules may be found for combining the effects of the functional groups into the properties of the molecule.

Ingold considered that the individual effects could be electrical in nature: charges of varying magnitude and either sign. Series of experimental observations ("The Nature of the Alternating Effect in Carbon Chains," "Influence of Poles and Polar Linkings of the Course Pursued by Elimination Reactions," etc.) strengthened in him this viewpoint and in 1934 he published in Chemical Reviews a paper entitled "Principles of an Electronic Theory of Organic Reactions."

The theory may be summarized briefly as follows: Contributing to the polar effect of each group Ingold recognizes four subsidiary effects, the result of two separate subdivisions:

I. Electrical Classification

1. "Polarization" is the consequence of a permanently unsymmetrical electron bond. It occurs, for example, in the carbon-chlorine bond.

2. "Polarizability" is a deformation of the bond under the influence of an external agent. Thus a carbon-carbon bond is polarizable by the introduction of a halogen atom nearby as in

$$CH_3 \longrightarrow CH_2 \longrightarrow CH_2 \longrightarrow Cl$$

II. Electronic Mechanism

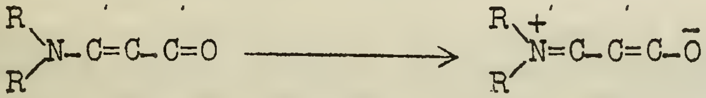
1. In the "general inductive" effect the positions of the bond electrons are highly localized as in the examples above.

2. In the "tautomeric" effect bond electrons move through distances comparable to interatomic distances.

Combination of these two subdivisions gives rise to the following table:

Electronic Mechanism	Electrical Classification	
	Polarization	Polarizability
General inductive	"Induction"	"Inductomerism"
Tautomeric	"Mesomerism"	"Electromerism"

Induction is a polarization in the ordinary sense. Inductomerism is a polarizability in the ordinary sense. Mesomerism is Ingold's term for resonance. Electromerism is a bond migration in multiple-bonded systems under the influence of an external agent:



Each of these effects had a predecessor in the theories of earlier workers; Ingold's contribution consists in their collection into a logically complete theory.

These effects of the individual groups may be combined into the properties of the molecule by Ingold's further hypothesis of transmission through the intervening carbon chain without change in sign but with diminution of magnitude, becoming practically negligible at the third carbon of a saturated chain.

Some of the inductive effects assigned by Ingold follow:

Electron Repulsion

$-\bar{N}R > -\bar{O}$

$-\bar{O} > -\bar{S} > -\bar{S}e$

$(CH_3)_3C- > (CH_3)_2CH- > CH_3CH_2- > CH_3-$

Electron Attraction

$-\overset{+}{O}R_2 > -\overset{+}{N}R_3$

$-\overset{+}{N}R_3 > -\overset{+}{P}R_3 > -\overset{+}{As}R_3 > -\overset{+}{Sb}R_3$

$-\overset{+}{O}R_2 > -\overset{+}{S}R_2 > -\overset{+}{Se}R_2 > -\overset{+}{Te}R_2$

$-\overset{+}{N}R_3 > -\overset{+-}{N}\bar{O}_2$; $-\overset{+-}{\overset{+-}{S}}\bar{O}_2R > -\overset{+-}{S}\bar{O}R$; $-\overset{+-}{\overset{+-}{S}}\bar{O}_2R > -\overset{+-}{\overset{+=}{S}}\bar{O}_3$

$-\overset{+}{N}R_3 > -NR_2$; $-\overset{+}{O}R_2 > -OR$; $-\overset{+}{S}R_2 > -SR$

$-F > -OR > -NR_2$ ($> -CR_3$)

$-F > -Cl > -Br > -I$

$=O > =NR > =CR_2$; $\equiv N > \equiv CR$

$=O > -OR$; $\equiv N > =NR > -NR_2$

$-C\equiv CR > -CR=CR_2$ ($> -CR_2-CR_3$)

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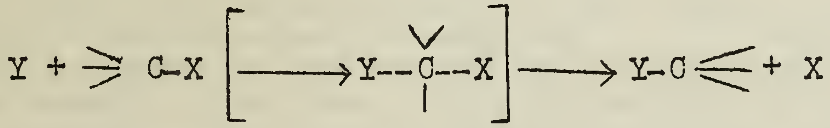
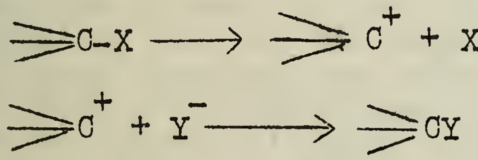
Two observations should be noted: (1) Alkyl groups are not so much polarized as polarizable: they are electron-repellant because, for example, the -COOH group is able to attract electrons more easily from R than from H in R-COOH and H-COOH. (2) Unsaturated hydrocarbon radicals behave as electron attractors, though in aryl radicals the general inductive effect is further complicated by tautomeric effects (resonance).

Another contribution of the theory is the classification of every reagent, acid or base, oxidation or reduction, substitution or addition, into one of two classes, nucleophilic and electrophilic, according as it donates or accepts electrons.

It was while searching for kinetic measurements in support of this theory that Hughes and Ingold came upon the experimental evidence which led to their second theory, on substitution mechanism, and a corollary, on solvent effect. Their view of substitution mechanism is this: Two mechanisms are operable. The first is bimolecular, involving simultaneous addition of the substituting reagent and dissociation of the substituted group:



The second is unimolecular and involves a dissociation of the substituted group followed by addition of the substituting reagent:



(slow, rate-controlling)

(rapid)

These mechanisms will apply to any of four possible electrical types of substitution:

(1) $Y^- + AlkX \longrightarrow AlkY + X^-$

e.g. $OH^- + AlkCl \longrightarrow AlkOH + Cl^-$

(2) $Y + AlkX \longrightarrow [AlkY]^+ + X^-$

e.g. $NH_3 + AlkCl \longrightarrow Alk\overset{+}{N}H_3 + Cl^-$

(3) $Y^- + [AlkX]^+ \longrightarrow AlkY + X$

e.g. $OH^- + Alk\overset{+}{N}(CH_3)_3 \longrightarrow AlkOH + (CH_3)_3N$

(4) $Y + [AlkX]^+ \longrightarrow [AlkY]^+ + X$

e.g. $(CH_3)_3N + Alk\overset{+}{S}(CH_3)_2 \longrightarrow Alk\overset{+}{N}(CH_3)_3 + (CH_3)_2S$

(no reaction of this type has yet been observed)

In a given case which of the two mechanisms will occur depends on:

(1) The polar contributions of the other substituents at the seat of substitution. In the reaction

$$R_3C{-}X + OH^- \longrightarrow R_3COH + X^-$$

increasing the electron-repulsive contributions of the R groups favors the unimolecular over the bimolecular reaction.

(2) The polarity of the substituting agent. In the reaction:

$$\overset{+}{\text{AlkNR}_3} + Y^- \longrightarrow \text{AlkY} + \text{NR}_3$$

decreasing the basicity of Y (as by substituting Cl^- for OH^-) favors the unimolecular over the bimolecular reaction.

(3) The nature of the solvent. The more powerfully ionizing the solvent (the higher its dielectric constant) the more is the unimolecular mechanism favored over the bimolecular.

The most important characteristic of the theory is the introduction of a true unimolecular mechanism. A. R. Olson in particular has objected to the concept of a dissociation. Considering, for example, reactions of electrical type 1 (the most extensively studied), Olson has pointed out that the heat of ionization of an alkyl chloride is roughly 160,000 calories whereas the heat of activation for the hydrolysis reaction is of the order of 25,000 calories, and further that the work of separation is done at such short distances that the dielectric constant of the solvent cannot affect it appreciably. Hughes and Ingold attribute the effect to solvation; and no mechanism other than the unimolecular one has been offered which is reconcilable with all of their experimental evidence. Olson has published evidence to show, 1, that solvation cannot account for the 135,000 calorie discrepancy, and 2, that if fugacity is measured rather than concentration, the kinetic data for the first-order hydrolysis of *tert*.-butyl chloride satisfy an equation considered to apply to a second-order mechanism.

Founded upon these basic concepts is Hughes' and Ingold's recent theory of steric orientation in substitution reactions. With Olson they consider that all bimolecular substitutions occur with inversion of configuration. In the unimolecular reactions, however, the steric course is entirely dependent upon the life of the carbon ion. If conditions are such that the ion is very short-lived, the separating cation and anion will not be far apart, the replacing reagent does not have a clear path to the carbon ion except from the opposite face, and substitution with inversion predominates. If the ion is longer-lived, the separating cation and anion will be sufficiently dispersed to have no shielding effect upon each other; the replacing group can then take the vacated place and retention of configuration results. In either case, prolonging the life of the ion (e.g., by decreasing the concentration of the substituting reagent) gives the ion more time to assume its stable planar configuration and increases the amount of racemization. In fact, substitution with retention of

configuration cannot occur unless the ion is abnormally stabilized in its pyramidal structure by such a substituent as the strongly polar carboxylate ion. Evidence is presented for each of the implications of the theory.

It is emphasized once again that the correctness of the theory is dependent on the occurrence of true unimolecular reactions.

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Olson, J. Chem. Phys., I, 418 (1933)
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59, 2644 (1937)
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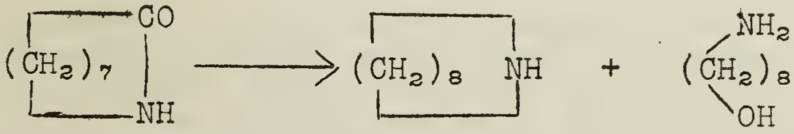
Reported by Hugh Gray
Harry Sutherland
January 5, 1938.

MANY-MEMBERED CYCLIC IMINES

Ruzicka -- Zurich

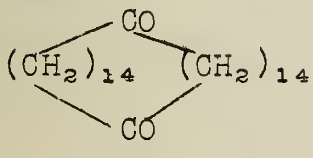
The largest cyclic imine reported in the literature before 1933 was the cycloheptamethylene imine reported by Müller and Bleier, obtained both by reduction of cycloheptanoneisoxime with sodium and alcohol and by condensation of 1,7 dibromoheptane with p-toluenesulfonamide (1 per cent yield).

In 1933, Ruzicka reported the preparation of the nine-membered cyclic imine by the same method (yields <10 per cent). The imine was always accompanied by 1-aminoöctane-8-ol. The cyclic amide (or isoxime) was obtained either by Beckmann rearrangement of the oxime or by the action of hydrazoic acid on the ketone.

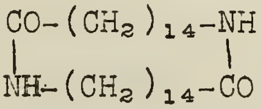


The isoxime was converted to the corresponding thioisoxime by treatment with phosphorous pentasulfide. Reduction of this compound with sodium in alcoholic acetic acid gave a 60 per cent, and electrolytic reduction an 85 per cent yield of cycloöctamethyleneimine. The 16- and 17-membered imines were also made by this process.

The 32-membered diimine was prepared from the diketone but its structure is questionable since cyclotriacontane-1,16-dione (I) may give rise to either (II) or (III) by Beckmann rearrangement of the dioxime. Therefore, the diimine may have the structure given either by (IV) or (V) or may be a mixture of both.



I



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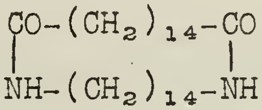

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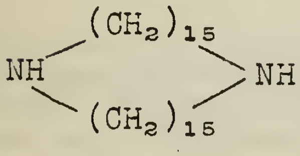

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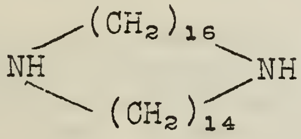
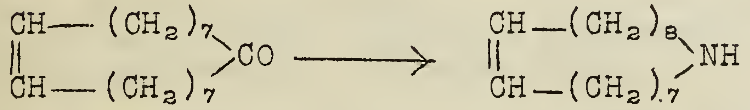


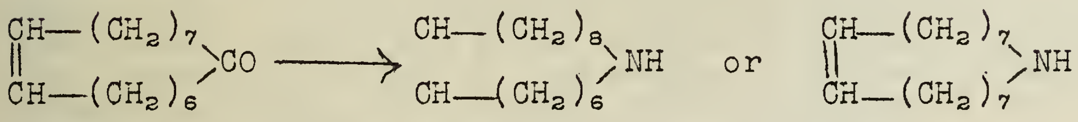
V

In a later publication, the 7-, 8-, 16-, and 18-membered saturated imines as well as the 17- and 18-membered unsaturated compounds from civetone (VI) and norcivetone (VII) were reported. The only possible imine obtained from civetone is

VIII, while norcivetone may give either IX or X. The position of the double bond in the compound obtained was not established.



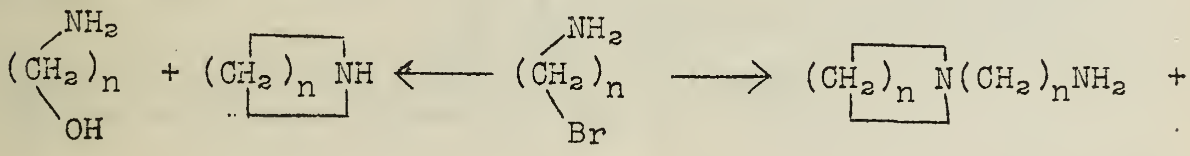
VI VIII

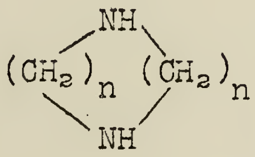


VII IX X

The 3- to 7-membered cyclic imines may be prepared easily by treatment of ω-halogen amines with alkali. Attempts by several workers to prepare larger rings by this method gave poor results, but in 1934 Ruzicka was able to obtain a 50 per cent yield of hexamethyleneimine by heating a solution 0.01 molar in ω-bromohexylamine and 0.1 molal in NaOH at 50° for one and one-half hours.

In the most recent work Ruzicka has studied the preparation of the 12-, 14-, 15-, and 17-membered rings by several days gentle refluxing of dilute alkaline solutions of the bromoalkylamines in 30 mol per cent aqueous isopropyl or ethyl alcohol solution. The imine was accompanied in every case by hydroxyalkylamines as well as dimeric products.





The yield of cyclic imine varied greatly with change in concentration of the amine and alkali but the total yield of the two monomeric products was always 60-70 per cent.

The maximum yields of the pure monomeric imine were 50 per cent cyclohexadecamethyleneimine, 42 per cent cyclopentadecamethyleneimine, 65 per cent cyclotridecamethyleneimine, and less than 5 per cent undecamethyleneimine. Not enough of this latter compound was obtained to determine any of its properties.

The cyclic imines having 3 to 9 and 14 to 18 members have been prepared. The density curve rises to a maximum between the 9- and 14-membered rings and has the same general form as that of the ketones. Several N-methylimines have been prepared and the density curve for these parallels that of the cyclic hydro-

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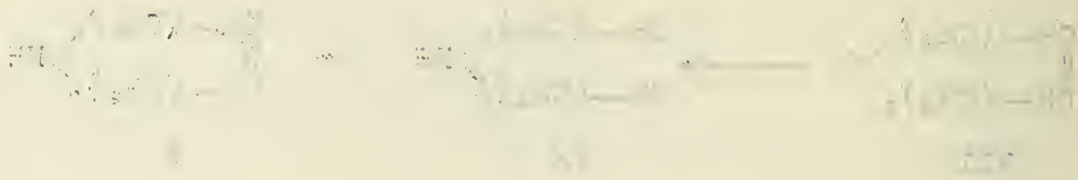

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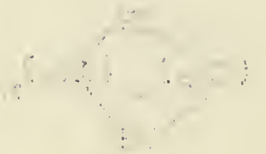

[illegible]

[illegible]

carbons. The melting points of the 14- to 18-membered imines were found to be almost identical with those of the ketones having the same number of carbon atoms.

The variations in odor of the known cyclic imines parallel closely those of the other known series of cyclic compounds. The 9-membered ring still exhibits the characteristic odor of piperidine. In the 14-membered ring, an amine odor is predominant but there is a trace of musk-like odor. This odor is very pronounced in the 15- and reaches a maximum in the 16- and 17-membered rings. The optimum odor is reached at the 17-membered ring in the case of the N-methylimines.

Pentadecamethyleneimine showed a strong local anesthetic action, and a similar but weaker action was observed in the 15- but not in the 17- and 18-membered rings. N-methylpentadecamethyleneimine showed no anesthetic action.

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17, 882 (1934); 18, 659 (1935);
20, 109 (1937).
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Müller and Bleier, Monatsh., 56, 391 (1930).

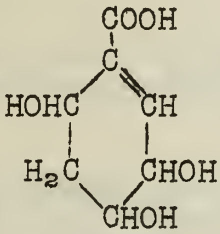
Reported by Wesley Fugate
January 12, 1937.

THE STRUCTURE AND CONFIGURATION OF SHIKIMIC ACID

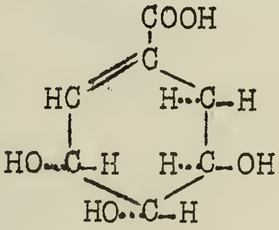
H. O. L. Fischer -- Anstalt für Organische Chemie, Basel
G. Dangschat -- Chemisches Institut der Univ., Berlin

Shikimic acid was first isolated by Eykman (1885) from the leaves of _Illicium religiosum_, poisonous star anise, called "shikimi" by the Japanese. It is present to the remarkable extent of 18 per cent in this plant and is also found in the true star anise, _Illicium verum_.

Eykman showed the compound to be a trihydroxy tetrahydro benzoic acid on the basis of its formation of triacyl esters and its absorption of one mole of hydrogen. On the strength of rather inconclusive evidence--stability of the double bond in the presence of alkalies and formation of _p_-hydroxy benzoic acid on dehydration--he assigned to it the structure:



Eykman had noted a relationship between shikimic acid and quinic acid, the tetrahydroxy pentahydro benzoic acid found in cinchona bark, coffee beans, beet leaves, and many other plants. Having proved the structure and configuration of quinic acid, H. O. L. Fischer employed similar methods to do the same for shikimic acid. On the basis of his experimental results he has assigned to it the following structure and configuration:



(I)

Shikimic acid

This formula is borne out by the following data: The methyl ester of I, upon reduction with one mole of hydrogen ($Pd-BaSO_4$) gave the ester of dihydroshikimic acid (II). This was oxidized with periodic acid to the aldehyde (IIIa) and the aldehyde oxidized to tricarballylic acid (III) with bromine water. The aldehyde was not isolated but was identified by means of the _p_-nitrophenylhydrazone. The reactions:

[illegible]

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[illegible]

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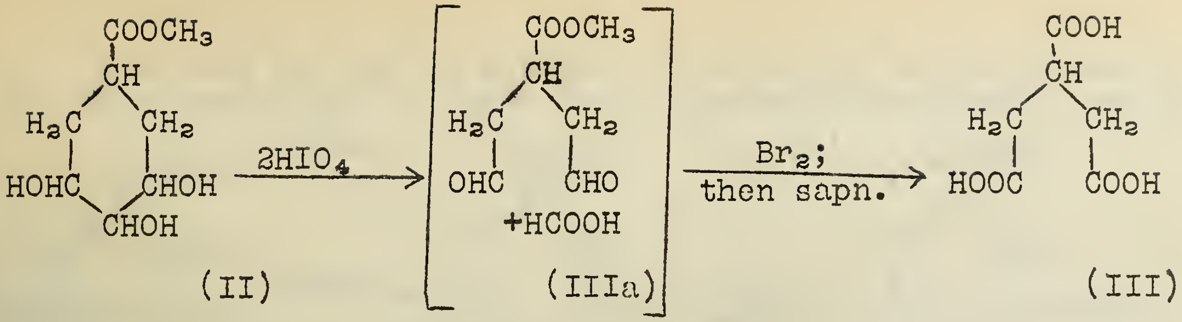
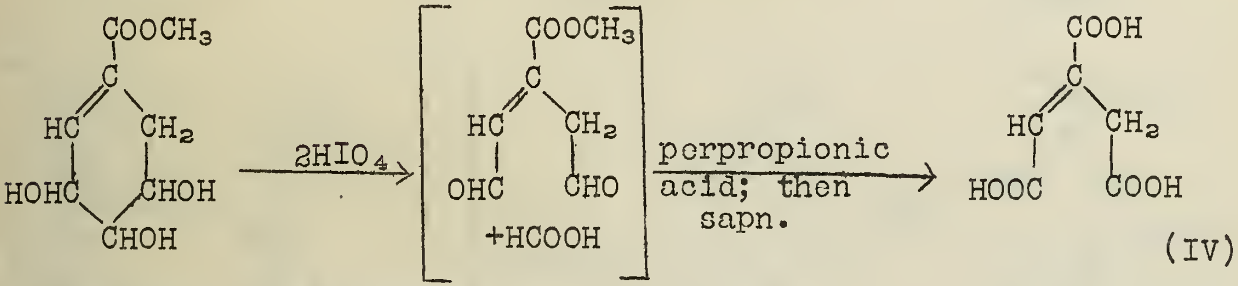
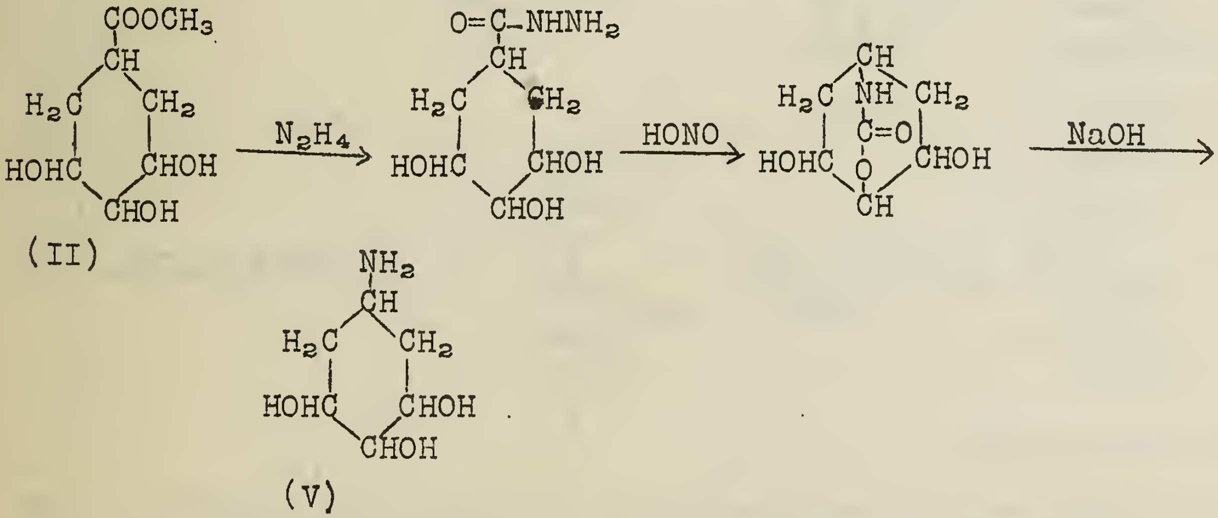


A similar series of reactions on shikimic acid or its ester resulted in the formation of trans-aconitic acid (IV):



Careful and precise work, including use of perpropionic acid in the second step, was necessitated by the presence of the double bond.

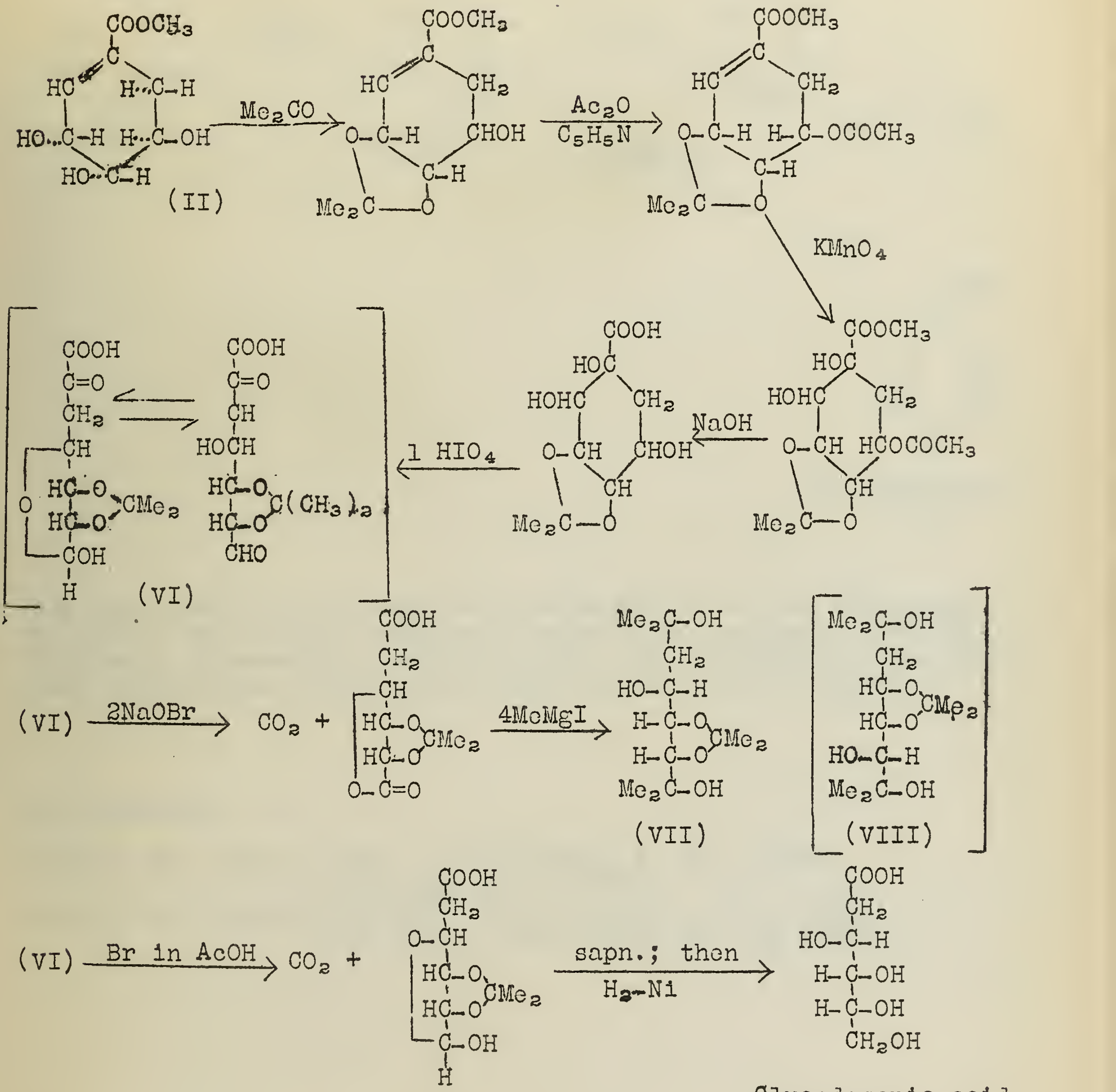
The absence of a hydroxyl group ortho to the carboxyl is further borne out by the following series of reactions: A Curtius degradation of dihydroshikimic acid hydrazide resulted in the formation of a cyclic urethane, which, upon vigorous hydrolysis, gave a trihydroxy cyclohexyl amine (V):



V, like II, requires only two moles of lead tetraacetate when titrated by the method of Criegee, whereas an $-NH_2$ group adjacent to an $-OH$ requires an extra mole of this reagent.

Dihydroshikimic acid forms an optically active lactone with the hydroxyl in the para position (consumes no lead tetraacetate); since such a lactone is otherwise symmetrical, the two hydroxyls in the meta positions must have a trans configuration.

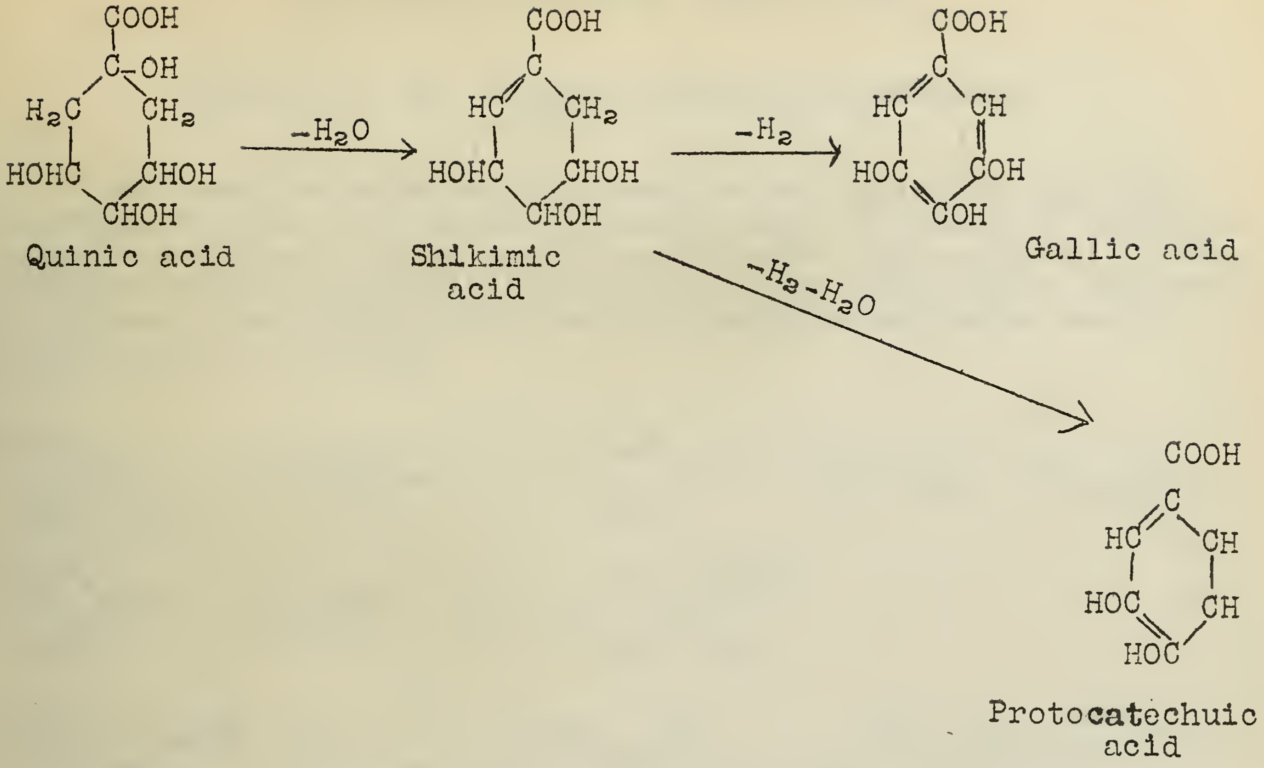
Assuming the -OH in position 5 to be cis to the p-hydroxyl, the double bond may be shown to lie between positions 1 and 6.



Glucodesonic acid

The position of the double bond is thus shown by two different methods. VIII is the formula of the compound that would have been obtained had the double bond been in the 1,2-position. This product should react with lead tetraacetate, while the product obtained did not.

The authors believe that, not only have they shown a relationship between a number of naturally-occurring plant acids:



but also that the conformity of configuration of the -OH groups in quinic and shikimic acid with those found on the corresponding carbons of glucose may furnish a basis for determining a relationship between the cyclic plant acids and the natural sugars.

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Ber., 24, 1278 (1891).
Fischer and Dangschat, Helv. Chim. Acta, 17, 1200 (1934);
18, 1204, 1206 (1935); 20, 705 (1937).

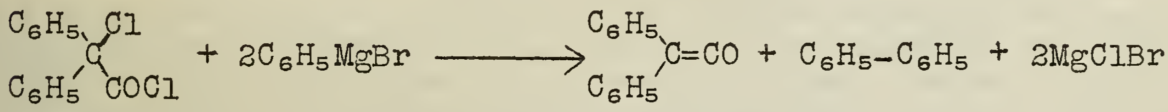
Reported by J. H. Clark
January 12, 1938.

REACTIONS OF GRIGNARD REAGENTS ON CHLOROACETYLCHLORIDE DERIVATIVES.

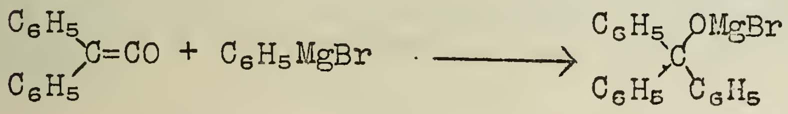
McKenzie -- St. Andrews University, Scotland

The reaction between phenylmagnesiumbromide and diphenylchloroacetylchloride proceeds anomalously. Although we might expect β-benzopinacolin or pentaphenylethanol these are not formed; instead we obtain phenyldesoxybenzoin. Diphenyl ketene appears to be formed as an intermediate so the reaction mechanism can be illustrated as follows:

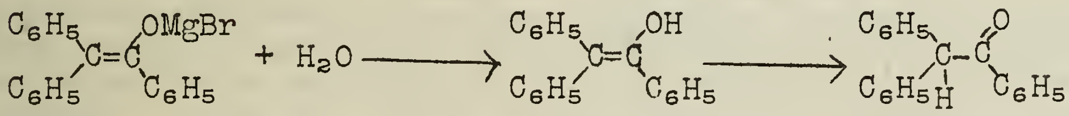
(a)



(b)

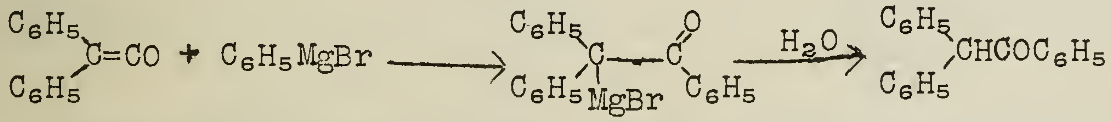


(c)



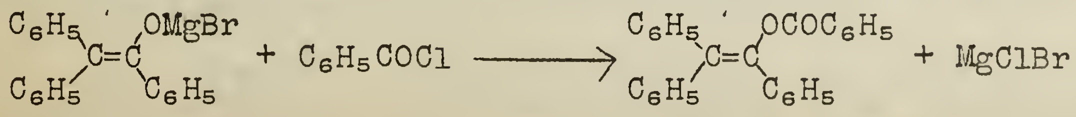
Assuming the intermediate formation of diphenylketene, the formation of diphenyldesoxybenzoin is readily understood since Staudinger obtained the latter compound by treating diphenylketene with phenylmagnesiumbromide. Staudinger interprets his reactions differently.

(d)



This mechanism is difficult to accept since Kohler and others have shown that the Grignard reagent never adds on to an ethylenic linkage in the 1:2 position. Gilman describes the reaction of benzoyl chloride on the additive compound of diphenylketene with phenylmagnesiumbromide. If Staudinger's view were correct then a 1:3 diketone should be formed.

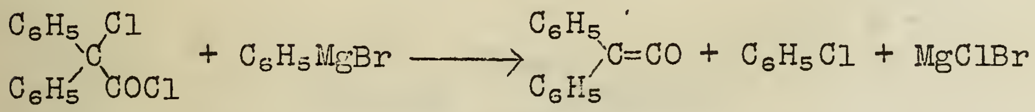
If, however, the mechanism expressed in (b) is correct then



is the reaction to be expected. Since the latter was obtained (b) is probably the correct mechanism.

The assumption involved in equation (a) is given support by the following considerations:

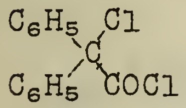
(1) Diphenyl is always formed in larger amounts than would be expected in the making of the Grignard reagent alone. For this reason the scheme (a) is preferred to the alternative scheme



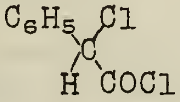
(2) When the experimental conditions are altered so that the Grignard reagent is added to the chilled solution of the diphenylchloroacetylchloride the course of the reaction is quite different than when added in the reverse order. After decomposition, the ether solution assumes an orange-red tint and this is the appearance of diphenylketene. The main product of this reaction is a resin probably consisting of polymerized diphenylketene.

(3) When the Grignard reagent was added to the diphenylchloroacetylchloride there was obtained a product in relatively small amount, melting at 256.5-257.5° whose analysis indicated it was an additive compound of diphenylketene and phenyldesoxybenzoin. It is well known that ketenes form additive compounds with many reagents.

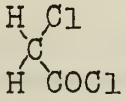
An attempt was now made to compare the reaction of phenylmagnesiumbromide on the acid chlorides:



I

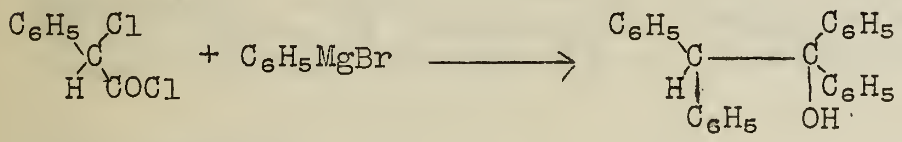


II



III

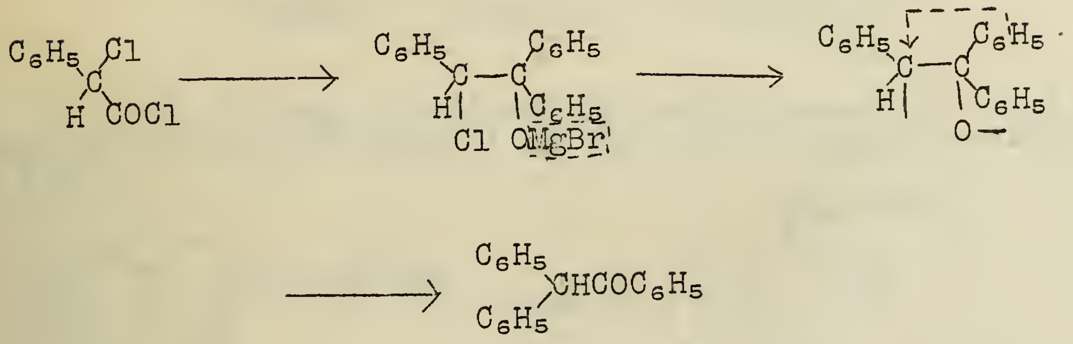
The chlorine atom of I is more readily removed than that of II, and that of II more readily than that of III. For II the experimental conditions play an important role. When II is added to the Grignard reagent the main reaction is:



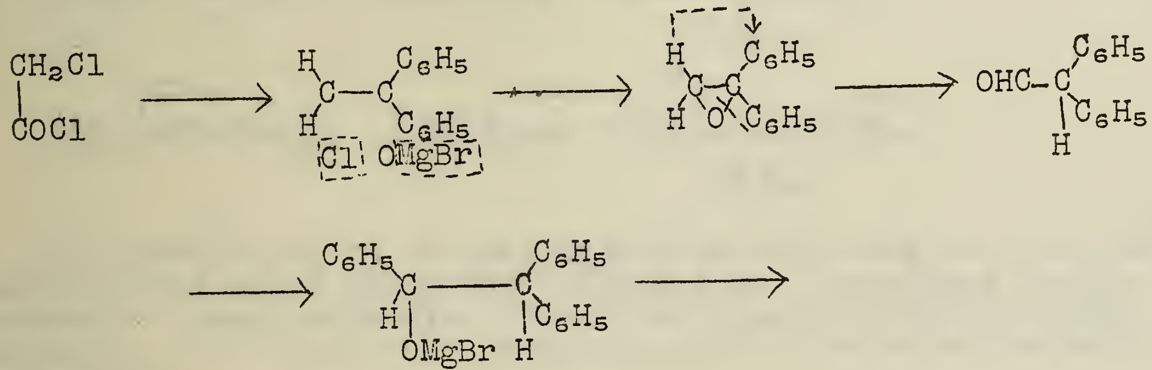
When, however, the Grignard reagent is added to II, phenyldesoxybenzoin is formed to a small extent; in the main, however, a resin is obtained, indicating a possible formation from phenylketene in the same manner as indicated in equation (a).

The formation of phenyldesoxybenzoin can scarcely be explained through an intermediate formation from triphenylethyleneoxide since if this were formed we should expect to isolate some of it, and this was not done.

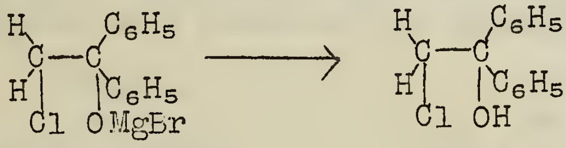
The most probable reaction mechanism appears to be:



The principle product of the reaction of phenylmagnesiumbromide on chloroacetylchloride is 1:2:2 triphenylethanol. The behavior of chloroacetylchloride is different from that of the diphenylchloroacetylchloride since at the beginning of this reaction ketene would be formed and acetophenone should be found; this product was not found at all.



A part of the intermediate product remained unattackable and when treated with water it was changed to diphenylchlorohydrin.



<u>Conclusion</u>: In order to account for all of the products obtained in the reaction of chloroacetylchloride derivatives with Grignard reagents we must use more than one reaction mechanism.

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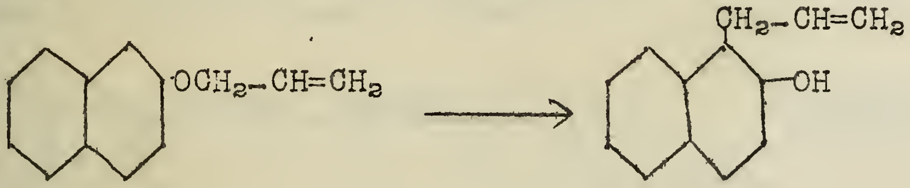
Boyle, McKenzie and Mitchell, Ber., 70, 2153 (1937).

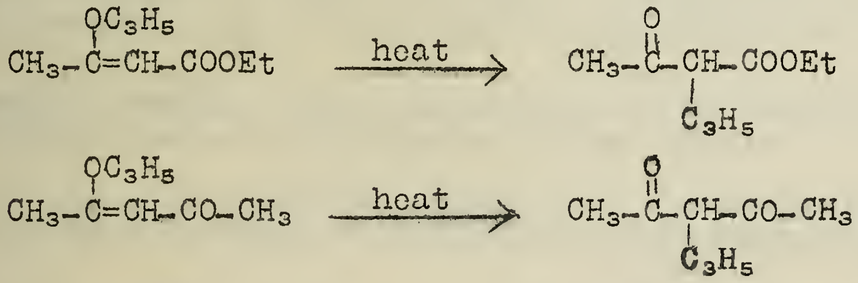
Reported by A. Berger
January 19, 1938.

Mumm and Möller -- University of Kiel
Chapman -- University of Sheffield

In 1912 Claisen described the rearrangement of allyl β-naphthyl ether to α-allyl, β-naphthol by the simple expedient of heating at 210°.



This was found to be a characteristic reaction not only of phenolic ethers but also of allyl ethers of enols. Thus,

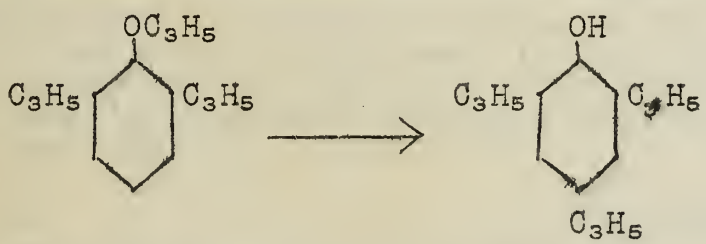


$$\mathrm{CH_3-\overset{OC_3H_5}{C}=CH-COOEt} \xrightarrow{\text{heat}} \mathrm{CH_3-\overset{O}{\overset{\|}{C}}-\underset{C_3H_5}{CH}-COOEt}$$

$$\mathrm{CH_3-\overset{OC_3H_5}{C}=CH-CO-CH_3} \xrightarrow{\text{heat}} \mathrm{CH_3-\overset{O}{\overset{\|}{C}}-\underset{C_3H_5}{CH}-CO-CH_3}$$

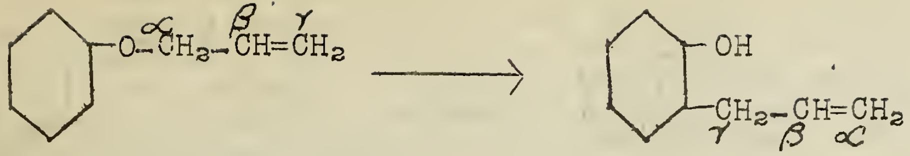
The technic of the rearrangement is very simple. The ether is usually heated at or below the boiling point, sometimes in the presence of inert solvents. Often the reaction is decidedly exothermic, while in other cases the heat of reaction is hardly perceptible.

In general, the allyl (or substituted allyl) residue goes to the <u>ortho</u> position. However, when the two <u>ortho</u> positions are occupied the ether will rearrange to give <u>para</u> substitution. Thus,

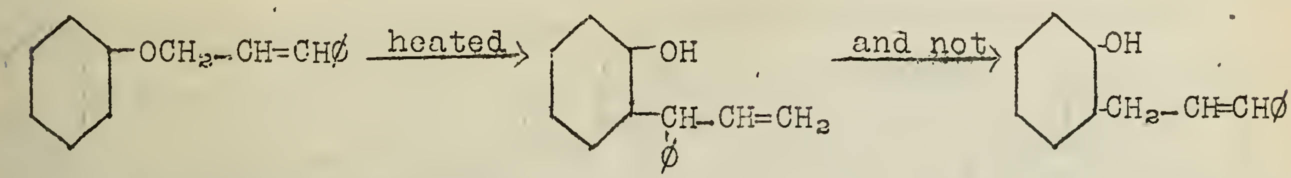


Methyl ethers, and those ethers having a normal chain fail to migrate. Secondary and tertiary alkyl groups can be introduced into the nucleus by an analogous method using a catalyst. In general, the yields are poorer and the mechanism is fundamentally different.

Claisen and Tietze showed that the α-allyl carbon atom, originally attached to the oxygen, is not the one which becomes attached to the nuclear carbon atom. It is the γ-carbon as shown below.

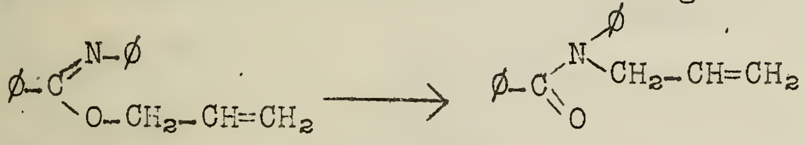


With a modifying group in the allyl chain such as phenyl, or brom, or methyl, it becomes possible to demonstrate the correctness of this statement. Thus,



While the rearrangement of a number of substituted phenyl allyl ethers has been studied, no examination has been made of an isomeric pair of the type $\phi\text{-O-}\underset{\text{R}}{\underset{|}{\text{CH}}}\text{-CH=CH}_2$ and $\phi\text{-CH}_2\text{-CH=CHR}$, the reason probably being the difficulty of obtaining the isomeric halides needed to synthesize these ethers.

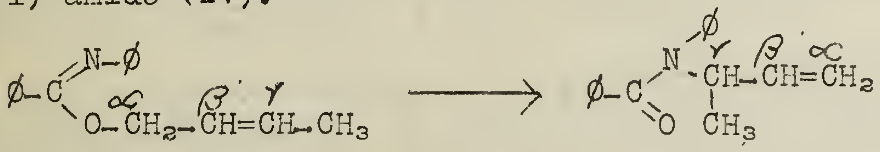
To gain a better insight into the mechanism of the rearrangement Mumm and Möller studied the rearrangement of imino ethers.



I II

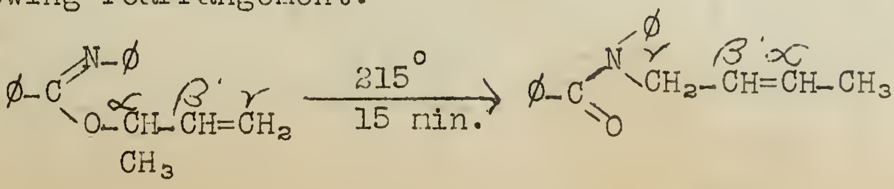
Here, only the allyl residue wanders and no interchange with a hydrogen atom occurs. The rearrangement of N-phenylbenzimino allyl ether (I) to the N-substituted amide (II) is quantitative after two and one-half hours to three hours at 210°.

Just as with the phenolic ethers, the γ-carbon of the allyl radical is the point of attachment in the amide. Thus, N-phenylbenzimino crotyl ether (III) upon being heated at 210° for only one-half hour is completely converted into benz-phenyl-(α-methylallyl)-amide (IV).



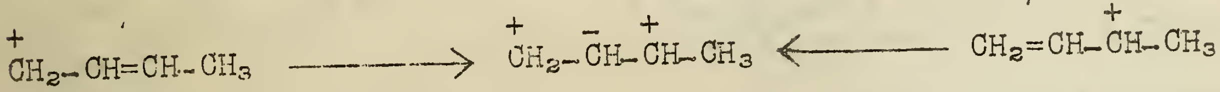
III IV

The fact that a γ-attachment results was shown conclusively by the following rearrangement.



V VI

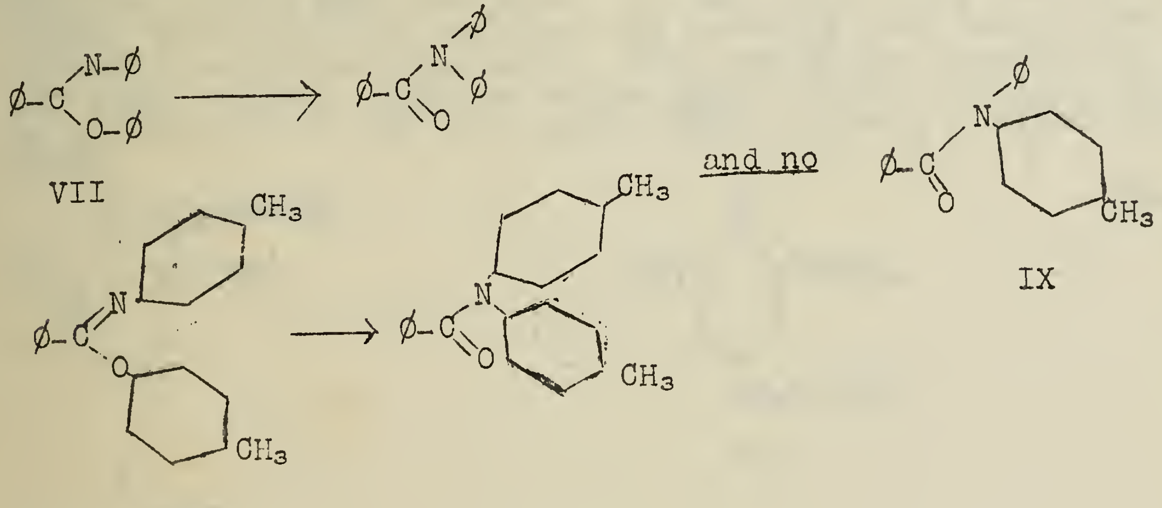
Thus, free radicals or ions are not to be considered as intermediates, for the wandering residues in each case have the same gross formula C_4H_7, the sole difference being that when the split occurs the free valence (or change) would first appear on different carbon atoms. Through a valence-chemical shift in the sense of Prévost or Burton and Ingold (Anionotropy) these two radicals or ions would become identical, e. g.,



$$\overset{+}{C}H_2-CH=CH-CH_3 \longrightarrow \overset{+}{C}H_2-\overset{-}{C}H-\overset{+}{C}H-CH_3 \longleftarrow CH_2=CH-\overset{+}{C}H-CH_3$$

so that (III) and (V) would give the same rearrangement product.

Chapman's work on the rearrangement of imino-aryl ethers furnishes further evidence that ions or free radicals are not involved in this type of migration. He found that an equimolar mixture of N-phenyl-benzimino-phenyl ether (VII) and N-*p*-tolyl benzimino-*p*-tolyl ether (VIII) upon being heated rearranged without the formation of a trace of benz-phenyl-*p*-tolyl amide (IX) which would have formed if a split into fragments (ions or radicals) had occurred.



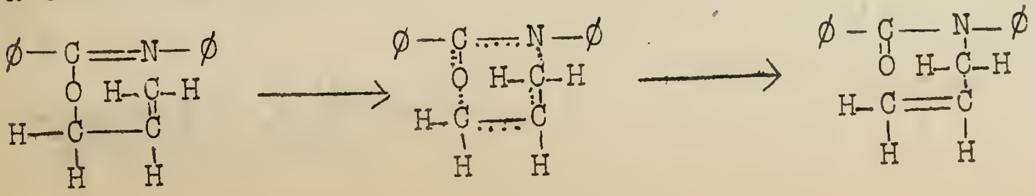
VII

IX

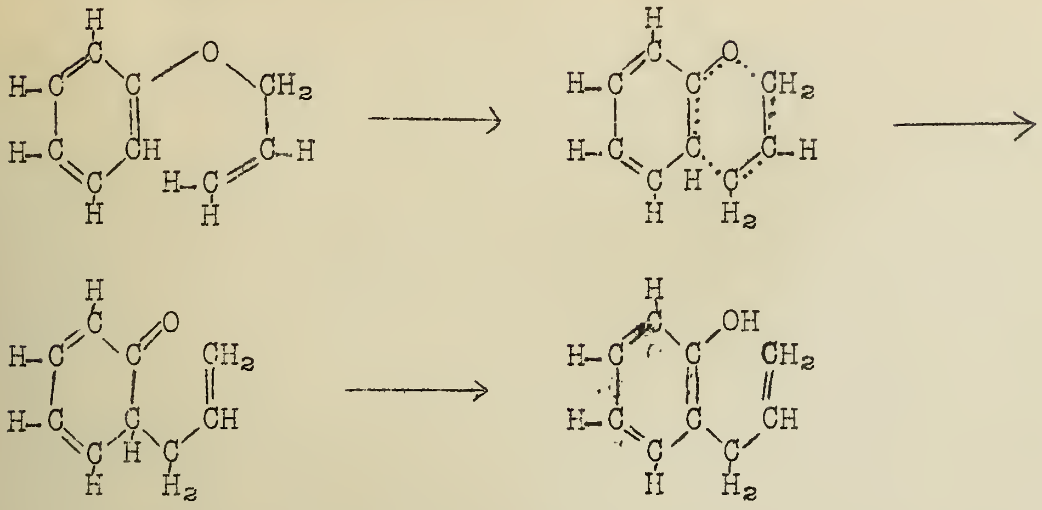
VIII

Mumm, Hesse and Volquartz had previously assumed that the migration was preceded by a gripping of the partial valences of the carbon on the oxygen, to the nitrogen atom.

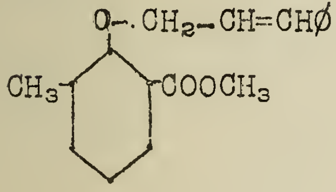
Mumm and Möller apply an electronic process suggested by Chapman to the rearrangement of imino allyl ethers and allyl phenyl ethers. They assume the formation of a six-membered ring through a shift of electrons throughout the allyl chain. In the following formulas a two electron bond is indicated by an unbroken line and a one-electron bond by a dotted line.



For the rearrangement of phenyl allyl ether the following is the reaction sequence:



When both ortho positions are blocked, the allyl residue migrates to the para position. In this case, ring formation is highly improbable, so that here we probably have ions or free radicals as the intermediates. Mumm and Möller showed that when the allyl radical migrates to the para position, it is attached to the nucleus by the same carbon which linked it to the oxygen. Thus,



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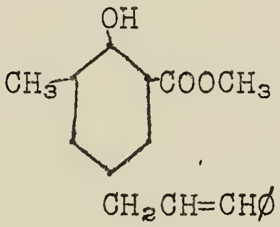

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Reported by N. Kornblum
January 19, 1938.

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R. L. Hicks

CHEMICAL EFFECTS ACCOMPANYING HYDROGEN BONDING

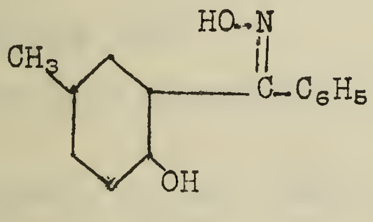
Blatt -- Howard University

In recent years much evidence has been advanced concerning the existence and nature of hydrogen bonds in organic compounds. Numerous physical properties of organic substances which had been vaguely attributed to various causes, are now readily explained by the theory of hydrogen bonding. For example, the abnormal freezing point depressions of alcohols in non-polar solvents is caused by the polymerization of the alcohol molecules,

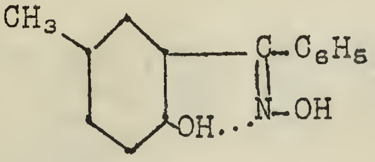
R R R
HO····HO····HO; the average length of polymer depends on the concentration of the alcohol. Another interesting example is that of the o-, m-, p-nitrophenols. The ortho compound forms an intramolecular hydrogen bond and it shows no tendency to polymerize in non-polar solvents; but the meta and para compounds, which are unable to form an intramolecular hydrogen bond, polymerize in non-polar solvents by forming intermolecular bonds. Huggins lists the following types of hydrogen bonds which may occur in organic compounds: OH····O, OH····N, NH····N, N····H-C, and O····H-C.

In 1913, Pfeiffer introduced the concept of hydrogen bonding into organic chemistry and since that time the idea has been used to account for deviations from expected physical properties of certain organic compounds. Until recently, investigations had centered mainly on physical properties rather than on chemical properties. Within the last two years, Blatt and coworkers have shown that the isomeric ketoximes such as those from o-hydroxybenzophenone differ from each other in that one contains a hydrogen bond between nitrogen and oxygen while the other does not. Isomeric oximes of this type offer a favorable opportunity to study the chemical effects accompanying hydrogen bonding.

The syn-form (non-bonded) of 2-hydroxy-5-methylbenzophenone oxime (I) and its derivatives react differently from the ante-form (bonded) (II) and its derivatives.

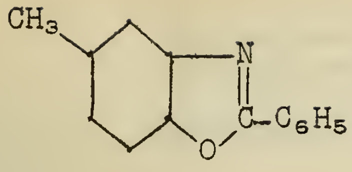


I

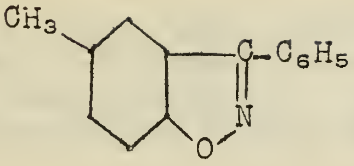


II

The oximino benzoates of both forms of the oxime hydrolyze with dilute sodium hydroxide to parent oxime. Treatment with sodium carbonate converts the non-bonded oximino benzoate to the parent oxime, but the bonded oximino benzoate gives the benzoxazole (III).



III



IV

The bonded oximino benzoate gives benzisoxazole (IV) on pyrolysis and the non-bonded oximino benzoate gives small amounts of III.

A study of the hydrolysis of the dibenzoates of I and II show a definite difference in the primary point of attack. This difference supports the structural formula given to the non-bonded oxime (see I).

The non-bonded oxime undergoes a normal Beckmann rearrangement, but the bonded oxime gives a benzoxazole. However, when the hydrogen bond is destroyed, the oxime derivative will undergo a normal Beckmann rearrangement.

The behavior of the trimethylbenzoates of the oximes shows that hydrolysis is an addition reaction which can be stopped by steric hindrance, but that benzoxazole formation, which is unaffected by hindrance, does not involve addition. The effect of hydrogen bonding is to facilitate the formation of the benzoxazole but the same result may also be effected by preventing the competing reaction of hydrolysis.

The strength of hydrogen bonds as measured by the energy required to break them is small compared with other types of bonds, but the bonding, nevertheless, reveals itself through characteristic chemical behavior.

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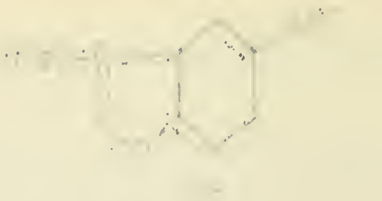
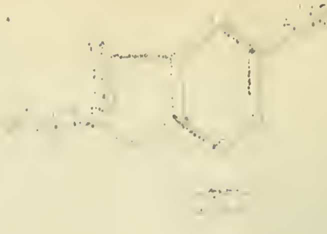
February 9, 1938.





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SUPER-AROMATICITY

Gilman -- Iowa State College, Ames, Iowa
Conant and Kistiakowsky -- Harvard University,
Cambridge, Massachusetts
Johnson -- Cornell University, Ithaca, New York

Before discussing aromaticity it is well to consider what is meant by aromatic properties. In general benzene and its derivatives show a remarkable resistance to such oxidizing agents as alkaline permanganate and nitric acid, which react readily with the olefins. The conjugate system in aromatic compounds is also very inert to the typical additive reagents of the olefinic double bond. As a result of this chemical inertness and the stability of the conjugated system, substitution reactions rather than addition reactions are characteristic of aromatic compounds.

From his work on heterocyclic systems of aromatic character Gilman enunciated a theory of "super-aromaticity." According to this theory certain heterocyclics were said to have properties more aromatic than benzene, and, therefore, were super-aromatic. In the case of furan four principal lines of evidence led him to this conclusion.

1. The splitting of organo-lead compounds with hydrochloric acid.

2. Comparative studies with the Friedel-Crafts reaction.

3. Comparative nitration.

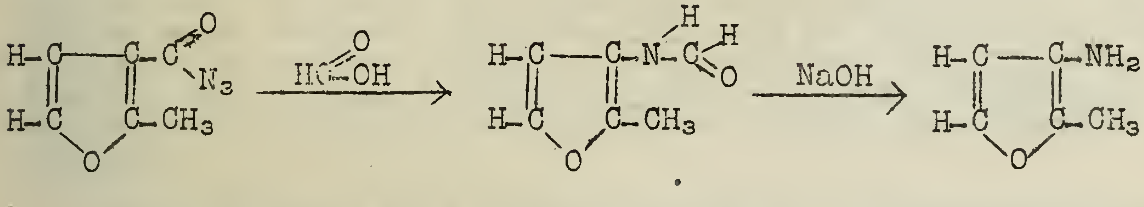
4. Comparative acidity of nuclear hydrogens derived from their reactions with organo-sodium compounds.

Since the enunciation of this theory, considerable evidence has been unearthed which suggests that furan, while aromatic in character, is not as aromatic as benzene. Conant's and Kistiakowsky's studies on heats of hydrogenation show that the stability of the unsaturated system in furan toward hydrogenation is intermediate between that of the cyclic olefins and of benzene.

			ΔH	ΔF°
$CH_2{=}CH{-}CH{=}CH_2$	$+ H_2 \longrightarrow$	$CH_3CH{=}CHCH_3$	-29.2	-20.3
$CH{=}CH{-}CH{=}CH$ CH_2CH_2	$+ H_2 \longrightarrow$	$CH_2CH_2CH{=}CH$ CH_2CH_2	-26.5	-17.7
$CH{=}CH{-}CH{=}CH$ CH_2	$+ H_2 \longrightarrow$	$CH{=}CHCH_2CH_2$ CH_2	-23.7	-14.8
$CH{=}CH{-}CH{=}CH$ O	$+ H_2 \longrightarrow$	$CH{=}CHCH_2CH_2$ O	-11.4	- 2.5
C_6H_6	$+ H_2 \longrightarrow$	$CH{=}CH{-}CH{=}CH$ CH_2CH_2	5.8	13.6

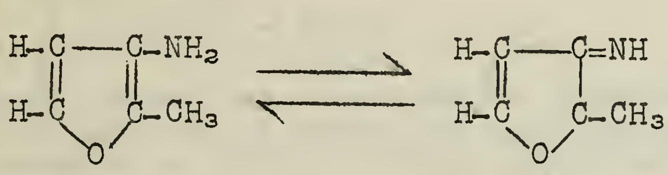
Likewise Johnson has shown that hydrocyanic acid and maleic anhydride add 1,4 to the conjugated double bonds in furan and that this is also the probable mechanism in nitration. Lutz's synthesis of 1,4-diketones by the oxidation of 2,5-diphenyl furans shows that the furan nucleus is more easily oxidized than the benzene nucleus.

Recently Johnson has prepared two simple amino-furans and compared their properties with those of the aromatic amines. His method of synthesis is as follows:



These amines give a strong carbylamine test but are easily hydrolyzed with hot dilute sulfuric acid to ammonia, acetic acid, and acetoin. They are very unstable to atmospheric oxygen, darkening on a few minutes exposure and resinifying after an hour or two. With sodium nitrite in excess dilute sulfuric acid, they give a transient blue-green color similar to that obtained on nitrosation. The diazonium salts so produced couple with β-naphthol but do not undergo the typical reactions with cuprous cyanide or alcohol.

From these reactions and by analogy with the corresponding oxygen derivatives, Johnson concludes that these amines are a mixture of two tautomers:



Eneamine   Ketimine

In conclusion it may be said that aromaticity is a matter of degree and not of kind and that furan, while more aromatic than the cyclic olefins, is less aromatic than benzene.

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Reported by W. S. Emerson
February 9, 1938.

DECOMPOSITION REACTIONS OF THE AROMATIC DIAZO COMPOUNDS

Waters - Durham

Despite the huge body of literature on the subject of the constitution and reactions of the diazo compounds, not one of the many theories proposed is as yet better than a good working hypothesis. Hitherto the mechanism of decomposition of diazonium salts has been considered chiefly in relation to reactions occurring in aqueous solution, from which no conclusive deductions can be made. In the absence of water, significant theoretical conclusions may be drawn from the experimental evidence.

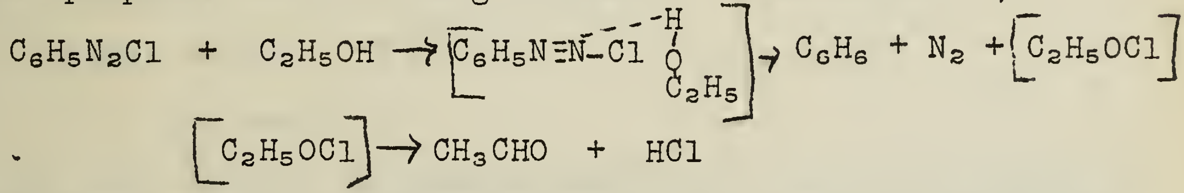
The reduction of a diazonium salt to a hydrocarbon is well known,

$$(1) \quad C_6H_5N_2Cl + C_2H_5OH \rightarrow C_6H_6 + N_2 + HCl + CH_3CHO$$

as is the formation of biaryls:

$$(2) \quad C_6H_5N_2Cl + C_6H_6 \rightarrow (C_6H_5)_2 + N_2 + HCl$$

Hantzsch proposed the following mechanism for reaction (1):



$$C_6H_5N_2Cl + C_2H_5OH \rightarrow \left[C_6H_5N{\equiv}N{-}Cl \; \overset{H}{\underset{C_2H_5}{O}} \right] \rightarrow C_6H_6 + N_2 + [C_2H_5OCl]$$

$$[C_2H_5OCl] \rightarrow CH_3CHO + HCl$$

The present author has considerable evidence supporting the view that in the absence of water the decomposition of a diazonium salt proceeds to form a neutral aryl radical and another neutral fragment:

$$(3) \quad (C_6H_5\overset{+}{N}{\equiv}N)\ \overset{-}{Cl} \rightarrow [C_6H_5N{=}NCl] \rightarrow N_2 + Cl\cdot + C_6H_5\cdot$$

$$(4) \quad C_6H_5N{=}NOCOCH_3 \rightarrow N_2 + CH_3COO\cdot + C_6H_5\cdot$$

(a single dot denotes an unshared electron)

Part of the experimental evidence relating to the non-aqueous decomposition of a benzenediazonium salt can be summarized as follows:

1. The production of benzene is a regular occurrence in a hydrogen-containing solvent and need not be attributed to a reducing agent.

2. Decomposition of diazobenzene acetate in acetic anhydride, carbon tetrachloride or carbon disulfide yields as one product carbon dioxide; this can not arise from an acetate ion, but must be evolved from a neutral acetate radical:

(5) $CH_3COO\cdot \longrightarrow CO_2 + CH_3\cdot\ (\longrightarrow C_2H_6)$.

3. Decomposition of benzenediasonium chloride in acetone yields chloroacetone. This must be formed from atomic chlorine, for neither the chloride ion nor a substituted ammonium chloride is a chlorinating agent.

4. Iodobenzene as well as chlorobenzene is formed by the decomposition of benzenediazonium chloride in ethyl iodide.

5. The decomposition of benzenediazonium chloride in the presence of metallic antimony yields triphenylstibine dichloride. Alkyl or aryl halides do not react with antimony alone; alkyl radicals do so instantly.

In the light of the free radical theory, the reduction in equation (1) can be interpreted as,

(6) $C_6H_5N_2Cl \longrightarrow N_2 + Cl\cdot + C_6H_5\cdot$

$C_6H_5\cdot + RH \longrightarrow C_6H_6 + R\cdot$

and the formation of biaryls is easily explained:

(7) $C_6H_5N_2Cl \longrightarrow N_2 + Cl\cdot + C_6H_5\cdot$

$C_6H_5\cdot + C_6H_6 \longrightarrow (C_6H_5)_2 + H\cdot$

$H\cdot + Cl\cdot \longrightarrow HCl$

The free radical hypothesis amplifies, but does not essentially contradict, the older theories of Hantzsch. It appears that careful reinvestigation of diazo reactions might shed considerable light on the Sandmeyer and Gattermann reactions, the mechanisms of which are still somewhat obscure.

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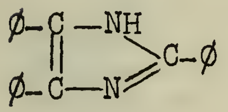
Reported by C. L. Fleming
February 16, 1938

THE ACTION OF AMMONIA ON BENZIL AND BENZOIN

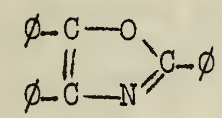
Davidson -- Brooklyn College

The action of ammonia on aldehydes and ketones is a rather complicated reaction. For instance, from different aldehydes, we can obtain urotropin, a simple addition compound, or a cyclic compound. From acetone we can get diacetone amine or triacetone amine. Other functional groups in the molecule further alter the course of the reaction. The effect of different solvents has also been observed. Davidson, while studying the preparation of murexide from alloxantine, used glacial acetic acid as a reaction medium and boosted the yield from the usual 2-5 per cent to a practically quantitative one. With this as a start, he determined to reinvestigate the action of carbonyl compounds and ammonia in glacial acetic acid as a reaction medium. The report deals with his findings in the cases of benzil and benzoin.

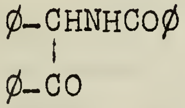
Early investigators had observed that benzil reacted with ammonia to give lophine (I), benzilam, originally poorly named azobenzil (II), benzilimide (III), and imabenzil (IV).



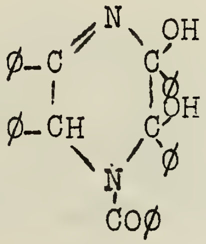
I



II

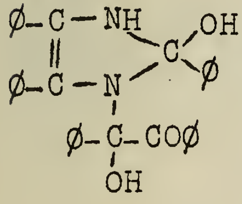


III



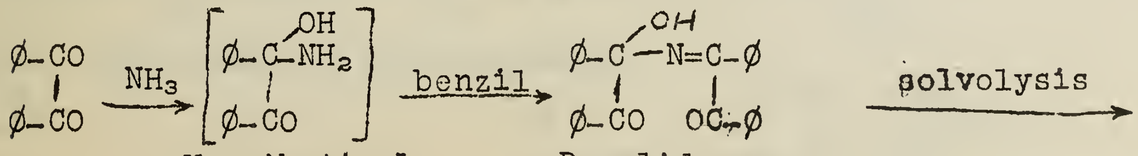
IV

Japp suggested formula II correctly, but offered an incorrect one for benzilimide. Pinner incorrectly proposed V as the formula for imabenzil, and Strain offered two modifications of this, both of which were wrong. At the time of Davidson's investigation, all that was known of imabenzil was its molecular formula, $C_{35}H_{28}N_2O_3$, and the fact that acids converted it to benzilimide, benzil, and ammonia. Both Radziszewski and Kulisch independently proved the structure of lophine; McKenzie and Barrow found the correct structure for benzilimide.



V

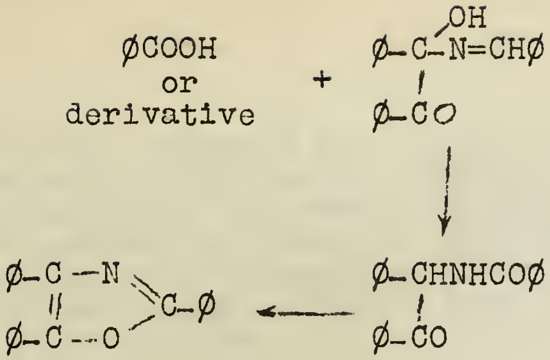
Japp's proposed mechanism of the reaction was incorrectly based upon the assumption of a scission of the benzil molecule. Davidson proposes the following mechanism.



Hypothetical benzil-ammonia

Desylidene-benzil-ammonia

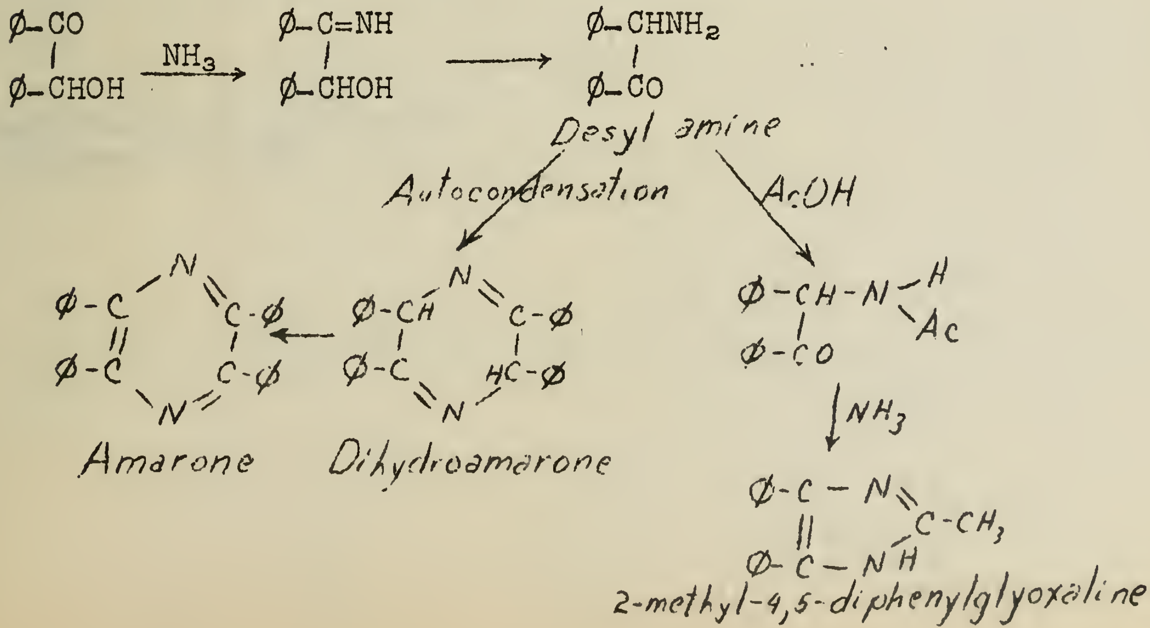
VI

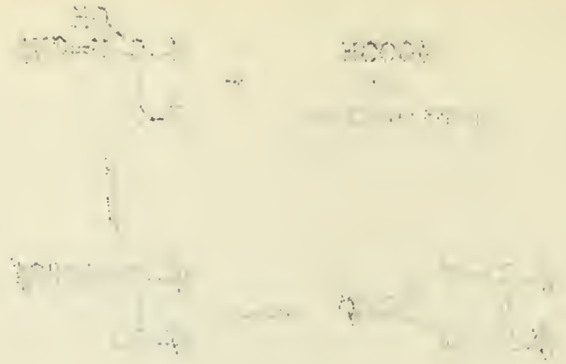


Formula VI possesses a particularly labile C-C bond between the azomethine carbon and the adjacent carbonyl group. This mechanism is analogous to the reaction of ammonia with α-keto acids. The formation of imabenzil is explained by assuming the interaction of benzilimide and the benzil-ammonia intermediate shown above. Benzilimide reacts with ammonia to form lophine, and this explains the disappearance of benzilimide as the reaction proceeds.

When the reaction is run in alcoholic or aqueous ammonia, benzilam is the principle product, but lophine is the main product when glacial acetic acid is the reaction medium. Thus glacial acetic acid is found to be suitable for the conversion of acyl derivatives of desylamine to glyoxaline by ammonia. Using this fact, a modified Radziszewski synthesis of glyoxaline is offered.

Early investigators found the reaction between benzoin and ammonia yielded three products, amarone, benzoinam, benzoinidam. Davidson found that with glacial acetic acid as the reaction medium benzoin gave amarone (main product), 2-methyl-4,5-diphenylglyoxaline, and dihydroamarone. From known reactions, it is reasonable to assume the following mechanism.





Structure II [illegible] the azomethine carbon and an adjacent methylene group. This [illegible]

[illegible]

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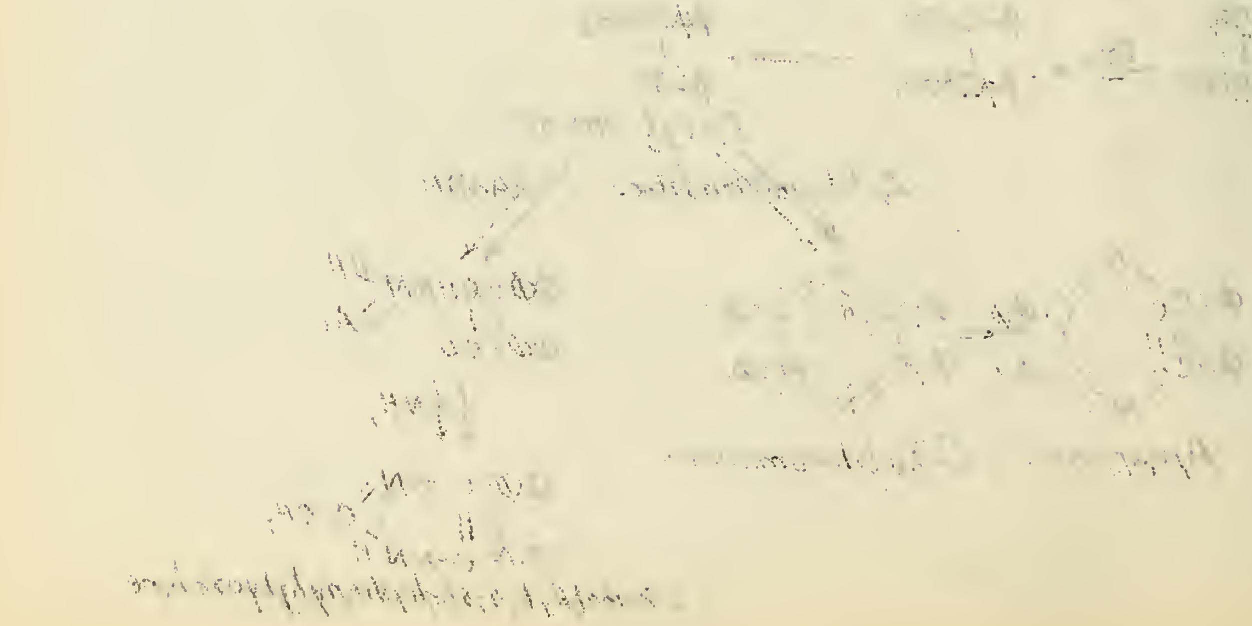

This mechanism has been supported by a study of the action of ammonia in the presence of formic acid, which suppresses the formation of pyrazines, enhancing the amount of glyoxaline formed. When esters of benzoin are used, it is demonstrated that it is the carbonyl group and not the carbinol group which is attacked. The use of benzoin esters offers a good method for the formation of oxazoles in good yields.

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Reported by F. J. Glavis
February 16, 1938

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[illegible]
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Reported by [illegible]
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A. ACTION OF DIAZOMETHANE ON AMINO ACIDS

Kuhn, Kaiser Wilhelm Institute

The equilibrium $\overset{+}{N}H_3RCO\overset{-}{O} \rightleftharpoons NH_2RCOOH$ in aqueous solution has been established by physical methods. Kuhn, intending chemical confirmation, employed the action of gaseous diazomethane on amino acids in aqueous solution.

It was found that betaines of aminocarboxylic acids formed only when the equilibrium was sufficiently far to the left that the aqueous solution was non-titratable. This was due to the fact that the O-methylation of the true acid was much more rapid than the N-methylation of the zwitterion. Results of the methylation were not predictable from dissociation constants.

No N-methylation occurred on the true acid. Aminophenols which form no zwitterions, gave only methoxyl compounds. Aromatic acids which yielded betaines in water yielded none in alcohol.

The more strongly acidic aminosulfonic acids, which were consequently readily titratable in water, yielded betaines exclusively because of the instability of the corresponding methyl esters.

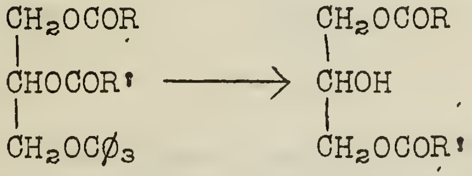
B. GLYCERIDE SYNTHESES USING TRITYL CHLORIDE

Verkade and van der Lee, Rotterdam

Researches instigated by natural formation of mixed triglycerides. Noteworthy results:

1. In support of Hudson's tritylation of β-methyl-α xyloside, tritrityl glycerol was found to form readily.

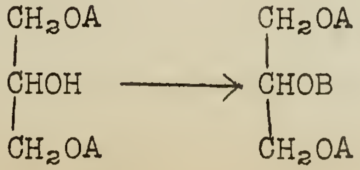
2. The rearrangement



$$\begin{array}{l} CH_2OCOR \\ | \\ CHOCOR' \\ | \\ CH_2OC\phi_3 \end{array} \longrightarrow \begin{array}{l} CH_2OCOR \\ | \\ CHOH \\ | \\ CH_2OCOR' \end{array}$$

on removal of the trityl group was found to occur if R' was aliphatic and not if it was aromatic. The general scheme of the proof was:

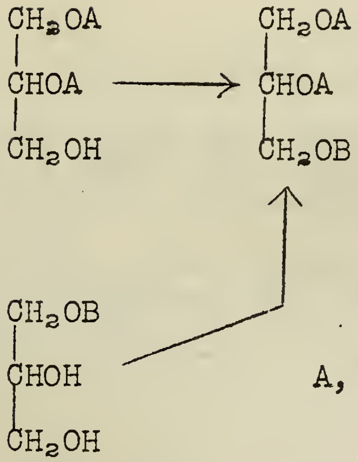
If rearranged



$$\begin{array}{l} CH_2OA \\ | \\ CHOH \\ | \\ CH_2OA \end{array} \longrightarrow \begin{array}{l} CH_2OA \\ | \\ CHOB \\ | \\ CH_2OA \end{array}$$

symmetrical

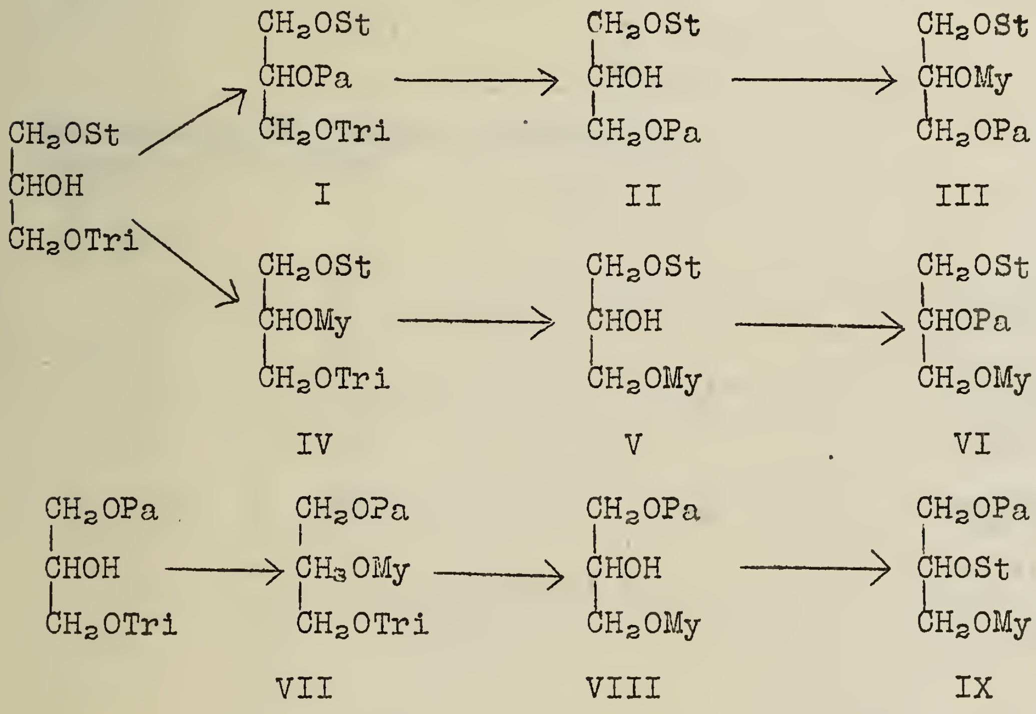
If not rearranged



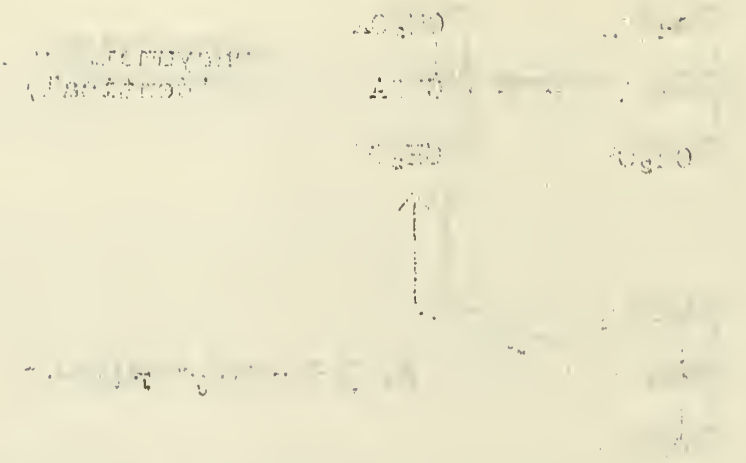
unsymmetrical
(identical)

A, B ≡ acyl radical

3. A smooth technic was developed for the formation of all permutations of tri-acid triglycerides. Example:



The rearrangement I → II had been previously proved. Since VI and IX were different, and neither identical with III, the rearrangements IV → V and VII → VIII must also have taken place.



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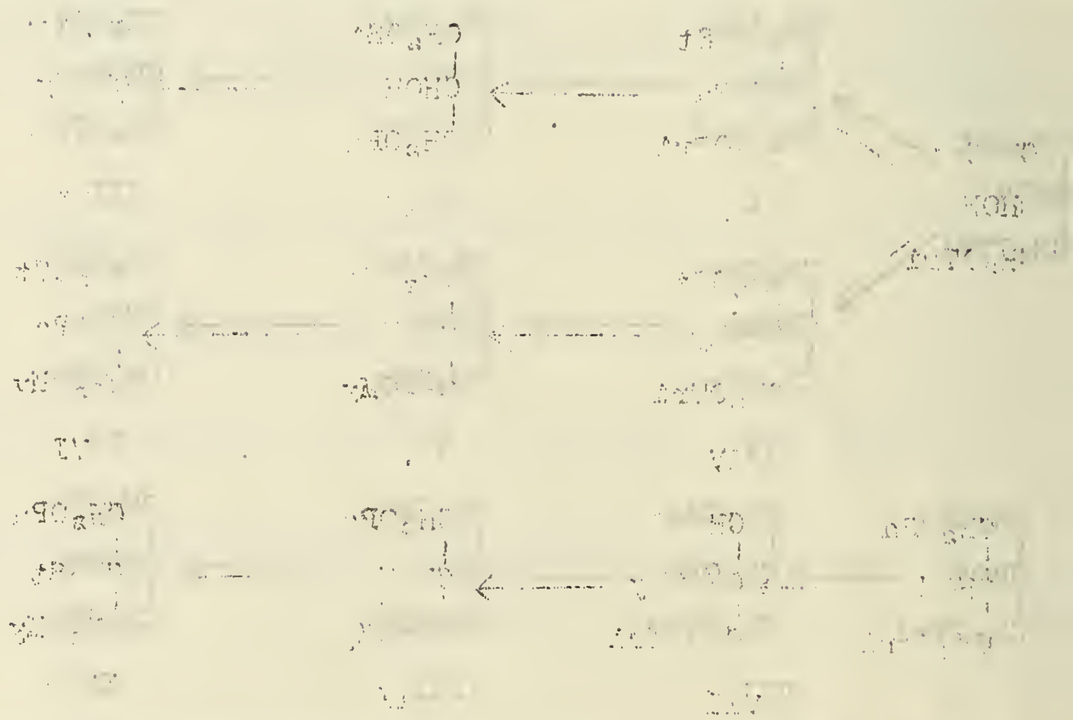

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Reported by William W. Williams
February 23, 1938.

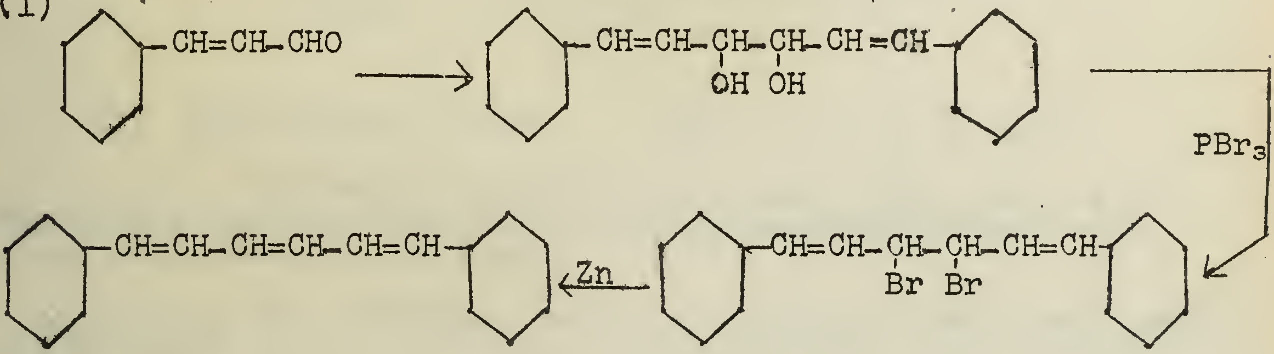
THE SYNTHESIS OF HIGHER POLYENES

R. Kuhn -- Kaiser Wilhelm Institute, Heidelberg

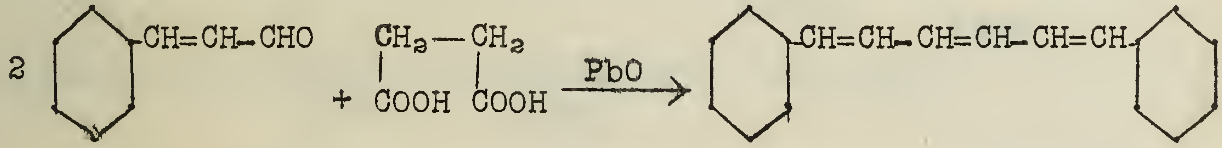
I. $C_6H_5-(CH=CH)_n-C_6H_5$ (n=1, 2, 3, 4, 5, 6, 7, 8)

In 1927 Kuhn and Winterstein first carried out the following reactions in order to find a suitable method for the preparation of the diphenylpolyenes.

(1)



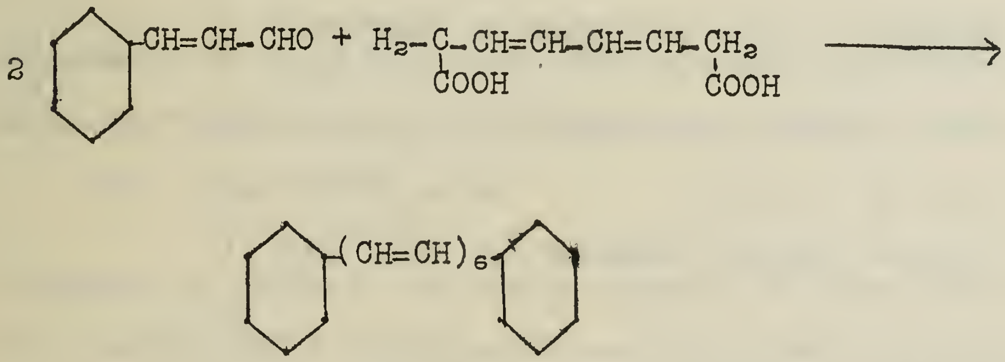
(2)



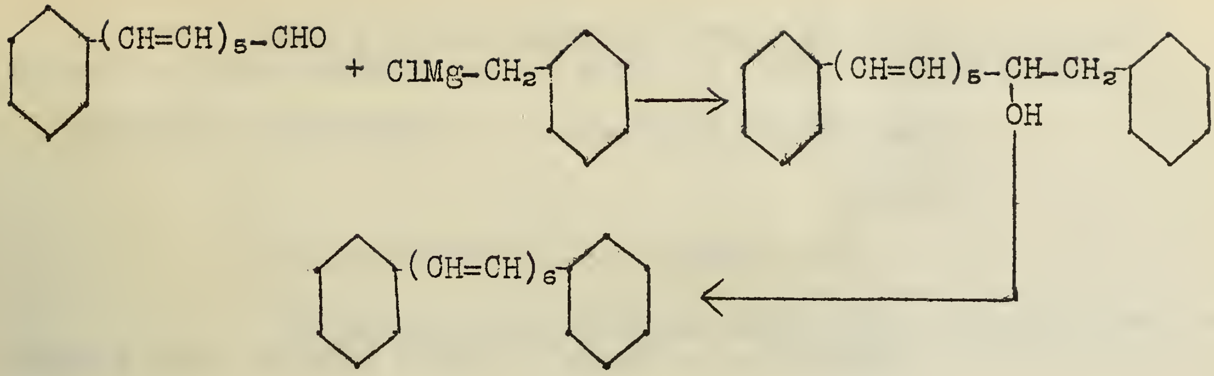
More recent investigations have led to the following methods of synthesis:

(3) For compounds containing an odd number of double bonds dihydromuconic acid is substituted for succinic acid in method 2.

(4) Using butadiene 1,4-acetic acid six carbon atoms are added.



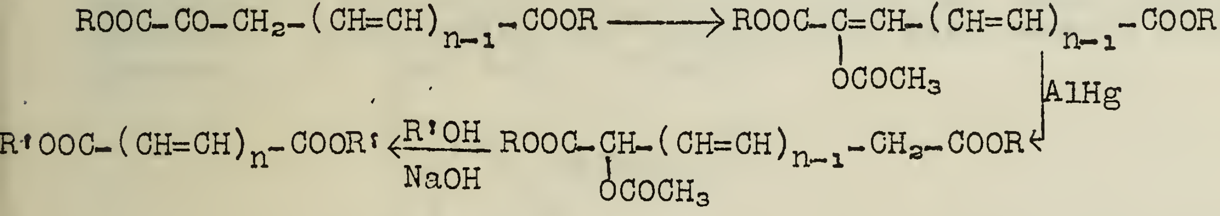
(5) Wallenfels, by the condensation of cinnamaldehyde and crotonic aldehyde in the presence of piperidine acetate, has been able to prepare the higher polyene aldehydes which can be converted to the diphenylpolyene by means of the Grignard reagent.



II. $HOOC-(CH=CH)_n-COOH$ (n=1, 2, 3, 4, 5, 6, 7)

Although diphenylpolyenes have been built up as far as n=8 the knowledge of the analogous dicarboxylic acids stops with muconic acid (n=2).

The following method of synthesis has been worked out by Kuhn:



$$ROOC-CO-CH_2-(CH=CH)_{n-1}-COOR \longrightarrow ROOC-\underset{OCOCH_3}{C}=CH-(CH=CH)_{n-1}-COOR \xrightarrow{AlHg}$$

$$R'OOC-(CH=CH)_n-COOR' \xleftarrow[NaOH]{R'OH} ROOC-\underset{OCOCH_3}{CH}-(CH=CH)_{n-1}-CH_2-COOR$$

It was also found that monocarboxylic acids of this type could be converted to the corresponding dicarboxylic acids containing the same number of carbon atoms by feeding the amide, methylamide, anilide of the acid, etc., to rabbits. There is probably an omega (ω) oxidation with subsequent conversion of the amide to the acid.

III. $HOOC-CH_2(CH=CH)_n-COOH$ (n=1, 2, 3, 4)

Compounds of this type can be prepared by the treatment of the α-keto acid with hydrogen peroxide.

$$HOOC-CO-CH_2-(CH=CH)_n-COOH \xrightarrow{H_2O_2} HOOC-CH_2-(CH=CH)_n-COOH$$

IV. $CH_3-(CH=CH)_n-CH_3$ (n=1, 2, 3, 4, 5, 6)

Kuhn uses the Grignard reagent and the unsaturated aldehyde to prepare the higher members of this series of compounds.

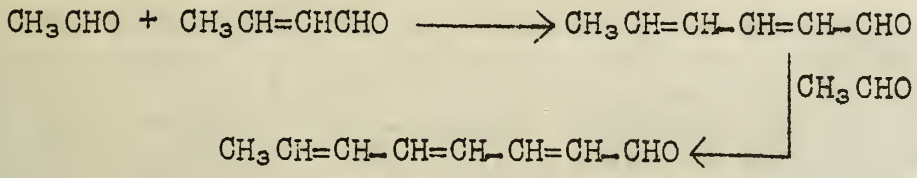
$$CH_3(CH=CH)_3-CHO + BrMgCH_2-CH_3 \longrightarrow CH_3(CH=CH)_3CHOH-C_2H_5$$

$$CH_3-(CH=CH)_4-CH_3 \longleftarrow$$

V. $CH_3-(CH=CH)_n-CHO$ (n=1, 2, 3, 4, 5, 6, 7) and

$CH_3-(CH=CH)_n-COOH$ (n=1, 2, 3, 4, 5, 6, 7, 8)

The polyenealdehydes are best prepared by the action of acetaldehyde upon itself or upon crotonaldehyde.



$$CH_3CHO + CH_3CH{=}CHCHO \longrightarrow CH_3CH{=}CH{-}CH{=}CH{-}CHO \xrightarrow{CH_3CHO} CH_3CH{=}CH{-}CH{=}CH{-}CH{=}CH{-}CHO$$

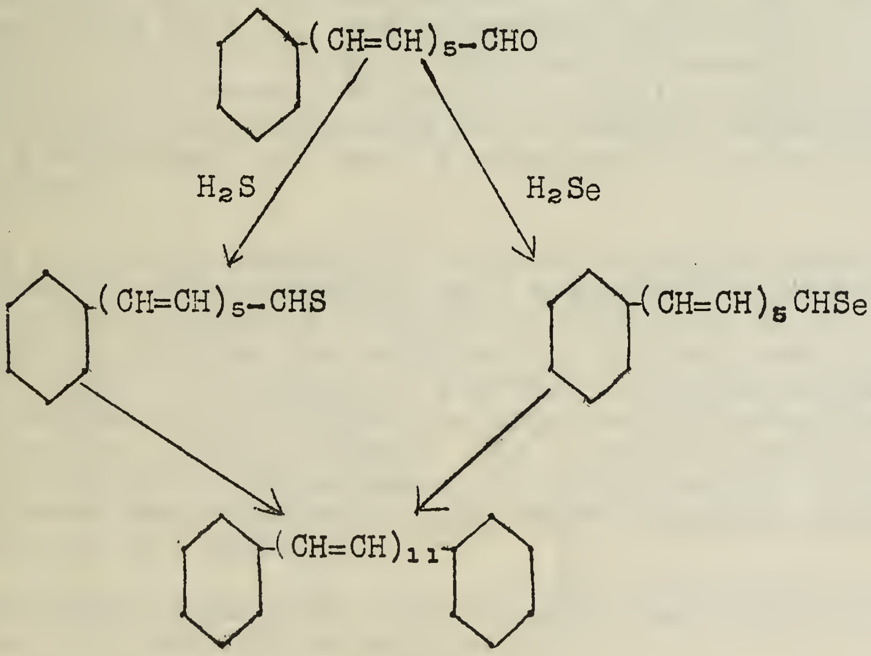
To prepare the polyene acids the aldehydes are condensed with malonic acid in pyridine solution.

$$CH_3CH{=}CH{-}CH{=}CH{-}CH{=}CH{-}CHO + CH_2(COOH)_2 \longrightarrow$$

$$CH_3CH{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH{=}CHCOOH + CO_2 + H_2O$$

VI. Syntheses with thio- and selenopolyenealdehydes.

By means of the polyenealdehyde prepared by the above method it is possible to prepare the corresponding thio- and selenopolyenealdehydes which are extremely useful in the synthesis of long chain unsaturated compounds. Kuhn used this process in synthesizing his Vitamin A and also uses it in the preparation of long chain polyenes.



Bibliography:

Richard Kuhn and coworkers, Angew. Chem., 50, 703 (1937)
(The article gives 16 additional references).

Reported by R. M. Haskins
February 23, 1938.

Borcherdt and Adkins -- Wisconsin
Winkel and Proske -- Kaiser Wilhelm Institute

The polarograph is an instrument for measuring the "depolarization potential" of a reducible substance. The method is based on the fact that a dropping mercury electrode is polarized to a very great extent. For example, if a cell is set up consisting of a dropping mercury cathode, a layer of mercury as anode and $ZnSO_4$ as electrolyte, a potential may be applied across this cell with practically no current flow until a potential of about 1.3 V is reached. At this potential the current flow rises sharply but soon attains a new constant value. This potential is the depolarization potential for zinc, and is characteristic. By plotting applied voltage against current flow a curve is obtained which shows this sudden rise in current at a definite potential. The height of this rise (the wave height) is a function of the concentration of the substance in solution and measurements of these wave heights give rise to quantitative determinations.

Heyrovsky in 1925 incorporated these principles into the polarograph. In the original Heyrovsky instrument the potential was gradually increased and the current flow recorded photographically by a reflecting galvanometer. Leeds and Northrup manufacture an instrument in which the potential increase and the recording of the current flow are both accomplished by a "Microwax" automatic potentiometer. The samples used ranged in size from 0.005 to 5 cc. and the method works best at concentrations of 10^{-2} to 10^{-4} normal. The current sensitivity must be from 10^{-8} to 10^{-9} amps. Potentials usually encountered range up to 2.3 V and for two compounds to be readily differentiated there must be a difference in their depolarization potentials of from 150 to 200 mV.

The method as applied to organic compounds consists of making up a solution of the compound in a supporting electrolyte, whose depolarization potential is greater than that of the compound being investigated, placing the solution in the cell and turning on the current. Since the amount of substance reduced during the taking of a polarogram is negligible as many as 100 determinations may be carried out on a single sample. In a solution which contains a mixture of reducible substances clear-cut breaks in the current-voltage curve are obtained as the characteristic potentials for each compound are reached.

Compounds containing the following functional groups have been characterized polarographically:

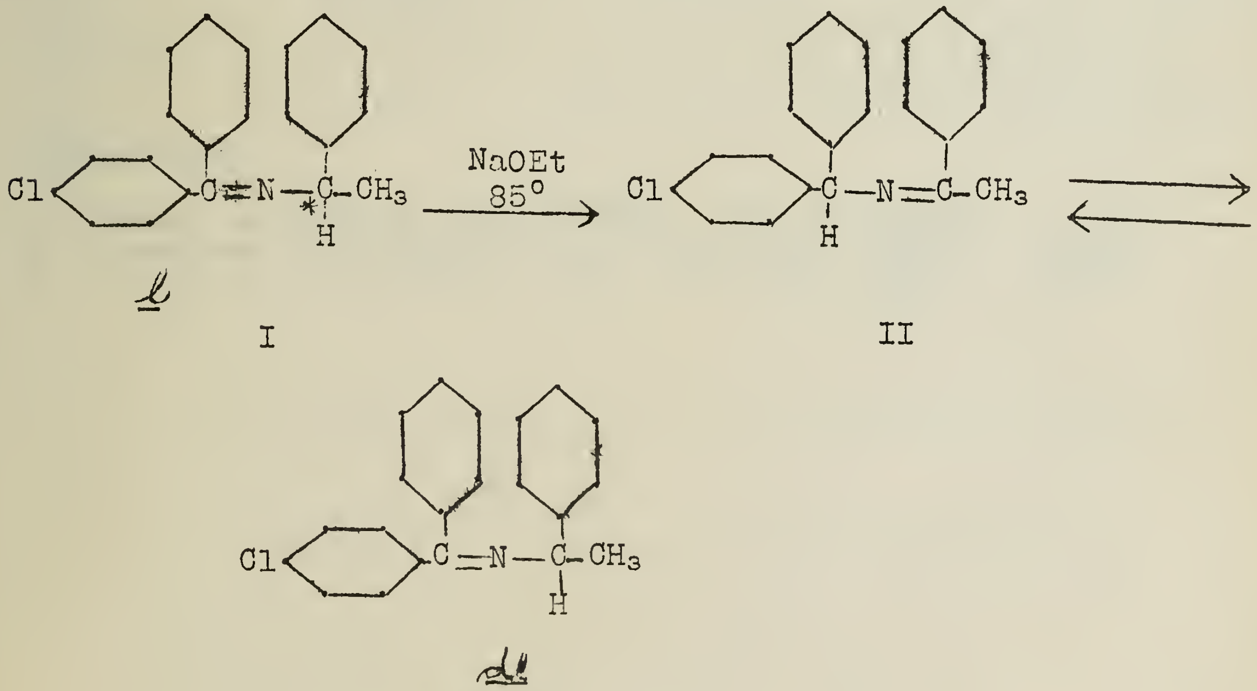
$-CHO$ and $>CO$, aromatics more readily than aliphatics.
Sugars (aldoses and ketoses)
$-NO_2$ and $-N=N-$.
Ethylenes and acetylenes.

Alcohols have not been reduced by this method.

Besides actual qualitative and quantitative work on organic compounds the instrument is useful in the determination of the

purity of compounds. For example: aldehyde-free alcohol or peroxide-free ether gives no polarographic waves. Considerable work has been done relating changes in depolarization potentials with alterations in structure. For example, the potential for formaldehyde is 1.38, for acetaldehyde or propionaldehyde 1.60, while acetone cannot be reduced.

In a tautomeric equilibrium A $\rightleftarrows$ B it is generally assumed that this equilibrium is a dynamic one and that at the equilibrium point A is actually being converted into B and vice versa. However, Adkins and Borcherdt have pointed out that all known facts concerning such an equilibrium could be explained by assuming that the rate of conversion of A to B is gradually slowed up by the accumulation of B until at equilibrium there is no interconversion of A and B and a state of "static" equilibrium exists. To obtain definite experimental evidence with respect to the nature of such an equilibrium they have studied a tautomerization $A^* \longrightarrow B \rightleftarrows A$ using two independent methods to measure the rates of conversion. The first method depends on measuring the rate of reaction by following the loss in optical activity of the solution and the second method depends on measuring the concentration of A^* plus A throughout the reaction. Adkins and Borcherdt make the statement that if the rate of reaction measured by the decrease in optical activity is less than the rate measured by the second method then support will be given to the concept of static equilibrium. These measurements were carried out and the rate constants found by the two methods agreed very well and the conclusion is drawn that this fact is evidence to show the actual existence of a dynamic equilibrium. The compounds studies were:



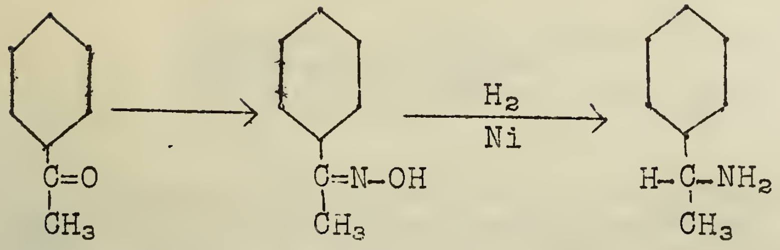
I

II

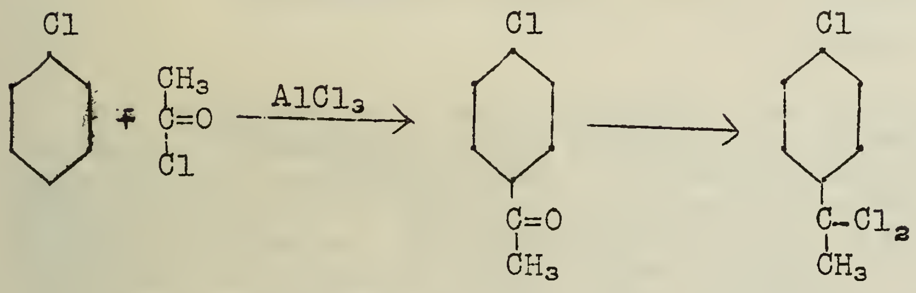
V

The concentration of I plus V was measured by means of a polarogram on the hydrolyzed reaction mixture, from which the ratio of p-chlorobenzophenone (from hydrolysis of I and V) to acetophenone (from hydrolysis of II) was calculated.

These were synthesized by the following series of reactions:



III



IV

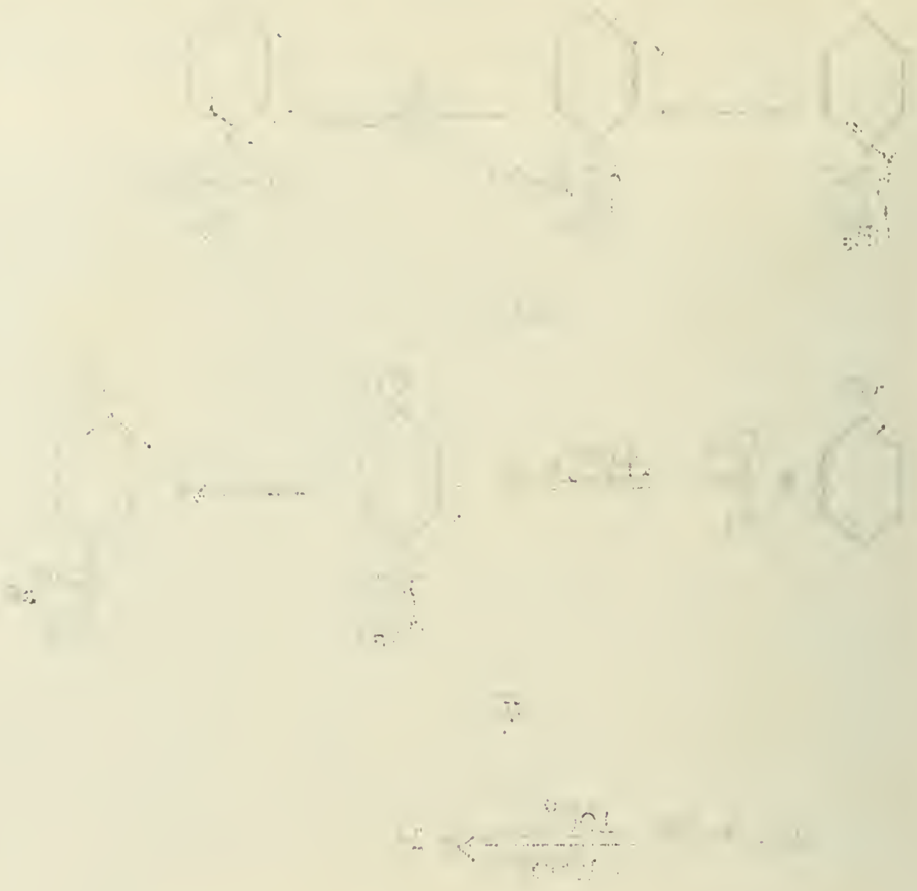
$$\text{III} + \text{IV} \xrightarrow[\text{4 hours}]{100^{\circ}} \text{I}$$

Bibliography:

1. Winkel and Proske, Angew. Chem., <u>50</u>, 18 (1937)
2. Borcherdt and Adkins, J. Am. Chem. Soc., <u>60</u>, 3 (1938)

Reported by T. L. Cairns
March 2, 1938.

[illegible]



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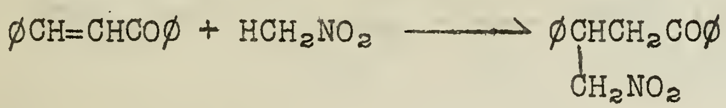
THE ADDITION OF REACTIVE METHYLENE GROUPS TO α,β-UNSATURATED KETONES

Mannich -- Pharm. Inst. Univ. of Berlin
Robinson -- Oxford
Reichert -- Pharm. Inst. Univ. of Berlin

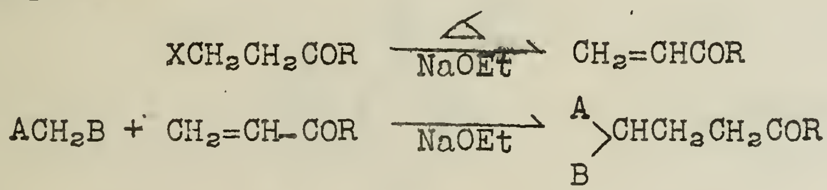
Compounds which contain a reactive methylene group usually add readily to α,β-unsaturated ketones. Thus malonic ester, acetoacetic ester or nitromethane add smoothly to substituted benzylidene acetophenones.



$$\phi CH{=}CHCO\phi + HCH_2NO_2 \longrightarrow \phi \underset{\displaystyle CH_2NO_2}{\underset{|}{C}}HCH_2CO\phi$$

If the β-carbon is unsubstituted, the yields are very poor due to the tendency of vinyl ketones to polymerize under the experimental conditions used. It has now been found that certain derivatives of such vinyl ketones react readily to give the desired compounds. Thus XCH_2CH_2COR (where X is chlorine or dialkylamino) readily undergo decomposition with formation of the vinyl ketone and the substance containing the reactive methylene group will react and the same product is produced as if the substance had added to the double bond of the vinyl ketone.

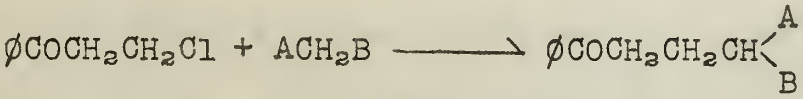
These reactions are usually carried out in hot alcoholic solution with sodium alkoxide as catalyst. It has been suggested that the compound undergoes decomposition with gradual liberation of the vinyl ketone which will then react with the substance containing the reactive methylene group which is also present in the reaction mixture. The reaction, therefore, proceeds in two steps.



$$XCH_2CH_2COR \xrightarrow[NaOEt]{\Delta} CH_2{=}CHCOR$$

$$ACH_2B + CH_2{=}CH{-}COR \xrightarrow[NaOEt]{} {}^{A}_{B}\!\!>\!CHCH_2CH_2COR$$

C. F. H. Allen[1] allowed β-chloropropiophenone to react with various compounds containing a reactive methylene group.



$$\phi COCH_2CH_2Cl + ACH_2B \longrightarrow \phi COCH_2CH_2CH\!<^{A}_{B}$$

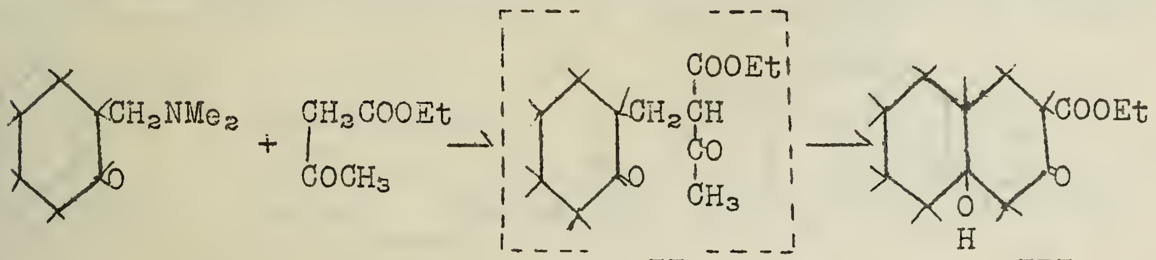
A =	CN	CN	CN	H	ϕ	ϕCO	$>CH_2$
B =	COOMe	$CONH_2$	CN	NO_2	NO_2	ϕ	

In more recent work, β-dialkylamino ketones or the quaternary salts of these have been used as starting material. Mannich and coworkers[2] have developed an advantageous synthesis of these.

$$R'COCH_2R + HCHO + R_2NH_2^+Cl^- \longrightarrow R'COCHRCH_2NR_2"H^+Cl^- + H_2O$$

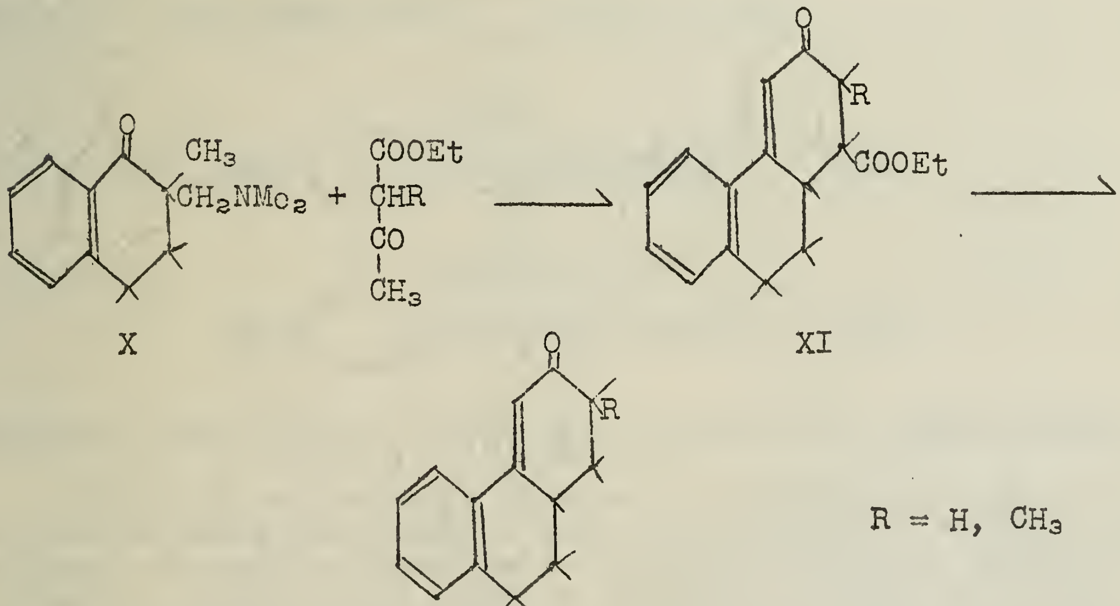
$$ArCOCH_2R + HCHO + R_2"NH_2^+Cl^- \longrightarrow ArCOCH_2(R-H)CH_2NR_2^{H}H^+Cl^- + H_2O$$

Recently Mannich[3] has condensed 2-dimethylaminomethyl cyclohexanone I with acetoacetic ester. Compound II should have been isolated. Apparently it underwent ring closure since compound III was actually isolated.



I II III

Acetoacetic ester and methyl acetoacetic ester were also condensed with X. The product XI was converted to the monoketone XII.



X XI

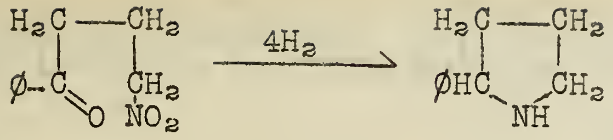
XII

R = H, CH_3

Reichert[4] was able to condense nitromethane with certain 1,3-dialkylamino ketones. He showed that dimeric and trimeric products may be formed. With ω-dimethylaminopropiophenone three products were isolated (formulas XIII, XIV and XV).

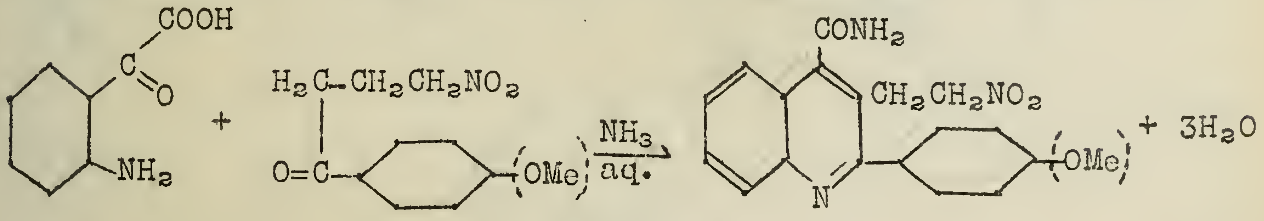
$\varnothing COCH_2CH_2CH_2NO_2$	$(\varnothing COCH_2CH_2)_2CHNO_2$	$(\varnothing COCH_2CH_2)_3CNO_2$
XIII	XIV	XV

However, with the p-methoxy derivative only the monomeric form could be prepared. With the 3,4-dimethoxy derivative a dimeric but no trimeric form was produced. Compound XI was reduced with the formation of α-phenylpyrrolidine (XVI).

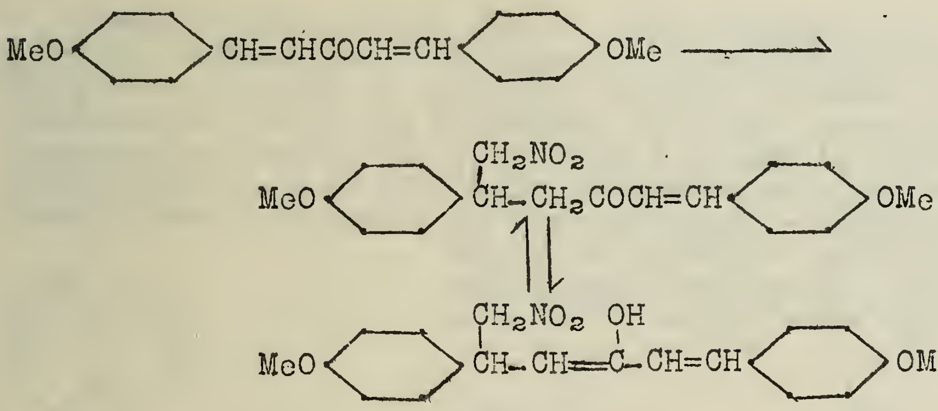


XVI

ω-Nitrobutyrophenone and the p-methoxy derivative could not be condensed with benzaldehyde but were condensed with isatin.



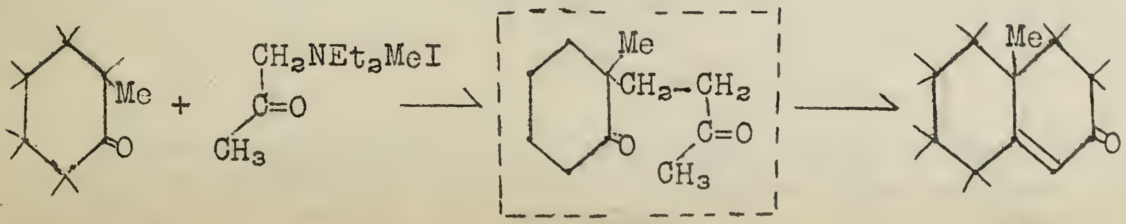
An attempt was made to add two mols of nitromethane to di-α-β-unsaturated ketones. However, only one mol would add.



Both the keto and enol forms were isolated and characterized.

Robinson[5] has recently carried out reactions of this type with a view to using the reaction for the synthesis of sterols. An attempt was made to condense 2-methylcyclohexanone with β-chlorobutanone. A very poor yield of compound XVII was obtained. As a result, β-dialkylamino ketones, prepared by Mannich's method, were converted to the quaternary salts with methyl iodide and used as such.

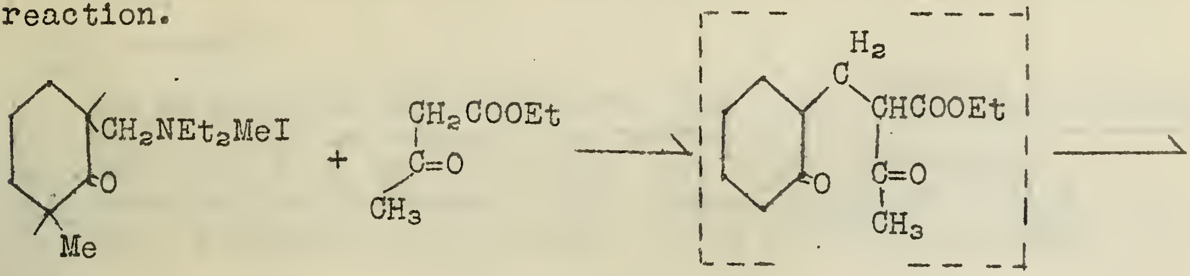
The quaternary salt of β-diethylaminobutanone (compound A) was condensed with 2-methylcyclohexanone. Compound XVIII underwent ring closure as compound XVII was isolated.

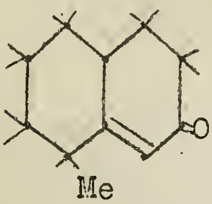


XVIII

XVII

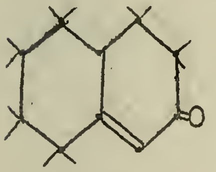
Acetoacetic ester was also condensed with 2-methyl-6-diethylaminomethylcyclohexanone. Compound XIX was isolated. The intermediate ester was hydrolyzed and decarboxylated during the reaction.



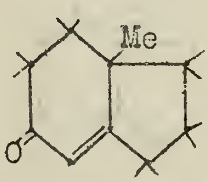


XIX

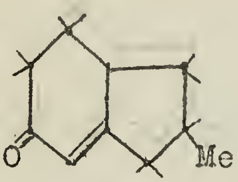
Cyclohexanone could not be used successfully in these reactions because cyclohexylidene cyclohexanone is also formed. This is difficult to separate from the product desired. However, 2-carbethoxy could be condensed with the compound A. The intermediate believed to be formed undergoes hydrolysis and decarboxylation to yield the same product that cyclohexanone should have. Compound XX was isolated. 2-Methyl cyclopentanone was also condensed with acetoacetic ester and compound A. Compounds XXI and XXII respectively were formed.



XX



XXI



XXII

β-Decalone was also condensed with compound A with the formation of compound XXIII.

XXIII

By means of reactions of this type, these workers hope to be able to synthesize the sterol nucleus. They suggest that probably the sterols are synthesized by similar reactions *in vivo* rather than from isopentenes.

Bibliography:

1. C. F. H. Allen and coworkers, Can. Jour. Res., 11, 40 (1934)
2. Mannich and coworkers, see reference 4
3. Mannich, Kock and Borkowsky, Ber., 70, 355 (1937)
4. Reichert and Posemann, Arch. Pharm., 275, 67 (1937)
5. Feu, McQuillin and Robinson, Jour. Chem. Soc., 1937, 53.

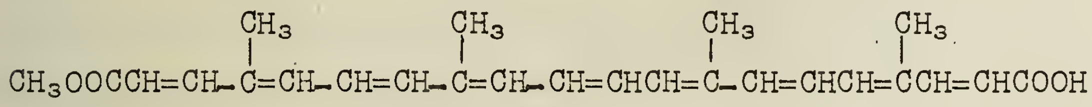
Reported by F. J. Sprules
March 2, 1938.

SOME CHEMICAL REACTIONS OF BIXIN

P. Karrer — Zurich

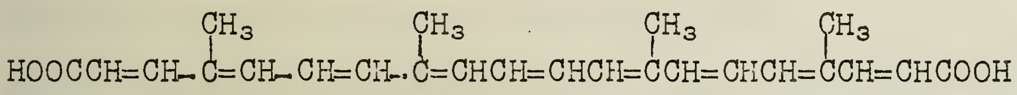
Karrer et al, while working with bixin, an α,ω-dicarboxylic polyene plant pigment, assigned the following structures to bixin and its analogs.

Bixin



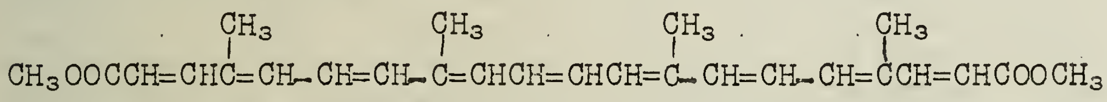
$CH_3OOCCH{=}CH{-}\overset{CH_3}{C}{=}CH{-}CH{=}CH{-}\overset{CH_3}{C}{=}CH{-}CH{=}CHCH{=}\overset{CH_3}{C}{-}CH{=}CHCH{=}\overset{CH_3}{C}CH{=}CHCOOH$

Norbixin



$HOOCCH{=}CH{-}\overset{CH_3}{C}{=}CH{-}CH{=}CH{-}\overset{CH_3}{C}{=}CHCH{=}CHCH{=}\overset{CH_3}{C}CH{=}CHCH{=}\overset{CH_3}{C}CH{=}CHCOOH$

Bixin methyl ester



$CH_3OOCCH{=}CH\overset{CH_3}{C}{=}CH{-}CH{=}CH{-}\overset{CH_3}{C}{=}CHCH{=}CHCH{=}\overset{CH_3}{C}{-}CH{=}CH{-}CH{=}\overset{CH_3}{C}CH{=}CHCOOCH_3$

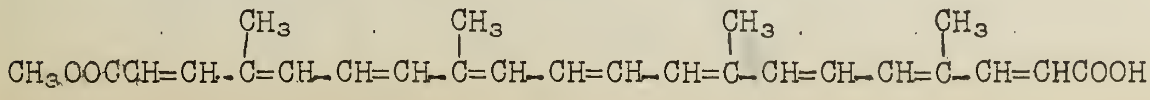
Bixin was converted to an isomeric compound, isobixin, on treatment with iodine in glacial acetic acid, norbixin was converted to isonorbixin by treatment with aqueous potassium hydroxide, and bixin methyl ester was converted to isobixin methyl ester by means of iodine in glacial acetic acid. These three iso compounds differed from the original in physical properties, such as melting point and absorption spectrum were different. The iso compounds were then given the prefix "stable," and the compounds from which they were obtained the prefix "labile."

It was assumed that inasmuch as the conversion of a labile form to a stable form involved no change in the number of double bonds, and no change in the functional groups, that the labile and stable forms were merely <u>cis-trans</u> isomers. It was also assumed that the same double bond was involved in the three isomeric changes shown above, inasmuch as stable norbixin on esterification yielded the same stable bixin methyl ester obtained from labile bixin methyl ester.

Labile norbixin ⟶ stable norbixin ⟶ stable bixin methyl ester ⟵ labile bixin methyl ester

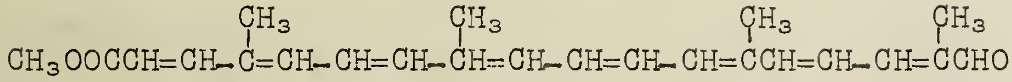
Karrer and his coworkers were successful in oxidizing labile bixin stepwise, and isolating some of the intermediate compounds. Dilute permanganate was the oxidizing agent employed, and in the three cases cited below, the aldehydes were isolated.

Labile bixin (I)



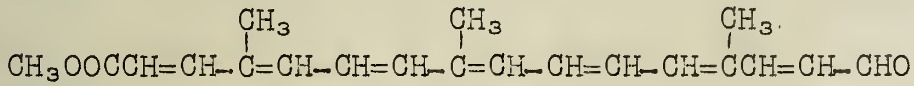
$CH_3OOCCH{=}CH{-}\overset{CH_3}{C}{=}CH{-}CH{=}CH{-}\overset{CH_3}{C}{=}CH{-}CH{=}CH{-}CH{=}\overset{CH_3}{C}{-}CH{=}CH{-}CH{=}\overset{CH_3}{C}{-}CH{=}CHCOOH$

Apo-1-norbixinal methyl ester (II)



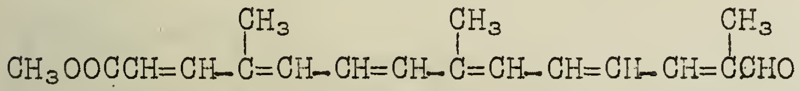
$$\mathrm{CH_3OOCCH{=}CH{-}\overset{CH_3}{C}{=}CH{-}CH{=}CH{-}\overset{CH_3}{CH}{=}CH{-}CH{=}CH{-}CH{=}\overset{CH_3}{C}CH{=}CH{-}CH{=}\overset{CH_3}{C}CHO}$$

Apo-2-norbixinal methyl ester (III)



$$\mathrm{CH_3OOCCH{=}CH{-}\overset{CH_3}{C}{=}CH{-}CH{=}CH{-}\overset{CH_3}{C}{=}CH{-}CH{=}CH{-}CH{=}\overset{CH_3}{C}CH{=}CH{-}CHO}$$

Apo-3-norbixinal methyl ester (IV)

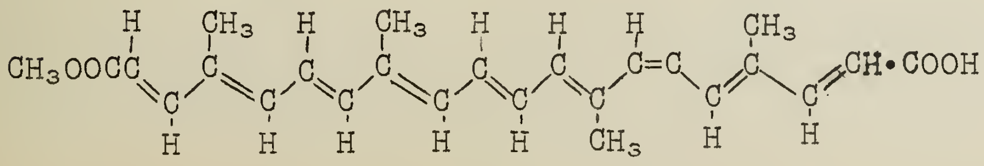


$$\mathrm{CH_3OOCCH{=}CH{-}\overset{CH_3}{C}{=}CH{-}CH{=}CH{-}\overset{CH_3}{C}{=}CH{-}CH{=}CH{-}CH{=}\overset{CH_3}{C}CHO}$$

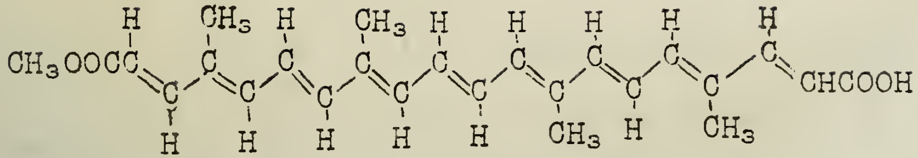
In the nomenclature employed here, apo refers to a degradation product, while the number following the term apo refers to the double bond oxidized. From the reaction mixtures, II and IV were isolated in larger amounts than III. All three aldehydes formed oximes and semicarbazones, but III was not obtained in the crystalline form, due to insufficient quantities isolated. Saponification of these apo-norbixinal methyl esters with alcoholic sodium hydroxide yielded the corresponding apo-norbixinals.

Stable bixin yielded three apo-norbixinal methyl esters on permanganate oxidation. The main product was an apo-1-norbixinal methyl ester, completely different from II. The apo-2-norbixinal methyl ester was obtained in such small amounts that it could not be isolated in the crystalline form. However, absorption spectra data showed it to be different than III. The apo-3-norbixinal methyl ester isolated was identical with IV. Since II and III differed from the isomers obtained by the oxidation of stable bixin, but the two apo-3-norbixinal methyl esters were identical, it was concluded that the third double bond from the free carboxyl was responsible for the isomerism between labile and stable bixin. Another fact which supported this conclusion was that II could be converted to the apo-1-norbixinal methyl ester obtained from the oxidation of stable bixin by the use of iodine in glacial acetic acid. This same reaction was carried out in the case of III, and the apo-2-norbixinal methyl ester was identical with the one obtained by the oxidation of stable bixin. From this series of reactions, the formulas of the labile and stable bixin are pictured graphically as follows:

Labile bixin



Stable bixin



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Lennard-Jones, Proc. Roy. Soc., (A) 158, 280 (1936)

Reported by C. F. Segal
March 9, 1937.

Adickes -- Tübingen

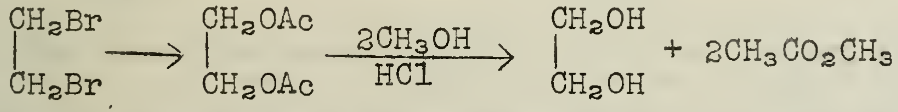
Transesterification is the reaction of an ester with an alcohol to form a new ester and a new alcohol as follows:

$$RCO_2C_2H_5 + R'OH \rightleftharpoons RCO_2R' + C_2H_5OH$$

It was first described in 1852 by Duffy who found that by heating fats with alcoholic sodium ethoxide he could make ethyl stearate and likewise amyl stearate.

Many catalysts have been used to bring about this reaction, probably the most common is alkali alcoholates. The Zemplén method for alcoholysis of sugar acetates uses methanol and sodium methoxide. α-Cellobiose octaacetate treated with methanol and sodium methoxide gives cellobiose in good yield. Fischer and Bergmann obtained glucose by treating the pentaacetate with sodium ethoxide and ethanol in 75 per cent of the theoretical yield.

Acid catalysts are common. Haller obtained methyl esters of myristic, palmitic and stearic acids by treating fats with excess methanol in the presence of hydrogen chloride. Willstätter and Stoll split phytol from chlorophyll with methanol and hydrochloric acid. Fischer and Bergmann obtained salicylic acid in 84 per cent yield from acetyl salicylate with excess methanol and hydrogen chloride. The common method of preparing glycol uses hydrogen chloride as catalyst.



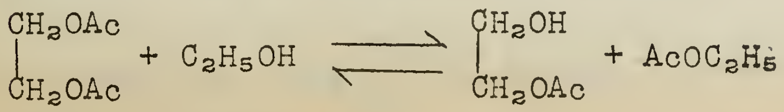
$$\begin{array}{l}CH_2Br\\ |\\ CH_2Br\end{array} \longrightarrow \begin{array}{l}CH_2OAc\\ |\\ CH_2OAc\end{array} \xrightarrow[HCl]{2CH_3OH} \begin{array}{l}CH_2OH\\ |\\ CH_2OH\end{array} + 2CH_3CO_2CH_3$$

Phillips' revised method for acetyl determinations is dependent upon transesterification with ethanol in the presence of p-toluenesulfonic acid.

Dilute alkalies are common catalysts. Kremann reports transesterification of glycoldiacetate, triacetin and mannose hexaacetate to the extent of 93 per cent, 86 per cent and 88 per cent respectively with excess ethanol in dilute sodium hydroxide. Toyama reports nearly quantitative alcoholysis of olive oil in the presence of alcoholic sodium hydroxide. The preparation of acetol is an example of transesterification in dilute alkali.

$$CH_3COCH_2Br + HCO_2K \longrightarrow CH_3COCH_2OCHO \xrightarrow[KOH]{CH_3OH} CH_3COCH_2OH + HCO_2CH_3$$

Transesterification has been observed without catalysts. The first experiments were carried out by Demole in 1875. He split glycol diacetate with ethanol.

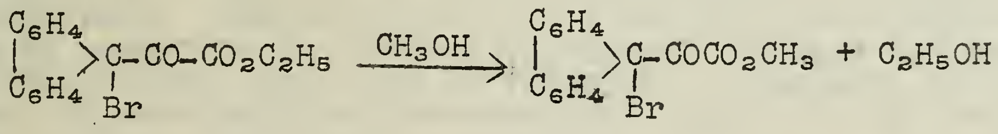


$$\begin{array}{l}CH_2OAc\\ |\\ CH_2OAc\end{array} + C_2H_5OH \rightleftharpoons \begin{array}{l}CH_2OH\\ |\\ CH_2OAc\end{array} + AcOC_2H_5$$

Grün reports that tristearin with absolute ethanol at 200° shows 12 to 13 per cent conversion to ethyl stearate. Similar treatment with isoamyl alcohol gave 14 per cent of the isoamyl ester.

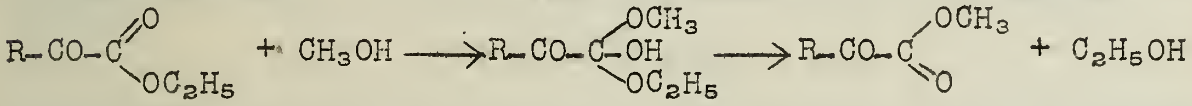
Numerous patents have been issued for alcoholysis especially of fats. One patent reports treatment of cottonseed oil with glycerol in the presence of dilute phosphoric acid to form edible fatty esters. Mono- and diglycerides are prepared by heating the fat with the required amount of glycerol at 170° to 205° with various catalysts, alkali metal alcoholates, soaps and dilute acids. Glycerides treated with excess aliphatic alcohols give the alkyl fatty acid esters and glycerol.

The relation of the structure of carboxylic acids to the extent of methanolysis of their ethyl esters has been studied by Adickes. His study was started by the observation that ethyl-β-diphenylene-β-bromopyruvate was readily changed to the methyl ester by warming with methanol.



$$\mathrm{(C_6H_4)_2C(Br){-}CO{-}CO_2C_2H_5 \xrightarrow{CH_3OH} (C_6H_4)_2C(Br){-}COCO_2CH_3 + C_2H_5OH}$$

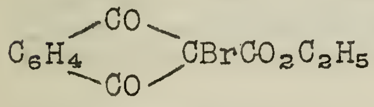
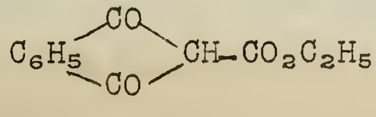
He believes the reaction depends upon the ability of the ester to add alcohol:



$$\mathrm{R{-}CO{-}C(=O)OC_2H_5 + CH_3OH \longrightarrow R{-}CO{-}C(OCH_3)(OH)OC_2H_5 \longrightarrow R{-}CO{-}C(OCH_3){=}O + C_2H_5OH}$$

The reactions were carried out by refluxing the ethyl esters of the various acids studied in a 5- to 10-mole excess of absolute methanol for eight hours. The alcohol was distilled off and the iodoform test made on the distillate. The residual methyl esters were isolated.

Esters of acids similar to β-diphenylene-β-bromopyruvic acid failed to undergo interchange (namely tribromopyruvic, β-diphenylene-β-benzylpyruvic, β-diphenylene-α-hydroxyacrylic and diphenylene acetic) indicating that its reaction is in a high degree dependent upon its particular structure.

Ethyl-2-bromo-1,3-diketohydrindene-2-carboxylate  (I) with the bromomethine group in the α-position and the carbonyl group in the β-position underwent the interchange to nearly an equal extent. The specificity of the structure is less marked here because ethyl-1,3-diketohydrindene-2-carboxylate  which may have an enol form

underwent the transesterification but to a lesser extent. However, the chloroanalog of I was entirely inactive. This failure to react was explained as due to difference in structure of the two halogen compounds.

Replacement of the diketohydrindene group by benzoyl gave inactive esters (benzoyldibromoacetate, benzoylmethylbromoacetate and benzoylacetoacetate).

Numerous other esters with various types of structure gave negative results. Slight interchange was noted with the ethyl esters of formic, benzoylformic, dihydroxymalonic and ketomalonic acids.

Ethyl formate with benzyl alcohol was readily converted to benzyl formate in 50 per cent yield. Ethyl oxalate, however, gave only about 2 per cent benzyl oxalate.

Adickes concludes that the presence of an α- or β-keto group is necessary for rapid conversion to the methyl ester under the conditions used. However, this is not the only requirement as may be seen by comparing the unreactive esters. He does not believe that the halfacetal which may be formed is a necessary intermediate. No more definite statement was made as to the relative activity of the ester group.

The relative activity of various alcohols in terms of their replacing power in alcoholysis has been studied by Adkins.

$$\mathrm{AcOR} + \mathrm{R'OH} \rightleftharpoons \mathrm{AcOR'} + \mathrm{ROH}$$

The relative replacing powers of twenty-seven alcohols compared with methanol given a value of 1 are reported. The following conclusions of significance are drawn: 1) In two homologous series of primary and secondary alcohols studied no progressive alteration in replacement values occurs as the series is ascended. 2) In a series of primary straight chain alcohols containing 1 to 12 carbon atoms methanol and pentanol-1 have the nearly identical replacement values of 1 and 0.98 respectively. 3) Ethanol, propanol-1, and butanol-1 are nearly identical in reactivity, about 0.8. 4) Hexanol-1, heptanol-1, nonanol-1 and decanol-1 have a value of about 0.88. 5) In a series of straight chain secondary alcohols pentanol-2 has the highest replacement value of 0.8. Propanol-2 and butanol-2 are lower with values of 0.55 and 0.53. 6) A comparison of the series of primary alcohols with secondary alcohols shows that with a given carbon content, the secondary alcohol is 0.16 to 0.25 lower in replacement value than the primary alcohol. 7) Introduction of unsaturation as in allyl alcohol reduces reactivity.

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Hatch and Adkins, J. Am. Chem. Soc., 59, 1694 (1937)

Reported by Donald E. Wolf
March 9, 1938.

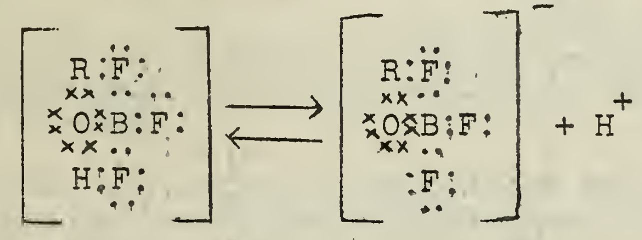
ORGANIC REACTIONS USING BORON FLUORIDE

Meerwein -- University of Marburg
Nieuwland and Sowa -- University of Notre Dame

The purpose of this discussion is to show the application of boron fluoride in syntheses of organic compounds.

Preparation.--The boron fluoride is made by warming a mixture of boric oxide and calcium fluoride with concentrated sulfuric acid. The boron fluoride may be passed directly into the reaction flask, or added from a stock solution prepared by absorbing it in methyl alcohol, ethyl acetate, or ether.

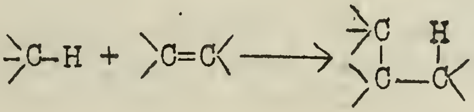
Coordination Compounds.--Boron fluoride forms addition compounds with water, alcohols, acids, esters, ethers, phenols, ammonia, amines, nitriles, etc. Two compounds of ethyl alcohol with boron fluoride, $BF_3 \cdot C_2H_5OH$ and $BF_3 \cdot 2C_2H_5OH$, have been reported. The following structure has been suggested for the former,



The dialcoholate may be purified by distillation. The monoalcoholate decomposes on distillation.

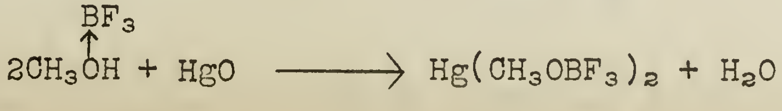
Polymerization.--Olefins are polymerized even by very small amounts of boron fluoride. This catalyst had no effect on paraffins under the conditions used.

Reaction of Paraffins with Olefins.--Ipatieff has shown that olefins react with paraffins to give higher paraffins in the presence of nickel, a small amount of water and boron fluoride according to the following equation:



Naphthenes containing a tertiary carbon atom like methyl cyclopentane and methyl cyclohexane are readily alkylated by olefins in the presence of boron fluoride.

Acetals and Ketals.--Numerous acetylenic compounds and alcohols have been condensed by boron fluoride and mercuric oxide to give acetals and ketals which could not be prepared by any other means. A suggested mechanism for acetal formation is the following:



$$2CH_3\overset{\overset{BF_3}{\uparrow}}{O}H + HgO \longrightarrow Hg(CH_3OBF_3)_2 + H_2O$$

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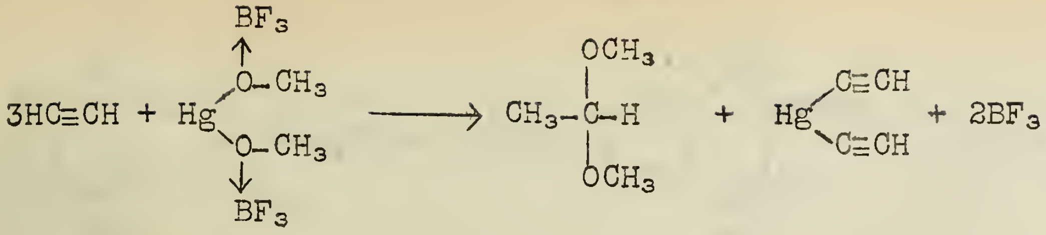
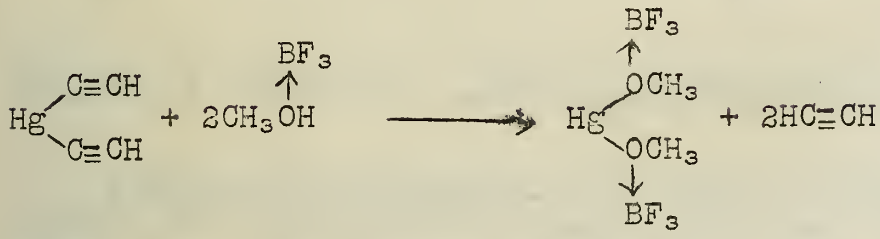




Esters.--Esters may be prepared,

(1) by the action of an acid boron fluoride compound with an alcohol.

(2) by the cleavage of ethers in the presence of an acid and boron fluoride. The yields of esters are generally low when this method is used.

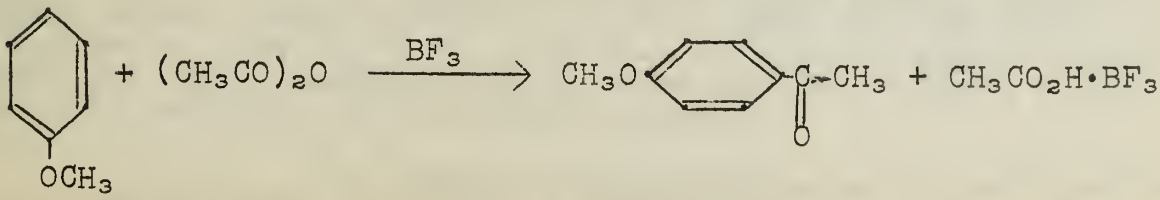
(3) by the action of alcohol or phenols on amide-boron fluoride compounds with the splitting out of monoammino-boron fluoride, $NH_3 \cdot BF_3$.

(4) by the action of olefins on acids in the presence of boron fluoride. No action takes place in the nucleus in the case of benzoic, *o*-chlorobenzoic, *p*-nitrobenzoic, phenyl acetic and furoic acids. Nuclear substitution occurs in the case of salicylic acid.

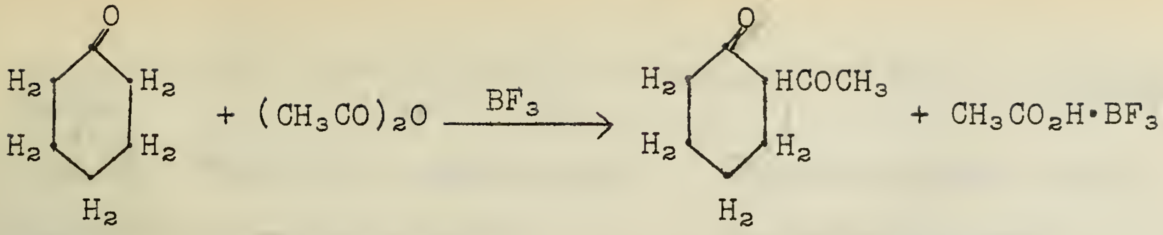
Nitriles.--When acetamide boron fluoride was treated with a small amount of acetic acid, acetonitrile was formed in almost quantitative yields.

Substituted Amides.--Aniline and acetamide boron fluoride give almost the theoretical yield of acetanilide after being warmed for only a few minutes together.

Simple Ketones and Beta-Diketones.--A Friedel and Craft type of reaction using ethers and anhydrides with boron fluoride and aromatic compounds yield ketones with the elimination of the boron fluoride compound of the alcohol or acid.

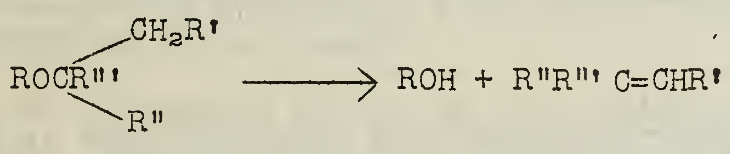


Good yields of *beta*-diketones are obtained by the action of anhydrides on ketones in the presence of boron fluoride.



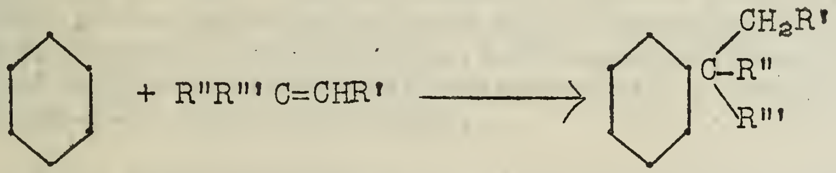
$$CH_3COCH_3 + (CH_3CO)_2O \xrightarrow{BF_3} CH_3COCH_2COCH_3 + CH_3CO_2H{\cdot}BF_3$$

Alkylation of Benzene.--Four types of compounds have been used in the alkylation of benzene. Olefins, alcohols, esters, and ethers react with benzene to give mono-, di-, and trialkylated benzenes. When sulfuric acid and boron fluoride were used as joint catalysts propylene was absorbed by benzene with considerable evolution of heat. The ratio by weight of mono- to diisopropyl benzene formed varied with the ratio of boron fluoride to sulfuric acid present. With boron fluoride practically no meta-compound is obtained. Approximately 98 per cent of the di-compound is para and the remainder is ortho. The tri-derivative is 1,3,4-triisopropylbenzene. The reaction of alcohols, esters, and ethers probably takes place in the same manner. There is first a cleavage of the compound at the oxygen atom which coordinates with the boron fluoride to give an olefin. The olefin then reacts in the manner as given for propylene and benzene.



$$ROCR''' (CH_2R')(R'') \longrightarrow ROH + R''R'''C{=}CHR'$$

Where R is a hydrogen atom for alcohols, formate radical for esters, or an alkyl or aryl group for ethers.



No sulfuric acid was required with the boron fluoride for alkylating benzene with alcohols, esters, or ethers.

Alkyl Phenols.--

1. Rearrangement of alkyl phenyl ethers.--Alkyl phenyl ethers rearrange readily under the influence of boron fluoride to give fifty to sixty-five per cent yields of alkyl phenols. When isopropyl phenyl ether was rearranged it gave a 65 per cent yield of o-isopropyl phenol.

2. Phenol and propylene.--As a continuation of the rearrangement given above substituted phenols were formed directly from phenol and propylene in which the ether intermediate rearranged to give an alkyl phenol. On further treatment with

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propylene the reaction proceeds similarly to give a polyalkylated phenol.

$C_6H_5OH + CH_3CH{=}CH \longrightarrow C_6H_5OC_3H_7$ (isopropylphenyl ether) I

$C_6H_5OC_3H_7 \longrightarrow C_6H_4(C_3H_7)OH$ (*o*-isopropylphenol) II

$C_6H_5(C_3H_7)OH + C_3H_6 \longrightarrow C_6H_4(C_3H_7)OC_3H_7$ (*o*-isopropylphenyl isopropyl ether) III

$C_6H_4(C_3H_7)OC_3H_7 \longrightarrow C_6H_3(C_3H_7)_2OH$ (2,4-derivative) IV

$C_6H_3(C_3H_7)OH + C_3H_6 \longrightarrow C_6H_3(C_3H_7)OC_3H_7$ V

$C_6H_3(C_3H_7)OC_3H_7 \longrightarrow C_6H_2(C_3H_7)_3OH$ VI

$C_6H_2(C_3H_7)_3OH + C_3H_6 \longrightarrow C_6H_2(C_3H_7)_3OC_3H_7$ (2,4,6-derivative) VII

3. *Phenol and alcohols*.--Alcohol reacts with phenol to give ethers and alkyl substituted phenols. The alcohol first loses water and goes to the olefin which then reacts with the phenol.

Substituted Phenolic Carboxylic Acids.--

1. *Rearrangement of alkyl salicylates*.--Isopropyl salicylate rearranges in the presence of boron fluoride to give 2-hydroxy-3-isopropyl benzoic acid.

2. *Propylene and o-, m-, and p-hydroxybenzoic acids*.--Salicylic acid condenses with propylene to give isopropyl salicylate which readily rearranges to 2-hydroxy-3-isopropylbenzoic acid which again combines with propylene to form the ester and so on. The products isolated were: isopropyl salicylate, 2-hydroxy-3-isopropylbenzoic acid, isopropyl-2-hydroxy-3-isopropylbenzoate, 2-hydroxy-3,5-diisopropylbenzoic acid, isopropyl-2-hydroxy-3,5-diisopropylbenzoate, and a trace of isopropyl-2-hydroxy-5-isopropylbenzoate.

With *p*-hydroxybenzoic acid and propylene the following products were obtained, 4-isopropoxybenzoic acid, isopropyl-4-isopropoxybenzoate and isopropyl-3-isopropyl-4-isopropoxybenzoate.

Propylene condensed with *m*-hydroxybenzoic acid to give 3-isopropoxybenzoic acid, isopropyl-3-isopropoxybenzoate, isopropyl-4-isopropyl-3-isopropoxybenzoate and a small amount of isopropyl-*m*-hydroxybenzoate.

3. *Salicylic acid and alcohols*.--Both *n*-propyl and isopropyl alcohol with salicylic acid yield the same products as propylene and salicylic acid as far as the reaction was permitted to go although not enough alcohol was used to allow the reaction to go to completion.

Preparation of Phenolphthalein and Fluorescein.--Phthalic anhydride, resorcinol and boron fluoride in benzene gave after a three-hour reflux a practically theoretical yield of fluorescein. Phthalic anhydride, phenol, and boron fluoride gave a 72 per cent yield of crude phenolphthalein after heating for one hour.

Rearrangements.--Boron fluoride is an active isomerizing agent in the following rearrangements: the benzidine rearrangement of diazoamino benzene to aminoazobenzene, phenylacetate to p-oxyacetophenone, and the Beckmann rearrangement for oximes.

Summary.--Almost any reaction requiring an acid catalyst is catalyzed by boron fluoride.

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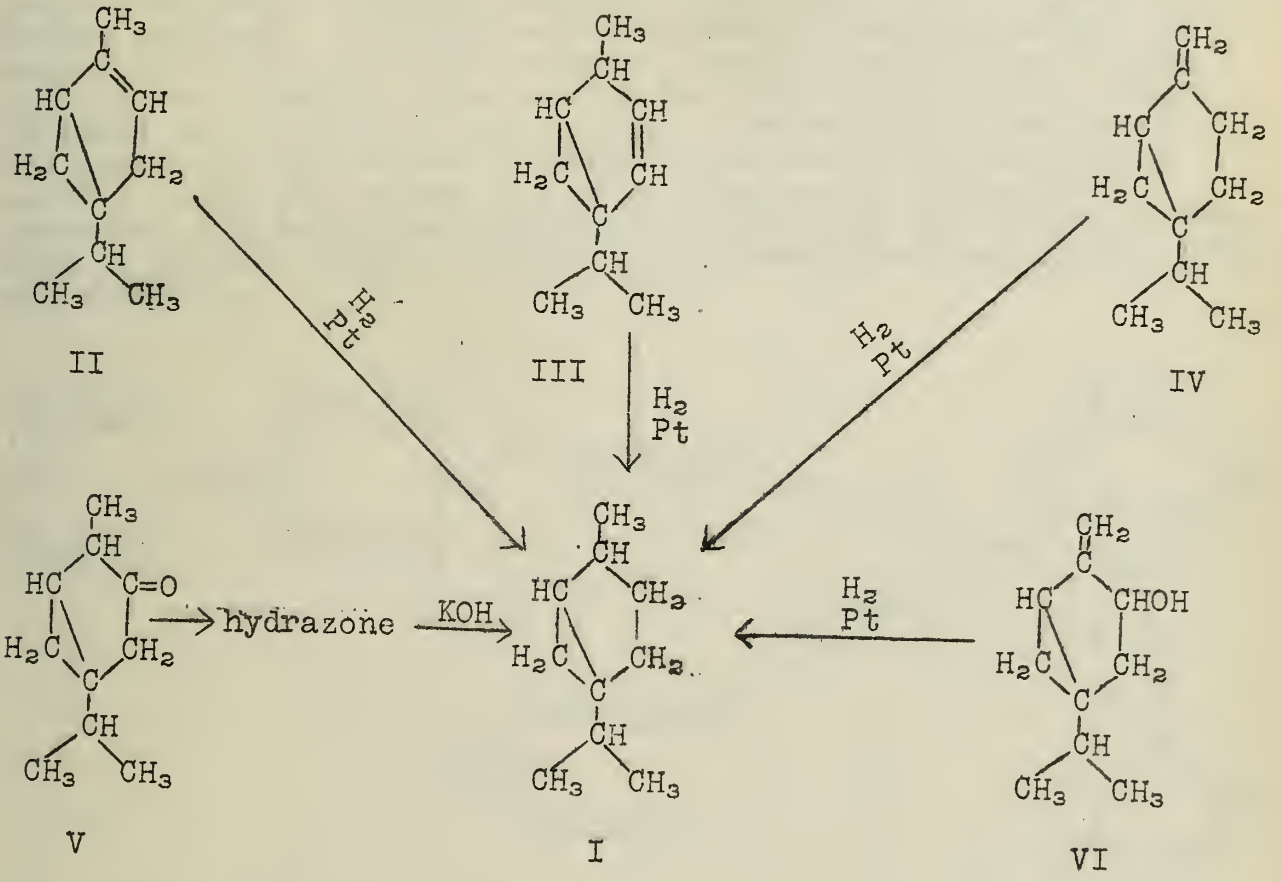
Ipatieff and Grosse, J. Am. Chem. Soc., 57, 1616 (1935)
Ipatieff, et al, ibid., 57, 1722 (1935)
Nineteen articles in a series and about five supplementary articles by Nieuwland, Sowa, and coworkers in the Journal of the American Chemical Society of which the latest is
Dorris and Sowa, J. Am. Chem. Soc., 60, 358 (1938)

Reported by G. F. Grillot and
A. Berger
March 16, 1938.

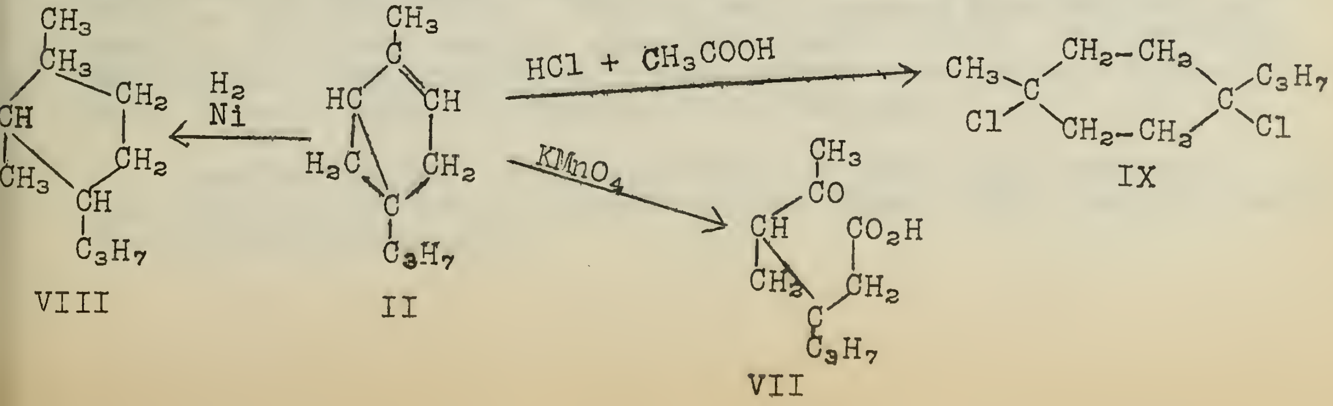
SYNTHESIS OF THUJANE

Guha — Indian Institute of Science, Bangalore

Thujane (I) was first obtained in 1910 by Tschugaev and Fomin as the product of reduction of α-thujene (II), β-thujene (III) and sabinene (IV). The density, refractive index, and boiling point were the same regardless of the source of the thujane, but the specific rotation was different in each case. Thujane has also been obtained from thujone (V) and sabinene (VI).

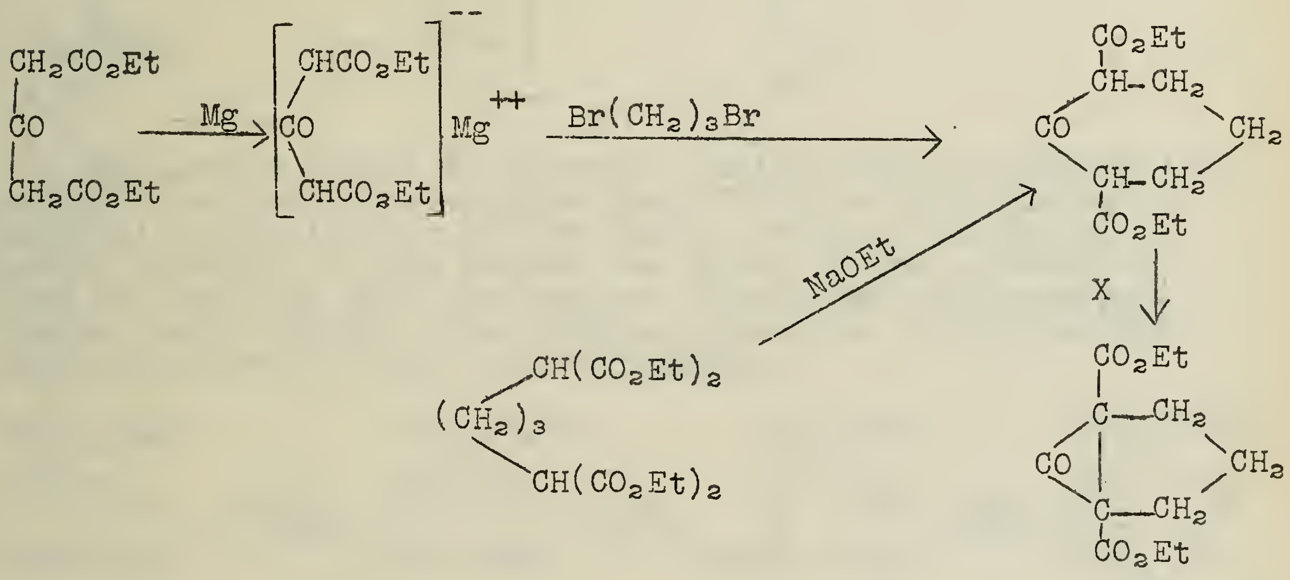


Cyclopropane, cyclopentane, and cyclohexane derivatives have been formed in the study of the structures of members of the thujane group. For example, α-thujene (II) gives thujaketonic acid (VII) when oxidized with permanganate, 1,2-dimethyl-5-isopropylcyclopentane (VIII) by reduction in the presence of nickel, and 1,4-dichloro-1-methyl-4-isopropylcyclohexane (IX) by treatment with hydrogen chloride in acetic acid.



Only a few compounds containing the bicyclo (0,1,3) hexane ring structure have been prepared. Guha's synthesis of thujane represents the first total synthesis of a member of this series, although Ruzicka and Koolhaas prepared thujone from thujaketonic acid.

Guha's first problem in the synthesis of thujane was to prepare suitable materials for the formation of the bicyclo-(0,1,3)-hexane skeleton. Diethyl-1-cyclohexanone-2,6-dicarboxylate (X) seemed to be the most satisfactory starting material since the only active hydrogen atoms are in the 2- and 6-positions. This compound was obtained by the action of trimethylene bromide on the magnesium derivative of diethyl acetone-1,3-dicarboxylate as well as by the action of sodium ethylate on tetraethyl-pentane-1,1,5,5-tetracarboxylate. By treating the sodium derivative of X with bromine, diethyl northujone-1,3-dicarboxylate (XI) was obtained.

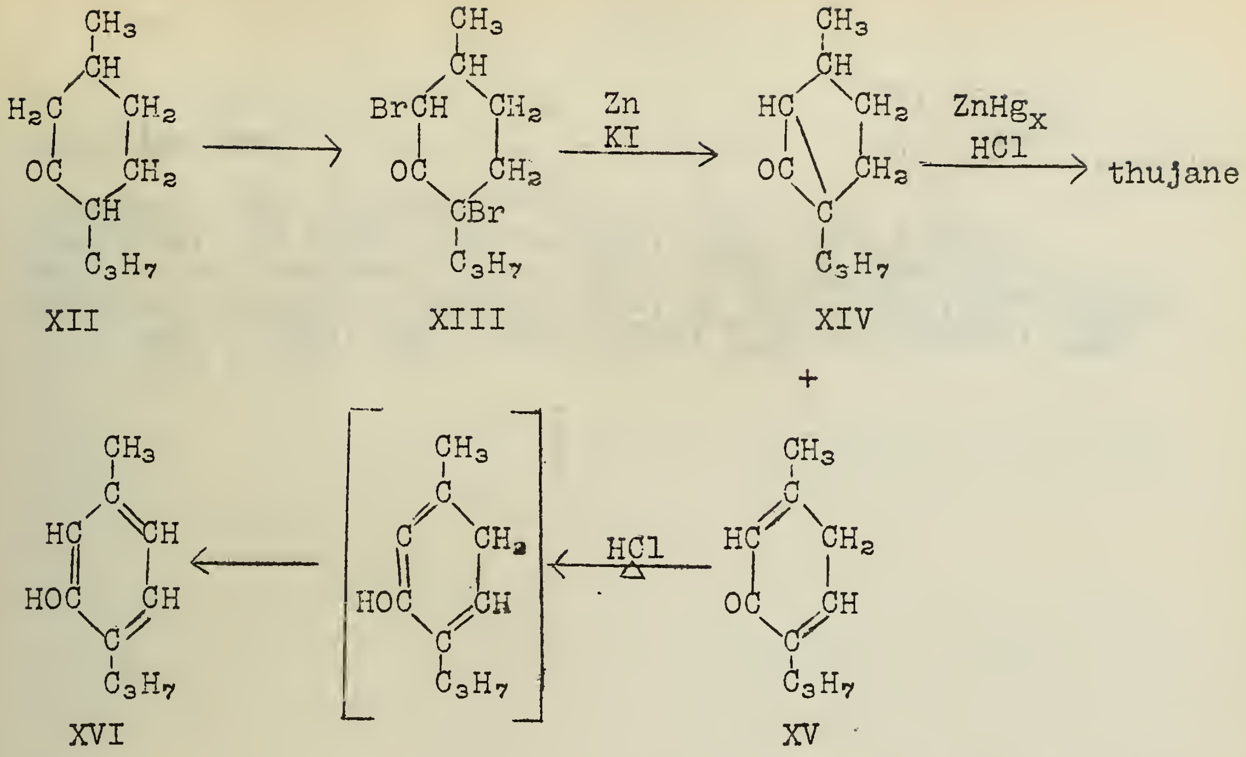


X

XI

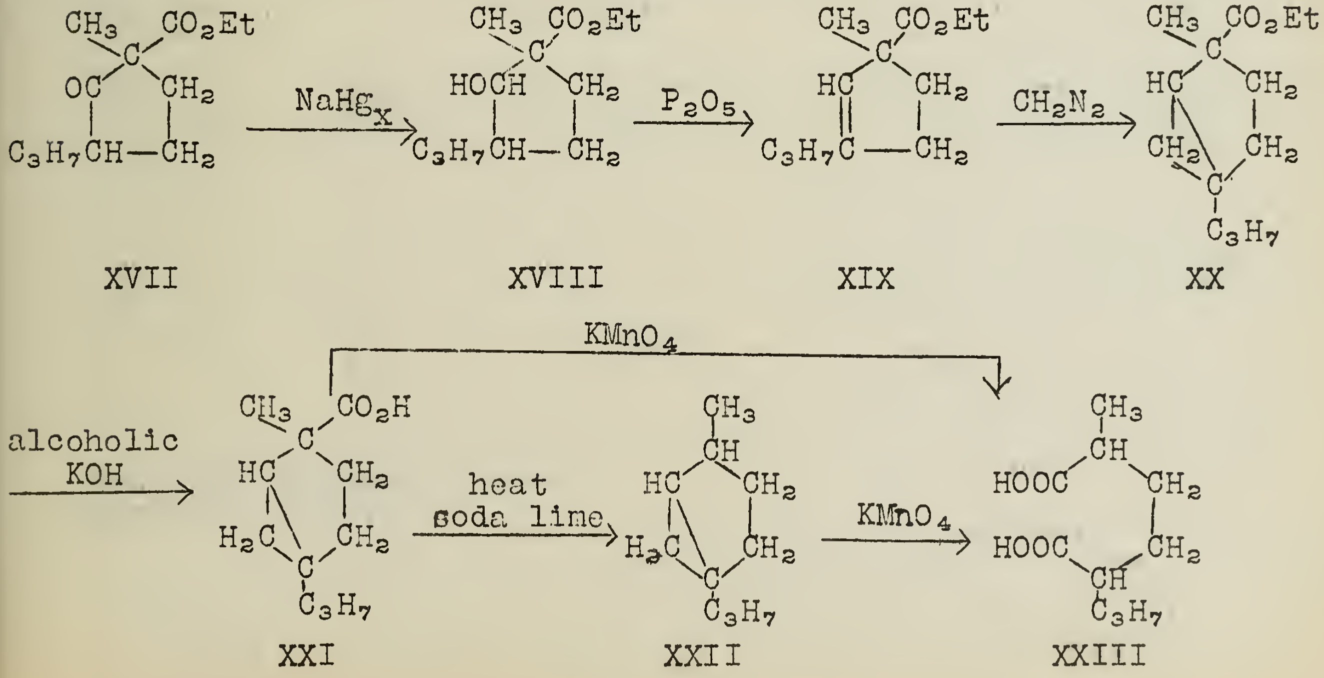
Thujane was prepared by two methods. In the first of these, *l*-menthone (XII) was brominated and the resulting dibromide (XIII) treated with zinc in the presence of potassium iodide. The principal product was optically active and was, therefore, the bicyclo compound (XIV). Thujane was prepared from XIV by reduction with zinc amalgam and hydrochloric acid. The physical properties (except specific rotation) of this product agreed with those of thujane prepared from thujone.

Another product of the reaction of XIII with zinc was identified as XV by its conversion to thymal (XVI) when refluxed with hydrochloric acid.



XII XIII XIV XV XVI

The second method of synthesis, using ethyl-1-methyl-3-isopropyl-2-cyclopentanone-carboxylate (XVII) as the starting material is outlined in XVII to XXII. Evidence for the cyclohexane structure of the product was given by the oxidation of both XXI and XXII with permanganate to α-methyl-α'-isopropyladipic acid (XXIII). The physical properties of the product agreed with those of the natural thujane.



XVII XVIII XIX XX

XXI XXII XXIII

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Reported by Wesley Fugate
March 23, 1938.

DETERMINATION OF cis-trans ISOMERISM IN CYCLIC COMPOUNDS

Knowledge of methods of determining cis or trans configurations is essential in the field of sterols and related compounds. It is of theoretical interest in connection with the actual structure of molecules. The methods are:

1. Resolution.--Many cis forms of simple compounds are meso. The corresponding trans forms are resolvable. Its use is limited.

2. Physical data.--Both isomers must be compared. The cis form usually has the higher boiling point, the greater density, refractive index, and smaller molecular refraction. The cis form is less associated.

3. Chemical reactions.--

(a) The formation of a lactam or lactone is usually easier with the cis isomer.

(b) Dehydration occurs most readily with the trans isomer.

(c) Degradation to a known cis or trans isomer may be undertaken usually by oxidation. Rearrangement may occur.

(d) Hydrogenolysis occurs at the same rate with similar compounds of the cis form to differentiate them from the slower reacting trans isomers.

4. Synthesis.--A reaction which is supposedly general is the catalytic hydrogenation of compounds with platinum in acetic acid solution to give the cis isomer. In neutral or basic solution the trans isomer is formed.

5. Special cases.--The 1,2-diols may be assigned a cis configuration if a boric acid solution has a high augmentation of conductivity, or if it reacts with acetone and hydrochloric acid to give an acetal.

With the exception of the first they are merely observations, and, unfortunately, are not as general as they should be.

The explanations in order to correlate these seemingly irrelevant facts are based on the steric positions of the groups in the molecule. Thus, a cis form should be more sterically hindered, which would lead to a smaller molecular weight and a slower reaction rate. This is generally true.

Hückel has recently undertaken an investigation of the decalol and hydrindol series to add to these studies. He found exceptions. *Cis*-α-decalol (m. p. 93°) (obtained by an acid hydrogenation of *cis*-α-decalone) has a greater saponification rate than *cis*-α-decalol (m. p. 55°). But he found the former alcohol to have an unusually high activation energy and suggests that other exceptions might also be found to have high activation energies. He could not explain the fact, however, that the saponification rates of the succinates and phthalates of the 4-*cis* hydrindols did not agree with each other. From this and the rather inconclusive data on the other isomers, he decides that the positions of the groups other than the fused ring positions cannot be ascertained due to the mobility of the rings.

He, then, describes the latest method of distinguishing *cis* or *trans* isomers, namely:

6. *The thermal stability of the toluene sulfonic esters.*---The compounds produced by acid hydrogenation are the most unstable, decomposing in an hour's time to an unsaturated hydrocarbon. Not a single exception has been found to date. This might indicate a factor other than steric hindrance, but it is too recent to predict its true worth.

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Reported by D. Pearson
March 23, 1938.

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THE WALDEN INVERSION

Walter Hückel -- Chemical Institute, Gottingen

In studying the Walden inversion on compounds containing one asymmetric center, there is always some difficulty in correlating the configuration of the starting material with that of the substitution product. Hückel believed that if one were to work upon a compound with more than one asymmetric carbon atom, this task would be simplified. He chose to work upon derivatives of decalin and hydrindane.

Ortho-methyl cyclohexanone upon reduction yields two isomeric alcohols. By varying the conditions of the reduction it is possible to obtain either one of the possible isomers in practically pure condition. Thus catalytic hydrogenation in acid solution with a platinum catalyst leads to practically pure cis-methyl cyclohexanol, while reduction with sodium in ethyl alcohol leads to the pure trans-isomer. This generalization holds for the reduction of all hydro-aromatic compounds having an alkyl group substituted on the carbon next to the carbonyl group. It is also known to hold for many monocyclic compounds having substituents in the 3 and 4 positions, but here there are exceptions. Reduction of the oximes of such ketones also gives two pure isomeric amines under the two sets of conditions. It is Hückel's chief assumption that the alcohol and amine produced under the same experimental conditions will have the same spacial configurations.

He prepared alcohols and amines as indicated in Table I; treated the amines with nitrous acid and separated the products shown. The last column shows whether or not the Walden inversion has occurred.

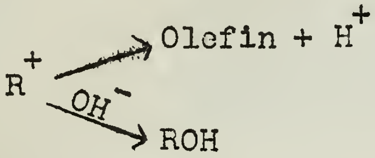
In the case of the isomeric methyl cyclohexanols, it has been shown that reduction with sodium in alcohol yields the trans-isomer, while reduction with hydrogen and platinum in acid solution yields the cis-form. The absolute configuration of the decalols and hydroxyhydrindanes discussed in this paper have not been proved with certainty. However, for our purpose this is not necessary. Take for purposes of illustration a specific example--the reduction products of trans-β-decalol melting at 75°. Reduction of the oxime of trans-β-decalone gave an amine which when treated with nitrous acid gave a 100 per cent yield of the alcohol melting at 75°. Therefore, it may be concluded that in this replacement no Walden inversion occurred. On the other hand, the decalol produced by reduction of the ketone with hydrogen and platinum in acid solution melted at 53°. The amine produced by the reduction of the oxime under the same experimental conditions, when treated with nitrous acid yielded 70 per cent unsaturated hydrocarbon and only 30 per cent β-decalol, but 90 per cent of this alcohol was the isomer melting at 75°. Hence, in this case the Walden inversion has occurred.

Casual examination of the results as shown by the table would make one despair of ever finding a generalization which will explain all of the cases. However, Hückel makes the following attempt:

The decomposition of an aliphatic diazonium ion is assumed to proceed according to the following scheme:

$$RNH_2 + ONOH + H^+ = RN_2]^+ + H_2O$$
$$RN_2]^+ = R^+ + N_2$$

The substitution is then just an addition of a negative ion to the positive radical. This requires that the positive radical be stable for a length of time greater than that required for substitution. However, the positive radical may stabilize itself by either of two reactions:



This explains the observed formation of unsaturated hydrocarbons in many of the reactions. Next consider the possible mechanisms for the formation of the alcohol. Since there is no localization of the positive charge on one side or the other of the ion, from an electrostatic viewpoint there is no apparent reason why the entering ion should choose one side of the positive radical rather than the other. On the other hand, if the radical is sterically stable for a time after the loss of the N_2, the corner vacated by the nitrogen should be easily attached, while the opposite side should be sterically hindered by the other three groups on the carbon. Therefore, addition without inversion should go readily, while the other should not. This conclusion cannot explain the cases in which an inversion is observed. However, it is conceivable that in more complicated molecules, the opening left by the removal of the N_2 is closed by the hindrance of atoms not adjacent to the asymmetric carbon. If this were the case the reaction leading to formation of an alcohol would be slowed down giving the olefin-forming reaction a chance to assert itself, thus explaining the frequent appearance of olefin formation with inversion.

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Reported by Max Mueller
March 30, 1938.

TABLE I

	Ketone	Melting Point of Corresponding Alcohol	Products from the Treatment of the Corresponding Amine with HNO_2	Walden Inversion
Trans-Ring	α-Decalone			
	[1]I	63°	100% α-decalol, m.p. 63°	-
	II	49	70% hydrocarbon; 30% α-decalol of which 90% melted at 63°	+
	β-Decalone			
	I	75	100% β-decalol, m.p. 75°	-
	II	53	70% hydrocarbon; 30% β-decalol of which 90% melted at 75°	+
Cis-Ring	α-Decalone			
	I	55	25% hydrocarbon; 75% α-decalol of which 10% melted at 93°	(-)
	II	93	100% α-decalol, m.p. 93°	-
	β-Decalone			
	I	18-31	100% β-decalol, m.p. 105°	+
	II	105	30% hydrocarbon; 70% β-decalol of which 90% melted at 18-31°	+
	4-Ketohydrindane			
	I	liqu.	20% hydrocarbon; 80% 4-hydroxyhydrindane of which 20% melted at 16-31°	(-)
	II	16-31	100% 4-hydroxyhydrindane, m.p. 16-31°	-
	5-Ketohydrindane			
	I	20	20% hydrocarbon; 80% 5-hydroxyhydrindane, m.p. 43°	+
	II	43	40% hydrocarbon; 60% 5-hydroxyhydrindane of which 80% melted at 20°	+
	α-Hydrindanone			
	I	liqu.	35% hydrocarbon; 65% α-hydrindanol of which 20% melted at 18°	(-)
	II	18	30% hydrocarbon; 70% α-hydrindanol which was a liquid	+
	β-Hydrindanone			
	I	10		
	II	5	100% β-hydrindanol of which 80% melted at 10°	+

---

1. I - Reduction with Na and EtOH
   II - Reduction with H_2 and Pt in acid solution.

SYNTHESIS IN THE HYDROAROMATIC SERIES

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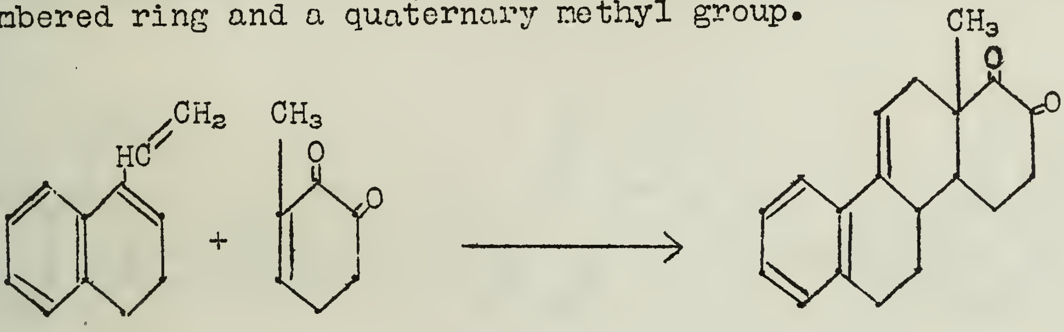
The object of this research is to work out methods for preparing hydrogenated polycyclic ring systems such as cyclopentanoperhydrophenanthrene, of which the sterols, bile acids, sex hormones, suprarenal cortex hormones, Vitamin D, plant heart poisons and toad poisons are derivatives. Specifically, the object of the work described is 1) to prepare a methyl cyclopentene derivative and 2) to condense this derivative with a suitable diene to form a tetracyclic ring system containing a 5-membered ring and a quaternary methyl group.

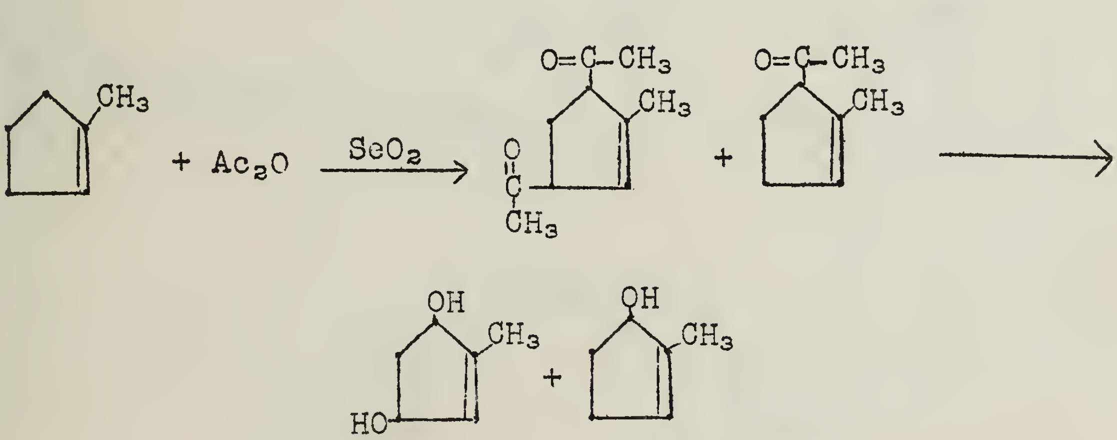
I



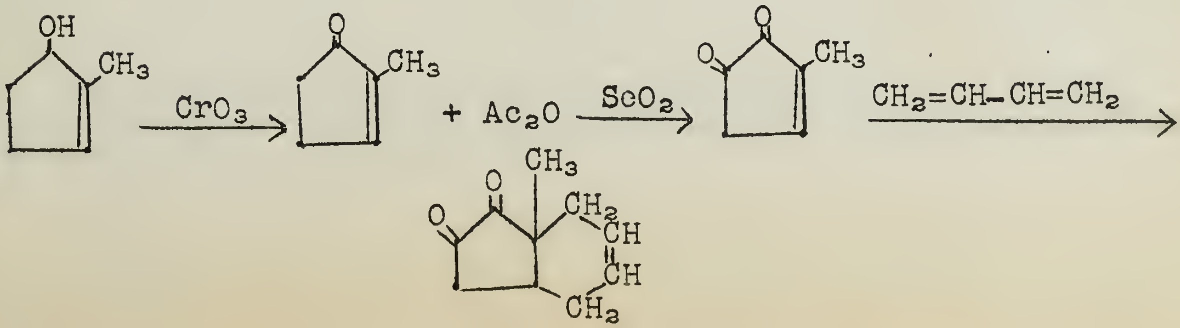
Attainment of the second objective has not yet been reported. The difficulties in preparing the sterol nucleus are caused by the quaternary aliphatic groups, the variety of possible isomers due to the number of asymmetric carbon atoms and <u>cis-trans</u> forms, and the amount and position of unsaturation.

Methyl cyclopentenedione was prepared from methyl cyclopentene. This ketone was active enough to react with butadiene.

II



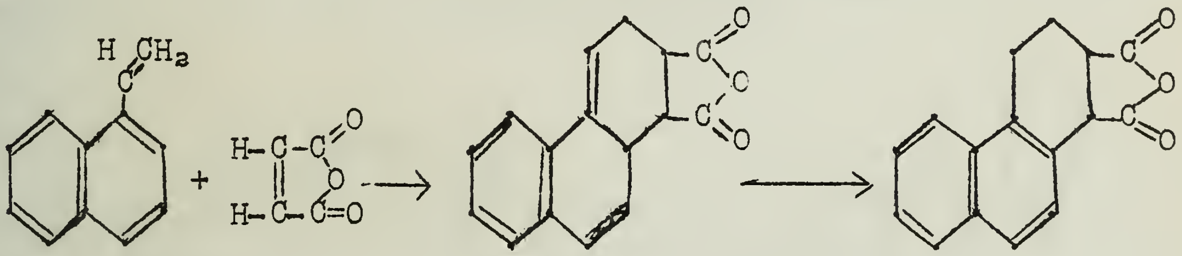
III



This indicated a similar reaction with a diene like that in equation I should occur.

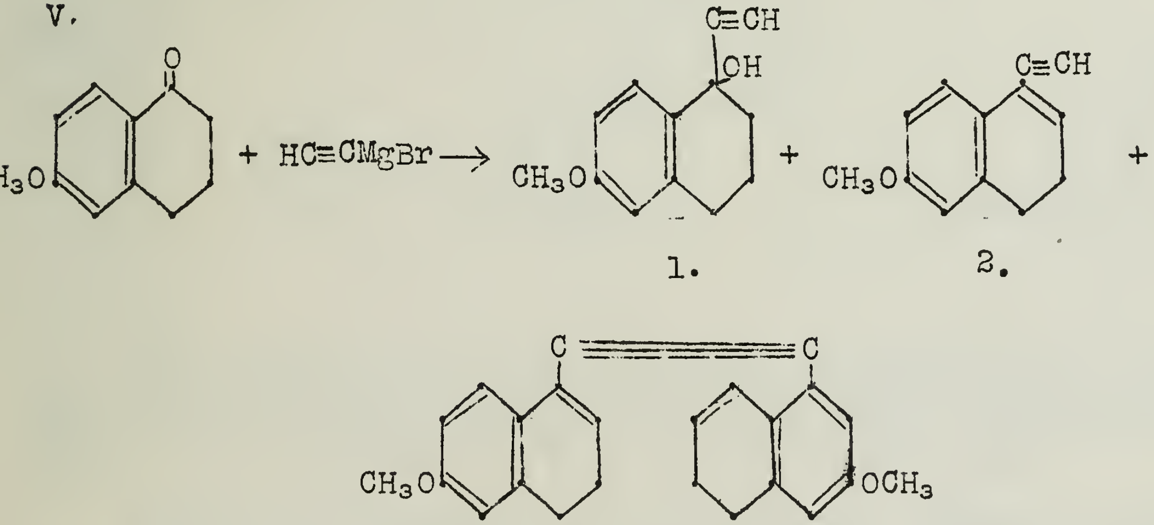
The next step was the preparation of such a diene. R. Robinson had treated α-tetralone with ethyl bromoacetate, reduced the ester to the alcohol and hoped to dehydrate the alcohol to the olefin. However, reduction to the alcohol also reduced the double bond in the ring and the saturated compound was useless for a diene synthesis. A. Cohen has reported a diene synthesis from 1-vinyl naphthalene.

IV



The present authors after some modification of the usual methods, prepared 1-vinyl-6-methoxy-3,4-dihydronaphthalene by treating 6-methoxy tetralone with acetylene Grignard. A very large excess of Grignard must be present. The products obtained were the acetylene alcohol (1), the simple acetylene (2), and the condensed acetylene (3).

V.

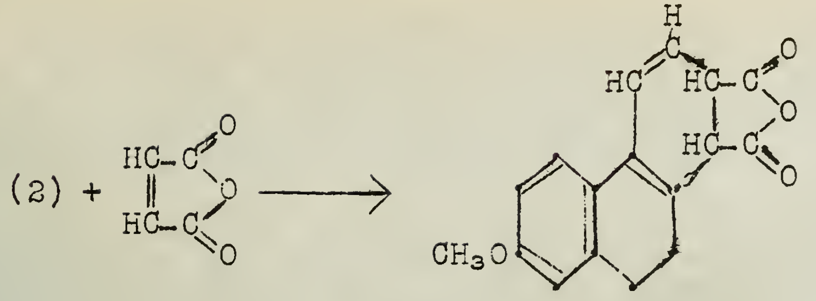


1. 2.

3.

The simple acetylene (2) was separated and found to add maleic anhydride easily to form 7-methoxytetrahydrophenanthrene-1,2-dicarboxylic anhydride (4).

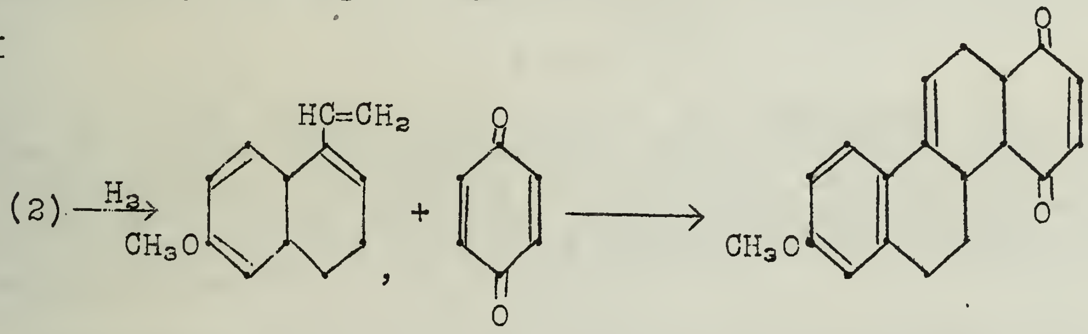
VI



4.

1-Ethinyl-6-methoxy-3,4-dihydronaphthalene (2) will not add quinone directly but if it is reduced to the vinyl derivative, quinone adds, forming a chrysene derivative.

VII

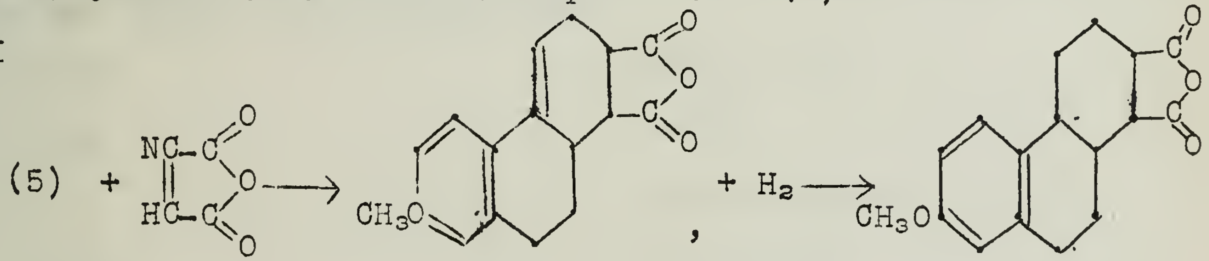


5.

6.

Maleic anhydride also adds to (5)⟶(7) which, when reduced, forms 7-methoxy-octahydrophenanthrene-1,2-dicarboxylic anhydride, (8) identical with the reduction product of (4).

VIII



7.

8.

The unsubstituted vinyl derivative corresponding to (5) has also been prepared but not the acetylene derivative corresponding to (2). It is claimed that the addition of maleic anhydride to a system $-CH=CH-C\equiv CH$ has not been described previously.

A methyl cyclopentene derivative active enough to enter into a diene synthesis and furnish an angular methyl group has been prepared. 1-Vinyl-6-methoxy-3,4-dihydronaphthalene has been prepared and its ability to enter into a diene synthesis shown. If it can be combined with the cyclopentene derivative the reaction should be useful for preparing compounds containing a steroid nucleus.

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Reported by L. H. Dunlap
March 30, 1938.

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THE USE OF ULTRA-VIOLET ABSORPTION SPECTRA

The study of the spectra of atoms and diatomic molecules has been carried on intensively by physicists. It has given them an insight into the structure of atoms and of the physical forces involved in molecules. From it they have developed a complex mathematical theory to explain their data.

The complexity of polyatomic molecules allows of no such calculations and thus their spectra are of little theoretical value to the physicist. They are, however, of value to the chemist as a characteristic property of a molecule or a molecular type.

When light is shone through a solution it has been found that the amount of light that gets through decreases logarithmically with the concentration of the solution C and the length of the path of the light beam through the solution l. Or stated mathematically

$$I = I_0 10^{-\epsilon C l}$$

where I_0 is the initial intensity of the light beam and I is the intensity of the light transmitted. ϵ is a constant which expresses the probability of absorption for the given compound and for a specific wave length of light. It is called the molecular extinction coefficient. The plot of ϵ against the wave length is the absorption spectrum of the compound.

Absorption of ultra-violet light is due to an electronic excitation of the molecule. Those groups which will cause absorption in the range that is readily observable (2000-6000 Å) are known as chromophores. Below 2000 Å quartz and gelatin absorb causing difficulties in the technic of measuring the spectra. The important simple chromophores are:

1. $>C=C<$

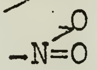
2. $-C\equiv C-$

3. $>C=O$

4. $>C=N-R$

5. $-N=N-$

6. $\geqslant C-N\longrightarrow O$

7. 
$-\overset{\nearrow O}{N}=O$

8. Free radicals

9. C-Halogen

In general compounds containing these chromophores will absorb at a wave length which increases in the order that the structures are listed in the table.

An auxochrome is a group that will not of itself cause absorption but will most markedly alter the absorption of a chromophore

$$-NR_2 > -OR > -SR.$$

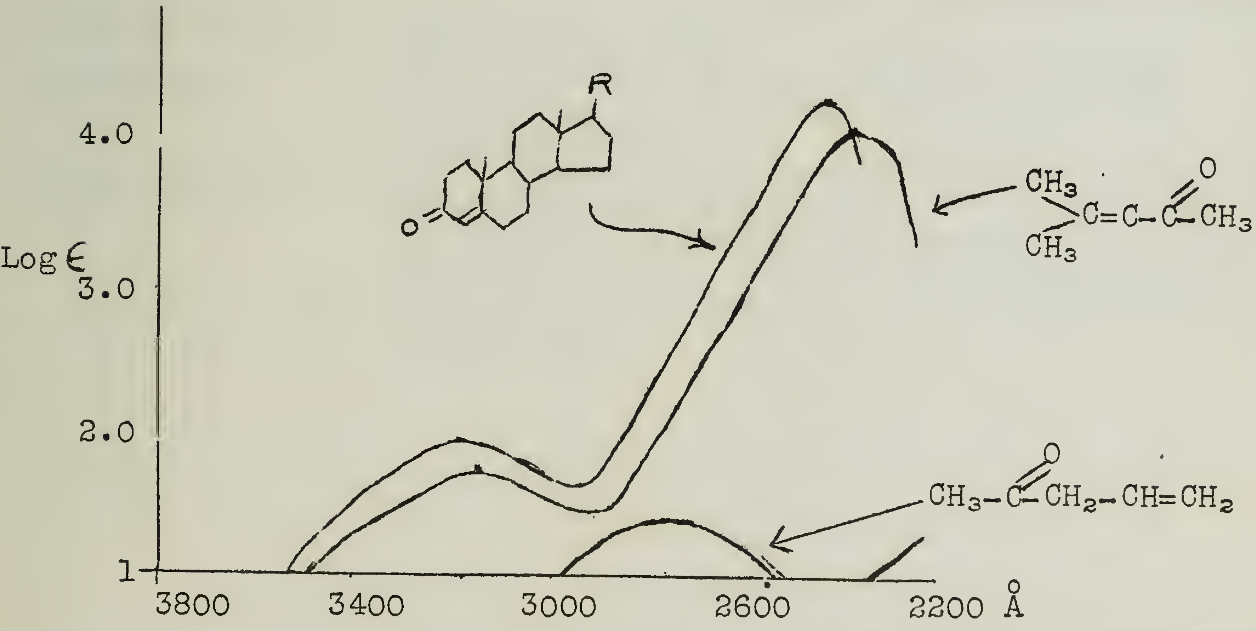
A combination of two or more chromophores when conjugated form a new or complex chromophore. Complex chromophores have much higher values of ϵ, i.e., are more absorptive. An auxochrome is only effective when it is on the end of the conjugated chain or in a benzene ring when it is p to an unsaturated substituent.

Polar solvents displace the absorption of simple chromophores away from the visible and complex chromophores towards the visible. The best solvent is, therefore, hexane but alcohol and water are more frequently used because of their solvent properties.

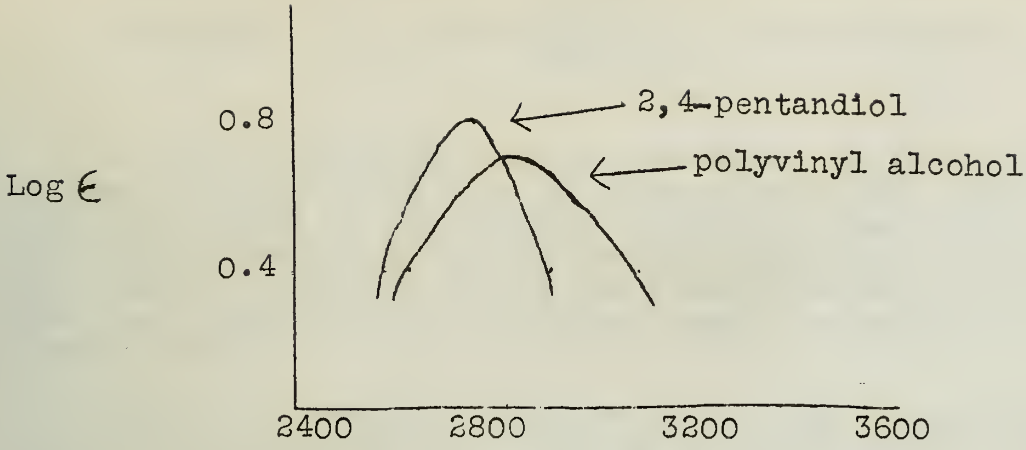
The most obvious use of the absorption spectrum of a compound is as an empirical constant for analytical purposes. Its advantage here is that we obtain the spectrum of one compound independent of what else may be present that does not absorb in the region studied and the analysis may be made on very small amounts of material. It may be used to identify unstable intermediates formed during the course of a reaction and to direct fractionations of mixtures when other physical properties are not successful.

The more potent use of absorption spectra is using it as characteristic of a chromophore or molecular grouping. Spectral analysis has been very helpful in suggesting possible structures for natural products or products of complex reactions. It is even possible to distinguish between _cis_ and _trans_ forms of isomers when care is exercised.

An example of the use of absorption spectra is the proof that cholestenone contains a carbonyl conjugated to a double bond. Androstendione and cortical preparation E give spectra that are identical with cholestenone.



Another example is the comparison of polyvinyl alcohol with 1,2- and 1,3-glycols.



2,3-Butanediol has no absorption in this region $\log \epsilon > 0.2$ showing polyvinyl alcohol to be a 1,3 or "head to tail polymer."

In structure determination the more concrete the question to be decided, the more certainly absorption spectra will be of value. The more general the problem the more data are necessary and the more a variety of closely related compounds must be studied. Where a chromophoric group is intimately connected with the questionable part of the molecule absorption spectral analysis is a real help.

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Reported by E. C. Kirkpatrick
April 6, 1938.

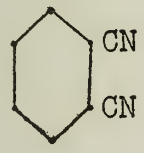
PHTHALOCYANINE PIGMENTS AND RELATED COMPOUNDS

Linstead -- Imperial College of Science and Technology,
London
Halberger - Org. Chem. Institute der Technischen Hochscule,
München

In 1927 de Diesboch and Von der Weid, while attempting to prepare phthalonitrile from *o*-dibromobenzene and cuprous cyanide, obtained instead of the expected nitrile, a deep blue, insoluble, very stable complex of the following composition, $C_{32}N_8H_{16}Cu$. This reaction, because it was not considered important at that time, was forgotten until Linstead began the study of the phthalocyanine pigments.

Linstead's original compound was a deep blue, iron complex obtained as a by-product in the synthesis of phthalimide from phthalic anhydride in the presence of iron.

The first investigation was on the possible dehydration and rearranged products of the phthalimide synthesis.



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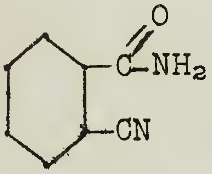
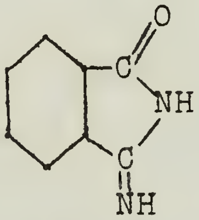


II



III

Phthalonitrile (I), *o*-cyanobenzamide (II) and imino phthalimide (III) all react in an exothermic reaction with metals or metal salts (carbonates, oxides, hydroxides, halides and sulfides) to form similar complexes if the metal is different and the same complex if the same metal is employed. The derivative obtained from copper is identical with that of de Diesboch and Von der Weid.

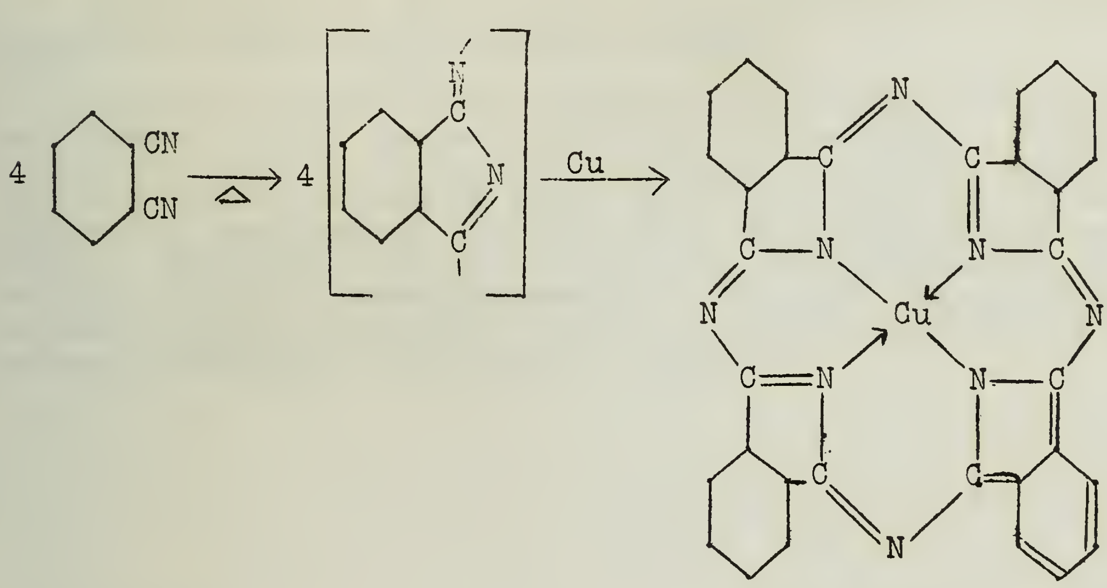
The reaction is still more general, 1,2- and 2,3-dicyanonaphthalenes undergo the reaction dissolving the massive metals to form naphthocyanines. Likewise *o*-dicyano pyridone, *o*-dicyanothiophen and α',α'-diphenyl maleic nitrile also react.

The metal-free phthalocyanine itself is a deep blue, very stable compound of the composition $(C_{32}N_8H_{16})H_2$ and can be prepared dissolving the magnesium derivative in concentrated sulfuric acid, then pouring the resulting solution on ice.

The metallic derivatives possess a remarkable stability which makes them ideal for paint pigments. They are unaffected by concentrated sulfuric acid, molten alkalies, mild oxidizing and reducing agents, concentrated hydrochloric acid and light. Vigorous oxidizing agents decompose them into phthalimide-metallic salts and nitrogen. Dry distillation with soda-lime gives benzonitrile and ammonia. They may be heated in air to temperatures around 300° C without being oxidized and sublimed at temperatures above 500° C in an inert atmosphere and low

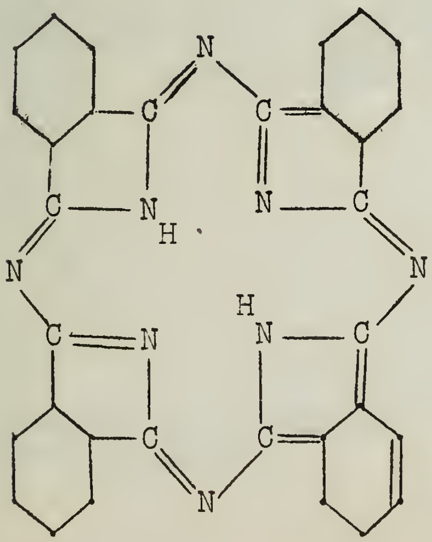
Linstead proposed a porphyrin-like structure for these compounds on a basis of their similarity to the natural pigments such as chlorophyll and haemin. The natural and synthetic pigments have similar stabilities, colors, derivatives, etc.

The ease of formation of a porphyrin-like ring having four $-N=$ bridges instead of $-\overset{H}{C}=$ is shown for the copper derivative.

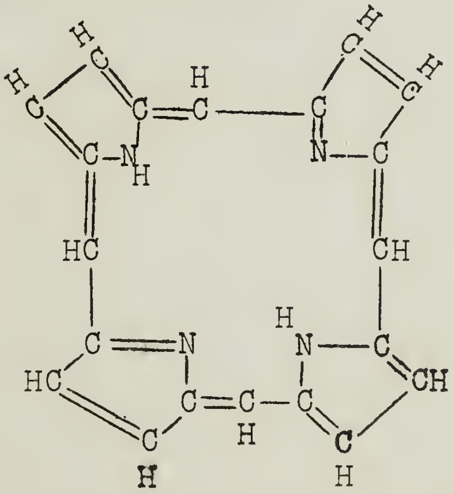


Copper phthalocyanine
Copper tetra benzo tetra
azaporphin

The structure of phthalocyanine as compared to porphyrin is shown in the two following diagrams.



Phthalocyanine
tetra benzo tetra
azaporphin



Porphyrin

Phthalocyanines are now named as porphyrin derivatives. The prefix aza indicating a=N-1 bridge. Thus the metal-free pigment is tetra benzo tetra azaporphin.

An extension of the condensations has been to prepare molecules containing the methine bridges.

Dent has prepared from methylene phthalimide, phthalonitrile and copper, a green copper tetrabenzo-triazaporphin. Halberger by reacting *o*-bromo acetophenone and cuprous cyanide has obtained copper tetrabenzo-monoazaporphin and by carrying out the condensation in the presence of phthalonitrile the diazaporphin can be formed. Halberger also has isolated by chromatographic adsorption on Al_2O_3 the iron tetrabenzoporphin. The last compound was formed in small amounts along with the diaza- and monoazaporphins from *o*-cyanoacetophenone and metallic iron.

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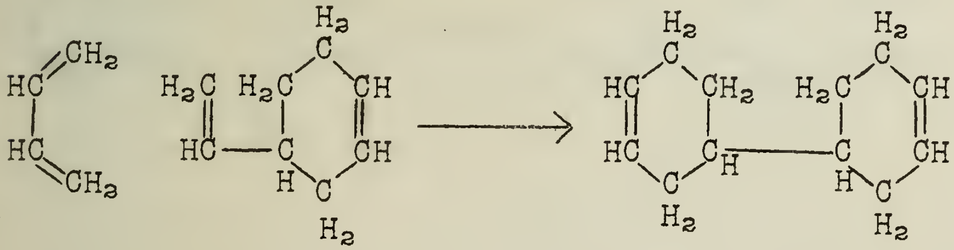
Reported by M. Miller
April 6, 1938.

STYRENE AND INDENE AS "ACTIVE OLEFIN" COMPONENTS IN THE DIELS-ALDER REACTION

Alder and Rickert
Hauptlaborat. d. I.-G. Farbenindustrie A.-G.,
Leverkusen

This paper is primarily concerned with the ability of the double bonds in styrene and indene, which are activated by unsaturation in the benzene ring, to function as "active ethylene" components in a Diels-Alder reaction.

Alder and Rickert prepared a trimer of butadiene by heating Δ^3-vinylcyclohexene and butadiene together for fourteen hours at 180°. Chain polymerization was inhibited by the addition of a small amount of acetylene dicarboxylic acid. The trimer was identified as $\Delta^{3,3'}$-octahydrobiphenyl (I).



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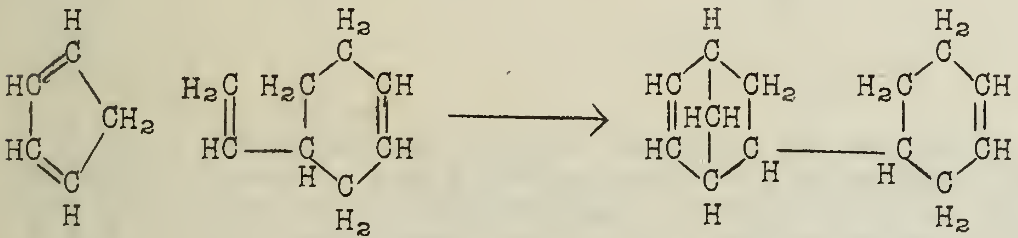
Cyclopentadiene reacted with Δ^3-vinylcyclohexene in a similar manner to yield 2,5-endomethylene-$\Delta^{3,3'}$-octahydrobiphenyl (II).



II

The above two reactions are only special cases of diene syntheses. Although the yields were low, seven and ten per cent respectively, it is of importance to note that a simple vinyl group functioned in the role of an "active ethylene."

Cinnamaldehyde gives excellent yields in Diels-Alder reactions. Alder and Rickert postulated that styrene should occupy a position midway between cinnamaldehyde and Δ^3-vinylcyclohexene, because although it would miss the activating influence of the carbonyl group, the double bond should be influenced by the adjacent unsaturation in the benzene ring, which is absent in Δ^3-vinylcyclohexene. They proceeded to investigate the reactions between

[illegible]

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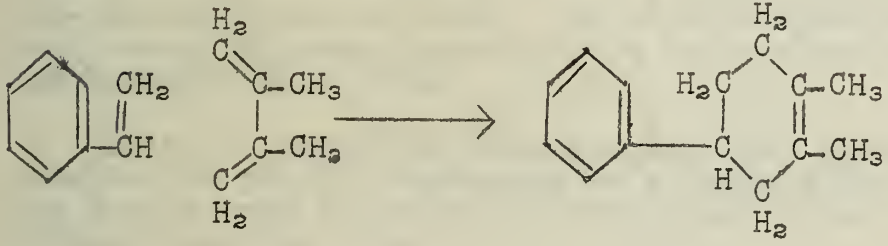
styrene and three conjugated systems, namely, butadiene, 2,3-dimethylbutadiene and cyclopentadiene. The products and yields are indicated below.

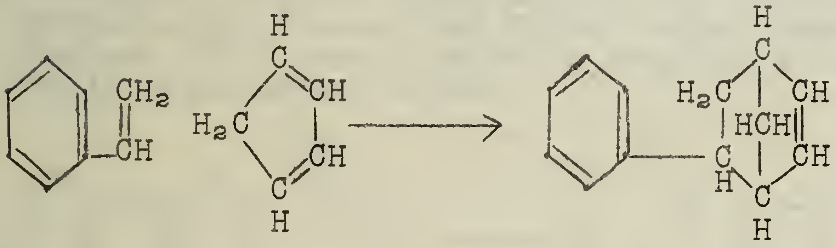
33 per cent yield

III



39 per cent yield

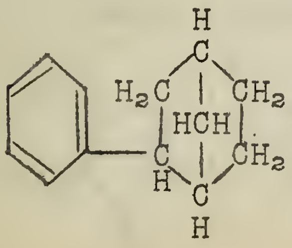
IV



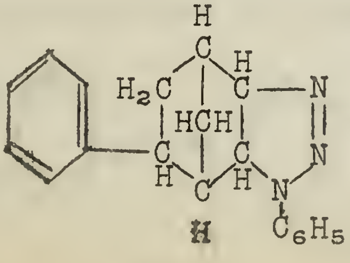
22 per cent yield

V

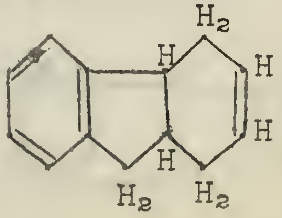
The structure of III was verified by catalytic reduction to phenylcyclohexane and dehydrogenation with selium to biphenyl. The structure of V was confirmed by reduction to 2,5-endomethylene-1,2,3,4,5,6-hexahydrobiphenyl (VI), and conversion to a hydrotriazole whose quantitative analysis for elements corresponded to those required of compound VII.



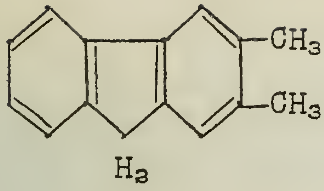
VI



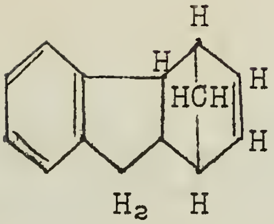
VII



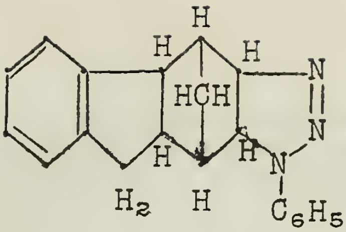
VIII



IX



X

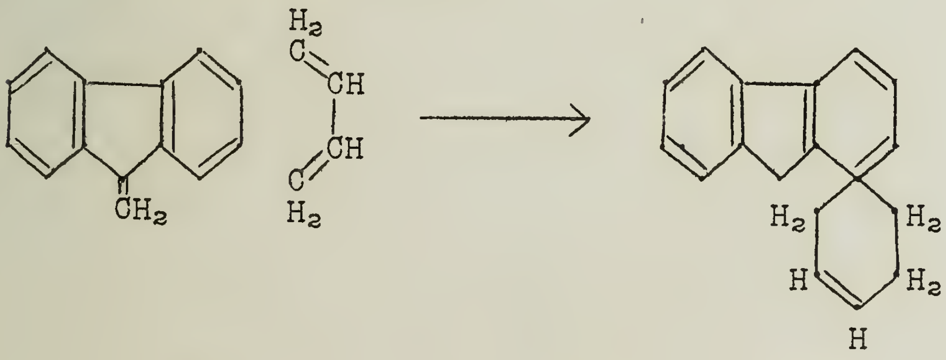


XI

Substitution of indene for styrene led to partially hydrogenated fluorene ring systems. The addition of butadiene to indene yielded Δ^2-tetrahydrofluorene (VIII), which upon dehydrogenation with selium was converted into fluorene. The addition product of 2,3-dimethylbutadiene and indene yielded upon dehydrogenation 2,3-dimethylfluorene (IX). The addition product of cyclopentadiene and indene (X), was characterized by conversion to the corresponding hydrotriazole (XI).

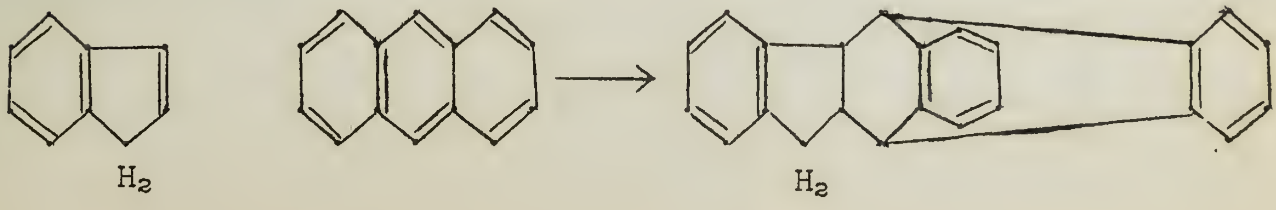
This investigation demonstrated that styrene and indene can function as olefin components in a Diels-Alder reaction, since the double bond is evidently activated by the unsaturation in the adjacent benzene ring.

These results add additional evidence in confirmation of the structural formulas advanced for two compounds that were recently synthesized. Wieland and Probst added butadiene to biphenylene ethylene (XII), and obtained a compound believed to be a spirocyclic hydrocarbon (XIII).



XII XIII

Mameli described the addition of indene to anthracene.



The above two reactions may be regarded as diene syntheses. The double bonds serving in the role of "active ethylene" perform in a manner as might be predicted on the basis of the work described by Alder and Rickert.

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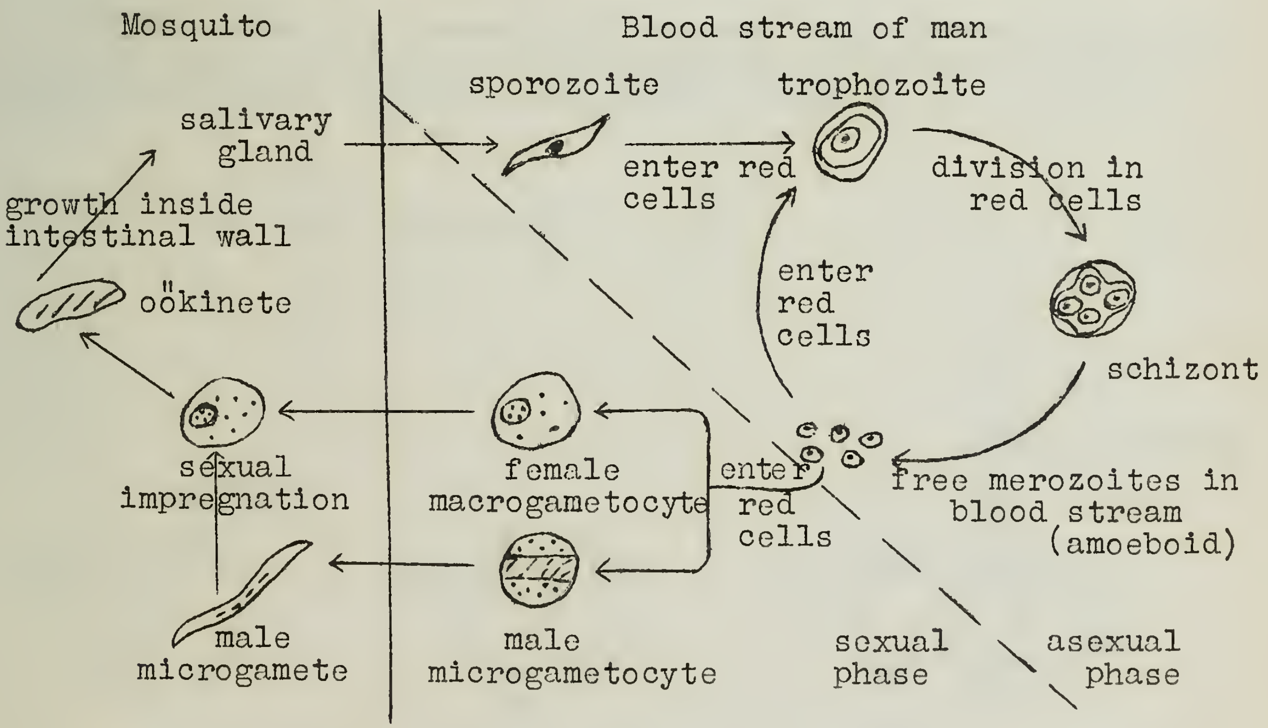
Reported by Joseph Dec
April 13, 1938.

SYNTHETIC ANTIMALARIALS

Fourneau -- Laboratory of Therapeutic Chemistry
Pasteur Institute, Paris
Magidson -- Chemopharmaceutical Research Laboratory,
Moscow
Robinson -- Oxford

Malaria[2] is the name given to a disease of man characterized by a regularly occurring fever, accompanied by other definite symptoms. The interval between attacks permits a distinction in the kinds of fever: In quotidian malaria fever recurs daily; in the tertian type, every second day; and in the quartan type, every third day. Different species of the genus Plasmodia are the causative agents.

The disease starts in man when an infected Anopheles mosquito bites the victim and injects into the wound saliva containing the sporozoite form of the parasite. This quickly enters the red blood cells where growth and division to the schizont form occur. It is the schizonts which are responsible for the symptoms of the disease. These then break up into merozoites which then enter new red blood cells to originate another fever cycle. Some merozoites invade new erythrocytes and develop instead into gametocytes, the sexual forms. These are the forms in which the malarial infection is retransmitted by man to the mosquito in the blood absorbed from the bitten victim. There then occurs sexual generation of a new crop of sporozoites, ready to be injected at the next bite.



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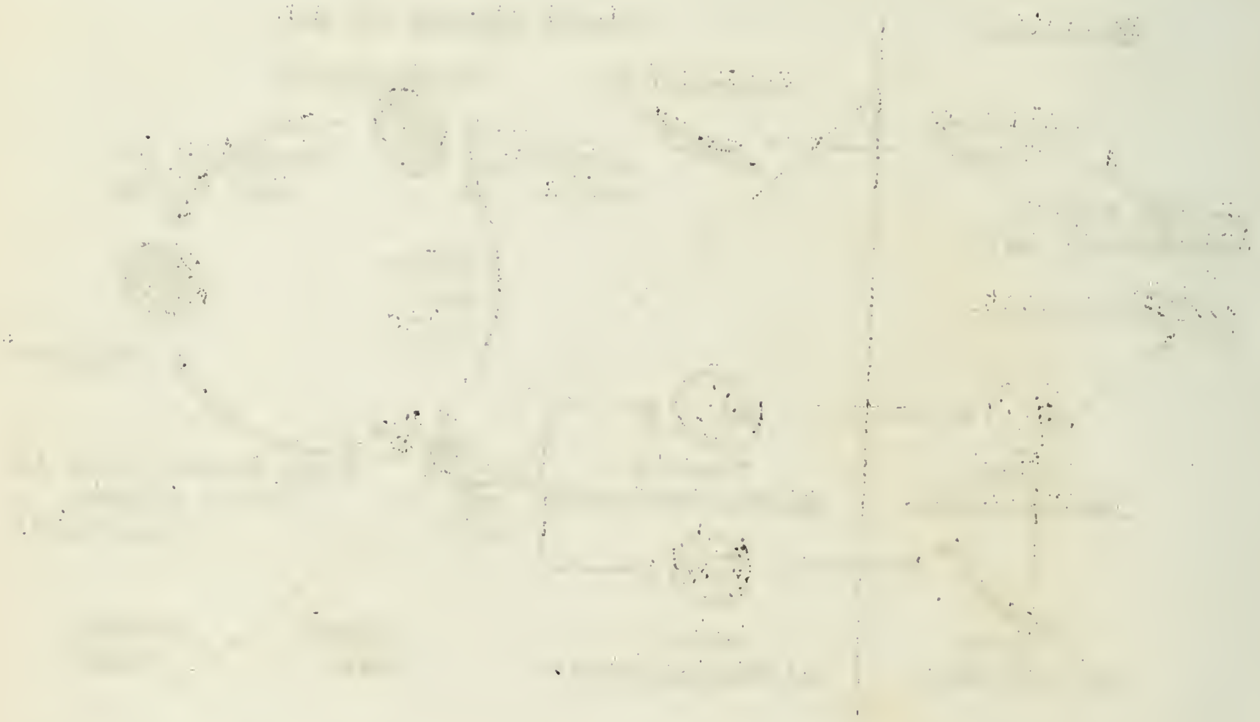

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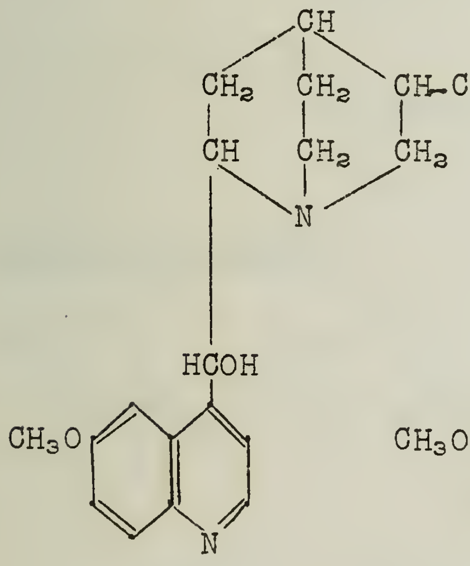
Recent work has indicated that the asexual forms (schizonts and merozoites) and the sexual forms (gametocytes) of the parasite require different drugs for treatment, and a biological method has been devised to distinguish schizonticidal and gametocidal drugs. A definite retardation of the onset of bird malaria in canaries or siskins is used to indicate schizonticidal activity, while gametocidal action is tested in Java sparrows. These birds are almost always infected with a parasite similar to the malaria organisms, and a gametocidal drug causes the disappearance of gametocytes from the peripheral circulation of Java sparrows.

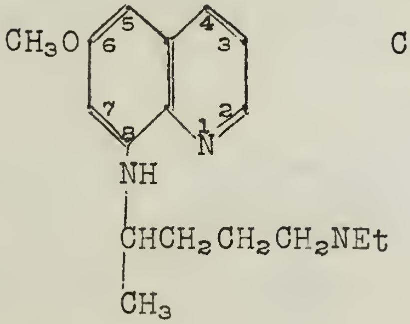
In testing the efficiency of a drug, two determinations are made, the maximal tolerated dose (T) and the minimal curative dose (C). The ratio T/C is called the chemotherapeutic index. Many other factors must be considered, besides the relative toxicity to host and parasite, before a drug is accepted for clinical use; but a favorable index is the most important way of selecting drugs for further investigation.

For well over one hundred years the only effective antimalarial was quinine (I). This is a schizonticidal drug with an index given variously as 4 to 10. It is, therefore, fairly efficient in checking the symptoms of the disease in humans, but has no effect on the spread of the disease.

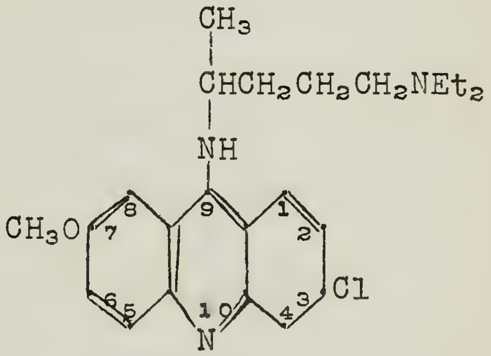
After extensive research Schulemann, Schönhofer and Wingler[3] of I. G. Farbenindustrie in 1926 developed plasmoquin (II), a gametocidal agent having a therapeutic index of 40. In 1930



I



II



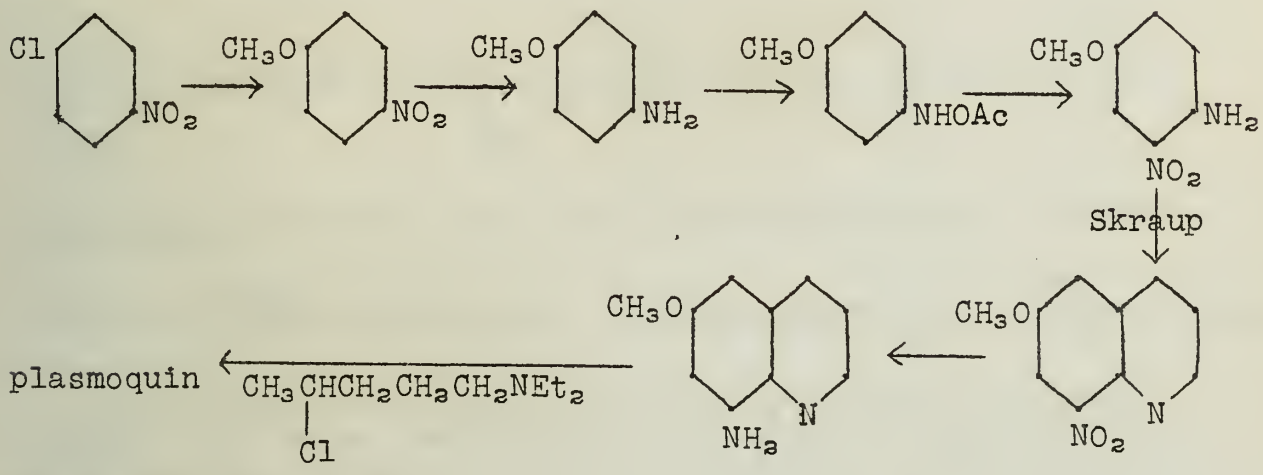
III

Mauss and Mietzsch[4] of the same organization developed atebrin (III), a schizonticidal drug having an index of 30. In the now common treatment for malaria plasmoquin is administered together

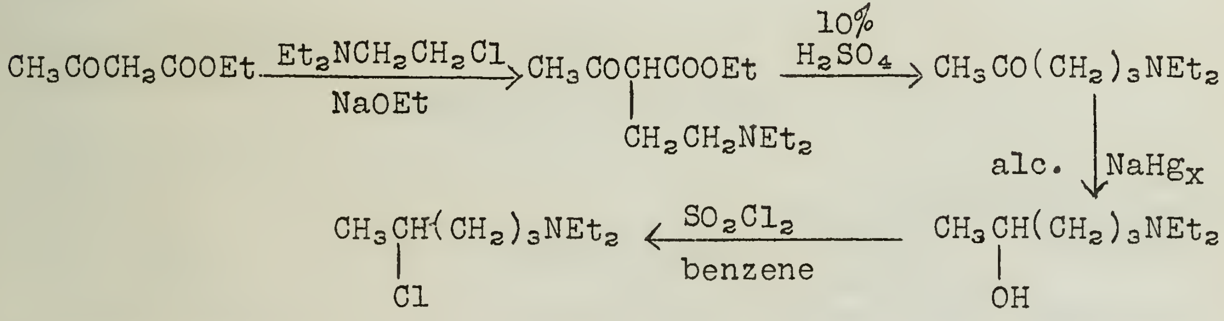
with atebrin or quinine, thus curing the disease and at the same time preventing its spread.

The best syntheses for these compounds now recorded in the literature are shown below:

Plasmoquin[5]

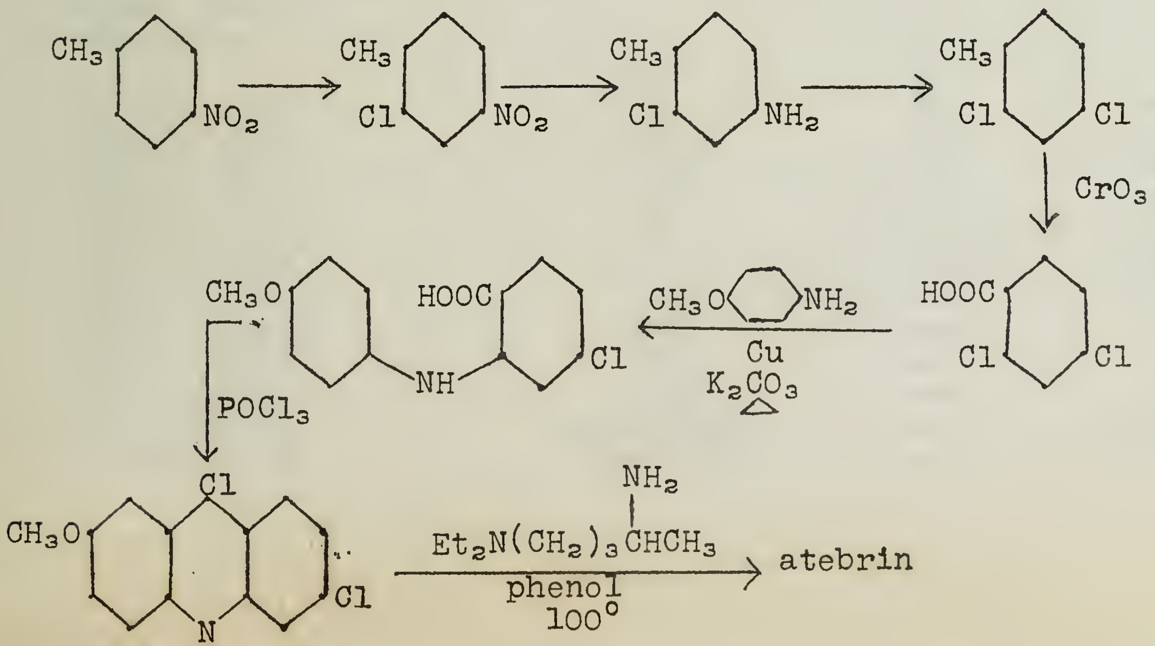


Plasmoquin side chain[6]

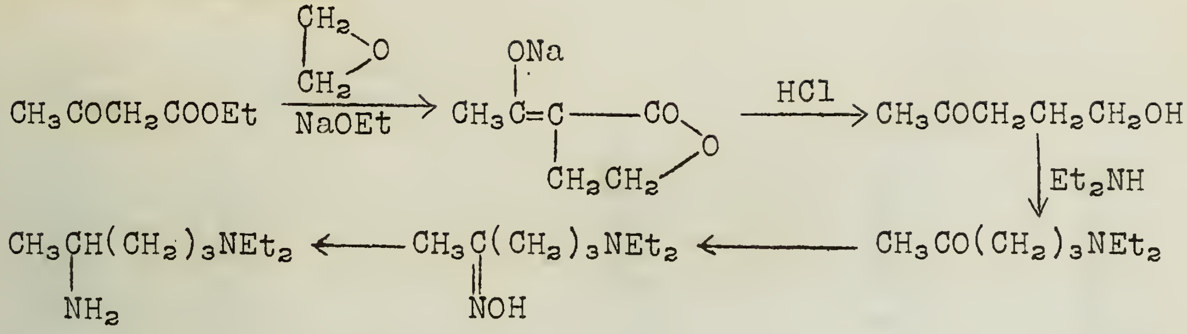


$$CH_3COCH_2COOEt \xrightarrow[NaOEt]{Et_2NCH_2CH_2Cl} \underset{CH_2CH_2NEt_2}{CH_3CO\underset{|}{C}HCOOEt} \xrightarrow[]{10\%\ H_2SO_4} CH_3CO(CH_2)_3NEt_2 \xrightarrow[alc.]{NaHg_x} \underset{OH}{CH_3\underset{|}{C}H(CH_2)_3NEt_2} \xrightarrow[benzene]{SO_2Cl_2} \underset{Cl}{CH_3\underset{|}{C}H(CH_2)_3NEt_2}$$

Atebrin (acrichin)[7]



Atebrin side chain[8]



Side chains of other lengths are prepared from the dibromide:[9]

$$Br(CH_2)_nBr \xrightarrow{KOAc} Br(CH_2)_nOAc \xrightarrow{Et_2NH} Et_2N(CH_2)_nOH \xrightarrow{HBr} Et_2N(CH_2)_nBr$$

Extensive research[1] has been done by Fourneau in France, Magidson in Russia, and Robinson in England on the effect of modifying the structures of these compounds. Below are tables showing the variation in substituents and in the corresponding therapeutic index.

Table I

Quinoline Derivatives

Chain in 8 position	Substituent in 6 position	Therapeutic Index Gametocidal (Java sparrows) (Fourneau)[1]	Therapeutic Index Schizonticidal (Siskins) (Magidson)[1]
Effect of change of alkoxy group in 6 position			
$-NH(CH_2)_3NEt_2$	H	80	—
$-NH(CH_2)_3NEt_2$	HO	40	—
$-NH(CH_2)_3NEt_2$	MeO	100	—
$-NH(CH_2)_3NEt_2$	EtO	4	—
$-NH(CH_2)_3NEt_2$	Me	inactive	—
$-NH(CH_2)_2NEt_2$	HO	—	13
$-NH(CH_2)_2NEt_2$	MeO	—	6
$-NH(CH_2)_2NEt_2$	EtO	—	4
$-NH(CH_2)_2NEt_2$	PrO	—	1
$-NH(CH_2)_2NEt_2$	BuO	—	1
$-NH(CH_2)_2NEt_2$	iso-$C_5H_{11}O$	—	inactive
$-NH(CH_2)_2NEt_2$	n-$C_8H_{17}O$	—	inactive

Effect of lengthening chain in 8 position

$-NH(CH_2)_2NEt_2$	MeO	40	6
$-NH(CH_2)_3NEt_2$	MeO	100	26
$-NH(CH_2)_4NEt_2$	MeO	20	11
$-NH(CH_2)_5NEt_2$	MeO	150	25
$-NH(CH_2)_6NEt_2$	MeO	150	13
$-NH(CH_2)_7NEt_2$	MeO	---	34
$-NH(CH_2)_9NEt_2$	MeO	---	40*
$-NH(CH_2)_{11}NEt_2$	MeO	10	5
$-NH(CH_2)_2NEt_2$	H	inactive	---
$-NH(CH_2)_3NEt_2$	H	80	---
$-NH(CH_2)_4NEt_2$	H	20	---
$-NH(CH_2)_5NEt_2$	H	40	---
$-NHCHMe(CH_2)_3NEt_2$ (plasmoquin)	MeO	40	---

*Bovet found a value of 100 in canaries.

From the first part of this table the conclusions can be drawn that:

(a) The 6-alkoxy group is not indispensable, since replacement by H or OH leaves products of high therapeutic index. Replacement by a methyl group, however, gives an inactive product.

(b) Increasing weight in the alkoxy group lowers the therapeutic index.

The second part of the table shows the alternation in activity in the homologous series, $-NH(CH_2)_nNEt_2$, as n is varied:

(a) Schizonticidal activity is higher when n is odd, and increases to a maximum where n is 9. Where n is even, the maximum is at $n = 6$.

(b) Gametocidal activity varies also as n is even or odd, and the maximum effectiveness is reached when n is 5 or 6.

The difference in the positions of the maxima ($n = 5$ and $n = 9$) substantiates the view of Bovet[10] that lengthening of a chain increases schizonticidal action at the expense of gametocidal activity.

Table II

Quinoline Derivatives

Chain in 8 position	Alkoxy Group in 6 position	Schizonticidal Therapeutic Index (Canaries) (Tate and Vincent)[11]
$-NHCHMe(CH_2)_3NEt_2$	MeO	30
$-NH(CH_2)_3NH_2$	MeO	16
$-NH(CH_2)_3NH_2$	EtO	16
$-NH(CH_2)_3NH_2$	BuO	8
$-NH(CH_2)_3NBu_2$(*n*-)	BuO	4
$-NH(CH_2)_2O(CH_2)_2NH_2$	MeO	8
$-NH(CH_2)_2O(CH_2)_2NBu_2$(*n*-)	MeO	8
$-NH(CH_2)_3NHBu$(*n*-)	MeO	8
$-NH(CH_2)_3NHPr$(*n*-)	MeO	8

From Table II the following conclusions can be drawn:

(a) Increasing weight in the alkoxy group lowers the therapeutic activity.

(b) No marked change is produced by the introduction of an oxygen atom in the center of the $-(CH_2)_n-$chain.

(c) In general, the $-NEt_2$ group gives a higher level of activity to the molecule than any other group.

Variations in the substituents on the acridine nucleus have also been made, and it is clear that effective drugs can be produced as long as the position and type of chain in the 9 position are maintained; considerable variation in the 3- and 7-substituents is also possible.

Table III

Dialkylaminoalkylaminoacridines

		Substituent at		Schizonticidal Therapeutic Index (Siskins) (Magidson)[1]
Chain in 9 position	2	3	7	
$-NH(CH_2)_2NEt_2$	—	Cl	MeO	8
$-NH(CH_2)_3NEt_2$ (Acrichin N5)	—	Cl	Meo	15
$-NH(CH_2)_4NEt_2$ (Acrichin N8)	—	Cl	MeO	20
$-NH(CH_2)_5NEt_2$	—	Cl	MeO	6
$-NH(CH_2)_6NEt_2$	—	Cl	MeO	5
$-NHCH_2CHOHCH_2NEt_2$	—	Cl	MeO	6
$-NHCH_2CHOHCH_2NEt_2$	NO_2	—	MeO	4
$-NH(CH_2)_2NEt_2$	—	NO_2	EtO	inactive
$-NH(CH_2)_2NEt_2$	NO_2	—	EtO	1.5
$-NH(CH_2)_3NEt_2$	—	Cl	MeO	15
$-NH(CH_2)_3NEt_2$	—	—	MeO	inactive
$-NH(CH_2)_3NEt_2$	—	Cl	EtO	7.5
$-NH(CH_2)_3NEt_2$	—	Cl	Me	6

$-NH(CH_2)_3NEt_2$	--	Cl	MeO^6 MeO^7	inactive
$-NHCHMe(CH_2)_2NEt_2$	--	Cl	MeO	6.6
$-NHCHMe(CH_2)_3NEt_2$ (Atebrin)	--	Cl	MeO	15*
$-NH(CH_2)_3NEt_2$[12]	--	CN	MeO	10
$-NHCHMe(CH_2)_3NEt_2$[12]	--	CN	MeO	23
$-NHCHMe(CH_2)_3NEt_2$[12]	--	CN	MeS	1

*Kikuth[13] found 30 in canaries.

Conclusions from Table III:

(a) The optimum length of the $-NH(CH_2)_nNEt_2$ comes at n=4.

(b) The -Cl or -Cn group in the 3 position is essential, but activity may be partially restored in its absence by a $-NO_2$ group in the 2 position but not in the 3 position.

(c) Increase in the 7-alkoxy group is disadvantageous, and the addition of a 6-methoxyl inactivates the molecules.

(d) The effects of branching are not consistent. The change from $-(CH_2)_4-$ to $-CHMe(CH_2)_2-$ lowers the index, while the change from $-(CH_2)_5-$ to $-CHMe(CH_2)_3-$ raises it.

(e) The methylmercapto group cannot replace the alkoxy group.

It is not known yet whether these therapeutic agents attack the parasites directly or whether they stimulate the leucocytes to attack them better. All effective current antimalarials contain a quinoline nucleus, if acridine can be thought of as quinoline with a fused benzene ring. The parasiticidal portion of each can be assumed to be the quinoline nucleus, while the rest of the molecule serves to enable this nucleus to come into contact with the parasite and to exert its toxic action. An effective drug, then, must be one which successfully combines these two factors with the other essential characteristics necessary for clinical use. Much more investigating must be done before these relationships are understood.

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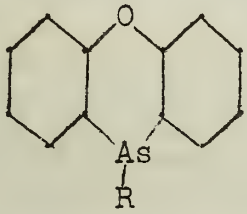
Reported by E. J. Matson
April 13, 1938.

THE CONFIGURATION OF HETEROCYCLIC COMPOUNDS

Turner -- University of London

The optical activity of 10-substituted phenoxarsine-2-carboxylic acids (I) has been explained as being due to a folded configuration of the molecule, stabilized as a result of the particular sizes of the atomic radii and valency angles of the oxygen and arsenic atoms. On the other hand, the asymmetry may be due to the asymmetric arsenic atom rather than to molecular asymmetry.



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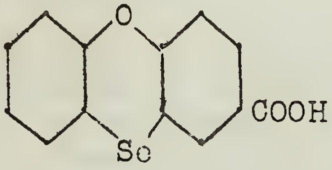
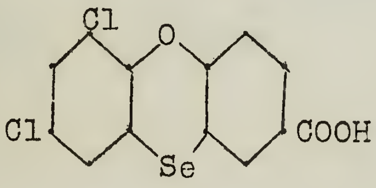


II

Turner has prepared similar compounds (formulas II and III) containing selenium in place of arsenic. The absence of a substituent in position 10 makes them particularly important as this eliminates the asymmetric atom and allows only molecular asymmetry due to the folded molecule. The stability of the selenium compounds should be comparable to the arsenic compounds since selenium has approximately the same atomic radius as that of arsenic. Assuming a value of 120-130° for the oxygen valency angle the angle of fold for the phenoxselenine structure would be 140-150°.

Phenoxselenine-2-carboxylic acid (II) was synthesized. Several resolving agents were employed but the diasterisomeric salts showed no signs of resolution.

6,8-Dichlorophenoxselenine (III) was also prepared but no resolution was obtained.



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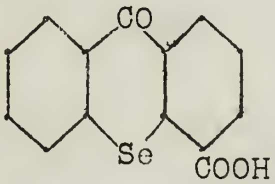
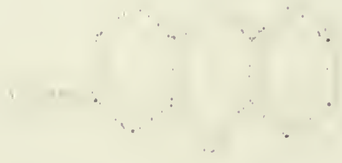
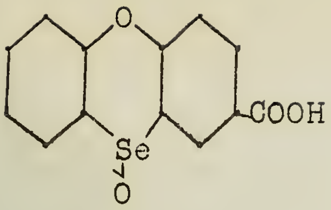


IV

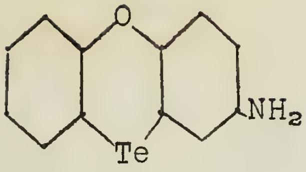
A third type of molecule which should give rise to molecular asymmetry are the substituted selenoxanthones. Of this type selenoxanthone-1-carboxylic acid (IV) was synthesized but all attempts at resolution failed.

Since theoretically the selenoxides should exist in optically active forms (both molecular asymmetry and atomic asymmetry) 2-carboxy phenoxselenine-10-oxide (V) was prepared. This showed no signs of resolution.





V



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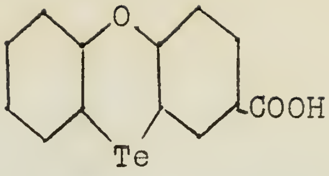


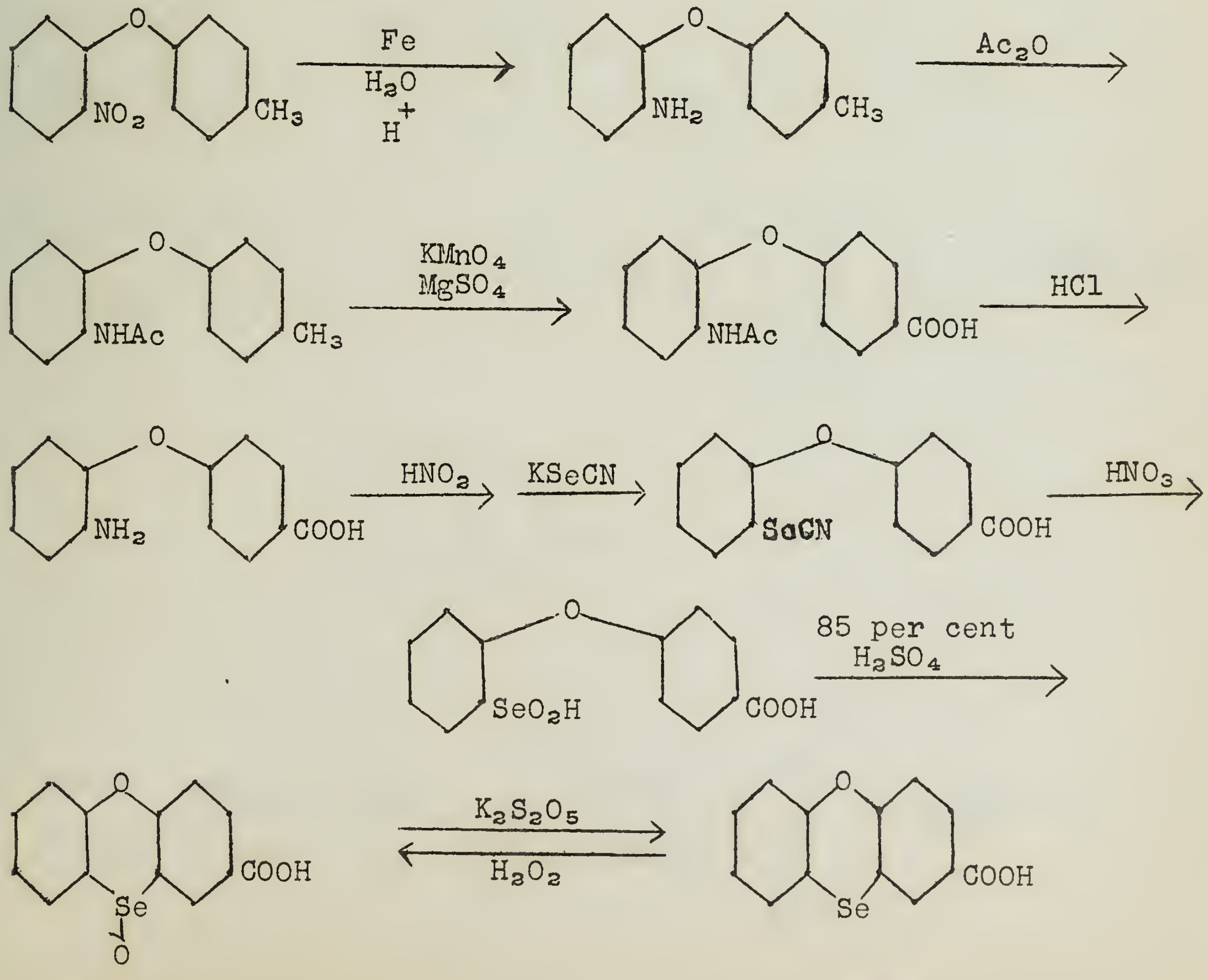
VII

In the tellurium series two compounds were synthesized: 2-Aminophenoxtellurine (VI) and phenoxtellurine-2-carboxylic acid (VII). Neither of these could be resolved.

Although negative evidence is never satisfactory these experiments indicate that these compounds, if optically active, are extremely difficult to resolve due to similarity of the diastereoisomeric salts used in resolution. Nonresolution may on the other hand be due to the flexibility of the folded molecule.

The synthesis of some of these compounds follow:

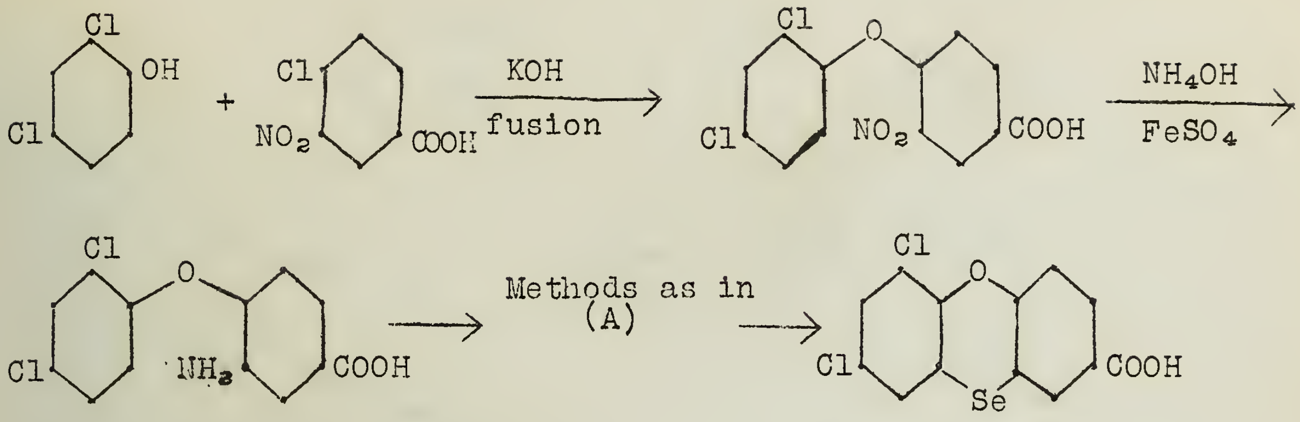
(A)



V

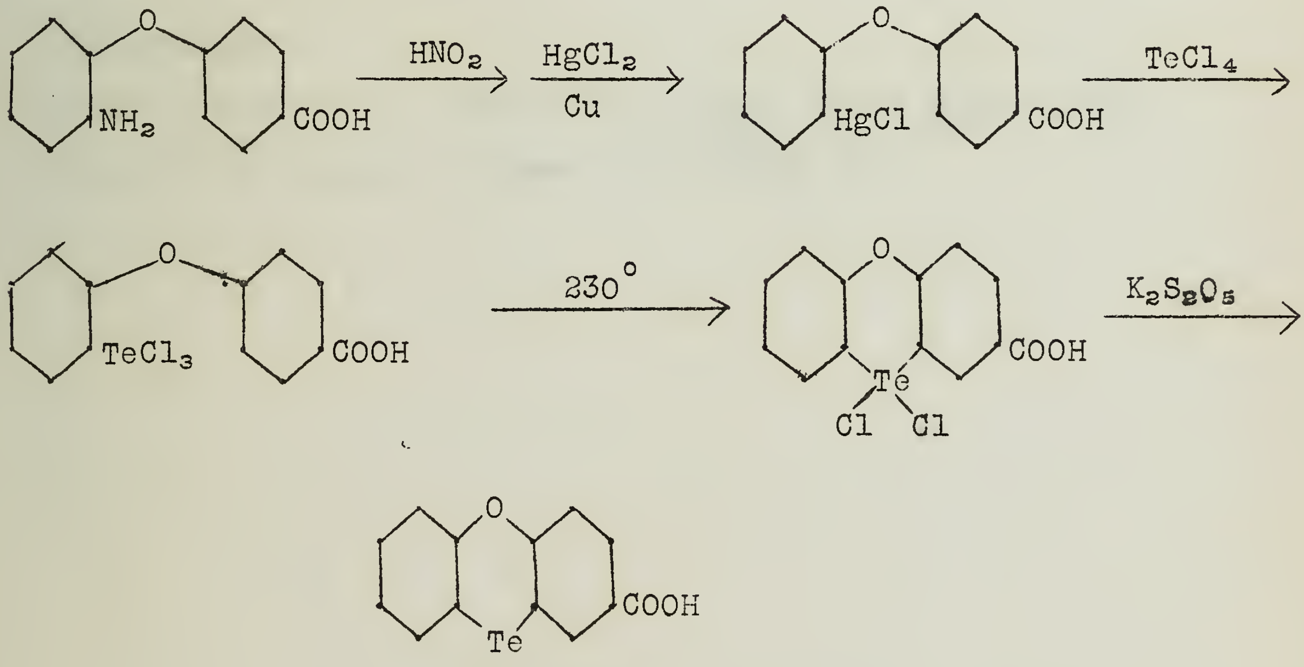
II

(B)


Cl
OH
Cl
+
Cl
NO₂
COOH
KOH
fusion
Cl
O
Cl
NO₂
COOH
NH₄OH
FeSO₄
Cl
O
Cl
NH₂
COOH
Methods as in (A)
Cl
O
Cl
Se
COOH

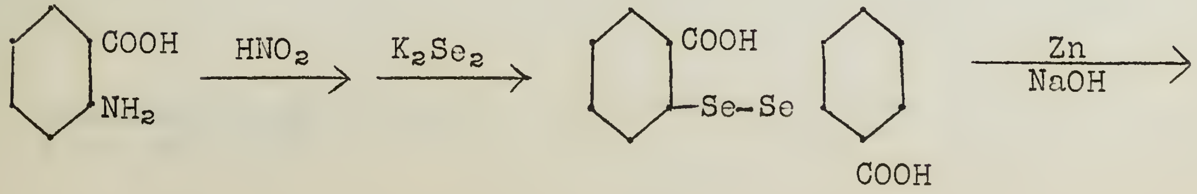
III

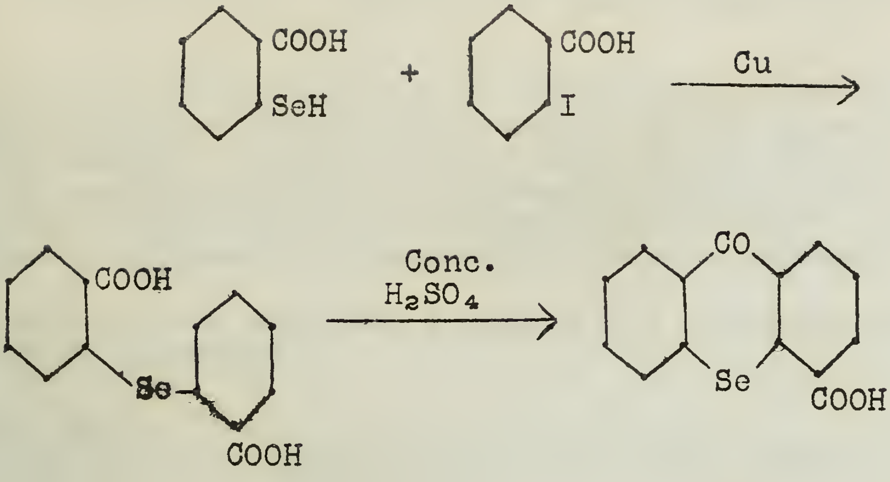
(C)


O
NH₂
COOH
HNO₂
HgCl₂
Cu
O
HgCl
COOH
TeCl₄
O
TeCl₃
COOH
230°
O
Te
Cl
Cl
COOH
K₂S₂O₅
O
Te
COOH

VII

(D)


COOH
NH₂
HNO₂
K₂Se₂
COOH
Se–Se
COOH
Zn
NaOH



IV

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Anderson and Turner, J. Chem. Soc., 1938, 29.

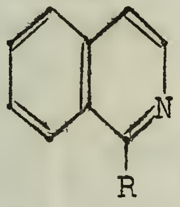
Reported by Wm. R. Dial
April 20, 1938.

A SYNTHESIS OF SUBSTITUTED ISOQUINOLINES

Walter Krabbe -- Organ. Chem. Institute A. Tech.
Hochschule Berlin-Charlottenburg.

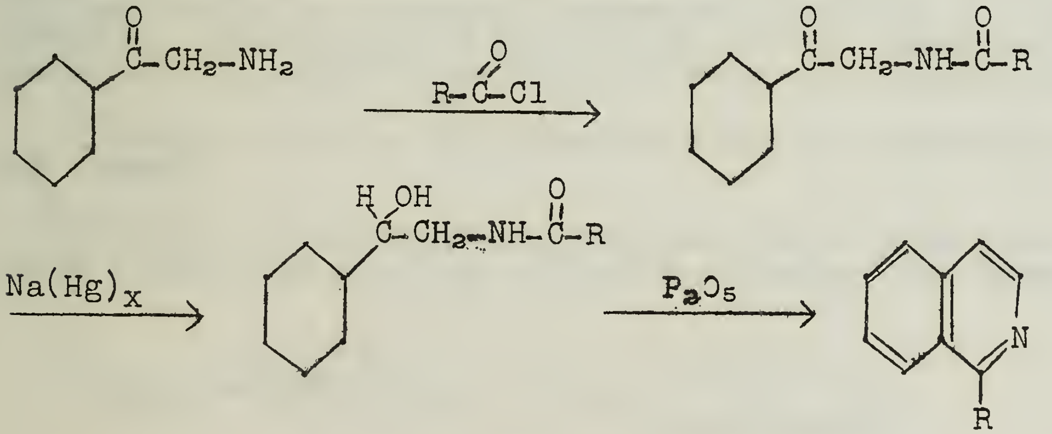
Isoquinoline and substituted isoquinolines have been synthesized by ring closure of benzene derivatives of the types C_6H_5-C-N-C-C and C_6H_5-C-C-N-C. Isoquinoline itself can be very easily prepared by heating the oxime of cinnamic aldehyde with phosphorus pentoxide. The oxime first undergoes the Beckmann rearrangement and this is followed by dehydration and ring closure.

Pictet in 1910 reported a method for synthesizing the 1-substituted isoquinolines.



where R may be H-, CH_3-, C_6H_5- and C_6H_5-CH_2-.

ω-Aminoacetophenone is acylated with a suitable acid chloride, and the resulting acylated amine is reduced to the carbinol with sodium amalgam. The carbinol is dehydrated to the corresponding isoquinoline by refluxing with phosphorus pentoxide in an inert solvent such as benzene or toluene.

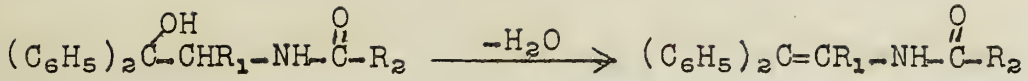


To prepare isoquinoline itself in this manner anhydrous formic acid is used to prepare the intermediate formamide.

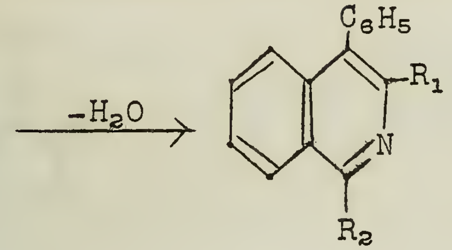
Krabbe in 1937 extended this method to the preparation of the 1,3,4-substituted isoquinolines and showed that the dehydration takes place in two well-defined steps.

acylaminocarbinol $\xrightarrow{-H_2O}$ acylvinylamine $\xrightarrow{-H_2O}$ isoquinoline

Most of Krabbe's work was on compounds of the following type.



$$(C_6H_5)_2C(OH)-CHR_1-NH-\overset{O}{\overset{\|}{C}}-R_2 \xrightarrow{-H_2O} (C_6H_5)_2C=CR_1-NH-\overset{O}{\overset{\|}{C}}-R_2$$



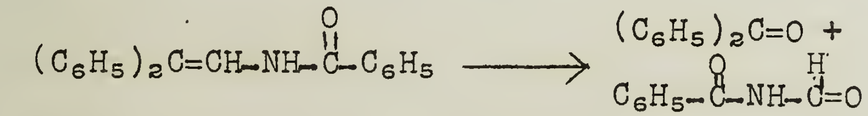
where R_1 = H–, and C_6H_5–,
and R_2 = H–, CH_3–, and C_6H_5–.

Aminomethyldiphenyl carbinol is prepared by the reaction of phenyl magnesium bromide on the ethyl ester of glycine. In a similar manner, amino triphenyl ethyl alcohol is prepared from aminophenylacetic acid. The acylating agents are anhydrous formic acid (R_2=H–), acetic anhydride (R_2=CH_3–), and benzoyl chloride (R_2=C_6H_5).

The primary dehydration to the vinylamine takes place by refluxing for a short time with phosphorus pentoxide in benzene, but the yields are poor as the dehydration is hard to control. Yields of 80-90 per cent of the vinylamine are obtained by simply distilling the acylaminocarbinol at atmospheric pressure. Only in the case of the 1,3,4-triphenyl isoquinoline has it been impossible to isolate the intermediate vinylamine. The final dehydration to the substituted isoquinoline is accomplished by refluxing the vinylamine with an excess of phosphorus pentoxide in xylene or tetralin. Krabbe reports good yields for all these substituted isoquinolines except those obtained from the formylamines.

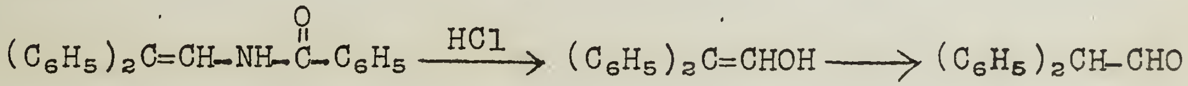
Cleavage of the acylvinylamines gives the expected products. For example:

Oxidation of N-benzoyl diphenylvinylamine with ozone in anhydrous formic acid solution yields benzophenone and formyl benzamide.



$$(C_6H_5)_2C=CH-NH-\overset{O}{\overset{\|}{C}}-C_6H_5 \longrightarrow (C_6H_5)_2C=O + C_6H_5-\overset{O}{\overset{\|}{C}}-NH-\overset{H}{\overset{|}{C}}=O$$

Cleavage with alcoholic hydrogen chloride gives diphenylacetaldehyde.



$$(C_6H_5)_2C=CH-NH-\overset{O}{\overset{\|}{C}}-C_6H_5 \xrightarrow{HCl} (C_6H_5)_2C=CHOH \longrightarrow (C_6H_5)_2CH-CHO$$

Oxidation of the substituted isoquinolines with alkaline permanganate yields among other products the dicarboxy substituted pyridines. Decarboxylation produces the substituted pyridines.

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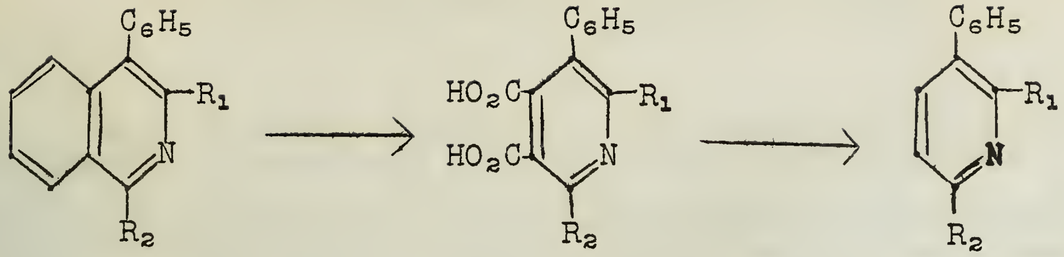

Though only a few of the 1,3,4-substituted isoquinolines were prepared this seems to be a general method where R groups may be any alkyl or aryl group.

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Krabbe, Ber., 71, 64 (1938)
Pictet, Ber., 43, 2384 (1910)

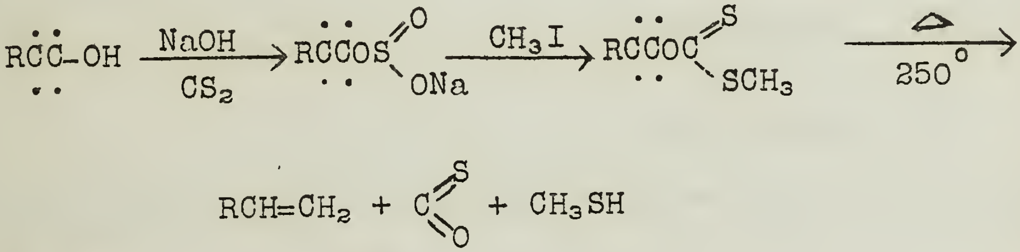
Reported by H. G. Cooke
April 20, 1938

DEHYDRATION OF ALCOHOLS

Whitmore -- Pennsylvania State College
Linstead -- Imperial College, London
Bacon and Farmer -- Imperial College,
London

A great many investigators have worked on the dehydration of alcohols. The methods generally used are as follows:

(1) Distillation from a small amount of concentrated HBr, H_2SO_4, aromatic sulfonic acid or anhydrous oxalic acid.
(2) Distillation from a crystal of iodine.
(3) Distillation from anhydrous cupric sulfate (15 grams of $CuSO_4$ per 100 grams of alcohol).
(4) Heating ROMgX to 250-300°.
(5) Flowing over hot H_3PO_4 in silica gel.
(6) Mixing with a large amount of 85-90 per cent H_2SO_4 at room temperature, then distilling under vacuo.
(7) Tchugaeff's xanthic method (produces no rearranged products)



Mechanisms and Rearrangements.--Whitmore, in a series of articles dealing with the dehydration of aliphatic alcohols, proposed the following mechanism of reaction for compounds of the type

(1) $:\underset{\cdot\cdot}{\ddot{A}}:\underset{\cdot\cdot}{\ddot{B}}:X$ and (2) $\ddot{A}::\ddot{B}:\underset{\cdot\cdot}{\ddot{D}}:X$ (X is electronegative and A, B, and D are elements from the center of the periodic table).

Step 1 -- Removal of X which takes with it a complete octet of electrons

$$:\underset{\cdot\cdot}{\ddot{A}}:\underset{\cdot\cdot}{\ddot{B}}:\underset{\cdot\cdot}{\ddot{X}}: \longrightarrow :\underset{\cdot\cdot}{\ddot{A}}:B + :\underset{\cdot\cdot}{\ddot{X}}:$$

Step 2 -- (a) The fragment may combine with any negative ion $:\underset{\cdot\cdot}{\ddot{Y}}:$ in solution,

$$:\underset{\cdot\cdot}{\ddot{A}}:B + :\underset{\cdot\cdot}{\ddot{Y}}: \longrightarrow :\underset{\cdot\cdot}{\ddot{A}}:\underset{\cdot\cdot}{\ddot{B}}:\underset{\cdot\cdot}{\ddot{Y}}:$$

(b) If A has an attached H atom, the fragment may be stabilized by loss of a proton (olefin formation)

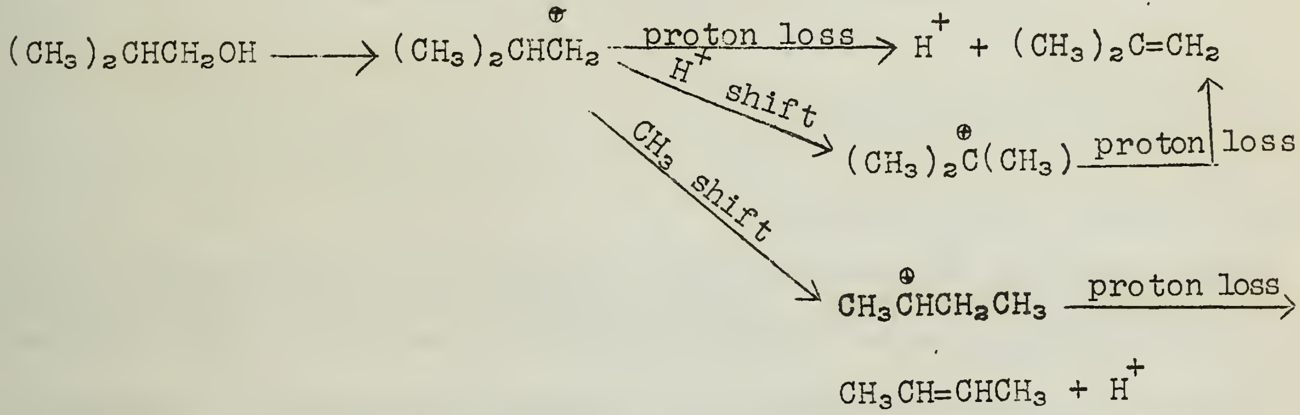
$$:\underset{\cdot\cdot}{\ddot{A}}:B \longrightarrow \underset{\cdot\cdot}{\ddot{A}}::\underset{\cdot\cdot}{\ddot{B}} + H^+$$

(c) Environment may be such that B has a greater electron attraction or that A can more readily dispose of an electron pair

$$:\underset{\cdot\cdot}{\ddot{A}}:B \longrightarrow \underset{\cdot\cdot}{\ddot{A}}:\underset{\cdot\cdot}{\ddot{B}}:$$

The new fragment may then combine with X or Y or, if B has an attached H atom, may lose a proton with the formation of an olefin either identical or different from that in (b). This mechanism fits all types of rearrangements which involve the transfer of an atom or group from one atom to an adjacent one, such rearrangements as pinacol, Beckmann, Hoffman of type 1, and allyl of type 2.

The dehydration of alcohols may be summed up as first the loss of $:\ddot{O}:H$ and second, the stabilization by (a), the loss of a proton to give an olefin or (b) rearrangement and then the loss of a proton. For example, the dehydration of isobutyl alcohol (⊕ indicates two missing electrons)



Though no good rule could be devised, Whitmore came to a few very general conclusions:

(1) The tendency to rearrange increased with the number of C atoms attached to "A" in the two atom system.
(2) Tertiary alcohols tend to give the normal products in about 3:1 ratio.
(3) Secondary alcohols gave predominantly rearranged products.
(4) The Tschugaeff method yielded only normal products.

A few of the alcohols dehydrated were:

Isopropyl tertiary butyl carbinol → no normal products
→ 5 per cent 2,4,4-trimethyl-pentene-1

Tertiary butyl methyl carbinol → tetramethylethylene
→ unsymmetrical methyl isopropyl ethylene

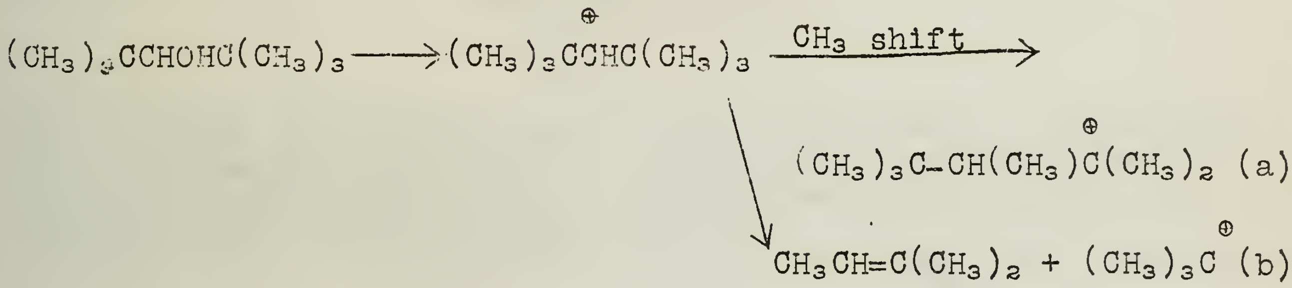
4,4-dimethyl pentanol-2 → 4,4-dimethyl pentene-2 80 per cent
4,4-dimethyl pentene-1 20 per cent

Methylethyl tertiary butyl carbinol → 3,4,4-trimethyl pentene-2 80 per cent
→ 3,3,4-trimethyl pentene-4 20 per cent

Dimethyl tertiaryamyl carbinol ⟶ 2,3,3-trimethyl pentene-1

2,2-Dimethyl hexanol ⟶ 2-methyl heptene-2
2-methyl heptene-1
3-methyl heptene-3
3-methyl heptene-2
2-ethyl hexene-1 (this one not observed)

A case of special interest is the dehydration of ditertiary butyl carbinol.

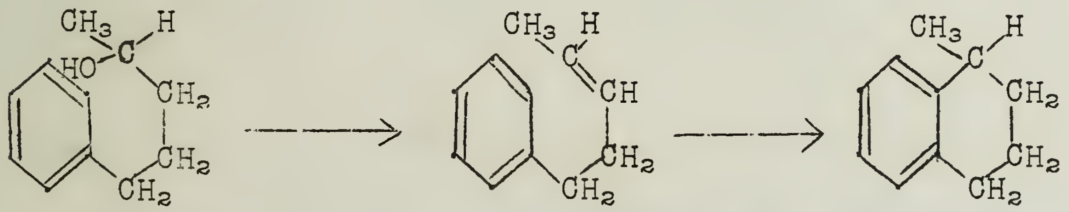


$$(CH_3)_3CCHOHC(CH_3)_3 \longrightarrow (CH_3)_3C\overset{\oplus}{C}HC(CH_3)_3 \xrightarrow{CH_3\ shift} (CH_3)_3C{-}CH(CH_3)\overset{\oplus}{C}(CH_3)_2 \quad (a)$$

$$(CH_3)_3C\overset{\oplus}{C}HC(CH_3)_3 \longrightarrow CH_3CH{=}C(CH_3)_2 + (CH_3)_3\overset{\oplus}{C} \quad (b)$$

(b) is explained by the assumption that an electron pair may shift without carrying along its organic group. This would leave a + fragment much in the same way that a proton leaves the molecule.

Dehydration of phenylated alcohols (cyclization).--Roblin, Davidson, and Bogert dehydrated twenty-four aromatic alcohols (method b). They found that some formed only olefins and polymers but others yielded indanes and tetralins. The latter is probably a two-step reaction, first the formation of an olefin and then subsequent cyclization.



The presence of the olefin could be shown if the reaction was interrupted and the reaction mixture titrated with bromine.

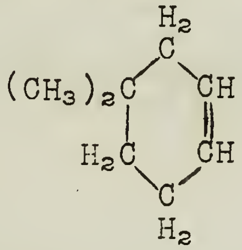
The unsaturation of these phenylated olefins is of such a character that it can apparently occupy different locations in the side chain and still form the same cycle. Thus 1-methyl tetralin is formed from 1-phenyl pentanol when the OH group is in position 2,3,4, or 5. Two alcohols, $C_6H_5CH_2CH(OH)CH(CH_3)CH_2CH_3$ and $C_6H_5CH_2CH_2C(CH_3)OHCH_2CH_3$, yielded both 1,2-dimethyl tetralin and 1-methyl-1-ethyl indane. The presence of a gem dimethyl group in every case led to indane formation, otherwise the six-membered ring formation was more prevalent.

Dehydration of unsaturated alcohols.--Linstead in 1936 devised a method of synthesis of compounds containing an angular methyl group by the dehydration of the appropriate alcohol. It had

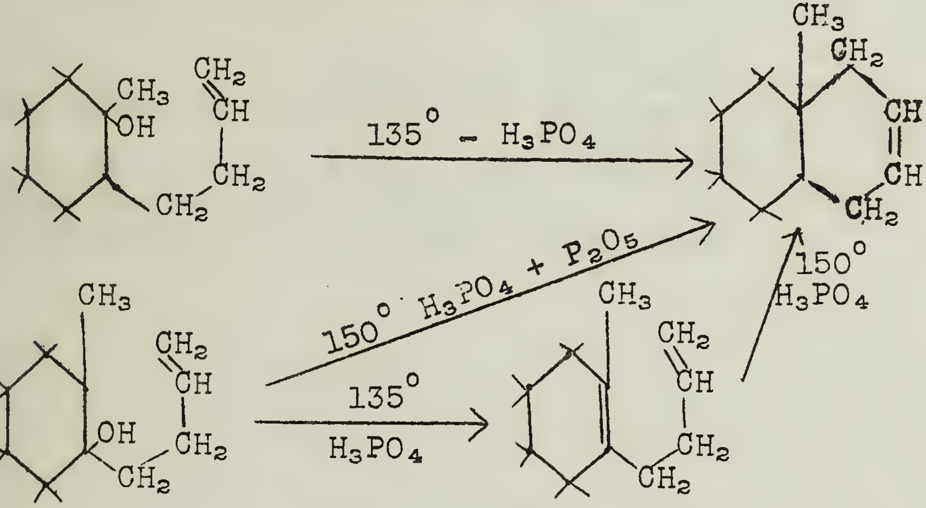
previously been shown that compounds of the type

$$RCH=C(CH_3)CH_2CH_2CH=C(CH_3)_2$$

could be cyclized in good yield by H_2SO_4 or H_3PO_4. Linstead dehydrated $C(CH_3)_2OHCH_2CH_2CH_2CH=CH_2$ and obtained 80 per cent yield of



From this he anticipated that 1-methyl-2$\Delta^{3'}$-butenyl cyclohexanol (I) would readily cyclize to a 9-methyl octalin (II). The isomeric 2-methyl-1Δ^{3}-butenyl cyclohexanol (III) was also dehydrated and yielded the same product.



I

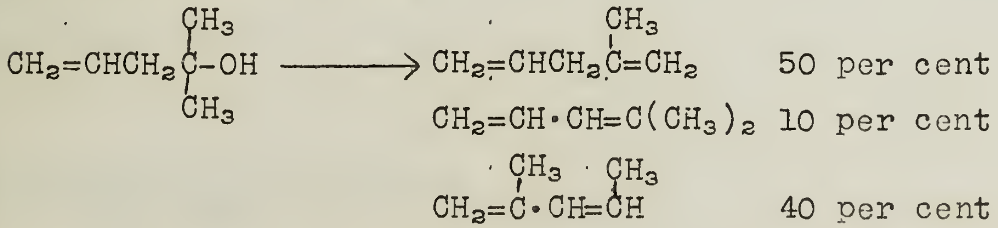
II (89 per cent)

III

IV

Under the proper conditions IV could be isolated.

Bacon and Farmer synthesized several dienes by the dehydration of unsaturated alcohols. They refluxed the alcohol with a small amount of concentrated HBr and then distilled out the hydrocarbon and water.



$$CH_2=CHCH_2\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-OH \longrightarrow CH_2=CHCH_2\overset{\displaystyle CH_3}{C}=CH_2 \quad \text{50 per cent}$$

$$CH_2=CH\cdot CH=C(CH_3)_2 \quad \text{10 per cent}$$

$$CH_2=\overset{\displaystyle CH_3}{C}\cdot CH=\overset{\displaystyle CH_3}{CH} \quad \text{40 per cent}$$

They likewise dehydrated $(CH_3)_2CHCHOHCH=CHCH_3$, $CH_3CH=CH-C(CH_3)_2OH$, $(CH_3)_2C=CHCHOH(CH_3)$ and attempted dehydration of

$$CH_3\cdot CH(CH_3)CHOHCH=CH_2.$$

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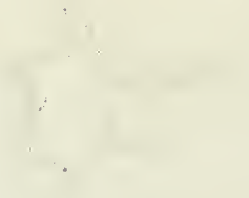

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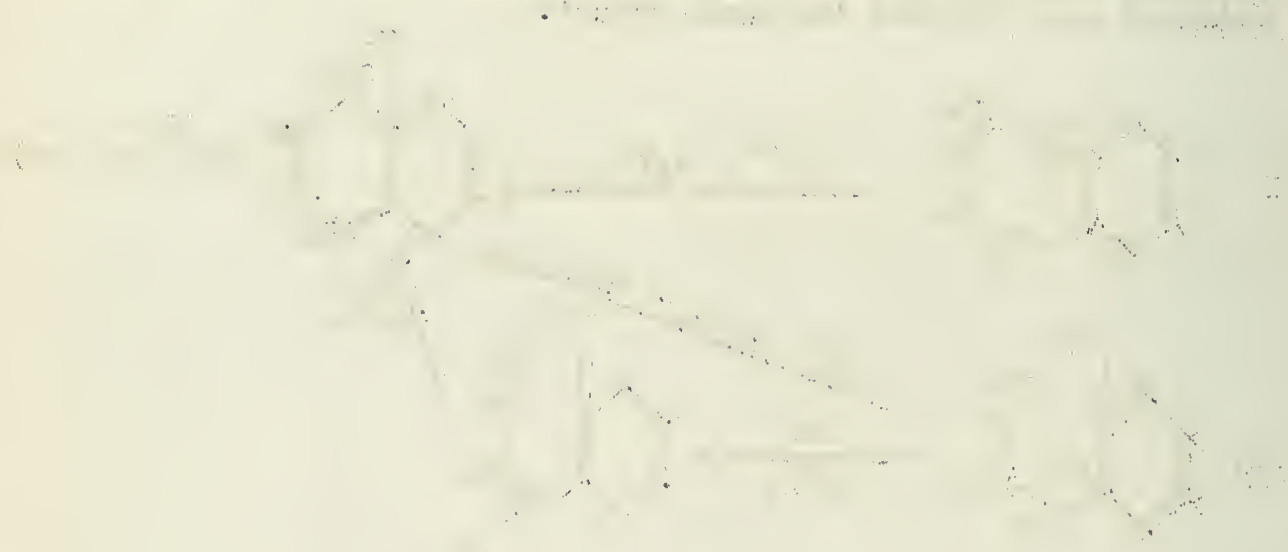

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The products were identified by oxidation with three per cent potassium permanganate to the corresponding acids, and the reaction of maleic anhydride which gives a crystalline derivative with α,γ-dimethylbutadiene, but only polymeric products with α,α-dimethylbutadiene. At no time could they prepare pure α,α-dimethylbutadiene for there were always rearrangements with the formation of the isomeric α,γ-dimethylbutadiene. At present they are investigating the use of phenylcarbimide as a dehydrating agent.

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Ibid., 55, 812, 1106, 1119, 1528, 3428, 3721, 3732, 3809, 4153, 4194 (1933)
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Roblin, Davidson, and Bogert, J. Am. Chem. Soc., 56, 186, 959 (1934); 57, 151 (1935)
Meyer and Tuot, Comp. Rend., 196, 1231 (1933)
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Reported by C. H. McKeever
April 27, 1938.

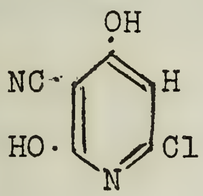
POLYMERIZATION OF CYANACETYL CHLORIDE; RICININE

Schroeter -- Berlin
Späth -- Vienna

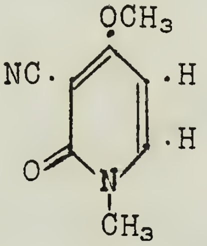
Cyanacetyl chloride changes on standing to a yellow solid from which 2,4-dihydroxy-6-chloronicotinic acid nitrile (I; chloronorricinine) can be obtained in good yields. The reaction is given by the equation:

$$3NC\cdot CH_2COCl \longrightarrow I + \left[(C_3H_2NOCl)\cdot HCl\right]_x \quad (II)$$

The mechanism for this change undoubtedly involves the α-hydrogen atom, since α-cyanopropionyl chloride and α-cyanophenylacetyl chloride polymerize on standing (more slowly than cyanacetyl chloride); while α-cyanodimethyl- and α-cyanodiethylacetyl chlorides do not polymerize even after long standing at room temperature.



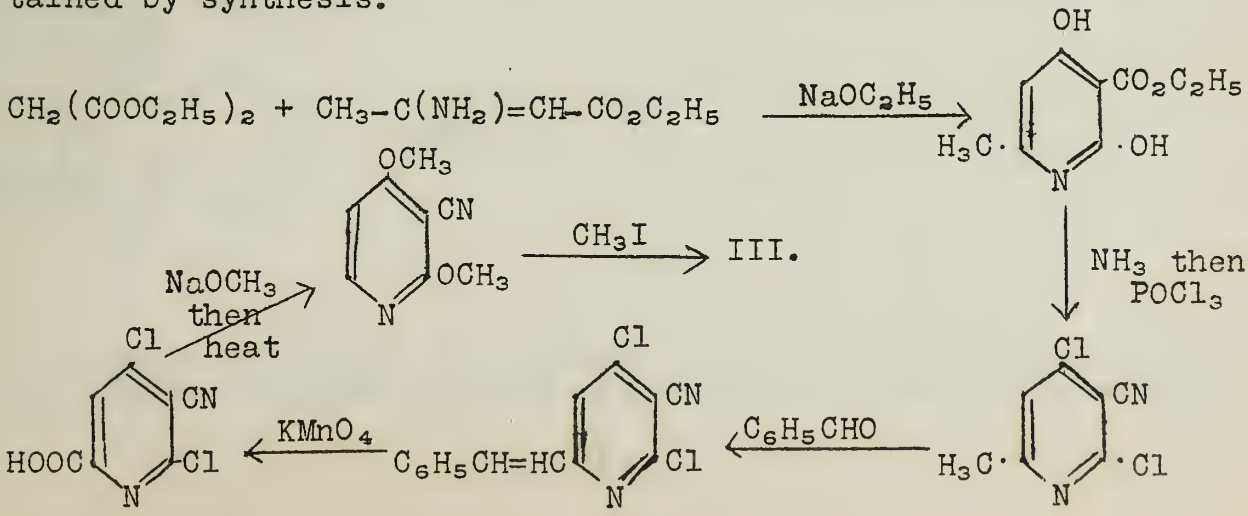
I



III

II seems to be a polymeric substance of high molecular weight and of unknown structure. On gentle hydrolysis, II yields mainly cyanoacetic acid and some malonic acid and ammonium chloride.

I is particularly interesting because of its close resemblance to ricinine (III), an alkaloid found principally in the castor bean. The structure of ricinine was determined by Späth from degradation experiments. Proof of the structure was later obtained by synthesis:



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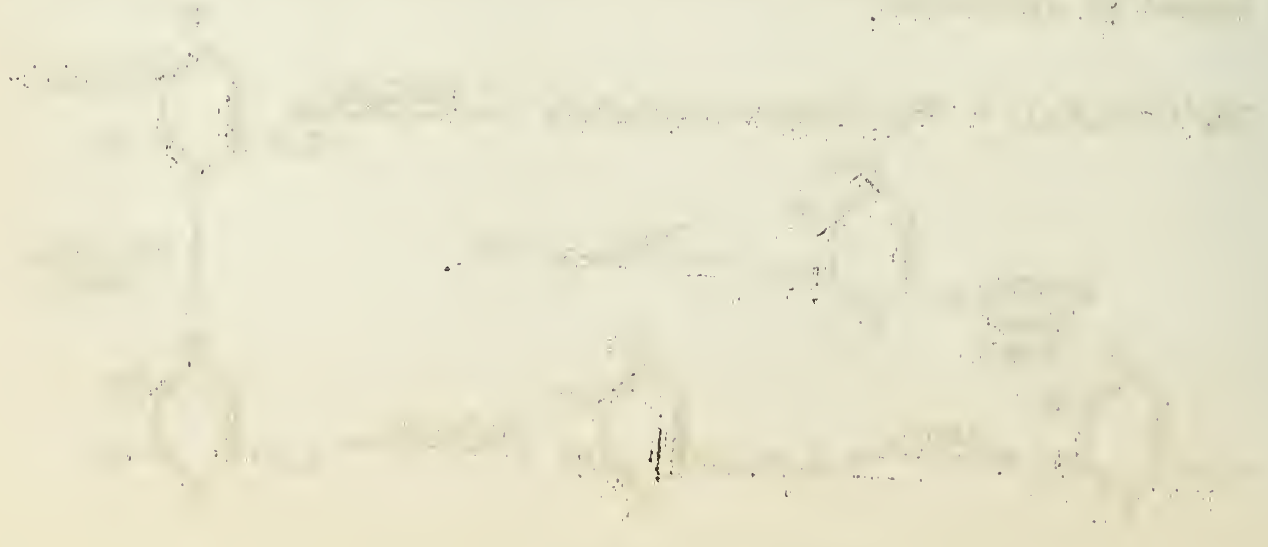
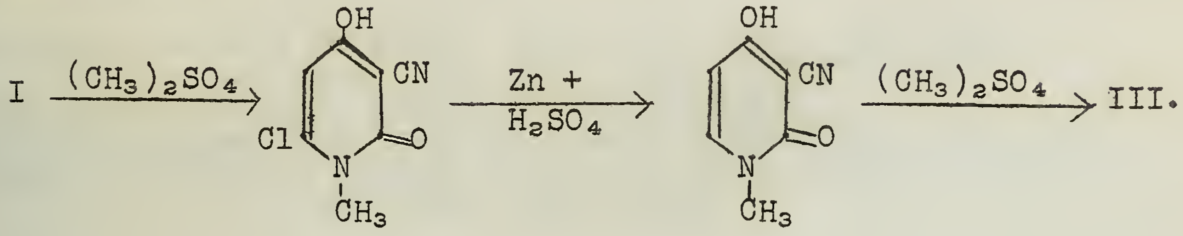


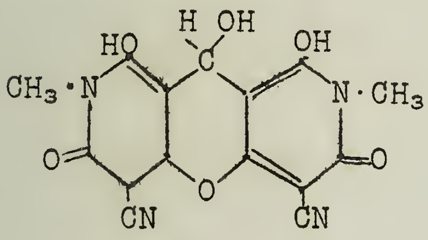
The synthesis from chloronorricinine is simpler and gives better yields:



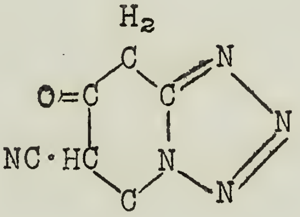
chlororicininic acid

ricininic acid

Numerous substituted pyridine derivatives have been made by Schroeter, but compounds of the fluoricininic acid (IV) and the pyridotetrazol (V) types are the most important. Fluoricininic acid is an orange dye prepared by heating formic acid with 6-hydroxyricininic acid.



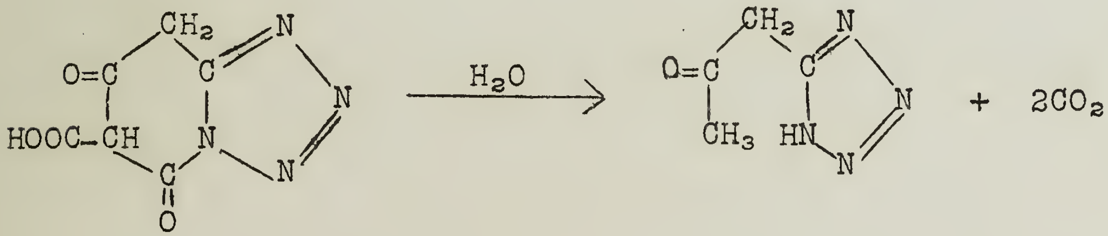
IV



V

1,3-diketotetramethyleneo-tetrazole-carboxylic acid-(2)-nitrile

V is prepared by treating 6-hydrazinonorricine with nitrous acid. The keto form of V is prepared because of the ease of hydrolysis, first to the amide, then the acid and finally to C-acetonyltetrazol (VI).



The amide of V gives some promise of being an effective heart stimulant, although the acid and nitrile are without beneficial action.

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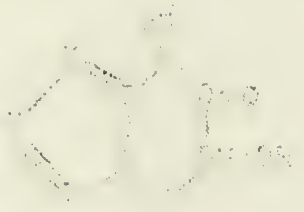

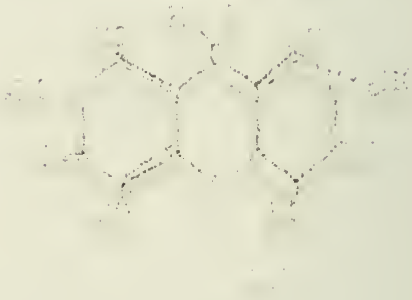

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Reported by Joseph Corse
April 27, 1938.

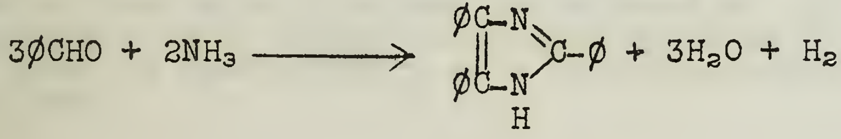
CHEMILUMINESCENCE

Drew -- Queen Mary College, University of London
Dougherty -- Princeton University
Petsch -- University of Jena

Chemiluminescence has been defined as light produced by molecules or atoms which have been excited by a chemical reaction. Many reactions are accompanied by the evolution of light. A few of these include neutralization of CaO, BaO, or K_2O with concentrated H_2SO_4: Decomposition of H_2O_2 by means of Ag, Pt, Os, Ag_2O, PbO_2, MnO_2, etc.; various reactions involving Grignard reagents, e.g., nitro compounds with Grignards, Wedekind's reaction between chloropicrin and phenylmagnesium bromide, and the oxidation of *p*-chloromagnesium bromide; and the Trantz-Shorigin oxidation of pyrogallol-formalin solutions in K_2CO_3 by means of 30 per cent H_2O_2. Many natural products such as coffee, cayenne pepper, black pepper, tea, cocoa, yeast, mustard, and others luminesce when treated with alkaline hypochlorite solutions.

Of more recent note and by far the most spectacular are the oxidation of lophine (I) with alkaline hypochlorite and H_2O_2; alkaline oxidation of the phthalhydrazides (II); and the decomposition of H_2O_2 by means of biacridylium salts (III) in alkaline solution.

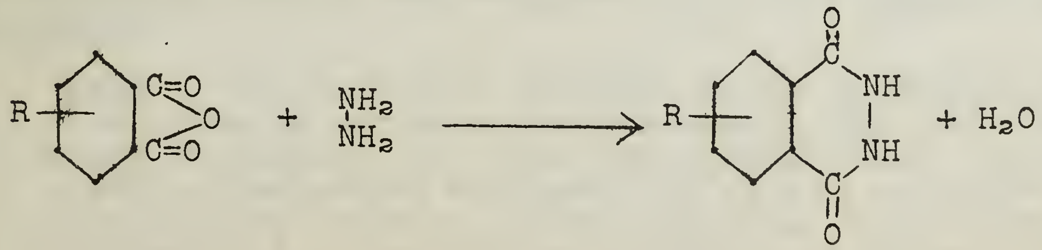
Lophine (triphenylglyoxaline) is easily prepared by the action of ammonia on benzaldehyde. The hydroxamide cake which forms is heated to obtain crude lophine of sufficient purity for experimentation.



Lophine

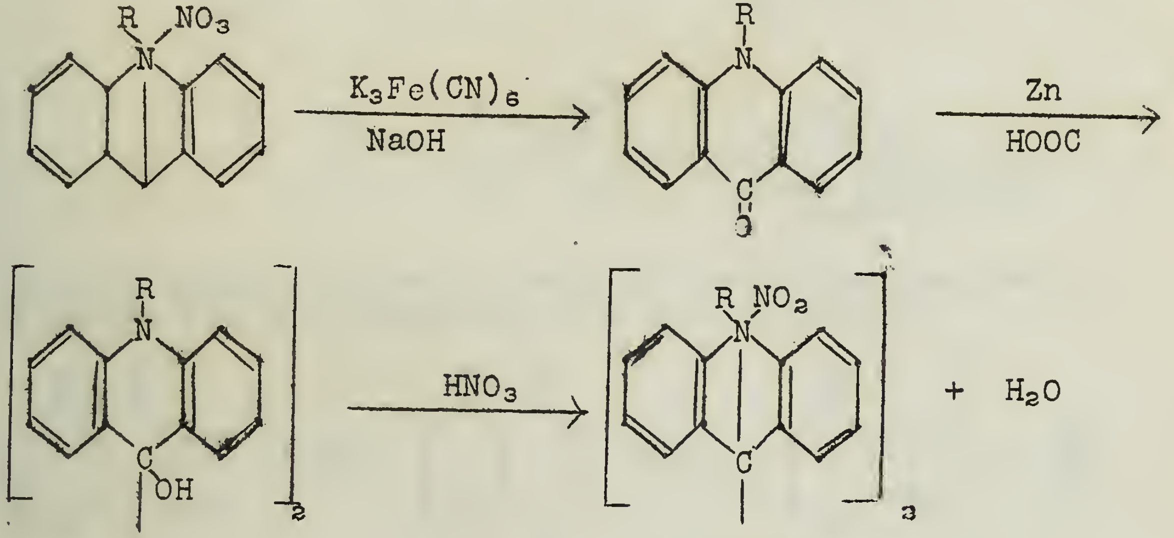
I

The substituted phthalhydrazides are usually made by the condensation of the proper substituted phthalic anhydride with hydrazine or hydrazine hydrate. In the case of the amino hydrazides the nitro compound is usually condensed with the hydrazine and subsequently reduced.



II

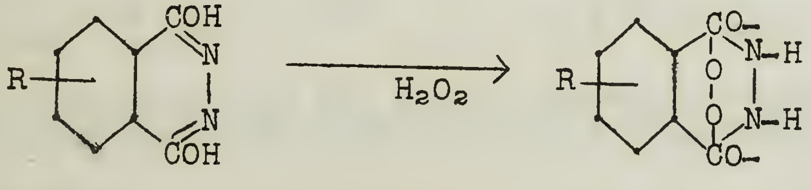
The biacridylium (luzigenin) salts are made as follows: By oxidation of an alkyl nitrate salt of acridine with alkaline potassium ferricyanide the alkyl acridone is produced. This compound is reduced with zinc and glacial acetic acid, and the product resulting is dissolved in hot dilute nitric acid. When the solution is cooled, the crystalline luzigenin salt separates.



III

The mechanism involved in the production of light is in all cases obscure and little understood. Several investigators have proposed different theories, but experimental proof is lacking.

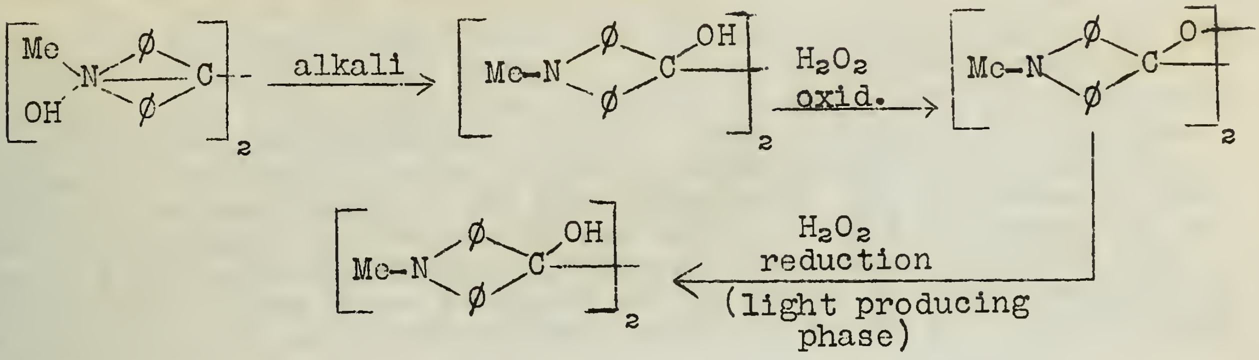
In the case of the phthalhydrazide series Drew has shown that if one of the imino hydrogens is replaced by an immobile group, the molecule is no longer chemiluminescent on oxidation. He states that there is some evidence of a peroxide formation by addition to the dienol,



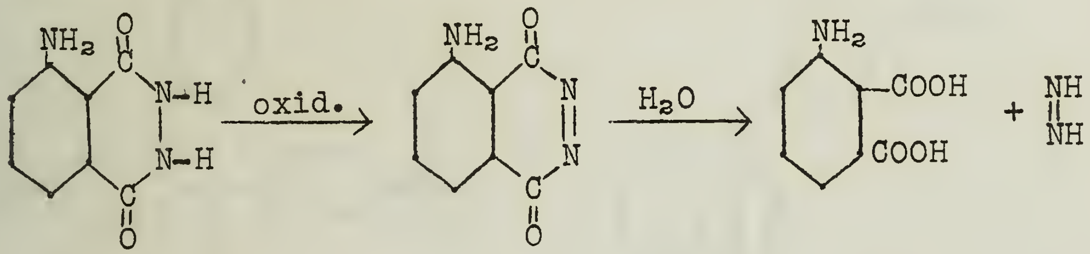
and proposes that the chemiluminescence follows the oxidation of the imino hydrogen of the peroxide with the consequent elimination of an oxygen molecule and regeneration of the original phthalhydrazide.

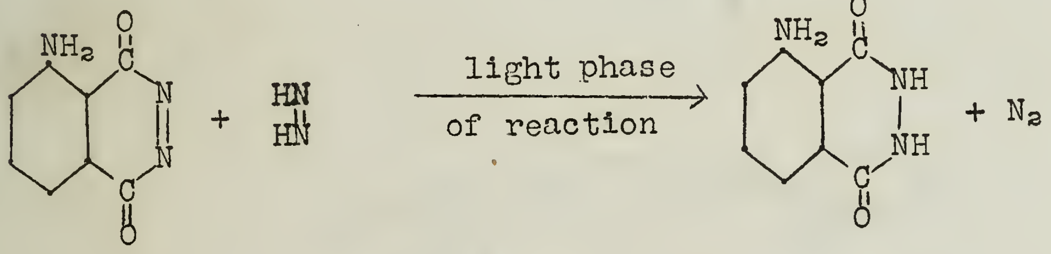
Study of the influence of alkali on the production of light and on the rate of oxidation as evidenced by the evolution of nitrogen led Dougherty to a different postulation. Since increasing alkali concentration increased the rate of oxidation but decreased the light emission, he says that the dienol form of the phthalhydrazide is first oxidized yielding energy rich fragments which then excite the keto form to chemiluminescence. The effect of the alkali is thus to increase the dienol concentration and at the same time decrease the keto form which is responsible for the light.

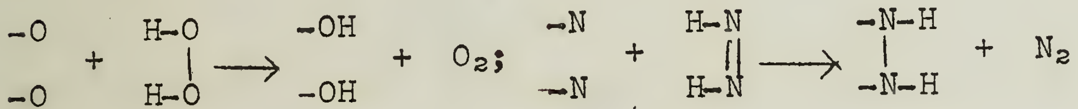
Petsch postulates the following series of reactions to explain the luminescence of the luzigenin salts.



He also draws the parallel with the mechanism proposed by Albrecht for the phthalhydrazide series, namely:







$$\begin{matrix}-O\\-O\end{matrix} + \begin{matrix}H-O\\ \vert\\ H-O\end{matrix} \longrightarrow \begin{matrix}-OH\\-OH\end{matrix} + O_2; \quad \begin{matrix}-N\\-N\end{matrix} + \begin{matrix}H-N\\ \Vert\\ H-N\end{matrix} \longrightarrow \begin{matrix}-N-H\\ \vert\\ -N-H\end{matrix} + N_2$$

5-Aminophthalhydrazide and 10,10'-dimethyldiacridylium nitrate are the most strongly chemiluminescent compounds yet developed.

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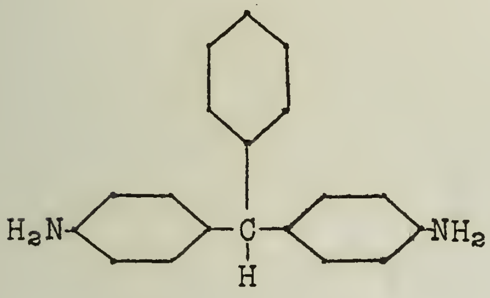
Reported by L. S. Keyser
May 4, 1938.

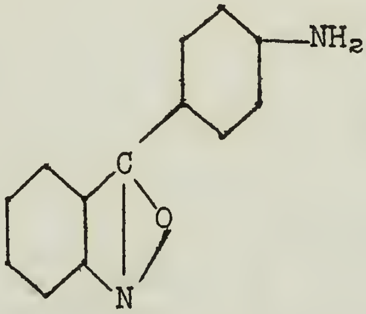
REACTIONS OF *o*-NITROBENZALDEHYDE

Ioan Tanasescu -- University of Cluj, Roumania

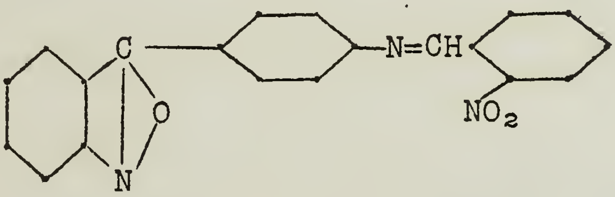
The condensation of *o*-nitrobenzaldehyde with aniline does not yield the expected Schiff base but instead gives a mixture of three products which have been shown to be 2-nitro-4',4''-diaminotriphenylmethane (I), *p*-aminophenylanthranil (II), and *o*-nitrobenzylidene-*p*-aminophenylanthranil (III). Renouf carried out the condensation originally using anhydrous zinc chloride and aniline sulfate but was unable to do more than prove the presence of the triphenylmethane derivative in the crude product by reduction to the 2,4',4''-triaminotriphenylmethane. Tanasescu effected the separation of the three products on the basis of their respective solubilities in cold hydrochloric acid and in 96 per cent alcohol.



I



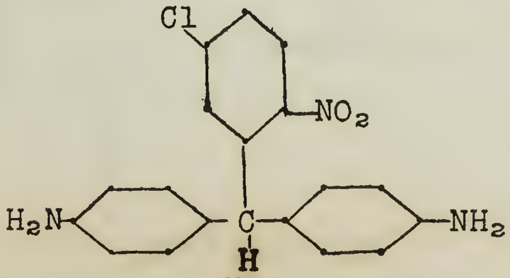
II



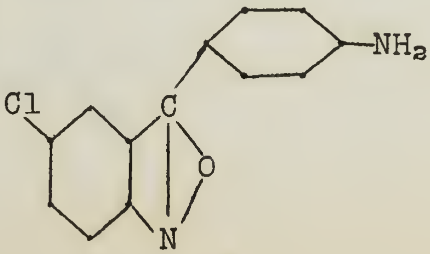
III

The expected derivatives were obtained in each case. III was also obtained by the condensation of an alcoholic solution of *p*-aminophenylanthranil with *o*-nitrobenzaldehyde.

He next studied the condensation of 2-nitro-5-chlorobenzaldehyde with aniline sulfate under the same conditions. In this case only IV and V were obtained.



IV

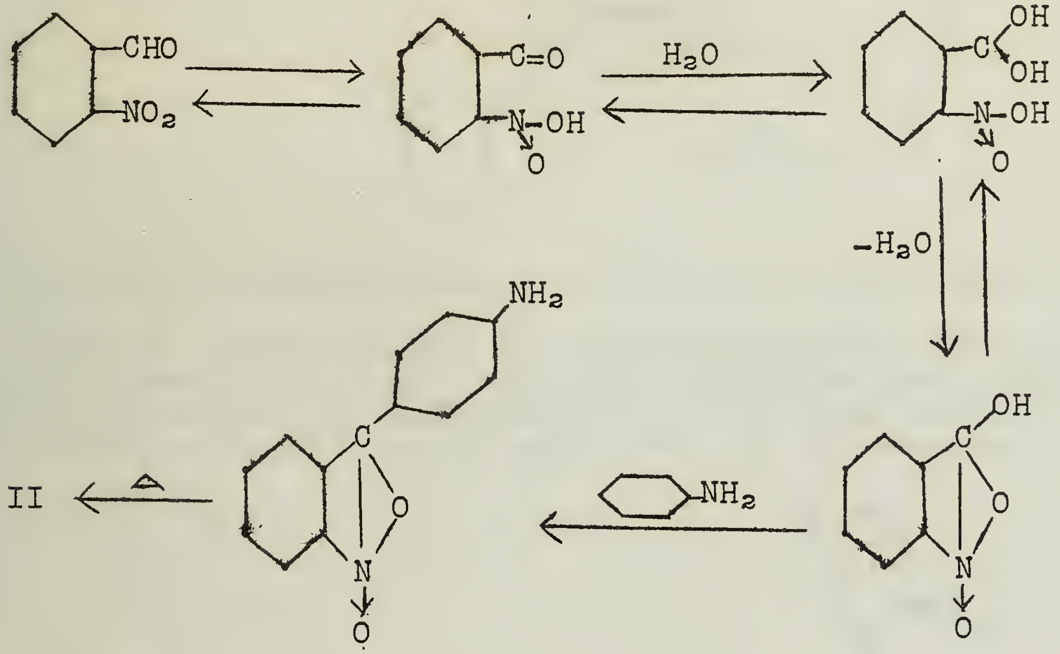


V

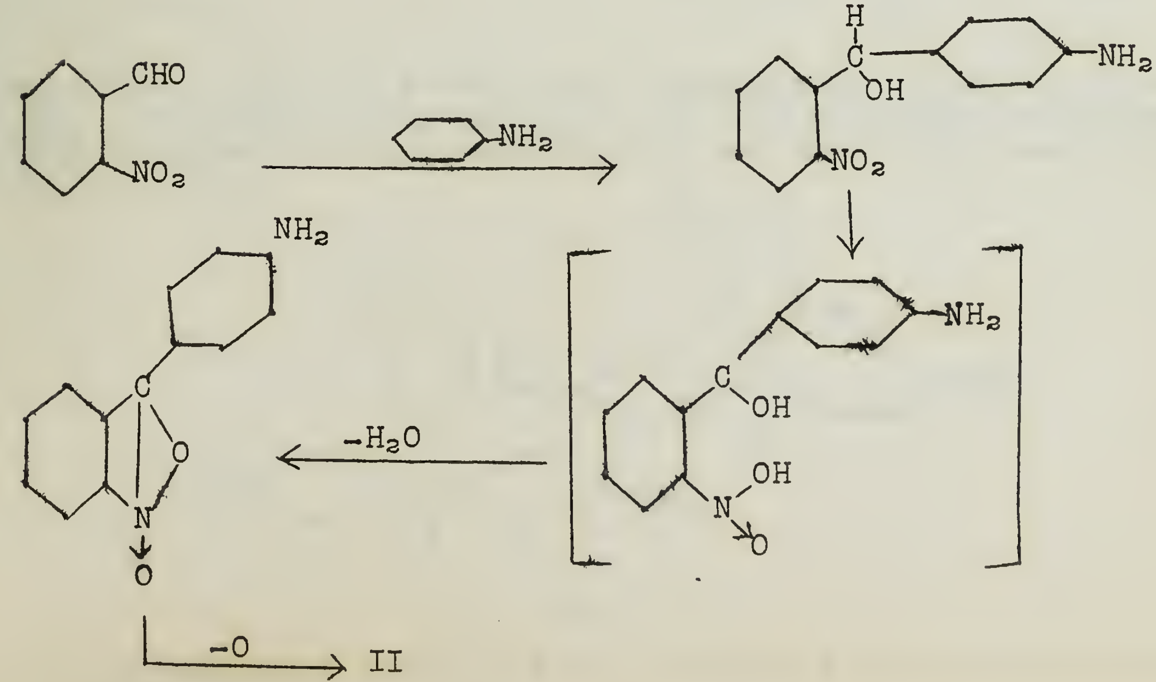
The usual derivatives were obtained from these compounds.

Tanasescu postulates two mechanisms for the formation of the anthranils but has been able to prove neither. The first mechanism is quite logical if one admits that o-nitrobenzaldehyde may tautomerize as shown.

(a)



(b)



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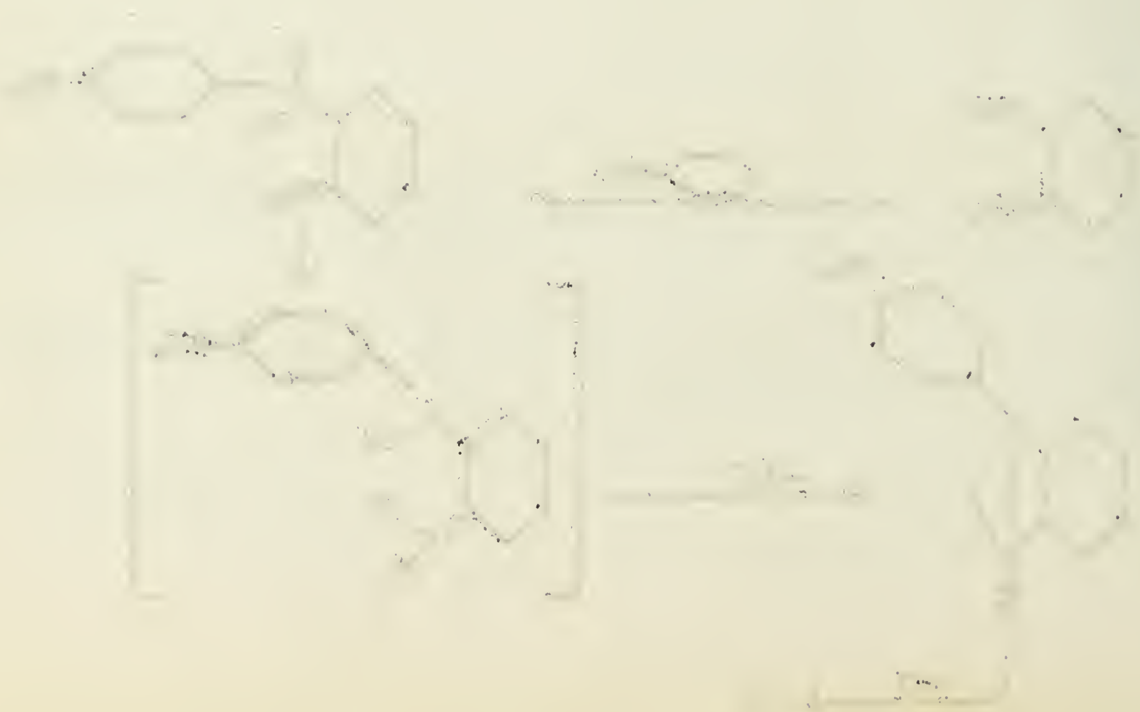
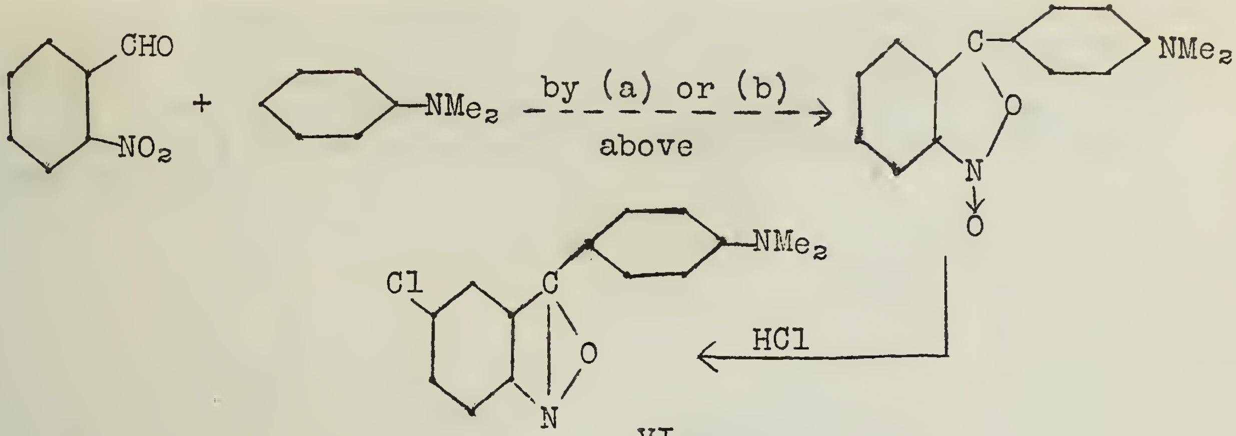


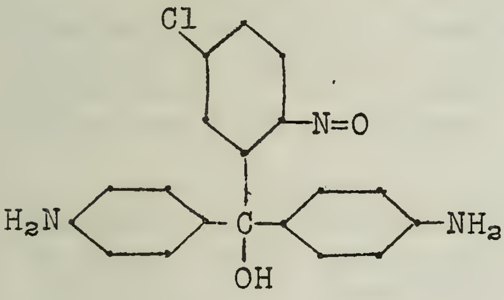
If the condensation is carried out in hydrochloric acid with dimethylaniline the chloro derivative (VI) is obtained, supposedly by the following mechanism:



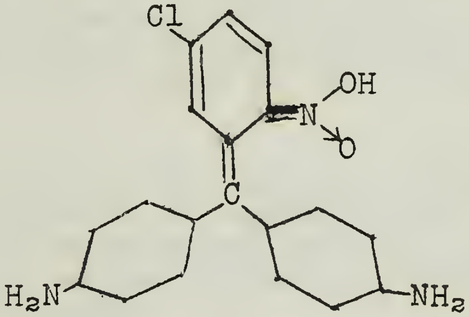
VI

The last step is characteristic of N-oxides of this type.

Both the anthranils and the triphenylmethanes react characteristically when irradiated. With the triphenylmethanes the first step is undoubtedly an isomerization to a nitroso carbinol (VII) if in pyridine or to a pseudo acid (VIII) if in benzene.

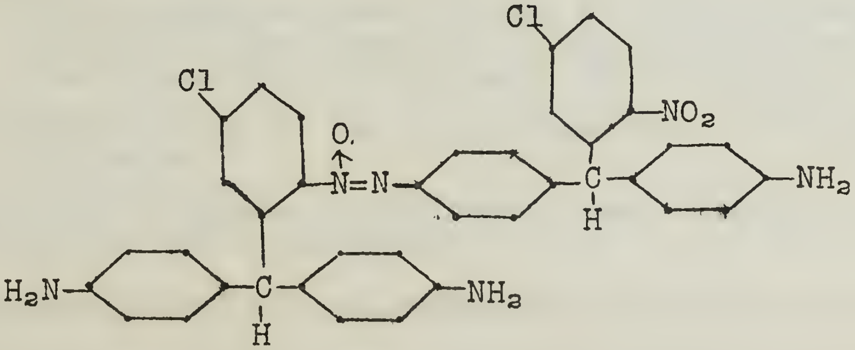


VII



VIII

The final product is a dark blue substance of polymeric character (IX). In addition they obtained a yellowish-orange substance which analyzes for $C_{38}H_{30}O_3N_6Cl_2$ and for which they postulate the structure,



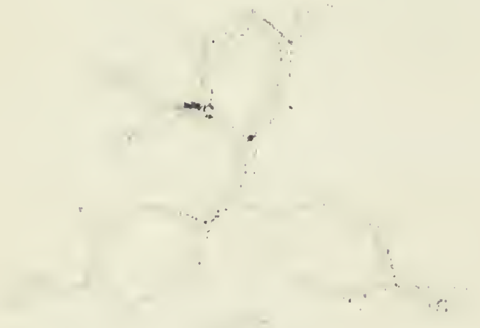
X

Irradiation of X gives IX so evidently X is an intermediate in the polymerization.

[illegible]

[illegible]

[illegible]

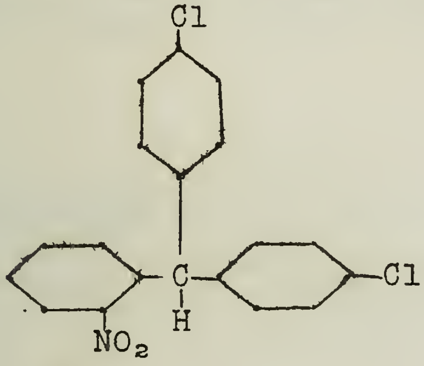


[illegible]

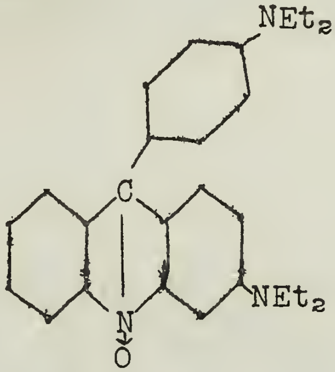
[illegible]

Oxidation of the hydrochlorides with hydrogen peroxide gives a similar dark blue precipitate which has not as yet, however, been proven to be identical with IX.

In an attempt to synthesize I they prepared XI by a Friedel and Crafts reaction between chloro-benzene and o-nitrobenzal chloride. However, heating of XI in a sealed tube fifteen hours at 180° with concentrated ammonia and copper sulfate gave, instead of I, a yellow substance for which they postulate the structure XII.



XI



XII

Irradiation of the anthranils in benzene solution also causes a definite transformation to brown substances which are evidently polymers. As yet no information concerning either the structure of the polymer or the probable course of the polymerization has been proffered.

Condensation of o-nitrobenzaldehyde with benzene, chlorobenzene, and bromo-benzene in the presence of concentrated sulfuric acid led in each case to the corresponding N-oxo, C-oxy-acridine. Reduction with sodium amalgam appears to reduce the C-hydroxyl but does not touch the N-oxygen.

Many condensations were carried out between o-nitrobenzaldehyde and substituted acetophenones generally with the aid of sodium phosphate as the condensing agent. The following regularities were noted:

1) Electronegative substituents in the acetophenone molecule favor the formation of the addition product while electropositive substituents favor chalcone formation.

2) Substituents in the 2 position cause unfavorable steric hindrance.

3) Electronegative substituents favor indigo formation by the action of alkali.

The products obtained all exhibited the following characteristics:

1) Treatment with alcoholic alkali gives a red substance of acidic character which upon treatment with a large amount of concentrated hydrochloric acid precipitates indigo.

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

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[illegible]

[illegible]

2) Reduction yields α-substituted quinolines.

3) Irradiation yields substances of acidic character for which a structure is not yet forthcoming.

Use of alcoholic alkali as the condensing agent generally leads to chalcone formation. The reactions of the chalcones are analogous to those of the corresponding keto alcohols.

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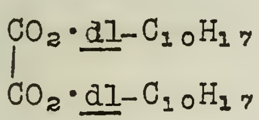
Reported by R. S. Long
May 4, 1938.

STEREOISOMERISM IN ESTERS OF DIBASIC ACIDS

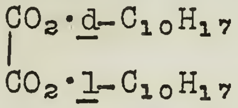
McKenzie and Abbot -- St. Andrews, Scotland

Hückel, in 1933, reported that esterification of oxalic acid with each of two α- and two β-racemic decalols produced two optically inactive normal esters. His experiments showed that one of these was a resolvable racemic form and the other a meso modification. These esters had, presumably, the following structures:



$$\begin{array}{l} CO_2\cdot\underline{dl}\text{-}C_{10}H_{17} \\ | \\ CO_2\cdot\underline{dl}\text{-}C_{10}H_{17} \end{array}$$

(racemic)

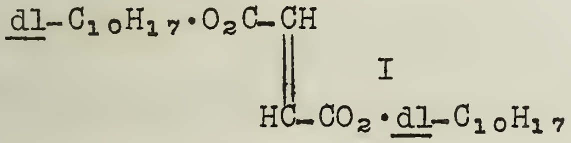


$$\begin{array}{l} CO_2\cdot\underline{d}\text{-}C_{10}H_{17} \\ | \\ CO_2\cdot\underline{l}\text{-}C_{10}H_{17} \end{array}$$

(meso)

He did not, however, succeed in identifying any one of the esters prepared with either of the forms shown above.

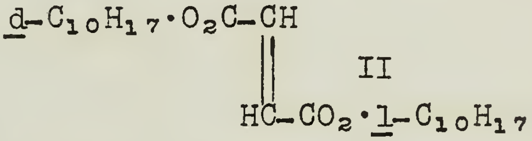
In 1934, McKenzie and Abbot succeeded in preparing and isolating two optically inactive bornyl esters of furmaric acid. These esters have the structures:



$$\begin{array}{ll} \underline{dl}\text{-}C_{10}H_{17}\cdot O_2C\text{-}CH & \\ \quad\quad\quad\quad\quad \| & \\ \quad\quad\quad\quad\quad HC\text{-}CO_2\cdot\underline{dl}\text{-}C_{10}H_{17} & \end{array}$$

I

dl-dibornyl fumarate



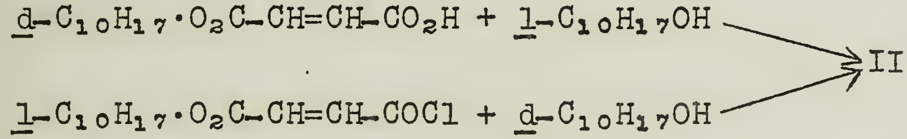
$$\begin{array}{l} \underline{d}\text{-}C_{10}H_{17}\cdot O_2C\text{-}CH \\ \quad\quad\quad\quad\quad \| \\ \quad\quad\quad\quad\quad HC\text{-}CO_2\cdot\underline{l}\text{-}C_{10}H_{17} \end{array}$$

II

d-bornyl *l*-bornyl fumarate

It will be noted that the optical inactivity of II is due to the presence of a center of symmetry in the molecule.

This ester was prepared in a number of ways. Esterification of the optically active acid ester with the alcohol of opposite sign gave yields of about 50 per cent while use of the corresponding acid chloride resulted in a yield of 80 per cent:



$$\left.\begin{array}{l} \underline{d}\text{-}C_{10}H_{17}\cdot O_2C\text{-}CH{=}CH\text{-}CO_2H + \underline{l}\text{-}C_{10}H_{17}OH \\ \\ \underline{l}\text{-}C_{10}H_{17}\cdot O_2C\text{-}CH{=}CH\text{-}COCl + \underline{d}\text{-}C_{10}H_{17}OH \end{array}\right\} \rightarrow II$$

It was also produced, along with I and the racemic acid ester by the esterification of fumaric acid with *dl*-borneol.

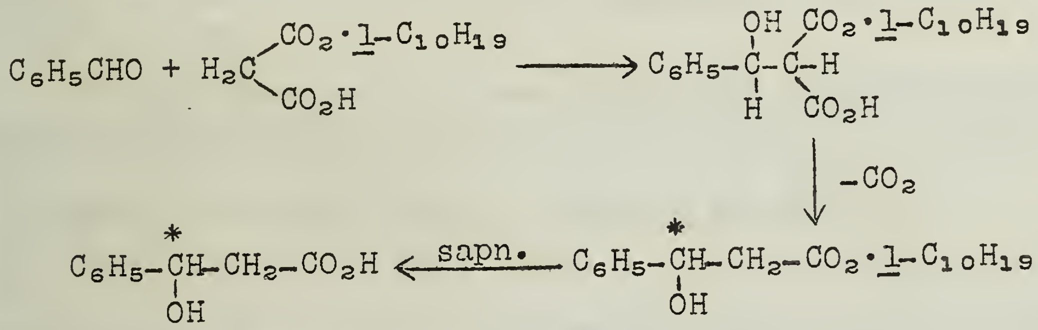
Efforts to obtain analogous dimenthyl esters of malonic acid produced only the racemic form. Difficulties in crystallizing the products obtained interfered with efforts to isolate the internally compensated form.

Repetition of the experiment using borneol with malonic acid esters gave a normal ester with a melting point well above that of the racemic ester. After repeated recrystallization, however, the product still had a slight optical activity whose sign depended on the method of preparation. This result was apparently due to the formation of mixed crystals of the internally compensated ester with an active form.

In contrast with the results obtained with the decalols by Hückel, only one inactive dibornyl oxalate, the racemic, was obtained by McKenzie and Abbot. Efforts to prepare the internally compensated form were unsuccessful due to the instability of the acid esters.

Some evidence was obtained for the formation of *d*-bornyl-*l*-bornyl-*d*-tartrate but the compound could not be isolated.

l-Monomenthyl malonate was used in the asymmetric synthesis of β-hydroxy-β-phenylpropionic acid according to the following scheme:



(*levo*-rotatory)

β-Hydroxy-β-phenylpropionic acid

Among the compounds prepared in this study were some interesting examples of racemic compounds and racemic solid solutions. The melting point curve for mixtures of *d*- and *l*-dibornyl fumarate has the two minima and one maximum characteristic of racemic compounds. But the molecular weight of the racemic form determined in boiling $CHCl_3$ was the same as that of the pure isomers.

dl-Monobornyl fumarate is dimorphous, one form melting at 118-119°, the other at 125-126°. The melting point curve showed one form to be a racemic solid solution and the other a racemic compound.

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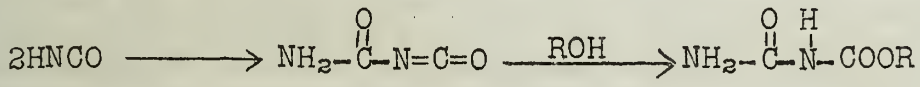
Reported by J. H. Clark
May 11, 1938.

VITAMIN E

Bergel, Todd and Work -- Lister Institute, London
Evans and Emerson, University of California, Berkeley
Fernholz -- Merck and Company, Rahway, New Jersey
Karrer -- University of Zurich

The first attempt to concentrate Vitamin E was made by Evans and Burr in 1927. By treatment of the nonsaponifiable matter from wheat germ oil with solvents a red oil was obtained, of which a single 10-mg. dose enabled test rats to bear litters. Other materials rich in Vitamin E are cottonseed oil, palm oil and lettuce leaves.

In 1936 Evans and Emerson found that treatment of the concentrate with cyanic acid gave three crystalline allophanates (I).



$$2HNCO \longrightarrow NH_2-\overset{O}{\overset{\|}{C}}-N=C=O \xrightarrow{ROH} NH_2-\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{|}{N}}-COOR$$

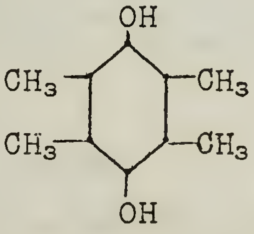
(I)

Upon hydrolysis of these allophanates three liquid alcohols were obtained, of which only two were physiologically active. One of these, active in a single dose of 3 mg., was named α-tocopherol. The optical rotation of its allophanate is either zero, or very low. Analysis gave $C_{29}H_{50}O_2$ for the alcohol.

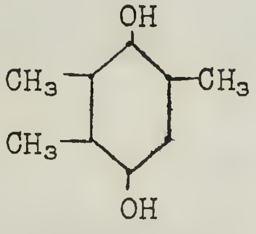
The second allophanate appears to be isomeric with a α-tocopheryl allophanate. Biologically the alcohol from this allophanate is less potent than α-tocopherol, 8 mg. being the minimal effective dose. It is known as β-tocopherol, and is optically active. The neo-tocopherol of Karrer and cumo-tocopherol of John are now believed to be identical with β-tocopherol.

In 1937 Evans isolated γ-tocopherol from cottonseed oil. It is effective in a single 8 mg. dose. It appears to have the empirical formula $C_{28}H_{48}O_2$ and shows a slight optical activity.

Fernholz in 1937 showed that α-tocopherol on thermal decomposition gave durohydroquinone (II) plus an unsaturated hydrocarbon, possibly $C_{18}H_{36}$.



II



III

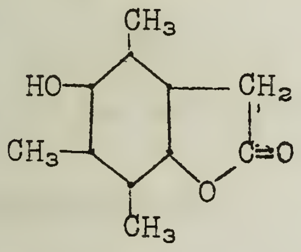
This, coupled with the fact that the reducing property of α-tocopherol is not present in its esters, led to the assumption that α-tocopherol is a mono ether of durohydroquinone. John found that β-tocopherol on pyrolysis gave pseudocumo-hydroquinone (III), and suggested that this alcohol is the mono ether of III.

Recently Fernholz, Todd, and Karrer have independently shown the mono ether concept to be untenable. They used as their lines of evidence the following facts:

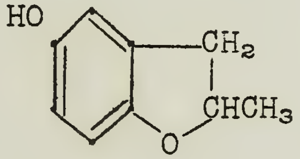
1. Synthetic mono ethers of durohydroquinone, e.g., cetyl, phytyl and octadecyl all have in common an absorption spectrum which differs from that of the tocopherols.

2. These mono ethers reduce silver nitrate much more slowly than the tocopherols. This type of oxidation gives duroquinone in the case of the synthetic ethers, whereas α-tocopherol undergoes but slight alteration in its molecular weight. The failure of α-tocopherol to split off duroquinone makes it likely that the alkyl portion is connected to the aromatic ring not only by means of an ether bond, but also by a carbon bridge. α-Tocopherol would then be derived from chromane or coumarane. This postulate is in keeping with the failure of ether splitting reagents to bring about the formation of durohydroquinone.

Todd, Bergel and Work prepared the following coumarane derivative (IV)



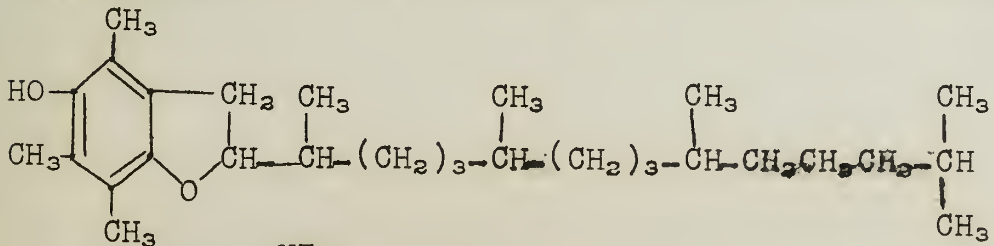
IV



V

and found a striking resemblance to α-tocopherol in both its absorption spectrum and reducing properties. They admit that a chromane nucleus is also a possibility.

Karrer synthesized 2-methyl-5-hydroxycumarane (V) and found its absorption spectrum and reducing action in line with those of α-tocopherol. He proposes as a provisional structure (VI)



VI

but admits of the possibility of a chromane structure.

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[illegible]

[illegible]

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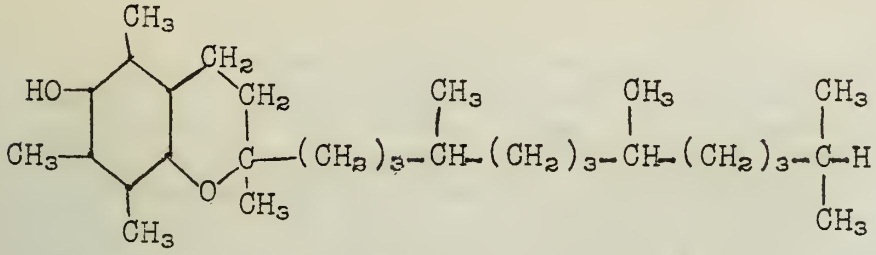
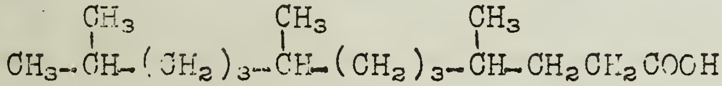
[illegible]

Fernholz has arrived at the following structure for α-tocopherol (VII) by a series of oxidative



VII

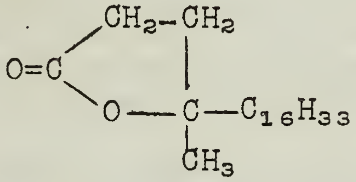
degradations. The products isolated are acetone, diacetyl, dimethyl maleic acid, and acid $C_{16}H_{32}O_2$. (VIII)



$$CH_3-\overset{CH_3}{CH}-(CH_2)_3-\overset{CH_3}{CH}-(CH_2)_3-\overset{CH_3}{CH}-CH_2CH_2COOH$$

VIII

a lactone $C_{21}H_{40}O_2$ (IX),



IX

and a ketone $C_{18}H_{36}O$.

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Reported by N. Kornblum
May 11, 1938.

Kuhn and Wallenfels -- Kaiser Wilhelm Institute,
Heidelberg

Well known compounds containing cumulated carbon-carbon double bonds are carbon suboxide and the allenes. From the tetrahedral structure of the carbon atom, it is seen that compounds with a larger number of carbon-carbon double bonds appearing together is an unbroken chain, that is, :C:C:C:C:C:C: are capable of existence. Compounds of this type are called cumulenes, reserving the name, polyenes, for compounds possessing a conjugated system of double bonds.

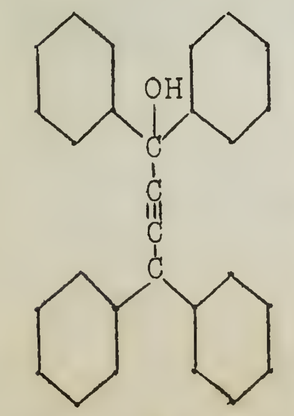
Theoretical considerations concerning the stereochemistry of compounds containing this system of cumulated double bonds were made by van't Hoff, who pointed out that allenes of the type XYC:C:CXY should be capable of resolution into optical antipodes. Maitland and Mills and Kohler have shown such to be the case. van't Hoff also predicted that in a butatrien, XYC:C:C:CXY, *cis-trans* isomerism would occur just as in the case of fumaric and maleic anhydride; in a pentatetraen, XYC:C:C:C:CXY, *dextro* and *levo* isomers, in a hexapentaen, XYC:C:C:C:C:CXY, *cis-trans* isomerism again, and so on. Atom models demonstrate that such possibilities do exist, and also that the structure is a very rigid one. Knowledge concerning the chemistry of these higher cumulenes is limited by a lack of suitable methods of preparation.

Brand was the first to obtain a hydrocarbon containing three cumulated double bonds. By allowing alcoholic potassium hydroxide to react with tetraphenyl-2,3-dichlorobutene, he isolated 1,1-4,4-tetraphenylbutatrien.

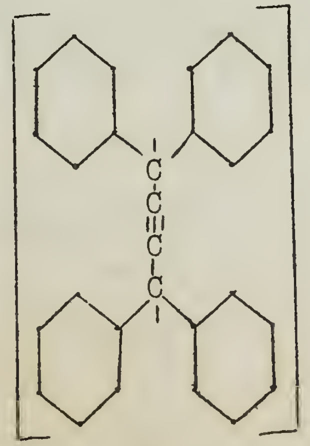
$$(C_6H_5)_2CH\cdot CCl{:}CCl\cdot CH(C_6H_5)_2 \xrightarrow[\text{alcohol}]{\text{2KOH}} (C_6H_5)_2C{:}C{:}C{:}C(C_6H_5)_2 + 2KCl + 2H_2O$$

Various homologs of this compound have since been prepared.

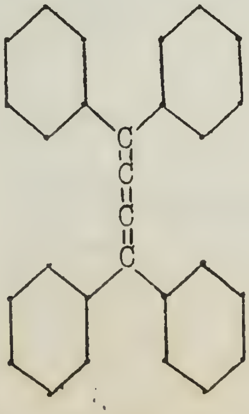
When acetylene glycols are treated with P_2I_4, cumulenes are formed, that is, when the tetraphenylbutindiol I is treated with P_2I_4, the tetraphenylbutatrien III is formed.



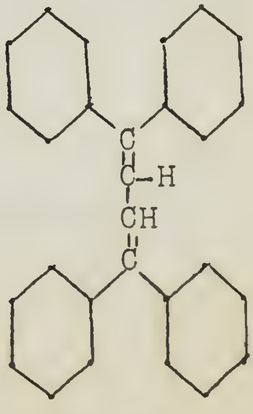
I



II



III

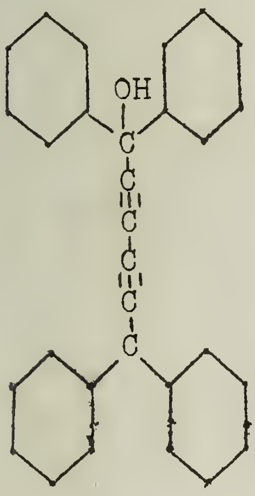


IV

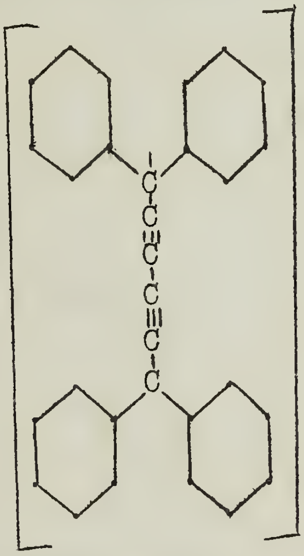
The acetylene glycol, I, is readily prepared from acetophenone and acetylene dimagnesium bromide, so the starting materials are readily available.

In the formation of these cumulenes, Kuhn postulates an intermediate diradical, II, the same as he postulates in the syntheses of polyenes. The hydrocarbon, III, differs from the polyene, IV, in its yellow color and higher melting point. Syntheses of higher tetraphenyl cumulenes show that in compounds with the same number of double bonds the light absorption is shifted more strongly toward longer wave lengths by cumulenes than by conjugated double bonds.

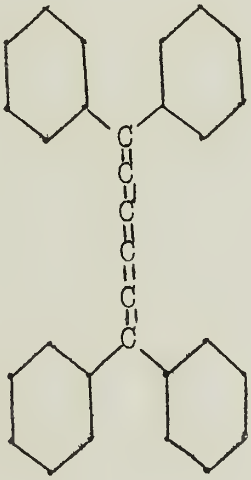
Diacetylene and ethyl magnesium bromide react readily with the formation of diacetylene dimagnesium bromide. Straus, Kollek, and Hauptmann have used it in preparing diacetylene glycols of acetaldehyde, acetone, and acetophenone. Kuhn and Wallenfels obtained compound V from acetophenone and diacetylene dimagnesium bromide in good yields. Upon treatment with P_2I_4, the scarlet red hydrocarbon, VII, is formed. In absorption spectra and in all its chemical properties, it behaves like an analog of tetraphenylbutatrien.



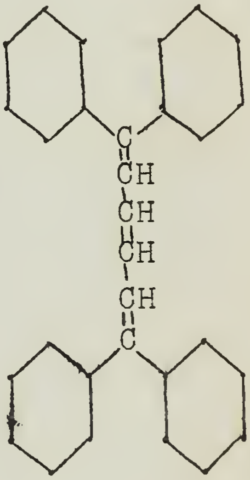
V



VI

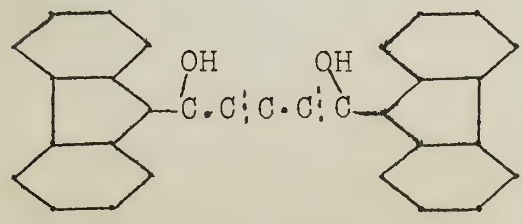


VII

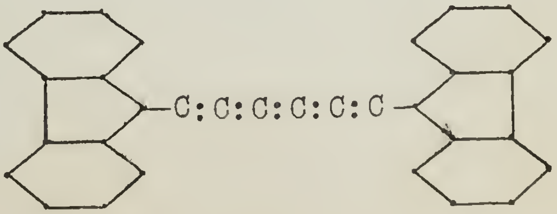


VIII

From fluorenon and diacetylene magnesium bromide, Kuhn also prepared 1,6-dibiphenylenehexadien-(2,4)-diol-(1,6), IX, and on decomposition with P_2I_4. X was produced.



IX



X

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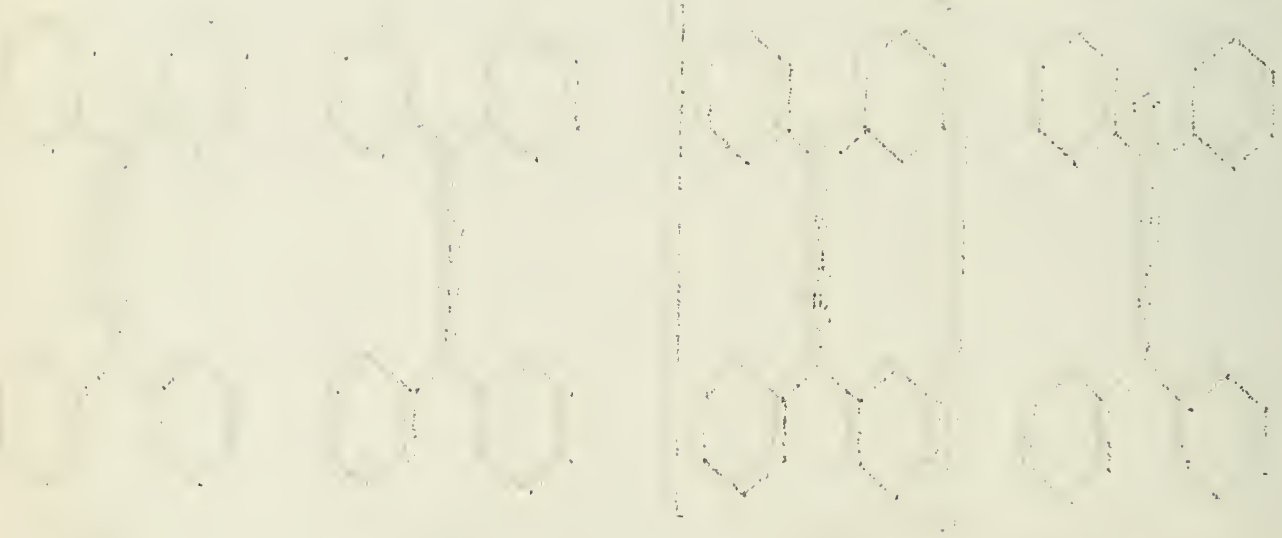
[illegible]



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These compounds are very stable toward molecular oxygen and toward $KMnO_4$, indifferent to maleic anhydride and $C(NO_2)_4$, but very sensitive to nascent and catalytic hydrogen, O_3, Br_2, and I_2. During catalytic hydrogenation of these compounds, a striking fluorescence is observed while none is detectable at the beginning and the end. Kuhn gives this as evidence of the intermediate formation of polyenes.

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Reported by L. N. Whitehill
May 18, 1938.

SEMIQUINONES

Leonor Michaelis -- Rockefeller Institute

The oxidation-reduction systems of quinoid-benzenoid forms, although involving two electrons, may occur stepwise, one electron at a time. One-electron systems are not very common in organic compounds occurring chiefly in tervalent carbon and divalent nitrogen compounds. Univalent oxidation of a benzenoid form gives a radical with a structure between a quinoid and a benzenoid form.

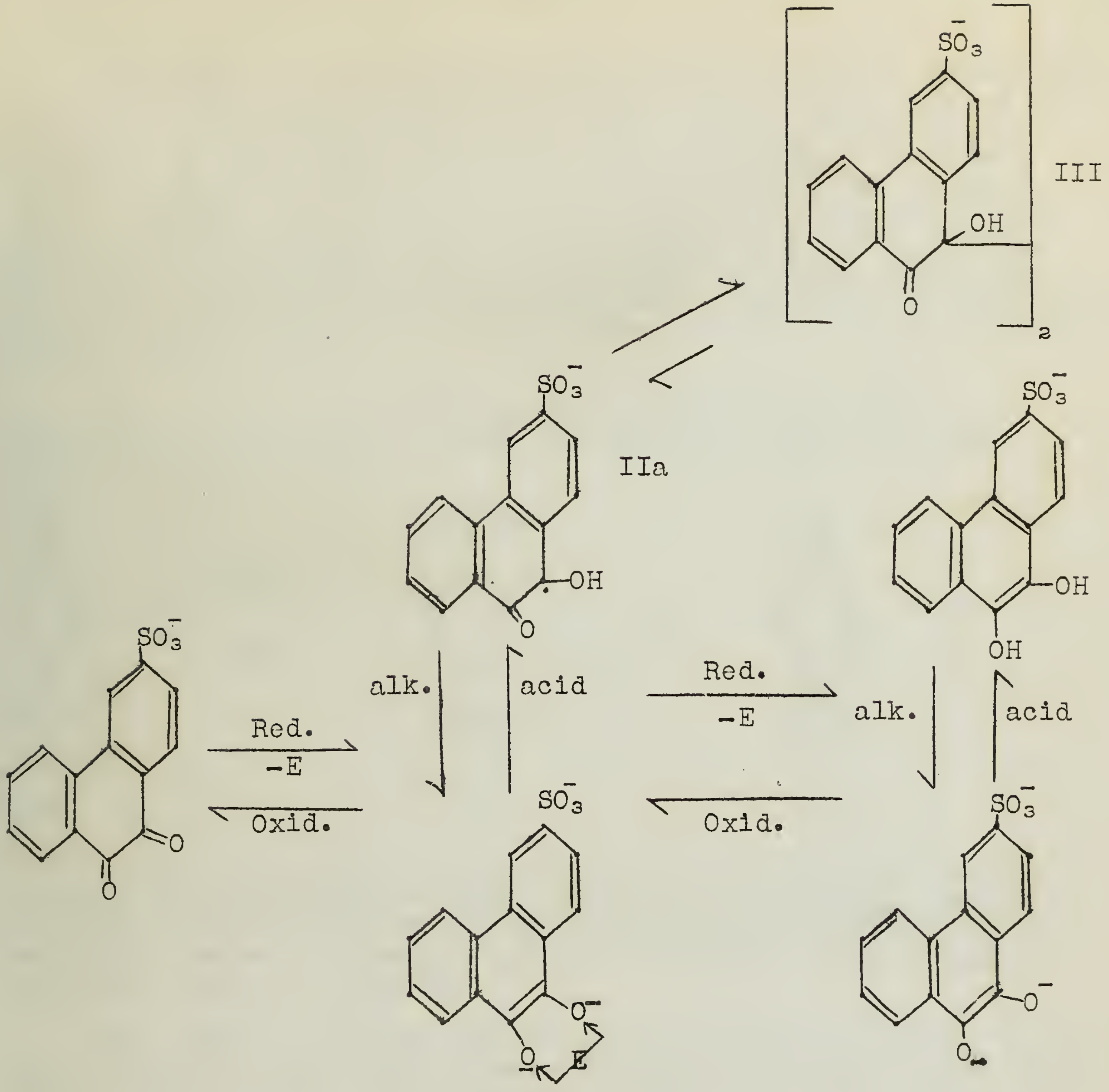
Quinhydrone is believedto be such a compound. The prevalent idea of the structure of quinhydrone considers it as a molecular compound of a hydroquinone and a quinone molecule. Willstätter proposed that an oscillation of bonds occurs between the reduced and oxidized halves, which are held together by secondary valence forces, so that the reduced and oxidized halves alternate.

Hantzsch on the basis of absorption spectra, and Weitz using boiling point data, were the first to suggest a monomeric formula for partially reduced quinoid types.

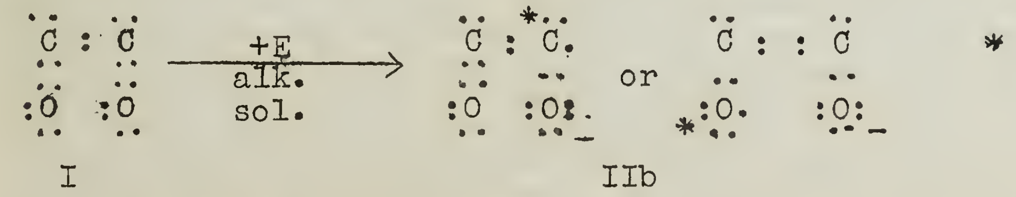
Since molecular weight determinations are almost impossible with most of these compounds, Michaelis and other workers used a potentiometric method of study. From these studies it was ascertained whether an oxidation involving two steps gave the semiquinoid intermediate, or if the intermediate involved was the dimeric quinoid (meriquinoid) form. The formation constants under different conditions could also be determined. Since these substances are acids or bases, the amount of semiquinoid depends on the pH of the solution.

The occurrence of the semiquinoid depends, firstly, on the thermodynamic factor, that is, its formation constant, which in turn depends on pH. Also the semiquinoid may be insoluble, hence, existsonly in the solid state. Secondly, being an unsaturated radical the stability may be small due to irreversible secondary rearrangements.

The simplest anionic semiquinone is quinhydrone. However, in alkaline solution where the semiquinone is possible, the irreversible dismutation into quinone and hydroquinone occurs. Michaelis found that the semiquinone of phenanthrenequinone-3-sulfonate was of sufficient stability for studies in various ranges of pH.

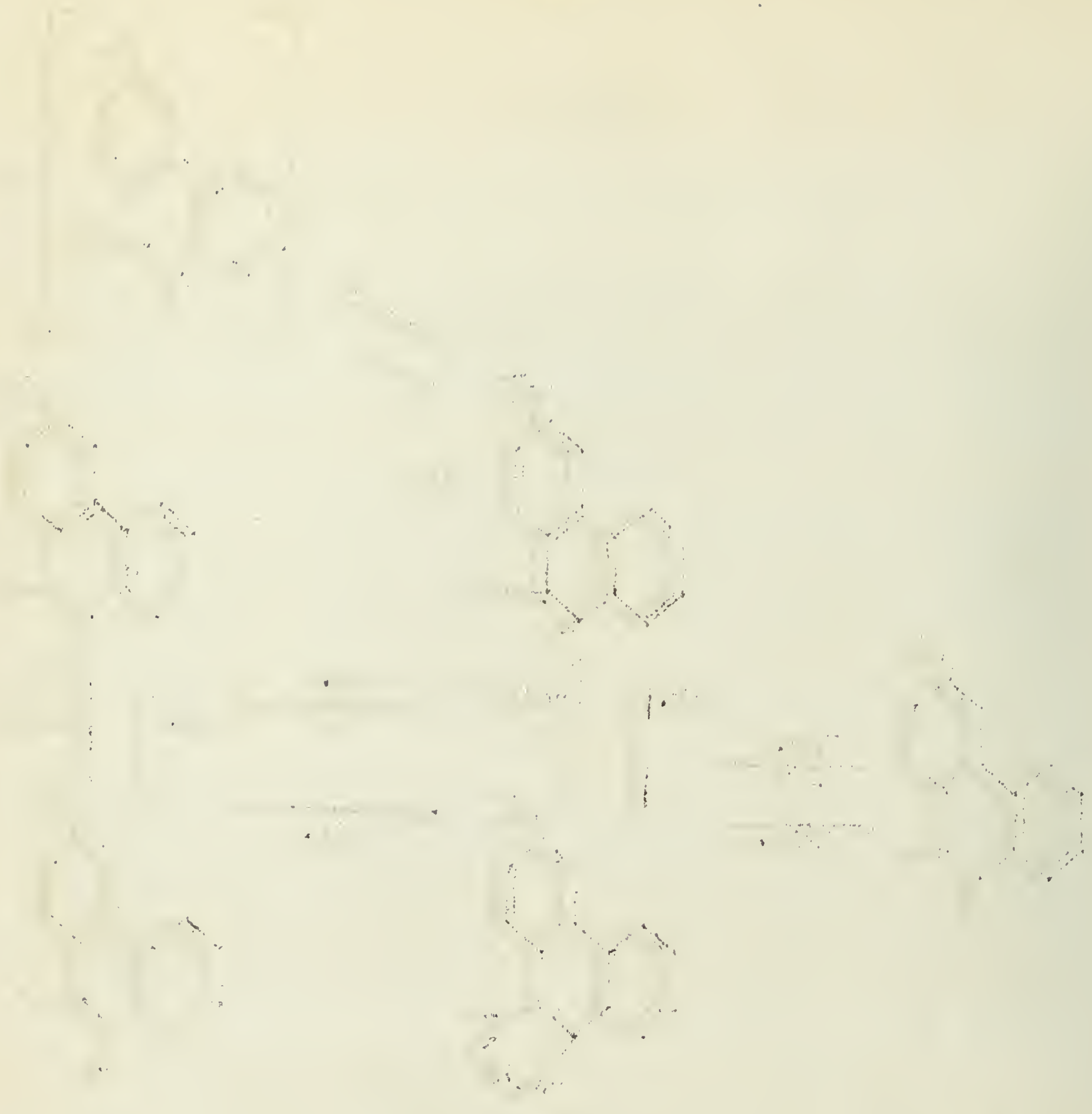


Whereas IIa is represented as a quinoid structure with the odd electron on the carbon, it could just as readily be shown in the IIb benzenoid form with the odd electron on an oxygen. Similarly IIb may resonate to the IIa type of structure. The change to semiquinone can be represented electronically as follows:



* Indicates atom with an odd electron.

The octet of electrons can be on either oxygen as can be the charge. The odd electron resonates between the carbon and oxygen atoms. Actually IIb has only one negative charge, with the electron resonating between the oxygens.



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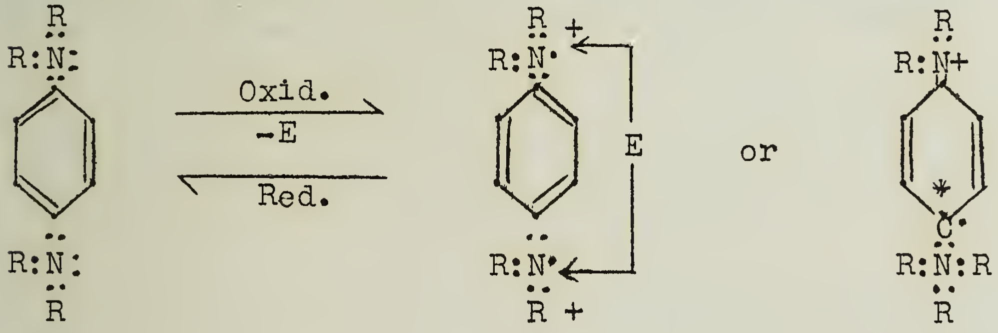
Reduction of I in alkaline solution gives IIb, a symmetrical structure with many resonance forms and hence stable. Since it is ionic, electrostatic repulsion helps prevent dimerization. This results in little dimer and a high concentration of free radical. In acid solution the less symmetrical (IIa) forms. Free exchange of the electron is more difficult because of the proton, and the molecule has less resonance. In acid solution the dimeric meriquinone, III, is the chief product. These are all labile equilibria, and all forms may be present, the quantities depending on the substance, conditions, and resonance or stability of the radical formed.

The cationic semiquinones have a similar structure illustrated by the one-electron oxidation of substituted p-phenylenediamines (IV).

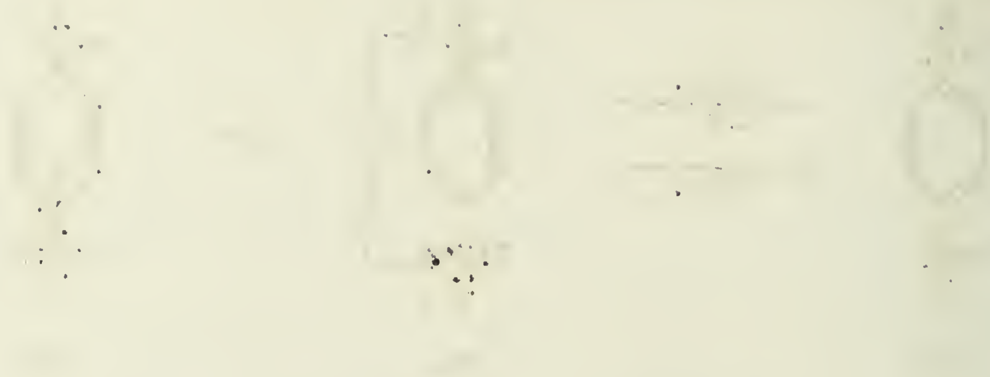


IV Va Vb

In this case the resonance forms Va and Vb having the odd electron on a nitrogen or carbon atom and the charged nitrogen can exist. The stability increases with increasing acidity, probably because in alkaline solution formation of an uncharged quaternary base is favored.

This type of charged radical differs from the neutral triaryl methyl type in being quite stable in aqueous solution under proper pH conditions, and, except under special conditions, have little tendency to dimerize. They have not been observed to abolish their unsaturation by reacting with substances like oxygen, nitric oxide or any of the usual triaryl methyl reagents.

The odd electron oscillating between carbons and oxygens or nitrogens should and does give semiquinones, distinctive colors and absorption bonds. It should also make the molecule paramagnetic. This would be evidenced by a lowering of the diamagnetism of the solvent. Recently, Michaelis carried out such determinations on the semiquinone of phenanthrenequinone-3-sulfonate, I, and qualitatively substantiated the potentiometric data. In acid reductions little paramagnetism was evidenced indicating the dimeric meriquinohe, III. In alkaline reductions an appreciable paramagnetism was found, indicating the semiquinone, IIb, was predominant. Katz found the solid quinhydrone of pyocyanine (a cationic semiquinone) to be paramagnetic in the solid state.



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Reported by E. Ginsberg
May 18, 1938.

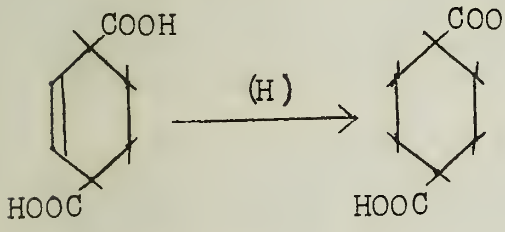
GEOMETRICAL ISOMERISM OF HEXAHYDROTEREPHTHALIC ACID DERIVATIVES

Malachowski -- Univ. of Lwow (Lemberg, Poland)
Mills -- Cambridge

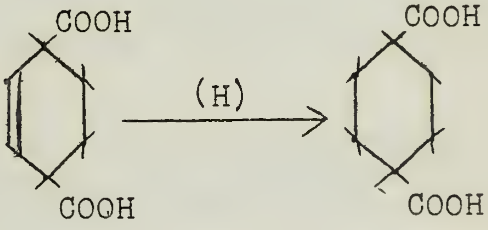
The two isomeric hexahydroterephthalic acids first prepared by Baeyer, and designated as cis and trans on the basis of melting points and solubilities, have been definitely identified and the original nomenclature confirmed by two independent investigations.

Malachowski prepared linear polymeric anhydrides from both the cis and trans acids using acetic anhydride. Decomposition of both these polymers by heating in vacuo gave the same unimolecular inner anhydride, which upon hydrolysis gave only the cis acid as expected. Apparently the trans polymer was converted to the cis anhydride under these conditions.

Mills based his investigation upon resolution of the Δ^2-tetrahydroterephthalic acids, followed by catalytic hydrogenation, again verifying the original nomenclature.



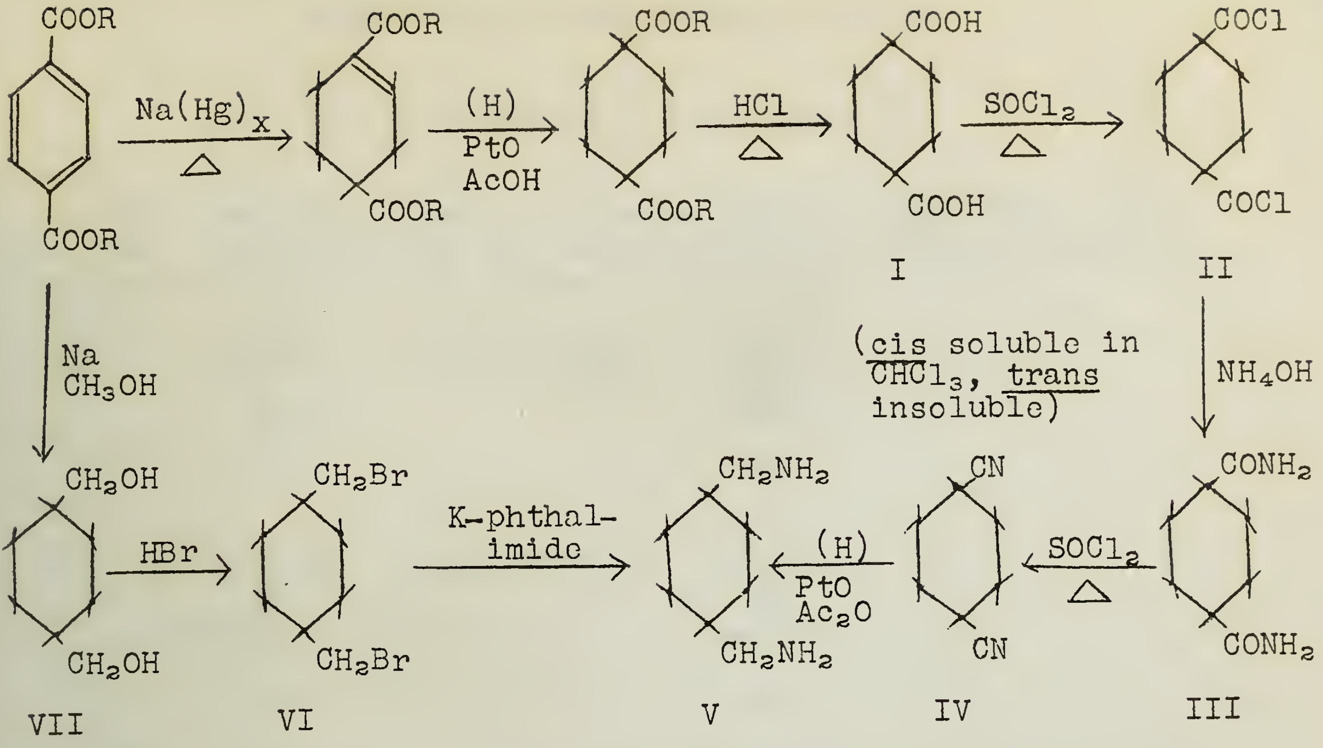
Resolvable (Racemic) — trans



Non-resolvable (Meso) — cis

In an attempt to find indications of isomerism of the cyclohexane ring itself, Malachowski prepared various derivatives of hexahydroterephthalic acid. However, in no case was any isomerism noted other than that due to the cis-trans relation of the substituent groups. Thus, proof of the existence of boat and chair forms of the cyclohexane ring is still lacking.

The following series of preparations was successfully carried out for both the cis and trans derivatives:

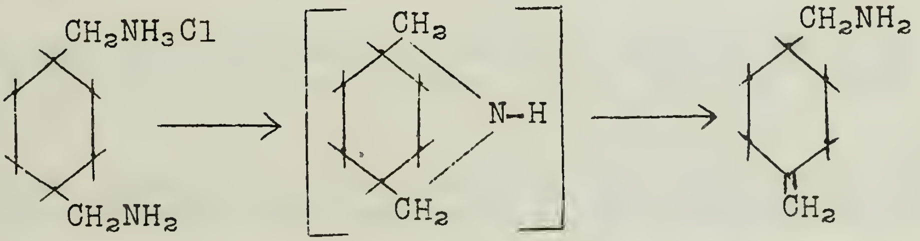


(*cis* soluble in $CHCl_3$, *trans* insoluble)

(Benzoylate,
cis soluble in
ethanol and ether,
trans insoluble)

In every case the *trans* isomer was higher melting and less soluble than the *cis*, in conformity to the general rule for such isomers. There are some exceptions however, notably in the case of isophthalic acid derivatives.

The two geometric isomers of I and III were convertible to equilibrium mixtures by heating. Heating the hydrochloride of the *cis* diamine (V) in an attempt to obtain ring closure to an imine gave instead an unsaturated monoamine.



Measurement of dissociation constants showed that the *trans* acid is slightly stronger than the *cis*.

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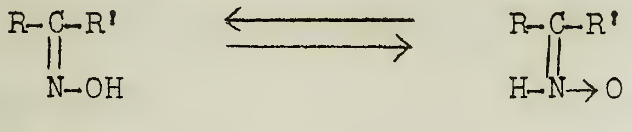
Reported by Hugh Gray
May 25, 1938.

ISOMERISM OF PHENACYLAMINE-OXIMES

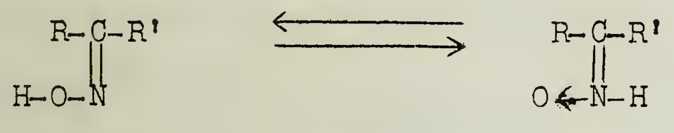
Busch -- University of Erlangen

Ketoximes are known to exist in syn and anti forms (Ia and IIa). There is also the possibility that these forms may tautomerize into the structures Ib and IIb.



$$\underset{\text{N-OH}}{\overset{\text{R-C-R'}}{\|}} \rightleftarrows \underset{\text{H-N}\rightarrow\text{O}}{\overset{\text{R-C-R'}}{\|}}$$

Ia Ib

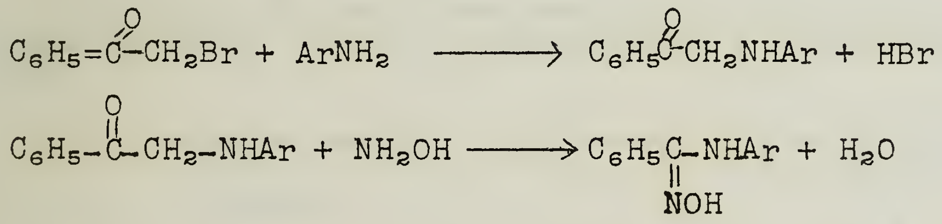


$$\underset{\text{H-O-N}}{\overset{\text{R-C-R'}}{\|}} \rightleftarrows \underset{\text{O}\leftarrow\text{N-H}}{\overset{\text{R-C-R'}}{\|}}$$

IIa IIb

The chief evidence for such a tautomerization is the fact that both oxygen and nitrogen alkyl derivatives may be produced by alkylation.

The present study is concerned with the oxines of phenacylamines whose reactions have been found to offer additional evidence for tautomerization. These oximes were synthesized by the following reactions:

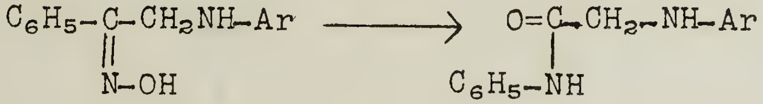


$$C_6H_5{=}\overset{O}{\overset{\|}{C}}{-}CH_2Br + ArNH_2 \longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}{-}CH_2NHAr + HBr$$

$$C_6H_5{-}\overset{O}{\overset{\|}{C}}{-}CH_2{-}NHAr + NH_2OH \longrightarrow C_6H_5\underset{NOH}{\underset{\|}{C}}{-}NHAr + H_2O$$

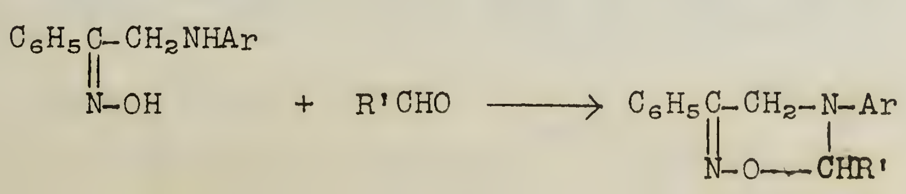
In most cases two forms were obtained. The low melting form may be denoted as the α-oxime and the higher melting isomer as the β-oxime.

The α-oxime generally corresponds to the syn-methyl form. They undergo the Beckmann rearrangement to give arylaminoacetanilides.



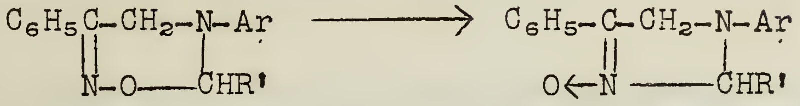
$$C_6H_5{-}\underset{N-OH}{\underset{\|}{C}}{-}CH_2NH{-}Ar \longrightarrow O{=}\underset{C_6H_5-NH}{\underset{|}{C}}{-}CH_2{-}NH{-}Ar$$

They condense with aldehydes to give oxadiazines:

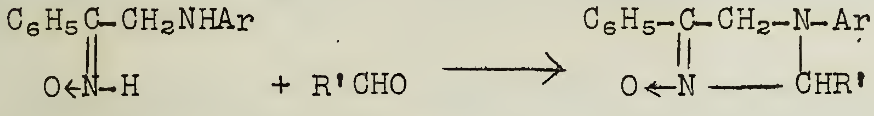


$$C_6H_5\underset{N-OH}{\underset{\|}{C}}{-}CH_2NHAr + R'CHO \longrightarrow C_6H_5\underset{N-O}{\underset{\|}{C}}{-}CH_2{-}\underset{CHR'}{\underset{|}{N}}{-}Ar$$

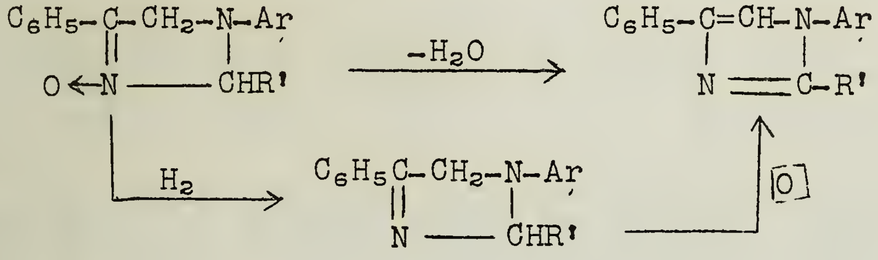
Treatment of the oxadiazines with glacial acetic acid causes rearrangement into oxoimidazoles:



The β-oximes do not undergo the Beckmann rearrangement. They condense with aldehydes to give oxoimidazoles:

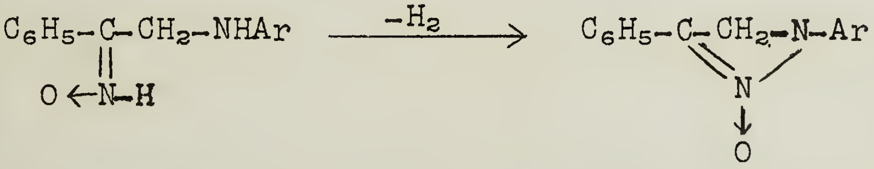


The latter undergo the following changes:

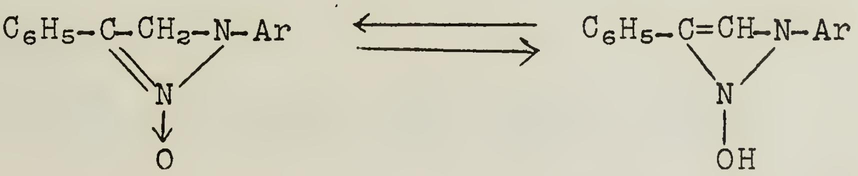


The β-oximes give a red color with ferric chloride in alcohol solution. Complex salts are also formed with cobalt and nickel salts.

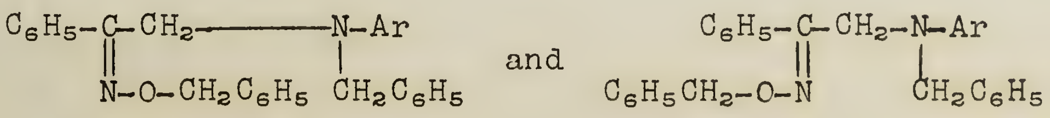
Oxidation of the oximes results in the loss of two hydrogens to give a cyclic molecule designated as a dehydro-phenacylamine-oxime:



Treatment of the β-oxime with PCl_5 gives a product identical with the dehydro compound. Methane is produced by the Zerewitinoff test indicating that under the influence of CH_3MgI a partial enolization takes place:



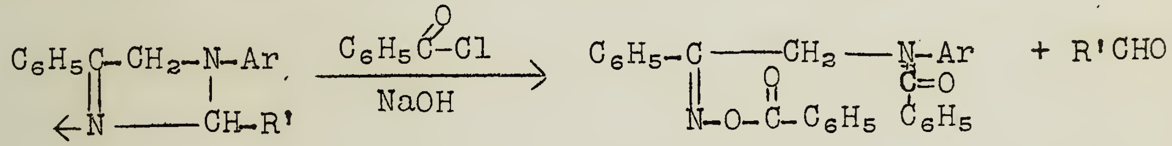
Benzyl chloride reacts with the alkali salt of the isomeric oximes to give two isomeric dibenzyl derivatives:



Benzyl chloride reacts with the isomeric oximes in the absence of alkali to give monobenzyl derivatives in which the arylamine nitrogen is benzylated.

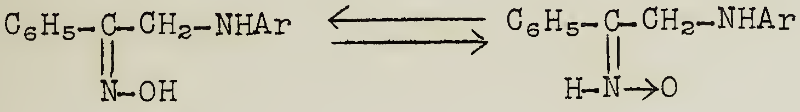
Application of the Schotten-Baumann reaction to the two isomeric oximes yields the same dibenzoyl derivative. One mole of benzoyl chloride in the presence of pyridine produces the monobenzoyl derivative in which the arylamine nitrogen is benzoylated--the latter is also produced by saponifying the dibenzoyl derivative with alkali.

Benzoylation of the oxadiazine or the oxoimidazole produces the dibenzoyl derivative. Thus it was shown that benzoylation produces a rearrangement from the anti into the syn forms:



The authors conclude that the α-oxime reacts as a normal oxime while the β-oxime reacts as an amine oxide or "isoxime" which on benzoylation is transposed into the normal form. It appears that the isomers exist in solution in the following tautomeric equilibria:

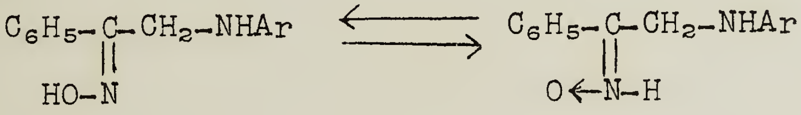
α-oxime



$$C_6H_5-\underset{\underset{N-OH}{\|}}{C}-CH_2-NHAr \rightleftarrows C_6H_5-\underset{\underset{H-N\rightarrow O}{\|}}{C}-CH_2-NHAr$$

Ia Ib

β-oxime



$$C_6H_5-\underset{\underset{HO-N}{\|}}{C}-CH_2-NHAr \rightleftarrows C_6H_5-\underset{\underset{O\leftarrow N-H}{\|}}{C}-CH_2-NHAr$$

IIa IIb

Bibliography:

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Reported by R. L. Hicks
May 25, 1938.