SEMINAR REPORTS

I Semester 1944-45

THE CHEMISTRY OF COLCHICINE

Colchicine (XV) is an alkaloid occurring to the extent of 0.5-0.9 per cent in the autumn crocus (Colchicum autumnale) and also in some other plants. Although it has long been used as a drug for the treatment of gout, its greatest interest lies in the fact that it has the ability to arrest cell division and to cause bizarre mitotic effects. Its property of increasing the number of chromosomes (polyploidy) in plants gives promise of considerable use in agriculture, since it can be used for producing new species and also to grow giant specimens of fruits, vegetables, and flowers.

The chemical history of colchicine can be divided into three periods: (1) the preliminary work of Zeisel and his coworkers, (2) the main structure proof by Windaus, and (3) recent research concerned with various fine points of structure.

(1) The Work of Zeisel and His Group (Vienna): Zeisel (7) was the first to purify crystalline colchicine sufficiently for careful analysis. He and his group established the following facts:

Colchicine ($C_{22}H_{25}NO_6$) has four methoxyl groups, one readily hydrolyzed by alkali or dilute acid, all removable by hydriodic acid.

Colchicine has one acetyl group attached to a primary amino group (proof by hydrolysis and reacetylation experiments; amino group shown to be primary by exhaustive methylation).

Colchicine has one methylene group readily oxidized to a carbonyl group.

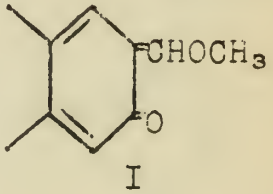
These facts allow the following conclusion:

$$(CH_3O)_3(C_{16}H_9O)(OCH_3)(NHCOCH_3);\ C_{22}H_{25}O_6N$$

Zeisel concluded further that the molecule contained a carbomethoxyl group, but Windaus later showed that this was not the case.

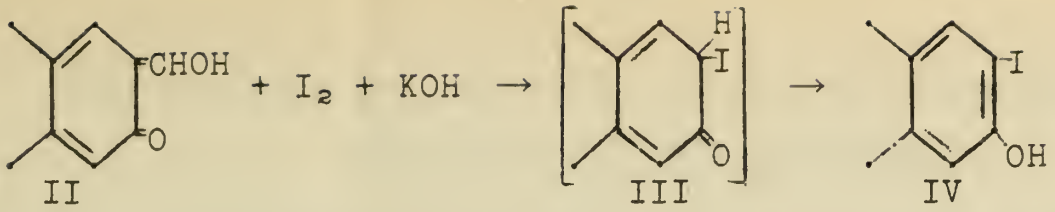
(2) The Work of Windaus (Göttingen)(9):

a. Windaus postulated the presence of the grouping



I

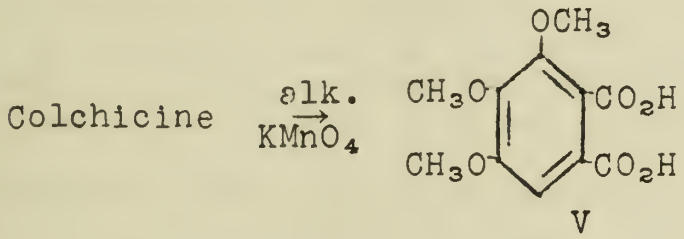
Evidence: Easy hydrolysis of one methoxyl group in colchicine. The product (colchicein) gives a positive ferric chloride test. Colchicein reacts with iodine and potassium hydroxide to give a compound (N-acetyliodocolchinol) in which an iodine atom has replaced (CHO):



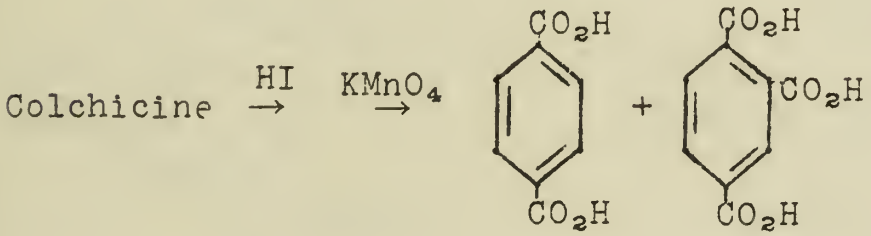
II III IV

This reaction parallels the formation of α-iodo-β-naphthol from α-aldehydo-β-naphthol. Colchicein (colchicine with one methoxyl hydrolyzed) was thought to have the structure of the vinyl alcohol (II) rather than an aldehydo phenol because it gave no aldehyde test (hydroxylamine). It does have many of the color reactions of ortho-hydroxy aldehydes, however.

b. Oxidative and Other Degradations of Colchicine:



V



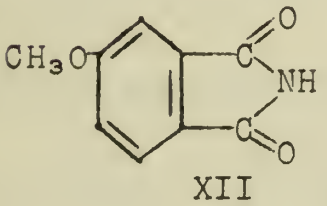
VI VII

Colchicein $\xrightarrow[KOH]{I_2}$ N-Acetyliodo colchinol (VIII) ($C_{14}H_{19}O_4N$)(C_6H_4(I)(OH)) → Methyl ether

Methyl ether $\xrightarrow{KMnO_4}$ Iodomethoxyphthalic Acid (IX)

Iodomethoxyphthalic Acid (IX) $\xrightarrow[(-I)]{Zn}$ N-Acetylcolchinol methyl ether (XI)

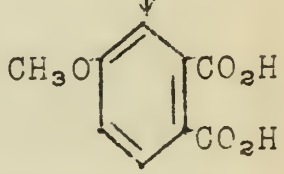
Iodomethoxyphthalic Acid (IX) $\xrightarrow[HOAc]{Zn}$ X



XII

N-Acetylcolchinol methyl ether (XI) $\xleftarrow[H_2SO_4]{CrO_3}$ XII

N-Acetylcolchinol methyl ether (XI) $\xrightarrow[CH_3OH]{HCl}$ Colchinol methyl ether XIII ($-COCH_3$)



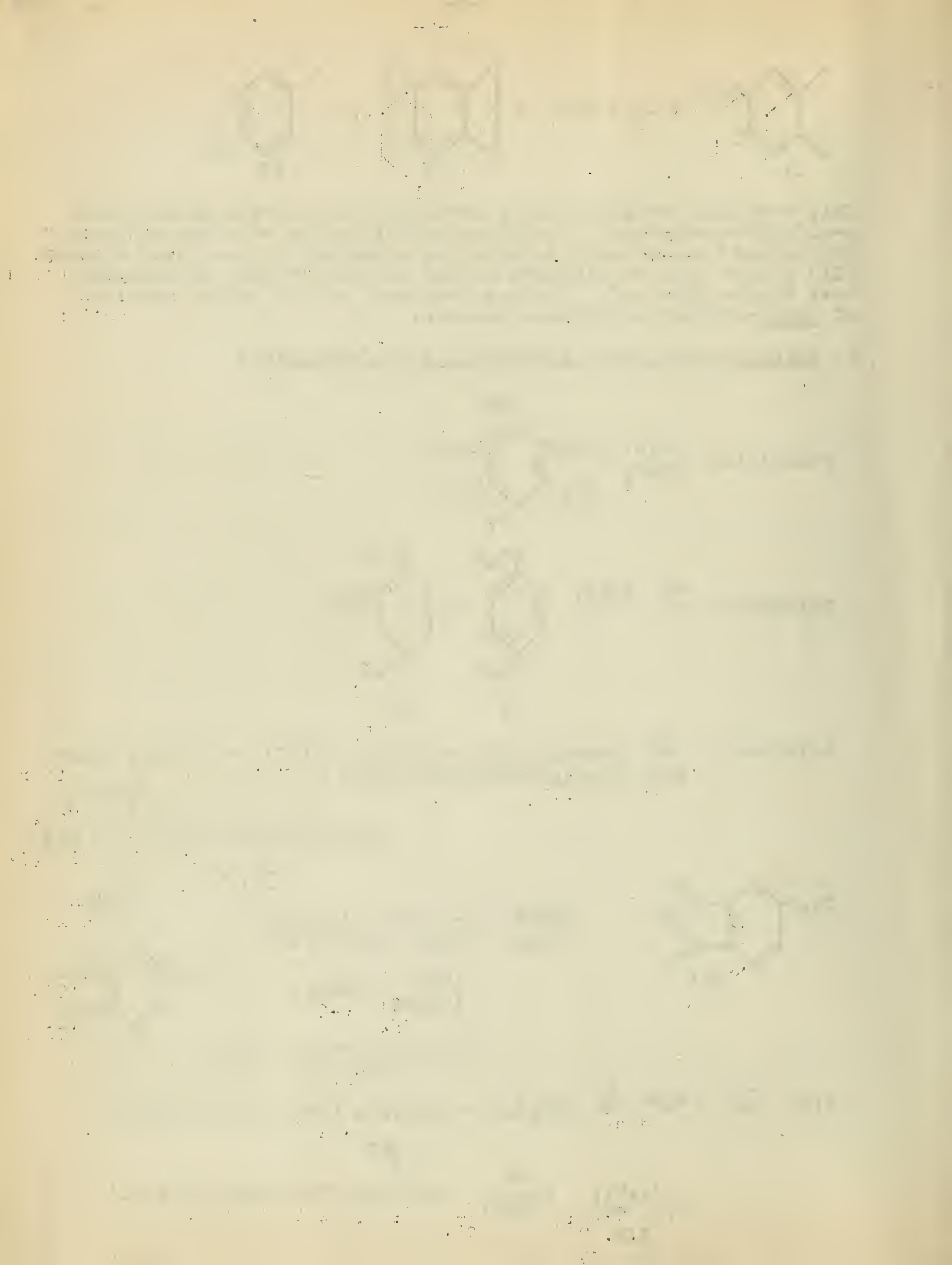
X

XIII $\xrightarrow{CH_3I}$ $\xrightarrow{Ag_2O}$ $\triangle$ $(CH_3)_3N$ + $C_{19}H_{20}O_4$ (Tetramethoxy cpd.)

$C_{19}H_{20}O_4$ (Tetramethoxy cpd.) $\xrightarrow{HI}$ $C_{15}H_{12}O_4$ (Tetrahydroxy cpd.)

$C_{15}H_{12}O_4$ (Tetrahydroxy cpd.) $\xleftarrow[dist.]{Zn}$ $C_{15}H_{12}$ m.p. 88°

XIV



This evidence indicates three different six-membered rings:

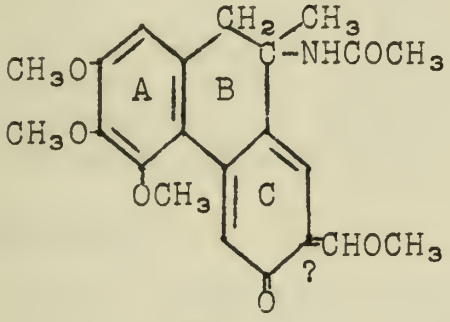
$$(CH_3O)_3(C_{15}H_9)(OCH_3)(NHCOCH_3)$$

The $-C_{15}H_9-$ carbon-hydrogen ratio further indicates that all the rings must have common carbon atoms. A methylphenanthrene or methylanthracene appeared to Windaus to be the most likely structure for the $C_{15}H_{12}$ derivative melting at 88° (XIV). All the possible isomeric methylanthracenes and methylphenanthrenes were known except 4- and 9-methylphenanthrenes. 9-Methylphenanthrene was synthesized and found to be identical with XIV (10,11).

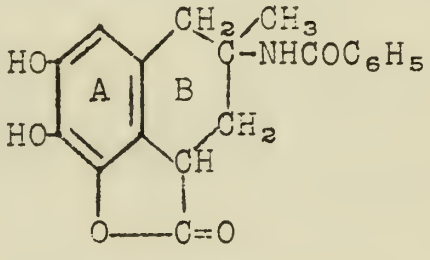
c. Structure of colchicine and its derivatives:

1. Colchicine is a dihydro derivative of 9-methylphenanthrene.
2. The dihydro ring is the center one and contains a methylene group. It also has one N-acetylamino group.
3. One other benzene ring carries three vicinal methoxyl groups.

A structure (XV) was then written as follows:



XV



XVI

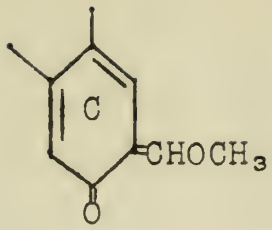
The positions of the three vicinal methoxyls of Ring A were proven to be 2,3, and 4, as shown, by an ingenious degradation to a lactone (XVI) which linked the peri positions of Rings A and B.

The positions of the groups on Ring C were left in doubt by Windaus.

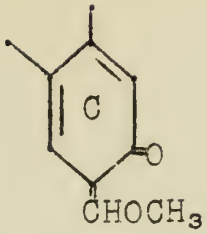
(3) Recent Investigations:

Bursian (Göttingen)(12) has studied the hydrogenation of colchicine, showing that a hexahydro derivative forms readily, but the double bond between Rings B and C is resistant to hydrogenation.

Grewe (Göttingen)(13) has synthesized 3-iodo-4-methoxyphthalic acid and 5-iodo-4-methoxyphthalic acid and found that the latter is identical with Compound IX obtained in the degradative studies of Windaus. This narrows the possibilities for Ring C to either XVII or XVIII:



XVII



XVIII

Cook and his coworkers (London)(14,15) have also carried out recent investigations on colchicine and throw some doubt on the structure of Ring B. Their experiments have not yet pointed to an improved structure, however.

BIBLIOGRAPHY

Occurrence and Isolation:

1. Pelletier and Caventou, Ann. Chim. Phys., 14 (2), 82 (1820).
2. Geiger, Ann., 7, 274 (1833).
3. Zeisel, Monatsh., 7, 557 (1886).
4. Clewer, Green, and Tutin, J. Chem. Soc., 107, 835 (1915).
5. Chemnitius, J. prakt. Chem., 118, 29 (1928).
6. Niemann, Pharm. Acta Helv., 8, 92 (1933); C. A., 27, 5893 (1933).

Chemistry:

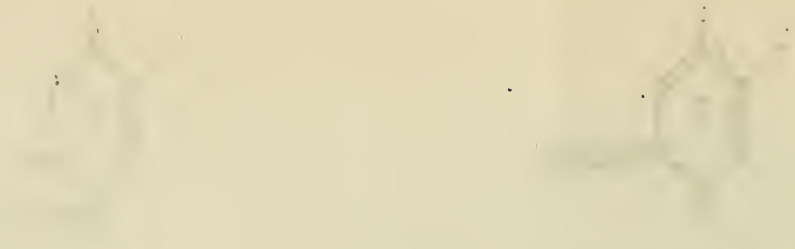
7. Zeisel, Monatsh., 4, 162 (1883); 7, 557 (1886); 9, 1 (1888); Johanny and Zeisel, ibid., 9, 865 (1888); Zeisel and v. Stockert, ibid., 34, 1181, 1327, 1339 (1913).
8. Windaus, Heidelberg Akad. Wiss., 1910, 1; 1911, I, 1637; (18) 1914; C. A., 4, 2665 (1910); 5, 3417, 3418 (1911); 9, 1481 (1915).
9. Windaus, Ann., 439, 59 (1924).
10. Windaus and Eickel, Ber., 57, 1871 (1924).
11. Windaus, Jensen, and Schramme, ibid., 57, 1875 (1924).
12. Bursian, ibid., 71, 245 (1938).
13. Grewe, ibid., 71, 907 (1938).
14. Cohen, Cook, and Roe, J. Chem. Soc., 1940, 194.
15. Cook and Engel, ibid., 1940, 198.

Physiological Action:

16. For discussion and leading references see Goodman and Gilman, "The Pharmacological Basis of Therapeutics," Macmillan, New York, 1941, pp. 239-241.

17. Freud, Laqueur, and Mühlbock, Ann. Rev. Biochem., VIII, 313 (1939).
18. Dermen, Botan. Rev., 6, 599 (1940).
19. Taylor, Readers' Digest, May, 1940, p. 69.

Reported by R. L. Frank
October 18, 1944

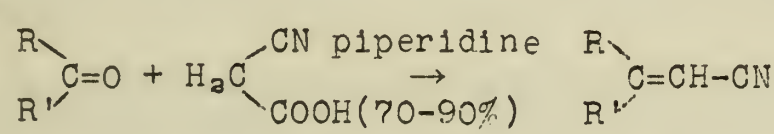


PREPARATION OF α,β-UNSATURATED NITRILES

For a review of the reactions of α,β-unsaturated nitriles, and especially acrylonitrile, the reader is referred to the seminar abstract of Dr. Mahan (1). The individual papers of Bruson of Röhm and Haas and his American Chemical Society address before the Illinois Section provide further details of interesting cyanoethylation reactions with acrylonitrile. Since analogous reactions can be carried out with other α,β-unsaturated nitriles, it becomes of interest to review general methods of preparing such nitriles. The present review is not intended to be exhaustive but rather to be a limited survey of some of the less well known methods of preparation of these α,β-unsaturated nitriles.

Catalytic methods of preparation of acrylonitrile to be found in the patent literature (2) include dehydration of cyanhydrin over activated alumina, removal of acid from a cyanoalkyl ester over hot metals, and dehydrohalogenation of α-halonitriles over $FeCl_3$ or TiO_2. Dehydration of cyanhydrins can be carried out on a laboratory scale to produce α,β-unsaturated nitriles, as can dehydrohalogenation of α-alkyl-β-chloronitriles, in 80-90% yield, by heating with pyridine (3). In cases where mixtures of cis and trans isomers are obtained, these can be separated by repeated fractional distillation. The cis isomer has the lower boiling point and less pronounced ultraviolet absorption bands than the trans variety (4).

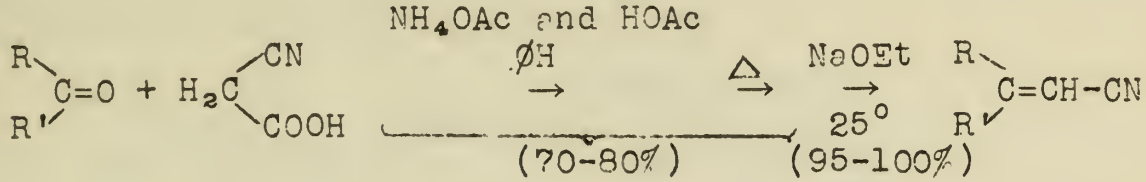
A. Preparation of α,β-unsaturated nitriles by the Knoevenagel type condensation.--Trakhtenberg and Shemyakin (5) have recently improved the Knoevenagel approach to substituted acrylonitriles by refluxing ketones with cyanoacetic acid in piperidine for two to four hours:



Pyre cyanoacetic acid was obtained by hydrolysis of ethyl cyanoacetate with dilute nitric acid, based on an earlier method of Phelps and Tillotson (6). Practical cyanoacetic acid is commercially available and can, of course, be prepared from chloroacetic acid (7). The Russian workers reported that no intermediate cyanoacid appears in the product of the condensation of ketones with cyanoacetic acid in piperidine (8). With aliphatic ketones, the α,β-unsaturated nitrile is produced predominantly, and α-hydrindone likewise gives the α,β-unsaturated nitrile, since the product does not take up bromine. Acetophenone and benzophenone did not react.

Whyte and Cope (9) carried out condensations of cyclohexanone and diethyl ketone with ammonium acetate in benzene and acetic acid. Water formed during the condensation was removed continuously. The alkylidene cyanoacetic acids were not isolated, but were decarboxylated directly by heating the reaction mixture following removal of the solvent. The β,γ-unsaturated nitriles obtained by heating at 140° and 50-60 mm. for 2-3 hrs. were 1-cyclohexenylacetonitrile (79% overall yield) and 3-ethyl-3-pentene-

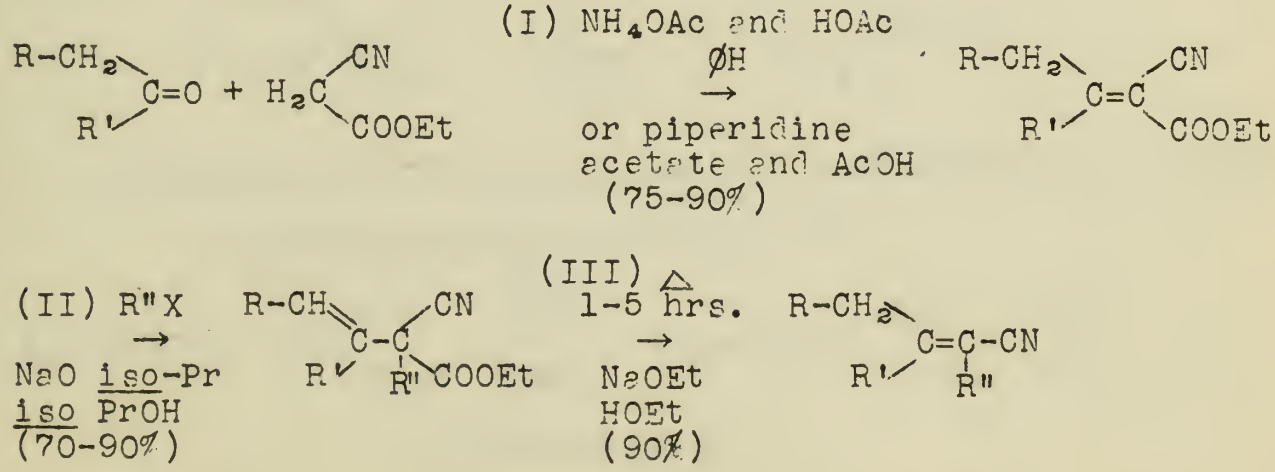
nitrile (72%), respectively. The pyrogenic decomposition of α,β-unsaturated cyanoacids to produce unsaturated (mainly β,γ) nitriles is based upon earlier work of Birch and Kon (10) and Bruylants (11). Although the β,γ-unsaturated nitrile predominates as a product, 95-100% equilibration to the α,β-unsaturated nitrile is possible by treatment with sodium ethoxide at room temperature (12). The steps in this method of synthesis are outlined below:



It should be noted that any method for the preparation of a β,γ-unsaturated nitrile (possessing at least one hydrogen on the α-C atom) is a potential method of obtaining an α,β-unsaturated nitrile by the equilibration reaction.

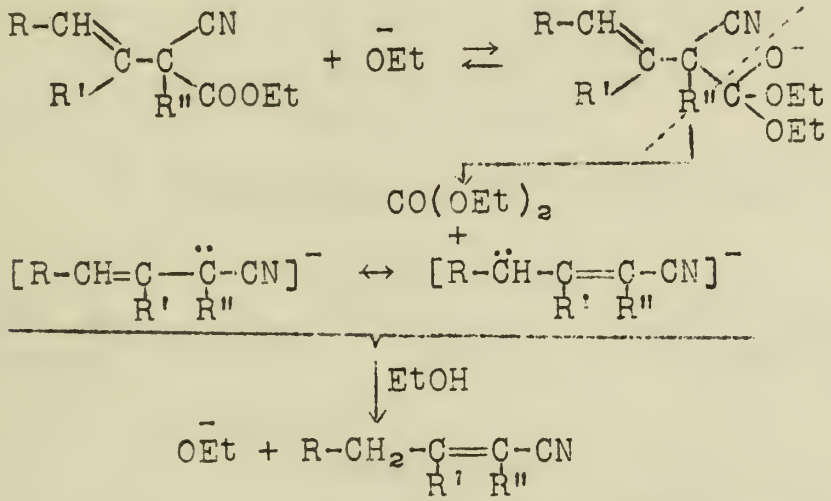
Of the two types of unsaturated nitriles, the α,β- has an exaltation in the molecular refraction and usually has a higher boiling point. Chemical methods of distinguishing between the two include (a) oxidation and identifaction of the products, (b) titration with iodine and mercuric chloride in ethanol (α,β does not take up iodine appreciably) (12), (c) titration with bromine (α,β does not react) (11), and (d) a modified Radziszewski reaction. Murray and Cloke (13) have shown that, in general, α,β-unsaturated nitriles give substituted glycidamides with hydrogen peroxide and sodium carbonate in acetone (nearly quantitative yields) whereas β,γ-unsaturated nitriles form the unsaturated amide. Analysis of the product would of course indicate the presence of the extra oxygen where the glycidamide is formed.

B. Preperation of α,β-unsaturated nitriles through alkylidene cyanoacetic esters.--The reactions involved in the preparation of certain substituted α,β-unsaturated nitriles is indicated in the following scheme (13,14,15,16,17):

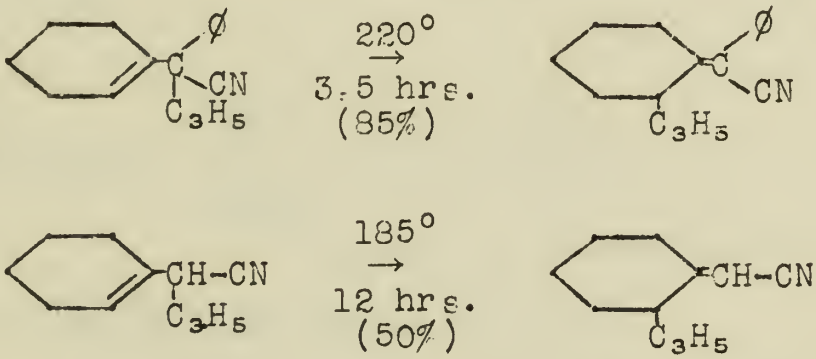


In reaction I, ammonium acetate, acetic acid and benzene are used for the condensation of ketones; piperidine acetate and acetic

acid, for aldehydes. Acetamide in acetic acid is also an effective catalyst for ketone condensations. The water formed during the condensation is removed continuously in every case. In reaction II, alkyl halides or sulfates with sodium isopropoxide in isopropyl alcohol give the highest yields in the alkylation which involves an α,γ-shift. In reaction III, cleavage of the (dialkylvinyl)-alkylcyanoacetic ester by refluxing with sodium ethoxide has produced 90% yields of α,β-unsaturated nitrile in every case tried. The mechanism suggested is as follows:

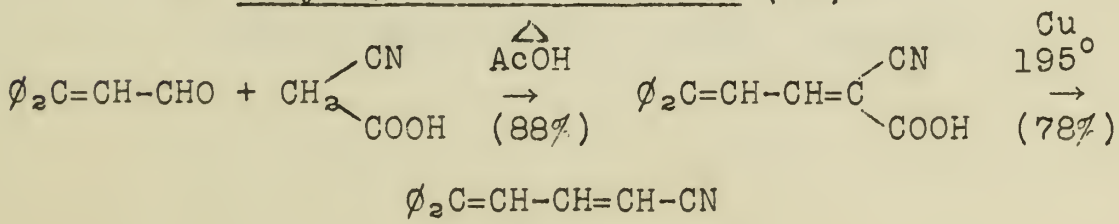


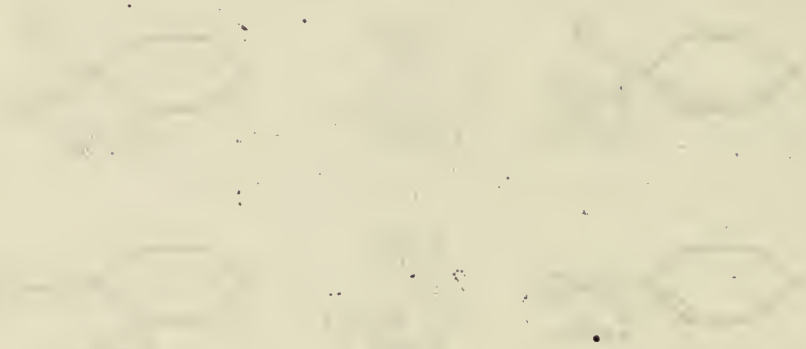
C. Preparation of α,β-unsaturated nitriles by allylic rearrangements.--Dr. Shepherd reviewed recently an example of allylic rearrangement which may be considered at the same time to be a means of preparing certain special α,β-unsaturated nitriles (18). Type reactions are outlined below (9):



D. Preparation of special types of α,β-unsaturated nitriles.

1. Polyunsaturated nitriles (19):



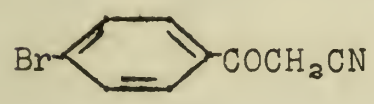


2. "β-Iminonitriles" (20):

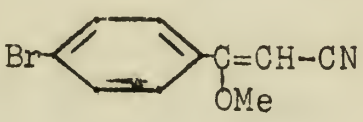
$$2RCH_2CN \xrightarrow[\text{Thorpe reaction (50\%)}]{\text{Na in ØH}} R\text{-}CH_2\text{-}C(=NH)\text{-}CH(R)\text{-}CN, \text{ actually } R\text{-}CH_2\text{-}C(=NH_2)\text{=}C(R)\text{-}CN$$

Hydrogenation evidence favors the β-amino-α,β-unsaturated nitrile structure for the product of this reaction. This enamine structure is also favored by evidence based on molar refraction and dispersion (21) and Raman spectra.

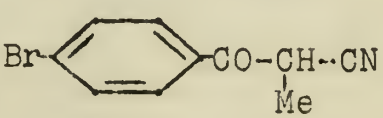
3. β-Methoxy-α,β-unsaturated nitriles (22,23):

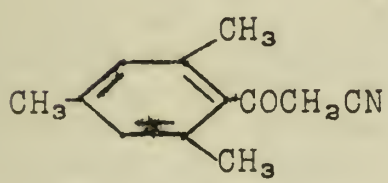


$Me_2SO_4 + KOH \xrightarrow{(30\%)}$

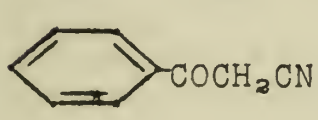


$NaOEt + MeI \rightarrow$

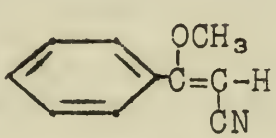




$NaOEt + MeI \rightarrow$ O-Me and C-Me derivs. in equal amounts



$CH_2N_2 \xrightarrow[\text{ether (100\%)}]{}$



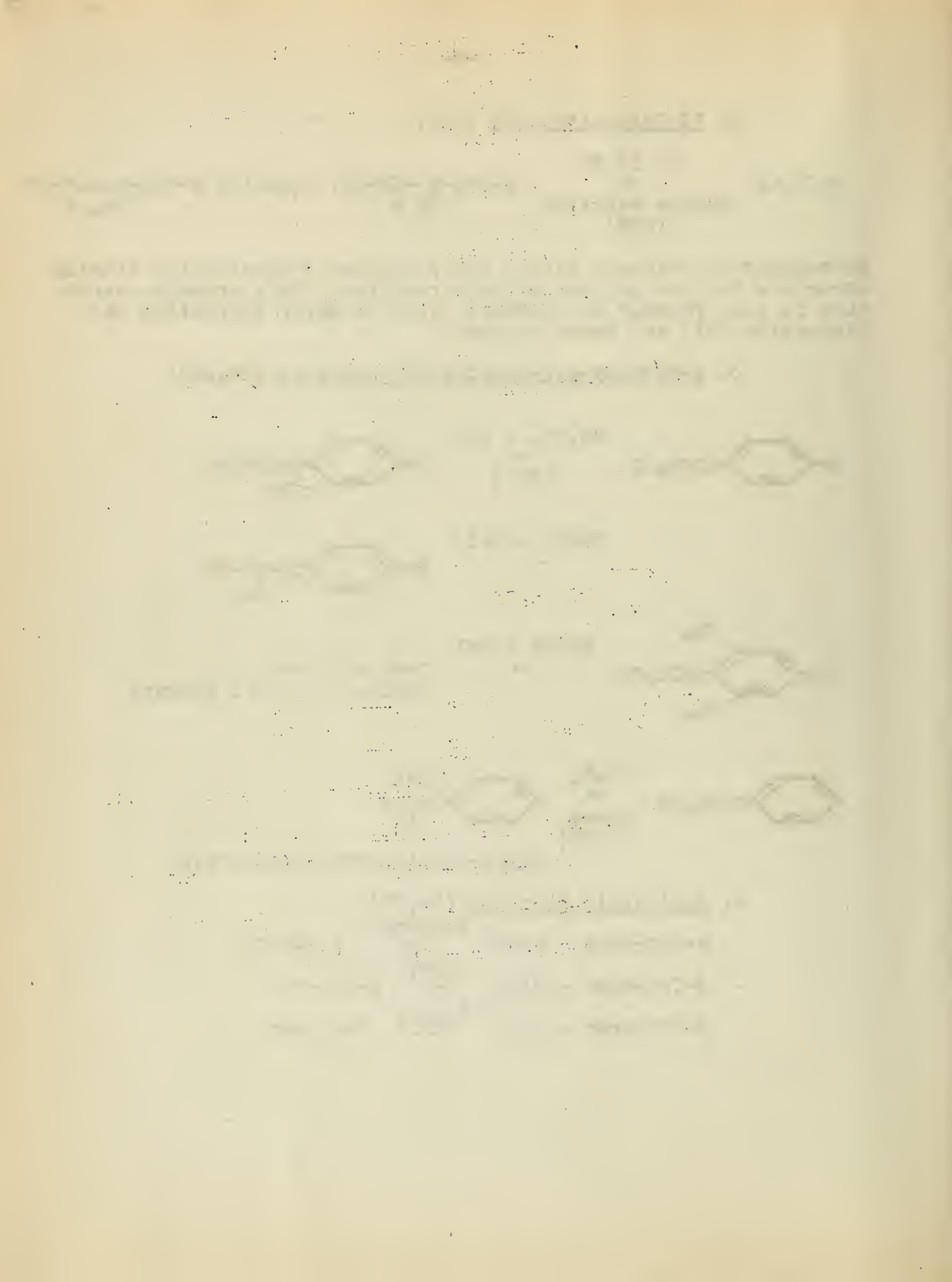
trans-β-methoxycinnamonitrile

4. Acetylenic Nitriles (24,25):

$$R\text{-}C\equiv C\text{-}MgBr + ClCN \xrightarrow{(60\text{-}70\%)} R\text{-}C\equiv C\text{-}CN$$

$$Ø\text{-}C\equiv C\text{-}MgBr + ClCN \xrightarrow{(60\%)} Ø\text{-}C\equiv C\text{-}CN$$

$$Ø\text{-}C\equiv C\text{-}MgBr + BrCN \xrightarrow[\text{but (80\%)}]{} Ø\text{-}C\equiv C\text{-}Br$$



BIBLIOGRAPHY

1. Mahan, Organic Seminar Abstracts, Univ. of Ill., Feb. 10, 1943.
2. Spence and Mitchell, Ger. 725,277; I.G.F., Ger. 673,427; Lichty, U.S. 2,208,328; Loder, U.S. 2,175,810; Pieroh, U.S. 2,174,756; I.G.F., Fr. 790,262.
3. Verhulst and Glorieux, Bull. soc. chim. Belg., 41, 501 (1932).
4. Vandewyer, Bull. soc. chim. Belg., 44, 376 (1935); Castille and Ruppol, ibid., 44, 351 (1935); Bruylants, Acad. roy. Belg., Classe sci., Mem. 14 [7] (1936).
5. Trakhtenberg and Shemyakin, J. Gen. Chem. (USSR), 13, 477 (1943).
6. Phelps and Tillotson, Chem. Zentr., 1908 II, 1248.
7. Org. Syn., Coll. Vol. I, second edition, p. 254.
8. Shemyakin and Trakhtenberg, Compt. rend. acad. sci. (USSR), 24, 763 (1939).
9. Whyte and Cope, J. Am. Chem. Soc., 65, 1999 (1943).
10. Birch and Kon, J. Chem. Soc., 123, 2440 (1923).
11. Bruylants, Bull. soc. chim. Belg., 41, 309 (1932).
12. Kandiah and Linstead, J. Chem. Soc., 1929, 2139.
13. Cope, J. Am. Chem. Soc., 59, 2327 (1937).
14. Cope, Hofmann, Wyckoff, and Hardenbergh, ibid., 63, 3452 (1941).
15. Cope and Hancock, ibid., 60, 2903 (1938).
16. Cope and Hancock, ibid., 61, 776 (1939).
17. Osmon and Cope, ibid., 66, 881 (1944).
18. Shepherd, Organic Seminar Abstracts, Univ. of Ill., Nov. 17,
19. Wittig, Kethur, Klein, Wietbrock, Ber., 69B, 2078 (1936).
20. Adkins and Whitman, J. Am. Chem. Soc., 64, 150 (1942).
21. Auwers and Wunderling, Ber., 64, 2758 (1931).
22. Fuson and Wolf, J. Am. Chem. Soc., 61, 1940 (1939).
23. Arndt, Loewe, Ozsoy, Ogut, Arslan and Bagevi, Ber., 71B, 1631 (1938).
24. Grignard and Perrichon, Ann. Chim. [10], 5, 5 (1926).
25. Grignard and Courtot, Bull. soc. chim., 17, 228 (1915).

Reported by Nelson J. Leonard
October 18, 1944

A MECHANISM FOR SOME SOLVOLYSIS REACTIONS OF TERTIARY BUTYL ESTERS

SAUL G. COHEN, PITTSBURGH PLATE GLASS CO.

Day and Ingold, in a review published in 1941, observed that there are a multiplicity of mechanisms to explain solvolytic reactions of esters (4). They have suggested the following classification of these mechanisms which is based on both the chemical and physical observations of numerous investigators.

TABLE I

Type of mechanism	Entity attacked	Known reactions	Type of bond fission* Acyl-oxy	Alkyl-oxy
Base	R'COOR	Hydrolysis only	---	$B"_1$
			B'_2	$B"_2$
Acid	$(R'COOHR)^+$	Hydrolysis	A'_1	$A"_1$
	$(R'COOH_2)^+$	Esterification	A'_2	$A"_2$(?)†

*Subscripts refer to the kinetic order of the reaction.
†Not yet experimentally confirmed.

Cohen and Schneider (3) and Cohen (2) have recently presented some chemical evidence in support of the fission of the alkyl-oxygen bond during solvolysis reactions of esters of t-butyl alcohol. The data for these alcoholysis and acetolysis reactions is summarized in tables II and III, respectively.

Alcoholysis.--The alcoholysis of esters leads to different products depending upon which bond is broken. The usual acyl-oxygen fission results in the familiar transesterification giving the new ester and the corresponding alcohol. Fission of the alkyl-oxygen bond produces an ether and the corresponding acid. This reaction is well established for the alkylation reactions of the esters of sulfonic acids (6). Although this reaction is general for the primary esters of the strong acids it has been observed only with the tertiary alkyl esters of the weak carboxylic acids.

TABLE II

Ester	Solvent	Conditions	Products
$\phi COOC(CH_3)_3$	Anhy. MeOH	reflux 4 days	Benzoic acid 22.6% Me. benzoate 61.9% Me. t-Bu. ether 60.7% t-Bu. alcohol none
"	"	10 mol%NaOMe reflux 4 days	Me. benzoate 71.6% t-Bu. alcohol 81.7% no ether detected

Ester	Solvent	Conditions	Products
MesCOO*t*-Bu.	"	reflux 7 days	Mesitoic acid 6.1% *t*-Bu. Me. ether 12.5% MesCOO*t*-Bu. 82.5% recovered.
"	"	NaOMe. reflux 7 days	no reaction
"	Water	20%NaOH reflux 1 hour	no reaction
"	Anhy. MeOH	39.5% HCl gas 0°C., 30 min.	Mesitoic acid 96.5%
"	Water	18% HCl reflux 1 hour	" " 97%
MesCOOMe	Anhy. MeOH	39.5% HCl 0°C., 30 min.	no reaction

T-Butyl mesitoate and *t*-butyl benzoate are readily and quantitatively hydrolyzed to mesitoic acid and benzoic acid, respectively, by the hydrion-catalyzed reaction in either water or anhydrous methanol solution. The reaction probably follows the $A"_1$ mechanism since it seems not to be sensitive to steric effects. Stuart models indicate that there is practically no hindrance of the oxygen atoms of these two esters to electrophilic attack, whereas the carbonyl carbon atom of *t*-butyl mesitoate is highly hindered to nucleophilic attack. As was expected, basic hydrolysis of the mesitoate could not be accomplished since the reaction involves nucleophilic attack of hydroxyl ion at the carbonyl carbon.

Methyl mesitoate is not hydrolyzed when subjected to acidic conditions similar to those causing complete hydrolysis of *t*-butyl esters. This is in accord with the observed order of rates of the hydrolysis of esters (I < II < III) (9), and with the order of ease of formation of carbonium ions (I < II < III). The A'_2 mechanism is highly sensitive to steric interference to the approach of the solvent molecule.

That the esters of *t*-butyl alcohol react by the normal B'_2 mechanism during treatment with alkali is indicated by the fact that *t*-butyl benzoate produces methyl benzoate and *t*-butyl alcohol when refluxed with methanol and sodium methoxide.

When the nearly-neutral condition of boiling methanol was used *t*-butyl benzoate produced methyl *t*-butyl ether in good yield and *t*-butyl mesitoate gave the ether very slowly. It was observed also that a mixture of *t*-butyl alcohol, a carboxylic acid and methanol did not produce any ether when refluxed a comperable length

of time. It is impossible to say whether this reaction is $A"_1$ or $A"_2$ since there is no convenient method of studying the kinetics. Cohen formulates the course of the reaction as follows:

$$\text{ØCOOC(CH}_3)_3 + \text{HA} \rightleftarrows \left[\begin{matrix}\text{H}\\ \text{O}\\ \text{ØCOOC(CH}_3)_3\end{matrix}\right]^+ + \text{A}^- \quad .$$

$$\downarrow\uparrow$$

$$\text{ØCOOH} + \text{C(CH}_3)_3^+$$

$$\text{C(CH}_3)_3^+ + \text{HOCH}_3 \rightarrow \text{CH}_3\text{OC(CH}_3)_3 + \text{H}^+$$

The reaction is probably initiated by the solvent methanol to give a small amount of the products and then the acid thus produced acts as the catalyst for the major portion of the reaction.

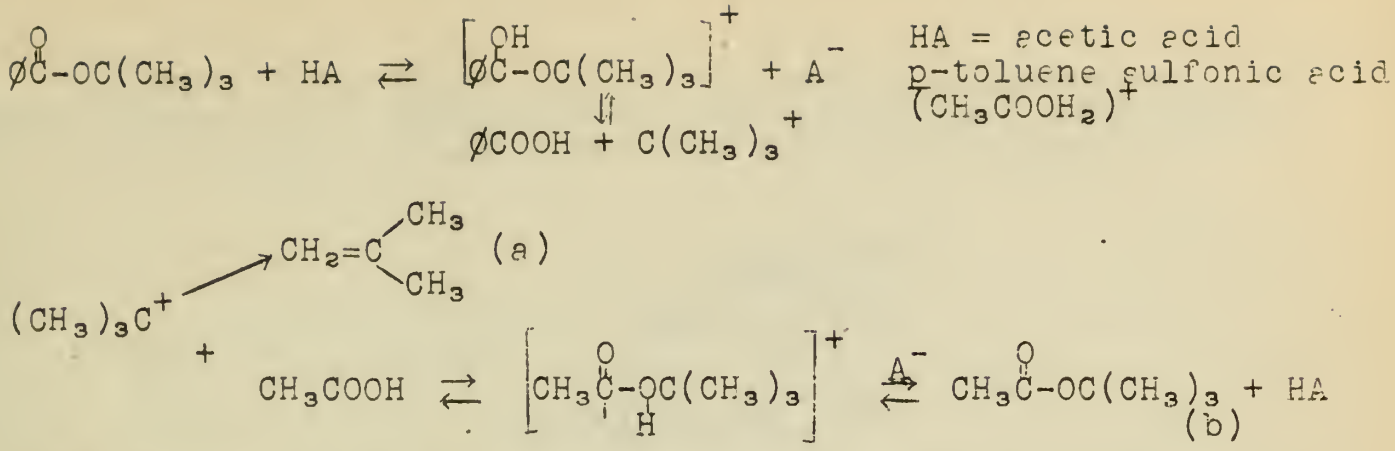
Acetolysis.--The reaction of an acid and an ester to produce the corresponding acid and ester was observed as early as 1861 when Lowig (7) produced methyl oxalate from oxalic acid and methyl carbonate. Gault and Chably (5) found the reaction to be reversible and several investigators have determined equilibrium constants for various esters with acetic and other acids (5,1,8). Sowa showed that the reaction was acid-catalyzed. Cohen described a case catalyzed by base.

Cohen has extended the reaction to esters of tertiary alcohols.

TABLE III
Reaction with Acetic Acid

Ester	Conditions	Catalyst	Products	
t-BuOOCØ	20 hours reflux	none	Recovered ester Benzoic acid t-Butyl acetate	17% 72% 8.5%
"	2 days at room temp.	p-Toluene sulfonic acid	Recovered ester t-Butyl acetate Benzoic acid isobutylene	25% 65%)of con- 61%)sumed 6.5%)ester
"	2.5 hours reflux	"	Benzoic acid t-Butyl acetate	76% none

With much more rigorous conditions isopropyl benzoate produced only a small amount of the products and methyl benzoate was recovered without a trace of the products being found. Thus the order of reactivity of the esters is the same as in alcoholysis (III > II > I). Cohen has proposed a mechanism for the reaction which is consistent with all of these observed facts and with the general theory of ester solvolysis reactions.



The formation of isobutylene probably presents a higher activating energy barrier since it takes place only when considerable energy is supplied in the form of heat. This mechanism is superior to that of Sowa (8) who suggested that the alkyl group of the ester undergoes loss of the elements of the acid producing an olefin as an intermediate, which then adds the acetic acid. This was suggested to explain the production of from 2 to 5% of s.-butyl acetate from n-butyl esters. However, the rearrangement of primary and secondary carbonium ions is well established.

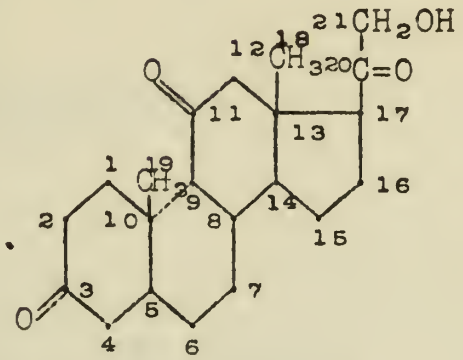
BIBLIOGRAPHY

1. Berkenbus, Roswell and Mitts, J. Am. Chem. Soc., 62, 1261 (1940).
2. Cohen, J. Am. Chem. Soc., 66, 1395 (1944).
3. Cohen and Schneider, ibid., 63, 3382 (1941).
4. Day and Ingold, Trans. Faraday Soc., 37, 686 (1941).
5. Gault and Chahlay, Compt. Rend., 203, 729 (1936).
6. Lapworth and Ferns, J. Chem. Soc., 101, 273 (1912); Olson and Miller, J. Am. Chem. Soc., 60, 2687 (1938).
7. Lowig, J. Prakt. Chem., (1) 83, 130 (1861).
8. Sowa, J. Am. Chem. Soc., 60, 654 (1938); Sowa, et. al., ibid., 60, 656 (1938).
9. Tronov and Subgatullen, Ber., 62B, 2850 (1929).

Reported by Herman I. Enos, Jr.
October 25, 1944

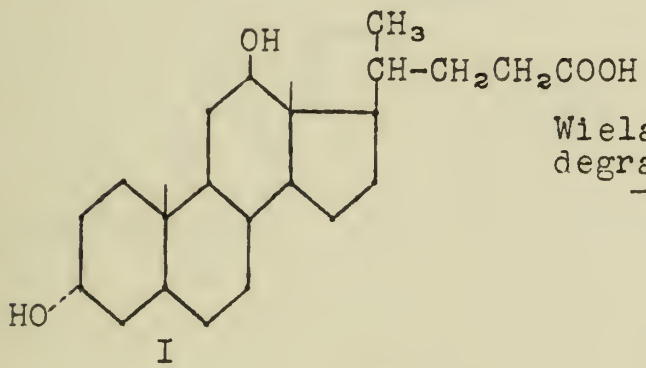
PARTIAL SYNTHESIS OF DEHYDROCORTICOSTERONE

Dehydrocorticosterone, one of the hormones isolated from the adrenal cortex, is a derivative of the hydrocarbon, allopregnane, and the ring system is numbered in the following fashion.



This hormone along with corticosterone and other compounds with an oxygen atom (either as a hydroxyl or a keto group) in the 11-position plays an important role in carbohydrate metabolism (1). It has been found that compounds with oxygen in the 11-position are very beneficial in treating Addison's disease (2), which is caused by an insufficiency of the adrenal glands. Therefore, it would be desirable to have synthetic corticosterone or dehydrocorticosterone readily available. Difficulties in synthesizing the compound have involved the inability of introducing oxygen in the 11-position. Recently, however, the synthesis has been worked out by Reichstein (3,4,5, and 6).

The starting material for Reichstein's synthesis, 3α,12β-dihydroxyetiocholanic acid is prepared from desoxycholic acid, a bile acid (7). The conversion of desoxycholic acid to the desired starting material involves the important Barbier-Wieland degradation.



I

desoxycholic acid

Wieland degradation →

$R-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-COOH$

nordesoxycholic acid

Wieland degradation →

$R-\underset{\displaystyle CH_3}{\underset{|}{CH}}-COOH$

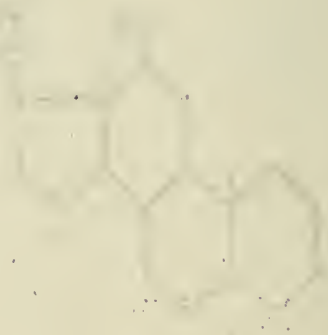
bis-nordesoxycholic acid

Wieland degradation →

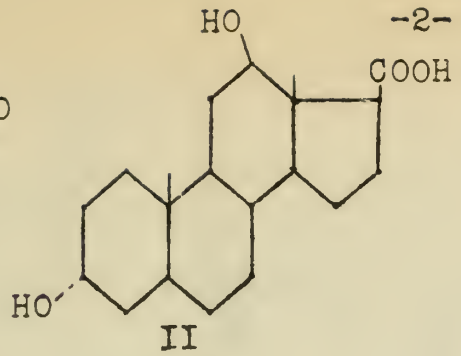
$R-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3$

C_6H_5CHO, $NaCC_2H_5$ →

$R-\overset{\displaystyle O}{\overset{\|}{C}}-CH=CH-C_6H_5$



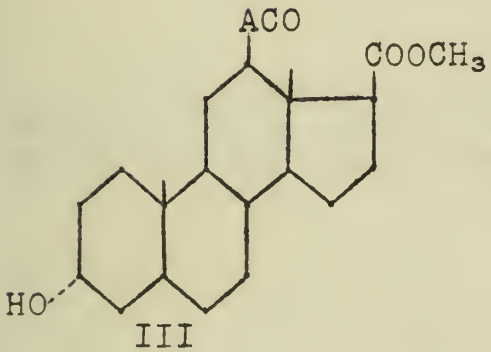
$\xrightarrow{O_3}$ $\xrightarrow{HIO_4}$ $\xrightarrow{H_2O}$



II

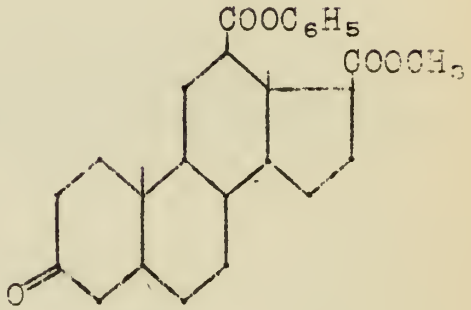
$\xrightarrow{CH_2N_2}$ then Ac_2O $\xrightarrow{1\%\ HCl}$ CH_3OH

3α,12β-dihydroxyetiocholanic acid



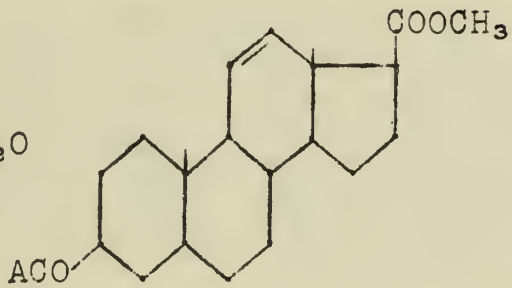
III

$\xrightarrow{CrO_3}$ $\xrightarrow{KOH}$ then CH_2N_2 $\xrightarrow{C_6H_5COCl}$ pyridine



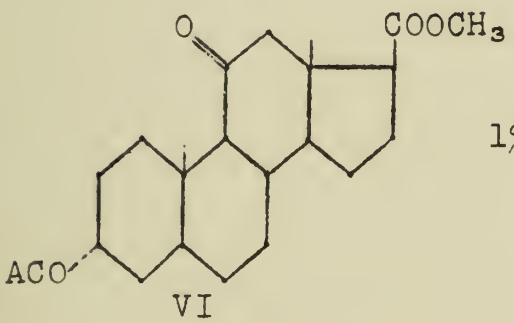
IV

$\xrightarrow[12\ mm.]{340^\circ}$ $\xrightarrow{Meerwein\ Pondorf}$ $\xrightarrow{Ac_2O}$



V

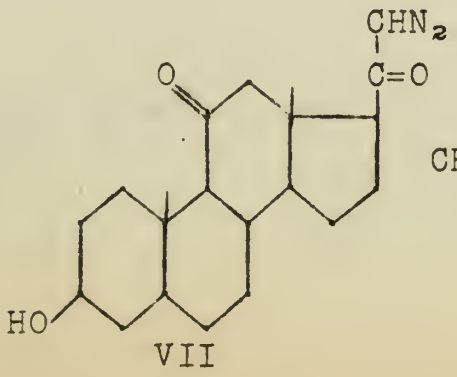
$\xrightarrow{HOBr}$ $\xrightarrow{CrO_3}$ $\xrightarrow{Zn\ dust}$



VI

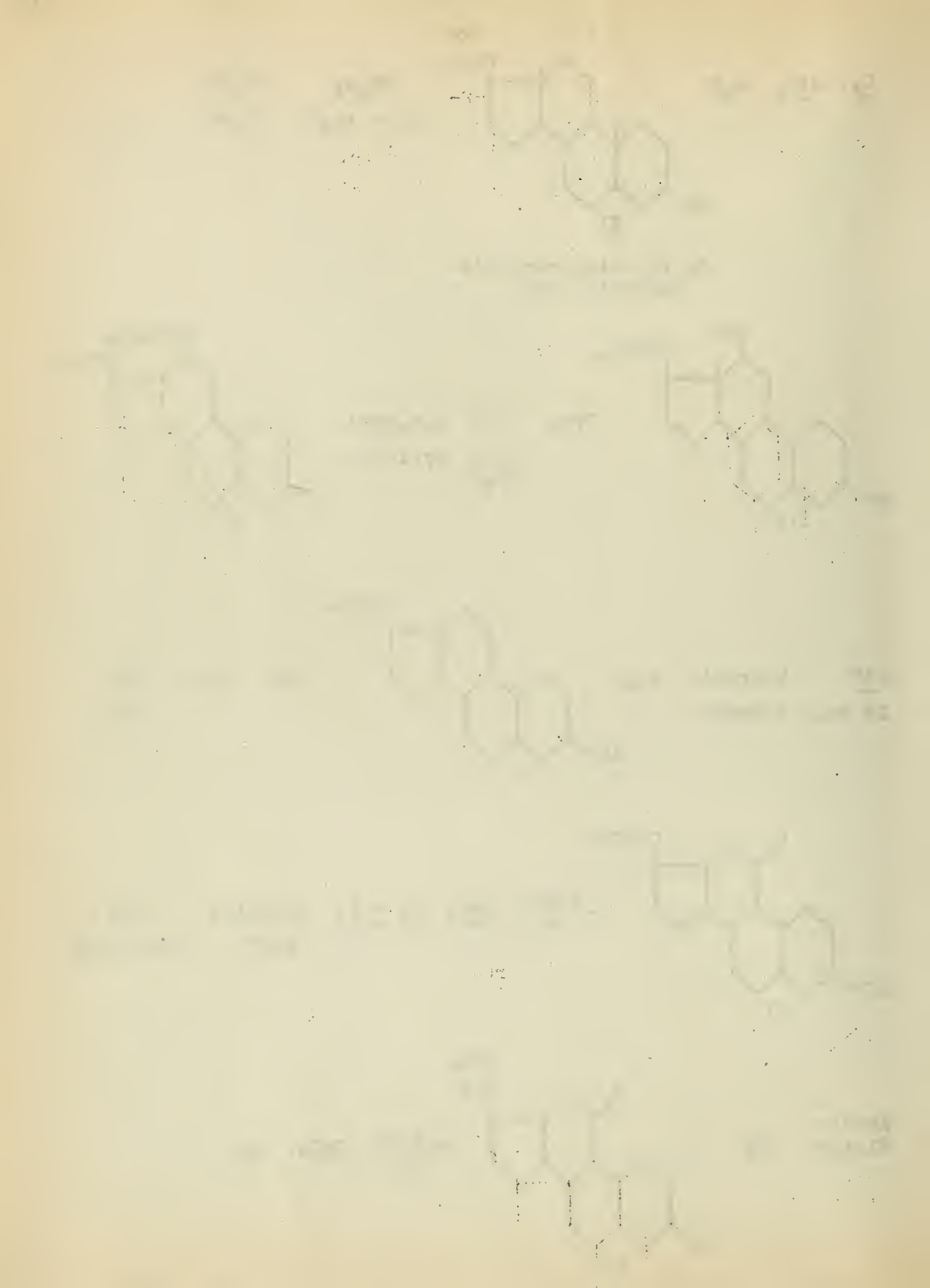
$\xrightarrow{1\%\ HCl}$ $\xrightarrow{CrO_3}$ $\xrightarrow{H_2 + Pt}$ $\xrightarrow[Ac_2O]{pyridine}$ $\xrightarrow[then\ Ac_2O]{KOH}$

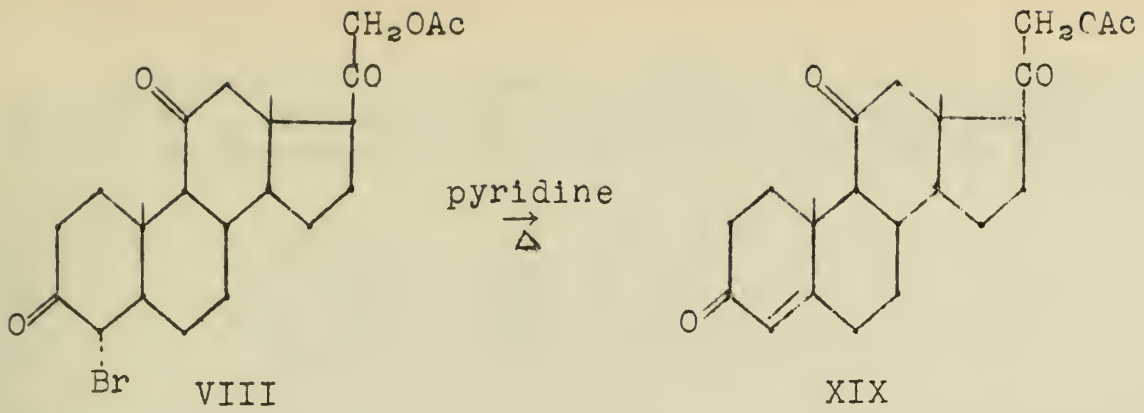
Arndt-Eistert $\xrightarrow{KOH}$



VII

$\xrightarrow[\triangle]{CH_3COOH}$ $\xrightarrow{CrO_3}$ $\xrightarrow{Br_2}$





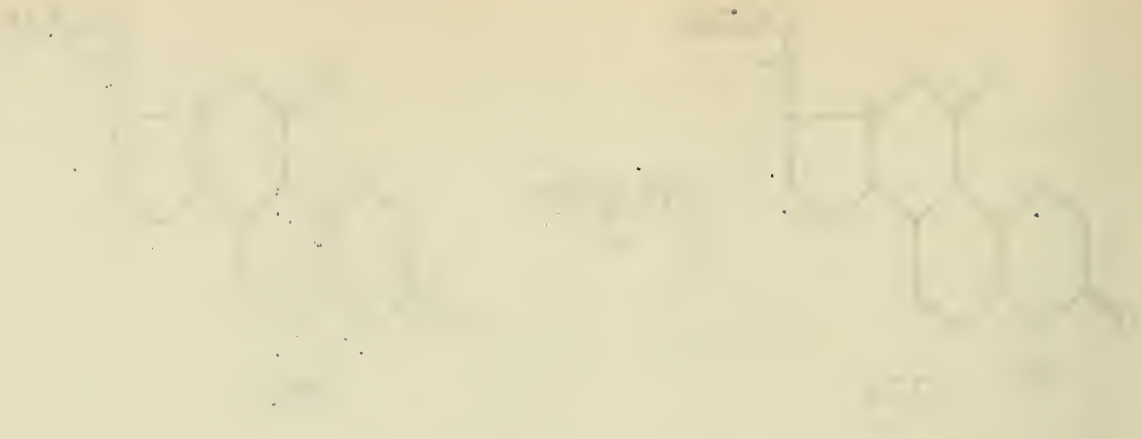
VIII XIX

This acetate can be readily hydrolized to dehydrocorticosterone, which agrees with the natural product as to melting point, mixed melting point, and specific rotation.

BIBLIOGRAPHY

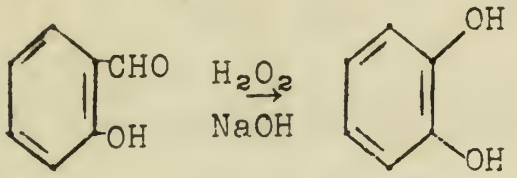
1. Long, Katzin, and Fry, Endocrinology, 26, 309 (1940).
2. Thorn, et al., J. Clin. Investigation, 19, 813 (1940).
3. Lardon and Reichstein, Helv. Chem. Acta, 26, 747 (1943).
4. Reich and Reichstein, ibid., 562 (1943).
5. Lardon and Reichstein, ibid., 26, 705 (1943).
6. Lardon and Reichstein, ibid., 26, 607 (1943).
7. Hoehm, J. Am. Chem. Soc., 60, 1493 (1938).

Reported by G. W. Stacy
October 25, 1944

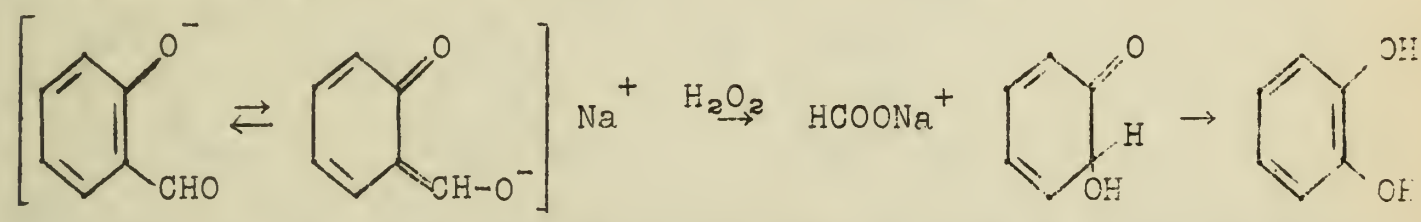


THE DAKIN REACTION

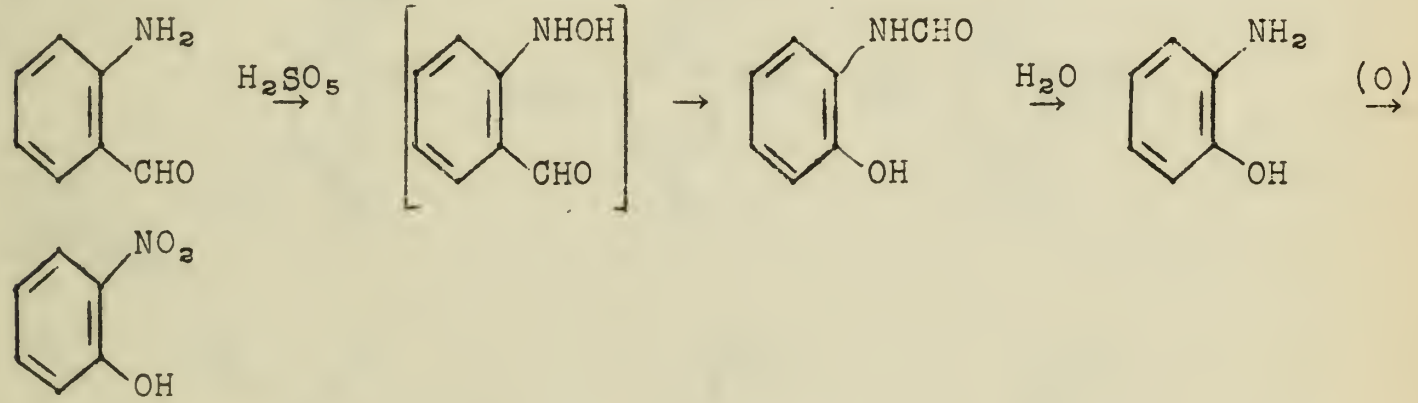
The reaction reported in 1909 by H. Dakin consisted of the oxidation of o or p-hydroxy derivatives of benzaldehyde and acetophenone with aqueous alkaline hydrogen peroxide to diphenols; e.g.



In addition to hydrogen peroxide other peroxides such as sodium peroxide, perbenzoic acid, and Caro's acid were found to work satisfactorily, but ordinary oxidizing agents yielded no diphenol. Dakin suggested a mechanism for the reaction based on the assumed existence of a quinoid form of the phenolate ion:

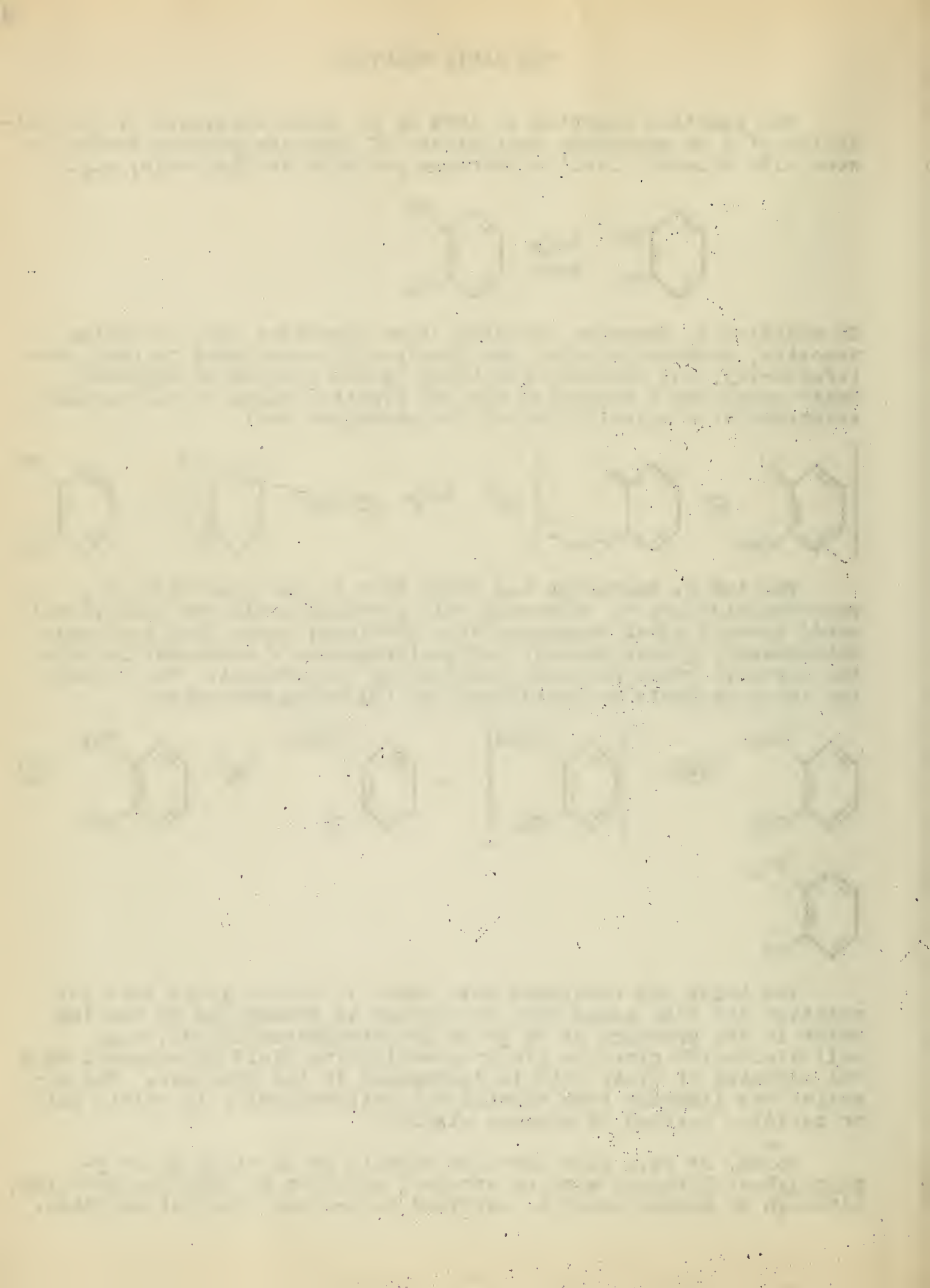


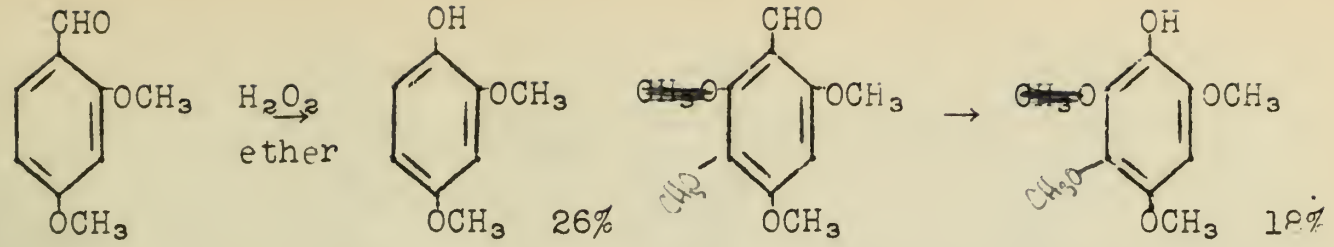
Earlier E. Bamberger had found that in the oxidation of o-aminobenzaldehyde to anthranil with peroxymonosulfuric acid (Caro's acid) several other compounds were obtained; among them o-formylaminophenol, o-aminophenol, and o-nitrophenol - compounds in which the carbonyl group has been replaced by an hydroxyl. To account for these products he postulated the following mechanism:



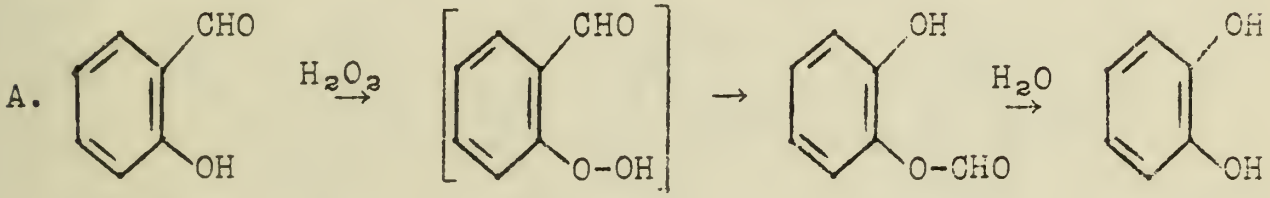
von Wacek and coworkers have shown in recent years that the reaction can take place when an ozonide is decomposed by boiling water in the presence of an o- or p-hydroxybenzaldehyde, e.g. salicylaldehyde gives an almost quantitative yield of catechol when the peroxide of oleic acid is decomposed in its presence. The reaction has likewise been carried out satisfactorily in acetic acid or pyridine instead of aqueous alkali.

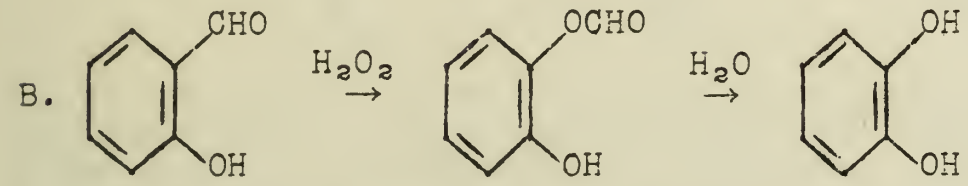
Späth, et al., also obtained phenols by treating o- or p-methoxybenzaldehydes with an ethereal solution of hydrogen peroxide, although no phenol could be obtained in aqueous alkaline solution.



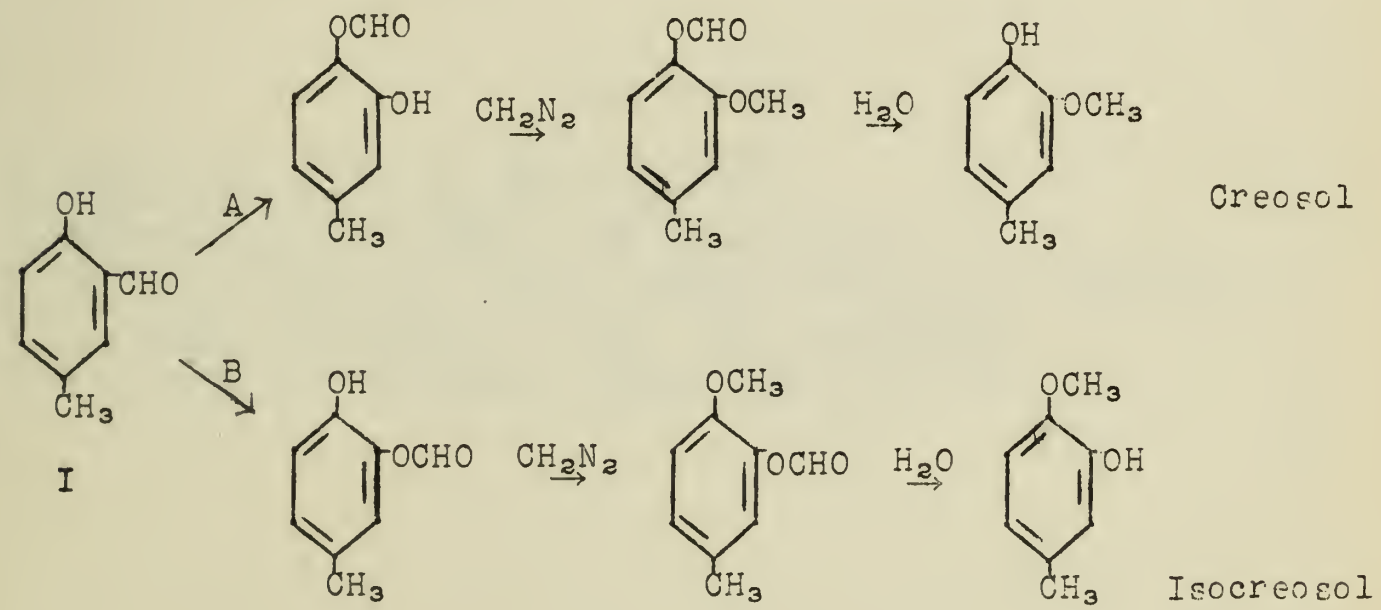


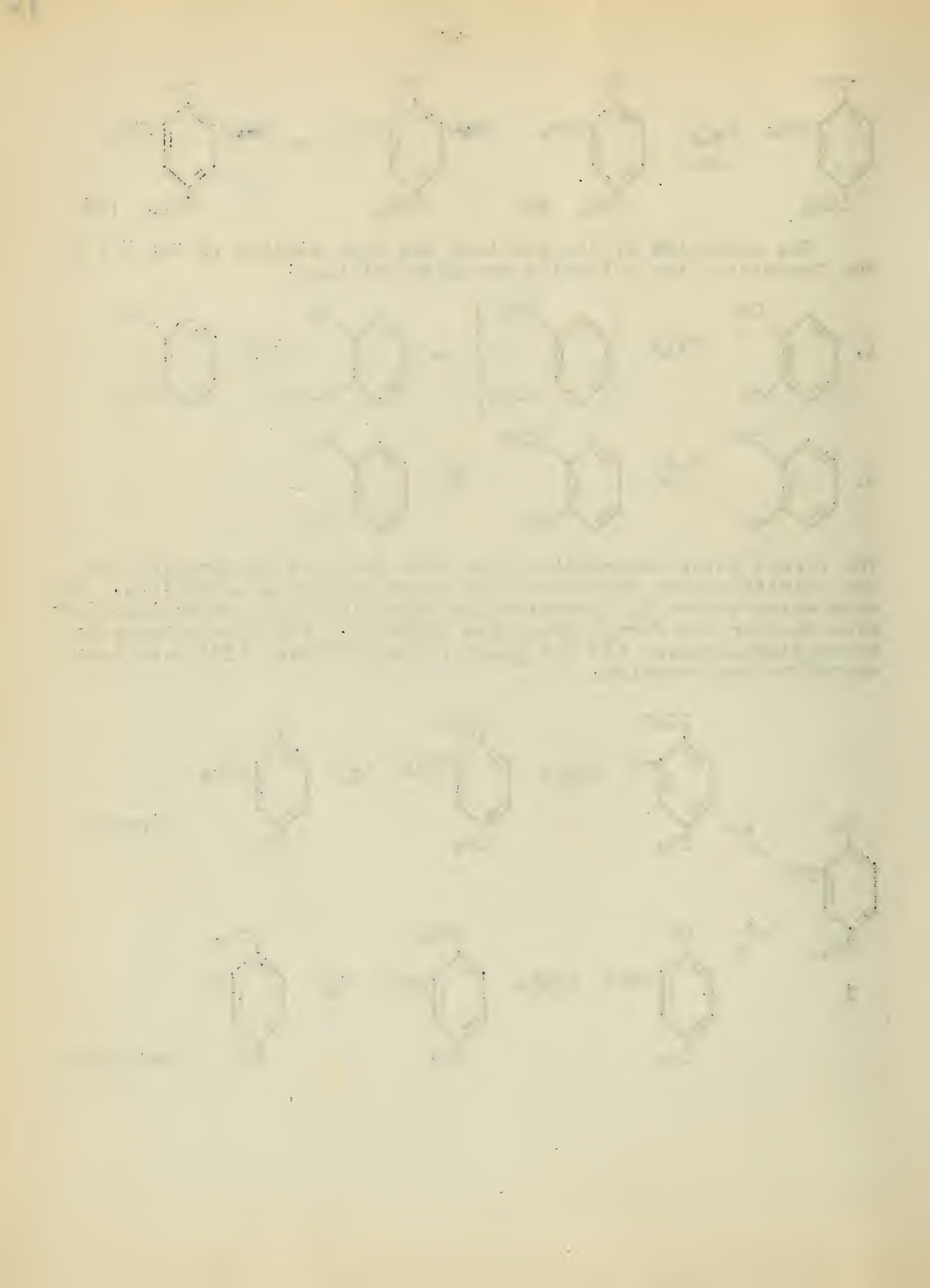
The mechanism of the reaction has been studied by von Weerk. who formulates the following two possibilities:

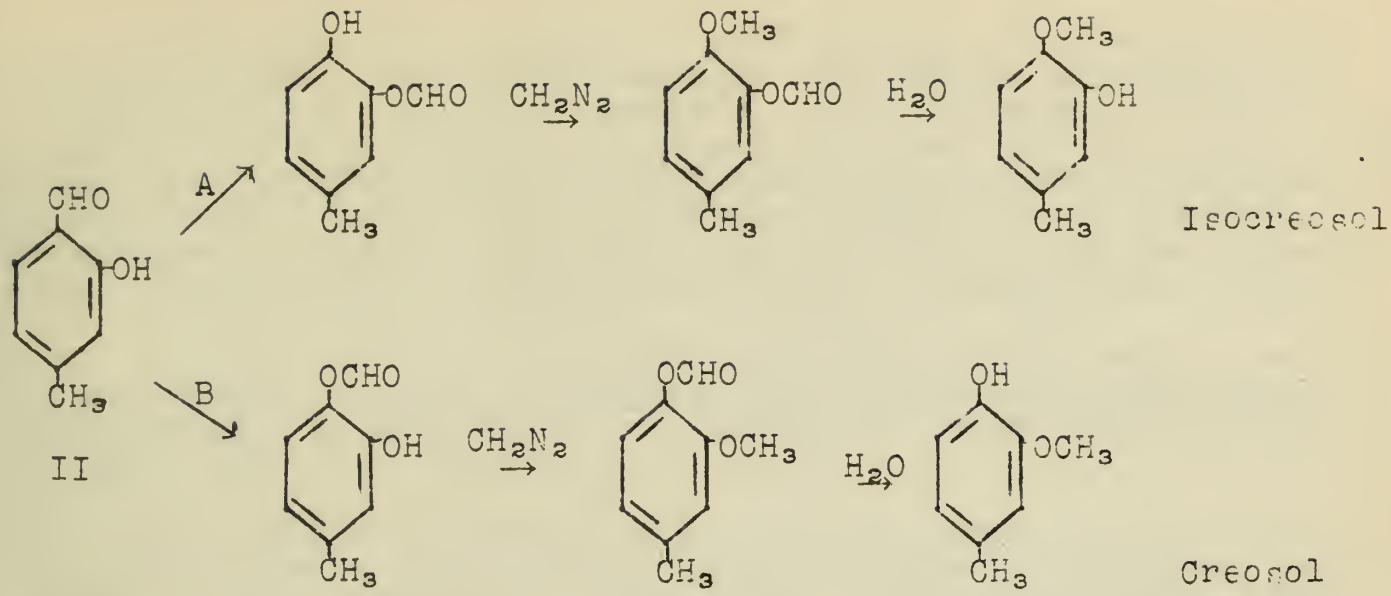




The formyl ester intermediate has been isolated by carrying out the oxidation with peracetic acid under anhydrous conditions. To show which course the reaction has taken it is necessary to determine whether the formyl group has migrated. For this purpose p-homosalicylaldehyde (I) and m-homosalicylaldehyde (II) were submitted to the reaction.





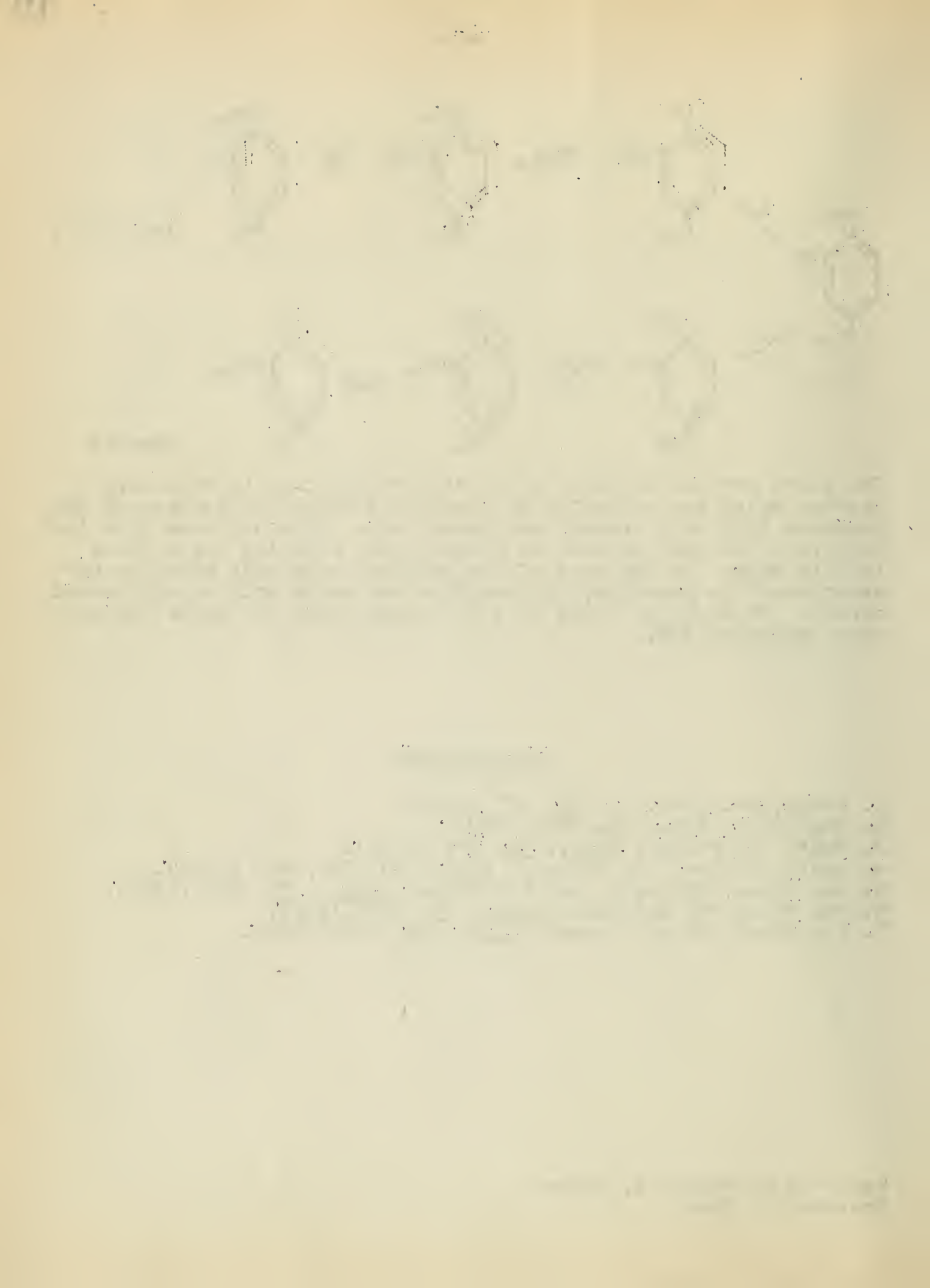


The final product of this series of reactions was in each case a mixture which was separated by fractional recrystallization of the picrates into both creosol and isocreosol. It would seem then that when free hydroxyl groups are present, the reaction takes place in both ways. In the case of the methoxyl compounds where no rearrangement is possible, the reaction can occur only in the second manner. It is to be noted that the yields here are lower, in no case exceeding 30%.

BIBLIOGRAPHY

1. Dakin, Am. Chem. J., 42, 477 (1909).
2. Bamberger, Ber., 36, 2042 (1903).
3. Späth and Pailer, ibid., 73, 238 (1940).
4. Späth, Pailer, and Gergely, ibid., 73, 795, 935 (1940).
5. von Wacek, Eppinger, and von Bezard, ibid., 73, 521 (1940).
6. von Wacek and Eppinger, ibid., 73, 644 (1940).
7. von Wacek and von Bezard, ibid., 74, 845 (1941).

Reported by Robert A. Bauman
November 1, 1944

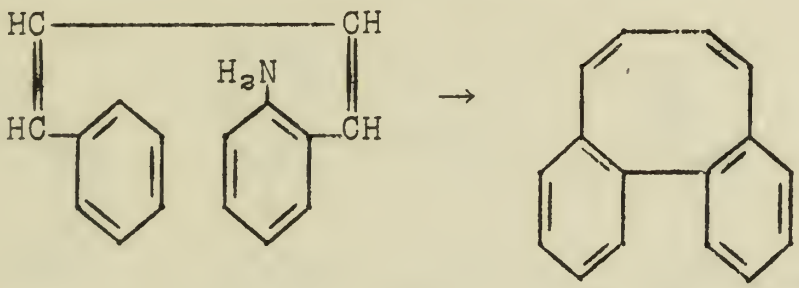


SUBSTITUTED CYCLOOCTATETRAENE

Ever since its synthesis by Willstätter, cyclooctatetraene has been widely used in theoretical discussions concerning the structure of the aromatic neucleus. Its symmetrical structure assigned by its discoverer was accepted without any doubt until 1938 when the striking similarity between cyclooctatetraene and styrene was noticed. In 1939 Hurd and Drake examined the Willstätter synthesis more closely and came to the conclusion that the symmetrical structure was not supported strongly by experimental facts.

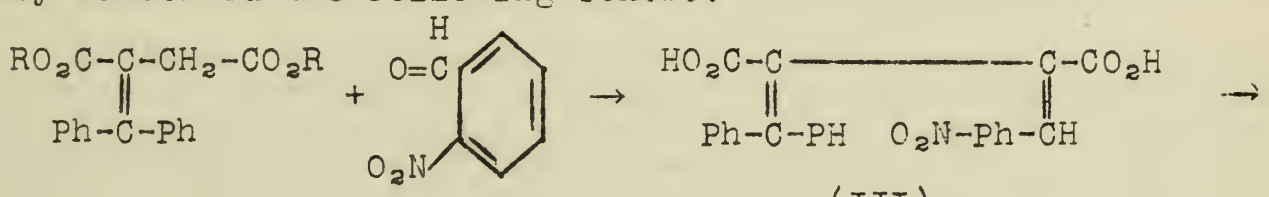
In April 1941, Dr. Wawzonek reviewed in this seminar several unsuccessful attempts to prepare this interesting hydrocarbon. The material of this report has been drawn from six papers published since that time.

Believing that substituted cyclooctatetraene may be easier to make and more stable, the attention of several chemists was drawn to this direction. Bachman and Heoglin reported in 1943 their failure at the attempt to prepare 1,2,3,4-dibenzo-1,3,5,7-cyclooctatetraene (II) by subjecting 1-phenyl-4-(o-aminophenyl)-1,3-butadiene to the Pschorr reaction.

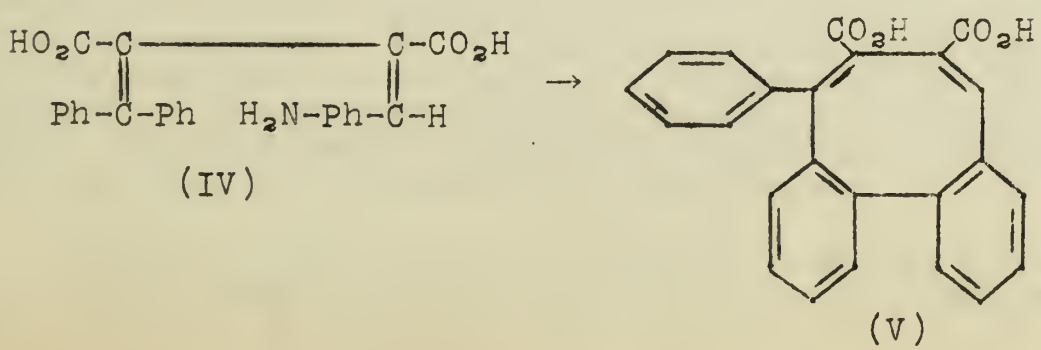


(I) (cis-cis) (II)

Of the four possible isomers, the cis-cis form is the only one in which the two phenyl groups approach each other close enough to make condensation between them likely. However, they were unable to find a suitable method for preparing this isomer. Instead, they conceived the following scheme:



(III)

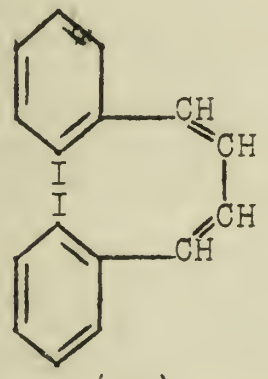


(IV) (V)

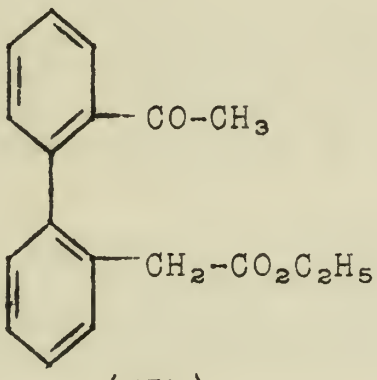
They pointed out that (a) the configuration of the double bond on the left of compound IV is invariably cis for one of the phenyl groups, (b) the replacement of the hydrogen atom in 1-position by a phenyl group prevents a coupling from occurring at that position, and (c) in the event of a successful ring closure, it is possible to determine whether the cyclooctatetraene ring is puckered or whether the bond angles are strained and the ring is planar. If it is puckered, the two benzene rings would not necessarily occupy the same plane and the system would be optically active. Resolution might be effected through the carboxyl groups.

Compound III was obtained easily and reduced to IV which was diazotized without difficulty. However, all efforts to cause the desired ring closure were unsuccessful - only resinous products could be obtained.

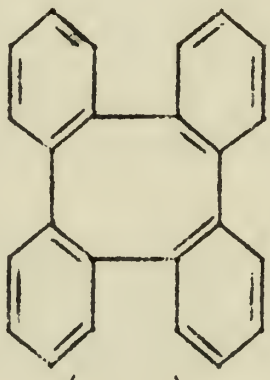
Their failure was preceded by Rapson and Shuttleworth in 1941, when the latter workers tried to prepare II by three different methods without any success. Whereas the condensation between biphenyl-2,2'-dialdehyde and succinic acid failed, treatment of 1,4-bis-o-iodophenyl-1,3-butadiene (VI) with copper-bronze alone



(VI)



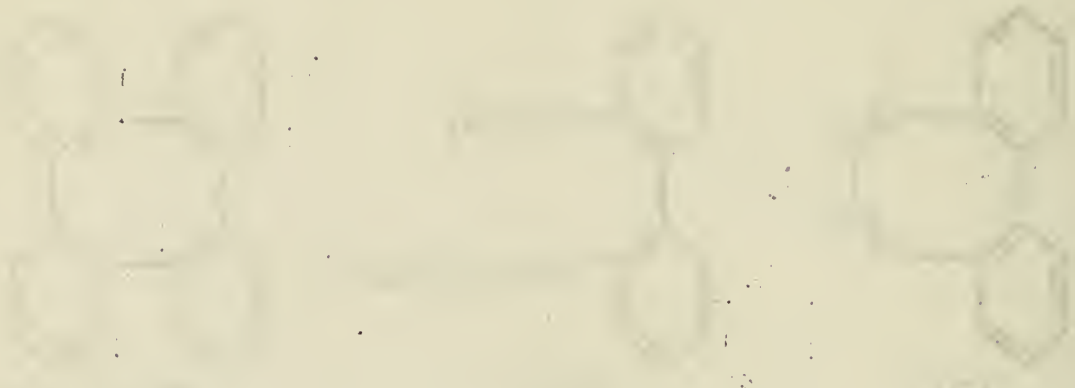
(VII)

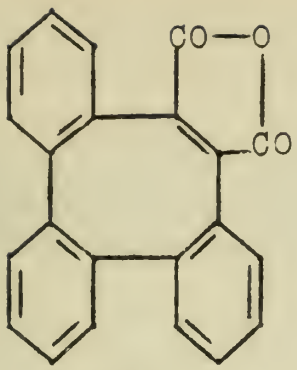

(VIII) m.p. 233°

or in quinoline, yielded intermolecular condensation products. They were also unable to find a suitable method of preparing (VII) from which the desired ring system should be accessible.

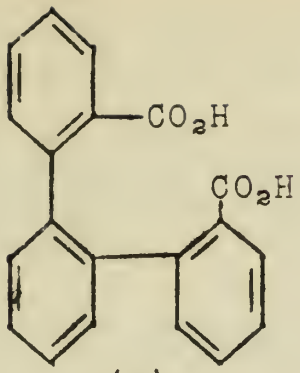
However, in 1943, they reported their success in synthesizing tetraphenylene which is a completely substituted cyclooctatetraene. This compound was obtained along with diphenylene when the Grignard reagent from one mole of 2,2'-dibromobiphenyl and 1.2 moles of magnesium was treated with 2.16 moles of dry cupric chloride. It is very stable, being recovered unchanged after treatment with potassium permanganate. It did not form an addition compound with trinitrobenzene, picric acid, or styphnic acid. Bromination in the presence of a catalyst yielded a monobromotetraphenylene melting at 182°. Treatment with a nitric acid-concentrated sulfuric acid mixture yielded tetranitrotetraphenylene.

Oxidation with chromium trioxide in glacial acetic acid yielded the anhydride of a dicarboxylic acid which was assigned the structure of 1,2,3,4,5,6-tribenzo-1,3,5,7-cyclooctatetraene-7,8-dicarboxylic anhydride (IX, deep yellow prisms, m.p. 228-229°.

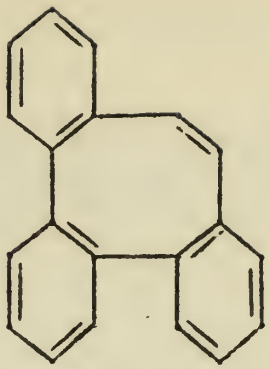




(IX)



(X)

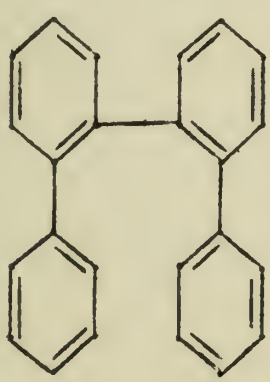


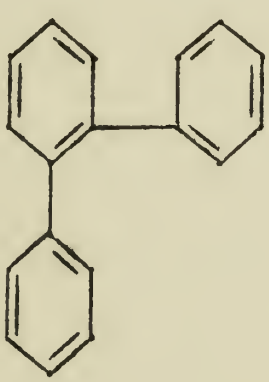
(XI)

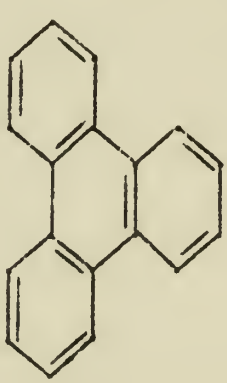
Further oxidation converted (IX) into o-diphenylbenzene-2',2"-dicarboxylic acid (X), identical with a specimen prepared by the action of copper on a mixture of ethyl 2-iodobiphenyl-2'-carboxylate with a large excess of ethyl o-iodobenzoate.

The anhydride was decarboxylated by heating with a mixture of copper-bronze and anhydrous barium hydroxide. The product assumed the form of colorless prisms, m.p. 138.5-139°. Its formulation as 1,2,3,4,5,6-tribenzo-1,3,5,7-cyclooctatetraene (XI), follows from the isolation of the acid (X). Treatment with bromine in carbon tetrachloride converted the hydrocarbon into an addition product of the mpirical formula $C_{20}H_{14}Br_2$. Hydrogenation with platinum oxide catalyst yielded a dihydro derivative as colorless prisms, m.p. 111-113°, which was believed to be 1,2,3,4,5,6-tribenzo-1,3,5-cyclooctatriene.

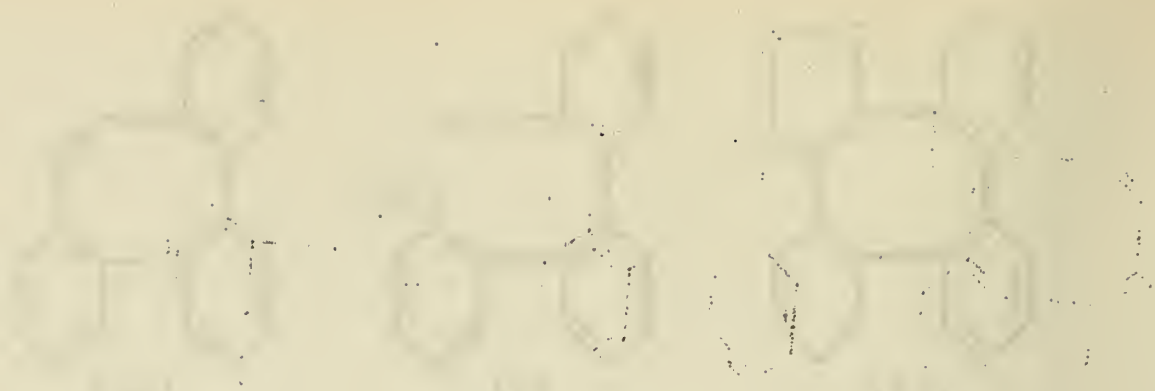
The absorption spectra of tetraphenylene and 1,2,3,4,5,6-tribenzo-1,3,5,7-cyclooctatetraene were found to be closely similar to those of 2,2'-diphenylbiphenyl and 2-phenylbiphenyl. But the absorption spectrum of triphenylene is markedly different. Whereas





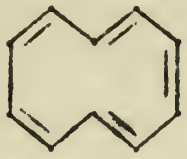


the presence of the central cyclohexatriene ring in triphenylene causes a profound difference between its absorption spectrum and that of 2-phenylbiphenyl, the presence of the central cyclooctatetraene ring in tetraphenylene causes no such difference between its absorption spectrum and that of 2,2'-diphenylbiphenyl. This seems to indicate that in tetraphenylene the cyclooctatetraene ring contributes little to the resonance, and therefore a non-planar structure for the tetraphenylene molecule is probable. Similar



conclusions must be drawn in the case of 1,2,3,4,5,6-tribenzo-1,3,5,7-cyclooctatetraene. They also cited substituting evidence from X-ray and electron diffraction studies.

Bachman pointed out that a cyclodecapentaene molecule of the following structure should be nearly planar and very little more strained than naphthalene. It may be relatively stable because of the high resonance.



BIBLIOGRAPHY

1. Wawzonek, Org. Seminar, II Semester, 1940-1941.
2. Bachman and Hoaglin, J. Org. Chem., 8, 300 (1943).
3. Rapson and Shuttleworth, J. Chem. Soc., 487 (1941); 33 (1942); 326 (1943); 71 (1944); 73 (1944).

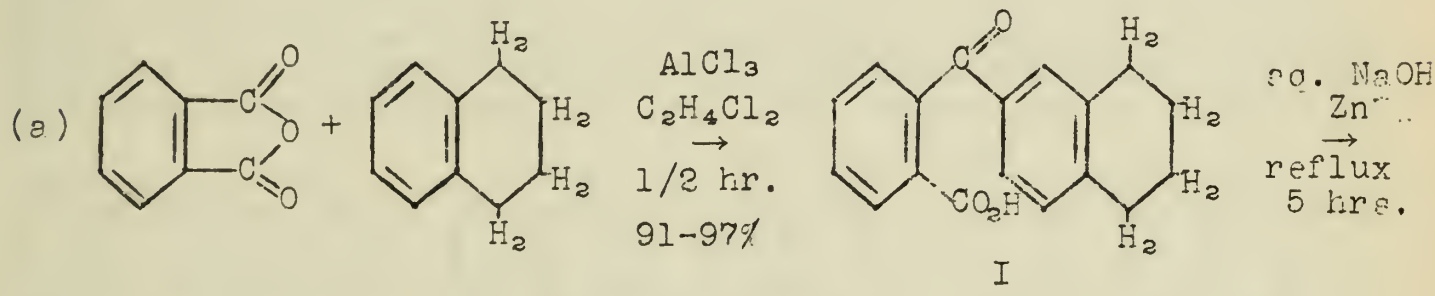
Reported by K. H. Chen
November 1, 1944

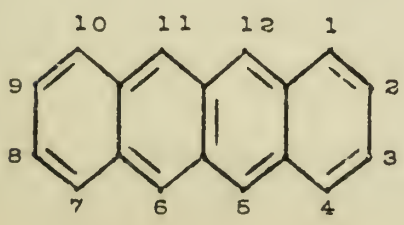
LINEAR POLYNUCLEAR HYDROCARBONS

Polynuclear hydrocarbons are benzologs of benzene, the simplest being naphthalene. This hydrocarbon has two monobenzologs; in one, anthracene, the three benzene rings are in a straight line. This arrangement is said to be linear. The other is phenanthrene, in which the arrangement is angular. Because of its convenience, the term, linear polynuclear hydrocarbons, has come to signify linear benzologs of anthracene; they have been grouped according to certain properties, especially color. Most of these properties are shown to a lesser degree by anthracene. The linear hydrocarbon having four benzene rings is naphthacene, or tetracene ($C_{18}H_{12}$); the nomenclature is regular thereafter, e.g., pentacene, hexacene, heptacene. The positions on the ring are numbered clockwise, starting at the top carbon on the right-hand ring.

Naphthacene occurs in small amounts in coal tar; it persists as an impurity in many other polynuclear hydrocarbons isolated from coal tar and may be responsible for their yellow color. The other linear compounds are obtained by synthetic methods.

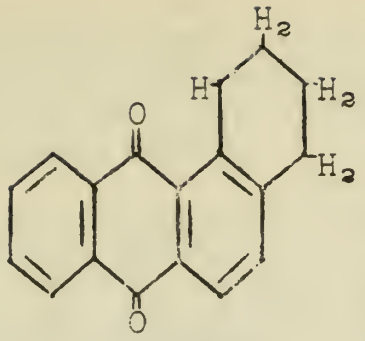
The syntheses require the addition of rings in a linear position, which is not an easy process because of the tendency to form angular compounds. The only practical general method involves the use of a phthalic anhydride in a Friedel-Crafts reaction, and cyclization of the O-benzoylbenzoic acid thus formed. Advantage is taken of the tendency of reduced ring systems or those bearing suitable substituents to close linearly. The following synthesis of naphthacene (1) indicates the general method used to synthesize these hydrocarbons.





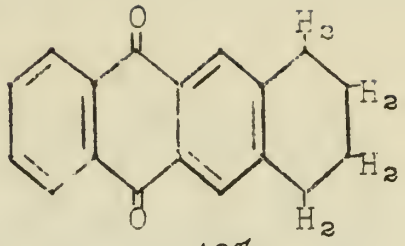
Naphthacene
IV

(b) I $\xrightarrow[25\%\ SO_3]{H_2SO_4}$ (2)



33%

+



40%

$\xrightarrow[700^\circ]{Zn}$ 40%

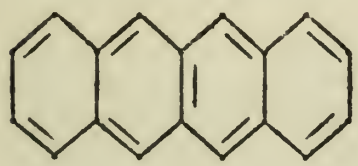
IV

Pentacene (4), hexacene (5,6), and heptacene (5) have been obtained by analogous procedures.

The linear polynuclear hydrocarbon that attracted the most attention was called "rubrene" by its discoverers, Moureu and Dufraisse (7). After a prolonged study Dufraisse showed that rubrene is 5,6,11,12-tetraphenylnaphthacene, and his conclusions have been verified by several syntheses (8,9).

Several varieties of polyarylated tetracenes and pentacenes are known. Most of them have been secured by the action of appropriate organometallic compounds upon the linear polynuclear quinones, by suitable manipulations. Hydroxy- and aminoquinones are also known.

The outline structures of these hydrocarbons is usually determined in the quinones, which are easily cleaved to readily recognizable fragments by an alkaline fusion. Now that preparative procedures are largely standardized, the method of synthesis serves as an independent proof of structure. The location of the bonds is not so easily settled. It is generally accepted that the preferred bond structures of these hydrocarbons are as shown below.



Naphthacene

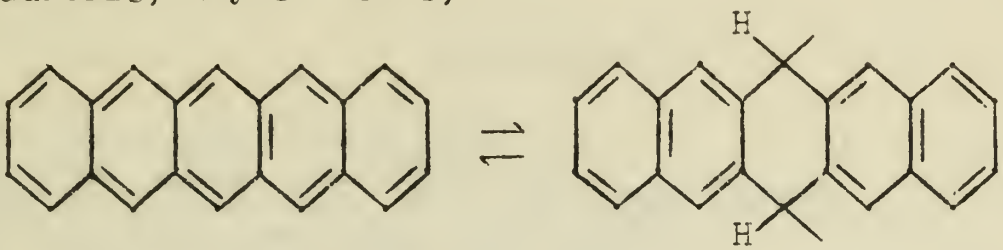
Pentacene

Hexacene

Heptacene

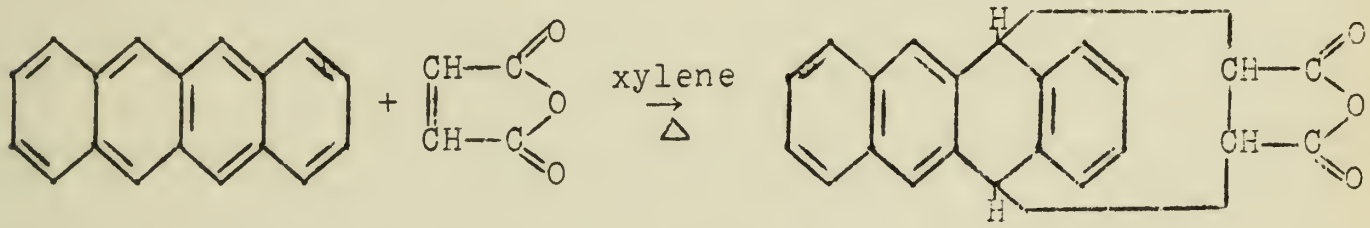
The location of certain bonds in the quinones has been demonstrated by the formation of 1,4- addition products with Grignard reagents (10).

The most striking physical property of the linear polynuclear hydrocarbons is their deep colors; naphthacene is orange-red; pentacene is reddish-blue, and hexacene and heptacene are green. Clar (11) suggested that the hydrocarbons were in equilibrium with free radicals, diyls. Thus,

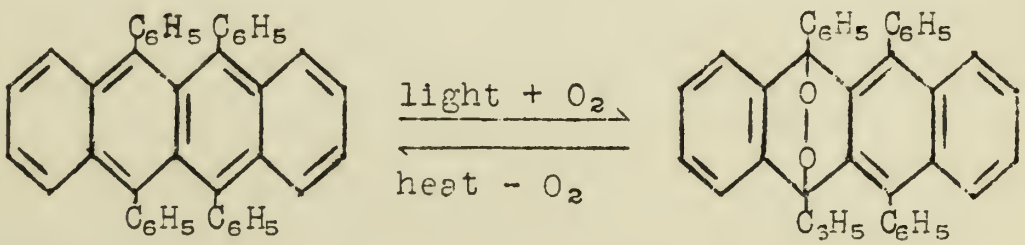


The free radicals would account for the color and reactivity of the hydrocarbons. Such an explanation seems improbable, for the substances do not exhibit paramagnetism (12); at best the diyl can be considered only as a transitory phase in reactions. An alternate interpretation (13) is that even the most stable possible arrangement of the double bonds in terms of the ordinary Kekulé formulation gives a pentacyclic system with three quinoid rings and a hexacyclic structure with four quinoid rings. The deepening in color in the series seems attributable to the accumulation of conjugated double bonds, particularly in the quinoid rings, and a somewhat analogous case is encountered in the series of the diphenylpolyenes.

Chemically, these hydrocarbons are very reactive and unsaturated. They combine rapidly, by addition (and are simultaneously decolorized), with oxygen, hydrogen, bromine and maleic anhydride.



The most spectacular property of these hydrocarbons, first noticed with rubrene (14) is the formation of a colorless photo-oxide ("dissociable oxide") when benzene or, better, carbon disulfide, solutions are shaken with air in the light. The photo-oxides undergo thermal dissociation with the liberation of oxygen.



Oxidation by chemical reagents results in the formation of mono or diquinones. The long conjugated systems of double bonds are partially or completely missing in the quinones, so that the unusual properties associated with the hydrocarbons are no longer encountered.

No carcinogenic activity has been observed with the linear polynuclear hydrocarbons.

BIBLIOGRAPHY

1. Clar, Ber., 75, 1271 (1942).
2. Schroeter, ibid., 54, 2242 (1921).
3. Dufraisse, Bull. soc. chim., 3, 1880 (1936).
4. Clar and John, Ber., 62, 3021 (1929).
5. Clar, ibid., 75, 1283, 1330 (1942).
6. Marschalk, Bull. soc. chim., 6, 112 (1939).
7. Moureu and Dufraisse, Compt. rend., 182, 1440, 1584 (1926).
8. Allen and Gilman, J. Am. Chem. Soc., 58, 937 (1936).
9. Wittig, J. prakt. chem., 160, 242 (1942).
10. Allen and Bell, J. Am. Chem. Soc., 64, 1253 (1942).
11. Clar, Ber., 63, 2967 (1930).
12. Muller and Muller-Rodloff, Ann., 517, 134 (1935).
13. Fieser, J. Am. Chem. Soc., 53, 2329 (1931).
14. Bergman and McLean, Chem. Rev., 28, 367 (1941). See also Herbrandson, Org. Chem. Sem., May 17, 1944, University of Illinois.

Reported by Lester Reed
November 8, 1944

CARBOXYLIC ACIDS OF MEDICINAL VALUE

(Karl Kindler, Universität Innsbruck)

Many substituted phenylacetic and phenylpropionic acids have proved to be active bactericides, and derivatives of these acids are important therapeutics. In order to make new acids of this type available, Karl Kindler developed several methods of synthesis.

Substituted Phenylacetic Acids

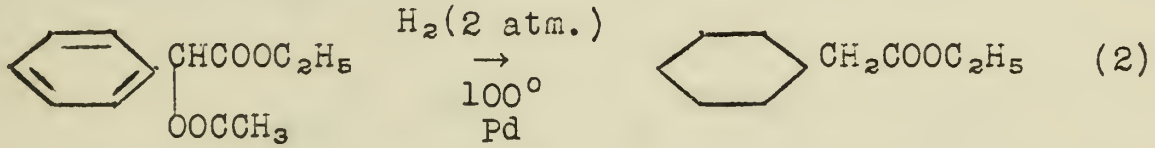
Substituted phenylacetic acids were prepared from readily available aldehydes according to the following equation.

$$\mathrm{ArCHO} \xrightarrow[\mathrm{KCN}]{\mathrm{C_6H_5COCl}} \mathrm{ArCH(OOCC_6H_5)CN}\ (\mathrm{I}) \xrightarrow[\mathrm{Pd}]{2\mathrm{H}} \mathrm{ArCH_2CN} + \mathrm{C_6H_5COOH} \qquad (1)$$

$$\mathrm{ArCH_2CN} \xrightarrow{\mathrm{H_2O}} \mathrm{ArCH_2COOH}$$

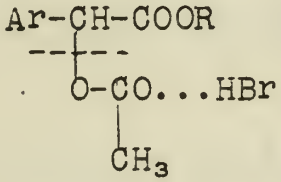
With tetralin as hydrogen donor and palladium black as catalyst, the nitriles were obtained in yields averaging 70 per cent.

Since amines were sometimes obtained as by-products in the above reduction, it was often desirable to convert the nitrile (I) into the ester before reduction. Reduction of the ester also presented difficulties, since molecular hydrogen was absorbed so rapidly that the hydroaromatic derivative resulted.



(2)

In compounds having an alkoxy group as substituent on the aromatic ring, the formation of the hydroaromatic compound was especially rapid. However, the reduction of the aromatic ring could be prevented by the addition of hydrobromic acid or $ZnCl_2$-HCl. The action of such an additive involved the formation of a molecular compound by coordination with the carbonyl oxygen.



(3)

This weakened the C-O bond indicated, and allowed the replacement of the acetate group by hydrogen.

Substituted phenylacetic acids were also prepared by hydrogenating the phenylglyoxylic esters obtained from the Friedel-Crafts reaction between ethyloxalyl chloride and an aromatic hydrocarbon or alkylaryl ether. Overall yields averaged 55 per cent.

$$ArH + ClCOCOOC_2H_5 \xrightarrow[C_6H_5NO_2]{AlCl_3} ArCOCOOC_2H_5 \xrightarrow[H_2SO_4]{Pd-H_2} ArCH_2COOC_2H_5 \qquad (4)$$

Substituted β-Phenylpropionic Acids

Esters of aromatic carboxylic acids condense with acetic ester in the presence of sodium to form aroylacetic esters. Kindler obtained β-phenylpropionic acids in 50-70 per cent yields by reduction of aroylacetic esters in the presence of concentrated sulfuric acid.

$$ArCOCH_2COOC_2H_5 \xrightarrow[Pd]{H_2} ArCHCH_2COOC_2H_5 \xrightarrow[H_2SO_4]{-H_2O} ArCH{=}CHCOOC_2H_5$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad (5)$$
$$\xrightarrow[Pd]{H_2} ArCH_2CH_2COOC_2H_5$$

β-Aryl propionic acids bearing easily reducible substituents such as halogens or alkylthio groups cannot be prepared in the above manner. Kindler developed a method of synthesis employing arylethyl ketones. Upon reaction with dimethylamine and sulfur, the ketones yielded N,N-dimethylthioamides, which were hydrolyzed to β-arylpropionic acids.

$$ArCOCH_2CH_3 \xrightarrow{NHR_2} ArC(NR_2)(OH)CH_2CH_3 \xrightarrow{S} ArC(S{:}NR_2)(OH)CH_2CH_3 \xrightarrow{-H_2O}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad (6)$$
$$\left[ArC(S{:}NR_2){=}CHCH_2.H\right] \rightarrow R_2N{-}C(=S){-}CH_2CH_2Ar \xrightarrow{H_2O} ArCH_2CH_2CO_2H$$

Aryl-substituted acetic acids were produced from arylmethyl ketones in a similar manner.

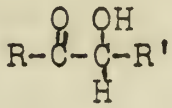
BIBLIOGRAPHY

Kindler and Peschke, Arch. Pharm., 271, 431 (1933)
Kindler and Gehlhaar, Arch. Pharm., 274, 377 (1936)
Kindler, Ber., 74, 315 (1941)
Kindler and Li, Ber., 74, 321 (1941)
Kindler, Metzendorf, and Dschi-yin-Kwok, Ber., 76, 308 (1943)
Kindler and Peschke, Arch. Pharm., 272, 236 (1934). (Synthesis of papaverine using the methods described above.)

Reported by Edgar Howard, Jr.
November 8, 1944

ACYLOINS

An acyloin, as considered in this seminar, will possess the type formula



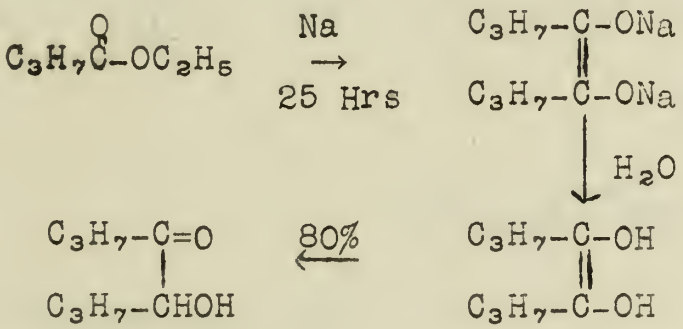
where R and R' are, in general, both aliphatic.

Acyloins are of interest both academically and industrially. Patents have been issued covering the preparations of cyclic acyloins useful as perfumes (1), and of sulfated acyloins which are suitable for use as dye-bath assistants in the textile industry. (2) Recently, attention has been called to the presence of the α ketol grouping in the side chains of sterols of the type of dehydrocorticosterone; subsequently compounds containing this grouping have been synthesized which possess biological activity (3).

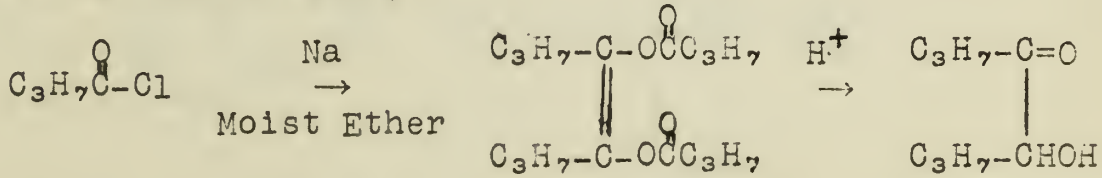
Preparation

Because synthetic methods of real value are few whereas specific preparations are many, only those of greatest interest will be considered.

1. Condensations using sodium.
   a. On esters (4).

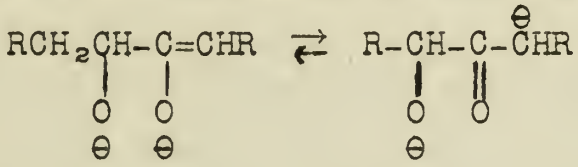


   b. On acid chlorides (5).

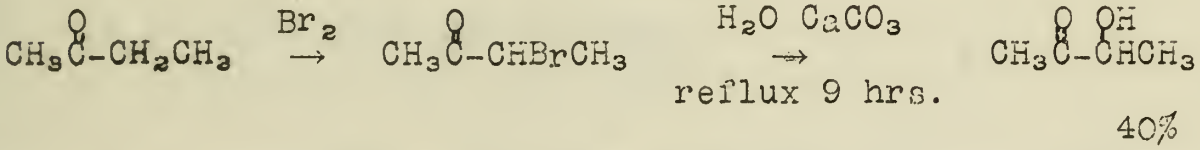


The preparation of acyloins using sodium and an ester is that employed by Organic Syntheses (6) for the preparation of butyroin, pivaloin, etc. The synthesis fails when used with unsaturated acid esters because of the formation of resins. The mechanisms of these reactions as first proposed and so listed above have been subjected to some criticism. Scheibler and Emden (8) believe that

RCONa=CONaR is an intermediate because treatment of a reaction mixture with ethyl bromide yields the 1,2-diethoxyethylene. Kharasch has developed the theory further and postulates other intermediates, but according to him this enolate is present in the reaction mixture (9). Woodward (10), however, cites some convincing proof that the enolate rather has the ionic form.



2. Hydrolysis of α-chloro ketones (11).

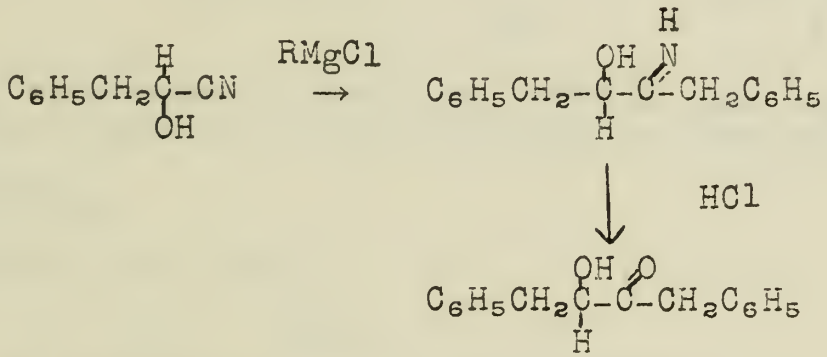


40%

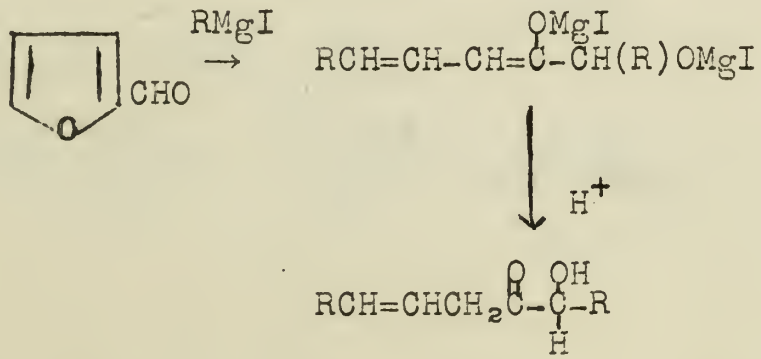
Although general, this method at times fails because of difficulties both in preparing the halogenated ketone and in the hydrolysis.

3. Action of Grignard Agents.

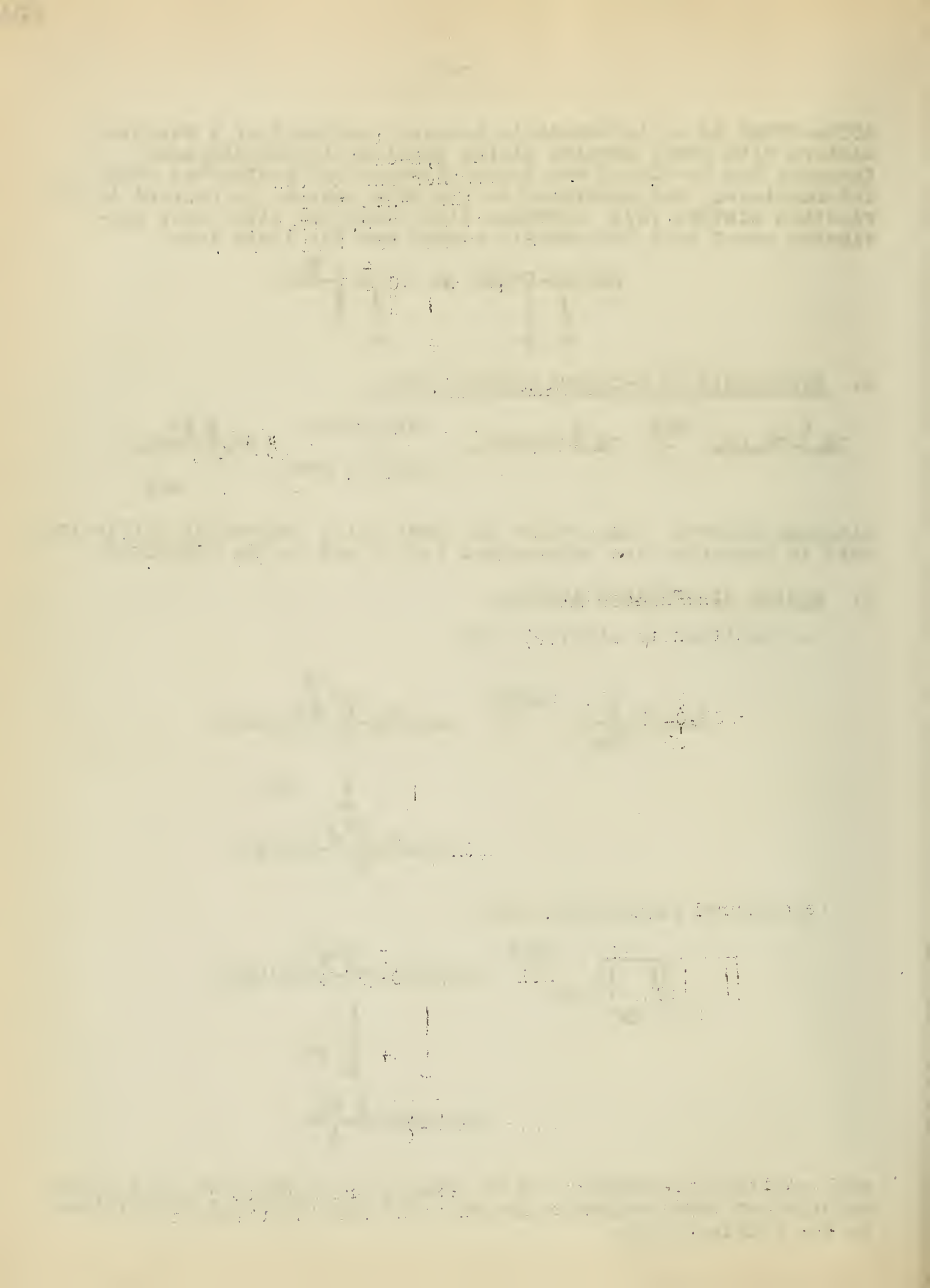
a. Addition to nitriles (12)



b. Use of furaldehyde (13).



This reaction is carried out by adding excess Grignard to a xylene solution of furaldehyde in the cold and then bringing the mixture to the boiling point.



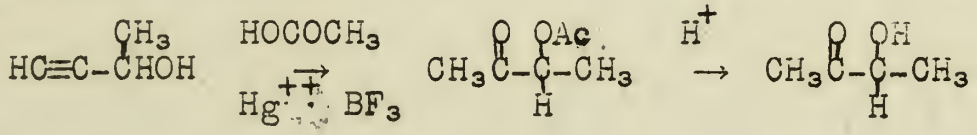
4. Enzymatic and Photochemical Preparation.

a. Addition of CH_3CHO to a yeast suspension containing glucose gives acetoin (14). Although the yields are poor (3-5%), it is possible that the process may be developed for there exists a German patent in which optically active acyloins are prepared by fermentation of o-hydroxybenzaldehyde in the presence of acetaldehyde and glucose (15).

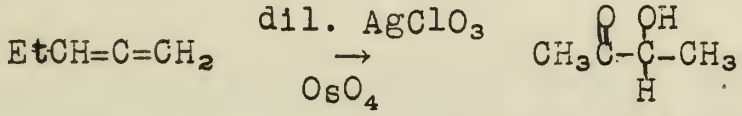
b. Aqueous solutions of pyruvic acid or acetaldehyde whe irradiated with ultra-violet light give acetoin in almost quantitative yields (16). This method has not as yet been extended to other acyloins with great success, although AcCHOHPh has been prepared in small yield by decomposing pyruvic acid in the presence of benzaldehyde.

5. Use of acetylenes and allenes.

a. Acetylenic compounds (17).



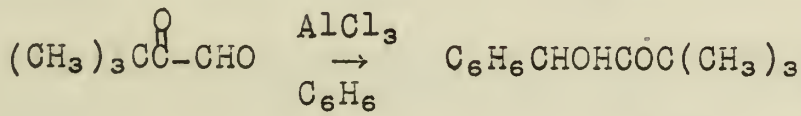
b. Allenes (18).



Commercially, compounds of the type, R-C≡C-R have been oxidized by H_2O_2 in the presence of OsO_4 in t-BuOH to give acyloins (19).

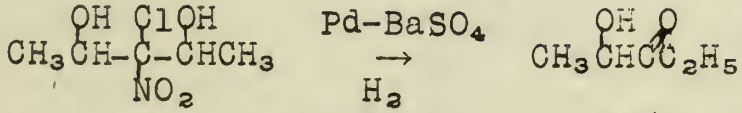
6. Miscellaneous.

a. Friedel Crafts (20).



52%

b. Reduction of $=CClNO_2$ (21).



60%

Reactions.

Acyloins may be considered as simple ketoses, this character being demonstrated both by the formation of osazones (22) with phenyl hydrazine, and the formation of compounds of glycosidic

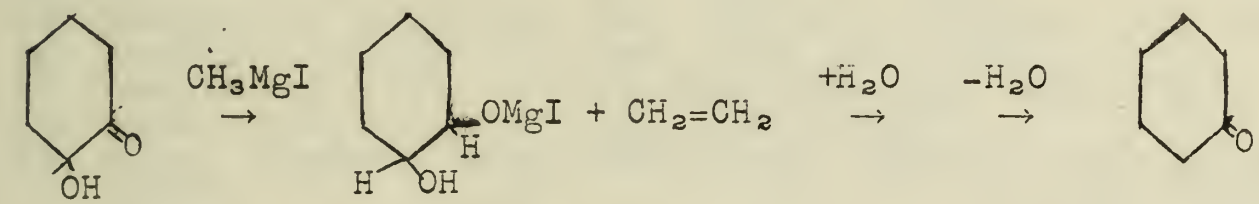
structure with CH_3OH (23).

Much work has been done on the isomerisation of acyloins and it has been found that traces of either acids or bases can cause the rearrangement: (24)

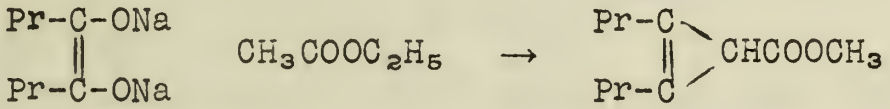
$$RCOCHOHR' \underset{\text{or } OH^-}{\overset{H^+}{\rightleftharpoons}} RCHOHCOR'$$

Oxidation studies using $Pb(OAc)_4$, HIO_4, and catalytic agents such as S_2O_2-H_3PO_4 have also been carried out on acyloins. The cleavage with $Pb(OAc)_4$ gives an acid and an aldehyde and proceeds only in the presence of H_2O, EtOH, or HCN (25).

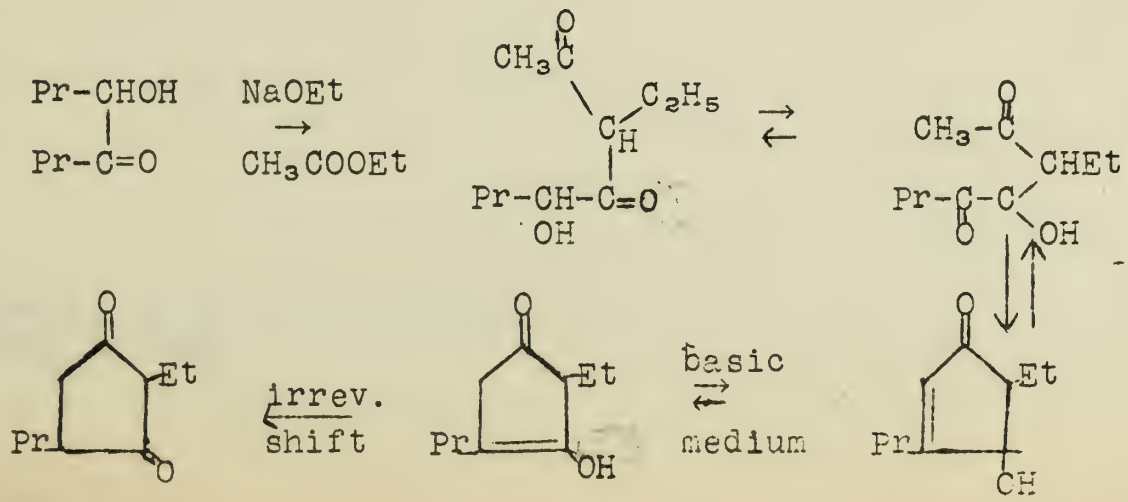
Some cyclic acyloins investigated by Katz (26) when treated with a Grignard underwent an interesting reaction.

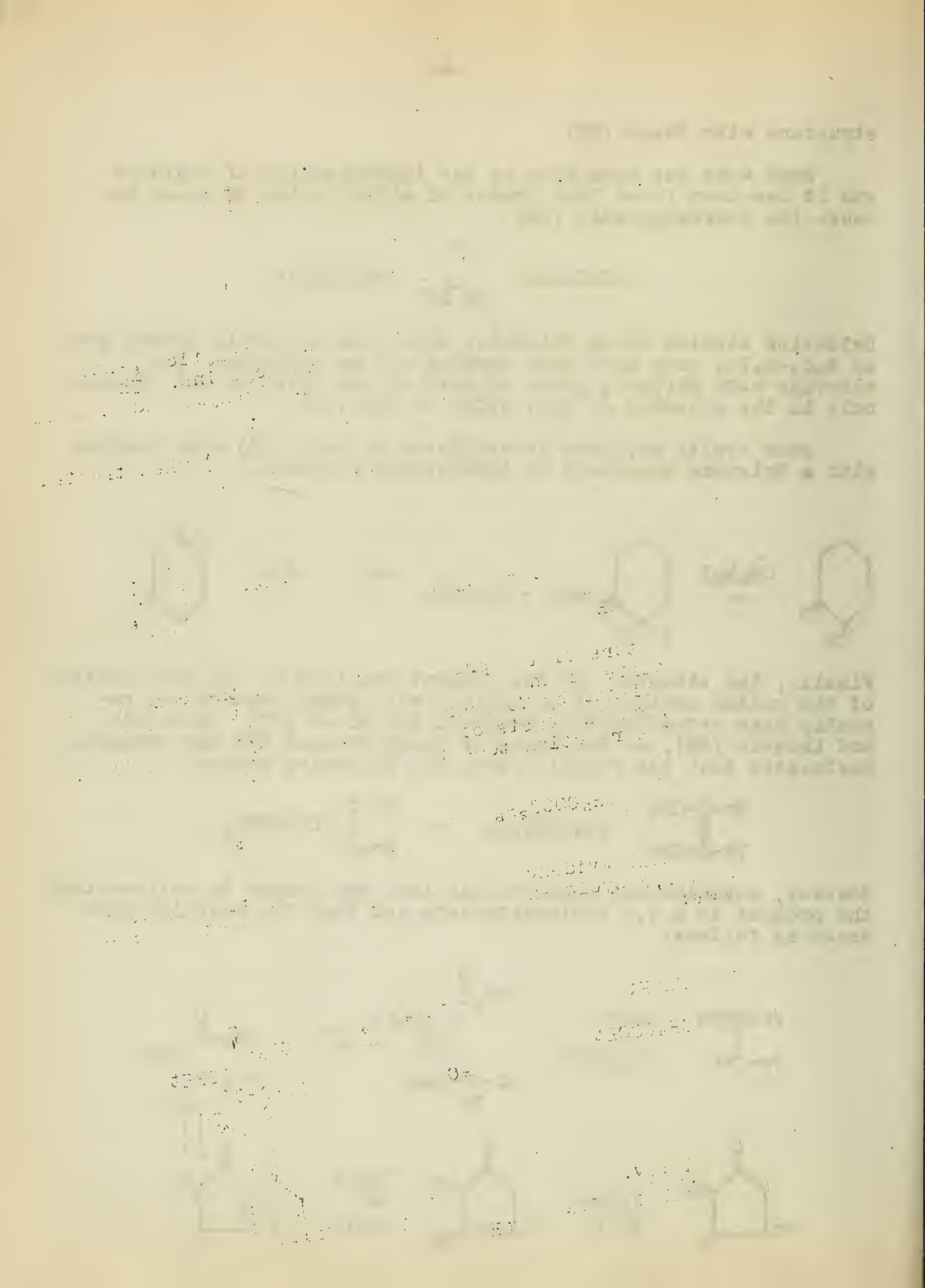


Finally, the structure of the product obtained by the condensation of the sodium enolate of an acyloin with ethyl acetate has recently been established by Woodward and Blout (27). Bouvealt and Locquin (28), on the basis of their formula for the enolate, postulated that the reaction took the following course:



However, experimental evidence has led the former to believe that the product is a 1,3 cyclopentadione and that the reaction proceeds as follows:

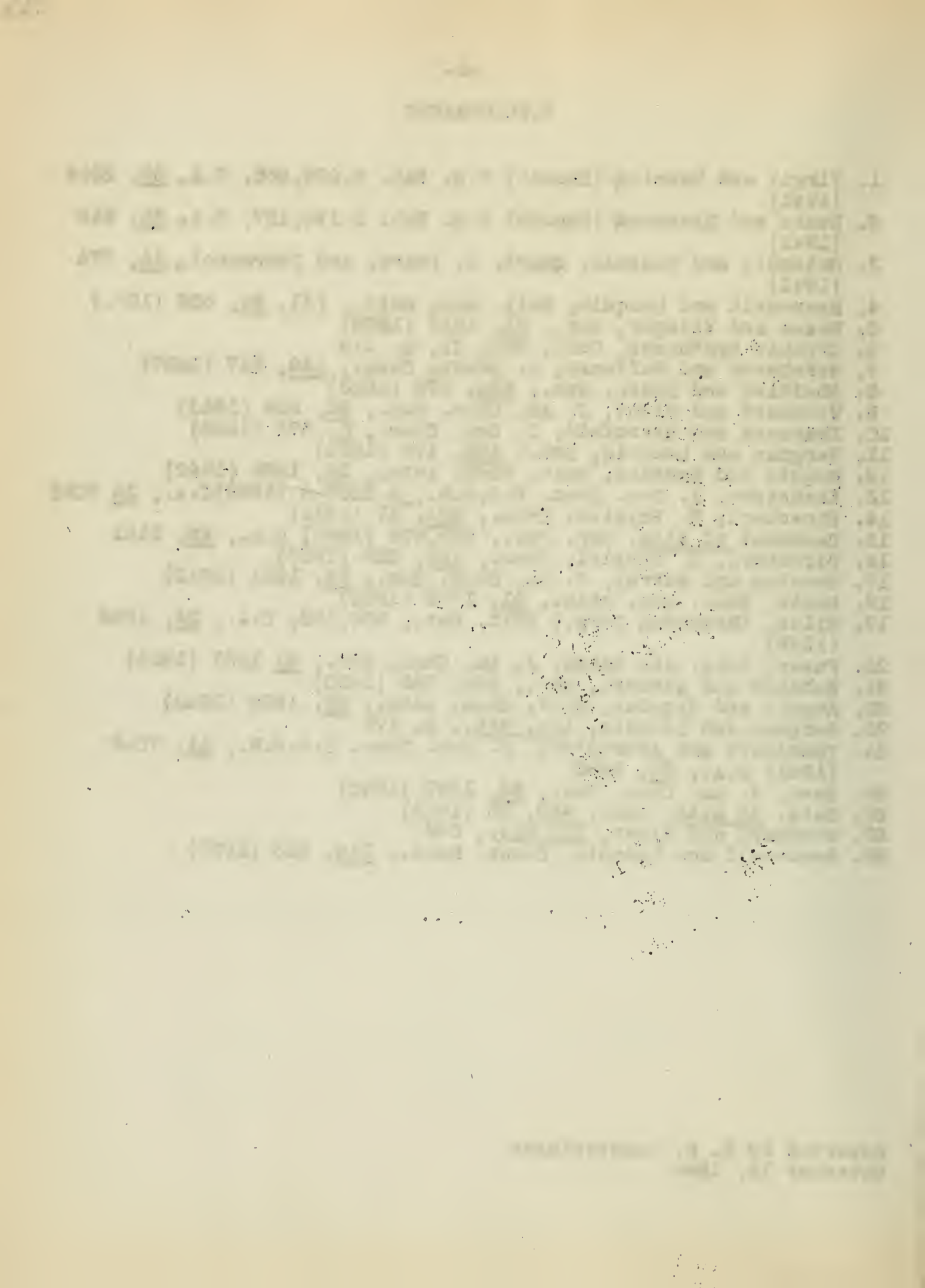




BIBLIOGRAPHY

1. Virgil and Hansley, (Dupont) U.S. Pat. 2,228,268, C.A., 35, 2534 (1941)
2. Henke and Redemond, (Dupont) U.S. Pat. 2,174,127, C.A., 35, 552 (1941)
3. Grinnell and Roushdi, Quart. J. Pharm. and Pharmacol., 14, 274 (1941)
4. Beauvealt and Locquin, Bull. soc. chim., [3], 35, 638 (1906)
5. Basse and Klinger, Ber., 31, 1217 (1898)
6. Organic Syntheses, Coll. Vol. II, p. 114
7. Bernhauer and Hoffmann, J. prakt. Chem., 149, 317 (1937)
8. Sheibler and Emden, Ann., 434, 272 (1923)
9. Woodward and Blout, J. Am. Chem. Soc., 65, 564 (1943)
10. Kharasch and Sternfeld, J. Org. Chem., 5, 373 (1940)
11. Bergman and Ludewig, Ann., 436, 178 (1924)
12. Ruggli and Hegedus, Helv. Chem. Acta., 25, 1289 (1942)
13. Kuznetsov, J. Gen. Chem. U.S.S.R., 9 2263-8 (1939) C.A., 34 5052
14. Dirscherl, Z. Physiol. Chem., 201, 47 (1931)
15. Bachmuhl et alia, Ger. Pat., 555,409 (1930) C.A., 26, 5101
16. Dirscherl, Z. Physiol. Chem., 188, 229 (1930)
17. Hennion and Murrey, J. Am. Chem. Soc., 64, 1221 (1942)
18. Bouis, Bull. soc. chim., 51, 1778 (1932)
19. Milos, (Research Corp.) Brit. Pat., 508,526, C.A., 34, 1032 (1939)
20. Fuson, Gray, and Ganza, J. Am. Chem. Soc., 61 1937 (1939)
21. Schmidt and Ascherl, Ber., 58B, 356 (1925)
22. Ruggli and Hegedus, Helv. Chem. Acta., 25, 1290 (1942)
23. Bergman and Ludewig, loc. cit., p. 175
24. Temnikova and Aforos'eva, J. Gen. Chem. U.S.S.R., 11, 70-6 (1941) C.A., 35, 6580
25. Baer, J. Am. Chem. Soc., 62, 1597 (1940)
26. Katz, et alia, Ann., 400, 58 (1913)
27. Woodward and Blout, loc cit., 563
28. Beauvealt and Locquin, Compt. Rend., 144, 853 (1907)

Reported by E. M. VanHeyningen
November 15, 1944



1. Preparations

Chloral can be prepared by passing Cl_2 into dry ethanol or acetaldehyde.

Chloral hydrate easily forms when water is added to chloral.

2. Distinction

Chloral is a colorless liquid freezing at -57.5°; chloral hydrate is a crystalline solid melting at 51.7°. It has been shown that the water in the hydrate is not held as water of crystallization. Chloral hydrate does not give the Fuchsin test. The two compounds also differ strikingly in their behavior toward aliphatic ortho esters (1).

$$CCl_3CH(OH)_2 + HC(OC_2H_5)_3 \xrightarrow[45\ min.]{Reflux} CCl_3CH(OH)OC_2H_5 + C_2H_5OH + HCO_2C_2H_5$$

Chloral does not react even in the presence of acid catalysts.

3. Reactions

a. Oxidation

$$CCl_3CHO \xrightarrow{HNO_3} CCl_3CO_2H$$

$$CCl_3CHO \xrightarrow[sunlight]{O_2(xs)} H_2O + Cl_2 + CO_2$$

b. Reduction

Zinc and hydrochloric acid act upon chloral to produce acetaldehyde while the reactive metal alkyls, such as aluminum ethyl, produce trichloroethanol in good yields (2).

The action of the Grignard reagent has been extensively studied. With RMgX compounds having groups like CH_3-, $C_6H_5CH_2$-, and C_6H_5- the main reaction is addition to the carbonyl group; those having the groups $C_6H_5(CH_2)_2$-, $C_6H_5(CH_2)_3$-, $C_6H_5(CH_2)_4$- reduce chloral to trichloroethanol (3).

The action of aluminum ethoxide on chloral produces trichloroethanol in 84% yield (4).

c. Polymerization

meta-Chloral, prepared by treating chloral with concentrated sulfuric acid below 0°, is an insoluble, amorphous solid of unknown constitution. The same reaction at 25° produces, in addition to meta-chloral, a small amount of α- and β-chloral. These are trimers and, presumably, are isomers of the cis-trans type (5).

d. Additions and Condensations

Chloral has much greater additive power than the ordinary aldehydes. It reacts normally with hydrogen cyanide, sodium bisulfite, acetic anhydride, and glycols. Stable intermediates can be isolated with hydroxylamine, alcohols, and semicarbazide.

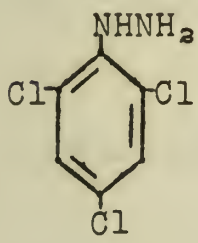
$$CCl_3CHO \xrightarrow{NH_2OH} CCl_3CH(OH)NHOH \xrightarrow{-H_2O} CCl_3C{=}NOH$$

$$CCl_3CHO \xrightarrow{C_2H_5OH} CCl_3CH(OH)OC_2H_5 \xrightarrow{C_2H_5OH} CCl_3CH(OC_2H_5)_2$$

$$CCl_3CHO \xrightarrow{H_2NNHCONH_2} CCl_3CH(OH)NHNHCONH_2 \xrightarrow[H_2O]{Hot} HOOCCH{=}NNHCONH_2$$

Ammonia reacts with chloral to form the stable chloral ammonia, $CCl_3CH(OH)NH_2$.

Phenylhydrazine reacts so rapidly that the reaction has been little studied. Halogen atoms on the phenyl nucleus moderate the reaction (6).



$$\xrightarrow[HCl]{Chloral,\ H_2O} RNHN{=}CHCCl_3 \rightleftarrows RN{=}NCH{=}CCl_2 + HCl$$

$$\Big\downarrow AcOH$$

$$RNHN{=}CHCOOH$$

Aliphatic amides and urethans form substituted ethers with chloral (7).

$$H_2NCOR(OR) \xrightarrow{chloral} CCl_3CH(OH)NHCOR(OR) \xrightarrow[Ac_2O]{NaOH} \begin{matrix} CCl_3CHNHCOR(OR) \\ O \\ CCl_3CHNHCOR(OR) \end{matrix}$$

α-Hydroxy acids form chloralides.

$$RCH(OH)COOH \xrightarrow{chloral} CCl_3CH\begin{matrix} O{-}CHR \\ | \\ O{-}CO \end{matrix}$$

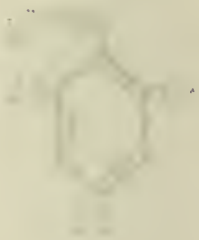
Carbonyl compounds containing active hydrogen undergo aldol condensations with chloral (8).

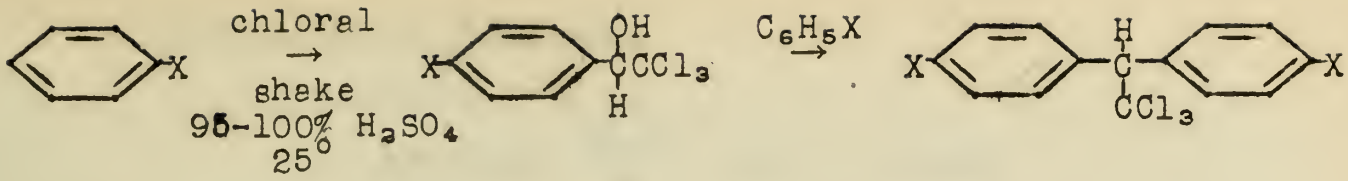
$$CH_3COCH_3 \xrightarrow{chloral} CCl_3CH(OH)CH_2COCH_3 \xrightarrow{H_2SO_4} CCl_3CH{=}CHCOCH_3$$

$$CH_3COCH_2CO_2C_2H_5 \xrightarrow[25^\circ,\ 5\ days]{chloral} CH_3COCHCO_2C_2H_5 \xrightarrow{\Delta} CCl_3CHO + CH_3COCH_2CO_2C_2H_5$$

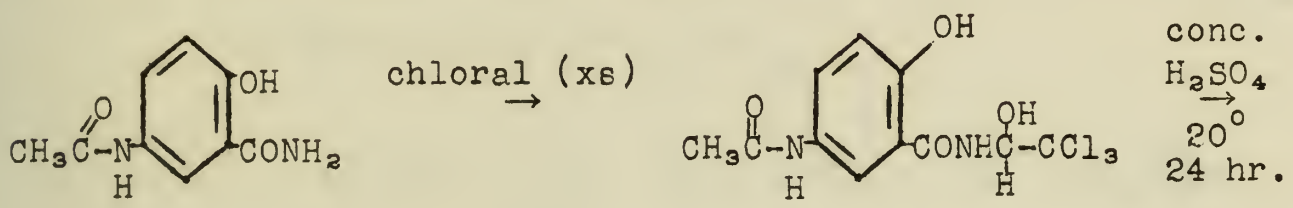
$$\begin{matrix} HCOH \\ CCl_3 \end{matrix}$$

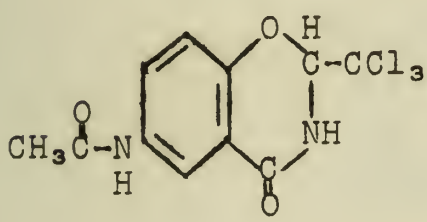
Aromatic hydrocarbons and halobenzenes react in two stages to produce diaryl-trichloro-ethanes (9).





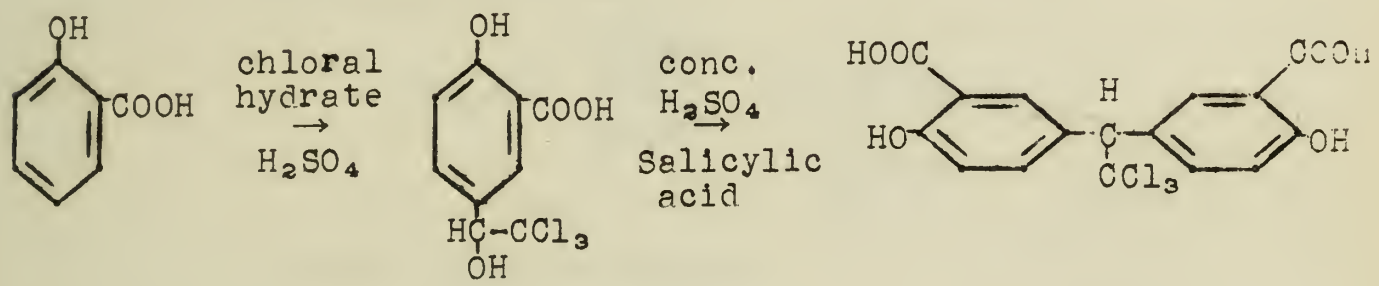
Benzamides add to form products of the type $ArCONHCH(OH)CCl_3$. Functional groups in the o-position may cause formation of cyclic compounds (10).





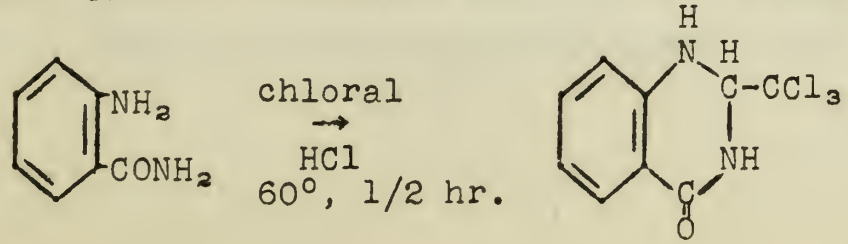
Some substituents in certain positions tend to inhibit condensation.

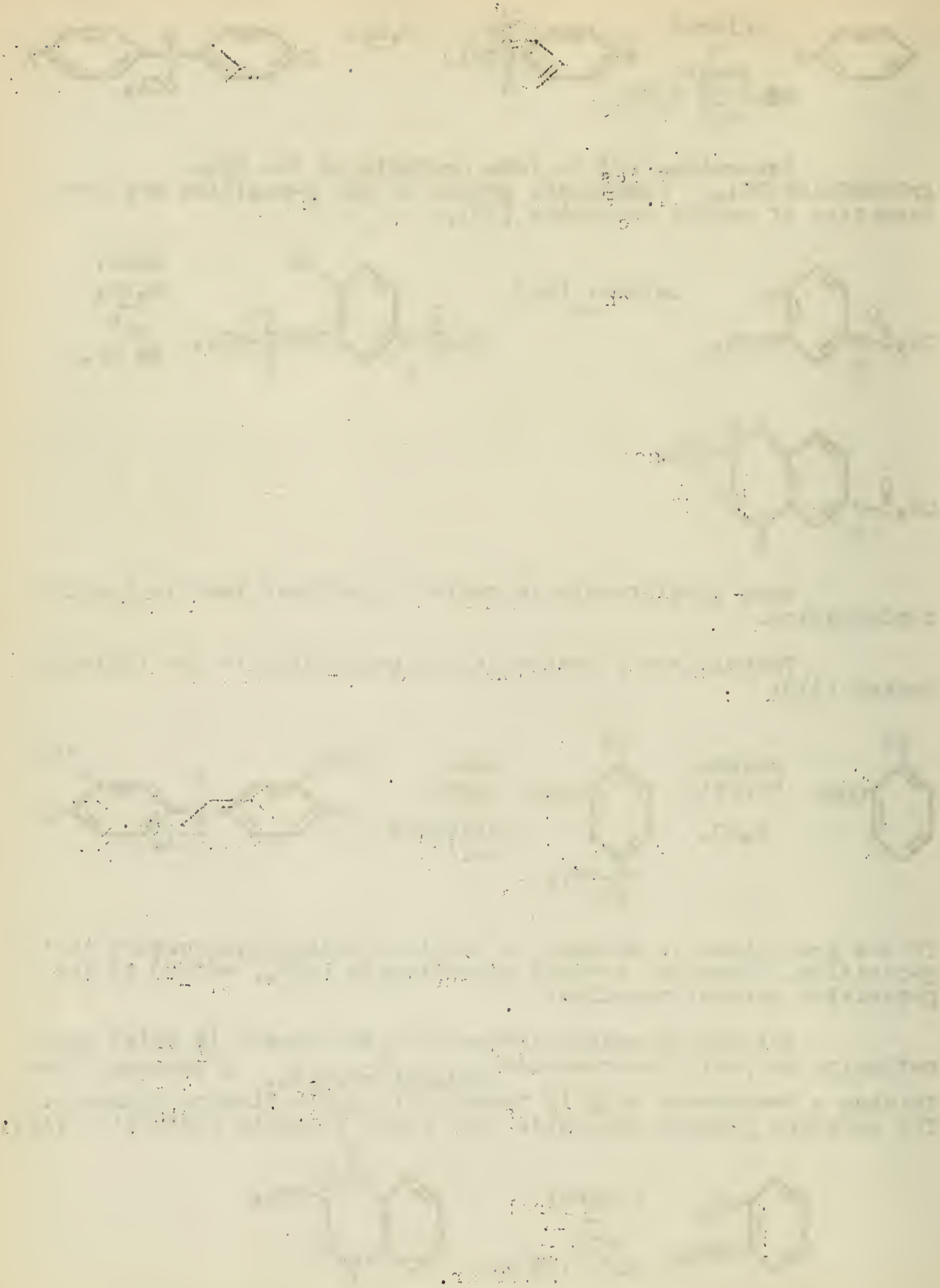
Phenols are attacked in the p-position in the following manner (11):



If the p-position is blocked, a similar condensation occurs in the o-position. However, certain substituents ($-NO_2$, -COOH) in the p-position prevent reaction.

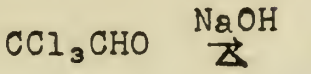
Aniline (2 moles) condenses with chloral (1 mole) upon refluxing to yield the compound $CCl_3CH(\overset{H}{N}\text{-}C_6H_5)_2$. A compound containing a 7-membered ring is formed with o,o'- diamino diphenyl. The compound o-amino benzamide also forms a cyclic derivative (12).



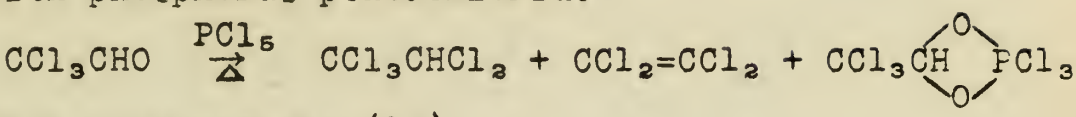


e. Miscellaneous Reactions

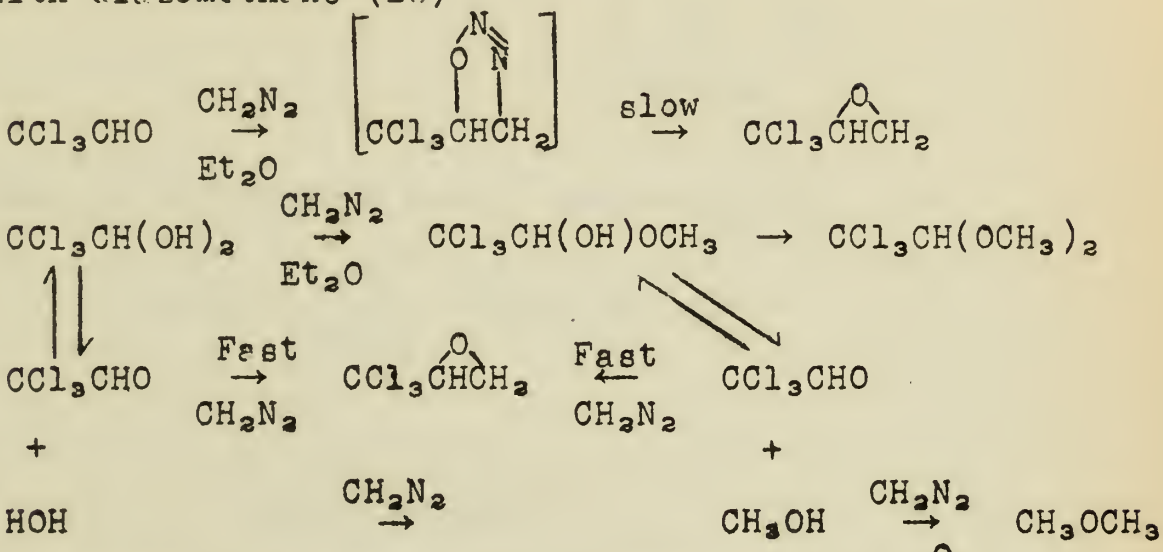
1. With alkali



2. With phosphorus pentachloride

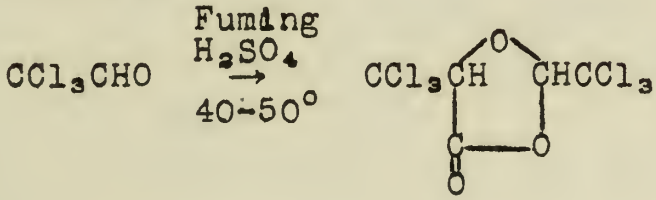


3. With diazomethane (13)

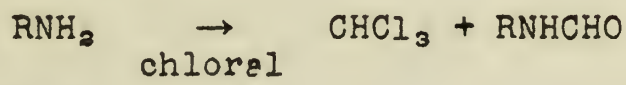


Chloral hydrate catalyzes the formation of CCl_3CHCH_2.

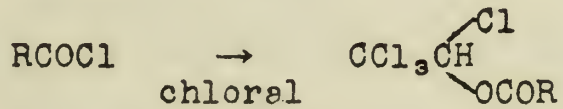
4. With sulfuric acid



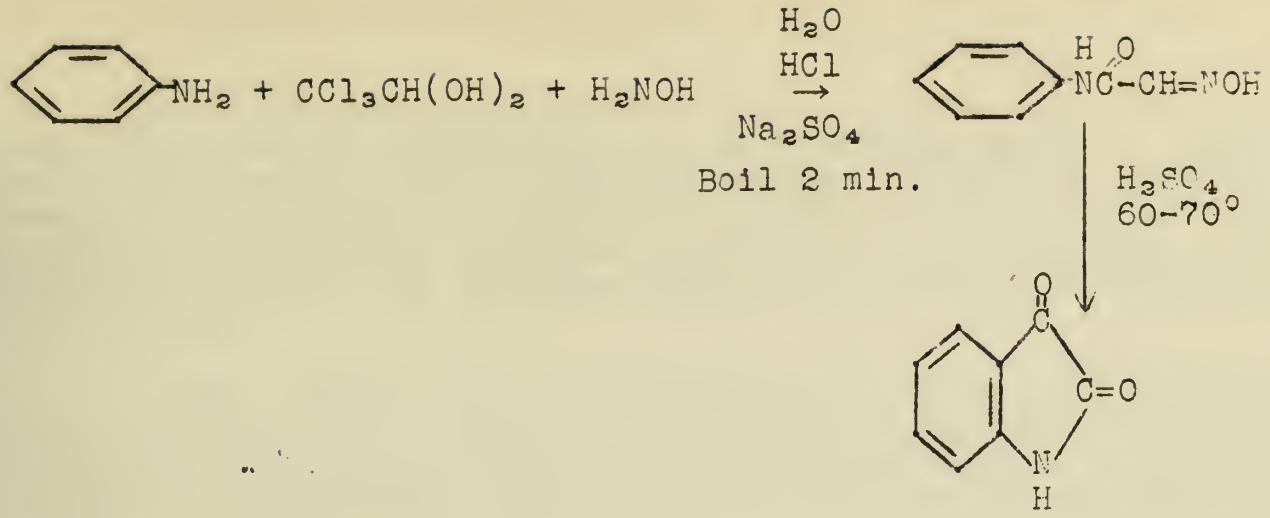
5. With aliphatic amines



6. With acid chlorides



7. With aniline and hydroxylamine (14).



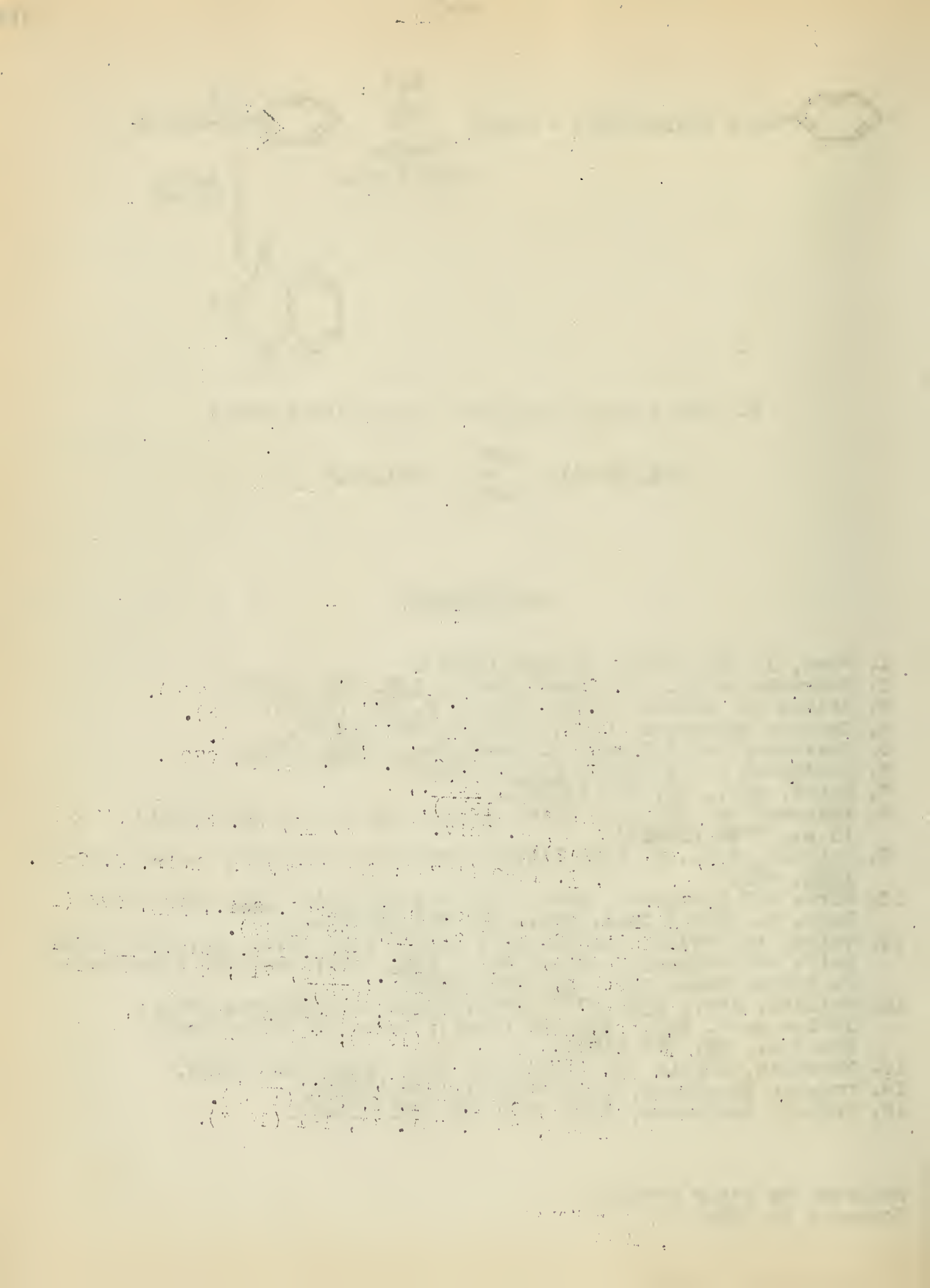
8. With calcium carbonate and sodium cyanide

$$CCl_3CH(OH)_2 \xrightarrow[CaCO_3]{NaCN} CHCl_2CO_2H$$

BIBLIOGRAPHY

1. Post, J. Org. Chem., 6, 830 (1941).
2. Meerwein et al., J. prakt. Chem., 147, 226 (1936).
3. Gilman and Abbot, J. Org. Chem., 8, 224 (1943).
4. Organic Syntheses, Coll. Vol. II, 598 (1943).
5. Chattaway and Kellett, J. Chem. Soc., 1928, 2709.
6. Chattaway and Kellett, ibid., 27568.
7. Feist, Ber., 45, 945 (1912).
8. Kulkarni and Shah, J. Univ. Bombay, 10, Pt. 3, 120 (1941). (C.A., 3795 (1942)).
9. Zeidler, Ber., 7, 1180 (1874); Chattaway and Muir, J. Chem. Soc., 1934, 701.
10. Hirwe and Deshpande, Proc. Indian Acad. Sci., 13A, 273 (1941); Rana, J. Indian Chem. Soc., 19, 299 (1942).
11. Valvet and Mejuto, Anales soc. espan. fis. quim., 34, 641 (1936); Balfe and Webber, J. Chem. Soc., 1942, 718; Shah and Alimchandani, J. Indian Chem. Soc., 13, 475 (1936).
12. Wallach, Ann., 173, 274 (1874); Hirwe and Kulkarni, Proc. Indian Acad. Sci., 13A, 49 (1941); Weiss and Chledowski, Monatsh., 65, 357 (1935).
13. Meerwein, Bersin and Burneleit, Ber., 62B, 999 (1929).
14. Organic Syntheses, Coll. Vol. I, 327 (1941).
15. Organic Syntheses, Coll. Vol. II, 181 (1943).

Reported by Peter Kovacic
November 15, 1944



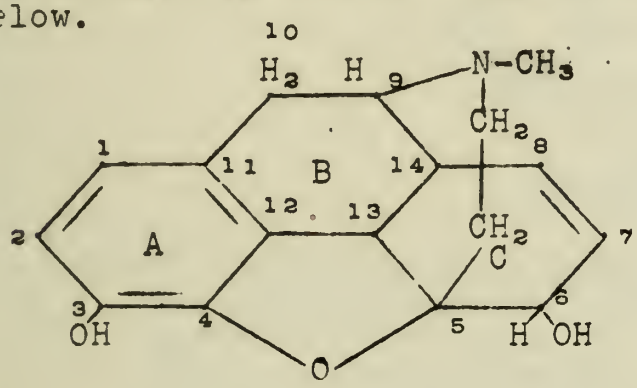
MORPHINE CHEMISTRY

(Knorr, Wieland, Robinson, Schöpf, Grewe, Fieser)

Opium contains approximately twenty alkaloids. These opium alkaloids can be divided into two well-defined groups: (1) The Papaverine group, (2) The Morphine group. Morphine, the most important of the opium alkaloids, is the one to which most of the physiological effects of opium are due. In this seminar, only morphine, codeine and thebaine (part of the morphine group) will be discussed.

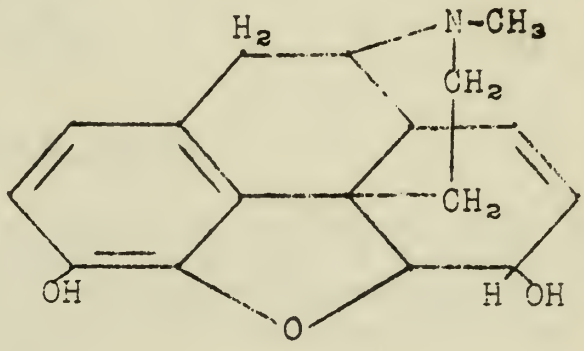
In 1803, Derosne (1) by extraction of opium with water and precipitation of the extract with potassium carbonate obtained a crystalline substance which he named salt of opium. Serturner (2) of Einbeck in Hannover described the isolation of the pure base in 1805.

In spite of the numerous attempts to interpret the enormous amount of research on morphine in terms of a structural formula, the constitutional problem of morphine must still be regarded as not completely solved. The two most probable structures are given below.



I

Knorr-Horlein (1907) as modified by Wieland and Kotake (1925)



II

Gulland and Robinson (1925)

Evidence for the Knorr-Wieland formula and the Robinson formula is summarized below.

(1) Empirical formula: $C_{12}H_{19}O_3N$
   (a) Eykman (3) and Von Klobukow (4) (also confirmed by other investigators)

(2) Morphine contains a phenolic hydroxyl group:
   (a) Morphine (5) dissolves readily in alkalies to form metallic salts.
   (b) Morphine (6) gives a good ferric chloride test for phenols.

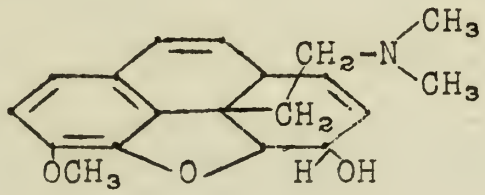
(3) Morphine contains an alcoholic hydroxyl group.
   (a) Morphine on gentle treatment with acid chlorides or anhydrides suffers replacement of two hydrogen atoms with acyl groups (heroin).

(b) Phosphorus pentachloride (7) and thionyl chloride (8) yield a chloromorphide with the retention of a phenolic hydroxyl group.

(c) Methylation of morphine yields codeine with no phenolic properties. Excellent methods of methylating morphine are described in the patent literature (9,10,11).

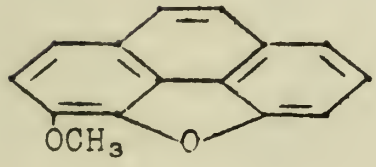
(4) Morphine contains a phenanthrene nucleus. The nitrogen on codeine and morphine is bound in a ring and carries a methyl group.

(a) Exhaustive methylation: The methiodide of morphine itself cannot be degraded by the usual Hofmann method because of the tendency of the quaternary ammonium hydroxide to form a phenol-betaine type of compound. Codeine methiodide, when boiled with dilute alkali, yields α-methylmorphimethine (III).

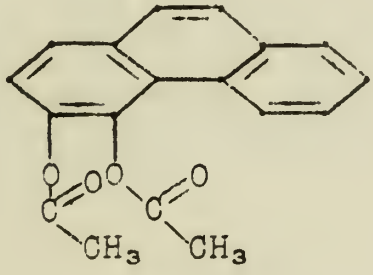


III
α-Methylmorphimethine

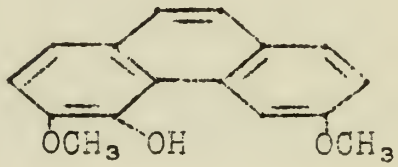
(b) The methohydroxide (12,13) of III does not break down in the manner expected in the normal course of a Hofmann degradation but loses the entire nitrogen-containing side chain as trimethylamine, ethylene and water. The other product is methylmorphenol (IV).



IV
Methylmorphenol



V
Diacetylmorphol



VI
Thebaol

(c) Diacetylmorphol (14,15) (V) is formed when morphine methiodide or α-isomorphine methiodide is heated with acetic anhydride.

(d) The high hydrogen content indicated that the phenanthrene nucleus in these bases must be partially hydrogenated.

(5) The position of the oxygen atoms in morphine.

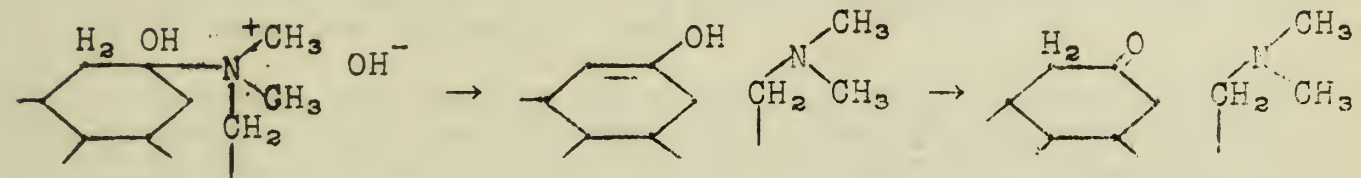
(a) The determination of the structure of methylmorphol and theboal (VI) made certain the position of two of the oxygen atoms in morphine and of all three in thebaine. The relation between thebaine and codeinone (16) also was known and conversion of the latter to methylthebaol (3,4,6-trimethoxyphenanthrene) indicated the location of all the oxygen atoms in morphine.

(6) The attachment of the nitrogen atom to the phenanthrene nucleus.

(a) Pschorr, Pfaff and Herrschmann (17) proved that the ethanamine chain could not be attached to the nucleus through oxygen.

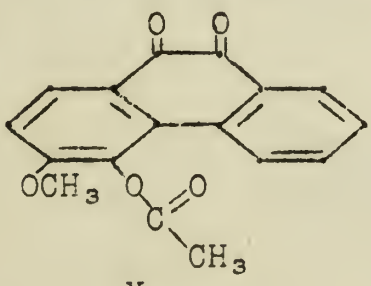
(b) Knorr and Pschorr (18) concluded in 1905 that the three morphine alkaloids are derivatives of 3,6-dihydroxyphenanthylene oxide in which an ethanamine chain (CH_2-CH_2-N-CH_3) is attached to a partially reduced aromatic ring.

(c) 1. By degradation of hydroxycodeine, Knorr (19,20) was able to show that the ethamine chain is linked through nitrogen to one of the hydrogenated bridge carbon atoms, C (9) or C (10).



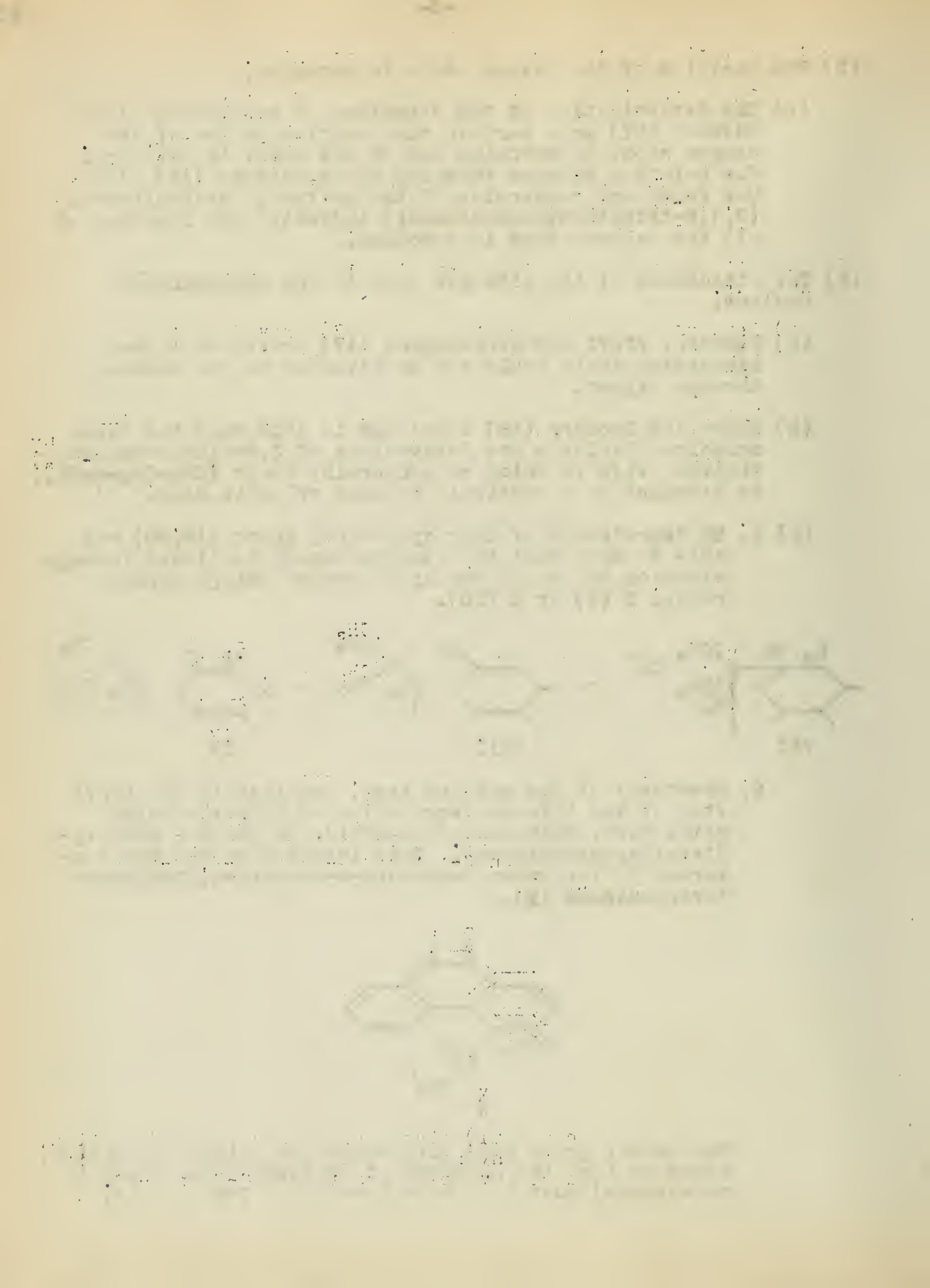
VII VIII IX

2. Treatment of the methine base, obtained in the first step of the Hofmann degradation of hydroxycodeine methiodide, with acetic anhydride produces a methoxydiacetoxyphenanthrene. This latter compound was converted to the known 3-methoxy-4-acetoxy-9,10-phenanthrenequinone (X).

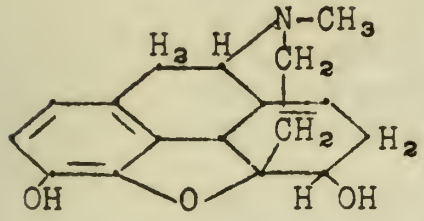


X

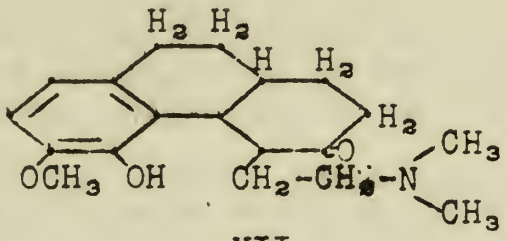
One acetyl group (21) disappeared in quinone formation, hence it (and the hydroxyl of hydroxycodeine which it represents) must have been located on C-9 or C-10.



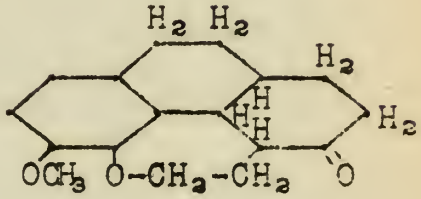
(7) A study of the isomeric codeines caused Knorr (20) to propose the following formula (XI) which dominated for nearly 20 years the theory of morphine structure.



XI
Knorr-Horlein, 1907



XII



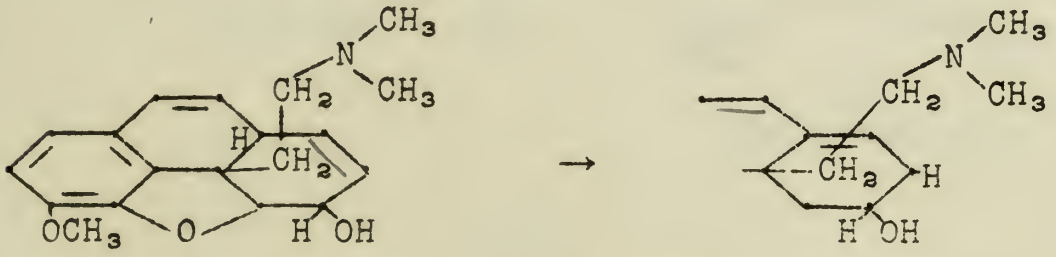
XIII

(8) Further studies on the attachment of the nitrogen-containing ring to the phenanthrene nucleus.

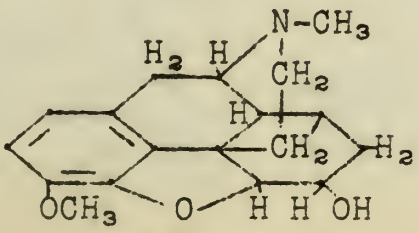
(a) Wieland (22,23) advanced the following argument for locating the nitrogen ring on C-5 in ring C in the phenanthrene nucleus. The ketone (XII) was prepared from tetrahydromethylmorphimethine or from dehydrothebaine by methods which, presumably, do not cause a shift in the side chain. The ketone could be degraded to thebenone (XIII), showing that the side chain must be in a position favorable for ring closure with the phenolic hydroxyl at C-4 (i.e., it must be on C-13 or C-5).

However, the ketone (XII) yielded only one condensation product with benzaldehyde or piperonal, as did thebenone. If the side chain is attached to C-13, the presence of two active methylene groups adjacent to the carbonyl group should make possible formation of more than one such condensation products.

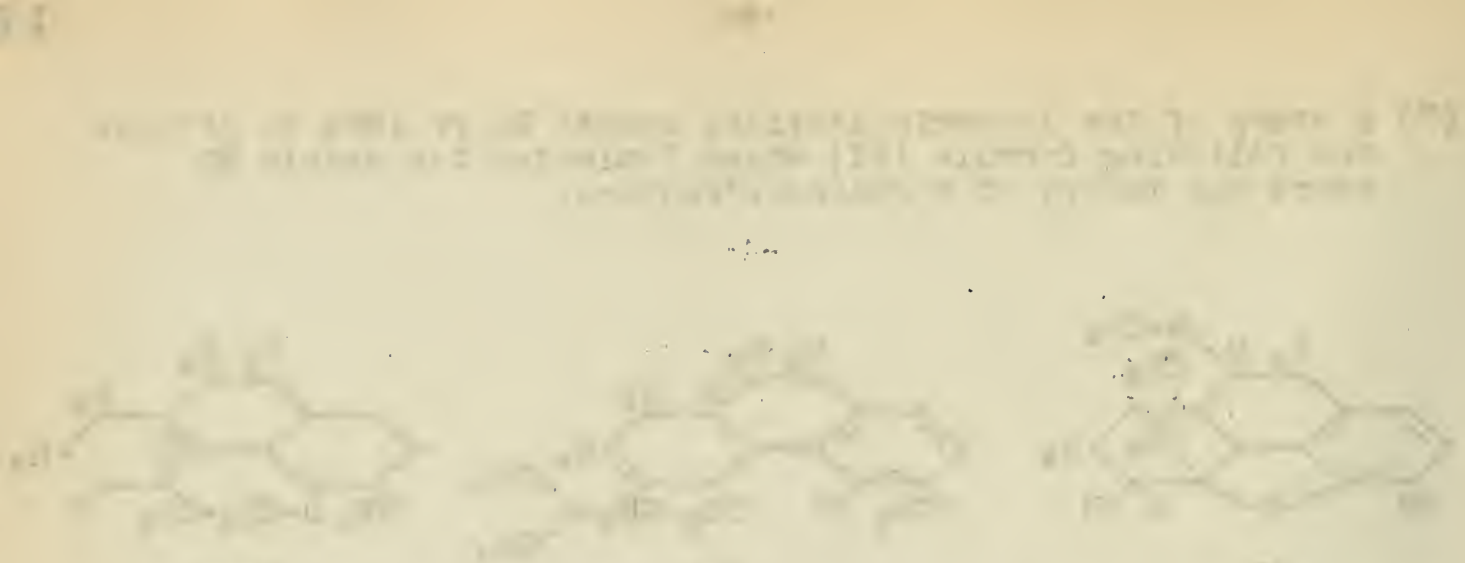
(9) The double bond in ring C was placed between C-7 and C-8. This clarified the relationship of the isomeric methylmorphimethines. The change from α-methylmorphimethine (XIV) to β-methylmorphimethine (XV) consists solely of a shift of the double bond to a position of conjugation, from C-7,8 to C-8,14.



XIV XV

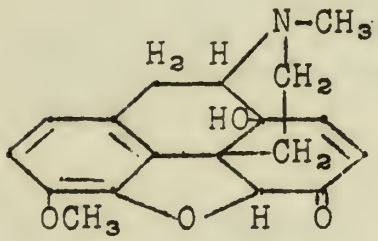


XVI

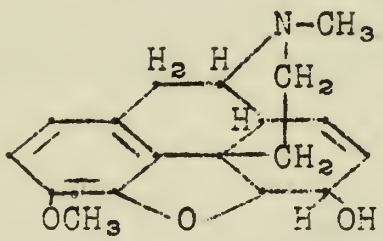


(10) The Robinson Formula

(a) Speculation in regard to the products from many degradative process led Robinson (24) to propose a new formula (XVI) for codeine in 1923. However, Gulland and Robinson (25) showed that hydroxycodeinone did not contain the group ($-\overset{O}{\overset{\|}{C}}-CH_2-$) but that dehydrohydroxycodeinone did. These facts are best explained by the presence of the arrangement $-\overset{O}{\overset{\|}{C}}-CH=C-\overset{OH}{\overset{|}{C}}-$ in hydroxycodeinone. It follows that codeine would contain the system $-\underset{OH}{CH}-CH=CH-CH-$ and not the bridge linkage previously proposed in XVI. This is in better accord with the ease of hydrogenation of codeine and its addition of two hydroxyl groups with permanganate in the manner of a substance containing an ethylenic bond. Therefore, codeine was assigned formula XVIII.



XVII
Hydroxycodeinone

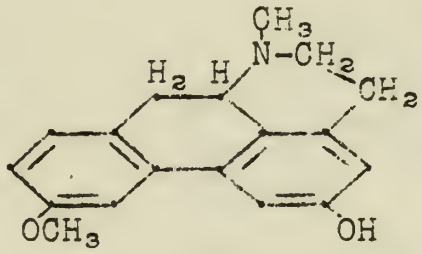


XVIII
Codeine
(Gulland-Robinson, 1925)

(11) The experiments of Schöpf.

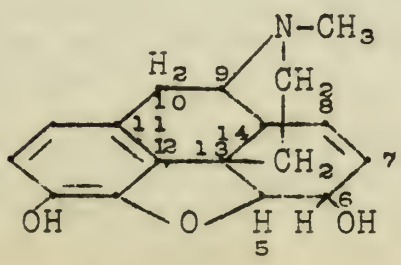
(a) According to Schöpf's (26) speculation, the Robinson formula is capable of explaining in a reasonable way the remarkable changes of thebaine or codeinone to morphothebaine (XIX), and of morphine to apomorphine (XX).

(A) Codeinone / Thebaine $\xrightarrow{\text{fuming HCl}}$

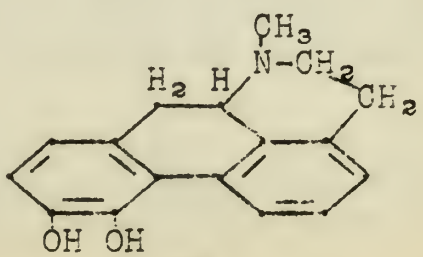


XIX
Morphothebaine

(B)

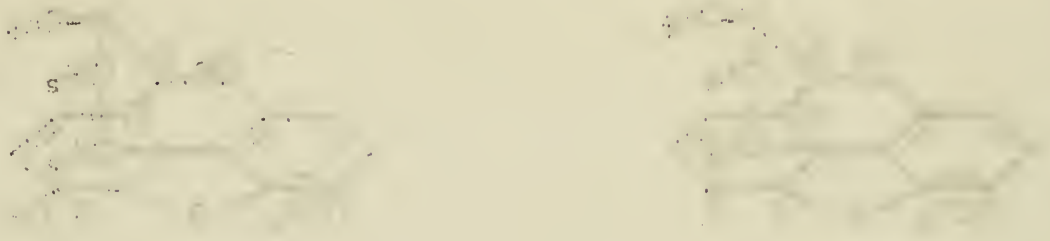


$\xrightarrow{\text{strong acid}}$



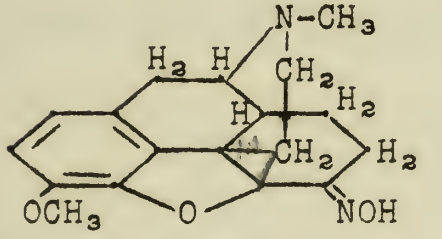
Morphine

XX
Apomorphine

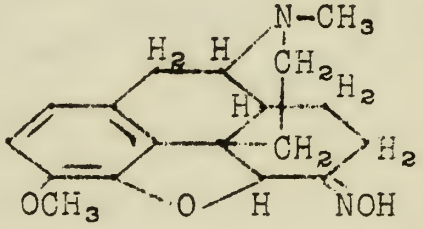


Reaction A is assumed to take place through hydrolysis of the enol ether group of thebaine, and addition of hydrogen chloride to the 8,14-double linkage followed by a rearrangement, whereby the ethanamine chain shifts from C-13 to C-14. The tendency of ring III or C to become aromatic on heating with concentrated hydrochloric acid forces a further shift of the side chain from C-13 to C-8, resulting in morphothebaine. The formation of apomorphine (XX) (reaction B) also is explained in a similar manner. The first step, loss of water from ring III (ring C) of morphine, results in two conjugated double linkages, and the tendency for aromatization is then strong enough to cause a shift of the side chain from C-13 to C-8.

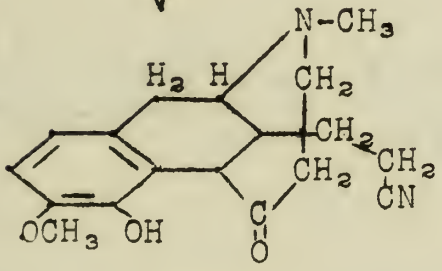
(b) Schopf (27) sought to obtain direct evidence for the location of the ethanamine chain by subjecting dehydrocodeinone (XXI or XXII) oxime to a Beckman rearrangement. If the Robinson formula is correct the isooxime resulting must be an aldehyde (XXIV) whereas if the Knorr-Wieland formula is correct a ketone must be obtained (XXIII).



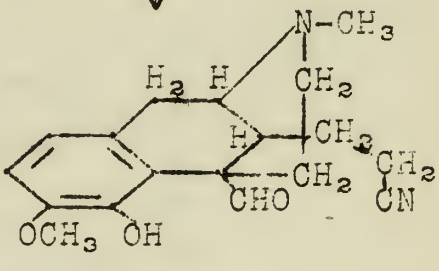
XXI



XXII



XXIII



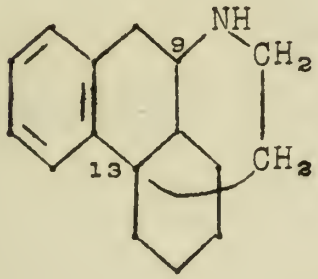
XXIV

Neither the isooxime itself nor its methyl ether yielded the desired proof, and only after a long series of transformations could the conclusion be drawn that the isooxime must have an aldehyde structure as in the Robinson formula.

The formula of Gulland and Robinson, while as yet not established beyond dispute, probably accounts best for the complicated array of evidence accumulated in the field of morphine chemistry.

B. Synthesis Which Might Lead to a Morphine Ring System

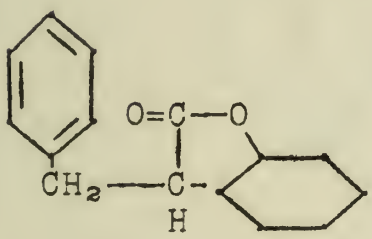
The fundamental morphine nucleus (XXV) has not yet been synthesized; however, partially hydrogenated phenanthrene derivatives with substituents at the 9 and 13 carbon atoms have been prepared with the obvious intent of synthesizing the morphine ring structure. It should be possible to synthesize system XXV from 9-13 substituted derivatives provided that one of the groups contains nitrogen, and provided that the two groups can undergo ring closure.



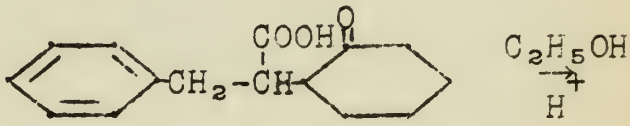
XXV

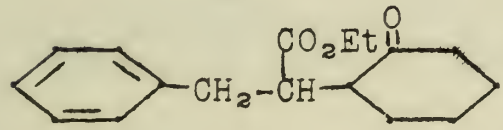
Rudolph Grewe, a former student of Wieland now at the University of Gottingen, has synthesized several 9-13 substituted partially hydrogenated phenanthrene derivatives (28-32). A typical synthesis is that of 13-methyl-6,7,8,9,10,13,14-octahydrophenanthrene-9-carboxylic acid (XXVI) (29).

1. 

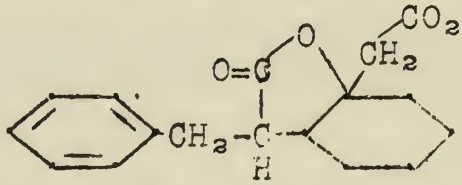


saponified
then 150° in vac.



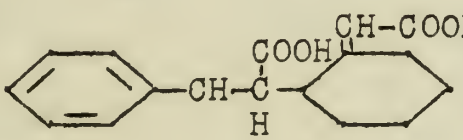


Reformatsky
$BrCH_2COOEt$

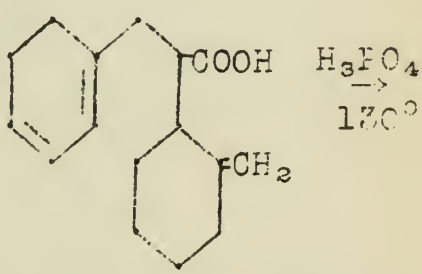


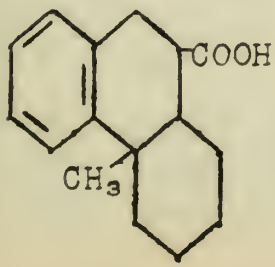
75%

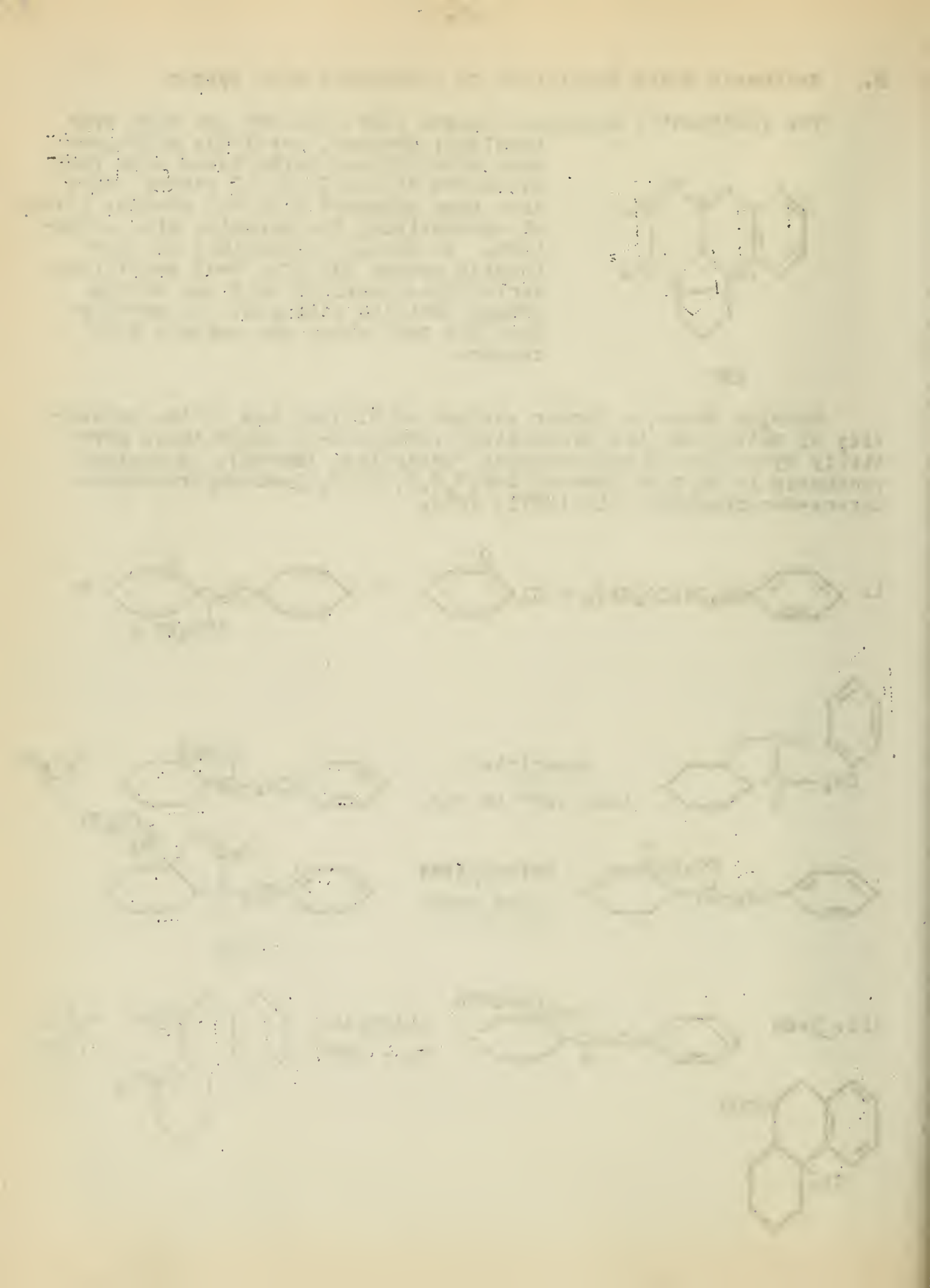
dil. NaOH



quinoline
Cu - 200°

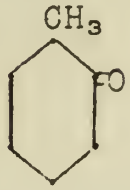
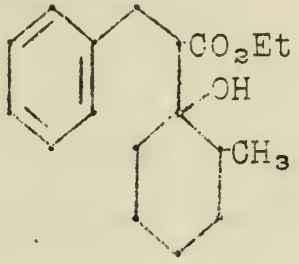


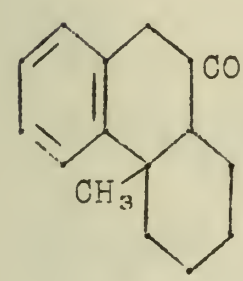
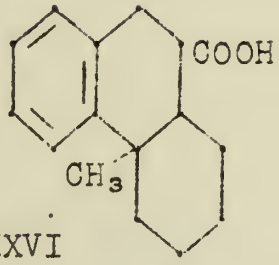




2. A second and more satisfactory scheme for XXVI (32) is outlined below.

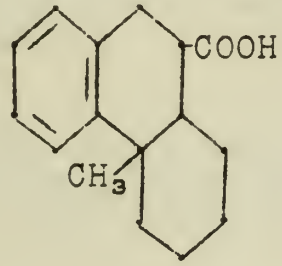
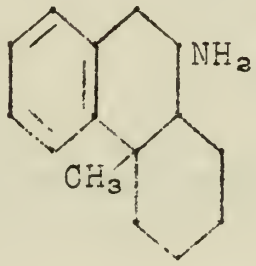
$PhCH_2CH(CO_2Et)_2 \xrightarrow[100^\circ]{KOH} PhCH_2CH(CO_2H)_2 \xrightarrow{Br_2} PhCH_2CBr(CO_2H)_2 \xrightarrow{120^\circ}$

$PhCH_2CHBrCOOH +$  $\xrightarrow[45\%]{\text{Reformatsky}}$  $\xrightarrow[90^\circ]{H_3PO_2}$ 71% yield

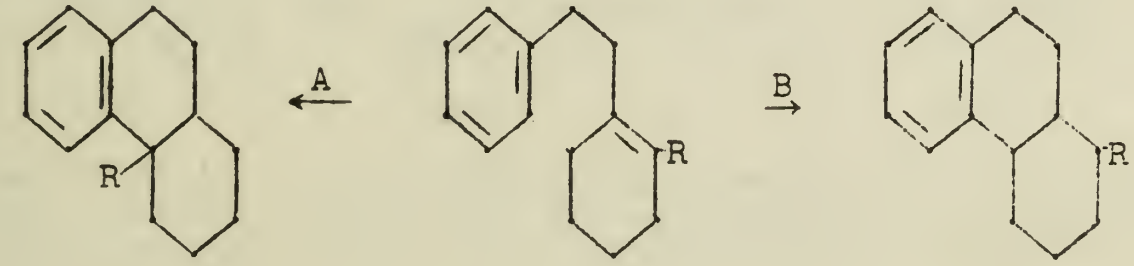
 $\xrightarrow{hyd.}$ 

XXVI

In this 9-methyl-13-carboxy derivative (XXVI), Grewe succeeded in replacing the carboxy group with an amine group (32).

 $\xrightarrow[60\%]{\text{Curtius}}$ 

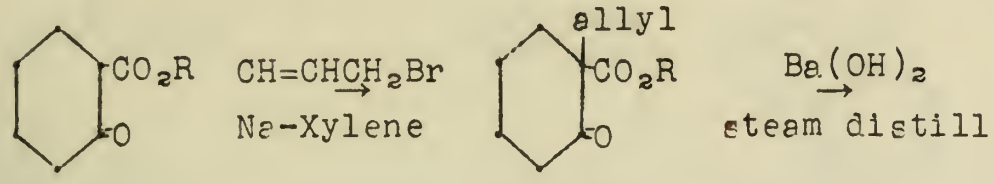
Attempts to substitute polar groups for the methyl group at C_{13} led exclusively to 1-substituted phenanthrene derivatives according to scheme B (30).

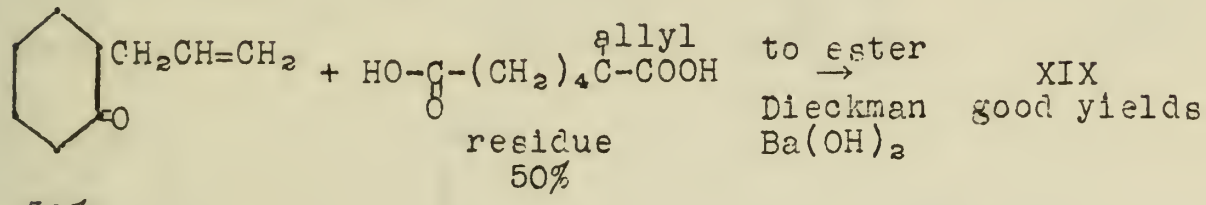


XXVII XXVIII

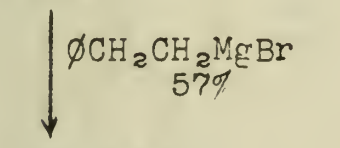
XXVII was synthesized where R is $-CH_2CH_2N(CH_3)_2$ and $-CH_2COOH$ by a scheme analogous to that described below to prepare compound XXX (30,31).

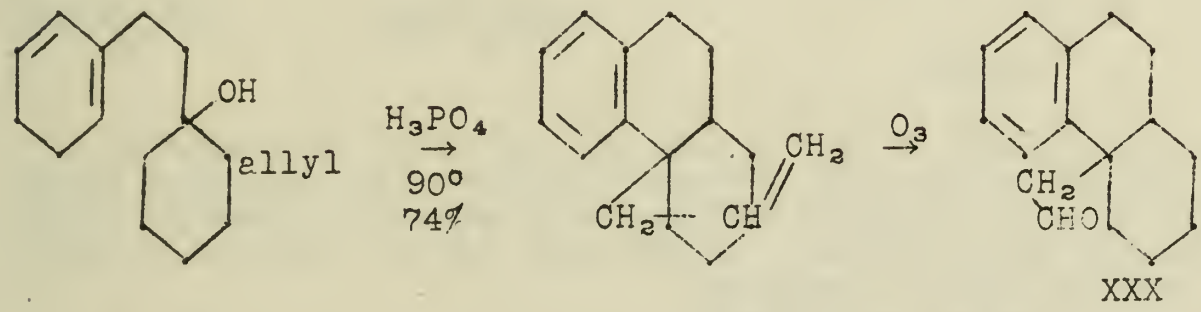
A very interesting synthesis involving the non-polar allyl group led to the 9-acetaldehyde derivative (XXX) (31).



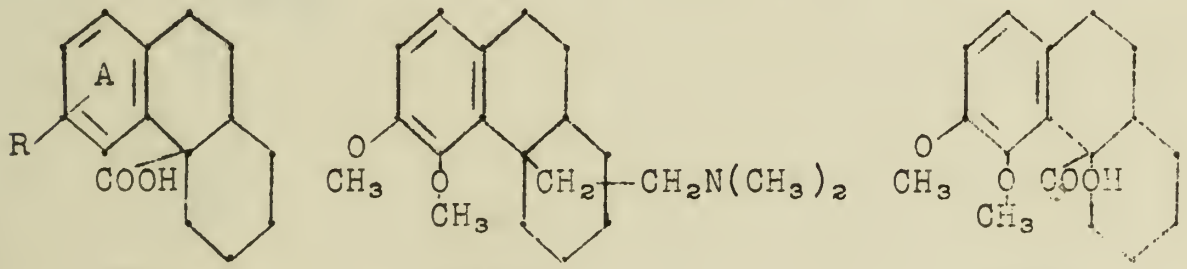


50%
XIX

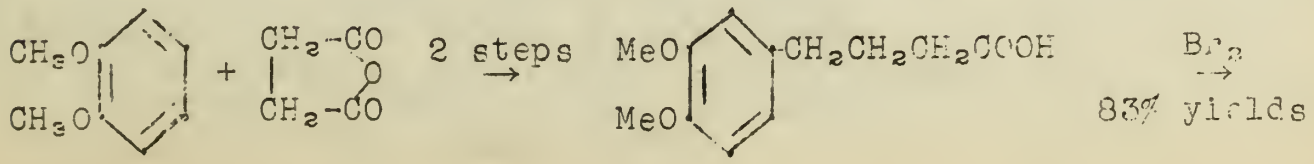


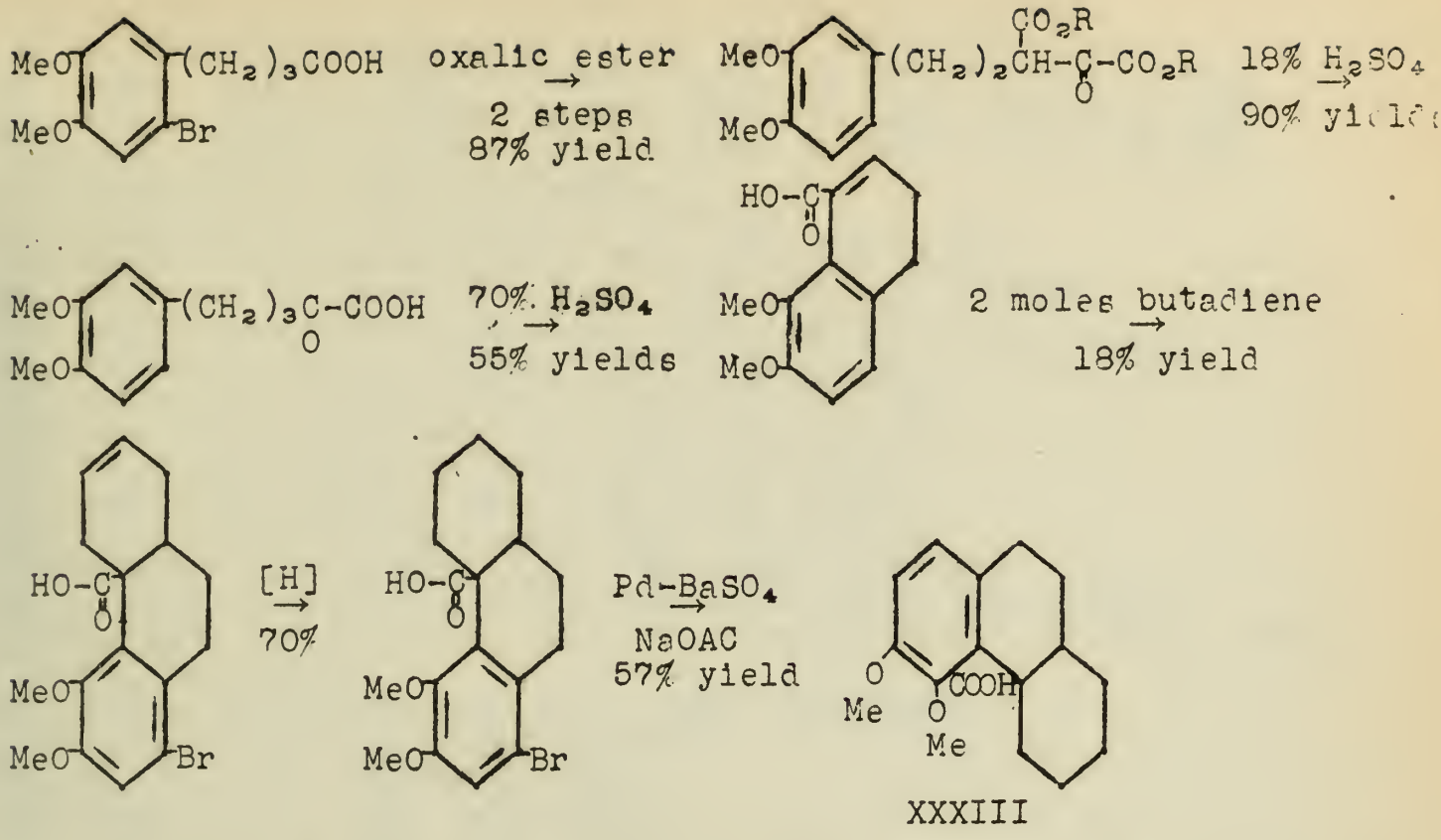


Fieser and Holmes (33) have developed a rather general method for the preparation of 13-carboxyoctahydrophenanthrene derivatives (XXXI) in which ring A can be substituted. Speyer and Kouler (34)

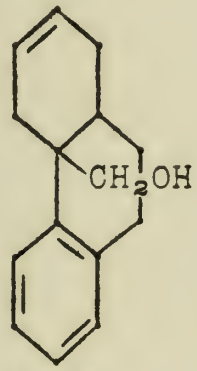


had obtained, as the methoide, a substance with a probable structure of XXXII. Fieser and Holmes succeeded in synthesizing 3,4-dimethoxy-5,6,7,8,9,10,13,14-octahydrophenanthrene-13-carboxylic acid (XXXIII).





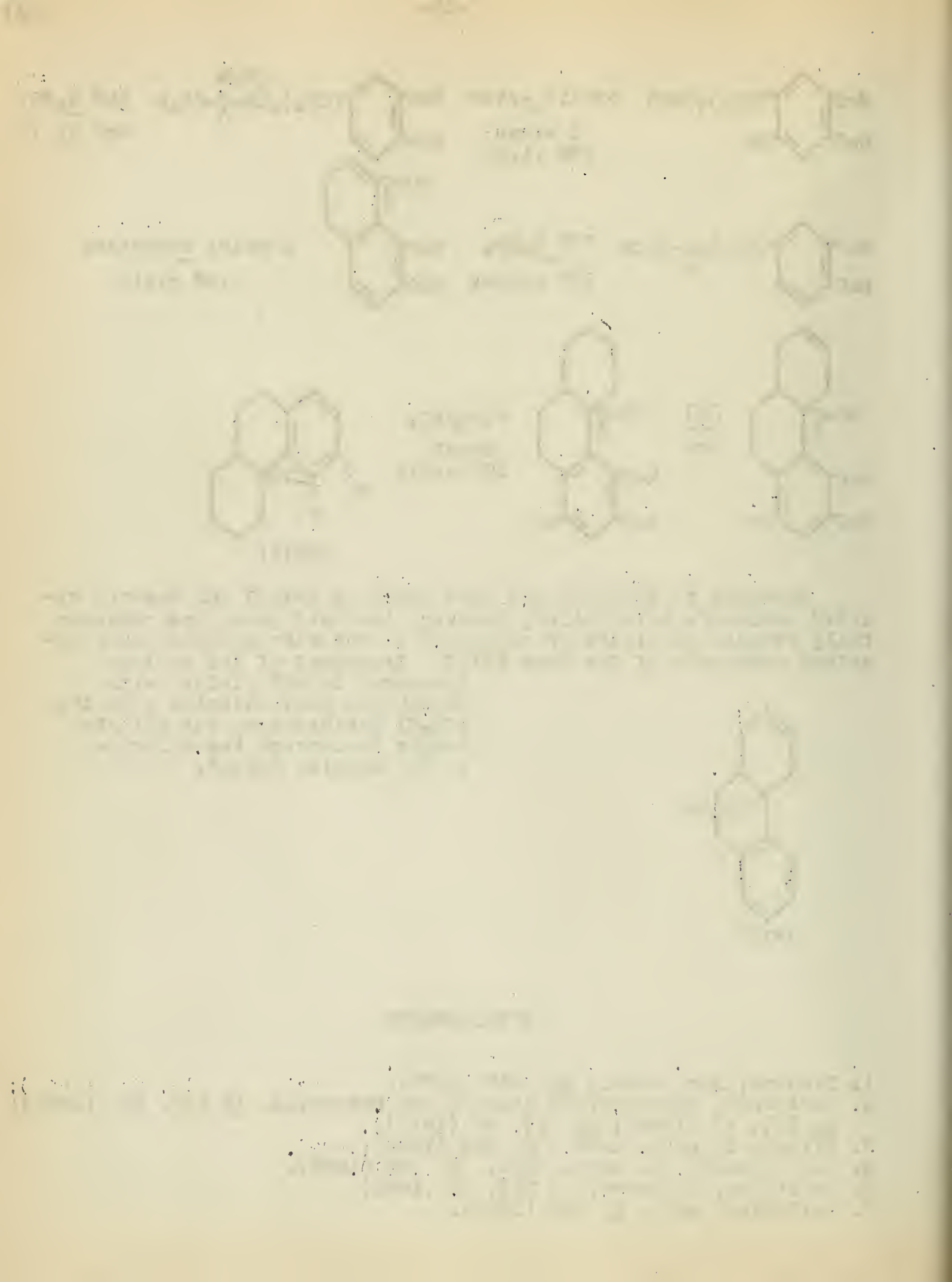
Attempts to build up the side chain in XXXIII and several related compounds have failed; however, the acid group was successfully reduced in yields of about 70% to the corresponding hydroxymethyl compounds of the type XXXIV. Treatment of the acetate (prepared in 80% yields) with phosphorus pentachloride gave the RCH_2Cl derivatives, but all attempts to convert the chloride to the nitrile failed.



XXXIV

BIBLIOGRAPHY

1. Derosne, Ann. chim., 45, 257 (1803).
2. Serturner, Trommsdorffs Journal der Pharmazie, 13 [1], 234 (1805); 14 [1], 47 (1806); 20 [1], 99 (1811).
3. Eykman, Z. phys. chem., 2, 964 (1888).
4. Von Klobukow, Z. phys. chem., 3, 476 (1889).
5. Chasteing, J. pharm., 4 [5], 19 (1881).
6. Pelletier, Ann., 5, 150 (1833).

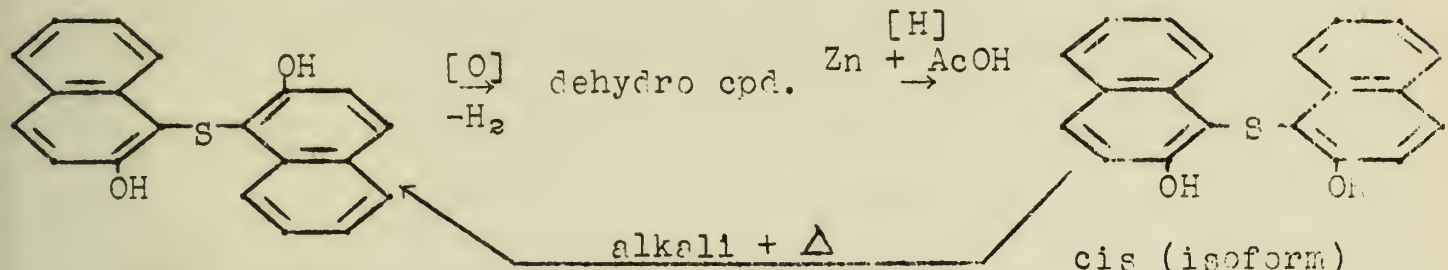


7. Schryver and Fees, J. Chem. Soc., 77, 1024 (1800).
8. Wieland and Kappelmeier, Ann., 382, 306 (1911).
9. Merck, D.R.P.-102634 (1898); Frdl. 5, 807; Houben I, 711.
10. Merck, D.R.P.-107225 (1898); Frdl. 5, 808; Houben I, 776.
11. Merck, D.R.P.-108075 (1898); Frdl. 5, 808; Houben I, 787.
12. Knorr, Ber., 22, 181 (1889).
13. Vongerichten, Ber., 29, 65 (1896).
14. Fisher and Vongerichten; Ber., 19, 792 (1886).
15. Schryver and Lees, J. Chem. Soc., 19, 792 (1886).
16. Speyer and Sarre, Ber., 57, 1422 (1924).
17. Pschorr, Pfaff and Herrschmann, Ber., 38, 3160 (1905).
18. Knorr and Pschorr, Ber., 38, 3172 (1905).
19. Knorr and Schneider, Ber., 39, 1414 (1906).
20. Knorr and Hörlein, Ber., 40, 2042 (1907).
21. Knorr and Hörlein, Ber., 39, 3252 (1906).
22. Wieland and Kotake, Ann., 444, 69 (1925).
23. Wieland and Garbsch, Ber., 59, 2490 (1926).
24. Gulland and Robinson, J. Chem. Soc., 123, 980 (1923).
25. Gulland and Robinson, Mem. Proc. Manchester, Lit. Phil. Soc., 69, 79 (1925).
26 Schöpf and Borkowsky, Ann., 458, 148 (1927).
27 Schöpf, Ann., 452, 211 (1927).
28. Crewe, Ber., 72, 426 (1939).
29. Crewe, Ber., 72B, 785 (1939).
30. Crewe, Ber., 72B, 1314 (1939).
31. Crewe, Ber., 76, 1072 (1943).
32. Crewe, Ber., 76, 1076 (1943).
33. Fieser and Holmes, J. Am. Chem. Soc., 60, 2548 (1938).
34 Speyer and Kaulen, Ann., 438, 34 (1924).

Reported by C. G. Overberger and W. E. Parham
November 22, 1944

THE SULFUR ISOMERISM OF ORGANIC SULFIDES AND CERTAIN OF THEIR DERIVATIVES

In 1894 Henriques observed that the compound 2,2'-dihydroxy-di-α-naphthyl sulfide (α-naphthol sulfide) existed in two forms which he thought might be <u>cis</u> and <u>trans</u> forms of the type indicated below.

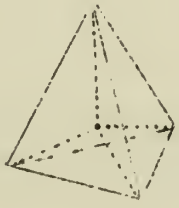


trans (normal form)
m.p. 211°
colorless

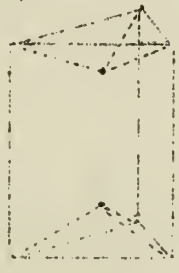
cis (isoform)
m.p. 152°
yellow

In 1916 Hinsberg postulated that the origin of this isomerism lay within the sulfur atom itself. In a series of papers extending from 1916 to 1920 he proposed and developed his "valence center" hypothesis which states that the elements of group V to VII of the periodic table posess multiple "valence centers," and with the aid of this hypothesis he claimed to be able to correlate and explain certain hitherto obscure aspects of the chemistry of these elements. The hypothesis was related to the physical concepts of the Rutherford-Bohr atom by the postulate that the multiple valence centers of the atom correspond to multiple-charged atomic nuclei, each of which controls a certain number of valence electrons.

As applied to the type of isomerism indicated above, the hypothesis states that the sulfur atom contains two of these valence centers and that, just as the valence bonds of the carbon atom are directed toward the corners of a regular tetrahedron, so the valence bonds of the sulfur atom are directed toward the corners of an elongated triangular prism.

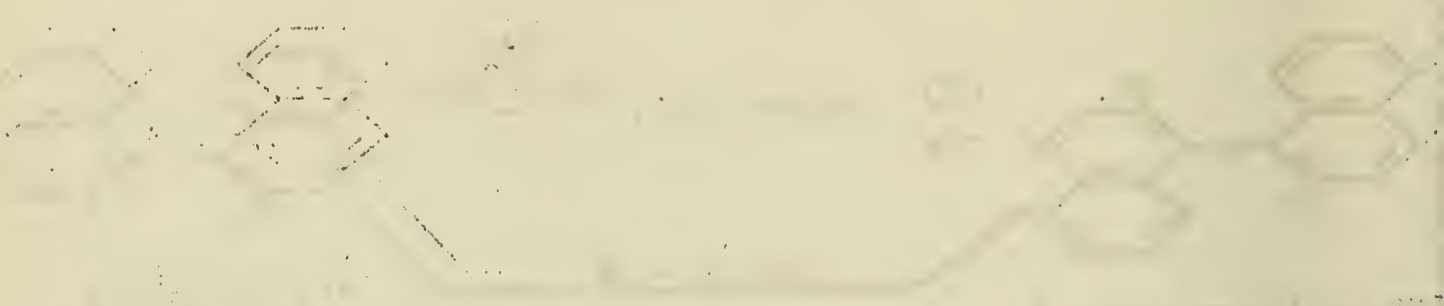


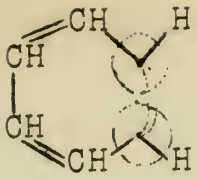
C



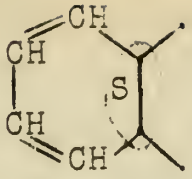
S

Hinsberg cites the hypothesis as applicable to the explanation of the close similarity between benzene and thiophene, in which a sulfur atom replaces a vinyl group.



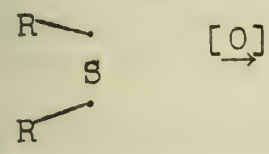


benzene



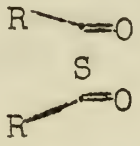
thiophene

According to the hypothesis, the isomerism of sulfides, sulfoxides, and sulfones is represented as follows:

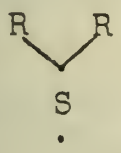


α-sulfide

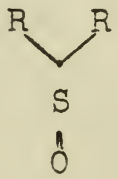
α-sulfoxide



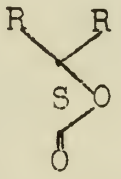
α-sulfone



β-sulfide

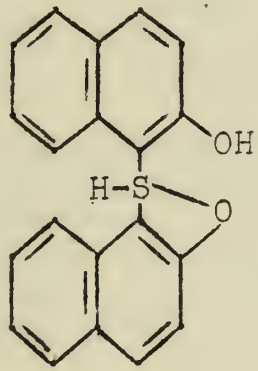


β-sulfoxide



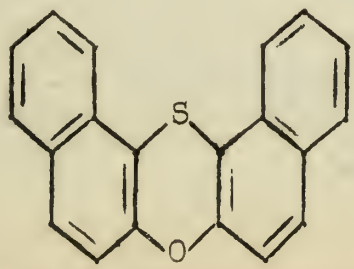
β-sulfone

In 1923, Lesser and Gad stated that the isomerism of the β-naphthol sulfide mentioned previously might be explained structurally and that the assumption of a special sulfur isomerism was unnecessary. They assumed the normal structure for the normal or α-sulfide and the following structure for the β-sulfide:

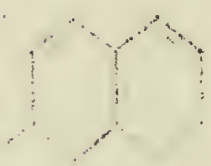


Hinsberg then pointed out that while the isomerism of the sulfide itself could be explained in this way, that of certain of its derivatives (namely the two naphthothioxins of Nolan and Smiles could not.

β-naphthol sulfide $\xrightarrow[-H_2O]{POCl_3}$



naphthothioxin m.p. 166°



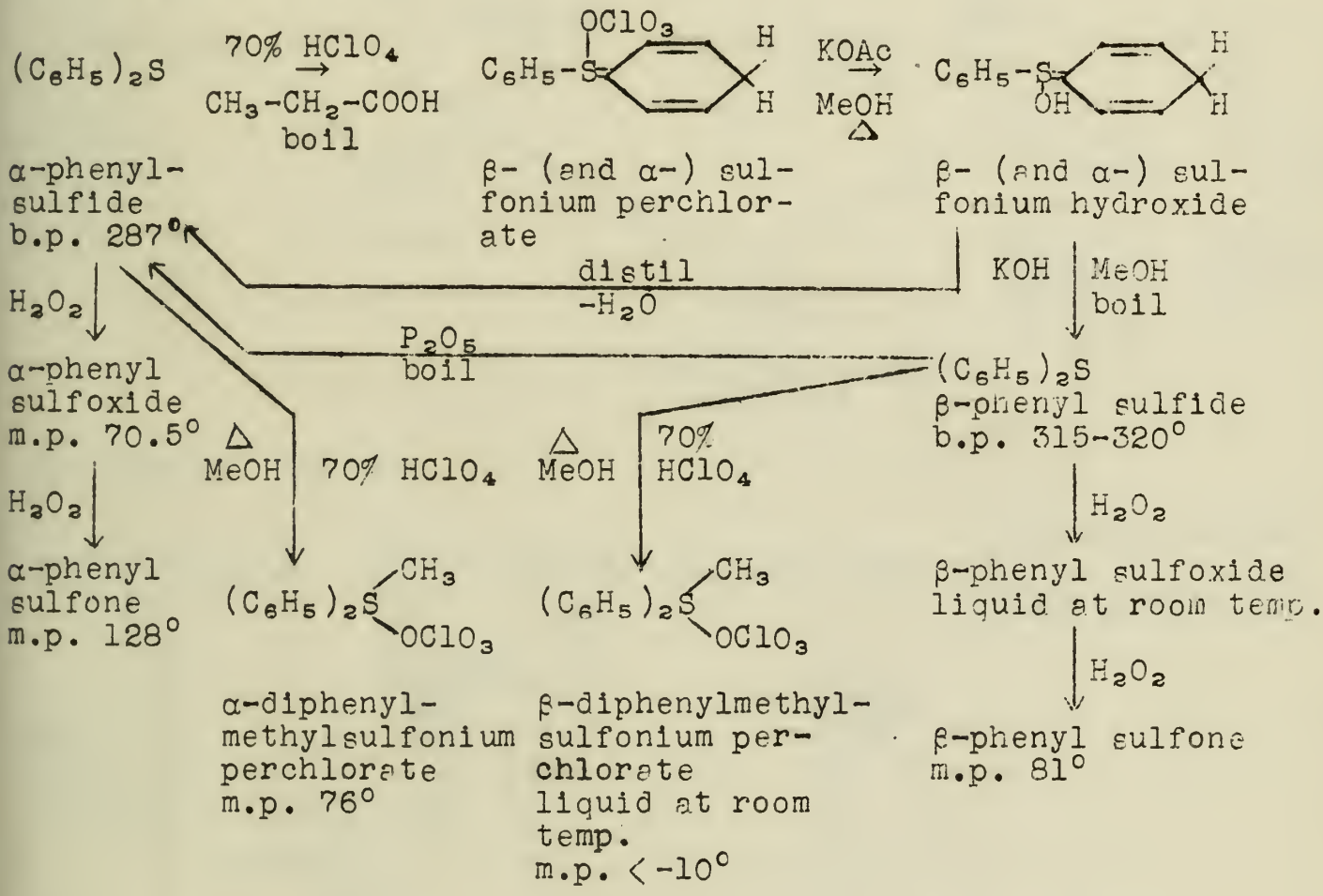
iso-β-naphthol sulfide $\xrightarrow[-H_2O]{POCl_3}$ iso-naphthothioxin
m.p. 152°

A mixture of these two compounds melted at 120°.

In a series of papers published from 1929 through 1937, Hinsberg examined the sulfur isomerism of several simple, unsubstituted aryl, alkyl and aralkyl sulfides.

He found that, in general, if a sulfide was heated with perchloric acid, a sulfonium perchlorate was formed which was decomposed by heating with alkali with the formation of an isomeric sulfide differing from the original in chemical and physical properties.

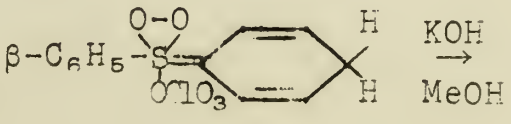
I. Phenyl Sulfide



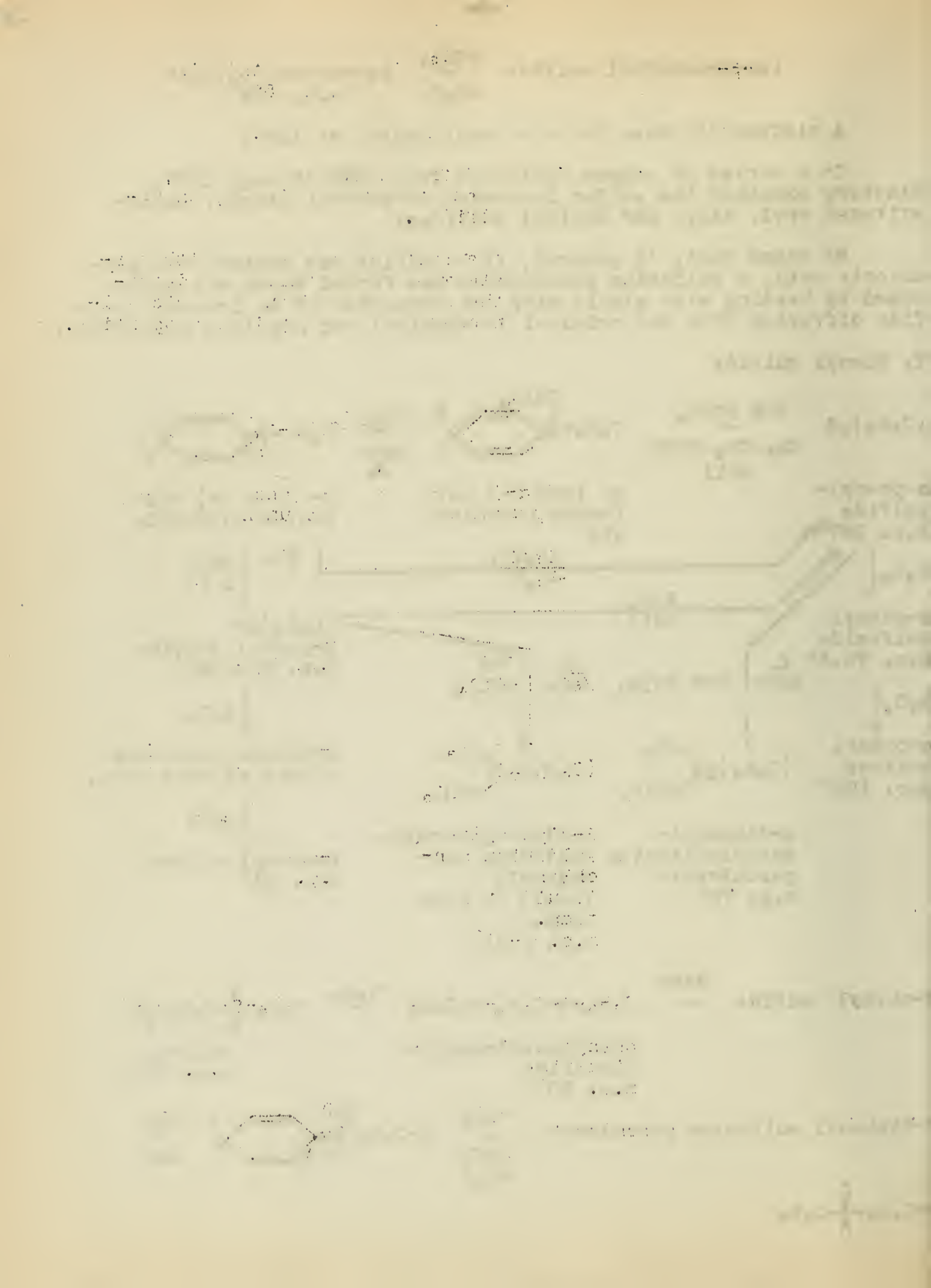
β-phenyl sulfide $\xrightarrow{350°}$ $C_6H_5-S-C_6H_4-S-C_6H_5$ $\xrightarrow{H_2O_2}$ $C_6H_5-\overset{O}{\underset{O}{S}}-C_6H_4-\overset{O}{\underset{O}{S}}-C$

phenylenediphenyl-disulfide
m.p. 80°

sulfone
m.p. 229°

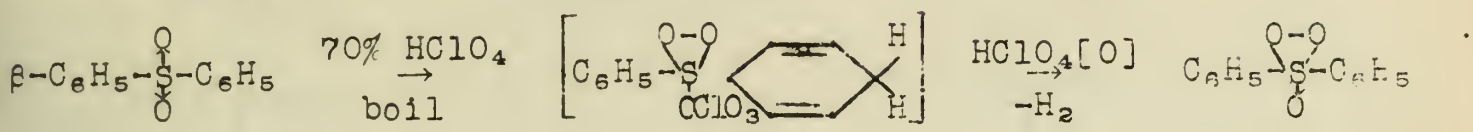
β-diphenyl sulfonium perchlorate $\xrightarrow[AcOH\ Ac_2O]{H_2O_2}$  $\xrightarrow[MeOH]{KOH}$

$\beta\text{-}C_6H_5-\overset{O}{\underset{O}{S}}-C_6H_5$



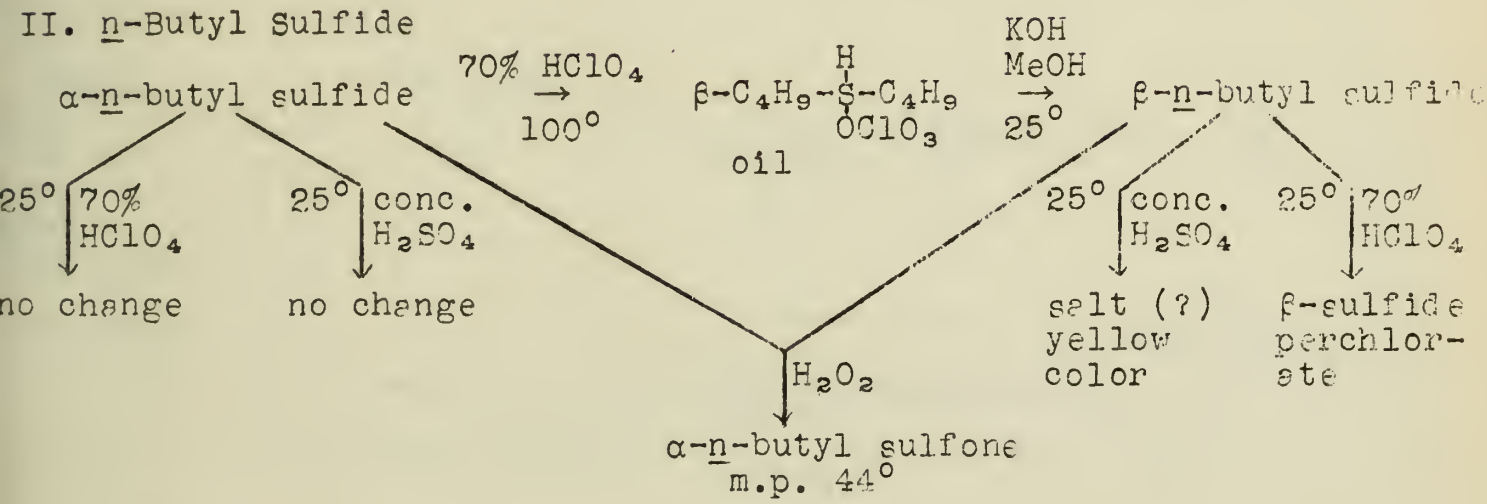
α-diphenyl sulfonium perchlorate $\xrightarrow[AcOH,\ Ac_2O]{H_2O_2}$ no change $\xrightarrow[MeOH]{KOH}$

α-C_6H_5-S-C_6H_5

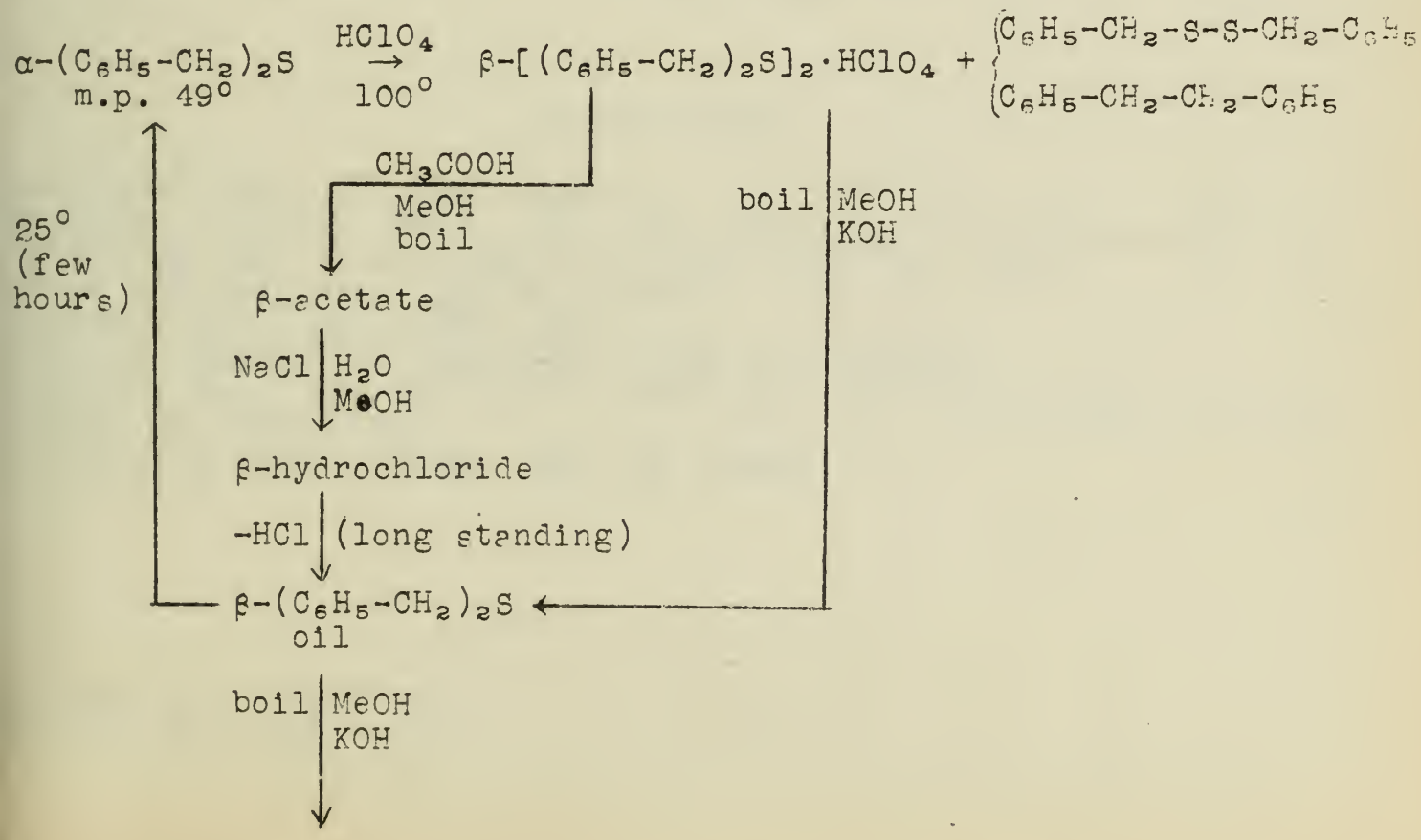


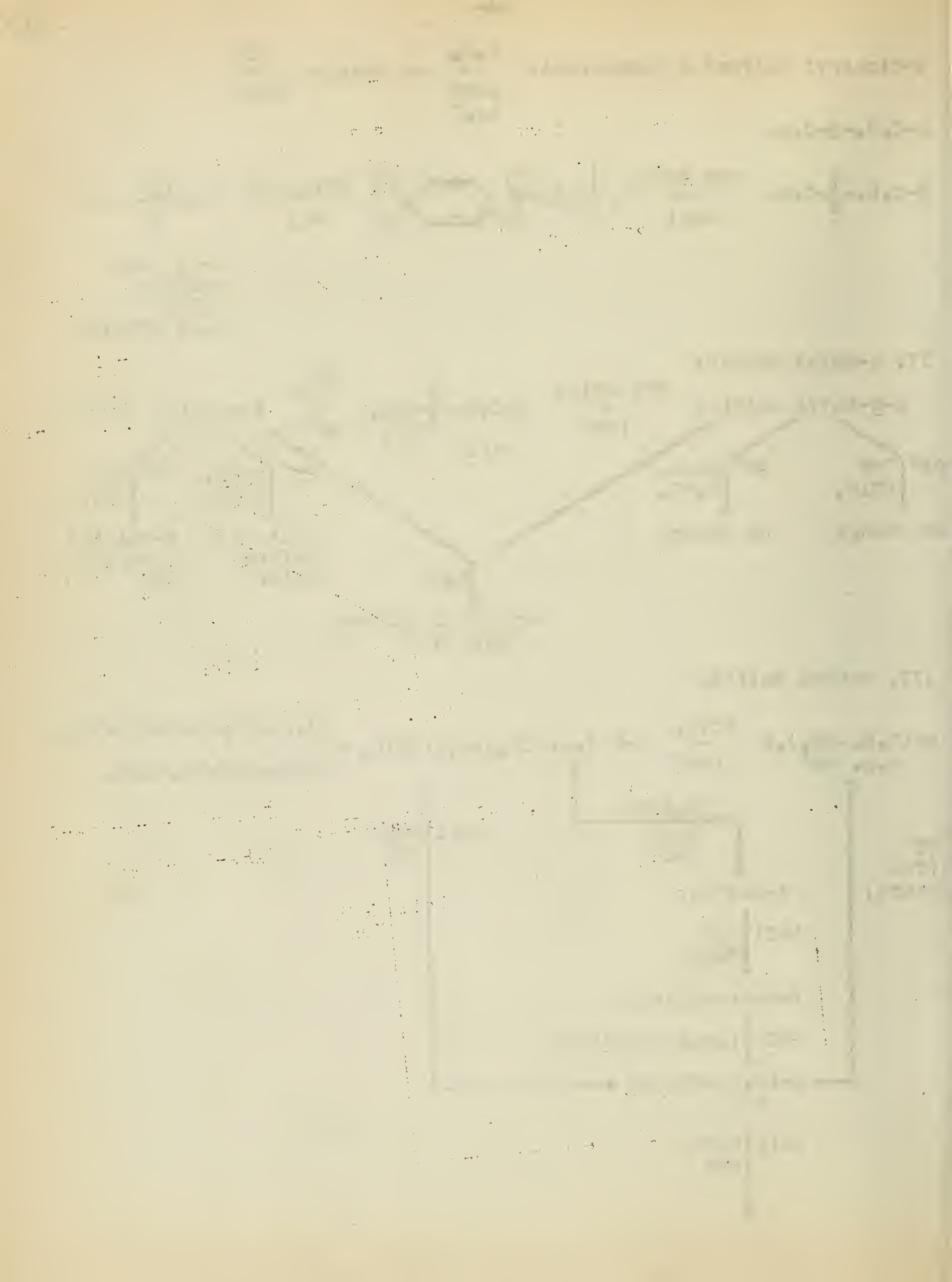
β-diphenyl sulfone oxide
m.p. 120-122°

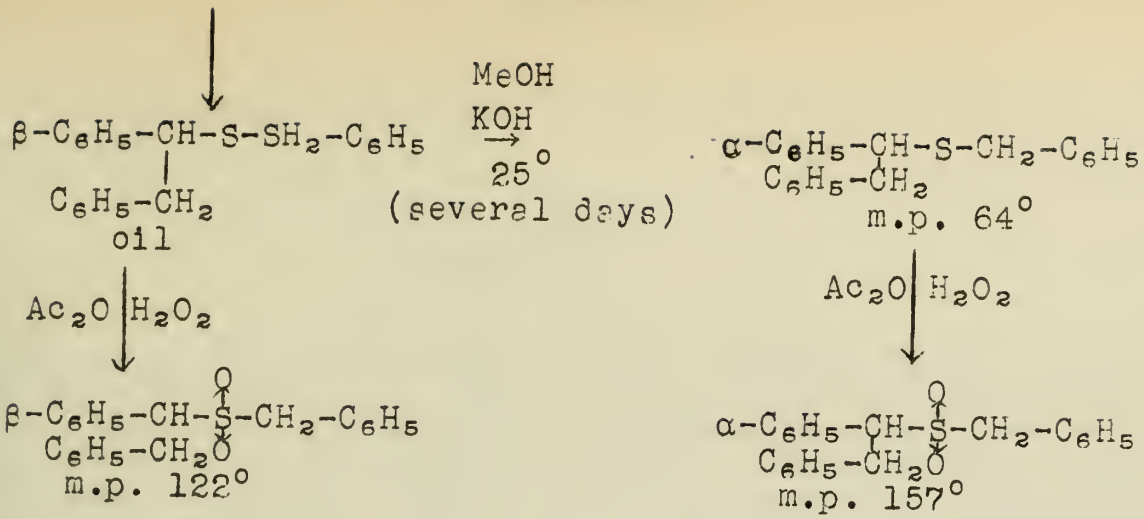
II. n-Butyl Sulfide



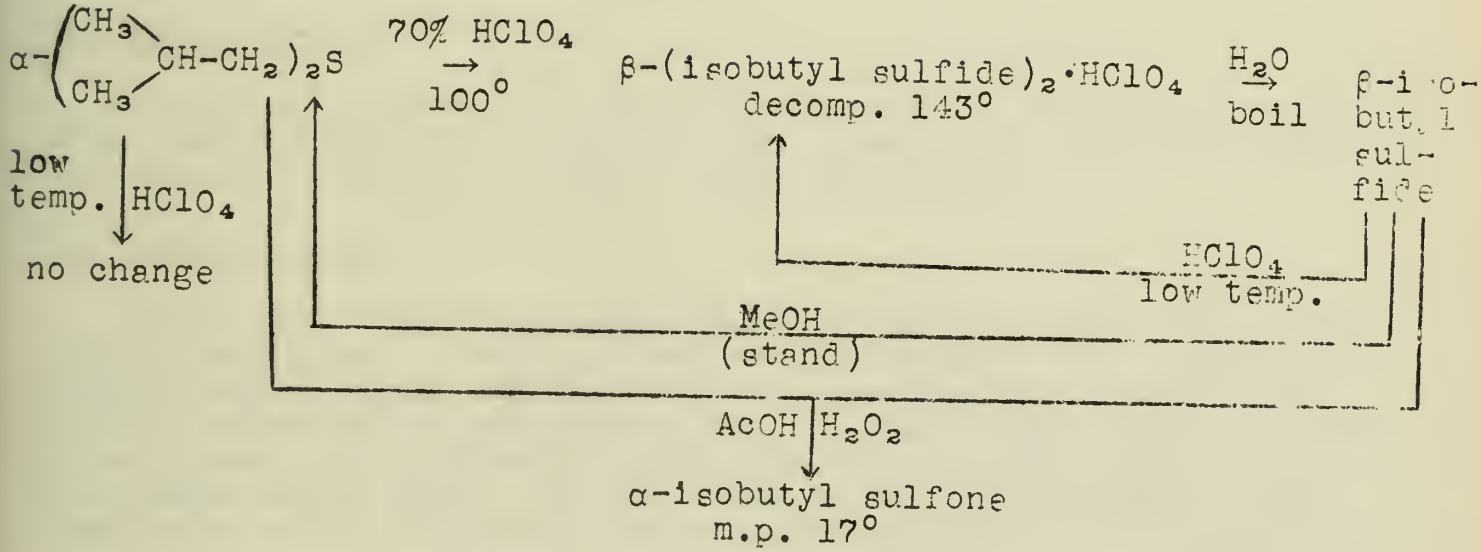
III. Benzyl Sulfide







IV. Isobutyl Sulfide



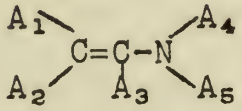
BIBLIOGRAPHY

Henriques, Ber., 27, 2993 (1894).
Hinsberg, J. prakt. Chem., 93, 302 (1916); 94, 179 (1916); 95, 121 (1917); 96, 166 (1917); 99, 232 (1919); 101, 97 (1920).
Lesser and Gad, Ber., 56, 963 (1923).
Hinsberg, Ber., 56, 1735 (1923).
Nolan and Smiles, J. Chem. Soc., 103, 901 (1913).
Hinsberg, Ber., 62, 127, 2166 (1929); 69, 492 (1936); 70, 936, 2027 (1937); 64, 2500 (1931).
Hinsberg, J. prakt. Chem., 140, 65 (1934).

Reported by J. B. Ziegler
November 29, 1944

VINYLAMINES

The vinylamines discussed in this seminar will be of the general type:



where A_1, A_2, and A_3 are alkyl, aryl, halogen, ether, or H; and A_4 and A_5 are alkyl, aryl, acyl, or H. The vinylamine derivatives will be discussed in the order of increasing number of substituents. The preparation of the simplest member of this series, vinylamine itself, was reported by Gabriel (1) who subjected bromoethylamine to dehydrohalogenation. This base was shown later (2,3) to be dimethyleneimine, a cyclic imine.

One Substituent

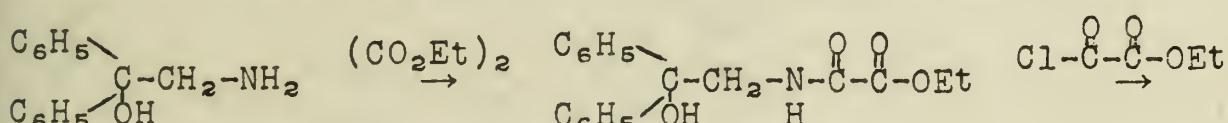
Only two compounds of this type have been reported, propyleneamine (4) and N-methylvinylamine (5); these two compounds also were proven to have the cyclic imine structure.

Two Substituents

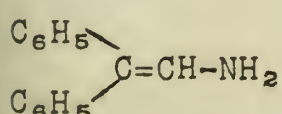
These types are the simplest of the substituted vinylamines and are relatively stable. N,N-Dimethylvinylamine was reported synthesized by Meyer and Hopff (6) by the dry distillation of neurine chloride ($CH_2=CH-N(CH_3)_3^+Cl^-$). This amine is stable for a few hours under ordinary conditions, but it soon polymerizes to a hard, white mass. In the presence of acids N,N-dimethylvinylamine easily decomposes into acetaldehyde and dimethylamine.

N,N-Diarylvinylamines have been prepared by a patented process (7) which involves the treatment of diarylamines with acetylene at temperatures between 100° and 200°C. and pressures between 20 and 25 atmospheres in the presence of a strong basic catalyst. For example, N,N-diphenylvinylamine has been prepared by this method.

The first report of a disubstituted vinylamine with no substituents on the N- atom was made by Krabbe and Schmidt (8) These workers synthesized diphenylvinylamine as follows:



I



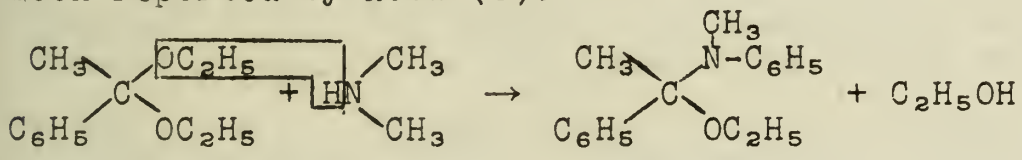
II

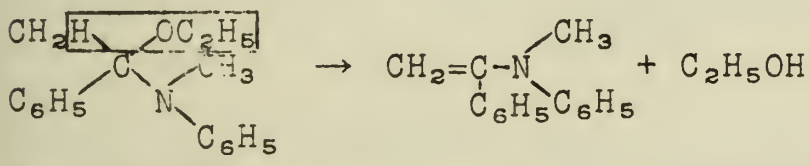
Two other methods to prepare II were later described by Krabbe: (a) treatment of the aminocarbinol I with concentrated sulfuric

acid (8); and (b) treatment of diphenylacetaldehyde with ammonia in methyl alcohol at 0°C. (93%) (13). Diphenylvinylamine (II) is stable enough to recrystallize, but decomposition soon occurs Apparently a molecule of ammonia from two molecules of the amine is eliminated to give an unsaturated secondary amine, $[(C_6H_5)_2C{=}CH]_2NH$. Acids greatly accelerate this decomposition. The ethylenic linkage in II behaves in a peculiar manner. Diphenylvinylamine does not add bromine, and it is not attacked by basic potassium permanganate solution with any degree of rapidity. Krabbe proposed the enamine structure (II) on the basis of molecular refraction measurements and ozonolysis experiments.

Three Substituents

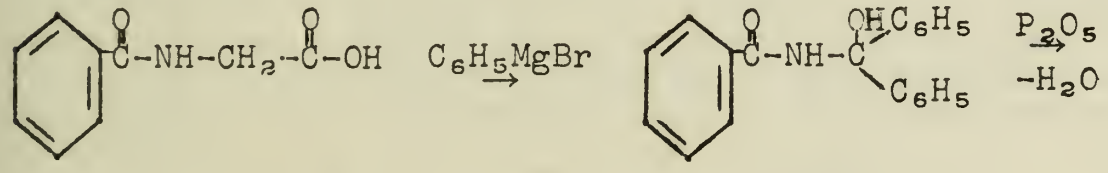
A general method to prepare N,N-disubstituted vinylamines where A_3 is aryl and A_4 and A_5 can be either aryl or alkyl, has been reported by Hoch (9).

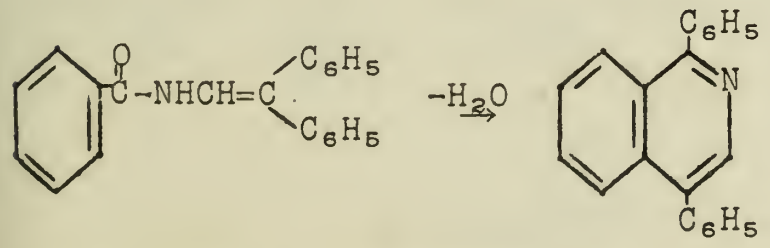




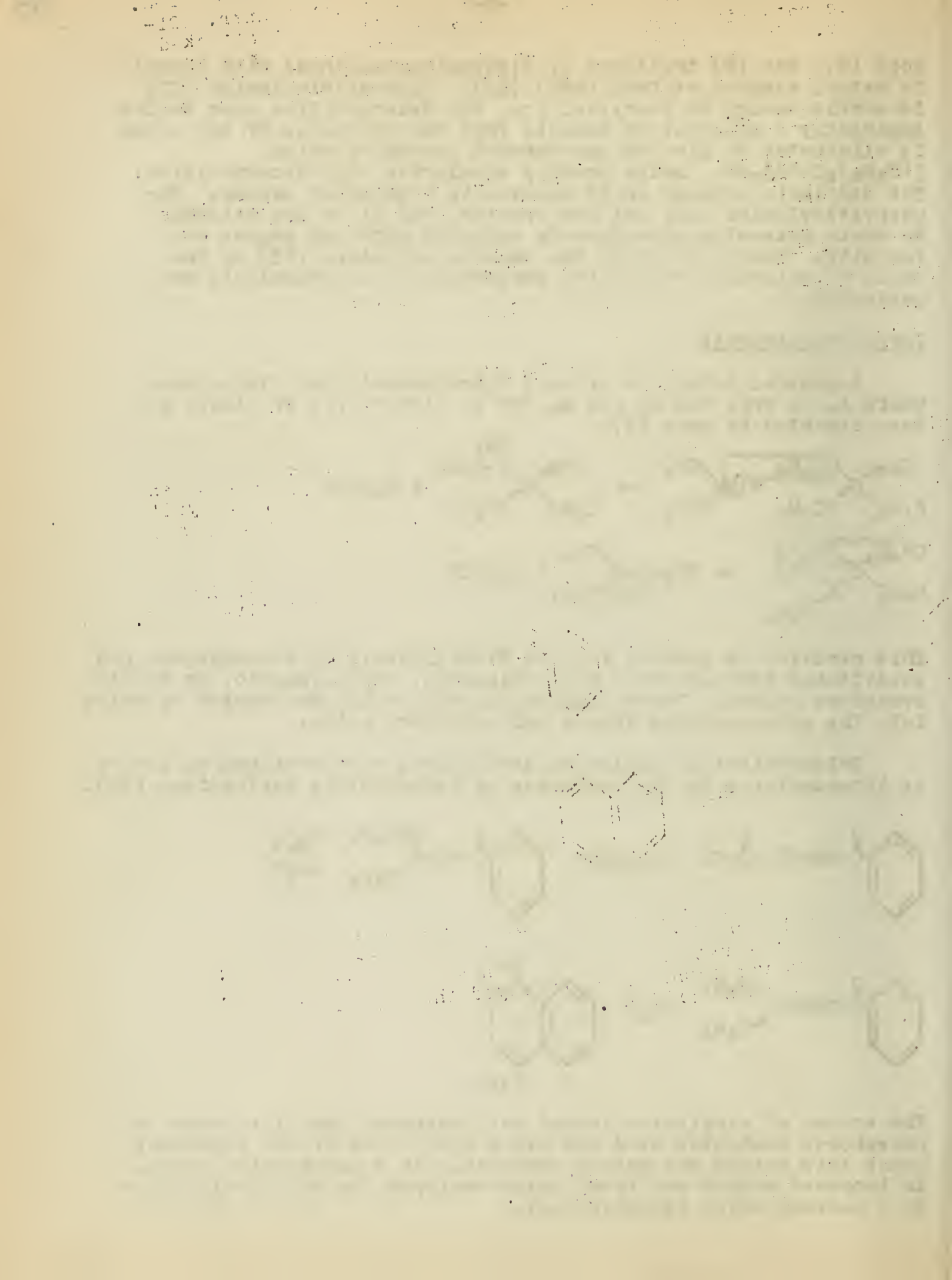
This reaction is general for the diethylketals of acetophenone and substituted acetophenones with aliphatic, arylaliphatic, or cyclic secondary amines. These vinylamines are easily decomposed by acids into the corresponding ketone and secondary amine.

Trisubstituted vinylamine derivatives were obtained by Krabbe as intermediates in the synthesis of isoquinoline derivatives (10).

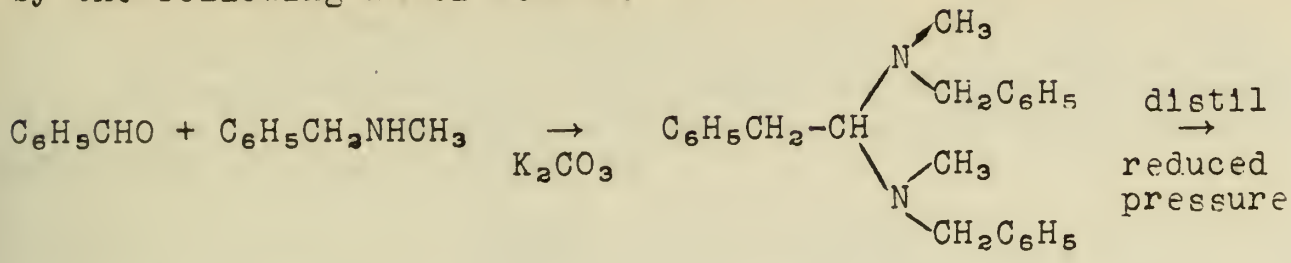




The amount of vinylamine formed was dependent upon the amount of phosphorus pentoxide used and other conditions of the reaction; hence this method was rather unreliable in a preparative sense. An improved method was found which employed the dry distillation of a corresponding aminocarbinol.

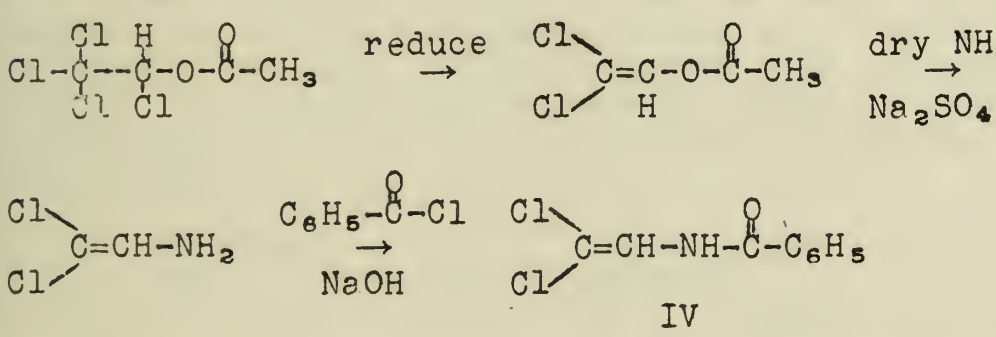


Mannich and Davidsen (11) have prepared tertiary vinylamines by the following novel method.



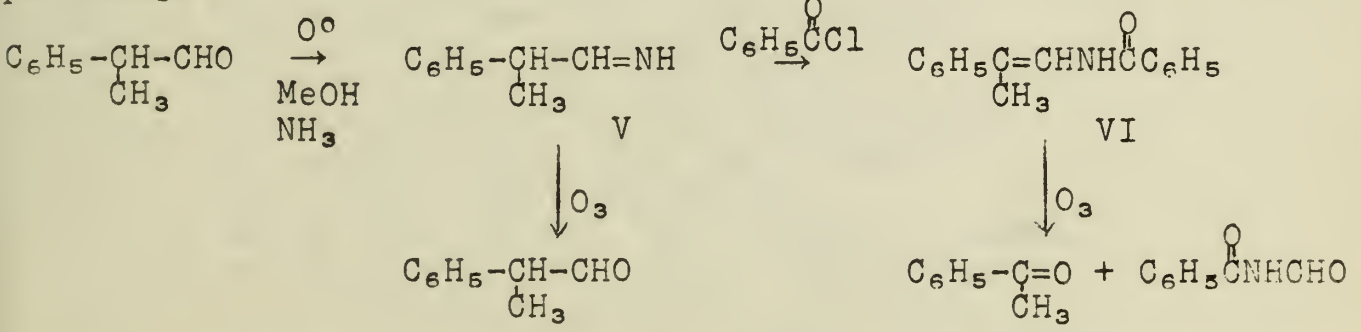
This reaction is reported to be general for most aldehydes and secondary amines.

Some chlorosubstituted vinylamines have been prepared by Deodhar (12) by the reduction of chloralacyl chlorides and subsequent reaction with dry ammonia and sodium sulfate.



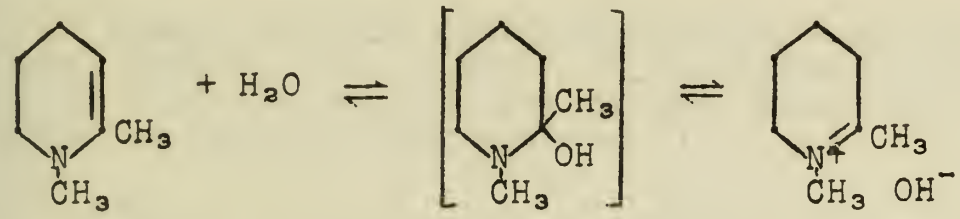
The benzoyl derivative (IV), however, was unstable and resinified in a short time.

Krabbe and coworkers (13) have attempted to distinguish between the imido and the enamine forms of some unsubstituted amines by ozonization experiments. The imido form of methylphenylvinylamine (V) was prepared and its ozonization product identified. The imido form then was converted to the N-benzoyl methylphenylvinylamine (VI), the enamine form, and identified by its ozonolysis products.



Additional evidence for the existence of imido and enamine forms was supplied by Raman spectra measurements on these compounds and numerous other compounds with known similar structure.

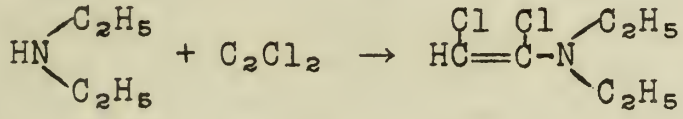
Basicity studies on some tertiary vinylamines have been made in this laboratory by Adams and Mahan (14). These workers concluded that the tertiary vinylamines studied were more basic than the corresponding saturated compounds. In order to explain this increased basicity an equilibrium was suggested between the vinylamine and a hydration product, the corresponding quaternary hydroxide, in aqueous solution.



The quaternary ammonium hydroxides are known to exceed all tertiary amines in basic strength.

Four and Five Substituents

These vinylamine derivatives may be prepared by the same general procedures discussed previously. Their properties are in general the same as the N-substituted, trisubstituted vinylamines. An interesting tetrasubstituted chloro derivative has been prepared by the action of dichloroacetylene on diethylamine (15).



This compound decomposes in air, but is stable for some time if stored under CO_2 or ether.

BIBLIOGRAPHY

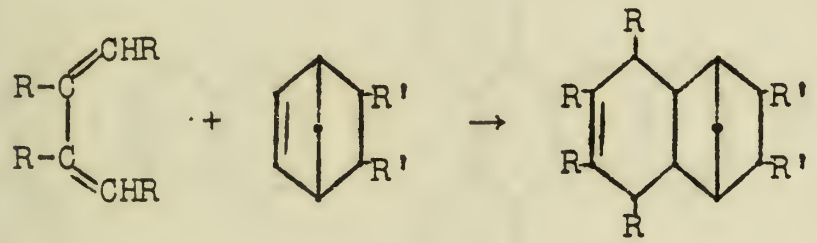
1. Gabriel, Ber., 28, 2929 (1895).
2. Howard and Marckwald, Ber., 32, 2036 (1899).
3. Marckwald, Ber., 33, 764 (1900).
4. Gabriel and Hirsch, Ber., 29, 2747 (1896).
5. Knorr and Meyer, Ber., 38, 3133 (1905).
6. Meyer and Hopff, Ber., 54, 2274 (1921).
7. German Patent 642,424, C.A., 31, 3504 (1937).
8. Krabbe and Schmidt, Ber., 72B, 381 (1939).
9. Hoch, Compt. Rend., 200, 938 (1935).
10. Krabbe, Böhlk, and Schmidt, Ber., 71B, 64 (1938).
11. Mannich and Davidsen, Ber., 69B, 2106 (1936).
12. Deodhar, J. Indian Chem. Soc., 11, 83 (1934).
13. Krabbe, Seher, and Polzin, Ber., 74B, 1892 (1941).
14. Adams and Mahan, J. Am. Chem. Soc., 64, 2588 (1942).
15. Ott, Dittus, Weissenburger, Ber., 76B, 84 (1943).

Reported by J. D. Young
November 29, 1944

THE DIELS-ALDER REACTION WITH CYCLOÖLEFINS

The usual philodienic component in the Diels-Alder reaction is an α,β-unsaturated carbonyl compound. Other groups which promote resonance (C≡N, C_6H_5, etc.) also serve to activate an ethylenic or acetylenic bond so that it may undergo the Diels-Alder reaction.

Simple olefinic hydrocarbons have not been known to condense readily with dienes. It was known, however, that bicyclo [2.2.1]-2-heptene derivatives react with 1,3-dienes to form the tricyclic derivatives.

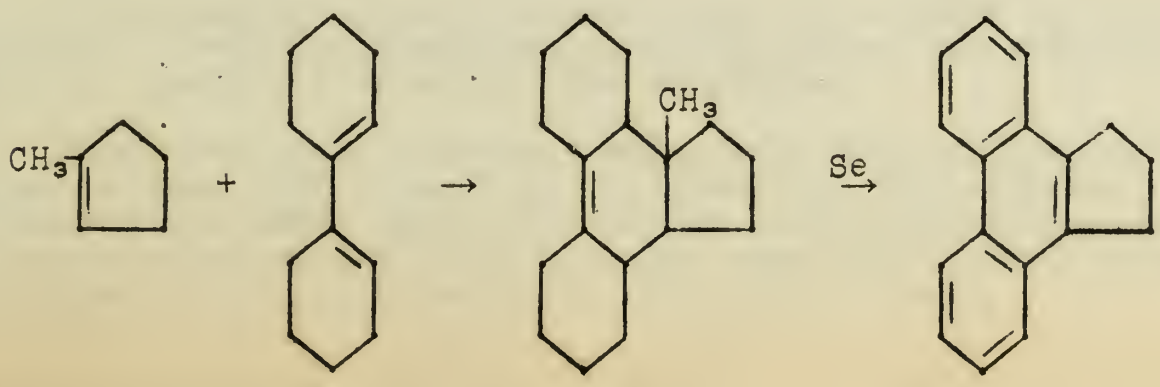


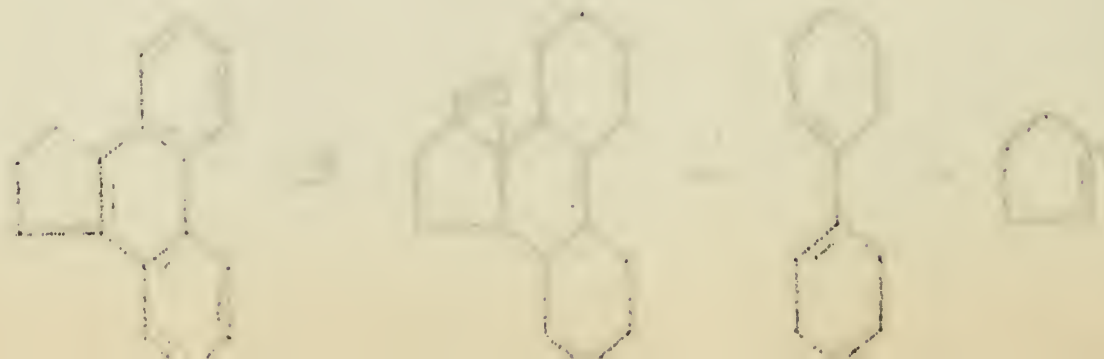
This reaction was considered a special case attributable to exceptional reactivity of the double-bond due to strain in the ring system.

Joshel and Butz recently have demonstrated that ethylene could react with butadiene or 2,3-dimethylbutadiene to give the corresponding cyclohexenes. These reactions took place only under drastic conditions. Since cyclohexenes are obtained as a reaction product it is indicated that other cycloölefins would not undergo the Diels-Alder reaction.

Bergmann and Weizmann, in attempting to prepare some aromatic hydrocarbons, used cycloolefins in a Diels-Alder reaction. This was done to avoid using other olefins which contained carbonyl groups and gave quinone adducts which could be converted to hydrocarbons.

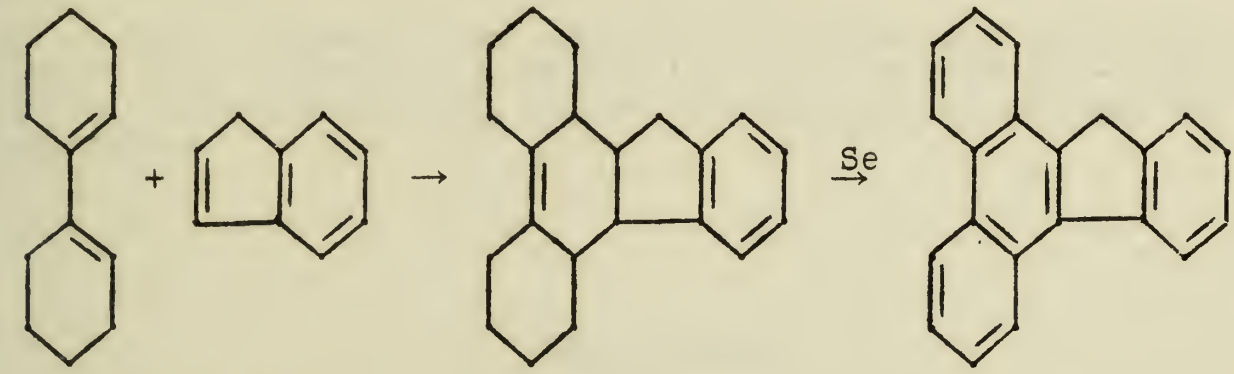
Bergmann and Eschinazi showed that bicyclohexenyl reacted with maleic anhydride and trans-cinnamic acid in good yields. This indicates that this diene is quite reactive towards philodienes. The diene was treated with cyclohexene, 1-methylcyclohexene, and 4-methyl-1,2-dihydronaphthalene under varibus conditions without success. However, 1-methylcyclopentene gave a positive result. It yielded an adduct which was dehydrogenated to 9,10-cyclopenteneophenanthrene.





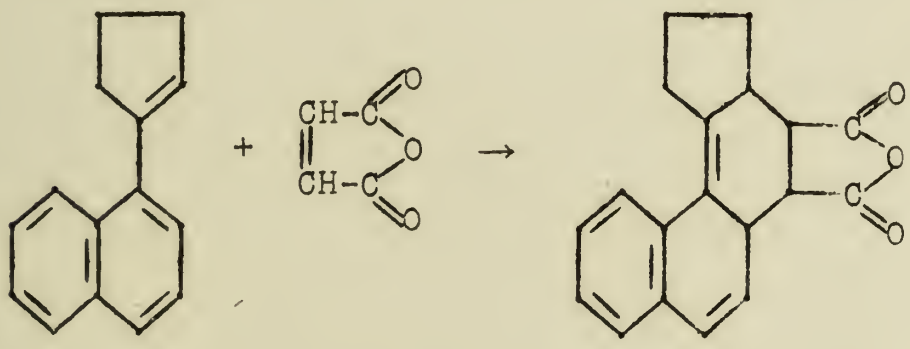
Bachmann and Kloetzel had isolated this latter compound by the cyclization of β-(10-phenanthryl)-propionyl chloride with aluminum chloride in nitrobenzene to 1'-keto-9,10-cyclopentenophenanthrene followed by reduction to 9,10-cyclopentenophenanthrene.

Bergman found that indene and 1,3-dimethylindene react with bicyclohexenyl to give adducts which can be dehydrogenated readily.



Other dienes besides bicyclohexenyl failed to give a reaction with cyclohexenes. Among the dienes tried were 2-isopropenylnaphthalene and 2-(1,2-dimethylvinyl)-naphthalene.

This unreactiveness of cyclohexenes as compared to the activity of cyclopentenes in the Diels-Alder reaction, is similar to the differences observed when either cycle belongs to a butadienic system in which one double-bond forms part of the aromatic nucleus. Thus Bachmann and Kloetzel found that 1-(α-naphthyl)-cyclopentene-1 and maleic anhydride gave a mixture of 3,4-cyclopentano-1,2,3,10-α-tetrahydrophenanthrene-1,2-dicarboxylic acid and the corresponding acid anhydride.



1-(α-naphthyl)-1-Cyclohexene will not undergo the above reaction. 9-Cycloalkenylphenanthrenes showed the same difference in reactivity toward maleic anhydride.

There are other instances which show that differences exist between cyclohexenyl or cyclopentenyl derivatives. Dieckmann has shown that ethyl cyclopentanone-2-carboxylate is in equilibrium with 4.5% of its enol form while ethyl cyclohexanone-2-carboxylate contains about 76% of enol.

Bergmann explains the difference in reactivity of the cyclopentenes and cyclopentanes as due to differences in strain. The cyclopentane ring is nearly coplanar and has but little strain but the cyclopentene ring is formed with some strain. Both the cyclohexane and cyclohexene ring are practically strainless. This would cause the cyclopentene ring to pass very readily to the cyclopentane ring structure while the opposite is true of cyclohexene rings. This difference of ring stability is an indication of the ease with which the two cycloölefins will undergo the Diels-Alder reaction.

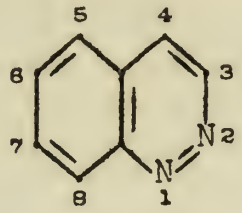
These arguments are supported by Alder and Stein who have shown that introduction of strain into a cyclohexene ring, as in the bicycloheptenes, allows the compound to undergo the reaction.

BIBLIOGRAPHY

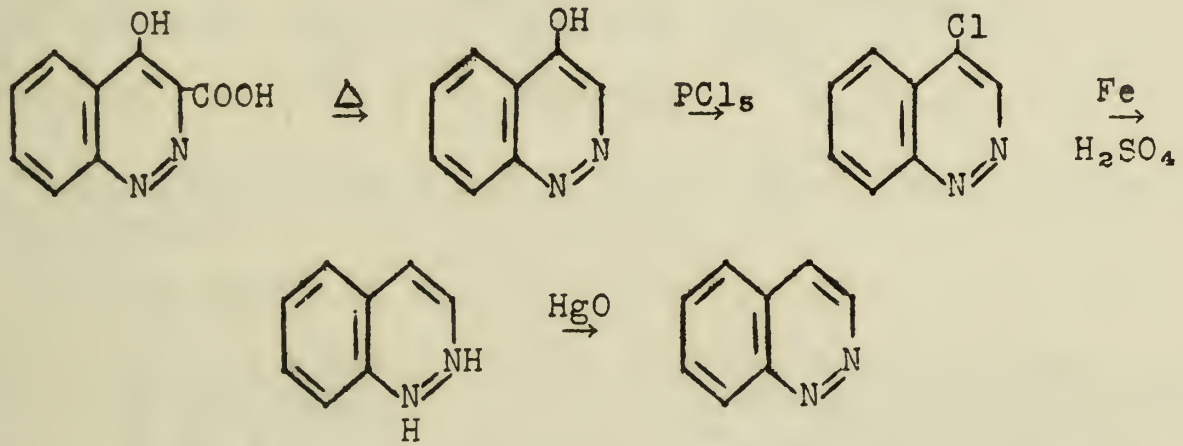
Bergmann and Weizmann, J. Org. Chem., 9, 352 (1944).
Bergmann and Eschinazi, J. Am. Chem. Soc., 65, 1405 (1943).
Joshel and Butz, J. Am. Chem. Soc., 63, 3350 (1941).
Bachmann and Kloetzel, J. Am. Chem. Soc., 59, 2207 (1937).
Bergmann and Bergmann, J. Am. Chem. Soc., 60, 1805 (1938).
Bachmann and Kloetzel, J. Am. Chem. Soc., 60, 2204 (1938).
Dieckmann, Ber., 55, 2470 (1922).
Alder and Stein, Ber., 71, 2409 (1938).

Reported by T. G. Klose
December 6, 1944

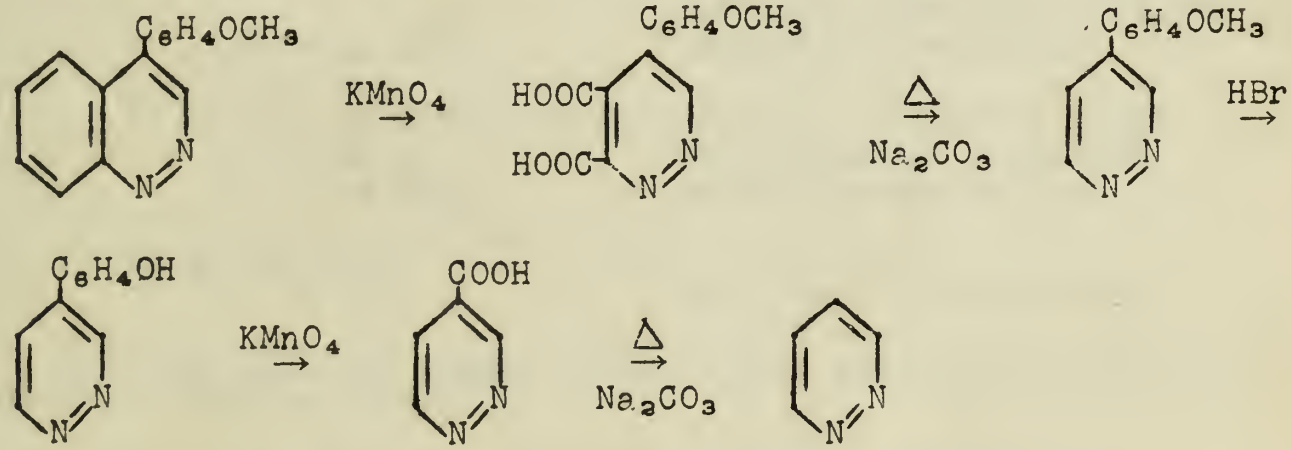
Introduction:--The cinnolines are derivatives of a heterocyclic binuclear base containing two vicinal nitrogen atoms.



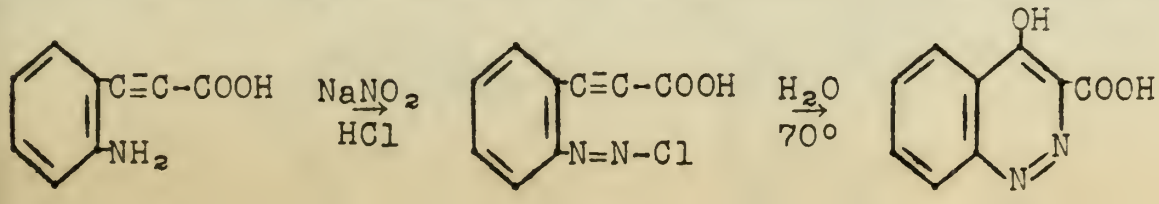
Cinnoline itself has been synthesized only through reduction of 4-chlorocinnoline and oxidation of the resulting dihydro compound.

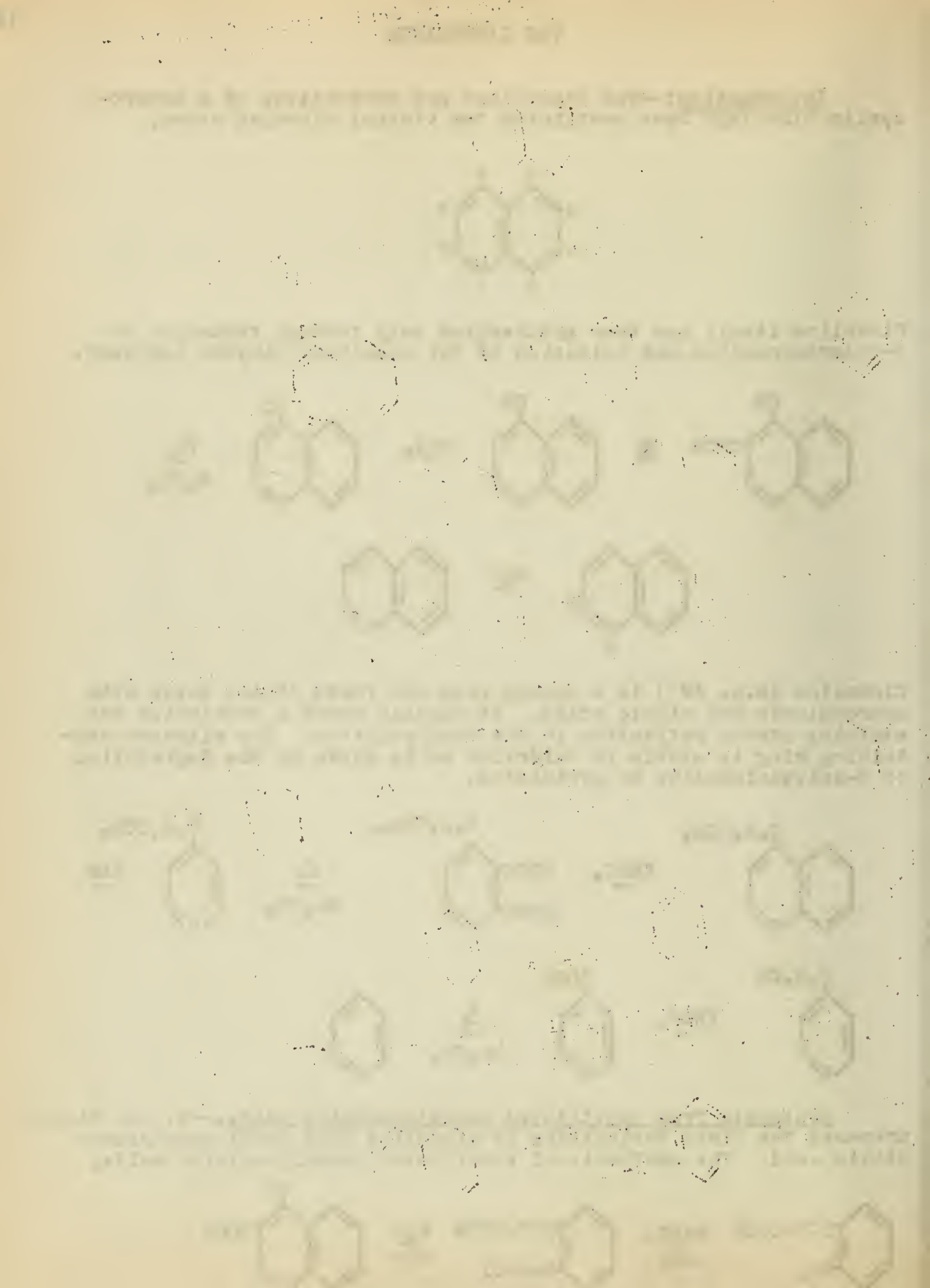


Cinnoline (m.p. 39°) is a strong base and forms stable salts with hydrochloric and picric acids. It readily forms a methiodide and exhibits strong activation in the four position. The nitrogen containing ring is stable to oxidation as is shown by the degradation of 4-anisylcinnoline to pyridazine.



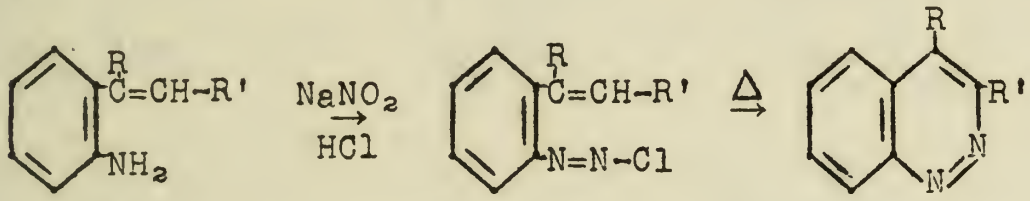
Synthesis from substituted phenylpropiolic acids.--V. von Richter prepared the first derivatives of cinnoline from o-aminophenylpropiolic acid. The synthesis of substituted phenylpropiolic acids,





however, is so difficult that this method for preparing the cinnolines has not been applied further.

The Widmann-Stoermer reaction:--The formation of cinnolines from substituted o-aminophenylethylenes, discovered by Widmann and developed by Stoermer, is the only general procedure for the synthesis of cinnolines. The Widmann-Stoermer reaction is carried out by the same procedure as the phenylpropiolic acid method, and Widmann advanced a mechanism for his reaction similar to that of Richter for the phenylpropiolic acid synthesis. The equation for the general Widmann-Stoermer reaction is as follows.



The substituents R and R' have a great effect on the course of the reaction.

A. The effect of R:

1. R is alkyl	cinnoline formation
2. R is aryl	increased tendency to cyclize
3. R is COOH	no cinnoline formation
4. R is OH, Br	cinnoline formation

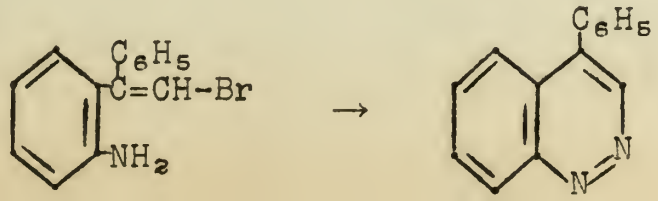
B. The effect of R':

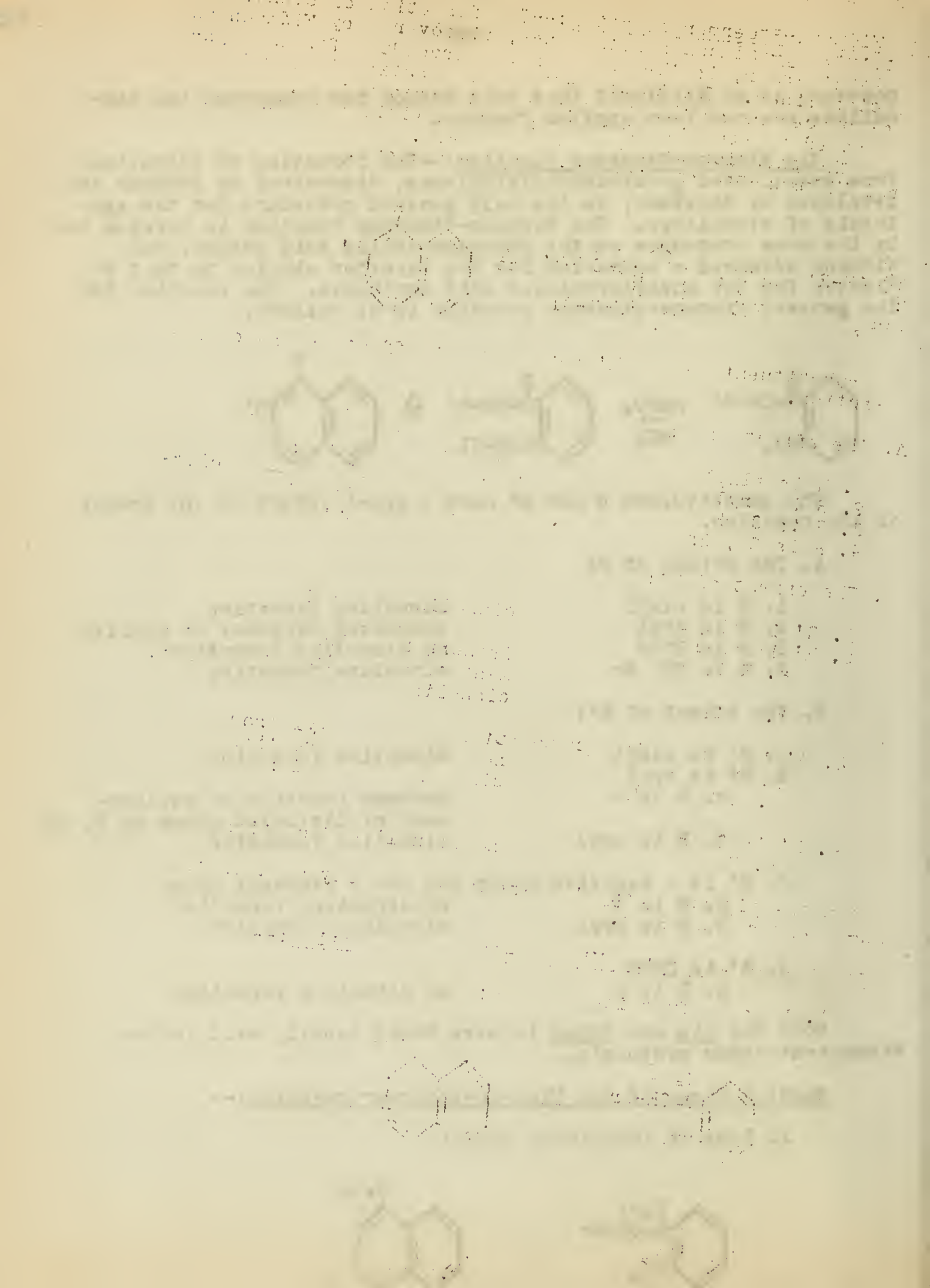
1. R' is alkyl	cinnoline formation
2. R' is aryl	
a. R is H	Pschorr reaction or replacement of diazonium group by H, OH.
b. R is aryl	cinnoline formation
3. R' is a negative group but not a carboxyl group	
a. R is H	no cinnoline formation
b. R is aryl	cinnoline formation
4. R' is COOH	
a. R is H	no cinnoline formation

Both the cis and trans isomers react equally well in the Widmann-Stoermer synthesis.

Special cases of the Widmann-Stoermer reaction:--

1. Loss of functional group:

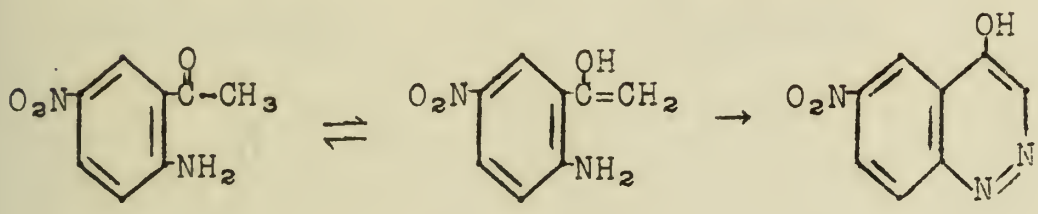


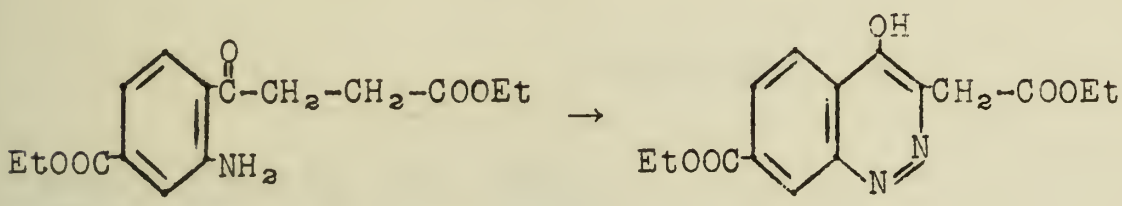


This is the only case in which loss of a functional group has been observed.

2. Enolization:

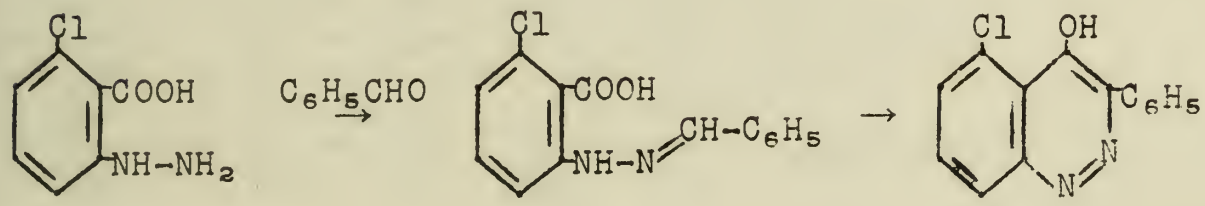
Although the following reactions do not appear to belong to the Widmann-Stoermer type, they can be considered with that group if the enolate is assumed to be the active form.



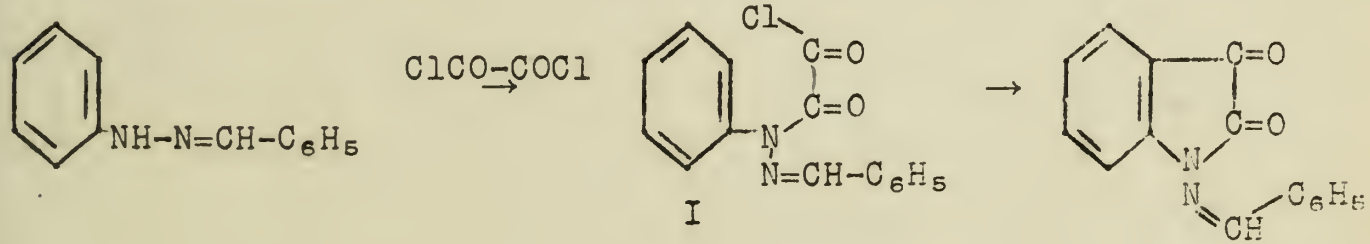


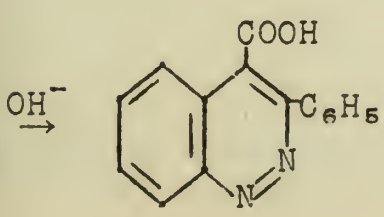
Special methods:--

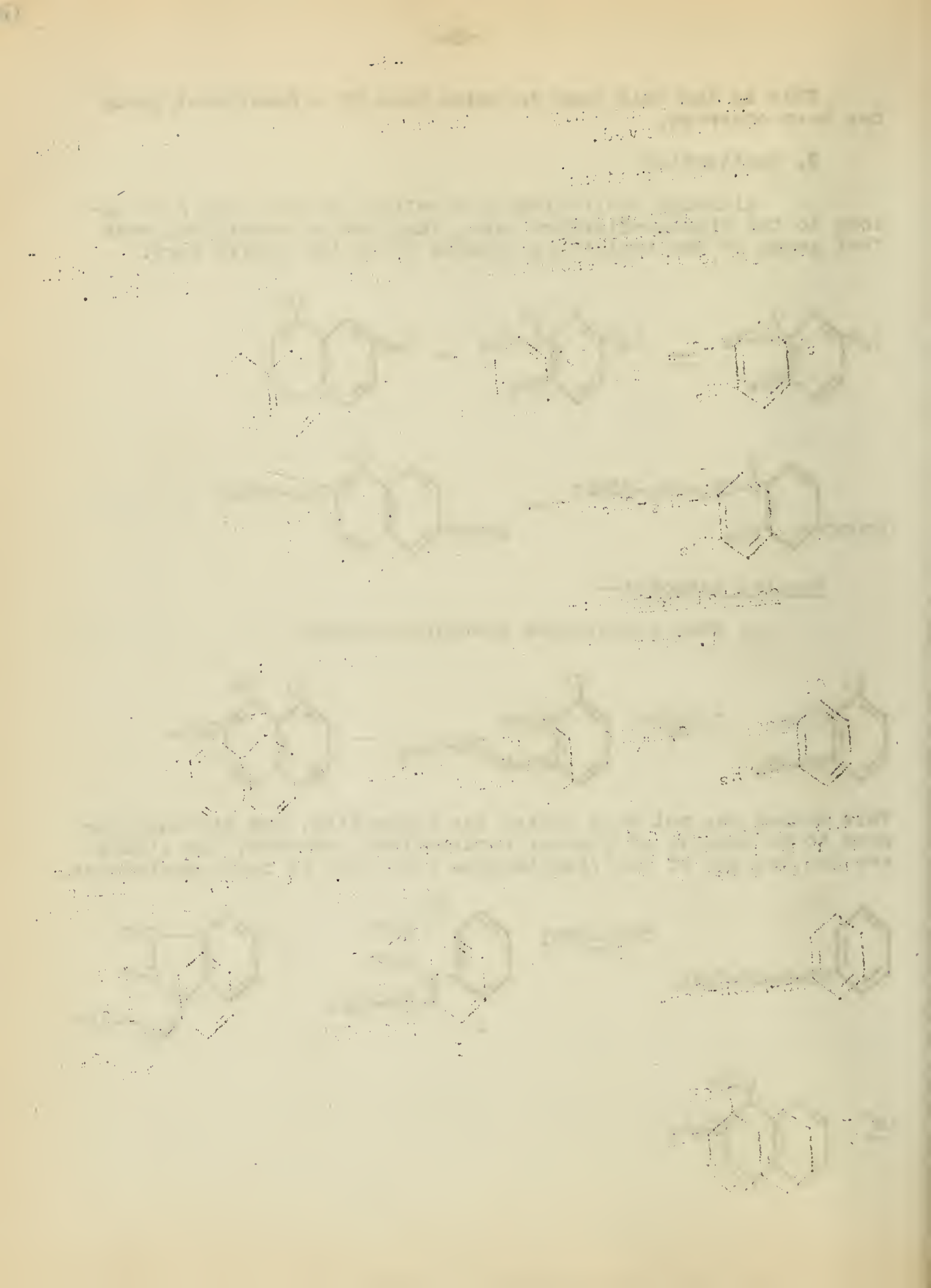
1. From substituted phenylhydrazones:



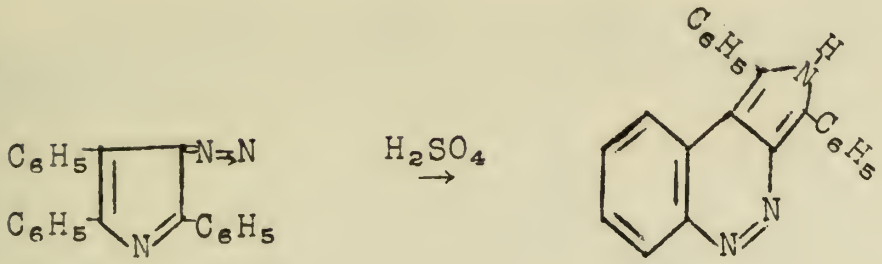
This method has not been tested for generality, but it would appear to be capable of general application. However, the yields are low because of the simultaneous formation of benzopyrazolones.







2. From 2,4,5-triphenyl-3-diazopyrrole:



II

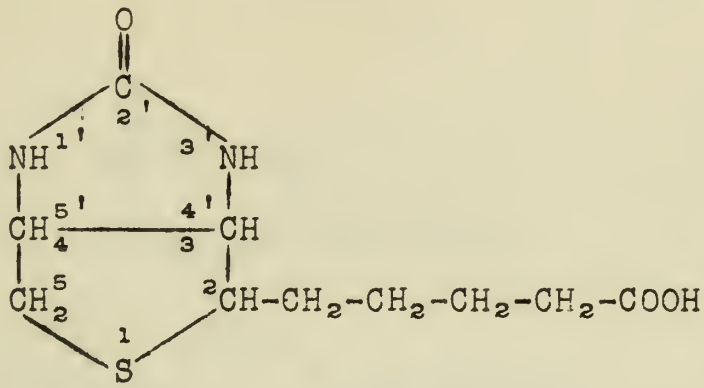
BIBLIOGRAPHY

Richter, Ber., 16, 677 (1883).
Widmann, Ber., 17, 722 (1884).
Busch and Klett, Ber., 25, 2847 (1892).
Busch and Rast, Ber., 30, 521 (1897).
Stoermer and Fincke, Ber., 42, 3115 (1909).
Stoermer and Gaus, Ber., 45, 3104 (1912).
Stolle and Becker, Ber., 57B, 1123 (1924).
Pfannstiel and Janecke, Ber., 75B, 1096 (1942).
Borsche and Herbert, Ann., 546, 293 (1941).
Koelsch, J. Org. Chem., 8, 295 (1943).
Simpson and Stevenson, J. Chem. Soc., 1942, 353.
Simpson, J. Chem. Soc., 1943, 447.

Reported by Elliot N. Marvell
December 6, 1944

SYNTHESIS OF BIOTIN

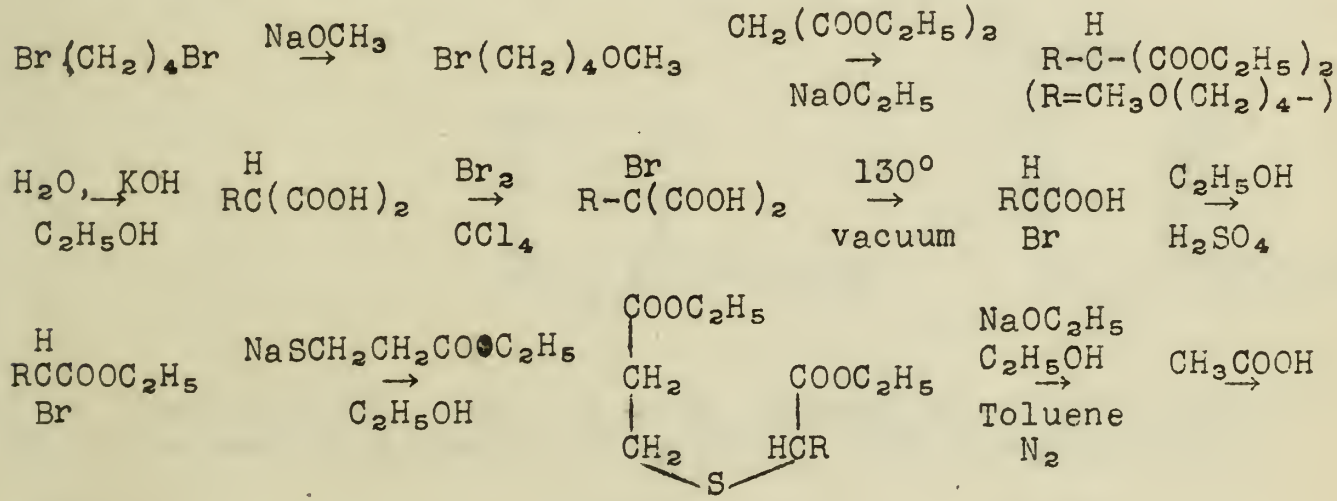
In December, 1942, the complete structure of biotin was established as 2'-keto-3,4-imidazolido-2-tetrahydrothiophene-valeric acid.

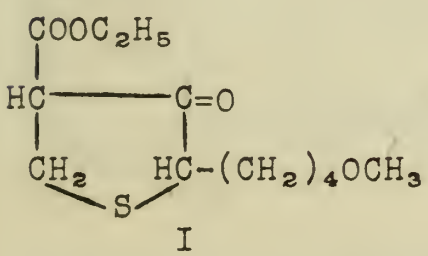


Biotin

A review of the work leading up to the assignment of this structure was presented in a seminar (December, 1942) by Dr. P. L. Southwick. This structure has now been verified by synthesis.

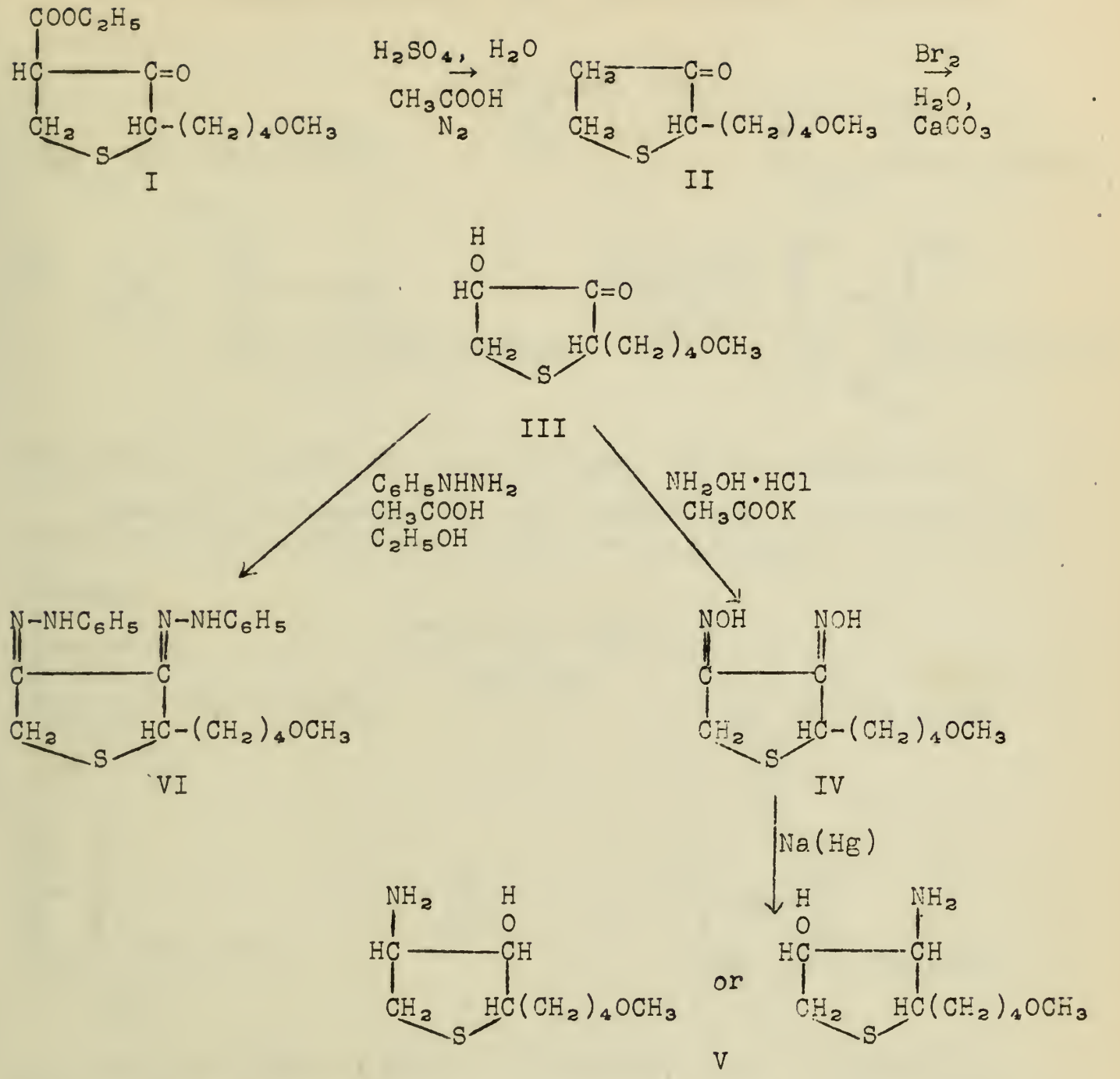
Karrer and Schmidt published a series of papers on derivatives of tetrahydrothiophene which are related to biotin. Compound I was prepared by the following method.



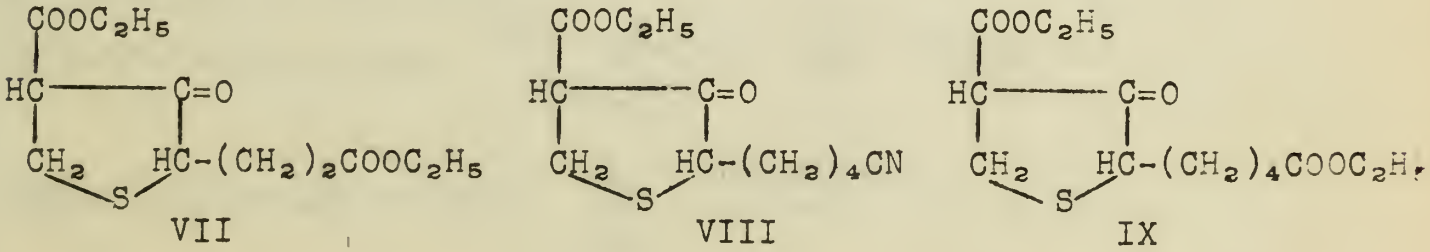


I

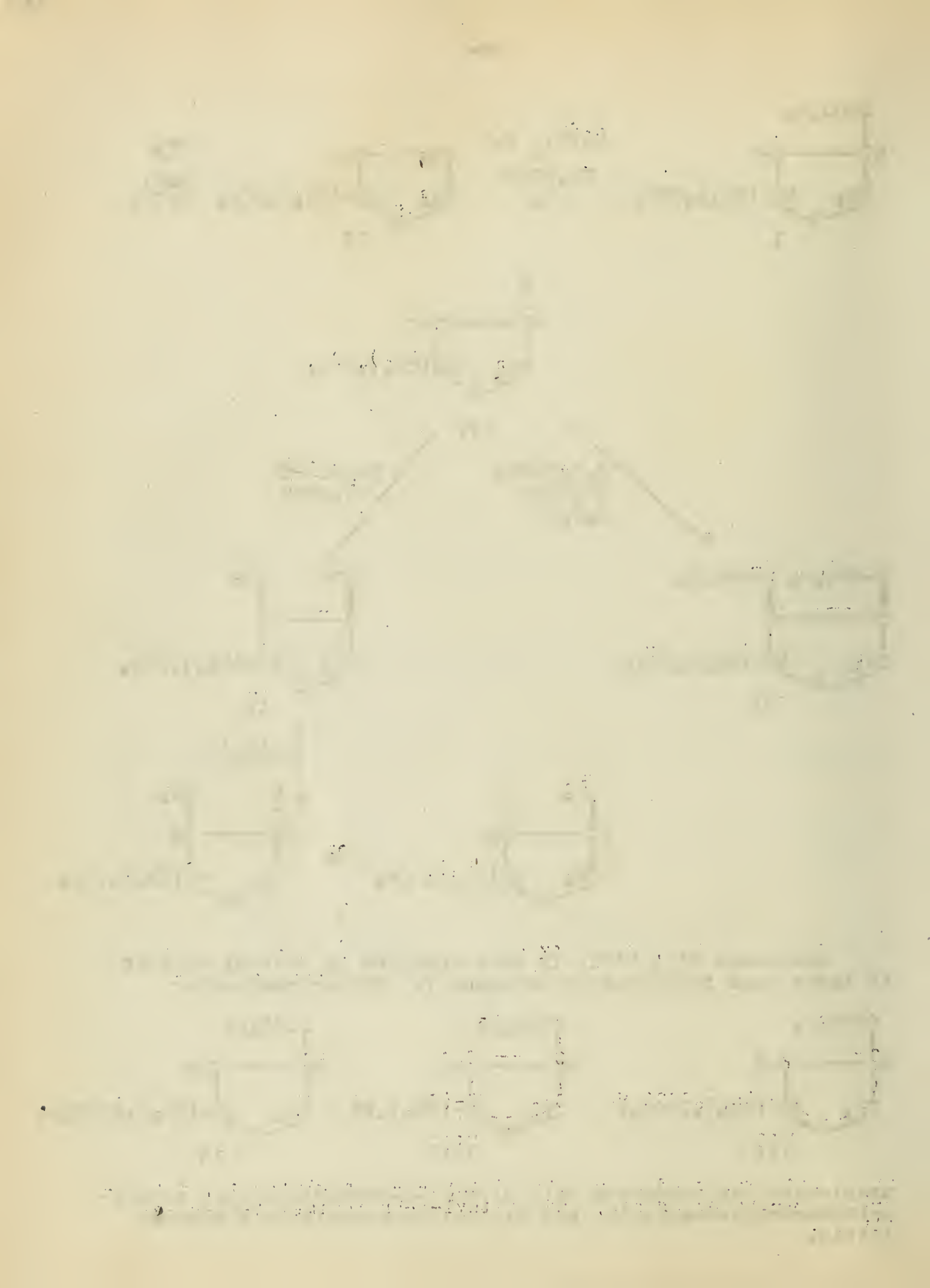
A series of interesting reactions was then carried out on this compound.



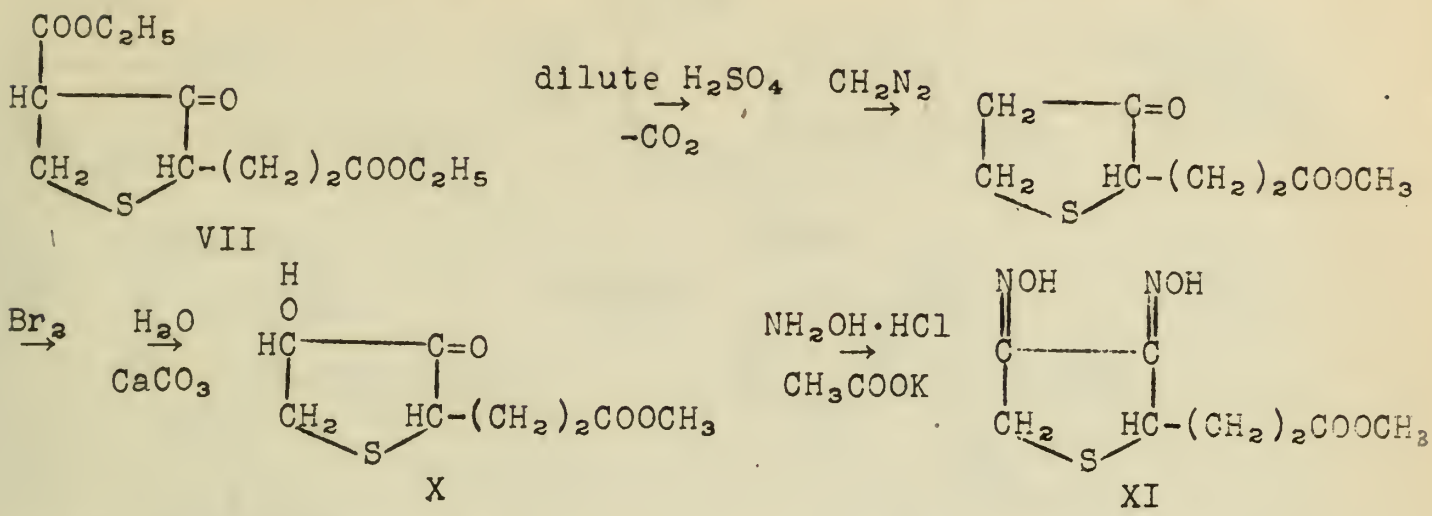
Compounds VII, VIII, IX were prepared by methods similar to those used in preparing compound I. Ethyl-β-mercapto-



propionate was condensed with diethyl-α-bromoglutarate, methyl-α-bromo-ω-cyanocaproate, and diethyl-α-bromopimelate respectively.

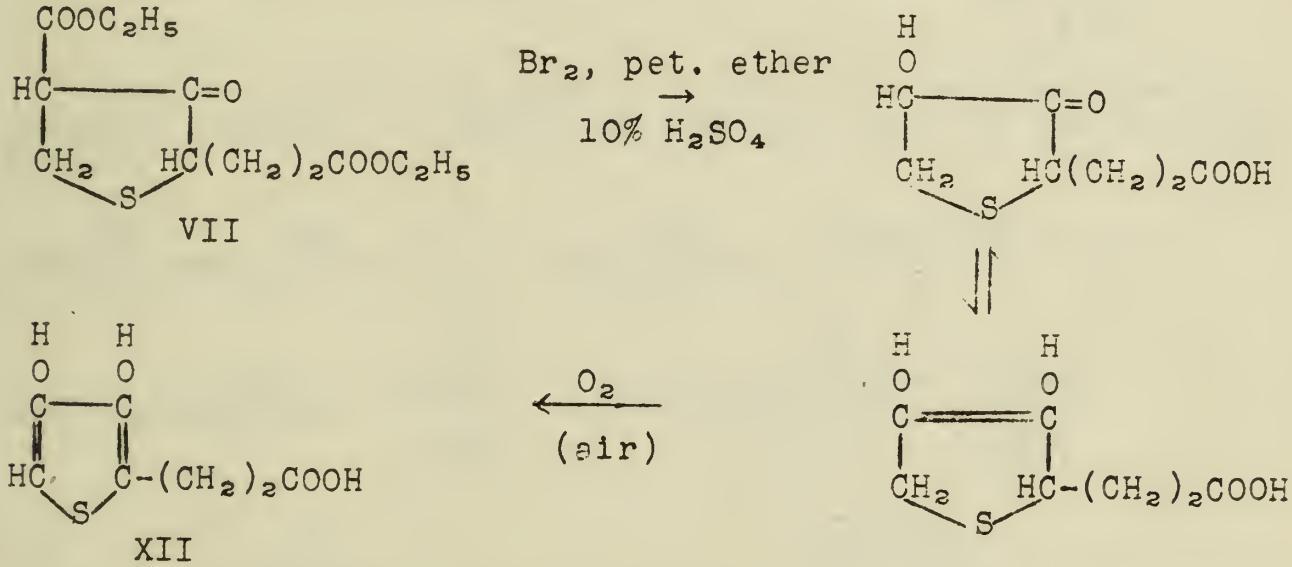


The following reactions were carried out on compound VII.



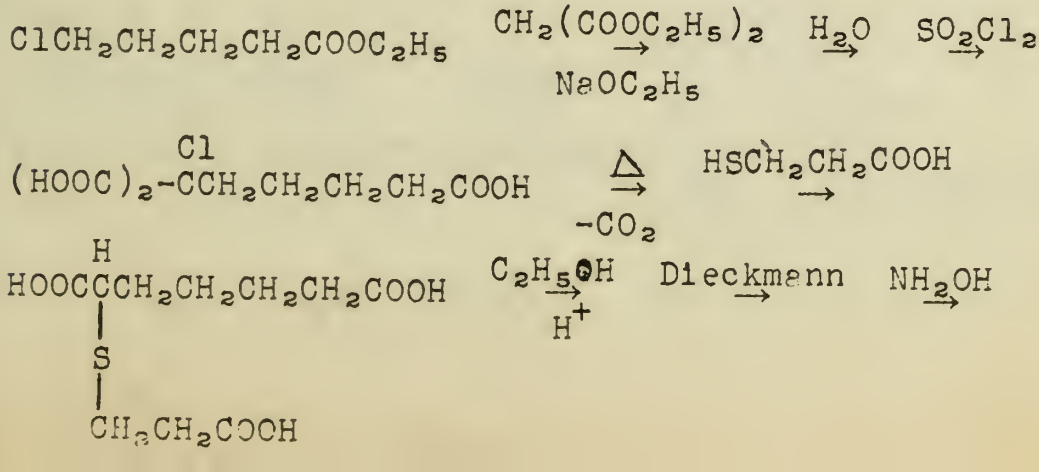
On reduction compound XI lost nitrogen, as did compound IV.

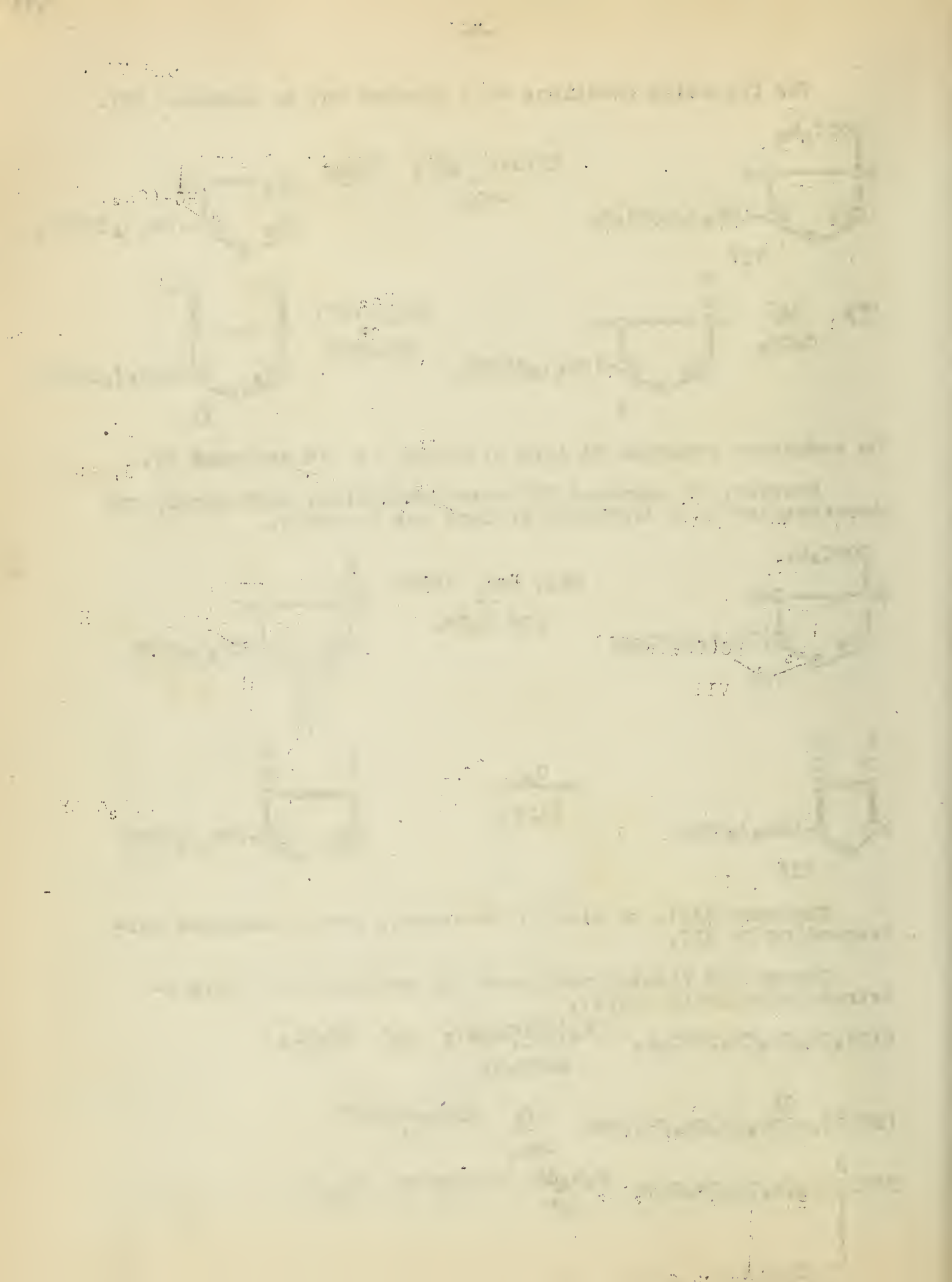
However, if compound VII were brominated, hydrolyzed, and decarboxylated, a different product was isolated.

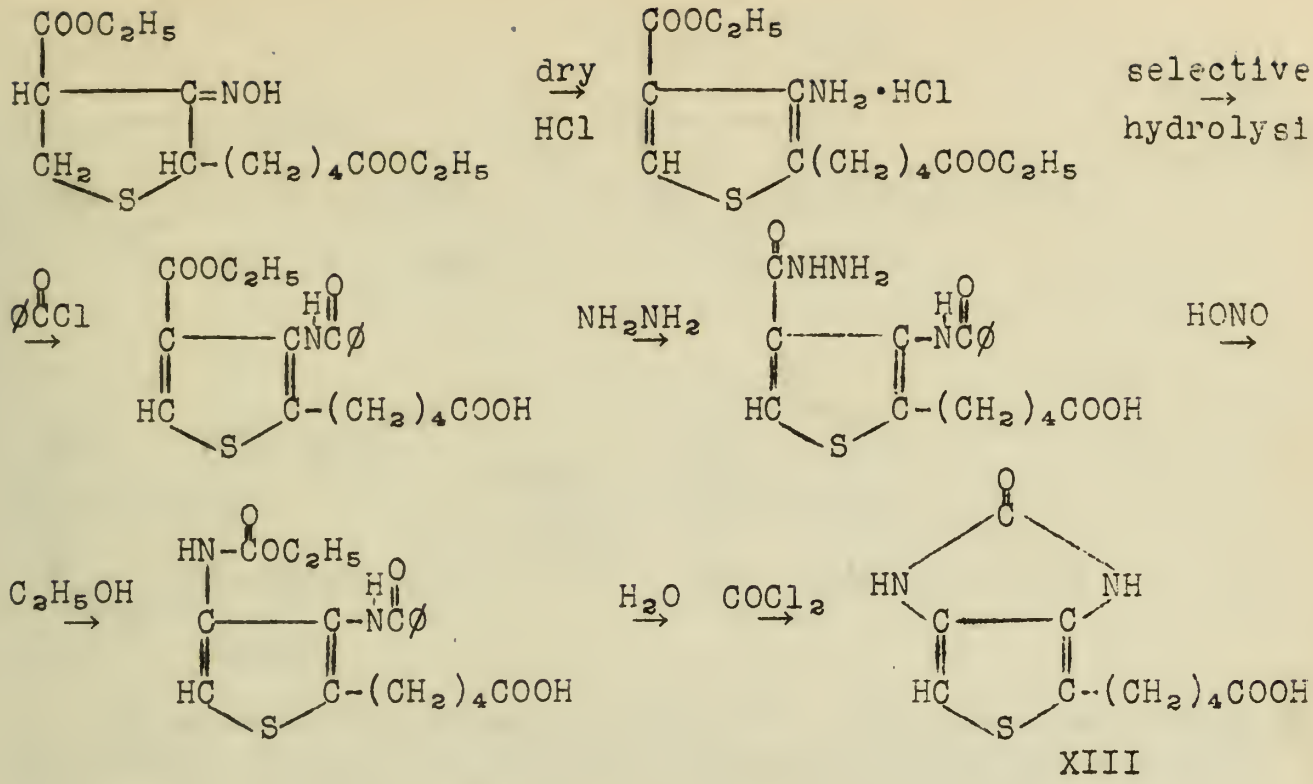


Compound VIII, on similar treatment, gave a compound corresponding to XII.

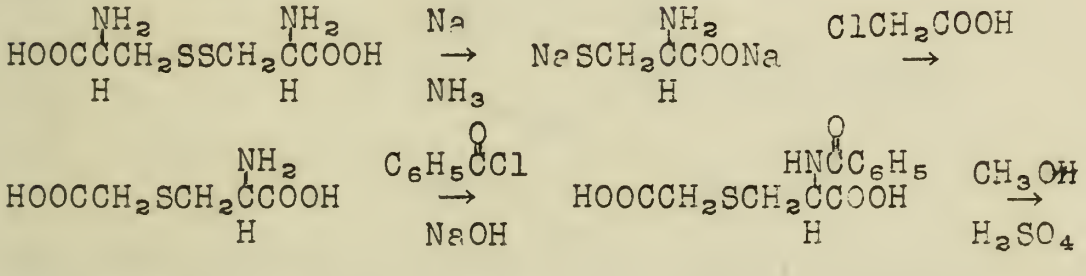
Cheney and Piening published the synthesis of 2,3,4,5-tetradehydrobiotin (XIII).

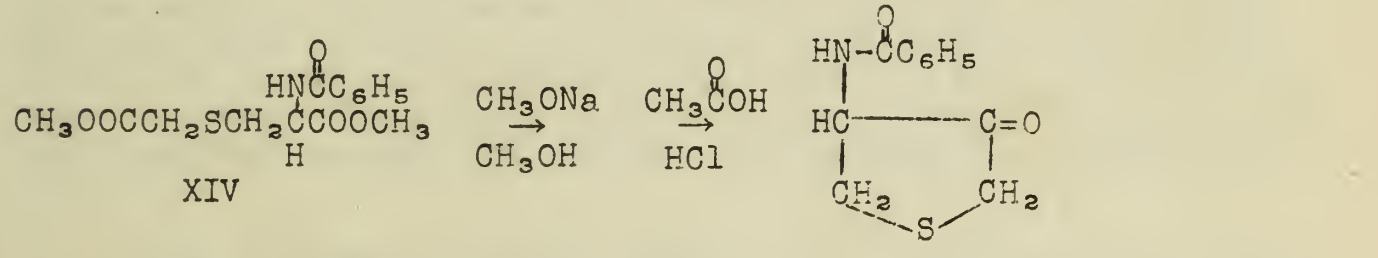




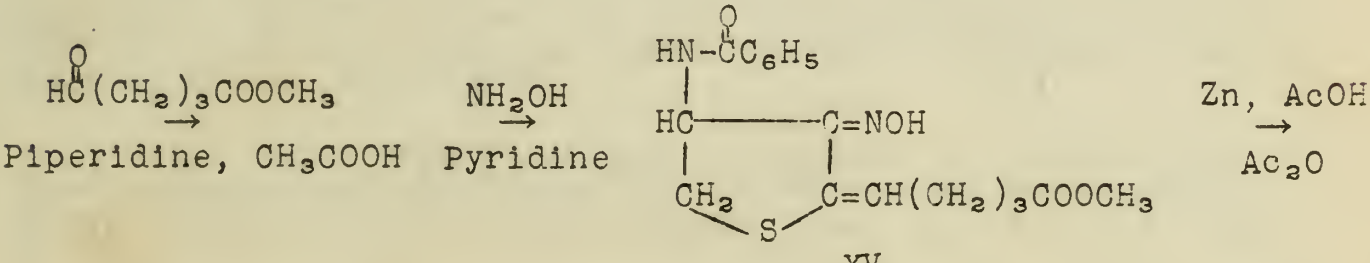


The successful synthesis of biotin was accomplished by a group of chemists at Merck and Company, Inc., in the following manner.

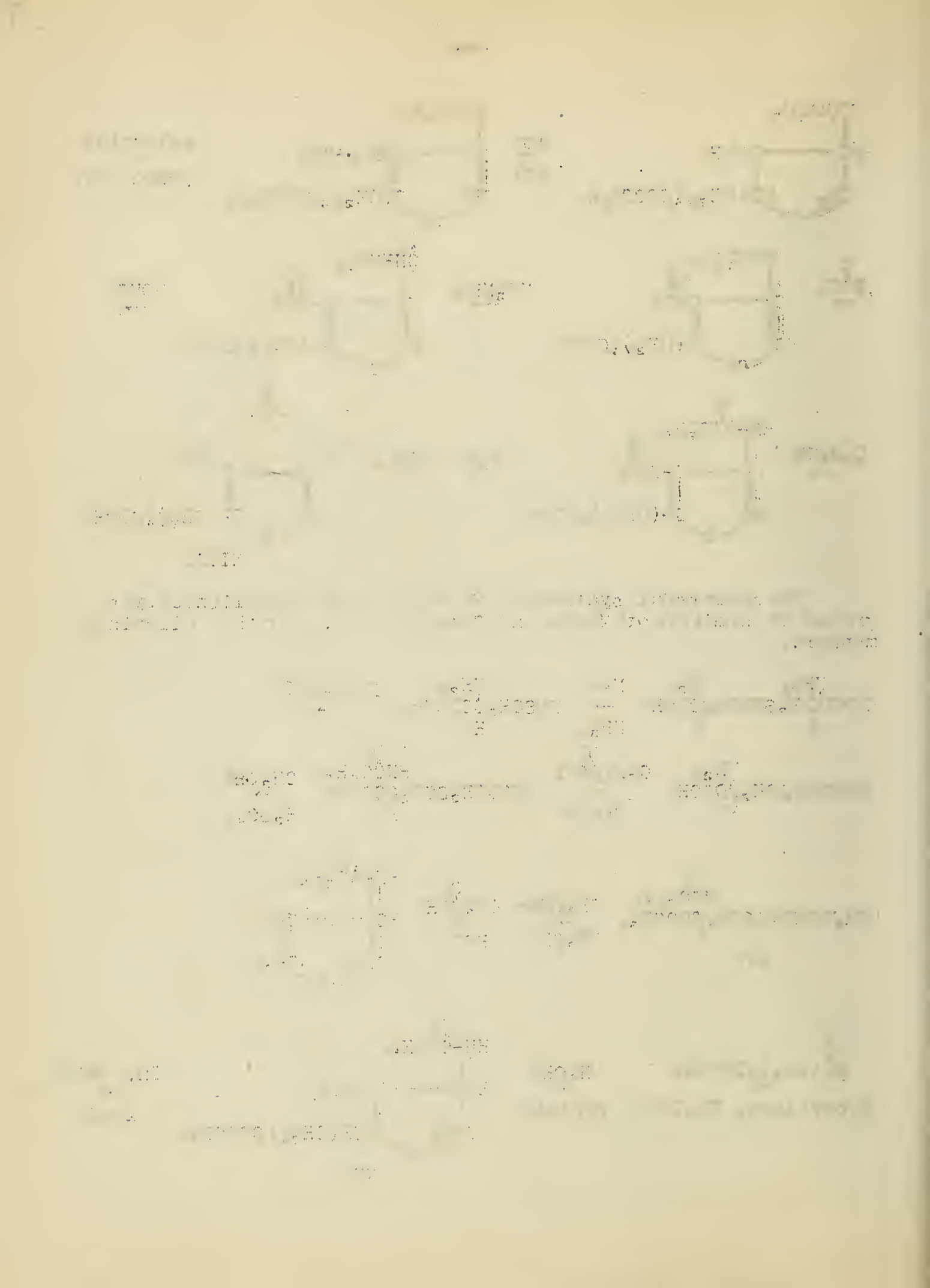


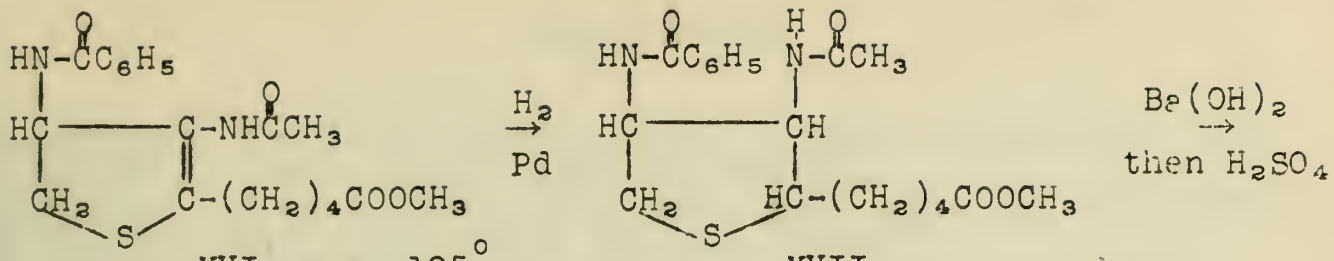


XIV

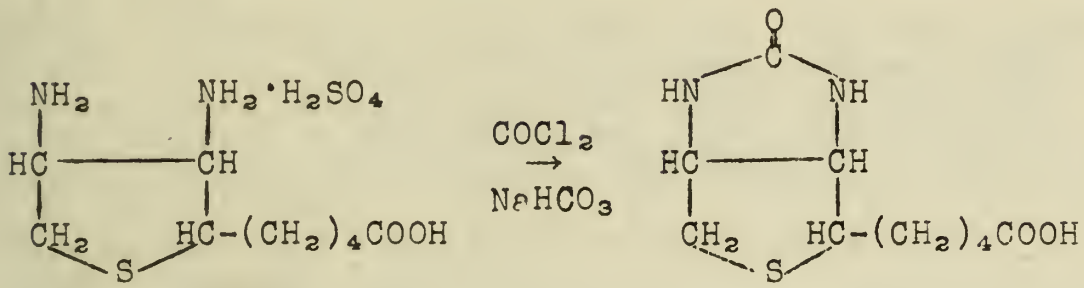


XV



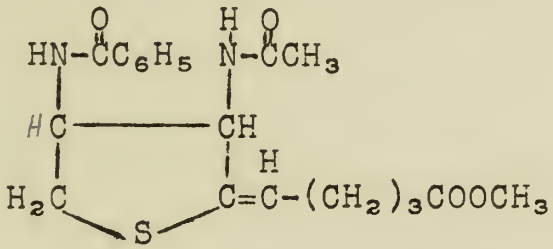


XVI, m.p. 185°



XVIII

Compound XVI melted at 185-186°. From the same reaction an isomer, XVI-A, was isolated whose melting point was 162-163°. This probably had the following structure.



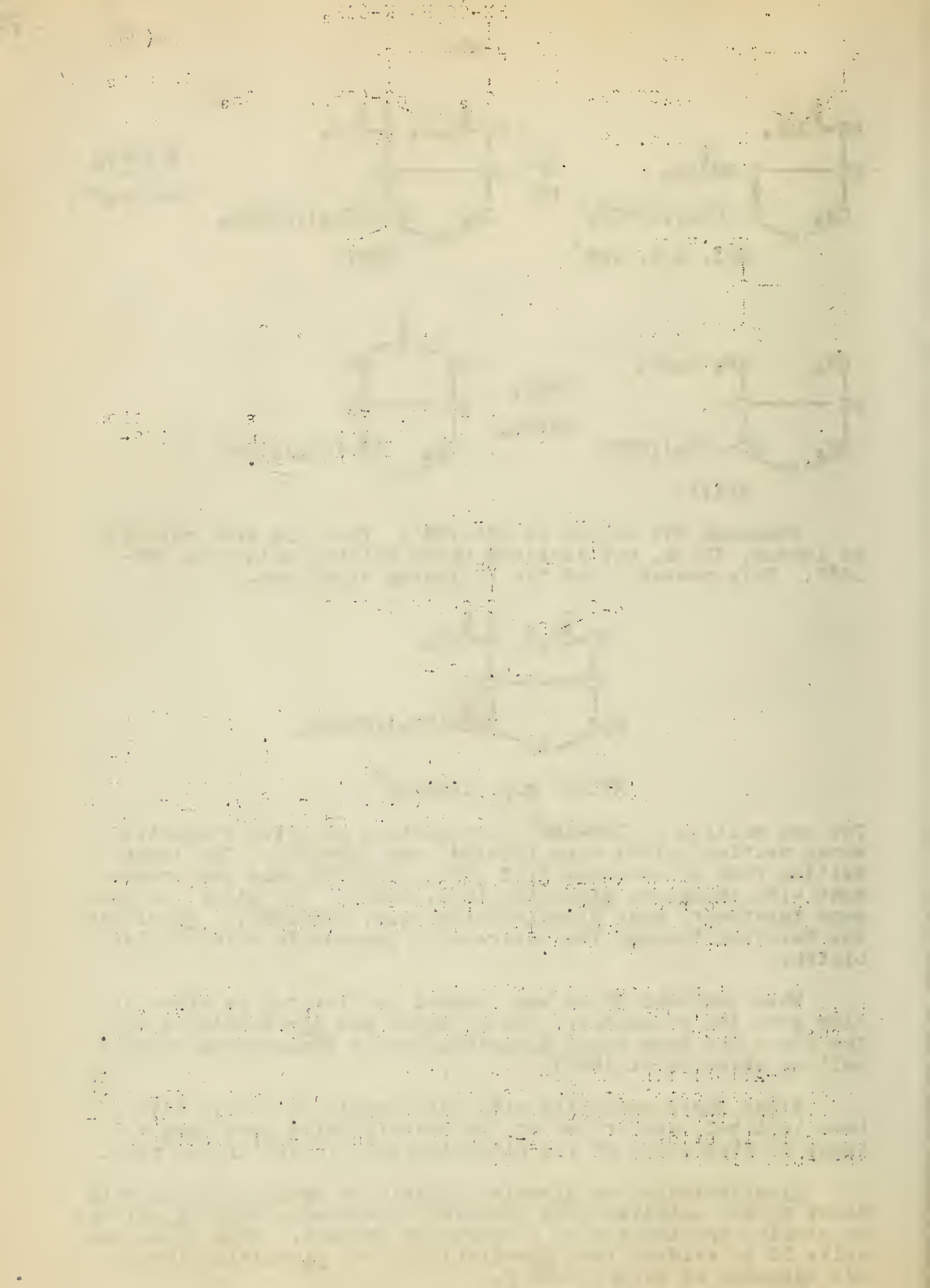
XVI-A, m.p. 162-163°

The one melting at 185-186° on reduction gave two racemates whose melting points were 153-154° and 172-173°. The lower melting form of compound XVII gave, on hydrolysis and treatment with phosgene, dl-biotin (m.p. 232°). The other, on the same treatment, gave dl-allobiotin (m.p. 194-196°). dl-Biotin was resolved through its esters with l-mandelic acid to give biotin.

When compound XVI-A was reduced and treated as above it also gave two racemates. One of these was dl-allobiotin and the other has been named dl-epiallobiotin (decomposes without melting starting at 195°).

Since three racemates with the formula of biotin have been isolated, one or two of the racemic pairs must have a trans configuration of its nitrogen atoms in its ureide ring.

dl-Allobiotin and dl-epiallobiotin on hydrogenolysis with Raney nickel catalyst gave identical compounds, while dl-biotin on similar treatment gave a different product. From these results it is evident that dl-allobiotin and dl-epiallobiotin are epimeric at carbon atom 2.



BIBLIOGRAPHY

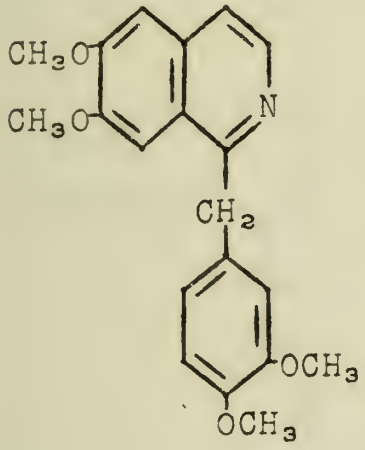
duVigneaud, Melville, Folkers, Wolf, Mozingo, Keresztesy, and Harris, J. Biol. Chem., 146, 475 (1942).
P. Karrer and H. Schmid, Helv. Chim. Acta, 27, 116, 124 (1944).
H. Schmid, Helv. Chim. Acta, 27, 127 (1944).
P. Karrer and F. Kehrer, Helv. Chim. Acta, 27, 142 (1944).
P. Karrer, R. Keller, and E. Usteri, Helv. Chim. Acta, 27, 237 (1944).
Cheney and Piening, J. Am. Chem. Soc., 66, 1040 (1944).
F. Kögl and E. ten Ham, Zeits. physiol. Chem., 279, 121 (1943).
Harris, Wolf, Mozingo, Anderson, Arth, Easton, Heyl, Wilson, and Folkers, J. Am. Chem. Soc., 66, 1756 (1944).
Harris, Easton, Heyl, Wilson, and Folkers, J. Am. Chem. Soc., 66, 1757 (1944).
Harris, Mozingo, Wolf, Wilson, Arth, and Folkers, J. Am. Chem. Soc., 66, 1800 (1944).
Harris, Wolf, Mozingo, Folkers, Science, 97, 447 (1943).

Reported by Nelson R. Easton and Herbert E. Freier
December 13, 1944

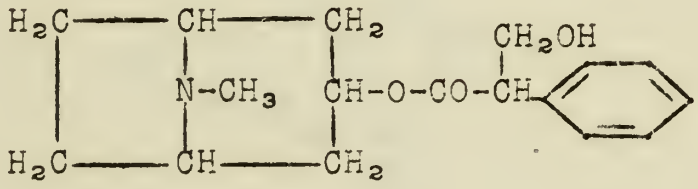
ANTISPASMODICS

Pharmacologically and physiologically, antispasmodics may be classed in two basic types: (1) Musculotropic - those that act irrespective of any innervation or in effect directly upon the muscle cell and (2) neurotropic - those that act to prevent nervous stimulation. Isolated strips of rabbit intestine are generally used as test objects. Musculotropic spasm can be simulated with barium chloride solution and neurotropic spasm with a solution of acetylcholine. The value of a substance as an antispasmodic can be measured in terms of concentration required to abolish the spasm induced in these ways. A kymograph record of the movements of the muscle shows whether or not relaxation has been produced.

Synthetic antispasmodics have been patterned after two naturally occuring drugs, papaverine (I) and atropine (II).



I



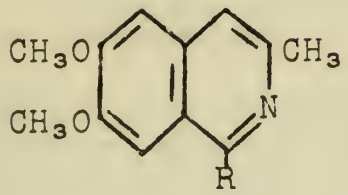
II

Papaverine exhibits musculotropic activity and atropine neurotropic activity. A single molecule combining both forms of antispasmodic activity would be invaluable from a clinical standpoint. An antispasmodic could be prescribed without the necessity of knowing the mechanism responsible for the particular spasm.

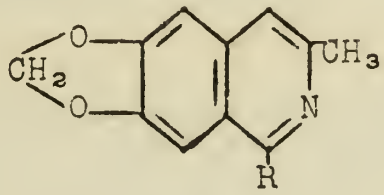
Papaverine is isolated incidental to the extraction of morphine from opium. The limited quantity available and the high cost of isolation has led to the development of numerous practical syntheses. The most recent synthesis reported is that of Kindler.

Attention has also been directed to the synthesis of papaverine-like compounds. The main efforts have been devoted to changing the substituents in the various rings, varying the side chain attached to the isoquinoline nucleus at position one, and introducing different groups at position three. Bruckner, during studies on the relation of structure to activity, prepared compounds of types (III) and (IV), in which the R group was C_6H_5-, $C_6H_5CH_2$-, 3,4-$CH_2O_2C_6H_3$-, 3,4-$CH_2O_2C_6H_3CH_2$-,

3,4-$(CH_3O)_2C_6H_3$-, 3,4-$(CH_3O)_2C_6H_3CH_2$-, p-$CH_3OC_6H_4$-, and 3,4,5-$(CH_3O)C_6H_2$-. In general these compounds were equal or

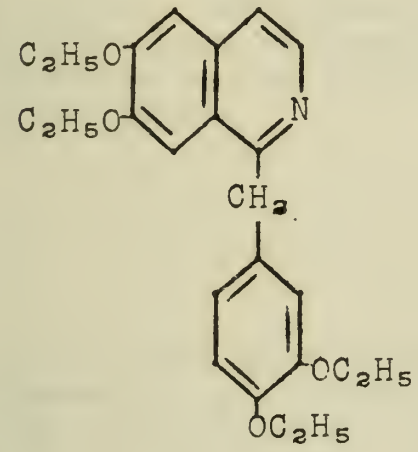


III

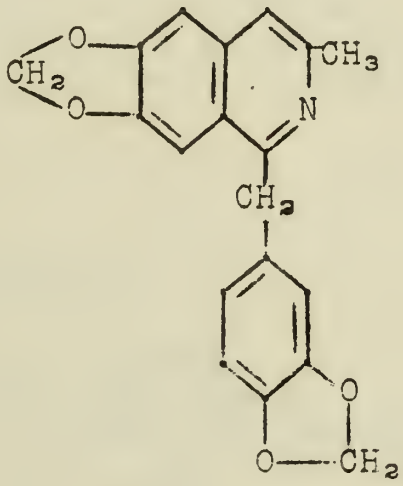


IV

superior to papaverine and less costly to manufacture. Of special interest was that the presence of the CH_2 group between the heterocyclic ring and the aromatic ring is by no means necessary for pharmocological activity. Eupaverine (V) and Perparine (VI) are probably the best known of the papaverine-like drugs. Despite the numerous modifications of the papa-



VI

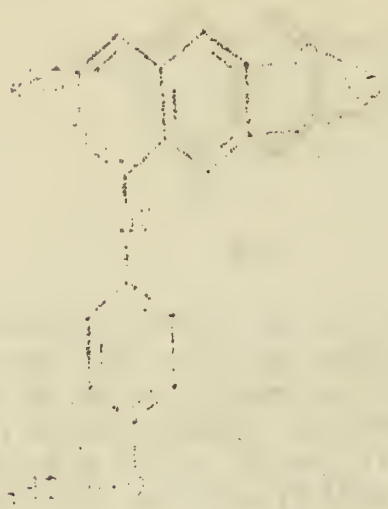


V

verine structure the compounds remained strictly musculotropic in action.

The largest amount of research in the field of synthetic antispasmodics has been devoted to the preparation of basic esters. A great number of basic esters of tropic acid has been prepared and tested. The evidence demonstrates that the basic alcohol may be much less complex than the one found in atropine and still be an effective antispasmodic. One of these esters, β,β-dimethyl-γ-diethylaminotropate, is sold under the name of Syntropan. The esters of tropine have not been studied to any great extent.

Hundreds of esters in which the alcoholic and the acyl radical are different from those in atropine have been prepared and tested in connection with antispasmodic investigations. In this class, Trasentin (β-diethylaminoethyl diphenylacetate) and



Trasentin-H (β-diethylaminoethyl phenylcyclohexylacetate) have exhibited favorable properties. The latter seems to be the most satisfactory compound. Its neurotropic activity almost equals that of atropine and its musculotropic activity is greater than that of papaverine.

Blicke has recently prepared and tested a number of basic alkyl esters similar to Trasentin. These were basic esters of substituted p-xenyl, α-naphthyl, and α-thienylacetic acids. At the present time it is especially among basic ethyl or propyl esters of disubstituted acetic acids that useful antispasmodics are sought.

One other type of basic ester of interest may be illustrated by Demerol (ethyl 1-methyl-4-phenylpiperidine-4-carboxylate). The basic nitrogen is present in the acyl instead of the alcoholic radical.

Other classes of compounds have been studied and found to be active. Antispasmodic activity is not limited to one particular class of compounds, and within a given class of active compounds no one specific radical seems to be responsible for the activity.

BIBLIOGRAPHY

Blicke, Ann. Rev. Biochem., 13, 549 (1944).
Raymond, J. Am. Pharm. Assoc., 32, 249 (1943).
Kindler and Peschke, Arch. Pharm., 272, 236 (1934).
Bruckner and Kramli, J. Prackt. Chem., 145, 291 (1936).
Bruckner and Fodor, Ber., 71B, 541 (1938).
Miescher and Hoffmann, Helv. Chim. Acta, 24, 458 (1941).
Blicke and Grier, J. Am. Chem. Soc., 65, 1725 (1943).
Blicke and Feldkamp, J. Am. Chem. Soc., 66, 1087 (1944).
Blicke and Tsao, J. Am. Chem. Soc., 66, 1645 (1944).
Eisleb, Ber., 74, 1433 (1941).

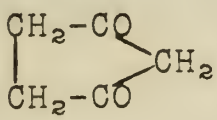
Reported by Albert Pohland
December 20, 1944

Received by Alfred Peltier
December 21, 1964

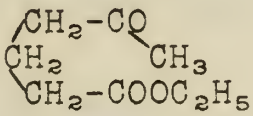
FORMATION AND REACTIONS OF CERTAIN ENOL-LACTONES

Paul Ruggli, University of Basel

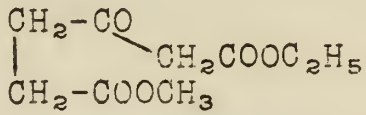
The work described here grew out of recent attempts by Ruggli and his co-workers to prepare derivatives of 1,3-cyclopentanedione (I). The parent compound is not known, and only a few derivatives of definitely established structure have been reported.



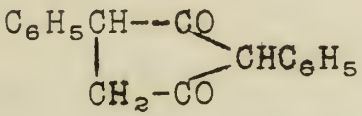
I



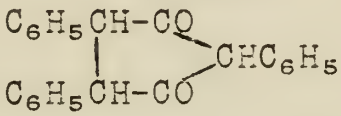
II



III



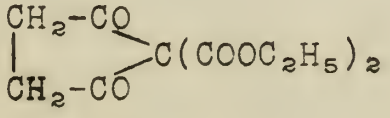
IV



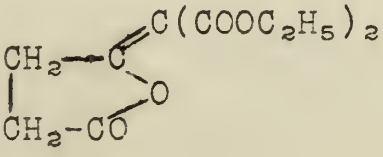
V

By analogy to the ready formation of 1,3-cyclohexanedione from ethyl δ-ketocaproate (II) (1), one would expect the desired cyclopentane analog from the ring closure of the ester of levulinic acid, but an attempt to effect this cyclization failed (2). The first attack on the problem by Ruggli and Maeder (3) involved the use of compound III with the hope that the more active methylene would induce cyclization, but this also failed to give the desired product. A second method of approach also failed to produce the cyclic diketone, but led to a field of investigation which is possibly more interesting and important than the original plan. (A measure of success has now been attained on the first problem; Ruggli and Schmidlin (4) have prepared 2,4-diphenyl-1,3-cyclopentanedione (IV) by two different methods. Koelsch and Wawzonek (5) obtained the triphenyl derivative (V) in 1941 and reported it to be completely enolic; this agrees with the observed properties of Ruggli's diphenyl derivative.)

The second unsuccessful attempt mentioned above involved the reaction of succinyl chloride with sodio-malonic ester. This reaction had been studied many years before by Reuber (6), Scheiber, and Lungwitz (7), and said by the latter two authors to produce "succinyl-malonic ester" (VI).

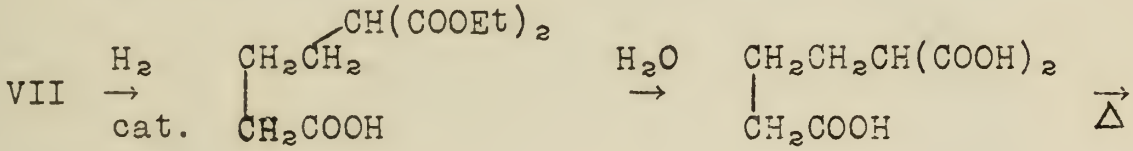


VI

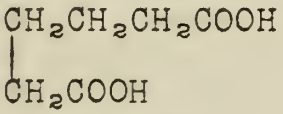


VII

The compound which Ruggli isolated was identical with their product in melting point and analysis, but has now definitely been shown to have the unsymmetrical structure VII. Previous attempts at reduction of the product had resulted in cleavage of the molecule so that no indications of the structure were given; however, Ruggli succeeded in hydrogenating the substance by the use of platinum oxide catalyst in alcohol at room temperature to produce compound VIII in good yield. Saponification of VIII gave the crystalline acid IX, and decarboxylation yielded adipic acid.

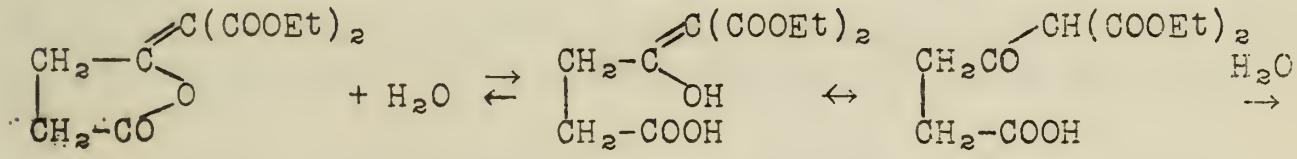


VII VIII IX

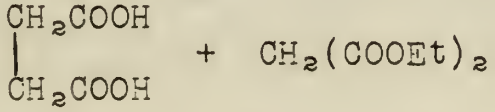


Formula VI is excluded by this work, since under these mild conditions cleavage of the β-diketone would certainly not occur, and the greatest extent of reduction would be to produce the diol. In contrast to this, the smooth catalytic hydrogenation of γ-unsaturated lactones to saturated acids under similar experimental conditions has been observed often (8).

Compound VII is very sensitive towards hydrolysis. The primary product (X or XI) may be isolated by treatment with cold

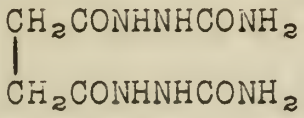


VII X XI

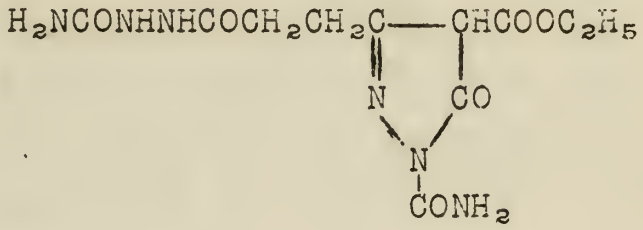


sodium carbonate closely followed by neutralization, and may be reconverted to the lactone by heating with anhydrous sodium acetate in benzene. This ease of hydrolysis is more characteristic of a true acid anhydride than of a lactone. However, Ruggli points out that structure VII is of a very special type, since the product of hydrolysis (XI) is at once a γ-hydroxy-acid and a β-ketoester, and therefore VII should be considered

an enol-lactone. The further similarity of this enol-lactone to an acid anhydride is shown by the following reactions. Dilute aqueous alkali and amines cleave the molecule to produce succinic acid and malonic ester, since the initial product (X or XI) is also easily hydrolyzed. Without solvent or in organic media, amines produce succinyl diamides. Reaction with semicarbazide leads to the formation of XII and XIII.

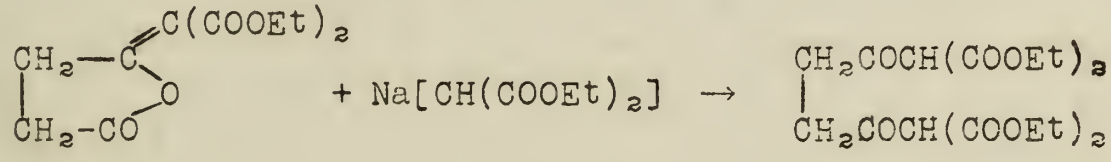


XII



XIII

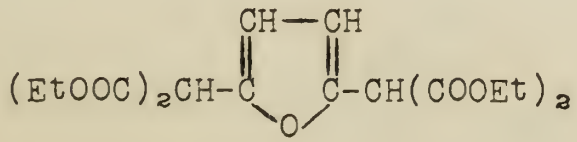
Reuber had found that succinic anhydride as well as succinyl chloride would react with sodio-malonic ester to produce "succinyl-malonic ester." Hence, Ruggli presumed that the enol-lactone itself, in keeping with its anhydride-like nature, should react further with sodio-malonic ester. Although Reuber and Lungwitz were unable to effect this reaction, product XIV was isolated in nearly quantitative yield by Ruggli.



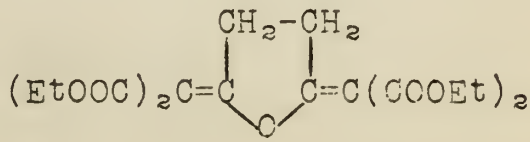
VII XIV

This tetra-ester differs distinctly from the enol-lactone VII in its reactions. It is stable towards hot water and cold dilute alkali.

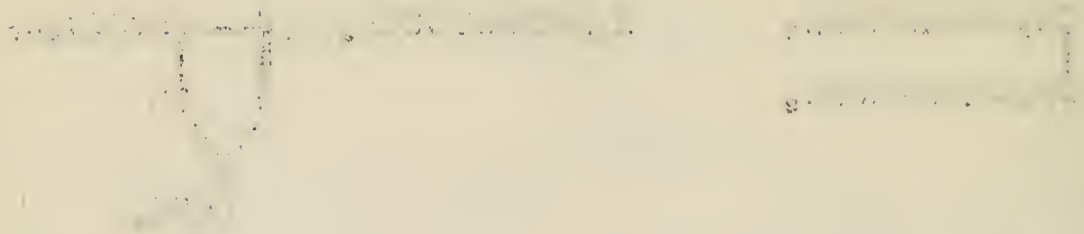
When succinyl chloride was treated with two moles of sodio-malonic ester, the main product (VII) was obtained in about 45% yield. Investigation of the crude reaction residue showed that it consisted of malonic ester, small amounts of VII, its hydrolysis product XI, and XIV. In addition, a new product, XV or XVI, was found and identified (9).



XV

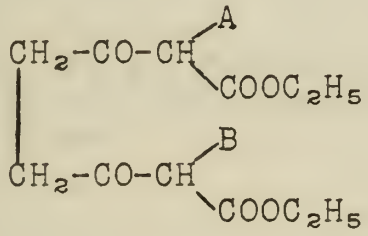


XVI



The chief interest in this residue was the possible presence of the true C-acylation product with the structure VI, which had been erroneously ascribed to the enol-lactone (VII). Some indications of the transitory existence of this form were obtained from the observation of some rather extraordinary color phenomena, but no definite conclusions were reached.

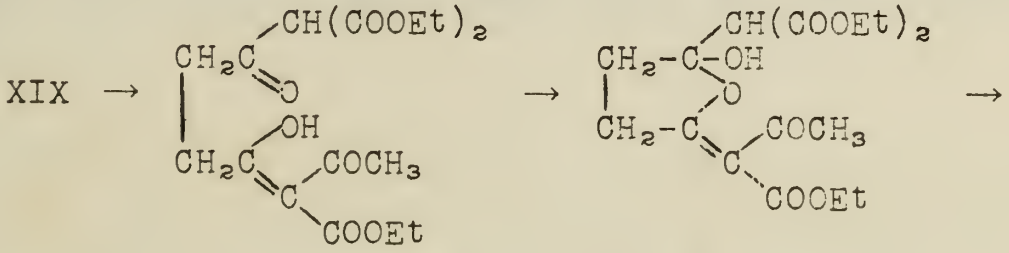
The cleavage of the enol-lactone (VII) by sodio-malonic ester to form the 1,4-diketone XIV, which is also a β-ketoester, was seen by Ruggli to offer preparative possibilities. By using succinic anhydride in place of succinyl chloride the yield of VII was raised to 63%. The substitution of other active methylene compounds for malonic ester was investigated and a new, generally applicable process for the preparation of compounds of type XVII is presented (10).

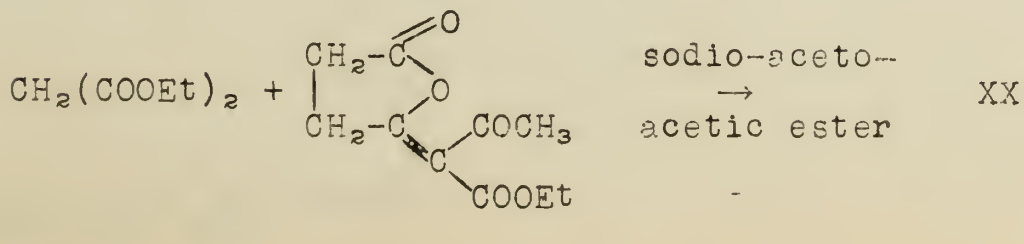


XVII

XIV: A and B = $COOC_2H_5$
XVIII: A = $COOC_2H_5$, B = CN
XIX: A = $COOC_2H_5$, B = $COCH_3$
XX: A and B = $COCH_3$

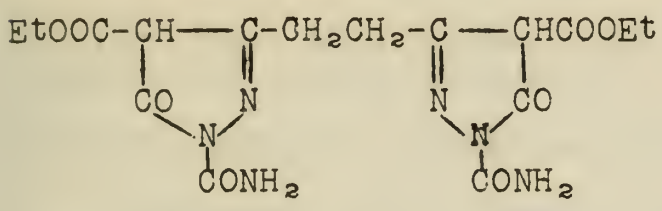
Treatment of VII with sodio-cyanoacetic ester gave compound XVIII. The reaction of succinic anhydride with an excess of sodio-acetoacetic ester gave directly compound XX, evidently through the intermediate formation and cleavage of an enol-lactone analogous to VII, but even more sensitive, since it could not be isolated. When VII was treated with sodio-aceto-acetic ester a mixture of XIX and XX was produced. The mechanism proposed to explain this substitution occurring along with condensation was based partly on the earlier observation by Ruggli (3) that, in the presence of catalytic amounts of trimethylamine, XIV decomposed to VII and malonic ester.



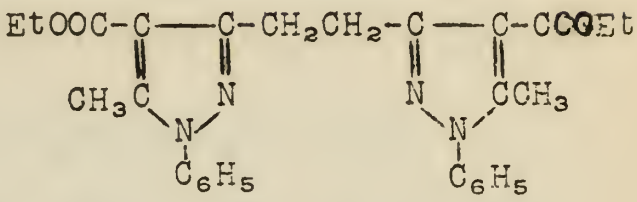


XX

The β-ketoesters and β-diketones produced by this synthesis react with semicarbazide and phenylhydrazine to form the expected substituted pyrazolones and pyrazoles, of which examples XXI and XXII may be given.



XXI



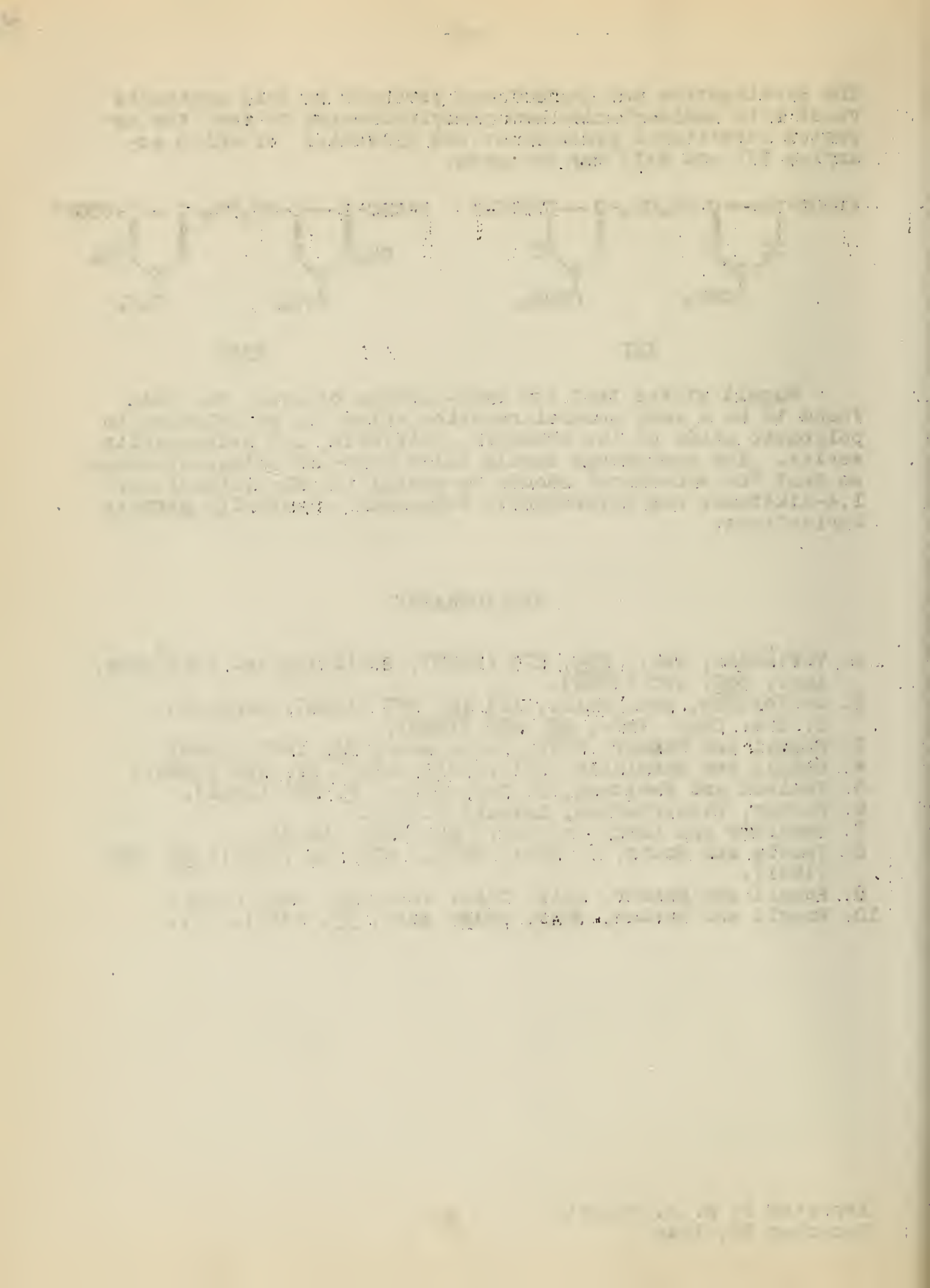
XXII

Ruggli states that the enol-lactone cleavage has been found to be a very general reaction which may be extended to polybasic acids of the aromatic, alicyclic, and heterocyclic series. The end-groups should allow acid- or ketone-cleavage so that the substances should be useful in the synthesis of 1,4-diketones and heterocyclic compounds, especially pyrrole derivatives.

BIBLIOGRAPHY

1. Vorländer, Ann., 294, 270 (1897); Schilling and Vorländer, Ann., 308, 190 (1899).
2. de Rosambo, Ann. chim., (9) 19, 327 (1923); Bergmann, J. Soc. Chem. Ind., 58, 465 (1939).
3. Ruggli and Maeder, Helv. Chim. Acta, 26, 1476 (1943).
4. Ruggli and Schmidlin, Helv. Chim. Acta, 27, 499 (1944).
5. Koelsch and Wawzonek, J. Org. Chem., 6, 684 (1941).
6. Reuber, Dissertation, Leipzig (1897).
7. Scheiber and Lungwitz, Ber., 42, 1320 (1909).
8. Jacobs and Scott, J. Biol. Chem., 87, 601 (1930); 93, 139 (1931).
9. Ruggli and Maeder, Helv. Chim. Acta, 26, 1499 (1943).
10. Ruggli and Maeder, Helv. Chim. Acta, 27, 436 (1941).

Reported by R. M. Roberts
December 20, 1944



THE REACTION OF N-METHYLOLAMIDES WITH AROMATIC COMPOUNDS

Sachs, in 1898, prepared N-methylolphthalimide by heating together phthalimide and aqueous formaldehyde.

$$C_6H_4(CO)_2NH + CH_2O \rightarrow C_6H_4(CO)_2NCH_2OH.$$

He found that this product would react with aniline to form a substituted methylenediamine.

$$C_6H_4(CO)_2NCH_2OH + C_6H_5NH_2 \rightarrow C_6H_4(CO)_2NCH_2NHC_6H_5 + H_2O.$$

Tscherniac, in a German patent dated 1902, claimed the condensation of N-methylolphthalimide with aromatic compounds such as hydrocarbons, nitro compounds, phenols and phenol ethers, tertiary bases, sulfonic acids, etc., to form the corresponding N-benzylphthalimides. These products could in turn be hydrolyzed to the corresponding benzylamines:

$$C_6H_4(CO)_2CH_2OH + ArH \rightarrow C_6H_4(CO)_2NCH_2Ar \xrightarrow{H^+}$$

$$C_6H_4(CO_2H)_2 + ArCH_2NH_2$$

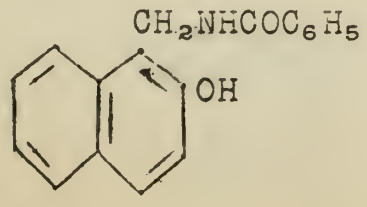
The condensation was carried out in the presence of concentrated sulfuric acid and took place quite readily when the aromatic component was benzene, nitrobenzene, m- and p-nitrotoluene, o-nitroanisole, dimethylaniline, etc.

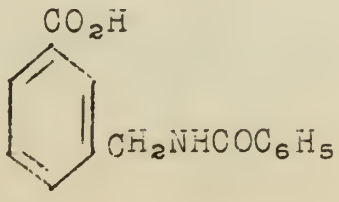
Einhorn and coworkers, in two papers published in 1905 and 1908, respectively, announced the preparation of the N-methylol derivatives of a large number of amides by a method which involved allowing the amide and formaldehyde to stand in the presence of a base such as sodium hydroxide, sodium carbonate, barium hydroxide, triethylamine, or potassium cyanide.

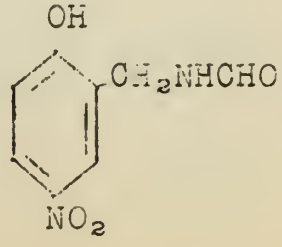
$$RCONH_2 + CH_2O \rightarrow RCONHCH_2OH$$

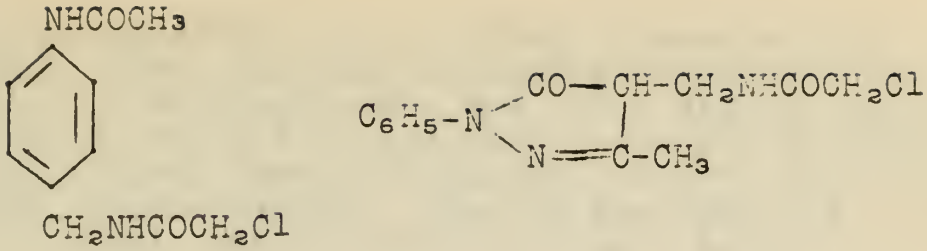
In this fashion were prepared N-methylol derivatives of amides of mono- and poly-basic acids. The reaction also was found to be applicable to amides of the aliphatic, aromatic, and heterocyclic series.

Einhorn extended the work of Tscherniac by carrying out condensations of his N-methylolamides with several aromatic compounds. Among the methylol derivatives used were those of benzamide, chloroacetamide, salicylamide, and formamide. Below are representative condensation products obtained by Einhorn.



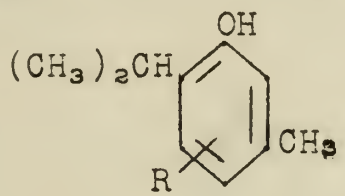
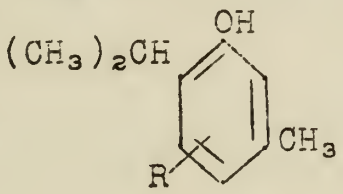
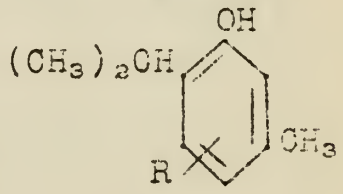
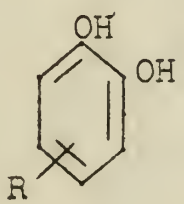
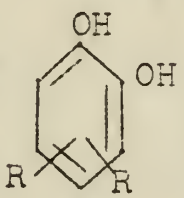
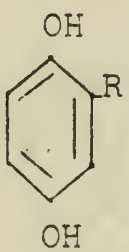
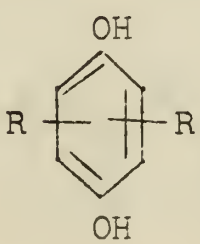
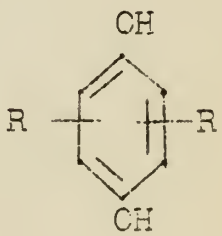
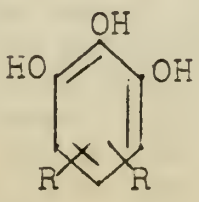
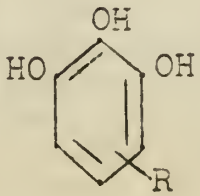
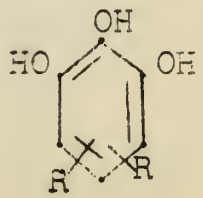


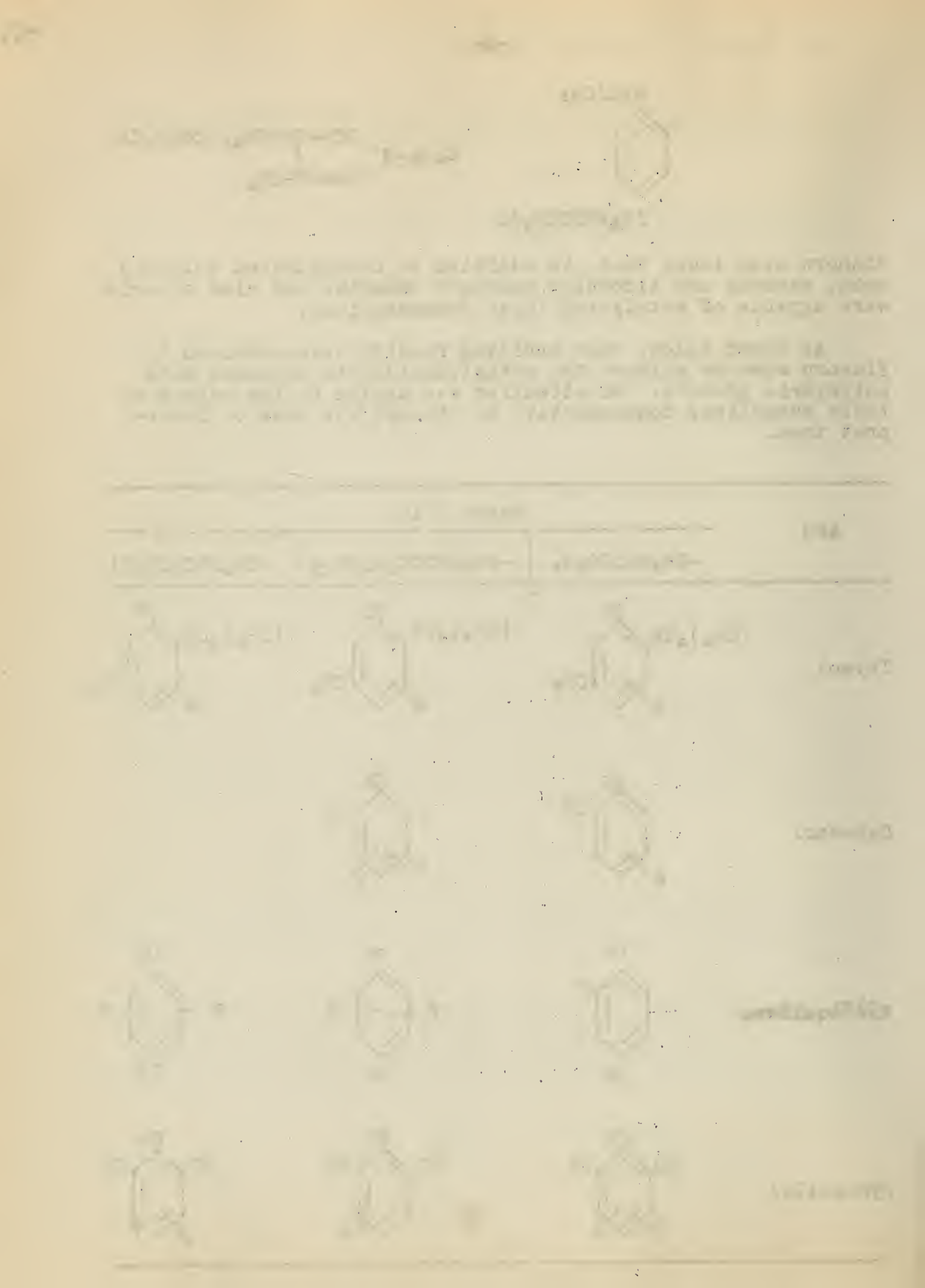




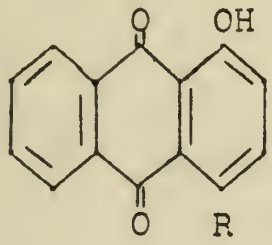
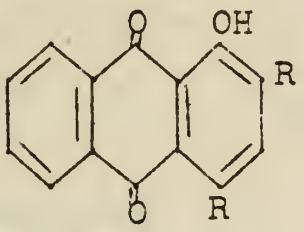
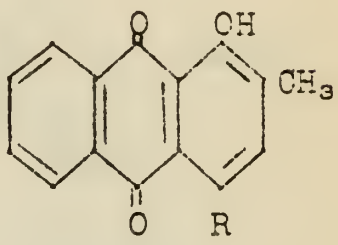
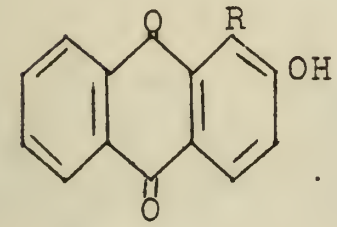
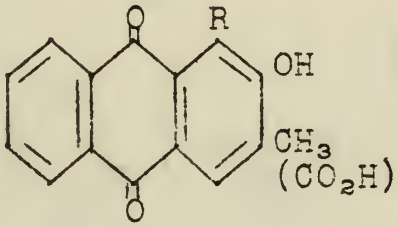
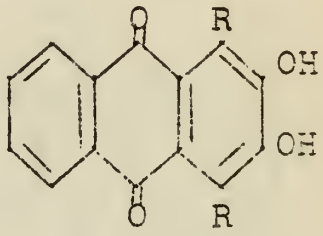
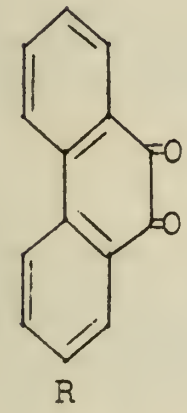
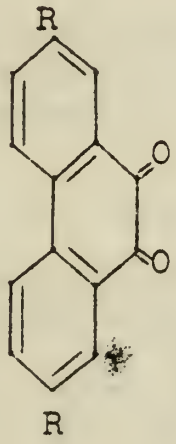
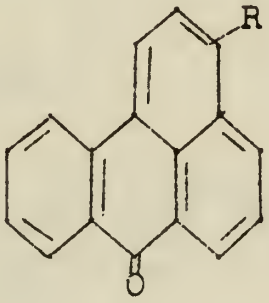
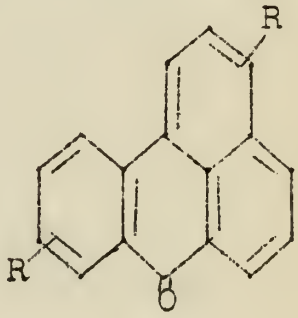
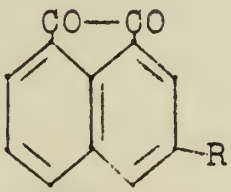
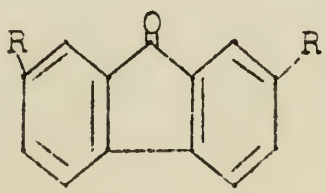
Einhorn also found that, in addition to concentrated sulfuric acid, aqueous and alcoholic hydrogen chloride and zinc chloride were capable of catalyzing these condensations.

As shown below, some striking results were obtained by Einhorn when he allowed the methylolamides to condense with polyhydric phenols. No attention was called by the author to these anomalies; consequently, no attempt was made to interpret them.

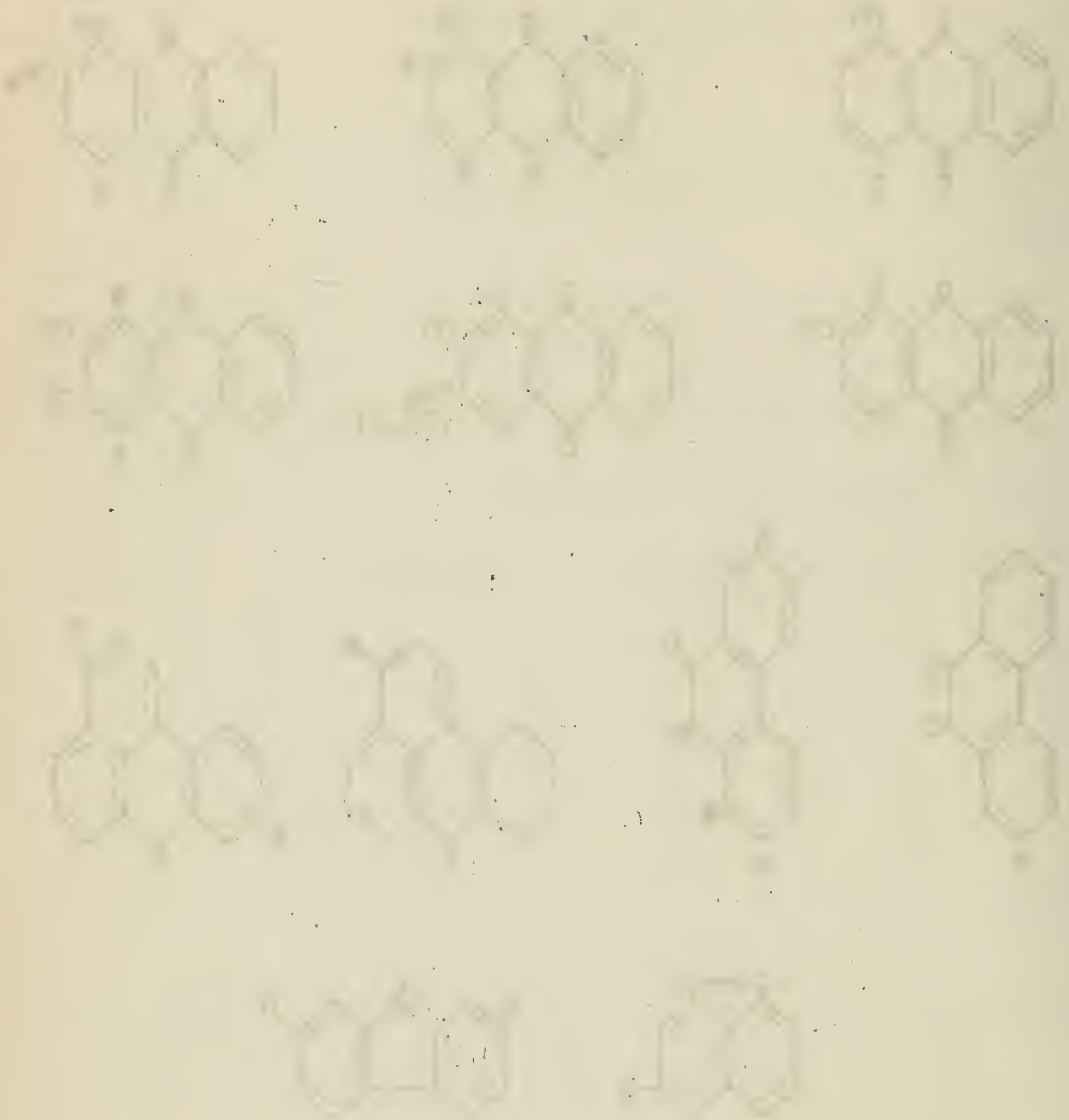
ArH	Where R is		
	$-CH_2NHCOC_6H_5$	$-CH_2NHCOC_6H_4OH$-o	$-CH_2NHCOCH_2Cl$
Thymol			
Catechol			
Hydroquinone			
Pyrogallol			



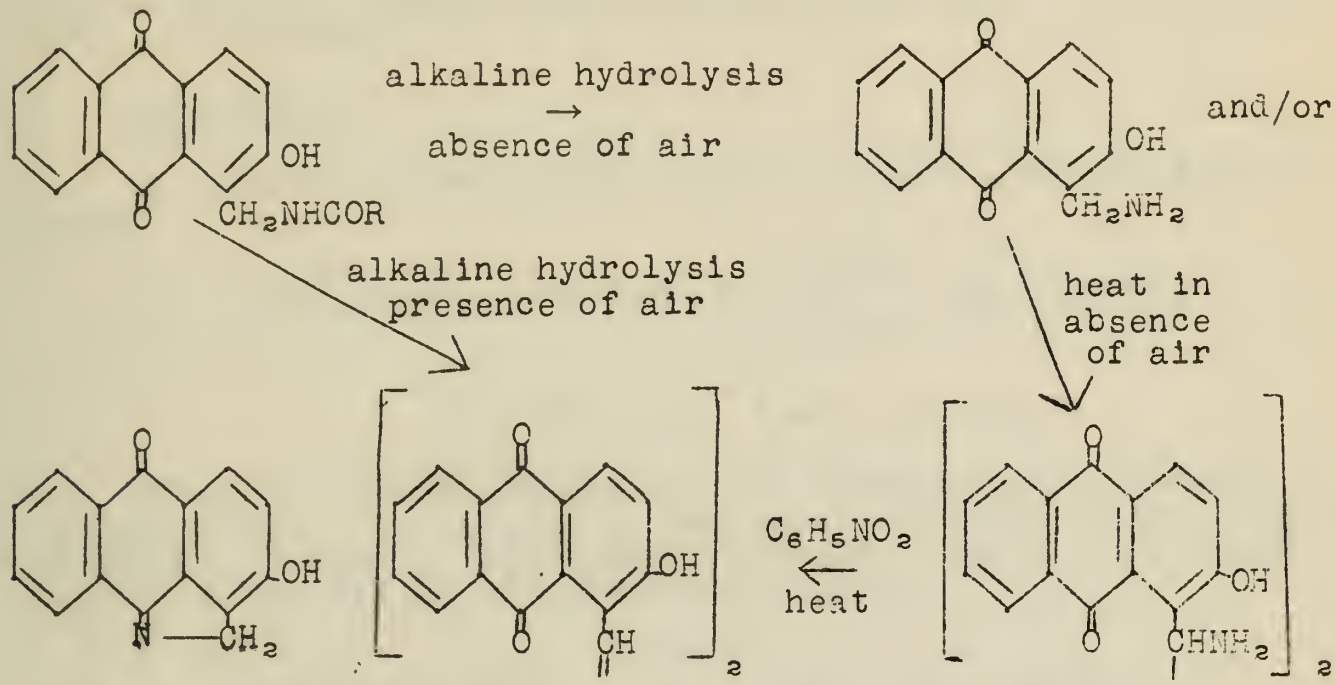
de Diesbach and coworkers, in a series of studies extending from 1928 to 1940, applied the condensation reaction of N-methylolamides to anthraquinones and other higher quinones and aromatic ketones. The N-methylolamides employed in these studies were those derived from phthalimide, chloroacetamide, trichloroacetamide, and benzamide. Some of the types of products obtained in this manner are illustrated below.

Benzophenone cannot be made to condense with the methylolamides, but the methylbenzophenones undergo reaction to yield mono- and di-acylaminomethyl derivatives, while the hydroxybenzophenones yield the disubstituted product exclusively. The three toluic acids undergo condensation in the usual fashion to give the product bearing the acylaminomethyl group in the position meta to the carboxyl group.



In attempting to hydrolyze the acylaminomethyl derivatives of the anthraquinone series, de Dreisbach found that the hydrolysis products depended on the mode of operation. In the case of the acylaminomethyl derivative of 2-hydroxyanthraquinone, the following transformations have been observed

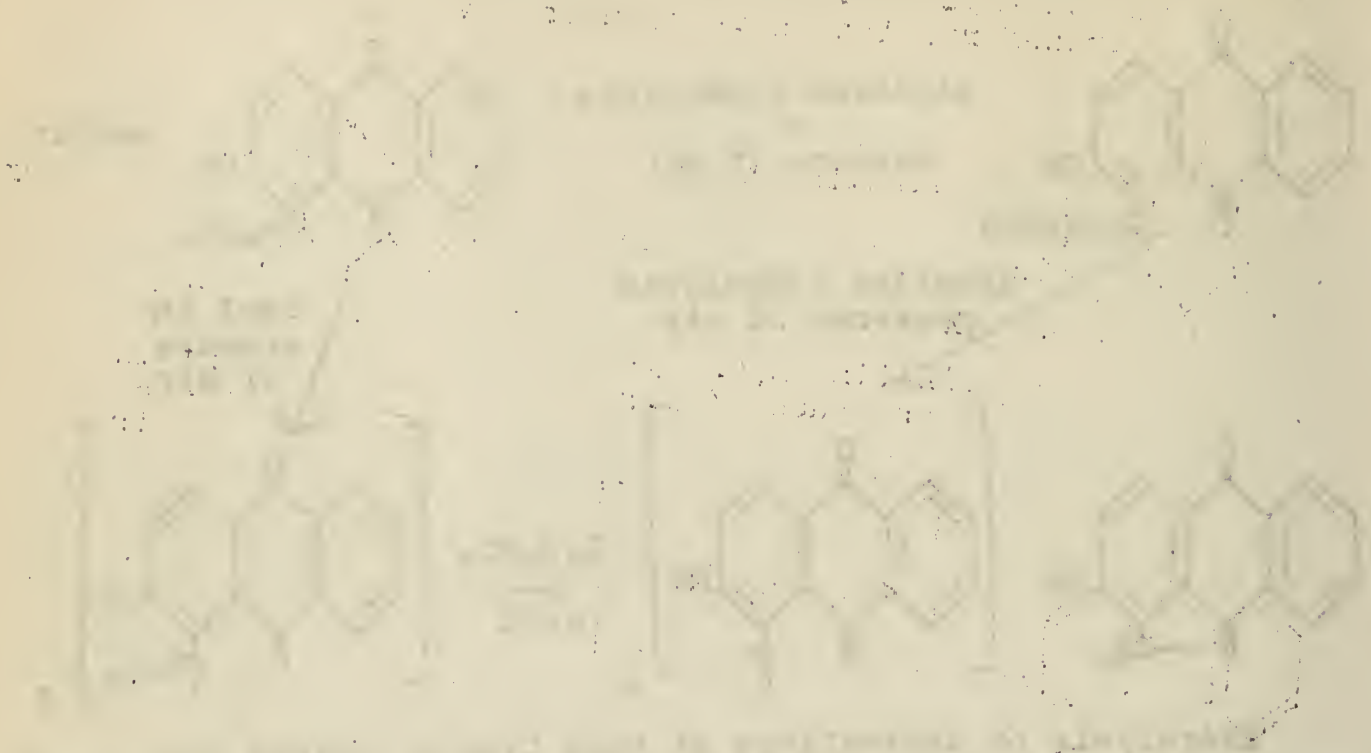


Hydrolysis of derivatives of this type is always accompanied by the formation of a certain amount of high-molecular-weight, polymeric material.

BIBLIOGRAPHY

Sachs, Ber., 31, 3230 (1898)
Tscherniac, DRP 134979; Frdl., VI, 143 (1902)
Einhorn et al., Ann., 343, 207 (1905); 361, 113 (1908)
de Driesbach et al., Helv. Chim. Acta, 11, 1098 (1928); 13, 120, 1265 (1930); 23, 1232 (1940)

Reported by Samuel Boyd
January 3, 1945



KETENE ACETALS

(McElvain et al, University of Wisconsin)

The purpose of this seminar is to review briefly the chemistry of the ketene acetals that has been covered in previous seminars and to discuss several recent publications that are concerned with this subject.

I. Preparation.

A. Elimination of hydrogen bromide from α-bromoacetals by bases.

$$BrCH_2CH(OR)_2 + KOC(CH_3)_3 \xrightarrow[\text{reflux}]{\text{t-BuOH}} CH_2 = C(OR)_2$$

R = Et, n-Pr, iso-Bu, isoamyl

This is the best method for the preparation of ketene diethylacetal. An attempt to extend this method to the preparation of $RCH_2CH = C(OEt)_2$ failed since the elimination of hydrogen bromide proceeded in an unfavorable manner.

$$RCH_2CHBrCH(OEt)_2 \xrightarrow{KOBu(t)} RCH = CH - CH(OEt)_2$$

Ketene acetals are not intermediates since compounds of the type $RCH = C(OEt)_2$ will not rearrange under these conditions.

B. Elimination of elements of alkyl hypohalites, ROX from orthoesters by metals.

$$RCHBr\text{-}C(OEt)_3 + 2Na \rightarrow RCH{=}C(OEt)_2 + NaBr + NaOEt$$

C. Pyrolysis of orthoresters.

$$C_6H_5CH_2C(OEt)_3 \xrightarrow{\triangle} C_6H_5CH = C(OEt)_2$$

This method if limited because the ketene acetal formed in the reaction is unstable to heat. It will, however, serve as a source of ketene acetal in a reaction which will remove the ketene acetal as soon as it is formed. A typical illustration is outlined below.

$$CH_3C(OEt)_3 \xrightarrow{200^\circ C} [CH_2 = C(OEt)2] \xrightarrow{C_6H_5OH} CH_3C\begin{matrix}(OEt)_2\\ OC_6H_5\end{matrix} \rightarrow$$

$$CH_3COOEt + C_6H_5OEt$$

It was through such reactions that McElvain studied the reactivity of OR group by their elimination from $RCH_2C(OR)_2OR'$

$BrCH_2C(OEt)_3 \xrightarrow{\Delta} CH_2 = C(OEt)_2$ $Br_2CHC(OEt)_3 \xrightarrow{\Delta} BrCH = C(OEt)_2$
(not Cl)

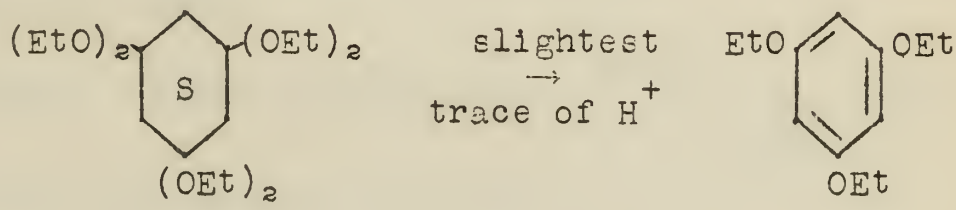
II Reactions.

A. Polymerization of Ketene Diethylacetal.

Strong acids such as hydrochloric acid and metal salts such as cadmium chloride produced a glass-like, "head-to-tail" polymer.

$$CH_3C(OEt)_2 - [CH_2C(OEt)_2 -]_n CH_2C(OEt)_3 \qquad n = 20, 21$$

A 1% solution of ketene diethylacetal and 5% hydrogen fluoride in ether gave 12-14% dimer and 40-45% trimer. Half the trimer or 22% was shown to be I.



I

Methylketene diethylacetal does not polymerize with either hydrogen fluoride or cadmium chloride.

B. Reaction with "Active Hydrogen" Compounds.

$$(1)\ CH_2 = C(OEt)_2 + HX \rightarrow [CH_3C(OEt)_2X] \rightarrow CH_3COOET + EtX$$

where X = OH, halogen, RCOO- or ArO-.

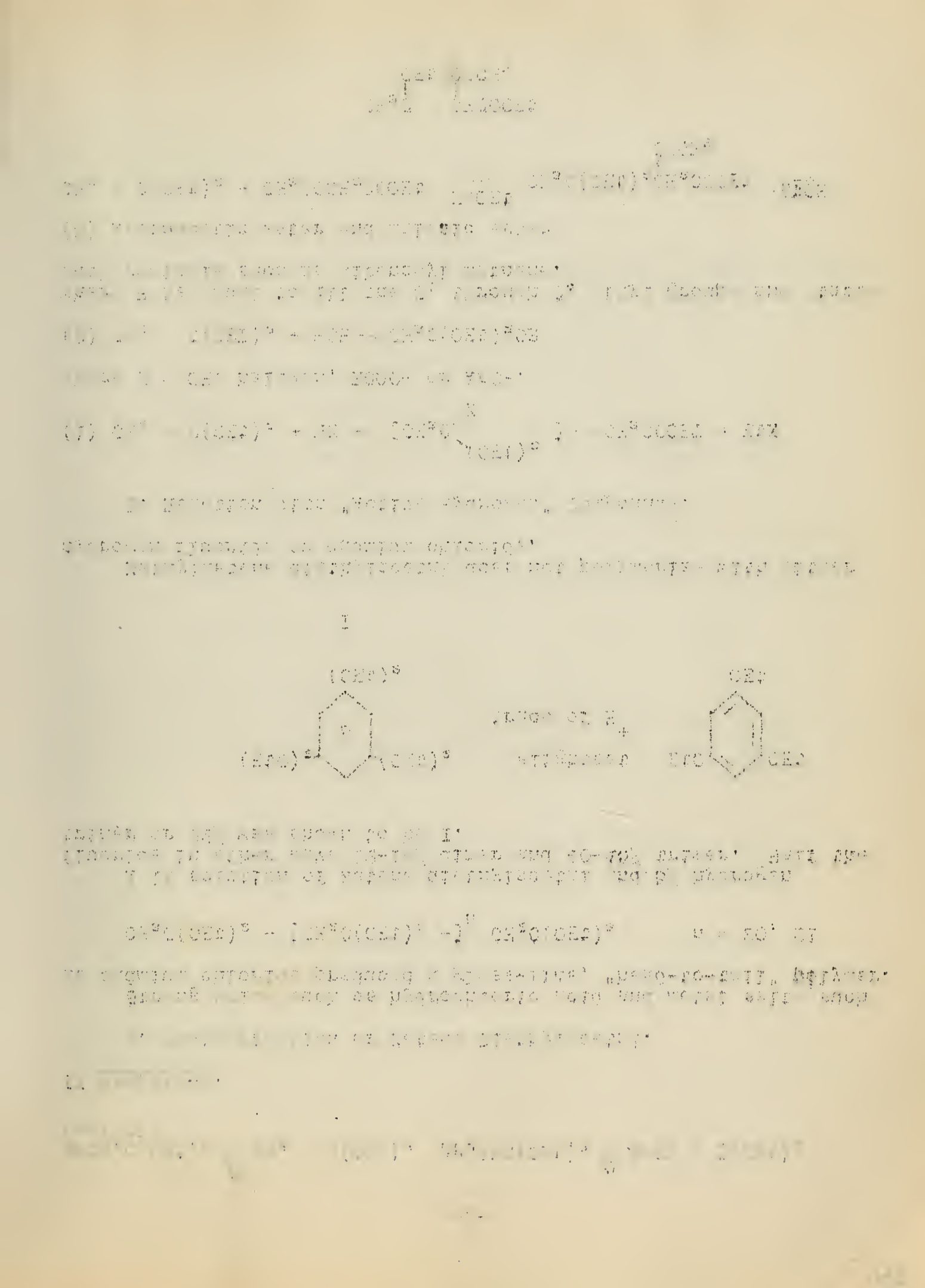
$$(2)\ CH_2 = C(OET)_2 + ROH \rightarrow CH_3C(OEt)_2OR$$

where R is equal to all the C_1 through C_4 alkyl groups and stable enol radicals such as dibenzoyl methane.

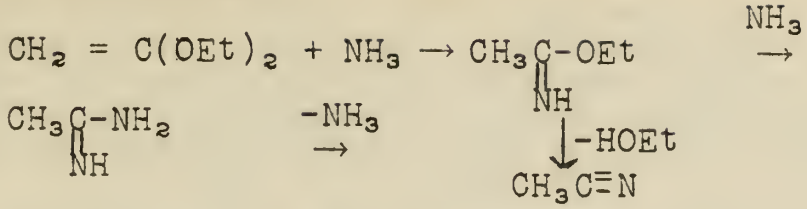
(3) Acetoacetic ester and malonic ester

$$CH_2 = C(OEt)_2 + CH_3COCH_2COOEt \xrightarrow{NaOEt} CH_3C(OEt)_2\underset{\displaystyle COCH_3}{\underset{|}{CH_2}}COOEt \xrightarrow{-EtOH}$$

$$CH_3\underset{\displaystyle OEt}{\underset{|}{C}} = \underset{\displaystyle COCH_3}{\underset{|}{C}}HCOOEt$$

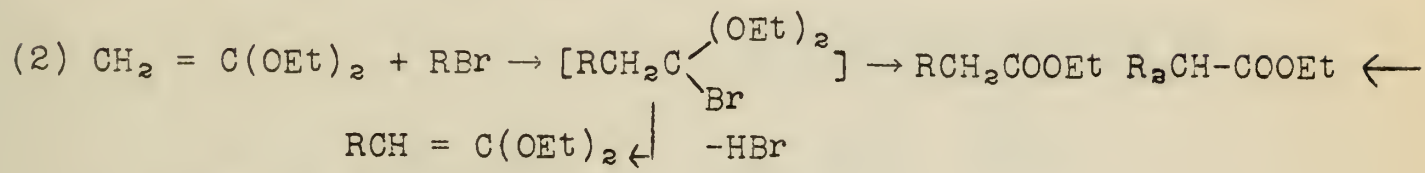


(4) Nitrogen Compounds.

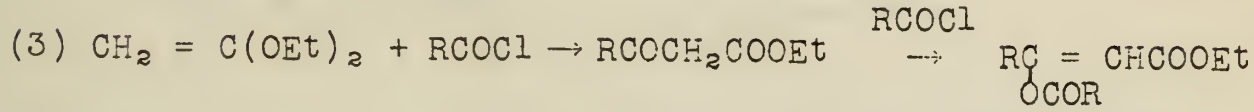


C. Reaction with Acyl and Alkyl halides.

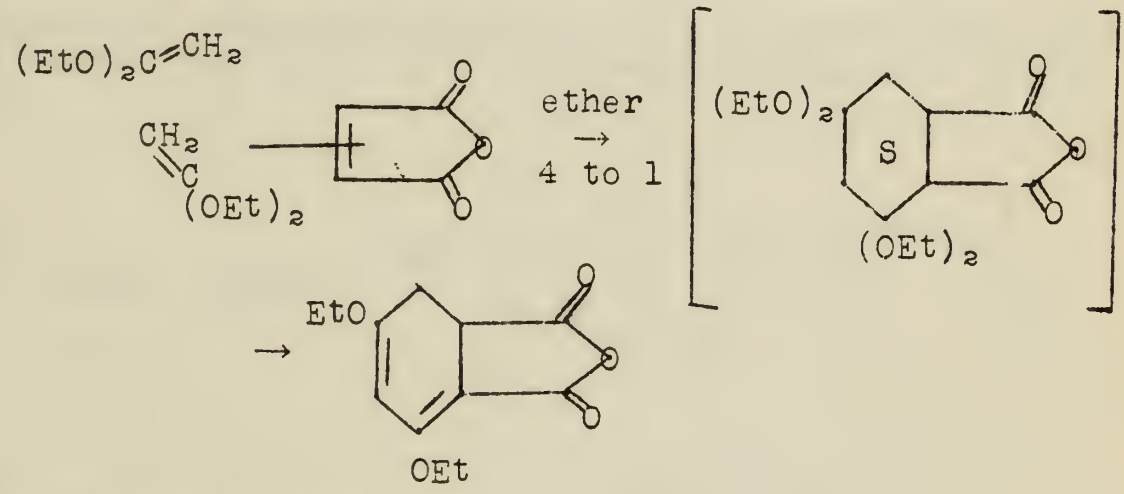
(1) $CH_2 = C(OEt)_2 + C_4H_9Br \rightarrow C_4H_9CH_2COOEt + EtBr$



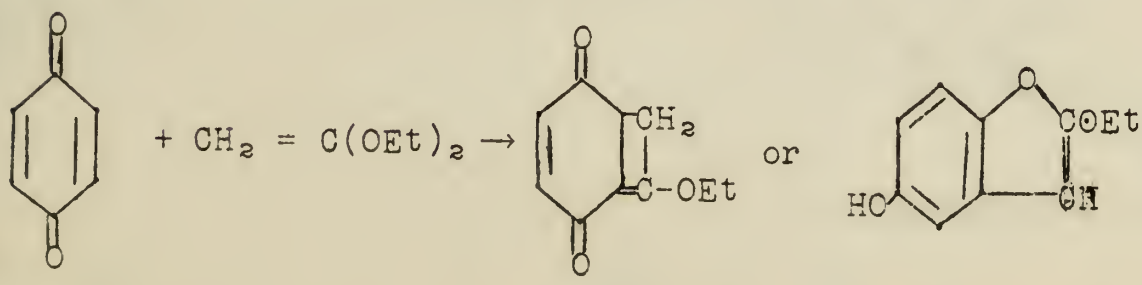
R = allyl or benzyl



D. Reaction with Maleic Anhydride.



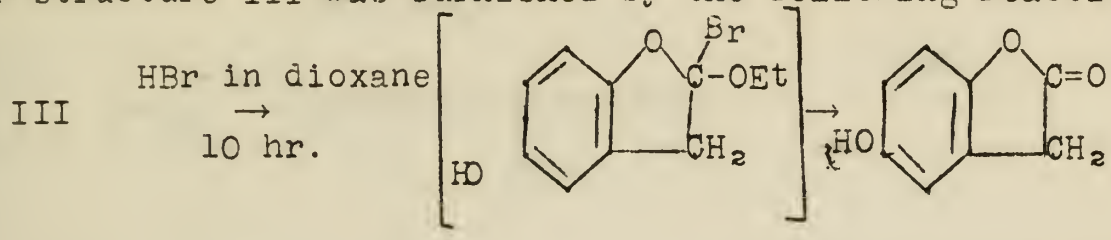
E. Reaction with Quinones.



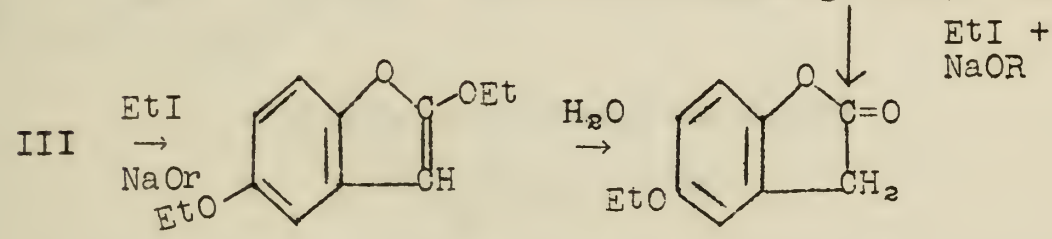
II III

II was originally reported to be the correct structure since the product did not show any tendency to form a polyester and it did not react with excess ketene acetal.

It was later shown however that m-Xyloquinone also gave an addition product; the product (II or III) contained a free hydroxyl group (by acetylation and Grignard machine) and this same product did not add Grignard reagent. Additional evidence for structure III was furnished by the following reactions.

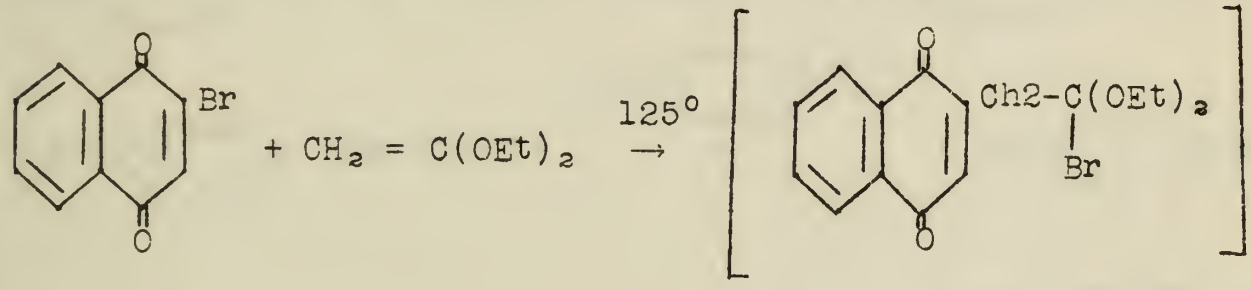


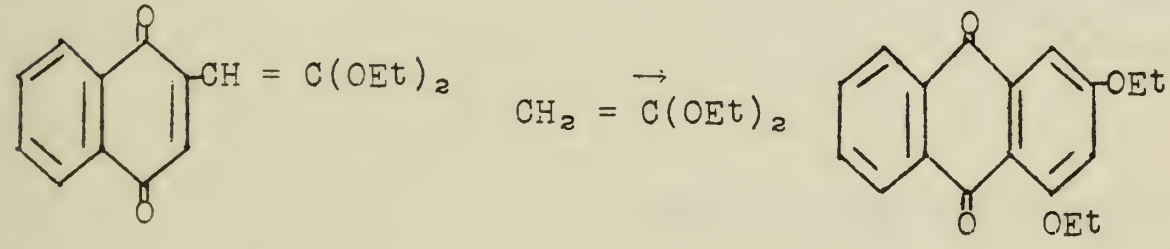
5-hydroxycoumaranone-2
(homogentisic lactone)



5-ethoxycoumaranone-2

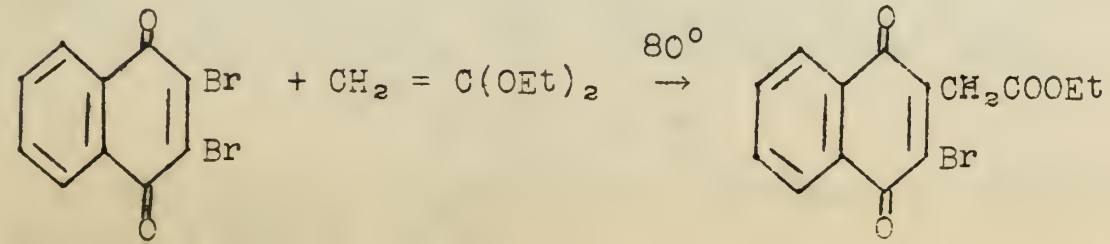
m-Xyloquinone, bromobenzoquinone, and α-naphthoquinone reacted in similar fashion but bromo- and dibromonaphthoquinone behaved differently.

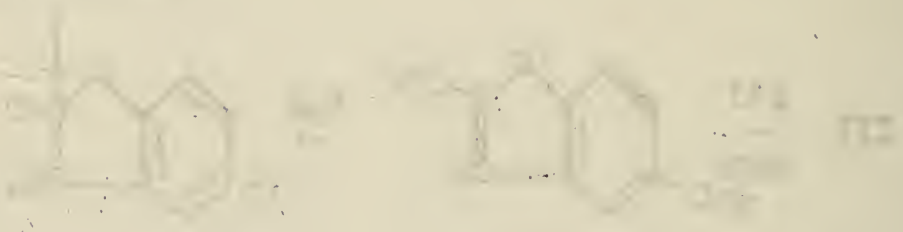


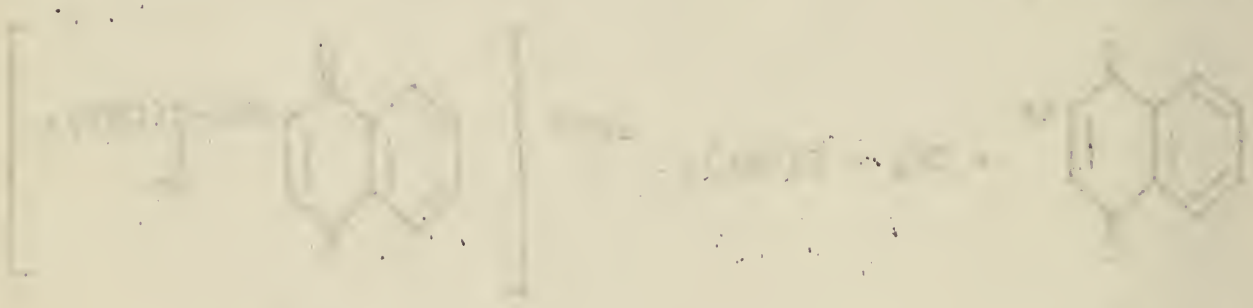


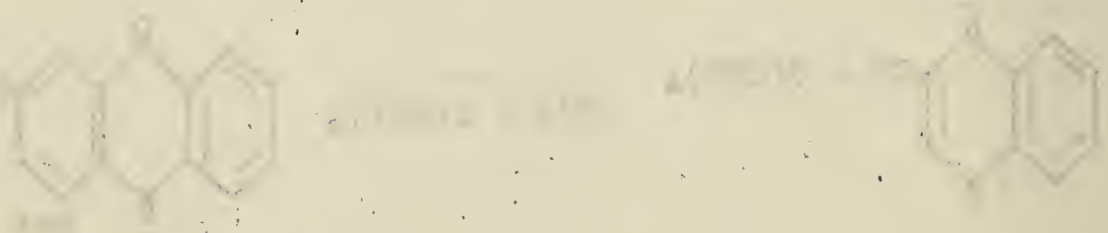
(21% yield)

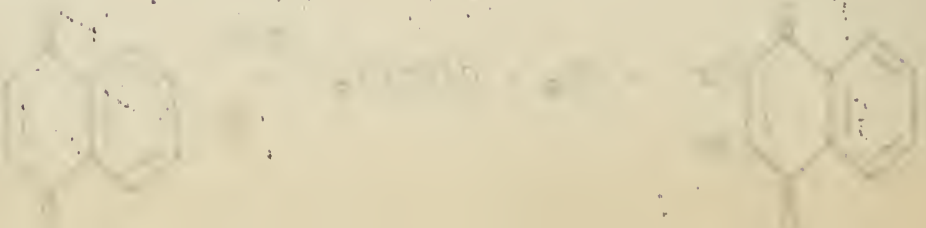
Xanthopurpurin diethylether



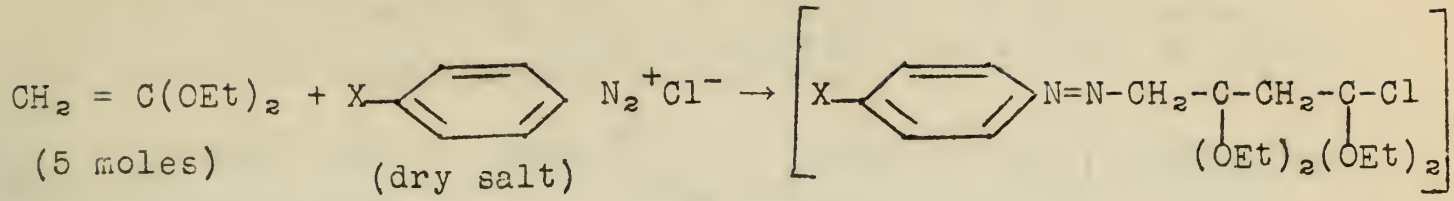




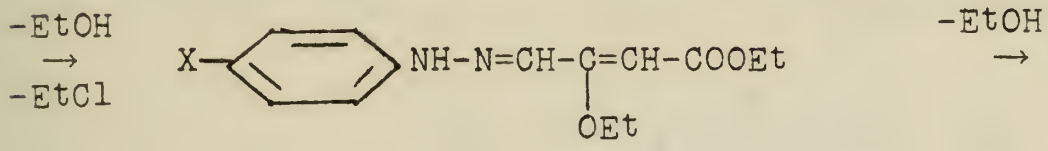


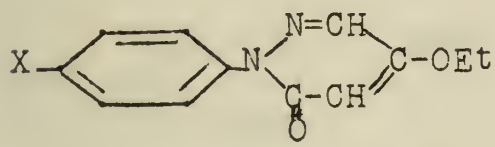


F. Reaction with Diazonium Salts.



(5 moles) (dry salt)



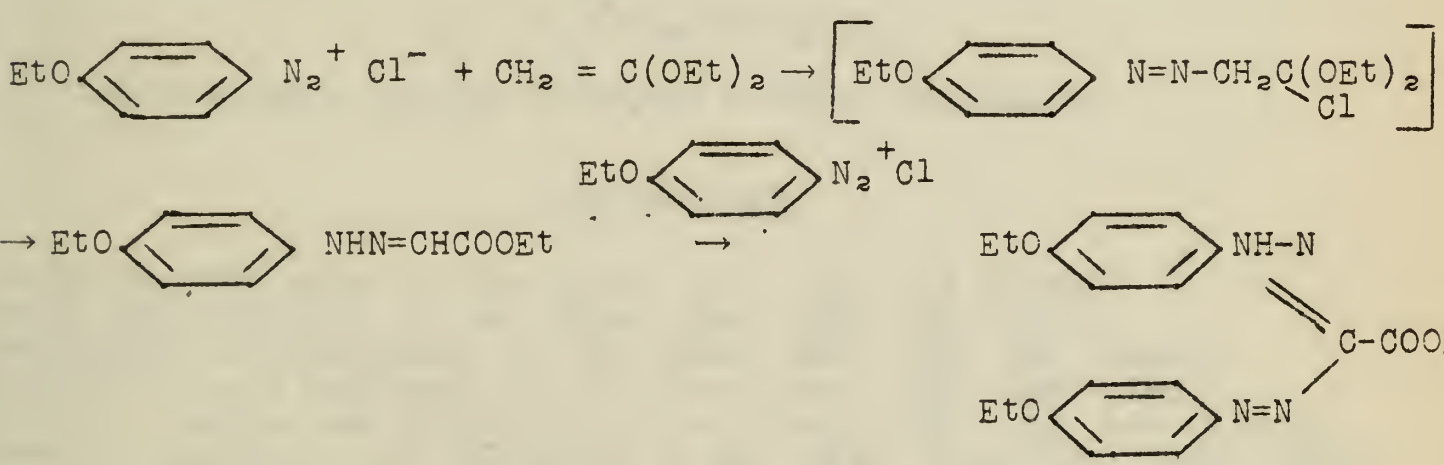


(25-35% yield)

1 phenyl-4-ethoxypyridazone-6

X = H, EtO, NO_2 or COOEt

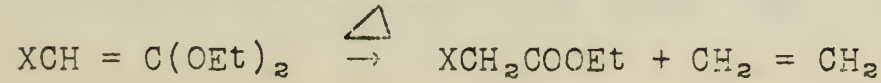
An additional 27% of the reaction product was shown to be IV. The formation of this compound can be explained by the following reactions.



IV

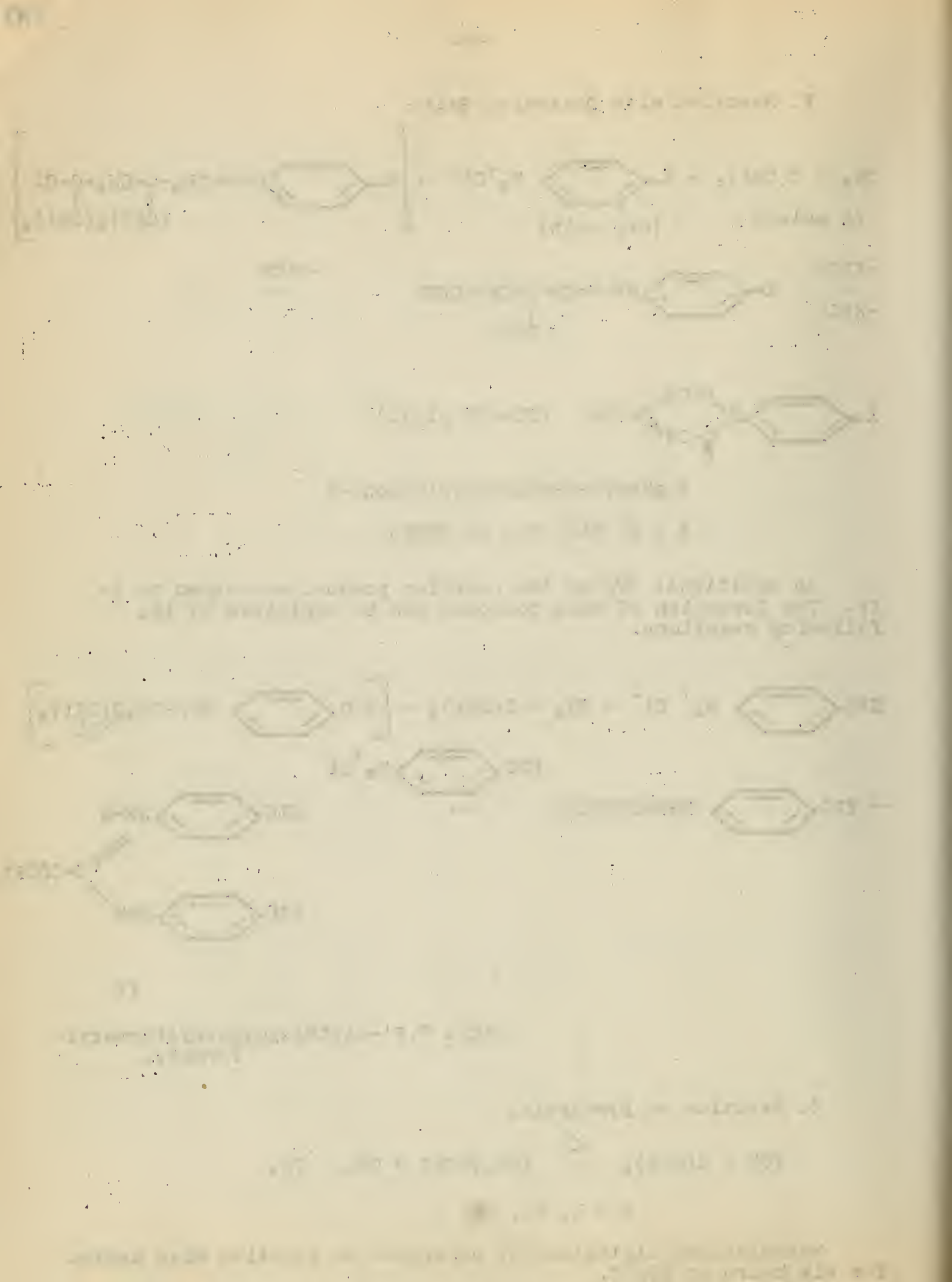
ethyl p,p'-diethoxydiphenylformazyl-formate.

G. Reaction on Pyrolysis.

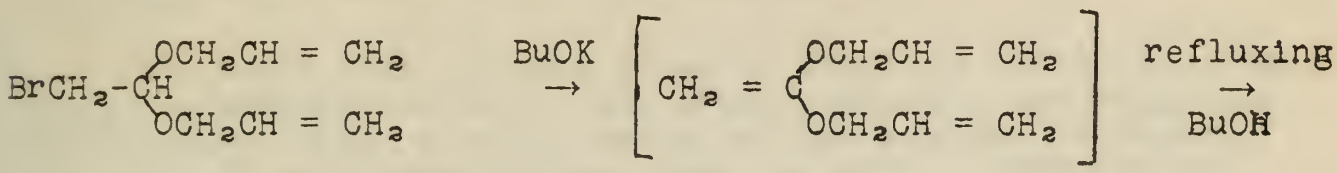


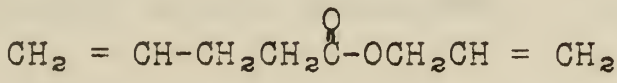
X = H, Cl, Br

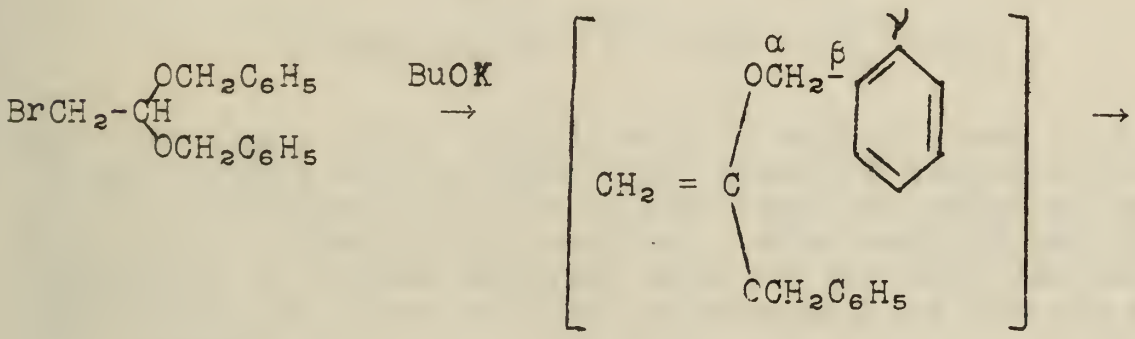
Methylketene diethylacetal undergoes no reaction when heated for six hours at 200°C.

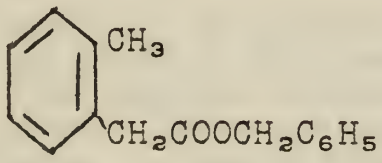


Ketene diallylacetal and ketene dibenzylacetal have the system $\rangle C = C-O-CH_2-C=C\langle$ which is necessary for the Claisen or allylic rearrangement. This rearrangement takes place so readily that the ketene acetal cannot be isolated.







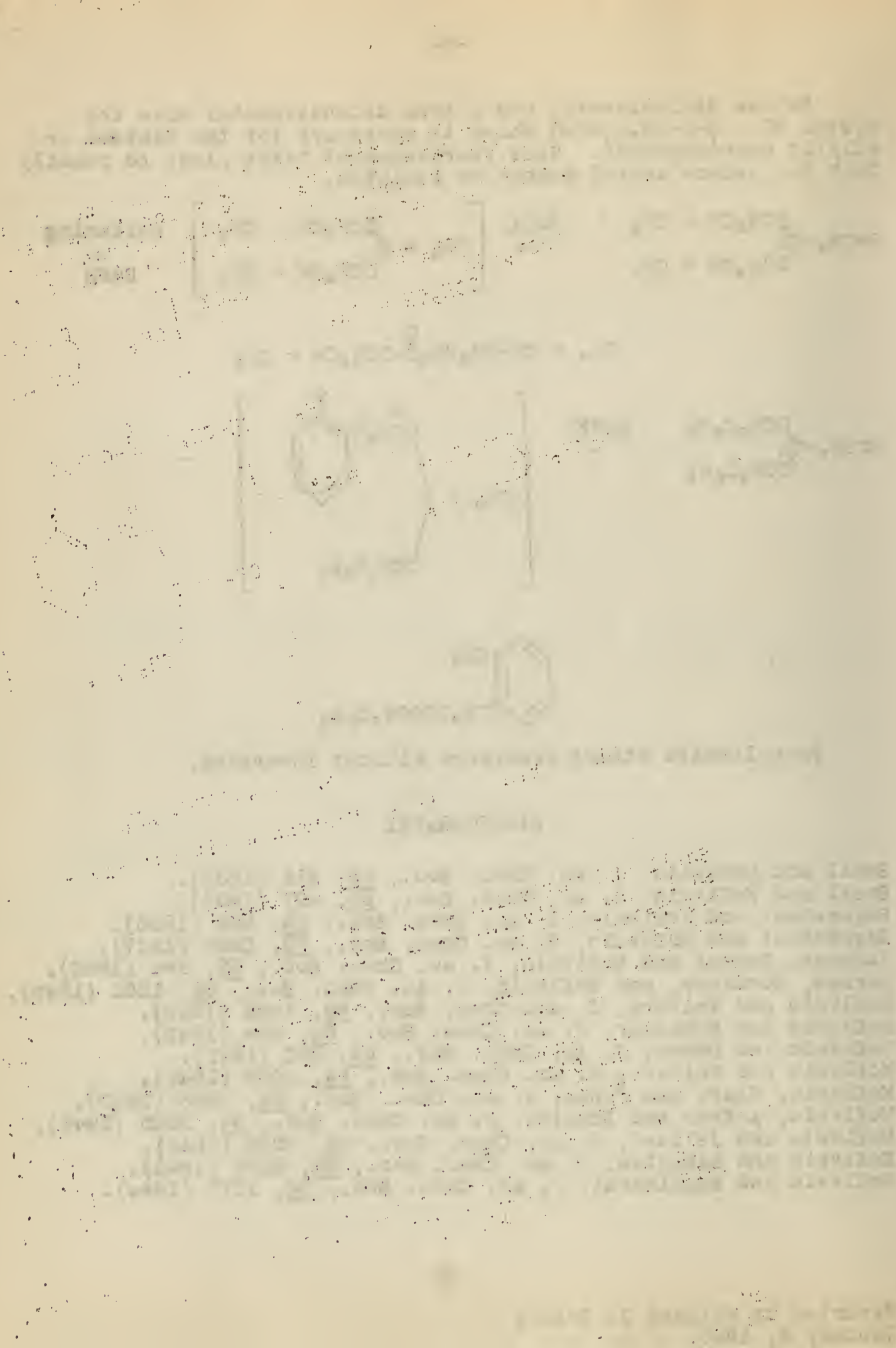


Phenylbenzyl ethers rearrange without inversion.

BIBLIOGRAPHY

Snell and McElvain, J. Am. Chem. Soc., 55, 416 (1933).
Snell and McElvain, J. Am. Chem. Soc., 55, 427 (1933).
Beyerstedt and McElvain, J. Am. Chem. Soc., 58, 529 (1936).
Beyerstedt and McElvain, J. Am. Chem. Soc., 59, 2266 (1937).
Johnson, Barnes and McElvain, J. Am. Chem. Soc., 62, 964 (1940).
Barnes, Kundiger, and McElvain, J. Am. Chem. Soc., 62, 1281 (1940).
McElvain and Walters, J. Am. Chem. Soc., 62, 1482 (1940).
McElvain and Kundiger, J. Am. Chem. Soc., 64, 254 (1942).
McElvain and Cohen, J. Am. Chem. Soc., 64, 260 (1942).
McElvain and Walters, J. Am. Chem. Soc., 64, 1059 (1942).
McElvain, Clark and Jones, J. Am. Chem. Soc., 64, 1966 (1942).
McElvain, Anthes and Shapiro, J. Am. Chem. Soc., 64, 2525 (1942).
McElvain and Jelinek, J. Am. Chem. Soc., 65, 2236 (1943).
McElvain and Langston, J. Am. Chem. Soc., 65, 2239 (1943).
McElvain and Engelhardt, J. Am. Chem. Soc., 66, 1077 (1944).

Reported by William J. Bailey
January 3, 1945.



THE REACTION OF β-HALO ETHERS WITH METALS

E. D. Amstutz, Lehigh University

The scope of the reaction is indicated by the following examples.

Treatment with (1) magnesium in ether or (2) sodium converted β-bromophenetole to the metal phenolate and ethylene. In the first case, a small amount of the product of Wurtz coupling, 1,4-diphenoxybutane, was isolated. β-Bromoethyl alkyl ethers were cleaved in the same manner by magnesium in ether (3).

$$BrCH_2CH_2OR \xrightarrow{Mg} ROH + CH_2 = CH_2$$

When the alkyl group contained five carbon atoms or less, yields of the alcohol were 28-46%. The yield of ethylene was 30-50%. It is to be noted that the Gilman test for Grignard reagent was negative during the reaction. When carried out in an atmosphere of carbon dioxide, none of the acid was obtained which would be expected from the reaction of the gas with Grignard reagent.

Boord and his coworkers (4) in 1930 utilized a similar reaction for the syntheses of olefins by treating alkyl β-bromoethyl ethers with zinc. The simpler olefins of the type $RCH=RCH_2$ were prepared in 65-90% yield. This synthesis has since been developed rather extensively. A modification of the reaction was used by Dykstra, Lewis, and Boord for the preparation of 1,4-pentadiene.

$$CH_2 = CHCH_2Br + CH_2BrCHBrOEt \xrightarrow{Mg} \xrightarrow{Br_2} CH_2BrCHBrCH_2CHBrCH_2Br$$

$$\xrightarrow{Zn} CH_2 = CHCH_2CH = CH_2 \qquad (28\%)$$

Presumably the allyl magnesium bromide first formed couples with the α-bromoether and the coupled product is then cleaved with excess magnesium.

Tetrahydrofurfuryl bromide reacted with magnesium as might be expected (5).

$$CH_2Br \xrightarrow{Mg} CH_2 = CH(CH_2)_3OMgBr \qquad (58\text{-}62\%)$$

The reaction could be run in wet or alcoholic ether---reagents which would normally react with a possible intermediate Grignard reagent.

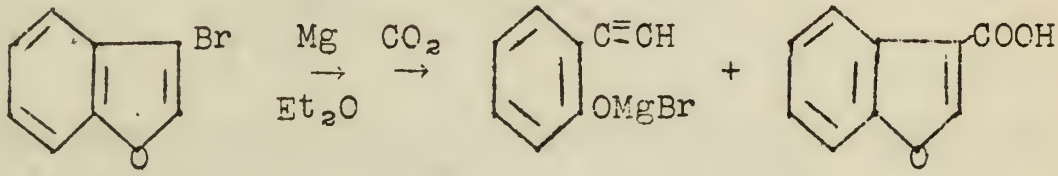
Although β-bromotetrahydrofuran failed to react with magnesium in ether it did react with lithium to give a low yield of lithium vinylethylate (14).

In at least one case a β-haloether has been made to undergo a coupling reaction with zinc rather than the usual cleavage (6).

$$\begin{matrix} CH_2Br \\ CHDR \\ CH_2Br \end{matrix} \xrightarrow[NaI,\ Na_2CO_3,\ AcNH_2]{Zn \quad 130^\circ} \triangle_{OR}$$

Triple bond formation has been brought about by the action of metals on aryl β-bromovinyl ethers (7,8).

$$PhOCH = CHBr \xrightarrow[90^\circ]{Na} PhOH\ (98\%) + CH \equiv CH\ (21\%\ \text{isolated as tetrabromide})$$



(3 g.) (0.5 g.) (0.028 g.)

Phenoxyethynyl magnesium iodide, when heated in butanol, gave an 86% yield of phenol and a small amount of an amorphous material (7).

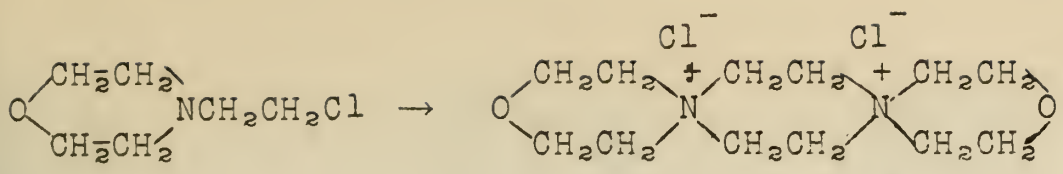
The formation of a vinyl ether by the reaction of sodium with β-chloroethyl acetal has been observed (9).

$$ClCH_2CH(OEt)_2 \xrightarrow[140^\circ]{Na} CH_2 = CHOCH_2CH_3$$

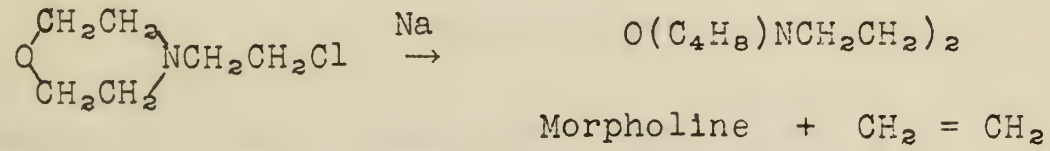
Sulfur and Nitrogen Analogs.--As might be expected the place of the oxygen atom in the ether linkage may be taken by other elements. β,β'-Dichlorodiethylsulfide reacted with zinc in 95% ethanol to give an 8% yield of ethylene which was isolated as the tetrabromide. Numerous other products were obtained (10).

Although β-chloroethyl phenyl sulfide failed to react with magnesium in ether the analogous bromo compound gave unspecified amounts of ethylene, thiophenol, and a product believed to be the result of Wurtz coupling (14).

Mason and Block (11) were unable to prepare the Grignard reagent of N-(β-chloroethyl)-morpholine. Instead the magnesium catalysed the dimerization.



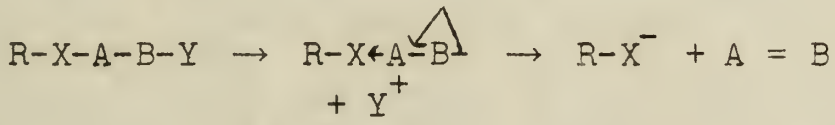
However, Amstutz (14) found that treatment of this chloroamine with sodium slightly above its melting point readily converted it to ethylene acid morpholine, isolated as the p-toluenesulfonamide. A small amount of coupled product was also obtained. No yields were given.



Morpholine + $CH_2 = CH_2$

Mechanism of the Reaction

Amstutz writes the generalized reaction as



and suggests that three conditions must be satisfied in order that reactions of this type can take place.

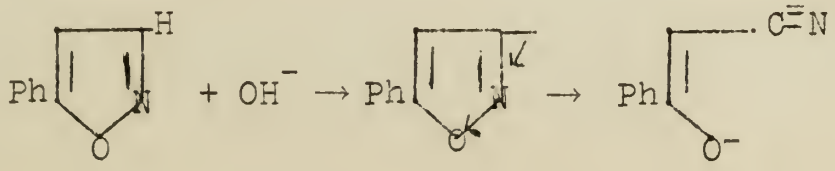
(1) Group Y must be removed without its pair of bonding electrons.

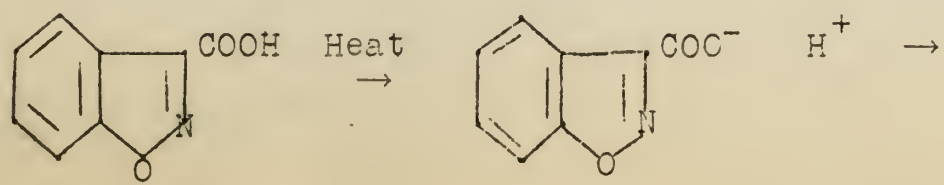
(2) Atom X must have a higher effective nuclear charge than atom B.

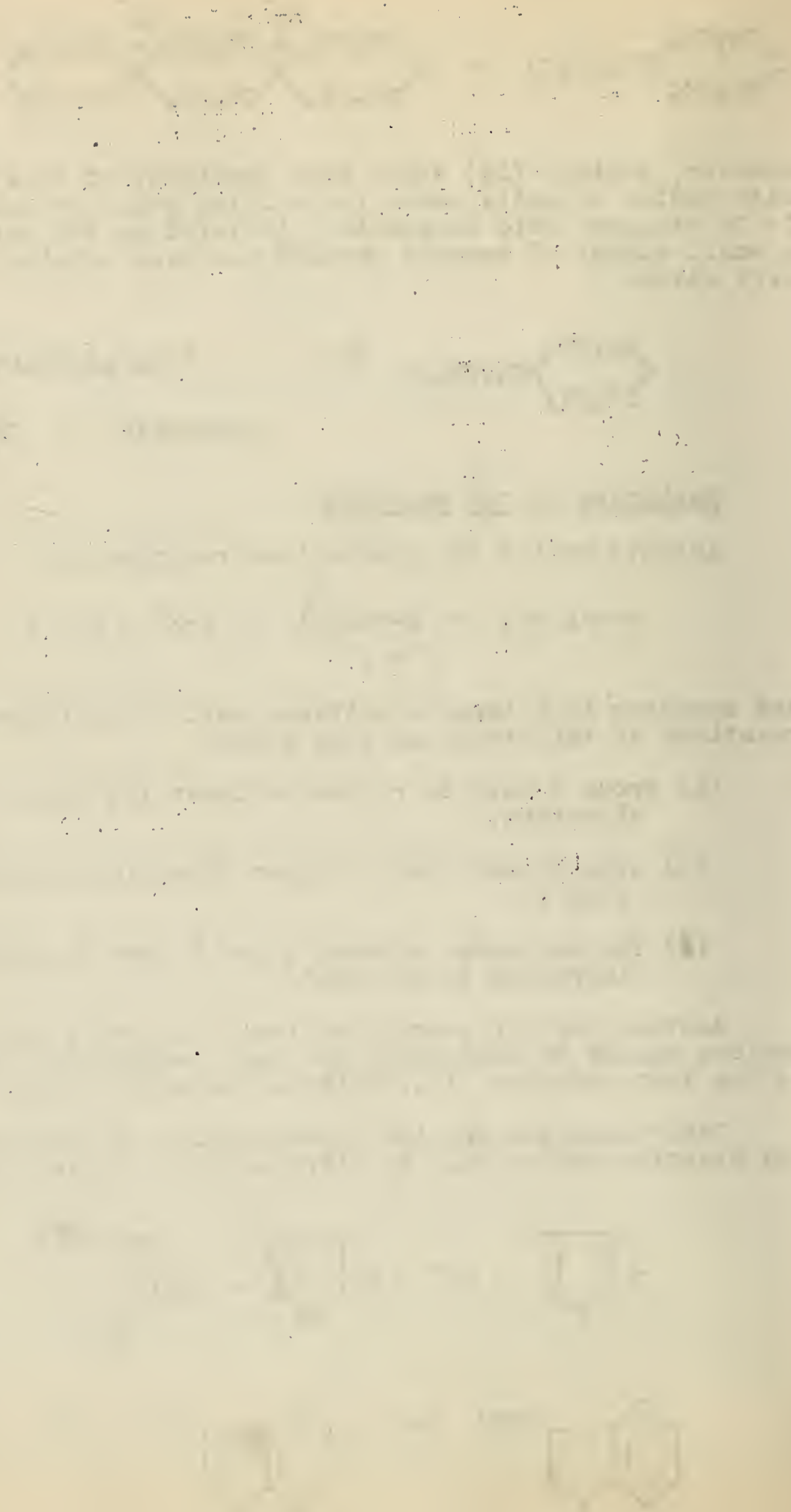
(3) The covalence between A and B must be capable of being increased by one unit.

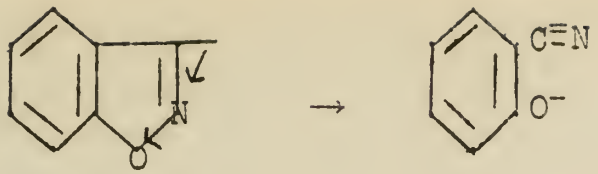
Amstutz further points out that some other well-known reactions appear to proceed by the same mechanism. The most familiar is the debromination of 1,2-dibromides with metals.

Other examples are the isomerization of isoxazoles (12) and benzoisoxazoles (13) to nitriles under suitable conditions.







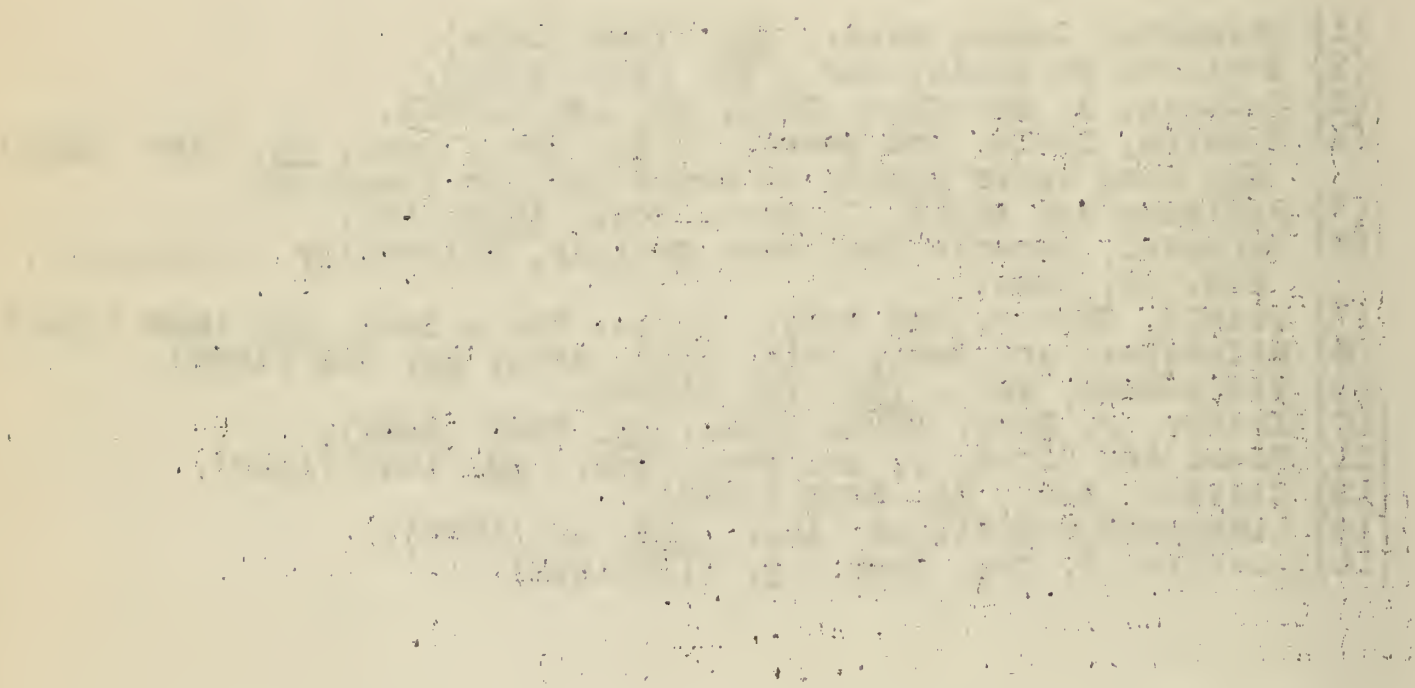


+ CO_2

BIBLIOGRAPHY

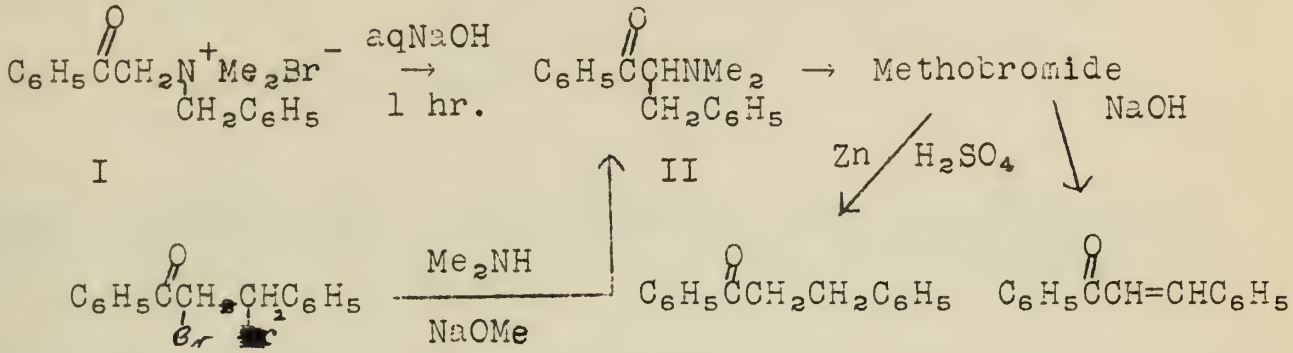
(1) Grignard, Compt. rend., 138, 1048 (1904).
(2) Wohl and Berthold, Ber., 43, 2175 (1910).
(3) Tallman, J. Am. Chem. Soc., 56, 126 (1934).
(4) Dykstra, Lewis, and Boord, J. Am. Chem. Soc., 52, 3396 (1930) See also later papers of Boord and his coworkers.
(5) Robinson and Smith, J. Chem. Soc., 1936, 195.
(6) Jarowski, Organic Chemistry Seminar, University of Illinois, Feb. 16, 1944.
(7) Jacobs, Cramer, and Weiss, J. Am. Chem. Soc., 62, 1849 (1940).
(8) Reichstein and Baud, Helv. chim. acta, 20, 892 (1937).
(9) Wislicenus, Ann., 192, 106 (1878).
(10) Kretov, J. Russ. Phys. Chem., 61, 2345 (1929).
(11) Mason and Block, J. Am. Chem. Soc., 62, 1447 (1940).
(12) Claisen, Ber., 36, 3672 (1903).
(13) Lindemann and Cissee, Ann., 469, 44 (1929).
(14) Amstutz, J. Org. Chem., 9, 310 (1944)

Reported by D. Curtin
January 10, 1945



FLUORENYLIDES AND THE STEVENS REARRANGEMENT

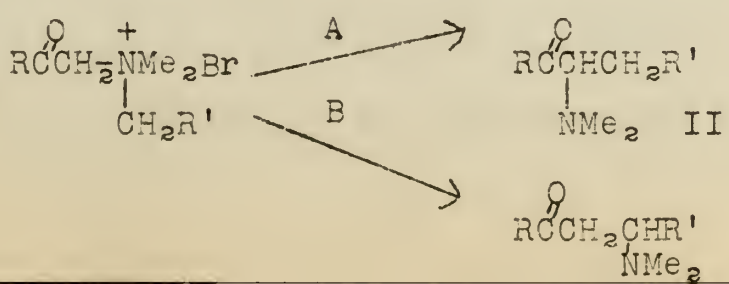
In 1928 Stevens and his coworkers described an Emde reaction using phenacyl-benzyl-dimethylammonium bromide (I) which produced a new carbon skeleton rather than the dealkylated product expected. The reaction proceeded equally well with various basic reagents such as aqueous alkali, sodium alkoxides, and sodamide.



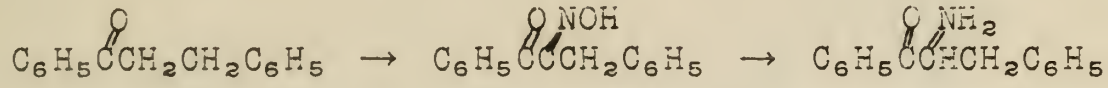
In subsequent articles the scope of the reaction has been quite clearly defined. Nitro, methyl, methoxy, or halogen groups on either aryl group will not prevent the occurrence of the reaction. The nature of the substituent does affect the reaction velocity greatly. The phenacyl group has been replaced by acetonyl, allyl, benzyl, and 9-fluorenyl without alteration of the course of the reaction. Instead of the benzyl group benzhydryl, 9-flourenyl, phenacyl, allyl, and phenylpropargyl groups have been used successfully. Groups lacking an active hydrogen such as nitrile, carbometoxy, methyl, phenyl, and phenylethyl could not be used.

The preparation of these quaternary salts was accomplished in either of two ways. Phenacyl bromide or its derivatives and the tertiary amine were refluxed in benzene solution for one-half to one hour. The second method was addition of the benzyl halide to the substituted aminoacetophenone. Several attempts further to clarify the scope of the reaction had to be abandoned when neither of the above methods yielded the necessary quaternary salt. A third aryl group could not be introduced, and the authors suggested that this failure might be due to steric hindrance, pointing to the failure of tribenzylamine to combine with benzyl chloride in much earlier work. Likewise, neither triphenylethyl-dimethylamine nor phenyl-isopropyl-dimethylamine would combine with phenacyl bromide.

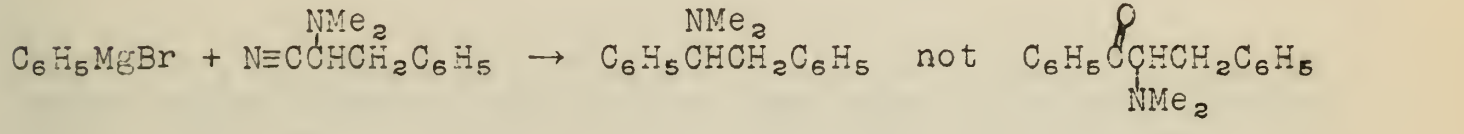
The carbon skeletons of the compounds produced were shown by degradation to the related chalcones or hydrochalcones. However, the reaction still might have proceeded in either of two directions.

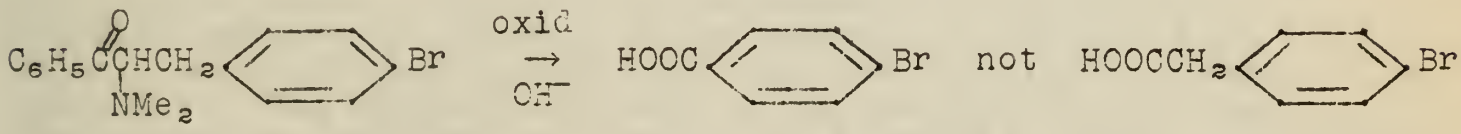


Several synthesis were attempted in order to determine definitely which course had been taken. The proof of structure II, already indicated, did not completely satisfy the authors, The corresponding primary amine was obtained but could not be alkylated.

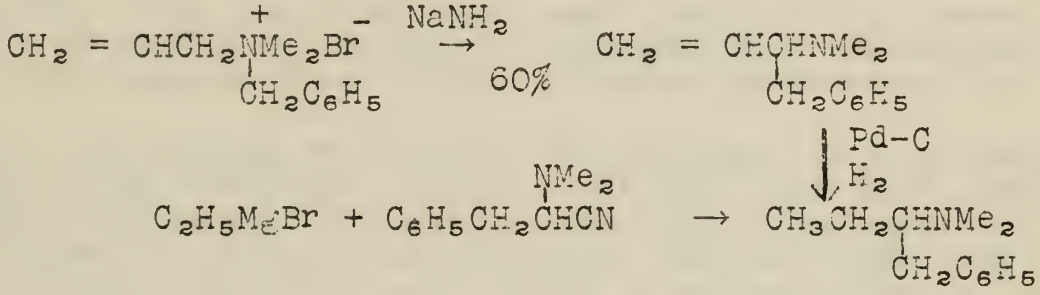


Two other unsuccessful attempts followed.



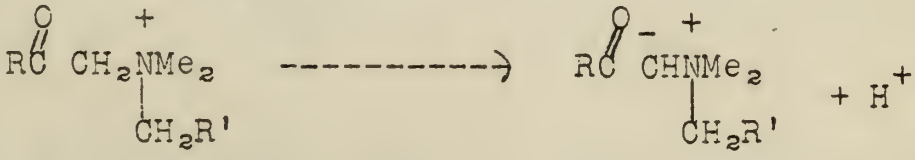


The fact that the hydrogen of the phenacyl group is the most labile can be taken as a strong indication that path A was followed. In addition, the most rigorous proof was obtained for the rearrangement of allyl-benzyl-dimethylammonium bromide.



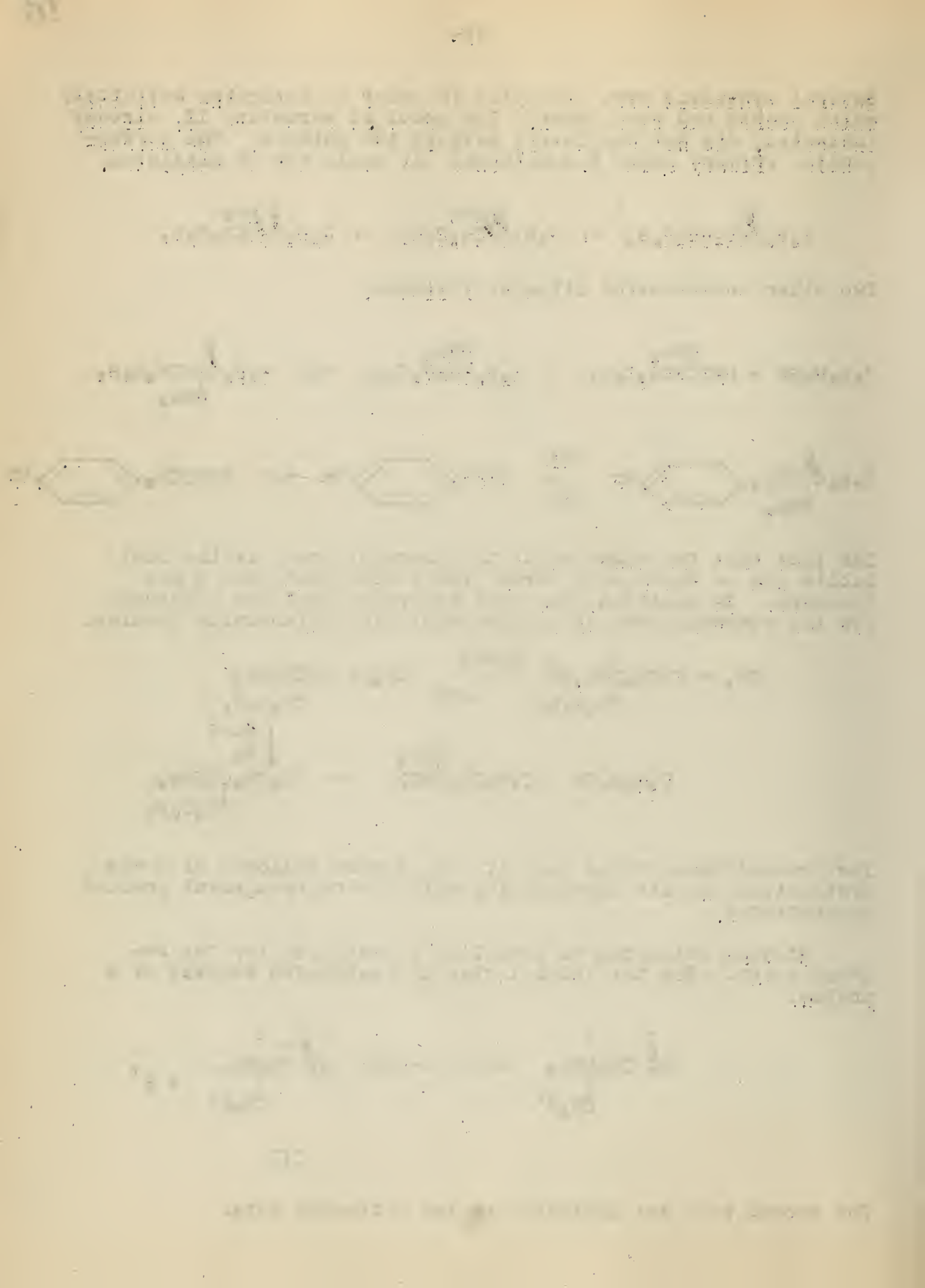
The product which would form if path B were followed also was synthesized and its non-identity with the rearrangement product demonstrated.

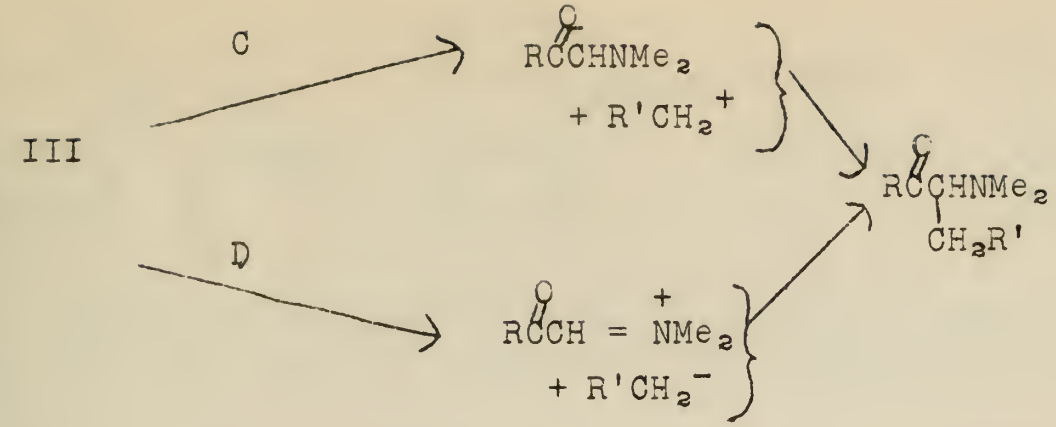
Stevens attempted to establish a mechanism for the rearrangement. For the initial step he postulated removal of a proton.



III

The second step was indicated in two different ways.

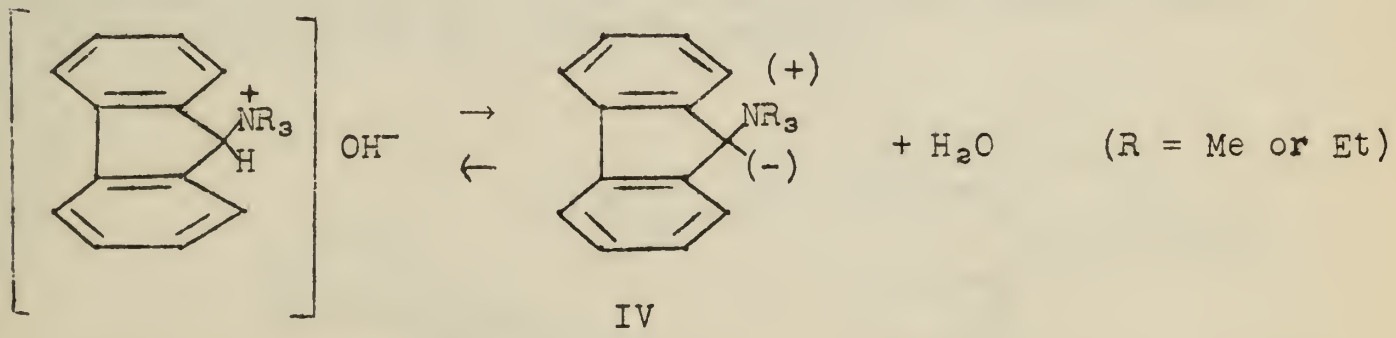




Suggestion of path D was prompted by the fact that the p-nitrobenzyl group migrates much faster than does the p-methoxybenzyl group. Neither of these ideas is completely satisfactory. A more likely scheme involves a simultaneous attack at the negative carbon and cleavage of the benzyl to nitrogen bond. This is substantiated by the fact that the reaction is intramolecular. The enhanced activity of the p-nitrobenzyl group could then be explained as a result of a shifting of the electrons toward the nitro group leaving the methylene group greater capacity for accepting electrons from a donor.

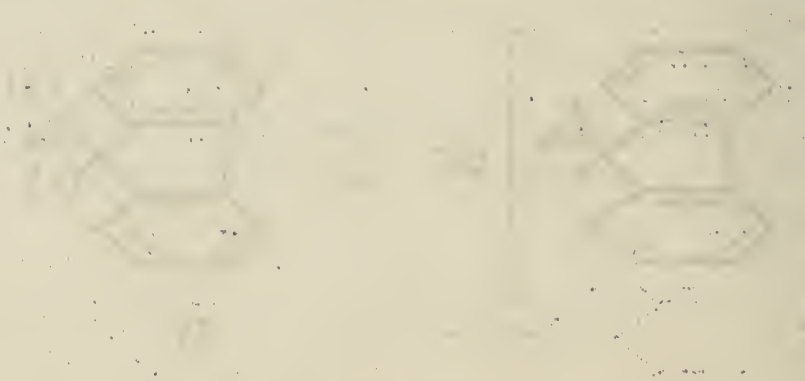
Negative groups which increased the reaction velocity when on the benzyl ring would decrease the velocity when on the phenacyl ring. Use of a stronger basic catalyst in these cases often was successful in forcing a rearrangement indicating that removal of the proton is a critical factor in the reaction.

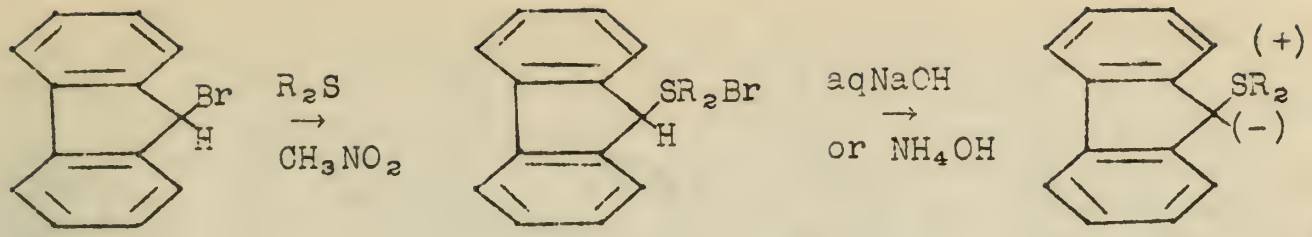
Ingold and Jessop postulated the presence of a compound which has a bond structure identical to III. In 1929 they reported that 9-fluorenyl-trimethyl- and triethyl-ammonium hydroxides in aqueous solution were colored, whereas their salts were colorless. This they attributed to an equilibrium established between the quaternary hydroxide and its anhydride (IV).



IV

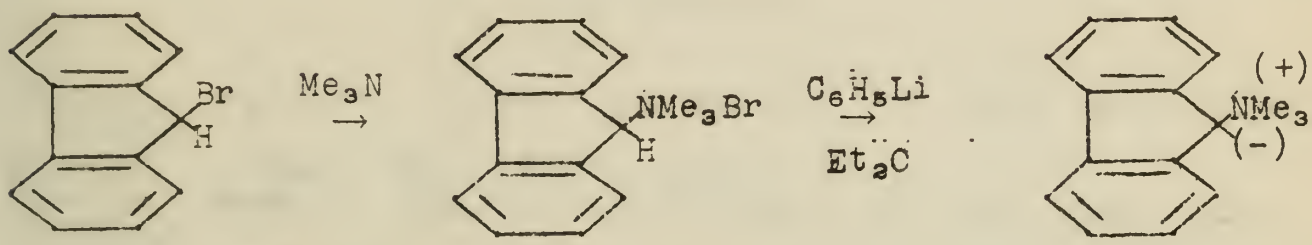
They were unable to isolate IV, but due to an equilibrium far to the **right** in the case of the sulfur analogue they did isolate V which was stable enough to permit analysis.





V

Wittig and Felletschin recently claimed to have isolated IV as one of a class of compounds they designate as fluorenylides.

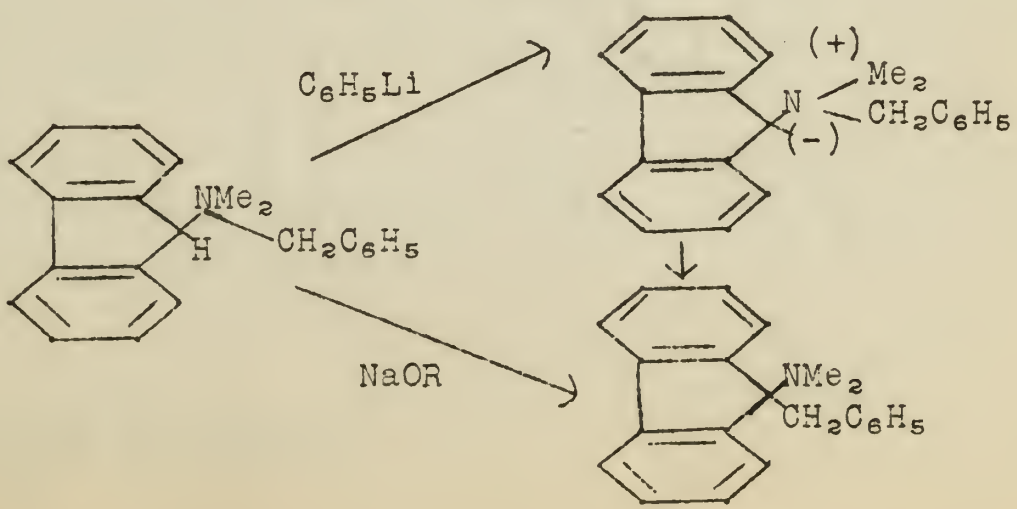


VI IV

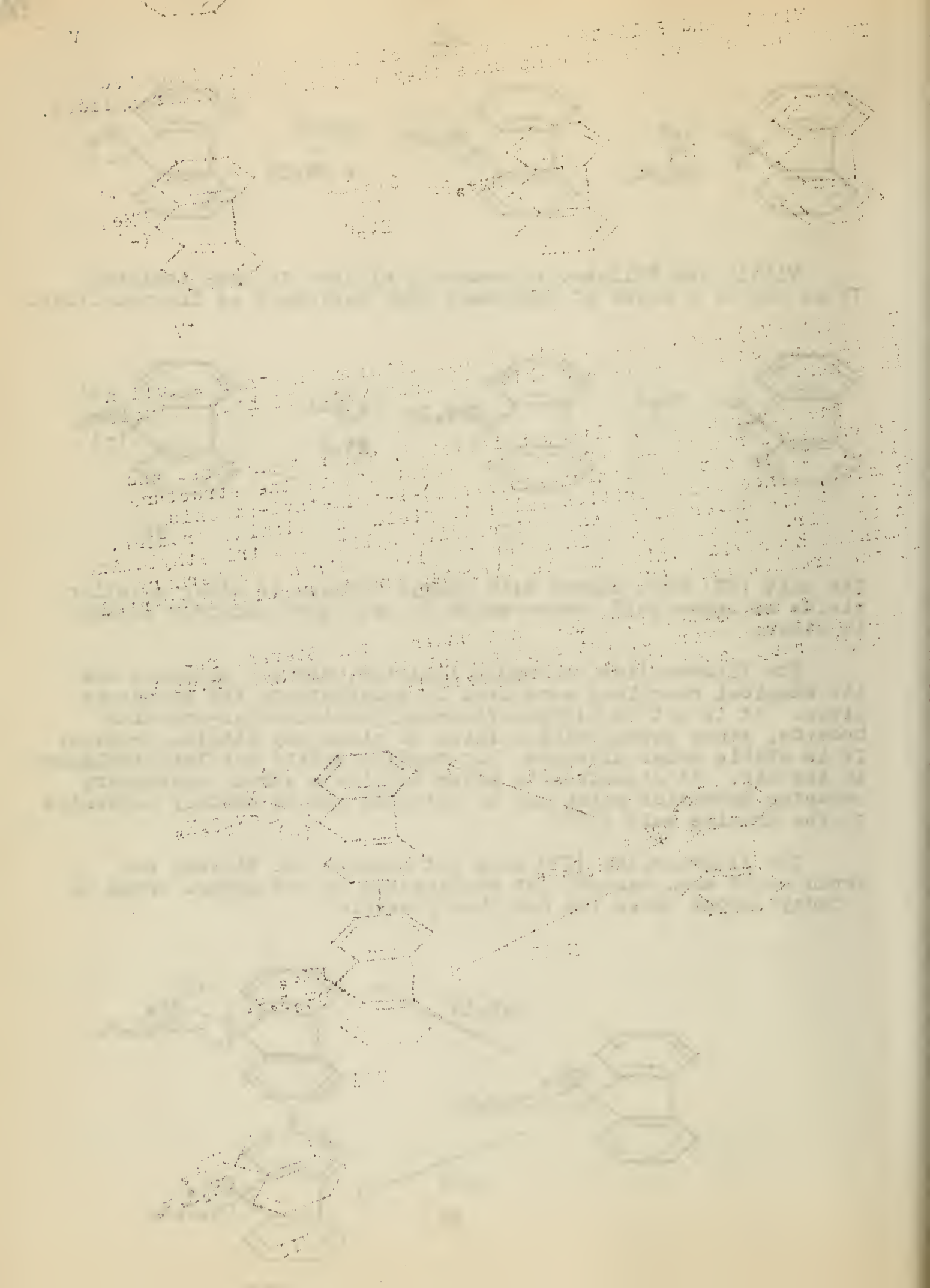
The salt (VI) when shaken with phenyl lithium in ether solution yields an ocher-gold powder which is only very slightly soluble in ether.

The fluorenylide, although isolated, was not analyzed and its chemical reactions were used to substantiate the structure given. It is not (9-lithium-fluorenyl)-9-trimethyl-ammonium bromide, since decomposition fails to yield any lithium bromide. IV is stable under nitrogen, but readily splits out trimethylamine in the air. It dissolves in water to give a strong quaternary ammonium hydroxide which may be titrated and is readily converted to the bromide salt (VI).

The fluorenylide (IV) does not undergo the Stevens rearrangement when warmed, but replacement of one methyl group by a benzyl group makes the reaction possible



VII



Use of the Stevens conditions produced a dark red color in the solution of the ammonium salt and considerable heat. A nearly quantitative yield of (9-benzyl-fluorenyl)-dimethylamine (VII) was obtained. VII could be converted readily to the previously synthesized (9-benzyl-fluorenyl)-9-trimethylammonium bromide. The fluorenylide is indicated as the intermediate compound in the rearrangement since an ether suspension of the salt with phenyl lithium evolved heat, formed a similar red color, and VII could be isolated from the reaction mixture.

BIBLIOGRAPHY

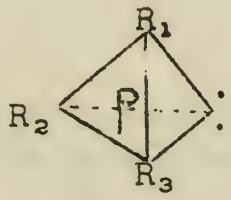
Stevens, Creighton, Gordon, and MacNicol, J. Chem. Soc., 3193, (1928).
Stevens, J. Chem. Soc., 2107, (1930).
Stevens, Snedden, Stiller, and Thompson, J. Chem. Soc., 2119, (1930).
Thompson and Stevens, J. Chem. Soc., 55, (1932).
Thompson and Stevens, J. Chem. Soc., 69, (1932).
Thompson and Stevens, J. Chem. Soc., 1926, (1932).
Thompson and Stevens, J. Chem. Soc., 1932, (1932).
Dunn and Stevens, J. Chem. Soc., 279, (1934).
Ingold and Jessop, J. Chem. Soc., 713, (1930).
Wittig and Felletschin, Ann., 555, 133, (1944).

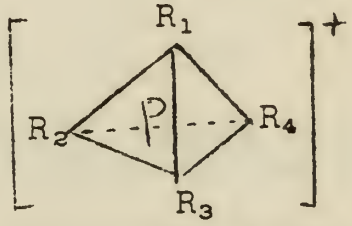
Reported by Robert H. Reitsema
January 10, 1945

STEREOCHEMISTRY OF ORGANIC PHOSPHORUS COMPOUNDS

In 1908, Meinsenheimer (1) successfully resolved ethylmethylphenylamine oxide into its dextro and levo forms through the d-camphorsulphonate salts. This excited immediate interest in the synthesis and possible resolution of various organic derivatives of the remaining elements comprising group V of the periodic table. Perhaps the most interesting series of investigations of compounds in this category is that dealing with the phosphorus compounds.

For a compound to be resolvable, it is necessary that the configuration of groups about either a tri- or tetra-covalent phosphorus atom should be definitely non-planar and presumably tetrahedral in arrangement.

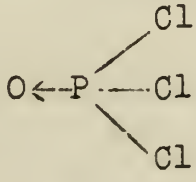




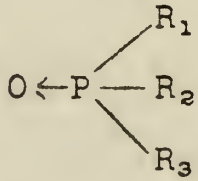
A discussion of the various phosphorus compounds which fit (in theory) this requirement may be presented conveniently under three divisions.

I. Phosphoric and Phosphonic Acids:

Through a systemmatic investigation of the configuration of various derivatives of phosphoryl chloride, Caven (2) concluded that the three chlorine atoms on phosphoryl chloride (I) occupied equivalent positions in space and therefore, a molecule of the type (II) would exist in a non-planar form, theoretically making resolution possible.



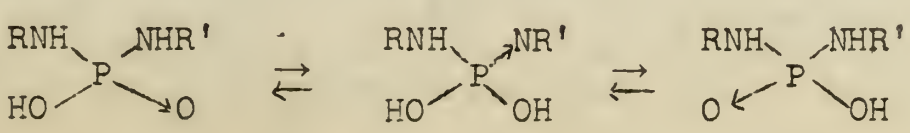
(I)

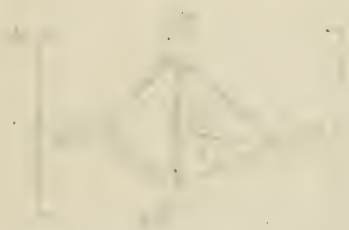


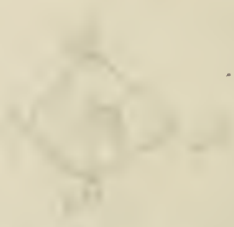
(II)

Caven tested his conclusion on anilino-p-toluidinophosphoric acid and on methoxy-p-toluidinophosphoric acid, but was unable to obtain resolution of either compound. As an explanation of this failure Caven suggested a possible tautomerism of the active hydrogen atom, which would result in racemization.

Luff and Kipping (3) prepared salts of phenyl-p-tolylphosphoric acid with eight different optically active bases but were unable to obtain separable diasteroisomers. They postulated the following mechanism for racemization.

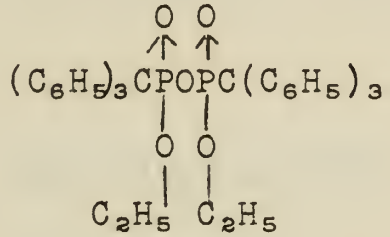






In support of the racemization theory, these workers found that while the d-hydrindamide made from phenyl-p-tolylphosphoryl chloride was composed of two separable diastereoisomers, decomposition of the active amides produced the same optically inactive acid.

The neatest evidence for the existence of asymmetric phosphorus in this group of compounds was obtained by Hatt (4). He separated the substituted pyrophosphate (III) into two forms which he labeled meso and racemic.



III

As expected, decomposition of the separated isomers yielded identical substituted phosphoric acids with no optical activity.

II. Phosphonium Salts:

In contrast to the experience of organic chemists working in the nitrogen series, the phosphonium salts have defied resolution (5) (6) (7).

One explanation given for the failure of these compounds to undergo resolution is the difficulty in obtaining good crystalline salts. A more likely explanation advanced by Davies and Cox (8) is the type of decomposition equilibrium of -onium salts in solution which actually has been observed in the ammonium series.

$$(abcdP)X \rightleftarrows abcP + dX$$

Davies and Mann (9) have pointed out that all phosphonium compounds tested had contained at least one alkyl radical and they suggest as a final test of resolution the preparation of a tetraaryl phosphonium salt which might be prepared through a novel reaction discovered by Chatt and Mann (10).

$$(C_6H_5)_2PCl \xrightarrow[AlCl_3]{2\ C_6H_5Br} \xrightarrow{KI} \left[(C_6H_5)_4P\right]^+ I^-$$

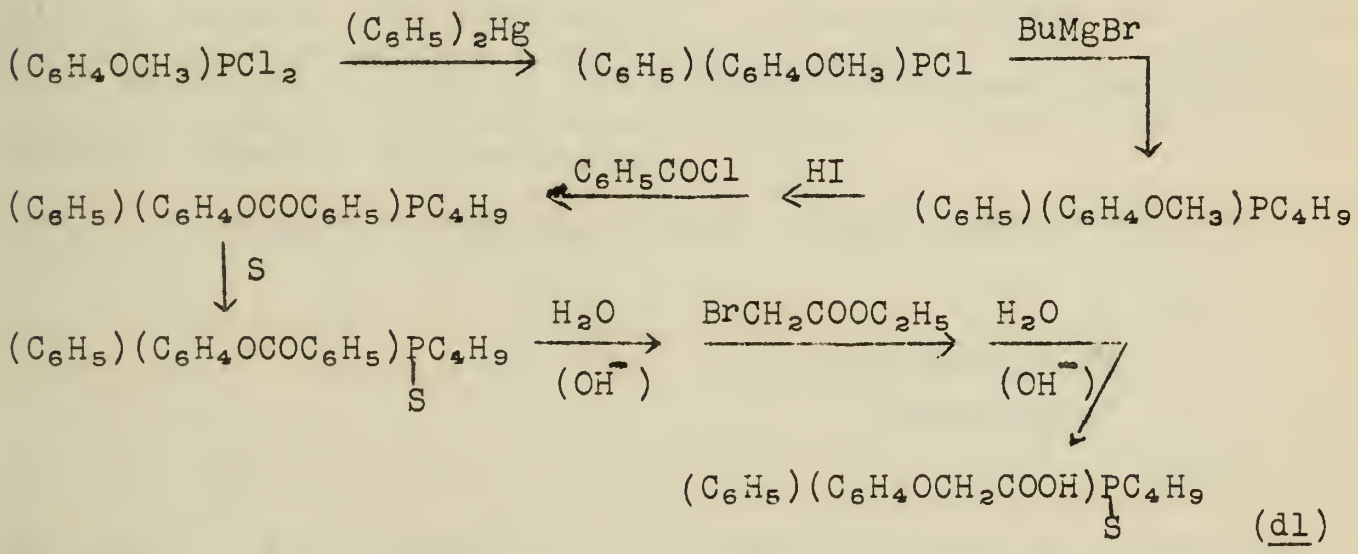
The reaction would need to be modified so that different aryl groups would enter the molecule. Prosecution of this research awaits the end of the war.

III. Tertiary Phosphine Oxides and Sulphides:

Following his resolution of ethylmethylphenylamine oxide, Meisenheimer (1) proceeded to synthesize and test the corresponding phosphorus compound. In 1911, he and Lichtenstadt (11) reported the successful resolution of ethylmethylphenylphosphine oxide through the d-bromocamphorsulfonate salt. Meisenheimer also reported in 1926 (12) that methylphenylbenzylphosphine oxide

had been resolved after a fractional crystallization requiring more than a year. At the same time, he reported his failure to resolve methylphenylbenzylphosphonium camphorsulfonate.

Assuming that Meisenheimer's difficulty in obtaining crystalline compounds had been lack of sufficient reactivity on the active bases, Davies and Mann (9) undertook to synthesize trisubstituted phosphines with a carboxymethoxy-group on one of the aryl substituents for ease in resolution. They report the successful synthesis of phenyl-p-(carboxymethoxy)-phenyl-n-butylphosphine sulfide and its resolution through the d-α-phenylethylamine salts.



Acidification of the active salts produced active acids with molecular rotation of ±9.6 degrees. Davies and Mann propose to prepare oxides and selenides as well as the sulfides of this type of compound in order to compare their effects upon the optical activity of the substituted phosphines.

BIBLIOGRAPHY

1. Meisenheimer, Ber., 41, 3966 (1908).
2. Caven, J. Chem. Soc., 81, 1362 (1902).
3. Luff and Kipping, J. Chem. Soc., 95, 1993 (1909).
4. Hatt, J. Chem. Soc., 1936, 776.
5. Wedekind, Ber., 45, 2933 (1912).
6. Radcliffe, Chem. and Ind., 42, 64 (1923).
7. Michaelis, Ann., 315, 54 (1901).
8. Davies and Cox, J. Chem. Soc., 1937, 614.
9. Davies and Mann, J. Chem. Soc., 276 1944.
10. Chatt and Mann, J. Chem. Soc., 1940, 1192.
11. Meisenheimer and Lichtenstadt, Ber., 44, 356 (1911).
12. Meisenheimer, Ann., 449, 224 (1926).

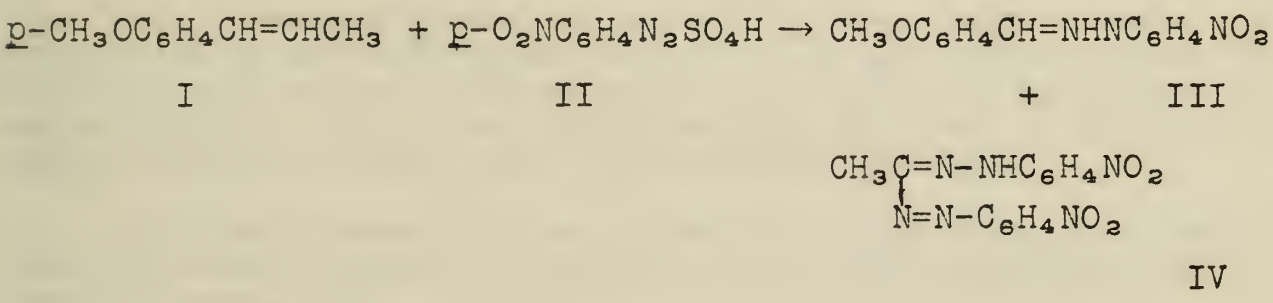
Reported by Robert E. Jones
January 17, 1945

THE ANAMOLOUS COUPLING OF DIAZO COMPOUNDS WITH UNSATURATED COMPOUNDS

Adolfo Quilico, et al.; Reale Politecnico, Milano

Marked similarities were found by Quilico to exist in the reactions of sulfamic acid and of diazo compounds with amines, phenols and phenolic ethers. Since phenolic ethers substituted with a propenylic side-chain are sulfonated on the lateral chain, a study of the action of diazo compounds on phenolic ethers with unsaturated side-chains was undertaken.

The reaction between anethole (I) and p-nitrobenzenediazonium sulfate (II) was first investigated. The coupling reaction with anisole proceeds only very slowly, but Quilico found the reaction with anethole in glacial acetic acid or alcohol leads smoothly to an 80-90 per cent yield of a compound which was identified as the p-nitrophenylhydrazone of anisaldehyde. A small amount of a secondary product is also formed.

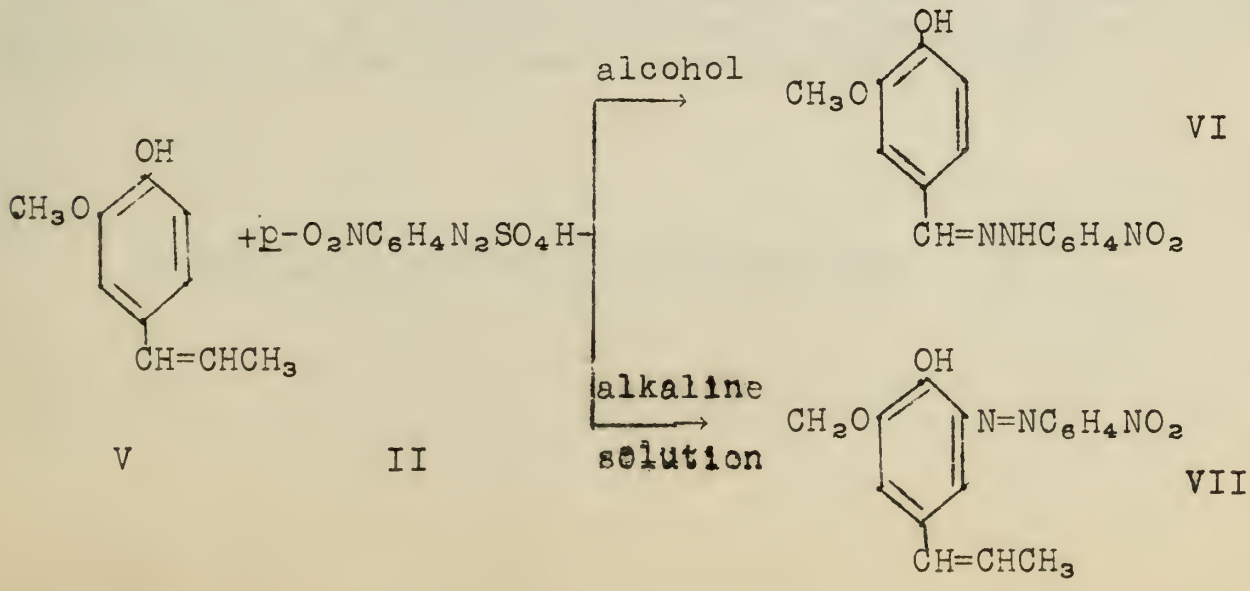


I II + III

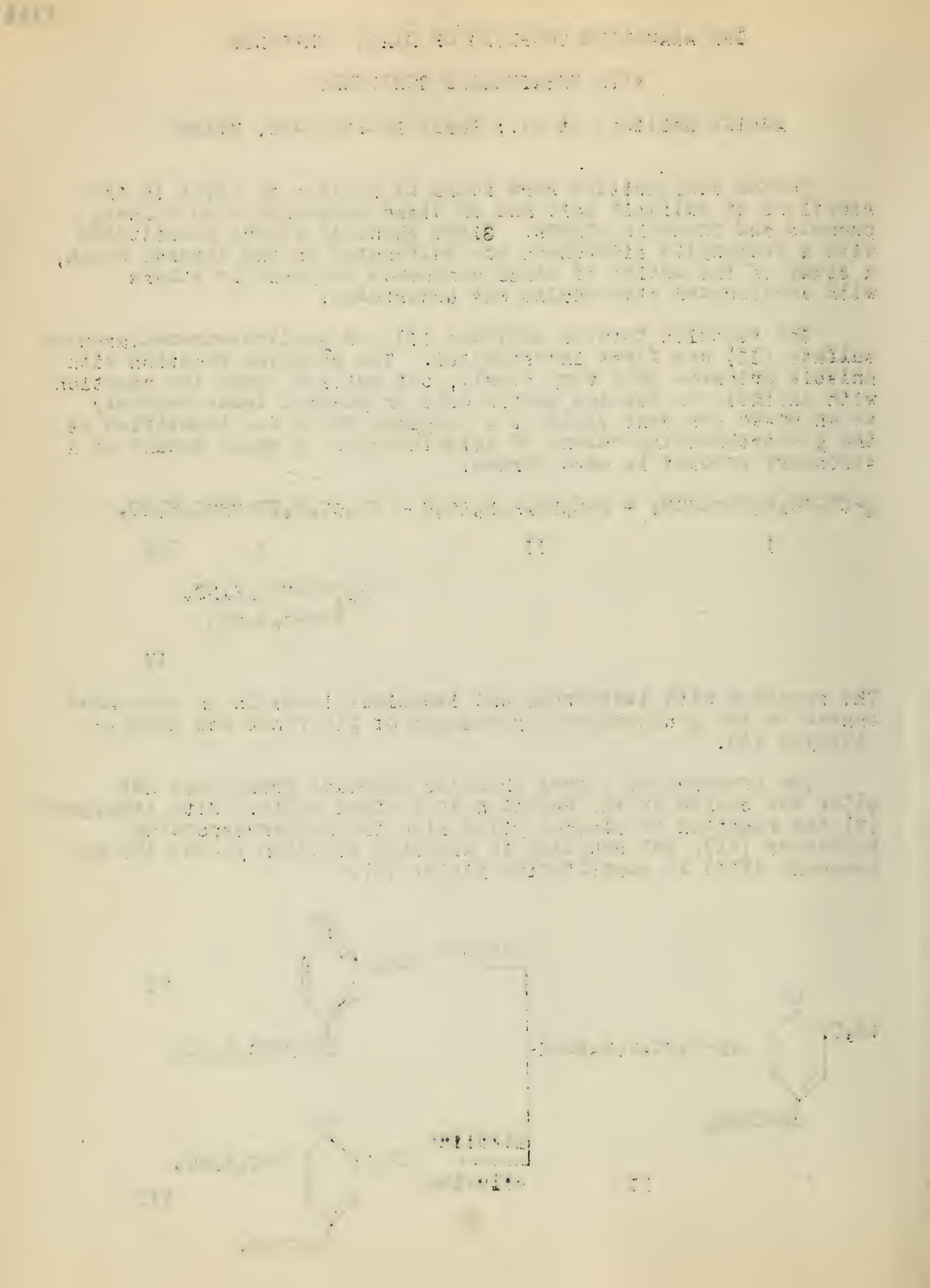
IV

The reaction with isosafrole and isoapiole leads in an analogous manner to the p-nitrophenylhydrazones of piperonal and apiolic aldehyde (1).

The presence of a free phenolic hydroxyl group does not alter the course of the reaction in neutral media. With isoeugenol (V) the reaction in alcohol gives rise to the corresponding hydrazone (VI), but coupling in alkaline solution yields the azo compound (VII) in quantitative yields (2).



V II VI VII



Likewise, with o-and p-hydroxypropenylbenzene coupling in alkaline, solution proceeds normally, but from alcoholic solution the hydrazones are obtained in 60 per cent yield (3).

A study of the secondary products of the reaction which were obtained in each of the above experiments showed that they were all identical and had the structure of p-nitromethylformazyl (IV). It is probable the compound is formed by the coupling of the p-nitrophenylhydrazone of acetaldehyde (VIII) with the diazo compound (4).

$$CH_3CH{=}{=}NNHC_6H_4NO_2 + p\text{-}O_2NC_6H_4N_2SO_4H \rightarrow CH_3C(-NNHC_6H_4NO_2)=N-NC_6H_4NO_2$$

VIII II IV

With cinnamic acid, ethyl cinnamate, cinnamyl alcohol, styrene, and safrole no comparable reaction takes place (2).

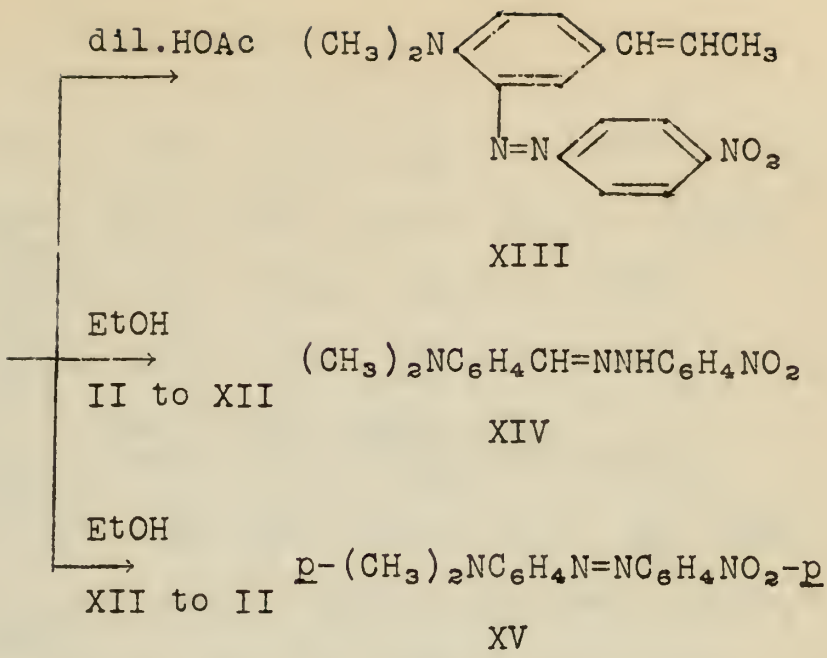
Ainley and Robinson, in extending the study of this reaction, found that p-methoxystyrene reacts in an analogous manner with 2,4-dinitrobenzenediazonium sulfate to give the hydrazone of anisaldehyde. They also confirmed the findings of Quilico that styrene does not give rise to a similar reaction.

p-Nitrobenzenediazonium chloride reacts with p-methoxyphenylacetylene in alcoholic solution to yield the hydrazone of p-methoxyphenylglyoxal (5).

$$p\text{-}CH_3OC_6H_4C{\equiv}CH + p\text{-}O_2NC_6H_4N_2Cl \rightarrow CH_3OC_6H_4C(=O)CH=N-NC_6H_4NO_2$$

With p-dimethylaminopropenylbenzene the reaction may be forced to proceed in any one of three directions. The normal coupling reaction in dilute acetic acid leads to the azo compound. However, when p-nitrobenzenebiazonium sulfate in alcohol is added to a cold, alcoholic solution of p-dimethylaminopropenylbenzene the hydrazone of p-dimethylaminobenzaldehyde is formed. Finally, when the order of mixing is reversed, 4-dimethylamino-4'-nitroazobenzene is formed in nearly quantitative yields.

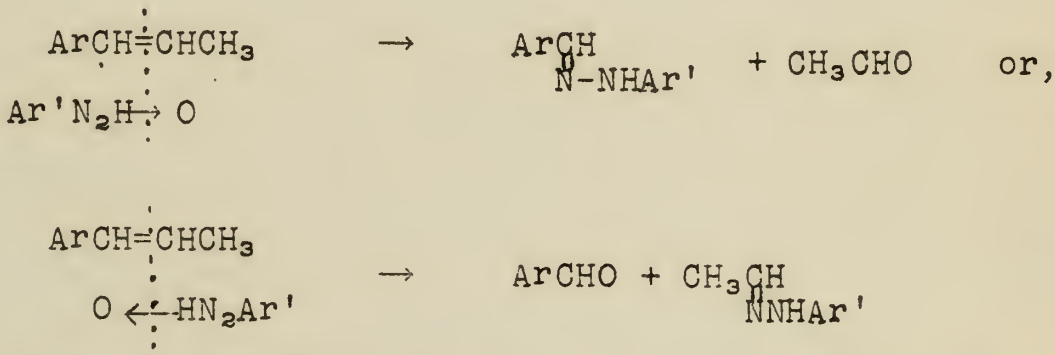
$$p\text{-}(CH_3)_2NC_6H_4CH=CHCH_3 + p\text{-}O_2NC_6H_4N_2SO_4H \rightarrow$$



The last reaction has also been carried out with p-dimethylaminobenazldehyde and di-(p-dimethylaminophenyl)carbinol (6).

Mechanism

The mechanisms for the above reactions are obscure, and until more is known of the structure of aromatic diazo compounds and their action as oxidizing agents the exact mechanisms will lie in doubt. Quilico (7) points out other cases of oxidation with aromatic diazo compounds: e.g., the Griess reaction and the oxidation of pyrrole to pyrrole black. Angeli (8) using his postulated structure for the normal diazohydrate, and Quilico (9) consider the reaction as proceeding by the mechanism outlined below.



In the latter case the hydrazone is not isolated as such but reacts with a second molecule of the diazohydrate to yield the formazyl compound.

In the reaction with p-dimethylaminopropenylbenzene to yield the abnormal azo compound, no secondary reaction product has been isolated. Quilico postulated that the propenyl group is expelled to yield propionaldehyde, and with the aldehyde the formyl group is expelled to yield formic acid (6).

The reaction with aromatic acetylenes is more easily explained by a 1-2 addition of the diazohydroxide (5).

BIBLIOGRAPHY

1. Quilico and Freri, Gazz. chim. ital., 58, 380 (1928); C.A., 23, 597 (1929).
2. Quilico and Fleischner, Gazz. chim. ital., 59, 39 (1929); C.A., 23, 3675 (1929).
3. Quilico and Freri, Gazz. chim. ital., 59, 600 (1929); C.A., 24, 599 (1930).
4. Quilico and Freri, Gazz. chim. ital., 60, 606 (1930); C.A., 25, 932 (1931).
5. Ainley and Robinson, J. Chem. Soc., 1937, 369.
6. Quilico and Freri, Gazz. chim. ital., 62, 253 (1932); C.A., 26, 4312 (1932).
7. Quilico, Gazz. chim. ital., 61, 326 (1931); C.A., 25, 5150 (1931).
8. Angeli and Polverini, Atti accad. Lincei, 11, 542 (1930); C.A., 24, 4770 (1930).
9. Quilico, Atti accad. Lincei, 12, 341 (1930); C.A., 25, 2683 (1931).

Reported by H. F. Herbrandson
January 17, 1945

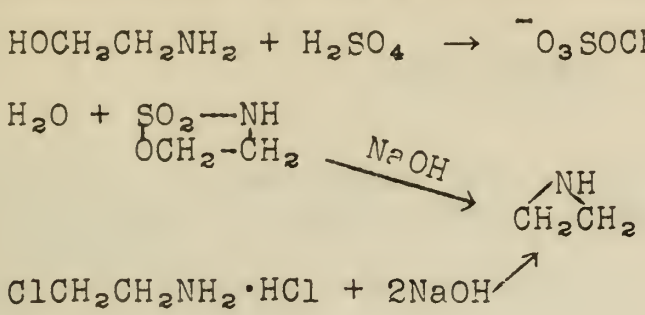
SEMINAR TOPICS

II Semester 1944-45

POLYMERIZATION OF ETHYLENIMINE

Giffin D. Jones, State University of Iowa

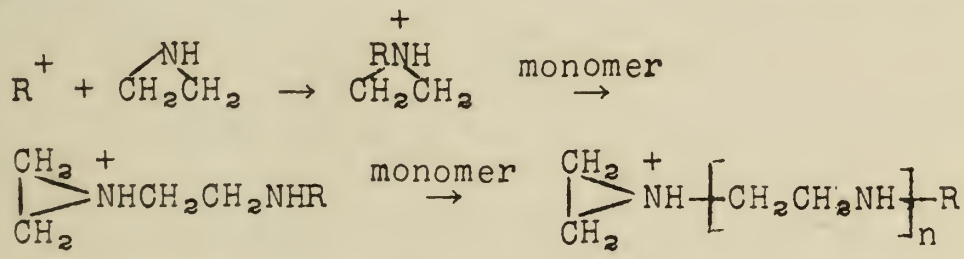
Ethylenimine may be prepared by the method of Wenker from ethanolamine, or by the method of Berchet from β-chloroethylamine hydrochloride. It is a liquid boiling at 56°; it will



remain unchanged indefinitely in the absence of carbon dioxide. Catalysts which will bring about polymerization are (1) acids, (2) alkylating agents, (3) oxidizing agents, (4) other electron acceptors, and (5) ammonia. Polymerization is often violent.

Kern and Brenneisen have pointed to the following evidence as being in support of a condensation mechanism of polymerization: the ineffectiveness of alkaline catalysts, the failure of quinone as an inhibitor, and the large fraction of dimer found in the product. Such a condensation might go by way of β-chloroethylamine formed as an intermediate by the action of hydrogen chloride catalyst.

An addition mechanism has been presented by Jones. This is not the slow, stepwise addition such as that found by Perry and Hibbert for the polymerization of ethylene oxide, but a rapid chain reaction starting from an active center according to the scheme



It is believed that this occurs, not by an ionic procedure involving a preliminary opening of the ring, but by an S_N2, or bimolecular inversion, reaction. Branching may occur through proton transfer.

The stability of ethylenimine in the absence of acid catalysts seems to preclude any stepwise addition mechanism. Jones was able to show that under anhydrous conditions hydrogen chloride will cause polymerization although no β-chloroethylamine appears to be present, and this compound alone polymerizes only very slowly at room temperature although it causes rapid polymerization

of ethylenimine; these facts oppose a condensation mechanism. The structure of the low polymers isolated from the polymerization of unsymmetrically substituted ethylenimines favors bimolecular inversion rather than an ionic ring opening.

BIBLIOGRAPHY

Perry and Hibbert, J. Am. Chem. Soc., 62, 2599 (1940).
Kern and Brenneisen, J. prakt. Chem., 159, 193 (1941) (from C. A., 37, 5637 (1943)).
Jones, Langsjoen, Neumann, and Zomlefer, J. Org. Chem., 9, 125 (1944).
Jones, J. Org. Chem., 9, 484 (1944).

Reported by G. E. Inskeep
February 14, 1945

MECHANISMS OF ELIMINATION REACTIONS

Hughes and Ingold, University College, London

During the period from 1927 to 1940, Hughes, Ingold, and coworkers determined, by studies of reaction kinetics, the mechanisms by which substitution and elimination reactions occur. Their work on elimination reactions will be the subject of this paper; the substitution mechanisms which they established will, however, be reviewed first (1), as they show great similarities to the elimination mechanisms.

Briefly, Hughes and Ingold have shown that substitutions may occur by either of two mechanisms. If the hydrolysis of alkyl halides by hydroxide ions in the presence of a solvent is used as an example, these two mechanisms may be formulated as follows.

$$1)\quad OH^- + RX \rightarrow ROH + X^- \qquad (S_N2)$$

The reaction is experimentally bimolecular; the speed of reaction is proportional to the concentration of the hydroxide ion and also of the alkyl halide. The attack by OH^- and the release of X^- occur simultaneously.

$$2)\quad RX \xrightarrow[\text{solvent}]{\text{slow}} R^+ + X^- \qquad (S_N1)$$

$$R^+ + OH^- \xrightarrow{\text{rapid}} ROH$$

The reaction is experimentally unimolecular; the speed is proportional to the concentration of the alkyl halide only, and is independent of the hydroxide ion concentration. The ionization of RX is the slow rate-determining step.

Factors which determine which of the above mechanisms will operate in any particular case include:

a) Nature of R. An increase in electron-release in R favors S_N1 relative to S_N2. For example, in alkaline aqueous alcohol, MeX and EtX undergo S_N2, iso-PrX undergoes S_N1 and S_N2, and t-BuX undergoes S_N1 substitutions (2). In general, primary halides undergo S_N2, and secondary and especially tertiary halides undergo S_N1 substitutions.

b) Nature of X. An increase in electron-affinity of X favors S_N1 to a greater extent than S_N2. For example, $[Et\overset{+}{S}(Et)_2]$ and Br^- in acetone solution form EtBr by an S_N1 substitution; EtCl and Br^- in acetone form EtBr by S_N2 ($\overset{+}{S}(Et)_2$ is more electron-attractive than Cl^-) (3).

c) Nature and concentration of base. An increase in basicity or in concentration of the base favors S_N2.

d) Nature of solvent. An ionizing solvent favors S_N1.

Further work by Ingold and Hughes (4,5,6,7,8,9) has demonstrated experimentally that elimination reactions also occur by two mechanisms, similar to those for substitutions.

$$I)\quad OH^- + H\text{-}CR_2\text{-}CR_2\text{-}X \rightarrow HOH + CR_2{=}CR_2 + X^- \qquad (E2)$$

The reaction is experimentally bimolecular; the speed of reaction is proportional to the concentrations of both OH^- and RX. All electronic transfers occur simultaneously.

$$II)\quad H\text{-}CR_2\text{-}CR_2\text{-}X \xrightarrow[\text{solvent}]{\text{slow}} H\text{-}CR_2\text{-}CR_2^+ + X^- \qquad (E1)$$

$$H\text{-}CR_2\text{-}CR_2^+ \xrightarrow{\text{rapid}} CR_2{=}CR_2 + H^+$$

The reaction is experimentally unimolecular; the speed of reaction is proportional to the concentration of RX only, and is independent of the OH^- concentration. The rate-determining step is the slow ionization.

An independent proof of the unimolecular elimination mechanism comes from a study of the change in the reaction rates and in the percentages of olefin formed in a series of alkyl halides, where R is constant but X varies. If the reaction is proceeding by a unimolecular mechanism, the relative rates of the total reaction (both substitution and elimination) should vary as X varies, since each of the alkyl halides will ionize at an independent rate. But the percentage of olefin formed should be approximately constant as X varies, since it depends only on the inherent tendency of R^+ either to lose H^+ (elimination) or to gain OH^- (substitution).

These theoretical predictions have been confirmed for β-n-octyl chloride and bromide. The rates of the total first order reaction (k_1) are in the ratio 1:33; but the proportion of olefin formed $\left(\frac{kE1}{k1}\right)$ is approximately the same, 0.13 for the chloride and 0.14 for the bromide. Similar results were obtained with the corresponding t-Bu and t-amyl compounds.

The factors determining which mechanism will operate in any particular case are the same as those influencing the mechanism of the substitution reaction.

A) Nature of RX. Unimolecular eliminations have been found with secondary and tertiary, but not with primary halides. This is expected, as secondary and tertiary alkyl groups are more electron-repulsive than primary.

B) Nature and concentration of the base. Previous literature contained many discrepancies in regard to the percentage of

olefins formed from halides. Brusoff (10), for example, found the sequence secondary > tertiary, while Segaller (11) found secondary < tertiary. Hughes and Ingold have been able to reconcile all previous results by taking into account the differences in the concentrations of the bases and in the basicity of the bases used in the different studies.

When a given halide is treated with a strong base, it is found experimentally and deduced theoretically that the percentage of olefin formed remains approximately constant so long as the total order of the reaction remains constant. For a unimolecular reaction, the percentage of olefin is given by $\frac{E1}{S_N1 + E1}$. As the alkalinity is increased, the mechanism gradually changes to a bimolecular one; and the percentage of olefin formed gradually changes to a new, larger, and again approximately constant value, given by $\frac{E2}{S_N2 + E2}$. The percentage of olefin formed by either the pure bimolecular or the pure unimolecular mechanism is generally greater for a tertiary halide than for a secondary halide; but the change from E1 to E2 kinetics as the alkalinity increases occurs sooner for the secondary halide. Consequently, during the period of changing order, the secondary halide may show a greater tendency for olefin formation than the tertiary halide (Brusoff sequence); while at either higher or lower concentrations of alkali, the Segaller sequence is maintained.

For a weakly basic reagent, such as $C_6H_5O^-$ or AcO^-, the nucleophilic activity for H is low, but the nucleophilic activity for C is still appreciable. Hence the percentage of olefin formed in the bimolecular reaction will be small, as the substitution (attack on C) will be favored over the elimination (attack on H). If the percentage of olefin formed by the bimolecular reaction falls below that of the unimolecular, but the tertiary halides still show greater olefin production than the secondary for the kinetically pure reactions, there will be no inversion such as was found with strong bases. The tertiary halides will show over the whole concentration range a higher percentage of olefin produced. This explains Mereshkowsky's and Segaller's results (12), where the sequence tertiary > secondary was found over the whole concentration range, using $C_6H_5O^-$ and AcO^- as bases.

C) Nature of solvent. With an increase in solvating (ionizing) power of the solvent, the pure bimolecular mechanism will gradually change to the pure unimolecular mechanism. The change from bimolecular to unimolecular kinetics will come earlier for the tertiary than for the secondary halide. If the percentage of olefin formed is greater for the tertiary compounds for both the pure uni- and the pure bimolecular mechanism, an inversion (such as was found with strong bases) may occur in a solvent of intermediate solvating power.

It is evident that, with a knowledge of the manner in which the reaction rates for S_N1, S_N2, E1, and E2 vary with constitutional, reagent, and solvent changes, a study of only a few members of a series will enable one to make semi-quantitative predictions as to the course of reaction of the other members.

BIBLIOGRAPHY

1. Jones, Organic Seminar, Dec. 3, 1941.
2. Watson, Ann. Reports Chem. Soc., 35, 210 (1938).
3. Hughes, Trans. Faraday Soc., 34, 195 (1938).
4. Hughes, Ingold, and Scott, J. Chem. Soc., 1937, 1271.
5. Hughes, Ingold, and Shapiro, J. Chem. Soc., 1937, 1277.
6. Cooper, Hughes, and Ingold, J. Chem. Soc., 1937, 1280.
7. Hughes and MacNulty, J. Chem. Soc., 1937, 1283.
8. Hughes, Ingold, Masterman, and MacNulty, 1940, 899.
9. Watson, Ann. Reports Chem. Soc., 35, 226 (1938).
10. Brusoff, Z. physikal. Chem., 34, 139 (1900).
11. Segaller, J. Chem. Soc., 1913, 1430.
12. Mereshkowsky, Ann., 431, 231 (1923).

Reported by Clara L. Deasy
February 14, 1945

WURTZ TYPE REACTIONS

A. A. Morton, Massachusetts Institute of Technology

Extensive work has been carried out on the mechanism of the Wurtz reaction. Three mechanisms for this reaction have been offered, involving the formation of free radicals,

$$2RX + 2M \rightarrow 2R\cdot + 2MX$$

$$2R\cdot \rightarrow RR$$

the intermediate formation of an organoalkali intermediate,

$$RX + 2M \rightarrow RM + MX$$

$$RM + RX \rightarrow RR + MX$$

and a combination of the two.

Because of the number of products obtained from this reaction the free radical mechanism has received considerable support. The products usually obtained are: (1) a saturated hydrocarbon R-R; (2) a saturated hydrocarbon RH; (3) an unsaturated hydrocarbon R(-H); and (4) polymeric material.

Bachman and Clarke obtained triphenylene and o-diphenylbenzene from a reaction mixture of sodium and chlorobenzene. Their formation can be satisfactorially explained on the basis of intermediate phenyl radicals which in turn may unite to give triphenylene.

$$2C_6H_5\cdot \rightarrow C_6H_6 + C_6H_4<$$

$$3C_6H_4< \rightarrow C_6H_4(-C_6H_4-)C_6H_4$$

or the phenylene and phenyl radicals can combine to give o-diphenylbenzene

$$C_6H_5\cdot + C_6H_4 + C_6H_5\cdot \rightarrow C_6H_5C_6H_4C_6H_5$$

Another characteristic common to Wurtz reactions is the appearance of color, usually blue, which later fades. Such an appearance of color is sometimes taken as an indication of the presence of free radicals.

Additional kinetic studies by Richards on the action of ethyl iodide and sodium indicated that the reaction was first order with respect to the iodide concentration and led him to assume there was a high concentration of radicals at the sodium surface. These radicals could react by disproportionation to give ethane and ethylene, or with the less concentrated ethyl iodide to give butane.

Proponents of the organoalkali intermediate mechanism have more direct evidence to substantiate their theory. Morton and co-workers have carried out the most extensive studies of this reaction.

Gilman and Pacevitz poured the reaction mixture of sodium and amyl chloride on solid carbon dioxide and isolated caproic acid showing that there was one amyl radical for every sodium rather than a mixture of "amylidene disodium." This same observation was made with butyl sodium. The importance of this work is that it brings the formation of alkyl malonic acids into line with that observed for phenyl malonic acid. The malonic acid is a product of a secondary reaction thus eliminating the necessity of assuming the intermediate free radical which accounted for the supposed disodium compound

$$RCH_2Na \xrightarrow{CO_2} RCH_2COONa \xrightarrow{RCH_2Na}$$

$$RCH(Na)COONa \xrightarrow{CO_2} RCH(COONa)_2$$

Morton found that highest yields of the organometallic compound could best be obtained by the presence of an excess of finely divided sodium, the absence of a protective coating on the sodium and an unreactive carbon-halogen bond.

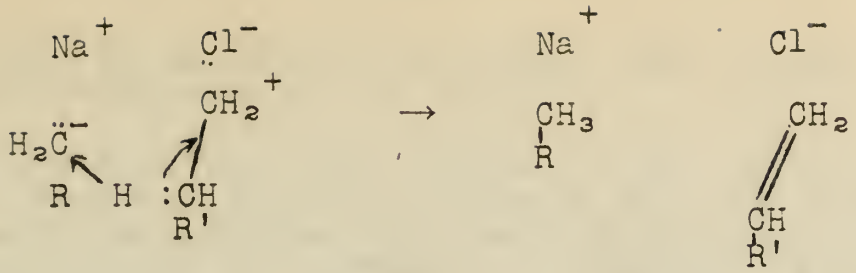
In order to fulfill the first requirement a method was devised for preparing extremely finely divided sodium sand.

Microscopic observation of a sodium partical indicated that a primary halide produced an insoluble, colloidal, jelly-like mass which was gradually pushed out as more of the halide diffused into the sodium. Secondary halides, on the other hand, apparently produced hard impenetrable coatings.

Best results for securing organometallic compounds were obtained with alkyl halides that would not react too readily with the organometallic compound.

If the Wurtz reaction can be divided into two steps in which the first step is the formation of the organometallic intermediate, the products obtained can be explained by reaction of this intermediate with an alkyl or aryl halide to form the second step.

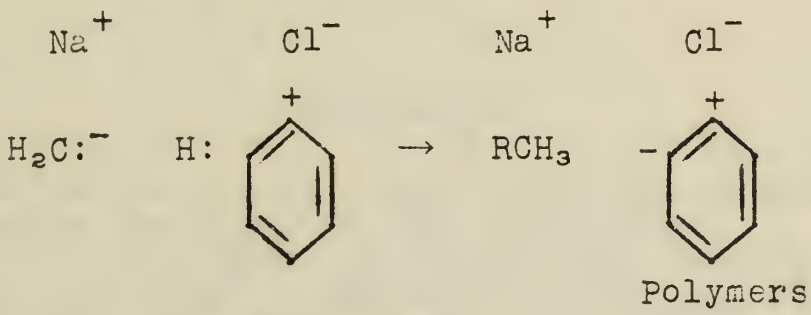
Disproportionation has been generally accepted as an indication of free radicals; however, a mechanism for this phenomenon by way of an organometallic intermediate is possible. If an alkyl halide and an alkyl sodium come together in such a way that, while the sodium halide is being formed, the alkyl chains are adjacent to one another, the two alkyl residues will be drawn to one another and the proton will be drawn to the alkyl residue having the two unsaturated electrons.



If this is to be accepted, the olefin produced must come from the halide rather than at random. This conclusion is obscured by the fact that metal-halogen interchange does take place and the olefin appears to be formed somewhat at random. Morton, Davidson, and Hakan treated octyl sodium and amyl sodium with various halides and found that in all cases the alkane of the sodium compound predominated over the alkene from the halide.

The formation of polymers can also be explained by the organometallic mechanism. A reaction between amyl sodium and chlorobenzene produced more polymer than when the phenyl sodium was reacted with amyl chloride.

Use of the organometallic mechanism explains the above observation and indicates that ortho substituted polymer should predominate and the polymers should have more phenyl units in it than any other type. This is borne out by experimental evidence.



Metalation of Ring Compounds

Reaction of amyl sodium with bicyclic compounds and carbonation of the mixture showed that metalation occurred readily in a number of places. The end-products from naphthalene were both mono-carboxylic acids, at least three dicarboxylic acids and some tricarboxylic acid. Acenaphthene and decalin were both readily attacked.

By proper control of the temperature, quantity of reagents used and efficiency of stirring, benzene and toluene can be dimetalated. Carbonation of the dimetalated products gives isophthalic and homoisophthalic acids respectively.

The fact that the dimetalated products of benzene and toluene are exclusively meta substituted can be explained if it is assumed that the monometalated compound is formed first. If this product is a salt and acts as an ion-pair then the

sodium ion will be so close to the anion that it will exert a meta directive influence on the anion.

The m- and p-xylenes are attacked on the methyl groups exclusively, whereas, o-xylene undergoes some nuclear metalation, presumably after one sodium atom has been introduced to a methyl group. Alkylation of the monometalated products yields the corresponding methylhexylbenzene. Carbonation of the dimetalated products yields the corresponding phenylene diacetic acids. The alkylation and metalation of the xylenes proceeds with greater difficulty than the corresponding reaction of toluene.

The results indicate that the presence of alkyl or methyl groups causes the metalation to proceed with difficulty. The maximum effect could be expected when the alkyl group is adjacent to the position being attacked and might alone be sufficient to explain the observed results.

Amyl sodium introduces a second sodium atom into furan with little difficulty. Carbonation of the disodium compound yields 2,5-furandicarboxylic acid. At first glance it would appear that the result would be in direct disagreement with those observed for benzene and toluene in which the substitution was exclusively in the meta position. It is possible that the meta-directing influence of the sodium ion is overcome by a strong ortho-directing influence such as the ether linkage in furan.

BIBLIOGRAPHY

Bachmann and Clarke, J. Org. Chem., 49, 2089 (1927).
Richards, Trans. Faraday Soc., 36, 956 (1940).
Morton, et al; J. Am. Chem. Soc., 64, 2240 (1942); 63, 327 (1941); 60, 1426 (1938); 59, 2387 (1937); 64, 2240 (1942); 60, 1429 (1938); 64, 2250 (1942); 65, 1339 (1943).
Gilman and Pacevitz, ibid., 62, 1301 (1940).
Marvel, Hager, and Coffman, ibid., 49, 2323 (1927).

Reported by A. Deutschmann
February 21, 1945

DEVELOPMENTS IN THE CHEMISTRY OF ORGANIC SILICON COMPOUNDS. THE SILICONES.

The study of organic silicon compounds was begun nearly eighty-five years ago and the basic work on the silicones was done over forty years ago.

Kipping suggested a method of nomenclature such that the silicon compounds would parallel their carbon analogs. Though the literature does not conform to any one system of nomenclature some characteristic terminology is as follows.

SiH_4	Silane or silicane
$Si(C_6H_5)_4$	Tetraphenylsilane
$SiH_3(OH)$	Silicol or silicanol
$Ph_3Si(OH)$	Triphenylsilicol
$SiH_2(OH)_2$	Silicanediol
Et_2SiO	Diethylsilicone
$RSiO_2H$	A siliconic acid or a metasilicic acid
$Si(OC_2H_5)_4$	Ethyl orthosilicate
$C_2H_5Si(OC_2H_5)_3$	Ethyl ethane orthosilicate (or siliconate)

Early work in the field of organic silicon compounds was published in 1866 by Friedel and Crafts. At that time they described their procedures for synthesizing ethyl orthosilicate from silicon tetrachloride, and the procedures for making the di- and trichloro derivatives as well.

$$SiCl_4 + 4CH_3CH_2OH \rightarrow Si(OC_2H_5)_4 + 4HCl$$
$$3Si(OC_2H_5)_4 + SiCl_4 \rightarrow 4ClSi(OC_2H_5)_3$$
$$2ClSi(OC_2H_5)_3 + SiCl_4 \rightarrow 3Cl_2Si(OC_2H_5)_2$$

They also demonstrated the chlorination of the orthosilicates by acetyl chloride, and the substitution of alkoxyl groups by refluxing the chloro compound with an alcohol.

$$Si(OC_2H_5)_4 + CH_3COCl \rightarrow ClSi(OC_2H_5)_3 + CH_3COOC_2H_5$$
$$ClSi(OC_2H_5)_3 + C_5H_{11}OH \rightarrow (H_{11}C_5O)Si(OC_2H_5)_3$$

Ladenburg in 1874 brought about the introduction of alkyl and aryl groups into the silicon compounds by the use of zinc and mercury alkyls and aryls, so that a direct C-Si bond was established.

$$Si(OC_2H_5)_4 + Zn(CH_3)_2 \rightarrow CH_3Si(OC_2H_5)_3 + ZnCH_3(OC_2H_5)$$
$$SiCl_4 + Hg(C_6H_5)_2 \rightarrow C_6H_5SiCl_3 + HgC_6H_5Cl$$
$$SiCl_4 + 2Zn(C_2H_5)_2 \rightarrow Si(C_2H_5)_4 + 2ZnCl_2$$
$$2SiC_6H_5Cl_3 + 3Zn(C_2H_5)_2 \rightarrow 2SIC_6H_5(C_2H_5)_3 + 3ZnCl_2$$

Polis did further work on the synthesis of compounds of this type, and converted some to the hydroxy derivatives. He first made triphenyl silicol from tetraphenyl silane by chlorinating then hydrolyzing with dilute ammonium hydroxide.

$$(C_6H_5)_4Si \xrightarrow[PCl_5]{} (C_6H_5)_3SiCl$$

$$(C_6H_5)_3SiCl \xrightarrow[NH_4OH]{} (C_6H_5)_3SiOH$$

The Silicol, in turn, can be transformed into the oxide (ether) by boiling with 10% hydrochloric acid.

$$(C_6H_5)_3SiOH \xrightarrow[10\% \text{ aqueous}]{HCl} [(C_6H_5)_3Si]_2O$$

It was not until Kipping became interested in the field of organo-silicon compounds that intensive investigations were carried out. It was while studying the by-products of the reaction to form tetraphenylsilane that he encountered a product which analyzed for diphenyl silicone, $(C_6H_5)_2Si = O$. He reported that it bore little or no resemblance to its carbon analog and thought the material to be a polymer.

Discovery in 1903 that $SiCl_4$ could react with Grignard reagents opened a new field for research. Kipping thus prepared the ethyl, propyl, phenyl and benzyl derivatives of silane.

$SiCl_4 + EtMgBr \rightarrow EtSiCl_3 + MgClBr$
$EtSiCl_3 + MgPhBr \rightarrow EtSiPhCl_2 + MgClBr$
$EtSiPhCl_2 + MgPrBr \rightarrow EtSiPhPrCl + MgClPr$
$EtSiPhPrCl + MeMgI \rightarrow EtSiPhPrMe + MgClI$

The chlorides can then be easily hydrolyzed to the corresponding hydrols.

$(C_6H_5CH_2)_3SiCl \xrightarrow[H_2O]{} (C_6H_5CH_2)SiOH$ tribenzyl silicol

$(C_6H_5CH_2)_2SiCl_2 \xrightarrow[H_2O]{} (C_6H_5CH_2)_2Si(OH)_2$ dibenzyl silicanediol

$(C_6H_5CH_2)SiCl_3 \xrightarrow[H_2O]{} (C_6H_5CH_2)_2SiO_2H$ benzyl siliconic acid or benzyl metasilicic acid

The silicol can be converted to the oxide by heating with 10% hydrochloric acid. Ethyl and tolyl metasilicic acid can be converted to the oxide by merely heating to 100°, but the benzyl is unchanged after seven hours at 150°, or even in boiling acetic anhydride.

The silicanediols can be dehydrated by heat or chemical agents to the corresponding silicones and condensation products. The silicones undergo condensation and polymerization so readily that much difficulty was encountered in identifying the reaction products.

$$(C_6H_5)_2Si(OH)_2 \xrightarrow[-H_2O]{} HOSiPh_2OSiPh_2OH$$

$$\xrightarrow{-H_2O}$$

<u>tri</u>- and <u>tetra</u>-dehydration products $\xrightarrow[-H_2O]{} HOSiPh_2OSiPh_2OSiPh_2OH$

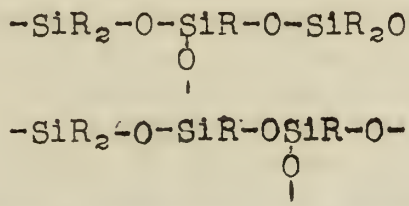
The formation of cyclic products of the type $(SiPh_2O)_3$ was also noted. These then condense further with heat to give polymers of a probable unit structure $[-R_2SiO-]$.

The mono- and trihydric silicols similarly yield condensation products.

$$2R_3SiOH \rightarrow R_3SiOSiR_3 \qquad 2RSi(OH)_3 \rightarrow (RSiO)_2O$$

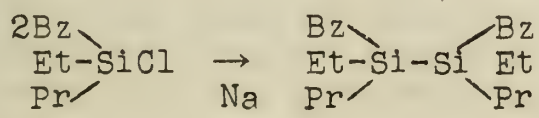
In the case of diethyl silicon dichloride, the dihydrol form was not isolated and apparently the product spontaneously eliminated water to form the silicone and condensation products. It had previously been reported that the silicones and siliconic acids bore little if any resemblance to their carbon analogs and would not undergo typical ketone and carboxyl reactions. The formation of the condensation products very probably account for this.

Intermolecular condensation of the silicanediols and the silicanetriols has yielded solid polymers probably with a cross-linked structure.



These complex condensation and polymerization products are the chief constituents of the widely-heralded silicone rubber.

In addition to linkage through oxygen, as exemplified by the silicone condensates, direct silicon-silicon bonds have been formed by coupling alkyl and aryl chlorosilanes with the aid of sodium.



Post and Hofrichter prepared orthosilico propionates, valerates, benzoates, etc., by the use of the desired Grignard reagent, followed by refluxing with the appropriate alcohol.

$$Si(OC_2H_5)_4 + C_2H_5MgBr \rightarrow C_2H_5Si(OC_2H_5)_3 + C_2H_5OMgBr$$

$$C_2H_5Si(OC_2H_5)_3 + 3C_3H_7OH \rightarrow C_2H_5Si(OC_3H_7)_3 + 3C_2H_5OH$$

71.3% yield

Silicoketals were also prepared by the action of Grignard reagents on ethyl orthosilicate as shown previously by Helferich and Hausen.

Alkyl orthosiliconates can be acetylated with acetic anhydride to form mono- and diacetylation products. Post and Hofrichter have proposed the following reversible ionic mechanism for the formation of these products.

$$C_2H_5Si(OR)_3 \rightleftarrows C_2H_5Si(OR)_2^+ + OR^-$$
$$(CH_3CO)_2O \rightleftarrows (CH_3COO)^- + (CH_3CO)^+$$
$$C_2H_5Si(OR)_2^+ + (CH_3COO)^- \rightleftarrows CH_3COOSiC_2H_5(OR)_2$$
$$(CH_3CO)^+ + OR^- \rightleftarrows CH_3COOR$$

For the diacetylation product a second ionization is necessary. For example the case of ethyl orthosilicate.

$$CH_3COOSi(OC_2H_5)_3 \rightleftarrows CH_3COOSi(OC_2H_5)_2^+ + (OC_2H_5)^-$$
$$CH_3COOSi(OC_2H_5)_2^+ + (CH_3COO)^- \rightleftarrows (CH_3COO)_2Si(OC_2H_5)_2$$

Intermolecular decomposition can be predicted to take place to form high molecular weight products.

$$CH_3COOSi(OC_2H_5)_3 \rightleftarrows (CH_3CO)^+ + [OSi(OC_2H_5)_3]^-$$
$$CH_3COOSi(OC_2H_5)_2^+ + [OSi(OC_2H_5)_3]^- \rightarrow \text{High mol. wt. products}$$

Whitmore has studied the reactivity of carbon-chlorine bonds in various positions relative to the silicon atom by use of Grignard reagents. If n-propyl trichlorosilane is chlorinated with sulfuryl chloride, a mixture of the monochlorination products is obtained in 90% yield, 13.3% going alpha, 46.7% beta, and 40.0% gamma. Hydrolysis also indicates a similar order of reactivity with the beta C-Cl bond approaching that of the Si-Cl bond. While the alpha chloro- product is not attacked by Grignard reagents the beta chloro- product yields the tetra substituted product and ethylene. The mechanism of this is explained by Whitmore and

$$CH_2ClCH_2SiCl_3 + 4CH_3MgBr \rightarrow (CH_3)_4Si + CH_2{=}CH_2 + 4MgBrCl$$

colleagues as follows: The trisubstitution product is first formed by the reaction which coordinates at the beta chlorine atom with the Grignard reagent resulting in an electrons displacement away from the beta chlorine atom.

$$R_3SiCH_2CH_2Cl + RMgBr \rightarrow R_3SiCH_2CH_2Cl \rightarrow \begin{matrix} MgR \\ Br \end{matrix}$$

Magnesium chlorobromide is then eliminated leaving the beta carbon with an open sextet. A simultaneous shift of the electron pair from the C-Si bond to the deficient carbon, results in the formation of ethylene.

$$R_3SiCH_2CH_2Cl \rightarrow \begin{matrix} MgR \\ Br \end{matrix} \rightarrow R_3SiCH_2CH_2^+ + R:^- + MgBrCl$$
$$R_3\overset{\frown}{SiCH_2CH_2}^+ \rightarrow R_3Si^+ + CH_2{=}CH_2$$

The electrically deficient silicon then combines with the alkyl group of the Grignard.

$$R_3Si^+ + R:^- \rightarrow R_4Si$$

The only organo-silicon compounds which have become commercially important as yet are the silicone and ethyl (ortho) silicate, the latter having been reported used as a binder in sane molds. The silicones are of greater national interest, at present, and seemingly have a broad field of uses.

Though the Grignard synthesis has heretofore been regarded mainly as a laboratory tool, it appears that in the case of the silicones it is used on a commercial scale that may assume gigantic proportions. Some of the silicones upon which patent rights are sought are the dimethyl, diethyl, diphenyl; mono-, di-, tri-, and polyhalogenated phenyl, polyalkylated phenyl, naphthyl, tetrahydronaphthyl, and various combinations of alkyl, aryl, and substituted aryl groups.

The uses of the finished product are too numerous to mention. The individual, copolymerized, or mixed silicones can be incorporated into other materials of varied nature, such as rubber tar, pitch, resins of all kinds, cellulosic materials and other organic plastic compounds. Lower molecular weight polymers can be dissolved in drying oils, can be plasticized alone, or made up in other manners to give heat resistant paints. They can be mixed with wood flour, talc, glass, etc. and be used for molding plastics.

Some uses of the finished products are for heat resisting gaskets, electrical insulating materials, for rendering materials water-repellent; for stop cock grease, laminated products, molding compositions, hoses, golf balls, and innumerable other uses.

BIBLIOGRAPHY

Friedel and Crafts, Ann. Chim. [IV], 9, 5 (1866).
Ladenburg, Ann., 173, 143 (1874).
Polis, Ber., 18, 1542 (1885).
Kipping and coworkers, J. Chem. Soc., 79, 449 (1901); 91, 209 (1907); 93, 439 (1908); 95, 302 (1909); 101, 2106, 2108, 2125, 2142, 2156 (1912); 105, 671 (1914); 107, 459 (1915); 119, 647, 830 (1921); 123, 2590, 2598 (1923).
Helferich and Hausen, Ber., 57, 1427 (1928).
Post and Hofrichter, J. Org. Chem., 4, 363 (1939).
Post and Hofrichter, ibid., 5, 443, 572 (1940).
Rochow and Gilliam, J. Am. Chem. Soc., 63, 798 (1941).
Gilliam, et al., J. Am. Chem. Soc., 63, 801 (1941).
Hyde and DeLong, ibid., 63, 1194 (1941).
U. S. Patent 2,258,219; 2,258,220; 2,258,222 (1941).
U. S. Patent 2,286,763 (1942).
Abstracts of Papers, 106th meeting Am. Chem. Soc., September, 1943, page 13M.
Abstracts of Papers, Am. Chem. Soc. meeting, September, 1944, pages 14M-15M.

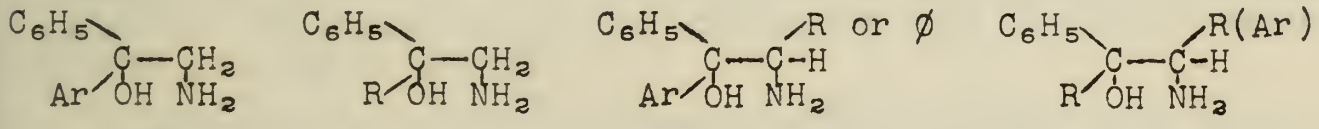
Reported by James R. Blegen
February 21, 1945

SOME REACTIONS OF AMINOALCOHOLS

Aminoalcohols have received much attention because of their widespread occurrence in natural products and because of their use as medicinals (novocaine, etc.). Little attention has been paid to their reactions. However over a period of years many reactions of amino alcohols have been recorded. The purpose of this seminar is to collect some of these reactions.

Deamination of β-Aminoalcohols by Nitrous Acid

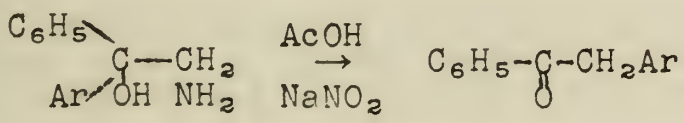
Like 1,2-glycols, β-aminoalcohols readily undergo a pinacolinic rearrangement when deaminated by nitrous acid. They undoubtedly do so by a similar mechanism. Unlike glycols, the functional group to be removed is predetermined (the NH_2 group). The following four types of compounds have been studied, principally by Tiffeneau, Mills, and McKenzie.



I II III IV

Ar=α-napthyl(5) R=CH_3,C_2H_5 Ar=anisyl, R=benzyl (4)
=anisyl, (7) p-tolyl(7)
veratryl(6) =α-napthyl,
p-tolyl (3) (1)(2)(3)(4)

In type I the aryl group migrates.

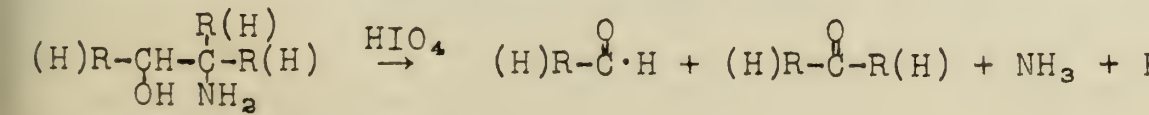


With types II, III, and IV the phenyl group migrates. In type III, by analogy with 1,2-glycols, the aryl group (anisyl, p-tolyl, etc.) would be expected to migrate in preference to the phenyl group.

Whitmore has applied his theory of molecular rearrangements to this semipinacolinic deamination. He has also shown that a Walden inversion takes place at the amino-carbon atom (8).

Oxidation of Aminoalcohols

Primary and secondary β-alkanolamines have been shown to be quantitatively oxidized (9) by periodic acid in a moderate length of time. Tertiary amines do not react at a significant rate.



R = CH_3

and $(HOCH_2CH_2)_2NH \rightarrow 4HCHO + NH_3$

This reaction is also quantitative for β-hydroxy-α-amino acids. For example Serine ($HOCH_2CH_2(NH_2)COOH$) may be determined quantitatively by periodic acid (10). Contiguously substituted dihydroxy amino compounds react in the expected manner (11). 1-Amino-2,3-dihydroxy-n-hexane requires two moles of lead tetraacetate or periodic acid.

Tertiary alkanolamines have been found to undergo oxidation by lead tetraacetate (12). The speed of oxidation decreased as the number of carbon atoms between the amino group and the hydroxyl group increased. From the products isolated it was shown that cleavage of a C-N bond instead of a C-C bond occurred when a tertiary amino group was involved.

Aminoalcohols have been shown to reduce chloronitrobenzenes and nitrobenzene to the corresponding anilines and azobenzenes (13). Ammonia was given off and the presence of an aldehyde was demonstrated. The reducing ability decreased with increased separation of the functional groups.

Although the tertiary amines, triethanolamine and triisopropanolamine, were good reducing agents, diethylaminoethylalcohol was extremely weak.

Dehydration of Alkanolamines

With aminoalcohols containing contiguous hydroxyl and tertiary amino groups it seems plausible that dehydration must produce the corresponding vinylamine or allylamine; usually the former.

2-Dimethylamino-1,1-dimethylethanol-1 could be dehydrated by pyrolysis of its Grignard complex to 1-dimethylamino-2-methyl-1-propene, identified by its hydrolysis products (14).

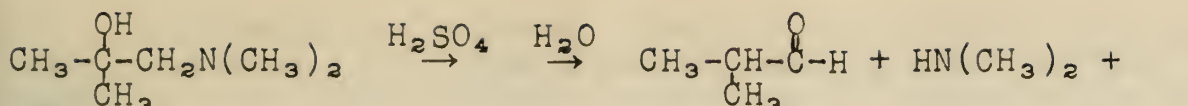
$$CH_3-\underset{CH_3}{C}=CH-N(CH_3)_2 \xrightarrow[H_2O]{OH^-} CH_3-\underset{CH_3}{CH}-\overset{O}{\overset{\|}{C}}-H + (CH_3)_2NH$$

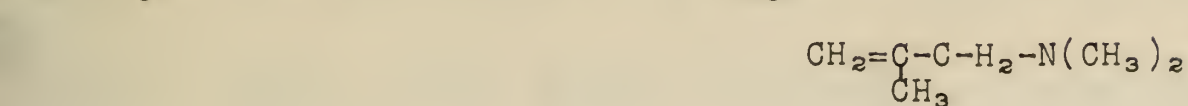
Krabbe has dehydrated a series of N-acyl-β-ethanolamines by a similar procedure and obtained vinyl amines (15).

Frequently the methods used for working up the product after dehydration by a strong acid give rise to conditions (dilute acid) which would hydrolyze any vinylamine formed. The hydrolysis of vinylamines, however, is thought to proceed as follows (16).

$$-\underset{|}{C}=\underset{|}{C}-N= \rightarrow -\underset{|}{\overset{H}{C}}-\underset{|}{\overset{O}{\overset{\|}{C}}} + NH=$$

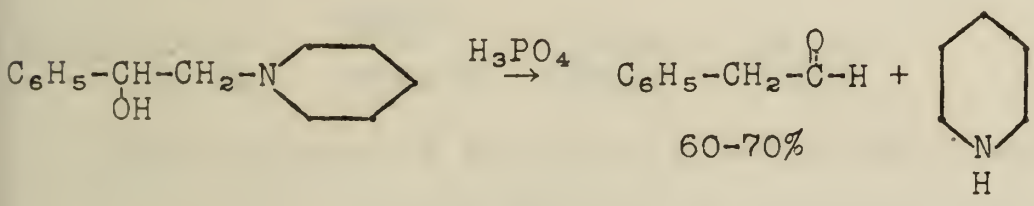
The following reactions have been shown to occur with concentrated sulfuric acid (14,17).

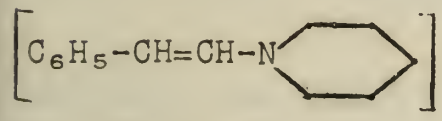


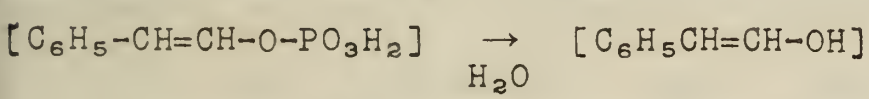


Krabbe has produced N-acyl vinylamines by dehydration with concentrated sulfuric acid (18).

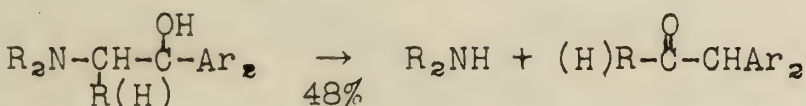
Krohnke and Schulze, using concentrated phosphoric acid, cleaved 1-phenyl-2-piperidinoethanol-1. They proposed the following mechanism for this type of reaction (19).



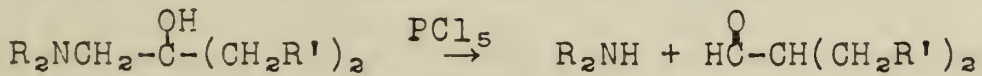




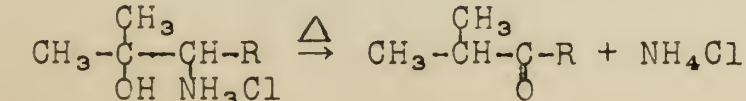
Treatment of <u>tertiary</u> akanolamines with 48% hydrobromic acid resulted in this same type of reaction (20).

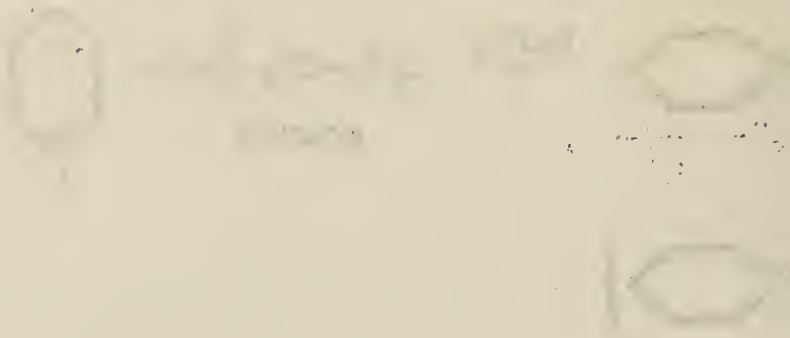


Phosphorous pentachloride gave similar results (20).

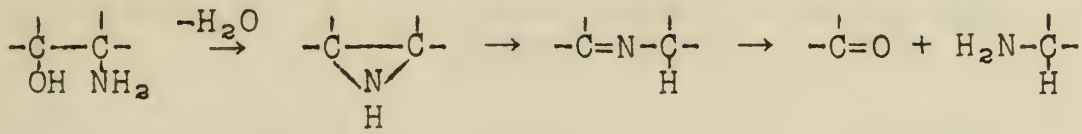


Those amino alcohols whose corresponding glycols will rearrange to aldehydes or ketones when heated with acid will likewise rearrange to aldehydes or ketones (21).when their hydrochloride salts are heated.



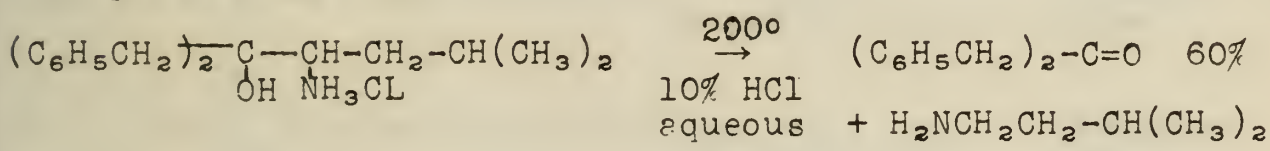


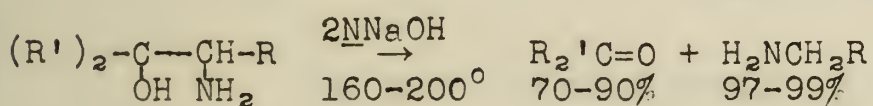
Dehydration of primary alkanolamines may proceed to give ethyleneimines, the imine rearrangement product of the ethylene imine, or the hydrolysates of the imine. Undoubtedly this is not



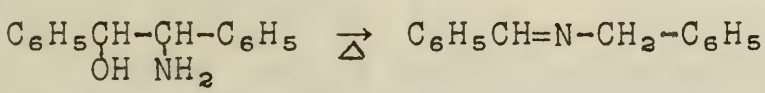
the whole picture.

Bettzieche and Ehrlich have shown that the following reactions take place (22, 23).

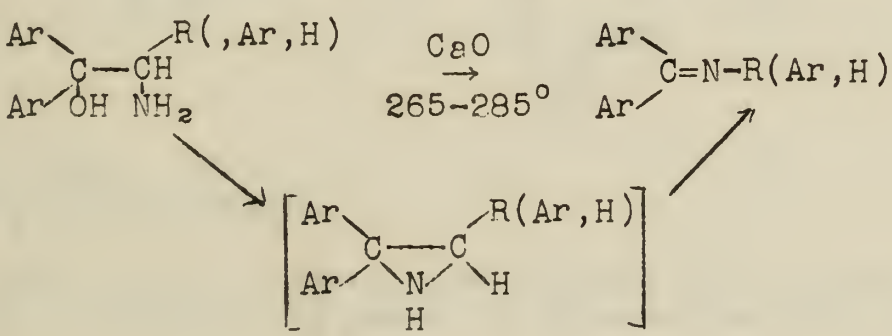




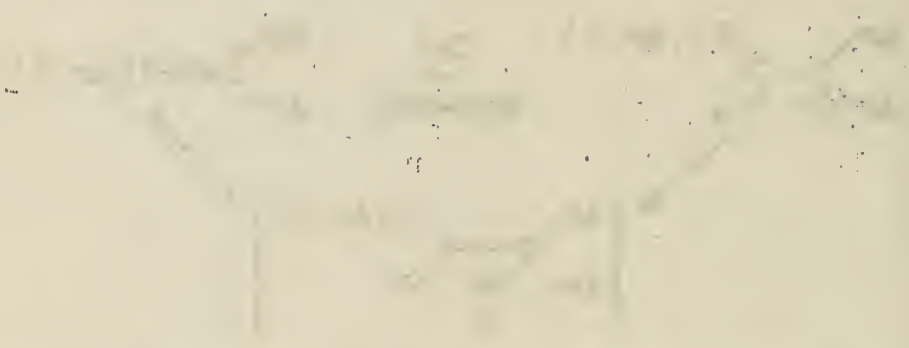
Heat alone will dehydrate 1,2-diphenylethanolamine (24).



Campbell and Campbell in 1943 showed that this rearrangement could proceed by way of an intermediate ethylenimine (25).



The amino group because of its electron attracting nature should produce in an adjacent tertiary hydroxyl group a tendency to act as a primary hydroxyl. As the number of carbon atoms between the two groups increases this effect should decrease. Campbell and Campbell (14) investigated a series of four amino alcohols and found this to be the case.

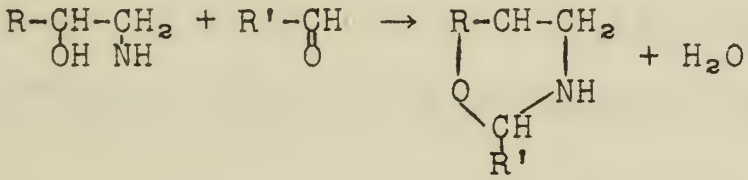


		Reaction with Benzoyl chloride	$CuSO_4$ 200°	KOH 200°
I	$CH_3-\overset{OH}{\overset{\vert}{C}}(CH_3)-CH_2N(CH_3)_2$	instantaneous esterification	no dehydration	no dehydration
II	$CH_3-\overset{OH}{\overset{\vert}{C}}(CH_3)-CH_2-CH_2-N(CH_3)_2$	instantaneous esterification	dehydration	no dehydration
III	$CH_3-\overset{OH}{\overset{\vert}{C}}(CH_3)-CH_2-CH_2-CH_2-N(CH_3)_2$	slow esterification	dehydration	no dehydration
IV	$CH_3-\overset{OH}{\overset{\vert}{C}}(CH_3)-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$	no esterification	dehydration*	dehydration

*I_2 will dehydrate only IV.

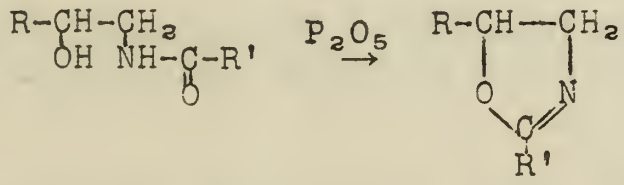
Oxazolines and Related Compounds

Substituted β-ethanol amines may be condensed with aldehydes, in the presence of a base, to form oxazolidines (26, 27).



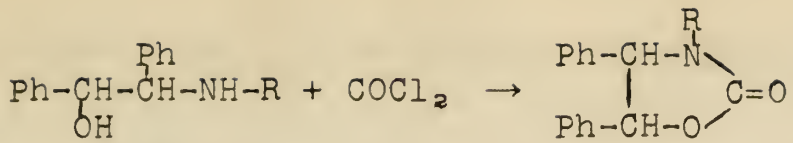
R' = Ph, H, CH_3
R = H, CH_3, $(CH_3)_2CH_2CH_2$

The amide from a substituted ethanolamine condenses in the presence of a dehydrating agent to form an oxazoline (28).



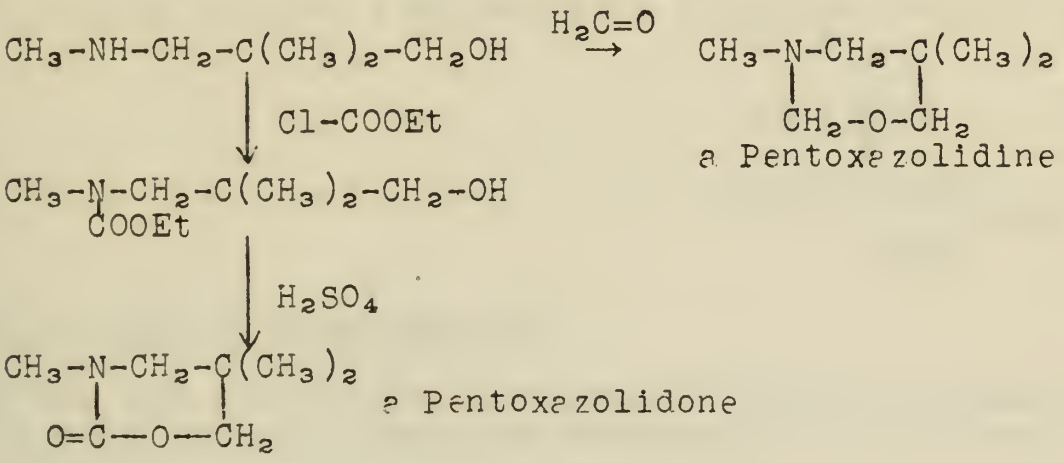
R' = H, CH_3, CH_3CH_2, Ph

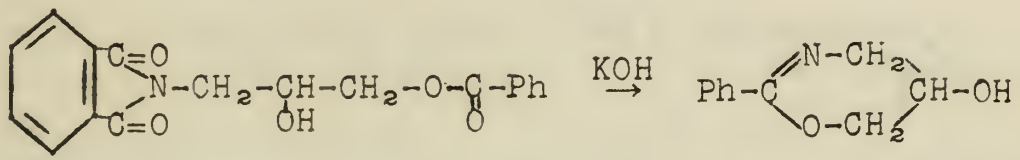
Oxazolidones may be formed by the condensation of a carbonic acid derivative with substituted ethanol amines (29).



R = m-C_7H_7, p-C_7H_7, β-$C_{10}H_7$, C_6H_5 failed with R = o-C_7H_7

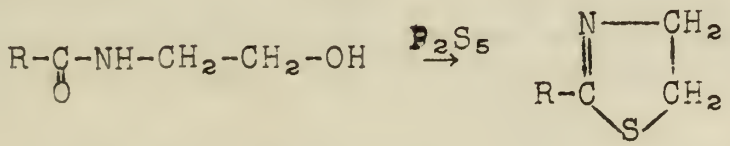
In a similar manner one may form Pentoxazolidines, Pentoxazolines and Pentoxazolidones from substituted 1,3-amino alcohols (30, 31).





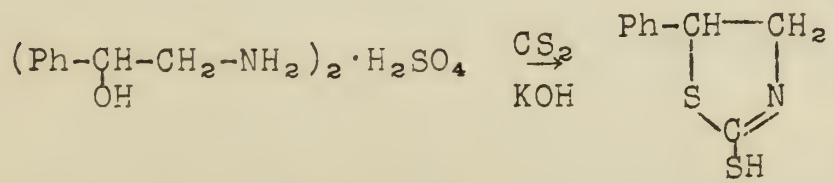
a Pentoxazoline

Thiazolines may be formed by treating N-acyl-2-aminoethanols with P_2S_5 (28).

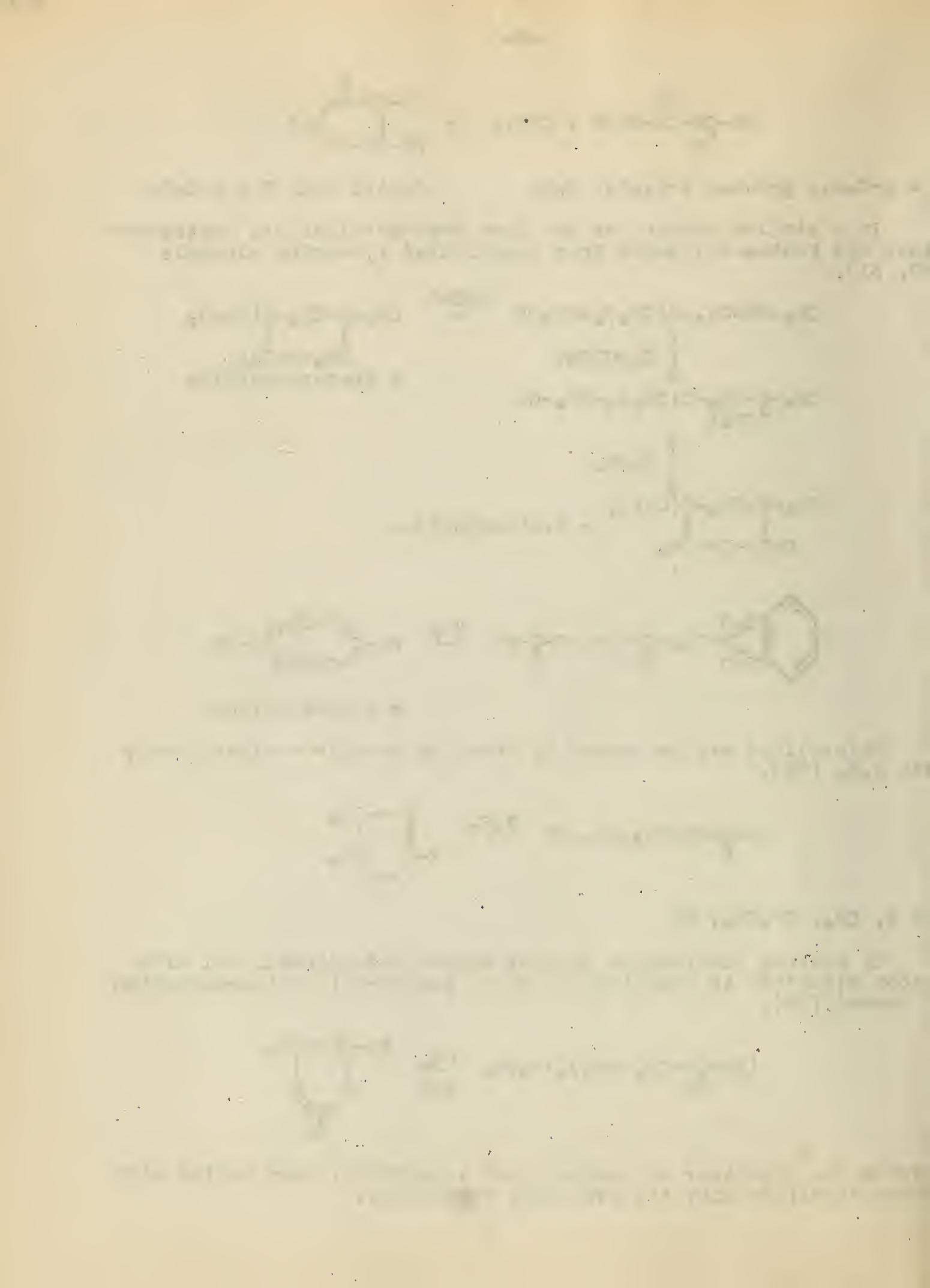


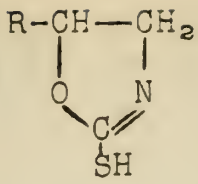
R = H, CH_3, CH_3CH_2, Ph

By heating the sulfate salt of 2-phenyl-2-aminoethanol with carbon disulfide in alkaline solution, phenyl-thiazoline-mercaptan is formed (32).



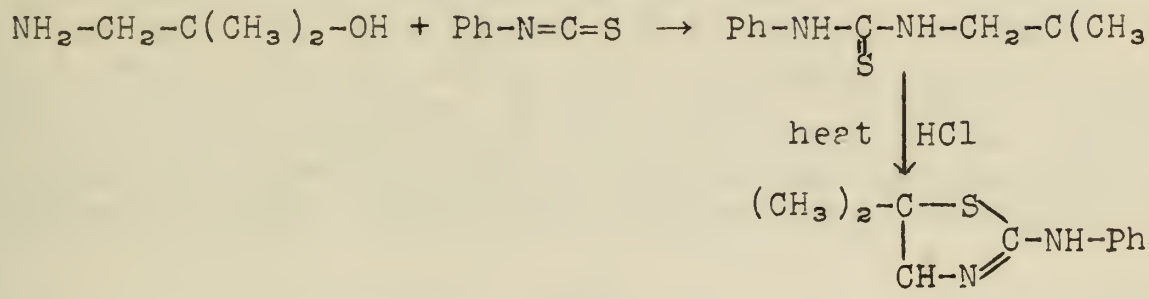
However the alkamines of anethole and isosafrole, when heated with carbon disulfide give the oxazoline mercaptans.





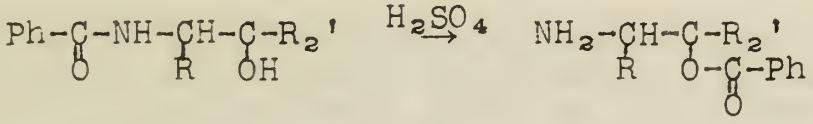
R = $CH_3OC_6H_4$, $CH_2O_2C_6H_3$

Thiazoline amines may be formed from substituted ethanolamines and isothiocyanates (33).



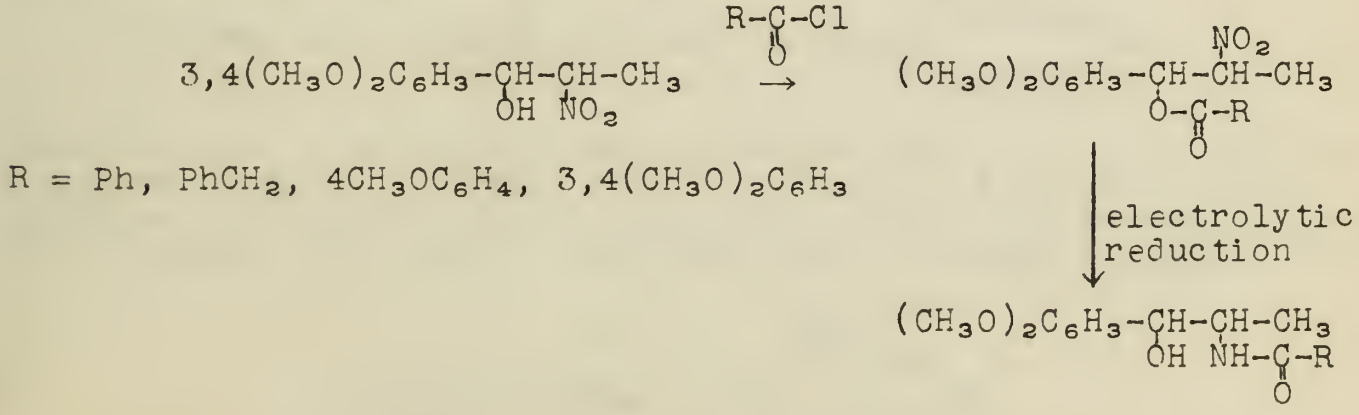
The Amide-to-ester Rearrangement

It has been noted that upon treating hydroxy amides with sulfuric acid the acyl group may migrate from the nitrogen to the oxygen, forming an ester (34).



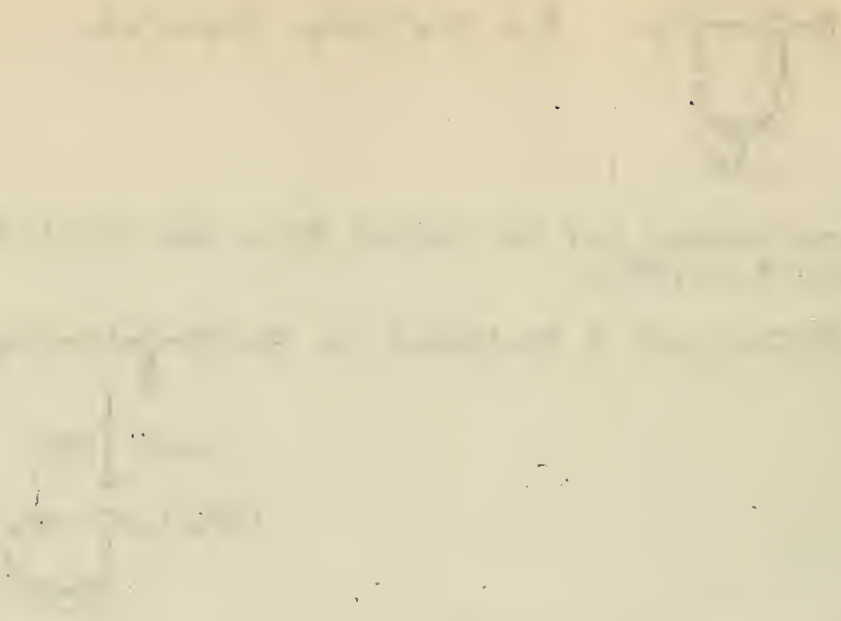
R =	Migration occurred			Doubtful		Negative		
	Ph	Me	Ph	H	Me	H	Me	Ph
R' =	Me	Et	Et	$PhCH_2$	$PhCH_2$	Ph	Ph	Ph

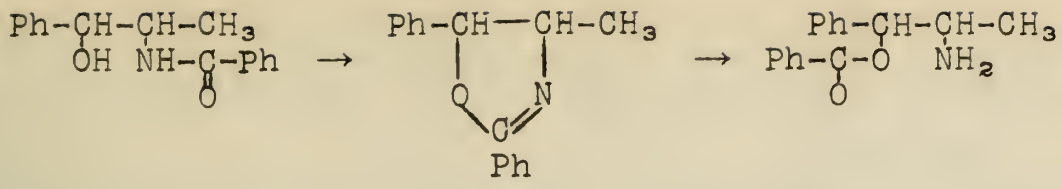
Migration from the oxygen to the nitrogen may occur when an excess of base is added to the ester amine salt (36). The following method has also been used to demonstrate this (35).



R = Ph, $PhCH_2$, $4CH_3OC_6H_4$, $3,4(CH_3O)_2C_6H_3$

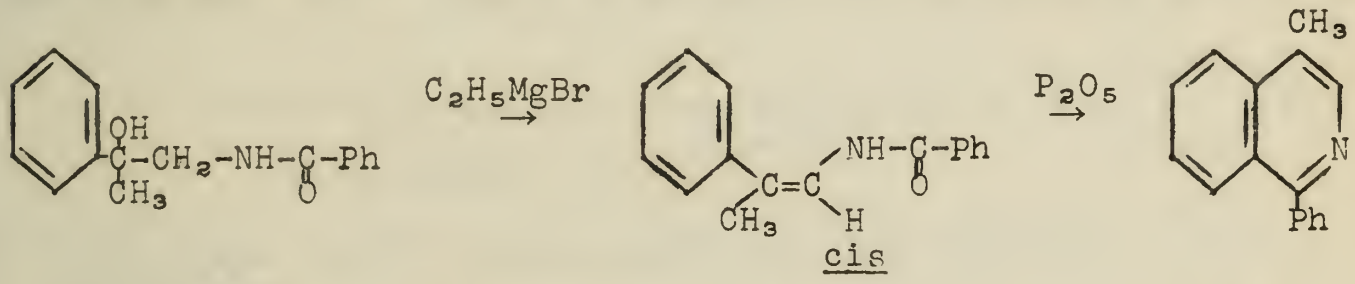
It was then found that, under suitable conditions, the oxazoline could be isolated as the intermediate product which would yield the ester upon addition of further acid (37).





Isoquinoline synthesis

Substituted isoquinolines can be formed by the method of Pictet and Gams (38) from phenyl (amido methyl) carbinols. More recently Krabbe (15) has shown that vinylamines may be intermediates in this synthesis. By the use of a Grignard reagent, Krabbe was able to obtain good yields (50-75%) of the vinylamine, which could be separated into two forms. The cis form was easily transformed into the substituted isoquinoline. During the ordinary

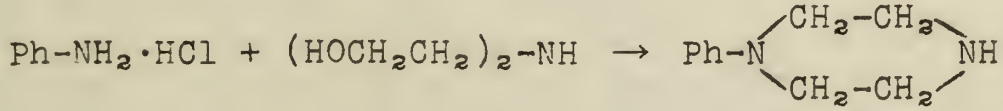


cis

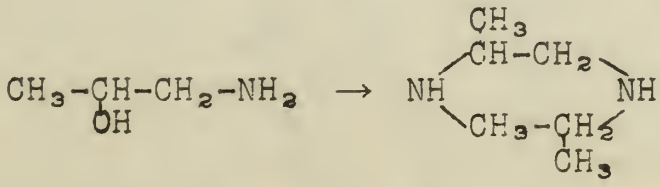
single step Pictet and Gams synthesis with phosphorus pentoxide, an appreciable amount of oxazoline derivative is formed from the amido alcohol, if it has one small group on the carbinol such as the methyl group, although not if both groups are phenyl. If, however, the vinylamine is formed first, this difficulty is not encountered.

Piperazines

Pollard and MacDowell formed N-phenylpiperazine by the reaction of aniline hydrochloride with diethanolamine at 240° (39).

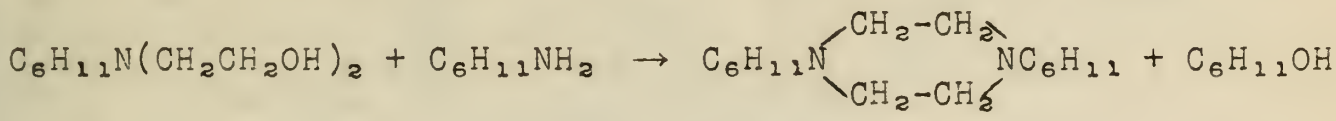


This does not seem to be general, however, for it failed with diisopropanolamine. However, isopropanolamine at 250-275° with hydrogen and copper chromite catalyst formed 2,5-dimethylpiperazine (40). Similar treatment of diethanolamine yielded 1,4-bis-β-



hydroxyethylpiperazine, and of phenylethanolamine yielded diphenylpiperazine. The yields in this reaction are somewhat low. Bain and Pollard account for this by the replacement of the amino

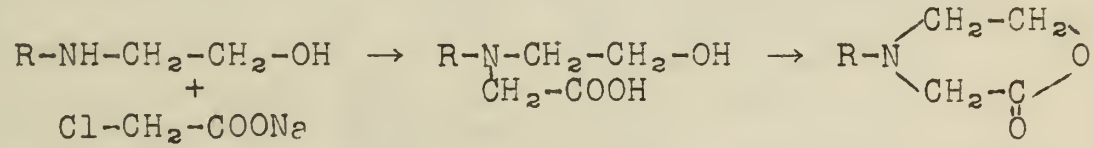
group by a hydroxyl group from the water liberated in the reaction. In forming dicyclohexylpiperazine, they found appreciable quantities of cyclohexanol. It was then shown that diethyl cyclohexyl-



amine reacted with water to give a 33% yield of cyclohexanol under the same conditions.

Morpholones

It has been found that N-substituted morpholones may be formed by the action of sodium chloracetate on N-substituted ethanolamines (41). When R is aromatic the reaction goes in one



R = CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, i-C_4H_9, C_6H_5, $C_6H_5CH_2$, o- and p-$CH_3C_6H_4$

step, but when R is alkyl, the second step is accomplished by distillation in vacuo.

BIBLIOGRAPHY

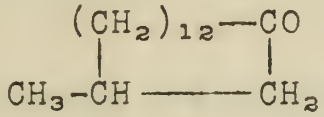
1. McKenzie and Denler, J. Chem. Soc., 125, 2105 (1924).
2. McKenzie and Mills, Ber., 62, 1784 (1929).
3. McKenzie, Mills and Myles, Ber., 63, 904 (1930).
4. Mills, J. Chem. Soc., 1565 (1934).
5. Luce, C. R. Ac. Sc., 180, 71 (1925).
6. Tiffeneau, Orekhoff and Roger, Bull., 49, 1757 (1931).
7. Tiffeneau, Levy and Ditz, Bull. Soc. Chim. [5], 2, 1866 (1935).
8. Whitmore and Bernstein, J. Am. Chem. Soc., 61, 1324 (1939).
9. Jones, J. Assoc. Official Agr. Chem., 27, 462 (1944); Chem. Abs., 38, 6276 (1944).
10. Nicolet and Shinn, J. Am. Chem. Soc., 61, 1615 (1939).
11. Nieman, Benson and Mead, J. Org. Chem., 8, 398 (1943).
12. Leonard and Rebenstorf, J. Am. Chem. Soc., 67, 49 (1945).
13. Kremer and Kress, Ber., 60, 1031 (1938).
14. Campbell and Campbell, Ber., 60, 1372 (1938).
15. Krabbe, Polzin and Culemeyer, Ber., 73B, 652 (1940).
16. v. Braun and Steindorff, Ber., 38, 3106 (1905).
17. Bettzeiche, Manger and Wolf, Z. physiol. Chem., 160, 263 (1926).
18. Krabbe and Schmidt, Ber., 72B, 381 (1939).
19. Köhnke and Schulze, Ber., 75B, 1154 (1942)
20. Phou-Ti Sou, Bull. faculte sci. univ. franco-chinoise Peiping, No. 5, 1 (1935); Chem. Abs., 30, 4463 (1936).

21. Krasuskii, Ukrainskii Khem. Zhurnal, 4, Sci. Pt., 61 (1929); Cent., 106 [2], 2174 (1929).
22. Bettzieche and Ehrlich, Z. physiol. Chem., 160, 1 (1926).
23. Bettzieche and Menger, Z. physiol. Chem., 172, 69 (1927).
24. Erlynmeyer, Ann., 307, 136 (1899).
25. Campbell and Campbell, J. Org. Chem., 9, 178 (1944).
26. Knorr and Matthes, Ber., 34, 3484 (1901).
27. W. Davies, J. Chem. Soc., 1580 (1932).
28. H. Wenker, J. Am. Chem. Soc., 57, 1079 (1935).
29. Crowther and McCombie, J. Chem. Soc., 103, 29 (1913).
30. Mannich and Wieder, Ber., 65B, 385 (1932).
31. Gabriel and Ohle, Ber., 50, 804 (1917).
32. J. Takeda, J. Pharm. Soc. Japan, 422, 281 (1917); C. A., 11, 2456 (1917).
33. Dersin, Ber., 54B, 3158 (1921).
34. Bettzieche, Z. Physiol. Chem., 146, 227 (1925).
35. Vinkler and Bruckner, J. Prackt. Chem., 151, 17 (1938).
36. J. Takeda, J. Pharm. Soc. Japan, 426, 691 (1917); C. A., 11, 3241 (1917).
37. Nagai and Kanao, Ann., 470, 157 (1929).
38. Pictet and Gams, Ber., 43, 2384 (1910).
39. Pollard and MacDowell, J. Am. Chem. Soc., 56, 2199 (1934).
40. Bain and Pollard, Ber., 61, 532, 2704 (1939).
41. Kiprianov, Tselskii and Ushenko, Chim. Refrat. Zhur 2, 4, 54 (1939); C. A., 34, 1023 (1940).

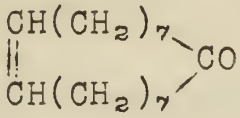
Reported by F. E. Woodward and R. R. Chambers
February 28, 1945

THE SYNTHESIS OF LARGE CARBOCYCLES

The possibility for the existence of molecules with large rings was demonstrated for the first time in 1926 by L. Ruzicka who proved that the naturally-occurring compounds, muscone and civetone, were macrocyclic ketones with the following structures.

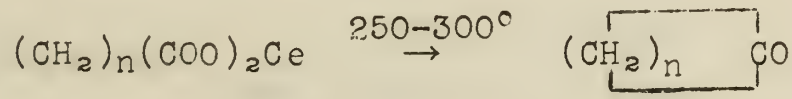


l-muscone



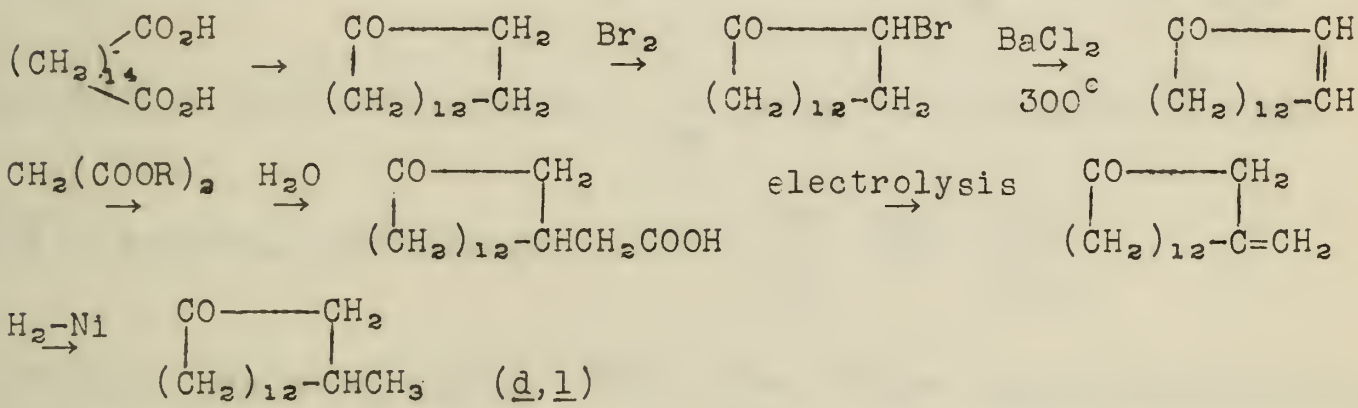
civetone

This initiated extensive work by Ruzicka on the general problem of synthesizing macrocarbocycles. His method involved dry-distillation of thorium or cerium salts of polymethylene-α,ω-dicarboxylic acids. The ketones obtained could be reduced by the Clemmensen method to alicyclic hydrocarbons.

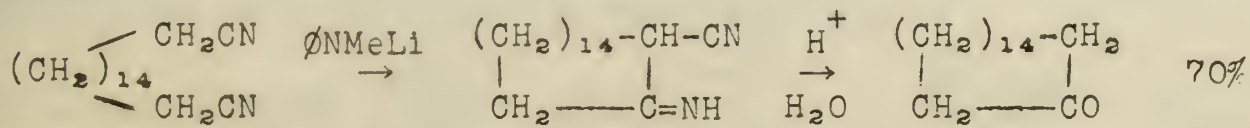


Yields of 2-5% of the larger rings were obtained, but the method fails almost completely for the 9-13 membered rings. However, many macrocyclic compounds were prepared in this way and their physical and chemical properties studied.

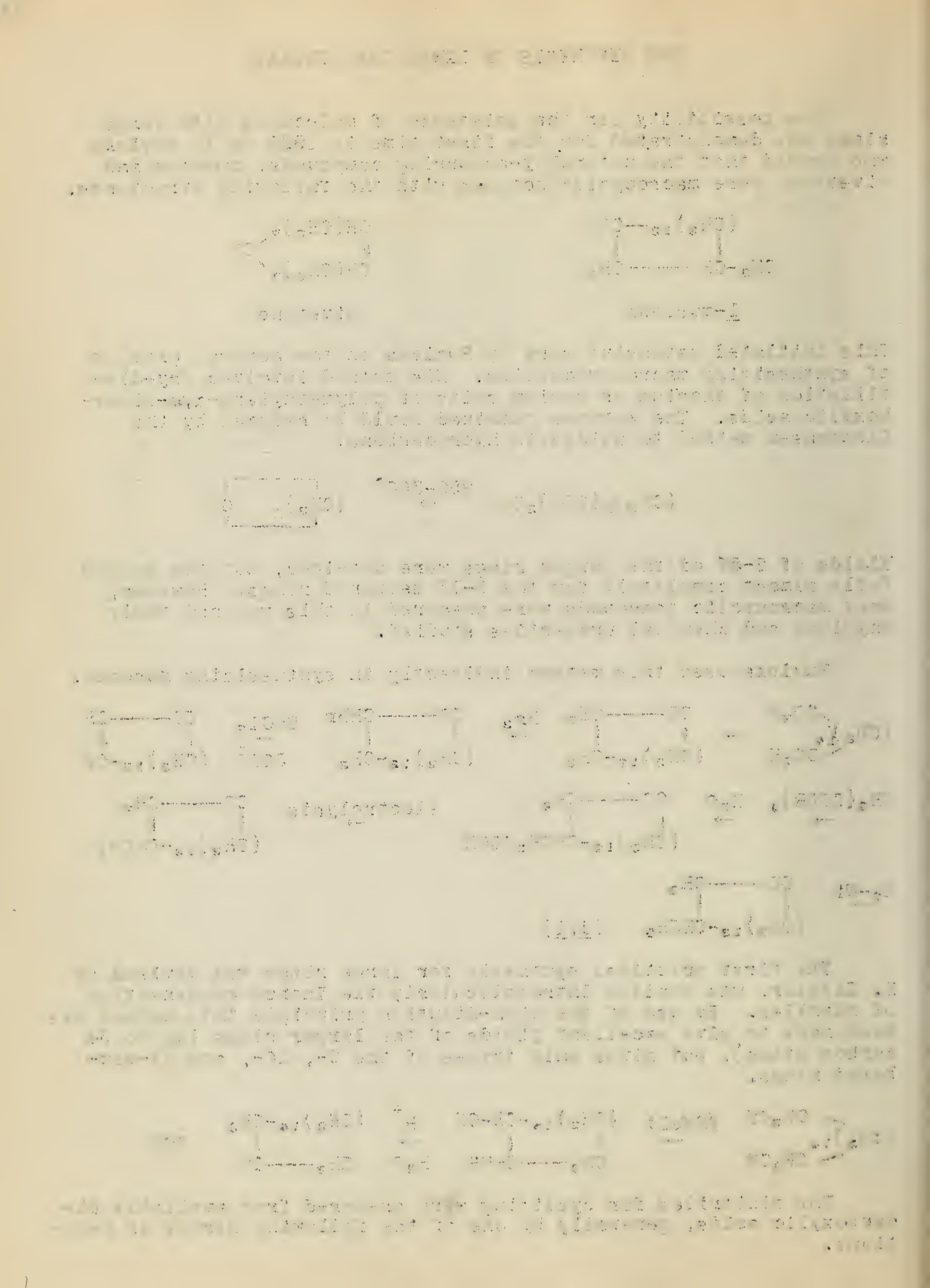
Ruzicka used this method indirectly in synthesizing muscone.



The first practical synthesis for large rings was devised by K. Ziegler, who applied intramolecularly the Thorpe condensation of nitriles. By use of the high-dilution principle this method has been made to give excellent yields of the larger rings (up to 34 carbon atoms), but gives only traces of the 9-, 10-, and 11-membered rings.



The dinitriles for cyclizing were prepared from available dicarboxylic acids, generally by one of the following series of reactions.



1. $HOCO(CH_2)_nCOOH \rightarrow I(CH_2)_n + {}_2I \rightarrow MeOC_6H_4O(CH_2)_n + {}_2I \rightarrow$

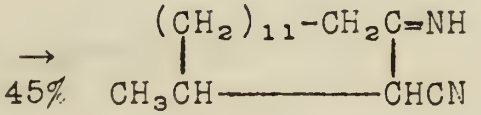
$MeOC_6H_4O(CH_2)_{2n} + {}_4OC_6H_4OMe \rightarrow I(CH_2)_{2n} + {}_4I \rightarrow CN(CH_2)_{2n} + {}_4CN$

2. $HOCO(CH_2)_nCOOMe \xrightarrow{\text{electrolysis}} MeOCO(CH_2)_{2n}COOMe \rightarrow CN(CH_2)_{2n}CN$

This method was used by Ziegler for the first synthesis of muscone.

$Br(CH_2)_{10}Br \xrightarrow{M.E.} Br(CH_2)_{10}CH(COOR)_2 \xrightarrow{MeI} Br(CH_2)_{10}C(CH_3)(COOR)_2$

$\xrightarrow{M.E.} HOCO(CH_2)_{11}CH(CH_3)COOH \xrightarrow[C_5H_{11}OH]{Na} HOCH_2(CH_2)_{11}CH(CH_3)CH_2OH \xrightarrow{HBr}$

$\xrightarrow{NaCN} CN(CH_2)_{12}CH(CH_3)CH_2CN \xrightarrow[45\%]{}$  $\rightarrow$ dl-muscone

Ruzicka has recently made the dinitrile intermediate in the preparation of civetone but has not reported its cyclization.

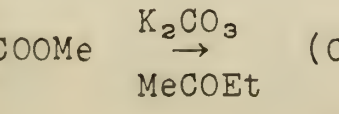
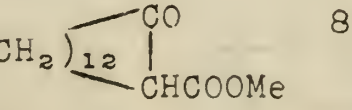
$CH_2=CH(CH_2)_8COOH \xrightarrow{Br_2} \xrightarrow{KOH} CH_3C\equiv C(CH_2)_7COOH \xrightarrow[H^+]{MeOH}$ ester $\xrightarrow[48\%]{Na}$

$CH_3C\equiv C(CH_2)_7COCHOH(CH_2)_7C\equiv CCH_3 \xrightarrow[40\%]{}$ diol $\rightarrow$ diacetate $\xrightarrow{O_3} 46\%$

$\xrightarrow{KMnO_4} HOCO(CH_2)_7CHOHCHOH(CH_2)_7COOH \xrightarrow[53\%]{HBr} \xrightarrow{CH_2N_2} \xrightarrow[86\%]{Zn}$

$MeOCO(CH_2)_7CH=CH(CH_2)_7COOMe \xrightarrow{SOCl_2} \xrightarrow[60\%]{NH_3} \xrightarrow{SOCl_2} CN(CH_2)_7CH=CH(CH_2)_7CN$

More recently another type of ring closure has been applied successfully by Hunsdiecker to the formation of 14-17 membered rings. This involves the self-alkylation of an ω-haloalkylaceto-acetic ester. The starting material is obtained by acylation of acetoacetic ester followed by acid cleavage.

$I(CH_2)_{12}COCH_2COOMe \xrightarrow[MeCOEt]{K_2CO_3}$  $\xrightarrow{80\%\ H_2SO_4}$ 

43%

This method has been used in another synthesis of muscone.

$CH_3CH{=}CHCOOMe \xrightarrow{M.E.} MeOCOCH_2CH(CH_3)CH_2COOMe \rightarrow MeOCOCH_2CH(CH_3)CH_2COOH$ (I)

$CH_2{=}CH(CH_2)_8COOH \rightarrow Br(CH_2)_{10}COOH \rightarrow MeO(CH_2)_{10}COOH$ (II)

$I + II \xrightarrow{electrolysis} MeOCOCH_2CH(CH_3)(CH_2)_{11}OMe \xrightarrow{HBr} \xrightarrow{SOCl_2}$

$ClCOCH_2CH(CH_3)(CH_2)_{11}Br \rightarrow CH_3COCH(COOEt)COCH_2CH(CH_3)(CH_2)_{11}Br$

$\xrightarrow{NaOMe} \xrightarrow{H^+} MeOCOCH_2COCH_2CH(CH_3)(CH_2)_{11}Br \xrightarrow{NaI} \xrightarrow[68\%]{K_2CO_3}$

$MeOCOCHCOCH_2CH(CH_3)(CH_2)_{11}$ (ring closed between CH and $(CH_2)_{11}$) $\rightarrow$ <u>dl</u>-muscone

Hunsdiecker has also published the first complete synthesis of civetone.

$HO(CH_2)_6CHOHCHOH(CH_2)_7COOH \xrightarrow[95\%]{HBr} Br(CH_2)_6CHBrCHBr(CH_2)_7COOH \xrightarrow[70\%]{Zn}$

$Br(CH_2)_6CH{=}CH(CH_2)_7COOH \xrightarrow{SOCl_2} \xrightarrow{CH_3COCH_2COOR}$

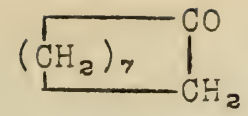
$Br(CH_2)_6CH{=}CH(CH_2)_7COCH(COCH_3)CO_2Et \xrightarrow[70\%]{NaOMe} Br(CH_2)_6CH{=}CH(CH_2)_7COCH_2COOMe$

$\xrightarrow{NaI} \xrightarrow[90\%]{K_2CO_3}$ $\begin{matrix} CH(CH_2)_6CHCOOMe \\ \| \qquad\qquad | \\ CH(CH_2)_7CO \end{matrix}$ $\xrightarrow[86\%]{KOH}$ $\begin{matrix} CH(CH_2)_7 \\ \| \qquad\quad CO \\ CH(CH_2)_7 \end{matrix}$ α-civetone (trans?)

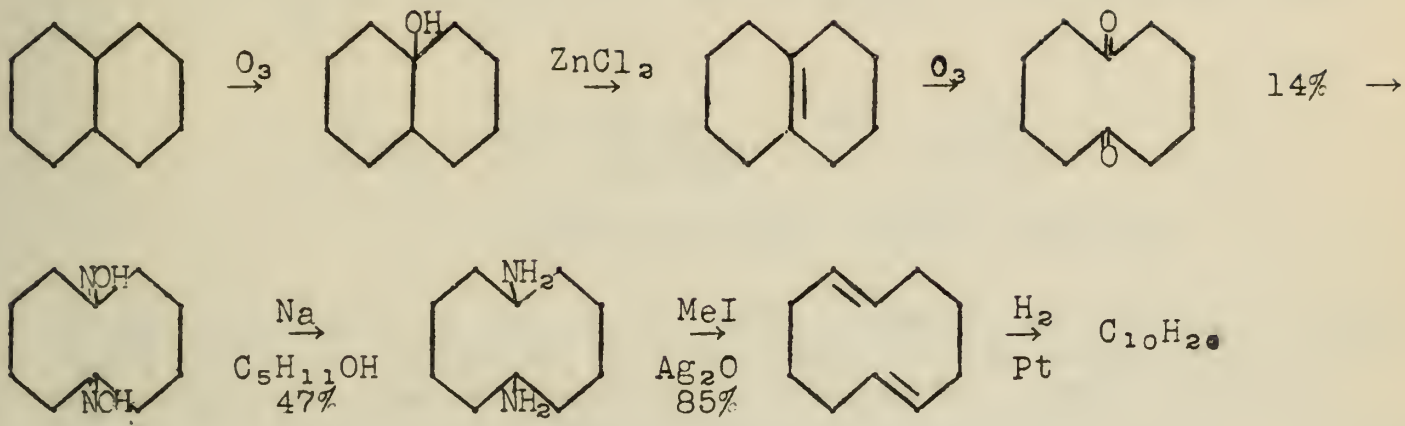
These general methods have been used in preparing the larger rings, but for the intermediate-sized rings (9-11 carbons) special methods have had to be developed.

<u>Cyclononanone</u>.

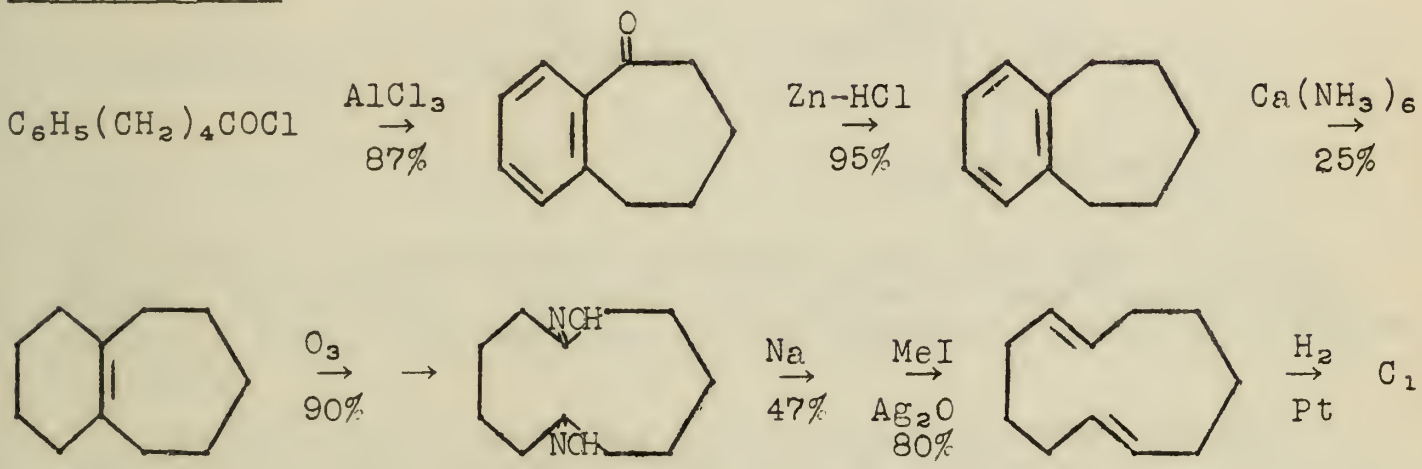
$(CH_2)_7CO$ (ring) $\underset{0^\circ}{\overset{HCN}{\rightleftharpoons}}$ $(CH_2)_7C(OH)(CN)$ (ring) $\xrightarrow[Pt,\ 20\%]{H_2}$ $(CH_2)_7C(OH)(CH_2NH_2)$ (ring) $\xrightarrow[57\%]{HNO_2}$



Cyclodecane.



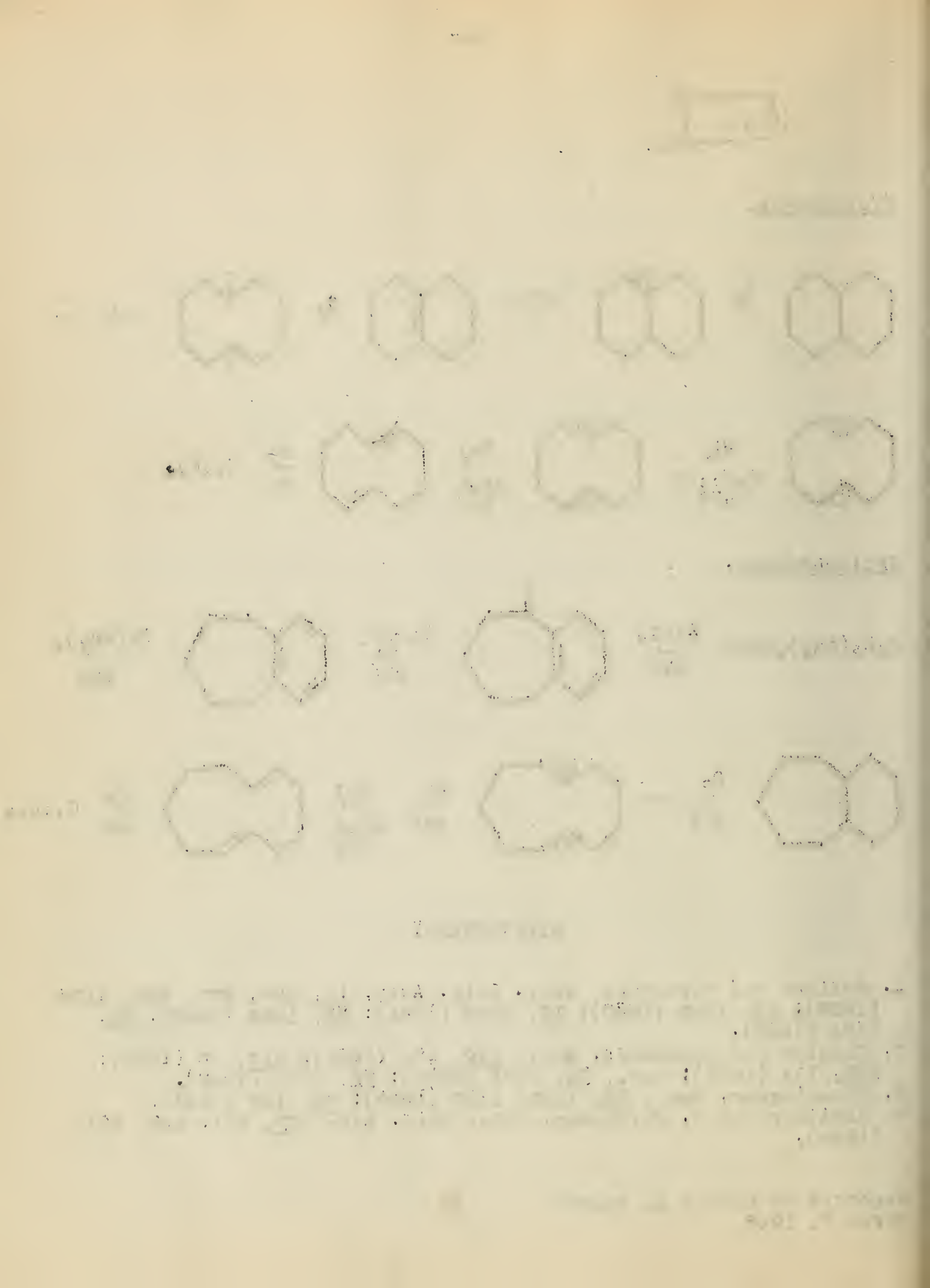
Cycloundecane.



BIBLIOGRAPHY

L. Ruzicka and coworkers, Helv. Chim. Acta, 11, 496, 670, 686, 1174 (1928); 13, 1152 (1930); 17, 1308 (1934); 25, 1086 (1942); 26, 1631 (1943).
K. Ziegler and coworkers, Ann., 512, 164 (1934); 513, 43 (1934); 528, 114 (1937); Ber., 70, 1275 (1937); 75, 1715 (1942).
H. Hunsdiecker, Ber., 75, 1191, 1197 (1942); 76, 142 (1943).
P. Plattner and J. Hulstkamp, Helv. Chim. Acta, 27, 211, 220, 801 (1944).

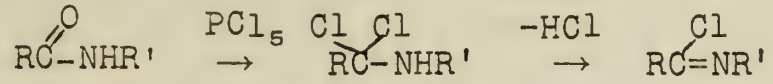
Reported by Robert A. Bauman
March 7, 1945



IMIDO CHLORIDES

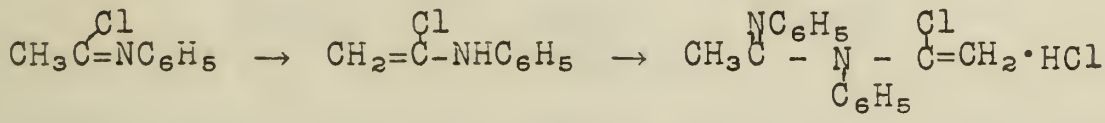
Since 1877, when Wallach (1) first prepared benzanilide imido chloride, a large number of investigations have been carried out on this type of compound. The material presented here reviews some of the more important aspects of the chemical properties of imido chlorides.

Preparation.--The most generally used method for the preparation of imido chlorides is the reaction of phosphorus pentachloride with an amide.



Amido chloride Imido chloride

If the R group is aromatic the imido chloride is stable, but when the R group is aliphatic, the stability of the imido chloride is dependent upon the nature of R as well as R'. This is due to the fact that the following change readily occurs in the aliphatic imido chlorides.



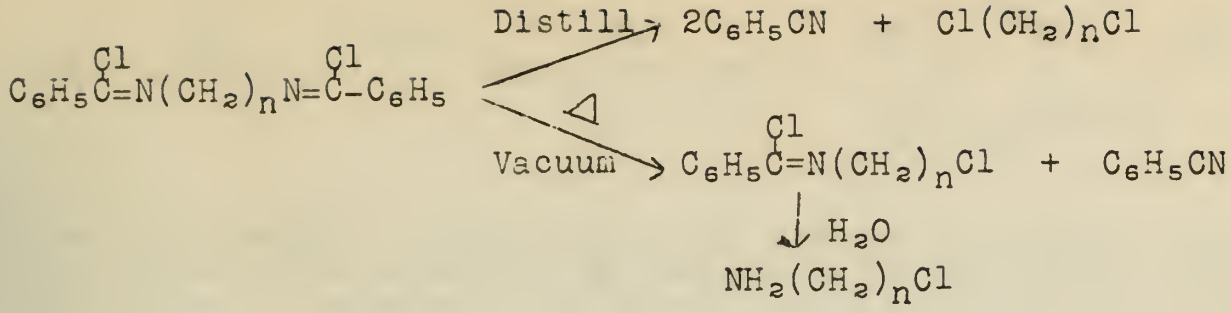
chlorovinylamidine

An aliphatic imido chloride is stable when R = R_3C-, Cl_3C-, Cl_2CH-, or $R_2CH{=}CH$-. When R' is a properly substituted ortho aromatic ring, the migration of the hydrogen is greatly retarded (2,3,4).

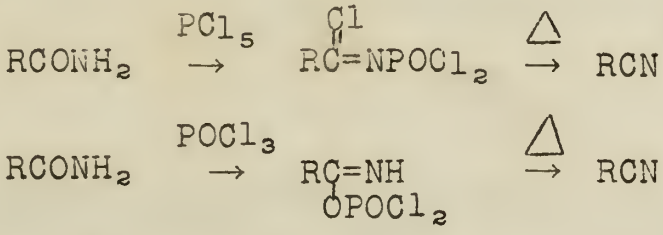
It has been recommended by von Braun (5) that thionyl chloride be used for the preparation of aromatic imido chlorides, because of facility in handling, the formation of sulfur dioxide as the only by-product, and the lack of formation of phosphorus complexes which are so commonly obtained when phosphorus pentachloride is used. Thionyl bromide cannot be used due to its instability and because of its brominating action on aromatic rings. Even the simple aliphatic amides such as acetanilide form sulfur containing products with thionyl chloride.

Uses and Transformations

Preparation of alkyl halides.--Benzoyl derivatives of higher aliphatic diamines react with phosphorus pentachloride to form imido chlorides which can be decomposed to give either an alkyl dihalide or an amino alkyl halide (6).

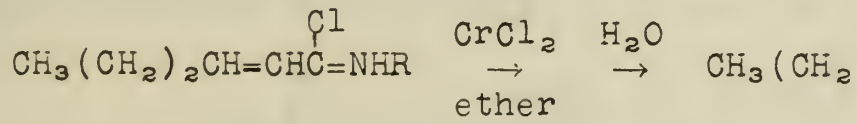


Preparation of nitriles.--As illustrated by the above equations nitriles can also be obtained by the decomposition of the imido chlorides. In a study of acetanilide and its chlorine derivatives, it was found (7) that a phosphorus complex was always an intermediate product in the formation of nitriles from these amides. It was further established that all aliphatic acid amides can be converted into nitriles by heating with phosphorus oxychloride.

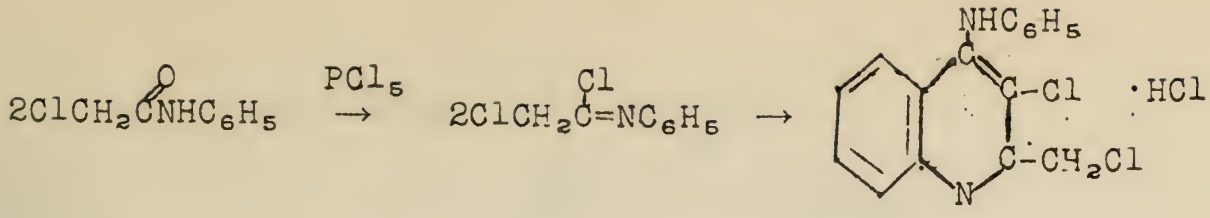


Preparation of α-halo acids.--Amides of the type RCH_2CONHR' where R and R' are either aliphatic and (or) aromatic residues, are converted by excess (at least three mole) phosphorus pentachloride into di-α-chloro imido chlorides which can be hydrolyzed successively to $RCCl_2CONHR'$ and $RCCl_2CO_2H$ (8).

α,β-Unsaturated aldehydes.--The reduction of α,β-unsaturated imido chlorides could not be accomplished with stannous chloride; however, by using an ether or benzene solution of the chloride and adding the precipitate obtained by digesting chromous acetate with hydrochloric acid, fifty per cent or less yields of the aldehyde could be obtained (9). Imido chlorides of aromatic acids and of cinnamic acid could readily be reduced by stannous chloride as well as by chromous chloride. Aliphatic compounds with no adjacent double bonds are not reduced.

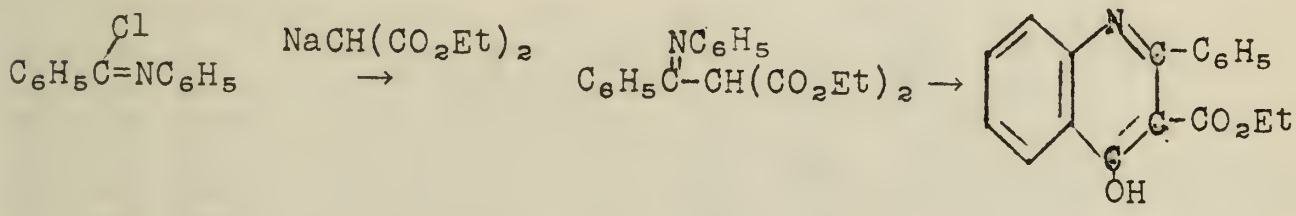


Amidines and nitrogen heterocycles.--As mentioned previously, amidines are formed when two moles of an aliphatic imido chloride condense with the loss of one mole of hydrochloric acid. This type of coupling is usually characteristic of aliphatic imido chlorides; however, it was found that chloroacetanilide when treated with phosphorus pentachloride condensed to form a quinoline (10).



It was impossible to force this reaction in the amidine direction, while acetanilide could not be forced in the quinoline direction. Derivatives of propionic and phenylacetic acid also form quinolines, and ring formation takes place readily and in good yield.

Amidines can also be prepared by condensing an imido chloride with an amine (11). Reaction of an aromatic imido chloride with sodiomalonic ester results in a product which undergoes cyclization to form a substituted quinoline (12, 13).

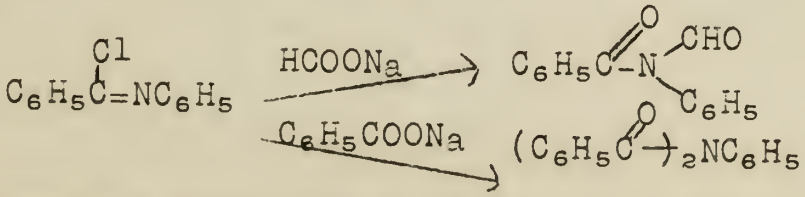


By substituting the sodium derivative of urethan for malonic ester in the above reaction, a product is obtained which under the influence of heat cyclyzes to form a quinazoline (14).

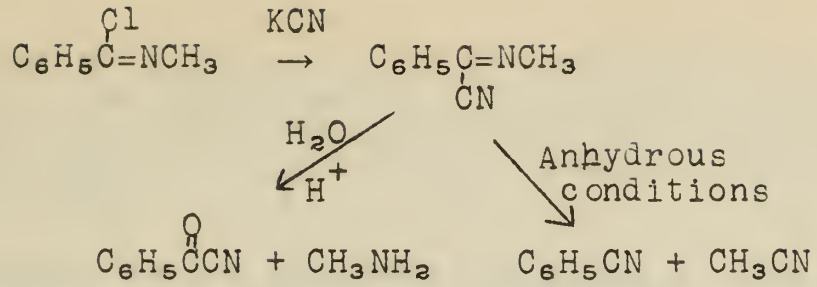
Friedel and Crafts reaction.--The condensation of benzanilide imido chloride with dimethylaniline in the presence of aluminum chloride results in good yields of p-dimethylaminobenzophenone. This type of reaction was found to be general for the benzanilide derivative with dimethyl o-, m-, and p-toluidine, diethyl-o-toluidine, dimethyl-α-naphthylamine, benzylmethyl- and benzylethylaniline (15).

It was further found that by simply heating a mixture of benzanilide, dimethylaniline, and phosphorus oxychloride 70 to 80 per cent yields of p-dimethylaminobenzophenone were obtained (16).

Reaction with acid salts.--The imido chlorides react very readily with the sodium salts of organic or inorganic acids (17).



Reaction of N-methyl benzamide imido chloride with potassium cyanide leads to a compound which is very unstable.



When benzanilide is used the nitriles which is formed is a stable crystalline compound.

BIBLIOGRAPHY

1. Wallach and Hoffman, Ann., 184, 79 (1877)
2. von Braun, Jostes, and Heymons, Ber., 60B, 92 (1937)
3. von Braun and Silbermann, Ber., 63B, 498 (1930)
4. von Braun and Heymons, Ber., 62B, 409 (1929)
5. von Braun and Pinkernelle, Ber., 67B, 1218 (1934)
6. von Braun and Muller, Ber., 38, 2340 (1905); 39, 2018 (1906)
7. von Braun and Rudolph, Ber., 67B, 1762 (1934)
8. von Braun and Heymons, Ber., 63B, 502 (1930)
9. von Braun, Rudolph, Kroper, and Pinkernelle, Ber., 67B, 269 (1934)
10. von Braun, Heymons, and Schnitzpahn, Ber., 63B, 3191 (1930)
11. Rao and Wheeler, J. Chem. Soc., 1643 (1937)
12. Just, Ber., 18, 2623,2632 (1885); 19, 979, 1541 (1886)
13. Shah and Heeramanek, J. Chem. Soc., 428 (1936)
14. Shah and Ichaporia, J. Chem. Soc., 431 (1936)
15. Shah and Chaubel, J. Chem. Soc., 650 (1932); Shah and Ichaporia, J. Chem. Soc., 894 (1935)
16. Shah, Deshpande, and Chaubel, J. Chem. Soc., 642 (1932)
17. Mumm, Volquartz, and Hesse, Ber., 47, 751 (1914); Mumm, Ber., 43, 886 (1910)

Reported by B. H. Velzen
March 7, 1945

ABSORPTION SPECTROPHOTOMETRY IN STRUCTURE ELUCIDATION

This paper will attempt a brief presentation of the theory and use of the spectrophotometer by the organic chemist. It will be mainly concerned with the ultraviolet and visible regions since infrared work requires equipment and technique which limit its use to specialists.

A spectrophotometer measures the ratio of the transmission of a monochromatic light beam through a liquid or solution to that for a reference liquid or the solvent. The absorption spectrum or curve is a graph of some function of this ratio (y-axis) plotted against some function of the wave length (x-axis).

Symbols and Calculations.--Recent attempts to unify the treatment of data have led to the following recommendations:

X-Axis:

Plot increase of light energy from left to right, i.e., frequency left to right, wave length right to left. The preferred unit of frequency is the Fresnel, f, (10^{-12} x frequency or 10^{-12} x velocity of light/wave length). The energy associated with a light beam is directly proportional to its frequency.

$$f = 10^{-12}\nu = 10^{-12}\ c/\lambda = 3 \times 10^{-2}\ /\lambda\ (cm) = 3 \times 10^{6}\ /\lambda\ (Å).$$

$$\text{Energy of beam (cal/mole)} = 95.3\ f = 2.86 \times 10^{8}\ /\lambda\ (Å).$$

Y-Axis:

Plot increasing values upwards of the extinction, E, or, preferably, the molecular extinction coefficient, ϵ. The extinction is defined as $\log I_o/I$, where I_o and I are the intensities of light transmitted by the solvent and solution, respectively. Application of the Beer-Lambert law to solutions requires that

$$E = \log I_o/I = \epsilon c l$$

where c is the molarity of the solution and l is the path length through the solution (cm.). When ϵ varies between inconveniently wide limits, $\log \epsilon$ may be graphed. Gibb devotes a chapter to the theory, calculations and applications of spectrophotometry.

Solvents.--The solvent should be chosen for its ease of purification and for its high and uniform transparency in the spectral region under investigation. Cyclohexane, hexane, alcohol and chloroform are widely used. The polarity of the solvent is of consequence for solutes capable of ionization, association, dissociation, solvation or tautomerism. Thus, the absorption curve of quinoline (Fig. 1) is identical in alcohol or hexane, but those of mesityl oxide (Fig. 2) and phenol (Fig. 3) vary with the solvent. The spectra of acidic or basic molecules in buffered aqueous media depend strongly upon the pH.

Concentration.--Except in the operation of such phenomena as association, etc., mentioned above, the absorption of solutions is governed by the Beer-Lambert law. ϵ is seen to be a physical

constant of the solute, dependent only upon the solvent, temperature, and wave length of incident light. Thus the extinction is proportional to ϵ and a shrewd guess at the value of the latter, gained from comparison with known spectra of similar compounds is usually superior to a dilute and try procedure. The optimum working concentration with the Beckman instrument is such that the extinction values are near but less than unity for the absorption peaks. Thus 10 mg./l. (20 micromolar) atebrin in water is quite satisfactory.

Literature.--The development of the Beckman Quartz Spectrophotometer with its simplicity of operation has been largely responsible for the recent flood of absorption curves in the journals. The International Critical Tables have a very extensive though old (1939) compilation of nearly two hundred carefully plotted graphs and a bibliography, arranged by formula, of about a thousand additional compounds. There is no modern collection of ultraviolet curves to parallel that for the infrared region by Barnes and his collaborators. Of the abstracts, Zentralblatt gives full coverage under "Spektra", giving breakdowns into ring systems, types of compounds, etc.

Analysis of Data.--The field is so new that it is largely empirical, although much fundamental progress is discernable. Thus the position of absorption maxima have been related to the ionization constant and to the threshold energy for certain photolytic decompositions. Lewis and Calvin have reviewed absorption and the theory of color, and Pestemer has summarized recent studies of conjugated chromophors. Carr and Stücklen have shown the maxima for all of the C_4-C_8 mono-olefins which they investigated to be dependent only upon the number of alkyl groups attached to double-bonded carbon. The absorption of a molecule is not a simple sum of its absorbing centers because of interactions such as resonance and conjugation. Substituents have been classified by Dadieu as those which alter the nature of curves and those which merely shift the position of peaks. The bathochromic properties (shift of absorption toward red) of groups usually parallel their electronegativity (Fig. 4).

Except for the case of simple compounds: olefins, polyenes, aromatic hydrocarbons, etc., the organic chemist would probably find the ultraviolet spectrum of a new compound to furnish contributary rather than absolute proof of its structure. Where independent hints are available, however, and especially when the spectra of somewhat similar systems are known, the spectrum is of invaluable aid. An excellent example of its importance was in the isolation and subsequent production by irradiation of vitamin D, which has been described by Ellis and Wells. The cinchona alkaloids form a large group which has been intensively investigated by spectrophotometric methods.

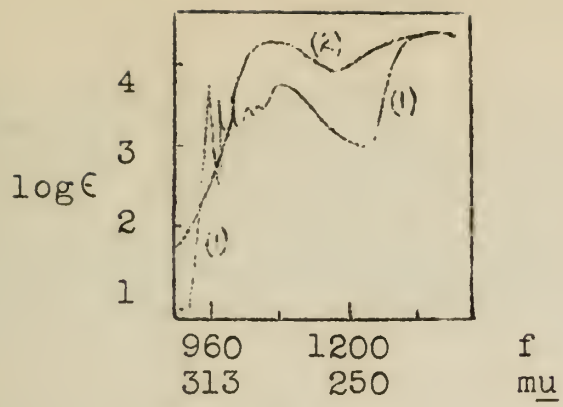


Fig. 1

(1) Quinoline in alcohol or hexane.
(2) Quinolinic acid in hexane
I.C.T. 5, 363.

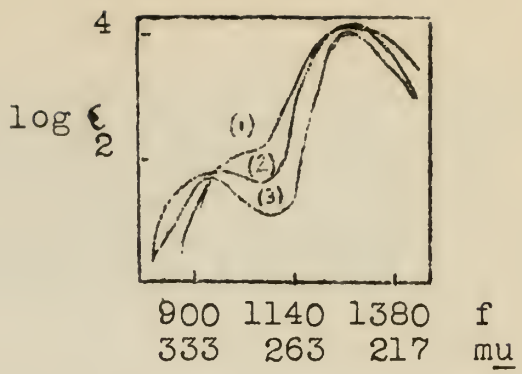


Fig. 2

Mesityl oxide in
(1) water
(2) alcohol
(3) hexane
I.C.T. 5, 372.

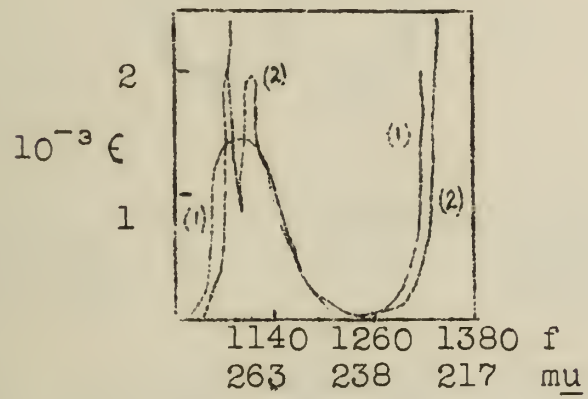


Fig. 3

Phenol in
(1) alcohol)
(2) pentane
I.C.T. 5, 361.

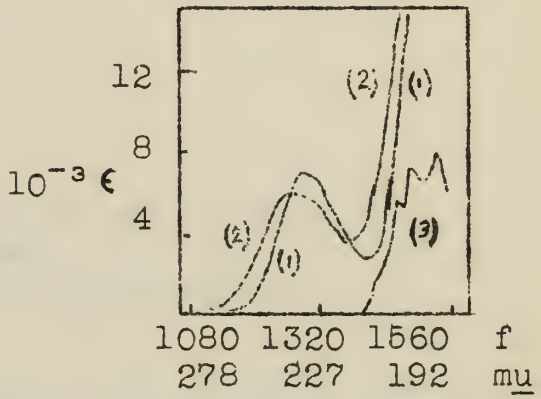


Fig. 4

(1) aniline
(2) p-toluidine
(3) benzene in hexane
I.C.T. 5, 362.

BIBLIOGRAPHY

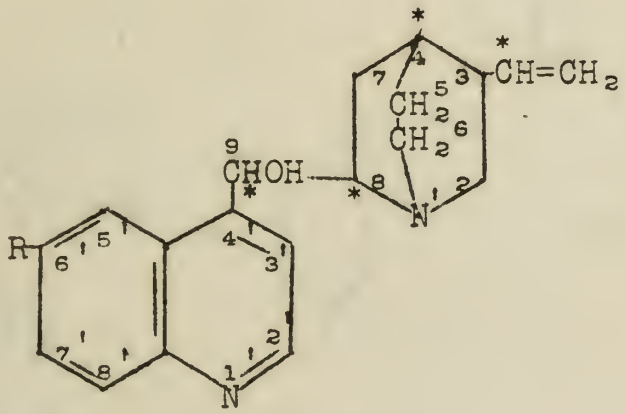
Gibb, "Optical Methods of Chemical Analysis," McGraw-Hill, New York (1942) p. 75.
Lewis and Calvin, Chem. Rev., 25, 273 (1939).
Pestemer, Z. Elektrochem., 49, 361 (1943).
Carr and Stücklen, Proc. Seventh Summer Conference on Spectroscopy and its applications. (M.I.T.) July, 1939.
Dadieu, Z. Elektrochem., 35, 283 (1929).
Ellis and Wells, "The Chemical Action of Ultraviolet Light," Reinhold, New York (1941) p. 791.

Reported by W. G. Jackson
March 14, 1945

STERIC CONFIGURATION OF THE PRINCIPAL CINCHONA ALKALOIDS

Vlado Prelog

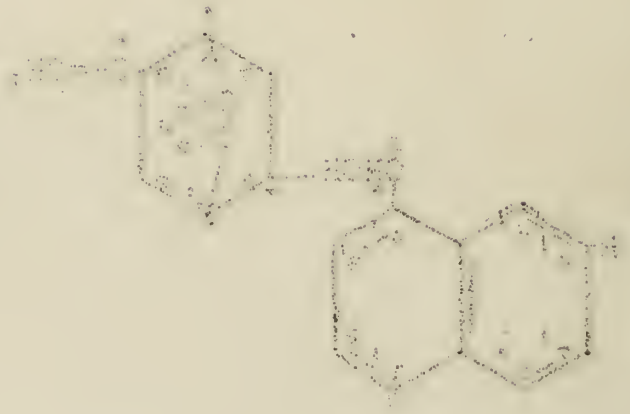
The cinchona alkaloids have received considerable attention from chemists for many years. It is appropriate that the elucidation of the steric configuration of quinine should follow so closely upon its synthesis. The present seminar is devoted entirely to steric considerations of the cinchona alkaloids; the work on structure elucidation and synthesis have been quite adequately summarized elsewhere (1).

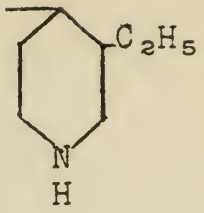


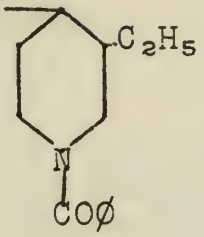
If R = H, formula represents cinchonine and cinchonidine.
R = OH, " " cupreine.
R = OCH_3, " " quinine and quinidine.

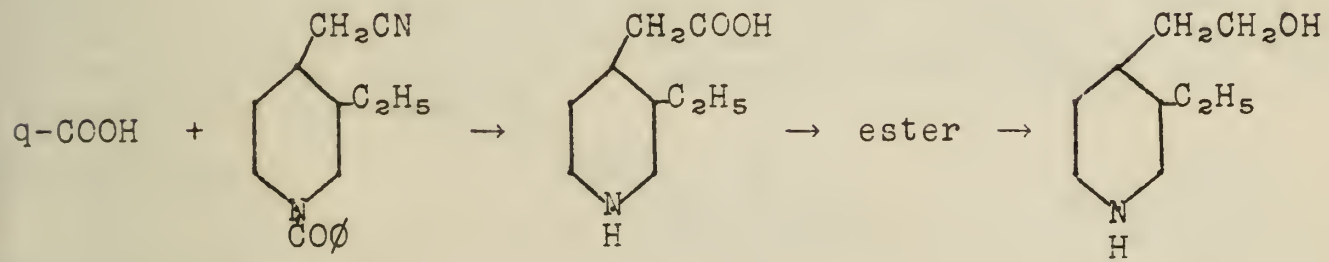
The five most important alkaloids of the cinchona group are quinine, quinidine, cinchonine, cinchonidine, and cupreine. These are illustrated by the general formula above. Inspection of the formula reveals that carbon atoms 3,4,8 and 9 are asymmetric. The task of determining the steric configuration of each of these alkaloids would indeed be exceedingly difficult were it not for certain simplifying relationships. Quinine, cinchonidine and cupreine have been shown by interconversion to possess the same steric configuration. Likewise cinchonine and quinidine are similar sterically. Furthermore, all of the naturally occurring cinchona alkaloids on degradation yield the same quinuclidine derivatives. Therefore the configuration of carbon atoms 3 and 4 must be the same for all of the cinchona alkaloids.

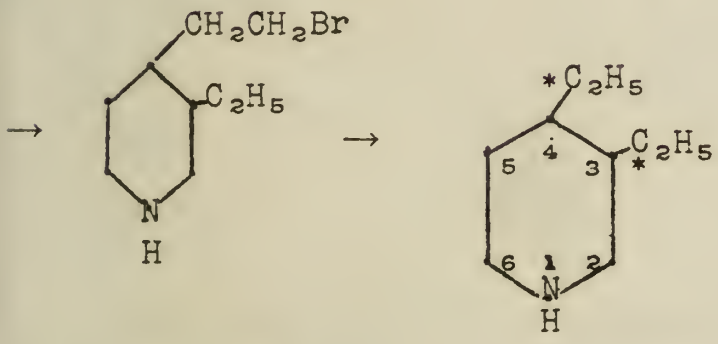
In view of these facts it would be well to begin by discussing the configuration of carbon atoms 3 and 4. In the degradation employed by Prelog and Zalan cinchonine was converted to a 3,4-diethylpiperidine (2).



cinchonine → dihydrocinchonine $\xrightarrow[\text{acid}]{\triangle}$ q-C(=O)-CH_2CH_2  →

benzoyl derivative $\xrightarrow{HNO_2}$ q-C(=O)-C(=NOH)-CH_2  $\xrightarrow{C_7H_7SO_2Cl}$



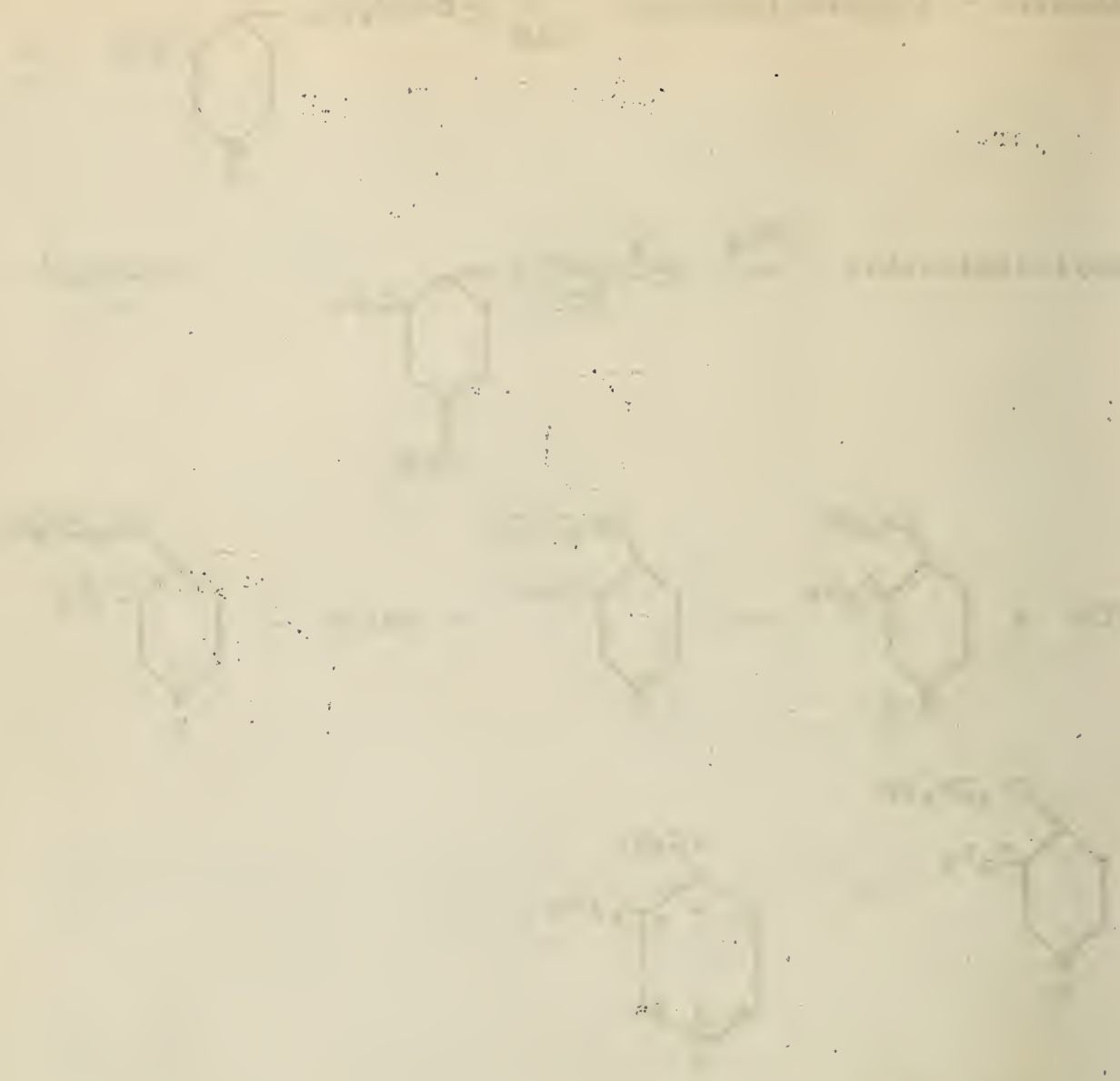


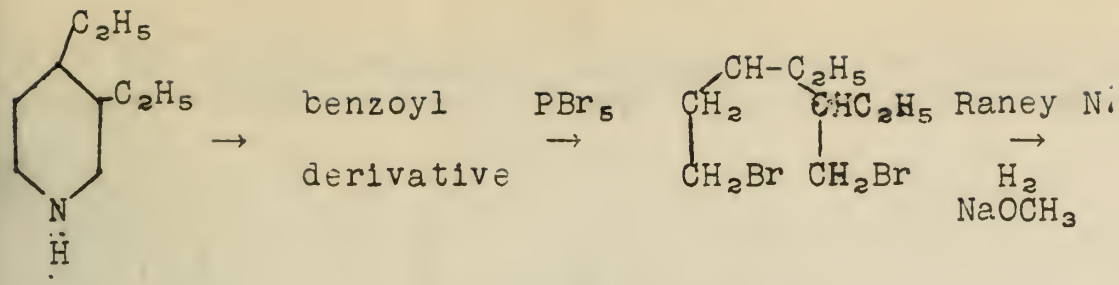
q = quinolyl group.

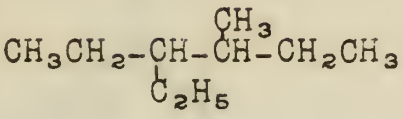
None of the above reactions involved the centers of asymmetry at carbon atoms 3 and 4, and therefore the resulting 3,4-diethylpiperidine should possess a configuration similar to that of the quinuclidine nucleus in the alkaloids.

A study to determine the configuration of the 3,4-diethylpiperidine was made by Koelsch and Stratton (3). By an ingenious synthetic approach they were able to synthesize separately the cis and trans forms of 3,4-diethylpiperidine. However, publication of the work of Prelog and Zalan halted their study before comparison to the 3,4-diethylpiperidine from the degration was made.

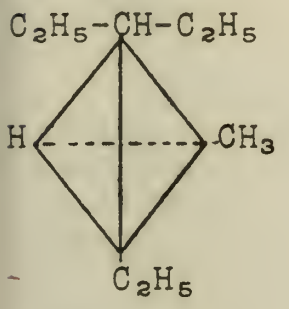
Prelog and Zalan clarified the configuration of carbon atom 3 by converting the 3,4-diethylpiperidine obtained in the degration to (-) 3-ethyl-4-methylhexane.



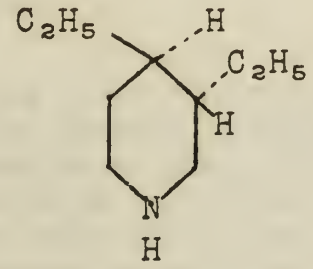




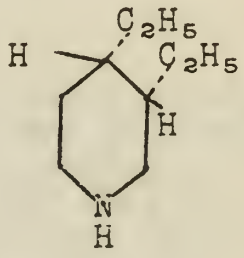
The 3-ethyl-4-methylhexane was found to be levorotatory. In view of the extensive work which Levene and Marker have done on the absolute configuration of such hydrocarbons, it could be assumed that the compound belonged to the (-) series shown by the space formula IV. However Prelog and Zalan avoided any assumption by synthesizing a compound of structure IV and showing that this compound was levorotatory.



IV

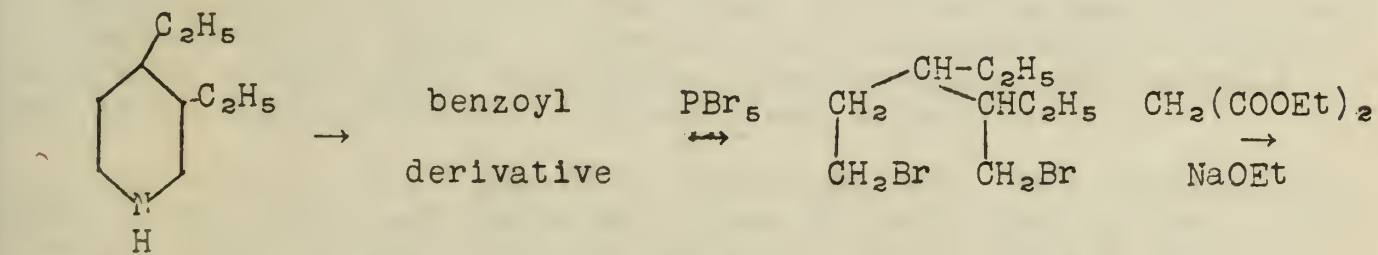


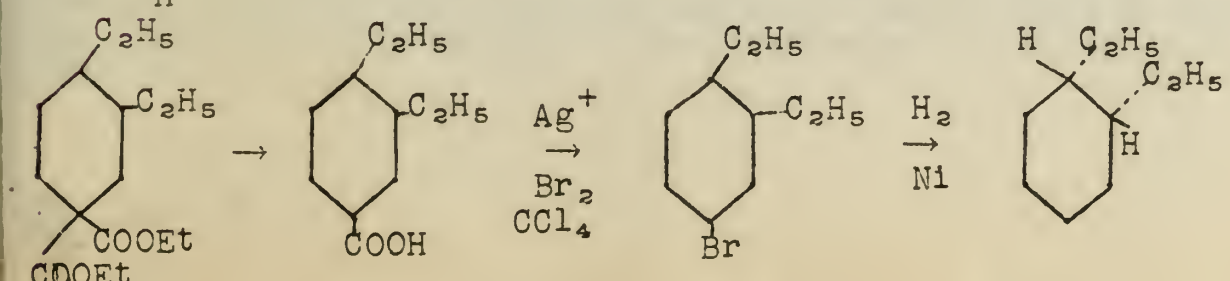
V

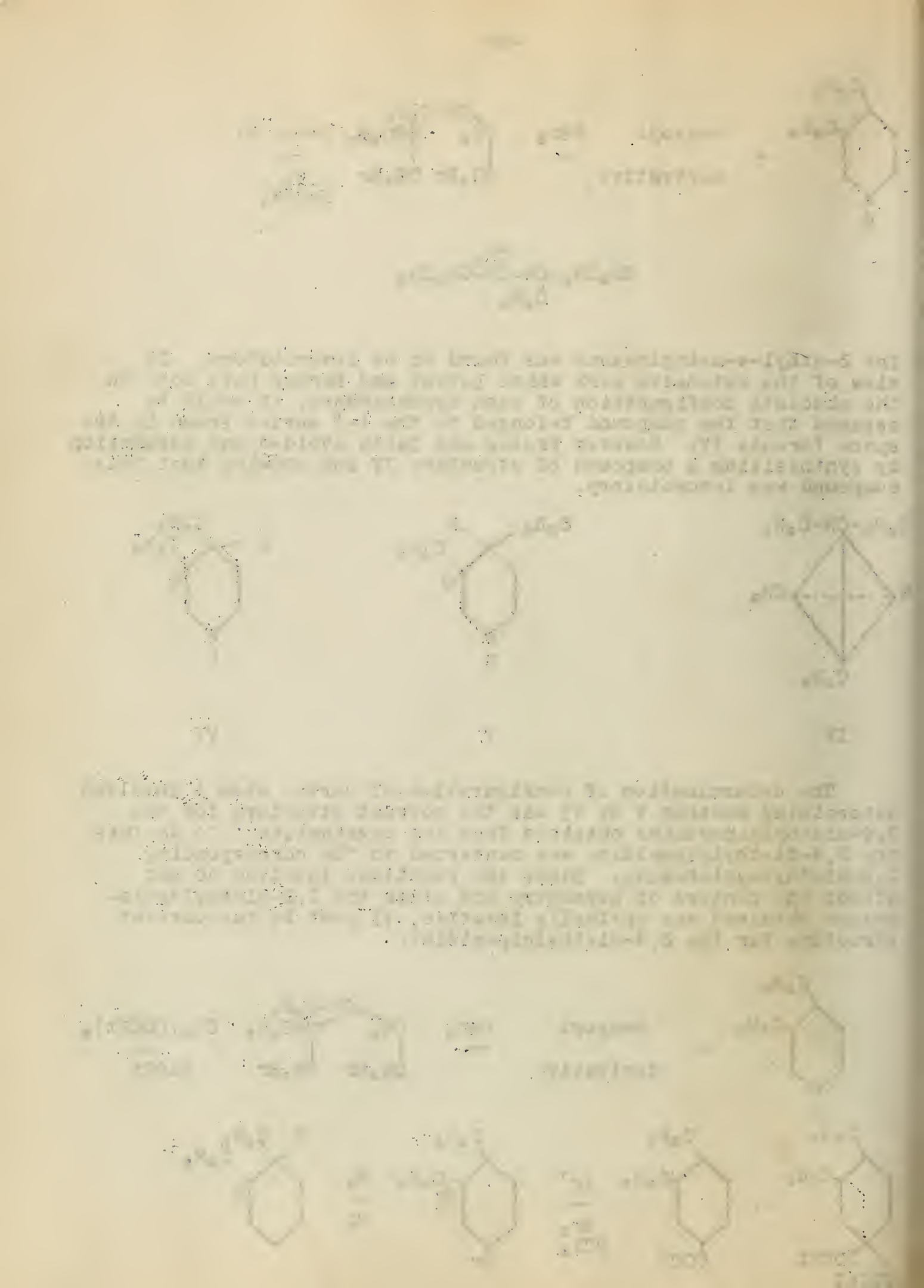


VI

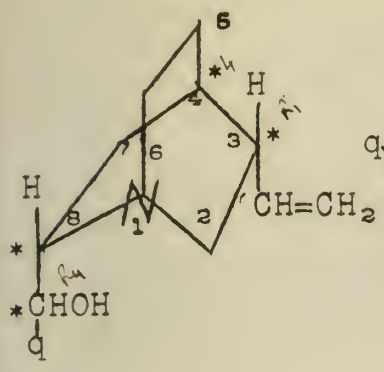
The determination of configuration of carbon atom 4 involved determining whether V or VI was the correct structure for the 3,4-diethylpiperidine obtained from the degradation. To do this the 3,4-diethylpiperidine was converted to the corresponding 1,2-diethylcyclohexane. Since the reactions involved do not affect the centers of asymmetry and since the 1,2-diethylcyclohexane obtained was optically inactive, VI must be the correct structure for the 3,4-diethylpiperidine.



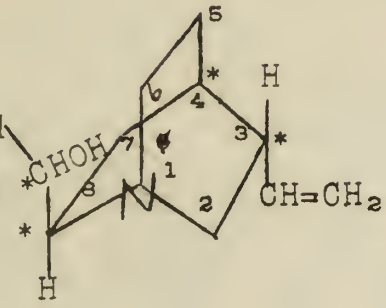




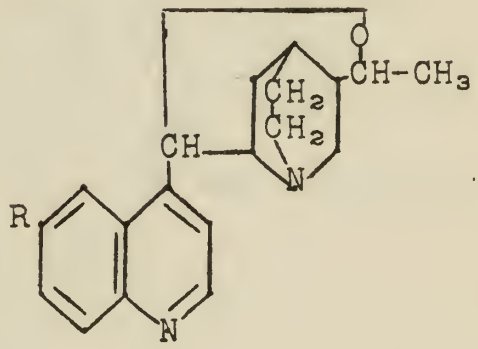
The establishment of configuration for carbon atoms 3 and 4 allows two structures, VII and VIII, for the quinuclidine nucleus.



VII



VIII

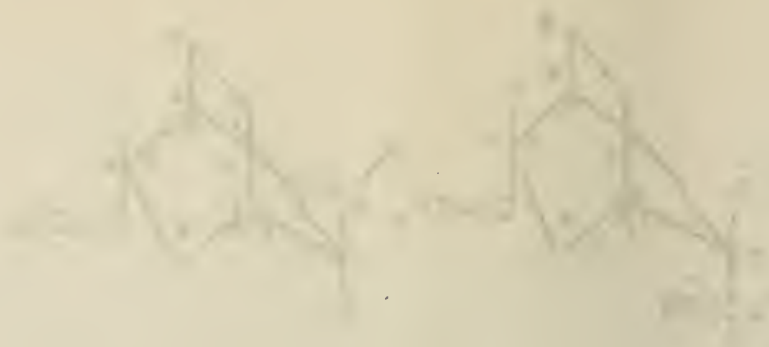


IX

It has long been known that cinchonine and quinine on conversion to the corresponding desoxy compounds give two different compounds. Therefore cinchonine must differ from quinine in steric configuration at carbon atom 8. Further evidence in this direction is obtained from the fact that cinchonine and quinidine can be converted to compounds corresponding to structure IX. Under the same experimental conditions quinine, cinchonidine, and cupreine give no reaction. A study of models of these compounds shows that in order for an ether linkage to be established as in IX, the alkaloid must have structure VII. Thus cinchonine and quinidine have structure VII; quinine, cinchonidine, and cupreine have structure VIII.

The steric configuration of the remaining asymmetric carbon atom 9 can be deduced from consideration of the specific rotations. Quinine, cinchonidine, and cupreine are levorotatory and have high values of specific rotation. Cinchonine and quinidine are dextrorotatory and likewise have high values of specific rotation. The difference between the levorotatory group and the dextrorotatory group is far too great to be accounted for by one asymmetric center alone. Therefore the configuration of carbon atom 9 is levorotatory in quinine, cinchonidine, and cupreine and is dextrorotatory in cinchonine and quinidine.

In conclusion it should be mentioned that this outstanding work which Prelog and Zalan have done in establishing the steric configuration of the cinchona alkaloids is in reality only an experimental confirmation of predictions made by Kenner in 1922 (4).



BIBLIOGRAPHY

1. C. G. Overberger, U. of Illinois Seminar, 1943.
   C. C. Price, U. of Illinois Seminar, 1944.
   Gilman, "Adv. Treatise of Org. Chemistry," pp. 1202, John Wiley and Sons, New York.
2. Prostenik and Prelog, Helv. Chim. Acta, 26, 1965 (1943)
   Prelog and Zalan, Helv. Chim. Acta, 27, 535 (1944)
   Prelog and Zalan, Helv. Chim. Acta, 27, 545 (1944)
3. Koelsch and Stratton, J. Am. Chem. Soc., 66, 1881 (1944)
4. Kenner, Ann. Rep. Chem. Soc., 19, 156 (1922)
5. Levene and Marker, J. Biol. Chem., 91, 405,761 (1931); 92, 455, (1931); 95, 153 (1932)
   Marker, J. Am. Chem. Soc., 58, 976 (1936)

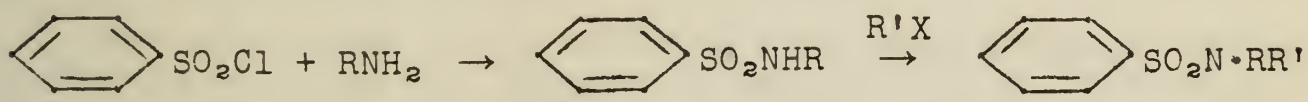
Reported by V. Boekelheide
March 21, 1945

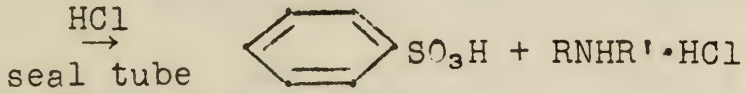
SYNTHESIS OF SECONDARY AMINES BY HYDROGENOLYSIS

Aliphatic primary and tertiary amines are in general easily obtained by various reductive procedures; however, most of the methods for the preparation of secondary aliphatic amines leave much to be desired in the way of yield, time required and purity of product. It is the purpose of this seminar to review briefly the more widely used methods for the preparation of secondary aliphatic amines with special emphasis on hydrogenolysis, or catalytic debenzylation, since this is one of the more satisfactory methods for the preparation of these compounds.

I. Methods which are more frequently employed for the preparation of secondary aliphatic amines.

1. The Hinsberg Method (1).

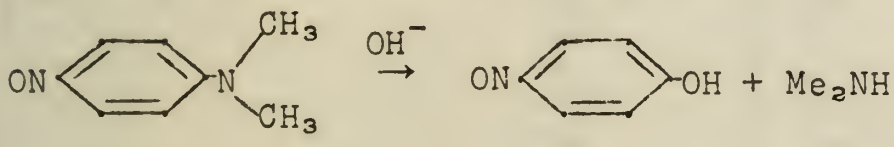




This procedure is somewhat involved, is not rapid, and frequently the overall yield is low.

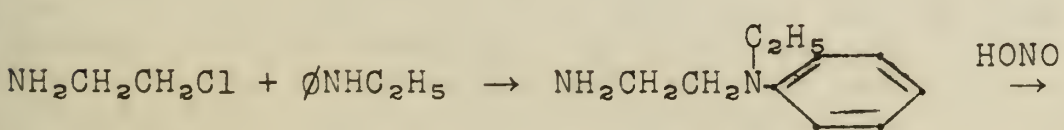
2. Stepwise alkylation of aniline with subsequent nitrosation and alkaline hydrolysis (2):

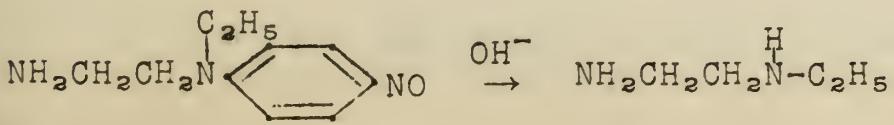
Pure dimethylamine can be prepared free from methylamine and trimethylamine by the hydrolysis of p-nitroso-dimethylaniline. Although this method cannot be used for the synthesis

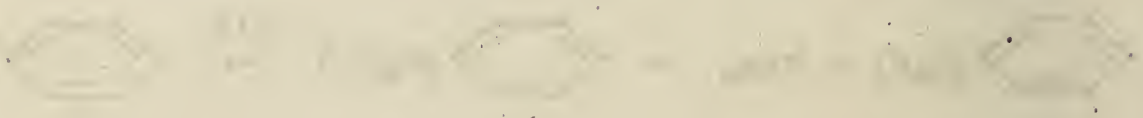


of high molecular weight amines (e.g. di-n-hexyl) (3) it has various other applications (4):

a. For the preparation of monoalkyl aliphatic diamines:

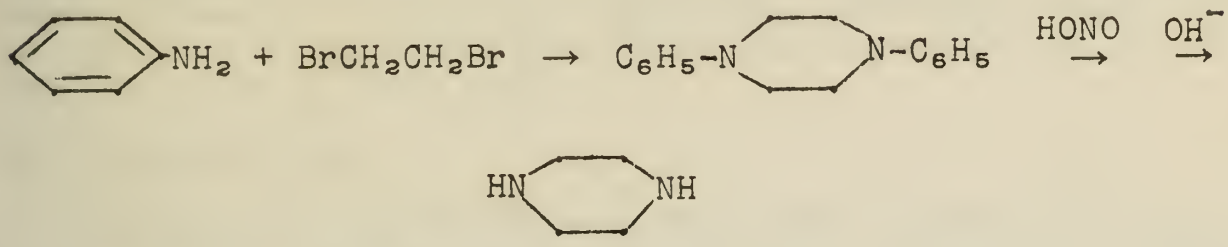






b. For the preparation of heterocyclic compounds.

Piperazine is formed only in poor yield by the action of ammonia on ethylene dibromide. It can be prepared in good yield, however, by the following scheme:



3. Reductive Alkylation

The well known method of using a carbonyl compound and ammonia was reviewed in a seminar by Emerson (5) in 1940 and will not be considered here. Henze and Humphrey (6) (Texas) have recently developed an improved procedure for the preparation of secondary amines by this method. The anil need not be isolated.

$$RCHO + R'NH_2 \xrightarrow{-10^\circ} RCH{=}N{-}R' \xrightarrow[75^\circ \text{ 3000 lbs.}]{Ni(H_2)} RCH_2NHR'$$

Some amines and the yield obtained by this method are given below.

Prepared by Henze and Humphrey

C_4H_9NHR	
R	Yield
Ethyl	31
n-propyl	31
i-propyl	52
i-butyl	56
s-butyl	51
i-amyl	41
n-amyl	51

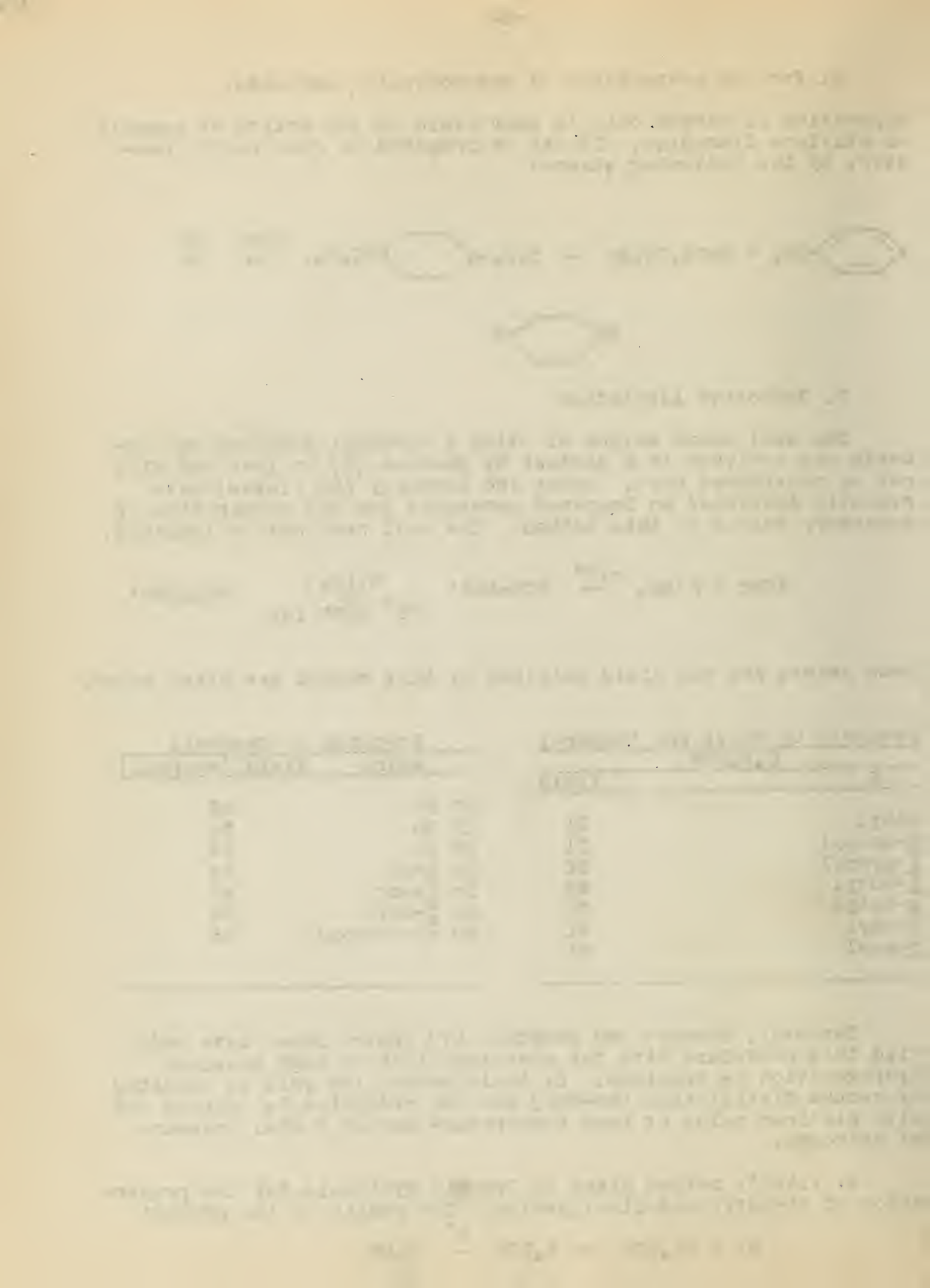
Prepared by Campbell

Amine	Yield (overall)
Et Pr	43
Et Bu	52
Pr Bu	54
Pr i-Bu	63
Pr i-amyl	47
Bu i-amyl	58
Bu cyclohexyl	45

Campbell, Sommers and Campbell (7) (Notre Dame) have modified this procedure with the advantage that no high pressure hydrogenation is required. By their method the anil is isolated by vacuum distillation (60-80%) and the reduction is carried out with platinum oxide at room temperature and at 3 atm. pressure of hydrogen.

4. Vliet's method given in Organic Synthesis for the preparation of di-butyl and di-allyamine. The purity of the product

$$RX + Na_2NCN \rightarrow R_2NCN \xrightarrow{H^+} R_2NH$$



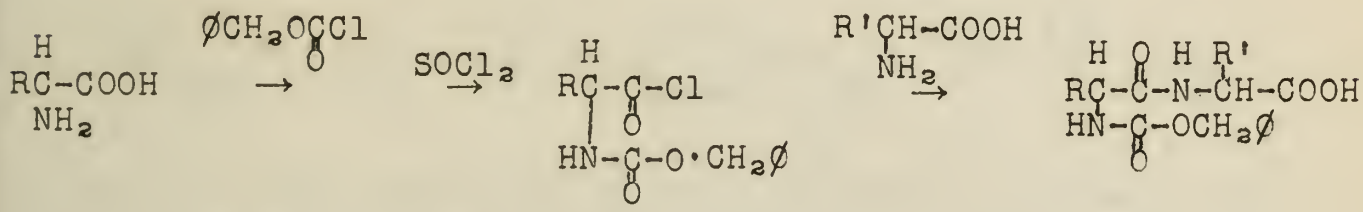
is very high; however this method is limited to lower molecular weight amines (3).

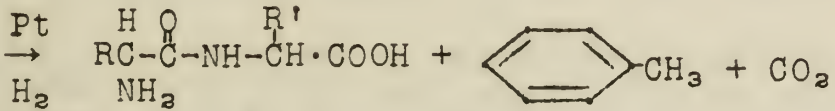
5. Ammonolysis of an Alkyl halide (8).

If the proper conditions are known this method frequently finds application for the synthesis of symmetrical secondary amines; however, in general, application of this scheme leads to a mixture of products from which the secondary amine can be isolated only in low yield.

II. Hydrogenolysis

It has been known for some time that esters and ethers of benzyl alcohol can be easily catalytically cleaved to toluene and the free acid or alcohol. It was by application of this O-debenzylation that Bergmann (9) (Dresden) was able to prepare various polypeptides. By using I as the starting amino acid

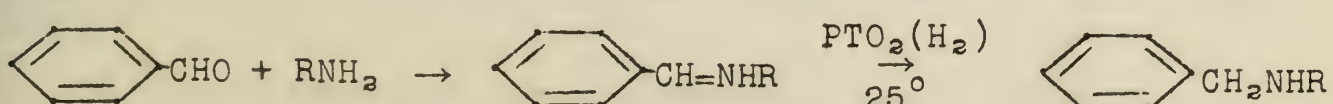




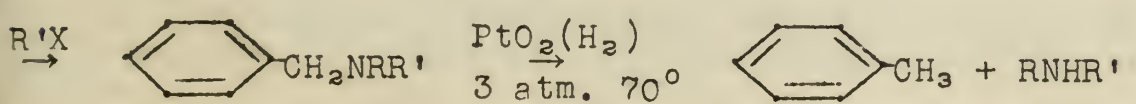
I

and by repeating this process several times polypeptides were prepared in which both the nature and position of the R groups were known.

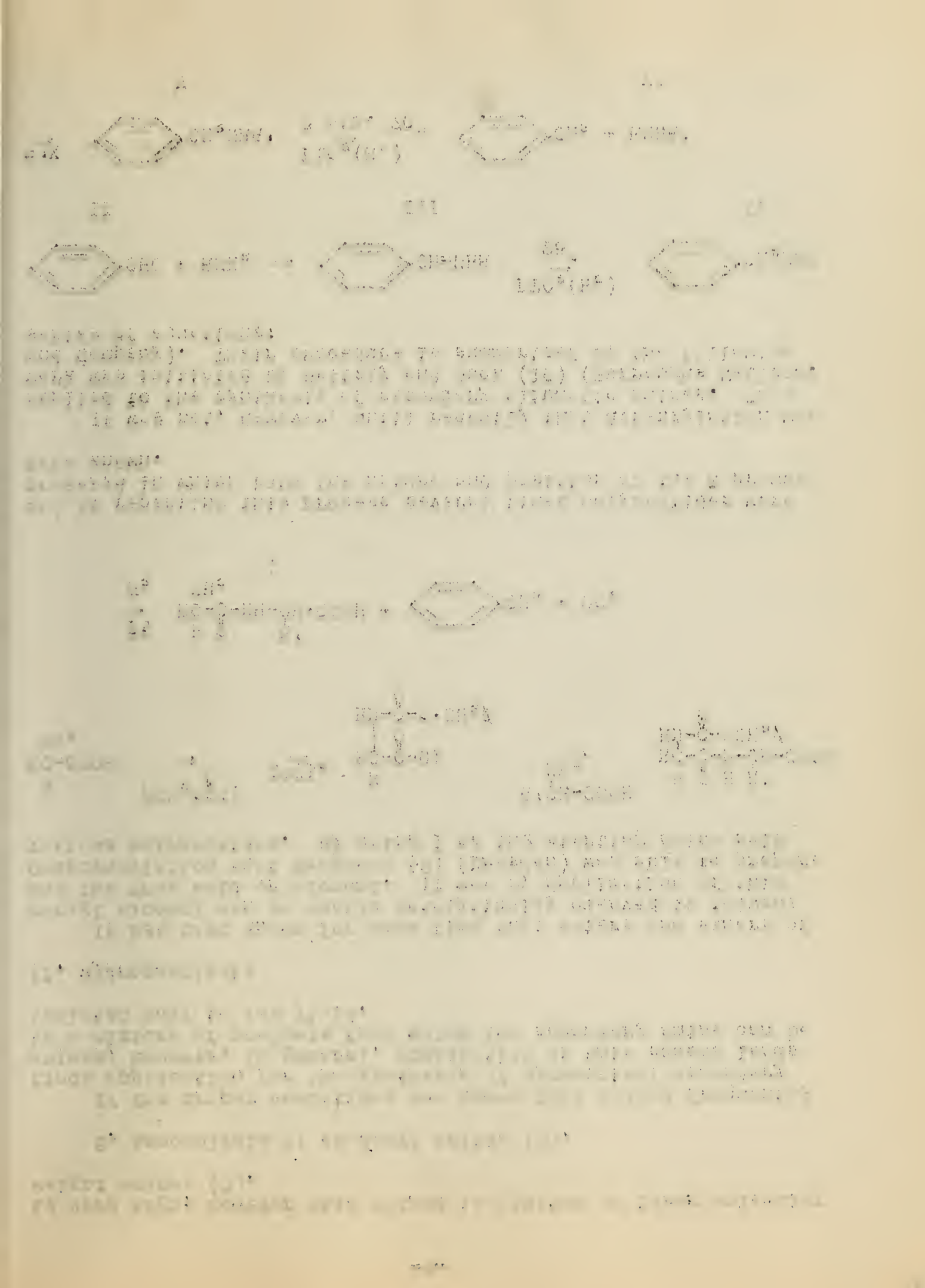
It was not, however, until recently that debenzylation was applied to the synthesis of secondary aliphatic amines. This work was initiated by Baltzly and Buck (10) (Burroughs Wellcome and Company). Their procedure is summarized by the following series of equations:



II III IV



V VI



The Schiff base III is not isolated. Stage II → IV is virtually quantitative and stages IV-V and V → VI give very high yields (60-98%).

When one of the R groups is methyl the alkylation of IV is not achieved with a methyl halide. Instead, a method reported by Clarke, Gillespie and Weisshaus (11) is used. The yields by

$$RNH_2 + CH_2O + HCOOH \xrightarrow{100^\circ} RN(CH_3)_2 + CO_2 + H_2O$$

$$R_2NH + CH_2O + HCOOH \xrightarrow{100^\circ} R_2N\text{-}CH_3 + CO_2 + H_2O$$

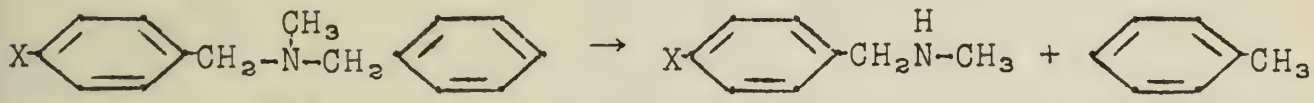
this method are virtually quantitative, but the method is applicable only to amines carrying no other functional group.

King and Work (12) (London) prepared a series of hexyl and nonyl secondary amines using essentially the same method, starting with the alkyl halide instead of the alkyl amine. The yield

III

of III was lower (65%) than when benzaldehyde was used as the starting material; however this variation is useful when the corresponding primary amines are not available.

Because of the growing synthetic importance of debenzylation procedures, Baltzly and Buck (13) have started an investigation to see whether the lability of the benzyl group can be increased by convenient substitution. They found that in molecules of type VII, where X is methoxy, chlorine, methyl or amine,



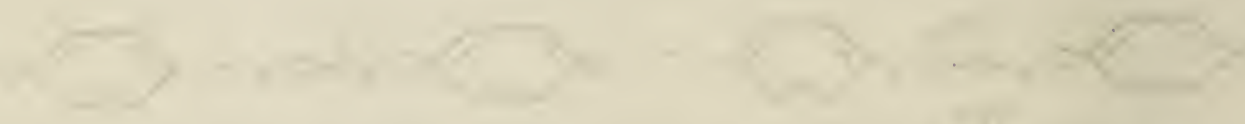
VII

the unsubstituted benzyl group was removed, to all appearances, exclusively. The only groupings so far examined that have proved more labile than the unsubstituted benzyl group are in effect more extended aromatic systems. α-Menaphthyl, β-menaphthyl and β-phenylbenzyl groups are removed in preference to the benzyl group.

Leonhard Birkofer (14) (Heidelberg) has carried out a rather extensive investigation of N-debenzylation and the results of his investigation are summarized below.

1. Benzylamine, dibenzylamine and monoalkyl benzylamines (III) are stable under the conditions used for reductive debenzylation.

2. The hydrogenation of quaternary ammonium hydroxides containing the benzyl group proceeds to the secondary amine.



3. Tertiary bases containing cyclic secondary amines connected to a benzyl group are smoothly cleaved.

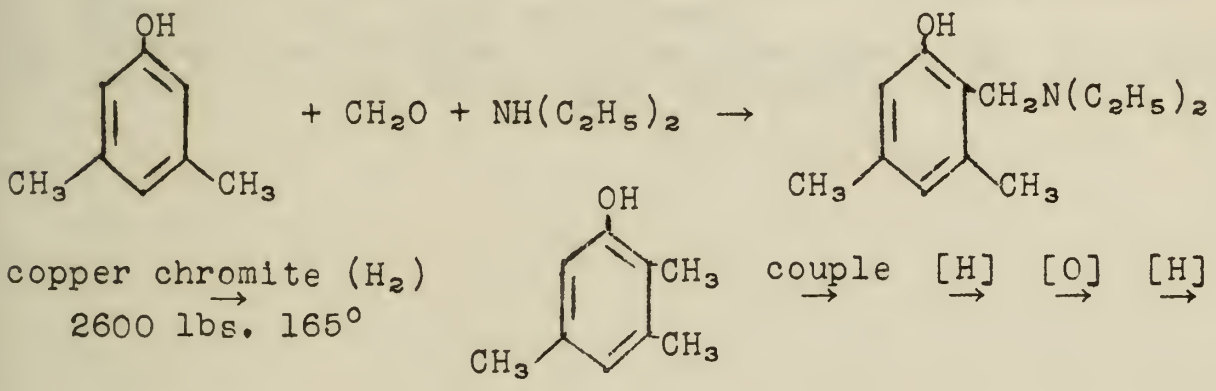
4. Aromatic rings, carboxyl groups and cyano groups have an activating effect so that the benzyl group of a secondary N-atom can be removed.

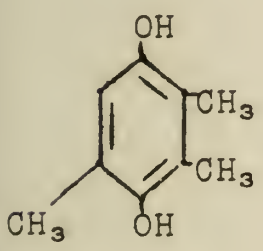
5. Benzyl amides are not cleaved under the conditions used for catalytic debenzylation.

III. Other Applications of Nitrogen Debenzylation.

1. Nuclear Methylation of Phenols (15).

2,3,5-Trimethylhydroquinone (VIII) is an intermediate in the synthesis of α-tocopherol. It has been synthesized by the following scheme.

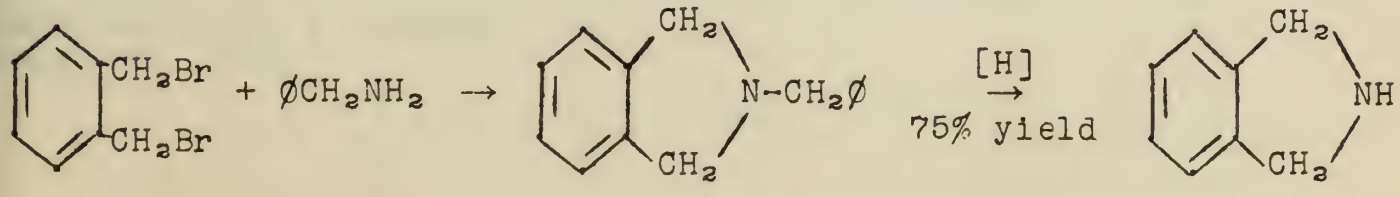


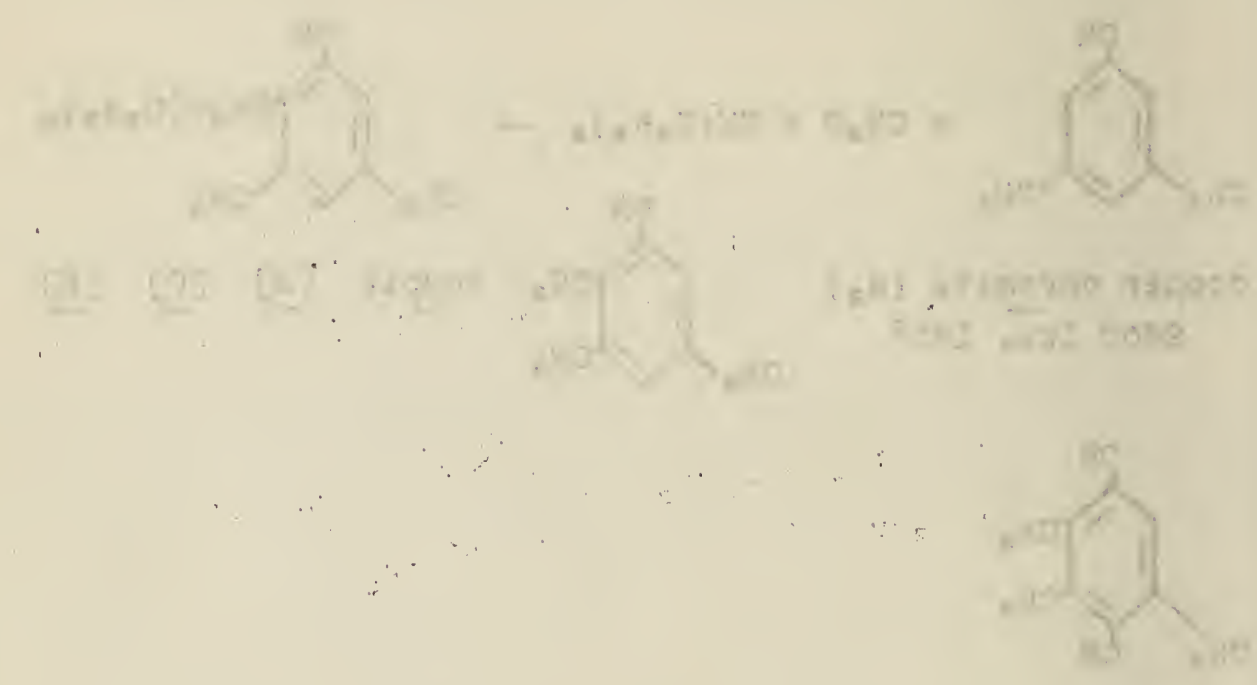


VIII

Decombe (17) had previously shown that the Mannich reaction goes predominately ortho on phenols.

2. Synthesis of Heterocyclic Compounds (16).





BIBLIOGRAPHY

1. Hinsberg, Ann., 265, 178 (1891).
2. Bayler and Caro, Ber., 7, 963 (1874).
3. King and Work, J. Chem. Soc., 1307 (1940).
4. Sidgwick, Organic Chemistry of Nitrogen, page 221.
5. Emerson, Organic Seminar, University of Illinois, February 7, 1940.
6. Henze and Humphreys, J. Am. Chem. Soc., 64, 2878 (1940).
7. Campbell, Sommers, Campbell, J. Am. Chem. Soc., 66, 82 (1944).
8. Westphal and Jerckel, Ber., 73B, 1002 (1940).
9. Bergmann and Zervas, Ber., 65, 1192 (1932).
10. Baltzly and Buck, J. Am. Chem. Soc., 63, 1964 (1941).
11. Clarke, Gillespie and Weissbaus, J. Am. Chem. Soc., 55, 4571 (1933).
12. King and Work, J. Chem. Soc., 1940, 1307.
13. Baltzly and Buck, J. Am. Chem. Soc., 65, 1984 (1943).
14. Birkofer, Ber., 75B, 429 (1942).
15. Caldwell and Thompson, J. Am. Chem. Soc., 61, 765 (1939).
16. Decombe, Compt. Rend., 196, 866 (1933).

Reported by W. E. Parham
March 28, 1945

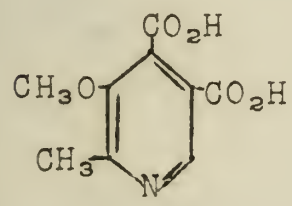
PYRIDOXINE

Pyridoxine, vitamin B_6, is that factor of the B complex which prevents or cures an acrodynia-like dermatitis in rats and promotes growth. Apparently pyridoxine also prevents microcytic hypochromic anemia and is related to the utilization of unsaturated fatty acids by the body.

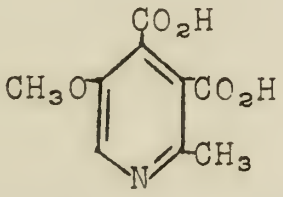
Keresztesy and Stevens have isolated pyridoxine from rice bran and determined its structure. The free base, $C_8H_{11}O_3N$, (III) obtained from the hydrochloride, melts at 160°. The compound is optically inactive, contains no alkyloxy or N-alkyl residues, gives a positive ferric chloride test, indicating a phenolic hydroxyl group. The base is stable toward acid and alkali and does not react with nitrous acid. One C-methyl residue and three active hydrogen atoms are present in the molecule. Ultra-violet absorption spectrum data indicate that it is a derivative of β-hydroxypyridine.

The free base reacts with diazomethane to form a monomethyl ether, $C_9H_{13}O_3N$, m.p. 101-102°. The methyl ether is readily oxidized by barium permanganate at room temperature. Two products are obtained, a lactone, $C_9H_9O_3N$ (XIV), and a dibasic acid, $C_9H_9O_5N$ (I).

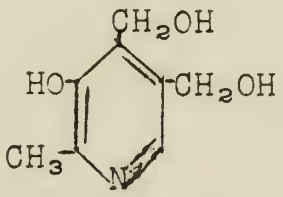
The acid gives no color with ferrous sulfate, indicating that neither carboxyl is α in the pyridine ring. Fusion with resorcinol gives a phthalein which exhibits a green-yellow fluorescence, indicating that the two carboxyls are vicinal. Therefore they must be attached to the 4,5 positions. The dibasic acid contains the original C-methyl residue and therefore must be compound (I) or (II).



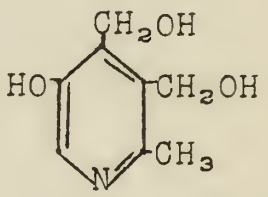
I



II



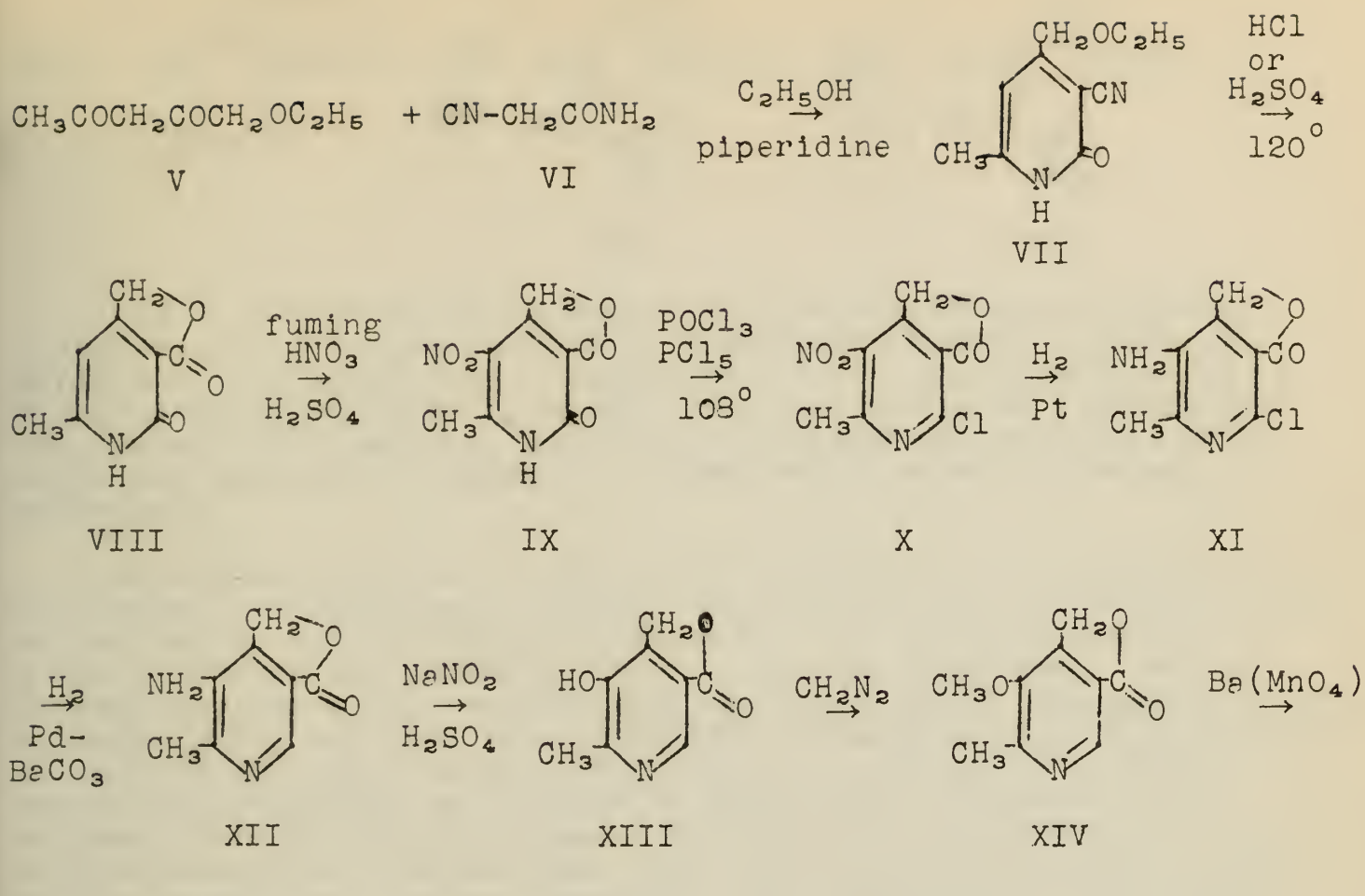
III

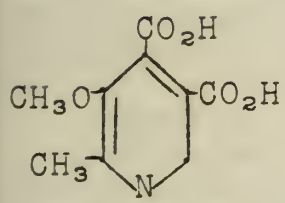


IV

The dibasic acid was formed from the methyl ether of the vitamin by the gain of two atoms of oxygen and loss of four atoms of hydrogen. Since the vitamin has three active hydrogen atoms in its molecule, it must be compound (III) or (IV). The dichloroquinone chloroimide test indicates that the compound is a phenol which is unsubstituted in the <u>para</u>-position. Hence pyridoxine must be compound (III).

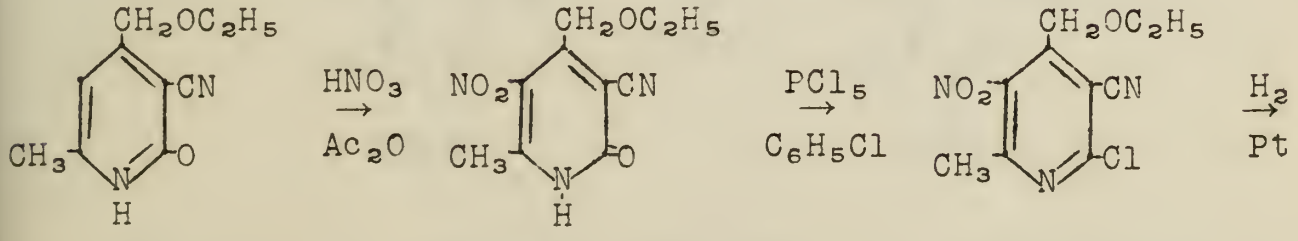
Harris, Stiller, and Folkers have synthesized the dibasic acid (I) and lactone (XIV) obtained by the oxidation of the methyl ether of pyridoxine. This confirms the work of Keresztesy and Stevens and proves pyridoxine to be 2-methyl-3-hydroxy-4,5-dihydroxymethylpyridine (III). The synthesis is outlined below.

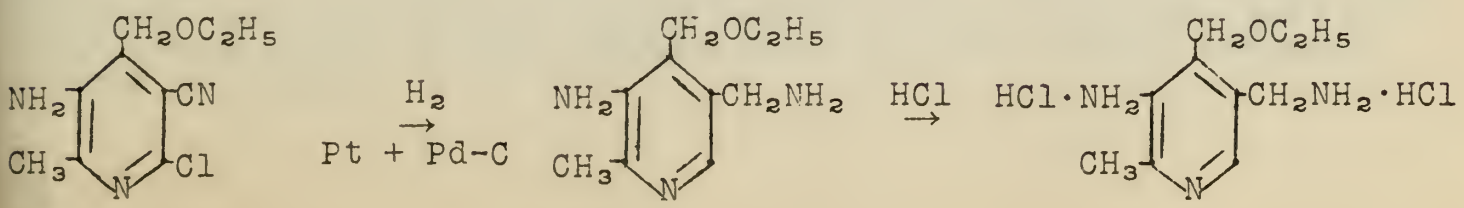


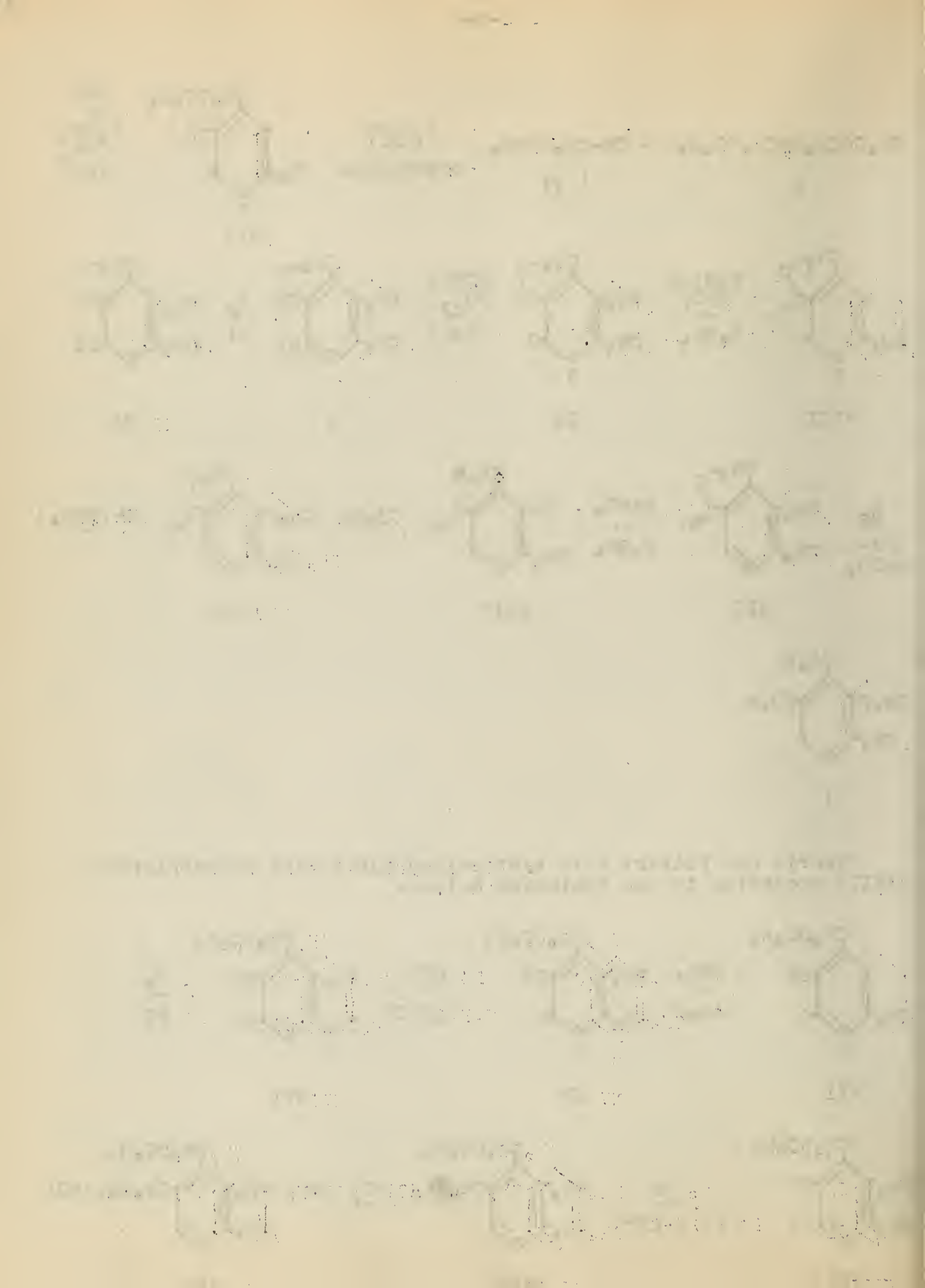


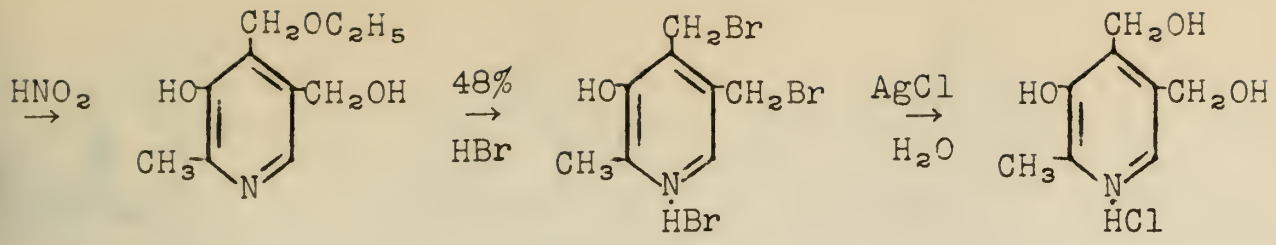
I

Harris and Folkers have synthesized pyridoxine hydrochloride (XXII) according to the following method.







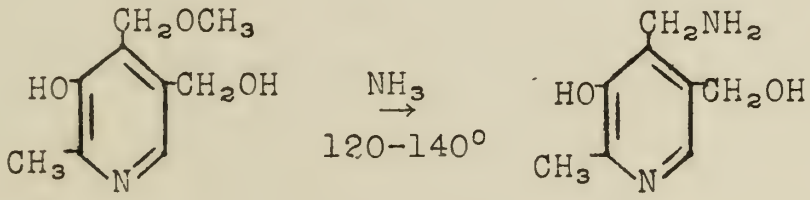


XX XXI XXII

Snell has presented evidence for the occurrence in natural materials of an active substance, "pseudopyridoxine," which is different from pyridoxine. Experimental data shows that an amine with increased activity is formed when pyridoxine or its esters are heated with ammonia. Also by heating pyridoxine with certain oxidizing agents an aldehyde is formed which shows increased activity.

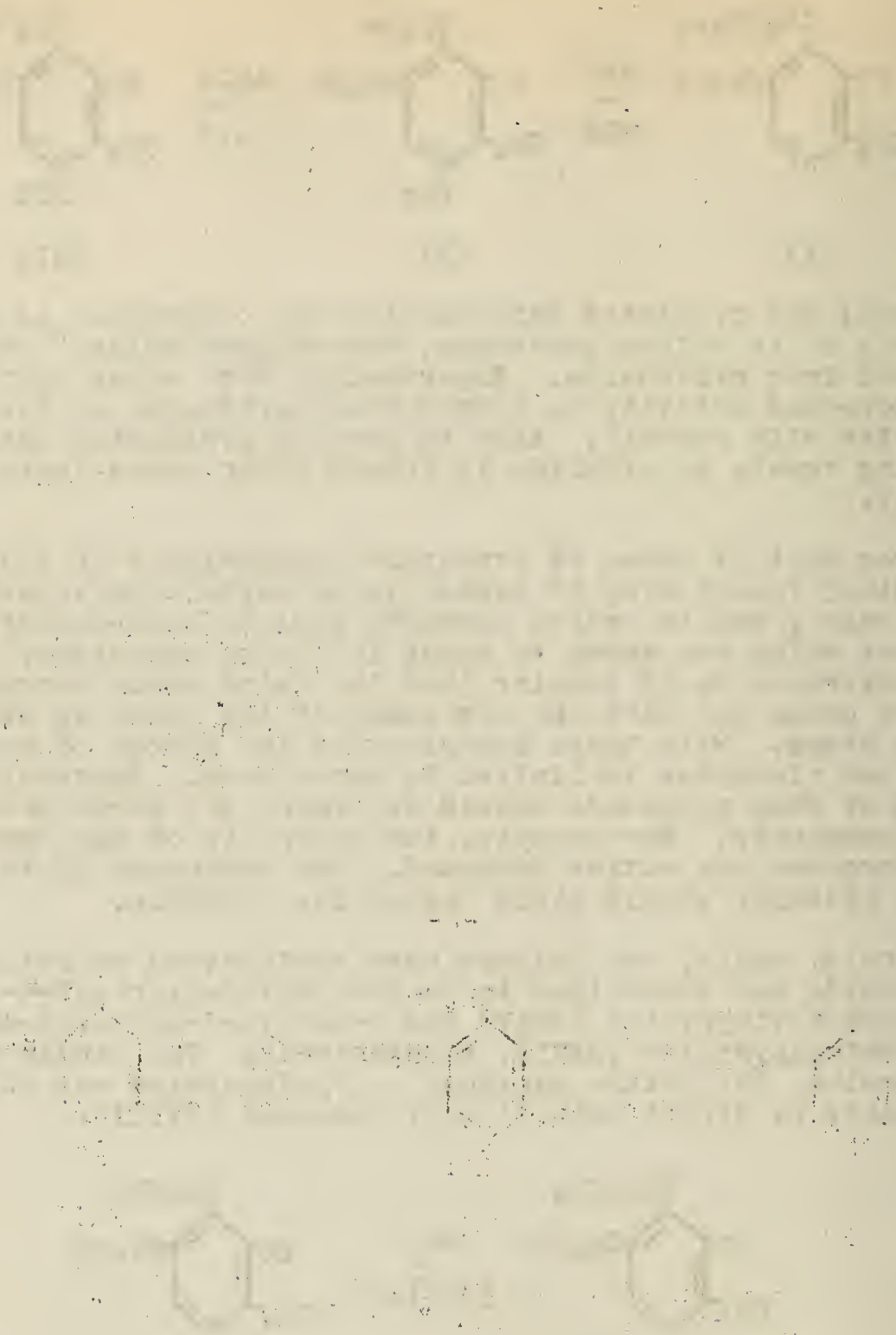
From what is known of structural specificity in relation to biochemical functioning it seems almost certain that pyridoxine, an active amine, and an active aldehyde must be interconvertible by processes which are known to occur in living organisms. Such interconversion would require that the amino group correspond to the aldehyde group and that the remainder of the molecule be identical in both cases. With these restrictions the number of possible amines and aldehydes is limited to three each. Synthesis of a minimum of four compounds should determine the structures of the active compounds. For example, the synthesis of the three amines should produce one active compound. The synthesis of the corresponding aldehyde should yield the active aldehyde.

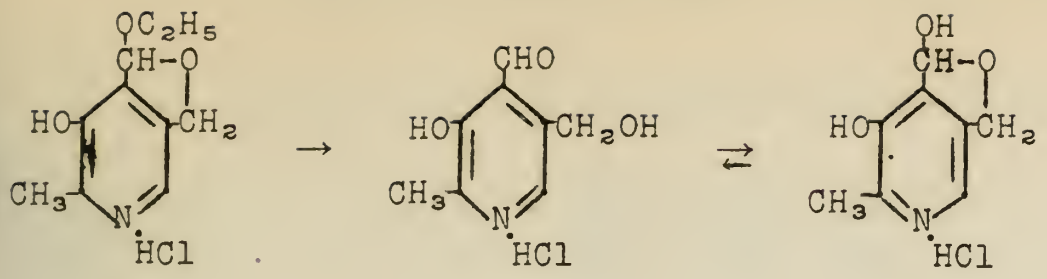
Harris, Heyle, and Folkers have synthesized an active amine and aldehyde and shown them to be 2-methyl-3-hydroxyl-4-aminomethyl-5-hydroxymethylpyridine (XXIV) and 2-methyl-3-hydroxyl-4-formyl-5-hydroxymethylpyridine (XXVI), respectively. The former was called pyridoxamine, the latter pyridoxal. Pyridoxamine was obtained in best yields by direct amination of compound (XXIII).



XXIII XXIV

Oxidation of pyridoxine with potassium permanganate produced an aldehyde which was isolated as the oxime. On decomposition of the oxime with nitrous acid and treatment with alcohol and hydrogen chloride the cyclic acetal (XXV) was obtained. Compound (XXV) was easily hydrolysed to the aldehyde which may have either structure (XXVI) or (XXVII).





XXV XXVI XXVII

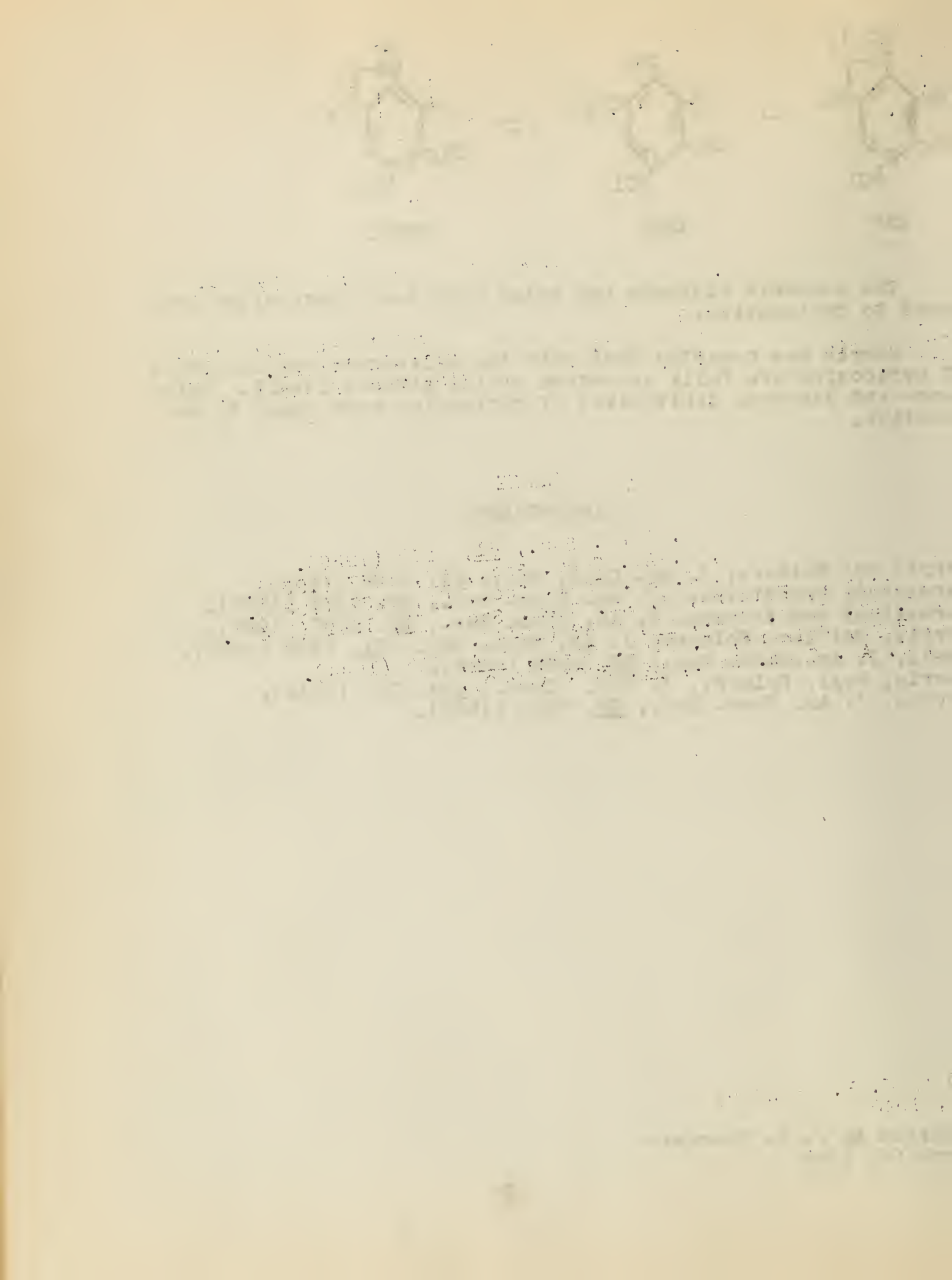
The isomeric aldehyde and amine have been synthesized and found to be inactive.

Harris has reported that both the triacetate and diacetate of pyridoxine are fully as active as the vitamin itself. Both mono- and didesoxy derivatives of pyridoxine were found to be inactive.

BIBLIOGRAPHY

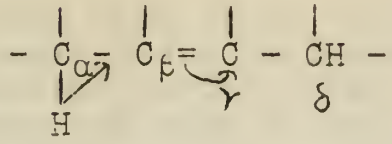
Harris and Folkers, J. Am. Chem. Soc., 61, 1245 (1939).
Keresztesy and Stevens, J. Am. Chem. Soc., 60, 1267 (1938).
Keresztesy and Stevens, J. Am. Chem. Soc., 61, 1237 (1939).
Harris, Stiller, Folkers, J. Am. Chem. Soc., 61, 1242 (1939).
Snell, J. Am. Chem. Soc., 66, 2082 (1944).
Harris, Heyl, Folkers, J. Biol. Chem., 154, 315 (1944).
Harris, J. Am. Chem. Soc., 62, 3203 (1940).

Reported by J. H. Saunders
March 28, 1945

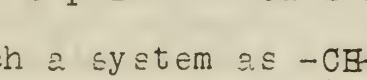


α-METHYLENIC REACTIVITY IN OLEFINIC SYSTEMS

The system involved in substitutive reactions of olefins is:

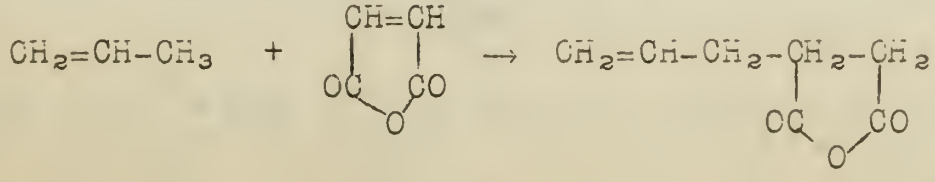


The reactivity most commonly expected of such a simple olefinic system is addition at the double bond. However, resonance in this system, in which a C-H bond is conjugated with an unsaturated (olefinic) system should give rise to increased reactivity of the α-methylene hydrogen atoms, probably smaller in magnitude than, but similar to that which arises from suitable conjugation with other activating unsaturated groups such as carbonyl, H-C=C=O, or cyano, H-C-C≡N (1). The system should, and does, possess in addition to its additive properties a marked tendency to undergo substitution at Cα (or Cδ), which process is referred to as "substitution in the allyl position." A variety of these substitution reactions are known. Doubtless the reaction mechanisms of these processes differ from example to example. In some of the substitution reactions of olefins, such as peroxidation and high temperature halogenation, the α-methylenic hydrogen atoms tend to come off as atoms, and a free radical reaction mechanism is probably involved (2). Other of the so-called substitutive reactions of olefins probably involve attack at the double bond, followed by double bond reformation. These different possibilities will be discussed in connection with the individual reactions.

Of particular interest is the influence on α-methylenic substitution of (a) reaction conditions and (b) alkyl substitution at the ethylenic carbon atoms. Available evidence suggests that inductive effects due to alkyl groups attached to ethylenic carbon atoms of olefins facilitate substitutive as well as additive attack and serve to determine the point of substitutive as well as of additive attack. In such a system as  substitution appears in practice more likely to occur at Cα than Cδ (3).

Reaction with Maleic Anhydride and Esters of Azodicarboxylic Acid

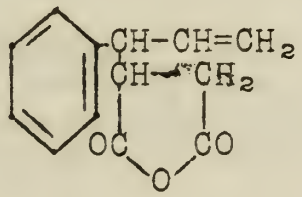
Alder and co-workers (4) have undertaken a systematic investigation of the reaction capacity of simple unsaturated hydrocarbons toward α,β-unsaturated compounds, especially maleic anhydride. The authors found that propylene reacts with maleic anhydride at 230° and 110 atm. to produce allyl succinic anhydride in low yield.



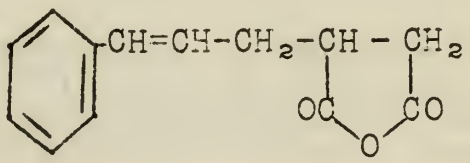
Similar products were obtained with n-butylene, isobutylene, n-hexylene, n-octylene and cyclic olefins such as cyclohexene.

The authors concluded from these findings that addition of the olefinic compound takes place on the carbon atom adjacent to the double bond (α-methylene carbon atom) whereby a hydrogen atom leaves this position and adds to the maleic anhydride. This process, which is a purely thermal, uncatalyzed addition, is referred to by Alder as "substituting addition in the allyl position."

An unexpected result was obtained when the reaction was carried out with allylbenzene. The resulting product was not the expected adduct (I) but the anhydride of a (γ-phenyl-allyl)-succinic acid (II):



I



II

Esters of diazocarboxylic acid react with olefins to produce similar products.

Peroxidation Reactions

With little doubt peroxidation constitutes the first step in all auto-oxidations of olefins, although many or all of the peroxide groups formed may undergo decomposition before the end of the reaction. In all the (unconjugated) systems examined by the authors (3,5), the oxygen appears to enter at the methylenic carbon atoms in the α-position to the double bond and there form hydroperoxide groups.

Farmer and co-workers suggest the following course for the peroxidation reaction:

$$-CH-C=C- \; + \; .OO. \; \rightarrow \; -\overset{\bullet}{C}-C=C- \; + \; .OOH$$

$$-C-C=C- \; + \; .OO. \; \rightarrow \; -\underset{\bullet}{\underset{|}{C}}-C=C-$$
$$\qquad\qquad\qquad\qquad\qquad\quad OO.$$

$$-\underset{|}{C}-C=C- \; + \; -CH-C=C- \; \rightarrow \; -\underset{|}{C}-C=C- \; + \; -C-C=C-$$
$$\quad OO. \qquad\qquad\qquad\qquad\quad OOH \qquad\qquad\qquad\quad \bullet$$

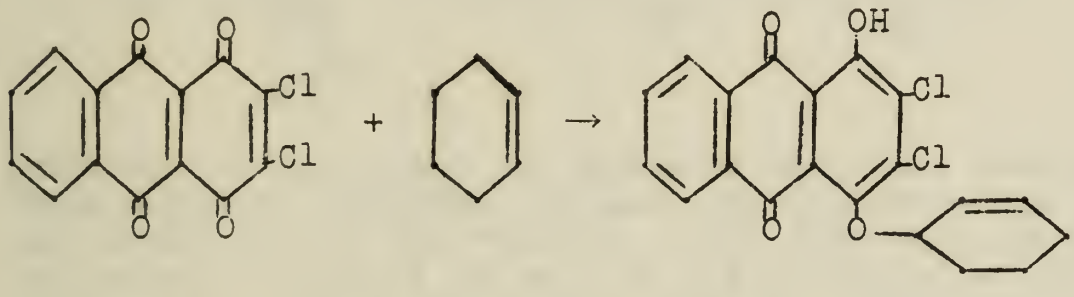
If the first stage of peroxidation consists in severance (presumably by molecular oxygen) of a thermally or photochemically activated C-H bond, so leaving an olefinic free radical, it may be expected that resonance between the two three-carbon forms,

$-\dot{C}H-C=C$ and $-C=C-\dot{C}H-$ will immediately follow, so there will be
3 2 1 3 2 1
an approximately equal tendency for the .OOH group to appear at positions 1 and 3. Changes in the arrangement of the double bonds have actually been observed in the peroxidation of polyenes.

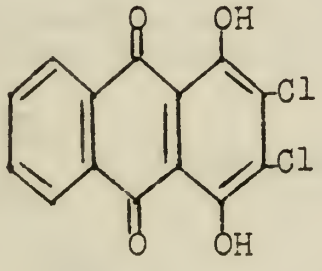
Peroxide decay generally occurs side by side with new peroxidation. The hydroperoxide groups themselves revert to hydroxyl groups (in some circumstances to keto groups) and concurrently the active oxygen is used in oxidizing either the adjacent or some remote double bond.

Reaction of Quinones

In the maleic anhydride reaction described above there is no tendency for the fragments formed by dissociation of the olefin to unite at the oxygen terminals of the system O=C-CH=CH-C=O
present in the anhydride. When the anhydride is replaced by a suitable quinone, however, such a reaction can be realized. Reaction between cyclohexene and the chlorodiquinone (I) occurs readily on heating, giving the adduct (II) (6). Simple benzoquinones do not react.



I II



III

At a higher temperature these hydroquinones (II) decompose, giving cylcohexadiene and the hydroquinone (III), so that the net result of the reaction carried out at high temperature is dehydrogenation of the olefin and reduction of the quinone.

Halogenation Reactions

The importance of α-methylenic reactivity is very evident in halogenation reactions. Both substitution and addition occur when an olefin in gaseous form is mixed with chlorine at low or

non-elevated temperatures. For substitution to become easy, however, and to compete successfully with addition, the lability of the α-methylenic hydrogen atoms requires enhancing either by structural modification of the normal olefinic chain or by using high temperatures.

A survey of the literature shows that at normal temperatures, direct halogenation of the type $-\overset{|}{C}=C-\overset{|}{C}H \rightarrow -\overset{|}{C}=C-\overset{|}{C}-X + HX$ is limited to hydrocarbons in which one of the unsaturated carbon atoms is fully substituted. The substitutive reaction in this case is found to be a liquid-phase reaction occurring in liquid films on the walls of the vessel. At a suitable rate of gas flow isobutylene (1 mol) reacts with chlorine (1 mol) to give mainly (a) $CH_2Cl-CMe=CH_2$ (0.87 mol), (b) $CH_3CMe=CHCl$ (0.03 mol) and (c) $CH_3CMeCl-CH_2Cl$ (0.06 mol), and the ratio of the yield of (a) to (b) changes little with varying conditions from ca. 97/3. Concerning the mechanism of this halogenation, it is now believed to involve attack at the double bond, followed by elimination of a proton and double bond reformation as shown below.

$$CH_3 \rightarrow \overset{\downarrow}{C}(CH_3)=CH_2 \rightarrow (CH_3)_2\overset{+}{C}-CH_2Cl \; (Cl^-) \rightarrow CH_2=C(CH_3)-CH_2Cl + HCl$$

(with Cl_2 adding across the double bond)

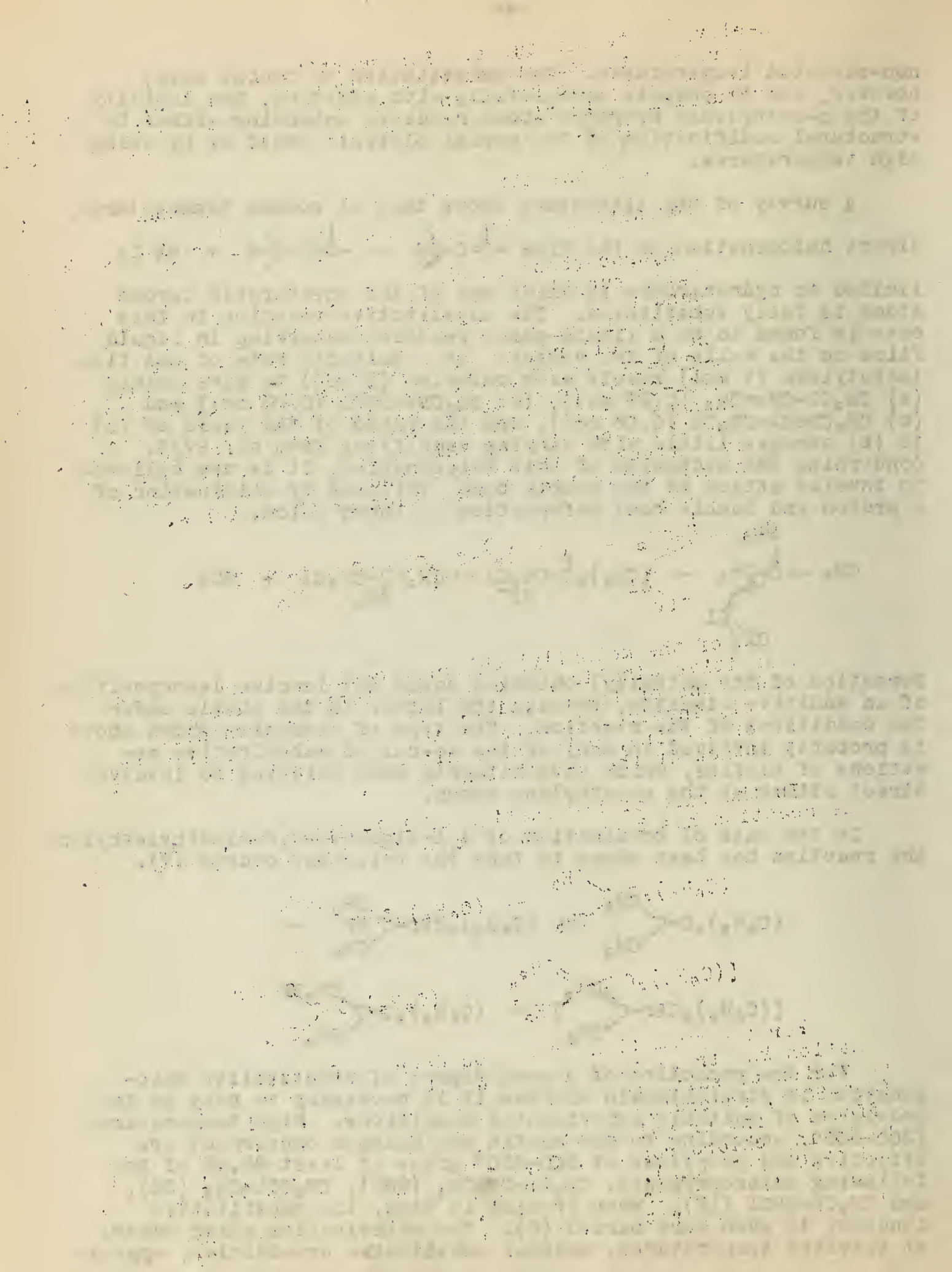
Formation of the methallyl chloride could not involve decomposition of an additive dihalide, because the latter is too stable under the conditions of the reaction. The type of mechanism shown above is probably involved in many of the so-called substitutive reactions of olefins, which have hitherto been believed to involve direct attack at the α-methylene group.

In the case of bromination of 1,1-diphenyl-2,2-dimethylethylene the reaction has been shown to take the following course (7).

$$(C_6H_5)_2C=C(CH_3)_2 \rightarrow (C_6H_5)_2CBr-C(CH_3)_2Br \rightarrow$$

$$[(C_6H_5)_2CBr-C(=CH_2)CH_3] \rightarrow (C_6H_5)_2C=C(CH_2Br)CH_3$$

For the promotion of a good degree of substitutive halogenation in straightchain olefins it is necessary to rely on the provision of suitable experimental conditions. High temperatures (300-600°, according to the olefin and halogen concerned) are effective and propylene at 600-650° gives at least 85.5% of the following chloropropenes, $CH_2Cl-CH=CH_2$ (96%), $CH_3CCl=CH_2$ (3%), and $CH_3CH=CHCl$ (1%). When bromine is used, the substitutive tendency is even more marked (8). The chlorination which occurs at elevated temperatures, whether substitutive or additive, appears



to be mainly (not exclusively) of radical character (9).

Application of this high temperature halogenation process is limited to olefins which do not decompose under such strenuous conditions. Ziegler and co-workers (10) have devised a general method for bromination in the allyl position which involves the use of N-bromosuccinimide. The latter reagent is very specific for the substitution reaction--addition of this reagent to the double bond has never been observed. The general conditions are excess olefin in carbon tetrachloride as solvent. The time of reaction for most of the olefins investigated varied from 5 minutes to 1 hour. When equivalent amounts of reactants were used, yields of 50-60% of the substituted allyl bromides were obtained. When an excess of the olefin was used, the yield was increased in some cases to 80%. A free radical mechanism has been suggested (11) to explain bromination of N-bromosuccinimide, but it should be remembered that the halogen in all N-halogen compounds is positiv and a mechanism such as that involved in the halogenation of isobutylene may be involved.

Oxidation by Lead Tetraacetate

Criegee (12) found that lead tetraacetate reacts directly with cyclohexene to give mainly cyclohexenylacetate. Diacetoxyl-cyclohexenes and 1,2-diacetoxyl-cyclohexane were also formed. This means that acetoxyl groups add at the double bond of the olefin, and also substitute at one or both of the α-methylene groups to give 3-, 3,6-, and 3,3-derivatives. Usually both addition and substitution reactions occur concurrently, the former generally predominating. The reaction appears to be of a free radical type, involving the following thermal decomposition.

$$Pb(OAc)_4 \rightarrow Pb(OAc)_2 + 2AcO\cdot$$

The acetoxyl radicals thus formed attack the double bond or an α-methylene group of the olefin.

Oxidation by Selenium Dioxide

Selenium dioxide exhibits a remarkable regularity in attacking olefins, aldehydes and ketones at the α-methylene groups. The point of attack in the case of olefins is very precisely determined by alkyl substitution in the chain. This is shown by the action of selenium dioxide in the presence of acetic acid on the following systems (13), in which attack occurs at the points marked.

$CH_3-\overset{*}{C}Me=\overset{*}{C}HMe$	$CH_3-\overset{*}{C}H_2-CMe=\overset{*}{C}H_2$	$CH_3-\overset{*}{C}(iso\text{-}Pr)=\overset{*}{C}HMe$
$CH_3-\overset{*}{C}Me=\overset{*}{C}HEt$	$CH_3-\overset{*}{C}H_2-C\overset{*}{P}h=\overset{*}{C}HMe$	$RCH_2-\overset{*}{C}Et=\overset{*}{C}HCH_2R$

When the reaction is carried out by heating the olefin with powdered selenium dioxide, the methylene groups attacked are oxidized to carbonyl groups. If a fatty acid is present, the fatty acid ester of the corresponding alcohol is obtained. The

exact course of the reaction, which does not appear to be normally of ionic type, is as yet undetermined.

Attack by Other Oxidizing Agents

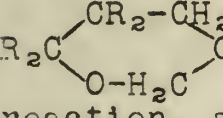
Oxidative attack at α-methylene groups in olefinic systems by ozonized oxygen, perbenzoic acid and chromic acid has been reported to occur (2).

Double-bond Displacement

Hydrogen can be displaced as an ion from the α-methylene groups of olefinic chains when strong caustic alkali is used as reagent at a sufficiently high temperature (14). Thus, linolenic acid is converted to a conjugated isomeride when heated with alkali.

Prins Reaction

A claim is made in a British patent that olefins of the type $R^1R^2C=CR^3CH_3$ (R^3 = Alkyl, alicyclic, alphyl or aryl; R^1,R^2 = the same or H) react at room temperature with trioxymethylene in the presence of catalysts such as zinc chloride, stannous chloride, zinc dichloroacetate, etc., in dry inert solvents such as ether, chloroform or saturated hydrocarbons to give unsaturated alcohols of the type $R^1R^2C=CR^3CH_2CH_2OH$. Under the usual conditions of the Prins reaction (trioxymethylene in the presence of acetic-sulfuric acids) the main products are the diacetate $R_2C(OAc)-CR_2-CH_2OAc$ of the 1,3-diol together with the corresponding formal



. Thus, whereas under the conditions of the Prins reaction, a normal acid-catalyzed addition to the olefinic linking occurs, the not very dissimilar conditions described in the patent are stated to give rise to reaction at the α-methylenic hydrogen atoms (1).

Free Radical attack on Olefins: - Vulcanization by Dibenzoyl Peroxid

Dibenzoyl peroxide decomposes thermally to give Ph. and Ph-CO-O. radicals. When an excess of cyclohexene is heated with this peroxide, numerous products are formed, but attack by the radicals at the α-methylene groups greatly exceeds their attack at the double bond (15).

In the vulcanisation of rubber by dibenzoyl peroxide it is believed that the rubber chains are extensively substituted at the α-methylene groups by benzoate and (to a lesser extent) by phenyl groups, and at the same time are in some degree cross-linked by bonds (intermolecular or intramolecular) joining the methylene groups of different rubber units or bonds joining α-methylene groups to double bonds (3).

Sulfur Vulcanisation

Sulfur vulcanisation is believed to involve attack at the α-methylene groups producing intermolecular links, usually considered to be sulfur bridges (sulfide, disulfide), but possibly to some extent C-C bonds. Extensive incorporation of sulfur at the later stages of sulfur vulcanisation, with concurrent loss of unsaturation of the rubber, is probably a secondary attack involving the double bonds (3).

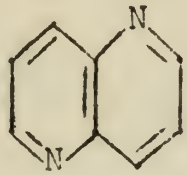
BIBLIOGRAPHY

1. Baker, J. Chem. Soc., 296 (1944).
2. Farmer, Trans. Faraday Soc., 38, 340 (1942).
3. Farmer, Bloomfield, Sundralingam and Sutton, Trans. Faraday Soc., 38, 348 (1942).
4. Alder, Pascher and Schmitz, Ber., 76, 27 (1943). See also Rabjohn, Organic Seminars, 1943-44.
5. Farmer, Koch and Sutton, J. Chem. Soc., 541 (1943).
6. Criegee, Ber., 69, 2758 (1936).
7. Ziegler and Bahr, Ber., 62, 1695 (1929).
8. Groll, Hearne, Rust and Vaughan, Ind. Eng. Chem., 31, 1239, 1413, 1530 (1939).
9. Rust and Vaughan, J. Org. Chem., 5, 472 (1940).
10. Ziegler, Späth, Schaaf, Schumann and Winkelmann, Ann. 551, 80 (1942). See also Jones, Organic Seminars, 1943-44.
11. Bloomfield, J. Chem. Soc., 114 (1944).
12. Criegee, Ann., 481, 263 (1930).
13. Guillemonat, Ann. Chim., 11, 143 (1939).
14. Farmer, Trans. Faraday Soc., 38, 356 (1942).
15. Farmer and Michael, J. Chem. Soc., 513 (1942).

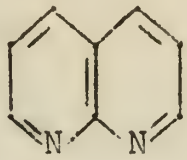
Reported by L. J. Reed
April 4, 1945

1,5- AND 1,8-NAPHTHYRIDINES

Of the six possible ring systems composed of two pyridine rings fused through adjacent carbon atoms, only two isomers have been studied extensively, the 1,5-naphthyridines (I) and the 1,8-naphthyridines (II). Early investigators were inter-



(I)

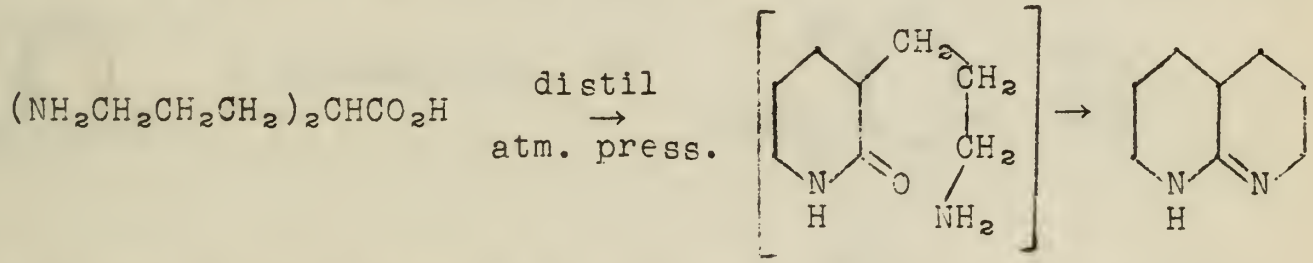


(II)

ested in naphthyridines by reason of their close similarity to the pyridines and quinolines; however, research in the last two decades has been directed in an increasing measure toward the synthesis of therapeutics containing the naphthyridine nucleus. Chronologically, the 1,8-naphthyridines were synthesized before the 1,5-analogs, and that sequence will be followed here.

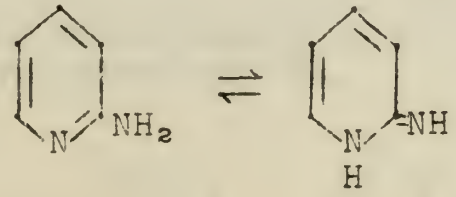
I. Synthesis of 1,8-Naphthyridines

In 1893 Reissert (1) prepared the first derivative of 1,8-naphthyridine, the octahydro compound. This was accomplished by distilling the proper dialkylaminoacetic acid at atmospheric pressure, as indicated by the following equation. It should be

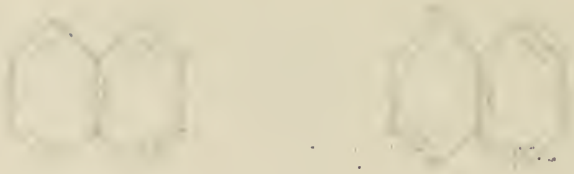


noted that in this method a substituted pyridine appeared only as an intermediate, whereas, in all later syntheses, pyridines were employed as starting materials.

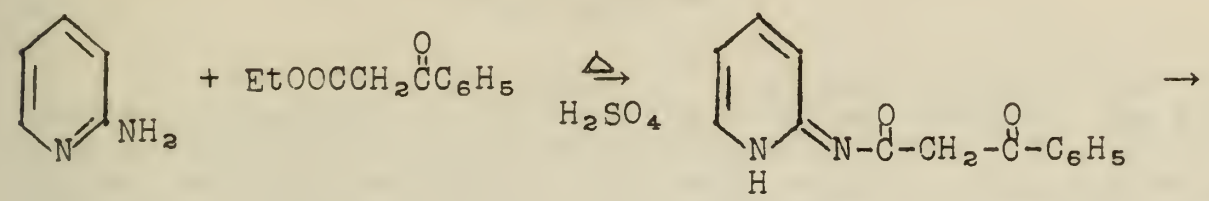
In the first attempts to prepare 1,8-naphthyridines from α-aminopyridines, ring closure on the β-carbon atom of the pyridine nucleus could not be effected. Chichibabin (2) has shown that α-aminopyridines react in two tautomeric forms, one of which has an active hydrogen on the nuclear nitrogen. This

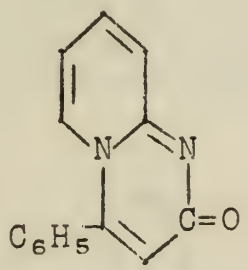


hydrogen is so activated that unless the pyridine ring is properly substituted, ring closure will occur by way of the

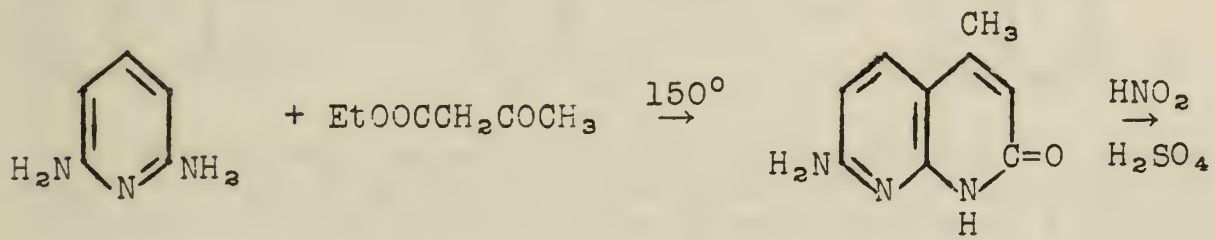


nuclear nitrogen rather than on the β-carbon atom. Thus, Seide (3) showed that Palazzo and Tamburini (4) obtained a dihydroketopyrimidine in their attempt to prepare 2-hydroxy-4-phenyl-1,8-naphthyridine by the Knorr quinoline synthesis.

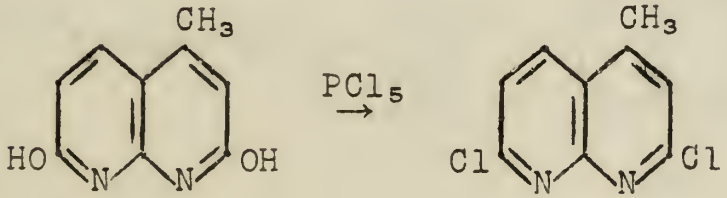




Oskar Seide (Moscow, 1926) found that activation of the pyridine ring by the substitution of an amino group in the α'-position would direct the Knorr ring closure to the β-carbon atom as desired (5).

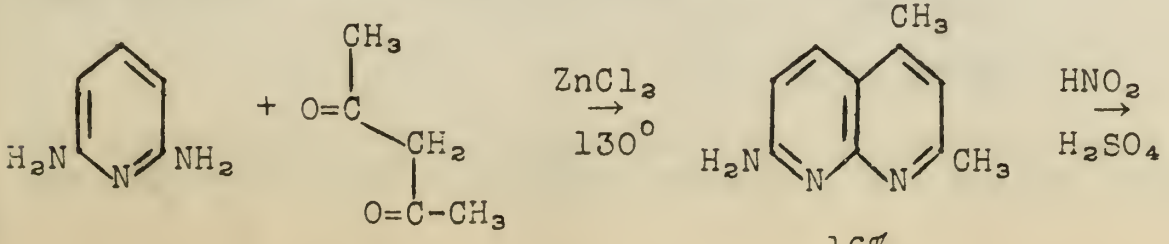


37%

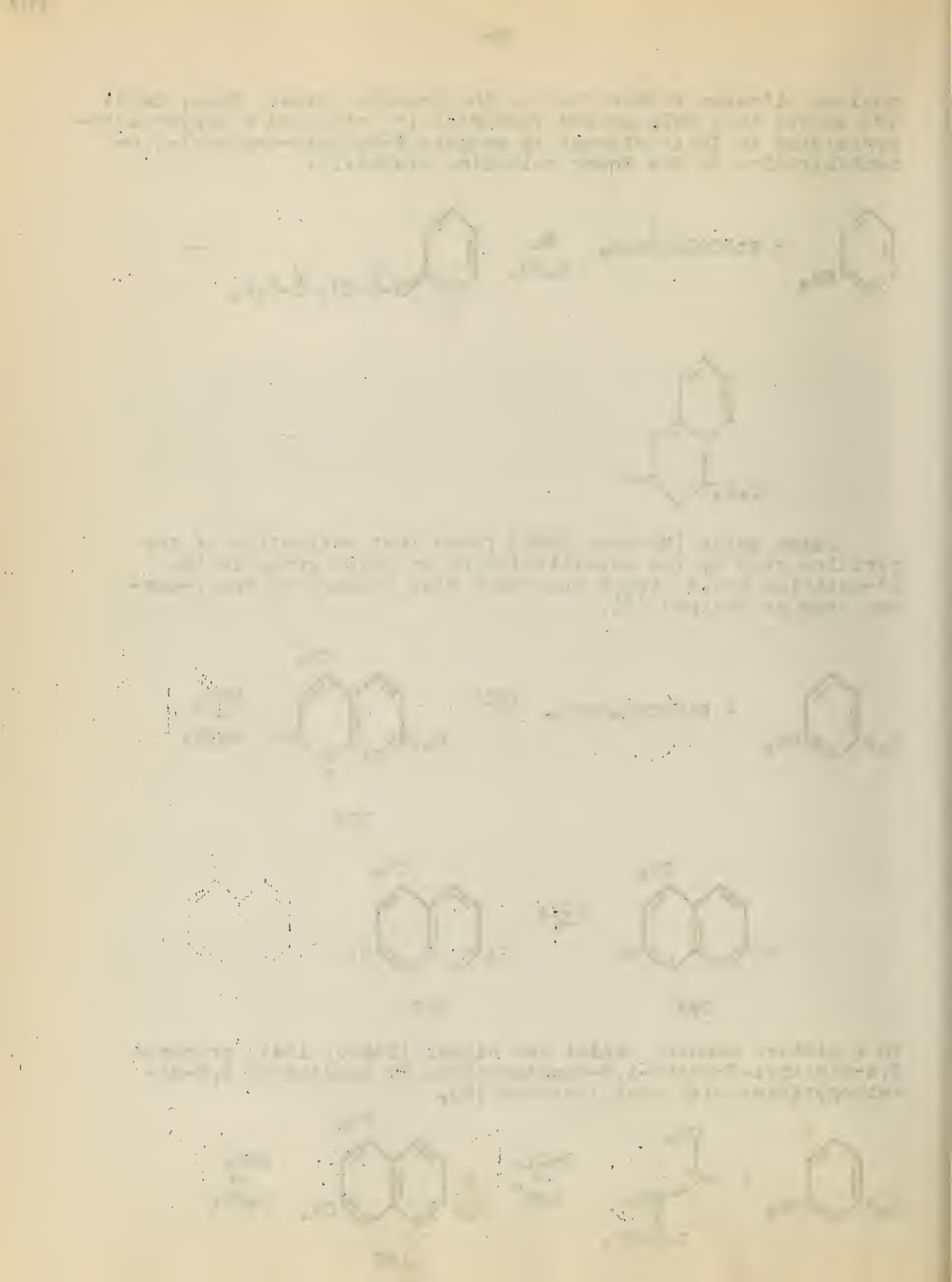


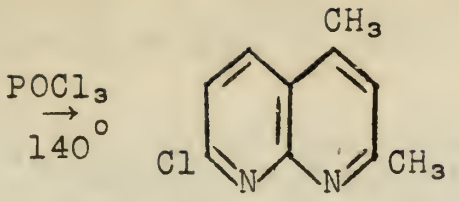
92% 90%

In a similar manner, Ochiai and Miyaki (Tokyo, 1941) prepared 2,4-dimethyl-7-amino-1,8-naphthyridine by condensing 2,6-diaminopyridine with acetylacetone (6).

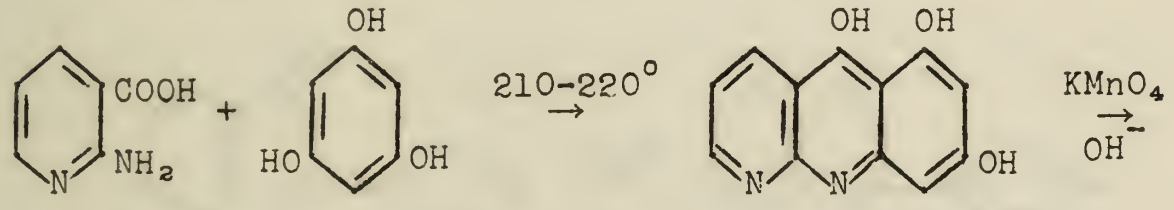


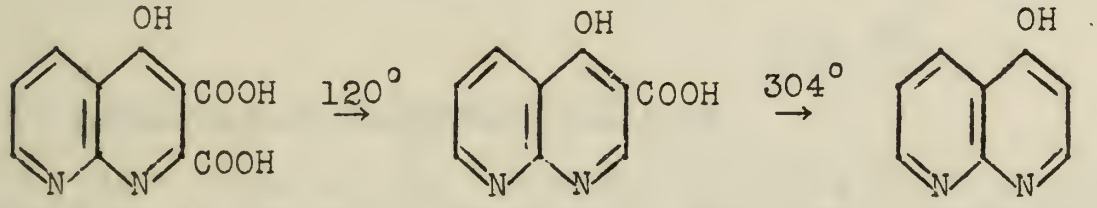
16%



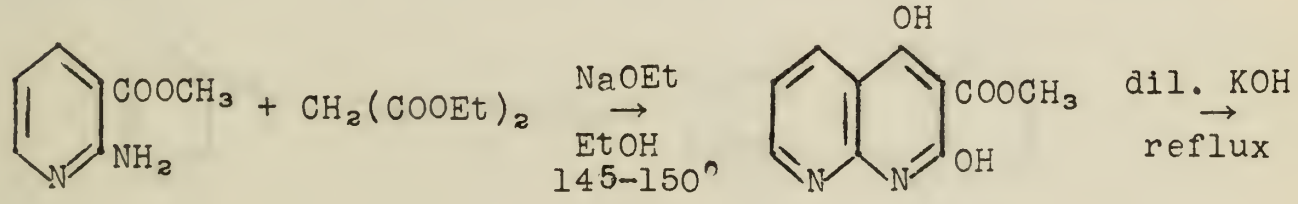


In 1920, Sucharda (Lwow) (7) prepared substituted 1,8-naphthyridines by an interesting indirect method. By condensing phloroglucinol with 2-aminonicotinic acid, the difficulty of an immobile β-hydrogen atom was avoided. The phloroglucinol residue, activated by the hydroxyl groups, was easily cleaved by permanganate or nitric acid. Either partial or complete decarboxylation of the oxidation product could be carried out, depending on the temperature employed.

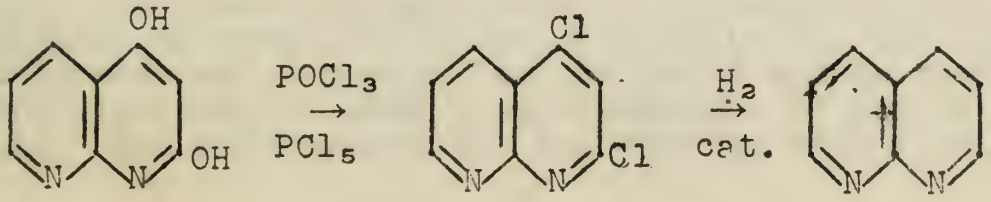




The malonic ester synthesis of 2,4-dichloro-1,8-naphthyridine, developed by Koller (Wien) (8, 17), is of interest because it led to the isolation of the parent compound, 1,8-naphthyridine.



57%

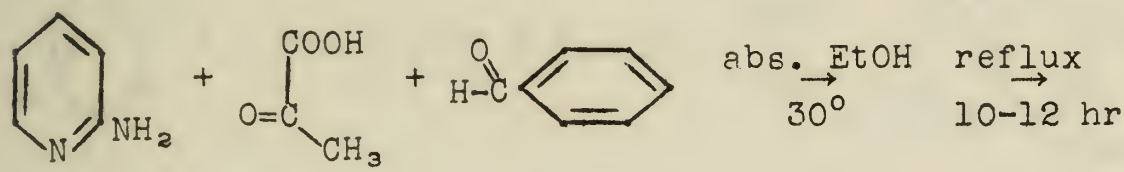


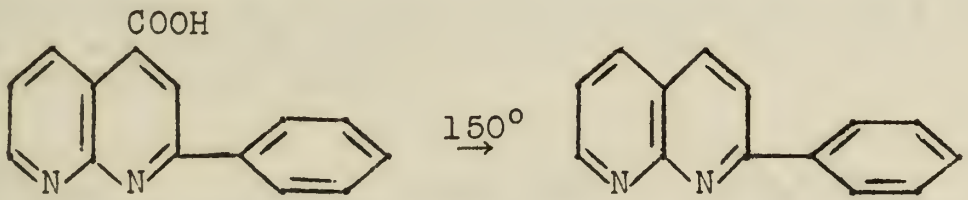
m.p. 98-99°

The inactivity of the β-hydrogen atom in pyridine made impossible the preparation of 1,8-naphthyridine by the Skraup synthesis;

in fact, reduction of chlorine-containing derivatives remains the only reported method of synthesizing this unsubstituted base.

Recently the use of the Doebner quinoline synthesis for the preparation of 2-phenyl-1,8-naphthyridine has been reported by Mazza and Migliardi (9, 10). The original literature reference is, however, not available; hence, in view of previous difficulties with α-aminopyridine, it is not known whether conclusive proof of the indicated structure was presented.

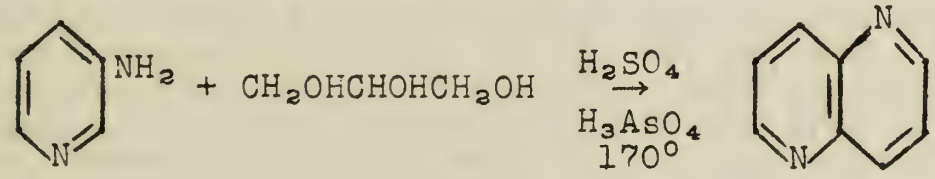




m.p. 97°

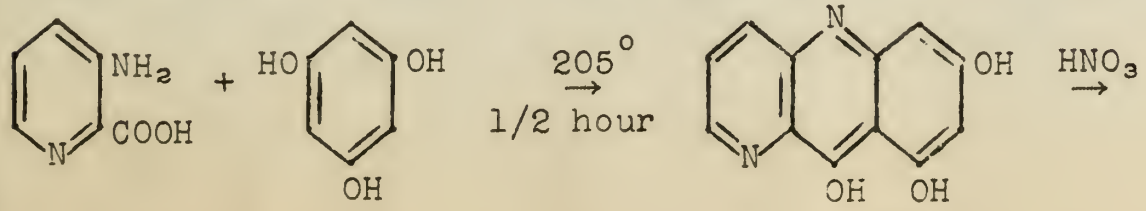
II. Synthesis of 1,5-Naphthyridines

As a study of the 1,8-naphthyridines has indicated, the β-position in the pyridine ring is relatively inactive; however, the hydrogen atoms in the α- and γ-positions have considerable mobility. The synthesis of 1,5-naphthyridine by ring closure on the α-position of β-aminopyridine has been effected by the Skraup method with little difficulty (11, 12, 13).

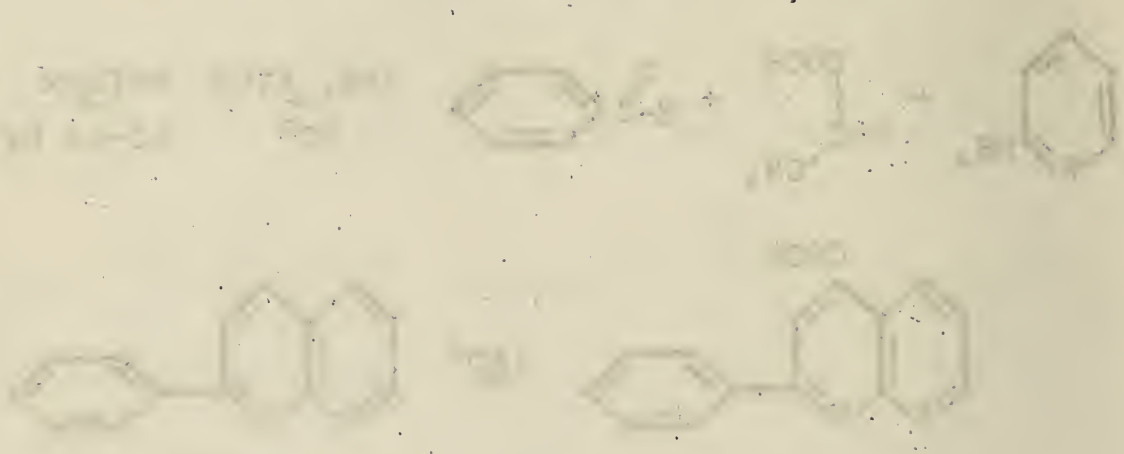


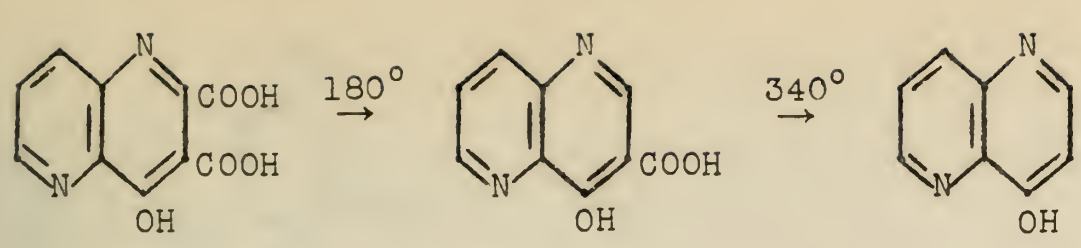
m.p. 75°

The remaining syntheses of 1,5-naphthyridines are modifications of reactions given previously for the 1,8-naphthyridines. Klisiecki and Sucharda (14) prepared 4-hydroxy-1,5-naphthyridine-2,3-dicarboxylic acid by condensation of 3-amino-2-picolinic acid with phloroglucinol, followed by oxidation.

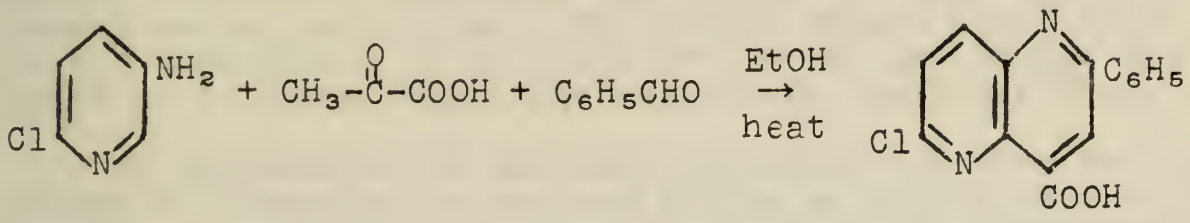


40%

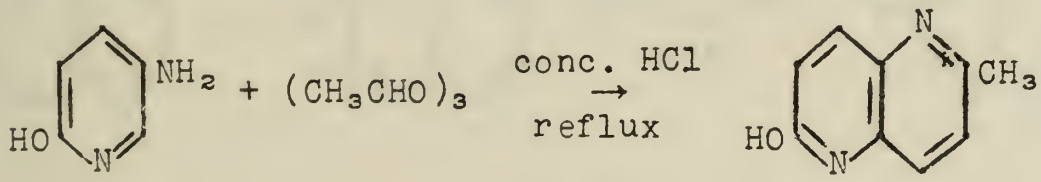




The Doebner synthesis was used to advantage in the preparation of substituted 1,5-naphthyridines (15).



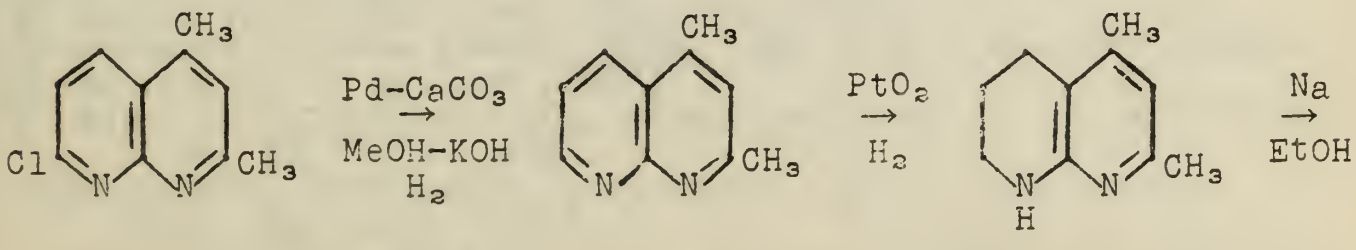
Paraldehyde and 2-hydroxy-5-aminopyridine were the reactants in a patented modification of the Doebner-von Miller quinoline synthesis (11).

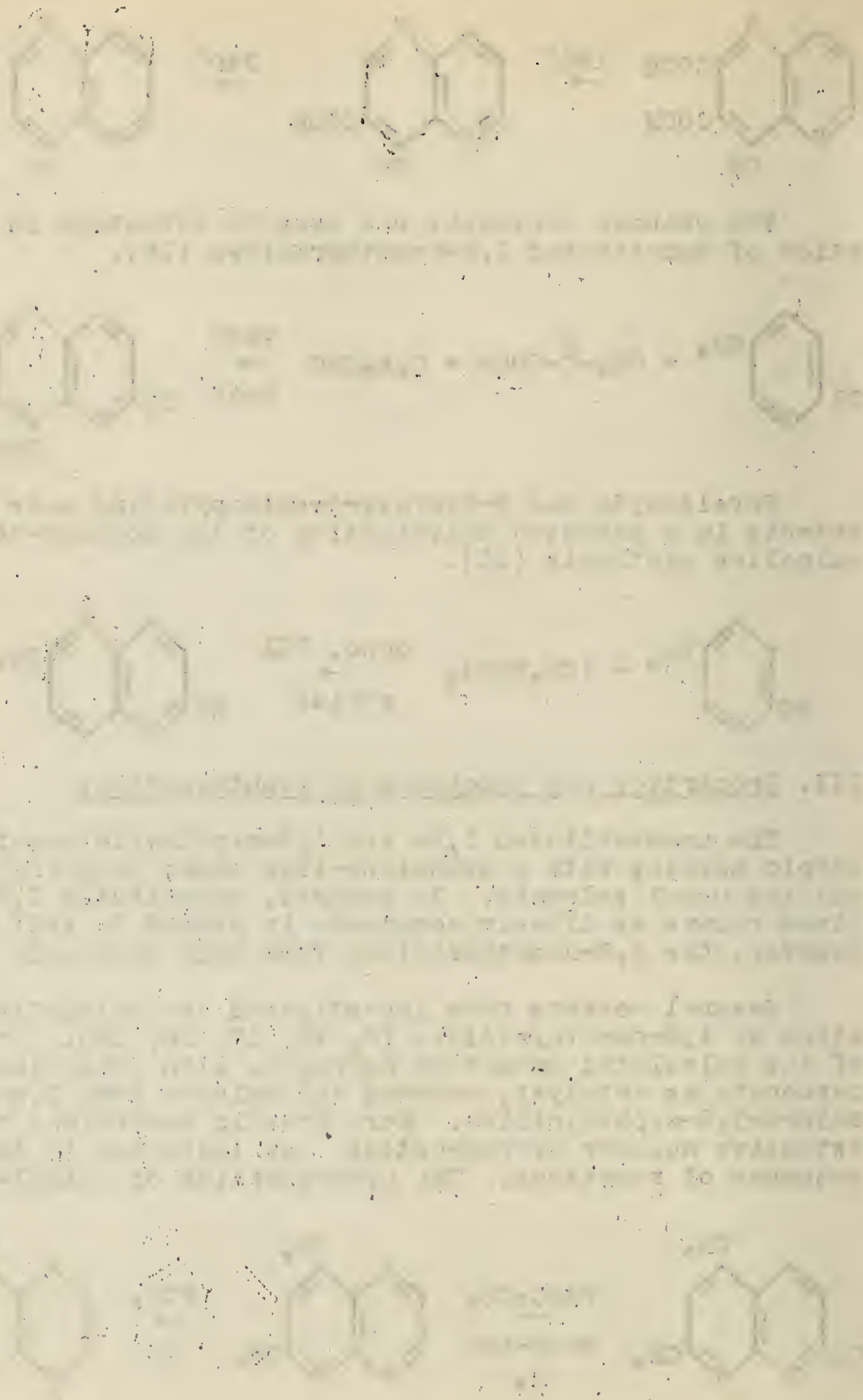


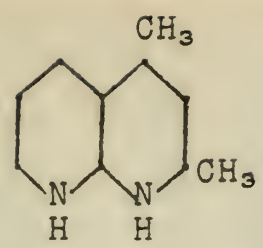
III. Properties and Reactions of Naphthyridines

The unsubstituted 1,5- and 1,8-naphthyridines form hydroscopic needles with a quinoline-like odor; they are soluble in all the usual solvents. In general, substituted 1,5-naphthyridines behave as dibasic compounds in regard to salt formation; however, the 1,8-naphthyridines form only monobasic salts.

Several workers have investigated the catalytic dehalogenation of 1,8-naphthyridines (6, 16, 17, 18, 19). The addition of the calculated amount of hydrogen, with palladium on calcium carbonate as catalyst, removed the halogen from 2,4-dimethyl-7-chloro-1,8-naphthyridine. More drastic conditions resulted in extensive nuclear hydrogenation , as indicated in the following sequence of reactions. The hydrogenation of methyl-substituted

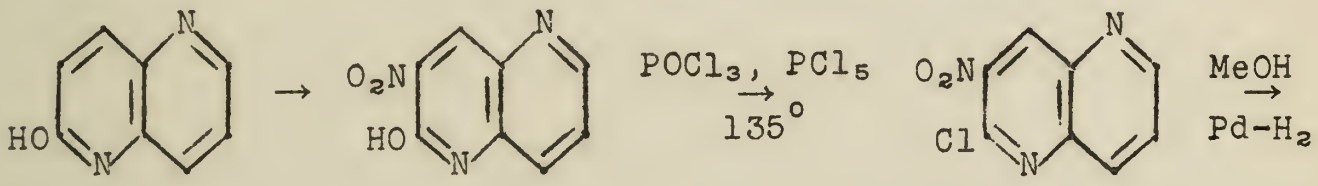


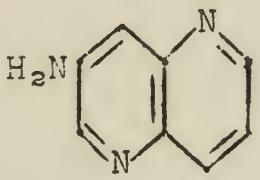




1,8-naphthyridines to the tetrahydro compounds occurred in a manner similar to that observed in the hydrogenation of the corresponding quinolines. The methyl groups deactivated the α- and γ-positions by an inductive effect and caused the hydrogenation to occur almost exclusively in the other ring.

An application of the dehalogenation reaction to the synthesis of therapeutics appears in the patent literature (20). 3-Amino-1,5-naphthyridine was prepared by the simultaneous dehalogenation and reduction of 2-chloro-3-nitro-1,5-naphthyridine.





BIBLIOGRAPHY

1. Reissert, Ber., 26, 2137 (1893).
2. Chichibabin, Ber., 57, 1168 (1924).
3. Seide, Ber., 58, 352 (1925).
4. Palazzo and Tamburini, Atti accad. Lincei, 20, I, 37; C. A., 5, 1586 (1911).
5. Seide, Ber., 59, 2465 (1926).
6. Ochiai and Miyaki, Ber., 74, 1115 (1941).
7. Sucharda, Kosmos (Lwow), 1920, 123; C. A., 22, 2948 (1928).
8. Koller, Ber., 60, 407 (1927).
9. Mazza and Migliardi, Atti accad. sci. Torino, 75, 438 (1940); C. A., 36, 5477 (1942).
10. Migliardi, Atti accad. sci. Torino, 75, I, 548 (1940); C. A., 38, 1507 (1944).
11. Schering-Kahlbaum A.-G., Ger. Patent 507,637; C. A., 25, 716 (1931).
12. Bobranski and Sucharda, Roczniki Chem., 7, 241 (1927); C. A., 22, 777 (1928).

13. Bobranski and Sucharda, Ber., 60, 1081 (1927).
14. Klisiecki and Sucharda, Roczniki Chem., 7, 204 (1927); C. A., 22, 777 (1928).
15. Deut. Gold- and Silber-Scheidenstalt, Brit. Patent 259,973; C. A., 21, 3425 (1927).
16. Koller, Ber., 60, 1572 (1927).
17. Koller, Ber., 60, 1918 (1927).
18. Koller and Kandler, Monatsh., 58, 213 (1931).
19. Miyaki and Kataoka, J. Pharm. Soc. Japan, 60, 367 (1940); C. A., 35, 1404 (1941).
20. Schering A.-G., Ger. Patent 700,862; C. A., 35, 7422 (1941).

Reported by Edgar Howard, Jr.
April 4, 1945

HYDROGENOLYSIS OF GROUPS ON THE BENZENE RING

I. Replacement of Halogen

Methods for the replacement of aromatic halogen groups by hydrogen may be divided into three general classifications: electrolytic, chemical and catalytic.

The electrolytic method has had very little application. Aryl bromides in alkaline methanol solution may be cleaved using palladium, copper or lead cathodes to give good yields of the desired hydrocarbon.

The most generally used chemical reduction of halogen groups involves the use of hydrogen iodide and phosphorus. Klages studied this reaction extensively and found the following trends.

(1) The ease of splitting out of halogen increases with the size from fluorine to iodine. In a compound containing different halogen groups those of higher weight can be selectively cleaved by control of temperature.

(2) The effect of temperature on the rate of reaction is considerable.

(3) The ease of splitting out of halogen is facilitated by small alkyl groups in the ortho and para positions. Alkyl groups in the meta position do not influence the reaction. If the alkyl groups in the ortho positions are large, steric hindrance decreases the ease of cleavage.

(4) Halogen atoms do not influence ease of cleavage of other halogens--bromobenzene, p-dibromobenzene, s-tribromobenzene and hexabromobenzene all being completely reduced at 300°.

(5) Hydroxyl and alkoxyl groups in ortho and para positions activate halogens more than alkyl groups do. Their effect in the meta position is small.

(6) The carboxyl group is indifferent.

(7) Nitro groups have no effect on replaceability by hydrogen but after reduction to amino groups a considerable effect is noted--an ortho or para amine group facilitating the removal of halogen.

The catalytic removal of halogen from aromatic compounds can be effected by a variety of catalysts under the proper conditions. Palladium on carbon, palladinized calcium carbonate, reduced nickel, colloidal palladium on gum arabic, palladinized barium sulfate and platinum black are among the most effective catalysts for removal of halogen by low pressure hydrogenation. In most cases alkaline alcohol as solvent greatly increases the yield, and a suspension of the compound in aqueous alkali ofter gives good results.

Schwenk, Whitman, Papa and Ginsberg have recently reported the replacement of halogen by hydrogen when compounds are treated with nickel-aluminum alloy (Raney) and aqueous alkali. This displacement is independent of the number, position, or presence of other groups. The reduction appears to be due to liberation of hydrogen which is then activated by the presence of the nickel. Addition of toluene or alcohol facilitates reductions of alkali-insoluble compounds. Other easily reduced groups, such as $-NO_2$, $-CHO$, $-CH=CH_2$, and $-COCH_3$, present in the compounds will be simultaneously reduced, but the unsaturated bonds in the ring are not affected.

Table I

Halogens

Compound	Product	Yield
1. Bromobenzene*	benzene	100%
2. m-Chlorobenzoic acid	benzoic acid	100%
3. p-chloronitrobenzene*	aniline	65%
4. p-chlorobenzaldehyde	toluene	60%
5. 5-chloro-2-hydroxybenzaldehyde	o-cresol	75%
6. p-bromoacetophenone*	ethylbenzene	67%
7. β-(p-chlorobenzoyl)-propionic acid	γ-phenylbutyric acid	70%

*25 cc. of alcohol used as solvent.

II. Hydrogenolysis of Groups other than Halogen by Means of Raney Alloy and Aqueous Alkali.

Hitherto, displacement of sulfonic acid groups by hydrogen has been limited to α-sulfonic acid groups in naphthalene, only a few instances of similar displacements being noted for β-compounds. By the method of Schwenk and coworkers, α- and β-naphthalenesulfonic acid groups as well as benzenesulfonic acid groups are replaced.

Table II

Sulfonic Acids

Compound	Product	Yield
1. benzenesulfonic acid	benzene	10%
2. o-sulfobenzoic acid	benzoic acid	40%
3. m-sulfobenzoic acid	benzoic acid	50%
4. naphthalene β-sulfonic acid	naphthalene	40%
5. 2-naphthol-6-sulfonic acid	β-naphthol	30%
6. 2-naphthol-3-6-disulfonic acid	β-naphthol	30%

Two organometallic compounds were investigated, arsanilic acid and phenyl mercuric acetate, the former yielding aniline and

Table I

[illegible]

[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]

[illegible]

[illegible]

Table II

[illegible]

[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]

the latter diphenyl upon reduction.

Of the compounds studied only halogen and sulfonic acid groups are displaced by hydrogen from mono-substituted benzene derivatives. In disubstituted compounds alkoxyl groups may also be displaced--this depending on the nature and position of the other substituent. In general, when meta-directing groups are present in the ortho- and para-positions to the alkoxyl group displacement occurs. In compounds having an ortho-para directing group as the other substituent, or in compounds having a meta-directing group in the meta position, no displacement occurs.

Table III

Disubstituted Benzene Derivatives

Compound	Product	Yield
1. o-methoxybenzaldehyde	o-cresylmethylether	45%
	toluene	15%
	benzoic acid	20%
2. o-methoxybenzoic acid	benzoic acid	100%
3. o-methythiobenzoic acid	benzoic acid	75%
4. o-benzyloxybenzoic acid	salicylic acid	75%
5. diphenyl ether	recovered unchanged	
6. p-methoxybenzyl alcohol*	p-cresylmethyl ether	50%
	toluene	15%
7. p-methoxybenzaldehyde	p-cresyl methyl ether	30%
	toluene	45%
8. p-nitroanisole*	p-anisidine	70%
	aniline	20%

*25 cc. of alcohol used as solvent.

Benzyloxyl compounds are split in the same manner as observed in other reduction methods, o-benzyloxybenzoic acid yielding toluene and salicylic acid.

The introduction of a hydroxyl or alkoxyl group as the third group in the ring alters considerably the course of the displacement reaction. Thus, in trisubstituted benzene derivatives of the general formula $RC_6H_3R'R''$, where R is a meta-directing group other than carboxyl, R' is either an hydroxyl or alkoxyl group, and R'' is an alkoxyl group, displacement of the meta-directing groups by hydrogen was observed, this displacement being independent of the position relationship of the three groups.

BIBLIOGRAPHY

Klages and Liecke, J. prakt. chem., 61, 307-329 (1900).
Sabatier and Mailhe, Compt. rend., 138, 245 (1904).
Kelber, Ber., 50, 305 (1917).
Rosenmund and Zetzsche, Ber., 51, 578 (1918).

Ellis, Hydrogenation of Organic Compounds, p. 259.
DeLange, Rec. trav. chim., 45, 19-60 (1926).
Busch and Schmidt, Ber., 62B, 2612 (1929).
Gautier, Bull. Soc. Chim., [5], 4, 219-225 (1937).
Busch and Weber, Ber., 70B, 744 (1937).
Vavon and Mathieu, Compt. rend., 206, 1387 (1938).
Busch, Weber, and Zink, J. prakt. chem., 155, 163-176 (1940).
Miyaki and Kataoka, J. Pharm. Soc. Japan., 60, 367 [C.A., 35, 1404 (1941)].
Schwenk, Papa and Whitman, J. Org. Chem., 7, 588 (1942).
Schwenk, Papa, Whitman, and Ginsberg, J. Org. Chem., 9, 1 (1944).
Schwenk, Papa, Whitman, and Ginsberg, J. Org. Chem., 9, 175 (1944).

Reported by John M. Stewart
April 11, 1945.

TANNINS AND WOOD PIGMENTS

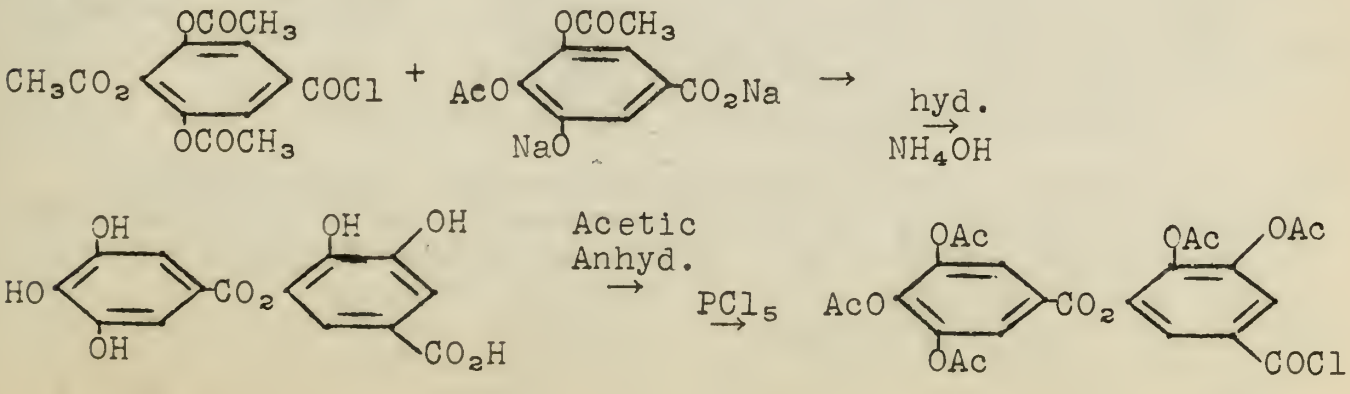
The natural tannins are polar-solvent-soluble extractives from plant tissue which are strongly absorbed and irreversibly fixed by raw skins, converting the proteins of the hide to tough, insoluble leather. All tannins are polyhydroxy phenols, are easily oxidized, and exist as amorphous, often hygroscopic solids which are difficult to purify without effecting decomposition and which, in many cases, decompose in air and light. While the tannins have been the subject of much study, their intractable properties, the failure of chemists to recognize the existence of different types of tannins, and the prevalence of theoretical speculation without adequate experimentation contributed to general confusion in the field. In the last fifteen years, however, research in tannin chemistry has been based on more careful and constructive work, and some progress seems apparent.

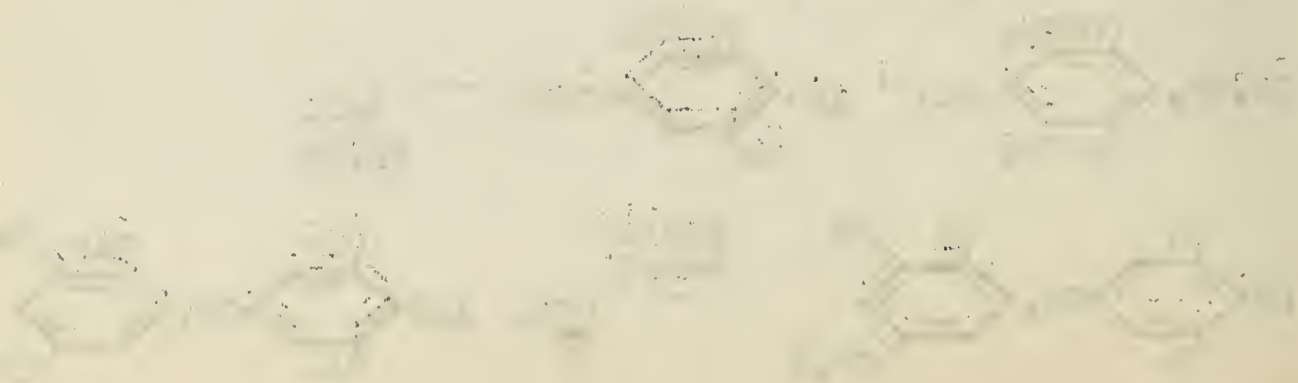
Classification of Tannins. On a chemical basis the natural tannins have been divided by Everest and Perkin into three groups.

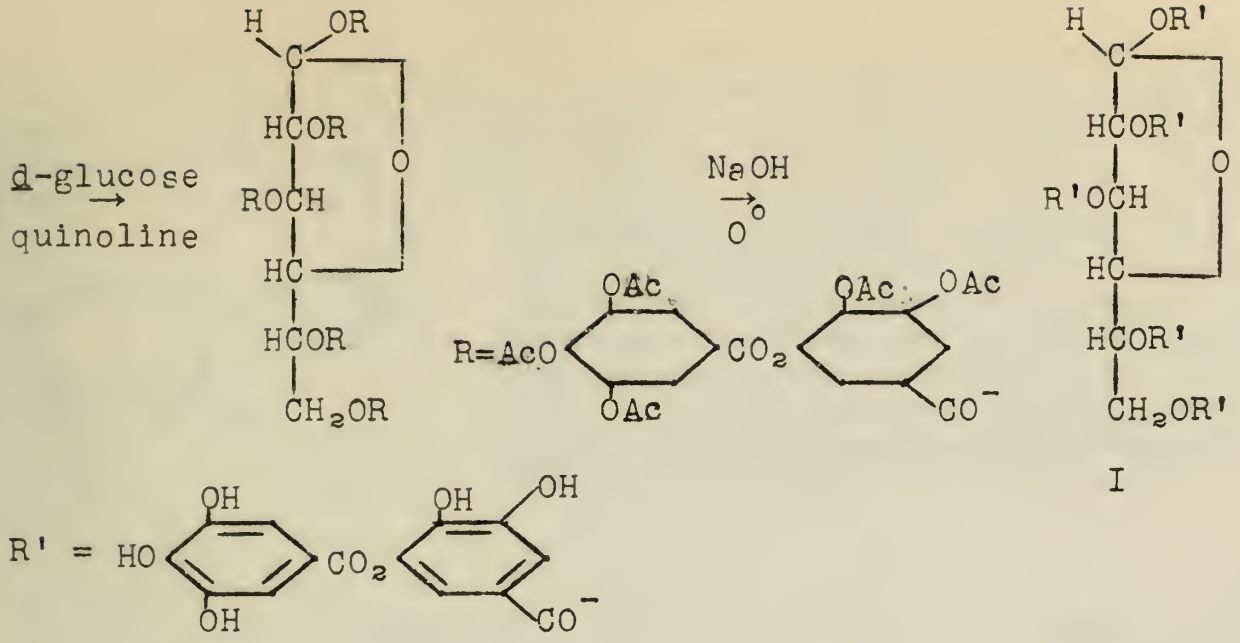
I. Tannins related to depsides
II. Tannins related to diphenyldimethylolid
III. Phlobaphene-producing tannins or phlobatannins

Tannins of groups I and II are hydrolyzed by boiling dilute mineral acids to give glucose and gallic acid and glucose, gallic acid, and ellagic acid, respectively; the phlobatannins are completely converted by this treatment to darkly colored, insoluble phlobaphenes. Other chemical methods of differentiating these classes are given by Russell.

Tannins Related to Depsides. The only natural tannin which is known to be related to the depsides is gallotannin, which occurs chiefly in the galls on the leaves and buds of certain species of oak and sumac. Fischer and Freudenberg found that gallotannin, on hydrolysis with dilute mineral acids, yielded nearly one molecule of glucose to ten molecules of gallic acid. Since Herzig and Tscherne had previously shown that the hydrolysis of completely methylated gallotannin yielded 3,4,5-trimethoxygallic acid and 3-hydroxy-4,5-dimethoxygallic acid, Fischer postulated the structure of gallotannin as penta-m-digalloylglucose (I). With Bergmann and Lipschitz he prepared the compound in the following manner.



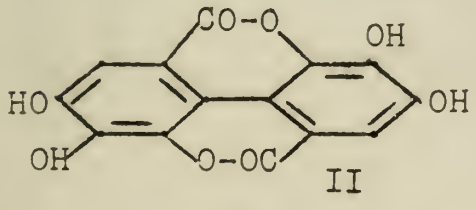




Although both are amorphous the synthetic product compared very closely with natural gallotannin.

While Fischer also prepared glucose pentagallate, he did not evaluate it as a tanning agent, and Russell, with several others (1942-1944) in a study directed toward the correlation of chemical constitution and tanning effect, has prepared and tested a series of simple esters and polyesters of gallic acid. It has been found that tanning properties are not exhibited by the simple gallates but are shown increasingly as the number of galloyloxy groups in the molecule is increased. Various pentagallates of glucose and mannose and a tetragallate of arabinose have tanning properties equal to gallotannin, but, surprisingly, fructose pentagallate is not a tanning agent.

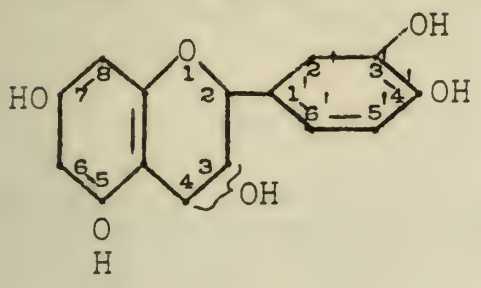
Tannins Related to Diphenyldimethylolid. Ellagitannin, occurring widely but in greatest amount in the nuts, pods, and woods of various trees, notably chestnut and oak, is the only natural tannin which has been identified positively as being related to diphenyldimethylolid. On acid hydrolysis it gives ellagic acid (II), gallic acid, and glucose and is probably a glucoside (Russell, 1935; Reichel, 1941). Although the structure of the tannin is not known, the synthesis of ellagic acid has been effected by the oxidation of gallic acid with arsenic acid, iodine and water, or potassium persulfate.



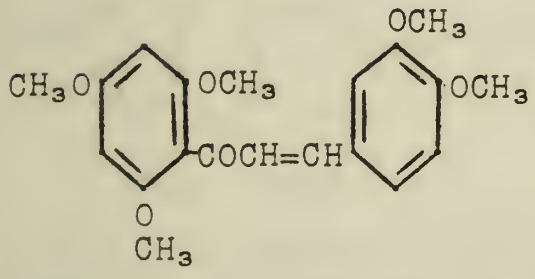
II

Phlobatannins. The remaining known natural tannins are all phlobatannins and are characterized by the property of forming insoluble phlobaphenes on treatment with boiling dilute mineral acids. A typical tannin of this class is catechu tannin which occurs with a pigment, catechin, in Uncaria gambier. Since both the tannin and catechin give the same products on alkali fusion it is of interest to examine the chemistry of catechin itself.

Catechin ($C_{15}H_{14}O_6$) is a difficulty-crystalline material which gives phloroglucinol and protocatechuic acid on alkali fusion. Oxidation by permanganate of its tetramethyl ether produces veratric acid and phloroglucinol dimethyl ether, leading Perkin to ascribe to it the formula 3 (or 4) 5,7,3',4'-pentahydroxyflavan (III). Evidence for this formulation came from Freudenberg who found that reduction of catechin tetramethyl ether and methylation of the product gave a compound (V) identical with that obtained by the reduction of 2',4',6',3,4-pentamethoxychalcone (V) with hydrogen and platinum.

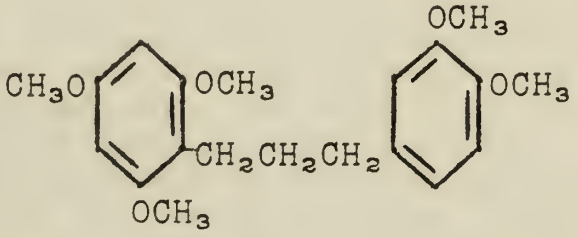


III



V

$\xrightarrow[Pt]{H_2}$

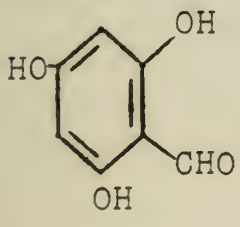


IV

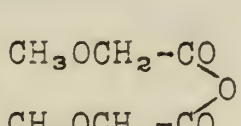
$\xleftarrow{\text{methyl-lation}}$

$\xleftarrow[Pt]{H_2}$ III

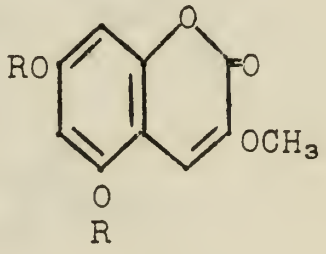
The final proof of structure of catechin was the synthesis by Freudenberg, Fikentscher, Harder, and Schmidt of its pentamethyl ether (VI) by reduction of the pentamethyl ether of cyanidin chloride (VII) of known structure, previously prepared by Willstätter, Zechmeister, and Kindler. The essential steps in the entire synthesis are.



+

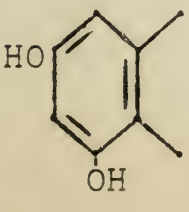


$\xrightarrow{CH_3COCH_2CO_2Na}$ Perkin Cond.

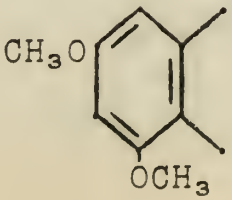


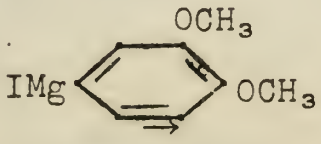
R = CH_3OCH_2CO-

$\xrightarrow{NaOH}$

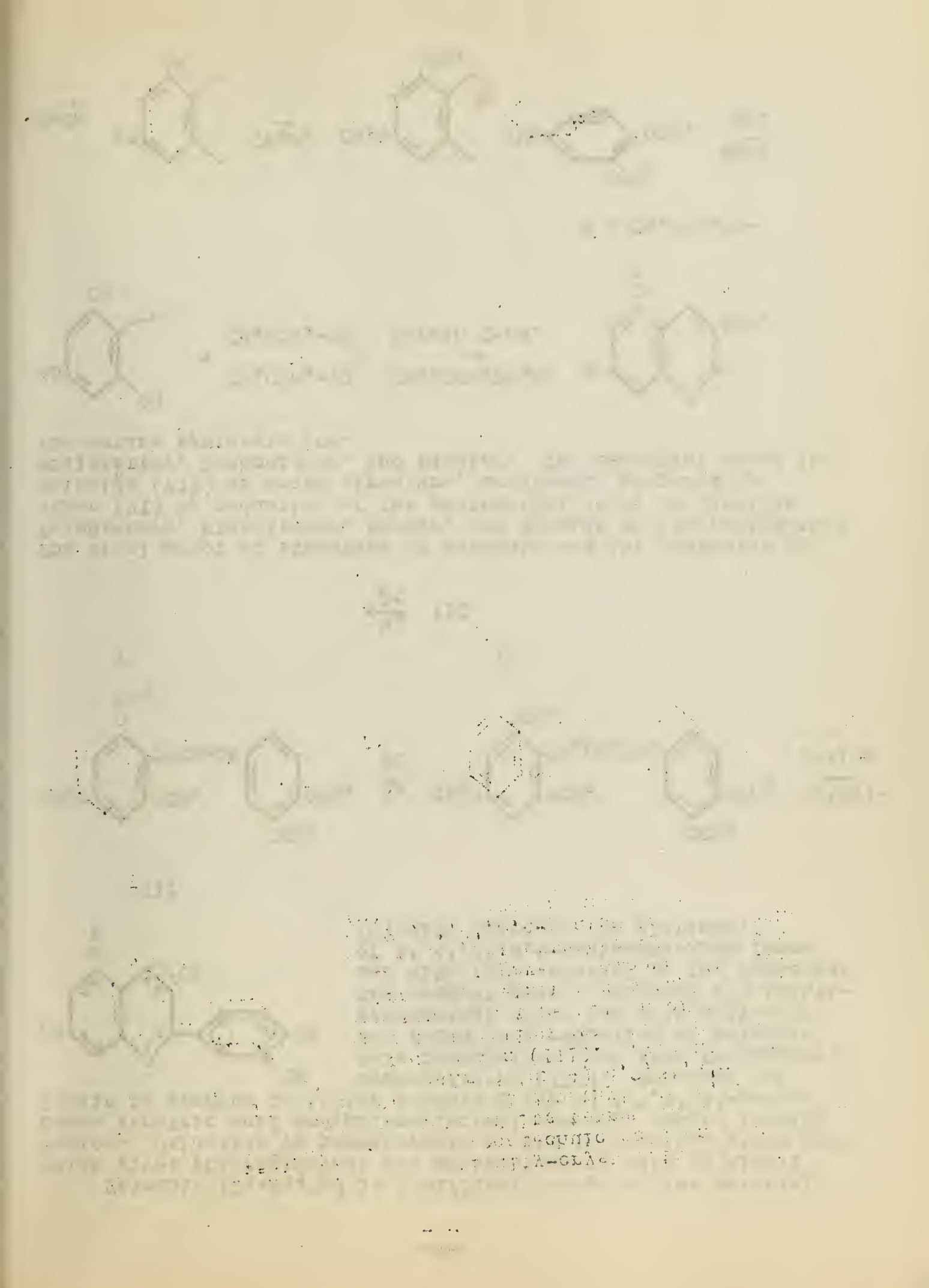


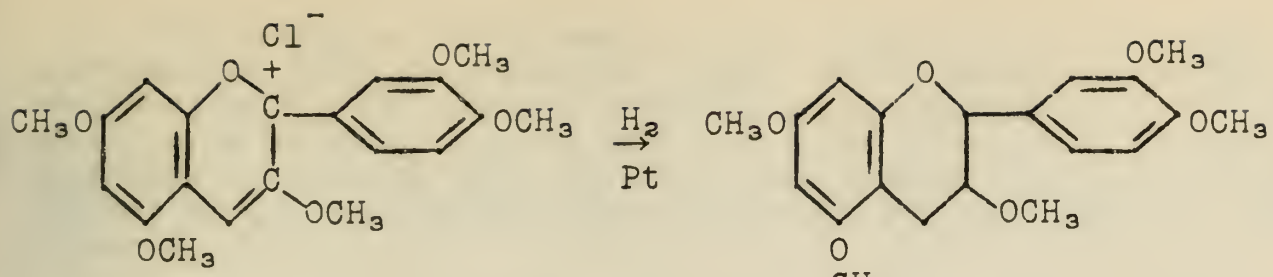
$\xrightarrow{CH_2N_2}$





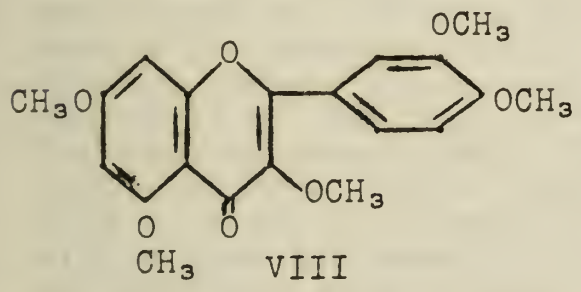
$\xrightarrow[HCl]{AgCl}$





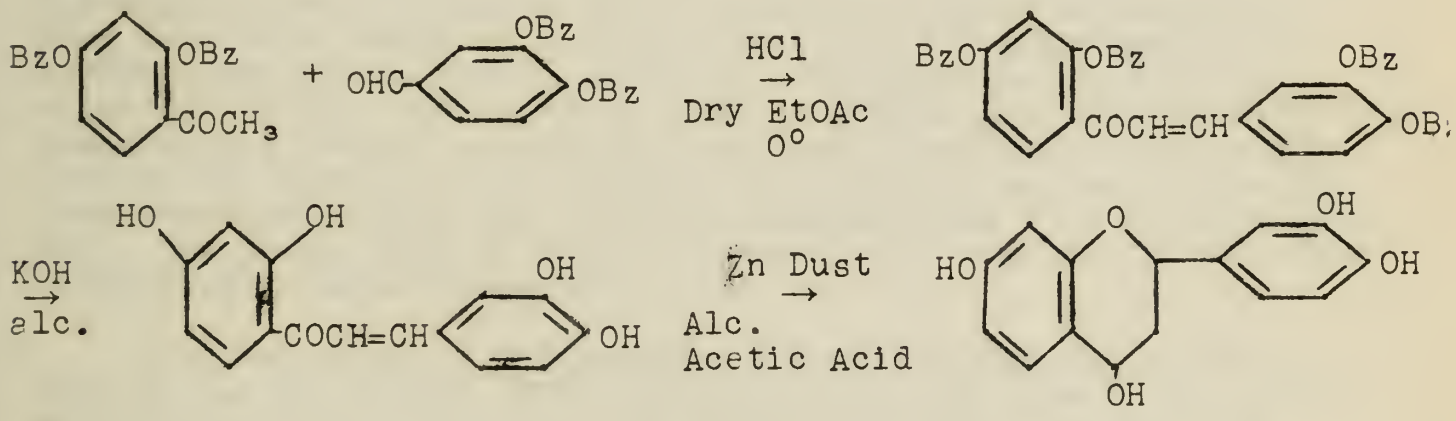
VII VI

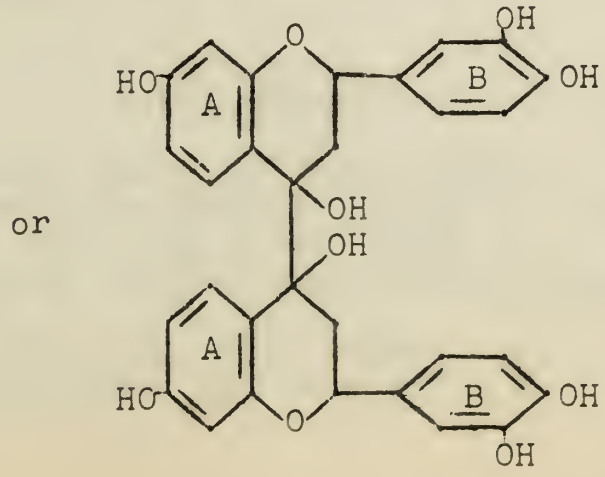
Similarly catechin was obtained from cyanidin chloride, and catechin pentamethyl ether was obtained from quercitin pentamethyl ether (VIII).



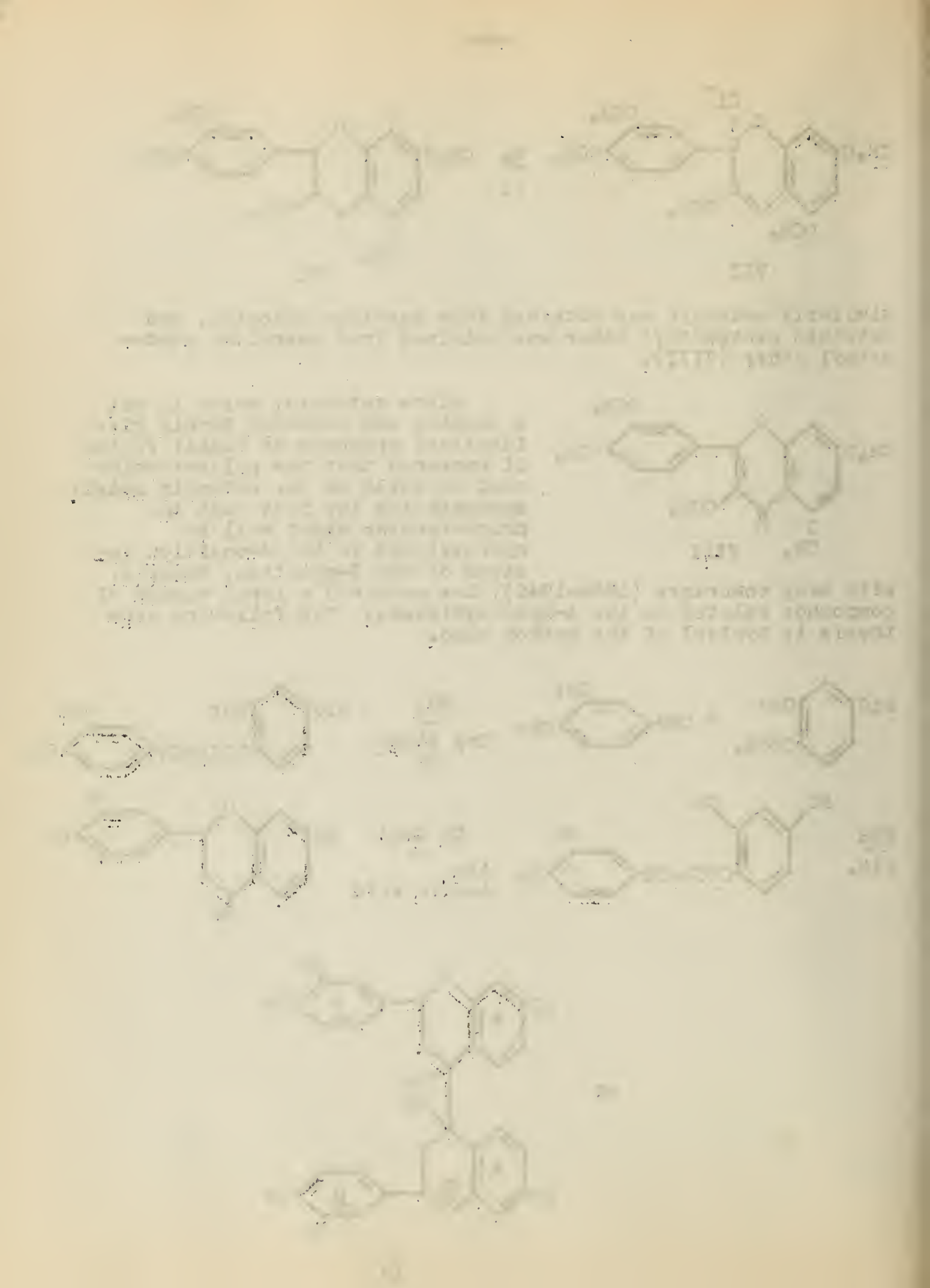
VIII

Since catechin, which is not a tannin, and catechin tannin give identical products on alkali fusion it appeared that the phlobatannins must be built on the catechin model. Appreciating the fact that the phlobatannins might well be hydroxylated in the 4-position instead of the 3-position, Russell, with many coworkers (1934-1942), has prepared a large number of compounds related to the 4-hydroxyflavans. The following synthesis is typical of the method used.





IX



The evidence is in favor of the formation of the bis-flavpinacol type of structure (IX). The product is amorphous while catechin and similar compounds are crystalline; the reduction of various ketones under similar conditions produces bis-type compounds; and, finally, the hydrogen uptake in the reduction is only sufficient to account for formation of the pinacol.

The series of flavpinacols has been extended by the use of o-hydroxylacetophenone, resacetophenone, phloracetophenone, and gallacetophenone as ketones and protocatechualdehyde, vanillin, and p-hydroxybenzaldehyde as aldehydes in various combinations in the above synthesis. With the exception of the water-insoluble flavpinacols from the latter two aldehydes, the products are amorphous, water-soluble compounds which tan leather, have absorption spectra very close to the natural tannins, and, in general, have a close qualitative similarity to them. The hydroxyls at positions 3' and 4' in ring B (IX) are sufficient for tanning properties. The number and disposition of substituents in ring B have a greater effect on solubility than in ring A, while the number and disposition of substituents in ring A have the greatest effect on color, which is intensified by increased substitution in that ring.

Using similar technics to those described above Russell and his students have prepared various polyhydroxy chalcones, flavanones, and anthocyanidins, as well as one flavpinacol, from 2,5-dihydroxyacetophenone and a variety of hydroxy aldehydes. They have also prepared a number of substituted 2-phenyl-1-α-naphthopyrylium chlorides (analogs of 2-phenylbenzopyrylium chloride) by the condensation with anhydrous hydrogen chloride of β-naphthol aldehyde and substituted acetophenones and have effected the synthesis of a number of chalcones and one flavanone from 9-anthraldehyde and various acetophenones in a similar manner. The properties of these compounds are similar to the corresponding benzene compounds.

The mechanism of phlobaphene formation from the phlobatannins is not clear. The available data indicate that a polymerization occurs, eliminating water, in which the phenolic groups do not take part.

BIBLIOGRAPHY

Fischer and Freudenberg, Ber., 45, 2709 (1912).
Fischer, Bergmann, and Lipschitz, Ber., 51, 45 (1918).
Fischer and Bergmann, Ber., 51, 1760 (1918).
Freudenberg, Fikentscher, Harder, and Schmidt, Ann., 444, 135 (1925).
Herzig and Tscherne, Ber., 38, 989 (1905).
Reichel, Naturwissenschatten, 29, 16 (1941).

Russell, J. Chem. Soc., 1934, 218.
Russell and Todd, J. Chem. Soc., 1934, 1066, 1506; 1937, 421.
Russell, Todd, and Wilson, J. Chem. Soc., 1934, 1940.
Russell, Chem. Rev., 17, 155 (1935).
Russell and Clark, J. Am. Chem. Soc., 61, 2651 (1939).
Russell and Speck, J. Am. Chem. Soc., 63, 851 (1941).
Russell and Happoldt, J. Am. Chem. Soc., 64, 1101 (1942).
Russell and Tebbens, J. Am. Chem. Soc., 64, 2274 (1942); 66, 1866 (1944).
Russell, Tebbens, and Arey, J. Am. Chem. Soc., 65, 1472 (1943).
Willstätter, Zechmeister, and Kindler, Ber., 57, 1938 (1924).
Wise, "Wood Chemistry," Reinhold Publishing Corporation, New York, 1944, Chapter 12, p. 385.

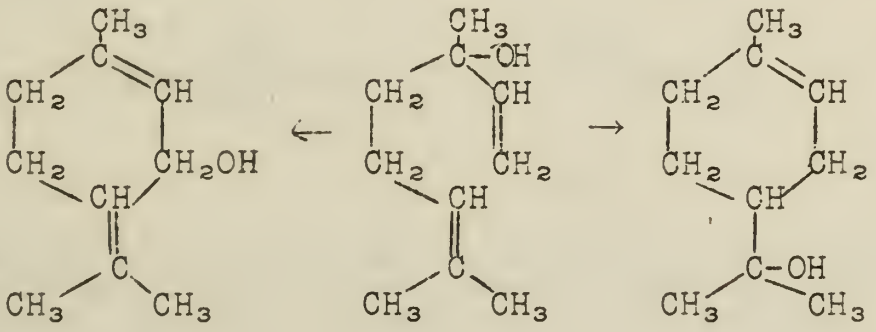
Reported by D. A. Shepherd
April 11, 1945

SYNTHESES OF ALIPHATIC TERPENE ALCOHOLS FROM ISOPRENE

Lennartz, Research Institute of Chemical Therapeutics, Frankfurt

Isoprene is a structural unit of terpenes, carotinoids and rubber. Many investigators have devoted considerable time to the identification of naturally occurring terpenes and terpene alcohols, but only in recent years have investigators prepared and identified such compounds from the fundamental unit, isoprene. Also much thought has been given to the possible biological genesis of terpenes and terpenoids from 2-methylbutadiene or its derivatives and to the possible mechanism of the reaction.

Wagner-Jauregg treated isoprene <u>in vitro</u> with 0.3 per cent sulfuric acid in glacial acetic acid and was able to isolate and identify geraniol (I) and α-terpineol (II) from the complex mixture of products obtained. Cyclic terpene ethers, alcohols and

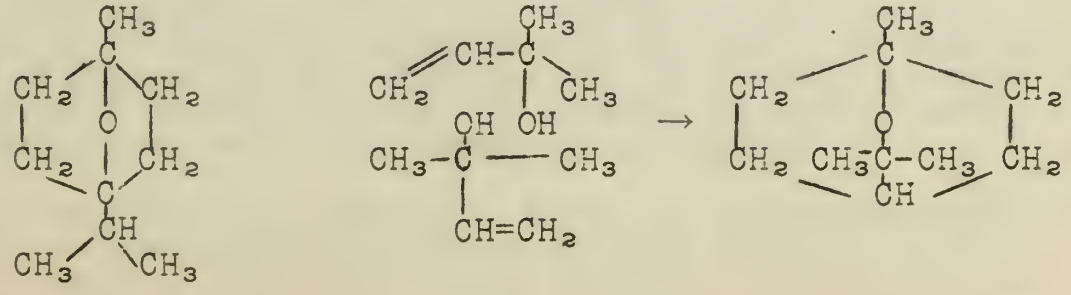


I VII II

hydrocarbons were indicated to be present in the reaction mixture, but definite known compounds were not isolated.

Wagner-Jauregg suggested that the complicated composition of the reaction mixture obtained by reaction of isoprene in sulfuric acid-glacial acetic acid could be explained by simultaneous polymerization and hydration of isoprene under ideal conditions for isomerization (cyclization, migration of double bonds and acetylation) and for the splitting out of acetic acid from the molecule.

By treatment of isoprene with dilute sulfuric acid a mixture of hydrocarbons and ethers was obtained in addition to free alcohols. It was possible to isolate 1,4-cineol (III) and 1,8-cineol (IV) through their addition complex with ferrocyanic acid. The identity with natural products was shown through crystalline



III IV

derivatives. In the laboratory, 1,4-cineol has been prepared by the elimination of water from 1,4-terpin by means of oxalic acid. 1,4-Terpin might possibly be an intermediate in the synthesis of 1,4-cineol from isoprene. The formation of 1,8-cineol could be indicated through the loss of water between two molecules of dimethylvinylcarbinol (V).

The later research of Favorski and Lèbèdèva definitely indicated that prenol (VI) (2-methylbutene-(2)·ol-4) was an intermediate in the synthesis of terpene alcohols from isoprene. Favorski and Lèbèdèva isolated from the reaction products obtained by shaking dimethylvinylcarbinol with 20 per cent sulfuric acid, in addition to isoprene and dimethylvinylcarbinol, the terpene alcohols linalool (VII) geraniol (I), and terpin hydrate (1,8-terpin). The allylic rearrangement of dimethylvinylcarbinol (V) to prenol (VI) was shown to be reversible. This transformation

$$CH_3-\underset{\underset{OH}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH=CH_2 \rightleftarrows CH_3-\overset{\overset{CH_3}{|}}{C}=CHCH_2OH$$

V VI

was also carried out in 50 per cent yield in the presence of sulfuric acid in glacial acetic acid by Lennartz in order to identify prenol obtained synthetically from isoprene by treatment of the hydrocarbon with 0.9 per cent sulfuric acid in glacial acetic acid in the presence of inhibitors such as hydroquinone and cupric acetate. Lennartz concluded that water adds to isoprene in the 1,2-manner rather than in the 1,4-manner and that 1,2-addition is followed by allylic rearrangement.

In addition to the acetate of prenol there was obtained in good yield from the reaction mixture geraniol (I), two other primary aliphatic terpene alcohols (designated as EI and EII)with a lavender odor, isomeric with geraniol but lower boiling; the sesquiterpene alcohol, Farnesol (VIII), and an aliphatic diterpene alcohol $C_{20}H_{34}O$. Linalool (VII) and another tertiary terpene alcohol were also identified.

$$CH_3-\overset{\overset{CH_3}{|}}{C}=CH-CH_2CH_2-\overset{\overset{CH_3}{|}}{C}=CH-CH_2-CH_2-\overset{\overset{CH_3}{|}}{C}=CHCH_2OH$$

VIII

For investigation of the ester mixture resulting from the polymerization of isoprene it was found advisable to separate by fractional distillation the acetates of the terpene alcohols from the greater part of the hydrocarbons formed simultaneously, which, in this connection, were not further investigated.

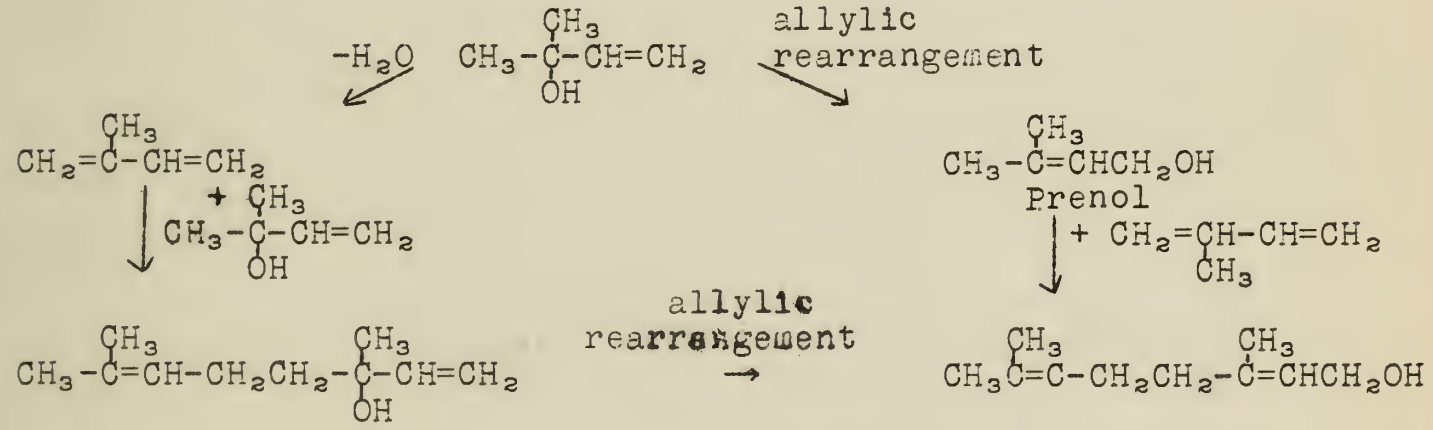
Geranyl acetate was separated from the crude ester mixture of monoterpene alcohols and identified through a crystalline derivative compared with the natural product. The other two primary alcohols (EI and EII) which were isomeric with geraniol also gave crystalline derivatives but could not be identified with

certainty.

The mixture of tertiary alcohols and hydrocarbons remaining after the separation of the primary alcohols was rearranged according to the procedure of Ruzicka and Firmenich by means of phosphorous tribromide in pyridine followed by potassium acetate in acetone. After the separation of the primary alcohols with phthalic anhydride two fractions were obtained by fractional distillation. The first of these showed extensive agreement in physical properties with the primary alcohol, EI, mentioned earlier, and the second proved to be geraniol. Hence one of the tertiary alcohols was linalool (VII). Thus the suggestion made by Wagner-Jauregg that linalool might be a precursor of geraniol seems reasonable.

The conclusion of Wagner-Jauregg that hydration of isoprene takes place at least in part before the dimerization was confirmed by Lennartz, in that, as a result of allylic rearrangement of dimethylvinylcarbinol, there appears beside prenyl acetate a small amount of terpene acetate having the boiling point of geranyl acetate as well as isoprene. Undoubtedly water is split from a part of the carbinol and the resultant isoprene can react with prenyl acetate in the 1,4-manner. Lennartz also demonstrated that the primary dimethylvinylcarbinol could react with isoprene to form the tertiary alcohol, linalool (VII, which, in turn, rearranges to peranyl acetate.

The following diagram summarizes the possible paths by which dimethylvinylcarbinol may form geraniol.



Linalool

Geraniol

The higher-boiling fractions of terpene alcohols which contained the sesquiterpene acetate of farnesol was separated into three fractions through high vacuum distillation. Farnesol (VIII) was obtained from the middle fraction and identified by comparison with the natural substance. The origin of farnesol can be thought of in analogy to gernaiol as resulting from isoprene and geraniol. The continuation of long chains with isoprene leads to geranylgeraniol (protophytol) and higher terpene alcohols.

A diterpene fraction was isolated which contained an alcohol

$C_{20}H_{34}O$, which was almost identical with geranylgeraniol prepared by Ruzicka and Firmenich from farnesylacetone and acetylene. The higher boiling fractions contained only cyclic products and hydrocarbons which were not investigated.

BIBLIOGRAPHY

Lennartz, Ber., 76B, 831 (1943).
Wagner-Jauregg, Ann., 496, 52 (1932).
Wallach, Ann., 392, 62 (1912).
Favorski and Lébédéva, Bull. Soc. chim. France, Mém., (5) 6, 1347 (1939).
Späth and Bruck, Ber., 71, 2709 (1938).
Lennartz, Ber., 76, 248 (1943).
Ruzicka and Firmenich, Helv. chim. Acta, 22, 392 (1939).
Semmler and Jones, Ber., 47, 2081 (1914).

Reported by H. W. Johnston
April 18, 1945

THE STRUCTURE OF SEROLOGICAL PRECIPITATES

Linus Pauling, California Institute of Technology, Pasadena

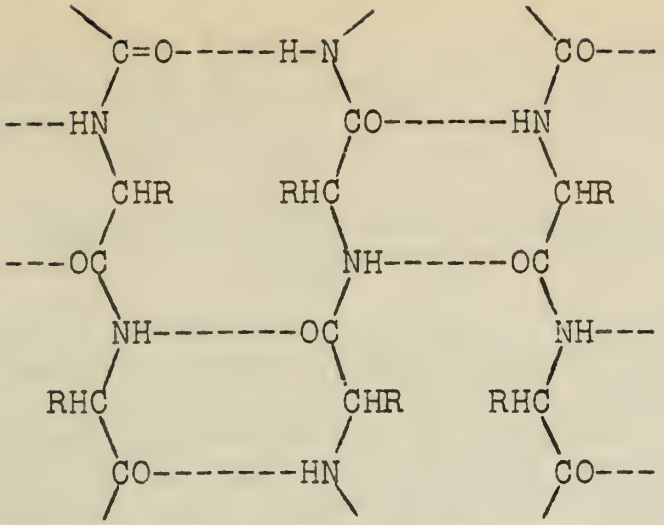
In a paper appearing in 1940 Pauling developed and discussed a detailed theory of the structure and process of formation of antibodies and the nature of serological reactions which is more definite and more widely applicable than any earlier theory. It is compatible with our present knowledge of the structure of simple molecules as well as with most of the empirical information about antibodies. It must be pointed out that the experimental observations in the field of immunology are so complex and so extensive that up to the present time no one has been able to deduce a theory of structure from the observational material alone.

Anti bodies are known to be of the same amino-acid composition as one or the other of the fractions of serum globulin of the animal producing the serum. The present and quantitative treatment is based on the fraction which has a molecular weight of about 160,000 (rabbit, monkey) and has a composition similar to that of the gamma fraction of serum globulin (Svedberg).

The fundamental assumption is that in the antibody molecule the order of amino acid residues in the polypeptide chain is exactly the same as in the normal globulin molecule and differs from it only in the configuration of the chain. Thus, in directing the folding or coiling of the polypeptide chain of the antibody the function of the antigen molecule is like that of the polypeptidases in the determining the configuration of the normal globulins.

The chemical evidence and the meager x-ray data support the polypeptide chain theory of protein structure. It is also well established that the native proteins have definite configurations, being coiled in a definite way and held in position by forces acting between parts of the chain. It should be noted here that the phenomena of denaturation involves the loss of configuration by partial or complete uncoiling of the chains.

Hydrogen bonds probably are the strongest of the forces involved in the retention of the native configuration. They may be formed by the carbonyl and imino groups of the peptide chain as well as by carboxy, amino, hydroxy, and other oxygen and nitrogen containing groups in the side chains of the amino acid residues. The most stable configuration will be that in which as many strong hydrogen bonds as possible exist. Below is illustrated an idealized case showing the formation of compact layers.



Inspection of proline and hydroxyproline stereo-models shows that they are capable of causing the polypeptide chain to turn through an angle of 180 degrees thus enabling it to fold back on itself.

To account for the formation of a great many different antibodies from the same globulin molecule it is further assumed that in the globulin molecule the amino acid residues are so arranged that a preponderance of proline, hydroxyproline and large R-group containing amino acids occur in the end-group structures of the polypeptide chain. These end-group structures must contain about 200 amino acid residues. Such an arrangement allows for a more stable central structure and for less stable end-group structures in which more possible configurations exist due to the skewed arrangements brought about by the steric interference of these large groups.

In order that the antibody be able to form a precipitate with the antigen more than one region of surface configuration complimentary to the antigen is required. The rule of parsimony suggests only two such regions; and, indeed, the experimental observations can be reconciled to such a reasonable assumption.

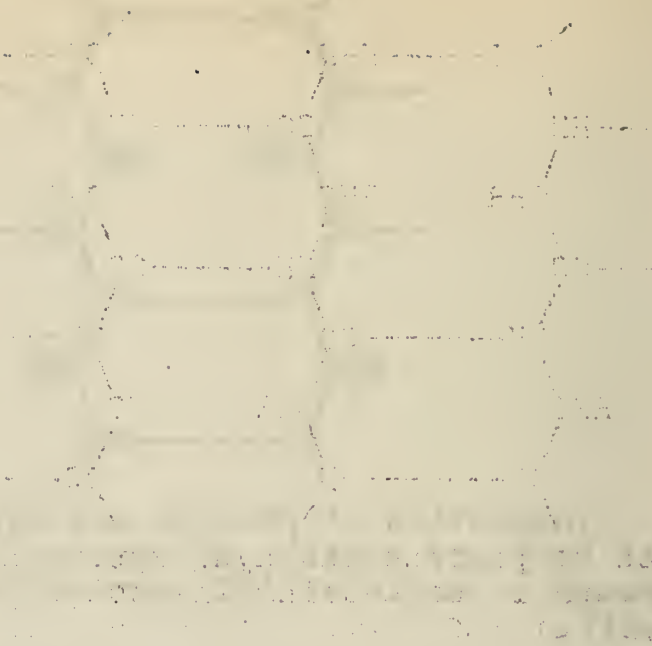
The framework theory is based on the idea that the precipitate is a network of antibody and antigen molecules in which each antibody molecule grasps two antigen molecules and the antigens are grasped by several antibody molecules. Precipitates with all intermediate structures are possible depending upon the antibody/antigen ratio and other factors in effect during their formation.

Some prediction of the theory which are verified by existing experimental data are the following:

1. Serum homologous to a given antigen must not be homogeneous, but heterogeneous, containing antibody molecules of greatly varied configurations.

2. Antigens are multivalent while antibodies are bivalent.

3. For idealized spherical molecules with the antigen equal to or smaller than the antibody, the ratio of antibody in

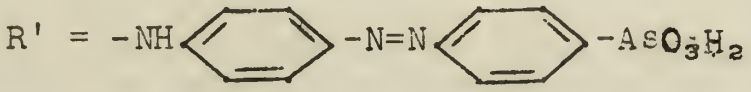


the saturated precipitate must be larger than two and but not more than six. Considering the many deviations from ideality, this is in good agreement with observed values which all lie within 2.5 and 15.

4. One antigen molecule acts as the template for the formation of both end-group structures of the antibody molecule.

Quantitative study of serological properties is complicated by the fact that the both antibody and antigen molecules are proteins. The discovery by Landsteiner (1932) that anaphlyxis could be produced by resorcinol or tyrosine coupled to two haptenic groups which had been present in the antibody-producing antigen provided a convenient point of departure for developing means of obtaining quantitative data.

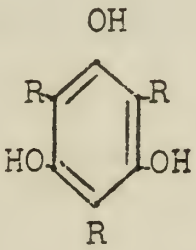
The following hapten groups were chosen:



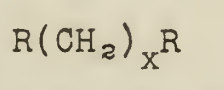
The antisera are prepared in the usual way from sheep serum. Precipitation with the following types of simple molecules is then studied.

X=OH, NH_2

(I)



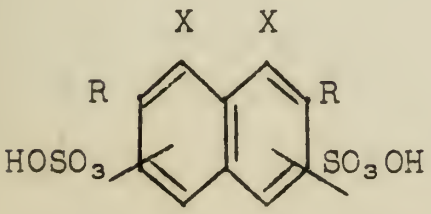
(II)



x = 0 to 8

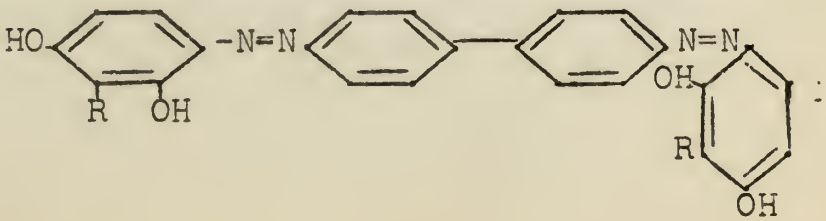
(III)

(IV)

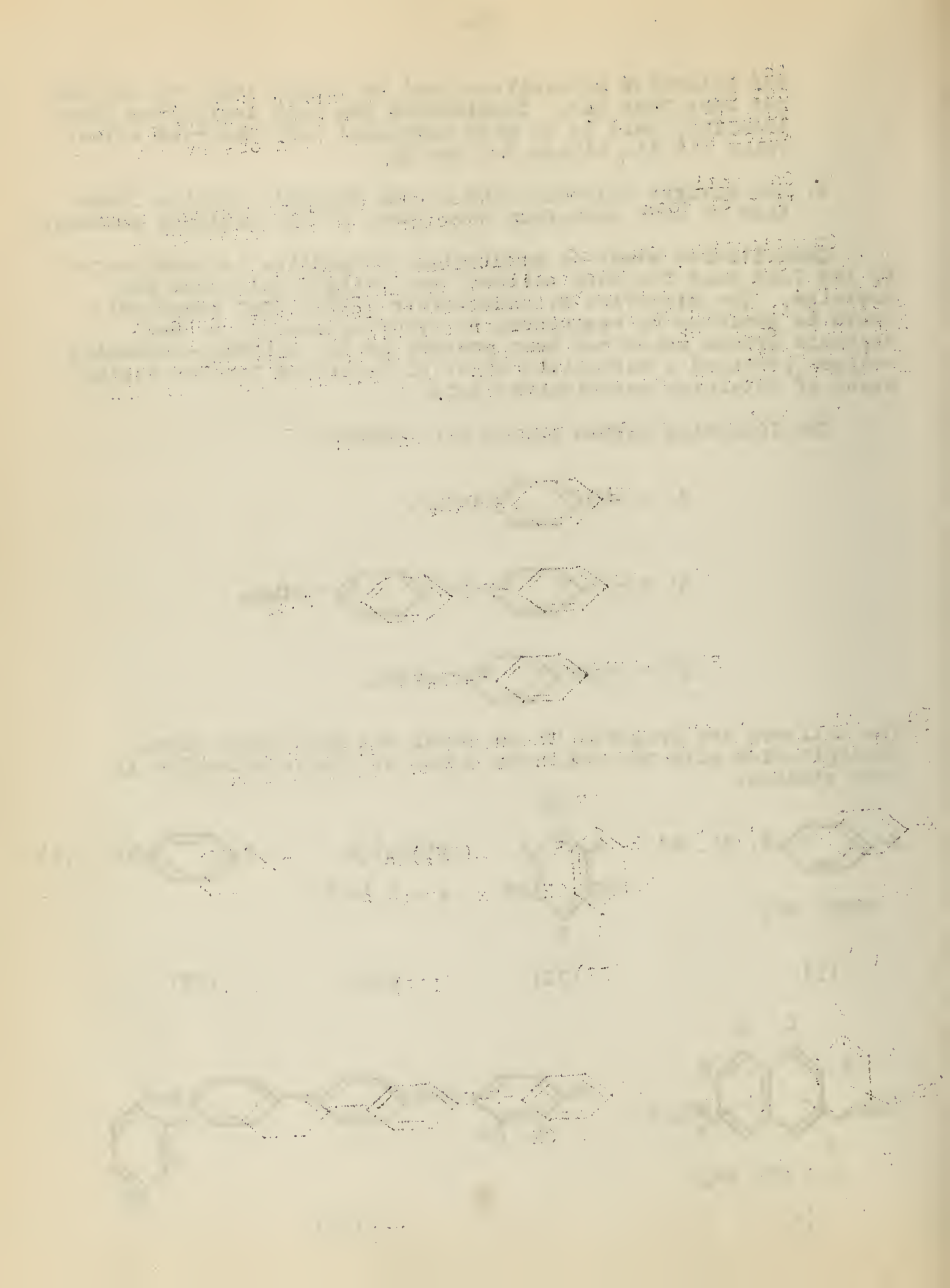


X = OH, NH_2

(V)



(VI)



None of the mono-haptenic substances causes precitation but all of the poly-haptenic substances do, with those of type II and VI being the most effective. The mono-haptenic substances however inhibit the precipitation of the antisera by either the antigen or poly-haptenic substances. Studies of the inhibiting power of a number of these substituted simple mono-haptenic substances has shown those with *para* substitutients to be the most active; *para* > *meta* > *ortho* and, as an approximation *para* = 2x *meta* = 4x *ortho*. *para*-Substitutients in azophenylarsonic acid in order of decreasing inhibiting power are: $HOC_6H_4N_2$, CH_3CONH, NO_2, C_6H_5CONH, I, Br, Cl, CH_3, OH, H, NH_2, COOH.

Precipitation of a mixture of two specific antisera by a di-hapten of type V containing the two specific haptenic groups has been studied also. The effective antibody valence was 2.8. Precipitation of either pure antisera by this molecule does not occur, and its presence inhibits precipitation of each pure antisera by its antigen. Further the precipitates are soluble in the presence of a large excess of antisera. This demonstrates that both haptenic groups enter the action and that both are essential. It is also clear evidence against the formation of insoluble protein-dye complexes as first suggested by Landsteiner.

Calculation of the antibody-hapten bond strength constants for each hapten and the heterogeneity index for the antisera has been made.

BIBLIOGRAPHY

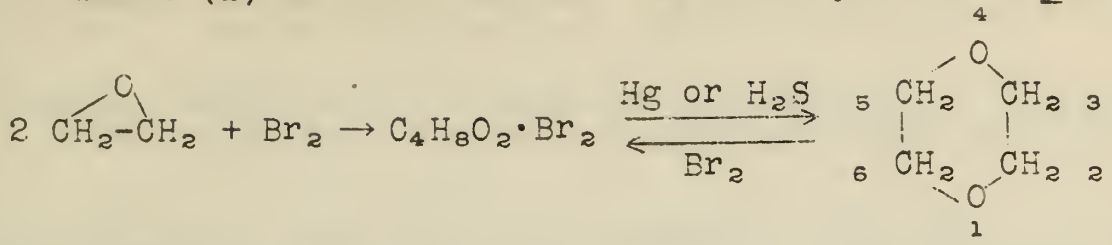
Pauling, *et al.*, J. Am. Chem. Soc., 62, 2643 (1940); 64, 2994, 3003, 3010, 3015 (1942); 65, 728 (1943); 66, 330, 784, 1731 (1944): Proc. of the Nat. Acad. of Sci., 27, 125 (1941): Physiol. Rev., 23, 203 (1943).

Reported by H. I. Enos
April 18, 1945

p-DIOXANES

Preparation

1. Wurtz (1) in 1862 was the first to synthesize p-dioxane.



2. Lourenco (2), a year later, prepared dioxane by heating a mixture of ethylene glycol and ethylene dibromide at 160°.

3. Favorski (3), in 1907, first applied the method of synthesis which is in use today--distillation of a mixture of ethylene glycol with 4% of concentrated sulfuric acid. Although modifications of this method have appeared (4,5), Favorski's procedure is still preferred.

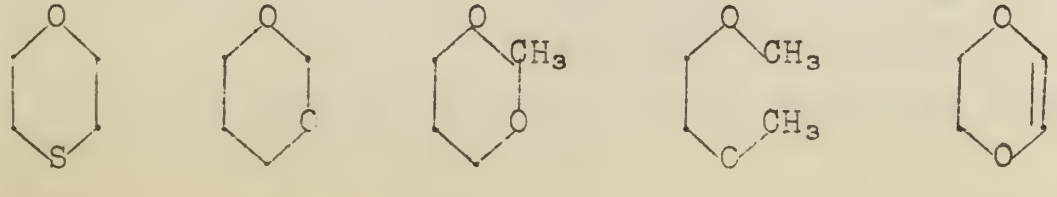
Physiological Action (6).--Although vapors of dioxane irritate the eyes, nose and throat, they are not harmful under ordinary conditions of usage. The toxicity of the substance is believed due to its oxidation products, oxalic and diglycolic acids.

Physical Properties (6).--p-Dioxane boils at 101.5°, freezes at 11.7°, and is completely miscible with water and most organic solvents. With water it forms an azeotrope (b.p. 83.8°) containing 80% by weight of dioxane and a eutectic (f.p. -15.4°) at 40% by volume of the di-ether.

Chemical Properties.--Dioxane is purified by heating with hydrogen chloride and then with sodium (7). The presence of impurities in dioxane promotes the formation of peroxides unless an inhibitor such as metallic copper is used (6).

Dioxane possesses an unusual amount of basic character; it forms molecular compounds with a large number of acidic substances, e.g., H_2SO_4, SO_2, SO_3, $AsCl_3$, $HClO_4$, halogens, metallic halides, organic iodides and picric acid. Baer (8) has suggested that the compound with phosphoric acid ($C_4H_8O_2 \cdot 2H_3PO_4$) might be substituted for crystalline phosphoric acid when a dry solution of this acid is required.

This distinctive property of p-dioxane is displayed to a much lesser degree by p-thioxane (I) and 1,3-dioxane (II), while other related substances (III, IV, V) are perfectly neutral (9).

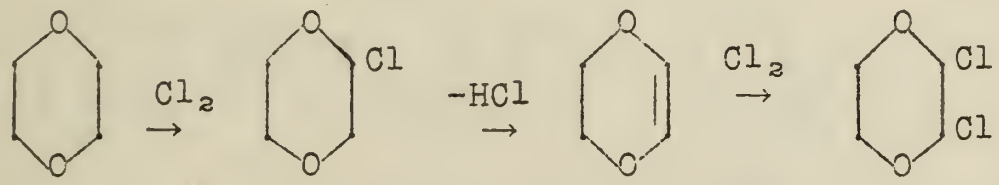


I II III IV V

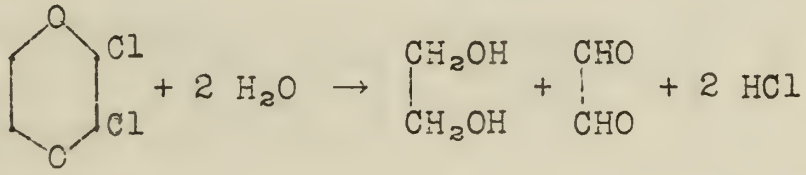
Dioxane is very stable to acids, alkalis, oxidizing agents, sodium metal, etc. For example, under conditions by which ethyl ether is converted by nitric acid into ethyl nitrate, dioxane merely yields an addition product. Nevertheless, at elevated temperatures, strong reagents can rupture the molecule.

Dioxane should never be used in hydrogenations with Raney nickel, for an explosive reaction occurs which may burst the bomb.

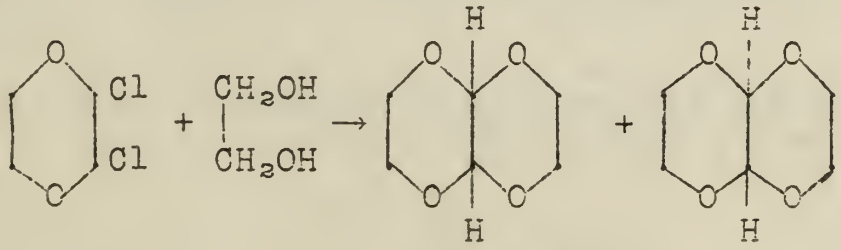
Chlorination.--Boeseken and coworkers (10) first prepared a 2,3-dichlorodioxane by treatment of dioxane with chlorine at 90°. Apparently only one isomer (m.p. 30°), believed to be the cis (?), was formed. The failure to obtain a monochloro derivative was later shown to be due to the instability of monochlorodioxane (11).



By catalytic chlorination, Kucera and Carpenter (12) obtained 2,3-dichlorodioxane in 96% yield. At higher temperatures, (140°), 33% of the symmetrical and 52% of the unsymmetrical tetrachlorodioxanes were formed (12, 13). 2,3-Dichlorodioxane and the symmetrical 2,3,5,6-tetrachlorodioxanes are convenient sources of glyoxal, since they are quantitatively hydrolyzed by boiling water.

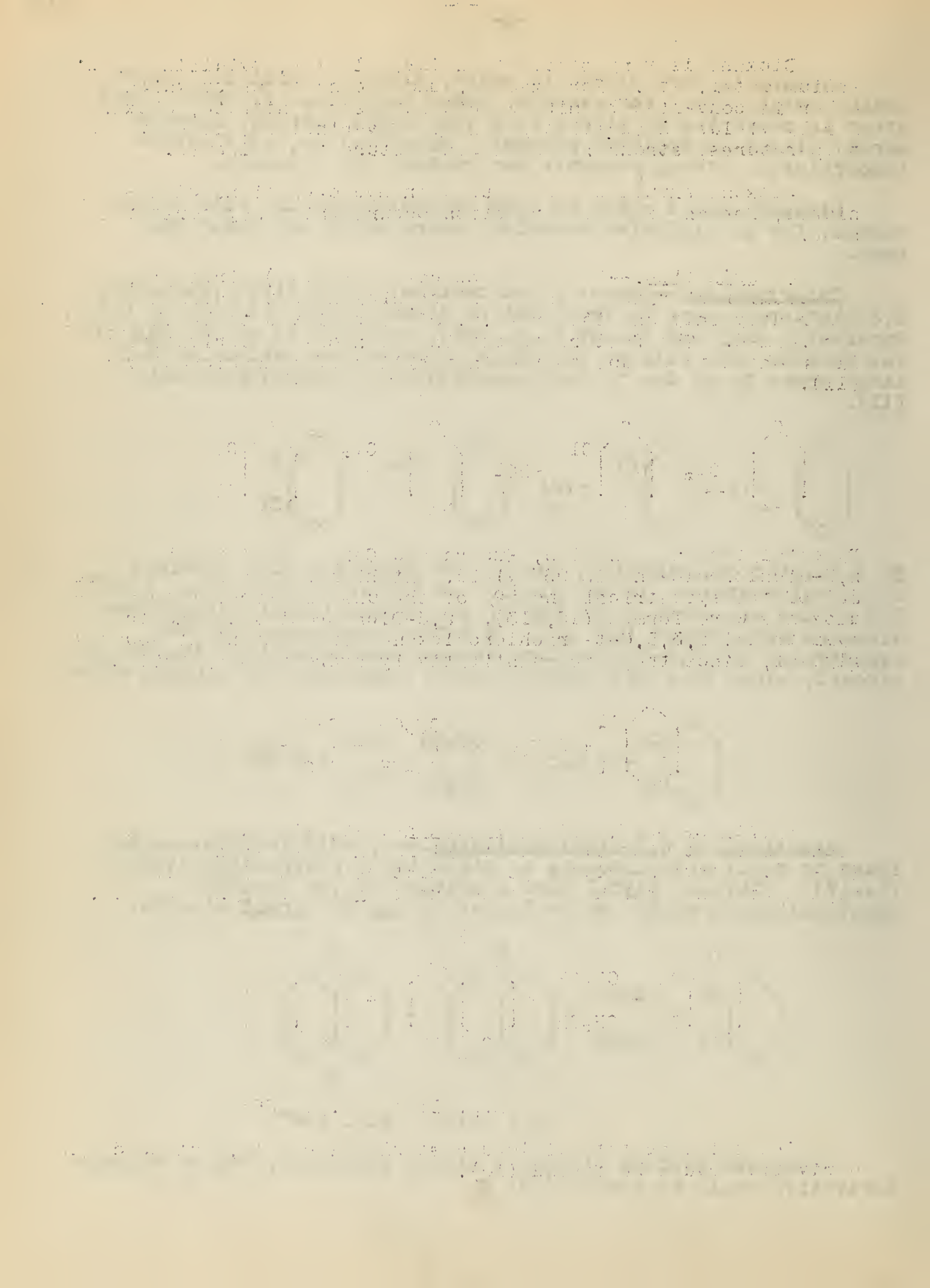


Reactions of 2,3-Dichlorodioxane.--2,3-Dichlorodioxane was found to react with alcohols to yield the corresponding ethers (14-17). Ethylene glycol gave a mixture of two isomeric naphthodioxanes which are analogous to cis and trans decalin.

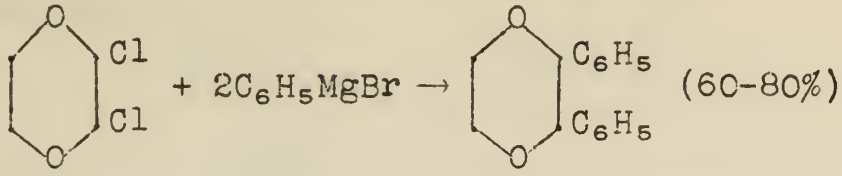


m.p. 111° m.p. 136°

Potassium acetate yielded a stable diacetate, but no dicyano derivative could be formed (18).

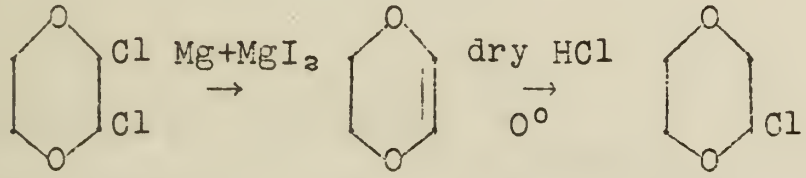


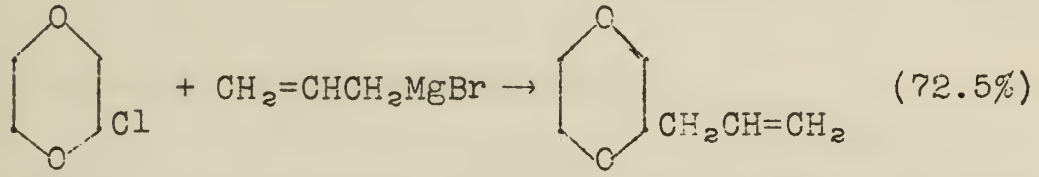
Summerbell and coworkers (11, 19-21) prepared a number of alkyl and aryl derivatives of dioxane from the dichloro compound.



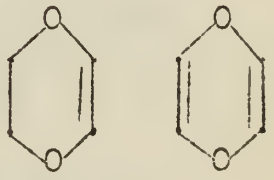
With the alkyl Grignard reagents, dehalogenation was so extensive that it was necessary to use the less reactive zinc or cadmium compounds.

In a similar manner, monosubstituted dioxanes were prepared; in this case, the alkyl Grignard reagents reacted normally.





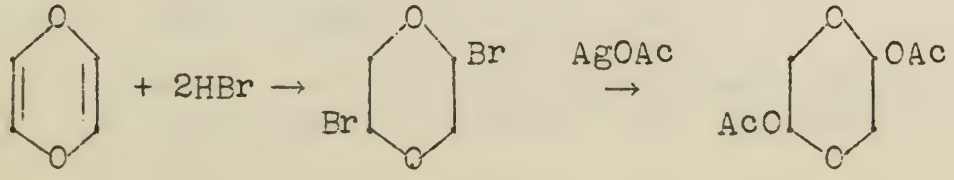
Dioxene and Dioxadiene.--The synthesis of dioxene (V) was revealed above. Dioxadiene (VI) was prepared in a similar fashion from 2,3,5,6-tetrachlorodioxane (22).



V VI

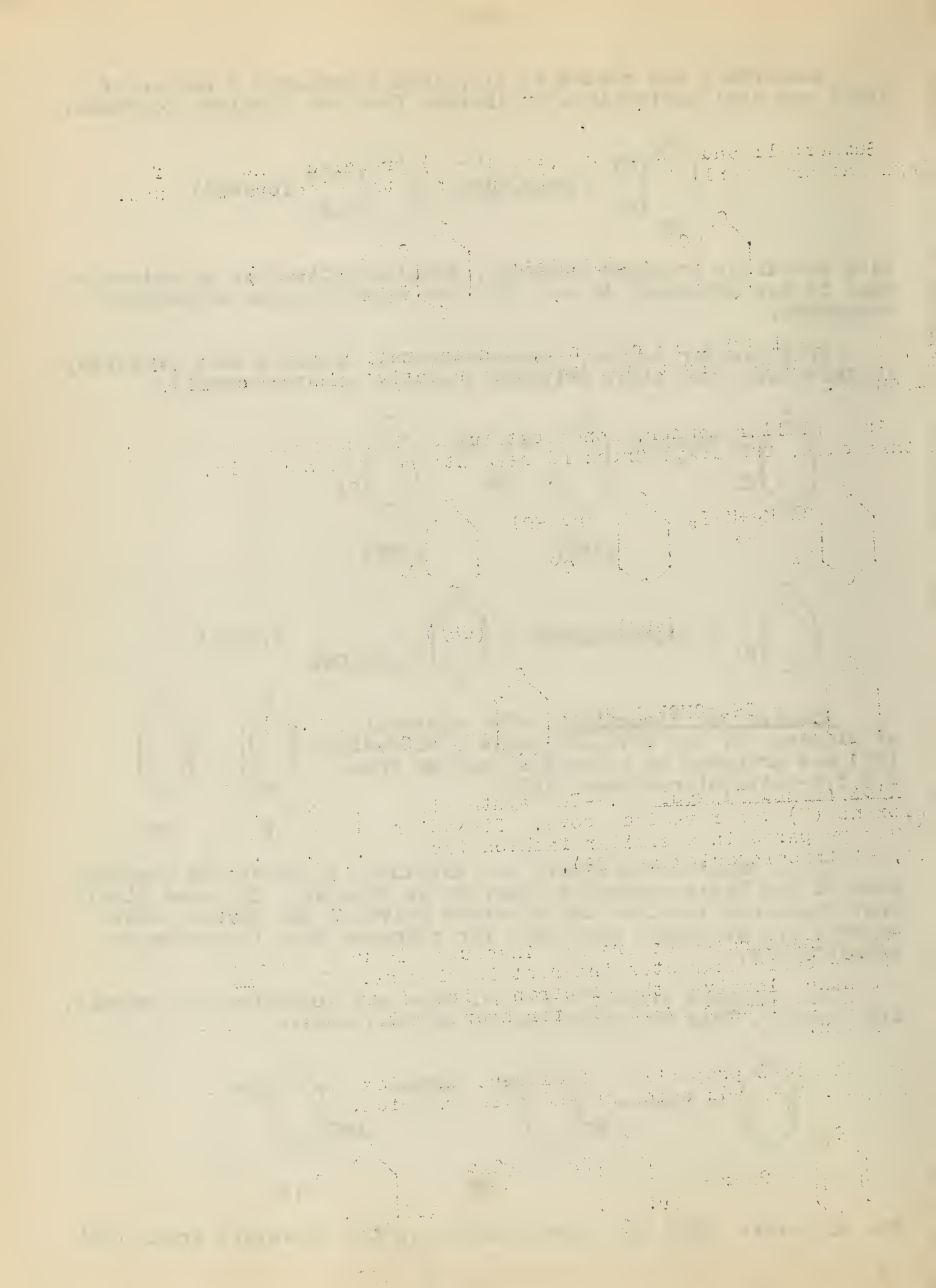
These unsaturated ethers are insoluble in water and possess none of the basic character inherent in dioxane. It seems likely that resonance involves the electron pairs of the oxygen atoms so they are no longer available for hydrogen bond formation or coordination.

The chemical properties of dioxene and dioxadiene are normal; for example, they add halogens and halogen acids.

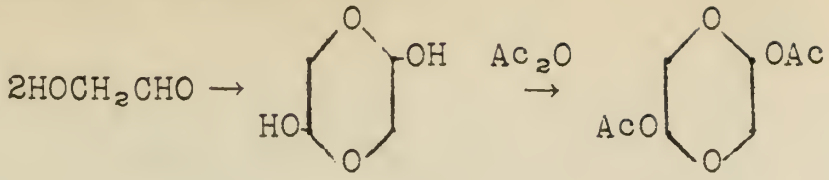


VII

The diacetate (VII) has proved useful in the structure proof (23)



of glycolaldehyde dimer (VIII).

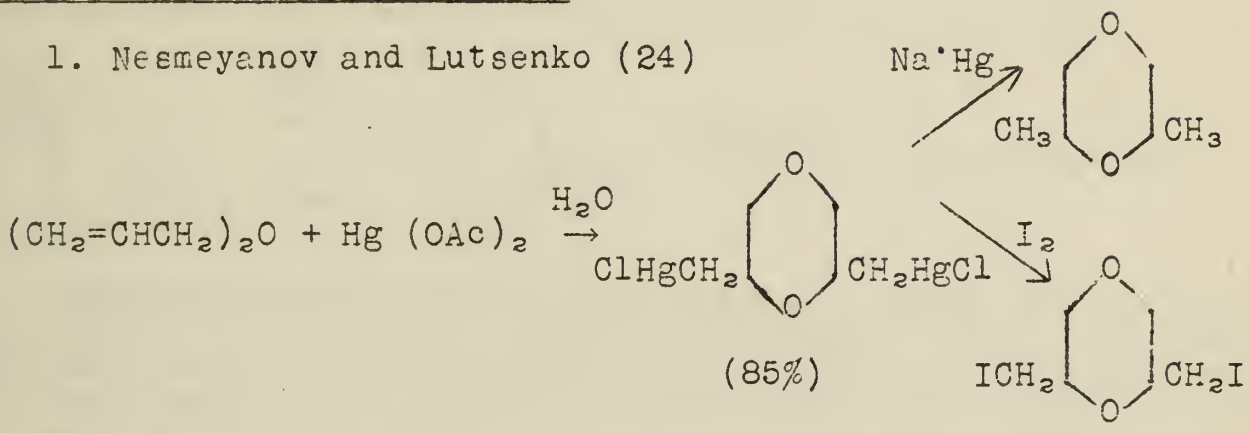


VIII

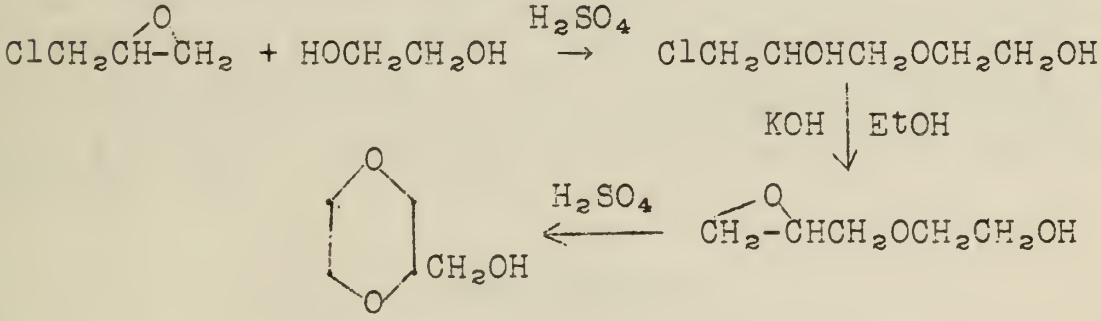
Dioxadiene polymerizes in two to three weeks to a hard, colorless, high-melting solid.

Other Derivatives of p-Dioxane

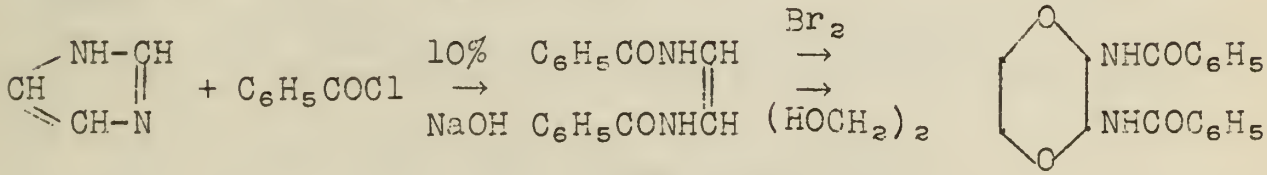
1. Nesmeyanov and Lutsenko (24)



2. Kharasch and Nudenberg (25)



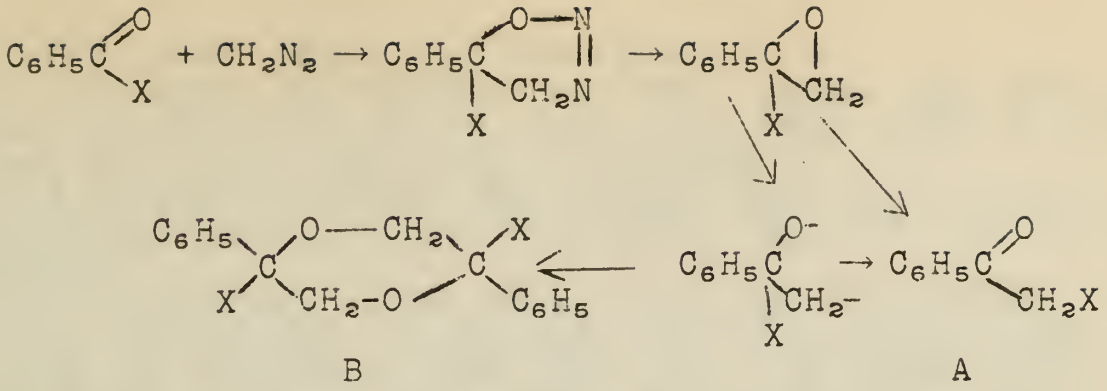
Ruggli, Ratti and Henzi (26)



(87%)

4. Lewis, Nierenstein and Rich (27)

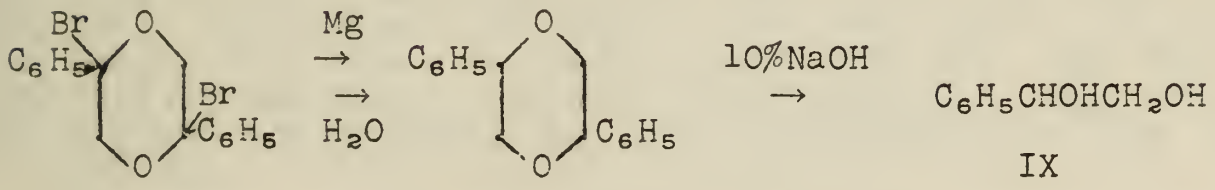
The reaction of acyl bromides with diazomethane does not yield the expected phenacyl bromides, but 2,5-dibromo-2,5-diaryldioxanes are formed.



B A

X = Cl gives 72% of A; X = Br gives 62% of B.

Compound B was readily converted into styrene glycol (IX).



IX

Industrial Applications.--Dioxane is an excellent solvent for many natural and synthetic resins and is often used in lacquers. Most oils and oil-soluble dyes dissolve readily in dioxane and it is a great aid in the dyeing of fibres which are wetted by water only with difficulty (6).

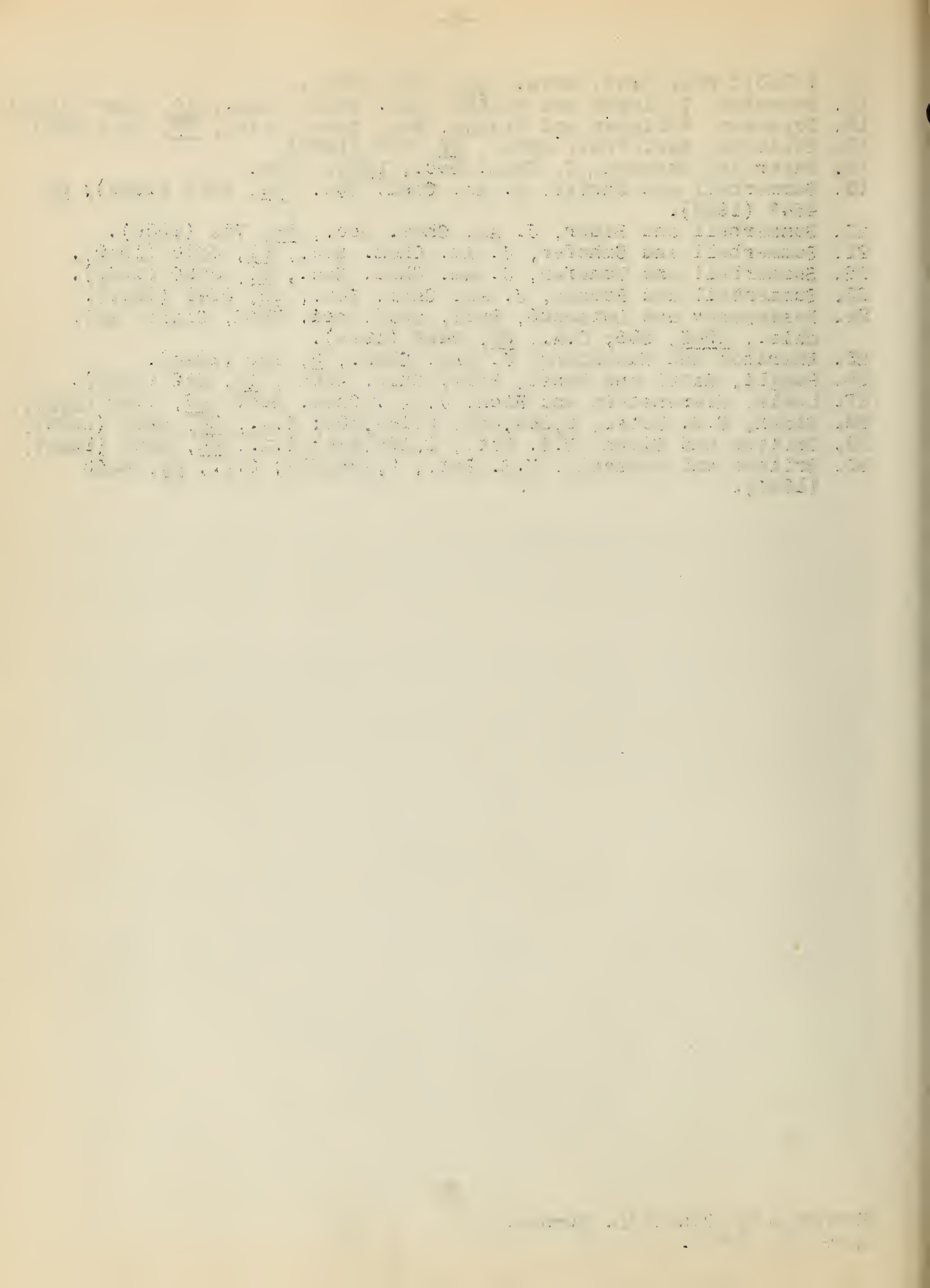
Dow Chemical Company has patented a process by which esters of 1,4-dioxane-2,3-diol are prepared by heating 2,3-dichlorodioxane with a carboxylic acid (28). These compounds are used as plasticizers and insecticides. Dow also holds patents for the preparation of unsaturated ethers of the 2,3-diol and for their use as modifiers in the polymerization of styrene and in copolymers with styrene (29, 30).

BIBLIOGRAPHY

1. Wurtz, Ann., 122, 354 (1862); Ann. chim. phys., (3) 69, 317 (1863).
2. Lourenco, Ann. chim. phys., (3) 67, 288 (1863).
3. Favorsky, J. Russ. Phys. Chem. Soc., 38, 741 (1906); Zentr. 1907I, 16.
4. U.S. Pat., 2,072,101; C.A., 31, 2613 (1937).
5. van Alphen, Rec. trav. chim., 49, 1040 (1930).
6. Regeoffe, Rev. prod. chim., 42, 229 (1939).
7. Hess and Frahm, Ber., 71B, 2627 (1938).
8. Baer, J. Am. Chem. Soc., 66, 303 (1944).
9. Clarke, J. Chem. Soc., 101, 1788 (1912).
10. Boeseken, Tellegen and Henriquez, Rec. trav. chim., 50, 909 (1931).
11. Summerbell and Bauer, J. Am. Chem. Soc., 57, 2364 (1935).
12. Kucera and Carpenter, J. Am. Chem. Soc., 57, 2346 (1935).
13. Butler and Cretcher, J. Am. Chem. Soc., 54, 2987 (1932).
14. Boeseken, Tellegen and Henriquez, J. Am. Chem. Soc., 55, 1284

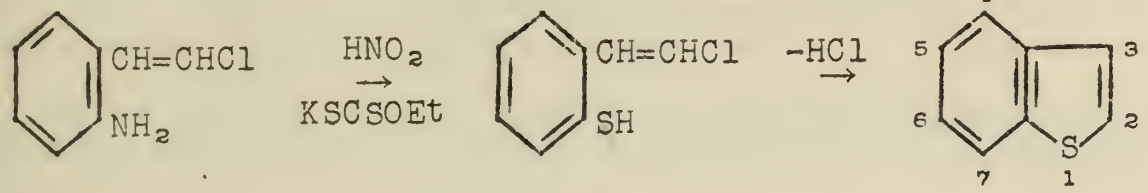
(1933); Rec. trav. chim., 54, 733 (1935).
15. Boeseken, Tellegen and Maltha, Rec. trav. chim., 52, 1067 (1933).
16. Boeseken, Tellegen and Plusje, Rec. trav. chim., 57, 73 (1938).
17. Tellegen, Rec. trav. chim., 57, 677 (1938).
18. Baker and Shannon, J. Chem. Soc., 1933, 1598.
19. Summerbell and Christ, J. Am. Chem. Soc., 54, 3777 (1932); 55, 4547 (1933).
20. Summerbell and Bauer, J. Am. Chem. Soc., 58, 759 (1936).
21. Summerbell and Umhofer, J. Am. Chem. Soc., 61, 3016 (1939).
22. Summerbell and Umhofer, J. Am. Chem. Soc., 61, 3020 (1939).
23. Summerbell and Rochen, J. Am. Chem. Soc., 63, 3241 (1941).
24. Nesmeyanov and Lutsenko, Bull. acad. sci. URSS, Classe sci. chim., 1943, 296; C.A., 38, 5498 (1944).
25. Kharasch and Nudenberg, J. Org. Chem., 8, 189 (1943).
26. Ruggli, Ratti and Henzi, Helv. Chim. Acta., 12, 332 (1929).
27. Lewis, Nierenstein and Rich, J. Am. Chem. Soc., 47, 1728 (1925).
28. Slagh, U.S. Pats., 2,164,355, 2,164,356; C.A., 33, 8210 (1939).
29. Britton and Slagh, U.S. Pat., 2,195,386; C.A., 34, 5091 (1940).
30. Britton and Marshall, U.S. Pat., 2,186,359; C.A., 34, 3405 (1940).

Reported by Donald M. Burness
April 25, 1945.



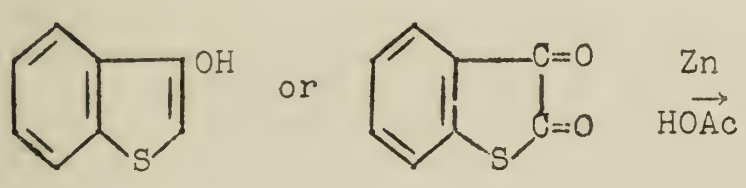
THIANAPHTHENES

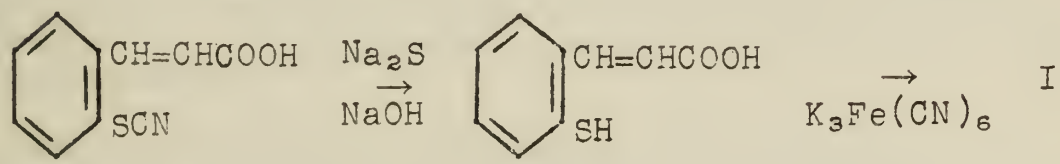
2,3-Benzothiophene, or thianaphthene, was prepared first by Gattermann and Lockhart in 1893. Since that time it has been found in lignite tar, shale oil and coal tar. It can be obtained from coal tar by separation of the acids formed by sulfonation of the crude naphthalene fraction. Synthetically, it has been prepared in several ways.

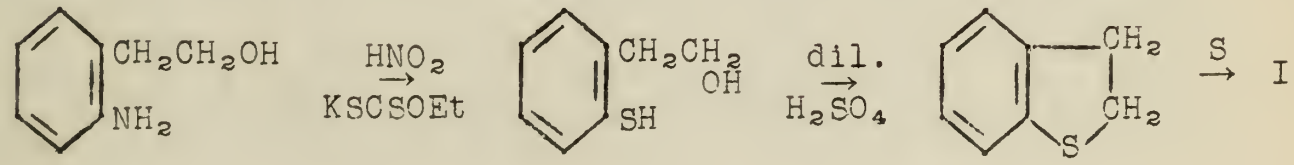
1. 

I

2.  I

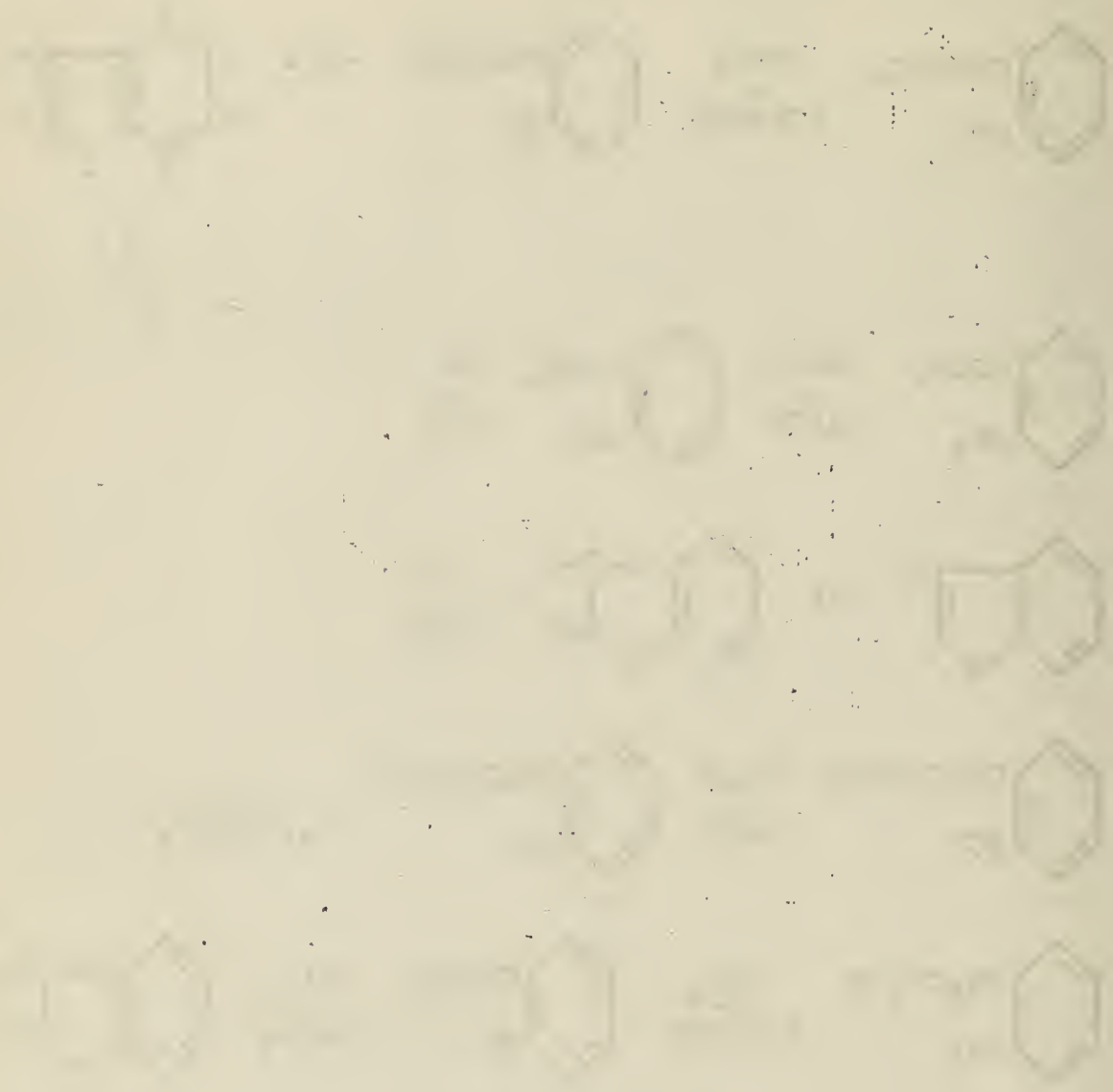
3.  I

4.  I

5. 

6. $HC{\equiv}CH + CH_4 + H_2S \xrightarrow[\text{catalyst}]{650\text{-}670^\circ}$

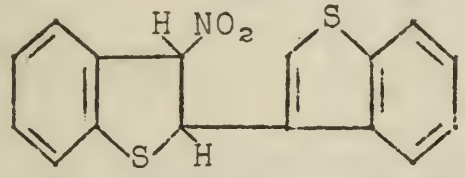
Treatment with hydrogen peroxide in acetic acid gives the sulfone. With potassium hydroxide at 300-330° it is cleaved to o-thiocresol and formic acid. Ozone cleaves thianaphthene to o-hydroxyphenyl disulfide or o-benzaldehyde disulfide. Reduction with sodium in ethanol cleaves it to 2-ethylthiophenol.



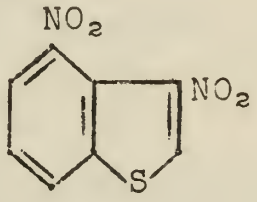
Substitution takes place first in the 3-position. With mercuric acetate thianaphthene forms a 3-acetoxymercuri- derivative at room temperature and a 2,3-di(acetoxymercuri)- derivative at higher temperatures. Acyl halides in the presence of aluminum chloride react with thianaphthene to form 3-acylthionaphthenes.

Chlorination in chloroform gives a dichloro compound, probably 2,3-. Bromine in chloroform gives 3-bromothianaphthene. Bromine water forms a dibromo derivative.

Fuming nitric acid in acetic acid gives 3-nitrothianaphthene, along with some 3-nitro-2,3-dihydro-2,3'-dithianaphthenyl (II).



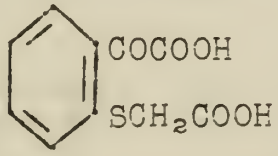
II



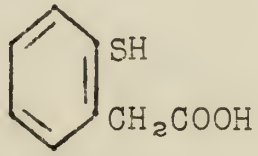
III

A 3,4-dinitro derivative (III) is also formed by nitration of thianaphthene. Treatment of III with hydrogen sulfide converts it to 4-nitrothianaphthene which may be reduced to 4-nitrothianaphthene. 2-Aminothianaphthene is not known. The 3-amino derivative, isolated only as the acetate or acid salt, is unstable and readily dimerizes to form di-3-thianaphthylamine. Thus, reduction of 3-nitrothianaphthene gives only traces of 3-aminothianaphthene. Dilute acids readily hydrolyze the amine to 3-thianaphthenol.

Thianaphthenyl-2-carboxyllic acid is formed when thianaphthene is treated with ethylmagnesium bromide in dimethylaniline, and then with carbon dioxide. The 3-acid may be prepared by means of the Grignard agent formed from 3-bromothianaphthene or by oxidation of 3-acetothianaphthene. The 2,3-diacid is formed when phenylthioglycolic-o-glyoxylic acid (IV) is treated with strong alkali.



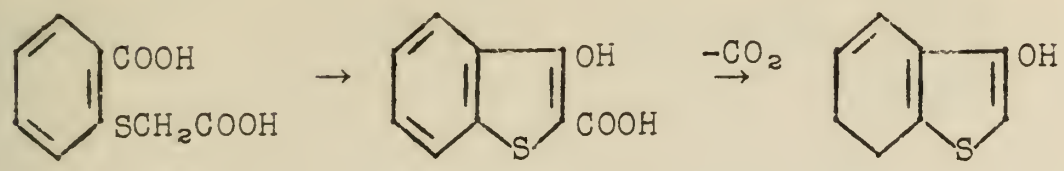
IV



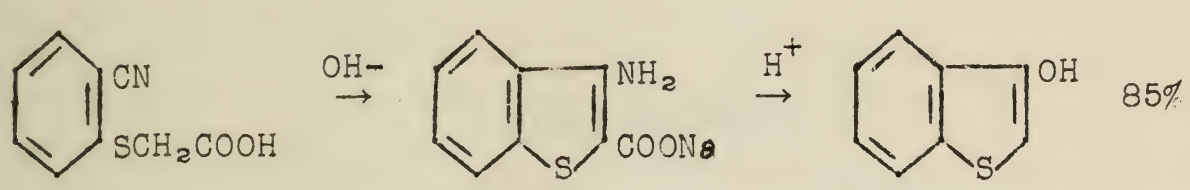
V

2-Thianaphthenol may be prepared from o-mercaptophenylacetic acid (V) by the elimination of water. It exists also in the keto form (thiooxindole). 3-Thianaphthenol has been prepared in a number of ways, many of which appear in the patent literature.

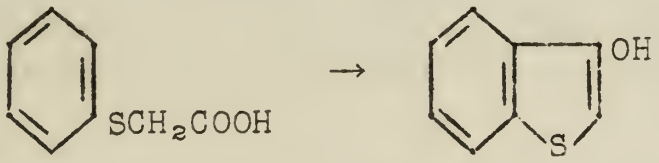
1. From o-carboxyphenylthioglycolic acid by heating in alkali, acetic anhydride or high-boiling inert solvents.



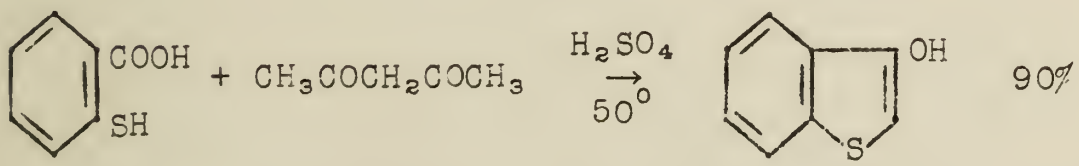
2. From o-cyanophenylthioglycolic acids by ring closure with alkali and decomposition of the intermediate with dilute acids.



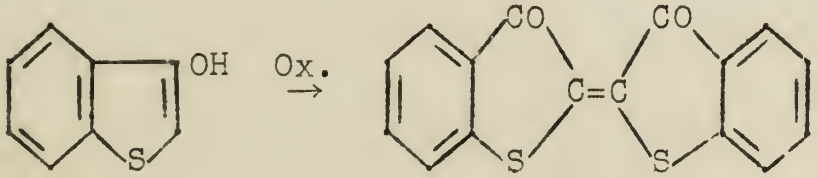
3. By cyclization of phenylthioglycolic acid with aluminum chloride, phosphorus pentoxide, sulfuric acid or other catalyst.



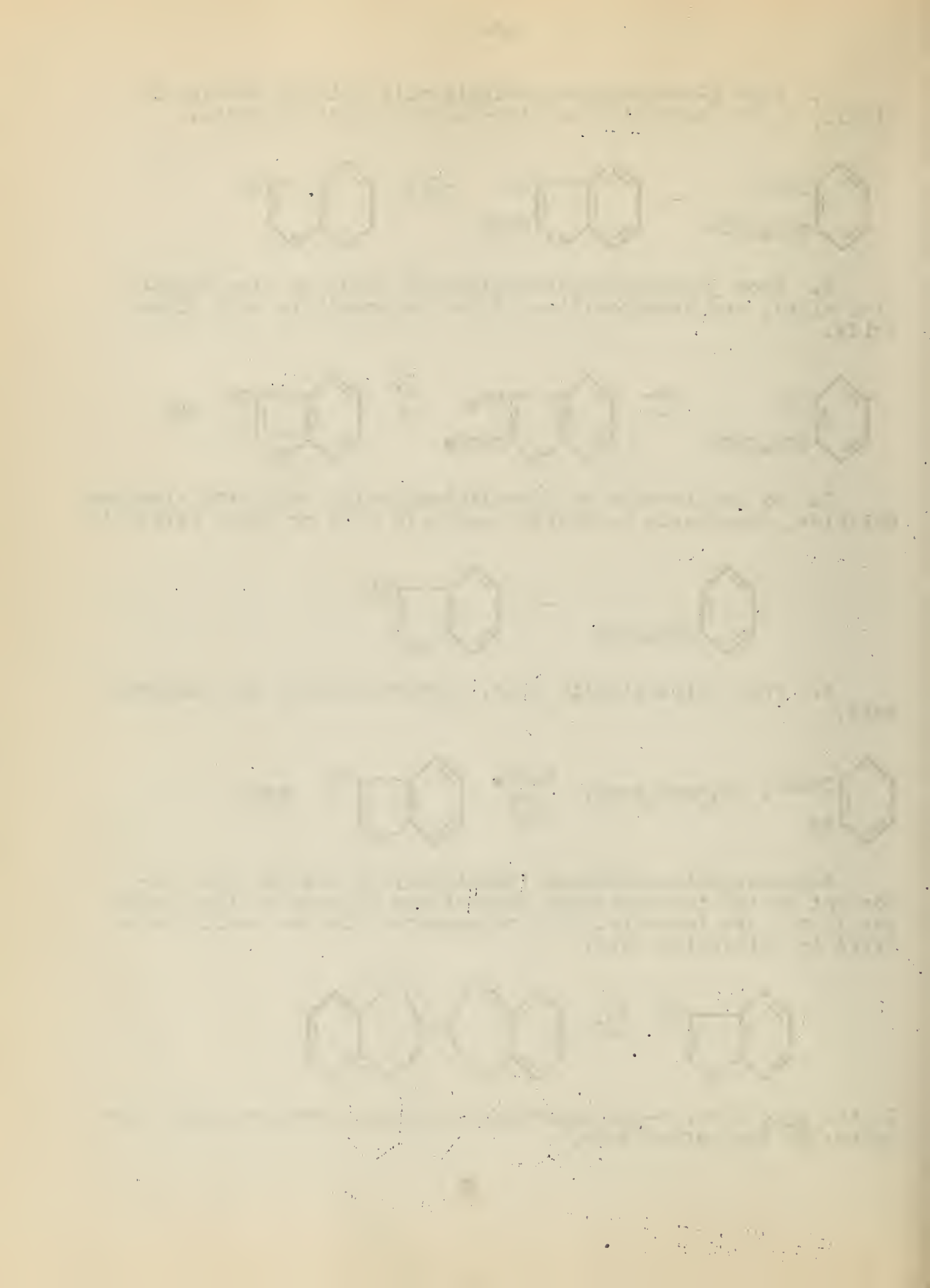
4. From thiosalicylic acid, acetonylacetone and sulfuric acid.

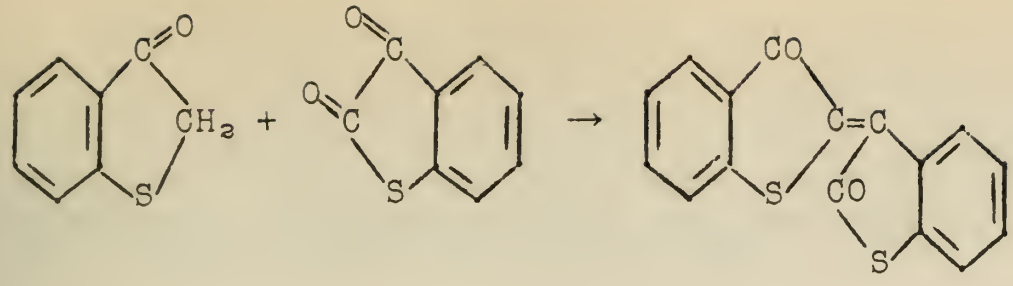


3-Hydroxythianaphthenes (thioindoxyls) are the most important of the thianaphthene derivatives because of their wide use in the dye industry. The thianaphthenols are easily oxidized to thioindigo dyes.



In the keto form, 3-thianaphthenol condenses with carbonyl compounds to form other dyes.





Indorubin

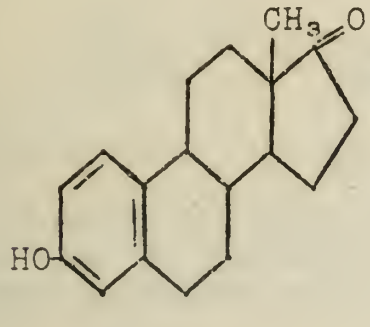
BIBLIOGRAPHY

"Die Chemie des Thiophens," W. Steinkopf, Theodor Steinkopff, Dresden und Leipzig, 1941.
Fricke and Spilker, Ber., 58, 24 (1925).
Wacek, Eppinger and Bezard, Ber., 73B, 521 (1940).
Bennett and Hofez, J. Chem. Soc., 1941, 287.
Harley-Mason and Mann, J. Chem. Soc., 1942, 405.

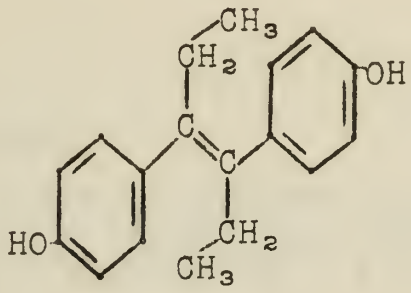
Reported by W. R. Hatchard
April 25, 1945

STILBESTROL

Stilbestrol is a synthetic female hormone comparable in activity to estrone. It was first synthesized by Dodds and co-workers in 1938 while they were conducting a study on the relation of structure to estrogenic activity. Examination of the structural formulas does show some resemblance between these two compounds and further experiments have been made to investigate the actual significance of this fact.



Estrone



Stilbestrol

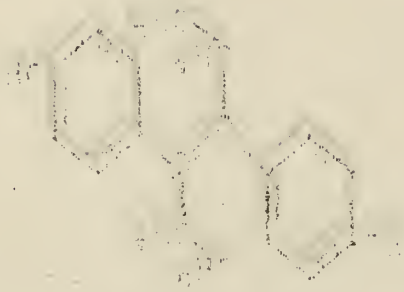
Linnell and Sharma prepared 3,4'-dihydroxy-α,α'-diethyl-stilbene and 3,3'-dihydroxy-α,α'-diethylstilbene and discovered that although the formal resemblance to estrone was greater in the former than in stilbestrol, its activity was equal. Placing both hydroxy groups meta to the alkyl group decreases activity, for the latter compound was less active.

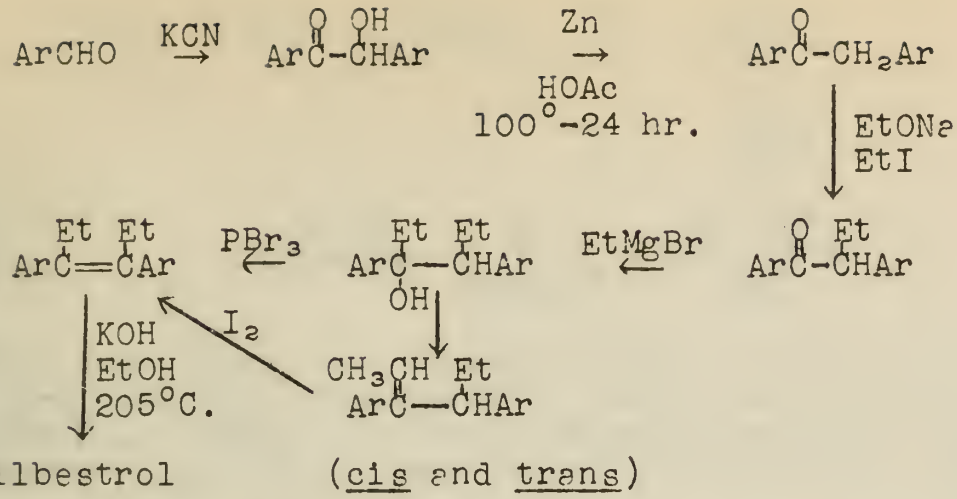
The effect of replacing the ethyl groups with other alkyl groups or hydrogen tends to decrease activity. Dodds has synthesized dihydroxyhexahydrochrysene which has a closer structural relation to estradiol than stilbestrol but whose activity is one-thousandth that of stilbestrol.

Other evidence for some sort of relationship between natural and synthetic estrogens and their activity is found in the cis and trans isomers formed in the synthesis of stilbestrol. Only one of these isomers is extremely active and it has been proved by hydrogenation experiments to be the trans isomer. Only the trans isomer can assume a spatial configuration similar to that of natural estrogens.

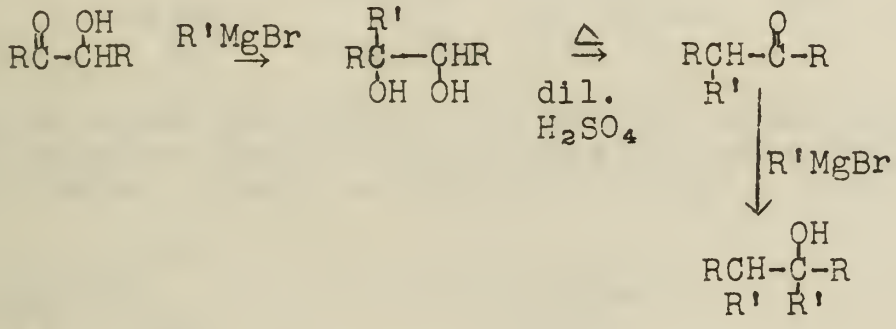
Because of its great activity and comparatively ready availability, stilbestrol is important as a substitute for natural female hormones. Consequently, a quick, inexpensive method of synthesis would be desirable. Attempts to find such a synthesis have been made and this seminar plans to deal with those proposed. (Ar represents the p-anisyl group.)

Dodds' original synthesis was as follows.

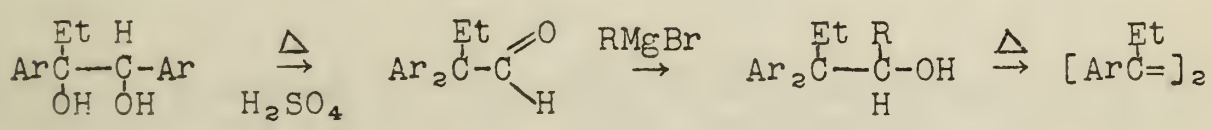




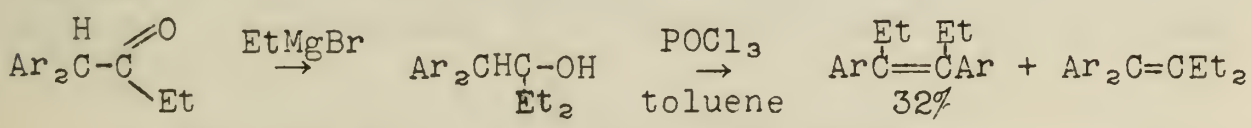
Kuwada has developed two slightly modified procedures for preparing the carbinol used in the dehydration. The following general equation applies where R = Ar and R' = Et, or R = Et and R' = Ar.



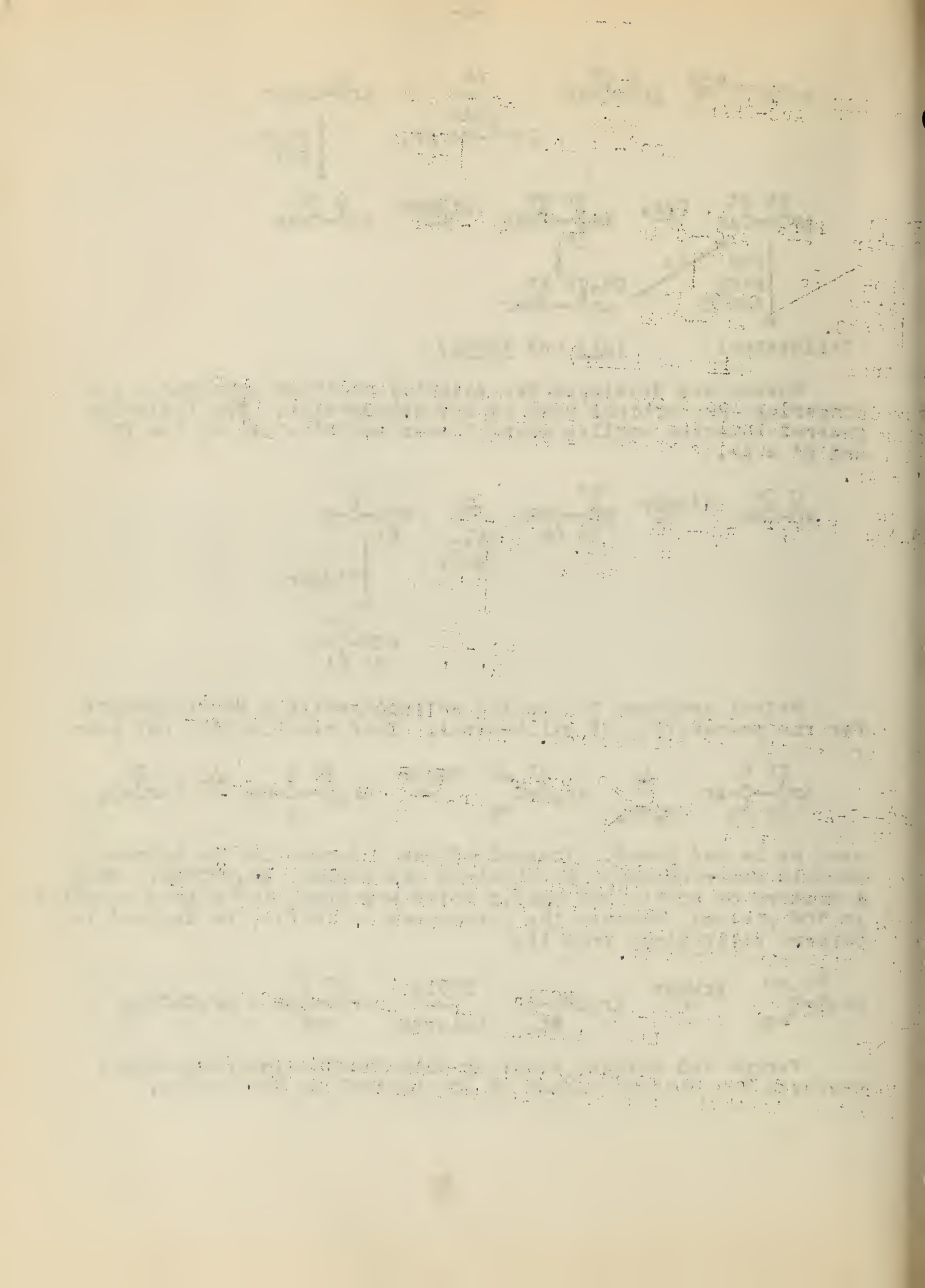
Peteri proposed to use the retropinacolinic rearrangement for the preparation of stilbestrol. This reaction did not pro-

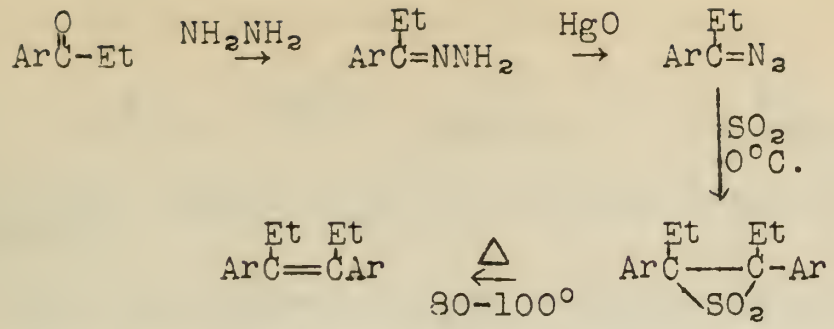


ceed as he had hoped. Instead of the aldehyde in the hydrobenzoin rearrangement, he obtained the ketone, $Ar_2CHCOEt$. When a mixture of acetic and oxalic acids was used, the ketone resulted in 70% yields. Because the ketone was available, he decided to prepare stilbestrol from it.



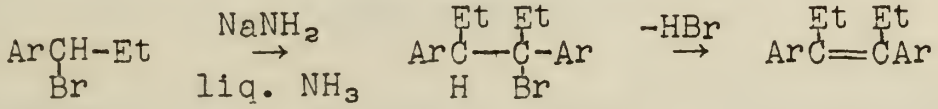
Vargha and Kovacs, starting with *p*-methoxypropiophenone, prepared the dimethyl ether of stilbestrol in 25% yields.



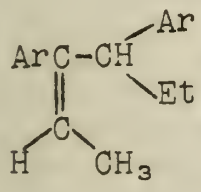


Linnell and Sharma had reported their attempt at this reaction but they had been unsuccessful, obtaining only the ketazine, $(ArEtC{=}N)_2$. Barber and Slack recently employed this reaction to prepare p,p'-dicyano-α,α'-diethylstilbene in small yields.

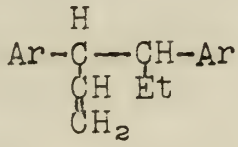
In 1943 Kharasch published the best synthesis to date. Reasoning on the conversion of allyl chloride to hexatriene, he thought stilbestrol could be made similarly. It was found,



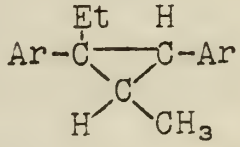
however, that the product was not the dimethylether of stilbestrol but a compound which on hydrogenation gave dihydrostilbestroldimethylether. Three possibilities exist. Since von Wesseley had



I



II

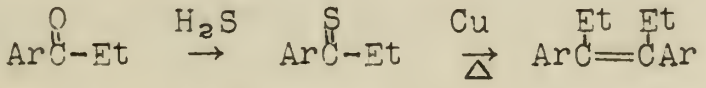


III

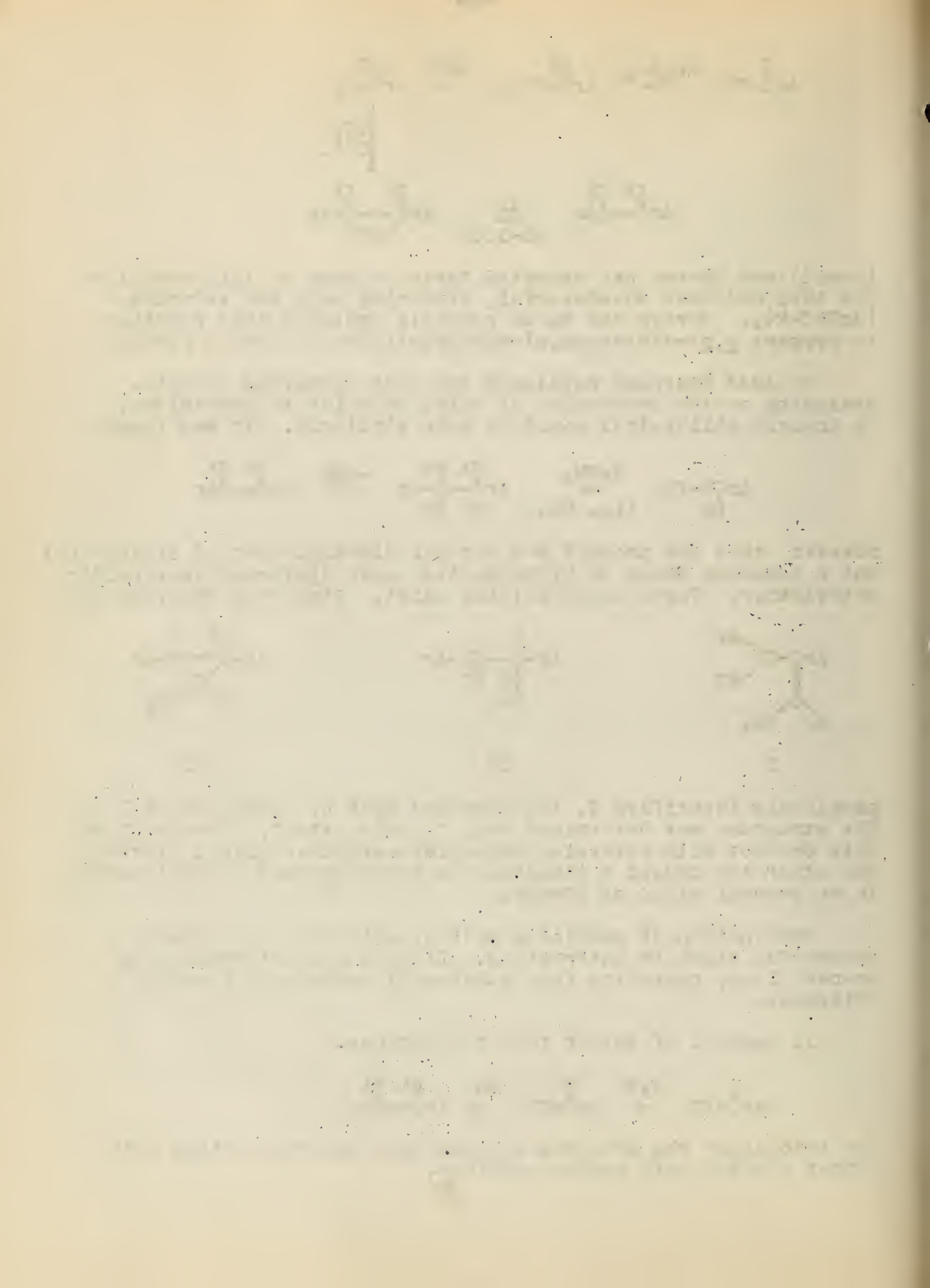
previously identified I, the compound must be either II or III. The structure was determined only to this extent. Treatment of this product with potassium hydroxide - ethylene glycol cleaved the ether and caused a simultaneous rearrangement to stilbestrol in an overall yield of 20-22%.

Examination of published methods which have not proved successful might be interesting. Linnell has attempted many preparations, reasoning from successful syntheses of simple stilbenes.

1. Removal of sulfur from thioketones.



The thioketone was prepared successfully but the heating with copper yielded only cyclic sulfides.



2. Removal of nitrogen from a ketazine.

$$ArC(=O)-Et \xrightarrow{NH_2NH_2} (ArC(Et)=N-)_2 \xrightarrow{\Delta} [ArC(Et)=]_2$$

In this preperation the ketazine could not be thermally decomposed.

Foldi and Demjen in 1941 attempted the following reaction.

$$ArC(=O)-CHAr \xrightarrow{SOCl_2} ArC(Cl)-CHAr \xrightarrow{EtMgBr} Ar_2CH-COHEt_2 \xrightarrow{-H_2O}$$

Hydrogenation of the final product did not give the expected hexestrol. It was shown by oxidation that the Grignard had caused a rearrangement.

BIBLIOGRAPHY

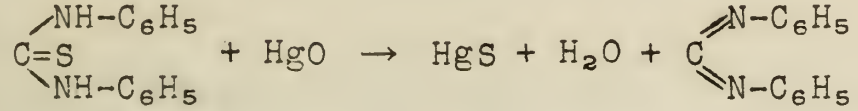
Dodds, Golberg, Lawson, Robinson, Nature, **141**, 247 (1938).
Jones, Annual Reports, 40, 137 (1943). A review.
Linnell and Sharma, Quart. J. Pharm. and Pharmacol., 14, 259 (1941).
Dodds, Golberg, Lawson, Robinson, Nature, 142, 34 (1938).
von Wesseley and Welleba, Ber., 74, 727 (1941).
von Wesseley and Kleedorfer, Die Naturwiss., 27, 567 (1939).
Kuwada and Sasagawa, J. Pharm. Soc. Jap., 60, 93 (1940); (C. A., 34, 4066 (1940)).
Kuwada, Sasagawa, Nisikawa, ibid., 60, 553 (1940); (C. A., 35, 1779 (1941)).
Peteri, J. Chem. Soc., 1940, 833.
Vargha and Kovacs, Ber., 75, 794 (1942).
Linnell and Sharma, Quart. J. Pharm. and Pharmacol., 12, 263 (1939).
Barber and Slack, J. Chem. Soc., 1944, 612.
Kharasch and Kleiman, J. Am. Chem. Soc., 65, 11 (1943).
Foldi and Demjen, Ber., 74, 930 (1941).

Reported by E. VanHeyningen
May 2, 1945

CARBODIIMIDES

The first member of this series, carbodiimide, is not known, but its isomer, cyanamide, is well characterized. However, Kahovec and Kohlraush have found that the spectrum of cyanamide indicates that two or more forms exist; cyanamide, $H_2NC{\equiv}N$, carbodiimide, HN=C=NH, and an associated form.

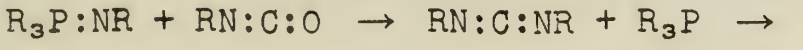
The first carbodiimide was prepared in 1874 by Weith. His method consisted in the treatment of the substituted thiourea with mercuric oxide:



This method is used today for the preparation of most carbodiimides and gives high yields, especially when there are aromatic substituents on the nitrogen atoms.

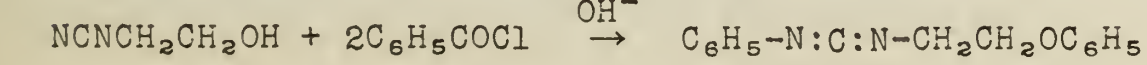
The most satisfactory and general method of preparing these compounds is that of Weith as modified by Zetzsche and also by Schmidt. The former has replaced the mercuric oxide with lead oxide in a solvent such as xylene or toluene. However, it was necessary to carry out the reaction in the boiling solvent and this led to an increase in polymeric products. Schmidt and coworkers have found that very pure and dry mercuric oxide in the finely divided state will transform the diaryl or dialkyl thioureas to the corresponding carbodiimides in yields of 80%.

Staudinger and Hauser have prepared carbodiimides from phosphinimines and isocyanates. The reaction seems to take the following course:



They have also found that aliphatic phosphinimes will react with carbon dioxide to give carbodiimides without intermediate products.

A method of preparing carbodiimides from cyanamide salts has been reported by Fromm and Honold.

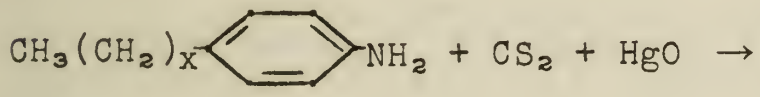


The best yields have been obtained by Schmidt and Striewsky who have found it unnecessary to use the thiourea as the starting material. They have prepared alkyl (methoxymethyl) carbodiimides in high yields by means of the following reaction.

$CH_3OCH_2NCS + RNH_2 + HgO \rightarrow CH_3OCH_2N=C=N-R + HgS + H_2O$

The reaction is carried out in cold, dry ether. R may be methyl, n-propyl, isopropyl, isohexyl or cyclohexyl. Later it was shown that when a 50-50 mixture of water and ether is used, the yields are high as 90% in each case.

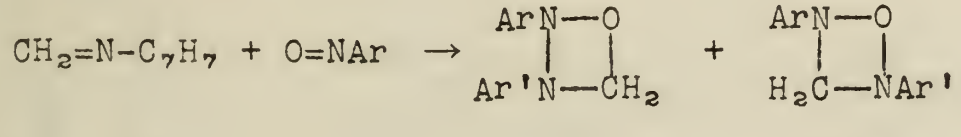
A patented method for preparing carbodiimides involves treatment of alkyl-substituted aromatic amines with carbon disulfide followed by subsequent desulfurization with mercuric oxide.



x = 9 or more

A 0.5 to 1.0% benzene solution of the compound is a valuable cloth finishing and impregnating material.

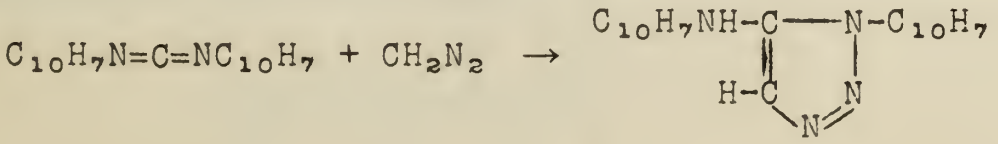
Ingold reports a method of making carbodiimides from azomethines and nitroso compounds. These substances combine very readily at ordinary temperature without the use of condensing agents to form two possible four membered rings.

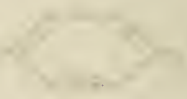


(I) (II)

Thermal decomposition gives as the chief product the carbodiimide Ar-N=C=NAr'. Ingold has never found formaldehyde or an azo-compound in the reaction mixture, thus showing that water split out of the four-membered ring (II). This indicates that this ring is the one present under the conditions of the dehydration.

Reactions.--Rotter and coworkers report that carbodiimides form triazoles upon treatment with diazomethane.





Carbodiphenylimide forms a similar triazole and also reacts with the methyl Grignard reagent.

$$C_6H_5N{=}C{=}NC_6H_5 + CH_3MgBr \rightarrow C_6H_5NH{-}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}{=}NC_6H_5$$

Guanidines are formed when aniline is used in place of the Grignard reagent.

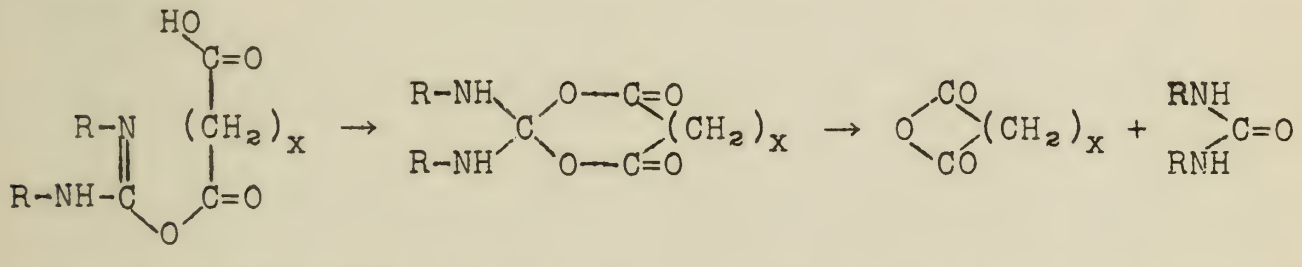
$$RN{=}C{=}NR + C_6H_5NH_2 \rightarrow RHN{-}\underset{\displaystyle N{-}C_6H_5}{\overset{\displaystyle |}{C}}{-}NHR$$

Zetzsche and coworkers have done extensive work on the use of carbodiimides in the characterization of acids as the ureides. This work was reviewed in a seminar by Dr. Ludington a few years ago.

The reaction between acids and carbodiimides is almost quantitative in most cases and is useful for many sensitive acids since it proceeds under mild conditions without a catalyst.

$$RN{=}C{=}NR + R'CO_2H \rightarrow RNH\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}{-}\underset{\displaystyle COR'}{\overset{\displaystyle R}{N}}$$

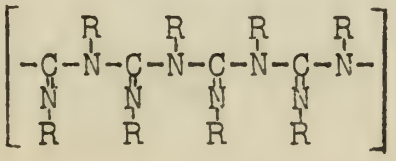
However, with low molecular weight dicarboxylic acids, the corresponding acid anhydride is formed along with the urea. Zetzsche and Lindlar propose the following course for the reaction:



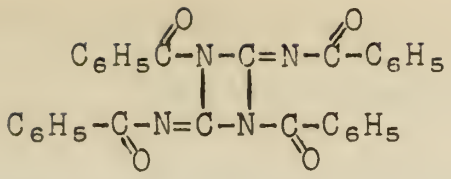
Carbodiimides react with water to form ureas and with hydrogen selenide to give selenoureas.

$$R{-}N{=}C{=}N{-}R + H_2Se \rightarrow RNH{-}\underset{\displaystyle |}{\overset{\displaystyle Se}{C}}{-}NHR$$

The carbodiimides polymerize readily either by heating or treatment with sodium. Zetzsche and Fredrich suggest the following structure for the polymer.



They have also found that some diaryl substituted carbodiimides form dimers as dibenzoylcarbodiimide does on standing in the air.



BIBLIOGRAPHY

Kahovec and Kohlraush, Z. Physik. Chem., B37, 421 (1937).
Weith, Ber., 7, 10 (1874).
Zetzsche, Meyer, Overbeck and Nerger, Ber., 71B, 1512 (1938).
Zetzsche and Lindlar, Ber., 71B, 2095 (1938).
Zetzsche and Fredrich, Ber., 72B, 363 (1939); 73B, 1114 (1940).
Zetzsche and Pinske, Ber., 74B, 1022 (1941).
German patent #707,025; C. A., 36, 2164 (1942).
Staudinger and Hauser, Helv. Chim. Acta, 4, 881 (1921).
Fromm and Honold, Ber., 55B, 902 (1922).
Rotter and Schaudy, Monatsh., 58, 245 (1931); 47, 353 (1926).
Schmidt, Hitzler, Lahde, Herbeck and Pezzati, Ber., 71B, 1933 (1938).
Schmidt and Striewsky, Ber., 73B, 286 (1940); 74B, 1285 (1941).
Ingold, J. Chem. Soc., 125, 87 (1924).

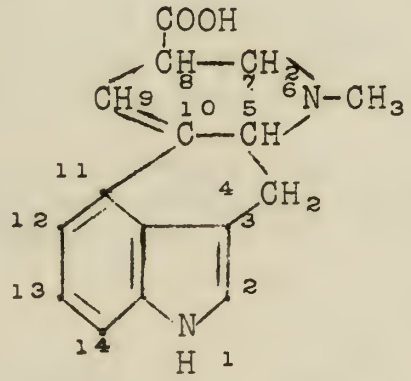
Reported by T. G. Klose
May 2, 1945

LYSERGIC ACID

(Jacobs and Craig, Rockefeller Institute for Medical Research)

Lysergic acid is a product of aqueous alkaline hydrolysis of all known ergot alkaloids, which occur in the mycelia of a fungus, Claviceps purpurea, found on grasses and cereal crops. Lysergic acid is the factor responsible for the unique pharmacodynamic activity of these alkaloids, and consequently many amides of lysergic acid are widely used clinically during childbirth.

The structure proposed by Jacobs and Craig for lysergic acid is given below.

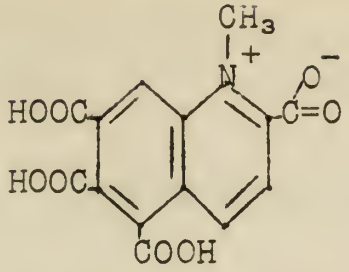


Evidence for this structure is outlined below.

(1) General
- (a) Empirical formula: $C_{16}H_{16}O_2N_2$ (Supported by analysis of the methyl ester)
- (b) Lysergic acid contains one N-methyl group and one carboxyl group.
- (c) Tests for a primary or secondary amino grouping on lysergic acid and its dihydro derivative fail, indicating that both nitrogen atoms are tertiary, or that perhaps one may be contained in an indole or pyrrole ring. Since lysergic acid, when heated to 210-230°C, yields carbon dioxide and methylamine, it is unlikely that a methyl group is on such a pyrrole or indole nitrogen atom.
- (d) Color reactions suggest an indole derivative, which may be biogenetically related to tryptophane.

(2) Ring System
- (a) Alkali fusion of lysergic acid yields as one product 1-methyl-5-aminonaphthalene. In the production of the naphthylamine derivative methylamine is produced almost quantitatively, and there is no contamination of the naphthylamine with the N-methyl derivative; hence the source of the amino grouping must be an indole nitrogen with no methyl group.
- (b) Nitric acid oxidation of lysergic acid yields an N-methyl quinoline betaine tricarboxylic acid. The authors suggest

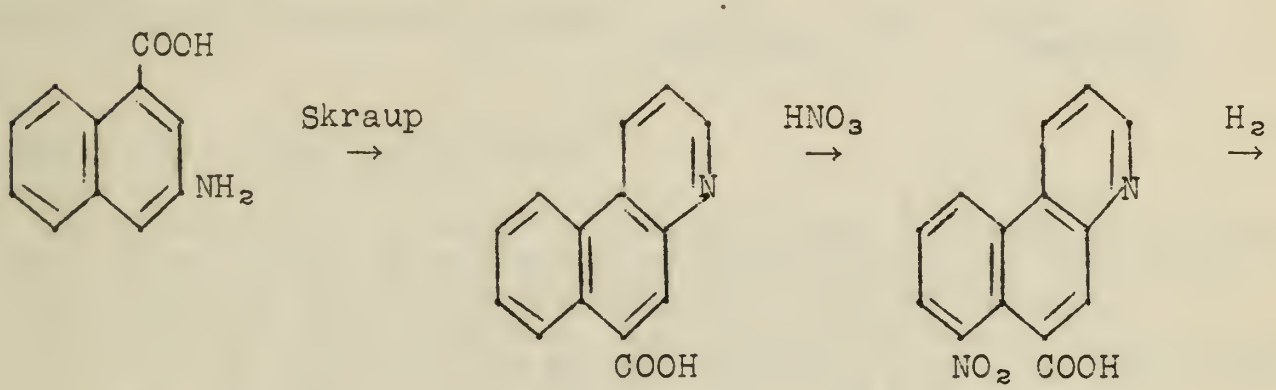
the structure given below.

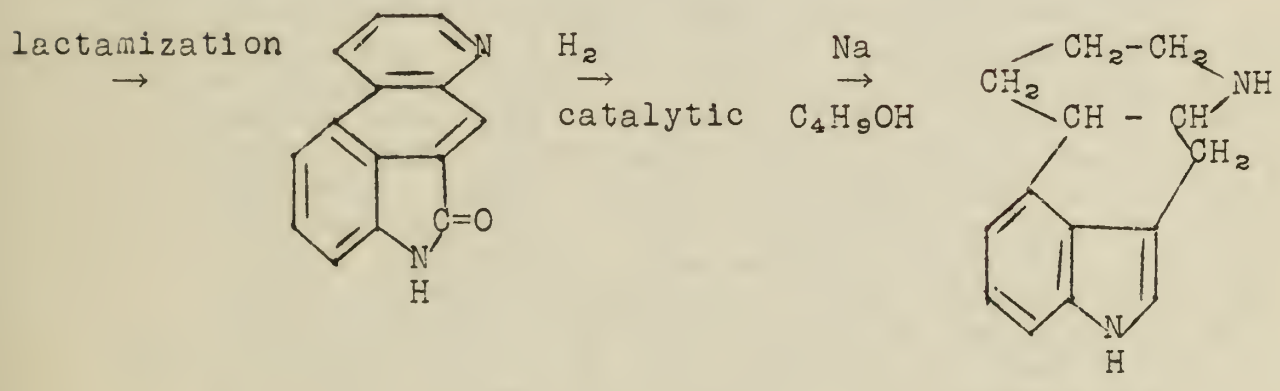


This compound, on distillation with soda lime, yields quinoline. This indicates the presence of a quinoline ring system in lysergic acid. Also, the formation of such a quinoline derivative shows that the hydroquinoline nucleus must be substituted in three positions other than that occupied by the original carboxyl group.

(c) Additional evidence for the presence of an indole nucleus was obtained by ultra-violet absorption spectra measurements.

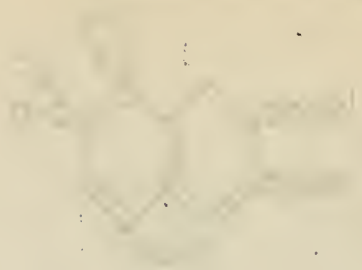
(d) On the basis of these facts, the authors proposed the basic ring system and were able to synthesize ergoline, a compound containing it.

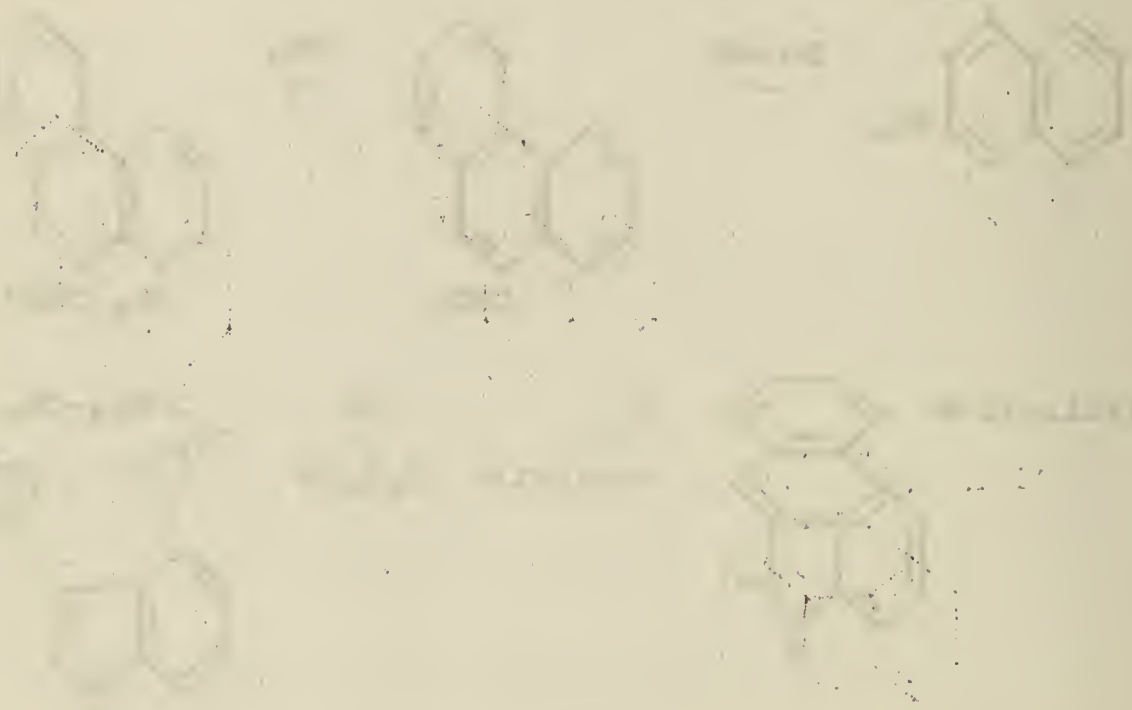




Ergoline gave similar color reactions to those of lysergic acid. 6-Methylergoline was also synthesized and likewise gave similar color reactions.

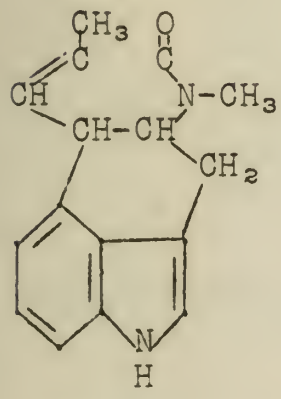
(e) Additional proof of the structure of the ring system was offered by the degradation of lysergic acid to dl-6,8-dimethylergoline identical with a synthetic product. The synthetic material was prepared by a scheme similar to that outlined above for ergoline using the α, γ-



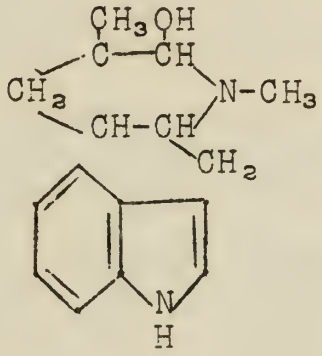


dimethyl ether of β-methylglycerol in place of glycerol in the initial Skraup reaction. A sample of dl-lysergic acid from ergotinine then subjected to the following series of reactions to obtain the same compound.

dl-lysergic acid $\xrightarrow[C_4H_9OH]{Na}$ dl-dihydrolysergic acid $\xrightarrow[\text{under reduced pressure}]{\text{sublime}}$



$\xrightarrow[\text{catalytic}]{H_2}$ $\xrightarrow[C_4H_9OH]{Na}$



$\xrightarrow{\text{sublime}}$

dehydro-dl-6,8-dimethylergoline $\xrightarrow[\text{catalytic}]{H_2}$ dl-6,8-dimethyl-ergoline

(3) Position of the Double Bond

(a) Quantitative catalytic hydrogenation followed by examination of the hydrogenated products indicated that there was only one double bond outside the indole nucleus.

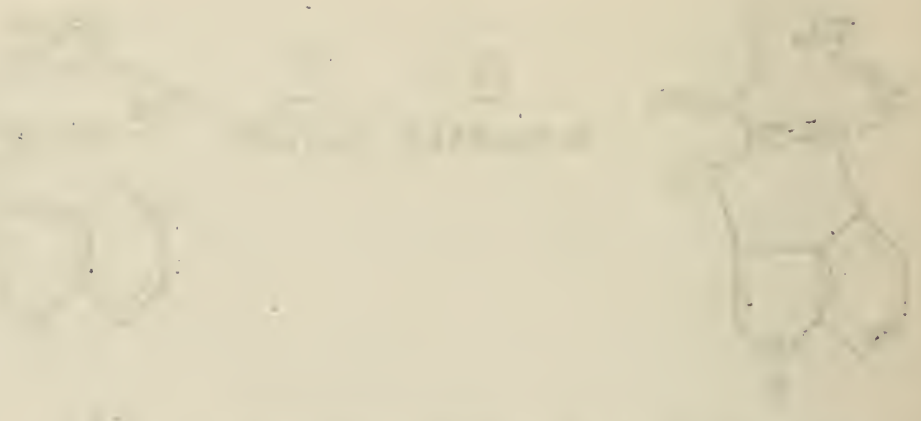
(b) Studies of ultraviolet absorption spectra of lysergic acid and its dihydro derivative suggested that the double bond was conjugated with those in the indole nucleus.

(c) Two isomeric lysergic acids were isolated from the ergot alkaloids. In a study of the basic dissociation constants of these two acids, it was found that lysergic acid was a weaker base than isolysergic acid. Since the position of a double bond near an amino group affects the basicity of that amino group, it was concluded that in one acid the ethylenic linkage is in an α-position, and in the other it is in a β-position. The authors suggested that the double bond in lysergic acid was between carbon atoms 5 and 10 and in isolysergic acid between carbon atoms 9 and 10.

(d) Basicity studies of some tertiary vinylamines by Adams and Mahan have shown that tertiary vinylamines are stronger bases than the corresponding saturated amines and, on the basis of this evidence, these authors suggest that the positions of the double bond assigned by Jacobs and Craig should be reversed for the two acids.

(4) Position of the Carboxyl Group

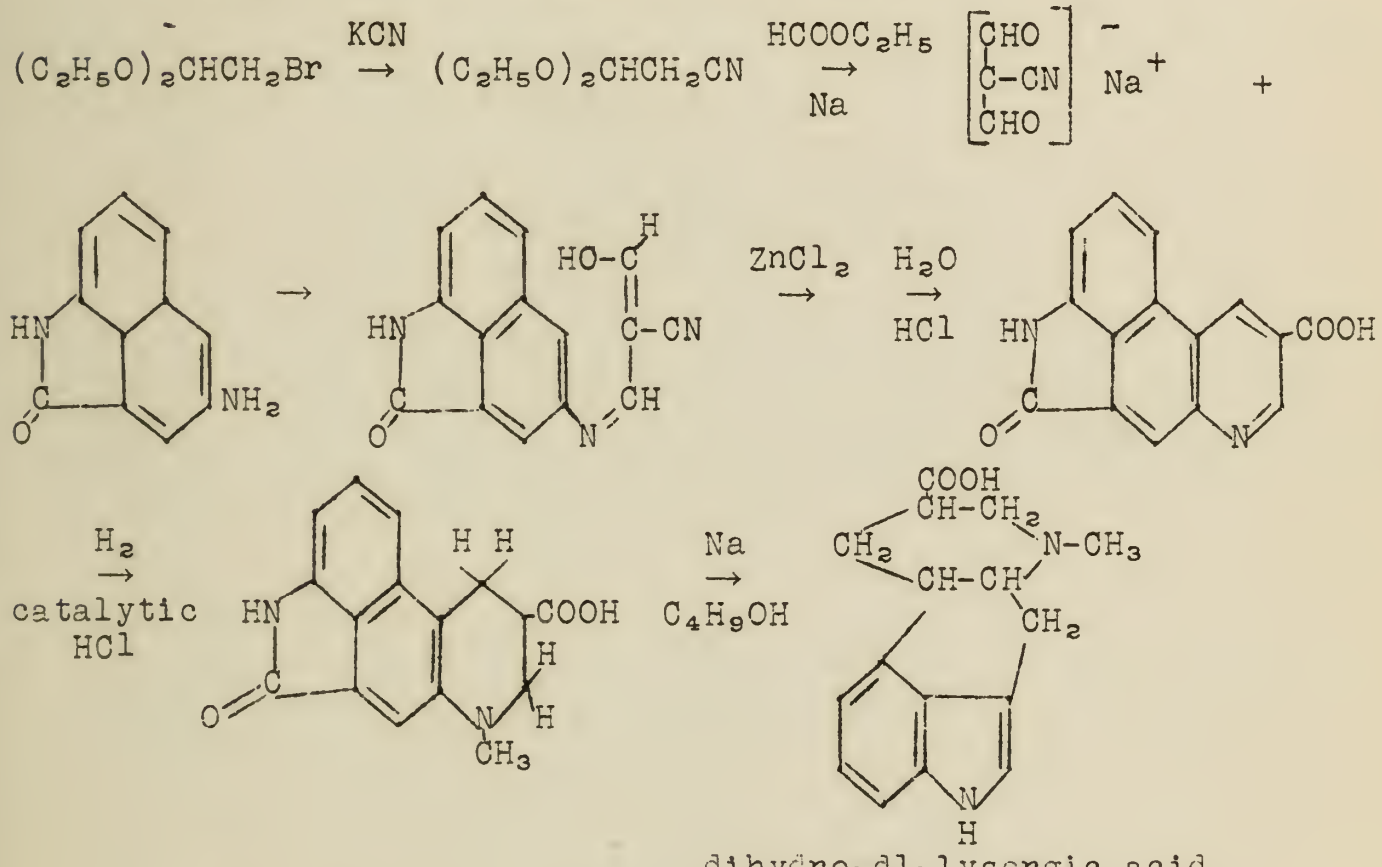
(a) Position 9 is eliminated because migration of the double bond between 5-10 and 10-9 would cause racemization. No evidence of racemization was detected.



(b) Position 4 is eliminated because of the stability of the carboxyl group in dihydrolysergic acid. If the carboxyl group were at position 4, the compound would be a substituted indole-acetic acid, which should lose carbon dioxide readily upon heating.

(c) The basic dissociation constant of α-dihydrolysergic was about 0.32 lower than that of synthetic 6-methylergoline. It is known that substitution of a carboxyl group in an aliphatic amine alpha to the amino group reduces the basic dissociation constant by 1.0 unit, while substitution in the beta position reduces the constant by only 0.5 unit. This evidence indicates that the carboxyl group is located at position 8.

(d) Additional proof of the position of the carboxyl group and also of the structure of the ring was given by the following synthesis of dl-dihydrolysergic acid.



dihydro-dl-lysergic acid

This synthetic dihydro-dl-lysergic acid was identical in all respects with that obtained from dl-lysergic acid.

BIBLIOGRAPHY

Jacobs, Craig, et al., J. Biol. Chem., 104, 547 (1934); 106, 393 (1934); 111, 455 (1935); 113, 759,767 (1936); 115, 227 (1936); 120, 141 (1937); 125, 289 (1938); 126, 67 (1938); 128, 715 (1939); 130, 399 (1939); 145, 487 (1942); Science, 82, 16,421 (1936); 83, 37,166 (1936); 85, 248 (1937): J. Am. Chem. Soc., 60, 1701 (1938): J. Org. Chem., 10, 76 (1945).

Smith and Timmis, J. Chem. Soc., 674 (1934); 1440 (1936).
Adams and Mahan, J. Am. Chem. Soc., 64, 2588 (1942).

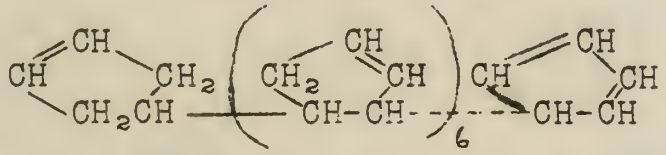
Reported by J. D. Young
May 9, 1945

CYCLOPENTADIENE

Cyclopentadiene was apparently first described by Roscoe in 1886 having been isolated as its dimer from the volatile hydrocarbon fraction obtained by the pyrolysis of phenol. Some physical properties are: d_{20}^{4} 0.8021; m.p. -85°; b.p. 42° (760mm); n_{D}^{20} 1.4429. It has both a conjugated system of double bonds and an active methylene group hence has chemical properties characteristic of these two groups.

It has some possible economic importance in polymer formation. Bruson and Staudinger described a colloidal material prepared by polymerizing cyclopentadiene in the presence of various halides especially stannic chloride, in chlorofrom solution at 0°. A white glistening rubber was precipitated on addition of absolute alcohol. Vulcanization could be carried out with sulfur chloride and controlled to produce a soft gel or an ebonite material.

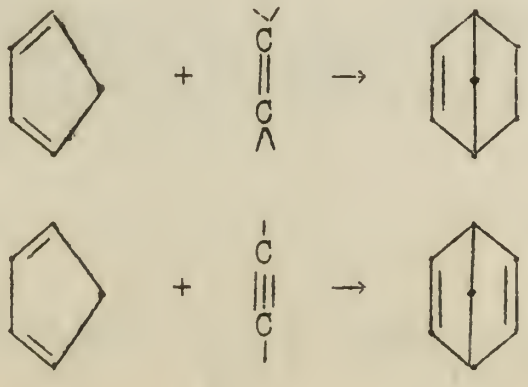
As a possibly important monomer in resin production, Carmody Sheehan, and Kelly prepared a resin of desirable characteristics by heating cyclopentadiene in the presence of a metal catalyst. They suggested that it was largely an octamer.



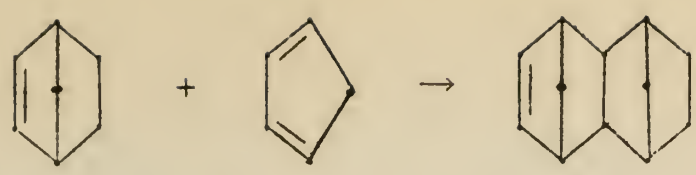
Several patents have been described in Chemical Abstracts dealing with the polymerization of cyclopentadiene under various conditions to produce resinous materials. Such resins are formed by polymerizing the alkyl or aryl cyclopentadienes or by forming copolymers, as the condensation of cyclopentadiene with acrylonitrile to produce a resin of the alkyd type.

Diene Synthesis.

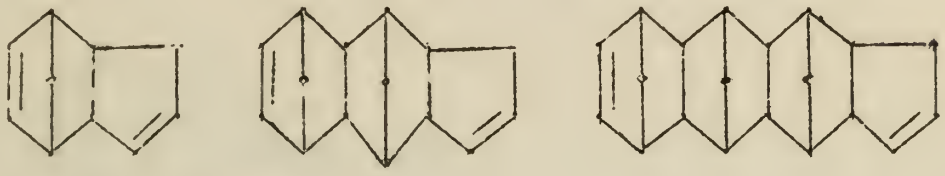
One of the most general of the chemical reactions of cyclopentadiene is its reaction as a conjugated double bond system in the Diels Alder diene synthesis.



In some cases a second molecule adds to the available double bond of the adduct:



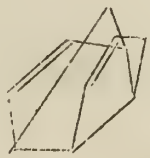
A typical example of this is described by Alder and Stein in the thermal polymerization of cyclopentadiene giving a series of polymers having the bicycloheptene ring structure:



etc.

The stereochemistry of the additions was reviewed by Norton and in this seminar by Chadwick and McPherson. It will suffice to recall here that in the diene reaction of cyclopentadiene alone at lower temperatures the <u>endo</u> form is produced.

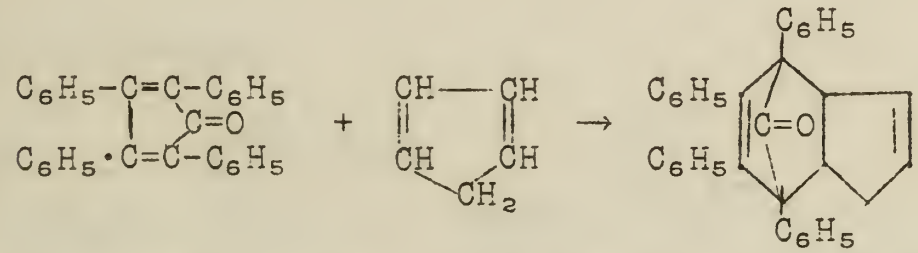
<u>endo</u>



<u>exo</u>

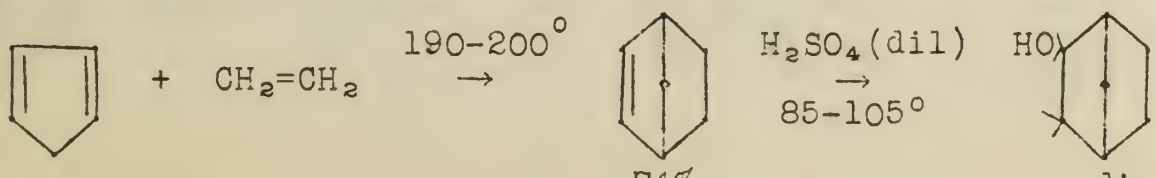
In higher addition products the endomethylene bridges all lie on one side of the ring system.

Examples have been given, as by Grummitt, Klopper, and Blenkhorn in which cyclopentadiene acts as the dienophile:



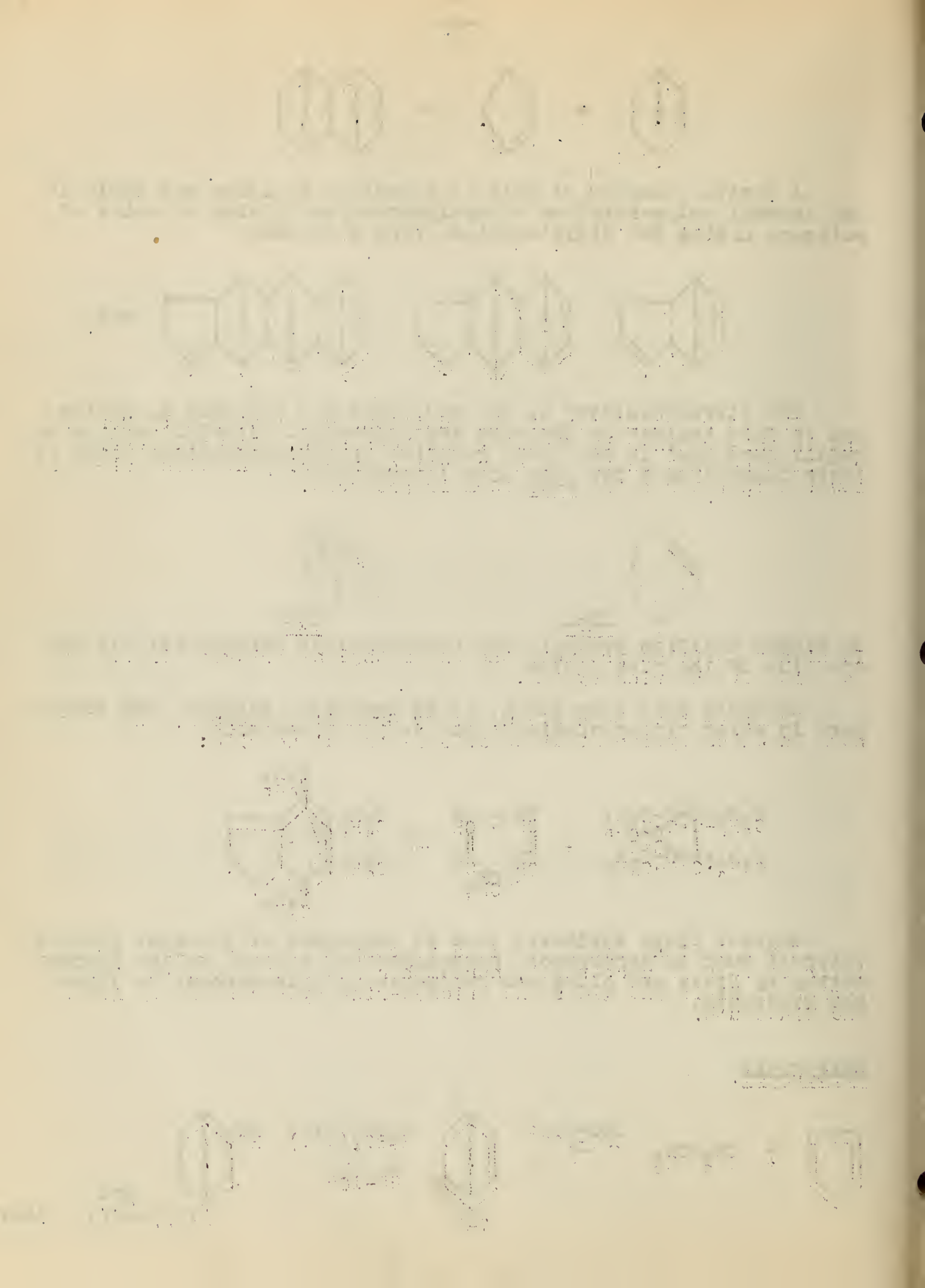
Several diene syntheses lead to compounds of somewhat greater interest such as norborneol, norcamphor and santene in the terpene series by Diels and Alder and bridged-ring hydrocarbons by Alder and Windemuth.

<u>Norborneol</u>.

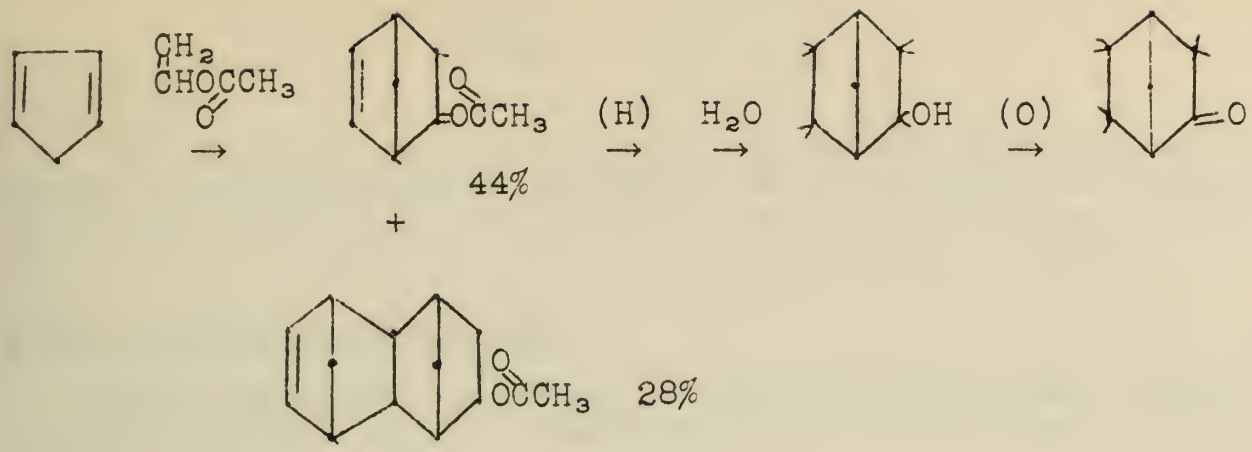


74%

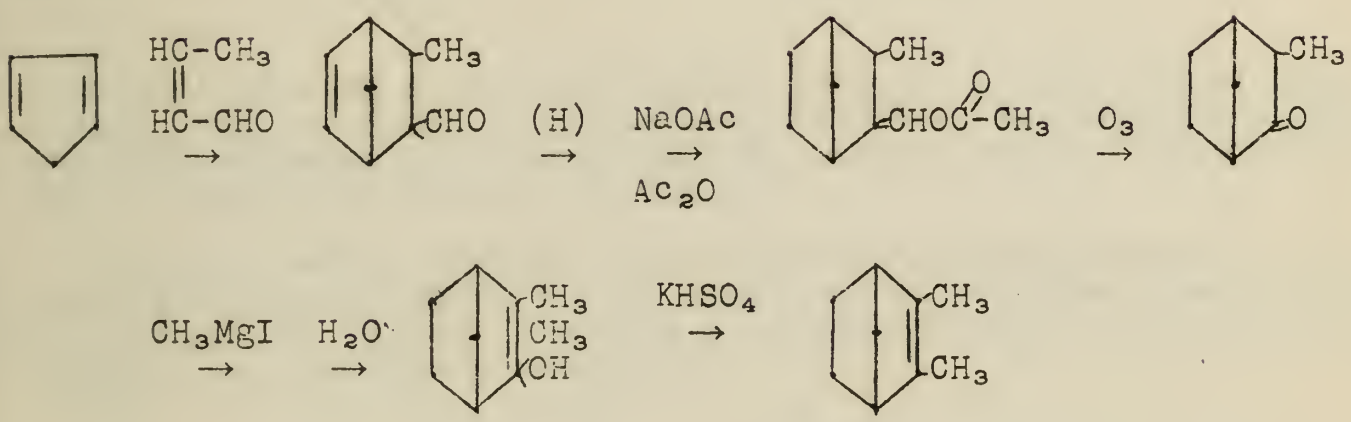
and dinorbornyl ether



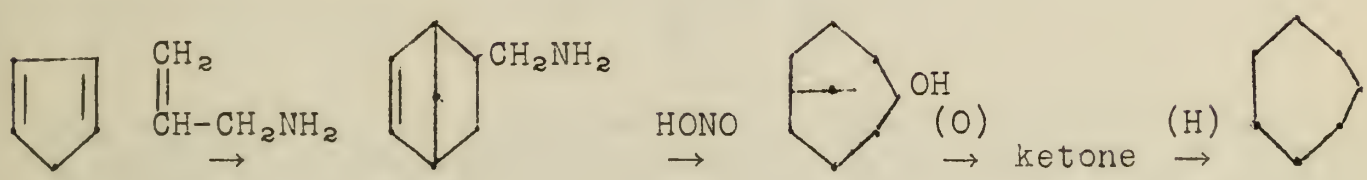
Norcamphor.



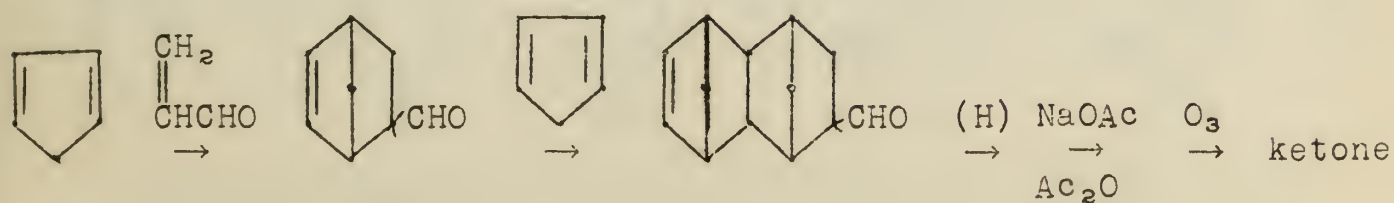
Santene.

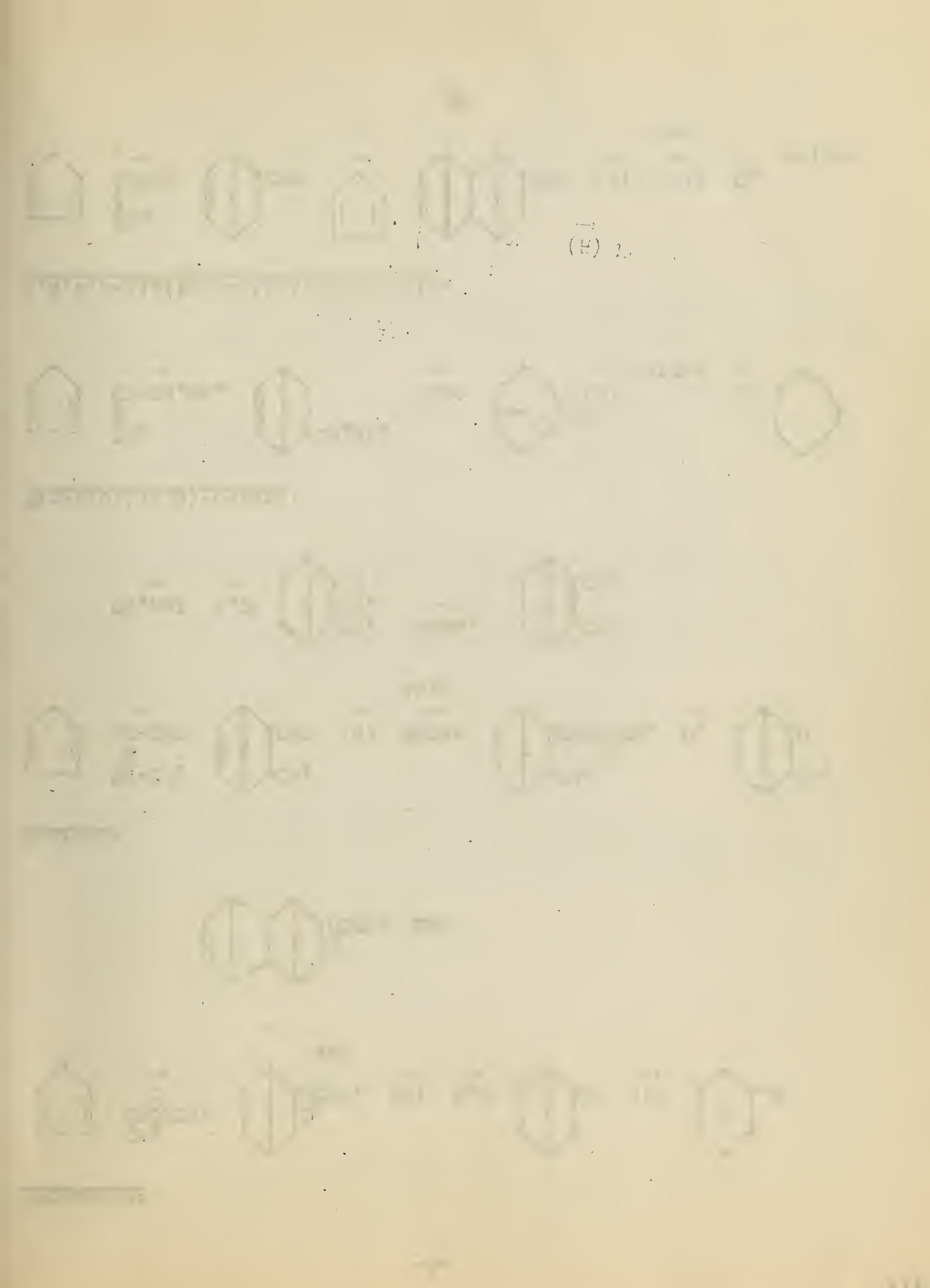


Bicyclo(1:2:3)-octane.



1,4,5,8-bis(Endomethylene)decalin.

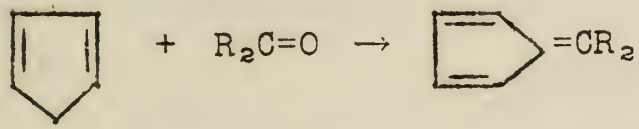




Addition of sulfite or bisulfite to the cyclopentadiene-maleic anhydride adduct, its mono- or di- amides, or esters is said to produce sulfonates of excellent wetting and detergent activity.

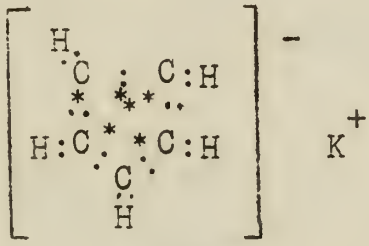
Active Methylene Reactions.

Some important reactions of cyclopentadiene are due to the active methylene group. The preparation of fulvenes is an example.

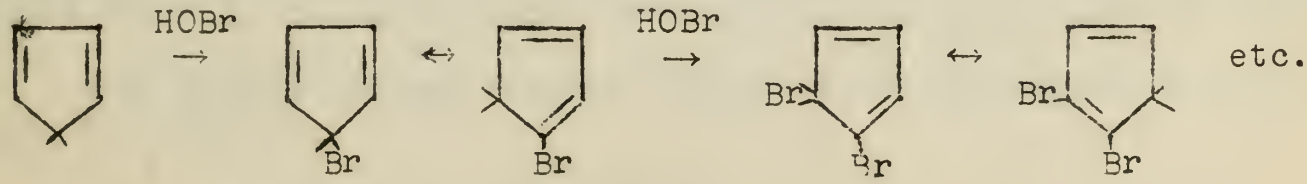


Condensation with N,N-diethyl amino acetone, α-,β-, and pseudo-ionone, and cyclopentanone has been described by Kohler and Kable and with anisaldehyde, benzaldehyde, acetone oxime, ethyl nitrite ethyl oxalate and others, by Thiele.

Active metals displace hydrogen from cyclopentadiene. The metal derivative, according to Alder and Holzrichter (reviewed by P. B. Welldon) either undergoes a tautomeric shift or possesses a symmetrical electron arrangement:

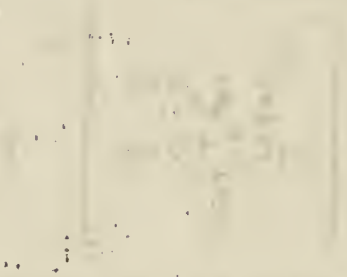


This supposition is supported by two other reactions. Bruson treated cyclopentadiene with acrylonitrile in the presence of "Triton B" and obtained polycyanoethylation products up to the hexa-derivative. Also Straus et al obtained the hexa-halogen derivative upon treating cyclopentadiene with hypohalites:



Grignard reagents metalate cyclopentadiene at the active methylene group.

$$C_5H_6 + RMgX \rightarrow RH + C_5H_5MgX$$

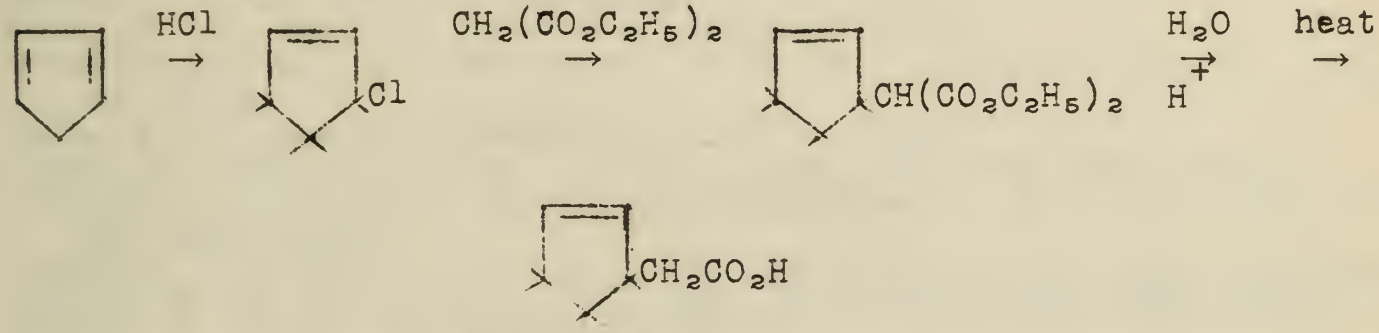


The resulting cyclopentenylmagnesium halide reacts in the usual fashion.

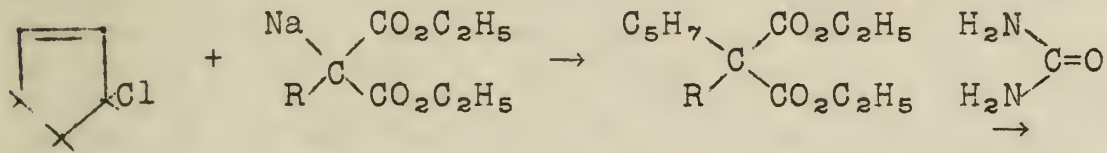
Addition.

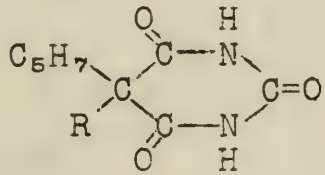
Because of the conjugated system additions to cyclopentadiene usually take place in the 1,4- manner. The stereochemistry in bromine addition was studied by Farmer and Scott, and by Wilson and Wells indicating that the trans isomer is produced at low temperatures and is the stable form.

Dry hydrogen chloride apparently adds 1,4- to produce cyclopentenyl chloride used by Noller and Adams in the preparation of a homolog of chaulmoogric acid.



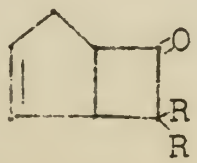
It was also used by Chaux in the production of barbiturates.



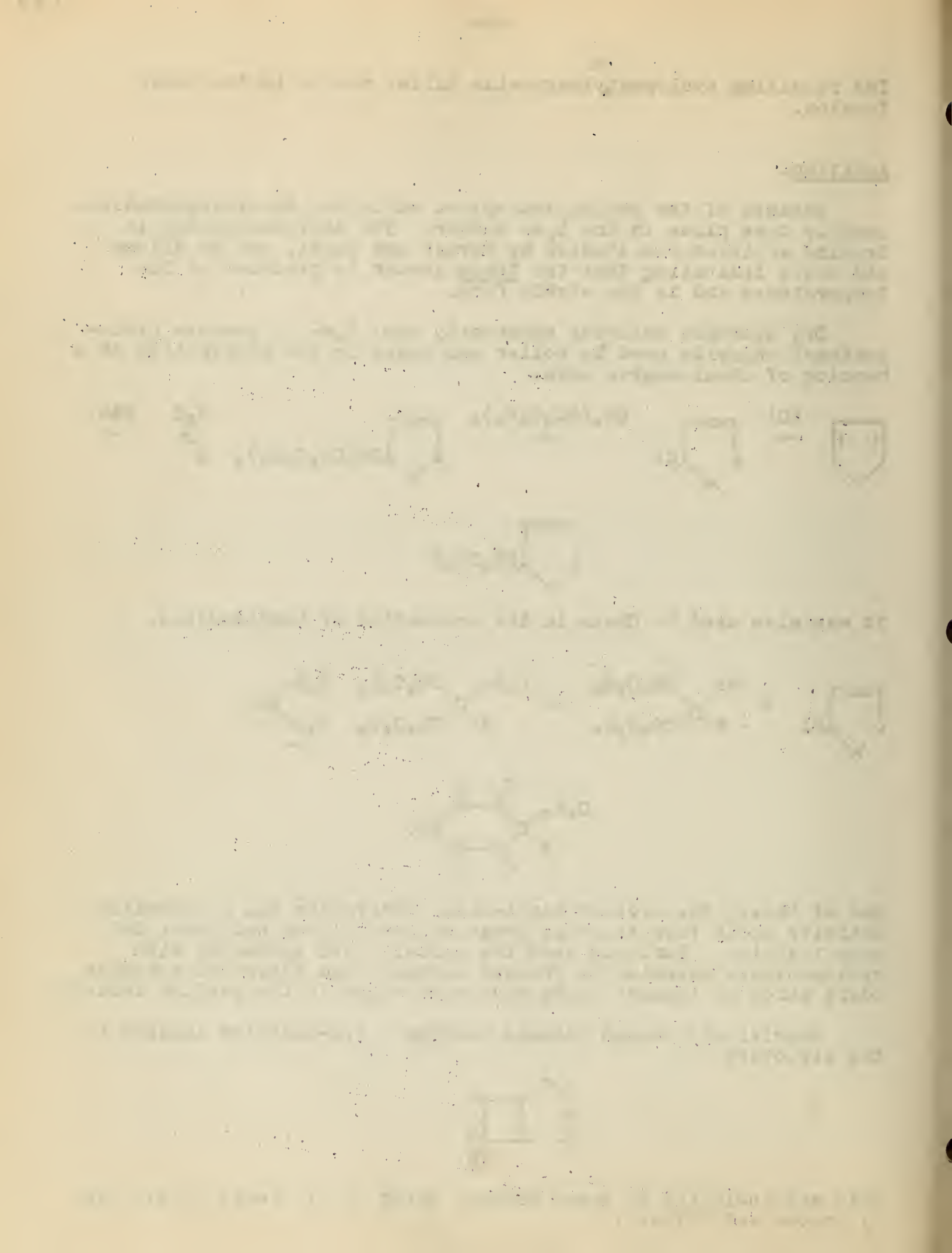


One of these, the cyclopentenyl-allyl derivative had a soporific activity about four times as great as Veronal and had about the same toxicity. Horclois used the malonic acid synthesis with cyclopentenyl chloride to produce lactones and esters of pleasant odors which he thought might have some value in the perfume industry

Suprisingly enough ketenes undergo a 1,2-addition leading to the structure:



This was indicated by three groups, Smith et al, Lewis et al, and by Brooks and Wilbert.



Oxidative addition leads to 1,4- or 1,2- attack depending upon conditions. Seguin, using hydrogen peroxide in the presence of selenium dioxide obtained the 1,2-diol, as did Criegee using lead tetraacetate and osmium tetraoxdie in dry ether. Milas and Maloney, using osmium tetraoxide in t-butyl alcohol, obtained the 1,3-diol.

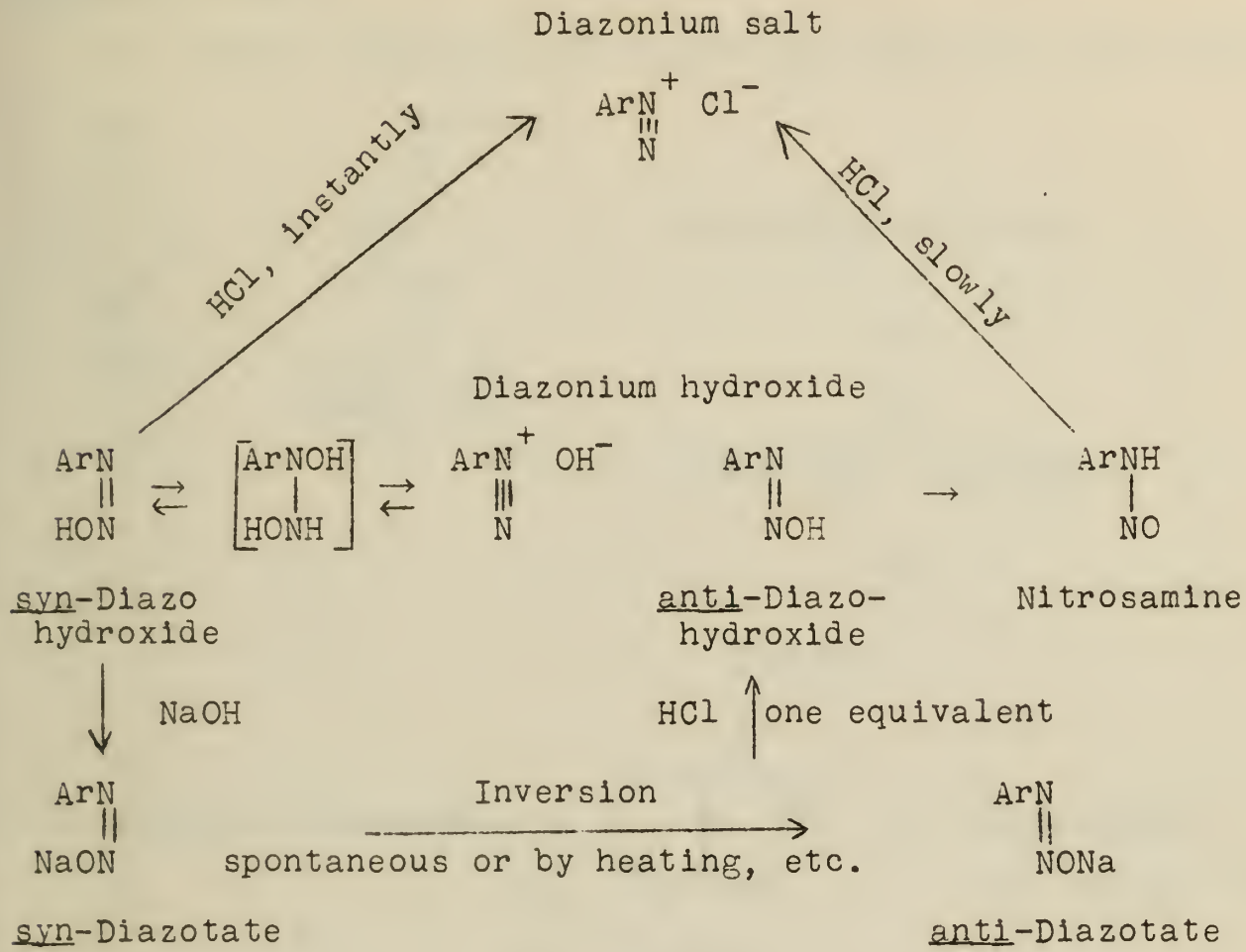
BIBLIOGRAPHY

Roscoe, Sir H. E., Ann., 232, 348 (1886).
Bruson, H. A. and Staudinger, H., Ind. Eng. Chem., 18, 381(1926).
Carmody, W. H., Sheehan, W., and Kelly, H., Ind. Eng. Chem., 30, 245 (1938).
Alder, K. and Stein, G., Angew. Chem., 47, 837 (1934).
Norton, J. A., Chem. Reviews, 31, 319 (1942).
Gold, M. H., Seminar Abstracts, Jan. 11, 1937.
Chadwick, D. H., and McPherson, J. B. Jr., Seminar Abstracts, April 21, 1943.
Ward, M. L., Seminar Abstracts, Feb. 21, 1940.
Alder, K., and Windemuth, E., Ber., 71B, 2404 and 2409 (1938).
Grummitt, O., Klopper, R. S., and Blenkhorn, C. W. J. Am. Chem. Soc. 64, 604 (1942).
Diels, O. and Alder, K., Ann., 470, 62 (1929); Ann., 486, 202 (1931)
Kohler, E. P. and Kable, J., J. Am. Chem. Soc., 56, 2756 (1934).
Thiele, J., Ber., 33, 666-673 (1900).
Thiele, J. and Balhorn, H., Ann., 348,1(1906).
Alder, K. and Holzrichter, H., Ann., 524, 145 (1936).
Welldon, P. B., Seminar Abstracts, October 23, 1940.
Bruson, H. A., J. Am. Chem. Soc., 64, 2457 (1942).
Straus, F., Kolleck, L. and Heyn, W., Ber., 63B, 1868 (1930).
Grignard, V. and Courtot, C., Compt. rend., 158, 1763 (1914).
Farmer, E. H. and Scott, W. D., J. Chem. Soc., 1923, 172.
Wilson, P. J., Jr., and Wells, J. H., Chem. Reviews, 34, 1 (1944).
Noller, C. R. and Adams, R., J. Am. Chem. Soc., 48, 2444 (1926).
Chaux, R., Compt. rend., 194, 1193 (1932).
Horclois, R., Chim. et Industrie Special No. 357 (1934).
Smith, L. I., Agre. C. L. Leekley, R. M. and Prichard, W. W., J. Am. Chem. Soc., 61, 7 (1939).
Brooks, B. T. and Wilbert, G., J. Am. Chem. Soc., 63, 870 (1941).
Seguin, P., Compt. rend., 216, 667 (1943).
Criegee, R., Ann., 481, 268 (1930).
Milas, N. A. and Maloney, L. S., J. Am. Chem. Soc., 62, 1841 (1940).
Criegee, R., Marchand, B., and Wannowius, H., Ann., 550, 99 (1942).

Reported by W. Alexander
May 9, 1945

THE STRUCTURE OF DIAZOTATES

Early in this century, progress in the chemistry of diazo-compounds had reached the point where Hantzsch was able to present the following summary of the evidence, direct and indirect, for the structures of the various compounds which had been isolated.



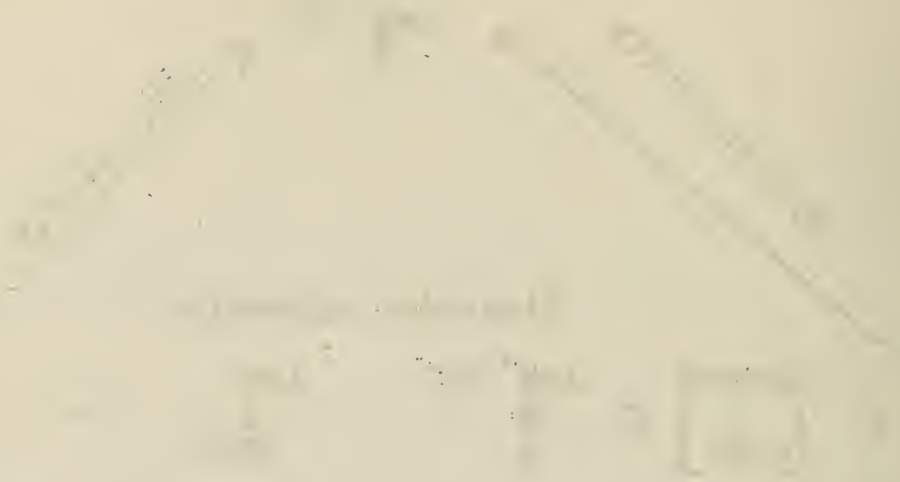
The syn-diazotate has been called the normal or labile form; the anti-diazotate the iso or stable form.

The syn-diazotates are very reactive and couple readily; the anti-diazotates are unreactive and couple with great difficulty. The anti-diazosulfonates undergo oxidation readily to give the diazonium sulfates which also couple very readily.

The structure of the diazonium salt has been proved to be $ArN^{+}_{\|}N\ X^{-}$ but the structure of the diazotates has caused considerable discussion.

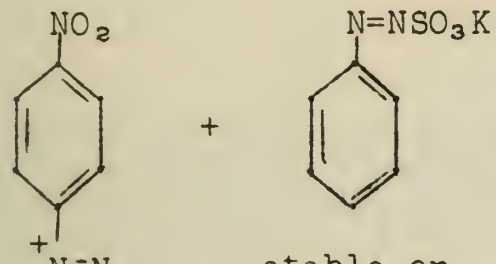
Recently Hodgson and Marsden have published new evidence in this field. They obtained chemical evidence that the different forms were structural rather than geometrical isomers. They also showed that the supposed syn form of potassium benzenediazosulfonate was a mixture rather than a pure compound.

The stable form of potassium benzenediazosulfonate was coupled

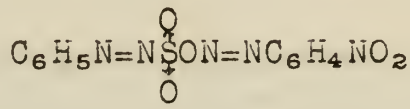


with p-nitrobenzenediazonium chloride, and the resulting compound was treated with alkaline β-naphthol. The products obtained were α-p-nitrobenzene-azo-β-naphthol (II) and the stable form of potassium benzenediazosulfonate. The latter could be isolated as such or oxidized and coupled with β-naphthol to give α-benzene-azo-β-naphthol (III).

The authors suggested the following course for the reactions:

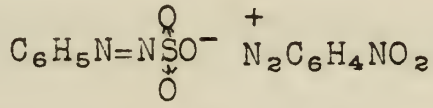


stable or anti form

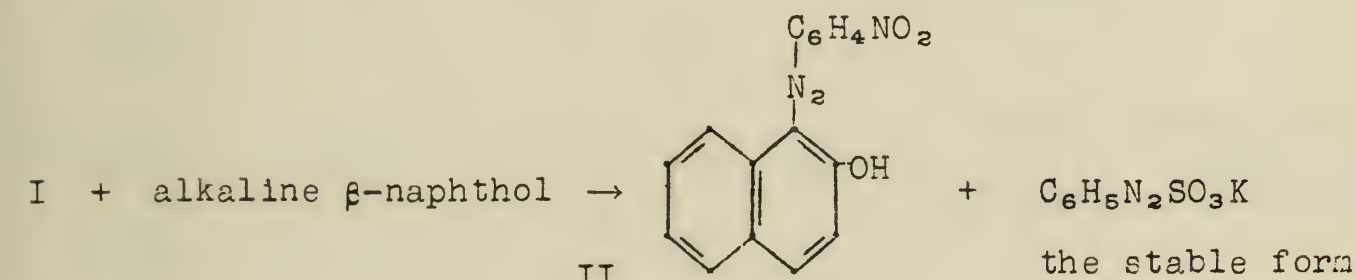


Ia

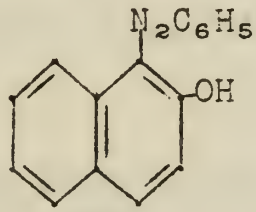
or



Ib



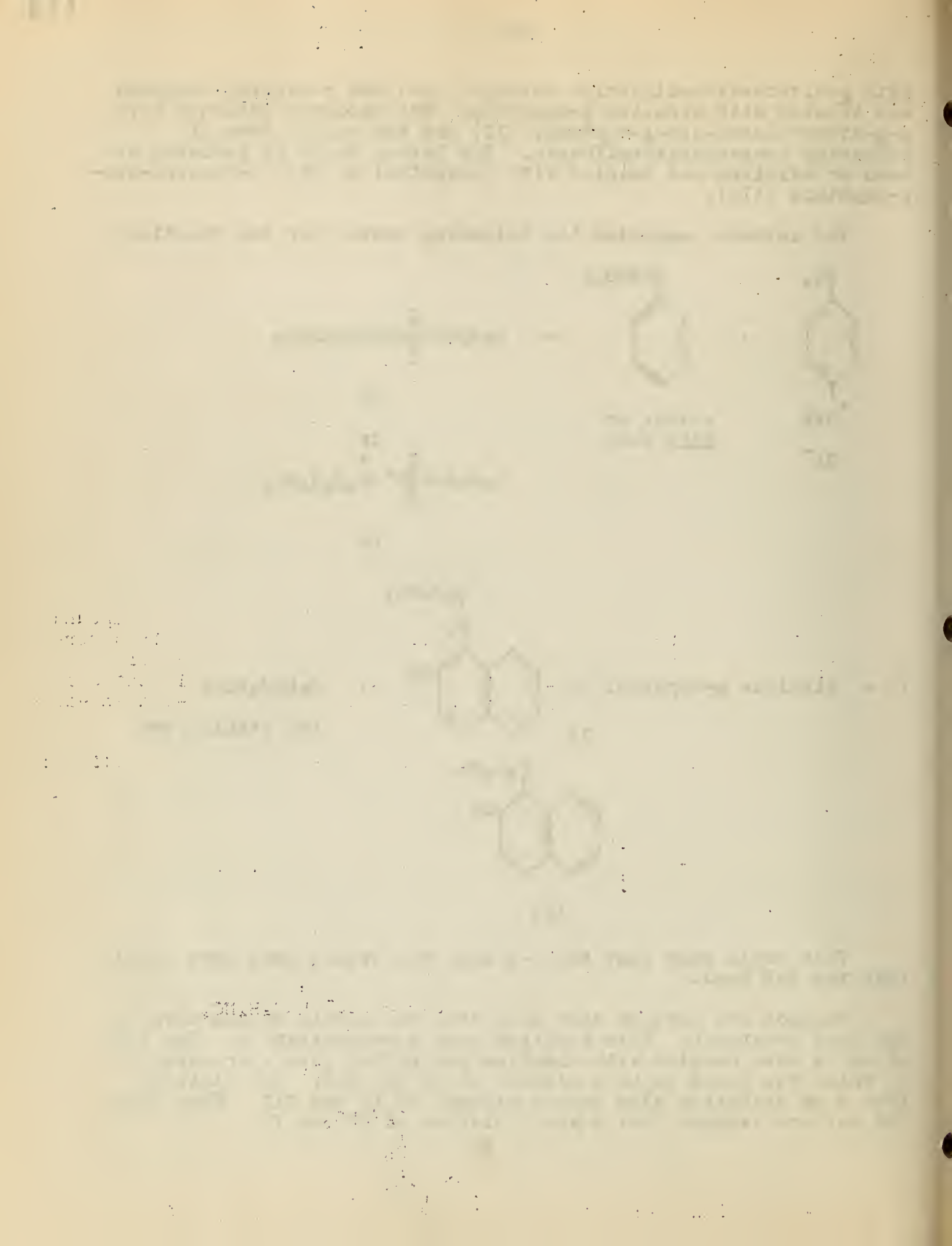
II

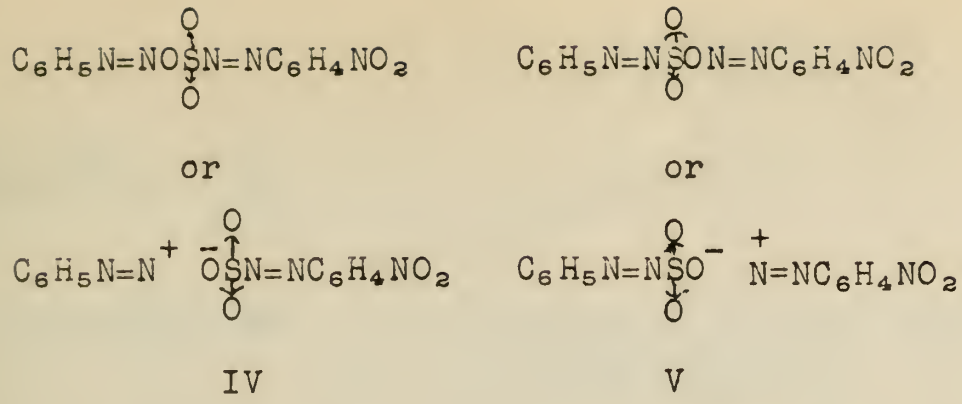


III

This would mean that the O-N bond was broken much more easily than the N-S bond.

Hodgson and Marsden next subjected the labile or cis form to the same treatment. This reaction gave a precipitate A. The substance A when coupled with alkaline β-naphthol gave a precipitate B, which was found to be a mixture of II and III. The filtrate from B on oxidation also gave a mixture of II and III. From this the authors assumed that A was a mixture of IV and V.

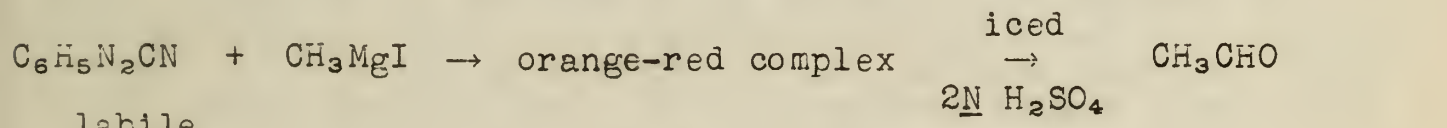


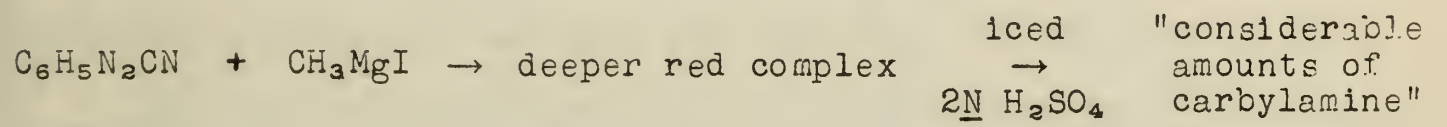


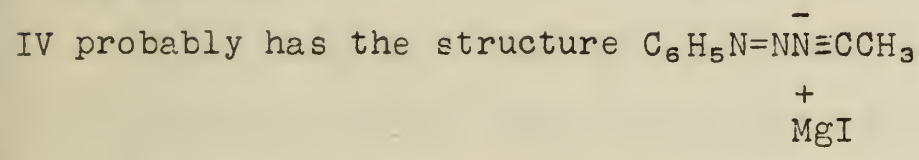
IV V

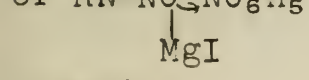
Reasoning from the reaction with the anti form, IV coupled with alkaline β-naphthol should give compound III and the stable form of potassium-p-nitrobenzenediazosulfonate; V under similar treatment should give compound II and the stable form of potassium benzenediazosulfonate.

Hodgson and Marsden also examined the diazocyanide. The stable and labile forms were allowed to react with methylmagnesium iodide.

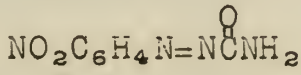




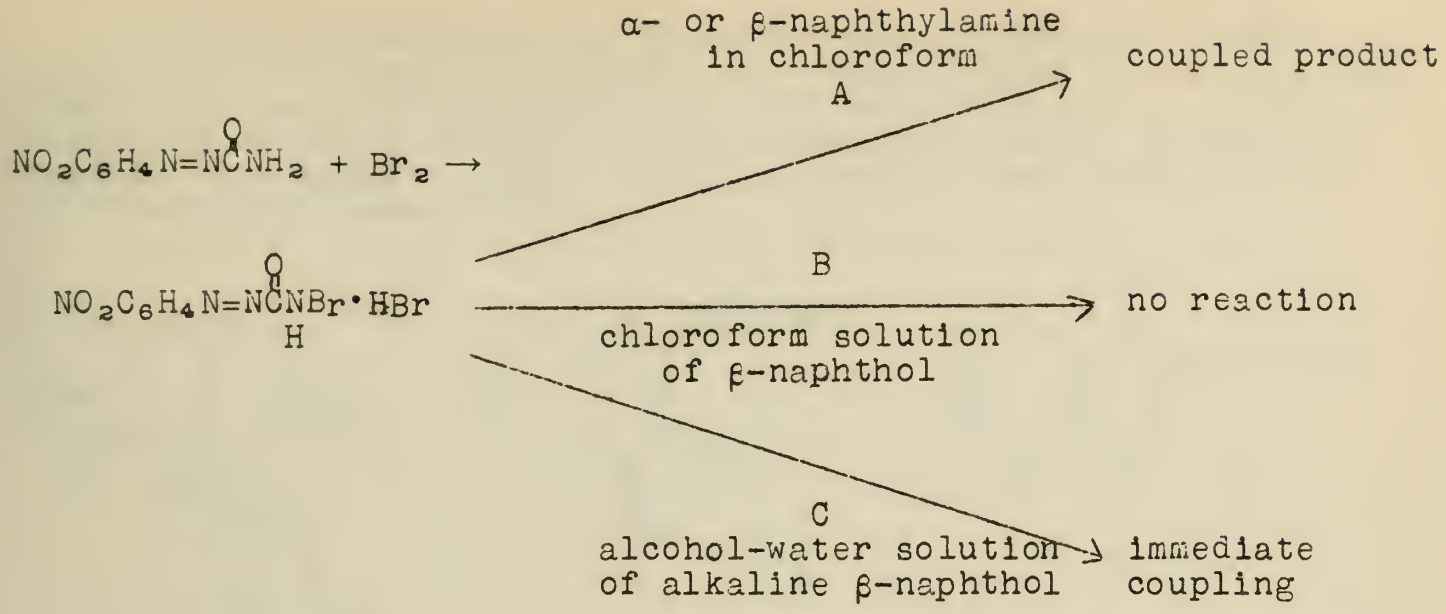
IV probably has the structure 

The authors suggested that V might contain considerable amounts of  and that this would decompose to give phenyl isocyanide.

Hantzsch had previously reported that the hydrolysis of both the labile and stable forms of p-nitrobenzenediazocyanide gave the same compound.



The following set of reactions was carried out using this compound:



The authors explain this behavior in the following manner. The original amide would not couple; hence, the N-C bond would not break. However, in reaction A the Hofmann rearrangement takes place giving a -N=N-N- system in which the N-N bond breaks and coupling occurs. In B, since no base is present, no such reaction can take place, hence, no coupling. In C the authors suggest that the N-bromoamide is hydrolyzed to $NO_2C_6H_4N=NCNOH$; this would undergo the Lossen rearrangement and give the same type of reaction as in A.

It was also pointed out that the difference in bond energy of N-N and C-N bonds is 28 K cal./mole; whereas the difference in energy of the stable and labile form is 21-22 K cal./mole.

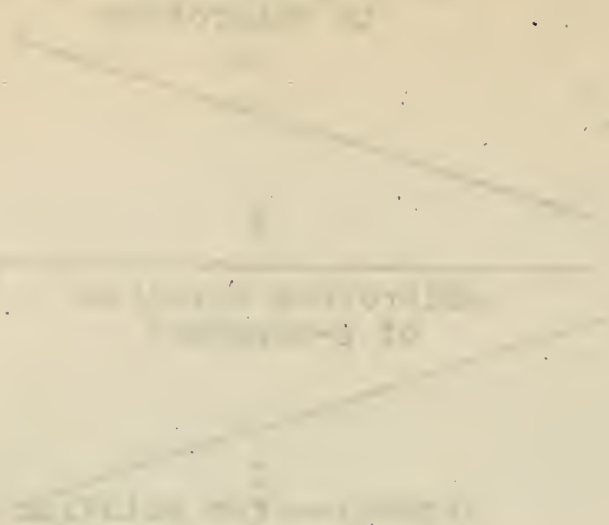
From these facts the authors deduce that the structures of the labile diazosulfonate and diazocyanide should be ArN=NOSOK and ArN=NN=C; whereas the stable forms have the chemical structure assigned by Hantzsch, but cannot yet be assigned either the <u>syn</u> or <u>anti</u> configurations.

ArN=NSOK and ArN=NCN

BIBLIOGRAPHY

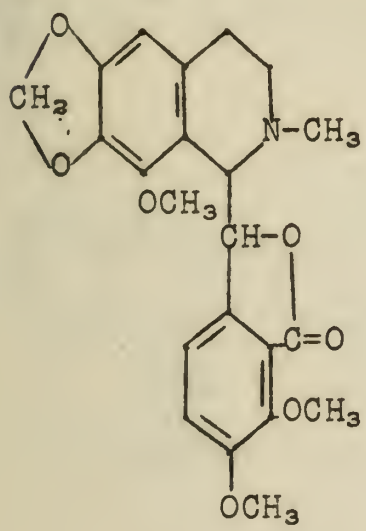
Saunders, K. H., "The aromatic Diazo Compounds," Longmans, Green and Co., New York.
Taylor and Baker, "Sidgwick's Organic Chemistry of Nitrogen," Oxford University Press, London.
Hantzsch and Schultz, Ber., 28, 666 (1895).
Hodgson and Marsden, J. Chem. Soc., 1943, 470-2; 1944, 395-8.
Le Fevre and Vine, J. Chem. Soc., 1938, 431.
Stephenson and Waters, J. Chem. Soc., 1939, 1796.

Reported by Nelson R. Easton
May 16, 1945.



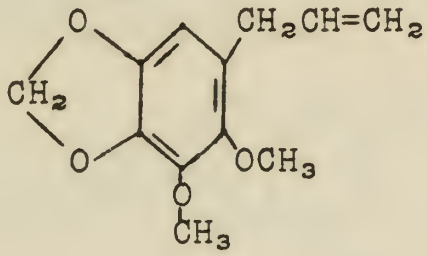
AROMATIC METHYLENEDIOXY COMPOUNDS

Aromatic methylenedioxy compounds are of interest because of their wide occurrance in nature. An example of an opium alkaloid that contains a methylenedioxy ring is narcotine (I). A series of compounds isolated from dill and parsley seeds known as apioles contain this group. Safrol (III), isosafrol, and piperonal are wellknown representatives.



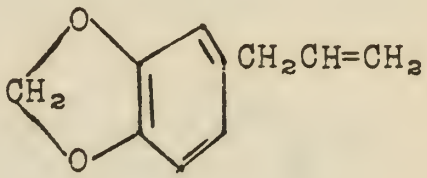
Narcotine

I



Dillapiole

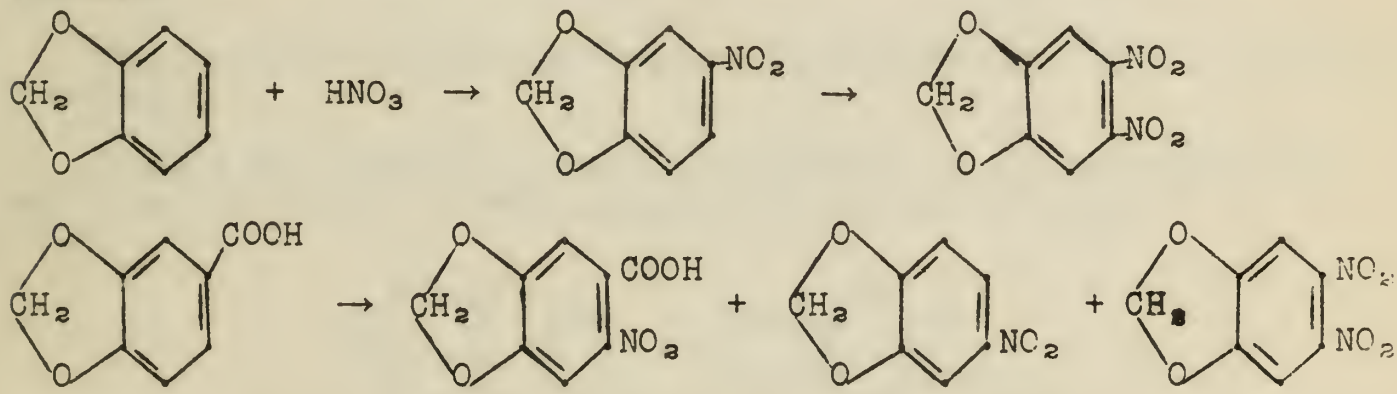
II



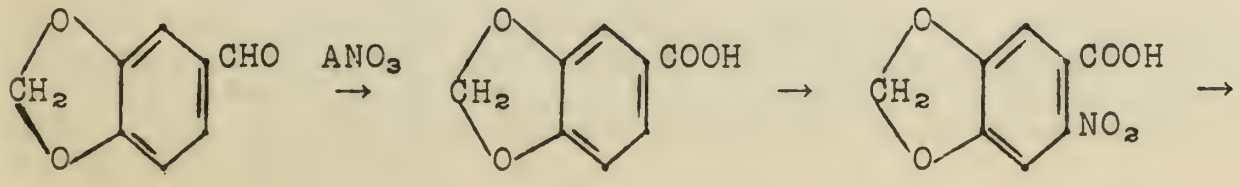
Safrol

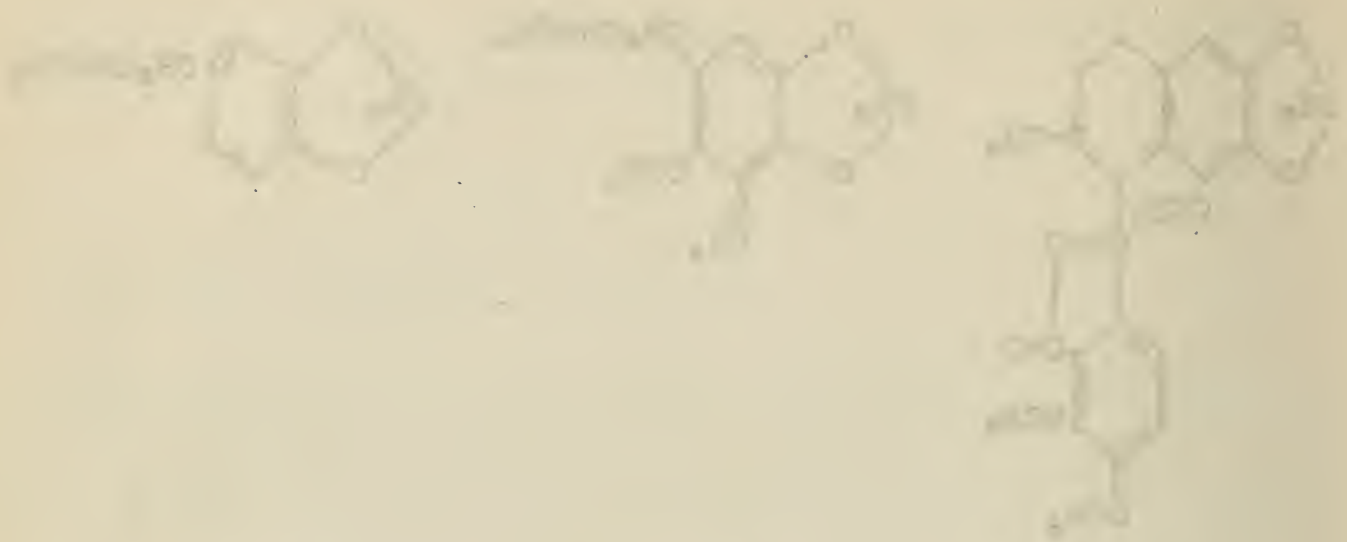
III

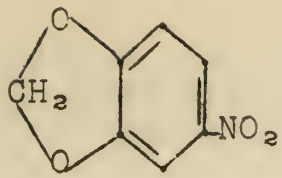
One of the most characteristic features of the methylenedioxy ring system is the fact that orientation cannot be predicted using the classical rules for aromatic substitution. A few examples follow.



The formation of 4-nitromethylenedioxybenzene (IV) from piperonal might proceed as follows.

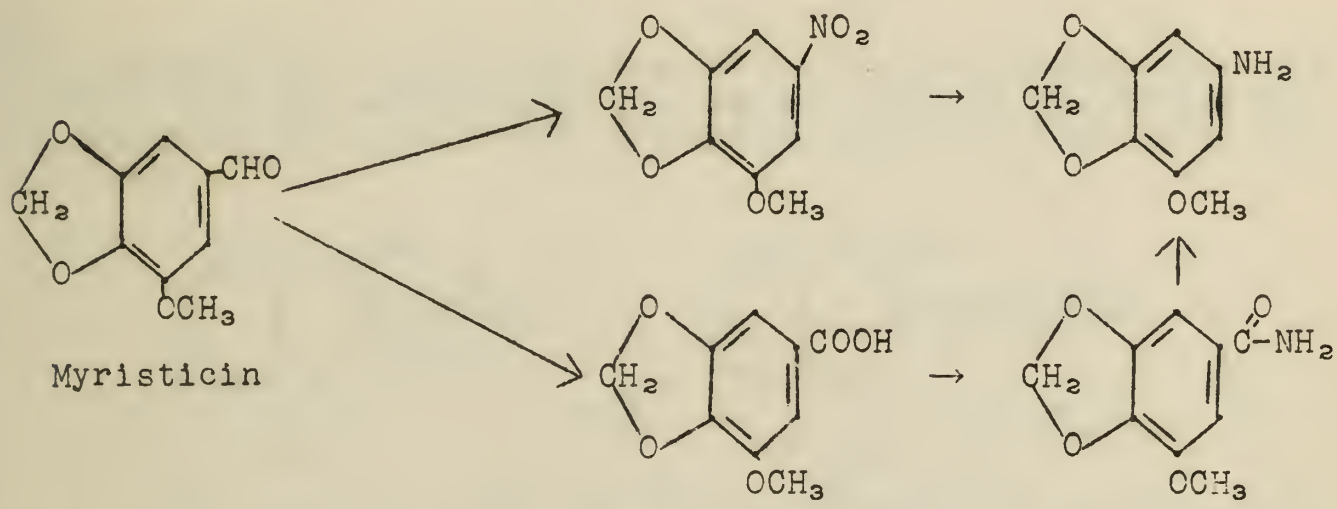






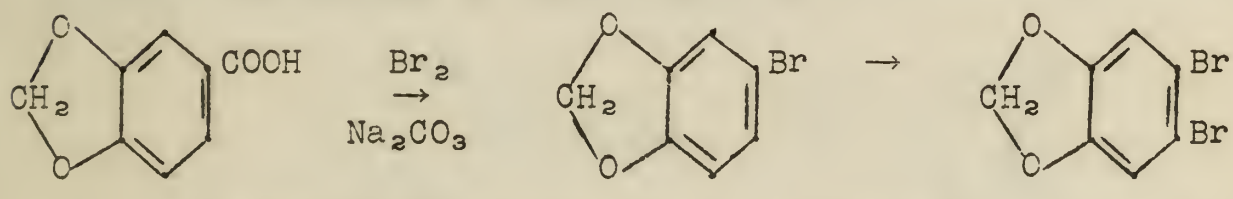
IV

Salway found that the reaction does not occur as above but proceeds by direct replacement of the carbonyl or carboxyl group as shown in the following reactions.



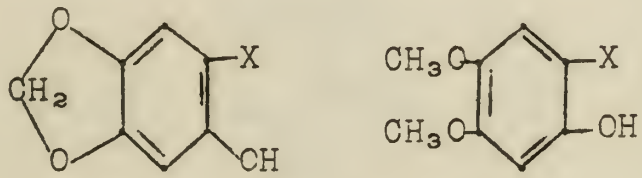
Myristicin

Bromination appears to proceed in a similar fashion.



The 4-carboxy-5-bromomethylenedioxybenzene is stable to further bromination.

Arnold and Bordwell prepared compounds of the following two series and measured the dissociation constants of each.



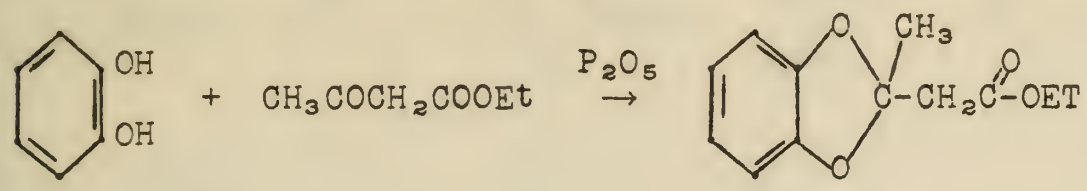
X = CHO, CN, COOH.

In every case the dissociation constant of the methylenedioxy compound was slightly higher than that of the dimethoxy compound. They interpreted this as evidence to indicate a Mills-Nixon effect which would give a more pronounced double bond character between carbon four and five.

Like other acetals the methylenedioxy compounds are cleaved by

IV

acid but unlike other acetals some methylenedioxy compounds are cleaved by base. Arnold, Bortnich and McMullen prepared a series of methylenedioxy esters by condensing catechol with keto esters.

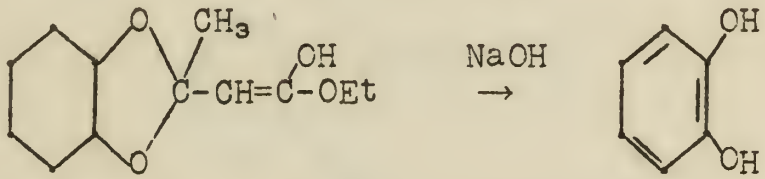


V

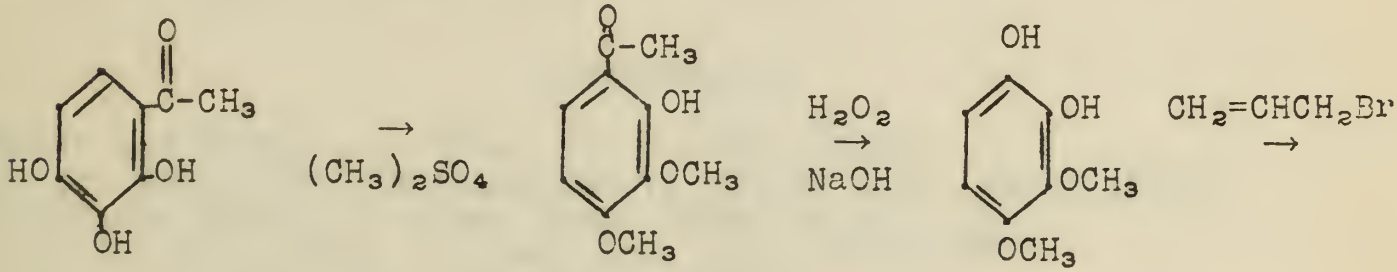
In attempting to hydrolyze the ester (V) with sodium hydroxide, they found that the methylenedioxy ring was cleaved in the process. The methylenedioxy ring in the following esters (VI and VII) were stable in base.

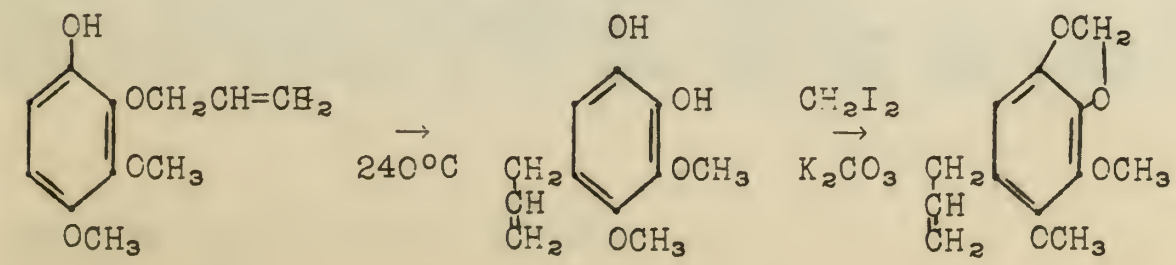
VI VII

They explained this unexpected cleavage by assuming that the intermediate was the enol of the ester which is a vinylog of the unstable hemiacetal or hemiorthoester.

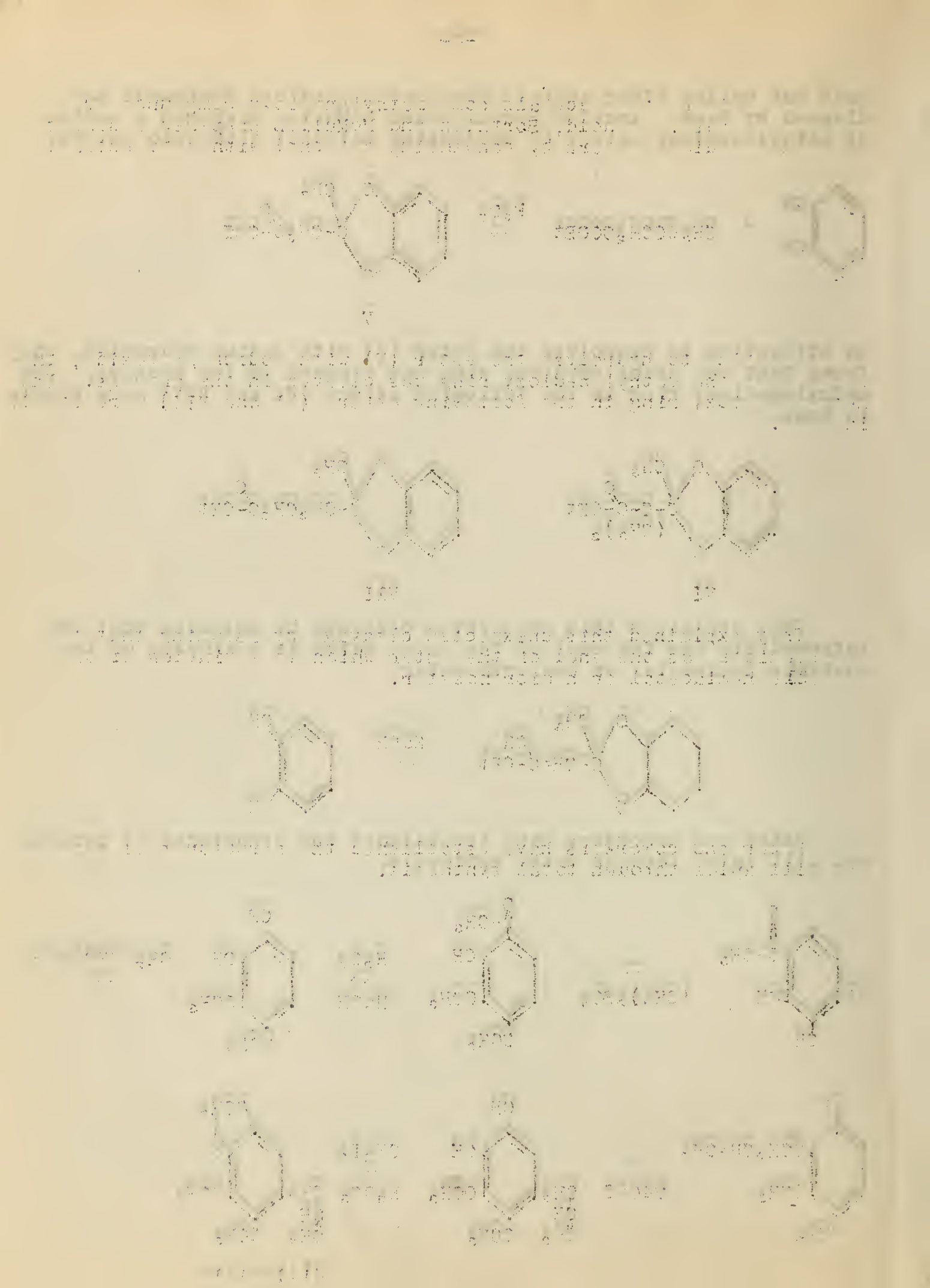


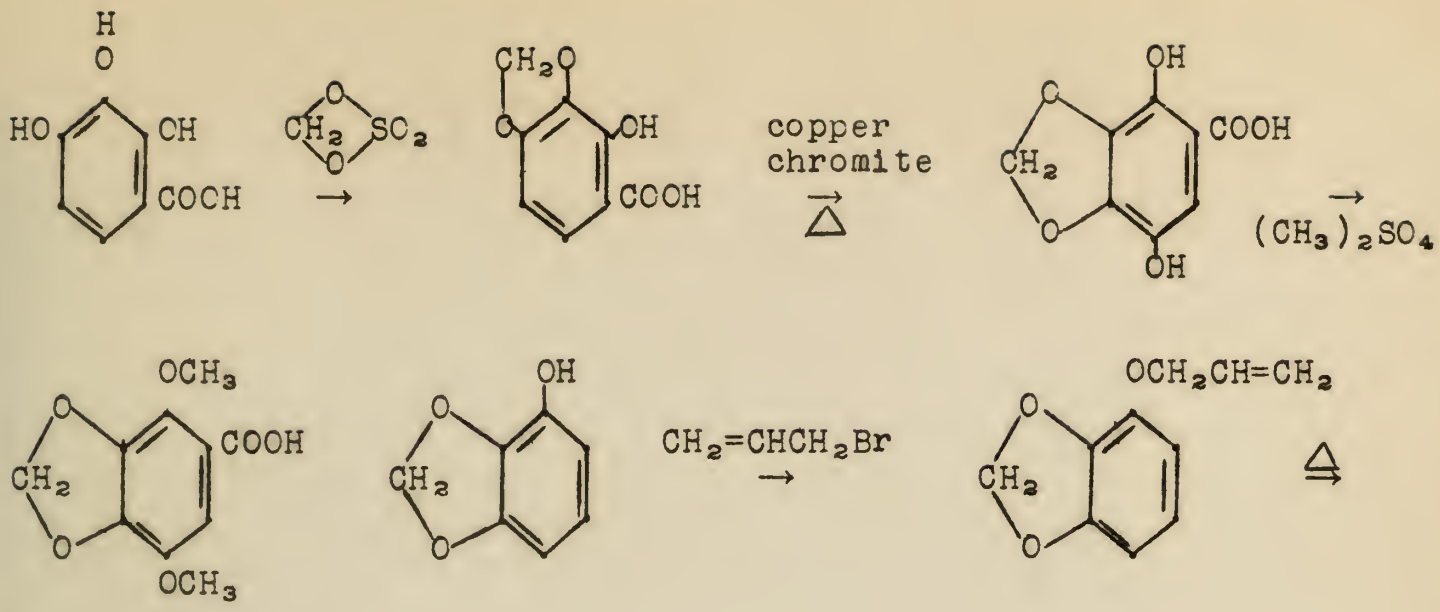
Baker and coworkers have established the structures of parsley and dill apiol through total synthesis.



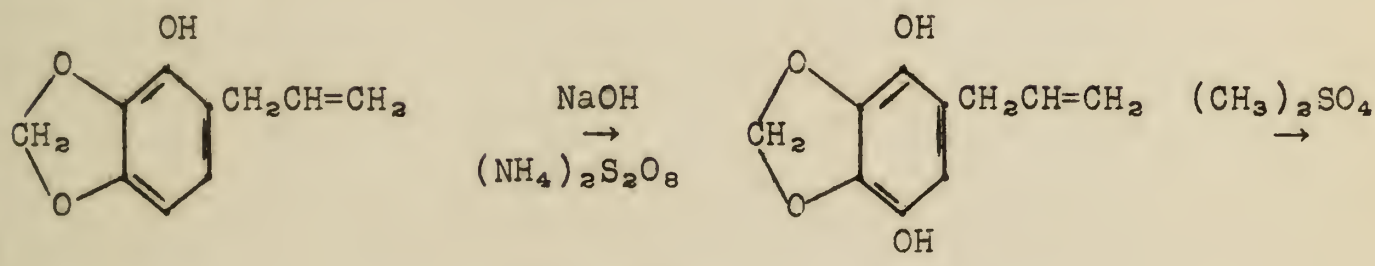


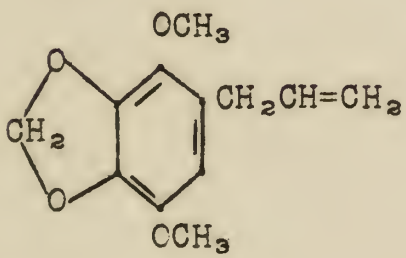
dillapiole





parsley
apiolic acid





parsley apiole

BIBLIOGRAPHY

Baker and Savage, J. Chem. Soc., 1609 (1938).
Baker, Jukes, and Subrahmanyan, J. Chem. Soc., 1681 (1934).
Baker and Smith, J. Chem. Soc., 2542 (1931).
Robinson and Jones, J. Chem. Soc., 111, 903 (1917).
Salway, J. Chem. Soc., 95, 1155 (1908).
Sloof, Rec. Trav. Chim., 54, 905 (1935).
Arnold, Bortnich, and McMullen, J. Am. Chem. Soc., 64, 1410 (1942).
Arnold and Bordwell, J. Am. Chem. Soc., 64, 2983 (1942).

Reported by William J. Bailey
May 16, 1945.