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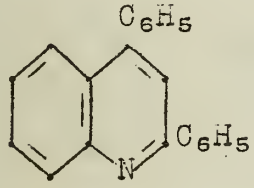
REACTIONS INVOLVING THE AZOMETHINE LINKAGE OF PYRIDINE

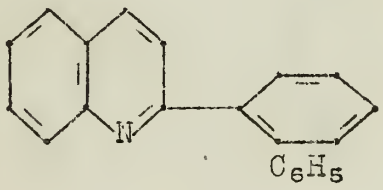
When an excess of Grignard reagent is heated with pyridine, alkyl- and arylpyridines are produced. With phenylmagnesium bromide the 2-phenylpyridine which is formed is accompanied by lesser amounts of 2,6-diphenylpyridine. This result indicates that the primary addition compound loses MgBrH or its equivalent to yield 2-phenylpyridine which in turn can react to form the diphenylpyridine.

Lithium alkyls and aryls react in a similar way but more smoothly and at lower temperatures. When phenyllithium is heated with pyridine for eight hours in toluene a 40-50% yield of 2-phenylpyridine is obtained (2).

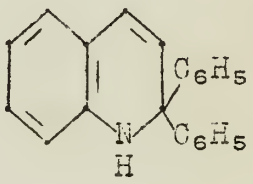
Quinoline has been shown to behave in a surprising manner, yielding a diphenylquinoline as well as the expected 2-phenylquinoline (3). The diphenyl compound (m.p. 86-87°) could be prepared also by the action of phenyllithium on 2-phenylquinoline, and it was considered likely that addition of the reagent to 2-phenylquinoline had occurred in the 1,4 manner. The new base was not 2,4-diphenylquinoline (I), however; this compound is known and melts at 112°. It differed also from 2(o-biphenyl)quinoline (II), a compound which might be formed by a 1,4-addition involving the phenyl radical.



I



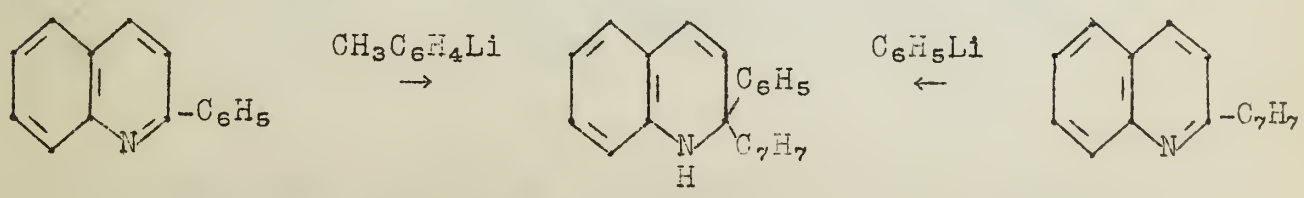
II



III

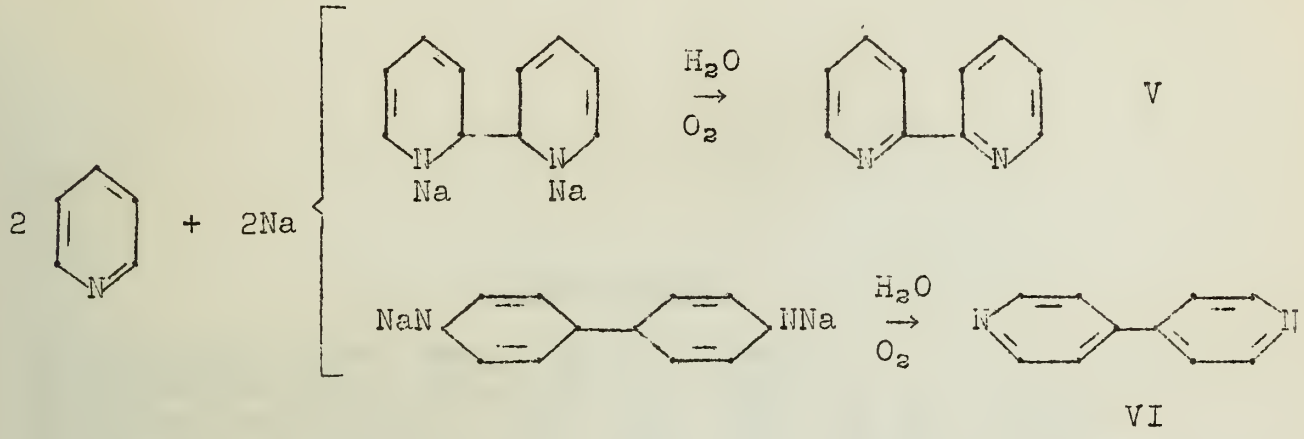
The compound was finally shown to be 2,2-diphenyl-1,2-dihydroquinoline (III), arising from 1,2 addition to 2-phenylpyridine.

This structure was confirmed by the observation that the reaction of 2-phenylquinoline with p-tolyllithium gave the same product as the condensation of 2-p-tolylquinoline with phenyllithium, namely, 2-phenyl-2-p-tolyl-1,2-dihydroquinoline (IV).

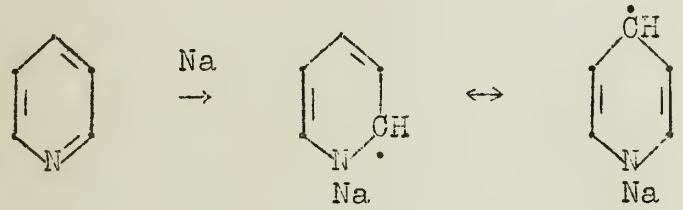


IV

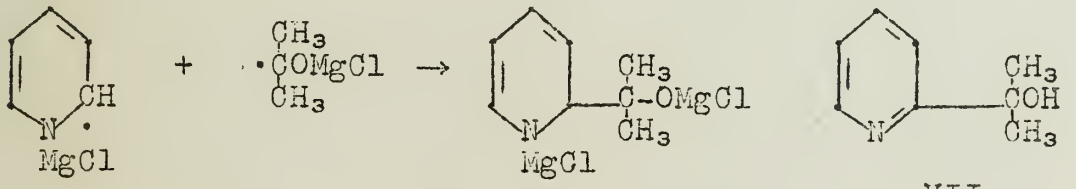
A few years ago a new type of reaction involving the azomethine group was discovered by Emmert and Asendorf (4). It had long been known that when the sodium derivative of pyridine is treated with water 2,2'-dipyridyl (V) and 4,4'-dipyridyl (VI) are formed, the corresponding tetrahydro compounds being intermediates.



There are good reasons for believing that these reactions involve a free radical which might be written with the unpaired electron in the 2 or the 4 position.



Emmert and Asendorf conceived the idea that it might be possible to cause such radicals to unite with ketyls from ketones, producing compounds analogous to pinacols. They were able to prepare these compounds by treating a mixture of pyridine and a ketone with magnesium in the presence of mercuric chloride. From acetone, for example, they obtained 2-(2-hydroxyisopropyl)-pyridine (VII).



This remarkable synthesis has been modified by Bachman and Micucci (5) who obtained yields of 29% based on the magnesium.

Similar results were obtained by Emmert and Asendorf with methyl ethyl ketone, acetophenone and benzophenone. The new reaction was applied successfully also to α- and β-picolines.

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Reported by R. C. Fuson
September 17, 1948

RECENT INVESTIGATIONS OF CALABASH CURARE

Since the last Seminar report (1) on the alkaloids of curare there have been four papers from the laboratories of Karrer (2,3,4) and Wieland (5) dealing with structure studies and with the isolation of new alkaloids from calabash curare. Earlier studies (1) in Wieland's laboratory had established the presence of the following substances in various specimens of calabash curare.

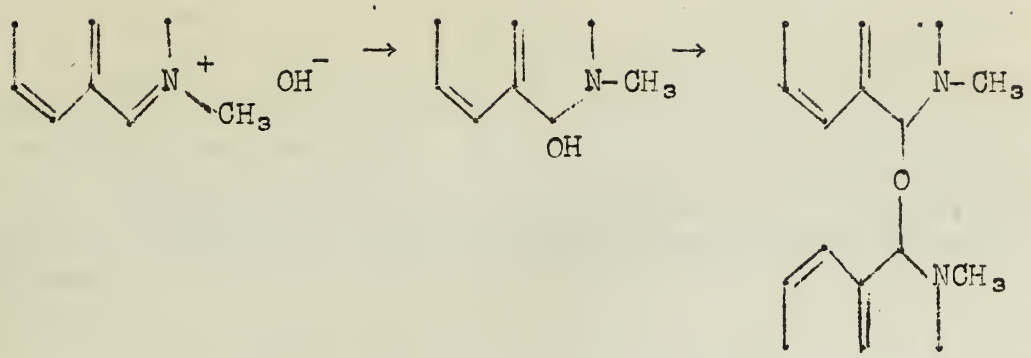
C-Curarine-I*	$C_{20}H_{21}N_2Cl$
C-Curarine-II	$C_{20}H_{23}N_2Cl$
C-Curarine-III	$C_{20}H_{21}N_2Cl$
C-Toxiferine-II	$C_{20}H_{23}N_2Cl$
C-Dihydrotoxiferine-I	$C_{20}H_{23}N_2Cl$
C-Isodihydrotoxiferine-I	$C_{20}H_{23}N_2Cl$

*The prefix C, an abbreviation for calabash, denotes the source of the alkaloid.

Other related substances, toxiferine-I ($C_{20}H_{23}ON_2Cl$), toxiferine-IIa ($C_{20}H_{25}O_2N_2Cl$) and toxiferine-IIb, along with toxiferine-II, had been isolated in Wieland's laboratory from the bark of Strychnos toxifera, a vine known to be employed by some of the Indians in the preparation of curare.

In the recent studies, Karrer and Schmid fractionated 200 g. of dry calabash curare and obtained eight new alkaloids: "alkaloid A", $C_{20}H_{23}ON_2Cl$; "alkaloid B", $C_{20}H_{25}N_2Cl$; C-calebassine, $C_{20}H_{25}ON_2Cl$, C-toxiferine-I, $C_{20}H_{23}ON_2Cl$, C-calebassinin, $C_{19}H_{23}O_2N_2Cl$; C-fluorocurine, $C_{20}H_{23}O_2N_2Cl$; C-alkaloid-UB, $C_{19}H_{23}O_3N_2Cl$(?); and C-alkaloid-X. C-Curarine-I is the principal alkaloid isolated both by Karrer and by Wieland. C-Toxiferine-I is said to be the most active alkaloid known, the limiting toxic dose for the dog being about 0.01 mg./kg. (subcutaneous injection). Karrer and Schmid believe C-toxiferine-I to be identical with the toxiferine-I of Wieland.

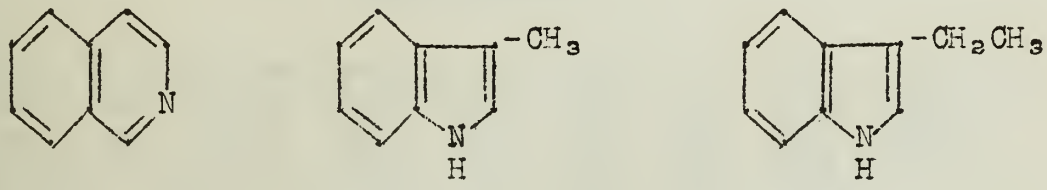
The most extensive structure studies have been carried out on C-curarine-I and C-dihydrotoxiferine-I. From the earlier work it was believed that one of the nitrogen atoms of C-curarine-I was a quaternary ammonium nitrogen. Pyrolysis (300°) at 10^{-4} mm. converts the substance to nor-C-curarine-I and methyl chloride. The methiodide of nor-C-curarine-I can be converted to the chloride and picrate, both of which are identical with the corresponding salts of C-curarine-I. Thus the quaternary nitrogen atom is attached to at least one methyl group. Treatment of C-curarine-I with strong bases leads to a dimeric ether ($C_{40}H_{42}ON_4$). This reaction appears to be that of a quaternary quinoline or isoquinoline nucleus, the quaternary hydroxide changing to a pseudobase and thence to an ether. Comparison of the pK value of nor-C-curarine-I with values for various aromatic and hydroaromatic



quinoline and isoquinoline compounds suggests that a tetrahydroisoquinoline system is present.

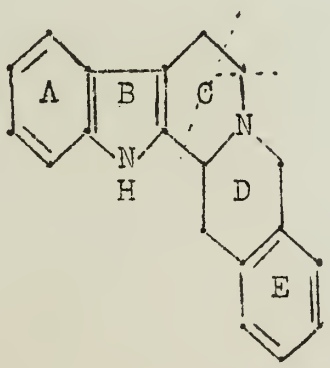
The second nitrogen atom of C-curarine-I is neutral. In zinc dust distillations the unmistakable odor of indole is evident.

Heating of C-dihydrotoxiferine-I with sulfur or zinc produces isoquinoline (I), and the reaction with zinc yields in addition substances believed to be skatole (II) and β-ethylindole (III).



I II III

It thus appears likely that this alkaloid contains the ring system shown in structure IV.



IV

Cleavage of ring C along either path indicated by the dotted lines and dehydrogenation would give rise to isoquinoline and skatole or

β-ethylindole. Wieland has postulated that C-dihydrotoxiferine-I contains the nucleus shown in structure IV. Karrer independently suggested the presence of the tetrahydro-β-carboline system (rings A, B, and C in structure IV) in C-toxiferine-I on the basis of similarities in color reactions of the alkaloid and known tetrahydro-β-carboline derivatives. The formula of the C-dihydrotoxiferine-I corresponds to a methochloride of a dihydro derivative of IV. The substance IV has been synthesized (6) in connection with studies of yohimbine, but its physiological action has not yet been reported.

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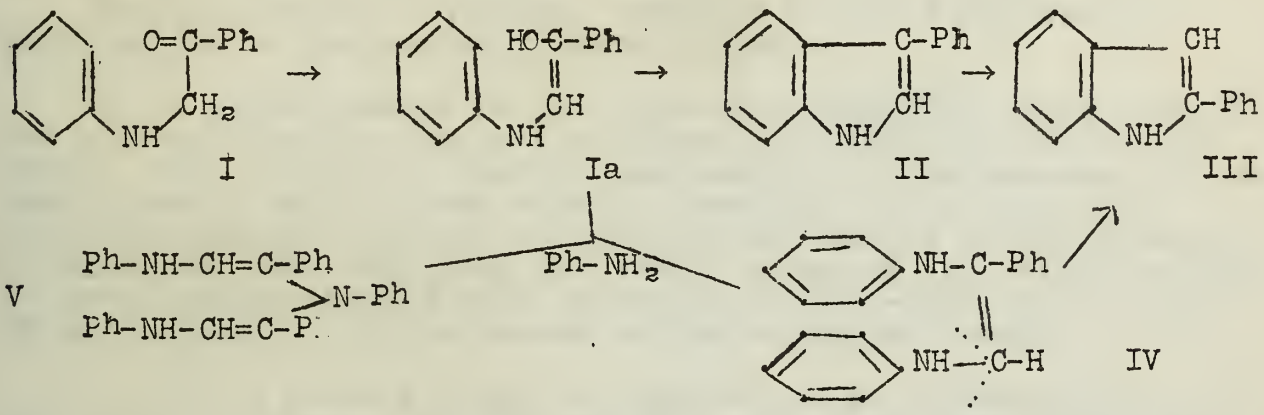
Reported by H. R. Snyder
September 17, 1948

THE MECHANISM OF INDOLE FORMATION FROM PHENACYLARYLAMINES.

Möhlau[1] discovered that phenacylaniline was converted to 2-phenyl indole, when exposed to air, or heated with phosphorus pentachloride or aniline. The mechanism of this reaction has remained obscure, in spite of much investigation[2] and controversy.

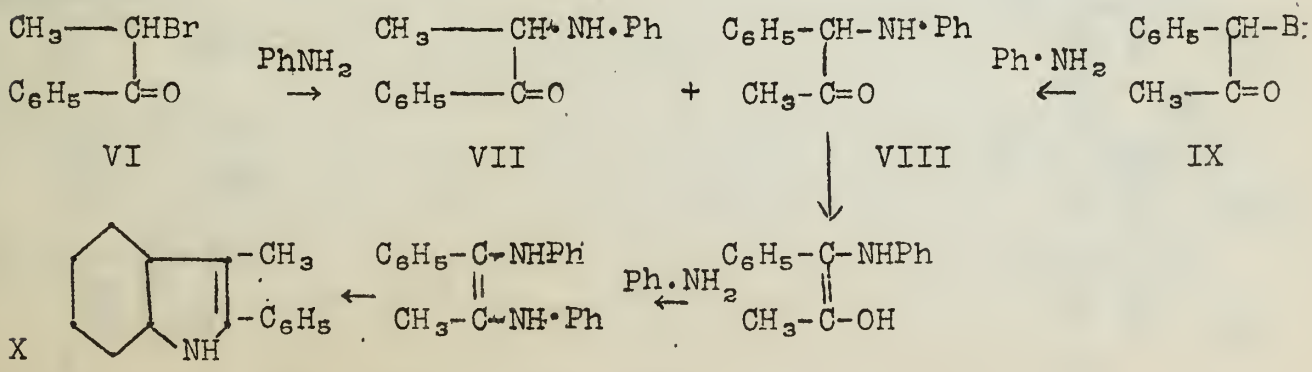
Fischer and Schmidt[3] proposed that phenacylaniline in its enol form (Ia) cyclised to 3-phenyl indole, which then isomerised to 2-phenyl indole and offered some experimental evidence.

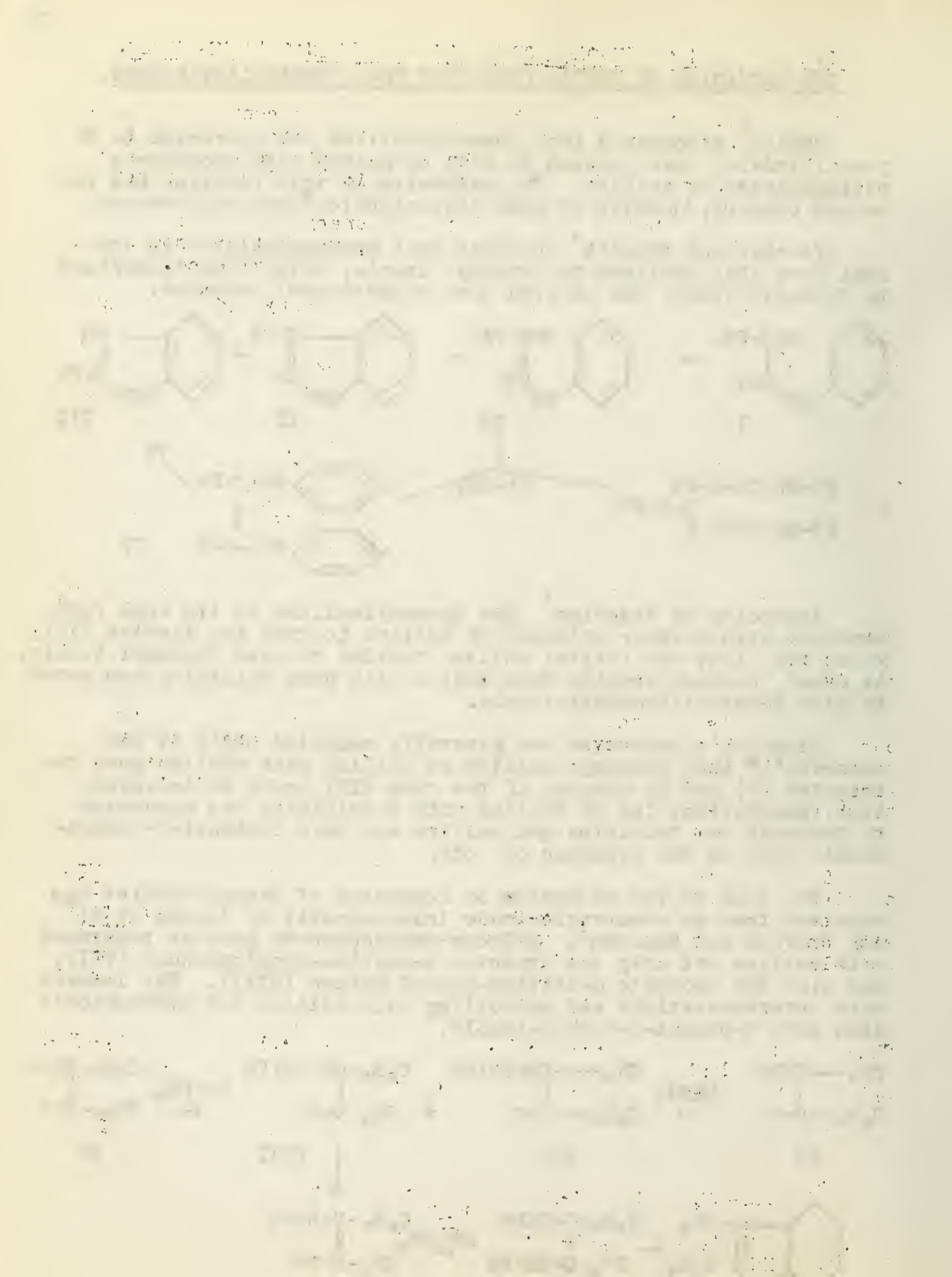


According to Bischler[4], the phenacylaniline in its enol form combined with another molecule of aniline to give the diamine (IV), which then lost the initial aniline residue to give 2-phenyl indole. As proof, phenacylbromide when boiled with para toluidine was shown to give 2-phenyl-5-methyl-indole.

Bischler's mechanism was generally accepted until it was observed[5,6] that phenacyl aniline on boiling with aniline gave the triamine (V) and no diamine of the type (IV) could be isolated. Also, phenacylaniline on boiling with o-toluidine was converted to phenacyl -o- toluidine and aniline and gave 2-phenyl-7-methyl-indole only in the presence of acid.

The clue to the mechanism of formation of 2-aryl-indoles was obtained from an observation made independently by Julian et al[7] and Stevens and Mcgeoch[8]. α-Bromo-propiophenone gave on treatment with aniline not only the expected α-anilino-propiophenone (VII), but also the isomeric α-anilino-benzyl ketone (VIII). The isomers were interconvertible and on boiling with aniline and hydrochloric acid gave 2-phenyl-3-methyl-indole.





Julian et al[7] concluded that the isomerization of VII to VIII may be the first step, followed by enolization, replacement by an aniline residue and final cyclization through loss of an aniline molecule. They showed that in the conversion of desylaniline to 2,3-diphenyl-indole, the intermediate desylanilineanil that should be formed according to the above mechanism could be isolated. The fact that α-anilino-propiomesitylene could not be cyclized to the corresponding indole was considered further proof that aniline addition was an essential step, since in this particular case steric hindrance may prevent aniline addition.

Recent essential findings[9] relevant to the mechanism of indolization of phenacylarylamines follow:

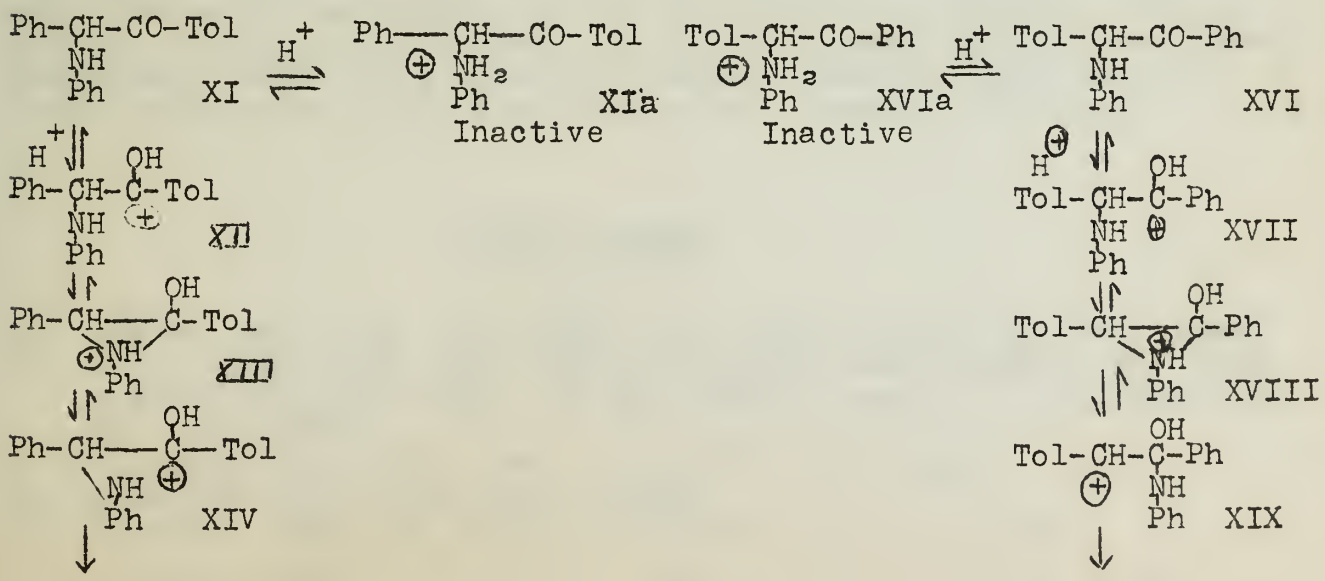
1. A phenacylamine of the type Ph.NH.CHR.COR' where R and R' are both aryl groups may have considerable stability in the pure state. When heated to moderate temperature in the presence of small quantities of acid, it may readily isomerize to the phenacyl compound PhNH.CHR'.COR and at higher temperatures in the presence of acids may then indolise; the indole obtained from either of the isomeric phenacylamines will therefore be 2-R'-3-R-indole formed by the cylization of the second and more stable isomer.

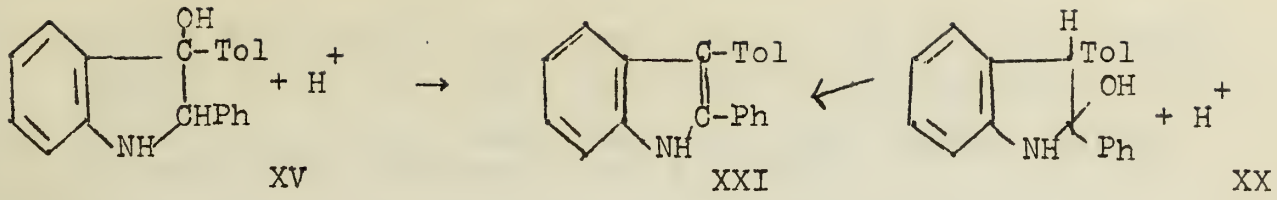
2. If an N-alkyl group is inserted in the phenacylamines, the two resulting isomers Ph.NR".CHR.COR' and Ph.NR".CHR'.COR do not undergo detectable interconversion and under vigorous conditions cyclize directly giving different indoles.

3. The pure dry hydrobromides of phenacylamines do not yield indoles on heating but decompose.

4. In the case of phenacyl primary amines, aniline hydrobromide was a more effective catalyst than aniline hydrochloride or N-ethyl aniline hydrobromide.

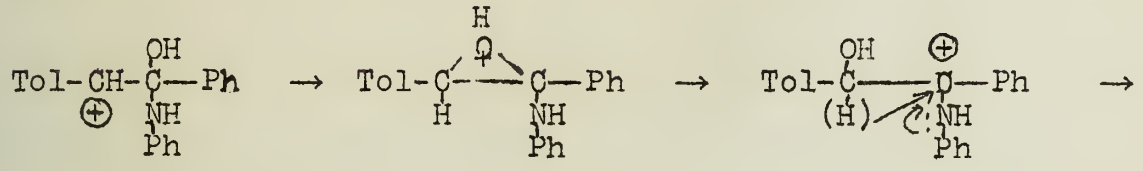
The mechanism postulated by Brown and Mann[9] has been modified slightly and is presented below with the reactions of the isomeric 1-phenyl-p-methylphenacylaniline and 1-p-tolylphenacylaniline as example.



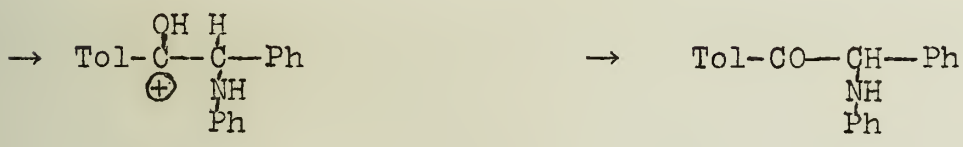


XV XXI XX

A plausible mechanism for the conversion of XI to XVI would be:



XIX XXII XXIII



XXIV XI

The mechanism clarifies the following experimentally observed facts:

1. The pure dry phenacylamine hydrobromides do not give indoles, because only the cations XIa and XVIa will be present and these are clearly inactive.

2. Aniline hydrochloride the salt of a stronger acid and N-ethyl aniline hydrobromide the salt of a stronger base are less dissociated and are therefore less effective than aniline hydrobromide as catalysts in this reaction, which depends on proton addition.

3. With phenacylalkylanilines, proton addition will favour the preponderance of the inactive cations of the type XIa and XVIa over the active carbonium ions of the type XII and XVII, because of the strong basic character of alkylanilines. Under the vigorous conditions required, direct cyclisation precedes isomerization, there being very little formation of the isomeric indoles.

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T. R. Govindachari
September 24, 1948

DISPLACEMENT REACTIONS

Probably the most important type of reaction in organic chemistry is a displacement reaction of the general form.

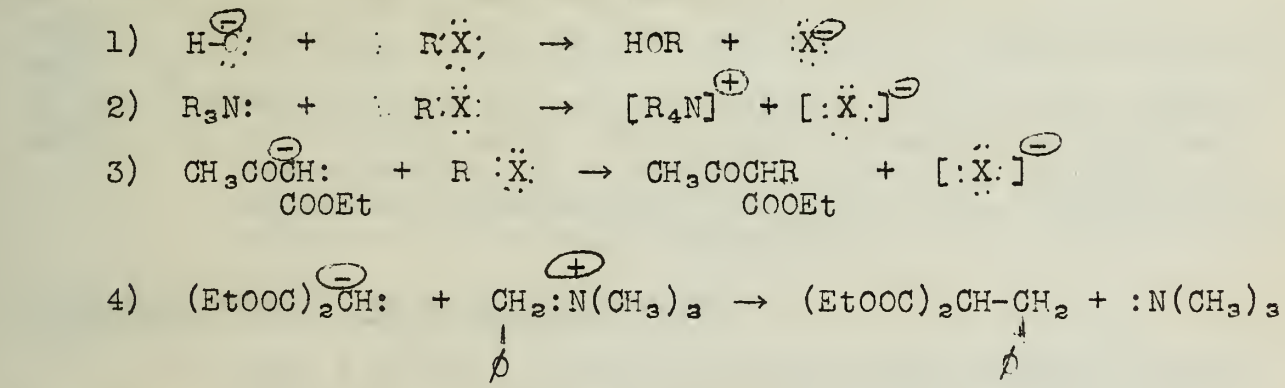
$$A + BC \rightarrow AB + C$$

Depending upon the electronic structure of A there are two different processes whereby this transformation may be effected.

Examples of Reactions Initiated by Electrophilic Attack:

1) Carbonium ion reactions 2) Aromatic substitution reactions

Examples of Reactions Initiated by Nucleophilic Attack:



Routes leading to substitution at carbon:

In many instances of substitution at a carbon atom it is found that if a homologous series is arranged in the order of increasing chain branching the total rate of reaction passes through a minimum:

Relative rates of reaction with hydroxide ion[2]

CH_3Br	2140
CH_3CH_2Br	171
$(CH_3)_2CHBr$	5
$(CH_3)_3CBr$	1010

With the first members of the series the rate is proportional to the concentration of hydroxide ion and to the concentration of the alkyl halide. In the region of the minimum no simple mathematics obtains, and with the highly branched members of the series the reaction is completely independent of hydroxide ion.

The most widely accepted explanation for the phenomenon is to assume that substitution at a carbon atom can occur by two paths:

A) $:\ddot{A}:^{\ominus} + :\ddot{C} - \ddot{X}: \rightarrow :\ddot{A}:\ddot{C}: + :\ddot{X}:^{\ominus}$

rate = $k[:\ddot{A}:]\,[:\ddot{C} - X]$

Substitution at carbon Nucleus - Bimolecular, kinetically 2nd order $\therefore S_N2$

B) $:\ddot{C} - \ddot{X}: \underset{\text{slow}}{\rightleftharpoons} :\ddot{C}^{\oplus} + :\ddot{X}:^{\ominus}$

$:\ddot{A}:$ (fast) $\downarrow$

$:\ddot{C}:A + :\ddot{X}:^{-}$

rate= $k\,[:\ddot{C} - X]$

Substitution - at carbon Nucleus - kinetically 1st order $\therefore S_N1$

Principal Evidence for S_N1 and S_N2:

S_N2. - 1) Kinetics 2) Always accompanied by Walden Inversion

S_N1. - 1) Verification of expected kinetic effects upon addition of an inert salt. 2) Always accompanied by extensive racemization. 3) Hydrolysis of certain compounds is rigorously independent of hydroxide ion. (α-phenylethyl chloride[6] and t-butyl chloride[7]).

Principal objections to S_N1 Mechanism:

1) Some inversion frequently accompanies extensive racemization. 2) The solvated carbonium ion must have a separate momentary planar configuration before it reacts with the solvent shell to form a protonated alcohol molecule:

$[(H_2O)_n\,(CH_3)_3C^{\oplus}] \rightarrow (CH_3)_3C-\overset{H}{\underset{\oplus}{O}}H + (n-1)\,H_2O$

Interpretation of the S_N1 Process as a Termolecular Reaction:

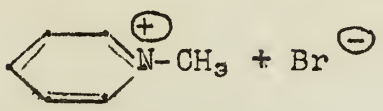
Since S_N1 reactions usually have been carried out in the presence of a large excess of solvating molecules, it has not been possible to determine the kinetic order with respect to the solvent. Recently, however, Swain has studied a number of solvolytic reactions in an inert solvent (benzene) with relatively small amounts of added tertiary amines, methanol, and phenol. In this system it has been found possible to determine the kinetic order of any of the components in the reaction mixture[8,9]. Surprisingly enough the reaction was found to be strictly third order in all cases. The following equations summarize some experiments which seem to be particularly pertinent:

1) $\phi_3CCl + CH_3OH + \text{pyridine} \rightarrow \phi_3COCH_3 + \text{pyridine.HCl}$

rate= $k_1\,[\phi_3CCl]\,[CH_3OH]^2$ (Indep. of pyridine)

2) $\phi_3CCl + CH_3OH + \text{phenol} \rightarrow \phi_3COCH_3 + HCl + \text{phenol}$ (no phenol consumed)

$$\text{rate} = k_2[\phi_3CCl]\,[CH_3OH]\,[\phi\ OH] \quad (k_2 \text{ seven times } k_1)$$

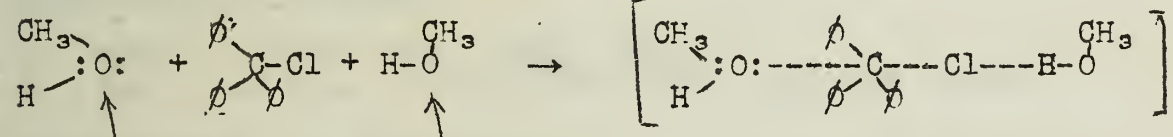
3) $CH_3Br + CH_3OH + \text{pyridine} \rightarrow$ 

$$\text{rate} = k_3[CH_3Br]\,[CH_3OH]\,[\text{pyridine}]$$

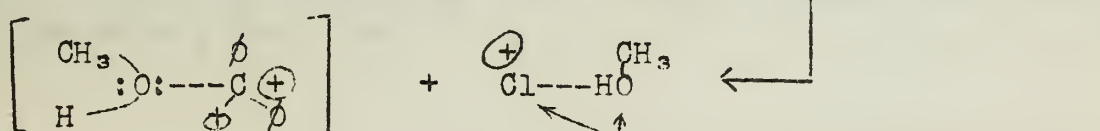
4) $CH_3Br + CH_3OH + \text{phenol} \rightarrow CH_3OCH_3 + HBr + \text{phenol}$

$$\text{rate} = k_4[CH_3Br]\,[CH_3OH]\,[\phi OH]$$

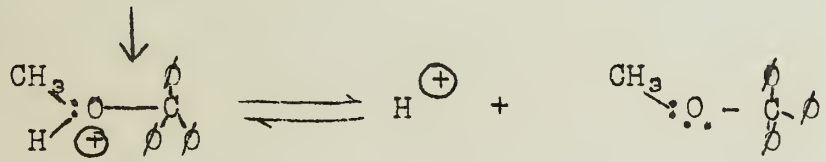
In the light of these data[5], Swain believes that neither a simple "push" (S_N2) nor a simple "pull" (S_N1) is sufficient to effect a displacement reaction. He suggests that all displacements actually proceed by a termolecular process in which reaction is a result of simultaneous nucleophilic and electrophilic attack. For the solvolysis of triphenylmethyl chloride, (a reaction which has been regarded traditionally as an example of S_N1), the process may be outlined as follows:



nucleophilic reagent — electrophilic reagent — transition complex

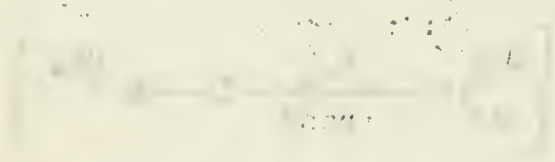


solvated carbonium ion — hydrogen bonded chloride ion



protonated ether molecule

According to this point of view phenol enters the rate equation in 2) and 4) without undergoing reaction because it acts exclusively as an aid toward removing the chloride ion by hydrogen bonding. In equation 3) methanol is a better acceptor than pyridine. Failure of hydroxide ion to accelerate the hydrolysis of certain halides in aqueous solution may be interpreted as due to steric hindrance or to the fact that water is already quite adequate to effect the "push-pull" operation of the termolecular process. Although hydroxide ion might be expected to perform this operation even more efficiently, Swain has pointed out that the amount of hydroxide ion



which can be added to a reaction mixture is small in comparison to the concentration of water molecules present. Consequently the effect of hydroxyl ion might not be detected.

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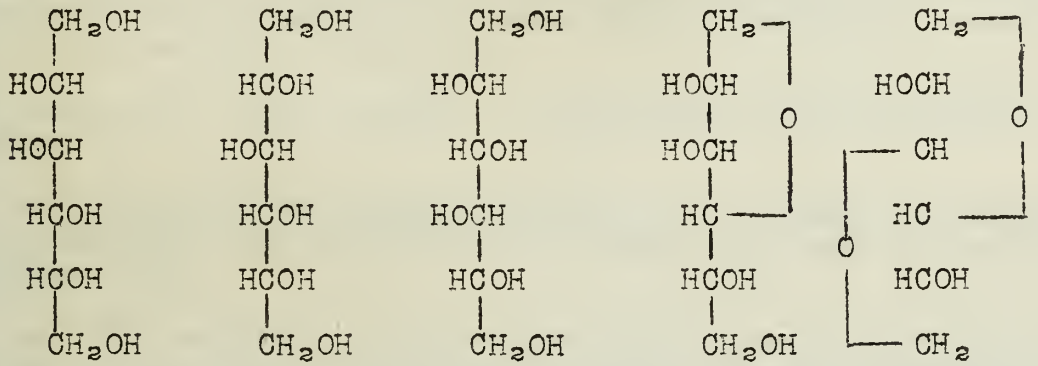
E. R. Alexander
September 24, 1948

HYDROFURANOL DERIVATIVES OF THE HEXITOLS

Anhydro hexitols containing rings of three, four, five, six, and seven members are known. This seminar however is limited to those derivatives of mannitol (I), sorbitol (II), and iditol (III) containing five membered anhydro rings. Both monoanhydro and dianhydro hexitols have been prepared; representatives of these types are 1,4-anhydromanitol or 1,4-mannitan (IV) and 1,4,3,6-dianhydromannitol or isomannide (V). In the older literature, various anhydro derivatives were described, but the structures of these compounds were not proved (1,2,3,4).



(I) (II) (III) (IV) (V)

Methods of preparation of the monoanhydro hexitols:

1. By heating the hexitol. For example, 1,4-mannitan (IV) results from mannitol on dry distillation (4).

2. By heating the hexitol in the presence of acid. Thus 1,4-sorbitan is obtained when sorbitol is heated *in vacuo* in the presence of sulfuric acid (5).

3. By reduction of the corresponding anhydro sugar. When 3,6-anhydromannose is reduced with sodium-amalgam, 3,6-mannitan, identical with (IV), is obtained (6). Likewise 3,6-sorbitan has been prepared by the sodium-amalgam reduction (7) and the catalytic reduction (8) of 3,6-anhydroglucose.

4. By deamination. Glucamine (1-aminosorbitol) is converted easily into 1,4-sorbitan by the action of nitrous acid (9).

5. By heating certain derivatives with acid or base. The conversion of 1,6-dibenzoylmannitol into "2,5-anhydro-1,6-dibenzoylmannitol" and "2,4-anhydro-1,6-dibenzoylmannitol" on heating with acid has been reported (10). However the former product has been shown to be 2,5-anhydro-1,6-dibenzoylsorbitol caused by a Walden inversion at C_2 (11) while the latter product has been demonstrated to be 1,4-anhydro-2 or 3,6-dibenzoylmannitol (12). Another example of such a Walden inversion was noted in the conversion of 1,6-ditosylsorbitol to 1-tosyl-2,5-anhydro-L-iditol by alcoholic sodium hydroxide (13).

Methods of preparation of the dianhydro hexitols:

1. By heating the hexitol or certain derivatives. Isomannide has been obtained from mannitol by dry distillation (4) and by heating 1,6-dichloromannitol *in vacuo* (14).

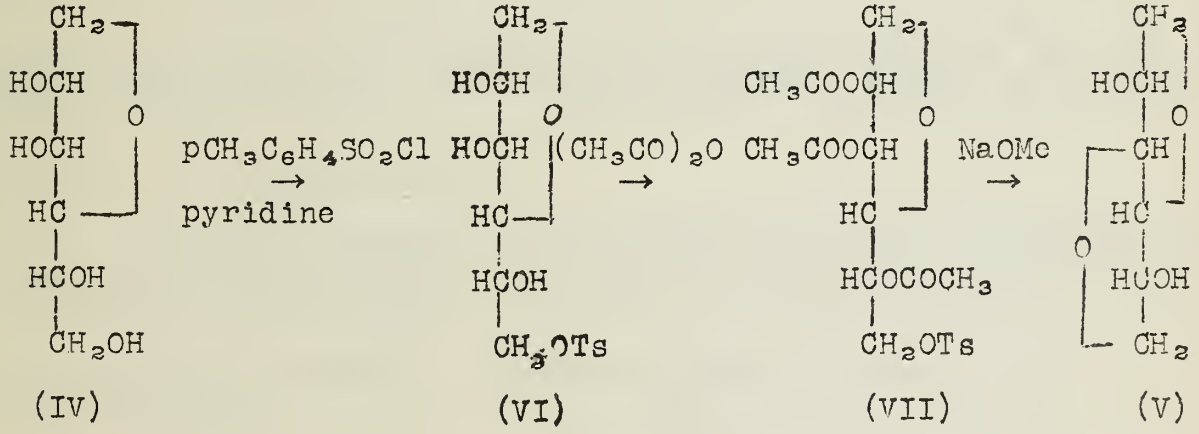
2. By heating the hexitol or monoanhydrohexitol with acid. Mannitol, sorbitol, and iditol can be dehydrated to isomannide (V), isosorbide (1,4,3,6-dianhydrosorbitol), and isoidide (1,4,3,6-dianhydroiditol) respectively by the action of heat and hydrochloric acid (4,8,14,15,16) or heat and sulfuric acid (12,15,17,18). Isomannide and isosorbide are obtained by heating 1,4-mannitan and 1,4- or 3,6-sorbitan with acid.

Less frequently used methods of synthesis of the dianhydro hexitols include:

3. Raney nickel dehydrogenation and subsequent hydrogenation partially converts isosorbide and isomannide into 1,4,3,6-dianhydro-L-iditol (18).

4. In addition 1,4-mannitan (IV) may be converted into isomannide by selective tosylation to give 6-tosyl-1,4-anhydromannitol (VI) which is then acetylated to 6-tosyl-2,3,5-triacetyl-1,4-anhydromannitol (VII). By treating (VII) with methanolic sodium methoxide, isomannide (V) is formed (14). Similarly isosorbide may be synthesized from 1,4- or 3,6-sorbitan (8).

5. By heating in tetrachloroethane with a trace of p-toluenesulfonic acid, 1,6-dibenzoylsorbitol and 1,6-dibenzoylmannitol are converted in part into the corresponding 2,5-dibenzoylisosorbide and 2,5-dibenzoylisomannide (10,17).



(IV) (VI) (VII) (V)

Properties of the anhydro hexitols:

1. Ring stability. The hydrofuranol derivatives of the hexitols possess ring structures which are extremely stable to base, being unattacked by several hours' heating with sodium methoxide.

They are also stable to mild, dilute acid but are cleaved by strong acid. Thus isomannide, heated with fuming hydrochloric acid, is converted to 1,6-dichloromannitol (14), while ring scission of isosorbide with hydrochloric acid leads to both 1,6-dichlorosorbitol and 6-chloro-1,4-anhydrosorbitol (19). The ring system is stable to oxidizing agents such as nitric acid at 100°; the dimethyl derivative of isomannide can be recovered unchanged after several hours' heating with this reagent (14).

2. Reactivity of the free hydroxyl groups. The primary hydroxyl groups present in the 1,4- and 3,6-anhydro hexitols react preferentially in the formation of , say, 6-tosyl-1,4-mannitan (see equation IV - VII above). The secondary hydroxyls of the dianhydro hexitols undergo a variety of reactions, such as etherification, esterification, and replacement (15, 20, 21, 22).

Proof of the structure of isomannide:

1. According to Hockett, Fletcher, Sheffield, Goepp, and Soltzberg: (12):

(a) 1,4-anhydro-2 or 3,6-dibenzoylmannitol is converted on heating with acid into dibenzoyldianhydromannitol which can be partially hydrolyzed to 1,4-mannitan with barium hydroxide (10)--proves the existence of the 1,4- or 3,6- ring in isomannide.

(b) Of the 27 possible dianhydro structures, only six possess the 1,4- or 3,6- ring, These are: 1,2,3,6-, 1,4,2,3-, 1,4,2,5-, 1,4,2,6-, 1,4,3,5-, and 1,4,3,6. Since isomannide does not react with lead tetraacetate, 1,2,3,6- and 1,4,2,3- are eliminated. Likewise the absence of primary hydroxyls was shown by experiments with triphenylmethyl chloride which eliminates the 1,4,2,5- and 1,4,3,5-dianhydro structures.

(c) The 1,5,3,6- structure was synthesized (23) and was not identical with isomannide. Therefore the structure must be 1,4,3,6-dianhydromannitol.

2. According to Wiggins (14):

(a) Isomannide undergoes ring scission to 1,6-dichloromannitol with fuming hydrochloric acid (pressure). Therefore carbons 1 and 6 are involved in the rings.

(b) Lead tetraacetate is without action, indicating no adjacent hydroxyls.

(c) Isomannide treated with thionyl chloride and pyridine yields 2,5-dichlorodianhydromannitol.

(d) Thus the rings must be either 1,4,3,6- or 1,3,4,6-.

(3) Mannitan can be converted into isomannide using only neutral or alkaline reagents and therefore isomannide contains the 1,4,3,6- ring structure.

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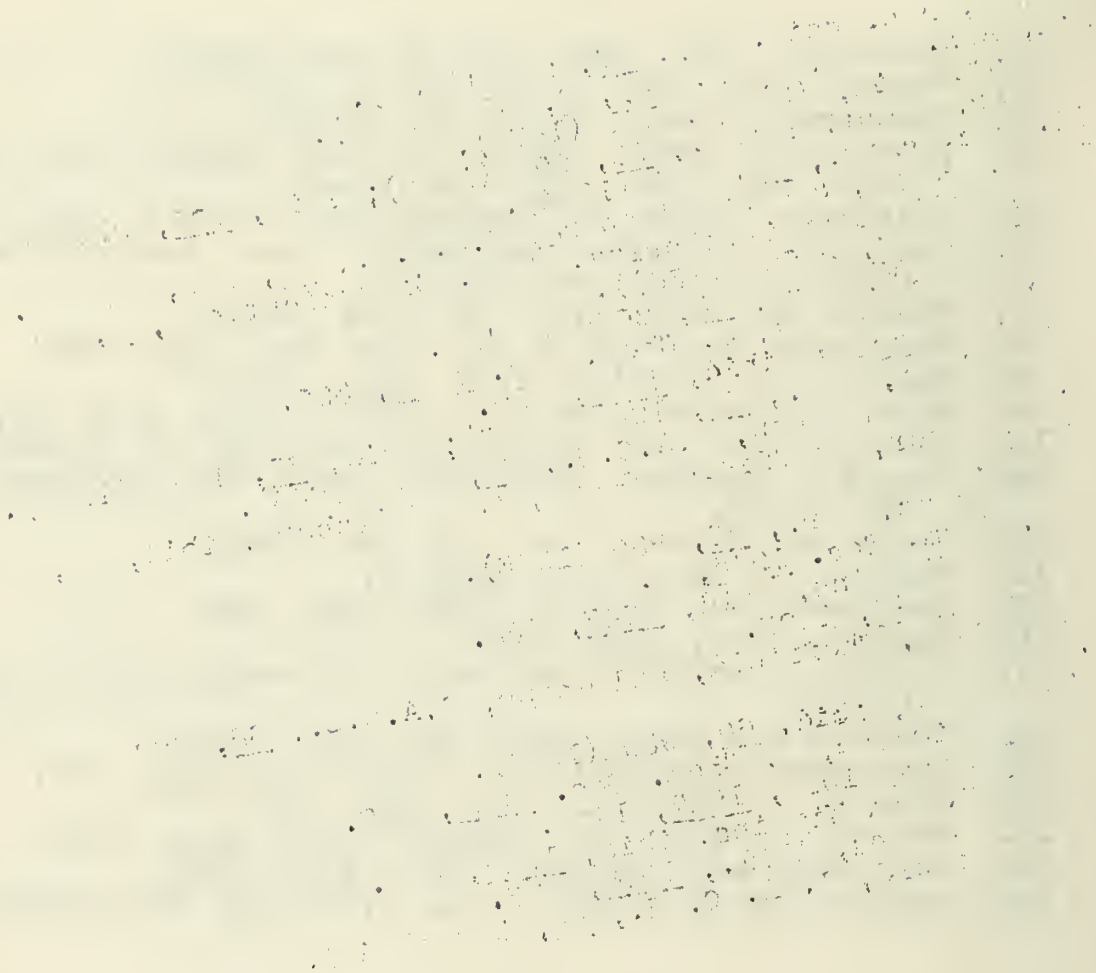
Reported by John Lynde Anderson
October 1, 1948



1-CYANO-1,3-BUTADIENE AND ITS REACTIONS

I Preparation

Coffman first reported the preparation of 1-cyano-1,3-butadiene, obtained by the action of sodium cyanide on 1-chloro-2,3-butadiene (1). He believed that the reaction proceeded in two steps as shown, although the intermediate was not isolated.

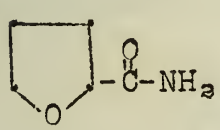
$$CH_2=C=CHCH_2Cl + NaCN \xrightarrow{CH_3OH} [CH_2=C=CHCH_2CN] \rightarrow CH_2=CHCH=CHCN$$

Coffman established the structure of his new compound by cold alkaline hydrolysis to β-vinylacrylic acid, reduction to n-amyl amine, and alkaline permanganate oxidation to oxalic acid.

Of several patented preparative methods the most general are the pyrolysis of esters of crotonaldehyde cyanohydrin (2-4) or of the diesters of acetaldol cyanohydrin (5,6). Others are given below:

$$CH_2=CHCH=CHX \text{ (in aqueous emulsion)} + NaCN_{(aq.)} \rightarrow CH_2=CHCH=CHCN \quad (7)$$
X=Cl or Br

$$CH_2=CHC\equiv CH + HCN \xrightarrow[\text{CuCl catalyst}]{} CH_2=CHCH=CHCN \quad (8)$$



$$\xrightarrow[400^\circ - 500^\circ C]{\text{dehydration catalyst}} CH_2=CHCH=CHCN \quad (9)$$

The most convenient method of preparation (60% yields) is the pyrolysis of the benzoate of crotonaldehyde cyanohydrin (10).

$$CH_3CH=CHCHO \xrightarrow[-10^\circ]{NaCN, C_6H_5COCl} CH_3CH=CH-CHCN \xrightarrow{575^\circ} CH_2=CHCH=CHCN + C_6H_5COOH$$
(OCOC$_6$H$_5$)

II cis-trans Isomers

Slight variations in the boiling point and index of refraction of products from different runs provided the first evidence for the existence of cis and trans forms of 1-cyano-1,3-butadiene (10). Likewise, variations were noted in reaction rates of different samples in copolymerizations with butadiene. Fractionation of the product of pyrolysis produced two isomeric fractions, one boiling at 49.5°/31.5 mm, the other at 53.0°/31.5 mm.

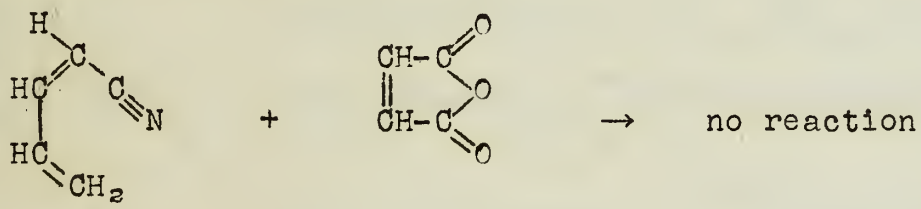
Copolymerization studies with butadiene showed that the higher boiling fraction reacted at a faster rate than did the low boiling fraction. Also, of the two rubber-like polymers so

obtained, only the one produced with the high boiling cyanobutadiene had a strong odor, previously noted in copolymers made with the mixture of cis- and trans 1-cyanobutadiene.

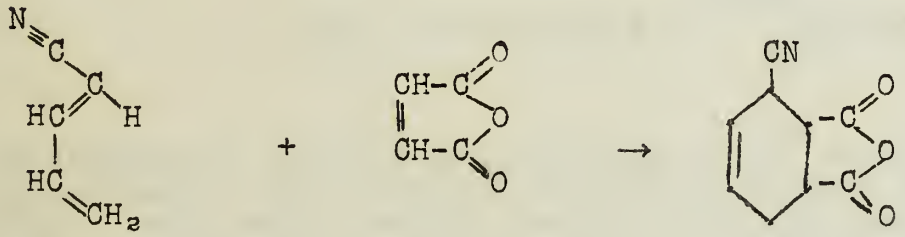
III Diels-Alder Reactions

To explain the presence in the rubber-like polymer of a by-product which was volatile enough to have a strong odor, it was suggested that a Diels-Alder reaction may have occurred between the more reactive high boiling 1-cyanobutadiene and butadiene (10). Tests with liquid butadiene permitted the isolation of a Diels-Alder adduct with the high boiling fraction, but none was obtained with the low boiling fraction. Similarly, the high boiling fraction formed an adduct with maleic anhydride, whereas the low boiling fraction did not.

Reasoning by analogy to cis- and trans-piperylene, provisional assignment of configuration of the isomeric 1-cyano-1,3-butadienes has been made. It has been shown that only trans-piperylene gives Diels-Alder adducts with maleic anhydride or acrylonitrile (11). Thus the more reactive higher boiling 1-cyano-1,3-butadiene is assigned the trans configuration. The reduced reactivity of the cis-form is explained on the basis of steric hindrance. The shape of the cis-molecule is such as to prevent the dienophile from close approach to the ends of the diene system.

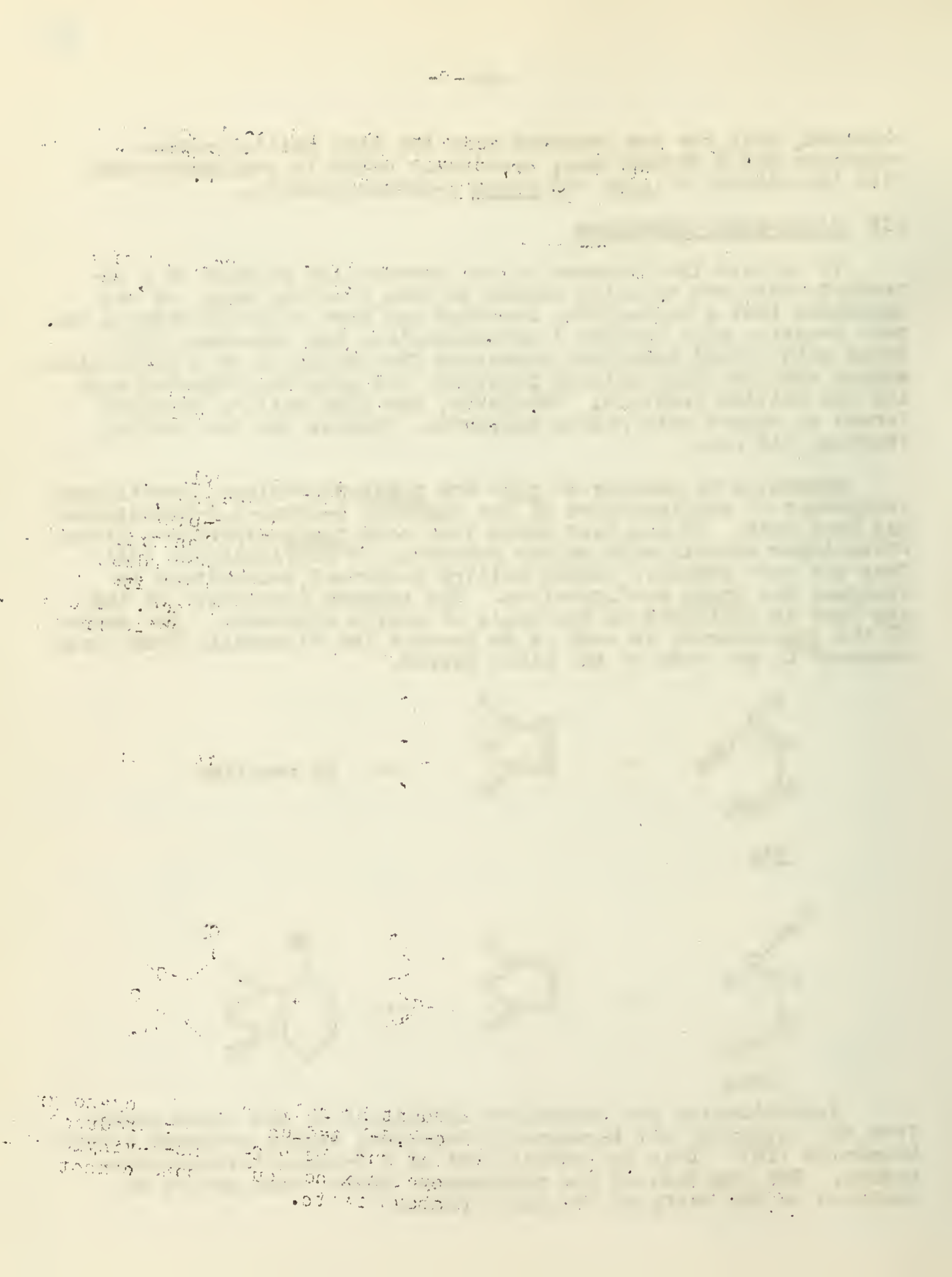


cis



trans

Aromatization and subsequent hydrolysis of the cyano group from the butadiene and 1-cyano-1,3-butadiene adduct produced 2-vinyl benzamide (12). Thus the adduct must be a 2-cyano-1-vinylcyclohexene. The position of the cyclohexene double bond cannot be assigned on the basis of the above facts.



IV Reactions with Active Methylene Compounds

The value of 1-cyano-1,3-butadiene as a preparative intermediate has been further demonstrated (13,14). A five carbon chain may be readily introduced into organic compounds possessing sufficiently active hydrogen atoms by a reaction resembling cyanoethylation. In general, the reaction may be represented by the following, where the H in RH is an active hydrogen.

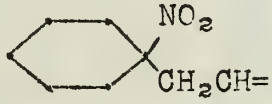
$$R{\cdot}H + CH_2{=}CHCH{=}CHCN \rightarrow RCH_2CH{=}CHCH_2CN$$

All additions studied were catalyzed by a 38% aqueous solution of triethylmethylammonium hydroxide. Addition was 1,4 across the conjugated diene system in all cases studied.

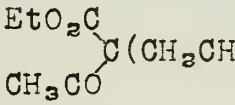
1) 1-cyano-1,3-butadiene + 2-nitropropane → $CH_3-\underset{NO_2}{\overset{CH_3}{C}}-CH_2CH=CHCH_2CN$ (13)

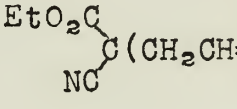
2) " + nitroethane → $CH_3-\underset{NO_2}{C}(CH_2CH=CHCH_2CN)_2$ (13)

3) " + nitromethane → $O_2N{=}C(CH_2CH=CHCH_2CN)_3$ (13)

4) " + nitrocyclohexane →  (13)

5) " + ethyl malonate → $(EtO_2C)_2C(CH_2CH=CHCH_2CN)_2$ (14)

6) " + ethyl acetoacetate →  (14)

7) " + ethyl cyanoacetate →  (14)

To illustrate possible applications of the reaction, adducts from nitro alkanes were converted to saturated nitro cyanides, nitro acids, amino acids, amino cyanides, and diamines, and unsaturated amino cyanides and amino acids by appropriate operations on the functional groups present (13).

The adducts 5) to 7) were unstable and lost one molecule of 1-cyano-1,3-butadiene when heated (14). However, the bis-adducts could be hydrogenated to give 5-substituted-1,9-dicyano nonanes. The mono-adducts can also be modified as in the preceeding paragraph.

It was reported that the methylene groups in benzylcyanide, acetophenone, and desoxybenzoin were insufficiently active to add across 1-cyano-1,3-butadiene (14).

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Reported by Bruce Englund
October 1, 1948

SODIUM HYDRIDE IN ORGANIC CHEMISTRY

Sodium hydride has recently become available in large quantities; preliminary investigations have demonstrated a usefulness that partially overlaps that of metallic sodium or alkali alkoxides but is also unique in some important respects.

I. Properties of pure NaH (1).

1. Grey to white, crystalline, free flowing powder insoluble in inert solvents.
2. Infusible (Dissociates into Na and H_2 at 400-430° C).
3. Decomposes readily in damp air. $NaH + H_2O \rightarrow NaOH + H_2$.
4. Ionizable. $NaH \rightarrow Na^+ + H^-$ (2).
5. Ignition point (in pure dry oxygen) $>$ 230° C; I.P. of Na (dry air) = 120° C.

II. The handling of NaH. Traces of Na may be removed from the commercial material by treatment with liquid ammonia (1). For some purposes a finer grained material is required; this is readily obtained by adding ceramic spheres as an abrasive to the reaction flask (3). Waste material may be destroyed in much the same manner as Na.

III. Applications to organic chemistry.

1. Catalytic reduction of aromatic hydrocarbons (8 references in (1)).

   a. Naphthalene $\xrightarrow[NaH]{T,\ p}$ Tetralin only T = 250-300° C; p = 500-1000 p.s.i.

   b. Other similar polynuclear condensed systems containing bonds of relatively high olefinic character $\xrightarrow[NaH]{T,p}$ Partial reduction products

In the case of naphthalene, by using NaH in excess of the amount required for conversion of any sulfur present to sodium sulfide, it is possible to effect hydrogenation and desulfurization simultaneously. It is stated that NaH should be generally useful in this manner, but evidence of its use with other compounds is not presented

2. Polymerization catalyst. NaH has been employed successfully in the polymerization of butadiene (4), crotonaldehyde and others, but it has not demonstrated any special value to justify its use in preference to other catalysts.

3. Catalyst for the cyanoethylation reaction (5).

4. Preparation of sodio derivatives of active H compounds.

   a. $CH{\equiv}CH + NaH \xrightarrow[liq.\ NH_3]{} CH{\equiv}CNa + H_2$ (1)

This reaction produces no acetylene reduction compounds as by-products unlike the related reaction with Na.

b. $CH_2(COOR)_2 + NaH \xrightarrow{\text{tr. alcohol}} [CH(COOR)_2]^- Na^+ + H_2$ (1)

This is the best way in which to prepare sodio malonic ester free of ethoxide ion; the reaction goes to completion rapidly.

c. Alkoxides are easily prepared by dropping the alcohol on a suspension of the NaH in an inert solvent; the reaction is not prolonged by deactivating surface effects such as are noted with Na. Certain alcohols susceptible to Na reduction are convertible to their alkoxides only by using NaH. Ex., furfuryl alcohol or eleostearyl alcohol $CH_3(CH_2)_3(CH{=}CH)_3(CH_2)_7COOH$ (1).

5. Action on carbonyl compounds.

a. Introduction. Swamer and Hauser (6) proved both of the following prototypical carbonyl reactions to occur with NaH:

(I) $-\overset{|}{C}H\overset{||}{C}- + NaH \rightarrow [-\overset{|}{C}\overset{||}{C}-]^- Na^+ + H_2$

(II) $-\overset{|}{C}\overset{||}{C}- + NaH \rightarrow -\overset{|}{C}\overset{|}{C}H- \quad (O^-Na^+)$

The latter type reaction (II) has been observed only with aldehydes and ketones containing no α H-atom. Thus, benzophenone on treatment with NaH in boiling xylene and subsequent hydrolysis yields benzhydrol. Benzyl benzoate in 92% yield is obtained from benzaldehyde using 0.05 equiv. NaH probably by first forming Na benzylate which then acts in the usual manner (7). Methyl benzoate is stable to NaH in boiling xylene.

The same investigators (6) attempted to prepare ketone anions, but they found that either self-condensation or no reaction at all occurred.

b. Ester-ester condensations. In general, the use of NaH holds these advantages:

(1) Simpler equipment and less time for completeness of reaction are required than with an alkoxide.
(2) The preparation of a particular ester does not necessitate the use of the corresponding alkoxide.
(3) NaH may be employed at higher temperatures than Na without producing competitive reactions like acyloin formation.

Esters up to and including the C_{18} acid ester are self-condensed in better than 90% yield, and it is interesting to note they were all cleaved in excellent yield to the corresponding ketones (8). Ex.,

$$2CH_3(CH_2)_{16}COOCH_3 + 2NaH \rightarrow CH_3(CH_2)_{15}\underset{CO(CH_2)_{16}CH_3}{CHCOOCH_3} \rightarrow [CH_3(CH_2)_{16}]_2CO$$

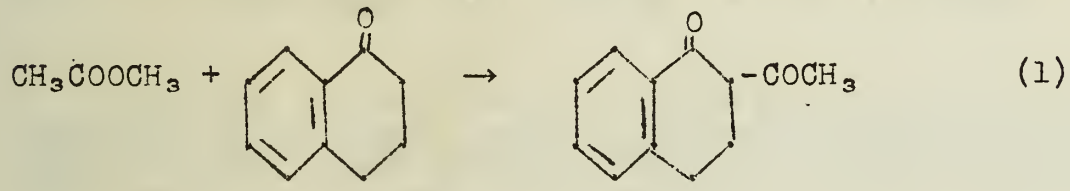
Early work failed to establish that the hydride and not the alkoxide formed by reaction with traces of alcohol present was the actual catalyst. This was demonstrated by the successful self-condensation of ethyl isovalerate using NaH (6) and the failure to effect this reaction with sodium ethylate (9).

As yet only one ineffectual attempt to condense an ester with only one α H-atom (ethylisobutyrate) has been reported (6).

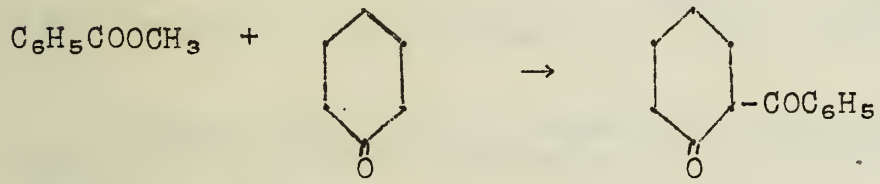
Succino succinic ester has been prepared with NaH in a Dieckmann type cyclization (3).

c. Ketone-ester condensations. Sodium hydride has demonstrated a particular utility with reactions involving high molecular weight compounds. Thus, the following condensations are best carried out using NaH.

$$CH_3(CH_2)_8COOCH_3 + CH_3COCH_3 \rightarrow CH_3(CH_2)_8COCH_2COCH_3 \quad (1)$$



(1)



(6)

Sodium hydride has been shown to work very well in the Stobbe type condensation involving a ketone plus succinic ester (10). It is also recommended in the synthesis of carbethoxy and ethoxalyl derivatives by the reaction of ketones with ethyl carbonate and ethyl oxalate (11).

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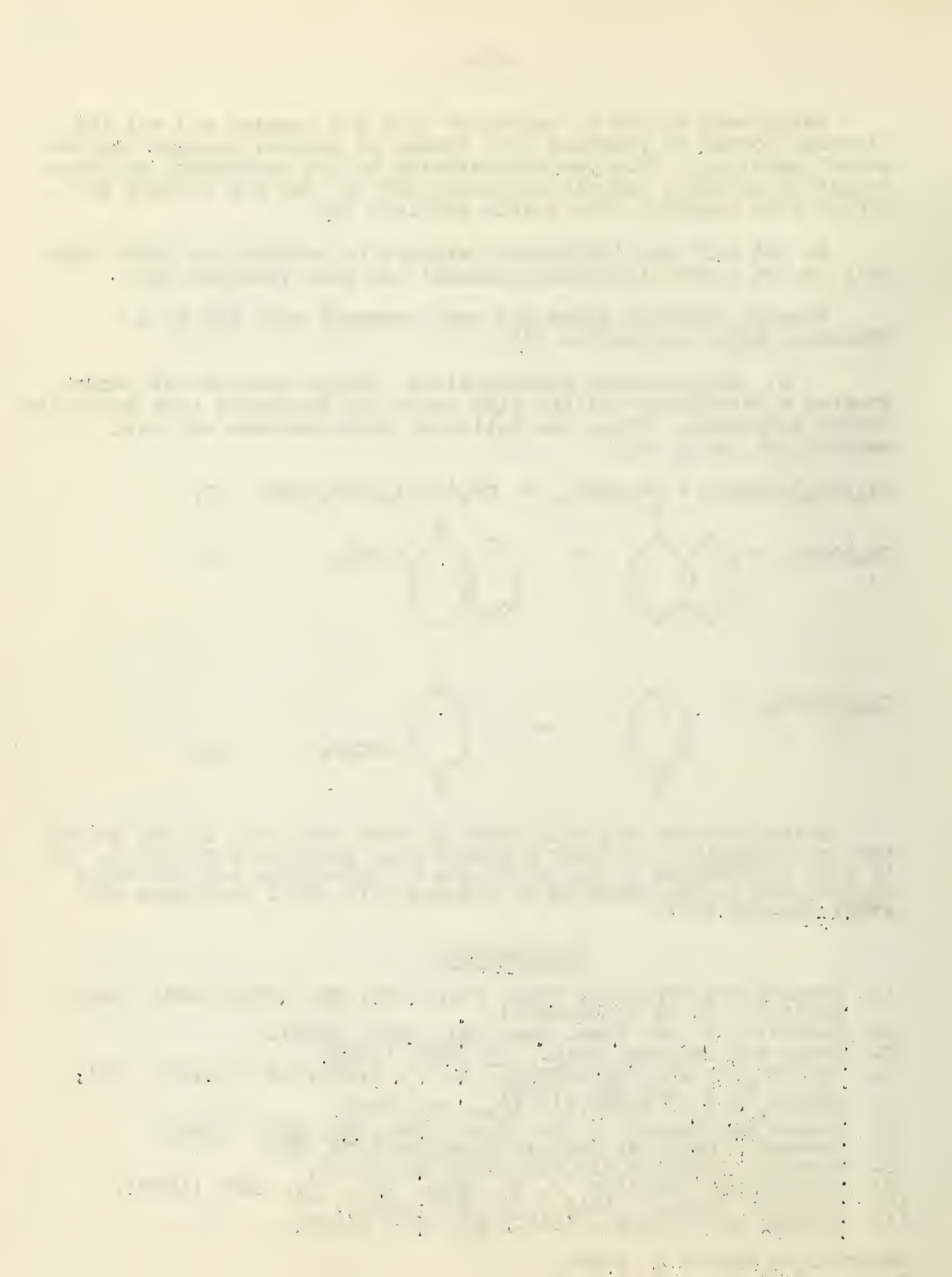
Reported by Melvin I. Kohan
October 8, 1948



SYNTHESIS OF AMIDINES

Amidines are of interest as medicinals - for example, some have recently been found effective against typhus infections. Amidines are also used to synthesize a large number of heterocyclic compounds, particularly pyrimidines.

Several common methods, all of which possess peculiar disadvantages, have been used for the synthesis of amidines (1). They may be represented as follows:

I. $$RCN + ROH \xrightarrow{HCl} R\text{-}C(=NH)\text{-}OR \cdot HCl \xrightarrow{NH_3} R\text{-}C(=NH)\text{-}NH_2 \cdot HCl$$

II. $$R\text{-}C(=O)\text{-}NHR \xrightarrow{PCl_5} R\text{-}C(Cl)=NR \xrightarrow{RNH_2} R\text{-}C(=NR)\text{-}NHR$$

III. $$RCN + RNH_2 \xrightarrow{Na} R\text{-}C(=NNa)\text{-}NHR \xrightarrow{H^+} R\text{-}C(=NH)\text{-}NHR$$

Recently, several new methods have been developed for the synthesis of amidines. Amidines or mono-N-substituted amidines result in good yield from the reaction of alkyl and aryl nitriles with ammonium or primary amine salts of sulfonic acids (2).

IV. $$RCN + [R'SO_3^-][R''NH_3^+] \xrightarrow{180\text{-}300^\circ} R\text{-}C(=NH)\text{-}NHR'' \cdot R'SO_3H$$

Amidines may also be prepared by merely heating together carboxylic acids and sulfonamides (3). The following overall equation applies:

V. $$RCOOH + 2R'SO_2NH_2 \xrightarrow{heat} R\text{-}C(=NH)\text{-}NH_2 \cdot R'SO_3H + R'SO_3H$$

It has been proposed that the reaction occurs in five steps:

1. $RCOOH + R'SO_2NH_2 \rightleftarrows RCONH_2 + R'SO_3H$
2. $RCONH_2 + R'SO_3H + R'SO_2NH_2 \rightleftarrows RCONHSO_2R' + R'SO_3NH_4$
3. $RCONHSO_2R' \rightleftarrows R\text{-}C(=NH)\text{-}OSO_2R'$
4. $R\text{-}C(=NH)\text{-}OSO_2R' \rightleftarrows RCN + R'SO_3H$
5. $RCN + R'SO_3NH_4 \rightleftarrows R\text{-}C(=NH)\text{-}NH_2 \cdot R'SO_3H$

The series of steps has been substantiated by the isolation of several of the intermediate compounds in good yield.

Carboxylic acids react with N-substituted sulfonamides to yield N,N'-disubstituted amidines (4).

$$\text{VI.}\quad RCOOH + 2R'SO_2NHR'' \rightarrow R-\overset{\overset{NR''}{\|}}{C}-NHR'' \cdot R'SO_3H + R'SO_3H$$

A series of reaction steps, partially identical to those given for reaction V, were proposed to explain the reaction.

This type of reaction is made more versatile by initially preparing the mixed imides which occur above as intermediates. The mixed imides are prepared from acid chlorides and N-substituted sulfonamides in the presence of base. They may then be reacted with ammonium or primary or secondary amine salts of sulfonic acids to yield mono-, di- or tri-N-substituted amidines.

$$\text{VII.}\quad RCOCl + R'SO_2NHR'' \xrightarrow{NaOH} RCONR''SO_2R'$$

$$\text{VIII.}\quad RCONR''SO_2R' + [R'SO_3^-][\overset{+}{N}H_2R''R'^{IV}] \rightarrow R-\overset{\overset{NR''}{\|}}{C}-NR''R'^{IV}.R'SO_3H + R'SO_3H$$

This general method of synthesis of amidines is very useful since amidines of all degrees of substitution can be prepared and in which all of the N-substituents can be different if desired.

Amidines may also be prepared by heating nitriles with ammonium thiocyanate or substituted ammonium thiocyanates (5).

$$\text{IX.}\quad RCN \xrightarrow[180^\circ]{R'R''NH_2SCN} R-\overset{\overset{NH}{\|}}{C}-NR'R'' \qquad (R' \text{ and } R'' \text{ may be H})$$

The yields are sometimes quite high but the reaction conditions are quite critical.

Amidines result in fair yield from the decomposition of the complexes formed from alkyl or aryl nitriles and aminomagnesium halides (6).

$$\text{X.}\quad R'R''NH + C_2H_5MgBr \rightarrow R'R''N-MgBr + C_2H_6$$

$$\text{XI.}\quad R'R''N-MgBr + RCN \rightarrow R-\overset{\overset{NMgBr}{\|}}{C}-NR'R'' \xrightarrow{H_2O} R-\overset{\overset{NH}{\|}}{C}-NR'R''$$

This reaction fails with the halomagnesium derivatives of primary amines and of diarylamines.

2-Substituted-4,5-dihydroglyoxalines, of recent interest as medicinals, can be prepared in excellent yields by heating nitriles with a sulfonic acid salt of ethylene diamine (7).

XII. $RCN + [R'SO_3^-][NH_3^+-CH_2CH_2-NH_2] \xrightarrow{230^\circ} [R-C(=NH)-NH-CH_2CH_2-NH_3^+][R'SO_3^-]$

$$R'SO_3NH_4 + R-C\begin{matrix}=N-CH_2\\ \\ NH-CH_2\end{matrix}$$

Bases containing two dihydroglyoxaline nuclei are readily prepared from dinitriles. Yields from the reaction are so good that it can be used for the identification of nitriles. Tetrahydropyrimidines are conveniently prepared from nitriles and the salt of trimethylene diamine.

N,N-Disubstituted amidines may be prepared from nitriles and amines, using Friedel-Craft type catalysts (8).

XIII. $RCN + R'R''NH \xrightarrow{AlCl_3} R-C(=NH)-NR'R''$

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STRECKER DEGRADATION

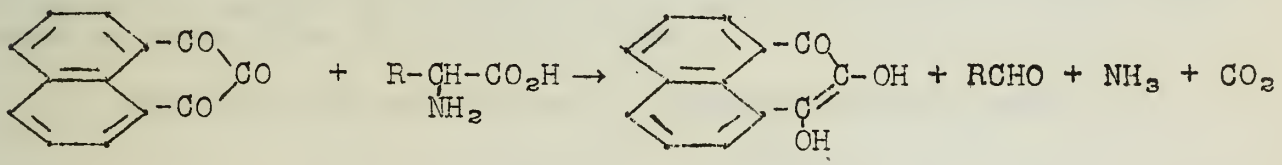
In 1862 Strecker (1) observed for the first time, that alloxan reacted with alanine to give acetaldehyde and carbon dioxide. The interaction of α-amino acids with carbonyl compounds in aqueous solution or in suspension to give aldehydes and ketones with one carbon atom less, has been termed the "Strecker Degradation".

Various workers in this field have studied the degradation of α-amino acids and many substances such as dehydroascorbic acid, alloxan, and 2-methyl-1,4-naphthaquinone were found to be effective. A detailed investigation on the scope and limitations was made by Schönberg and co-workers (2) at the Fouad University in Egypt. Their results may be summarized as follows.

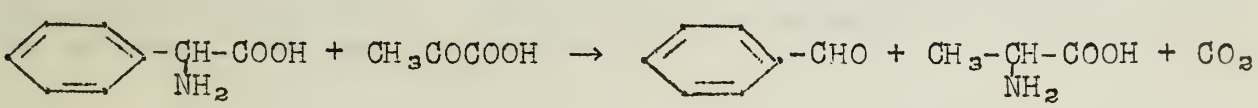
1. Natureof α-Amino Acids:-The two hydrogens on the nitrogen atom must be unsubstituted. However the hydrogens on the α-carbon atom may be substituted; thus α-aminoisobutyric acid yields acetone when treated with p-benzoquinone (4), or with methyl-glyoxal (5). Proline, an α-secondary amino acid does not undergo degradation with ninhydrin (3).

2. Final State of the Amino group of the α-Amino Acid Subjected to Strecker Degradation:-The character of the reaction products depends upon the nature of the carbonyl compound employed.

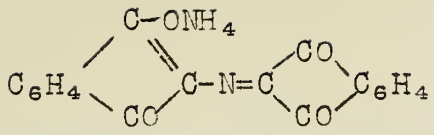
(a) The amino group may be eliminated as ammonia.



(b) The amino group may become linked to the carbonyl compound which affects the degradation converting it into an amino compound of similar structure (Transamination). Thus alanine is formed when α-aminophenylacetic acid is subjected to degradation by the action of pyruvic acid.

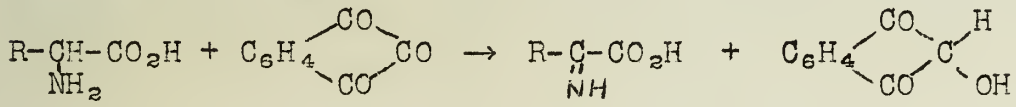


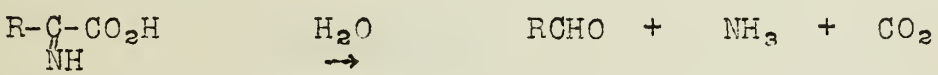
(c) The amino group may enter into combination with the carbonyl compound used as the degrading agent producing a nitrogenous compound of a complicated character. Thus triketoindane, when used in the degradation, is transformed into a violet-blue imino compound (3).



3. Nature of Carbonyl Compounds which bring about the Strecker Degradation:-The degradation is not effected by mono carbonyl compounds. Experiments with various carbonyl compounds have shown (2) that only those containing the group $-CO-(CH=CH)_n-CO-$ are effective. However, there are exceptions such as parabanic acid, s-bibenzoylethylene and dibenzoylstilbene which are ineffective in aqueous media probably due to their inability to form Schiff's base, which is an essential step in the degradation.

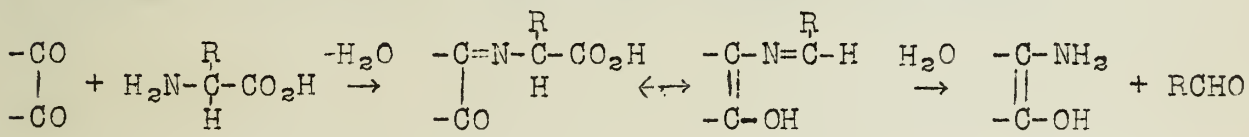
4. Reaction Mechanism of Strecker Degradation:-Grassmann and Arnim (3) suggested the following scheme for the degradation.



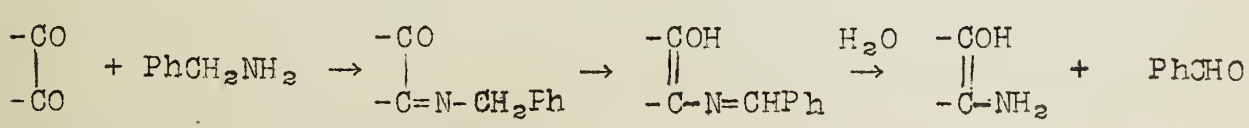


The triketoindane functions only as a dehydrogenating agent. However the degradation has been brought about by such weak dehydrogenating agents as anthraquinone and not by the stronger ones such as azobenzene or methylene blue.

Schönberg and co-workers (2) advance another mechanism.



This scheme explains the necessity of the two hydrogen atoms on the nitrogen atom, as well as the formation of aldehydes from non-acidic substances. Benzaldehyde is formed from benzylamine by the action of alloxan or isatin.



Schönberg's scheme appears to be more generalized than that suggested by Herbst (6) for the interaction of a ketonic acid and an α-amino-acid.

$$RCO\text{-}CO_2H + R'\underset{NH_2}{\underset{|}{C}}H\text{-}CO_2H \xrightarrow{-H_2O} R\underset{CO_2H}{\underset{|}{C}}=N\text{-}\underset{CO_2H}{\underset{|}{C}}HR' \rightarrow R\underset{CO_2H}{\underset{|}{C}}H\text{-}N=\underset{CO_2H}{\underset{|}{C}}R'$$

$$\xrightarrow{+H_2O} R\text{-}\underset{NH_2}{\underset{|}{C}}H\text{-}COOH + R'CHO + CO_2$$

This involves first the condensation of the carbonyl group of the ketonic acid with the amino group, followed by the migration of a hydrogen from the α-carbon of the amino acid to the α-carbon of the ketonic acid. Subsequently decarboxylation takes place, an aldehyde is split off and a new amino acid is obtained.

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RECENT ADVANCES IN THIOPHENE CHEMISTRY

Introduction

Since the Seminar report (1) and Steinkopf's treatise (2) on the chemistry of thiophene, a commercial process for the preparation of this compound has been developed (3,4) which has made it available in large quantities for the first time. The resultant renewal of interest in thiophene has been marked both in the fields of organic and biological chemistry. In the former, at least one important point has been established. Thiophene is more properly considered an anolog of phenol rather than benzene (5). This discussion will be limited to four types of organic reactions which best illustrate this fact.

Alkylation

The alkylation of thiophene with olefins was not reported until the last two years. Since then a wide selection of olefins has been used as alkylating agents in the presence of such catalysts as:

Activated silica-alumina type clays (6)
Phosphoric acid on kieselguhr (7)
Sulfuric acid of 70-96% concentration (8)
Boron fluoride complexes (8)
Anhydrous aluminum chloride and others (8)

The tardy discovery of this reaction can only be explained by the assumption that prior attempts failed because of the selection of alkylating conditions based on the old benzene-thiophene analogy.

The following general precepts may be found useful in the selection of optimum conditions for the alkylation of thiophene.

1. Alkylation with reactive olefins, such as isobutylene, is catalyzed best by sulfuric acid of 70-80% concentration, boron fluoride ether complex, or other mild catalysts at temperatures of the order of 70-80°. Alkylation with the less reactive straight-chain olefins, such as 1-octene or 1-hexadecene, requires active catalysts, such as concentrated sulfuric acid (combined with the olefin first) or boron fluoride water complex.

2. Sulfuric acid or dihydroxyfluoboric acid generally give products rich in monoalkylthiophene; boron fluoride complexes give products rich in dialkylthiophenes.

3. The preparation of the α-isomers is favored by mild reaction conditions and short reaction times. Considerable quantities of the β-isomers occur at elevated temperatures in the presence of strong catalysts. This was noted by Appleby and coworkers (7), who used phosphoric acid on kieselguhr as the catalyst at 270°.

Acylation

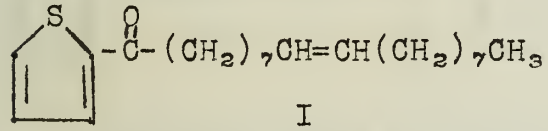
Although thiophene like benzene can be acylated with acylhalides in the presence of mole equivalents of metal halides (9),

more economic methods for the synthesis of low molecular weight thienylketones have recently been reported (10-14). It was found that thiophene can be acylated with acid anhydrides in the presence of catalytic amounts of anhydrous zinc chloride, iodine, or hydriodic acid; or by passing the reagents over activated clays or ortho-phosphoric acid.

Aluminum chloride and stannic chloride in catalytic amounts do not promote acylation of thiophene and higher concentrations of zinc chloride tend to decrease the yield. It is reasonable to assume that the zinc chloride does not form the complex usually associated with acylation reactions catalyzed by metal halides. Benzene, phenol, and resorcinol do not acylate this way.

The mechanism by which traces of iodine or hydriodic acid catalyze the acylation has not been elucidated. Iodic anhydride, bromine, hydrochloric and hydrobromic acids fail as catalysts.

Since acyl halides proved to be less efficient acylating agents with these catalysts, these methods are limited practically to the use of available anhydrides. However, a good method for the preparation of higher molecular weight thienylketones was reported (15) in which molecular equivalents of phosphorus pentoxide were used to promote the acylation of thiophene with organic acids. Benzene was used as the solvent since it is completely inert in this reaction. The yields, in general, increase with increasing molecular weight of the acid employed. With oleic acid, a 42% yield of an acylated, unidentified dimer is obtained in addition to a 55% yield of 2-(△9,10-octadecenoyl)-thiophene (I). Strangely, a 23% yield of 2,5-didecanoylthiophene (II) is obtained with decanoic acid in addition to a 42% yield of the mono-derivative. This does not occur with the lower molecular weight derivatives. 2,5-Diacetothiophene has been isolated but in less than 5% yields.

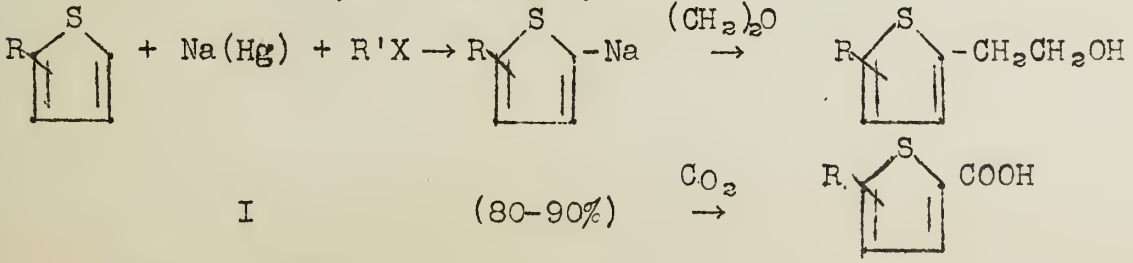


I

II

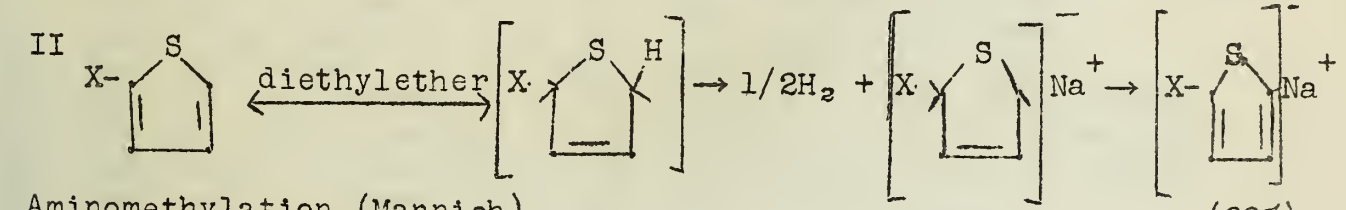
Metalation

In recent studies (16-18) thiophene and its homologs were found to undergo transmetallation with sodium amalgam and an alkyl or aryl halide as shown in reaction I. Subsequent treatment of the thienyl sodium with carbon dioxide or ethylene oxide offers an excellent method for the preparation of alkylthienyl carboxylic acids or ethanols, respectively.



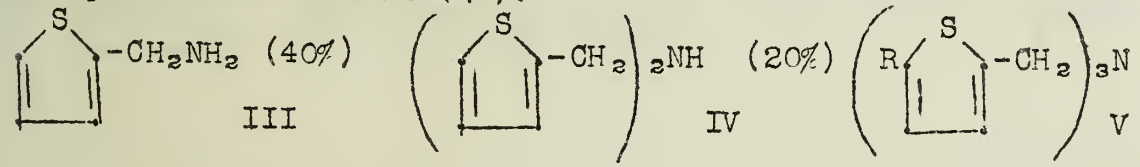
I (80-90%)

The products obtained in the metalation of 2-chlorothiophene were found to be dependent on the solvent employed. In benzene, an 84% yield of thienyl sodium is obtained; in anisole or butyl ether there is no metalation of the thiophene. Of particular interest is the fact that high yields of 5-chloro-2-thienyl sodium are obtained using diethyl ether as the solvent. The mechanism shown in reaction II was suggested to account for the product obtained. Neither lithium nor potassium behave in this manner.

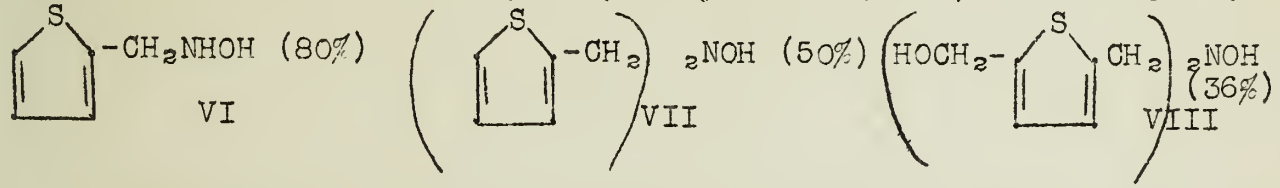
II 

Aminomethylation (Mannich)

Recently it has been found (19-21) that thiophene and its homologs possess hydrogens of sufficient reactivity to undergo a type of Mannich reaction in the presence of formaldehyde and ammonium chloride. The products after neutralization consist of a mixture of primary (III) and secondary (IV) amines, together with a considerable quantity of sub-resinous amines of unknown structure. No tertiary amines were isolated unless one of the α-positions on the thiophene was blocked (V).



Analogous products are obtained with hydroxylamine hydrochloride. Depending on the conditions us ed, substantial yields of 2-thenylhydroxylamine (VI), di-(2-thenyl)-hydroxylamine (VII), or di(5-hydroxymethyl-2- thenyl)-hydroxylamine (VIII) can be isolated.



Thiophene does not enter into the Mannich reactions with alkylamine hydrochlides, probably because of side reaction.

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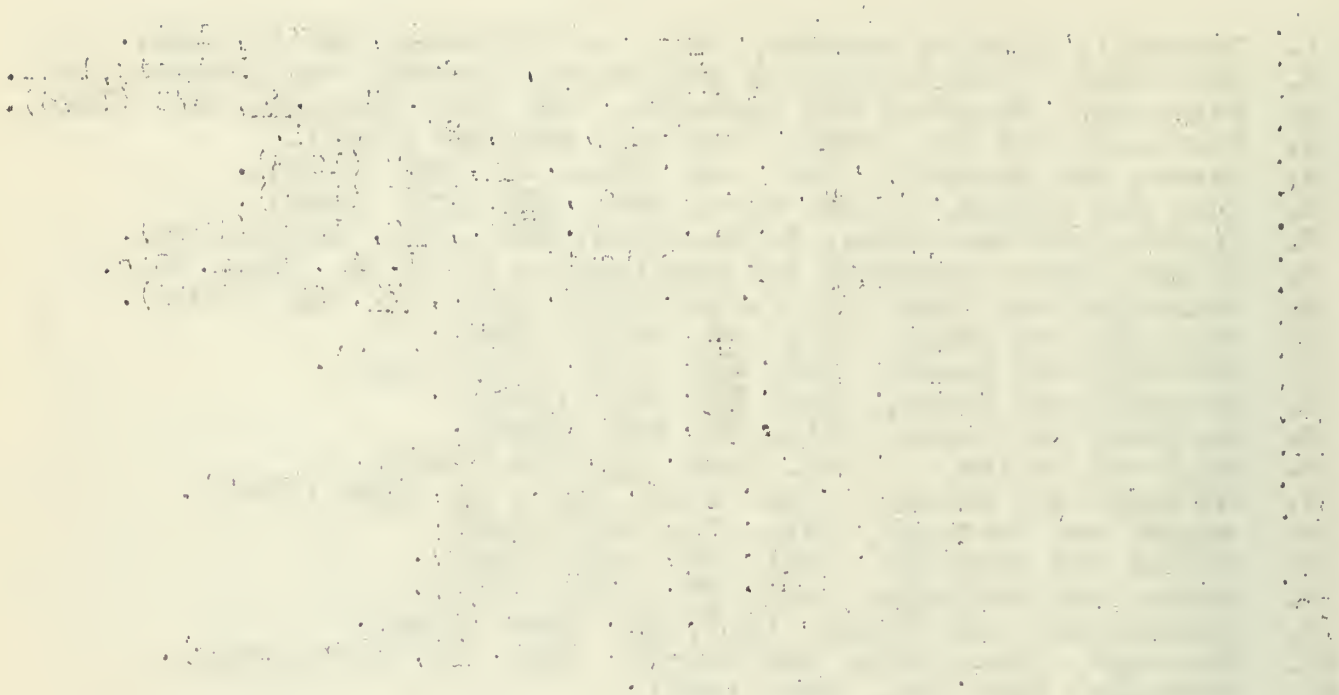
Reported by P. D. Caesar
October 15, 1948



REACTIONS OF DIHYDROPYRAN AND RELATED COMPOUNDS

I Preparation: In 1933 Paul (2) first prepared 2,3-dihydro-1,4-pyran (or 3,4-dihydro-1,2-pyran) in 44% yield by passing tetrahydrofurfuryl alcohol over Al_2O_3 at 370-80°. A thorough study of reaction conditions has improved the yields from 66-70% (11) to as high as 85-90% (12).

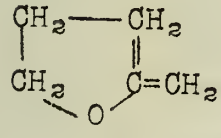
Paul (2) proved the structure of dihydropyran as follows:

1. The position of the oxygen was verified by the reaction sequence:

dihydropyran $\xrightarrow{H_2}$ tetrahydropyran $\xrightarrow[HOAc]{2HBr}$ 1,5 dibromopentane

aniline $\rightarrow$ N-phenylpiperidine

Any of the following structures would give 2-methyl-N-phenylpyrrolidine under similar treatment.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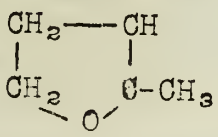


2. Two structural isomers are possible for dihydropyran with different positions of the double bond. Partial hydrolysis with .1N H_2SO_4 at room temperature to an aldehyde and the instability of the dibromide adduct are results consistent only with the 3,4-dihydro-1,2-pyran structure. Recently Paul and Tchelitcheff (10) synthesized the other isomer; 5,6-dihydro-1,2-pyran, and found their chemical reactivities distinctly different.

II Ring Nuclear Reactions (Reactions of Double Bond)

A. Hydrogenation: Dihydropyran may be easily reduced catalytically (10,14) to tetrahydropyran.

B. Halogenation: Dihydropyan may be halogenated with Br_2 (4,7,14) or with Cl_2 in CCl_4 (9) to the corresponding 2,3-dihalotetrahydropyran. The relatively unstable dibromide upon distillation dehydrohalogenates to 1,5-epoxy-2-bromo-1-pentene. The analagous chloro compound is obtained by distilling the stable dichlorotetrahydropyran with diethylaniline (9).

C. Addition of HBr: Dry hydrogen bromide adds to dihydropyran to yield 2-bromotetrahydropyran (7,8) which is unstable and resinifies on standing.

D. 2-Alkyl or Aryl Derivatives via Grignard Reagents: The addition of RMgX to 2-bromotetrahydropyran may be effected at low temperatures (6,8). Further treatment of the resulting product with HBr under suitable conditions produces the corresponding 1,5-dibromoparaffin. Under similar conditions the dibromo and dichloro-tetrahydropyrans also undergo alkylation with slightly lower yields. Only the 2-halogen of the ring is replaced.

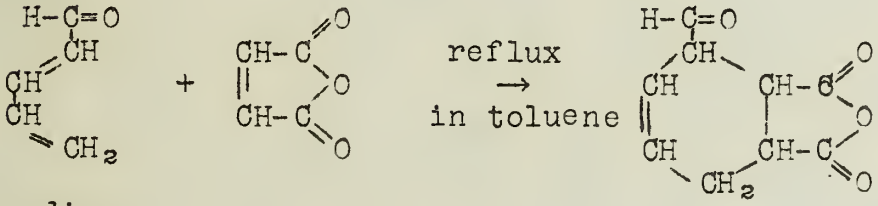
E. 2-Alkoxy Derivatives: In the presence of a trace of acid, alcohols and phenols add readily to dihydropyran, to produce the acetals, 2-alkyoxy or aryloxy tetrahydropyrans (15). Dihalotetrahydropyrans, when treated with an alcohol in the presence of the corresponding sodium alkoxide, yield the 2-alkoxy-3-halotetrahydropyrans (9, 14).

III Ring Opening Reactions (Involving Oatom)

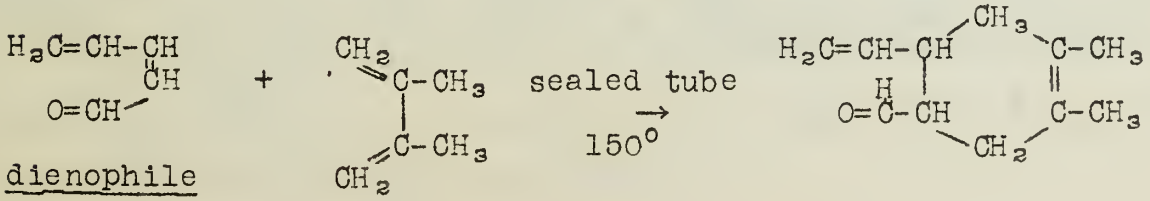
A. Hydrolysis: Dihydropyran is hydrolyzed to 5-hydroxypentanal with dilute HCl (3,12,13,17). The 5-hydroxypentanal exists in solution almost completely in the form of the cyclic hemiacetal, 2-hydroxytetrahydropyran (12). Reduction of 5-hydroxypentanal by a variety of methods (3,12,13) produces 1,5-pentanediol in excellent yields.

Amino alcohols are produced by reductive amination of 5-hydroxypentanal with liquid ammonia or the appropriate amine using Raney nickel and hydrogen under pressure (13) The side chain of the antimalarial SN 13,276 [8-(5-isopropyl aminoamylamino)-6-methoxyquinoline] was synthesized using a similar method (1).

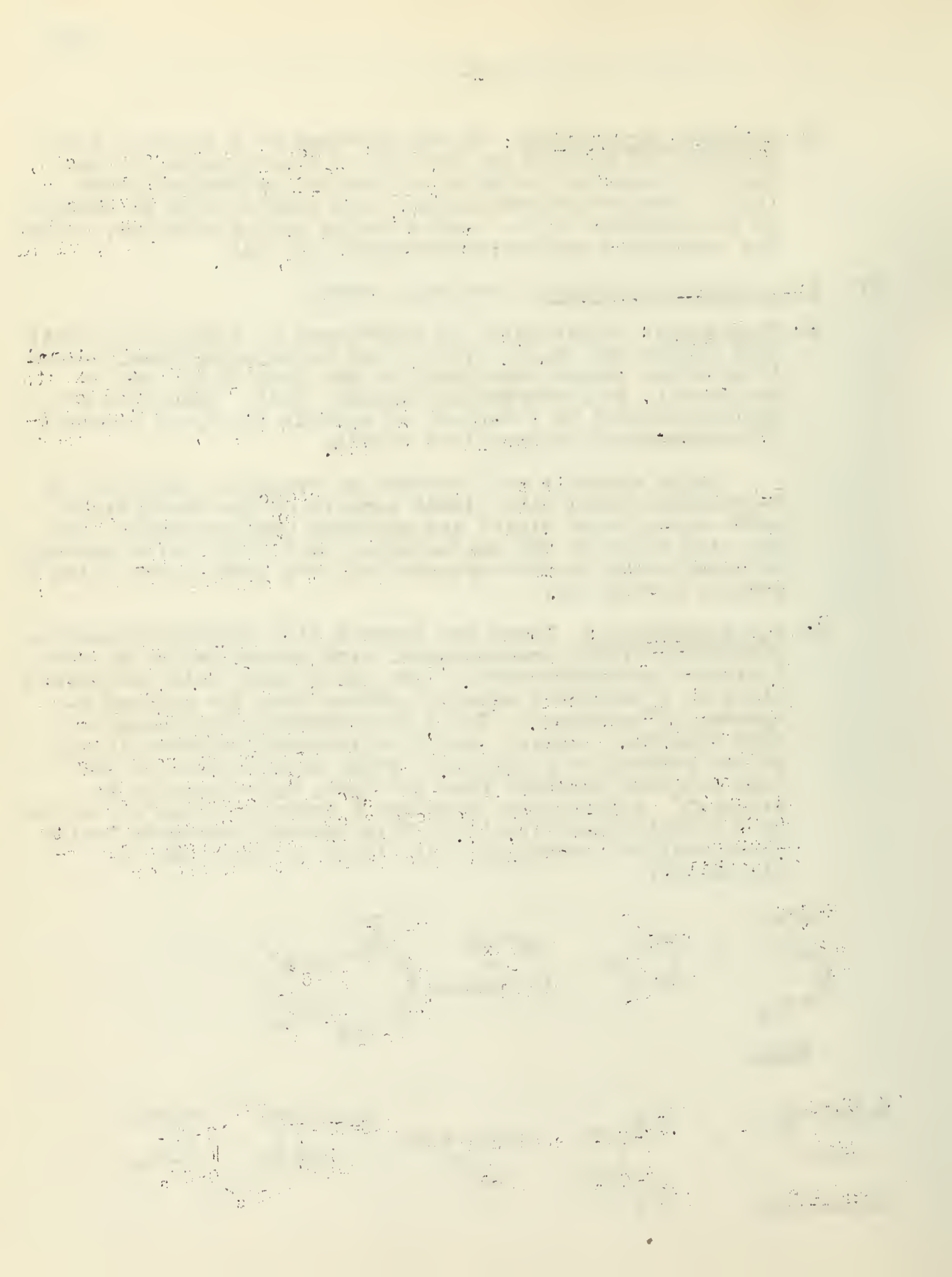
B. 2,4-Pentadienal: Woods and Sanders (14) dehydrohalogenated 2-ethoxy-3-bromotetrahydropyran with alcoholic KOH to form 2 ethoxy-Δ^3-dihydropyran. The latter upon acid hydrolysis yield ed a polymeric material rather than the desired 5-hydroxy-Δ^2-penteral. The 2,4-dinitrophenylhydrazone of this aldehyde, however, could be isolated by hydrolizing in the reagent as a solvent. Steam distillation of the acid solution obtained from the H_3PO_4 hydrolysis of 2-ethoxy Δ^3 dihydropyran produced a compound which proved to be 2,4 pentadienal (14,16). This product undergoes Diels-Alder addition reactions (16) either as the diene or dienophile.



diene



dienophile



2,4-Pentadienal + C_6H_5MgBr

The reaction of phenyl magnesium bromide with 2,4-pentadienal did not produce the alcohol expected by 1,2 addition (16). The alcohol produced is unstable in air, and cinnamaldehyde can be isolated from the decomposed mixture. Reduction of the alcohol with Raney nickel and hydrogen gave 5-phenyl-1-pentanol. The reaction is presumed to proceed as follows:

$$CH_2{=}CH{-}CH{=}CHCHO \xrightarrow{C_6H_5MgBr} CH_2{=}CHCH{=}CHC(OH)C_6H_5 \rightarrow \text{tar} + C_6H_5CH{=}CHCH$$

(Double Allylic shift of (OH))

$$C_6H_5CH{=}CH{-}CH{=}CHCH_2OH \xleftarrow[H_2]{Ni} C_6H_5(CH_2)_4CH_2OH$$

Woods and Schwartzman (18) produced 1,3,5-hexatriene by the following reactions:

$$CH_2{=}CH{-}CH{=}CHCHO \xrightarrow{CH_3MgBr} CH_2{=}CH{-}CH{=}CH{-}CH(OH)CH_3 \xrightarrow{Al_2O_3}$$

$$CH_2{=}CH{-}CH{=}CH{-}CH{=}CH_2$$

The cis isomer is the open chain analog of benzene.

IV Miscellaneous Reactions

A. Pyrolysis: Pyrolysis of 3,4-dihydro-1,2-pyran in presence of equal parts of Al_2O_3 and SiO_2 as catalysts (10,20) cleaves it into ethylene and acrolein. Pyrolysis of 5,6-dihydro-1,2-pyran produces formaldehyde and butadiene (10).

B. Dihydropyran, when passed over Al_2O_3 at 400° in a stream of H_2S (19), is converted in 60% yield to dihydrothiapyran.

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Reported by Sidney Baldwin
October 22, 1948

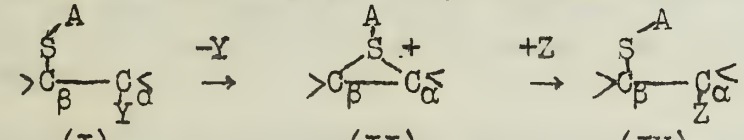
A GENERAL THEORY OF NEIGHBORING GROUPS AND REACTIVITY IN NUCLEOPHILIC REPLACEMENT REACTIONS

Two mechanisms for nucleophilic replacement reactions at a saturated carbon atom are currently recognized (1,2). One is the now familiar (3) bimolecular, S_N2, substitution with complete Walden inversion.

The second mechanism has been termed unimolecular, S_N1 (1,2,4). It seems to consist of at least two steps, the most probable rate-determining step being an ionization.

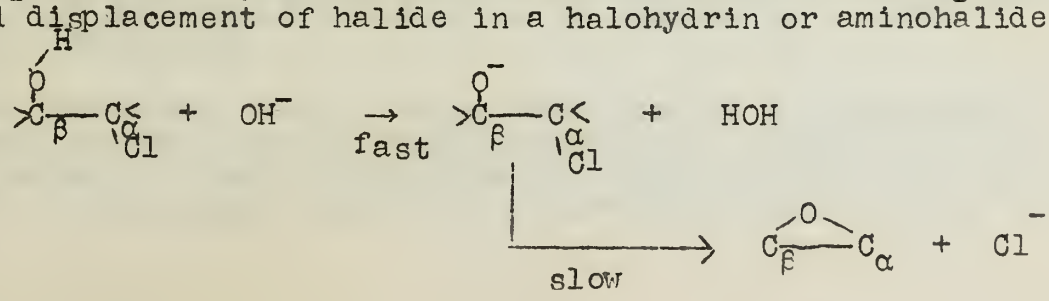
Ionization to an ion-pair, solvated in a way characteristic of ions, may be thought to be the rate-determining step in the S_N1 mechanism. Solvation of the ions makes this step feasible; therefore, the rate varies with the arrangement of solvent molecules around what is to be the ion-pair. Solvent molecules must be included in the transition state, without, however, drawing bonds between the solvent molecules and the carbonium ion (5). If the carbonium ion is very reactive it will react preferentially with a molecule in the solvation cluster to give inversion as the major steric result (1). If the reaction of the carbonium ion takes place after dissociation of the ion-pair, complete racemization is the steric result (4).

To understand the rates and steric results of nucleophilic replacement reactions of the most complex compounds it is necessary to demonstrate and understand the effects of substituent groups other than their supply or withdrawal of electrons to the seat of substitution by induction and resonance (1). One of the most interesting effects is that of participation of a group on a neighboring carbon atom in a replacement process at a carbon atom. Thus, a replacement reaction might really consist of two steps, the first one an intramolecular S_N2 reaction, the second the opening of a ring. Two inversions or apparent retention will be the steric result. This is symbolized (6a) below, Y and Z indicating the leaving and entering groups, respectively.

(A) 

(I) (II) (IV)

Participation of neighboring groups in displacement reactions has long been known with such groups as O^- (from OH) and NH_2, prior ring closure (7) to isolable oxide or imine occurring on attempted displacement of halide in a halohydrin or aminohalide.

(B) 

In these cases the groups are those which also take part in known bimolecular, S_N2, displacements (2) symbolized in equations (C) and (D).

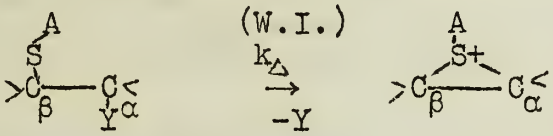
(C) $RO^- + R'X \rightarrow ROR' + X^-$

(D) $RNH_2 + R'X \rightarrow (RNH_2R')^+ + X^-$

Of equal interest is the participation in nucleophilic displacement reactions by such neighboring groups as OAc, Br and OCH_3. Winstein and co-workers (6) have accumulated a great deal of data which seems to indicate that these groups, when bonded to a neighboring carbon atom, do participate in the reaction by the formation of an intermediate of type (II), (see equation A).

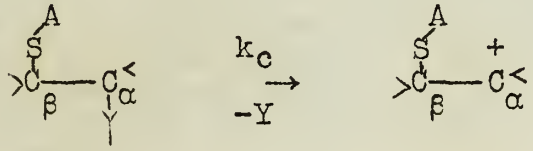
In this connection, rate measurements lead to an understanding of the rate-determining ionization step. This may be a one-stage ring closure to the cyclic intermediate (II) with Walden inversion (W.I.) at C_α, an ionization to the substituted carbonium ion (III), or both (6a).

(E)



(I) (II)

(F)



(I) (III)

There are several indications that the carbonium ion intermediate, (III), is, in some respects, quite unfree (2). For example, the steric result of reaction by this mechanism generally is predominant inversion.

Winstein and co-workers (6) observed the expected insensivity of solvolysis rate to changes in structure, solvent and departing groups in the S_N1 reaction through intermediate (III). However, in dealing with some compounds which were shown to have a first order rate constant, the solvolysis rate was found to vary widely with structure, and this was attributed to the operation of both mechanisms, (E) and (F).

These trends are exactly those predicted by a qualitative theory which recognizes that alpha substitution stabilizes (II) and, to a greater extent, (III), and that beta substitution stabilizes (II). Thus, beta substitution increases k_Δ and k_Δ/k_c

while alpha substitution increases both k_Δ and k_c and decreases k_Δ / k_c.

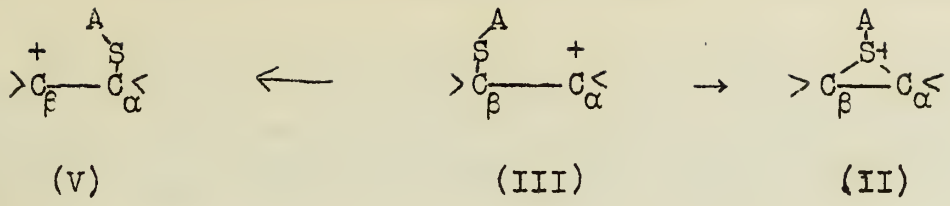
An alternative mechanism was considered in which mechanism (F) was the sole one, the open carbonium ion always being formed in the rate-determining step. In this interpretation, deviations of the solvolysis rate from the calculated values, k_s/k_h, would be due to polarization of the neighboring groups, and to steric effects such as envisioned by Brown (8) and termed "B"-strain. However, a steric effect of the kind postulated appears to be too small to be of sufficient importance in calculating deviations from the calculated solvolysis rate. In addition, polarization of a neighboring group does not predict the contrast between Cl on the one hand and Br and I on the other. With Cl as the neighboring group, the solvolysis rate is not sensitive to structure and the reaction proceeds by mechanism (F); with Br and I it is, the reaction proceding predominantly by mechanism (E).

The qualitative theory explains the trends observed in rates of closure of the ethylene oxide ring from variously substituted ehtylene chlorohydrins. Similarly, it is in accord with the favorable effect of alpha methyl substitution for closure of the ethylene imine (9) and the beta-lactone ring.

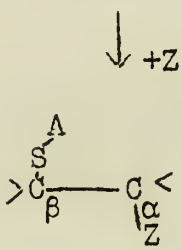
Sterochemistry and Products:--To control steric results of mucleophilic displacement reactions it is often necessary to assess the relative tendencies for bimolecular displacement with inversion, or for unimolecular type displacement which can lead to various steric results of which, perhaps, the most interesting is retention of configuration in the presence of a suitable neighboring group. For this purpose, a knowledge of the rates in reactions of the unimolecular type of the substituted compounds is essential, and toward this end Winstein's rate work (6) so far reported is useful.

Correlating the present work on rates of unimolecular solvolysis with previous (6e,f,g,h) work on the stereochemistry and products of such reactions, it becomes clear that most of the previous work has dealt with cases in which the rate-determining reaction step was the type (E). Inversion of configuration to form intermediate (II), followed by a second inversion thereby converting (II) to product (see reaction A), accounts for the clean-cut retention of configuration.

For the situation where the rate work indicates the ionization is at least partly by mechanism (F), there is little information on products and stereochemistry. In the cases where the rate-determing step is (F), the rate constants refer to the rate of formation of open carbonium ion (III) and do not yield information on the reaction paths (III) follows. The ion (III) may close to (II), it may coordinate with reagent or solvent (Z) to give product (IV), or it may rearrange either to new ion (V) or in other ways, to mention some of the possibilities (6m).



(V) (III) (II)



(IV)

Also, the sterochemical results may be controlled by restriction of rotation around the C_β——C_α bond.

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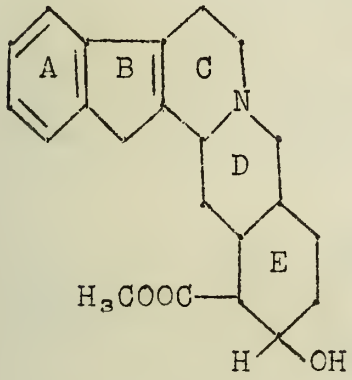
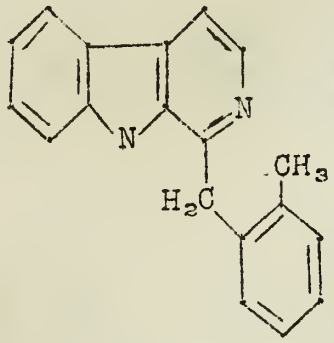
Reported by R. W. Meikle
October 22, 1948

THE STRUCTURE AND SYNTHESIS OF KETOYOBYRINE

The selenium dehydrogenation of yohimbine (I) gives two bases, yobyrine (II), and tetrahydroisoyobyrine (III), and ketoyobyrine, a neutral substance having the formula $C_{20}H_{16}ON_2$. The structures of yobyrine and tetrahydroisoyobyrine, and of yohimbine itself, have been established beyond question. (1,2)



I



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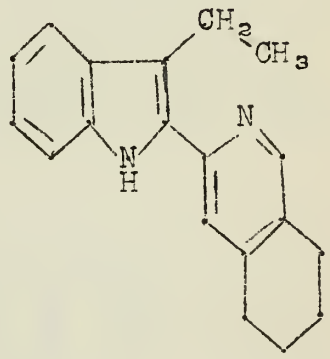
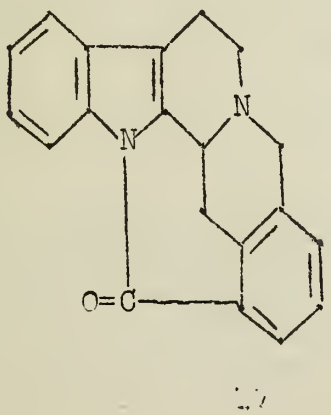


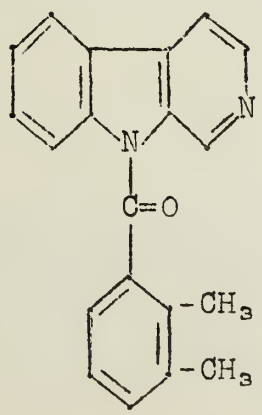
III

Scholz (3), in 1933, proposed the structure (IV), for ketoyobyrine. The facts that ketoyobyrine is optically inactive, that it is the product of a drastic dehydrogenation, and in particular that it has no basic properties, are incompatible with that formula. Also, ketoyobyrine is cleaved smoothly by amyl alcoholic potassium hydroxide to norharmane and hemellitylic acid.

This cleavage was used as a basis for formula (V), proposed by Witkop (2) in 1943. However, this formula also can not be reconciled with the basic character of ketoyobyrine. In addition, Raymond-Hamet (4) has made Witkop's formula doubtful on spectroscopic grounds.



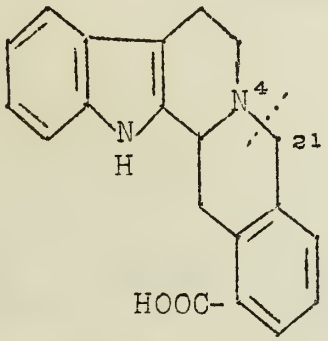
IV



V

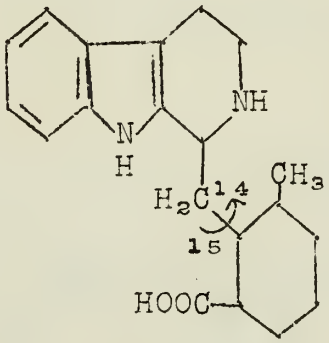
This year, almost simultaneously, Schlitter and Speitel (5) and Woodward and Witkop (6) proposed a new structure (VI) for ketoyobyrine. Both groups deduced the formula from that of yohimbine on the basis of the following considerations: (a) when yohimbine is heated with selenium, loss of the hydroxyl group through dehydration may be followed to some extent by the dehydrogenation of ring E; (b) the resulting intermediate (VII), as a benzylamine, should be subject to ready reduction cleavage between N·4 and C·21 to give (VIII); (c) by rotation through 180° about the C·14-C·15 bond, (VIII) is in a position to undergo lactamization to (IX); (d) selenium may effect the further dehydrogenation of the dihydroisoquinolone (IX) to (VI).

yohimbine $\xrightarrow{Se}$



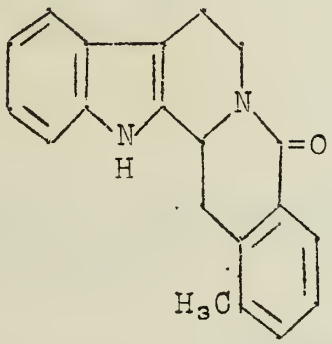
VII

$\rightarrow$



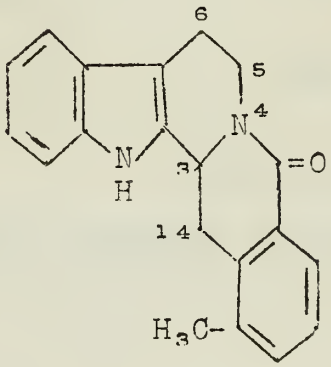
VIII

$\rightarrow$



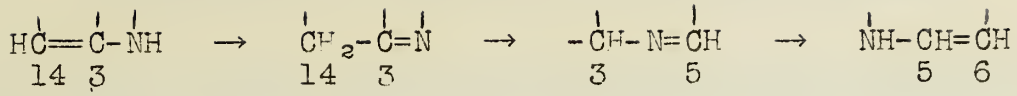
IX

$\rightarrow$

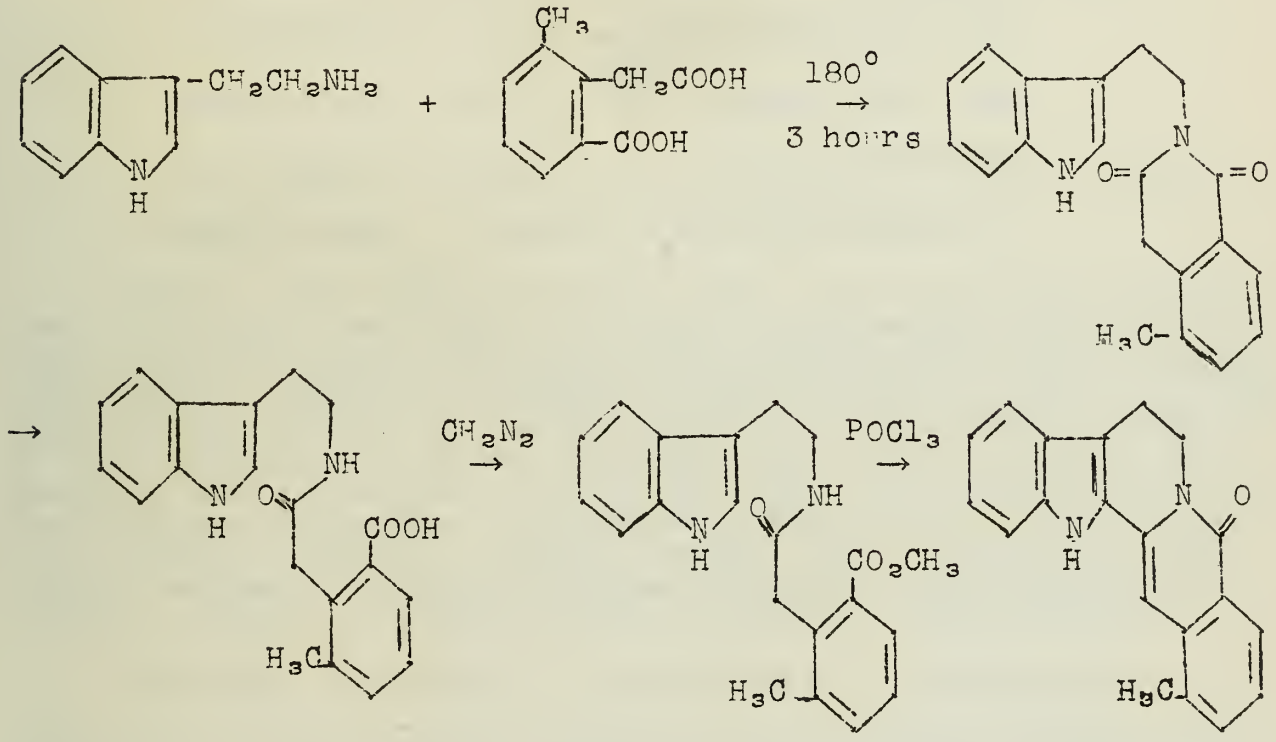


VI

The cleavage of ketoyobyrine by amyl alcoholic potassium hydroxide may be readily explained on the basis of this newly proposed structure. According to Woodward and Witkip, the opening of the amide link is followed by the migration of the $\Delta^{3,14}$ double bond to $\Delta^{5,6}$ by three prototropic shifts. The resulting dihydropyridine derivative then suffers loss of the side chain, giving norharmane and 2,3-dimethylbenzoic acid.



Schlitter and Speitel (5) and Julian, et. al. (7) have reported, independently, the synthesis of ketoyobyrine. The methods of synthesis were almost identical.



Ketoyobyrine

Comparison of the ultraviolet absorption spectrum of synthetic ketoyobyrine with that of the product of natural origin showed the two to be identical.

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Reported by William E. Goode
October 22, 1948

THE ADDITION OF AMINES TO ACETYLENIC KETONES

With the recent interest in the chemistry of acetylene compounds, much is being done with additions to the ethynylcarbonyl system, -C≡C-CO-, (1-8).

In general, the laboratory preparation of acetylenic ketones has utilized the following types of reactions.

1. $R-C\equiv C-Na + R'-COCl \rightarrow R-C\equiv C-CO-R'$ (1,9,10,11,12)

2. $R-C\equiv C-C\equiv C-R' + H_2O \rightarrow R-CH_2-C\equiv C-CO-R'$ (13)

3. $R-C\equiv C-CO-Cl + R'H \xrightarrow{AlCl_3} R-C\equiv C-CO-R'$ (8)

4. $R-C\equiv C-MgX + R'-CO_2-R'' \rightarrow R-C\equiv C-CO-R' + R''OMgX$ (8,15)

5. $Ar-C\equiv C-CO_2Et + ArMgX \rightarrow Ar-C\equiv C-CO-Ar$ (8)

Recently, the work of Bowden, Jones, and co-workers (2) and of Liang (15) upon the oxidation of the corresponding carbinols has made readily available the acetylenic ketones. The most satisfactory method of oxidation consists of the addition of CrO_3 in dilute H_2SO_4 to the carbinol in acetone solution. With proper adjustment of the concentration of the reagents, the reaction mixture will separate into two layers of which the upper one consists mainly of the carbonyl in acetone. In this way, the carbonyl is protected from further oxidation. By this method, use is made of the convenient action of acetylene Grignard reagents upon aldehydes and ketones to give the ethynylcarbinol compounds (16,17,18,19).

$$R-C\equiv C-MgX + R'-CHO \rightarrow R-C\equiv C-CHOH-R' \rightarrow R-C\equiv C-CO-R'$$

Chauvelier (6) has found a practical way to prepare symmetrical diacetylenic ketones by the reaction of acetylene Grignard reagents upon ethyl formate.

$$R-C\equiv C-MgX + HCO_2Et \rightarrow R-C\equiv C-CHOH-C\equiv C-R \rightarrow R-C\equiv C-CO-C\equiv C-R$$

The reaction of ammonia and primary and secondary amines with ethynyl carbonyl compounds gives products in which the addition takes place across the triple bond to give a beta substituted ethylene carbonyl compound (1,2,6,11,16).

$$R-C\equiv C-CO-R' + R''NH_2 \rightarrow R-C(R''NH)=CH-CO-R'$$

With compounds of the ethynyl-ethylene carbonyl type, the addition is across the triple bond.

$$R-C\equiv C-CO-CH=CH-R' + R''NH_2 \rightarrow R-C(R''NH)=CH-CO-CH=CH-R'$$

By the addition of diethyl amine to a vinylog of an acetylenic ketone the expected product (2) was obtained.

$$CH_3\text{-}CO\text{-}CH{=}CH\text{-}C{\equiv}CH \;+\; (C_2H_5)_2NH \rightarrow CH_3\text{-}CO\text{-}CH{=}CH\text{-}CH{=}CH\text{-}N(C_2H_5)_2$$

This product is unstable and was characterized merely by absorption spectrum. Other nitrogen compounds, hydrazine sulfate, hydroxy amine hydrochloride, guanidine nitrate, and ammonium sulfate add to benzoyl acetylene to give respectively 3-phenylpyrazole (70%), 5-phenylisooxazole (90%), 2-amino-4-phenylpyrimidine (25%), and 5-benzoyl-2-phenylpyridine (3).

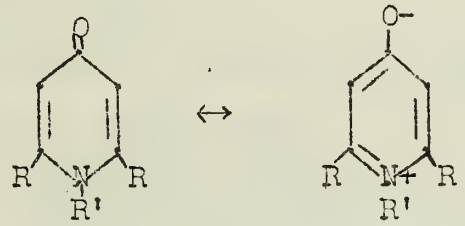
The addition of ammonia and primary and secondary amines to symmetrical diacetylene ketones proceeds as might be expected to give mono-addition products which have been well characterized (2,6).

$$R\text{-}C{\equiv}C\text{-}CO\text{-}C{\equiv}C\text{-}R + R'NH_2 \rightarrow R\text{-}C(R'NH){=}CH\text{-}CO\text{-}C{\equiv}C\text{-}R$$

These products exist in two isomeric forms both of which have been isolated and interconverted. In all probability, these are cis-trans geometric isomers. To date, the addition of two moles of amine has not been reported.

When the addition products of primary amines are heated above their melting points or boiled with xylene, a rearrangement takes place and the corresponding tri-substituted lutidones are produced in good yield.

$$R\text{-}C(R'NH){=}CH\text{-}CO\text{-}C{\equiv}C\text{-}R \rightarrow$$

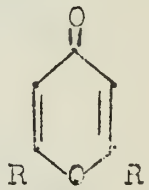


The addition products of secondary amines do not undergo this rearrangement. The existance of a resonate zwitterion accounts for the lack of color found.

Hydrolysis of the amino addition products (primary or secondary) with water and acid produces beta diketones from acetylenic ketones and gamma pyrones from di-acetylenic ketones by way of an unstable intermediate (6,20) acetylenic diketone.

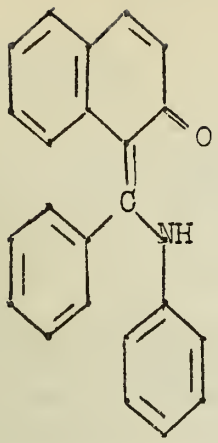
I. $R\text{-}C(R'NH){=}C\text{-}CO\text{-}R'' \rightarrow R\text{-}CO\text{-}CH_2\text{-}CO\text{-}R''$

II. $R\text{-}C(R'NH){=}C\text{-}CO\text{-}C{\equiv}C\text{-}R \rightarrow R\text{-}CO\text{-}CH_2\text{-}CO\text{-}C{\equiv}C\text{-}R \rightarrow$

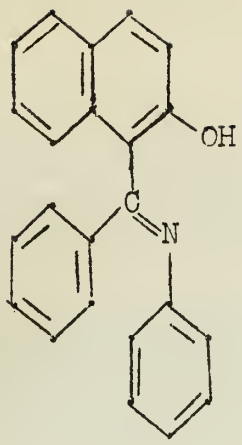


This intermediate is converted by heating almost explosively to the pyrone. (20).

When aniline addition products of bis-ethynyl ketone are treated to effect cyclization to the lutidone, only 30% of this product is obtained. From this reaction mixture, a red compound has been isolated and from its absorption spectrum and degradation to benzoic acid, phthalic acid, benzanilid, and carbon dioxide, it appears to have the following structure.



or its isomer



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Reported by Carl S. Hornberger
October 29, 1948

RECENT STUDIES OF THE JACOBSEN REATION

Introduction

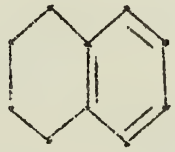
The name Jacobsen Reaction is given to those reactions involving the migration of an alkyl group or a halogen atom of the sulfonic acid derived from a polyalkylbenzene, a halogenated polyalkylbenzene, or a polyhalogenated benzene, in the presence of concentrated sulfuric acid (1).

The reaction was first discovered by Herzig who, in 1881, noted the rearrangement of a polyhalogenated benzenesulfonic acid. It is named however after Jacobsen who was the first to observe the rearrangement of polyalkylbenzenesulfonic acids in 1886 (2).

Studies of Cyclic Systems

Hydrindene (I) and tetralin (II), and their derivatives, may be considered as ortho-dialkylbenzenes, and might be expected to undergo rearrangements under the conditions of the Jacobsen Reaction (3).

(I)



(II)

A rearrangement of this type was observed by Schroter and Gätzky (4) who in preparing octahydroanthracene-9-sulfonic acid found that under prolonged heating and high temperatures, this compound was transformed into the octahydrophenanthrenesulfonic acid.

Arnold and Barnes (3) subjected s-hydrindacene (III), 5,6,7,8-tetrahydrobenz(f)indan (IV), 5-ethyl-6-methylhydrindene (V), 6,7-diethyltetralin (VI), and octahydroanthracene to the conditions of the Jacobsen Reaction.

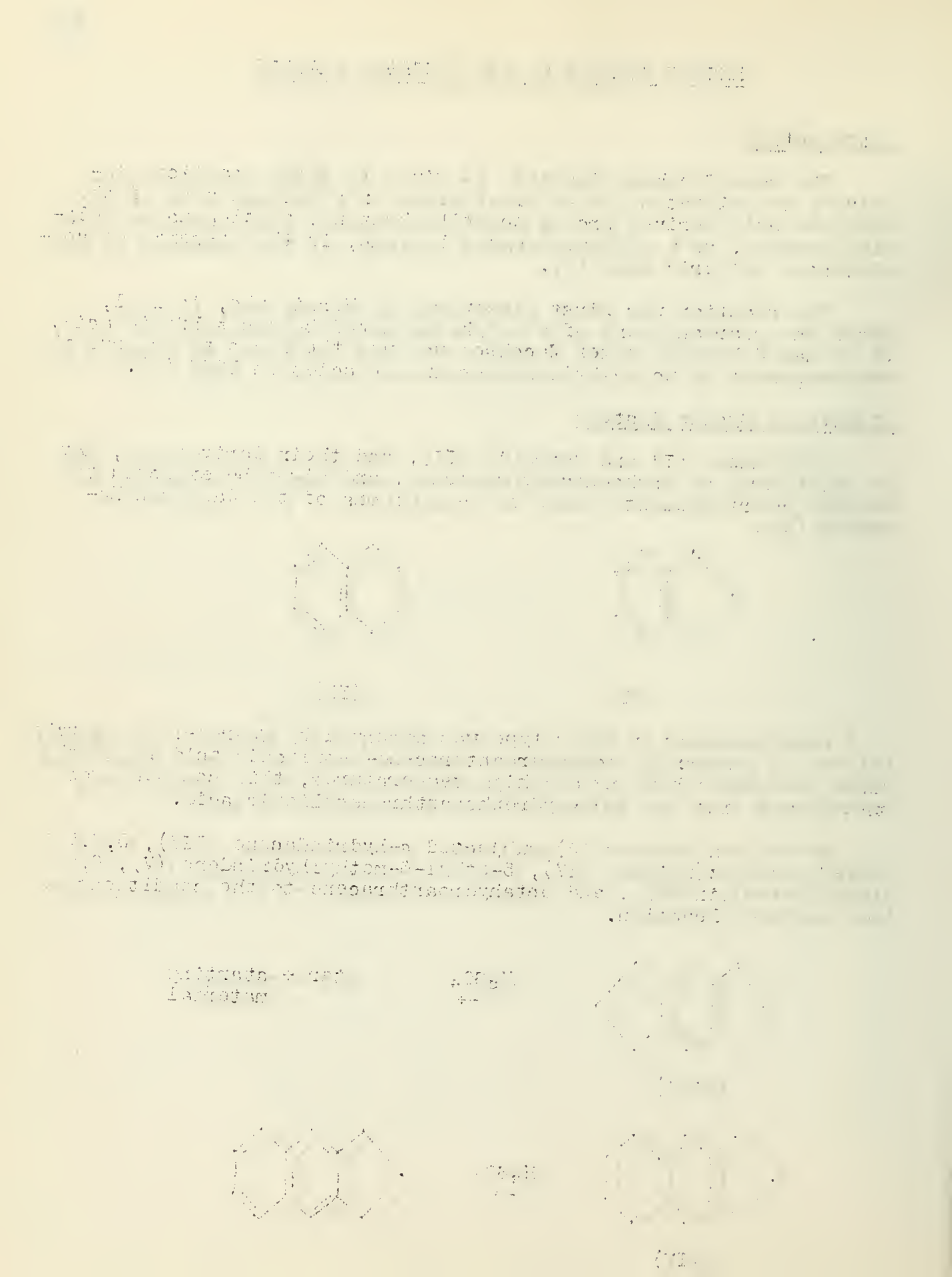
H_2SO_4 →

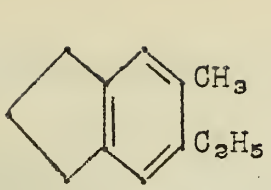
tar + starting material

(III)

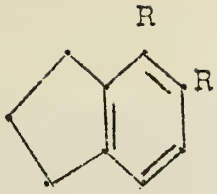
H_2SO_4 →

(IV)



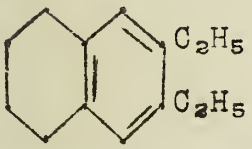


H_2SO_4 →

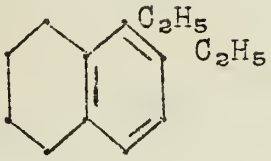


R = CH_3 or C_2H_5

(V)



H_2SO_4 →



(VI)

Octahydroanthracene $\xrightarrow{H_2SO_4}$ Octahydrophenanthrene

Reaction Mechanism

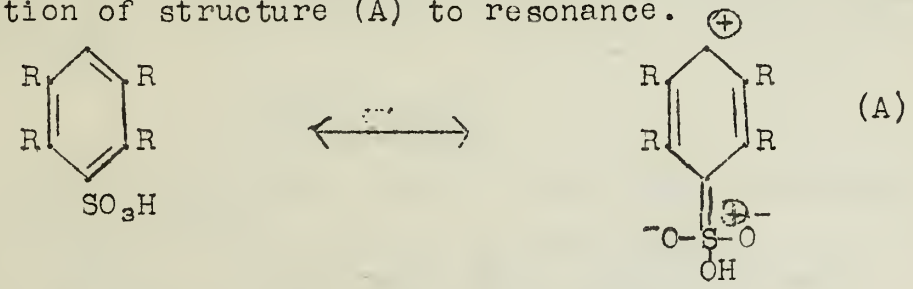
From the results of the above reactions, and other work which indicated that the steric effect of a methylene group present in various groupings, increase in the order,

5-membered ring (hydrindene) < 6-membered ring (tetralin) < CH_3,

Arnold and Barnes postulated the following regarding the mechanism of this reaction (3):

1. The reaction proceeds by an initial sulfonation, replacement of an alkyl group by a second sulfonic acid group, and subsequent replacement of the first sulfonic acid group by the alkyl cation.

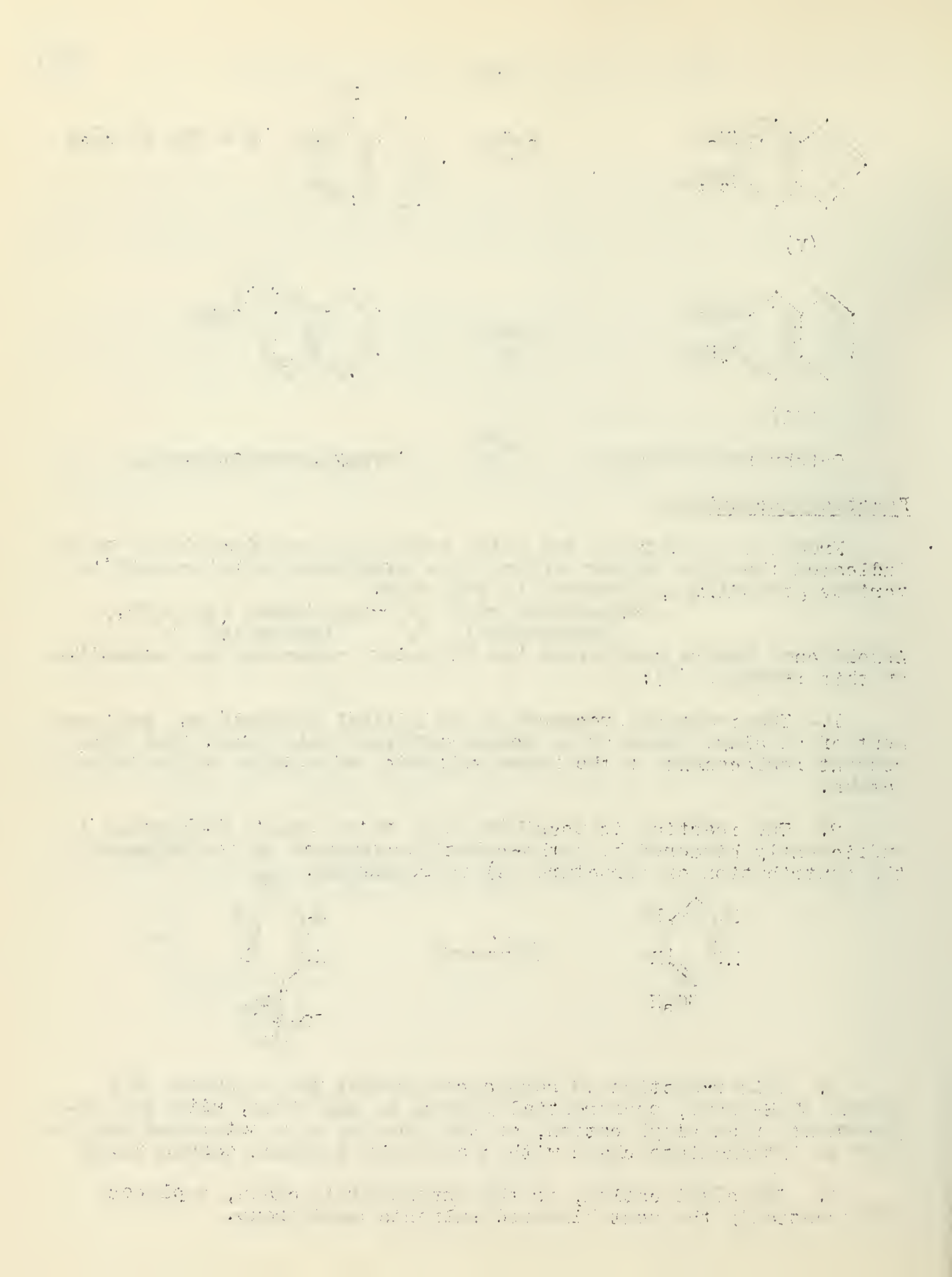
2. The reaction is possible only if the first SO_3H-group is sufficiently hindered by ortho-substituents such as to decrease the contribution of structure (A) to resonance.



(A)

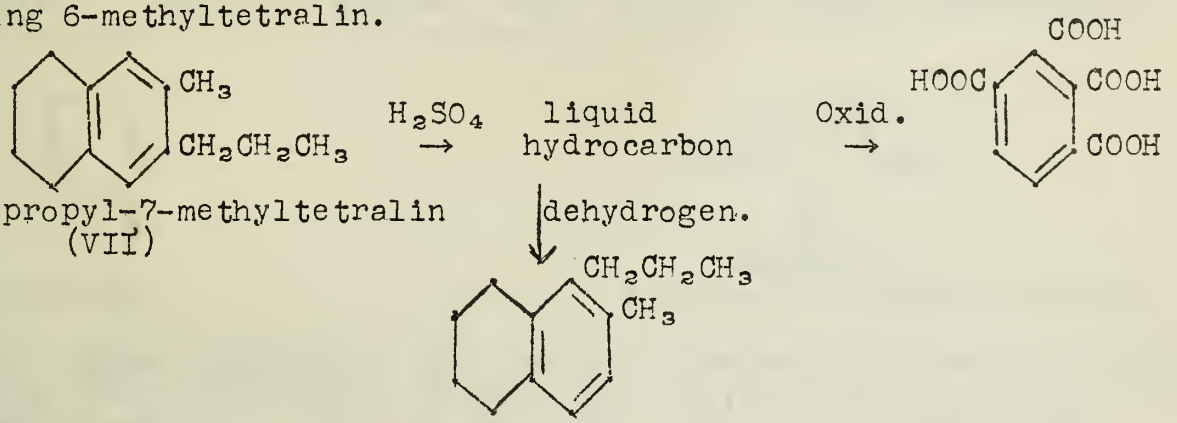
3. This reduction of resonance permits the entrance of a second SO_3H-group, preferentially meta to the first, with the replacement of an alkyl cation, or the opening of a saturated ring to form an intermediate chain with a cationic terminal carbon atom.

4. The alkyl cation, or the intermediate chain, replaces preferentially the most hindered sulfonic acid group.



Further Studies of Cyclic Systems

Smith and Lo (5) have reported further studies of 6,7-dialkyltetralins. The 6,7-dimethyltetralin gave the expected 5,6-dimethyl tetralin. 6-Isopropyl-7-ethyltetralin and 6,7-di-n-propyltetralin yielded small amounts of unidentified oils. 6-Isopropyl-7-methyltetralin on treatment with sulfuric acid lost the isopropyl group giving 6-methyltetralin.



There are two ways that (VII) can undergo rearrangement to give the liquid hydrocarbon which was identified as the 5-n-propyl-6-methyltetralin:

(a) The 6-n-propyl-group may migrate to the 8-(or 5-) position

(b) The tetramethylene ring may open and close ortho to the propyl group.

According to the mechanism theory of Arnold and Barnes (3), the product from (a) should be 5-isopropyl-6-methyltetralin since during the course of the reaction a free n-propyl cation would be existent, and this would rearrange to the more stable isopropyl cation. Smith and Lo conclude therefore that the reaction proceeds according to (b).

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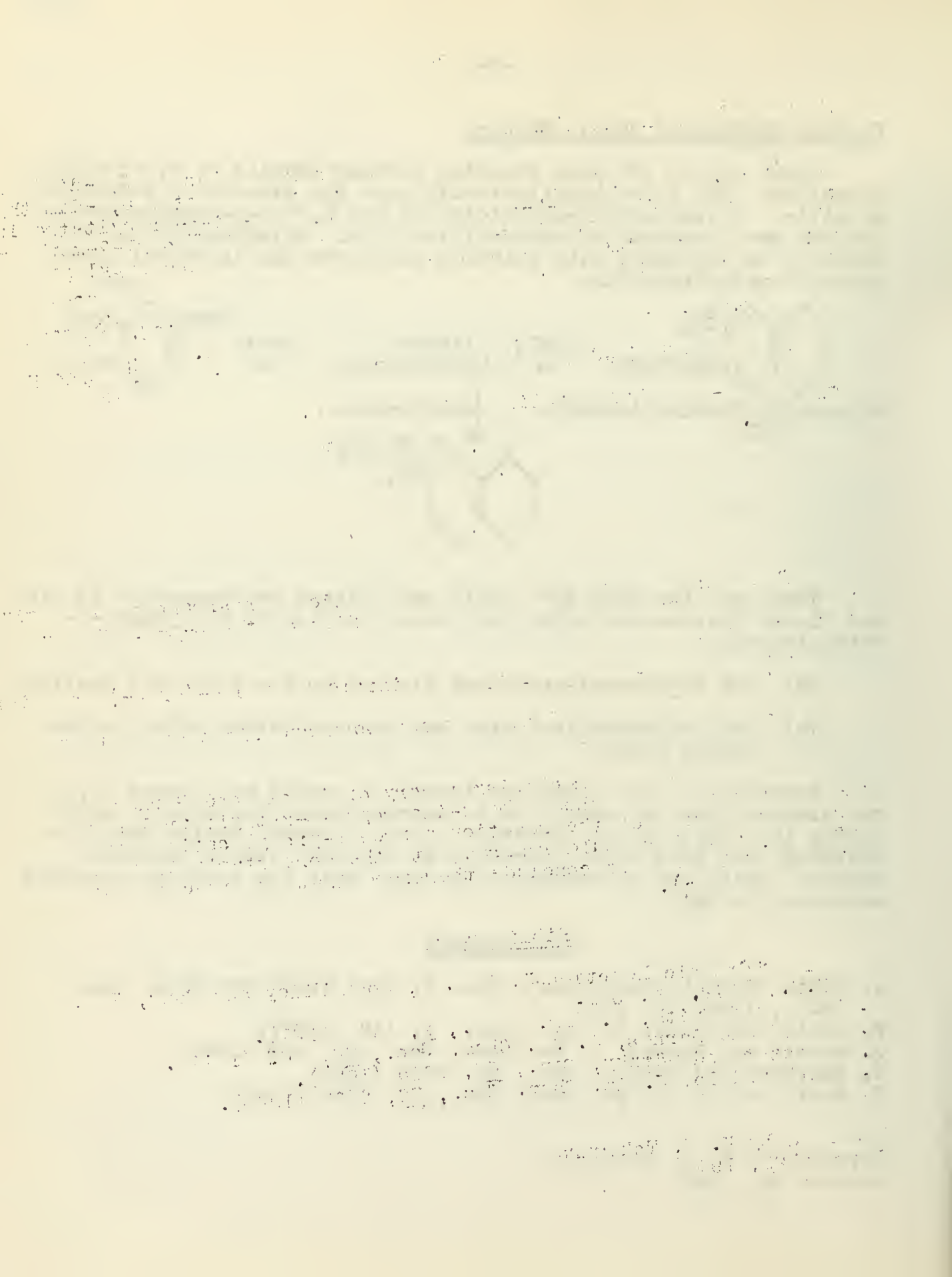
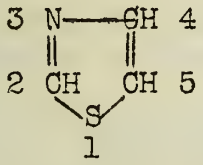
Reported by K. H. Takemura
October 29, 1948

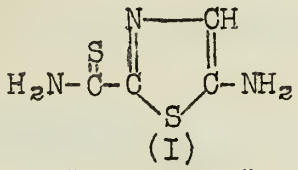


SYNTHESES OF 5-AMINOTHIAZOLES

In view of the use of the well-known sulfathiazole (the sulfanilamide derivative of 2-aminothiazole) as an important sulfa drug, interest arose in the synthesis of the 4- and 5-aminothiazoles and their derivatives. Although 2-aminothiazole was synthesized as early as 1889, the isomeric 4-aminothiazole and 5-aminothiazole are not known. Recently, however, derivatives of these compounds have been prepared by a variety of methods (1-8).



Thiazole



(I)

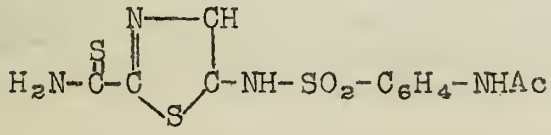
"Chrysean"

5-Amino-2-thioamidothiazole

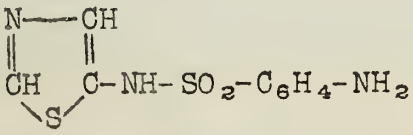
A. From "chrysean". Wallach (1) obtained chrysean in 15-20% yield by passing hydrogen sulfide into a saturated solution of potassium cyanide. Later it was shown (2,3) to be 5-amino-2-thioamidothiazole, (I). The chrysean molecule is fragile, and the 5-aminothiazole cannot be prepared by the nitrile, carboxylic acid, and decarboxylation route.

Hellsing (2) prepared 5-aminothiazole-2-nitrile from chrysean by treatment with lead or silver salts, but attempts to hydrolyze this to the acid usually result in rupture of the ring, especially under alkaline conditions. Cautions acid hydrolysis has given 5-amino-thiazole-2-carboxylic acid in poor yield. On the other hand, in neutral solution with excess of $CaCO_3$ the nitrile gives 5-aminothiazole-2-amide in very good yield. Acylation of the amino group permits normal degradation of the thioamide group, but the products are all so resistant to hydrolysis that the acyl group cannot be removed.

Arnold and Scaife (3) prepared 5-(p-acetamidobenzenesulfonamido)thiazole-2-thioamide, (II), from chrysean and p-acetamidobenzenesulfonyl chloride. 5-(p-Aminobenzenesulfonamido)thiazole, (III), was obtained from the 2-thioamide, (II), by converting this into the 2-nitrile with lead carbonate and boiling the solution with sodium hydroxide; deacetylation, hydrolysis of the nitrile group, and decarboxylation then took place. It was found that against streptococcal infections in mice, (III) was active but has no advantage over established sulfonamide drugs, whereas (II) is inactive.



(II)



(III)

B. From thiazole-5-carboxylic esters by the Curtius reaction (4,5). Starting with ethyl 2,4-dimethylthiazole-5-carboxylate, which was prepared from thioacetamide and ethyl α-chloroacetoacetate the corresponding 5-amino compound was obtained by the Curtius reaction. The ethereal solution of the azide obtained from the ester was added to a mixture of acetic acid and acetic anhydride. After decomposition of the azide and neutralization with Na_2CO_3, the acetamino compound separated in 99% yield. Hydrolysis with HCl yielded the amino compound in 90% yield.

The following esters, (a-c), gave the corresponding 5-acetamino compounds.

(a) Ethyl 4-methylthiazole-5-carboxylate.
This ester was prepared from thioformamide and ethyl α-chloro (or bromo) acetoacetate.

(b) Ethyl 2-chloro-4-methylthiazole-5-carboxylate.
The reaction of ammonium thiocarbamate and ethyl α-chloroacetoacetate gave ethyl 2-hydroxy-4-methylthiazole-5-carboxylate. Refluxing with $POCl_3$ gave (b), the corresponding 2-chloro compound.

(c) Ethyl 2-amino-4-methylthiazole-5-carboxylate.
This compound was prepared from thiourea and ethyl α-chloroacetoacetate.

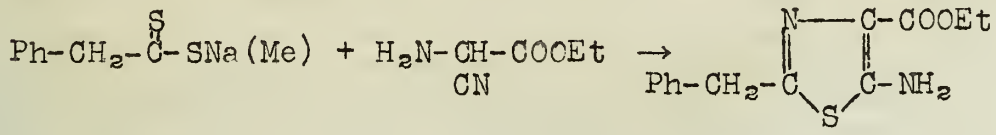
C. From 5-acetylthiazoles by the Beckmann rearrangement. 4-Methyl-5-acetylthiazole, prepared from thioformamide and chloroacetylacetone, and 2,4-dimethyl-5-acetylthiazole, prepared from thioacetamide and chloroacetylacetone, were converted to the corresponding 5-acetamino compounds in 30% and 10% yields, respectively, by treatment of their oximes with PCl_5. Treatment of their oximes with acetic anhydride and hydrogen chloride gave the acetates of the oximes. (4)

D. From the reduction of 5-nitrothiazoles (4). Nitration of 2-acetaminothiazole with concentrated sulfuric acid and fuming nitric acid yielded 2-acetamino-5-nitrothiazole, but reduction failed to give the 5-amino compound. Nitration of 2,4-dimethylthiazole, prepared from thioacetamide and chloroacetone, gave 2,4-dimethyl-5-nitrothiazole. This nitro compound could be reduced with iron to the amino compound which on acetylation gave 2,4-dimethyl-5-acetaminothiazole.

E. From the reduction of 5-azothiazoles (4). 2-Hydroxy-4-methylthiazole, prepared from ammonium thiocarbamate and chloroacetone, underwent coupling with diazotized p-toluidine to yield an azo dye which on reduction with sodium hydrosulfite furnished 2-hydroxy-4-methyl-5-aminothiazole. This method has limited applicability, for 2,4-dimethylthiazole or 2-amino-4-methylthiazole did not couple with diazotized p-toluidine.

F. From aminoacetonitriles and dithioacid derivatives. In connection with the study of penicillin, Heilbron (6) examined the reaction between sodium or methyl dithiophenylacetate and ethyl-

aminocyanoacetate (prepared by reducing ethyl nitrosocyanoacetate with amalgamated aluminum). The product was at first thought to be acyclic, but subsequent investigation showed that it was 5-amino-4-carbethoxy-2-benzylthiazole, (IV). Similarly, aminoacetonitrile



(IV)

and sodium dithiophenylacetate afforded an excellent yield of 5-amino-2-benzylthiazole.

By employing sodium dithioformate and ethyl aminocyanoacetate, 5-amino-4-carbethoxythiazole was obtained. In the same way α-aminobenzyl cyanide and sodium dithioformate afforded 5-amino-4-phenylthiazole.

This appears to be the most general synthesis of the 5-amino-thiazoles. It is noteworthy also that these ring syntheses take place at room temperature, several of them in aqueous neutral solution.

G. From α-amino-nitriles and carbon disulfide (7). The reaction between carbon disulfide and α-aminobenzyl cyanide was easily effected at room temperature to yield 5-amino-2-mercapto-4-phenyl-thiazole. When this was treated with alkali and Raney nickel in hot ethanol, removal of one atom of sulfur proceeded spontaneously to give the known 5-amino-4-phenyl-thiazole.

Ethyl aminocyanoacetate and carbon disulfide gave 5-amino-2-mercapto-4-carbethoxythiazole. This was confirmed again by desulfurization with Raney nickel to a known thiazole.

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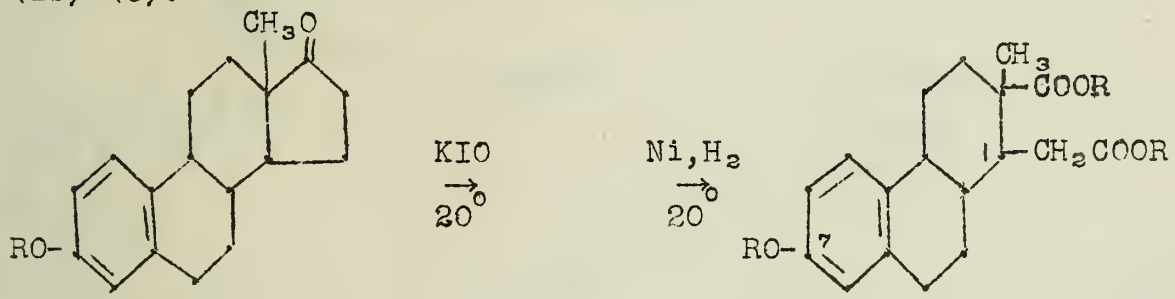
Reported by Alex Kotch
October 29, 1948

THE TOTAL SYNTHESIS OF (+)-ESTRONE

The total synthesis of the natural estrogenic hormone (+)-estrone was reported at the beginning of this year in a brief communication by Anner and Miescher (1). Several investigators have attempted to synthesize the hormone but have succeeded only in obtaining mixtures of sterioisomers or structural isomers (2). As a result of extensive research in the stereochemistry and synthesis of the marrianolic and doisynolic acids, Miescher and coworkers have been able to limit the number of stereoisomers in each of the intermediate steps in the synthesis and have therefore been able to obtain the correct one of the sixteen possible stereoisomers of estrone.

"Natural" (+)-marrianolic acid (IIa) has been obtained most conveniently from (+)-estrone (Ia) via the estrone benzyl ether (Ib) (3).

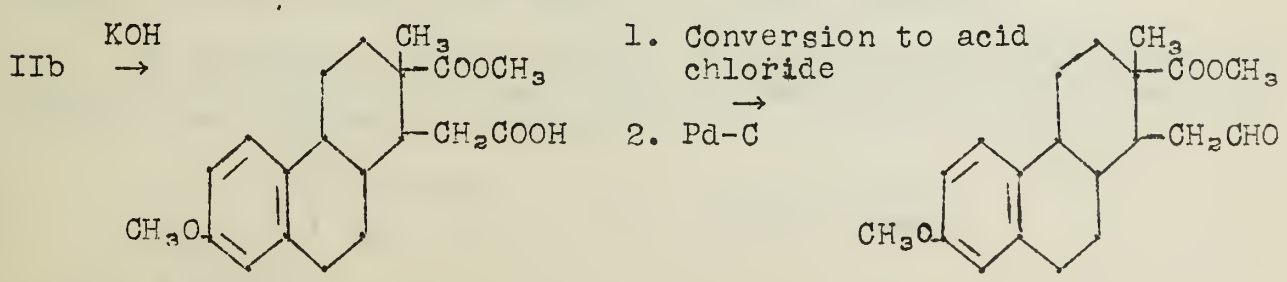


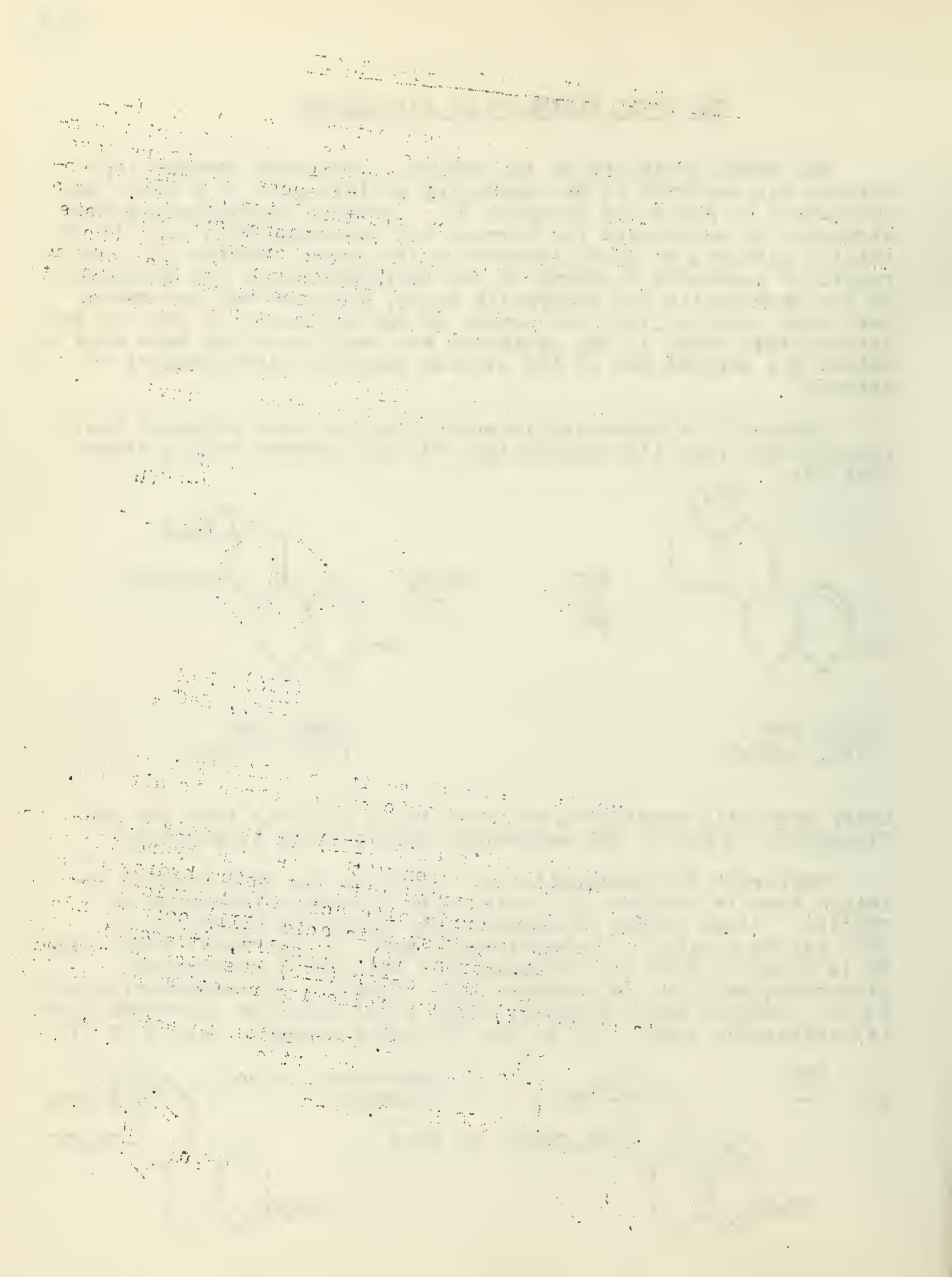
(Ia), R=H
(Ib), R=$CH_2\phi$

(IIa), R=H
(IIb), R=CH_3

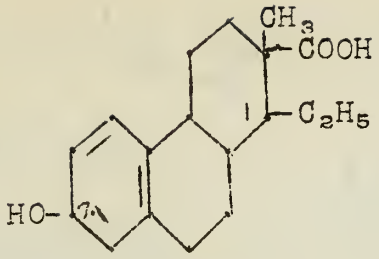
Under such mild conditions as these it is unlikely that the configuration at any of the asymmetric carbon atoms is altered.

"Natural" (+)-doisynolic acid (III) is the only product obtained from (+)-estrone by fusion with potassium hydroxide at 275° (3). Since fusion of estriol with potassium hydroxide at 275° yields a single (+)-marrianolic acid (4) identical with (IIa), it is probable that the (+)-doisynolic acid (III) corresponds stereochemically to (+)-estrone (5). Finally, (+)-marrianolic acid as the 7-methyl ether dimethyl ester (IIb) has been converted into (+)-doisynolic acid (III) in the following reaction series (6,7):



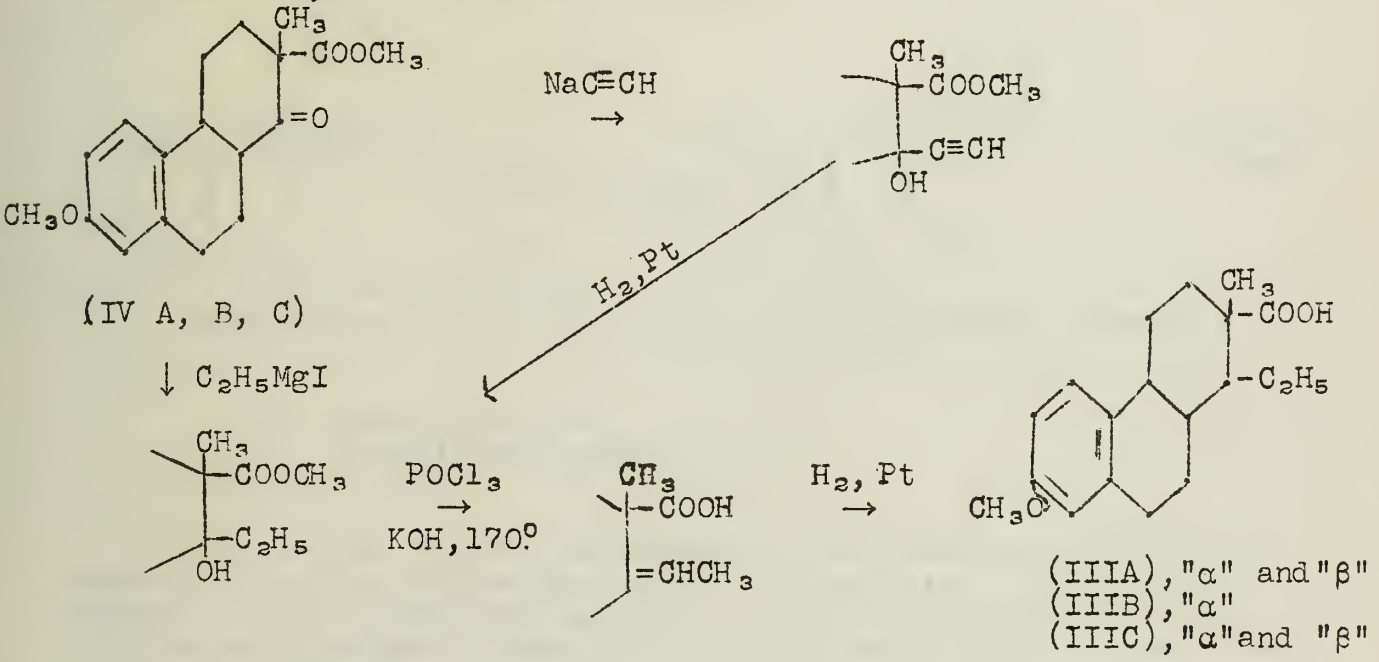


1. $Na_1Clycol$, N_2H_4, 190°
2. Pyridine-HCl



(III)

The key to the total synthesis of (+)-estrone was the keto ester IV which both Robinson (8) and Bachmann (9) had obtained only as a liquid mixture of racemates. Robinson (10) had little success in his attempt to synthesize estrone from this mixture. Anner and Miescher (11) were able to separate the mixture into three crystalline, racemic substances (IVA,B and C) by fractional crystallization With these compounds as starting materials, they were able to accomplish the total synthesis of five out of the eight possible racemic doisynolic acids as follows:

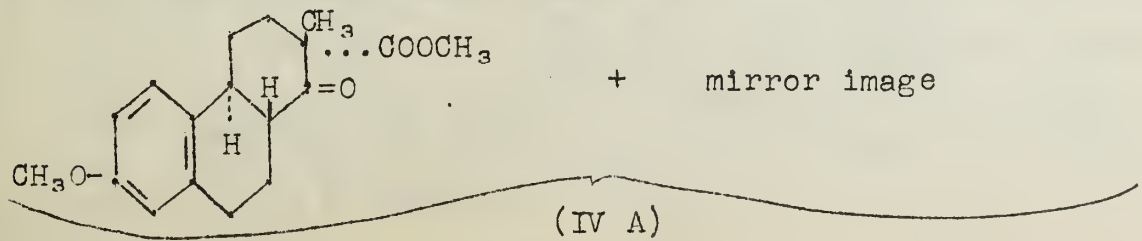


(IV A, B, C)

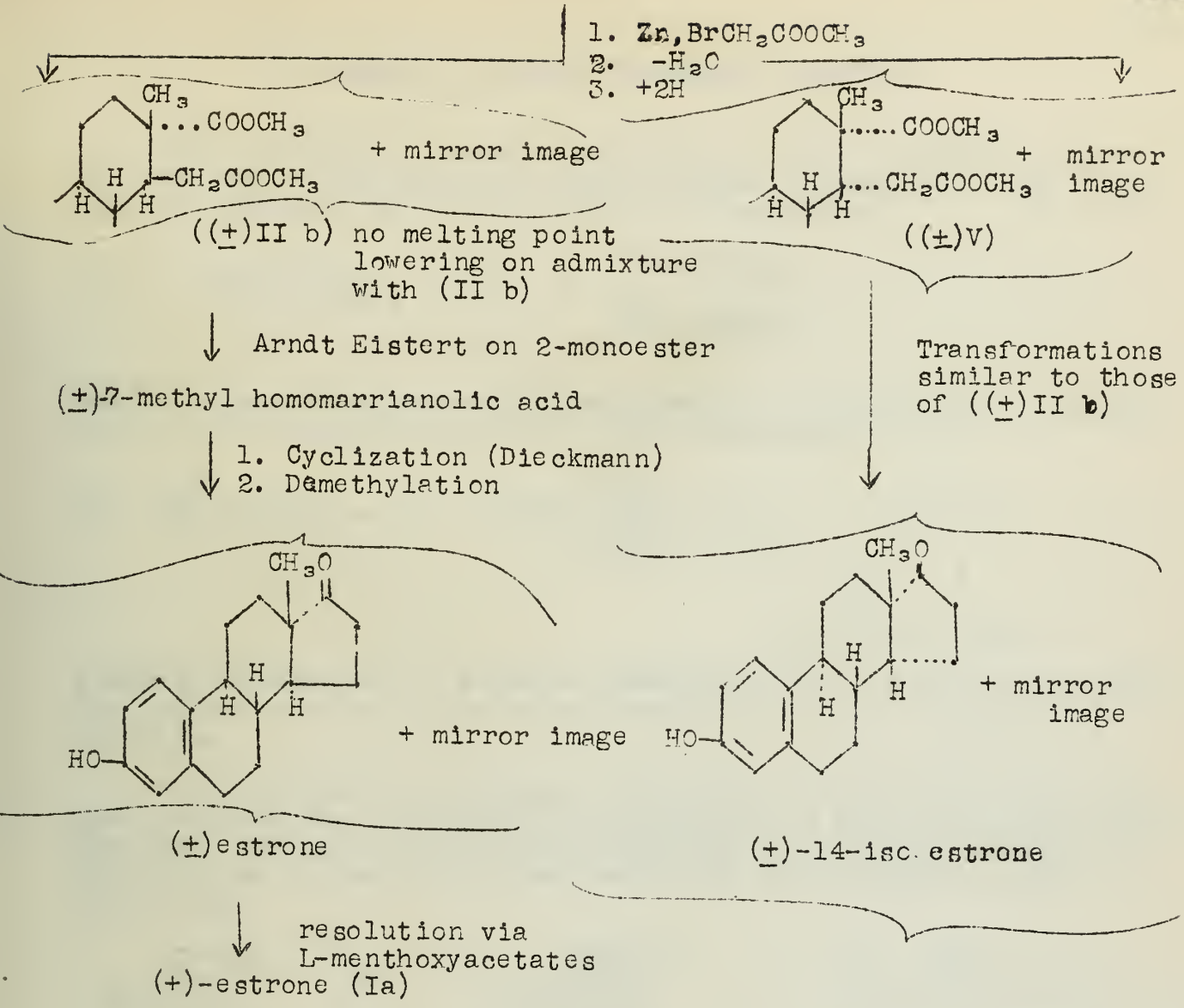
(IIIA), "α" and "β"
(IIIB), "α"
(IIIC), "α" and "β"

The racemic (III A), (±)-"β"-7-methyl doisynolic acid, did not depress the melting point of the "natural" (+)-7-methyl doisynolic acid and, similarly, the (III B), "α" racemate corresponded to (+)-7-methyl lumidoisynolic acid (differs from the "natural" doisynolic acid only in configuration at C_2). The (III A), "α" racemic 7-methyl doisynolic acid has been related to 14-iso estrone.

The synthesis of (+)-estrone started with the keto ester (IV A) since it was believed to have the requisite configuration at each of the three asymmetric centers.



(IV A)



This is also a total synthesis of "α" estradiol since "α" estradoil is a reduction product of (+)-estrone. In a similar manner $\Delta^{8,9}$-monodehydroisoestrone has been synthesized from (±)-"α"-7-methyl monodehydromarrianolic acid which has, in turn, been obtained by total synthesis (12,13,14).

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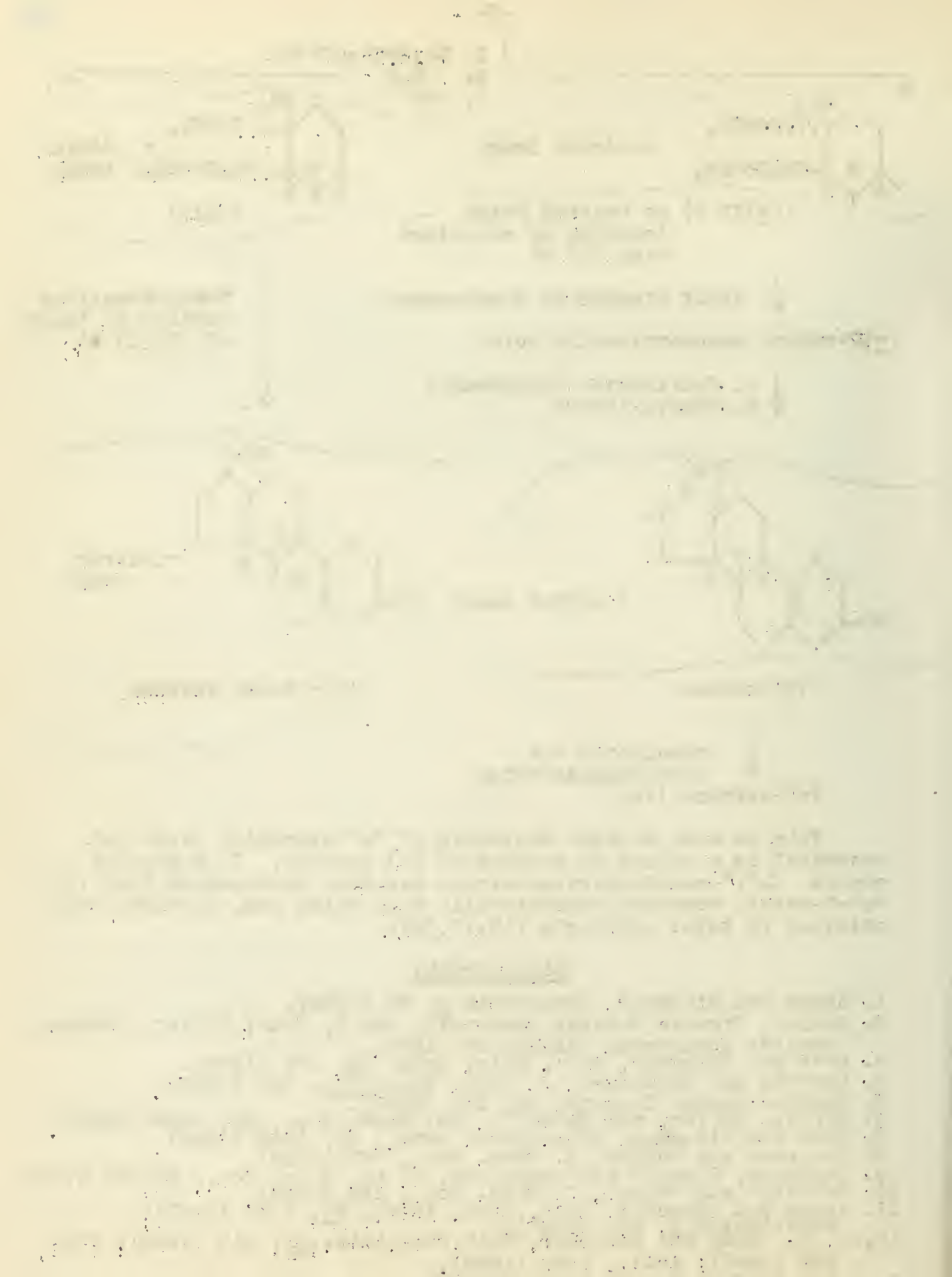
Reported by Janet B. Peterson
November 5, 1948



BY PRODUCTS IN THE REFORMATSKY REACTION

The Reformatsky reaction produces several by products, some of which may be expected and others rather unexpected. The ones usually expected (6) are the product of coupling

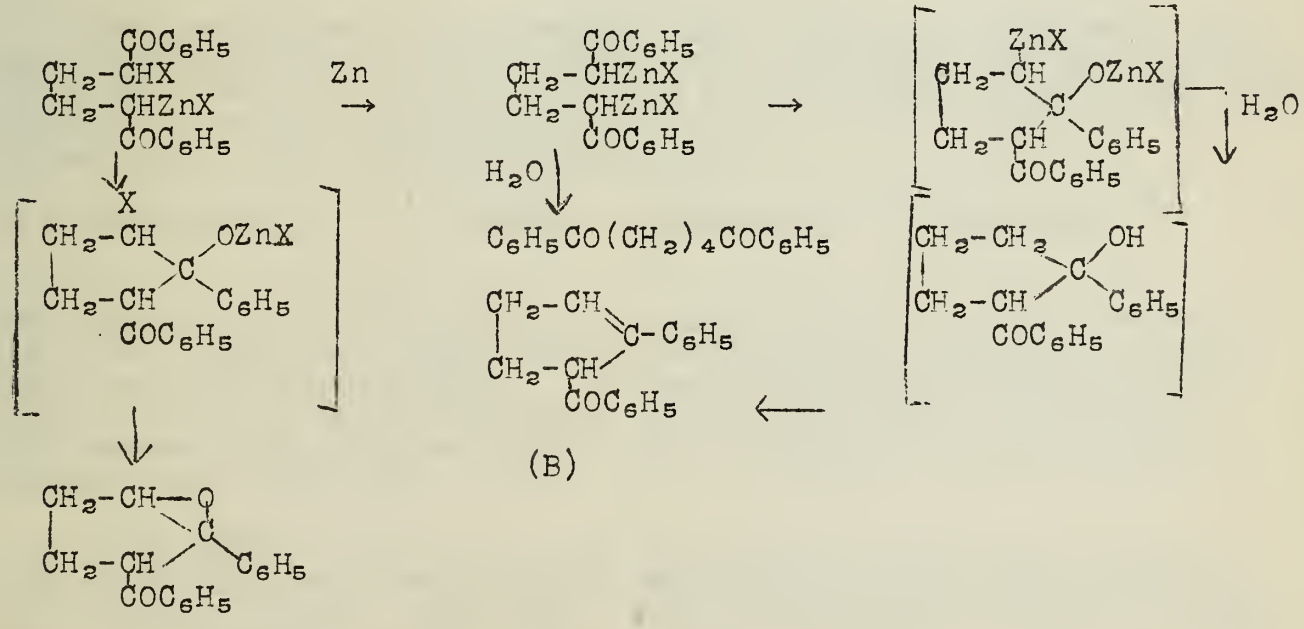
(1) $2BrCH_2COOC_2H_5 + Zn \rightarrow \begin{matrix} CH_2\text{-}COOC_2H_5 \\ | \\ CH_2\text{-}COOC_2H_5 \end{matrix}$

and a γ-bromo-β-ketoester (3) produced by the addition of one mole of the zinc halide to a mole of the bromoester.

(2) $2CH_2(Br)COOC_2H_5 + Zn \rightarrow BrCH_2\text{-}C(OZnBr)(OC_2H_5)\text{-}CH_2COOC_2H_5 \rightarrow C_2H_5OZnBr + BrCH_2C(=O)CH_2COOC_2H_5$

Aliphatic aldehydes or ketones sometimes undergo aldolization under the influence of the zinc salts forming the usual condensation products.

Upon treating 1,4-dibromo-1,4-dibenzoyl butane (1) with zinc they obtained two cyclopentane derivatives, A and B, and the reduced dibenzoyl butane instead of the expected cyclobutane derivative. The proposed course of the intramolecular Reformatsky reaction is as follows:



(A)

When 5,8-dimethyl-1-tetralone (3) was treated with zinc and (a) ethyl bromoacetate (b) ethyl α-bromopropionate and (c) ethyl α-bromoisobutyrate the principal by products were the reduced

ester and the corresponding β-ketoester, $R_2CHCOCR_2COOC_2H_5$. By using an excess of the bromoester and zinc to compensate for these by products the yields of the desired products increased from 25% to 85% with ethyl α-bromoacetate and from 17% to 82% with ethyl α-bromopropionate. No Reformatsky product was obtained with ethyl α-bromoisobutyrate. In each case about the same amount of reduced ester was obtained, 10-15%. In addition a considerable amount of the corresponding β-ketoester was obtained; 15% of ethyl aceto-acetate, 35% of ethyl α-propionyl propionate and 69% of ethyl α-isobutrylisobutyrate. They were unable to detect any of the halogenated β-ketoester or coupled product. The proposed reaction path for the formation of the β-ketoester is as follows:

(3) $[R_2CCOOEt]ZnBr + R_2CBrCOOEt \rightarrow$

$R_2CBrC(OEt)(OZnBr)-CR_2COOEt \xrightarrow{-EtOZnBr} R_2CBrCOCR_2COOEt$

$R_2CBrCOCR_2COOEt \xrightarrow{Zn} [R_2CCOCR_2COOEt]ZnBr$

$[R_2CCOCR_2COOEt]ZnBr \xrightarrow{H_2O} R_2CHCOCR_2COOEt$

The experimental support for this reaction path is the fact that, even in the absence of carbonyl compounds, ethyl α-bromopropionate reacts vigorously with zinc to give 16% of the reduced ester and 39% of the ethyl α-propionylpropionate. Ethyl α-bromoisobutyrate gave traces of the reduced ester and a 65% yield of ethyl α-isobutrybutryate when treated in like manner.

The occurrance of the reduced ester has been explained in two ways, neither of which is satisfactory in itself. The first explanation (5) postulates the enolization of the ketone which reacts with the organometalic intermediate analogously to the formation of methane in a Zerwitinoff determination:

(4) $[RCHCOOEt]ZnBr + RCOCH_2R \rightarrow [RCOCHR]ZnBr + RCH_2COOEt$

This postulate was confirmed by treating acetomesitylene, which is known to react with other organometalics (4) by enolization, with zinc and methyl bromoacetate. It was possible to distill methyl acetate from the reaction mixture before hydrolysis showing that the reduced ester did not arise from a reaction of the bromozinc intermediate with water.

Since appreciable amounts of the reduced ester are obtained when no ketone is present in the reaction mixture it was necessary to postulate another mechanism. The one proposed involves an acid-base type reaction involving the acidic hydrogen of the bromoester.

(5) $[RCHCOOEt]ZnBr + RCHBrCOOEt \rightarrow RCH_2COOEt + [RCBrCOOEt]ZnBr$

This type of mechanism is supported by the fact that no reduced ester is produced in the self condensation of ethyl α-bromoisobutyrate, a bromo ester which contains no α hydrogen.

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Reported by C. W. Fairbanks
November 5, 1948

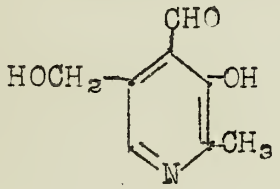
STUDIES ON THE STRUCTURE OF PYRIDOXAL PHOSPHATE

Enzymes are organic catalysts produced by living organisms. Thus far, every enzyme isolated has been found to be a protein. Most usually, enzymes are named and classified in terms of the reaction or reactions which they catalyze and by their behavior toward substrates (the substances acted upon).

An enzyme may be considered as a combination of a protein carrier (apoenzyme) and a coenzyme, an organic, heat-stable molecule which is a specific activator.

Gunsalus et al. (1,2) have shown that the ability of suspension of Streptococcus fecalis and Escherichia coli to decarboxylate tyrosine and other amino acids is slightly stimulated by pyridoxal (I), but is markedly stimulated if supplied with pyridoxal and adenosine triphosphate or if the pyridoxal is treated previously with chemical phosphorylating agents (3,4,5). The methods of phosphorylation used were: (a) treatment with thionyl chloride, followed by silver dihydrogen phosphate; (b) treatment with phosphoric acid in the cold; (c) treatment of an aqueous solution of pyridoxal hydrochloride with sodium hydroxide and phosphorus oxychloride.

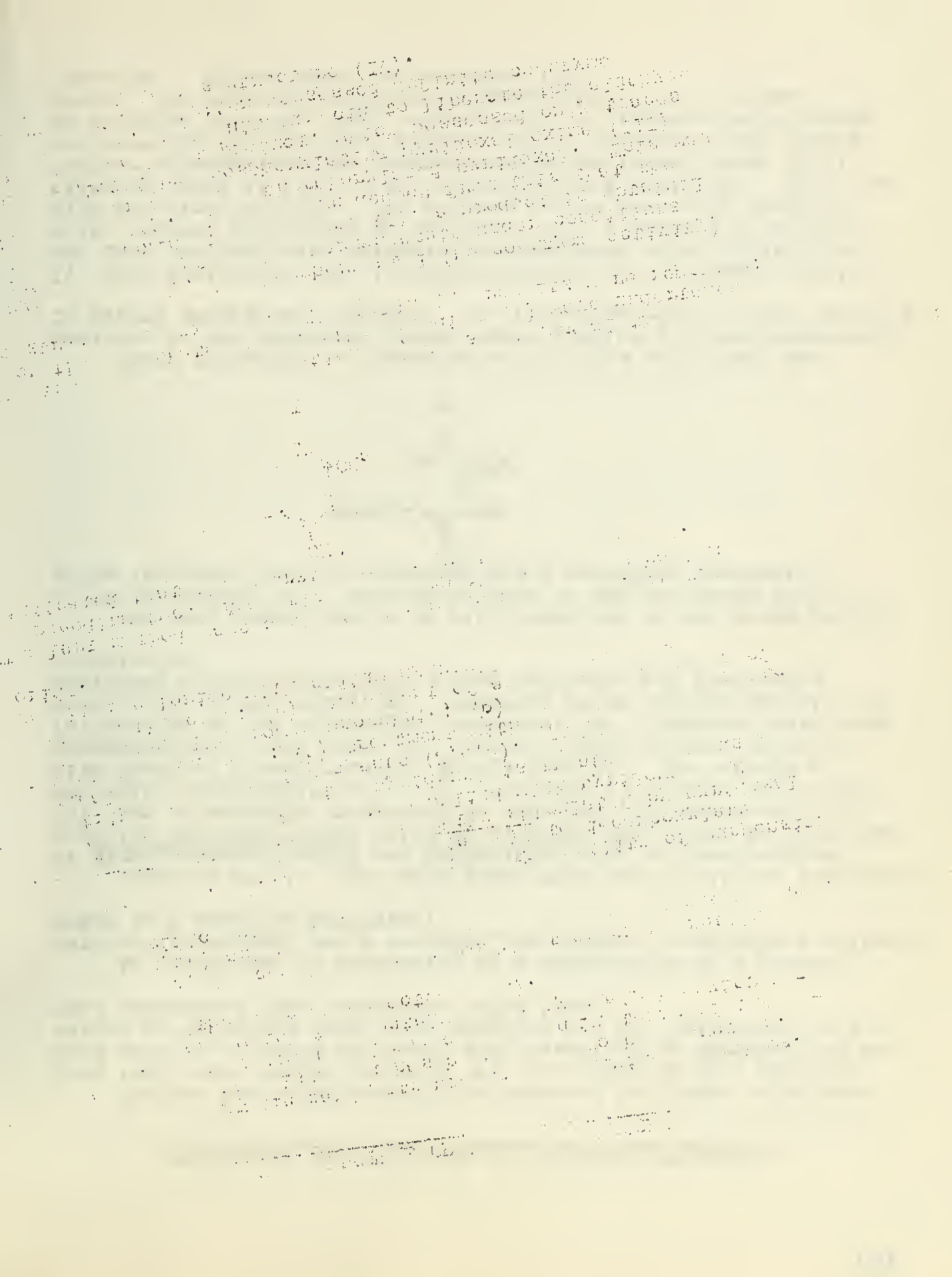
The last method gave a 5% yield compared to the trace yields of the preceding two. Analytical data on the amorphous barium salts indicated that the coenzyme was a pyridoxal phosphate.

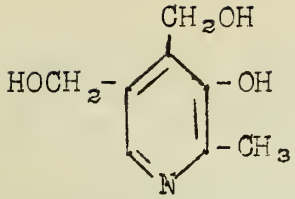


I

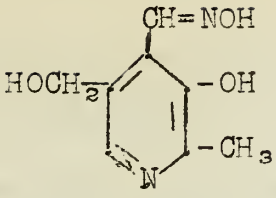
Since the method of preparation (6) does not reveal the position of the phosphate group, other studies (7) were undertaken to secure structural evidence. The following results were reported:

1. When pyridoxine (II) is phosphorylated (no coenzyme activity) and then oxidized with potassium permanganate under conditions which convert pyridoxine to pyridoxal (I), a product is obtained with coenzyme activity. The authors deduce from this that the aldehyde group is free in the phosphorylated pyridoxal. This was further substantiated by phosphorylating pyridoxal oxime (III) and treating the resultant product, which possessed only traces of coenzyme activity, with nitrous acid to liberate the aldehyde group. The resulting solution possessed definite coenzyme activity. This eliminates structure (IV).

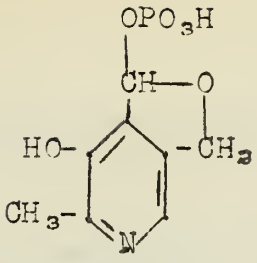




II

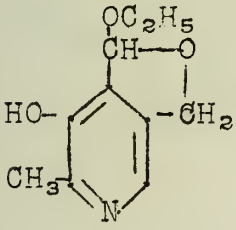


III



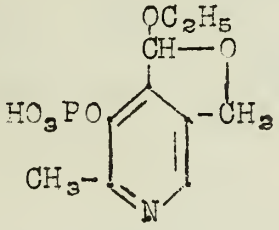
IV

2. The following evidence indicates that the phenolic hydroxy group of pyridoxal is free: (a) The cyclic ethyl acetal of pyridoxal (V) was converted into the oxime of the phosphate (VII) by phosphorylation, followed by the action of hydroxylamine. The oxime (VII) differs from the oxime of the phosphorylated pyridoxal. (b) If the phenolic hydroxyl were phosphorylated, the absorption maximum at 2900 Å which is present in acid solution should be maintained under alkaline conditions, as is the case with pyridoxin-3-methylether (VIII). This does not occur.



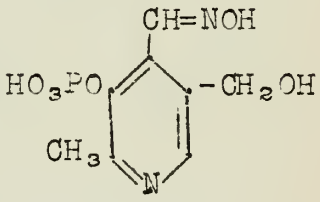
V

$POCl_2$ in pyridine → Then water

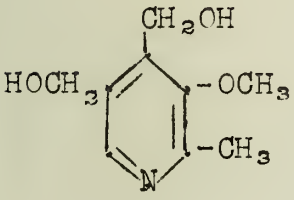


VI

NH_2OH → HCl

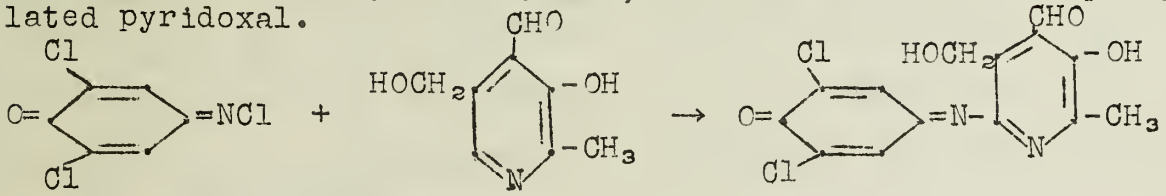


VII



VIII

3. Coupling of 2,4-dichloroquinone chlorimide (8) in the 6-position of pyridoxal readily takes place, but does not occur in phosphorylated pyridoxal.



Karrer and Viscontini (9) reported that the synthetic cyclic ethyl acetal of pyridoxal-3-phosphate (VI) possessed co-decarboxylase activity. These results could not be duplicated by Gunsalus and Umbreit (10), due possibly to the difference in the enzymes used in the subsequent testing.

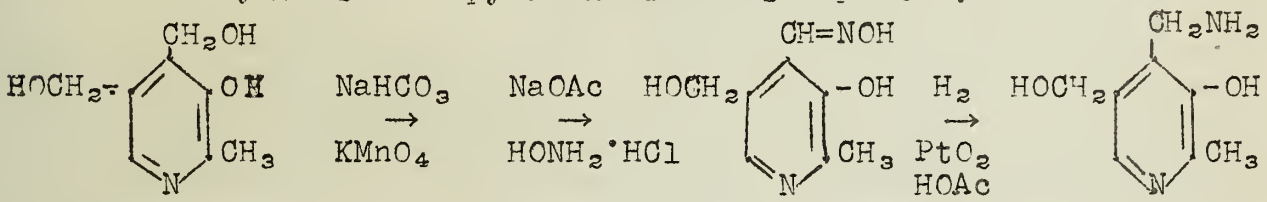
Karrer verified his postulated structure for acetal pyridoxal-3-phosphate (VI) by its failure to couple with 2,4-dichloroquinone

chlorimide. Since this is a positive test for p-unsubstituted phenols, he concludes the phenolic hydroxyl must have been modified by esterification to the phosphate.

Karrer (11) claimed that the loss of the absorption maximum at 2900 Å was to be expected, since compound VI existed in acid solution as a cation and in alkaline solution as an anion.

He showed that (VI) or the hydrolyzed product, pyridoxal-3-phosphate was at least as active a coenzyme of l-tyrosine-decarboxylase as a mixture of pyridoxal and adenosinetriphosphate. Attempts to phosphorylate the primary hydroxyl group of pyridoxal or of its various derivatives were unsuccessful.

A new synthesis of pyridoxamine was reported:



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Reported by S. E. Neuhausen
November 5, 1948

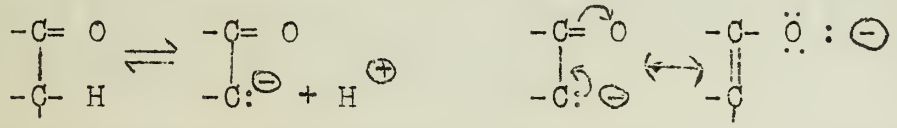
HYPERCONJUGATION

I INTRODUCTION: The concept of hyperconjugation (or no-bond resonance) was first proposed by Baker and Nathan (1) in 1935. Since that time a large body of physical and chemical evidence supporting the theory has accumulated, and it is further substantiated by quantum mechanical calculations. These facts have been reviewed recently (2, 3) and will not be presented here. This seminar will be limited to a qualitative discussion of carbon-hydrogen hyperconjugation and a presentation of the recently proposed carbon-carbon hyperconjugation.

II CARBON-HYDROGEN HYPERCONJUGATION:

A. General Expression of the Concept: Hyperconjugation occurs, to a greater or lesser extent, whenever a saturated carbon atom (holding one or more hydrogen atoms) is attached to an unsaturated carbon atom. In general it is the tendency of the electron pair of one of the C-H bonds of the saturated group to drift toward the unsaturated atom. In the extreme state the C-H bond is broken and there is an accompanying polarization of the double bond (see sections B and C below).

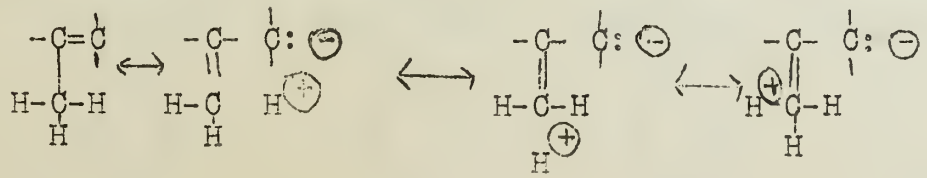
B. Analogy to Carbonyl-type Resonance: The acidic properties of carbonyl compounds having a hydrogen atom attached to the adjoining carbon atom can be attributed to resonance stabilization of the negative ion.



Hyperconjugation merely extends this idea to olefinic unsaturation. The position of the equilibrium (I) is again further to the right than might be expected, because of the resonance structures (II and III), which stabilize the negative ion.

I II III

It is of importance to note that the formation of the proton does not necessarily precede the electronic shift, and for this reason structures of the following type may occasionally contribute appreciably to the resting state of the molecule:



C. Order of Electron-releasing Tendencies of Alkyl Groups: Assuming that only the alpha hydrogen atoms can participate in hyperconjugation, the order of electron-releasing tendency of alkyl groups attached to an unsaturated system is:

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

The order for the inductive effect is the reverse of this.

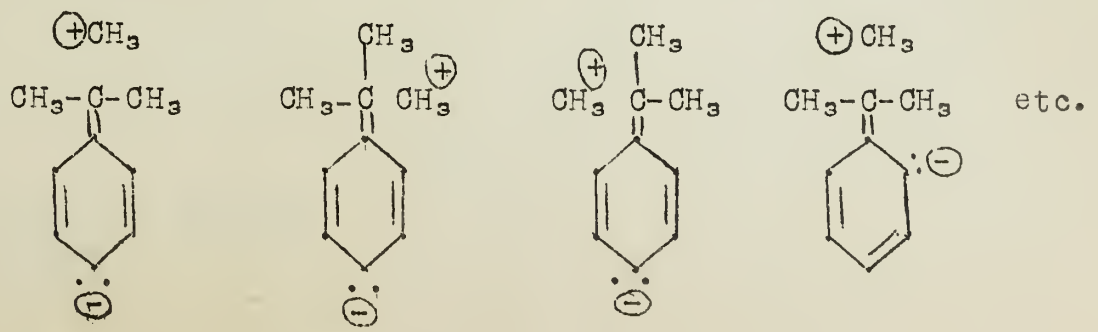
D. Examples of Carbon-Hydrogen Hyperconjugation:

1. Addition of HCl to a 2-pentene:
Since there are more C-H bonds in the methyl group than in the methylene group adjacent to the double bond in this molecule, hyperconjugation predicts the observed preferential formation of 2-chloropentane whereas the Markownikoff rule is not applicable because each unsaturated atom holds one hydrogen atom.

2. Bromination of Toluene:
Toluene is brominated about four times faster than t-butyl benzene. This is the expected result on the basis of the order of electron-releasing tendencies (section C).

III CARBON-CARBON HYPERCONJUGATION: Berliner and Bondhus have recently suggested (4, 5) that a carbon-carbon single bond of a saturated group attached to an aromatic nucleus can participate in hyperconjugation in much the same way as a carbon-hydrogen bond, although to a lesser degree.

A. The Necessity for Carbon-Carbon Hyperconjugation: When benzene and t-butyl benzene compete for an insufficient amount of bromine, the ratio of the rates of bromination is overwhelmingly in favor of the t-butyl benzene (115:1 at 45°C). The inductive effect can explain the direction of this result but probably not the extent, nor the strong ortho-para orienting influence in t-butyl benzene. Carbon-hydrogen hyperconjugation offers no assistance, because t-butyl benzene has no C-H bonds alpha to the unsaturated system. Since no satisfactory explanation based on a recognized theory has been advanced, Berliner believes that resonance structures of the following type must be utilized to account for the considerable electron-releasing character of the t-butyl group in t-butyl benzene:



Extension of C-C hyperconjugation to other alkyl groups gives an order of electron release identical with the order of the inductive effect: methyl < ethyl < i-propyl < t-butyl.

B. Justification of Carbon-Carbon Hyperconjugation:

1. Participation of C-C single bonds in hyperconjugation is allowed by quantum mechanics.
2. The origin and physical significance of the inductive effect is obscure. Therefore, it is advantageous to consider all electron release by alkyl groups as a resonance effect.
3. Physical constants indicate that increasing contributions to resonance are obtained as the number of carbon-carbon single bonds available for hyperconjugation is increased.
   a. Resonance energies of alkyl benzenes: methyl < i-propyl < t-butyl
   b. Dipole moments of alkyl benzenes: methyl < ethyl < i-propyl < t-butyl
   c. Molecular exaltations of alkyl benzenes: methyl < ethyl < i-propyl > t-butyl

IV CONCLUSION: The facts suggest that there are two opposing orders of electron release by alkyl groups attached to an unsaturated system. One of these orders can be explained by carbon-hydrogen hyperconjugation. Either the inductive effect or carbon-carbon hyperconjugation can be used to account for the opposing effect. Neither can be accepted without reservation, since the concept of carbon-carbon hyperconjugation has not been adequately tested, and the inductive effect is ill-defined with respect to its origin and physical nature.

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Reported by Aaron B. Herrick
November 12, 1948

THE SYNTHESIS OF dl-LYSINE

The l-form of lysine ($\alpha,\mathcal{E}$-diaminocaproic acid) is one of the essential amino acids.

Previous to this year four methods (1,2,3,4) for the synthesis of dl-lysine had been reported.

The first method was that of Fischer and Weigert (1).

$$NaCH(COOC_2H_5)_2 + ClCH_2CH_2CH_2CN \rightarrow CN(CH_2)_3CH(COOC_2H_5)_2$$

$$CN(CH_2)_3CH(COOC_2H_5)_2 + C_2H_5ONO \xrightarrow{Na} CN(CH_2)_3C(NOH)COOC_2H_5$$

$$CN(CH_2)_3C(NOH)COOC_2H_5 \xrightarrow{Na,\ C_2H_5OH} \xrightarrow{H^+} NH_2(CH_2)_4CHNH_2COOH$$

Sörensen's (2) synthesis was similar in principle, but involved the reduction and hydrolysis of $\mathcal{T}$-cyanopropylphthalimidomalonic ester in the final step.

The method of v. Braun (3) provided the first practical synthetic procedure.

$$\text{piperidine} + C_6H_5COCl \rightarrow \text{N-benzoylpiperidine} \xrightarrow{PCl_5} C_6H_5CONH(CH_2)_5Cl$$

$$\rightarrow C_6H_5CONH(CH_2)_5CN \xrightarrow{\text{aq. KOH}} C_6H_5CONH(CH_2)_5COOH \xrightarrow{P,\ Br_2}$$

$$C_6H_5CONH(CH_2)_4CHBrCOOH \xrightarrow{NH_4OH} \xrightarrow{H^+,\ H_2O} NH_2(CH_2)_4CHNH_2COOH$$

dl-Lysine has been synthesized from acrolein (4), but this method has not proved practical.

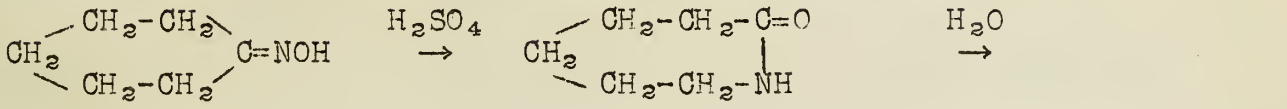
$$CH_2=CHCHO \xrightarrow[C_2H_5OH]{\text{dry HCl}} ClCH_2CH_2CH(OC_2H_5)_2 \rightarrow CN(CH_2)_2CH(OC_2H_5)_2$$

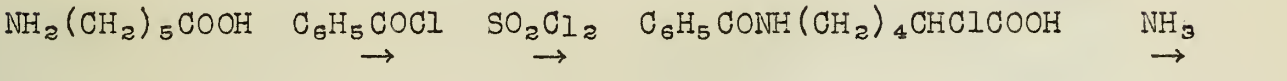
$$\xrightarrow[C_2H_5OH]{Na} NH_2(CH_2)_3CH(OC_2H_5)_2 \xrightarrow{C_6H_5COCl} \xrightarrow{H^+,H_2O} C_6H_5CONH(CH_2)_3CHO$$

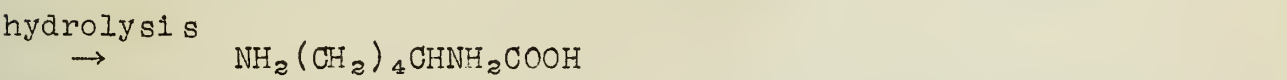
$$C_6H_5CONH(CH_2)_3CHO + CH_2(COOH)_2 \xrightarrow[C_5H_{11}N]{C_5H_6N\ \text{sol'n}} C_6H_5CONH(CH_2)_3CH=CHCOOH$$

$$\xrightarrow{H_2,\ \text{cat.}} C_6H_5CONH(CH_2)_3CH_2CH_2COOH \rightarrow \text{continue according to v. Braun's method}$$

The current laboratory synthesis is that of v.Braun (3) as improved by Eck and Marvel (5) and later by Galat (6).

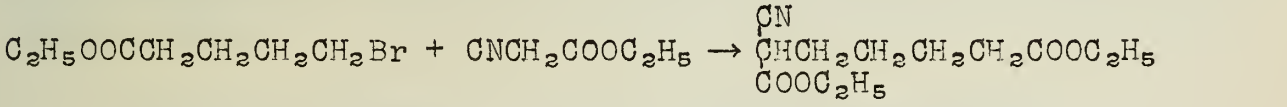


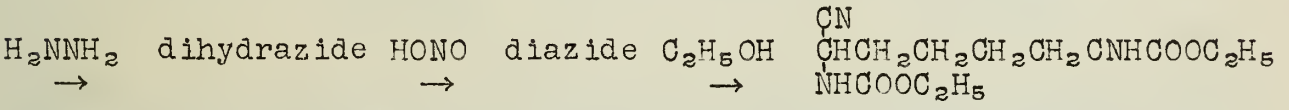


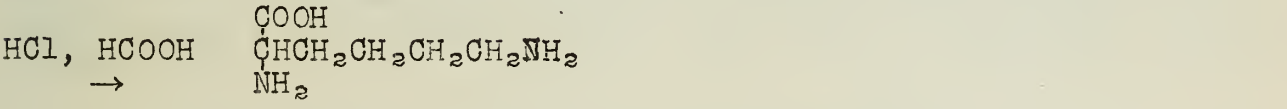


This year three new methods have appeared. One of these permits the introduction of C^{14} which is desirable for metabolic studies.

One method involves the Curtius degradation of diethyl-α-cyanopimelate (7).

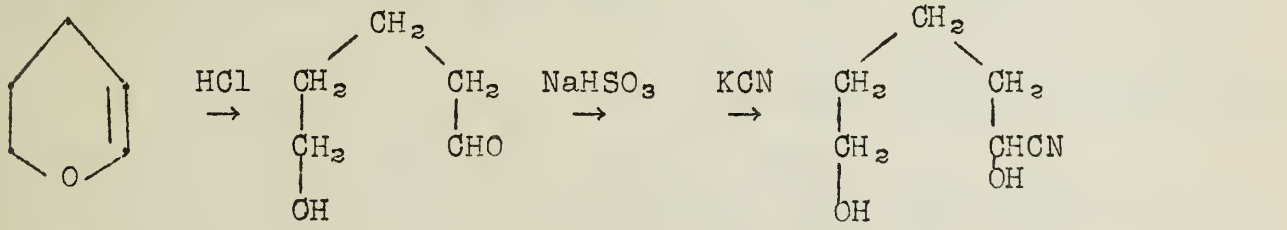


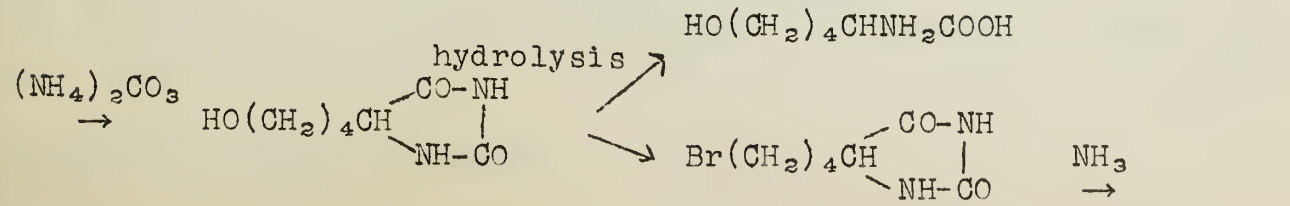


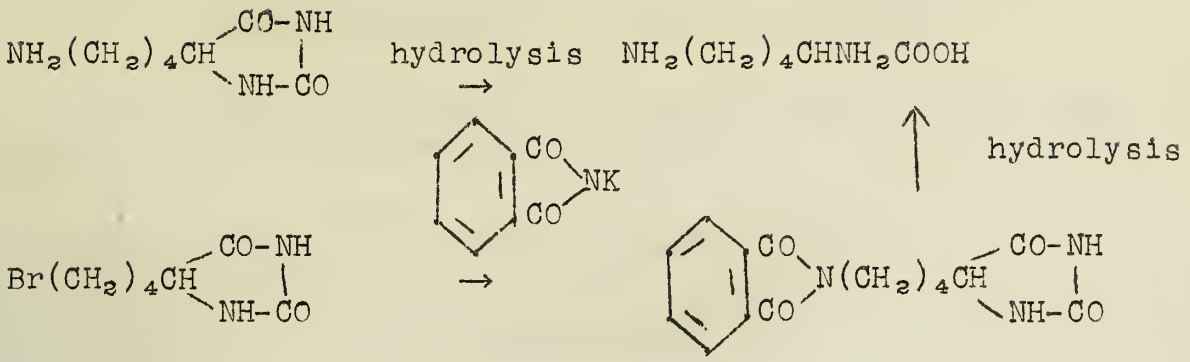


This method does not seem to be of any great preparative significance since the yield is low (10%) and no other advantages are apparent.

The cleavage of dihydropyran to 5-hydroxypentanal (8) provides the basis for an excellent preparative method (9).







This method affords a 40% yield as compared to 23% obtained by the modified method of v. Braun. Both methods use readily available materials and employ reactions which proceed with a minimum of difficulty.

For the introduction of C^{14} into the lysine molecule, δ-chloro-α-acetamidovaleric acid was considered a useful intermediate (10) since it could be resolved before the introduction of the radioactive carbon.

$$ClCH_2CH_2CH_2CHCOOH \xrightarrow{KC^{14}N} C^{14}NCH_2CH_2CH_2CHCOOH$$
$$\qquad\qquad NHCOCH_3 \qquad\qquad\qquad\qquad\qquad\qquad NHCOCH_3$$

However, all attempts to prepare this intermediate failed. The introduction of C^{14} was achieved by a modified Fischer-Weigert synthesis using γ-chlorobutyronitrile containing a radioactive nitrile carbon atom.

$$Cl(CH_2)_3Br + KC^{14}N \rightarrow Cl(CH_2)_3C^{14}N$$

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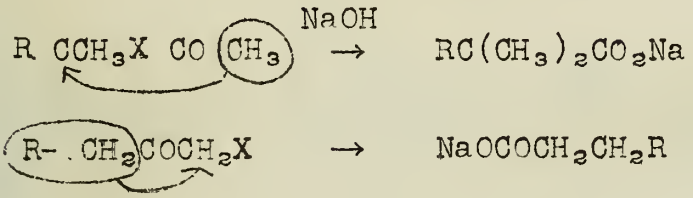
Reported by Robert E. Carnahan
November 12, 1948

THE REARRANGEMENT OF ALPHA HALOKETONES

When alpha haloketones are treated with a strong base, a carbon chain rearrangement often occurs.



Treatment of the same haloketone with alkoxides produces the methyl or ethyl esters (Route A) and occasionally hydroxy acetals corresponding to the original ketone (Route B).

The following examples have been observed; (1) $C_6H_5CHClCOCH_3$ when treated with KOH or $NaOCH_3$ in ether gives potassium or methyl hydrocinnamate;

(2) $C_6H_5CHClCOCH_3 \xrightarrow[CH_3OH]{NaOCH_3} C_6H_5CH_2CH_2COOCH_3 + C_6H_5CHOH\text{-}C(OCH_3)_2CH_3$;

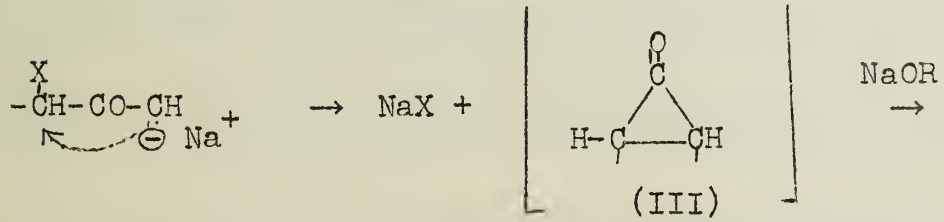
(3) $C_6H_5CH_2COCH_2Cl \xrightarrow[CH_3OH]{NaOCH_3} C_6H_5CH_2CH_2COOCH_3$

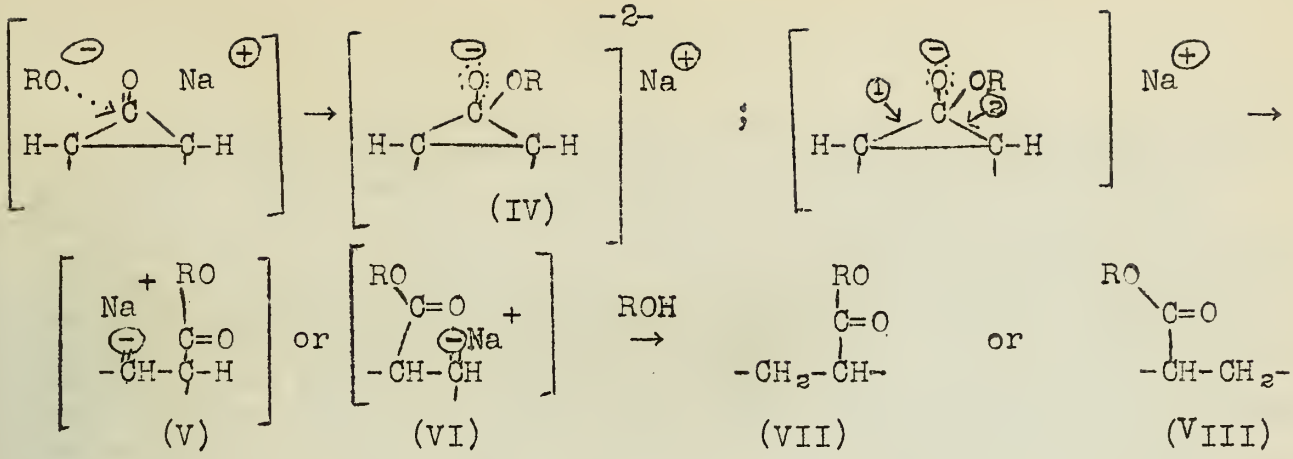
(4) $CH_3\text{-}CBrCH_3COCH_3 \xrightarrow[C_2H_5OH]{NaOC_2H_5} CH_3COHCH_3C(OC_2H_5)_2CH_3 + (CH_3)_3CCO_2C_2H_5$

A number of mechanisms (3)(4)(5)(6) have been advanced for this transformation but none of them is completely general. One mechanism of interest is the following:

Route A $-CHX\text{-}CO\text{-}CH_2- \xrightarrow{NaOR} HOR + -\overset{X}{C}H\text{-}CO\text{-}\overset{\ominus}{C}H\text{-}\ Na^+$

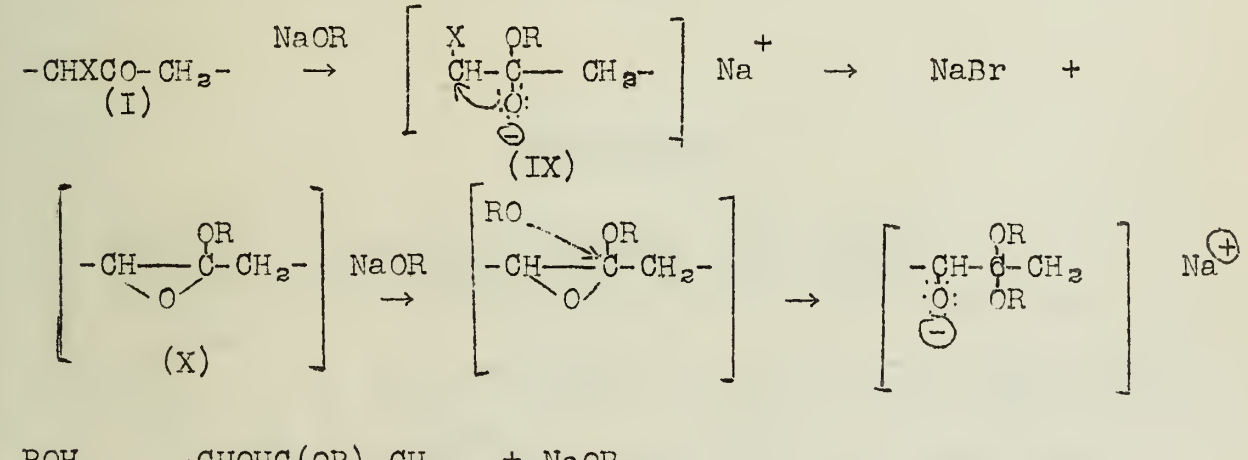
(I) (II)





The carbonion ion (II) undergoes immediate intramolecular alkylation forming the highly strained cyclopropanone derivative (III). Addition of the sodium alkoxide to the carbonyl group follows to give the alkoxide adduct (IV). This adduct cleaves at (1) or (2), as indicated, to give the intermediates (V) or (VI) which then abstract a proton from the alcohol which was formed (I-II) to produce the ester.

Route B. Formation of the hydroxyacetals:



The following statements offer evidence for Routes A and B.

Route A. (1) This mechanism satisfactorily explains the fact that $C_6H_5CHClCOCH_3$ and its isomer $C_6H_5CH_2COCH_2Cl$ give the same ester.

Route B. (1) The rearward attack by the alkoxide ion on the ethylene oxide intermediate (X) is reterded by using a larger or secondary alkoxide ion.

The location of the halogen atom or either side of the α or α' carbon atom of the ketone is inmaterial. However, the ketone must be able to form a three membered ring, which requires at least one hydrogen on one of the carbon atoms. α-Chloroisobutrophenone is inactive and does not rearrange.

The above mechanism does have some difficulties; (1) It fails to explain why α-haloacetone does not undergo rearrangement but gives the normal metathesis product when treated with sodium methoxide and methanol. Experimental evidence indicates that a branched chain is necessary in order for α-halo alphatic ketones to undergo the above rearrangement; (2) The point of cleavage of the proposed cyclopropanone intermediate does not follow a definite pattern. For example, isopropyl propyl ketone and isobutyl propyl ketone cleave between the tertiary carbon atom and the carbonyl group in the cyclic derivative from the former compound and between the secondary carbon atom and the carbonyl group in the cyclic derivative from the latter compound. The corresponding esters of isopropyl butyrate and dimethylbutyl acetate are produced in excellent yields; (3) Routes A and B do not explain the evidence that the ester rearrangement is favored when solid alkoxide and ether are used, nor do they explain the fact that the hydroxy acetal predominates when alkoxide and alcohol are used as the reagents.

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Reported by H. A. DeWalt, Jr.
November 12, 1948

FORMATION OF CARBON-SILICON BONDS

It is the purpose of this seminar to discuss the preparation of simple organosilicon compounds by methods which involve the formation of carbon-silicon bonds.

Use of Organozinc Compounds. The earliest method of forming carbon-silicon bonds involved the use of zinc alkyls as indicated by the equation:

$$2ZnR_2 + SiCl_4 \xrightarrow[\text{sealed tube}]{150\text{-}200^\circ} SiR_4 + 2ZnCl_2 \qquad (1)$$

where R is either alkyl or aryl. Since such a substitution proceeds in a stepwise manner, a mixture of substitution products containing from one to four groups is obtained. However by controlling the molar quantities of reagents, it is possible to make one of the products predominate. Obvious disadvantages of the method are the sealed tube conditions, the preparation and handling of the highly flammable and toxic zinc alkyls and the separation of products.

Use of Organosodium Compounds. It will be noted that this method is essentially that of the Wurtz reaction.

$$SiCl_4 + 4RCl + 8Na \rightarrow SiR_4 + 8NaCl \qquad (2)$$

The method finds its greatest use in the preparation of tetraalkyl- and tetraaryl-silanes.

Use of Grignard Reagents. This represents the most universal method of preparing simple organosilicon compounds.

$$3RMgX + SiCl_4 \rightarrow R_3SiCl \qquad (3)$$

$$3RMgX + SiHCl_3 \rightarrow R_3SiH \qquad (4)$$

It is difficult to prepare tetraalkyl- or tetraaryl-silanes by this method. If an excess of the Grignard reagent is used, the trialkyl or triaryl product usually predominates. Tetraphenylsilane may be prepared by this method only if the reaction mixture is heated to 160-180° for 3-4 hours. However if R is a group such as isopropyl, only two groups may be substituted.

Recently Grignard reagents containing silicon have been employed as indicated by the following equations:

$$(CH_3)_3SiCH_2MgCl + (CH_3)_3SiCl \rightarrow [(CH_3)_3Si]_2CH_2 \qquad (5)$$

$$(CH_3)_3SiCH_2MgCl + (CH_3)_2SiCl_2 \rightarrow [(CH_3)_3SiCH_2]_2Si(CH_3)_2 \qquad (6)$$

If silicon tetrafluoride is used, the main product is R_3SiF along with smaller amounts of R_4Si. No mono- or di-substituted products are formed.

Use of Organolithium Compounds. It has been found advantageous to use organolithium coumpounds when the corresponding Grignard reagents give low yields or fail.

$$SiCl_4 + 4RLi \rightarrow SiR_4 + 4LiCl \qquad (7)$$

In the case of the simple alkyl- or aryl-lithium compounds, the above reaction goes quite readily. However introduction of the fourth R group is slow and sometimes impossible with some sterically hindered lithium compounds. It should also be noted that trialkyl- and triaryl-silanes react with organolithium compounds.

$$R_3SiH + RLi \rightarrow R_4Si + LiH \qquad (8)$$

The following table indicates the products obtained with various lithium derivatives:

Starting Material	R	Product	% Yield
$SiCl_4$	Et	R_4Si	92
$SiCl_4$	i-Pr	R_3SiCl	68
$SiHCl_3$	i-Pr	R_3SiH	64
i-Pr_3SiH	i-Pr	No reaction	--
i-Pr_3SiH	C_6H_5	i-$Pr_3SiC_6H_5$	36
i-Pr_3SiH	o-tolyl	No reaction	--
$SiCl_4$	n-Bu	R_4Si	98
$SiCl_4$	t-Bu	R_2SiCl_2	44
$SiCl_4$	C_6H_5	R_4Si	99

Addition of $SiCl_4$ and $SiHCl_3$ to Unsaturated Compounds. Silicon tetrachloride can be made to add to ethylene or other olefinic hydrocarbons under conditions of high temperature and high pressures in the presence of $AlCl_3$.

$$CH_2=CH_2 + SiCl_4 \rightarrow ClCH_2CH_2SiCl_3 \qquad (9)$$

$$HC\equiv CH + SiCl_4 \rightarrow ClCH=CHSiCl_3 \qquad (10)$$

The addition of trichlorosilane to olefins in the presence of peroxides is quite general.

$$RCH=CH_2 + SiHCl_3 \xrightarrow{\text{peroxide}} RCH_2CH_2SiCl_3 \qquad (11)$$

Silicon tetrachloride will not add in an analogous manner.

Direct Method. The direct union of alkyl or aryl halides with metallic silicon in the presence of finely divided copper is a good method for preparing dialkyl- and diaryl-dichlorosilanes. Both this method and the Grignard method are being used commercially.

$$RCl + Si \xrightarrow[150\text{-}300^\circ]{Cu} R_2SiCl_2 \qquad (12)$$

If R is phenyl, finely divided silver has been found to be more effective.

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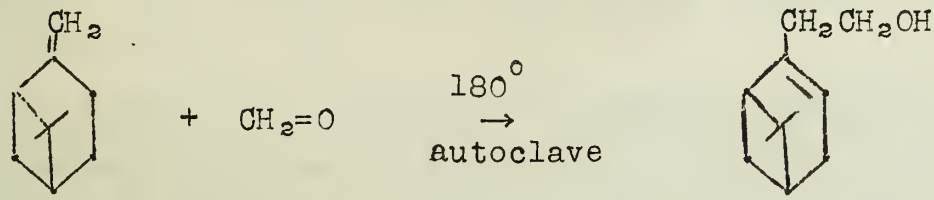
Reported by H. W. Hill, Jr.
November 19, 1948.

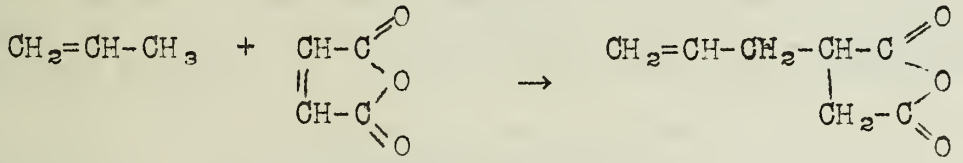
THE REACTION OF MONOÖLEFINS WITH MALEIC ANHYDRIDE, SULFUR TRIOXIDE, FORMALDEHYDE AND AZODICARBOXYLIC ESTER

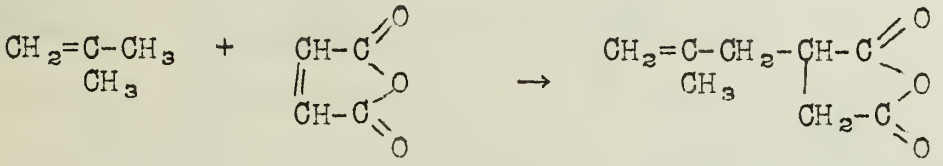
Monoölefins have been shown to react with maleicanhydride, sulfur trioxide, formaldehyde, and azodicarboxylic ester to form 1-1 adducts in which the original olefinic bond has migrated to an adjacent position. B-Pinene (I), for example, reacts with formaldehyde at 180° to give "nopol" (II) in almost quantitative yields.(1



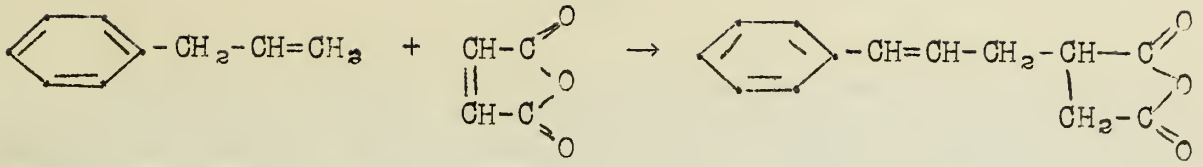
I II

As a result of various patent claims describing the addition of hydrocarbons with isolated double bonds to maleic anhydride, Alder (2) undertook a systematic study of the behavior of simple olefins toward this reagent. At elevated temperatures, 200° and under pressure, ethylene gave no simple addition product with maleic anhydride. However, propene, 2-butene, isobutylene, n-hexylene, n-heptylene, cyclopentene and cyclohexene reacted to give 1-1 adducts. In general, the yields increased with increasing molecular weight of the olefin. A few representative reactions are shown. Propene reacts to give allyl succinic anhydride and isobutylene gives 2-methylallyl succinic anhydride.





Alder regarded this reaction as a typical substitution in the allyl position, the allyl H atom migrating to saturate the maleic residue. He termed it a "substitution addition" reaction. However allyl-benzene reacted with maleic anhydride to give 3-phenylallyl succinic anhydride.



Such a product is not in accord with the postulated substitution at the allyl position.

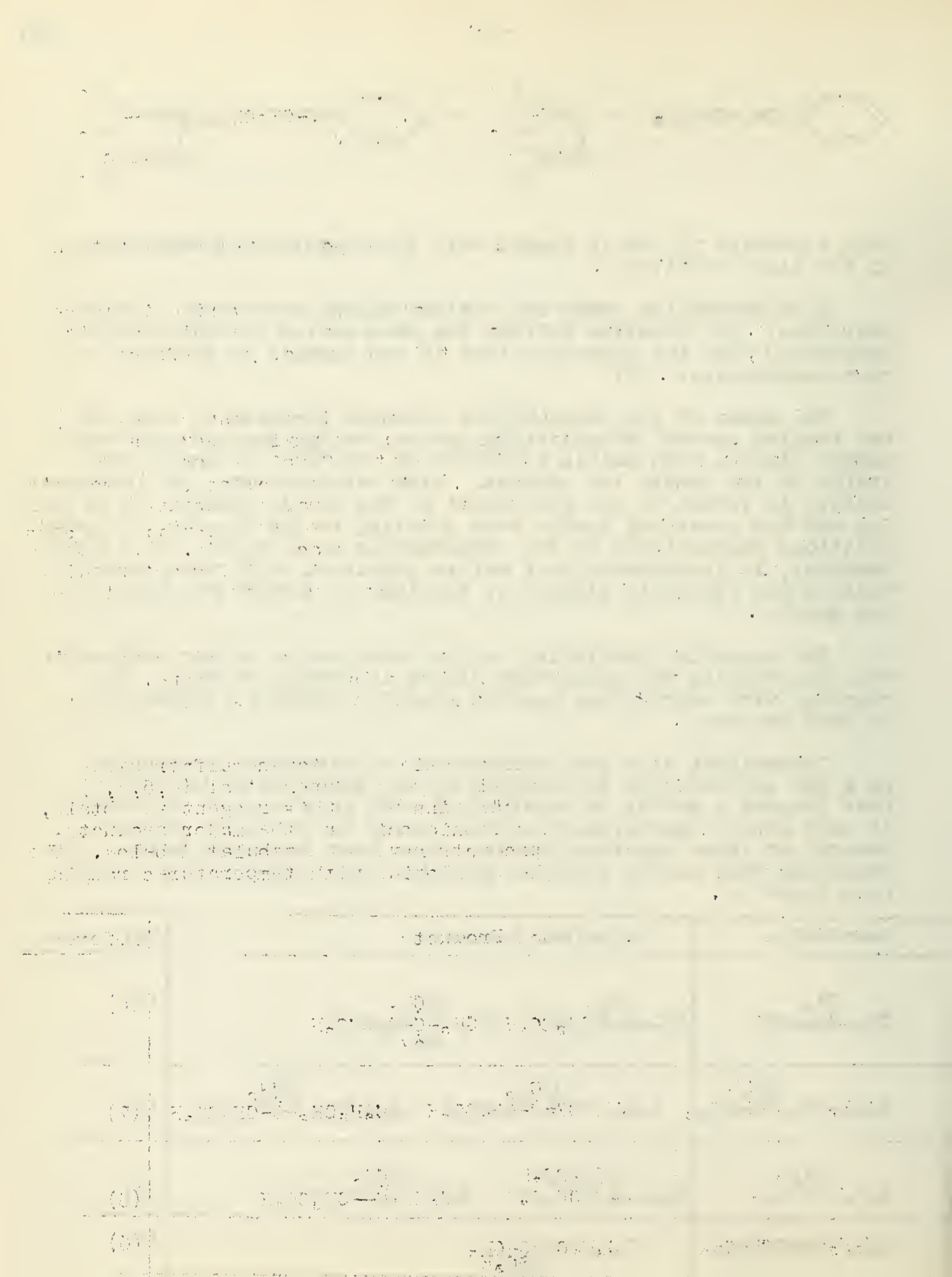
Azodicarboxylic ester can replace maleic anhydride in these reactions. The reaction follows the same course as with maleic anhydride, with the advantage that it can usually be effected at room temperature. (2)

The scope of the reaction was extended somewhat by Ross (3) who treated several monoölefinic esters, methyl undecylenate and methyl oleate, with maleic anhydride at 200-250° to obtain good yields of the simple 1-1 adducts. With methyl oleate, an isomeric mixture is formed by the attachment of the maleic residue to C_9 or C_{10} and the remaining double bond shifting to the C_{10}-C_{11} or C_9-C_8 positions respectively of the octadecanoic acid chain. From these examples, it is apparent that maleic anhydride will react readily whether the ethylenic linkage is terminal or toward the center of the chain.

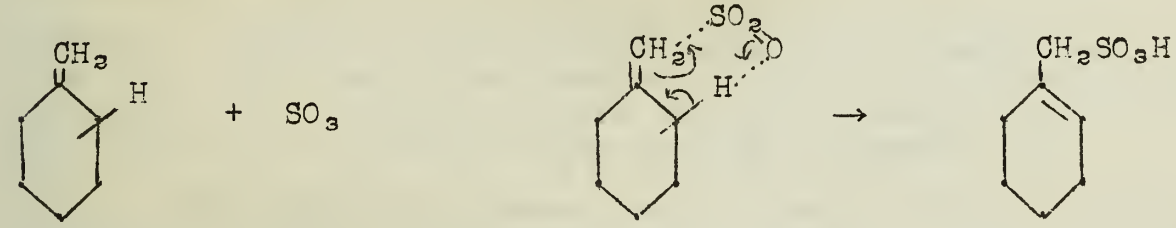
The essential similarity in the reactions of maleic anhydride with monoölefins and conjugated dienes is worthy of note. The reaction with monoölefins however usually requires a temperature of 200° or more.

Concomitant with the introduction of dioxanesulfotrioxide as a new sulfating or sulfonating agent, Suter et al (4,5,6,7) have treated a series of monoölefins with this reagent to obtain, in many cases, unsaturated sulfonic acids as the major products. Several of these reaction products have been tabulated below. The reactions were run in ethylene chloride with temperatures ranging from 0-20° C.

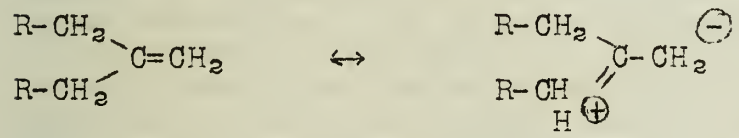
Monoölefin	Principal Products	Reference
$CH_3-\overset{CH_3}{\underset{}{C}}=CH_2$	$CH_2=\overset{CH_3}{\underset{}{C}}-CH_2SO_3H$ $CH_3-\overset{CH_3}{\underset{OH}{C}}-CH_2SO_3H$	(5)
$C_6H_5-CH_2-\overset{CH_3}{\underset{}{C}}=CH_2$	$C_6H_5-CH=\overset{CH_3}{\underset{}{C}}-CH_2SO_3H$ $C_6H_5CH_2-\overset{CH_2}{\underset{}{C}}-CH_2SO_3H$	(7)
$C_6H_5-\overset{CH_3}{\underset{}{C}}=CH_2$	$C_6H_5-\overset{CH_2SO_3H}{\underset{}{C}}=CHSO_3H$ $C_6H_5-\overset{CH_2}{\underset{}{C}}-CH_2SO_3H$	(6)
$C_6H_5-CH=CH-CH_3$	$C_6H_5CH=\underset{SO_3H}{\underset{\vert}{C}}-CH_3$	(6)
$C_6H_5-CH_2-CH=CH_2$	$C_6H_5CH=CH-CH_2SO_3H$ $C_6H_5CH_2-\underset{OH}{\underset{\vert}{CH}}-CH_2SO_3H$	(6)



Arnold and Dowdall (8) have characterized the products obtained by the reaction of methylenecylohexane and the reagents paraformaldehyde, maleic anhydride, and sulfur trioxide. In each case, the reaction is accompanied by a shift of the exocyclic double bond into the six membered ring. These men regard the formation of these adducts as occurring via transient cyclic complex, which is formed by a simultaneous attack of the reagent at the terminal carbon atom of the olefin and an α-methylenic group, necessarily followed by a shift of the double bond.



The unusual reactivity shown by the isobutylene type olefins might be attributed partly to hyperconjugation.



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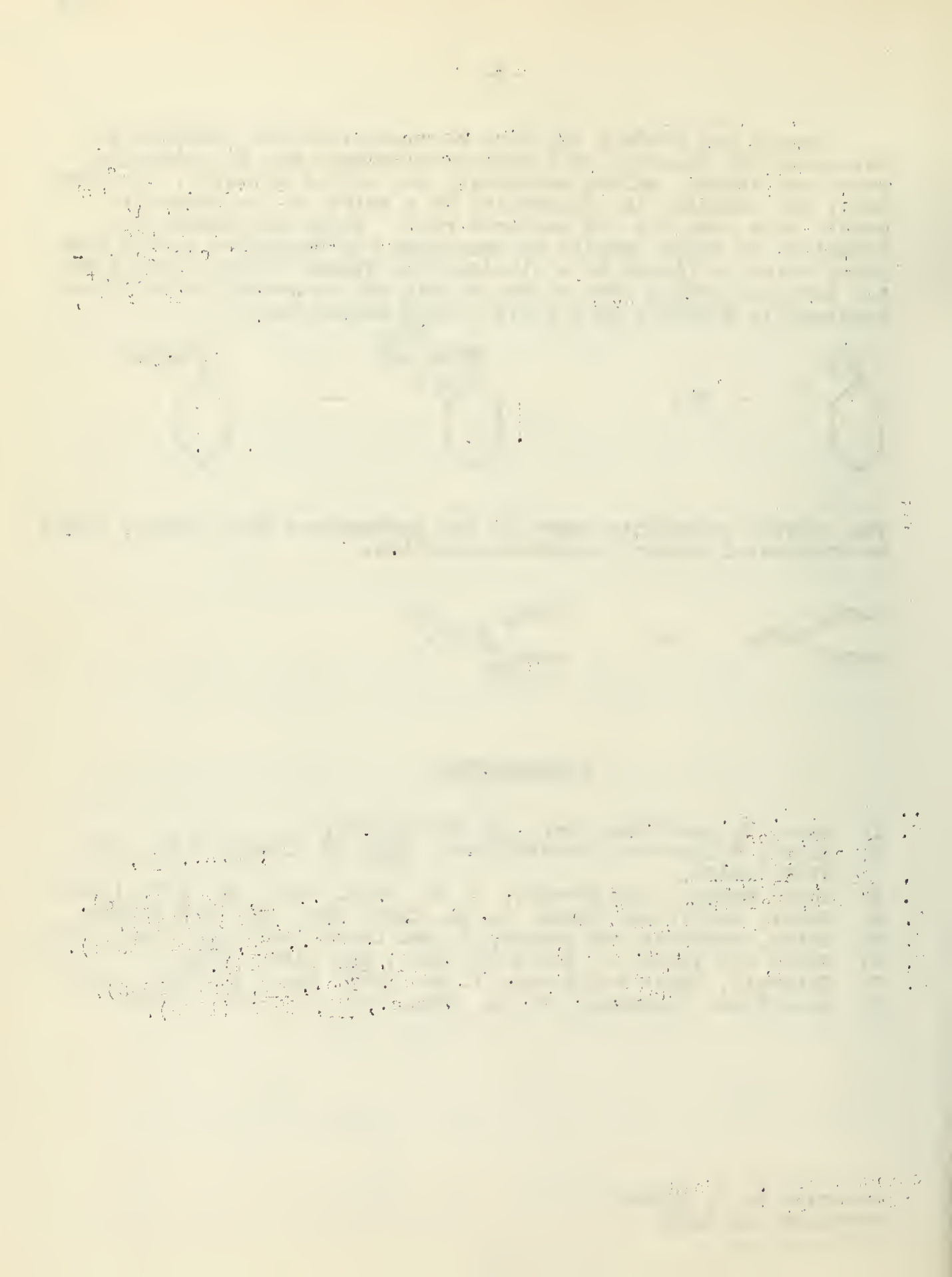
Reported by H. DeWald
November 19, 1948



NEW ORGANIC INSECTICIDES

The success achieved in combating insect pests with DDT and its analogs has stimulated a search for other organic compounds with practical insecticidal properties. This report is concerned mainly with the few of many insecticides tested which have shown sufficient promise to be of economic importance.

I. CHLORINATED HYDROCARBONS

A. BENZENE HEXACHLORIDE (1,2,3,4,5,6-hexachlorocyclohexane). Although benzene hexachloride has been known for a long time (1), its insecticidal properties were not discovered until 1941-1942 (2). It was developed in England during World War II and found to be toxic to a wide variety of insects (1).

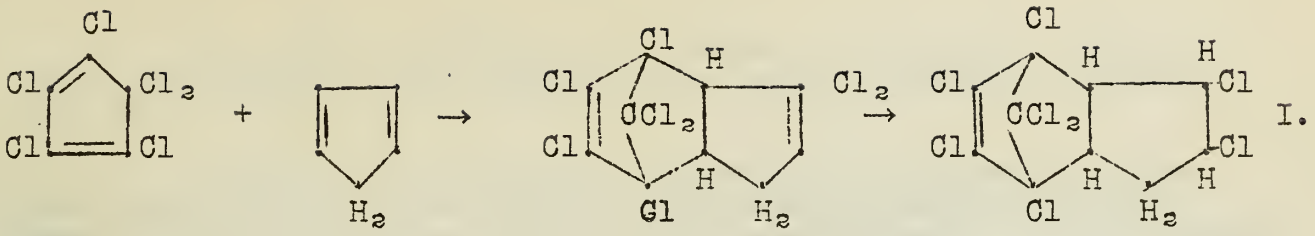
The principle process used in making benzene hexachloride consists of adding gaseous chlorine to benzene in the presence of light (3). Technical benzene hexachloride contains five stereoisomers (1,5) (α, β, γ, δ and ϵ) but only the gamma isomer has appreciable insecticidal activity. Normally only 10-12% active isomer is obtained and so processes for concentrating the gamma isomer by extraction of the technical product with cyclohexane, trichloroethylene, chloroform, toluene, xylene, etc. are used (2,4). It has recently been reported (6) that the chlorination of benzene in methylene chloride solution under the influence of a peroxide catalyst produces 18% gamma isomer. The configuration of only the beta isomer has been established with certainty (1,7,8).

A serious deterrent to the more widespread use of benzene hexachloride is the objectionable musty odor of the technical material. This odor is due to an impurity which can be only partially removed by a variety of treatments (2, 2a, 9, 10, 11).

The problem of finding analytical methods for gamma benzene hexachloride was difficult due to the chemical similarity of the stereoisomers. Differences in the rates of dehydrochlorination of the isomers is the basis of one method (8, 12). Other useful methods for analysis are based on infrared absorption spectra (13), cryoscopic measurements (14), partition chromatography (15, 16) and polarographic methods (17).

B. CHLORDANE. Chlordane is a chlorinated hydrocarbon, $C_{10}H_6Cl_8$, which was found to be toxic to a variety of insects by Kearns (18) in 1945. Its action is similar to DDT and benzene hexachloride and it shows much promise in controlling some insect species (19).

The active constituent of chlordane is 1,2,4,5,6,7,8-octachloro-4,7-methano-3a,4,7,7a-tetrahydroindane(I) which is made (2b) by adding chlorine to one of the double bonds of the Diels-Alder adduct formed from perchlorocyclopentadiene and cyclopentadiene.



I.

C. CHLORINATED TERPENES. Chlorination of camphene (2) to a chlorine content of 67-9% produces a material with the empirical formula $C_{10}H_{10}Cl_8$ which has been found toxic to a considerable number of household and agricultural insect pests.

It has been shown (20) that cis-1,8-dichloroparamenthane and, to a lesser extent, bornyl chloride exhibit insecticidal activity. These compounds are made by treating α-or β-pinene with hydrogen chloride.

II. ORGANIC PHOSPHOROUS COMPOUNDS

A. TETRAETHYL PYROPHOSPHATE. The Germans developed a substitute for nicotine in aphid control during the last war which they termed Bladan (21, 22, 23). The active principle was thought to be hexaethyl tetraphosphate, a product obtained by the reaction of triethyl orthophosphate with phosphorous oxychloride (24, 25) or phosphorous pentoxide (26) at 150°. It has been shown (27, 28) however that the insecticidal principle is tetraethyl pyrophosphate (II) which is produced in these reactions to the extent of about 15-8% along with ethyl metaphosphate. Approximately 40% tetraethyl pyrophosphate is produced by increasing the proportion of triethyl orthophosphate (2). Toy (29) has described the preparation of pure tetraethyl pyrophosphate in good yield by the controlled hydrolysis of diethyl chlorophosphate in pyridine.

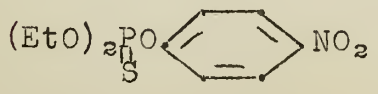
$$2(EtO)_2POCl + H_2O + 2C_5H_5N \rightarrow (EtO)_2PO_2PO(OEt)_2 \qquad \text{II.}$$

Tetraethyl pyrophosphate is a highly toxic compound to both insects and warm-blooded animals, but hydrolyzes rapidly to non-toxic products (27).

B. PARATHION. Another insecticide developed in Germany during the war is O,O-diethyl-O-p-nitrophenyl thiophosphate (III) which was designated E-605 by the Germans (30, 31, 32, 33) and was given the name Parathion in this country.

Parathion is synthesized by the following sequence (33).

$$PCl_3 + S \xrightarrow[2\text{ hr}]{130^\circ} PSCl_3 \xrightarrow[EtOH]{NaOEt} (EtO)_2PSCl \xrightarrow[C_6H_5Cl,\ 130^\circ]{p\text{-}NO_2C_6H_4ONa}$$



III.

C. OTHER PHOSPHATES. A number of compounds closely related to parathion were prepared and tested by German chemists (31, 33).

A series of 46 organic phosphates and phosphites have been tested by Ludvik and Decker (34) against various aphids. These workers found that some of the pyrophosphates, triphosphates and tetrapyrophosphates tested were superior to nicotine as aphicides.

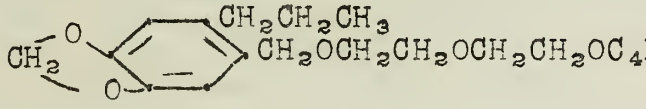
III. MISCELLANEOUS

A. BIS(p-CHLOROPHENOXY)METHANE. This compound has been shown to be a highly effective miticide (35). It is prepared by treating p-chlorophenol with an equimolar quantity of sodium in a solvent such as absolute ethanol and subsequently treating the phenolate dispersion with methylene chloride (36).

B. 1,1-BIS(p-CHLOROPHENYL)ETHANOL. Also termed di(p-chlorophenyl)methyl carbinol (DMC), 1,1-bis(p-chlorophenyl)ethanol is another very effective miticide. This compound is made from 4,4'-dichlorobenzophenone and methyl magnesium bromide (2d).

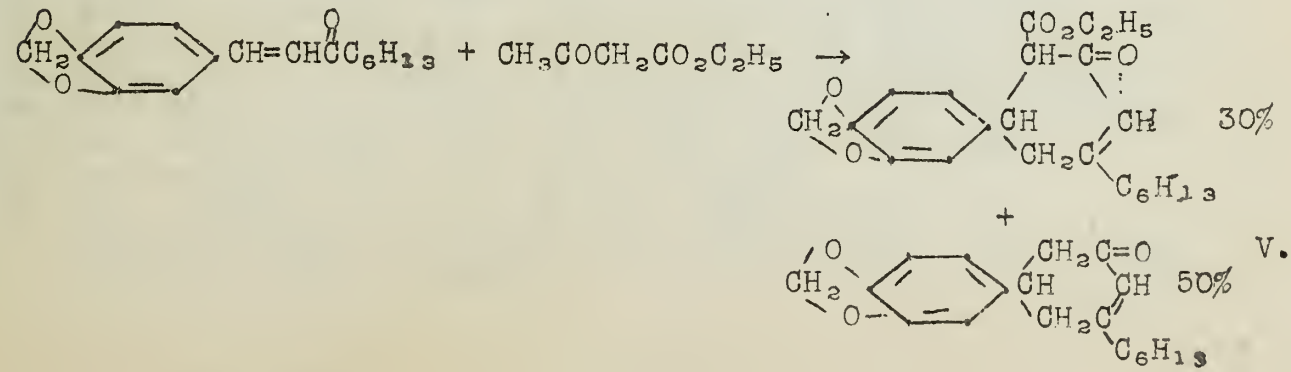
C. PYRETHRIN SYNERGISTS. The pyrethrins, which are the active alkaloids of pyrethrum, possess a more rapid paralytic effect on insects than any synthetic organic insecticide known. Pyrethrum is less toxic to warm-blooded animals than the synthetic insecticides, but relatively expensive. It has been found that compounds with a methylene dioxyphenyl grouping increase the toxicity of the pyrethrins (2, 37, 38). Several of the more important of these activators or synergists are listed below.

1. PIPERONYL BUTOXIDE (39, 41) contains 80% of α-[2-(2-butoxyethoxy)ethoxy]-4,5-methylenedioxy-2-propyltoluene (IV).



IV.

2. PIPERONYL CYCLONENE (39, 40) (V) is obtained by condensing ethyl acetoacetate with cyclohexyl-3,4-methylenedioxystyrylketone.



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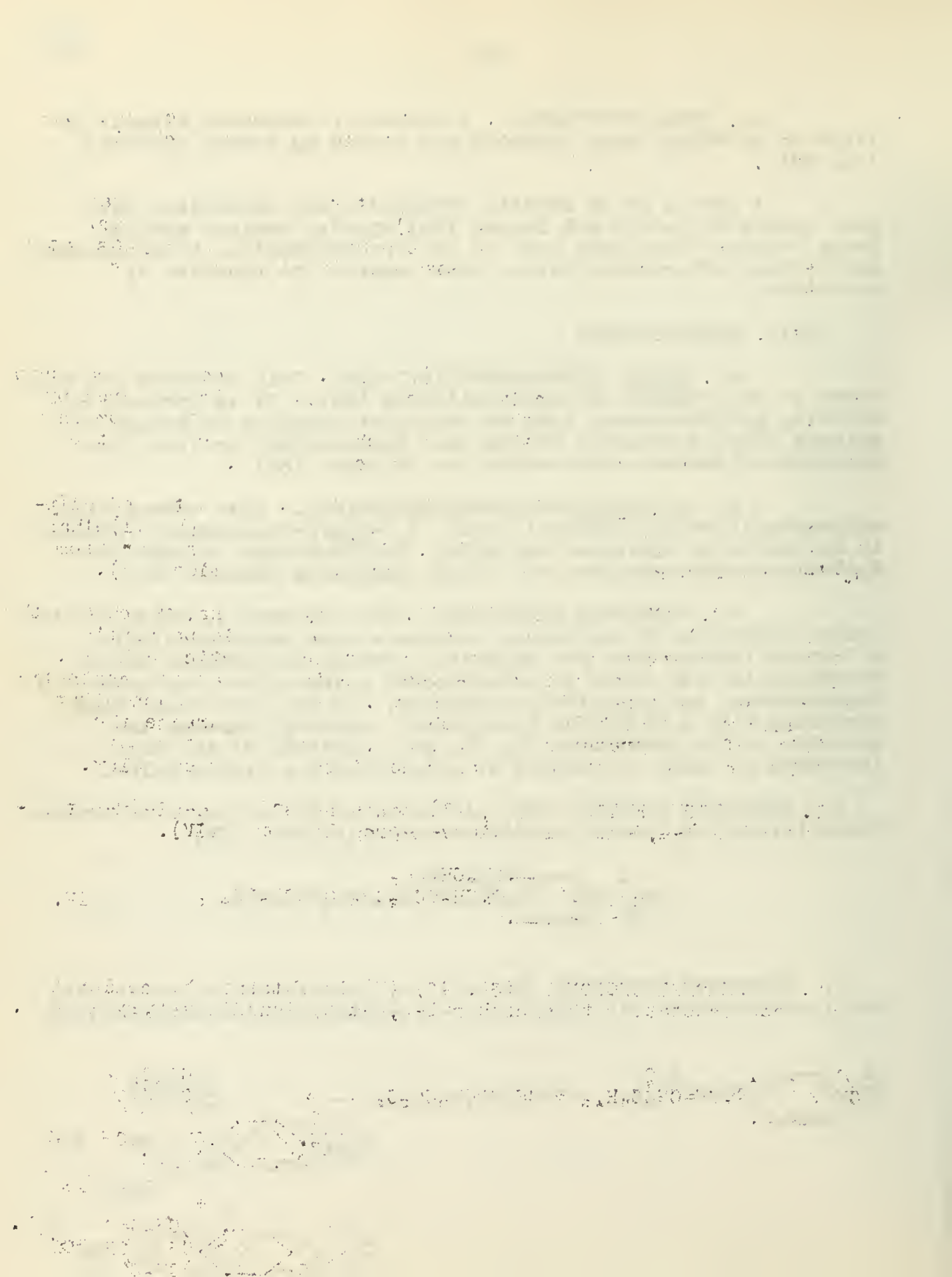
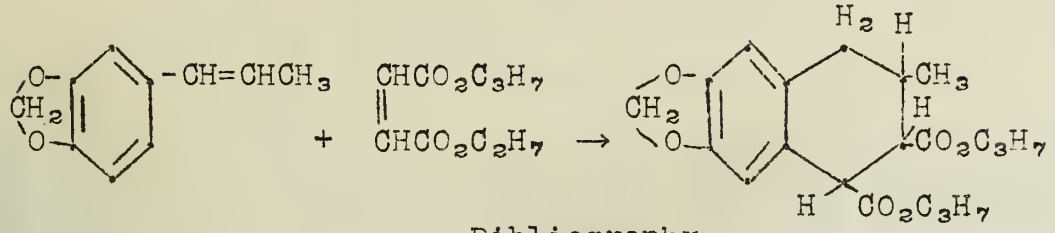


3. PROPYL ISOME(2c, 42) (VI) is prepared by a Diels-Alder reaction between n-propyl maleate and isosafrole.



VI.

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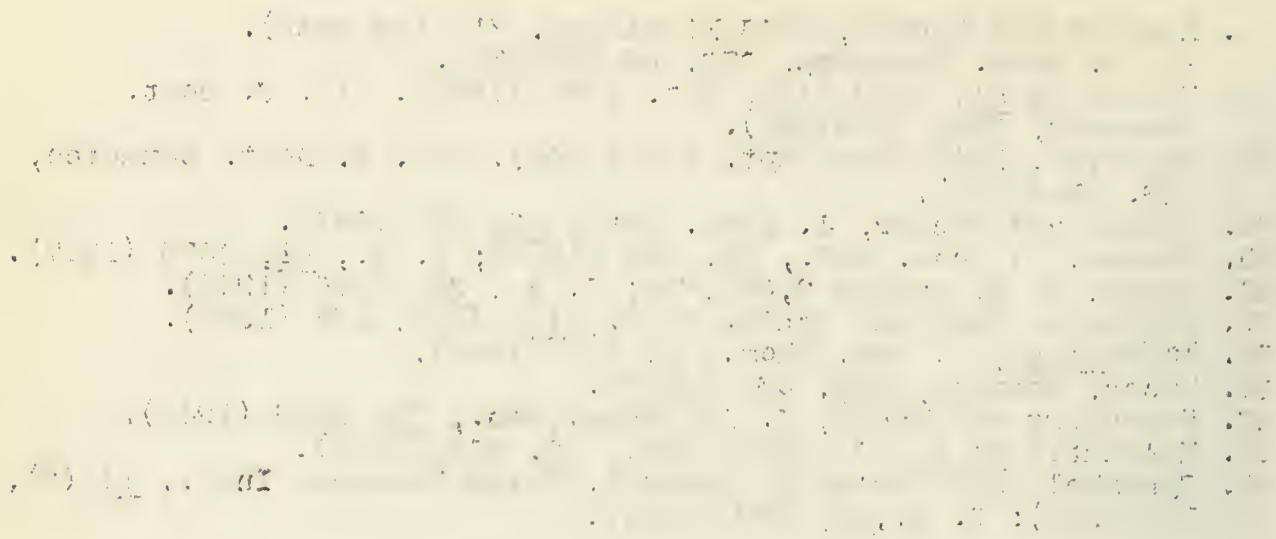
Reported by George I. Poos
November 19, 1948

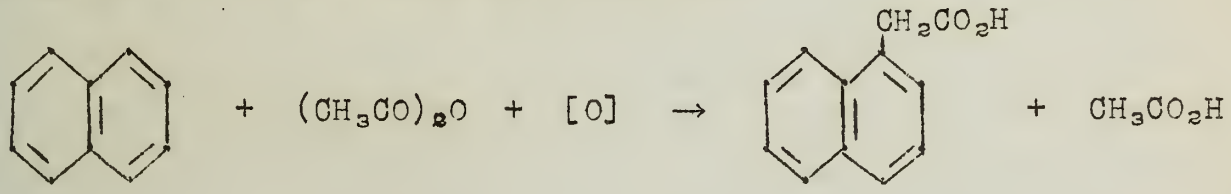


A NEW SYNTHESIS OF ARYLACETIC ACIDS

This paper describes the use of potassium permanganate in free radical reactions producing arylacetic acids.

Griehl (1) has prepared α-naphthylacetic acid by adding powdered potassium permanganate slowly to an excess of naphthalene in boiling acetic anhydride. Eighty percent of the naphthalene was recovered, and the yield of α-naphthylacetic acid was 66% of the naphthalene consumed. No by-products were isolated. Hydrogen peroxide and diacetyl peroxide were used also, but the yields seemed better with permanganate.

Griehl termed the reaction an oxidative dehydrogenation and represented it by the following equation:



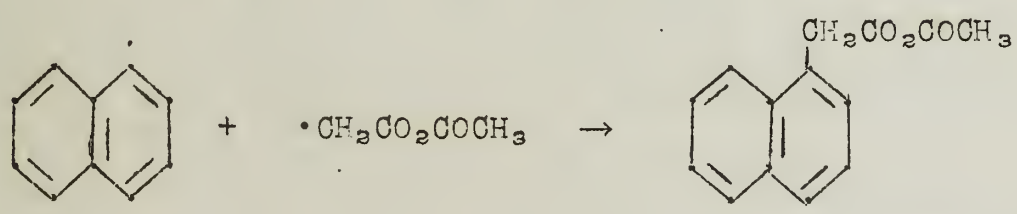
In view of recent studies of free radical reactions (2,3,4) and the concept that certain oxidations involving metallic oxidizing agents proceed via free radicals (5), it seems reasonable that the course of this reaction could be represented by a series of steps involving free radicals, such as the following:

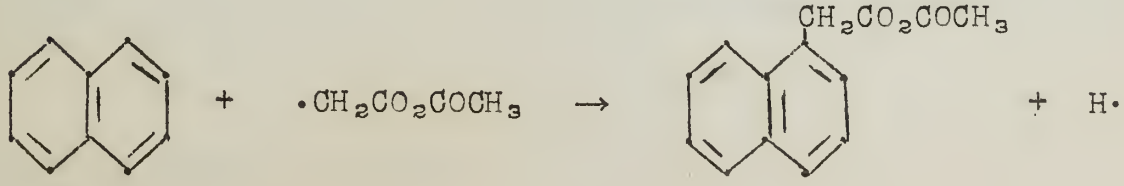
(1) $4(CH_3CO)_2O + KMnO_4 \rightarrow 5CH_3COO\cdot + CH_3CO_2K + (CH_3CO_2)_2Mn$

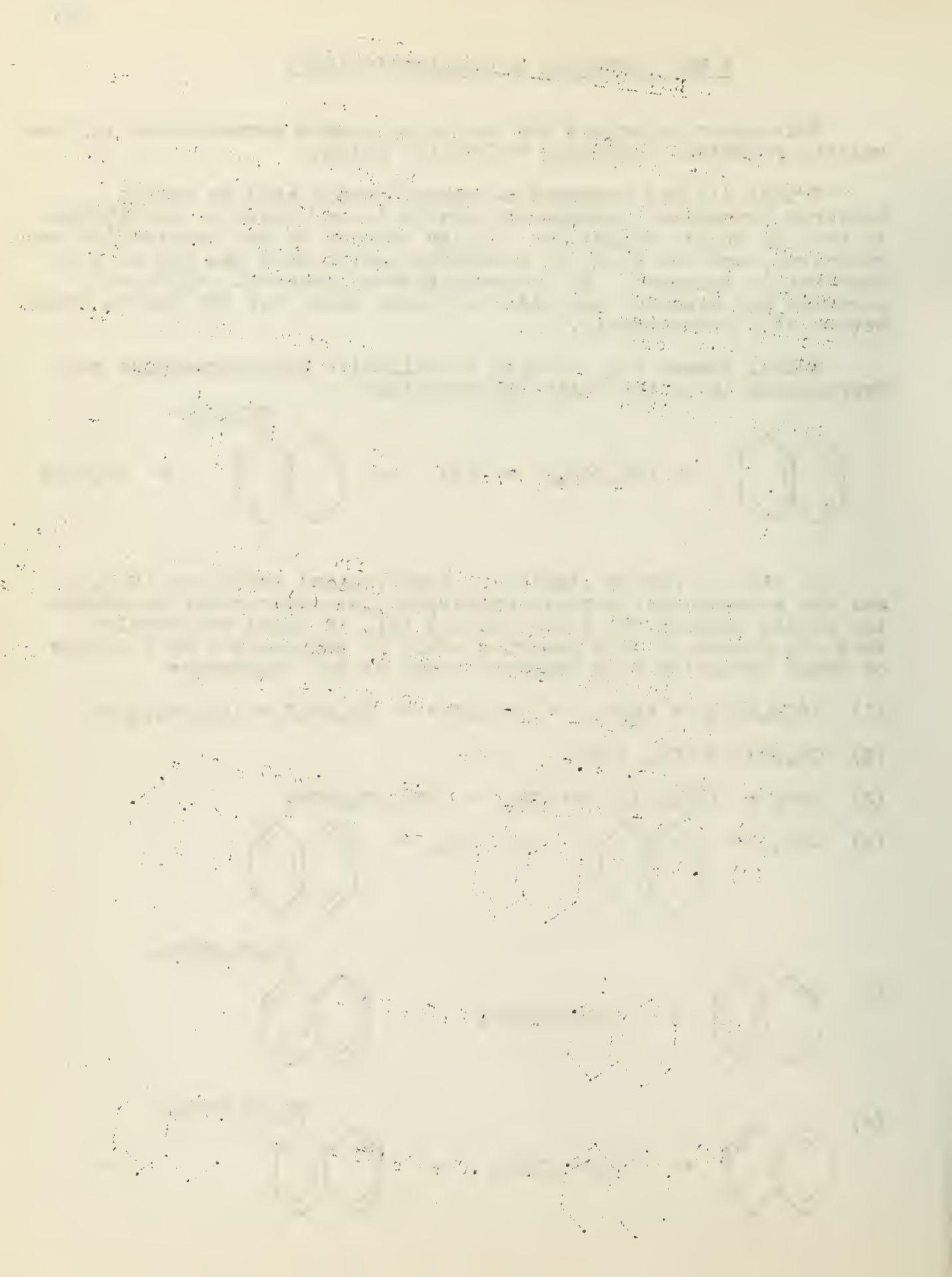
(2) $CH_3COO\cdot \rightarrow \cdot CH_3 + CO_2$

(3) $\cdot CH_3 + (CH_3CO)_2O \rightarrow CH_4 + \cdot CH_2CO_2COCH_3$

(4) 

(5) 

(6) 



Step (1) is more easily explained if traces of acetic acid are assumed to be present. It is well known that the permanganate ion is unstable toward reduction by water in acid solution; the reaction is regarded as proceeding through the hydroxyl radical, the permanganate ion being reduced stepwise to manganous ion (6). By analogy, with acetic acid, step (1) may be written as

$$2CH_3CO_2H + [O] \rightarrow 2CH_3COO\cdot + [H_2O]$$

$$[H_2O] + (CH_3CO)_2O \rightarrow 2CH_3CO_2H$$

with acetic acid being reformed as it is oxidized.

Uses of the Reaction. This synthesis of α-naphthylacetic acid, being a decided improvement over the best previous method (7), is of possible commercial interest, since α-naphthylacetic acid has considerable importance as a plant-growth regulator. In a similar manner, Griehl produced β-hydroxy-α-naphthylacetic acid from β-naphthol, p-phenylphenylacetic acid from biphenyl, and o-methoxyphenylacetic acid from anisole. Aralkanes reacted in a different manner, producing dimers of the sort encountered by Kharasch (3) by means of decomposition of diacetyl proxide in alkylbenzenes. For example, n-propylbenzene, treated with acetic anhydride and permanganate, gave 3,4-diphenylhexane. It is interesting that permanganate with acetic anhydride alone gave a 40% yield of succinic anhydride. Kharasch (2) obtained a 50% yield of succinic acid by allowing diacetyl peroxide to decompose in acetic acid.

The use of permanganate to form arylacetic acids is obviously limited to compounds without groups easily oxidized. Also, the reaction must be carried out using insufficient permanganate, since the products are subject to further oxidation by permanganate. Its advantage is twofold; the reagents are cheap and the handling of peroxides is eliminated.

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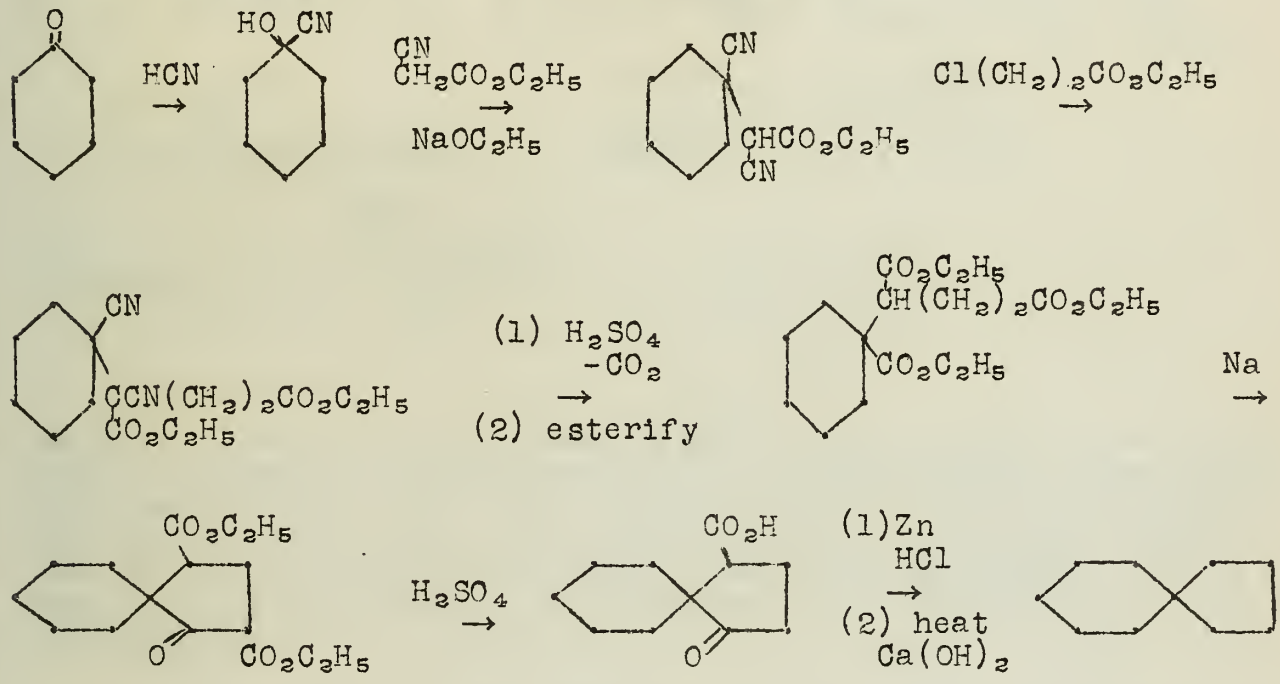
Reported by Harold J. Watson
December 3, 1948

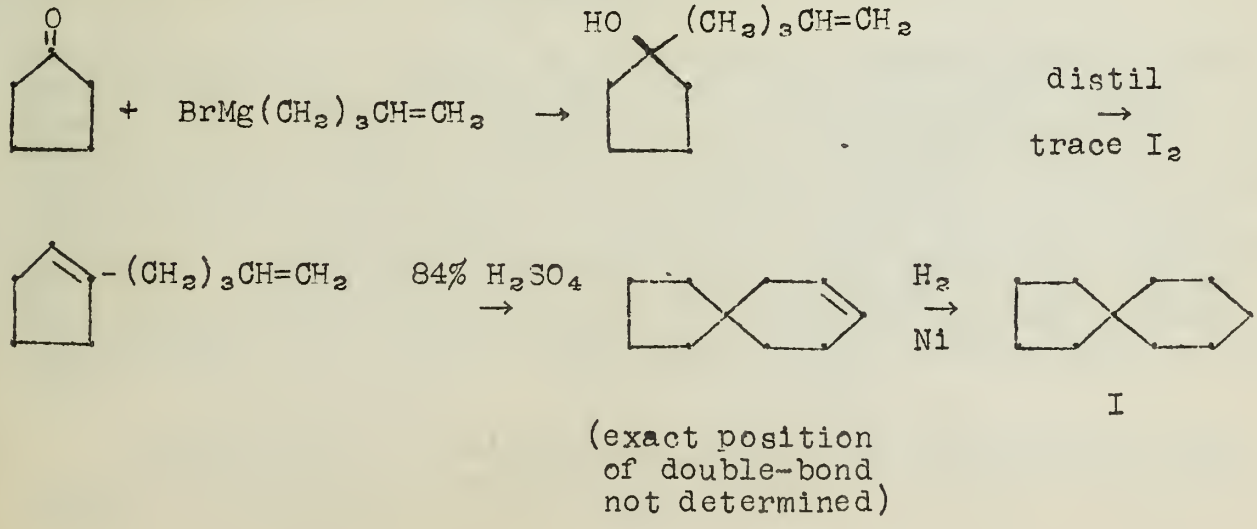
RECENT SYNTHESES OF SPIRANES

Spiro compounds are composed of two or more rings, two of which have a single atom in common. Spiranes, then, are saturated spiro hydrocarbons. These compounds are named by adding the prefix "spiro" to the name of the normal aliphatic hydrocarbon of the same number of members.

Relatively few spiranes have been prepared. The following synthesis, taken from the last seminar on this subject (1), is typical of the syntheses used up to 1941:

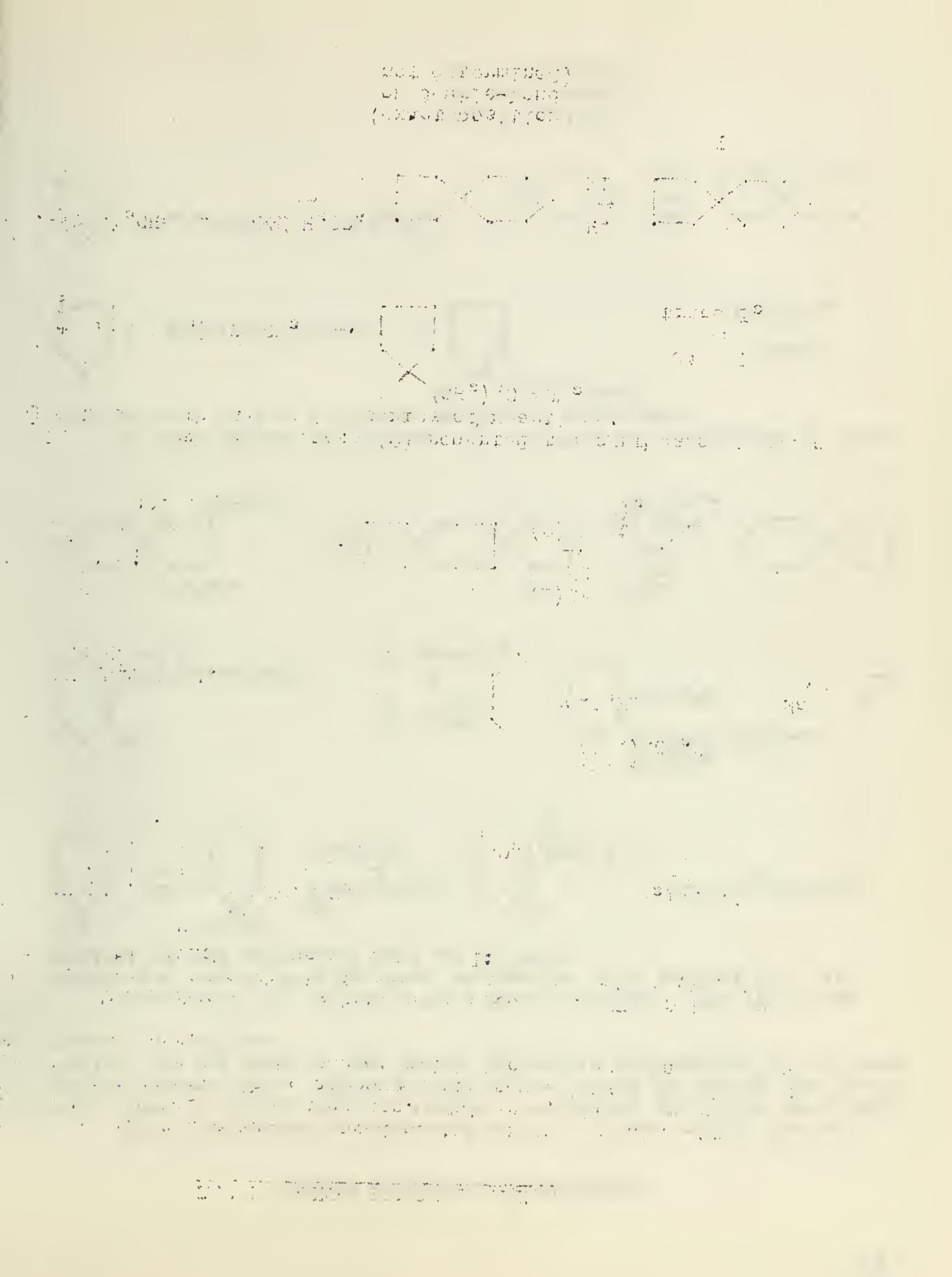


In 1941 Marvel and Brooks (2) reported the synthesis of spiro [4.5] decane by the following series of reactions:



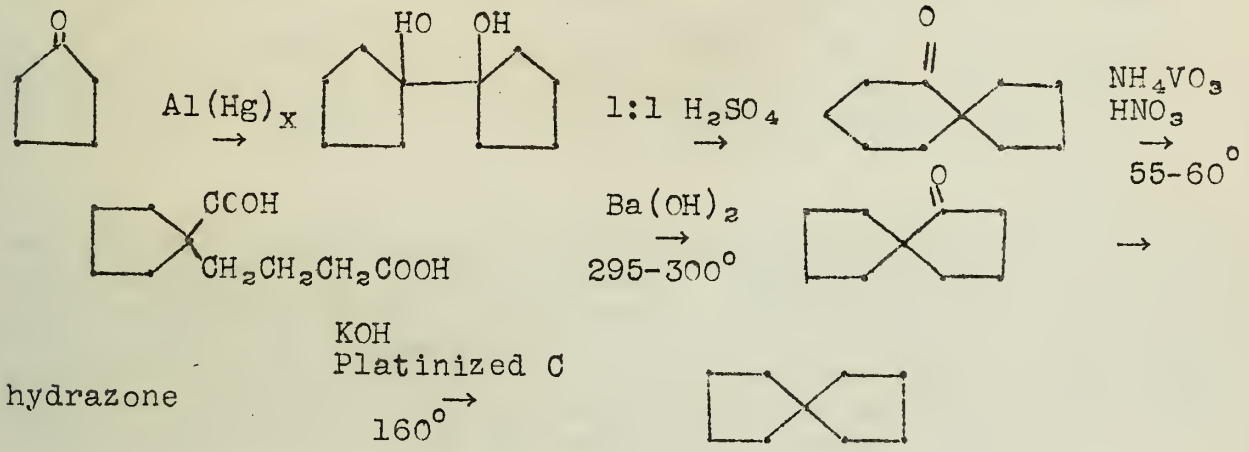
I

(exact position of double-bond not determined)



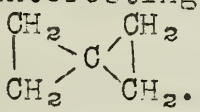
3-Methylcyclopentanone gave the analogous 3-methylspirane. The spirane I gave no reaction with bromine and on dehydrogenation over platinum or palladium on charcoal gave 33-5% naphthalene. The 3-methylderivative on similar treatment gave 31% 2-methylnaphthalene. Neither spirane could be dehydrogenated with selenium.

Spiro [4.4] nonane has been synthesized by Zelinskii and Elagina (3) in the following manner:



II

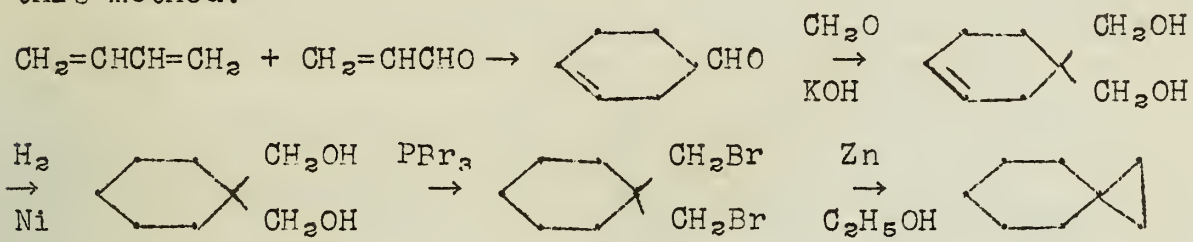
The final reduction took place in 68.7% yield to give a colorless, mobile liquid of terpene-like odor. On hydrogenation over platinized charcoal (4) mixtures of isomeric nonanes and cyclopentane homologs were obtained. In a carbon dioxide atmosphere, treatment with platinized charcoal at 305-10° gave o-ethyltoluene. It is hypothesized that bicyclo[4.3.0]nonane is an intermediate in this rearrangement.

Perhaps the most interesting spirane currently being investigated is spiropentane,  The obvious method of preparing this simplest spirane, by treatment of pentaerythrityl tetrabromide with zinc, has been believed not to give the desired product (5). However in 1944 Murray and Stevenson (6) showed, by means of Raman spectra, that the product of this reaction in aqueous methanol contained an unexpected component. Use of molten acetamide as the solvent, together with the addition of sodium iodide and sodium carbonate, conditions unfavorable for rearrangement (7), increased the yield of this component to 40%. Further investigation (8) indicated that this compound was the desired spiropentane. It has now been shown (9) that the reaction may be carried out successfully in ethanol solution.

Hydrogenation of spiropentane (10) gives a mixture of neopentane, dimethylcyclopropane and 2-methylbutane. No ethylcyclopropane or n-propane was isolated.

A recent patent states that 5 to 25% spiropentane in gasoline hydrocarbons gives an aviation fuel of improved performance (11).

Recently a new synthesis of other spiranes, making use of the reaction utilized for the preparation of spiropentane, has been devised (12). The preparation of spiro[2.5]octane will illustrate this method:



III

4-Methylspiro[2.5]octane has also been synthesized, starting with crotonaldehyde rather than acrolein. Hydrogenation of III gives 1,1-dimethylcyclohexane, the 4-methyl analog giving 1,1,2-trimethylcyclohexane. From these reactions and the results of the hydrogenation of spiropentane (10), the generalization has been made (12) that cleavage of these compounds seems to occur exclusively at the bond opposite the gem-substituted carbon atom.

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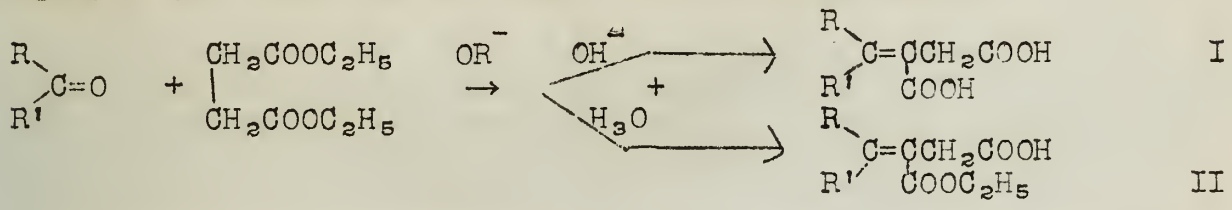
Reported by William R. Miller
December 3, 1948

RECENT STUDIES OF THE STOBBE CONDENSATION

Introduction

The term Stobbe Condensation is applied to those alkoxide-catalyzed reactions between ketones and diethyl succinate which result in the formation of dibasic unsaturated acids.



I

II

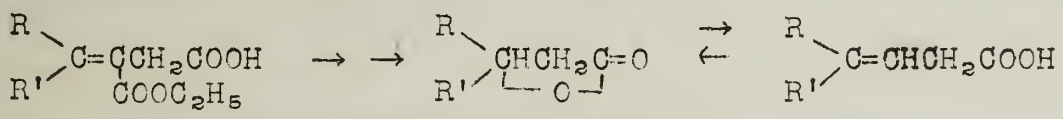
Since the previous report (1) on the Stobbe Condensation, several papers have been published dealing with both the modification and extension of the reaction (3,4,5,6).

Modified Stobbe Condensation

In 1945, Johnson and coworkers (2) introduced the use of potassium t-butoxide in t-butylalcohol in place of classical sodium ethoxide for effecting the condensation. This modified procedure has since been extended to the reaction of a number of different type ketones (3,4,5). In almost all cases, potassium t-butoxide was found to be a far superior agent for the reaction by giving both higher yields and purer products during shorter reaction times.

Decarbethoxylation Reaction

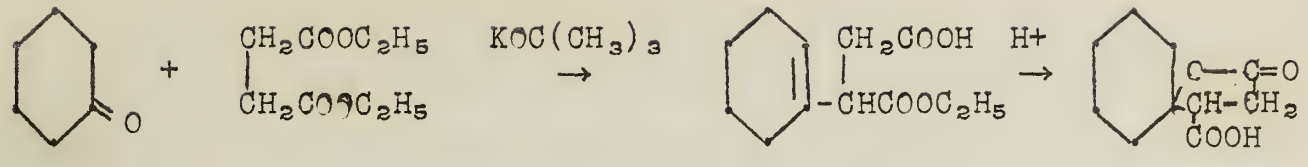
Decomposition of the product of the Stobbe Condensation is generally brought about by an acid-catalyzed decarbethoxylation reaction to give the lactone and/or the unsaturated acid. Recently it has been shown that the γ-lactones and unsaturated acids thus produced are interconvertible in a true acid-catalyzed γ-lactoenoic tautomerism (3).



III IV

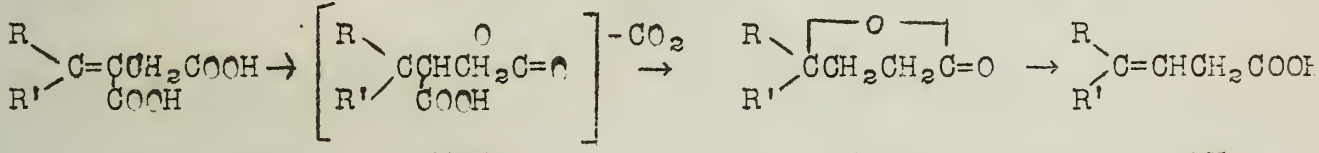
In the polycyclic series it was noted that the decarboxylation proceeded more rapidly than the tautomerism, making it possible to stop the process before equilibrium was reached. When this was done, the lactone was always found in higher proportion than at equilibrium, suggesting that the lactone is the precursor of the unsaturated acid.

When the Stobbe Condensation was effected with cyclohexanone and the resulting half-ester (or its alkaline hydrolysis products) was treated with a strong mineral acid, a high yield of the paraconic acid was obtained (5).



V VI

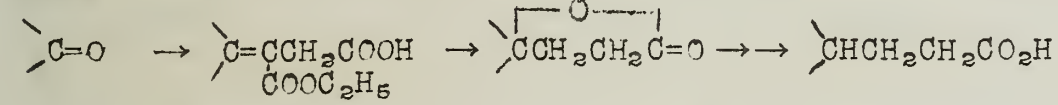
This evidence (V → VI), together with the conclusion that the γ-lactones are precursors of the unsaturated acids, offers support to the hypothesis that paraconic acids are intermediates in the decarboxylation reaction. The following mechanism may then be postulated for the decarboxylation of the itaconic acid:



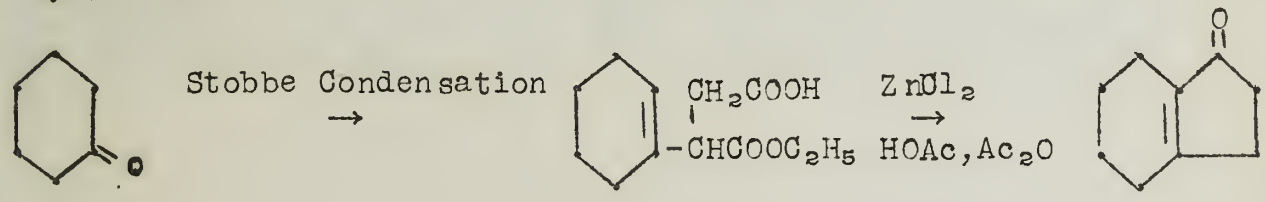
VII VII IX

Synthetic Applications

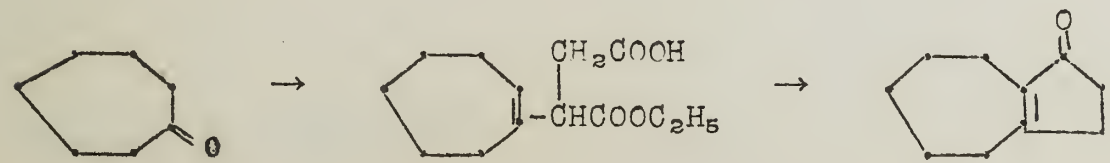
When the acid-catalyzed decarbethoxylation of the half-ester (formed by the Stobbe Condensation) is followed by reduction of the resulting product, a method is afforded for introducing a propionic acid residue at the site of the carbonyl group of a ketone Thus:



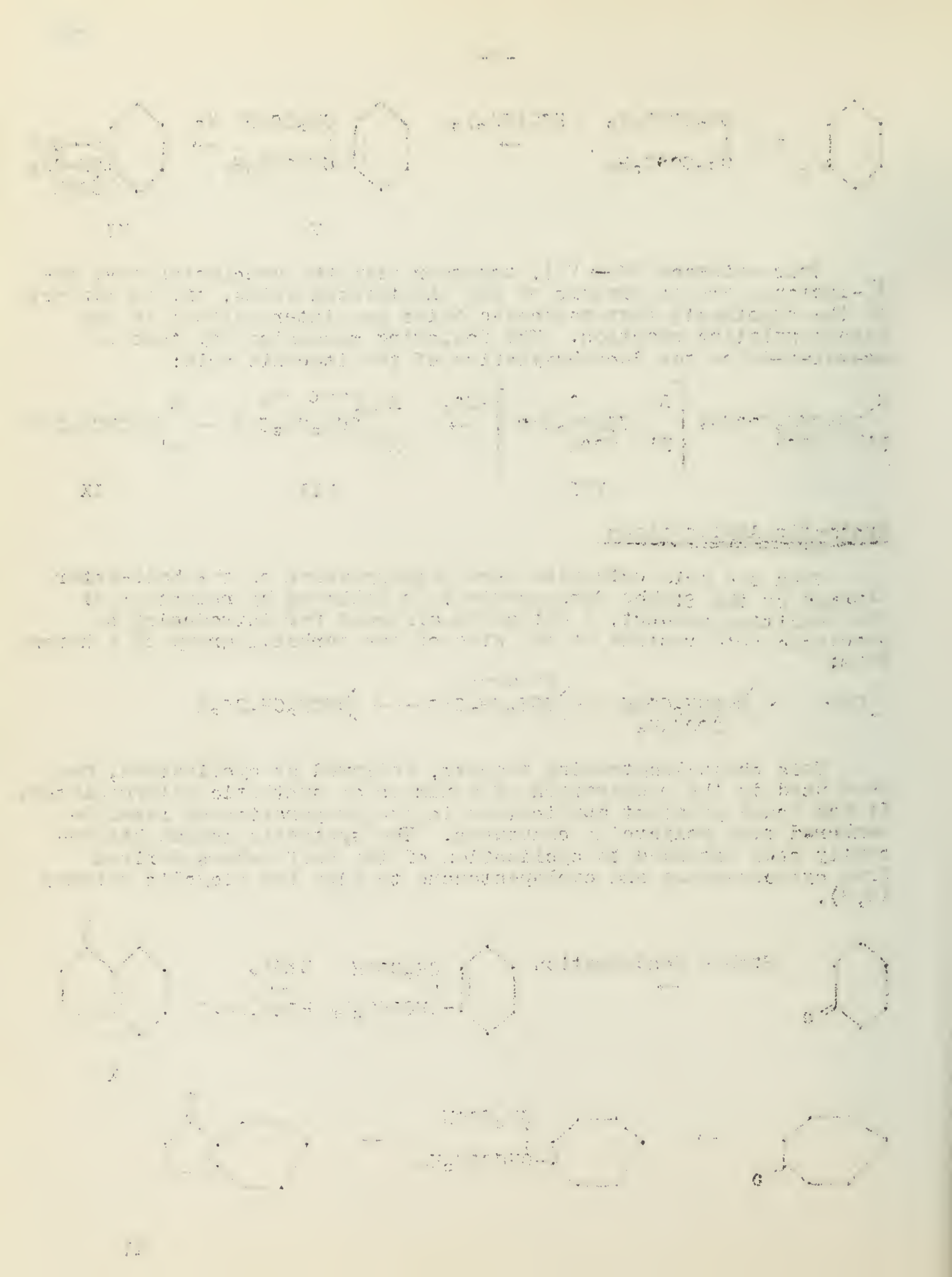
This chain-lengthening process, followed by cyclization, has been used in the preparation of a number of synthetic intermediates. It has found greatest application in the preparation of fused 5-membered ring polycyclic compounds. The synthetic scheme has recently been extended to cyclization of the half-esters derived from cyclohexanone and cyclopentanone to give the bicyclic ketones (5,6).



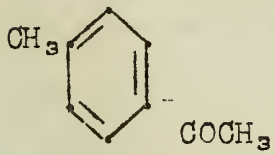
X



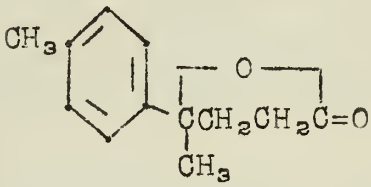
XI



Johnson has applied the process to methyl p-tolyl ketone and has utilized the resulting acid in a new, improved synthesis of cadalene (4). The steps in the synthesis are as follows:



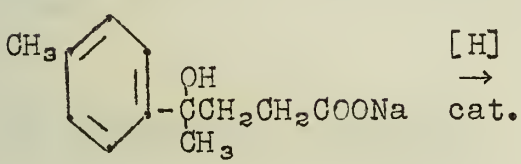
(1) Stobbe Condensation
(2) Decarbethoxylation



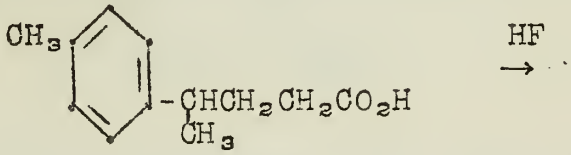
dil. NaOH

XII

XIII



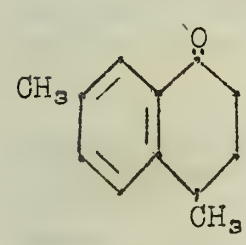
[H] cat.



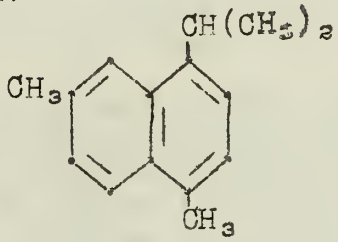
HF

XIV

XV



(1) $(CH_3)_2CHMgBr$
(2) Dehydrogenation



XVI

XVII

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Reported by H. Rosenberg
December 10, 1948

SCOPE OF THE ARBUZOV REACTION

The Arbuzov reaction is a very general method for the preparation of phosphonic acid esters. Recent work has described its wide applicability and has outlined its limitations. Arbuzov (1) found that phosphite esters could be isomerized to phosphonic acid esters by heating with an alkyl halide, as shown in equation I

$$(RO)_3P + R'X \xrightarrow{\Delta} R'P(=O)(OR)_2 + RX \qquad \text{I}$$

The procedure is sometimes modified, as in equation II, by using sodium dialkyl phosphites, which are less expensive than the trialkyl phosphites and usually permit milder reaction conditions.

$$NaOP(OR)_2 + R'X \xrightarrow{\Delta} R'P(=O)(OR)_2 + NaX \qquad \text{II}$$

1. Monohalogen compounds

Alkyl halides:- Primary bromides and iodides give best results; secondary halides do not react. Tertiary halides of the type Ar_3CBr give excellent yields (2).

Ethane and methane phosphonates are formed in 95% yields. Though butyl and amyl bromides react much more slowly with trialkyl phosphites and give poor yields, hexyl and larger bromides work more smoothly (3). With further increase in chain length more drastic conditions and longer reaction periods are required (4). However, the entire series has been obtained in yields of 80% by use of sodium dibutyl phosphite under mild conditions (5).

Aralkyl halides:- A variety of substituted benzyl chlorides have been converted to phosphonates, both by use of triethyl phosphite (6) and sodium dibutyl phosphite (7). The chloromethyl group attached to the ring is active, so that the yields by both methods are 70-90%. Kosolapoff (8) has also prepared dibutyl α-thienylmethane phosphonate similarly.

The chlorine atom in 9-chloroacridine was found to be active though to undergo this reaction with triethyl phosphite. However, when sodium dibutyl phosphite was used, a quantitative yield of acridone was obtained (9).

Alkyl halides with other functional groups present:- Halogen substituted carboxylic esters yield phosphonocarboxylic esters in limited cases.

$$(RO)_2PONa + XCH_2CO_2Et \rightarrow (RO)_2P(=O)-CH_2CO_2Et$$

Successful results have been obtained with α-haloacetic esters (10,11,12), β-iodopropionic ester (13), and bromomalonic ester. The latter yielded its phosphonate only with trialkyl phosphites (10,12). When sodium dialkyl phosphites are used, self coupling of the organic ester is an important side reaction. In several instances, the coupling products along with disproportionation products are the only organic compounds formed (11).

α-Nitrobromo compounds do not give the expected α-nitrophosphonates with triethyl phosphite. Instead, ethyl phosphate is formed; the nitrobromo compound is decomposed (14).

Acyl halides yield α-ketophosphonates (15).

$$(RO)_3P + CH_3C(=O)-Cl \rightarrow CH_3C(=O)-P(=O)-(OR)_2$$

2. Polyhalogen compounds

Methylene halides:-In general it is possible to obtain two principal products from a reaction with methylene halides, depending upon the relative amounts of reactants (16,17,18,3):

$$(RO)_2P(=O)-(CH_2)_n-P(=O)(OR)_2 \quad \text{and} \quad (RO)_2P(=O)-(CH_2)_nBr, \quad n=1,2,3$$

Carbon tetrachloride:- When excess carbon tetrachloride is used just one of the chlorine atoms is reactive (9).

$$CCl_4 + (RO)_3P \rightarrow Cl_3C-P(=O)-(OR)_2$$

3. Ethylene oxide (19,20,21,22)

The phosphites formed from ethylene oxide and phosphorus trichloride can undergo intramolecular Arbuzov reactions.

$$PCl_3 + H_2C(-O-)CH_2 \rightarrow ClCH_2CH_2OPCl_2 \xrightarrow[\text{pyr.}]{ROH} ClCH_2CH_2OP(OR)_2$$

or

$$(RO)_2PCl + H_2C(-O-)CH_2 \rightarrow ClCH_2CH_2P(=O)(OR)_2$$

However, when arylchlorophosphites, $(ArO)_2PCl$, are treated with ethylene oxide, the products, $ClCH_2CH_2OP(OAr)_2$, do not isomerize as expected in a normal Arbuzov reaction; instead ethylene diphosphonic esters are formed.

Excess ethylene oxide on PCl_3 or PBr_3 gives the corresponding trihaloethyl esters which are difficult to obtain pure since they isomerize on distillation.

4. Glycols (23,24)

Cyclic phosphites can be prepared by action of PCl_3 on a glycol in presence of a tertiary base. The 5 and 6 membered ring phosphites are stable and are formed in poor yields; those with 7 and 8 membered rings are formed in good yields and polymerize easily. In isomerization, the ring may or may not be opened. This seems to depend on the substitution on the ring.

(a)
$$PCl_3 + \begin{matrix}CH_2OH\\CH_2OH\end{matrix} \xrightarrow[\text{in } Et_2O]{\text{pyridine or } \phi NEt_2} \text{[CH}_2\text{CH}_2\text{O-P-O, Cl]} \xrightarrow[ROH]{\text{dry}} \text{[CH}_2\text{CH}_2\text{OP-O, OR]} \xrightarrow[\Delta]{R'Br} R'-P(=O)(OR)(OCH_2CH_2Br)$$

(b) $PCl_3 + \begin{matrix}CH_2OMe\\ CHOH\\ CH_2OH\end{matrix} \xrightarrow{"} MeOCH_2CH_2CH_2OP(Cl)O \xrightarrow{"} MeOCH_2CH_2CH_2OP(OR)O \xrightarrow[\Delta]{R'Br}$

$MeOCH_2CH_2CH_2OP(=O)(R')OR$

5. Organometallic reagents

Cacodyl phosphonic esters have been prepared from ethyl alkyl arsenous iodides and sodium diethyl phosphite (25). The P-As bond in these esters is much weaker than the corresponding P-C bond; on attempted hydrolysis to the phosphonic acid with 15% HCl at 150° the esters decompose. Analagous tin derivatives have been prepared using both dialkyl and trialkyl tin halides on trialkyl phosphites (26,27). In these esters the P-Sn bond is quite weak since it is cleaved by dilute HCl at room temperature. This preparation has also been tried with lead alkyl halides, but only disproportionation products result (27).

Mechanism of the Reaction

The Arbuzov reaction is generally considered to procede through an addition intermediate, with subsequent splitting out of alkyl halide. For example:

$$P(OEt)_3 + MeI \rightarrow \left[EtO-\overset{\oplus}{P}(OEt)-Me \; I^{\ominus} \right] \rightarrow EtO-P(=O)(OEt)-Me + EtI$$

Arbuzov (1), who postulated this mechanism, found evidence for such an intermediate by preparing crystals of $[CH_3P(OC_6H_5)_3]I$; more recently Kamai and Belorossova (25) obtained a quantitative yield of $[EtBuAsP(OEt)_3]I$, crystals, m.p. 182°.

In the intramolecular Arbuzov reaction, the intermediate is said to be a cyclic one (19).

$$[(ClCH_2CH_2O)_2P(Cl)-OCH_2CH_2]$$

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Reported by Claire Bluestein
December 10, 1948

PUNCHED CARDS FOR THE INDIVIDUAL ORGANIC CHEMIST

The punched card is a mechanical device which can be used to reduce the laborious repetitive work for literature searching. It has already achieved wide use in business and government applications, and is finding increasing use in science.

Punched cards are divided into two main classes according to the way they are sorted.

I. Machine-Sorted Punched Card

This is the type used in accounting and computing operations; it has little use for the individual organic chemist. Where files can be planned of more than about 10,000 items, it should be investigated.

A. Advantages
   1. cheap - about $1.10 per thousand.
   2. large punching capacity - 80 twelve-punch columns.
   3. machine operated - this card can be punched, interpreted, verified, sorted, serialized, alphabetized, duplicated, collated and tabulated by machine.

II. Hand-Sorted Punched Card

This is the type recommended for personal files and individual applications. The cards may be obtained from the McBee Company, ("Keysort"), Athens, Ohio, and the Charles R. Hadley Company, ("Rocket"), Los Angeles, California.

A. Advantages
   1. large informational capacity - body of card on both sides can be used.
   2. simple sorting - knitting needle and gravity.

B. Sorting Procedure

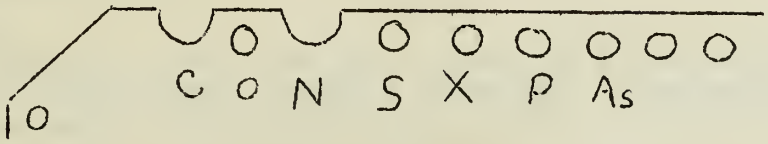
Punched cards to be sorted manually have holes cut in them near the margins. When this margin is cut away from a particular hole on a card, leaving an open slot, the card may be sorted by means of a knitting needle. The needle is thrust through the deck at the particular position and lifted; slotted cards will drop out. A double row of holes will give three categories.

C. Coding Procedure

The most difficult and most important part of preparing a punched card file is the selection of a suitable code. This should be based on an outline covering the complete subject. For a most useful procedure, see Cox, Bailey and Casey (6). This procedure will insure coding into the file only information likely to be sought later.

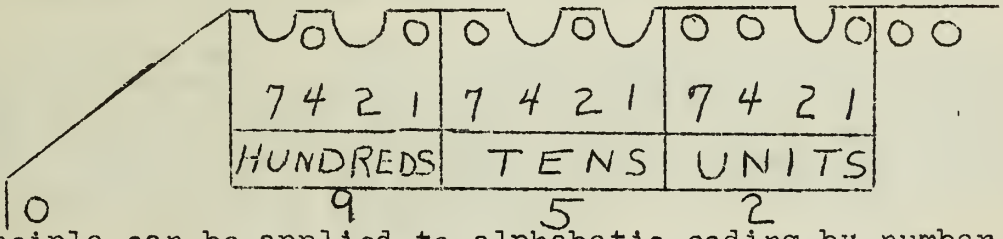
There are three general methods of coding information on punch cards.

1. The so-called "direct" coding (better described as single-position punching, or unit punching) uses only one hole for a specific item of information. The presence of carbon and nitrogen in a compound can be indicated as

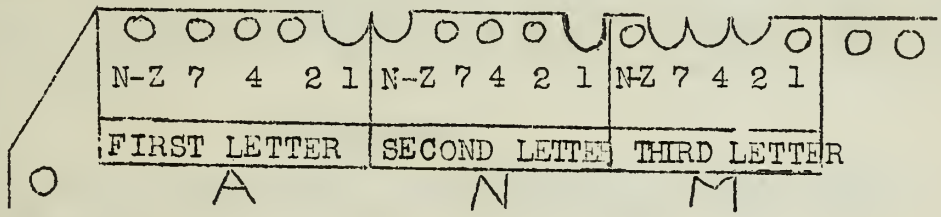


This type uses the most holes, but is the easiest to sort: one pass selects the desired cards. The items need not be mutally exclusive.

2. Numeric (and alphabetic) coding makes use of a group of adjacent holes, called a "field," to indicate an item. To code the number 952 (which might indicate a process like hydrogenation of C-C double bonds, or a concept like the theory of reaction mechanisms at C-X linkages) the following punching would result:



The principle can be applied to alphabetic coding by numbering each letter. ANM would be coded



(5)

More complex systems have been developed which effect a saving in holes (4-7).

This coding allows a great many items of information to be entered, but only one item per field, and a separate code index is required. A feature of this type is that if the field or group of fields is sorted in order, hole by hole, from right to left across the card, with the cards that drop placed in back, the resulting deck will be in serial or alphabetic order.

3. Random coding* consists of the superposition of randomly-chosen designations on the same set of holes, allowing a statistical distribution to control the number of cards which result from chance sorting. This can be controlled to any degree of fineness.

Sorting is more complex, but allows the use of a file containing unrelated topics. The best plan for "unrelated topics," for the individual, is to make a separate file for each. This makes for ease of sorting and specificity.

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* The patent status of this system is unclear at present and some caution should be used in its application.

"Direct" coding should be used where space is available, but generally both it and numeric (or alphabetic) coding will be used on the same card. Where random coding is used, it is best to employ all the holes on the card as one field.

A point of first importance is to leave room on the final card lay-out for expansion.

D. Uses

In general, there are two types of files which are of interest to the individual organic chemist: a chemical compound file and a literature reference file.

The compound file usually contains information on elements present, physical properties, and some structural indication, among others. Complete structural codes are in the process of development

A file of literature references is ordinarily kept alphabetically, but punched cards can be kept in, and sorted from, random order. Other items often included are date of publication, major and minor subjects treated, language of original, junior authors, etc. Each of these types of information takes the place of another whole file of ordinary cards.

Correlations can be made by simultaneous or serial sorting. Thus, if one is interested in all organic compounds containing both N and As, and having a density between 1.5 and 2.0, it is relatively easy to arrive at these compounds using punched cards, and somewhat difficult other ways. More complicated multiple sorts can be made in subject classifications. It is here that the advantages of a well-made outline and coding system appear.

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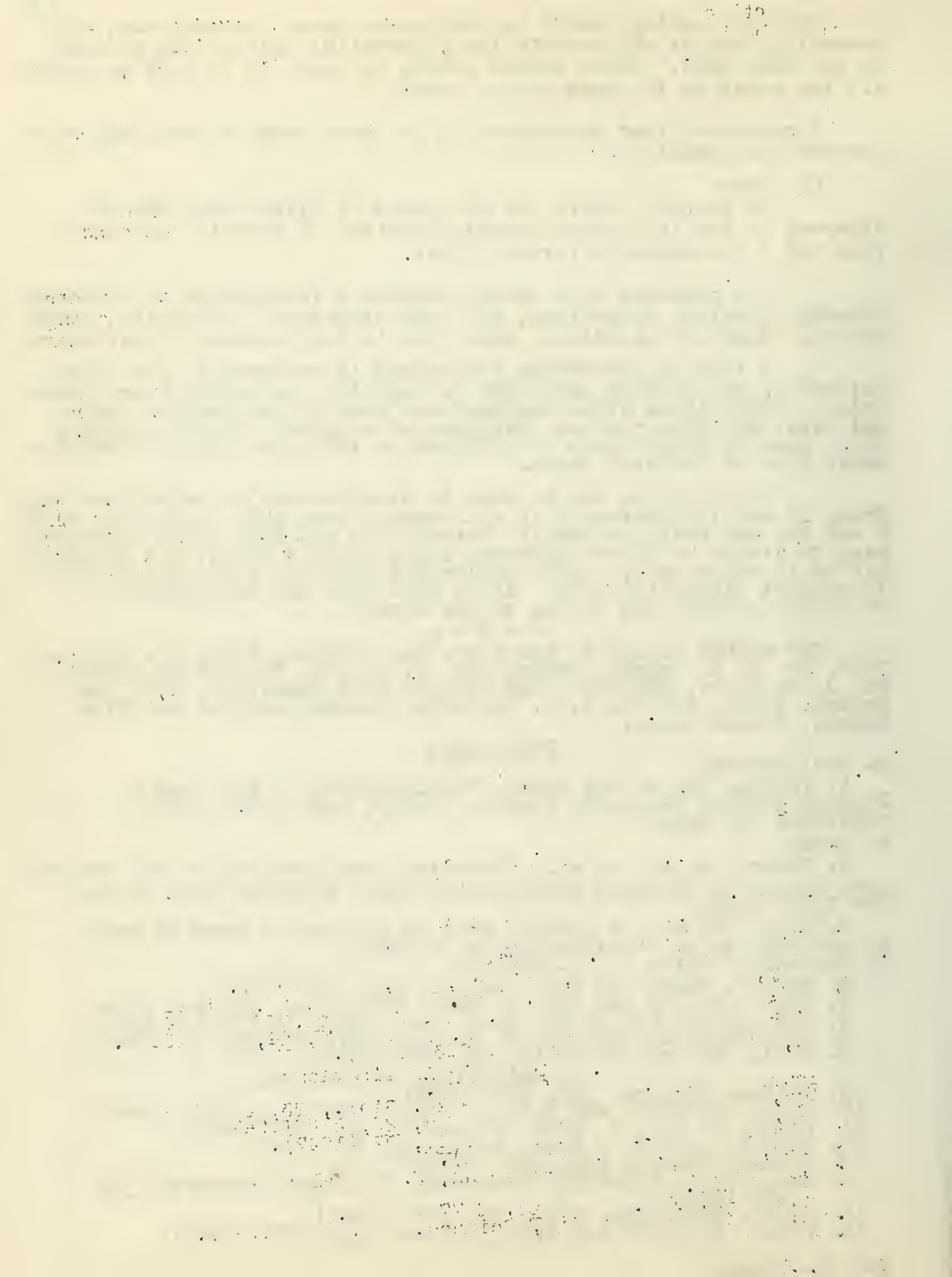
Karl F. Heumann
December 10, 1948



CARBODIIMIDES

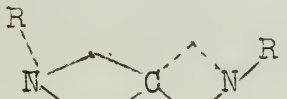
I. Nomenclature

Carbodiimides have the general structure R-N:C:N-R'. If R = cyclohexyl- and R' = phenyl-, the compound may be called carbocyclohexylphenyldiimide,or cyclohexylphenylcarbodiimide.

II. Steriochemistry

Carbodiimides of the type A and B are theoretically structurally similar to the allenes (1).

A



B

If the nitrogen atom has a fixed tetrahedral structure, a pair of mirror images may exist, since the two substituted R groups are in planes different from those of the C=N linkages. No optically active carbodiimides of this type have been reported.

Optically active carbodiimides have been prepared by the use of optically active reagents (2). Dibornyl- and dimenthylcarbodiimides were prepared from the corresponding thioureas. Their optical rotations lie between those of the corresponding ureas and thioureas.

III. Preparation

Carbodiimides are best prepared by desulfurization of thioureas.

$$(I):\quad SC(NHR)_2 + HgO \rightarrow HgS + H_2O + C(:NR)_2$$

Numerous side reactions are also possible: II, the addition of water to the carbodiimide forming the urea; III, the reaction of the thiourea and carbodiimide to form the guanadine and isothiocyanate; IV, the reaction of urea with carbodiimide to form the isocyanate and guanidine; V, polymerization reactions.

In the original method of Weith (3), the aromatic thiourea was boiled in benzene with mercuric oxide. This treatment was too vigourous, resulting in low yields as a result of reactions II and V. Rotter (4) attempted to avoid reaction II, but the urea formation could not be prevented.

For the preparation of aliphatic carbodiimides, pure, freshly prepared dry thioureas and freshly precipitated yellow mercuric oxide were shaken in dry ether, benzene, or carbon disulfide at room temperature, thus repressing polymerization reactions (5,6,7,8). In cases where urea formation was greatly favored, the desulfurization velocity was increased by using freshly prepared, undried

mercuric oxide; the carbodiimide was formed before reaction II could occur. Di-isopropyl-, di-n-propyl-, propyl-cyclohexyl-, and propyl-isopropylcarbodiimides were prepared in two to fifteen minutes in over 90 per cent yield by this method.

The applicability of the above method is limited by the solubility of the thiourea in the solvent at room temperature. A modification of the method was subsequently sought which would be applicable to the difficulty soluble aromatic thioureas (9). The desulfurization velocity is increased by the use of sulfur as a catalyst, by increasing the reactive surface of the metal oxide, and by using acetone as a solvent, thus preventing harmful accumulation of water on the metal oxide-sulfide surfaces. Sulfur also inhibits urea formation and resinification. 90 per cent yields of most aromatic carbodiimides were achieved. This method is not applicable to aliphatic thioureas (9).

Carbodiimides are also prepared by the action of phenylisocyanate on phosphinimines, and aromatic acid chlorides on cyanaminoethyl alcohol.

IV. Stability toward polymerization

Aliphatic carbodiimides with two primary residues are very unstable; stability in the primary residue increases with the number of carbon atoms. The stabilizing effect of secondary groups is larger than a proportional increase in the primary group size (7). Two secondary groups show greater stability, while tertiary residues are the most stable (8).

There is a wide variation in the polymerization tendencies of aromatic carbodiimides. For example, di-p-iodophenylcarbodiimide and carbo-p-dimethylaminophenyl-phenyl- carbodiimide polymerize readily; diphenyl-, p-tolyl-p-bromophenyl-, di-p-bromophenyl-, and di-p-tolylcarbodiimide moderately; di-p-dimethylaminophenyl- and di-α-pyridylcarbodiimide tend to polymerize only slightly.

V. Reactions

A. With Grigard Reagents- R'MgX adds across one C=N double bond of R-N:C:N-R forming the addition product, R-N=C(R')-N(MgX)=NR, which is subsequently hydrolyzed to a substituted amidine, R'C(NHR)=NR (10).

B. With Phenols- Diphenylcarbodiimide when heated with phenol yields the O-ether of diphenyl-Ψ-carbamide, PhN:C(OPh)NHPh. Acid treatment yields phenol and diphenyl urea. p-cresol, α- and β-naphthol were also used (11).

C. With Aromatic Amines- Aromatic guanidine derivatives.

D. With Carboxylic Acids- (See Uses).

E. With Hydrazoic Acid- Carbodiimides add HN_3 forming 1,2,3,4-tetrazoles.

F. With Diazomethane- The reaction of carbodiimides with diazomethane yields triazoles.

VI. Uses of Carbodiimides

A. Characterization of Carboxylic Acids

1. As Ureides

Depending upon the solvent, the temperature, the carbodiimide, and the acid, carbodiimides react in two ways with carboxylic acids (12,13,14):

a) With one mole of acid to form the ureide (N-acyl, N,N'-disubstituted urea.

b) With two moles of acid, forming the acid anhydride and a disubstituted urea.

If carbodicyclohexylimide is boiled in alcohol with carboxylic acids, it is possible to make ureide formation the chief reaction. Ureides of butyric, benzoic, and stearic acids are readily prepared. A similar reaction with aromatic carbodiimides in ether or benzene solution at room temperature results almost exclusively in the formation of the anhydride.

2. A Test for α-, β-unsaturated Acids (12)

Ureides with $C(:NC_6H_4N\text{-}Me_2\text{-}p)_2$ and RCOOH are colored when R = R'CH=CH- or R'C ≡ C-; those having an unsaturated link in any position other than α,β-, are colorless.

3. A Test for α-haloaliphatic Acids (9)

Like the α,β-unsaturated acids, the α-haloaliphatic acids form colored ureides with $C(:NC_6H_4N\text{-}Me_2)_2$. β,γ- and other halogens do not produce a deepening of color. Bromide and iodide cause a greater effect than chloride.

4. Detection of Free Carboxylic Acids in Anhydrides

As little as 0.1 per cent free acid will form a precipitate with carbodi cyclohexylimide (13).

5. Preparation of Acid Free Anhydrides

Same method as above.

B. Industrial Applications

1. Deacidification of animal and vegetable oils and fats.
2. Textile finishing and impregnating agents.
3. Preparation of films, fibers, and various molded products.

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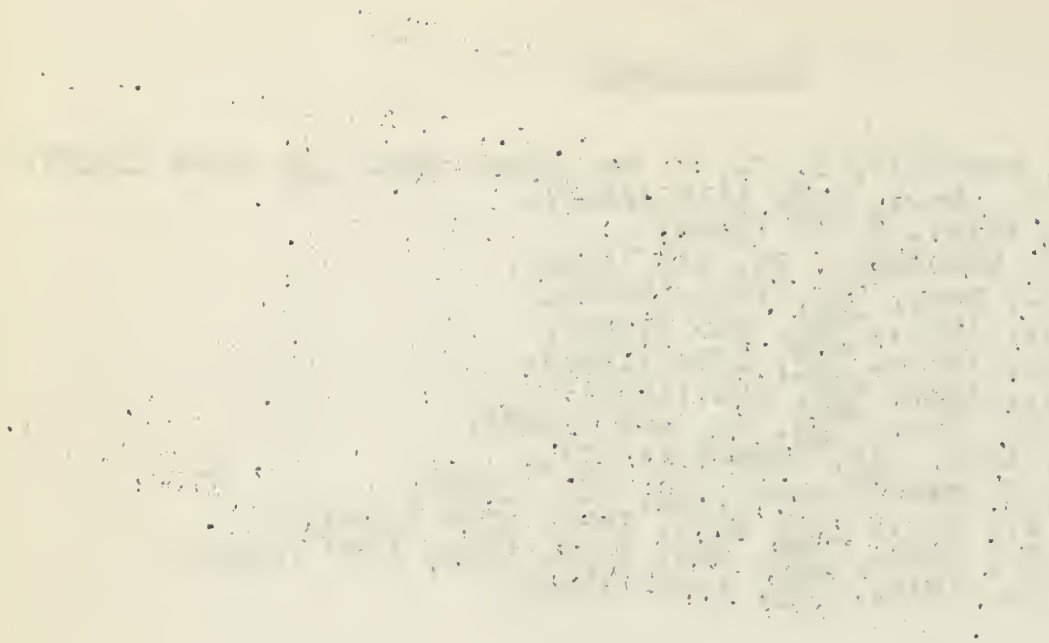
Reported by Edward F. Elslager
December 17, 1948

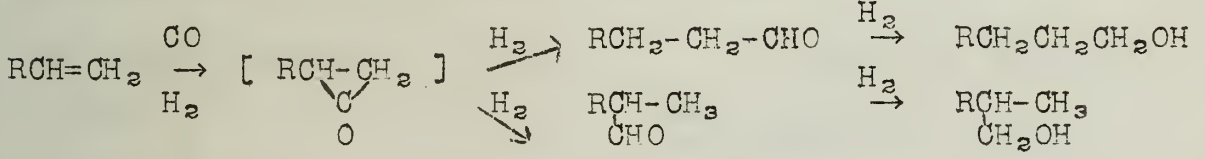


THE OXO PROCESS

A new aldehyde synthesis, disclosed in a patent (1) issued to Roelen in 1943, involves the combination of olefins with carbon monoxide and hydrogen in the presence of a catalyst containing cobalt. The aldehyde slurry is then subjected to hydrogenation resulting in reduction of the aldehydes to primary alcohols. The alcohols are then separated from the reaction mixture by distillation.

A wide range of pressures and temperatures may be used in both stages (2). The pressure range usually employed is 150 to 200 atmospheres. The temperature in the first stage is usually about 140° C. and in the second or hydrogenation stage about 180° C.

Mechanisms have been proposed for this reaction but sufficient evidence has not been put forth which proves any postulated. The reaction may be illustrated by the following:

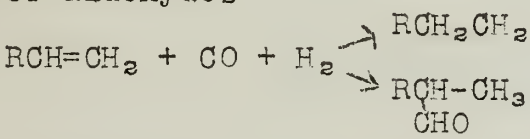


As a general rule, about 60 percent branched and 40 percent straight chain alcohols are obtained.

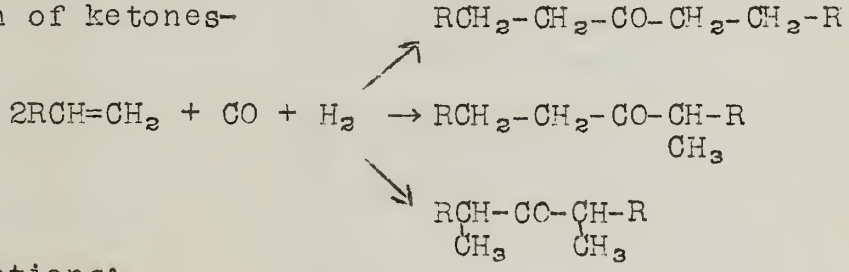
NATURE OF PRODUCTS

(1) Primary Reactions:

(a) Formation of aldehydes-



(b) Formation of ketones-



(2) Secondary Reactions:

(a) Formation of alcohols-
Occurs possibly as a result of a Cannizzaro-type reaction.

(b) Formation of acids-
This also is due apparently to the Cannizzaro-type reaction

(c) Formation of esters.

(d) Formation of high-molecular-weight compounds-
Formed by polymerization and condensation reactions.

(e) Formation of saturated hydrocarbons-
Corresponding to starting material.

DOUBLE BOND ISOMERIZATION

This is an important feature of the oxo process. Using pure 1-dodecene, in the absence of hydrogen it has been shown that all dodecene isomers in almost equal ratios are formed. Using cobalt metal in the presence of an inert gas, under the usual conditions of the oxo reaction, no isomerization takes place. The isomerization agent is apparently the dicobalt octacarbonyl, $[Co(CO)_4]_2$, itself. It has been stated that the oxo reaction and isomerization proceed simultaneously but that the former takes place with the greater velocity since when terminal olefins are used, the formation of branched products is not as great as would be predicted from laboratory experiments on the isomerization of olefins in the presence of carbon monoxide but in the absence of hydrogen.

Below are listed the results (4) obtained by using various olefins:

Base Material	Alcohols Obtained
Propene	60% n-Butanol 40% 2-Methyl-Propanol-1
Butene-1	50% n-Butanol 50% 2-Methyl-Butanol-1
Butene-2	50% n-Pentanol 50% 2-Methyl-Butanol-1
Isobutene	3-Methyl-Butanol-1 (Only)
Pentene-1	50% n-Hexanol 40% 2-Methyl-Pentanol-1 10% 2-Ethyl-Butanol-1
Pentene-2	55% n-Hexanol 35% 2-Methyl-Pentanol-1 10% 2-Ethyl-Butanol-1
n-Hexene	50% n-Heptanol 30% 2-Methyl-Hexanol-1 20% 2-Ethyl-Pentanol-1
2-Methyl-Pentene-3	30% 2,4-Dimethyl-Pentanol 40% 5-Methyl-Hexanol-1 30% 3-Methyl-Hexanol-1
2,4,4-Trimethyl-Pentene-1 2,4,4-Trimethyl-Pentene-2	3,5,5-Trimethyl-Hexanol-1

The results may be summarized as follows:

(1) Addition of a formyl group to a tertiary carbon atom does not occur at all. No quaternary carbon atoms are formed.

(2) Addition of a formyl group adjacent to a quaternary carbon atom does occur.

(3) Addition of a formyl group adjacent to a tertiary carbon atom is strongly hindered, but it may occur to a small extent.

(4) Addition of a formyl group is not hindered by an isolated tertiary carbon atom.

(5) Isomerization of the double bond generally accompanies the formylation, but does not necessarily occur.

ADDITION TO DIOLEFINS (5,6)

(a) $CH_2=\underset{\underset{CH_3}{|}}{C}-CH_2-CH_2-\underset{\underset{CH}{|}}{C}=CH$ — 40% Diol, 60% C_9 Monol

(b) $CH_3-\underset{\underset{CH_3}{|}}{C}=CH-CH=\underset{\underset{CH_3}{|}}{C}-CH_3$ — 100% C_9 Monol

(c) $CH_3-CH=CH-S-CH=CH-CH_3$ — Non-identifiable products

$CH_3-CH=CH-O-CH=CH-CH_3$

It was assumed that the low yield of the diol in (a) was brought about by the oxo reaction itself since the presence of conjugated bonds could not be established in the original olefin or after heating it with a catalyst to 130°.

It was expected that a higher yield of diol would be formed in (c) since the sulfur atom or the oxygen atom should prevent the double bond migration to form a conjugated system. The resulting products boiled from 100° to 400° but no fraction had an appreciable hydroxyl number.

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Reported by Edward F. Riener
December 17, 1948

THE BEHAVIOR OF ORGANIC ACIDS AND ESTERS IN SULFURIC ACID

Because of its strong acidity and convenience for cryoscopic measurements, concentrated sulfuric acid is an excellent solvent for studying the basic ionization (in the Brönsted-Lowry sense) of organic substances. The magnitude of the freezing-point depression compared to the depression produced by a non-electrolyte (known as the van't Hoff "i" factor) is accepted as a relatively accurate measure of the number of ions produced by the solution of one molecule of solute.

Hantzsch (1) discovered that many organic oxygen compounds ionize almost completely as monoacid bases. Most acids and esters ionize as follows:

$$\text{(A)} \qquad RCOOR' + H_2SO_4 = RCOOR' \cdot H^+ + HSO_4^- \quad (i=2)$$

Such solutions conduct electricity and yield the original compound unchanged upon dilution with water or alcohol. Certain strong acids, such as trichloroacetic acid, behave as non-electrolytes ($i=1$), while dichloroacetic acid ionizes only partially. The behavior of aldehydes and ketones resembles that of acids and esters, but most alcohols have an i factor of 3 and yield alkyl sulfuric acids on dilution with water.

Further investigations by Hammett (2,3,4) and later by Newman (5,6,7,8) disclosed an unusual type of ionization by certain sterically hindered acids and esters (such as mesitoic acid):

$$\text{(B)} \qquad RCOOR' + 3\ H_2SO_4 = RCO^+ + H_3O^+ + R'OSO_3H + 2\ HSO_4^-$$

The i value is 4 when R'=H and 5 when R' is an alkyl group. Dilution with water yields the corresponding acid in either case, while dilution with an alcohol yields the corresponding ester. This is particularly surprising, since sterically hindered acids are not esterified by the usual acid catalysis while (as seen above) ordinary acids are recovered unchanged from dilution of their sulfuric acid solutions with alcohol. Newman (5) utilized this reaction as a method of preparing esters of sterically hindered acids (yields 60-80%).

In the series of compounds studied by Hammett, acylization (see B) occurred only when there were two ortho-methyl groups. 2-Methyl-6-nitrobenzoic acid ionized normally, as did 2,4,6-tribromobenzoic acid (possibly because of its strong acidity, $K=4\times10^{-2}$) Dibromomesitoic acid exhibited partial acylization in pure sulfuric acid, but when a little water was present the i factor sank to 2. Hammett therefore postulated that acylization takes place in two non-overlapping steps:

$$RCOOH + H_2SO_4 = RCO_2H_2^+ + HSO_4^-$$

$$RCO_2H_2^+ + H_2SO_4 = RCO^+ + H_3O^+ + HSO_4^-$$

Confirming this, Newman found that the presence of HSO_4^- ion partially inhibits acylization even in mesitoic acid.

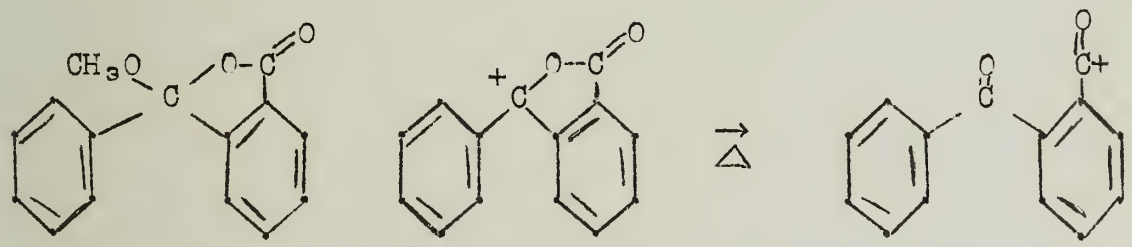
Until recently, it was believed that the effect of the alcohol group in an ester had no effect on acylization. However, Kuhn and Corwin (9) have found that such esters as cellosolve benzoate and trichloroethyl acetate have μ values of 4.4 and 3.5. Furthermore, when the sulfuric acid solutions of these esters were diluted with alochol, the free acid was obtained. The investigators postulated that the benzoyl and acetyl cations are unstable in sulfuric acid and react as follows:

$$RCO^+ + HSO_4^- = RCOOSO_3H$$

As proof, they prepared acetyl and benzoyl sulfate and found that they react with alcohols to form free acetic and benzoic acid.

Kuhn and Corwin also found that anisic acid and its esters form acyl cations (the first known instance of acylization without ortho substituents), while Corwin and Straughn (10) have investigated selective acylization in pyrryl dicarboxylic esters.

Newman (6,7,8) has investigated o-benzoyl benzoic acid, which is unusual in that the free acid and its pseudo methyl ester (I) undergo acylization while the normal ester does not. Newman postulates a cyclic acyl cation (II) because the pseudo ester is obtained when the sulfuric acid solution of the acid or pseudo ester is diluted with methanol. He further postulated that a new



I II III

acyl cation (III) of higher energy content is obtained upon heating (II). This would explain why anthraquinone is not obtained in the cold, since (III) can react to form the quinone while (II) cannot. Newman also found that both the normal and pseudo methyl esters of 2-benzoyl-6-methyl-benzoic acid are acylized.

Smith and Smith (11) recently attempted to prepare the methyl ester of triphenylacetic acid by Newman's method, but the product obtained was the methyl ether of triphenylcarbinol. Presumably the intermediate acyl cation $(C_6H_5)_3CCO^+$ is formed, which then loses carbon monoxide to form the triphenyl carbonium ion. However, this reaction suggested a simplified procedure for the preparation of such ethers from triphenyl carbinol in concentrated sulfuric acid (yields 86-97%).

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Reported by R. G. Bannister
December 17, 1948

ENOLIZATION TENDENCY IN AROMATIC β-DIKETONES

When there is a methylene group situated between two carbonyl groups in a 1,3-diketone the existence of tautomeric forms is very probable. The nature of the structure of the tautomeric enolic form, if stable, depends largely upon the groups or radical attached directly to the carbonyls.

In the aromatic series it has been shown that substitution in the ring influences the enolized form, also certain relationships as to o, m or p-substitution in the ring have been pointed out (1,2,8). Attempts have been made to explain these substitution effects by the various theories of electron releasing tendency and electron attracting ability of the substituent groups.

TABLE I

	Compound	Enolized Form
1.	p-bromodibenzoylmethane	resonating forms
2.	p-methoxydibenzoylmethane	p-CH_3O-C_6H_4-C(=O)-CH=C(OH)-C_6H_5
3.	m-nitrodibenzoylmethane	m-NO_2-C_6H_4-C(=O)-CH=C(OH)-C_6H_5
4.	3-nitro-4' methoxydibenzoylmethane	3-NO_2-C_6H_4-C(=O)-CH=C(OH)-C_6H_4-OCH_3-4
5.	Benzoylmesitoylmethane	C_6H_5-C(OH)=CH-C(=O)-Mes
6.	o-methoxybenzoylmesitoylmethane	O-CH_3O-C_6H_4-C(OH)=CHC(=O)-Mes
7.	Mesitoyl-o-nitrobenzoylmethane	Mes-C(=O)-CH=C(HO)-C_6H_4-NO_2-O
8.	Mesitoyl-m-nitrobenzoylmethane	Mes-C(OH)=CH-C(=O)-C_6H_4-NO_2-m
9.	Mesitoyl-p-nitrobenzoylmethane	Mes-C(OH)=CH-C(=O)-C_6H_4-NO_2-p

The comparitive substituent effect in the direction of enolization can be seen from this table.

GENERAL METHOD OF SYNTHESIS OF β-DIKETONES

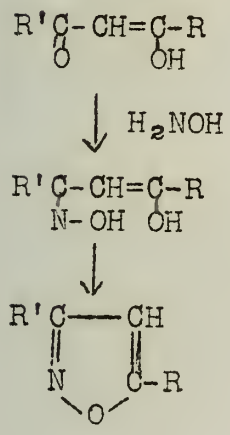
$$RC(=O)H + CH_3C(=O)R' \xrightarrow[10\%]{NaOH} RCH=CHC(=O)R' \xrightarrow{Br_2} RCH(Br)-CH(Br)-C(=O)R'$$

$$RCH(Br)-CH(Br)-C(=O)R' \xrightarrow{\text{KOH in methanol}} [RC\equiv CHC(=O)R'] \xleftarrow{H^+} RC(OCH_3)=CH-C(=O)R' \rightleftarrows RC(OH)=CH-C(=O)R'$$

This method is well known and the mechanism is firmly established (3,4). Isomeric β-unsaturated ketones may be prepared in this way by the proper selection of aldehyde and ketone for condensation.

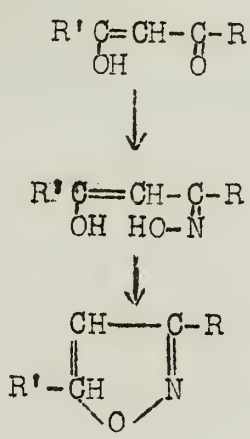
GENERAL METHOD OF CHARACTERIZATION (3,5)

Series A

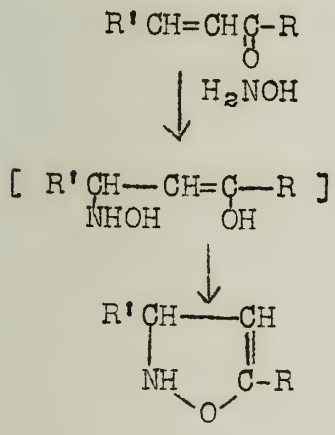


Isomeric isoxazoles

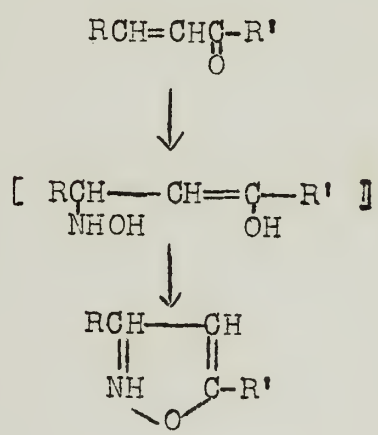
Series B



The enolic compounds listed in Table I gave rise to a single isoxazole, indicating only one form. The structure of the isoxazole was determined by isoxazoline formation and oxidation according to the following scheme (6):



Isomeric isoxazolines



These isomeric isoxazolines are then oxidized to the isoxazoles. The position of the nitrogen is thus fixed and the direction of enolization of the β-diketone shown.

Compounds 7, 8, 9 in Table I, because of the presence of the mesityl nucleus together with a nitro group substituted in the other ring, exhibit some interesting and varied properties. (7,9).

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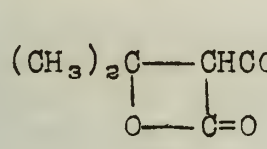
Reported by Alfred S. Spriggs
January 7, 1949

THE STRUCTURE OF MELDRUM'S ACID

In 1908, Meldrum (1) reported that he had treated a suspension of malonic acid in acetic anhydride-sulfuric acid mixture with acetone and obtained a crystalline product melting at 97°.

$$(CH_3)_2CO + CH_2(COOH_2 \xrightarrow[\text{Room temp.}]{Ar_2O\text{-}H_2SO_4} H_2O + C_6H_8O_4$$

This compound proved to be a monobasic acid, the properties of which did not correspond to those of the previously prepared (2,3,4) isopropylidene malonic acid or β-methyl crotonic acid, so Meldrum concluded that the compound must be β,β-dimethyl-β-propiolactone-α-carboxylic acid (I).



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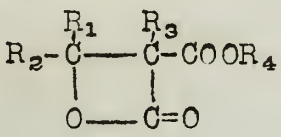
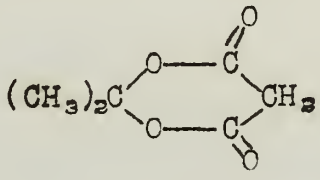


Ia



II

Since that time his conclusion had been accepted as demonstrated fact by numerous investigators until Davidson and Bernhard (5) recently proposed that the properties of the compound did not justify Meldrum's conclusion. They have pointed out the fact that the reactions of Meldrum's acid indicate that the methylene group of malonic acid still exists in the molecule, and that the compound is actually isopropylidene malonate (II).

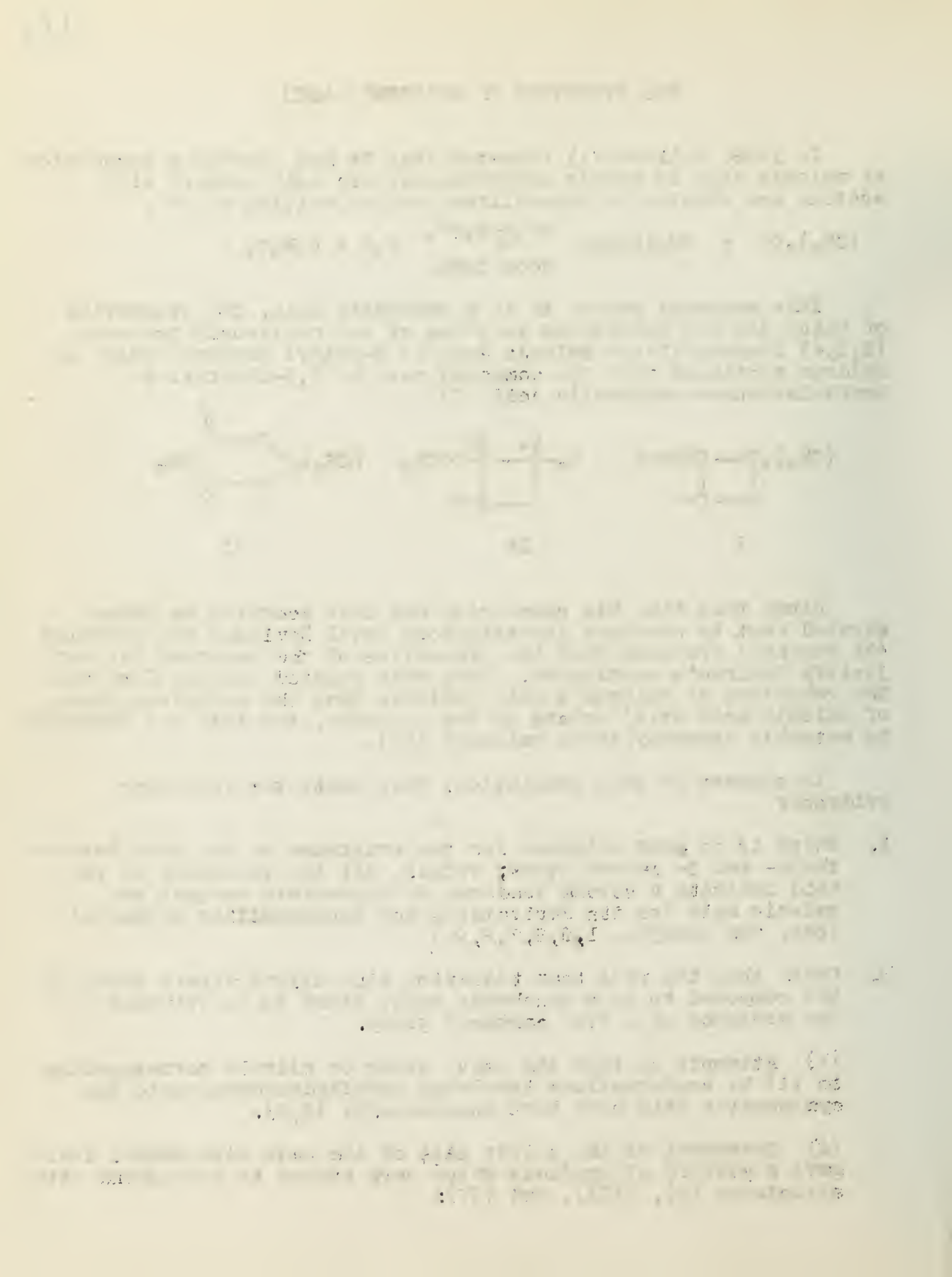
In support of this conclusion, they quote the following evidence:

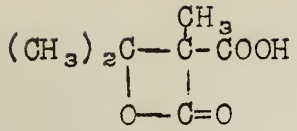
A. There is no good evidence for the existence of the bond between the α- and β- carbon atoms; rather, all the reactions of the acid indicate a strong tendency to regenerate acetone and malonic acid (or its derivatives and decomposition products). (See, for example, 1,5,6,7,8,9.)

B. Other than the fact that titration with dilute alkali shows the the compound to be a monobasic acid, there is no evidence for the presence of a free carboxyl group.

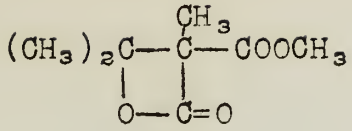
(1) Attempts to form the ethyl ester or nitrile corresponding to (I) by condensations involving ethylhydrogenmalonate and cyanoacetic acid have been unsuccessful (6,9).

(2) Treatment of the silver salt of the acid with methyl iodide gave a mixture of products which were stated to correspond with structures (I), (III), and (IV):

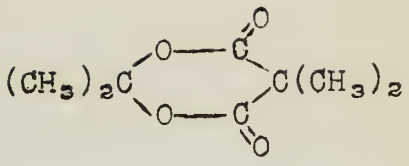




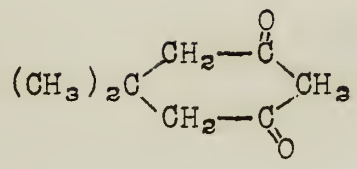
III



IV



V



Va

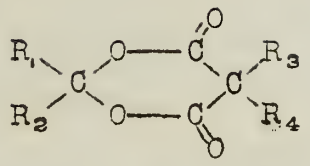
No evidence was presented in support of structure (IV), but it was reported that pyrolysis of this derivative yielded acetone, carbon dioxide, and dimethylketene (6,13,16). On the basis of this fact, Davidson and Bernhard theorized that the compound represented by (IV) is actually isopropylidenedimethylmalonate (V).

C. Hydrolysis of the dimethyl derivative (V) with dilute hydrochloric acid gives high yields of dimethylmalonic acid, whereas structure (IV) would be expected to give monomethylmalonic acid (5).

D. Meldrum's acid has several properties which are the same as those of methone (Va), to which the proposed structure (II) is analogous.

	Meldrum's acid	Methone
Ka	8.0×10^{-6}	6.3×10^{-6} (10)
Reaction with:		
(a) $NaNO_2$ (11)	gives purple product	gives violet salt of nitroso derivative.
(b) Br_2	reacts with 2 moles	reacts with 2 moles (10
(c) RCHO	gives precipitates in the cold	gives precipitates in the cold (12)

Numerous other compounds with structures represented by (Ia) have been synthesized by the investigators whose reports have been quoted here, usually by Meldrum's method or by Ott's modification. Experimental data on these compounds are so incomplete that it is not possible to reach a definite conclusion at this time, but their reported properties have all been the same as those of Meldrum's acid. In view of this fact, it seems that these compounds should be thoroughly investigated on the basis of the strong possibility that they have structures of the cyclic type (VI).



VI

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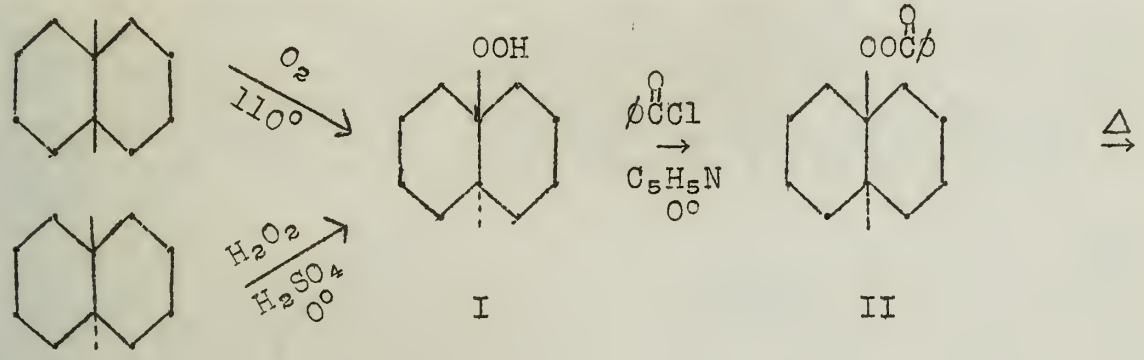
Reported by Richard H. Tennyson
January 7, 1949

REARRANGEMENT OF SOME PEROXIDE ESTERS

Criegee (1,2) in 1944 reported that the benzoate (II) of decalin hydroperoxide (I) rearranged into the isomeric benzoate (III) on warming and that alkaline saponification of III yielding cyclodecanol-6-one (IV), thus providing a convenient route from decalin to the cyclodecane series.



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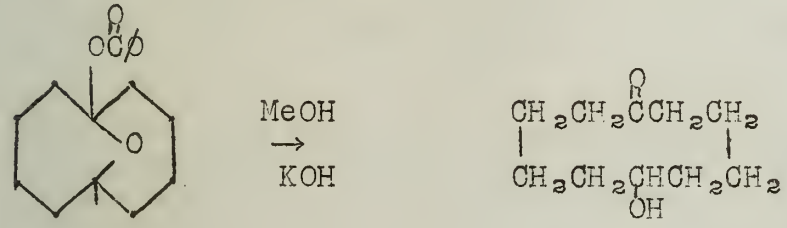


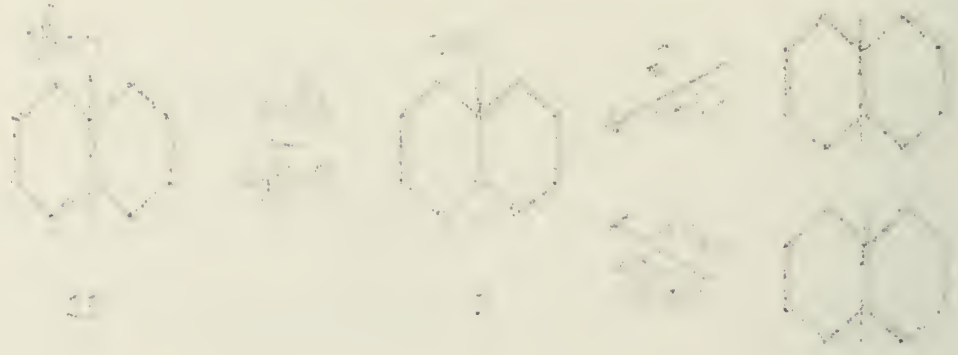
III IV

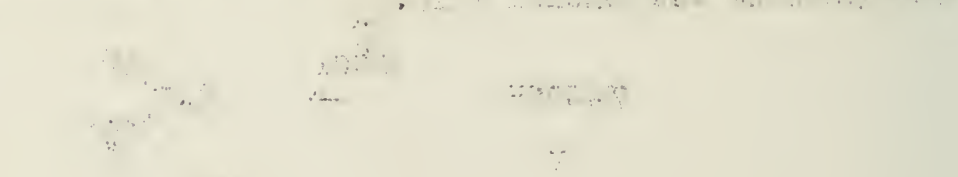
Wieland and Maier (3) had previously described a similar rearrangement in the attempted preparation of benzoyl triphenylmethyl peroxide. When trityl hydroperoxide (V) was treated with benzoyl chloride in the presence of sodium hydroxide, the only product obtained had none of the characteristics of a peroxide and subsequently was assigned the structure of the benzoylated hemiacetal of benzophenone and phenol (VI).

V VI

More recent work by Criegee (4) has been undertaken to study the mechanism of the rearrangement of esters of decalin hydroperoxide.

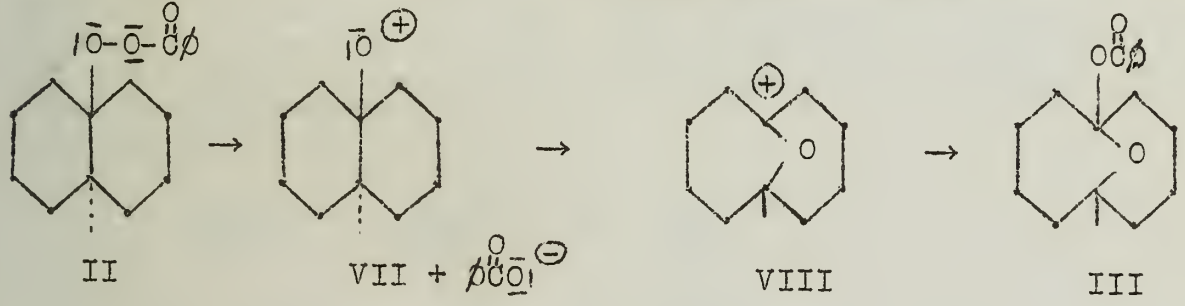
The rearrangement has been shown to be dependent on three factors: 1) the strength of the acid in the ester, 2) the acidity of the peroxide, and 3) the solvent used. It was found that the stronger the acid used for esterification, the greater the tendency for rearrangement. Of the numerous hydroperoxides prepared, only





trityl and decalin hydroperoxide fail to form sodium salts with 30% sodium hydroxide (5), thus indicating their weak acidity. Because these two hydroperoxides are the only ones for which the rearrangement has been demonstrated, it is assumed that the rearrangement takes place only if the peroxide is a very weak acid. In general, the rearrangement is much more rapid in polar solvents.

The experimental facts indicate that the cause of the rearrangement may lie in a strong polarization of the O-O bond in the peroxide ester, the decomposition of which results in the formation of a benzoate anion and a species which contains an electronically deficient oxygen atom. A Whitmore shift produces the carbonium ion VIII, which combines with the benzoate anion to yield the rearranged ester III.

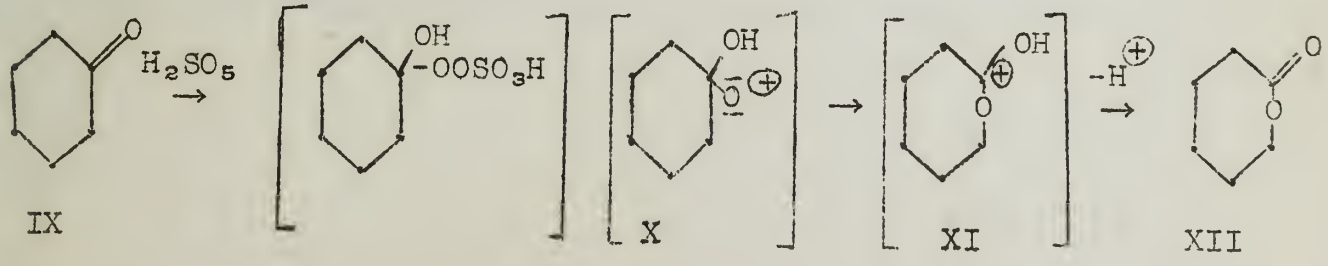


II VII + ϕCO_2^- VIII III

In accord with all carbonium-like processes, complete dissociation of the benzoate anion is not assumed. However, influences which favor a polarization of the O-O bond in the direction of such a dissociation, i.e. a strong acid used in the esterification, a weakly acidic peroxide, and a polar solvent, facilitate the rearrangement.

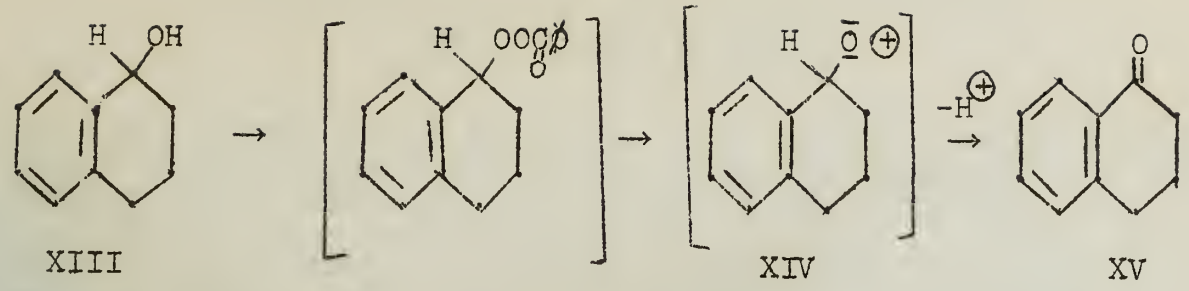
Several other reactions may be considered as involving cationic oxygen in an intermediate state.

1) If the conversion of cyclic ketones to lactones with Caro's acid involves first the addition of the reagent to the carbonyl double bond as postulated by Stoll (6), the formation of the intermediate X would follow analogously to that from decalin peroxide benzoate. Rearrangement of X to the carbonium ion XI, followed by the loss of a proton would yield the lactone (XII).



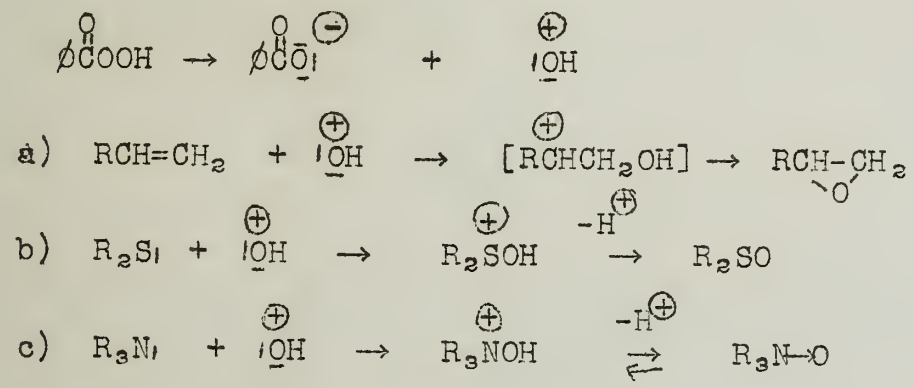
IX X XI XII

2) Tetralin hydroperoxide (XIII) on attempted benzoylation loses a molecule of water to form α-tetralone (XV). The intermediate XIV is stabilized by the loss of a proton.



XIII XIV XV

3) The derivatives of hydrogen peroxide which are the strongest oxidizing agents in the cold are the peracids. Presumably this is due to the strong electron attracting nature of the carbonyl group which tends to weaken the O-O bond and thus facilitates the formation of + O-H. The assumption of such an intermediate will account for the ready formation of epoxides, sulfoxides and amine oxides when olefins, thioesters, and tertiary amines are treated with peracids.



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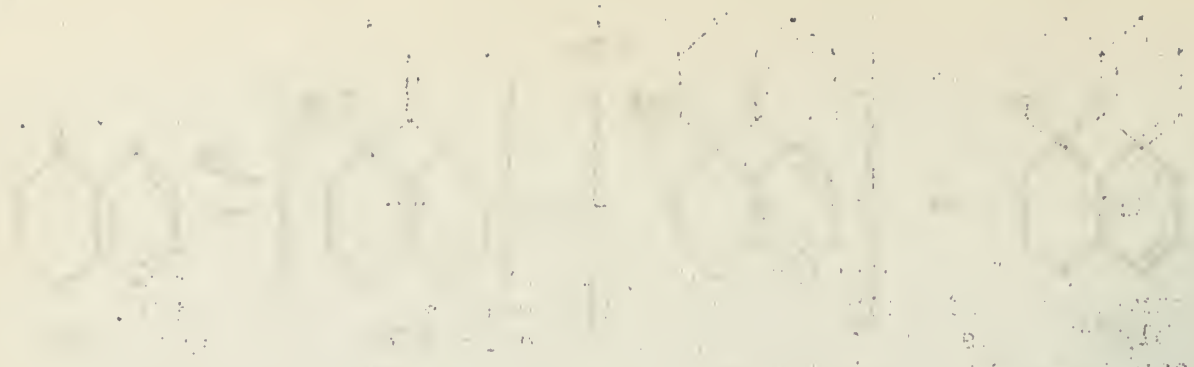
Reported by Jean V. Crawford
January 7, 1949



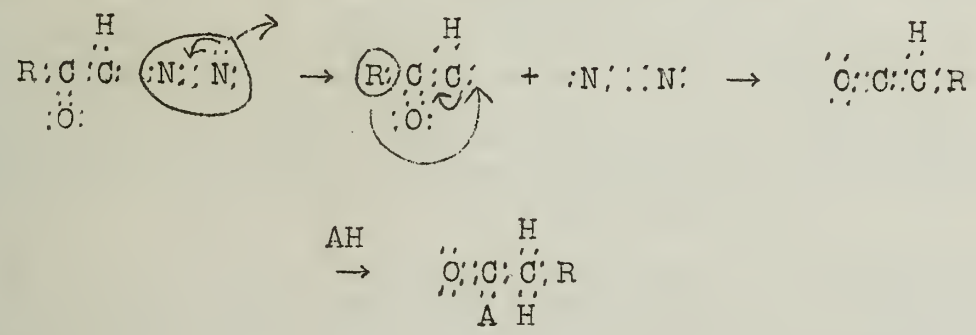
THE USE OF HIGHER DIAZOHYDROCARBONS IN THE ARNDT-EISTERT SYNTHESIS

The Arndt-Eistert synthesis (1,2) offers a means of converting a carboxylic acid into its next higher homologue or a derivative thereof. The following reactions are involved.

$$RCOOH \xrightarrow[\text{etc.}]{SOCl_2} RCOCl \xrightarrow{CH_2N_2} RCOCHN_2 \xrightarrow[Ag]{AH} RCH_2COA$$

Where A=HO, R'O, NH_2, or RNH

The accepted mechanism (2,3) for the last step of the synthesis is as follows.



On the basis of this mechanism the use of higher diazohydrocarbons, such as diazoethane or 1-diazopropane, in place of diazomethane would be expected to lead to carboxylic acids, or derivatives, bearing an alpha-alkyl substituent. It is rather surprising that until very recently there had been only one recorded attempt to extend the generality of the reaction in this manner. In 1941 Eistert (4) reported the successful rearrangement of the diazoketone from p-nitrobenzoyl chloride and diazoethane to the anilide of alpha-(p-nitrophenyl)propionic acid.

This year Wilds and Meader (5) have reported the successful use of diazoethane and diazopropane in the Arndt-Eistert synthesis of a variety of carboxylic acids. In connection with this work a new and more dependable method for rearranging diazoketones was developed.

In the early stages of the work it was learned that the diaketones obtained from diazoethane would not consistently undergo rearrangement under the usually employed conditions, i.e., in the presence of colloidal silver in methanol. The rearrangement could be effected, however, by using the already known procedure of dropping the diazoketone into boiling aniline (1). This method had the disadvantage that the difficultly hydrolyzable anilides of the rearranged acids were obtained, and so Wilds and Meader devised a new procedure. According to their innovation the diazoketone is heated to 170-180° in a mixture of gamma-collidine and benzyl alcohol, whereupon the easily saponified benzyl esters

of the rearranged acids are formed. This method not only made practicable the use of diazoethane and diazopropane in the Arndt-Eistert synthesis but was also found to be an improvement over the colloidal silver-methanol procedure when applied to diazoketones made from diazomethane. The new method gave more consistent results.

It was found that other tertiary amines and high boiling alcohols could be substituted for gamma-collidine and benzyl alcohol without greatly lowering the yields in the rearrangement, and the reaction temperature proved not to be highly critical.

In preparing diazoketones from acid chlorides and higher diazohydrocarbons the reaction temperature had to be controlled more carefully than when diazomethane was used, and even under optimum conditions the diazoketones often were not completely crystalline, part of the product appearing as an oil. For instance, in the preparation of 1-p-chlorobenzoyl-1-diazoethane the most suitable temperature was found to be -20°. Changing the temperature by 10°, up or down, caused the yield of crystalline diazoketone to fall from 71 to 61%. Diazomethane, on the other hand, gave practically quantitative yields of crystalline diazoketones at temperatures ranging from 0° to room temperature.

In the following tables are presented the results obtained when Wilds and Meader subjected various acids to the Arndt-Eistert reaction using diazoethane and diazopropane and carrying out the rearrangement of the diazoketones in gamma-collidine-benzyl alcohol mixture.

TABLE I

Arndt-Eistert Synthesis Using Diazoethane

Starting acid	Yield of diazoketone	Yield of rearranged acid based on starting acid
p-Chlorobenzoic	71% + 7% oil	61-70%
p-Toluic	51% + 16% oil	55-70%
p-Nitrobenzoic	76%	50%
1-Naphthoic	(oil)	58%
2-Naphthoic	60%	40-48%
β-1-Naphthyl-propionic	(oil)	47%

TABLE II

Arndt-Eistert Synthesis Using Diazopropane

Starting acid	Yield of diazoketone	Yield of rearranged acid based on starting acid
p-Chlorobenzoic	(oil)	58%
p-Nitrobenzoic	81%	45%
p-Anisic	(oil)	37%

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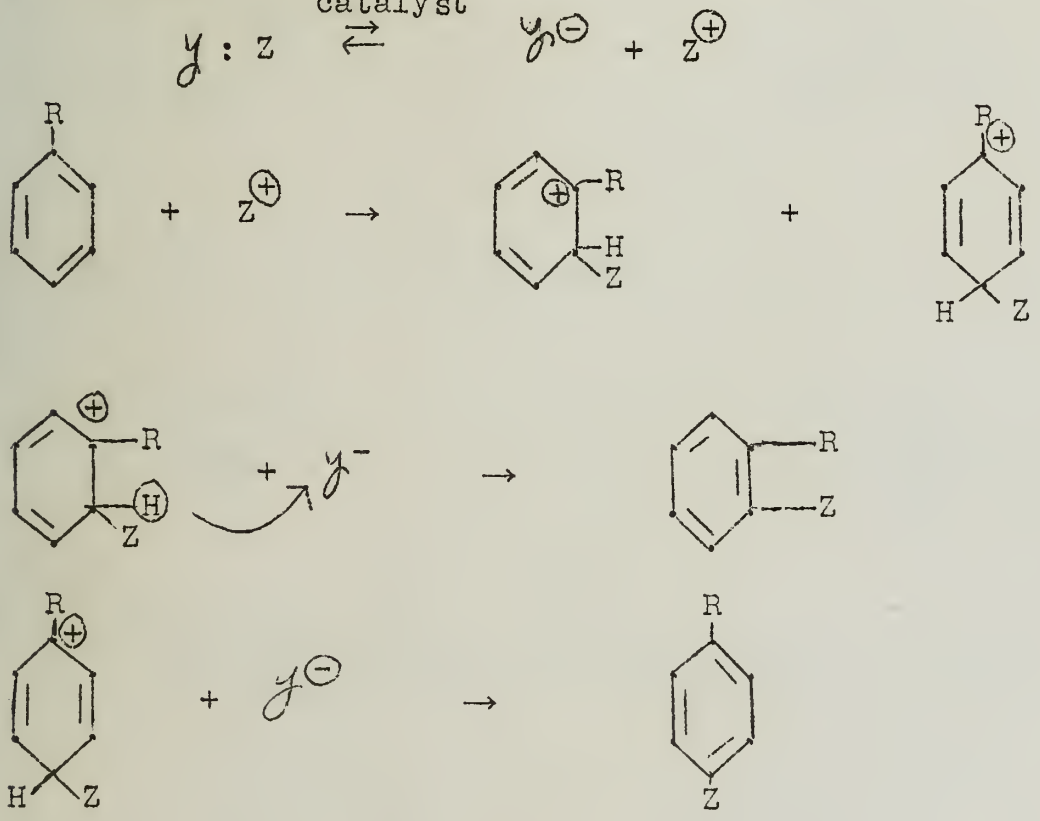
Reported by Paul M. Mader
January 14, 1948

THE SIGNIFICANCE OF THE TRANSITION STATE IN AROMATIC SUBSTITUTION

Recently it has been suggested (1) that the most important consideration in aromatic substitution is the energy content of the intermediates through which the reaction progresses. More commonly, the tacit assumption is made that substitution occurs at the point of highest electron density and attention has been focused upon the factors which produce such charges. Consideration of the energy of the transition state, however, permits the correlation of several seemingly unrelated phenomena, including: a) the predominance of the para isomer in ortho-para substitution in the benzene series; b) the almost complete inertness of the 3-position in such compounds as β-naphthol and isoquinoline; and c) the position to which entering groups are directed in polynuclear aromatic and heterocyclic compounds.

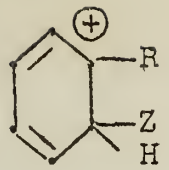
It is generally accepted that aromatic substitution proceeds as follows: (2)



The transition state theory proposes that the reaction will proceed through the intermediate (transition state complex) which is most readily formed (the one with the lowest energy content).

Examples: (The intermediate of the favored product is underlined.)

A. Para substitution predominates over ortho.



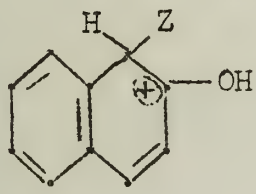
III

IV

Explanation: The p-quinoid complex is more readily formed by analogy with the fact that p-quinone has a lower energy content than o-quinone. (As shown by their oxidation-reduction potentials. (3,1))

B. Position of substitution in other aromatic systems.

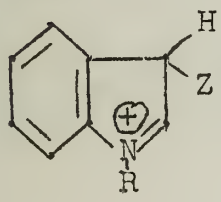
1. The 3-position in β-naphthol is inert.



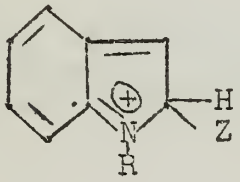
V

VI

2. The substitution of indole.

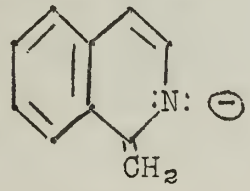


VII

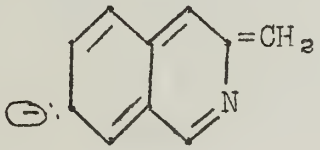


VIII

3. Reactivity if the the methyl groups in 1-methyl and 3-methyl isoquinoline.

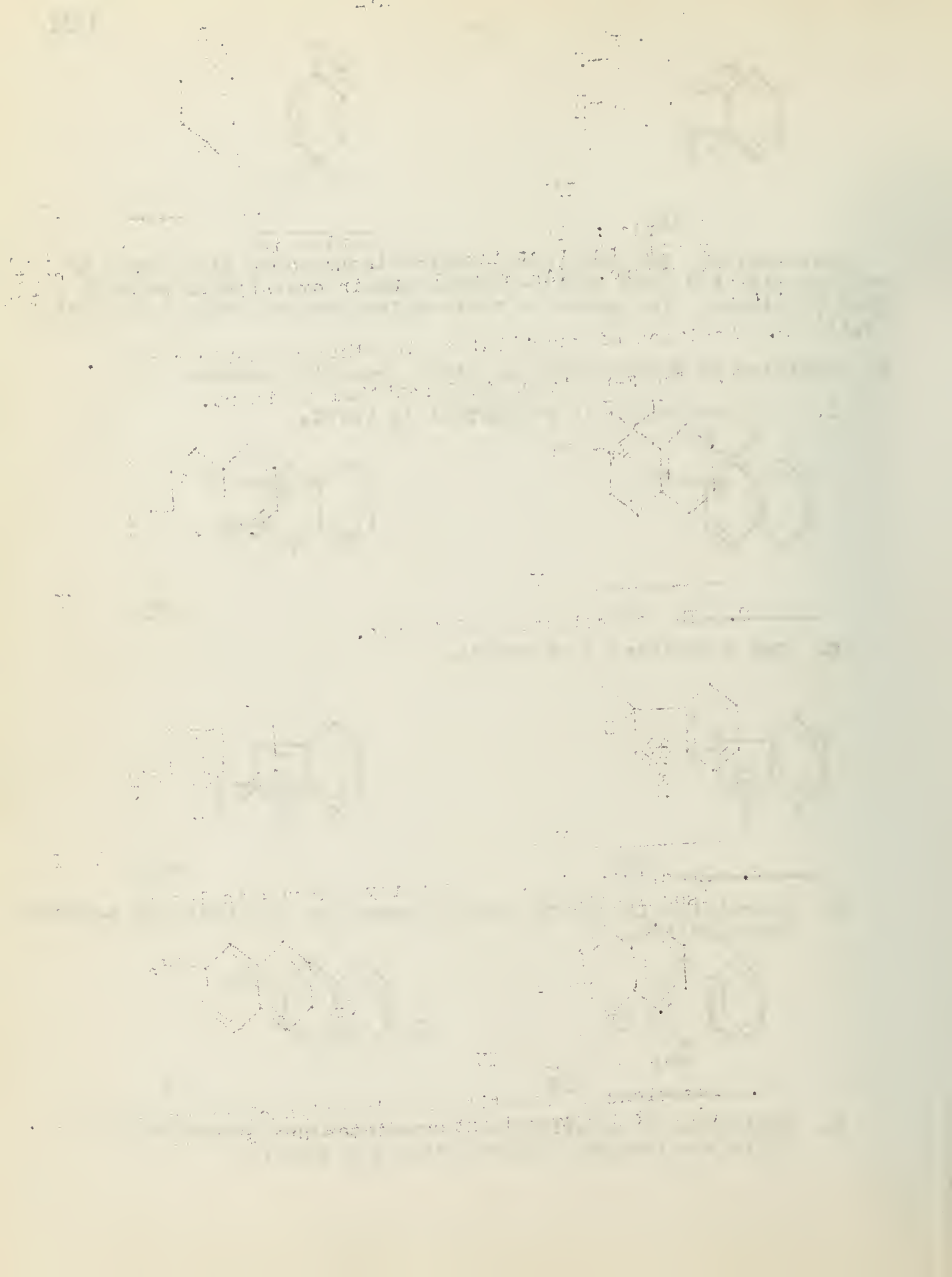


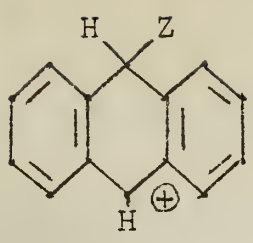
IX



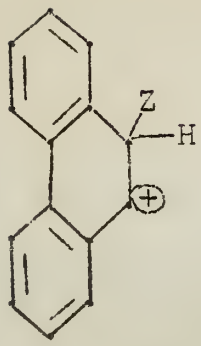
X

4. Positions of substitution in polynuclear hydrocarbons. (Only the favored intermediates are shown.)

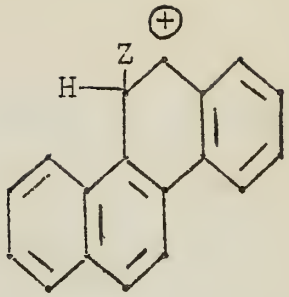




XI



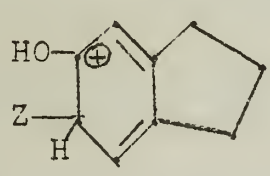
XII



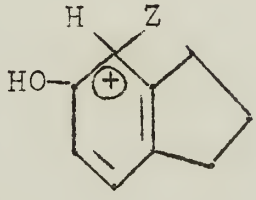
XIII

Explanation: Reaction occurs at such points that benzenoid resonance is interrupted in the fewest number of rings. (Note the similarity of Fries rule.) (4)

C. Substitution of 5-hydroxyindane.



XIV



XV

Explanation: XIV is favored because the bond common to both rings is stretched by the five membered ring to a length near that of a single bond. (5)

It has been suggested that free radical substitution can also be explained by similar considerations. It would not be surprising if elucidation of the free radical mechanism proved this so. (1,6)

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Reported by George R. Coraor
January 14, 1949

SEMINAR TOPICS

CHEMISTRY 435 II Semester 1948-49

THE NAPHTHENIC ACIDS

Reported by H. E. Baumgarten February 11, 1949

The naphthenic acids are saturated alicyclic acids, the majority of which have the empirical formulas, $C_nH_{2n-2}O_2$ and $C_nH_{2n-4}O_2$. They are probably naturally occurring constituents of all crude petroleum oils, occurring in amounts variously estimated as between 0.03 and 3% (1). The methods used for the separation of the naphthenic acids from petroleum, their purification, and their uses have been discussed in a review (1).

Structure Studies.

The first acidic compounds from petroleum were reported by Pebal (2) in 1860 (cf., however, (3)) and from that date until about 1930 the major contributions to the knowledge of the naphthenic acids structures were vague and often incorrect generalizations.

1. The Naphthene Nucleus.

As early as 1874 Hell and Medinger (4) suggested that the naphthenic acids have a cyclic nucleus. Markovnikov (5) related the acids to the cyclic hydrocarbons, the naphthenes, and was the first to call them "naphthenesauren." Actually most petroleum acids are mixtures of aliphatic (fatty) and alicyclic (naphthenic) acids in which the former usually occur to the extent of approximately 5%, the exact amount depending on the source and treatment of the crude acids. In general crude naphthenic acids contain aliphatic acids up to C_{10}, monocyclic naphthenic acids from C_6 to C_{13}, bicyclic naphthenic acids above C_{12}, and polycyclic naphthenic acids above about C_{14} (some as high as C_{29}) (6,7,8,9,10,11).

2. Size of the Ring.

For many years some workers believed that there were either very few or no natural naphthenic acids having the six-membered ring (1,12), but today we know from complete structural studies that both cyclopentane and cyclohexane derivatives are found in the naturally occurring naphthenic acids. Apparently five-membered rings predominate. Goheen (11) reports that very high molecular weight naphthenic acids contain two to three five-membered rings per molecule. As yet no one has reported the presence of the six-membered ring in the polycyclic naphthenic acid molecule.

3. Linkage of the Carboxyl.

Primary, secondary, and tertiary acids have been isolated and identified from naphthenic acid fractions. In general primary and secondary acids predominate (6,7,8) with the primary probably the more abundant of the two (cf.,however, (6)). For new structure studies the methods used for determining the linkage of the carboxyl are of considerable importance. The method of von Braun (7,13) is probably the most satisfactory.

(a) $RCH_2CONHR' + 3PCl_5 \rightarrow RCCl_2\overset{NR'}{\overset{\|}{C}}-Cl + POCl_3 + 2PCl_3 + 3HCl$

$RCCl_2\overset{NR'}{\overset{\|}{C}}-Cl + H_2O \rightarrow RCCl_2CONHR' + HCl$

(b) $R_2CHCONHR' \xrightarrow[2.\ H_2O]{1.\ 2PCl_5} R_2CClCONHR'$

(c) $R_3CHCONHR' \xrightarrow[2.\ H_2O]{1.\ PCl_5} R_3CCONHR'$

R = aliphatic or naphthenic

R' = ethyl, methyl, or phenyl

The methods of Chichibabin (6) and Lapkin (8) are less satisfactory. The method of Whitmore and Crooks (14) has given erroneous results in the naphthenic acid series (15).

Although all of the primary acids identified to date have been acetic acid derivatives, von Braun (7,13) has presented evidence that there may be as many as three methylene groups between the ring and the carboxyl in some naphthenic acids, i.e., the structure $-CH_2CH_2CH_2CO_2H$.

$$C_9H_{17}COOH \xrightarrow[2.\ EtOH\ \ 3.\ \emptyset NEt_2\ \ 4.\ KOH + H_2O]{1.\ P + Br_2} C_7H_{13}CH=CHCOOH \xrightarrow{H_2SO_4} [C_6H_{11}CH=CHCH_2COOH] \rightarrow$$

$$C_6H_{11}CH(-O-)CH_2-CH_2-C=O \xrightarrow{HNO_3} HO_2C-CH_2CH_2-CO_2H$$

(yield of lactone: 20% overall)

4. Isomers.

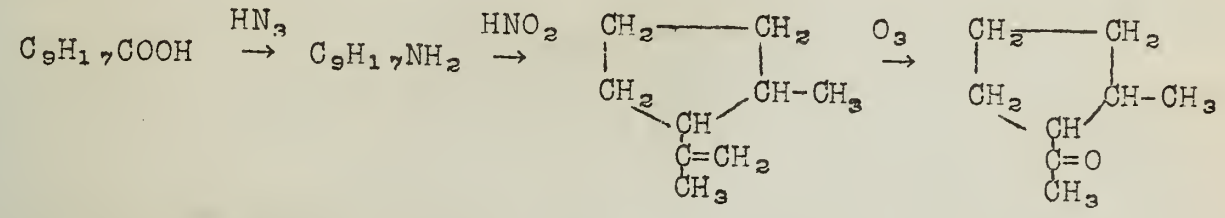
A tremendous number of structural isomers are possible for most of the naphthenic acids and the indications are that a large of such isomers do exist. Both optical (16) and cis-trans (17) isomers occur in the natural naphthenic acids.

5. The Individual Acids.

At the present time about a dozen naphthenic acids have been isolated from petroleum and identified more or less satisfactorily. Some of these have been isolated and identified through rather conventional analytical procedures; others have been identified through degradative studies. All of the acids whose structures are reasonably well known are listed in Table II. Some of the more interesting studies are listed here.

a. "trans-"2,2,6-Trimethylcyclohexanecarboxylic Acids.

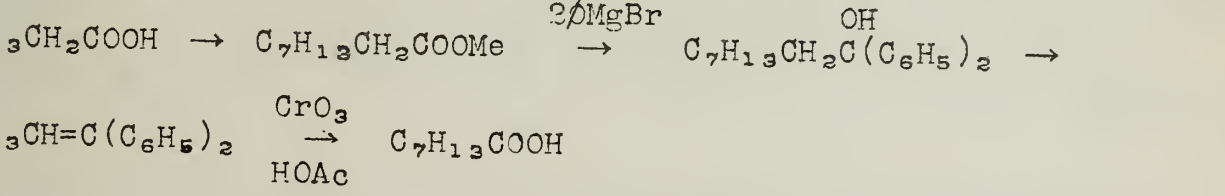
Shive, Horeczy, Wash, and Lochte (15) isolated a solid acid (m.p. 83° C.) from California petroleum. Application of the von Braun method showed it to be secondary. The acid was degraded as follows:



The ketone was identified through comparison with an authentic sample. Since a Dem'yanov rearrangement was possible in the nitrous acid treatment, all of the amines which could rearrange (by Whitmore' theory (18)) to give the olefin indicated were formulated. Then all of the acids corresponding to these amines were synthesized. Final identification was through comparison of the natural and the synthetic acids.

b. 2,3-Dimethylcyclopentaneacetic Acid.

Ney, Crouch, Rannefeld, and Lochte (17) isolated this acid through fractional distillation of the methyl ester and fractional neutralization of the acid. The von Braun method indicated a primary acid. The acid was degraded by the Barbier-Wieland method following the directions of Skraup and Schwamberger (19):



The acid of one less carbon atom than the original was identified through comparison with an authentic sample. 2,3-Dimethylcyclopentaneacetic acid was synthesized and was shown to be identical with the original acid.

c. 3,3,4-Trimethylcyclopentaneacetic Acid.

von Braun (7,20) isolated a C_{10} fraction of naphtheni acids from various sources. He was unable to purify it satisfactoril through distillation of the acids or their methyl esters. Purification through distillation of the amine (Schmidt reaction) and recrystallization of the amine acid oxalate was more satisfactory. The acid was degraded as follows:

$$C_9H_{17}COOH \xrightarrow{HN_3} C_8H_{15}CH_2NH_2 \rightarrow C_8H_{15}CH_2(CH_3)_3OH \xrightarrow{KOH} \rightarrow$$

$$C_9H_{16} \xrightarrow{O_3} \begin{matrix}\text{Aldehydes}\\ \text{Ketones}\\ \text{Acids}\\ \text{Condensation products}\end{matrix} \xrightarrow{H_2O_2} C_8H_{14}O_2 + C_8H_{14}O$$

One-third of the final product was the ketone, $C_8H_{14}O$, which was purified through distillation and crystallization of the semicarbazone. The ketone reacted with two moles of p-nitrobenzaldehyde to give a di-p-nitrobenzal derivative, indicating the structure $-CH_2-CO-CH_2-$. This bit of evidence eliminated all but eleven of the eight carbon ketones. von Braun was able to synthesize or obtain data on only ten of these ketones. von Braun's ketone and its derivatives did not correspond to any of these ten ketones, so by elimination von Braun concluded that his ketone must be the ketone he could not synthesize, 3,3,4-trimethylcyclopentanone. From the purified ketone he regenerated the original acid (through a Reformatsky reaction, followed by dehydration, then reduction). For ketone properties see Table I.

In 1942 Buchman and Sargent (21) were able to synthesize 3,3,4-trimethylcyclopentanone by two independent routes (the product of the second route was identified in terms of the first). Comparison of their synthetic product with the degradation product of von Braun indicated to them that the two ketones could not be identical. Thus, they claimed von Braun's structure to be in error. For comparison of ketones see Table I.

In 1948 Mukherji (22) synthesized 3,3,4-trimethylcyclopentanone by a third route and obtained a ketone having very nearly the same properties as the von Braun ketone. The ketone was converted to the naphthenic acid by approximately the same route as that used by von Braun; the properties of the synthetic acid were very nearly identical with those reported by von Braun for the natural naphthenic acid. See Table I.

The von Braun ketone has been obtained as an impurity in the degradation products from a nine carbon naphthenic acid isolated from Aruba petroleum (23). A ketone that appears to be identical with the von Braun ketone was isolated from wood extracts by Pringsheim (24). See Table I.

TABLE I

Ketone Source	b.p.	m.p. Semicarbazone	m.p. Di-p-nitrobenzal	b.p. Oxime		
von Braun	172-174	162-163	188-190	116-20(14mm.)	1.4390	0.895
Buchman-Sargent	172-173	213.5-214.0	α204.7-05.1 β202.0-02.5	(m.p.=99.8-100.0)	1.4386*	0.892
Mukherji	174	172	190-191	---	---	---
Aruba acids	174.5	165.5-67	190-191	---	---	0.895
Pringsheim	60-63 (12 mm.)	168	---	115 (12mm.)	1.4515	---

*Measured at 25°.

TABLE II

Naphthenic acid identified:	Reference
Cyclopentanecarboxylic acid	(17,25)
Cyclohexanecarboxylic acid (hexahydrobenzoic)	(6,17)
2-Methylcyclopentanecarboxylic acid	(17)
3-Methylcyclopentanecarboxylic acid	(17)
p-Hexahydrotoluic acid	(26,27*)
Cyclopentaneacetic acid	(17,25)
3-Methylcyclopentaneacetic acid	(17,25)
2,3-Dimethylcyclopentaneacetic acid	(17)
cis-2,2,6-Trimethylcyclohexanecarboxylic acid	(17)
trans-2,2,6-Trimethylcyclohexanecarboxylic acid	(15)
dl-Camphonanic acid (1,2,2-trimethylcyclopentanecarboxylic	(28)
3,3,4-Trimethylcyclopentaneacetic acid (?)	(7,20)

*Abstract of (27) called acid m-hexahydrotoluic acid, but properties listed were those of p-hexahydrotoluic acid; hence, the listing here.

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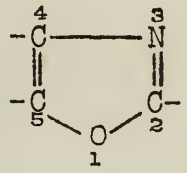
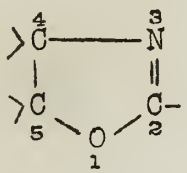
RECENT SYNTHESES OF OXAZOLES AND 2-OXAZOLINES

Reported by R. M. Ross February 11, 1949

Oxazoles and 2-oxazolines are represented by the following structural formulas:



an oxazole



a 2-oxazoline

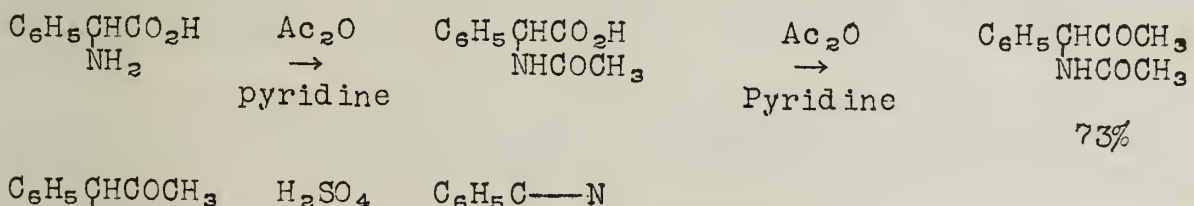
Interest shown in this class of compounds stems from their pharmacological action, their close relationships to naturally occurring products, and their unusual chemical properties. Although two review articles are available which discuss these heterocycles, the chemistry of oxazoles and 2-oxazolines is relatively incomplete.

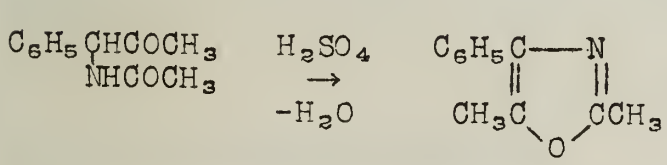
The remainder of this seminar will be limited to a discussion of some newer preparations of various oxazoles and 2-oxazolines. No attempt will be made to cover the entire synthetic field; for such information those interested are referred to Wiley's publications (1,2) and the Ph. D. theses of Leffler (3) and Sparks. (4)

Oxazoles

From α-Amino Acids

Starting with certain α-amino acids, Wiley (5,6) has modified Wrede's and Feurriegel's (7) early work to the point wherein quite respectable over-all yields of substituted oxazoles may be obtained.

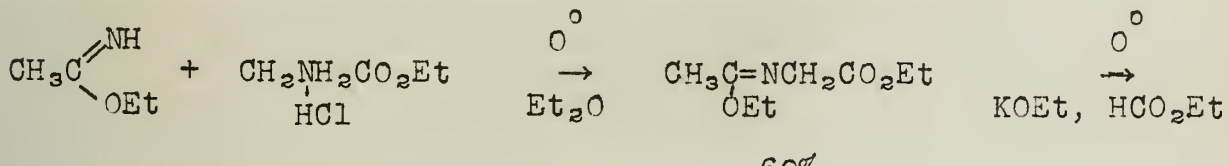




The final step in the process, i.e., dehydration of the N-acyl ketone, is a classical oxazole synthesis to be credited to Robinson (8). Using Wiley's procedure it is possible to prepare 2,5-dimethyl derivatives with varying substitutents on carbon atom four. The method is straightforward and easily carried out. Thus far, Wiley's procedure and that of Wrede and Feurriegel have been applied successfully to the following α-amino acids: glycine, alanine, valine, leucine, phenylalanine, tyrosine and glutamic acid; the use of asparagine, tryptophan and formyl glycine has been unsuccessful.

The Cornforth Synthesis (9)

Recently, Cornforth and Cornforth reported an excellent synthesis of oxazoles which not only offers good yields, but which shows promise of being applicable to a wide variety of substituted oxazoles. Starting with ethyl iminoacetate and ethyl glycinate hydrochloride, the following process leads to the formation of either 2-methyl-4-carbethoxyoxazole or 2-methyloxazole.



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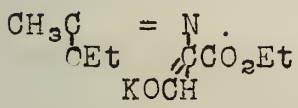

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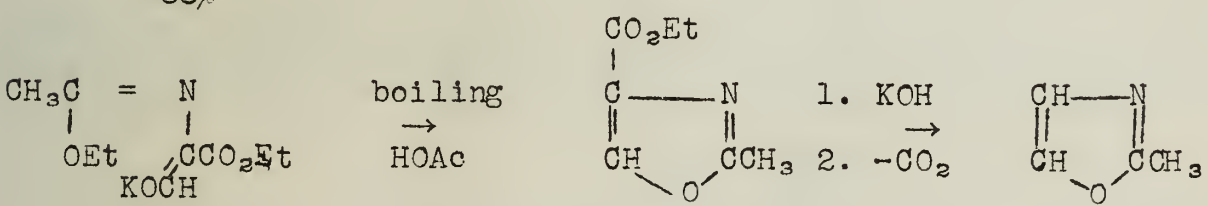


75% 80%

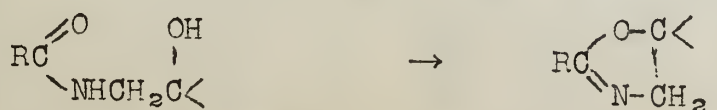
Until the Cornforth synthesis was reported, no preparation of oxazole itself had been effected. A minor variant of the procedure shown was employed by the Cornforths to yield the parent member of the series, oxazole. The method was extended to the preparation of 2-benzyl-4-carbethoxyoxazole (10) last year with good results. Because of this, the Cornforth synthesis would seem to be applicable to the synthesis of 2-phenyloxazole, which was obtained for the first time in 1942 by Cass, (11) in quite poor yields.

It should be pointed out that the intermediates in the Cornforth synthesis are attacked readily by moisture, air, etc. Therefore, no undue delay should be allowed in carrying out the preparation.

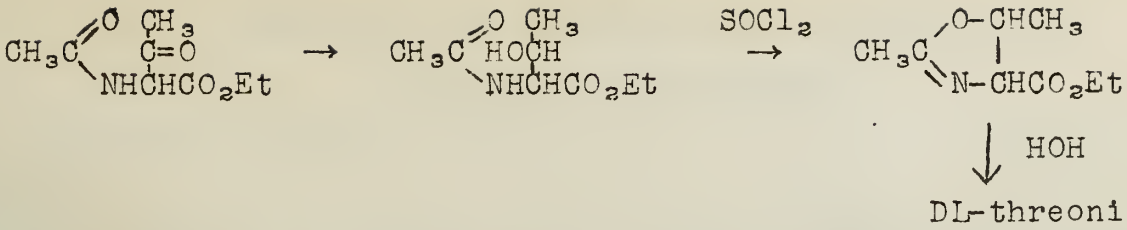
2-Oxazolines

From N-Acyl-β-Amino Alcohols

Cyclization of N-acyl-β-amino alcohols using sulfuric acid (12) or thionyl chloride (13) has resulted in the formation of a number of 2-oxazolines in very good yields.



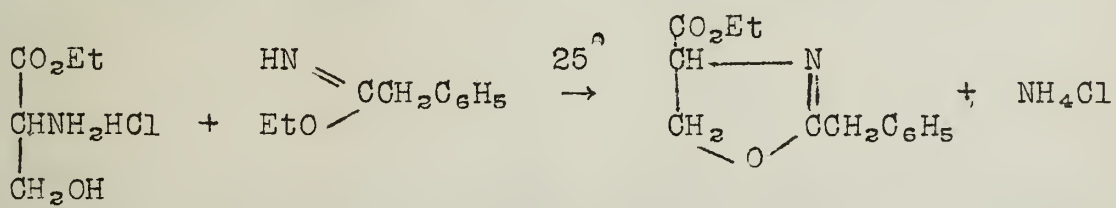
In 1948 an application of the thionyl chloride cyclization proved most fruitful in obtaining 2,5-dimethyl-4-carbethoxy-3-oxazoline, the key intermediate in a novel synthesis of DL-threonine. (14)



Ring closure by the sulfuric acid method is limited to amides in which the hydroxyl group is on a secondary or tertiary carbon atom. Amides containing hydroxyl groups on primary, secondary or tertiary carbon atoms, however, have been cyclized using thionyl chloride.(3) Some 2-oxazolines prepared by these routes are: 2,5-diphenyl-, 2-phenyl-5-carbomethoxymethyl-, 2-phenyl-4-carbomethoxymethyl-, and 2-p-nitrophenyl-5,5-dimethyl-.

From Imino Esters

Bockmühl and Knoll (15) reported successful condensations of imino ester hydrochlorides, derived from fatty acids, with α-amino-β-hydroxy compounds to produce substituted 2-oxazolines. A similar type of condensation has been applied recently to the preparation of 2-benzyl-4-carbethoxy-2-oxazoline (10) with good results.



Among the 2-oxazolines reported by the Bockmühl and Knoll process are 2-pentadecyl-5-diethylaminomethyl-2-oxazoline and 2-heptadecyl-5-diethylaminomethyl-2-oxazoline.

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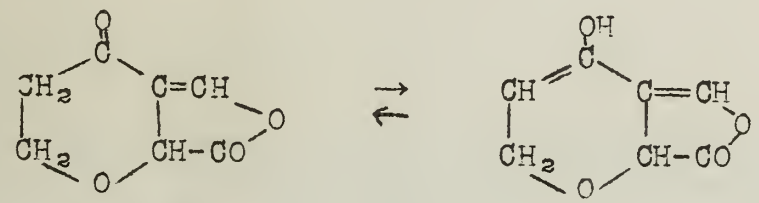
THE STRUCTURE OF PATULIN AND INVESTIGATIONS RELATING TO ITS SYNTHESIS

Reported by Robert A. Hardy, Jr. February 18, 1949

Patulin is a bactericidal compound obtained from a variety of mould organisms, and has been variously named according to the source from which it is isolated. Patulin from Penicillium patulum Banier (1), claviformin from Penicillium claviforme (2), clavacin or clavatin from Aspergillus clavatus (No. 129) (3), and expansine from Penicillium expansum Westl. (4) are the same compound as is conclusively shown by comparison of the physical and chemical properties of these substances (4,5,6,7). Structural investigations (1,4,8) have shown that this compound is probably anhydro-3-hydroxymethylenetetrahydro-γ-pyrone-2-carboxylic acid (I) and/or its keto-enol isomer (II).

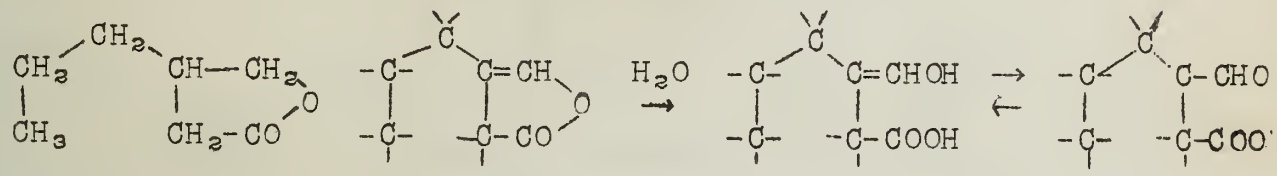


I II

Patulin, $C_7H_6O_4$, is an optically inactive, neutral compound which is soluble in water and most organic solvents. The presence of one carbonyl group is shown by the formation of a mono-phenylhydrazone and a mono-oxime (8). Patulin forms an easily hydrolyzed mono-acetate (1) (and other esters (4)); the mono-acetate when treated with a HCl solution of phenylhydrazine gives the same phenylhydrazone as that formed from patulin itself. A Zerewitinoff determination shows the presence of one active hydrogen per molecule. This evidence would indicate a keto-enol grouping. Decolorization of cold alkaline permanganate (1), bromine titration (4), and perbenzoic acid oxidation (4) show the presence of at least one double bond; one mole of bromine adds very rapidly followed by gradual utilization of 1-2 additional moles which may involve cleavage of the molecule. A freshly prepared aqueous solution of patulin does not give a coloration with $FeCl_3$, or a Schiff test, but reduces cold ammoniacal silver nitrate and Fehling's solution when warmed (1). After standing, the aqueous solution becomes acid and now gives a positive Schiff test and a typical enol reaction with $FeCl_3$ (4). No methoxyl groups could be found by Zeisel determination (4), and only traces of C-methyl were found by the Kuhn-Roth method (1,4). An attempted periodic acid oxidation showed that patulin does not contain two adjacent carbon atoms bound to oxygen.

The behavior of patulin in alkaline solution (1,4) suggests a lactone, as the ring is slowly opened forming an acid, and two moles of alkalai are consumed. Also, a lactone has been isolated

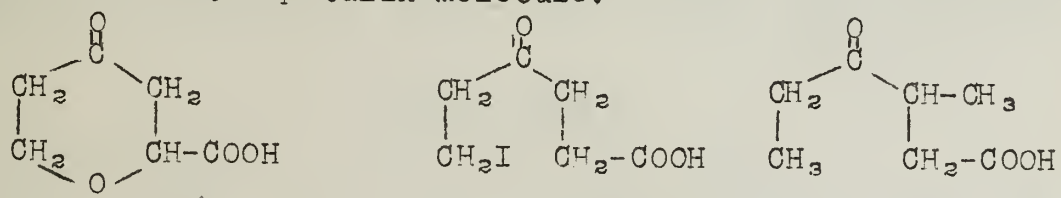
as a degradation product of patulin; hydrogenation followed by treatment with HBr and a second hydrogenation (to remove bromine) has yielded β-n-propyl butyrolactone (III) (8). The reduction of cold ammoniacal silver nitrate and a positive color test with sodium nitroprusside (Legal's test) (4) indicate that patulin contains an unsaturated lactone grouping, probably a $\Delta\beta,\gamma$-unsaturated-γ-lactone. Piecing this information together patulin must contain the grouping shown by IV, which is the lactone of a β-aldehydo acid.



III IV V VI

Opening the ring to form an acid which colors $FeCl_3$ solution and also gives a positive Schiff test would be represented by conversion to structures V and VI. The structure shown in IV would also explain the formation of formic acid on ozonolysis (4,8), the formation of a dimethone derivative (4), and the slow uptake of a second molecule of hydroxylamine during titration (4).

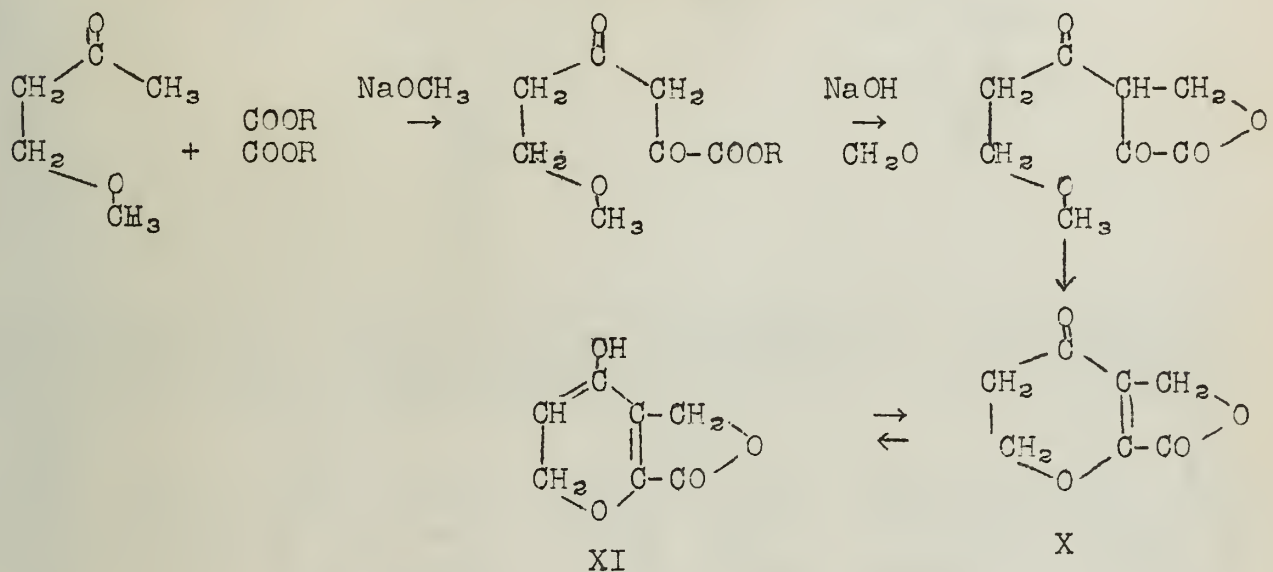
A study of the products of acid hydrolysis will settle the remaining structure of the patulin molecule, including the position of the free carbonyl group. Raistrick and co-workers (1) have isolated one mole of formic acid and a 10% yield of inactive tetrahydro-γ-pyrone-2-carboxylic acid (VII). This establishes the γ-pyrone ring and also the location of the free carbonyl group, and leads to structure I for the patulin molecule.



VII VIII IX

Other degradation products which have been isolated are γ-keto-ε-iodo-n-hexanoic acid (VIII) by treatment with concentrated HI (1), γ-keto-β-methyl-n-hexanoic acid (IX) (8), the lactone of β-methyl-γ-hydroxy-n-hexanoic acid (1) and β-methylcaproic acid (1). After ozonolysis (4,8) the products isolated include one mole of CO_2, one mole of formic acid, glycolic aldehyde, glyoxal, and oxalic acid. All of these degradation products are consistent with structures I and II for the patulin molecule.

Attempts at synthesis have not yielded a compound identical with the natural product, but have given an isomer which is an $\Delta\alpha,\beta$-unsaturated lactone while patulin contains the $\Delta\beta,\gamma$-unsaturated lactone ring. This synthesis has been carried out by two different groups of investigators (9,10) working independently. The general method involves the Claisen condensation of the appropriate methyl ketone to yield a 2,4-diketo ester, followed by treatment of the sodium enolate with formaldehyde. This gives the corresponding α-keto-β-acyl-butyrolactone which is cyclized to the dihydropyrone. The following reactions illustrate this synthesis:



The product of this synthesis is not identical with patulin. It has a lower melting point, very little bacteriostatic action compared to patulin, and differs from patulin in its chemical behavior (10). Attempts to form a mono-acetate under the same conditions which patulin forms a mono-acetate left X unchanged.

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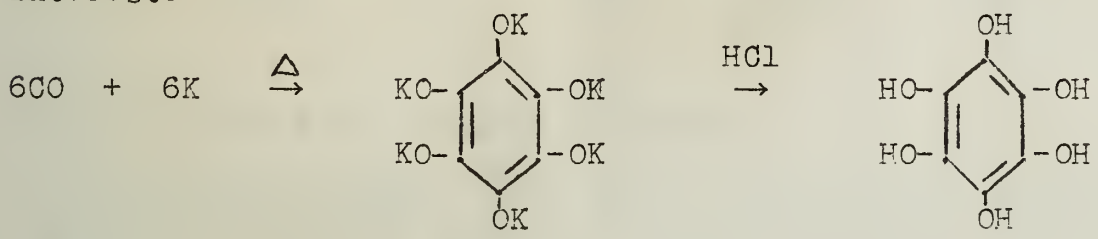
HEXAHYDROXYBENZENE (BENZENE HEXOL)

Reported by I. Moyer Hunsberger February 18, 1949

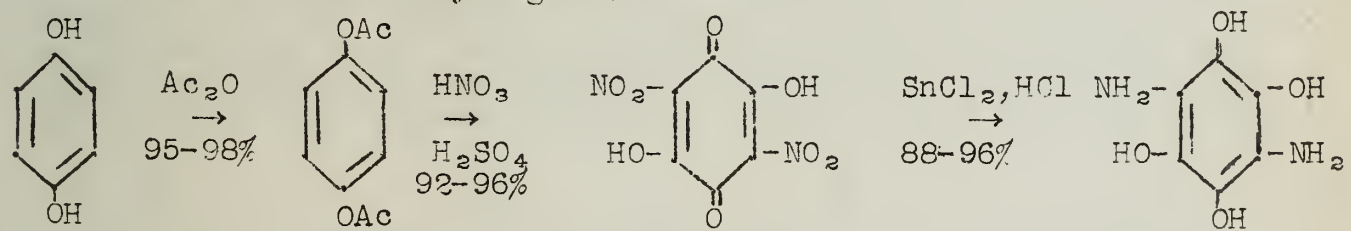
I. Syntheses of Hexahydroxybenzene.

A. In 1862 Lerch (1) unwittingly prepared hexahydroxybenzene (I) by the reactions outlined below. Because of the peculiar nature of this synthesis (2,3,4) the structures of II and I were not elucidated until 1885 (5). At present this method possesses only historical interest.

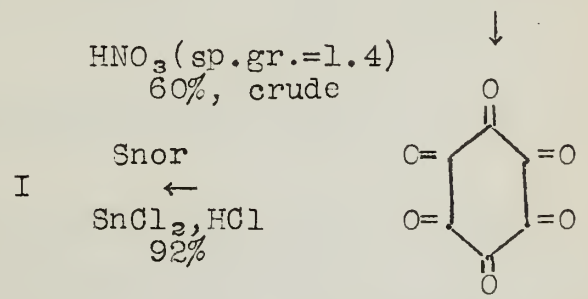


II I

B. The following synthesis (6,7,8) has definite preparative value despite the highly reactive intermediates. Very recently, the overall yield has been reported (9) as only 20%, but earlier claims were considerably higher.

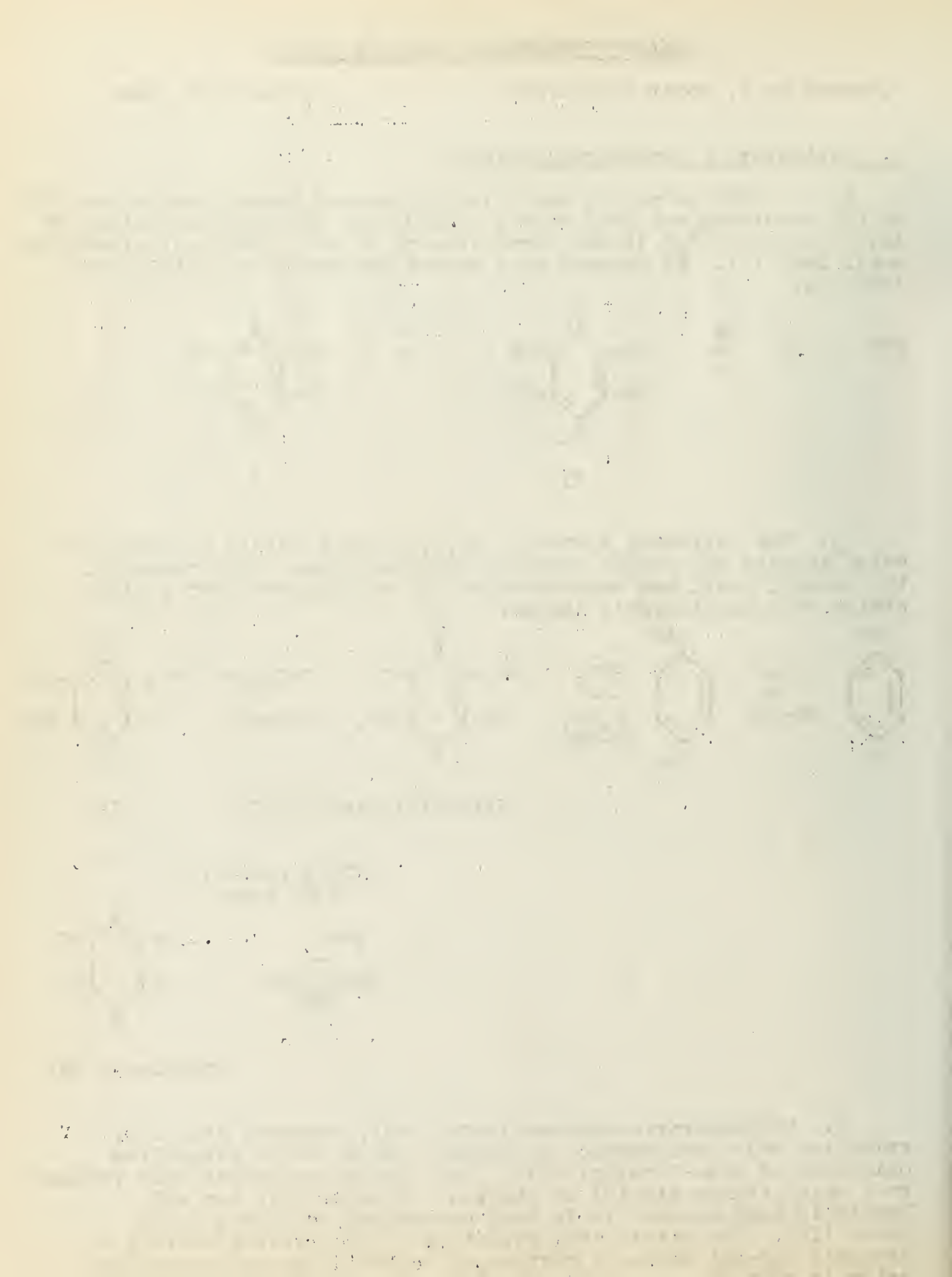


Nitranilic Acid (III) IV

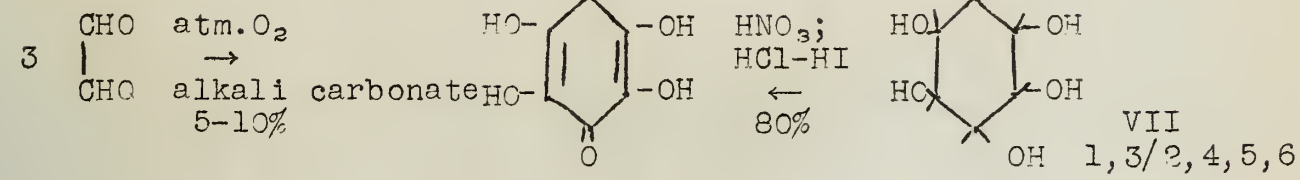


Triquinoyl (V)

C. Tetrahydroxy-p-benzoquinone (VI), prepared either by oxidative self-condensation of glyoxal (8-11) or by controlled oxidation of meso-inositol (VII) (12), can be satisfactorily reduced to I using either tin (8) or stannous chloride (9), but 45% hydriodic acid apparently is most convenient and gives a 70% yield (12). The nitric acid oxidation of VII gives a variety of products (13-15) unless a mixture of hydrochloric and hydriodic acids is added to stop the oxidation at VI (12). The preparation



of I from VII appears to be the most desirable of all the available methods.

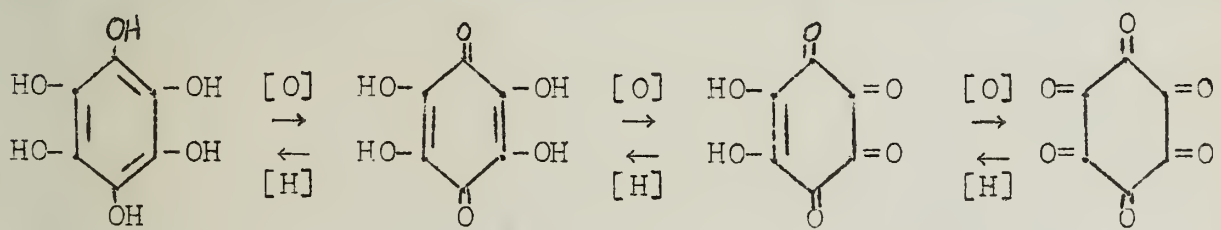


VI

II. Properties of Hexahydroxybenzene.

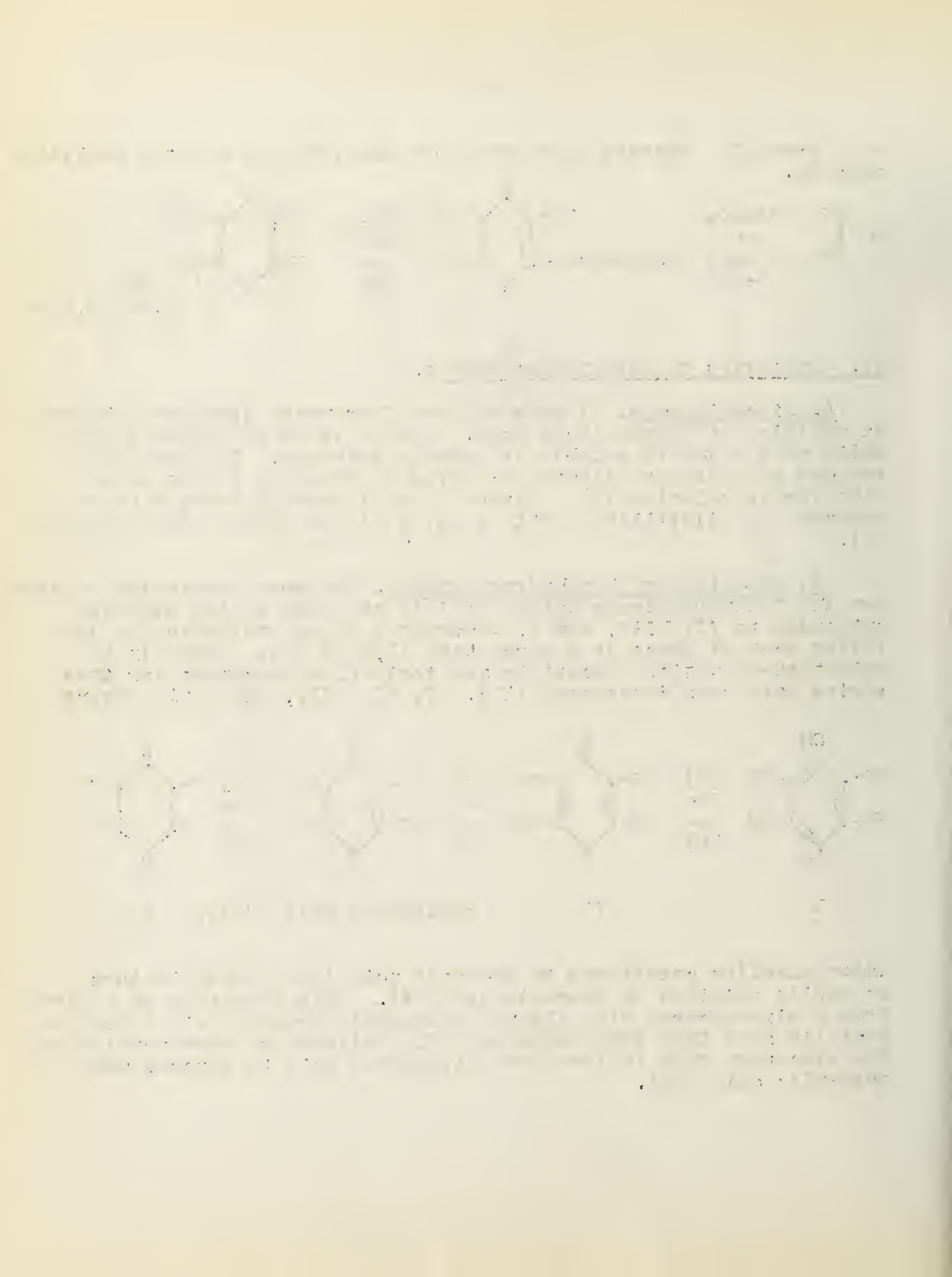
A. Miscellaneous. I crystallizes from water (stannous chloride) on addition of hydrochloric acid. Pure I is an infusible grayish solid only slightly soluble in organic solvents. It instantly reduces cold silver nitrate and gives a transient violet color with ferric chloride (6). Either I or II readily forms a hexa-acetate. On distillation with zinc, I yields benzene and diphenyl (6).

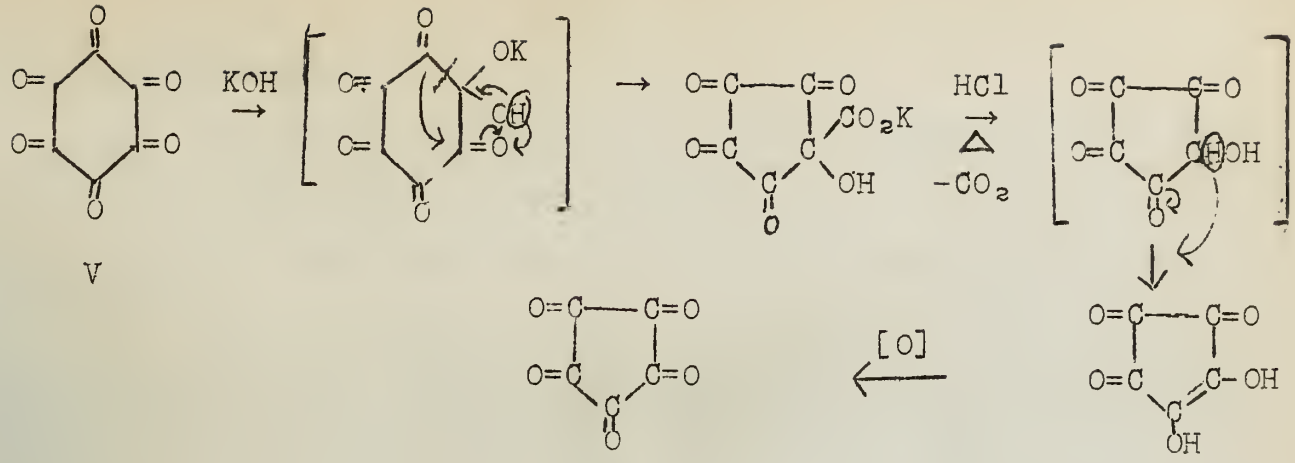
B. Oxidation of Hexahydroxybenzene. The most convincing evidenc for the trihydroquinone nature of I is afforded by its stepwise oxidation to VI, VIII, and V, procedures being available for isolating each of these in a pure state (1,6,15,16). Recently the oxidation-reduction potentials and ionization constants for this series have been determined (17). I, VI, VIII, and V all revert



I VI Rhodizonic Acid (VIII) V

under alkaline conditions to croconic acid (IX), which in turn is easily oxidized to leuconic acid (X). This formation of a five- from a six-membered ring (18-20) presumably proceeds via a benzil-benzilic acid type transformation (21) followed by decarboxylation. The structure of X follows from its hydrol ysis to glyoxal and mesoxalic acid (22).

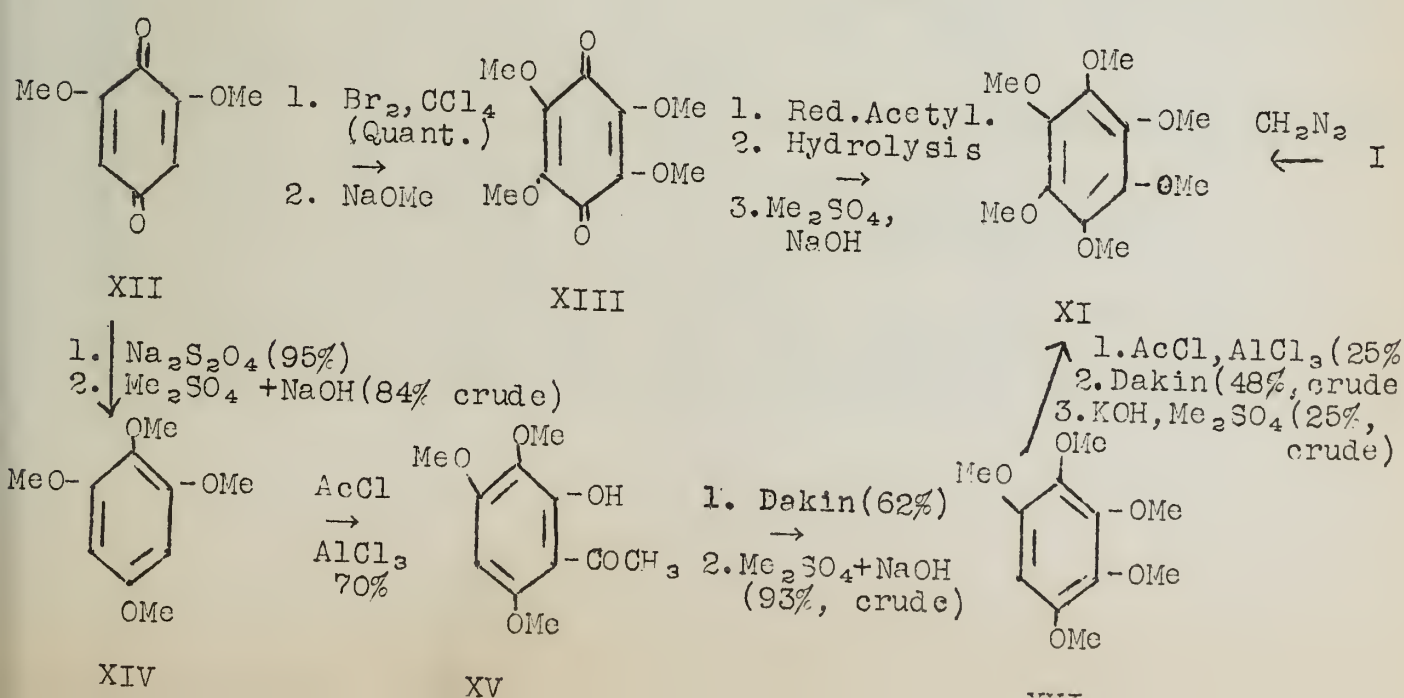




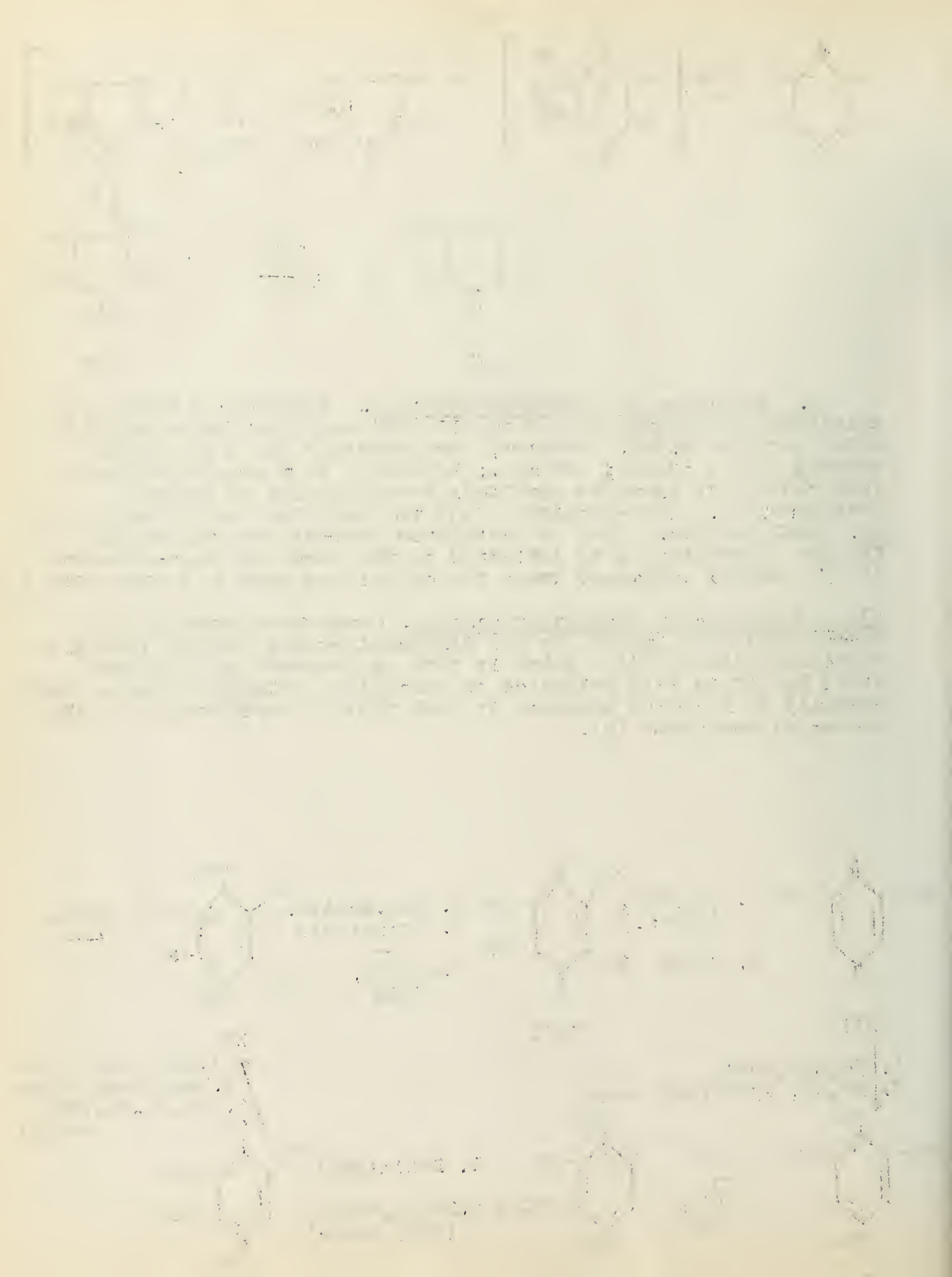
V X IX

C. Reduction of Hexahydroxybenzene. Wieland and Wishart's catalytic hydrogenation of I to VII (23) could not be repeated by later workers (9,24). However, very recently (9) I was hydrogenated (Raney nickel; 100 atm.; 125-150°) to a complex mixture from which five isomeric cyclitols were isolated by tedious fractionation. Meso-inositol (VII) and scyllitol were obtained in ca. equal amounts. That the catalytic process was responsible for the isomerization is indicated by the fact that meso-inositol (VII) remained unchanged under the conditions used to hydrogenate I.

III. Syntheses of Hexamethoxybenzene. Hexamethoxybenzene (XI) became available in 1941 by two different routes (25,26) from 2,6-dimethoxyquinone (XII), which in turn is prepared in excellent yield by nitric acid oxidation of pyrogallol trimethyl ether. Very recently XI has been produced in high yield by methylating I with excess diazomethane (9).



XII XIII XI I XIV XV



IV. Miscellaneous.

A. Some twenty aliphatic and aromatic esters of I have been prepared. Interesting correlations exist between the structure and melting points of these esters (8,12).

B. I,VI, and V increase the electrical conductivity of boric acid (27).

C. It seems reasonable that the I-VI-VIII-V equilibrium may be involved in the oxidation-reduction processes of living cells (17), for VII is widely distributed in nature and is an accessory growth factor for many organisms (28). Furthermore, certain bacteria can convert VII to calcium rhodizonate (29), and the rat is able to convert VII to glucose (24).

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SYNTHESIS OF t-CARBINAMINES

Reported by Karl F. Heumann February 25, 1949

Carbinamines are related to methylamine in the same manner that carbinols are related to methyl alcohol.

The earliest preparation of a t-carbinamine (specifically, t-butylamine) is that of Linneman and Brauner (1) who used the following procedure (yield about 45%):

1. $2AgNCO + (CH_3)_2CHCH_2I \rightarrow AgI + (CH_3)_2C{=}CH_2 + O{=}C(HN{-}C{=}O)\text{-}N\text{-}Ag$

2. $O{=}C(HN{-}C{=}O)\text{-}N\text{-}Ag + (CH_3)_2CHCH_2I \rightarrow AgI + O{=}C(HN{-}C{=}O)\text{-}N\text{-}C(CH_3)_3$

3. $O{=}C(HN{-}C{=}O)\text{-}N\text{-}C(CH_3)_3 + 4KOH \rightarrow 2K_2CO_3 + NH_3 + (CH_3)_3CNH_2$

Coleman, et al. (2) reported the preparation from t-butylmagnesium chloride and chloramine (NH_2Cl), but the instability of the latter made the reaction undesirable:

$$RMgX + NH_2Cl \rightarrow RNH_2 + MgXCl \quad (60\%)$$

A high yield (85%) characterized the preparation of Klages, et al. (3):

$$(CH_3)_2C{=}N\text{-}N{=}C(CH_3)_2 + CH_3MgBr \xrightarrow[\text{ice}]{HCl} \text{t-BuNHNH}_2\cdot HCl \xrightarrow[170^\circ]{H_2\text{-}Ni} \text{t-BuNH}_2$$

A general method was reported by Mentzer, et al. (4):

$$ArCH_2Cl + Na\text{-}C(R)(R')(O)\text{-}C\text{-}\phi \rightarrow ArCH_2C(R)(R')(O)\text{-}C\text{-}\phi \xrightarrow{NaNH_2} ArCH_2C(R)(R')\text{-}CONH_2$$

$$\xrightarrow{KOBr} ArCH_2C(R)(R')\text{-}N{=}C{=}O \xrightarrow{HCl} ArCH_2C(R)(R')\text{-}NH_2\cdot HCl$$

(R and R' may be alkyl, aryl or aralkyl)

Henze, Allen and Leslie (5) prepared carbinamines by the reaction of an active nitrile and a Grignard:

$$EtOCH_2CN + 2CH_2{=}CHCH_2MgBr \rightarrow (CH_2{=}CHCH_2)_2C(CH_2OEt)\text{-}NH_2$$

An interesting reaction was used by Karabinos and Serijan (6) to prepare t-$BuNH_2$ in 70% yield:

$$(CH_3)_2C\!-\!CH_2 \;(N,\ H) \xrightarrow[130^\circ,\ 700\#]{H_2,\ Ni} (CH_3)_3CNH_2 \quad \text{(no isobutylamine)}$$

Campbell, Sommers and Campbell (7) repeated the hydrogenation at low pressure (60#, 60°, Raney Ni, in dioxan).

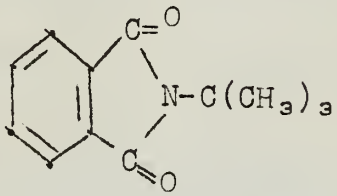
The 2,2-dimethylethyleneimine was made by the method of Cairns (8):

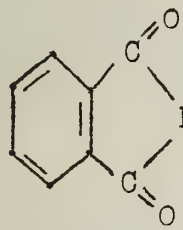
$$(CH_3)_2C(NH_2)\text{-}CH_2OH \xrightarrow{H_2SO_4} (CH_3)_2C(NH_2)\text{-}CH_2OSO_3H \xrightarrow{NaOH} (CH_3)_2C\!-\!CH_2 \;(N,\ H)$$

(This compound was originally prepared to test the asymmetry of the N atom, but it was not resolved; see also Adams and Cairns (9)).

By 1945 the best method of synthesis of t-butylamine consisted of three steps (Smith and Emerson (10)):

1. t-BuOH + urea $\xrightarrow[15^\circ]{H_2SO_4}$ t-$BuNHC(=O)NH_2$

2. t-$BuNHC(=O)NH_2$ + phthalic anh. $\xrightarrow{240^\circ}$ 

3.  + $NH_2NH_2\cdot H_2O$ $\xrightarrow{EtOH}$ $\xrightarrow{HCl}$ t-$BuNH_2\cdot HCl$ (89%)

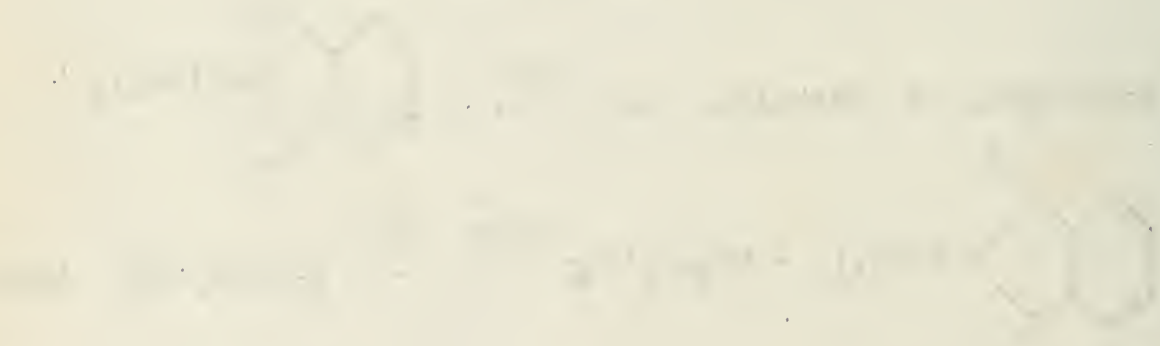
Brown and Jones (11) prepared primary amines by action of O-methylhydroxylamine on the Grignard (yield 70%):

$$2RMgCl(or\ Br) + MeONH_2 \rightarrow RNH\cdot MgCl \rightarrow RNH_2\cdot HCl$$

Very recently a new reaction has been turned to a general method of preparation of t-carbinamines. Ritter and Minieri (12) reported the reaction of alkenes with nitriles in the presence of concentrated sulfuric acid to form amides, and postulated the following as occurring:

$$(CH_3)_2C{=}CH_2 + H_2SO_4 \rightarrow (CH_3)_3C\text{-}OSO_3H + CH_3CN \rightarrow$$

$$CH_3C(OSO_3H){=}N\text{-}C(CH_3)_3 \xrightarrow{H_2O} [CH_3C(OH){=}N\text{-}C(CH_3)_3] \rightarrow CH_3C(=O)\text{-}NH\text{-}C(CH_3)_3$$



This has been tried on a number of compounds and appears to be general; it is recommended as a source of solid derivatives for the identification of both nitriles and olefins. When HCN is present in the nitrile used, N-alkyl formamides are formed.

Ritter and Kalish (13) employed as starting material a tertiary alcohol or alkene in glacial acetic acid solution to which an equivalent of NaCN has been added; the reaction occurs spontaneously when sulfuric acid is added and simple dilution generates the formamide:

$$\left.\begin{matrix} R_3COH \\ R_2C{=}CHR(H) \end{matrix}\right] \xrightarrow{H_2SO_4} R_3C{-}OSO_3H \xrightarrow{HCN} R_3C{-}N{=}\overset{OSO_3H}{\overset{|}{C}}H \xrightarrow{H_2O}$$

$$[R_3C{-}N{=}\overset{OH}{\overset{|}{C}}H] \rightarrow R_3CNHCHO \xrightarrow{\text{aq. alk.}} R_3C{-}NH_2$$

The N-alkylformamides were hydrolyzed with aqueous alkali to t-carbinamines. Other amides are more difficult to hydrolyze.

The following compounds were reported in reference (13) (with approximate yields):

$(CH_3)_3C{-}NH_2 \cdot HCl$ (I) (50%)

$\phi CH_2{-}\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}{-}NH_2$ (II) (55%)

$CH_3{-}\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}{-}CH_2{-}\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}{-}NH_2$ (III) (70%)

$\phi CH_2{-}\overset{CH_3}{\overset{|}{C}}H{-}NH_2$ (IV) (30%)

Compound (IV) is amphetamine, included because of the interest in beta-phenylethylamines as medicinals. It was not obtained from a formamide but by hydrolysis (with HCl for 11 hours) of its acetyl derivative formed from allylbenzene and acetonitrile.

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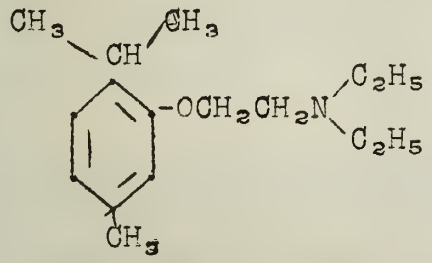
ANTIHISTAMINIC DRUGS

Reported by George I. Poos February 25, 1949

It was reported (1) in 1937 from the Pasteur Institute that certain organic compounds exert a specific antagonism to the powerful physiological action of histamine. Of more than thirty aryl ethers and amines investigated, 2-thymoxyethyldiethylamine (F929)(I) and N,N-diethyl-N'-ethyl-N'-phenylethylenediamine (F1571) (II) proved to be the most active although both were found to be too toxic for human use.



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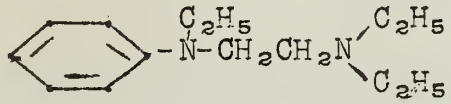
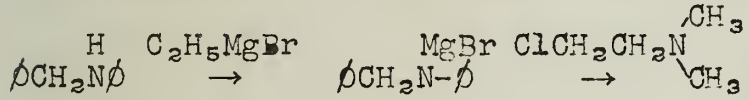
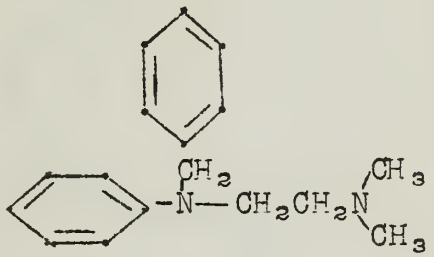


II

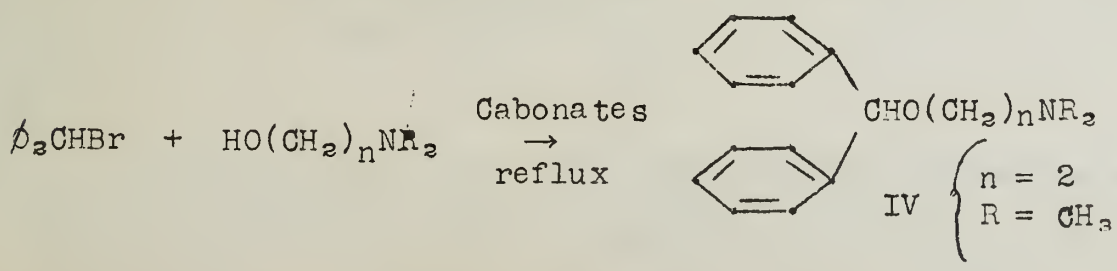
The first compound with antihistaminic activity to receive extensive clinical trial was N-benzyl-N',N'-dimethyl-N-phenylethylenediamine (Antergan)(Dimetina)(R.P. 2339)(III)(2). The following scheme has been patented for its preparation (3):





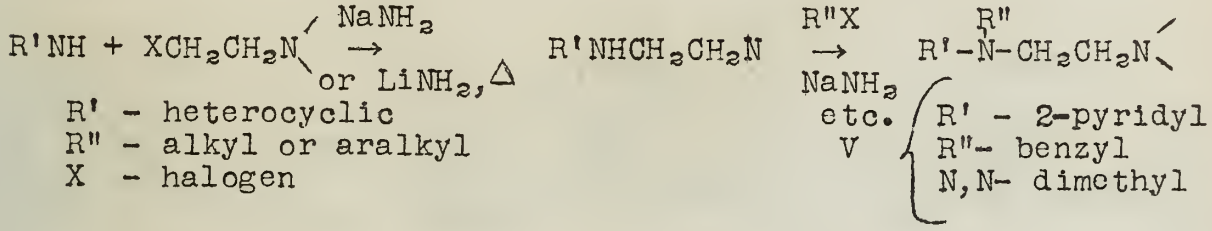
III

Several types of more active histamine antagonists appeared soon after the success with Antergan had been announced. Rieveschl and Huber investigated (4) a number of benzhydryl alkamine ethers, prepared from diphenylmethyl bromide and appropriate amino alcohols (5). The 2-(N,N-dimethylamino)ethyl benzhydryl ether (Benadryl)(IV)



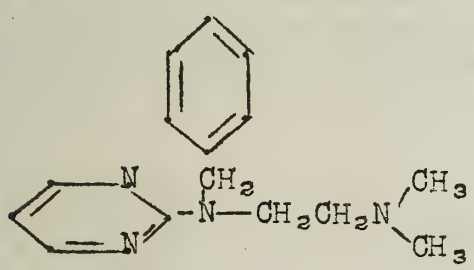
proved the most effective of twenty-one compounds tested (6) and has received widespread clinical use. The marked side reactions induced by Benadryl, especially the saporific action, make its use less desirable than some of the newer less toxic drugs.

Another important agent is N-benzyl-N',N'-dimethyl-N-(2-pyridyl)-ethylenediamine (Pyribenzamine)(V), the most active of twenty similar compounds prepared (7). The method of preparation (used in general for compounds of this type) involves successive alkylations of the appropriate heterocyclic amine with alkyl and aralkyl halides in the presence of sodamide or lithamide (8).



Pyribenzamine has been used extensively as a histamine antagonist and is probably less toxic than Benadryl (9).

Many analogs and substituted derivatives of Pyribenzamine equal or excell the potency of the parent compound. N-Benzyl-N',N'-dimethyl-N-(2-pyrimidyl)-ethylenediamine (Hetramine)(VI)(10); N,N-dimethyl-N'-p-methoxybenzyl-N-(2-pyrimidyl)-ethylenediamine (Neohetramine)(Thonzyl amine)(VII)(11); and N,N-dimethyl-N'-p-methoxybenzyl-N-(2-pyridyl)-ethylenediamine (Neoantergan)(Pyranisamine)(R. P. 2786)(VIII)(12) increase in activity in the order given (2b).



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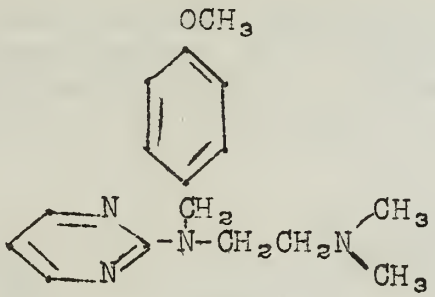
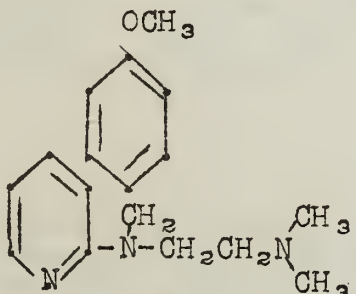


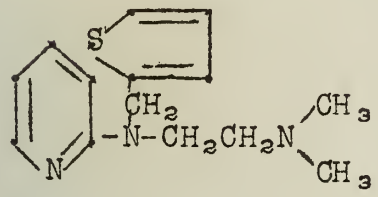
VII



VIII

Recently it has been shown that certain Pyribenzamine thenyl analogs compare very favorably with Pyribenzamine. N,N-Dimethyl-N'-(2-pyridyl)-N'-(2-thenyl)-ethylenediamine (Histadyl)(Thenylene)(Antihistamine 01013)(IX)(13,14) and the corresponding 2-halogen-2-thenyl compounds (Chlorothen and Bromothen)(14) have been prepared and tested (15). N,N-Dimethyl-N'-phenyl-N'-(2-thenyl)-ethylenediamine (Diatrin)(W-50)(X)(16) and N,N-dimethyl-N'-furfuryl-N'-(2-pyridyl)-ethylenediamine (XI)(17) are reported to be very

effective and of low toxicity. Other thiophene analogs of antihistaminics thus far prepared and tested have less activity than the corresponding phenyl compounds (18).



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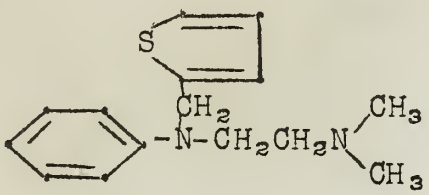

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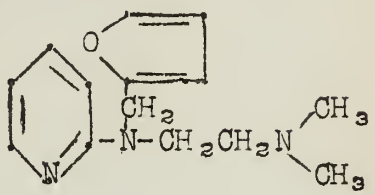
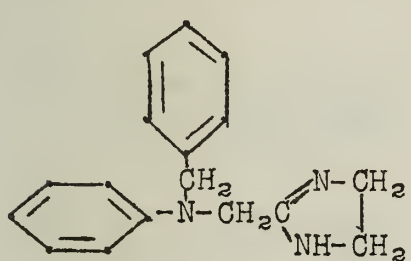


XI

Replacement of the dimethylaminoethyl grouping by the 2-methylimidazoline group leads to another series of active drugs. 2-(N-Benzyl-N-phenylaminomethyl)-imidazoline (Antistine)(Phenazoline) (XII) (19) is well established while 2-(aryloxymethyl)-imidazolines (20) such as 2-(benzhydryloxymethyl)-imidazoline (XIII) show promise.

It has been reported (21) that certain phenothiazines such as N-(dimethylaminoisopropyl)phenothiazine (R. P. 3277)(XIV) have a very high order of antihistaminic activity subsequent tests (2b) have shown the phenothiazines to be too toxic for human use.



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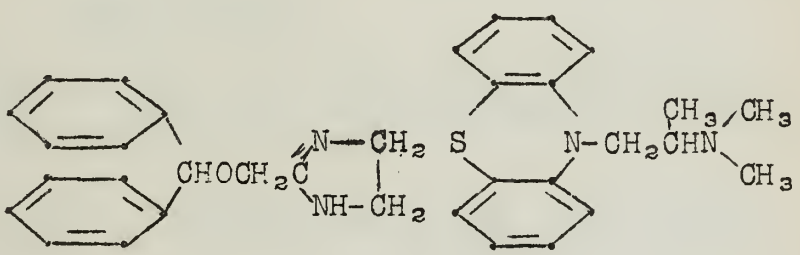
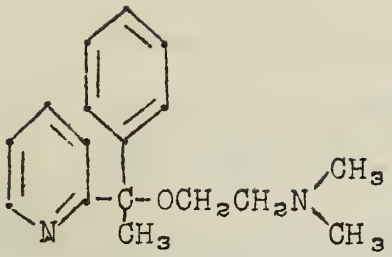


XIII XIV

2-Dimethylaminoethyl ethers of 2-substituted pyridine methanols have recently been reported to be active histamine antagonists (22). The most active of these compounds is 2-[α-(2-dimethylaminoethoxy)-α-methylbenzyl]-pyridine (Decapryn)(Doxylamine) (XV). Among other compounds reported to have specific antihistaminic activity may be included 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (Thephorin)(Phenindamine)(XVI) (23); 4-phenyl-1-(2-dimethylaminoethyl)-piperazine (XVII)(24) and 1-phenyl-1-(2-pyridyl)-2-dimethylaminopropane (Trimeton)(Prophenpyridamine) (XVIII)(25).



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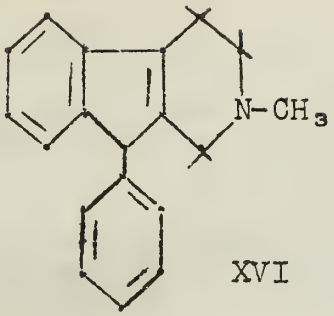
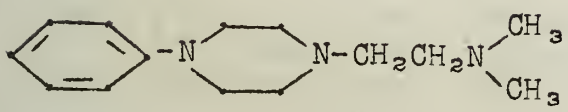
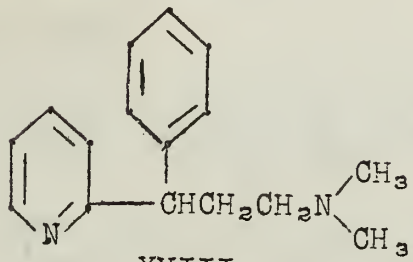


XVI



XVII



XVIII

The results of a recent clinical comparison of seven important histamine antagonists show the following order of decreasing anti-histaminic activity (26): Neoantergan > Histadyl > Antistine > Pyribenzamine >> Benadryl >> Neohetramine > Thephorin.

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ORIENTATION IN ALIPHATIC CHLORINATION

Reported by John Lynde Anderson March 4, 1949

Although orientation in aromatic substitution reactions has been rather thoroughly investigated, the directive effects in aliphatic substitutions have received little attention until recent years. Both ionic and free radical substitution reactions are known in the aliphatic series. The free radical aliphatic chlorination reaction has been studied in the most detail, and this seminar will be limited to a discussion of this type of reaction.

Chlorinations of unsubstituted aliphatic hydrocarbons: The vapor phase chlorination at 300° and the liquid phase chlorination at 25° of unsubstituted paraffins have been investigated (1). It has been shown that hydrogen atoms are replaced in the order primary < secondary < tertiary; the relative rates are 1.00 to 3.25 to 4.43. As the temperature of both types of reaction is increased, the ratio of rates approaches unity, the limiting ratio in liquid phase reactions being reached at much lower temperatures.

Chlorinations of substituted aliphatic hydrocarbons: The directive effects of various substituents in aliphatic hydrocarbons have been indicated by a number of recent investigations. Thus the liquid phase chlorination of 1-chloro-, 1,1-dichloro-, and 1,1,1-trichlorobutane using sulfuryl chloride as the chlorinating agent (2,3,4) shows that the effect of each chlorine substituent is to direct further chlorination to more remote positions in the molecule (see Table I). Ash and Brown (5) believe this effect is due to deactivation of the adjacent carbonhydrogen bonds rather than to activation of the more remote bonds. From an inspection of these data, it is apparent that two or more chlorine atoms are sufficient to deactivate the beta position.

The directive influence of fluorine atoms and the orienting effect of the trichlorosilyl group are also shown in Table I. The products are in accord with prediction, for fluorine is more electronegative than chlorine and carbon is more electronegative than silicon.

The chlorination of acids and acid chlorides is markedly affected by the reaction conditions employed. Thus chlorination of butyryl chloride in the presence of iodine or phosphorus leads only to alpha substituted derivatives (via the ionic reaction); however when very pure reagents and equipment are used, the peroxide-catalyzed chlorination of n-butyryl chloride leads to only three percent alpha substitution (4).

The directive effects of the acetoxy (4), the trichloroacetoxy (6), the methyl (1), and the phenyl groups (4) are indicated in Table I. Obviously the effect of the methyl and phenyl groups is to activate the neighboring position in contrast to the deactivating effects of the other groups.

TABLE I (5)

Relative percentage substitutions in the chlorination of 1-substituted propanes.

C - C - C - X

-	-	50	C_6H_5
20	40	40	CH_3
25	51	24	CH_2Cl
35	45	20	$OOCCH_3$
41	46	13	$SiCl_3$
38	50	12	$CHCl_2$
45	45	10	COOH
45	45	10	Cl
48	49	3	COCl
47	50	3	$OOCCCl_3$
51	49	0	CCl_3
55	45	0	CF_3.

Discussion: Ash and Brown have discussed the theoretical aspects of aliphatic free radical chlorinations in their most recent paper (5). Agreeing with Tischenko (7), they consider the best explanation of these directive influences to be due to the inductive effect of the group X. Thus the separation of a hydrogen atom from the 2-carbon atom in 1-chlorobutane is predicted to be more difficult than in butane itself. This prediction is in accord with the observed fact. That the effect is additive as more chlorines are introduced into the 1-carbon of normal butane is indicated by the results for the chlorination of the three chlorobutanes. In Table I the groups X are listed in the order of decreasing activating effect, that is increasing negative inductive effect.

In vapor phase chlorinations above a critical temperature, little or no 1,2-dichloroalkanes are isolated. For example, when 1-chlorobutane is chlorinated at temperatures in excess of 312°, the 1,2-dichlorobutane is absent or present in only very small amounts (8). Ash and Brown postulate that this apparently anomalous result, the "vicinal effect", is due to the instability of the free radical (I) which eliminates a chlorine atom to form the olefin (II).

$$CH_3CH_2\dot{C}HCH_2Cl \rightleftharpoons CH_3CH_2CH=CH_2 + Cl\cdot$$

(I) (II)

Analogously, ethyl chloride in the absence of free halogen is quite stable up to 415°, but in the presence of chlorine, it decomposes to ethylene and hydrogen chloride at temperatures as low as 280° (9). This "vicinal effect" has been observed only in vapor phase reactions.

The free radical stability factor in the chlorination reaction is well indicated by a comparison of the attack of a chlorine atom and a methyl free radical on isobutyric acid. In the first case, 15 percent of alpha- and 85 percent of beta-chloroisobutyric acid is formed (10), while the reaction of isobutyric acid in the presence of acetyl peroxide leads exclusively to tetramethylsuccinic acid (11). Ash and Brown believe that the initial attack is at the beta position predominantly (a) which is in accord with the data in Table I. They also postulate that the reaction with chlorine is very fast (c). However, in the case of the methyl free radical initiation, the beta free radical, predominantly formed at first, reacts with unchanged isobutyric acid to form the alpha free radical which is considerably more stable due to resonance (b). The slow coupling reaction leads only to the formation of tetramethylsuccinic acid (d).

(a) $(CH_3)_2CHCOOH + CH_3\cdot(Cl\cdot) \rightarrow \begin{matrix} CH_3 \\ \cdot CH_2 \end{matrix}\!\!>\!CHCOOH(P\cdot) + CH_4(HCl)$

$\searrow$

$(CH_3)_2\dot{C}COOH(T\cdot)$

(b) $P\cdot + (CH_3)_2CHCOOH \rightleftharpoons \begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CHCOOH + T\cdot$

(c) $P\cdot + Cl_2 \rightarrow PCl + Cl\cdot$

$T\cdot + Cl_2 \rightarrow TCl + Cl\cdot$ } fast

(d) $T\cdot + T\cdot \rightarrow TT$ slow

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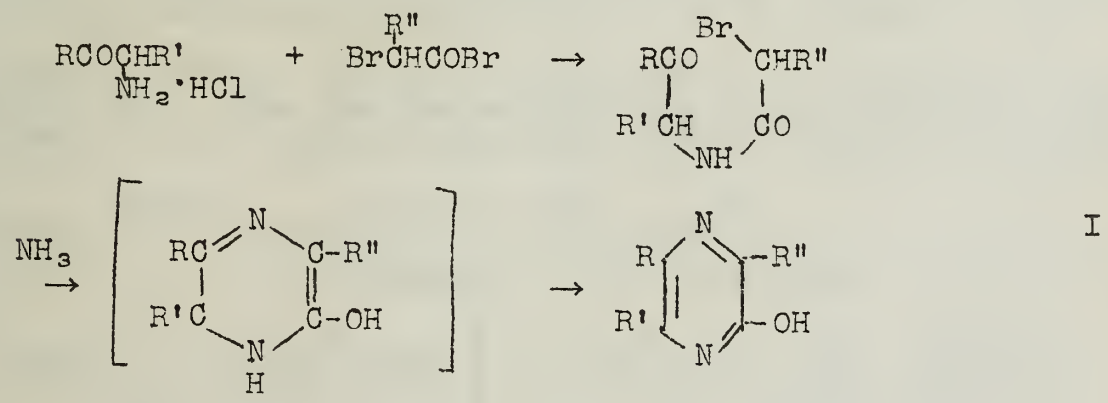
HYDROXYPYRAZINES

Reported by Claire Bluestein March 4, 1949

The hydroxypyrazines are of interest because of their relation to physiologically active compounds. Early investigators were limited in working with the isolated pyrazine nucleus because of low yields in the methods of preparation and the resistance of the ring to the usual aromatic substitutions. A thorough review of pyrazine chemistry up to 1946 has been made by Krems and Spoerri (1). Since that time there have been further extensions.

Syntheses of the Ring

1. The method developed by Tota and Elderfield (2) appeared to be a very general one for hydroxypyrazines. However, more recent work (3,4) has shown that the method is applicable mainly to the preparation of 5,6-disubstituted or 3,5,6-trisubstituted-2-hydroxypyrazines. This method is outlined in equation I.

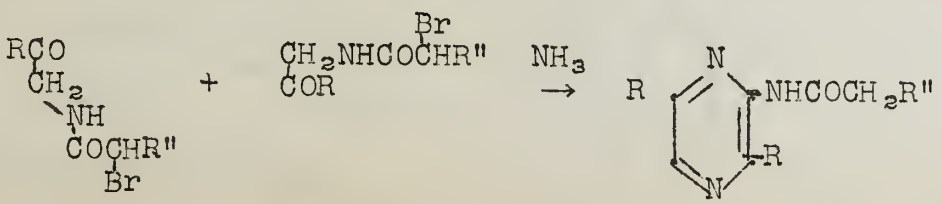


I

The condensation between the α-aminoketone and the bromoacyl bromide is best carried out by using N-methylmorpholine in anhydrous chloroform (4).

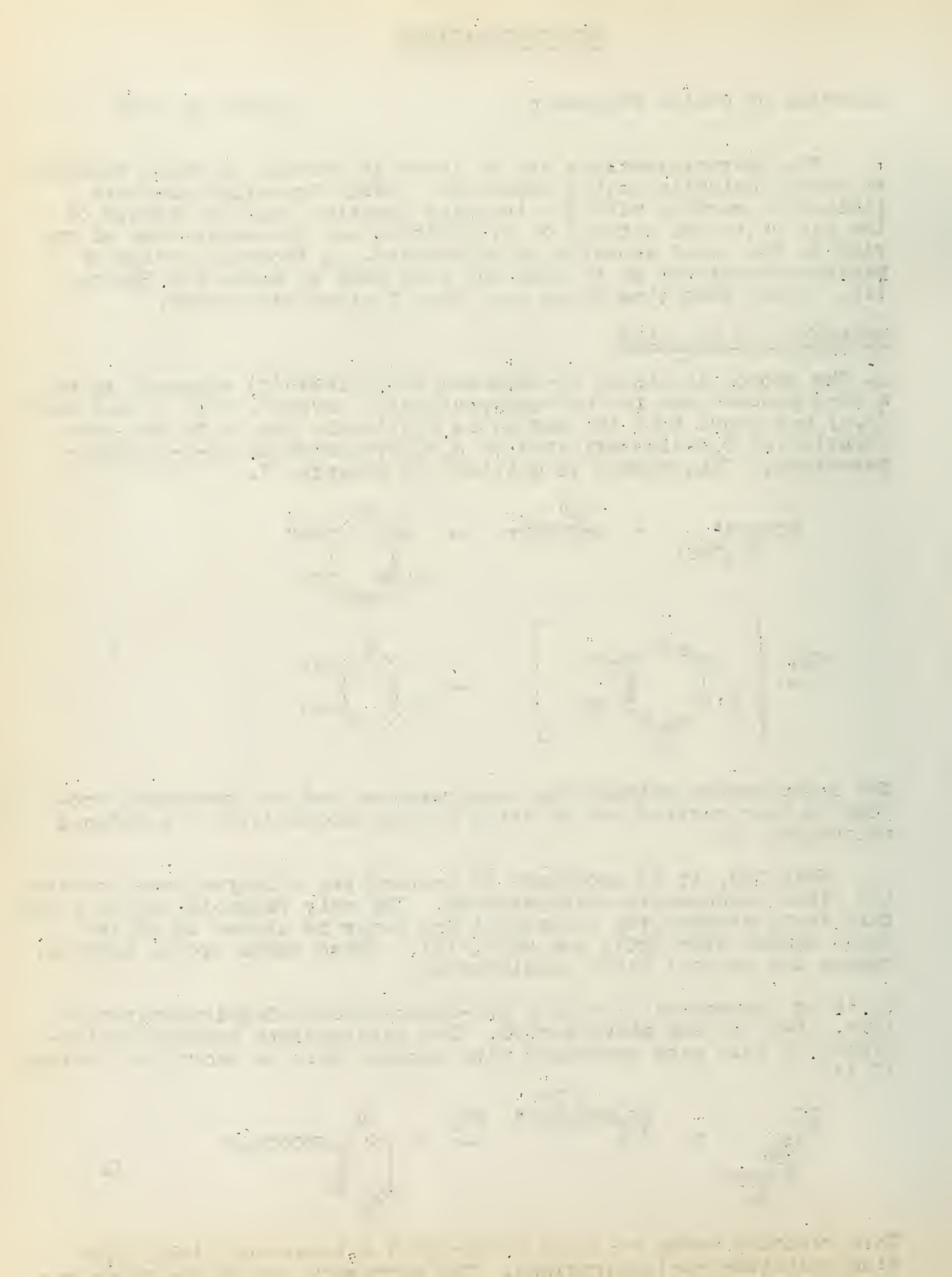
When R=H, it is necessary to protect the aldehyde group before the final condensation with ammonia. The only feasible way of doing this is to prepare the thioacetal and later to cleave it in the usual manner with $HgCl_2$ and $CdCO_3$ (3). These added steps, however, reduce the overall yield considerably.

2. It is impossible to make a 3,5-disubstituted-2-hydroxypyrazine (i.e. R'=H) by the above method. The intermediate bromoacylamidoketone in this case condenses with ammonia only as shown in equation II (4).



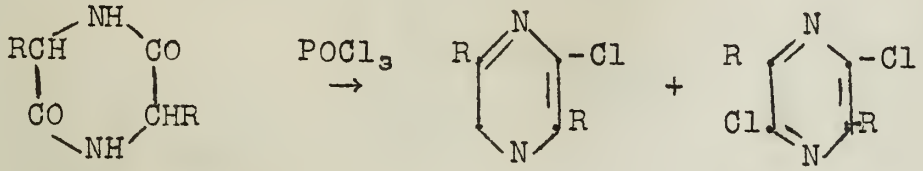
II

This reaction works well for aminomethyl ketones and yields 3,6-disubstituted-2-aminopyrazines. The corresponding hydroxypyrazines



can be obtained by treatment with nitrous acid (5) or nitrosyl sulfuric acid (6).

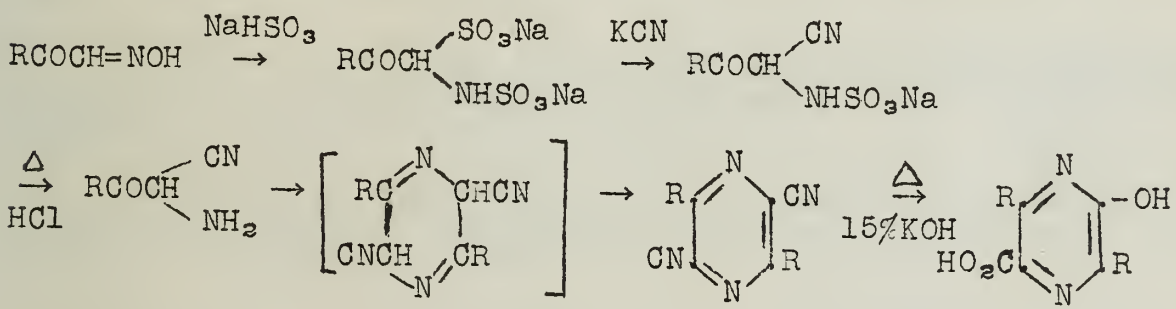
3. Diketopiperazines, which are amino acid anhydrides, are tautomeric with dihydrodihydroxypyrazines. They are most conveniently prepared by heating the amino acid with ethylene glycol (7). There is no direct method of oxidation to the hydroxypyrazines, but Baxter and Spring (8) have achieved conversion to the mono- or dichloropyrazines by use of phosphorus oxychloride (equation III).



III

The monochloropyrazines can be converted to hydroxypyrazines by hydrolysis methods, and the dichloropyrazines to hydroxychloropyrazines and also to dialkoxypyrazines, but it has been impossible to obtain a dihydroxypyrazine because the ring cleaves first (9).

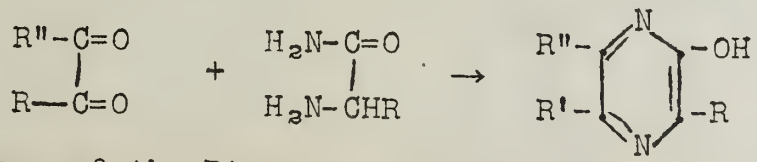
4. Another method, the use of which has been extended, is that of Gastaldi (10). The starting material is an oximinomethyl ketone. The steps in the improved synthesis (11) are outlined in equation IV.



IV

If desired, the final product can easily be decarboxylated to the 3,6-disubstituted-2-hydroxypyrazine.

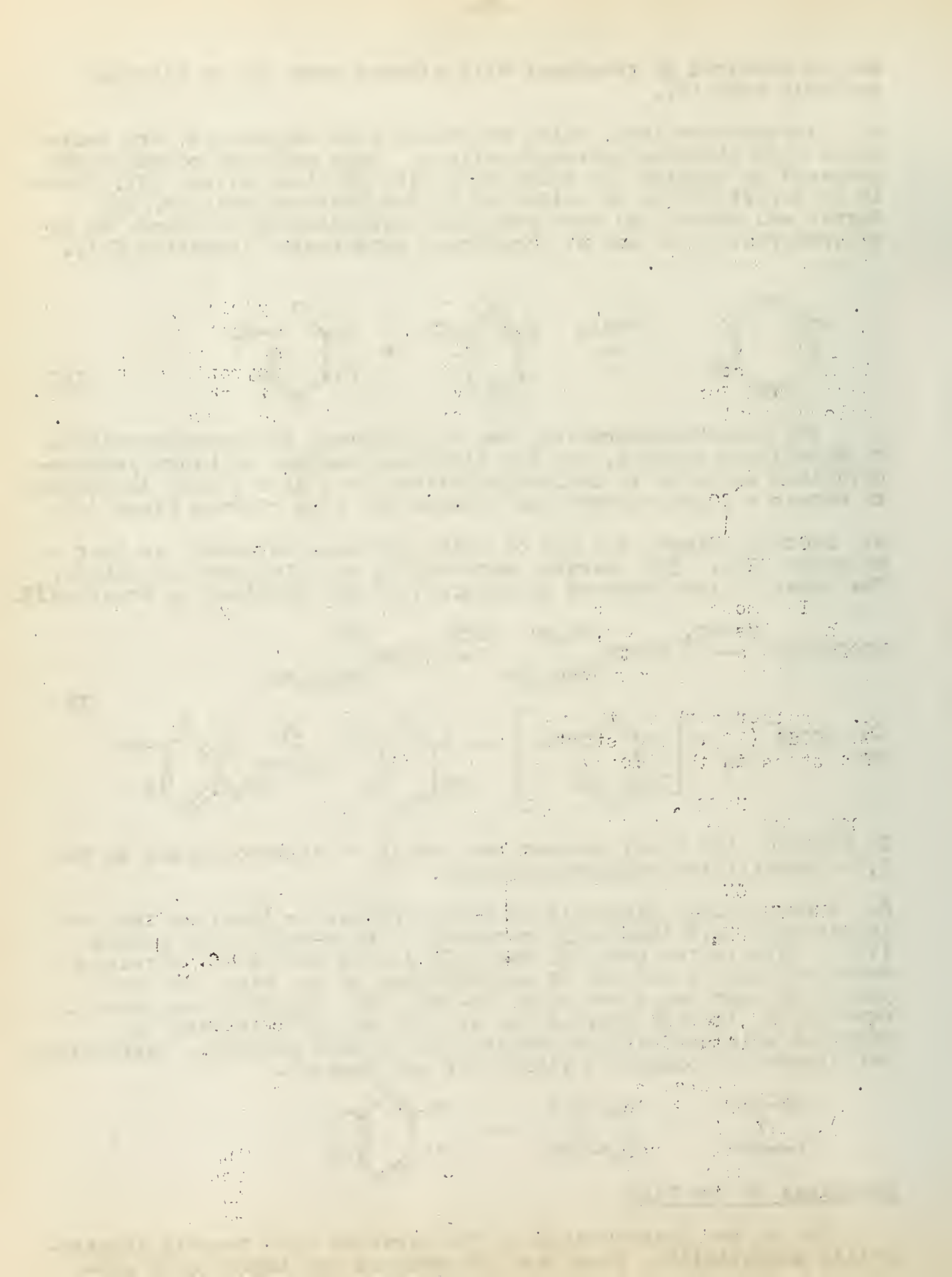
5. A new general synthesis of hydroxypyrazines involves the condensation of 1,2-dicarbonyl compounds with α-amino acid amides (12). This is the simplest and most direct method for obtaining compounds with a variety of substituents on the ring, and the yields in most cases are high, 75-95%. The reaction, as shown in equation V, is best carried out at -10° to -20°C in water or methanol solution with one equivalent of NaOH present. Unsymmetrical dicarbonyl compounds yield only one product.



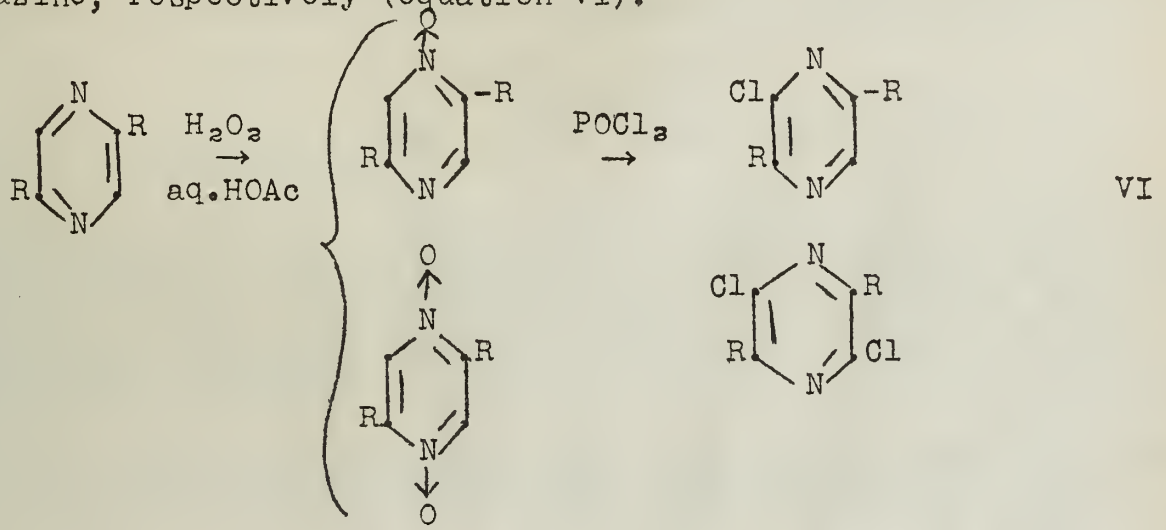
V

Reactions of the Ring

Due to the deactivation of the pyrazine ring towards electrophilic substitution, there are few methods for introducing sub-



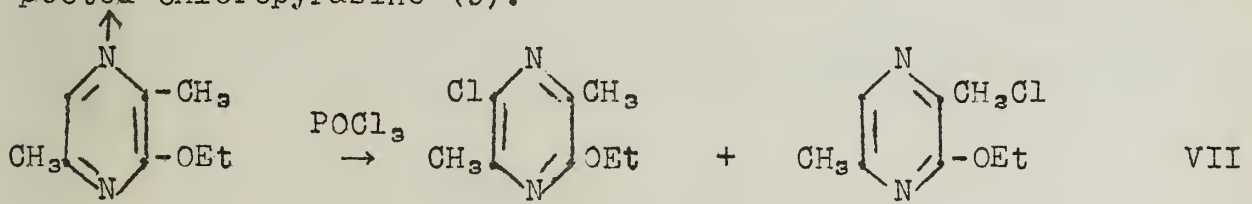
stituents directly into the ring (1). Hydroxypyrazines are obtained chiefly through synthesis or by replacement of the amino group as mentioned previously. A chloropyrazine, if available, can be hydrolyzed conveniently with KOH (8). Recently a fairly direct method for introducing chlorine easily into the pyrazine nucleus has been devised (13). The pyrazine is treated with hydrogen peroxide, which gives the mono- and di-N-oxides. These can be separated by means of their solubility, and further treatment of each with phosphorus oxychloride yields the mono- or dichloropyrazine, respectively (equation VI).



VI

If there is already a Cl on the pyrazine ring, the peroxide oxidation will yield only one mono-N-oxide, that in which the oxidized N is not adjacent to the Cl (9).

Treatment of the N-oxide shown in equation VII with phosphorus oxychloride yields a chloromethyl pyrazine in addition to the expected chloropyrazine (9).



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THE USE OF $LiAlH_4$ AND RELATED COMPOUNDS IN ORGANIC CHEMISTRY

Reported by H. Wayne Hill, Jr. March 11, 1949

Since the discovery of $LiAlH_4$, much attention has been given to its use both as a reducing agent and in quantitative organic chemistry.

Lithium aluminum hydride is readily prepared by the action of $AlCl_3$ on LiH under anhydrous conditions in ether solution (2).

$$4LiH + AlCl_3 \rightarrow LiAlH_4 + 3LiCl$$

Both LiH and $LiAlH_4$ are now sold by Metal Hydrides, Inc. of Beverly, Massachusetts.

Reductions with $LiAlH_4$ Lithium aluminum hydride is a powerful reducing agent for organic compounds, its chief advantage being that side reactions are at a minimum. Most of the reductions to be mentioned in this seminar are conveniently carried out at room temperature, the general technique being quite similar to that used in Grignard syntheses.

The equations for the reaction of carboxylic acids will serve to indicate the stoichiometry of the reduction (10).

$$4RCOOH + 3LiAlH_4 \rightarrow LiAl(OCH_2R)_4 + 2LiAlO_2 + 4H_2$$

$$LiAl(OCH_2R)_4 + 4H_2O \rightarrow RCH_2OH + LiOH + Al(OH)_3$$

This represents an excellent means of reducing an acid directly to the corresponding alcohol.

In order to effect the reduction of alkyl halides, it is necessary to use somewhat more vigorous conditions. The reduction is conveniently carried out in boiling tetrahydrofuran (b.p. 65°) as solvent using LiH with a small amount of $LiAlH_4$ as the hydrogen carrier (5).

$$RX + LiH \xrightarrow{LiAlH_4} RH + LiX$$

Alicyclic and aryl halides are very unreactive.

Although carbon-carbon double bonds in general are not reduced by the reagent, it has been noted that ethylenic bonds of the type $C_6H_5CH{=}CHX$ where X is NO_2, COOH, CHO, COR, etc. are reduced in the normal reduction procedure (addition of a solution of the compound to the hydride solution). However if the order of addition is reversed, it is possible to reduce X without affecting the carbon-carbon double bond (4). Reduction of double bonds proceeds slowly.

The following table illustrates the types of compounds which may be reduced and their reduction products. In many cases the yields are almost quantitative.

Type Compound	Intermediate	Product	Reference
RCHO	$LiAl(OCH_2R)_4$	RCH_2OH	9
R_2CO	$LiAl(OCHR_2)_4$	R_2CHOH	9
RCOOR'	$LiAl(OR')_2(OCH_2R)_2$	RCH_2OH	9
RCOCl	$LiAlCl_2(OCH_2R)_2$	RCH_2OH	9
$(RCO)_2O$	$LiAl(OCH_2R)_4$	RCH_2OH	9
RCOOH	$LiAl(OCH_2R)_4$	RCH_2OH	10
RCHOHCOOH	$LiAl\begin{pmatrix}-OCHR\\-OCH_2\end{pmatrix}_2$	$RCHOHCH_2OH$	10
$RCHNH_2COOH$	$LiAl\begin{pmatrix}-NHCHR\\-OCH_2\end{pmatrix}_2$	$RCHNH_2CH_2OH$	10
RCOCOOH	$LiAl\begin{pmatrix}-OCHR\\-OCH_2\end{pmatrix}_2$	$RCHOHCH_2OH$	10
RX	-----	RH	5
RCN	$LiAl(NCH_2R)_2$	RCH_2NH_2	11
$ArNO_2$	-----	ArN=NAr	11
RNO_2	$LiAl(NR)_2$	RNH_2	11
$ArN{=}\overset{\uparrow}{N}Ar$ (O above)	-----	ArN=NAr	11
ArCH=NAr	$LiAl(ArCH_2NAr)_4$	$ArCH_2NHAr$	11
$RCH\text{-}CH_2$ (O below)	$LiAl[OCH(CH_3)R]_4$	$RCHOHCH_3$	11
$RCONH_2$	-----	RCH_2NH_2	11, 14

Reductions with $NaBH_4$ Since sodium borohydride is potentially a cheaper material than $LiAlH_4$, it has been of interest to investigate its action as a reducing agent in organic chemistry (1). It has been found that $NaBH_4$ can be used in aqueous or ethanolic solution, thus offering a great advantage in convenience as compared with $LiAlH_4$. It may also be possible to reduce ether-insoluble compounds such as sugars, by this method. $LiAlH_4$ is of little use in the reduction of such compounds.

Sodium borohydride is superior to $LiAlH_4$ in selective reductions. Thus in aqueous solution, aldehydes and ketones are reduced to alcohols, whereas acids, acid chlorides, esters, nitriles and acid anhydrides are not reduced. However in aqueous solution, the alkaline conditions may effect hydrolysis of easily hydrolyzable groups. Acid chlorides may be reduced in inert solvents, while acids, acid anhydrides, esters and nitro compounds are not affected under the same conditions. $LiAlH_4$ affords no selectivity in such cases.

Active Hydrogen Determinations with $LiAlH_4$ (3,7,8,15) Many compounds containing active hydrogen atoms decompose ether solutions of $LiAlH_4$ to liberate hydrogen. Thus by measuring the hydrogen evolved, it is possible to calculate the number of active hydrogens in a molecule.

$$4ROH + LiAlH_4 \rightarrow 4H_2 + LiAl(OR)_4$$

In the majority of cases, results similar to those obtained by the Grignard method were observed. One notable difference was with keto-enol tautomers. These compounds react with the Grignard reagent as though they exist in the enol form only, whereas with $LiAlH_4$ they behave as though they are only partially enolized.

With compounds containing more than one active hydrogen, such as primary amines and unsubstituted amides, a rather long reaction time (an hour or more) was required for the complete liberation of hydrogen. However in most of these cases, the first hydrogen was liberated rapidly (5-10 minutes).

Determination of Reducible Groups with $LiAlH_4$ (3,15) In connection with the determination of active hydrogens, $LiAlH_4$ may be used to determine reducible groups, such as: carbonyl, ester, carboxylic acid, nitrile and amide. The procedure consists in treating a weighed amount of the compound with a known amount of the hydride and measuring the hydrogen gas evolved to get the number of active hydrogens. The reaction mixture is then allowed to stand for some time (during which the reduction occurs) and is treated with alcohol to decompose the excess hydride. Again the evolved hydrogen is measured. Thus the amount of hydride used in effecting the reduction is obtained by difference, no hydrogen being liberated in the reduction process.

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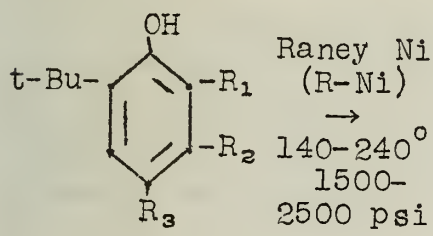
RECENT DEVELOPMENTS IN THE CATALYTIC HYDROGENATION OF ORGANIC COMPOUNDS

Reported by Melvin I. Kohan March 11, 1949

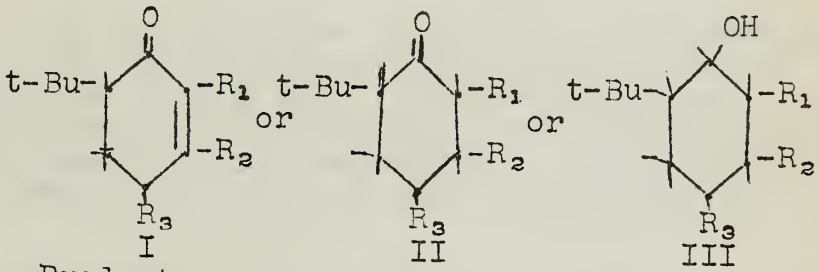
Catalytic hydrogenation is largely an empirical art so that success in any given case is assured only by experiment. Not only the extent but also the direction of a reduction depends importantly on many factors: the kind, method of preparation and amount of catalyst; the compound to be reduced (hydrogen acceptor); temperature, pressure, solvent, promoters and poisons. Any process depending upon the balance of so many variables is obviously complex, but an attempt can be made to understand many phenomena on the basis of the Langmuir concept of a unimolecular film adsorbed on the catalyst and proximate centers of activity (1). This seminar reviews the recent work and the explanations of the results obtained.

I. Hydrogenation of the Benzenoid Ring (2).

1. Polyalkyphenols (3). Whitaker studied the effect of steric hindrance on the reduction of phenols and observed the following:



Raney Ni (R-Ni) → 140-240° 1500-2500 psi



I II III

R_1	R_2	R_3	Product
H	CH_3	H or t-Bu	III only
CH_3	H	H or t-Bu	II or III
t-Bu	H	CH_3 or t-Bu	I or II

The following guide for the hydrogenation of phenols over R-Ni (in the absence of promoters) is therefore proposed:

	compound	product
a.	one ortho position unsubstituted	cyclohexanol derivative only
b.	one ortho position occupied by CH_3 and one by t-Bu	cyclohexanol or cyclohexanone derivative
c.	both ortho positions occupied by t-Bu	cyclohexanone or cyclohexene-one derivative

2. β-Naphthol. Using R-Ni Stork (4) found that in basic solution the product is the tetralol, but in neutral or acid media the unsubstituted ring is attacked preferentially. The effect of base in increasing the ease of reduction of phenolic compounds had been established earlier by Ungnade and co-workers (5). Since copper-chromium oxide, which attacks carbon-to-oxygen in preference to carbon-to-carbon double bonds, can be used to hydrogenate phenolic compounds but not their ether derivatives (6) and since the carbonyl group is known to react more readily in the presence of base (7), the base effect can be interpreted as facilitating tautomerism to the ketonic structure. However, the methyl ether of

β-naphthol exhibits a similar behavior over R-Ni so Stork proposes that the effect is one of increased adsorption of a positive center on the catalyst through coordination with the base. On this basis also, he explains the fact (8) that by the addition of a little NaOH the R-Ni hydrogenation of benzylcyanide gives almost exclusively the primary amine.

It has also been shown that this behavior of β-naphthol is essentially independent of the type R-Ni (9) used and that triethylamine can serve as the base instead of NaOH (10).

3. Pyrogallol (11). This compound (1,2,3-trihydroxybenzene) has been hydrogenated as the monosodium salt over R-Ni to the ene-diol, dihydropyrogallol (2,3-dihydroxy-2-cyclohexene-1-one). The stopping of the reduction at this stage is attributed to the resonance stabilization of the anion of the 1,3-diketone system.

4. Hydroxyphenyl Aliphatic Acids. The reduction of this type compound has been complicated since hydrogenolysis of the hydroxyl group occurs with noble metal catalysts and decarboxylation with R-Ni (12). This problem has been resolved by use of R-Ni with the ester to which 0.3 mole per cent of the sodium salt has been added (13). (Cf. base effect, above.)

5. Use of Adams Catalyst at High Pressure (14). The hydrogenation of an aromatic ring using the Adams Pt catalyst at low pressures can be accomplished if glacial acetic acid (15) or alcohol containing HCl or HBr (16) is the solvent employed. The high pressure reaction also depends critically on the solvent and, in general, proceeds more readily although an anomalous failure was observed in the case of aniline.

6. Polymethylbenzenes and Polymethylbenzoic Acids. Smith and coworkers have undertaken a study of the hydrogenation of the benzenoid nucleus using the Adams datalyst in HOAc at low pressures. The behavior of phenyl substituted aliphatic acids and alkylated benzenes (17) indicated the importance of symmetry, e.g. p-cymene reduces faster than i-propyl benzene. Examination of almost all of the polymethylbenzenes and polymethylbenzoic acids (18) confirmed this fact: as the number of groups increases, the rate of hydrogenation (19) decreases; for a given number of groups, as the symmetry of the molecule increases the rate increases.

II. Hydrogenation of Esters to Alcohols (20, 21, 22, 23). The use of a 1:1 or higher ratio of catalyst to hydrogen acceptor lowers the temperature required for the hydrogenation of esters and, in so doing, gives high yields of alcohols where previously only the corresponding saturated compounds have been obtained. Thus, benzoates give benzyl alcohols; malonates, 1,3-glycols; β-keto and -hydroxy esters, 1,3-glycols; α-keto and -hydroxy esters, 1,2-glycols; α- and β-amino esters, 1,2- and 1,3-amino-alcohols. High pressures (5000 psi) and temperatures of 125-150°C with CuCrO or 25-75° with W-6 R-Ni are used. Copper-chromium oxide is preferred in general and in particular with the β-substituted esters unless temperatures below 100° are necessary. If R-Ni is used the amino-esters reduce faster than the keto or hydroxy esters unless triethylamine is added (Cf. base effect, above). This development is

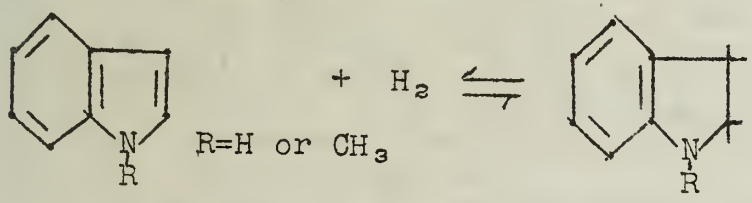
considered to be the most important advance in recent years in catalytic hydrogenation.

III. Reversibility of Catalytic Hydrogenations. The following equilibrium over copper-chromium oxide at 240-60°C and 200-300 atmospheres of hydrogen pressure has been definitely established (24):

$$RCOOCH_2R' + 2H_2 \rightleftharpoons RCH_2OH + R'CH_2OH$$

It is evident that compounds such as $RCOOCH_2R$, $R'COOCH_2R'$ and $R'COOCH_2R$ are possible in such a reaction. The isolation of such compounds has never been accomplished since the concentration of ester is only about 1%. Subsequent experiments (25) used for the sake of simplicity compounds which can give only one ester and one alcohol: $CH_3(CH_2)_6COO(CH_2)_7CH_3$, $(CH_3CH_2)_2CHCOOCH_2CH(CH_2CH_3)_2$ and $(CH_3)_3CCOOCH_2C(CH_3)_3$. The position of the equilibrium was shown to depend profoundly on the hydrogen pressure; at 10 atmospheres the conc. of ester is 80%. This would indicate the reaction has potentiality for the preparation of hindered esters from the corresponding alcohols. A similar reaction attempted over R-Ni yielded only a hydrocarbon with one less carbon (25, 26).

Similarly, over copper-chormium oxide at 150-70°C (25, 27):



2,3-Dimethylindole gives a lower conc. of the indoline at comparable pressures. However, the reduction of 3,3-dimethylindole proceeds irreversibly at 35 atmospheres of hydrogen pressure.

IV. Preparation of Raney Nickel Catalyst. A number of catalysts (9) have been prepared from a 50% Ni-Al alloy, but there are basically three kinds: a slightly alkaline catalyst (commercial, W-3,-4,5), a highly alkaline catalyst (W-7), and one with a large amount of adsorbed hydrogen (W-6). The commercial type serves for most purposes. W-6 is the most active and is sometimes the only effective catalyst; it has been used especially in the low temperature hydrogenation of esters (above) and in the low pressure technique ordinarily employed with the noble metal catalysts (9d). W-7 is especially useful, even at low pressures, for aldehydes, ketones and nitriles (9d).

The affect of the composition of the alloy has been subjected to further study, and it is claimed that an alloy containing only 20% Ni gives not only a superior but also a non-pyrophoric catalyst (28).

V. Selective Hydrogenation of α,β-Unsaturated Ketones (28,29). The low pressure hydrogenation of α,β-unsaturated ketones over R-Ni is known to give a saturated alcohol, but a recent paper states that if $CHCl_3$ or HCl is present the saturated ketone is obtained. For example, the reduction of benzalacetone to benzylacetone and dibenzalcyclohexanone to dibenzylcyclohexanone are cited. It is also claimed that complex systems such as difurfuralacetone can be selectively hydrogenated by controlling the amount of $CHCl_3$ added.

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THE WILLGERODT REACTION

Reported by P. D. Caesar March 18, 1949

Reviews of the Willgerodt reaction and its various modifications complete through 1946 can be found in "Organic Reactions," vol. III, and in a past seminar (1).

Mechanism Studies

Two mechanisms have been proposed, either of which can be used to explain most of the experimental facts.

A. The mechanism proposed by Carmack and coworkers (2) follows the route:

Ketone $\rightleftarrows$ hydroxylamine $\rightleftarrows$ unsaturated amine $\rightleftarrows$ acetylene $\rightleftarrows$ unsaturated amine.....

When the labile amine group reaches the end of the chain, an irreversible oxidation reaction takes place between the sulfur and the nitrogen compound to produce a thioamide. Subsequent hydrolysis gives amide and acid.

Objections to this theory include the need of a separate mechanism to get the labile group past a branched chain, the unsubstantiated unsaturated amine intermediate, and the unexplained final oxidation step.

B. King and coworkers (3) suggested the route:

Ketone $\rightleftarrows$ thioketone $\rightleftarrows$ thiol $\rightleftarrows$ olefin $\rightleftarrows$ thiol....

Again when the labile group, this time a mercaptan group, reaches the end of the chain an irreversible reaction with sulfur takes place to produce a thioamide.

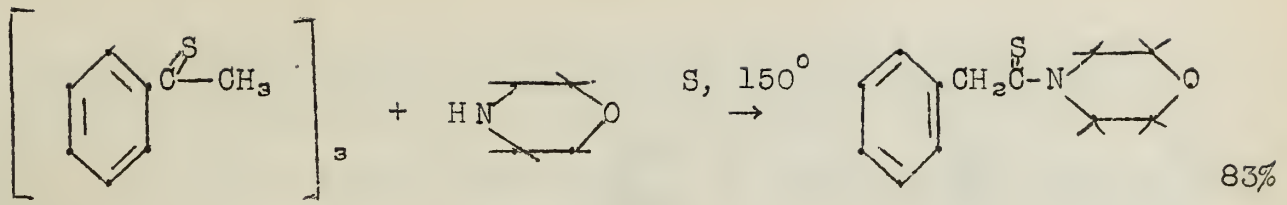
This mechanism offers an adequate explanation for the migration of the SH-group past a side chain:

$$RC{=}\overset{C}{\underset{C}{}}{-}C \rightleftarrows RC{-}\overset{C}{\underset{SH}{C}}{-}C \rightleftarrows RC{-}\overset{C}{C}{=}C$$

and accounts for the poor yields obtained, since t-thiols, when used as starting materials in the Willgerodt reaction gave very poor yields of the amides. Moreover, with the aid of some recent investigations all intermediates proposed in this mechanism have been shown to be feasible starting materials, and the steps in the final oxidation reaction have been thoroughly analyzed.

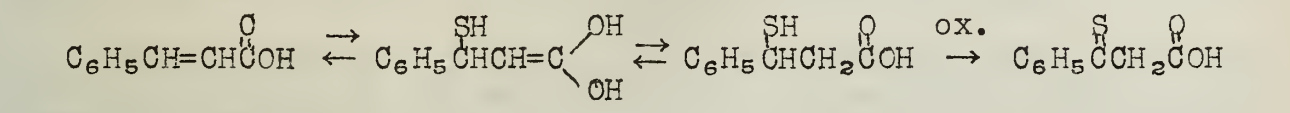
Thioketones as Intermediates

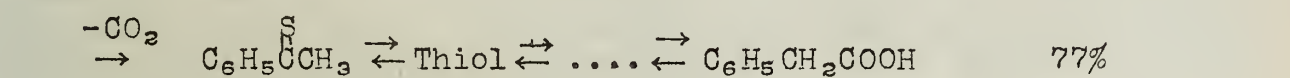
Confirmation of the probable participation of thioketones in the Willgerodt reaction was obtained (4) when trithioacetophenone was found to give better yields of the thioamide than did acetophenone.



83%

Moreover, α, β-unsaturated acids lose the original carboxyl carbon with conversion of the α-carbon to a carboxyl (5). Using cinnamic acid as a typical example, King's mechanism could be applied in this manner.



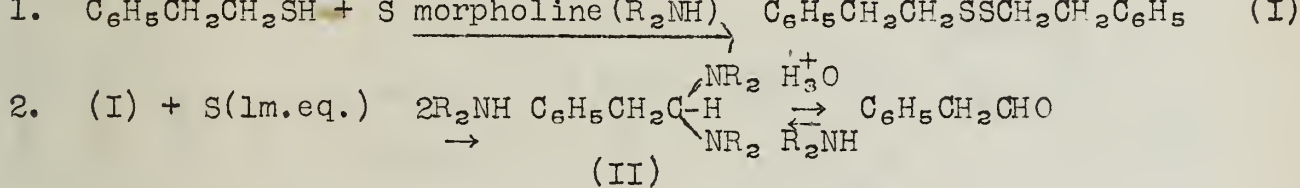


77%

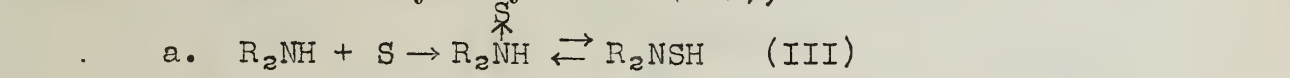
These experiments coupled with the negative results obtained with certain secondary alcohols give substance to the ketone-thioketone-thiol-olefin route. However, easily dehydrated alcohols can be used as starting materials, so that analogous ketones may by-pass the thioketone step.

Oxidation of Primary Thiols (6)

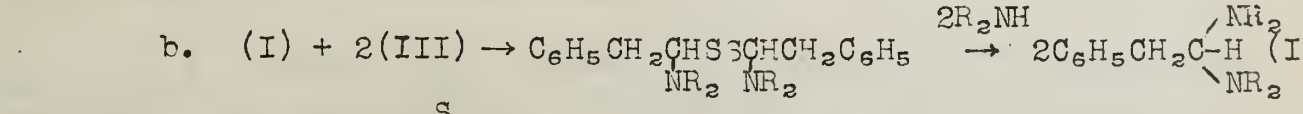
The oxidation reaction of a primary amine to a carboxylic acid derivative is unique. The steps will be illustrated, where possible, by compounds actually employed.



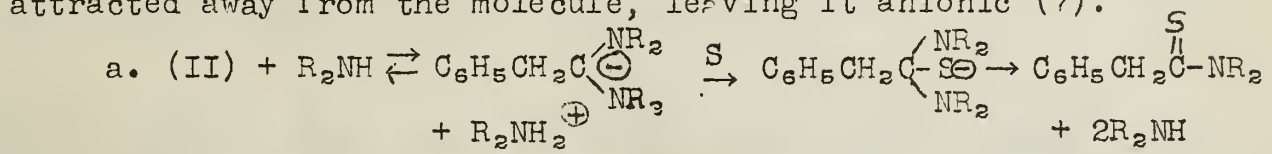
In this step phenyl acetaldehyde was isolated upon hydrolysis of the product when the sulfur used was insufficient to carry the reaction to completion. The best of several methods of accounting for this seemed to be the assumption that the amine and sulfur react to form a thiohydroxylamine (III),



which then reacts with disulfide.

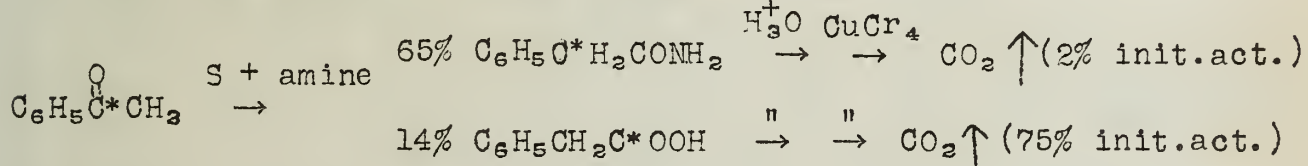


In this step it is assumed that the amino groups tend to activate the hydrogen at the central bond so that it can be attracted away from the molecule, leaving it anionic (7).



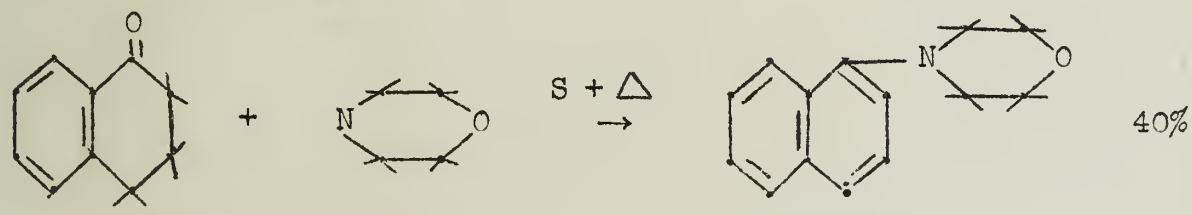
It should be noted that this course of oxidation can not be applied to tertiary thiols (8) past step 1. or to secondary thiols past step 2. Therefore, the reaction must proceed to the primary thiol before reaching the irreversible oxidation stage.

Tracer studies (9) using C^{14} in the carbonyl group have shown that in addition to the major yield of unrearranged amide, a substantial quantity of acid is formed in which the C^{14} has migrated to the carboxyl group. This work in its complete form is now in press and the findings do not differ from those specified in the previous Communication to the Editor.



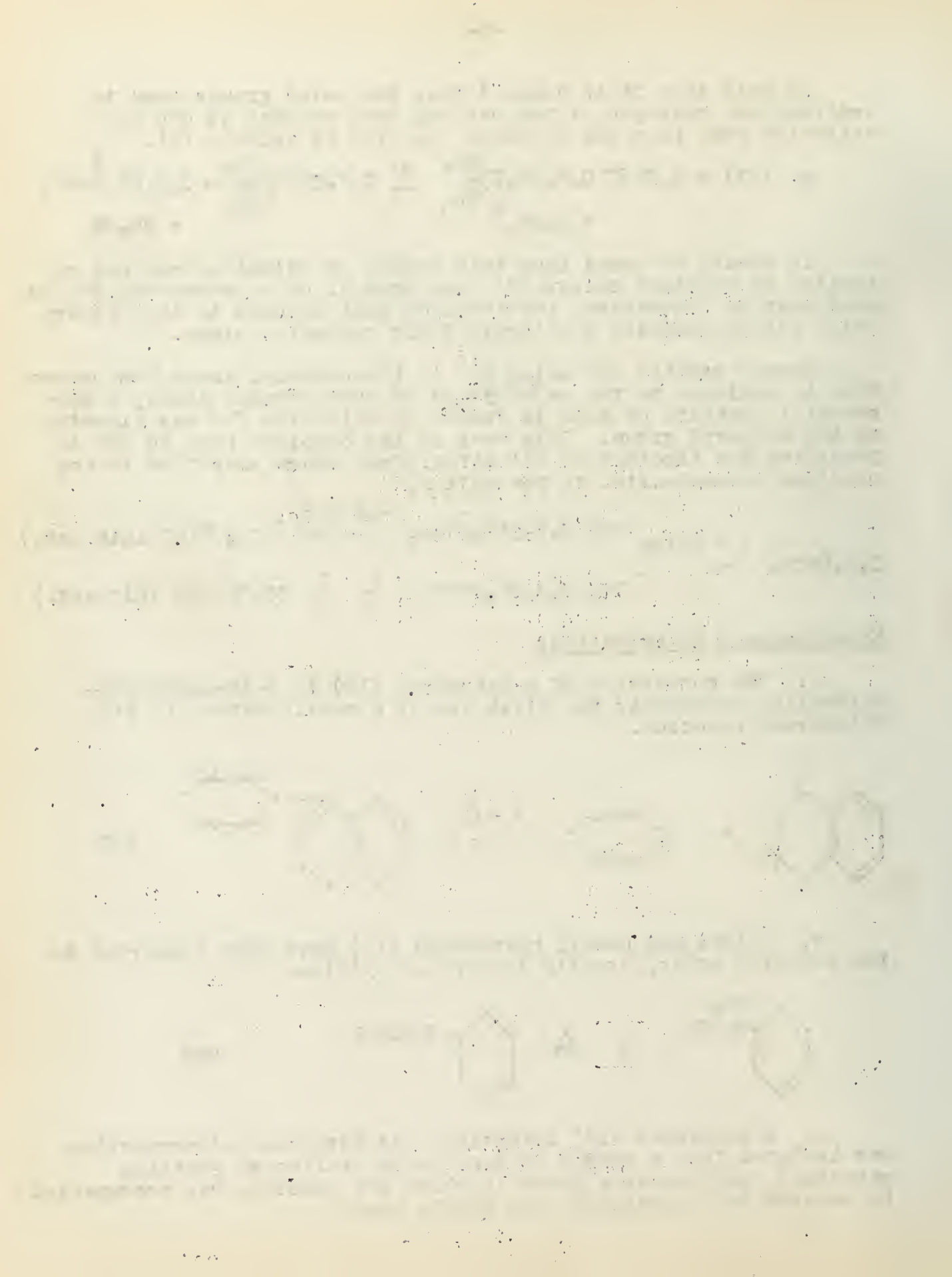
Miscellaneous Contributions

1. The conversion of α-tetralone (10) to 4-(2-naphthyl)-morpholine represents the first use of a cyclic ketone in the Willgerodt reaction.

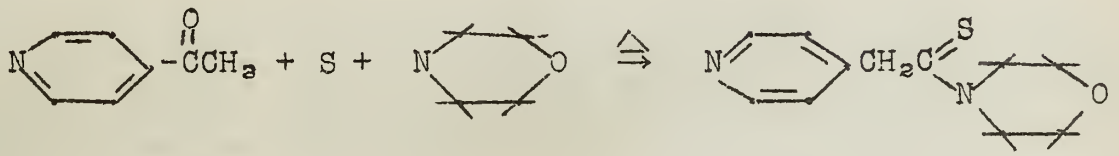


2. Oximes and phenyl hydrazones (11) have been converted to the expected acids, usually in very low yields.

3. A substance (12) idientified as dithiooxalodimorpholide was isolated from a number of runs using olefins as starting materials, particularly those in which the reaction was accompanied by substantial cleavage at the double bond.



4. Several heterocyclic ketones have been employed (13,14). α-Thienyl methyl ketone gave tarry products only, but the pyridyl and quinolyl methyl ketones reacted normally.



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THE MECHANISM OF THE FRIES REACTION

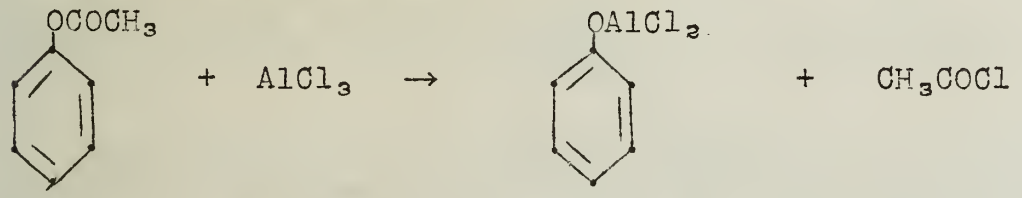
Reported by Robert E. Carnahan March 18, 1949

The Fries reaction consists in the conversion of a phenyl ester into an ortho- or para-hydroxyphenylketone under the action of an acid catalyst such as aluminum chloride. In most cases by the proper choice of the reaction conditions, primarily one isomer or the other may be obtained (1).

Mechanisms

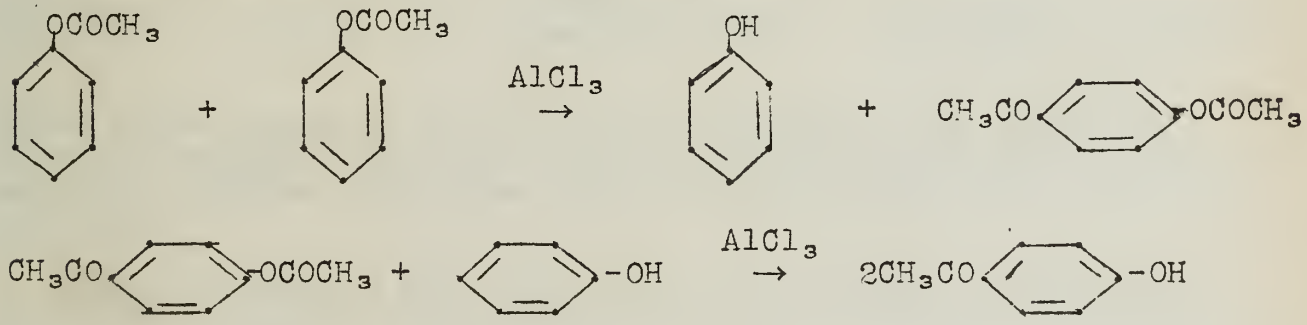
Previous to 1940, three mechanisms for the Fries reaction had been presented (2). Each of these had evidence which supported it but did not exclude the others.

I. Cleavage of the ester to yield an acid chloride which could then acylate the aromatic nucleus.



This was supported by the fact that acetyl chloride could be isolated when m-cresylacetate was submitted to the Fries reaction in the presence of o-chlorobenzoyl chloride.

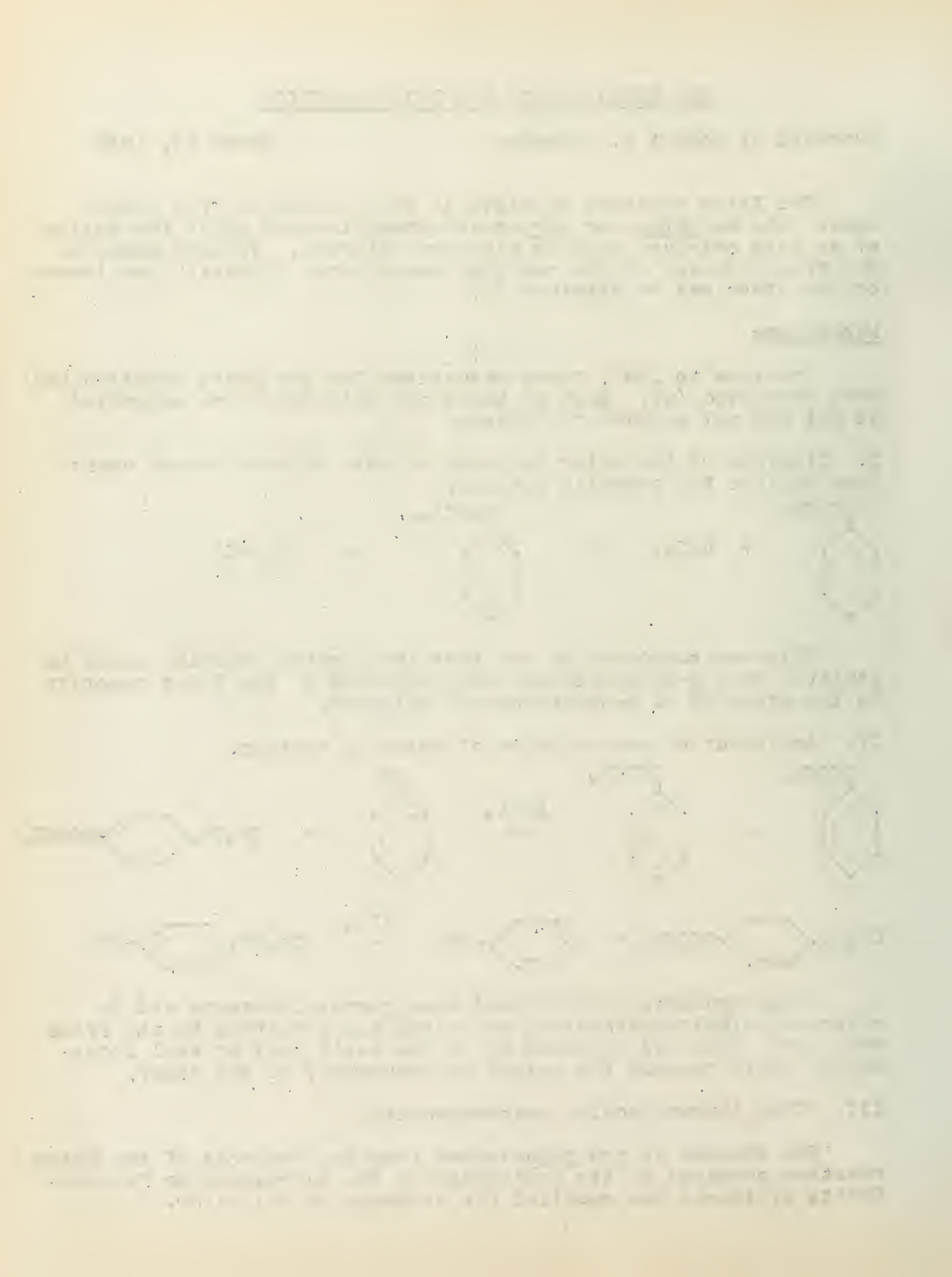
II. Acylation of one molecule of ester by another.

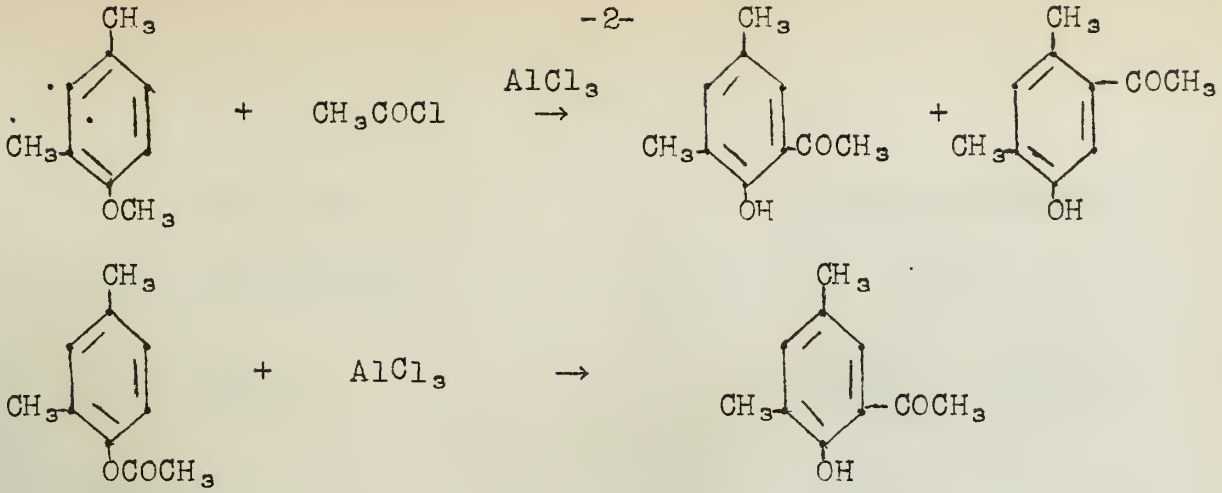


Cross-products are obtained when p-cresylbenzoate and 2-chloro-4-methylphenylacetate are mixed and submitted to the Fries reaction. This was objected to on the basis that an acyl interchange could precede the actual rearrangement of the ester.

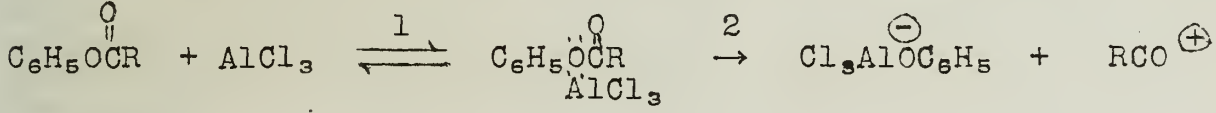
III. True intramolecular rearrangement.

The absence of the meta-isomer from the products of the Fries reaction compared to its production in the corresponding Friedel-Crafts synthesis was supplied for evidence of this view.

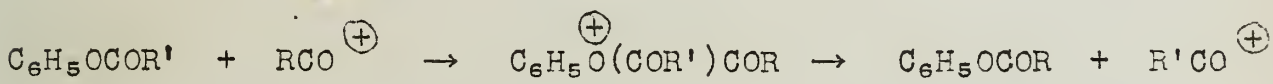




Actually the two intermolecular mechanisms above are one and the same (3). Each of these mechanisms is basically a Friedel-Crafts type of reaction. The crucial part of such a mechanism involves the attack of an oxo-carbonium ion on the aromatic nucleus. The most logical route for the production of this ion is as follows.



The possibility for an acyl interchange to precede an intramolecular rearrangement in a case where mixed products are obtained is excluded. This would involve the attack of the oxo-carbonium ion, $RCO^{\oplus}$, on a molecule of ester to form the ion $C_6H_5O(COR)COR'$ which would then dissociate into a molecule of ester and the other oxo-carbonium ion, $R'CO^{+}$.



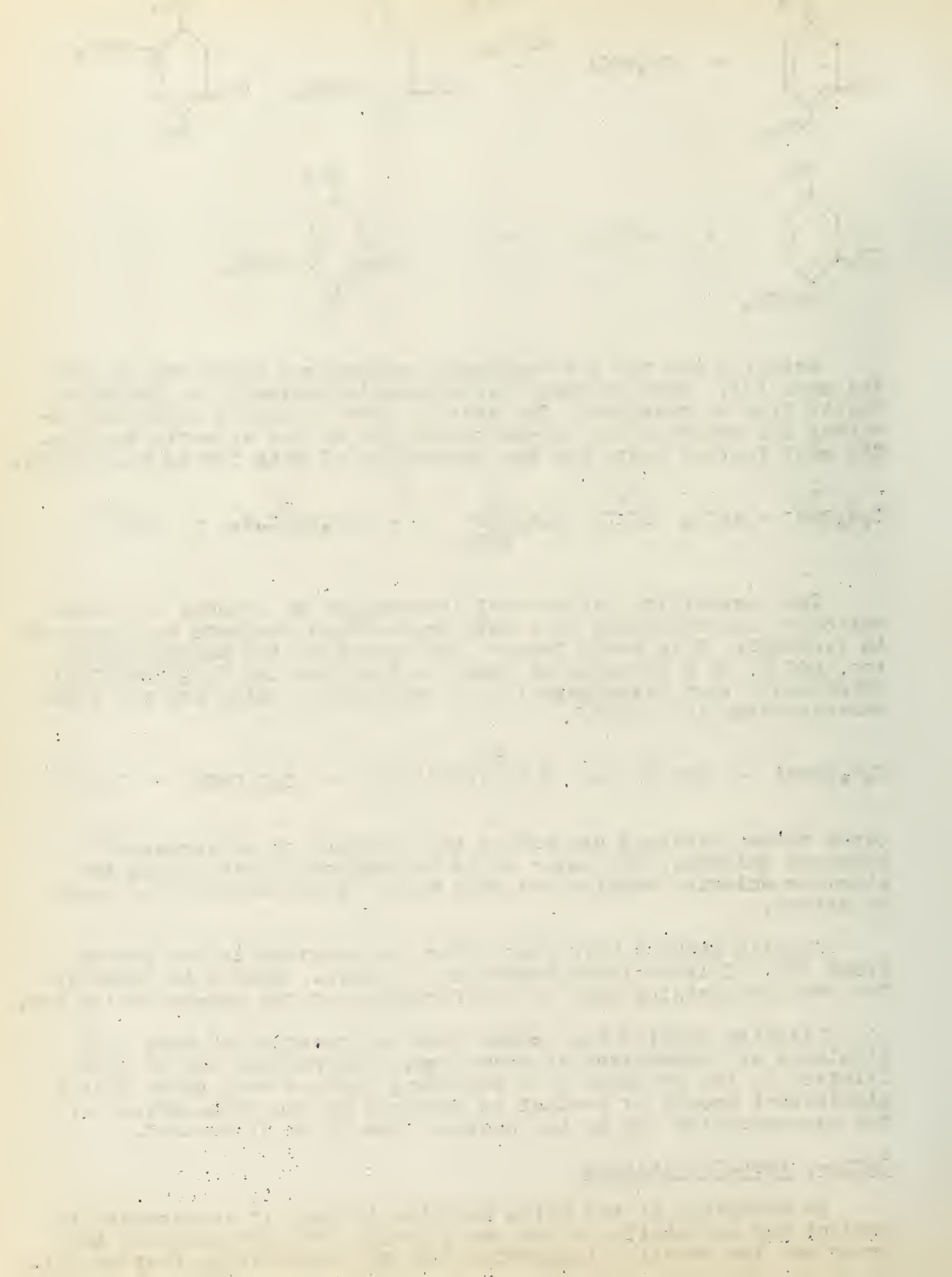
Since these reactions are run in the presence of an excess of aluminum chloride, the ester would be completely tied up as the aluminum chloride complex and thus would be unavailable for such an attack.

Kinetic studies have shown that the reaction is not second order (3). This excludes mechanism II above. Step 2 is probably the rate determining step in the formation of the oxo-carbonium ion.

Dilution studies have shown that the reaction at best only simulates an intramolecular mechanism. Experiments run at high dilution in the presence of a competing nucleus have shown that a significant amount of product is obtained by the chance attack of the oxo-carbonium ion on the nucleus from which it seceded.

Ortho-, Para-Orientation

An advantage of the Fries reaction is that it is possible to predict the orientation of the acyl group. The structure of the group and the reaction temperature are the determining factors (4).



Acyl Group	Isomer Produced
aromatic-aliphatic (e.g. phenylacetyl)	ortho-
aliphatic (e.g. acetyl)	ortho- or para- depending upon the temperature
aromatic (e.g. benzoyl)	para-

In the case of the aliphatic esters, a high reaction temperature (about 160°) in the absence of a solvent leads to ortho-orientation. A low reaction temperature (60° or less) in the presence of a solvent such as nitrobenzene leads to para-orientation. It is interesting to note that with aromatic-aliphatic and strictly aromatic esters, orientation is temperature independent. A correlation between the enolization tendency of the ester and the ortho-orientation of its acyl group has been made (4). It has been found that those esters which have a strong tendency to enolize give rise to ortho-orientation while those which cannot enolize give only the para-isomer regardless of the reaction conditions. On the basis of this, an intramolecular mechanism for the ortho-shift, involving enolization as the first step, was presented.

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THE AUTOXIDATION OF TETRALIN

Reported by Robert G. Bannister March 25, 1949

Because of its activated methylene groups, tetralin undergoes autoxidation with measurable speed under mild conditions; moreover, its primary oxidation product, tetralin hydroperoxide, is a relatively stable compound which can be isolated in crystalline form at least 98% pure. The reaction has therefore been studied in detail in an effort to shed light on hydrocarbon oxidation in general. Previous work has been concerned chiefly with kinetic studies based on oxygen uptake, but recently the identification of numerous by-products has made possible a more thorough understanding of the reaction.

When a current of air is passed into tetralin at 76° for 50-80 hours, a viscous reddish-orange oil is produced. The oxidation has been shown (1,2,3) to take place in four distinct stages in which the reaction is at first barely perceptible, then accelerates rapidly, reaches a steady state, and finally tapers off after about 30% of the tetralin has been oxidized. It is impracticable to oxidize the last 30-40% of the tetralin.

The mechanism of the primary oxidation process involves the chain formation of peroxides: this reaction accounts for at least 95% of the oxygen uptake (2).

(a) $>CH\cdot + O_2 \rightarrow >CHOO\cdot$

(b) $>CH_2 + >CHOO\cdot \rightarrow >CHOOH + >CH\cdot$

Tetralin hydroperoxide is itself an autoxidation catalyst, so that the initiation of the above reactions can be attributed to the minute quantities of the peroxide always found in tetralin as well as adventitious catalysis by active spots on the surface of the vessel, etc. After 80 hours reaction time the concentration of tetralin hydroperoxide is 25%; at earlier stages it is even higher (35-40%).

After the reaction mixture has been heated to destroy the peroxides (130-150°) and the unreacted tetralin has been removed, the chief reaction products, α-tetralone and α-tetralol, may be distilled off. Several workers (3,4,5) have recently shown that α-tetralol, which cannot be separated from the ketone by distillation alone, constitutes 20-30% of this fraction. Robertson and Waters (3) were also able to isolate the following by-products in small amounts from the residue: (I) γ-o-hydroxyphenylbutyraldehyde, (II) β-o-carboxyphenylpropionic acid, and (III) γ-o-hydroxyphenylbutyric acid together with polymeric products and saponifiable substances, probably esters of tetralol with acids (II) and (III). The tetralin fraction was also found to contain a small percentage of 1,2-dihydronaphthalene. All of these products were also obtained by thermal decomposition of tetralin hydroperoxide.

Robertson and Waters account for the production of tetralone and tetralol by reactions of the type:

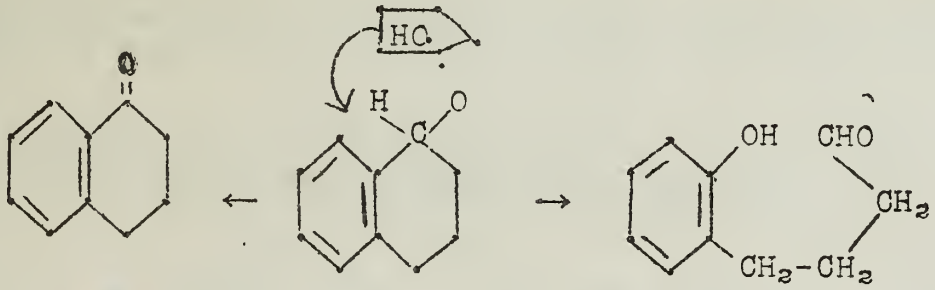
(c) $C_{10}H_{11}OOH \rightarrow C_{10}H_{10}O + H_2O$ (see below)

(d) $C_{10}H_{11}OO\cdot + .OH \rightarrow C_{10}H_{11}OH + O_2$

(e) $C_{10}H_{11}O\cdot + RH \rightarrow C_{10}H_{11}OH + R\cdot$

The fact that equation (d) plays some part in the formation of α-tetralol is shown by the observed evolution of oxygen; however, most of the tetralol is probably derived from $C_{10}H_{11}O\cdot$ radicals which have oxidized (dehydrogenated) other organic matter according to equation (e).

The aldehyde (I) is regarded as a product of the direct decomposition of the peroxide, analogous to the known decomposition of

(f) $H_2O +$ 

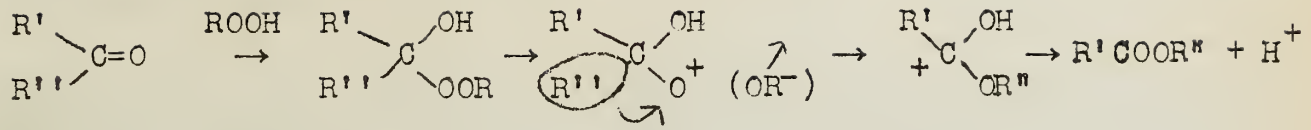
(I)

triphenylmethane hydroperoxide to benzophenone and phenol. Most of the peroxide, however, decomposes to form tetralone, as shown also in equation (c), indicating the tendency to break the C-H bond rather than the C-aryl link.

The investigators have found that the phenolic aldehyde (I) and acid (III) are inhibitors of the autoxidation when added at any stage of the reaction and therefore attribute to their formation the fact that the autoxidation does not proceed to completion.

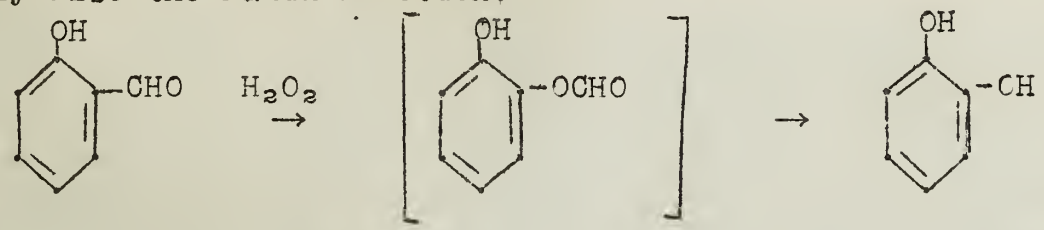
The dicarboxylic acid (II) probably results from the further autoxidation of α-tetralone in the β position, followed by fission of the α,β-carbon-carbon bond. Pure α-tetralone undergoes slow autoxidation at 100° to form the 1,2-diketone and unidentified acids, while the analogous autoxidation of cyclohexanone gives both the diketone and adipic acid (as well as its hemi-aldehyde) in good yield.

The investigators regard the phenolic acid (III) as the product of a reaction between α-tetralone and tetralin hydroperoxide since they were able to prepare the same acid (in the form of the lactone) by oxidation of tetralone with Caro's acid (which is, of course, itself a hydroperoxide). They have postulated the following general mechanism for peroxide oxidation of ketones:



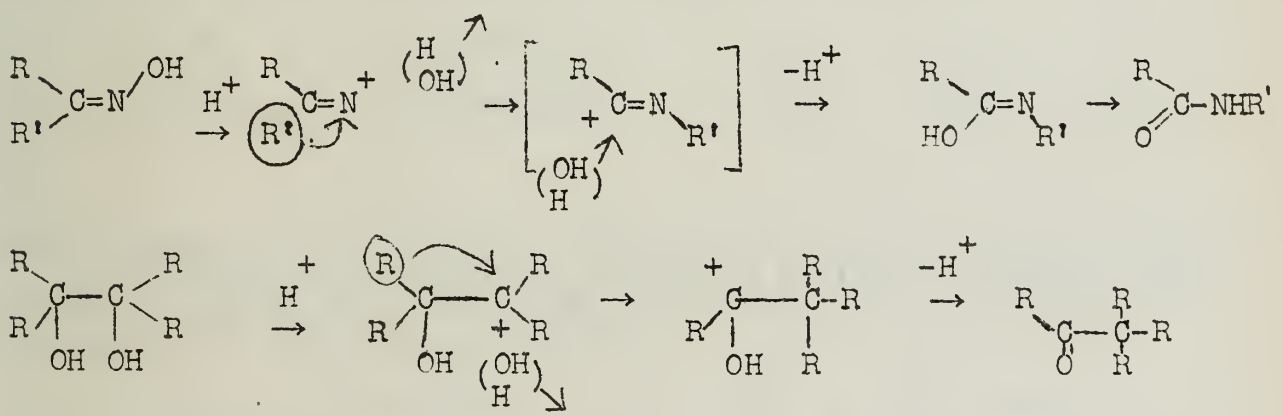
(R=$C_{10}H_{11}$, SO_3H, etc.)

The postulated mechanism seems to be applicable to many types of peroxide reactions: Caro's acid oxidation of ketones, peroxide ester rearrangements as reported in a recent seminar (6), perbenzoic acid oxidation of ketones (7): $C_6H_5COAr \rightarrow C_6H_5OOCAr$, and probably also the Dakin reaction:



The formate intermediate in the above reaction has been isolated by carrying out the reaction with peracetic acid in glacial acetic acid (8).

It is interesting to note the similarity of the above mechanism to those of the Beckmann and pinacol rearrangements:



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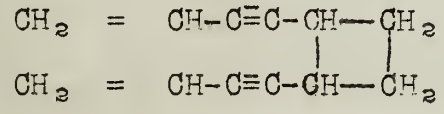
SYNTHESIS OF THE CYCLOBUTANE RING

Reported by Aaron B. Herrick March 25, 1949

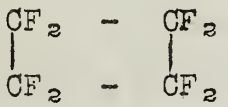
Introduction: The synthesis of cyclobutane and its derivatives is difficult because of the strain involved in forming four-membered rings. Few synthetic methods leading to cyclobutanes were known until recently, and most of these result in poor yields. In recent months cyclobutane has been prepared for the first time in good yield; a few general method of preparing alkyl cyclobutanes has appeared, and fluorinated cyclobutane derivatives have been obtained in large numbers.

Historical: Perkin in 1883 prepared the first cyclobutane derivative, the mono-carboxylic acid, from trimethylene bromide and malonic ester in the presence of sodium ethoxide, followed by saponification and decarboxylation (2). The two dicarboxylic acids were also prepared by Perkin in a similar manner. A method using sodium cyanide as the condensing agent affords the 1,2-dicarboxylic acid in better yield (3). In a similar fashion trimethylene bromide and benzyl cyanide condense in the presence of sodamide to yield 1-cyano-1-phenyl-cyclobutane.

The only other general source of cyclobutane derivatives is a number of dimerization reactions. Cinnamic acid dimerizes to a mixture of truxinic and truxillic acids; divinyl acetylene dimerizes to a cylcobutane derivative (I), and octafluorocyclobutane is obtained upon heating tetrafluoroethylene. (II) (4).

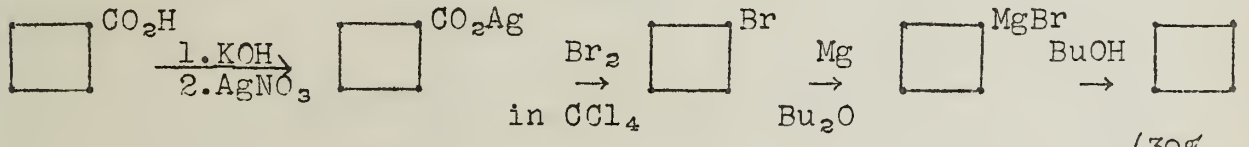


I



II

Preparation of cyclobutane: Willstadter obtained a small amount of cyclobutane by a series of reactions in 1907. However this compound was not prepared in appreciable yield until Cason (5) developed the following synthesis:



(39% Overall)

Cason also obtained cyclobutane in 7% yield from tetramethylene bromide by a Wurtz reaction employing sodium in boiling xylene. Although this appears to be a poor yield, the best previously obtained was approximately 1%.

Preparation of tetrafluorocyclobutanes: A large number of tetrafluorocyclobutane derivatives have been reported recently (6). They are produced by the reaction of tetrafluoro ethylene with a variety of unsaturated compounds. The products are one to one adducts, and

they are obtained by heating the reagents at 100-150° in a high pressure bomb.

$$CF_2 = CF_2 + CH_2 = CH - X \xrightarrow[\text{bomb}]{100\text{-}150^\circ} \begin{matrix} CF_2\text{-}CH_2 \\ | \quad | \\ CF_2\text{-}CH\text{-}X \end{matrix}$$

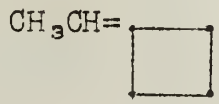
Table of Representative Tetrafluorocyclobutanes

Starting material	X	Percent Yield
$CH_2 = CH_2$	-H	40
$C_6H_5CH = CH_2$	$-C_6H_5$	85
$CH_2 = CHCl$	-Cl	23
$CH_2 = CH\text{-}CN$	-CN	84
$CH_2 = CH\text{-}CHO$	-CHO	12
$CH_2 = CH\text{-}CH_2OH$	$-CH_2OH$	45
$CH_2 = CH\text{-}COCH_3$	$-COCH_3$	18
$CH_2 = CH\text{-}CH{=}CH_2$	$-CH = CH_2$	90
$CH_2 = C = CH_2$	$=CH_2$	14

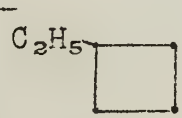
These "cycloalkylations" proceed in higher yield at lower temperatures than the dimerization reaction mentioned previously. The relative ease of reaction is: dienes > $CH_2 = CHR$ > $RCH = CHR$.

Preparation of Alkyl cyclobutanes: Boord (7) and coworkers have recently outlined a novel synthesis of alkyl cyclobutanes from neopentyl type tribromides using a zinc dehalogenation in molten acetamide (the Hass-McBee procedure). The yield of alkylidene cyclobutane is usually 40-50% of theory. Some of the other products of the reaction, differing only in the position of the double bond, can be hydrogenated to the same alkylcyclobutane. The synthesis of ethyl cyclobutane illustrates this method.

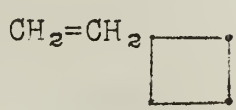
$$CH_3CH_2C(CH_2OH)_3 \xrightarrow[59\%]{PBr_3} CH_3CH_2C(CH_2Br)_3 \xrightarrow[Na_2CO_3,\ NaI\ (90\%)]{Zn,\ CH_3CONH_2}$$



(50%)

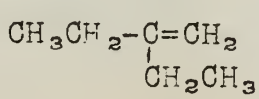


30%

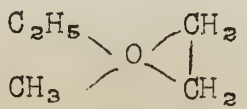


70%

(18%)



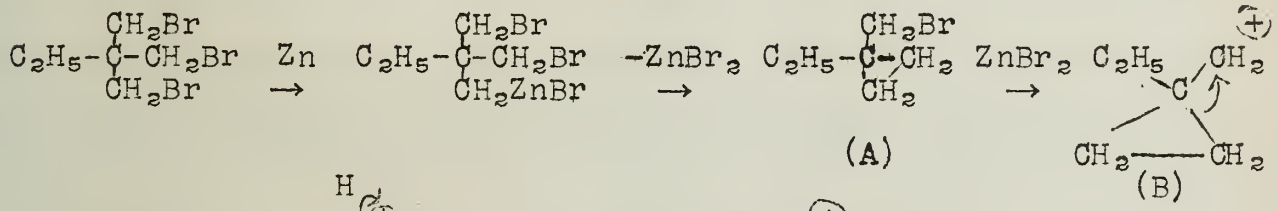
(12%)



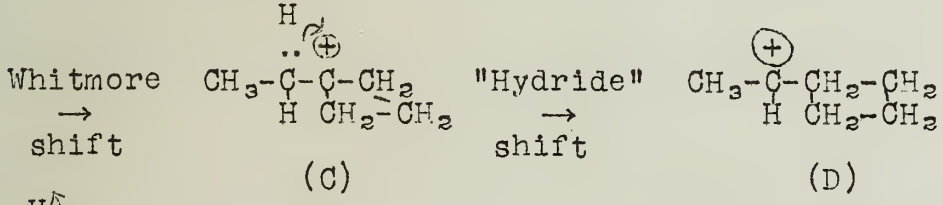
(3%)

Starting with the appropriate tribromide, the corresponding methyl and isopropyl cyclobutanes were also obtained by this method. Methylene cyclobutane and methyl cyclobutane were obtained in better yield from the dehalogenation of the tetrabromide from pentaerithritol using zinc in ethanol (Gustavson procedure) (8). However, the Boord synthesis appears to be the only general route to monoalkyl and monoalkylidene cyclobutanes.

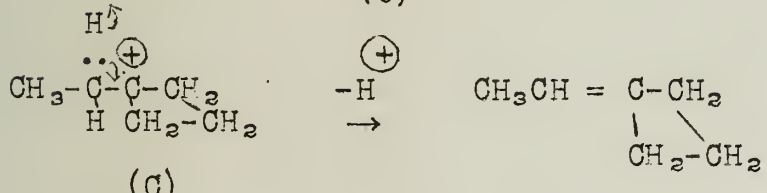
A mechanism suggested by Boord to account for the products obtained (above) involves the preliminary formation of a bromoethylcyclopropane (A) which is further converted by zinc bromide to the carbonium ion (B), which then undergoes a rearrangement (Whitmore shift) to the cyclobutyl carbonium ion (C). By a "hydride shift" (6) rearranges to (D), another carbonium ion. Familiar operations on these four intermediates lead to the products obtained.



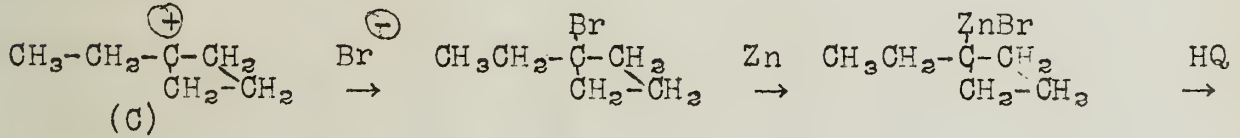
(A) (B)



(C) (D)



(C)



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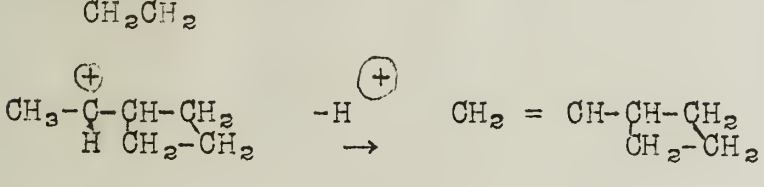

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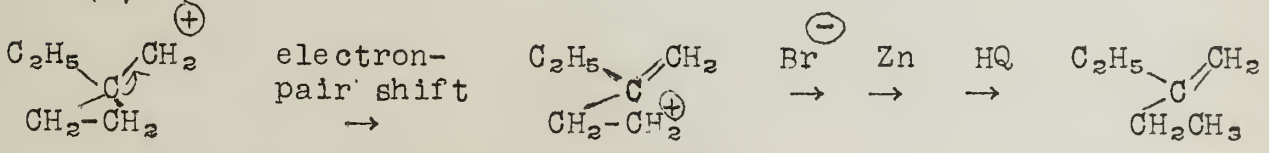
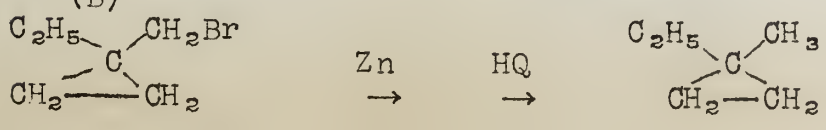


(B)



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SURVEY OF DECARBOXYLATION REACTIONS

Reported by H. A. DeWalt, Jr. April 1, 1949

The well known use of decarboxylation reactions in organic synthesis has instigated numerous studies of this reaction. The influences of substituents, pH, solvents, biochemical enzymes, and optically active catalyst for asymmetric decarboxylations have been studied (1,2,3). Unfortunately, all of these investigations with their different points of view did little to correlate this general reaction. From the results of these investigations and the modern concept of organic reactions Schenkel et al (4,5,6,7) have treated decarboxylation reactions as outlined in this abstract.

In general, the decarboxylation of an acid follows the mechanism:

$R: | \overset{O}{\overset{\parallel}{-}}O: | H \rightarrow R:H + \overset{O}{\overset{\parallel}{C}}=O$. The bond between the R group and the carboxyl group is cleaved with retention of the electron pair by the R group. This is followed by the lost of carbon dioxide with simultaneous electrophilic attack of the carbanion by the proton. The following two electrophilic mechanisms have been formulated and verified by experiment.

S_E1 $\quad H^{+} + R\text{-}COOH \rightarrow RH + CO_2H^{\oplus}$

The rate determing step is the displacement of the carboxyl group by the hydrogen ion. Anthracene-9-carboxylic acid decarboxylates according to this mechanism, and the prediction that the rate of decarboxylation increases with increasing acidity of the solvent has been experimentally verified.

S_E2 $\quad RCOOH \rightarrow R:^{\ominus} + COOH^{\oplus} \rightarrow CO_2 + H^{\oplus}$

$R:^{\ominus} + H^{\oplus} \rightarrow RH$

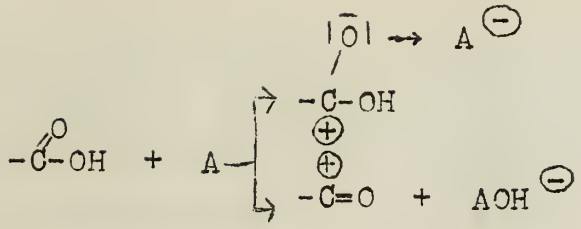
The rate determing step is the dissociation of the bond between the R and the carboxyl groups. The strong organic acids - such as trichloroacetic, tribromoacetic, nitroacetic, and 2,4,6 trinitrobenzoic acids -- were found to decarboxylate by this mechanism.

II. The Catalyzed Reaction.--The sensitivity of certain decarboxylation reactions to catalysts is well known. Schenkel (6) explains the action of the catalyst with the assumption of a donor-acceptor reaction between the carboxylic acid and the catalyst exclusive of the dielectric properties of the solvent.

Further correlation is possible by considering the separate influence of the R and the carboxyl groups upon the decarboxylation mechanism.

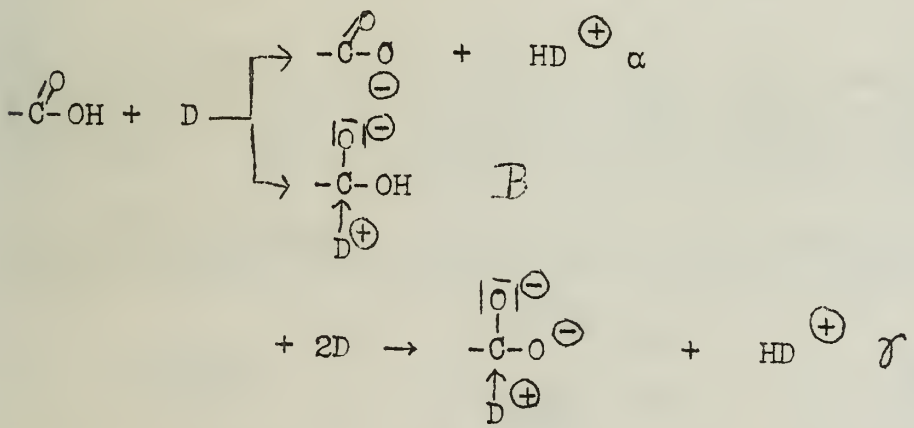
A. Reactions with the COOH, CO

1. Where the acceptor molecule is an acid molecule, the following reactions are possible.



Thru polarization of the carbonyl group, the CO group becomes positive or electron deficient and impedes decarboxylation. Studies on the energy of activation for decarboxylation of trichloroacetic and trinitrobenzoic acids in water dioxane solutions show a decrease energy requirement with increasing dioxane content. Hydrogen bonding between the oxygen atom of the carbonyl group and the hydrogen atoms of the water molecules causes the CO group to become positive. A higher energy of activation is then required to push the electrons towards the CO to complete the electron octet and permit decarboxylation.

2. When the donor molecule is a basic molecule, the CO group possesses two acidic atoms, the hydrogen atom and the carbon atom according to the Lewis concept. Either of these acidic atoms can be neutralized singly or at the same time by basic molecules.



In each of the above equations the CO becomes negative and will decarboxylate.

Route α is the well known decarboxylation in alkaline medium. Equation B explains the catalytic effect of tertiary amines on decarboxylation of beta ketoacids. The following experimental facts are offered as evidence for this mechanism:

(1) Since the anion is stable towards decarboxylation, the increased decarboxylation rate of the free acid in the presence of an amine can not be due to route α.

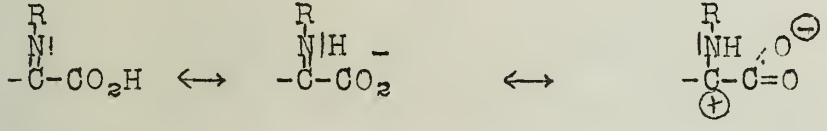
(2) The catalytic effect of the tertiary amine in acid solution is retarded due to the lose of its co-ordinating electron in salt formation.

Route γ is observed by the kinetic investigations on the rate of decarboxylation of trichloroacetic acid in aniline - benzene or toluene solution. The greatest yield of product was obtained when two moles of aniline were present for every mole of acid.

B. Reaction with the rest of R-

The general treatment of catalytic addition to the R group of carboxylic acids must be postponed until this part of the problem has been more throughly investigated. However, the following cases represent two interesting examples.

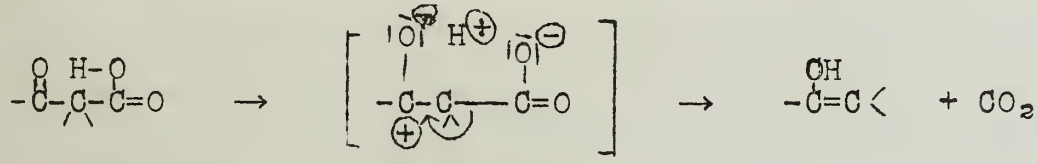
Alpha ketoacids.-- These acids can be catalytically decarboxylated by the SE1 mechanism. The required primary amine converts the ketoacid into an iminoacid which on account of the strong basicity of the nitrogen atom exists in the immonium carboxylate form (I).



(I) (II)

The resonance of (I) to (II) permits the formation of a strongly positive or electron deficient alpha carbon atom which attracts the electron pair of the bond connecting the negative CO group to itself. Decarboxylation then stabilizes the molecule.

Beta-ketoacids.--Since these free acids are readily decarboxylated, Schenkel (6) proposes the following mechanism.

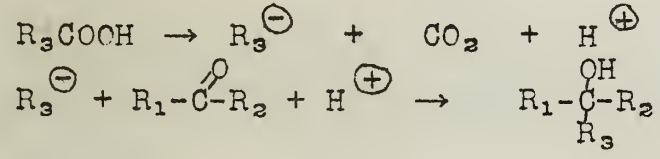


This decarboxylation proceeds through intramolecular neutralization of the polarized beta carbonyl group by a proton from the CO group. The beta carbon atom becomes positive and induces the dissociation of bond between the alpha carbon atom and the negatively charged CO group. Double bond formation between the alpha and beta carbon atoms meutralizes the latter's electron deficiency. This mechanism predicts the following: (1) Beta-keto-acids should decarboxylate according to SE1. (2) Anions can not be decarboxylate. (3) [5,5] bicyclo beta-keto-acids should be stable to non catalytic carboxy lation since double bond formation between the alpha and beta carbon atoms is prohibited by Bredt's rule.

Experimentally, beta-keto-acids have been found to decarboxylate according to SE1 and their anions are not decarboxylated. 7,7 dimethyl-bicyclo-[1,2,2]-2-heptanone-1-carboxylic acid has been found stable towards non-catalytic decarboxylation.

This same decarboxylation mechanism has been applied to acetoned carboxylic, dihydroxymaleic, and dibromomalonic acids where the carboxyl group beta to the carbonyl is the one that decarboxylates. However, in these acids the mechanism fails to explain why the free acids decarboxylate slower than the singly charged anion.

III. Miscellaneous Reactions.--Hammick and coworkers (9,10) in their study of decarboxylation reactions boiled alpha picolinic, quinoline-2-carboxylic, and isoquinoline-1-carboxylic acids in benzaldehyde and isolated secondary alcohols instead of the expected products. When acetophenone or benzophenone was used as solvent, tertiary alcohols were isolated. The products of the decarboxylation reaction were similer to those obtained if the previously mentioned carbonyl compounds were treated with alpha pyridzyl, 2-quinolyl, 1-isoquinolyl magnesium bromides. These workers offered the following mechanism.



Further studies to prove the generality of this reaction indicated that only those heterocyclic acids containing the structure -N=C´ would produce carbinols when decarboxylated in the presence of carbonyl compounds. The -N=C´ structure is similar to the cyanide ion [N≡C]⁻ where one of the nitrogen to carbon bonds is replaced by a ring, [N=C]⊖. It, therefore, follows that the formation of carbinols by decarboxylation of these three alpha imino acids is similar to the analogous cyanohydrin formation with hydrogen cyanide and carbonyl compounds.

Of all the various carboxylic acids isomers of the pyridine, quinoline and isoquinoline series, only those molecules containing the alpha imino acid group decarboxylate most readily. This case of decarboxylation can be explained as due to the resonance of the imino group which is described in the alpha keto acid section of this abstract.

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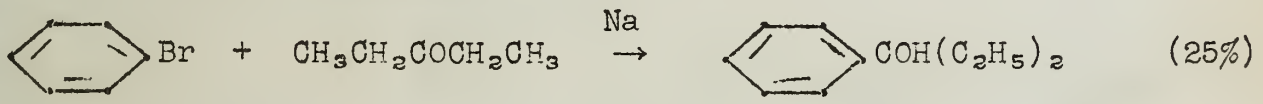
THE USE OF SODIUM IN THE PREPARATION OF TERTIARY ALCOHOLS

Reported by Carl S. Hornberger, Jr. April 1, 1949

The preparation of tertiary alcohols by the reaction of Grignard reagents upon carbonyl compounds is limited by steric factors to components which are not highly hindered. Often with branched aliphatic reactants, normal addition is not found and the reaction products are those obtained by dehydrohalogenation, enolization, coupling, and reduction (1,2,3). These difficulties have been overcome in part by the use of organolithium compounds which have a greater tendency to undergo normal addition to the carbonyl group (4). However, these seem to be limited to compounds which are no more highly branched than in the case of diisopropyl ketone and isopropyl lithium which react to form triisopropyl carbinol (5).

An early work by Morton and Stevens (6) indicated that ketones and organic halides could be condensed in the presence of sodium to give carbinols analogous to those obtained through the use of Grignard reagents.



In 1945, the first successful synthesis of tri-t-butyl carbinol was achieved by an extension of this reaction (7).

$$(CH_3)_3CCOC(CH_3)_3 + (CH_3)_3CCl \xrightarrow{Na} [CCH_3)_3C]_2COH \qquad (8.5\%)$$

The synthesis of carbinols with a great degree of branching was thus facilitated by the utilization of increasingly specific reagents. (Na > Li > Mg)

Recently, the use of sodium has been investigated more thoroughly so that now the reaction seems applicable to a wide variety of highly branched alcohols (8).

Preparation from ketones When a solution of ketone and organic halide is added to sodium sand dispersed in solvent, a reaction takes place which yields after hydrolysis an alcohol.

(1) $(CH_3)_2CHCOCH(CH_3)_2 + CH_3CH_2CH_2Cl \xrightarrow{Na} [(CH_3)_2CH]_2COH(CH_2CH_2CH_3$ (32%)

(2) $(CH_3)_2CHCOCH(CH_3)_2 + (CH_3)_2CHCH_2Cl \xrightarrow{Na} [(CH_3)_2CH]_2COH[CH_2CH(CH_3)_2$ (14%)

(3) $(CH_3)_3CCOCH(CH_3)_2 + (CH_3)_2CHCl \xrightarrow{Na} [(CH_3)_3C]COH[CH(CH_3)_2]_2$ (42%)

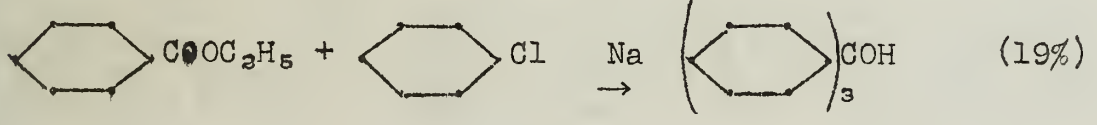
(4) $(CH_3)_3CCOCH(CH_3)_2 + (CH_3)_3CCl \xrightarrow{Na} [(CH_3)_3C]_2COHCH(CH_3)_2$ (16%)

The diisopropyl ethyl carbinol corresponding to the first example has been prepared using the ethyl Grignard reagent in a somewhat greater yield (9). This seems to indicate that on the basis of yield, there is little choice between the two methods when using a straight chain halide. The isopropyl Grignard reagent will not add to diisopropyl ketone but gives 68% enolization and 21% reduction of the ketone (10). Isopropyl lithium will add to this ketone to give the carbinol in 19% yield.

With the methyl ketone, pinacolone, the reaction was one of self condensation.

$$(CH_3)_3CCOCH_3 + CH_3CH_2CH_2CH_2Cl \xrightarrow{Na} (CH_3)_3CC(CH_3)=CHCOC(CH_3)_3$$

Preparation from esters The reaction with esters leads to the formation of several products.

(5)  (19%)

(6) $(CH_3)_2CHCOOCH_3 + (CH_3)_3CCl \xrightarrow{Na}$ (Grignard 7%)

$[(CH_3)C]_2COH[CH(CH_3)_2]$ (19%)

+

$(CH_3)_3CCOCH(CH_3)_2$ (50%)

+

$(CH_3)_3CCHOHCH(CH_3)_2$ (7%)

(7) $CH_3CH_2CH_2COOCH_3 + (CH_3)_3CCl \xrightarrow{Na}$

$(CH_3)_3CCOCH_2CH_2CH_3$ (6%)

+

$(CH_3)_3CCHOHCH_2CH_2CH_3$ (5%)

(8) $(CH_3)_3CCOOCH_3 + (CH_3)_3CCl \xrightarrow{Na}$

$[(CH_3)_3C]_3COH$

+

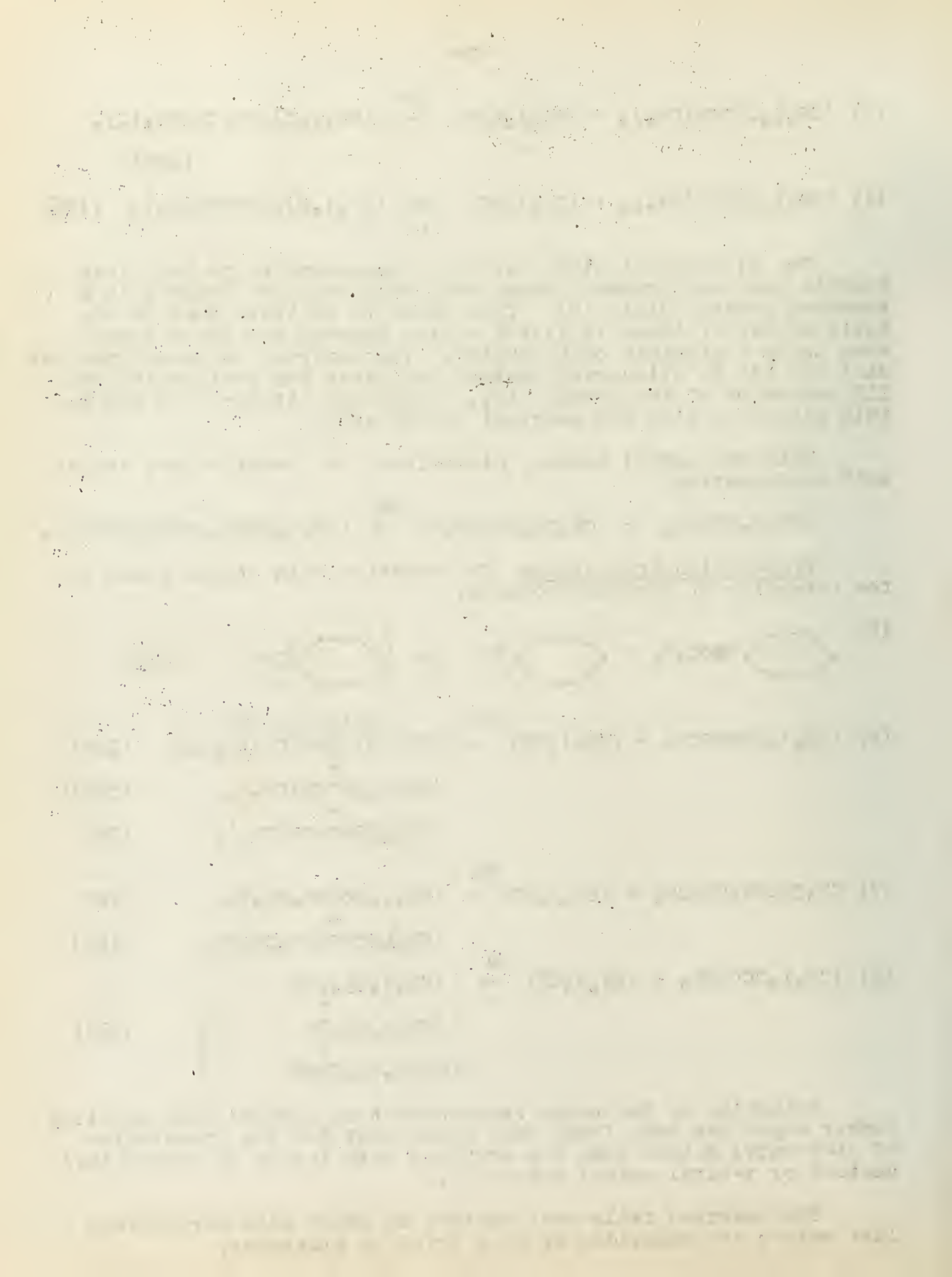
$[(CH_3)_3C]_2CO$ } (71%)

+

$[(CH_3)_3C]_2CHOH$ }

Oxidation of the crude carbinol-ketone mixture from reaction number eight has been found more convenient for the preparation of di-t-butyl ketone than the previous methylation of pentamethyl acetone or t-butyl methyl ketone (7).

The reaction fails when applied to other acid derivatives like amides or anhydrides or when tried on aldehydes.



Mechanism Since it has been established that both carbonyl compounds and esters form a disodium derivative, a metathetical reaction may take place (11).

$$RCl + Na-\overset{R}{\underset{R}{C}}-ONa \rightarrow NaCl + (R)_3CONa$$

A more likely mechanism seems to be based on the reaction of a ketyl free radical to form the sodium alkyl as follows:

$$RCOR + Na^{\bullet} \rightarrow (R)_2\dot{C}ONa$$

$$(R)_2\dot{C}ONa + RCl \rightarrow R^{\bullet} + NaO-\overset{R}{\underset{R}{C}}-Cl$$

$$NaO-\overset{R}{\underset{R}{C}}-Cl \rightarrow NaCl + (R)_2CO$$

$$R^{\bullet} + Na^{\bullet} \rightarrow RNa$$

$$RNa + (R)_2CO \rightarrow (R)_3CONa$$

When this reaction is used in the laboratory, it seems to be easier to carry out than the corresponding Grignard reaction. It is a one step reaction which is suitable to rather large scale (65 mole) and is one from which a major portion of the unreacted starting material may be recovered.

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SOME 1,4-ADDITION REACTIONS OF CONJUGATED SYSTEMS

Reported by Emil W. Grieshaber April 8, 1949

The ability of a conjugated system containing a hetero atom at a terminal position to undergo 1,4-addition has been related to similar abilities of longer conjugated systems to add 1,6 and possibly 1,8. As a result, the term "Conjugate Addition" has been proposed as a general name to include all such addition reactions. This seminar is limited to examination of the mechanism, to a brief consideration of some normal 1,4 addition reactions and to a review of an abnormal addition of this type.

A simple conjugated system may be described by the following resonance structures:

$$\underset{\text{I}}{RCH{=}CH{-}\overset{R}{\overset{|}{C}}{-}O^{(+)(-)}} \leftrightarrow \underset{\text{II}}{RCH{=}CH{-}\overset{R}{\overset{|}{C}}{=}O} \leftrightarrow \underset{\text{III}}{RCH^{(+)}{-}CH{=}\overset{R}{\overset{|}{C}}{-}O^{(-)}} \qquad (1)$$

The addition of a negative fragment to positions 2 or 4 in these systems may proceed with either polarized structure I or III with the attachment of a positive fragment to position 1 followed by rearrangement of the enol so formed. Support for the polarized structures as indicated is lent by the fact that the negative ion invariably attaches itself to a carbon at position 2 or 4, usually the latter.

$$RCH{=}CH{-}\overset{R}{\overset{|}{C}}{=}O + HX \rightarrow RCH(X){-}CH{=}\overset{R}{\overset{|}{C}}{-}OH \rightarrow RCH(X){-}CH_2{-}\overset{R}{\overset{|}{C}}{=}O \qquad (2)$$

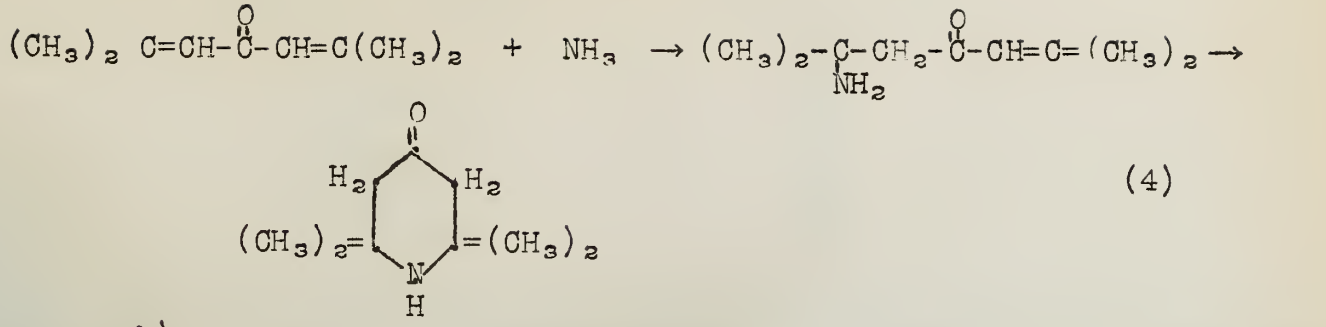
In many instances the product of a 1,2 addition is unstable and the reaction is reversible so it is not isolated. On the other hand, 1,4 additions are thought not to be readily reversible. That the addition is actually 1,4 and not 3,4 as an examination of the product would lead one to believe is established by the addition of a Grignard reagent to a conjugated system.

$$C_6H_5CH{=}CH{-}\overset{C_6H_5}{\overset{|}{C}}{=}O + C_6H_5MgBr \rightarrow \rightarrow (C_6H_5)_2CH{-}CH_2{-}\overset{C_6H_5}{\overset{|}{C}}{=}O \qquad (3)$$

Had the addition gone 3,4 the carbonyl group would have been exposed to further attack by excess Grignard Reagent to yield a carbinol. Further, enols have been isolated in the form of peroxides (6).

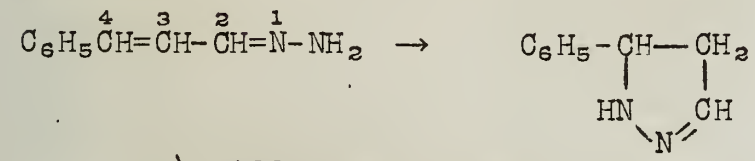
Reagents which add to the conjugate system in this manner include water, hydrogen halides, sulfhydryl compounds, ammonia and amines, Grignard reagents, hydrogen cyanide, sodium bisulfite and active methylene compounds. The latter group is usually classified as a Michael condensation and is not considered here. The general reaction is given in equation (2). Special examples include:

a). Addition of ammonia to phorone to form triacetoneamine



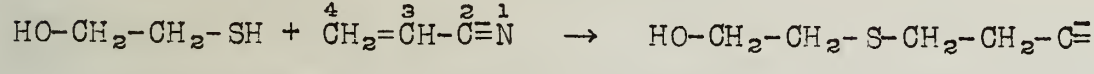
(4)

b). Addition of cinnamalhydrazone to itself to form 5-phenyl pyrazoline



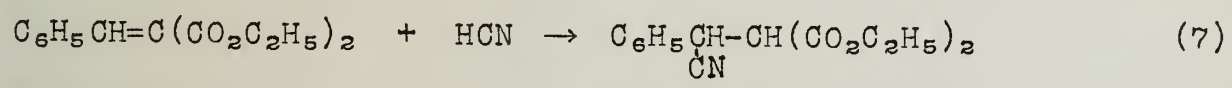
(5)

c). Addition of 2-mercaptoethanol to acrylonitrile



(6)

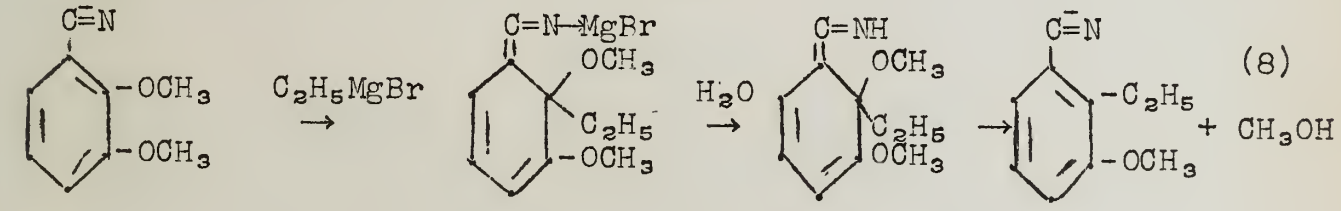
d). Addition of hydrogen cyanide to ethylbenzalmalonate (7)



(7)

The above reactions involve systems which are terminated by a keto carbonyl group, a nitrile group, an imino linkage and an ester carbonyl group.

Recently a 1,4 addition reaction accompanied by replacement has been reported by Richtzenhain (9, 10, 11). 2,3-Dimethoxybenzonitrile IV (4,8) was found to react with ethylmagnesium bromide to give 2-ethyl-3-methoxybenzonitrile V. This amounts to replacement of the 2-methoxyl group by the alkyl group of the Grignard reagent. A mechanism which allows for 1,4 addition with subsequent elimination of methyl alcohol or its equivalent is necessary to rationalize the course of this reaction (5,9).



(8)

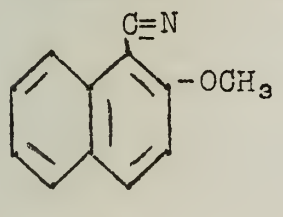
IV V

The related 2,3-dimethoxy-5-methylbenzonitrile underwent a similar replacement when treated with ethylmagnesium bromide. It was found that methylmagnesium bromide gave only the normal 1,2 addition product which could be hydrolyzed to the 2,3-dimethoxyacetophenone. Other alkyl Grignard reagents found to add as does the ethyl reagent are listed with yields of methoxyl group replacement product as indicated.

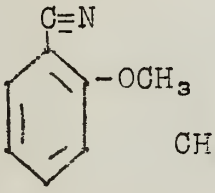
Grignard reagent	Percent yield
ethyl	60
isopropyl	81
butyl	80
isobutyl	45
heptyl	62
cyclohexyl	68

Although phenylmagnesium bromide had been reported earlier to add 1,2 to IV, (2) Richtzenhain obtained approximately equal amounts of 1,2 and 1,4 addition. Apparently the earlier investigators were not anticipating a replacement. Benzylmagnesium chloride does not condense with IV (1). In general, aromatic Grignard reagents add with lower yields of replacement product than do alkyl reagents. Richtzenhain therefore employed tetrahydro Grignard reagents and aromatized the addition product to obtain better yields (10).

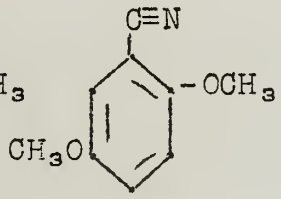
The function of the adjacent methoxyl groups is not yet known. 2-Methoxy-1-naphthonitrile VI would seem to offer enhanced possibilities of 1,4 addition since it is known that the naphthalene derivatives possess a greater double bond character between the 1- and 2-positions. The behavior of 2-methoxybenzonitrile VII should test the necessity of the methoxyl group in the 3-position. If this group is exerting an important influence on the cyano group, 2,5-dimethoxybenzonitrile VIII should undergo replacement. A doubled opportunity for replacement is available in 2,6-dimethoxybenzonitrile IX, which might exhibit steric inhibition of the competing 1,2 addition to the cyano group. None of these compounds could be shown to give the desired replacement; rather, good yields of the normal products were isolated (3).



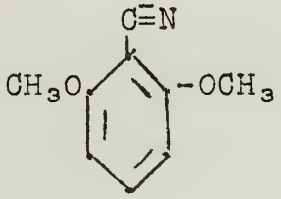
VI



VII



VIII



IX

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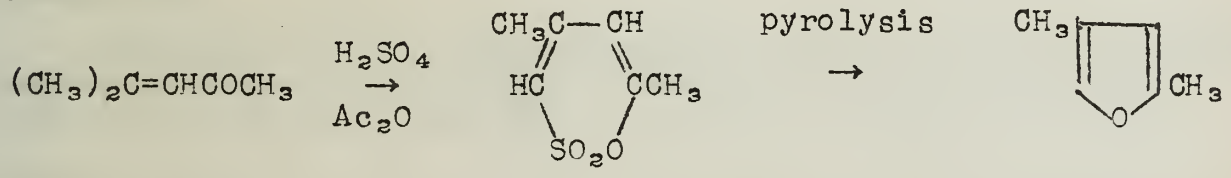
RECENT STUDIES ON FURAN

Reported by William R. Miller April 8, 1949

Structural considerations and the common reactions of furan were discussed in the last seminar on this subject (1). The conclusion reached in that discussion was that furan possesses a degree of unsaturation less than that of a 1,3-diene but greater than that of benzene. This seminar will discuss the more recent work on furan which, in general, appears to bear out this conclusion.

Synthesis

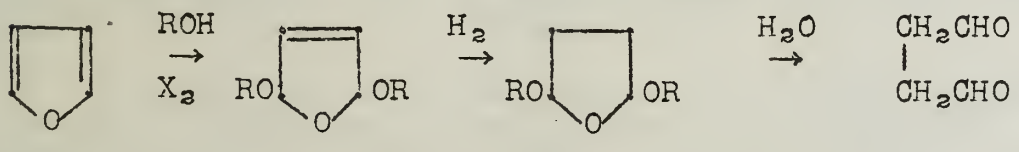
The methods of synthesis of substituted furans have been well discussed in a recent article by Wright and Gilman (2). A new general synthesis was reported last year (3): An alpha, beta-unsaturated ketone is treated with sulfuric acid and acetic anhydride to form a delta-sultone. This compound is then pyrolyzed to give the furan. The synthesis of 2,4-dimethylfuran illustrated the procedure:



It is necessary that the ketone be branched in the position beta to the carbonyl. This synthesis may be adapted to give 2,4-, 2,3,4-, 2,3,5- and 2,3,4,5-substituted furans.

Nuclear Oxidation

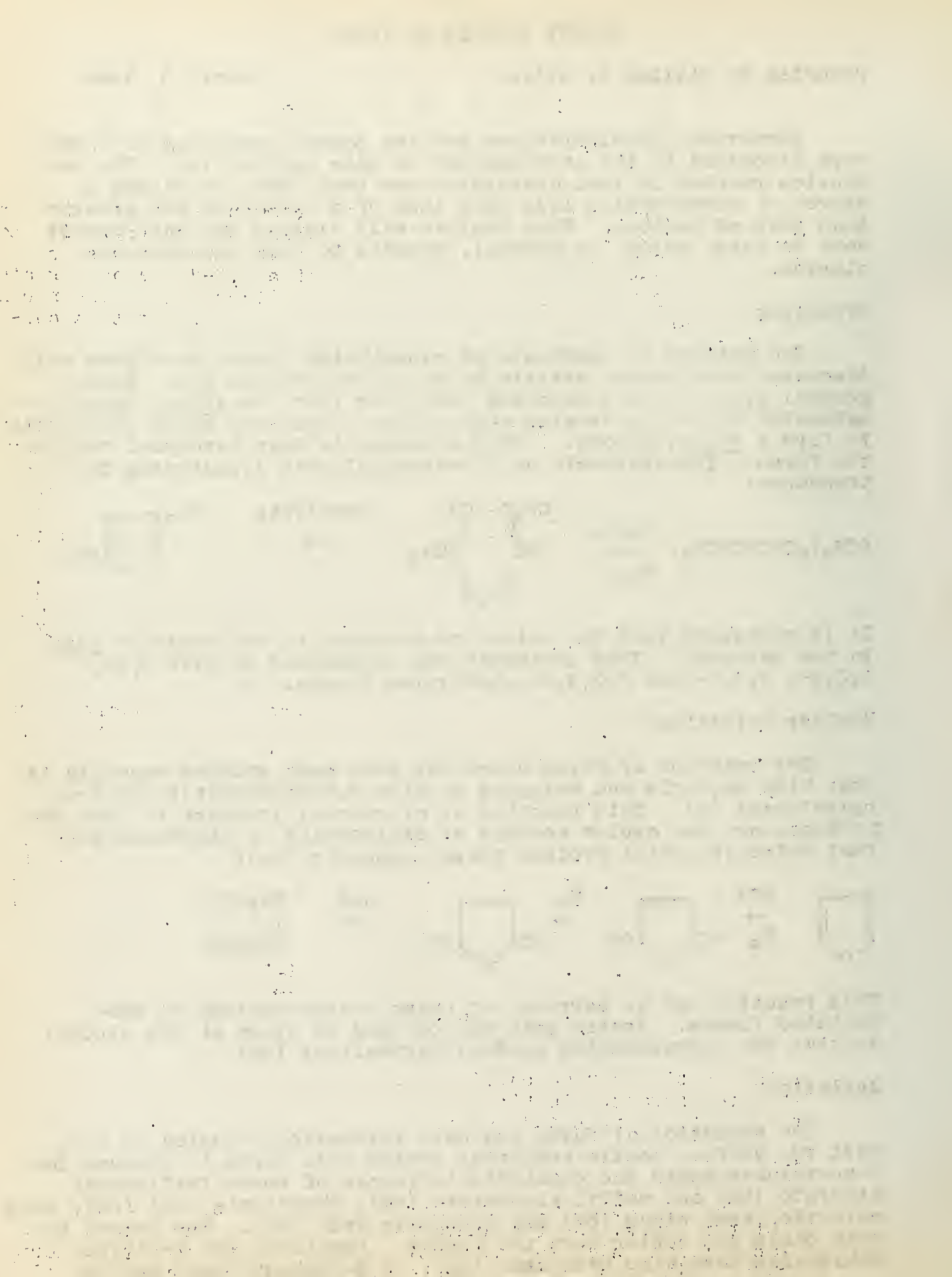
The reaction of furan which has been most studied recently is that with alcohols and halogens to give 2,5-disubstituted-2,5-dihydrofurans (4). This reaction is of special interest in that the products are the cyclic acetals of dialdehydes or diketones and that hydrolysis will produce these compounds (4a):



This reaction may be carried out using a wide variety of substituted furans. Acetic acid may be used in place of the alcohol to give the corresponding acetoxy derivatives (4b).

Acylation

The acylation of furan has been extensively studied in the past two years. Acetic anhydride reacts with furan to produce the 2-acetofuran under the catalytic influence of boron trifluoride etherate (5a) and methyl alcoholate (5b), phosphoric acid (5c), zinc chloride, acid clays (5d) and hydriodic acid (5e). The longer the acid chain the better were the yields. Propionic and n-butyric anhydrides have also been used (5a). 2,5-Diphenylfuran may be



acylated in the 3-position by means of acetic anhydride and stannic chloride (6).

Sulfonation

Russian workers have made an extensive study of the sulfonation of furan (7). Furan is best sulfonated by pyridine-sulfur trioxide in a sealed tube at 100° for eight to ten hours. Furan gives the 2-furansulfonic acid. Sylvan (2-methylfuran) gives the 5- and 3,5-disulfonic acids. 2,5-Dimethylfuran gives the 3-sulfonic acid (7b).

Halogenation

Furan can be chlorinated to give 2-chlorofuran provided that the temperature is maintained at 50° and the HCl formed is immediately removed from the reaction mixture (8a). Low temperature chlorination (at -40° to -20°) will give a mixture of mono-, di-, tri- and tetrachlorofurans as well as 2,2,3,4,5,5-hexachloro-2,5-dihydrofuran but the 2-chlorofuran may be separated by distillation (8b).

The bromination of beta-(2-furyl)-acrylic acid and its esters may be so regulated as to give a variety of products of both addition and substitution (9).

Other Reactions

Both sylvan and furfuryl alcohol will undergo the Mannich reaction to give the 5-aminomethyl derivative (10).

Methyl furoate can be chloromethylated to give the methyl 5-chloromethylfurate. The alpha-chloroethyl derivatives can also be readily prepared (11). The chloromethylation of 2,5-diphenylfuran gives only the 3,4-di-(chloromethyl)-2,5-diphenylfuran (12).

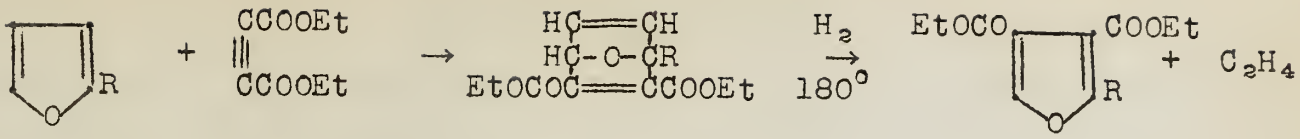
Furan is metalated in the 2-position by n-butyllithium (13a). With sodium and amyl chloride, followed by carbonation and reaction with diazomethane, 27% of methyl furoate and 19% of dimethyl 2,5-furandicarboxylate are obtained (13b).

Furan reacts with diazonium salts in the presence of base or with N-nitrosoacetanilides to give 2-arylfurans (14). With p-nitrobenzenediazonium chloride in alcohol solution, however, 2,5-dimethylfuran is cleaved and the final product is 1-p-nitrophenyl-3-acetyl-5-methylpyrazole (15).

Sylvan condenses with alpha, beta-unsaturated ketones and aldehydes to give beta-(5-methyl-2-furyl) carbonyl compounds (16).

Diene Reactions

Furan derivatives have been condensed with diethyl acetylene-dicarboxylate to give an intermediate which, on partial hydrogenation loses ethylene to form the 3,4-dicarboxy-2-substituted furan (17):



The reaction of furan with maleic anhydride has recently been reinvestigated by Woodward (18) and it has been shown that in ether solution an exo-cis adduct is formed while in water solution maleic acid adds to furan to form an endo-cis adduct.

Furan will condense with ethylene, in the presence of a little hydroquinone, to form 3,6-epoxycyclohexene (19).

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ETHYLENE IMINE KETONES

Reported by Sidney Baldwin April 22, 1949

I. Synthesis: (1,3,4)

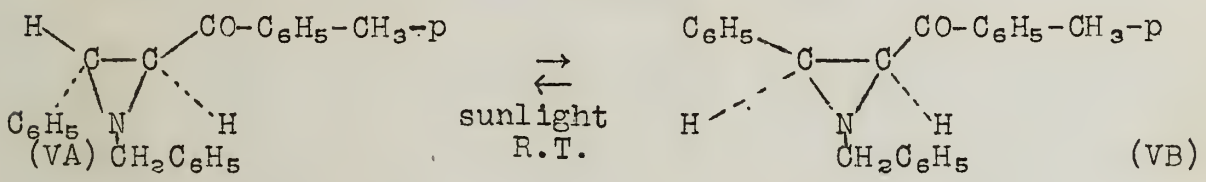
Cromwell and coworkers have prepared ethylene imine ketones by the reaction of the corresponding α,β-dibromo ketones with the respective amines thus:

$$RCH(Br)-CH(Br)-CR' + 3R''NH_2 \xrightarrow{<40^\circ} R-\underset{\displaystyle N-R''}{\overset{2}{CH}}-\overset{3}{CH}-\overset{1}{C}(=O)-R' + 2R''NH_3^{\oplus}Br^{\ominus}$$

The following ethylene imine ketones have been prepared in about 25% yields by this method: 1-benzyl-2-phenyl-3-benzoylethyl-enimine (I), 1-cyclohexyl-2-phenyl-3-benzoyl ethylenimine (II), 1-methyl-2-phenyl-3-benzoyle thylenimine (III), 1-benzyl-2-(m-nitrophenyl)-3-benzoylethylenimine (IV), 1-benzyl-2-phenyl-3-(p-toluyl)-ethylenimine (V), and 1-benzyl-2-(p-tolyl)-3-benzoyl-ethylenimine (VI). In addition, (I) and (II) were prepared from the corresponding amine and α-bromobenzalacetophenone; while (I) was also produced from benzylamine and α,β-dichlorobenzylaceto-phenone.

II. Isomerism and Ultra-Violet Absorption Spectra: (6,2)

The yield of ethylene imine ketones is low, and diphenylethylenimine is known to exist in cis and trans forms (9). This indicated that ethylene imine ketones may also exhibit cis-trans isomerism. The low yields may have resulted from the failure to isolate the more soluble isomer, or from side product formation, such as piperazines and α-imino ketones. When benzyl-amine was allowed to react with α-β-dibromobenzyl-p-methylaceto-phenone in dry benzene at 20°, the isomeric products (VA) (29%) and (VB) (37%) were isolated.



(VA) (VB)

trans m.p. 120-121°

cis m.p. 70-74°

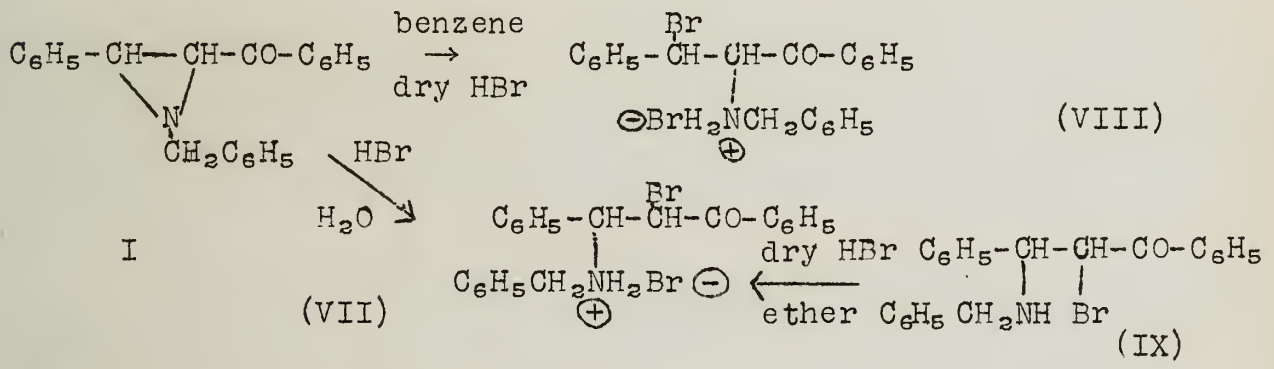
The low melting isomer (VB) was partially decomposed and rearranged to the higher melting form (VA) when its saturated petroleum ether solutions were exposed to sunlight at room temperature. Scale models of the isomers demonstrate that racemate (VB) would be a more highly strained structure than racemate (VA). Thus the more labile form (VB) might be expected to rearrange to the less strained form (VA). Only one form of the imine (I), however, could be isolated. (m.p. 108°, presumably trans).

In contrast to the unsaturated amino ketones, these ethylene imine ketones, which do not have conjugated unsaturation, show only a maximum similar to that of the parent unsaturated

ketones. The maximum absorption band of the isomer (VB) was 30-80 Å nearer the red (visible), with a 2000-3000 greater extinction coefficient value, as compared with (VA). This is in agreement with the view that the more strained structure (VB) should absorb light of longer wave-lengths.

III. Reaction with Hydrogen Bromide: (1,3)

α-Bromo-β-benzylaminobenzylacetophenone hydrobromide (VII) was produced from the reaction of the imine (I) with aqueous hydrogen bromide. On the other hand, if the imine (I) is treated with dry hydrogen bromide in dry benzene solution, the cleavage product is the isomeric β-bromo ketone hydrobromide (VIII). An authentic sample of (VII) was also prepared from (IX) as shown below:

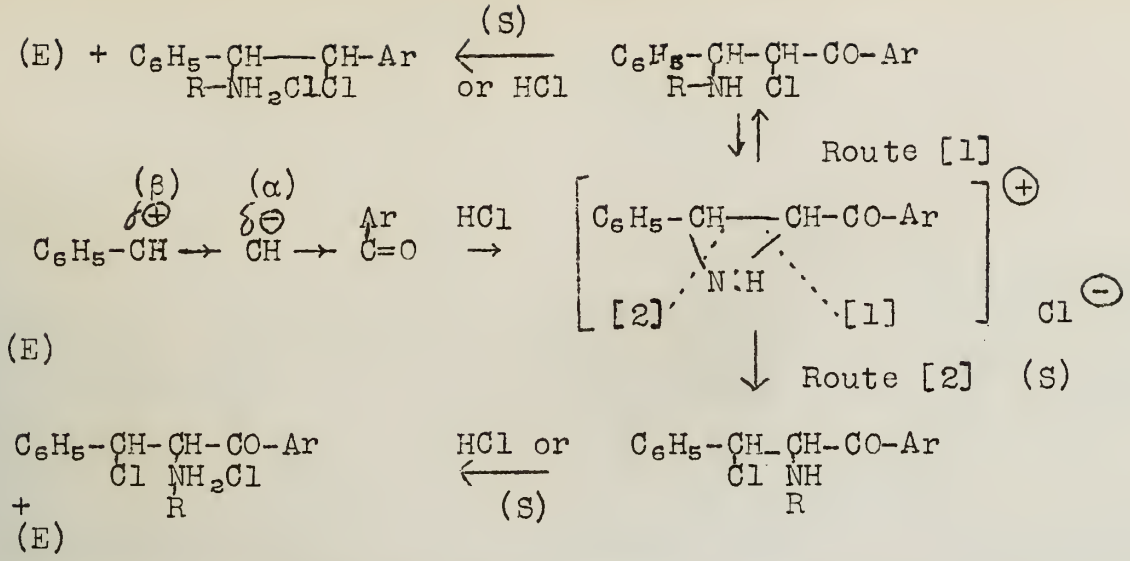


The α-bromo ketone (VII) released iodine (3) from acidified potassium iodide solutions at room temperature in thirty minutes, whereas the β-bromo-ketone (VIII) gave no reaction under identical conditions.

IV. Reaction with Hydrogen Chloride: (1,3,5,6,7)

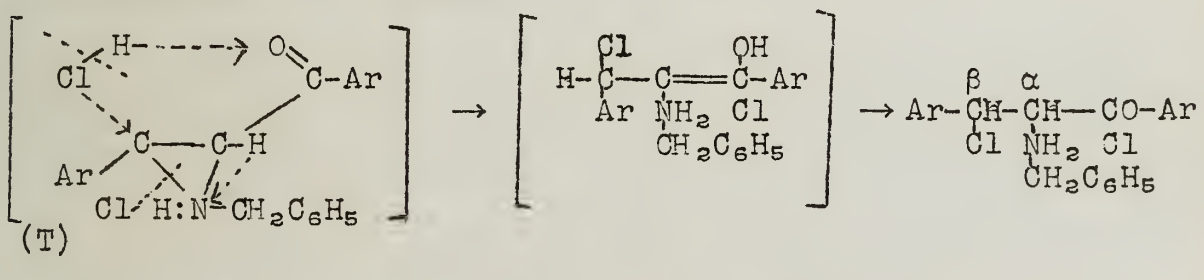
Excess amounts of dry or aqueous hydrogen chloride react with the imine (I) (presumably trans) and with the trans imine (VA) to yield the β-chloro-α-aminoketone hydrochlorides. With minimum amounts (i.e. the proper number of equivalent amounts) of dry hydrogen chloride, the trans imine (I) gave 73.5% of the α-chloro ketone and 26.5% of the β-chloro isomer, while the trans imine (VA) gave 78% of the α-chloro ketone and 22% of the β-chloro ketone. The cis form (VB) reacts very rapidly with excess or minimum amounts of dry hydrogen chloride to yield nearly equal amounts of the α-chloro and β-chloroketones in both cases.

A mechanism consistent with the above results is proposed as follows: (7)



A hydrochloride of the type (S) has been isolated (1). An S_n1 mechanism would cleave the ring mainly according to scheme [1], if the α-carbon atom has the higher electron density. Course [2] should be followed if an S_n2 mechanism came into play, especially if the β-carbon atom is more electrophilic than the α. Excess chloride ion concentration should favor the S_n2 mechanism and course [2].

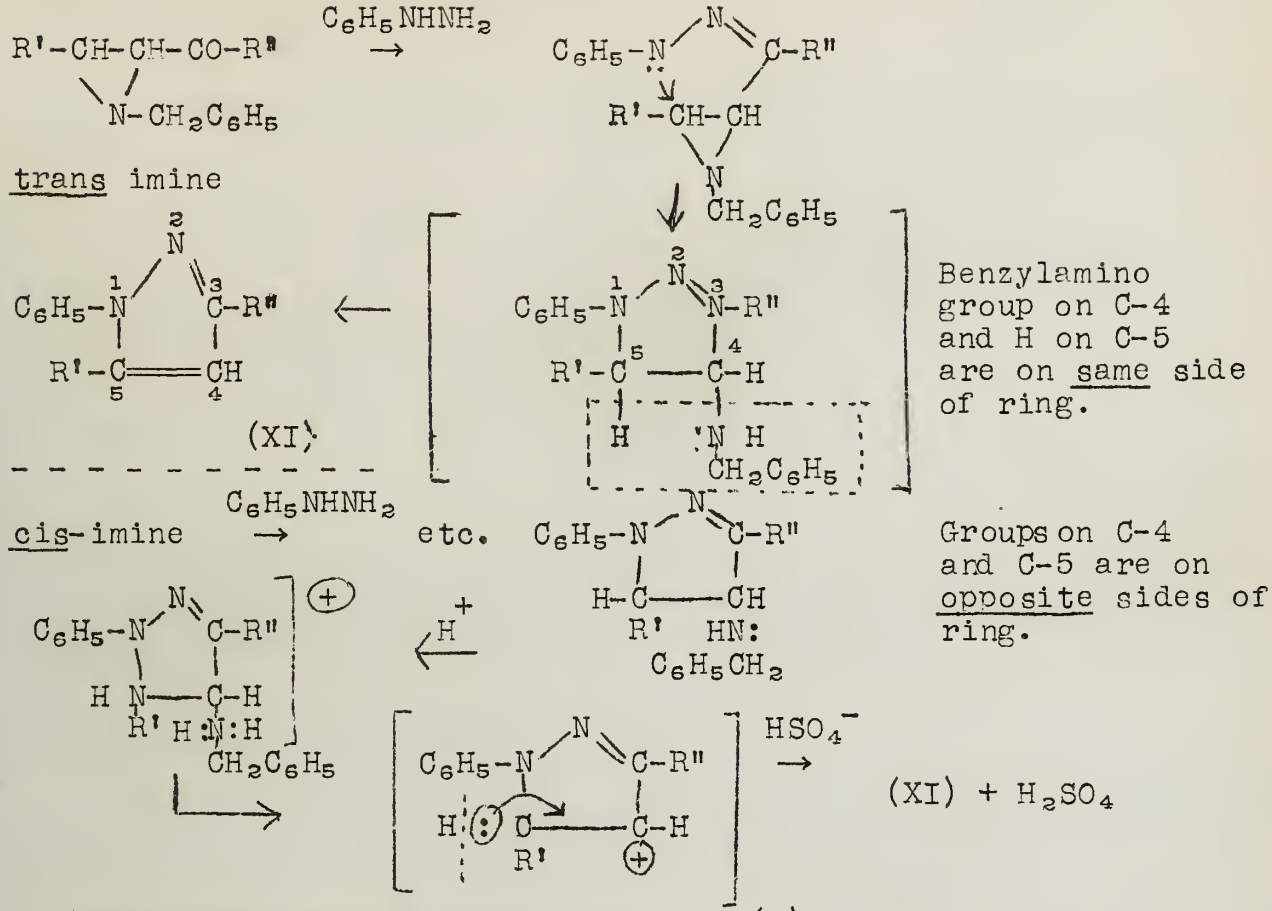
Under the influence of excess hydrogen chloride, the salt might also undergo ring cleavage via a carbonyl directed 1,4 attack as outlined below:



Scale models demonstrate that trans structures could form a transition complex (T) with ease, but that the cis form should not because of the repulsion of the chlorine in hydrogen chloride by the aryl group on the β-carbon atom.

V. Reactions with Phenylhydrazine: (8)

Trans ethylene imine ketones react with phenylhydrazine in glacial acetic acid to produce the corresponding pyrazoles and N-acetylphenylhydrazones. Hydrolysis of the latter with boiling 20% sulfuric acid produced the respective pyrazoles in 90-100% yield. Pyrazoles corresponding to (I), (V), and (VI) (all trans) were prepared in this way. Cis ethylene imine ketones give excellent yields of the intermediate 4-amino-pyrazolines. The latter are stable in neutral or basic solution but lose benzylamine in strongly acid solution to produce the pyrazoles.



VI. Reactions with Grignard Reagents: (4)

Grignard reagents add to the carbonyl group of ethylenimine ketones to give a new class of compounds, enimine carbinols, in excellent yields. The addition reactions took place rapidly, indicating that the imine ring offers very little hindrance to the carbonyl group. Furthermore, the Grignard reagent does not open the imine ring, nor does it cleave the aliphatic chain. This shows that the imine ring is stable and is further chemical evidence for the ethylene imine ketone structure.

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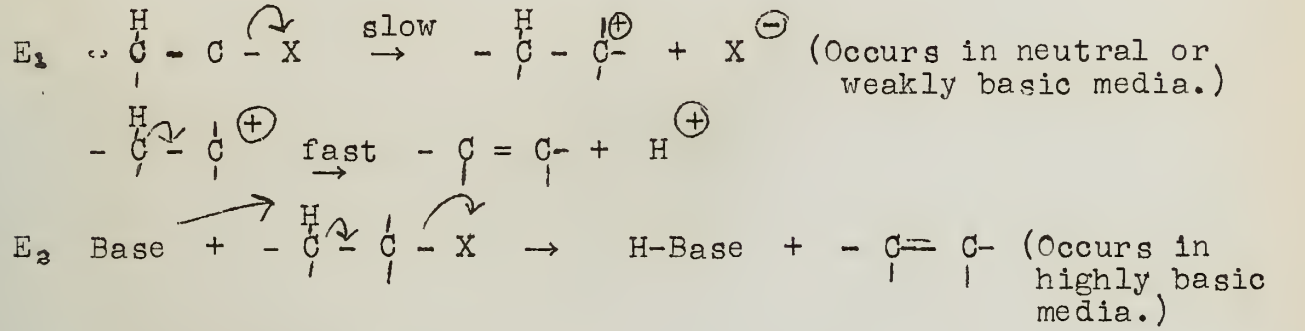
FACTORS INFLUENCING ELIMINATION REACTIONS

Reported by George R. Coraor April 29, 1949

Most elimination reactions proceed by one of the following mechanisms:



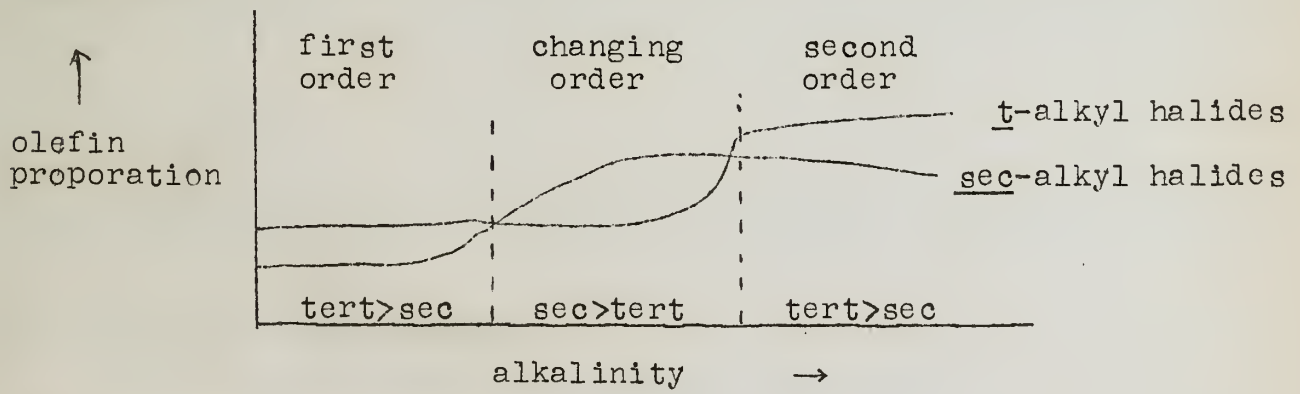
Elimination and substitution proceed under the same conditions, hence are always in competition. A knowledge of factors which favor the reaction desired is of practical as well as theoretical importance.

A. Concentration of base:

The rate of E_1, like S_{n_1}, is unaffected by changes in the concentration of base. The proportion of olefin to substitution product is thus unaffected. (1)

The rate of E_2 reactions is increased greatly with increasing concentration of base. The olefin proportion is unchanged because the rate of Sn_2 reactions increases in a parallel manner.

In mild alkali, both E_1 and E_2 processes proceed simultaneously. This situation caused many disagreements in the older literature over the ease of elimination in secondary and tertiary alkyl halides. The diagram below explains how differing results are possible.



B. Polarity of Solvent:

Solvent effects arise from the difference between the solvation energy of the transition state and the initial state.

Solvation results from the attraction of the dipole charges of a polar solvent for partial or unit charges on the solute. If the magnitude of charge on the solute is decreased or spread over a larger volume, solvation is decreased. To decrease solvation, energy must be supplied because the net effect is that the forces holding solvent to solute have been overcome. To decrease solvation of a more polar solvent (one held more firmly because of its greater dipole charges) more energy is required. Therefore, if the charge on a reactant is decreased or more widely dispersed in the transition state than in the initial state, the reaction will be hindered by a polar solvent. Conversely, if the charge is increased or concentrated, a polar solvent will facilitate the reaction. The olefin proportion is affected by virtue of the fact that the dipole charges are spread over a 5 carbon system in the transition state of elimination, but only over a 3 carbon system in the transition state of substitution. Hence, if the charge is dispersed in progressing to the transition state, it is more widely dispersed in elimination than in substitution. The table below summarizes the predicted solvent effects on two common types of elimination reactions. Using the considerations stated above, similar predictions can be made of other types of elimination.

Rxn	Disposition of charges: initial state	Disposition of charges: transition state	Effect of activation on charges	Effect of more solvent on: Reaction rate	Effect of more solvent on: Olefin proportion
Sn_2	$Y^{\ominus}$ + RX	$Y^{\delta-}..R..X^{\delta+}$	dispersed	small decrease	small decrease
E2	" "	$Y^{\delta-}..H..C..C..X^{\delta+}$			
as	($OH^{\ominus}$ + RCl)				
Sn_2	$Y^{\ominus}$ + $RX^{\oplus}$	$Y^{\delta-}..R..X^{\delta-}$	reduced	large decrease	?
E2	" "	$Y^{\delta-}..H..C..C..X^{\delta-}$			
as	($OH^{\ominus}$ + $RNMe_3^{\oplus}$)				

The reaction rates are affected as predicted above. A decrease in olefin proportion was also observed in the cases so predicted. In the case designated as questionable, no trend could be discerned (3).

C. Temperature:

The proportion of olefin increases with temperature for both first and second order reactions. No adequate explanation has as yet been offered (4).

D. Constitutional Factors:

There are two empirical rules of elimination:

1) Hofmann rule: Elimination in quaternary amine salts will yield the olefin with the least alkyl substitution on the β carbon.

$$CH_3CH(\overset{\oplus}{N}Me_2)CH_2CH_3 \xrightarrow{E_2} \underset{26\%}{CH_3-CH:CH-CH_3} + \underset{74\%}{CH_3-CH_2-CH:CH_2}$$

2) Saytzeff rule: Alkyl halides dehydrohalogenate to yield the olefin with the most alkyl substitution on the β carbon.

$$CH_3CHBrCH_2CH_3 \xrightarrow{E_1 \text{ or } E_2} \underset{82\%}{CH_3\text{-}CH\text{:}CH\text{-}CH_3} + \underset{18\%}{CH_3\text{-}CH_2\text{-}CH\text{:}CH_2}$$

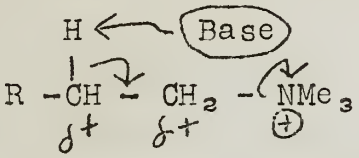
A careful study (5) has revealed that the rules are more general than stated above. Their applicability is as follows:

1) Only bimolecular eliminations of onium ions follow the Hofmann rule.

2) Unimolecular onium ion eliminations and eliminations of all neutral molecules follow the Saytzeff rule.

Interpretation of Hofmann type elimination: (6)

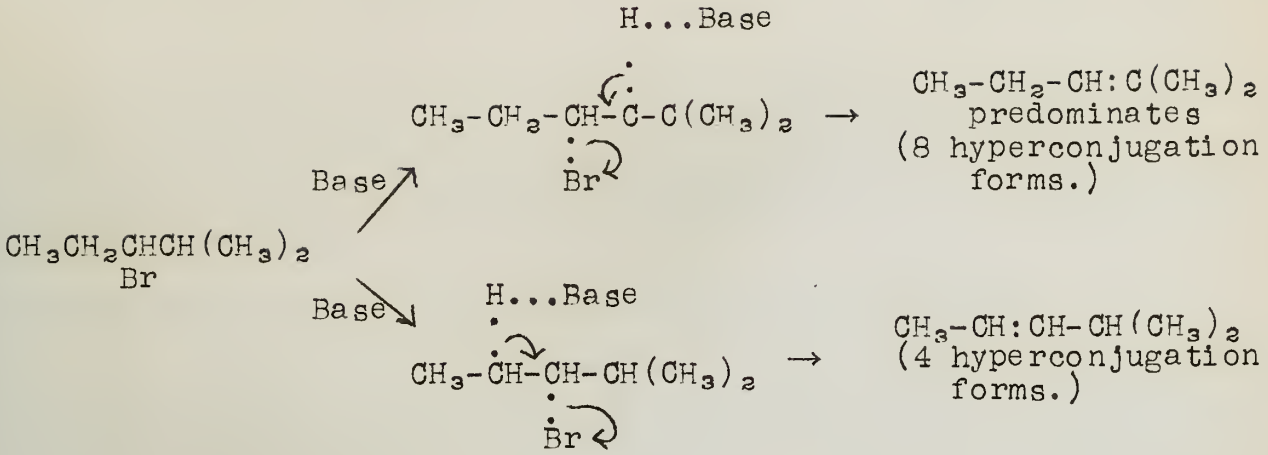
The proton is removed by collision with a basic ion.



The positive nitrogen induces a partial positive charge on the carbon atoms of the chain, thus facilitating the hydrogen's removal. If, however, the group R is electron releasing and neutralizes the partial positive charge on the β carbon atom, the hydrogen is less easily removed. Consequently, the hydrogen attached to the β carbon atom with the least alkyl substitution is removed.

Rationalization of the Saytzeff type elimination: (6)

The weakening of the carbon-hydrogen bond in the Hofmann type elimination is the result of induction. Apparently, in the Saytzeff type elimination hyperconjugation is more important than induction. Olefin (a) below is more stabilized by hyperconjugation than olefin (b). Quantum mechanics suggests that the transition state leading to (a) is also more stabilized than that leading to (b). Consequently, the olefin formed will be the one with the greatest number of allyl hydrogen atoms. Here, α alkyl substitution as well as β substitution must be taken into consideration, for <u>all</u> allyl hydrogen atoms can participate in hyperconjugation.



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   Dhar, Hughes and Ingold, ibid., 1948, 2058-65; 2065-72
   Hughes, Ingold, and Maw, ibid., 1948, 2072-77
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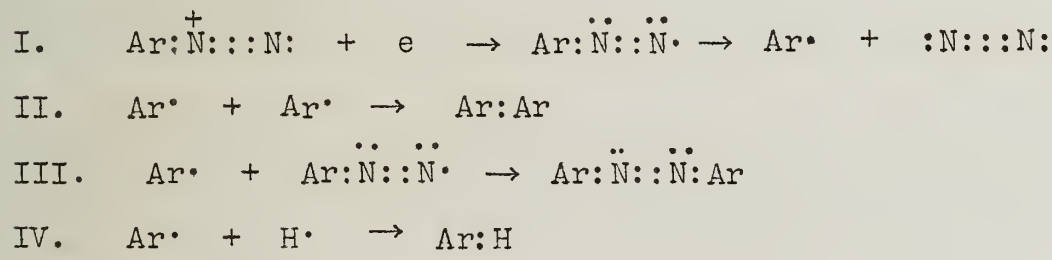
AN ELECTRONIC INTERPRETATION OF THE DECOMPOSITION REACTIONS OF AROMATIC DIAZO-COMPOUNDS IN AQUEOUS SOLUTION

Reported by K. H. Takemura April 29, 1949

Decomposition reactions of aromatic diazo-compounds in aqueous solutions have been explained largely by assuming that the diazo-compound decomposes into molecular nitrogen and free radicals. Recently Hodgson (2) has presented an electronic theory to explain some of these reactions without the use of this free radical hypothesis.

Decomposition in the Presence of Mild Reducing Agents.

1. Prior to the work mentioned above, Hodgson and co-workers (3) had potulated essentially the following series of reactions to explain the decomposition of a number of aryl diazo-compounds in sulfuric acid solution in the presence of cuprous hydroxide as a reduxing agent:



I. $Ar:\overset{+}{N}:::N: + e \rightarrow Ar:\ddot{N}::\ddot{N}\cdot \rightarrow Ar\cdot + :N:::N:$

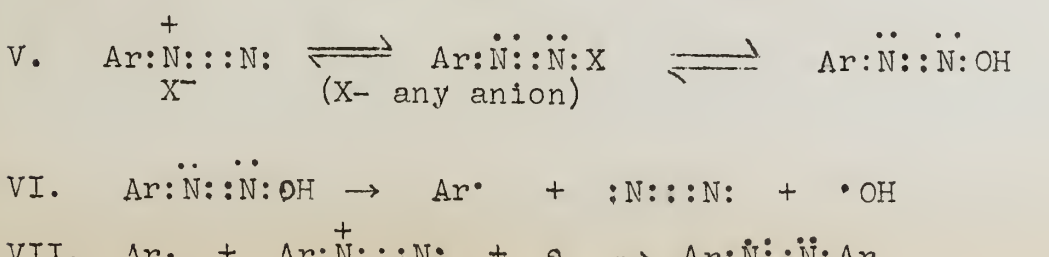
II. $Ar\cdot + Ar\cdot \rightarrow Ar:Ar$

III. $Ar\cdot + Ar:\ddot{N}::\ddot{N}\cdot \rightarrow Ar:\ddot{N}::\ddot{N}:Ar$

IV. $Ar\cdot + H\cdot \rightarrow Ar:H$

The course taken was found to depend upon the positivity of the carbon atom to which the diazo-group was attached. If this positivity was great, the odd electron of the free radical was so restrained that it could combine only with nascent hydrogen; e.g., diazotized 2-nitro-1-naphthylamine gave only the nitronaphthalene on decomposition. With slightly less restraint, biaryl-formation occurred; and when the restraint was small or even reversed, azo-formation occurred. Any one or all of these reactions took place to a greater or less extent depending upon the nature of the aryl diazo-compound and the conditions.

2. Saunders and Waters (6) arrived at another series of reactions from their work with diazo-compounds in aqueous solutions near the neutral point in the presence of ammoniacal cuprous oxide. Their mechanism differed primarily in the initial step in which a homolytic cleavage of the diazo-hydroxide to give free radicals with the liberation of nitrogen was postulated (VI).



V. $Ar:\overset{+}{N}:::N: \underset{X^-}{} \rightleftharpoons Ar:\ddot{N}::\ddot{N}:X \rightleftharpoons Ar:\ddot{N}::\ddot{N}:OH$ (X- any anion)

VI. $Ar:\ddot{N}::\ddot{N}:OH \rightarrow Ar\cdot + :N:::N: + \cdot OH$

VII. $Ar\cdot + Ar:\overset{+}{N}:::N: + e \rightarrow Ar:\ddot{N}::\ddot{N}:Ar$

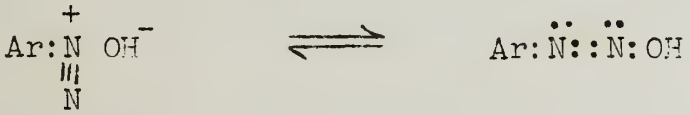
Saunders and Waters regarded the mechanism postulated by Hodgson et al as improbable since they considered the driving force of the reaction to be the liberation of nitrogen gas through the homolysis of the covalent diazo-compound with the simultaneous formation of two free radicals. Hodgson (2) later pointed out that his mechanisms dealt with ionic diazonium compounds in acid solution and not with covalent compounds in neutral solution. He then set forth an electronic theory to explain a number of decomposition reactions without the use of the homolytic cleavage exemplified by the free radical hypothesis.

Electronic Theory versus The Free Radical Hypothesis.

1. Ortho, Para-Substitution. According to the free radical hypothesis, the invariable p- and/or o-substitution in reactions of the Gomberg type has been explained by assuming that the free aryl radical which is formed (VI above) is amphoteric in type; that is, the free radical may function either as a cationoid or as a anionoid reagent as the occasion demands (5). Thus the reaction of diazotized aniline with nitrobenzene has been found to give a 33% yield of 4-nitrobiphenyl; and the diazotized p-nitroaniline with nitrobenzene gave a 69% yield of 4,4'-dinitrobiphenyl (1).

In as much as nitrogen, :N:::N:, is evolved in the reaction, Hodgson considers it more reasonable to have the nitrogen in the triple-bonded state as is the case in the diazonium ion, with only one bond to break, rather than the double-bonded state with two bonds to break in the case of the covalent compound.

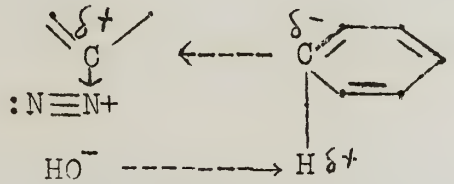
VIII.



(A) (B)

According to Hodgson's theory, the diazonium ion attacks the anionoid reactant (usually benzene) at an anionoid carbon causing its hydrogen to become cationoid and to attract the anion of the diazonium salt (usually hydroxide or acetate). Equation IX.

IX.



The hydrogen is then assumed to split off as a proton, with electron release, to form HOH, with the liberation of nitrogen and formation of the biaryl.

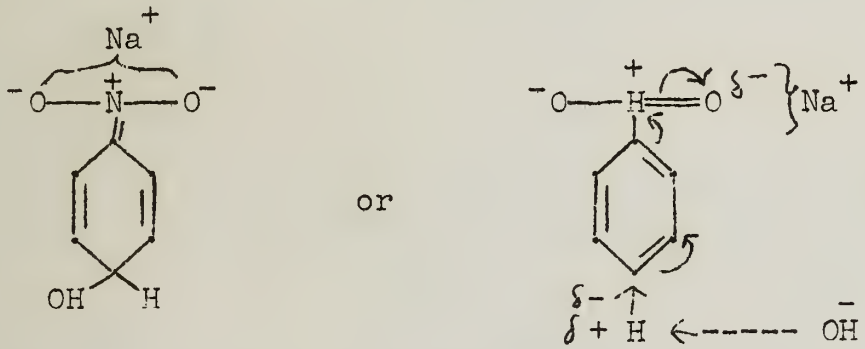
2. Non-Formation of Sym-Biaryls. This mechanism does not involve any free radicals and hence the formation of sym-biaryls

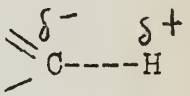
does not occur. This point is another difficulty found in the free radical hypothesis, according to which the assumed free radicals react preferentially with relatively unreactive molecules, rather than with themselves to form sym-biaryl compounds. Hence, biphenyl is formed in the Gomberg reaction from diazotized aniline only in the presence of benzene.

3. o,p-Activity of Nitrohydrocarbons. The anomalous behavior of nitrohydrocarbons at the o- and p-positions has been one of the main arguments in favor of the free radical hypothesis.

Hodgson attributes this to a reversal of the cationoid character of the o,p-positions to an anionoid one by solvent action on the nitro-group. m-Dinitrobenzene and s-trinitrobenzene have been found to form stable salts with NaOH and KOH in methanol. Hodgson therefore assumes incipient salt formation of nitrobenzene with NaOH.

X.

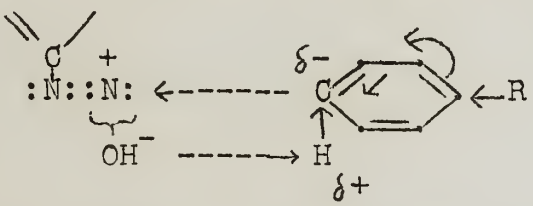


The diazonium ion and the hydroxide ion then attacks the  bond as in IX to form the biaryl compound.

Further Applications of the Electronic Theory.

1. Azo-Formation. The formation of azo-compounds can be explained by the attack of the diazo-compound in the form VIII(B). Whether an azo-compound will form depends upon the anionoid character of the second reactant. If this is sufficiently great, the diazonium ion can attack the anionoid carbon as shown in XI:

XI.

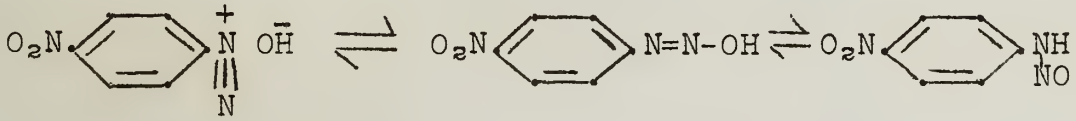


Thus, there is complete azo-formation with phenol and β-naphthol, and partial azo-formation with biphenyl.

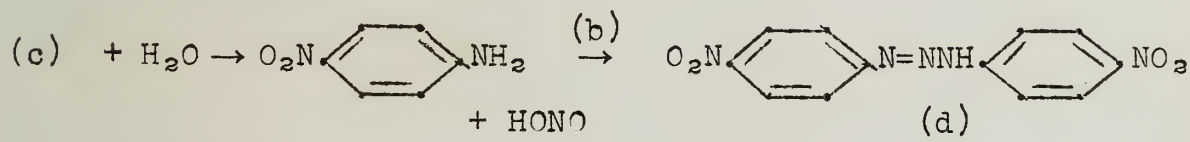
The main driving force in the usual azo-coupling reactions is the formation of water or weakly ionized acetic acid. Where the anionoid character of the second reactant is small, e.g. benzene,

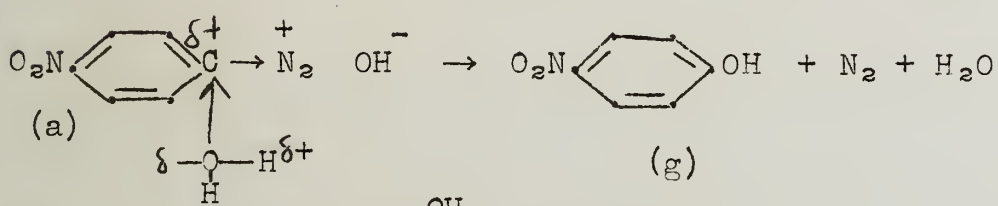
the driving force must be augmented by the liberation of nitrogen and biaryl formation occurs. Usually both reactions occur to varying degrees depending upon this anionoid character of the second reactant.

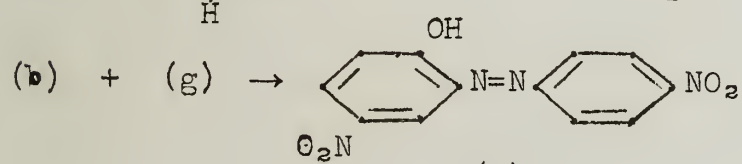
2. Decomposition of p-Nitrodiazonium Sulfate in Neutral Solution. (4). An aqueous sulfuric acid solution of diazotized p-nitroaniline, neutralized with calcium carbonate, and allowed to decompose yielded a solid product from which was isolated (d) p,p'-dinitrodiazoaminobenzene (ca. 40%); (e) 4-nitro-2-p-nitrobenzeneazophenol (ca. 10%); and a small amount of p,p'-dinitrodiphenylamine (f). The remainder of the solid, ca. 50%, was an inseperable tar. A small amount of p-nitrophenol (g) was isolated from the residual liquid of the decomposition mixture. The formation of these products can be explained by the equations below:

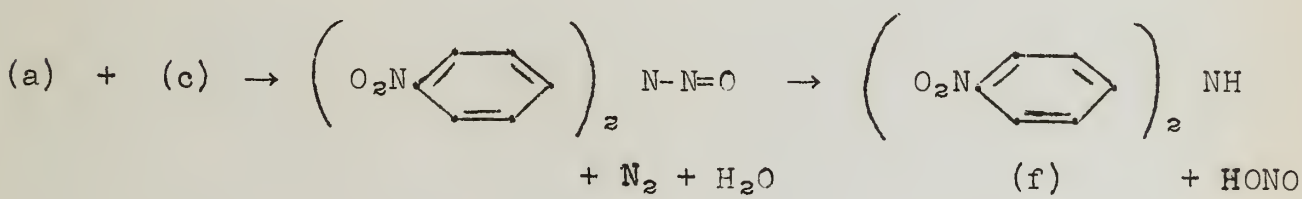


(a) (b) (c)









Reduction of the reaction mixture gave no benzidine which indicates that no sym-biaryl, p,p'-dinitrobiphenyl, was formed.

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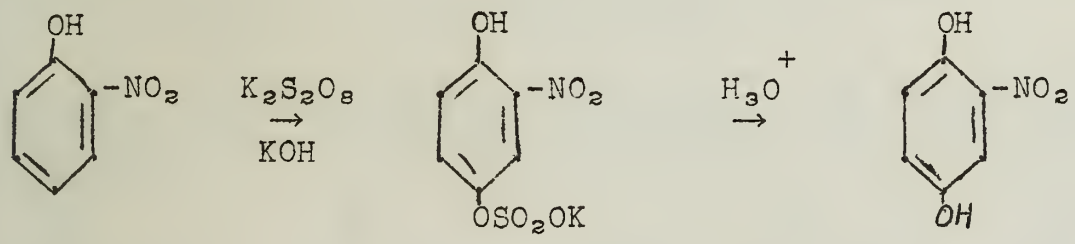
THE ELBS PERSULFATE OXIDATION OF PHENOLS

Reported by H. A. DeWald May 6, 1949

Phenols may be oxidized by potassium persulfate in alkaline solution to give hydroquinone or catechol derivatives. If the p-position to the phenolic group is free, then hydroquinone derivatives are produced; if the para position is occupied a derivative of catechol is formed although usually in much smaller yield.

The reaction was first studied by Elbs (1) in the favorable case of o-nitrophenol (I) which gave nitrohydroquinone (III) in 30-40% yield, about half of the starting material being recovered. Early German work showed that the reaction proceeds via the intermediate formation of a hydroxyphenylpotassium sulfate (II) which is subsequently hydrolyzed in acid solution to the hydroquinone.

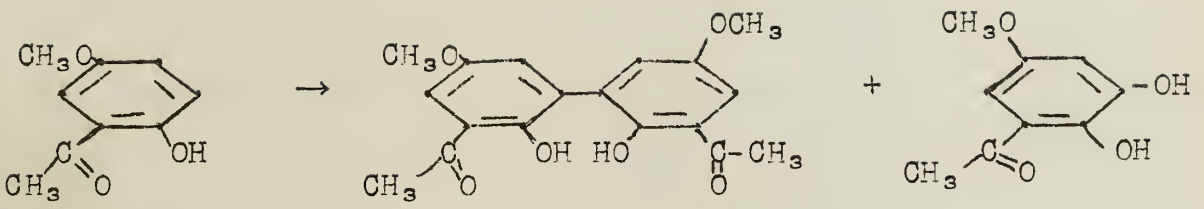


I II III

A recent study of the oxidation of a number of simple phenols has established certain optimum reaction conditions (2) and may indicate certain structural requirements of the phenols in order to obtain respectable yields. In the para-oxidations, the yields are increased by (a) the presence of an electron attracting group and (b) by increasing ring substitution-particularly if the substitution exerts an effect to make the position para to the hydroxyl group relatively rich in electron density. The ortho oxidation of p-substituted phenols gives catechol derivatives in very poor yield and tarry matter is simultaneously produced.

The oxidation is effected quite simply by the slow addition of a saturated solution of potassium persulfate to a stirred solution of the phenolic compound dissolved in excess 10% sodium hydroxide, kept at 20° or lower. The reaction mixture is allowed to stand overnight, acidifed to Congo red, and extracted with ether to remove unreacted starting material. The aqueous layer is then treated with excess HCl, heated for a short time and the dihydric phenol extracted with ether.

Although the oxidation product is generally quite pure, a side reaction has been observed in several instances. (3) When 2-hydroxy-5-methoxyacetophenone (IV) is oxidized with alkaline persulfate, the principal product is a biphenyl derivative (V) with only a small yield of the expected catechol (VI).

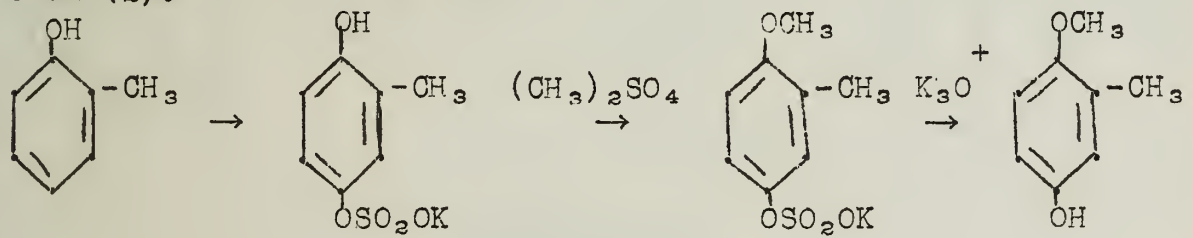


IV V VI

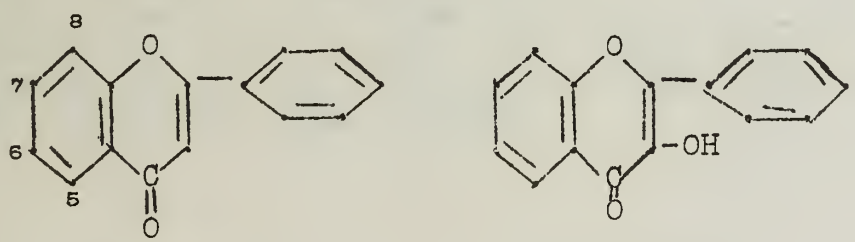
Synthetic Applications

The reaction is sometimes a convenient method for the introduction of a para hydroxyl group into a phenolic compound having an oxidizable side chain. Gentisaldehyde (2,5-dihydroxybenzaldehyde) has been prepared by persulfate oxidation of salicyladehyde or m-hydroxybenzaldehyde (4).

The phenyl potassium sulfate derivative is stable under alkaline conditions and may be alkylated, then hydrolyzed in acid solution to give a hydroquinone monoalkyl ether of known orientation (2).

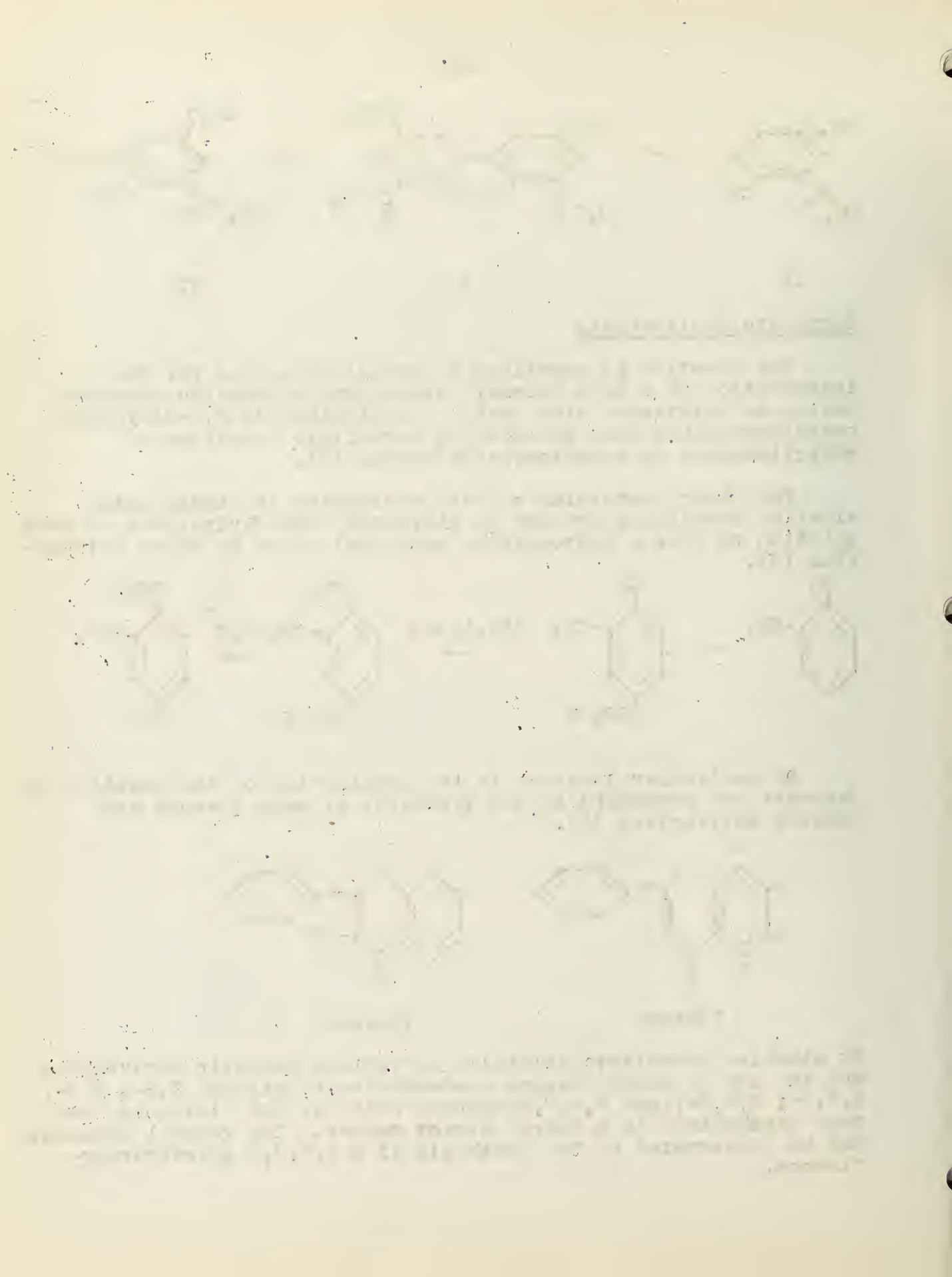


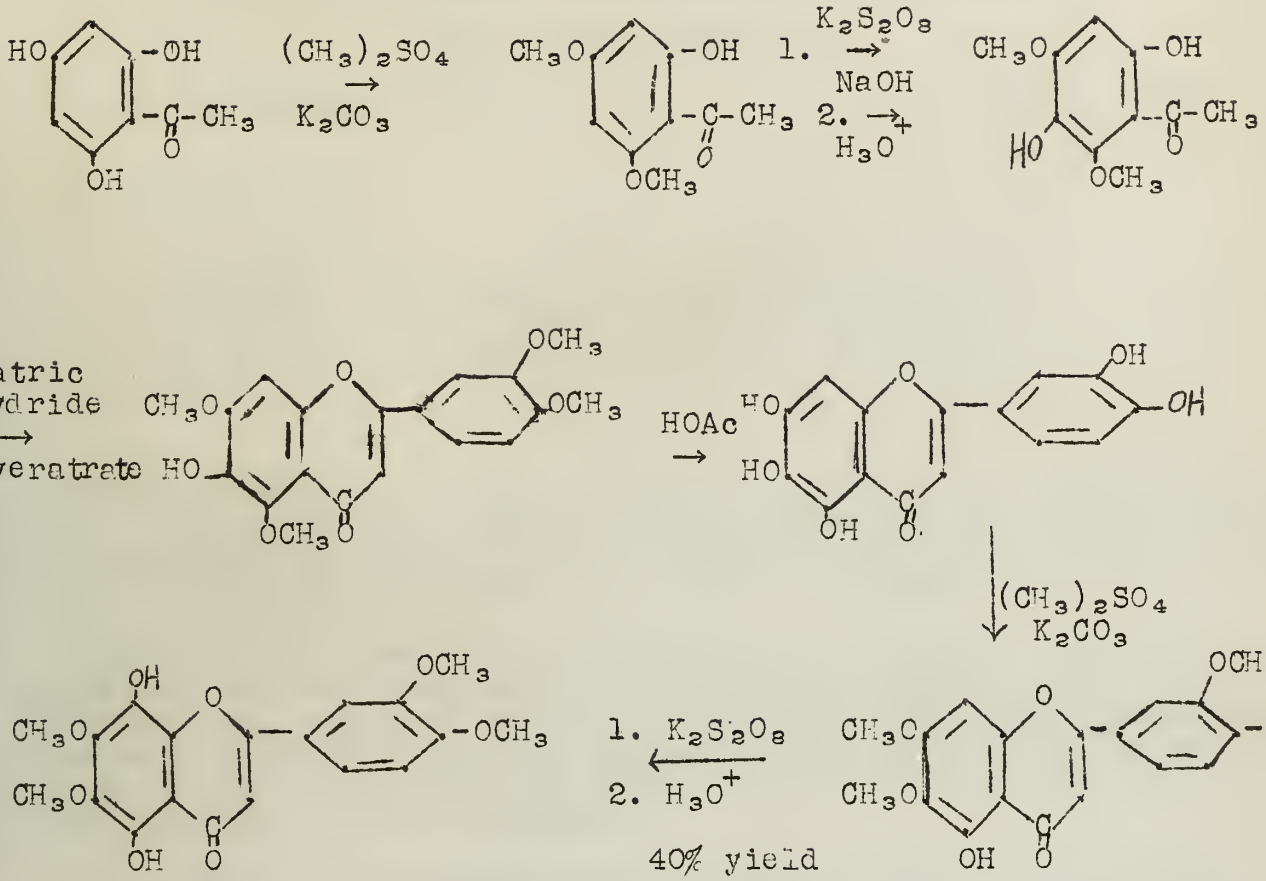
Of particular interest is the application of the reaction by Seshadri and coworkers to the synthesis of many flavone and favanol derivatives (5).



flavone flavanol

By alkaline persulfate oxidation of various phenolic derivatives and the use of known flavone condensation reactions, 5,8-; 5,7-; 5,6,7-; 5,7,8-; and 5,6,7,8-hydroxy flavones and flavanols have been synthesized in a fairly direct manner. The general procedure may be illustrated by the synthesis of a 5,6,7,8 tetrahydroxyflavone.





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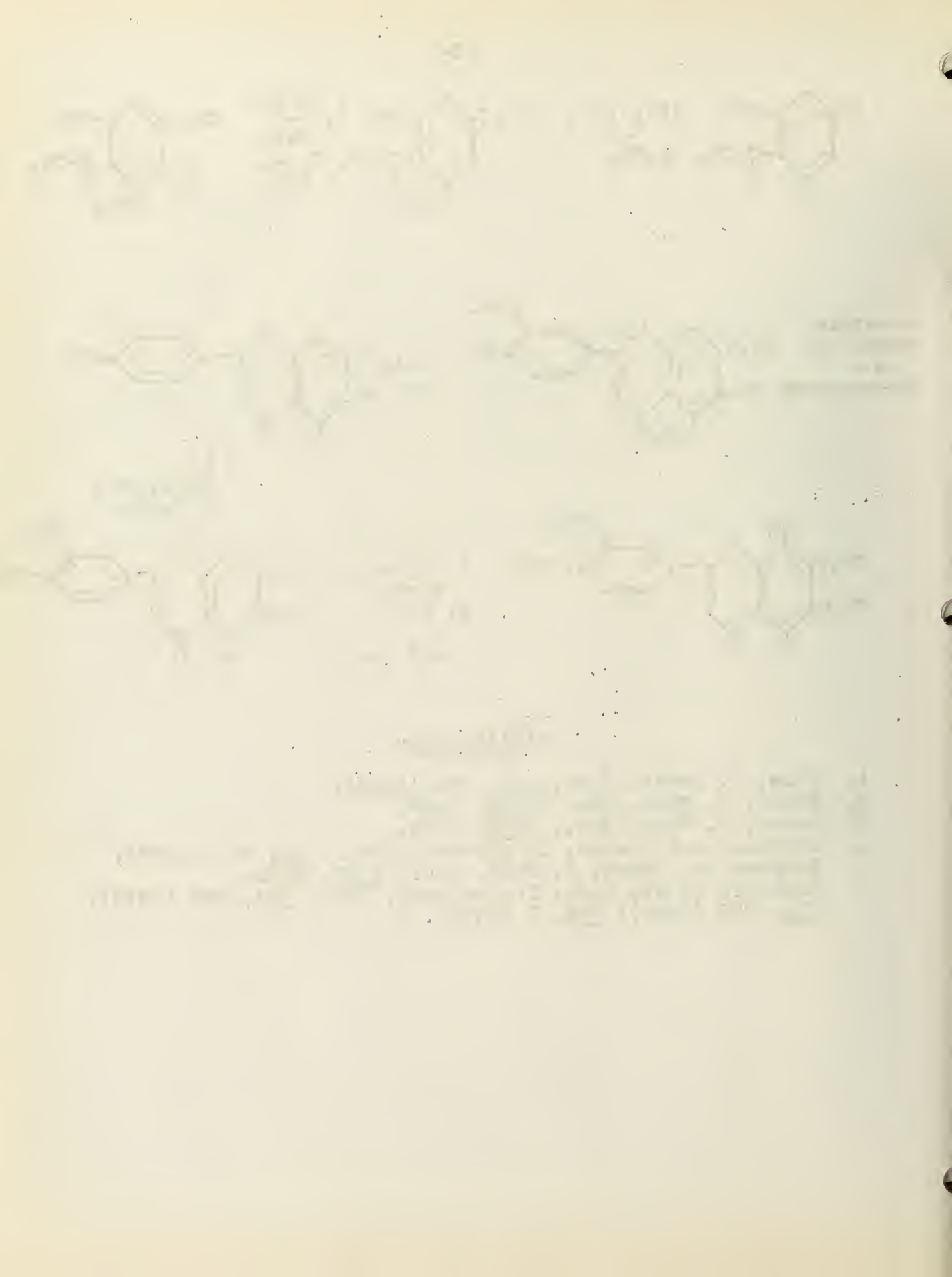
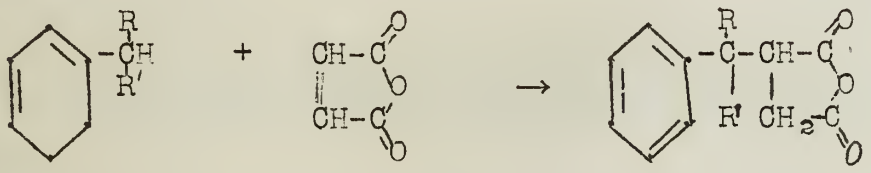


"PEROXIDE CATALYZED REACTION OF ALKYL BENZENES WITH MALEIC ANHYDRIDE"

Reported by Edward F. Riener May 6, 1949

The reaction



was discovered by Dr. Joseph Binapfl (1,2,3,4,5) of Germany before 1935. The conditions used were temperatures of the order of 300° and pressures of about 400 psi. Reaction times were short, of the order of 5-30 minutes under the cited conditions.

It was claimed that any α,β-unsaturated aliphatic acid was operable, such as itaconic or citraconic anhydrides, maleic acid, fumaric acid, mesaconic acid or citric acid (which dehydrates on heating). Binapfl described the use of iodine, sulfur, or copper bronze as catalysts, but his evidence does not show that the catalysts were at all necessary.

An aliphatic side chain with an alpha hydrogen was necessary for reaction under these conditions; neither benzene nor naphthalene reacted. It was found that the reactivity of the side group was in the following increasing order:

$$-CH_3 \qquad -CH_2- \qquad -\overset{\diagup}{\underset{\diagdown}{CH}}$$

When the aromatic nucleus contained more than one side chain, as in diethyl benzene or triisopropyl benzene, only one group reacted.

Clar (6) reported that when fluorene and maleic anhydride were gently heated for forty hours at 210°C, there was obtained a 28 per cent yield of 9-fluorenylsuccinic anhydride. Acenaphthene and maleic anhydride gave 23 per cent yield of acenaphthenylsuccinic anhydride.

Beavers (7) recognized the possibilities of this reaction and investigated it further. He postulated that the reaction was actually a free radical reaction and, therefore, should be catalyzed by peroxide catalysts. Using various peroxide catalysts, he discovered that the reaction could be run under comparatively simple conditions. The addition of a hydrocarbon solution of the catalyst to a hydrocarbon solution of maleic anhydride at about 110 C gives rise to good yields of α, α'-dialkyl benzylsuccinic anhydrides.

Below is a list of hydrocarbons which react with maleic anhydride and respective yields:

DONOR	YIELD
Isopropylbenzene	64.2%
Tetramethylbenzene (mixed isomers)	23.3%
Ethylbenzene	49.5%
m-Xylene	23.5%
p-Xylene	41.2%
Mesitylene	25.9%
Triisopropylbenzene	15.4%

Under the same conditions, the expected product was not obtained in significant amounts from any of the following donors:

o-Xylene
Toluene (8)
p-Methylacetophenone
1-Methylnaphthalene
Ethyl acetoactate
Diethyl malonate
2-Methylthiophene
o-Nitrotoluene
Dihydropyran

With isopropylbenzene as the donor in all cases, the following potential acceptors did not give the expected products:

Chloromaleic anhydride
Mesityl oxide
Dibutyl maleate
n-Butyl crotonate
Crotonic acid
Quinone
n-Butyl vinyl ether
Naphthalene
Furan

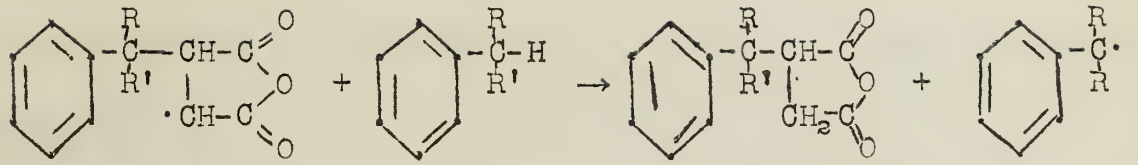
The mechanism of the reaction is a free radical chain reaction since only 0.04 mole of peroxide per mole of maleic anhydride is sufficient to catalyze it. This mechanism is illustrated as follows:

1) $[CO]_2O_2 \rightarrow \cdot O + CO_2 +$ other products

2) $\cdot O + \text{C}_6\text{H}_5\text{-C(R)(R')-H} \rightarrow \text{C}_6\text{H}_5\text{-C}\cdot\text{(R)(R')} + O\text{H}$

(A)

3) $\text{C}_6\text{H}_5\text{-C}\cdot\text{(R)(R')} + \text{CH-C(=O)-O-C(=O)-CH} \rightarrow \text{C}_6\text{H}_5\text{-C(R)(R')-CH-C(=O)-O-C(=O)-CH}\cdot$

4) 

This mechanism formulates a cycle by which one free radical from the peroxide may cause the formation of many molecules of the product. The initiating step, to give (A), has been demonstrated by Kharasch. (9)

Notable is the fact that when isopropylbenzene was treated with an unsaturated carbonyl compound under the conditions stipulated before, symmetrical diphenyltetramethylethane was obtained in low yield.

Marvel et al, (10) found that when dimethyl maleate was treated with peroxide in the presence of dioxan, dimethyl dioxanylsuccinate was obtained as a by-product. The mechanism of the formation of this compound is the same as that between alkyl benzenes and maleic anhydride.

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ALKENE SULFIDES

Reported by Edward F. Elslager May 13, 1949

I. INTRODUCTION

Compounds containing the ethylene sulfide ring (thiirane), by analogy to those composed of the ethylene oxide ring (oxirane), would be expected to be very reactive and should undergo numerous transformations involving the degradation of this ring.

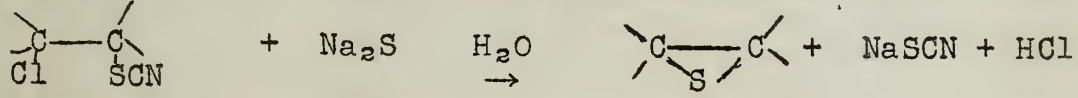
II. PREPARATION

A. Addition of sulfur to olefinic bonds

Several investigators (1,2) have reported the formation of alkene sulfides by the addition of sulfur across olefinic double bonds. Complex mixtures were formed, and the yields of olefinic sulfides were very low. This procedure needs further investigation.

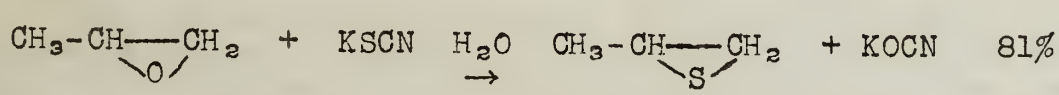
B. From 1,2-dithiocyano- and 1-chloro-2-thiocyanoethanes

The action of sodium sulfide on 1-chloro-2-thiocyano- and 1,2-dithiocyanoethanes in aqueous solution yields ethylene sulfides in low yields (3,4,5). This method was one of the earlier methods and is not extensively used at the present time.

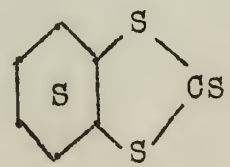


C. From analogous epoxides (6,7,8,9,10,11)

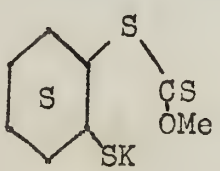
Ethylene oxide and its derivatives, when treated with aqueous potassium thiocyanate or thiourea, are converted to the corresponding ethylene sulfide derivatives. The yields are very good, and this is by far the best method for the preparation of alkyl olefin sulfides.



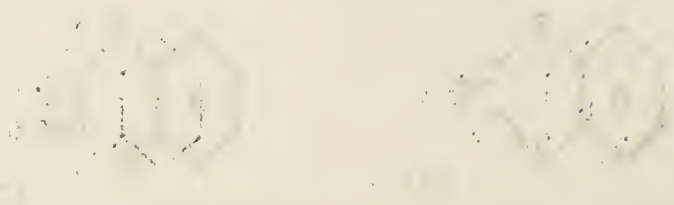
It was found that the action of two moles of metallic xanthates on ethylene oxide yielded 97 per cent of ethylene trithiocarbonate (I), by means of the intermediate (II) (10).



(I)

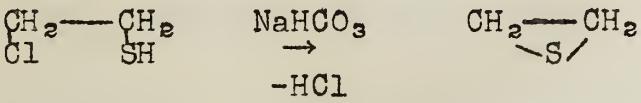


(II)



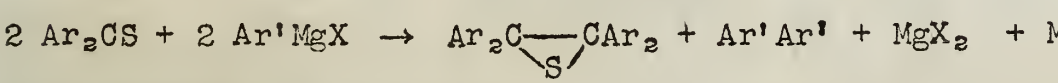
D. Dehydrohalogenation of an α-chlorothiol

In the presence of an alkaline reagent, α-chlorothiols are dehydrohalogenated to ethylene sulfides (12). According to the patent, 50 to 90% yields of ethylene sulfide are obtained, and this procedure may be commercially important.



E. From Grignard reagents

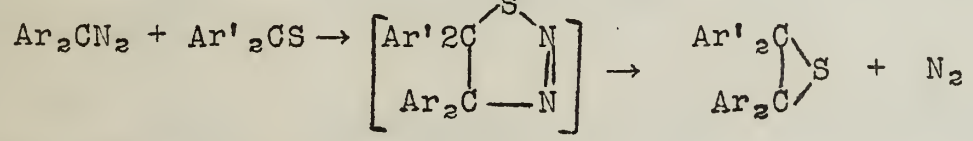
Tetraarylethylene sulfides are produced by the action of a Grignard reagent on a diarylthioketone (13,14).



This reaction may be regarded as the bimolecular reduction of thiocarbonyl compounds by Grignard reagents, and the reaction is very general. This reduction is also effected with magnesious iodide (15).

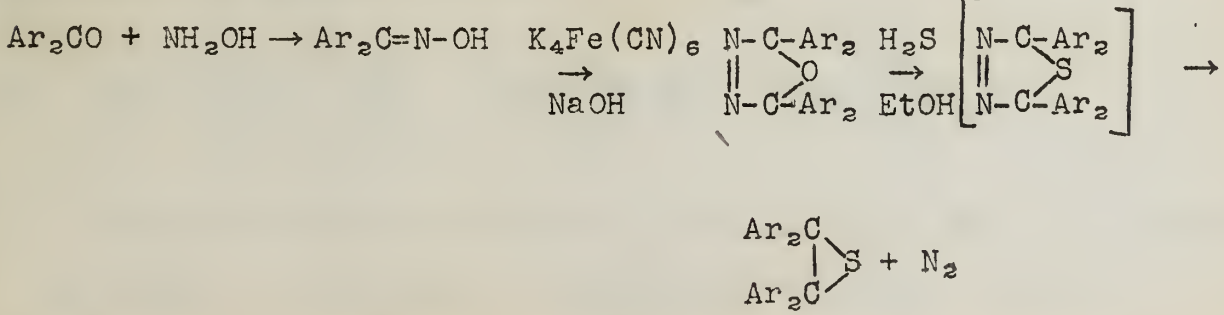
F. From diaryldiazomethanes

Another synthesis of tetraarylethylene sulfides involves the reaction between a diaryl diazomethane and a diaryl thioketone. It is believed that an unstable 4,4,5,5-tetraaryl-4,5-dihydro-1,2,3-thiadiazole is first formed; it subsequently loses nitrogen to form the olefin sulfide (16,17,18,19). In contrast to the above method, this scheme is used when one wishes to make Ar and Ar' different.



G. From substituted oxadiazoles

2,2,5,5-Tetraaryl-2,5-dihydro-1,3,4-oxadiazoles when treated with hydrogen sulfide in ethanolic solution yield the corresponding thiadiazoles, which decompose into nitrogen and the ethylene sulfide derivative (20).



This synthesis is especially useful in those instances where the starting diarylthioketone is not readily available.

III. REACTIONS - Reactions C, D, I, J and K appear to be the most important.

A. $CH_2\!-\!S\!-\!CH_2 + HNO_3 \rightarrow HO_3S\text{-}CH_2COOH + HO_3SCH_2CH_2SCH_2COOH$ (21)

B. " $\xrightarrow[\text{trace}]{HCl}$ amorphous polymer (21)

C. " $\xrightarrow[\text{cool}]{\text{3 pts HCl}}$ $HSCH_2CH_2Cl + HSCH_2CH_2SCH_2CH_2Cl$ (21)

D. " $\xrightarrow[\text{Bz. } 50^\circ]{NaHSO_3}$ $HSCH_2CH_2SO_3Na \xrightarrow{H^+}$ acid (22)

E. " $\xrightarrow[\text{cool}]{RCOCl}$ $ClCH_2CH_2SCOR$ (23,24)

F. " $+ H_2S \rightarrow$ $SHCH_2CH_2SH$ (49%) + $S(CH_2CH_2SH)_2$ (16%) (11)

G. " $+ C_5H_{11}SNa \rightarrow$ $C_5H_{11}SCH_2CH_2SH$ (75%) + $C_5H_{11}SCH_2CH_2SCH_2CH_2SH$ (25%)

H. " $\xrightarrow[\text{weak alk.}]{I_2}$ $ICH_2CH_2S\text{-}SCH_2CH_2I$ (25)

I. " $\xrightarrow[100^\circ]{PhNH_2}$ $PhNHCH_2CH_2SH$ $\xrightarrow{CH_2\!-\!S\!-\!CH_2}$ $PhN(CH_2CH_2SH)_2$ (8,26)

J. " $\xrightarrow[100^\circ]{R_2NH}$ $R_2NCH_2CH_2SH$ $\xrightarrow{CH_2\!-\!S\!-\!CH_2}$ $R_2NCH_2CH_2SCH_2CH_2SH$ (8,26)

K. $CH_3\text{-}C(CH_3)\!-\!S\!-\!CH_2$ $\xrightarrow[NaOEt]{\text{xs. } RSH}$ $CH_3\text{-}C(CH_3)(SR)\text{-}CH_2SH$ + $CH_3\text{-}C(CH_3)(SH)\text{-}CH_2SR$

The reaction products are capable of reacting further as follows:

$R_2C(SR)\text{-}CH_2SH + R'_2C\!-\!S\!-\!CH_2 \rightarrow R_2C(SR)\text{-}CH_2SC(R'_2)CH_2SH$ (27,8)

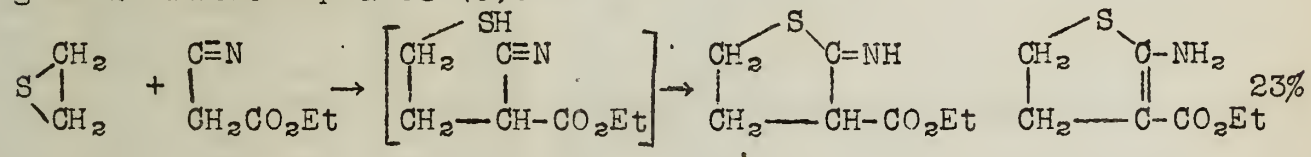
L. With alcohols - The same authors (8) reported the condensation of primary alcohols with alkene sulfides in the presence of boron fluoride catalysts; the products were β-alkoxy mercaptans.

M. With benzene and $AlCl_3$ - Propylene sulfide reacts with benzene in the presence of $AlCl_3$ to yield a polymer, which, when heated, yields 1,2-diphenyl propane (24).

N. With acetic acid - Acetic acid gives only a 15% yield of primary addition product when reacted with propylene sulfide. This product is a mixture of the isomers:

$$CH_3\text{-}\underset{SH}{C}HCH_2OCOCH_3 \quad \text{and} \quad HSCH_2\underset{CH_3}{C}HOCOCH_3 \qquad (24)$$

O. Synthesis of 2-iminothiophanes - Ethyl cyanoacetate and olefin sulfides were found to react in the presence of sodium ethoxide to give 2-iminothiophanes (9).



P. Polymerization - Polymerization was one of the first reactions of the olefin sulfides to be noted, and although the polymeric sulfides have been described as amorphous solids, little work has been done to determine their structure. When treated with mineral acids or concentrated alkali, the polymerization proceeds with the liberation of much heat. Ethylene oxide polymerizes spontaneously even at 0°; by the addition of small amounts of aliphatic mercaptan, the polymerization is inhibited. Cyclohexene sulfide can be stored in the refrigerator for several days without polymerizing, and isobutylene sulfide has been stored at room temperature for several months without any appreciable change (8).

Tetraarylethylene sulfides when heated decompose to the corresponding olefin and sulfur, or ring close with the loss of HCl forming the corresponding benzothiophene derivative.

IV. APPLICATIONS

The products resulting from the action of amines on olefin sulfides are useful in the preparation of dyes, vulcunization accelerators, and textile assistants. Ethylene sulfides are found to react with wool fiber forming a polymer which greatly decreases the shrinkage characteristics of the wool. The condensation of ethylene sulfide with cyanamide in water produces a substance which has good insecticidal properties.

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THE SYNTHESIS AND STRUCTURE OF SEMPERVIRINE

Reported by Charles W. Fairbanks May 20, 1949

The American "Yellow Jasmine", gelsemium sempervirens, has afforded the following crystalline alkaloids (2): Gelsemine ($C_{20}H_{22}O_4N_2$), sempervirine ($C_{19}H_{16}N_2$), and gelsemicine ($C_{20}H_{25}O_4N_2$) as well as other amorphous constitutents of unknown composition.

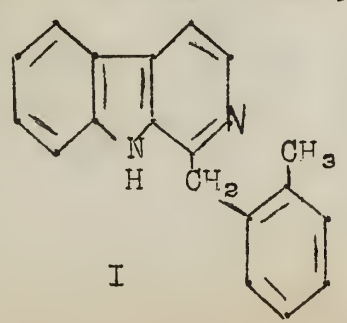
By treating gelsemium root in a modified Sayre and Watson procedure sempervirine and gelsemine were obtained in a ratio of 19 to 29.

Sempervirine absorbs three molecules of hydrogen over palladium and five molecules of hydrogen over Adams catalyst. The former product could not be crystallized nor could any crystalline derivatives be isolated as the material rapidly resinified. The latter product could be crystallized but contained oxygen and rapidly absorbed more oxygen from the air. Sempervirine affords a quaternary mono-methiodide upon treatment with methyl iodide. No definable product could be obtained on degradation with aqueous alkali. No useful results were obtained by oxidation with permanganate, nitric acid or hydrogen peroxide - osmium tetroxide; by heating with palladium in air or oxygen, or by potash fusion (2).

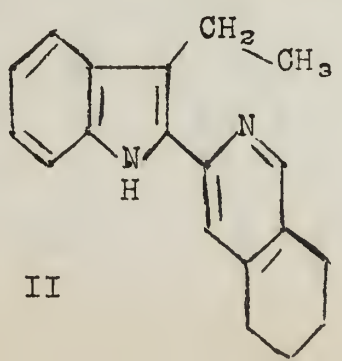
The free alkaloid crystallizes from chloroform in reddish brown needles, is slightly soluble in alcohol and water and is almost insoluble in ether, benzene and petroleum ether. The hydrochloride is readily soluble in water and alcohol and is precipitated by nitric, tannic and picric acids. Yellow precipitates are obtained by treatment with potassium chromate, platinic chloride, sodium chloride and sodium nitrite (5).

Sempervirine has an active hydrogen as shown by means of a Zerwitinoff determination. The N-methyl determination was negative. The ultraviolet absorption spectra of sempervirine shows a strong series of absorption bands; these bands are almost identical in alkaline and neutral alcoholic solutions (4).

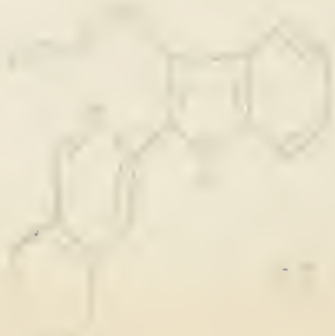
Sempervirine is isomeric with yobyrine (I). In attempting to relate the two it was found that upon heating sempervirine with selenium it was changed to yobyrine, as determined by mixed melting points and ultraviolet absorption spectra. Sempervirine, when heated with Raney nickel in xylene solution, gave poor yields of tetrahydroisoyobyrine (II) as determined by mixed melting points and ultraviolet absorption spectra (4).



I



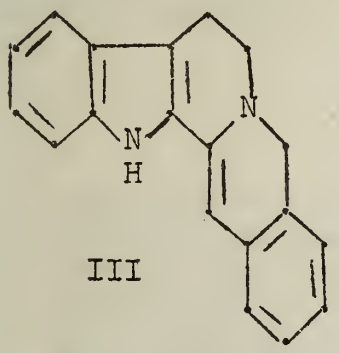
II



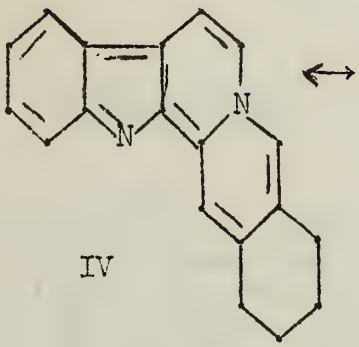
These experiments appeared to have clarified the ring structure of sempervirine; however, they still left the position of the double bonds undetermined. Upon considering the ultraviolet absorption spectra, which requires an extended chromophoric system conjugated with the aromatic system, Prelog proposed the structure (III) as a possible formula for sempervirine.

All N-unsubstituted indole derivatives are characterized by an intense sharp band at 2.9. Sempervirine shows no such band. When sempervirine methochloride is treated with selenium a new base, N-methylyobyrine, is obtained. Its ultraviolet spectrum is nearly identical with that of yobyrine and its infrared spectrum possesses no NH band. The base was identified by direct comparison with a synthetic sample.

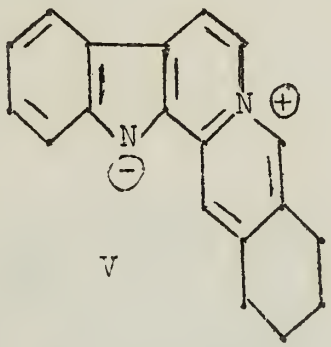
These considerations led Woodward (6) to propose a new structure (IV) for sempervirine. This structure implies an important contribution of the fully aromatic ionic structure (V). This view explains the color of the alkaloid and its high basicity (pK 10.6).



III



IV

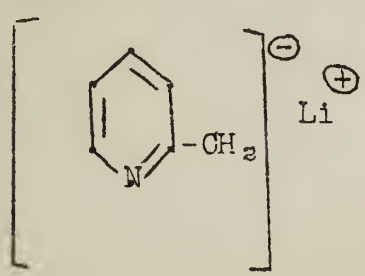


V

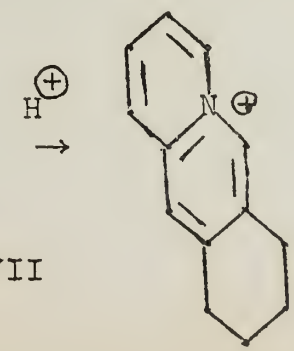
The formation from sempervirine of a mole of methane in the Zerewitinoff determination can be attributed to the presence in (IV$\leftrightarrow$ V) of a virtual (substituted) γ-picolinium system.

Final proof of the structure of sempervirine was obtained through the synthesis of sempervirine methosalts by an unambiguous route.

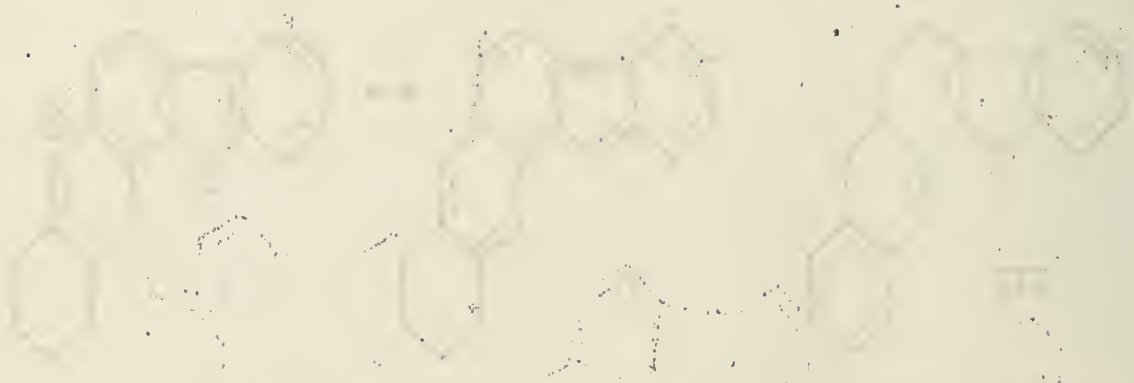
In a model experiment, the lithium derivative of α-picoline was condensed with isopropoxymethylene cyclohexanone (VI), salts of the dehydroquinolizinium cation (VII) being readily obtained from the acid-treated reaction-mixture.



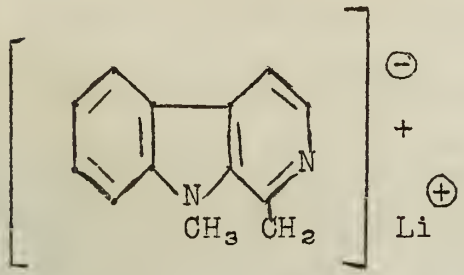
VI



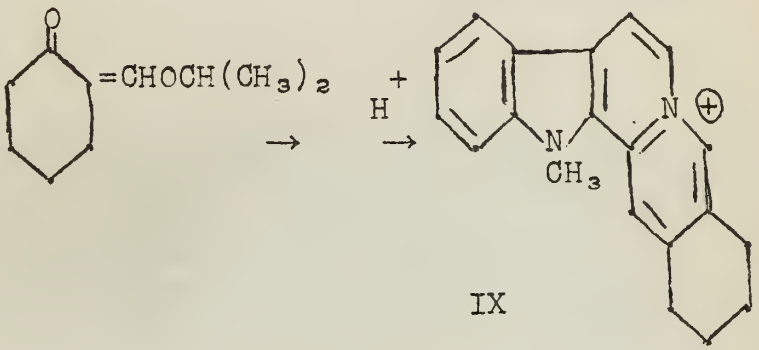
VII



In a similar reaction, the lithium derivative of N-methylharman (VIII) led to the smooth synthesis of salts of the methylsempervirinium cation (IX).



VIII



IX

Synthetic samples of sempervirine methopicrate and sempervirine methochloride showed no depression in melting point on admixing with the corresponding salts prepared from the natural sempervirine. Further corroboration for formula (IV) was obtained through the reproduction of the characteristic ultraviolet absorption spectra.

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ISOMERISM OF LYSERGIC ACID

Reported by Allen B. Simon May 20, 1949

Importance of Lysergic acid.

Lysergic acid is the most important fission product of the ergot alkaloids, and the only product common to all ergot alkaloids upon alkaline hydrolysis (2). The great difference in physiological activity between the almost inactive dextrorotatory and the active levorotatory series of alkaloids clearly depends only on the lysergic acid moiety (5) and seems to be determined by a steric shift on an asymmetric center, as will be shown in this seminar.

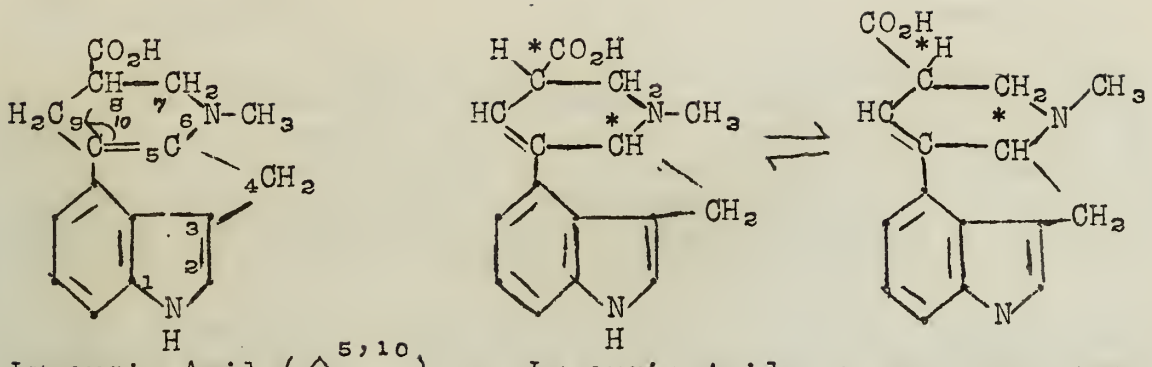
Ergot, the source of the alklaoids, is a fungus which grows on the rye plant. Eating of the infested plant causes a severe form of gangrene and, in pregnant women, abortion (3). When pharmacologically administered, ergot induces a prolonged, rhythmic contraction of the puerperal uterus.

Lysergic acid is also of chemical interest since the ergoline ring system, the basic tetracyclic ring structure of lysergic acid, represents the only known example of an indole derivative condensed in the 3,4 position to other nuclei (7) Diagram I.

Previous Work.

The basic ring structure of lysergic acid and of its isomer, isolysergic acid, was confirmed by the synthesis of dihydro-d,l-lysergic acid (8). This, however, still left unanswered the question of the position of a non-aromatic double bond present outside of the indole nucleus. Ultraviolet absorption studies indicated that in both lysergic acid and isolysergic acid this double bond is conjugated with one of the double bonds in the indole nucleus. Jacobs (5) assumed that the isomerism between lysergic acid and isolysergic acid is brought about by a shift in the position of this double bond. Positions 4-5 and 5-10 would place the double bond equidistant from the NCH_3 group (position 6). These positions were excluded when the difference in basicity of the tertiary amine groups in the two compounds were ascribed to difference in distance from the non-aromatic double bond to the NCH_3. The basic group in lysergic acid is weaker than that in isolysergic acid (2); by analogy with the findings of an earlier study on dissociation constants (4), it was concluded that the double bond in isolysergic acid is 9-10, the farther position, while the double bond in lysergic acid is 5-10, the nearer position (2). When further study showed that vinyl tertiary amines are more basic than unsaturated tertiary amines not in the vinyl position (1), it was proposed that the positions of the double bonds are reversed.

Diagram I



Lysergic Acid ($\Delta^{5,10}$)
Isolysergic Acid ($\Delta^{9,10}$)
(Jacobs)

Lysergic Acid
(Stoll)

Isolysergic Acid

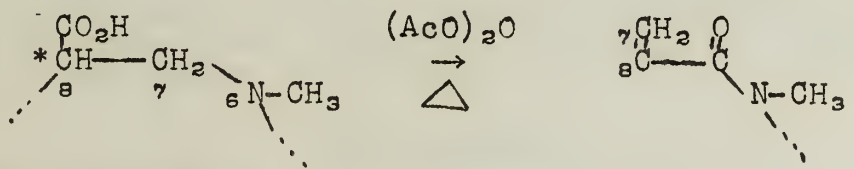
Isomerism Explained as Stereoisomerism (6)
Formation of the Lactam

Stoll, Hofmann, and Troxler began their investigation of the position of the non-aromatic double bond by the removal of the C8 asymmetry. This was unexpectedly accomplished when treatment with acetic anhydride yielded the lactam. Both lysergic and isolysergic acids yielded the identical lactam which was opitcally active.

From this experiment the following conclusions were drawn. The double bond in lysergic acid and isolysergic acid is 9-10. The large displacement of the ultra-violet absorption spectrum of the lactam towards the region of the long wave lengths indicates that the new double bond in 7-8 is conjugated with those already present. That could only be possible if the non-aromatic double bond is 9-10.

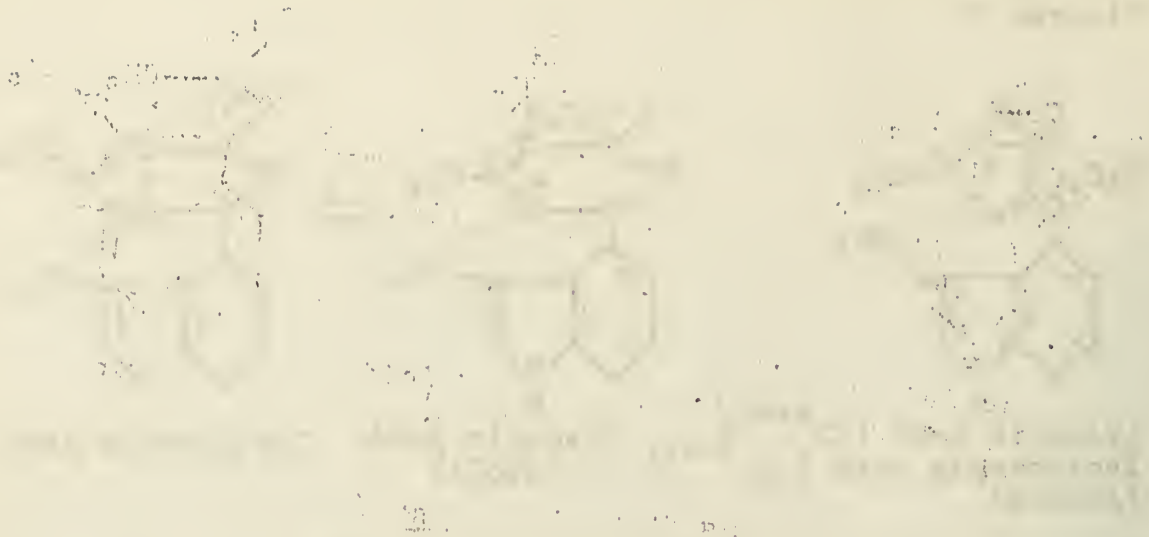
Lysergic acid and isolysergic acid differ only by the steric arrangement about C8 since removal of C8 asymmetry produces the identical compound from both acids. Therefore, they are diastereoisomers and not structural isomers as hypothesized by Jacobs.

Diagram 2



Hofmann Degradation

The removal of asymmetry from C5 was attempted by the Hofmann degradation method, using stable derivatives of the lysergic acids as starting reagents. The products from both reagents proved to be identical, optically active, and with C5 still asymmetric. The ring had broken between positions 6-7.



The degradation was continued to give a product which was no longer optically active, confirming the assumption that C5 and C8 are the only asymmetric atoms in lysergic and isolysergic acids.

Number of Isomers

If the double bond is fixed in the 9-10 position in both acids then upon racemization two racemates should be formed. Two racemates of the lysergic acids and two of the hydrazides are known. If the formulas of Jacobs are correct, then one racemate of lysergic acid and two racemates of isolysergic acid are possible. Stoll, Hofmann, and Troxler have made repeated attempts to discover a third racemate but have always been unsuccessful.

The saturation of the double bond, 9-10, of lysergic acid with hydrogen causes the formation of a new center of asymmetry at C5 with the possibility of two stereoisomers. Up until now, however, only one isomer has been found. With isolysergic acid the saturation of the double bond again causes the formation of a new center of asymmetry at C5 with the possibility of two isomers. Here both isomers have been found. Under definite conditions one of the isomeric dihydroisolysergic acids can be irreversibly converted into the dihydrolysergic acid. Therefore, the two dihydroacids differ only in the steric arrangement about C8. The steric arrangement about the newly formed center of asymmetry, C10, is identical.

Importance of 9-10 Unsaturation for Isomerism

Lysergic acid and isolysergic acid are easily converted one into the other. If the carboxyl group is replaced, however, the interconversion can no longer be brought about. Ester derivatives do isomerize and the alkyl portion of the ester influences the speed of isomerization. If the 9-10 double bond is saturated, isomerism can no longer occur except that the one isomer of dihydroisolysergic acid can irreversibly change to dihydrolysergic acid.

Although most of these observations had previously been used as evidence for the hypothesis that the isomerism is due to a shifting of the double bond (5), Stoll considers them readily explainable on the basis of his theory. The presence of the 9-10 double bond enhances the enolization of the carbonyl portion of the carboxyl group; it permits the formation of a completely conjugated double bond system from the enol double bond to the double bond system of indole. Since the enol form of C8 is symmetrical, it permits the formation of equal amounts of the enantiomorphs upon tautomerization back to the keto form. Therefore, it could be expected that saturation would hinder isomerization.

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