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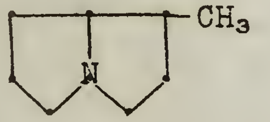
SEMINAR REPORTS

I Semester 1941-42

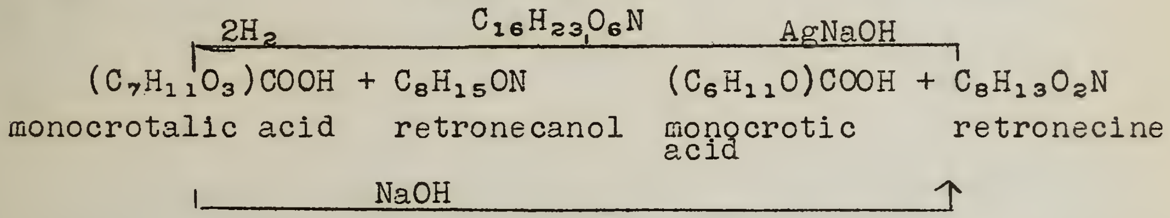
ALKALOIDS OF CROTALARIA, SENECIO,
HELIOTROPIUM TRICHODESMA, AND ERECHTITES

Crotalaria is a genus of leguminous plants, many species of which are commonly used in the southern part of the United States as soil-enriching legumes. All contain smaller or larger quantities of alkaloids. At present Crotalaria spectabilis is the most widely planted. Its alkaloid, extracted by alcohol, has the formula $C_{16}H_{23}O_6N$. Through its chemical reaction it has been shown to be closely related to alkaloids extracted from various species of Senecio, Heliotropium, Trichodesma, and Erechtites. In view of the fact that Senecio alone has over 1200 species, the alkaloids of this general type promise to be the largest single class known. Of the 20-30 thus far characterized, not a single one has had its structure clarified. These alkaloids are esters, made up of an acid containing eight or ten carbons (typical formulas are $C_8H_{12}O_5$, $C_8H_{10}O_4$, $C_{10}H_{14}O_4$, $C_{10}H_{16}O_6$) and a bicyclic nitrogen base containing two hydroxyls, at least one of which is esterified with a carboxyl of the acid. All the bases appear to be derivatives of methyl pyrrolizidine.



This report will be confined to the experiments on monocrotaline, the alkaloid of Crotalaria spectabilis. The two most important reactions which cleave the molecule into parts more suitable for structural study are (1) hydrolysis with alkali; (2) hydrogenolysis with platinum of nickel catalyst and hydrogen.

Monocrotaline



$C_{16}H_{23}O_6N$

$2H_2$ — AgNaOH

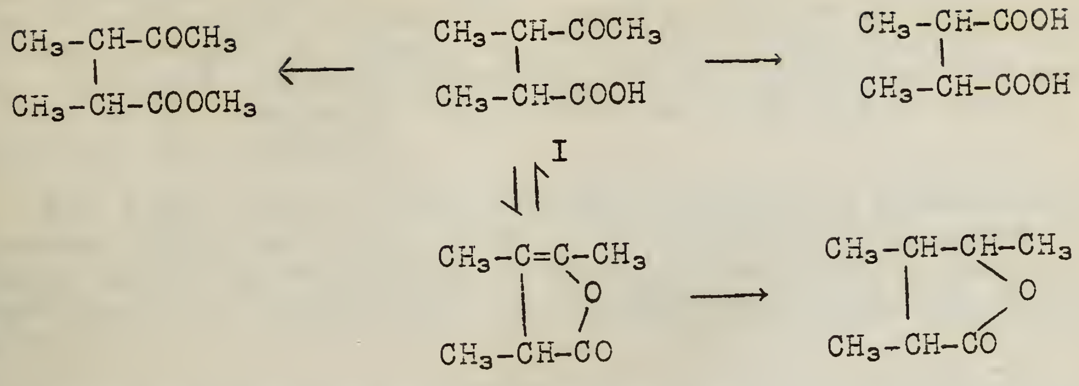
$(C_7H_{11}O_3)COOH + C_8H_{15}ON$ — $(C_6H_{11}O)COOH + C_8H_{13}O_2N$

monocrotalic acid — retronecanol — monocrotic acid — retronecine

NaOH

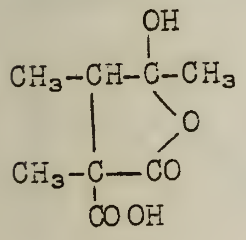
Monocrotalic acid (optically active) loses carbon dioxide upon treatment with alkali to give monocrotic acid (I). Its properties follow: (1) optically inactive; (2) monomethyl ester with diazomethane; (3) forms a dinitrophenylhydrazone; (4) gives iodoform with iodine and alkali; (5) oxidizes with sodium hypobromite to a mixture of meso and racemic α,α'-dimethylsuccinic acids; (6) on heating loses water to give an unsaturated neutral substance reconverted to the acid by hydrolysis. Monocrotic acid thus appears to be α,β-dimethyl levulinic acid which was established by synthesis.

Monocrotic Acid


I

II

Monocrotalic acid is obviously closely related to dimethyl levulinic acid. Monocrotalic acid was shown to have the following properties: (1) back titration from alkali indicates a carboxyl and lactone linkage; (2) monomethyl ester with thiazomethane which shows one active hydrogen; (3) heat decomposition gives α,β, γ-trimethylangelicalactone (II); (4) heat decomposition of methyl monocrotalate gives an unsaturated ester by loss of a molecule of water; the unsaturated ester can be reduced to a saturated ester which is hydrolyzed to a stable, crystalline, lactonic acid; the unsaturated ester can be hydrolyzed with acid to the lactone obtained by heat decomposition of monocrotalic acid. These facts may be explained by any of three formulas which decarboxylate in alkaline solution to the tautomeric form of dimethyl levulinic acid and whose esters dehydrate to unsaturated lactone. They are the lactone forms of γ-keto acids.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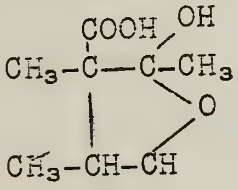
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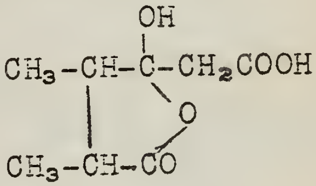
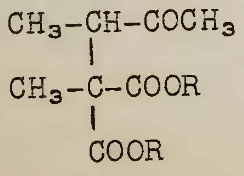
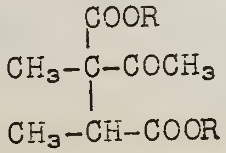

V

The observation that monocrotalic acid esterifies with great difficulty with acid and methanol led to the elimination, perhaps uncorrectly, of V. The necessity of high pressure reduction made unlikely the unsaturated ester corresponding to IV. Originally III was accepted as the most likely. However, the results of the study of compounds VI and VII led to different conclusions.


VI


VII

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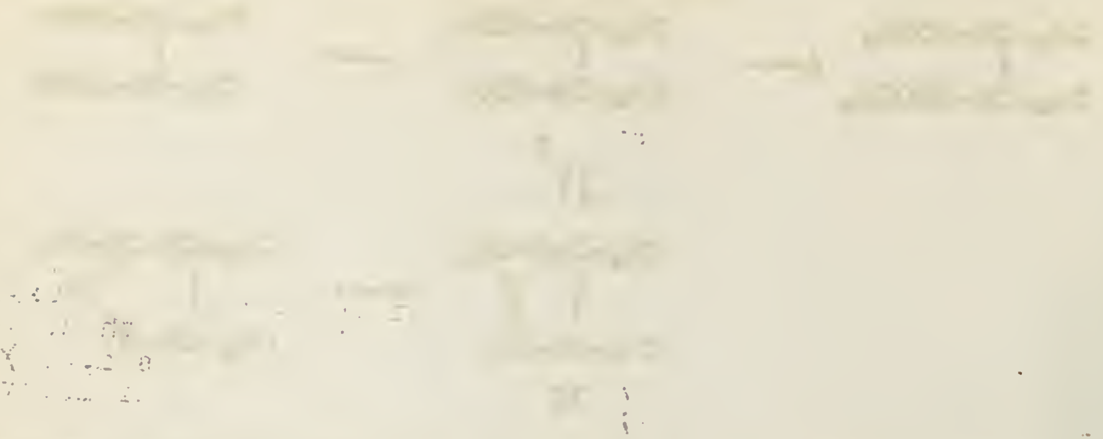

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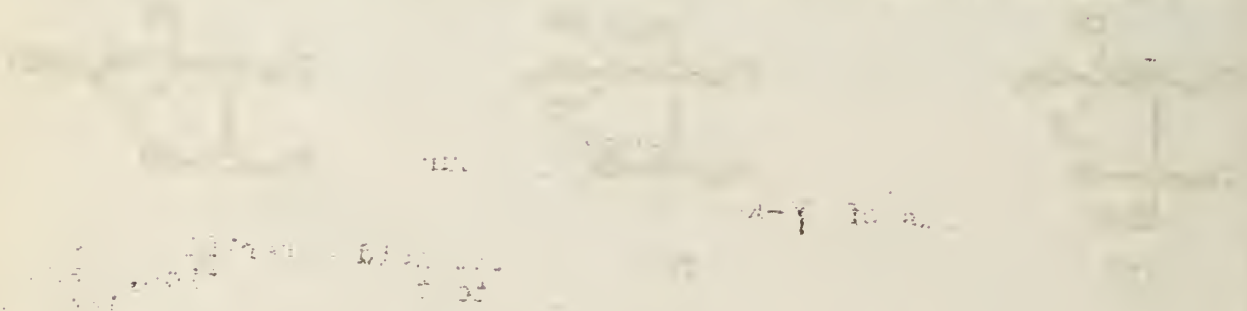

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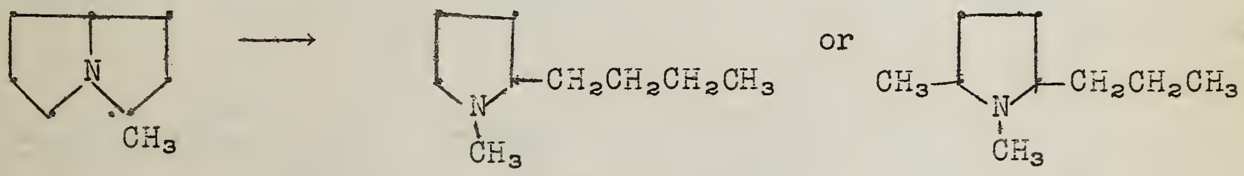
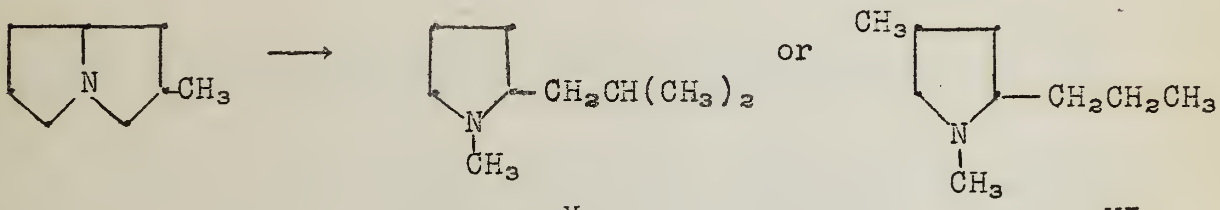
Acid hydrolysis of compound VI resulted in formation of dimethyl levulinic acid (I) which indicates this configuration is unstable to acid while monocrotalic acid is stable to acid. Alkali saponification gave a dibasic acid and no decarboxylation took place. Acid and alkaline hydrolysis of VII also gave dimethyl levulinic acid. Compound V now seems the most likely formula but no proof is yet available.

The basic part of the molecule obtained by saponification is retronecine which has been shown by previous investigators to be a dihydroxy methyl pyrrolizidine containing one double bond. By hydrogenolysis of retronecanol a monohydroxy methyl pyrrolizidine results.

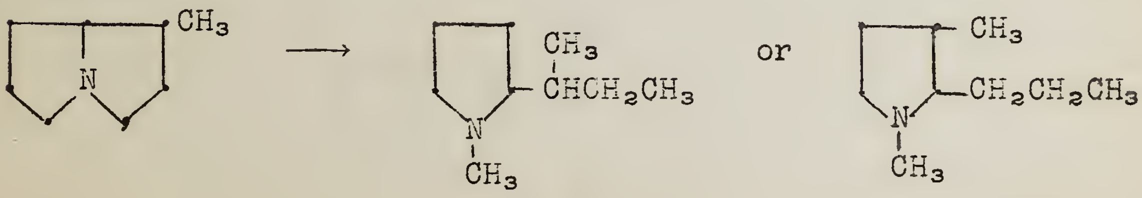
Menshikov dehydrated retronecanol to the corresponding unsaturated compound and reduced this product to the saturated base. His proof that this substance, called heliotridane, $C_8H_{15}N$, is 1-methyl pyrrolizidine was as follows: it had the following properties -- (1) a tertiary base and no N-alkyl groups, thus it must be a bicyclic molecule with a nitrogen atom, common to both rings. Exhaustive methylation followed by reduction gave a pyrollidine derivative shown by its smooth dehydrogenation to a pyrrol. Subsequent reduction gave an optically inactive pyrollidine, a synthesis for which by Menshikov failed. He prepared all of the possible pyrrolidines which could be formed theoretically except the desired one and drew his conclusions by elimination. Thus the three possible methyl pyrrolizidines would yield an exhaustive methylation depending on the point of attack on the molecule the following compounds.



VIII IX

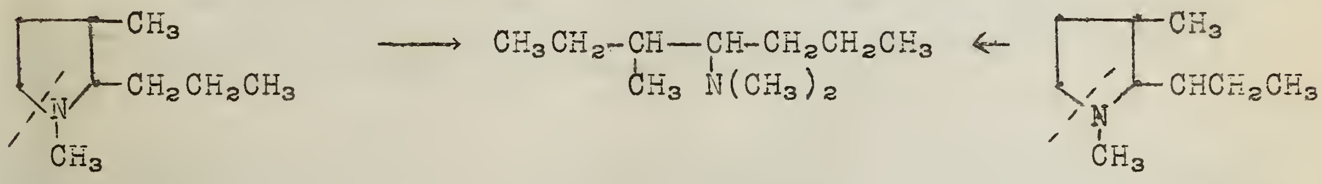


X XI



XII XIII

All the pyrrolidines except XIII were synthesized and the solid picrates compared in m.p. with the picrate of the optically inactive product obtained by degradation of heliotridane. None were identical. Menshikov degraded further the natural pyrrolidine base and obtained an open chain compound which gave a picrate identical with that obtained by a similar reaction with XII.

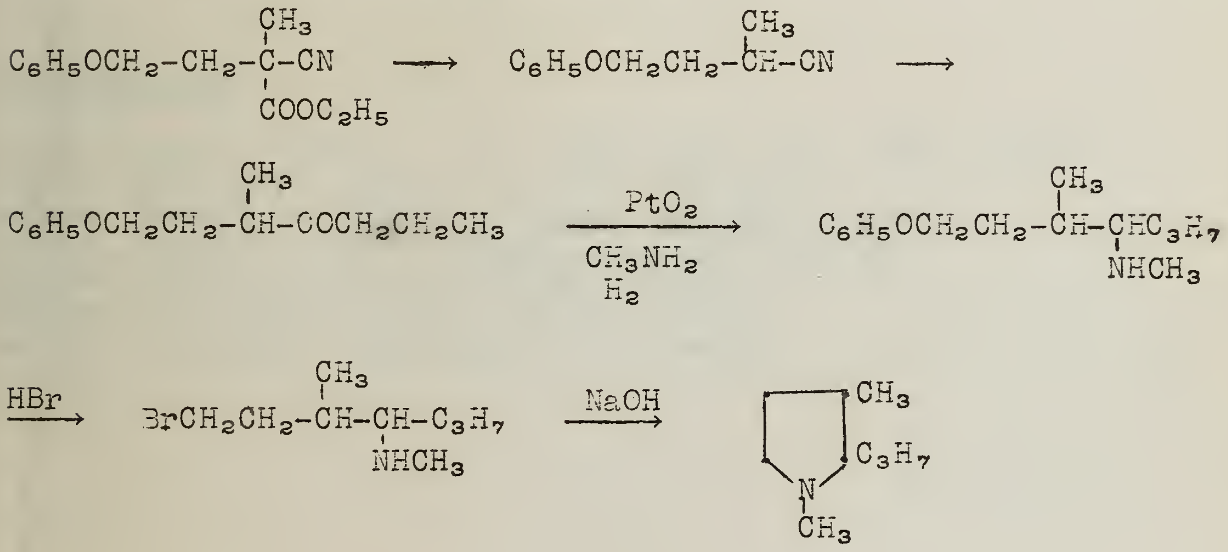


XIII

XII

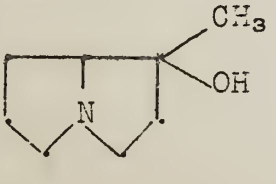
This reaction establishes the structure except for one point. Compound XII can exist in two stereochemical forms and Menshikov may have isolated the one not identical with the compound from the natural product.

In this laboratory compound XIII was synthesized and shown to give an identical picrate (m.p. 116°).



Use of copper chromite, dry methyl amine and hydrogen gave a diastereoisomeric pyrrolidine picrate (m.p. 126°).

Placement of the hydroxyls and double bond has not yet been completed. On the basis of the exhaustive methylation of retronecanol, Menshikov claimed he obtained a tertiary alcohol. Accepting this as correct, retronecanol would have the structure



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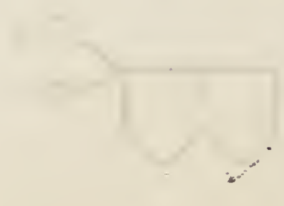
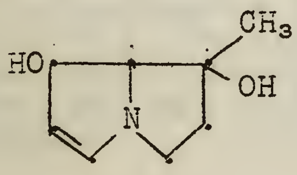
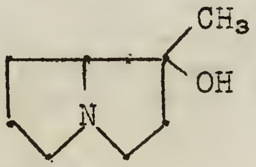


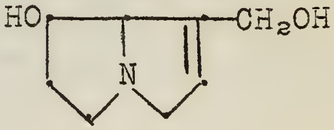
The following experimental facts were used to place the other hydroxyl and double bond in retronecine. (1) One hydroxyl is readily replaced by hydrogen; (2) after reducing the double bond both hydroxyls are stable to reduction; (3) hydroxyls in the saturated molecule esterify at different rates; (4) no enol group; (5) saturated dihydroxy compound readily forms an internal ether. The only formula satisfactorily fulfilling these conditions is shown in XIII, assuring retronecanol to be XIV.



XIII



XIV



XV

Compound XV represents another structure on the assumption of no tertiary hydroxyl. It satisfies all the other facts and also the stability which might not be true of a vinyl amine type, (XIII).

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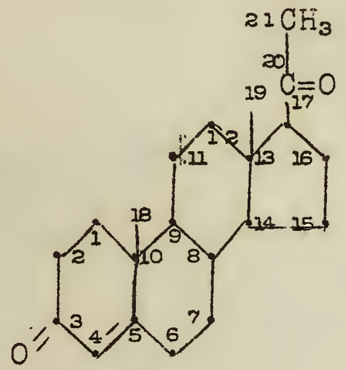
Reported by Roger Adams
September 24, 1941

PROGESTERONE AND RELATED COMPOUNDS

Progesterone is the female sex hormone produced in the corpus luteum, a small yellow body in the ovary. Its function is to condition the uterus for fertilization.

The isolation of pure crystalline progesterone from sows' ovaries was first announced by Butenandt and his coworkers at the Kaiser-Wilhelm Institute in Berlin in 1934 (only shortly before similar announcements by Slotta, Allen and Wintersteiner, and Hartmann and Wettstein). Its structure was first suggested by Slotta but was confirmed largely through the synthetic work of Butenandt and his collaborators, who synthesized the hormone from pregnanediol and from stigmasterol.

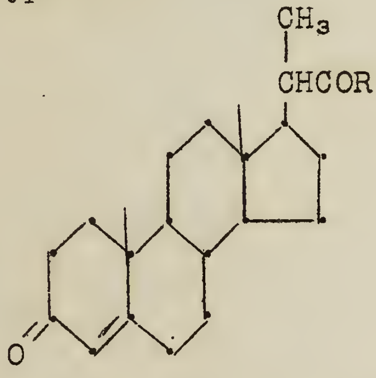
I



Progesterone

Progesterone is the most highly specific of the sex hormones. Very few of the compounds related to it show any of its biolcgical activity. Some of those which do are the 3-enol acetate of progesterone (100%), testosterone (low), 17-methyltestosterone (low), 17-ethinyltestosterone (good), 6-dehydroprogesterone (50%), 6-hydroxyprogesterone acetate, 21-hydroxyprogesterone, 21-methylprogesterone, and 20-norpregnanolone.

Cole has very recently announced the preparation of a number of compounds of the type II:



R = Me, Et, or phenyl

II

These were prepared by the addition of dialkylcadmium or zinc compounds to the acid chloride of Δ^5-3-acetoxybisnorcholenic acid (from stigmasterol). The pure products were inactive, but the crude materials showed progestational activity.

Considerable research has been carried out since 1934 in an effort to find practical syntheses for progesterone from the cheaper sterols such as cholesterol, stigmasterol, the bile acids, and the

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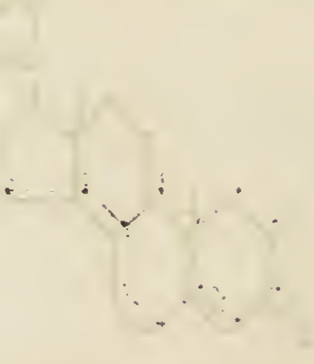

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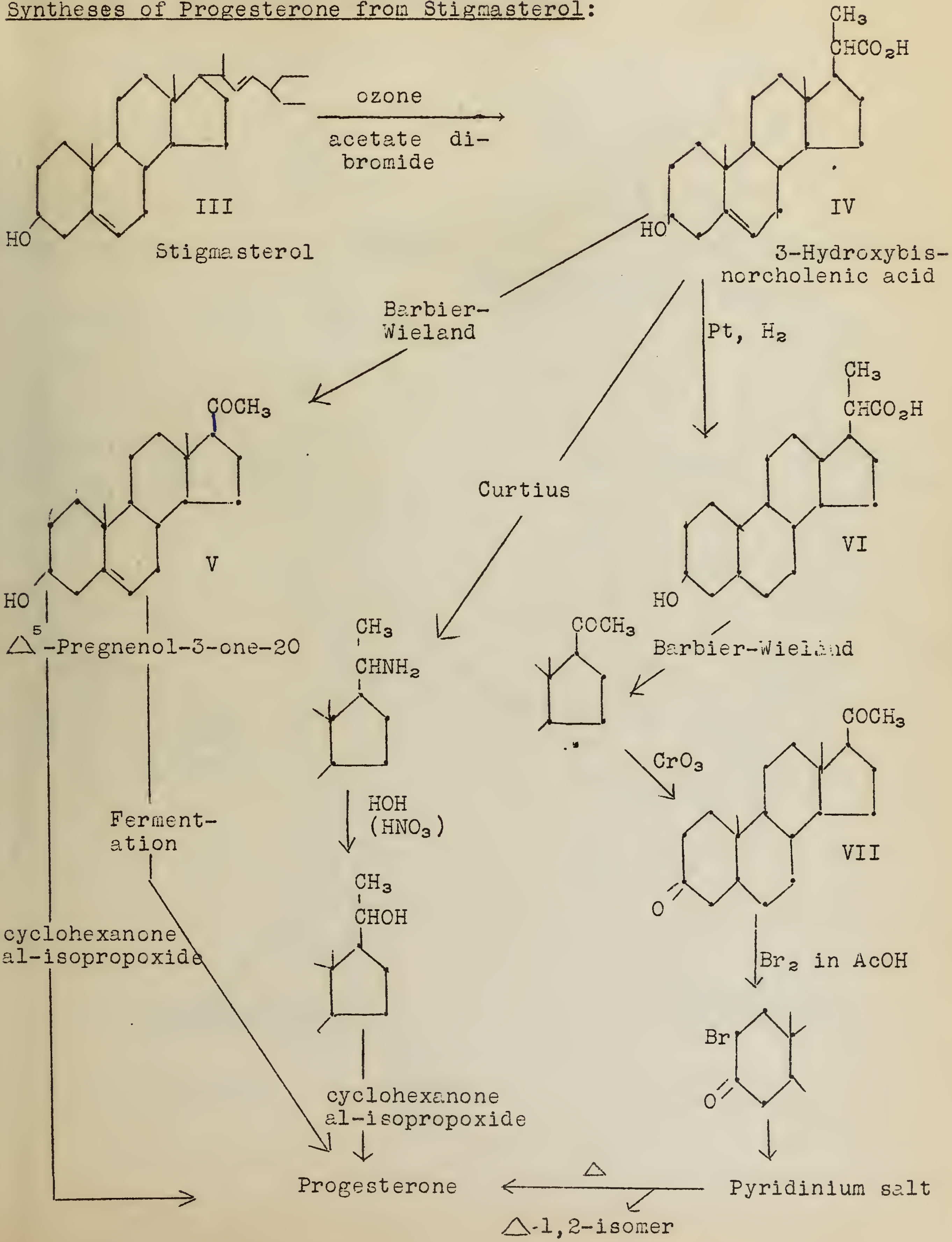
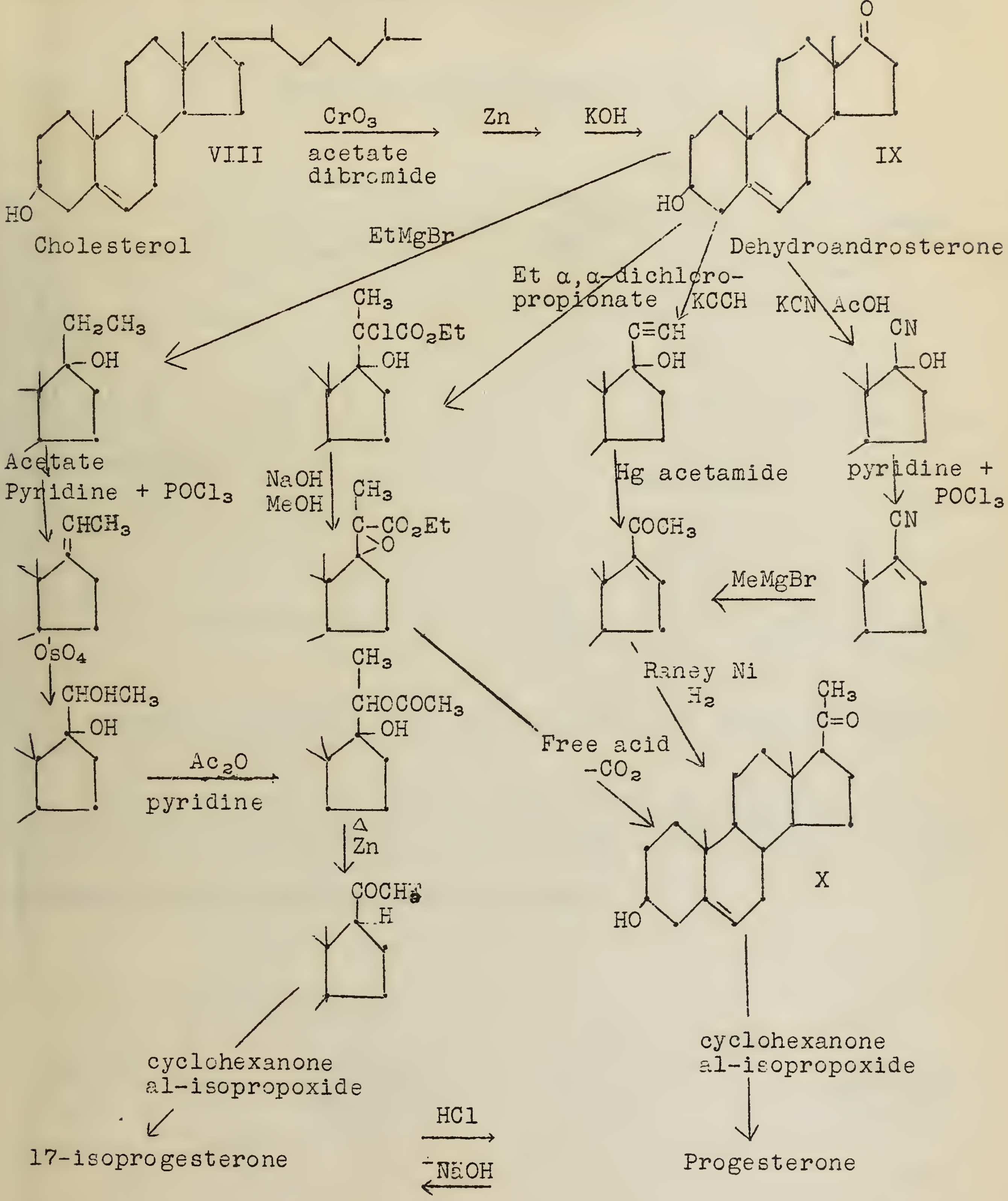
saponins. At attempt has been made to summarize this synthetic work in the following pages.

Syntheses of Progesterone from Stigmasterol:

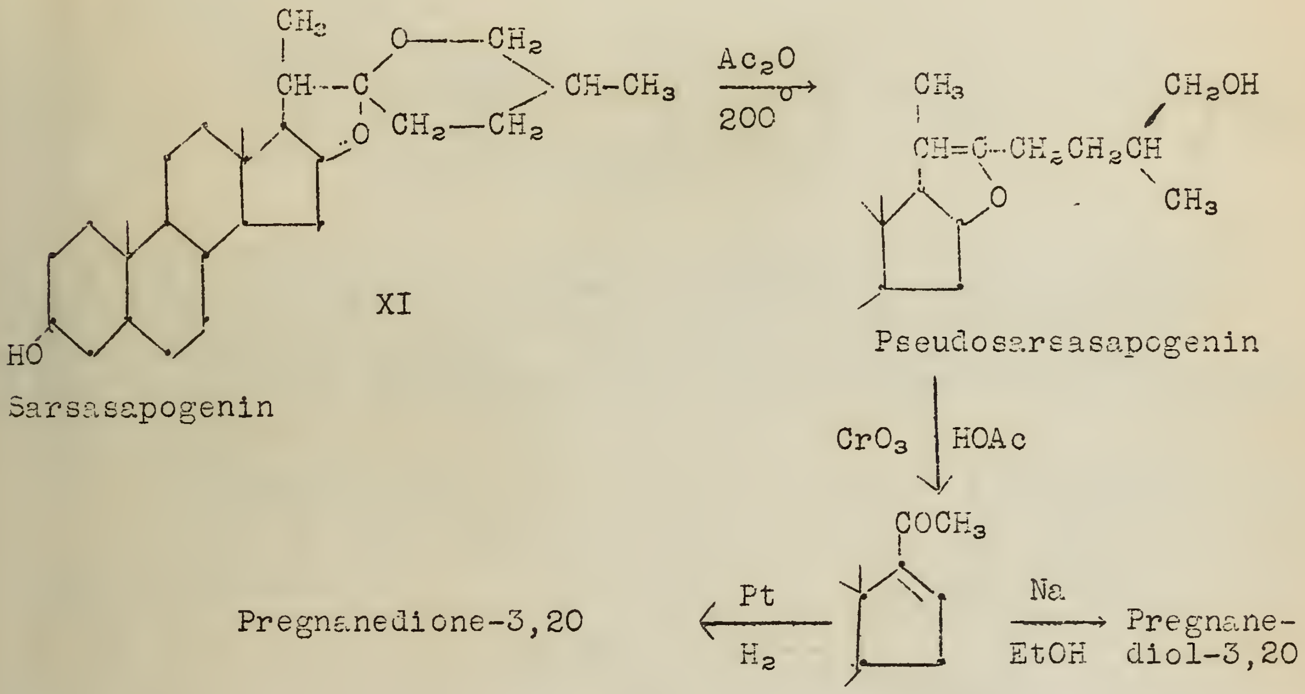


Syntheses of Progesterone from Cholesterol



Spielman and Meyer have developed a method of oxidizing dibromocholesterol directly to progesterone by means of acid permanganate. The yield is 0.2% and the product is not isolated in a pure state, but the concentrates have been found to be satisfactory in biological work.

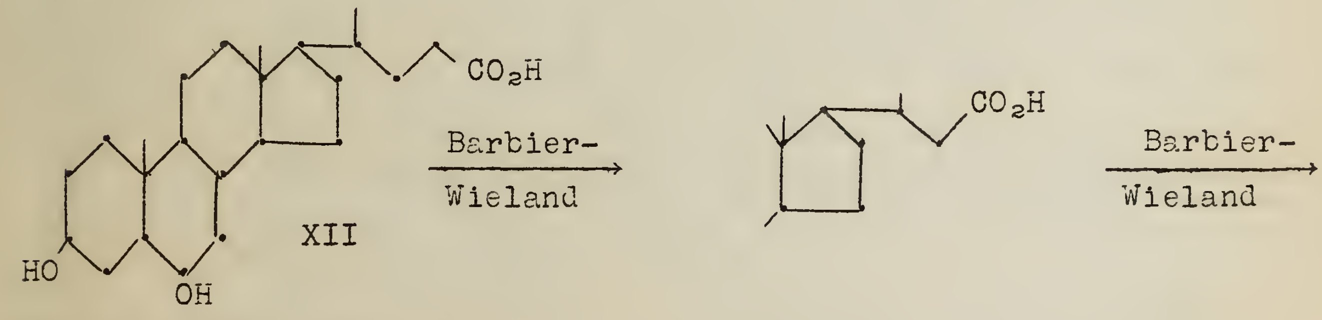
Conversion of Sapogenins to Pregnane Derivatives



Tiogenin (differing from sarsasapogenin in having an allo-H at C_5) can be similarly transformed.

Marker has recently applied this series of reactions to diosgenin, which has a double bond at $C_{5\ 6}$, and obtained progesterone in good yields (See Organic Seminar by E.H. Riddle, April 30, 1941).

Synthesis of Progesterone from Bile Acids



Hyodesoxycholic acid

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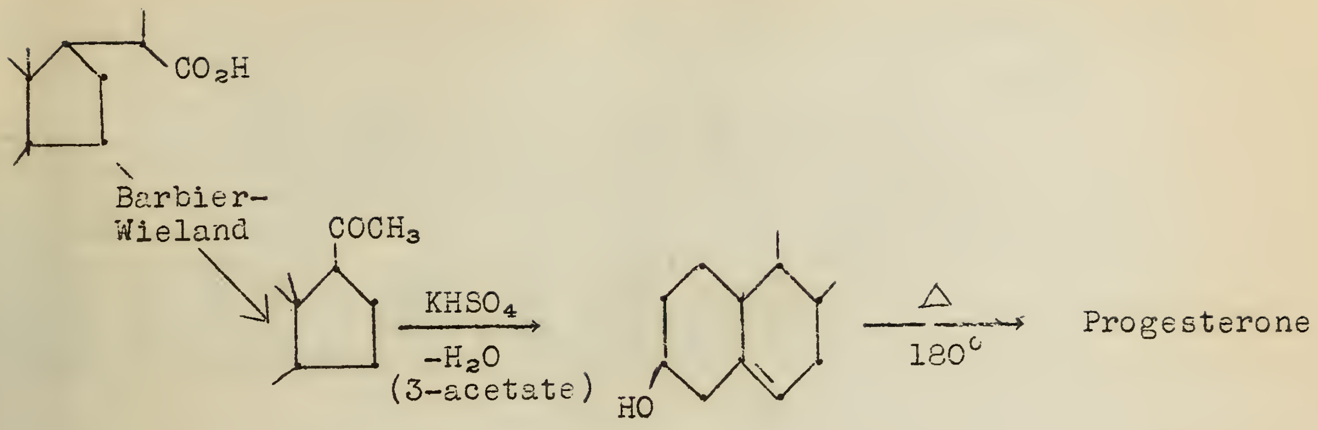
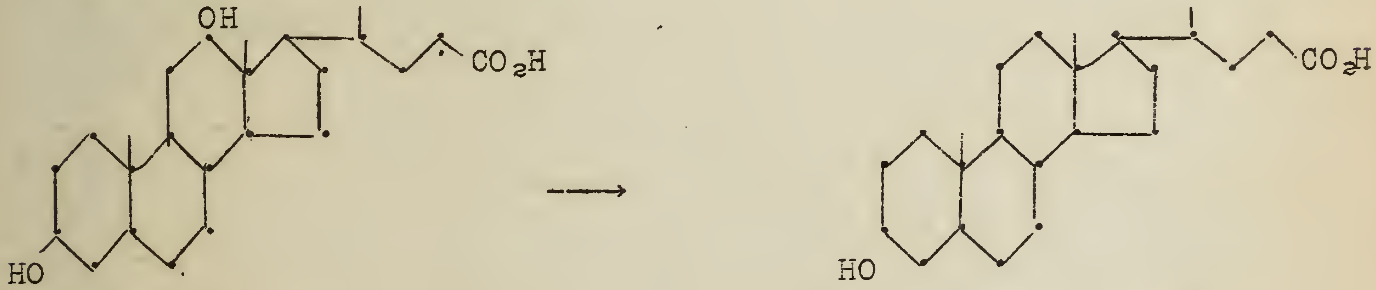


Hoehn and Mason have prepared lithocholic acid from desoxycholic acid (from bile) in 50 per cent yield by preferential esterification of the 3-OH and oxidation of the hydroxyl at position 12 to a keto group. This was then removed by Wolff-Kishner reduction. Lithocholic acid can be converted to progesterone by known steps.



Desoxycholic Acid

Lithocholic Acid

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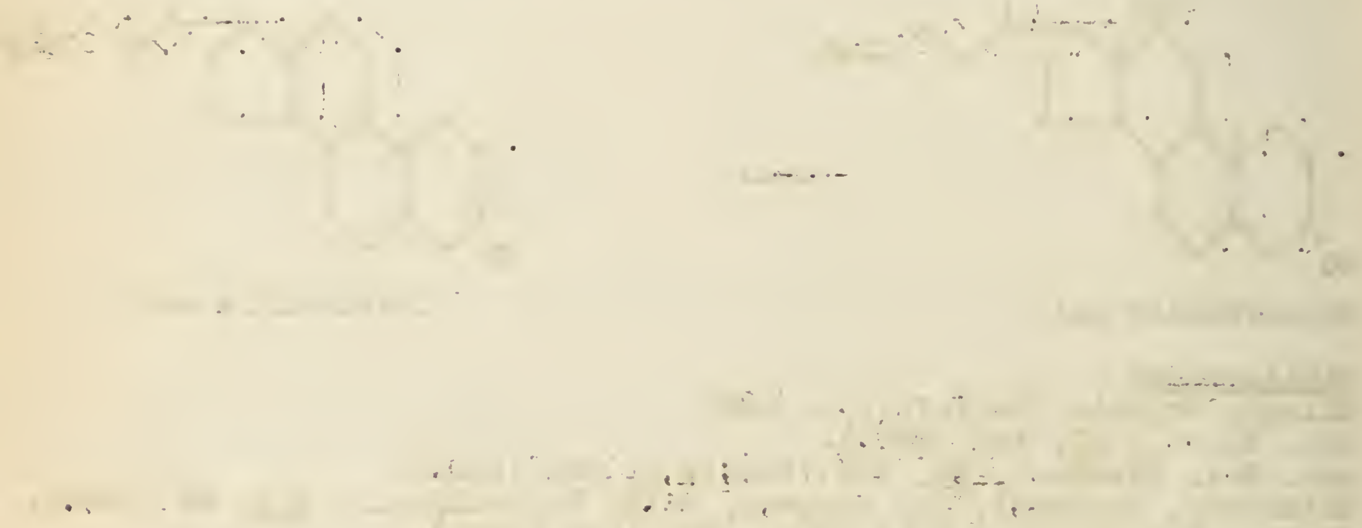

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Reported by Robert L. Frank
October 1, 1941

KOELSCH'S WORK ON CYCLIC DIKETONES

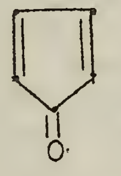
Koelsch's work on diketones derived from cyclopentane may be divided into two parts: (1) Enolizability; (2) Reactivity of the carbonyl groups when adjacent to each other.

A survey of the literature indicated that the following generalities could be made concerning the enolization of polyketocyclopentanes:

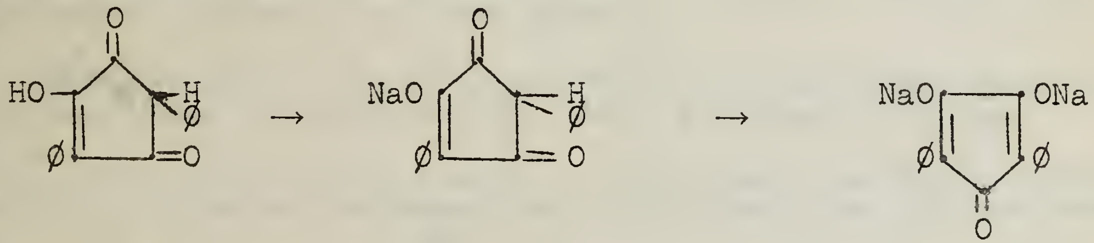
(1) Cyclopentanes containing more than one ketone group and having the ability to enolize twice, exist as mono enols.

(2) If the ketone is a derivative of cyclopentene, enolization is hindered.

Under the influence of reagents which produce enolization such as alkali, the above statements do no hold. Treatment with base, depending upon the amount used, forms a yellow or red sodium salt of the compound if only one double bond is present in the ring, or a purple one if a second double bond is introduced. Necessary conditions for the fulfillment of these effects are the presence of the following chromophonic groupings:

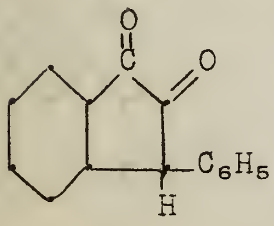


One example of this behavior in the literature is oxalyldibenzylketone.

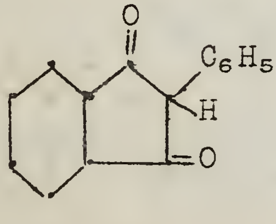


yellow yellow purple

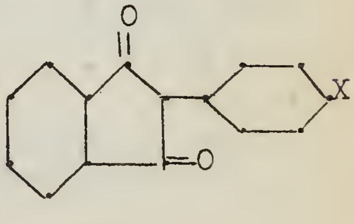
Exceptions to these generalities were the following:



(A)



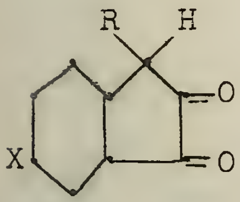
(B)



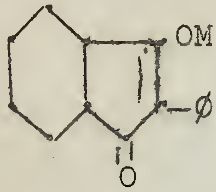
(C)

1,2-Diketo-3-phenylhydrindene(A) is completely enolic while 1,3-diketo-3-phenylhydrindene (B) is predominantly enolic in polar solvents. 1,3-Diketo-p-iodophenylhydrindene (C) gave two crystalline forms, depending upon the solvents used. From acetic acid red violet prisms were obtained, while from non-polar solvents colorless needles were obtained.

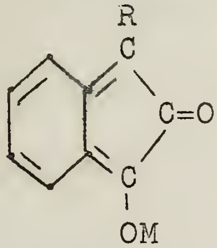
The colors of the salts of the compounds in this series were likewise peculiar. Compounds of type (D) are red and dissolve easily in alkali to give deep blue or green salts. 1,3-Diketo-2-phenylhydrindene (B) dissolves in aqueous alkali to give a deep red sodium salt the structure of which is written as E. von Braun, who worked with compounds of type D primarily on the basis of the difference in color, assigned the ortho-quinoid structure (F) to these compounds. Koelsch, using 1,2-diketo-3-phenylhydrindene as a representative of group D, investigated the enolate structure of this compound. He found that the deep blue alkali salt when methylated with $(CH_3)_2SO_4$ gave a red O-methyl derivative which had an absorption spectra similar to the enol itself and to 2,3-diphenylindone. The compound added one mole of C_6H_5MgBr to give G, since on oxidation O-dibenzoylbenzene was obtained. This behavior indicated that the ortho-quinoid structure was not present.



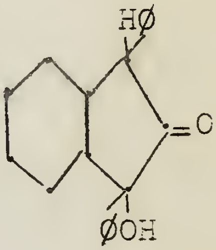
(D)



(E)



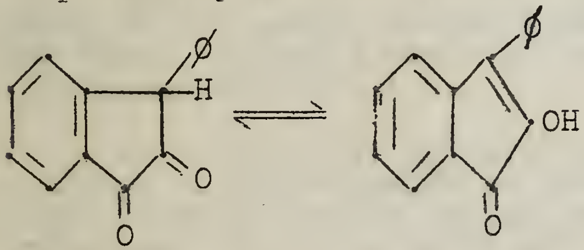
(F)

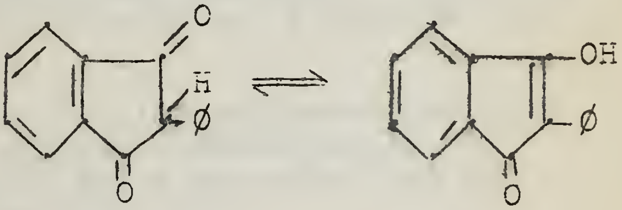


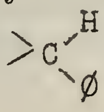
(G)

Turning now to the enolization of the diketones themselves, two explanations are possible for their abnormal behavior.

1. The double bond common to both rings can migrate totally or partially into the benzene ring, depending upon the environment.

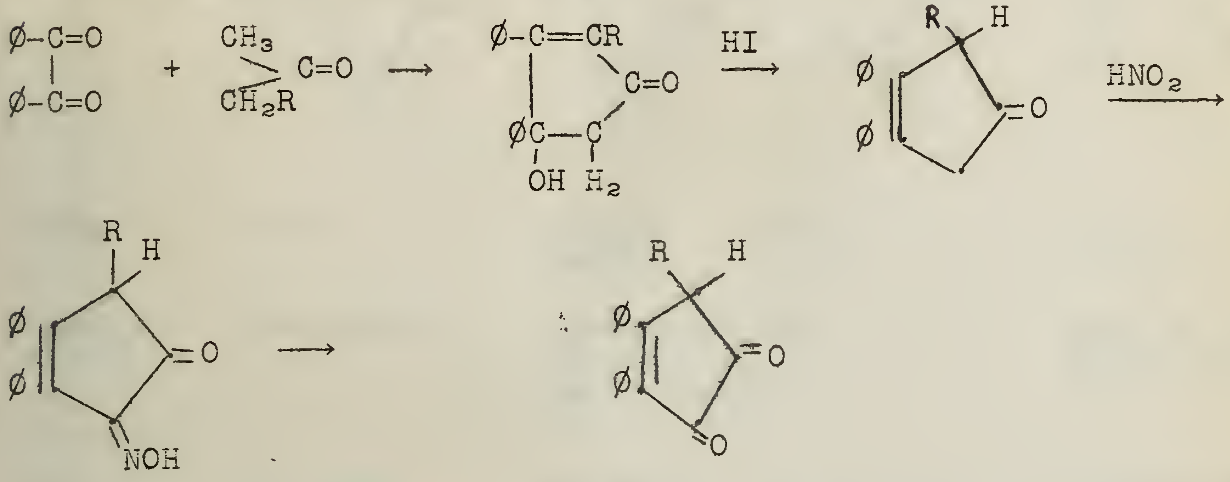


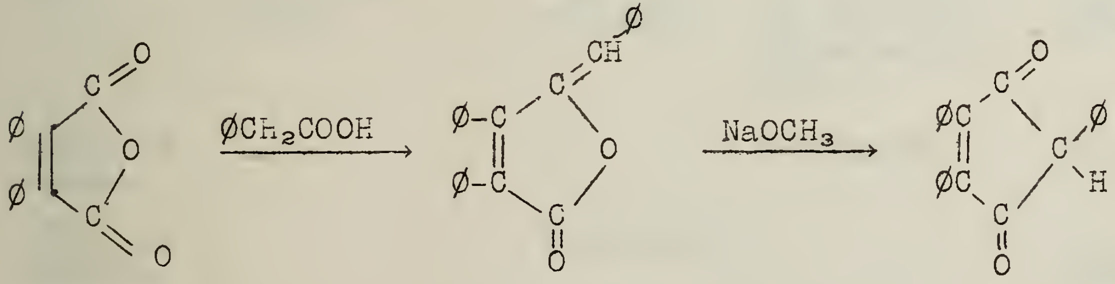


2. Since 1,2-diketohydrindene and 1,3-diketohydrindene are both ketonic, the grouping  $>C\genfrac{}{}{0pt}{}{H}{Ø}$ influences the enolization in such systems.

To distinguish between these two possibilities, 1,2-diketo-3,4,5-triphenylcyclopentene-3, 1,2-diketo-3,4-diphenylcyclopentene-3 and 1,3-diketo-2,4,5-triphenylcyclopentene-4, analogs to the above in which the double bond is fixed, were synthesized and their enolizations compared with corresponding hydrindenes.

Methods of synthesis used were as follows:





A comparison of reactions is given in Table I (page 4).

Results point to a ketonic character for the cyclopentene analogs and, therefore, indicate that the first explanation was the correct one. Reduction products in this series are enolic.

In the second part of the work the purpose was to find out which of the groups in the cyclic α-diketones was more reactive and how this reactivity compared with that of carbonyl groups in an acyclic α-diketone.

Activation of carbonyl groups is usually characterized by a tendency to add alcohols or water. Acyclic α-diketones are apparently not active enough to do this but α-ketoaldehydes and triketones (2,3,4-triketopentane) apparently are.

To study this activation cyclic diketones were chosen which showed no tendency to enolize. A summary of the observations made is given in Table II (page 5).

TABLE I

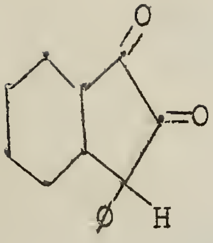
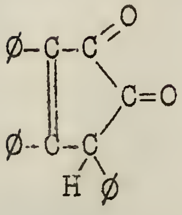
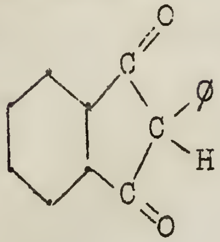
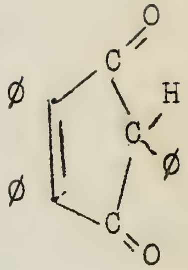
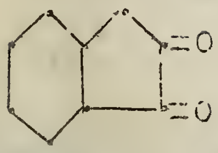
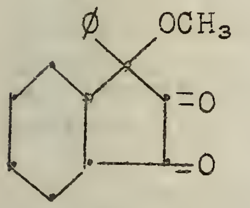
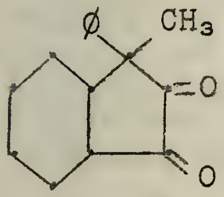
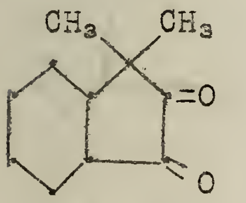
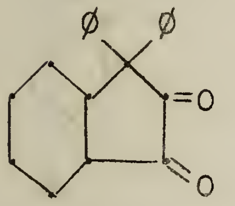
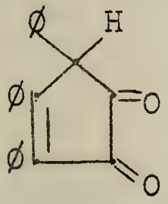
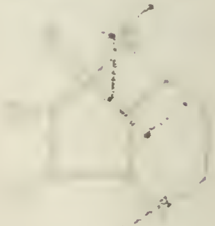
Reagent	Compounds			
				
color	red	orange yellow	white	yellow
color in alkali	blue-green	blue-green in alcoholic alkali	red	blue in alcoholic alkali
Br_2	in cold CCl_4	Reacts in hot HOAc	in cold alcohol but not in ether or $CHCl_3$	Reacts in hot HOAc
ØCOCl in alkali			O-benzoate	C-benzoate
ØCOCl in pyridine		O-benzoate		C-benzoate + O-benzoate
ØMgBr	1 mole addition	2 moles addition	1 mole addition	Reduction

TABLE II

Compound	ROH	1 eq. NH_2OH	1 eq. ØMgBr
	Unstable acetal	carbonyl-2 oximated	
	carbonyl-2-gives acetal		
	carbonyl-2 gives acetal	carbonyl-2 oximated	
	no rx		
	carbonyl-2 gives acetal	carbonyl-2 oximated	carbonyl-1 reacts
	no rx	carbonyl-1 oximated	
	no rx		

[illegible]



From the table one can conclude that in compounds bearing no phenyl group on carbon-3, carbonyl-2 shows more activation than a carbonyl group in acyclic α-diketone. One phenyl group diminishes this activation while two removes it entirely.

One explanation for the greater activity of the 2-carbonyl group is that the double bond conjugated with the 1-carbonyl tends to lessen the polarization of this group. Therefore in the reversible reactions of oxime or hemiacetal formation, any reagent attacking the more exposed 1-carbonyl is eventually given up to the 2-carbonyl. Phenylmagnesium bromide in its addition being irreversible adds to the 1-carbonyl.

The effect of the phenyl groups is to deactivate the 2-carbonyl through electron donation. If the effect were one of steric hindrance alone only the rate of reaction would be diminished.

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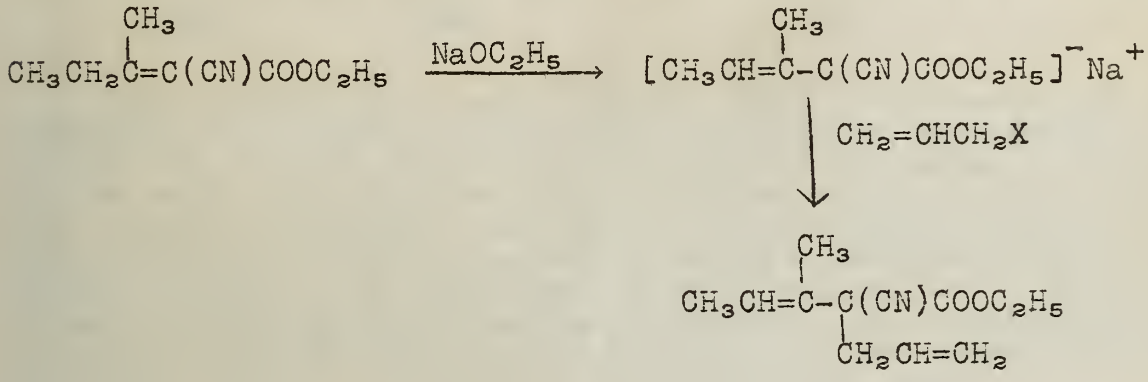
Koelsch and LeClaire, ibid., 6, 516 (1941).
Wawzonek, Thesis, University of Minnesota, 1939.

Reported by S. Wawzonek
October 1, 1941

THE REARRANGEMENT OF ALLYL GROUPS IN THREE-CARBON SYSTEMS

Cope, et al

While carrying out an investigation of the alkylation of cyanoacetic ester, Cope and Hardy found that when the sodium derivative of ethyl (1-methylpropylidene)-cyanoacetate was treated with allyl halides the expected product I was obtained.



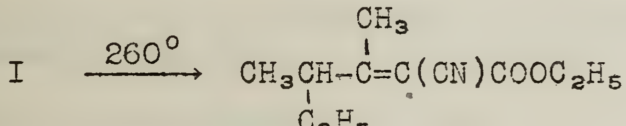
$$CH_3CH_2\overset{CH_3}{\overset{|}{C}}=C(CN)COOC_2H_5 \xrightarrow{NaOC_2H_5} [CH_3CH=\overset{CH_3}{\overset{|}{C}}-C(CN)COOC_2H_5]^-Na^+$$

$$\Big\downarrow\ CH_2=CHCH_2X$$

$$CH_3CH=\overset{CH_3}{\overset{|}{C}}-\underset{CH_2CH=CH_2}{\underset{|}{C}}(CN)COOC_2H_5$$

I

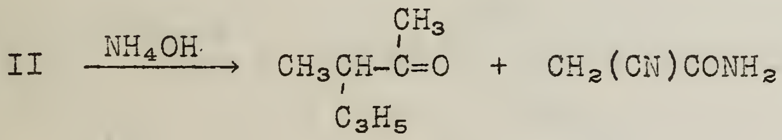
Although the ester I was sufficiently stable to permit purification by means of distillation under reduced pressure, repeated distillations caused isomerization with the formation of a new compound having a higher boiling point and a higher index of refraction. A good yield of the isomer could be obtained by refluxing I at atmospheric pressure. That the isomerization involved a shift of the allyl group from the *alpha*- to the *gamma*-position was shown by establishing the structure of the product as ethyl (1,2-dimethyl-4-pentenylidene)-cyanoacetate (II).



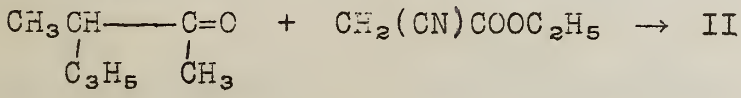
$$I \xrightarrow{260^{\circ}} CH_3\underset{C_3H_5}{\underset{|}{C}}H-\overset{CH_3}{\overset{|}{C}}=C(CN)COOC_2H_5$$

II

The structure of II was established by cleavage with aqueous ammonia to *unsym*-methyl allyl acetone and cyanoacetamide, and verified by synthesis from the same ketone and ethyl cyanoacetate.

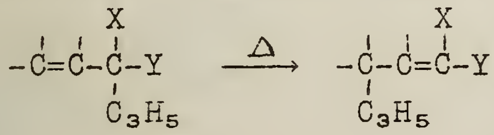


$$II \xrightarrow{NH_4OH} CH_3\underset{C_3H_5}{\underset{|}{C}}H-\overset{CH_3}{\overset{|}{C}}=O \quad + \quad CH_2(CN)CONH_2$$



$$CH_3\underset{C_3H_5}{\underset{|}{CH}}\text{——}\underset{CH_3}{\underset{|}{C}}=O \quad + \quad CH_2(CN)COOC_2H_5 \rightarrow II$$

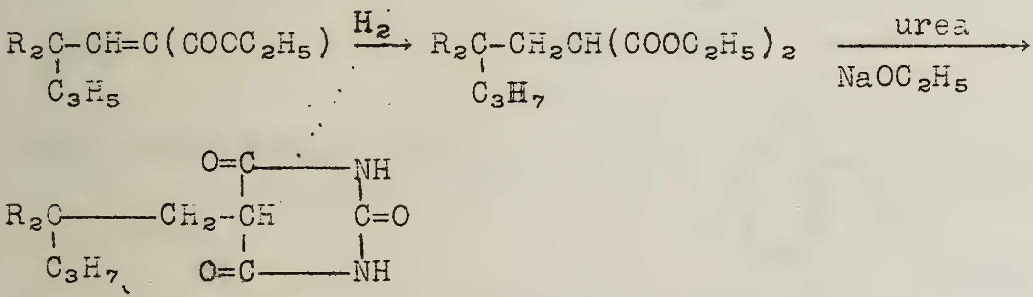
Recently the investigation has been extended to include several additional cyanoacetic esters, as well as malonic esters and malononitriles. All three classes of compounds were found to undergo the rearrangement involving a shift of the allyl group from the α- to the γ-carbon atom with an accompanying shift of the double bond from the β, γ- to the α, β-position.



$$-\overset{|}{C}=\overset{|}{C}-\underset{C_3H_5}{\overset{X}{C}}-Y \xrightarrow{\Delta} -\underset{C_3H_5}{\overset{|}{C}}-\overset{|}{C}=\overset{X}{C}-Y$$

X and Y = CN or $COOC_2H_5$

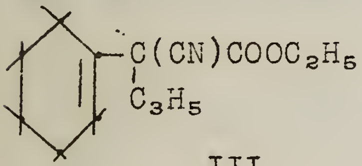
The isomerizations were brought about by refluxing the pure compounds in a partial vacuum, the pressure being regulated to produce the desired boiling temperature of the liquid. Since in all the cases investigated the refractive index of the rearrangement product was higher than that of the starting material, completion of the reaction was evidenced by a constant value after a steady increase. The structure of the products was established either by cleavage with ammonia to ketones, as illustrated for II, or by reduction followed by condensation of the reduced compound with urea to give a derivative of barbituric acid.



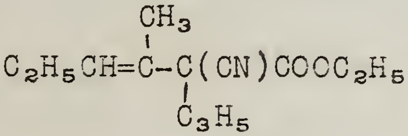
In some instances the structure was verified by means of an independent synthesis.

Cyanoacetic Ester Series

Six cyanoacetic esters, disubstituted by an alkyl vinyl and an allyl group, were rearranged and the products identified by cleavage with ammonium hydroxide.

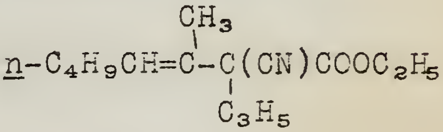


III



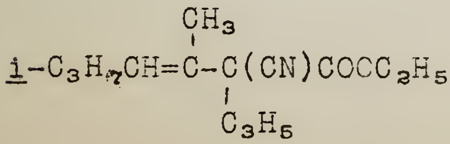
$C_2H_5CH=\overset{CH_3}{C}-\underset{C_3H_5}{C}(CN)COOC_2H_5$

IV



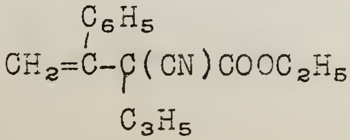
$\underline{n}-C_4H_9CH=\overset{CH_3}{C}-\underset{C_3H_5}{C}(CN)COOC_2H_5$

V



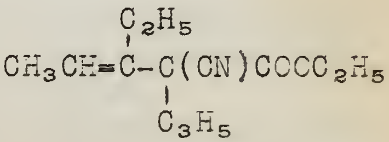
$\underline{i}-C_3H_7CH=\overset{CH_3}{C}-\underset{C_3H_5}{C}(CN)COOC_2H_5$

VI



$CH_2=\overset{C_6H_5}{C}-\underset{C_3H_5}{C}(CN)COOC_2H_5$

VII



$CH_3CH=\overset{C_2H_5}{C}-\underset{C_3H_5}{C}(CN)COOC_2H_5$

VIII

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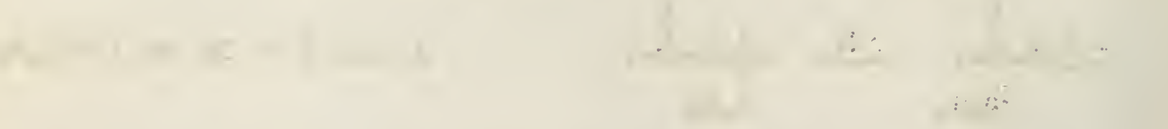

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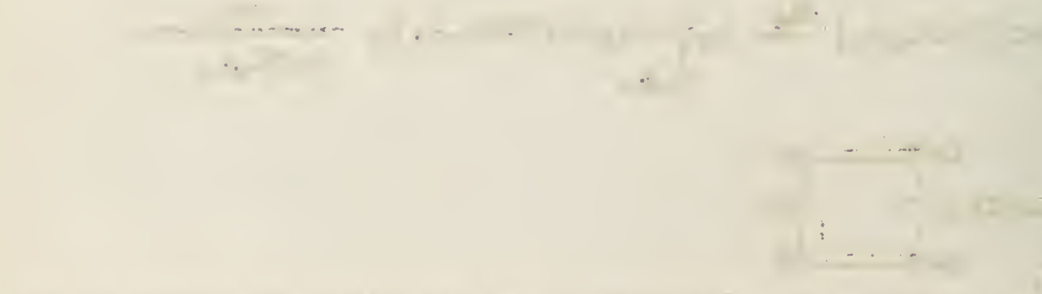

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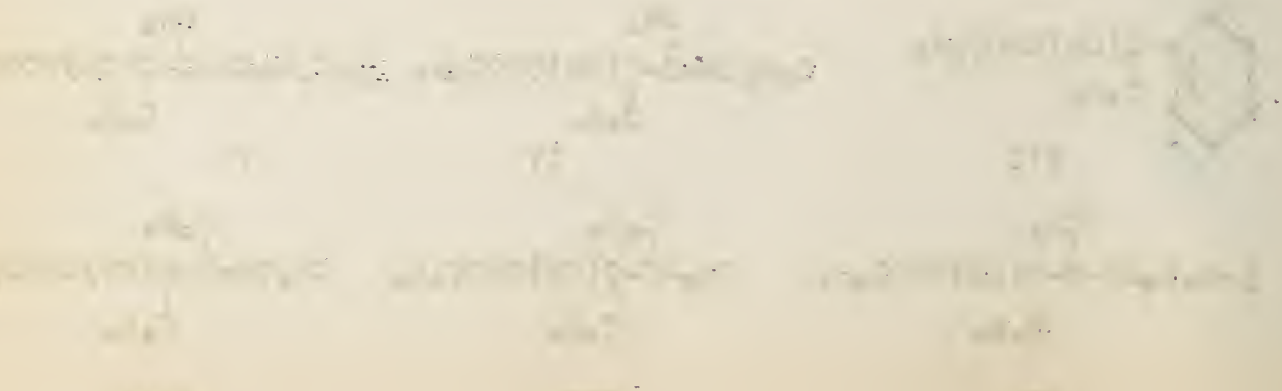
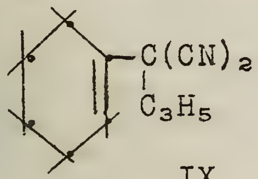
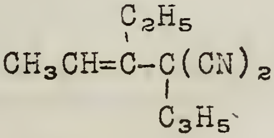


Malononitrile Series

Two representatives of this class, 1-cyclohexenyl-allylmalononitrile (IX) and 1-ethylpropenyl-allylmalononitrile (X) were found to isomerize very readily. The structures of the rearrangement products were established by cleavage with aqueous ammonia



IX

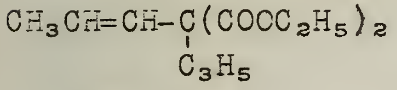


$CH_3CH{=}\overset{C_2H_5}{C}{-}\underset{C_3H_5}{C}(CN)_2$

X

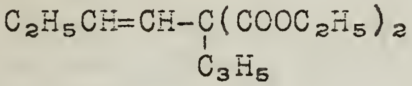
Malonic Ester Series

Of the four disubstituted malonic esters investigated, only two, ethyl propenylallylmalonate (XI) and ethyl (1-butenyl)-allylmalonate (XII), could be rearranged with the formation of pure products. Side reactions occurring during the rearrangement of the higher molecular weight esters (XIII and XIV) produced mixtures of indefinite boiling points.



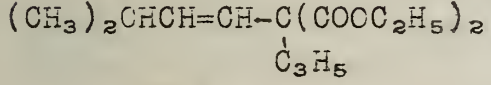
$CH_3CH{=}CH{-}\underset{C_3H_5}{C}(COOC_2H_5)_2$

XI



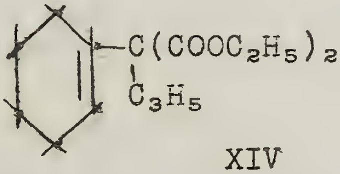
$C_2H_5CH{=}CH{-}\underset{C_3H_5}{C}(COOC_2H_5)_2$

XII



$(CH_3)_2CHCH{=}CH{-}\underset{C_3H_5}{C}(COOC_2H_5)_2$

XIII



XIV

The structures of the isomers produced by the rearrangement of XI and XII were established by reduction followed by condensation with urea. The barbituric acid derivative thus obtained was compared with an authentic sample.

The rates of the rearrangements were studied for the ten compounds above which gave clean reactions. The progress of the reactions was followed by means of the increasing refractive index and rate constants were calculated from the following equations:

$$k_1 = \frac{1}{t_2 - t_1}\ 2.303 \log \frac{1 - x_1}{1 - x_2}$$

x_1 and x_2 = fraction rearranged at times t_1 and t_2

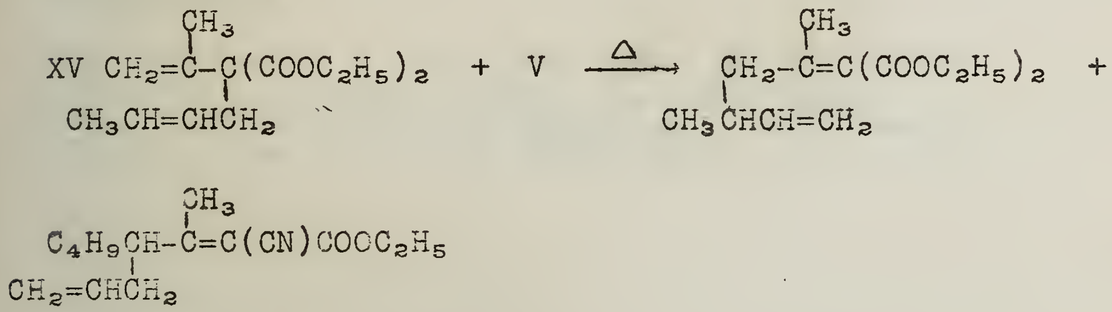
per cent rearranged at time t =

$$\frac{n_t - n_i}{n_t - n_i} \times 100$$

n_i = refractive index of starting material

n_t = refractive index of product.

Good first order rate constants were obtained in all cases except the malonic ester XII, the rearrangement of which was accompanied by side reactions affecting the refractive index. Correspondence of the rates to first order kinetics was interpreted as strong evidence that the rearrangement is intra- rather than inter-molecular. This view received support when it was found that there was no interchange of groups when mixtures were rearranged. For example, rearrangement of a mixture of ethyl isopropenyl crotylmalonate (XV) and ethyl (1-methyl 1-hexenyl)-allylcyanoacetate (V) yielded no crotylcyanoacetate or allylmalonate derivatives.



$$\text{XV}\ \underset{CH_3CH=CHCH_2}{CH_2=\overset{CH_3}{C}-C}(COOC_2H_5)_2 + V \xrightarrow{\Delta} \underset{CH_3CHCH=CH_2}{CH_2}-\overset{CH_3}{C}=C(COOC_2H_5)_2 +$$

$$\underset{CH_2=CHCH_2}{C_4H_9CH}-\overset{CH_3}{C}=C(CN)COOC_2H_5$$

A great difference in ease of isomerization of the three classes of compounds was found. The most striking difference in rate exists between the malononitriles, which rearrange much faster than the cyanoacetic esters, which in turn isomerize faster than the malonic esters.

In order to determine whether the allyl group undergoes inversion during the rearrangement, the crotyl derivatives XV and XVI were isomerized.

$$\underset{CH_3CH=CHCH_2}{CH_3CH=\overset{CH_3}{C}-C}(CN)COOC_2H_5 \xrightarrow{180^\circ} \underset{CH_3CHCH=CH_2}{CH_3CH}-\overset{CH_3}{C}=C(CN)COOC_2H_5$$

XVI

In both cases, the only product was the one resulting from an inversion of the crotyl group.

The authors conclude that the rearrangement of allyl groups in acyclic or alicyclic three-carbon systems is a general reaction when the α-carbon atom is attached to two nitrile or carbethoxyl groups, or to one of each of these groups. The isomerization is similar in type to the Claisen rearrangement of allyl ethers of phenols and enols in which the allyl group shifts from the electron attracting oxygen atom to a carbon atom.

$$-\overset{|}{C}=\overset{|}{C}-O-C_3H_5 \longrightarrow C_3H_5-\overset{|}{C}-\overset{|}{C}=O$$

In the isomerization involving a three-carbon system, the allyl group becomes detached from the α-carbon atom, electron attracting because of the two negative groups attached to it, and recombines

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$$[illegible]$$

$$[illegible]$$

[illegible]

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$$[illegible]$$

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$$[illegible]$$

[illegible]

with the γ-carbon atom which is less electron attracting. It is generally accepted that one motivating force responsible for the Claisen rearrangement is the unequal sharing of the electron pair binding the allyl group to the α-atom. The fact that the nitrile group is more electron attracting than the carbethoxyl group offers a ready explanation for the greater ease with which a malononitrile isomerizes as compared with the cyanoacetic and malonic esters.

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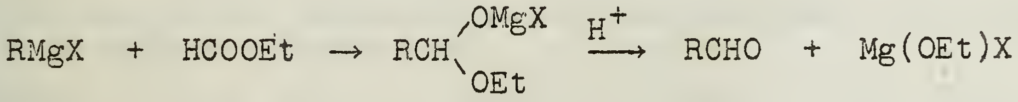
Reported by Clay Weaver
October 8, 1941

SYNTHESES OF ALDEHYDES THROUGH GRIGNARD REAGENTS

Formic Esters

The first preparation of aldehydes by means of Grignard reagents was reported by Gattermann and Maffezzoli, who treated various Grignard reagents with a three-molar excess of ethyl formate at -50°C. Aldehydes were formed in yields varying between ten and fifty per cent.



$$RMgX + HCOOEt \rightarrow RCH\begin{matrix} OMgX \\ OEt \end{matrix} \xrightarrow{H^+} RCHO + Mg(OEt)X$$

Other esters of formic acid, namely methyl and amyl formates, have also been used in this reaction. At the low temperature prevailing throughout, secondary alcohol formation was minimized.

Ethyl Orthoformate

That Grignard reagents could be caused to react with ethyl orthoformate to yield aldehyde acetals was simultaneously recorded by Tschitschibabin and by Bodroux.

$$RMgX + HC(OEt)_3 \rightarrow RCH(OEt)_2 + Mg(OEt)X$$

Tschitschibabin added the orthoformate to an ether solution of the Grignard reagent, refluxed, and then evaporated most of the ether. After most of the ether had been removed, a very vigorous reaction occurred and considerable heat was evolved. The pasty reaction mixture was acidified and the acetal isolated by distillation. The yields ranged between fifteen and eighty per cent.

Tschitschibabin and his coworkers were able to show that large excesses of Grignard reagent and increasingly strenuous conditions resulted in two, or even three, of the ortho ester ethoxyl groups being replaced by the organic portion of the Grignard reagent.

In general, it has been shown, aliphatic and arylaliphatic Grignard reagents give better yields of aldehydes than do the aromatic compounds.

Formic Acid

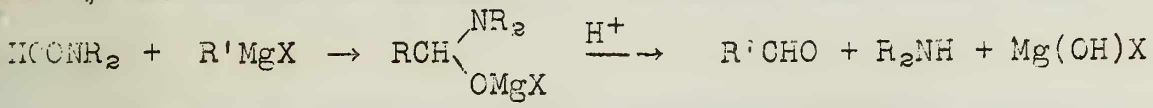
Zelinsky found that aldehydes were formed when Grignard reagents were treated with formic acid.

$$HCOOH + RMgX \rightarrow HCR(OMgX)_2 \xrightarrow{H^+} RCHO + Mg(OH)X$$

Houben investigated this reaction and reported that the yields were never greater than thirty per cent. Use of copper and other salts of formic acid in place of the acid itself failed to improve the reaction.

Disubstituted Formamides

Bouveault showed that disubstituted formamides reacted with Grignard reagents to give products which formed aldehydes on hydrolysis.



$$HCONR_2 + R'MgX \rightarrow RCH\begin{matrix}NR_2\\OMgX\end{matrix} \xrightarrow{H^+} R'CHO + R_2NH + Mg(OH)X$$

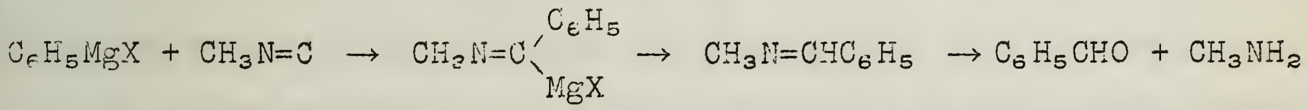
He reported no yields, although he pointed out that a secondary reaction is prominent in some cases.

$$HCON(CH_3)_2 + 2C_5H_{11}MgCl \rightarrow HC(C_5H_{11})_2N(CH_3)_2 + MgO + MgCl_2$$

A number of Grignard reagents were used, and a variety of secondary amines was studied. In addition to the simultaneous reactions indicated above, other side reactions occurred in special cases, and the reaction was generally undependable. Yields of aldehyde ranged from twenty to fifty per cent. In all cases twenty to forty per cent of the substituted amide was recovered unchanged.

Isocyanides

Sachs and Loevy reported that benzaldehyde was formed when phenylmagnesium bromide was treated with methyl isocyanide.



$$C_6H_5MgX + CH_3N{=}C \rightarrow CH_3N{=}C\begin{matrix}C_6H_5\\MgX\end{matrix} \rightarrow CH_3N{=}CHC_6H_5 \rightarrow C_6H_5CHO + CH_3NH_2$$

Gilman and Heckert later investigated this reaction and discovered that the particular case studied by Sachs and Loevy was the only one of the general type which could be made to occur. Even this reaction produced benzaldehyde in negligibly small yield.

Ethoxymethylene Aniline

Monier-Williams showed that aldehydes are produced when Grignard reagents are treated with ethoxymethylene aniline.

$$RMgX + C_6H_5N{=}CHOEt \rightarrow EtOMgX + RCH{=}NC_6H_5 \rightarrow RCHO + C_6H_5NH_2$$

He reported yields of thirty to sixty per cent.

Carbodithio Acids

Wuyts prepared aldehydes from Grignard reagents by means of a series of reactions, with the carbodithio acid as the predominant intermediate.

$$RMgX \xrightarrow{CS_2} RCSSH$$

$$RCSSH + H_2NCONHNH_2 \longrightarrow RCSNHCONHNH_2 + H_2S$$

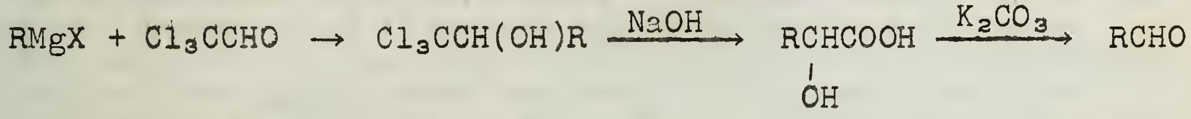
$$RCSNHCONHNH_2 \longrightarrow RCH{=}NCONHNH_2 + S$$

$$RC{=}NCONHNH_2 \longrightarrow RCHO$$

Wuyts and his coworkers found that semicarbazide was superior to other well-known nitrogenous aldehyde-ketone reagents in this reaction. Side reactions are prominent, however, in this preparation. Most troublesome of these is nitrile formation. Aromatic aldehydes are formed in better yield than aliphatic aldehydes, since reactions leading to the latter frequently stop after the second step.

Chloral

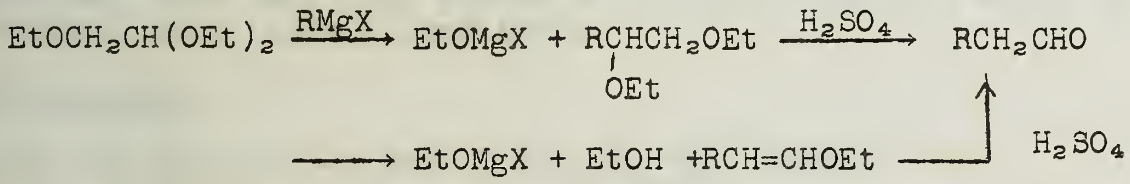
Savariau reported yields of aldehydes of about fifty per cent from the reaction of Grignard reagents with chloral



$$\mathrm{RMgX + Cl_3CCHO \rightarrow Cl_3CCH(OH)R \xrightarrow{NaOH} R\underset{OH}{C}HCOOH \xrightarrow{K_2CO_3} RCHO}$$

Aldehyde Syntheses in which the Group -MgX is replaced by a Formyl Homologue

Spath prepared substituted acetaldehydes by means of the reaction between Grignard reagents and ethoxyacetal.



$$\begin{tikzcd}
\mathrm{EtOCH_2CH(OEt)_2} \arrow[r, "\mathrm{RMgX}"] \arrow[dr] & \mathrm{EtOMgX + R\underset{OEt}{C}HCH_2OEt} \arrow[r, "\mathrm{H_2SO_4}"] & \mathrm{RCH_2CHO} \\
 & \mathrm{EtOMgX + EtOH + RCH{=}CHOEt} \arrow[ur, "\mathrm{H_2SO_4}"'] &
\end{tikzcd}$$

It was demonstrated that aldehyde was formed from both intermediates.

A clever preparation of substituted acetaldehydes from Grignard reagents was devised by Herschberg, who coupled Grignard reagents with allyl bromide.

$$\begin{tikzcd}
\mathrm{RMgX + BrCH_2CHCH_2} \arrow[r] & \mathrm{MgXBr + RCH_2CH{=}CH_2} \arrow[r] & \mathrm{Dibromide} \arrow[d] \\
\mathrm{RCH_2CHO} & \mathrm{Glycol} \arrow[l] & \mathrm{Diacetate} \arrow[l]
\end{tikzcd}$$

Either ethoxyacetic ester or its phenoxy analogue was used as a starting material for a Grignard synthesis of disubstituted acetaldehydes by Behal and Sommelet.

$$\mathrm{ROCH_2COOEt + R'MgX \rightarrow ROCH_2C(OH)R_2' \rightarrow R_2'C{=}CHOR \rightarrow R_2'CHCHO}$$

$$\mathrm{EtOCH_2COR + R'MgX \rightarrow RR'C(OH)CH_2OEt \dashrightarrow RR'CHCHO}$$

Comparative Studies by Smith and Nichols

Of the Grignard reactions leading to aldehydes in which the -MgX group is replaced by the formyl group, Smith and Nichols selected those involving ethyl orthoformate, ethoxymethylene aniline, and carbodithio acids as the ones showing the greatest promise. Grignard reagents were prepared from a series of bromomethyl- and bromopolymethylbenzenes which ranged from *o*- and *p*-bromotoluene to bromopentamethylbenzene and compared the yields of aldehydes obtained when each Grignard reagent was converted to the corresponding

aldehyde by each of the three different methods. Best of the three methods proved to be that involving ethoxymethylene aniline, by means of which the aldehydes were produced in yields of sixty to eighty per cent. The yields obtained in this synthesis were four to seventeen per cent better than those obtained by means of ethyl orthoformate, which ranged between forty-five per cent and seventy-five per cent. Only the Grignard reagent from o-bromotoluene produced a respectable yield of aldehyde by means of the carbodithio acid synthesis, o-tolualdehyde being formed in sixty per cent yield. In all other cases the reaction was useless as a preparative method.

An outgrowth of this work which is worthy of mention is the study of the formation of bisulfite addition products of these hindered aldehydes. It has long been recognized that benzaldehydes having at least one *ortho* group unsubstituted formed bisulfite addition products rapidly and in good yield. Smith and Nichols were able to show that aldehydes having both *ortho* positions occupied by hindering groups but its *para* position unsubstituted formed bisulfite addition products in excellent yield, although slowly. If, however, both *ortho* positions and the *para* position were substituted, only very poor yields of bisulfite product could be obtained, even after a long time.

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All previous references are cited in the above two papers

Reported by R. B. Carlin
October 8, 1941

SYNTHETIC ESTROGENIC COMPOUNDS

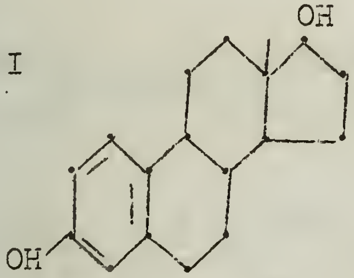
Dodds, Lawson, et al, Courtauld Institute of
Biochemistry, London

Robinson, et al, Oxford University

Estrone and estradiol, the female sex hormones secreted by the Graafian follicle, possess the physiological function of preparing the vagina and uterus for fertilization.

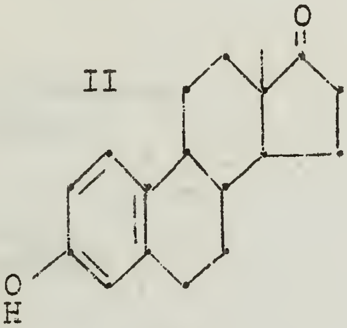
These hormones are very expensive because (1) they do not occur naturally in great quantities, (2) they cannot be prepared cheaply from related natural compounds such as cholesterol, stigmasterol, or equilenin, and (3) great difficulty has been encountered in synthesizing them from cheap starting materials. Consequently, much work has been done in recent years to synthesize more accessible compounds which would possess estrogenic activity.

I



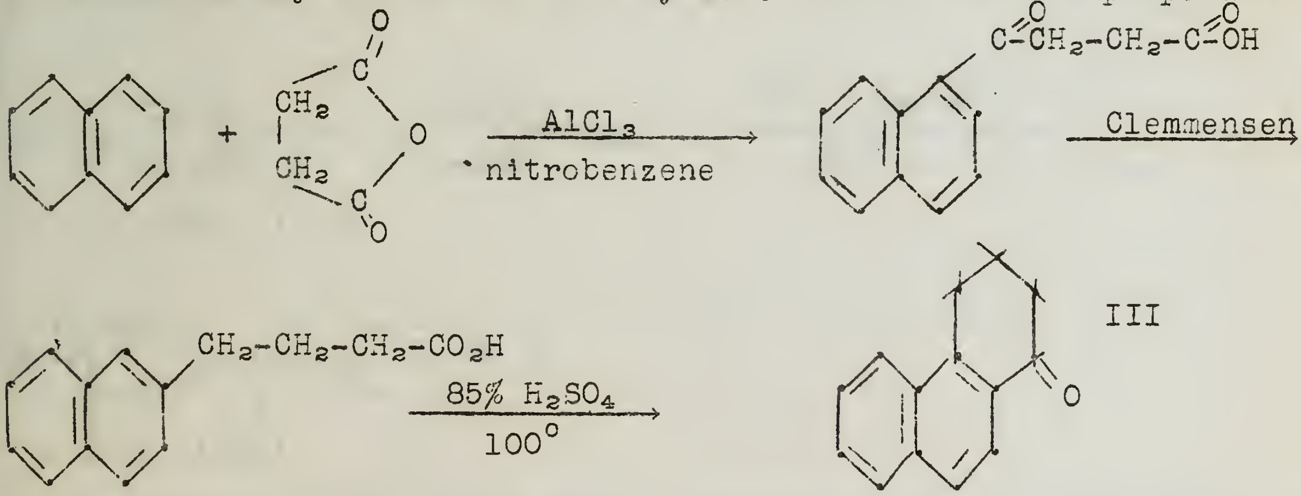
Estradiol

II



Estrone

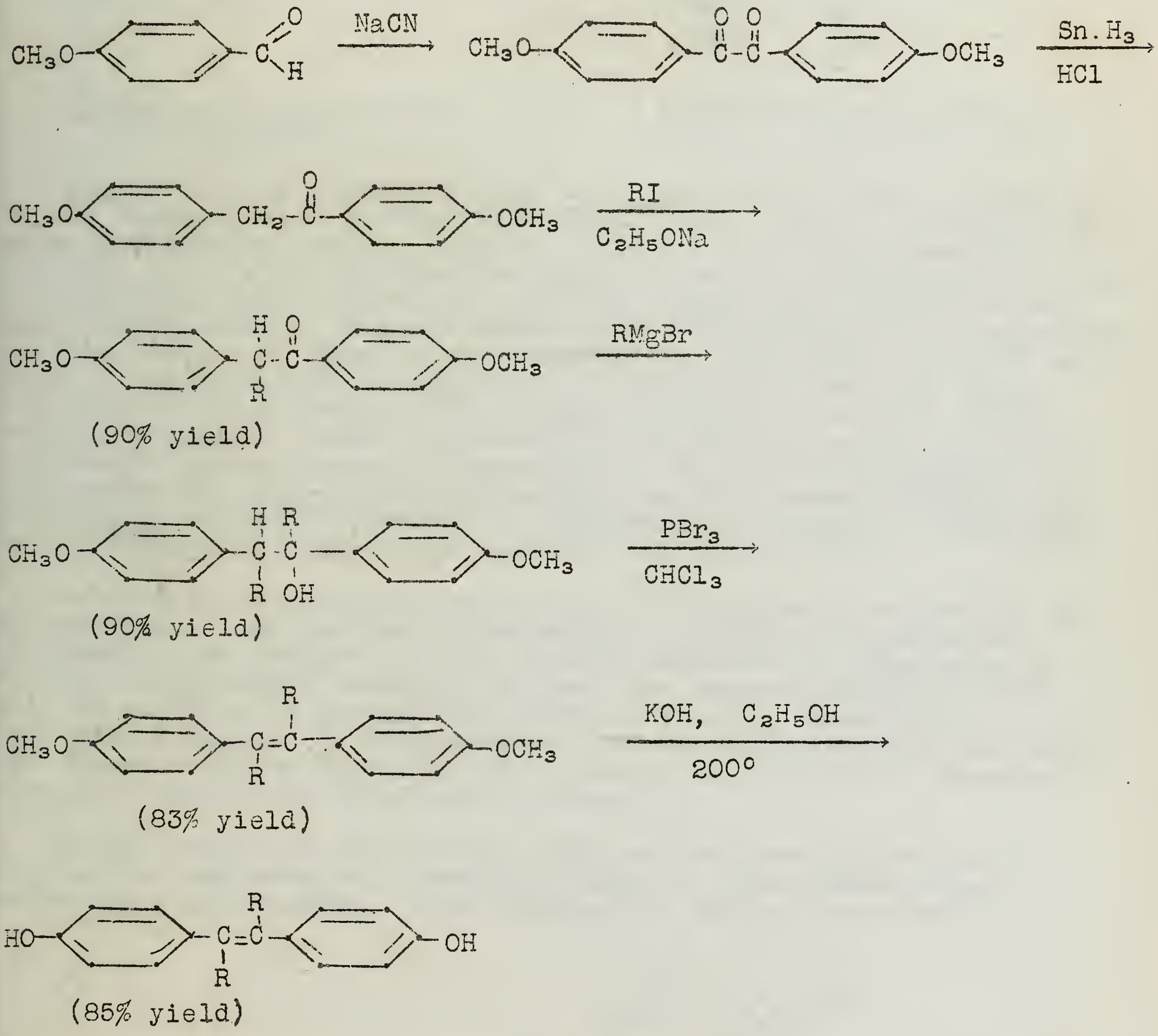
Dodds and Lawson in 1934 started a study to determine the molecular structure essential for a compound to exhibit estroegnic activity. It was found that a cyclo-pentano-phenanthrene structure was not essential when they discovered that 1-keto-1:2:3:4-tetrahydrophenanthrene (III) displayed marked estrogenic activity. They synthesized this by the method used by R.D. Haworth for its preparation:



They next found that a compound need not contain a phenanthrene-type structure in order to be estrogenically active. As an example,

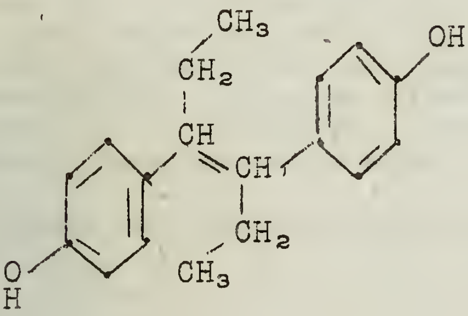
diphenyl-α-naphthyl-carbinol was moderately active. However, the corresponding β-naphthyl-carbinol was not effective. Of much greater importance was the fact that while 4:4'-dihydroxybiphenyl was moderately active, 4:4'-dihydroxystilbene displayed a much greater activity.

On observing these facts, Robinson noted that both hydroxyl groups might well be phenolic, although only one is phenolic in estradiol, and that a stilbene type of compound seemed to have an enhanced activity. Consequently, he synthesized a series of C-alkylated derivatives of 4:4'-dihydroxystilbene by the following method which used anisole as the starting material:

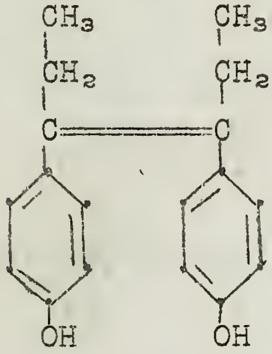


Biological tests showed that a remarkable peak in estrogenic activity was found when R=Ethyl, and that this compound is two to

three times as active as estrone itself. The reason for this activity probably is that it is closely related stereochemically to estradiol:



Trans-Diethylstilbestrol
"Stilbestrol"



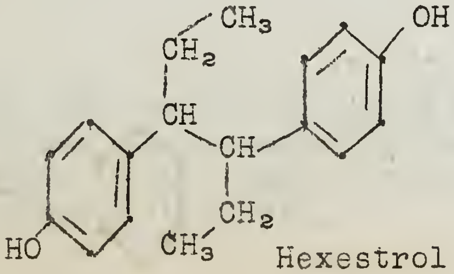
cis-Diethylstilbestrol

One difficulty connected with this synthesis is that in addition to the highly active diethylstilbestrol (m.p., 171°), a less active geometrical isomer (m.p., 141°) is obtained. By stereochemical analogy, it is apparent that the trans-isomer is more closely related to estradiol, and, therefore, that the trans-isomer should be the more active isomer. Wessely showed that this is true by hydrogenating the two isomers of dimethylstilbestrol, the structures of which are known. Hydrogenation of cis-dimethylstilbestrol gives the meso-compound, while hydrogenation of trans-dimethylstilbestrol gives a racemic compound. Since hydrogenation of the more active diethylstilbestrol gives a racemic compound, it must have the trans-configuration. Cis-diethylstilbestrol can be converted completely into trans-diethylstilbestrol by exposure to sunlight, so that none of the less active cis-isomer need be obtained.

Another difficulty connected with this synthesis is that in the dehydration of the carbinol intermediate by means of phosphorus tribromide, the dehydration can give an unsaturated side-chain as well as the stilbene compound, so that two racemic mixtures could result in addition to diethylstilbestrol. Wessely showed that this really happens by isolating the two racemic mixtures. He found that these could be converted into diethyl stilbestrol by warming them in a chloroform solution of iodine.

In the course of their work, Dodds and Robinson hydrogenated stilbestrol and obtained a compound which is even slightly more active than stilbestrol. This compound is called "hexestrol."

Diethyl stilbestrol $\xrightarrow{H_2}$

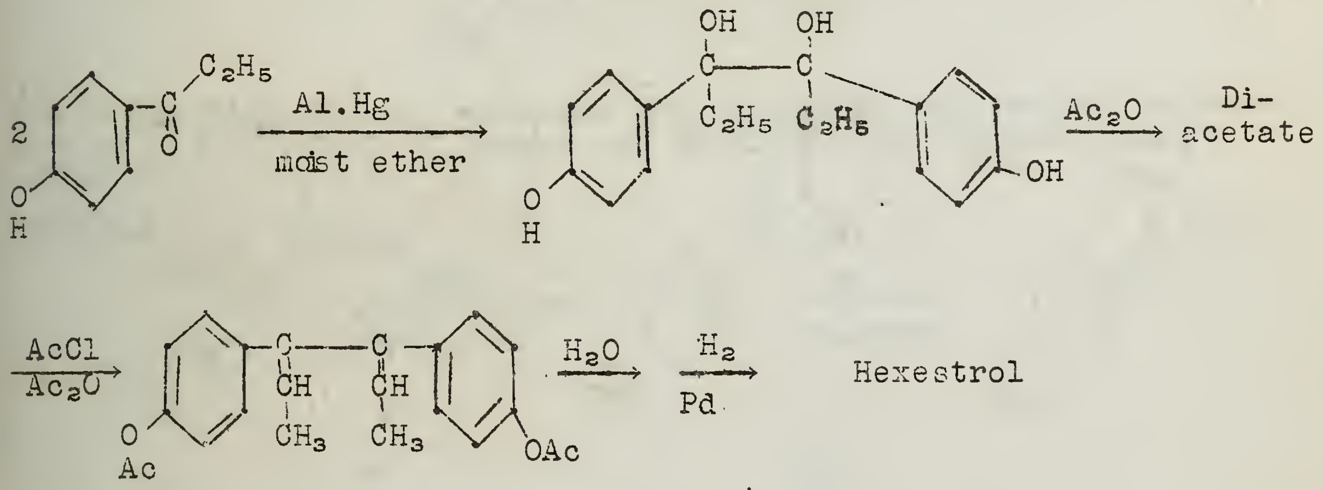


IV

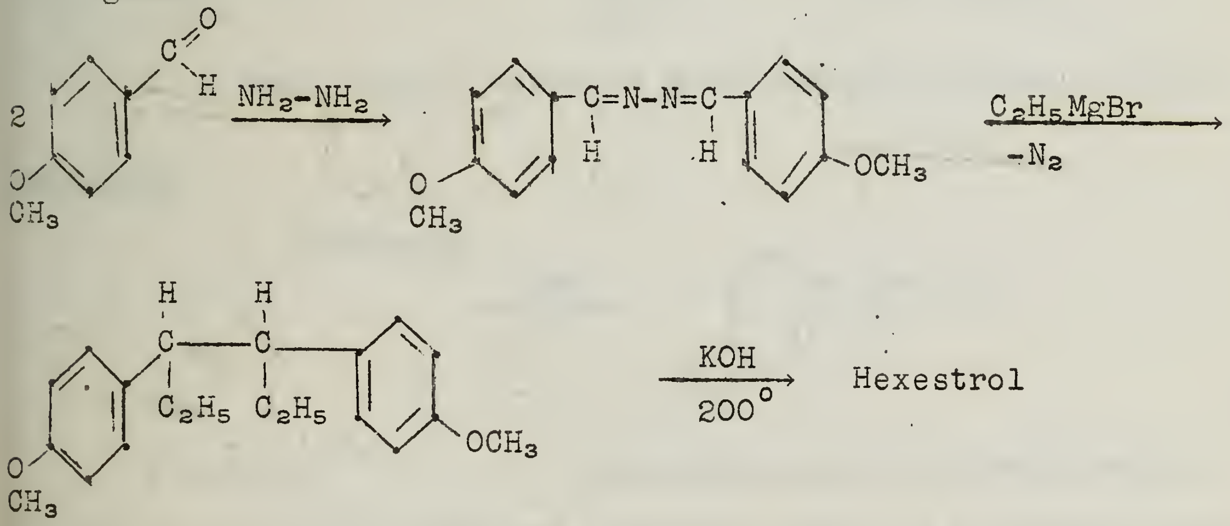
Hexestrol

cis-Stilbestrol on hydrogenation in the presence of platinum oxide yields a compound melting at 184°, while the *trans*-isomer on hydrogenation in the presence of a palladium catalyst yields a compound melting at 128°. The estrogenic activity of the lower-melting form is much less than that of the higher-melting form. As shown by Figure IV, the compound analagous stereochemically to estradiol is the meso compound, so it was postulated that the active, higher-melting compound was the meso compound, and that the less active, lower-melting form was a racemic mixture. Wessely has shown this to be true by resolving the lower-melting product by means of its α-bromo-π-camphor-sulfonate.

Dodds and Robinson also prepared hexestrol by the following method:



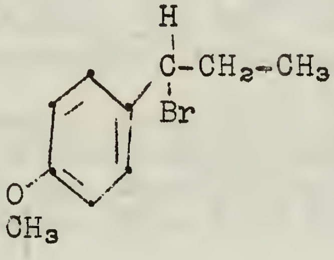
Still another method of preparation of hexestrol is that developed simultaneously by Dodds and by Bretschneider whereby ethyl magnesium bromide is added to anisaldazine with simultaneous loss of nitrogen:



It was possible to isolate both the racemic dimethoxyhexestrol and the *meso*-dimethoxyhexestrol, and it was found that the racemic mixture could be converted into the highly active *meso*-compound by heating in the presence of a palladium-charcoal catalyst.

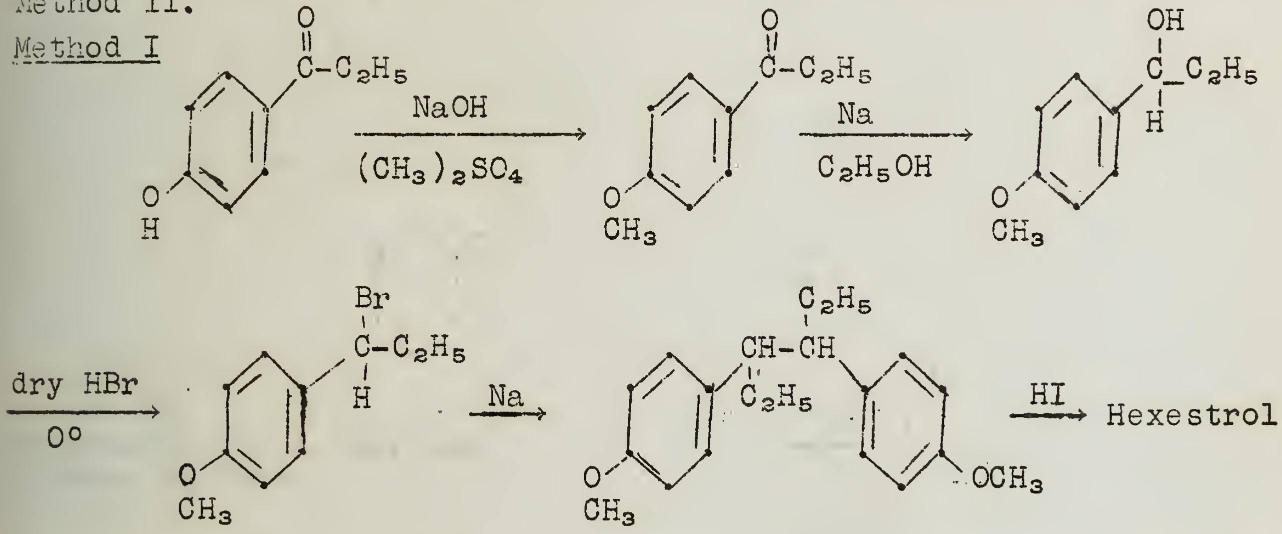
Since the over-all yield in the latter synthesis employing the aldazine intermediate is low, and since the hydrogenation of stilbestrol to hexestrol is very difficult, various investigators have been investigating possible new methods of synthesis of hexestrol in order to develop a cheap way of preparing this compound.

Two syntheses which are promising necessitate the preparation of the intermediate, α-*p*-methoxyphenyl-α'-bromopane,



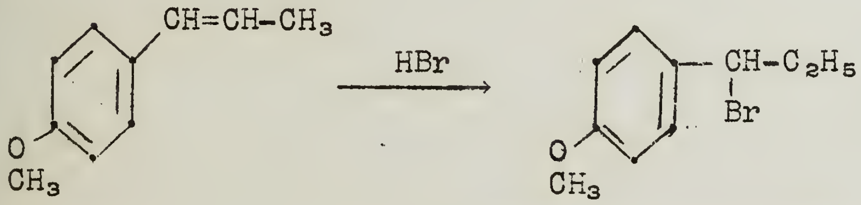
The method employed by Bernstein and Wallis is represented below by Method I, while that of Docken and Spielmann is represented by Method II.

Method I



Overall yield, based on *p*-hydroxypropiophenone, about 7%

Method II



Anethole

α-*p*-methoxyphenyl-α'-bromopropane

Docken and Spielmann obtained hexestrol from the α-*p*-methoxyphenyl-α'-bromopropane by coupling the propane derivative with magnesium, followed by demethylation at high temperatures by means of potassium hydroxide. The over-all yield, based on anethole, is 10-15%.

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Reported by C. F. Jelinek
October 15, 1941

DERIVATIVES OF METHALLYL CHLORIDE

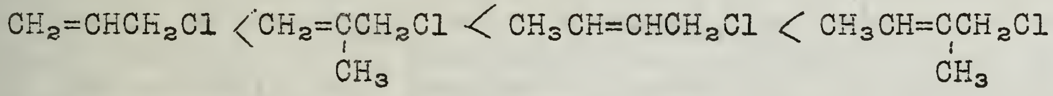
Shell Development Company, Emeryville, California

As a result of the recent advances in the chlorine substitution of isobutylene on a commercial scale methallyl chloride (β-methylallyl chloride) has assumed importance as a synthetic intermediate. The presence of a reactive chlorine atom and an olefin linkage makes possible a large number of useful reactions.

Commercial methallyl chloride containing 4% of β,β-dimethylvinyl chloride is prepared by allowing a mixture of chlorine and liquid isobutylene to react for 0.006 second at such a temperature (0-150° C) that a liquid film on the walls will catalyze substitution, and then passing the reaction products into water to reduce secondary reactions of HCl on the olefins present. The impurity of vinylic chloride, which is extremely inert, is of little importance in replacement reactions; this is not true for reactions involving the double bond.

Metathesis Reactions of Methallyl Chloride

The reactivity of the chlorine atom in this molecule has been measured by means of the reaction velocity with potassium iodide; thus a comparison shows that allyl < methallyl < crotyl < 1-chloro-2-methyl-2-butene.



$$CH_2{=}CHCH_2Cl < CH_2{=}\underset{CH_3}{C}CH_2Cl < CH_3CH{=}CHCH_2Cl < CH_3CH{=}\underset{CH_3}{C}CH_2Cl$$

The chloride is readily hydrolyzed by alkali, the product depending upon the temperature, alkalinity, and agitation. Inefficient mixing may cause local points of acidity and rearrangement to isobutyraldehyde; high alkalinity favors formation of dimethallyl ether from the methallyl alcohol and unreacted methallyl chloride. The necessity for a large excess of water and careful pH control indicates that allylic chlorides are capable of reacting in two ways; i.e. by a unimolecular reaction with the solvent (alcohol or water) and by a bimolecular replacement of the chlorine atom by a hydroxyl or alkoxyl group. It is interesting to note that methallyl chloride is structurally incapable of eliminating HCl. Careful control will give the alcohol in 90% yield.

Methallyl chloride is so reactive that many of its ethers can be made by heating with the alcohol and concentrated aqueous sodium hydroxide. Thus, formation of dimethallyl ether in 90% yield is maintained by the exothermic reaction of the chloride and alcohol in 50% alkali. The ethers from the more highly dissociated alcohols - methyl, ethyl, isopropyl, and phenol - which furnish a more favorable ratio of alkoxyl to hydroxyl ions give good yields of the corresponding ether even in the presence of water. Acid-catalyzed dehydration of the alcohol fails because methallyl alcohol rearranges to isobutyraldehyde in acid medium. The isobutyl group can be introduced into phenols without formation of tertiary phenols by rearranging methallyl phenyl ether to isobutyl phenol (Claisen Rearrangement), followed by hydrogenation.

Treatment of methallyl chloride with aqueous ammonia in an autoclave for two minutes yields 56% primary, 26% secondary, 8% tertiary, and 5% quaternary amines; the high percentage of secondary amine shows that primary methallyl amine is more reactive than ammonia. By including ammonium chloride in the reaction mixture the amount of secondary amine is reduced, since the primary amine forms a hydrochloride salt as produced.

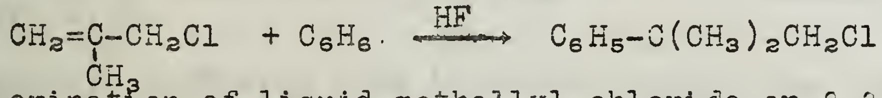
Methallyl chloride reacts with many metal salts, such as KBr, KI, Na_2S, NaSH, NaSCN, to form the bromide, iodide, sulfide, mercaptan, and thiocyanate respectively. Cuprous cyanide must be used in preparing the cyanide since the alkali cyanides cause a shift of the double bond. Substituted barbituric acids can be prepared from methallyl chloride, a monosubstituted barbituric acid, and caustic or by the chloride with malonic ester and sodium, followed by urea.

Magnesium gives first the Grignard reagent, which immediately couples to form dimethallyl. However, 90% Grignard reagent may be obtained by using a large excess of magnesium and ether. The Barbier reaction has been applied to utilize the Grignard as formed - for example, acetone yields 2,4-dimethyl-4-penten-2-ol.

Reactions Involving the Double Bond

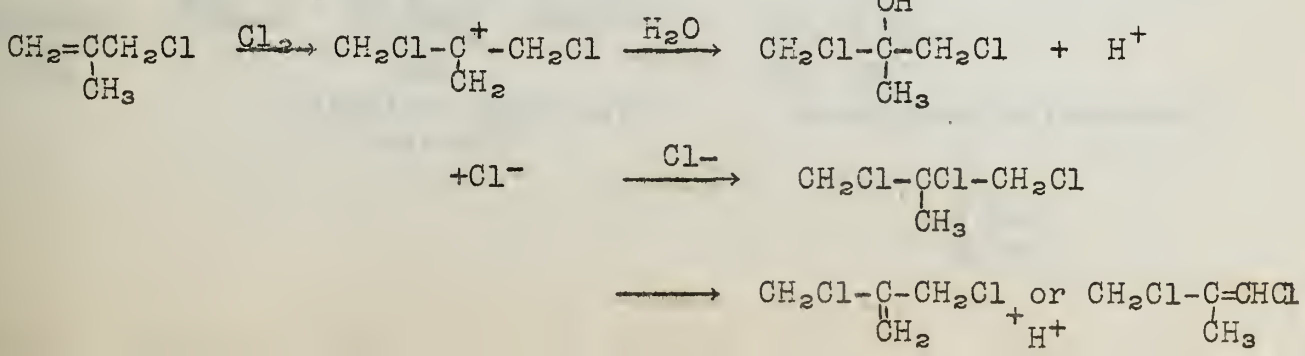
Stirring methallyl chloride with 80% sulfuric acid at 10°, then decomposing the sulfuric ester with ice yields 65% of isobutylene chlorohydrin (chloro-tert. butyl alcohol), the remainder of the methallyl chloride being rearranged to β,β-dimethylvinyl chloride. At 40° the sulfuric acid treatment causes 85% rearrangement; the removal of unreacted methallyl chloride from the vinylic chloride is effected by saponifying with KOH.

Concentrated HCl adds to the double bond; it has been reported that HF catalyzes the addition of methallyl chloride to benzene to form (chloro-tert.butyl) benzene.



$$CH_2{=}\underset{CH_3}{C}{-}CH_2Cl + C_6H_6 \xrightarrow{HF} C_6H_5{-}C(CH_3)_2CH_2Cl$$

Chlorination of liquid methallyl chloride or β,β-dimethylvinyl chloride results in 70% of the unsaturated dichlorides; bromine gives 93% addition. A solution of chlorine in water gives chiefly dichloro-tert.butyl alcohol, along with some dichloro-isobutylenes, trichlor-alcohols and trichloropropane. A reasonable mechanism postulates that chlorine substitutes to form a positive charge on the tertiary carbon atom, to which water or chloride ion may add or from which a proton may be expelled to cause unsaturation at different points in the chain.



$$CH_2{=}\underset{CH_3}{C}CH_2Cl \xrightarrow{Cl_2} CH_2Cl{-}\underset{CH_2}{C^+}{-}CH_2Cl \xrightarrow{H_2O} CH_2Cl{-}\overset{OH}{\underset{CH_3}{C}}{-}CH_2Cl + H^+$$

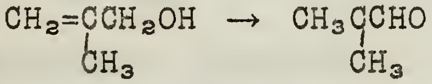
$$+Cl^- \xrightarrow{Cl-} CH_2Cl{-}\underset{CH_3}{C}Cl{-}CH_2Cl$$

$$\longrightarrow CH_2Cl{-}\underset{CH_2}{\overset{}{C}}{-}CH_2Cl + H^+ \text{ or } CH_2Cl{-}\underset{CH_3}{C}{=}CHCl$$

In comparing isobutylene and methallyl chloride, it is seen that the former is more reactive, as evidenced in polymerization, addition of HCl, and chlorine substitution.

Reactions of Methallyl Alcohol

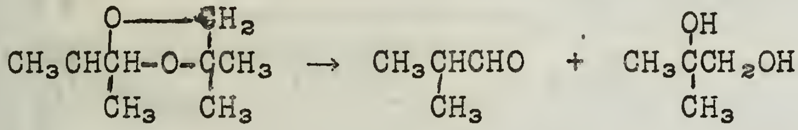
Methallyl alcohol is rearranged by 12% sulfuric acid in almost quantitative yield to isobutyraldehyde; any impurity of dimethallyl ether is also hydrolyzed and rearranged.



$$CH_2{=}\underset{CH_3}{C}CH_2OH \rightarrow CH_3\underset{CH_3}{C}CHO$$

This aldehyde can be oxidized to isobutyric acid; the overall conversion from isobutylene to isobutyric acid is 75%.

Refluxing methallyl alcohol and isobutyraldehyde in 25% sulfuric acid gives isobutyleneglycol-isobutyracetal, which is decomposed to the glycol and aldehyde on heating with dilute acid.



$$CH_3CH\underset{CH_3}{\overset{O}{C}}H\text{-}O\text{-}\underset{CH_3}{\overset{CH_2}{C}}CH_3 \rightarrow CH_3\underset{CH_3}{C}HCHO + CH_3\underset{CH_3}{\overset{OH}{C}}CH_2OH$$

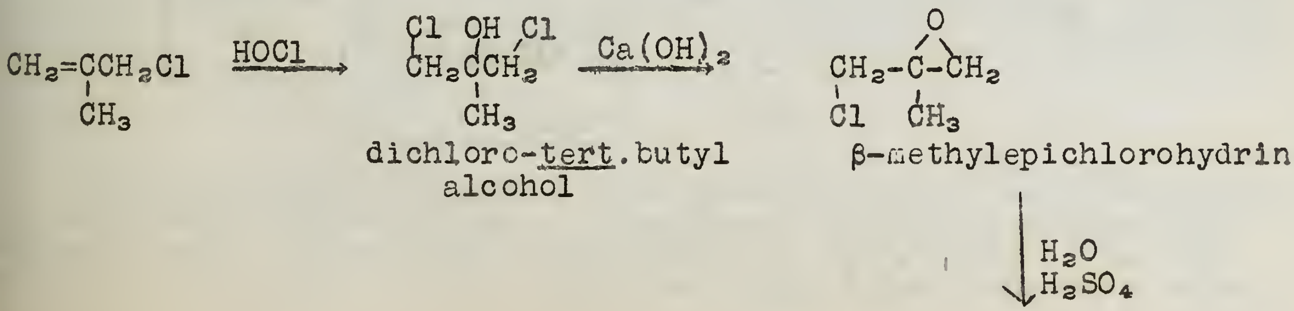
Esterification proceeds by distilling the organic acid with methallyl alcohol. Again, use of mineral acid must be avoided because of rearrangement to the aldehyde. Methallyl alcohol, its esters, and ethers may be hydrogenated below 200° over nickel to the corresponding isobutyl compound.

Methacrolein is prepared either by dehydrogenation or oxidation of methallyl alcohol; the oxidation process is employed because of less rearrangement to isobutyraldehyde. The process consists of passing alcohol and air over silver gauze at 500°. Unless inhibited, methacrolein polymerizes on standing at room temperature to a white granular solid.

Methallyl xanthate, used in ore-flotation, can be made from methallyl alcohol, alkali, and carbon disulfide.

β-methyl glycerol and its Derivatives

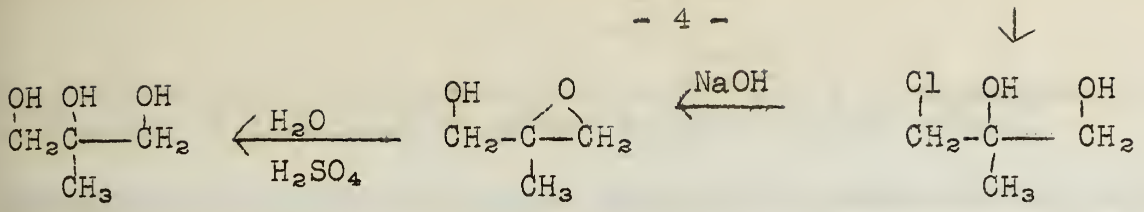
Methallyl chloride has a series of derivatives similar to those of allyl chloride, hence the "β-methylglycerol" homologs.



$$CH_2{=}\underset{CH_3}{C}CH_2Cl \xrightarrow{HOCl} \overset{Cl}{CH_2}\underset{CH_3}{\overset{OH}{C}}\overset{Cl}{CH_2} \xrightarrow{Ca(OH)_2} \underset{Cl}{CH_2}\text{-}\underset{CH_3}{\overset{O}{C}}\text{-}CH_2 \xrightarrow{H_2O,\ H_2SO_4}$$

dichloro-tert.butyl alcohol

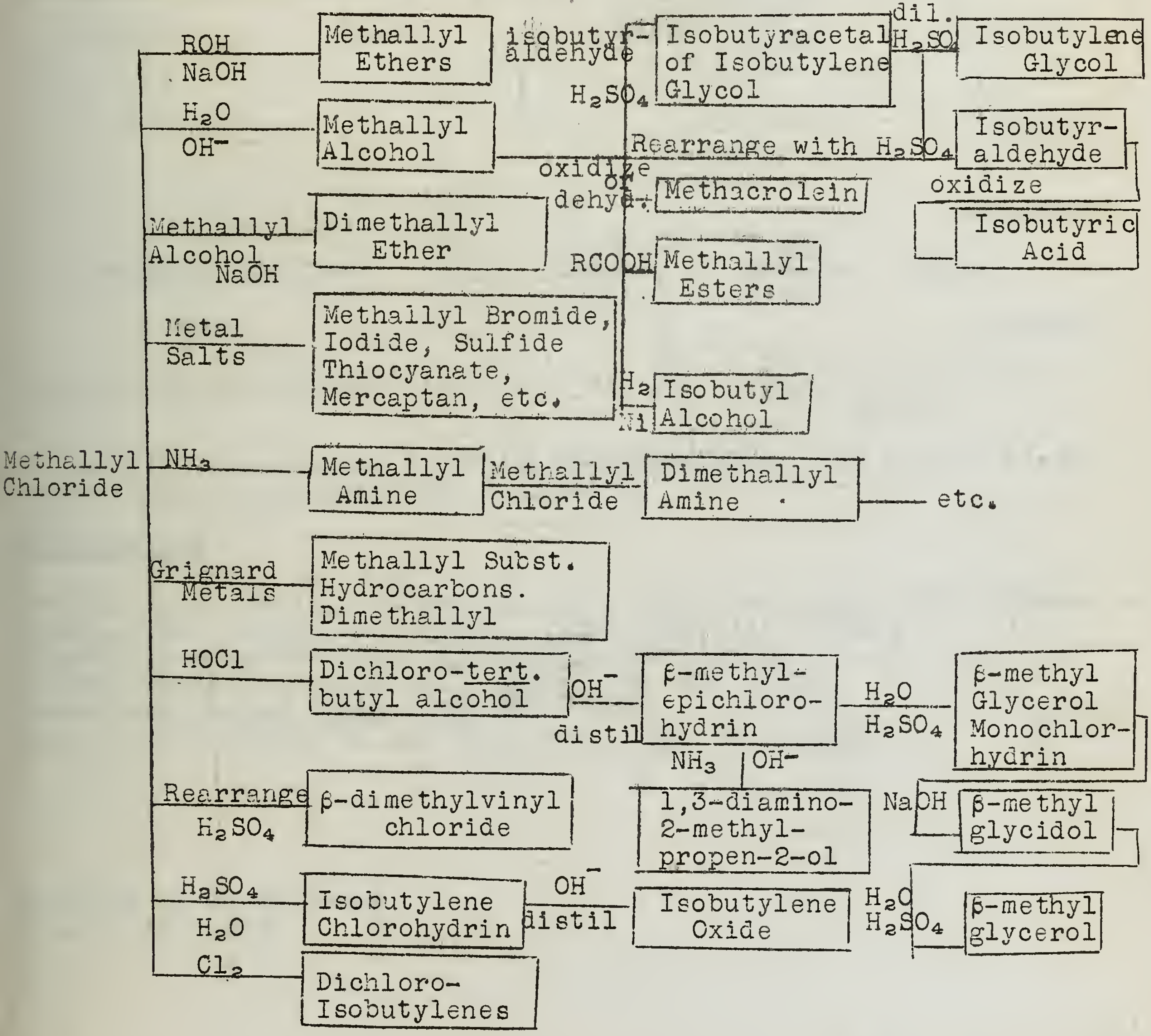
β-methylepichlorohydrin



β-methylglycerol β-methylglycidol β-methylglycerol monochlorohydrin

The advantage of this series of reactions over the direct hydrolysis of dichloro-<u>tert</u>.butyl alcohol or β-methylglycerol monochlorohydrin is that the salt need not be removed from the glycerol produced.

<u>Derivatives of Methallyl Chloride</u>

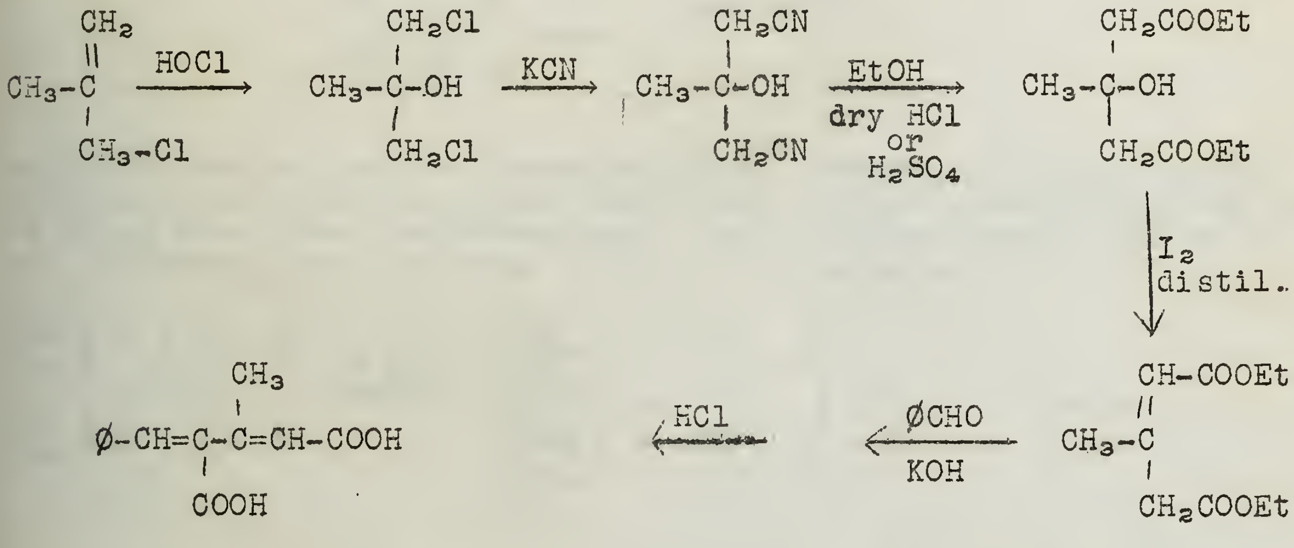


β-methyl glycerol differs from glycerol in its easy conversion to the unsaturated aldehyde by atmospheric distillation from 12% sulfuric acid. These same conditions give methacrolein from any member of the above series. Trichloro-<u>tert</u>.butyl alcohol, a minor

by-product from the chlorohydrination, gives an analagous series containing a chloromethyl group in place of the methyl.

Compounds Containing Conjugate Unsaturation from Methallyl Chloride.

Methallyl chloride affords a feasible approach to the synthesis of substituted isoprenedicarboxylic acids through β-methylglutaconic ester.



α-benzal-β-methylglutaconic acid

β-methylglutaconic ester

By use of β-cyclocitral in place of benzaldehyde, this gives a new route to the caratenoids and Vitamin A.

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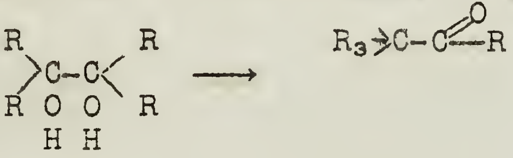
Reported by R. S. Voris
October 15, 1941

PINACOL REARRANGEMENTS

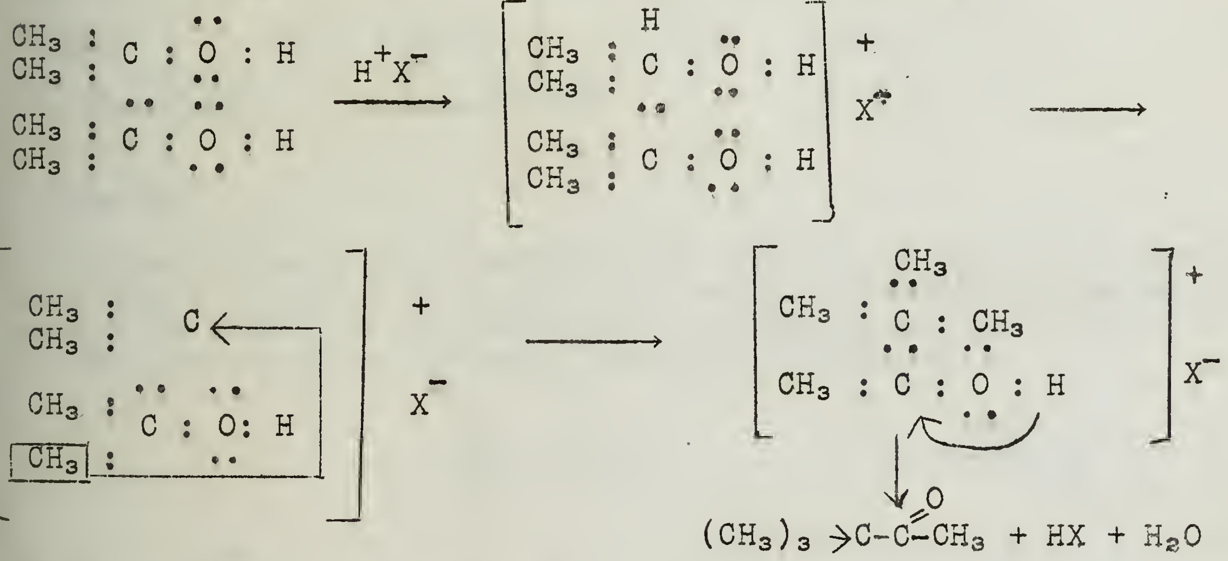
The rearrangements of tri- and tetrasubstituted ethylene glycols and α,β-amino alcohols are summarized in this report.

I. Pinacol-pinacolone rearrangement

When tetrasubstituted ethylene glycols (pinacols) are dehydrated, they rearrange to form pinacolones.

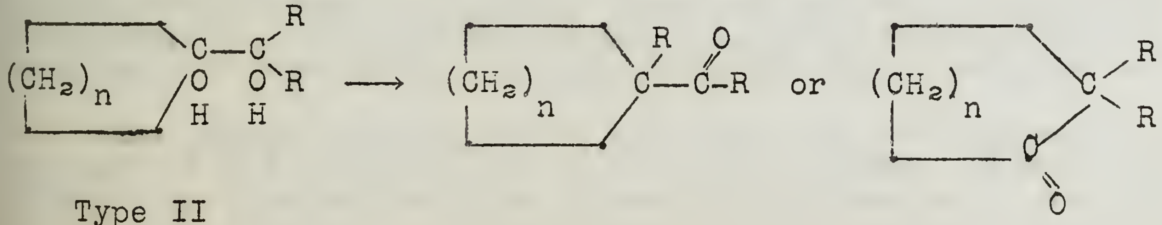


Sulfuric acid of various concentrations, hydrochloric acid, acetyl chloride, and acetic acid and iodine are the most common reagents used to bring about the transformation. The mechanism usually given is the following, using pinacol itself as an example.

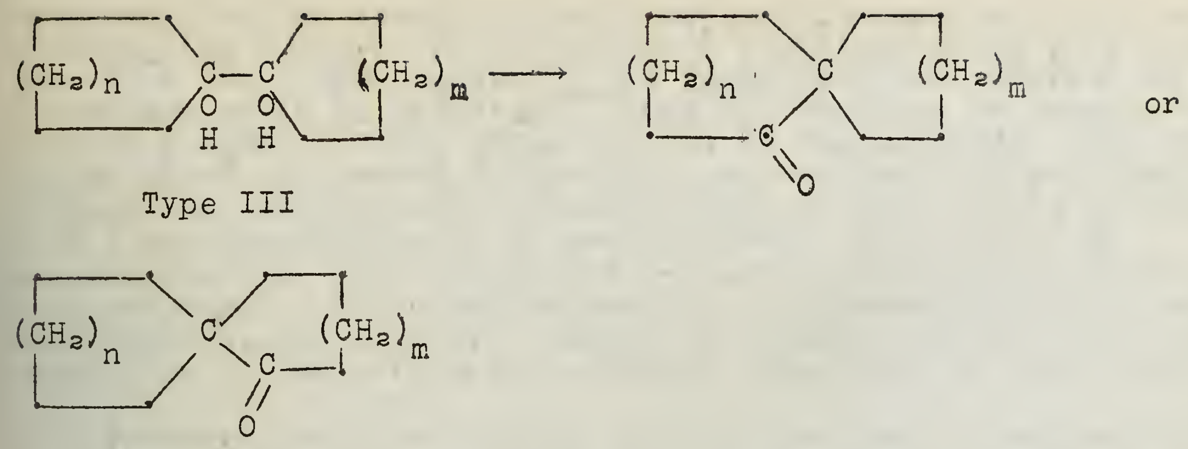


There are four types of pinacols, which can undergo the types of reaction shown.

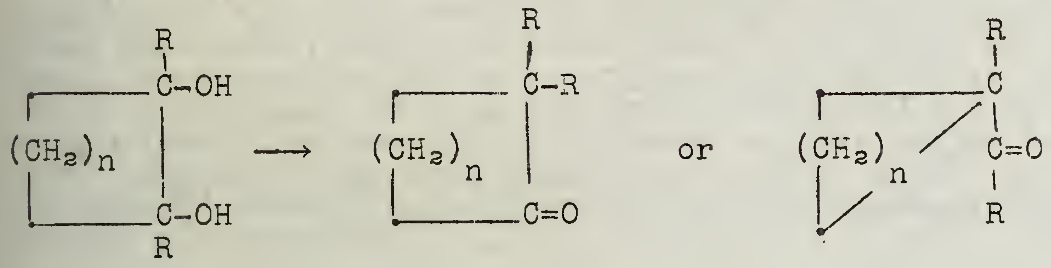
Type I



Type II

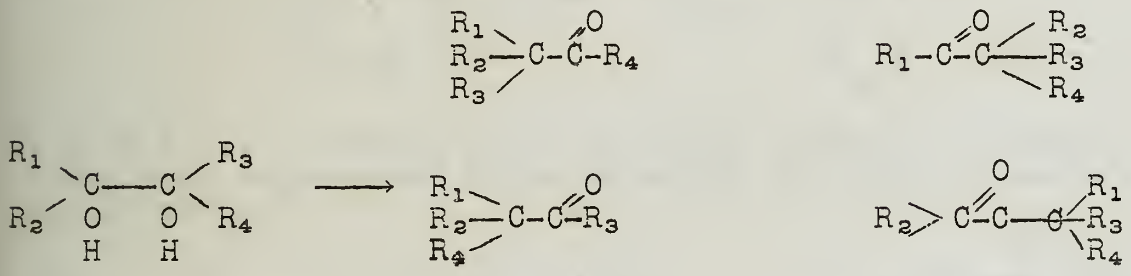


Type III



Type IV

The course of the rearrangement depends, first, on which carbon atom loses an hydroxyl group, and, secondly, on which radical migrates to stabilize the molecule. In type I, if the radicals were all different, four different products could result.



Since the hydroxyl group takes with it a pair of electrons, it will be lost from the carbon atom having the greater capacity for electron release. The second consideration is the migratory ability of the groups on the other carbon atom. The migrating group carries a pair of electrons so that its electron-attracting power, of affinity capacity, is important. In the aliphatic series there is an inverse relationship between migratory power and affinity capacity while in the aromatic series the two go hand-in-hand, showing that in one case or the other there is another factor under observation.

The pinacol rearrangement has been used to compare the affinity capacities and migratory power of various groups. Bachmann has studied the rearrangement of symmetrical pinacols of the type ArAr'C(OH)C(OH)ArAr'. The question of which hydroxyl group is lost is eliminated and the product depends solely on the relative migratory tendencies of Ar and Ar'. In all cases both products were

Type III

Type IV

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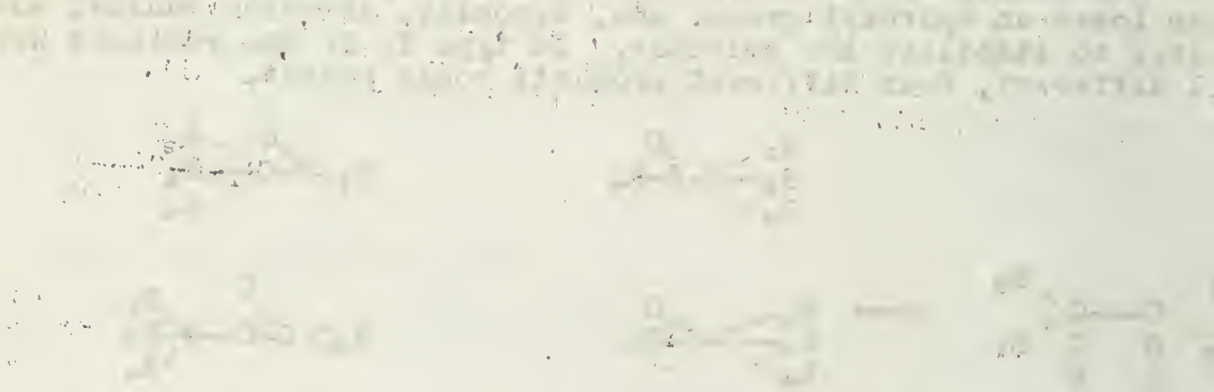

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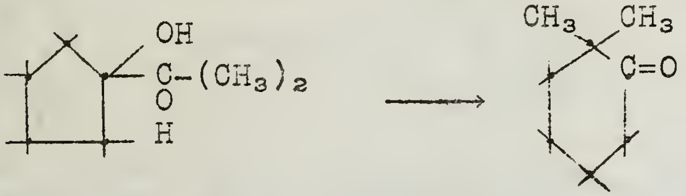
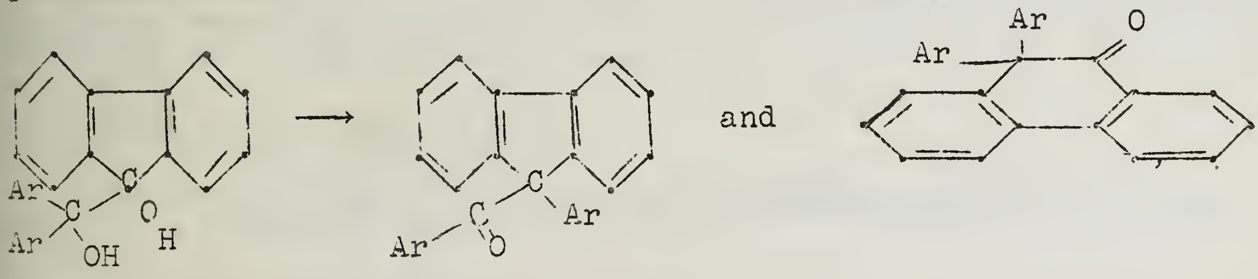
obtained, but the amounts of each gave an indication of the migratory power of the groups. If the relative migratory power of A and B and that of A and C were known, it was found that the behavior of B and C together could be predicted. Thus the tendency to migrate was shown to be a property of the group and not of the molecule. The following series gives the relative migratory power of various aryl radicals (phenyl = 1; anisyl, 500; phenetyl, 500; *p*-tolyl, 15.7; *p*-biphenyl, 11.5 ; *p*-isopropylphenyl, 9; *p*-ethylphenyl, 5; *m*-tolyl, 2; *m*-methoxyphenyl, 1.6; phenyl and *p*-iodophenyl, 1; *p*-bromophenyl, 7; *p*-chlorophenyl, .66; *o*-methoxyphenyl, .3; *m*-bromophenyl, *o*- and *m*-chlorophenyl, nearly zero. Except for steric factors this series is comparable to the series for affinity capacities of these groups.

Bachmann has also studied the rearrangement of unsymmetrical pinacols of the type ArArC(CH)C(OH)Ar'Ar'. The migrating tendencies found here were greatly different from those found in the symmetrical type. They bore no simple relationship to the other values and could not be predicted. This is because the ease of loss of hydroxyl group rather than the migratory power was the factor under observation. Apparent migratory capacities in this series are as follows: *p*-biphenyl > phenyl > *m*-tolyl > *p*-tolyl > *p*-chlorophenyl > phenetyl anisyl > *p*-fluorophenyl.

The rearrangement of pinacols of types II, III, and IV is governed not only by the two factors mentioned above, but also by the size of the ring. Thus, in type II, if *n* is four, a ring enlargement will take place, as is shown by the following example:



If *n* is five, a mixture of the possible products is formed. Pinacols of the type represented below rearrange to both fluorenes and phenanthrenes.



Bachmann investigated pinacols of type IV in the phenanthrene series. Only one reaction was found to take place.

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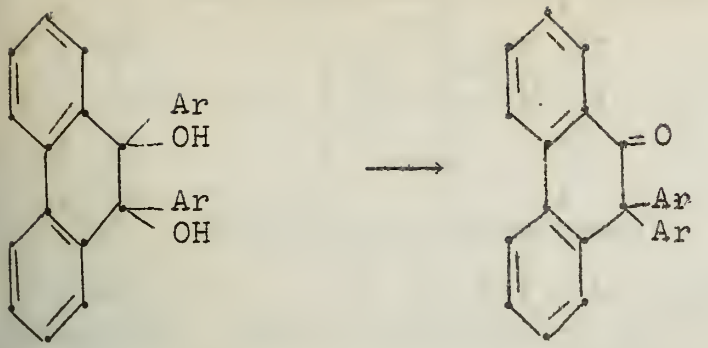
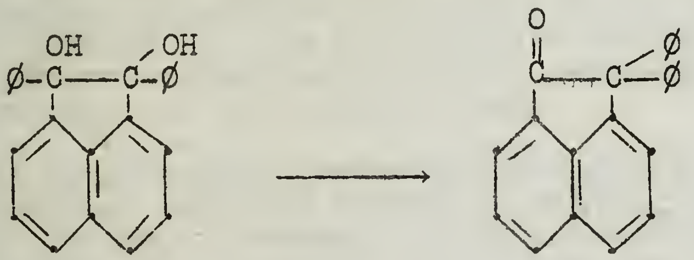


Ar = anisyl, *p*-tolyl, *m*-tolyl, *p*-chlorophenyl, *p*-fluorophenyl, *p*-biphenyl, and α-naphthyl

In the alicyclic series, type IV gives a ring contraction in one case.

Recently it has been suggested that the pinacol rearrangement involves a Walden inversion. Bartlett has studied the rearrangement of the *cis*- and *trans*- forms of 7,8-diphenylacenaphthenediol-7,8.

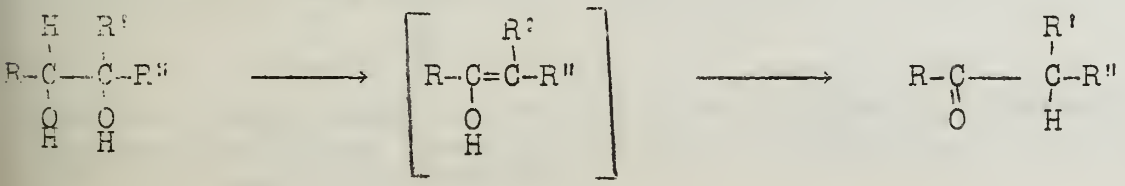


Both geometrical isomers gave the same product, but the kinetics of the reaction showed that the rearrangement of the *trans*- form was much slower, corresponding to conversion to the *cis*- form before rearrangement. Some *cis*-pinacol was actually isolated from a partially rearranged portion of *trans*-pinacol. Since the *cis*- form is the one which can rearrange by Walden inversion, that procedure seems most likely in the light of these facts.

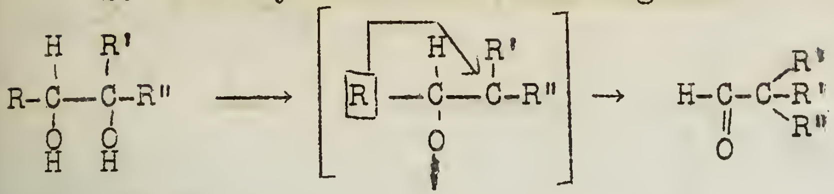
II. Semipinacol Rearrangement

The dehydration of trisubstituted ethylene glycols can take place in a number of ways.

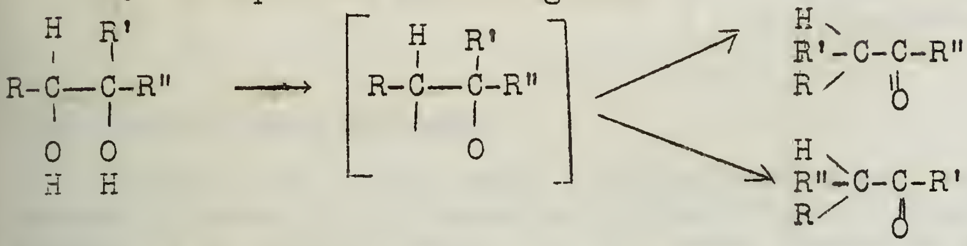
1. vinyl dehydration



2. Semihydrobenzoin rearrangement



3. Semipinacol rearrangement



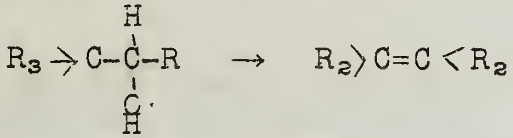
In the first two reactions, the tertiary hydroxyl group is eliminated, but in the last one the secondary hydroxyl group is eliminated. The removal of one or the other is controlled by the nature of the groups attached to the respective carbon atoms as well as by the nature of the reagent. Concentrated acid promotes reaction 3, while milder conditions favor reaction 2. Dehydration of aryl dialkyl glycols, $ArCH(OH)C(OH)RR$, with oxalic acid or dilute sulfuric acid gives aldehydes (reaction 2) and with concentrated sulfuric acid gives ketones (reaction 3). As the radicals become larger the tertiary hydroxyl group is stabilized and the semipinacol rearrangement takes place regardless of the reagent used.

Alkyl hydrobenzoins $C_6H_5CH(OH)C(OH)RC_6H_5$, give desoxybenzoins by loss of tertiary hydroxyl when R is methyl, isobutyl, or phenyl. When R is ethyl, propyl, isopropyl, butyl, isoamyl, and cyclohexyl, of desoxybenzoins and benzhydryl alkyl ketones, $(C_6H_5)_2CH-\underset{R}{C}=O$ are produced. Evidently the size of the radical is not the determining factor in the rearrangement of alkyl hydrobenzoins.

It has been shown that the presence of an aryl group on the carbon atom carrying the secondary hydroxyl group is necessary before a semipinacol rearrangement can occur.

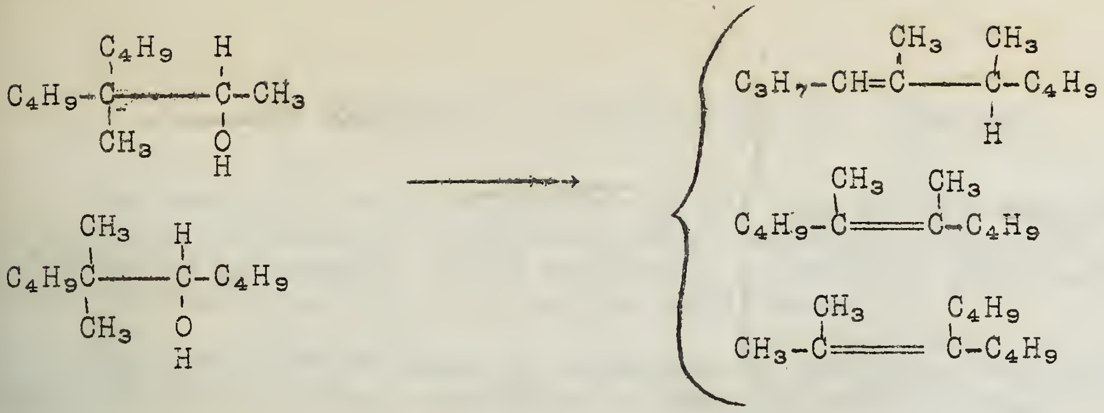
III. Retropinacol rearrangement

The dehydration of alcohols derived from pinacolones is accompanied by the reverse pinacol rearrangement.



$$R_3{\to}C-\overset{H}{\underset{OH}{C}}-R \rightarrow R_2{>}C=C{<}R_2$$

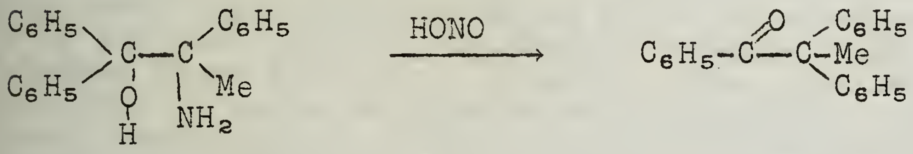
Mixtures result when the radicals are different. Whitmore studied the dehydration of two isomeric pinacolyl alcohols and found that they gave the same three products.



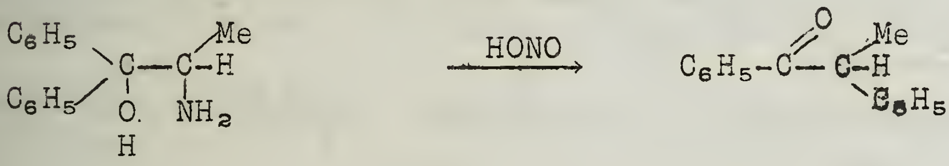
IV. Deamination reactions

Pinacol and semipinacol rearrangements may take place if one hydroxyl group of a pinacol or trisubstituted ethylene glycol is replaced by an amino group. In this case there is no question of the course of the reaction. The amino group is always eliminated and migration takes place away from the carbon atom carrying the hydroxyl group.

1. Pinacolic deamination



2. Semipinacolic deamination



The relative ease of migration of aryl groups may be determined by making the groups different.

Whitmore has shown that semipinacolic deamination involves a Walden inversion. The optically active amino alcohol was used in reaction 2 above and an optically active ketone resulted. By relating the configuration of starting material and product to compounds of known configuration, it was proved that a Walden inversion has occurred.

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Complete references given.
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Whitmore, ibid., 55, 1528 (1933); 61, 1324 (1939).
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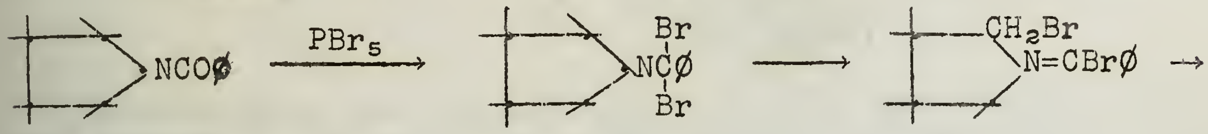
Reported by J. O. Corner, October 22, 1941

NEW SYNTHESES OF HEXATRIENES AND SQUALENE

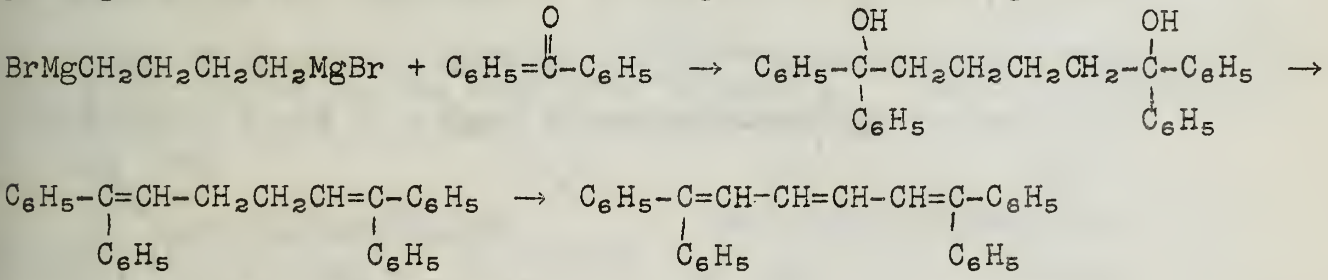
The basis of these syntheses is the use of the Grignard compound of 1,4-dibromobutane in reactions with carbonyl compounds to form 1,6-glycols by regular (1,2) addition, subsequent dehydration and dehydrogenation giving the desired hexatriene.

The 1,4-dibromobutane is obtained by treating N-benzoyl pyrrolidine with PBr_5 according to the von Braun method:



$BrCH_2CH_2CH_2CH_2Br + \text{Ø}CN$

When an ether solution of benzophenone is added to a solution of the Grignard compound of 1,4-dibromobutane, the solution turns carmine, and the reaction product separates as a viscous mass. It has been shown that this product is 1,1,6,6-tetraphenyl-1,6-hexanediol. It is the same product that Bouvet obtained when he let excess C_6H_5MgBr react with ethyl adipate. When this impure alcohol is dissolved in water, a spontaneous dehydration takes place giving almost quantitative yields of 1,1,6,6-tetraphenyl-1,5-hexadiene. If the purified hexadiene is dissolved in glacial acetic acid and heated with SeO_2, one obtains 1,1,6,6-tetraphenyl hexatriene upon recrystallization of the product from acetic anhydride. It is in the form of pale green plates - the color arising from the conjugation.



$$BrMgCH_2CH_2CH_2CH_2MgBr + C_6H_5=\overset{O}{\overset{\|}{C}}-C_6H_5 \rightarrow C_6H_5-\underset{C_6H_5}{\overset{OH}{C}}-CH_2CH_2CH_2CH_2-\underset{C_6H_5}{\overset{OH}{C}}-C_6H_5 \rightarrow$$

$$C_6H_5-\underset{C_6H_5}{C}=CH-CH_2CH_2CH=\underset{C_6H_5}{C}-C_6H_5 \rightarrow C_6H_5-\underset{C_6H_5}{C}=CH-CH=CH-CH=\underset{C_6H_5}{C}-C_6H_5$$

The hexadiene may also be converted to the hexatriene by heating it with *p*-benzoquinone at 170-180°.

Fluorenone was also made to react with the Grignard solution of 1,4-dibromobutane to form 1,6-difluorenyl-1,6-hexanediol. This turned out to be so very insoluble that ordinary recrystallization was quite difficult. Hence the impure alcohol was heated with benzenesulfonic acid in acetic anhydride, which eliminated the water to give the hexadiene. This was converted to the hexatriene by means of SeO_2 in glacial acetic acid as above. The result was 1,6-dibiphenylene hexatriene.

THE PREPARATION OF [illegible] AND [illegible]

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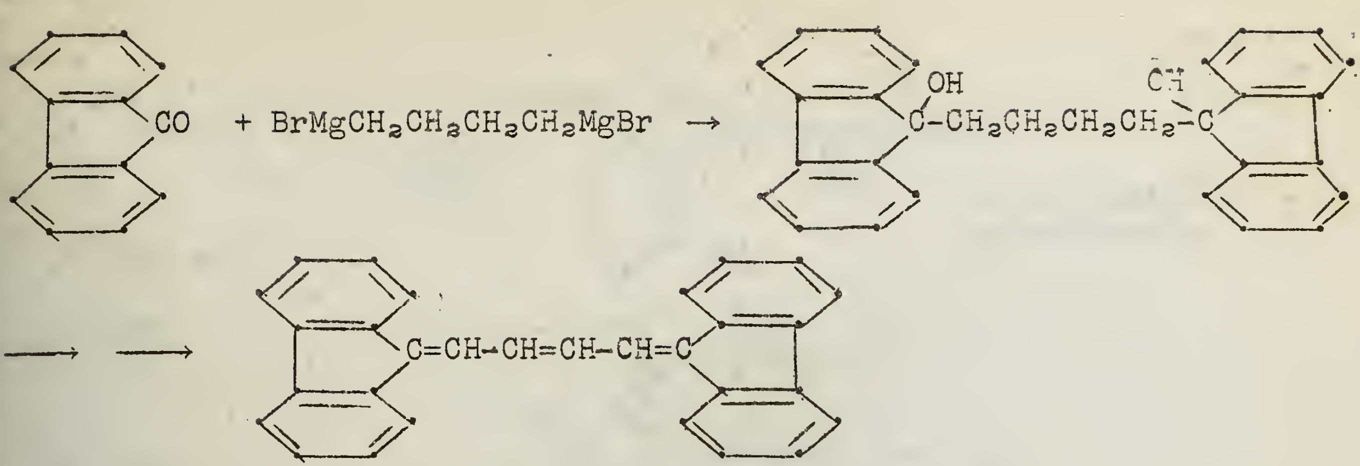
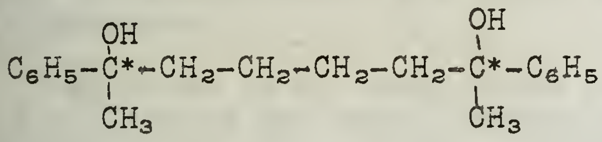


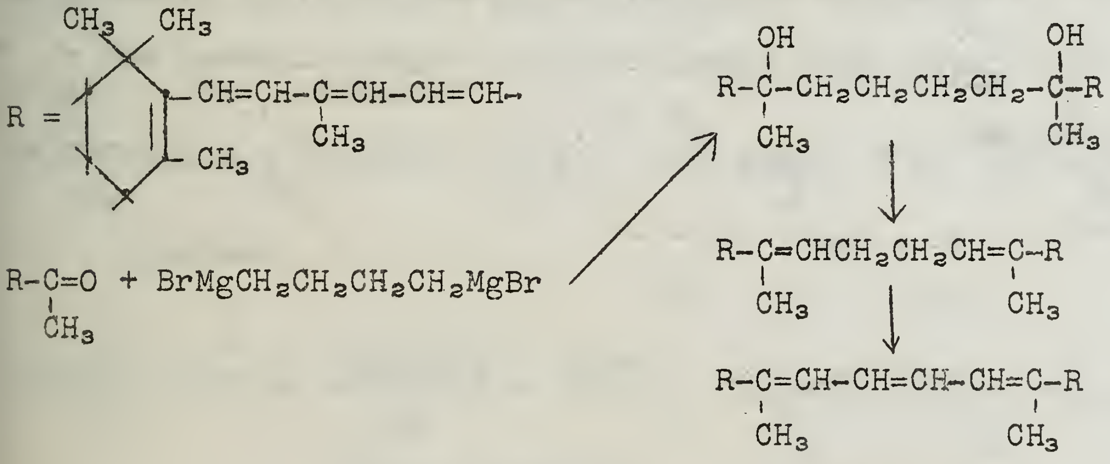
Acetophenone and benzaldehyde were also used in this reaction; good yields of the hexatriene were obtained in each case. It is interesting to note that the 1,6-diphenyl-1,6-dimethyl-1,6-hexanediol from the acetophenone gives rise to two forms -- one a racemic modification and the other a meso form. This results from the two similar asymmetric carbon atoms which the molecule possesses.



$$C_6H_5-\underset{CH_3}{\overset{OH}{C^*}}-CH_2-CH_2-CH_2-CH_2-\underset{CH_3}{\overset{OH}{C^*}}-C_6H_5$$

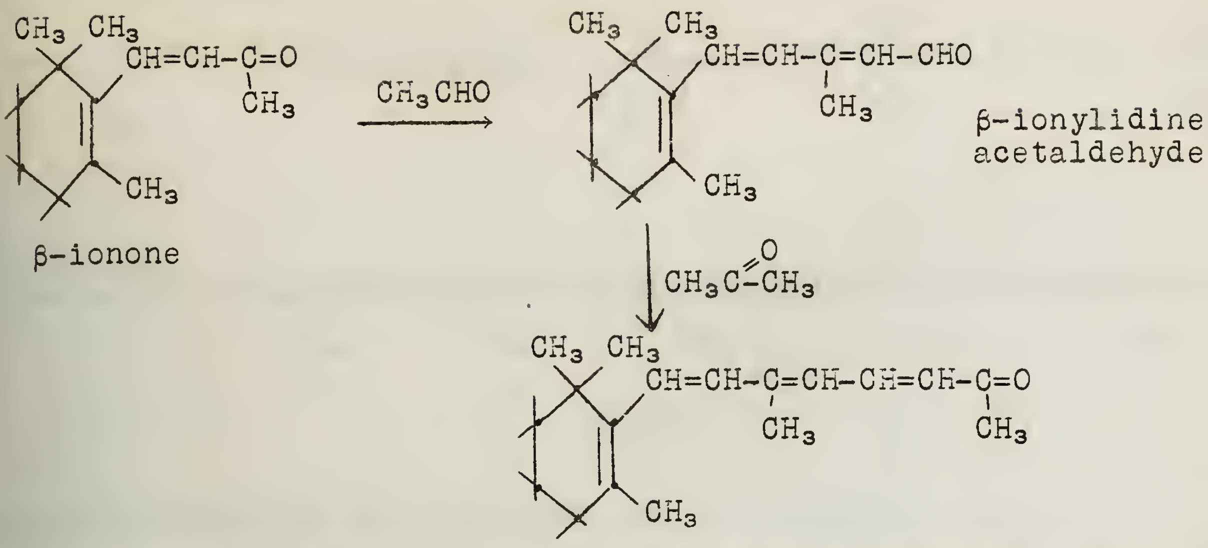
There are few classes of natural products that are harder to synthesize than the carotenoids.
This is mainly due to the long branched carbon chain and the extensive system of conjugated unsaturations which are characteristic of this class of compounds.

One of the most important of the carotenoids is β-carotene which can be converted by the body into Vitamin A. The new synthesis of hexatrienes gives us a good means of producing β-carotene:



β-carotene

However it should be noted that the ketone with which this synthesis starts is not know but it has been well established that it could be produced by condensing β-ionylidene acetaldehyde with acetone:



β-ionone

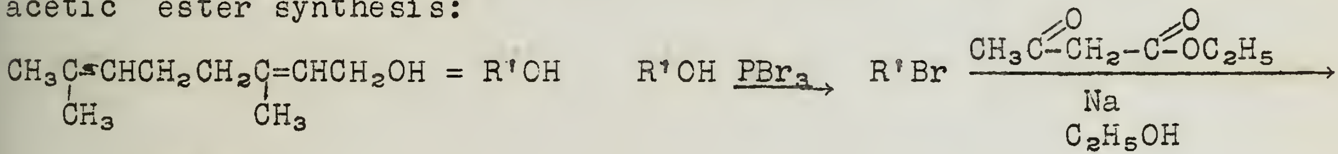
β-ionylidine acetaldehyde

It would seem simpler to use 1,4-dibromo-2-butene and thereby omit the dehydration, but this is not possible - only the pinacol is isolated.

Squalene is an unsaturated hydrocarbon which occurs in the liver oil of fish of the shark family and also in yeast. It is made up of six isoprene units and gives crystalline compounds with HCl and HBr that are suitable for its characterization.

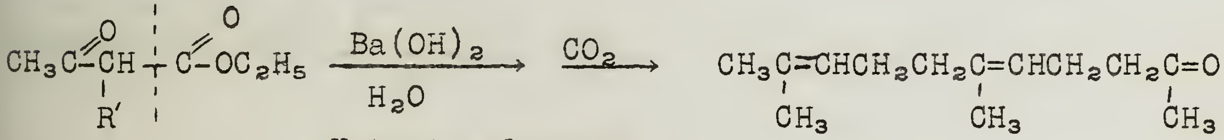
It is interesting to note that the Barbier reaction is employed instead of the Grignard reaction in this synthesis of squalene. In the Barbier reaction the 1,4-dibromobutane is added to the geranyl acetone in an absolute ether solution of Mg with a crystal of iodine as catalyst, and the "nascent" Grignard reagent reacts in a normal manner before complicating side reactions can set in. A vigorous reaction takes place and the diol is formed. This is converted into squalene by distillation under diminished pressure.

The geranyl acetone is first formed from geraniol by an acetoacetic ester synthesis:



$$CH_3\underset{CH_3}{C}{=}CHCH_2CH_2\underset{CH_3}{C}{=}CHCH_2OH = R'CH \qquad R'OH \xrightarrow{PBr_3} R'Br \xrightarrow[\substack{Na \\ C_2H_5OH}]{CH_3\overset{O}{C}-CH_2-\overset{O}{C}-OC_2H_5}$$

geraniol

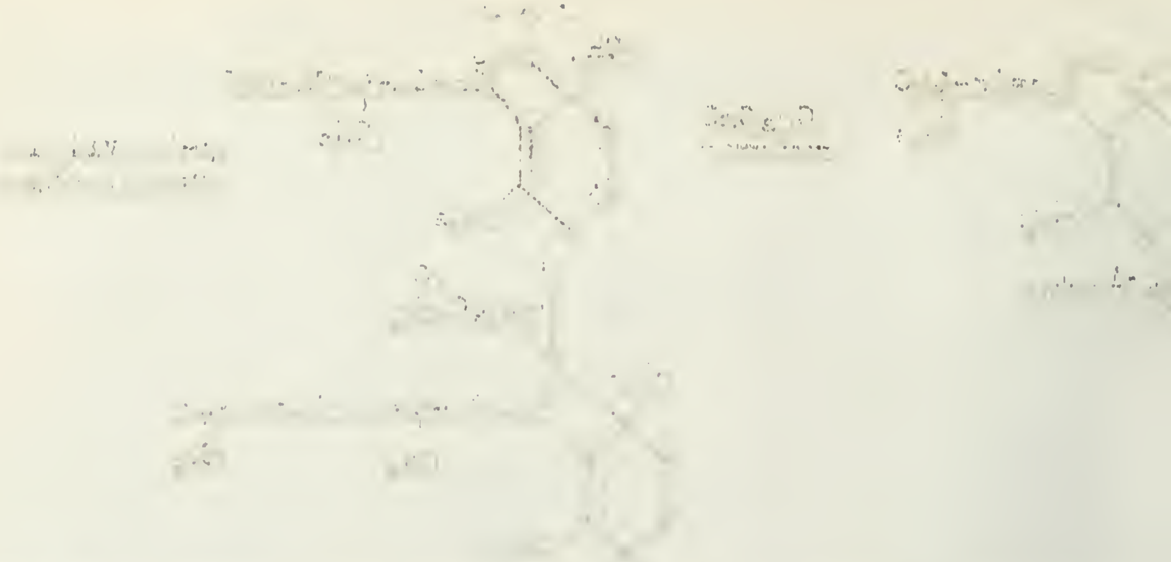


$$CH_3\overset{O}{C}-\underset{R'}{CH}-\overset{O}{C}-OC_2H_5 \xrightarrow[H_2O]{Ba(OH)_2} \xrightarrow{CO_2} CH_3\underset{CH_3}{C}{=}CHCH_2CH_2\underset{CH_3}{C}{=}CHCH_2CH_2\underset{CH_3}{C}{=}O$$

Ketonic cleavage

geranyl acetone

Then the Barbier reaction is carried out, using 1,4-dibromobutane with the above product:



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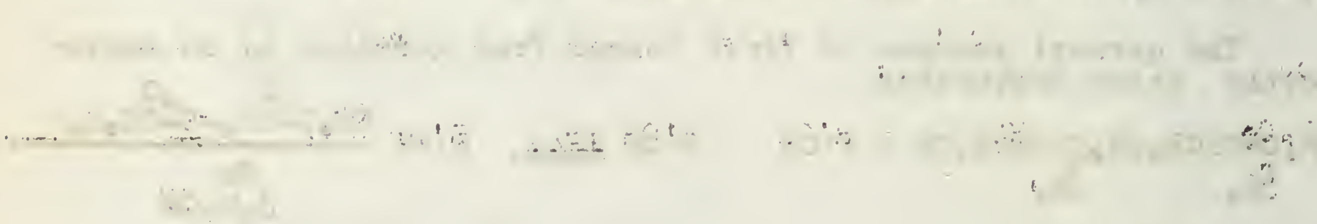

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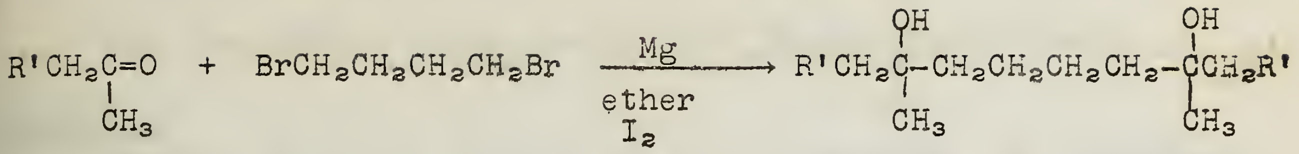
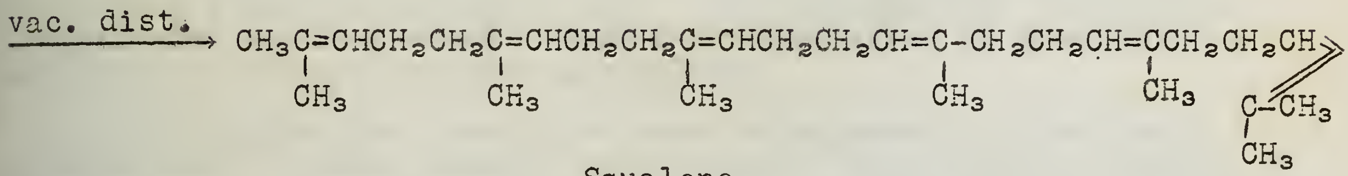


$$R'CH_2\underset{CH_3}{C}=O + BrCH_2CH_2CH_2CH_2Br \xrightarrow[\text{ether}\ I_2]{Mg} R'CH_2\underset{CH_3}{\overset{OH}{C}}-CH_2CH_2CH_2CH_2-\underset{CH_3}{\overset{OH}{C}}CH_2R'$$



$$\xrightarrow{\text{vac. dist.}} CH_3\underset{CH_3}{C}=CHCH_2CH_2\underset{CH_3}{C}=CHCH_2CH_2\underset{CH_3}{C}=CHCH_2CH_2CH=\underset{CH_3}{C}-CH_2CH_2CH=\underset{CH_3}{C}CH_2CH_2CH=\underset{CH_3}{C}-CH_3$$

Squalene

The advantages of this squalene synthesis are:

(1) Cheaper and more easily obtainable starting materials

(2) Squalene is produced in better yields and in purer crystalline form.

The old preparation started with farnesol → farnesyl bromide $\xrightarrow{MgBr}$ squalene. See reference to Karrer.

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Reported by P. F. Warfield
October 22, 1941

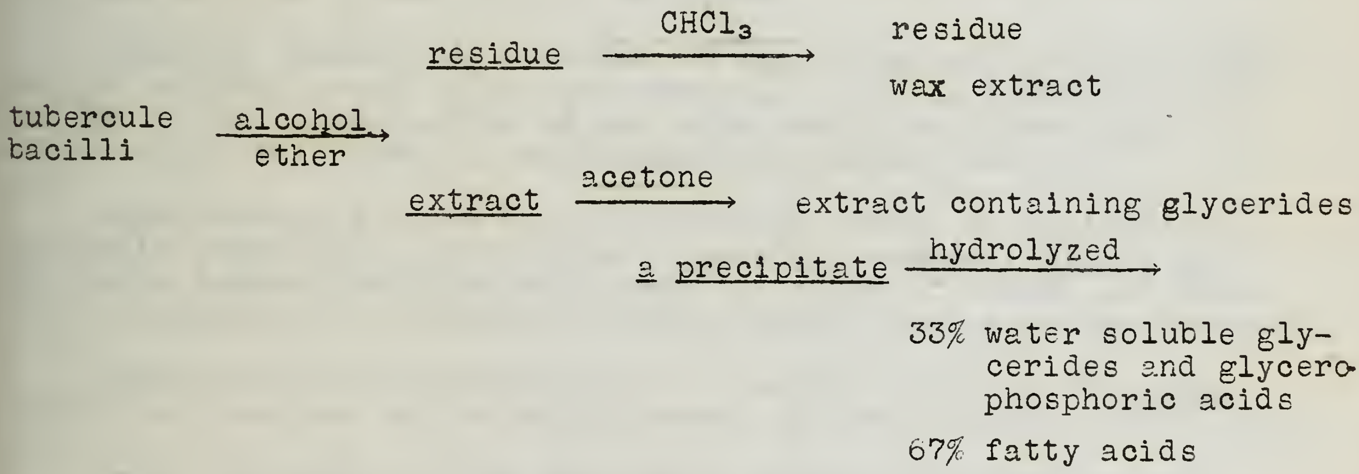
ATTEMPTS TO DETERMINE THE STRUCTURE OF PHTHIOIC ACID

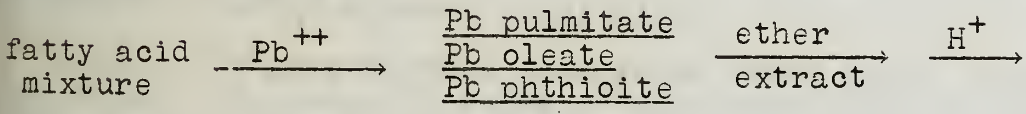
From the 1940 Presidential Address by Robert Robinson

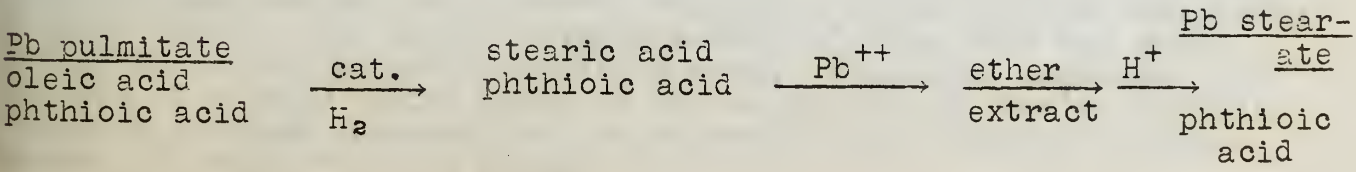
Isolation

Phthoic acid was isolated by R. J. Anderson. He extracted moist live tubercule bacilli with an equal mixture of alcohol and water. The residue was further extracted with chloroform. The chloroform fraction yielded a wax. The alcohol-ether extract was treated with acetone which caused a precipitation of phosphatides and left in solution various glycerides.

The phosphatide precipitate was decomposed by hydrolysis, yielding 33% of water soluble constituents, consisting of carbohydrates and glycerophosphoric acid, and 67% of a mixture of fatty acids. This mixture of acids was converted into a corresponding mixture of lead soaps. This mixture was extracted with ether, leaving a residue, which yielded pulmitic acid on decomposition with acid. The ether extract was hydrogenated catalytically and the resulting mixture of acids was converted to the lead salts and extracted with ether. A residue was left which, when decomposed, yielded stearic acid. The stearic acid resulted from the hydrogenation of oleic acid present inthe original mixture of fatty acids. The ether extract was decomposed yielding a yellow oil which solidified on cooling. The melting point of the resulting solid was 21°, the rotatory power $[\alpha]^{20}_{D}$ was +11.96° and analysis showed an empirical formula $C_{26}H_{52}O_2$. Anderson named this product phthioic acid.

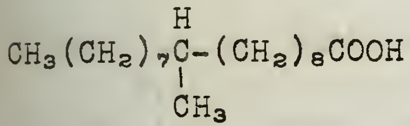




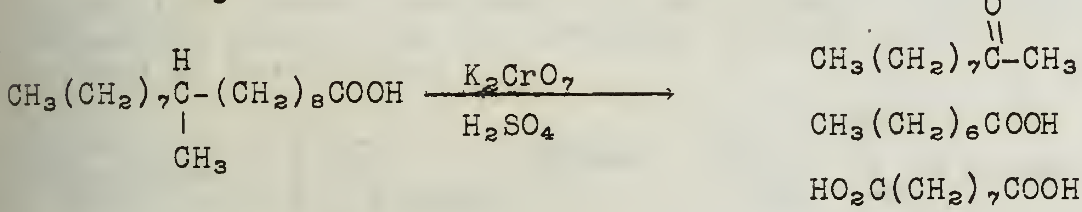


A mixture of fatty acids was also obtained from the wax fraction. On distillation at low pressure two fractions were isolated; a low boiling one, which proved to be a single compound, was called tuberculostearic acid, the high boiling fraction was shown to be identical with phthioic acid.

Spielman oxidized tuberculostearic acid with chromic acid and obtained n-octyl ketone, azelaic and n-octoic acids. He, therefore, showed tuberculostearic acid to be --



$$CH_3(CH_2)_7\overset{H}{\underset{CH_3}{C}}-(CH_2)_8COOH$$



$$CH_3(CH_2)_7\overset{H}{\underset{CH_3}{C}}-(CH_2)_8COOH \xrightarrow[H_2SO_4]{K_2CrO_7} \begin{array}{l} CH_3(CH_2)_7\overset{O}{\overset{\|}{C}}-CH_3 \\ CH_3(CH_2)_6COOH \\ HO_2C(CH_2)_7COOH \end{array}$$

Attempt to determine the structure

Phthioic acid, when oxidized with chromic acid, gave a compound with the formula $C_{11}H_{22}O_3$, which was claimed to be different from n-undecoic acid because two derivatives melted 20° too low. This evidence is not thought to be conclusive in view of the small quantities used and the probability of mixtures.

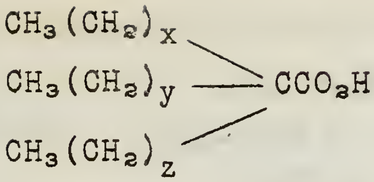
Charguff synthesized a number of C_{26} acids and, from the fact that the melting point of the n-hexacosanic acid is lowered 20-30° from 88° by the introduction of one side chain, concludes that phthioic acid must have at least three hydrocarbon chains.

Wagner-Jaureyg found by the Kuhn-Roth method of estimating side chain methyl that phthioic acid gave 2.4 moles of $C_2H_4O_2$ per mole while tuberculostearic acid gave 1.4 moles of $C_2H_4O_2$ per mole. This is suggested as evidence for three carbon chains in the molecule.

Anderson believes that there is a methyl group in the alpha position and another in the neighborhood of the eleventh carbon atom.

X-Ray reflections from multilayer films of the barium salt showed that the length of the molecule was that of a chain of twelve to fourteen carbon atoms.

Phthioic acid differs from known fatty acids in that it is in thin films. On water it forms a very compressed unimolecular layer collapsing at an area of $38A^{o2}$ per molecule. On the other hand, n-decyl-n-dodecylacetic acid forms a much more expanded film collapsing at about $60A^{o2}$. The surface dipole moment of this film was much smaller than that formed by phthioic acid. Stenhagen suggests the presence of a small alkyl group in the α-position to the carboxyl because this might account for the observed close packing of the chains. He suggested the formula --

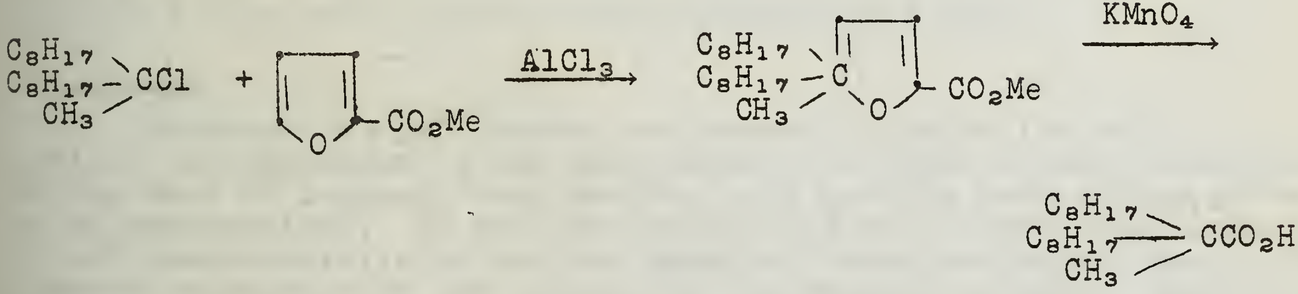


$$\begin{matrix} CH_3(CH_2)_x \\ CH_3(CH_2)_y \\ CH_3(CH_2)_z \end{matrix} \Big\rangle CCO_2H$$

in which x and y are about 10-12 and different and z = 0 or 1, the most probable formula thought to be the one in which z = 1, x = 9, y = 11.

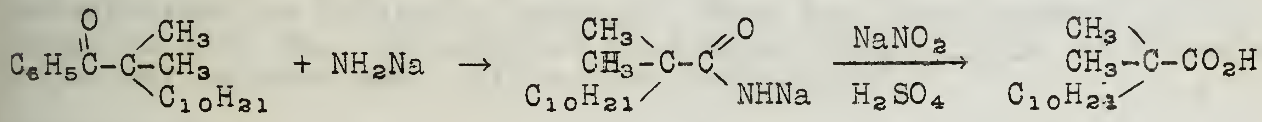
Synthesis of Substances of the phthioic acid type

With the ultimate purpose of synthesizing phthioic acid, Birch synthesized several compounds of the phthioic acid type. Methyl di-*n*-octyl acetic acid was produced by application of the method devised by Reichstein.



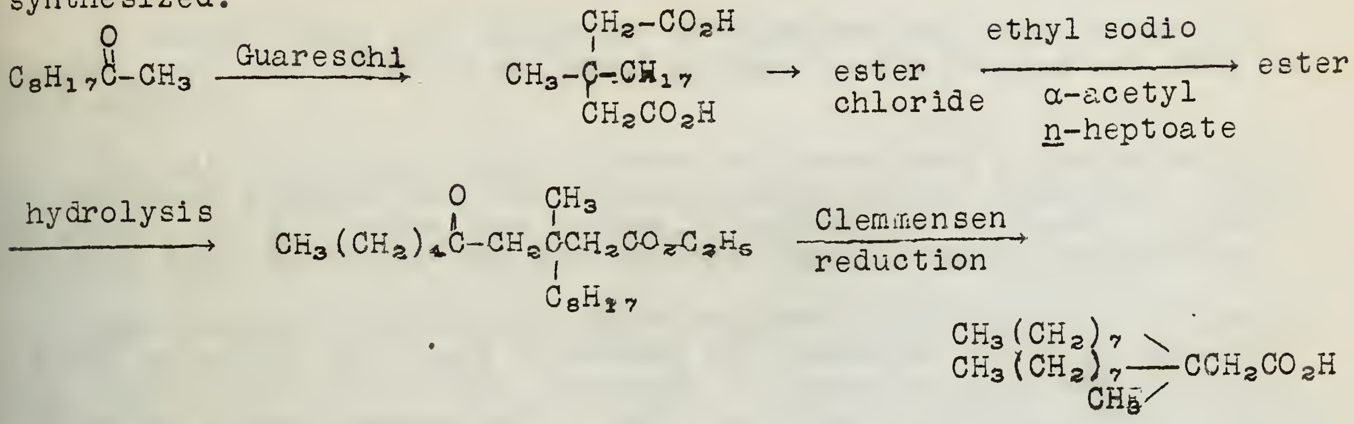
This acid formed the compressed films of the phthioic acid type.

α,α-Dimethyl *n*-decyl acetic acid was synthesized according to the directions of Haller.



This acid also produced films of the type shown by phthioic acid.

After several attempts β,β-di-n-octylbutyric acid was synthesized.



This acid also gives films of the phthioic acid type.

Conclusion

Tuberculosis and leprosy are caused by infection with bacilli characterized by the possession of a fatty or waxy envelope. In the case of leprosy, chaulmoogric acid and its derivatives prove to be bactericidal. It has been shown that the bactericidal action is not characteristic of any one group of atoms but rather due to the physical character of the molecule. The bacilli probably suffer an impairment of the fatty envelopes in the presence of chaulmoogric acid and its derivatives. It has also been shown that the best results were obtained with molecules containing 16 or 17 carbon atoms. Molecules of the phthioic acid type synthesized by Robinson and Birch, especially β,β-di-n-octyl butyric acid, are found to be bactericidal to tubercule bacilli. From the above analogy it is expected that the compounds of this type containing 16 or 17 carbon atoms may be even more active when synthesized.

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Reported by R. G. Chase
October 29, 1941

THE OPTICAL ISOMERS OF CIS-9-METHYL-1-DECALONE

Plentl, et al

In recent years the synthesis of steroids has been of special interest, but the question of their optical isomerism has not been so fully studied.

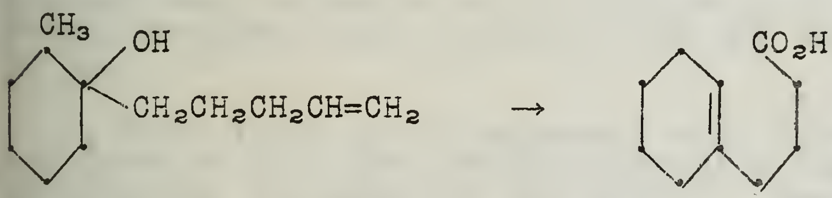
The ultimate aim of all of these syntheses was a comparison of the synthetic steroid with its corresponding natural compound. Since the latter, in all cases, are optically active the synthetic steroid must be a pure substance and not contain stereoisomeric impurities.

<u>cis</u>-9-Methyl-1-decalone, first reported by Chuang, was selected as a raw material for study to obtain an isomer of definite composition. This compound has the advantage of possessing an angular group at C_9 which gives dissymmetry as well as being a general characteristic of all steroids. From this compound, methods are available for the preparation of both perhydrophenanthrenes and cyclopentenophenanthrenes.

Methylcyclohexenylbutyric Acid

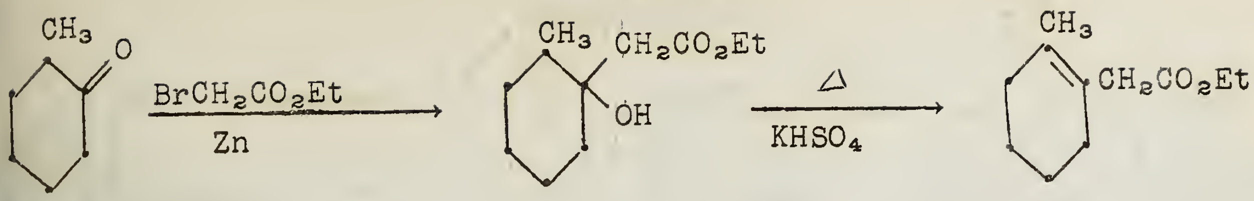
The only methods reported for the preparation of 9-methyl-1-decalone are dependent on the synthesis of methylcyclohexenylbutyric acid; consequently the method previously worked out by Elliot and Linstead was tried. In this a Grignard reaction is run with 5-bromo-1-pentene and methylcyclohexanone with permanganate oxidation of the tertiary alcohol, followed by dehydration of the hydroxy acid.

$CH_2{=}CHCH_2CH_2CH_2Br \rightarrow CH_2{=}CHCH_2CH_2CH_2MgBr \rightarrow$



However, appreciable amounts of methylcyclohexanol were found in the Grignard reaction, which is in agreement with the observation of Butenandt that aliphatic magnesium bromides with moderately long side chains have reducing properties. The dehydration of the hydroxy acid also forms a spirolactone. This need not be discarded but is simply converted to ethyl methylcyclohexenylbutyrate in very good yields by boiling with thionyl chloride in benzene solution and pouring the mixture into absolute alcohol. γ-Lactones are usually split in this way and apparently the procedure is equally as good with δ-lactones.

Simultaneously with the above study a new synthesis of this acid was attempted by Plentl and Bogert which proved superior in many ways. This is shown in Flow Sheet A. Essentially the method is the elongation of the side chain of methylcyclohexenylacetic acid by two successive Arndt-Eistert rearrangements. The substituted acetic acid had previously been prepared by Chuang as follows:



cis-9-Methyl-1-decalone

This preparation is also outlined on Flow Sheet A, and is essentially a cyclization of the acid by the Darzens reaction, as modified by Cook and Lawerence, to the corresponding chloroketone which after removal of the HCl yields the unsaturated ketones.

Resolution

Only the purest fraction of cis-9-methyl-1-decalylamine was used for the resolution. Although Hueckel and Kuehn were able to resolve α-decalylamine using camphorsulfonic acid, this reagent was unsatisfactory here because of the excessive solubility of its salts. However, bromocamphorsulfonic acid formed salts which were sufficiently difficultly soluble in ethanol to be separated.

The amines were regenerated from these salts and allowed to react with nitrous acid to give a mixture of a hydrocarbon and a partially inverted alcohol. The hydrocarbon was probably $\Delta^{1,2}$-9-methyloctalin and was not further studied. The conversion to the alcohols seemed to involve partial inversion at C_1, since the mixtures obtained from the d- and l-amines could not be brought to equal and opposite rotation. However since oxidation of the mixture gave quite pure d- and 1-9-methyl decalone, this indicated that the Walden inversion was confirmed to C_1.

These facts are in agreement with Hueckel's observations that in compounds of this type partial inversion occurs, although he was unsuccessful in isolating the alcohol. Further evidence is found here that the compound is cis and not trans, since in trans compounds of this type Hueckel showed that no inversion occurs.

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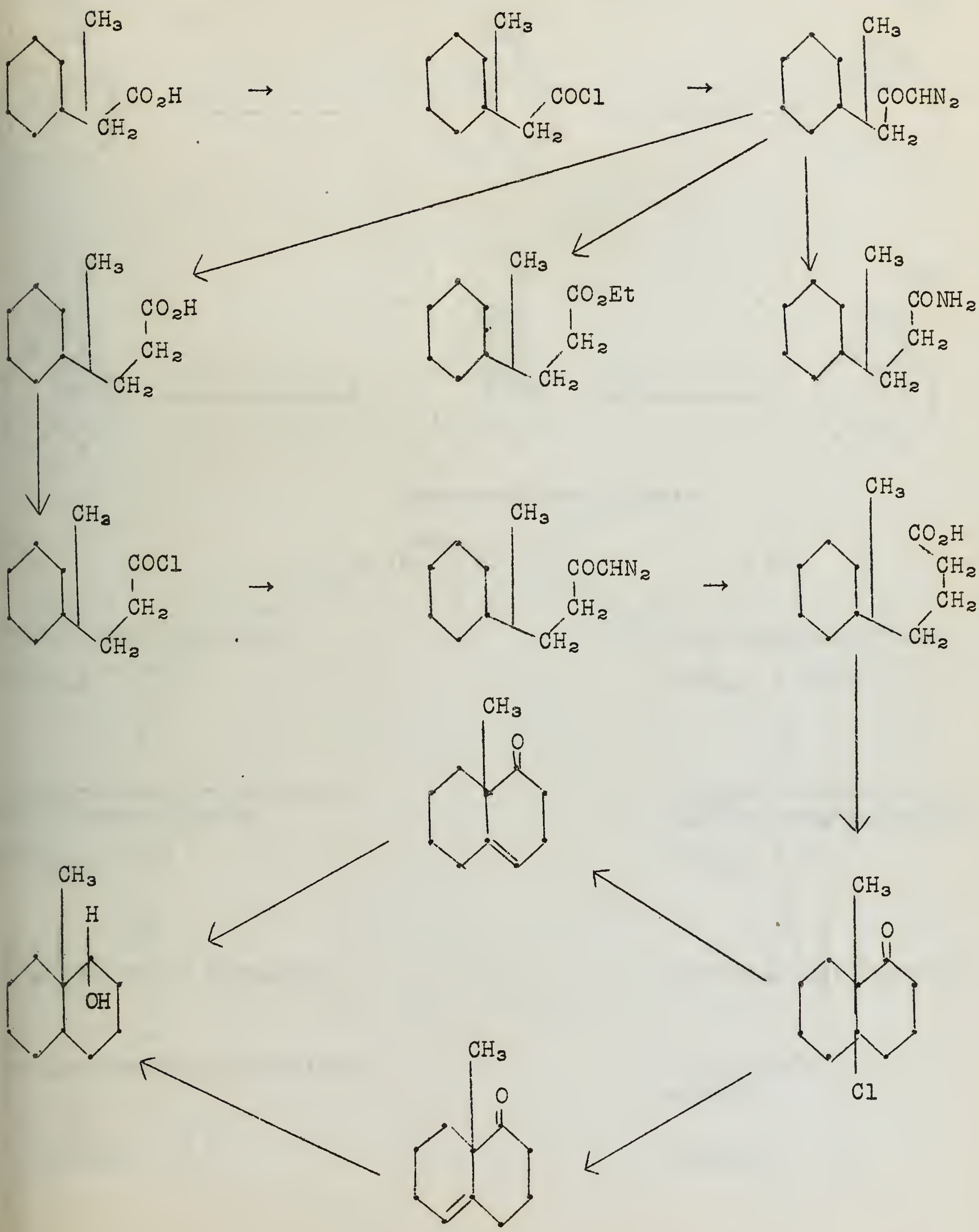
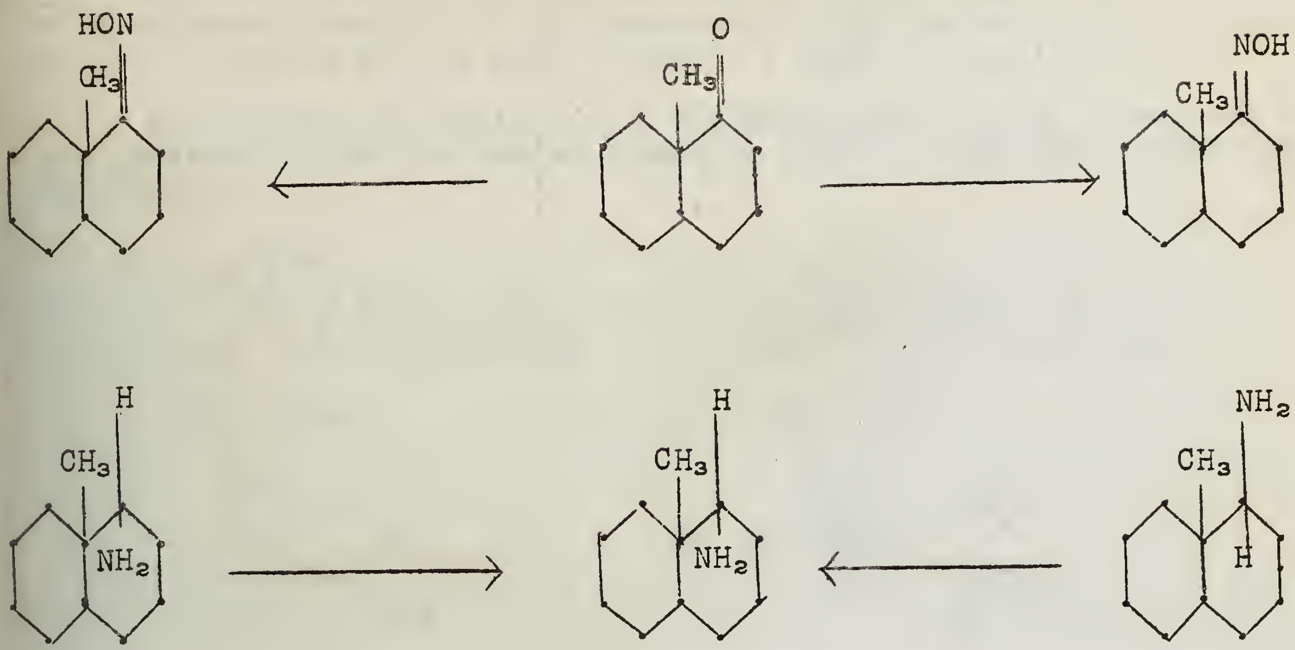
Reported by J. D. Garber
October 29, 1941

FLOW SHEET A


CH₃
CO₂H
CH₂
CH₃
COCl
CH₂
CH₃
COCHN₂
CH₂
CH₃
CO₂H
CH₂
CH₂
CH₃
CO₂Et
CH₂
CH₂
CH₃
CONH₂
CH₂
CH₂
CH₃
COCl
CH₂
CH₂
CH₃
COCHN₂
CH₂
CH₂
CH₃
CO₂H
CH₂
CH₂
CH₂
CH₃
O
CH₃
H
OH
CH₃
O
Cl
CH₃
O

FLOW SHEET B



Bromocamphorsulfonate

$[\alpha_D]_{H_2O}$ + 73°

↙ ↘

Bromocamphorsulfonate

$[\alpha_D]_{H_2O}$ + 59.2°

↓

(-)<u>cis</u>-9-Methyl-1-decalylamine hydrochloride

$[\alpha_D]_{H_2O}$ - 6.9°

↓

Stereoisomeric decalols

↓

(-)<u>cis</u>-9-Methyl-1-decalone

$[\alpha_D]_{EtOH}$ - 3.9°

Bromocamphorsulfonate

$[\alpha_D]_{H_2O}$ + 68.8°

↓

(+)<u>cis</u>-9-Methyl-1-decalylamine hydrochloride

$[\alpha_D]_{H_2O}$ + 7.0°

↓

Stereoisomeric decalols

↓

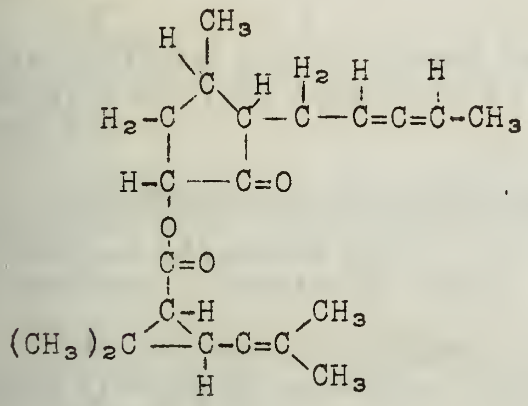
(+)<u>cis</u>-9-Methyl-1-decalone

$[\alpha_D]_{EtOH}$ + 4.2°

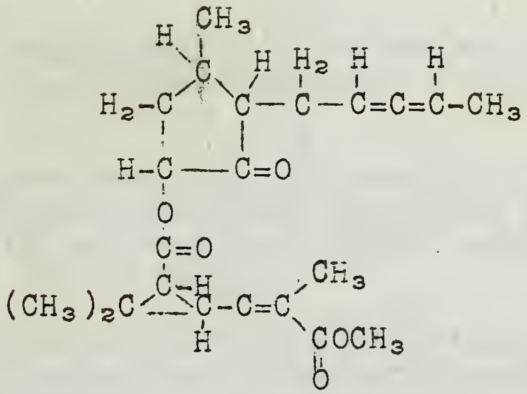
STRUCTURES OF PYRETHRINS I AND II

Pyrethrins I and II are the active insecticidal constituents of Pyrethrum flowers. It is important to determine their structures so that attempts may be made to produce them synthetically.

Staudinger and Ruzicka did the first work on the structure of the pyrethrins and arrived at formulas I and II for the respective pyrethrins:



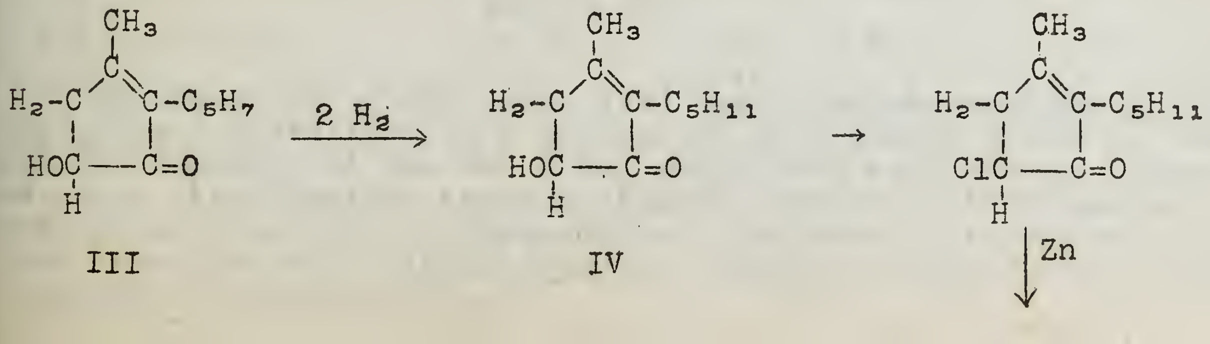
I



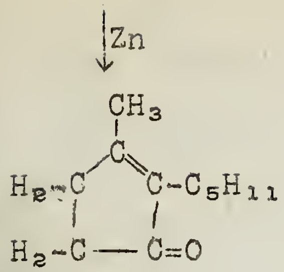
II

Structure of the Acid Components.--Staudinger and Ruzicka on saponification of pyrethrin extracts were able to isolate but one alcohol which they called pyrethrolone and two acids which they named chrysanthemum monocarboxylic acid and chrysanthemum dicarboxylic acid corresponding to the acid portions of I and II. Some chrysanthemum dicarboxylic acid monomethyl ester was also separated, which indicates which -COOH group is attached to the pyrethrolone nucleus. Ozonolysis of chrysanthemum monocarboxylic acid yielded acetone and l-trans-caronic acid; ozonolysis of chrysanthemum dicarboxylic acid yielded l-trans-caronic acid and pyruvic acid, thus establishing the structures of the acids as shown in I and II. LaForge and Haller discovered a third acid constituent whose formula is $C_{16}H_{30}O_2$ but have not identified it.

Structure of the Pentenolone Nucleus.--The results of Staudinger and Ruzicka indicated the structure shown in I and II for the cyclopentanolone nucleus. LaForge and Haller showed that the analyses of pyrethrolone, tetrahydropyrethrolone, and their semicarbazones indicated two less H atoms than represented by their empirical formulas. They reduced pyrethrolone (III) to tetrahydropyrethrone (V):



III IV

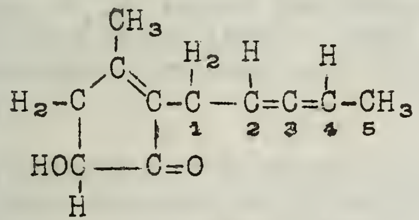


V

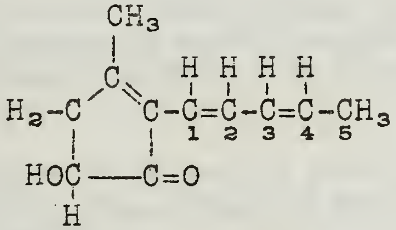
Mixed melting points showed the semicarbazone of tetrahydropyrethrone (V) to be identical to that of dihydrojasmone of known structure V.

Structure of the Sidechain.--Studies of the structure of the sidechain have attracted considerable attention, for if it has the structure indicated by VI, it will be the first natural product known to contain a cumulated system of double bonds.

Staudinger and Ruzicka postulated structure VI in the sidechain from their studies. Later Ruzicka and Pfieffer abandoned VI in favor of VII.



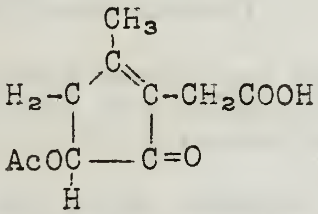
VI



VII

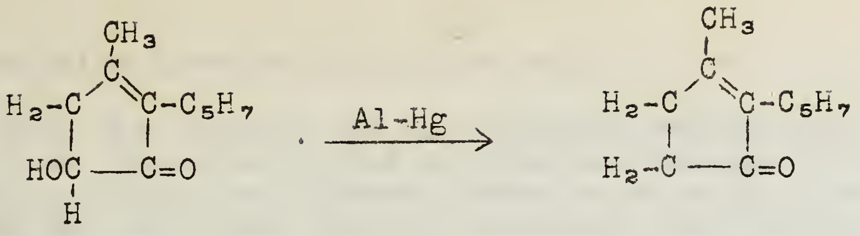
LaForge and Haller's early work was evidence against a conjugated system but did not allow a definite choice.

Ozonolysis yielded acetaldehyde, establishing the position of the 3,4-double bond. Further oxidation with hydrogen peroxide yielded malonic acid which is evidence for the cumulated system. Only in one instance was an acid of probable structure VIII isolated in small yield from the ozonolysis.



VIII

Treatment of pyrethrolone (VI) with aluminum amalgam should have given 1,4-addition if a conjugated system were present. Subsequent reduction of the -OH group would have resulted in jasmone. Reduction with aluminum amalgam yielded pyrethrone (IX) however. Pyrethrone on catalytic hydrogenation furnished a tetrahydro derivative identical with dihydrojasmone. (Nuclear double bond is very resistant to hydrogenation.)



VI IX

Pyrethrolone and pyrethrone do not form characteristic products with maleic anhydride or α-naphthoquinone.

Pyrethrone absorbed one mole bromine readily in an indifferent organic solvent. If 1,4-addition had occurred, the product should have yielded jasmone when reduced with zinc in acetic acid, but the original pyrethrone resulted. Evidently bromine added on adjacent carbon atoms and no choice could be made.

Addition of one mole of bromine in ethanol solution yielded a monobromo compound plus nearly one mole of hydrogen bromide. Consequently the bromine reaction was considered as one of substitution. Addition of two moles of bromine gave a dibromo compound plus nearly two moles of hydrogen bromide. Both bromo derivatives gave pyrethrone when reduced with zinc. Only the sidechains are involved in that tetrahydropyrethrolone and tetrahydropyrethrone do not decolorize bromine.

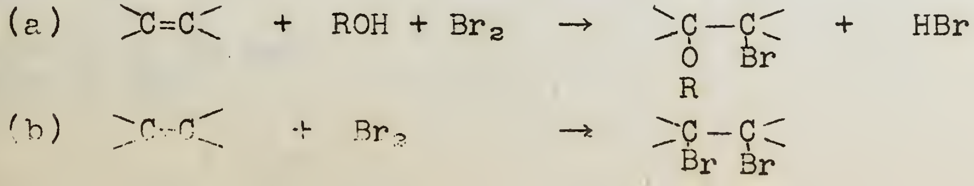
Pyrethrone was heated with sodium in a sealed tube and the product was treated with carbon dioxide resulting in the formation of an acid. This is typical of $>C=C=CHCH_3$.

No conclusion can be reached from the above results except that no such behavior has been noted with a conjugated system. The literature furnishes no clues of the behavior of cumulated systems toward halogens except that allene is stated to add four atoms of bromine to give an unstable tetrabromide. Therefore, Acree and LaForge prepared 1-phenyl-1,2-butadiene, 1-cyclohexyl-2,3-pentadiene, and 2,3-pentadiene to compare their reactions with halogens with those of pyrethrone and pyrethrolone.

The above allenes did not react with maleic anhydride or α-naphthoquinone (cf. pyrethrone above).

All three of the allenes mentioned gave dibromo and dichloro addition products with bromine and chlorine in indifferent organic solvents in the cold as did both pyrethrolone and pyrethrone.

Conant and Jackson and later Jackson and coworkers have reported that certain compounds with ethylenic linkage yield methoxybromo derivatives (a) as well as the normal dibromo derivatives (b) when treated with bromine in methyl alcohol.



$$(a)\quad >C=C< \; + \; ROH + Br_2 \; \rightarrow \; >\underset{\underset{R}{O}}{C}-\underset{Br}{C}< \; + \; HBr$$

$$(b)\quad >C=C< \; + \; Br_2 \; \rightarrow \; >\underset{Br}{C}-\underset{Br}{C}<$$

Both reactions proceed at a slow rate.

Both the dibromo and the methoxybromo products were formed when each of the above mentioned allenes was treated with bromine in methanol. Liberated hydrogen bromide amounted to 60-70% equivalent, showing that reaction (a) predominates. In contrast to ethylenic compounds, the allenes reacted instantly in the cold. Pyrethrone reacted analogously in methanol to give a methoxybromo and a dibromo derivative. Titration of liberated hydrogen bromide (60-70% equivalent) and methoxyl and bromine determinations showed that reaction (a) predominated. Reduction of the mixture of methoxybromo and dibromo products with zinc regenerated pyrethrone in excess of the amount expected from the dibromo derivative present. Evidently zinc gives an analogous reaction with the alkoxybromo compound. Analogy for this reaction is found in an article by Dykstra, Lewis and Boord who reported that α,β-alkoxybromo compounds are readily dehalogenated by zinc to form a double bond between the carbon atoms that carried the substituents.

All the above reactions of allenes and pyrethrone are compatible and the cumulated system of double bonds seems the most likely arrangement in the sidechain.

LaForge and Acree have reported the reactions of allenes with lead tetraacetate but have not reported comparable reactions for pyrethrone yet.

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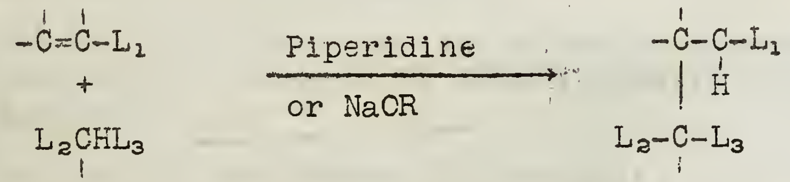
Reported by D. W. Hein
November 5, 1941

THE MICHAEL CONDENSATION: SOME RECENT INVESTIGATIONS

Connor, et al. University of Pennsylvania

The Michael condensation may be generally represented by the equation



$$\begin{array}{c} -\overset{|}{C}=\overset{|}{C}-L_1 \\ + \\ \underset{|}{L_2CHL_3} \end{array} \xrightarrow[\text{or NaCR}]{\text{Piperidine}} \begin{array}{l} -\overset{|}{C}-\underset{H}{\overset{|}{C}}-L_1 \\ \;\;| \\ L_2-\underset{|}{C}-L_3 \end{array}$$

in which L_1, L_2, and L_3 are labilizing groups. Examples have been reported in which L_1 is $-COOR$, $-COR$, $-CN$, $-CONH_2$, $-NO_2$, $-SO_2R$, and in which L_2, L_3, or both, are $-COOR$, $-COR$, $-CN$, $-CONH_2$, $-NO_2$, $-SO_2R$, $-CHO$. The acceptor may be acetylenic rather than olefinic, or it may be a quinone. Either the acceptor or addendum may be vinylogs of these structures.

Influence of Experimental Conditions and the Structure of the Acceptor on the Condensation

Connor's work has shown that secondary amines, for instance, piperidine, are the safest catalysts; they seldom cause any reaction other than normal condensation. However, amines often fail to bring about reactions that occur in the presence of NaOR, and the rate is so slow, even in favorable cases, that a long reflux is necessary. One-sixth to one-third of an equivalent of NaOR may bring about condensation when amines do not; the use of one equivalent of NaOR is most likely to cause condensation, as well as side reactions. With sodium alkoxides as catalysts, the best results are obtained by permitting the reaction mixture to stand at room temperature for twenty to one hundred and fifty hours. Higher temperatures may give lower yields, probably because side reactions and retrogression are favored.

Nature of L_1

Arrangement of groups in order of activation of double bond is not generally possible but unsaturated ketone > corresponding ester > nitrile. Examples in Table I.

TABLE I

	Acceptor	Addendum	% Yield	Conditions
1.	$\phi CH=CHCO\phi$	ϕCH_2COOEt	90	A, C
2.	$\phi CH=CHCOOEt$	ϕCH_2COOEt	0	A
3.	$\phi CH=CHCOOEt$	ϕCH_2COOEt	85	C
4.	$\phi CH=CHCN$	ϕCH_2COOEt	0	C
5.	$\underline{p}-O_2NC_6H_4CH=CHCO\phi$	$CH_2(COOEt)_2$	90	A
6.	$\underline{p}-O_2NC_6H_4CH=CHCOOEt$	$CH_2(COOEt)_2$	0	A

Conditions

A. Piperidine catalyst, long reflux
B. Small amount of sodium alkoxide, stand at room temperature
C. Equivalent amount of sodium alkoxide, hot.

Substitution on α and β atoms

(1) Reactivity of acceptor decreases as hydrogens are replaced.
(2) Reactivity decreased if substituent is alkyl, aryl, carbethoxyl or acyl.

Typical results are shown in Table II.

TABLE II

Acceptor	Addendum	% Yield	Conditions
1. ØCH=CHCOØ	$ØCH_2COOEt$	90	B, C
2. ØCH=C(COOEt)COØ	$ØCH_2COOEt$	0	C
3. ØCH=CHCOOEt	$ØCH_2COOEt$	85	C
4. ØCH=C(Ø)COOEt	$ØCH_2COOEt$	0	C
5. $CH_3CH=CHCOOEt$	$Ø CH_2COOEt$	90	C
6. $CH_3CH=C(CH_3)COOEt$	$ØCH_2COOEt$	40	C
7. $(CH_3)_2C=CHCOOEt$	$ØCH_2COOEt$	20	C

Remote Substitution

Groups not directly attached to the double bond of acceptor may have greater effect than would be expected (Cf. Table III).

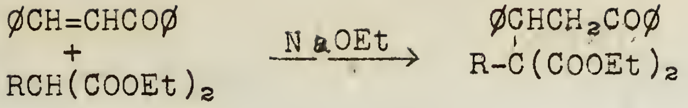
TABLE III

Acceptor	Addendum	% Yield	Conditions
o-$O_2NC_6H_4CH=CHCOOMe$	$CH_2(COOMe)_2$	70	B
m-$O_2NC_6H_4CH=CHCOOMe$	$CH_2(COOMe)_2$	95	B
p-$O_2NC_6H_4CH=CHCOOMe$	$CH_2(COOMe)_2$	0	B
ØCH=CHCO Mes	$CH_2(COOMe)_2$	70	B

Instability of some Addition Products

In some cases, there is an unusual difference in reactivity between a substituted active methylene compound and the next higher homolog.

[illegible]

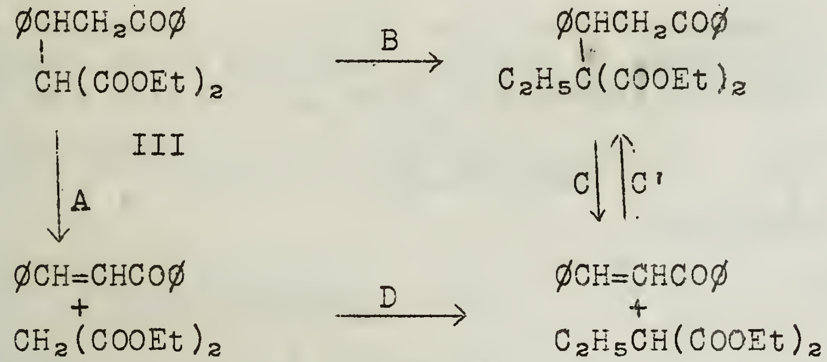


$$\phi CH{=}CHCO\phi + RCH(COOEt)_2 \xrightarrow{NaOEt} \underset{R-C(COOEt)_2}{\phi CHCH_2CO\phi}$$

I R = CH_3- 80%

II R = C_2H_5 0%

If the difference is due to spacial interference, II, once prepared, would be expected to be stable. An addition product of a Michael condensation was alkylated, as a possible synthesis of II.



$$\begin{tikzcd}
\underset{CH(COOEt)_2}{\phi CHCH_2CO\phi} \text{ III} \arrow[r, "B"] \arrow[d, "A"] & \underset{C_2H_5C(COOEt)_2}{\phi CHCH_2CO\phi} \text{ II} \arrow[d, shift right, "C"'] \\
\phi CH{=}CHCO\phi + CH_2(COOEt)_2 \arrow[r, "D"] & \phi CH{=}CHCO\phi + C_2H_5CH(COOEt)_2 \arrow[u, shift right, "C'"']
\end{tikzcd}$$

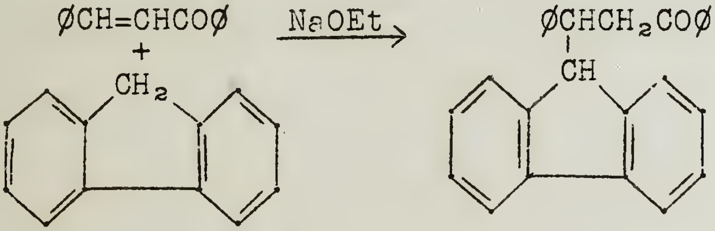
None of compound II was isolated even at -78°. Steric hindrance is improbable when one considers the results of Connor and Andrews obtained by the reaction of the sodium derivative of ethyl ethylmalonate with benzalacetophenone to give ethyl α-ethylcinnamate and ethyl benzoylacetate which must be the results of a Michael condensation.

Thus the data indicate that the expected product is so readily cleaved by NaOR that isolation is impossible and steric hindrance does not prevent reaction.

Activation of the Methylene Group by Carbon-Carbon Unsaturation

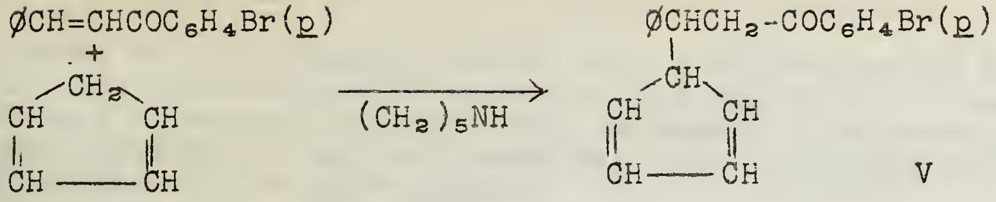
The possibility of L_2 and L_3 both being aromatic or olefinic was investigated by Connor. The reactivities of fluorene, cyclopentadiene and 1,4-pentadiene were studied.

Fluorene reacted with benzalacetophenone, benzal-p-bromoacetophenone, and benzalacetone in the presence of one equivalent of sodium ethoxide (yields 2-27%). No reaction occurred with α,β-unsaturated esters or m- or p-nitrobenzalacetophenone.



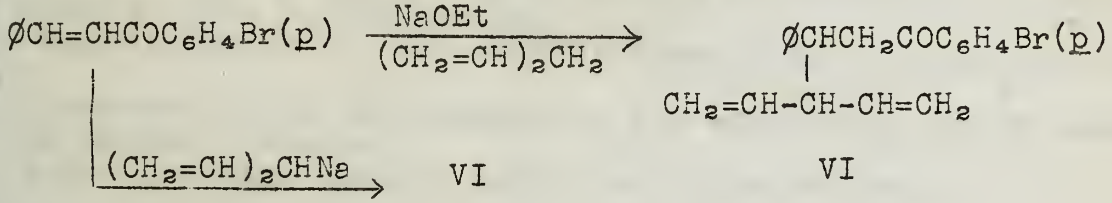
IV

Cyclopentadiene reacted with α,β-unsaturated ketones when piperidine was used as a catalyst. This indicates that it is a highly reactive compound. The reaction was carried out under pressure to prevent the loss of the hydrocarbon (yields 25-30%).



V

Pentadiene-1,4 reacted with benzal p-bromoacetophenone in the presence of an equivalent amount of sodium ethoxide. The same compound was obtained by using the sodium derivative of the diene.



VI

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Reported by R. E. Foster
November 5, 1941

REACTION OF ALKYL BENZOATES WITH SODIUM ALKOXIDES

McElvain, et al, University of Wisconsin

A study of the products formed when alkyl benzoates are heated with the corresponding sodium alkoxide led McElvain at Wisconsin to suggest that a reverse Tischtschenko occurred. The benzaldehyde and aliphatic aldehyde or ketone formed may then take part in one or several of the following reactions:

1. Forward Tischtschenko
2. Mixed aldol condensations followed by loss of CO to give alkyl phenyl carbinols which in turn give ketones.
3. Further condensation of the ketone, as acetophenone, with unreacted ester to give 1,3-diketones.
4. Saponification of the ester by water formed in various condensations.
5. Condensation of the alcohol or its ester with sodium alkoxide through the Guerbet reaction.
6. Acyl exchanges between esters and 1,3-diketones.

Adickes had treated ethyl benzoate with sodium ethylate and obtained not only more sodium benzoate than expected but also a 20 per cent yield of dibenzoylmethane. McElvain found that heating 4 moles of the ester with one mole of the alkoxide at 175-180° for two hours gave a maximum yield, 40%, of dibenzoylmethane from ethyl benzoates. These conditions were then employed for treating the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and neopentyl esters. Table I is a summary of most of the results.

The formation of benzylbenzoate as a common product is cited as evidence that although the reactions are apparently quite different they may follow a common initial course, a reverse Tischtschenko, and the benzaldehyde formed could then give benzylbenzoate by a forward Tischtschenko. Reverse Tischtschenkos with neopentyl benzoate and isobutyl benzoate would give trimethylacetaldehyde and isobutyraldehyde. These aliphatic aldehydes have either none or only one alpha hydrogen and might give esters by forward Tischtschenko reactions. Neopentyl trimethylacetate was found in good yield and enough isobutyl isobutyrate was formed to indicate that isobutyraldehyde might have functioned in a forward Tischtschenko.

If ethyl and propyl benzoates took part in a reverse Tischtschenko reaction the resulting aliphatic aldehydes would be capable of entering into aldol condensations with the benzaldehyde. The following mechanism is proposed to explain the origin of a 40 per cent yield of dibenzoylmethane from ethyl benzoates.

$$C_6H_5COOC_2H_5 \rightarrow C_6H_5CHO + CH_3CHO$$

$$C_6H_5CHO + CH_3CHO \rightarrow C_6H_5CHOHCH_2CHO \xrightarrow{-CO} C_6H_5CHOHCH_3$$

$$C_6H_5CHOHCH_3 \xrightarrow{-2H} C_6H_5COCH_3$$

In a similar manner propiophenone would be formed from propyl benzoate.

[illegible] WITH SODIUM ALCOHOLATES

[illegible], et al., University of [illegible]

A study of the [illegible] with the corresponding sodium alcoholate and [illegible]. The [illegible]

[illegible]

1. [illegible]
2. [illegible]
3. Further condensation of [illegible]
4. [illegible]
5. Condensation of [illegible] alcoholate [illegible]
6. [illegible]

[illegible]

The [illegible]

If [illegible]

[illegible]

[illegible]

[illegible]

In a similar [illegible]

Dibenzoylmethane, produced by the ethyl ester, could have been formed by a Claisen condensation.

$$C_6H_5COCH_3 + C_6H_5COOC_2H_5 \xrightarrow{NaOC_2H_5} (C_6H_5CO)_2CH_2$$

It is recognized that the loss of carbon monoxide by an alpha hydroxyaldehyde is without precedent in the literature. Those esters giving high yields of the carbinol also gave high yields of carbon monoxide. Trimethylacetaldehyde formed in the neopentyl benzoate reaction could not give an aldol condensation to form an alpha hydroxyaldehyde and this reaction did not liberate carbon monoxide.

The results from isopropyl benzoate are of particular interest because the acyl exchange reaction suggested proved to be of considerable importance when studied further.

$$C_6H_5COOCH(CH_3)_2 \xrightarrow{NaOCH(CH_3)_2} C_6H_5CHO + (CH_3)_2CO$$

$$C_6H_5COOCH(CH_3)_2 \xrightarrow{Claisen} C_6H_5COOCH_2COCH_3$$

$$C_6H_5COCH_2COCH_3 \xrightarrow{Acyl\ Exchange} (C_6H_5CO)_2CH_2 + CH_3COOCH(CH_3)_2$$

The presence of 2-methyl-1-pentanol among the reaction products of the *n*-propyl ester and of 2-ethyl-1-hexanol from the *n*-butyl ester can be explained as being formed by the Guerbet reaction.

Acyl Exchanges Between Esters with 1,3-Diketones and Esters with β-Keto Esters

The acyl exchange reaction mentioned above was investigated in more detail. If the reaction proposed is correct it should be possible to prepare 1,3-diketones and β-keto esters by such reactions as follows:

(1) $C_6H_5COCH_2COCH_3 + C_6H_5COOC_2H_5 \rightarrow C_6H_5COOCH_2COC_6H_5 + CH_3COOC_2H_5$

(2) $CH_3COCH_2COOC_2H_5 + C_6H_5COOC_2H_5 \rightarrow C_6H_5COCH_2COOC_2H_5 + CH_3COOC_2H_5$

Attempts to obtain the exchange products by heating at 130-160° with sodium ethoxide caused the ester, e.g. ethyl benzoate, to take part in the reverse Tischtschenko and subsequent reactions to such an extent that the acyl exchange was obscured. When the less basic sodium enolates of the 1,3-diketone or β-keto ester were employed good results were obtained. The sodium enolates were heated with a sufficient excess of the ethyl ester to form a homogeneous reaction mixture. The temperature employed was sufficiently high to permit the ethyl acetate formed to be removed by distillation. Results of the exchange are shown in Tables II and III.

In Table II it is to be noted that there are good yields and correlations between yields in runs 1,4, and 5 where the acetyl group is replaced by benzoyl and α-furyl. Since *p*-chlorobenzoyl did not replace benzoyl in run 7 it is believed that the *d*-*p*-chlorobenzoylmethane formed in run 2 (see footnote a) was formed by the reverse Tischtschenko and subsequent reactions.

The yield obtained in run 1 of Table III suggests a useful method of preparing acylacetic esters **provided** the esters employed have a [illegible] compared to the ethyl esters [illegible] in a Claisen condensation.

[illegible] $\xrightarrow{\text{[illegible]}}$ [illegible]

It is recognized that [illegible]

The results from [illegible]

[illegible] $\xrightarrow{\text{[illegible]}}$ [illegible]

[illegible] $\xrightarrow{\text{[illegible]}}$ [illegible]

[illegible] $\xrightarrow{\text{[illegible]}}$ [illegible]

The presence of [illegible]

[illegible]

The [illegible]

[illegible]) [illegible]

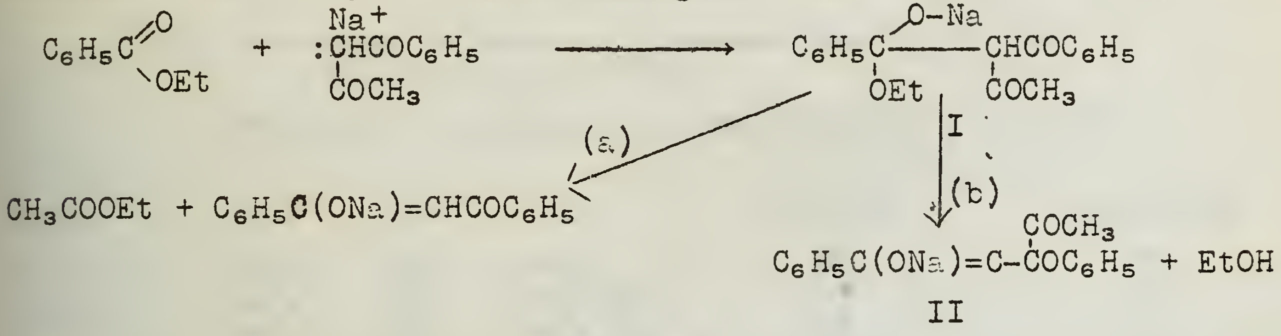
[illegible]) [illegible]

Attempts to obtain [illegible] Table II and III.

In Table II it is to be noted that [illegible]

The yield obtained in run 1 of Table III suggests a useful method [illegible] boiling point sufficiently high to permit the ethyl acetate formed to distil from the reaction mixture.

A mechanism is proposed for this exchange which accounts not only for the acyl exchange but also explains the origin of considerable alcohol which always distilled along with the volatile ester.



Intermediate I formed through a carbanion mechanism could decompose by path (a) to give the acyl exchange product II or by path (b) to give ethyl alcohol. Evidence is lacking for the formation of a triacyl methane, II, but it may have been hydrolyzed into a diacyl compound and an acid. Acids roughly equivalent to the alcohol distilled were separated from the mixture.

Under somewhat different conditions ethyl isobutyrate and ethyl benzoyldimethylacetate form ethyl benzoate and ethyl isobutyrylisobutyrate. The net result is an acyl exchange. This reaction proceeds in the presence of sodium ethoxide and triphenylmethane at ordinary temperature and is explained by Hauser as a series of forward and reverse acetoacetic ester condensations.

TABLE I

Ratio of Moles Product to Moles Unrecovered Ester for the Reaction of Four Moles of $C_6H_5CO_2R$ with One Mole of RONa at 175-180°

R-	Ethyl	Propyl	Iso-Propyl	n-Butyl	Isobutyl	Neopentyl
Unrecovered Ester, Moles	2.10	2.60	1.75	3.08	3.00	2.10
Benzoic Acid	.26	.35	.34	.87	.34	.41
ROH	.08	.60	1.00	.41	.47	.40
1,3-Diketone	.19	....	.09[a] .05[b]	....	...	...
Esters from Tischtschenko Reaction	.07[c]	Trace[c]	.06[c]	.013[c]	.05[c] .10[d]	.07[c] .06[e] .46[f]
$RCHOHC_6H_5$	...	.08 .12[g]	...	.11 .13[g]	.06 .09[g]	...
CO	.27	.41	...	.34	...	...
Guerbet Products	...	.015 .09[g]	...	.03 .08[g]	...	...

Table I (Cont')

[a] $C_6H_5COCH_2COC_6H_5$
[b] $C_6H_5COCH_2COCH_3$
[c] Benzyl benzoate
[d] Isobutyl isobutyrate
[e] Benzyl trimethylacetate
[f] Neopentyl trimethylacetate
[g] Benzoic ester of

TABLE II

Acyl Exchange Between the Sodium Enolate of 1,3-Diketones and Esters

$$RCOCHNaCOR' + R''CO_2Et \longrightarrow RCOCHNaCOR'' + R'CO_2Et$$

Run	R	R'	R"	% yield of R'CO₂Et	% yield of RCOCH₂COR"
1	C_6H_5	CH_3	C_6H_5	49	48
2	C_6H_5	CH_3	p-C_6H_4Cl	33[a]	b
3	C_6H_5	CH_3	$C_6H_5CH_2$	43	b
4	C_6H_5	CH_3	C_4H_3O (α-Furyl)	51	47
5	CH_3	CH_3	C_4H_3O	72	32[c]
6	C_6H_5	C_6H_5	CH_3	0	0
7	C_6H_5	C_6H_5	p-C_6H_4Cl	0	0

(a) a 40% yield of ethyl benzoate was also obtained
(b) a mixture of $C_6H_5COCH_2COC_6H_4Cl$ and $Cl\text{-}C_6H_4COCH_2COC_6H_4\text{-}Cl$ was obtained. Yield not given.

TABLE III

Acyl Exchange between the Sodium Enolate of β-Keto-Esters and Esters.

$$RCOCR'NaCO_2Et + R''CO_2Et \longrightarrow R''COCR'NaCO_2Et + RCO_2Et$$

Run	R	R'	R"	% yield of R'CO₂Et	% yield of R"COCHR'CO₂Et
1	CH_3	H	C_6H_5	56	49
2	CH_3	C_2H_5	C_6H_5	10[a]	61[b]
3	$(CH_3)_2CH$	C_2H_5	C_6H_5	72	50
4	CH_3	H	C_4H_3O (α-Furyl)	66	38
5	CH_3	H	C_5H_4N (β-Pyridyl)	73	4[c]
6	C_2H_5O	H	C_6H_5	10	16

(a) yield of 10% ethyl acetate and 60% ethyl butyrate
(b) This product was ethyl benzoylacetate
(c) Main product was a non-distillable tar.

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Reported by G. L. Schertz
November 12, 1941

THE STRUCTURE OF LIGNIN

Hibbert - McGill
Braun- Inst. of Paper Chemistry
Freudenberg - Heidelberg
Adkins - Wisconsin

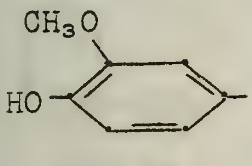
Lignin is a constituent of the woody portion of plants. Besides 50-55% of cellulose, wood contains 25-30% of lignin, 15-20% of sugars and other low molecular weight carbohydrates, and a few per cent of resins, fats, and proteins. Since wood contains so much lignin, the structure and properties of lignin have been studied extensively by the paper industry, both with a view to finding more efficient ways of separating it from cellulose and to discover uses for it after it is removed.

Lignin is not readily separated from the other wood constituents, being chemically combined with the lower carbohydrates through ether or glycoside linkages, and the whole being intimately mixed with the cellulose. Rather drastic chemical methods are necessary, such as heating a number of hours with sodium bisulfite, alcoholic hydrogen chloride or various acids. Whatever method is used, there is little doubt but that the amorphous brown solid which is finally obtained differs from the lignin as it originally occurs in wood. Moreover, the nature of lignin varies quite a bit depending both on its source and its method of isolation. For these reasons and the fact that lignin is a highly complex substance, the lignin problem is a difficult and controversial one.

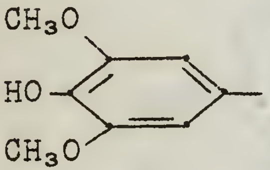
In spite of this, most authorities seem agreed as to the essential structure of lignin, differ though they may in some details. Just as a protein may be regarded as a condensation product of amino acids and a polysaccharide as a condensation product of monoses, so lignin is regarded as a condensation product of a number of closely related aromatic compounds. The units are believed to be derivatives of phenylpropane. Typical examples are:

I $RCOCHOHCH_3$ II $RCOCOCH_3$ III $RCH=CHCH_2OH$

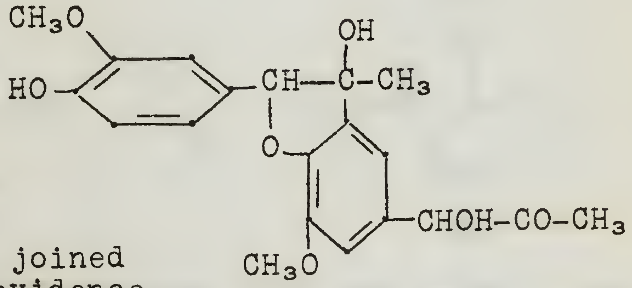
R is guaiacyl (IV) or syringyl (V)



IV



V



VI

These units are thought to be joined together as in VI. Most of the evidence indicates that this explanation is fundamentally correct and that lignin is comprised of structures such as VI and polymers of VI. Unpolymerized compounds like I, II, and III may also be present.

The proof of the above hypothesis rests upon analytical data and the general reactions of lignin as well as upon the products obtained by the degradation of lignin by caustic fusion, oxidation,

hydrogenation, sulfonation, and alcoholysis. Studies of known substances with structures similar to that assumed for lignin have also proved helpful.

Analytical Data and General Reactions

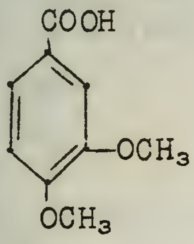
Lignin has a methoxyl content of around 16%. It has an hydroxyl content of about 10%. Color reactions and a certain acidity indicate the presence of phenol hydroxyl groups, but while dimethyl sulfate almost doubles the methoxyl content of the lignin, diazomethane increases it by only about 3%. This is taken to mean that most of the phenol hydroxyls of the guaiacyl and syringyl radicals are tied up in ether linkages as in VI.

Lignin can be chlorinated, brominated, nitrated, sulfonated, and mercurated in a way reminiscent of sensitive aromatic compounds. The absorption spectra of lignin sulfonic acid indicate an aromatic structure. A positive haloform reaction shows the presence of CH_3-CO- or CH_3-CHOH-.

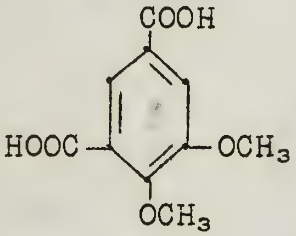
Brauns has isolated a lignin by merely soaking wood in alcohol for several days. On the basis of analytical data, he assigns it the formula $C_{42}H_{32}O_6(OCH_3)_4(OH)_4(CO)$ and says that it contains one phenol hydroxyl and an enolizable carbonyl group. This he believes is the fundamental building stone of lignin, an opinion not shared by Hibbert.

Degradation by Oxidation

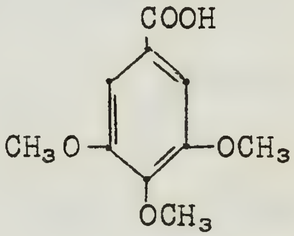
Methylation of phenol groups with diazomethane, treatment with alkali to break ether linkages, another methylation, and finally oxidation with permanganate, gives veratric acid VII, isohemipinic acid VIII, and trimethylgallic acid IX. The yields are very low, which is attributed to the fact that the acids themselves are not very resistant to permanganate. The isolation of isohemipinic acid is good evidence that the side chain of one phenylpropane unit has condensed with the benzene ring of another.



VII



VIII

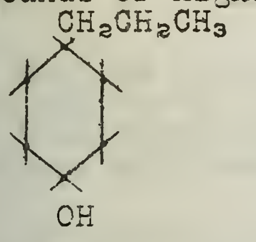


IX

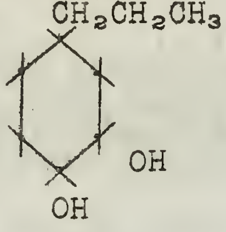
All three of these acids are obtained from hard wood lignin, but only veratric acid and isohemipinic acid are obtained from soft wood lignin. This is in line with other facts indicating that the guaiacyl radical IV is the only important radical in soft wood lignin, while both the guaiacyl radical and the syringyl radical V are important in hard wood lignin.

Degradation by Hydrogenation

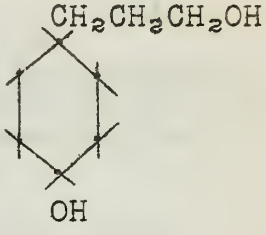
Adkins recently reduced lignin catalytically. His lignin was extracted by the relatively mild reagent methanol-dry hydrogen chloride. The lignin took up more hydrogen than a corresponding weight of benzene, and besides a large amount of methanol, a 40% yield of X, XI, and XII, all cyclohexylpropane derivatives, was obtained. Unidentified compounds of higher molecular weight were also found.



X



XI



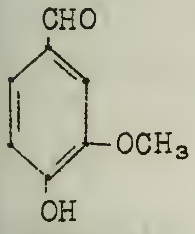
XII

When he hydrogenated lignin obtained industrially by the rather severe soda process, he isolated small amounts of X and XII plus some cyclohexanol, 4-methylcyclohexanol, and 4-ethylcyclohexanol. However, most of the products were alcohols and glycols related to polycyclic hydrocarbons with 20 to 70 or more carbon atoms in the molecule. None was identified. He concludes that lignin isolated by mild means is made up of phenylpropane units joined in chains, and that the soda process causes considerable cyclization, giving molecules very stable to hydrogenolysis. This is good evidence that lignin has a skeleton of many carbon atoms.

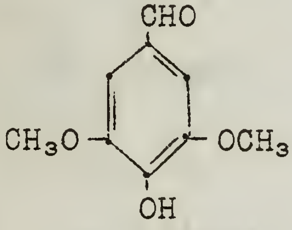
Degradation by Bisulfite and Alkali

Lignin sulfonic acid from the sulfite liquor of paper manufacture when treated with alkali in the presence of m-nitrobenzenesulfonic acid, gives as high as a 45% yield of vanillin, XIII, and syringic aldehyde, XIV. This process is actually being used commercially to prepare vanillin.

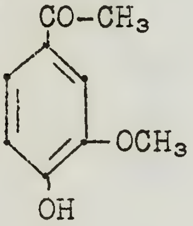
Small amounts of acetovanillone, XV, and acetosyringone, XVI, were also found.



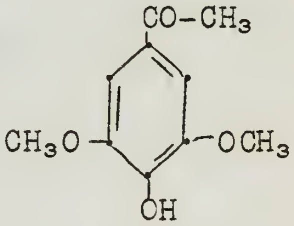
XIII



XIV



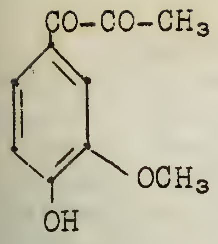
XV



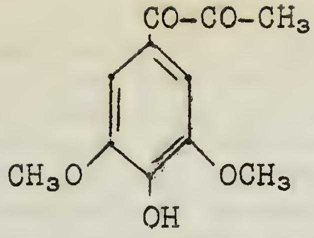
XVI

Degradation by alcoholysis

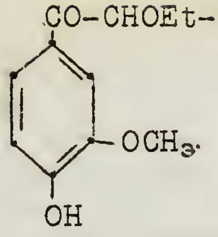
Refluxing wood with ethanolic hydrogen chloride, a relatively mild method of isolating lignin, gives a quantity of water soluble products, some of which have been identified recently by Hibbert as vanilloyl methyl ketone, XVII, syringoyl methyl ketone, XVIII, α-ethoxypropiovanillone, XIX, and α-ethoxypropiosyringone, XX.



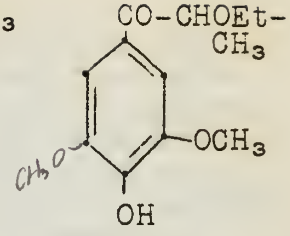
XVII



XVIII



XIX



XX

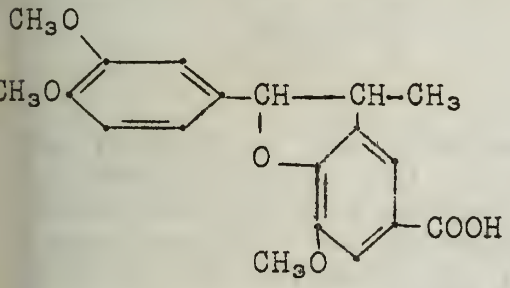
This is further proof that lignin is built up of phenylpropane units such as I, II, and III (this was originally postulated on somewhat theoretical grounds) and is the first good indication of the structure of the side chain of the phenylpropane units.

The ethoxy group in XIX and XX probably came from the ethyl alcohol with which the wood was refluxed.

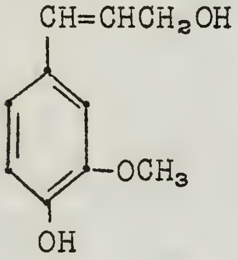
Studies of Lignin Models

The acid XXI has a structure very similar to that postulated for lignin. When heated with alkali, methylated, and then oxidized with permanganate, it gives the same products as does lignin under the same conditions (veratric acid, VII, and isohemipinic acid, VIII).

Coniferyl alcohol, XXII, which occurs in plants as the glucoside coniferin, is readily condensed by a trace of acid to an amorphous substance similar to lignin. Thus this substance gives the same oxidation products, reacts with bisulfite to give similar sulfonic acids, and has about the same composition. There seems to be a definite relationship between coniferin and lignin, but so little is known about the life processes of plants that it is hard to say just what it is. Likewise, although there is no lack of theories regarding the formation of lignin and its possible function in the plant, not much can be said with any degree of certainty.



XXI



XXII

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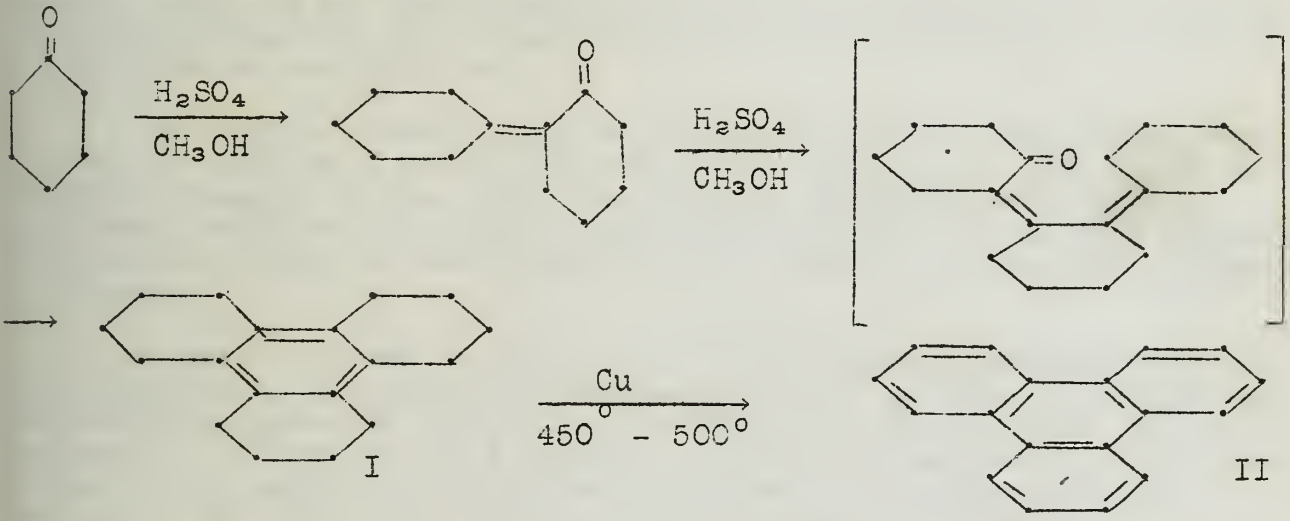
Hibbert, Paper Trade Journal, July 24, 1941.

Reported by B. McKusick
November 12, 1941

SYNTHESES IN THE TRIPHENYLENE SERIES

Until very recently little attention had been paid the triphenylene series, and few derivatives of triphenylene had been prepared. However, following the discovery of the carcinogenic properties of derivatives of 1,2-benzanthracene, an effort was made to prepare compounds in the triphenylene series isomeric with these. Several useful methods of synthesis have resulted. Moreover, patents have been issued within the past few years for several processes for the preparation of triphenylene derivatives suitable for use as dye intermediates. Thus, there is evidence of increasing interest in the chemistry of the triphenylene derivatives.

Triphenylene, the parent compound of the series, occurs to the extent of one to three per cent in the chrysene fraction of coal tar. The first useful synthesis of triphenylene was that developed by Mannich in 1907, although the formation of small amounts had previously been reported in the pyrolysis of benzene, and in treatment of bromobenzene with sodium. Mannich prepared it by heating cyclohexanone with a 30% solution of sulfuric acid in methanol. The reaction is apparently exactly analogous to that in which mesitylene is formed from acetone:



The product of the condensation, 1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrotriphenylene (I), is obtained in a yield of about 8%. By passing the vapors of this product in an atmosphere of carbon dioxide over a copper catalyst at 450-500°, Mannich dehydrogenated it almost quantitatively to triphenylene (II). Mannich assigned these compounds their correct structure on the basis of their oxidation to mellitic acid by fuming nitric acid in a sealed tube.

A modification of this method of preparation has recently been patented. Cyclohexanone or 1-cyclohexylidenecycylohexanone is condensed to the same dodecahydrotriphenylene by heating under pressure in the presence of a dehydration catalyst and a rare earth oxide.

Most of the recent work on the triphenylene series concerns the synthesis of derivatives by ring closure methods which could leave no doubt about the position of substituent groups. Compounds to be tested for carcinogenic activity must, of course, be of known

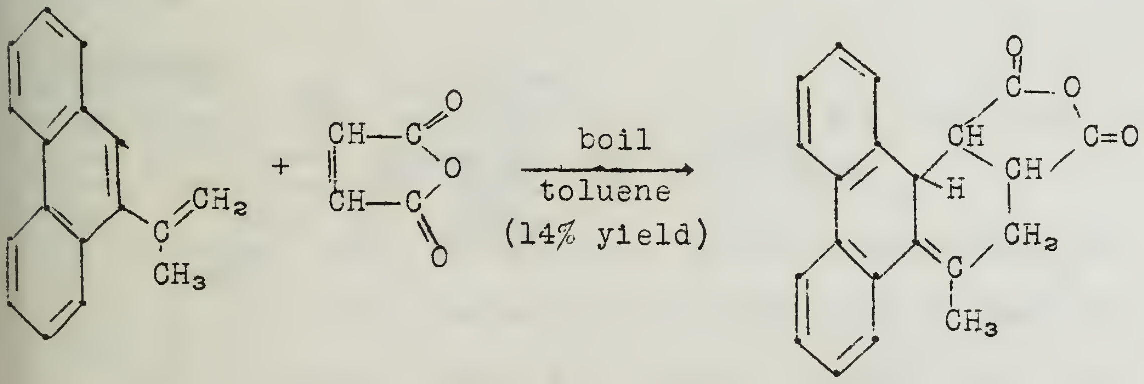
structure. Moreover, it was considered desirable to obtain reference compounds which could be used to determine the structures of new compounds in this series.

A few general methods have been developed for syntheses of this type. The first of these is that introduced by Bergmann and Blum-Bergmann, and subsequently extended and improved by Fieser and Joshel. Triphenylene, the 1- and 2-methyltriphenylenes, and 1,2-dimethyltriphenylene were prepared by the series of reactions shown in flow sheet A, starting with 9-bromophenanthrene. The percentages given under the arrows indicate the yields obtained.

Bachmann and Struve have prepared 1-methyltriphenylene by a similar series of reactions. Their synthesis, however, began with the preparation of β-[9-(1,2,3,4-tetrahydrophenanthroyl)] propionic acid by a Friedel-Crafts reaction between 1,2,3,4-tetrahydrophenanthrene and succinic anhydride. Phenanthrene itself could not be used, since, in the Friedel-Crafts it gives substitution mainly in the 3-position and to a lesser extent in the 2-position, not in the 9-position as desired here.

To prepare 1,4-dimethyltriphenylene, Fieser and Joshel were forced to adopt a different scheme after attempts to add the methyl Grignard reagent to the carbonyl group of β-(9-phenanthroyl) propionic acid and its methyl ester had failed. The method finally employed is shown in flow sheet B. It involves an unusual aldehyde synthesis.

A novel method of forming the triphenylene skeleton is that investigated by Bergmann and Bergmann. When various 9-vinylphenanthrenes were treated with maleic anhydride, a Diels-Alder reaction occurred. The necessary 1,3-diene system was furnished by the vinyl group of the side chain and the 9,10-bond of the phenanthrene nucleus. Examples are shown in the following equations:



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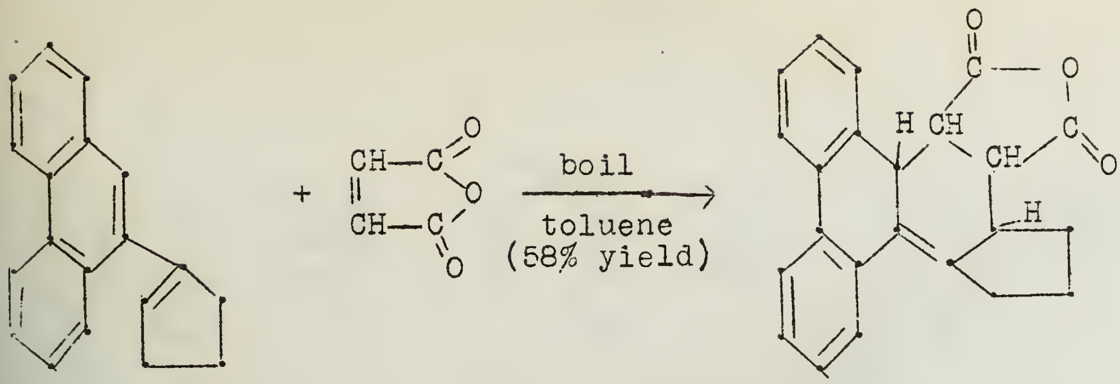

The most recent contribution to the field is the method worked out by Rapson. As in Mannich's original synthesis of triphenylene, the starting material was cyclohexanone. This was condensed to 1-cyclohexylidenecyclohexanone in almost quantitative yield when saturated with dry hydrogen chloride and allowed to stand. When this product is treated with arylmagnesiumbromides, carbinols result which can be cyclized to triphenylene derivatives. The equations in flow sheet C show the syntheses accomplished by Rapson using this procedure. Yields in the cyclization step seem to have been low in general, although they were not reported in all cases. This scheme, however, involves fewer steps than the other general methods, and gives more convenient access to some derivatives.

Within the last six years a number of processes for making derivatives in this series have appeared in patents. 2-Triphenylenesulfonic acid is made by the sulfonation of triphenylene in nitrobenzene solution. 2-Hydroxy-3-triphenylenecarboxylic acid is made by treating the alkali salt of 2-hydroxytriphenylene with carbon dioxide at high temperature and pressure. Various anilides of this acid are made by condensing it with substituted anilines such as the toluidines, the anisidines, and the chloroanilines. Triphenylenecarboxylic amides can be made directly by a Friedel-Crafts reaction between triphenylene and two moles of carbamic chloride. This method can be applied to other compounds having three or more condensed aromatic rings, or two benzene rings condensed with a heterocyclic ring. All of these products have been patented as dye intermediates.

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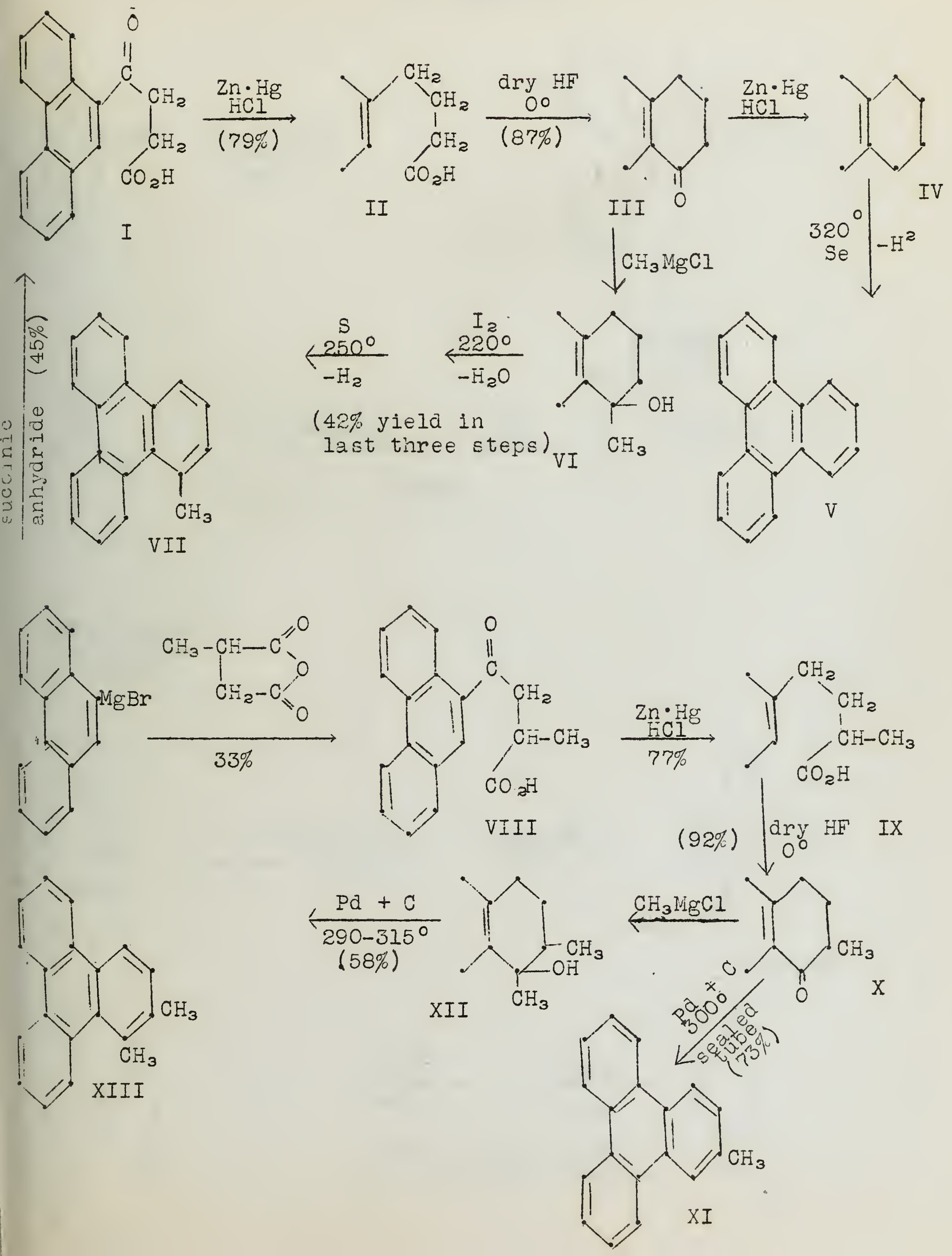
I.G. Farbenind, A.G., French Pat. 797,072 (1936); Chem. Abs., 30, 6389^7 (1936).

Reported by P. L. Southwick, November 19, 1941.

FLOW SHEET A


I
Zn·Hg
HCl
(79%)
II
dry HF
0°
(87%)
III
Zn·Hg
HCl
IV
320°
Se
-H2
V
CH3MgCl
VI
I2
220°
-H2O
S
250°
-H2
(42% yield in
last three steps)
VII
succinic
anhydride
(45%)
MgBr
33%
VIII
Zn·Hg
HCl
77%
IX
dry HF
0°
(92%)
X
Pd + C
300°
sealed
tube
(73%)
XI
CH3MgCl
XII
Pd + C
290-315°
(58%)
XIII

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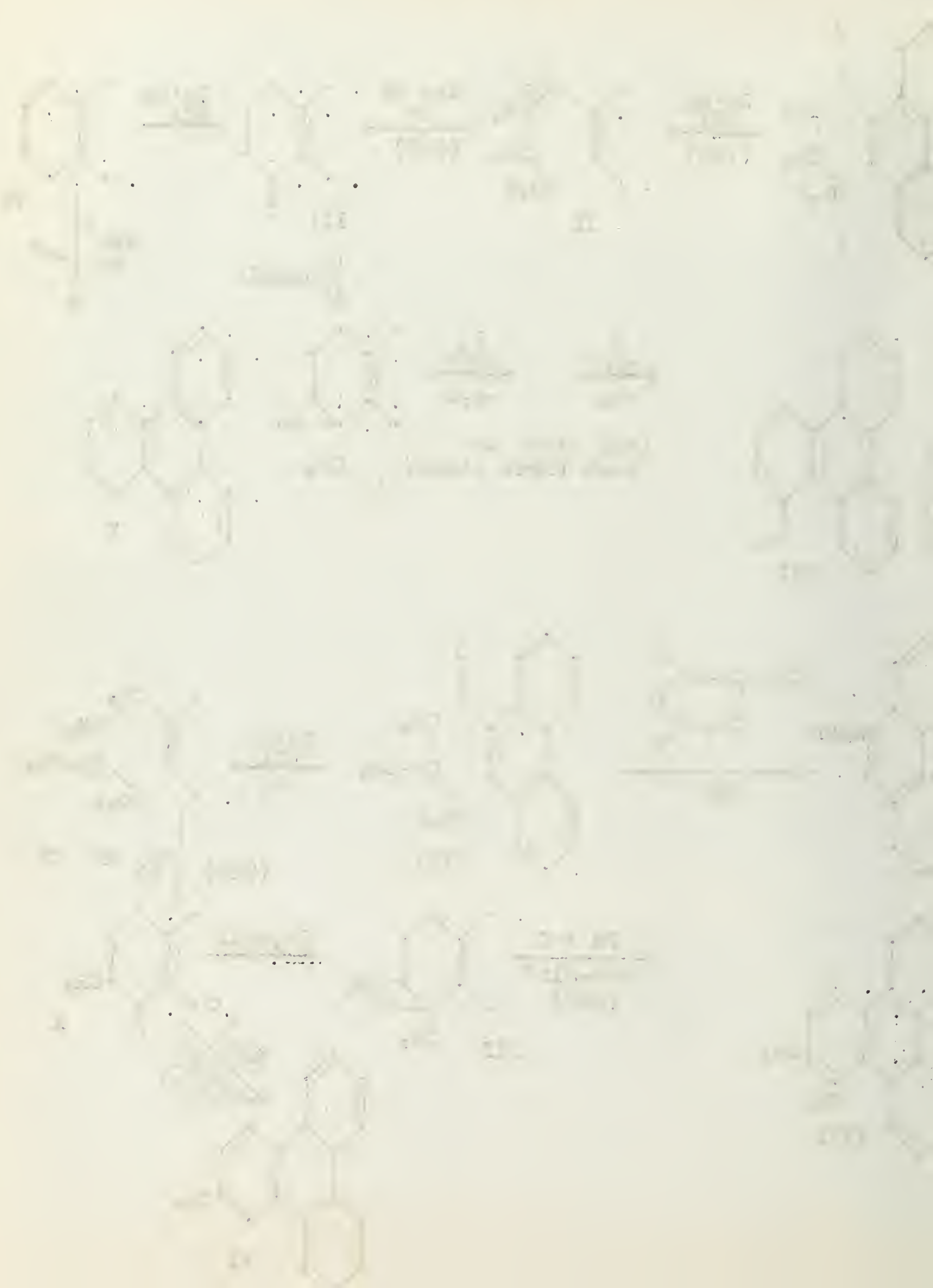
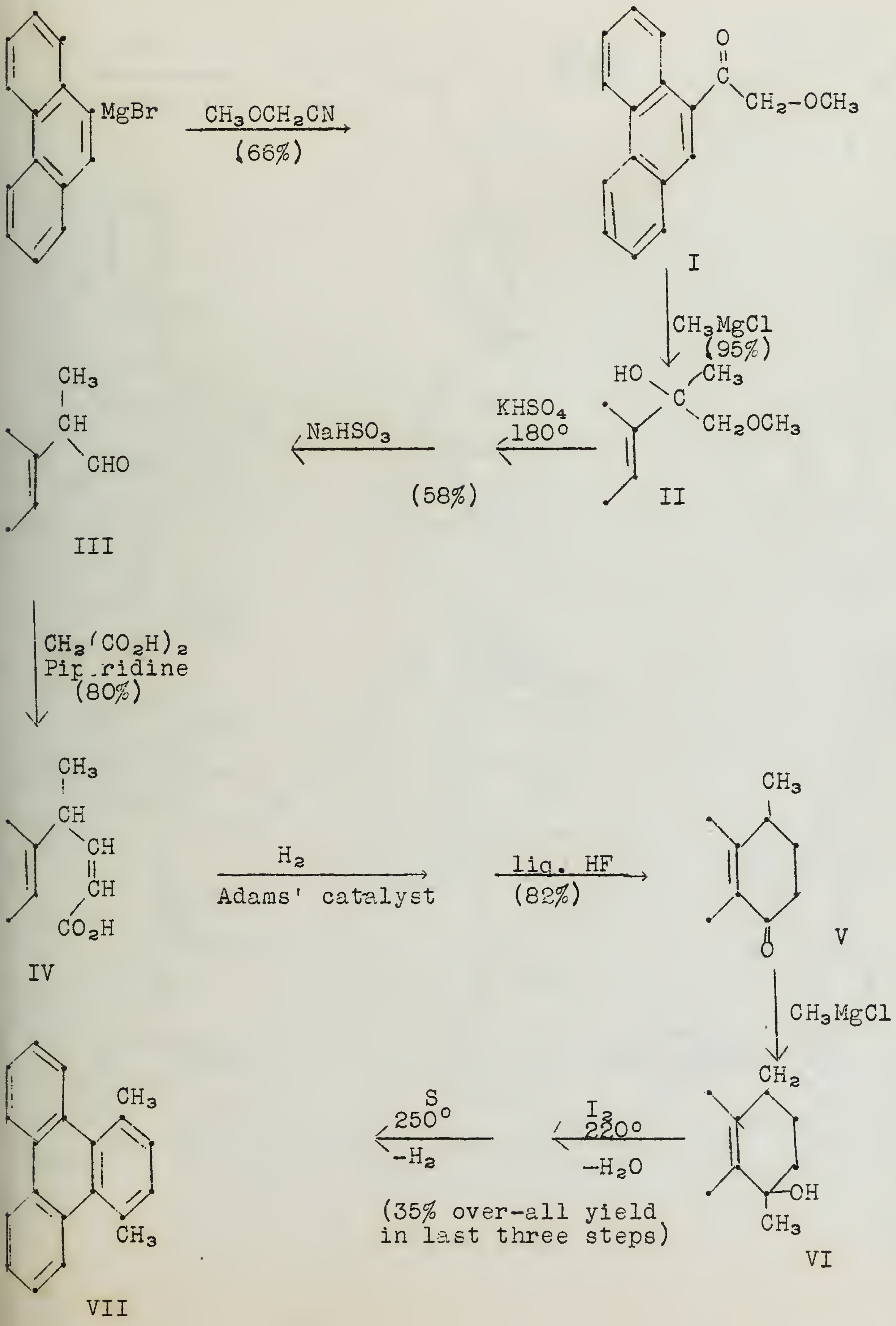
[illegible]

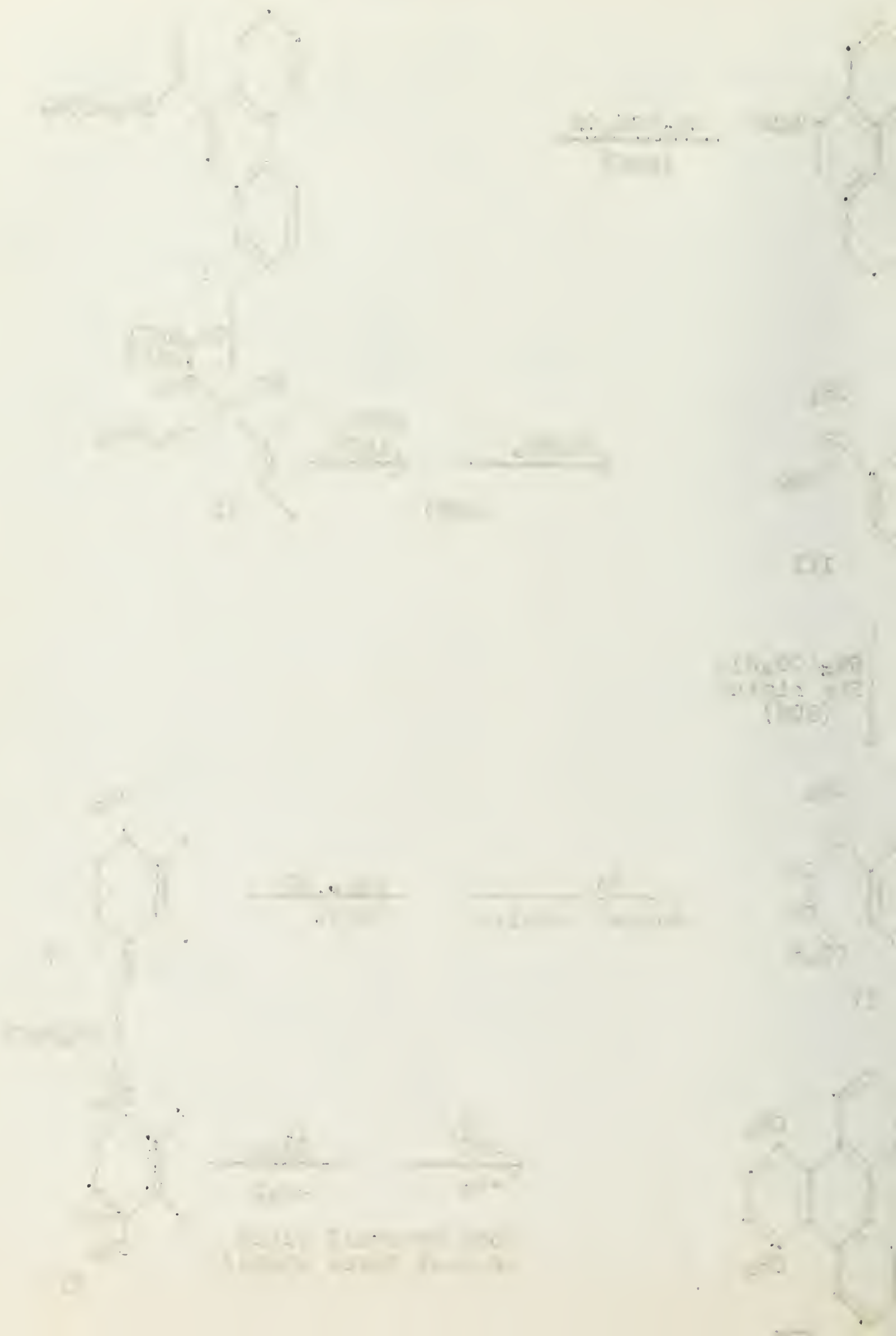


FLOW SHEET B

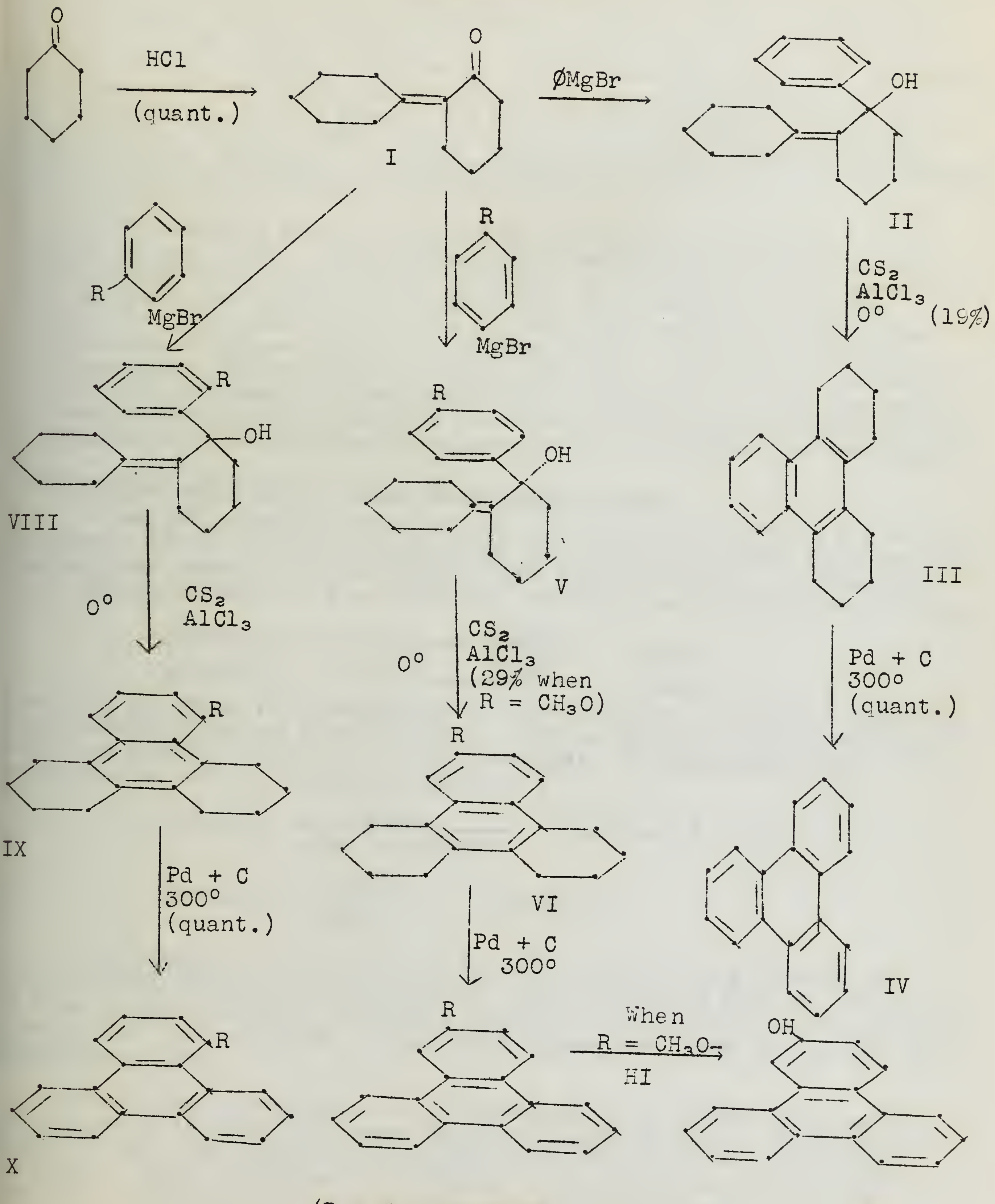

MgBr
CH_3OCH_2CN
(66%)
O
C
CH_2-OCH_3
I
CH_3MgCl
(95%)
HO
CH_3
C
CH_2OCH_3
II
$KHSO_4$
180°
$NaHSO_3$
(58%)
CH_3
CH
CHO
III
$CH_2(CO_2H)_2$
Piperidine
(80%)
CH_3
CH
CH
CH
CO_2H
IV
H_2
Adams' catalyst
liq. HF
(82%)
CH_3
O
V
CH_3MgCl
CH_2
OH
CH_3
VI
I_2
220°
$-H_2O$
S
250°
$-H_2$
(35% over-all yield
in last three steps)
CH_3
CH_3
VII

[illegible]

[illegible]

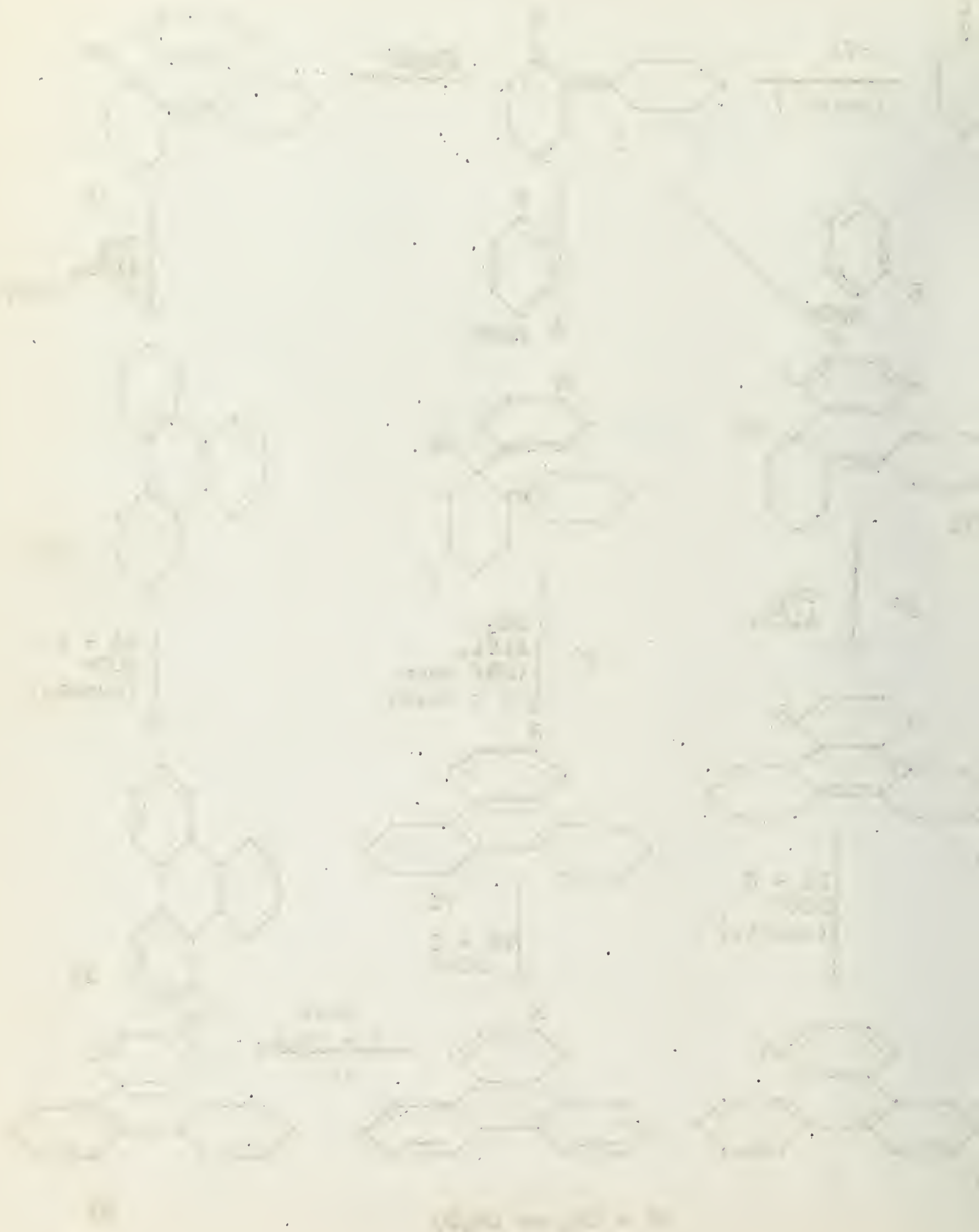


FLOW SHEET C



(R = CH$_3$ or CH$_3$O)

XI



HIGH OCTAINE AVIATION FUELS

It has been known for many years that hydrocarbons of different structures have varying efficiencies as fuel for the internal combustion engine. Thus, gasoline obtained by direct distillation of petroleum, because of its tendency to knock, can be used only in engines of low compression ratio. The power output and efficiency of the engine, however, improve as the compression ratio is increased. In a study of the antiknock qualities of pure hydrocarbons of the gasoline range, it has been found that highly branded hydrocarbons are superior fuels. Among the best is isooctane, while *n*-heptane is one of the poorest. In standardizing gasolines the fuel is compared to a mixture of isooctane and *n*-heptane.

The cracking process has brought a great improvement in the quality of gasoline. The unsaturated hydrocarbons produced have a good antiknock rating, and the cracking is accompanied by isomerization to more highly branched compounds. New processes for the production of airplane gasolines of very high quality involve the utilization of gases from the cracking units. The first of these was developed for the production of isooctane. When isobutylene is passed over sulfuric or phosphoric acid supported on inert material it reacts with itself to give a mixture of isooctenes. These are hydrogenated in the presence of a catalyst and isooctane is obtained.

Low Temperature Sulfuric Acid Alkylation Process

A valuable modification of this process consists in a similar treatment of the fraction containing all the four-carbon hydrocarbons. Isobutylene reacts preferentially with the butylenes. At the same time isobutane adds to the butylenes yielding saturated hydrocarbons.

$$\text{Isobutylene} + \text{butylene} \xrightarrow{H_2SO_4} \text{octenes}$$

$$\text{Isobutane} + \text{butylene} \xrightarrow{H_2SO_4} \text{octanes}$$

The last reaction is accompanied by the formation of higher and lower hydrocarbons (pentanes and decanes). Since *n*-butane does not enter into the desired reactions, it is converted to isobutane and butylenes by the following processes.

$$n\text{-butane} \xrightarrow[\text{oxide catalysts}]{\text{heat}} \text{butylenes} + H_2$$

$$n\text{-butane} \xrightarrow[AlCl_3]{\text{heat}} \text{isobutane}$$

The commercial development of the sulfuric acid process has gone forward very rapidly and it has been estimated that by the fall of 1940 plants had been installed capable of producing over 7,200,000 barrels per year of 92-94 octane fuel (unleaded) from C_4 olefins and isobutane alone.

The entire process may be summarized as follows: With pure hydrocarbons it has been shown that the reaction in the presence of sulfuric acid may be generally applied to the lower olefins except ethylene. Thus propylene, isobutene, 1- and 2-butene, trimethylethylene, together with lower polymerides of isobutene, di- and

triisobutene, and the butene-isobutene copolymer have all been shown to react with isobutane to give good yields of saturated products possessing octane numbers of 90+. Of the paraffins investigated, isobutane, isopentane, and isohexane reacted smoothly although the octane number of the saturated product falls off rapidly with increasing length of the carbon chain used.

The olefin is passed into a well-stirred mixture of the isoparaffin and 96-97% sulfuric acid kept at temperatures varying from -10 to 30°C. The overall yield of gasoline to the point where conversion was no longer considered economical in experiments with a C_4 cut containing 56% of unsaturated compounds, was 310% by weight of the acid used.

High Pressure Hydrogenation Process

The production of hydrogenated fuels to augment the natural supply has been made possible by the development of new catalysts for the high pressure hydrogenation operations. These catalysts possess the property of converting petroleum oils boiling outside the naptha range into lower boiling cyclic and branched chain compounds imparting desirable high octane values to the product. The fuels obtained by this method generally possess antiknock qualities superior to those of straight run naphthas.

A typical run gives conversions of 50-75% per pass and yields 80-95% of 75-78 octane gasoline as compared to 74 for natural aviation naphtha. The desirability of hydrogenated fuel is increased by its high octane number response on additions of lead tetraethyl.

In addition to the production of aviation naphthas high pressure hydrogenation is currently employed on a commercial scale for the preparation of blending agents. One of the principal blending agents thus made results from the hydrogenation of octenes available from copolymerization of iso- and *n*-butylenes. The hydrogenated codimer is not an aviation fuel in itself since it does not possess the boiling point range available for standard engine use. It is, therefore, principally employed as a blending agent to increase the octane number level of natural or hydrogenated aviation naphtha. In this case the increase in octane number is from 84 for the codimer to 100 for the hydrogenated polymers.

Mechanisms of Low Temperature Alkylations

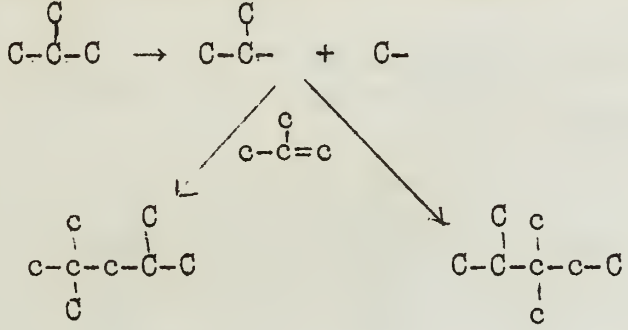
McAllister and his coworkers have postulated the following reaction mechanisms for these alkylations: ----

1. Simple addition of the isoparaffin to the double bond of the olefin. Most of the products obtained can not be explained by this mechanism.

2. Polymerization and depolymerization. The fact that a large proportion of octanes are obtained by the alkylation of isobutane with butylene trimers is evidence for this reaction.

3. Rearrangement of the primary products. This reaction undoubtedly occurs but not to a large extent under the given conditions.

4. Carbon-carbon cleavage and addition of the fragments to the double bond. Pauling has calculated that it takes less energy to cleave a C-C bond than it does to cleave a C-H linkage, hence this reaction is more plausible than dehydrogenation. The reaction of isobutylene and isobutane can be postulated as follows:

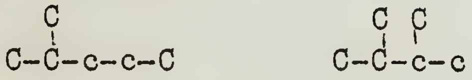


isooctane

Caesar and Francis propose a method whereby the formation of the observed compounds could be easily explained. They state that the olefin is able to wedge itself in between a methyl group and the rest of the isoparaffin so that the methyl group adds to one side of the double bond and the rest of the isoparaffin to the other. The methyl group <u>farthest</u> from the tertiary carbon is the one split off in the case of isopentane. Because it is necessary to use an <u>iso</u>paraffin they suggest as the first step that there is a bonding between the tertiary carbon, or its lone hydrogen atom, and the catalyst.

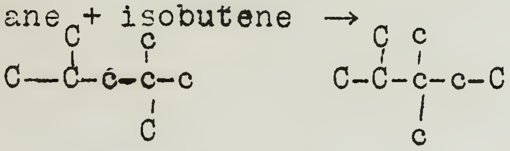
The following table gives the paraffins found and the manner in which they are explained by this method. ----

1. Isobutane + ethylene →



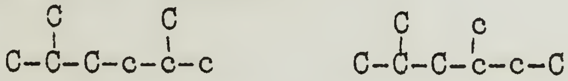
$\mathrm{C{-}\overset{C}{C}{-}C{-}C{-}C}$ $\qquad$ $\mathrm{C{-}\overset{C}{C}{-}\overset{C}{C}{-}C}$

2. Isobutane + isobutene →



$\mathrm{C{-}\overset{C}{C}{-}C{-}\underset{C}{\overset{C}{C}}{-}C}$ $\qquad$ $\mathrm{C{-}\overset{C}{C}{-}\underset{C}{\overset{C}{C}}{-}C{-}C}$

3. Isopentane + propylene →



$\mathrm{C{-}\overset{C}{C}{-}C{-}C{-}\overset{C}{C}{-}C}$ $\qquad$ $\mathrm{C{-}\overset{C}{C}{-}C{-}\overset{C}{C}{-}C{-}C}$

Consideration of the thermodynamic equilibria of isomeric paraffinic hydrocarbons show the following interesting point: "In any group of isomeric paraffins formed by this process, the relative amounts of the isomers agree closely with those computed by thermodynamic equilibria when those isomers are excluded which are not permitted by this mechanism." Thus in the case of the hexanes: ---

	ΔF (n = 0)	Equilibrium Per Cent	Per Cent in Alkylate	
			Calcd.	Found
n-hexane	0	4	0	0
2-methylpentane	-558	11	26	10-25
3-methylpentane	-558	11	0	0
2,2-dimethylbutane	-1341	42	0	0
2,3-dimethylbutane	-1165	32	74	75-90

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McAllister, et al., J. Org. Chem., 6, 647 (1941).
Caesar and Francis, Ind. Eng. Chem., 33, 1426 (1941).

Reported by Q. Soper
November 19, 1941

THE MECHANISM FOR THE COUPLING OF DIAZONIUM SALTS WITH AROMATIC AMINES AND PHENOLS

Bartlett and Wistar

Hauser and Breslow

The diazo compounds have been a most interesting subject of investigation since their discovery by Griess in 1858. They have been proven to be a most important and useful group of compounds.

The structure of these compounds has been a very controversial matter. Griess thought that both nitrogen atoms were attached directly to the benzene ring, but this idea was soon disproven by Kekule, who postulated the structures $C_6H_5N{=}NX$ for the salt, and $C_6H_5N{=}NOH$ for the free base. Shortly afterward, Blomstrand, Erlanger, and Strecker independently suggested the identical structure, $C_6H_5\underset{\substack{|\\ X}}{N}\equiv X$, but for different reasons.

For a number of years, little attention was devoted to the structure of these compounds, the major interest being in their uses. However, the issue was raised again in 1892 by von Pechmann, and for many years a tumultous controversy raged between Hantsch, Bamberger, Angeli, and many others over various suggested structures. The conflict between Hantsch and Bamberger was perhaps the most acrimonious in the history of Organic Chemistry. The matter has not been entirely clarified even at the present time.

The subject is complicated by the several isomeric compounds which are known, either directly or through their derivatives. Although many others have been suggested, supporting evidence exists for the following structures:

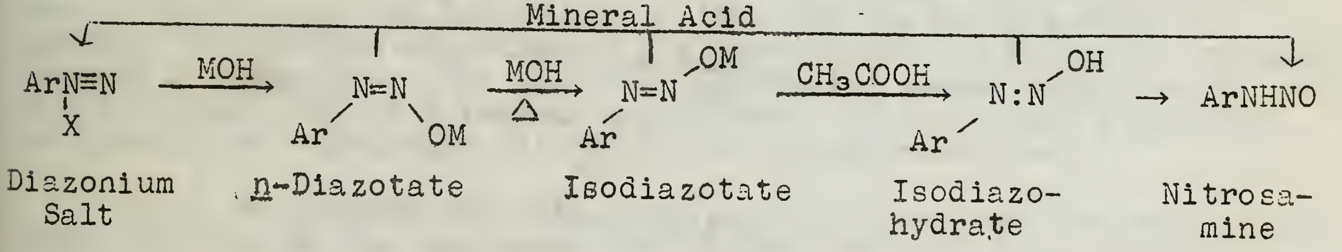
(1) Kekule's dizao formula, $ArN{=}NOH$

(2) Blomstrand's diazonium formula, $Ar\underset{\substack{|\\ X}}{N}\equiv N$

(3) Hantsch's stereoisomeric modification of Kekule's diazo formula

(4) von Pechmann's nitrosamine formula, $ArNHNO$

Probably all these formulas are correct under certain conditions. Taylor and Baker summarize the relationship in the following manner:



The limited scope of this report precludes a discussion of the evidence for and against the various structures which have been suggested from time to time. For further discussion of this point, your attention is directed to the General References listed with this report.

THE MECHANISM FOR THE FORMATION OF DIAZONIUM SALTS

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The primary interest of this discussion is not the possible structure of the diazo compounds, but the mechanism by which one of their most useful reactions occurs. It was discovered in 1870 by Kekule and Hidegh that diazo compounds would unite with substances such as phenols and amines to form stable azo compounds. Many hundreds of these substances have been and are now used as dyestuffs.

This coupling reaction occurs in weakly acidic or weakly basic solutions. The mechanism by which it occurs has been a source of uncertainty. It was generally supposed that the coupling took place between undissociated diazohydroxide and the phenol or amine. The reaction has been usually represented as follows:

$$\mathrm{ArN{=}NOH} + \mathrm{ArOH} \rightarrow \mathrm{ArN{=}NArOH} + \mathrm{HOH}$$

or

$$\mathrm{ArN{=}NOH} + \mathrm{ArNR_2} \rightarrow \mathrm{ArN{=}NArNR_2} + \mathrm{HOH}$$

Since the reaction did not go well in strongly acid solution, it was presumed that the addition of alkali to reduce the acidity simply converted the diazonium salt into the diazohydroxide, and thus promoted the coupling reaction.

This point of view does not appear consistent with the modern electronic conceptions of aromatic substitution, which require that the substituting reagent be an electron acceptor attacking a region of high electron availability. It seems more logical that the diazonium ion, which can readily serve as an electron acceptor, is the active reagent in the reaction. It is known that electron attracting substituents (such as the nitro group), which would increase the electrophilic character, activate the diazonium component. It is also known that the same substituents, which would reduce the electron donor tendency, deactivate the amine or phenolic component.

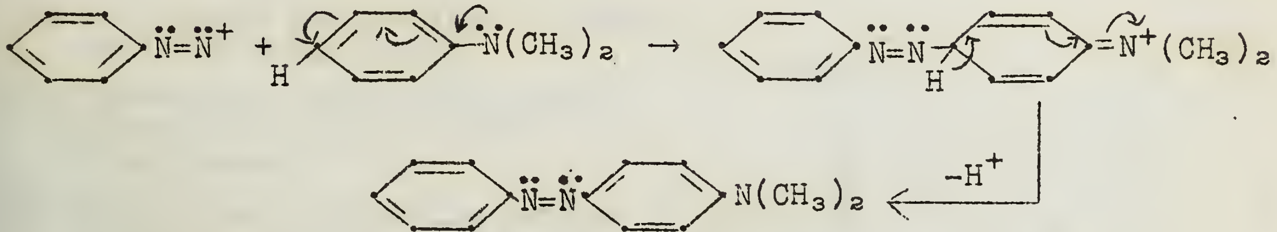
The diazonium ion may be represented in two resonance forms.

$$\underset{(A)}{\mathrm{Ar}:\overset{+}{\mathrm{N}}\vdots:\overset{\cdot\cdot}{\mathrm{N}}} \longleftrightarrow \underset{(B)}{\mathrm{Ar}:\overset{\cdot\cdot}{\mathrm{N}}::\overset{\cdot\cdot\,+}{\mathrm{N}}}$$

Although resonance form A probably contributes largely to the structure of the ion, it may be assumed that at the approach of an electron-donating molecule, resonance form B becomes the major structure. Similarly, the activation of the ion by the presence of electron attracting substituents in the aromatic ring can be explained by such a structure. The electron attracting substituents would cause resonance form B to contribute more to the ionic structure by drawing the electrons closer to the aromatic nucleus.

It also appears that the free amine rather than the substituted ammonium ion, or the phenoxide ion rather than the free phenol would have a greater tendency for electron donation, and hence would be more likely to serve as the other active component in the coupling reaction. Similarly, the presence of electron attracting groups in the aromatic nucleus would obviously reduce the tendency of this component to act as an electron donor.

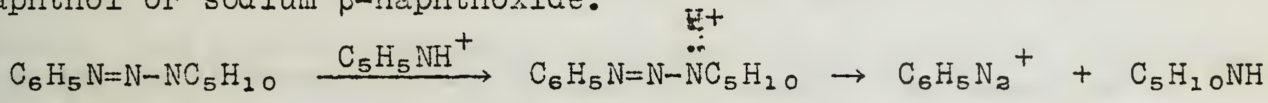
The most obvious mechanism for the coupling reaction would appear to be



Hauser and Breslow have shown that the diazonium ion is capable of entering directly into the coupling reaction. They used anhydrous media (pyridine), and observed that phenyldiazonium chloride couples readily with either β-naphthol or sodium β-naphthoxide to form 1-benzeneazonaphthol-2.

The argument might be made that a molecular oxy-azo compound (analogous to the diazohydroxide in aqueous solution) between the diazonium ion and the β-naphthol might be formed first, followed by a reaction between the oxy-azo compound and unchanged β-naphthol. In answer to this possible objection, investigation of the reaction of the nitrogen-azo compound benzenediazopiperidide (analogous to the hypothetical oxy-azo compound postulated above) with β-naphthol and its anion was made. Coupling did not occur. The nitrogen-azo compound was used because of the difficulty in obtaining the oxy-azo compounds in a pure state.

These results become even more convincing when we consider that addition of pyridinium chloride to the solution of benzenediazopiperidide and β-naphthol (or sodium β-naphthoxide) brings about some coupling almost immediately. The pyridinium ion effects the decomposition of the benzenediazopiperidide to form piperidine and benzenediazonium ion, which is then free to couple with the β-naphthol or sodium β-naphthoxide.



$$C_6H_5N{=}N{-}NC_5H_{10} \xrightarrow{C_5H_5NH^+} C_6H_5N{=}N{-}\overset{H^+}{\ddot{N}}C_5H_{10} \rightarrow C_6H_5N_2^{\ +} + C_5H_{10}NH$$

The above results seem to show conclusively that the diazonium ion is capable of serving as the active reagent in the coupling reaction, at least in anhydrous media.

Further evidence in favor of this mechanism has been obtained by Bartlett and Wistar, making use of an entirely different method of approach, i.e., from a kinetic study of the reaction. The fact that diazonium coupling with phenols and amines takes place only when the acidity of the solution was kept below a certain value suggested to Conant and Peterson that the rate of coupling is a function of the H^+ activity of the solution. They investigated this point with different diazonium salts and phenols. Heavily buffered dilute solutions of constant ionic concentration were used, and the progress of the reactions was followed colorimetrically. It was found that the reaction is strictly bimolecular and free from complications. Over the pH range investigated, when log k was plotted against pH, curves were obtained which had a slope of 1.

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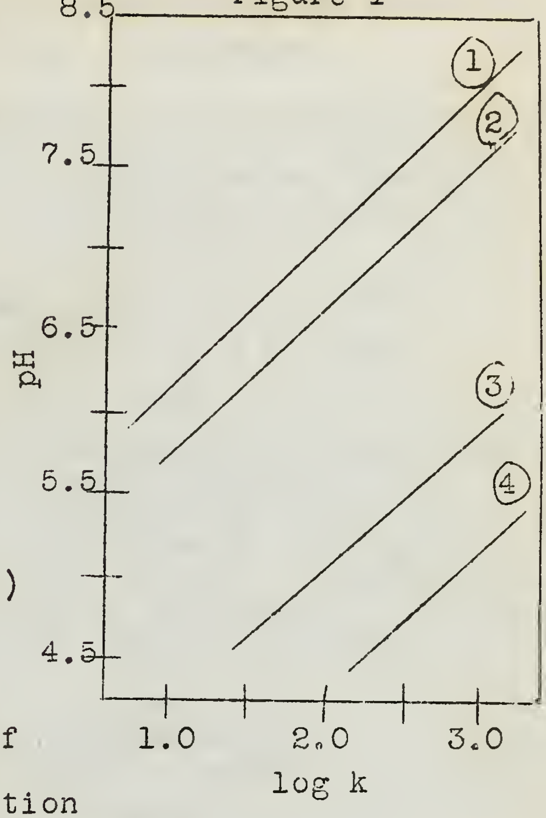
Figure I



(1) Diazotized o-anisidine + disodium-2-naphthol-3-6-disulfonate

(2) Diazotized o-anisidine + sodium-1-naphthol-4-sulfonate

(3) Diazotized sulfanilic acid + disodium 2-naphthol-3-6-disulfonate

(4) Diazotized sulfanilic acid + sodium 1-naphthol-4-sulfonate

A probable mechanism was suggested[1]

(1) $ArN_2X + OH^- \rightleftharpoons ArN{=}NOH + X^-$
(Fast and reversible)

(2) $ArN{=}NOH + P \rightleftharpoons ArN{=}NP + H_2O$
(Relatively slow and irreversible)

The equilibrium in the first step would be a function of the (OH^-) activity, which is a direct function of pH. The rate controlling reaction (2) would depend directly on the concentration of ArN=NOH, and thus the rate would be a direct function of the pH value of the solution.

It is to be noted that both of the reactants are capable of acid-base equilibria.

$$ArN_2^+ + OH^- \rightleftharpoons ArN_2OH$$

and

$$ArOH \rightleftharpoons ArO^- + H^+$$

However, the phenol equilibrium does not reach appreciable dissociation in the pH region in which coupling occurs, and hence is of little importance in the actual kinetic study.

Recently Bartlett and Wistar have investigated the coupling reaction using amines instead of phenols. Unlike the phenols, the acid-base equilibria of amines reaches 50% in the pH range where the coupling reaction occurs.

$$ArNH_2 + H^+ \rightleftharpoons ArNH_3^+$$

Hence, this equilibrium must be of practical importance in the reaction, and the curve, log k vs pH, cannot be a straight line, as in the case of phenols.

There are four possibilities for actual reacting components in diazonium salt-amine coupling.

(1) Diazohydroxide couples with the substituted ammonium ion

(2) Diazonium ion couples with the free amine

(3) Diazonium ion couples with the substituted ammonium ion

(4) Diazohydroxide couples with the free amine

In interpreting the results obtained, it is advantageous to consider the general shape of the curves (log K vs pH) resulting if the various possible combinations above are the active reactants. For simplicity, a model case with the following dissociation constants can be set up.

For the substituted ammonium ion ....$K = 1 \times 10^{-4}$

For the diazohydroxide ....$K = 1 \times 10^{-3}$

For the phenol ....$K = 1 \times 10^{-8}$

We can calculate the fractions of the total amine existing as free base and as substituted ammonium ion in buffer solutions of different pH values. Similarly we can calculate the fraction of the diazonium compound existing as the diazonium ion and as undissociated diazohydroxide in these same buffers. Likewise the fractions of phenol and phenoxide ion can be calculated. The results of these model case calculations are tabulated below.

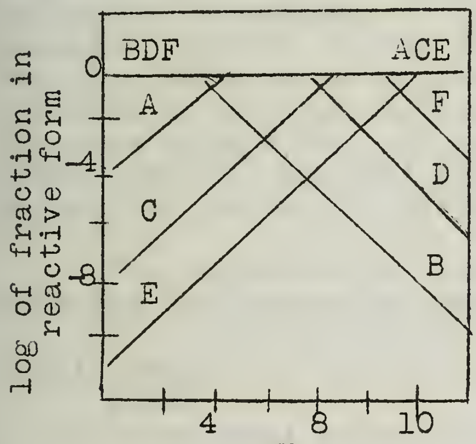


Figure 2

Effect of pH on fraction of each component in acid and basic form

(A) $$\frac{ArNH_2}{ArNH_3^+ + ArNH_2}$$

(B) $$\frac{ArNH_3^+}{ArNH_3^+ + ArNH_2}$$

(C) $$\frac{ArO^-}{ArOH + ArO^-}$$

(D) $$\frac{ArOH}{ArOH + ArO^-}$$

(E) $$\frac{ArN_2OH}{ArN_2OH + ArN_2^+}$$

(F) $$\frac{ArN_2^+}{ArN_2OH + ArN_2^+}$$

Referring back to the possible combinations of diazonium compounds and amines, if Case (1) represents the facts, then the velocity constant for the rate of coupling will change with pH in proportion to the change in product

$$\frac{(ArN_2OH)}{(ArN_2OH) + (ArN_2^+)} \times \frac{(ArNH_3^+)}{(ArNH_3^+) + (ArNH_2)}$$

Corresponding expressions will be obtained for the other three cases. Plots of these products, therefore, indicate the general slope of the Rate-pH curve which should result from each of the eligible mechanisms. The theoretical curves are listed below.

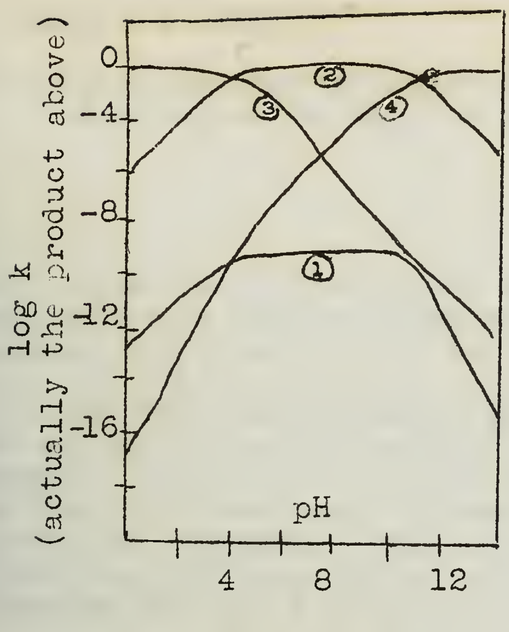


Figure 3

(1) $ArN_2OH + ArNH_3^+$

(2) $ArN_2^+ + ArNH_2$

(3) $ArN_2^+ + ArNH_3^+$

(4) $ArN_2OH + ArNH_2$

log k values plotted are actually the fraction product illustrated above.

The general shapes of these curves would be the same even if the ionization constants were not the same as in the assumed case, only the points of inflection being shifted. Actually the assumed values are near the constants for the amines and salts actually used. To be perfectly accurate, it is necessary to note that these curves are not strictly correct, since the acidic character of the diazohydroxide is neglected. Only the alkaline portion of the curves would be affected, however. Experimentally this is of no importance as the pH regions investigated included only those regions where this effect is negligible, i.e., pH range 2.04-6.25. It is to be noted that the curves for mechanisms (1) and (2) are identical with each other in general shape, but are quite different from those of mechanisms (3) and (4).

The experimental work consisted in a determination of the velocity constants at various pH values for the coupling of

(1) 1-Naphthyl amine 4-sulfonic acid with diazotized sulfanilic acid.
(2) 1-Naphthyl amine 8-sulfonic acid with diazotized aniline

Determinations were made in heavily buffered solutions of constant ionic concentration and temperature, duplicating the conditions used by Conant and Peterson exactly. Progress of the reaction was followed colorimetrically. Results were obtained as shown by the following curves.

Figure 4

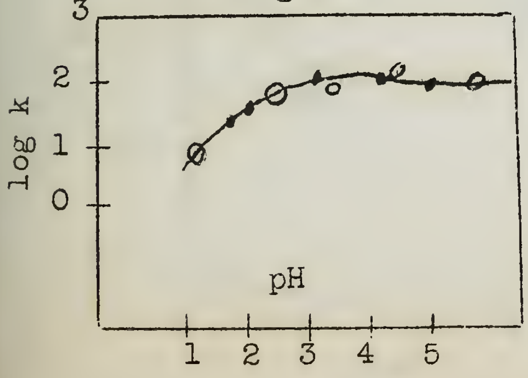


Figure 5

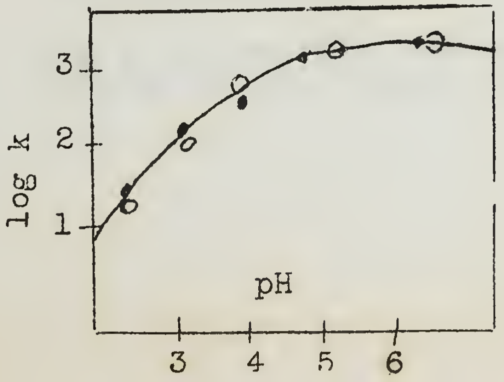


Figure 4 (Cont)

1-Naphthyl Amine-4-Sulfonic Acid + Diazotized Sulfanilic Acid

Figure 5 (Cont)

1-Naphthyl Amine-8-sulfonic Acid + Diazotized Aniline
(Solid circles are experimental points. Open circles are theoretical superposed values)

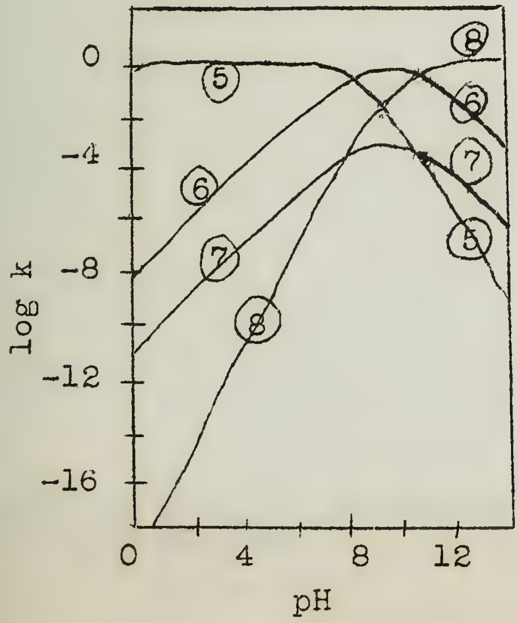
Only a portion of the curve is shown in each case as it is obviously impossible to obtain experimental results over the entire pH range. However, this portion is sufficient to establish the general shape.

Of the theoretically eligible mechanisms, it is seen that the curves for mechanisms (1) and (2) are similar to the experimental curves. In fact, by making the slight necessary change in assumed K, the exact coincidence between the theoretical and experimental curves is obtained. This has been done in the graphs above. Mechanisms (3) and (4) are definitely eliminated from consideration, although (4) has been usually considered as the most probable.

In deciding between mechanisms (1) (Diazohydroxide coupling with substituted ammonium ion) and mechanism (2) (Diazonium ion coupling with free amine), there appears to be little doubt that mechanism (2) is the correct one. In those cases where aromatic substitutions have been carried out on anilinium ions, these ions have proven both unreactive and powerfully meta directing. It appears most unlikely that such a substance could act as an active intermediate in a reaction which fails to occur except with highly activated benzene derivatives, and which always results in para or ortho substitution. On the other hand, mechanism (2) is perfectly in accord with the modern electronic theories of substitution.

The phenol coupling reactions studied by Conant and Peterson are subject to the same analysis. Theoretical curves are obtained as follows:

Figure 6



(5) $ArN_2^+ + ArOH$

(6) $ArN_2^+ + ArO^-$

(7) $ArN_2OH + ArOH$

(8) $ArN_2OH + ArO^-$

log k is actually the fraction product of the reacting pairs

Although for obvious reasons, complete experimental data is lacking, it is seen that only curves (6) and (7) have any portion that is linear with a slope of 1 as observed. The choice here is between the reactive pairs, diazohydroxide and phenol, or diazonium ion and phenoxide ion. On theoretical grounds, the second mechanism is to be preferred here also. Certainly it is quite definitely shown that the results of Conant and Peterson are not incompatible with the postulated mechanism.

Since two entirely independent and different lines of approach to the problem have led to the same conclusion, and since this conclusion is thoroughly in accord with modern electronic theory, it appears to be definitely established that the diazonium ion and the free amine or phenoxide ion are the active agents in the diazonium coupling reaction.

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Reported by W. E. Blackburn
November 26, 1941

A REVIEW OF THE ORGANIC CHEMISTRY OF ARSENIC

Since there are no naturally occurring organic arsenic compounds which might serve as starting material in a synthesis, one is immediately faced with the problem of preparing a compound with the desired C-As linkage. With this end in view a large number of arsonation reactions have been attempted with varying success. Of these many reactions only a few with general applicability can be picked out.

I. Methods of Arsonation.

A. Aliphatic

Cahours and Richie in 1854 found that by heating an alkyl halide, usually the iodide, with sodium arsenide they obtained a mixture of arsines.

$$RI + Na_3As \rightarrow R_2As{-}AsR_2 + R_3As + R_4As^+I^-$$

This reaction was important in pointing out the relationship between the various types of arsines then known, but is of little preparative value because of the mixture obtained. In 1859 Cahours announced an improvement of the synthesis.

$$RI + Zn_3As_2 \rightarrow R_4As^+I \cdot ZnI_2 \xrightarrow[KOH]{aqueous} R_4As^+I^- \xrightarrow[KOH]{distil} R_3As + RI$$

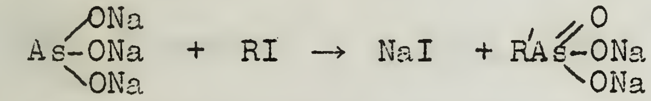
The cadmium salts could also be used.

Michaelis and Reese in 1882 advanced another more versatile method for preparing these arsines.

$$3RX + 6Na + AsX_3 \rightarrow R_3As + 6NaX$$

Using the following types of arsine halides, which are available from other reactions, $RAsX_2$ and $RR'AsX$, one can obtain tertiary arsines of the type $RAsR_2$ and $R'R''R'''As$ respectively.

The most widely used synthetic method which is also capable of industrial application is the Meyer reaction.



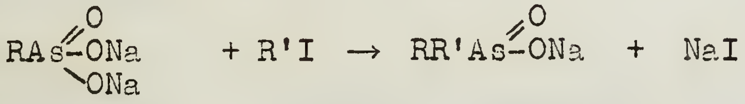
$$As(ONa)_3 + RI \rightarrow NaI + RAsO(ONa)_2$$

Meyer carried the reaction out in an aqueous medium usually under pressure to avoid the loss of the alkyl iodide being used. Dehn extended this reaction and found that he could improve the yields by using dilute alcohol solutions and potassium rather than sodium arsenite. He thus obtained an homogenous reaction medium.

The procedure as modified by Dehn still left much to be desired, because the higher homologs were obtained in increasingly small yields and because a considerable amount of alkyl iodide was lost due to ether formation with the solvent alcohol. Valeur and Delaby found, in contrast to Dehn, that they obtained better results with aqueous solutions which allowed better agitation and refrigeration. Adams and Quick selected this method for preparing higher aliphatic arsonic acid and found that better yields could be obtained by the use of alkyl bromides or chlorides. The sodium salts of the arsonic acids produced are soluble in the reaction

mixture and difficult to isolate. When the alkyl chloride or bromide was used these sodium salts could be converted to the free acids which are much less soluble. When the iodides were used the hydrogen iodide immediately reduced the arsonic acids.

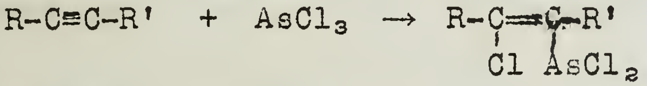
The reaction can be extended to further alkylation as follows:



$$RAs(=O)(ONa)ONa + R'I \rightarrow RR'As(=O)ONa + NaI$$

$$RR'As(=O)ONa + R''I \rightarrow RR'R''As{=}O + NaI$$

Still another method of importance because of its application especially to the production of lethal compounds of military value is the addition of arsenic halides to acetylenes.

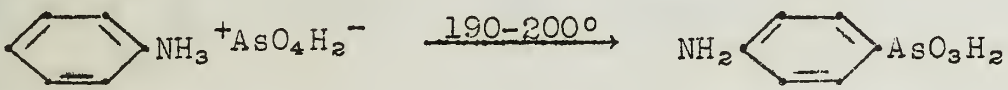


$$R{-}C{\equiv}C{-}R' + AsCl_3 \rightarrow R{-}\underset{Cl}{C}{=}\underset{AsCl_2}{C}{-}R'$$

The reaction has also been carried out on ethylene.

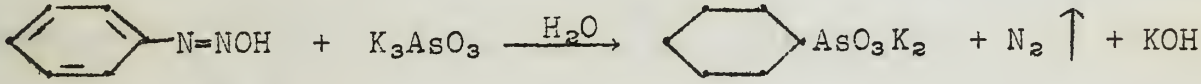
B.. Aromatic.

The oldest method of aronation in the aromatic series is that of Bechamp.



The reaction can be carried out on nuclear substituted amines with an open p or o position. If both the o and the p positions to the amine group are filled the reaction fails.

By far the most important method of aromatic arsonation is the Bart reaction or one of its various modifications.



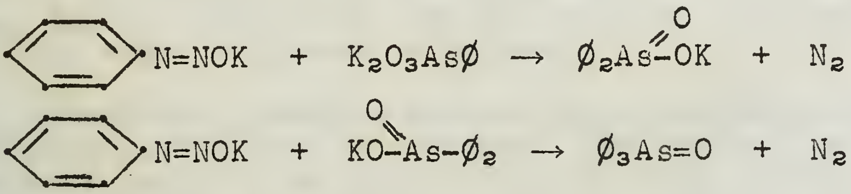
According to Bart's original procedure a solution of the diazonium salt was prepared and then made alkaline and heated to a rather high temperature, then with continued heating the arsenite solution was poured into the diazo solution. He later suggested the use of copper, nickel, silver, and cobalt and their salts as catalysts.

Since Bart's original procedure appeared it has undergone many modifications in the hands of other workers. Schmidt suggests the use of a neutral or even faintly acid medium with no catalyst. Mouneyrat uses alkaline, neutral, or acid reaction medium with a dual catalyst consisting of a metallic salt and reducing agent chosen with reference to the pH of the solution.

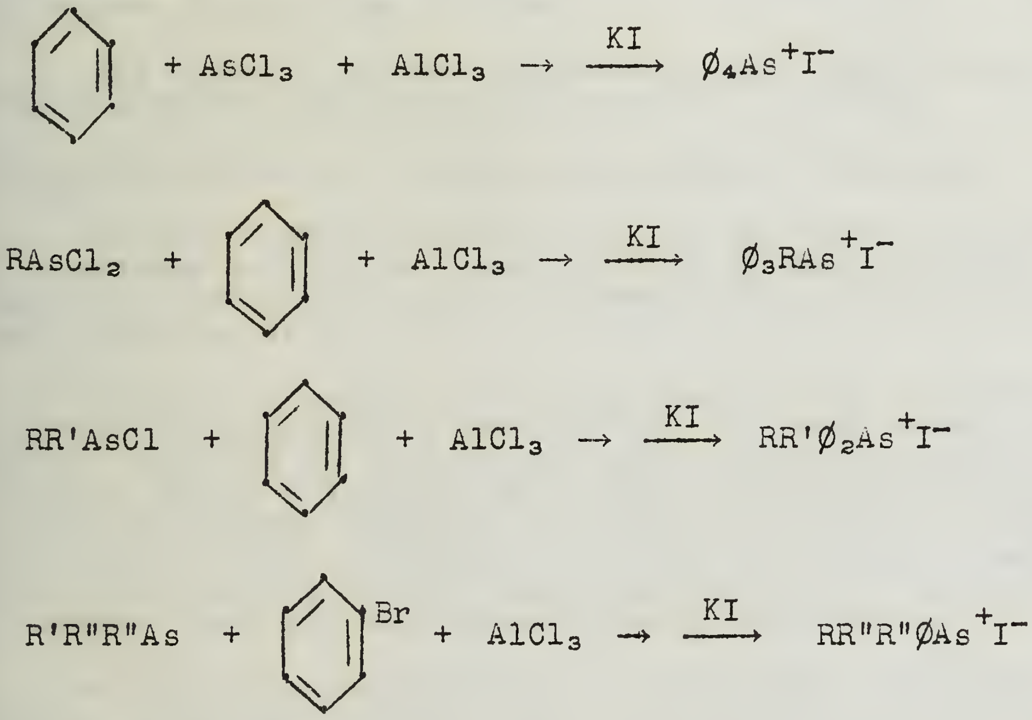
No blanket statement can be made in regard to the best conditions for carrying out the Bart reaction. The choice in any given case must be made after experimentation with the particular

amine under consideration. Even then the successful completion of the reaction is dependent on the technique employed so that two operators have difficulty in reproducing yields.

As in the case of the Meyer reaction the higher arylated arsinic acids and arsine oxides can be prepared by proper choice of starting material.



Chatt and Mann recently developed a method for making arsonium iodides of the type $As(abcd)^{+}I^{-}$. These compounds are of interest stereochemically.



Many attempts at direct arsonation of aromatic compounds by the Meyer reaction have been made. Rosenmund was successful in isolating benzene arsonic acid from bromobenzene and aqueous potassium arsenite. Hamilton and Leudeman confirmed this report and attempted to extend the reaction. They found that o-chlorobenzenearsonic acid could be arsonated in aqueous medium to arsonophthalic acid in good yields but that other compounds with equally active halogen gave poor yields or none at all. It thus appears that direct arsonation is not a general reaction in the aromatic series.

II. Transformations in the Arsenic Series

The presence of arsenic in an aromatic nucleus does not materially alter the aromaticity of the ring. The arsonic acid group has about the same m orienting effect as the sulfonic acid

group and activates the ortho and to a lesser extent the para positions. o-Chlorobenzenearsonic acid is sufficiently reactive to react with aromatic and aliphatic amines and with alcohols. The amino arsonic acids are of especial synthetic value since they undergo all of the characteristic aromatic amine reactions. The presence of an amine group or hydroxy group in the para position seems to weaken the C-As linkage and in this case the use of halogen containing reagents must be avoided since by some of them (i.e., PCl_3, SO_2Cl_2, $SOCl_2$, Cl, Br) the arsonic acid group is cleaved from the ring being replaced by halogen.

There are numerous derivatives of arsenic known due to its existence in multivalent states. The arsonic acids are the most important derivatives since they are most readily prepared. Since interconversion in the series is quite easy, all of the other derivatives may be prepared from the arsonic acids. There are noteworthy differences between the aliphatic and aromatic arsenicals of the same class, but they are differences, as a rule, of stability and degree rather than of kind.

The types of arsenic compounds, their nomenclature, and their interconversion are summarized in Tables I and II.

III. A Comparison of Nitrogen and Arsenic Chemistry

As can be seen from Tables I and II, there are several types of compounds similar in structure to well known nitrogen compounds. There are also many arsenic compounds whose nitrogen analog is not known and vice versa.

Arsenic compounds react very readily with halogens to give haloarsenic compounds; a reaction not observed in the nitrogen series. This is to be expected since inorganic arsenic halides are more stable and easier to prepare than nitrogen chlorides. The ability of arsenic compounds to become oxidized to a higher valence state is also more pronounced than in the nitrogen compounds. Indeed, with certain arsenic compounds their air oxidation occurs so rapidly that they are spontaneously combustible.

A study of the reactions and properties show that compounds of similar structural formula often show fundamental differences in their chemistry.

The arsonic acids most closely resemble the nitro compounds. The reactions due to the acidic hydrogens of arsonic acids, of course, have no parallel in the nitro compounds. The electronic arrangement of nitro compounds is suitable for the formation of a dibasic acid and the inability to do so has been attributed to the small atomic size of the nitrogen atom which will not permit it to coordinate the required number of groups. Arsonic acids can exist in the anhydride form $RAsO_2$, but unlike the nitro compounds, these are hydrolyzed by water to the arsonic acid. The arsonic acid group has no chromophonic properties, all the arsonic acids being white solids. Like the nitro group, the arsono group exerts a m directing effect on orientation and like the nitro compounds the arsonic acids can be reduced to any desired lower valence state by the choice of suitable reagents.

TABLE I

Aliphatic Arsenicals

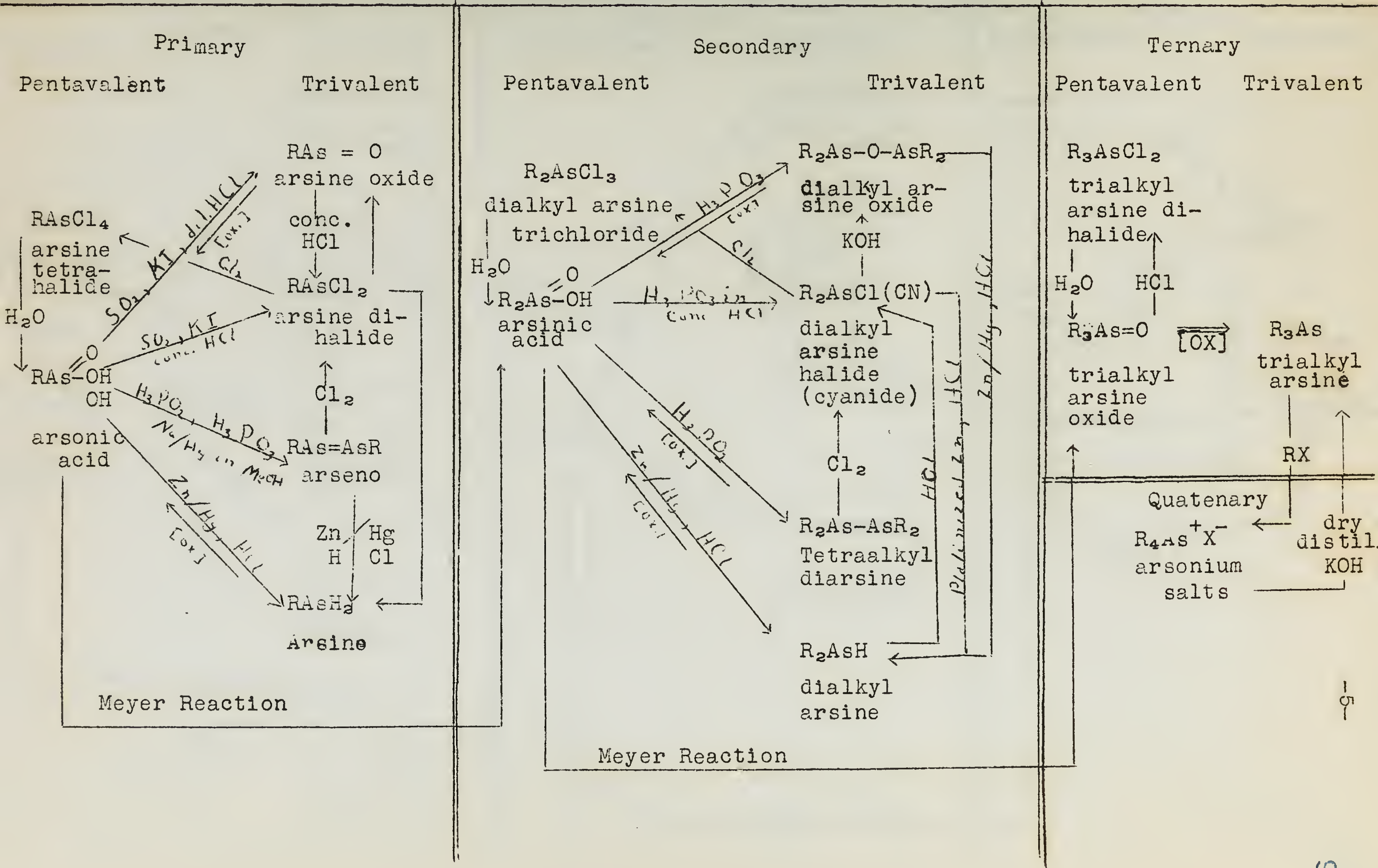
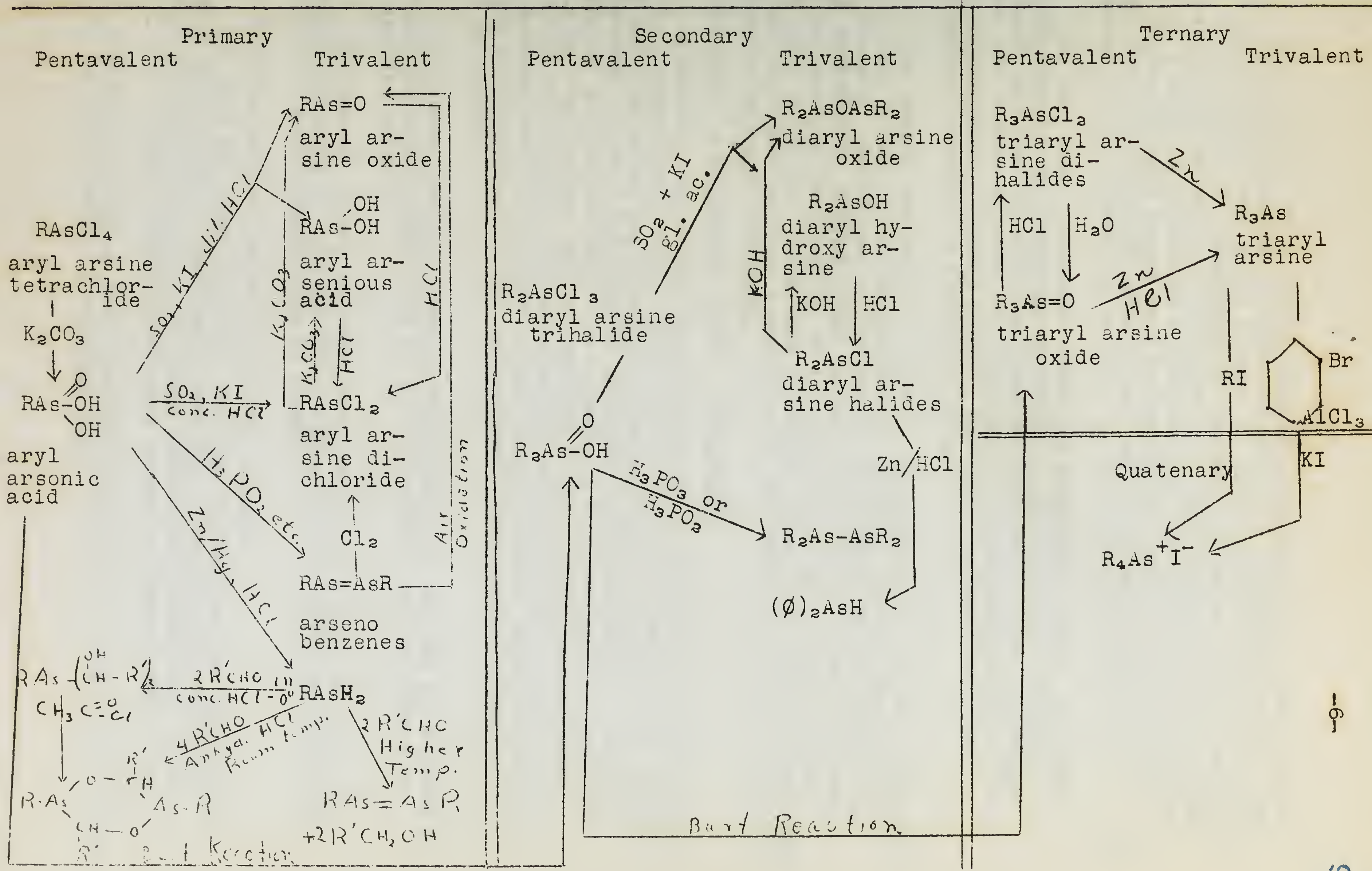


TABLE II

Aromatic Arsenicals



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The arsines bear little chemical resemblance to the amines. They are nearly devoid of basic properties. Methylarsine and the tertiary arsines are basic enough to form salts with halogen acids, but these salts are completely decomposed by water. The tendency to oxidize increases as the number of organic groups is increased. Arsine itself is stable to air oxidation, the mono organic arsines are fuming liquids which must be protected from air to preserve them, and the di-organo arsines are spontaneously combustible. The tendency to air oxidation is less in the aromatic series.

On the other hand, the arsonium compounds bear a striking resemblance to the ammonium compounds. The salts are highly ionized, and the arsonium hydroxides are strong bases absorbing water and carbon dioxide from the air. The arsonium iodides are not decomposed by aqueous alkali, but must be distilled from potassium hydroxide to decompose them.

The arseno compounds are quite dissimilar to the azo compounds. The arseno group is not chromophoric although some arseno compounds are colored. Oxidation of the arseno compounds occurs under very mild conditions, silver oxide being reduced by an arseno compound. The comparative instability of the arseno group is shown by the fact that halogens, sulfur and hydrogen cleave the As=As linkage and by the fact that heating a solution of two different arseno compounds causes an exchange reaction.

$$RAs{=}AsR + R'As{=}AsR' \rightleftharpoons 2RAs{=}AsR'$$

Likewise, the arsine oxides bear only structural resemblances to the nitroso compounds. The arsine oxides are amphoteric, giving with halogen acids the dihalogen arsines, and with bases the salts of hydroxy arsines $R_2As\text{-}ONa$ or arsenous acids $RAs(ONa)_2$. In the aliphatic series the acids corresponding to these salts cannot be isolated, but esters can be prepared with an alkyl halide under suitable conditions. In the aromatic series the arsenious acids and hydroxy arsines are not stable unless nuclear nitro or carboxyl groups are present. In the latter event the arsine oxides may be hard to obtain.

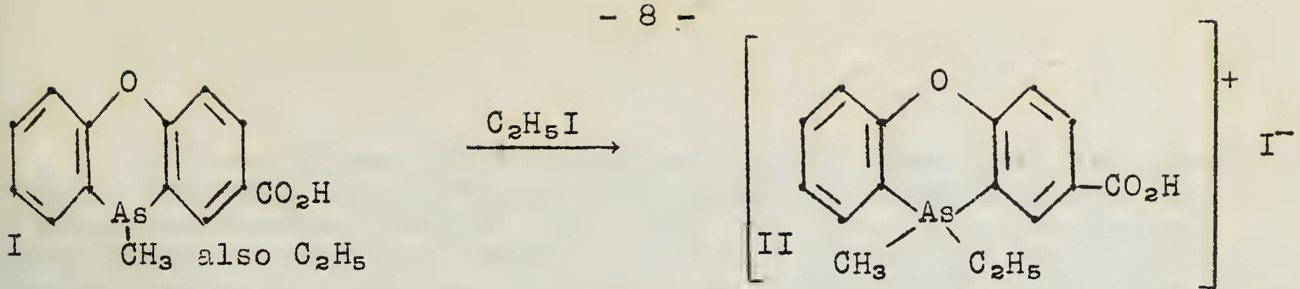
Compounds having a formal resemblance to the diazo, diazonium, hydrazo and azoxy groups and to the hydrazines are not known in the arsenic series.

In general it may be said that analogous reasoning from the nitrogen compound to its arsenic analog is not justified, although significant resemblances can be found.

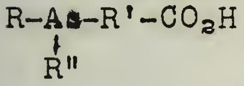
IV. The Stereochemistry of Trivalent Arsenic

To date the best physical evidence indicates that trivalent arsenic has a rather flattened pyramidal configuration with the arsenic atom at the apex. The bond angles are calculated to be $100^\circ \pm 3^\circ$. Recent chemical evidence seems to support this view.

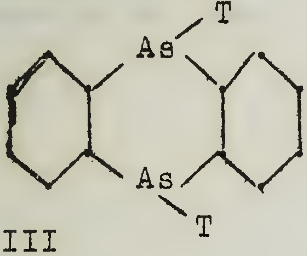
Lesslie and Turner have resolved compounds of type I and found them to be very stable to racemization.



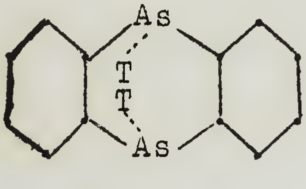
The optical activity of these compounds could be due to three causes: (a) The three rings could be coplanar with the optical activity due to the asymmetry of the molecule (i.e., methyl group in front or behind the plane.). (b) If arsenic has a pyramidal configuration the rings would have to be folded along the O to As axis. The asymmetry of the molecule would still be the cause of optical activity. (c) The optical activity could be due to an "asymmetric arsenic atom" which would impart optical activity even in the absence of an asymmetric molecule.

Kamai attempted the resolution of compounds of the type  $R\text{-}\underset{\substack{\mid\\R''}}{As}\text{-}R'\text{-}CO_2H$ but failed. This negative evidence, of course, does not rule out the third possibility. The evidence in favor of (b) is rather meager. Lesslie and Turner found that the optical isomers of I were very stable to racemization, being only slowly racemized in boiling benzyl alcohol. However, in ethyl alcohol in the presence of an alkyl iodide racemization was rapid. Treatment of I with ethyl iodide would produce II in which the arsenic atom, being no longer trivalent, would probably not have the pyramidal configuration. If II has a tetrahedral arsenic atom, then it should be resolvable, but all attempts at resolution have met with failure.

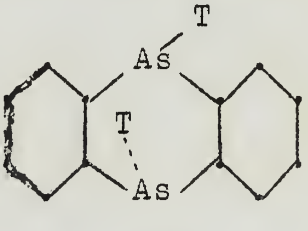
Chatt and Mann have advanced interesting evidence in favor of the pyramidal arsinic atom. They synthesized 9, 10 di-p-tolylarsanthrene (III, IV, or V) and found it to consist of a mixture of two forms which they separated by fractional crystallization. Assuming the pyramidal construction the following three compounds are indicated.



III



IV



V

The left hand ring is projecting from the plane of the paper toward the observer and a dotted line to the p-tolyl group indicates that it extends behind the plane of the paper and toward the center of the molecule. From an examination of the model for IV it is seen that the two p-tolyl groups are almost coincident in space. They offer this as an explanation of their failure to obtain a third form.

It thus appears that trivalent arsenic does have the pyramidal form. However, this pyramidal form might be stabilized by the fused ring systems present in I, III, and IV. The evidence on hand points to the fact that I is resolvable due to the asymmetry of the molecule but does not yet prove or disprove the existence of an "asymmetric arsenic atom."

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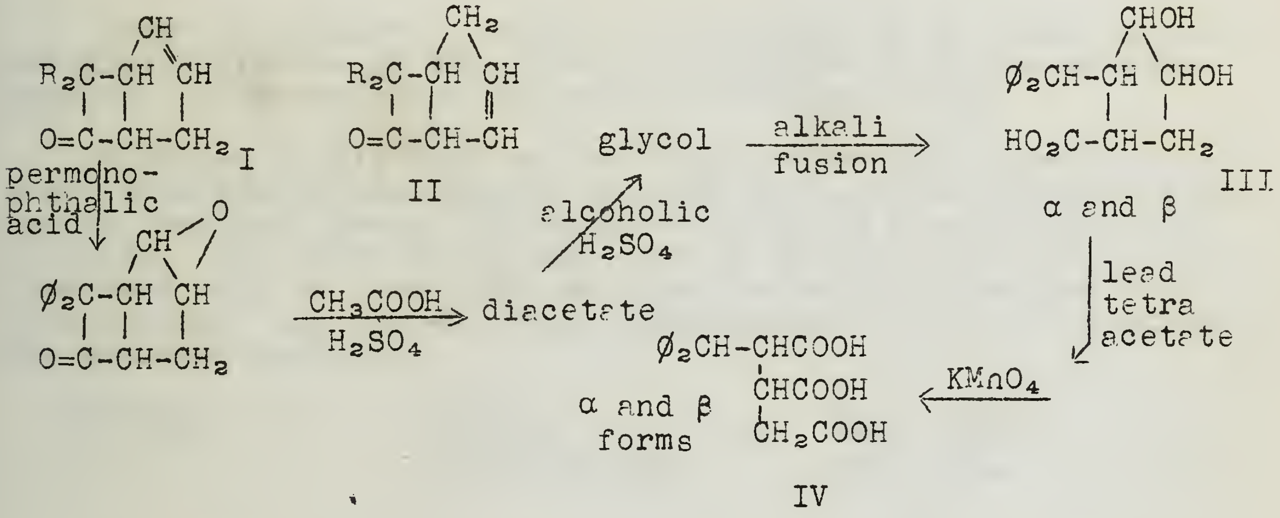
Reported by C. W. Theobald
November 26, 1941

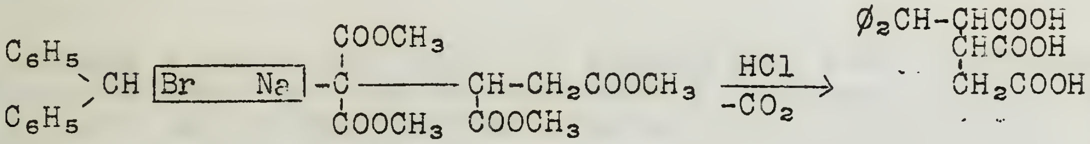
ADDITION PRODUCTS BETWEEN KETENES AND UNSATURATED HYDROCARBONS

Staudinger prepared several addition products between ketenes and unsaturated hydrocarbons and suggested that they were substituted cyclobutanones. In the past few years the structure of these addition products has been definitely established.

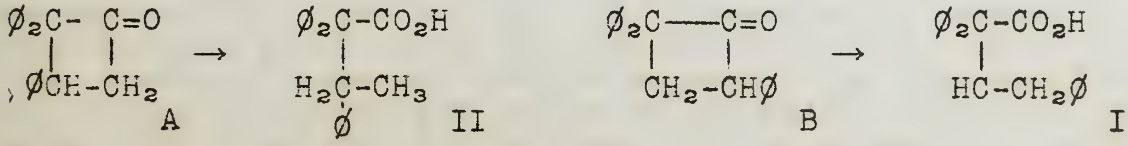
Diphenylketene and Cyclopentadiene.--Staudinger condensed dimethylketene and cyclopentadiene and obtained a dicyclic unsaturated ketone, $C_9H_{12}O$. He suggested I and II as two possible structures, where $R=CH_3$. After unsuccessfully attempting to characterize the degradation products of Staudinger's compound, Simonsen studied the compound in which $R=C_6H_5$ and proved the structure to be I.



The α and β forms of IV were synthesized by the hydrolysis of the condensation product of bromodiphenylmethane and methyl sodio-propane-α,α,β,γ-tetracarboxylate, one of the carboxyl groups being eliminated.



Diphenylketene and Styrene.--Structures A and B were suggested by Staudinger for the condensation product of diphenylketene and styrene. Hydrolytic fission (NaOH, H_2O) of the adduct gave an acid, $C_{22}H_{20}O_2$, which he suggested was α,α,γ-triphenylbutyric acid (I) or α,α,β-triphenylbutyric acid (II).



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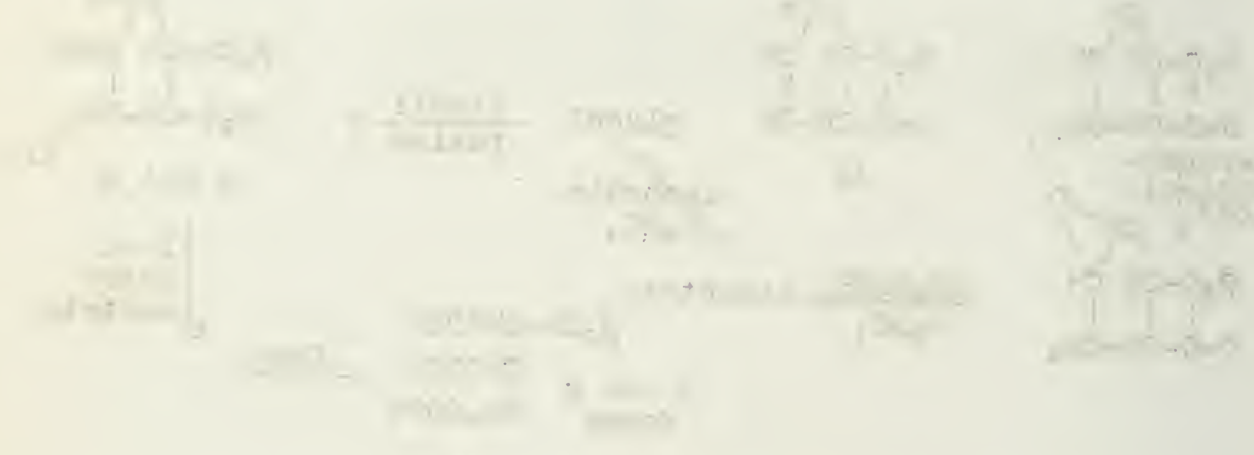
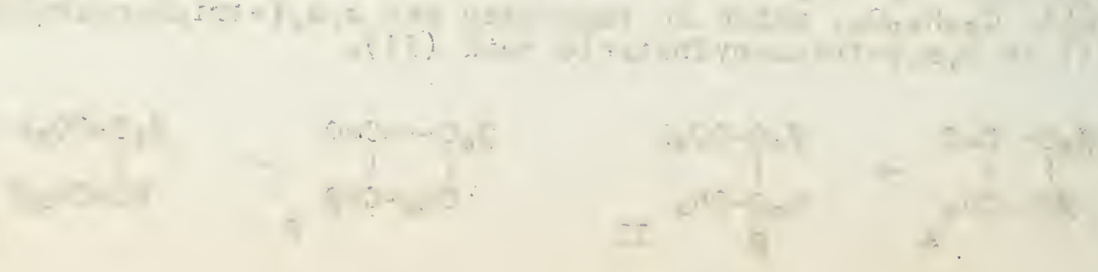


I

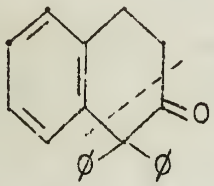
[illegible]

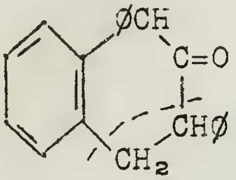
[illegible]



Both of these acids were synthesized by Bergmann and found to differ from Staudinger's acid.

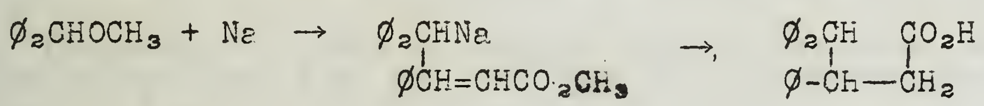
Addition of the ketene might involve reaction at the nuclear double bond (as with benzophenonephenylimide and phenylmagnesium bromide, and ethyl azodicarboxylate and styrene derivatives) to give compounds like:





Bergmann prepared a series of compounds which would result by hydrolytic fission of the above and analagously formed addition products; none was identical with Staudinger's acid.

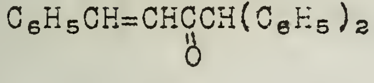
Simonsen in his work on the adduct with cyclopentadiene had found that hydrolytic fission occurred between the diphenyl carbon and the carbonyl group. A similar fission of A would give the acid III. This acid was synthesized by Bergmann and found to be identical with the acid derived from the addition product of diphenylketene and styrene, thus establishing A as the structure of the addition product.



$$\text{Ø}_2\text{CHOCH}_3 + \text{Na} \rightarrow \begin{array}{l}\text{Ø}_2\text{CHNa}\\ \text{ØCH=CHCO}_2\text{CH}_3\end{array} \rightarrow \begin{array}{ll}\text{Ø}_2\text{CH} & \text{CO}_2\text{H}\\ \text{Ø-Ch} & \text{—CH}_2\end{array}$$

III

Structure B was also ruled out by the consideration that it would not account for the isomerization of the original adduct to



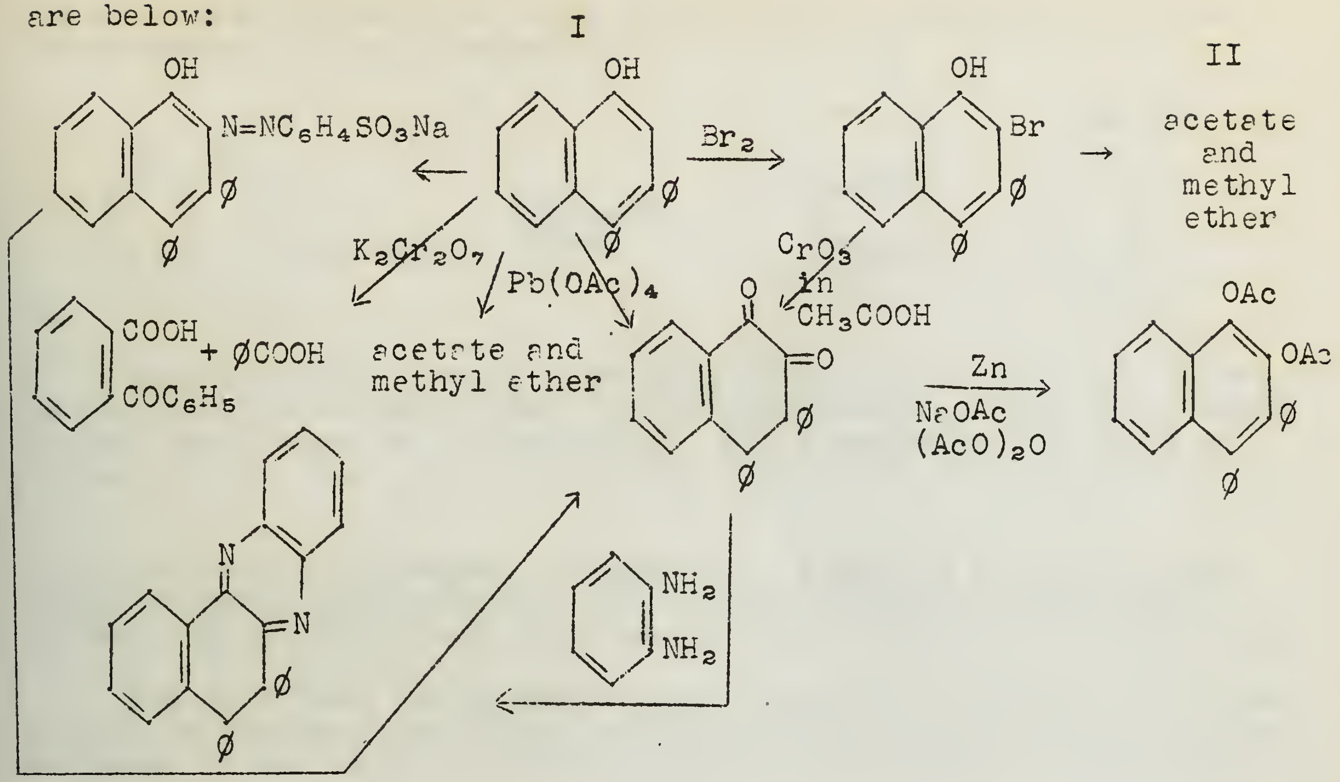
$C_6H_5CH{=}CH\overset{}{\underset{\overset{\|}{O}}{C}}CH(C_6H_5)_2$.

Using a different method of degradation Smith confirmed Simonsen's structure for the adduct with cyclopentadiene. Smith also found that diphenylketene reacted with cyclohexadiene and with 2,3-dimethylbutadiene. However, 1,4-dimethylbutadiene did not react and neither did cyclopentadiene react with ketene.

Farmer and Farooq found that diphenylketene reacted with cyclohexene, cyclopentadiene, cyclohexadiene, dimethylbutadiene and piperylene. However tetramethylethylene would not react.

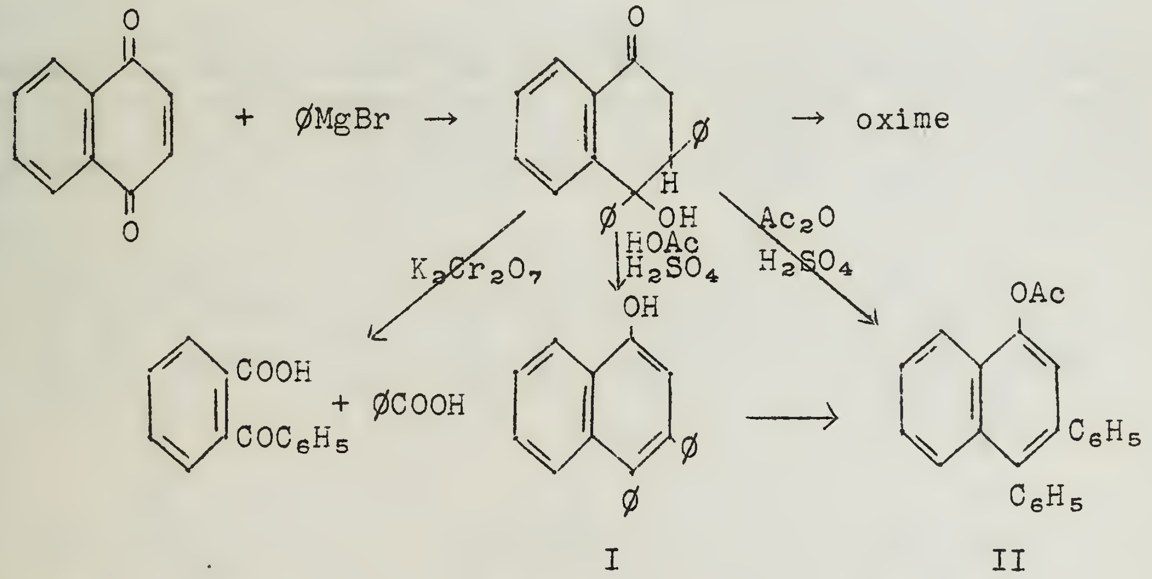
<u>Diphenylketene and Phenylacetylene</u>.--In an attempt to obtain further evidence that styrene and diphenylketene reacted to give cyclobutanone derivatives Agre and Smith tried the reaction between diphenylketene and phenylacetylene. The compound obtained was soluble in methanolic potassium hydroxide and gave a positive phenol test (Folin). The Grignard machine showed one active hydrogen and no addition of reagent. The principal reactions

are below:



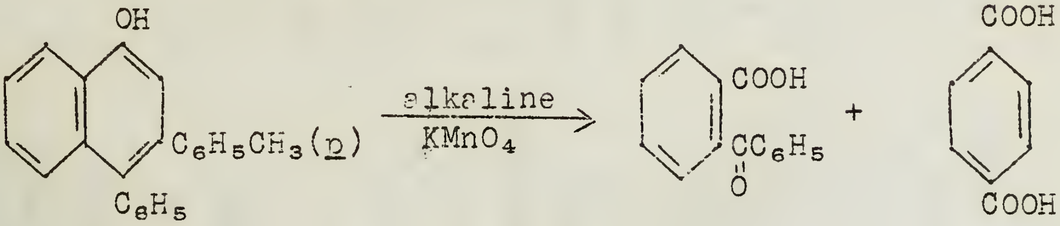
All the reactions were adequately explained by structure I, but the reactions would be just as consistent with the β-naphthol.

Following the lead of earlier work by Franssen, Smith and Hoehn synthesized I by the addition of 1,4-naphthoquinone to an excess of 5 moles of phenyl magnesium bromide.



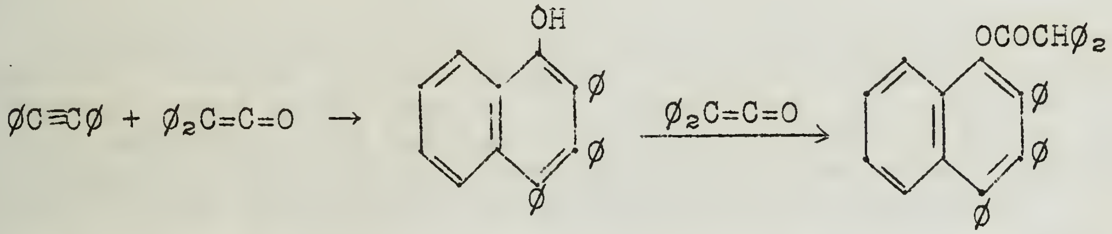
Because of the unexpected nature of the addition product an attempt was made to determine the mechanism of the reaction. The first step was to determine the location of the aryl group from the acetylene. The reaction between *p*-tolyl acetylene and diphenyl-

ketene indicated that the aryl group from the acetylene goes to the 3-position in the naphthalene.

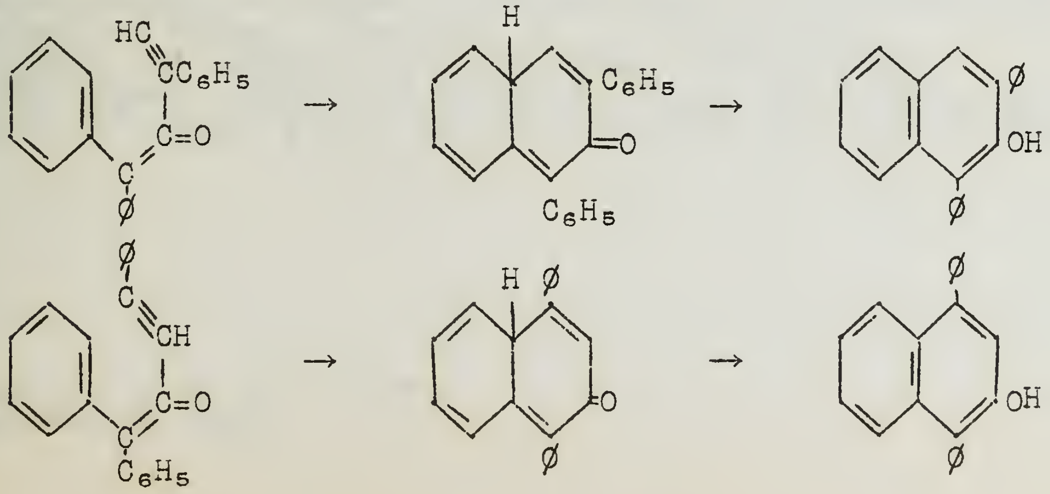


Diphenylketene reacts with many compounds with active hydrogen to give compounds containing the diphenylacetyl group. This might be the first step in the reaction. The compound which would be formed if this were the first step, $Ø_2CH\underset{\overset{\|}{O}}{C}C\equiv CØ$, was prepared by the reaction between $ØC\equiv CMgBr$ and $Ø_2C=C=O$. Attempts to cyclize the phenyldiphenylacetylacetylene with fused $ZnCl_2$ in acetic acid failed. This eliminated this compound as a possible intermediate.

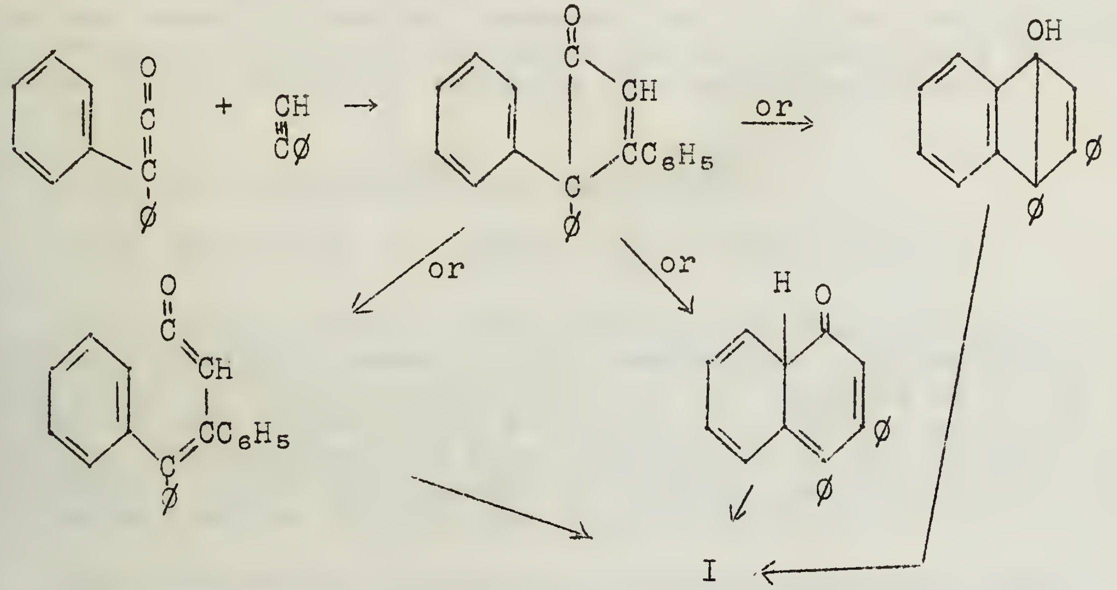
The fact that the disubstituted acetylene reacted in the same manner as the monosubstituted acetylene indicated that the active hydrogen of the phenyl acetylene was not necessary to the reaction.



The addition between diphenylketene and phenylacetylene resembles the Diels-Alder reaction in that no catalyst is required and that elevated temperatures are not needed. The diphenylketene supplies a 1,4 conjugated system, if a double bond of a ring is included. But the diene synthesis could only lead to β-naphthols.



The work of Staudinger, Simonsen, Farooq, and Bergmann had demonstrated that ketenes react with ethylenic compounds to give substituted cyclobutanones. It is therefore quite probable that a cyclobutanone is an intermediate of the reaction with acetylenes.



The cyclobutanone is the first and most important intermediate. It explains the formation of an α-naphthol, why the acetylenic aryl group goes to the 3 position, why both mono- and diarylacetylenes give analagous products. The bond which is broken in subsequent steps is the same one which breaks upon hydrolytic fission of the adducts of diphenylketene and ethylenes.

Attempts to obtain direct evidence for the existence of the cyclobutanone intermediate have been unsuccessful.

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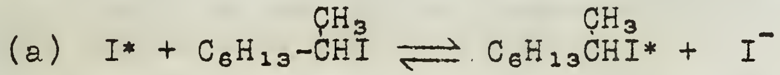
Reported by W. H. Kaplan
December 3, 1941

SOLVOLYTIC REACTION MECHANISM

Hammett-Columbia; Ingold, Hughes-University College, London;
Bartlett-Harvard

Second-order replacement reactions by (a) anions or (b) electron donating neutral reagents are quite well established as occurring by a bimolecular inversion mechanism. This Lewis-London-Polanyi-Olson mechanism explains the Walden inversion.



$$\text{(a)}\quad I^* + C_6H_{13}\text{-}\overset{CH_3}{C}HI \rightleftharpoons C_6H_{13}\overset{CH_3}{C}HI^* + I^-$$

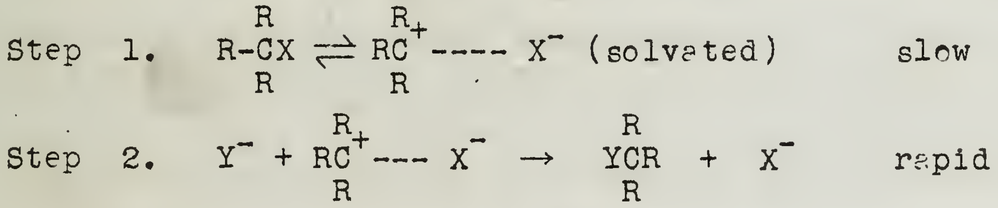
$$\text{(b)}\quad NH_3 + RCl \rightarrow RNH_3^+ + Cl^- \quad \text{(Menschutkin)}$$

It is almost equally well established that not all anion replacement reactions occur by this mechanism. For example: α-phenylethyl chloride is hydrolyzed to the alcohol at a rate independent of the hydroxyl ion concentration, converted to the ethyl ether by alcoholysis at a rate independent of the ethoxyl ion concentration, and to the acetate in glacial acetic acid at a rate independent of the acetate ion concentration.

Such first-order replacements occur in solvents such as water, alcohols, phenols, carboxylic acids, and sulfur dioxide and the reaction rate is influenced by the solvent concentration when a diluent is used.

To explain this first-order (in the presence of large excess solvent) replacement, Ward in 1937 proposed a solvolytic ionization mechanism, which Hammett and Ingold have accepted with modifications. It is unlike the bimolecular mechanism where the energy to eliminate the departing anion is partly furnished from the energy of the bond forming with the simultaneously entering anion.

In the solvolytic mechanism the rate-determining and energy-providing step is the solvation with insipient ionization of the anion-forming part of the molecule. The electron donating or



$$\text{Step 1.}\quad R\text{-}\overset{R}{\underset{R}{C}}X \rightleftharpoons \overset{R}{\underset{R}{C}}{}^{+}\text{----}\;X^-\ \text{(solvated)} \qquad \text{slow}$$

$$\text{Step 2.}\quad Y^- + \overset{R}{\underset{R}{C}}{}^{+}\text{---}\;X^- \rightarrow Y\overset{R}{\underset{R}{C}}R + X^- \qquad \text{rapid}$$

"nucleophilic" reagent Y^- is not involved in the rate-determining step 1.

The hypothesis that step 2 occurs with the anion being removed not over 1 Å away explains why inversion of configuration occurs with large but incomplete racemization when optically active compounds are being substituted on the asymmetric carbon.

The ionization mechanism will be favored relatively to the bimolecular mechanism by large electron-release from R, strong electron-affinity in X, low nucleophilic activity (basicity) and low concentration of Y, and high ionizing capacity of the solvent. Such a mechanism is not possible when the group is held very firmly as in aryl halides and applies essentially to substitution at a saturated carbon atom and in solution.

Primary halides tend to react by the bimolecular mechanism; secondary and tertiary, by the ionization mechanism. The "mechanistic critical point" is illustrated in work of Hughes and Ingold on the decomposition of sulfonium hydroxides and salts in water at 100°.

$$OH^- + RS^+R_2' \rightarrow ROH + R_2'S$$

$$\begin{array}{llll}
(CH_3)_3S^+ & \xrightarrow{k_1} CH_3OH & \text{second-order} & \\
 & & & k_1 = 9\ k_2 \\
(C_2H_5)_3S^+ & \xrightarrow{k_2} C_2H_5OH & \text{second-order} & \\
CH_3\overset{+}{S}(C_3H_7\text{-}i)_2 & \xrightarrow{k_3} C_3H_7OH & \text{first-order} & \\
 & & & k_4 = 2600\ k_3 \\
(CH_3)_2\overset{+}{S}C_4H_9\text{-}t & \xrightarrow{k_4} C_4H_9OH & \text{first-order} &
\end{array}$$

Trimethyl sulfonium salts were decomposed in alcohol.

$$\xleftarrow{\text{basicity}}$$

$$\text{anions:}\quad \underbrace{\bar{O}H > \bar{O}C_6H_5}_{\text{decreasing rate, second-order}} \qquad \underbrace{CO_3^{=} \quad Br^- \quad Cl^-}_{\text{first-order and equal rate}}$$

In addition to the three characteristics illustrated, (1) an ionization favoring solvent, (2) a first-order reaction rate independent of the concentration of the replacing ion, (3) an inductive effect in reverse to that of bimolecular replacement, the solvolytic mechanism can be diagnosed stereochemically.

$$\begin{tikzcd}
\text{\underline{d}-\underline{sec}-octyl bromide} \arrow[r, "1N\ NaOH\ 80^\circ", "60\%\ EtOH"'] \arrow[d, "acid"] & \text{\underline{l}-alcohol less than 10\% racemized} \\
\text{\underline{l}-alcohol 65\% racemized} &
\end{tikzcd}$$

(probably due to secondary reaction)

Some of the other evidence for the mechanism is as follows:

1. In a mixed solvolysis experiment a linear rate dependency on water was observed in the alcoholysis of benzhydryl chloride; however, it was not a case of two superimposed bimolecular reactions because less than 1/4 the theoretical proportion (calculated from the relative rates) of benzhydrol to benzhydrylethyl ether was formed. The water facilitated ionization but entered step 2 to a minor extent.

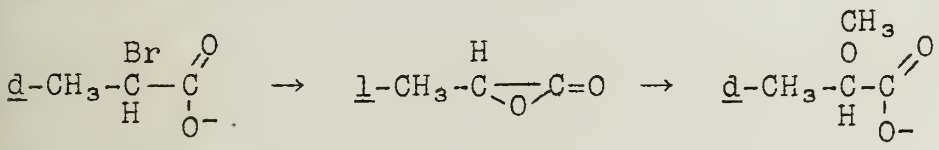
2. In the solvolytic hydrolysis of p,p'-dimethylbenzhydryl chloride in aqueous acetone the two steps do not have widely different rates; therefore, a mass effect can be observed. Due to building up chloride concentration there is a progressive decrease in the overall reaction rate; furthermore a 0.05M addition of chloride ion depresses the reaction rate one-third.

3. Only those halides which cause Friedel-Craft alkylation were effective in racemizing α-phenylethyl chloride and the order of racemizing effectiveness coincided with alkylating effectiveness ($SbCl_5 > BCl_3 > SnCl_4 > ZnCl_2 > HgCl$). The solvolytic ionization is analogous to that caused by these strongly electrophilic reagents; it is presumably less in degree and due to hydrogen bonding.

   Bartlett has found that phenols exhibit hydrogen bonding with hydrogen chloride.

4. Because the rate of hydrolysis of benzhydryl chloride in acetone increases nearly thirtyfold for a tenfold increase in water concentration, and other similar results, Hammett refers to "polymolecular solvolysis." Dimeric water must be more effective in solvolysis than monomeric.

An unusual case is the alcoholysis of d-bromopropionic acid to methoxypropionic acid. The reaction is mainly second-order at sodium methoxide concentrations from 0.5 to 1 M, but mainly first-order from 0.03 to 0.06 M. The second-order reaction inverts the configuration but the first-order reaction does not and is accompanied by no racemization. The interpretation of the first-order reaction involves cyclization and double inversion; the reaction may or may not be solvolytic.



The hydrolysis of ethyl benzene sulfonate shows the characteristics of solvolytic replacement.

First-order elimination reactions have been formulated by Hauser as occurring by the solvolytic initial step.

As a result of this work, to quote Hammett, "It seems very probable that every displacement on an asymmetric carbon the rate of which is proportional to the concentration of the nucleophilic displacing ion or molecule involves an inversion of configuration."

Another step was taken toward the chemical explanation of homogeneous catalysis when it was shown that the solvent is kinetically important in first-order replacements.

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Reported by G. D. Jones
December 3, 1941

AROMATIZATION OF ALIPHATIC HYDROCARBONS

In recent years steps toward more efficient utilization of natural hydrocarbon resources have led to development of such processes as cracking, nitration, chlorination, and aromatization of gaseous hydrocarbons. The conversion of aliphatic hydrocarbons to aromatic hydrocarbons is by no means a recent discovery but the practical solution of the problem is the latest success of the petroleum industries.

A bulk production of aromatics from open chain compounds in industry obviously must make use of suitable naphtha cuts from petroleum sources, light oils arising from low temperature distillation of coal, and the fractions of light spirit derived from either high pressure hydrogenation of coal or from synthetic processes for hydrocarbon production starting with water gas (Fischer-Tropsch synthesis).

Aromatization is best approached by consideration of thermal decomposition of paraffin hydrocarbons. This might proceed in the following manner in the case of <u>n</u>-hexane:

1. $2C_6H_{14} \rightarrow C_{12}H_{26} + H_2$,
2. $C_6H_{14} \rightarrow C_6H_6 + 4H_2$,
3. $C_6H_{14} \rightarrow C_6H_{12} + H_2$,
4. $C_6H_{14} \rightarrow C_6H_{12}(\text{cyclic}) + H_2$,
5. $C_6H_{14} \rightarrow C_5H_9CH_3(\text{cyclic}) + H_2$,
6. $C_6H_{14} \rightarrow C_6H_{10}(\text{cyclic}) + 2H_2$,
7. $C_6H_{14} \rightarrow C_5H_{10} + CH_4$,
8. $2C_6H_{14} \rightarrow C_5H_{12} + C_7H_{16}$,
9. $C_6H_{14} \rightarrow 6C + 7H_2$.

The maze of conceivable reactions may be simplified to a certain extent by a thermodynamic consideration of the possibility of each transformation at different temperature intervals. By means of linear equations expressing the free energies of formation of the hydrocarbons from graphite and hydrogen in the range 300° to 1000° A, the standard free energies accompanying the various transformations can be determined. The conclusions to be drawn for a thermal decomposition at atmospheric pressure are: a reforming reaction (1) cannot proceed since conditions favor the reverse reaction; cyclization and dehydrogenation to benzene (2) begin about 500° A and the equilibrium is well on the aromatic side at 600°A; dehydrogenation to hexene (3) or cyclohexene (4) is not appreciable below 800° A; cyclization to methylcyclopentane (5) sets in about 350° A; cracking (7), disproportionation (8), and decomposition to carbon and hydrogen (9) are appreciable above 400° A.

Reactions 3,4,5 serve to produce substances which can form benzene by further dehydrogenation so that successful solution of the problem of aromatization of *n*-hexane hinges on the suppression of reactions 7,8,9 which involve fission of the C-C bond. The partial or complete elimination of these reactions will depend upon the choice of catalyst. The catalyst, moreover, must be specifically a dehydrogenation catalyst since the energies of the C-C and the C-H bonds are, respectively, 58600 and 87300 cal./mole. Such selective action has been realized in mixtures of oxides of elements of groups VI, V, and IV (in order of their effectiveness) of the periodic table. The most common catalyst is amorphous Cr_2O_3 suspended on an inert carrier such as alumina, magnesia, or silica gel but mixtures containing molybdenum, vanadium, and sometimes titanium and cerium in addition to the chromium give the best results. The method of preparation of these catalysts as well as the ratio of the different oxides is very important to the activity of the catalyst.

Because investigators have employed different catalysts, reaction temperatures, and rates of flow, their results are not usually directly comparable. Nevertheless, the following table summarizes yields obtained in a few dehydrocyclizations for a single passage of the hydrocarbon over the catalyst.

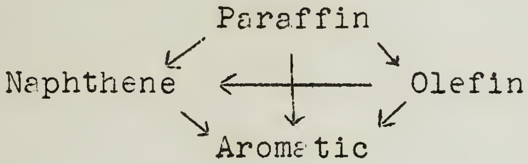
	Composition of liquid product in weight per cent of starting material			
Hydrocarbon	Aromatics	Naphthenes	Olefins	Paraffins
2-Methylpentane	4.3	2.2	14	53
n-Hexane	17.0 (benzene)	2.2	14	54
2-Methylhexane	28.0 (toluene)	0	18	44
2,5-Dimethylhexane	46.0 (80% *p*-xylene)	0	16	26
n-Heptane	30.0 (toluene)	1	9	43
	26	-	-	-
	*12.1	0	11.5	75.5
2,6-Dimethylheptane	82.0 (*m*-methylisopropylbenzene)			
n-Octane	38.0 (55% *p*-xylene, 35% *o*-xylene, 5% *m*-xylene, 5% ethylbenzene)			
n-Nonane	52.0 (greater than 90% methylethylbenzene)			
Butylbenzene	12.0 (naphthalene)			

What would seem to be low yields of aromatics in the table are in most cases satisfactory since the olefins and paraffins appearing in the product are converted to aromatics on recycling. Thus, the latest experimental data on the dehydrocyclization of *n*-heptane (starred data in table), show that there was obtained 98.1 weight per cent of liquid products consisting of 12.1 weight per cent of toluene. The calculated recycle yield (yield obtained by repassing olefins and paraffins over the catalyst) of toluene is 89 weight per cent or 97 per cent of the theoretical.

All paraffin hydrocarbons with the exception of methane have been converted to aromatics with the expected variations in yield. Those hydrocarbons whose structure permits formation of a six-membered ring are aromatized to a marked extent. Branched chain paraffins having less than six carbons in a straight chain give low yields presumably due to the difficulty of the necessary isomerization to a six-membered chain. Extent of aromatization increases with the number of carbons and generally the more ways a cyclization can take place the greater the extent to which it occurs. Nevertheless, all possibilities of ring formation are not realized to an equal extent. It seems that the shortest sidechains (on aromatic rings) are formed preferentially.

The nature of the predominating aromatic products is governed by the reaction temperature. High temperatures favor formation of naphthalene and anthracene. However, the present value of the conversion of aliphatics to pure aromatics lies in the production of toluene and benzene.

The aromatization of paraffins may be conceived as taking place in one of various ways. Thermodynamically, all are possible. Evidence indicates that the olefin is an intermediate in the reaction and not merely a by-product. The next step, cyclization, is considered to involve the double bond in a 5 or 6 position. This is in harmony with the observation that those olefins that have not undergone reaction and are isolated in the product contain the double bond in a 2 or 3 position. These remain only because a shift of the double bond must constitute a step preliminary to cyclization.



In no case have appreciable quantities of naphthenes been isolated from the reaction product. This does not eliminate the naphthene structure as an intermediate in the process since it would be dehydrogenated more easily than the other reactants (probably before it could leave the surface of the catalyst). Under a given set of conditions the extent and ease of aromatization from the following starting materials increases in the order: paraffin < corresponding olefin < six-membered naphthene < corresponding cycloölefin.

Aromatization of relatively pure hydrocarbons proceeds smoothly without formation of large amounts of by-products. On the other hand, the economic cracking of heavy petroleum residues to aromatics depends on the disposal of considerable quantities of gas, tar, and carbon.

The latest variation of the dehydrocyclization reaction is the hydroforming process, a dehydrogenation carried out in the presence of hydrogen. By this process, utilizing low octane heavy naphtha, there may be obtained either a product consisting of 40 to 50 per cent aromatics (high grade gasoline) or one having upwards of 80 per cent aromatics (toluene production)

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Reported by S. P. Rowland
December 10, 1941

THIAZOLES: SOME SYNTHESES AND REACTIONS

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E. Ochiai - University of Tokyo
T. B. Johnson - Yale University

Thiazoles contain a five-membered ring with two hetero-atoms, nitrogen and sulfur, separated by a carbon atom. In numbering the ring, one begins with the sulfur atom and proceeds in a manner such that nitrogen is the number three atom.

Recently there has been a great amount of interest in the pharmacological properties of thiazoles. Johnson has synthesized many thiazoles with a 3,4-dihydroxyphenyl group in the 2-position. They possess definite analgesic and anesthetic action and are equally effective when administered intravenously, subcutaneously or orally. Three of the most recent chemotherapeutic agents are thiazoles-- 2-sulfanilamidothiazole (sulfathiazole), 2-sulfanilamido-4-methylthiazole (sulfamethylthiazole) and 2-sulfanilamido-4-phenylthiazole (sulfaphenylthiazole). They are superior to sulfanilamide and sulfapyridine in their bacteriostatic action on pneumococci types I, II and III, on β-hemolytic streptococcus A and on gonococcus. The 4-methyl derivative is even more effective then sulfathiazole itself. 4-Methyl-5-(β-hydroxyethyl)-thiazole is the sulfur-containing portion of vitamin B_1.

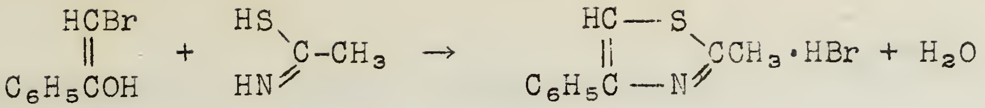
The thiazole nucleus is important in the dye industry. A yellow dye, primuline, was the first thiazole dye. There is still a demand for Thioflavine T discovered by Green in 1889 because it is one of the few dyes giving yellow shades with a prized greenish tone.

In 1921 it was reported that mercaptobenzothiazole was a very powerful vulcanization accelerator. At present the organic accelerator most widely used in industry is mercaptobenzothiazole, known to the trade as "Captax." Other popular accelerators are its zinc salt (Zenite) and its benzoyl derivative (Ureka C). These accelerators have nearly flat vulcanization curves making the vulcanization of thick rubber articles practical.

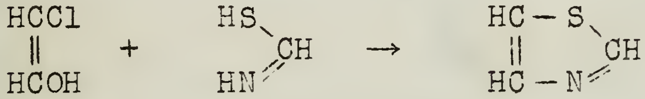
Syntheses of Mononuclear Thiazoles.--(1) The condensation of α-halogen aldehydes and ketones with thioacid amides.

This, one of the most important methods, was worked out by Hantzsch. The reaction is vigorous and is controlled by the use of a diluent such as alcohol, water or ice.

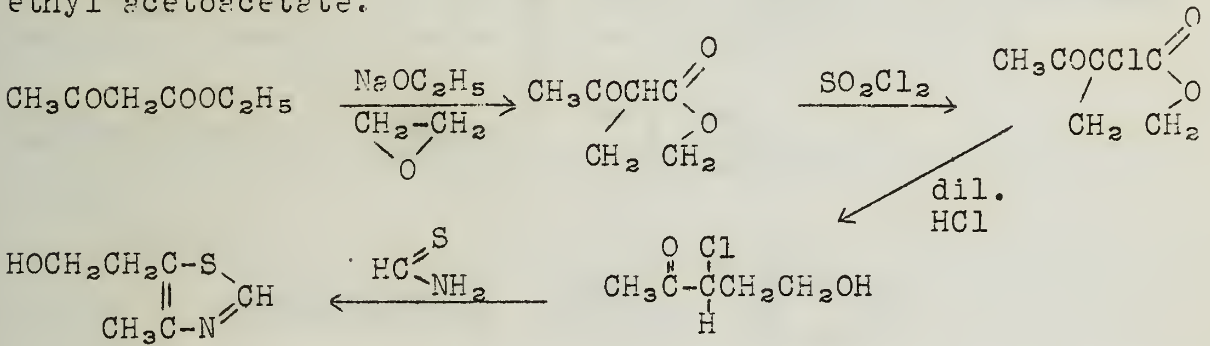
2-Methyl-4-phenylthiazole is obtained from α-bromoacetophenone and thioacetamide.



Thiazoles in which the 2-position is unsubstituted are obtained when thioformamide are used.

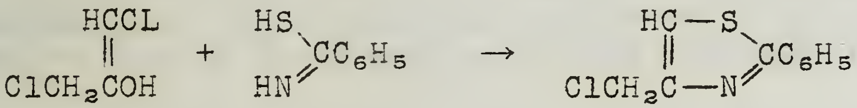


The thiazole portion of vitamin B_1 has been synthesized by three groups of workers. Buchman's synthesis, reported to be the best, yields 8 - 12 grams of the thiazole from 100 grams of ethyl acetoacetate.



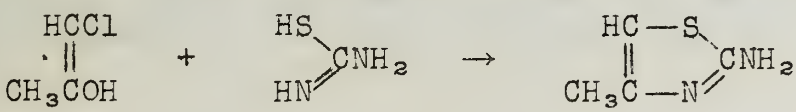
Several recent patents appear to be based on this synthesis.

Johnson has made 4-(α-chloromethyl)-thiazoles by using symmetrical dichloroacetone and thiobenzamide or its derivatives.



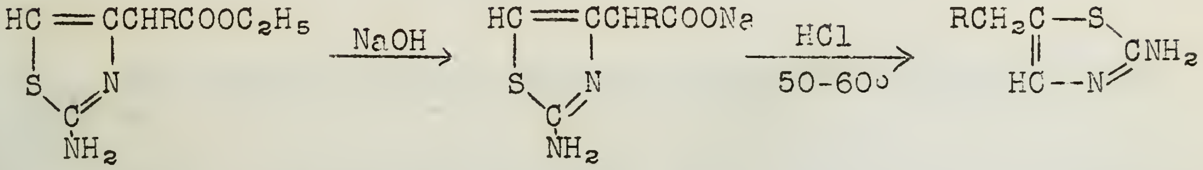
(2) Condensation of α-halogen aldehydes and ketones with thioureas.

This synthesis was first employed by Traumann in the preparation of 2-aminothiazoles. It is illustrated by the synthesis of 2-amino-4-methylthiazole given in Organic Syntheses.



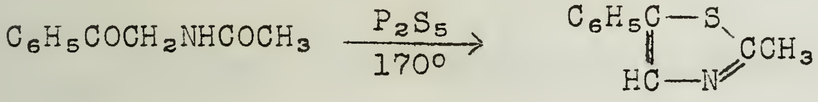
In a search for new sulfanilamide derivatives, Ziegler has used it recently for the preparation of 2-amino-4-alkylthiazoles.

$$CH_3COCHRCOOC_2H_5 \xrightarrow[CS_2]{Br_2} BrCH_2COCHRCOOC_2H_5 \xrightarrow{NH_2CSNH_2}$$

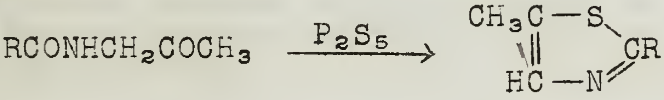


(3) Treatment of α-acylated aminoaldehydes and aminoketones with phosphorus pentasulfide.

This reaction was first used by Gabriel in the synthesis of 2-methyl-5-phenylthiazole from acetaminoacetophenone.

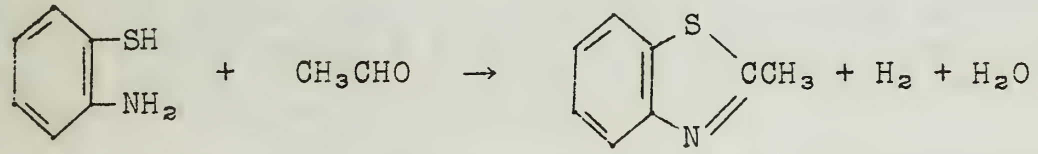


Similarly:

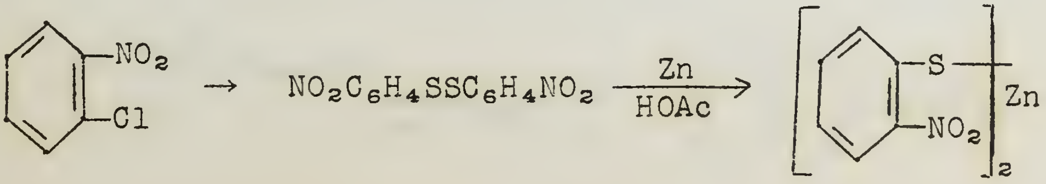


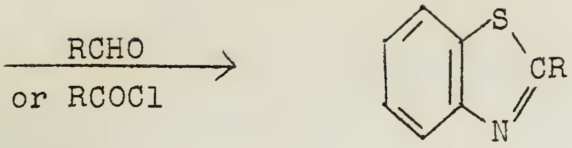
Syntheses of Benzothiazoles.--(1) Condensation of o-aminophenylmercaptans with acids, acid anhydrides, acid chlorides, aldehydes and ketones.

Hofmann developed this reaction for the preparation of benzothiazoles. Condensing acetaldehyde with o-aminophenylmercaptan results in the formation of 2-methylbenzothiazoles.



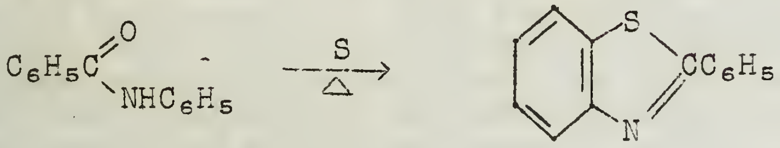
However, these mercaptans are frequently unavailable since they are usually prepared from the benzothiazoles and are often unstable. With some modification, this method has been especially fruitful in the hands of Bogert and his coworkers.





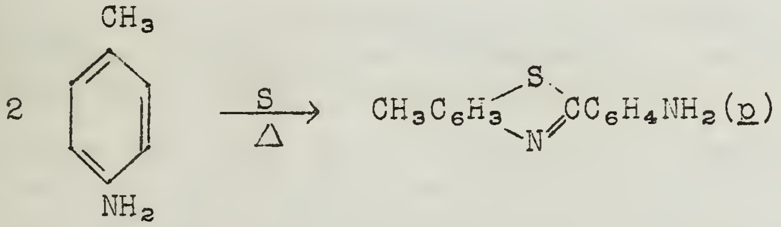
(2) Heating aromatic amines and their derivatives with sulfur.

Bogert and Abrahamson report that the fusion of benzanilide with sulfur is the best method for the synthesis of 2-phenylbenzothiazole.



Similarly, benzothiazole itself would be obtained from formanilide.

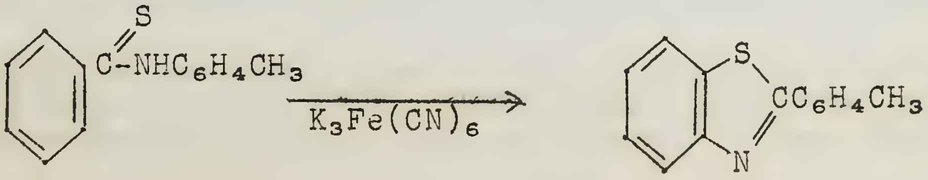
The principal product from the fusion of p-toluidine with sulfur for the manufacture of thiazole dye intermediates is dehydrothio-p-toluidine.

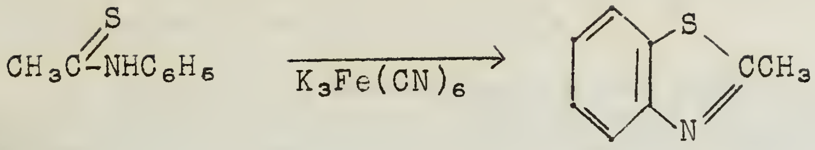


A larger molecule is obtained upon further heating with sulfur. The sodium salt of the sulfonic acid obtained by the action of fuming sulfuric acid on this molecule is primuline. An entire series of dyes is obtained by diazotizing and coupling primuline with amines and phenols.

(3) Rearrangement of compounds with the group CH-N-C-S- .

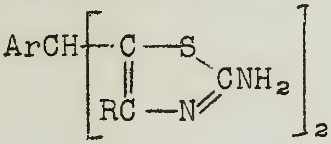
Jacobson found that thioanilides and phenylthiourethans are oxidized by alkaline potassium ferricyanide at room temperature to benzothiazoles. Bogert and Meyer used this method in the synthesis of 2-(p-tolyl)-benzothiazole.





Properties and Reactions of Thiazoles.--The benzothiazoles resemble the quinolines. They are stable to acids but yield an o-aminophenylmercaptan and an acid when boiled with alcoholic alkali or fusing with potassium hydroxide.

The thiazoles resemble the pyridines. Their aqueous solutions react neutral and they form stable salts with acids which have an acid reaction. They are oxidized by potassium permanganate. They are unaffected by most reducing agents but sodium amalgam and alcohol cleave the ring with the formation of an amine and a mercaptan. 2-Aminothiazoles can be diazotized and then treated as any primary aromatic amine. 2-Amino-4-alkylthiazoles couple in the 5-position with diazotized amines to form azo dyes. Two molecules of the 2-amino-4-alkylthiazole will also condense with an aromatic aldehyde to form a compound of the type



The chlorine atom in the 2-phenyl-4-(α-chloromethyl)-thiazoles is comparable to that in benzyl chloride. Ammonia will replace it with an amino group at room temperature.

Most of the work on the substitution reactions of thiazoles has been done in the last three years by Ochiai and his coworkers. Brominations were conducted by treating the thiazole in ice cold dilute sulfuric acid with bromine and allowing it to stand overnight and by allowing the thiazole to stand overnight with chloroform and bromine. The 4-methyl and 5-methyl thiazoles were unaffected while the 2-hydroxy and 2-aminothiazoles gave the 5-bromo derivative. 2-Bromothiazoles are obtained when thiazoles are brominated in the vapor phase at 250° and 400°. The 2-bromo derivative is also obtained when benzothiazole is brominated at 450°.

4-Methylthiazole cannot be nitrated. 2-Hydroxy-4-methylthiazole gives the 2-hydroxy-4-methyl-5-nitrothiazole. The analogous 2-aminothiazole gives the corresponding 4-methyl-2-nitramino-5-nitrothiazole. When a phenyl group occupies the 4- or the 5-position, a p-nitrophenyl derivative is obtained.

4-Methylthiazole-5-sulfonic acid is obtained when 4-methylthiazole is sulfonated. The 2-amino derivative yields 2-sulfamino-4-methylthiazole when sulfonated in the cold.

Further treatment produces the corresponding 2-sulfamino-4-methylthiazole-5-sulfonic acid.

A thiazole unsubstituted in the 2-position is obtained when 2-mercaptothiazoles are oxidized by acid or neutral hydrogen peroxide. Oxidation with alkaline hydrogen peroxide produces the 2-sulfonic acid.

2-Hydroxy-4-methylthiazole undergoes the Friedel-Crafts reaction with acetylchloride to give 2-hydroxy-4-methyl-5-acetylthiazole; with benzoyl chloride to give 2-hydroxy-4-methyl-5-benzoylthiazole. 4-Methylthiazole would not undergo the Gattermann reaction but 2-hydroxy-4-methylthiazole did, forming the 5-aldehyde.

An amino group is introduced in the 2-position both of thiazoles and benzothiazoles when they are treated with sodamide at 140-150°.

Fox and Bogert have observed that 6-alkoxy-7-nitrobenzothiazoles, in the presence of alcohols and small amounts of dilute caustic alkali, exchange their alkyls for those of the alcohol used.

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Reported by G. W. Cannon
December 10, 1941

HIGH PRESSURE HYDROGENATIONS OVER NICKEL AND COPPER CHROMITE

Adkins et. al. University of Wisconsin

The use of hydrogen at high pressures and temperatures in laboratory syntheses has been made practical by the work of Adkins and his students. For the most part, this seminar is concerned with the results which they have obtained. In a previous seminar, the reactions of organic molecules over platinum, palladium, and other catalysts at low pressures were covered. These data will not be included in this report.

Hydrogen reacts with organic molecules either by addition to a multiple linkage (hydrogenation) or by cleavage of the molecule (hydrogenolysis). For convenience, the reaction of hydrogen with common functional groups will be considered before discussion of the selective hydrogenation of polyfunctional molecules.

The most widely used catalysts for these hydrogenations are copper chromite and nickel. Nickel catalyst is prepared either on a support such as kieselguhr or as "Raney" nickel. It is a highly active, versatile catalyst even at room temperatures and at low hydrogen pressures. In many partial hydrogenations it is difficult to stop the reaction when the calculated amount of hydrogen has been taken up. In cases like these the "limited (16) hydrogenation" procedure of Adkins and Durland can be used. This procedure is carried out by filling the bomb with nitrogen at 100 atmospheres and then adding the calculated amount of hydrogen. The nickel functions as a catalyst until the partial pressure of hydrogen approaches zero.

Copper chromite (Adkins' catalyst) is a highly useful, stable catalyst prepared by the decomposition of copper ammonium chromate. It is active at temperatures above 100° and at hydrogen pressures greater than 20 atmospheres, and is particularly useful for the hydrogenation of esters to alcohols and amides to amines. It is notably inactive for the hydrogenation of the benzenoid nucleus and, therefore, may be used for the hydrogenation of aryl compounds without much danger of saturating the benzene ring. As an example, naphthalene can be hydrogenated over copper chromite to tetralin, at which point the reaction stops. With nickel as catalyst tetralin can only be obtained by interrupting the reaction when the theoretical amount of hydrogen has been absorbed. A review of the preparation and properties of these catalysts is given in recent publications. (1,2)

Hydrogenation of the alkene linkage: In general the alkene linkage is easily and quantitatively reduced. A selected list of examples is given below. Of all the hydrocarbons, the only carbon-carbon bond which is easily cleaved is the ethane bond in phenylated ethanes. For example, tetraphenylethane undergoes hydrogenolysis (cleavage) of the carbon-carbon bond. The corresponding cyclohexyl derivatives have a stable ethane bond.

Hydrogenation of Alkenes

Compound	°C	Time(Min.)	Catalyst*	Products**	
styrene	20	25	Ni(k)	ethyl benzene	(3)
styrene	125	7	CuCrO	ethyl benzene	(3)
1,1,2,2,-tetraphenyl ethylene	100	130	Ni(k)	1,1,2,2,-tetraphenyl ethane	(3)
1,1,2,2-tetraphenyl ethylene	150	15	CuCrO	1,1,2,2-tetraphenyl ethane	(3)
cyclohexene	165	1	CuCrO	cyclohexane	(4)

*Ni(k) - nickel on kieselguhr **The yields averaged 95-100%

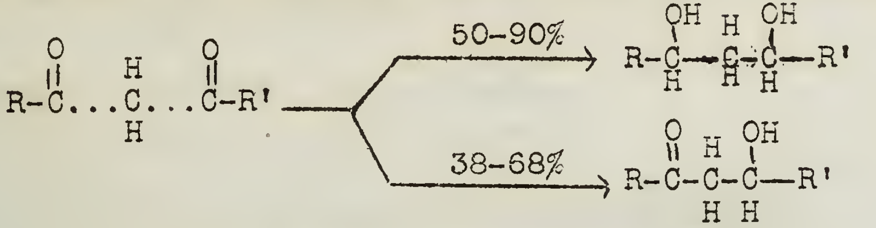
Hydrogenation of carbonyl compounds: The carbonyl group in aldehydes, ketones, esters, and lactones is of varying reactivity. Hydrogenation of the carbonyl group in amides will be discussed separately.

(a) Aldehydes and ketones generally react with hydrogen under conditions as mild as those required for the reduction of the alkene link. The yield of alcohol is practically quantitative even with aldo or keto esters and alcohols. Carbonyl compounds which are reduced to benzyl alcohols or to 1-3 or 1-4 glycols can undergo hydrogenolysis of the C-OH bond. This side reaction is a function of the conditions; the higher the temperature and the longer the duration of the reaction, the greater will be the amount of hydrogenolysis. For example, benzaldehyde is reduced in 92% yield to benzyl alcohol; however, reduction of ethyl benzoate requires high temperatures and gives a quantitative yield of toluene rather than benzyl alcohol.

(b) Esters are hydrogenated over copper chromite at 200-250° to give almost quantitative yields of the corresponding alcohols or glycols. Esters which are reduced to unstable alcohols or glycols give lower yields. To reduce diethyl succinate to tetramethylene glycol (74% yield) the reaction is carried out as rapidly as possible in order to cut down the cleavage of the 1-4 glycol.

(c) 1-3 Diketones can be reduced either to the keto alcohol, or to the 1-3 glycol as well as undergoing hydrogenolysis of the carbon-carbon bond. Keto alcohols have been isolated in the reduction of a series of 1-3 diketones in 35-68% yield. The corresponding 1-3 glycols could be prepared in 50-90% yield. If the methylene carbon of the diketone is substituted, hydrogenolysis

takes place quite readily. The labile carbon-carbon bonds in 1-3 diketones are shown by dotted lines in the formula below --



(11)

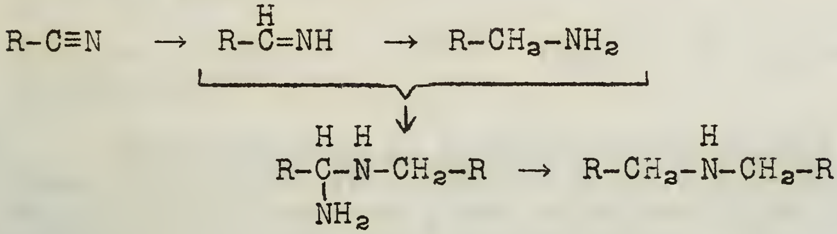
(12)

Hydrogenation of Carbonyl Compounds

Compound	T°C	Time	Catalyst	Yield	Product
acetone	125	13m	Ni(k)	100	propanol-2 (3)
cyclopentanone	100	6 hr	Ni(k)	100	cyclopentanol (6)
acetophenone	150	30 m	CuCrO	95	phenylmethylcarbinol (7)
acetophenone	110	10mn	Ni(R)	91	phenylmethylcarbinol (7)
benzophenone	160	1 hr	Ni(k)	87	diphenylcarbinol (6
benzil	125	1 hr	Ni(k)	90	1,2-diphenylethylene glycol (6)
benzaldehyde	180	1 m	CuCrO	92	benzyl alcohol (4)
benzylalcohol	125	10 m	Ni(k)	88	toluene (5)
ethyl benzoate	250	--	CuCrO	100	toluene (8)
acetophenone	175	6 m	Ni(k)	88	ethylbenzene
benzophenone	175	1 hr	CuCrO	97	diphenylmethane (4
ethyl caproate	250	5 hr	CuCrO	95	hexanol-1 (8)
ethyl stearate	250	3 hr	CuCrO	95	octadecanol-1 (9)
diethyl succinate	250	1-1/2 hr	CuCrO	74	tetramethylene glycol (10)
				18	butyrolactone
diethyl adipate	250	--	CuCrO	95	hexanediol-1-6 (10
diethyl α-methyl succinate	250	3 hr	CuCrO	30	2-isopropylbutanediol,1-4 (10)
diethyl α-phenyl succinate	250	6 hr	CuCrO	12	2-phenylbutanediol, 1-4
				67	3-phenylbutanol-1 (10)

The functional group in cyanides, imines, hydroxylamines, oximes and nitro compounds is readily reduced under mild conditions to give good yields of amines. Formation of secondary amines is a side reaction in the reduction due to the reaction of an imine with the primary amine. This secondary amine formation can be reduced to a large extent by carrying out the reduction

rapidly, and by using methanol-ammonia as solvent. By this procedure alkyl cyanides can be reduced to primary amines in yield as high as 95%.

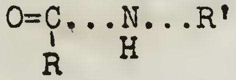


$$R{-}C{\equiv}N \rightarrow R{-}\overset{H}{C}{=}NH \rightarrow R{-}CH_2{-}NH_2$$

$$R{-}\underset{NH_2}{\overset{H}{C}}{-}\overset{H}{N}{-}CH_2{-}R \rightarrow R{-}CH_2{-}\overset{H}{N}{-}CH_2{-}R$$

n-butyl cyanide	125°	30 m	Ni(R)	67%	n-pentyl amine (8)
				16	di-n-pentyl amine
n-butyl cyanide	methanol-ammonia			95	n-pentyl amine (13)
benzal aniline	65	5 m	Ni(k)	97	phenyl benzyl amine
benzal aniline	175	25 m	CuCrO	97	phenyl benzyl amine (15)

Reduction of amides to amines: Although this hydrogenation requires drastic conditions (temperature 250-265°, pressure 200-300 atmospheres) the yield of amines is very good. With substituted amides, the yields range from 80-95% while with simple amides the yield is lowered due to formation of secondary amines at the high temperature necessary for the reduction. In addition to reduction of the carbonyl, the linkages shown by dotted lines in the formula below are subject to hydrogenolysis. For the most part side reactions due to cleavage of these bonds are small. (1)

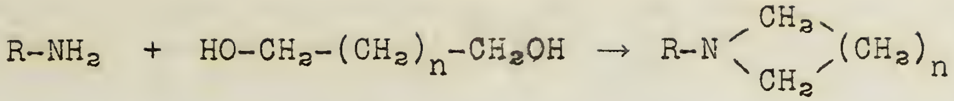


$$O{=}\underset{R}{C}\cdots\underset{H}{N}\cdots R'$$

Reduction of Amides (CuCrO catalyst)

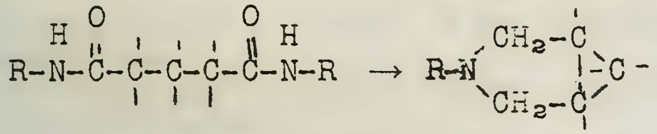
Lauramide	250°	42 m	48	n-duodecylamine (10)
Heptamide	250	4 hr	49	di-n-duodecylamine
Heptamide	250	4 hr	39	n-heptylamine (10)
			58	di-n-heptylamine
Salicylamide	250	2 hr	80	o-cresol (10)
Lauroylpiperadine	250	1 m	2	n-duodecyl alcohol (10)
			92	N-n-duodecyl piperadine
N-diethylheptamide	250	1 hr	64	n-heptylethylamine (10)
			4	n-heptyldiethylamine
			25	di-n-heptylamine

Reaction of glycols with amines: Secondary and tertiary amines can be prepared in 30 to 70% yields by reaction of glycols with amines in the presence of copper chromite. When 1-4, 1-5, or 1-6 glycols are used the corresponding pyrrolidine, piperidine, and hexahydroazepine is produced. The yield of the seven member ring compound (hexahydroazepine) is low (17%), but that of pyrrolidines and piperidines averages 50-75%.



Pentane 1-4 diol *n*-amylamine	250	CuCrO	60	1-*n*-amyl-2-methylpyrrolidine (17)
hexane 1-5 diol *n*-amylamine	250	CuCrO	75	1-*n*-amyl-2-methylpiperidine (17)

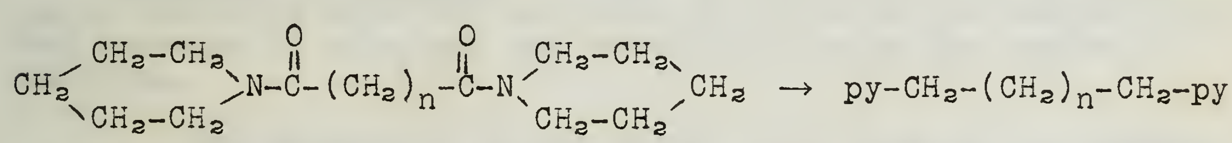
Hydrogenation of N-substituted amides of dicarboxylic acids: When the amides are prepared from 4,5,6-carbon chain dicarboxylic acids, hydrogenation gives excellent yields of pyrrolidines, piperidines, and hexahydroazepines. By this method β and γ substituted piperidines can be prepared by starting with the appropriate substituted glutaramide.



R amyl, benzyl, phenylethyl

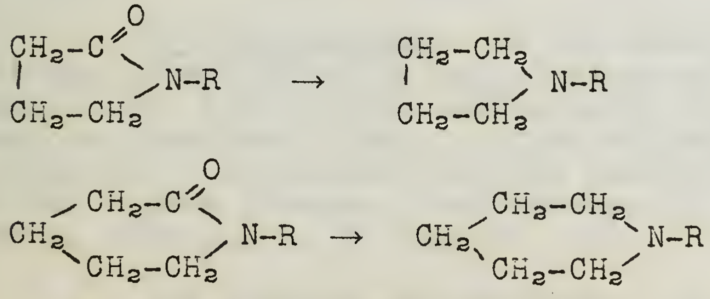
Adipamides cyclize in this reaction to give hexahydroazepines in 35% yield

In the case where the piperidine amide of these acids is reduced, ring closure is impossible and straight chained substituted cadaverines are formed.



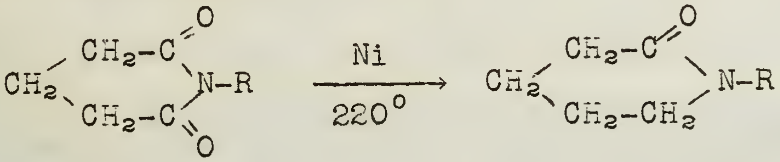
N-*n*-amylsuccimide	200	30 m	CuCrO	79	N-*n*-amylpyrrolidine (10)
glutaramide	250	2 h	CuCrO	70	piperadine (14)
di-N-*n*-amyl-β, β dimethyl glutaramide	250	4-1/2 h	CuCrO	69	1-*n*-amyl-4,4'-dimethyl piperidine (14)
β-methylglutarimide	250	1-1/2	CuCrO	50	4-methyl piperidine (14)

Hydrogenation of pyrrolidones and piperidones: (14)



It is not impossible that these cyclic imides would be intermediates in the hydrogenation of amides of dicarboxylic acids to cyclic amines. However, the yield of cyclic amines by

reduction of these compounds is less than the overall yield from the straight chained amides. The piperidones and pyrrolidones are prepared in excellent yield by partial reduction of the appropriate cyclic imides. Nickel is used as a catalyst in this reduction.



Preparation of amines from aldehydes and ketones: The reduction of aldehydes and ketones in the presence of ammonia or amines (Mignonac's method) is a very satisfactory preparative method for secondary and tertiary amines.

butyraldehyde	125	2 hr	Ni(k)	70	dicyclohexylamine	(15)
piperidine				93	N-*n*-butylpiperadine	(15)
cyclohexanone	125	2 hr	Ni(k)	70	dicyclohexylamine	(15)
cyclohexylamine						

In hydrogenation reactions today the critical problem is not better, but more selective hydrogenation. By selective hydrogenation is meant the use of the proper catalyst and conditions so as to bring about the preferential hydrogenation of the important functional groups in the presence of each other.

Control of reaction: Success in selective hydrogenation depends primarily upon the selection of the catalyst, temperature, and duration of reaction, and secondarily upon the medium of reaction.

(a) Catalyst: Proper choice of a catalyst is perhaps the one most important factor to be recognized in choosing conditions for a selective hydrogenation. For an example, copper chromite is relatively inactive toward benzenoid nuclei, hence aldehydes, ketones, esters, and amides containing an aryl group may be hydrogenated to the corresponding alcohols or amines containing the benzenoid ring. Nickel, on the other hand, is inactive toward oxygen-containing groups as the amido and carbalkoxyl groups, so compounds of these types containing aryl groups may be converted to the corresponding amides or esters containing cyclohexyl groups. Other selective catalysts will be encountered later.

(b) Temperature: In the discussion of hydrogenation reactions it was noted in many instances that one functional group reacts at a temperature sufficiently below that required for another functional group to make selective hydrogenation easily attainable. An example of this is the selective hydrogenation of the alkene linkage in preference to other unsaturated carbon-carbon linkages as in benzene, etc.

(c) Duration of reaction: In the preparation of β-phenylethyl alcohol from ethyl phenylacetate, the optimum yield of

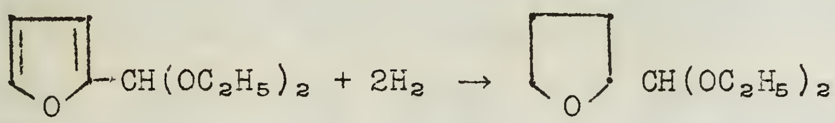
phenylethyl alcohol is obtained only by interrupting the hydrogenation before all the ester has undergone the first step in the following reaction: (29)

(1) $C_6H_5CH_2COOC_2H_5 + 2H_2(CuCrO) \xrightarrow{250^\circ} C_6H_5CH_2CH_2OH + C_2H_5OH$

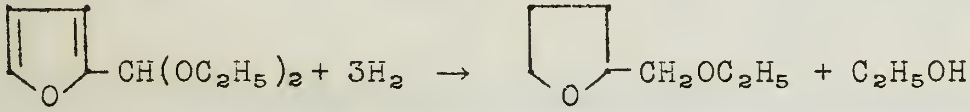
(2) $C_6H_5CH_2CH_2OH + H_2(CuCrO) \xrightarrow{250^\circ} C_6H_5CH_2CH_3 + HOH$

(d) Modification of reaction medium: If diethyl furfural acetal is hydrogenated two principal products are obtained:

(1)



(2)



Over a nickel catalyst reaction (2) takes place to give the ether in 95% yields. However, if a little sodium carbonate, sodium ethoxide, or any one of several amines is added, reaction (1) takes place and the saturated acetal is obtained in 30-80% yields. (5)

Structure and ease of hydrogenation: Attempts to summarize the relative ease of hydrogenation of a series of monofunctional compounds will embody contradictory facts which have no immediate explanation. However, on the basis of present data, the following qualitative list may be proposed:

1. Alkynes
2. Alkenes
3. Imides
4. Oximino
5. Nitro-nitroso
6. Cyanides
7. Aldehydes
8. Ketones
9. Furanoid
10. Pyridinoid (subst.)
11. Benzenoid
12. Pyrroloid (N-subst.)
13. Esters
14. Amides

The relative ease of reaction of two compounds with different functional groups taken separately is not a safe basis of prediction as to the relative rates of hydrogenation of the two compounds in a mixture or of the two groups when both are in the same molecule. *d*-Alpha pinene is hydrogenated much more rapidly than cinnamic acid, yet in a mixture of the two, cinnamic acid is completely hydrogenated to the exclusion of the pinene. Likewise in a single molecule the functional group which taken alone is most reactive is not always the most active when the molecule contains a second functional group.

Selective hydrogenations:

1. Hydrogenation of unsaturated esters: Despite the fact that the carbon to carbon double bond in alkenes is

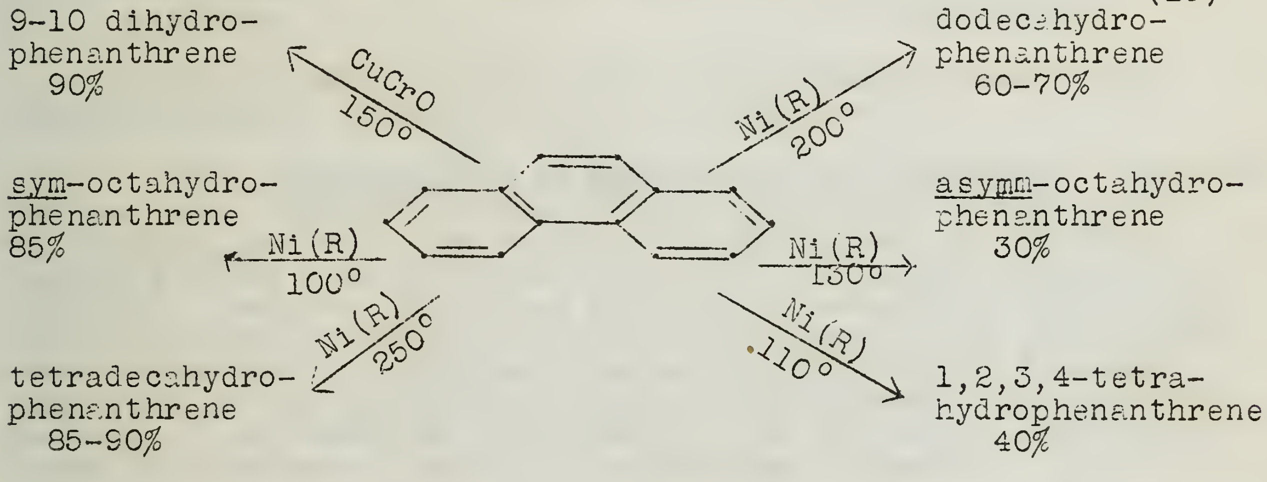
hydrogenated under as mild conditions as is any other functional group, and despite the fact that the carbalkoxyl group requires a temperature of over 200° and pressures exceeding 100 atmospheres, certain unsaturated esters have been hydrogenated to the corresponding unsaturated alcohols using zinc chromite as a catalyst. (18)

Butyl oleate	300°	11 h	ZnCrO	65	octadecenol
Butyl erucate	300°	11 h	ZnCrO	68	ducosenol

2. Hydrogenation of benzenoid type compounds: The benzenoid nucleus requires more drastic conditions for hydrogenation than most other functional groups.

Benzene	150°	1 h	Ni(R)	100	cyclohexane (30)
Toluene	175°	5 m	Ni(R)	100	methylcyclohexane (30)
Mesitylene	200°	4 h	Ni(R)	92	1,3,5-trimethylcyclohexane (30)

(a) Selective Hydrogenation of Phenanthrene (16) (19)



3. Hydrogenation of furanoid type compounds: Hydrogenation of the furanoid nucleus occurs under somewhat milder conditions than those used for the benzenoid ring and also differs in that the furan ring is a cyclic ether and hence subject to hydrogenolysis.

2-Methyl furane	150°	1 h	Ni(k)	83	2-methyl tetrahydrofurane (20)
Furfuryl alcohol	125°	2.5h	Ni(k)	85	tetrahydrofurfuryl alcohol (21)
Furoin (in EtOH)	150°	0.5h	Ni(k)	93	1,2-dihydroxy-1,2-ditetrahydrofurfuryl ethane (21)
Diethyl furfuryl acetal (1 g. amyl amine)	175°	5 h	Ni(k)	76	diethyl tetrahydrofurfural acetal (21)

4. Hydrogenation of pyridinoid type compounds: Pyridine requires a somewhat higher temperature for conversion to piperidine than does the transformation of benzene to cyclohexane. However, derivatives of pyridine are generally more readily hydrogenated than are derivatives of benzene. This is evidenced by the preferential hydrogenation of the pyridine ring in compounds such as quinoline and phenyl pyridine.

Pyridine compounds with substituents, viz., carbethoxy, benzyl, etc., in the 2 or 2,6-positions are hydrogenated rapidly at lower temperatures than is pyridine itself. This is no doubt due to the effect of the substituents in lowering the tendency of the nitrogen to "poison", i.e., to combine with, the catalyst.

Refs. (22)(4)

pyridine	200°	7 h	Ni(R)	83	piperidine
3-acetyl pyridine	145°	4.5h	Ni(R)	28	3-ethyl piperidine
				61	3-piperidyl methyl ketone
2-methyl pyridine	200°	0.6h	Ni(R)	90	2-methyl piperidine
2-benzyl pyridine	100°	3 h	Ni(R)	85	2-benzyl piperidine
2,6-dicarbethoxy pyridine	137°	0.01h	Ni(R)	66	2,6-dicarbethoxy piperidine

Copper chromite is also active for hydrogenation of the pyridine ring in compounds such as quinoline.

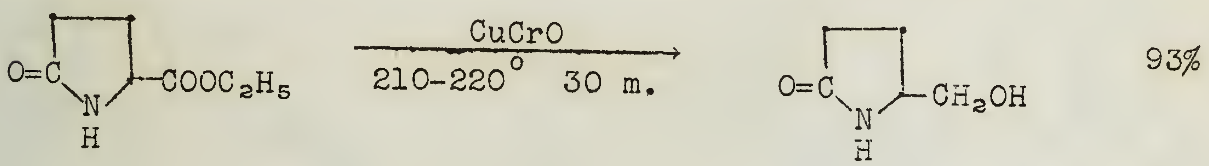
5. Hydrogenation of pyrroloid type compounds: Pyrroles are far less reactive toward hydrogen than are the derivatives of benzene, pyridine, or furane. The 2,3,4 and (or) 5-alkyl pyrroles react with hydrogen over nickel or copper chromite at 200-250°. However, the 2,3,4 and (or) 5-carbethoxy pyrroles require such drastic conditions that hydrogenation of the nucleus does not occur without simultaneous hydrogenation and hydrogenolysis of the carbethoxyl group. On the other hand, pyrroles bearing a carbethoxy or aryl group on the nitrogen atom readily react with hydrogen from room temperatures upward.

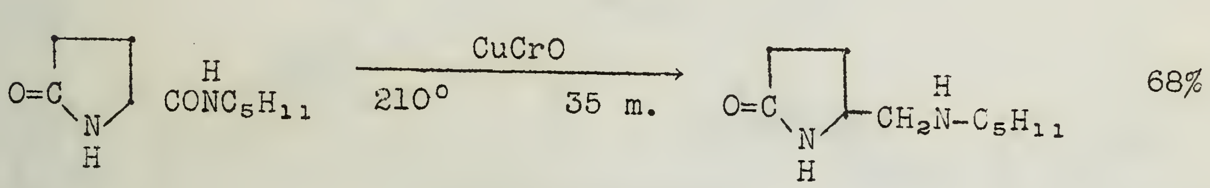
Because of the resistance of the nucleus toward hydrogenation, acyl pyrroles have been converted to alkyl pyrryoles in excellent yields over copper chromite. Similarly carbethoxy pyrroles have been converted to methyl pyrroles although careful control of the reaction is necessary so as to avoid excessive formation of pyrrolidines.

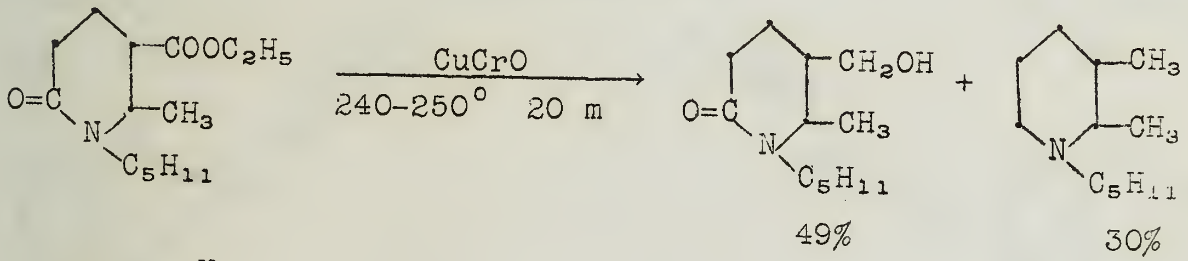
a. Pyrrole	180°	1 h	Ni(R)	47	pyrrolidine (23)
b. 1-Phenyl pyrrole	135°	1 h	Ni(R)	63	1-phenylpyrrolidine (23)
c. 1-Carbethoxy pyrrole	70°	0.3h	Ni(R)	93	1-carbethoxypyrrolidine (24)
d. 2,4-diacetyl-3,5-dimethyl pyrrole	160°	0.3h	CuCrO	94	2,4-diethyl-3,5-dimethyl pyrrole (23)
e. 2,4-dicarbethoxy-3,5-dimethyl pyrrole	220°	0.3h	CuCrO	53	3-carbethoxy-2,4,5 trimethyl pyrrole (23)
				5	2,3,4,5-tetramethyl pyrrolidine

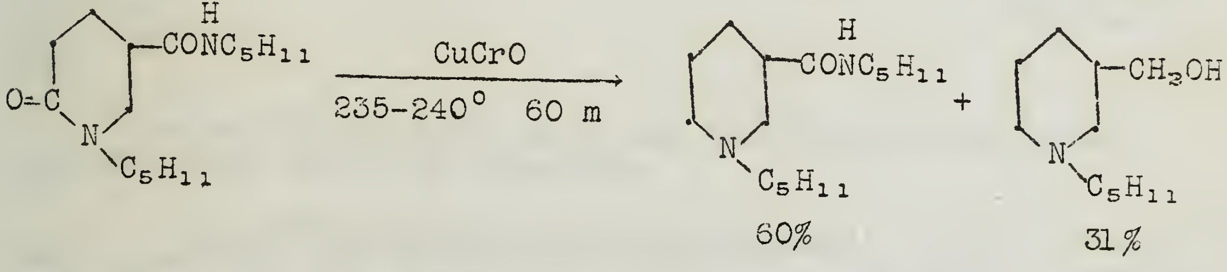
f.	1,2-dicarbethoxy pyrrole	200°	1 h	CuCrO	42	2-methyl pyrrole (23)

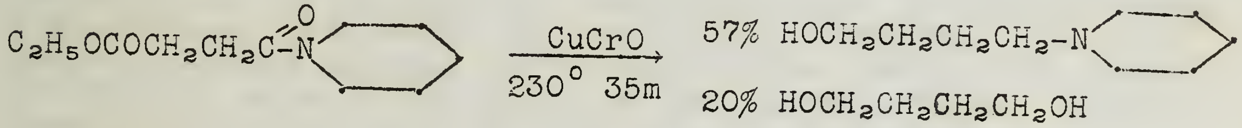
6. Hydrogenation of substituted amides: As previously stated, hydrogen under 200-300 atmospheres reacts with amides at 200-260° under the influence of copper chromite to give amines. A study of the reaction of various substituted pyrrolidones and piperidones and open chain amido esters with hydrogen offers an excellent example of selective hydrogenation. (25)







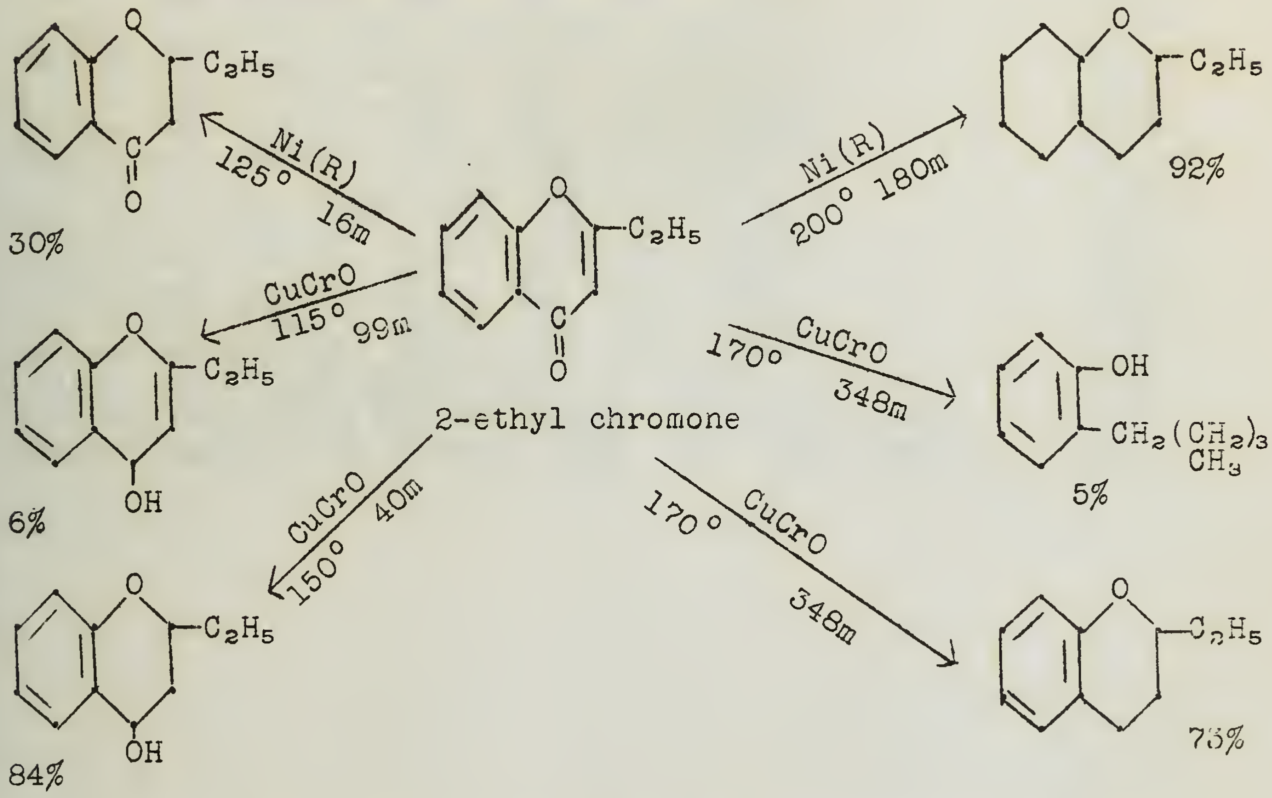




From the above data it is observed that a carbethoxy or amido group in the 5-position in a pyrrolidone-2 is more reactive toward hydrogen than is the lactam group of the ring. In the piperidine series this same relationship holds with respect to the carbethoxy derivatives but with the amido derivatives, preferential hydrogenation of the lactam group in the ring occurs. In the open chain amido esters, both the ester group and amido group undergo simultaneous hydrogenation (and hydrogenolysis) since no evidence was found for either the hydroxy amide or the amino ester.

D'Ianni and Adkins/(26) have shown that under the influence of either Raney nickel or copper chromite various N-pentamethylene amides having a hydroxyl group in the α, γ, δ, or ε positions are converted to the corresponding amino alcohols in yields of 51-79%. In the case of the β-hydroxy amide the hydroxyl group is eliminated and the chief product is the alkyl piperidine.

7. Hydrogenation of Pyrones (27)



Flavone (2-phenylchromone) can be hydrogenated to the corresponding series of compounds.

8. Hydrogenation of β-ketonitriles: Wiley and Adkins/(28) have found that the products obtained from the easily reduced ketonitriles depend upon the temperature used in the hydrogenation process. At 35-40° over nickel the ketoamines were isolated in 10-60% yields, but hydrogenations carried out rapidly at 150-250° gave 30-60% yields of the aminoalcohols. Hydrogenolysis also occurred to some extent at 150-200°.

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Reported by C. M. Himel
R. C. Gunther
December 17, 1941

THE CHEMISTRY OF ORGANOBORON COMPOUNDS

Organic compounds containing boron comprise a field which for many years has received relatively little attention, and is still generally unfamiliar. In recent years interest in these compounds has grown, for several reasons. For one thing boron is situated next to carbon in the periodic table and hence is very similar in effective nuclear charge ant atomic radius; therefore, one may expect studies of organic boron compounds to be of value in interpreting the behavior of analogous carbon electronic systems. Another emphasis is placed on boron compounds because of the ease of effecting nuclear disintegration of the boron atom. Kruger has recently shown that when neoplastic tissue which has been impregnated with boric acid is bombarded with slow neutrons the tumor cells are killed very effectively by the boron disintegration products. His experiments were carried out in vitro, but he concludes that the same results could be obtained in the living body if the boron could be applied to the diseased tissue. This suggests the possibility of developing organic compounds containing boron which may be specifically absorbed by the tissue.

Therefore, it is the purpose of this report to briefly outline the preparation and properties of the different classes of organoboron compounds, with reference also to certain mechanism explanations.

I. Trialkyl and Triaryl Borines (R_3B)

A. Preparation: The first organoboron compounds were prepared by Frankland in 1862; he obtained trimethyl- and triethylborine by the interaction of zinc alkyls and ethyl borate. Krause and Nitsche have more recently obtained good yields of the borines by the action of Grignard reagents on the etherate of boron trifluoride. Johnson, Snyder, and Van Campen have also produced these compounds from methyl borate and Grignard reagents, but find the BF_3 method preferable.

$$3ZnR_2 + (EtO)_3B \xrightarrow{N_2} R_3B + 3ZnROEt$$

$$3RMgX + Et_2O{:}BF_3 \xrightarrow{N_2} R_3B + 3MgXF + Et_2O \quad (80\% \text{ yield})$$

$$3RMgX + (MeO)_3B \xrightarrow{N_2} R_3B + 3MgXOMe \quad (50\% \text{ yield})$$

(R = alkyl or aryl)

B. Properties: The aliphatic borines have been studied more thoroughly recently. Trimethyl borine is a gas - the only gaseous organometallic compound; the higher members of the series are colorless liquids.

(1) These compounds are so easily oxidized that they are spontaneously inflammable in air. (2) They are stable toward water, in sharp contrast to the organic derivatives of the

neighboring elements Be and Al. (3) With dry HBr a hydrocarbon is produced by the removal of one alkyl group:

$$R_3B + HBr \rightarrow R_2B\text{-}Br + R\text{-}H$$

In the presence of water the boron bromide is hydrolyzed to $R_2B\text{-}OH$, but with anhydrous HBr the reaction is clear-cut, and the dialkyl boron bromide produced is a new type compound which may be important in the synthesis of other new organoboron compounds. (5) With dry Br_2 more complex reactions take place, with some substitution of bromine in the alkyl groups forming HBr which may then react with the borine as shown above; however, it is definitely shown that <u>two</u> alkyl groups are split off. This will be mentioned later. (6) As would be expected, NH_3 forms an addition complex; a more unusual reaction is the addition of the alkali metals - the latter is specific for the aromatic borines, it seems.

II. Boronic and Borinic Acids, Alkyl Boron Oxides [$RB(OH)_2$, R_2BOH, RBO]

1. Aromatic

A. Preparation: These were first prepared by Michaelis and Becker in 1880 by use of an organomercurial. Several better methods have been developed since then: Krause obtained the acids by careful oxidation of triaryl borines prepared from BF_3 and RMgX.

$$R_3B \xrightarrow[AIR]{(O)} R_2B\text{-}OR \xrightarrow{(O)} RB(OR)_2 \xrightarrow{H_2O} RB(OH)_2$$

Khotinsky and Melamed used methyl borate and aryl magnesium bromide.

$$RMgBr + (MeO)_3B \rightarrow RB(OMe)_2 \xrightarrow{H_2O} RB(OH)_2$$

Konig and Scharrnbeck modified this procedure by the use of iso-butyl borate, and Bean and Johnson by the use of <u>n</u>-butyl borate. The last method is probably the best of the lot.

Diaryl borinic acids are formed as by-products in the above reactions.

B. Properties: The acids are crystalline white solids, soluble in organic solvents, sparingly soluble in water. They are fairly stable substances, for benzene boronic acid has been nitrated and the nitro compound reduced to the amine without cleavage of the C-B bond by Johnson and his coworkers. This bond may be cleaved, however, upon warming with metallic salts such as $HgCl_2$, $ZnCl_2$, and by aqueous H_2O_2 or bromine water. They do not undergo atmospheric oxidation. Upon treatment with ammoniacal Ag_2O the hydrocarbon R-H is formed.

2. Aliphatic

A. Preparation: Frankland first prepared an aliphatic boronic acid by the careful oxidation of triethyl borine, followed by hydrolysis. They are now prepared by the same methods used for the aromatics. Snyder, Kuck, and Johnson have obtained the best results using the method of Khotinsky and Melamed, with slight modification, to prepare a series of aliphatic boronic acids. The borinic acids may be prepared by the action of aqueous HBr on trialkyl borines, but are very easily dehydrated, giving $R_2B\text{-}O\text{-}BR_2$. Their esters may be obtained by careful oxidation of the borine, as shown above.

B. Properties: The aliphatic boronic acids are much weaker acids than their aromatic analogs, as evidenced by the fact that the latter can be titrated with standard alkali upon the addition of mannitol, whereas the former cannot. They are not cleaved by reagents which cleave the aromatics ($HgCl_2$, $Br_2\text{-}H_2O$), but do resemble them in being cleaved by H_2O_2. They undergo autooxidation in the air very rapidly.

$$RB(OH)_2 \xrightarrow[\text{air}]{H_2O_2} ROH + H_3BO_3$$

H_2O_2, R = aryl or alkyl
air, R = alkyl only.

They react quite differently with ammoniacal Ag_2O also, giving the R-R hydrocarbon instead of R-H:

$$2\underline{n}\text{-}C_4H_9\text{-}B(OH)_2 + Ag(NH_3)_2^+ + 2H_2O \rightarrow \underline{n}\text{-}C_8H_{18} + \underline{Ag} + 2H_3BO_3 + 2NH_3$$

An interesting change takes place if the aliphatic boronic acids are dried over P_2O_5 or concentrated H_2SO_4:

$$RB(OH)_2 \xrightarrow{-H_2O} RBO$$

The products are called alkyl boron oxides. Although they have the composition RBO, molecular weight determinations show them to be trimeric. This suggests a cyclic trimer analogous to the paraldehydes. Thus it is seen that the aliphatic boronic acids show a definite similarity to the aliphatic aldehydes: (1) They combine with molecular oxygen, (2) they reduce ammoniacal Ag_2O, (3) they undergo cyclization to a 6-membered ring structure. This may be attributed to analogous electronic configurations.

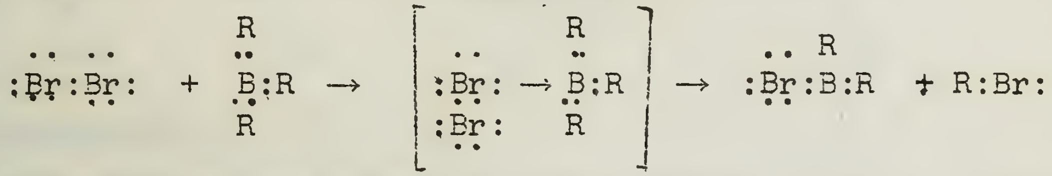
To show the distinction between aromatic and aliphatic boronic acids still more clearly, Johnson, Van Campen, and Grummitt prepared benzyl-, t-butyl-, 2-furyl-, and 2-thienyl-boronic acids and tested them with $Ag(NH_3)_2^+$ and air oxidation. The first two were shown to react definitely as aliphatic, the last pair as aromatic - confirming the well known aromatic character of these groups.

III. Mechanism Studies

Mention was made on page 2 of the reaction of dry bromine with trialkyl borines, and it was noted that the significant point of the reaction is that two alkyl groups are cleaved from B

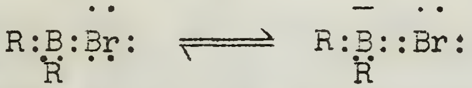
This dibromide formed ($RB-Br_2$) must come from the action of bromine on the monobromide (R_2B-Br) since the latter has been shown to be inert toward HBr.

These reactions may be considered as proof of the theory that many organic reactions take place through a mechanism in which one group acts as an electron acceptor, the other as a donor. Here, the electron shell of the B atom may be completed by an unshared electron pair of a Br atom. This would cause a surge of electron density in the direction $B \rightarrow R$, and increase the mobility of the potential alkyl anion; an irreversible $\alpha - \gamma$ shift within the complex would complete the reaction.



$$:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Br}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Br}}: \;+\; \underset{R}{\overset{R}{\underset{\cdot\cdot}{\overset{\cdot\cdot}{B}}}}:R \;\rightarrow\; \left[\begin{array}{l} :\overset{\cdot\cdot}{\underset{\cdot\cdot}{Br}}: \rightarrow \underset{\cdot\cdot}{\overset{R}{\overset{\cdot\cdot}{B}}}:R \\ :\underset{\cdot\cdot}{Br}: \quad\;\; R \end{array}\right] \;\rightarrow\; :\underset{\cdot\cdot}{\overset{\cdot\cdot}{Br}}:\overset{R}{B}:R \;+\; R:Br:$$

Failure of HBr to effect cleavage of more than one group may be attributed to the diminuished acceptor activity of B after the compound R_2B-Br is formed, due to an internal resonance effect:



$$R:\underset{R}{B}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{Br}}: \;\rightleftharpoons\; R:\underset{R}{\overset{-}{B}}::\overset{+}{\underset{\cdot\cdot}{Br}}:$$

Br_2 undergoes coordination even with this weaker acceptor effective enough to produce sufficient mobility of the alkyl group, but HBr does not.

Investigation was carried further in this field by Johnsc and Van Campen, who studied the results of oxidation by aqueous H_2O_2 and autooxidation in air:

$$R_3B \xrightarrow{(O)} \underset{I}{R_2BOR} \xrightarrow{(O)} \underset{II}{RB(OR)_2}$$

They concluded that these reactions also go through a coordination complex, because they found that the reaction would be stopped at stage I in the presence of water, and would not go at all with the ammonate of the borine ($R_3B \leftrightarrow NH_3$).

A survey of the behavior of various alkyl boron compounds toward HBr, Br_2, H_2O_2, O_2, etc., indicates a definite gradation of reactivities: $R_3B < R_2BOH > RB(OH)_2$, and this is nicely explained by reference to resonance possibilities within the molecule, leading to lessened reactivity.

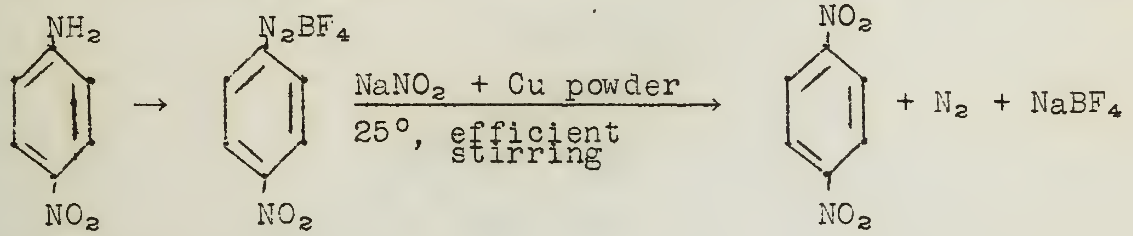
IV. Use of Diazonium Borofluorides in Synthesis.

Dunker, Starkey, and Jenkins have shown that the diazonium borofluorides may be readily prepared as follows:

$$Ar\_NH_2 + NaNO_2 + 2HBF_4 \xrightarrow[0^\circ]{} Ar-N_2BF_4 + NaBF_4 + 2H_2O \text{ (90-97\% yields)}$$

They were interested in these compounds because when they are

obtained. More recently, Starkey has used these diazonium compounds for synthesizing molecules in which the nitro group is _ortho_ or _para_ to a nitro, carbonyl, or similar group. For example, his method is included in Organic Syntheses for the preparation of _p_- and _o_-dinitro benzenes in yields of 67-82% and 33-38% respectively. His reactions are carried out according to the following equation:



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January 7, 1942.

CARDIAC AGLYCONES OF THE STROPHANTHIDIN GROUP

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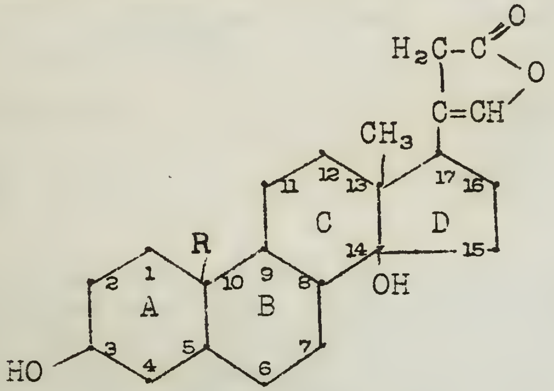
R.C. Elderfield - Columbia University

Plants of the digitalis-strophanthus group contain glycosides which have a characteristic and powerful action on cardiac muscle. The nucleus, which is common to all the aglycones of this group, is given below (I):



I

Recent evidence indicates an α,β unsaturated lactone.

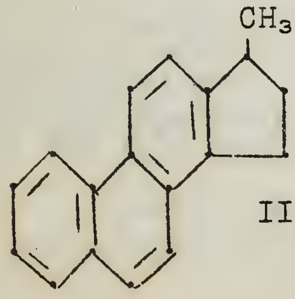
The following table lists the best known aglycones.

Aglycone	OH Groups	C_3-OH/R*	Rings A/B*	R	Plant Source
Digitoxigenin	3, 14	trans	cis	CH_3	Digitalis
Thevetigenin	3, 14	cis	cis	CH_3	Thevetia
Uzarigenin	3, 14	cis	trans	CH_3	Uzara tree
Digoxigenin	3, 11, 14	trans	cis	CH_3	Digitalis
Gitoxigen	3, 14, 16	trans	cis	CH_3	Digitalis
Periplogenin	3, 5, 14	trans	cis	CH_3	Periploca
Sarmentogenin	3, 11, 14	trans	cis	CH_3	Strophanthus
Strophanthidin	3, 5, 14	trans	cis	CHO	Strophanthus

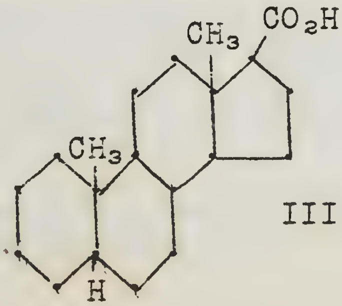
* Probable structures

In the glycosides the sugar residue is linked through the C_3-OH.

In 1934 Tschesche elucidated the cyclopentanoperhydrophenanthrene ring system by selenium dehydrogenation of monoanhydrouzarigenin to Diels' hydrocarbon (II) and also by degradation of the same material to etioallocholanic acid (III).



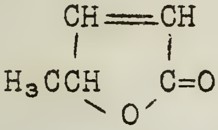
II



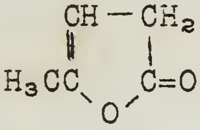
III

Correlation of the above results with the extensive work, principally by W. A. Jacobs from 1922 on, made it possible to infer the complete structures of the more important aglycones.

The highly important and characteristic lactone group may be titrated with alkali at moderately elevated temperatures. It absorbs one mole of hydrogen to give a saturated lactone. The β,γ unsaturation was inferred from the behavior of the aglycones on treatment with sodium nitroprusside (Legal's test) and ammoniacal silver solution (Tollens' reagent) which resembled that of $\Delta^{\beta,\gamma}$ angelica lactone (V) and not that of $\Delta^{\alpha,\beta}$ angelica lactone (IV).

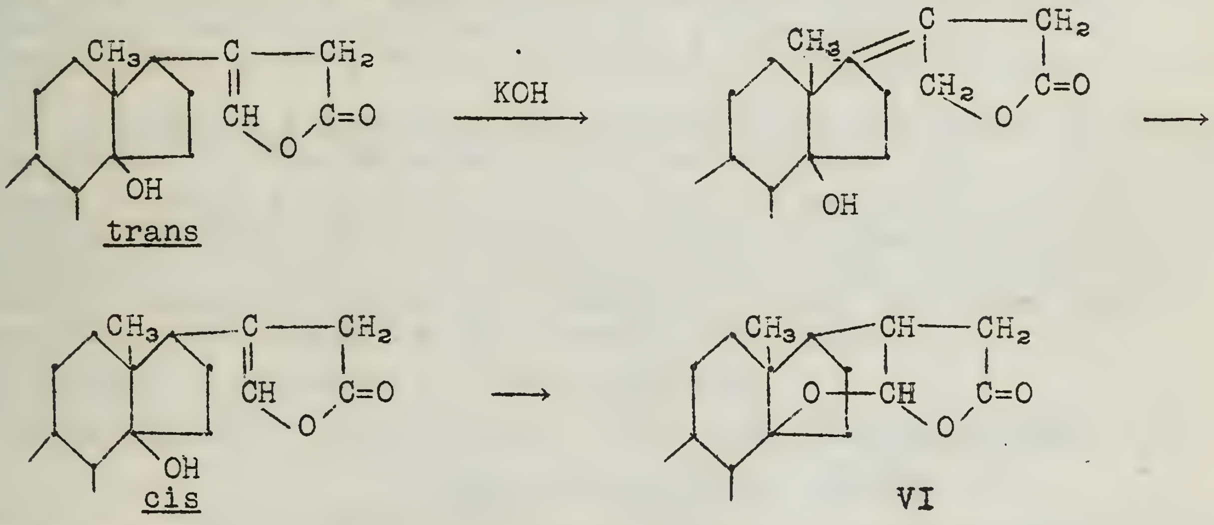


IV



V

Therefore, the side chain appeared to be the lactone of an enolized aldehydo acid. Upon saponification and then acidification or merely by treatment with alcoholic alkali without saponification, a characteristic rearrangement of either the aglycone or the unhydrolyzed glycoside to a saturated isomer (VI) takes place. Jacobs inferred that it was preceded by a stereochemical inversion on C_{17} by which the lactone and the C_{14}-OH, originally <u>trans</u>, assumed a <u>cis</u> relationship.



The structure of the isomer (VI) is well established.

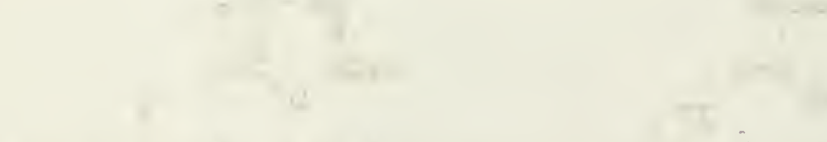
Evidence for the positions of the other functional groups of strophanthidin follows:

C_{14}-OH. One molecule of water is split out on mild treatment (alcoholic HCl) of strophanthidin. The anhydrogenin cannot be isomerized. The C_{14} position alone allows the hydroxyl to be both tertiary and γ or δ with respect to the aldehyde group of the side chain.

C_3-OH. The secondary hydroxyl has been located at C_3 by degradations involving the opening of ring A.

[illegible]

[illegible]



[illegible]

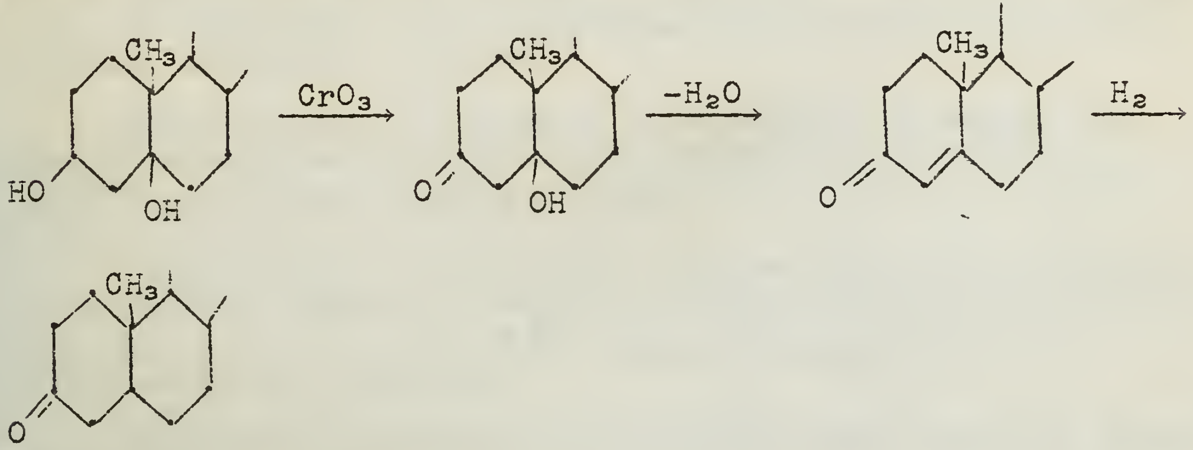
[illegible] (VII) [illegible]

[illegible]

[illegible]

[illegible]

C_{10}-CHO. Wolff-Kishner reduction of a strophanthidin derivative gave a derivative of periplogenin. Conversion of this to a derivative of digitoxigenin was accomplished as follows:

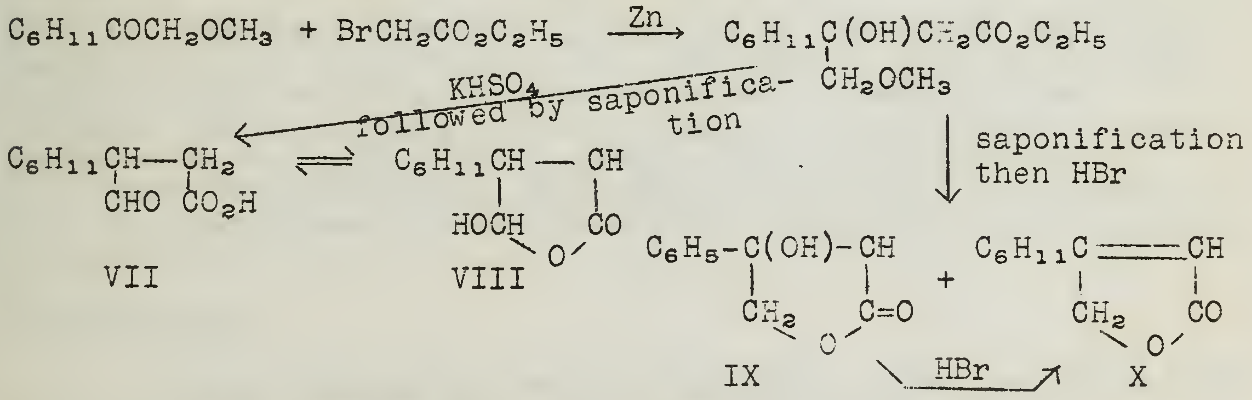


Digitoxigenin has been degraded to etiocholanic acid (a stereoisomer of III).

C_5-OH. A second tertiary hydroxyl has been demonstrated. The extremely easy dehydration of the hydroxyketone in the previous transformation suggested a β hydroxyketone. To be both tertiary and β to C_3 the OH must be attached to C_5.

Recently Elderfield has considered the synthesis of cardiac aglycones by transformations of other steroids. His attempts to prepare model β substituted $\Delta^{\beta,\gamma}$ unsaturated lactones have thrown new light on the structure of the lactone ring in the aglycones. His more successful syntheses made use of the fact that half-ethers of primary-tertiary glycols are converted smoothly into aldehydes when heated with acids:

$$C_6H_{11}MgBr + CH_3OCH_2CN \rightarrow C_6H_{11}COCH_2OCH_3$$



$$C_6H_{11}COCH_2OCH_3 + BrCH_2CO_2C_2H_5 \xrightarrow{Zn} C_6H_{11}\underset{CH_2OCH_3}{C}(OH)CH_2CO_2C_2H_5$$

$$\xleftarrow{\text{KHSO}_4 \text{ followed by saponification}} \qquad \downarrow \text{saponification then HBr}$$

$$\underset{VII}{C_6H_{11}\underset{CHO}{CH}-\underset{CO_2H}{CH_2}} \rightleftharpoons \underset{VIII}{C_6H_{11}\underset{HOCH-O-}{CH}-\underset{CO}{CH}}$$

$$\underset{IX}{C_6H_5-C(OH)-CH \;\; CH_2-O-C{=}O} + \underset{X}{C_6H_{11}C{=}CH \;\; CH_2-O-CO}$$

$$IX \xrightarrow{HBr} X$$

It was not possible to dehydrate VII to an unsaturated lactone.

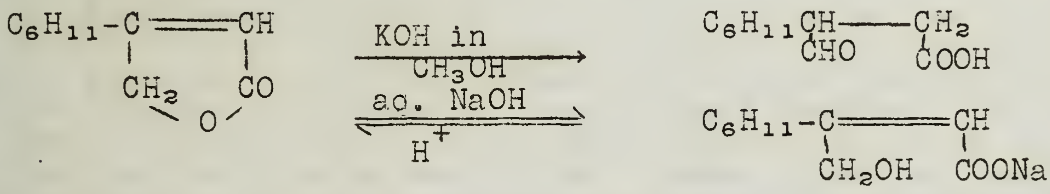
The following considerations have led Elderfield to suggest that the lactone in the aglycones is really $\Delta^{\alpha,\beta}$ unsaturated:

The comparison of the lactones of keto acids (angelica lactones) with lactones of aldehydo acids is not justified. X and strophanthidin gave identical color reactions with a modified Legal test and with ferricyanide while $\Delta^{\beta,\gamma}$ angelica lactone differed remarkably. $\Delta^{\alpha,\beta}$ angelica lactone gave only a slow response to Legal's reagent.

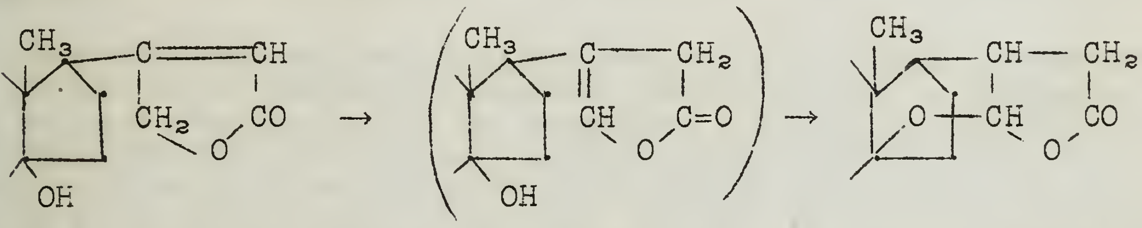
Representative aglycones, X, and ethyl crotonate have similar absorption spectra. Vinyl acetate (comparable to $\Delta^{\beta,\gamma}$ lactones) differed greatly.

Hydrogenation of X and the aglycones yielded exclusively the saturated lactones. When the double bond is at the point of lactonization (as in the $\Delta^{\beta,\gamma}$ type), varying amounts of desoxy-acids are obtained.

The action of alkali on X parallels that noted in aglycone derivatives.



The isomerism of the glycosides and aglycones by alkali may be formulated as follows:



Here the lactone is assumed *cis* to the C_{14} hydroxyl and no inversion on C_{17} is necessary. The observed failure of the glycoside uzarin and of allostrophanthidin to isomerize is probably due to a *trans* configuration. Allostrophanthidin is produced by the action of an enzyme found in strophanthus seed upon strophanthidin. Allostrophanthidin has been shown to be a diastereoisomer of strophanthidin for which C_{17} or C_{14} is responsible.

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Reported by R. F. Phillips

PREPARATION OF NITRILES BY THE USE OF CUPROUS CYANIDE

J. F. Koelsch, University of Minnesota

Cuprous cyanide has been used as a reagent to produce nitriles by the replacement of halogen atoms in aryl halogen compounds, vinyl halides, allyl halides, and acyl halides. These reactions will be discussed in order.

The Rosenmund-Von Braun nitrile synthesis,

$$2\ ArX + Cu_2(CN)_2 \rightarrow 2\ ArCN + Cu_2X_2$$

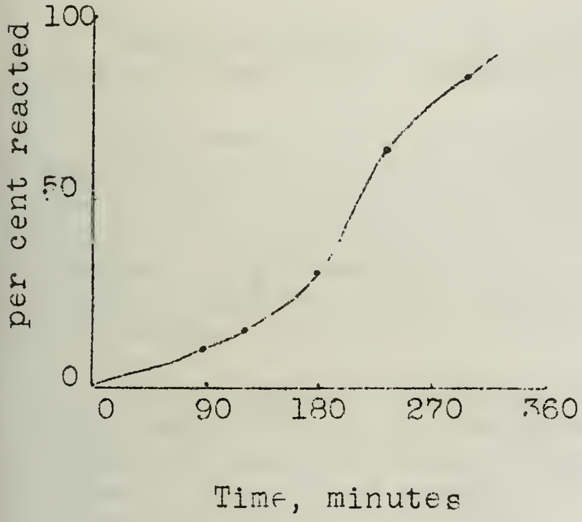
is best known. Reactions reported in the literature vary widely in experimental conditions. Koelsch found that iodo- and bromodiphenylindones mixed with cuprous cyanide and heated at 240-250°C. for three hours gave nearly quantitative yields of the nitriles. Fieser and Seligman found that when pyridine was added to a mixture of 4-chloro-7-methylhydrindene and cuprous cyanide the temperature necessary for reaction was lowered from 265° to 225°C., the time of heating could be cut from eighteen hours to two hours, and the yield of nitrile was higher. Newman has given the most detailed directions for the use of pyridine in the Rosenmund-Von Braun synthesis. Quinoline has also been used as a solvent to aid reaction.

Recently Koelsch and Whitney carried out a study to determine the mechanism of the transformation involved in this synthesis, and optimum conditions for the reaction. Though the reaction could be simply written, it was not free of complications. Reaction between cuprous cyanide and p-bromotoluene was only 15 per cent completed after sixty minutes at 250°, but was 75 per cent completed in the next thirty minutes. This induction period indicated an auto-catalytic reaction.

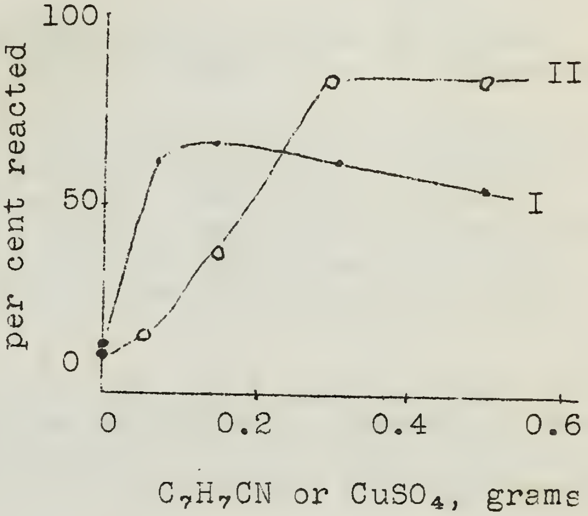
The catalyst might be the aromatic nitrile, forming a complex with cuprous cyanide and bringing the solid into solution. To test this assumption p-tolunitrile was added to the reaction mixture. Small amounts increased the rate of reaction; larger amounts were less advantageous. The induction period was not entirely eliminated.

The authors believed that peroxides might act as anticatalytic agents. These if present at the start of the reaction would be destroyed during its course. Accordingly, small amounts of hydroquinone were added. The induction period was almost doubled.

This suggested the use of an oxidizing agent. Cupric sulfate was found to have a pronounced catalytic effect. The actions of both cupric sulfate and p-tolunitrile on the reaction of p-$(C_6H_5)_2CHC_6H_4Br$ with two equivalents of cuprous cyanide are shown in the graphs below. The rate of reaction for this compound without catalysts is also shown, illustrating the induction period.



p-$(C_6H_5)_2CHC_6H_4Br$
2 equiv. CuCN



0.5 g. p-$(C_6H_5)_2CHC_6H_4Br$
with I. p-C_7H_7CN, 45 mins.
II. $CuSO_4$, 60 minutes

A mechanism was suggested to explain the catalytic effect of cupric sulfate in the Rosenmund-Von Braun synthesis:

$$\begin{aligned}
&ArX + Cu^{++} && \rightarrow && (ArX \rightarrow Cu)^{++} \\
&(ArX \rightarrow Cu)^{++} + Cu^{+} && \rightarrow && (ArX \rightarrow Cu)^{+} + Cu^{++} \\
&(ArX \rightarrow Cu)^{+} && \rightarrow && Ar^{+} + CuX \\
&Ar^{+} + CN^{-} && \rightarrow && ArCN
\end{aligned}$$

This mechanism rests on assumptions that: (1) The aryl halide does not form a complex through the halogen atom with cuprous copper; (2) The cuprous complex can decompose to give an aryl ion.

The study led to the formulation of a practical synthetic procedure. To a mixture of an aryl halide with excess cuprous cyanide is added a few drops of tolunitrile, and a little cupric sulfate. The whole is placed in a bath at 250°C. Completion of the reaction, as indicated by marked dimunition in volume of solid copper salts and formation of a dark liquid phase follows rapidly (ten to thirty minutes).

The nine compounds used in Koelsch's experiments were rated as to relative reactivity with cuprous cyanide by measuring the time required for fifty per cent of a substance to react with cuprous cyanide. The order of reactivity was: p-bromotriphenylmethane < m-bromotoluene < p-bromobenzophenone < o-bromotoluene < bromobenzene < bromomesitylene < α-bromonaphthalene < p-bromobenzoic acid.

Many examples in the literature show that bromine or iodine is much more easily replaced by the nitrile group than is chlorine.

The reaction of vinyl halides with cuprous cyanide should be similar to the reaction of aromatic halogen compounds. Koelsch found that triphenylvinylbromide heated two hours with cuprous cyanide at 240° gave a quantitative yield of triphenylacrylonitrile. However, α-p-bromophenyl-β,β-diphenylvinylbromide under similar conditions gave only a black resin and at lower temperatures did not react.

Allyl cyanide has been made by shaking allyl chloride for eight days with a concentrated solution of potassium cyanide. The yield was ten per cent. Bruylants obtained a 95 per cent yield by refluxing allyl iodide or bromide one hour with a five per cent excess of cuprous cyanide.

α-Ketonitriles have been prepared from the lower members of the fatty acid series in sixty to eighty-five per cent yields by refluxing the acyl bromide and cuprous cyanide, without solvent, for one and a half to two hours. This is the method of Tschelinzeff and Schmidt. Previously silver cyanide had been used with acid chlorides. An autoclave was necessary, and there were many side reactions.

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Reported by A. V. McIntosh, Jr.
January 14, 1942

THE REDUCTION OF MULTIPLE CARBON-CARBON BONDS

Because of the ease of replacement of the hydrogen atoms of acetylene by sodium or by the MgX group, substituted acetylenes may be readily prepared in a pure state. These should afford a source of the corresponding olefins, provided that a satisfactory reagent or catalyst for partial reduction can be found.

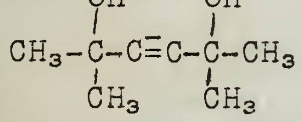
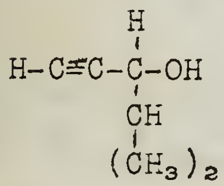
The ordinary catalysts, nickel, palladium, and platinum, in their various forms, have been used successfully for this process Zalkind has reduced a great many substituted acetylenic glycols using the noble metal catalysts and in all cases has found that there is a definite break in the curve at half-reduction. Campbell and O'Connor have continued some of the earlier work of duPont using Raney nickel on variously substituted acetylenes. Their results may be summarized as follows:

Type	Half-reduction
$R-C\equiv C-H$	Very slight change in slope
$R-C\equiv C-R'$	Noticeable change, especially if $R = R'$
$Ph-C\equiv C-H$ and $Ph-C\equiv C-Me$	No change
$Ph-C\equiv C-Ph$	Stops at one mole

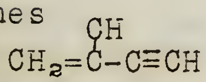
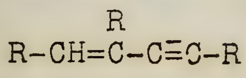
Analysis and Raman spectra indicate that there is better than 99.5% olefin at the half-way point.

Less familiar methods include the use of chromous chloride, "Raney" iron, and sodium in liquid ammonia. The iron catalyst, prepared exactly as Raney nickel, was developed by Paul and Hilley and was found to be almost specific for triple bonds. It failed in only a few isolated cases; for example, tolane is completely reduced to diphenylethane in the presence of this catalyst. Thompson and Wyatt have extended the use of the catalyst to the reduction of various alkynes, enynes, and dienynes.

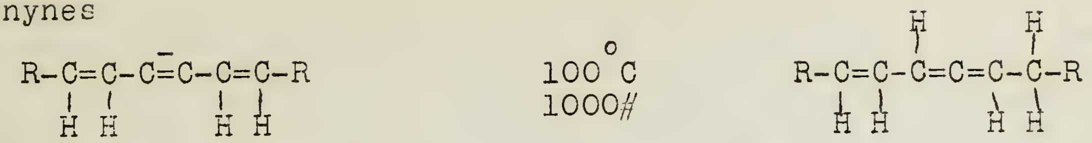
Alkynes

 $CH_3-\underset{CH_3}{\overset{OH}{C}}-C\equiv C-\underset{CH_3}{\overset{OH}{C}}-CH_3$	$150\,^{\circ}C$ 1400#	80% olefin
 $H-C\equiv C-\underset{\underset{(CH_3)_2}{CH}}{\overset{H}{C}}-OH$	$100\,^{\circ}C$ 1000#	2nd mole of H enters one fourth as fast as first

Enynes

 $CH_2=\overset{CH}{C}-C\equiv CH$	$100\,^{\circ}C$ 1000#	50% isoprene
 $R-CH=\overset{R}{C}-C\equiv C-R$	$100\,^{\circ}C$ 1000#	Stops at diolefin

Dienynes



$$\mathrm{R{-}CH{=}CH{-}C{\equiv}C{-}CH{=}CH{-}R} \xrightarrow[1000\#]{100^{\circ}\,C} \mathrm{R{-}CH{=}CH{-}CH{=}C{=}CH{-}CH_2{-}R}$$

(R is CH_3 or C_6H_{11})

Sodium in liquid ammonia is a reducing agent developed by Lebeau and Picon and has been used to prepare olefins, especially trans olefins, by Campbell and Eby. Several trans octenes, hexenes, and decenes as well as butadiene have been prepared from the corresponding acetylenes by this method. They recommend it, incidentally, as the most satisfactory for obtaining terminal ethylenic compounds.

As regards the stereochemical course of reduction reactions, it may be said that in general catalytic methods lead to cis forms whereas chemical methods produce trans modifications. Bourguel, Gredy, Sherrill and Zalkind have all used metal catalysts and have obtained cis compounds in 90-100% yields. The melting points of known compounds and the Raman spectra data on the unknowns have been offered as evidence.

Interesting work in this field has been done by Schroter, Ott, and Farkas. Shroter found that by using the same batch of catalyst over and over in the reduction of ethyl acetylenedicarboxylate, the ratio of ethyl fumarate to ethyl maleate gradually increased. Changing the amount of catalyst or the introduction of a catalyst poison such as carbon monoxide or hydrogen sulfide diminished the rate of hydrogen absorption but did not change the nature of the product. This led Ott to postulate in a later paper that the production of the more labile form is favored by an increase in the activity of the catalyst. He recognized that the velocity of the reaction on a catalytic surface is not measurable in terms of hydrogen absorbed. He assumed that the activity of catalysts is similar in nature to the reduction potential of the ordinary reducing agents. A metal of low potential should give a stable trans form, one of higher potential would give more of the cis isomer, and one high in the electromotive series which gives hydrogen of extremely high potential would carry the reduction all the way to the ethane. Propiolic acid was reduced chemically by the following combinations with the results indicated:

Cr-HCl	100% trans cinnamic acid
Zn-alkali	90% trans
Mn-Alkali	30% cis, 4% trans, and an oily mixture
Mg, Na, etc.	gave mixtures of the saturated hydrocinnamic acid and unreduced propiolic acid.

Thus between zinc and manganese lies the critical area, within which ordinary catalysts probably belong as far as reduction potential or activity is concerned.

Farkas and Farkas have also reviewed the literature and summarized the results rather briefly. Catalytic methods add two hydrogen atoms simultaneously, thus giving a cis form; nascent

hydrogen on the other hand adds stepwise giving the opportunity for the more stable modification to result, and with most olefinic pairs the malenoid form is the more labile, the fumaroid form the more stable. This may be carried further into the reduction of olefins to ethanes and in general the <u>meso</u> form resembles the <u>cis</u> and the racemic modification the <u>trans</u>. Most reductions conform to the following scheme:

Modification reduced	Product from	
	Nascent hydrogen	Catalytic hydrogen
C≡C	<u>trans</u>	<u>cis</u>
C=C (<u>cis</u>)	<u>dl</u>-pair	<u>meso</u>
C=C (<u>trans</u>)	<u>meso</u>	<u>dl</u>-pair

If the temperature is too high or if enolization is possible, then catalytic reduction may lead partially or totally to the <u>trans</u> modification.

So far, the work on these methods of partial reduction has been confined to the laboratory only. The industrial research in this field has been limited almost entirely to attempts to prepare butadiene from vinylacetylene. Most important patents are to du Pont for the catalytic reduction of vinylacetylene, to Jasco for reduction by metallic zinc in alkaline solution, and to I. G. Farbenindustrie for the reduction by sodium and zinc in the presence of butyl naphthalenesulfonate. Hurukawa has published results indicating a 60% yield of the diene from an electrolytic reduction at a palladium black cathode. There is also a process for the semi-reduction of most of the common acetylenes by means of palladium on clay and there is another patent for the reduction of several substituted dienynes to mono-olefins in the presence of nickel.

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Reported by John C. Robinson, Jr.
January 14, 1942

POLYENES AND CUMULENES

Richard Kuhn and Coworkers - Kaiser Wilhelm Institut

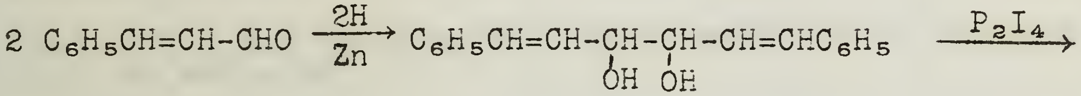
REVIEW OF POLYENES

Kuhn defines 'polyene' as referring to those substances th contain many ethylenic linkages in open chains. It is usually understood that the double bonds are conjugated.

Methods of Synthesis.--

Type A - $C_6H_5\{CH=CH\}_nC_6H_5$ (n = 1,2,3,4,5,6,7,8,11,15)

1. Treatment of hydrobenzoins with phosphorous iodide (P_2I_4):

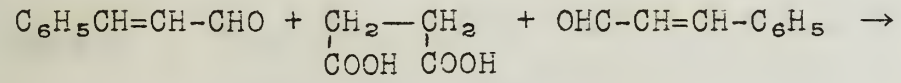


$$2\ C_6H_5CH=CH-CHO \xrightarrow[Zn]{2H} C_6H_5CH=CH-\underset{OH}{CH}-\underset{OH}{CH}-CH=CHC_6H_5 \xrightarrow{P_2I_4}$$

$C_6H_5CH=CH-CH=CH-CH=CHC_6H_5$

This method is suitable for 1,4- and 1,6-glycols also. They are prepared by the action of $BrMgC{\equiv}CMgBr$ and $BrMgC{\equiv}C-C{\equiv}CMgBr$ on polyene aldehydes.

2. Condensation of polyene aldehydes with $HOOC-CH_2\{CH=CH\}_nCH_2-COOH$ (n = 0,1,2) using lead oxide:



$$C_6H_5CH=CH-CHO + \underset{COOH}{CH_2}—\underset{COOH}{CH_2} + OHC-CH=CH-C_6H_5 \rightarrow$$

$C_6H_5-CH=CH-CH=CH-CH=CH-CH=CH-C_6H_5$

3. Action of benzylmagnesium chlorides on polyene aldehydes:

(a) $C_6H_5CH=CH-CHO + CH_3-CH=CH-CHO \xrightarrow[acetate]{piperidine}$

$C_6H_5\{CH=CH\}_5CHO$ and $C_6H_5\{CH=CH\}_7CHO$

(b) $C_6H_5\{CH=CH\}_nCHO + C_6H_5CH_2MgCl \rightarrow$

$C_6H_5\{CH=CH\}_nCHOHCH_2C_6H_5 \rightarrow C_6H_5\{CH=CH\}_{n+1}C_6H_5$

4. Coupling of thio- and seleno-aldehydes:

$C_6H_5\{CH=CH\}_nCHO \xrightarrow{H_2S(H_2Se)} C_6H_5\{CH=CH\}_nCHS \xrightarrow[piperidine]{Cu,\ CaCO_3}$

$C_6H_5\{CH=CH\}_{2n+1}C_6H_5$

In this manner, $C_6H_5\{CH=CH\}_{15}C_6H_5$ was prepared. It is the highest known member of the polyene series. The solid is greenish black and its solutions are violet-red.

Type B - $CH_3\{CH=CH\}_nCHO$ (n = 1,2,3,4,5,7,9) and

$CH_3\{CH=CH\}_nCOOH$ (n = 1,2,3,4,5,6,8)

Aldehydes, chiefly crotonaldehyde are condensed by means of piperidine acetate to give higher polyene aldehydes, $CH_3\{CH=CH\}_nCHO$. These aldehydes will condense with malonic acid:

$$CH_3\{CH=CH\}_nCHO + CH_2(COOH)_2 \rightarrow CH_3\{CH=CH\}_nCH=C(COOH)_2 \xrightarrow{-CO_2}$$

$$CH_3\{CH=CH\}_{n+1}COOH$$

By this method the total synthesis of stearic acid and cetyl alcohol was effected.

Type C - $CH_3\{CH=CH\}_nCH_3$ (n = 1,2,3,4,6)

Polyene aldehydes react normally with alkylmagnesium halides to form the carbinols. These are dehydrated by treating with a 1-2% solution of p-toluenesulfonic acid in ether:

$$CH_3\{CH=CH\}_nCHO + CH_3CH_2MgBr \rightarrow CH_3\{CH=CH\}_nCHOHCH_2CH_3 \xrightarrow{-H_2O}$$

$$CH_3\{CH=CH\}_{n+1}CH_3 \qquad (n = 2,\ m.p.\ 52^{\circ})$$

Type D - $HO_2C\{CH=CH\}_nCOOH$ (n = 1,2,3,4,5,7) and
$HO_2C-CH_2\{CH=CH\}_nCOOH$ (n = 1,2,3,4)

1. Claisen Condensation:

$$EtO_2C-CO_2Et + CH_3\{CH=CH\}_nCO_2R \xrightarrow[\text{pyridine}]{EtOK}$$

$$EtO_2C-COCH_2\{CH=CH\}_nCO_2R \xrightarrow{Ac_2O}$$

$$EtO_2C-\underset{\substack{|\\ OAc}}{C}=CH\{CH=CH\}_nCO_2R \xrightarrow{Al,\ Hg}$$

$$EtO_2C-\underset{\substack{|\\ OAc}}{CH}\{CH=CH\}_nCH_2CO_2R \xrightarrow{R'OH,\ NaOH}$$

$$R'O_2C\{CH=CH\}_{n+1}CO_2R'$$

The free oxalo-polyene carboxylic acids are obtained by saponification. Treatment with hydrogen peroxide removes carbon monoxide:

$$HO_2C\text{-}COCH_2\text{-}CH{=}CH\text{-}COOH \xrightarrow{H_2O_2} HO_2C\text{-}CH_2\text{-}CH{=}CH\text{-}CO_2H$$

2. Biological Oxidation:

Kuhn discovered that if polyene mono-carboxy acid amides were fed to rabbits, the mono-amide of the corresponding dicarboxy acid would be obtained from the rabbit's urine:

$$CH_3\{CH{=}CH\}_3CONH_2 \rightarrow HO_2C\{CH{=}CH\}_3CONH_2$$

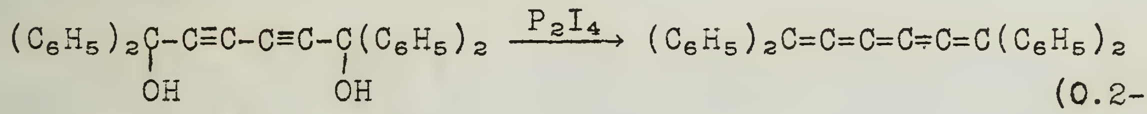
Yields of 20-80 per cent have been obtained.

CUMULENES

Cumulenes are compounds containing an uninterrupted series of double bonds.

Methods of Synthesis:--

The first method used by Kuhn was the treatment of acetylene or diacetylene glycols with P_2I_4:

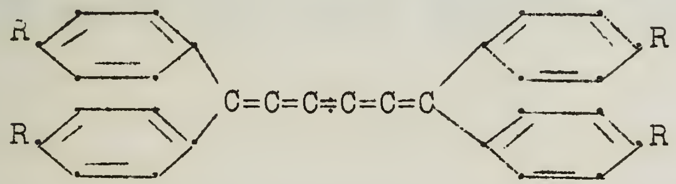


$$(C_6H_5)_2\underset{OH}{C}\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}\underset{OH}{C}(C_6H_5)_2 \xrightarrow{P_2I_4} (C_6H_5)_2C{=}C{=}C{=}C{=}C{=}C(C_6H_5)_2$$

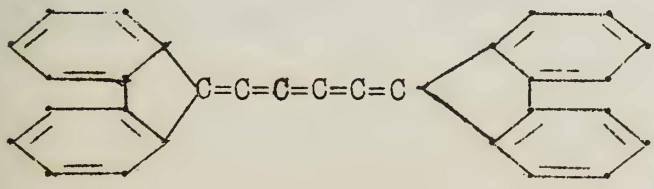
(0.2-0.3%)

I

The yields were greatly improved by treating (I) in ether solution with dry HCl and VCl_2 or $CrCl_2$. Yields of around 90 per cent were obtained. In this manner the following cumulenes were prepared:

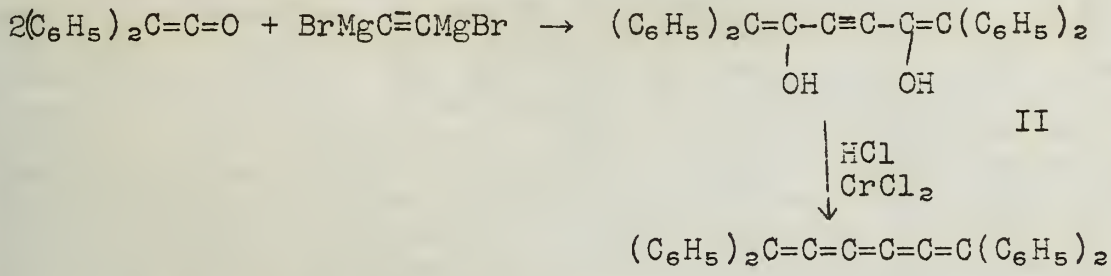


R = H
Cl
CH_3



Attempts were made to prepare unsymmetrical cumulenes in order to test out the van't Hoff theory. Unsymmetrical benzophenones were treated with $BrMgC{\equiv}CMgBr$ and the corresponding acetylene diols obtained. These, however, could not be converted into the butatrienes.

Kuhn attempted to prepare cumulenes from diphenylketene by the following reactions:



$$2(C_6H_5)_2C{=}C{=}O + BrMgC{\equiv}CMgBr \rightarrow (C_6H_5)_2C{=}\underset{OH}{C}-C{\equiv}C-\underset{OH}{C}{=}C(C_6H_5)_2$$

II

$$\xrightarrow{HCl,\ CrCl_2} (C_6H_5)_2C{=}C{=}C{=}C{=}C{=}C(C_6H_5)_2$$

Instead of (II), however, he obtained a diol of some other structure, as yet undetermined.

Properties of Cumulenes and Polyenes:

As compared to the corresponding saturated compounds, polyenes and cumulenes are more highly colored, have higher melting points and lower solubility, and have absorption bonds in the higher wave lengths.

Cumulenes are much more highly colored than polyenes and have higher melting points. They give a negative Baeyer test, do not react with maleic anhydride, and give no color reaction with $C(NO_2)_4$. They are destroyed by H_2O_2 and are readily reduced.

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Reported by Stanley B. Speck
January 21, 1942

REACTIONS OF PYRIDINE

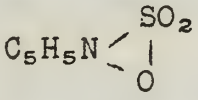
Pyridine is a well-known organic base which occurs in small amounts in coal tar. It is a weaker base than ordinary tertiary amines but does form soluble, stable salts. It may be considered more aromatic than benzene, as shown by the oxidation of quinoline, and may be compared in many of its reactions and properties to nitrobenzene.

It is, however, more easily reduced than benzene. The selective reduction of phenyl and benzyl derivatives of pyridine has been accomplished by sodium and alcohol and by hydrogenation over Raney nickel. The salts may be reduced by Adams' platinum catalyst. The ease of reduction is quite different for isomeric alkyl or aryl derivatives. Thus it has been reported that 4-phenylpyridine is not reduced with Adams' catalyst under conditions which effect reduction of 4-benzylpyridine. With Raney nickel the following is the order of decreasing ease of reduction of the pyridine ring: 2-benzyl, 2-methyl, 2-phenyl, pyridine, 4-phenyl. The reduction and alkylation of pyridine to methylpiperidinium formate by refluxing a mixture of methanol, formic acid, and pyridine has been reported.

Pyridine undergoes a number of substitution reactions, few of which may be carried out except under strenuous conditions. In general, the product formed by chlorination, bromination, iodination, sulfonation, or nitration is the three or the three-five derivative. However, conditions and catalysts have a pronounced effect upon the nature of the product. Under the strenuous conditions necessary to obtain any substitution at all it is difficult to prevent the simultaneous formation of some di- and poly-substituted derivatives. The mechanism of the substitution of pyridine is not known but sufficient data are at hand to show that it is not a simple one.

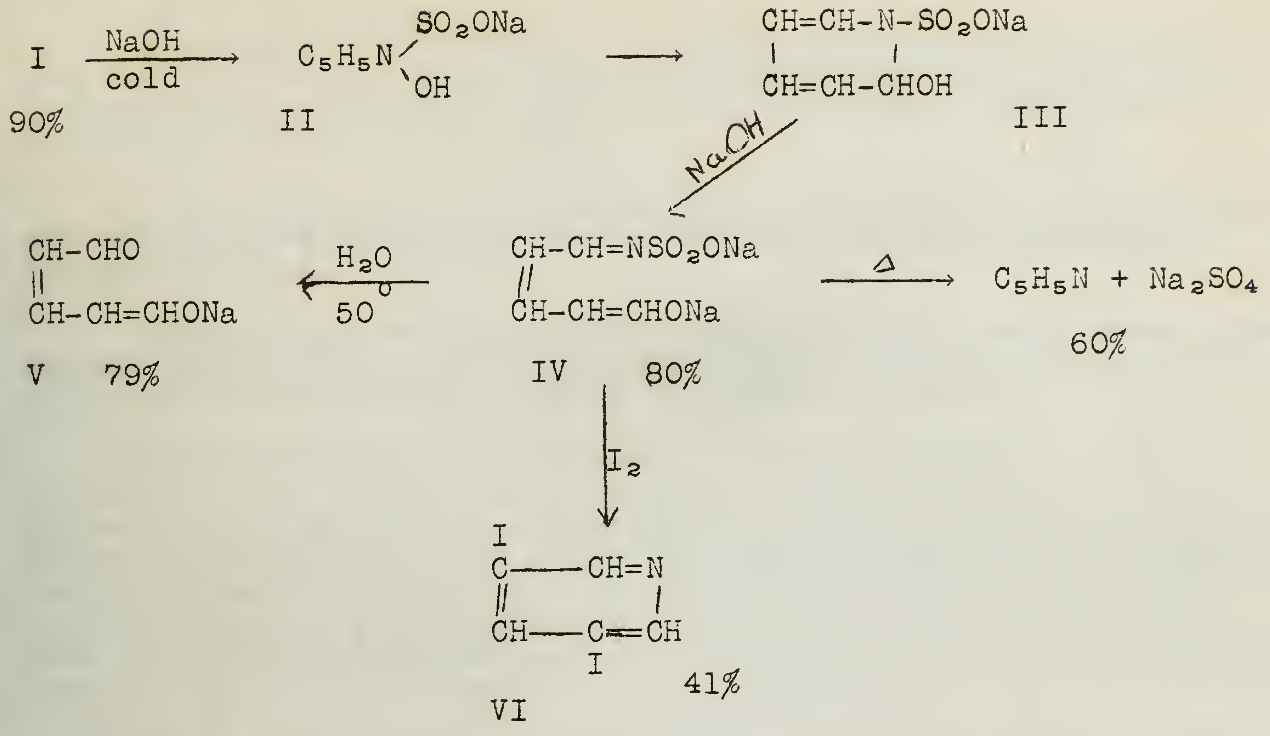
The sulfonation of pyridine is best carried out in the presence of mercuric salts with fuming sulfuric acid at a temperature of 270°. The main product is pyridine-3-sulfonic acid, although some of the 2-derivative is reported. No disulfonic acids are produced. The compound (I) has been prepared by treatment of

(I)



$C_5H_5N\langle SO_2, O\rangle$

pyridine with $(SO_3)_2$ and has been proposed as an intermediate in the sulfonation reaction. A few reactions of (I) which show the nature of the problem encountered are listed. It is noteworthy that one of the best methods for the iodination of pyridine involves the use of fuming sulfuric acid as an oxidizing agent. In this case the predominant product is 3-iodopyridine.



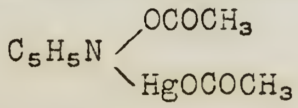
If pyridine is chlorinated at 170-220°, 3- and 3,5-derivatives are formed while at 260-420°, 2- and 2,6-derivatives are formed. When bromination is carried out in the absence of metallic salts, some of which tend to lower the temperature necessary for substitution and affect the course of the reaction, definite transition ranges are noted. Thus at 300° the 3- and 3,5-derivatives are formed; at 400° a mixture, the 2-, 3-, 2,6-, and 3,5-derivatives are obtained; while at 500° the product is mainly 2- and 2,6. It is apparent from these facts that some sort of a polar mechanism as opposed to a free radical type mechanism must apply and that possibly the character of the nitrogen atom is changed when the higher temperatures are reached. The formation of 2-chloropyridine by treatment of pyridine with sulfuryl chloride has been advanced as evidence that substitution in this position takes place on some sort of an N-oxide or peroxide derivative.

Nitration of pyridine produces practically negligible yields of 3-nitropyridine but if the pyridine ring is substituted it is possible to obtain the nitro compounds in yields as high as 90 per cent.

When pyridine is heated with sodamide to 160-180° 2-amino- or 2,6-diaminopyridine is obtained depending upon the ratio of the reactants. This reaction may involve an addition of the sodamide across the C=N linkage.

Treatment with mercuric acetate produces only the 3-mercuri-derivative under mild conditions and tars under more strenuous conditions. An intermediate, probably VII, is first formed.

VII



$$C_5H_5N\begin{matrix}\diagup OCOCH_3\\ \diagdown HgOCOCH_3\end{matrix}$$

In general the orientation effects of groups already present are the same as the same groups in nitrobenzene and good yields of the substitution products may be obtained if the substituent is one which activates the ring.

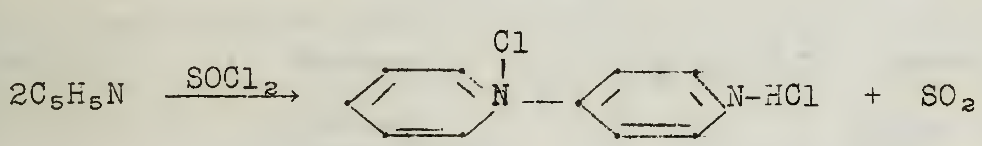
Cases of 1-2 and 1-4 addition to the bond system of pyridine are encountered when pyridine is treated with phenylmagnesium bromide or phenyl lithium.

Since all three derivatives are isolated in most cases, free radical substitution probably does occur when pyridine is treated with diazotized aromatic amines in alkaline solution.

The comparison to nitrobenzene may be extended to the activity of the groups already present. Thus halogen in the 2- or 4-position is activated much the same as in *o*-chloronitrobenzene. Methyl or alkyl groups in these positions undergo active methylene condensations with aldehydes and esters and this method may be used to separate β-picoline from the mixture which is obtained from coal tar in the same manner that *m*-nitrotoluene is separated from the *o*- and *p*-isomers.

The treatment of amino pyridines with nitrous acid gives unstable diazonium salts which behave in replacement reactions much like the corresponding benzene derivatives. The conversion of 5-chloro-2-aminopyridine to 5-chloro-2-nitropyridine in 40% yield by treatment with sulfuric acid and hydrogen peroxide has been reported.

The other amino pyridines may be obtained from the corresponding halogen compounds by treatment with ammonia in an autoclave. 3-Aminopyridine may be obtained by the Hofmann degradation of nicotinamide and 4-aminopyridine is obtained by treatment of 4-pyridyl-N-pyridinium dichloride with ammonia (VIII).



VIII 94%

Some reactions of VIII are shown:

VIII $\xrightarrow[150^\circ]{NH_3}$ 4-aminopyridine + pyridine 41%

VIII $\xrightarrow[150^\circ]{HOH}$ 4-hydroxypyridine + pyridine 84%

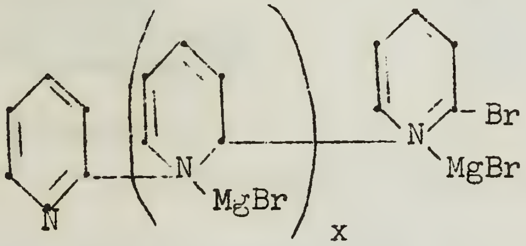
VIII $\xrightarrow{C_6H_5OK}$ 4-phenoxypyridine + pyridine 56%

Pyridine-2-sulfonic acid has been produced by oxidation of the thiol obtained by treatment of 2-bromopyridine with sodium hydrosulfide. The sulfonic acids may be fused with alkali, metal hydroxides, or cyanides to produce the corresponding hydroxide or cyanide.

The hydroxy derivatives may be produced by diazotization of the amine, by alkali fusion of the sulfonic acid or by hydrolysis of compounds of the type VIII.

The preparation of nicotinonitrile by the heating of 3-bromopyridine with cuprous cyanide has been reported. Nicotinic acid may also be produced by the treatment of 3-bromopyridine with butyl lithium followed by carbonation and hydrolysis, a process which is reported to produce yields as high as 70 per cent.

The treatment of 2-bromopyridine with magnesium apparently produces a polymer to which structure IX was assigned. It was possible to produce phenyl-2-pyridylcarbinol in 50 per cent yields by treatment of this polymer with benzaldehyde.



A table showing the yields and isomers obtained by some of the substitution reactions of pyridine is included.

TABLE

Reaction	Product	% yield	Remarks	Ref.
chlorination	2-chloro 2,6-dichloro	46 1	copper tube 270°	10
bromination	3-bromo 3,5-dibromo polybromo	39 12 4	mercury salts pumice 300°	13
iodination	3-iodo 3,5-diiodo	18	fuming sulfuric	9
sulfonation	3-sulfonic acid	40	mercuric sulfate 230°	7
nitration	3-nitro	3	18% fuming HNO_3 160-180°	14

Table (Cont)

Reaction	Product	% yield	Remarks	Ref.
amination	2-amino 2,6-diamino	50 51		15 16
phenylmagnesium bromide	2-phenyl	44	autoclave	18
ethylmagnesium bromide	2-ethyl	45	autoclave	18
phenyl lithium	2-phenyl	40-50	110°-toluene	19
sodium benzene diazotate	2-phenyl 3-phenyl 4-phenyl	24 10 10		20
benzyl chloride	2-benzyl 4-benzyl 2,6-dibenzyl 2,4-dibenzyl	50 trace trace trace	benzyl chloride heat and copper powder	
mercuration	3-mercuri	49	160-180°	17

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Reported by F. J. Wolf, January 21, 1942

SEMINAR REPORTS

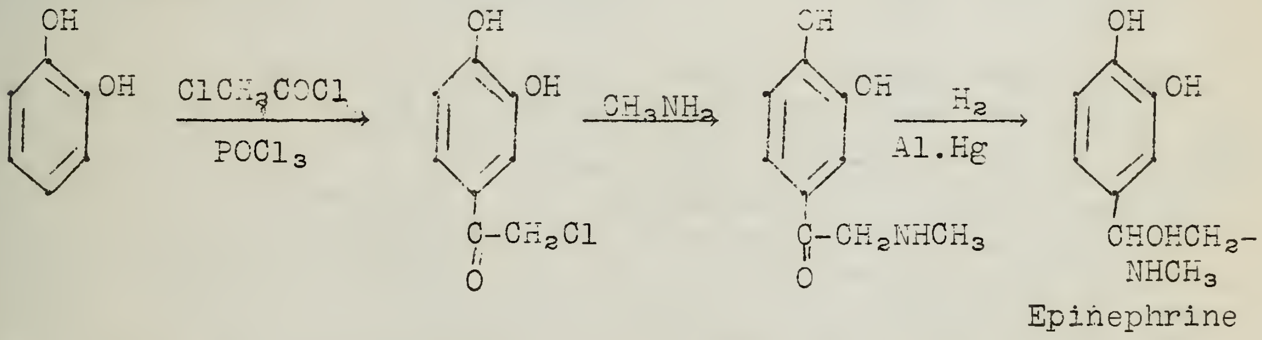
II Semester 1941-42

EPINEPHRINE AND RELATED COMPOUNDS

The Influence of Structure on Physiological Activity

Although rapid progress has been made, the relationship between the chemical structure and the physiological activity of medicinal products is still not clearly understood. However, evidences that there is some such relationship are apparent in several well-known chemical series, such as the alcohols, amines, barbiturates, phenols, and "sulfas." The individual importance and purpose of each intimate group or radical within each series has yet to be determined. That this relationship is of value to discover, is essential to the chemist synthesizing products which combat disease. By such information, scientific approach can be made towards specific medicinals where formerly success was often only by chance.

The earliest and best known study in attempting to correlate chemical constitution and physiological behavior was made with "pressors" or compounds which produce a rise in blood pressure. Interest in these compounds was first aroused when Oliver and Schaefer in 1894 found that extracts of the suprarenal glands produced a rise in blood pressure when injected into the blood vessels of animals. Immediately an intensive study of this gland in an effort to isolate its active principle was made by chemists, physiologists, and pharmacologists, credit finally going to Abel and his coworkers, who first isolated the hormone (as the poly-benzoyl derivative) in 1897. Once isolated, the formula for epinephrine was quickly established and this formulation confirmed by synthesis of the hormone carried out by Stolz in 1904, and is as follows:



Since the levo compound is the only one used in medicine, the racemic mixture obtained is resolved through d-tartaric acid.

Biologically, epinephrine is an extremely active compound. It has been found to exert an effect on the isolated frog heart in dilution as low as one part in five billion. Its value as a drug is based on the effects that it produces. These are chiefly, (1) its action on smooth muscles to relieve asthma, hay fever and severe colds; (2) its hyperglycemic effect to convert muscle and liver glycogen into glucose; and (3) its pressor action to cause a high rise in blood pressure or locally to arrest hemorrhage.

[illegible]

[illegible]

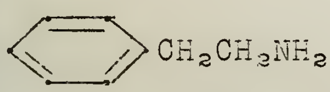
[illegible]

[illegible]

[illegible]

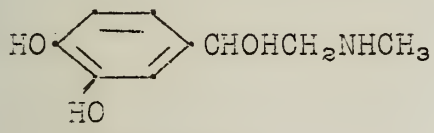
While the interest in epinephrine was increasing, a substance isolated from putrified meat, acting as a pressor, was identified by Barger and Dale to be tyramine. Their investigations on a group of compounds of putrefactive origin were reported in a classic which first shows this correlation of physiological character and structural similarity. Accordingly, when Chen in 1923 brought to light the medicinal virtues of ephedrine, a drug used by the Chinese for over five thousand years, workers in this field intensified their efforts to coordinate these physiologically related chemical compounds.

A comparison of the structure of the better known naturally occurring pressors (which follows) reveals that the β-phenylethylamine skeleton is common to all.

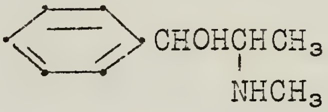


β-Phenylethylamine

Tyramine



Epinephrine



Ephedrine

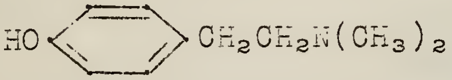
As is noted, however, there are significant structural differences between each compound. How, then, do these differences affect their relative physiological behaviors? Such modifications of structure will next be considered.

It seems appropriate at this point to discuss very briefly the usual method by which such compounds are compared. Since pressor action is common to all of these substances, assay is made by administration to a test animal and recording the resulting rise or fall in blood pressure. As epinephrine is the animal hormone and has been most widely studied, it serves as the comparative standard during the assay. It must be realized that in this, as in other biological assays, variations occur as a result of many factors. Hence, in accumulating evidence from many sources, contradictions and inconsistencies are unavoidable. Thus, for comparison, the different results of a single experimenter are the most reliable. Also, in interpreting results, the relative activities and toxicities must be compared before assigning a chemical compound a specific therapeutic value.

Considering now variation from the β-phenylethylamine nucleus, Barger and Dale investigated a series of compounds in which the relative positions of the phenyl and amino groups were varied. Aniline was without effect, benzylamine was slightly active, α-phenylethylamine more active, β-phenylethylamine had maximum activity, while γ-phenylpropylamine was again much less active. They concluded, therefore, that, in such a series, optimum pressor

activity was shown by compounds having a phenyl group removed from an amino group by two carbon atoms. More recently, these observations have been substantially confirmed by other workers, thus establishing the β-phenylethylamine skeleton as essential for optimum activity.

Naturally occurring compounds of the type under consideration include tyramine, epinephrine, and hordenine [hordenine or anhaline is an alkaloid isolated from germinating barley having the formula:



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primary, secondary, and tertiary amines, respectively. Let us then consider the variation in the amino group.

Barger and Dale in their early reports stated that for the non-phenolic compounds, methylation of the amino group makes no appreciable difference in pressor potency. However, a lengthy survey of reports by more recent workers indicates that for both phenolic and non-phenolic substances of this type (with one exception), the secondary amines are much less active and more toxic than the corresponding primary amines. Introduction of the higher alkyl groups in place of methyl is a step in the wrong direction. Toxicity becomes higher and <u>depressor</u> action results. Two methyl groups also work to a disadvantage, as in the case of hordenine which is distinctly of less value than tyramine. The effect of alkylating the amino group may best be summarized by Table I.

TABLE I

Effect of Substitution in Amino Group

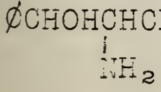
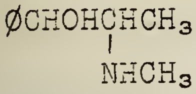
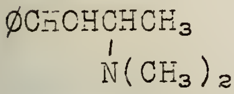
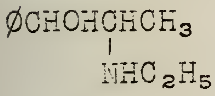
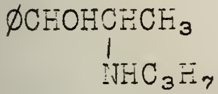
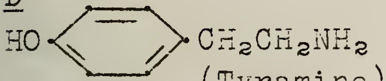
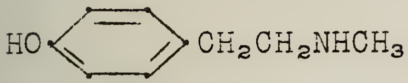
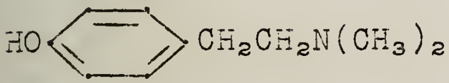
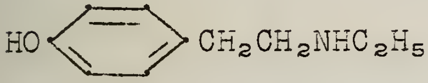
Compound	Pressor Activity Epinephrine = 1	Relative Toxicity
<u>A</u>		
Ø$CH_2CH_2NH_2$ (β-phenylethylamine)	1/350	Toxicity doubles on substitution
Ø$CH_2CH_2NHCH_3$	1/350	
<u>B</u>		
Ø$CHOHCH_2NH_2$	1/350	Toxicity about same
Ø$CHOHCH_2NHCH_3$	1/700	
<u>C</u>		
 Ø$\underset{NH_2}{CHOHCH}CH_3$ (Propadrine)	1/80	50% more toxic than primary amine

Table I (Cont')

C (cont')		
 $\phi CHOH\underset{\substack{\vert \\ NHCH_3}}{C}HCH_3$	1/95	
 $\phi CHOH\underset{\substack{\vert \\ N(CH_3)_2}}{C}HCH_3$	1/600	Toxicity progressively increases with alkylation
 $\phi CHOH\underset{\substack{\vert \\ NHC_2H_5}}{C}HCH_3$	1/150	
 $\phi CHOH\underset{\substack{\vert \\ NHC_3H_7}}{C}HCH_3$	Depressor	
D		
 (Tyramine)	1/150	
	1/150	Toxicity increases with alkylation
	1/700	
	1/200	

A second principal difference in chemical structure in the naturally occurring pressors, is the presence of one or more phenolic hydroxyl groups. As a result of the investigations of Barger and Dale, Alles, and Tainter, it can be stated that the intensity of action of phenolic pressor substances is much greater than that of the corresponding non-phenolic compounds. Although the ortho-hydroxyl has no apparent pressor influence, it does serve to increase the toxicity. The meta isomer increases the pressor activity as much as five times but also increases the toxicity. Finally, the para hydroxyl confers a pressor activity between the ortho and meta and, most important, it lowers the toxicity. Thus, it is not too surprising to find that the 3,4-dihydroxy compound indicates a maximum activity with a rather low toxicity. Further phenolic substitution only serves to decrease activity. With phenolic substitution, however, the action is more transitory, the duration of response being lowered. Table II summarizes such comparable compounds.

TABLE II

Effect of Phenolic Hydroxyls

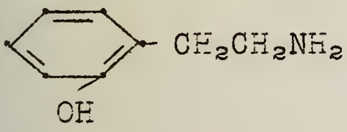
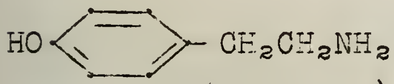
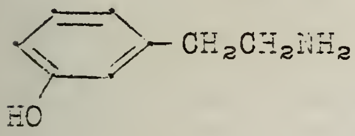
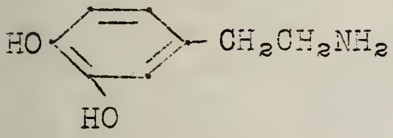
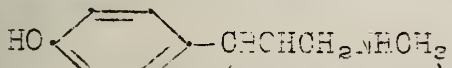
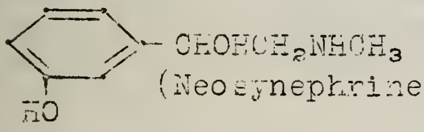
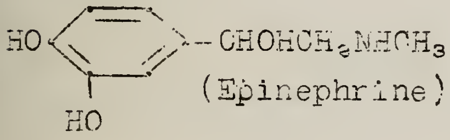
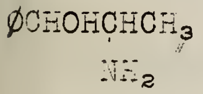
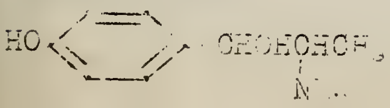
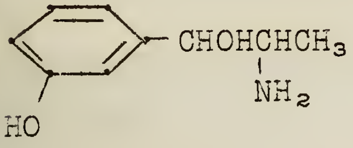
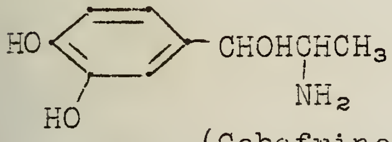
Compound	Pressor Activity Epinephrine = 1	Relative Toxicity
A		
$ØCH_2CH_2NH_2$ (I)	1/350	
	1/350	More toxic than I
 (Tyramine)	1/150	Less toxic than I
	1/70	More toxic than I
	1/35	Toxicity only slightly more than I
B		
 (II) (Synephrine)	1/35	
 (Neosynephrine)	1/5	More toxic than II
 (Epinephrine)	1	More toxic than II
C		
 $ØCHOH\underset{NH_2}{C}HCH_3$ (III) (Propadrine)	1/80	
	1/50	1/5 as toxic as III

Table II (cont')

C (cont')		
	1/25	3 times as toxic as III
 (Cobefrine)	1/4	1/100 as toxic as epinephrine

In the use of epinephrine as a therapeutic agent, its chief handicap is its complete inactivity when administered by mouth. Since ephedrine, a propane derivative, is orally active, is the length of the side chain responsible for this physiological difference? As studied by the Council on Pharmacy and Chemistry of the American Medical Association, phenylethanolamine is not active after oral administration, whereas phenylpropanolamine is. Chen, et al, in their investigations on the ephedrines attribute the oral efficacy of ephedrine to the presence of the third carbon of the side chain. Hartung and Munch from their results with the phenylpropylamines found that phenyl-1-amino-2-propane was orally active. Thus, such compounds as ephedrine, propadrine and benzedrine are all active when administered by mouth. However, further extension of the side chain gives results of a negative character. Thus, phenylbutanolamine is nearly inactive while phenylpentanolamine is a depressor with a marked toxicity.

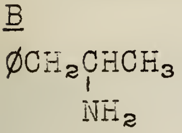
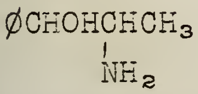
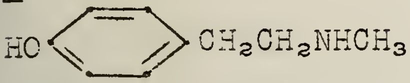
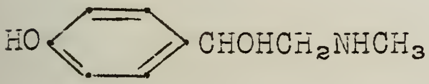
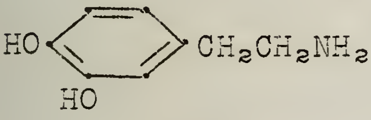
Finally, in a discussion of these pressor substances, it is noted that for some, a side chain hydroxyl group is in evidence. The effect of this group is not too well defined but all evidence points to an augmentation of the pressor activity and a lowered toxicity. An examination of Table III illustrates this rather clearly.

TABLE III

Effect of Alcoholic Hydroxyl

Compound	Pressor Activity Epinephrine = 1	Relative Toxicity
A		
Ø$CH_2CH_2NH_2$	1/350	
Ø$CHOHCH_2NH_2$	1/350	1/2 as toxic as simple amine

Table III (Cont')

<u>B</u>		
 $\phi CH_2\underset{NH_2}{C}HCH_3$ (Benzedrine)	1/350	1/3 as toxic as simple amine
 $\phi CHOH\underset{NH_2}{C}HCH_3$ (Propadrine)	1/80	
<u>C</u>		
	1/150	Less toxic than simple amine
	1/35	
<u>D</u>		
	1/35	
 (Arterenol)	$\frac{dl\text{-art.}}{dl\text{-epi.}} = \frac{3}{2}$ $\frac{dl\text{-art.}}{l\text{-epi.}} = \frac{1}{1.2}$	Less toxic than simple amine 1/3 toxicity of epinephrine

The above discussions and the resulting conclusions may be summarized as follows:

1. The optimum pressor activity (production of a rise in blood pressure) is found in those compounds in which the aromatic nucleus and the amino group are attached to neighboring or adjacent carbon atoms, thus Ar-C-C-N.

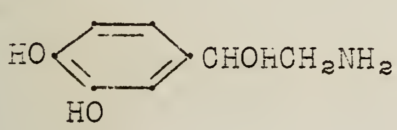
2. The primary amines are more active and less toxic, generally, than corresponding methylated, secondary amines.

3. Substitution of hydroxyl groups in the 3,4-positions of the phenyl nucleus confers optimum pressor activity.

4. Compounds with three carbon atoms in the side chain are much more active on the circulation after oral administration than are the homologs with only two carbon atoms in the side chain.

5. The alcoholic hydroxyl group increases the activity and decreases the toxicity or both.

In applying this information, the following two compounds are chosen as representatives of the synthetic field to surplant perhaps in their individual usefulness, the natural products:



Arterenol

Nearly as active as epinephrine
1/3 as toxic as epinephrine
Acts twice as long as epinephrine

Cobefrine

Orally active
1/100 as toxic as epinephrine
Acts twice as long as epinephrine
1/4 as active as epinephrine

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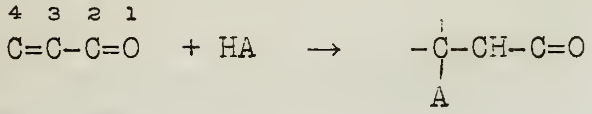
Jenkins, G.L. and Hartung, W.H., The Chemistry of Organic Medicinal Products, John S. Swift and Co., 274, (1941).

Reported by K. E. Hamlin, Jr.
February 11, 1942

ATTACK AT THE ALPHA CARBON ATOM OF ALPHA, BETA-UNSATURATED CARBONYL COMPOUNDS

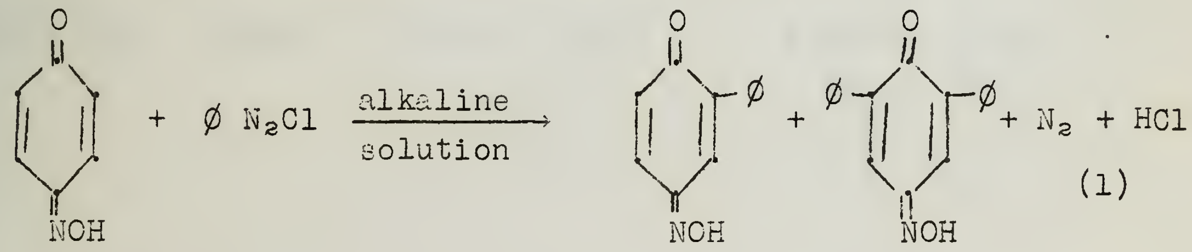
α,β-Unsaturated carbonyl compounds are well characterized by the addition reactions which they undergo with many different types of reagents. In a large number of cases addition occurs in such a manner that the elements H and A, of the reagent HA, finally become attached to carbon atoms 3 and 4, respectively.



$$\overset{4}{C}{=}\overset{3}{C}{-}\overset{2}{C}{=}\overset{1}{O} + HA \rightarrow -\underset{A}{\overset{|}{C}}-CH-C{=}O$$

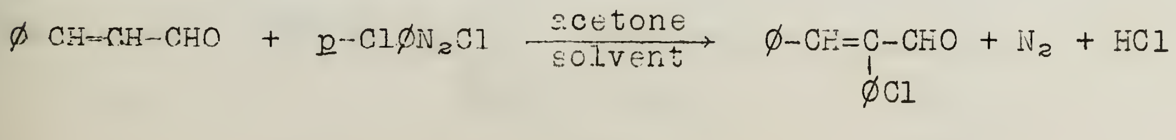
Kohler and his associates have definitely established that the initial reaction is a 1,4 addition in the case of Grignard reagents, and hence, it is generally assumed that most other HA reagents react by the same mechanism. However, there are a few reagents which apparently attack conjugated carbonyl compounds at the alpha carbon atom, and thus, are in contrast to the general scheme outlined above.

A. The first of these to be mentioned is the reaction of aromatic diazo compounds with substances containing a conjugated carbonyl system. The reaction was discovered in 1899 by Borsche who found that instead of obtaining an azo dye by the action of benzene diazonium chloride on p-nitrosophenol, a carbon-carbon linkage was established and 2-phenyl-4-nitrosophenol resulted along with some 2,6-diphenyl-4-nitrosophenol.

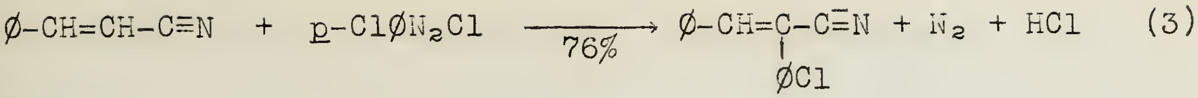


(1)

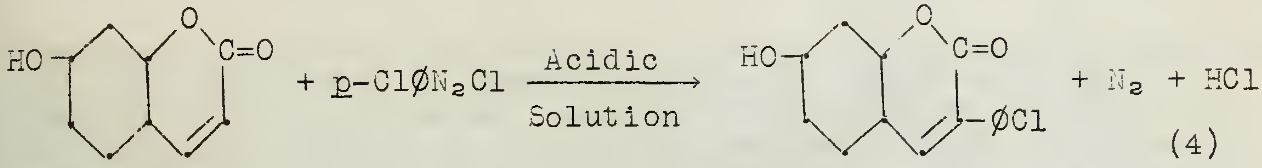
The nature of this reaction has been further studied and extended to various benzo- and naphthoquinones by Kvalnes; while Meerwein and coworkers have established definitely that the attack is at the α-carbon atom. The reaction is also the subject of a few patents in connection with the preparation of substituted quinones to be used as dye intermediates. The work of Meerwein, mentioned above, was reviewed by Mr. Rabjohn as a seminar topic in the fall of 1939, so only a few of the more interesting reactions are listed below:



$$\phi\,CH{=}CH{-}CHO + p\text{-}Cl\phi N_2Cl \xrightarrow[\text{solvent}]{\text{acetone}} \phi{-}CH{=}\underset{\phi Cl}{\underset{|}{C}}{-}CHO + N_2 + HCl \quad (2)$$

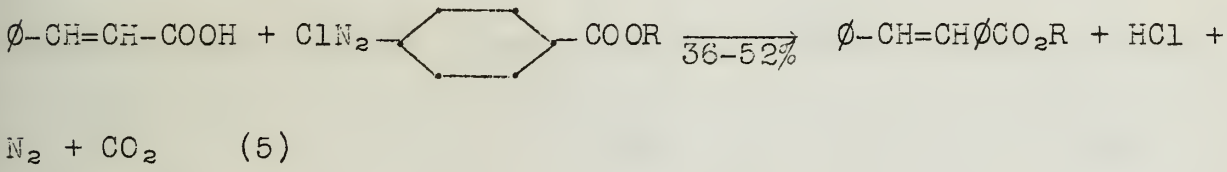


$$\phi\text{-CH=CH-C}\equiv\text{N} + p\text{-Cl}\phi\text{N}_2\text{Cl} \xrightarrow[76\%]{} \phi\text{-CH=}\underset{\phi\text{Cl}}{\text{C}}\text{-C}\equiv\text{N} + \text{N}_2 + \text{HCl} \qquad (3)$$

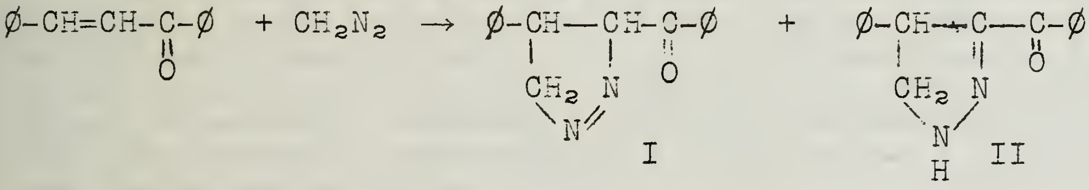


Umbelliferone

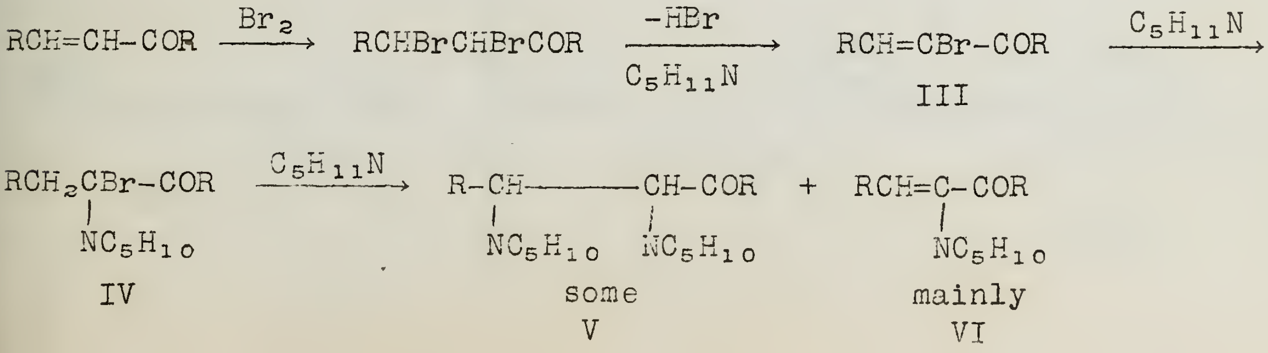
Methyl cinnamate and cinnamic acid are also attacked at the alpha carbon atom, however, in the case of cinnamic acid carbon dioxide is eliminated and a stilbene results. This reaction has been used in this Laboratory by Fuson and Cooke to prepare the methyl and ethyl esters of 4-carboxystilbene.



It should be pointed out that although aromatic diazo compounds attack the conjugated system at the α-carbon atom, aliphatic diazo compounds attack these substances in such a way that a new carbon link is established at the β-carbon atom. Thus benzalacetophenone and diazomethane give the two pyrazolines I and II.

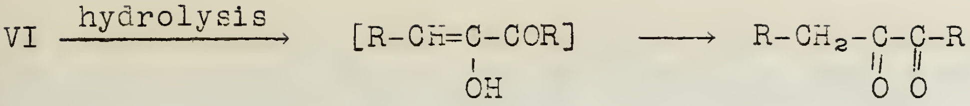


B. In 1927 Dufraisse and Moureu discovered that α,β-unsaturated ketones could be converted into α-diketones (40-80% yields) by bromination, treatment with piperidine, and subsequent hydrolysis. After a careful examination of the reaction the authors formulated it as follows:



$$\text{RCH=CH-COR} \xrightarrow{\text{Br}_2} \text{RCHBrCHBrCOR} \xrightarrow[\text{C}_5\text{H}_{11}\text{N}]{-\text{HBr}} \underset{\text{III}}{\text{RCH=CBr-COR}} \xrightarrow{\text{C}_5\text{H}_{11}\text{N}}$$

$$\underset{\text{IV}}{\text{RCH}_2\underset{\text{NC}_5\text{H}_{10}}{\text{C}}\text{Br-COR}} \xrightarrow{\text{C}_5\text{H}_{11}\text{N}} \underset{\substack{\text{some}\\ \text{V}}}{\text{R-}\underset{\text{NC}_5\text{H}_{10}}{\text{CH}}\text{---}\underset{\text{NC}_5\text{H}_{10}}{\text{CH}}\text{-COR}} + \underset{\substack{\text{mainly}\\ \text{VI}}}{\text{RCH=}\underset{\text{NC}_5\text{H}_{10}}{\text{C}}\text{-COR}}$$

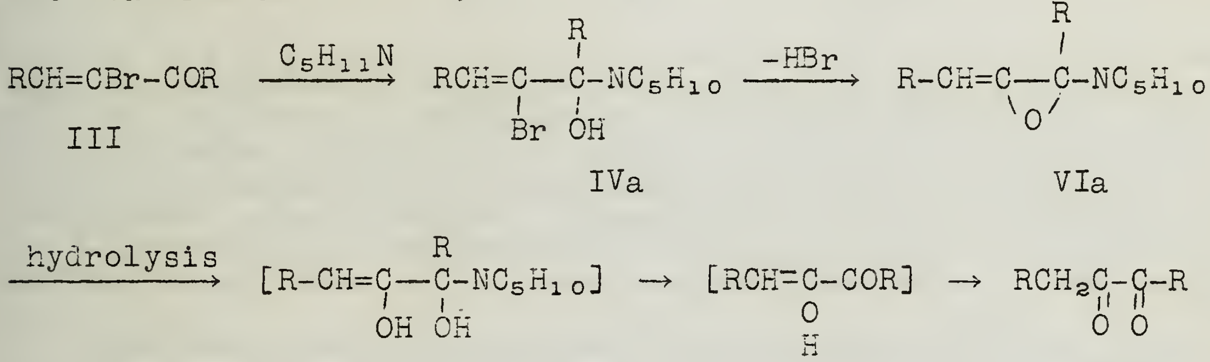


$$\text{VI} \xrightarrow{\text{hydrolysis}} [\text{R-CH=}\underset{\text{OH}}{\text{C}}\text{-COR}] \longrightarrow \text{R-CH}_2\text{-}\underset{\overset{\|}{\text{O}}}{\text{C}}\text{-}\underset{\overset{\|}{\text{O}}}{\text{C}}\text{-R}$$

VII

The French investigators wrote V as the α,α-dipiperidino compound but the recent work of Cromwell indicates rather definitely that it is the α,β-isomer. The transformation of III into IV is of particular interest since it involves an inverse addition to the conjugated carbonyl system. Compound VI (R=Ø) is a deep red crystalline compound and was first prepared by Watson, although he considered it to be β-piperidinobenzalacetophenone.

Kohler and Addinall refused to accept either the mechanism of Dufraisse and Moureu or their structure VI (R=Ø) for the red piperidino compound. Instead Kohler and Addinall, who had been studying the action of alcoholates on β-dibromoketones, formulated the reaction as follows:



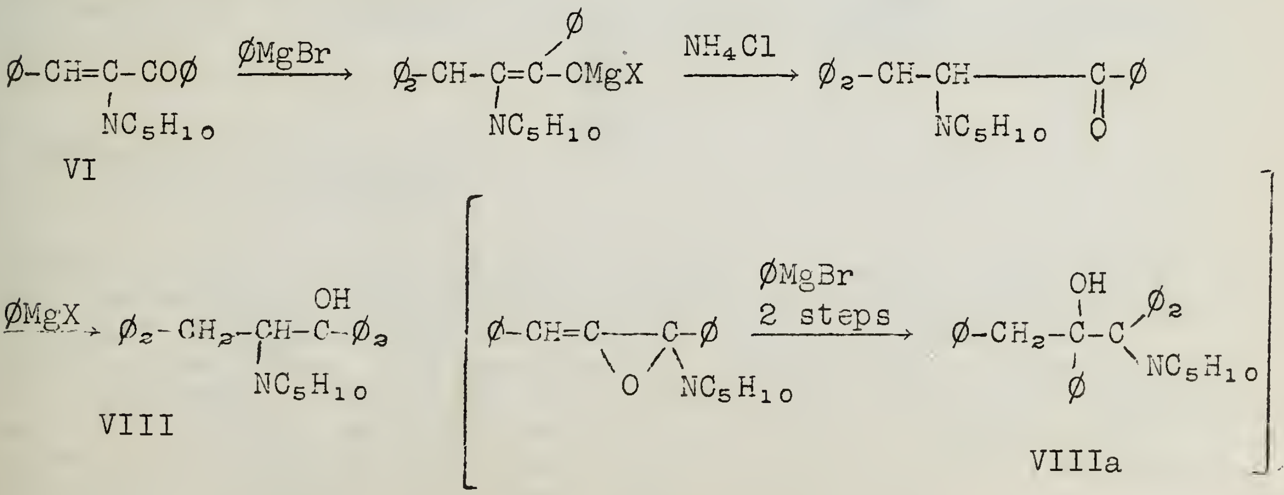
$$\text{RCH=CBr-COR} \xrightarrow{C_5H_{11}N} \text{RCH=}\underset{\text{Br}}{\text{C}}\text{—}\overset{\text{R}}{\underset{\text{OH}}{\text{C}}}\text{-NC}_5\text{H}_{10} \xrightarrow{\text{-HBr}} \text{R-CH=}\underbrace{\text{C—}\overset{\text{R}}{\text{C}}}_{\text{O}}\text{-NC}_5\text{H}_{10}$$

III IVa VIa

$$\xrightarrow{\text{hydrolysis}} [\text{R-CH=}\underset{\text{OH}}{\text{C}}\text{—}\overset{\text{R}}{\underset{\text{OH}}{\text{C}}}\text{-NC}_5\text{H}_{10}] \rightarrow [\text{RCH=}\underset{\underset{\text{H}}{\text{O}}}{\text{C}}\text{-COR}] \rightarrow \text{RCH}_2\underset{\overset{\|}{\text{O}}}{\text{C}}\text{-}\underset{\overset{\|}{\text{O}}}{\text{C}}\text{-R}$$

VII

In order to prove which of these two mechanisms was correct a rigorous proof of structure of the compound represented by VI or VIa was necessary and in so doing the questionable inverse addition would be clarified. This work was done by Kohler and Bruce and after an exhaustive study they reluctantly concluded that the structure represented by VI as assigned by Dufraisse and Moureu was correct. In brief, their most conclusive proof of structure was as follows:



$$\phi\text{-CH=}\underset{\text{NC}_5\text{H}_{10}}{\text{C}}\text{-CO}\phi \xrightarrow{\phi\text{MgBr}} \phi_2\text{-CH-}\underset{\text{NC}_5\text{H}_{10}}{\text{C}}\text{=}\overset{\phi}{\text{C}}\text{-OMgX} \xrightarrow{\text{NH}_4\text{Cl}} \phi_2\text{-CH-}\underset{\text{NC}_5\text{H}_{10}}{\text{CH}}\text{———}\underset{\overset{\|}{\text{O}}}{\text{C}}\text{-}\phi$$

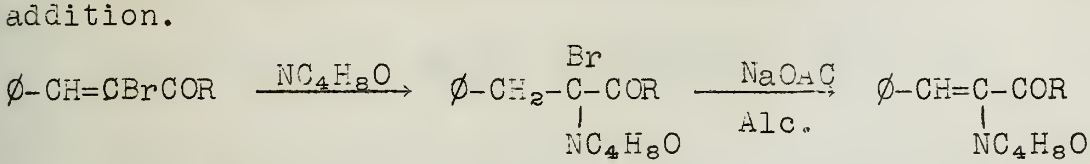
VI

$$\xrightarrow{\phi\text{MgX}} \phi_2\text{-CH}_2\text{-}\underset{\text{NC}_5\text{H}_{10}}{\text{CH}}\text{-}\overset{\text{OH}}{\text{C}}\text{-}\phi_2 \qquad \left[\phi\text{-CH=}\underbrace{\text{C——}\underset{\text{NC}_5\text{H}_{10}}{\text{C}}}_{\text{O}}\text{-}\phi \xrightarrow[\text{2 steps}]{\phi\text{MgBr}} \phi\text{-CH}_2\text{-}\overset{\text{OH}}{\underset{\phi}{\text{C}}}\text{-C}\begin{matrix}\phi_2\\ \text{NC}_5\text{H}_{10}\end{matrix}\right]$$

VIII VIIIa

To decide which of the two formulas, VIII or VIIIa, was correct for the carbinol which they obtained was easy; oxidation with chromic acid gave two moles of benzophenone instead of one as would be expected from VIIIa.

More recently Cromwell has further investigated the reactions of α-bromo-α,β-unsaturated ketones with amines. He has demonstrated that morpholine reacts in cold ether, or petroleum ether, with α-bromobenzalacetone, IX, and α-bromobenzalacetophenone, X, to give the α-bromo-α-morpholino compounds XI and XII by inverse addition.



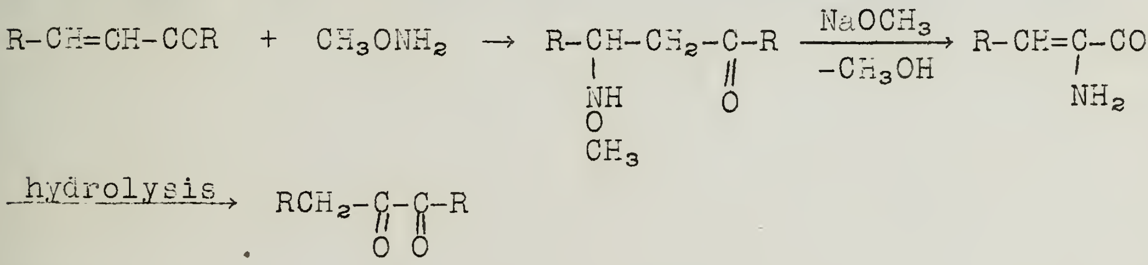
$$\phi\text{-CH=CBrCOR} \xrightarrow{NC_4H_8O} \phi\text{-CH}_2\text{-}\overset{Br}{\underset{NC_4H_8O}{C}}\text{-COR} \xrightarrow[Alc.]{NaOAc} \phi\text{-CH=}\underset{NC_4H_8O}{C}\text{-COR}$$

(IX; R = CH_3) (XI; R = CH_3) (XIII; R = CH_3)
(X; R = ϕ) (XII; R = ϕ) (XIV; R = ϕ)

When XI and XII were treated with sodium acetate in alcohol solution the α-morpholino-α,β-unsaturated ketones XIII and XIV resulted. The latter two compounds, however, could not be induced to add another molecule of morpholine, nor could this base be added to β-morpholinobenzalacetophenone which also contains the conjugated carbonyl system. Pyrrolidine has been found to add to α-bromobenzalacetophenone X in the same manner as morpholine, but the weaker base, 1,2,3,4-tetrahydroquinoline will not react.

Now when benzalacetone and benzalacetophenone react with morpholine only saturated β-morpholino ketones result, thus indicating that amines attack the α-carbon atom of α,β-unsaturated ketones only when there is a halogen atom substituted on the α-carbon.

In studying the reaction of methoxylamine witn α,β-unsaturated ketones, Blatt has shown that this reagent adds smoothly and reversibly in the absence of a catalyst to produce saturated β-methoxyamino ketones.

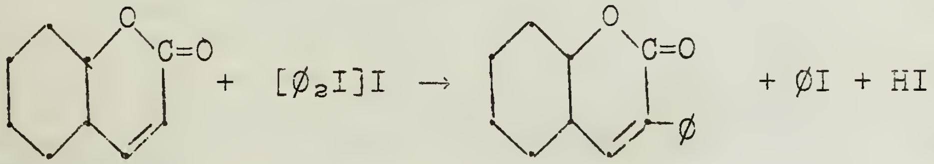


$$\text{R-CH=CH-CCR} + CH_3ONH_2 \rightarrow \text{R-}\underset{\substack{NH\\O\\CH_3}}{CH}\text{-CH}_2\text{-}\underset{O}{\overset{}{C}}\text{-R} \xrightarrow[-CH_3OH]{NaOCH_3} \text{R-CH=}\underset{NH_2}{C}\text{-COR}$$

$$\xrightarrow{hydrolysis} \text{RCH}_2\text{-}\underset{O}{C}\text{-}\underset{O}{C}\text{-R}$$

However, when this reaction is carried out in the presence of a base or when the β-methoxyamino ketone is treated with sodium ethylate, methyl alcohol is removed, and an α-amino-α,β-unsaturated ketone is formed, which can be further hydrolyzed to an α-diketone. This shift of an amino group from the β to the α carbon is easily accomplished in yields which in many cases approximate 90% and thus constitutes a useful method for transforming α,β-unsaturated ketones into α-diketones.

C. It is reported in the paper of Meerwein, et al., that diphenyl iodinium iodide reacts with α,β-unsaturated carbonyl compounds to give substitution at the α-carbon atom just as in the case of diazo compounds. Thus



$$\phi\text{-CH=CH-COOH} + [\phi_2I]I \rightarrow \phi\text{CH=CH}\phi + \phi I + HI$$

There was no experimental detail, or reference to previous work given, merely the statement that the reaction was under investigation. To date nothing further on this reaction has been published.

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Reported by John E. Mahan
February 11, 1942

HYDROGEN BONDING BY C-H

Marvel, Copley and Zellhoefer

The concept of association through hydrogen bonding proposed by Latimer and Rodebush in 1920 to explain the abnormal properties of certain liquids has been utilized with considerable success in understanding the behavior of liquids and solutions. In particular it has proved useful in explaining and predicting abnormally high solubility of certain organic substances in various types of solvents, high heats of mixing, and other abnormal solution behavior.

The types of hydrogen bonds that have been found are OH ← O or N, XH ← O or N, NH ← O or N, SH → O or N, and CH ← O or N. The present work deals with the latter type.

There are a number of methods of determining the presence and strength of hydrogen bonds. One method involves shift in the C-H absorption frequency in the infra-red regions. The methods used at this school include measurement of the heat of mixing of liquid mixtures, vapor pressure - composition studies of a volatile solute in a relatively non-volatile solvent, and solubility measurements of polymers in various solvents. All of these methods give relative values of the strength of bond. Qualitatively they are in excellent agreement. Absolute values for the strength of a CH ← O bond, say for chloroform ether, are about 5,000 to 10,000 calories per mole of complex formed.

The CH hydrogen atom is capable of acting as an acceptor only when it is activated by some negative group such as halogen, nitro, nitrile, acetylenic linkage, and to a very slight extent the phenyl group. It has been found that as acceptors, $CHCl_3 > CHBr_3 > CHI_3$ and $CH_2Cl_2 > CH_2Br_2 > CH_2I_2$. This is quite in keeping with the order of electronegativity of the halogens: $Cl > Br > I$. It is the presence of the strongly electron-attracting halogen atoms on the carbon atom which loosen the hydrogen atom and make it available for coordination to the donor atom.

One very unusual case of an active CH hydrogen atom is in benzotrichloride. This compound is a vinylog of chloroform and most probably owes its bonding activity to the vinylogous action of the halogen atoms on the <u>para</u> (or <u>ortho</u>) hydrogen atom.

In the case of donor solvents the order of donor-ability appears to be, roughly and with a degree of overlapping: alkyl phosphates > 3° aliphatic amines > N,N-dialkyl amides > 1° aliphatic amines > ethers, ketones and esters > aromatic amines > nitriles > alkyl sulfates and sulfonates > nitrates and nitro compounds.

Solvents which form strong intramolecular hydrogen bonds such as alcohols, unsubstituted amides, and glycols exhibit little tendency to bond intermolecularly with other acceptors and hence are poor solvents for such compounds as haloforms. However, they

are good solvents for strong donors such as amines. Dinitriles, aliphatic nitro compounds, aromatic amines, and other compounds which form weak intramolecular hydrogen bonds show less tendency to form intermolecular bonds with either donor or acceptor molecules than do unassociated solvents. Similarly, chelation tends to decrease the solubility of diketones and keto esters in acceptor solvents.

A steric effect has been noted in the heat of mixing of chloroform and polyethylene glycol ethers. The curves indicate that every other oxygen atom bonds to a chloroform. This is similar to the result obtained with donor solvents and sym-tetrachloroethane. In this case with two adjacent active hydrogen atoms only one appears to bond.

Hydrogen bonding has been of some help in obtaining solvents for polymeric materials. In general, if the polymer contains a donor group an acceptor compound will be a good solvent. However, hydrogen bonding is only a partial explanation for solubility of polymers.

Hydrogen bonding is a very useful aid to the organic chemist, but it must be remembered that it is only a part explanation of solubility and not an infallible rule.

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Reported by E. Ginsberg
February 18, 1942

At the University of Texas, under the direction of Dr. H. L. Lochte and the late Dr. J. R. Bailey, sixty-five individual acidic and basic constituents of petroleum have been isolated and identified. Several more have been isolated but not yet identified. Only sixteen of these compounds had been previously reported, and thirteen of these were phenols and aliphatic acids. The compounds which have been isolated are listed in Table I.

TABLE I

Bases

Quinoline
Quinaldine
2,8-Dimethylquinoline
2,3-Dimethylquinoline
2-Methyl-8-ethylquinoline
2,3,8-Trimethylquinoline
2,3-Dimethyl-8-ethylquinoline
2,3-Dimethyl-8-*n*-propylquinoline
2,4-Dimethylquinoline
2,4,8-Trimethylquinoline
2,4-Dimethyl-8-ethylquinoline
2,4-Dimethyl-8-*n*-propylquinoline
2,4-Dimethyl-8-*s*-butylquinoline
2,3,4,8-Tetramethylquinoline
2,3,4-Trimethyl-8-ethylquinoline
2,3,4-Trimethyl-8-*n*-propylquinoline
2,3,4-Trimethyl-8-*i*-propylquinoline
2,3,8-Trimethyl-4-ethylquinoline
2,3-Dimethyl-4,8-diethylquinoline
2,3-Dimethyl-4-ethyl-8-*n*-propylquinoline
Isoquinoline
2-Picoline
4-Picoline
2,6-Dimethylpyridine
2,5-Dimethylpyridine
2,4-Dimethylpyridine
3,5-Dimethylpyridine
2,4,5-Trimethylpyridine
2,4,6-Trimethylpyridine
2-*sec*.-Butyl-4,5-dimethylpyridine
2,4-Dimethyl-6-"*trans*"-2,2,6-trimethylcyclohexylpyridine
2,3-Dimethylbenzo(h)quinoline
2,4-Dimethylbenzo(h)quinoline

Acids

Formic
Acetic
Propionic
n-Butyric
iso-Butyric
Valeric
iso-Valeric
n-Hexanoic
2-Methylpentanoic
3-Methylpentanoic
n-Heptanoic
2-Methylhexanoic
3-Methylhexanoic
4-Methylhexanoic
5-Methylhexanoic
n-Octanoic
n-Nonanoic
Dimethylmaleic anhydride
Phenol
o-Cresol
m-Cresol
p-Cresol
2,4-Xylenol
2,5-Xylenol
3,5-Xylenol
Cyclopentanecarboxylic
Cyclopentaneacetic
3-Methylcyclopentaneacetic
2,3-Dimethylcyclopentaneacetic
solid 4-methylcyclohexanecarboxylic
"*trans*"-2,2,6-Trimethylcyclohexanecarboxylic
cis-2,2,6-Trimethylcyclohexanecarboxylic

One of the interesting problems in connection with this research was the assignment of structure to a $C_{16}H_{25}N$ base, 2,4-dimethyl-6-trans-2,2,6-trimethylcyclohexylpyridine, and the structural correlation of this base with a $C_{10}H_{18}O_2$ acid, trans-2,2,6-trimethylcyclohexanecarboxylic acid, also isolated from petroleum.

The positive contributions toward determining the structure are diagramed on the Flow Sheet and may be listed as follows:

1. Isolation of pyridine-2,4,6-tricarboxylic acid from the oxidation products of the base with dilute nitric acid proved alkylation at positions 2,4, and 6.

2. Formation of a phthalone established the presence of a methyl group at position 2 or 6.

3. Condensation of the base with formaldehyde and nitric acid oxidation of the product yielded a dicarboxylic acid, $C_{14}H_{19}N(COOH)_2$, which was decarboxylated first to $C_{14}H_{19}N(COOH)_2$, which was decarboxylated first to $C_{14}H_{20}NCOOH$ and then to $C_{14}H_{21}N$, indicating the presence of two reactive methyl groups.

4. Formation of a dibenzal derivative also indicated the presence of two reactive methyl groups.

5. High pressure hydrogenation in the presence of Raney nickel as a catalyst resulted at 250° in the consumption of six atoms of hydrogen per molecule of the base. Dehydrogenation yielded the original base. The base with one mole of methyl iodide formed a quaternary ammonium salt which was not converted into a methylated free base by sodium hydroxide. The non-reactivity of the base with ammonium iodide and hydriodic acid in an atmosphere of carbon dioxide showed the absence of an N-alkyl group. All of these facts indicated that the base was a substituted pyridine.

One of the confusing facts about the base was its stability towards oxidizing agents. Alkaline permanganate as well as chromic acid has no effect at room temperature. Acid permanganate attacks the base but no product except carbon dioxide could be isolated.

Data to this point indicated that the compound contained a pyridine nucleus with two methyl groups and a C_9H_{17}-alicyclic radical as substituents in positions 2,4, and 6, the exact location of the individual groups being indefinite.

6. Ring cleavage and removal of the nitrogen atom was achieved by the method of von Braun, by which benzoylpiperidine may be converted to pentamethylenedibromide. The dibromide obtained was converted to a diene by alcoholic KOH and ozonized to obtain a $C_{10}H_{18}O_2$ acid, confirming the presence of a C_9H_{17}-substituent on the pyridine nucleus. Direct ozonization of the base followed by hydrolysis in alkaline peroxide gave the amide of the acid, establishing the C_9H_{17}-group as being in the 2-position.

7. The $C_{10}H_{18}O_2$ acid obtained from degradation of the base was found identical with one obtained from petroleum.

8. Conversion to the $C_9H_{17}NH_2$ amine was accomplished by the action of hypobromite on the amide or hydrazoic acid upon the acid. Treatment with nitrous acid gave an unsaturated hydrocarbon, C_9H_{16}, which gave 2-methylcyclopentyl methyl ketone, leaving only five possible structures (listed in the flow sheet) for the acid. Since the acid was not esterifiable by methyl alcohol-hydrogen chloride, the ester prepared from the acid chloride was not saponified by alcoholic KOH, the ester was not hydrogenated under 4000 pounds pressure at 250° in the presence of copper-chromium oxide, and the amide could not be prepared by ammonolysis of the ester, it appeared at first to be a tertiary acid. Whitmore's method of distinguishing between secondary and tertiary acids indicated that this acid was tertiary; so the structurally possible tertiary acids were synthesized.

After elimination of these tertiary acids, von Braun's imide chloride method showed the acid to be secondary, whereupon the two isomers of 2,2,6-trimethylcyclohexanecarboxylic acid were synthesized. The acid from petroleum and from the degradation of the base was identical with the higher melting form, tentatively assigned the trans configuration as the higher melting form.

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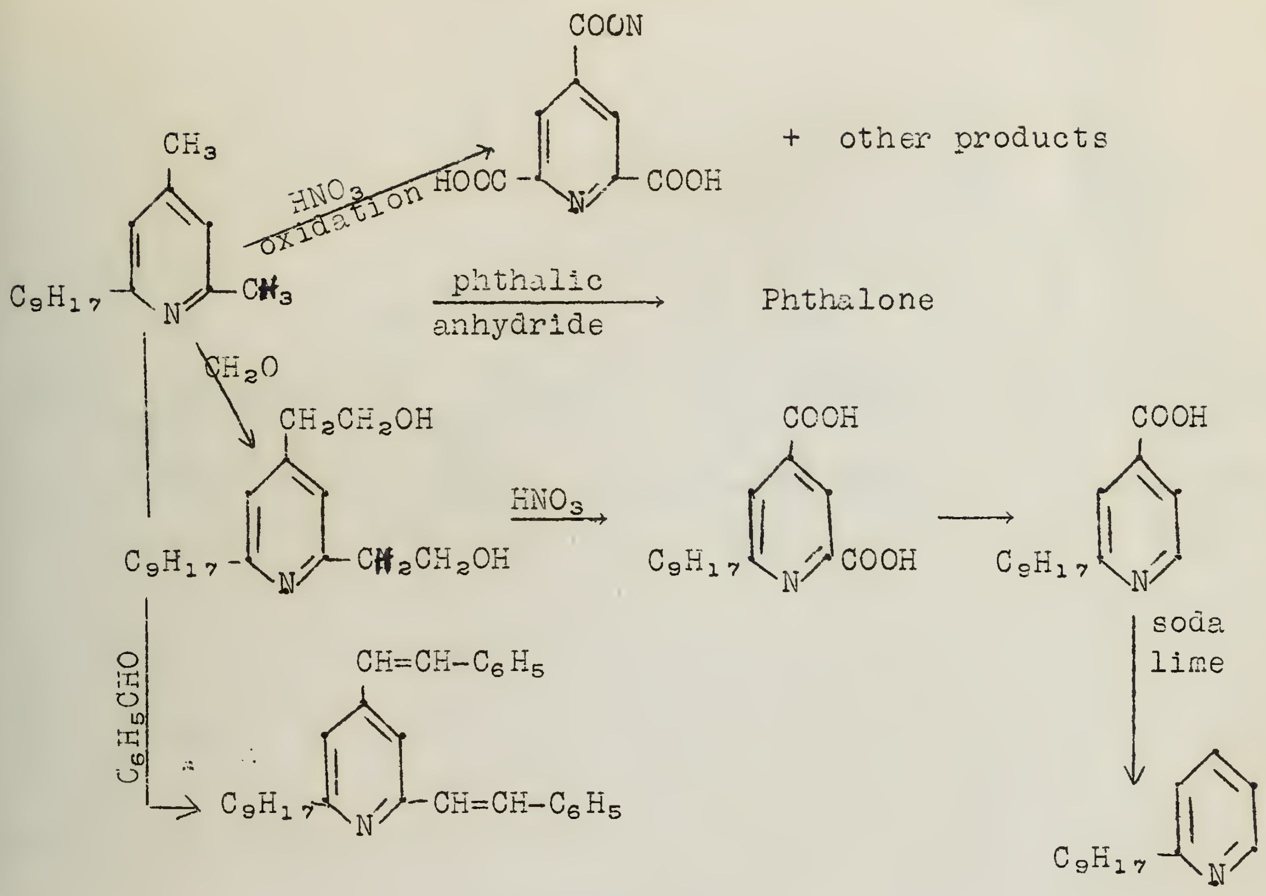
Reported by Billie Shive
February 18, 1942

FLOW SHEET

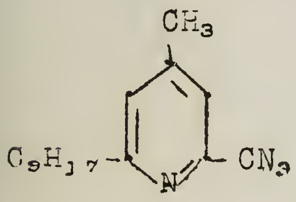
Degradation



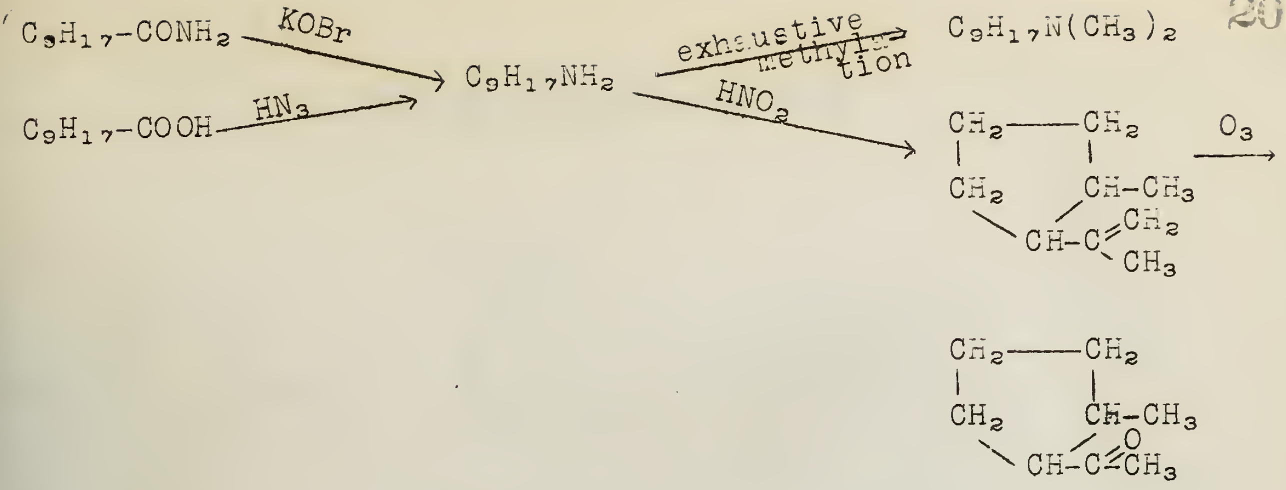
$C_{16}H_{25}N + 3H_2 \rightarrow C_{16}H_{31}N \xrightarrow{C_6H_5COCl} C_{16}H_{30}N-CO-C_6H_5 \xrightarrow{PBr_5}$

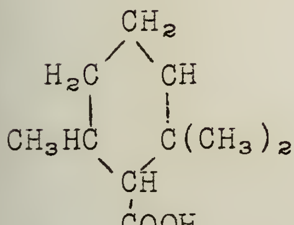
$C_{16}H_{30}NCBr_2(C_6H_5) \xrightarrow[\text{in vacuum}]{\text{distillation}} C_{16}H_{30}Br_2 \xrightarrow[KOH]{MeOH}$

$C_9H_{17}-CH=CH-CH(CH_3)-CH=CH-CH_3 \xrightarrow[H_2O_2]{O_3} C_9H_{17}COOH$



$\xrightarrow{O_3}$ ozonide $\xrightarrow[H_2O_2]{NaOH}$ $C_9H_{17}-CONH_2 + 2CH_3COOH +$
$2CO_2$

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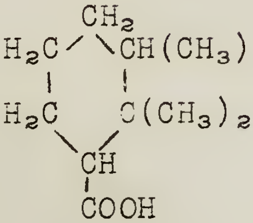
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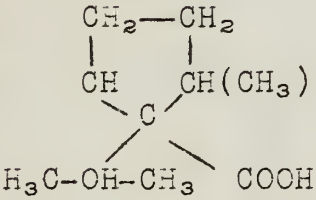
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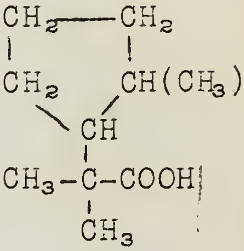
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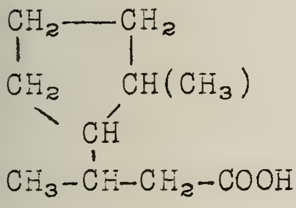
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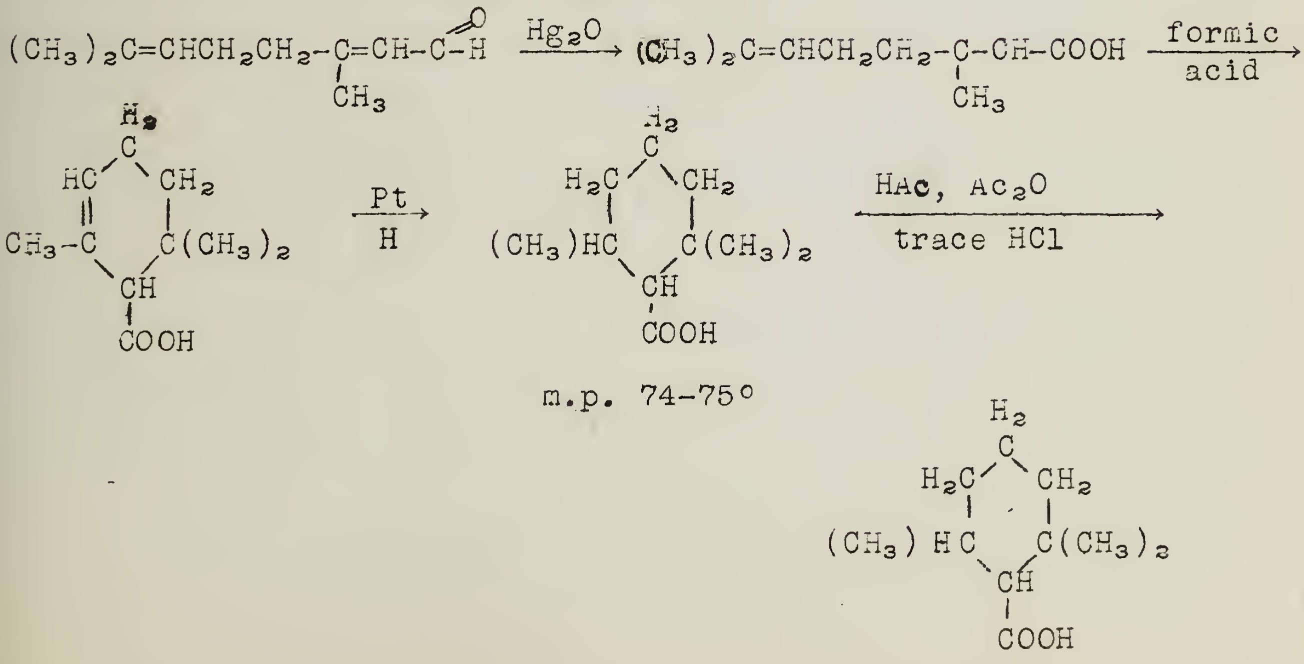
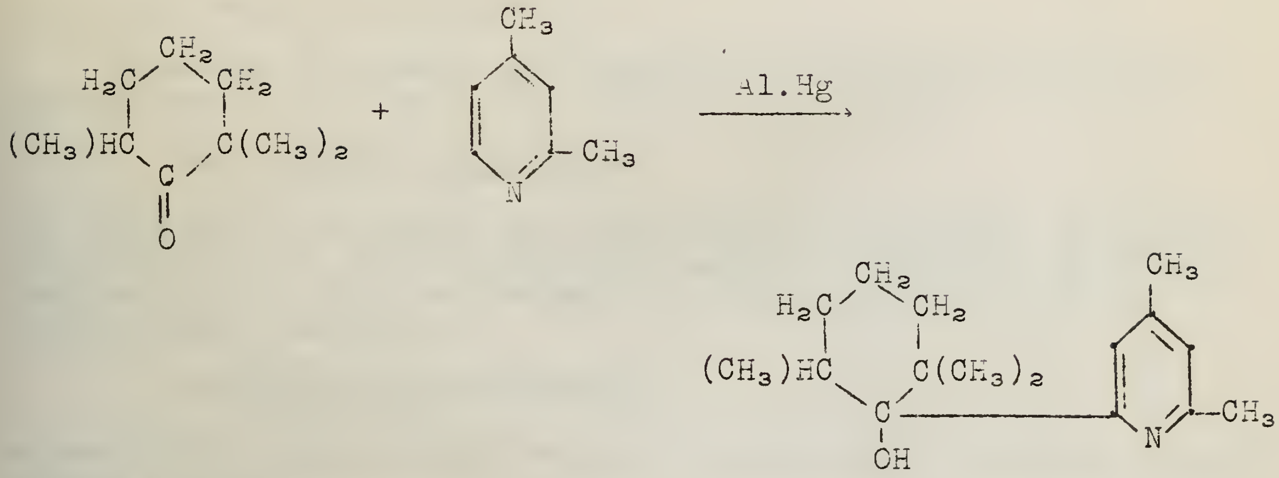
SYNTHESIS OF I



m.p. 74-75°

m.p. 82-83°

PROPOSED SYNTHESIS OF BASE



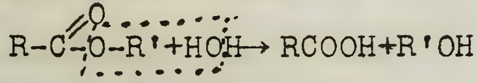
CLEAVAGE OF THE ALKLY-OXYGEN BOND IN THE HYDROLYSIS OF ESTERS

Cohen and Schneider (Harvard)

Although it appears that hydrolysis of sulfonic and other strong acid esters occurs in the following manner,

$$-SO_2-O-R+HOH \rightarrow -SO_2OH+ROH$$

it is generally accepted that hydrolysis of carboxylic esters and the formation of these esters are reactions which do not involve rupture of the alkyl carbon-oxygen bond but involve an acyl carbon-oxygen mechanism,

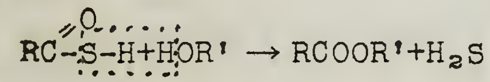


$$R-\overset{O}{\overset{\|}{C}}-O-R'+HOH \rightarrow RCOOH+R'OH$$

although the same products could be produced by the alkyl carbon-oxygen rupture.

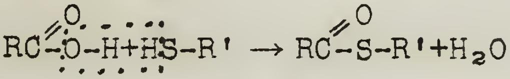
The evidence for the acyl carbon-oxygen mechanism can be summarized as follows:

1. Reid's work on the esterification of thio-acids and mercaptans, and the hydrolysis of thio-esters.
   (a) Esterification of thio-acids produced oxygen esters and hydrogen sulfide, rather than thio-esters and water.



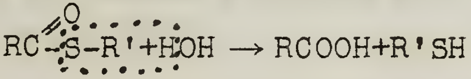
$$R\overset{O}{\overset{\|}{C}}-S-H+HOR' \rightarrow RCOOR'+H_2S$$

   (b) Carboxylic esterification of mercaptans produced thio-esters and water, rather than oxygen esters and hydrogen sulfide.



$$R\overset{O}{\overset{\|}{C}}-O-H+HS-R' \rightarrow R\overset{O}{\overset{\|}{C}}-S-R'+H_2O$$

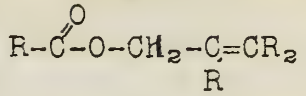
   (c) Hydrolysis of thio-esters produced carboxylic acids and mercaptans, rather than thio-acids and alcohols.



$$R\overset{O}{\overset{\|}{C}}-S-R'+HOH \rightarrow RCOOH+R'SH$$

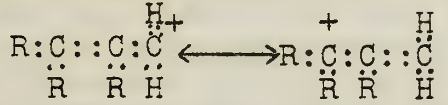
2. Retention of configuration when carboxylic esters of the type $R-\overset{O}{\overset{\|}{C}}-O-\underset{R''}{\overset{H}{C}}{}^{*}-R'$ are hydrolyzed. It is evident that if at any time during the hydrolysis, the asymmetric carbon become free, complete retention of the original configuration is not possible. Thus, retention of configuration is an indication that the alkyl-oxygen bond is not broken during the hydrolysis. There are many cases of such hydrolyses in the literature, and there is no simple instance of appreciable inversion of configuration of the alcohol.

3. Demonstration by Ingold and co-workers that single alcoholic products are obtained when esters of the



$$R{-}\overset{O}{\overset{\|}{C}}{-}O{-}CH_2{-}\underset{R}{C}{=}CR_2$$

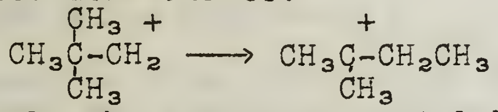
type are hydrolyzed. If the resonating ion becomes free at any time during the hydrolysis,



$$R{:}\underset{R}{C}{::}\underset{R}{C}{:}\overset{H+}{\underset{H}{C}} \longleftrightarrow R{:}\overset{+}{\underset{R}{C}}{:}\underset{R}{C}{::}\overset{H}{\underset{H}{C}}$$

a mixture of alcohols would be obtained.

4. Demonstration by Quayle and Norton that esterification of various acids with neopentyl alcohol produced no unsaturated products, and that hydrolysis of the resulting esters produced neopentyl alcohol as the only alcohol. Whitmore and his collaborators have demonstrated that a positive neopentyl group invariably rearranges to tertiary amyl, the rearrangement being accompanied by the formation of unsaturated derivatives.



$$CH_3\overset{CH_3}{\underset{CH_3}{C}}{-}\overset{+}{CH_2} \longrightarrow CH_3\overset{+}{\underset{CH_3}{C}}{-}CH_2CH_3$$

Apparently the oxygen-neopentyl bond is not broken during esterification or hydrolysis, even though the acid concerned is as strong as trichloracetic acid.

5. Direct evidence employing isotopically distinguished oxygen.
   (a) Alkaline hydrolysis of amyl acetate in an aqueous medium enriched in O^{18} resulted in the obtaining of amyl alcohol with the normal isotope ratio, thus indicating that the oxygen present in the alcohol was originally attached to the alkyl group in the ester.

   (b) Similar results were obtained by Ingold in the acid-catalyzed hydrolysis of methyl hydrogen succinate.

   (c) Urey and Roberts esterified benzoic acid with O^{18} enriched methyl alcohol, and found that the heavy isotope was not present in the water produced in more than the normal ratio, thus indicating that the oxygen of the water produced was obtained entirely from the benzoic acid.

There are a few exceptions to this mechanism in the case of some compounds, which because of special structural features, show unusual reactivity. These include β-lactones, the hypothetical α-lactones, and esters of a secondary allylic alcohol ($C_6H_5{-}CH{=}CH{-}CHOH{-}CH_3$).

The general conclusion for the mechanism has been based on a study of esters of primary and secondary alcohols, and apparently is perfectly valid for such cases. However, there is one instance reported in the literature in which a very limited racemization of a secondary optically active alkyl group occurred during esterification, i.e., the esterification of

β-n-octyl alcohol. An alternative mechanism was indicated. Since the tertiary alkyl-oxygen bond is more easily broken than is the secondary, an investigation of tertiary alkyl esters was thought to be worth-while.

Cohen and Schneider have made such investigations. Although the nature of the hydrolysis products would throw no light on the point of interest (unless optically active alkyl groups or isotopically distinguished oxygen were employed), the nature of the products obtained from a primary alcoholysis of an ester would provide pertinent information.

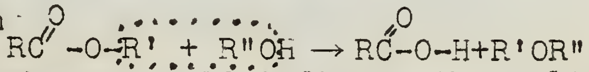
The two possibilities are:

(a) Ester Interchange

$$R\overset{O}{\overset{/\!/}{C}}-O-R'+HOR'' \longrightarrow R\overset{O}{\overset{/\!/}{C}}-O-R''+R'OH$$

and

(b) Acid and Ether Formation



$$R\overset{O}{\overset{/\!/}{C}}-O-R' + R''OH \rightarrow R\overset{O}{\overset{/\!/}{C}}-O-H+R'OR''$$

The occurrence of ester interchange would indicate the validity of the general conclusion as applied to tertiary esters, while the formation of acid and ether by alcoholysis would indicate a different mechanism, i.e. Alkyl carbon-oxygen cleavage.

Alcoholysis of t-butyl benzoate with methyl alcohol in initially neutral solution produced a good yield of t-butyl methyl ether and appreciable quantities of benzoic acid. Although considerable methyl benzoate was produced, this could have been formed by esterification of the benzoic acid produced by the acid-ether mechanism. It was also shown that t-butyl alcohol and methanol do not form t-butyl methyl ether in the presence of benzoic acid. No t-butyl alcohol (which would result from ester interchange) could be detected. Thus it appears that ester interchange does not play a very important part in this reaction, and that the alkyl carbon-oxygen cleavage is probable. Similar results were obtained with t-butyl acetate.

On the other hand, similar alcoholysis in the presence of alkali resulted in the normal ester interchange, and no evidence was found for the formation of t-butyl methyl ether, thus indicating the "normal" cleavage.

Further investigation was made using t-butyl 2,4,6-trimethyl benzoate. Incidentally, this compound could not be prepared by the action of the silver salt of the acid on t-butyl cloride, but action of the acyl chloride on the alcohol in pyridene produced the desired compound. This reaction is of interest because, although the action of acyl halides on tertiary alcohols normally produces tertiary alkyl halides, the presence of pyridine results in the removal of the hydrogen chloride as it is formed, permitting the formation of the esters. Esters of this acid are resistant to hydrolysis because of steric hindrance.

Results of the hydrolysis of esters of 2,4,6-trimethyl benzoic acid were as follows:

(1) Acid hydrolysis of t-butyl 2,4,6-trimethylbenzoate produced a nearly quantitative yield of the acid.

(2) Similar acid hydrolysis of the methyl ester was unsuccessful.

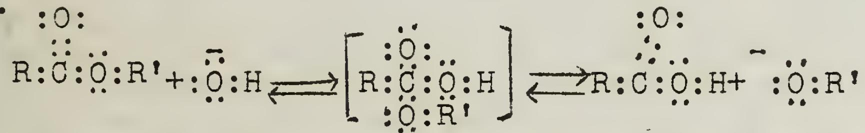
(3) Comparable basic hydrolysis of the t-butyl ester was unsuccessful. These results demonstrate that there is a deep-seated difference between the alkaline and the acid hydrolyses of the t-butyl ester, and that an equally important difference exists between the acid hydrolyses of the tertiary ester and of the primary ester.

When t-butyl 2,4,6-trimethyl benzoate was subjected to alcoholysis, results pointing to the same conclusion were observed, namely

(1) Initially neutral alcoholysis gave products obtainable from the acid-ether mechanism, although the yields were not nearly as great.

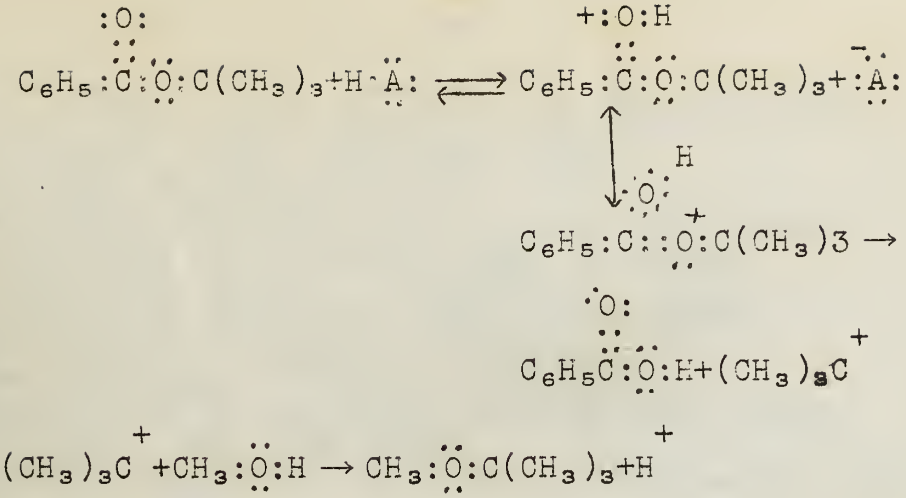
(2) Base catalyzed alcoholysis did not occur, indicating that the ester interchange mechanism is not active in the case of this sterically hindered compound.

The base-catalyzed ester interchange and hydrolysis reactions of esters probably proceed by a nucleophilic attack by an alkoxide or hydroxide ion on the carbonyl carbon atom of the ester.



A Stuart model of t-butyl 2,4,6-trimethylbenzoate shows that the carbonyl carbon atom is strongly hindered, and the reason for the failure of attempts at alkaline hydrolysis is readily apparent. The probable mechanism for the "normal" acid-catalyzed hydrolysis also involves the same difficulty, and the resistance of primary esters of this acid is understandable.

A possible course for the alcoholysis of tertiary esters to form the corresponding carboxylic acids and ethers is as follows. First, a slow reaction occurs in neutral solution involving hydrogen bonding between an alcohol molecule and the carbonyl oxygen atom of the ester, followed by ejection of the t-butyl group and the formation of the products. This uncatalyzed or solvolytic mechanism accounts for only a very small portion of the products. However, the acid produced catalyzes the faster and more important reaction.



$$\mathrm{C_6H_5{:}\overset{:O:}{C}{:}O{:}C(CH_3)_3 + H{\cdot}A: \rightleftarrows C_6H_5{:}\overset{+:O:H}{C}{:}O{:}C(CH_3)_3 + {:}\overset{-}{A}{:}}$$

$$\updownarrow$$

$$\mathrm{C_6H_5{:}\overset{\cdot O{:}H}{C}{::}\overset{+}{O}{:}C(CH_3)3 \rightarrow}$$

$$\mathrm{C_6H_5\overset{\cdot O:}{C}{:}O{:}H + (CH_3)_3\overset{+}{C}}$$

$$\mathrm{(CH_3)_3\overset{+}{C} + CH_3{:}O{:}H \rightarrow CH_3{:}O{:}C(CH_3)_3 + \overset{+}{H}}$$

The model of t-butyl 2,4,6-trimethylbenzoate shows that the carbonyl oxygen atom is not strongly hindered. Since the above mechanism involves this atom and not the carbonyl carbon, the above mechanism seems plausible, and would account for the acid hydrolysis of this ester as well as the alcoholysis products obtained from t-butyl benzoate in initially neutral solution.

There are relevant kinetic data available for hydrolysis of esters of the type CH_3COOR. As the group R is varied from CH_3 to C_2H_5, i-C_3H_7 and t-C_4H_9, the rate of the base-catalyzed hydrolysis falls off, while the rate of acid hydrolysis falls through a slight minimum and rises again, that of the t-butyl ester being about 15% faster than that of the methyl ester.

These facts are consistent with the following interpretation: in the base-catalyzed reactions, a single mechanism operates, the attack of the hydroxyl ion on the carbonyl carbon atom followed by the ejection of the alkoxyl group. The rate of this reaction diminishes as the alkyl group is changed from primary to tertiary. In the acid-catalyzed reaction, there is one mechanism available for esters of primary and secondary alcohols involving a rupture of the acyl-oxygen bond, and there is the alternative mechanism available for the tertiary alcohol ester, involving rupture of the alkyl-oxygen bond and ejection of the alkyl group.

Further investigation employing optically active tertiary esters or isotopically distinguished oxygen would provide further information on this question.

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Reported by W. E. Blackburn
February 25, 1942

SOME REACTIONS OF HYDROCARBONS IN AN ELECTRICAL DISCHARGE

It is possible to excite molecules, causing them to undergo subsequent chemical reactions, by exposing them to the action of heat, light, sound waves, α particles, and electrical discharges. Considering only the last method, we find that there are two distinct types of electrical discharge, the silent or non-disruptive and thedisruptive discharge. The silent discharge may take the form of the ozonizer, the semi-corona, the corona, the glow, or the electrodeless discharge, while the disruptive discharge may occur as the arc or the spark. The chemical reactions which take place in these two types of discharges are essentially different. In a given reaction, the important variables to be considered are: (1) the effective discharge intensity; (2) the effective residence time in the discharge.

Reactions of Hydrocarbons in the Silent Discharge

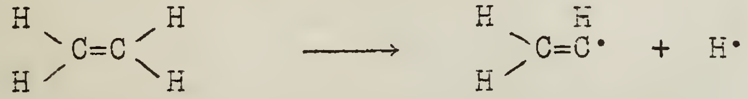
Ethylene is a fairly active hydrocarbon and requires only mild excitation to cause it to react. With ethylene and higher olefins reactions occur under mild conditions and are of a comparatively simple nature. In a static system, that is a system in which the ethylene was allowed to stay in the reaction chamber during the entire course of the discharge, it was found that when using a high frequency course discharge, the ethylene had completely reacted after a period of about ten hours. There appeared to be an induction period of about two hours which could be considerably shortened by the introduction of hydrogen into the reaction chamber. An analysis of the gaseous products showed 67% hydrogen and 20% saturated hydrocarbons. The liquid fraction consisted of a dark oil with a molecular weight of the order of five hundred.

The results of an experiment using a dynamic system are more informative. The ethylene was passed through the discharge in a stream and the products were condensed at -70°C. In the particular experiment cited a high frequency ozonizer discharge was used. The following products were obtained:

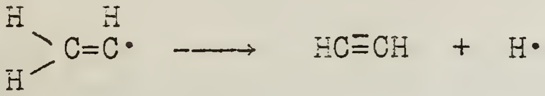
Uncondensed gases (H_2, C_2H_2, C_2H_6)	13%
Butane	45%
1-Butene	15%
a fraction boiling in the range 34-45°C	4%
a C_6 fraction	15%
Higher hydrocarbons	8%

In the C_6 fraction 1-hexene and paraffin hydrocarbons were isolated. In other experiments in which somewhat different experimental conditions were used, it was found that the chief product was acetylene or butadiene. In all cases the energy consumption was about twenty kilowatt hours per kilogram of ethylene which reacted. The products identified are thought to be evidence for the theory that ethylene undergoes two primary reactions:

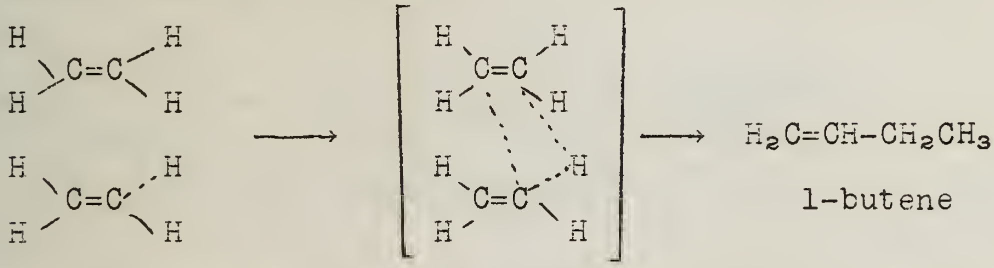
(1) Dehydrogenation of ethylene to produce acetylene and hydrogen;
(2) Polymerization to give higher molecular weight hydrocarbons. Egloff and others suggest that (1) may be accounted for by the assumption that the energy absorbed from the electrical discharge disrupts the C-H bond in ethylene leaving the vinyl radical.



The vinyl radical then decomposes to give acetylene and more hydrogen.



It is quite possible, however, that the C-H bond is not actually broken but merely activated. Under these conditions it is possible that two molecules of ethylene might react as follows:



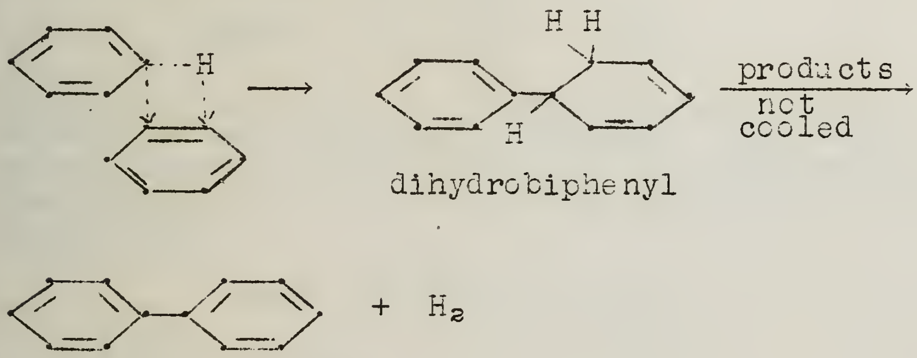
The butene is isolated in a great many cases. Furthermore, in the presence of hydrogen, hydrogenation to butane is possible which would account for the formation of this substance. It is also possible for the butene to react with another molecule of excited ethylene forming a hexene and then a hexane. However, this theory is not sufficient to account for all the observed products. In many cases the liquid products absorb oxygen from the air, a property common to acetylene polymers but not characteristic of ethylene polymers. This fact suggests the possibility that acetylene, after being formed, reacts to give polymers of the butadiene type.

With higher olefins, reactions similar to those of ethylene take place. In a static experiment using propene, it was found that 85-90% of the olefin reacted to form a liquid possessing an average molecular weight of 232. Isobutene polymerizes readily to give, as the largest fraction, a mixture of di- and triisobutenes.

Acetylene was found to react readily in an electrical discharge. When the reaction mixture was cooled to -60°C., a 70% yield of a colorless liquid was obtained. This liquid had a molecular weight of a trimer and from the reactions of the liquid it was concluded that it contained 1,5-hexadiyne, methyl pentadiyne and unidentified products.

When the reaction products were allowed to stand at room temperature, both liquid and solid products were formed. Some of the products seemed to have an unsaturated side-chain attached to the benzene ring. Thus it seems probable that the primary action of a silent discharge on acetylene is to form polymers. If the reaction products are quickly removed from the system and cooled, relatively simple polymers may be isolated. If allowed to react further, long-chain, highly unsaturated, aliphatic compounds or aromatics with unsaturated side chains may be formed. A spectroscopic examination of the light produced when acetylene is in the discharge indicates the presence of the C^+ ion, the carbon atom, and the hydrogen atom.

Benzene reacts in the silent electric discharge. The most commonly identified product is diphenyl but it is always accompanied by complex resinous material. In the gaseous products hydrogen and acetylene are found in considerable quantities. If the reaction products are quickly cooled, dihydrobiphenyl can be obtained.



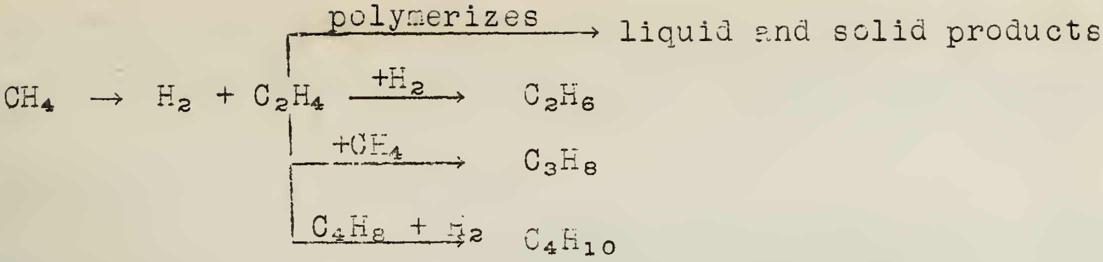
Thus benzene seems capable of undergoing two types of reactions.

C_6H_6 $\xrightarrow{60\%}$ polymerization and dehydrogenation (biphenyl)

C_6H_6 $\xrightarrow{40\%}$ depolymerization (acetylene)

A spectroscopic study of the light emitted during the reaction shows the presence of C^+ ions, carbon and hydrogen atoms, C_2 and CH molecules. This would indicate the presence of a complex mixture.

Paraffin hydrocarbons, being less reactive than olefins and acetylenes, require a more intense discharge to initiate a reaction. With the more intense discharge a high temperature is developed and thermal activation is at least partially responsible for the observed reactions. When methane is subjected to an ozonizing discharge at room temperature, the reaction is thought to take the following general course.



$$CH_4 \rightarrow H_2 + C_2H_4 \xrightarrow{\text{polymerizes}} \text{liquid and solid products}$$

$$C_2H_4 \xrightarrow{+H_2} C_2H_6$$

$$C_2H_4 \xrightarrow{+CH_4} C_3H_8$$

$$C_2H_4 \xrightarrow{C_4H_8 + H_2} C_4H_{10}$$

Very little ethylene was actually isolated, but it is not surprising for, if formed, it should immediately react in any discharge which is intense enough to activate methane. In a glow discharge methane can be made to yield acetylene but the products must be quickly removed from the reaction zone and cooled to prevent the acetylene from undergoing further reaction.

Ethane can undergo both dehydrogenation due to activation of the C-H bond and demethanation due to the activation of the C-C bond.

$$C_2H_6 \rightarrow C_2H_4 + H_2$$

$$2C_2H_6 \rightarrow CH_4 + C_3H_8$$

The latter reaction is characteristic of the saturated hydrocarbons in an electrical discharge. This reaction can possibly be accounted for by assuming the ion-cluster mechanism which was proposed to account for the reactions of hydrocarbons with α particles.

$$C_2H_6 \xrightarrow{\text{discharge}} C_2H_6^+ + e \quad (1) \text{ ionization}$$

$$C_2H_6^+ + C_2H_6 \rightarrow [C_2H_6.C_2H_6]^+ \quad (2) \text{ clustering}$$

$$[C_2H_6.C_2H_6] \rightarrow [CH_4.C_3H_8]^+ \quad (3) \text{ rearrangement of the valence bonds}$$

$$[CH_4.C_3H_8]^+ + e \rightarrow CH_4 + C_3H_8 \quad (4) \text{ decomposition}$$

It must be assumed that the ion-cluster is stable for a long enough period of time to allow the valence bonds to rearrange. Propane undergoes the same type of reactions.

Reactions of Hydrocarbons in Disruptive Discharges

The disruptive discharges consist of the arc and the spark. While there may be electrical effects on hydrocarbons in the spark discharge, there is reasonable doubt that there is any such effect in the arc. Both discharges cause the same type of reaction as does high temperature, i.e. above 1500°C. Carbon and hydrogen are the main products in most cases and there is usually a considerable amount of acetylene formed. Traces of ethylene, dipropargyl ($HC{\equiv}CCH_2CH_2C{\equiv}CH$), benzene, and naphthalene have been found when using methane, indicating a thorough-going disruption and recombination. In arc and spark discharges, the electrode

material is of considerable importance and there is some evidence to indicate that in the case of graphite electrodes, they may actually take part in the reaction. It has been noticed that benzene has a very distinct tendency to form carbon and hydrogen.

Activation of the Molecules

Most of the reactions typical of an electrical discharge take place in the silent discharge. Taking the glow discharge as an example of this type the process of activation will be considered in a little more detail. The activating electrons are produced at the cathode. Moving under the force of electrostatic repulsion away from the negative pole, they migrate to the Crookes dark space. This area is the region of greatest potential drop and the electron experiences an accelerating force toward the anode. During this acceleration, the electrons undergo three types of collisions with molecules.

(1) elastic collisions in which no energy is lost or gained
(2) ionizing collisions in which a secondary electron and a positive ion are formed
(3) activating collisions in which the quantum state of the molecule is raised

Each electron leaving the cathode is known to produce from 50 to 100 secondary electrons by ionizing collisions and since the energy of ionization is much greater than that required for activation, it is assumed that many times that number of activating collisions take place. At all pressures above .1 mm of Hg, electrons are thought to be the sole factors producing activation and ionization. The positive ions present are so heavy that there is not a sufficiently high potential drop to give them a high velocity, and they are large and, therefore, must hit other molecules very often. Both of these conditions operate to prevent the positive ions from ever acquiring sufficient energy to cause an ionizing or activating collision. Elastic collisions may be neglected as only the ionized and activated molecules have the energy necessary for chemical reaction. Very little is known about the reaction of hydrocarbon ions except what little can be deduced from the nature of the products. The course of the reaction of the activated molecules can be followed in many cases by analogy with reactions which take place under the influence of thermal activation.

Commercial Applications

The action of the silent discharge is being used on a commercial scale to produce and improve lubricating oils. The process is known as "Electrionization" in Belgium and as "Voltolization" in Germany. The oil is put in a large mechanical device which is arranged in such a way as to provide thorough mixing and a short exposure to the silent discharge. The reaction is run at about 80°C and the pressure is about 60-65 mm. The electrical energy is furnished by a 500 cycle discharge at approximately 4000 volts. The action of the discharge dehydrogenates the molecules which then polymerize. Fifteen per cent of the

product is blended with untreated oil. The mixture possesses the following desirable characteristics: (1) the viscosity is increased, (2) the viscosity temperature coefficient is decreased, (3) the pour point is lowered, (4) the sludge-forming tendency of the oil is decreased, (5) the tendency to form emulsions with water is increased.

The production of acetylene from methane on a commercial scale can be accomplished at the present time. In the carbide process we have the reaction:

$$CaO + 3C \rightarrow CaC_2 + CO \qquad \Delta F^{0}_{298} = 88,400 \text{ cal/mol}$$

For the discharge process:

$$2CH_4 \rightarrow C_2H_2 + 3H_2 \qquad \Delta F^{0}_{298} = 75,400 \text{ cal/mol}$$

Translated into electrical units this means the carbide process requires theoretically 5.6 kilowatt hours as against 4.7 for the discharge process per cubic meter of acetylene. In actual practise the energy consumption is considerably larger, requiring from 9 to 18 kilowatt hours, depending on the type of furnace. Various experiments have been carried out with methane. When the methane is diluted with two volumes of hydrogen to cut down the carbon forming reaction, it was found that 68% of the methane which reacted, 51% of the methane charged was converted to acetylene giving an energy consumption of 12 kilowatt hours per cubic meter of acetylene in an arc. It was possible with a glow discharge tube to obtain yields up to 90% of methane charged. Using liquid hydrocarbons, a process has been developed which requires 15.5 kilowatt hours per cubic meter of acetylene but, at the same time, 1.4 cubic meters of hydrogen are produced as a by-product.

Several other processes, i.e. the preparation of diphenyl from benzene, butadiene from fuel oil, and various processes for the preparation of gasoline hydrocarbons by cracking in an electrical discharge, have been patented. As far as is known, none of these are in actual operation at the present time.

It may be seen that an electrical discharge is a powerful tool in causing the activation and subsequent reaction of hydrocarbons. It is possible to expose the reactants to a wide variety of experimental conditions. The primary reactions seem to be dehydrogenation and polymerization. In many cases these are followed by various secondary reactions which give rise to a large number of products. One commercial process, i.e. Voltolization, has been in operation for a number of years and other useful products may be awaiting only the proper experimental conditions for large-scale production.

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Reported by R. G. Chase February 25, 1942

Perhaps the commonest classification of war gases is the physiopathological classification; that is, a classification based on the most characteristic action of the war gas on human beings. By this method, the gases usually are divided into the following classes:

(1) Lachrymators, or tear gases;

(2) Sternutators, or "sneeze" gases;

(3) Lung injurants;

(4) Toxic gases-those gases having a harmful systemic effect;

(5) Vesicants, or substances producing blisters on the skin.

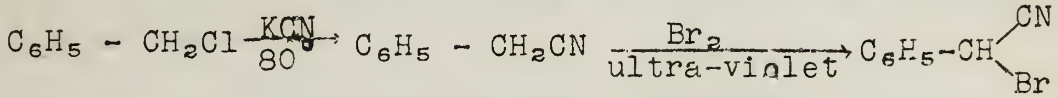
This classification is not rigid, since the biological action of these substances is complex. For instance, chloropicrin is a lachrymator, a toxic gas, and a lung injurant. Nevertheless, this classification is useful in helping to present a clear picture of this subject.

(A) Lachrymators

The many substances which have been used as lachrymators include α- and β-halogenated ethers, ethyl bromoacetate, acrolein and its halogenated derivatives, α-halogenated ketones, the benzyl and xylyl halides, o-nitrochlorobenzene, bromobenzyl cyanide, and phenylcarbylamine chloride.

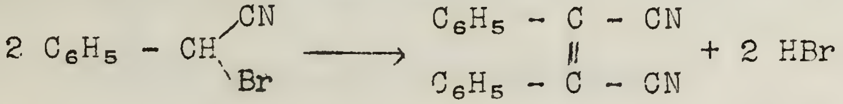
In general, it has been found that the aromatic compounds are more satisfactory than the aliphatic compounds. Of the substances mentioned above, bromobenzyl cyanide and chloroacetophenone are perhaps the most satisfactory lachrymators.

Bromobenzyl cyanide can be prepared in the following way:



$$C_6H_5 - CH_2Cl \xrightarrow[80^\circ]{KCN} C_6H_5 - CH_2CN \xrightarrow[\text{ultra-violet}]{Br_2} C_6H_5-CH\begin{matrix}CN\\Br\end{matrix}$$

Bromobenzyl cyanide is a low-melting solid. One method in which it may be used is to dissolve it in chloropicrin, which in itself is a war gas. On heating to 160°, it decomposes to form dicyanostilbene:



$$2\ C_6H_5 - CH\begin{matrix}CN\\Br\end{matrix} \longrightarrow \begin{matrix}C_6H_5 - C - CN\\ \| \\ C_6H_5 - C - CN\end{matrix} + 2\ HBr$$

For this reason, its use is limited because of its low stabaility to the explosion of a bursting shell. Another drawback is that it attacks metals, so that specially-lined containers

have to be used.

Chloroacetophenone can be prepared by the following method.

$$C_6H_6 + ClCH_2 - COCl \xrightarrow{AlCl_3} C_6H_5 - CO - CH_2Cl + HCl.$$

This substance is also a solid. One method of using it is to spray a benzene solution of it into the air. When the benzene evaporates, the chloroacetophenone is dispersed in a state of fine subdivision.

(B) Sternutators

Some of the representative sternutators are phenyl dichloroarsine, diphenyl chloroarsine, diphenyl cyanoarsine, and phenarsazine chloride (Adamsite).

(1) Phenyl Dichloroarsine and Diphenyl Chloroarsine

A mixture of the above two compounds was prepared by the Allies in the last war by the following method:

$$AsCl_3 + 3\ C_6H_5Cl + 6Na \longrightarrow (C_6H_5)_3\ As + 6NaCl$$

$$(C_6H_5)_3\ As + AsCl_3 \xrightarrow{350^\circ} \underset{60 - 65\%}{C_6H_5 - AsCl_2} + \underset{35 - 40\%}{(C_6H_5)_2 - AsCl}$$

This mixture, which was used without further treatment, solidifies to form a low-melting mass. When it was dispersed in the form of fine particles, it passed through the gas masks then in use, causing sneezing and vomiting. Since then, layers of felt have been put into the gas mask to mechanically filter the sternutator.

(2) Diphenyl Cyanoarsine

This substance can be prepared by the reaction of hydrogen cyanide with diphenyl arsenious oxide as shown by the following series of reactions:

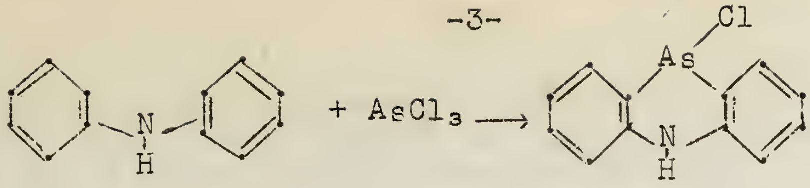
$$2\ (C_6H_5)_2 - AsCl + H_2O \longrightarrow HCl + [(C_6H_5)_2\ As]_2\ O$$

$$[(C_6H_5)_2\ As]_2\ O + 2\ HCN \longrightarrow 2\ (C_6H_5)_2\ AsCN + H_2O$$

This also is a low-melting solid, and is utilized in the same way as diphenyl chloroarsine.

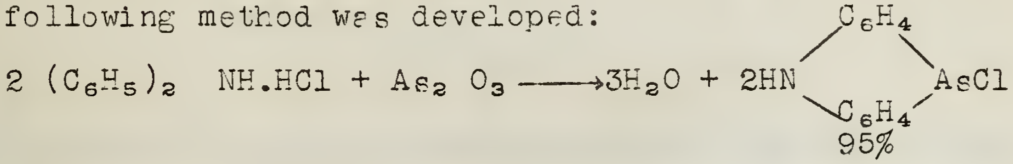
(3) Phenarsazine Chloride (Adamsite)

This compound was studied in 1918, but was not used in the last war. It was prepared at Edgewood by the reaction between diphenylamine and arsenic chloride:



Yield, 80%

Later, it was found that diphenylamine hydrochloride dissociates into the amine and hydrogen chloride at about 100°, so the following method was developed:



$$2\ (C_6H_5)_2\ NH.HCl + As_2\ O_3 \longrightarrow 3H_2O + 2HN\begin{matrix} C_6H_4 \\ C_6H_4 \end{matrix}AsCl \quad 95\%$$

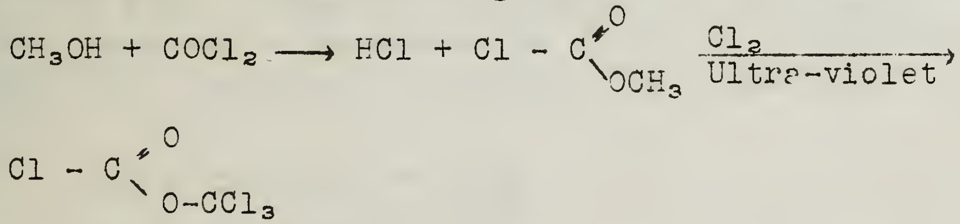
This substance melts at 190°, and is also employed in the form of a fine dust.

(C) Lung Injurants

Substances which have been employed as lung irritants include chlorine, thiophosgene, chloropicrin, phosgene, and trichloromethyl chloroformate.

Due to its low persistence, chlorine was not used to a great extent. In addition to being a lung injurant, phosgene is very injurious to the heart. Phosgene was used extensively, but it has the disadvantage of hydrolyzing easily.

On the other hand, trichloromethyl chloroformate is quite resistant to hydrolysis at ordinary temperatures. This compound can be prepared in the following way:



$$CH_3OH + COCl_2 \longrightarrow HCl + Cl - C\begin{matrix} \nearrow O \\ \diagdown OCH_3 \end{matrix} \xrightarrow[\text{Ultra-violet}]{Cl_2} Cl - C\begin{matrix} \nearrow O \\ \diagdown O{-}CCl_3 \end{matrix}$$

This substance is also known as diphosgene, since on heating it decomposes into two moles of phosgene. It is completely retained by filters of active carbon.

Chloropicrin was prepared by the action of calcium hypochlorite on picric acid, but now can be prepared by the action of chlorine on nitromethane:

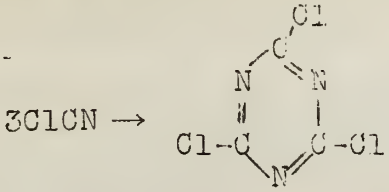
$$CH_3 - NO_2 + Cl_2 \xrightarrow{Ca\ (OCl)_2} Cl_3C - NO_2$$

Chloropicrin is not as toxic as phosgene or diphosgene, and of the war gases is one of those most easily held back by active carbon.

(D) Toxic Gases

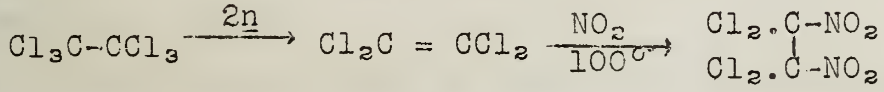
Among the toxic gases are cyanogen chloride, dimethyl sulfate, carbon monoxide, hydrogen cyanide, and tetrachloro dinitroethane.

Carbon monoxide and hydrogen cyanide are too volatile. Cyanogen chloride had a limited use as a war gas due to its tendency to trimerize to form cyanuryl chloride.



Dimethyl sulfate is unsuitable because of its low volatility.

Since the last war, it has been found that tetrachlorodinitroethane is a very effective toxic gas. It has been prepared as follows:



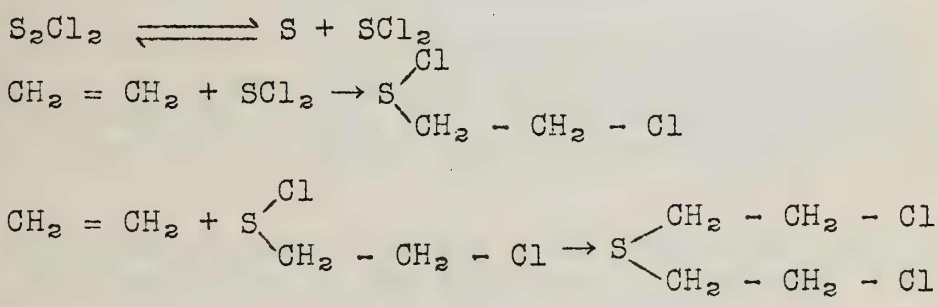
$$Cl_3C-CCl_3 \xrightarrow{2n} Cl_2C = CCl_2 \xrightarrow[100^\circ]{NO_2} \begin{array}{l} Cl_2.C-NO_2 \\ \quad | \\ Cl_2.C-NO_2 \end{array}$$

This substance is six times as toxic and eight times as lachrymatory as chloropicrin.

(E) Vesicants

The most important vesicant used in the last war was mustard gas, β,β'-dichlorodiethyl sulphide. In addition to being a vesicant, mustard gas is five times as toxic as phosgene.

The method of preparation used by the Allies was that developed by Pope in England and Levinstein in America. Ethylene is bubbled into sulfur monochloride while the temperature is kept below 35°. According to Conant, the following reactions take place:



$$S_2Cl_2 \rightleftharpoons S + SCl_2$$

$$CH_2 = CH_2 + SCl_2 \rightarrow S\begin{array}{l} Cl \\ CH_2 - CH_2 - Cl \end{array}$$

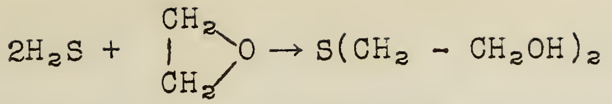
$$CH_2 = CH_2 + S\begin{array}{l} Cl \\ CH_2 - CH_2 - Cl \end{array} \rightarrow S\begin{array}{l} CH_2 - CH_2 - Cl \\ CH_2 - CH_2 - Cl \end{array}$$

The Germans prepared it from thiodiglycol and concentrated hydrochloric acid by the following series of reactions:

$$2OH - CH_2 - CH_2 -Cl + Na_2S \rightarrow S(CH_2 - CH_2OH)_2 \xrightarrow[50^\circ]{HCl}$$

$$S(CH_2 - CH_2Cl)_2$$

The Allied method was cheaper, but the German method was more easily controlled. Recently, a cheap method of preparation of thiodiglycol has been developed:

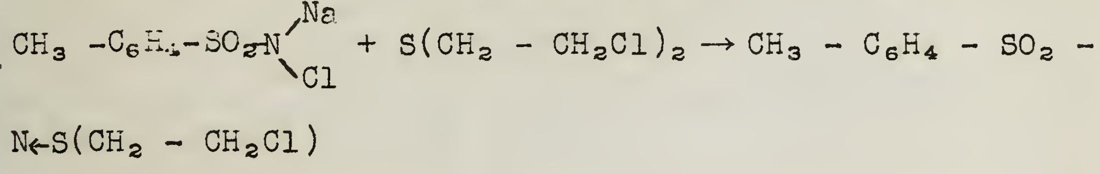


$$2H_2S + \underset{CH_2}{\overset{CH_2}{|}}\!\!>O \rightarrow S(CH_2 - CH_2OH)_2$$

Consequently, the thiodiglycol method of preparation of mustard gas may now be the preferable method.

Bleaching powder reacts with mustard gas both as an oxidizing agent and as a chlorinating agent, rendering it harmless. For this reason, bleaching power is used to decontaminate areas infected by mustard gas.

Chloramine-T reacts with mustard gas to form a sulfilimine:



$$CH_3 - C_6H_4 - SO_2 - N\genfrac{}{}{0pt}{}{Na}{Cl} + S(CH_2 - CH_2Cl)_2 \rightarrow CH_3 - C_6H_4 - SO_2 - N \leftarrow S(CH_2 - CH_2Cl)$$

Thus, chloramine-T can also be used as a decontaminant.

Lewisite is β-chlorovinyl dichloroarsine, $Cl_2-As(CH=CHCl)_2$, which is prepared from acetylene and arsenic trichloride:

$$CH \equiv CH + AsCl_3 \xrightarrow{AlCl_3} \left\{\begin{array}{l} Cl_2As - CH = CHCl \\ ClAs(CH = CHCl)_2 \\ As(CH = CHCl)_3 \end{array}\right.$$

The chlorovinyl dichloroarsine can be separated from the other two products by fractional distillation. The secondary and tertiary arsines can be converted into Lewisite by heating with arsenic trichloride, so that the over-all yield is satisfactory.

On oxidation, Lewisite yields chlorovinyl arsenic acid, $Cl - CH = CH - AsO_3H_2$, which is innocuous.

Lewisite, besides being a vesicant and a toxic gas, is an irritant to the eyes and lungs, so that it is potentially a very effective war gas. This gas was developed too late to be used in the last war, so that it has not been tested in actual combat.

The vesicants proved to be the most effective gases in the last war. For instance, in the last year of the war, 77% of the British gas casualties were caused by mustard gas.

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Reported by C. F. Jelinek
March 4, 1942

This report is an attempt to note only some of the high spots in recent developments of quantitative analytical technique. For clarity, brief descriptions of some methods in common use will be included.

Signer has introduced a process of molecular weight determination which, although not new, has received little attention. Clark describes the method, together with simplified apparatus for its application. Solutions of the unknown and of a known compound in the same solvent are placed in a sealed, isothermally insulated system so that their vapors are in contact. Following Raoult's law, the solvent from one solution will distill into the other until equilibrium is reached. A measurement of the volume of each solution will then give the molecular weight of the unknown according to the equation

$$M_x = \frac{G_x M V}{G V_x}$$

where M is molecular weight, G is weight, and V is solution volume of the standard, and the symbols with subscript x refer to these values for the unknown. The advantage of the method is its high accuracy (reported error usually less than 1%, frequently less than 0.4%); its principal disadvantage lies in the time consumed in reaching equilibrium (several days).

Most of the recent changes in the standard carbon-hydrogen combustion determination have been introduced to take care of the nitrogen oxides from N-containing compounds, because the lead dioxide fails to do so satisfactorily. Proposed substitutes include other metal oxides to absorb the nitrogen oxides or metals to reduce them, or an absorbing agent placed in a U-tube between the anhydrone and the ascarite absorption tubes. Tests by Elving and McElroy on a large number of these materials showed them to be unsatisfactory, either because of incomplete removal or because of a tendency to absorb CO_2 or water. They recommend a strong oxidizing agent (potassium permanganate or dichromate) in concentrated sulfuric acid solution placed in a U-tube between the two absorption tubes. Niederl and Whitman mix the sample with copper oxide and employ a stream of nitrogen; the oxide oxidizes the sample and the freshly reduced copper reduces the nitrogen oxides.

Several wet oxidation methods have been developed to simplify the apparatus required for combustion. Oxidizing agents used include permanganate, iodate, dichromate, or persulfate, in solution in concentrated sulfuric or phosphoric acid. The volume of evolved CO_2 may be measured, or it may be determined gravimetrically or volumetrically. Christensen has recently combined several previous methods in the following microprocedure: the sample is oxidized with potassium iodate and sulfuric acid; the carbon dioxide is absorbed in standard barium hydroxide solution and the excess base is titrated. Since such a procedure gives

only carbon content, Williams back-titrates the excess oxidizing agent (iodate or dichromate) and from this value of equivalent oxygen O_R he calculates hydrogen content.

$$\%H = (\%O_R + 100 - 11/3 \cdot \%C)/8.93$$

This equation is applicable to compounds containing only C, H, and O. He reports that the accuracy of the latter value is greater than that from the usual combustion procedure. Williams also uses the oxidation equivalent E and the exact molecular weight M of an unknown compound $C_xH_yO_z$ to obtain its formula:

$$12x + y + 16z = M$$
$$2x + 0.5y - z = M/E$$

This oxidation equivalent E is the number of grams of the compound equivalent to one gram-atom of required oxygen. M must be even, and M/E must be a whole number. The equations are solved for x and y in terms of z and a few trial values of z readily show which is correct. Compounds containing S and N can be determined similarly provided the content of these elements is known and certain corrections are made. Wet combustions fail with certain compounds. Acetic acid, phyhalic acid, and pyridine types are unresponsive to one or more of the oxidants mentioned. Also, dichromate frequently produces some carbon monoxide, and the use of phosphoric acid medium leads to oxidation of part of the ammonia from nitrogen compounds.

Dumas nitrogen microanalysis often gives high results, especially when the sample contains more than 40% N. Fischer ascribes this to oxygen from a carbon monoxide-cuprous oxide-oxygen equilibrium at the high temperature in the combustion tube and suggests a separate furnace kept at only 200°C for the farther end of the tube. He reports a result 0.28% high on a sample containing 80%N.

In the standard Kjeldahl amino nitrogen procedure the sample is digested with sulfuric acid and a catalyst to produce ammonium sulfate; the solution is made alkaline with strong caustic and the ammonia steam-distilled into a standard acid solution. This method is limited to amines, amides, and amino acids; nitro groups must be absent, and heterocyclic nitrogen is in general not attacked. Sometimes the method is used for total nitrogen by first reducing it, as in the Friedrich procedure which uses HI and red phosphorus. The excess HI is removed with sulfuric acid and heat. Belcher and Godbert have applied this method to a wide range of compounds, including those with hetero nitrogen; they recommend as a catalyst for the Kjeldahl digestion a mixture of potassium sulfate, mercuric sulfate, and selenium. The reported results were rather consistently low by about 0.1% N.

Huffman has perfected a way by which sulfur can be determined during carbon-hydrogen combustion. The oxides of sulfur are absorbed on silver pellets to form silver sulfate, and this

is electrolyzed in dilute aqueous isopropyl alcohol (so that an adherent plate may be obtained.) Halogens must be absent.

The standard Zerewitinoff procedure has been modified by Evans, Davenport, and Revukas for improving the accuracy of micro determinations of active hydrogen. They burn the hydrocarbon evolved and determine C and H in the usual manner. n-Butyl Grignard is used to obtain more weighable product per active hydrogen than methyl Grignard would give.

The classical method for determination of acetyl is by trans-esterification with ethanol, distillation of the ethyl acetate and its saponification in standard alkali. Matchett and Levine have eliminated the unwieldy procedure of introducing ethanol vapors during trans-esterification by employing an efficient fractionating column with total reflux; small fractions of the distillate at the top are removed at intervals. This also permits the use of HCl catalyst in place of the less available aromatic sulfonic acids.

Methoxyl or ethoxyl content is commonly found by a modification of the Zeisel method. The alkoxyl is converted by HI to the alkyl iodide, which is distilled into bromine solution. The excess bromine is destroyed by formic acid, potassium iodide is added, and the liberated iodine is titrated with thiosulfate. The reactions are:

$$RI + Br_2 \rightarrow RIBr_2 \rightarrow RBr + IBr$$

$$IBr + 2Br_2 + 3H_2O \rightarrow HIO_3 + 5HBr$$

$$HIO_3 + 5HI \rightarrow 3I_2 + 3H_2O$$

Lisle reports a rapid method for approximate determination of methoxyl. Evolved methyl iodide is passed over a test paper saturated with a palladium chloride-pyridine solution, which turns brown. After drying it is compared with a set of standards. The question of whether the methio group will react to the Zeisel procedure has been investigated. Arndt shows the relationship of structure to ease of splitting: S-alkyl > S-aryl > S-carbonyl. He concludes that the method is generally not applicable, but that at the same time methio groups will interfere in alkoxyl determinations.

An illustration of the applicability of absorption spectra to quantitative organic analysis is given by the work of Gore and Patberg on the determination of toluene purity. Most impurities are aliphatic hydrocarbons. The aliphatic C-H bond shows a marked absorption peak in the infrared region at 3.4μ, and another smaller peak at 3.49μ. The aromatic C-H bond exhibits a much lower peak at 3.3μ. Fig. 1 compares the absorption curves for cyclohexane (upper) and toluene. Small quantities of paraffin present in toluene will show themselves in the peak at 3.4μ in spite of the toluene methyl. By arbitrarily assuming a single compound as the impurity (e.g. cyclohexane) it is

possible to estimate the degree of purity of the toluene from the relative absorption at this wave length according to Beer's law:

$$\log I_0/I = kc$$

where I_0 and I represent intensity of radiation through pure toluene in solution and that through the sample containing impurity of concentration c. Results from pure toluene with added traces of cyclohexane gave fig. 2. The procedure is rapid and indicates relative purity of the toluene with sufficient accuracy for industrial purposes.

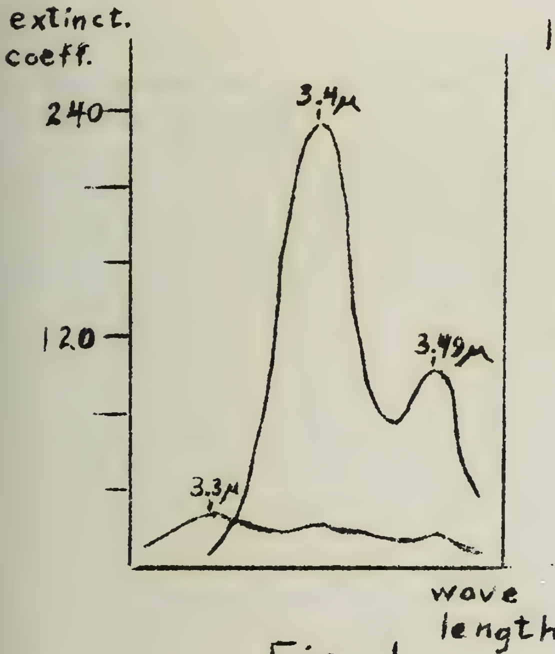

Fig. 1

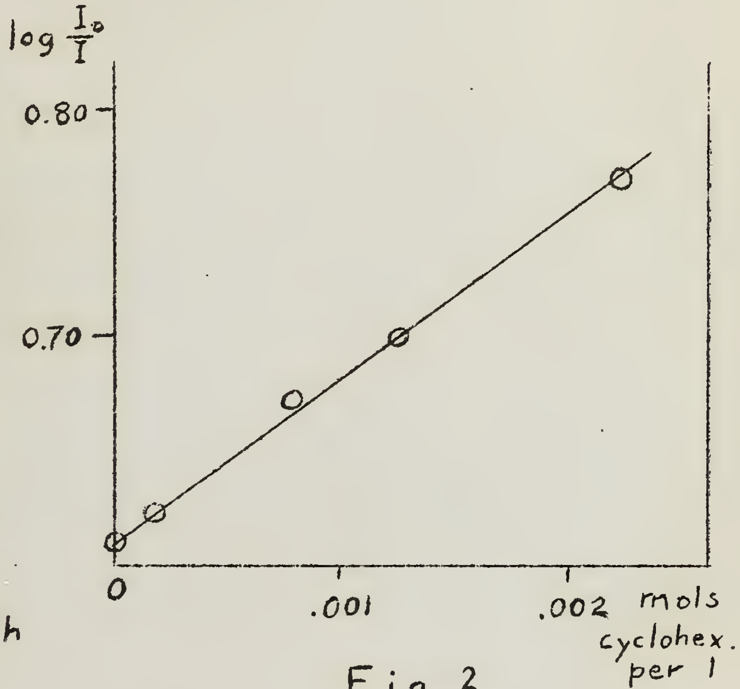

Fig. 2

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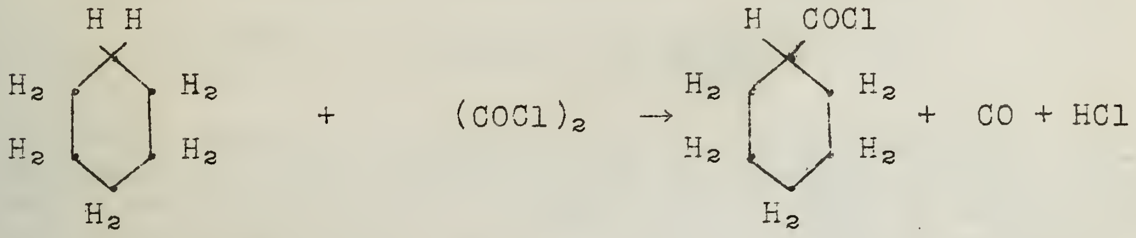
Reported by G. E. Inskeep
March 4, 1942

RECENT METHODS FOR MAKING ACIDS

I. Condensations with Oxalyl Chloride

In the presence of light and at room temperature oxalyl chloride and typical saturated hydrocarbons react with the formation of an acid chloride and the liberation of carbon monoxide and hydrogen chloride. The reaction appears to be general for paraffinic and cycloparaffinic hydrocarbons and may be represented as



The yields are quantitative--that is, a mole of acid chloride is produced for each mole of oxalyl chloride used. The conversions, however, vary from a few per cent for n-heptane to more than fifty per cent for cyclohexane. The chief cause of low conversions is the formation of colored matter in the reaction mixture which shields the oxalyl chloride from effective radiation.

Benzene inhibits the reaction, apparently by the absorption and degradation of the effective radiation. Toluene and related compounds do not react. This is presumed to be due to the effect of the aromatic ring on the transmission of the radiation reouired for activation of the oxalyl chloride.

From a consideration of the energy involved the following mechanism is proposed

Primary process:

$(COCl)_2 \rightarrow 2\cdot COCl$

$(COCl)_2 \rightarrow \cdot COCOCl + .Cl$

Secondary process:

$\cdot COCl \rightarrow CO + Cl\cdot$

$\cdot COCOCl \rightarrow 2\ CO + Cl\cdot$

$RH + Cl\cdot \rightarrow R\cdot + HCl$

$R\cdot + (COCl)_2 \rightarrow RCOCl + \cdot COCl$

$\cdot COCl \rightarrow CO + Cl\cdot$

$Cl\cdot + RH \rightarrow R\cdot + HCl$

It was found that the addition of small quantities of benzoyl peroxide to a reaction mixture of cyclohexane and oxalyl chloride induced a reaction in which the conversion was practically complete and the yield was sixty-five per cent.

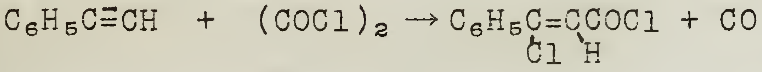
Neither light nor peroxides have any apparent effect upon the action of oxalyl chloride with unsaturated compounds. Gentle refluxing, however, brings about a reaction which may be

represented as

$$RHC{=\!=}CH_2 \;+\; (COCl)_2 \rightarrow RHC{=}CHCOCl + CO + HCl$$

Yields vary from over fifty per cent for 1,1-diphenylethylene to six per cent for 1-methylcyclohexene.

Phenyl acetylene reacts somewhat differently



$$C_6H_5C{\equiv}CH \;+\; (COCl)_2 \rightarrow C_6H_5\underset{Cl}{C}{=}\underset{H}{C}COCl + CO$$

Most unsaturated compounds do not react under these mild conditions but the effect of typical catalysts on the condensation was not studied. A highly polar double or triple bond is a prerequisite for reaction. The reaction is unaffected by the usual catalysts and inhibitors for reactions involving atoms and free radicals. The authors, therefore, believe that the reaction is strictly of the polar type.

II. Tertiary Carboxylic Acid Esters

Aston and his workers have shown that sodium alcoholates in ether act on α-bromo-α, α-dialkyl ketones to yield the ester of a tertiary acid. The following table gives some esters with the yield obtained using this method

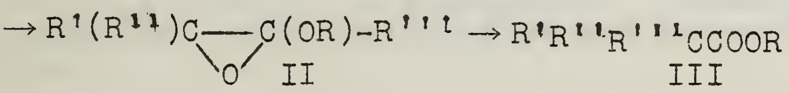
Isopropyl trimethylacetate	64%
Methyl timethylacetate	39%[1]
Methyl trimethylacetate	61.3%
Methyl methyl-t-butylacetate	73%
Methyl ethylmethylpropylacetate	75%[2]

[1]-the low yield is due to an excess of alcohol used in preparing the alcoholate.

[2]-a trace of methoxy ketone formed in the reaction is included in this yield.

The steps postulated for the reaction are:

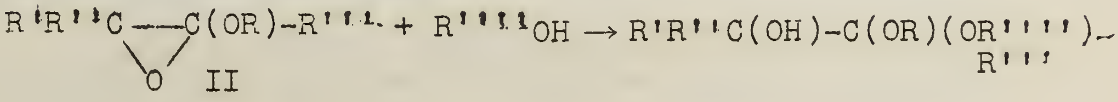
$$R'(R'')CBr\text{-}CO\text{-}R''' + NaOR \rightarrow \underset{\text{I}}{R'(R'')CBr\text{-}C(OR)(ONa)\text{-}R'''}$$



Two other reactions are possible:

1. Normal metathesis; e.g. 3-alkoxy-2-butanone from 3-bromo-2-butanone

2,



When no alcohol is present (sodium alcoholate suspended in ether), reaction (2) which requires alcohol is not possible. The possibility that a change of medium alone is the factor influencing the rearrangement to the ester is eliminated by the fact that if any alcohol is present a corresponding amount of hydroxy acetal is obtained in ether medium.

The formation of addition product (I) rather than the product of metathesis is ascribed to steric hindrance. That the presence of hydrogen on the α-carbon is not the determining factor is shown by the seventy-three per cent yield of the pure methyl ester of methyl-t-butylacetic acid obtained from 4,4-dimethyl-3-bromo-2-pentanone. The rearrangement is retarded by making the rearranging alkyl or aryl group larger. Thus α-bromoisobutyrophenone gave only the α-methoxyisobutyrophenone.

III. Glycolic Acid

Glycolic acid is produced by heating formaldehyde, carbon monoxide and water at 160-170° for one hour at pressures between five and fifteen hundred atmospheres. An inorganic acidic material such as sulfuric acid, dissolved in an organic acid such as acetic acid, serves as a catalyst. Other suitable catalysts are boron trifluoride, hydrochloric, phosphoric, formic and glycolic acids.

IV. Substituted Acetic Acids

Substituted acetic acids are formed when carbon monoxide, formaldehyde or one of its polymers and an inorganic acid react in the presence of an acidic catalyst according to the equation

$$n\,(HCHO) + n\,(CO) + H_nX \rightarrow X(CH_2COOH)_n$$

When an organic acid is used, acyloxyacetic acids are obtained. Thus propionoxyacetic acid would be obtained from formaldehyde, carbon monoxide and propionic acid.

V. Acetic and Propionic Acids

Acetic acid is produced when methyl alcohol and carbon monoxide are heated at a temperature of 125-180° and pressures greater than twenty-five atmospheres, 700-900 atmospheres being most suitable. Boron trifluoride and water are used as the catalysts.

By the use of ethyl alcohol and carbon monoxide under similar conditions, propionic acid is produced. Propionic acid is also made from a hydrating agent such as water, carbon monoxide, and ethylene using boron trifluoride and one to three moles of water as the catalyst.

In an analogous manner, polycarboxylic acids are obtained from polyhydroxy alcohols such as ethylene glycol, propylene glycol and glycerol.

The boron trifluoride catalyst is prepared by treating anhydrous liquid hydrogen fluoride with boric acid, its anhydride or a borate at temperatures below 10°. The reactants are used in such a proportion that $BF_3 \cdot 2H_2O$ or $BF_3 \cdot 3H_2O$ will be formed.

Dreyfus has patented a catalyst consisting of traces of copper and ammonium phosphate for the production of acetic acid by this procedure. The Eastman Kodak Company has a catalyst containing small amounts of the oxides of zinc and manganese and larger amounts of the oxides of copper with a binder such as sodium silicate or cellulose acetate. Other suitable catalysts are the fluorides of magnesium, calcium and titanium and the halides of numerous other metals.

VI. Maleic Acid

A process recently patented by the Standard Oil Development Company consists in passing a mixture of oxygen, an oxidizable unsaturated hydrocarbon containing at least four carbon atoms and water vapor over a catalyst at a temperature of 250-400°. The oxides or salts of vanadium, nickel, tungsten, chromium, manganese, molybdenum or mixtures of these are suitable catalysts.

VII. Fumaric Acid

Fumaric acid is produced by the oxidation of furfural. This is accomplished by moderate heating in a chlorate solution using vanadium trioxide and one or more of manganese trioxide, aluminum oxide or ferric oxide as the catalyst.

VIII. Soap-forming Carboxylic Acids

British and German patents describe a method for the preparation of soap-forming carboxylic acids or their salts by the oxidation of technical mixtures of hydrocarbons and fusion with alkali metal or alkaline earth metal bases. The hydrocarbon must contain one unsaturated link in an aliphatic chain and at least one saturated aliphatic chain not less than six carbon atoms in length. The unsaturated tar oils boiling at 200-350° obtained from the distillation of lignite, cracking-gas oil fractions boiling at 200-325° (seventy to seventy-five per cent of which are olefins having twelve to eighteen carbon atoms) and olefinic products from the hydrogenation of carbon monoxide are suitable starting materials.

Permanganates, persulfates, hypochlorites, hydrogen peroxide, chlorine, oxygen and air are used as oxidizing agents and in some cases the hydrocarbons are emulsified before oxidation. The use of solvents or diluents such as mineral oils or saturated hydrocarbons which may be present in the initial hydrocarbon mixture is beneficial.

In a typical example, a hydrocarbon having a boiling point above 250° is oxidized at 115° by means of air in the presence of heavy metal salts of unsaturated acids. The dried product may then be fused with alkali at 250-280°. The product consists of salts of stearic, palmitic, myristic, lauric and capric acids.

IX. α-Chloroacrylic Acid

Paraformaldehyde, trichloroethylene, 98% sulfuric acid and metallic copper (in the ratio 30-132-84-1 parts) are heated at 25-30°; the temperature finally being raised to 45°. α-Chloroacrylic acid is obtained from the reaction mixture.

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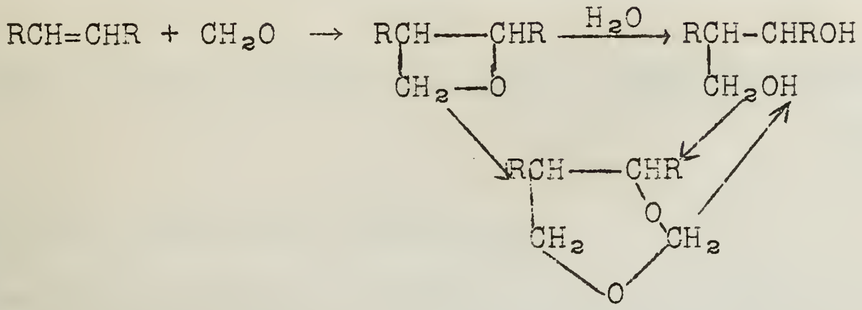
Reported by G. W. Cannon
March 11, 1942.

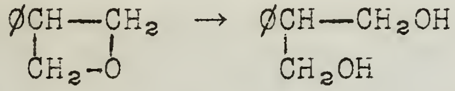
THE PRINS REACTION

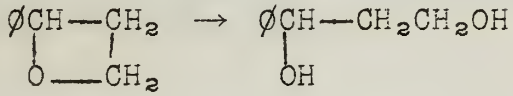
This reaction, discovered by Prins, is the condensation of formaldehyde with an olefin.



In some cases the 4-membered ring may rearrange, or the glycol may dehydrate, to give an unsaturated primary alcohol.. The condensation is brought about by sulfuric acid in acetic acid, formic acid, or water. Prins carried out his initial experiments on styrene, anethole, isosafrol, α-pinene, camphene, and cedrene.

With unsymmetrical olefins, for example styrene, the addition might proceed in two ways, giving rise to the products:

A.

$$\underset{CH_2-O}{\varnothing CH-CH_2} \rightarrow \underset{CH_2OH}{\varnothing CH-CH_2OH}$$

B.

$$\underset{O-CH_2}{\varnothing CH-CH_2} \rightarrow \underset{OH}{\varnothing CH-CH_2CH_2OH}$$

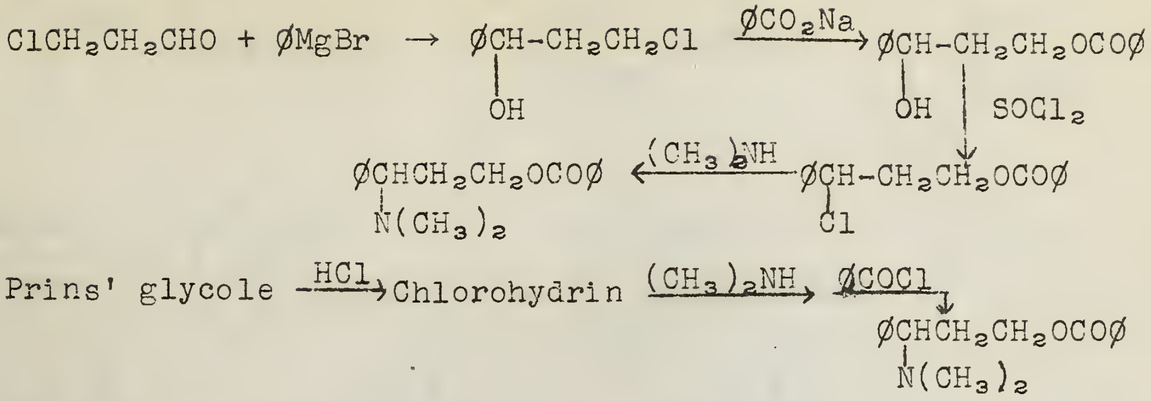
Only one product was obtained; Prins believed it to be of the structure A, since it gave a diacetate with boiling acetic anhydride, instead of cinnamyl acetate.

Fourneau, Benoît and Ferminich conclusively proved the structure to be the unsymmetrical glycol B. They based their conclusion on the following evidence:

1. Saponification of the diacetate yielded large quantities of cinnamyl alcohol.

2. The glycol, 1-phenyl-1, 3-propanediol prepared by Rupe by reducing ØCOCH=CHOH gave a dibenzoate of the same melting point (51°) as that from Prins' glycol.

3. The unsymmetrical glycol was prepared from a chlorohydrin of known structure.



$$ClCH_2CH_2CHO + \emptyset MgBr \rightarrow \underset{OH}{\emptyset CH}-CH_2CH_2Cl \xrightarrow{\emptyset CO_2Na} \underset{OH}{\emptyset CH}-CH_2CH_2OCO\emptyset \xrightarrow{SOCl_2} \underset{Cl}{\emptyset CH}-CH_2CH_2OCO\emptyset \xrightarrow{(CH_3)_2NH} \underset{N(CH_3)_2}{\emptyset CH}CH_2CH_2OCO\emptyset$$

$$\text{Prins' glycole} \xrightarrow{HCl} \text{Chlorohydrin} \xrightarrow{(CH_3)_2NH,\ \emptyset COCl} \underset{N(CH_3)_2}{\emptyset CH}CH_2CH_2OCO\emptyset$$

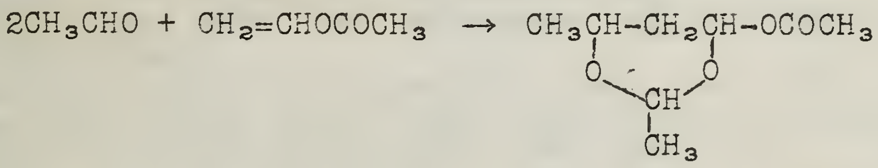
The two amino esters were identical.

Prins later offered an explanation as to the mode of addition of formaldehyde to an unsymmetrical olefin derivative. He assumed that the negative oxygen atom would add to the more positive carbon atom of the $>C=C<$, and he further assumed that a carbon atom would be the more positive when a hydrogen was substituted by an atom with a high electron affinity. Thus the reaction was studied with di-, tri-, and tetrachloroethylene. The neutralization of the charge on the carbon to which the oxygen became attached, activates the chlorine atom so that immediate hydrolysis occurs.

The reaction with dichloroethylene gave only a resin. Trichloroethylene yielded $CH_2OHCHClCOOH$ which lost water to form the ethereal acid $O(CH_2CHClCOOH)$. The oxygen attacks the CCl_2=group almost exclusively. Tetrachloroethylene yielded the dichloroacid CH_2OHCCl_2COOH.

<u>Recent Developments and Applications</u>.

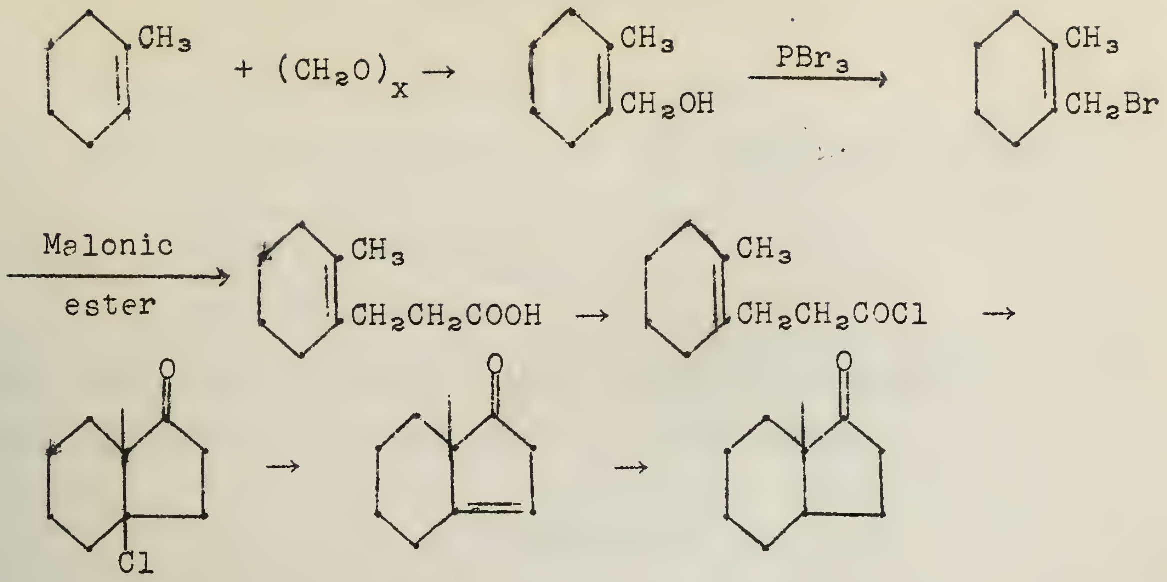
Marvel, Harmon, and Riddle found that acetaldehyde condenses with vinyl acetate in the presence of sodium to give a cyclic acetal reminiscent of the classical Prins reaction.



$$2CH_3CHO + CH_2{=}CHOCOCH_3 \rightarrow CH_3CH-CH_2CH-OCOCH_3$$

Acid condensing agents had no effect, and no other aldehyde could be made to undergo the reaction.

Nenitzescu and Przemetzky, in searching for new routes to 8-methyl-1-hydrindanone and similar compounds, discovered that the best method involved the Prins reaction.



A patent has been issued for the formation of a synthetic plastic from formaldehyde and a cracked petroleum oil fraction. The reaction is brought about by an acid condensing agent in the presence of a promoter such as acetic acid.

Cyclic formals can easily be synthesized by reacting one mole of an aliphatic monoolefin with about two moles of formaldehyde in the presence of an acid condensing agent. Similarly, a source of 1,3-butanediol is the reaction of formaldehyde hydrate with propylene at super-atmosphere pressures using HX and $ZnCl_2$ as catalysts.

The important acid, α-chloroacrylic acid may be manufactured by heating formaldehyde with trichloroethylene in concentrated sulfuric acid, and heating the subsequent mixture in the presence of water.

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Nenitzescu and Przemetzky, Ber. 74B, 676 (1941)
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Reported by R. E.Foster
March 11, 1942

Chlorosulfonic Acid As An Organic Reagent

I. Preparation of chlorosulfonic acid.

II. Action as a sulfonating and chlorosulfonating agent on:

- Hydrocarbons and derivatives
- Hydroxy compounds
- Aldehydes and ketones
- Acid derivatives

III. Reactions involving oxidation and chlorination.

IV. Reactions as a qualitative organic reagent.

I. PREPARATION

Numerous examples have been cited in the literature for the preparation of chlorosulfonic acid, $ClSO_3H$, but all are essentially based upon the production of hydrochloric acid and its reaction with sulfur trioxide:

$$HCl + SO_3 = ClSO_3H$$

For example, dry hydrogen chloride is passed into oleum until no further absorption occurs, and the chlorosulfonic acid separated by distillation in a stream of hydrochloric acid. Perhaps a more widely used method is the addition of solid sodium chloride to oleum containing 60-80 mole per cent of sulfur trioxide and finally separation by distillation.

Chlorosulfonic acid itself is a colorless, fuming liquid which boils at 158°, melts at -88°, and has a sharp unpleasant odor. It is very corrosive and therefore must be handled with care.

II. SULFONATION AND CHLOROSULFONATION

The action of chlorosulfonic acid as a sulfonating reagent, stressed by Gebauer-Fuelnegg and Haemmerle, is only one of its extensive and varied reactions.

Starting first with the aromatic hydrocarbons, the initial step in the reaction is the elimination of hydrochloric acid and the formation of the corresponding sulfonic acid which, in the presence of excess chlorosulfonic acid, reacts to form the sulfonyl chloride, thus:

$$C_6H_6 + ClSO_3H = C_6H_5SO_3H + HCl, \text{ (benzenesulfonic acid)}$$
$$C_6H_5SO_3H + ClSO_3H = C_6H_5SO_2Cl + H_2SO_4 \text{ (benzenesulfonyl chloride)}$$

The mechanism is perhaps oversimplified, for the products depend intimately upon the experimental conditions: the time of reaction, the temperature, the quantity of reagents, and the nature and order of additions of the reacting substances. The type of reaction is determined by the temperature of the reaction and the amount of chlorosulfonic acid. The results may be summarized by the following observations:

A. At low temperature, that is, room temperature although many reactions are run at 0° and below, and in the presence of equivalent quantities of the reacting substances, the sulfonic acid is produced.

B. At low temperature and in the presence of an excess of chlorosulfonic acid, the acid chloride is produced.

C. At higher temperatures, 150°, and in the presence of equivalent amounts of reacting substances, the sulfone is produced which may be chlorosulfonated further.

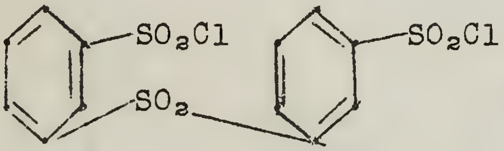
D. At the higher temperatures, and in the presence of excess chlorosulfonic acid, the product obtained is the sulfonyl chloride. Under these forced conditions, more than one sulfonyl group may be introduced.

To illustrate these:

$C_6H_6 + ClSO_3H$ (excess) $\xrightarrow[\text{temp.}]{\text{room}}$ $C_6H_5SO_2Cl$ (76%)
(benzenesulfonyl chloride)

$C_6H_5 + ClSO_3H$ (excess) $\xrightarrow[\text{3 hrs.}]{150^\circ}$ _m_-$C_6H_4(SO_2Cl)$ + sulfone.
(benzene-_m_-disulfonyl chloride)

$C_6H_5(20\text{ g.}) + ClSO_3H(15\text{ g.}) \xrightarrow[\text{10 min.}]{150^\circ} \xrightarrow[\text{5 hrs.}]{\text{excess}}$



(80%)

(diphenylsulfone-_m_-disulfonyl chloride)

Other organic compounds are indicated in the following table:

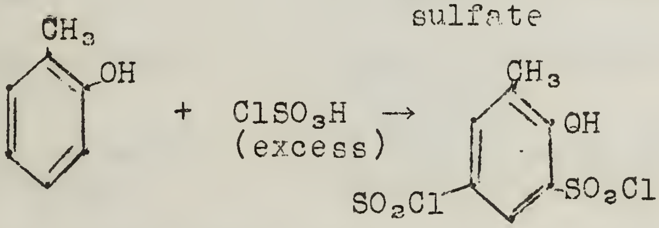
Hydrocarbon	Products isolated
Toluene	*o*-sulfonic acid
	p-sulfonic acid
	2,4-disulfonyl chloride
	di(*p*-methylphenyl-*m*-sulfonyl chloride) sulfone
o-xylene	3,5-disulfonyl chloride
m-xylene	1,3-dimethylphenyl-4-sulfone
p-xylene	1,4-dimethylphenyl-2-sulfone
	2-sulfonyl chloride
Naphthalene	1-sulfonic acid
	1-sulfonyl chloride
	1,5-disulfonyl chloride
Biphenyl	monosulfonic acid
	4,4'-disulfonyl chloride
Chlorobenzene	2,4-disulfonyl chloride
Chlorobenzene and	*p*-monosulfonic acid
Bromobenzene	dihalosulfobenzide
1-Chloro-4-nitro benzene	2-sulfonyl chloride
Ethyl phenyl sulfone	*m*-sulfonyl chloride
Aniline	2,4,6-trisulfonyl chloride
m-phenylenediamine	4,6 disulfonyl chloride

In its action on aliphatic compounds, chlorosulfonic acid is similar to sulfuric acid. Branched chain hydrocarbons are much more reactive, and these offer a possible means of purification. Ethylene adds $ClSO_3H$ to form $C_2H_5OSO_2Cl$.

Hydroxy compounds of the aromatic series have been studied very extensively and seem to bring about sulfonation by the following mechanism: A molecular addition compound is formed followed by the elimination of hydrochloric acid to form a sulfate which undergoes a Fries rearrangement producing the sulfonic acid, whence the sulfonyl chloride, the para position beimg selected preferentially. For example:

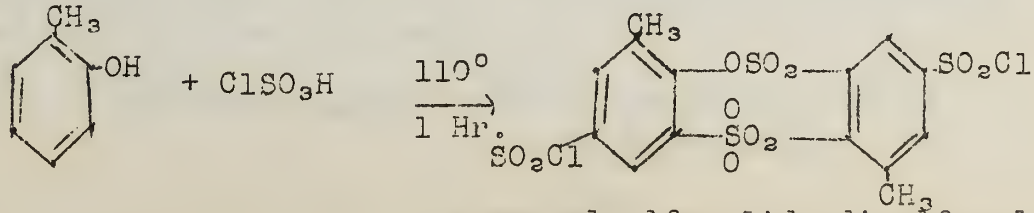
(1) $$C_6H_5OH + ClSO_3H \xrightarrow[-15^\circ]{CS_2} \underset{\text{phenyl hydrogen sulfate}}{C_6H_5OSO_3H} + \underset{\text{4-hydroxybenzene-sulfonic acid}}{p\text{-}HOC_6H_4SO_3H}$$

(2)



,2-hydroxytoluene-3,5-disulfonyl chloride.

(3)



m-cresolsulfonylide-disulfonyl

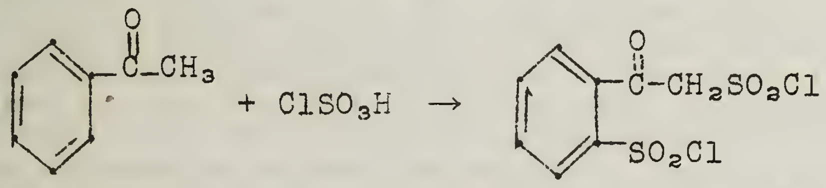
The sulfate of equation (1) is formed if the reaction is carried out in the presence of pyridine or some other tertiary base. Other examples are given in the following:

Reactant	Products
p-cresol	p-toluyl hydrogen sulfate 4,4'-dimethyldiphenyl-1,2,1',2'-sulfonylide-6,6'-disulfonyl chloride
2,3-dimethylphenol	4,6-disulfonyl chloride 2,3,2',3'-tetramethyldiphenyl-1,6,1',6'-sulfonylide-4,4'-disulfonyl chloride
2,4-dimethylphenol	6-sulfonyl chloride 1,3,1',3'-tetramethyldiphenyl-4,5,4'5'-sulfonylide

In the aliphatic series, hydroxy compounds tend to form the sulfuryl chloride, as ethyl alcohol produces $C_2H_5OSO_2Cl$. One interesting application is its use to produce sulfated sugars. These are converted to the acetates when treated with acetic anhydride.

Formaldehyde reacts with chlorosulfonic acid to produce $ClCH_2OSOCl$, CH_2SO_4, $(ClCH_2O)_2SO_2$, and $(ClCH_2)_2O$ as if the hypothetical $ClCH_2OH$ had been formed. Homologues are attached in the alpha position, producing sulfonic acids; however chloral, being stable in this position, produces $(CCl_3CHCl)_2O$ and chloralide.

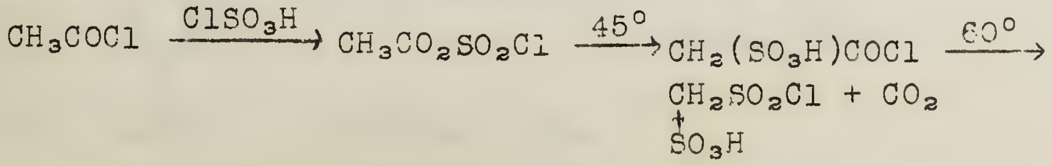
Acetophenone is of interest because of its unique reaction



Reactions on acid derivations are indicated in the following table:

Reactant	Products
Sodium acetate	acetic anhydride
CH_3OCOCl	CH_3OSO_2Cl
$ArSO_3K$	$ArSO_2Cl$
Salicylic acid	3,5-disulfonyl chloride
$CH_2(CONHR)_2$	disulfonic acids

The most spectacular reaction of this group is the action of chlorosulfonic acid on acid chlorides.



$$CH_3COCl \xrightarrow{ClSO_3H} CH_3CO_2SO_2Cl \xrightarrow{45^\circ} CH_2(SO_3H)COCl \xrightarrow{60^\circ} \underset{SO_3H}{\underset{|}{CH_2}}SO_2Cl + CO_2$$

Above 60°, a 3% yield of 2-methyl-1,4-pyrone-6-acetic acid was obtained. Propionyl chloride reacts similarly to form $CH_3CH(SO_3H)COCl$ and a by-product of α'-ethyl-β,β'-dimethylphorone; butuyryl chloride does not undergo these condensation reactions, but rather forms dipropyl ketone.

III. OXIDATION AND CHLORINATION

These reactions of oxidation or chlorination are more or less exceptions to the rule rather than general in application, however their presence is real and must be considered; besides they are interesting and unusual.

Reactant	Products
Hydroquinone	Chloranil Penta chlorophenol
Nitrobenzene	Chloranil
p-phenylenediamine	Chloranil
p-phenylenediamine ($ClSO_3Na$)	Tetrachlorophenylendiamine
Phloroglucinol	Pentachlorophenol
Resorcinol	Hexachlorobenzene
Naphthalene	Tetrachlorophthalic anhydride
Cyclohexadiene	Benzenesulfonyl chloride
Thiophenetole	Pentachlorothiophenetole
Thiophenol	Diphenyldisulfide

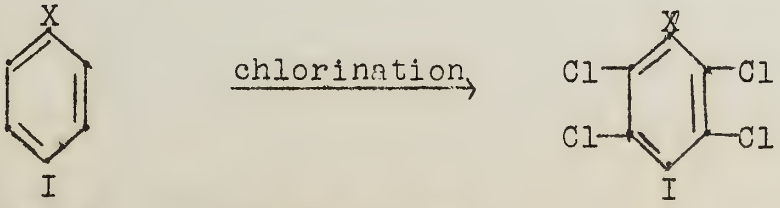
Huntress and co-workers recently applied this versatile and reactive substance to the identification of organic compound: aryl halide, alkyl aryl ethers, and alkyl benzenes. The results have proven very satisfactory, and a procedure has been standardized for the identification of such compounds. It consists of adding an excess of chlorosulfonic acid to a cold solution of the unknown in chloroform solution, separating the sulfonyl chloride and converting it to the amide by means of solid ammonium carbonate or concentrated ammonium hydroxide.

$$ArX \xrightarrow{ClSO_3H} XArSO_2Cl \xrightarrow{(NH_4)_2CO_3} XArSO_2NH_2$$

He found that under these conditions the para isomer where possible is invariably formed.

In general the halides of benzene, toluene, and naphthalene were studied. The iodo compounds all reacted abnormally, thus

(1)



(2) $C_6H_5I \rightarrow (p\text{-}IC_6H_4)_2SO_2$

Constituents in the <u>ortho</u> and <u>meta</u> positions of iodo compounds reacted according to (1); sulfones as in (2) were also produced from fluorobenzene, and from <u>o</u>-dichloro- and <u>o</u>-dibromobenzene.

Some forty-two alkoxybenzenes were studied and found to react analogously, with only biphenyl compounds behaving pecuriarly.

In the case of the alkylbenzenes, the para orientation was proven by permanganate oxidation to the corresponding sulfamidobenzoic acid where possible. That only one sulfamide group had been introduced under the conditions of the reaction was established by a nitrogen determination.

It was pointed out that even in the cases where abnormal reactions had taken place, the products served just as well for the purposes of identification.

<u>Bibliography</u>

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Reported by S. S. Drake
March 18, 1942

SOME DERIVATIVES OF THE POLYHYDROXYBENZENES

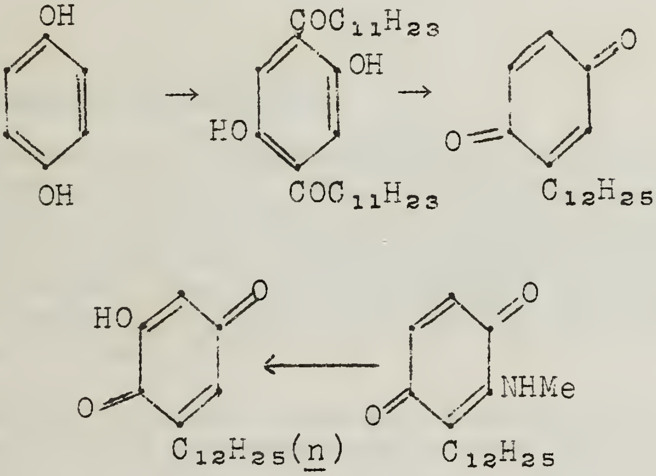
Wilson Baker, et al
Oxford University

This paper attempts to cover only a few of the many possible polyhydroxybenzene derivatives. It is chiefly concerned with certain tetra-, penta- and hexamethoxybenzenes and some naturally occurring compounds that may be derived from them.

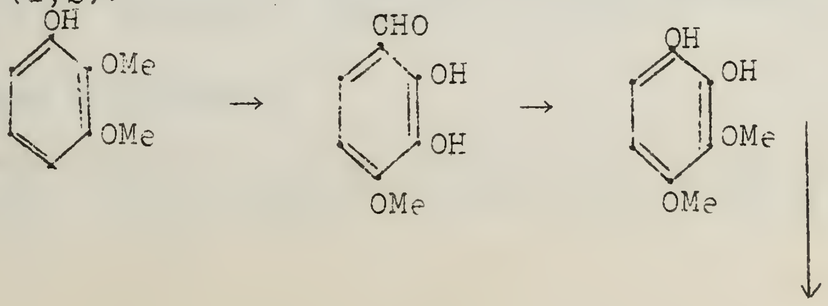
Tetrahydroxybenzene Derivatives

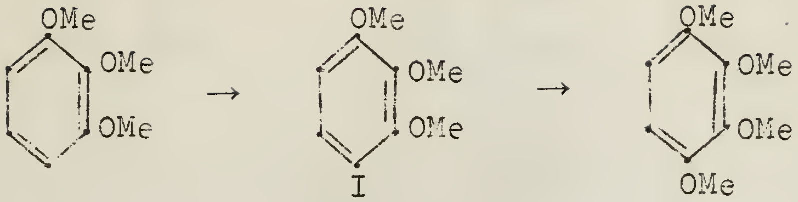
Compounds derived from tetrahydroxybenzene are not often found in nature, but of these substances the derivatives of 1:2:3:5-tetrahydroxybenzene occur most frequently. Many of these have been determined and found to be flavones, flavonols, and isoflavones.

Derivatives of 1:2:4:5-tetrahydroxybenzene are contained in certain lichen coloring matter, and in embelic acid (2:5-dihydroxy-3-lauryl-p-benzoquinone). The latter has been synthesized by Hasan and Stedman (9) as follows:

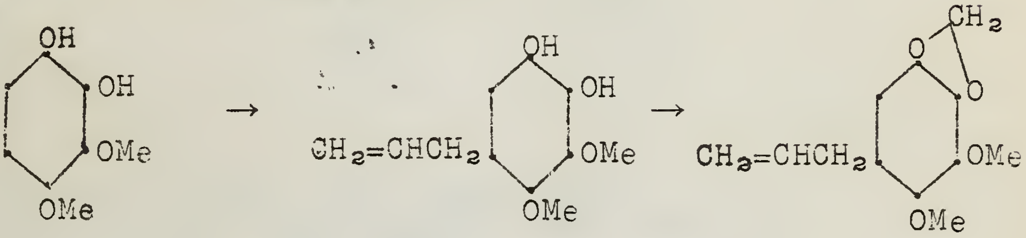


Derivatives of 1:2:3:4 -tetrahydroxybenzene are represented in nature by parsley apiole (1:4-dimethoxy-2:3-methylene dioxyallylbenzene), fraxetin (7:8-dihydroxy-6-methoxycoumarin), and dill apiole (3:4-dimethoxy-1:2-methylenedioxy-5-allyl-benzene). Two syntheses of the basic compound 1:2:3:4:tetramethoxybenzene are shown below (1,2):





The product, (1:2-dihydroxy-3:4-dimethoxybenzene), resulting from the first series of reactions, was used by Baker and Jukes (3) in their synthesis of dill apiole, which occurs in dill plants, matico oil, and sea-fennel oil.



Dill Apiole

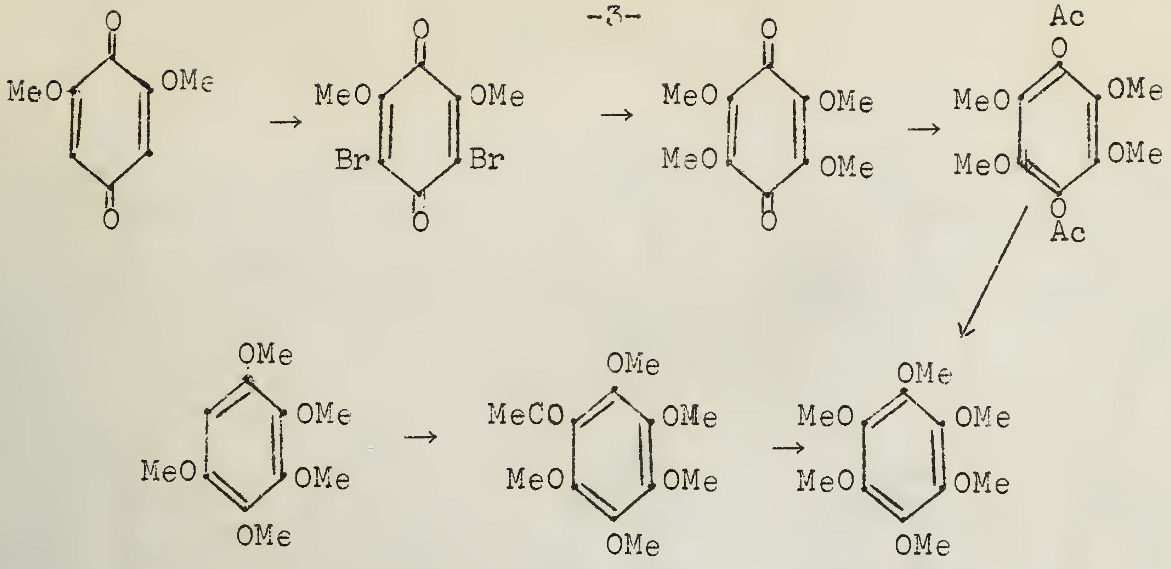
Pentahydroxybenzene Derivatives

Many derivatives of pentahydroxybenzene have been isolated from plant sources. Some of these include nobiletin (5:6:7:8:3':4'-hexamethoxyflavone), spinulosin (3:6-dihydroxy-4-methoxy-2:5-toluquinone), erianthin (5:7-dihydroxy-3:6:8:3':4'-pentamethoxy flavone), pedicin (2:3-dihydroxy-4:5:6-trimethoxyphenyl styryl ketone), and the closely related compound pedicellin (dimethyl ether of pedicin).

Four separate methods have been recorded in the literature for the preparation of pentahydroxybenzene derivatives, the yields varying and in general not good. Baker (5) has devised two relatively simple procedures which have been outlined in Flow Sheet A. Flow Sheet B shows some simple reactions of these compounds, and in Flow Sheet C are found two syntheses of pedicellin (5) and also one of funagatin as worked out by Baker and Raistrick (6). This latter product, 3-hydroxy-4-methoxy-2:5-toluquinone, can be isolated as maroon-colored needles from a mould metabolic product.

Hexahydroxybenzene Derivatives

The only derivative to be considered in this paper is hexamethoxybenzene. This compound has been prepared by Robinson and Vasey (4), and by Baker (5).



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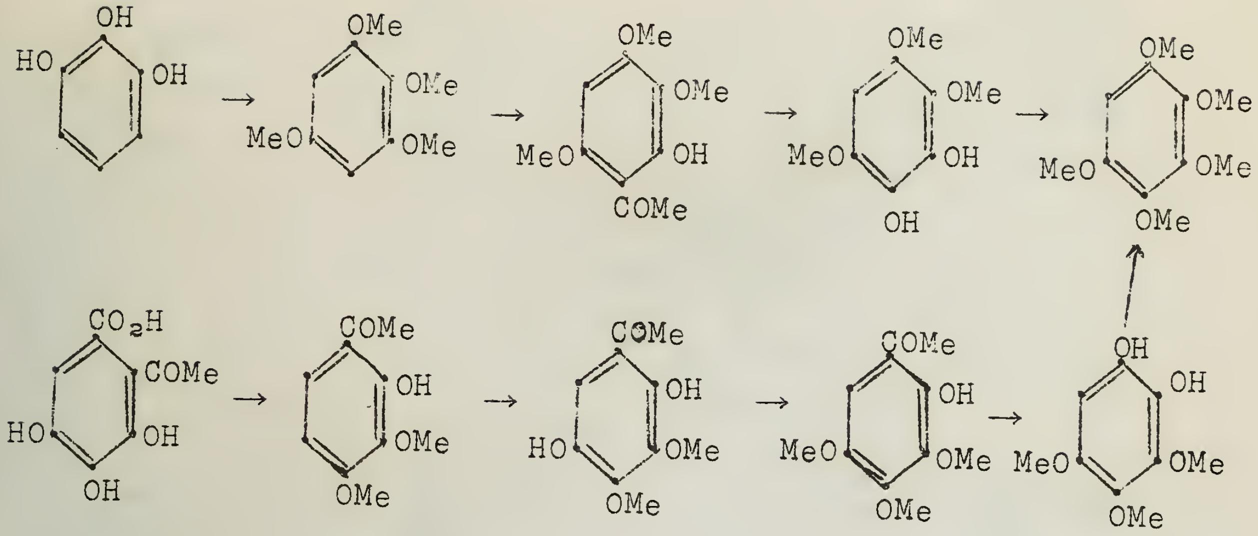
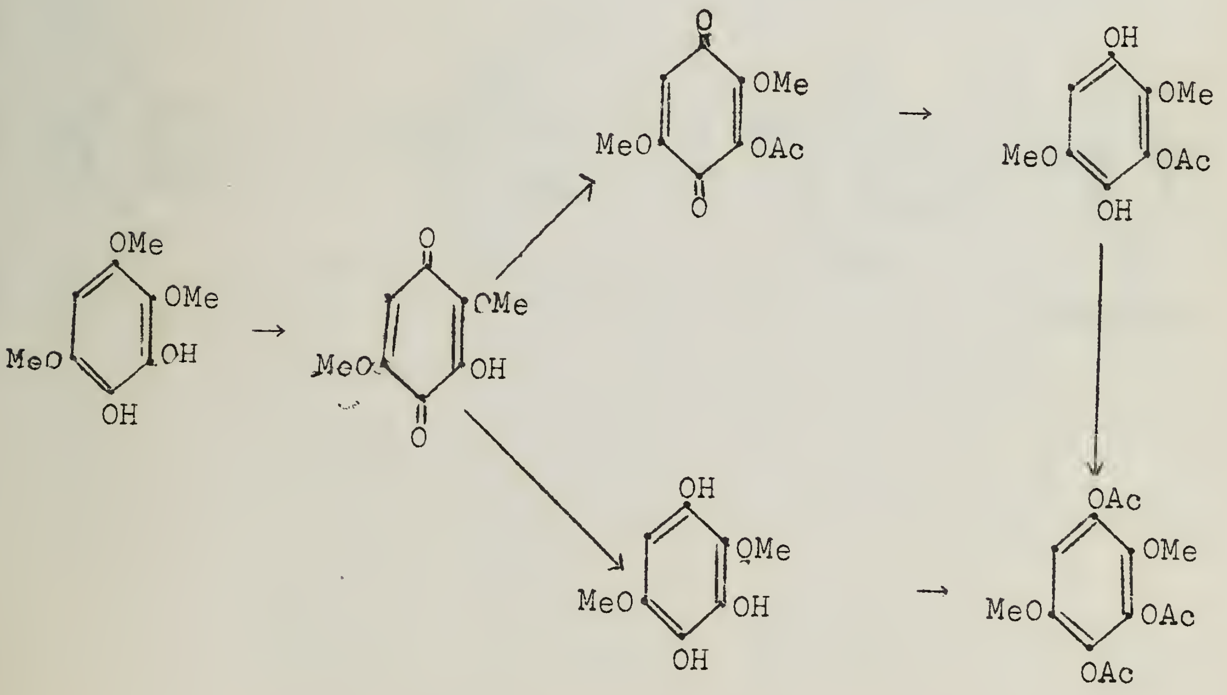
Reported by John D. Garber
March 18, 1942

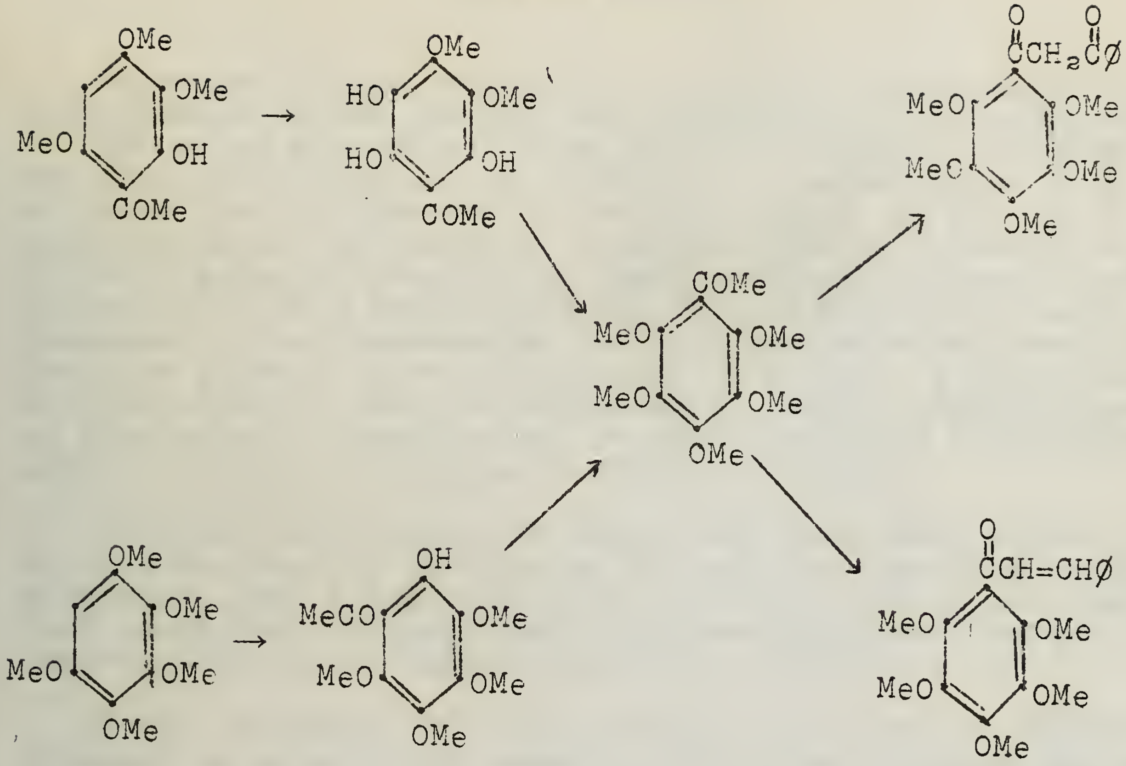
Flow Sheet A



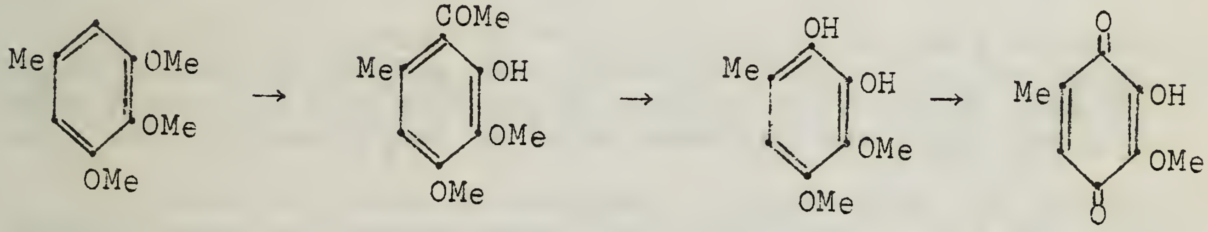
Flow Sheet B



Flow Sheet C



Pedicellin



Fumagatin

RELATION BETWEEN OPTICAL ROTATORY POWER AND CONSTITUTION OF THE STEROLS

Evidence for the correlation of optical rotatory power with constitution of the sterols was presented by Callow and Young in 1936 after a study of known pairs of compounds between which the only difference was an inversion of carbon atoms 3, 4, 5 or 17 or the introduction of a double bond. In 15 out of 18 cases there was an increase of dextro-rotatory power by a change of the 3 hydroxyl from <u>cis</u> to <u>trans</u> relative to the 10 methyl. Introduction of a double bond at the 4:5 position results in an increase in dextro-rotation, while introduction at the 5:6 position gives a decrease in dextro-rotation. A double bond at 8:14 brings a small decrease and at 14:15 a small increase in <u>d</u>-rotation. Changing the 17 ketone group to a secondary carbinol brings a decrease in dextro rotation.

However, the results of Callow and Young were merely qualitative; the sign of the change but not the magnitude could be predicted. And exceptions were not rare, even in the limited data available, although many of these might be ascribed to impure materials or uncertainty as to structure.

Gorin, Kauzmann and Walter showed that optical superposition depended on certain very special conditions to which the carbohydrate molecules readily conform. Steroid molecules in general cannot conform to these conditions and any method of optical superposition will not succeed.

Berstein, Kauzmann and Wallis have worked out a method which in effect divides the steroid molecule into two parts, the ring system and the side chain, each of which parts functions as a unit optically and is independent of the other part.

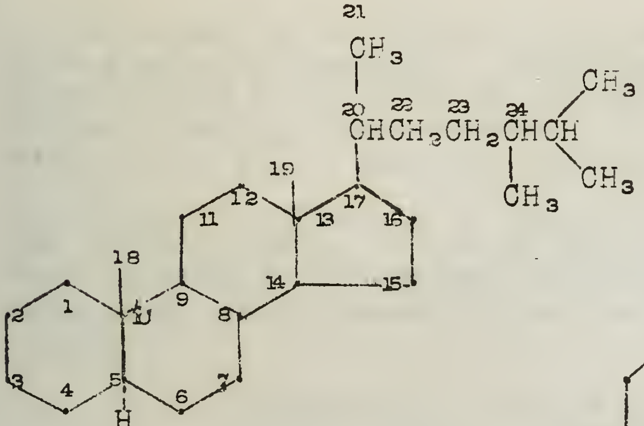
Consider the pairs of compounds, stigmastane and ergostane, stigmastanone and ergostanone (see next page). In each case the only difference is in the side chain, one having an ethyl the other a methyl on C-24. If the molecule is considered as being made up of two independent regions of asymmetry, the atoms in the neighborhood of C-3 and the side chain, then the difference in molecular rotation between the substances in each of the above pairs should be due only to the difference in effect of an ethyl and a methyl at C-24, and therefore both differences should have the same value.

stigmastane	+10,470°	stimastanone	+17,000°
ergostane	+ 7,670°	ergostanone	+13,960°
	+ 2,800°		+ 3,040°

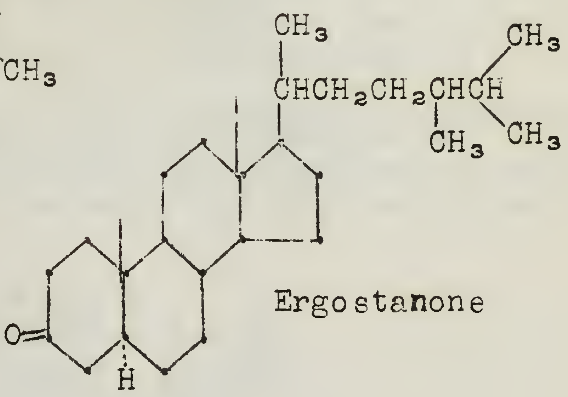
Since an error of 1000° in molecular rotation corresponds to about 2.5° of specific rotation, the agreement of these values is very good.

Now compare the pairs ergostane and ergostanone, stigmastane and stigmastanone. In this case the difference in rotation should be due to the effect of a methylene group and its environment and a carbonyl group and its environment at C-3.

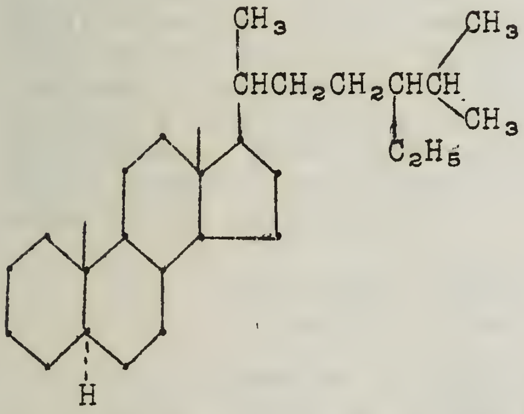
ergostanone	+13,960°	stigmastanone	+17,000°
ergostane	+ 7,670°	stigmastane	+10.470°
	+ 6,290°		+ 6,530°



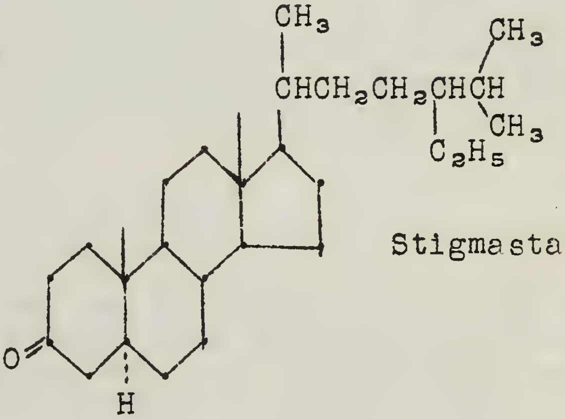
Ergostame



Ergostanone



Stigmastane



Stigmastanone

Whenever the environment of the C-3 is the same as in ergostane--that is, with saturated rings and with the C-5 hydrogen <u>trans</u> to the C-10 methyl--the difference in rotation between the methylene and carbonyl compound should be +6,400°.

cholestanone	+15,840°	γsitostanone	+15,760°
cholestane	+ 9,160°	γsitostane	+ 8,090°
	+ 6,680°		+ 7,670°

However, if the C-5 hydrogen is <u>cis</u> to the C-10 methyl, we would expect the difference between the rotations of the carbonyl and the methylene compound to have a different value.

coprostanone	+14,010°
coprostane	+ 9,430°
	+ 4,580°

In order to use these relationships more easily, we can set up a system of notation. Cholestane is taken as the reference compound and its molecular rotation is denoted by the letter C. In the change to cholestanone, we can symbolize the change in rotation as K_{3_t}. Thus the rotation of cholestanone is $C + K_{3_t}$. The change in rotation in going from cholestane to ergostane can be called Erg. Thus the rotation of ergostane is C + Erg. Then knowing the numerical values for the rotations of these molecules, we can easily find the value for the individual constants.

$$\text{cholestane} = +9{,}160^\circ = C$$
$$\text{cholestanone} = 15{,}840^\circ = C + K_{3_t}$$
$$K_{3_t} = 15{,}840^\circ - 9{,}160^\circ$$
$$\text{ergostane} = 7{,}670^\circ = C + \text{Erg}$$
$$\text{Erg} = 7{,}670^\circ - 9{,}160^\circ$$

Using this notation, we can indicate the rotation of ergostanone as $C + K_{3_t} + \text{Erg} + e$ where e represents the difference in interaction of the ergostane and cholestane side chains with the carbonyl and methylene groups at C-3. But since two centers of asymmetry which are far apart do not influence one another's contribution to the optical rotation, e should be negligible. Then since we already know the values of the other three symbols, we should be able to calculate the molecular rotation of ergostanone.

$$C + K_{3_t} + \text{Erg} = +14{,}350^\circ$$
$$\text{observed value} = +13{,}960^\circ$$

In this manner a table was set up (Table I) for the values of a large number of symbols which were assigned to specific changes on the sterol framework and then these values were used to calculate the rotation of a number of sterols (Table II). The calculated and observed values agreed fairly well in most cases. The authors ascribed large discrepancies to inaccuracies in observed values (difficulties of purification) or to errors in assigned structures.

In their most recent paper, Berstein, Wilson, and Wallis adapt a similar method to the calculation of the rotation of derivatives such as acetates, benzoates and <u>m</u>-dinitrobenzoates (Tables III and IV) and apply the method to recent experimental results.

Table I

Substance Used In Obtaining Constant	Environmental Change Cholestane as Reference	$[M]_D$ ($CHCl_3$)	$[M]_D$ in Terms of Constants	Symbol and Value of Constant	
Cholestane		+ 9,160	C	C	+ 9,160
Coprostane	C_5-H (cis)	+ 9,430	C + B	B	+ 270
Coprostanol	C_3-OH (cis) C_5-H (cis)	+ 9,580	C + N_c	N_c	+ 420
Cholestanol	C_3-OH (cis)	+ 8,920	C + N_t	N_t	- 240
Epi-coprostanol	C_3-OH (trans) C_5-H (cis)	+12,260	C + E_c	E_c	+ 3,100
Epi-cholestanol	C_3-OH (trans)	+11,460	C + E_t	E_t	+ 2,300
Δ^4-Cholestene	F-4:5	+23,740	C + $D_{4:5}$	$D_{4:5}$	+14,580
Δ^5-Cholestene	F-5:6	-20,830	C + $D_{5:6}$	$D_{5:6}$	-29,990
$\Delta^{5:6,7:8}$ Cholestadiene	F-5:6,7:8	-46,740	C + $D_{5:6,7:8}$	$D_{5:6,7:8}$	-55,900

Table II

Substance	[M] in Terms of Constants	$[M]_D$ Calc	$[M_D]$ Obs.	$[\alpha]_D$ Calc	$[\alpha]_D$ Obs
Pregnane	C + B + Et_D	+ 4,700	+ 5,700	+16.3	+19.8
γ-sitostene	C + γ-Sit + $D_{5:6}$	-21,910	-23,640	-55.1	-59.4
Stigmastanol	C + N_t + Stig	+10,230	+10,190	+24.6	+24.5
Epi-stigmastanol	C + E_t + Stig	+12,770	+10,610	+30.7	+25.5

Table II (continued)

Ergostanol	C + N_t + Erg	+ 7,430	+ 6,230	+18.5	+15.5
Epi-ergostanol	C + E_t + Erg	+ 9,970	+ 5,670	+24.8	+14.1
γ-sitostanol	C + N_t + γ-Sit	+ 7,840	+ 7,650	+18.8	+18.4
β-sitosterol	C + $ND_{5:6}$ + Stig	-13,940	-14,950	-33.7	-36.1
β-ergostenol	C + $N_tD_{14:15}$ + Erg	+11,630	+ 8,080	+29.1	+20.2

Table III

Substances Used for Calculating Constants	$[M]_D$Deriv. - $[M]_D$sterol. Value of Constant	Symbol for Constant
Cholestanol and acetate	- 4,100	$A_{C_3}N_t$
Cholestanol and benzoate	0	$B_{z_3}N_t$
Stigmastanol and <u>m</u>-dinitrobenzoate	- 2,260	$DNB_{z_3}N_t$
Cholesterol and acetate	- 3,500	$Ac_3ND_{5:6}$
Ergosterol and acetate	+11,820	$Ac_3ND_{5:6,7:8}$

Table IV

Compound	Obs $[\alpha]_D$ ($CHCl_3$)	Calc. $[\alpha]_D$ using obs. $[M]_D$ of Sterol	Calc $[\alpha]_D$ using Calc'd. $[M]_D$ of Sterol
Stigmastanol acetate	+15.4	+13.3	+13.4
γ-sitostanol acetate	+ 9.0	+ 7.8	+ 8.2
Ergostanol acetate	+ 6.8 (av.)	+ 4.8	+ 7.5
α_1-sitostanol acetate	+39.4	+15.6	
ergostanol *m*-dinitrobenzoate	+13.5 (av.)	+ 6.6	+ 8.6
Stigmasterol acetate	-55.6	-51.3	
β-sitosterol acetate	-41.0	-40.5	-38.2
Brassicasterol acetate	-65.0	-64.7	-60.3

(all tables abridged)

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Reported by W. H. Kaplan
March 25, 1942

The three chief methods of converting carbonyl groups to methylene groups are the Wolff-Kishner reduction, the Clemmensen reduction, and high pressure hydrogenation over copper chromite. Other methods which have occasional value are reduction with sodium and alcohol, zinc and alkali, or hydriodic acid and red phosphorus.

The Wolff-Kishner Reduction (1,2,3,4,5)

The classical method of Wolff is to heat the hydrazone of an aldehyde or ketone with 5-10% sodium ethoxide at 180-200° in a sealed tube.

$$\rangle C{=}O + N_2H_4 \cdot H_2O \rightarrow \rangle C{=}NNH_2 \xrightarrow[180\text{-}200^\circ]{NaOEt} \rangle CH_2 + N_2$$

The semicarbazone can also be used. In this case, the first step is decomposition to the hydrazone, which then reacts as above. If there is insufficient heating, the reaction may stop at the hydrazone stage.

$$\rangle C{=}NNHCONH_2 \rightarrow \rangle C{=}NNH_2 + CO_2 + NH_3$$

Often it is not necessary to isolate the hydrazone. The compound can be heated at 180-200° with sodium ethoxide and a slight excess of hydrazine hydrate in absolute alcohol, and the reduction product is obtained in one step.

Because of the sealed tube feature of the reaction, only small batches of a compound can be reduced, usually about a gram at a time. Bigger batches can be reduced if a bomb is available. Ruzicka recommends the use of sodium benzylate instead of sodium ethylate. Benzyl alcohol has a high enough boiling point (205°) so that the reaction can be run in an open vessel. A commoner means of doing the reaction at ordinary pressure is due to Kishner. He found that heating a hydrazone with powdered potassium hydroxide accomplishes the desired result. One refluxes the carbonyl compound with hydrazine hydrate in alcohol, distils off alcohol, water, and excess hydrazine, and adds powdered potassium hydroxide to the residual oil. The mixture is then heated until nitrogen is evolved, usually at 160-180°.

The reaction gives 40-90% yields with all ordinary types of aldehydes and ketones, including those which also contain hydroxyl groups, carboxyl groups, or double bonds. The product is readily purified. The chief side reaction is azine formation caused by water being present.

$$\rangle C{=}NNH_2 + HOH \rightarrow N_2H_4 + \rangle C{=}O \xrightarrow{\rangle C{=}NNH_2} \rangle C{=}N{-}N{=}C\langle$$

The Clemmensen Reduction (5,6,7)

In this reaction, the compound to be reduced is treated with zinc amalgam and hydrochloric acid. The oldest method is merely to reflux the compound six or eight hours. It is often well to

dissolve the compound in toluene, particularly if it is a compound melting above the boiling point of the hydrochloric acid solution or if it is very insoluble. This has the advantage that since the compound is in the toluene layer, well removed from the zinc, little if any of the resinous by-product often accompanying the older method forms. Another modification employs alcohol, dioxan, acetic acid, or other solvent miscible with the hydrochloric acid solution in order to form a homogeneous reaction mixture.

An advantage of the Clemmensen reduction is its extreme simplicity. The amalgam is prepared by shaking the zinc a few minutes with a 5-10% mercuric chloride solution containing a little hydrochloric acid. This solution is poured off, 20-40% hydrochloric acid and the compound (with or without toluene) are added, and the whole is refluxed. No stirring is necessary because the hydrogen evolved provides good agitation. The amounts of zinc and acid are unimportant as long as there is an excess of each.

The reaction has not been used with much success on aldehydes except for a few phenolic ones. Low molecular weight aliphatic ketones go fairly well, higher ones with difficulty. Many alicyclic compounds, including various sterols, have been reduced successfully. Aromatic-aliphatic ketones, including the important β-aroylpropionic acids, are usually reduced in good yield. Aromatic ketones are undependable, some reacting smoothly and others not at all.

Most other functional groups are safe from attack. Exceptions are: the hydroxy groups of α-hydroxy acids and benzyl alcohols; halogens alpha to a carbonyl or carboxyl group; and the double bonds in pyrroles, isoquinolines, and α-β unsaturated ketones or acids.

Catalytic Hydrogenation (8,9,10)

This is a relatively recent method which has not had much practical application as yet, but it seems destined to grow in importance as time goes on. Its use is limited to carbonyl groups directly attached to an aromatic ring. The compound is hydrogenated at 150-200° under a pressure of 2000-3000 pounds over a copper chromite catalyst. Yields are usually 80% or better and an easily purified product results. Furan nuclei are completely reduced. Pyrrole and benzene rings are not ordinarily affected.

Fieser found that keto acids were best reduced as an aqueous solution of the sodium salt. In other cases alcohol or no solvent at all was used.

Low pressure hydrogenation over a platinum catalyst sometimes reduces a ketone to a hydrocarbon in low yield, the main product being a carbinol.

Sodium and Alcohol (11,12)

This is an excellent method for reducing diaryl ketones to the corresponding diaryl methanes. Other ketones usually stop at the carbinol stage, as, indeed, do a few diaryl ketones. The sodium reduces even hindered ketones not susceptible to the Clemmensen or Wolff-Kishner methods. The yields are usually good, but are sometimes low due to cleavage of the ketone.

One merely drops chunks of sodium into a boiling ethyl or amyl alcohol solution of the ketone. The hot reaction mixture is poured into water and the product is filtered or extracted with ether.

Zinc and Alkali (6)

This method often works well on keto acids and anthrones. The zinc is activated by shaking it with a copper sulfate solution. When the blue color disappears, this solution is poured off and a sodium hydroxide or ammonium hydroxide solution of the compound is then refluxed 12 to 48 hours. High melting compounds insoluble in alkali are dissolved in toluene.

Hydriodic Acid and Red Phosphorus

Sometimes ketones which are hard to reduce to the methane are readily converted to the carbinol. The carbinol can then be reduced by means of hydriodic acid and red phosphorus. The carbinol may be changed to the halide first.

A method occasionally used as a last resort is to convert the carbonyl group to a 1,1 dichloride with phosphorus pentachloride and then reduce the product with the above reagent. An even more desperate measure involves the ketone, hydriodic acid, red phosphorus, and a sealed tube at 200°.

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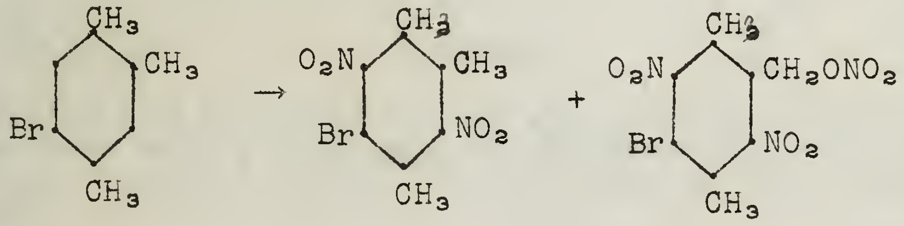
Reported by B. C. McKusick
March 25, 1942

THE REPLACEMENT OF ALKYL GROUPS DURING NITRATION

Halogens, methoxyl, carboxyl, sulfonic acid, and alkyl groups are all known to migrate or to be replaced by the nitro group during nitration in certain cases. The removal of an alkyl group was first noted in the case of thymol. In nitrating this compound with a mixture of nitric and sulfuric acids, 2,4,6-trinitro-m-cresol was obtained. Since that time many such replacements have been observed.

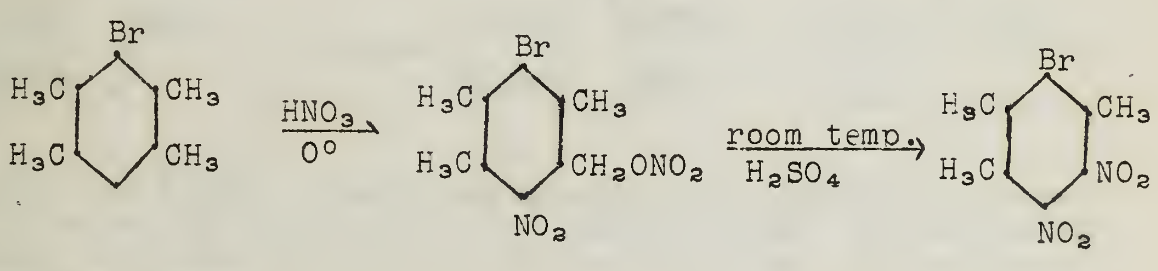
Although the methyl groups of toluene and of the xylenes have been replaced by the nitro group in electrolytic nitrations, such replacement is not the rule when more usual methods are used.

The trimethylbenzenes have never been known to lose a methyl group. If 5- or 6-bromopseudocumene is added to fuming nitric acid and concentrated sulfuric acid and heated, a reaction proceeds as follows:



The 3-bromopseudocumene does not give this result.

Continuing on to the tetramethylbenzenes, durene is not demethylated on nitration, but a nitric acid ester is obtained. If bromodurene is nitrated with fuming nitric acid or a mixture of nitric and sulfuric acids, not only can the nitric acid ester be formed, but on standing at room temperature in the presence of the acid, 3-bromo-5,6-dinitropsuedocumene is formed.



In connection with the effect of halide substitution on the ease of replacement of alkyl groups, Qvist has found that the more chlorine substituted on the ring of p-cymene, the easier the replacement of the isopropyl group by the nitro group.

Pentamethylbenzene and pentamethylbromobenzene act in an an analogous manner. The latter can have two methyl groups

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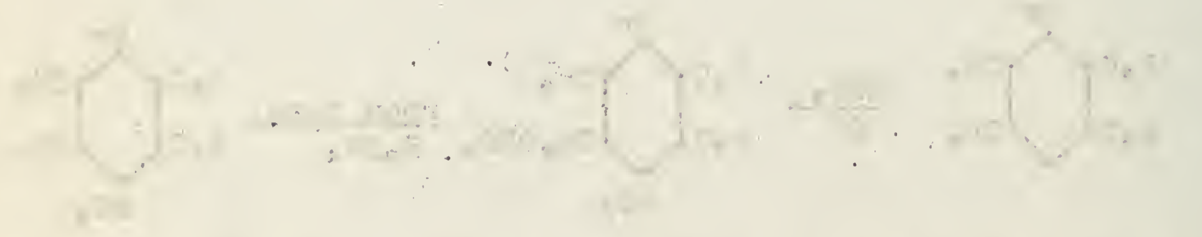

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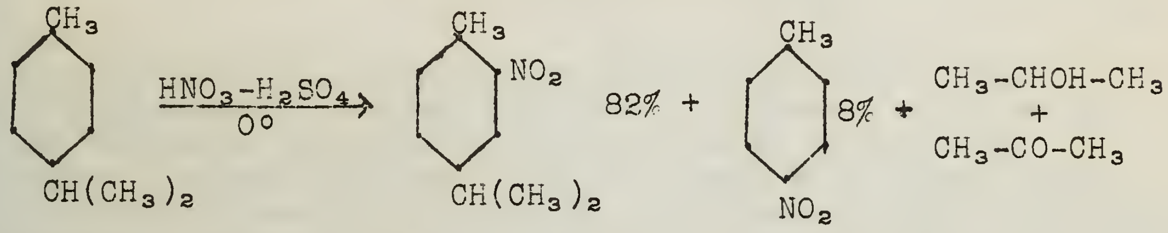
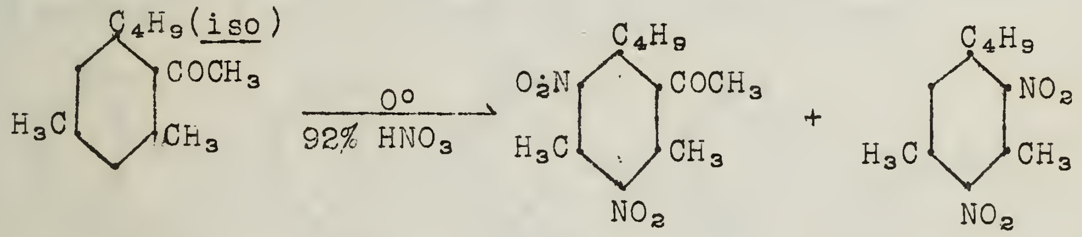
replaced by nitration with sulfuric and fuming nitric acids in chloroform at 0-5°.

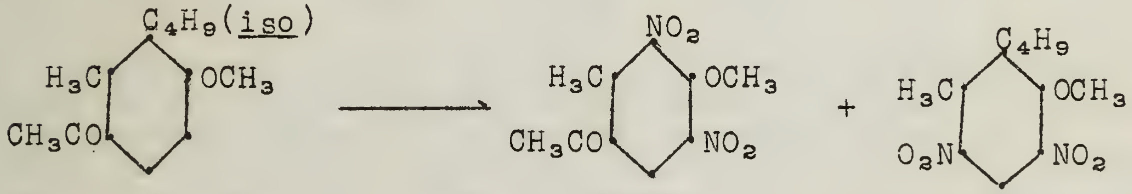
In those cases where dinitro compounds were produced by the elimination of one or two methyl groups, the ortho compound is formed to the exclusion of the para. In the case of hexa- and pentaethylbenzene, the para dinitro compound is formed to the exclusion of the ortho. The best method of preparing the p-dinitro, p-diamino, or p-quinone of tetraethylbenzene is through nitration of pentaethylbenzene rather than through nitration of 1,2,4,5-tetraethylbenzene.

The elimination of the isopropyl group was mentioned above. The latest reaction reported is the following:

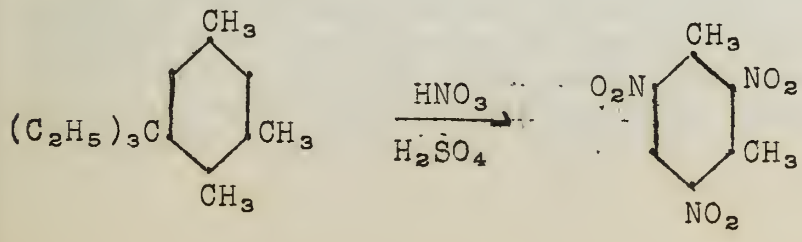


Barbier has done work on the elimination of butyl groups. He found that only groups meta to the first entering nitro group, were replaced. This is well shown by two examples from his work.





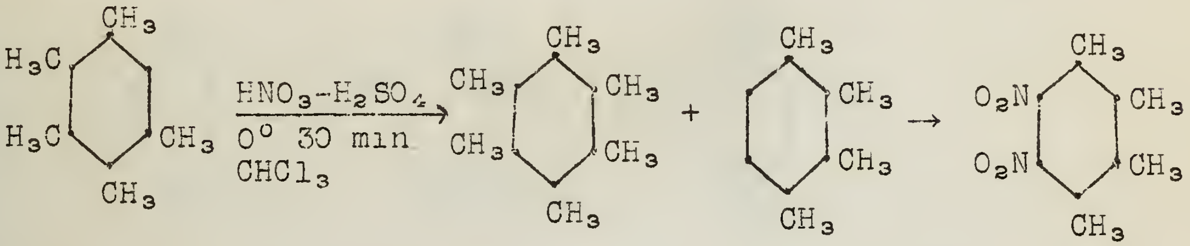
Amyl and heptyl substituent groups have also been observed to be affected by nitration of the benzene ring. In the latter compound, the heptyl group was eliminated but a nitro group did not take its place



MECHANISMS

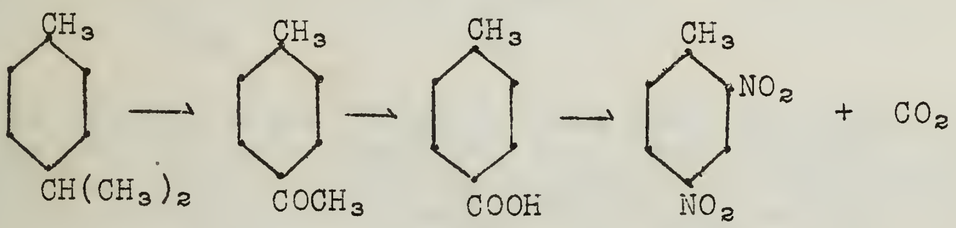
To date five mechanisms have been advanced to account for different instances of this type of replacement.

The first mechanism suggested was a Jacobsen Rearrangement mechanism.



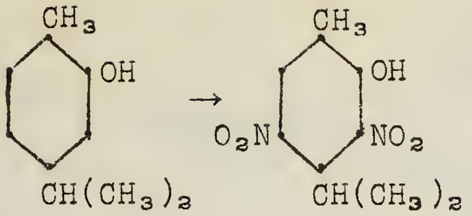
The yield in this particular nitration is 70% of the theoretical based on pentamethyl benzene. Such a yield would require that more than the prehnitene itself be nitrated. Therefore, a mechanism would still be required to explain the conversion of hexamethyl benzene to dinitroprehnitene. Furthermore, the low temperature and short time required for the reaction would permit only a negligible Jacobsen Rearrangement to take place.

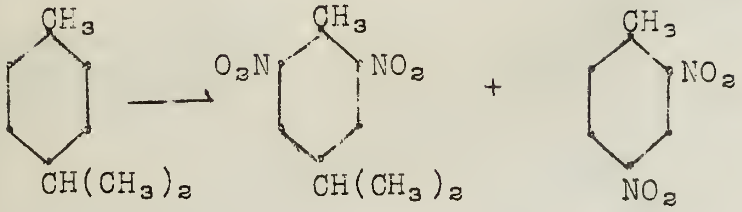
Another mechanism suggested is the one by Alfthan proposing that the alkyl group is first oxidized to a carboxyl and that this carboxyl is then replaced by the nitro group.

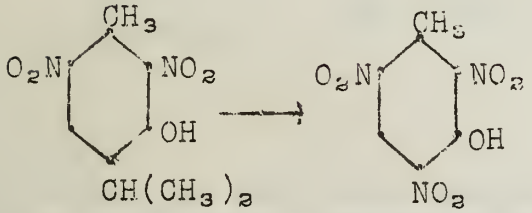


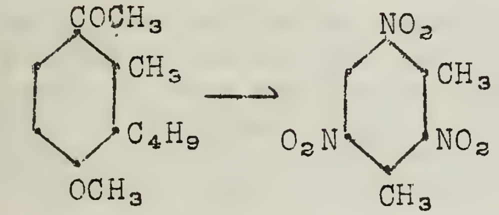
Alfthan was unable, however, to nitrate methyl-p-tolyl ketone to the nitrotoluene. It has been shown that in the case of polymethyl carboxylic acids, the carboxyl group can be almost quantitatively replaced. The objection to this mechanism lies in the fact that nitro replacement of a methyl group takes place in polymethyl compounds even under conditions which do not favor oxidation of the methyl group.

Barbier has advanced a mechanism which is in agreement with results of a large number of experiments. From his own work and from work on the elimination of halogens, carboxyl, alkoxy, and alkyl groups during nitration, Barbier suggested that elimination may take place when the alkyl group is meta to a nitro group which has entered the ring. This is in agreement with such results as the following.



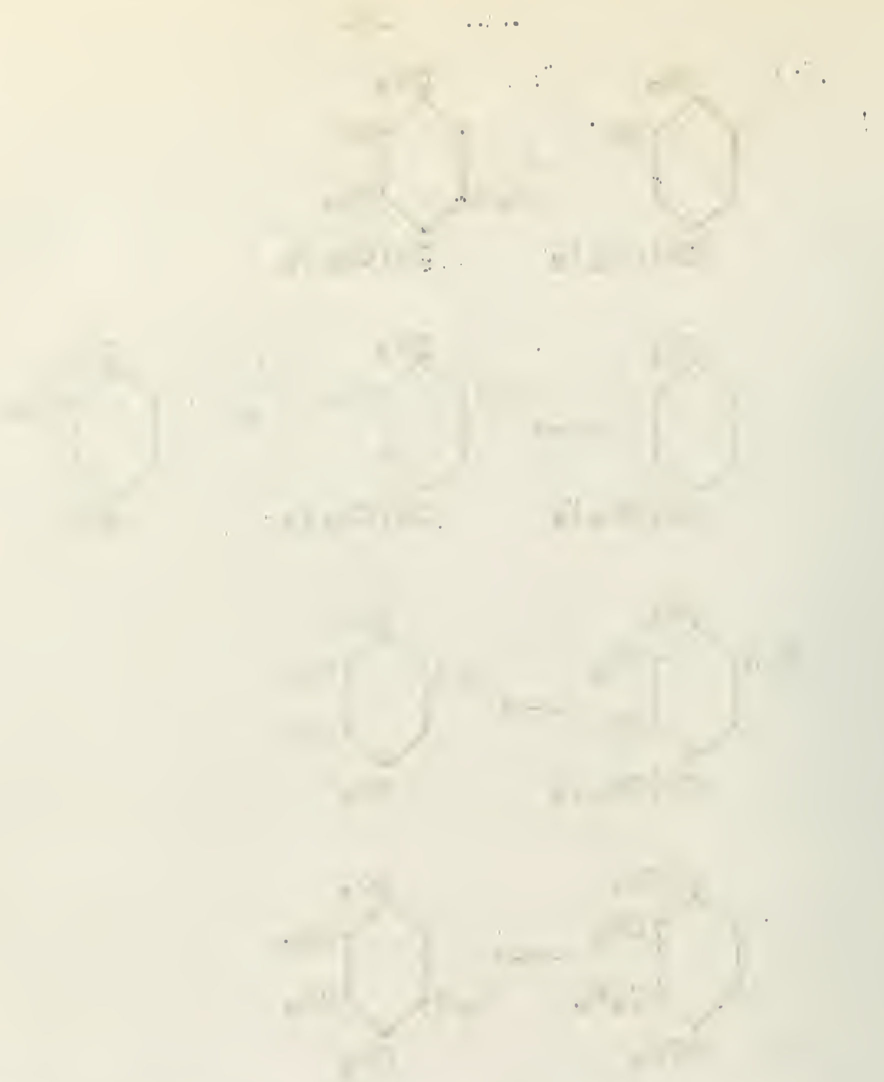






In certain cases, however, this mechanism fails to account for the products of a reaction, e.g., the nitration of p̲-cymene to give p̲-nitrotoluene and the nitration of chloro-substituted p̲-cymenes which have no free positions meta̲ to the isopropyl group. In the case of polymethyl and of polyethylbenzenes, the mechanism does not explain the facts at all. Pentamethylbenzene gives only the ortho̲ dinitro compound, and pentaethyl benzene gives only the para̲ dinitro compound.

From their work with polymethyl and polyethylbenzenes, L. I. Smith and coworkers have also advanced a mechanism. They propose that the first step is the nitration of the benzene ring if a position is open. After this nitration (or the first step if no position was open), another nitric acid molecule reacts to form a benzoyl alcohol ester of nitric acid. This ester then decomposes to give the nitrobenzene. The steps of the reaction are illustrated in the nitration of bromodurene shown above. This particular nitration constitutes one of the proofs that the reaction can take place in the steps postulated. Another similar nitration in which the intermediate products were isolated is the nitration of pentaethylbromobenzene.



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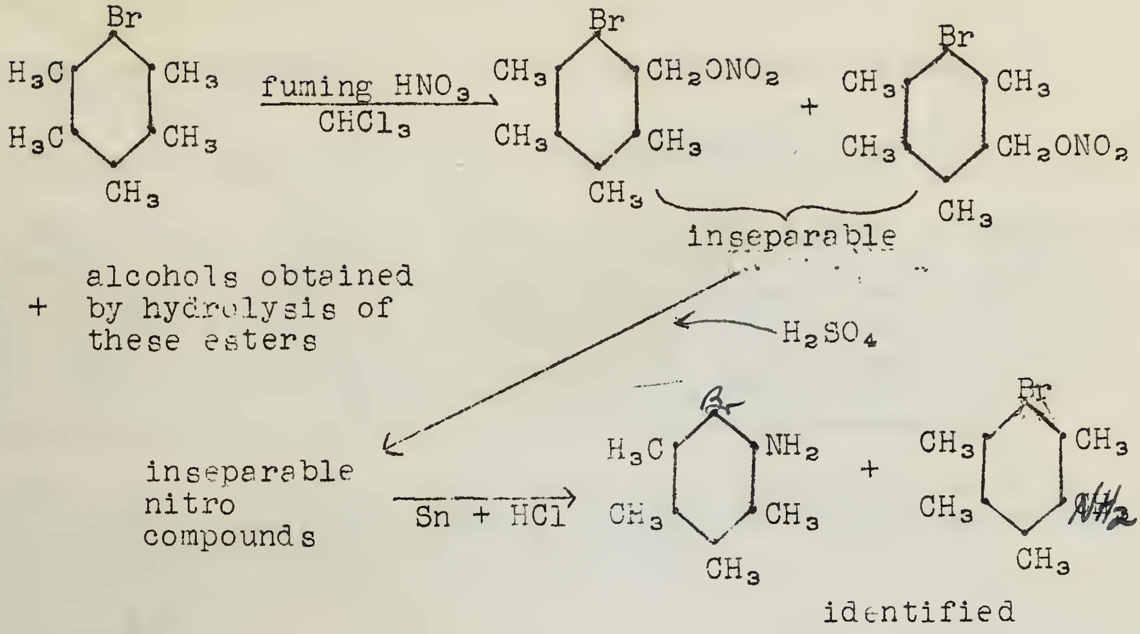

This mechanism obviously does not explain such orientation of reaction as shown in connection with Barbier's work.

The latest mechanism proposed suggests that the replacement occurs as a hydrolysis of the alkyl group from the benzene ring. The proponents of this mechanism state as their only support that p-cymene on treatment with nitric and sulfuric acids at zero degrees gives about 8% of p-nitrotoluene. Isopropyl alcohol can be recovered as well as acetone.

None of the above mechanisms by itself can account for all observed results. One mechanism, however, does not necessarily exclude all others and it is possible that a more complete mechanism may be formulated by incorporating elements from the different mechanism so far proposed.

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Reported by R. I. Meltzer
April 1, 1942

KETENE ACETALS

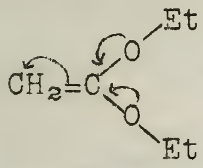
McElvain et al, University of Wisconsin

The most satisfactory method for preparing ketene diethylacetal is:

$$CH_2BrCH(OEt)_2 + KOC(CH_3)_3 \xrightarrow{\text{Butyl alcohol}} CH_2{=}C(OEt)_2 + HBr$$

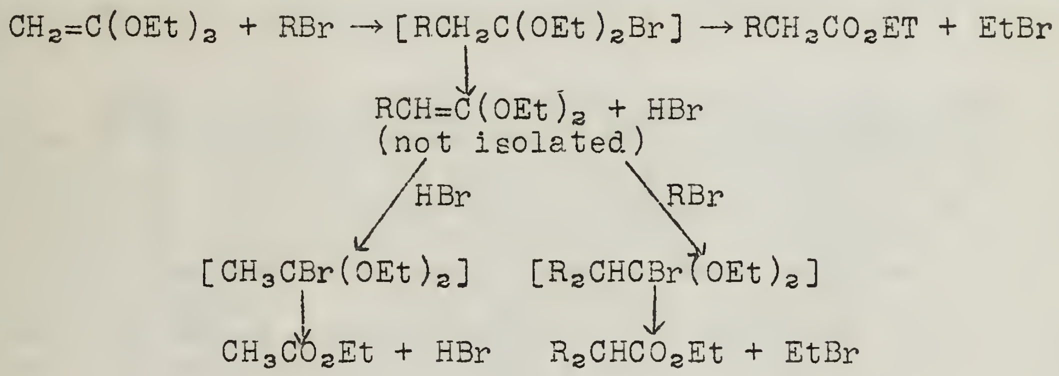
This ketene adds H_2O, EtOH, RCOOH, HX, C_6H_5OH, $CH_3COCH_2CO_2Et$, $CH_2(CO_2Et)_2$, NH_3, $C_6H_5NH_2$, $C_5H_{10}NH$, and H_2 across the double bond. In the presence of $CdCl_2$ dimers, trimers, and polymers have been produced and a head-to-tail structure has been indicated. These properties were discussed in this seminar last year. This report is concerned with the addition of active halogen compounds, acids, and α,β-unsaturated carbonyls.

Many of the additive reactions can be interpreted on the basis of the polarization that is characteristic of the heteroenoid structure of ketene diethylacetal:



1. <u>Addition of active bromides</u>.--The reaction with active bromides can be summarized as follows:

R = allyl or benzyl



$$CH_2{=}C(OEt)_2 + RBr \rightarrow [RCH_2C(OEt)_2Br] \rightarrow RCH_2CO_2ET + EtBr$$

$$[RCH_2C(OEt)_2Br] \rightarrow RCH{=}C(OEt)_2 + HBr \text{ (not isolated)}$$

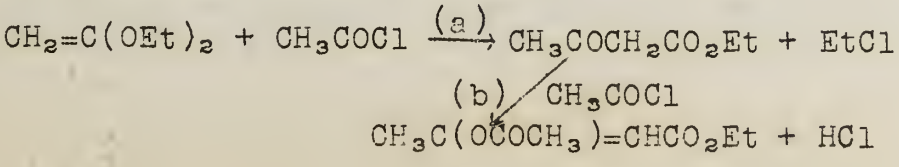
$$RCH{=}C(OEt)_2 \xrightarrow{HBr} [CH_3CBr(OEt)_2] \rightarrow CH_3CO_2Et + HBr$$

$$RCH{=}C(OEt)_2 \xrightarrow{RBr} [R_2CHCBr(OEt)_2] \rightarrow R_2CHCO_2Et + EtBr$$

$$RCH{=}C(OEt)_2 + EtOH \rightarrow RCH_2C(OEt)_3$$

Origin of the alcohol used in the last reaction is polymerization of some of the ketene.

2. <u>Addition of CH_3COCl</u>.--The products isolated indicate the following course of the reaction:

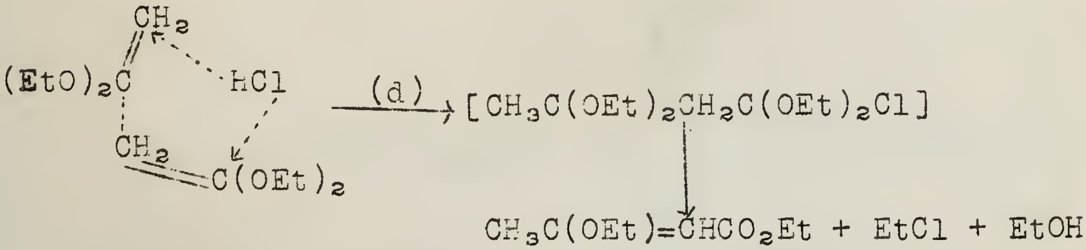


$$CH_2{=}C(OEt)_2 + CH_3COCl \xrightarrow{(a)} CH_3COCH_2CO_2Et + EtCl$$

$$CH_3COCH_2CO_2Et \xrightarrow[(b)]{CH_3COCl} CH_3C(OCOCH_3){=}CHCO_2Et + HCl$$

The hydrochloric acid formed by reaction (b) appears to react in two ways, (c) and (d). Notice that reaction (d) involves a 1,4 addition across two molecules of the acetal. This unusual reaction is substantiated by other additions.

$$CH_2{=}C(OEt)_2 + HCl \xrightarrow{(c)} CH_3CO_2Et + EtCl$$

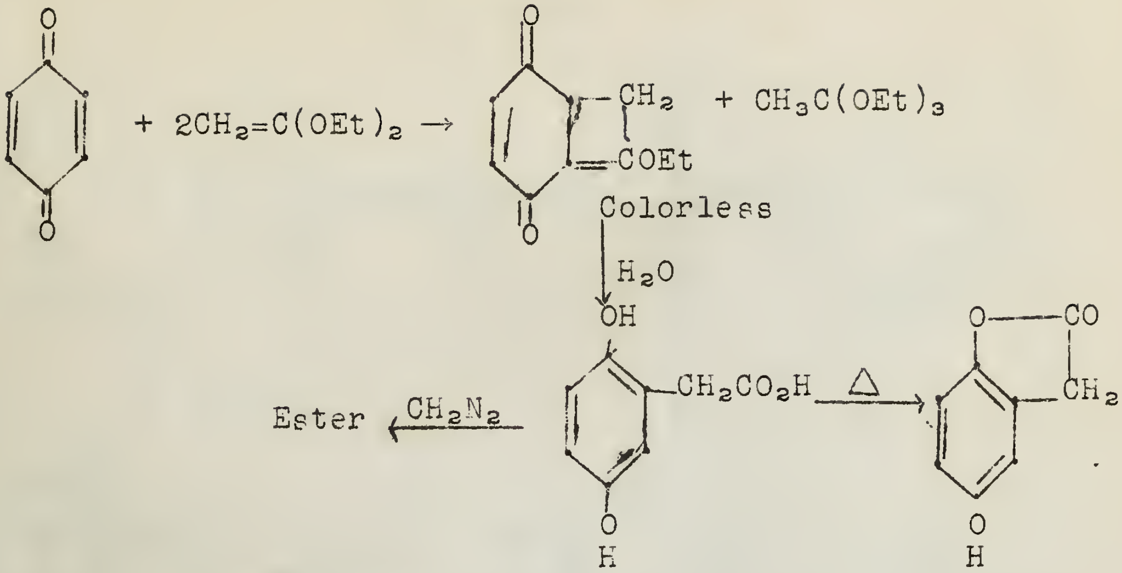


The validity of reaction (b) is indicated by the fact that acetoacetic ester is acetylated by acetyl chloride with either pyridine or ketene diethylacetal as reagents for the removal of HCl.

3. Addition of Acids.--1,4 addition of acids across two molecules is further indicated by similar addition to pure ketene diethylacetal by nine acids as, for example, hydrochloric, hydrobromic, trichloroacetic, formic, and acetic in yields of 10-38%. A minimum of acidity seems to be required for this type of addition since phenol and p-bromophenol added only as in (c) above but tribromophenol gave a 26% yield of the 1,4 product.

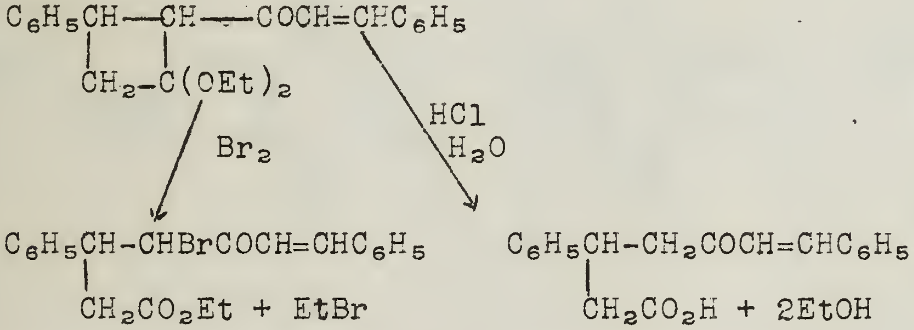
4. Addition to α,β-unsaturated carbonyl compounds.--The addition of maleic anhydride can also be considered as a 1,4 intermolecular addition in which the establishment of the 2,3 double bond of the ordinary type is replaced by a single bond that joins the two molecules of the ketene involved. The work with maleic anhydride is summarized on the flow sheet at the end of the abstract. Because the addition product, II, is insoluble in ether, only one mole of the anhydride adds in this solvent. In benzene II will add a second mole of maleic anhydride to give III. Chief support for the structure of II is its dehydrogenation to the known compound, 3,5-diethoxyphthalic anhydride, IV, and hydrolysis of IV to the corresponding phthalic acid. Heating either the anhydride or the acid with aniline gave the corresponding N-phenylphthalimide. Since reaction (b) involves the loss of an α-hydrogen, possible addition to dimethyl maleic anhydride was studied. No addition product was obtained.

Addition to quinone and proof of structure was as follows:



It is interesting to notice that I, a colorless compound, can be considered as a vinylog of an ester while quinone, from which it is derived, is vinylogous to the colored 1,2-diketones.

The addition to dibenzalacetophenone and proof of structure was as follows:



$$\begin{array}{l} C_6H_5CH-CH-COCH{=}CHC_6H_5 \\ \quad\ \ |\qquad\ | \\ \quad\ CH_2-C(OEt)_2 \end{array}$$

$$\xrightarrow{Br_2} \begin{array}{l} C_6H_5CH-CHBrCOCH{=}CHC_6H_5 \\ \quad\ \ | \\ \quad\ CH_2CO_2Et + EtBr \end{array}$$

$$\xrightarrow[H_2O]{HCl} \begin{array}{l} C_6H_5CH-CH_2COCH{=}CHC_6H_5 \\ \quad\ \ | \\ \quad\ CH_2CO_2H + 2EtOH \end{array}$$

Benzalacetophenone added in a similar manner.

<u>Bibliography</u>:

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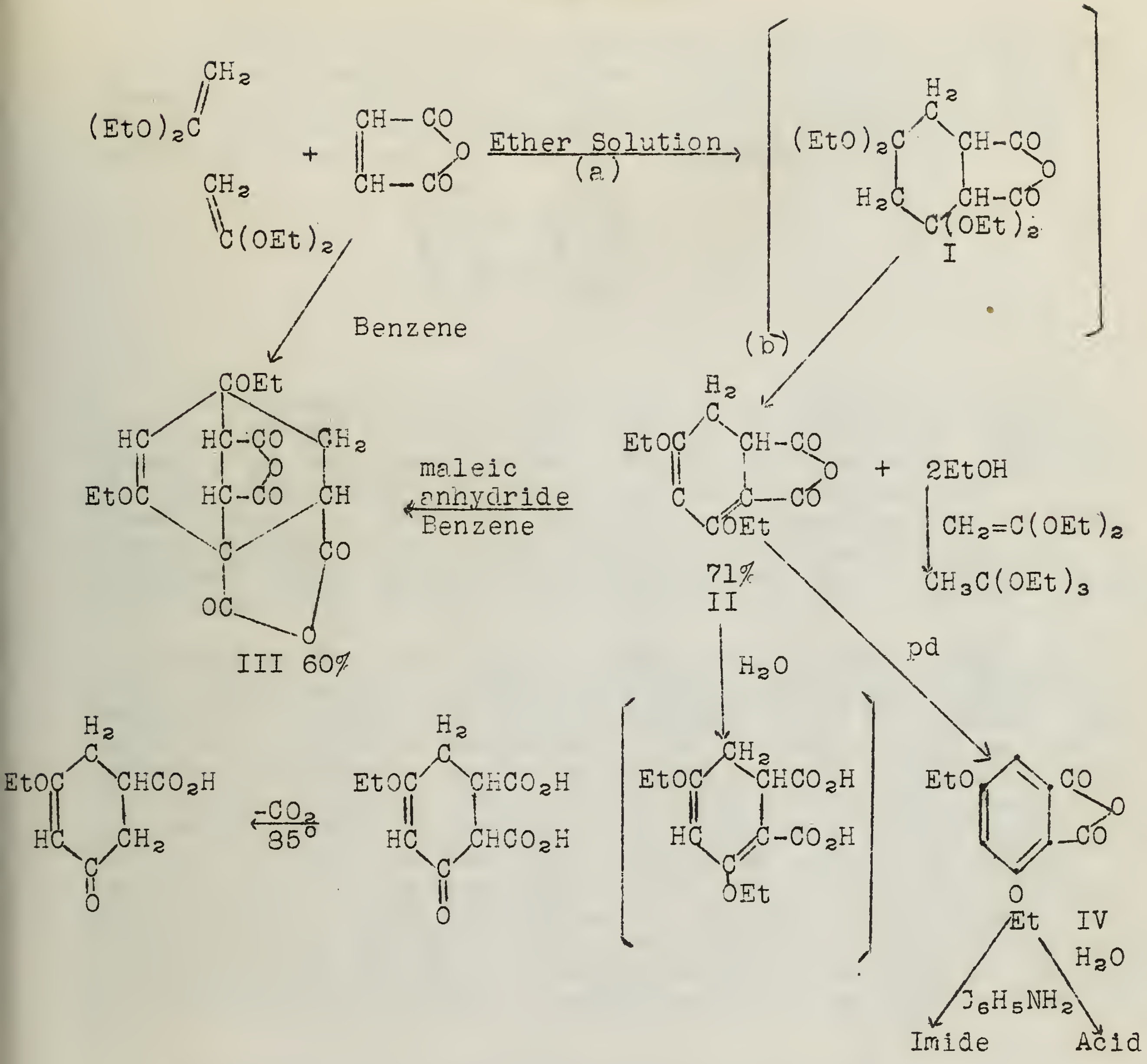
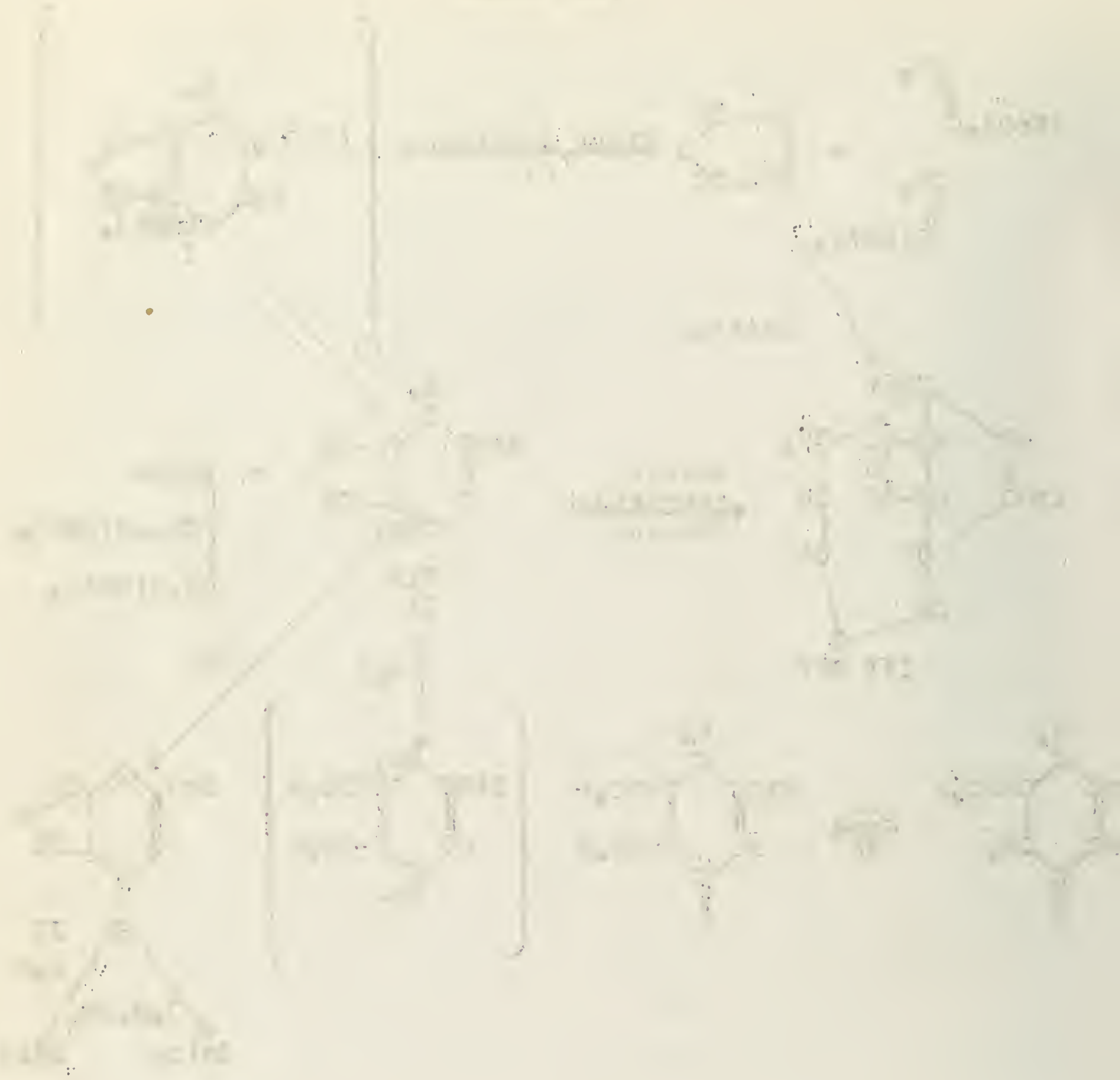
McElvain and Cohen, J. Am. Chem. Soc., 64, 260 (1942).

Reported by G. L. Schertz
April 1, 1942

FLOW SHEET


Ether Solution
(a)
I
Benzene
(b)
maleic anhydride
Benzene
III 60%
71%
II
+ 2EtOH
CH₂=C(OEt)₂
CH₃C(OEt)₃
pd
H₂O
-CO₂
85°
IV
H₂O
C₆H₅NH₂
Imide
Acid



BIPHENYLENE

Investigation of the interesting hydrocarbon biphenylene (I) has been carried out because it might contribute to the theory of aromatic chemistry as a whole, supplying in its central ring a possible cyclobutadiene system and at the same time affording an extreme case of the Mills-Nixon effect.

(I)

The history of its preparation is a series of repeated failures and of only one isolated and irreproducible success. Hosaeus, in 1893, carried out a Wurtz reaction with o-dibromobenzene, obtaining biphenyl as the only hydrocarbone. Niementowski, in 1901, on treating the diazonium salt of 2,2'-diaminobiphenyl with copper powder obtained carbazole. An attempted dehydration of 2-hydroxybiphenyl by Cullinane, Morgan, and Plummer also failed.

Dobbie, Fox, and Gauge in 1911 reported the preparation of the hydrocarbon in 100% yield by the prolonged action of freshly cut sodium on 2,2'-dibromobiphenyl in dry ether. They based their proof of structure of the compound $C_{12}H_8$ on the method of synthesis, on its oxidation in part to phthalic acid, and on its analysis. Reactions carried out on the compound indicated a strained central ring. Treatment with bromine opened the ring to give the starting material as well as a dibromo derivative of the hydrocarbon. The action of nitric acid on the hydrocarbon gave dibenzofuran, a dinitro, and a tetranitro derivative. Attempts by other investigators to repeat the work of Dobbie, Fox, and Gauge failed completely so that the existence of a compound containing a cyclobutadiene ring became questionable.

Lothrop has recently investigated biphenylene in connection with his work on the Mills-Nixon effect in aromatic compounds. His attempts to eliminate the bromine atoms from 2,2'-dibromobiphenyl by the action of hydrogen, lithium, sodium, and potassium were all successful, but the product in each case was biphenyl and a bromine containing oil. Magnesium reacted with only one of the bromine atoms and calcium, zinc, and pure copper had no effect. Cuprous oxide, however, gave a low yield of a new hydrocarbon which was volatile in steam and formed a scarlet picrate. Pyrolysis of biphenylene iodonium iodide with cuprous oxide gave a larger yield of the hydrocarbon with small amounts of 2,2'-diiodobiphenyl.

[illegible]

[illegible]

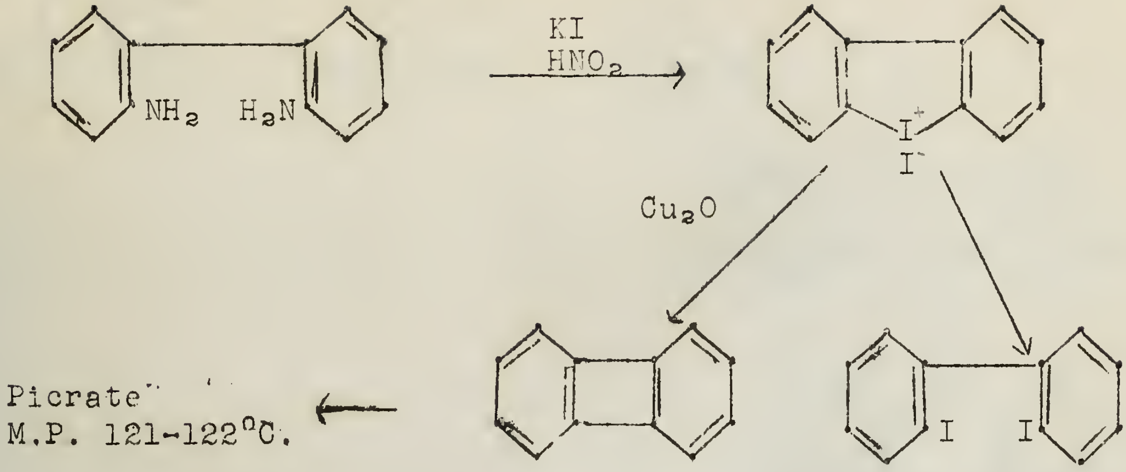
I

[illegible]

[illegible]

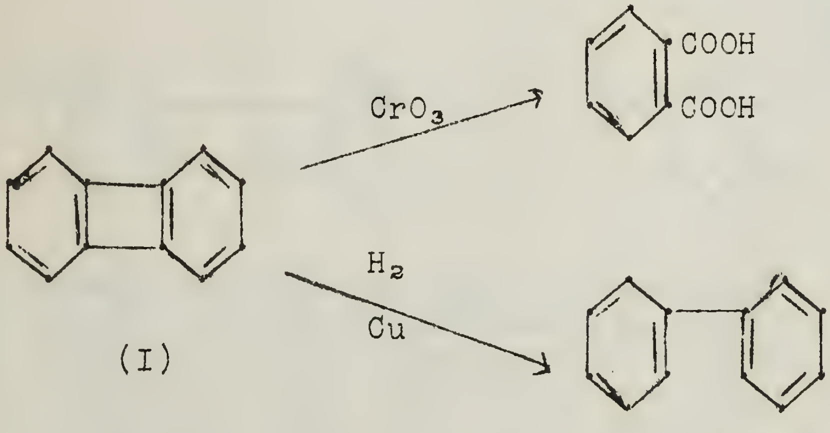
[illegible]

[illegible]

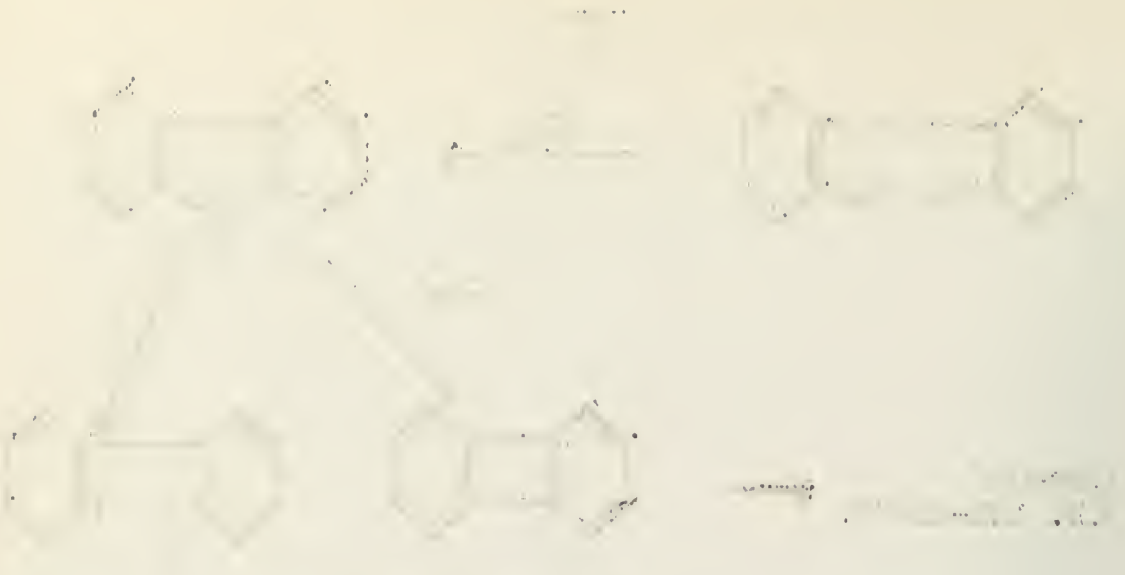


M.P. 109-110°C.
(I)

Molecular weight determinations in camphor and benzene agreed with the formula for biphenylene rather than for dimolecular coupling possibilities. Analyses of the hydrocarbon and its picrate agreed with the formula $C_{12}H_8$. Oxidation with chromic oxide gave phthalic acid, thus establishing the presence of ortho substitution. Reduction with hydrogen over red hot copper gave biphenyl.



2,7-Dimethylbiphenylene (II).--The 2,7-dimethyl derivative of biphenylene was prepared in the same manner in order to see whether the dehalogenation reaction could be considered general. This compound was prepared by two different routes, thus verifying the structural formula of biphenylene. This compound gave a deep crimson picrate.



[illegible]

[illegible]

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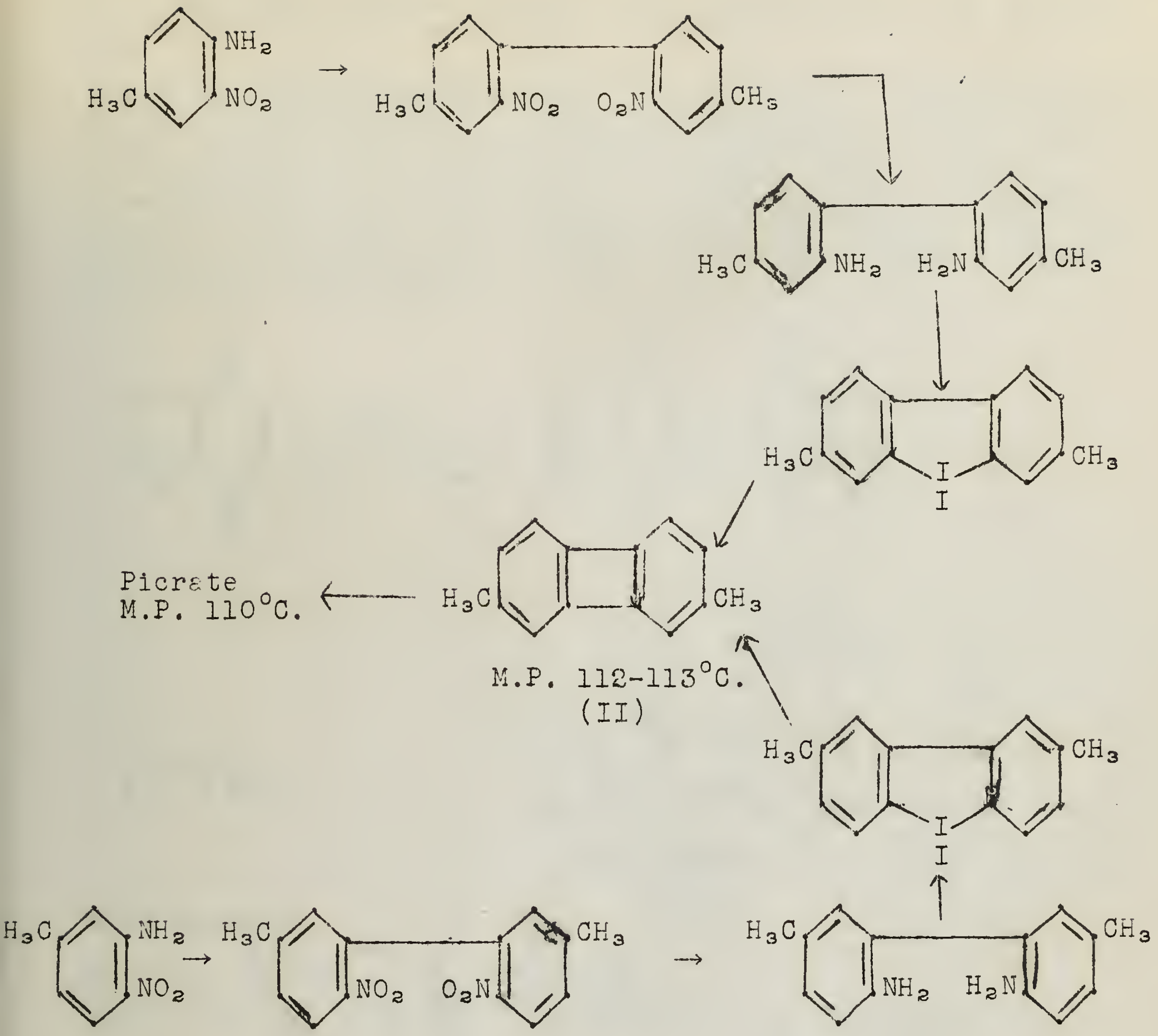
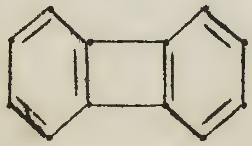
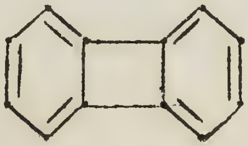
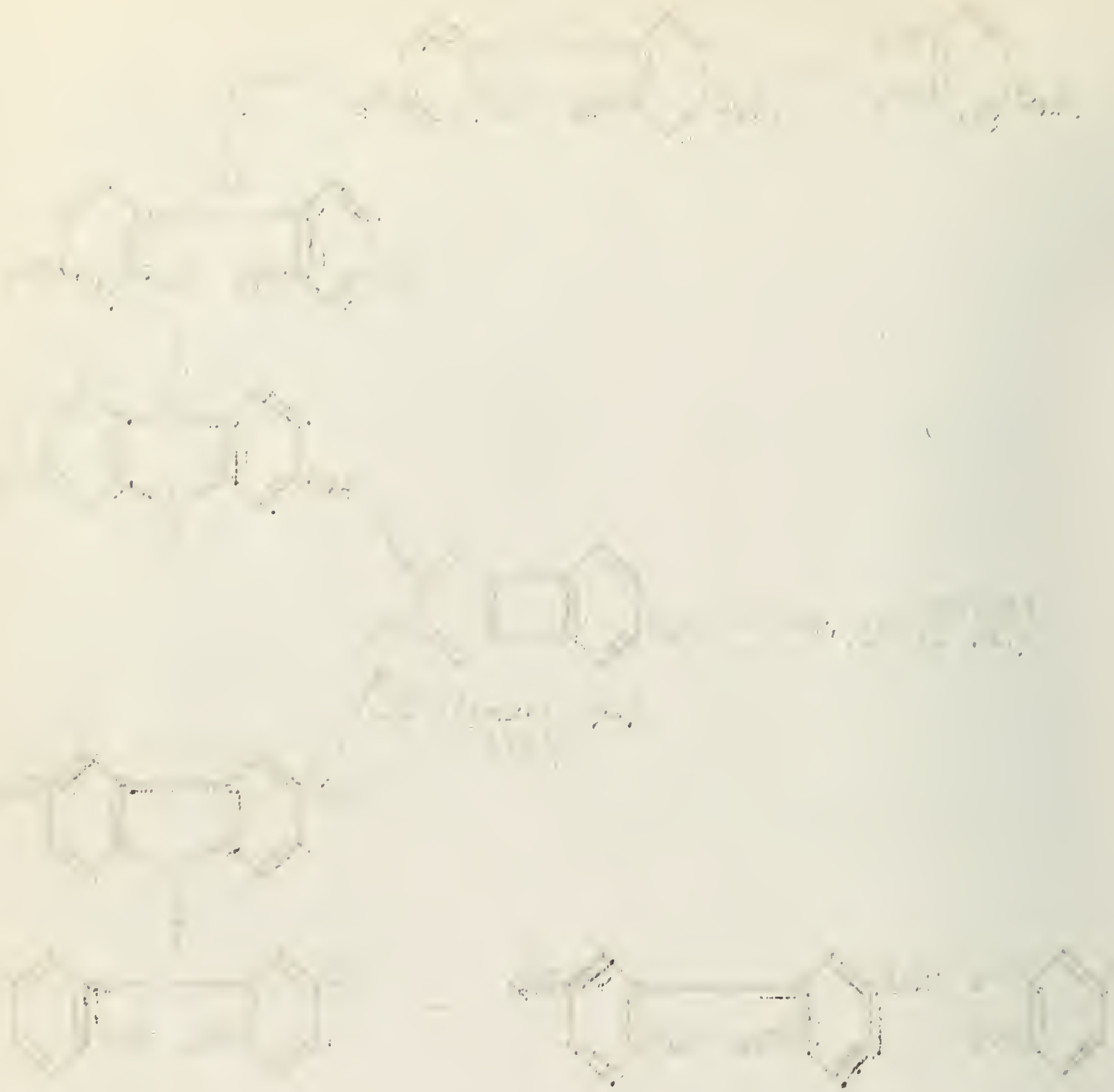


M.P. 112-113°C.
(II)

The formulas written for these hydrocarbons are supported by the complete agreement found between prediction and experiment, and suggest that the cyclobutadiene ring may not be too strained to exist if fused with two benzene rings (A), or that the Mills-Nixon effect may operate to stabilize the molecule in a less strained cyclobutane form (B), or that the coplanar molecule has considerable resonance energy.


(A)

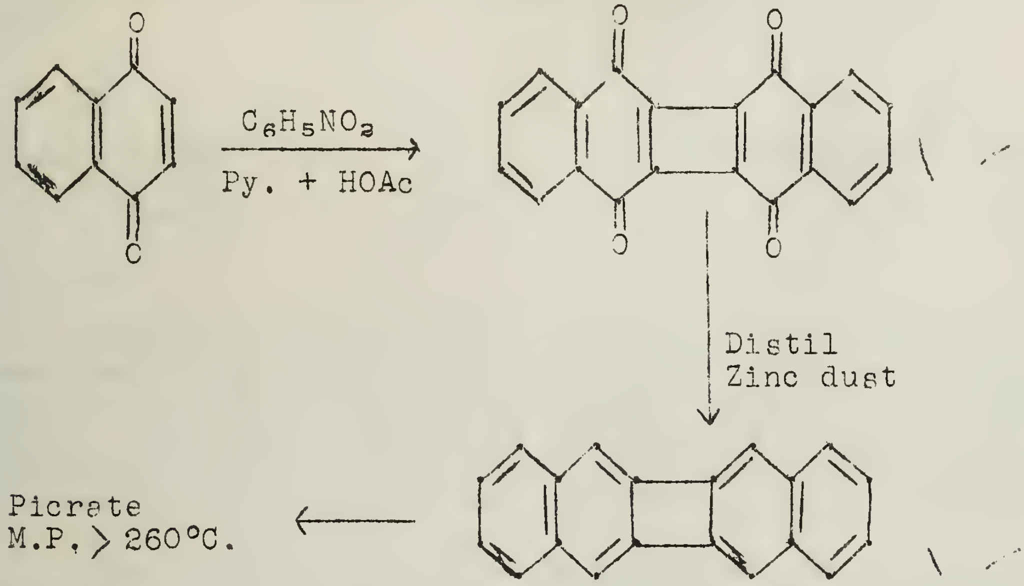

(B)



[illegible]

The fused system of three rings would seem to be confirmed by the formation of such stable and highly colored picrates.

2,3,2',3'-Binaphthylene (III).--The only other compound reported in the literature having a structure similar to biphenylene is 2,3,2',3'-binaphthylene, prepared by Rosenhauer, Braun, Pummerer, and Riegelbauer in connection with polymerization studies. 1,4-Naphthoquinone was condensed to form 2,3,2',3'-binaphthylene-1,4,1',4'-diquinone which, on distillation with zinc dust, gave 2,3,2',3'-binaphthylene in 15.5% yield. This compound formed an unstable red picrate.



M.P. 365°C.

(III)

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Dobbie, Fox, and Gauge, J. Chem. Soc., 99, 683, 1615 (1911); 103, 36 (1913).
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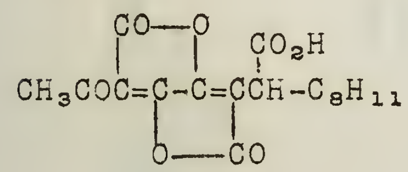
Mascarelli and Gatti, Gazz. chim. ital., 63, 654, 661 (1933).
Cullinane, Morgan, and Plummer, Rec. trav. chim., 56, 627 (1937).
Rosenhauer, Braun, Pummerer, and Riegelbauer, Ber., 70, 2281 (1937).
Lothrop, J. Am. Chem. Soc., 63, 1187 (1941).
Hammett, "Physical Organic Chemistry", McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 19

Reported by F. W. Spangler
April 8, 1942

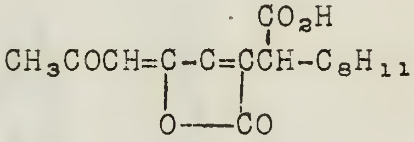
THE CONSTITUTION OF USNIC ACID

Usnic acid is a very widely distributed naturally occurring compound which has been found in more than 70 lichens. Usnic acid was isolated first by Rochleder and Heldt in 1843 and has been the subject of much investigation since that time. Widman in 1902 first advanced a formula for usnic acid (I), based on the observations of several earlier workers and on the results of his own degradation experiments. In 1927 Shopf, Heuck and Kraus turned up several new experimental facts which made it obvious that Widman's interpretation of his data was erroneous.



$$\begin{array}{l} \;\;\;\;\;\;\;\;CO{-}O\;\;\;\;CO_2H \\ CH_3COC{=}C{-}C{=}CCH{-}C_8H_{11} \\ \;\;\;\;\;\;\;\;\;O{-}CO \end{array}$$

I



$$\begin{array}{l} \;CO_2H \\ CH_3COCH{=}C{-}C{=}CCH{-}C_8H_{11} \\ \;\;\;\;\;\;\;\;\;\;\;\;\;\;\;\;\;O{-}CO \end{array}$$

II

Kraus demonstrated by a Zerewitinoff determination that usnic acid had three active hydrogens. Formula I would indicate only two if we assume complete enolization of the methyl ketone group. Moreover, one of the characteristic degradation products, decarbousnic acid, represented by Widman as II, was demonstrated by Shopf and Heuck to be an acidic enol, not a carboxylic acid.

The structure of usnic acid is most readily elucidated from its degradation products which are quite numerous. The more important are set forth in Chart I for future reference.

The decomposition through usnetic acid to usnetol has been of greatest aid in elucidating the nuclear structure of usnic acid and its derivatives. The structure of usnetol follows from the following degradations and synthesis.

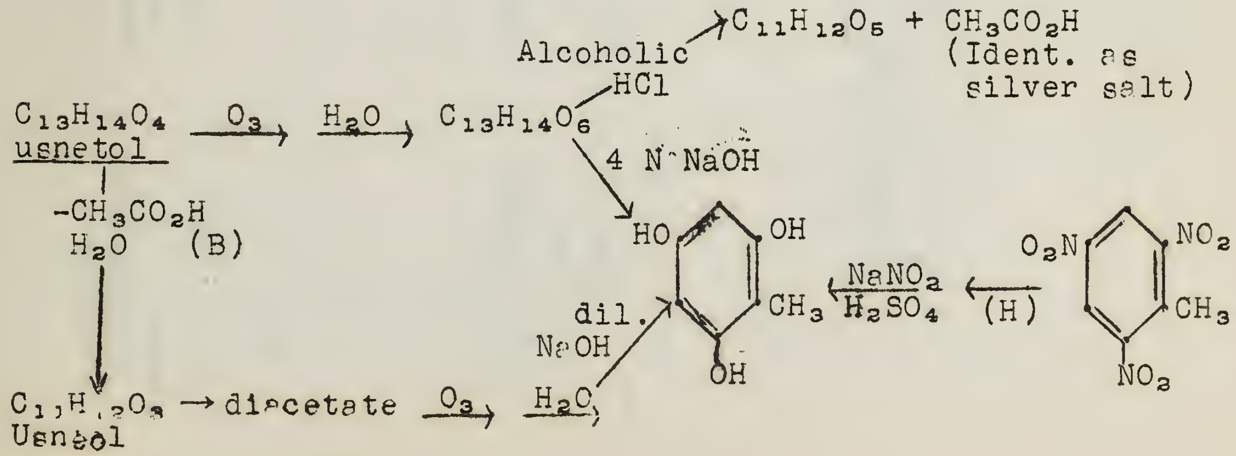
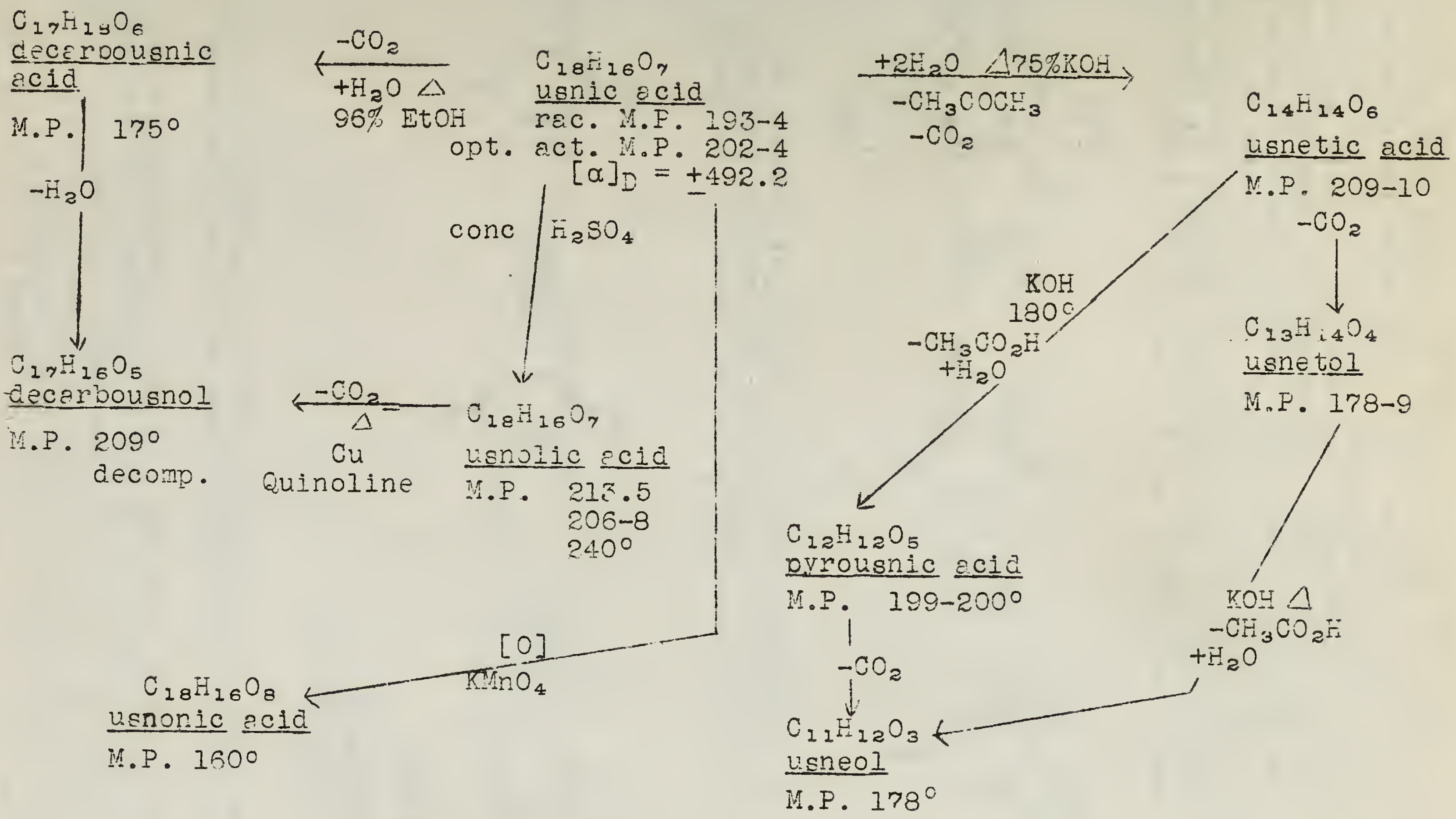
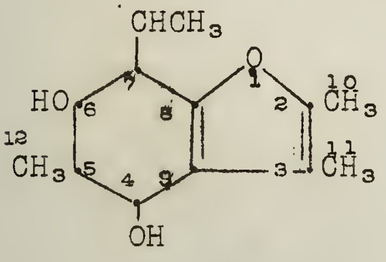


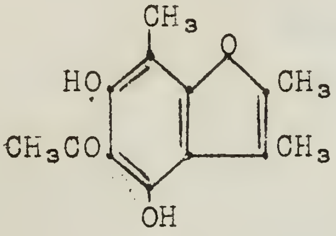
CHART I


$C_{17}H_{18}O_6$
decarbousnic acid
M.P. 175°
$-H_2O$
$C_{17}H_{16}O_5$
decarbousnol
M.P. 209°
decomp.
$-CO_2$
$+H_2O$ △
96% EtOH
$C_{18}H_{16}O_7$
usnic acid
rac. M.P. 193-4
opt. act. M.P. 202-4
$[\alpha]_D = \pm 492.2$
conc H_2SO_4
$-CO_2$
△
Cu
Quinoline
$C_{18}H_{16}O_7$
usnolic acid
M.P. 213.5
206-8
240°
[O]
$KMnO_4$
$C_{18}H_{16}O_8$
usnonic acid
M.P. 160°
$+2H_2O$ △75%KOH
$-CH_3COCH_3$
$-CO_2$
$C_{14}H_{14}O_6$
usnetic acid
M.P. 209-10
$-CO_2$
$C_{13}H_{14}O_4$
usnetol
M.P. 178-9
KOH
180°
$-CH_3CO_2H$
$+H_2O$
$C_{12}H_{12}O_5$
pyrousnic acid
M.P. 199-200°
$-CO_2$
$C_{11}H_{12}O_3$
usneol
M.P. 178°
KOH △
$-CH_3CO_2H$
$+H_2O$

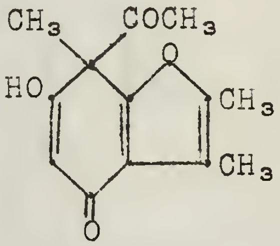
The isolation of the product $C_{13}H_{14}O_6$ after decomposition of the ozonide indicates a double bond in a ring system since no carbon atoms were lost. The ease with which this compound is hydrolyzed by alcoholic hydrochloric acid indicates an oxygen containing five or six memebered ring with one double bond. The alternative route of degradation (B̲) indicates one acetyl group, not present as an acetate. Structures III, IV or V would satisfy all of the above facts. The isolation of acetic acid and the compound $C_{11}H_{12}O_5$ by acid hydrolysis of the ozonolysis product rules out an isomeric structure with an ethyl group and a hydrogen at C-2 and C-3 instead of two methyls as shown.



III

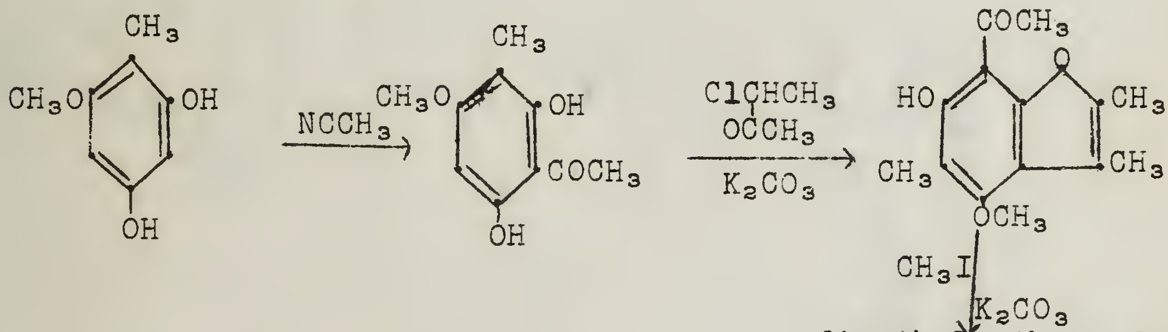


IV



V

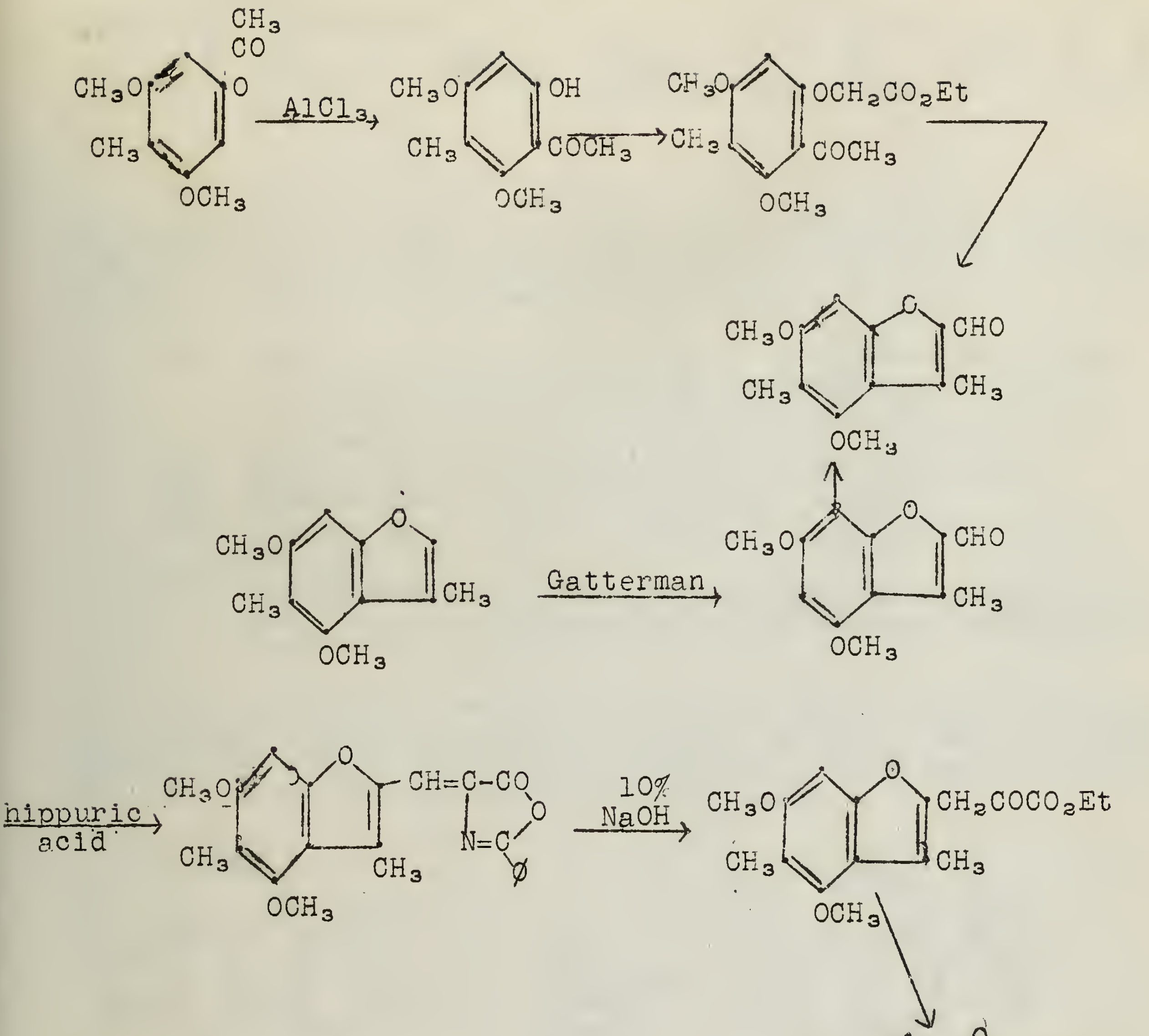
The correct structure (III) was established by the following synthesis of Curd and Robertson after they had established the structure of usneol as being III minus the acetyl group at C-7.

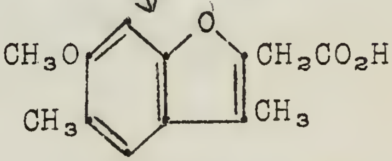


dimethyl ether of III
(no depression on mixed M.P.)

The establishment of the orientation of these substituted phloroglucinols is due to work by Robertson et al.

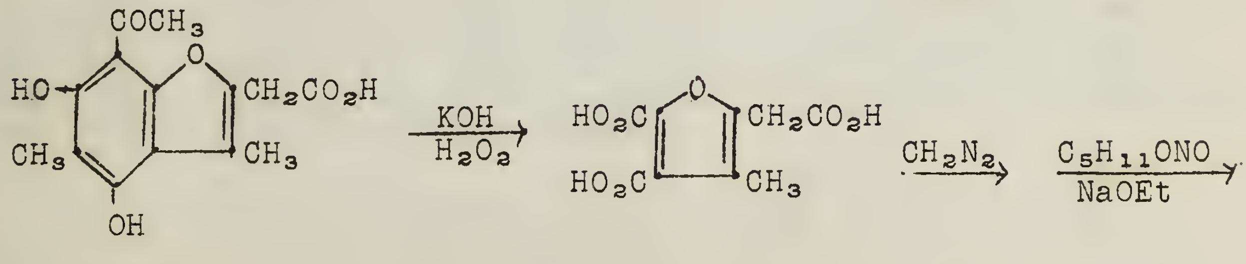
Usnetic acid must then have the same nuclear structure as usnetol with the addition of CO_2 to make the carboxyl group shown to be present. Because of the synthetic difficulties, usnetic acid itself was not synthesized but the structure of pyrousnic acid dimethyl ether (VI) arising from usnetic acid by loss of the nuclear acetyl group at C-7 has been established as follows.



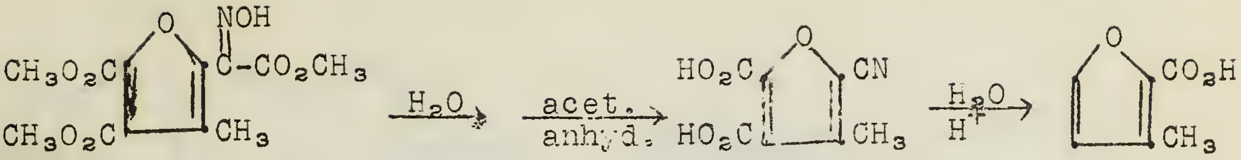


VI

This structure for usnetic acid (VII) has been confirmed by Asahina by the following degradation.



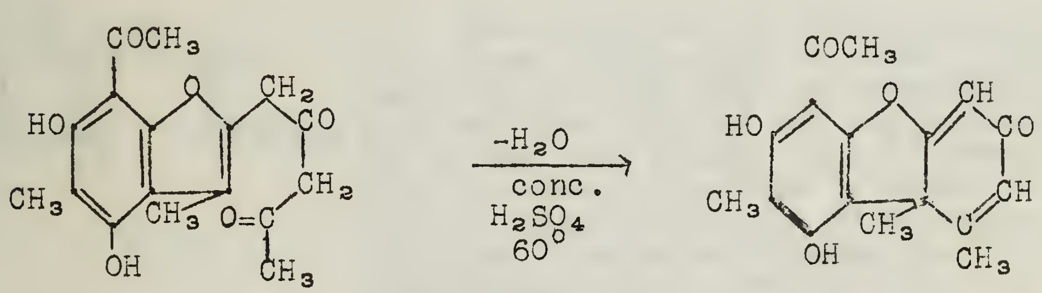
VII



The structure of decarbousnic acid has not been established by synthesis but there can be little doubt as to its structure. The following most pertinent facts must be considered in formulating a structure for decarbousnic acid.

(1) Ketonic reagents indicate a 1,3 diketone structure.
  a. Hydroxylamine gives an isoxazole derivative.
  b. Phenylhydrazine gives a pyrazole derivative.
  c. Semicarbazide gives a pyrazole derivative.
(2) Mono-di-tri-tetraacetyl derivatives are known.
(3) Decarbousnic acid is optically inactive.
(4) Decarbousnic acid is a dibasic acid containing no CO_2H group.
(5) Ozonolysis of diacetyl decarbousnic acid shows that decarbousnic acid has the characteristic substituted benzofurane nucleus.

The only formula which seems to fit all of these criterea and a mass of minor experimental facts is VIII. Experimental evidence for the side chain structure will be given in connection with the ozonolysis of diacetyl usnic acid.

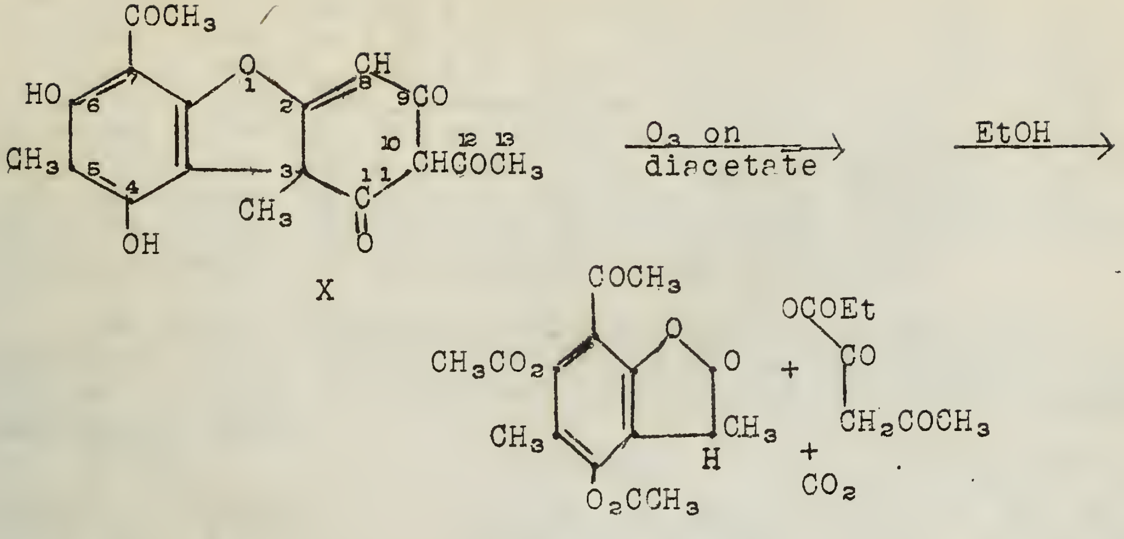


VIII

IX

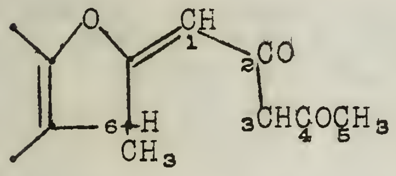
The cyclization of decarbousnic acid VIII to decarbousnol IX (postulated) was without precedent until Foster and Robertson (and Healy) showed that this type of reaction did occur and that the compounds so obtained were entirely analogous to decarbousnol and usnolic acid of similar structure.

The structure of usnic acid (X) itself is fairly well established without presupposing the structure of decarbousnic acid and the evidence thus obtained supports the proposed formula for decarbousnic acid. Shopf and Ross performed the following degradation.



XI XII

The isolation of the lactone XI and of acetoneoxalic ester XII clearly indicates the presence of the double bond as shown and consequently of the benzodihydrofuran nucleus, and the 1,3 diketonic nature of the side chain. The fact that all the degradation products of usnic acid have been demonstrated to be substituted benzofurans does not constitute a serious drawback since the reversion to the more stable conjugated form is to be logically expected when possible.



XIII

The nature of the degradation products indicates the partial structure XIII of usnic acid which must be considered as derived from XIII by the replacement of 2H by the -CO- group. One of these H atoms must be from C_6 in XIII in order to stabilize the dihydrocoumarin ring system. There are then four possibilities left; a) By enolization and removal of the H at C_2 a sixmembered cyclic lactone results, b) by the same process at C_4 an 8 membered cyclic lactone results, c) by removal of an H at C_3 a 6 membered cyclic triketone (X) results, d) by the same process at C_5 an 8 membered cyclic triketone results. Both lactone formulas are readily ruled out since the 1,3 diketonic system characteristic of usnic acid as well as decarbousnic acid would not be present. Of the remaining two the choice of the 6 membered triketone is preferred on two grounds, first the more ready occurance of 6 membered rings, but this choice is even more strongly indicated since 1,3, diketones in a ring structure do not show the characteristic behaviour of straight chain 1,3 diketones with ketonic reagents (i.e. dihydroresorcinol).

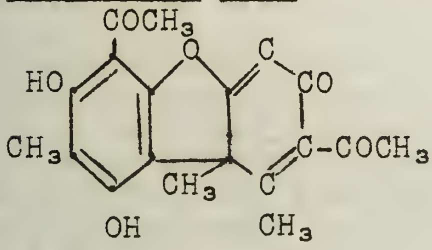
The isolation of the [illegible] alkaloid [illegible] degradation [illegible]

[illegible]

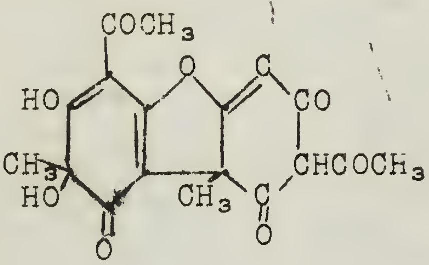
[illegible]

The structure advanced has some debatable features. It is necessary to assume that the linkage between C_3 and C_{11} in X is rather weak since in all the degradations of usnic acid this linkage is broken. This does not seem to be an unjustifiable assumption since the linkage under question is to a highly hindered quaternary C atom which is under the combined influence of several activating groups. The only serious objection without explanation is the easy racemizeability of usnic acid. This again may be considered as a property of the weakness of the C_3-C_{11} linkage but no adequate analogy is known.

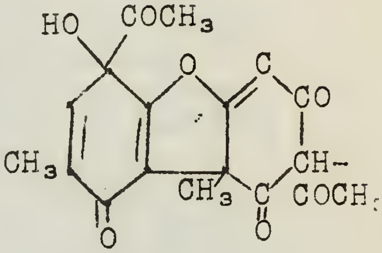
Two other compounds in Chart I which have had only a "nuisance value" in the elucidation of the structure of usnic acid are usnolic acid XIV and usnonic acid XV a or b (structures postulated only).



XIV



XVa



XVb

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Reported by C. W. Theobald, April 8, 1942

ALKYL CARBONATES IN SYNTHETIC CHEMISTRY

Wallingford, Homeyer, and Jones--Mallinckrodt Chemical Works

Until very recently the alkyl carbonates have found little application in synthetic organic chemistry. Within the last year a series of investigations have been carried out which have greatly extended the uses of this class of compounds and have made easily available certain types of compounds which before were difficult if not impossible to prepare.

I. Synthesis of Malonic Esters.

The first attempt to condense alkyl carbonates with esters was made by Wislicenus in 1887; he was unsuccessful, and concluded that alkyl carbonates were not suitable for Claisen type condensations. However, since then, several investigators (Lux, Nelson and Cretcher, Skinner) have succeeded in carrying out such condensations by use of sodium or potassium in benzene or ether solution, producing malonic esters in low yield. Wallingford and his associates point out that the difficulties encountered were due to the following factors: (1) The ester may condense with itself, (2) The metallic sodium and potassium used readily decompose alkyl carbonates, (3) A metal alcoholate in alcohol solution may not be used as a condensing agent because it has been shown by Cope and McElvain and by Connor that substituted malonic esters undergo alcoholysis according to the equation

$$RCH(COOEt)_2 + EtOH \xrightarrow{NaOEt} RCH_2COOEt + (EtO)_2CO$$

The Mallinckrodt workers have demonstrated that this reaction may be reversed. By applying the principles of mass action, they have developed a process which is quite general, and have prepared a large number of malonic esters by condensing alkyl carbonates with a variety of esters. The general reaction is

$$R'CH_2COOR + (RO)_2CO + MOR \rightarrow [R'C(COOR)_2]M + 2ROH$$

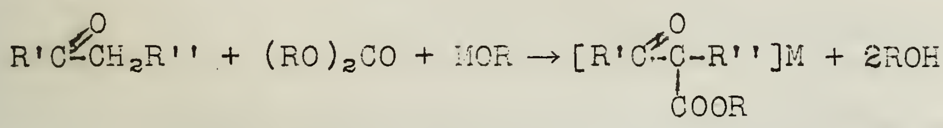
The essentials of the new procedure are (1) the use of a large excess of alkyl carbonate as a reaction medium or solvent and (2) removal of alcohol from the reaction mixture by distillation. The validity of the applied principles of mass action is shown by the fact that an 86% yield of diethyl phenylacetate was obtained from ethyl phenylacetate and diethyl carbonate whereas Nelson and Cretcher have shown that these two will not condense at all in an alcoholic solution of NaOEt.

It was noted in the carbalkoxylation of some of the lower aliphatic esters that an appreciable amount of alkylation occurred. For example, from ethyl <u>n</u>-butyrate and diethyl carbonate there was obtained diethyl diethylmalonate along with the expected diethyl ethylmalonate. This observation led to the work which will be mentioned later in this report.

Scope and Limitations: It may be seen from Table I that the carbalkoxyl group is introduced most readily into aryl substituted acetic esters; but the reaction also goes well with aliphatic esters up to ethyl stearate. The α-carbon must contain two hydrogen atoms. If the β-carbon of the ester is tertiary the yield is low. The esterified alcohol of the ester and of the carbonate should be the same.

II. Synthesis of β-Keto Esters.

It would be expected that if alkyl carbonates will condense with esters that they should condense with ketones, and such is the case. The general reaction may be represented as follows:



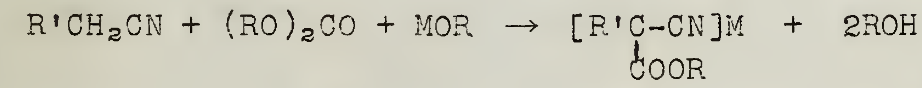
$$R'\overset{O}{\overset{\|}{C}}-CH_2R'' + (RO)_2CO + MOR \rightarrow [R'\overset{O}{\overset{\|}{C}}-\underset{COOR}{\underset{|}{C}}-R'']M + 2ROH$$

Wallingford and his associates have used the same procedure used in the carbalkoxylation of esters and have prepared a large number of β-keto esters from various ketones and alkyl carbonates; a few of these are shown in Table II. Such a general method of organic synthesis is particularly important since the products are one of the most reactive classes of organic compounds.

Limitations: Ketones which are so active that they condense with themselves or polymerize are not satisfactory. Unreactive ketones such as camphor give low yields. Forcing by heating above 100° is undesirable because of ether formation by the reaction between alcoholate and alkyl carbonate at that temperature. O-Acylation takes place with certain ketones (cyclohexanone, for example) giving the carbonic ester of the enol form of the ketone.

III. Synthesis of α-Cyano Esters.

Alkyl carbonates may be condensed with nitriles to give the corresponding α-cyano esters as follows:



$$R'CH_2CN + (RO)_2CO + MOR \rightarrow [R'\underset{COOR}{\underset{|}{C}}-CN]M + 2ROH$$

Although several authors have reported the condensation of diethyl carbonate with phenylacetonitrile by various procedures, none indicated that this reaction was applicable to other types of nitriles. The Mallinckrodt workers have employed the technique used with esters and ketones for nitriles and have prepared a variety of α-cyano esters, some of which are shown in Table III.

Alcohol introduced with the metal alcoholate and that produced in the condensation is removed by distillation. Cope and Hancock have shown that cyano esters undergo an alcoholysis

analogous to that of malonic esters, producing an alkyl carbonate and a nitrile. Therefore, here again the distillation of the alcohol favors completion of the reaction according to the mass law and prevents cleavage of the reaction product.

Scope and Limitations: Vinylacetonitrile and *p*-nitrophenylacetonitrile appear to be too active and result in tars. α-Phenylbutyronitrile failed to react. A general statement may now be made in regard to the use of alkyl carbonates for carbalkoxylation:

(1) The method is general for esters, ketones, and nitriles having two *alpha* hydrogen atoms.

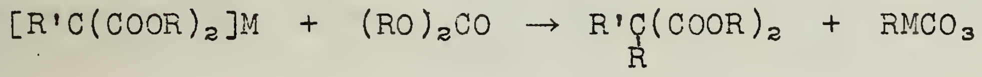
(2) Na and K alcoholates are equally effective as condensing agents; Mg and Al alcoholates are not effective.

(3) Primary alkyl carbonates react satisfactorily; the use of secondary carbonates is not practical.

(4) Lower members of each series give poor yields of carbalkoxylated products either because the low boiling point prevents forcing the reaction, or because of polymerization.

IV. Alkylation of Malonic Esters by Alkyl Carbonates.

It was noted in the synthesis of malonic esters with alkyl carbonates that as a side reaction the sodio derivative was alkylated; this was found to take place in the following manner:



$$[R'C(COOR)_2]M + (RO)_2CO \rightarrow R'\underset{\substack{|\\R}}{C}(COOR)_2 + RMCO_3$$

This is a new type of alkylation; organic esters, including alkyl carbonates, are known to act as alkylating agents in the Friedel-Crafts reaction, but metal enolates have not been alkylated by esters of organic acids before.

The alkylation may be carried out on the metal derivative of a malonic ester, or a mono-substituted acetic ester may be used as starting material since carbalkoxylation gives the malonic derivative. The reaction is carried out by refluxing at temperatures of 125-175° with a large excess of the alkyl carbonate.

Scope and Limitations: Ethyl, butyl, isobutyl, isoamyl, and benzyl groups have been introduced into a variety of esters (see Table IV). Secondary carbonates are poor alkylating agents. Malonic ester itself reacts to form tricarbalkoxymethane. If the first substituent is a *s*-aliphatic group, alkylation is poor. Best results are obtained if the alkyl carbonate, metal alcoholate, and malonic ester all have the same alkoxy group. Preliminary experiments with substituted α-cyanoacetic esters and acetoacetic esters gave negative results.

V. Alkyl Carbonates as Solvents for Metallation and Alkylation.

In the foregoing synthesis it will be noted that the product is in the form of the metal derivative. Not only is it easy to alkylate directly by means of the alkyl carbonate solution itself, but it has now been shown that alkyl carbonates are superior solvents for alkylation by means of alkyl halides.

Previously, esters containing a branched substituent such as the s-butyl group have been very difficult to alkylate further by the usual procedure using sodium alcoholate in alcohol. This has been ascribed to the incomplete formation of the sodio derivative according to the equation

$$R'CH(COOR)_2 + NaOR \rightleftharpoons [R'C(COOR)_2]Na + ROH$$

The alkyl halide when added reacts to a large extent with the NaOR present. Furthermore, as previously noted, the alkylated malonic ester formed may undergo alcoholysis. Both of these conditions may be avoided by using alkyl carbonates as reaction media. The above reaction may be forced to completion by removing the alcohol by distillation; the metal derivative may then be treated with the alkylating agent in alkyl carbonate solution with no danger of alcoholysis.

The alkylation of malonic, β-keto, and α-cyano esters were carried out in alkyl carbonate solution with alkyl halides as the alkylating agent. Excellent yields were obtained as shown in Table V. It may be seen that ethyl and allyl groups are readily introduced into diethyl s-butylmalonate whereas this is practically impossible in alcoholic solution. The method has also enabled Wallingford to introduce two s-alkyl groups as substituents, which has hitherto been impossible.

As would be expected, slight alkylation may take place by action of the alkyl carbonate, hence it is desirable to use as reaction medium the alkyl carbonate corresponding to the group to be introduced.

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Reported by R. M. Roberts, April 15, 1942.

TABLE I.

Starting Material	Product	% Yield
Ethyl acetate	Diethyl malonate	25
	Tricarbethoxymethane	10
Ethyl butyrate	Diethyl ethylmalonate	45
	Diethyl diethylmalonate	10
Ethyl stearate	Diethyl cetylmalonate	50
Ethyl phenylacetate	Diethyl phenylmalonate	86
Ethyl *p*-methylphenylacetate	Diethyl *p*-methylphenylmalonate	65

TABLE II.

Starting Material	Product	% Yield
Diethyl ketone	Ethyl β-keto-α-methylvalerate	20
Methyl isobutyl ketone	Ethyl β-keto-δ-methylcaproate	60
Di-*n*-propyl ketone	Ethyl β-keto-α-ethylcaproate	45
Acetophenone	Ethyl benzoylacetate	60
Dibenzyl ketone	Ethyl α,γ-diphenylacetoacetate	45
Propiophenone	Ethyl α-benzoylpropionate	37
	Ethyl 1-phenyl-1-propen-1-yl carbonate	25
Cyclohexanone	Ethyl 1-cyclohexen-1-yl carbonate	20

TABLE III.

Starting Material	Product	% Yield
Acetonitrile	Ethyl cyanoacetate	10
Butyronitrile	Ethyl α-cyanobutyrate	40
Capronitrile	Ethyl α-cyanocaproate	54
Stearonitrile	Ethyl α-cyanostearate	75
Phenyl acetonitrile	Ethyl α-cyanophenylacetate	78

TABLE IV.

Starting Material	Product	% Yield
Ethyl butyrate	Diethyl diethylmalonate	36
Diethyl ethylmalonate	Diethyl diethylmalonate	54
Ethyl δ-methylcaproate	Diethyl ethylisoamylmalonate	45
Diethyl *s*-butylmalonate	Diethyl *s*-butylethylmalonate	Poor
Dibutyl ethylmalonate	Dibutyl butylethylmalonate*	42
Dibutyl cetylmalonate	Dibutyl butylcetylmalonate*	83
Fluorene	Butyl 9-butyl-9-fluorenecarboxylate	45

TABLE V.

Starting Material	Alkyl Halide	Product	% Yield
Diethyl ethylmalonate	EtI	Diethyl diethylmalonate	83
Diethyl ethylmalonate	_i_-AmBr	Diethyl ethylisoamylmalonate	75
Diethyl _s_-butylmalonate	EtBr	Diethyl _s_-butylethylmalonate	95
Diethyl _s_-butylmalonate	AllylBr	Diethyl _s_-butylallylmalonate*	86
Diethyl _s_-butylmalonate	_s_-BuBr	Diethyl di-_s_-butylmalonate*	25

* New compound

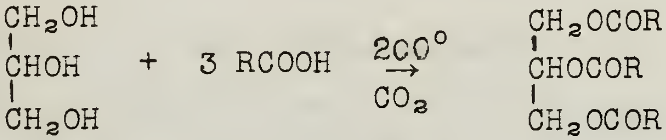
GLYCEROL DERIVATIVES

The specificity of triglycerides for various animal species has been shown. Structurally similar animals frequently elaborate similar kinds and proportions of fatty acids combined as triglycerides. Likewise it has been shown that the more complex fatty acid mixtures are found in fats of the simplest forms of plant and animal life, and a gradual simplification is observed both in structure and number of component acids on ascending the evolutionary scale of development. With recent developments in molecular distillation and fractional crystallization it is reasonable to assume that more work will be done in the near future in isolation and purification of the triglycerides, and their structures will have to be checked by syntheses.

Accordingly, some workers have been engaged in fundamental research on triglycerides. A brief summary of their successes in synthetic problems constitutes this seminar report.

Synthesis of Simple Triglycerides

No special procedures need be resorted to in preparing simple triglycerides. Merely heating three moles of the acid with one mole of glycerol yields the tri-ester in nearly quantitative amounts. The slight oxidation which occurs at such temperatures may be avoided by use of an inert atmosphere such as N_2, CO_2, or SO_2.

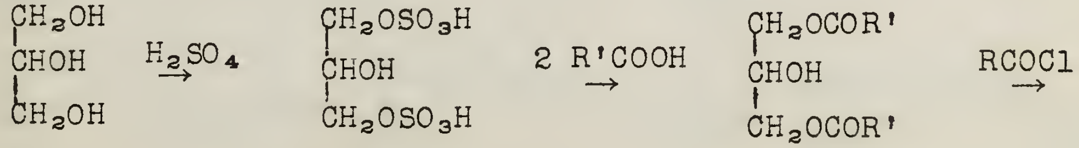


$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} + 3\ RCOOH \xrightarrow[CO_2]{200^\circ} \begin{array}{l} CH_2OCOR \\ | \\ CHOCOR \\ | \\ CH_2OCOR \end{array}$$

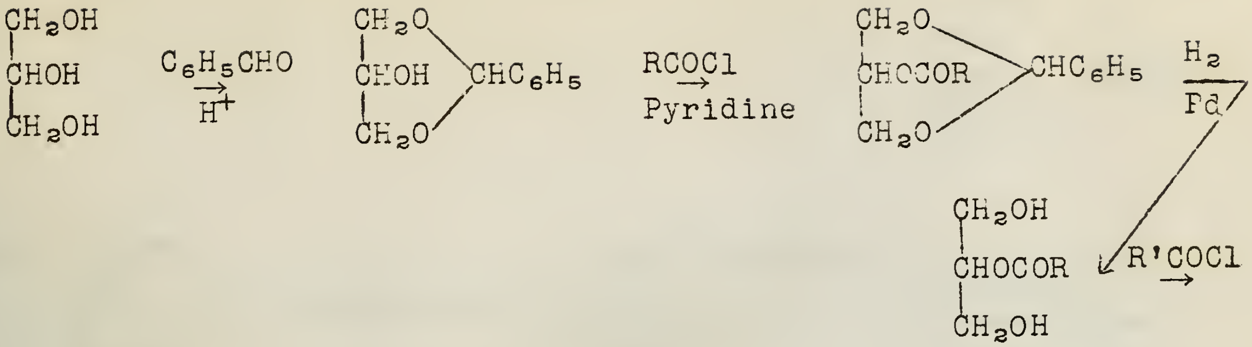
Syntheses of Symmetrical Mixed Triglycerides

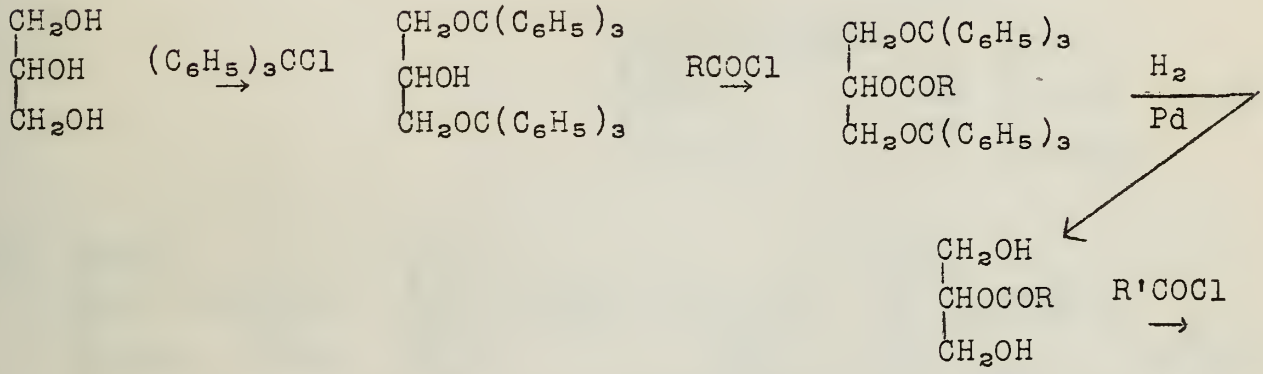
The preparation of mixed triglycerides cannot be effected by the above method, i.e., by heating in either order a mole of glycerol with a mole of one acid and then with two moles of another acid. Such a reaction yields a variety of triglycerides, and the usual methods of fractional crystallization and distillation can not be applied with any degree of success in attempting to purify any one product.

The following methods have been used:



$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} \xrightarrow{H_2SO_4} \begin{array}{l} CH_2OSO_3H \\ | \\ CHOH \\ | \\ CH_2OSO_3H \end{array} \xrightarrow{2\ R'COOH} \begin{array}{l} CH_2OCOR' \\ | \\ CHOH \\ | \\ CH_2OCOR' \end{array} \xrightarrow{RCOCl}$$





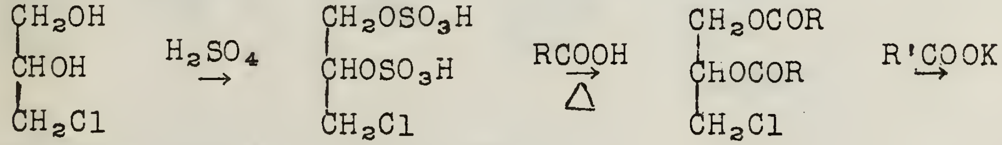
The final product in each of the above three equations is the same symmetrical triglyceride. The latter method is of more recent date and appears to be successful for a wider variety of glycerides.

Syntheses of Unsymmetrical Mixed Triglycerides

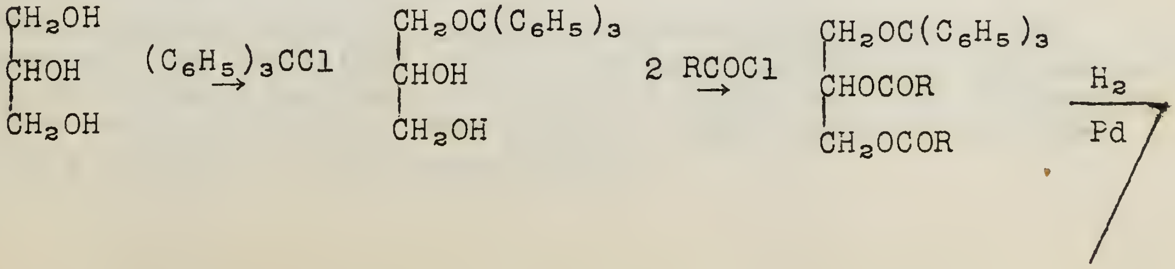
The preparation of unsymmetrical mixed triglycerides involves first, of course, the formation and isolation in the pure state of either the α-monoglyceride or α,β-diglyceride.

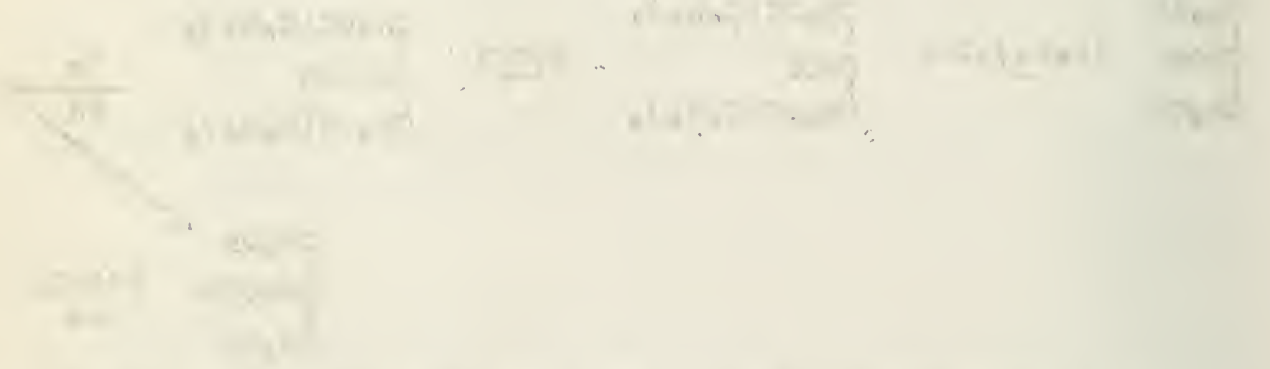
Among the following syntheses, I is only of historical interest, II, III, and IV represent fairly satisfactory methods of syntheses, and V's authenticity has been questioned because of its similarity to VI, which yields a product whose formation seems to involve a so-called acyl shift.

I.



II.





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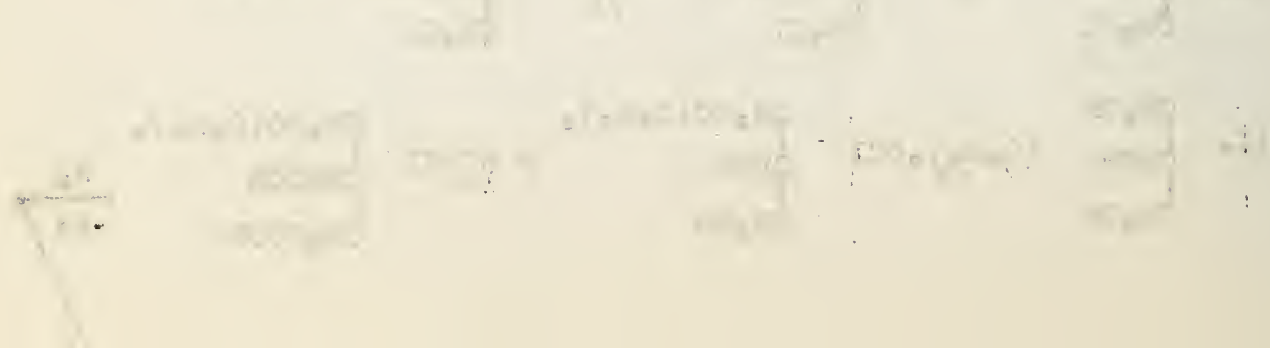
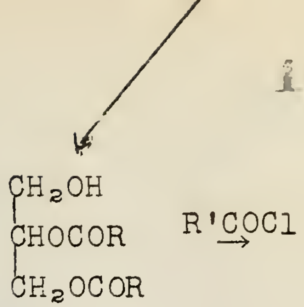
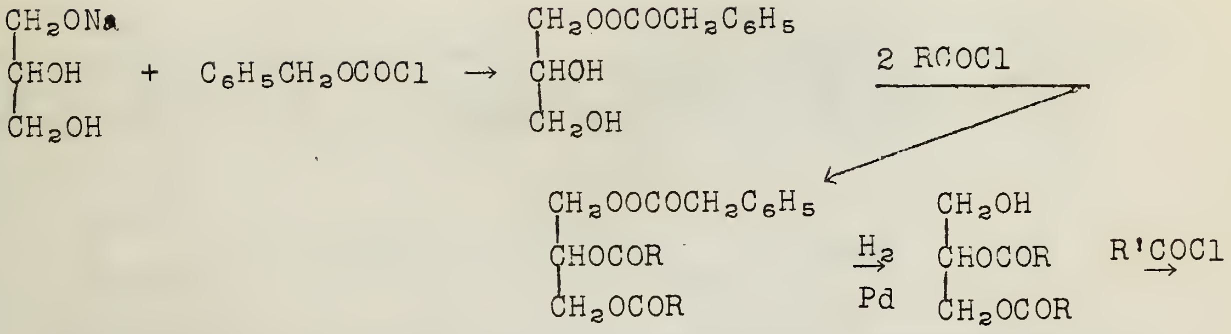
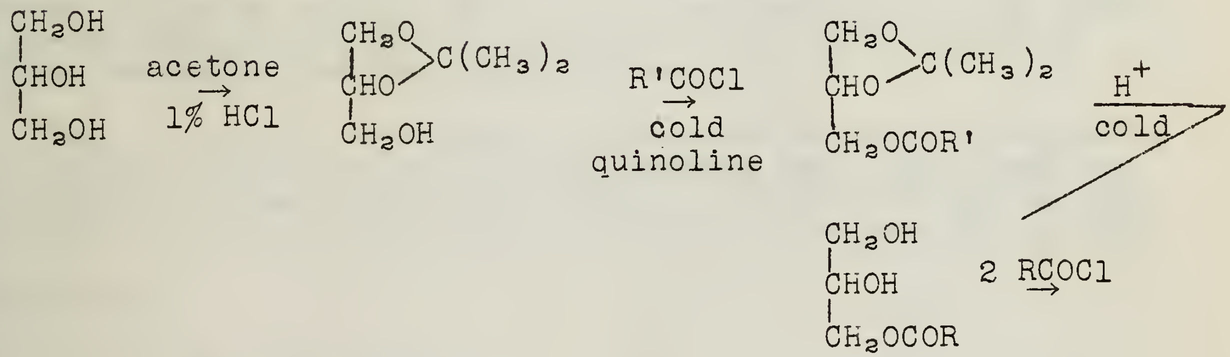




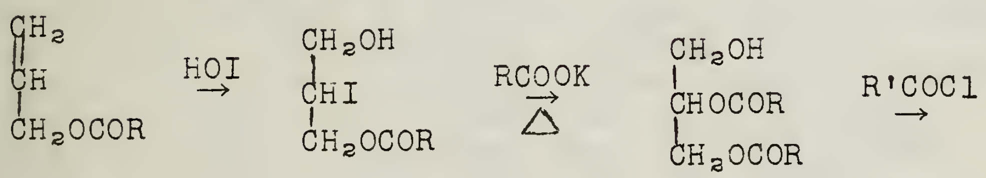
III.



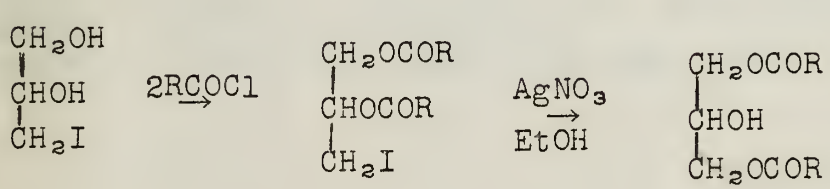
IV.



V.

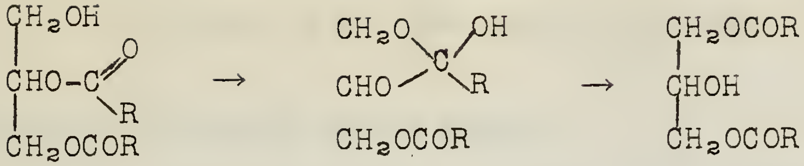


VI.

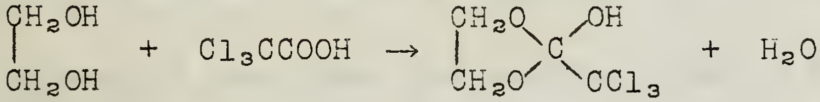


The α-β Acyl Shift in Diglycerides

The expected product from VI (above) would be the α,β-diglyceride, and isolation of the α,α'-diglyceride to the exclusion of any of the expected substance can be explained only by saying that the acyl group first went into the beta position and subsequently shifted to the alpha position.



Fischer postulated the above mechanism of acyl shift several decades ago. Hibbert and Grieg, in 1931, substantiated Fischer's hypothesis by obtaining a stable ring structure in the acylation of ethylene glycol with trichloroacetic acid.



Apparently the polarity occasioned by the presence of the three chlorine atoms serves to stabilize the oxolone structure. Hibbert and Grieg presume that in all such acylations of <u>alpha</u>-dihydroxy compounds there is an equilibrium between such an oxolone structure and the normal ester.

This α-β shift, seemingly, is applicable only to aliphatic acyl groups; several α,β-aryl diglycerides have been found to be stable. Further, this acyl shift is not encountered during such catalytic hydrogenations as shown in equations II and III.

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Reported by Jos. F. Shekleton
April 15, 1942

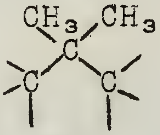
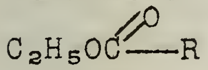
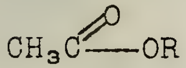
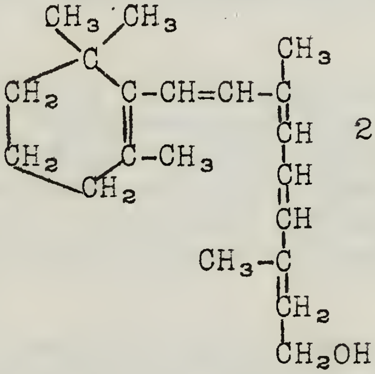
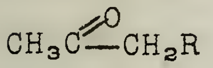
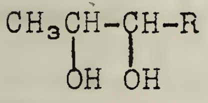
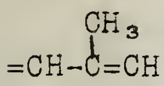
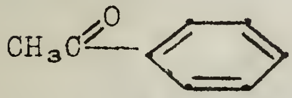
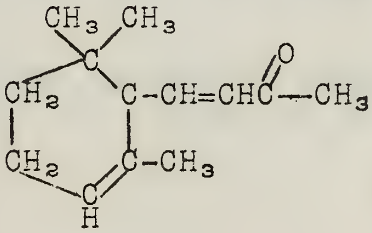
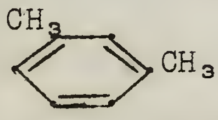
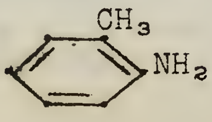
DETERMINATION OF BRANCH CHAIN METHYL, CITRIC ACID, AND ORGANIC HALOGEN

Determination of Branch Chain Methyl

Kuhn and L'Orsa developed a method for determining side-chain methyl groups in natural products (Vitamin A, Carotenoids, etc.) composed of isoprene units. The method consists in oxidizing the substance with chromic acid in sulfuric acid, then distilling and titrating the acetic acid formed. Pregl and Roth have adapted the process to micro-analytical work. King has applied the method to volatile materials by carrying out the oxidation in a micro bomb.

A variety of compounds has been analyzed in this way (Table I).

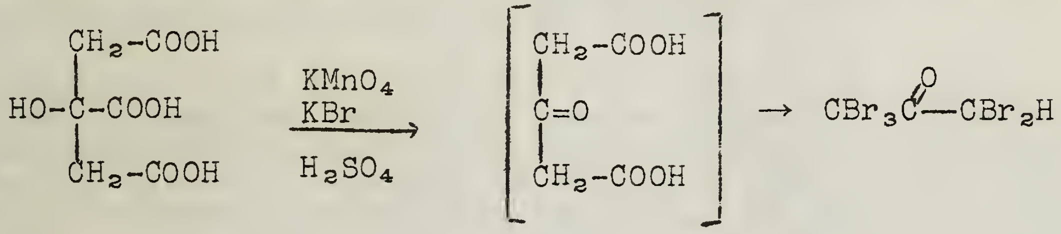
TABLE I.

Compound	Moles of Acetic Acid per mole of Compound	Compound	Moles of Acetic Acid per mole of compound
C_2H_5OH	1		
$C_2H_5OC_2H_5$	1		.40
 $C_2H_5OC(=O)-R$	.95-1		
 $CH_3C(=O)-OR$	1		
 $CH_3C(=O)-CH_2R$	.85		2.70
 $CH_3CH(OH)-CH(OH)-R$	.95		
$CH_3CH=CH-R$	.85		
 $=CH-C(CH_3)=CH$	.90		
	.10		
	.12		2.00
	.70		

It is evident from the figures given that the method is not as precise as might be desired. It has been most useful in choosing one of several possible formulas by comparing the amount of acetic acid found with that calculated from the figures given in Table I. For example, α-ionone would be expected to yield (0.4 + 0.90 + 0.85) = 2.15 molecules of acetic acid per molecule. There were found 2.0 molecules.

Determination of Citric Acid

Of the various methods used for the determination of citric acid, the pentabromoacetone method has produced the most satisfactory results. The details of the procedure are given by Deysher and Holm in a recent publication. The method consists of the oxidation of citric acid with potassium permanganate in the presence of bromine, under controlled conditions. The acid is converted quantitatively into pentabromoacetone, a white crystalline solid which can be determined gravimetrically.



Kunz was the first to utilize the reaction to determine the citric acid content of milk, wines, and other food products. The citric acid content of urine also has been determined by this method.

Because of the slight solubility and volatility of the pentabromoacetone, no absolute method can be prescribed for the complete recovery of citric acid as pentabromoacetone under all conditions. The method must be standardized with respect to the conditions and products employed. A complete discussion of various other methods and modifications is given by Lampitt and Rooke.

Kometiani determines the pentabromoacetone by treating it with hydrogen iodide in alcoholic solution to liberate six atoms of iodine per molecule. The iodine may then be determined volumetrically.

It seemed probable that compounds similar to citric acid might be determined in a like manner but a study of the literature disclosed no such examples.

Determination of Organic Halogen

The determination of organic halogen by the liquid ammonia-sodium process is both rapid and accurate. Chablay was the first to employ this reaction quantitatively. The method of Vaughn and Nieuwland, an adaptation of the Chablay method, does away

with all special apparatus, and gives increased rapidity and accuracy of analysis of insoluble materials. A small amount, 0.1 to 0.4 g. of the halogen-containing organic material is introduced into liquid ammonia contained in a beaker. If solution does not take place upon stirring, some organic solvent (as ether) inert toward sodium in liquid ammonia is slowly added until the material is dissolved. One gram of sodium is then added in small pieces and the covered beaker allowed to stand until the reaction is complete (usually 30 seconds to two minutes). The excess sodium is removed by ammonium nitrate, and the solution allowed to evaporate to dryness. The solids are taken up in water acidified with nitric acid and the halogen content determined with silver nitrate either gravimetrically or volumetrically by the method of Fajan or Volhard.

In some cases organic solids are produced during the decomposition. These must either be filtered off or put in solution by the addition of aldehyde-free acetone or other suitable solvent before precipitation of the halide.

Clifford noted that cyanides were formed with certain highly chlorinated compounds as carbon tetrachloride and hexachloroethane and caused high halogen values. He devised a method for removal of the cyanide which consists in boiling a nitric acid solution. Dains and Brewster investigated the action of sodium in liquid ammonia on 123 organic halogen compounds and found cyanide produced from only eight. In all these cases where cyanide was produced two or more halogens were attached to a single carbon atom. Methyl cyanide, benzyl cyanide, cyanoacetic ester evidently splits off sodium cyanide directly.

Organic fluorides also may be determined by following this procedure except that the fluoride is precipitated from the water solution with calcium nitrate as calcium fluoride and determined gravimetrically.

Some of the results of Vaughn and Nieuwland may give an idea of the reliability of the procedure.

Compound	% Halogen Present	% Halogen Found
Trichloracetic acid	65.11	65.19
Chloralhydrate	64.33	64.21
Hexachloroethane	89.86	89.91
Chlorobenzene	31.53	31.42
p-Dichlorobenzene	48.28	48.23
Hexachlorobenzene	74.73	74.80
Ethyl bromide	73.37	73.46
3,5-Dibromobenzoic acid	57.15	57.00
Styrene dibromide	60.56	59.95
n-Butyl iodide	68.98	68.86
Methylene iodide	94.77	94.84
Phenyl iodide	62.23	62.23
Fluorobenzene	19.79	19.78
1,3-Dimethyl-5-bromofluorobenzene	9.36	9.30
p-Chlorophenylfluoroform	31.58	31.36

The average per cent difference for all determinations run was .14 although the large majority ran below 0.1%.

This method has been used in this laboratory with good results.

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Reported by Curtis W. Smith
April 22, 1942

RECENT DEVELOPMENTS IN THE IDENTIFICATION
OF ORGANIC COMPOUNDS

I. Acids

Dewey and Shasky suggest the use of p-bromopseudothiouronium bromide as a reagent for the identification of acids. The reagent is prepared from p-bromobenzyl bromide and thiourea. When a hot alcoholic solution of this bromide is added to an acqueous solution of the sodium or potassium salt of the acid, the derivative precipitates out in the pure state on cooling. The p-chloropseudothiouronium chloride reagent has also been used but both have the disadvantage that the melting points of the salts formed cover only a small range (about 140-170°).

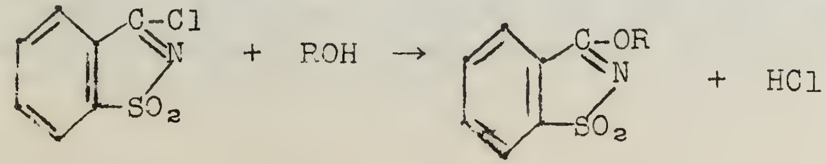
In addition to its use as a carbonyl reagent, phenylhydrazine has been used to form acid derivatives. Stempel and Schaffel tried this compound on aliphatic carboxy acids when they observed the success of its use on aliphatic sulfonic acids. To prepare the phenylhydrazide it is only necessary to boil a solution of the acid in phenylhydrazine for thirty minutes. The derivative precipitates on cooling or by the addition of benzene.

II. Alcohols

In order to identify the cellosolves, carbitols, and related glycols, Seikel and Huntress developed a procedure for the formation of the solid trityl ethers. The derivatives are formed by heating the alcohol and triphenylmethyl chloride in a mixture of pyridine and ether.

By means of a modified Schotten-Baumann reaction Lipscomb and Baker have discovered a good way to identify alcohols in an aqueous solution such as would result from the saponification of an ester. A solution of 3,5-dinitrobenzoyl chloride in benzene is made then a little ligroin is added to prevent freezing of the mixture during the reaction. This is shaken at 0° with the aqueous solution of alcohol, sodium acetate, and alkali.

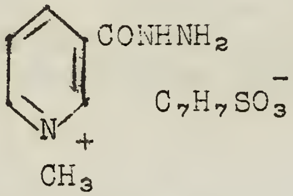
Alcohols may be identified by the use of saccharin chloride. The reagent is easily prepared from insoluble saccharin and phosphorus pentachloride. It reacts with alcohols in the absence of water to give saccharin alkyl ethers in which the alkyl group is attached to the carbon through the oxygen bridge.



The isomeric nitrogen ethers can be formed by the reaction of the alkyl halide on sodium saccharin. Saccharin chloride was used to identify primary and secondary alcohols.

III. <u>Aldehydes and Ketones</u>

By the use of the methyl p-toluenesulfonate addition product of nicotinic acid hydrazide it is possible to secure

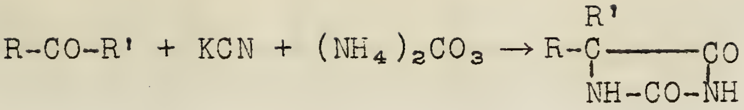


solid derivatives of aliphatic aldehydes having a melting point 40° higher than the corresponding 2,4-dinitrophenylhydrazones. It has the advantage in that the aldehyde is very easily recovered or it can be converted directly into another derivative such as the 2,4-dinitrophenylhydrazone. It gives oils with unsaturated ketones and the range of melting points for the C_6-C_{10} aldehyde derivatives is narrow.

Sah added another carbonyl reagent to his long list when he described the preparation and use of p-iodobenzhydrazide. This compound is easily prepared from methyl p-iodobenzoate and 40% aqueous hydrazine hydrate. Refluxing a mixture of the hydrazide, excess aldehyde, and two drops of acetic acid in pure alcohol gives the desired derivative. This reagent has two distinct advantages: (a) the yields are so high that it is easy to operate with 300 mg. of the aldehyde and still get enough material for a study of physical properties and analysis, and (b) the melting points of the derivatives of the alkanal series from C_6-C_{10} are widespread. This is not true of the 2,4-dinitrophenylhydrazones or semicarbazones for this series.

A new optically active carbonyl reagent of this type has been described by Woodward, Kohman, and Harris. This is prepared from l-menthol by conversion to l-menthylhydrazide. It gives very good derivatives with nice melting points and has the added advantage of having a characteristic specific rotation. It is of interest in that it was used in the first successful resolution of dl-camphor.

A new type ofcarbonyl derivative has been developed by Henze and Speer. In their work with keto ethers, they found that certain of their compounds did not give solid derivatives with the ordinary carbonyl reagents but did form solid hydantoins. The carbonyl compound was warmed in dilute alcoholic potassium cyanide and ammonium carbonate:



$$R\text{-}CO\text{-}R' + KCN + (NH_4)_2CO_3 \rightarrow R\text{-}\overset{R'}{\underset{|}{C}}\text{———}\underset{|}{CO} \atop \qquad NH\text{-}CO\text{-}NH$$

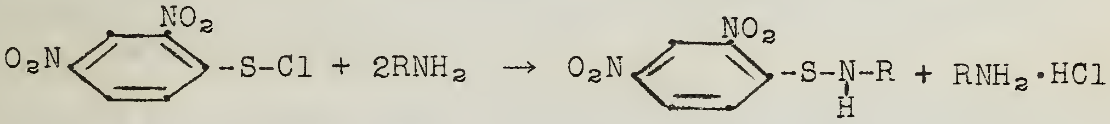
(R' can be H or R)

In most cases the hydantoin separates in a state of sufficient purity to eliminate further recrystallization. This is not useful for formaldehyde, certain unsaturated aldehydes, a few nitro- and hydroxy-aryl aldehydes and pyruvic acid. However, levulinic acid and acetoacetic ester are converted to the corresponding 5,5-disubstituted hydantoins.

IV. Amines

By the diazotization of p-iodobenzhydrazide, one can get p-iodobenzazide. When this reagent is refluxed in an anhydrous medium, usually toluene, the corresponding substituted urea is formed. Again, as in the case of the hydrazide, only a small amount (200 mg.) is necessary for a complete physical examination and analysis.

Billman et al used 2,4-dinitrobenzenesulfonyl chloride as a reagent for the identification of amines. The reagent is prepared from 2,2',4,4'-tetranitrodiphenyl sulfide and chlorine.



It can be used even with a 30% aqueous solution of the amine.

V. Hydrocarbons

Although it is not a new reagent and identification work with it is not new, trinitrobenzene has been found useful in identifying aromatic compounds. The derivatives, which are much like the corresponding picrates, have been listed for certain aromatic compounds: acids, aldehydes, amines, ethers, hydrocarbons, ketones, and nitriles; mostly for amines, hydrocarbons, phenols and phenol ethers. One interesting fact about this reagent is that the number of trinitrobenzene molecules used does not vary with the number of functional groups but with the number of aromatic nucleii. Certain pyrrole derivatives, which do not give picrates, do form the trinitrobenzene compound.

The identification of pure paraffinic hydrocarbons has usually been made only through the use of physical constants of the compounds. Huntress has developed desoxycholic acid as a reagent for the preparation of derivatives of these hydrocarbons. He has applied it to three pentanes, five hexanes, seven heptanes, eight octanes, three nonanes, eight decanes, and three higher

paraffins, making a total of thirty-seven hydrocarbons. The derivative is produced when desoxycholic acid in methanol is allowed to react with the hydrocarbon.

VI. Phenols

Phenols can be identified by the use of p-iodobenzazide (see first reagent under amines). In this case the result is a substituted urea.

VII. Sulfonic Acids

Although characterization of carboxylic acids by the formation of their p-nitrobenzyl esters has been a standard procedure, the analogous preparation of the corresponding sulfonates has hitherto proved impossible. By employing the silver salt of the sulfonic acid with p-nitrobenzyl chloride in pyridine, and taking advantage of the fact that the resultant silver chloride is less soluble in hot than cold pyridine, and that the solvent combines with the sulfonate to yield a readily crystallizable pyridium salt with sharp and significant melting point, Huntress has characterized twenty common aromatic sulfonic acids.

Chambers and Watt have extended the use of benzylisothiouronium hydrochloride to include 34 sulfonic acids. Impure sulfonic acids can be used but if there is an amino group present, the method usually fails.

If there is an amino group present and ordinary identification methods fail because of inner salt formation or sensitivity of the amino group, then Allen and Frame suggest the replacement of the amino group by a chlorine atom through the Sandmeyer reaction. The sulfonyl chloride, sulfonamide or sulfonanilide can then be made. The yields are good enough so that 1.5-2 gms. are all of the original acid that is necessary.

VIII. The Iodoform Reaction

Rothlin has developed a method whereby it is possible to distinguish between $R-CO-CH_3$ and $R-CHOH-CH_3$ by means of the iodoform reaction. Using a reagent made of one part potassium cyanide, four parts iodine, five parts ammonium hydroxide and fifty parts of water, a positive test can be obtained for the methyl ketone only. It may also be used quantitatively to determine the amounts of these two compounds in a mixture. By the ordinary iodoform reaction, the total amount of the two types can be determined; then by means of this second reagent the amount of methyl ketone can be found.

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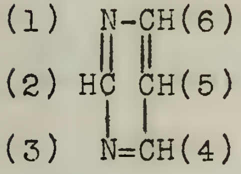
Reported by Q. F. Soper
April 22, 1942

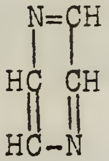
SULFADIAZINES

The antistreptococcic activity of Prontosil, 2,4-diaminoazobenzene-4'-sulfonamide was discovered in the laboratories of I. G. Farbenindustrie by Mietzsch, Klarer, and Domagk in 1935. That same year Tréfouël, Tréfouël, Nitti, and Bovet at the Pasteur Institute while synthesizing Prontosil derivatives found that sulfanilamide was just as active. During the next five years synthesis of about 1300 new derivatives was published. Among the most successful of these derivatives were sulfapyradine (2-sulfanilamidopyridine), sulfathiazole (2-sulfanilamidothiazole), sulfaguanidine, and sulfadiazine (2-sulfanilamidopyrimidine).

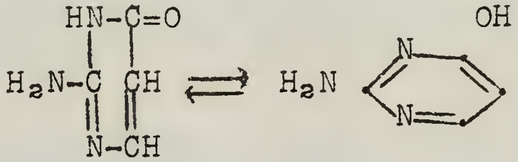
After its synthesis by Roblin and co-workers, sulfadiazine proved to be more effective, more soluble, and less toxic in general than the other active sulfa-drugs. As a result a great many pyrimidine and pyrazine derivatives of sulfanilamide were prepared.



pyrimidine



pyrazine



isocytosine

Synthesis of Isocytosine.

For the synthesis of isocytosine, an intermediate in the synthesis of several pyrimidine derivatives, Roblin and co-workers used a condensation of malic acid with guanidine sulfate in the presence of fuming sulfuric acid.

$$\mathrm{COOHCH_2CHOHCOOH + H_2NC(=NH)NH_2 \longrightarrow [COOHCH_2CHO + HN{=}C(NH_2)_2] \xrightarrow{} \uparrow \text{Isocytosine}}$$

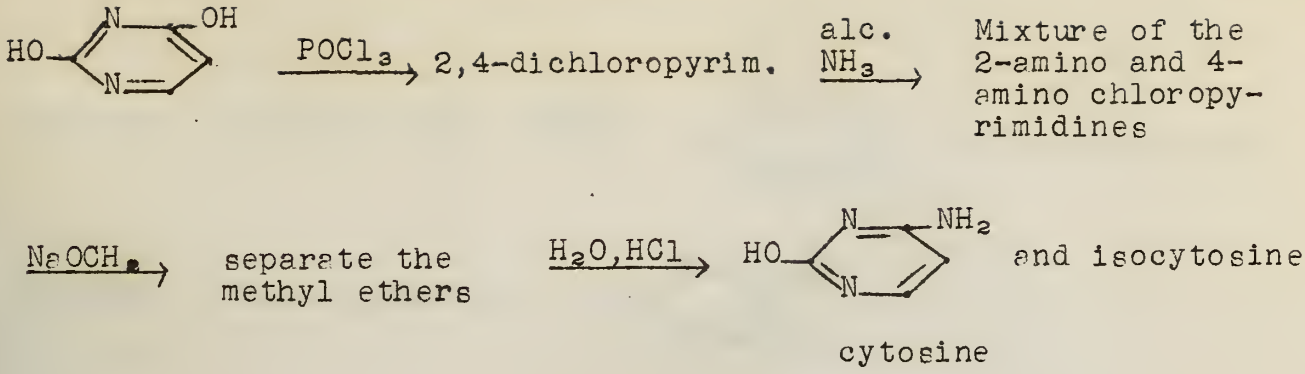
Among the earlier methods reviewed by Johnson and Hahn was the alkaline condensation of guanidine carbonate with the sodium salt of ethyl formylacetate.

$$\mathrm{C_2H_5OCO\text{-}CH{=}CHONa + HN{=}C(NH_2)_2 \longrightarrow \text{isocytosine}}$$

Davidson and Baudish developed a synthesis for uracil from urea and malic acid.

$$\mathrm{NH_2CONH_2 + HOOCCH_2CHOHCOOH \xrightarrow{fum. H_2SO_4} \text{uracil (2,4-diketopyrimidine)}}$$

Using this method Hilbert and Johnson synthesized cytosine and isocytosine from uracil according to the following reactions:



$\xrightarrow{POCl_3}$ 2,4-dichloropyrim. $\xrightarrow{\text{alc. } NH_3}$ Mixture of the 2-amino and 4-amino chloropyrimidines

$\xrightarrow{NaOCH_3}$ separate the methyl ethers $\xrightarrow{H_2O, HCl}$ and isocytosine

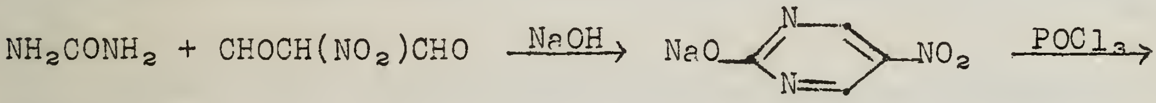
cytosine

Pyrimidine synthesis

In the preparation of 2-aminopyrimidine Roblin and his co-workers treated isocytosine with $POCl_3$ and then reduced off the chlorine in the (4) position with H_2 and $Pd(OH)_2$ on $CaCO_3$.

The same series of reactions starting with cytosine would lead to 4-aminopyrimidine. The reduction can also be carried out in either case with Zn and H_2O.

Using a procedure of Hale and Brill to obtain the sodium salt of 2-hydroxy-5-nitropyrimidine, Roblin worked out a synthesis of 5-aminopyrimidine.

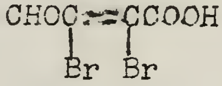


NH_2CONH_2 + $CHOCH(NO_2)CHO$ $\xrightarrow{NaOH}$ $\xrightarrow{POCl_3}$

2-chloro-5-nitropyrimidine $\xrightarrow{Fe, HOAc}$ 2-chloro-5-amino pyrimidine $\xrightarrow[Pd]{H_2}$ 5-aminopyrimidine

Nitromalondialdehyde can be made by the action of sodium nitrite on mucobromic acid according to Hill who used pyromucic acid and bromine as a source of the acid. Simonis was able to make mucobromic acid in good yield by the action of bromine on furfural.

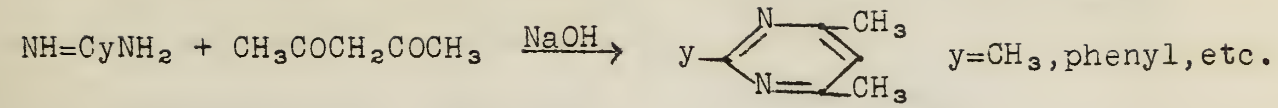
furfural + 5 Br_2 + 3 H_2O → [pyromucic acid] →

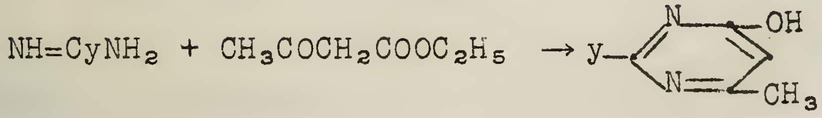


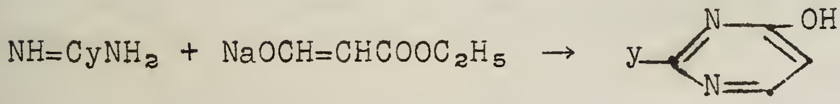
$CHOC(Br){=}C(Br)COOH$

$\xrightarrow{NaNO_2, \text{ dil. alc.}}$ $NaO_2N{=}C(CHO)_2$

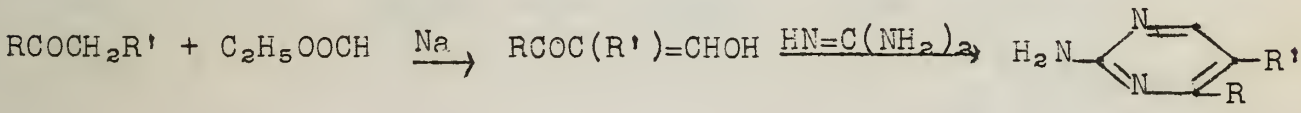
Other condensations lead to alkyl and aryl substituted pyrimidines. Gabriel has investigated a number of reactions between amidines and various diketones.



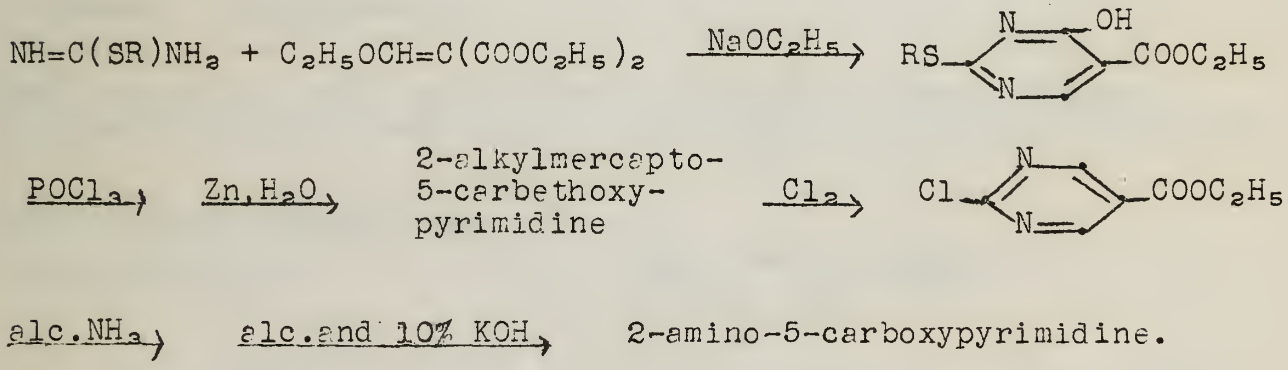




Caldwell and co-workers made 4,5-dialkylpyrimidines by refluxing the appropriate hydroxymethylene ketones with guanidine carbonate in alcohol. The ketones were prepared by a Claisen condensation of ethyl formate with the proper straight chain or cyclic ketone.



Ballard and Johnson synthesized 2-amino-5-carboxypyrimidine as follows:



The preparation of ethoxymethylene malonic ester was worked out by Wheeler and Johns.

$$CH_2(COOC_2H_5)_2 + CH(COOC_2H_5)_3 + (CH_3CO)_2O + ZnCl_2 \rightarrow C_2H_5OCH{=}C(COOEt)_2$$

Previously $C_2H_5OCH{=}C(CN)COOC_2H_5$ and $HOCH{=}C(CHO)COOC_2H_5$ had been used in the condensation. In the pseudothiourea R may be hydrogen, ethyl, or benzyl.

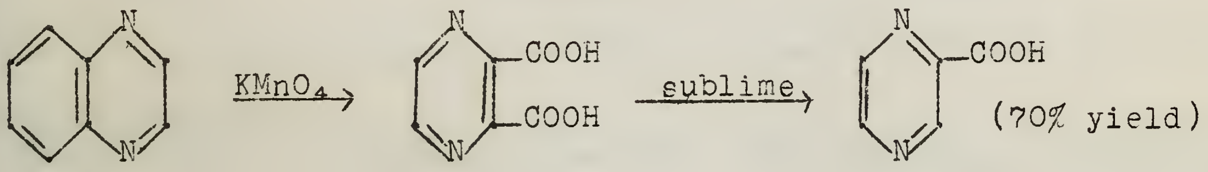
Roblin, Winnek and English obtained 5-chloro-2-aminopyrimidine from the condensation of chloromalondialdehyde with guanidine carbonate in fuming sulfuric acid. The chloromalondialdehyde was prepared from tetrachloropropene.

$$CHCl_2C(Cl)=CHCl + 95\%\ H_2SO_4 \rightarrow CHO\text{-}CHCl\text{-}CHO$$

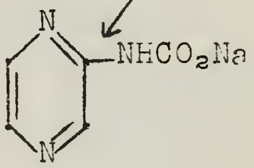
$$CHOCHClCHO + NH=C(NH_2)_2 \rightarrow \text{5-chloro-2-aminopyrimidine.}$$

Pyrazine Synthesis.

Hall and Spoerri prepared aminopyrazine starting with quinoxaline.



pyrazoic acid $\xrightarrow[HCl]{CH_3OH}$ ester $\xrightarrow[CH_3OH]{NH_3}$ amide $\xrightarrow{NaOCl}$

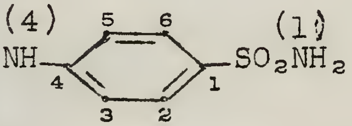


$\xrightarrow{H^+}$ aminopyrazine

The authors say that this is the first time a stable sodium carbamate has been isolated from the Hofmann hypobromite reaction.

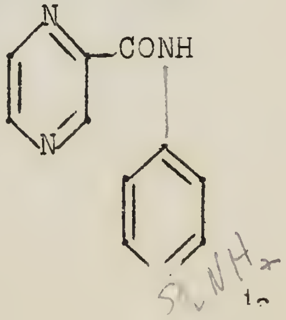
Sulfanilamide derivatives.

N^4-substituents:



The synthesis of N^4-pyrazinoyl sulfanilamide by Daniels and Iwamoto illustrates one method of preparing N^4-derivatives.

pyrazinoyl chloride + sulfanilamide $\xrightarrow[pyridine]{dry}$



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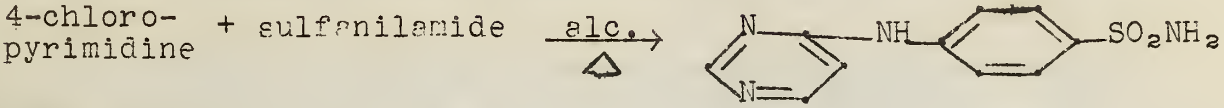
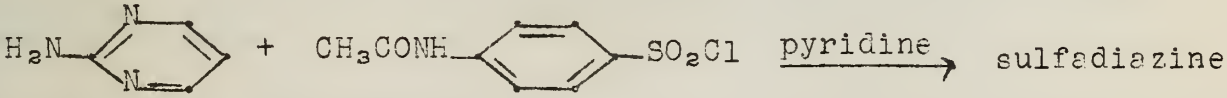
4-chloropyrimidine is used in the synthesis of 2-N^4-sulfonamidopyrimidine according to the method of de Suto-Nagy and Johnson.

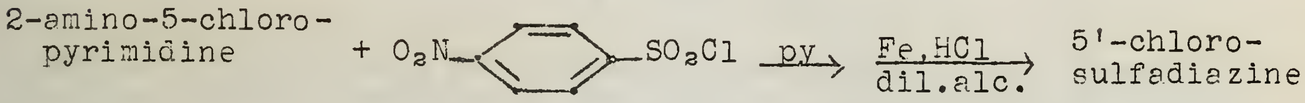


N -substituents:

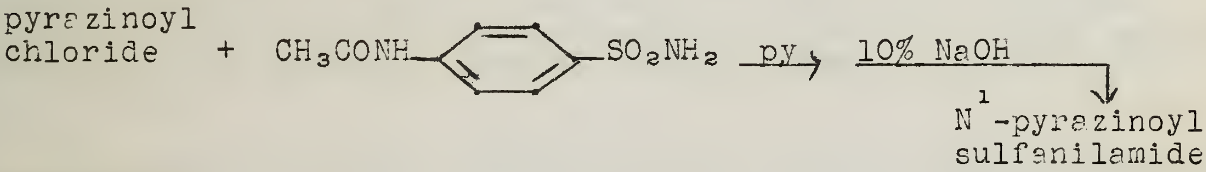
There are three main methods of preparing N^1-derivatives.
(1) The use of acetylsulfanylil chloride on an amine followed by hydrolysis.



(2) The use of p-nitrobenzenesulfonyl chloride followed by reduction



(3) The action of an acyl chloride on N^4-acetylsulfanilamide.



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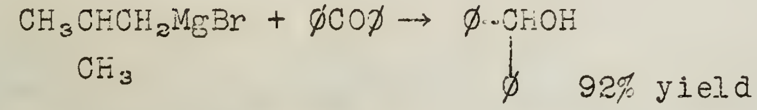
Reported by M. Chiddix
April 29, 1942

THE EFFECT OF CATALYSTS ON THE GRIGNARD REACTION

Kharasch et al, University of Chicago

It is known that several metals and metallic compounds have a significant effect upon the Grignard reaction -- the nature of the products, the rate of reaction, and the yield. In order to study this effect more closely Kharasch and his co-workers investigated the catalytic effect of several metallic halides upon certain Grignard reactions.

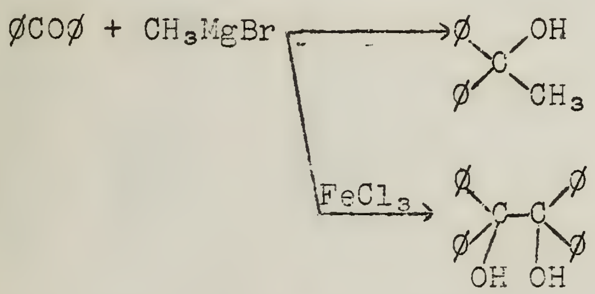
The first reaction to be studied was that of isobutyl magnesium bromide with benzophenone. Ordinarily this reaction goes as follows:



$$CH_3\underset{CH_3}{CH}CH_2MgBr + \phi CO\phi \rightarrow \phi\text{-}\underset{\phi}{CHOH} \quad 92\%\ \text{yield}$$

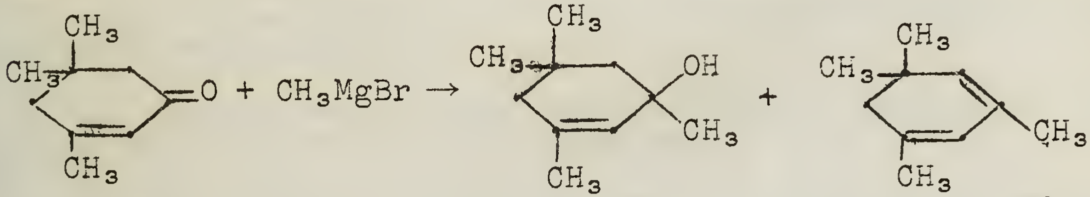
The reaction is thus a 2-electron Grignard reduction. However, when the reaction was run in the presence of manganous chloride, benzopinacol as well as benzohydrol was obtained, and the yield of benzopinacol varied directly with the amount of manganous chloride present up to 2 mol per cent of the latter. Chromic chloride and ferric chloride gave similar results but with smaller yields of benzopinacol. Cuprous chloride showed no effect upon the reaction.

The second reaction studied was that between methyl magnesium bromide and benzophenone. The reaction ordinarily yields diphenylcarbinol, but the presence of small amounts of metallic halides altered the reaction to yield either benzopinacol or the carbinol in quantitative amounts.

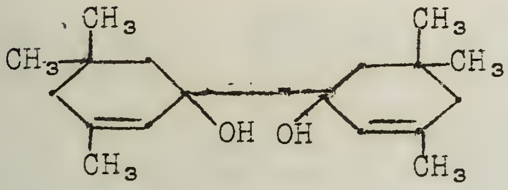


2 mol % catalyst used	% pinacol	% carbinol
Mg	0	95
CuCl	0	93
MnCl$_2$	0	93
FeCl$_3$	65	21
CoCl$_2$	93	2

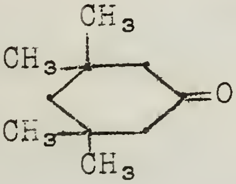
The last reaction studied was that of isophorone with methylmagnesium bromide. Ordinarily the addition of Grignard reagents to conjugated cyclic unsaturated ketones yields varying amounts of the 1,2 and 1,4 addition products, and in this case a yield of 71% of the tertiary alcohol and its dehydration product was obtained. However, in the presence of metallic halides various other products were obtained as shown in the following diagram and table.



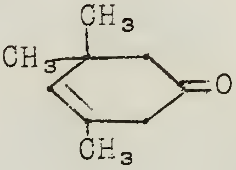
I II



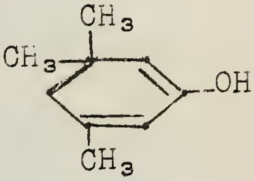
III



IV



Va

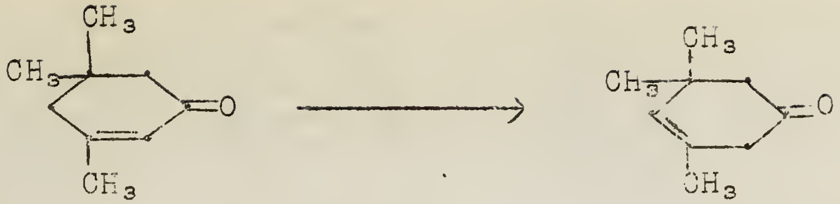


Vb

<u>Yields</u>

Mol %	1,2 addn.					
Catalyst	Diene	Carbinol	Cpd.V	Pinacol	1,4 addn.	Total
none	48.2	42.6				90.8
1.0 $FeCl_3$	2.2		81.6	9.46		94.0
1.0 CuCl	6.96				82.5	89.5
1.0 $NiCl_2$	7.3	22.6		61.1	4.73	96.0
1.0 $CoCl_2$			16.1	78.5		94.6
20 xs Mg	55.5	22.7		1.45		80.0
1.0 AgCl	57.7	35.0				92.7
1.0 $MnCl_2$	56.0	28.5				84.5
ordinary Mg	85.5	4.35			1.45	91.3

Determination of the structure of compound V proved to be difficult. On the basis of chemical evidence this compound should be either the enol form of isophorone or the isomer in which the double bond is in the β,γ position. If the latter structure is correct, then a remarkable rearrangement takes place when isophorone is treated with methyl magnesium bromide in the presence of 2 mol per cent of ferric chloride:



Following is the evidence for the existence of compound V as distinct from isophorone:

1. Carbon and hydrogen analyses show an empirical formula $C_9H_{14}O$, the same as that of isophorone.

2. The physical properties are different from those of isophorone.

	b.p. °C.	b.p.(atm.)	n_D^{20}	d^{20}
compound V	38.0-38.4 (4 mm.)	181-185	1.4620	0.9083
isophorone	69.0-69.3 (5 mm.)	210-211	1.4775	0.9215

3. Compound V absorbs oxygen much faster than isophorone. This property caused much difficulty in securing analyses, and the compound had to be distilled and kept in high vacuum to get consistent results.

4. Compound V slowly changes to isophorone at room temperature. This conversion is accelerated by a trace of acetic acid, and in the presence of potassium bisulfate at 150°, the change is complete in one hour.

5. The possibility that compound V might be the alcohol Δ^2-3,5,5,-trimethylcyclohexanol formed by the reduction of isophorone by methyl magnesium bromide was disproved by comparison of the physical properties of the two.

	B.p. °C.	n_D^{20}	d^{20}
Compound V	38-38.4 (4 mm.)	1.4620	0.9083
Alcohol	69 (5 mm.)	1.4717	0.9144

6. A comparison of the reactivity of compound V and isophorone toward semicarbazide was carried out. Compound V gave a precipitate immediately, but one to three hours were required for isophorone to form any precipitate. Both semicarbazones melted at 186-187°C., and they did not depress each other's melting points.

7. Compound V is evidently an isomer of isophorone. The enol form should give a test with ferric chloride, and compound V did not, but this test is not conclusive.

8. Each compound reacted with hydroxylamine to give an oxime melting at 78-79°, but an equimolar mixture of the two oximes melted at 50-52°-

Thus no definite conclusion could be reached as to the structure of compound V. The best method of deciding on one of the two proposed structures would seem to be their absorption spectra since the infra-red should reveal the presence of a hydroxyl group and the ultra-violet should show the presence of conjugation.

In attempting to explain the effects of the metallic halides, certain considerations must be kept in mind. The coupling by metallic halides has been studied many times, but in every case at least one mol of the halide was used:

$$2RMgX + MX_2 \rightarrow R\text{-}R + 2MgX_2$$

2 mols 1 mol 1 mol

However, when one mol of bromobenzene is dropped into a mixture of phenyl magnesium bromide (one mol) plus 3 mol% of cobaltous chloride, the bromobenzene acts as an oxidizing agent in converting the phenyl magnesium bromide to biphenyl. That the biphenyl is formed exclusively from the Grignard reagent is shown by the fact that the bromobenzene may be replaced by p-tolyl bromide, ethyl bromide, isopropyl bromide, and others with exactly the same results. The reaction is applicable to other biaryls, and p-p' bitolyl, o-o' bitolyl, 4-4' bianisyl, 2-2' biphenetyl, were obtained in yields better than those obtained using other coupling agents.

This reaction essentially involves the transfer of an electron to the halide from the organic radical of the Grignard reagent. The metallic halide acts as an oxidation-reduction catalyst since it is reduced by the Grignard reagent and oxidized back by the organic halide. The need of only small amounts of the metallic halide suggests a chain mechanism:

$$C_6H_5MgBr + CoCl_2 \rightarrow C_6H_5CoCl + MgBrCl$$

$$2C_6H_5CoCl \rightarrow C_6H_5\text{-}C_6H_5 + 2\ CoCl\cdot$$

$$CoCl\cdot + C_6H_5Br \rightarrow CoClBr + C_6H_5\cdot$$

$$XC_6H_5\cdot \rightarrow C_6H_6,\ C_6H_5\text{-}C_6H_5,\ C_6H_5\text{-}C_6H_4\text{-}C_6H_5,\ \text{etc.}$$

This mechanism also explains the pinacol rather than the carbinol in the first reaction studied:

$$CH_3MgBr + CoCl_2 \rightarrow CH_3CoCl + MgBrCl$$

$$2CH_3CoCl \rightarrow C_2H_6 + 2CoCl\cdot$$

$$2CoCl\cdot + 2\phi_2CO + MgBrCl \rightarrow 2CoCl_2 + (\phi_2C\text{-}OMgBr)_2$$

Not all Grignard reagents would react with bensophenone in the presence of cobaltous chloride to give the pinacol even

though the primary requirement, reaction of the Grignard reagent with the metallic halide, were fulfilled. The second step, decomposition of the RCoCl into R-R and CoCl, must be sufficiently rapid or the normal addition reaction will take place exclusively. Thus in attempting to alter the normal course of a Grignard reaction, the rate of normal condensation as well as the stability of the intermediate must be considered.

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Reported by A. B. Spradling
April 29, 1942

THE CHEMISTRY OF EXPLOSIVES

Because of the contemporary importance of explosives, their chemistry, both organic and inorganic, is a topic of extreme interest. Inasmuch as exact information of modern developments is unavailable, this report will summarize the practices of the explosives industry during and following World War I.

History

Historically, tradition records that Berthold Schwarz, a German monk, discovered black powder around 1250, but various documents indicate that Roger Bacon in the thirteenth century was the first European scholar acquainted with the use of saltpeter in incendiary mixtures. Even earlier, around the eighth century, the Byzantines and Greeks described various flame-throwers and pyrotechnics. After guns began to be used in the fourteenth century, the best proportion of potassium nitrate, charcoal, and sulfur (6:1:1) was found and later developments were chiefly in the manufacturing methods. As an improvement, the potassium nitrate and sulfur were replaced by ammonium nitrate to produce Ammonpulver, a cheap, powerful, flashless, smokeless propellant.

The discovery of smokeless powder by Pelouze (1838) and its development by Abel in the form of guncotton (nitrocellulose) marked the beginning of modern firearms; Nobel was the first to gelatinize guncotton and nitroglycerin with acetone.

Properties

The important physical properties to be considered are:

1. Shattering Power (brisance)
   a. Strength of Detonation- depends on volume of gas evolved and amount of heat liberated. Determined by measurement of the distension after explosion in a lead block (Trauzl test), by recoil of a pendulum in a ballistics gun, or by means of a crusher gauge in a manometric bomb.
   b. Velocity of Detonation- depends on constitution and packing density. Measured by a rotating-drum chronograph or by comparison with standard samples (Dautriche test).

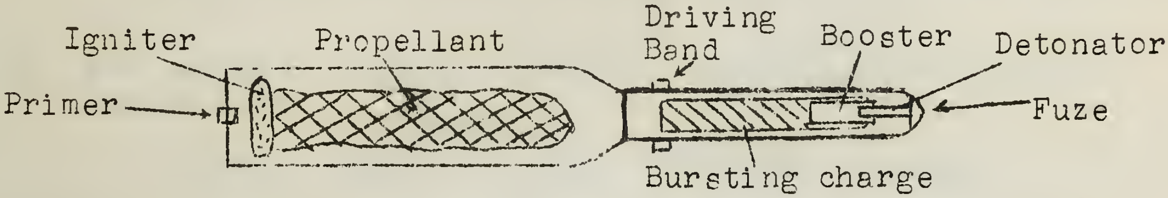
2. Sensitivity
   a. Impact
   b. Temperature of Ignition

3. Stability
   a. Time and temperature for NO_2 evolution
   b. Hygroscopic nature

Classification

Explosives may be classified conveniently by reference to their responses to the stimuli causing the explosions. Thus, there are primary explosives, propellants, and high explosives (with an intermediate sub-class of boosters).

The behavior of the various classes of explosives is best illustrated by considering a typical ammunition shell containing both a propelling charge and a bursting charge.



Thus, the firing pin causes the primer cap to produce a small flame, igniting the black powder in the primer. This in turn sets fire to the igniter, from which the large, hot flame causes burning of the grains of smokeless powder, the propellant. The gases from the combustion of the smokeless powder, which is colloided nitrocellulose of cylindrical grains with 1-7 longitudinal perforations, causes the projectile to move forward and to acquire a rotating motion as the rifling of the gun bites into the soft copper driving band. The proper burning of the powder is necessary to insure a gradual and powerful acceleration of the projectile.

If the shell is intended to explode a definite time after leaving the gun, a firing pin in the fuze undergoes set-back, striking a primer cap containing a primary explosive which ignites the slow-burning powder train adjusted by time rings. When this flame reaches the detonator and bursting charge, the shell explodes in flight. For detonation on striking the target, a percussion element is included. The centrifugal force causes a firing pin to rise up so that inertia will cause it to strike the cap, produce fire in the powder charge, and result in an explosion. The usual high explosive must be insensitive to tolerate the shock of the set-back. In general TNT is used for this purpose along with a booster of tetryl which aids in the detonation and reduces the quantity of primary explosive necessary. The bursting charge may also contain shrapnel or a war gas.

Naturally, there is some overlapping in the classification of explosives. For example, nitrocellulose may function as a propellant if ignited by fire, or as a high explosive if detonated by a primary explosive such as mercury fulminate. In all cases, adoption of a particular explosive depends to a large extent upon its stability, sensitivity, and reaction to climactic conditions in addition to its strength.

I. The Primary Explosives (initiators, detonators)

These compounds explode or detonate when heated or subjected to shock, but do not burn. Their uses vary with their brisance; mercury fulminate, lead azide, and nitromannite are by far the most common initiators.

1. Mercury fulminate - $Hg(ONC)_2$ - used with potassium chlorate and sometimes with powdered glass. Prepared by dissolving mercury in 60% nitric acid, adding alcohol, and separating the grey powder. Eleven times as sensitive as TNT.

2. Lead Azide - $Pb(N_3)_2$ - half as sensitive as fulminate. Prepared by

$$NaNH_2 + N_2O \xrightarrow{200^\circ} NaN_3 \xrightarrow{Pb(NO_3)_2} Pb(N_3)_2$$

3. Nitromannite - the hexa-nitrate of mannitol, which is made by electrolytic reduction of mannose. Nitrosorbitol is also used.

Others of lesser importance are lead picrate, trinitroresorcinol, m-nitrophenyldiazonium perchlorate, tetracene, nitrogen sulfide, copper acetylide, and nitrosoguanidine.

II. The Propellants (low explosives)

These are combustible materials containing within themselves all the oxygen for their combustion; they burn but do not explode and function by producing gas which explodes.

1. Black Powder - in the United States, it usually contains 75% sodium nitrate, 15% carbon, and 10% sulfur. It is now used chiefly in coal mining, as time fuses, and in shrapnel shells. Its products of combustion are 56% finely divided solids.

2. Smokeless Powder - Cellulose in the form of clean cotton or wood chips is nitrated by a nitric-sulfuric acid mixture to give a product containing 12.8% N, which corresponds to the formula $C_{24}H_{30}O_{10}(NO_3)_{10}$. This "nitrocellulose", plasticized by alcohol-ether and stabilized by diphenylamine, is forced through perforated dies, cut, and dried to give the desired guncotton. An improved military rifle powder now being made contains 13.1% N.

3. Cordite - a double-base powder developed by the British which contains nitrocellulose and about 30% of nitroglycerin, gelatinized by acetone. Burns more readily and faster and is well suited for trench mortars.

4. E. C. powder - semi-gelatinized nitrocellulose with small amounts of potassium or barium nitrate; used in hand grenades.

5. Nitroguanidine ($NH_2\overset{\overset{NH}{\|}}{C}NHNO_2$) made from guanidine nitrate, which comes from cyanamide by the addition of ammonia, then subsequent treatment with nitric acid. May be used with a chlorate or perchlorate.

III. <u>The High Explosives</u> (bursting charges)

These substances detonate under the influence of a suitable primary explosive. They do not function by burning and sometimes are not even combustible. They are not readily exploded by heat or shock but are extremely brisant once they are detonated. The chief members of this class are the dynamite and liquid oxygen types used for industrial purposes, and the nitro aromatics and newly developed nitro aliphatics employed in warfare.

1. NITROGLYCERIN AND DYNAMITE.--$C_3H_5(NO_3)_3$ - The trinitrate of glycerine is too sensitive; Nobel, however, discovered dynamite, a solid made by absorbing the liquid in kieselguhr. The filler now used in the United States is wood meal and sodium nitrate and acts as a cushion for the explosive during handling. A dynamite cartridge is fired by an electric spark in the sequence of primer mixture, fulminate, and dynamite.

   To eliminate the hazard of frozen nitroglycerin, ethylene glycol dinitrate or glycerin dinitromonochlorohydrin is usually added to lower the freezing point.

2. AMMONITES.--This term includes mixtures of ammonium nitrate with aromatic nitro compounds or combustibles such as sawdust and coal.

   dynamon - ammonium nitrate with wood chips, widely used in Russia.
   amatol - 20-80% mixtures of ammonium nitrate and TNT.
   ammonal - 15% TNT, 17% Al, 65% NH_4NO_3, 3% C.
   alumatol - same as above except for 3% Al; used in hand grenades.

3. BLASTINE.--60% NH_4ClO_4, 11% TNT, 22% $NaNO_3$, 7% wax; used in mines.

4. LOX.--Liquid oxygen absorbed on carbonaceous material contained in a canvas wrapper. Retardents such as diammonium phosphate solution may be used to reduce handling and storage hazards. Used chiefly in open-air mining.

5. CARDOX.--(liquid CO_2) in steel cylinders is ignited by a special electric spark; sometimes used in mining.

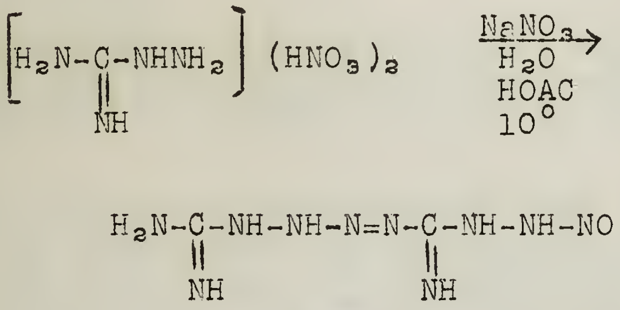
6. NITROSTARCH,__used as filler for hand grenades and mortar shells.

7. NIB - NITROGLYCERINE.--(nitroisobutylglycerol trinitrate; $(HOCH_2)_3CNO_2$) obtained from CH_3NO_2 and CH_2O is nitrated.

8. TETRANITROMETHANE.--from acetic anhydride and nitric acid.

9. NITROGUANIDINE, NITROCELLULOSE.--listed previously as propellants.

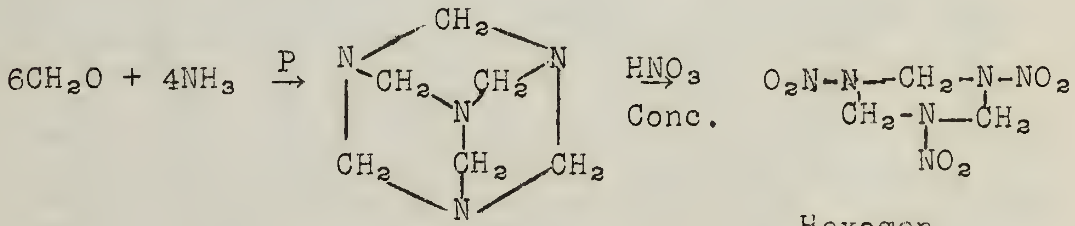
10. TETRACENE (guanyl-nitrosaminoguanyl-1-tetracene.)--This substance has a wide range of sensitivity depending upon its density. It varies from a slow burning compound to a detonator. However neither tetracene nor its mixtures with potassium chlorate are satisfactory substitutes for mercury fulminate. Commercial preparation:



$$\left[H_2N-\underset{\underset{NH}{\|}}{C}-NHNH_2\right](HNO_3)_2 \xrightarrow[\substack{H_2O\\HOAC\\10^\circ}]{NaNO_3} H_2N-\underset{\underset{NH}{\|}}{C}-NH-NH-N{=}N-\underset{\underset{NH}{\|}}{C}-NH-NH-NO$$

tetracene

11. HEXOGEN (trimethylenetrinitramine) (Syn. Cyclonite) Except for Penthrit this is one of the most brisant of all explosives. This high brisance makes it a useful underwater explosive for use in mines and in depth bombs. For this purpose it is usually mixed with 30-40% of TNT. It can be made quite cheaply because the apparatus required is very similar to that used in the high pressure process for making methanol. Commercial preparation:



Hexamethylene tetramine

Hexogen

12. PENTHRIT (pentaerythritol tetranitrate) This is the most powerful of the known military explosives. Like Hexogen, it has a high brisance which makes it a useful

underwater explosive, and also makes it useful as a bursting charge in artillery shells. It is stable, easily stored, can be prepared from coal, water, air, limestone and sulfuric acid, and hence can still be made by any country even though that country's imports are completely cut off.
Commerical preparation:

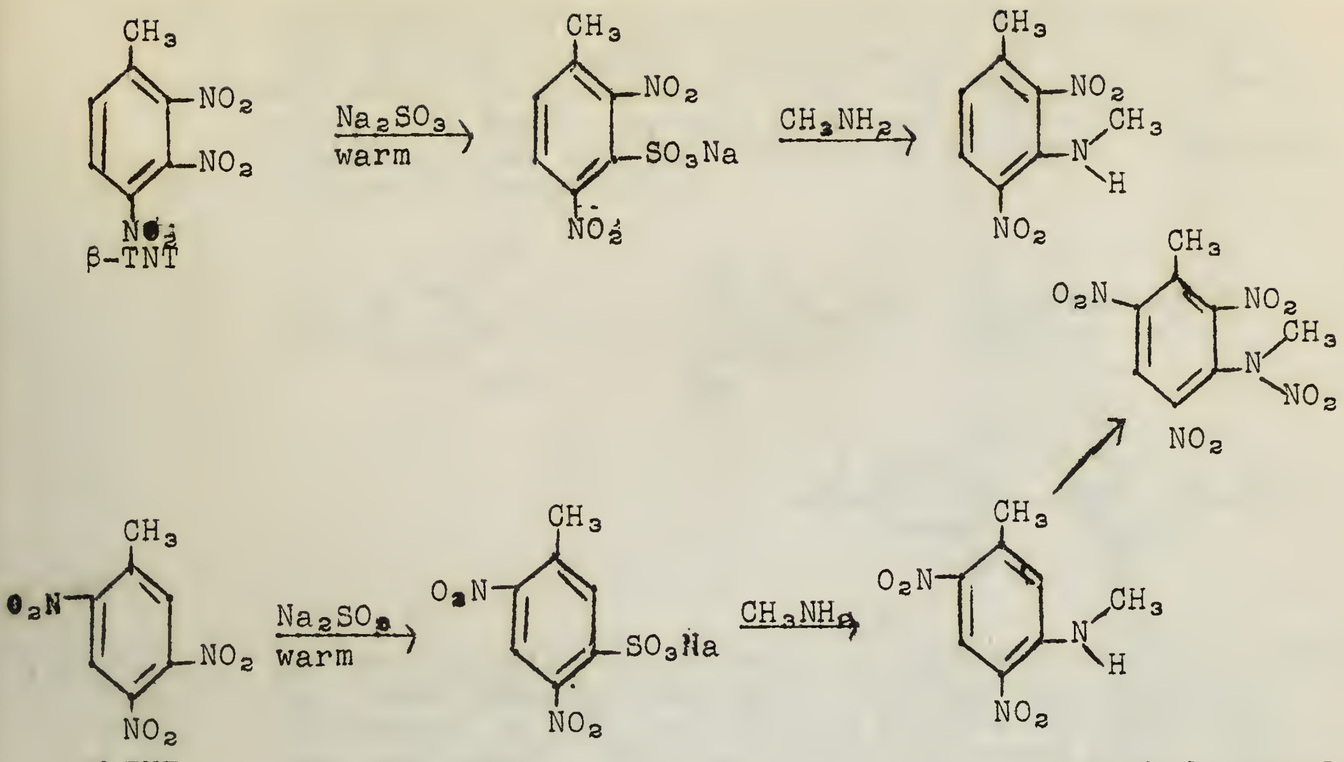
$$CH_3CHO + CH_2O \xrightarrow{Ca(OH)_2} C(CH_2OH)_4 \xrightarrow[H_2SO_4]{HNO_3} C(CH_2ONO_2)_4$$

13. PENTRINIT.--This is the name applied to mixtures of Penthrit and Nitroglycerol in various ratios. Pentrinit 60/40 (60% Penthrit and 40% Nitroglycerol) has the highest rate of detonation of any of the known explosives.

The Nitro Aromatics

Although several new and very good explosives have been developed in the aliphatic class, the aromatic nitro compounds still constitute the largest and most important class of the high explosives.

1. TNT (2,4,6-trinitrotoluene) (syn. Trotyl, Tolite).--This is probably the most widely used of the military high explosives. It is widely used in demolition shells, the TNT constituting as much as 60% of the weight of the shell.
Commerical preparation: A 3-stage direct nitration process is generally used in the commercial preparation of TNT from toluene, although 1- and 2-stage processes have been used.
Purification of product: The crude product which separates from the reaction mixture usually contains several impurities, the chief of which are: β-(2,3,4-), γ-(3,4,6-), and ζ-(2,3,6-) TNT, TNB (1,3,5-trinitrobenzene) and DNT (2,4-dinitrotoluene). There may also be impurities from the toluene used. However, this latter class of impurities is usually removed by an initial purification of the toluene. In spite of this, some TNX (trinitro-m-xylene) is usually present in the final product, but in such a small amount that it does no harm. Some of the DNT is removed by washing with sulfuric acid, and what little is left causes no trouble. It is not all removed because too large an amount of TNT would be dissolved by the sulfuric acid. The ζ-TNT is present in too small an amount to cause any trouble; however, the β- and γ-TNT must be removed. This is accomplished by treating the crude product with sodium sulfite. The products formed from the β- and γ-TNT are dissolved in water, and then converted to m-methyl tetryl:



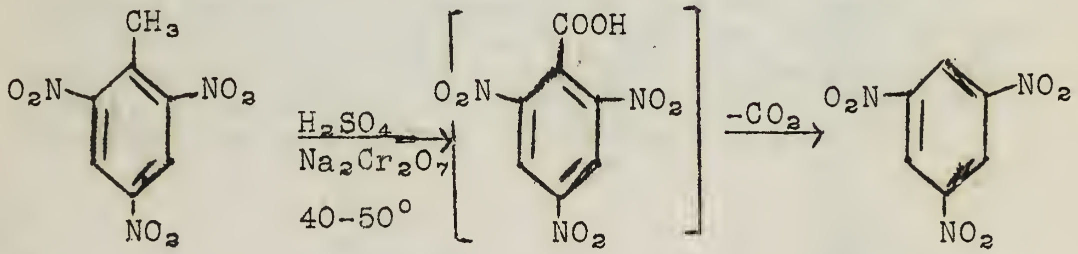
β-TNT

γ-TNT

m-methyl tetryl

these are H_2O sol.

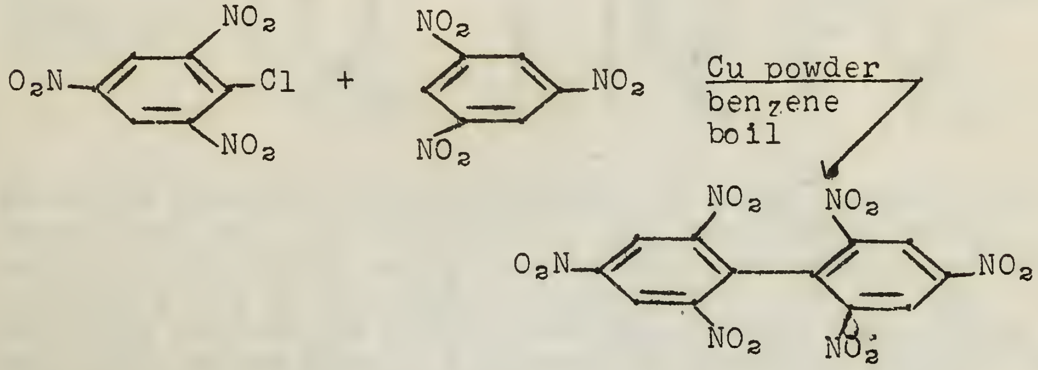
2. TNB (1,3,5-trinitrobenzene) This is the most powerful explosive among the nitro aromatics, and is less sensitive to impact than TNT.
Commercial preparation:



Although benzene can be nitrated directly to TNB, the process is too expensive of acid and heat to be used commercially.

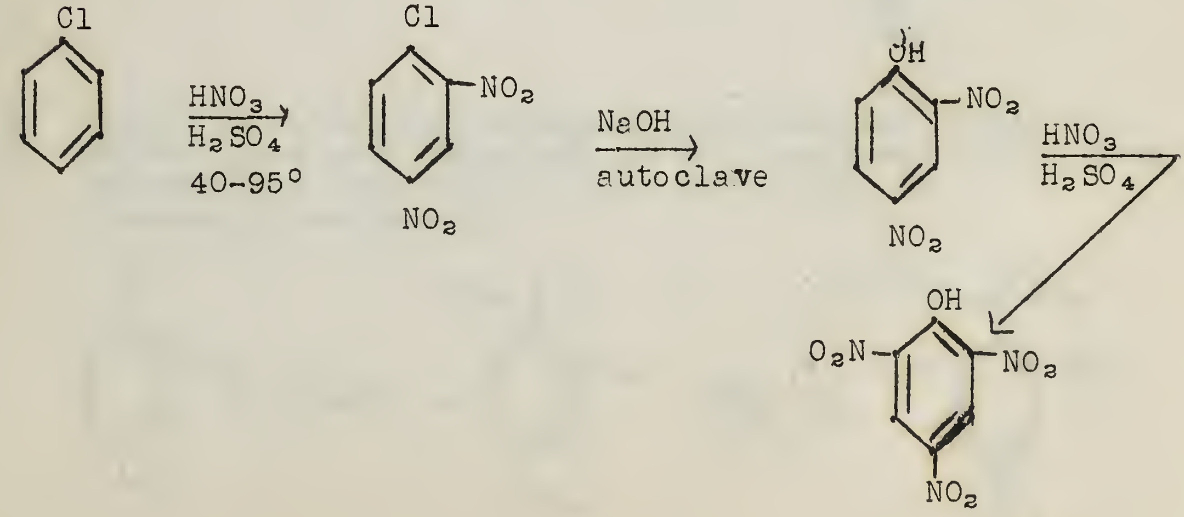
3. TNX (trinitro-m-xylene) This compound has a large excess of carbon in each molecule, so it is used with oxidizing agents such as NH_4NO_3. It is also used to lower the m.p. of compounds such as TNT and PA. However, it attenuates the explosive power of these compounds to some extent. TNX is prepared by a 3-stage nitration of m-xylene.

4. HEXANITROBIPHENYL (2,2',4,4',6,6'-) This compound is said to have explosive properties superior to those of hexil. It is also non-toxic and very stable chemically. It cannot be made by direct nitration of biphenyl since only the tetranitro compound is obtained. Commercial preparation:



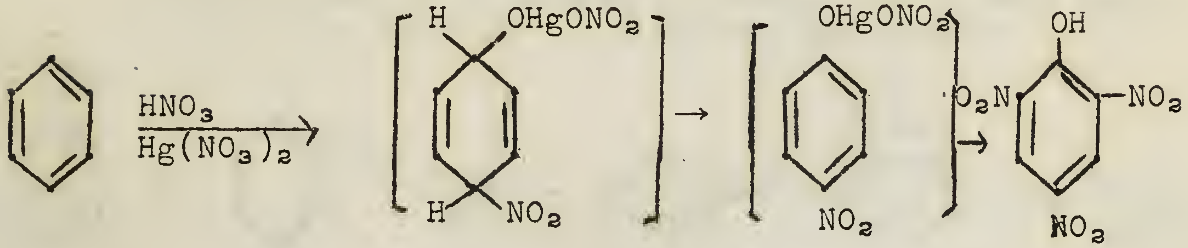
5. PA (Picric Acid) (Syn. Metinite, lyddite, shimose) This is a very powerful explosive, but has been largely supplanted by TNT, even though the latter is somewhat less explosive. This is because PA forms salts with the common metals (except Sn and Al), which are very sensitive to shock. (In fact lead picrate is an excellent detonator.) Because of this reaction with metals, use of PA in shells necessitates an inside coating of a varnish.

The straight nitration of phenol is not a satisfactory method for preparing PA for two reasons: 1. The -OH group weakens the ring and makes it more sensitive to oxidation. 2. Some o-nitrophenol is always lost because of its volatility. Therefore PA is made commercially by an indirect method:



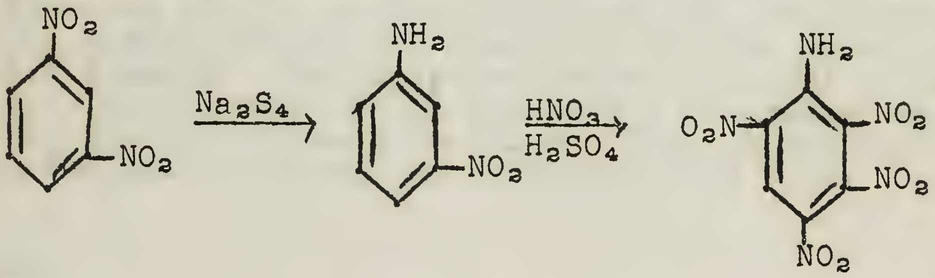
Picric Acid

There is also a catalytic process which is commercially feasible. This process gives the same overall yields as the above method.

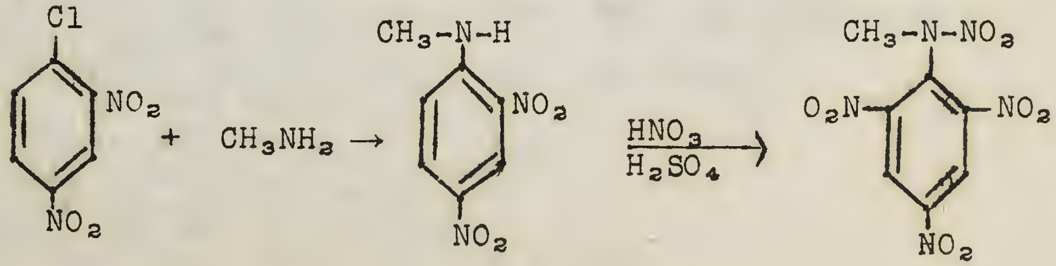


6. AMMONIUM PICRATE,--This explosive is less sensitive to shock than PA. In fact it is not even detonated by mercury fulminate, and a booster such as compressed PA or Tetryl has to be used to explode it. It is very suitable for use in armor piercing shells, especially for coast guard guns. A mixture of ammonium picrate and picric acid is known as "Explosive D" and is quite widely used in artillery shells in this country. Commercial preparation: PA is suspended in hot water and an excess of strong NH_4OH is added. The ammonium picrate separates on cooling.

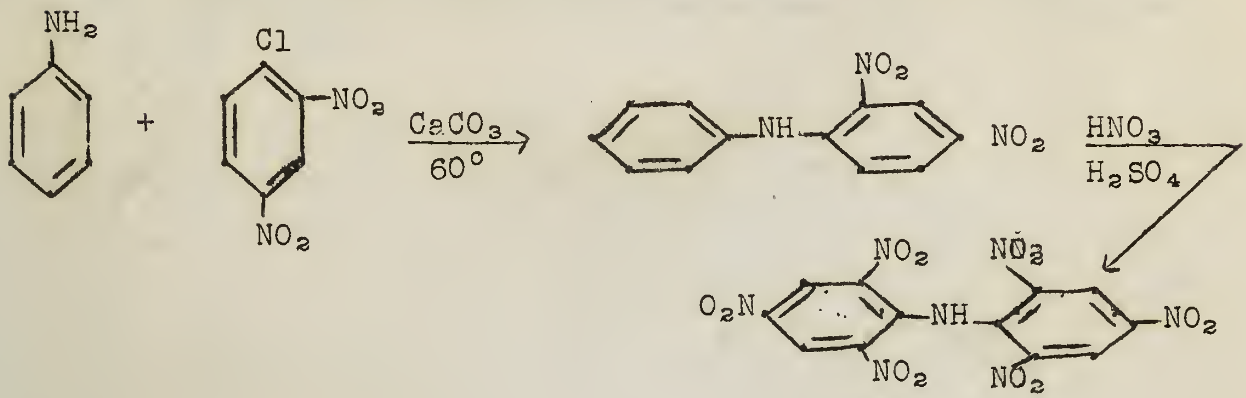
7. TNA (tetranitroaniline) This compound has a very high velocity of detonation, but it is too reactive chemically to be of much use. It does find some use as a booster, however.
   Commercial preparation:



8. TETRYL (1,3,5-trinitrophenylmethylnitramine) This is probably the most important of the boosters. It is more powerful and more brisant than TNT or PA.
   Commercial preparation:



9. HEXIL (2,2',4,4',6,6'-hexanitrodiphenylamine) This is another important booster like tetryl. It is slightly less sensitive to shock than tetryl, but it has the disadvantage of attacking the skin. It is made commercially from aniline and dinitrochlorobenzene:



EXPLOSIVE RIVETS

An important industrial use of explosives that has recently been patented is the use of explosive rivets. These are extremely valuable in the manufacture of airplanes, since they can easily be used when the riveter can reach only one side of the rivet.

The explosive rivet consists of a rivet with a hollow shank wherein is placed a very small charge of lead azide. The rivet is then placed in the hole and a riveting iron is applied to its head. This iron heats the rivet, causing the charge to explode within 1.5 to 2.5 seconds. The explosion causes the part of the shank that has passed through the plates to expand, thus locking the rivet firmly in place. This expansion of the rivet can be controlled to within 0.02 inch.

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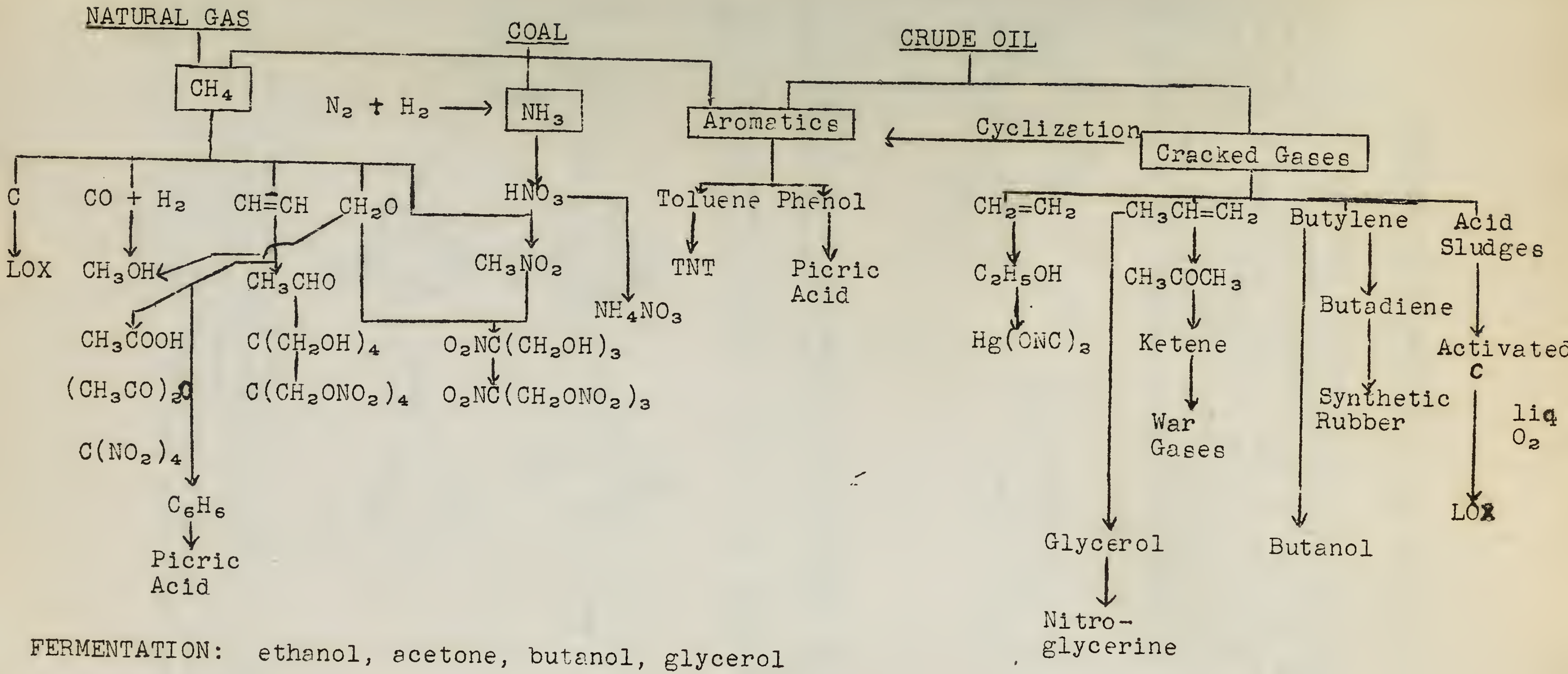
Reported by R. S. Voris
P. F. Warfield
May 6, 1942

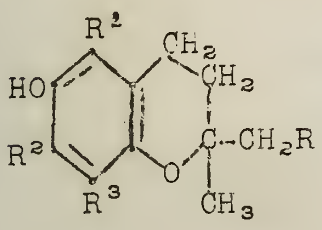


FERMENTATION: ethanol, acetone, butanol, glycerol

CARBOHYDRATES: starch → nitrostarch
cellulose → nitrocellulose
mannose → mannitol → nitromannite
sorbose → sorbitol → nitrosorbite

RECENT DEVELOPMENTS IN THE STUDY OF VITAMIN E

Although many p-hydroxychromans show slight vitamin E activity, it is not possible to modify the structure of α-tocopherol very much and without loss of part or all of the vitamin E activity. Karrer and coworkers have synthesized homologs of α-tocopherol in which R (formula I) has been modified by addition or subtraction of isoprene units. Also they have synthesized derivatives in which R^1,R^2 and R^3 has been varied. A summary of the homologs they have prepared is given in Table I.



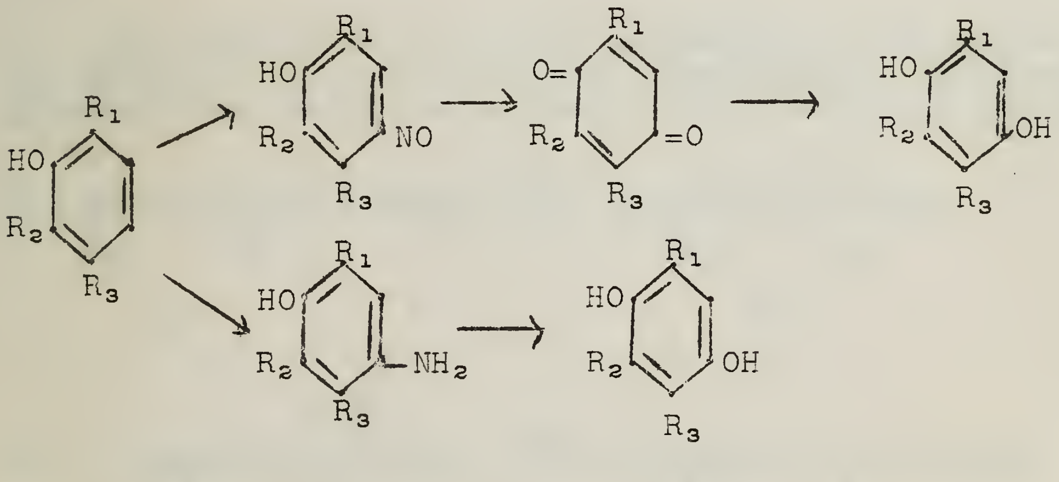
I

In α-tocopherol, $R^1,R^2,R^3 = CH_3$

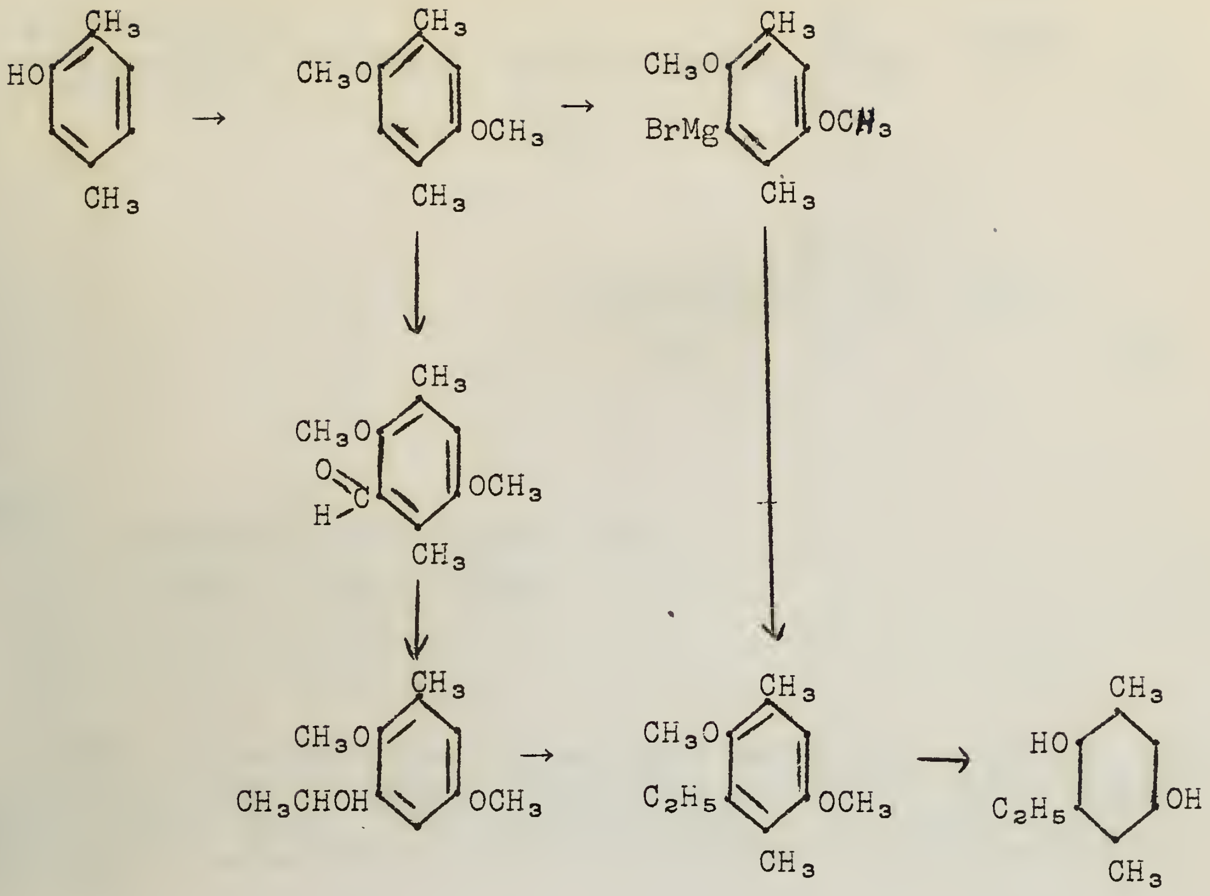
and $R = C_{15}H_{31}$ "3 isoprene units"

All of these compounds were obtained by condensing the proper hydroquinone derivative with the allyl bromide or alcohol.

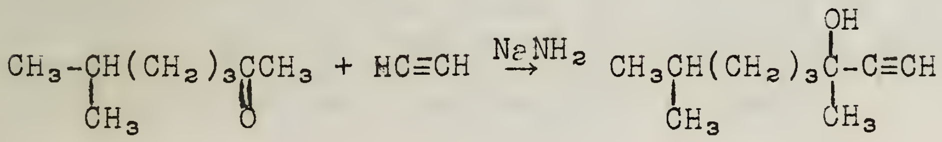
The general methods used for the synthesis of the hydroquinones are as follows:



The substituted hydroquinones were all synthesized by one of these methods, with only one exception, that being 2-ethyl-3,6-dimethyl-p-hydroquinone. In this case, the tri-substituted phenol necessary for the above syntheses could not be obtained readily by synthesis. For this particular case the following procedure was employed:

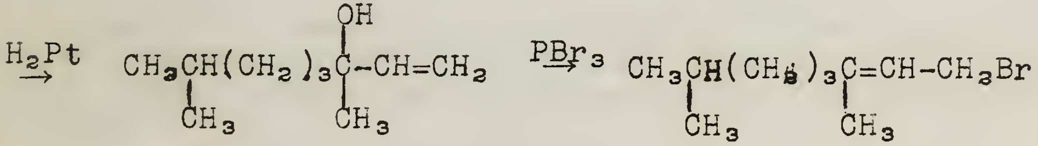


An application of Fischer's synthesis of phytol was used for the synthesis of allyl bromides. For example, 1-bromo-3,7,11-trimethyldodecene-2 was prepared in the following manner:



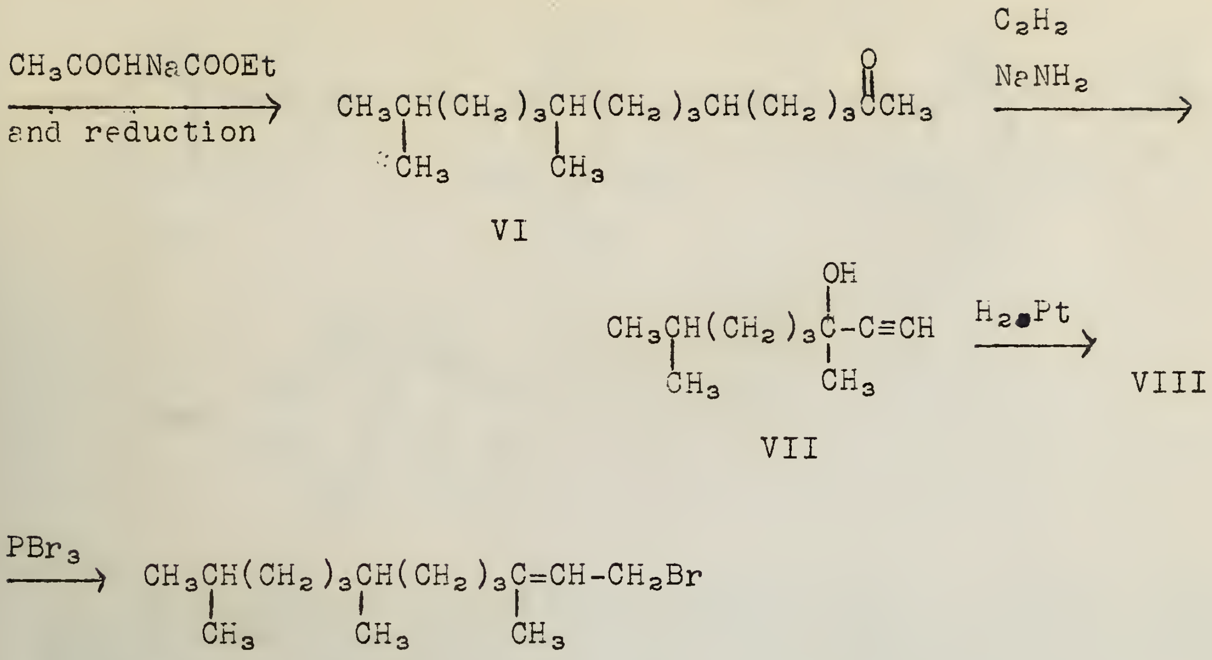
$$CH_3-\underset{CH_3}{CH}(CH_2)_3\underset{O}{\overset{\Vert}{C}}CH_3 + HC\equiv CH \xrightarrow{NaNH_2} CH_3\underset{CH_3}{CH}(CH_2)_3\underset{CH_3}{\overset{OH}{C}}-C\equiv CH$$

II III



$$\xrightarrow{H_2Pt} CH_3\underset{CH_3}{CH}(CH_2)_3\underset{CH_3}{\overset{OH}{C}}-CH=CH_2 \xrightarrow{PBr_3} CH_3\underset{CH_3}{CH}(CH_2)_3\underset{CH_3}{C}=CH-CH_2Br$$

IV V



$$\xrightarrow[\text{and reduction}]{CH_3COCHNaCOOEt} \underset{CH_3}{CH_3CH}(CH_2)_3\underset{CH_3}{CH}(CH_2)_3CH(CH_2)_3\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{C_2H_2,\ NaNH_2}$$

VI

$$\underset{CH_3}{CH_3CH}(CH_2)_3\overset{OH}{\underset{CH_3}{C}}-C\equiv CH \xrightarrow{H_2 \cdot Pt} \text{VIII}$$

VII

$$\xrightarrow{PBr_3} \underset{CH_3}{CH_3CH}(CH_2)_3\underset{CH_3}{CH}(CH_2)_3\underset{CH_3}{C}=CH-CH_2Br$$

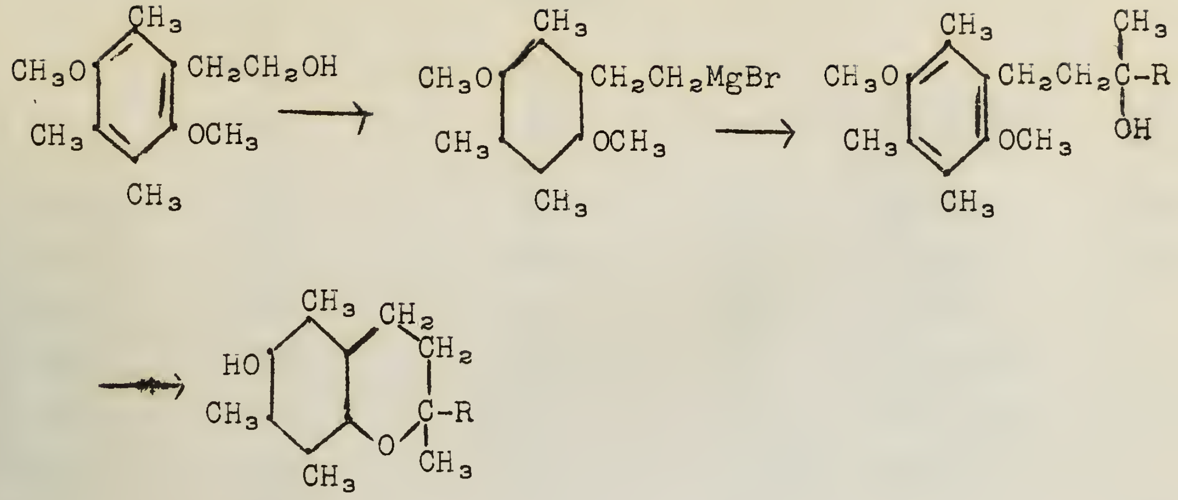
IX

The 1-bromo-3,7-dimethylpentene-2 which was needed for the synthesis of the homolog in which R(Formula I) is C_5H_{11} appears in the above scheme. The higher homolog, i.e., the one in which R is $C_{20}H_{41}$, was obtained from phytol by the same method as above.

One compound containing an unsaturated hetero-cyclic ring has been prepared by Karrer. The method of synthesis here was the condensation of trimethyl hydroquinone with the bromide obtained from the action of PBr_3 upon 3,7,11,15-tetramethylhexadecyn-1-ol-3. The latter was obtained by treating the ketone, resulting from the ozonolysis of phytol with acetylene and sodamide. It also occurs as one of the intermediates in the synthesis of phytol from compound IX above.

A New Method of Synthesis of Tocopherals

Smith and coworkers have devised another method of synthesis of 6-hydroxychromans which does not depend on the condensation of an allyl compound with hydroquinones. This method is as follows:



This method so far has been applied only to chromans containing methyl groups in the 2,5,7, and 8 positions. By varying the nature of the ketone, five 2,5,7,8-tetramethyl-2-alkyl-6-hydroxychromans have been prepared, namely, R=CH_3, C_2H_5, n-C_3H_7, iso-C_4H_9, and $C_{16}H_{33}$(4,8,12-trimethyl decyl).

For the preparation of α-tocopherol, the ketone was obtained from phytol by ozonolysis. The carbinol was prepared from trimethylhydroquinone dimethyl ether by bromination, conversion to the Grignard reagent and treating with ethylene oxide.

From a synthetic point of view, the proof of the structure of α-tocopherol until now has been based upon the assumption that phytol and its derivatives would behave in the condensation reaction as the simpler analogs do, i.e. to form a chroman ring. Since the new method of synthesis leads unquestionably to a chroman structure, the preparation of α-tocopherol by this method affords further proof, by synthesis, that the hetero ring in α-tocopherol is a chroman.

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Reported by F. W. Wyman
May 13, 1942

TABLE I

R	R^1	R^2	R^3	Complete Activity	No. Activity
$C_{20}H_{41}$	CH_3	CH_3	CH_3	30 mg.	3 mg.
$C_{15}H_{31}$	CH_3	CH_3	CH_3	3 mg.	1 mg.
$C_{15}H_{31}$	CH_3	H	CH_3	6 mg.	
$C_{15}H_{31}$	CH_3	CH_3	H	5-10 mg.	
$C_{15}H_{31}$	H	CH_3	CH_3	8-10 mg.	
$C_{15}H_{31}$	CH_3	CH_3	C_2H_5	16 mg.	
$C_{15}H_{31}$	CH_3	C_2H_5	CH_3		
$C_{15}H_{31}$	C_2H_5	CH_3	CH_3		
$C_{15}H_{31}$	CH_3	C_2H_5	C_2H_5	10 mg.	
$C_{15}H_{31}$	C_2H_5	CH_3	C_2H_5	10 mg.	
$C_{15}H_{31}$	C_2H_5	C_2H_5	H	10 mg.	4 mg.
$C_{10}H_{21}$	CH_3	CH_3	CH_3		20 mg.
C_5H_{11}	CH_3	CH_3	CH_3		40 mg.

THE ACYLATION AND ALKYLATION OF THE SODIUM ENOLATES OF ALIPHATIC ESTERS

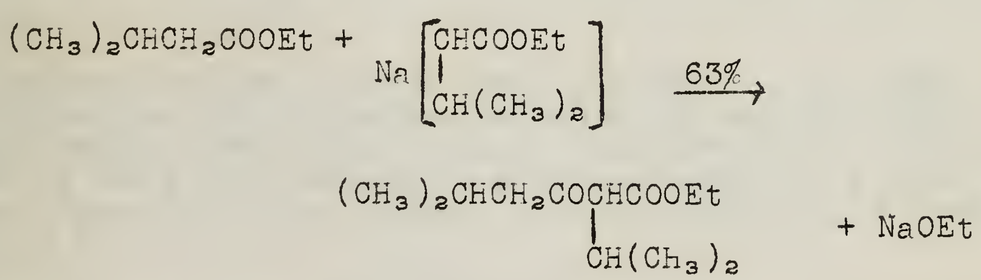
Hauser--Duke University

The scope of reactions of the sodium enolates of esters was limited until a base was found which would convert esters largely into their sodium enolates. The Claisen condensation of simple esters, for instance, required the presence of two alpha hydrogen atoms, if the condensing agent used was sodium ethoxide. Two esters qualifying in respect to having two alpha hydrogen atoms but failing to condense were ethyl isovalerate and ethyl t-butyl acetate. Also, esters belonging to the class which has only one alpha hydrogen atom did not condense.

In 1931 Schlenk, Hillemann and Rodloff showed that sodium triphenylmethyl converts methyl diphenylacetate into its sodium enolate, consequently the use of sodium triphenylmethyl has been extended to the condensations, acylations and alkylations of those aliphatic esters requiring a strong base to form the enolate. The enolate is formed according to the following equation:

$$(C_6H_5)_3CNa + \overset{|}{\underset{|}{H}}\text{-}C\text{-}COOR \rightarrow Na[\overset{|}{\underset{|}{C}}\text{-}COOR] + (C_6H_5)_3CH$$

Ethyl isobutyrate, which has only one alpha hydrogen atom, has been converted to ethyl isobutyrylisobutyrate by sodium triphenylmethyl; and ethyl isovalerate, which was noted above to be unaffected by treatment with sodium ethoxide, similarly undergoes self-condensation to give ethyl isovalerylisovalerate:



$$(CH_3)_2CHCH_2COOEt + Na\begin{bmatrix} CHCOOEt \\ | \\ CH(CH_3)_2 \end{bmatrix} \xrightarrow{63\%} (CH_3)_2CHCH_2CO\underset{\substack{|\\ CH(Ch_3)_2}}{C}HCOOEt + NaOEt$$

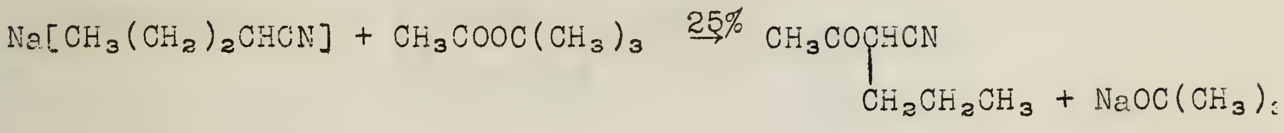
Spielman and Schmidt have shown that this same self-condensation also takes place in the presence of mesitylmagnesium bromide, although the yield is lower.

The acylation of the sodium enolate of an ester by a different ester is satisfactory only when the latter has no active hydrogen, for the sodium enolate apparently attacks an available active hydrogen of the second ester more readily than the carbonyl group to give a mixture of two enolates and two free esters, from which four beta-keto esters might be formed.

Nitriles having hydrogens alpha to the -C≡N group likewise exhibit this hydrogen interchange:

$$CH_3(CH_2)_2CH_2CN + Na[CH_2COOC(CH_3)_3] \rightarrow Na[CH_3(CH_2)_2CHCN] + CH_3COOC(CH_3)_3$$

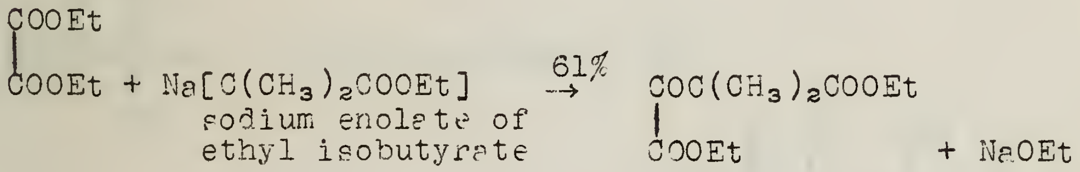
n-valeronitrile — sodium enolate of t-butyl acetate



$$Na[CH_3(CH_2)_2CHCN] + CH_3COOC(CH_3)_3 \xrightarrow{25\%} \underset{\displaystyle CH_2CH_2CH_3}{CH_3CO\overset{}{C}HCN} + NaOC(CH_3)_3$$

α-acetyl-n-valeronitrile

Ethyl oxalate, having no alpha hydrogens, reacts easily to give ethoxalyl derivatives, but ethyl formate gives low yields of formyl esters:



$$\begin{matrix}COOEt\\ |\\ COOEt\end{matrix} + Na[C(CH_3)_2COOEt] \xrightarrow{61\%} \begin{matrix}COC(CH_3)_2COOEt\\ |\\ COOEt\end{matrix} + NaOEt$$

sodium enolate of ethyl isobutyrate

$$HCOOEt + Na[C(CH_3)_2COOEt] \xrightarrow{16\%} HCOC(CH_3)_2COOEt + NaOEt$$

Hauser has also carried out a series of acylations with acid chlorides and the sodium enolates of esters having only one alpha hydrogen atom. This method, in contrast to that using esters as the acylating agent, gave satisfactory yields. The general reaction is as follows, and the results are summarized in Table I:

$$RCOCl + Na[CR_2COOEt] \rightarrow RCOCR_2COOEt + NaCl$$

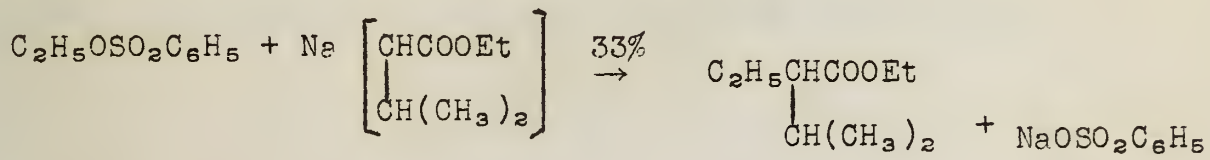
The α,α-disubstituted beta-keto esters so produced may be subjected to ketonic hydrolysis to give certain ketones of the type $RCOCHR_2$. The complete procedure represents an extension of the acetoacetic ester method of synthesis of these ketones. Table II lists the experimental results.

Finally, certain other reactions of the sodium enolates of esters might be listed:

1. With phenyl isocyanate the enolate of ethyl isobutyrate gives α,α-dimethylmalonanilide ethyl ester:

$$C_6H_5N{=}C{=}O + Na[C(CH_3)_2COOEt] \xrightarrow{33\%} C_6H_5NHCOC(CH_3)_2COOEt$$

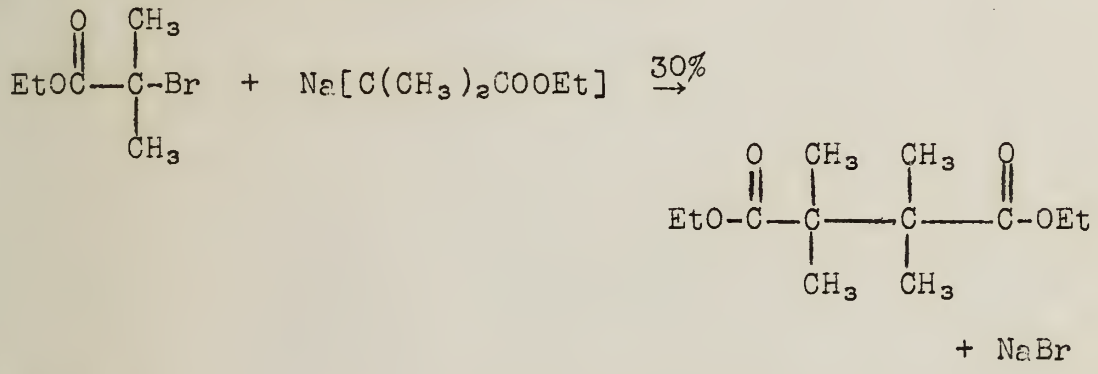
2. With ethyl benzenesulfonate the enolate of ethyl isovalerate gives ethyl α-ethylisovalerate:



$$C_2H_5OSO_2C_6H_5 + Na\left[CH(CH(CH_3)_2)COOEt\right] \xrightarrow{33\%} C_2H_5CH(CH(CH_3)_2)COOEt + NaOSO_2C_6H_5$$

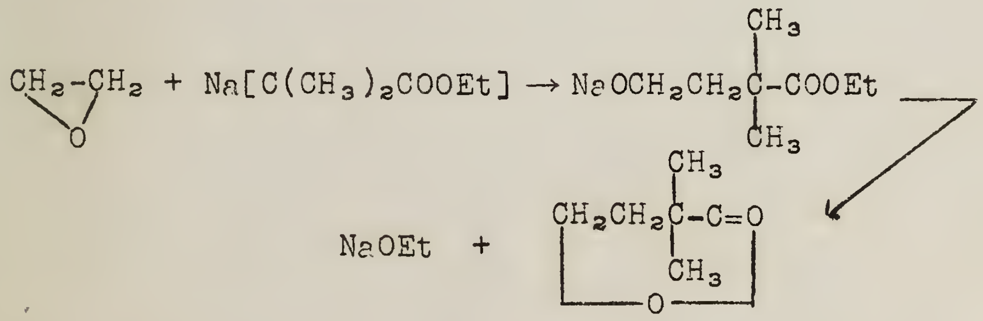
This method represents a gain of 11% in yield over that obtained when the same enolate was alkylated with ethyl iodide.

3. With ethyl α-bromoisobutyrate the enolate of ethyl isobutyrate gives diethyl tetramethylsuccinate:



$$EtOC(=O)-C(CH_3)_2-Br + Na[C(CH_3)_2COOEt] \xrightarrow{30\%} EtO-C(=O)-C(CH_3)_2-C(CH_3)_2-C(=O)-OEt + NaBr$$

4. With ethylene oxide the enolate of ethyl isobutyrate gives α,α-dimethylbutyrolactone:



A previous method due to Blanc for production of this compound involved the reduction of α,α-dimethylsuccinic anhydride, but this procedure also results in the formation of the isomeric β,β-dimethyllactone.

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Reported by John Whitson
May 13, 1942

TABLE I

Results of Experiments with Na[$CR_2COOC_2H_5$] and RCOCl

Ester Used, Ethyl			$(C_6H_5)_3CNa$	Acid Chloride Used			Yield of Keto Ester		B.P.	
	G	Mole	Mole		G	Mole	G	%	°C	Mm
Isobutyrate	23	0.198	0.195	Acetyl	32	0.408	15.7	51	75-6 183-4	15 760
Isobutyrate	22	.190	.185	*n*-Butyrl	21.5	.20	20.2	58	109-11	29
Isobutyrate	110	.95	.93	Isobutyryl	102	.95	128.0	74	92-94	15
Isobutyrate	102	.875	.85	Benzoyl	123	.875	122.0	65	146-8	15
Methylethylacetate	26	.20	.20	Propionyl	18.5	.20	19.3	52	97-102	15
Methylethylacetate	26	.20	.20	Isovaleryl	24.6	.20	21.7	51	116-19	15
Methylethylacetate	25.6	.197	.197	Benzoyl	27.7	.197	24.0	52	164	18
Diethylacetate	28	.20	.195	Benzoyl	28	.20	28.8	59	175-77	20

TABLE II

Ketonic Hydrolysis of Beta-Keto Esters

β-Keto Ester Used, Ethyl		Hydrolysis Mixture, cc.									
	G.	H_2SO_4	H_2O	CH_3-COOH	50% HI	Time, Hr.	Ketone	Yield G	%	B.P. °C	Mm.
Ethylbutyrylisobutyrate	14.8	10	10	30		4.0	Di-isopropyl	7.0	78	121-25	760
n-Butyryldimethylacetate	21.0	5	10	55		3.5	*n*-Propyl iso-propyl	10.2	79	134-36	760
Propionyldimethylacetate	14.2	4	4	40		8.0	Ethyl isopropyl	6.7	78	134-36	760
Isovalerylmethylethylacetate	14.0	8	5	38		14.0	Isobutyl *s*-butyl	7.0	75	165-67	760
Benzoyldimethylacetate	20.0	10	5	30		3.0	Phenyl isopropyl	13.4	81	102 218	15 760
Benzoylmethylethylacetate	13.0			75	75	48.0	Phenyl *s*-butyl	6.0	69	109	10
Benzoyldiethylacetate	15.0			75	75	48.0	Diethylacetophenone	8.0	75	117-18 247-49	10 760