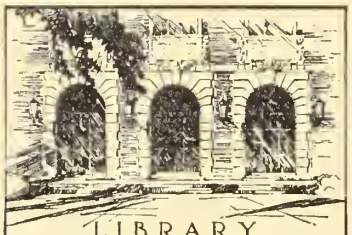
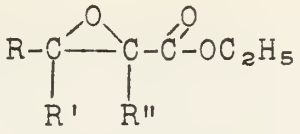


SEMINAR REPORTS

Summer Semester 1943

REACTIONS OF GLYCIDIC ESTERS

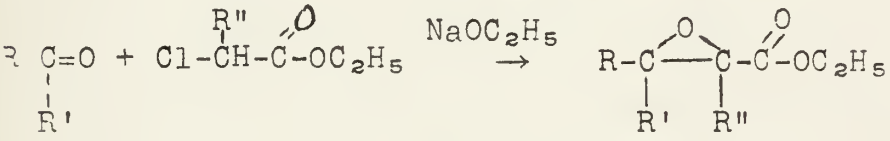
Glycidic esters first came into prominence in 1904 as the basis of a new aldehyde synthesis. Since that date, Darzens and coworkers have discovered many other interesting reactions of esters of this type, which will be presented in this seminar. Glycidic esters are ethylene oxidic esters of the general formula



where any or all of the R groups may be hydrogen.

A. Preparation of Glycidic Esters.

1. In general, the preparation associated with Darzen's name consists of the condensation of an aldehyde or ketone with an alpha-halo ester in the presence of sodium ethoxide.



60-65%

This reaction is general with ketones. Aliphatic and alicyclic ketones give better yields of the corresponding ester than semi-aromatic ketones do. In the aromatic series, sodamide must sometimes be used in place of sodium ethoxide.

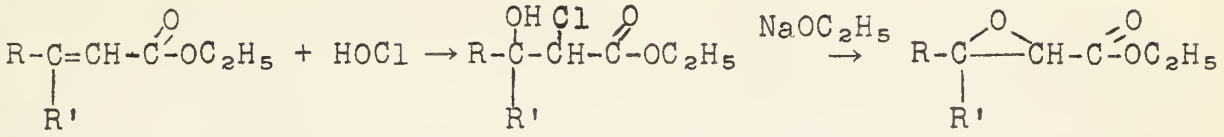
Carvone, pulegone, thujone, menthone, and isophorone give negative results with alpha-halo esters. It appears that the vicinal electro-negative methylene groups have an unfavorable influence on the reaction.

The reaction is not at all general for aldehydes. When ethyl-α-chloroacetate is used, only a few aromatic aldehydes, such as benzaldehyde, will condense. Ethyl α-chloropropionate will not condense with all aldehydes, but it is successful in many cases where the acetate fails. With acetaldehyde, propionaldehyde, and isovaleraldehyde, 20-30 per cent yields are possible. Aromatic aldehydes, piperonal, and furfural condense with it quite easily. Even paraformaldehyde reacts to give ethyl α-methyl-glycidate.

Condensations with ethyl α-chloroproprionate give better yields than the corresponding reactions with ethyl α-chloroacetate or ethyl α-bromopropionate.

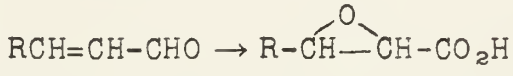
The glycidic esters act as saturated compounds, having no effect upon bromine solutions. The ordinary carbonyl reactions are not obtained, and failure to give a phenyl urethan proves the absence of an hydroxyl group.

2. A later development by Darzens utilizes α,β-unsaturated esters.



The elimination of hydrogen chloride by sodium ethoxide is quantitative. Inasmuch as one can start with any α,β-unsaturated ester and obtain the corresponding glycidic ester, this reaction is more general than the ketone-ester condensation.

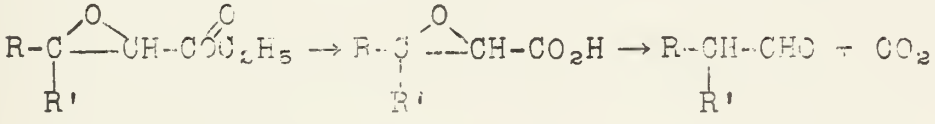
3. Patents have been issued for the oxidation of α,β-unsaturated aldehydes to the glycidic acids.



Hydrogen peroxide, or hypohalites, in the presence of sodium hydroxide have been used as oxidizing agents.

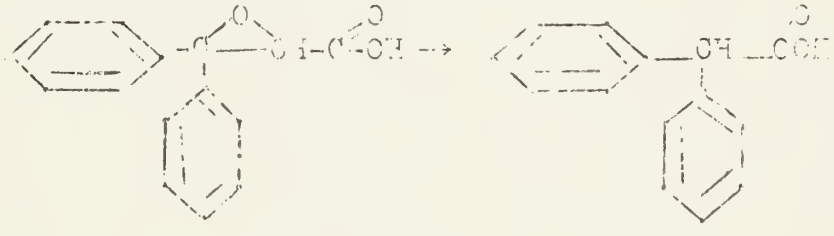
B. Preparation of Aldehydes

Glycidic esters having an alpha hydrogen can be decomposed to give aldehydes according to the following equation.



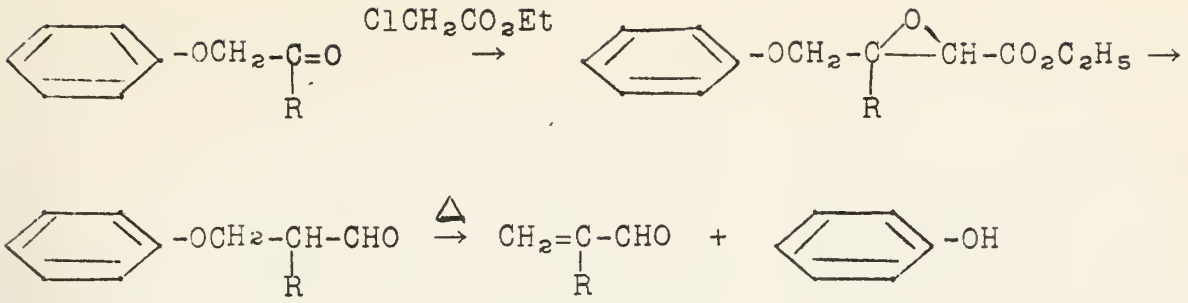
The esters, in general, are quite easily saponified forming unstable acids which readily lose carbon dioxide to form aldehydes. Usually carbon dioxide begins to escape at atmospheric pressure, the last traces being removed under vacuum.

Beta-di-aromatically substituted glycidic esters give acids upon decomposition instead of aldehydes.



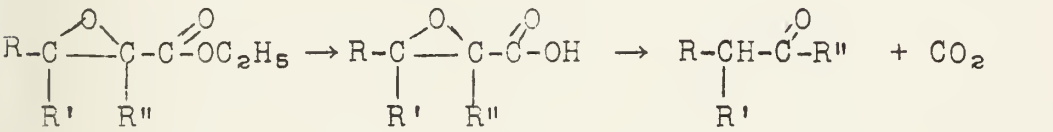
Often in aliphatic and hydroaromatic series, the aldehydes obtained polymerize easily.

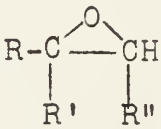
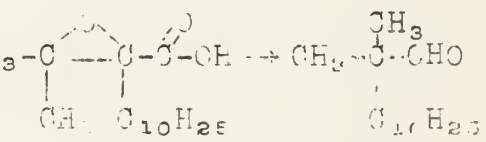
The following is an interesting preparation of alpha substituted acroleins.



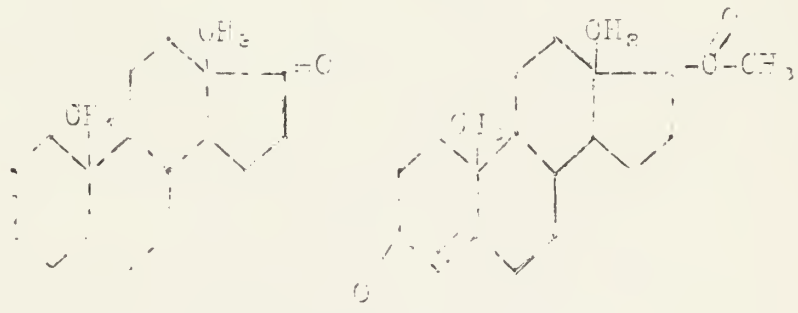
C. Preparation of Ketones

Glycidic esters possessing an alkyl group in the alpha position decompose in general to give ketones.



This suggests the intermediate formation of  , which rearranges to the ketone. However, if R" = C_5 or greater, the molecule rearranges to give an aldehyde. 

Yarnall and Wallis, in attempting to convert dehydroandiosterone to progesterone, developed two improved methods for decomposing the glycidic acid. The first of these was to treat the acid with



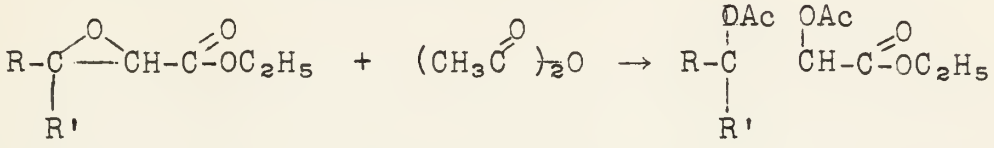
dehydroandiosterone progesterone

hydrogen chloride, thereby forming a chlorohydrin. This was dissolved in a sodium carbonate solution and steam distilled. Even better results were obtained by dissolving the chlorohydrin in pyridine. The second method involved treating the sodium salt of the acid with alkali. Both methods improved the yields considerably. Numerous other of their refinements of technique are to be recommended.

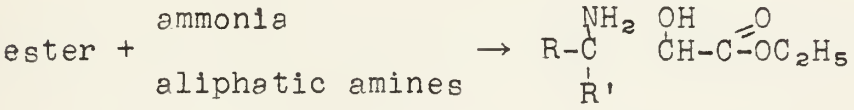
D. Reactions of Glycidic Esters with Various Reagents

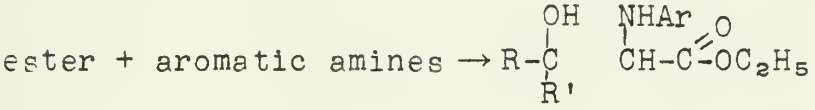
Although the glycidic esters are saturated compounds, the oxygen linkage makes them unusually reactive. Listed below are several typical reactions.

1. Reaction with acid anhydrides.

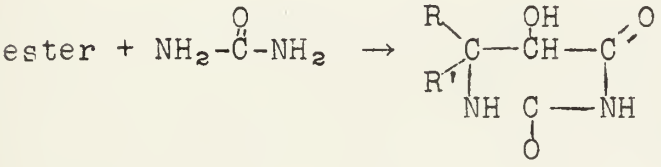


2. Reaction with ammonia and amines.



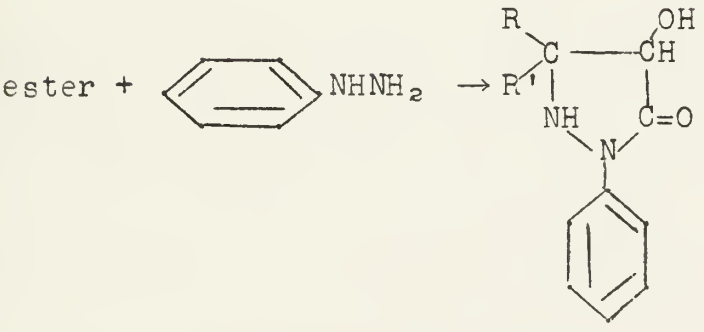


3. Reaction with urea



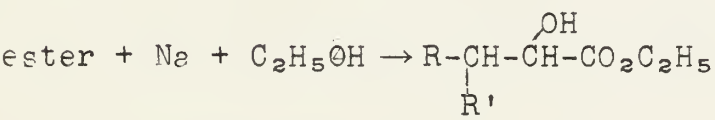
4,4-dialkyl-2,6-diketo-5-hydroxy-pyrimidine

4. Reaction with phenylhydrazine



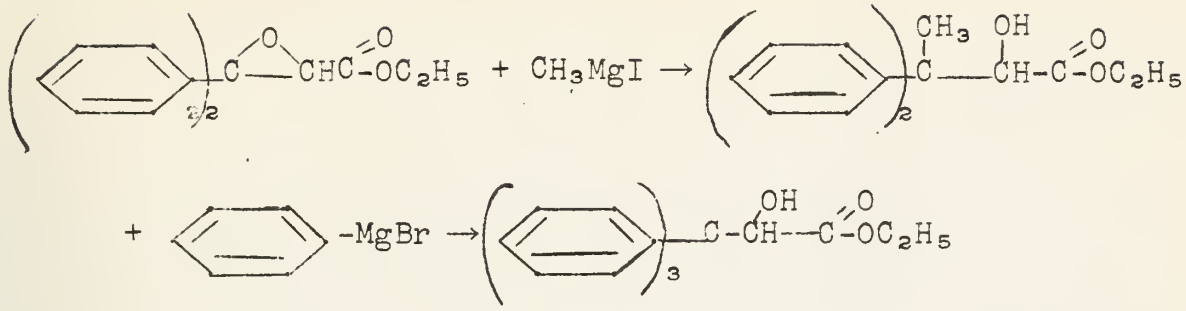
1-phenyl-3,3-dialkyl-4-hydroxy-5-pyrazalone

5. Reaction with Na and alcohol.



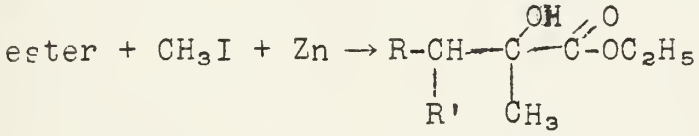
The group -ONa (or -OMgX in case of Grignard), which is formed as an intermediate in the alpha position to the ester group, renders the latter more inert, or almost entirely inert, towards the reagents used.

6. Reaction with Grignard reagent.



In general Grignard reagents react well with glycidic esters, but Darzens was unable to establish any principle concerning the product to be expected. He obtained mixtures of glycidic alcohols, hydroxy-esters, and glycols.

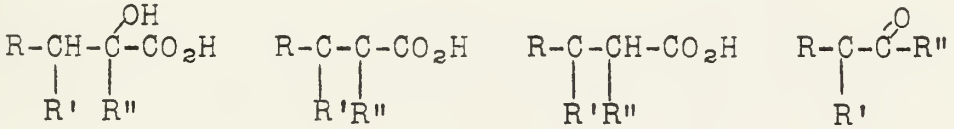
7. Reaction with alkyl bromides and iodides.



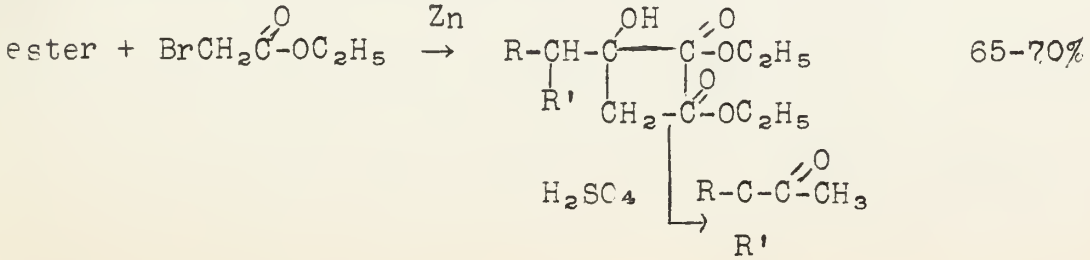
RZnX compounds will not react with the ester grouping, so the product is easily isolated. One might expect to obtain the α-hydroxy-β-methyl, or α-methyl-β-hydroxy product instead of the above. Its formula has been definitely established by the ease with which it is dehydrated and by comparison with known compounds. This condensation reaction is general, and proceeds even more easily with allyl bromide.

In all probability the glycidic ester rearranges to a pyruvic ester under the influence of the organo-zine compound. This would then react normally. The first fractions in the distillation of these glycidic esters give semicarbazones which check with the corresponding substituted pyruvic ester derivatives.

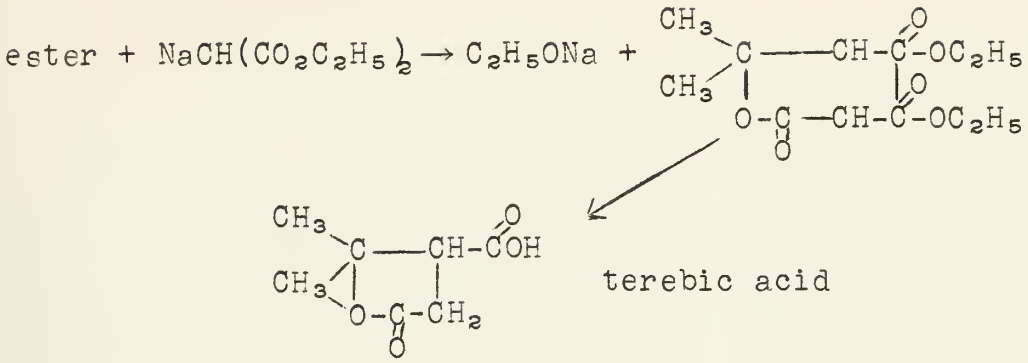
This reaction serves as a good method of preparation for compounds of the following types.



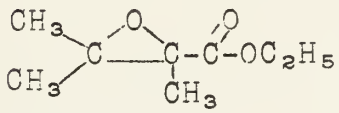
8. Reaction with alpha-bromo esters



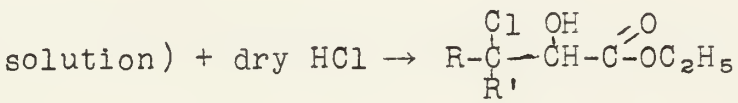
9. Reaction with sodium malonic ester



terebic acid

The ester  will not react, presumably because of steric hindrance.

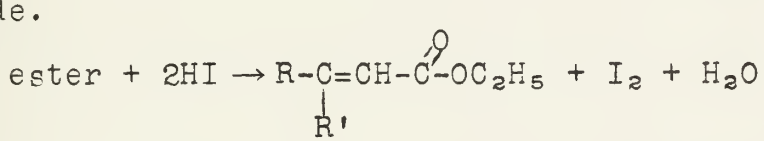
10. Reaction with hydracids



The structure was proven by the failure to split out water, and by comparison with the ester in which the hydroxyl was known to be in beta position. Sodium ethoxide in absolute alcohol regenerates the glycidic ester immediately.

Darzens tried to make the dimethyl pyruvic ester by splitting out hydrogen chloride with diethylaniline. As it did not work, he concluded that in the aliphatic series the glycidic form is more stable than the pyruvic form.

This reaction is general with any hydracid except hydrogen iodide.



This reaction also is general and permits the formation of any α, β-unsaturated ester from the corresponding glycidic ester.

In all of these reactions, one must operate in the absence of water to avoid the formation of glyceric esters.

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Haller and Blanc, ibid., 142, 1471 (1906).
Pointet, ibid., 148, 417 (1909)
Bardon and Ramart, ibid., 183, 214 (1926).
Rothstein, Bull. Soc. Chim., [5], 2, 653 (1935).
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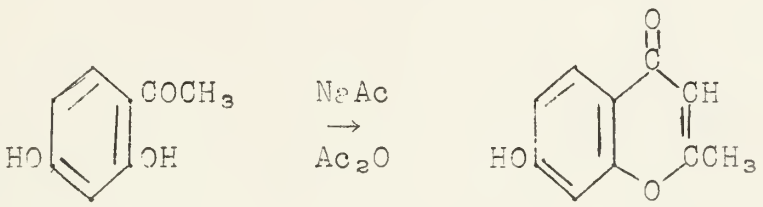
Reported by Paul V. Smith
June 23, 1943

THE KOSTANECKI-ROBINSON REACTION

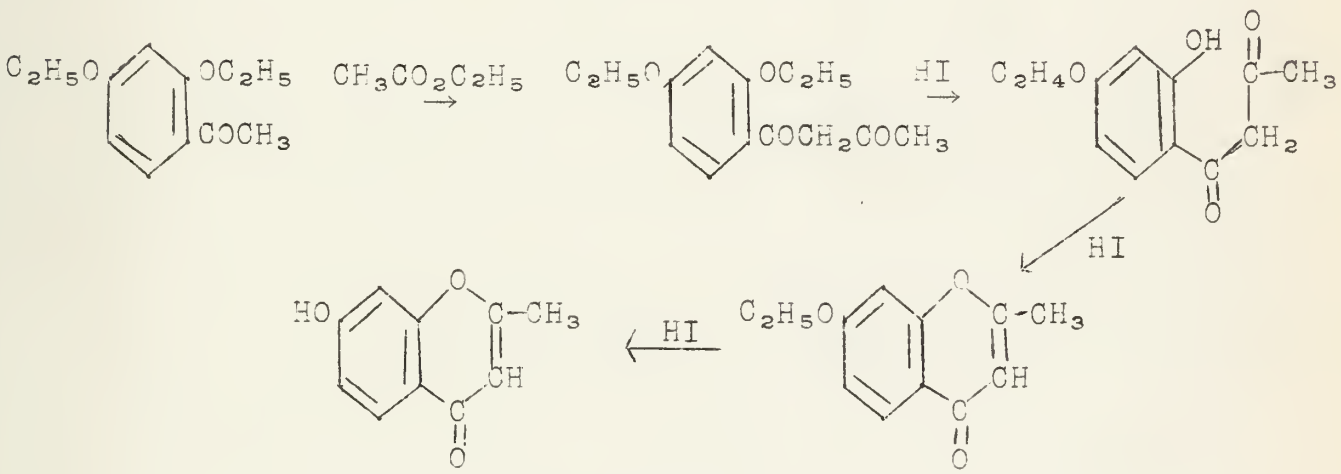
Introduction

The reaction of an o-hydroxy aryl ketone with an acid anhydride and the corresponding sodium salt of the acid, leading to the formation of chromones, coumarins, or mixtures of the two is usually referred to as the Kostanecki-Robinson reaction. Tahara[1], by treating resacetophenone with acetic anhydride and sodium acetate, isolated a product which he thought was dehydrodiacetylresacetophenone. Kostanecki[2], following up this work, proved that the compound formed was instead the 7-hydroxy-2-methyl-chromone.



7-hydroxy-2-me-chromone

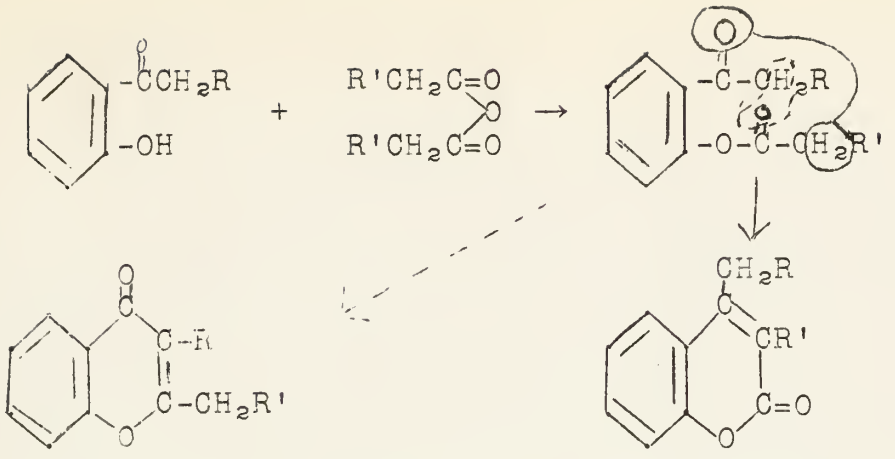
To verify the structure of this compound, Kostanecki[3] synthesized it by a different method.



This method has proved to be very general and useful in the proof of structure of many of the chromones which have been synthesized in the Kostanecki-Robinson manner.

Mechanism[4,5]

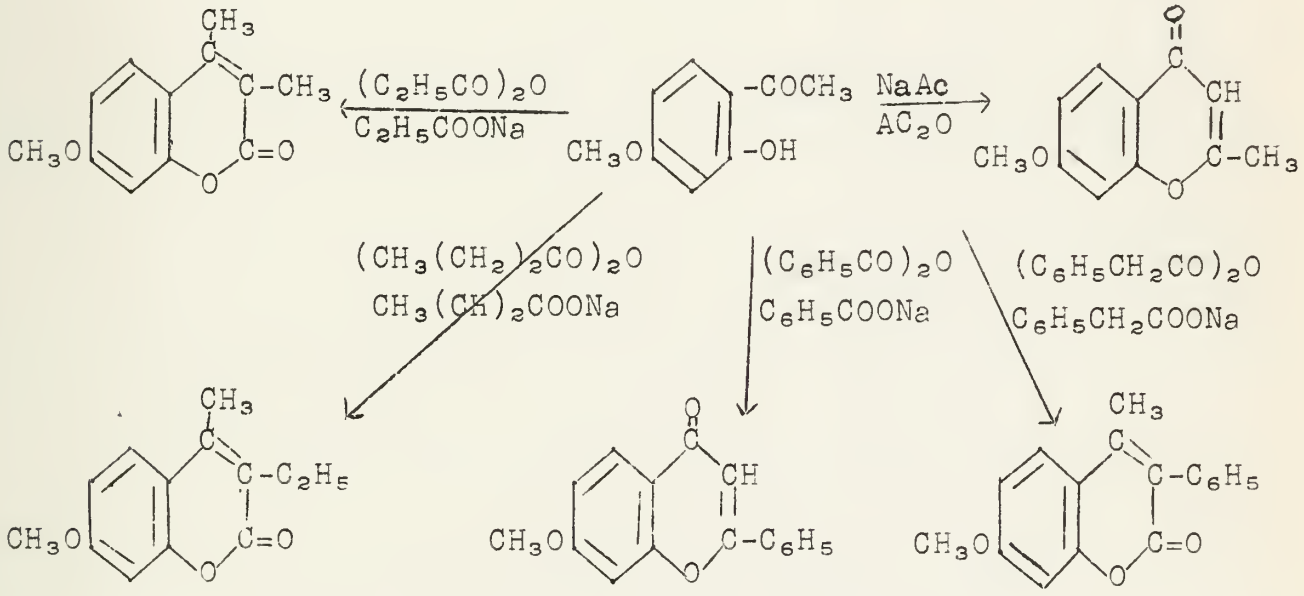
The formation of chromones or coumarins can be explained on the basis of the following mechanism.



Chromone Derivative Coumarin Derivative

o-Hydroxyaryl Methyl ketones[2,6,7]

The action of sodium acetate and acetic anhydride on o-hydroxy acetophenones results in chromone formation, while with propionic and butyric anhydride and the corresponding sodium salt of the acid the tendency is toward coumarin formation. Phenylacetic anhydride and the sodium salt gives coumarins while benzoic anhydride and sodium benzoate gives flavones[8] (2-phenyl-chromones). The results are



entirely analagous in the naphthalene series[9]. The α-hydroxy-β-naphthyl methyl ketones on acetylation yield the α,γ-naphthopyrones, while propionylation and butyrylation give the α,β-napthopyrones. Chakravarti[10] found that the introduction of halogen (chlorine and bromine) into the ring had no effect on the course of the reaction.

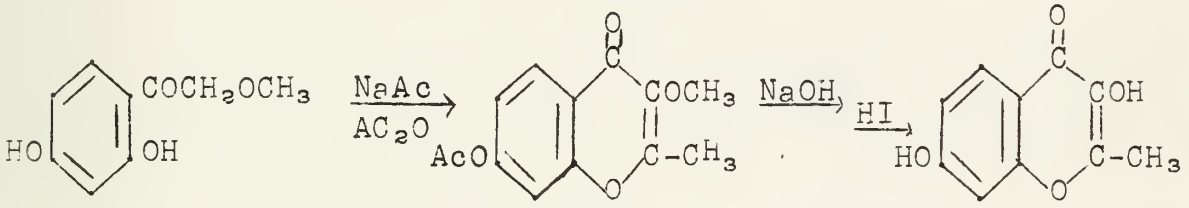
With the methyl ketones the most important effect is the acid radical that is used. Apparently the methylene group formed in the o-acylation is more active and loses water more readily than the hydrogens from the methyl ketones.

Recently extensive study has been carried out on the acylation of orcacetophenone[11] (2,4-dihydroxy-6-methyl acetophenone) and it has been found that acetylation, propionylation and butyrylation all result in coumarin formation, while benzoylation yields the 3-benzoyl flavone. However γ-orcacetophene[12] (2,6-dihydroxy-4-methyl acetophenone) yields the chromone on acetylation. The 6-methyl group in orcacetophenone seems to have a profound influence on the course of the reaction and it may be a steric factor. In general when a methyl ketone is used, increasing the acid length increases the tendency toward coumarin formation.

ω-Substituted-o-hydroxy aryl methyl ketones

Propiophenone derivatives, on acetylation, propionylation or butyrylation give mainly chromens. Curd and Robertson[13] prepared 7-hydroxy-2,3-dimethyl chromone by acetylation of respropiophenone. Heilbron[7] found that propionylation and butyrylation of 2-hydroxy-4-methoxy propionphenone gave mainly chromone derivatives. Hence the change from a methyl to an ethyl ketone has a greater effect than varying the sodium salt and the acid anhydride. Benzoylation produces chromones while phenylacetic anhydride always gives a coumarin, regardless of the ketone used.

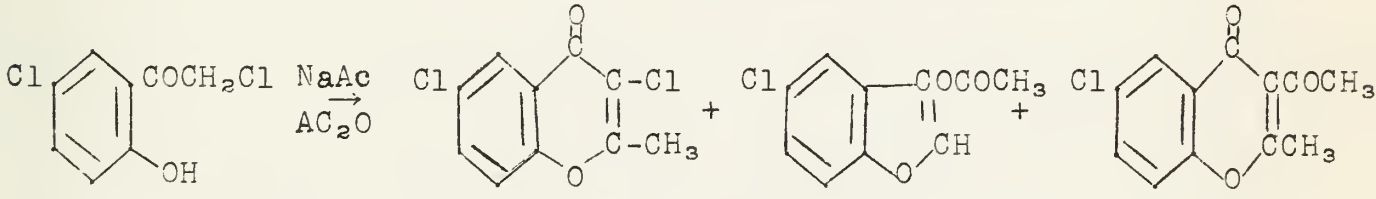
ω-Methoxy methyl ketones[8] yield methoxy chromones which then can be demethylated to give chromonols.



3,7-dihydroxy-2-methyl chromone

ω-Methoxy resacetophenone on benzoylation and subsequent hydrolysis gives 7-hydroxy-3-methoxy flavone.

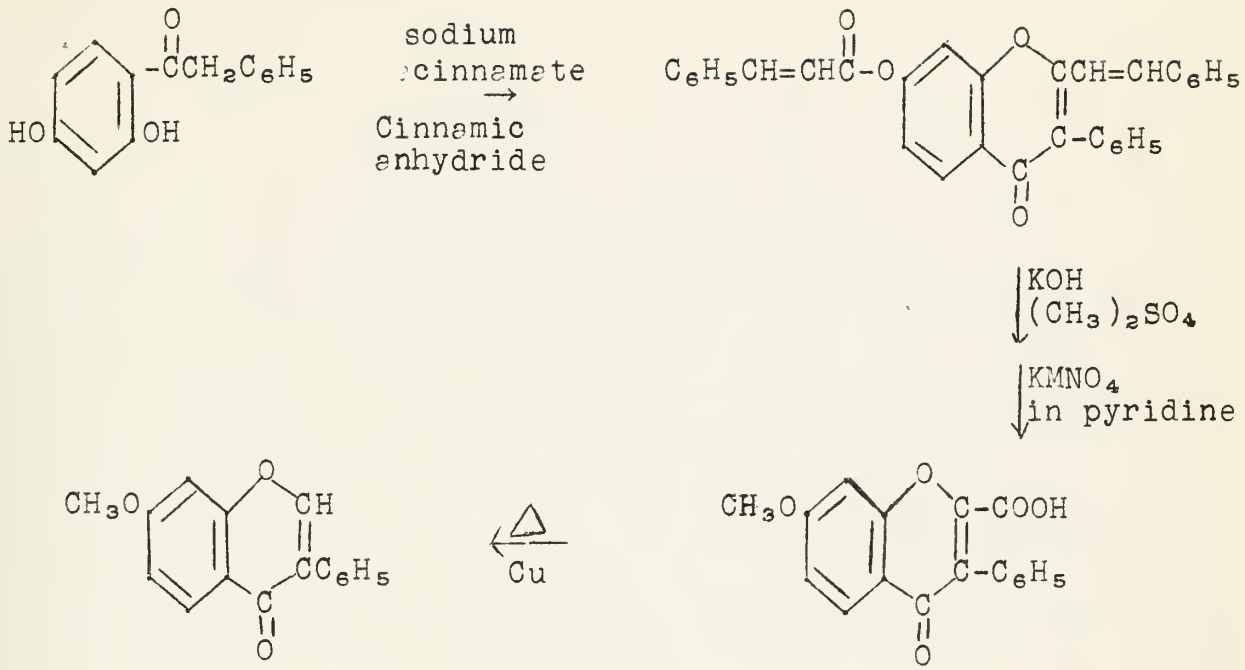
ω-Halo methyl ketones[5] generally produce mixtures.



o-Hydroxy-ω-bromacetophenone under similar conditions gives chiefly an ester of a chromonol.

Benzyl ketones give almost exclusive chromone formation with any of the acylating agents. Isoflavones substituted in the 2-position are quite readily obtained by the interaction of 2,4-dihydroxyphenyl benzyl ketones. The isoflavones in which the 2-position is unsubstituted are difficult to prepare. 7-Methoxy isoflavone is

prepared as follows.



The ω -substituent is always an aid to chromone formation and may from the point of view of increasing yield and ease of purification be arranged in the order: methoxyl, methyl, phenyl.[14] Chromone formation takes place as a rule more readily in the naphthalene series than in the benzene series and is often quantitative from derivatives of α-naphthol.

O-Hydroxy benzophenones

Acetylation of o-hydroxybenzophenones yields 4-phenyl coumarins or -O-acetyl derivatives of the ketone while a mixture of acetic anhydride and sodium phenylacetate gives 3,4-diphenyl coumarins.[14]

Experimental

Practically all o-hydroxy aryl ketones will react with the acid anhydrides if heated long enough, which may be from 2 to 24 hours at temperatures ranging from 100 to 200°C. Subsequent dilution with water will cause the product to separate. One good method of separating the chromone from the coumarin depends on the insolubility of the oxonium salt of the chromone in ether.[5] Another method depends on the use of sodium ethoxide in the cold.[15] This reagent forms an o-hydroxy-β-diketone from the chromone and a coumaric acid derivative from the coumarin. Acidification regenerates the coumarin which then can be separated from the o-hydroxy-β-diketone by alkali. Concentrated sulfuric acid will then regenerate the chromone.

In many of the reactions acylated chromones are formed. Sethna and Shah[11] have devised a method whereby stepwise elimination of the acyl groups can be accompalished. The O-acyl group can be smoothly removed by the use of concentrated sulfuric acid, leaving the 3-acyl group intact. The C-acyl group then can be removed by the use of alcoholic potassium hydroxide.

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Reported by B. H. Velzen
June 23, 1943

HYDROGENOLYSIS OF SULFUR COMPOUNDS BY RANEY NICKEL CATALYST

During a collaborative study of biotin by du Vigneaud and his coworkers and members of the research staff of Merck and Company a method for the replacement of sulfur by hydrogen was applied to the investigation of the structure of biotin.

It has been found that Raney nickel catalyst prepared in the usual way contains hydrogen which is not lost when the nickel is stored in the absence of oxygen. The hydrogen may be collected by heating the catalyst in the absence of oxygen. The means by which this hydrogen becomes attached to the nickel is not known at the present time. The amount of hydrogen present varies with the method of preparing the catalyst and it is this hydrogen which accomplishes the hydrogenolysis of sulfur containing compounds.

Bougalt, Cattelain and Chabrier have reported the reduction of aliphatic sulfhydryl compounds and disulfides with Raney nickel catalyst in neutral or alkaline solution. They have isolated the intermediate nickel mercaptides in most cases which then decompose to yield the sulfur-free compounds.

Mozingo and his coworkers have found that Raney nickel catalyst alone, in the presence of a solvent at a moderate temperature, removes either reduced or oxidized sulfur by cleavage from the remainder of the organic molecule. The reaction is postulated as taking one of the following two courses:

$$R\text{-}S\text{-}R' + Ni(H) \begin{cases} \xrightarrow{(a)} & R\text{-}R' + R\text{-}R + R'\text{-}R' \\ \xrightarrow{(b)} & R\text{-}H + R'\text{-}H \end{cases}$$

In the first of these the nickel functions as a metal, removing the sulfur in a Wurtz type reaction according to equation (a). In the presence of sufficient Raney nickel catalyst which contains a large excess of hydrogen, only the reaction (b) has been observed.

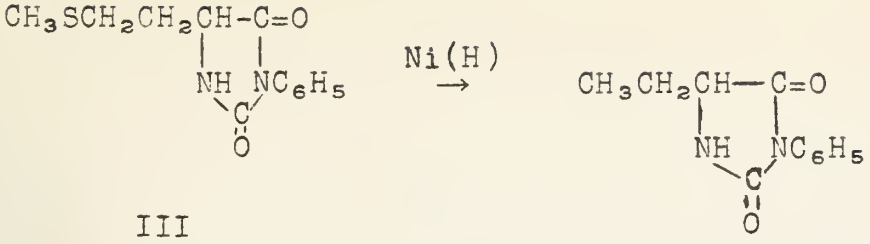
When benzyl sulfide (I) was treated with Raney nickel catalyst in boiling ethanol in the absence of a hydrogen atmosphere an 85% yield of toluene was obtained. Similarly, benzoyl methionine (II), methionine phenylhydantoin (III), and δ, δ'-thiodivaleric acid (IV) were prepared and subjected to the hydrogenolysis reaction with the corresponding sulfur-free compounds being obtained in good yields.

$$C_6H_5CH_2SCH_2C_6H_5 \xrightarrow{Ni(H)} 2C_6H_5CH_3$$

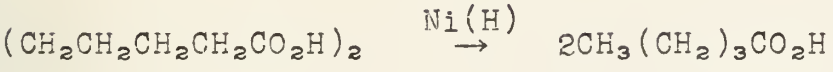
I

$$CH_3SCH_2CH_2\text{-}\underset{\displaystyle NHCOC_6H_5}{\underset{|}{CH}}\text{-}CO_2H \xrightarrow{Ni\ (H)} CH_3CH_2\underset{\displaystyle NHCOC_6H_5}{\underset{|}{CH}}\text{-}CO_2H$$

II



III

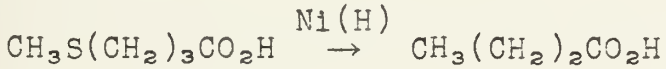


IV

The carbon-sulfur bond in an aromatic sulfide, is easily cleaved by Raney nickel catalyst, and simple refluxing in ethanol solution is sufficient to effect hydrogenolysis. Diphenyl sulfide was easily converted into benzene in 68% yield, while di-p-tolyl disulfide was converted into toluene in 87% yield.

A similar ease of cleavage was observed in the case of oxidized sulfur compounds. Diphenylsulfoxide when treated with the catalyst was reduced to benzene in 75% yield and a 75% yield of benzene was recovered from diphenylsulfone under the same conditions.

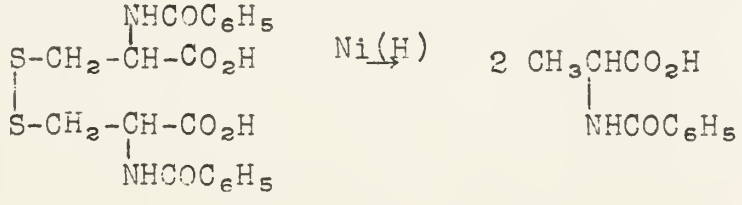
Reductions with Raney nickel take place quite readily in methanol as well as in ethanol. The hydrogenolysis of γ-methylmercaptobutyric acid (V) was carried out in methanol to give a 95% yield of butyric acid.



V

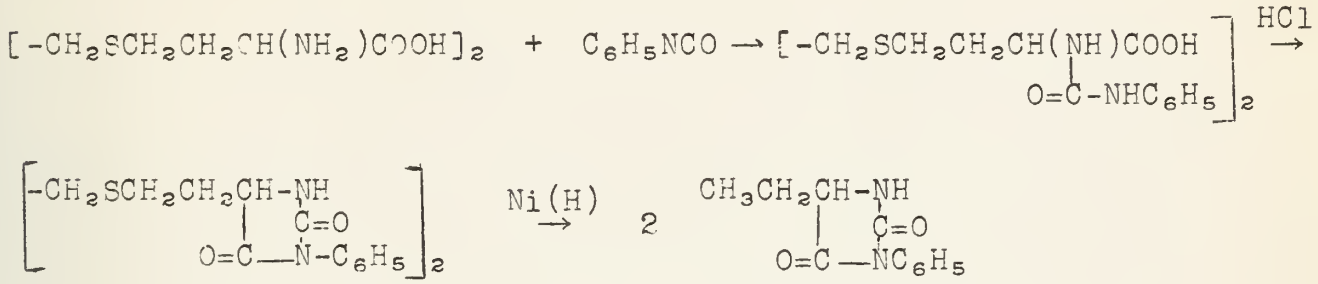
The time of heating may be as short as ten minutes as shown by the successful reductive cleavage of methyl-p-tolyl sulfide in ten minutes to give a 93% recovery of toluene.

Benzoyl-l-(-)-cystine was prepared from l(-)-cystine isolated from a natural source so that the configuration of the benzoyl derivative would be the same. This benzoyl derivative (VI) was easily reduced without disturbing the asymmetric center. The product was found to have the same configuration as the starting material with only a slight deviation in rotation being observed which was probably due to a small amount of racemization by the alkali used in the various steps of the process.



VI

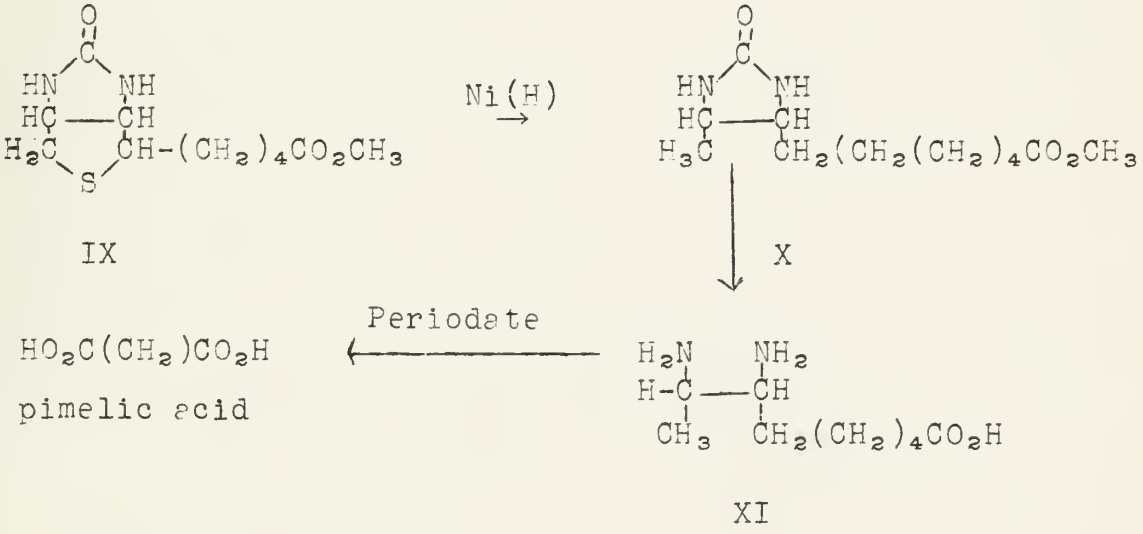
Snyder, Howe, Cannon and Nyman have successfully reduced ethylene bis [-B-(3-phenyl-5-hydantoin) ethylsulfide] (VII) obtained from "pseudomethionine" to dl-3-phenyl-5-ethyl hydantoin (VIII) in 75% yield.



VII VIII

The analysis of the gas in the reductive cleavage revealed a mixture of methane and ethane in the ratio of 44 to 56%. Reduction of "pseudomethionine" itself also gave a mixture of methane and ethane in the ratio of 34 to 66%. However, reductions carried out on three known compounds containing the ethylene disulfide linkage showed that methane as well as ethane could be a product of such a cleavage.

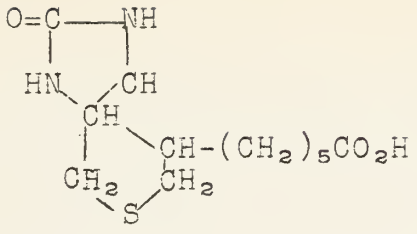
In a recent seminar Southwick reported du Vigneaud's work on the structure of biotin. The problem of deciding between two possible structures for biotin was successfully attacked by the reductive cleavage of biotin methyl ester with Raney nickel according to the method of Mozingo. Biotin methyl ester (IX) was reduced to "desthiobiotin" ester (X) which was hydrolyzed to give a diaminocarboxylic acid (XI). Oxidation of this acid yielded pimelic acid as was expected from formula (IX) and not α-methyl adipic acid as would be expected from formula (XII).



IX X

pimelic acid

XI



XII

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du Vigneaud, Melville, Folkers, Wolf, Mozingo, Keresztesy and Harris, J. Biol. Chem., 146, 475 (1942).
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Reported by H. W. Johnston
June 30, 1943

REACTIONS OF METHYLENE-BIS-AMINES AS AMMONO-ALDEHYDES

Feldman and Wagner; University of Pennsylvania

There exist structural analogies between methylene-bis-amines, considered as ammono-aldehydes or ammono-acetals, and the hydrate and acetals of formaldehyde. Methylene imines may probably be considered as functionally equivalent to methylene diamines in certain reactions, the two being related as are formaldehyde and formaldehyde hydrate.

$$HOCH_2OH \rightleftarrows CH_2O + H_2O$$

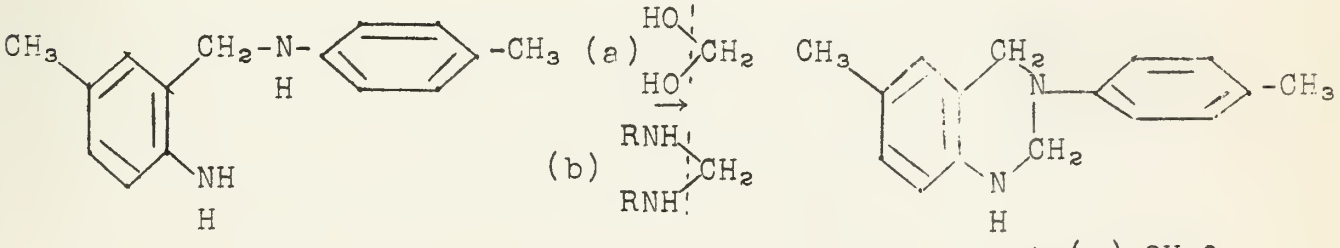
$$RNH\text{-}CH_2\text{-}NHR \rightleftarrows CH_2 = NR + RNH_2$$

Feldman and Wagner used formalin and certain methylene diamines interchangeably in reactions known to be characteristic of formaldehyde. In each group of comparable reactions, the main product was the same whether the methylene diamine or formaldehyde was used.

Methylene diamines are hydrolyzed by acid which made it necessary to conduct certain experiments with apparatus and reagents which had been scrupulously dried. If water were present the methylene diamine could possibly be hydrolyzed to formaldehyde and amine, the formaldehyde being the active reactant rather than the diamine. Thus only in the absence of water could conclusions be drawn to show that the methylene diamine reactions were analogous to those of formaldehyde.

The methylene diamines used were methylene-bis-p-toluidine (I), methylene-bis-p-chloroaniline (II), methylene-bis-p-bromoaniline (III), methylene-bis-p-anisidine (IV), methylene-bis-ethylaniline (V), methylene-bis-piperidine (VI), and methylene-bis-morpholine (VII). The first four are produced from primary amines; the last three, with no amino hydrogen, are ammonia-system analogs of formaldehyde acetals. Since acetals can be used instead of aldehydes in some reactions, it was expected these diamines would show a functional analogy with formaldehyde, which was experimentally shown to be true.

1. Formation of 3-p-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline

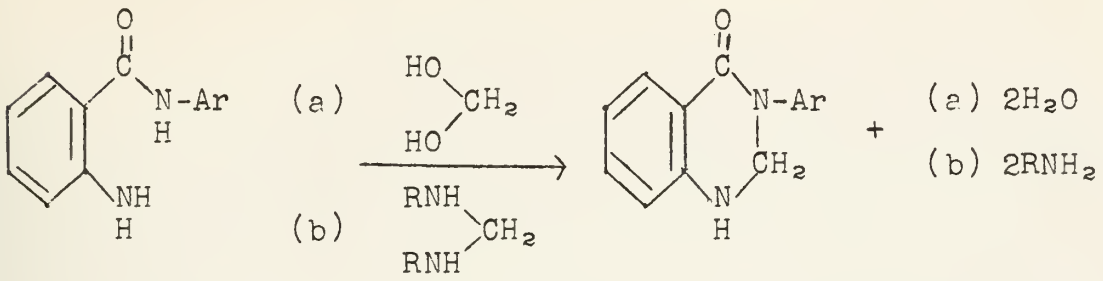


+ (a) $2H_2O$

(b) $2RNH_2$

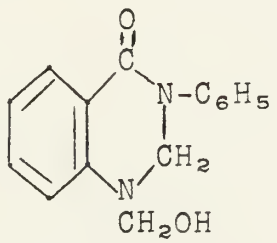
Each of the above named methylene-bis-amines reacted with o-amino-m-xylyl-p-toluidine to give the desired quinazoline.

2. Formation of 3-substituted-1,2,3,4-tetrahydroquinazolones from anthranilanilides

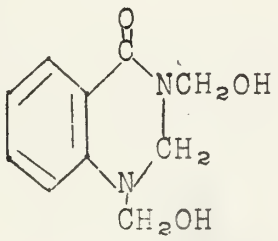


The anthranilanilides used were N-phenyl-, N-p-bromophenyl-, and N-p-anisyl-anthranilamide, giving 3-phenyl-, 3-p-bromophenyl-, and 3-p-anisyl-1,2,3,4-tetrahydroquinazolone-4.

Using a large excess of formalin on anthranilanilide at lower temperatures yielded



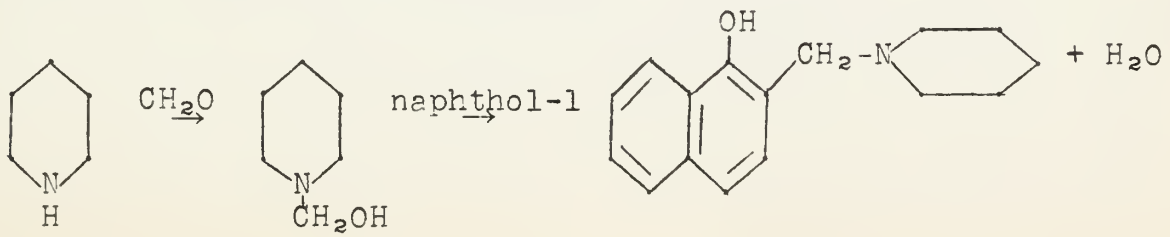
instead of the tetrahydroquinazolone. Interaction of anthranilamide with formaldehyde gave not tetrahydroquinazolone but yielded

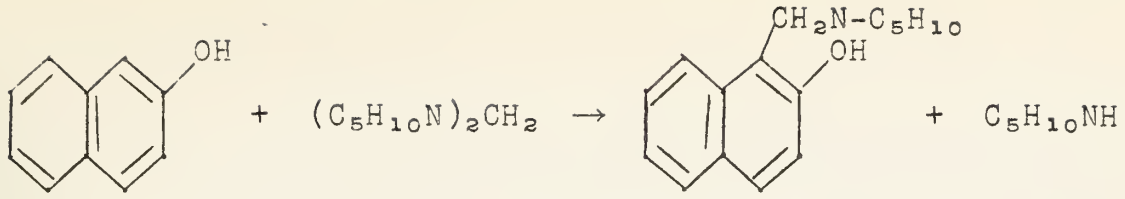


This reaction could not be paralleled using methylene diamines so was not studied further.

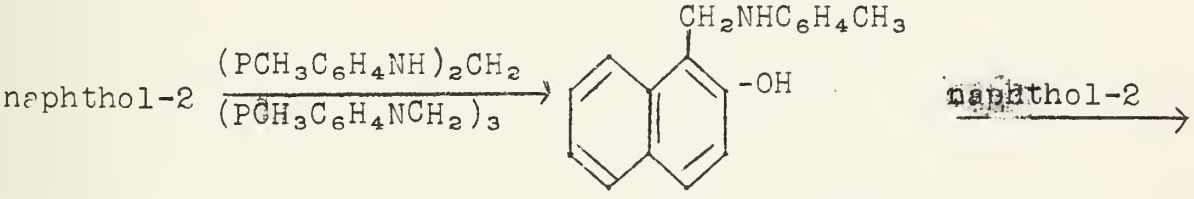
Alkali had a favorable effect on both reaction (a) and (b) although the absence of added alkali in (b) did not hinder its progress, indicating the methylene diamine itself, or the by-product amine, may serve as an alkaline promoter.

3. Formation of Aminomethylphenols

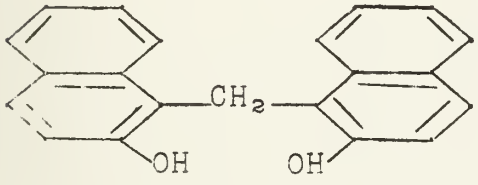




Methylene diamines I, II, and VI were used successfully on naphthol-1, naphthol-2, and carvacrol. In the presence of alkali the condensation of phenols, formaldehyde and secondary amines was found by Auwers and Dombrowski to go farther, yielding the bis (hydroxyaryl) methane compound. The same results were achieved using naphthol-2 with I and the trimeric Schiff base, of methylene-p-toluidine.



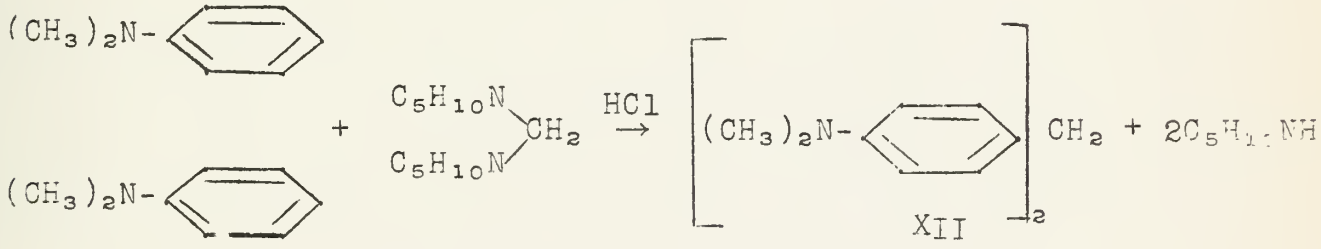
X



XI

In the absence of added alkali, the same reactants gave a mixture of X and XI, proof that the liberated amine acted as the alkaline promoter of the second stage of the reaction.

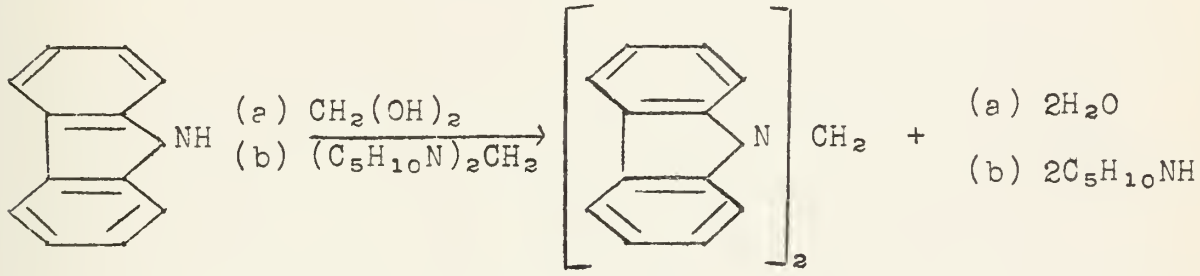
4. Formation of 4,4'-dimethylaminodiphenylmethane



Previously, XII was prepared by treatment of dimethylaniline with either formaldehyde or methylal. The above reaction would not proceed when the reagents were heated in absolute alcohol, but proceeded smoothly in the presence of hydrogen chloride.

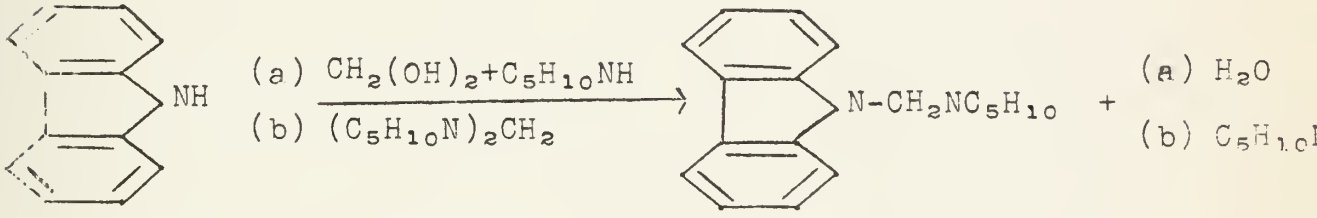
5. Interaction of Carbazole with Formaldehyde and Methylene-bis-piperidine

Votocek and Vesely have shown methylene-bis-carbazole to be formed by interaction of carbazole and formaldehyde or compounds containing methylene groups attached to oxygen or nitrogen if conducted in acid solution. The authors obtained methylene-bis-carbazole using either formaldehyde or VI in glacial acetic acid. When carbazole, piperidine, and formaldehyde were heated in aqueous alcohol solution in the absence of acid, product XIV was obtained. The same compound was obtained by heating carbazole and VI in the absence of both solvent and acid.



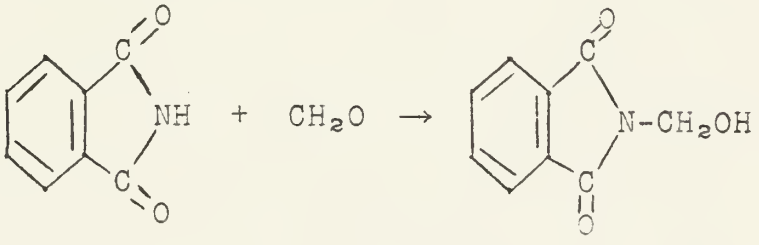
XIII

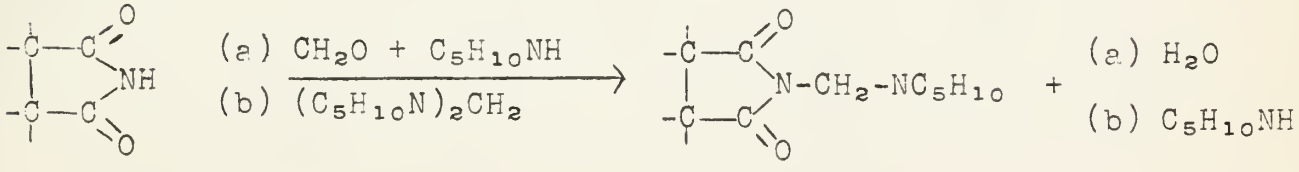
In absence of acid:



XIV

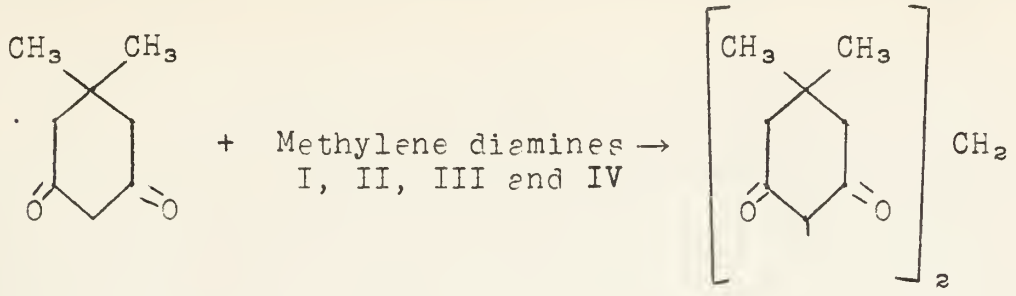
6. Formation of Aminomethylimides





Succinimide
or
Phthalimide

7. Interaction of Methylene Diamines and Dimethyldihydroresorcinol



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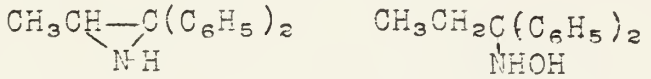
Reported by R. E. Allen
June 30, 1943

THE ACTION OF GRIGNARD REAGENTS ON MIXED KETOXIMES

In past years, few studies were made on the action of Grignard reagents on oximes. However, this unusual reaction has recently been studied thoroughly by Dr. K. N. Campbell of the University of Notre Dame.

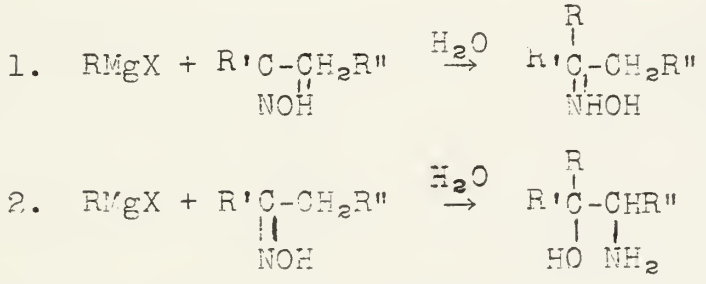
Busch and Hobein[1] reported the formation of diphenylanilinomethane instead of the expected hydroxylamine, when benzaldoxime was treated with phenylmagnesium bromide. Diels and ter Meer[2] found that the O-methyl ether of diacetyl monoxime, when treated with methylmagnesium iodide, reacted normally through the carbonyl group to give the corresponding carbinol. Orekoff and Tiffeneau[3] showed that this normal carbonyl reaction was general for all such isonitrosoketones.

More recently Hoch[4] has studied the action of Grignard reagents on ketoximes. He reported that propiophenone oxime and phenylmagnesium bromide react to give two compounds which were thought to be an ethyleneimine (I) and a hydroxylamine (II).



I II

Stieglitz discovered that the reaction of mixed ketoximes and Grignard reagents resulted in a new type of rearrangement leading to β-amino alcohols (2) rather than forming the expected hydroxylamines (1.).



The products obtained from the reaction of phenylmagnesium bromide with acetophenone, propiophenone and desoxybenzoin were 1,1-diphenyl-2-amino-ethanol, 1,1-diphenyl-2-aminopropanol and 1,1,2-triphenyl-2-aminoethanol. Since benzophenone contains no α-hydrogen atom, it did not lead to an amino alcohol.

As stated above, Hoch reported that propiophenone oxime and phenylmagnesium bromide gave a hydroxylamine and an ethyleneimine. However, the physical constants for his hydroxylamine and its derivatives are identical with those given by Stieglitz for the compound assumed to be 1,1-diphenyl-2-aminopropanol and its derivatives. Campbell[5] has prepared the latter compound by treating either propiophenone oxime or the ethyl ester of alanine hydrochloride with phenylmagnesium bromide. The products from both methods were identical, indicating that the amino alcohol formula is correct rather than the hydroxylamine structure assumed by Hoch.

Since the ketoximes do not react readily with Grignard reagents, certain conditions must be fulfilled. An excess of the Grignard reagent must be used; it must be concentrated; and the oxime must be added at an elevated temperature, generally about 160-165°C. Instead of concentrating the Grignard reagent, about half of the diethyl ether may be replaced by diisoamyl ether. If toluene is used to replace the ether, the reaction takes a different course and does not lead to the amino alcohol.

Campbell[5,6] has prepared numerous amino alcohols by this method (Table I). In each case the amino alcohol and its derivatives, usually the hydrochloride and the benzamide, were identical with those of authentic samples prepared by other methods.

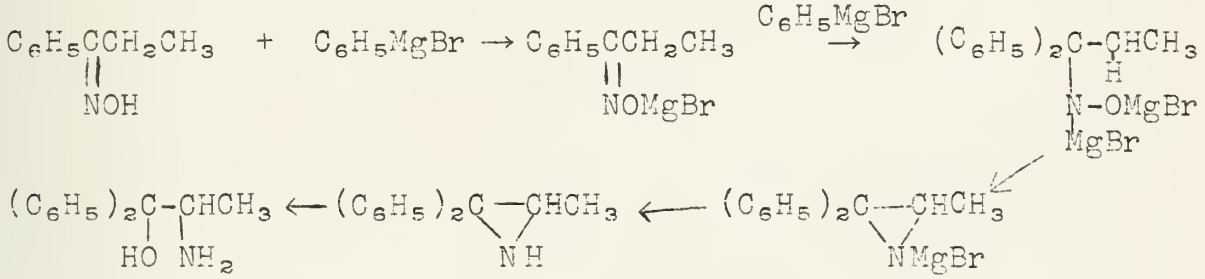
Table I.

Amino alcohol	Source
1,1-Diphenyl-2-aminopropanol	Propiophenone oxime and C_6H_5MgBr. Alanine ester hydrochloride and C_6H_5MgBr.
1-Phenyl-1-*p*-tolyl-2-aminoethanol	*p*-Methylacetophenone oxime and C_6H_5MgBr. Aminoacetophenone hydrochloride and *p*-$CH_3C_6H_4MgBr$.
1-phenyl-1-*p*-chlorophenyl-2-amino-ethanol	*p*-Chloroacetophenone oxime and C_6H_5MgBr. *p*-Chloro-α-aminoacetophenone hydrochloride and C_6H_5MgBr.
1-phenyl-1-α-naphthyl-2-amino-ethanol	Methyl-α-naphthyl ketoxime and C_6H_5MgBr. Aminoacetophenone hydrochloride and α-$C_{10}H_7MgBr$.
1-Phenyl-1-*p*-tolyl-2-amino-ethanol	Acetophenone oxime and *p*-$CH_3C_6H_4MgBr$ Phenacylamine hydrochloride and *p*-$CH_3C_6H_4MgBr$. Mixture
1-Phenyl-1-α-naphthyl-2-amino-ethanol	Acetophenone oxime and α-$C_{10}H_7MgBr$. Phenacylamine hydrochloride and α-$C_{10}H_7MgBr$ Mixture
1-Phenyl-1-*p*-anisyl-2-aminoethanol	Acetophenone oxime and $CH_3OC_6H_4MgBr$. Phenacylamine hydrochloride and $CH_3OC_6H_4MgBr$. Mixture.
1-Phenyl-1-biphenyl-2-aminoethanol	*p*-Phenylacetophenone oxime and C_6H_5MgBr. Amino-*p*-phenylacetophenone and C_6H_5MgBr.
1-Phenyl-1-*p*-tolyl-2-amino-propanol	Propiophenone oxime and *p*-$CH_3C_6H_4MgB$ Aminopropiophenone and *p*-$CH_3C_6H_4MgBr$ Mixture.

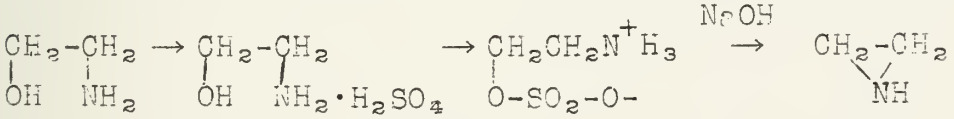
1,1-Diphenyl-2-aminobutanol	Butyrophenone oxime and C_6H_5MgBr. α-Aminobutyric ester and C_6H_5MgBr. Mixture.

Mechanism:

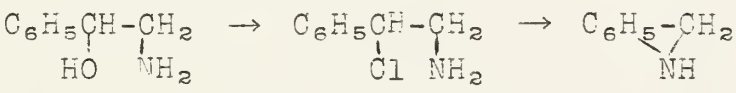
It was thought by Campbell[7] that the ethyleneimine which Hoch had reported from the action of Grignard reagents on oximes might be an intermediate in the formation of amino alcohols, as shown below. He therefore studied the ethyleneimines of propiophenone and butyrophenone oximes.



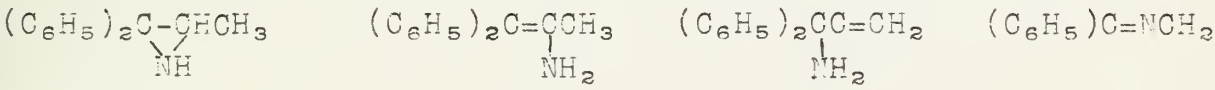
The ethyleneimines, unlike their analogs, the ethylene oxides, have not been studied extensively. Ethyleneimine itself can be prepared from the sulfate of the corresponding amino alcohol.



The ethyleneimines formed from aryl-substituted amino alcohols are more suitably prepared via the corresponding chloramines, a variation of this method was used by Campbell.



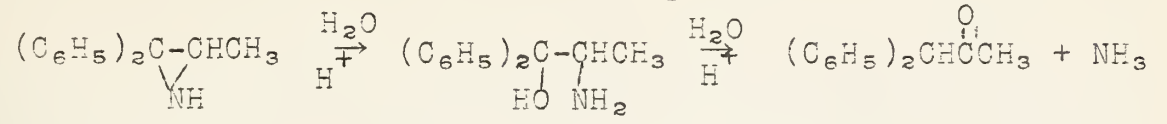
When propiophenone oxime was treated with phenylmagnesium bromide under the previously mentioned conditions and the complex was hydrolyzed with ice and acid, 1,1-diphenyl-2-aminopropanol was formed, which melted at 103-104°. But if no acid was used in the hydrolysis, a product melting at 72-73° was obtained. This same product could be obtained by carrying out the Grignard reaction in toluene and then hydrolyzing the complex without acid. Analysis of the compound indicated the formula $C_{15}H_{15}N$, and the four possible structures indicated below were proposed.



III IV V VI

The compound, m.p. 72-73°, readily formed a stable hydrochloride. It reduced an aqueous or acetone solution of potassium permanganate in the cold very slowly. When warmed for a short while with 2N sulfuric acid or 6N hydrochloric acid, it was converted quantitatively to 1,1-diphenyl-2-aminopropanol; longer warming led to a

mixture of diphenyl acetone, ammonia and the amino alcohol. The amino alcohol itself led to the same products on treatment with acid.



Benzophenone ethylimide (VI) melts at 62° and is very easily hydrolyzed in the cold by aqueous acid to benzophenone and ethylamine; furthermore it does not form a stable hydrochloride. A vinyl amine, such as structure IV, would be expected to yield only diphenylacetone and ammonia from hydrolysis, not an amino alcohol. An unsaturated amine (V) should be readily oxidized by potassium permanganate, whereas the compound in question was oxidized very slowly. These facts indicate that the ethyleneimine structure (III) is correct.

As further proof an attempt was made to prepare the ethyleneimine. Treatment of 1,1-diphenyl-2-aminopropanol with thionyl chloride and subsequent treatment with alcoholic potassium hydroxide gave an amine in low yield which melted at 72-73° and which did not depress the melting point of the ethyleneimine obtained from propiophenone oxime.

A corresponding intermediate was isolated from the action of phenylmagnesium bromide on butyrophenone oxime.

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Reported by J. B. McPherson, Jr.
July 7, 1943

NITROPARAFFINS AND THEIR DERIVATIVES

The commercial production of nitroparaffins began in 1940 as a result of ten years of research by Hass et al who applied the vapor-phase technique which had been so successful in chlorinating paraffins. Thus nitromethane, nitroethane, 1-nitropropane and 2-nitropropane were produced by the nitration of propane and subsequent rectification. Recently Hass and Boyd have succeeded in nitrating methane at a temperature of 475°C and a contact time of 0.18 sec. obtaining a 13% conversion to nitromethane per pass. The nitroparaffins are comparable in their field to the position of nitrobenzene in the aromatic field for they are both raw materials for chemical synthesis and good solvents.

Nitrohydroxy Compounds

The aldol condensation by which the nitrohydroxy compounds may be prepared requires a fine control of conditions and is general only in the case of formaldehyde. The major difficulties are 1) the ease with which the nitroalcohols produced are dehydrated to nitroolefins, 2) the unreactivity of secondary nitroparaffins and 3) the fact that when formaldehyde is used the second molecule condenses almost as easily as the first. Three methods for carrying out this condensation have been worked out the most general of which involved mixing a dilute solution of the sodium salt of the nitroparaffin with the sodium bisulfite addition product of the aldehyde and warming. By this method yields of 70-80% with primary and of 40% with secondary nitroparaffins have been obtained. A good yield of the monohydric alcohol is obtained with formaldehyde if a molal excess of the nitroparaffin and strong alkali are used. Strong alkali reverses the condensation.

$$CH_3(NO_2)C(CH_2OH)_2 + NaOH \rightarrow CH_3(CH_2OH)C = NOONa + HCHO + H_2O$$

Chloronitroalcohols may be prepared by appropriate aldol condensations.

1) $CH_3CH_2NO_2 + CH_2ClCHO \xrightarrow{Na_2CO_3} CH_3CH(NO_2)CHOHCH_2Cl$

2) $CH_3CH_2CH(Cl)NO_2 + HCHO \rightarrow CH_3CH_2C(NO_2)CH_2OH$ (Cl)

Nitrodiols may be prepared by using formaldehyde and any primary nitroparaffin. With higher aldehydes diol formation is obtained only with nitromethane and only in the presence of mild alkali.

$$CH_3NO_2 + 2C_2H_5CHO \xrightarrow[28\text{-}35^\circ,\ 4\ days]{K_2CO_3} C_2NCH(CHOHC_2H_5)_2$$

Nitrotriols may be obtained by condensing nitromethane or appropriate nitroalcohols or diols with formaldehyde.

$$CH_3CH_2CHOHCH_2NO_2 + 2HCHO \xrightarrow[30^\circ,\ 4\ days]{K_2CO_3} CH_3CH_2\underset{\displaystyle CH_2OH}{\overset{\displaystyle OH}{\overset{|}{C}}}-NO_2$$

The nitrohydroxy derivatives have found use in chemical synthesis and in a number of direct applications. For example, 2-nitro-2-methyl-1-propanol is an excellent heat sensitizer for rubber latex and 2-nitrobutanol is a good highboiling solvent for cellulose acetate.

Nitroolefins may be prepared by heating the nitroalcohols in the presence of zinc chloride or by treating the acetates of secondary nitroalcohols with hydrolytic agents.

$$C_6H_5CH(OCOCH_3)CH(NO_2)CH_3 \xrightarrow[0.1N]{NaHCO_3} C_6H_5CH = C(NO_2)CH_3$$

Reduction of nitroparaffins and their derivatives

Aliphatic amines are prepared in 90-97% yield from nitroparaffins either 1) by the action of iron and dilute hydrochloric acid at 100°C or 2) by hydrogen over Raney nickel at moderate temperature and a pressure of six to one hundred atmospheres. Oximes are obtained in 40% yield by the action of zinc and acetic acid. Alkylhydroxylamines are obtained if zinc dust and water are the reducing media.

Aminohydroxy compounds are always prepared by catalytic reduction, because the nitroalcohols and glycols are unstable in alkaline and acid media. Under certain conditions hydrogenolysis to

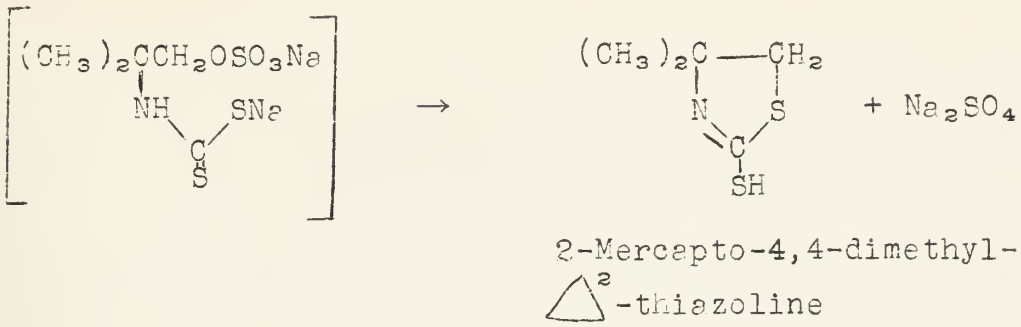
$$C_2H_5(NO_2)C(CH_2OH)_2 \xrightarrow[40\text{-}50^\circ,\ 700\ lbs.]{H_2,Ni} C_2H_5(NH_2)C(CH_2OH)_2 \quad (99\%)$$

give 2-amino-1-butanol takes place. The aminohydroxy compounds have found extensive use as emulsifying agents. The most versatile of these is 2-amino-2-methyl-1-propanol. Aminohydroxy compounds have found use in the synthesis of amides.

$$(CH_3)_2C(NH_2)CH_2OH + C_{17}H_{35}COOH \xrightarrow{\triangle} C_{17}H_{35}CONHC(CH_3)_2\underset{\displaystyle CH_2OH}{\overset{|}{}}$$

Substituted oxazolines, oxazolidines and mercaptothiazolines may also be prepared. The latter are of interest as vulcanization accelerators for rubber.

$$(CH_3)_2C(NH_2)CH_2OH + H_2SO_4 \rightarrow (CH_3)_2C(NH_2)CH_2OSO_3H \xrightarrow[CS_2]{NaOH}$$



2-Mercapto-4,4-dimethyl-Δ^2-thiazoline

Chloronitroparaffins

α-CHloronitroparaffins are used as anti-gelling agents for rubber cements and are prepared by the action of sodium hypochlorite solution on nitroparaffins. Either the mono or disubstituted chlornitroparaffin may be obtained as desired.

β-Chloronitroparaffins may be prepared under anhydrous conditions in the presence of strong light.

$$CH_3CHNO_2CH_3 + Cl_2 \xrightarrow{P_2O_5} CH_2ClCHNO_2CH_3$$

However if there is a γ-position it will be chlorinated also.

$$CH_3CH_2CH_2NO_2 \xrightarrow{Cl_2} CH_2ClCH_2CH_2NO_2 + CH_3CHClCH_2NO_2$$

Chloropicrin is prepared industrially by the action of hypochlorous acid on nitromethane in the presence of calcium carbonate. Chloropicrin undergoes an interesting reaction with ammonia to produce guanidine.

$$CH_3NO_2 \xrightarrow{OCl^-} Cl_3CNO_2 \xrightarrow{NH_3} NH_2\overset{NH}{\overset{\|}{C}}-NH_2$$

chloropicrin guanidine

Alkali metal salts of the nitroparaffins

Nitroparaffins do not dissolve in sodium carbonate solution, but do so readily in dilute sodium hydroxide.. These salts are used in a number of interesting syntheses.

Straight chain aldehydes and ketones may be prepared in 80-85% yield by adding a 10% sodium hydroxide solution of the nitroparaffin to excess 20% sulfuric acid. Branching of the chain greatly reduces the yield. For example, isobutyraldehyde is formed in only 35% yield.

$$2RCH{=}NOONa + 2H_2SO_4 \rightarrow 2RCHO + N_2O + 2NaHSO_4 + H_2O$$

Mercury fulminate may be prepared as follows:

$$2CH_2{=}NOONa + HgCl_2 \rightarrow Hg(ON{=}C)_2 + 2NaCl + 2H_2O.$$

Glycine may be prepared by the following steps.

$$2CH_2{=}NOONa \xrightarrow{NaOH} HON{=}CH{-}CH{=}NOONa \xrightarrow{-H_2O} N{\equiv}CCH{=}NOONa$$

Sod. methazonate

$$(\rightarrow NaOOCCH{-}NOONa \rightarrow O_2NCH_2COOH \rightarrow H_2NCH_2COOH)$$

1,2-Dinitroparaffins are obtained by the following type of condensation.

$$(CH_3)_2\overset{Cl}{C}NO_2 + CH_3)_2C{=}NOONa \rightarrow (CH_3)_2C(NO_2)C(CH_3)_2(NO_2) + NaCl$$

1,3-Dinitroparaffins may be prepared by condensing nitromethane with a ketone.

$$(CH_3)_2CO + 2CH_3NO_2 \xrightarrow{Cat.} (CH_3)_2C(CH_2NO_2)_2$$

dinitroneopentane

Aryl diazonium compounds couple with sodium nitronates to yield highly colored compounds, some of which make fast dyes for wool and silk.

$$ClN_2\text{-}C_6H_4\text{-}C_6H_4\text{-}N_2Cl + 2(CH_3)_2C{=}NOONa \xrightarrow{OH^-} (CH_3)_2 =$$

$$NO_2C\text{-}N{=}N\text{-}C_6H_4\text{-}C_6H_4\text{-}N{=}N\text{-}\overset{NO_2}{C}(CH_3)_2$$

Hydroxylamine

The preparation of hydroxylamine in commercial quantities by the hydrolysis of nitroparaffins with strong sulfuric acid has given new interest to certain uses of this compound. For example, it is now economical to make certain amines by the reduction of oximes. The hydroxamic acids and the amidoximes have received more attention.

$$CH_3COOH + NH_2OH \xrightarrow{\triangle} CH_3C(NOH)\text{-}OH$$

Acet-hydroxamic acid

$$CH_3CN + NH_2OH \rightarrow CH_3C(NOH)NH_2$$

Acetamide oxime

Diazomethane may be prepared by an unusual synthesis using hydroxylamine and N-dichloromethylamine.

$$NH_2OH + Cl_2NCH_3 \rightarrow CH_2N_2 + 2HCl + H_2O$$

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Reported by W. J. Shenk, Jr.
July 7, 1943

THE STRUCTURE OF STARCH

It has long been recognized that starch can be separated into two fractions of widely different physical properties. Meyer[1] named the two substances α-amylose and β-amylose. The general usage, however, is that of Maquenne and Roux[2] who designated the fractions as amylose and amylopectin.

Various methods have been employed to isolate the two starch fractions but no quantitative separation has yet been effected. Due to the variation in the degree of separation by the methods used, the amylose fraction in starch has been reported from 60 to 17% by different workers. According to the present methods of analysis of the fractions, the best separations are (a) that of Samec and Meyer,[3] by electrodialysis of an autoclaved suspension of starch, and (b) that of McCready and Hassid,[4] by diffusion of the amylose from starch grains swollen in water at 60 to 80°C.

The amylose is easily soluble, forming a slightly viscous solution, while the amylopectin is much less soluble, giving opalescent and highly viscous solutions. Although initially the amylose is more soluble than the amylopectin, after separation, precipitation and drying it is less soluble and the 0.1% which dissolves rapidly retrogrades from solution.

Amylose gives a much more intense coloration with iodine than amylopectin. McCready and Hassid[4] have used this property for a quantitative colorimetric determination of mixtures of the two fractions. By the use of this method, 19% amylose has been found in potato starch. This result checks very closely with other data obtained from β-amylase hydrolysis and end group determinations.

The enzyme β-amylase, prepared from ungerminated barley, is found to hydrolyze amylose completely to maltose. Amylopectin is only 54% hydrolyzed by β-amylase, which indicates a structural difference between the two fractions. Synthetic starch, prepared by the action of potato phosphorylase on the Cori ester, glucose-6-phosphate, and closely resembling amylose, is 98% hydrolyzed by β-amylase.

The molecular structure of the two starch fractions was first studied by Hirst, Plant and Wilkinson[5] in 1932. By means of hydrolysis of methylated starch and determination of the amount of tetramethylglucose, formed only from end groups, they concluded that both components were of essentially the same molecular structure, made up of chains of 24 and 30 glucopyranose units. The different physical properties were attributed to differences in the state of hydration and interlocking of chains to form micelles.

In 1940 Meyer, Werthem and Bernfield[6] using more highly purified fractions in similar methylation experiments showed that the two starch fractions possess different molecular structures. This work has since been confirmed by Hassid and McCready.[7] The amylose is first converted to the triacetate, which is simultaneously deacetylated and methylated by the repeated action of sodium hydroxide and methyl sulfate. The methylated amylose is insoluble in cold and hot water and by viscosity measurements has a molecular weight of 50,000. The methylated amylose is hydrolyzed with methanolic

hydrogen chloride; the cleavage products are separated and fractionally distilled under reduced pressure. The amounts of tri- and tetramethylmethylglucosides in each fraction are determined by correlation of rotations and indices of refraction as proposed by Hirst and Young.[8] This method allows the determination of the tetramethylglucose in the presence of large amounts of trimethylglucose and variation in the proportions of α- and β-forms of the glucosides. These values were also checked against methoxyl determinations. By this method amylose was found to yield 0.32% tetramethylglucose, which corresponds to an approximate chain length of 300 to 400 glucose units. This molecular weight is of the same order of magnitude as that obtained from viscosity measurements.

Methylated amylopectin is soluble in cold water but insoluble in hot water. Viscosity measurements indicate a molecular weight of 92,000 using the modified constant corresponding to that obtained by osmotic pressure measurements on natural starch. By means of a procedure similar to that used for amylose, methylated amylopectin on hydrolysis yielded 4.67% tetramethylglucose and 21% dimethylglucose. This would correspond to a repeating chain length of 25 glucose units, the short chains being combined to form a branched structure.

These structures explain the difference in behavior of β-amylose toward amylose and amylopectin. Hanes[9] first proposed that the enzyme can attack the chain only at the non-reducing end and proceed to split off successive terminal maltose fragments until some modification in structure is encountered. Freudenberg and Boppel[10], by isolation and identification of the dimethylglucose from hydrolysis of methylated starch as the 2,3-compound, have indicated that the side chains are attached to the sixth carbon of about every twentieth glucose unit by an "isomaltose" union. This linkage is probably responsible for the stopping of the highly specific enzyme hydrolysis. Amylose and synthetic starch are straight chains with no modifications so that the β-amylase hydrolysis continues until the whole molecule is degraded to maltose.

The evidence for the exclusive maltose or α-glucosidic linkage in starch is based on the work of Freudenberg[11] on the relationship between the optical rotation of a disaccharide and higher saccharides containing exactly similar chain units joined by identical glucosidic linkages. The molecular rotation of such a polysaccharide, $[\alpha]M$, is the sum of the individual contributions of the individual chain members, the average value for a very long chain being $\frac{[M]_\infty}{\infty}$. The values for the two end groups will of course differ from the average value and may be designated as $[M]_a$ for the reducing end and $[M]_e$ for the non-reducing end. Thus for a saccharide of n units:

$$[M]_n = [M]_a + (n-2)\frac{[M]_\infty}{\infty} + [M]_e = [M]_2 + (n-2)\frac{[M]_\infty}{\infty}$$

where $[M]_2$ is equal to the molecular rotation of the disaccharide. This equation would predict a linear relationship for the values of $\frac{[M]_n}{n}$ and $\frac{(n-1)}{n}$ if the linkages are all of the same type. This is

found to be the case for the methylated derivatives of starch, through the various dextrins to maltose.

Haworth[12] first brought out that the hexagonal model of six glucopyranose units was strainless. C. S. Hanes[9] extended this view to a spiral starch molecule, each coil containing exactly six glucose units. This structure was used to account for the splitting off of six glucose units by the hydrolytic action of α-maltamylose.

Freudenberg and co-workers[13] have by structural work substantiated this screw-like structure for the starch molecule, using five or six glucose units for each turn of the screw. This proof is based on the ring-like properties[14] of the α- and β-dextrins found by E. Schardinger to be derived from starch by the action of Bacillus macerans. Models of the α-dextrin, a pentosan, with the five oxygens of the 1,4 bonds arranged in an equilateral pentagan and the glucose units perpendicular to the plane of the ring, and β-dextrin, a hexosan, in which the linking oxygen atoms are in two planes, showed no tension when made according to the recent conception of size and attachment of atoms. These models have recently[10] been found compatable with the presence of side chains on the sixth carbon atom of the glucopyranose units. This screw shaped molecule is 15 to 20 A° thick and X-ray data indicates that they are arranged radially in the concentric layers of the starch granules.

Freudenberg[13] explains the iodine addition product colors by means of this structure. The iodine molecule, 6.3 by 3.8Å, in a perpendicular position can easily get inside of the spiral, which has an internal diameter of about 5Å. In this position, however, the iodine is held fast by the attraction of the CH groups surrounding it. Under this influence, the adsorption bands of the iodine molecule are modified and the characteristic colors are developed.

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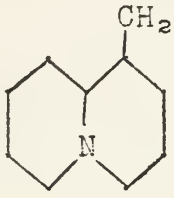
Reported by C. E. Adams
July 14, 1943

THE LUPINANE ALKALOIDS

The principal members of the group of lupin alkaloids are lupinine, sparteine (lupinidine), cytisine, anagyrine, and lupanine. Lupinine, $C_{10}H_{19}ON$, is the simplest member of the group and its ring system, known as octahydropyridocoline, also occurs in the others.



I Lupinine, $C_{10}H_{19}ON$

The pressure of a primary alcohol group was established in 1902 by Willstätter and Fourneau. The alkaloid gives a benzoyl derivative and a phenylurethane. On oxidation it yields lupininic acid, and it can be dehydrated to anhydrolupinine.

$$(C_9H_{16}N)\text{-}CH_2OH \xrightarrow{(O)} (C_9H_{16}N)\text{-}CO_2H$$

Lupinine $\xrightarrow{-H_2O}$ Lupininic acid

$$(C_8H_{15}N)\!>\!C\!=\!CH_2$$

Anhydrolupinine

Anhydrolupinine is optically inactive, and its formation from active lupinine indicates that the primary alcohol group ($-CH_2OH$) is attached to an asymmetric carbon.

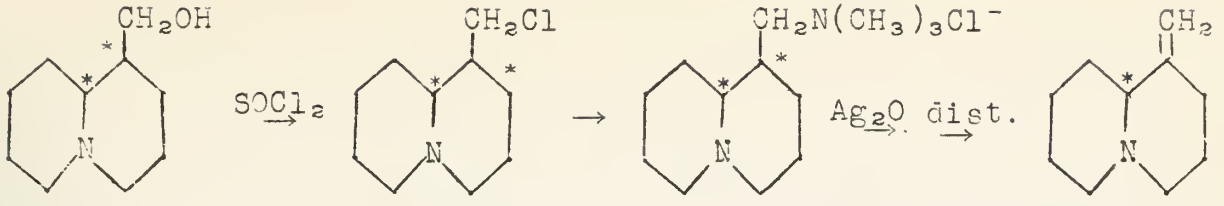
Schöpf and Thöma in 1928 prepared the methyl ester of lupininic acid and found that $[\alpha]D$ varied from -19.4° to $+5.8^\circ$ in different batches. The l-ester could be converted to the d-ester by the action of sodium methoxide. This epimerization was assumed to indicate the existence in lupininic acid of two centers of asymmetry.

Supporting this point of view is the fact that anhydrolupinine can be hydrogenated to a mixture of two inactive epimeric lupinanes, separable by crystallization of the picrates.

$$(C_8H_{15}N)\!>\!CHCH_2OH \xrightarrow{-H_2O} (C_8H_{15}N)\!>\!C\!=\!CH_2 \xrightarrow{(H)} (C_8H_{15}N)\!>\!CHCH_3$$

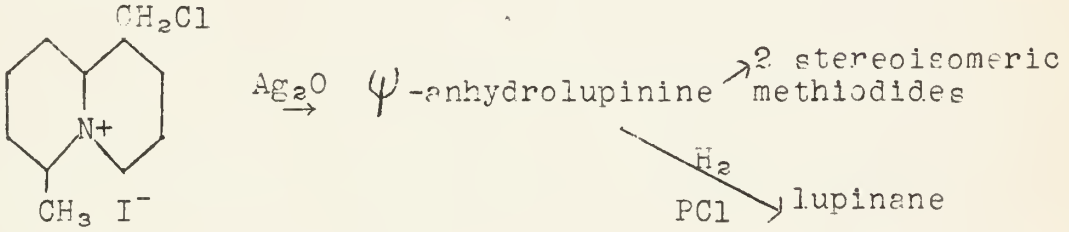
lupinine — anhydrolupinine — lupinane

Since the second asymmetric center must still be intact in the optically inactive anhydrolupinine, this compound must be a racemate. Karrer and Vogt were able to prepare an active anhydrolupinine $[\alpha]-49.3^\circ$, by the following series of reactions.

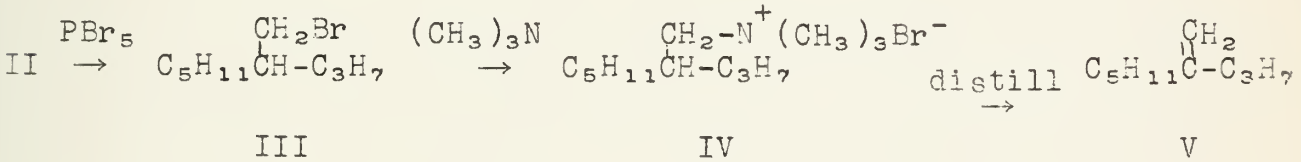


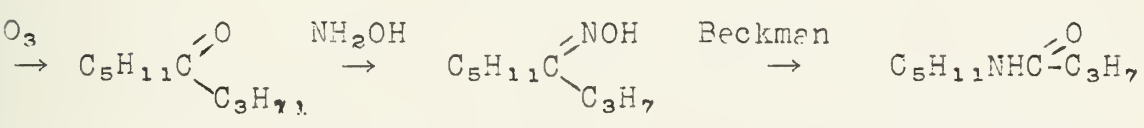
lupinine [α]D-32.9° anhydrolupinine [α]D -49.8°

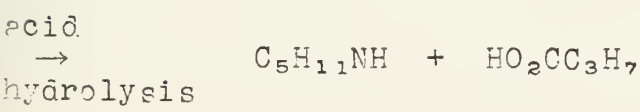
They claim that this levorotatory compound differs from the inactive one only in its optical activity. Clemo and Raper also prepared an optically active anhydrolupinine [α]D -35.3, but the physical properties and derivatives of their compound differ markedly from those of the previously obtained anhydrolupinine, so it was named ψ-anhydrolupinine. The differences have not as yet been satisfactorily explained.



In 1928, Karrer, Canal, Zohner, and Widmer were able to accomplish the Hofmann degradation of lupinine by hydrogenating the unsaturated intermediates at each stage. The final product was a mixture of two optically active unsaturated alcohols, $C_{10}H_{20}O$, which were hydrogenated to the corresponding saturated alcohol, $C_{10}H_{22}O$. This was identified as $CH_3(CH_2)_4\overset{CH_2OH}{\overset{|}{C}}H\text{-}CH_2CH_2CH_3$, II, by the following series of reactions.

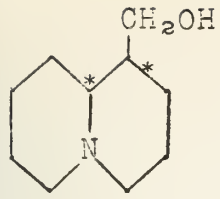




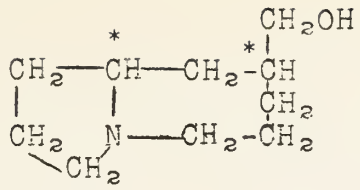


n-amylamine n-butyric acid

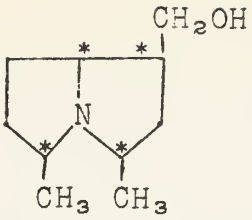
The optical activity disappeared in the unsaturated hydrocarbon V. The possible structure for lupinine which could give rise to this alcohol are as follows.



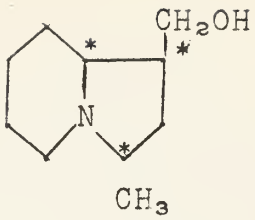
IX



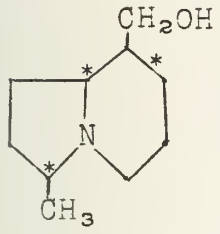
X



XI

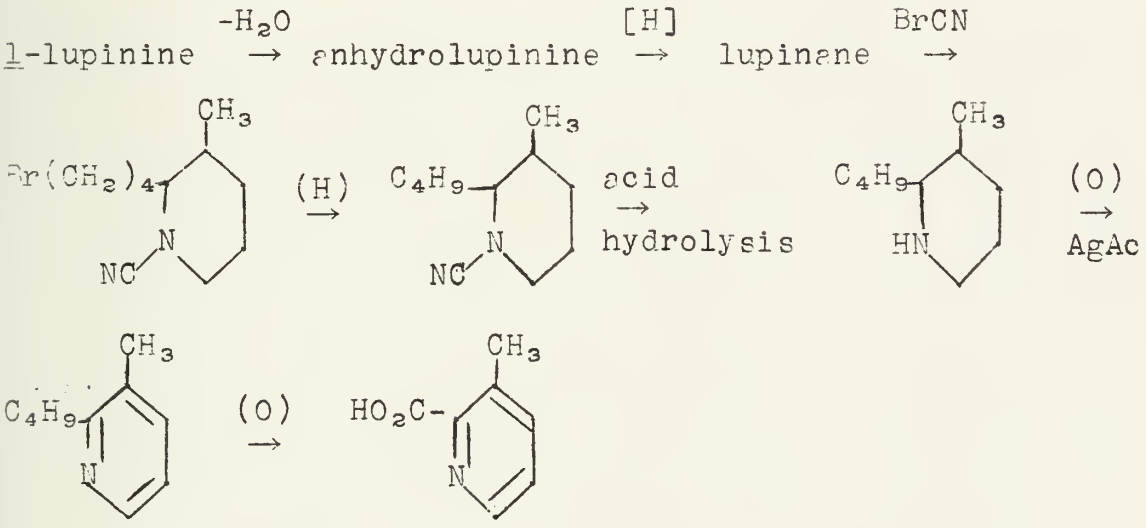


XII



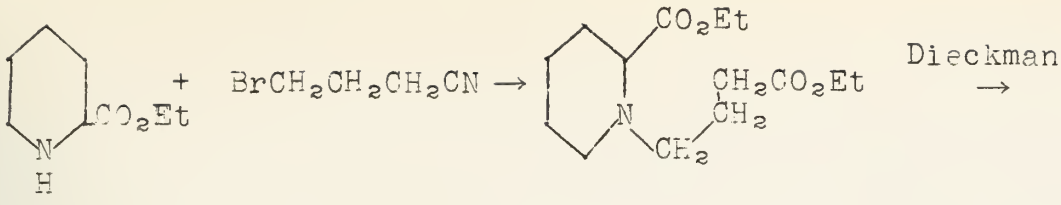
XIII

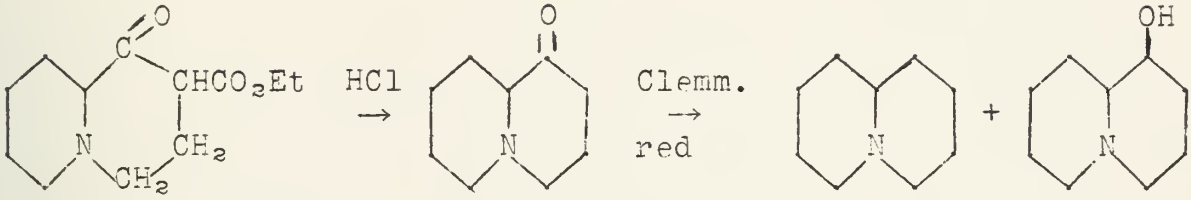
The authors thought IX the most probable. This was confirmed by the cyanogen bromide degradation carried out by Winterfeld and Holschneider.



This series of reactions restricted lupinine to structure IX or XIII.

The structure IX was confirmed by the synthesis of norlupinane which may be obtained from lupininic acid either by distillation with soda lime or by the milder conditions of the Curtius rearrangement. The first synthesis, due to Clemo and Ramage, led to an octahydropyridocoline, B, which was not identical with norlupinane, A.

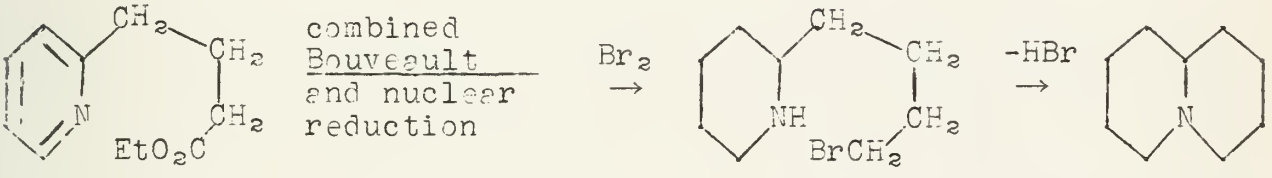




XIV B. octahydropyridocoline

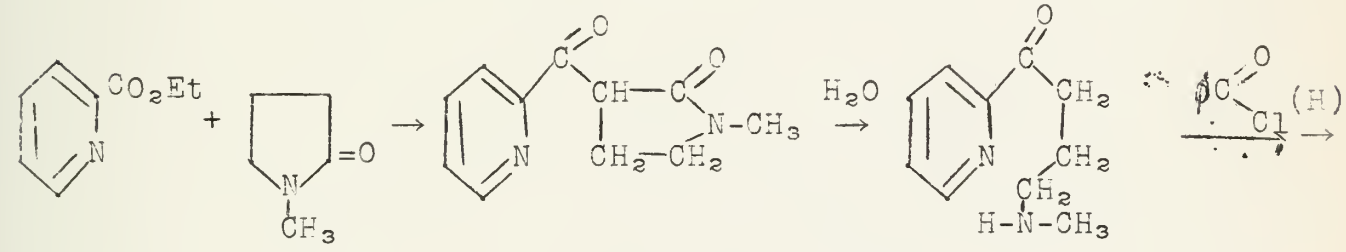
A and B could not be interconverted. It was not believed possible for the octahydropyridocoline ring to exist in stereoisomeric forms of the cis-trans decalin type, so the structure IX for lupinine was thrown into question. Later, however, norlupinane was synthesized in several different ways which left no doubt that it was an octahydropyridocoline.

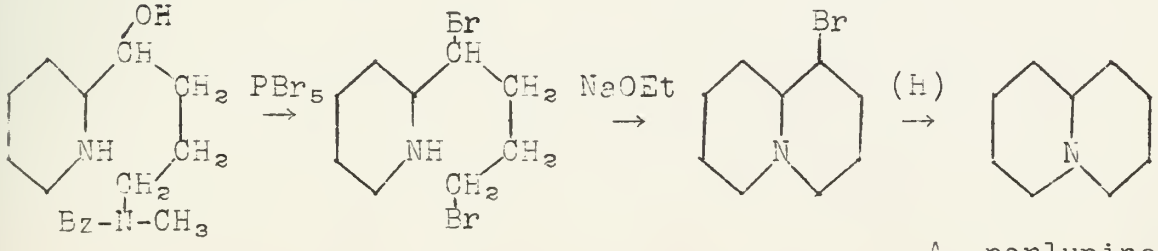
1. Clemo, Ramage, and Raper



A. norlupinane

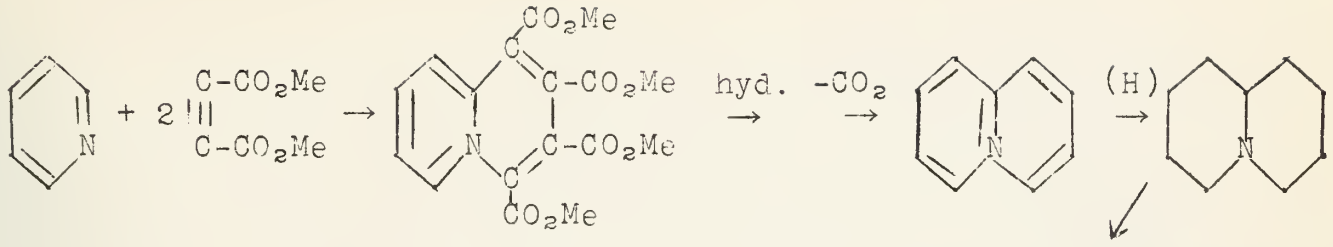
2. Winterfeld and Hoeschneider





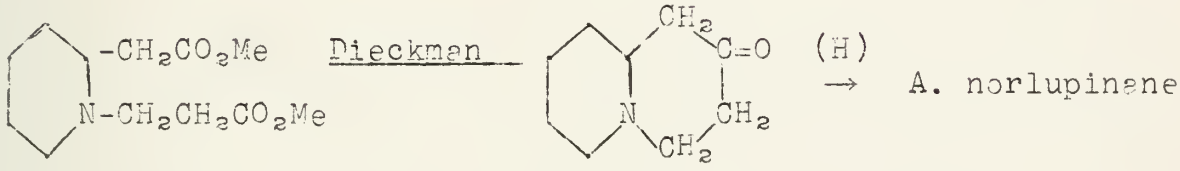
A. norlupinane

3. Diels and Alder



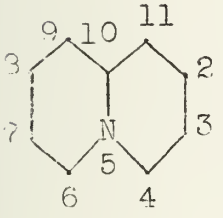
Picrate identical with norlupinane picrate, but aurichlorides were different.

4. Clemo, Metcalfe, and Raper



→ A. norlupinane

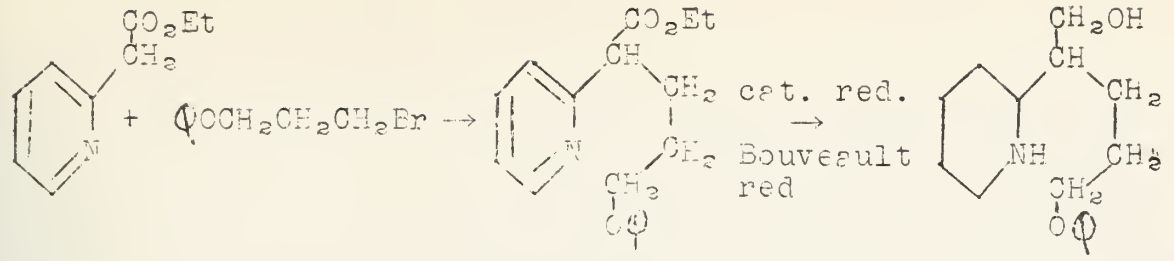
The last authors observed that of all the ring closures used to synthesize octahydropyridocoline, the only one leading to B is the Clemmenson reduction of the 1-keto compound, XIV. They therefore tried a Wolff reduction of XIV, and got pure norlupinane, A.

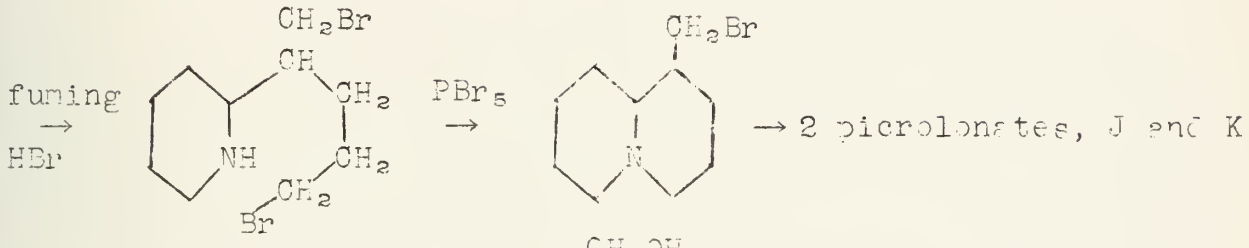


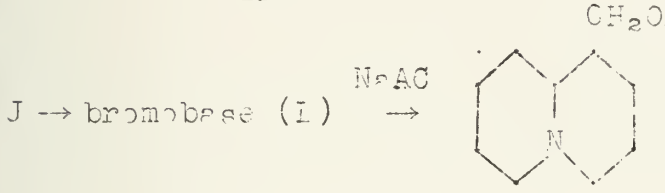
XIV

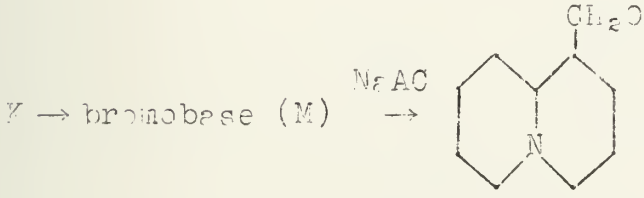
	picrate	picrolonate	methiodide
Clemm B →	213°	189°	281°
Wolff A →	194°	245°	321°

This, coupled with the fact that XIV can enolize by migration of the tertiary hydrogen at carbon 10, strongly supports the cis-trans formulation of A and B. The synthesis of lupinine itself was finally accomplished by Clemo, Morgan and Raper in 1938.









One of the two alcohols should be dl-lupinine, the other dl-isolupinine. N was resolved with d-tartaric acid, giving l-lupinine. $[\alpha]D$ -20.85°, m.p. 69-70°, not depressed by admixture with the bona fide alkaloid which had $[\alpha]D$ -21.3°. The picrolonates were identical.

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13. Diels and Alder, Ann., 498, 21 (1932); 505, 119 (1933)

Reported by Marion Dickman
July 14, 1943

CATALYTIC DEHYDROGENATION OF TETRALIN DERIVATIVES

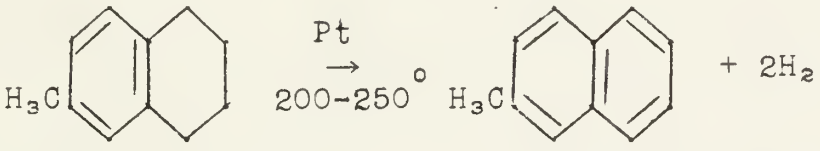
Catalytic dehydrogenation of hydroaromatic compounds was first observed in 1911 by Sabatier, who found that the use of nickel allowed the dehydrogenation of cyclohexane at 250-300°. Zelinsky showed that the noble metals, platinum and palladium, induce the same reaction at 170°.

$$C_6H_{12} \xrightarrow[170^\circ]{Pt} C_6H_6 + 3H_2$$

Platinum and palladium have been widely used in the dehydrogenation of tetralin derivatives in syntheses and in determinations of structure of polycyclic natural products. General behavior in "normal" dehydrogenations may be summarized by the examples below. ("Normal" dehydrogenations are those during which no carbon-carbon bonds are broken or formed.)

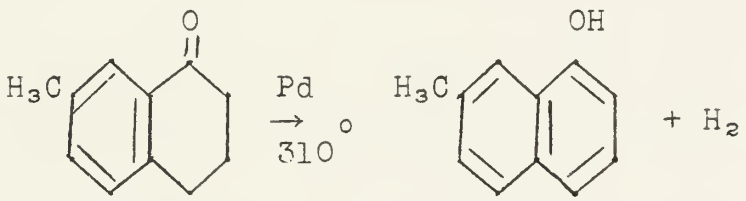
1. Normal Dehydrogenation

Linstead and coworkers showed that tetralin, 6-methyltetralin, and 1,6-dimethyltetralin give high yields of the corresponding naphthalenes over Pt or Pd at 200-250°.



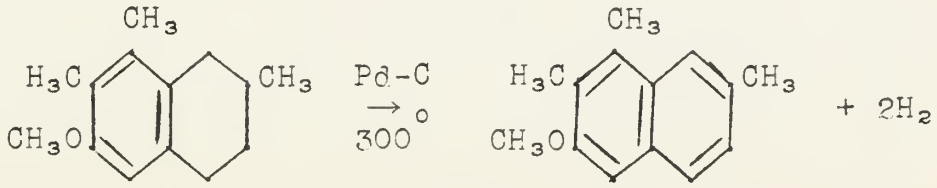
6-methyltetralin 2-methylnaphthalene

Ruzicka and Mörgeli, in studies on polyterpenes, utilized the conversion of 1-tetralones to the corresponding 1-naphthols in their syntheses.



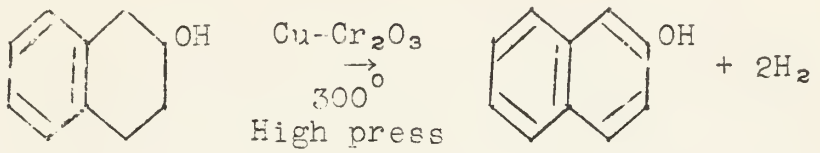
7-methyl-1-tetralone 7-methyl-1-naphthol

Ruzicka and coworkers also showed that a methoxyl group on the aromatic ring of a tetralin is not affected in dehydrogenation over palladium-charcoal.

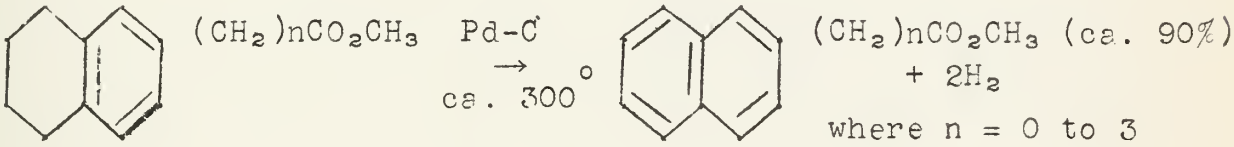


1,2,7-trimethyl-3-methoxytetralin 1,2,7-trimethyl-3-methoxy-naphthalene.

Adkins and Reid found that 1,2,3,4-tetrahydronaphthol-2 can be converted to 2-naphthol even by copper chromite, a catalyst which does not dehydrogenate tetralin.



Newman and Zahm investigated the dehydrogenation over palladium-charcoal of twelve tetralins substituted in the 2-position on the aromatic ring, the side chain in each compound carried at least one oxygen-containing group. In every case the alicyclic ring of the tetralin dehydrogenated readily. A carbomethoxy group alone on the side chain was not affected. A keto group or a carbon-oxygen single bond alpha to the ring was reduced. An unsaturated side chain was also reduced, but an aldehyde group on the ring lost CO. An acid chloride yielded no isolable product on dehydrogenation.



$$2\text{-}C_{10}H_{11}\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[270^\circ]{Pd\text{-}C} 2\text{-}C_{10}H_7CH_2CH_3 \quad (63\%) + 2\text{-}C_{10}H_7\overset{O}{\overset{\|}{C}}CH_3 \quad (19\%)$$

$$2\text{-}C_{10}H_{11}\overset{O}{\overset{\|}{C}}(CH_2)_2CO_2CH_3 \xrightarrow[290^\circ]{Pd\text{-}C} 2\text{-}C_{10}H_7(CH_2)_3CO_2CH_3 \quad (33\%) + 2\text{-}C_{10}H_7(CH_2)_3CO_2H \quad (37\%)$$

$$2\text{-}C_{10}H_{11}\overset{\frown O \frown}{CH}(CH_2)_2C{=}O \xrightarrow[310^\circ]{Pd\text{-}C} 2\text{-}C_{10}H_7(CH_2)_3CO_2H \quad (71\%) + H_2$$

$$2\text{-}C_{10}H_{11}CHOHCH_3 \xrightarrow[290^\circ]{Pd\text{-}C} 2\text{-}C_{10}H_7CH_2CH_3 \quad (28\%) + HOH + H_2$$

$$2\text{-}C_{10}H_{11}CH_2OH \xrightarrow[260^\circ]{Pd\text{-}C} 2\text{-}C_{10}H_7CH_3 + 2\text{-}C_{10}H_{11}CH_3 \quad (67\%) + HOH + H_2$$

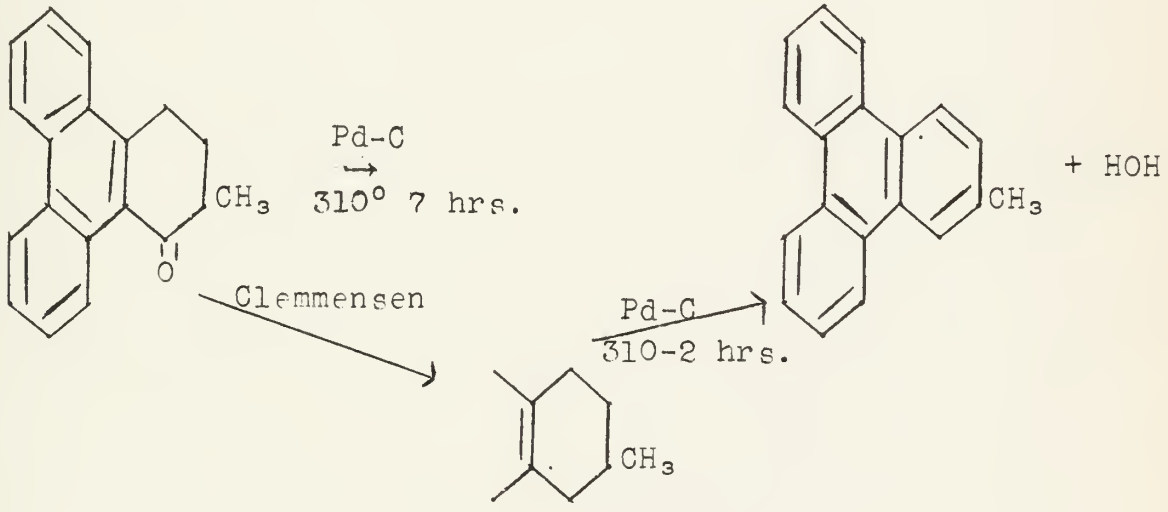
$$2\text{-}C_{10}H_{11}CH{=}CHCO_2CH_3 \xrightarrow[305^\circ]{Pd\text{-}C} 2\text{-}C_{10}H_7(CH_2)_2CO_2CH_3 \quad (89\%) + H_2$$

$$2\text{-}C_{10}H_{11}CHO \xrightarrow[275^\circ]{\text{Pd-C}} 2\text{-}C_{10}H_8 + CO + 2H_2 \qquad (95\%)$$

When reduction of a side chain substituent occurs during dehydrogenation, the yield of hydrogen escaping from the reaction mixture is small, probably indicating that the process is an intramolecular oxidation-reduction, promoted by catalyst-activated hydrogen.

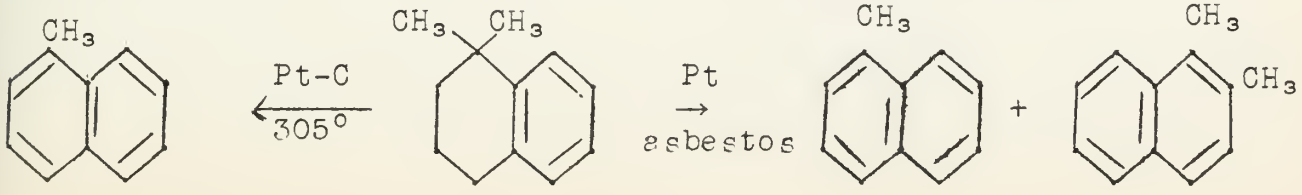
Newman and Zahm's work indicates the possibility of more convenient syntheses of certain 2-substituted naphthalenes. For example, pure gamma-(2-naphthyl-)butyric acid may more readily be prepared by succinoylation of tetralin, followed by esterification, dehydrogenation, and saponification, than by succinoylation of naphthalene, followed by separation of the resulting 1- and 2-isomers, then Clemmensen reduction of the 2-isomer.

Certain polycyclic compounds containing tetralin-like structures are of interest in syntheses involving dehydrogenation. 1-keto-2-Methyl-1,2,3,4-tetrahydro-9,10-benzphenanthrene has been found to dehydrogenate, over palladium-charcoal, directly to 2-methyltriphenylene. Thus, reduction of the keto group prior to dehydrogenation is unnecessary.

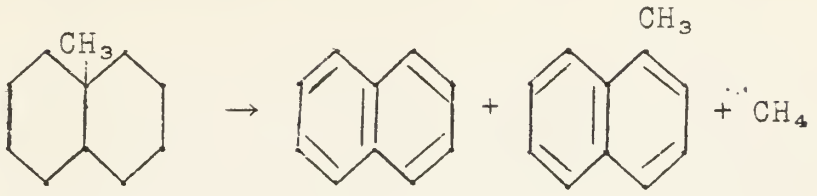


2. Abnormal Dehydrogenation

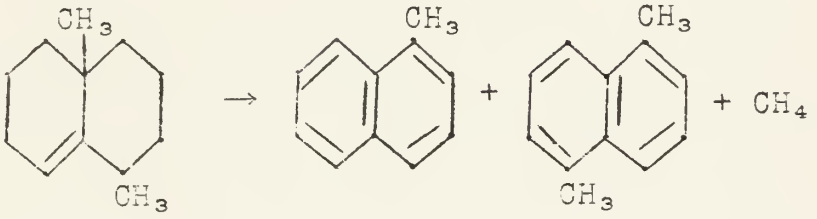
If a substituted tetralin having a quaternary carbon atom is dehydrogenated catalytically, cleavage or migration of an alkyl group will occur. Linstead and Thomas found that asbestos as a carrier for Pt and Pd seems to promote migration in 1,1-dimethyltetralin during dehydrogenation.



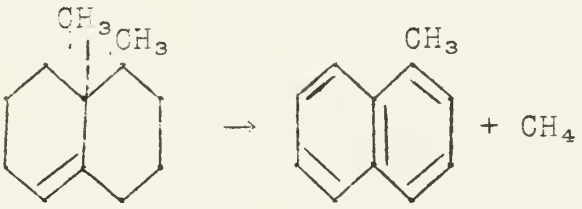
Angular groups also tend to cleave or wander during dehydrogenation of substituted octalins and decalins:



cis-9-methyldecalin

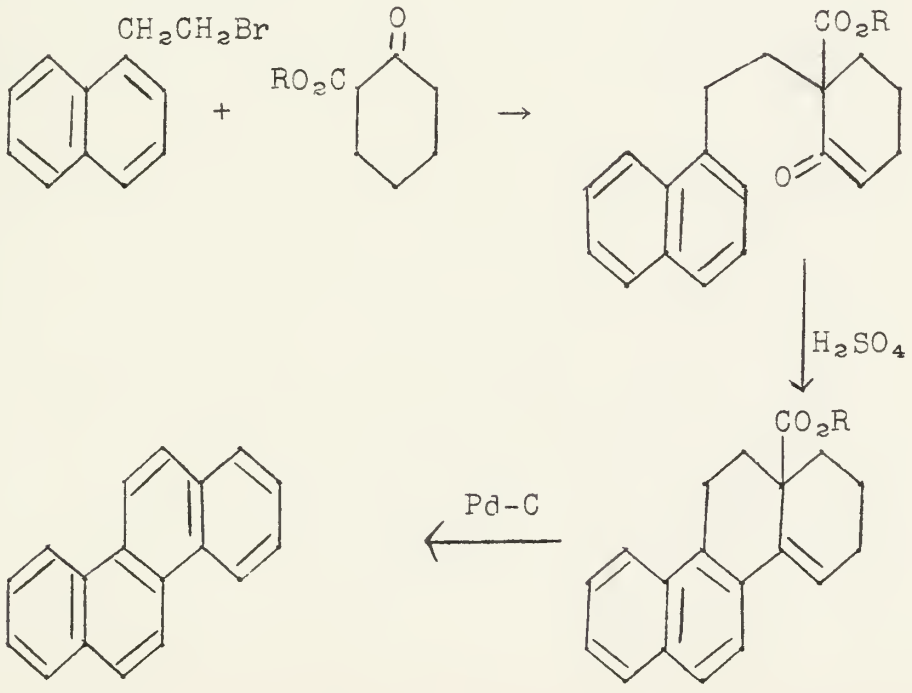


cis-4,9-dimethyloctalin



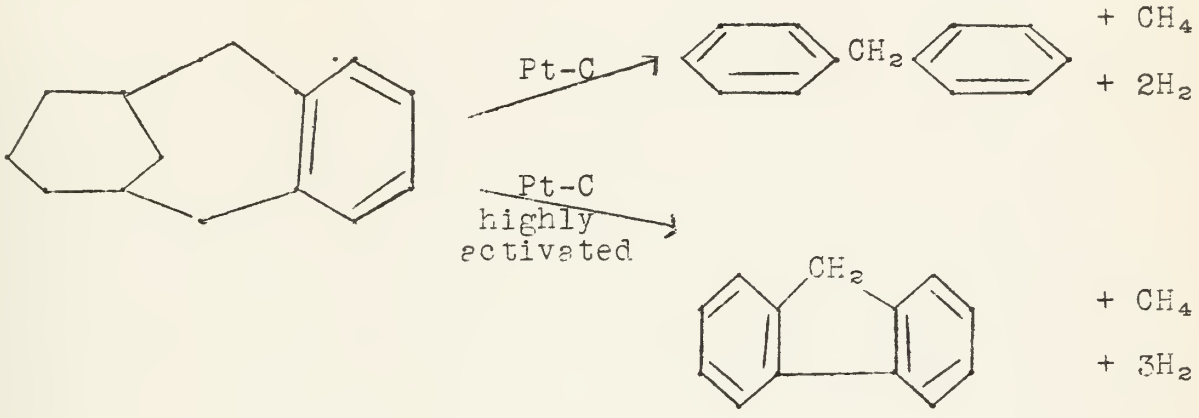
cis-1,9-dimethyloctalin

Zelinsky utilized the cleavage of an angular carboalkoxy group in the synthesis of chrysene.



chrysene

Plagina and Zelinsky accomplished an interesting change in structure in the hydroaromatic compound 2,3-benzobicyclo(3,3,1-)2-nonene. Dehydrogenation with platinized charcoal converted this compound into diphenylmethane, and a more highly activated catalyst changed it to fluorene.



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Reported by Cameron Lewis
July 21, 1943

THE LEUCKART REACTION

The reaction of aldehydes and ketones with either ammonium formate or formamide to yield amines was first discovered by Leuckart in 1885. Probably because of the inconvenient procedures and the mixtures of amines obtained, the reaction was little used until more recent investigators, notably Ingersoll and coworkers and Novelli, developed satisfactory methods for preparing primary, secondary and tertiary amines in good yields by this method.

Mechanism

The general reaction is illustrated below.

$$RCOR' + 2\ HCO_2NH_4 \xrightarrow{150\text{-}190^\circ} RCH(NHCHO)R' + 2\ H_2O + CO_2 + NH_3$$

$$RCH(NHCHO)R' \xrightarrow[\text{alkali}]{\text{acid or}} \underset{NH_2}{RCHR'} + HCO_2H$$

Wallach, in 1905, proposed a mechanism which explained the secondary and tertiary by-products which were obtained, and postulated the formyl compound as a secondary reaction product.

$$HCO_2NH_4 \rightleftarrows HCO_2H + NH_3$$

$$R_2CO + NH_3 \rightarrow R_2C\begin{matrix}OH\\NH_2\end{matrix} \xrightarrow{HCO_2H} R_2CHNH_2 + CO_2 + H_2O$$

$$R_2CO + R_2CHNH_2 \rightarrow R_2C(OH)\text{-}NHCHR_2 \xrightarrow{HCO_2H} (R_2CH)_2NH + CO_2 + H_2O$$

$$R_2CO + (R_2CH)_2NH \rightarrow R_2C(OH)\text{-}N(CHR_2)_2 \xrightarrow{HCO_2H} (R_2CH)_3N + CO_2 + H_2O$$

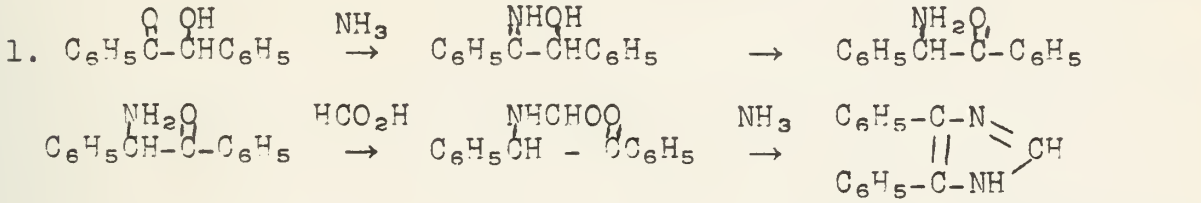
The formation of primary amines is favored by an excess of formic acid which, under the extreme conditions necessary for the reaction, converts the amines to the formyl derivative. The substituted formamide may be hydrolyzed to the amine by either acid or alkali.

Ingersoll, in his extensive investigation of the reaction, found that formamide gave much better yields of amines than did ammonium formate, and he postulates that it, rather than the salt, is the reactant.

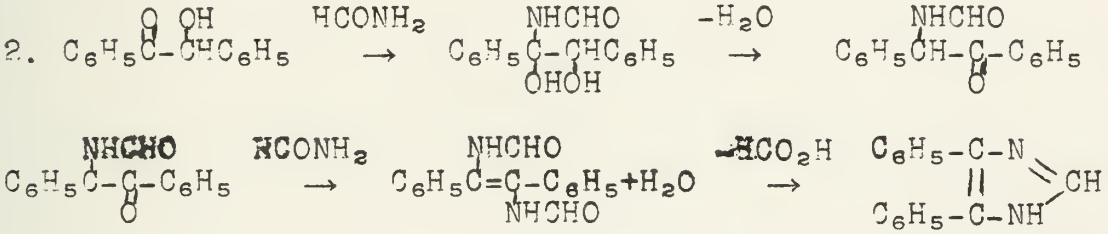
Applications

The Leuckart reaction is of special importance in the preparation of amines which cannot be prepared by the reduction of the oxime. It is found to give the best yields with water-insoluble ketones which boil above 120° C. A few aldehydes such as benzaldehyde, substituted benzaldehydes, and furfural have been success-

fully used in this synthesis. Aliphatic aldehydes yield tertiary amines. The method has been used to a considerable extent with terpenoid ketones. The reaction with aromatic acyloins is unique, giving a high yield of glyoxalines with a small amount of the pyrazine. Two mechanisms have been proposed for this reaction.[5,11]

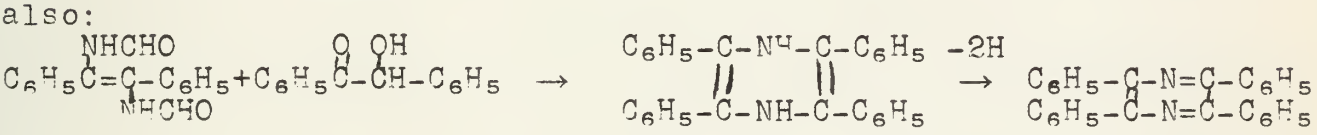


4,5-diphenylglyoxaline



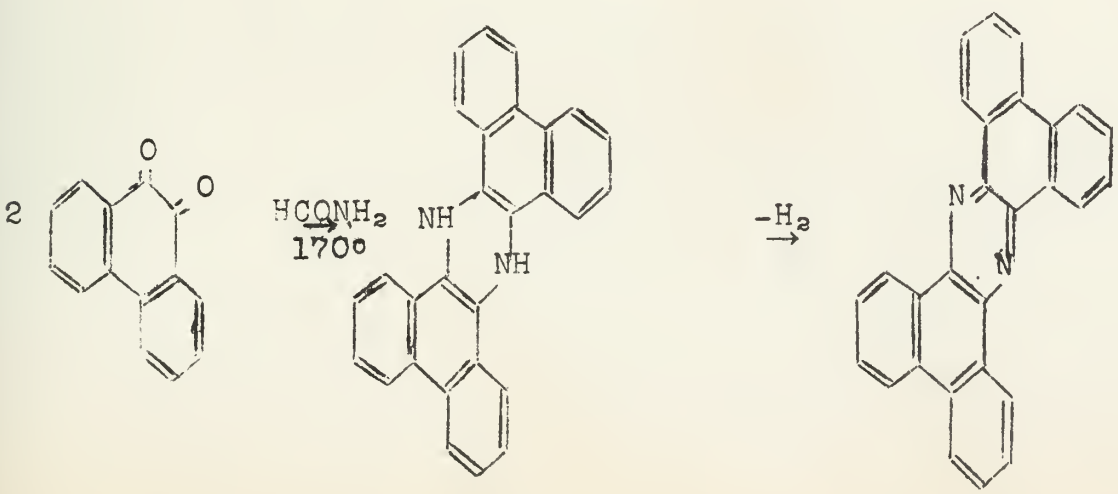
4,5-diphenylglyoxaline

also:



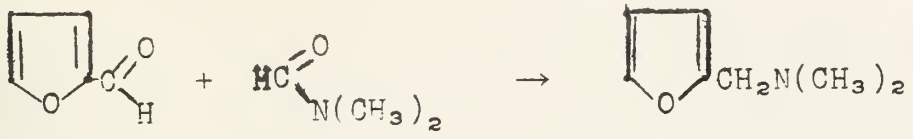
tetraphenyl-p-diazine

Para-quinones yield the corresponding di-formylamino compounds, but the use of ortho-quinones in this reaction leads to the formation of heterocyclic rings. An example of this condensation is the reaction of phenanthro-quinone (I) with formamide to yield the dihydrophenanthrazine (II). On recrystallization from tetralin, the compound loses hydrogen, and phenanthrazine (III) is obtained.



I II III

Either formamide or ammonium formate may be used in the Leuckart reaction. With the salt good yields are obtained only if water is allowed to distil from the reaction mixture as it is formed. N-Substituted formamides yield the correspondingly substituted amines.



Amines Prepared by the Leuckart Reaction

Carbonyl Compound	Amine Used (As formamide or formate)	Amine Prepared	Yield (%)	Ref.
Valeraldehyde	NH_3	triamyl	13	2
Valeraldehyde	aniline	N,N-diamylaniline	13	2
Valeraldehyde	methyl-aniline	N-methyl N-amylaniline	13	2
Carvomenthone	NH_3	carvamenthyl	20-25	3
Acetophenone		α-phenylethyl	72	4(19)
p-Methylacetophenone		α-p-tolylethyl	72	4(19)
m-Methylacetophenone		α-m-tolylethyl	70	4
p-Chloroacetophenone		α-p-chlorophenylethyl	82	4(19)
p-Bromoacetophenone		α-p-bromophenylethyl	79	4(19)
p-Methoxyacetophenone		α-p-methoxyphenylethyl	68	4
p-Phenylacetophenone		α-p-xenylethyl	77	4(19)
p-Phenoxyacetophenone		α-p-phenoxyphenylethyl	69	4
β-Acetonaphthone		methyl-β-naphtyl carbin	84	4(19)
m-Nitroacetophenone		α-m-nitro-phenylethyl	56	4
dl-Fenchone		dl-fenchyl	85	4
d-Camphor		d-bornyl + neobornyl	62 (83)	4(13)
Pinacolone		methyl-t-butyl carbin	52	4
Cyclohexanone		cyclohexyl	50	6
		dicyclohexyl	11	
o-Chlorobenzylmethyl ketone		α-o-chlorobenzylethyl	52	7
Benzylethyl ketone		α-benzylethyl	50-60	7
p-Tolylethyl ketone		α-p-tolylethyl	50-60	7

Acetone	α-naphtyl-amine	α-naphthylisopropyl		8
Cyclohexylmethyl ketone	NH_3	α-cyclohexylethyl		9
		di-α-cyclohexylethyl	20	
Acetophenone	methyl	methyl-α-phenylethyl	60	10
p-Methylaceto-phenone	methyl	methyl-α-p-methylphenyl-ethyl	50	10
p-Chloroaceto-phenone	methyl	methyl-α-p-chlorophenyl-ethyl	70	10
p-Bromoaceto-phenone	methyl	methyl-α-p-bromophenyl-ethyl	70	10
Acetophenone	ethyl	ethyl-α-phenylethyl	70	10
p-Methylaceto-phenone	ethyl	ethyl-α-p-methylphenyl-ethyl	60	10
p-Chloroaceto-phenone	ethyl	ethyl-α-p-chlorophenyl-ethyl	80	10
p-Bromoaceto-phenone	ethyl	ethyl-α-p-bromophenyl-ethyl	60	10
Acetophenone	butyl	butyl-α-phenylethyl	70	10
p-Methylaceto-phenone	butyl	butyl-α-p-methylphenyl-ethyl	50	10
p-Chloroaceto-phenone	butyl	butyl-α-p-chlorophenyl-ethyl	80	10
p-Bromoaceto-phenone	butyl	butyl-α-p-bromophenyl-ethyl	70	10
Benzoin	NH_3	4,5-diphenylglyoxaline	75	11
		tetraphenyl-p-diazine	10	11
Anisoin		di-p-methoxyphenyl glyoxaline	70	11
		tetra-p-methoxyphenyl pyrazine	10	11
Benzanisoin		p-phenyl-5-p-methoxy-phenyl glyoxaline		11
		diphenyl-di-p-methoxy-phenyl pyrazine		11
p-Toluoin		4,5-di-p-tolyl glyoxaline	75	11
		tetra-p-tolyl pyrazine	8	11
Phenylacetone	methyl	α-benzylethyl methyl	50-70	11
			22	13
Phenylacetone	ethyl	α-benzylethyl ethyl	50-70	11
Phenylacetone	butyl	α-benzylethyl butyl	50-70	11
Phenylacetone	amyl	α-benzylethyl amyl	50-70	11
Phenylacetone	dimethyl	α-benzylethyl dimethyl	50-70	11
Phenylacetone	diethyl	α-benzylethyl dimethyl	50-70	11
p-Fluorobenzyl-methyl ketone	NH_3	α-methyl-p-fluorophenyl-ethyl	41	13
α-Phenylethyl-methyl ketone		2-amino-3-phenyl butane	60	13
α-Phenylpropyl-methyl ketone		2-amino-3-phenyl pentane	63	13
α-Phenylbutyl-methyl ketone		2-amino-3-phenyl hexane	68.5	13
α-Phenylisopropyl-methyl ketone		2-amino-3-phenyl-3-methyl butane	76.5	13
α-Phenylethyl-methyl ketone	methyl	2-methyl amino-3-phenyl butane	16	13

Methyl-α-thienyl ketone	NH_3	1-(α-thienyl)-1-aminoethane	51	15
Methyl-α-thienyl ketone	methyl	1-(α-thienyl)-1-methylaminoethane	45	15
Ethyl-α-thienyl ketone	NH_3	1-(α-thienyl)-1-aminopropane	36	15
Ethyl-α-thienyl ketone	methyl	1-(α-thienyl)-1-methylaminopropane	27	15
o-Anisaldehyde	methyl	o-methoxybenzyl methyl		16
p-Anisaldehyde	methyl	p-methoxybenzyl methyl		16
o-Anisaldehyde	ethyl	o-methoxybenzyl ethyl		16
p-Anisaldehyde	ethyl	p-methoxybenzyl ethyl		16
Piperonylmethyl ketone	NH_3	2-(3,4-methylene dioxyphenyl) isopropyl	20	17
Furfural	di-methyl	di-methyl furfuryl		18
Furfural	di-ethyl	di-ethyl furfuryl		18

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Reported by H. F. Herbrandson
July 21, 1943

THE CORRELATION OF MOLECULAR STRUCTURE AND BACTERIOSTATIC ACTIVITY OF SULFANILAMIDE TYPE COMPOUNDS

Introduction

The discovery in 1935 by Domagk with prontosil and the Pasteur Institute with sulfanilamide that compounds related to sulfanilamide were effective as bacteriostatic agents began a period of hurried research on the synthesis and bacteriological testing of these compounds until, in 1940, Northey[1] was able to write that probably three thousand derivatives of sulfanilamide had been prepared. But with all this activity in the synthesis of the sulfa drugs, the correlation of structure and antibacterial properties could be made only with the usual vague generalizations which aided little in indicating the fundamental properties of the sulfanilamide molecules responsible for their activity. This correlation came only after the elucidation of the mechanism of bacteriostatic action of sulfa compounds, which proved increasingly interesting since it showed itself to be concerned with antibacterials other than sulfanilamide and with the very life processes of the cells themselves.

The Mechanism of Sulfanilamide Bacteriostasis.

It was suggested early that sulfanilamide probably acted by its influence in some fashion on the enzymes of the bacteria. Locke, Main, and Millon[2] held that the active form was the corresponding hydroxylamine which inhibited catalase to allow the accumulation of hydrogen peroxide in lethal amounts, while Shaffer[3] believed the hydroxylamine was active due to its high oxidation potential, an idea later disproved by Roblin and Bell[4]. Concurrent with these theories, experimental evidence began to accumulate suggesting that sulfanilamide exerted its effect by interfering with the nutrition of the bacterial cell[5]. Lockwood proposed that the proteolytic enzymes of the cell were inhibited, Stamp isolated from a streptococcus a sulfanilamide-antagonizing factor which he thought might be a coenzyme, and Green prepared from Brucella abortus a similar extract, the properties of which suggested it as a stimulant of a sulfanilamide-inhibited enzyme system.

In 1940, Woods[6] reported the isolation from yeast of a substance which, even in small amounts, inhibited the bacteriostatic action of sulfanilamide completely. Obtained by extraction with N/25 ammonium hydroxide at 37°C., the substance was very stable, being unaffected by heat, storage for three months at 0°C., or boiling with dilute alkali or 50% hydrochloric acid. The factor was precipitated by heavy metal cations and could be extracted with ether from acidic aqueous solutions, but not from basic ones. It could be esterified, confirming an acid group, diazotized, confirming a primary aromatic amine, and acetylated, showing either an hydroxyl or amino group. Its pK_a was 4-5. All the evidence indicated an aromatic amino carboxylic acid which did not exist as a zwitterion since it was soluble in ether. The similarity of the proposed structure to sulfanilamide itself was noted.

In growth tests with sulfanilamide, the factor was found to prevent inhibition of bacterial growth in amounts proportional to the quantity of sulfanilamide used, and, furthermore, it was shown that a stoichiometric reaction between the factor and the sulfa drug would require a molecular weight of one for the factor, if it were assumed that one mole of the factor reacted with one mole of the sulfanilamide. Therefore it was suggested that the observed facts could be explained on the basis that sulfanilamide and the factor were both competing for the same enzyme system in the organism.

While the chemical identity of the factor was not discovered, its properties suggested p-aminobenzoic acid, and trial of this compound gave results identical with those of the factor. Thus Woods was able to postulate that sulfanilamide acted by competing with p-aminobenzoic acid, an essential metabolite, for an enzyme system in the organism, and that the sensitivity of the organism to sulfanilamide would depend on its ability to synthesize p-aminobenzoic acid or on its availability in the medium.

Corroboration of Woods' work came rapidly. Selbie[7] and Strauss, Lovell, and Finland[8] showed the *in vitro* results to be valid *in vivo*. Landy and Wyeno[9] demonstrated that p-aminobenzoic acid inhibited sulfapyridine and sulfathiazole as required by Woods' general theory. Rubbo and Gillespie[10] closed two loopholes by proving p-aminobenzoic acid a growth factor for *clostridium acetobutylicum*, thus showing it an essential metabolite, and by isolating 2 mg. of benzoyl-p-aminobenzoic acid from 30 kg. of brewers yeast. It was shown by Wyss[11] and Wood[12], by mathematical analysis, that a competitive mechanism where one molecule of p-aminobenzoic acid antagonized 25,000 molecules of sulfa drug was consistent with the observed growth data. Finally it was demonstrated by Wood and Austrian[13] that thiamine and cocarboxylase would not antagonize sulfathiazole and that coenzymes would not antagonize sulfapyridine, indicating that the N' substituents of the sulfa compounds did not interfere with these cozymases in the cell, and that competition with p-aminobenzoic acid was the only significant function of sulfanilamide.

The Correlation of Molecular Structure and Antibacterial Activity

With the mechanism of sulfanilamide action clarified, Bell and Roblin[14] have used certain physical constants to bring the molecular structure and bacteriostatic activity of these compounds into effective correlation. Since the function of the sulfanilamide is to compete with p-aminobenzoic acid, its effectiveness should be determined by its similarity to the molecule which it replaces. The characteristic groups in the molecules concerned are the acidic groups and the basic amino groups para to them. Aside from their geometric configuration, the most important characteristic of these groups is their positive or negative character, which is reflected in their acidity or basicity. Measurement of the ionization constants for the basic amino groups in a great number of N' substituted sulfanilamides showed little variation from about 2.6×10^{-12}, which is very near that of p-aminobenzoic acid. However, a corresponding study of the acid dissociation constants revealed a variation from 10^{-3} to 10^{-11}, and the correlation of

bacteriostatic values with these constants showed that with increasing acidity, the bacteriostatic power of the compounds increased to a maximum at a pKa of about 6.5 and then decreased steadily.

An explanation of this fact is to be found in the consideration of several factors. p-Aminobenzoic acid is a strong enough acid (pKa 4.68) to be 99% dissociated in a solution buffered at pH 7, giving it a structure depicted in Figure 1a., while the sulfanilamides will exist in either an un-ionized (b) or ionized form (c) depending on the dissociation of the H attached to N'.

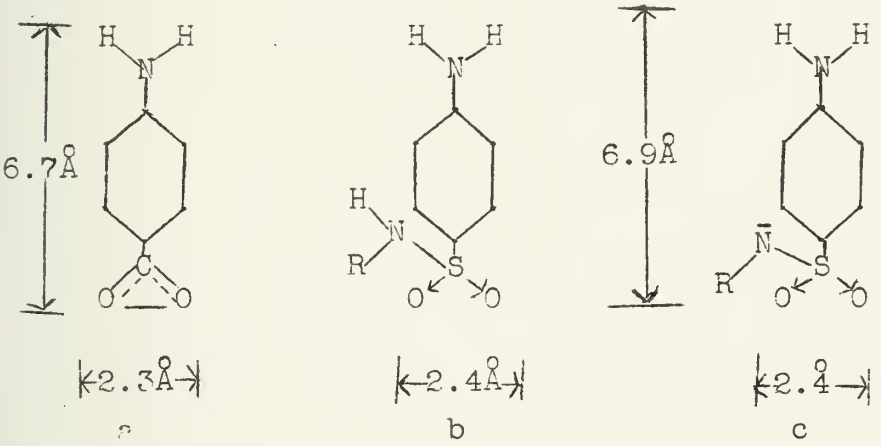

Figure 1

In view of the geometric similarity of these molecules, since the basicity of the amino groups does not seem to vary significantly, and since the $-CO_2^-$ group of p-aminobenzoic acid is more negative than the $-SO_2$ group of the sulfanilamide, it may be postulated that the more negative the $-SO_2$ group of the sulfanilamide, the closer it will resemble p-aminobenzoic acid and the greater its bacteriostatic powers will be.

Since the R group attached to N' is the only variable, the problem is one of correlating its properties with the acidity of the molecule and the negativity of the $-SO_2$ group. If the R group is to be an acid strengthening group, it must be electro-negative (electron attacting), in which case it functions by attracting electrons from the N-H bond to free the proton, leaving the sulfonamide group as an ion, in which form the negativity of the $-SO_2$ group is enhanced due to the ionic charge. But, the other effect of increasing electronegativity of the R group is to attract electrons from the $-SO_2$ group and, thus, decrease its negativity. Therefore, the overall effect of increasing the electronegativity of the N' substituent is first to increase the amount of the compound existing in ionic form to cause an increase in bacteriostatic power, and then, as this effect becomes proportionally less than the decrease in the negativity of the $-SO_2$ group due to increased competition by the R group for electrons, the bacteriostatic power decreases. Meanwhile, the acidity is increasing, and the observed variation of antibacterial activity with acidity is accounted for. The problem of maximum antibacterial activity is one of balancing the increase in activity due to an increase in ionization and the decrease in activity due to increased competition of the R group with

the $-SO_2$ group for electrons. A mathematical analysis based on theoretical considerations indicates the maximum activity at a pKa of 6.7, which checks the experimental data well. If the R group becomes electropositive, the $-SO_2$ group should become more negative and bacteriostasis should increase, but these compounds are such weak acids that no dissociation constants were obtained to check this.

With this theory, a more nearly accurate evaluation of the effect of anti-bacterial activity of N' substituents in compounds which are inhibited by p-aminobenzoic acid may be made, and these considerations should apply equally well to p-aminobenzoic acid-inhibited compounds in which the S is replaced by P, As, Se or other elements. Examples of substituents which increase activity are aromatic rings and alkyl chains substituted in the α position with strong electron attracting groups. Acyl and sulfonyl groups are so strongly electronegative that they decrease bacteriostasis, as do the slightly electropositive alkyl chains. Heterocyclic and substituted aromatic groups vary greatly in electronegativity and, hence, in their effect on activity. A second N' substituent on a compound which is capable of ionization will decrease activity by prohibiting ionization.

An interesting implication of the above theory is that the limit of anti-bacterial activity in the sulfanilamides has been reached, and that further research should be designed to increase efficiency of utilization in the biological system.

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Reported by D. A. Shepherd
July 28, 1943

ORGANO CADMIUM COMPOUNDS

Organo cadmium compounds were first prepared and studied extensively by Krauss in 1917. Since then Gilman and Nelson, and de Benneville have extended the study and have used both cadmium alkyls and aryls in the preparation of ketones.

Cadmium compounds can be prepared most readily by the action of cadmium halide on the Grignard reagent. Other organometallic compounds may be used but their greater expense and difficulty of preparation does not in most cases warrant their use. Contrary to Krause, Gillman and Nelson and de Benneville found that cadmium chloride is entirely satisfactory. This is significant for several reasons: (1) cadmium chloride is less expensive than other cadmium halides, (2) anhydrous cadmium chloride is easily prepared and stored (3) and it is more readily handled than the highly deliquescent zinc chloride.

The reaction with the Grignard reagent is easily effected and it is unnecessary to isolate either the R_2Cd or RCdX compounds inasmuch as subsequent reactions may be carried out in the same medium (ether). Organozinc compounds cannot be used in ether solutions in reactions with acid chlorides to form ketones because ether cleavage brings about the formation of esters. The only case of ester formation noted by Gilman and Nelson was in the case of diphenyl cadmium and benzoyl chloride and here only about 7% of ethyl benzoate was formed. De Benneville noted the formation of traces of esters when he used acid anhydrides in place of acid chlorides.

The Grignard reagent is usually prepared from the corresponding alkyl or aryl bromide, both because they are obtainable in good yields and because iodides may give side reactions which tend toward lower yields when the cadmium compound is used to prepare ketones.

The pure organo cadmium compounds may be isolated in 50-90% yields by distillation in nitrogen atmosphere under diminished pressure. They are colorless, highly refractive oils with a very unpleasant odor and an irritating action on the mucous membranes. The oils are stable in tubes filled with pure nitrogen and stored in the dark. In air they fume vigorously and may even burst into flame if allowed to fall in small drops. They are stable in an inert atmosphere up to temperatures of 150°. However the thermal instability seems to increase with branching and in the preparation of a ketone from di-t-butylcadmium it is advisable to cool the reaction mixture in an ether-dry ice bath. Di-isopropyl-cadmium should be cooled in ice bath and diethyl-cadmium may be used at room temperature.

The ether solution of dialkyl- or diaryl-cadmium reacts with acid chlorides to yield ketones. In case mixed aryl-alkyl ketones

$$RCOCl + R_2Cd \rightarrow RCOR'$$

are derived better yields are obtained when the di-aryl-cadmium is allowed to react with the alkyl acid chloride. The reaction is especially useful in preparing aryl ketones in which orientation is of major importance. Suter reported that he was unable to obtain

satisfactory yields of 3,5-dimethoxyphenyl alkyl ketones by use of either cadmium or zinc alkyls. He found that this type of ketone was more readily available through the action of an alkyl Grignard reagent on the corresponding dimethylamide.

An attempt to prepare an α-diketone from oxalyl chloride and diethyl-cadmium went beyond the α-diketone stage to form diethyl propionyl carbinol.

$$ClCOCOCl + (C_2H_5)_2Cd \rightarrow [C_2H_5COCOC_2H_5] \rightarrow (C_2H_5)_2COHCOC_2H_5$$

Apparently there is activation of one of the carbonyl linkages to that the ketone is converted to the tertiary alcohol.

Carter obtained satisfactory yields of diketones by using acid chlorides of dibasic acids. However when diphenyl-cadmium was reacted with phthalyl chloride a 49% yield of 3,3-diphenyl-phthalide was obtained. Some keto acid was also produced. When the ester was used in place of the acid chloride the yield of the acid chloride was decreased and the yield of the diketone increased. Addition of diethyl-cadmium to ethyl oxalyl chloride produced ethyl α-hydroxy-α-ethyl butyrate in 63% yields. When the diethyl ester was used the yield was increased to 83%.

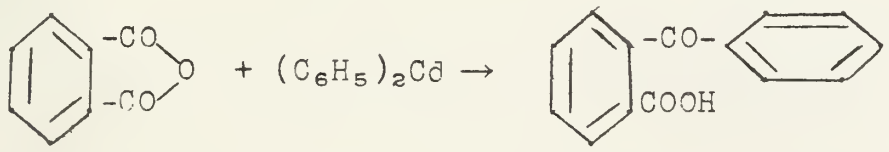
$$C_2H_5OCOCOOC_2H_5 + (C_2H_5)_2Cd \rightarrow (C_2H_5)_2COHCOOC_2H_5$$

The unusually rapid reaction of organo cadmium compounds with acid halides is in marked contrast with their slow reaction with benzaldehyde. This indicates that in ketone formation there may not be preliminary addition to the carbonyl linkage. There is a possibility that a simple acid chloride may react by metathesis and others (like oxalyl chloride) by addition to the carbonyl group.

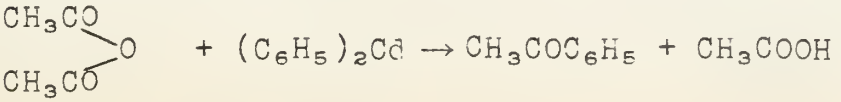
Phenyl-cadmium bromide reacts with ketene to give acetophenone.

$$C_6H_5CdBr + H_2C{=}C{=}O \rightarrow CH_3COC_6H_5$$

De Benneville treated cyclic acid anhydrides with organo cadmium compounds in preparing keto acids. He obtained a 64% yield of o-benzoyl-benzoic acid when phthalic anhydride was allowed to react with diphenyl-cadmium.



When non cyclic anhydrides were used the main product of the reaction was the ketone.



Comparison of yields shows that in most cases acid anhydrides and acid chlorides may be used interchangeably.

Phenyl isocynate and α naphthyl isocynate trimerize under the influence of diethyl-cadmium. Diphenyl-cadmium apparently condenses benzaldehyde and acetophenone to benzalacetophenone.

$$C_6H_5CHO + CH_3COC_6H_5 \xrightarrow{(C_2H_5)_2Cd} C_6H_5CH{=}CH_2COC_6H_5$$

There is a possibility that under the experimental conditions the diethyl-cadmium may have reacted with the acetophenone to give enolate ions.and the condensation might have gone through an intermediate salt of this type.

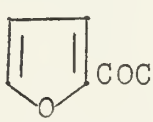
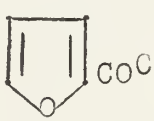
Diphenyl-cadmium reacts with benzenesulfonyl chloride after the general manner of organo metallic compounds.

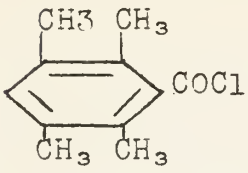
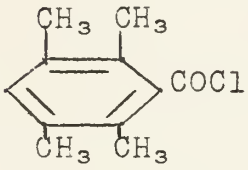
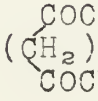
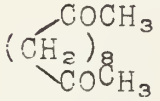
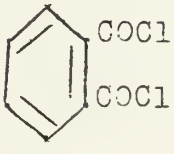
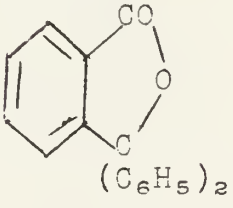
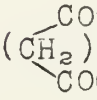
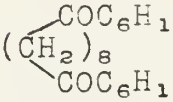
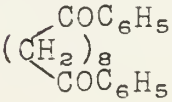
$$C_6H_5SO_2Cl + (C_6H_5)_2Cd \rightarrow C_6H_5SO_2C_6H_5 + C_6H_5SO_2H + C_6H_5Cl$$

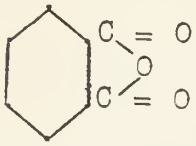
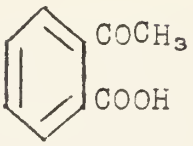
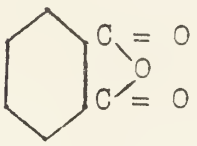
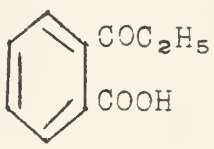
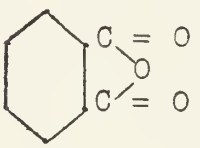
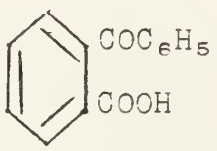
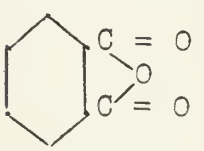
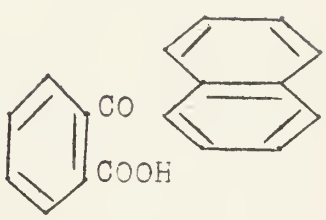
Di-n-butylcadmium and t-butyl chloride react to give primarily isobutylene. In these experiments the R_2Cd compound was not isolated but used in the mixture directly after preparation. The more reactive organo zinc compounds give R_4C types.

In his studies on reactivity of organo metallic compounds, Nelson found that diethylcadmium reacts with hydrogen attached to oxygen, sulfur and nitrogen only when these atoms are adjacent to a carbon atom holding a negative group. Only 60-80% of the active hydrogen was evolved in the reaction.

Ketones prepared from
Organo Cadmium Compounds

*Cadmium Compound	Acid Chloride	Product	Yield
$(CH_3)_2Cd$	C_6H_5COCl	$C_6H_5COCH_3$	85%
$(CH_3)_2Cd$	m-$CH_3C_6H_4COCl$	m$CH_3C_6H_4COCH_3$	83
$(CH_3)_2Cd$	p-$CH_3OC_6H_4COCl$	p$CH_3OC_6H_4COCH_3$	84
$(C_2H_5)_2Cd$	CH_3COCl	$CH_3COC_2H_5$	46
C_2H_5CdBr	CH_3COCl	$CH_3COC_2H_5$	50
$(C_2H_5)_2Cd$	C_6H_5COCl	$C_6H_5COC_2H_5$	50
$(C_2H_5)_2Cd$	n-$C_{17}H_{30}COCl$	n-$C_{17}H_{30}COC_2H_5$	65
$(C_2H_5)_2Cd$			61
(iso $C_3H_7)_2Cd$	nC_3H_7COCl	iso $C_3H_7COC_3H_7$	60
$(nC_3H_7)_2Cd$	CH_3COCl	$nC_3H_7COCH_3$	74
$(t\text{-}C_4H_9)_2Cd$	CH_3COCl	$t\text{-}C_4H_9COCH_3$	17
$(C_6H_5CH_2)_2Cd$	CH_3COCl	$C_6H_5CH_2COCH_3$	18
$(C_6H_5)_2Cd$	CH_3COCl	$C_6H_5COCH_3$	83%
C_6H_5CdBr	CH_3COCl	$C_6H_5COCH_3$	83

Cadmium Compound	Acid Chloride	Product	Yield
C_6H_5CdBr		$DurCOC_6H_5$	75
$(P(CH_3)_3CC_6H_4)_2Cd$		$P(CH_3)_3CC_6H_4CODur$	20
$(C_2H_5)_2Cd$	$ClCOCOCl$	$(C_2H_5)_2COHCOC_2H_5$	27
$(C_2H_5)_2Cd$	$C_2H_5OCOCOCl$	$(C_2H_5)_2COHCOOC_2H_5$	63
$(C_2H_5)_2Cd$	$C_2H_5OCOCOOC_2H_5$	$(C_2H_5)_2COHCOOC_2H_5$	83
$(CH_3)_2Cd$			4
		and 	33
$(CH_3)_2Cd$			88
$(C_6H_5)_2Cd$			49
$(n\text{-}C_6H_{13})_2Cd$			49
$(C_6H_5)_2Cd$			71

Cadmium Compound	Acid Chloride	Product	Yield
	Acid anhydride		
$(CH_3)_2Cd$			62
	Acid anhydride		
$(C_2H_5)_2Cd$			67
	Acid anhydride		
$(C_6H_5)_2Cd$			64
	Acid anhydride		
$\alpha C_{10}H_7)_2Cd$			57
$(C_6H_5)_2Cd$	Succinic	CH_2-COOH CH_2-COC_6H_5	30
$(nC_4H_9)_2Cd$	Acetic	$CH_3COC_4H_9$	56
$(C_6H_5)_2Cd$	Acetic	$CH_3COC_6H_5$	75
$(C_6H_5)_2Cd$	Propionic	$C_2H_5COC_6H_5$	68
$(C_2H_5)_2Cd$	Benzoic	$C_2H_5COC_6H_5$	53
$(isoC_3H_7)_2Cd$	Benzoic	$(CH_3)_2CHCOC_6H_5$	44
$(t\text{-}C_4H_9)_2Cd$	Benzoic	$tC_4H_9COC_6H_5$	40

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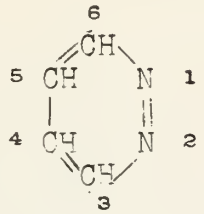
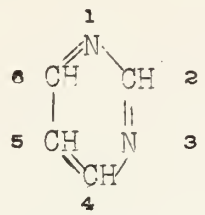
Reported by D. F. Meisner
July 28, 1943

SYNTHESIS OF DIAZINES

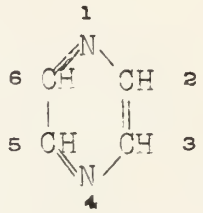
The three isomeric diazine rings are quite stable even to strong oxidation, but are readily reduced to the corresponding saturated heterocycles. They are numbered as follows:



pyridazine
(1,2-diazine; ortho-diazine)



pyrimidine
(1,3-diazine; metadiazine)

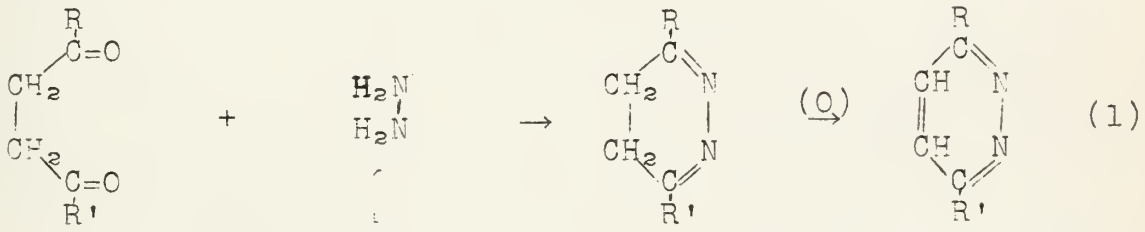


pyrazine
(1,4-diazine; paradiazine)

SYNTHESIS OF PYRIDAZINES

From 1,4-dicarbonyl compounds

Hydrazine reacts with 1,4-diketones in neutral or alcoholic solution to give substituted dihydropyridazines (I); the monohydrazone is presumably an intermediate.



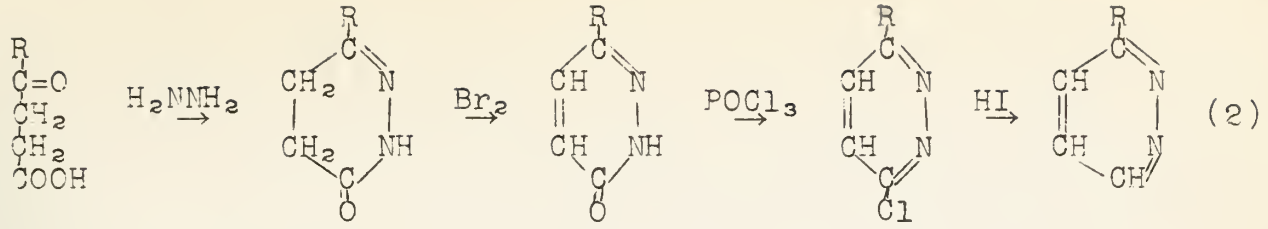
I II (1)

These dihydropyridazines are very readily oxidized to the corresponding pyridazines (II); some, in fact, can not be isolated in the presence of air. R and R' may be either aryl or alkyl; the ketone may be more highly substituted, to give substituents in the 4- or 5- positions in the product. The reaction is observed for such ketones as phenacylacetone, diphenacyl, desylacetophenone; ethyl diacetylsuccinate gives 3,6-dimethyl-4,5-dicarbethoxypyridazine.

If the dicarbonyl compound is unsaturated, no dihydro intermediate will be formed. Thus maleic aldehyde gives pyridazine, and dibenzoylethylene and ethyl dibenzoylmaleate give substituted pyridazines.

From γ-ketoacids

Hydrazine reacts with γ-ketoacids to give 3-keto-4,5-dihydropyridazines (III), which are converted to pyridazines as follows:



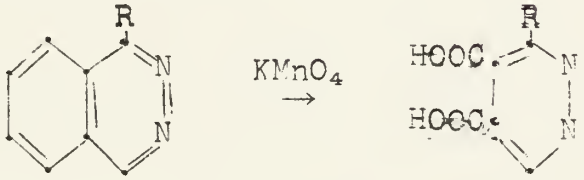
(2)

III IV

R is usually aryl; if R is p-anisyl, it may be oxidized to a carboxyl group and decarboxylated to give pyridazine. Aromatic groups may also appear on the other two carbon atoms. The bromine oxidation is unnecessary if the ketoacid is unsaturated, as with α-methyl-β-acetylacrylic acid.

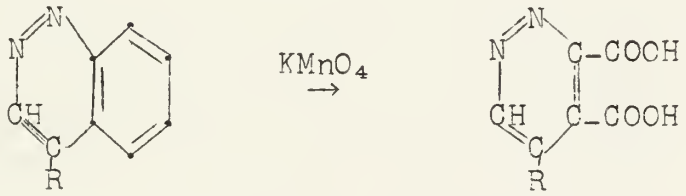
From fused ring systems

Phthalazines are oxidized by alkaline permanganate to pyridazine-4,5-dicarboxylic acids.



(3)

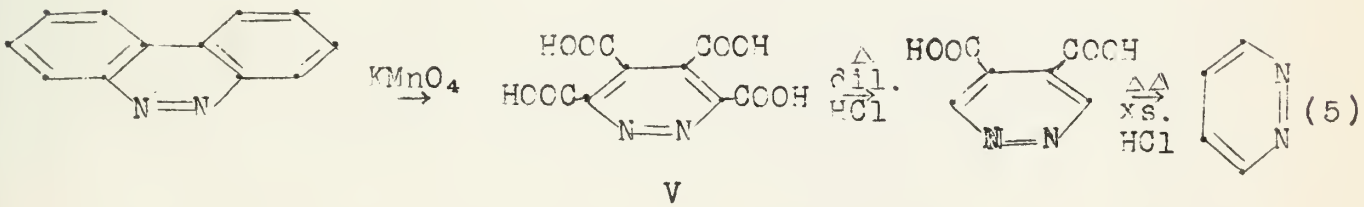
Cinnolines are similarly oxidized to the 3,4-dicarboxylic acids:



(4)

Cinnolines may be obtained by diazotization of aromatic amines having an unsaturated ortho-substituent; cyclization takes place spontaneously. R is usually aryl.

Phenazones give the tetracarboxylic acid (V) with neutral permanganate; this, like the mono- and dicarboxylic acids, is decarboxylated on heating, alone or with acids.



(5)

V

Phenazone is prepared by alkaline reduction of o,o'-dinitrobiphenyl.

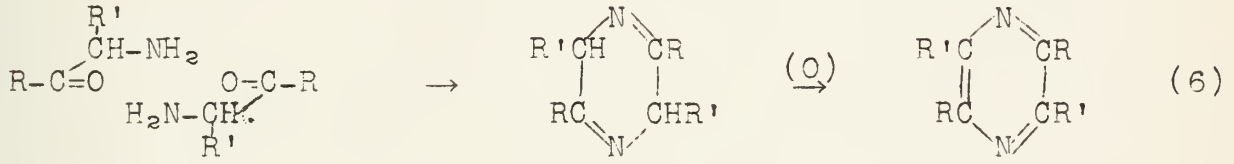
Aminopyridazine

When treated with alcoholic ammonia, 3-chloropyridazine (compound IV, R=H) gives 3-aminopyridazine. The sulfanilamide derivative has been made, but not extensively investigated.

SYNTHESIS OF PYRAZINES

From α-aminoketones

Generally α-aminoketones are unstable in the free state, condensing upon formation to give 3,6-dihydropyrazines (VI), which are oxidized by air to pyrazines (VII):



VI VII (6)

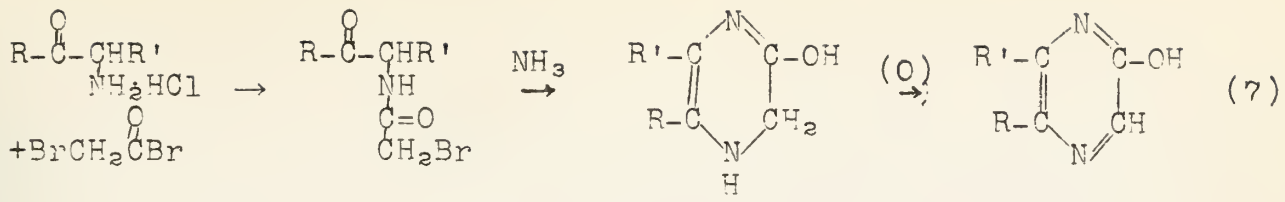
The dihydro intermediates often are not isolated, especially when R'=H; in other cases they are oxidized merely on warming in air or by mild oxidizing agents. R and R' may be alkyl or aryl; if the α-carbon atom is further substituted, usually no condensation occurs. Many aminoketones are prepared by the phthalimide synthesis; some, where R=CH_3, are obtained from amino acids and acetic anhydride, with subsequent decarboxylation and hydrolysis. With careful exclusion of air, the reaction may be reversed by boiling VI with dilute hydrochloric acid or concentrated hydriodic acid.

Similarly, aminoacetaldehyde gives pyrazine when oxidized by mercuric chloride in basic solution. Pyrazine is also obtained by catalytic dehydrogenation of ethanolamine; presumably the aminoaldehyde is an intermediate.

From α-haloketones

Treatment of α-chloro or α-bromoketones with ammonia, usually alcoholic, forms the aminoketones, and the condensation (6) follows. This reaction is also general; R and R' may even be joined, as in α-chlorocycloheptanone. However, reaction of phenacyl halides with ammonia may also give diphenacyl amine, which condenses with ammonia to give the 2,6-diphenylpyrazine in addition to the expected 2,5-diphenylpyrazine. Therefore it is often best to obtain the aminoketone by phthalimide synthesis.

Just as two like molecules condense to form a symmetrical pyrazine, the ring closure may be intramolecular.



(7)

R is alkyl; R' is either alkyl or aryl. In the first step the pH of the mixture must be kept slightly acid to prevent condensation of the first aminoketone.

From α-isonitrosoketones

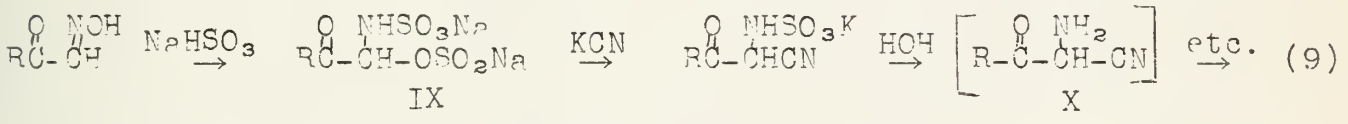
Alkaline reduction of α-isonitrosoketones likewise gives α-aminoketones (VIII), which condense on formation, according to series (6) above.

VIII.

(8)

Most acid reductions give the amine salt, but sometimes the condensation will occur even in acid media. While isonitrosoacetoacetic ester can give the amine salt with stannous chloride and hydrochloric acid, and with zinc and acetic acid, it condenses directly if reduced by zinc and formic acid; it also condenses on hydrogenation over Raney nickel.

Gastaldi prepared pyrazines from α-isonitrosoketones by way of their bisulfite addition products (IX), which on treatment with potassium cyanide and hydrolysis give α-cyano-α-aminoketones (X).



IX X

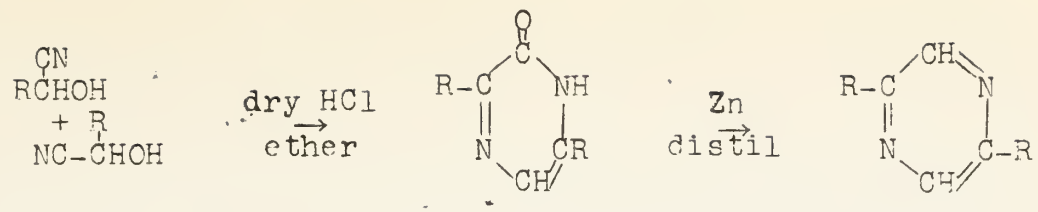
(9)

Thus R', in series (6), becomes -CN.

Similarly, alkaline reduction of dimethylglyoxime leads to tetramethylpyrazine; here the dioxime is first hydrolyzed to the monoxime and the reaction proceeds as above in (8) and (6).

From cyanohydrins

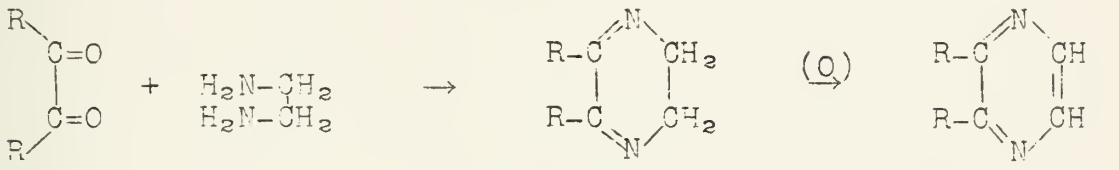
Aromatic cyanohydrins condense in the presence of dry hydrogen chloride to form ketodihydropyrazines (XI). Distillation from zinc dust then gives the 2,5-diarylpyrazines (XII). Cinnamaldehyde-cyanohydrin behaves analogously.



XI XII (10)

From 1,2-diketones and 1,2-diamines

Saturated 1,2-diamines condense with 1,2-diketones in alcohol or acetic acid; the 5,6-dihydropyrazines formed (XIII) can often be isolated, but are usually easily oxidized, on warming in solution or distilling, to the pyrazines (XIV).



XIII XIV (11)

Substituted diamines will give 4- or 5- substituted pyrazines. If the diamine is unsaturated, no dihydro intermediate will be formed; thus diaminomaleinitrile condenses with glyoxal, dimethylglyoxal or benzil to give cyanopyrazines directly.

From fused ring systems

Quinoxalines are oxidized by alkaline permanganate to pyrazine-2,3-dicarboxylic acids.

(12)

Quinoxalines substituted in the heterocyclic ring are prepared from o-phenylenediamine and suitable 1,2-dicarbonyl compounds, as in reaction (11). Here most substituents are unaffected by permanganate, but ethoxymethyl groups are oxidized. Decarboxylation of the acids is accomplished by heating in glacial acetic acid or distilling from lime.

Aminopyrazines

Hoffman degradation of the monocarboxylic acid amide gives as a stable product the sodium pyrazinecarbamate, which must be hydrolyzed with acid to obtain aminopyrazine. Recently direct amination of the ring with sodamide in dimethylaniline has been reported. Preliminary investigations on the sulfanilamide derivative show it to be rather effective against pneumococcus in mice.

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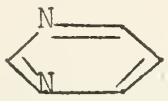
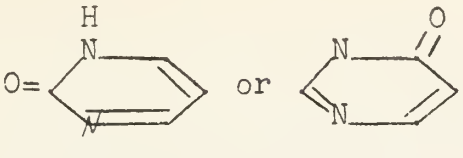
Reported by Elizabeth Peel
August 4, 1943.

SYNTHESIS OF PYRIMIDINES

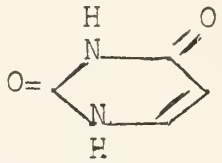
Pyrimidines may be classified according to the number of oxygen atoms on the ring.



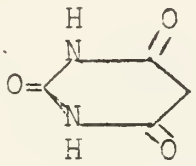
I. True pyrimidines

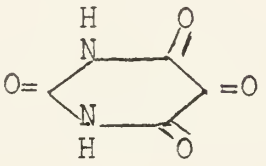


II. Monoxopyrimidines



III. Uracil

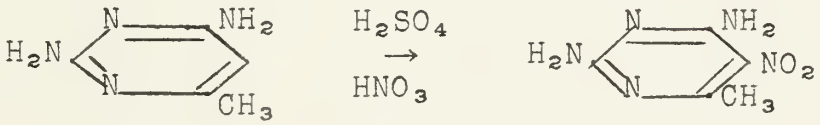


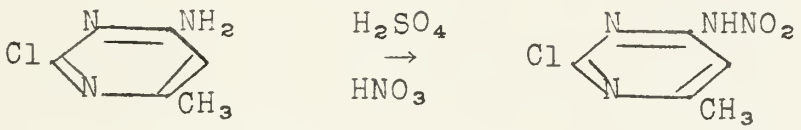


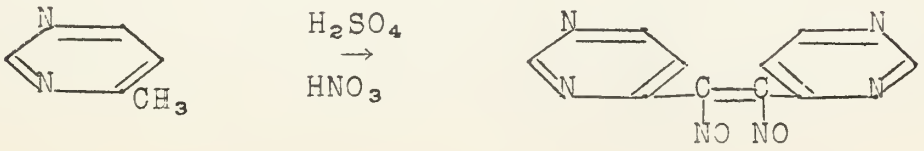
IV. Barbituric Acid V. Alloxan

The pyrimidine ring structure is somewhat analogous to pyridine. It is a heterocyclic carbon-nitrogen ring and as such possesses strongly basic properties. This basic nature can be seen in its formation of stable salts with mineral acids and formation of relatively insoluble complex salts with chlorides of gold and of platinum. For identification, the stable compounds formed with picric and picrolonic acid are used. Substitution of oxygen directly on the ring causes a decrease in the basic properties such that 6-oxypyrimidine is weakly amphoteric. Any additional increase in the number of oxygen atoms further decreases the basic nature until the compounds become acidic.

One problem in pyrimidine chemistry is due to the fact that one reagent will react in such a variety of ways with different pyrimidines. Nitration of three pyrimidines serves to illustrate this.





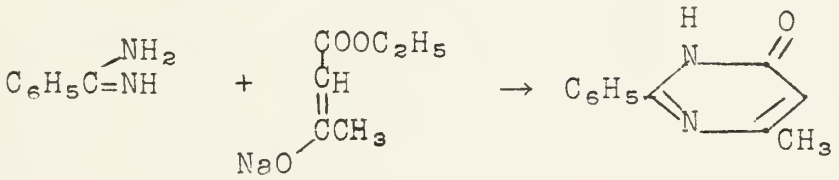


This series also serves to illustrate certain properties of the pyrimidine ring. The methyl group is active as can be seen

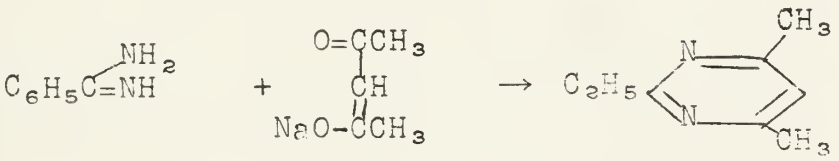
from the third reaction. It will condense with benzaldehyde in the Perkin manner. It also shows the active position of the pyrimidine ring toward replacement to be the 5-position. Chlorination and bromination also have been found to occur at the 5-carbon.

Alkyl Substituents

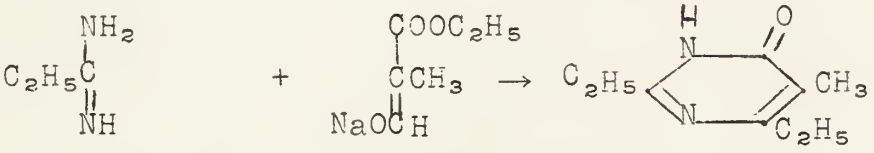
Alkyl groups are inserted in the 2-position by condensing amidines with β-Ketoesters.



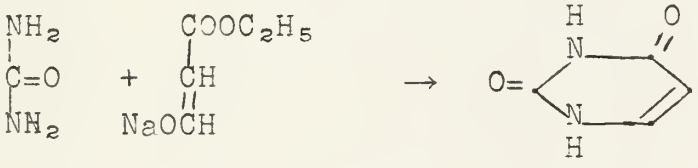
Alkyl groups in 4- and 6-position are introduced by varying the compound used with the amidine.

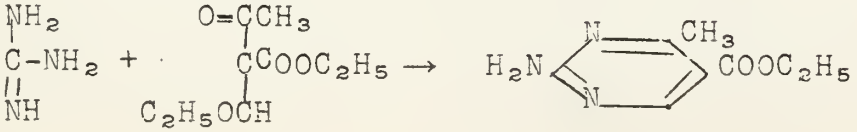


Alkyl groups in the 5-position may be inserted using a substituted β-ketoester.



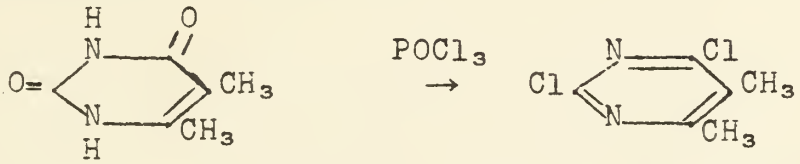
Guanidine carbonate or nitrate in place of the amidine yields a 2-aminopyrimidine. Urea similarly used gives oxygen in the 2-position which can be converted to the chloride and then to the amine. Benary used a procedure which inserted a formyl group on a β-ketoester using the ester and ethyl formate or ethyl orthoformate. The hydroxymethylene compounds thus synthesized broadened the synthetic possibilities.



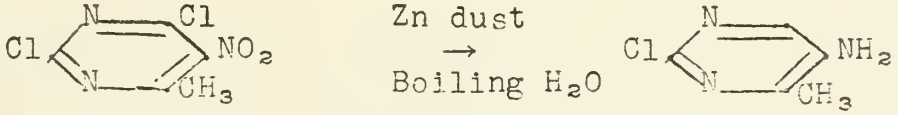


Chlorides

Chlorides in the 2-, 4-, and 6-positions are prepared from the corresponding oxy-compounds, using $POCl_3$ or PCl_5 although the former is preferred by Johnson.



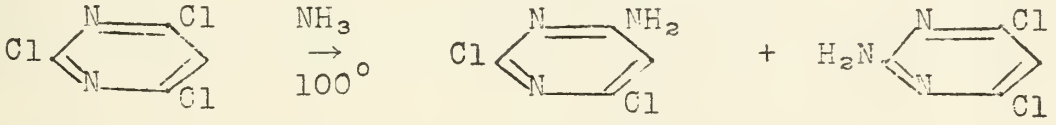
Zinc dust usually removes the chlorine on the ring although this may be a selective process.



The 2-chloro is here relatively inactive. Roblin and his co-workers have used catalytic reduction with palladium hydroxide to remove chlorine.

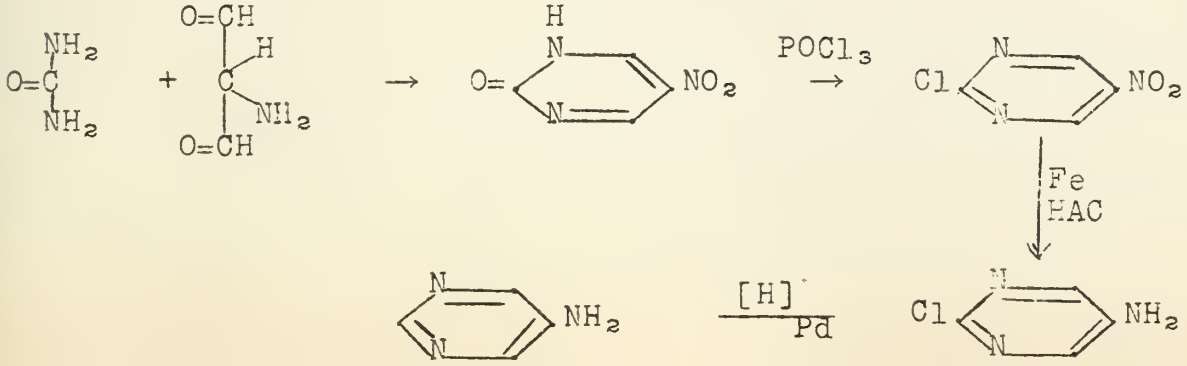
Amines

2-Aminopyrimidines are usually obtained by use of guanidine. Amine groups in the 4- and 6-positions may be derived from the corresponding chloro-compounds upon treatment with alcoholic ammonia.



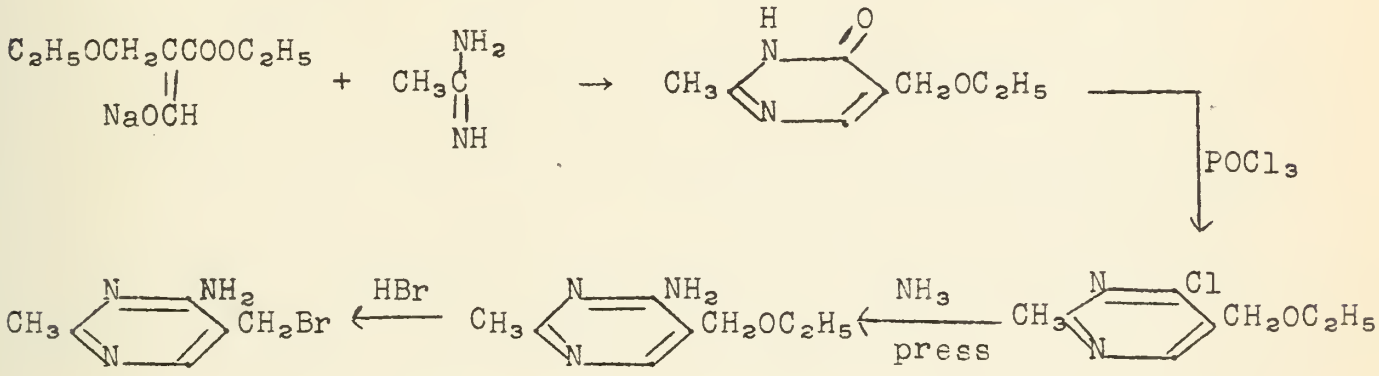
Replacement of the other chlorine atoms is possible. At 160°, two amine groups enter; at 300°, three amine groups are introduced.

5-Amino derivatives are prepared by nitration in the 5-position and subsequent reduction with zinc. Winnek and English used a variation of this in preparing 5-aminopyrimidine.

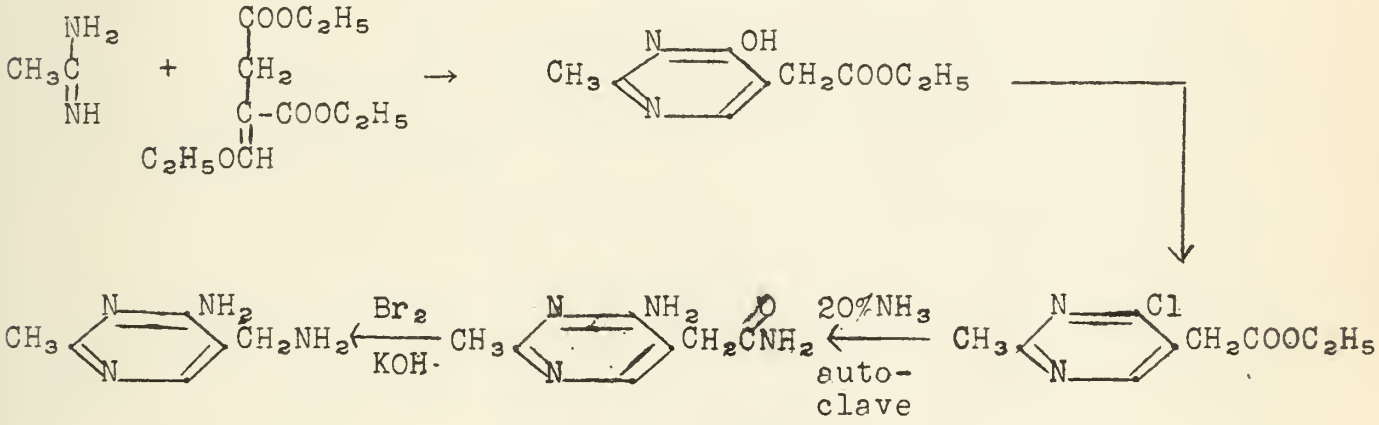


Important Pyrimidine Derivatives.

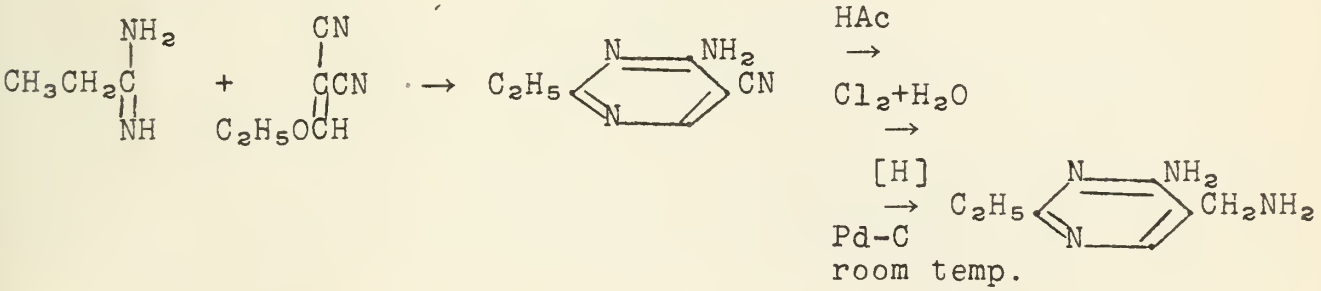
Thiamin (Vitamin B_1) has a pyrimidine portion of the molecule derived from 2-methyl-4-amino-5-halomethylpyrimidine. A British Patent issued to the Research Corporation gives the following procedure.



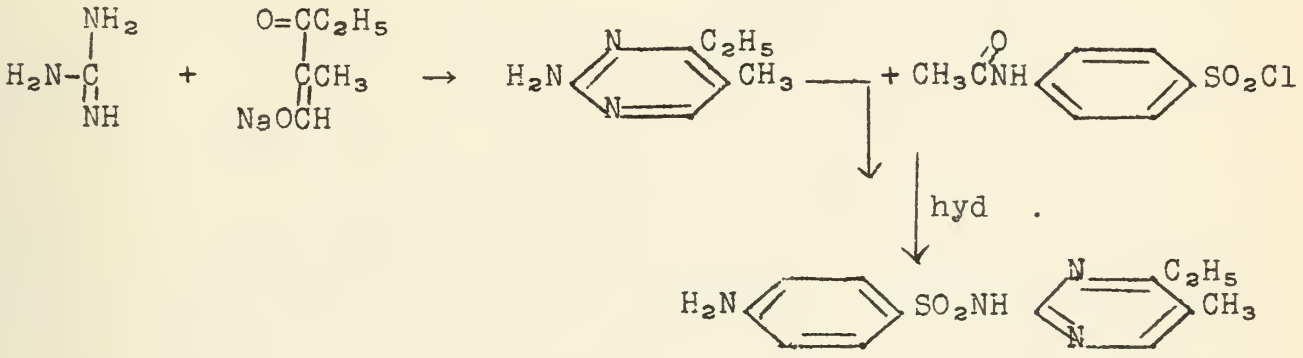
Andersag and Westphall outline an interesting procedure.



A method for the preparation of the ethyl analog is described by Hüber and Hölscher.



Many sulfa drugs derived from pyrimidines have been prepared, usually from the 2-aminopyrimidines by reaction with p-nitro or acetosulfanilylchloride. A preparation by Raiziss and Friefelder will illustrate this.



This compound has demonstrated good activity towards Penumococcus Type II, although it is too toxic to be useful.

The sulfanilyl group also has been put in the 3- and 5-positions. Small alkyl groups gave the greatest activity but several were high in toxicity. The active compounds included 4-methyl, 4-, 6-dimethyl, 4-, 5-nitro, and 5-chloro-2-sulfapyrimidines. Sulfadiazine itself was somewhat less effective in strepococci infections in mice than sulfanilamide; slightly less effective in pneumococcus infections than sulfathiazole or sulfapyridine. In certain specific cases of staphylococcus infections, they proved superior to sulfathiazole.

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Reported by Robert H. Reitsema
August 4, 1943

PENICILLIN

1. Discovery

In 1929 the English pathologist Alexander Fleming noticed a clear zone around a mold which had contaminated a petri dish of bacteria. He isolated the mold and found that it had the characteristics of a strain of Penicillium notatum. He demonstrated that filtrates of the mold culture possessed bacteriostatic properties. These active filtrates he designated penicillin. (1)

2. Production Methods

(a) Surface cultures.-The mold is grown in flat sided jars or bottles on a modified Czapek-Dox medium 1.5-2.0 cm. deep. (2) The addition of corn steep liquor greatly increases the concentration of penicillin produced. With present methods maximum penicillin production is secured in six to eight days. Strains of P.notatum have been developed which are more efficient in producing penicillin than those used a few years ago. By these techniques the yield of penicillin has been increased from four to one hundred fifty units per ml. in the crude medium.

(b) Submerged cultures.-Altho most of the penicillin produced up to now has been made by method (a) above, this procedure is unhandy for large scale production of the substance since a large number of bottles must be manipulated and the chances of bacterial contamination are high. Research is being carried out at various laboratories to develop a strain of P.notatum which will produce large quantities of penicillin when grown in a rotating drum. When this procedure is worked out, daily production or penicillin can be increased many times.

(c) Drip cultures.-A recent paper by Clifton (3) describes a constant flow method of producing penicillin similar to that used in making vinegar. Wood shavings are loosely packed in a long cylinder open at either end. The sterile shavings are inoculated with the fungus and sterile medium allowed to slowly drip thru the mass. Rate of flow from 400 to 1000 ml. daily per column produces a solution with as high a penicillin titer as a surface culture. Large amounts of penicillin can be produced with a minimum of equipment by this method.

3. Purification Methods

The crude medium is acidified, cooled and the active material extracted by an organic solvent, (4). Further purification of penicillin is effected by taking advantage of its solubility in aqueous solutions at pH's 5-7 and its solubility in organic solvents at acid reactions. A great increase in purity is obtained by chromatographing an ethereal solution of penicillin thru a column of silica gel on which is suspended an alkaline carbonate (5). The active layer is eluted with phosphate buffer and frequently the barium salt prepared as a dry powder. In this manner samples of penicillin have been obtained which possess an activity of 1500 units/mg. This is as far as present attempts at purification have proceeded. Penicillin or an active derivative of it has not yet been obtained in crystalline condition.

4. Assay Methods

In order to follow the purification of a biologically active substance an assay method is needed. The method should be rapid, quite accurate, and not require too much material. A number of such assays have been described by bacteriologists working on the problem.

(a) Plate cultures.-A sensitive organism is spread on the surface or mixed with an agar medium and placed in a petri dish. Penicillin is added either to a cylinder pressed against the agar or into a cup formed directly in the agar. When rigourous control of experimental conditions was established, the English workers (2) found that they could define an arbitrary 'unit of activity' as: "that amount of penicillin in 1 ml. of solution which will inhibit a specified strain of Staphyloccus aureus in an area of 24 mm. diameter after 24 hr. incubation at 37 C." This is commonly known as the 'Oxford unit' and provides a convenient measure of comparing results.

Foster (6) has recently described an assay which utilizes the spore forming properties of Bacillus subtilis as a means of obtaining a standard and uniform bacterial growth on the plates.

(b) Tube cultures.-

1. serial dilution- highest dilution of penicillin which will inhibit growth of Staph. aureus in liquid broth is determined. (1).

2. inhibition of hemolysis-Rammelkamp (7) determines highest dilution of penicillin which will inhibit hemolysis of blood by a culture of Strep. hemolyticus.

3. turbidity-Foster (8) adds various amounts of penicillin to standard cultures of Staph. aureus. He finds an inverse relationship between the amount of penicillin added and the turbidity of the culture after 18 hr. incubation.

5. Chemical Studies

Penicillin giving a homogeneous chromatogram appears to be an acid containing two titratable groups (4). It is doubtful that both acid groups are carboxylic. The free acid is soluble in many organic solvents whereas its salts are soluble in aqueous solutions. The free acid and its potassium, sodium and ammonium salts are all hygroscopic and they readily decompose unless kept in a vacuum. The barium and strontium salts are more stable.

Penicillin loses CO_2 on heating to 100° C. in acid, neutral or alkaline solution. The CO_2 does not come from an orginal acidic group as indicated by its titration curve after boiling. The electrometric titration curve after acid or alkaline inactivation suggests that the same part of the molecule is involved in either type but is broken down in different ways.

The English workers suggest a tentative formula of $C_{24}H_{32}O_{10}N_2Ba$ or $C_{23}H_{30}O_9N_2Ba$.

Absorption spectra measurements indicate several non-aromatic condensed rings. They also have evidence for one ketonic group, two acetylatable groups and one latent carboxyl group.

Meyer et al (9) have prepared a series of esters of penicillin by reacting the free acid with the corresponding diazo compound. The aliphatic esters are less active than penicillin in vitro against hemolytic sterptococci but are just as active in vivo (mice). The benzohydrol derivative on the other hand is as active as the starting material in vitro but does not protect mice against this organism.

Meyer suggests a formula of $C_{14}H_{19}O_6N$ or $C_{14}H_{17}O_5N.H_2O$

Catch, Cook and Heilbron (5) on a more active preparation suggest $C_{24}H_{34}O_{11}N$ Sr. After fission with NH_3 they isolated:

(A) colorless water soluble acid which on further hydrolysis yielded (a) an ether soluble acid
(b) an ether insoluble acid which gave a positive ninhydrin reaction. Thus (A) appears to be a simple peptide.

(B) yellow, water-insoluble pigment, $C_{16}H_{20}O_6$ or $C_{16}H_{18}O_5.H_2O$ which possesses absorption bands at 261 and 397 mu but does not appear to be a quinone. It titrates as a monobasic acid but is probably enolic. Degradation with alkaline permanganate yields at least 3 mols of oxalic acid.

(C) acetaldehyde plus a minute quantity of α-β-unsaturated aldehyde-$C_7H_{12}O$

Abraham et al (10) have reported the isolation of a crystalline substance which they term 'penicillamine' by hydrolysis of penicillin barium salt at 100°C. for 1 hr. in 0.1N H_2SO_4. Penicillamine is optically inactive and has three proton binding centers. They suggest formulae $C_6H_{11}O_4N.HCl$ or $C_6H_9O_3N.HCl.H_2O$. Nitrogen is present as $-NH_2$ and more than 90% of it is liberated in VanSlyke apparatus in 5 min. They suggest a relation to an amino sugar and ascorbic acid.

Duffin and Smith (11) found that in highly active penicillin solutions kept at pH2 a rise in optical rotation occurred until a maximum was attained. A dextrotatory, ether insoluble substance is formed by this treatment which they call 'penillic acid'. It can be extracted from the aqueous phase by butyl alcohol and is finally recrystallized from water. It is acid to litmus and has some properties of an amino acid. It forms a color with ninhydrin, readily decolorizes bromine water but does not give the blue color with $FeCl_3$ characteristic of penicillamine. They do not publish a molecular formula for the compound.

6. Clinical Trials

Since a rather accurate popular account of the clinical use of penicillin has appeared in the August, 1943 issue of the Reader's Digest, a list of the disease causing organisms against which penicillin is active will merely be given here.

organism	infection
Staph.aureus	boils, carbuncles, pyemia
N.gonorrheae	gonorrhea
N.meningitis	meningitis
Cl.tetani	lockjaw
Cl.welchii	gas gangrene
D.pneumococcus	pneumonia
B.anthracis	anthrax
B.septus	rhinitis
Strep.hemolyticus	scarlet fever, peritonitis, osteomyelitis, puerperal infection

Some remarkable recoveries from acute gonorrhea which had not responded to treatment by the sulfa drugs are reported from the Mayo clinic (12).

An interesting experiment has been reported by Hac and Hubert(13) on the use of penicillin in protecting mice and guinea pigs against experimental gas gangrene. Sulfadiazine or sulfathiazole was found to protect 50% of the mice tested against Cl.welchii infections. Fifty units of penicillin injected concurrently with the organism gave 98% survival. Delay in commencing penicillin therapy lowers survival rate but not appreciably unless the delay is over three hours. Penicillin was far superior to the sulfa drugs in this respect. Since this organism is one of the most common in war wounds, these results seem promising indeed.

One clinical disadvantage of penicillin is its rapid rate of excretion. Rammelkamp and Bradley (14) found that 58% of penicillin administered intravenously was excreted the first hour. They found that injection of diodrast (a mixture of 3,5-di-iodo-4-pyridone-N-acetic acid and diethanolamine) along with penicillin decreased the rate of penicillin excretion from two to four times.

7. Comparison with Sulfonamides

The main advantages of penicillin over the sulfa drugs are:

1. It is active against sensitive bacteria in higher dilutions, hence requires less to effect a cure.

2. It has fewer physiological complications. Even relatively impure penicillin seems to have no toxic effect on humans.

3. It is not inhibited in its anti-bacterial action by tissue exudates, pus, body fluids, etc. as are the sulfonamides.

4. It is not inhibited by the number of organisms present in the infection. To treat well-developed infections with the sulfa drugs requires that much higher concentrations be maintained than is ordinarily necessary to get the infection under control. Penicillin retains its efficiency under widely varying conditions.

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Reported by S. R. Dickman
August 11, 1943

SURVEY OF RUSSIAN CHEMISTRY

The development of science in Russia dates back to the reign of Peter the Great. In 1724 he founded the Academy of Science which was patterned after the French model. Tsar Peter and his successors depended a good deal for their academicians on importation from abroad. The idea was to invite outstanding scientists from other countries to come to Russia and carry on their work. Important positions and high salaries attracted many outstanding men of science in return for which Russia hoped to accelerate the progress of its scientific research.

However the activities of the Academy were limited for the later tsars were somewhat uncertain patrons of scientific progress.

An era of more vigorous advancement of science began in the 50's and 60's of the 19th century when a series of liberal reforms were carried out in Russia on the initiative of Tsar Alexander II and the serfdom of peasants was abolished.

During this period students went abroad for study and specialization in the sciences. This contact with western Science became a great stimulus to the development of Science in Russia. It was in this era of scientific awakening that the pioneer organic chemists emerged.

Suffice it to mention the names of Zinin, Butlerov, Markovnikov, Konovalov, Mendeleev and Kucherov. Zinin's research on organic chemistry enabled him to demonstrate that nitro compounds may easily be reduced to amines.

Butlerov was a student of Zinin and simultaneously with Kekule' worked on the development of the theory of organic compounds.

Butlerov's student, V. Markovnikov, pursued studies on Russian petroleum oils thru which his name has become known to all of us. As for Mendeleev, his genius is too well known to warrent comment.

Konovalov, who studied under Markovnikov, may be regarded as the originator of the synthesis of nitro-paraffins at the close of the 19th century.

The remarkable reaction of addition of water to acetylene in the presence of salts of mercury was discovered by Kucherov in the 80's of the last century. Little attention was paid to this discovery for a period of 30 years until, during World War I, the Germans began to employ this reaction for the preparation of acetic acid and ethanol.

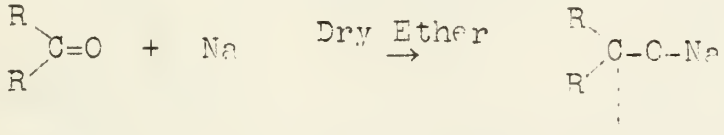
Much of this early work was published largely in German literature and hence many Russian researches were known in this country only as they were published in German science journals and their authors were not always recognized as Russians.

It may be of interest to mention that men like Feodor Beilstein, Wilhelm Ostwald and Tammann were born in Russia and started their careers there.

The progress of organic chemistry has been even more remarkable since the October Revolution in 1917. The extremely wide scope and great increase in fundamental research is attributable to the lavish Soviet budgets for scientific research. In contemporary Russia the Academy of Science is no longer an intellectual ornament as it was in former years. Today it functions as the General Staff of Soviet Science. Each year it drafts a general plan of research which the various scientific institutions in the Soviet Union follow.

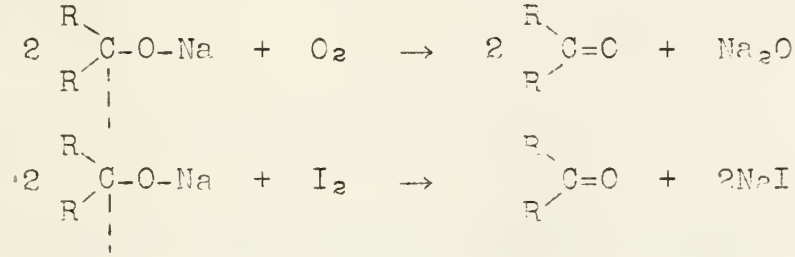
The purpose of the remainder of this seminar is to acquaint you with the names of many outstanding Soviet chemists and to give you an idea of their work. It should be mentioned that the following material was obtained from an article in the Journal of General Chemistry, p. 533 (1942) written by Tanilov which is entitled: "The Progress of Organic Chemistry in Russia since the time of the October Revolution." A literal English translation of this article will be available in our library.

Nazarow and Favorskii (1) were the first to prepare aliphatic ketyls. Ketyls are formed when ketones are treated with metallic sodium in anhydrous ether.

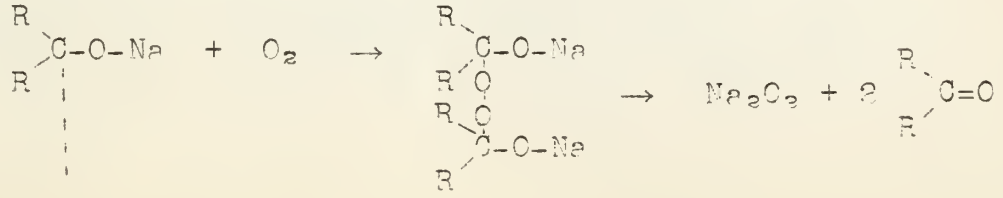


The intense colors of the compounds and their similar behaviour with I_2 and O_2 to that of the triarylmethyls indicate that the Na compounds are free radicals.

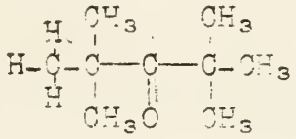
Thus:



The mechanisms of the reactions are:



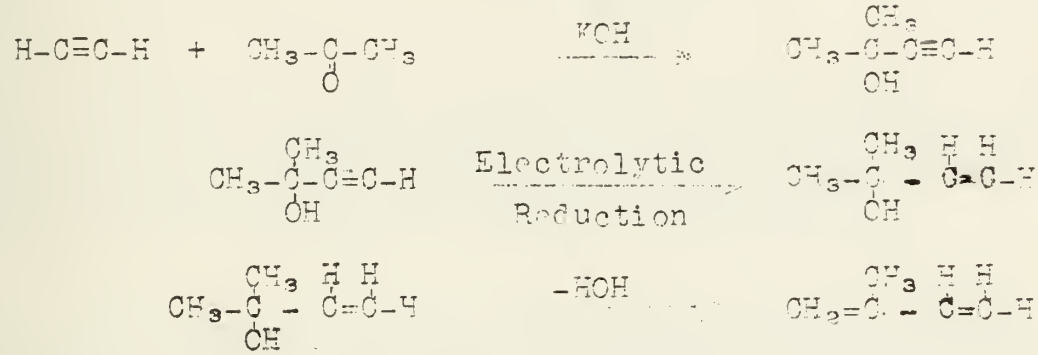
The Russian workers found that simple ketones of the aliphatic series invariably led to the formation of the corresponding pinacolate. In the case of highly branched ketones such as di-tertiary



butyl ketone stable ketyls are formed.

Favorskii has gained world-wide renown by his classical researches on isomeric transformations and intramolecular rearrangements of unsaturated hydrocarbons.

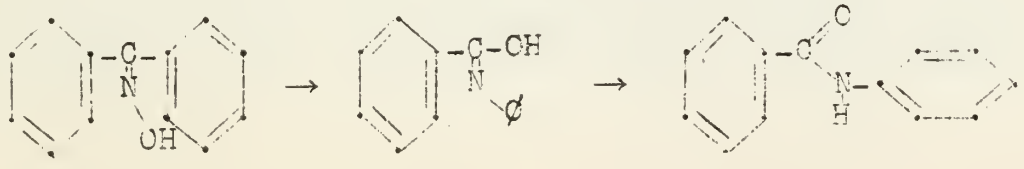
He and his coworkers have devised an interesting synthesis of isoprene (2). The reactions are as shown:

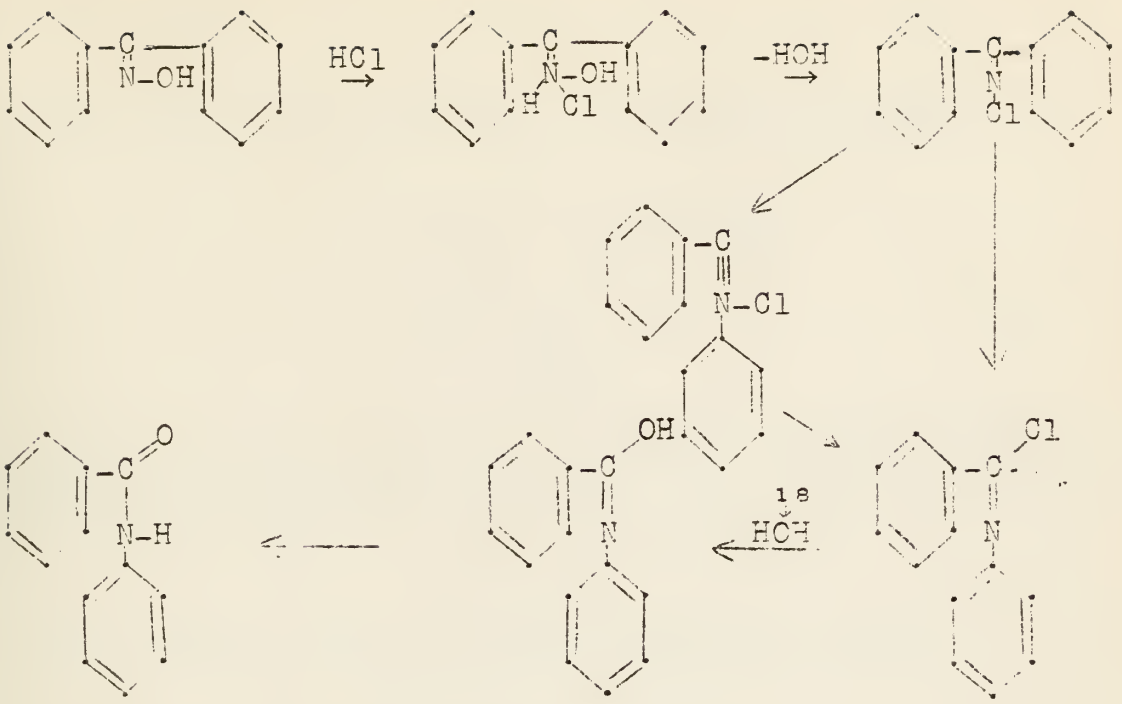


The isoprene thus procured was successfully polymerized by Leberdev to give a synthetic rubber possessing excellent properties as a substitute for the natural product. This method has been so well worked out by Leberdev that it is used by the Russian industry on a large scale.

Brodskii and his coworkers applied the isotopic method in the investigation of reaction mechanisms (3).

The Beckmann rearrangement of ketoximes according to Lachman proceeds by intramolecular rearrangement as shown:





Brodskii was able to demonstrate that Lachman's proposed mechanism was incorrect by carrying out the reaction in the presence of water enriched with heavy oxygen. Reduction of the resulting benzanilide gave water which contained O^{18}.

Shoruigin has carried out a great deal of research in several fields of organic chemistry. The titles of a few of his papers will illustrate his versatility.

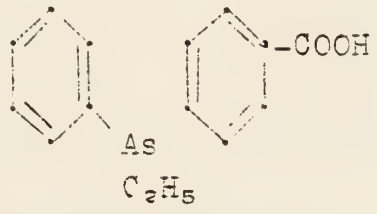
1) "The Relative stability of various alkyl radicals on the oxygen atom"
2) "The Tautomeric forms of toluene"
3) "Tribornyl borate and its use for the separation of borneol from camphor"
4) "Isosaccharinose"
5) "Glyceric ethers of cellulose"

Another outstanding Russian chemist, who has contributed a great deal of work on terpene-like compounds, is Nametkin.

Isocamphadiene, isobornylene, tertiary propyl borneol, 4-propyl-camphor, 5-methyl camphenylone and tertiary bornyl alcohol are examples of some compounds in which he and his coworkers were interested.

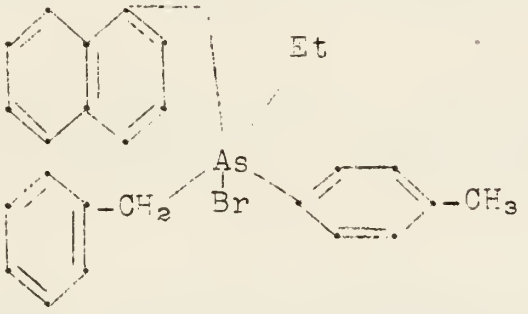
In the field of Stereochemistry we find such names as Nametkin, Kamai, and Arbuzov.

Kamai successfully prepared and resolved compounds containing asymmetric trivalent arsenic (4). An example is shown:



However when the phenyl was replaced by alkyl groups he was unsuccessful in procuring crystalline salts with the alkaloidal resolving agents employed.

Kamai likewise prepared and attempted to resolve



byinteration with the Silver salt of d- -bromcamphorsulfonic acid. However here again his results were not conclusive.

Phosphinic acids containing asymmetric phosphorous and thiophosphinic acids were prepared and resolved by Arbuzov (5).

The work of Nametkin was concerned with the stereochemistry of alicyclic compounds in relation to the form of addition to cyclic double bonds and the dehydration of aliphatic diols.

The Russian biochemists Blagoveshchenskii, Oparin and Kurssanov have carried out enzymic syntheses of polysaccharides.

Oparin, together with Kurssanov, showed that glucose and anfructose could be caused to recombine in the presence of invertase and phosphatase plus a small quantity of phosphate salts to yield sucrose (6).

Such recombination does not ordinarily occur because of an equilibrium which is set up between am-fructose and β-fructose:

β-fructose (2-6) ⟷ am-fructose (2-5)

This secondary reaction is cut down by introducing a phosphate ester group into the sucrose molecule on one of the hydroxyl groups of the fructose. When this sucrose molecule is hydrolyzed by invertase the reaction does not go to completion, but an equilibrium is set up when 40% is hydrolyzed in consequence of the synthesis which now occurs.

Blagoveshchenskii was able to synthesize raffinose by the action of emulsin upon a mixture of galactose and sucrose in acetone solution (7).

In the field of dyes the name of Porai-Koshitz stands foremost. His extensive researches have resulted in improved methods of synthesis and the discovery of new synthetic dyestuffs.

The names most frequently encountered in the fields of alkaloids are: Menshikov, Orekhov and Konovalova.

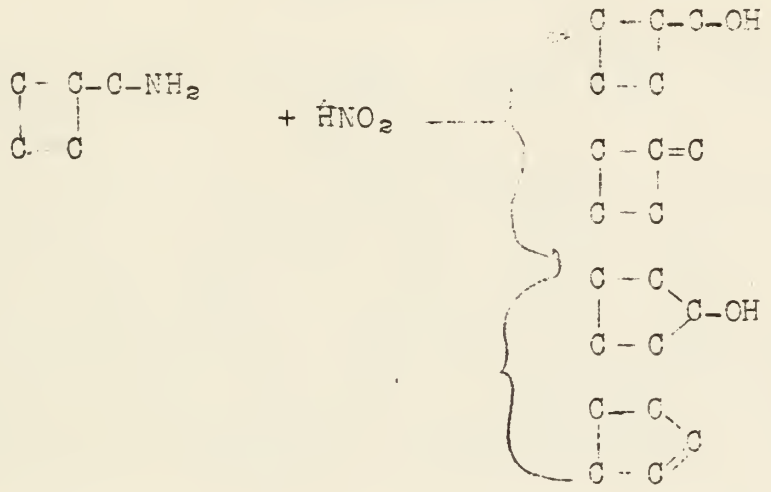
Konavalova recently isolated the alkaloid delphamine from species of delphinium. Her present work is concerned with the proof of its structure.

Menshikov and Orekhov were among the first to study the acid-alkanolamine alkaloids from heliotropium lasiocarpum. Their investigations were confined to the alkanolamine portion of the molecule which has been called retronecine. It is present in alkaloids of other species as well. Our own Dr. Adams became interested in the proof of structure of retronecine a few years ago. Just within the past two months, on the basis of the excellent researches of Drs. John Mahan and Nelson Leonard under the direction of Dr. Adams, its structure has been proven unequivocally to be

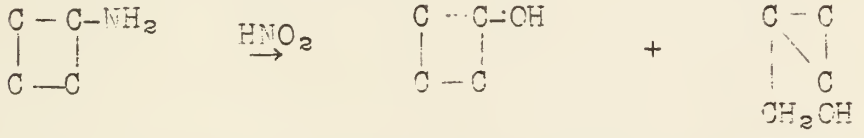
In the field of medicinal chemistry, Magidson and coworkers have been responsible for the introduction of new antimalarial drugs and anesthetics. They describe the synthesis of derivatives of 8-aminoquinoline which show definite anesthetic action. The synthetic derivatives of acridine and 6-methoxyl quinoline possess antimalarial action (8).

The classical rearrangement of alicyclic compounds which was first discovered by Dem'yanov is of course familiar (9).

He showed that when alicyclic amino compounds were treated with nitrous acid the following reactions occurred.



Ring contraction can likewise occur in certain cases, thus:



The study of this rearrangement was carried on by his students. Recently Feofilaktov was able to show that heterocyclic amines would rearrange similarly.

Putokhin extended the work to pyrrole derivatives and he was able, on the basis of Dem'yanov's rearrangement to convert them to indole, pyridine and quinoline derivatives (10).

Before concluding this seminar perhaps it would be desirable to discuss the Russian chemical journals which an organic chemist would find most useful. The Journal of the Russian Physical Chemistry Society was started in 1869 and it was replaced in 1930 by the Journal of General Chemistry. Of no less importance is the journal entitled: Compt. rend. of Academy of Science. The first two are found in our own library and the third is in the Physics library.

There has been an attempt to make the translation of Russian names into English uniform. The difficulty arose from the fact that the early Russian chemists published in German journals and the German spelling was carried over into English.

A good example is the older spelling of Dem'yanov: DEMJANOV.

Another point of interest about Russian names is that those ending in vowels such as a or ya are almost invariably the names of feminine chemists, whereas those ending in consonants or in ii are masculine.

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Reported by Charles Jarowski
August 11, 1943

TERTIARY ALKYL PRIMARY AMINES, $RR'R''CNH_2$

A reference to the literature indicates that primary amines of the type in which the amino group is attached to a tertiary aliphatic carbon atom have been prepared in a very limited number of cases. In fact, as recently as 1938 Adkins made the statement that "methods apparently are not available for the preparation in quantity of the aliphatic amines which bear the same relationship to primary amines that tertiary alcohols bear to primary alcohols." The recent investigations of Henze and his coworkers, however, present a new approach to the synthesis of these interesting compounds. A brief resumé of earlier methods of synthesis is also included in this seminar.

Reduction

A number of tertiary alkyl nitro compounds have been reduced to the corresponding primary amines. Both catalytic hydrogenation and chemical reduction have been used. This method is limited only to the availability of the desired nitro compound. With the recent development of the nitroparaffins this method may become more important. Several amines prepared in this manner are listed below.

$(CH_3)_3CNH_2$ $(C_2H_5)_3CNH_2$

$(CH_3)_2C(CH_2OH)NH_2$ $(CH_3)_2C(C_6H_5)NH_2$

$(CH_3)_2C(C_3H_7)NH_2$ $(CH_3)_2C(i\text{-}C_4H_9)NH_2$

The reduction of tertiary aliphatic nitroso compounds gives the corresponding primary amines. Tertiary butyl amine can be prepared according to the following scheme.

$$(CH_3)_3CMgCl \xrightarrow{NOCl} (CH_3)_3CNO \xrightarrow{H} (CH_3)_3CNH_2 \qquad (1)$$

Hofmann Hypobromite Degradation of Acid Amides

Montagne and Casteran have found that theoretical amounts of potassium hypobromite and α-trisubstituted amides give high yields of isocyanates. These are quite stable to alkali but furnish the corresponding primary amines when hydrolyzed with hydrochloric acid. In some cases appreciable amounts of the disubstituted urea are formed by the reaction of the isocyanate with the amine. The amine, however, can be recovered almost quantitatively by heating the disubstituted urea with lime. A few of the amines prepared in this manner are listed below.

$(CH_3)_3CNH_2$ $(CH_3)_2C(C_6H_5)NH_2$

$(CH_3)_2C(C_3H_7)NH_2$ $(C_2H_5)_2C(C_6H_5)NH_2$

$C_6H_5CH_2-\underset{\displaystyle C_2H_5}{\overset{\displaystyle C_6H_5}{\overset{|}{\underset{|}{C}}}}-NH_2$ $C_3H_7-\underset{\displaystyle C_2H_5}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-NH_2$

Reaction of Grignard Reagents with Monochloro-amine

Coleman and his coworkers have found that Grignard reagents react with monochloro-amine to give primary amines and ammonia according to the following equations.

$$RMgX + NH_2Cl \rightarrow RNH_2 + MgXCl \qquad (2)$$

$$RMgX + NH_2Cl \rightarrow RCl + MgXNH_2 \qquad (3)$$

The course of the reaction and the yields of amines and ammonia are much the same for Grignard reagents prepared from primary, secondary, or tertiary halogen compounds. If the Grignard reagent is represented by RMgX, then for a given radical R the yield of amine is greatest when X is chlorine and the least when X is iodine. When X is bromine the yield lies between the other two. The yield of ammonia increases as the yield of amine decreases. Tertiary butyl amine and tertiary amyl amine have been prepared by this method.

Reaction of Tertiary Alkyl Halides with Ammonia

Attempts have been made to prepare amines from tertiary alkyl halides and liquid ammonia or dry ammonia in a solvent such as ethanol or benzene, but the yields are very low. The tertiary alkyl halides do not react or the predominant reaction is the loss of HX to give olefins and NH_4X. Brander has prepared the following series of amines by this method.

$(CH_3)_3CNH_2$ $\qquad$ $(C_6H_5)_2C(CH_3)NH_2$

$(CH_3)_2C(C_6H_5)NH_2$ $\qquad$ $(C_6H_5)_3CNH_2$

Addition of Ammonia to Mesityl Oxide

Smith and Adkins have found that anhydrous ammonia adds to mesityl oxide to give excellent yields of dry diacetoneamine. This β-keto-carbinamine was acetylated, hydrogenated over Raney nickel, and hydrolyzed to the corresponding diacetonealkamine. Attempts to reduce or dehydrate these compounds to a tertiary hexylamine were unsuccessful.

$$(CH_3)_2C{=}CHCOCH_3 \xrightarrow{NH_3} (CH_3)_2C(NH_2)\text{-}CH_2COCH_3 \xrightarrow{Ac_2O} (CH_3)_2C(NHAc)\text{-}CH_2COCH_3 \qquad (4)$$

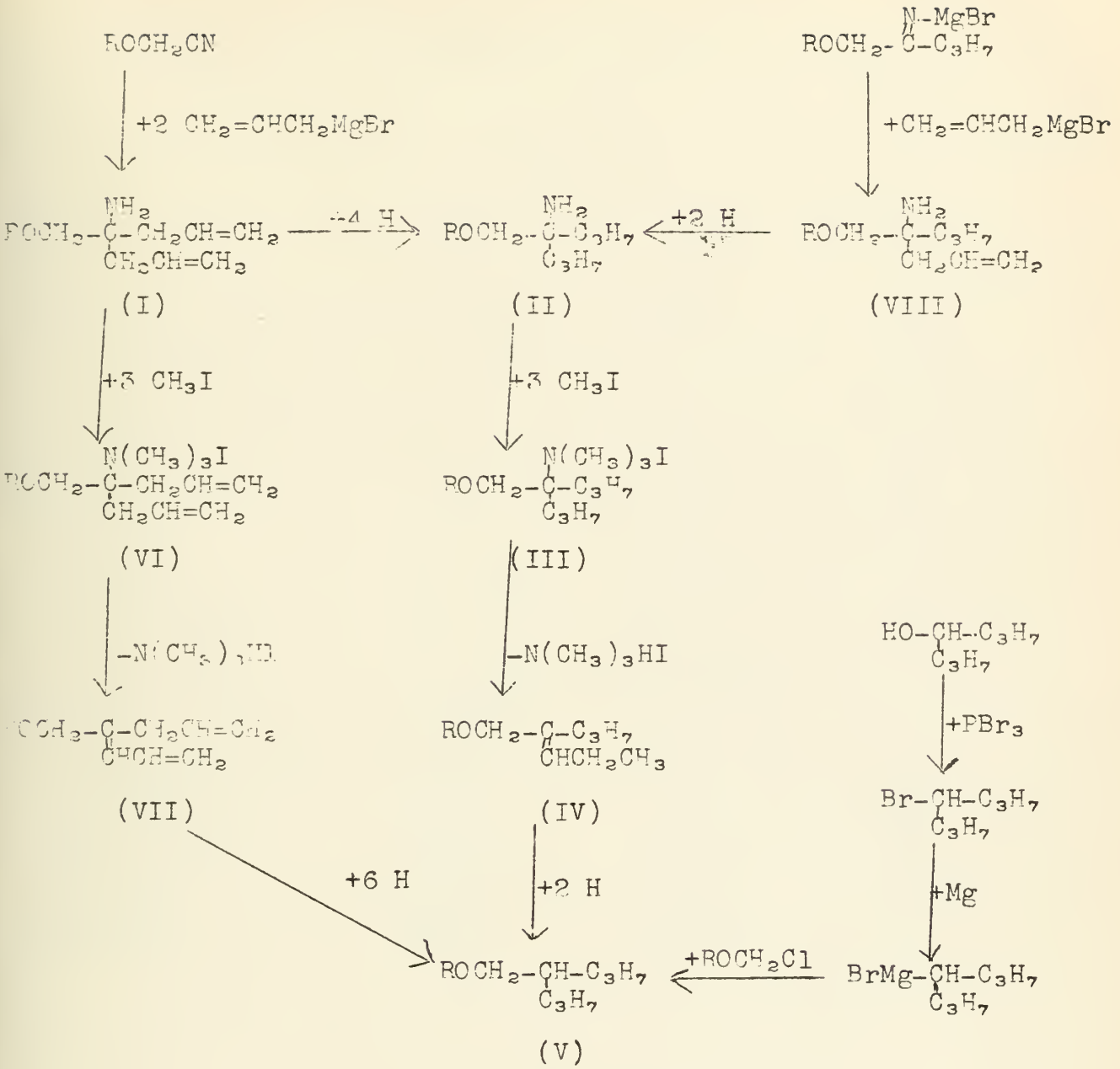
$$(CH_3)_2C(NHAc)\text{-}CH_2COCH_3 \xrightarrow{H_2} (CH_3)_2C(NHAc)\text{-}CH_2CHOHCH_3 \xrightarrow{H_2O} (CH_3)_2C(NH_2)\text{-}CH_2CHOHCH_3$$

Reaction of Allylmagnesium Bromide with Nitriles and Ketimines

In an attempt to prepare ethoxymethyl allyl ketone from ethoxyacetonitrile and allylmagnesium bromide, Allen and Henze observed an abnormal reaction which produced, instead of the anticipated ketone, a tertiary alkyl primary amine, ethoxymethyldiallylcarbinamine (I). This compound formed solid derivatives with picric acid and phenyl isocyanate, but failed to undergo the typical primary amine reaction of isonitrile formation. Molecular refraction values and the fact that one molecular weight of the amine reacted with three molecular weights of methyl iodide to form a methiodide required the substance to be a primary amine. Hydrogenation of (I) produced the corresponding saturated amine (II). Allylmagnesium bromide was found also to react with the addition product resulting from the interaction of ethoxyacetonitrile and propylmagnesium bromide yielding compound (VIII), an amine of structure intermediate between that of (I) and (II). Hydrogenation of (VIII) resulted in the formation of (II). Final proof of structure was obtained through degradation and through conversion into a substance of established structure, as indicated in chart 1. Attempts to synthesize the saturated amine (II) by known procedures were unsuccessful.

Further investigation of this reaction has indicated that allylmagnesium bromide is able to react with other alkoxyalkyl cyanides, as well as with alkyl cyanides, with aralkyl cyanides, with alkenyl cyanides, and with keto-nitriles to yield the corresponding carbinamines. The β-keto-carbinamines prepared in this manner are unstable at room temperature in that they decompose with the loss of ammonia to form unsaturated ketones. Carbinamines prepared by this method are listed in table 1.

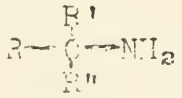
Chart 1



R represents CH_3CH_2-

Table 1

Yields of Amines Derived from Allylmagnesium Bromide



R	R'	R"	Yield, %
Methoxymethyl	Allyl	Allyl	65.3
Ethoxymethyl	Allyl	Allyl	78.7
Ethoxymethyl	n-Propyl	Allyl	60.7
Ethoxymethyl	n-Propyl	n-Propyl	98.9
i-Propoxymethyl	Allyl	Allyl	63.3
n-Butoxymethyl	Allyl	Allyl	59.
n-Butoxymethyl	n-Butyl	Allyl	54.
Allyl	Allyl	Allyl	52.
n-Propyl	Allyl	Allyl	30.
n-Butyl	Allyl	Allyl	56.
Benzyl	Allyl	Allyl	43.
n-Propyl	n-Propyl	n-Propyl	
1-Ethoxyethyl	Allyl	Allyl	35.
2-Ethoxyethyl	Allyl	Allyl	53.
1-Ethoxyethyl	n-Propyl	n-Propyl	94.5
2-Ethoxyethyl	n-Propyl	n-Propyl	93.
1-Ethoxyethyl	n-Propyl	Allyl	40.
n-Propoxymethyl	Methyl	Allyl	51.
n-Propoxymethyl	Methyl	n-Propyl	90.
i-Amoxymethyl	Methyl	Allyl	65.
i-Amoxymethyl	Methyl	n-Propyl	90.
Phenacyl	Methyl	Allyl	85.
Phenacyl	Methyl	n-Propyl	89.
Phenacyl	Ethyl	Allyl	89.
Phenacyl	Ethyl	n-Propyl	91.

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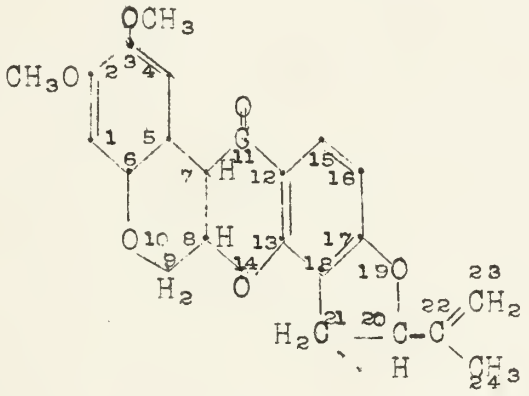
Reported by F. W. Spangler
August 18, 1943

THE STRUCTURE OF ROTENONE AND RELATED COMPOUNDS

The roots of certain plants of the family Fabaceae, of which the most important is derris, have long been used as insecticides and fish poisons. Their utility lies in their high toxicity to fish and insects and their low toxicity to humans when taken orally. Derris root, its concentrated extracts and rotenone itself are now articles of commerce.

The composition of extracts of these roots in various organic solvents varies widely with the species of plant, its source, and method of cultivation and the solvent used as extractant. From most extracts the principal constituent obtained is rotenone, which appears as optically active crystals on concentration of the extract. After complete removal of solvent an optically active uncrystalizable mixture of rotenone-like compounds is obtained, which in the case of derris is known as derris resin.

Rotenone is the most important compound of the group and is also the best insecticide. Its structure has been elucidated mainly through the combined efforts of three groups of chemists - Haller, LaForge, Smith and Clark in this country; Butenand et al. in Germany and Takei et al. in Japan. Its formula and numbering system are

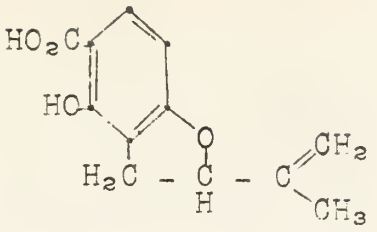


I. Rotenone

There are three asymmetric carbon atoms - nos. 7, 8, and 20.

Analytical data indicated the presence of two methoxyl groups a carbonyl group and three chemically inert oxygen atoms.

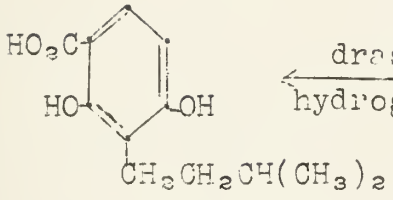
On cleavage with alkali a monobasic phenolic acid (II) called tubaic acid was obtained. The evidence leading to the proof of the skeletal structure of II is outlined below.



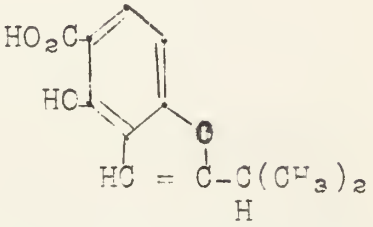
II. Tubaic acid (opt. act.)

alkali fusion

$2\ H_2$



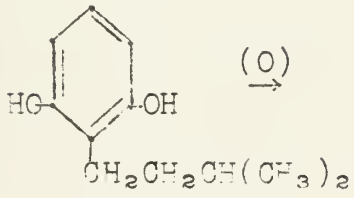
drastic hydrogenation



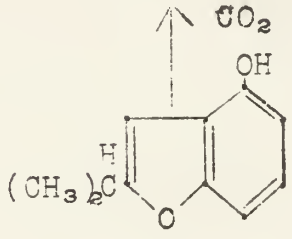
III. Tetrahydrotubaic acid (opt. inact.)

IV. Isotubaic acid (opt. inact.)

Δ $-CO_2$



(O) → isocaproic acid

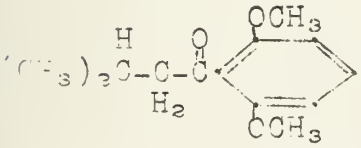


V. Tetrahydrotubanol

VI.

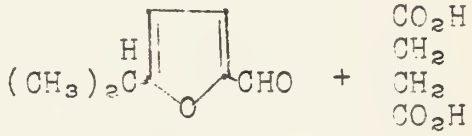
demethylate

(H)



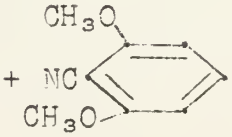
VIII.

alkali fusion



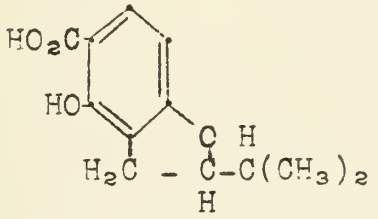
VII.

resorcinal + isovaleric acid

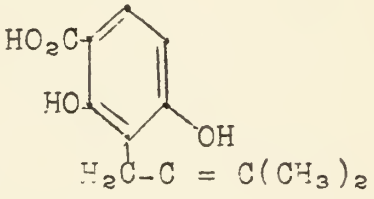
i-BuMgBr + 

IX.

The position of the aliphatic double bond was established as follows. Tubaic acid (optically active) absorbs one mol of hydrogen in neutral solution to give optically active dihydrotubaic acid (compound X below). In alkaline solution tubaic acid absorbs one mol of hydrogen to give optically inactive isodihydrotubaic acid (compound XI below). On oxidation tubaic acid gives acetic acid while dihydrotubaic acid (X) and isotubaic acid (compound IV above) give isobutyric acid. Both X and XI can be reduced to tetrahydrotubaic acid (III).



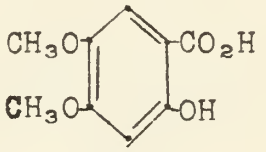
X. Dihydrotubaic acid (opt. act.)



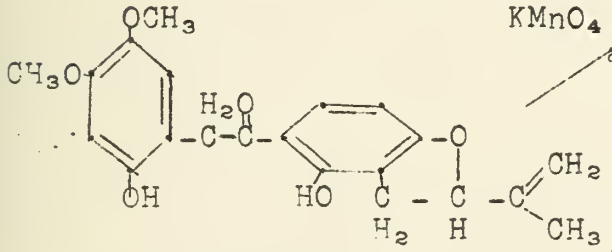
XI. Isodihydrotubaic acid (opt. inact.)

Rotenone undergoes the same transformations in the tubaic acid part of the molecule as does tubaic acid. Thus dihydrorotenone, isodihydrorotenone, tetrahydrorotenone and isorotenone were made available for study.

Treatment of rotenone with alcoholic alkali in the presence of a reducing agent such as zinc gave two main products - derritol (XII) and rotenol (XIII). Derritol gave the following reactions:



XIV.



XII. Derritol

$KMnO_4$, acetone

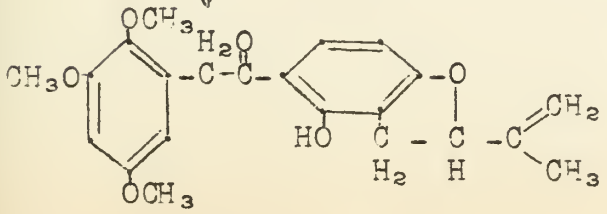
alkali → fusion

isotubaic acid

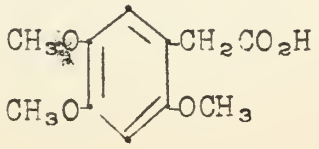
$KMnO_4$

tubaic acid

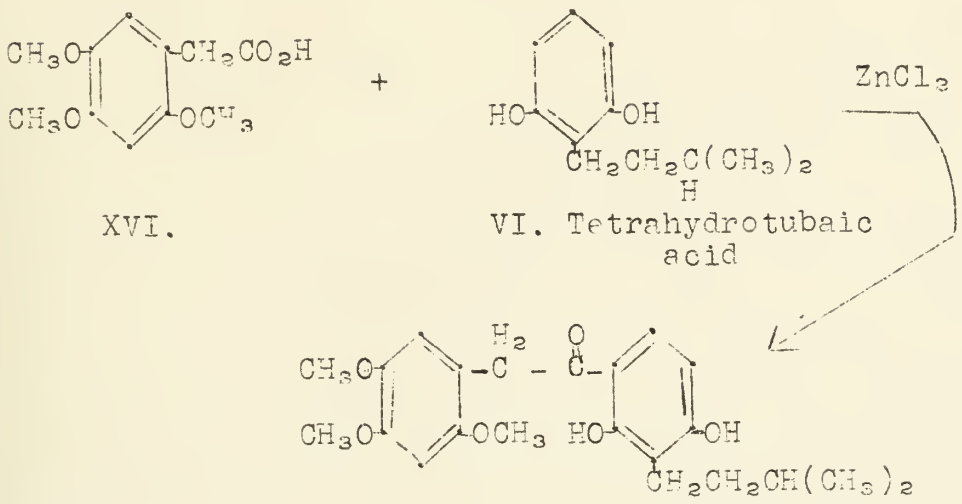
methylate



H_2O_2



The synthesis of compounds XIV and XVI has been accomplished. Also methyltetrahydroderritol (XVII) has been synthesized:

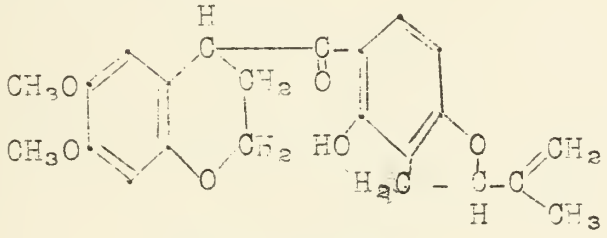


XVI.

VI. Tetrahydrotubaic acid

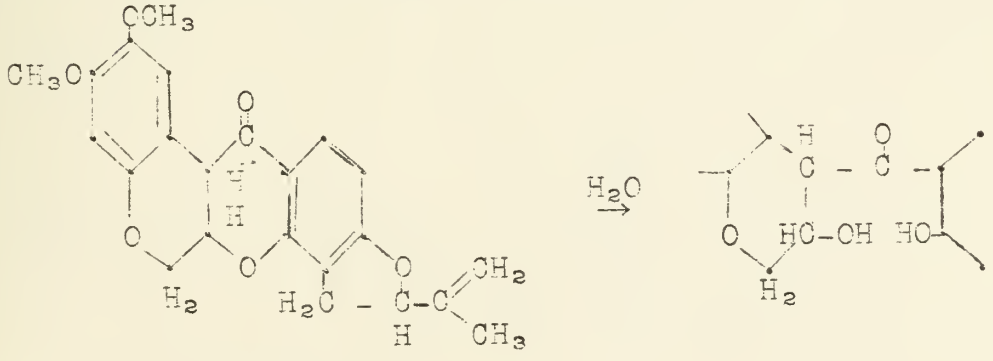
XVII. Methyltetrahydroderritol

By degradations similar to those used on derritol, rotenol was shown to be probably

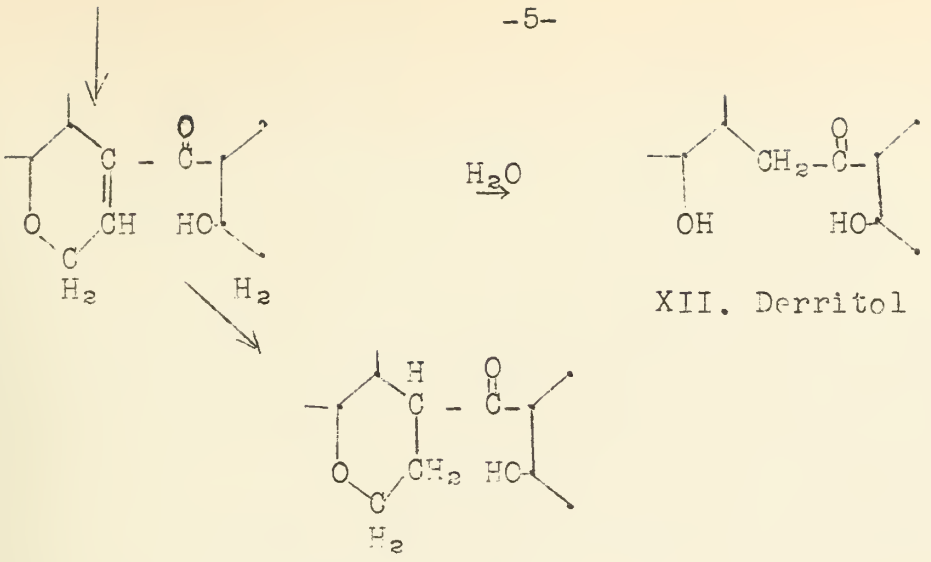


XIII. Rotenol

The following mechanism would account for the formation of derritol and rotenol from rotenone:



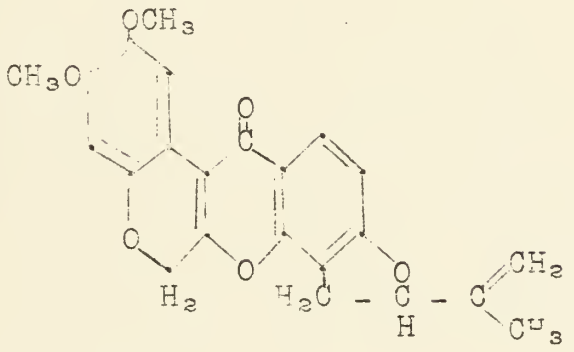
I. Rotenone



XII. Derritol

XIII. Rotenol

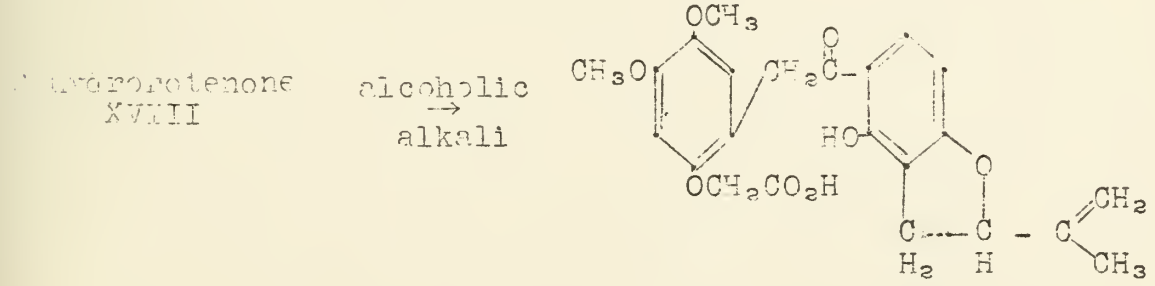
Rotenone on gentle oxidation loses two hydrogen atoms and becomes dehydrorotenone XVIII.



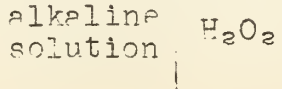
XVIII. Dehydrorotenone (opt. act.)

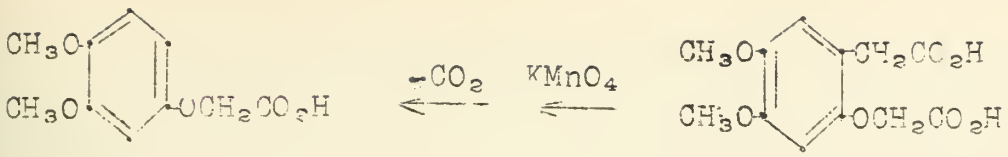
Isorotenone on undergoing a similar transformation gives an optically inactive compound. Hence oxidation had destroyed all asymmetry in the molecules except that in the tubaic acid part.

Dehydrorotenone can be degraded as follows.



XIX. Derrisic acid





XXI. XX. Derric acid

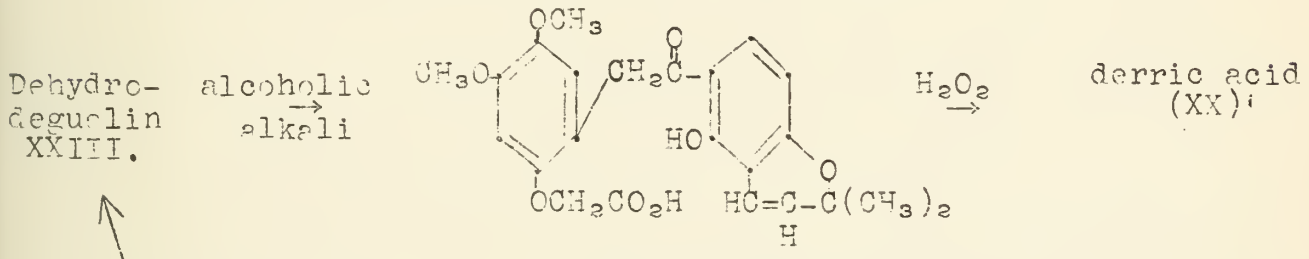
Derrisic acid was formed when the grouping $-CH_2CO_2C_2H_5$ was substituted on the active phenolic hydroxyl of derritol (XII).

Derric acid (XX) and compound XXI have been synthesized.

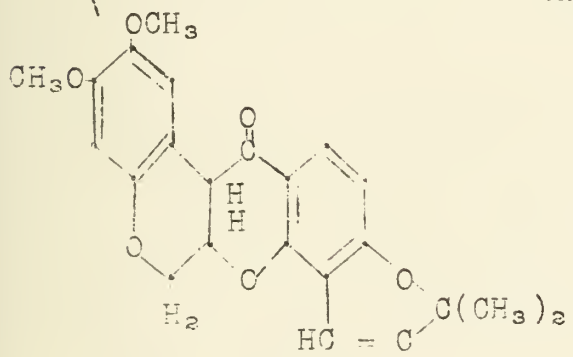
COMPOUNDS FROM DERRIS RELATED TO ROTENONE

On treatment of an alcoholic solution of derris resin with alkali E. P. Clark obtained three crystalline optically active compounds which he named deguelin, tephrosin and toxicarol.

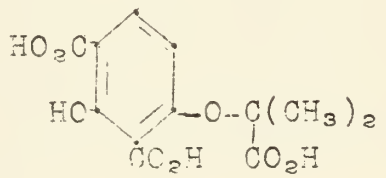
Structural proof of deguelin is as follows.



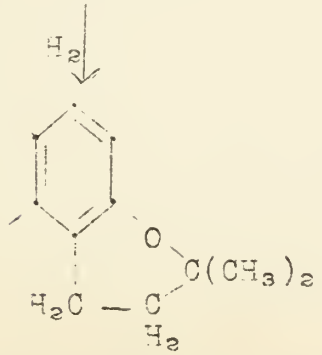
XXIV. Deguelic acid



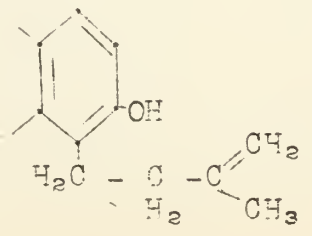
XXIII. Deguelin



XXV. Nicouic acid



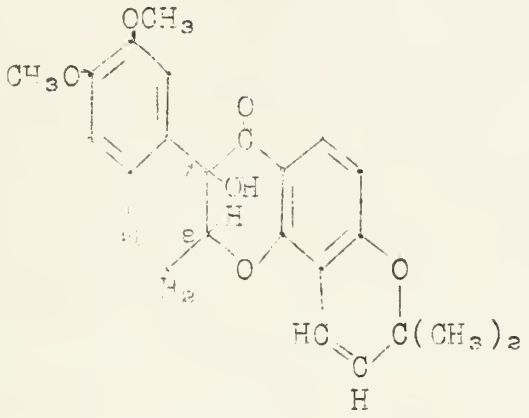
XXVI. Dihydrodeguelin



XXVII. Isodihydrorotenone

The l-form of deguelin was isolated from derris resin which had not been treated with alcoholic alkali and hydrogenation experiments indicated that the inactivity of deguelin after treatment with alcoholic alkali is due to racemization

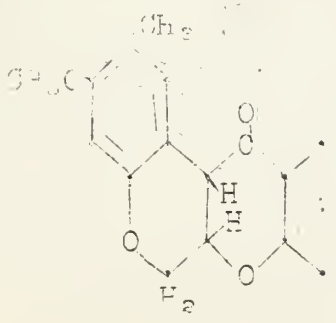
Tephrosin was found to be dehydrated to dehydrodeguelin. Two isomers of tephrosin were discovered, one of which is readily dehydrated to dehydrodeguelin and one of which is very resistant to dehydration. Deguelin in alkaline solution is readily oxidized to a mixture of tephrosins. Consequently the formula XXVIII below is thought to represent one of the tephrosins.



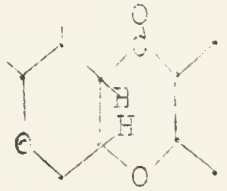
XXVIII. Tephrosin

It is not known whether the hydroxyl group is attached to position 7 or position 8. Cis-trans isomerism around carbon atoms 7 and 8 is also possible.

Toxicarol is isomeric with tephrosin but possesses a phenolic hydroxyl group. Like rotenone it yields on gentle oxidation a dehydro compound which adds two molecules of water with the formation of toxicarolic acid, which can be oxidized to derric acid. This type of degradation (dehydrogenation, hydrolysis to an acid of the deguelic type and hydrogen peroxide oxidation to derric acid) has been found to be characteristic of the grouping below, which involves the chromene-chromanone system.



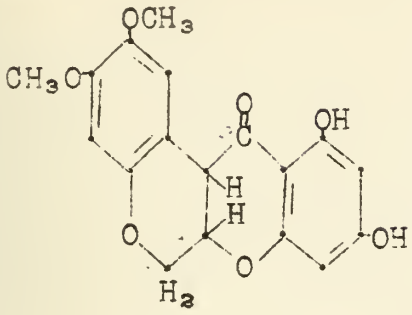
XXIX.



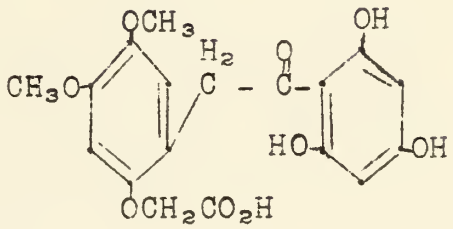
XXX. Chromane-chromanone system

Toxicarol therefore contains the grouping XXIX.

apotoxicarol to which the formula XXXI was assigned on the basis of



XXXI. Apotoxicarol

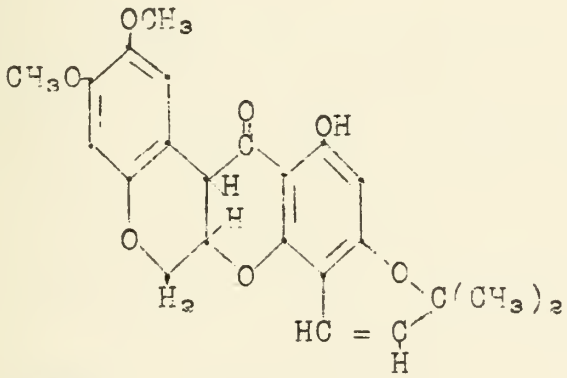


XXXII. Apotoxicarolic acid

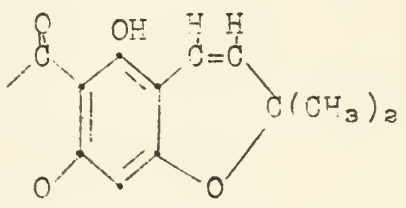
its empirical formula, the fact that it undergoes the reactions of the chromane-chromanone system (XXX) and the synthesis of apotoxicarolic acid (XXXII). Thus the presence of a free phenolic hydroxyl group on position 15 was indicated.

Toxicarol and deguelin yield acetone on treatment with alkali under proper conditions, indicating the presence of $(CH_3)_2C-$ and making it probably that toxicarol also contains the 2,2-dimethylchromene residue of deguelin.

On the basis of this evidence toxicarol was assigned the formula XXXIII.



XXXIII. Toxicarol (α)



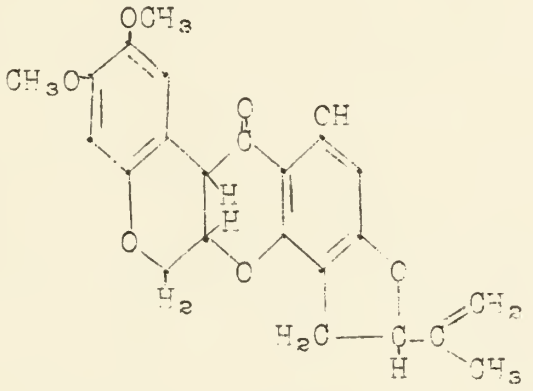
XXXIV. β-Toxicarol

On treatment with potassium carbonate in acetone solution toxicarol is partly changed to an isomer which is believed to be XXXIV.

An optically active toxicarol has been obtained from derris resin.

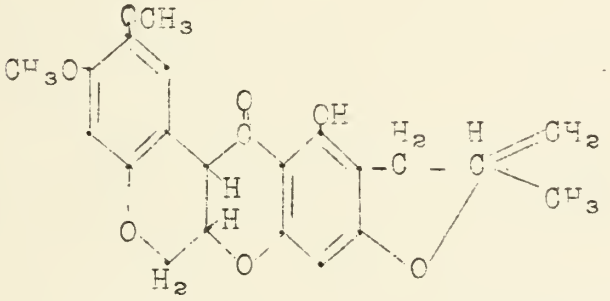
A compound called sumatrol was isolated from a Sumatratype derris resin, which contains no rotenone. Sumatrol is optically

active and isomeric with tephrosin and toxicarol. It gave a dehydro compound which furnished an acid of the derrisic type on hydrolysis. Sumatrol therefore contains a chromene-chromanone ring system. On hydrogenation sumatrol, like rotenone, yields a dihydro compound and a tetrahydro derivative. Both compounds are optically active and both form dehydro derivatives of which only the dihydrodehydro compound is optically active. Ferric chloride gave similar colors with both toxicarol and sumatrol, indicating the presence of a hydroxyl group on position 15. Synthesis of tetrahydrosumatrolic acid and dehydrotetrahydrosumatrol confirmed this deduction. Sumatrol is therefore considered to be XXXV.



XXXV. Sumatrol

The linear formula XXXVI has not been eliminated.



XXXVI. Sumatrol (linear formula)

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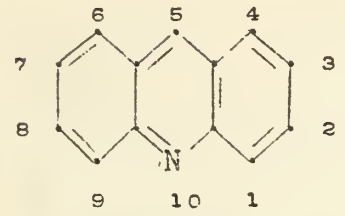
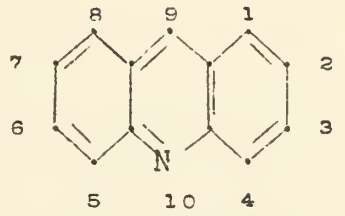
Reported by H. F. Kauffman, Jr.
August 18, 1943

SYNTHESIS OF ACRIDINES.

There are two general numbering systems for acridine.

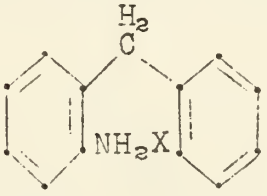


English



Chemical Abstracts

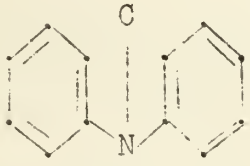
There are only a few types of syntheses of acridine compounds as in all cases it is the meso (middle) ring which is closed. The methods of synthesis may be put into one of three general classes. These classes are:

A. Elimination of HX from 

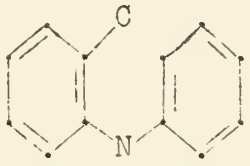
Where X is NH_2 or OH; followed by oxidation of the dihydro compound to the acridine.

B. From benzyl- or benzal-anilines, etc.

C. The meso carbon atom is supplied by a substituent carried by the nitrogen or by a group in the ortho position.



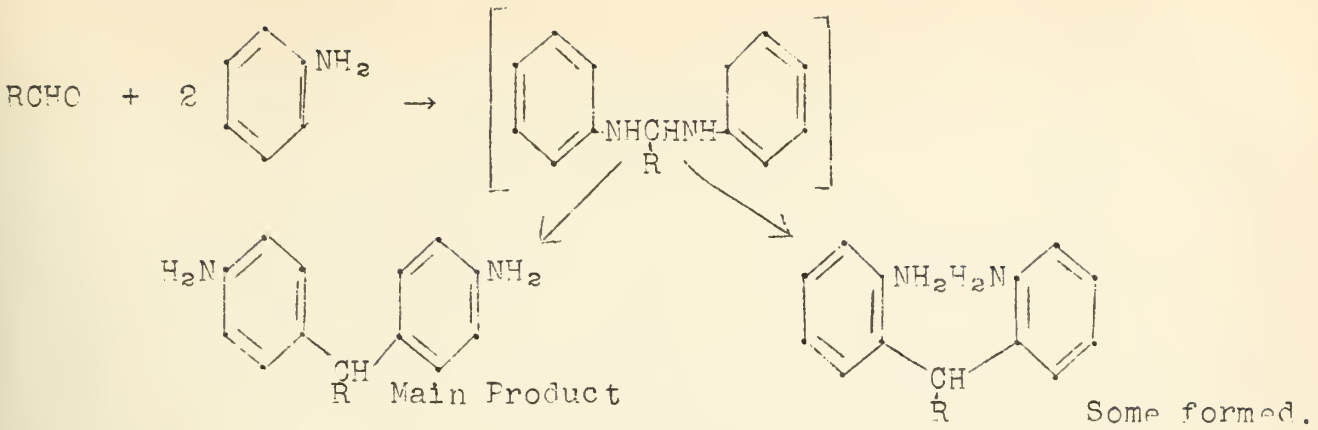
or



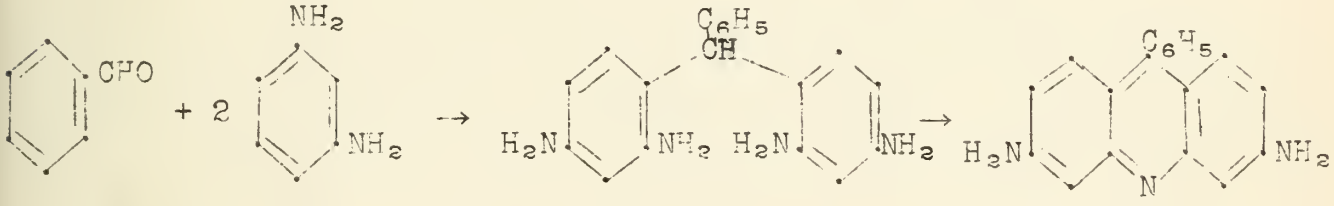
One of the most important methods is that under Class A. The trick of course here is that of preparing the o,o'-disubstituted diphenylmethane. The condensation is generally brought about with zinc chloride or hydrogen chloride.

There are various methods available for preparing these diphenylmethane derivatives.

When an aldehyde is condensed with an amine of the benzene series there is little tendency for the methylene group to take up the ortho position, the product being almost entirely the para derivative.

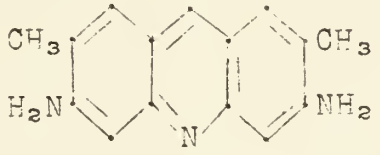


A simple way of ensuring that the product contain amino groups ortho to the aldehyde residue is to use a meta-diamine. Meyer and Gross prepared benzoflavine from benzaldehyde and m-phenylenediamine.

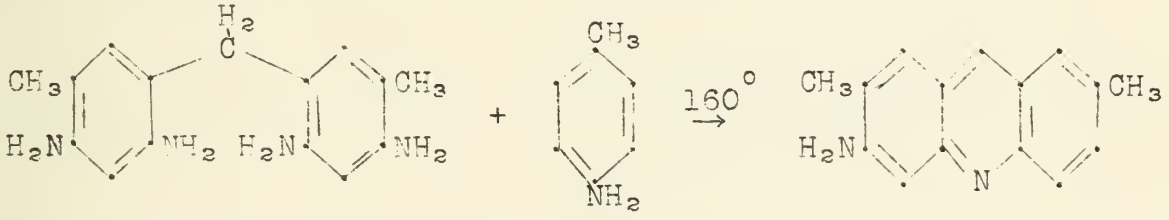


The hydrochloride salt was heated in a xylene-bath. This brings about the condensation to the acridine; the oxygen of the air oxidizes the dihydroacridine to the acridine.

In preparing acridine yellow from formaldehyde and m-tolylenediamine, hydrogen chloride under pressure is a better catalyst than zinc chloride.



Terisse and Darier found that p-toluidine displaces one equivalent of a m-diamine from its condensation product with formaldehyde, and acridination follows, giving a monoaminoacridine.



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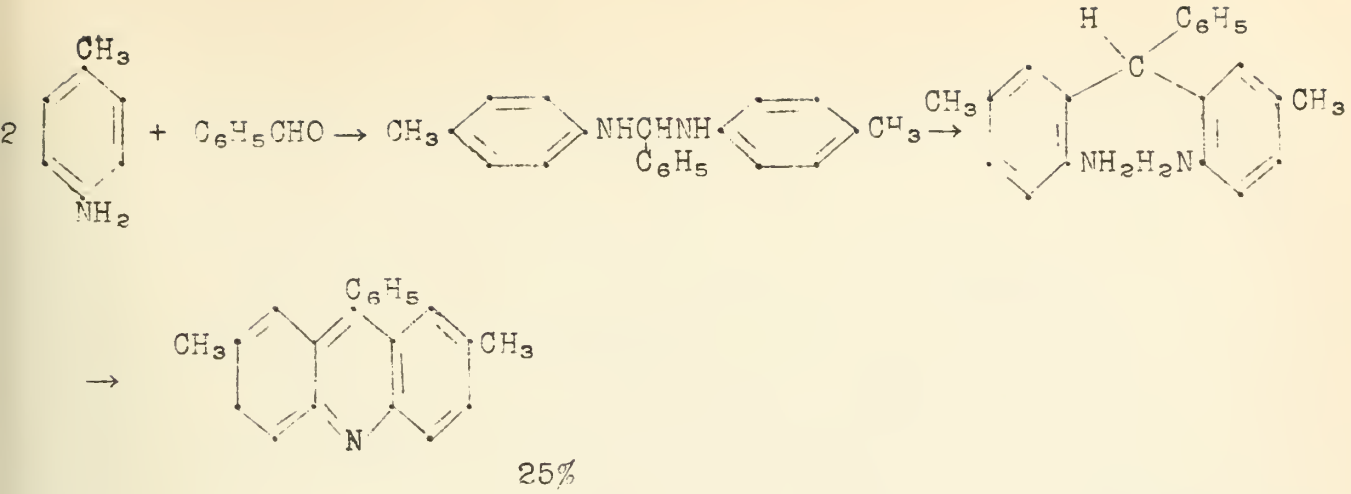
Another way of getting amino groups ortho to the methylene group in the diphenylmethane is by condensing a para-substituted aromatic amine with an aldehyde. The entering group is forced into the ortho position and the product can be converted into an acridine.



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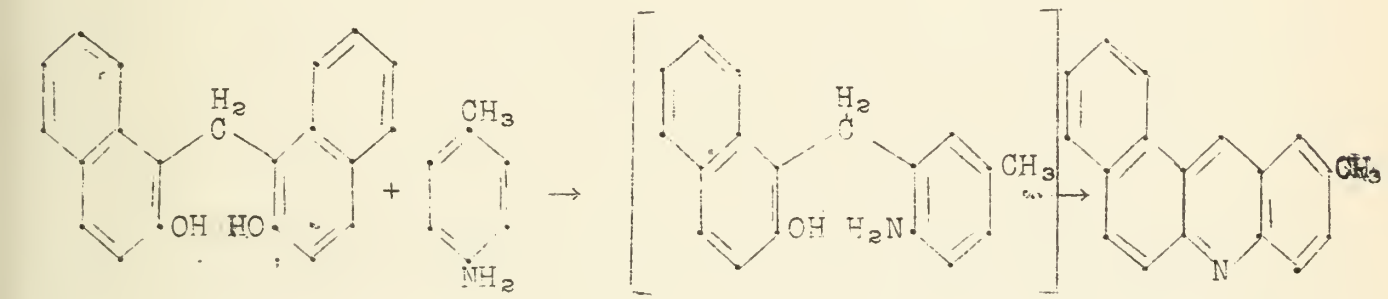
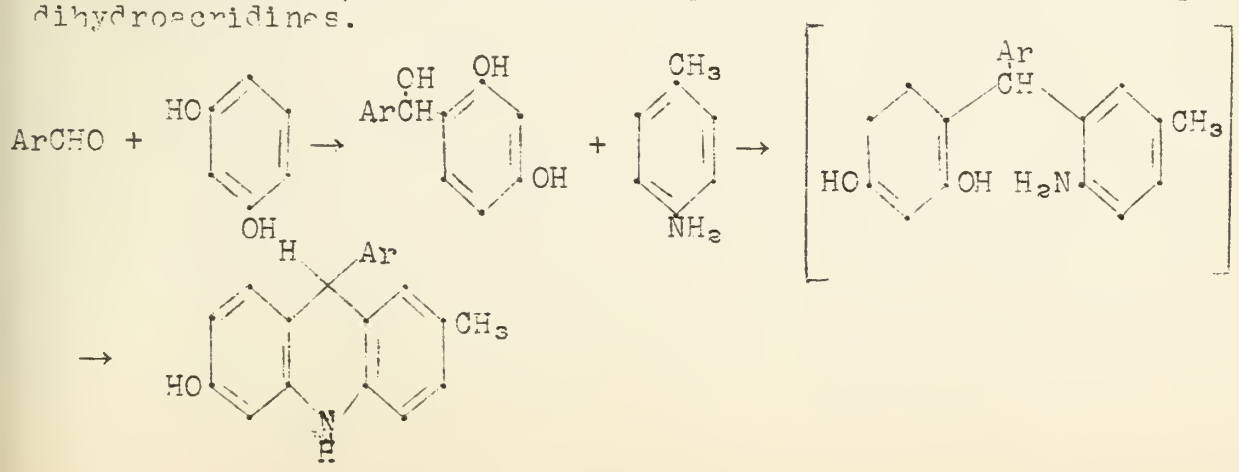
This method is general and can be used with aliphatic or aromatic aldehydes and with any para-substituted aromatic amine.

β-Naphthol condenses with formaldehyde to give methylene-di-β-naphthol. If this is heated with p-toluidine hydrochloride, one equivalent of β-naphthol is displaced by the base, and the product is a phenonaphthacridine.

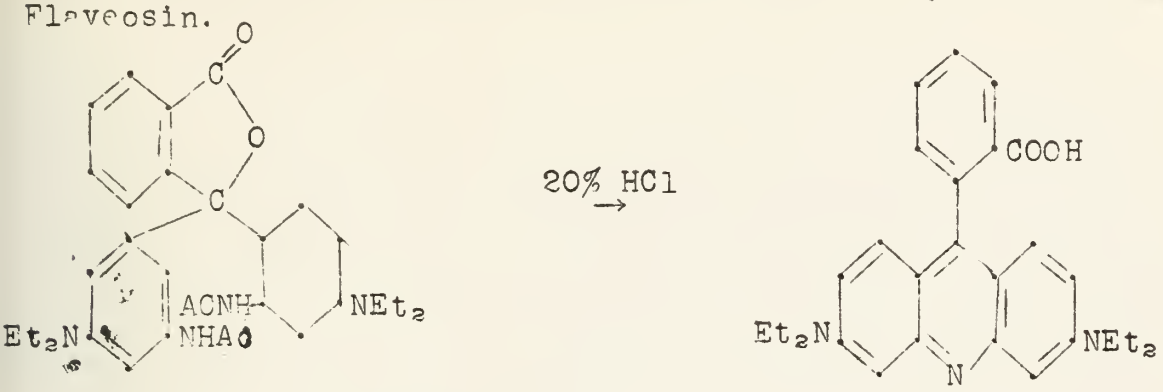


This reaction is general and has been applied to formaldehyde, benzaldehyde, and m- and p-nitrobenzaldehyde on one hand, and p-toluidine and m-xylidine on the other. In this way a large number of phenonaphthacridines and dinaphthacridines have been prepared. The yields vary from 10-93 per cent.

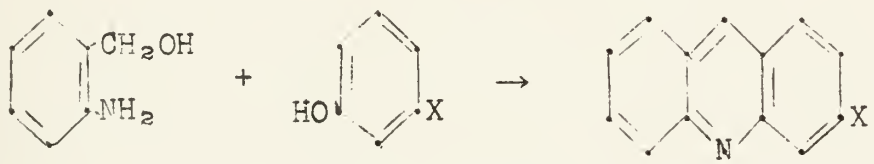
Pope and Howard prepared hydroxy derivatives by adding resorcinol to benzaldehyde or p-anisaldehyde. These react with p-toluidine and β-naphthylamines (p-substituted amines) to give dihydroacridines.



In place of aldehydes phthalic anhydride (which shows many of the reactions of a ketone) may be condensed with m-diamines, and the products give acridines when treated with zinc chloride or 20 per cent hydrochloric acid. Thus from diethyl-m-aminoacetanilide and phthalic anhydride in the presence of acetic anhydride a phthalein is obtained which is converted by sulfuric or hydrochloric acid to Flaveosin.



Ullmann and Baezner obtained acridines by condensing o-aminobenzyl alcohol with β-naphthols, resorcinol or diethyl-m-aminophenol.



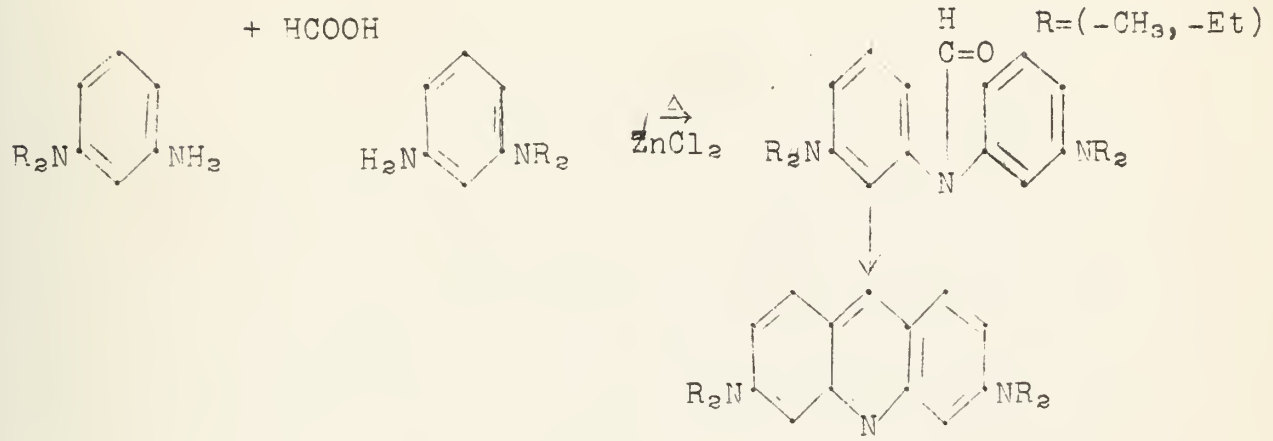
(X=OH or NEt_2)

This reaction was developed further by Baezner.

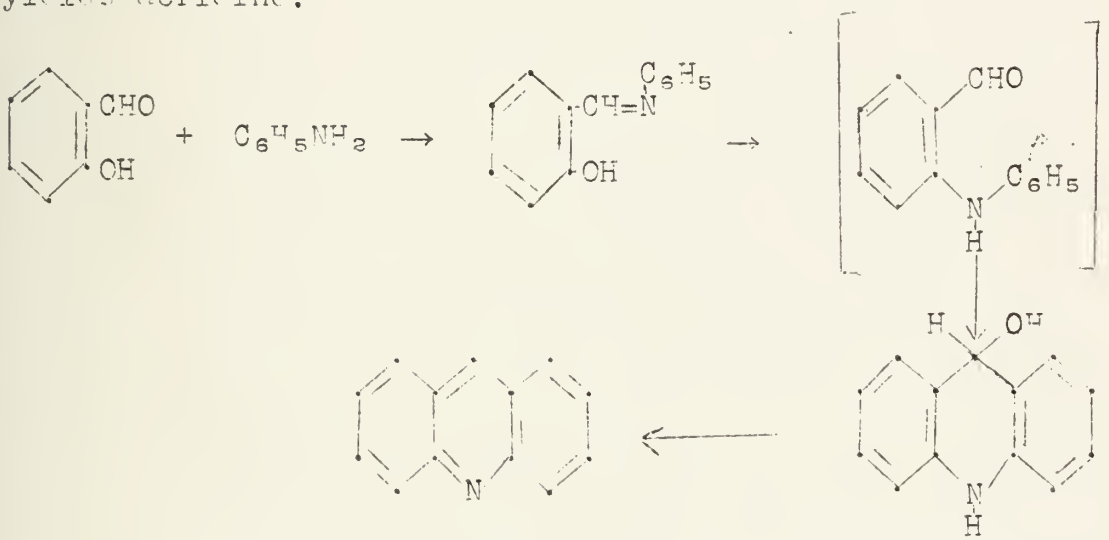
The second method for preparing acridines uses benzyl- or benzalanilines as starting materials. Meyer and Hofmann passed benzylaniline through a hot tube and formed acridine in considerable quantity. This is a convenient method for preparing acridine. Pictet and Erlich prepared α- and β-chrysidines (α- and β-naphthacridines) from benzal-α- and β-naphthylamines.

In the third general method the meso carbon atom is supplied by a substituent carried by the nitrogen or by a group in the ortho position. A general method starting with diphenylamines and acids was developed by Bernthsen in 1878, when he heated diphenylamine hydrochloride and benzonitrile at 230-250° and obtained 9-phenylacridine in 10 per cent yield. The same product was obtained more smoothly by heating benzoyl diphenylamine or a mixture of benzoic acid and diphenylamine with zinc chloride. The reaction has been extended to a large number of acylated diphenylamines. Acridine itself is obtained in only small yield by using formic or oxalic acids, but chloroform, especially in the presence of aluminum chloride, gives good results. The yields with other acids, aromatic or aliphatic, are from 40-60 per cent. Substituted diphenylamines give the corresponding acridines.

A modification of Bernthsen's method consists of heating the formyl derivative of a para-substituted arylamine (or of a meta-diamine) with the hydrochloride of a similar arylamine. An example is

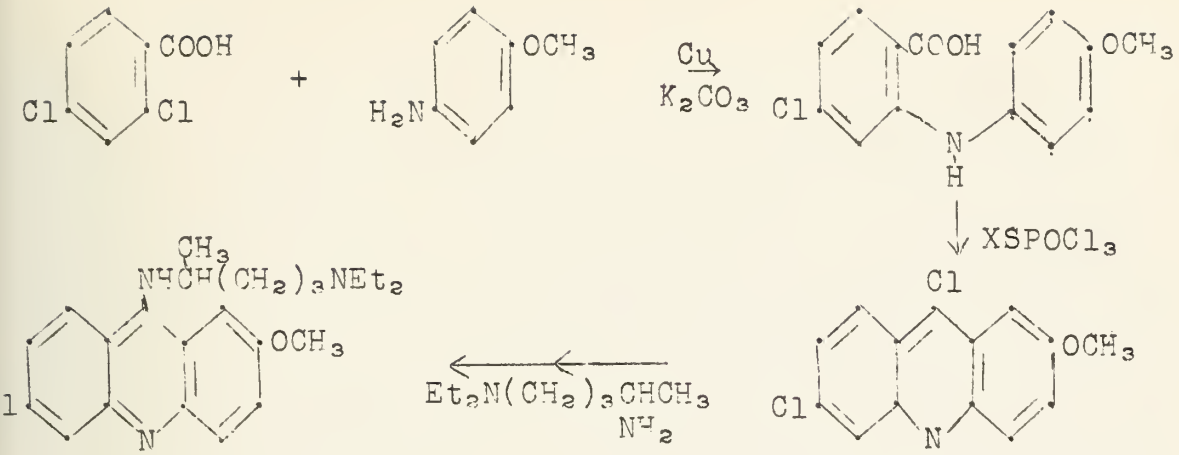


Aryl-o-aminoaldehydes can also be used as starting materials. For example, salicylaldehyde and aniline heated together at 260 yields acridine.



Certain acridines that are substituted in the 9-position with dialkylamino alkylamino groups show good antimalarial activity. It is interesting to see that only one general method is used in preparing these acridines. The synthesis ends up with an active chlorine on the 9-position that can be readily replaced by a secondary or primary amine.

This method involves first the condensation of a 2-chlorobenzoic acid with an aromatic primary amine to give an N-arylanthranilic acid. This condensation has been brought about in nitrobenzene with copper catalyst and potassium carbonate but Drozdov and Bekhli state that they get better results using copper acetate and potassium carbonate with amyl alcohol as the solvent. The anthranilic acid is then refluxed with excess of phosphorus oxychloride to produce the 9-chloroacridine derivative. The synthesis of atebrin is given be-



Atebrin

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Reported by N. K. Sundholm

August 25, 1943

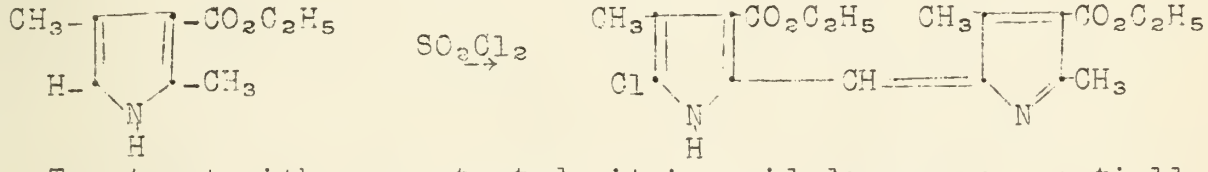
PYRROLES

The two general methods for the synthesis of pyrroles are the condensation of 1,4-carbonyl compounds with ammonia or primary amines and the condensation of an α-aminoketone with another ketone. By using a γ-keto ester in the first method, an α-hydroxypyrrole is obtained. The second method usually uses an isonitrosketone under reducing conditions rather than a primary amine. The Piloty synthesis employs a secondary aminoketone to prepare N-substituted pyrroles.

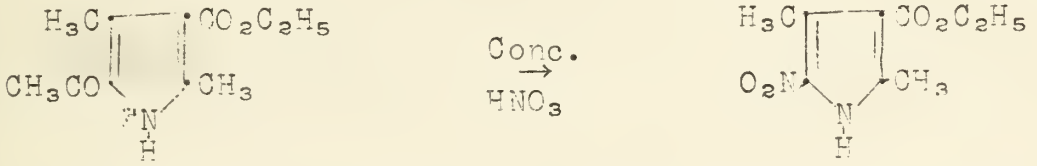
Pyrrole itself has been prepared: (1) by heating mucic acid with ammonia, (2) by heating glutamic or pyroglutamic acid, (3) by passing acetylene and ammonia through a hot tube, and (4) by the distillation of succinimide from zinc dust.

Patents have been issued for the synthesis of pyrroles: (1) from furan and ammonia at elevated temperatures and pressures, (2) from 1,4-dihydroxy compounds and ammonia, and (3) by the dehydrogenation of pyrroline and pyrrolidine.

In their aromatic reactions, pyrroles resemble phenols. Halogenation must be run in dilute solution, and the product is completely halogenated. Principle side-reactions include side-chain halogenation, replacement of an acyl group with halogen, and the formation of a dipyrryl methene if a trisubstituted pyrrole has an α-position free and a methyl group in the other α-position.



Treatment with concentrated nitric acid decomposes partially substituted pyrroles, but can replace acyl, carboxyl, halogens, or even alkyl groups in tetrasubstituted pyrroles. Direct nitration



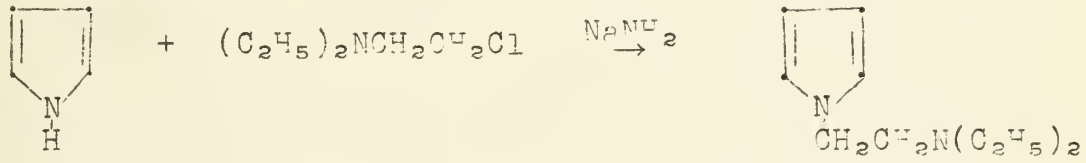
may be achieved by using ethyl nitrate and sodium ethylate.

Pyrroles are nitrosated in the β-position by treatment with amyl nitrite in the presence of sodium ethylate. In the absence of sodium ethylate, the nitroso compound is oxidized to the nitro compound. The nitroso compound is obtained as the sodium salt of the isonitroso form. The nitroso form may be obtained by acidification, but is not stable for alkyl pyrroles.

Diazonium salts couple with pyrroles, usually in the α-position, to give azo compounds. Nitro-, nitroso-, and azopyrroles can all be reduced to aminopyrroles by the usual methods.

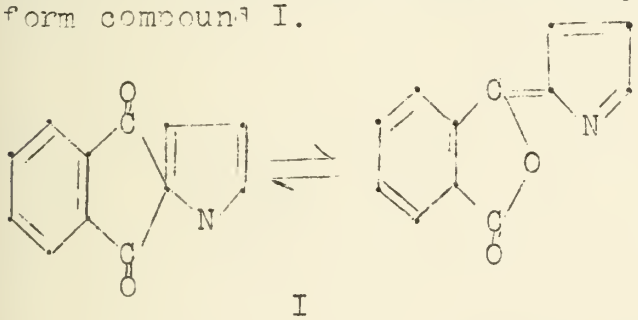
Pyrroles undergo the Gattermann, Houben-Hoesch, Reimer-Tiemann, and Friedel-Craft reactions, usually in the α-position. Pyrrole acids may be decarboxylated by heating in a vacuum, and pyrrole ketones may be deacylated by heating in dilute sulfuric acid.

Non-aromatic substitution reactions usually involve the N-hydrogen atom. The hydrogen may be replaced by potassium, and the resulting compound treated with an acyl or an alkyl halide to prepare N-substituted pyrroles. Heating pyrrole with a mixture of acid anhydride and the sodium salt of the acid gives a mixture of N- and α-acylated pyrrole. By using strongly alkaline conditions, it is sometimes possible to put an alkyl group on the nitrogen with an alkyl halide.

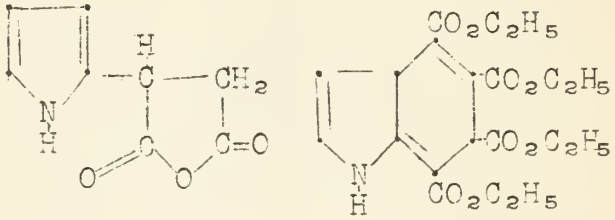


Grignard reagents react with the active hydrogen of pyrrole to give a pyrrylmagnesium halide. These react with the usual reagents to give α- (or β-) substituted pyrroles. Diazoacetic ester reacts with pyrrole to form α-pyrrylacetic ester.

Pyrroles with the α-position free or substituted with a carboxyl group have a number of typical reactions. They react with p-dimethylaminobenzaldehyde to form a colored compound by the so-called Ehrlich reaction. They form precipitates with mercuric chloride and arsenic oxide. They react with phthalic anhydride to form compound I.



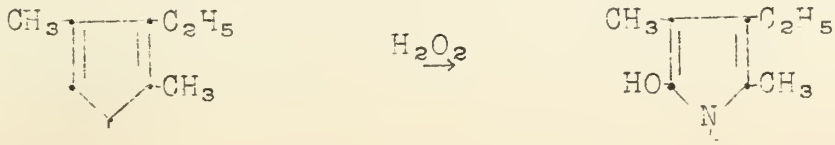
I



II

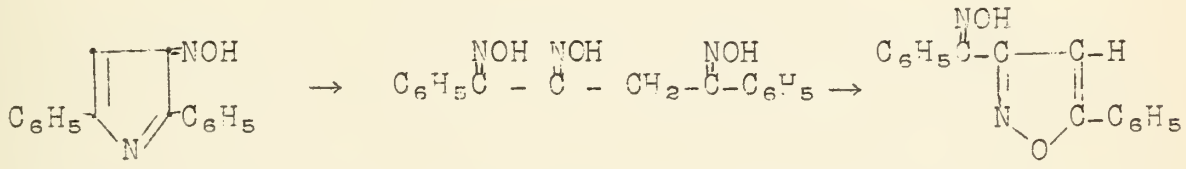
Pyrrole reacts with maleic anhydride to form compound II and with acethylenedicarboxylic ester to form compound III.

Pyrroles may be simultaneously oxidized and chlorinated with alkaline chlorine solutions, to form dichloromaleinimide. In one case, a trisubstituted pyrrole may be oxidized with hydrogen peroxide to form a hydroxypyrrole.

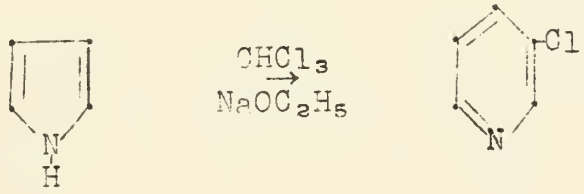


Reduction can occur by adding either one or two molecules of hydrogen. Zinc with hydrochloric acid or acetic acid adds one molecule of hydrogen to form a pyrroline. Hydriodic acid and phosphorus or catalytic hydrogenation add two molecules of hydrogen to form pyrrolidines.

Hydrolysis of pyrroles gives a 1,4-dicarbonyl compound and ammonia. Frequently, hydroxylamine is used in the hydrolysis, and the dioxime is obtained. Nitrosopyrroles, on hydrolysis in the presence of hydroxylamine, give trioximes which ring-close to form oxadiazoles.



On treatment with chloroform and sodium ethylate, pyrrole is converted to β-chloropyridine.



Nitrosopyrroles, on treatment with phosphorus pentachloride, are converted into pyrimidines.

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Reported by R. S. Ludington
August 25, 1943

1,2-EPOXY COMPOUNDS

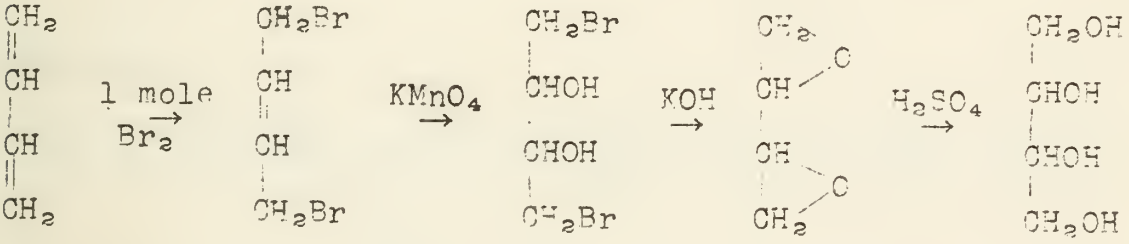
Nomenclature

Substances that contain the grouping $-\overset{O}{\overset{\diagup\diagdown}{C-C}}-$ are given several different names. The index of Chemical Abstracts lists them either as epoxy compounds (Geneva system) or as derivatives of ethylene oxide. These substances may also be called oxido compounds, or may be named as derivatives of cyclic ethers or of oxirane.

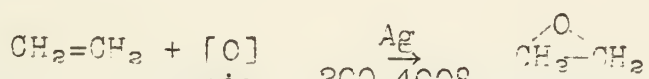
Preparation

There are five general methods for introducing the epoxy group into a molecule.

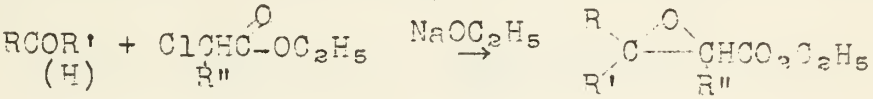
1. The most general method is the treatment of a halohydrin with an alkaline reagent. An interesting use of this method occurs in the following preparation of erythritol (1).



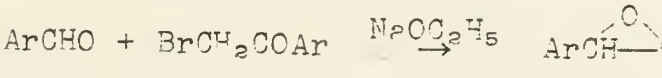
2. Many patents have been issued for the preparation of epoxy compounds, particularly ethylene oxide itself, by the use of a silver catalyst and air (2).



3a. Glycidic esters can be prepared by a condensation of a ketone or an aldehyde with ethyl chloroacetate, or one of its derivatives, in the presence of sodium ethoxide (3).

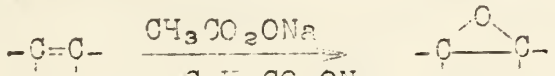


3b. A modification of the above method involves the condensation of an aromatic aldehyde with an aracyl halide. Sodium ethoxide is the condensing agent (4). (Widman method)

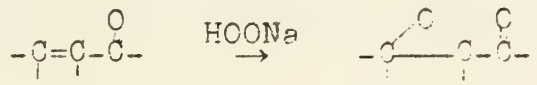


(Both methods 3a and 3b probably involve the intermediate formation of a halohydrin, and therefore can really be considered as modifications of the first method.)

4. The treatment of an aliphatic double bond with peracetic or perbenzoic acids results in the formation of the epoxy group (5,6,). (Prilezhaev reaction). Monoperphthalic acid may be used too, and has the advantage of being cheaper and more stable. (7)

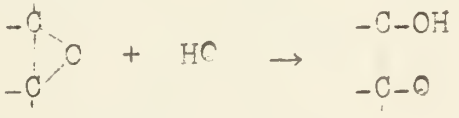


5. If there is a carbonyl group adjacent to the double bond, the Prilezhaev reaction will not take place (8). There are only two methods of preparing α-oxido carbonyl compounds. We can use the Widman method, or we can treat the olefin with alkaline hydrogen peroxide at room temperature (9).



Reactions

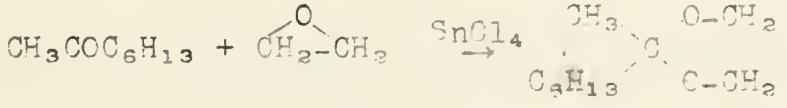
1. An epoxy compound will, in general, react with a molecule containing an active hydrogen in the following manner (10):



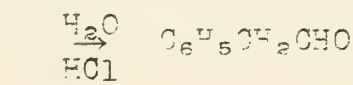
A specific example:

β-Halogenethyl esters can be prepared by treating ethylene oxide with acyl halides.

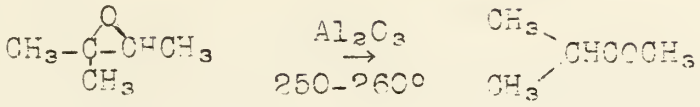
Cyclic acetals (dioxolanes) can be prepared by treating aldehydes with ethylene oxide in the presence of stannic chloride. Ketones will give cyclic ketals.



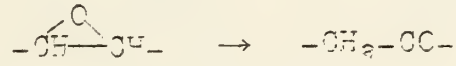
Dilute acids have a tendency to cause isomerization (11).



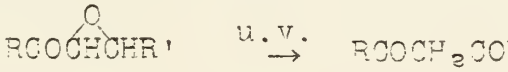
Isomerization can also be brought about by heating in the presence of alumina (12).



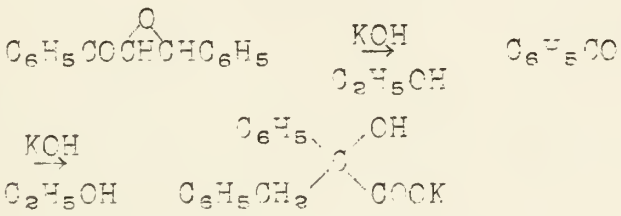
2. The α-oxido carbonyl compounds undergo some rather special reactions. In general it is easy to bring about the following transformation (13):



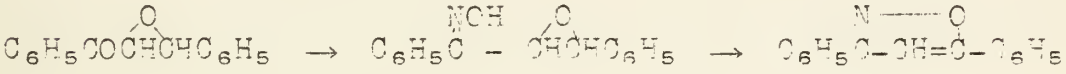
The usual catalysts for this reaction are acids and metal oxides such as Al_2O_3. Sometimes heat alone will suffice. Ultraviolet light has also been used.



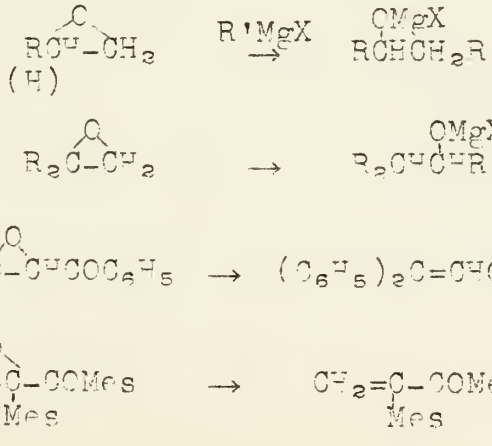
Alkaline reagents usually produce a 1,2-diketone (14, 15).



The epoxide may react with another part of the molecule:



3. The reaction of epoxides with the Grignard reagent is quite complex, and depends upon the particular epoxide used (16,17).



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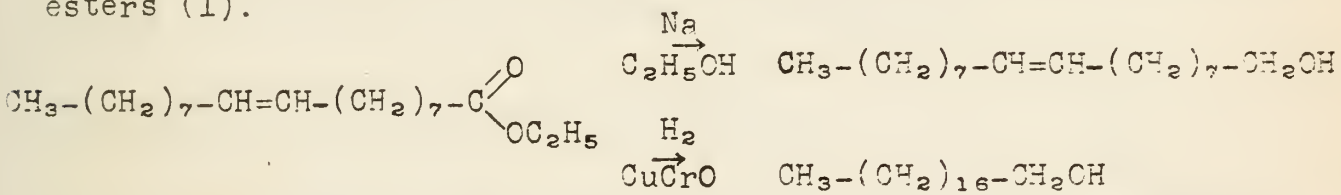
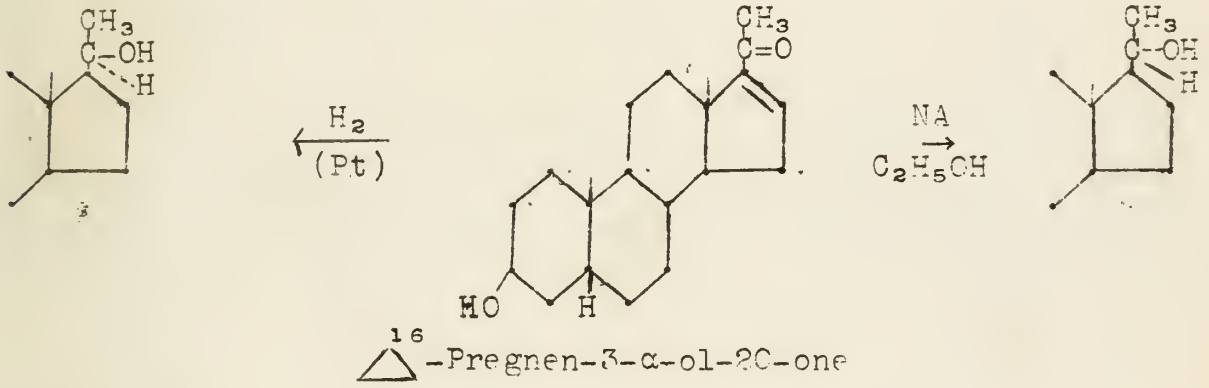
Reported by Peter F. Warfield
September 8, 1943

REDUCTION WITH SODIUM AND ALCOHOLS

Among the more important reduction methods is that embracing the use of sodium and an alcohol, commonly known as the Ladenburg or Bouveault-Blanc method. The reagent has a certain specificity for the C=O bond and for this reason has been supplemented rather than supplanted by the cheaper, more recent methods of catalytic hydrogenation. Since sodium and alcohol do not attack isolated ethylenic linkages, the Bouveault-Blanc method has been used widely for the preparation of unsaturated alcohols from the corresponding esters (1).



Moreover, reductions with sodium and alcohols follow a different steric course than hydrogenations over metal catalysts. An example is Marker's synthesis of the two isomeric 3-(α)-20-pregnanediols (2).



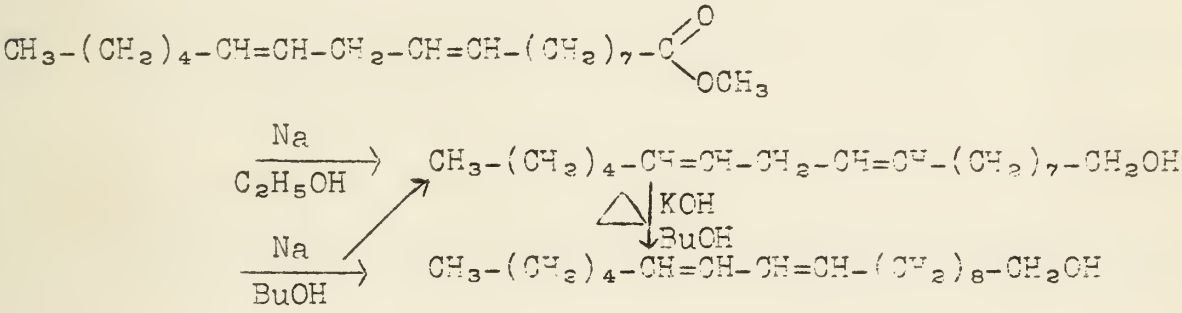
16-Pregnen-3-α-ol-20-one

A. Reduction of Esters

Esters are generally reduced to the corresponding primary alcohols (3) (Bouveault-Blanc) with the exception of those with the esterified carboxyl group directly attached to the ring. Esters of dicarboxylic acids are reduced to the corresponding diols. Since traces of water in the alcohol result in saponification of the ester and a lowering of the yield, the reduction must be run in absolutely dry alcohol. By use of a modification of Bouveault's procedure, Ziegler prepared the glycols corresponding to the C_{17}-C_{25} dicarboxylic acids in yields of 85% and better.(4). In the past fifteen years most of the commercially available higher primary alcohols have been made by catalytic reduction of the esters over copper chromite.

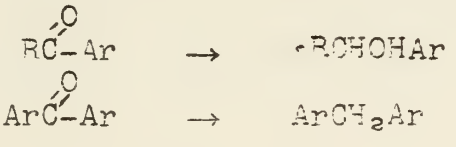
Since isolated multiple carbon-carbon bonds are not reduced by sodium and alcohols, this method affords a convenient synthesis

of ethylenic alcohols. The yields of unsaturated alcohols are considerably better than those from the catalytic reduction over zinc chromite (1,5). The more vigorous conditions of reduction with sodium and higher alcohols frequently cause a shifting of the double bonds of unsaturated esters (6). Reduction of methyl linoleate with sodium and butyl alcohol yields a mixture of the expected 9,12-octadiene-1-ol and the product of its rearrangement, 10,12-octadecadiene-1-ol. Milder reduction with sodium and ethyl alcohol yields only the 9,12-diene in 45% yield.

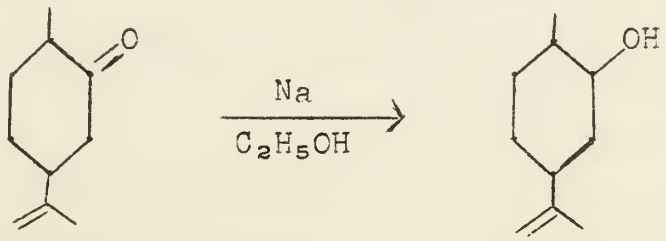


B. Reduction of ketones (Ladenburg)

Aliphatic ketones are reduced to secondary alcohols by sodium and alcohols. The yields, however, do not compare with those obtained from catalytic hydrogenation with Raney nickel. Fatty aromatic ketones likewise are reduced to the corresponding secondary alcohols, but diaryl ketones yield up to 90% of the hydrocarbons representing complete reduction of the carbonyl group to methylene (7,8).

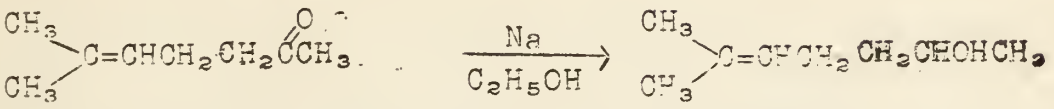


α,β-Unsaturated ketones are reduced to the corresponding saturated alcohols in good yields. This reaction typifies the ease with which conjugated systems are attacked by this reducing agent, a fact which has been widely exploited in the development of the chemistry of the terpenes and steroids. If the conjugated system is a 1,4-carbon-oxygen one, complete reduction to the saturated alcohol usually ensues. Thus carvone leads to dihydrocarveol (9).



If the carbon-carbon double bond be removed by one or more carbon atoms from the carbonyl group, the reagent exerts only its

usual reducing action on the C=O bond, e.g., the reduction of methyl heptenone to methyl heptenol (10).



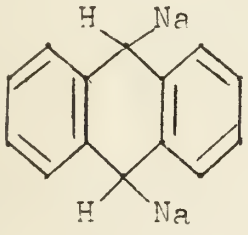
The extent and character of reduction obtained by this method is often closely dependent on the alcohol selected. In general, a higher temperature, secured by the use of an appropriate higher boiling alcohol, and maintainance of the reaction temperature at the boiling point of the alcohol during the course of the reduction, tend to give a stronger reducing action than is produced by the use of a lower boiling alcohol.

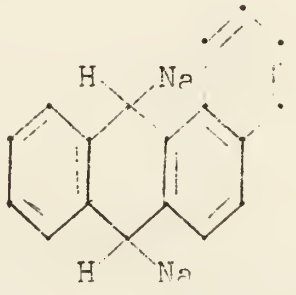
C. Reduction of multiple carbon-carbon bonds.

The use of sodium and alcohols in the reduction of non-aromatic ethylenic bonds has been discussed in a previous seminar (11).

With the exception of the benzene series, aromatic hydrocarbons are partially reduced by sodium and alcohols. On reduction with sodium and absolute alcohol naphthalene gives primarily Δ^1-dihydronaphthalene; if, however, 95% alcohol be used, the product consists of a mixture of Δ^1-dihydronaphthalene and Δ^2-dihydronaphthalene in the ratio of about 2:3. If amyl alcohol be used, tetrahydronaphthalene is formed (12). Anthracene yields the 9,10-dihydro compound (13).

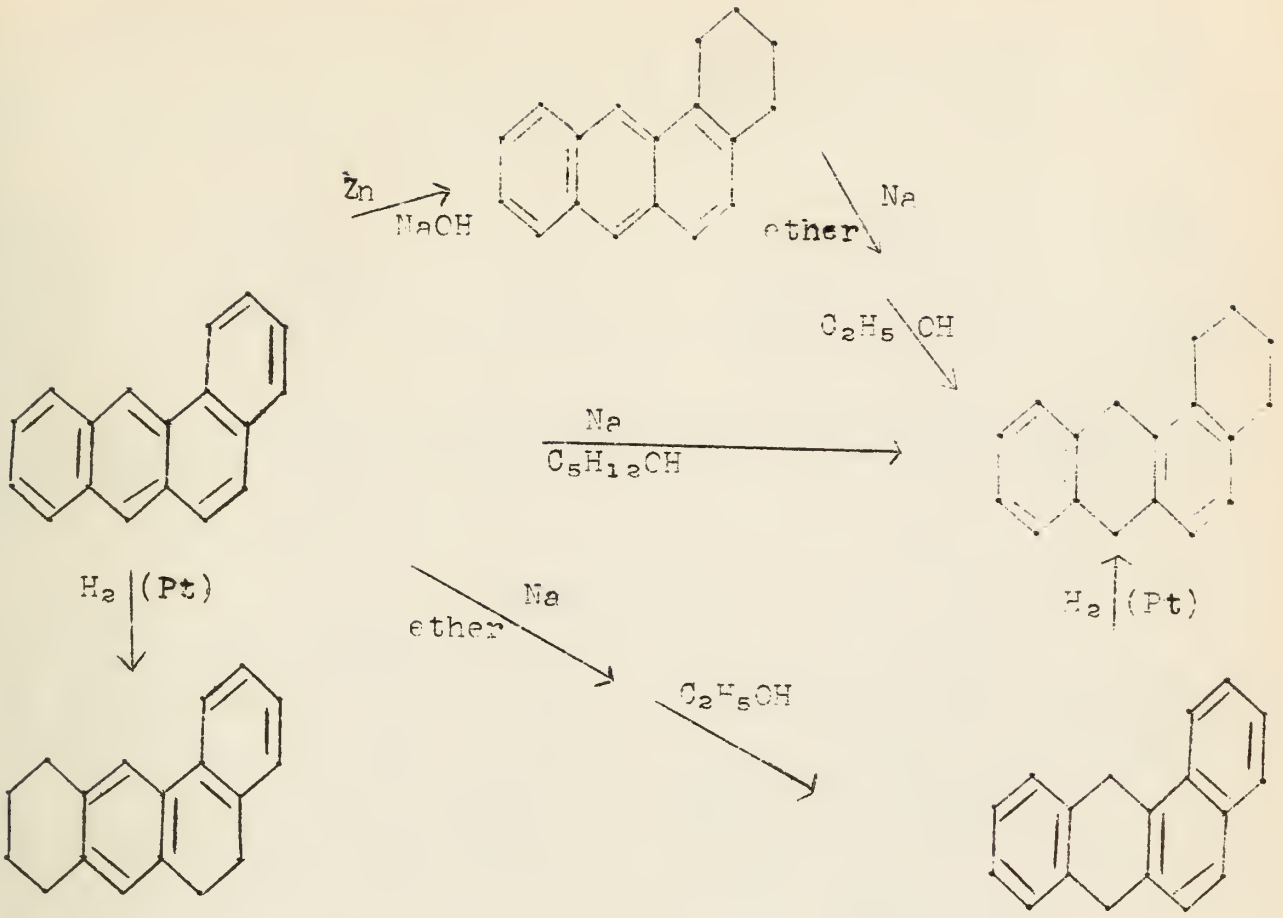
If the polycyclic aromatic compound in an ether-benzene solution is treated with sodium, a colored sodium addition product is formed. Schlenk postulates the following structures for the sodium addition compounds of anthracene and benzanthracene.



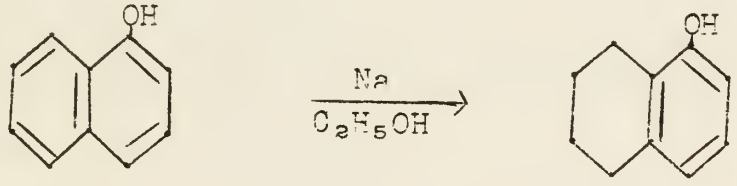


Treatment of the sodium adduct with alcohol yields the dihydrohydrocarbon.

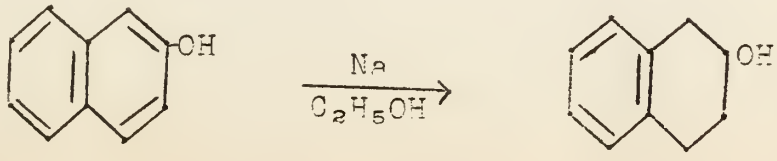
The effect of various reducing agents on benzanthracene is illustrated by the following equations.

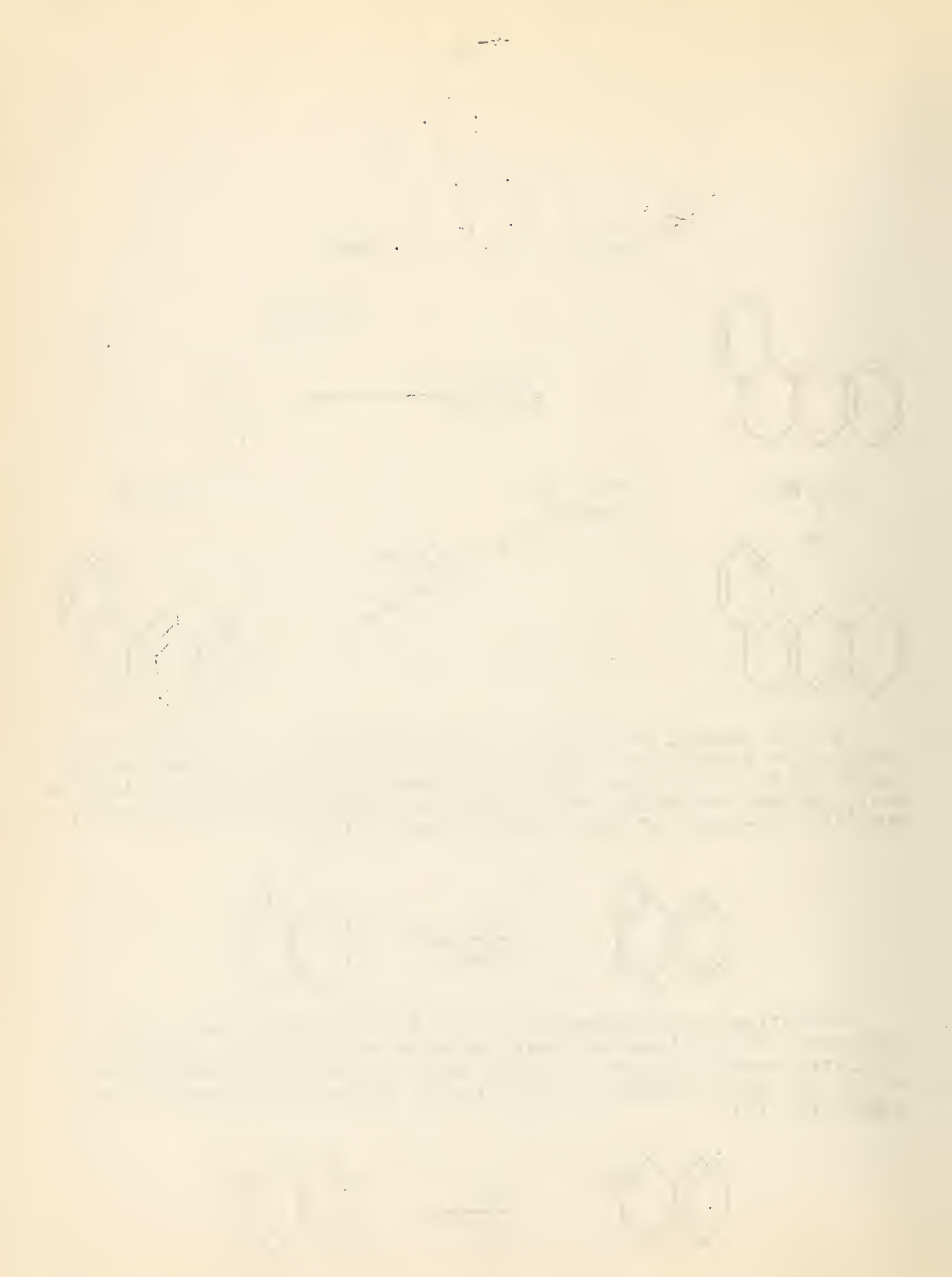


In the partial reduction of aromatic nuclei, the character and position of substituents play an important role in determining the course of the reduction. Thus α-naphthol and its homologs, in general, undergo reduction of the ring not carrying the substituent, with the formation of ar-tetrahydro derivatives:

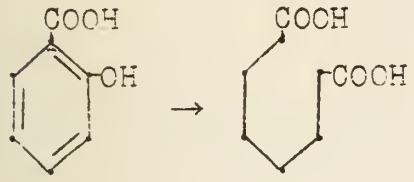


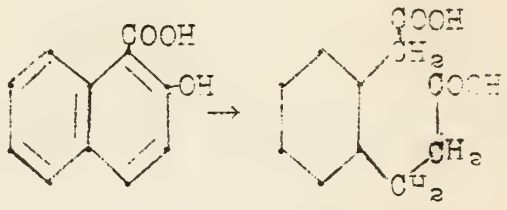
Reduction of β-naphthylamine and β-naphthols leads to ac-tetrahydro derivatives and small amounts of the ar-compounds (15). Catalytic reduction with platinum and a trace of hydrochloric acid yields the ar-derivative of both the α- and β-naphthylamines and naphthols (16).





Similarly, reduction of benzoic acid with sodium and amyl alcohol results in the formation of hexahydrobenzoic acid, whereas salicylic acid suffers ring cleavage of the intermediate tetrahydro acid to give pimelic acid; and β-hydroxy-α-naphthoic acid gives phenylenediaceticpropionic acid (17).





Anthranilic acid gives principally the hexahydro derivative whereas p-aminobenzoic acid loses the amino group to give hexahydrobenzoic acid (18).

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Reported by J. Mills
September 8, 1943

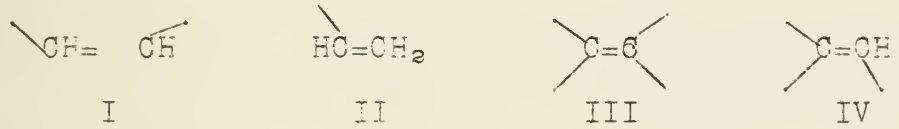
REACTIONS OF NITROSYL CHLORIDE WITH ORGANIC COMPOUNDS

The chemical behaviour of nitrosyl chloride is quite interesting, for although it is a remarkably stable compound, nevertheless it is very reactive, and there are few organic compounds with which it will not react in some manner. There are various methods to be found in the literature for the preparation of nitrosyl chloride, but most of these are modifications of two general methods, that of Tilden[1] and Girard and Pabst[2] and that of Gay-Lussac[3]:

$$HNOSO_4 + NaCl \rightarrow NOCl + NaHSO_4$$
$$2NO + Cl_2 \rightarrow 2NOCl$$

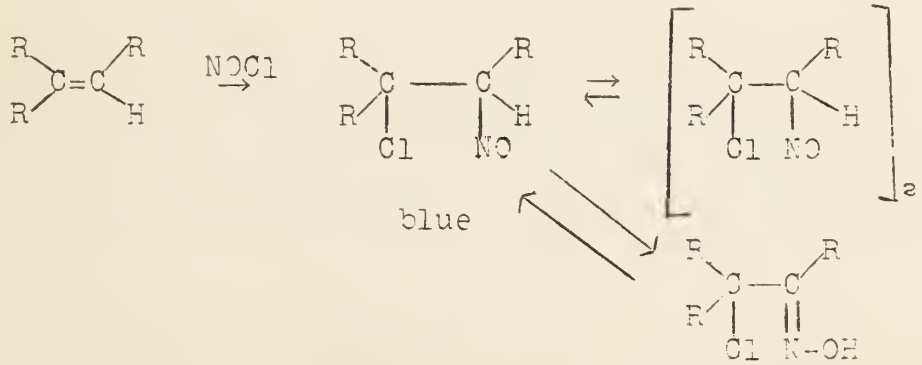
The best method of purification of nitrosyl chloride is by means of the stable molecular addition compounds which it forms with many metallic chlorides[4].

The most well-known and useful of the reactions of nitrosyl chloride is that of addition to the double bonds of unsaturated compounds to form nitrosochlorides. It is this reaction which proved to be of great assistance in the elucidation of the structures of the terpenes and other natural oils in the work developed chiefly by Wallach and Bayer. In this connection it should be noted that nitrosyl chloride itself is not often used but instead an alkyl nitrite such as amyl or ethyl nitrite and hydrogen chloride in alcoholic or aqueous solution. Many investigators have studied the formation of nitrosochlorides from ethylenic hydrocarbons, and Tuot[5] and Ipatieff[6] have found that compounds which have more than one hydrogen atom attached to a double bond carbon atom do not form solid nitrosochlorides. Thus compounds of types I or II do not yield solid nitrosochlorides.



I II III IV

The nitrosochlorides are usually sharply melting white solids which dissolve to give blue or colorless solutions. Nitroso compounds usually occur in the bimolecular (bisnitroso) form in the solid state, and it is this form or the isomeric isonitroso form which is colorless. The possible forms are shown in the following equation.



Perrot[7] has investigated the action of nitrosyl chloride on styrene and similar hydrocarbons and has found that in general nitrosochlorides are formed at low temperatures while at higher temperatures oxidation takes place. From styrene he obtained at room temperature a 95% yield of the nitrosochloride and also α,β-dichlorethylbenzene and β-nitrostyrene. More recently he has been able to obtain the nitrosochlorides of styrene, indene, stilbene, β-bromostyrene, and other hydrocarbons in good yields by working at temperatures around -50°[8]. He has also investigated the reactions at higher temperatures[9] and has found, that oxidation takes place. For example, tolane reacts with nitrosyl chloride at 150-200° to give benzoyl chloride.

$$\phi C{\equiv}C\phi + 2NOCl \rightarrow 2\phi COCl + N_2$$

Not only unsaturated hydrocarbons but also the paraffins have been shown to react with nitrosyl chloride. Lynn and Filton[10] have shown that paraffin hydrocarbons react in the presence of sunlight to form nitroso compounds which rearrange to form oximes, and these are easily hydrolyzed to the corresponding ketones. For example, n-heptane gives dipropylketone.

$$CH_3(CH_2)_5CH_3 \rightarrow [(CH_3CH_2CH_2)_2CH\text{-}NO] \rightarrow (CH_3CH_2CH_2)_2C{=}N\text{-}OH \rightarrow$$

$$(CH_3CH_2CH_2)_2CO$$

He later[11] reported the formation of benzaldehyde from toluene.

$$\phi CH_3 \rightarrow [\phi CH_2NO] \rightarrow \phi CH{=}N\text{-}OH \rightarrow \phi CHO$$

Mitchell and Carson[12] have found that most of the oxime formed in a reaction of the above type reacts with more nitrosyl chloride to give the chloronitroso compound, both functional groups being on the same carbon atom. Perrot[13] has found that at temperatures near 150° chlorination is the principal reaction and has obtained good yields of the corresponding chloro compounds from hydrocarbons such as toluene, ethyl benzene, and biphenyl.

$$\phi CH_3 \rightarrow \phi CH_2Cl$$

$$\phi CH_2CH_3 \rightarrow \phi CH_2CH_2Cl$$

If the compound which is treated with nitrosyl chloride contains an hydroxyl group, then it is this group which is attacked and not the hydrocarbon chain. Lee and Lynn[14] have subjected several aliphatic alcohols to the action of nitrosyl chloride by saturating the alcohol at -10° with the gas. In the presence of an equivalent amount of pyridine the corresponding nitrites are formed in yields of 60-80%.

The action of nitrosyl chloride on phenols has evidently been little investigated although there is a patent[15] on the production of nitrosophenols in this manner. A phenol free from reactive substituents when subjected to the action of nitrosyl chloride in aqueous medium at 6-8° gives the p-nitrosophenol.

With ketones nitrosyl chloride reacts in a manner analogous to that with the paraffin hydrocarbons, but in this case since the molecule contains active hydrogen, the reaction proceeds much more smoothly, and there is no need for catalysis by light. According to Lynn and Lee[16] the compounds formed are the isonitroso derivatives, substitution taking place in the position alpha to the carbonyl group.

$$RCOCH_2R' + NOCl \rightarrow RCOC(=N-OH)-R'$$

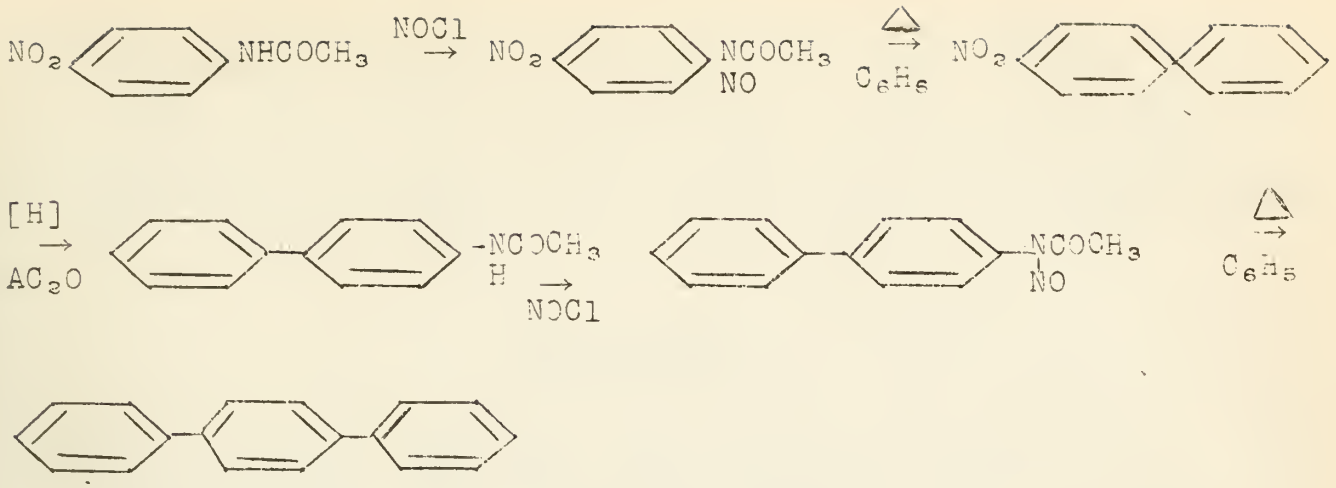
Pheinboldt and Schmitz-Dumont[17] have subjected many ketones to the action of nitrosyl chloride, and in all cases the chloroisonitroso ketones were formed. They have also shown[18] that ketoximes react with nitrosyl chloride to the form the chloroisonitroso compounds and later have found[19] that the product formed with a ketone depends upon whether or not a large excess of nitrosyl chloride is present and also upon the reactivity of the methylene group. Perrot[20] has found that with desoxybenzoin chlorination is the principal reaction at elevated temperature while the isonitroso compound is formed at moderate temperatures and in the absence of light.

$$\phi COCH_2\phi + NOCl \begin{cases} \xrightarrow{80^\circ} \phi COCHClO \\ \xrightarrow{20^\circ} \phi COC(=N-OH)-O \end{cases}$$

The reaction of nitrosyl chloride with amines and other nitrogen compounds has been studied fairly extensively, and it has been found that the compound reacts with almost every type, the reactions usually being similar to those of nitrous acid. Primary amines react to form diazo compounds, secondary amines form N- nitroso derivatives. With aliphatic primary amines the diazo compounds decompose to the chlorides and nitrogen, and rearrangement takes place to a certain extent during the process. Levene and Marker[21] have used this reaction to prepare the chloride from l-methyl-phenylethylamine

$$CH_3CH(\phi)CH_2NH_2 + NOCl \rightarrow \phi\text{-}CH(CH_3)CH_2Cl$$

and there is a commercial process for the preparation of aromatic diazo compounds from the amines by the use of nitrosyl chloride[22]. France, Heilbron, and Hey[23] have prepared the nitrosoacylarylamines in yields of 60-70% by the use of nitrosyl chloride in the presence of potassium acetate and phosphorus pentoxide, and form the products many of the terphenyls can be prepared in good yield.



Schiff bases have been shown to react with nitrosyl chloride to form the corresponding aldehydes and diazonium compounds[24] while with aldazines the aldehyde and dichloro compound are formed[25]

$$Ar\text{-}N{=}CH\text{-}R + N{-}Cl \;\|\; O \rightarrow Ar\text{-}N_2Cl + RCHO$$

$$\phi CH{=}N\text{-}N{=}CH\phi + 2NOCl \rightarrow \phi CHCl_2 + \phi CHO + N_2 + N_2O$$

The action of the reagent upon nitriles has been studied by Perrot[26] who has found that aliphatic nitriles yield the alpha oximino compounds in yields of 60-80%

$$\phi CH_2CN + NOCl \rightarrow \phi\text{-}\underset{\underset{N\text{-}OH}{\|}}{C}\text{-}CN$$

Aromatic nitriles react in a manner analogous to that of the corresponding hydrocarbons unless elevated temperatures are employed whereupon the acid chlorides are formed

$$\phi CN + NOCl \xrightarrow[150^\circ]{} \phi COCl + N_2$$

With amides nitrosyl chloride does not react unless the compound is treated with liquid nitrosyl chloride in a sealed tube. Then the corresponding acid is formed[27]

$$RCONH_2 + NOCl \rightarrow RCOCl + N_2 + H_2O,\quad RCOCl + H_2O \rightarrow RCO_2H + HCl$$

The reactions of nitrosyl chloride with certain sulfur compounds have also been investigated. Lecher and Siefkin[28] have found that there are several possible modes of combination of nitrosyl chloride with mercaptans or mercaptides

1) $2RSH + 2NOCl \rightarrow RSSR + 2HCl + 2NO$
2) $4RSH + NOCl \rightarrow 2RSSR + NH_2OH\text{-}HCl$
3) $RSH + NOCl \rightarrow RSNO + HCl$
4) $2RSNO \rightarrow RSSR + 2NO$
5) $2RSNO + O_2 \rightarrow RSSR + N_2O_4$

Working at -50° reaction 3) predominates, and the thionitrites or nitrosyl mercaptides can be produced in 80% yield. Further studies have shown[29] that tertiary thionitrites are stable toward oxygen and can easily be prepared by adding an excess of nitrosyl chloride to a solution of the mercaptan in ether at 0°. The thionitrites are fairly high boiling liquids or solids which gradually decompose, and they are very intensely colored.

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Reported by A. B. Spradling
September 15, 1943.

USES OF LITHIUM IN ORGANIC SYNTHESIS

Organolithium compounds are intermediate in activity between organomagnesium and organosodium compounds. They show the many-sided reactivity of the Grignard reagents and yet are easily prepared in contrast to the organosodium compounds.

Lithium alkyl and aryls may be prepared by the action of lithium on the appropriate halide.

$$RX + 2\ Li \rightarrow RLi + LiX$$

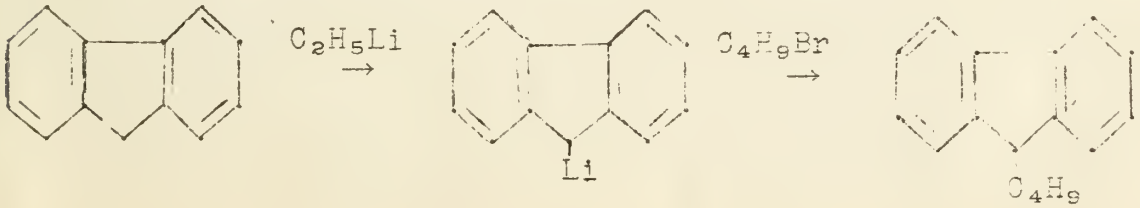
In order to obtain good yields oxygen must be excluded and the halide must be added to the lithium so as to prevent a Wurtz reaction. Excellent yields (90-95%) of lithium compounds may be obtained. In general the best yields of lithium alkyls are obtained from the chlorides; benzene, cyclohexane, petroleum ether and ether may be used as solvents. The yields are slightly better in benzene and cyclohexane and also solutions of lithium alkyls in benzene and cyclohexane are stable for long periods of time in an inert atmosphere, while on long standing they will react with ether to form lithium alcoholates.

$$RLi + R'OR' \rightarrow R'OLi + R'R$$

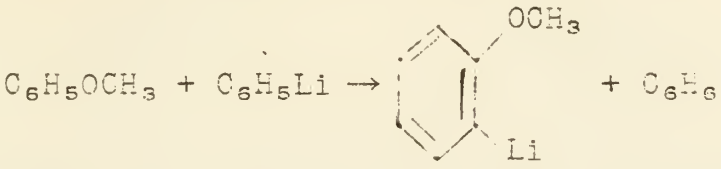
However, ether is the most widely used solvent since less care is necessary to maintain an inert atmosphere.

In making lithium aryls, the reaction proceeds a little less readily and generally the bromides are used with ether as a solvent. However, aryl chlorides can be used, this being an advantage over the Grignard, if the chloride and not the bromide is available. Lithium will react readily with certain halides with which magnesium either will not or does so only slowly. Thus p-bromodimethylaminobenzene gives a 95% yield of the desired lithium compound, but will not react with magnesium. This is also true of p-bromobiphenyl, chlorobenzene, p-chlorotoluene and α-chloronaphthalene among others. On the other hand dihalobenzenes, such as p-dibromobenzene, react much more readily with magnesium than with lithium.

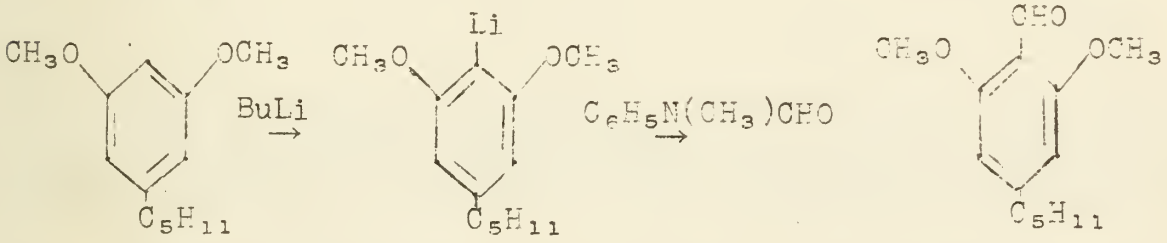
Many other organo-lithium compounds have been prepared by exchange reactions of a simple organo-lithium compound with a compound having a somewhat activated hydrogen atom. For example 9-fluoryllithium is prepared in ethereal solution practically instantaneously by the action of ethyl lithium on fluorene. The lithium compound can then be treated with butyl bromide to give a 40% yield of 9-butylfluorene, or with acetyl chloride to give a 60% yield of 9-acetofluorene.



Recently it has been established that a hydrogen on a benzene ring can be replaced by lithium in certain compounds. Thus phenol ethers and thiophenol ethers, when treated with butyl or phenyl lithium, exchange to form ortho- lithium compounds. With anisole itself, several hours heating at 100° with pehnyllithium are required to give a 70% yield of o-lithioanisole.

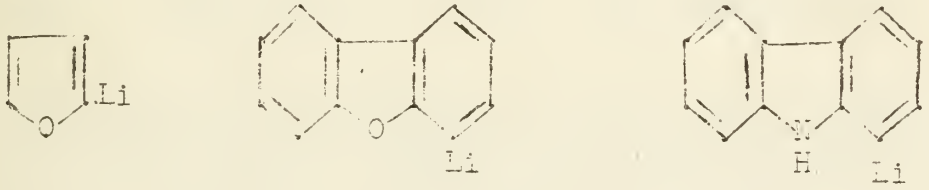


But when resorcinol dimethyl ether is allowed to stand in the cold for several hours with pehenyllithium and excellent yield of the 2-lithium resorcinol dimethyl ether is formed. Since the lithium enters between the two methoxyl groups, the lithium compounds can be used for the synthesis of the difficulty obtainable 2-resorcinol derivatives. For example, Adams and Carlin[2] have prepared olivetol dimethyl ether 2-aldehyde in this manner in 90% yield.

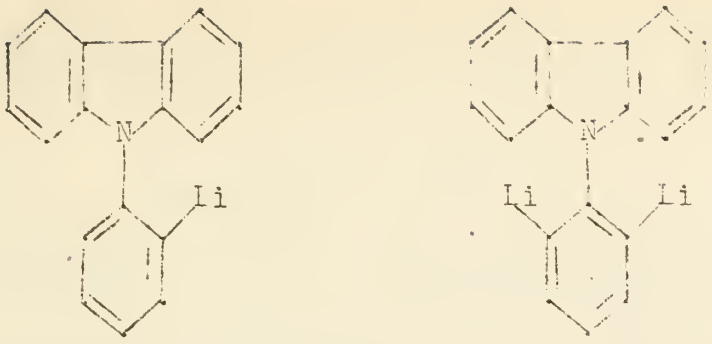


This method of preparing aldehydes appears to be quite general for lithium aryls.

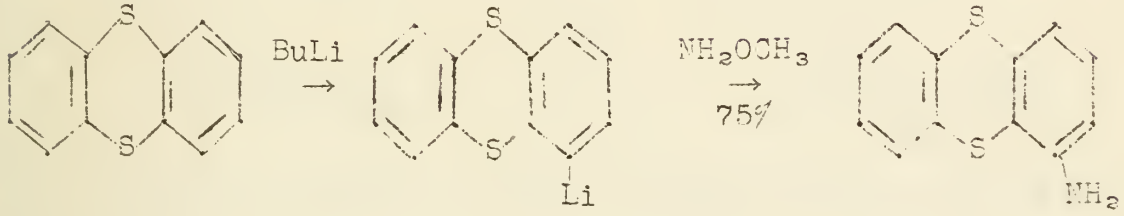
Similarly in heterocyclic compounds the positions ortho to the heterocyclic atom are easily replaced by lithium. Thus furan,



dibenzofuran and carbazole are easily metalated by treating the heterocycle with phenyllithium. The case of the metalation of 9-phenyl carbazole is an interesting one, Gilman[3] has shown that the mono and dimetallated products are formed.

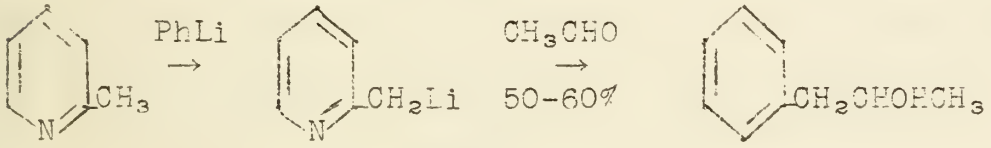


Recently Gilman[4] has synthesized 1-aminothianthrene by an interesting series of reactions.

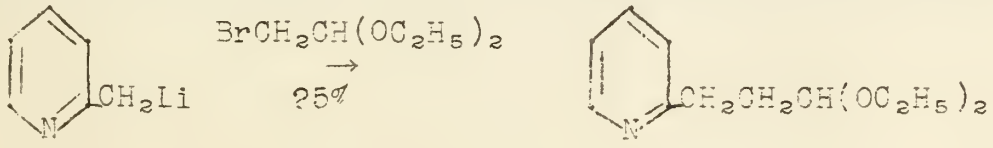


This use of α-methyl hydroxylamine appears to have been first discovered by Sheverdina and Kochechkov[5] and is also applicable to Grignard reagents. The best yields are, however, obtained with RMgCl compounds, the bromo- and iodo-compounds giving poorer yields.

Another interesting replacement reaction is the one which takes place with the α-picoline type compound. An example is the Organic Syntheses[6] preparation of 1-(α-pyridyl)-2-propanol.

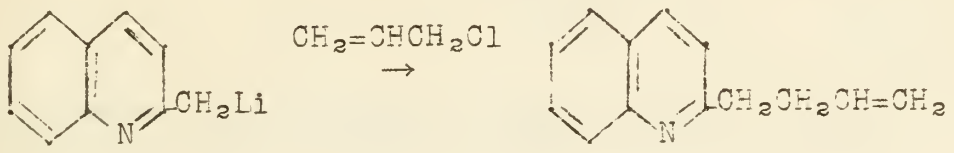


The condensation of α-picoline directly with acetaldehyde gives only 4% of the desired compound. The other possible method, the Tchitschibabin method, which accomplished the same purpose with sodamide, is more limited and frequently when it does work gives lower yields, besides the disadvantage of using sodamide. Wibaut and Beets[7] have used the method to synthesize dl-pelleterine acetal.

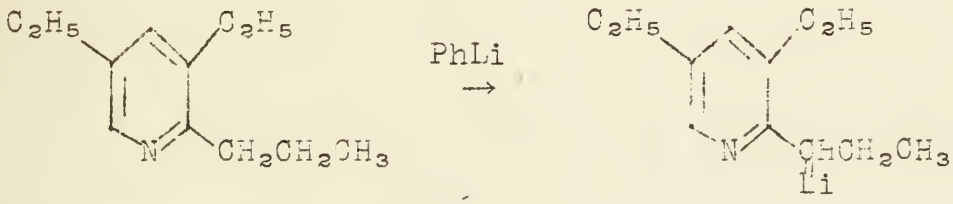


The use of sodamide in this condensation was completely unsuccessful. Other examples of its use are the synthesis of 2-propylpyridine[8] from picolinelithium by treatment with ethyl bromide (90% yield),

treatment with benzoyl chloride gives α-benzoyl-picoline. Treatment of the dilithium derivative of 2,6-lutidine with benzyl chloride gives 2,6-di-(β-phenylethyl)pyridine in excellent yield etc. Quinaldinelithium[9] reacts in the same manner thus among others:



Using an α-propylpyridine, lithium can be introduced on the carbon adjacent the ring.[10]



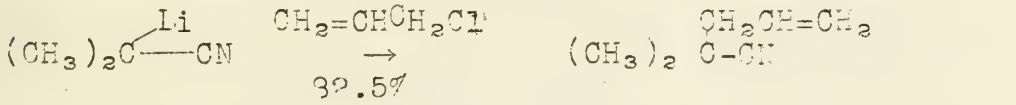
The resulting lithium compound can then be used in any of the above reactions.

Lithium secondary amines are also useful exchange agents. Butyllithium react with dimethylacetonitrile in the same way butyl magnesium bromdie would to give the ketimine. But, if the butyllithium is first treated with diethyl amine, metatation occurs.

$$C_4H_9Li + HN(C_2H_5)_2 \rightarrow LiN(C_2H_5)_2 + C_4H_{10}$$

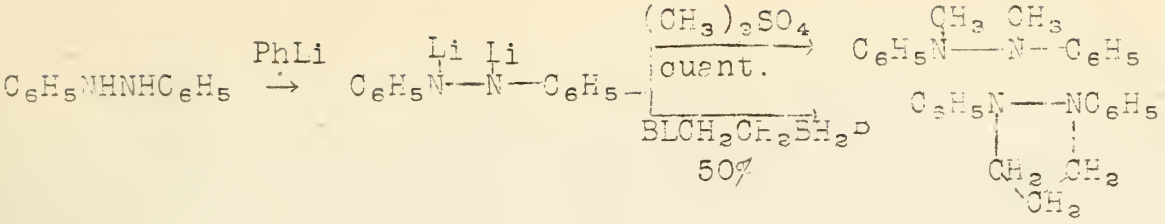
$$Li\ N(C_2H_5)_2 + (CH_3)_2CHCN \rightarrow (CH_3)_2C(Li)CN$$

This lithio compound can then be used in various syntheses.



This then serves as an elegant method for the synthesis of nitriles with a tertiary carbon. Lithium diethylamine has also been used as the condensing agent in the synthesis of large rings from dinitriles by the method of Ziegler.

Active hydrogens on nitrogens are also easily replaced, which leads to an easy synthesis of N,N'-disubstituted-hydrazobenzenes.



Halogen-metal interchange is also possible. The following interconversion occurs in a 97% yield.

$$\alpha\text{-}C_{10}H_7Br + nC_3H_7Li \rightarrow \alpha C_{10}H_7Li + nC_3H_7Br$$

The reaction is much more rapid than interchange with hydrogen, so that 4-bromoresorcinol dimethylether reacts with phenyllithium to give the 4-lithio compound rather than the 2-lithiocompound. An interfering side reaction is the Wurtz-Fittig reaction. The ease with which it takes place depends on the halogen. In the aromatic series, it takes place most readily with chloro-compounds, iodo-compounds giving almost exclusively exchange, while in the aliphatic series just the reverse is true. The reaction is of particular value in the synthesis of other lithium compounds which can not be prepared in any other way. For example, although no appreciable quantity of an RMgBr or RLi compound can be prepared directly from 3-bromo-2,4,5-triphenylfuran or 2-bromo-3,4,6-triphenylpyridine, the respective RLi compounds are readily prepared by halogen-metal interconversion with n-butyllithium.[11]

Also RLi compounds may be formed from compounds having otherwise reactive functional groups like -OH, -NH, -COOH, and =C=N-. The yields of acids formed in the following were in excess of 70%.

a) $o\text{-}BrC_6H_4OH \xrightarrow{1)BuLi,\ 2)CO_2,\ 3)H_2O} o\text{-}HOOCC_6H_4OH$

b) $p\text{-}BrC_6H_4NH_2 \xrightarrow{1)BuLi,\ 2)CO_2,\ 3)H_2O} p\text{-}HOOCC_6H_4NH_2$

c) $p\text{-}IC_6H_4COOH \xrightarrow{1)BuLi,\ 2)CO_2,\ 3)H_2O} p\text{-}HOOCC_6H_4COOH$

d)

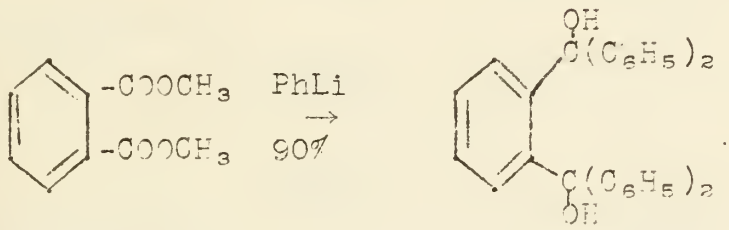
ADDITION REACTIONS

Many of the addition reactions are just the same as with Grignard reagents, we will try to mention here only some of the cases where differences occur. Most of the differences are due to the greater reactivity of the lithium compounds. Thus lithium compounds will add to unsaturated hydrocarbons with conjugated double

bonds.

$$(C_6H_5)_2C = CH_2 + C_6H_5Li \rightarrow (C_6H_5)_2\overset{Li}{C}\ CH_2C_6H_5.$$

In the addition to carbonyl containing compounds, Grignard reagents are generally used, although there are some cases, particularly with diketones and diesters, for which the lithium compounds are much more satisfactory.

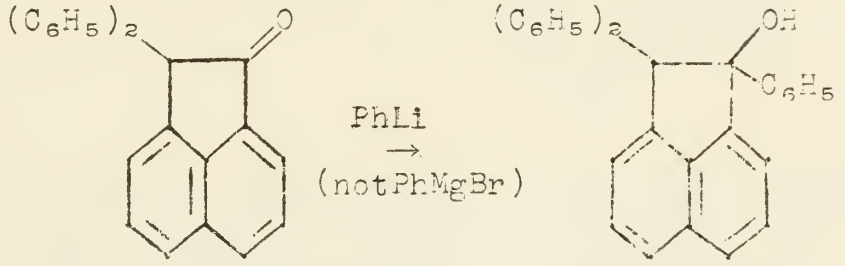


With phenylmagnesium bromide, none of the desired product was obtained. The smooth reaction of unsaturated dicarboxylic esters of the type $ROOCCH_2(CH=CH)nCH_2COOR$ with phenyl lithium makes possible the preparation of ω,ω'-tetraphenylpolyenes in excellent yields. For example tetraphenylhexatriene:

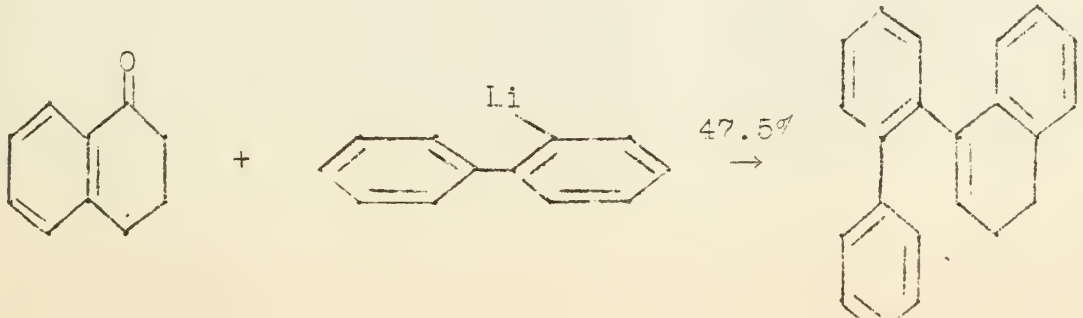
$$C_2H_5OOCCH_2CH=CHCH_2COOC_2H_5 \xrightarrow[75\%]{PhLi} (C_6H_5)_2CCH_2CH=CHCH_2C(C_6H_5)_2 \xrightarrow{95\%}$$

$$(C_6H_5)_2C=CHCH=CHCH=C(C_6H_5)_2$$

Organolithium compounds are very useful for treating carbonyl compounds which will not react with Grignard reagents because of steric hindrance.

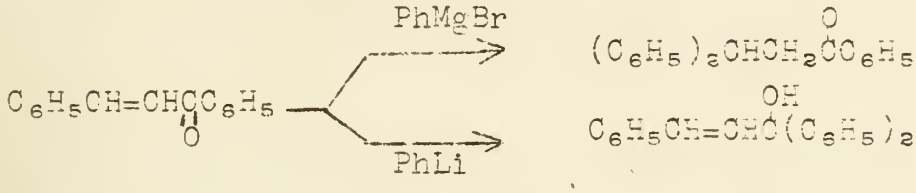


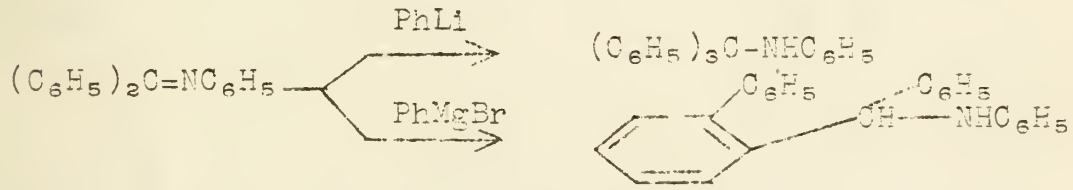
Another example is the addition of o-phenylphenyllithium to α-tetralone; the corresponding Grignard would only produce enolization.[12]



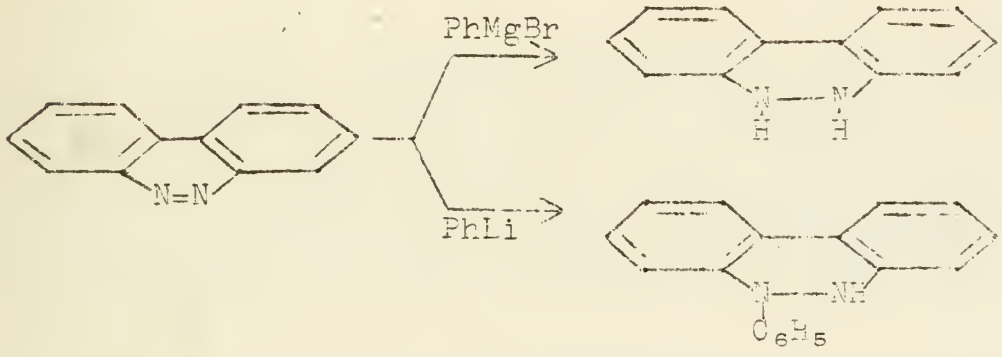
Wittig[1] says that phenyllithium is the most sensitive reagent for the detection of the carbonyl group that is available at the present time.

In general, lithium compounds have a much greater tendency to add 1,2 to a conjugated system than do Grignard reagents. Two examples are given below.

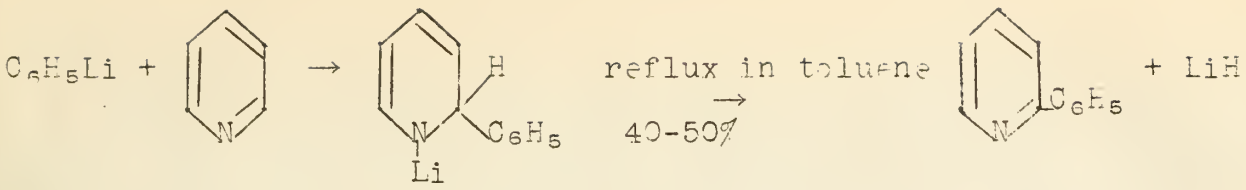




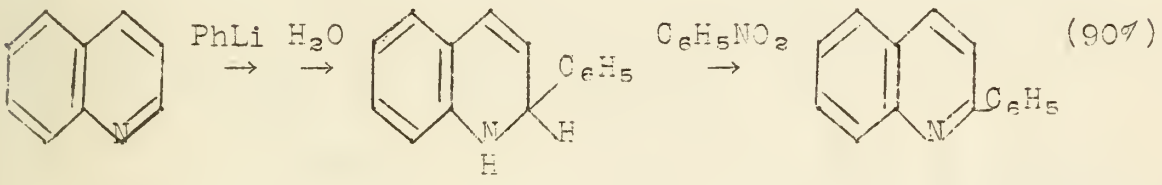
Also as a general rule, phenyllithium is less likely to act as a reducing agent than are Grignard reagents.

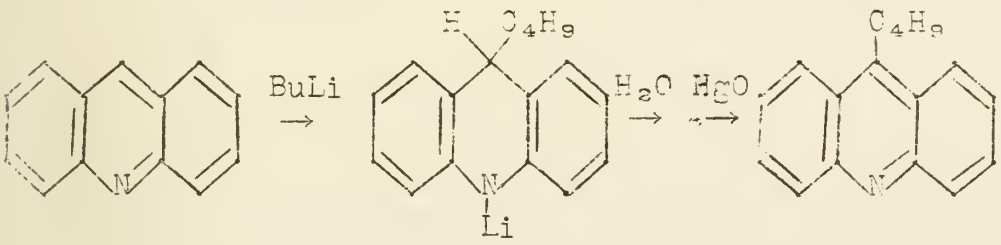


Another result of the higher reactivity of lithium alkyls and aryls as compared to magnesium compounds is that they react much more readily with =C=N- compounds. Ziegler and Zeiser[9] have shown that pyridine, quinoline, isoquinoline, and acridine react vigorously with lithium alkyls and aryls at room temperature. On hydrolysis the adduct give the substituted dihydro-product, which can be treated with a dehydrogenating agent such as nitrobenzene to give the alkylated or arylated pyridine homolog. The same result may be obtained by heating the adduct in a sealed tube to eliminate lithium hydride, or as Walters and McElvain[13] have shown by refluxing a solution of the adduct in toluene. An example of the use of the reaction is given in the Organic Syntheses[14] preparation of 2-phenylpyridine.



The elimination of lithium hydride is said to be practical only in the case of pyridine derivatives. In the other cases excellent yields have been obtained by dehydrogenation





There have been numerous other syntheses carried out using lithium. It appears now that chemists have realized that lithium is easy to work with and that no special apparatus is required, its uses will be still further extended. Even now it is difficult to find a journal without lithium mentioned in it someplace, whereas as recently as ten years ago it was a novelty. Wittig has predicted that within the next ten years lithium will have become almost as important a reagent as magnesium in organic chemistry.

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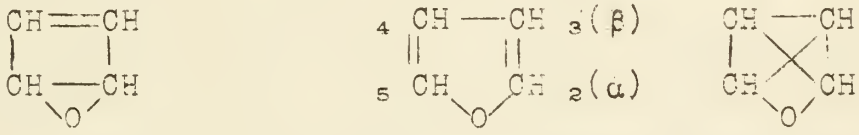
THE CHEMICAL NATURE AND REACTIONS OF FURAN

Introduction

Furan is an unsaturated compound of formula C_4H_4O, and has the structure of a heterocyclic ring with four carbon atoms and an oxygen atom. The longest known compound of the furan series is pyromucic acid, which is 2-furancarboxylic acid or α-furoic acid. It was discovered by Scheele in 1780, in the products of dry distillation of mucic acid. The corresponding aldehyde, furfural, was discovered in 1832 by Dobereiner during the oxidation of sugar with dilute sulfuric acid and manganese oxide. The parent compound was first prepared in 1870 by Limpricht, by heating barium furoate with sodium hydroxide. Limpricht erroneously believed that furan and its derivatives were derivatives of a cyclobutadiene structure, but Baeyer in 1877 showed that furan could only be an unsaturated cyclic ether, and that three possible structures might be written:



I II III

The structure most commonly used today is II, which is in accord with many of the reactions of the furan compounds, as well as with the synthesis of the furan ring itself; there is, however, good reason for believing that furan cannot be represented by a single structural formula, but rather that it is an equilibrium mixture of several structures. A resonating structure involving an unsaturated oxygen atom is indicated in several reactions.

The derivatives of furan have properties of two different types. In one respect, they closely resemble the corresponding benzenoid compounds; this type of property is greatly enhanced by the presence of negative substituents on the ring. Thus, furfural and furoic acid exhibit properties which are quite similar to benzaldehyde and benzoic acid, respectively. The aromaticity of furan compounds has been the subject of some discussion in the literature. Gilman has ascribed to α-substituted furans "supersromatic" properties, on the basis of a number of so-called typical aromatic reactions which occur preferentially in the furan nucleus of compounds which contain both the phenyl and furyl groups. These reactions were the selective cleavage of the organo-lead compounds, the preferential nitration, sulfonation, bromination, and Friedel-Crafts reaction in the furan nucleus in furyl phenyl ketone, and the reaction of furan with alkali aryls and alkyls. On the other hand, there are many reactions in which furan derivatives exhibit to a greater extent than the benzenoid compounds an unsaturated nature. This is illustrated by the addition of halogens, by the ease of hydrolysis of the ring, by the fact that furan and its simple derivatives take part in the Diels-Alder reaction, form definite preliminary addition products in halogenation and nitration reactions, by the fact that the α-furfuryl group undergoes certain allylic rearrangements which are not found in the benzene series, and by the fact that the simple amines of furan possess only to a limited extent

the properties most typical of the aromatic amines. These aspects of its behavior indicate that furan possesses a degree of unsaturation less than that of a 1,3-diene, but greater than that of benzene; hence, it appears to be weakly aromatic rather than superaromatic. The ready tendency of furan devatives to polymerize is further indication of their unsaturation.

Substitution Reactions of Furan

As has previously been indicated, furan undergoes most of the substitution reactions typical of benzene compounds. The question of the orientation of the incoming group has presented a rather difficult problem, and is not yet completely answered although a great amount of research has elucidated some rather clear cut orientation rules for the α-substituted furans. In an article in Chemistry Reviews, Gilman sums up the evidence as follows:

(1) Direct nuclear substitution of furan leads to the formation of mono-α-substituted furans, and no isomeric β-substituted furan is formed

(2) Direct nuclear substitution of a mono-α-substituted furan gives an α,α-disubstituted furan, apparently to the exclusion of any isomeric α,β-disubstituted furan.

(3) Direct nuclear substitution of an α,α-disubstituted furan yields generally but one α,α,β-trisubstituted furan. When the α-substituents are unlike, the β-position assumed by the third substituent is determined largely by the nature of the groups already present, and probably in essential accordance with the directing influence of groups in the benzene series. For example, 5-bromo-2-furoic acid on sulfonation yields 5-bromo-4-sulfo-2-furoic acid, and not 5-bromo-3-sulfo-2-furoic acid.

(4) Direct nuclear substitution of mono-β-substituted furans, now accessible by indirect means, involves the replacement of an α-hydrogen. Here again, the apparent absence of isomers is noteworthy, for despite the availability of two α-positions, only one α,β-disubstituted furan results.

The α-substituted derivatives are the ones of the greatest interest, since they not only are obtained exclusively in the substitution reactions, but also nearly all of the naturally occurring furans are the α-derivatives. Also, the products obtained from the commercially available furfural are the α-derivatives. The proof of the structure of furfural is due to Baeyer and Marckwald, who independently and by slightly different reactions, converted furfural to pimelic acid. Furfural and most of the simple mono-α-substituted furans are interconvertible by reliable reactions, thus enabling one to determine definitely the orientation of a particular compound.

Bromination.--The earliest work on halogenation of furan compounds was done by Malaguti in 1837. He found that treatment of ethyl furoate with dry chlorine gas yielded ethyl tetrachlorofurcate; Schmelz and Beilstein, a number of years later, found that treatment of furoic acid with the aqueous halogens gave mucobromic and mucochloric acids, while Limpricht, using aqueous bromine under somewhat more stringent conditions, obtained both fumaric acid and its half aldehyde from

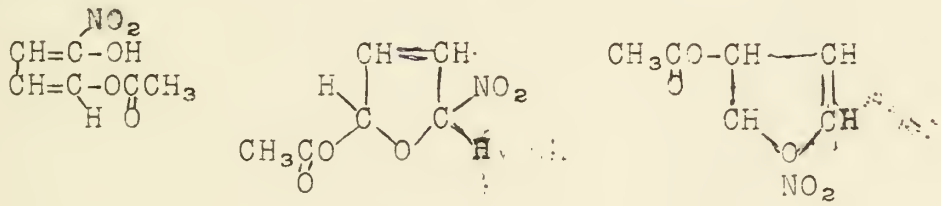
furoic acid, but reported that no reaction occurred with dry bromine. Alcoholic potassium hydroxide on the tetrabromo compound gives dibromofuroic acid, of which there are two isomers, and further treatment of either of these isomers with dilute ammonia and zinc dust yields the β-bromofuroic acid. The α-bromofuroic acid is obtained, of course, by direct bromination. Whittaker has found that the optimum conditions for the direct bromination are the use of one molecular equivalent of phosphorous to three molecular equivalents of the furoic acid, and the use of chloroform or carbon tetrachloride as solvent. The effect of the solvent is interesting; the maximum yields obtainable are 40-45 percent, while under identical conditions using acetone, ethanol, or pyridine as solvent, the yields are negligible. The maximum yield of 45 percent was obtained by bromination in carbon tetrachloride with antimony trichloride as a catalyst; while with no catalyst and either chloroform or carbon tetrachloride as solvent, the yields are 38-40 percent. The contrast to the conditions with benzene brominations should be noted. In the furan series, bromine substitution will occur in yields of 75-100 percent of the maximum obtainable in the absence of a halogen-carrier catalyst. The bromination of other furan derivatives may be carried out under similar conditions.

The mechanism of the bromination reaction is not clearly understood, but it is certain that it proceeds through an intermediate addition product; in several cases these addition compounds have been isolated. The nature of the addition compound is not definitely known; several possibilities might be entertained, depending on the particular structure for the furan ring which was selected. Rather good evidence indicates that it is of the nature of an oxonium compound.

Nitration.--Due probably to the fact that most of the furans are quite sensitive to strong oxidizing agents, the literature on the nitration of furans has been very brief. Klinkhardt, in 1882, obtained 5-nitro-2-furoic acid by treating pyromucic acid with nitric acid. Six years later, Hill and coworkers obtained several nitro derivatives by treating furoic acid first with sulfuric acid, and then with nitric acid. The first direct nitration of furan and its derivatives was carried out by Marquis, by adding the furan to a mixture of acetic anhydride and fuming nitric acid, maintained at -5°. The nitro derivative was not obtained directly, but a rather unstable oil, which could be converted to the nitro derivative by treatment with pyridine. This has been found to be a nearly general type of behavior with furan derivatives; the direct nitration yields an intermediate, which on treatment with pyridine, or any mild base, loses a molecule of acetic acid, and gives the nuclear nitro derivative. As with other substitution reactions, nitration gives the α-derivative if an α-position is unoccupied, or even if an α-position is occupied by an easily replaceable group such as the carboxyl or sulfonic. Rinkes has conclusively established the structures of the simple nitro compounds. Nearly all the simple furans have been nitrated. All except furoic acid itself and furylacrylic acid give the intermediates, and these two compounds give the nitro derivative directly; ethyl 5-acetamino-2-furoate, however, on nitration provides part of the product directly as the nitro compound, while more of the nitro compound may be obtained by treating the intermediate, which is also obtained, with a weak base.

The mechanism of the nitration reaction is even more obscure than in the case of the bromination. The most satisfactory nitrating agents are the previously mentioned acetic anhydride-fuming nitric acid mixture, and a mixture of cupric nitrate with three times its weight of acetic anhydride, the latter being by far the more satisfactory of the two. The active reagent in either case is assumed to be acetyl nitrate, since the intermediates, when obtained, have a composition which corresponds to the addition of one molecule of acetyl nitrate to the furan molecule. However, furfural diacetate, which is satisfactorily nitrated by the fuming nitric-acetic anhydride mixture, is not nitrated by pure acetyl nitrate in carbon tetrachloride, and ethyl furoate, when nitrated by an equimolecular mixture of acetic anhydride and nitric acid in an indifferent solvent, gives only a trace of a nitro compound. Inspection of the literature reveals that in two cases a crystalline intermediate was isolated from the oil which is directly obtained. These crystalline compounds (from methyl furoate and furfural diacetate) were converted quantitatively to the corresponding nitro compounds, while the oils were converted only in yields of 40-42 percent to the nitro compounds. The conclusion from the data at hand would indicate that there are two intermediate products formed, one of which is convertible to the nuclear nitro compound, the other not.

The method of addition of the reagent is not known, since the structure of the intermediate is unknown. Marquis found that the intermediate from furan, upon treatment with water, eliminated nitrous acid, and gave maleic dialdehyde. He postulated that the intermediate was an open-chain, unsaturated enol of the structure IV. Freuer and Johnson, however, found that the <u>crystalline</u> intermediate from methyl furoate gave no enol color with ferric chloride, no decolorization of bromine-carbon tetrachloride solution, but did show the characteristic reducing action of aldehydes. These workers concluded that the intermediate was formed by the 1,4-addition of nitric acid ($HO-NO_2$) to the furan ring, followed by acetylation of the hydroxyl group, giving the closed chain structure V. It might be pointed out here that nitration will occur under conditions where there is no free nitric acid. Still another suggestion as to the structure of the intermediate is that of Gilman, who postulates a compound of the



IV V VI

oxonium type (VI), formed by the addition of a molecule of acetyl nitrate to a conjugated system set up by the unsaturation emerging from the oxygen and one of the ethylenic linkages. This compound, on the elimination of a molecule of acetic acid from the molecule, rearranges to the carbon-nitrogen derivative. The fact that the intermediate oil, after thorough hydrogenation in the presence of platinum black, still yields a very significant amount of ethyl

5-nitro-2-furoate is a strong argument for structure VI.

Other Substitution Reactions.--As has been mentioned before, the Friedel-Crafts reaction, and the substitution of alkali metals in the furan ring will take place. Although furan itself is not sulfonated, the simple derivatives are. The Gattermen aldehyde synthesis will work with some simple furans, and chloromercuration is a general reaction of furan derivatives. The chloromercuri group may be replaced by iodine, giving a compound which readily reacts with magnesium, yielding the Grignard reagent. This Grignard reagent reacts normally, as, incidentally, does the Grignard reagent from furfuryl bromide.

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