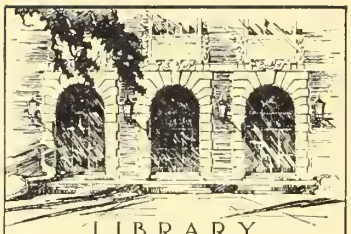


ORGANIC SEMINAR ABSTRACTS

I SEMESTER 1951-52

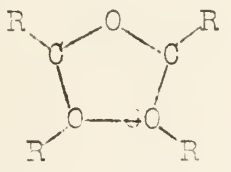
# SEMINAR TOPICS

CHEMISTRY 435 I SEMESTER 1951-52

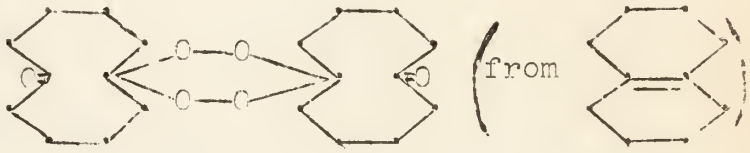
# OZONOLYSIS

Reported by D. Y. Curtin September 21, 1951

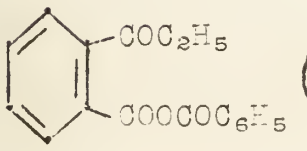
The reaction of ozone upon an olefin ordinarily has been represented as yielding an ozonide, of the type indicated by formula I, which upon suitable treatment (hydrolysis and oxidation or reduction) is converted to carbonyl compounds or acids. The ozonides have been isolated and analyzed only in rare instances, however. In recent work by Rudolf Criegee and his associates at Karlsruke (Techn. Hochschule), described by Criegee* at the Symposium on Reaction Mechanisms at the 120th meeting of the American Chemical Society, a number of substances previously described as ozonides have been reinvestigated. Most such compounds proved not to have structures of the type represented by I, but rather to be isomeric, dimeric or polymeric. Some examples of the products obtained by Criegee are given in structures II to IV.

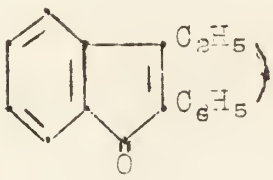


I

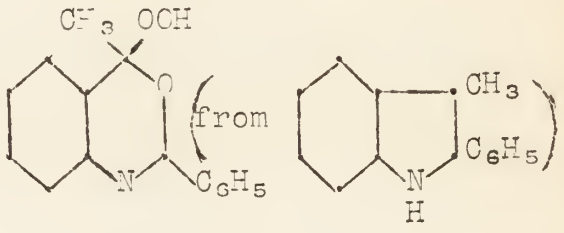


II



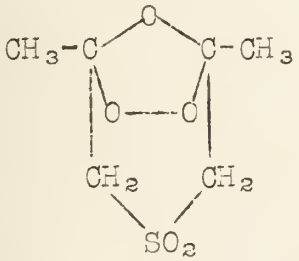


III

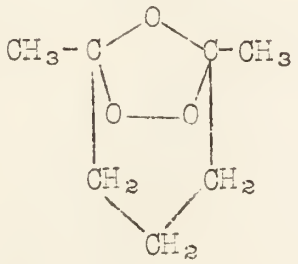


IV

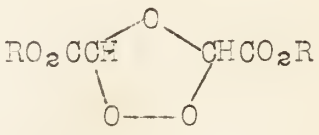
A few olefins gave true ozonides. Examples are shown in structures V to VII.



V



VI

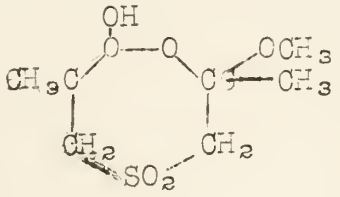


VII

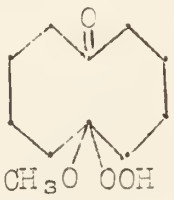
*Abstracts of Papers, 120th Meeting of the American Chemical Society New York, 1951, P.22M.

The ozonide VI, obtained from 1,2-dimethylcyclopentene, was also prepared from its cleavage product, 2,6-heptandione, by the action of hydrogen peroxide and phosphorus pentoxide. It is of particular interest that a similar simple ozonide was not obtained from 1,2-dimethylcyclohexene and that the ozonide VII was obtained from either the maleic or fumaric ester. The configuration of the ozonide VII is not known at present.

The simple ozonides and peroxides mentioned above were formed only in inert solvents like chloroform and petroleum ether. The use of hydroxylic solvents resulted in the formation of products of reaction with the solvents. For example, ozonization in methanol gave VII, rather than V, and IX rather than II.



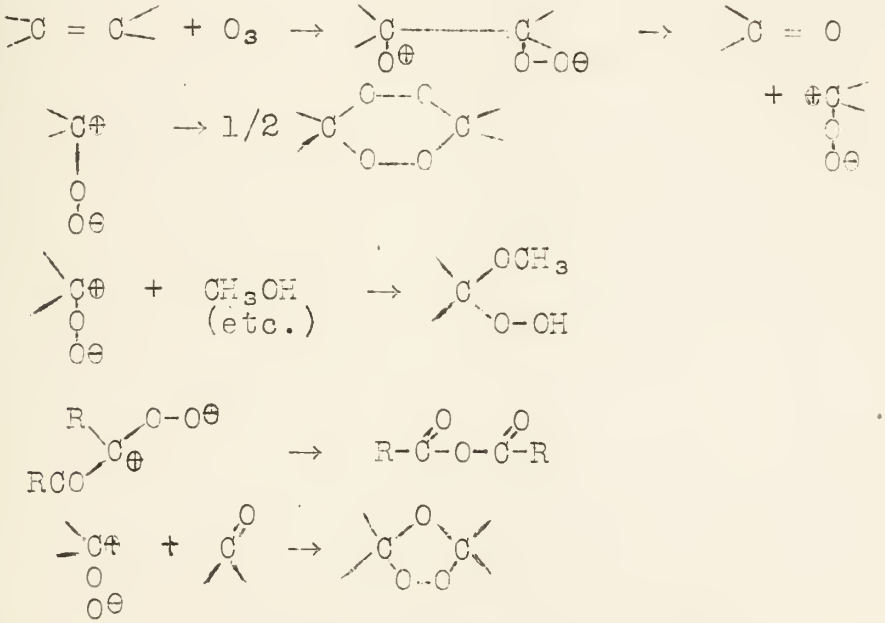
VIII



IX

The compound VIII was <u>not</u> obtained from the ozonide V by treatment with methanol. Thus it appears that the ozonide and the solvolysis product arise from a common intermediate.

Criegee believes that the following mechanism will account for the reactions observed.



In this representation the ozonide is formed by recombination of the fragments of the scission. In the ozonization of a cyclopentene the reacting functions are in close proximity and the product (containing 5-,6-and7-membered rings) is not highly strained. The ozonization of a cyclohexene does not produce a simple ozonide undoubtedly because such a product, containing 5,7-and 8-membered rings, would be highly strained.

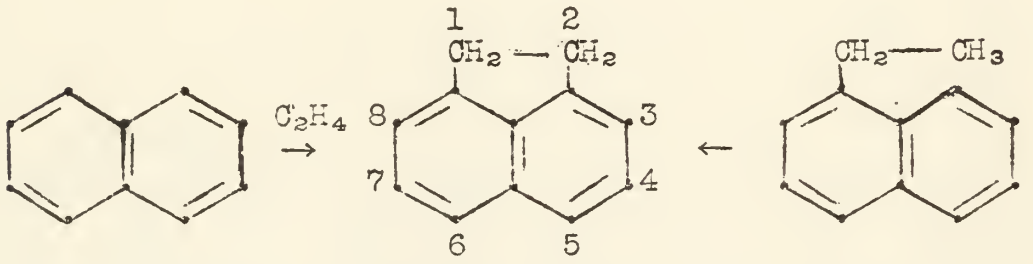
## ACKNOWLEDGEMENT

The speaker is indebted to Professor H. R. Snyder for the preparation of this abstract.

# THE FORMATION OF TWO-CARBON PERI BRIDGES IN NAPHTHALENE

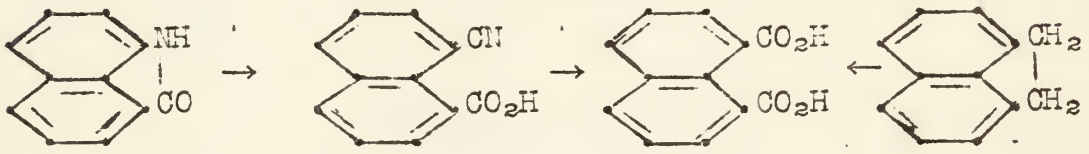
Reported by R. C. Fuson September 21, 1951

The formation of a peri bridge in napthalene was first acheived in 1866 when Berthelot prepared acenaphthene by passing a mixture of naphthalene and ethylene through a hot tube.[1]




Later acenaphthene was made by the pyrolysis of 1-ethylnaphthalene and was found in coal tar, which is its chief source.

The structure of acenaphthene was established by relating it to naphtholactam (I) by the following sequence of changes.[2]



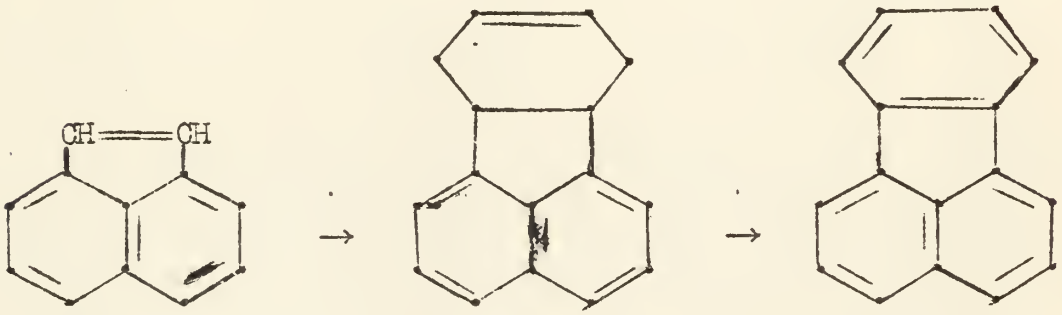

I

The bond distance between carbon atoms 1 and 2 in acenaphthene has been shown to be 1.8Å; thus the central bond of the bridge is stretched beyond the normal distance (1.54 Å).[3] Substitution occurs more readily than in naphthalene, preferably at the 5 and 6 positions. In particular, diacylation involving these positions occurs readily.

## Acenaphthylene

When acenaphthene vapors are passed through a column packed with a suitable catalyst and maintained at an elevated temperature, dehydrogenation occurs and acenaphthylene is produced; the yield may be as high as 90%.[4] The unsaturated hydrocarbon may be prepared also from 1-acetoxyacenaphthene by pyrolysis or by treatment with hydrogen bromide and pyridine in benzene solution.[5]

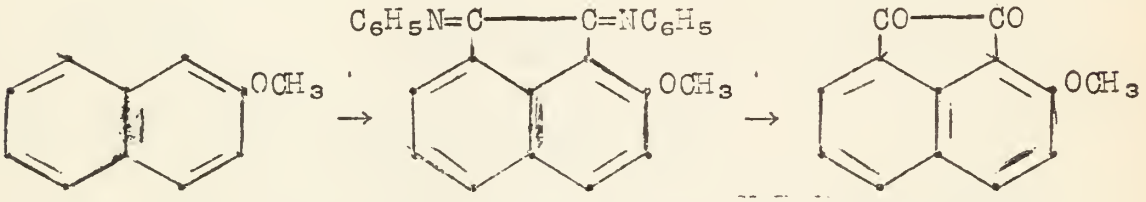
The resonance energy of acenaphthylene (92 kcal/mole) is greater than that of naphthalene (75 kcal/mole).[6] The resonance energy ascribed to the olefinic bridge (17 kcal/mole) is not significantly different from that of the ethylenic function of stilbene. The reactions of the two compounds reflect this similarity. In the Diels-Alder reaction acenaphthylene appears to be more reactive than stilbene. Advantage has been taken of this reactivity in the synthesis of fluoranthene (II).[5]




II

Acenaphthenequinone

Certain 2-naphthyl ethers react with oxalyl chloride to afford the corresponding acenaphthenequinone derivatives. The yields are greatly improved when diphenylimido chloride is employed as the acylating agent.[7] With 2-methoxynaphthalene the yield may be as high as 75%.



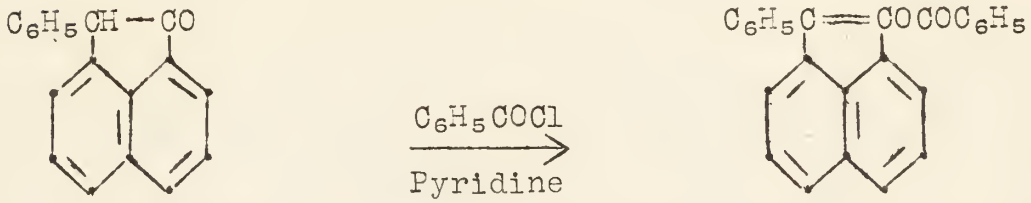

This type of reaction fails with acenaphthene; in fact, no two-atom bridge had ever been introduced at the 5 and 6 positions prior to the work of Kloetzel and Chubb[8] to be discussed later.

Acenaphthenone

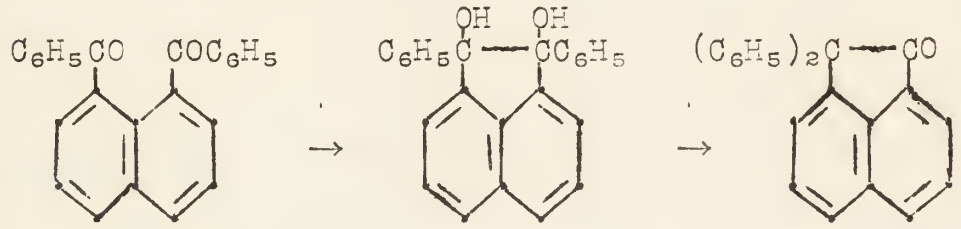
Formation of a two-carbon peri bridge occurs when 1-napnthylacetyl chloride is treated with aluminum chloride in nitrobenzene, the product being acenaphthenone.[9]

5-Bromo-[10] 2-phenyl-,[11] and 2,2-diphenyl-1-acenaphthenone[12] have been made in a similar way.

2-Phenyl-1-acenaphthenone forms a colored benzoate which is believed to be the enol ester. All acenaphthylenes are colored. However, 2-phenyl-1-acenaphthenone is colorless and reacts additively with phenylmagnesuim bromide.[11]

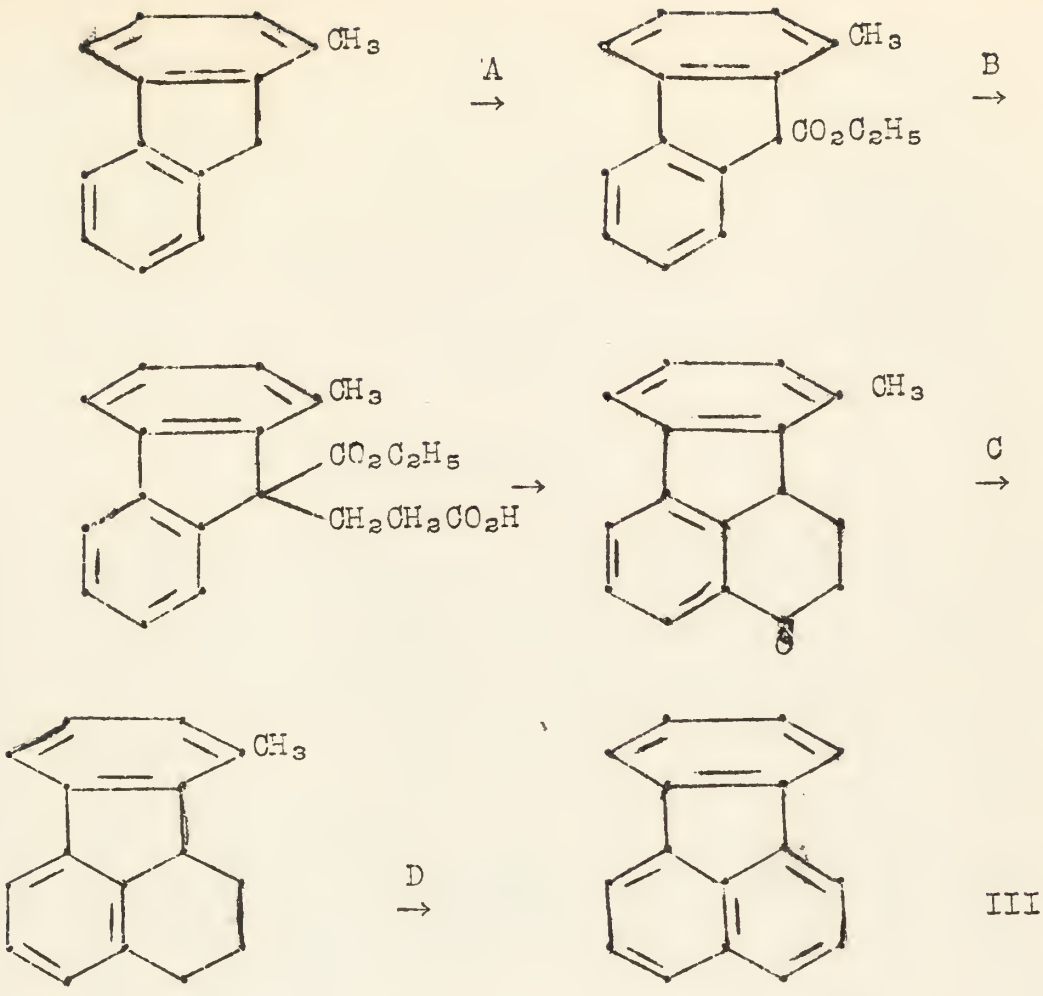



An indirect route to acenaphthenones is by rearrangement of the pinacols formed by condensing acenaphthenequinones with grignard reagents. The rearrangement is brought about by treating the glycol with a few drops of sulfuric acid in boiling acetic acid.[13] The pinacol from acenaphthenequinone and the phenyl Grignard reagent, formed in 81% yield, has the <u>trans</u> configuration. The <u>cis</u> form is obtained in 95% yield by reducing 1,8-dibenzoylnaphthalene with the binary mixture, mg + $mgI_2$. The <u>cis</u> form rearranges six times as fast as the <u>trans</u> isomer.[13] The reduction, it may be noted, involves the formation of a two-carbon <u>peri</u> bridge.

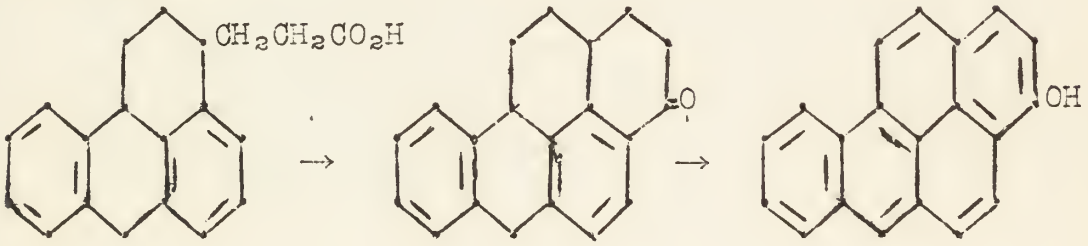



<u>The Use of Hydroaromatic Intermediates</u>

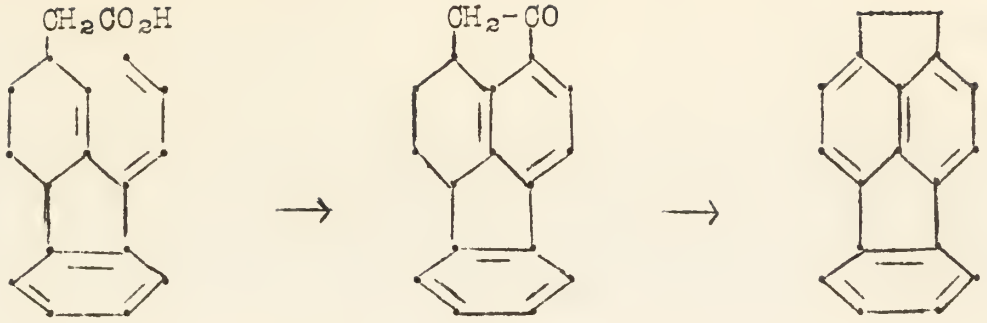
As might be expected the formation of <u>peri</u> bridges may be accomplished more readily if the ring closure involves a hydroaromatic system, which can be dehydrogenated subsequently. The synthesis of 7-methylfluoranthene (III) from 1-methylfluorene is an example.[5]




A similar example is involved in the following synthesis.[14]




The only fully authenticated example of a naphthalene ring with two two-carbon *peri* bridges, already alluded to, was made by establishing the second bridge while one of the central rings was hydroaromatic.[8]

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# POLYALKYLENE SULFIDES

Reported by C. S. Marvel September 28, 1951

The addition of a mercaptan to an olefin when initiated by free radicals is a rapid, quantitative reaction which produces a single non-Markowinkoff product. Hence, the reaction has the requisites for a polymer forming reaction, and it has been found that dimercaptans will add to non-conjugated diolefins to yield high molecular weight polyalkylene sulfides.

$$X\,HS(CH_2)_nSH + X.CH_2{=}CH{-}(CH_2)_{n-4}CH_2{-}CH_2 \longrightarrow \left[S{-}(CH_2)_n\right]_2X$$

Coffman (1) has prepared low molecular weight polymers from several dimercaptans with butadiene and vinylcyclohexene under the influence of ultraviolet light but he did not succeed in getting high molecular weight materials. His choice of olefins was responsible for the unsatisfactory results.

Chambers (2) working in this laboratory was able to get polymers of moderate molecular weights from a wide variety of dimercaptans with biallyl in cyclohexane solution when he initiated the reaction with ultraviolet light. The polymers were formed by non-Markownikoff addition since there were no methyl side chains in the polymers. Synthetic polymers made from 2,5-dibromohexane and sodium hexamethylenedimercaptide did show infrared absorption characteristics of such methyl side chains.

Others have applied emulsion polymerization techniques to the reaction and have been able to increase the size of the polymers produced to about 100,000 in molecular weight. Aldrich (3) demonstrated the reaction goes best in low pH, and Nowlin (4) showed the best results were obtained at a pH of 3.5. Markhart (5) showed that the reaction went with great rapidity under the best conditions. In five minutes at 30°, 95% of the mercaptan groups disappeared and a 100% yield of a polymer with a molecular weight between 40,000 and 50,000 was produced. Then the emulsion was agitated for another 18 hours, mercaptan groups were entirely absent, and a polymer of about 100,000 molecular weight was formed. The last reaction may be disulfide formation. This remains to be established.

When butadiene-1,3 is treated with hexamethylenedithiol under conditions which give polymers with biallyl (6) only the dicrotyl ether of hexamethylenedithiol was isolated (6). This result combined with the failure of the reaction with diallyl ether and the lack of polymerization of allyl mercaptan, indicate the double bond $\beta$-$\gamma$ to a S or O atom is not active in the reaction.

The polyalkylene sulfides obtained from symmetrical monomers are highly crystalline polymers and products with a molecular

weight of 20,000 melt sharply. If unsymmetrical units are present, the polymers are glassy even at very low temperatures. By using mixtures of monomers rubbery products can be produced (7). With aromatic dithiols high melting oriented polymers are with fiber forming properties have been obtained (8).

The reaction seems to be general for aliphatic and aromatic dithiols and for non-conjugated diolefins except those having O or S in the β- position to the double bond. The double bonds need not be terminal.

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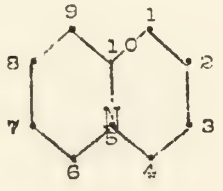
# STEREOCHEMISTRY OF THE LUPIN ALKALOIDS

Reported by Nelson J. Leonard September 28, 1951

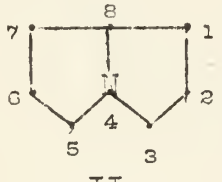
The "lupin alkaloids" are found in a wide variety of plants and small trees, such as broom, lupin, gorse, and laburnum, which are used diversely in gardens, for fodder, and as sand-binders. The alkaloids as a group are toxic, but as individuals find some use in veterinary medicine and in insecticide preparations. Chemical similarity rather than plant distribution links these alkaloids, since most of them contain--in actual or modified form--the quinolizidine ring structure (I). Structure determination,




I

total synthesis, and understanding of the intricate stereochemistry of the lupin alkaloids are successive goals which are being acheived at this time of reporting.

Perhaps it would be interesting in this discussion first to dispose of an exception among the lupin alkaloids--one that possesses the pyrrolizidine nucleus (II) rather than the ring-homologous quinolizidine nucleus (I). The alkaloid is laburnine, isolated by

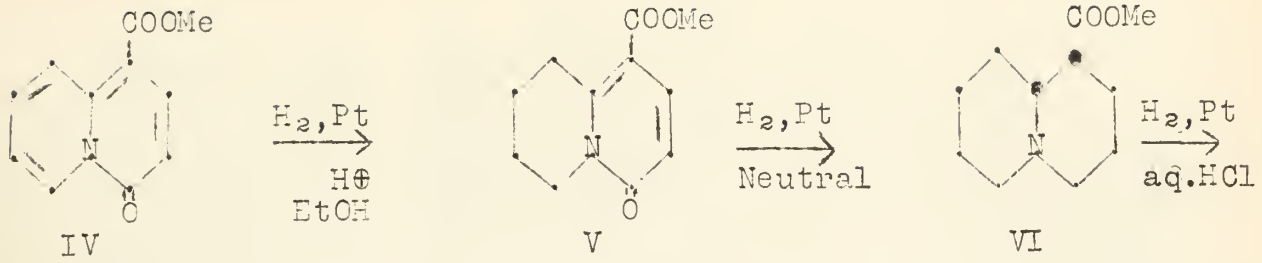



II

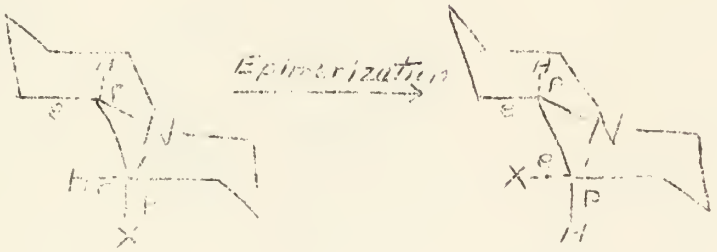

III

Galinovsky, Goldberger, and Pohm[1] from the seeds of *Cytisus laburnum* L., and shown to be one of the four possible optically active forms of 1-hydroxymethylpyrrolizidine. The most unusual feature of laburnine is that it belongs to the lupin family due to its source and to the *Senecio* alkaloid family[2] due to its constitution as a derivative of pyrrolizidine (II). Another unusual feature of laburnine is that it was synthesized by Felley[3] in this Laboratory prior to the knowledge of its natural occurrence as an alkaloid, The stereochemical structure of (*d*-)laburnine was also established, as represented in III, as one of the enantiomorphs with the hydrogens on $C_1$ and $C_8$ in the *trans* relation.[3]

Our knowledge of the stereochemistry of the lupin alkaloid, lupinine (VIII), has been advanced by a recent synthesis[4] of the racemic form corresponding to *dl*-lupinine. Since this synthetic route (IV→VIII) utilized hydrogenation over platinum in neutral medium to establish the asymmetric centers at $C_1$ and $C_{10}$ and since a homogeneous product consisting of only one of the diastereoisomeric racemates was obtained, the structure of (*l*-)lupinine can reasonably be assigned as one of the enantiomorphs with the



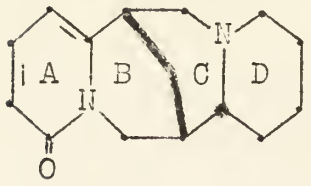

hydrogens on $C_1$ and $C_{10}$ in the cis relation (VIII). This assignment is in accord with the observed epimerization of VII by sodium methoxide and VIII by sodium, which would correspond to a shift from 1,10-polar, equatorial bonding to the preferred 1,10-diequatorial bonding.[5]



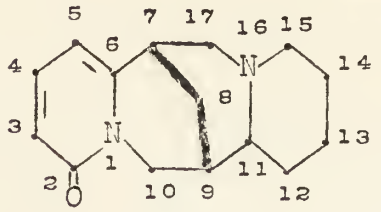

VII or VIII VIIa or VIIIa

The $C_{15}$ lupin alkaloids have been subjected to careful stereochemical analysis with the result that structures have now been assigned by Marion and Leonard[6] to the known alkaloids of this family, and structures for the missing members have been predicted. The steric interrelations within the family are shown in Fig. 1, as established from stereospecific hydrogenation reactions and certain conversions of the oxygenated derivatives of sparteine. The predicted structure of d-isosparteine as the cis-cis $C_{15}H_{26}N_2$ isomer has just had beautiful confirmation by x-ray analysis of crystalline d-isosparteine hydrate.[7]

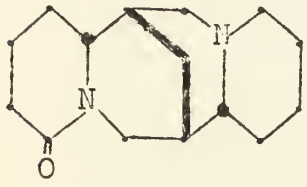
Fig. 1. Stereochemical Family - $C_{15}$ Lupin Alkaloids



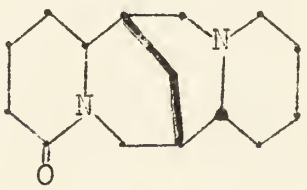

blank - cis
Thermopsine




blank - trans
Anagyrine

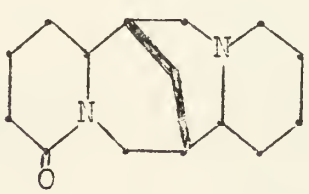


cis - cis
α-Isolupanine



trans - cis
?

cis - trans
Lupanine



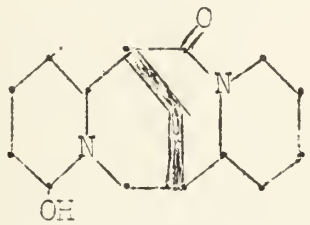
trans - trans
?

cis - cis
α-Isosparteine

cis - trans
Sparteine

trans - trans
β-Isosparteine

The total synthesis of dl-sparteine has been announced from no fewer than five laboratories, but the simplest method of preparation is that developed by Beyler in this Laboratory: a two-step process starting with ethyl 2-pyridylacetate. The total synthesis of dl-α-isosparteine was also effected in this Laboratory,[9] since this isomer accompanied sparteine in the product resulting from the second, or reductive-cyclization step. Following the total synthesis of α-isosparteine, the natural occurrence of l-α-isosparteine in Lupinus caudatus Kellogg was definitely established.[10] Most recently, the hitherto missing β-isosparteine has been obtained,[7] thus completing the stereochemical picture of the $C_{15}H_{16}N_2$ bases. The new lupin alkaloid, sericeine, from Lupinus sericeus,[11] was shown to have the formula $C_{15}H_{24}N_2O_2$ and a structure compatible with IX (stereochemistry indicated). The alkaloid has been converted to a $C_{15}H_{26}N_2$ base (X) by lithium aluminum hydride reduction. Since the latter is neither sparteine nor α-isosparteine, but can be converted to sparteine (XI) by dehydrogenation ($-1H_2$) with mercuric acetate, followed by catalytic hydrogenation, it must be β-isosparteine,[7] which has the trans-trans structure.[6]



$C_{15}H_{24}N_2O_2$

IX

$LiAlH_4$

$C_{15}H_{26}N_2$

X

$-H_2$

$2Hg(OAc)_2$

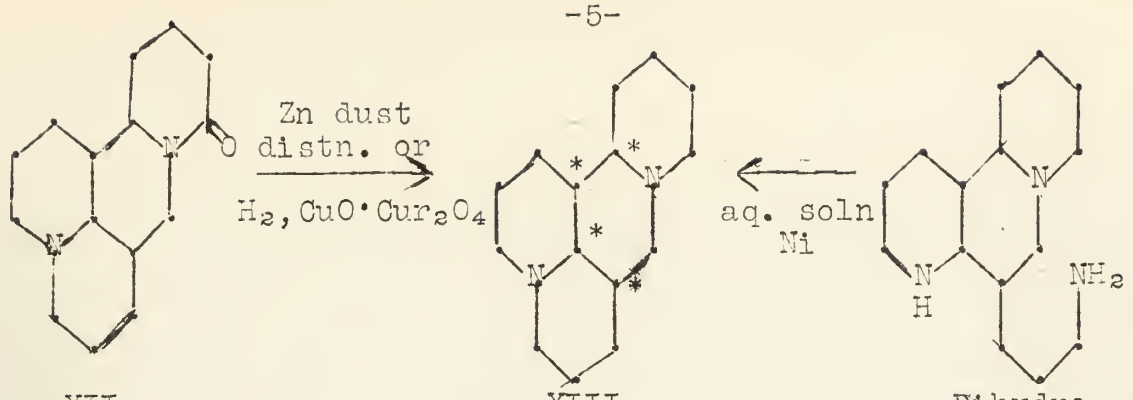
(not isolated)

$+H_2$

$C_{15}H_{26}N_2$

XI

In some quarters, the lupin alkaloid, matrine ($C_{15}H_{24}N_2O$), has been regarded as having the possible constitution required by one of the as yet unknown trans-cis or trans-trans $C_{15}H_{24}N_2O$ structures (see Fig. 1), although the accumulated evidence favors a different ring system.[12] Any doubt as to the ring structure of matrine (XII) has been dispelled by the brilliant synthesis by Schöpf and his coworkers [13] of matridine (XIII), the $C_{15}H_{26}N_2$ reduction product obtainable frim the alkaloid. The stereochemistry of matridine and matrine (XII and XIII each represent 16 optically active forms) remains to be determined.




XII XIII Dihydro-aldotripiperidein

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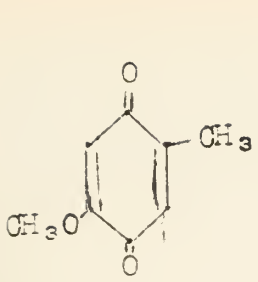
# A NEW TOTAL SYNTHESIS OF CORTISONE

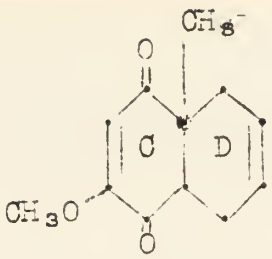
Reported by James M. Quinn October 5, 1951

In the spring of 1949 there was announced from the Mayo Clinic[1] the discovery that 17-hydroxy-11-dehydrocorticosterone; 3,11,20-triketo-17(β),21-dihydroxy-$\Delta^4$-pregnene; Kendall's Compound E; Wintersteiner's Compound F; Reichstein's Compound Fa; or cortisone(VI), one of the steroid hormones of the adrenal cortex gland, will rapidly relieve the symptoms of rheumatoid arthritis and perhaps other rheumatoid diseases. Since then great interest has arisen concerning the properties, isolation from nature and synthesis of this compound. However it does have some side effects and the results of its continued use are not fully known.[2,3,4] A seminar on the general nature and partial synthesis of cortisone has previously been given by Dr. Frank.[5]

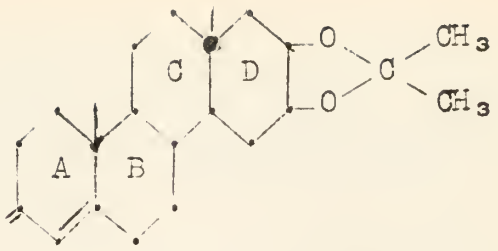
Recently there has been reported in the literature by Woodward, Taub and Sondheimer[6,7] a series of reactions which complete the total synthesis of cortisone. The reporting of these reactions is the topic of this seminar. The synthesis started by condensation of 5-methoxytoluquinone(I) with butadiene[6] in benzene to give cis-1,4-diketo-2-methoxy-4a,5,8,8a-hexahydronaphthalene(II). On acidification in basic aqueous dioxane under carefully controlled conditions this compound gave predominately the trans-isomer which was separated by seeding out with a crystal of the trans-isomer. Reduction with lithium aluminum hydride gave a dihydroxy compound which was acidified and treated with zinc and acetic anhydride which, followed by formylation and treatment with base, yielded a compound that was condensed with ethyl vinyl ketone in a Michael 1,4-Addition. There are two possible configurations but only the one in which the aldehyde group is above the plane of the rings is produced. Cyclization[8] by an aldol condensation with potassium t-butoxide in t-butanol and selective hydroxylation with osmium tetroxide in ether yielded a glycol. This glycol was converted to the acetonide by treating with acetone and dry hydrogen chloride. Selective hydrogenation in dry benzene with a palladium-strontium carbonate catalyst led to the corresponding αβ-unsaturated ketone. Solvents other than benzene led to a mixture of products. To block the 4-C position the ketone was treated with N-methyl aniline and ethyl acetate. The ketone with the α-position blocked was then condensed with acrylonitrile in the presence of Triton B in a t-butanol-benzene mixture and the product yielded a mixture of two isomers. This is the first mixture of isomers in the synthesis. Separation was easy as the α-form was a relatively high melting solid while the impure β-isomer, the most abundant of the two, was an oil. The β-isomer upon treatment with hot acetic anhydride and a trace of sodium acetate formed a β-enol lactone. Upon treatment with methylmagnesium iodide the lactone ring was opened. Base cyclization[9] gave dl-3-keto-16,17-dihydroxy-$\Delta^{4,9(11)}$-D-homoandrostadiene acetonide(III) in good yield. The action of periodic acid on (III) removed the acetonide group and cleaved ring D forming



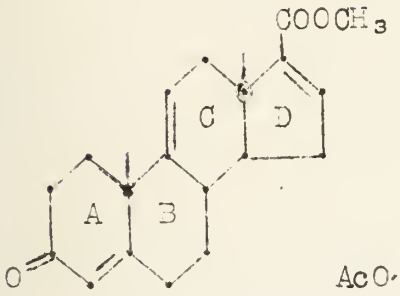
(I)



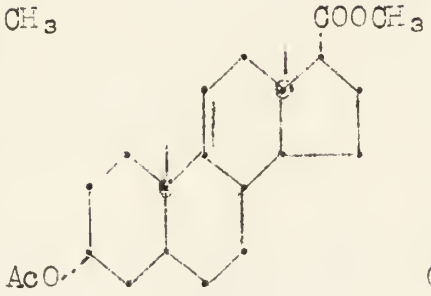
(II)



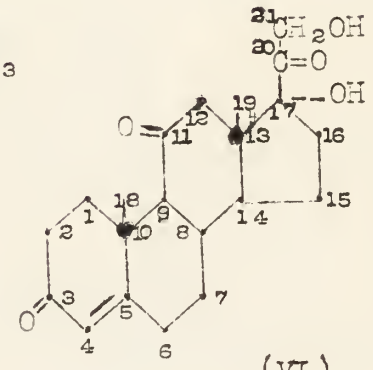
(III)



(IV)



(V)



(VI)

a dialdehyde. Upon treatment with hot aqueous dioxane, an internal aldol condensation occurred slowly due to the presence of the methyl group. This tetracyclic compound was oxidized with dichromate and then esterified with diazomethane forming methyl dl-keto-$\Delta^{4,9\,(11),16}$-etiocholatrienate(IV). Compound (IV) represents the second synthesis of a compound possessing the full hydroaromatic steroid nucleus of the correct stereochemical configuration. This racemate was resolved[7] by a four step process starting with a reduction by sodium borohydride and concentration of the precipitated complex was followed by an Oppenauer oxidation. The d-isomer was reduced by hydrogen over palladium on strontium carbonate in neutral medium and this crude hydrogenation product was then reduced further with sodium borohydride in ethanol. The resulting mixture of isomers was separated through precipitation of the β-isomer by digitonin leaving the desired α-isomer. Acetylation of the α-isomer then gave methyl 3(α)-acetoxy-$\Delta^{9\,(11)}$-etiocholenate(V).

At this point the synthetic work intersects the lines previously laid down in the extensive prior investigations by many groups on the partial synthesis, from natural sources, of cortisone(VI) and other cortical steroids. Heymann and Fieser[10,11] have recently converted the acetoxy-ester into an 11-keto compound by a series of five steps. These included treatment with perbenzoic acid, dichromate oxidation, addition of hydrogen bromide and reduction. This compound was converted to pregnane-3(α),21-diol-11,20-dione-21-acetate[12] by catalytic hydrogenation and acetylation[13]

followed by the diazo-ketone method in five steps. A 17(α)-hydroxy group was introduced[14] by another series of five steps. Finally the $\Delta^4$-double bond was introduced[15] in four steps which completed the synthesis of cortisone(VI). The entire synthesis comprises a total of approximately forty-five steps.

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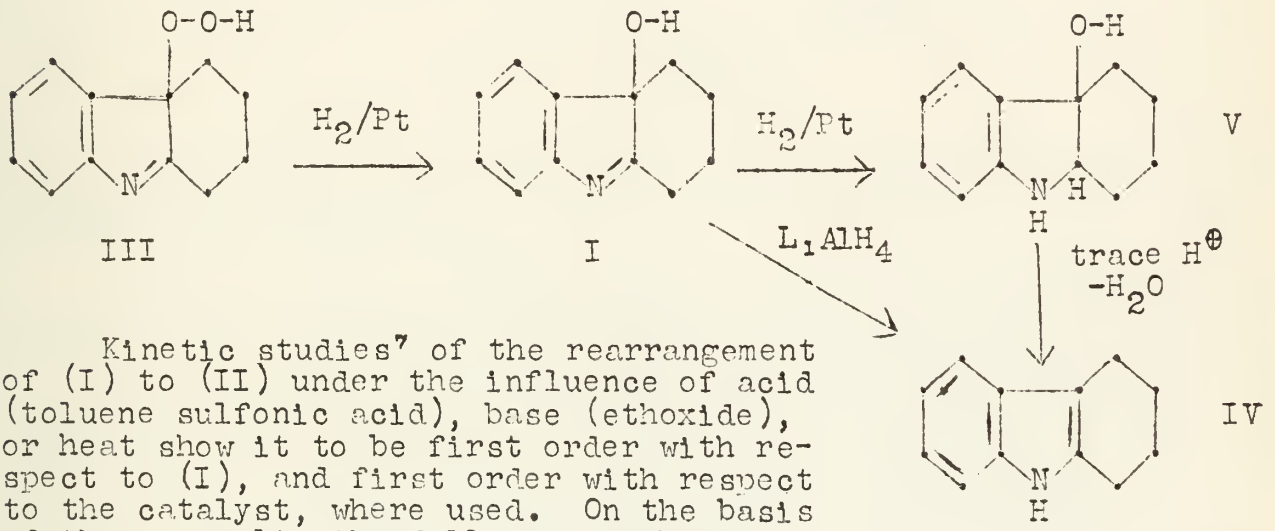
# REARRANGEMENTS OF TETRAHYDROCARBAZOLENINES AND PSEUDO-INDOXYLS

Reported by Thomas E. Young October 5, 1951

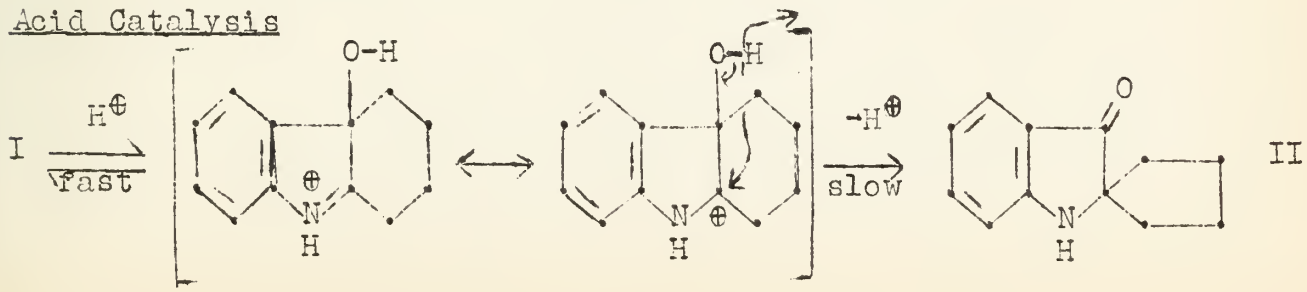
Introduction: In the course of some investigations of the mechanism of oxidation of indoles[3] it was shown that the 11-hydroxytetrahydrocarbazolenine,(I), reported in the literature[10] was in reality a rearrangement product, spiro (cyclopentane-1,2'-pseudo-indoxyl), (II),[1,11,12] while authentic (I) was obtained in 75% yield by catalyti reduction of 11-hydroperoxytetrahydrocarbazolenine,(III), prepared by catalytic oxygenation of tetrahydrocarbazole,(IV). Compounds (I), (II), and (III) undergo several interesting rearrangement reactions, which constitute the body of this report.

11-Hydroxytetrahydrocarbazolenine(I): Infrared examination of this compound shows a 3.02$\mu$ hydroxyl band and a 6.25$\mu$ peak characteristic of the indolenine system ($\phi$-N=C)[2] Further evidence for this structure consists of the catalytic reduction to 11-hydroxyhexahydro carbazole, (V), which in the presence of a trace of mineral acid is dehydrated to (IV). Lithium aluminum hydride reduction of (I) gives directly an almost quantitative yield of (IV). In this latter case, the Lewis acid character of the aluminum causes dehydration of the presumed intermediate,(V).

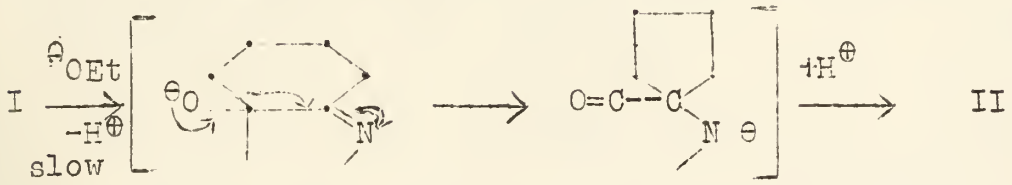



Kinetic studies[7] of the rearrangement of (I) to (II) under the influence of acid (toluene sulfonic acid), base (ethoxide), or heat show it to be first order with respect to (I), and first order with respect to the catalyst, where used. On the basis of these results the following mechanisms have been proposed.

Acid Catalysis

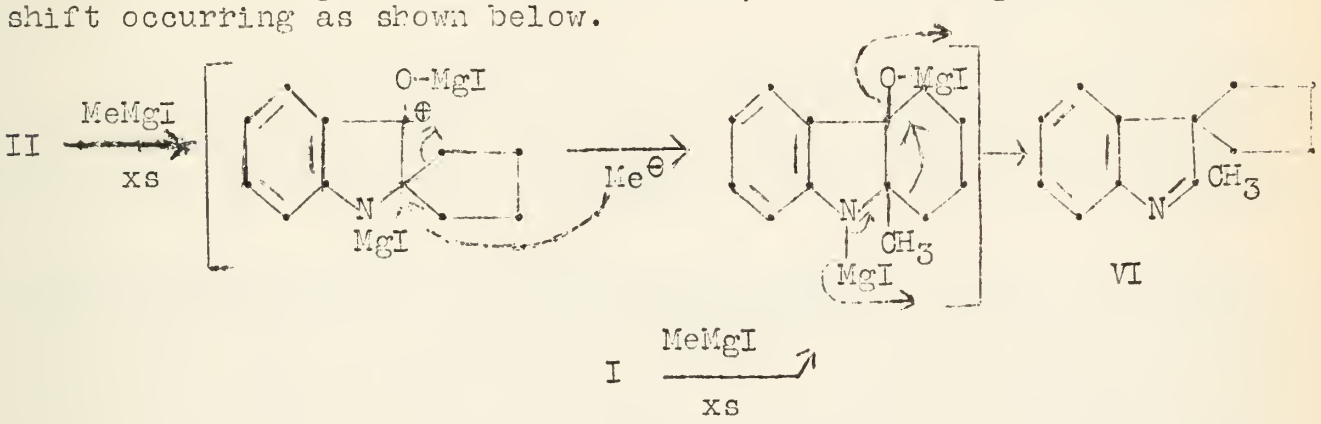


Base Catalysis (Cf. the benzilic acid rearrangement)



The yield in this rearrangement is about 85-90% and some by-products have been isolated.

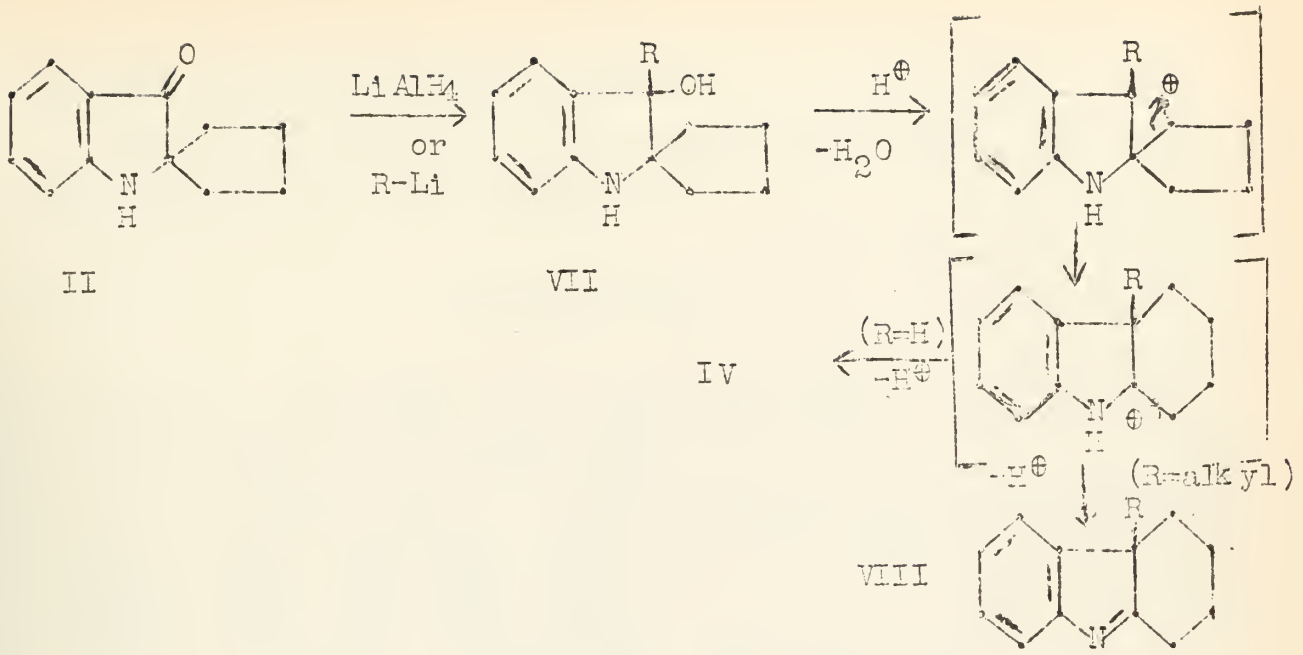
Reactions of (I) and (II) with Organometallic Compounds:[6] With methyl magnesium iodide 11-hydroxytetrahydrocarbazolenine gives an 80% yield of spiro (cyclopentane-1,3'-pseudo-2'-methylindole), (VI). The same product is obtained in much lower yield by the action of excess methyl magnesium iodide on (II), a double Wagner-Meerwein shift occurring as shown below.



Compound (VI) is also obtained from methylcyclopentyl ketone by the Fischer indole synthesis.

Lithium aluminum hydride reduces the spiro compound (II) to the alcohol (VII), which in the presence of acid is dehydrated and rearranged to tetrahydrocarbazole, (IV), with loss of the $C_{11}$ proton.[1]

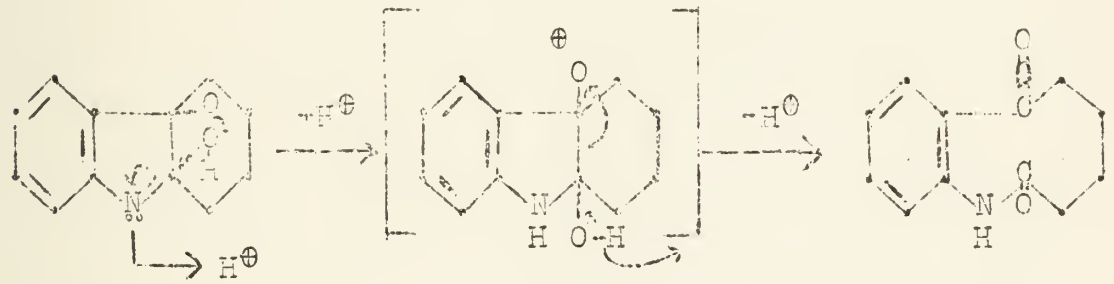
In the reaction of (II) with alkyl lithiums, 80-90% of the starting material is recovered. In this case the expected alcohol, (VII, R=Me,Et) is not isolated since acid is used in working up the reaction mixture. Again dehydration-rearrangement has occurred to form the 11-alkyltetrahydrocarbazolenine, (VIII), with loss of the $C_9$ proton.[3] These products have also been synthesized in poor yields from 2-alkylcyclohexanones by the Fischer method.




II VII IV VIII

Similar rearrangements have been observed accompanying lithium aluminum hydride reductions of other pseudo-indoxyls, in fact, in some of these cases the rearrangement could be attributed to the Lewis acid character of the aluminum compound present since no other acid was used in the treatment.[5]

11-Hydroperoxytetrahydrocarbazolenine, (III): In neutral solution in polar solvents or more rapidly in the presence of acid, this compound rearranges in good yield to the cyclic lactam of ζ-o-aminobenzoylvaleric acid, (IX).[3,4,8] Kinetic studies of this reaction have been made spectrophotometrically by following the rate of change of per cent transmission of the 6.0μ carbonyl band produced by the product.[6] The reaction rate is increased with increasing acid concentration, suggesting the following ionic mechanism in which the electron displacements may well be concerted.




III IIIa IX

Compound (IX) is produced directly by addition of perbenzoic acid to the N=C bond of (III), yielding the perbenzoate of (IIIa) as the presumed intermediate.

In connection with this work it is interesting to note that in the Fischer indole synthesis with cyclopentanone, a major by-product, identified as γ-o-aminobenzoylbutyric acid is formed, probably by a process like the one above, thus indicating significant

autoxidation of the indole produced.

Other ring homologs of the hydroperoxide,(III), have been shown to undergo similar rearrangement.[4,9]

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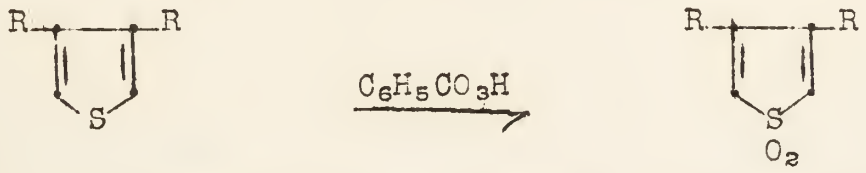
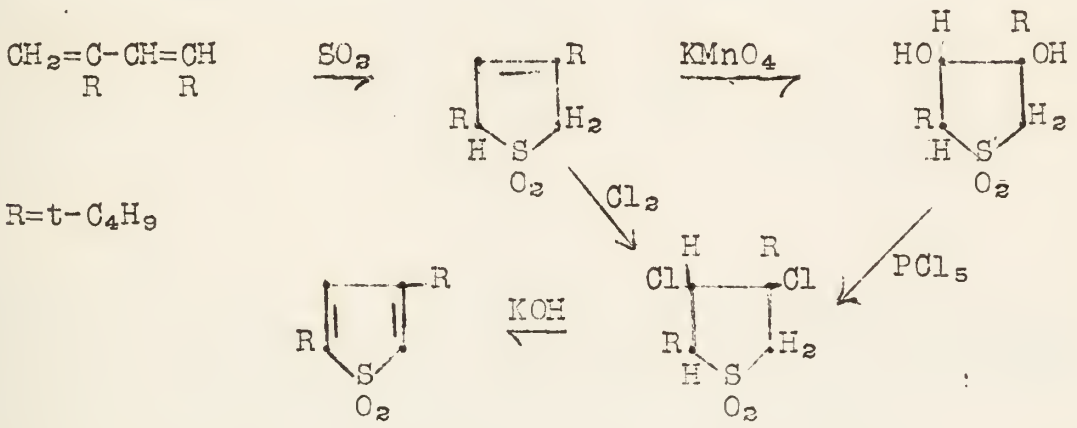
# THIOPENE DIOXIDES

Reported by Dale C. Blomstrom October 12, 1951

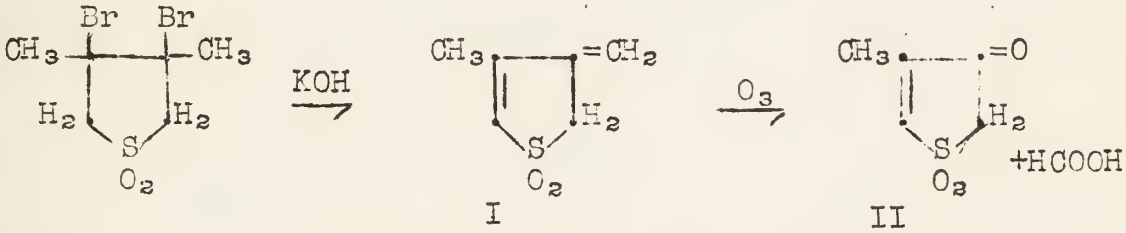
Preparation: Thiophene-1-dioxide was first prepared by Lanfry[1] by oxidation of thiophene with hydrogen peroxide. Oxidation of the corresponding thiophene derivative constitutes a general preparation of substituted thiophene dioxides. Later investigators[2,3] have used perbenzoic acid as the oxidizing agent.




A synthetic method applicable in certain cases involves halogenation of a substituted butadiene sulfone followed by dehydrohalogenation.[4]



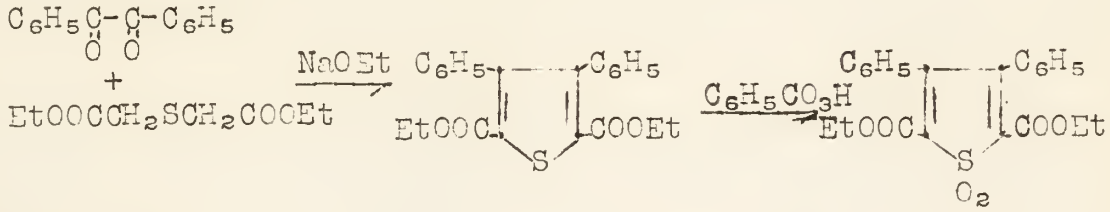

However if an alkyl group containing an α-hydrogen is attached to the ring at the 3- or 4-position, dehydrohalogenation may take place in such a manner as to form one double bond outside the ring. Thus, 3,4-dimethyl-3,4-dibromothiophene-1-dioxide yields 4-methyl-3-methylene-2,3-dihydrothiophene-1-dioxide (I) instead of 3,4-dimethylthiophene-1-dioxide when treated with potassium hydroxide.[5]

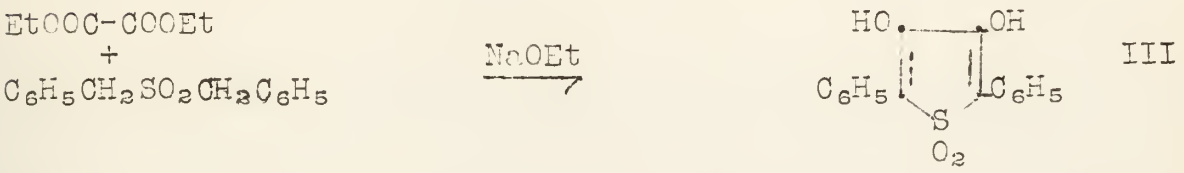



I II

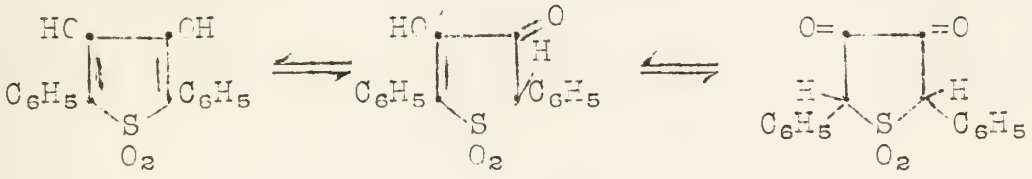
The structure of (I) was determined by ozonolysis. Formic acid and 3-keto-4-methyl-2,3-dihydro thiophene-1-dioxide (II) were formed. Ozone in glacial acetic acid at room temperature does not attack the α,β-double bonds in thiophene-1-dioxides.

A general synthesis is the condensation of compounds containing adjacent carbonyl groups with active methylene compounds using basic catalysts. The following reactions are examples:[3,6]





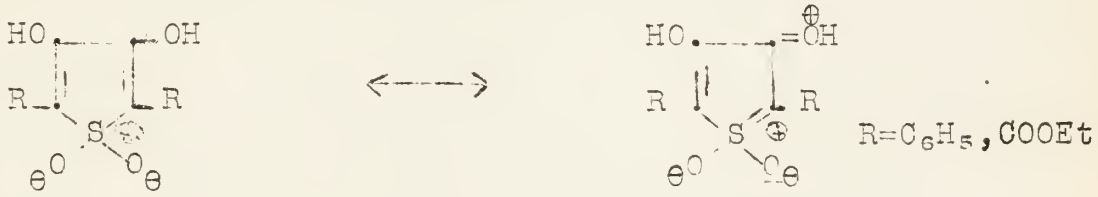
Properties and Reactions: Compound (III) apparently exists in keto and enol forms which are readily interconvertible:[6]



IIIa IIIb

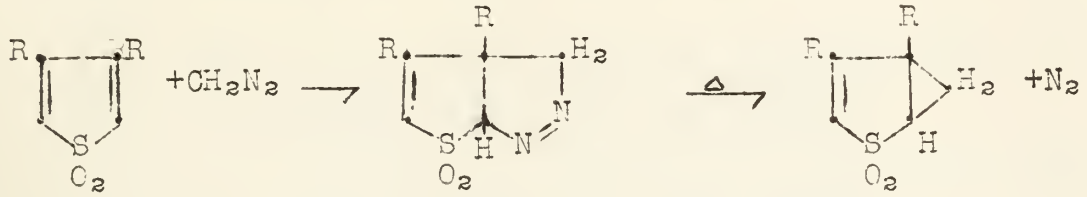
Evidence for the enol form (IIIa) includes formation of a ferric chloride coloration, solubility in dilute sodium carbonate, and formation of a dibenzoate. Presence of the keto form (IIIb) is indicated by the formation of a quinoxaline and by the ultra violet spectrum, which shows typical carbonyl absorption.

Measurements on the acidity of substituted 3,4-dihydroxy-thiophene-1-dioxides show that these compounds are much stronger acids than are the corresponding thiophene, thiophene-1-oxide, pyrr or furan derivatives.[7] The 2,5-diphenyl-3,4-dihydroxy-and 2,5-dicarbethoxy-3,4-dihydroxythiophene-1-dioxides are as strongly acidic as malonic and picric acids, respectively. This is interpreted as evidence that the molecules are hybrids to which resonance structure (IVa) makes an important contribution.

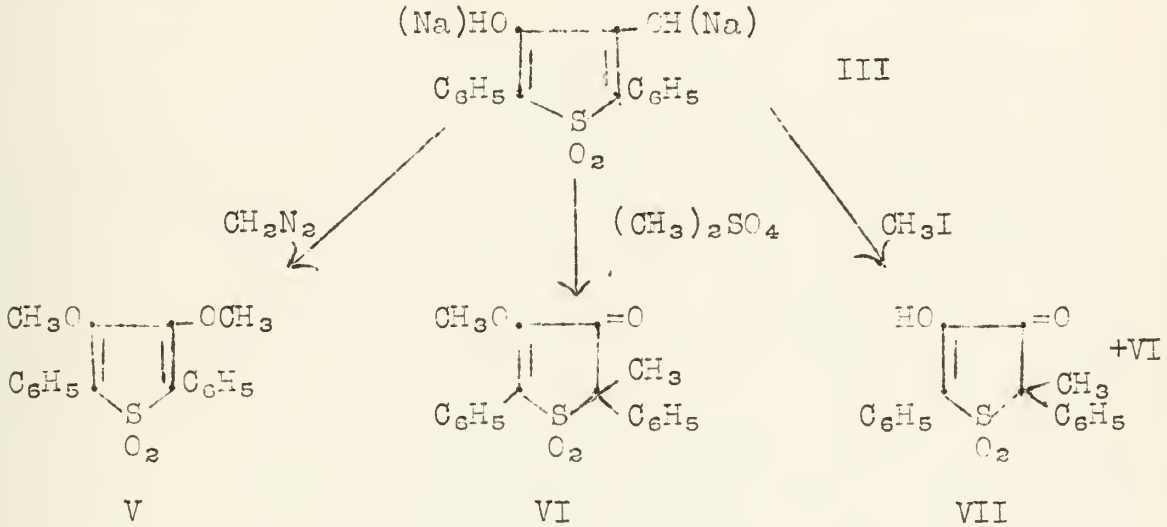


IV IVa

Thiophene-1-dioxides have been found to add a molecule of diazomethane at the double bond to form pyrazolines.[8] The orientation of the addition was the same as that found for the addition of diazomethane to straight-chain α,β-unsaturated sulfones. Pyrolysis of the pyrazolines yielded the corresponding cyclopropane compounds.



Methylation of 2,5-diphenyl-3,4-dihydroxythiophene-1-dioxide (III) with three different agents has been investigated.[9,10] Diazomethane reacted with (III) to form the expected 3,4-dimethoxy compound (V). However dimethyl sulfate and methyl iodide gave anomalous results. Reaction of the disodium salt of (III) with two equivalents of dimethyl sulfate produced 4-methoxy-3-keto-2,5-diphenyl-2,3-dihydrothiophene-1-dioxide (VI) in 39% yield as the only product. Treatment of the disodium salt of (III) with two equivalen of methyl iodide yielded two products--88% of 4-hydroxy-3-keto-2,5-diphenyl-2,3-dihydrothiophene-1-dioxide (VII) and 7% of (VI).



These structures were written on the basis of the following evidence: (1) analysis for methoxyl groups showed that (V) possessed two, (VI) one, and (VII) none; (2) the infrared spectra indicated carbonyl groups in (VI) and (VII); (3) (VII) formed a monoacetate and a quinoxaline, and was converted to (VI) by diazomethane. The proof of structures was completed by sodium hydroxide hydrolysis of the compounds to oxalic acid and a sulfone; (V) yielded dibenzylsulfone, (VI) and VII) yielded benzyl-α-phenethylsulfone. The hydrolysis probably involves a reversal of the original Claisen condensation, the methoxyl groups first being displaced by hydroxyl in the case of (V) and (VI).

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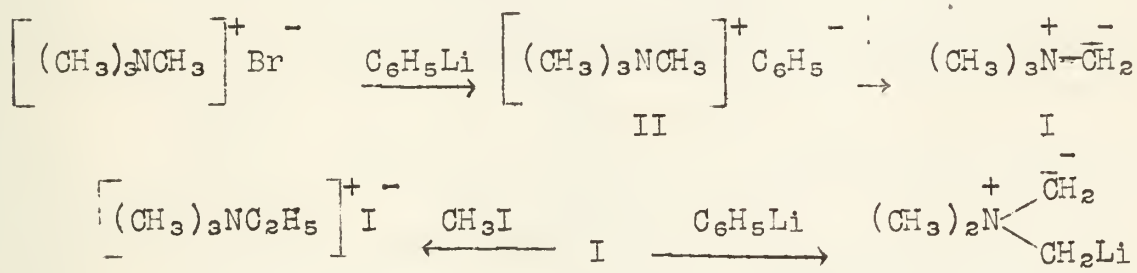
# YLIDS AND YLID REACTIONS

Reported by E. R. Lovejoy October 12, 1951

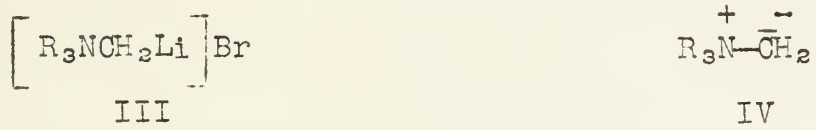
## Preparation[1]

Compounds have been prepared with a semipolar double bond between C and N, and C and P. It may be considered to be a combination of a single ionic bond with a single covalent bond. The term "ylid" which is given to these compounds is a combination of the German names for these bonds.

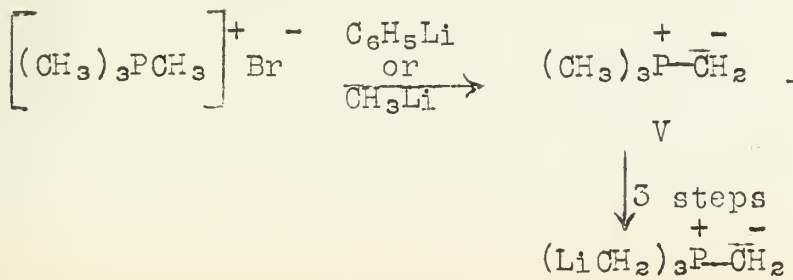
While attempting the synthesis of a compound similar to benzyl tetramethyl ammonia, Wittig isolated a product which proved to be the ylid trimethylammonium methylid (I) rather than the expected phenyl tetramethyl ammonia (II). The latter, which first forms, is unstable and decomposes into I and benzene. This decomposition occurs due to the great proton affinity of the phenyl anion. The ylid is capable of adding benzophenone and alkyl halides, and can be further metallated with phenyl lithium.



In contrast to the colorless methylid, trimethylammonium 9-fluorenylid is an ochre yellow. It can be freed completely from LiBr, an indication that an ylid is not a metal compound III but a semipolar one IV. It adds alkyl halides but not carbonyl compounds.



Pentaphenylphosphorus has been prepared and shown to be completely covalent. However, trimethylphosphonium methylid V is formed rather than pentamethylphosphorus in a similar reaction. The rate of formation of the P ylid is faster than that for the N ylid. This is to be expected since the H atoms on the methyl groups attached to the P atom are more mobile. In agreement with this, the P ylid can be metallated with 3 Li atoms as compared to only 1 for the N ylid. It also adds benzophenone and methyl iodide.



# Intramolecular Rearrangements of Ylids

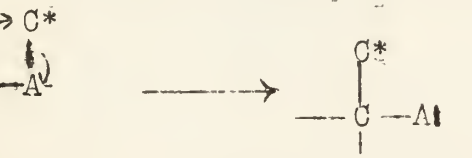
Stevens Rearrangement:

The Stevens Rearrangement involves a shift of an alkyl group from a quarternary N atom to an adjacent C atom under the influence of a base. Phenyl lithium, $NaOC_2H_5$, fused $NaOCH_3$ or $NaNH_2$, and $OH^-$ have been used to bring about the reaction. The intramolecular nature of the shift was shown by the fact that no cross-product was isolated when a mixture of salts was allowed to react. Sulfonium salts are likewise rearranged. Wittig[2] proposed that by the proton capturing influence of the base, an ylid VI is formed which isomerizes to the final product.

$$\left[(C_6H_5CH_2)_2N(CH_3)_2\right]^+ Br^- \xrightarrow[C_6H_5Li]{NaOC_2H_5 \text{ or}} C_6H_5\overset{-}{C}H-\overset{+}{N}(CH_3)_2 \quad | \quad CH_2C_6H_5 \longrightarrow C_6H_5CHN(C \quad | \quad CH_2C_6$$

VI

Hauser and Kantor[3] have been using as a working hypothesis for such rearrangements the internal displacement mechanism (1) which agrees with the experimental results of the relative rates of isomerization of a series of compounds VII as determined by Stevens.[4]

(1) 

A = positive N, S; neutral O

$$C_6H_5CO\overset{-}{C}H-\overset{+}{N}(CH_3)_2 \quad | \quad CH_2C_6H_4Y \longrightarrow C_6H_5COCHN(CH_3)_2 \quad | \quad CH_2C_6H_4Y$$

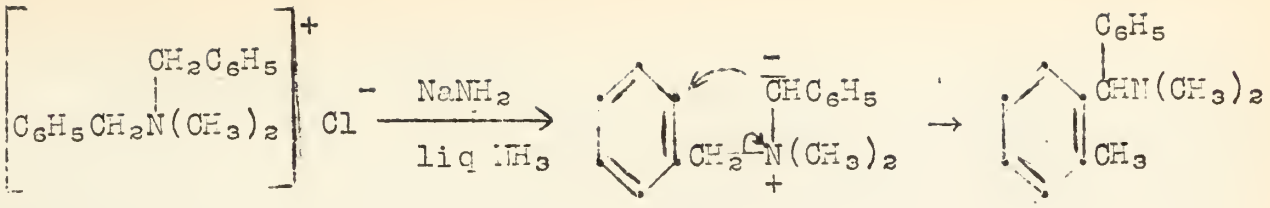
Y = $NO_2$, X, $CH_3$, H, $OCH_3$

VII

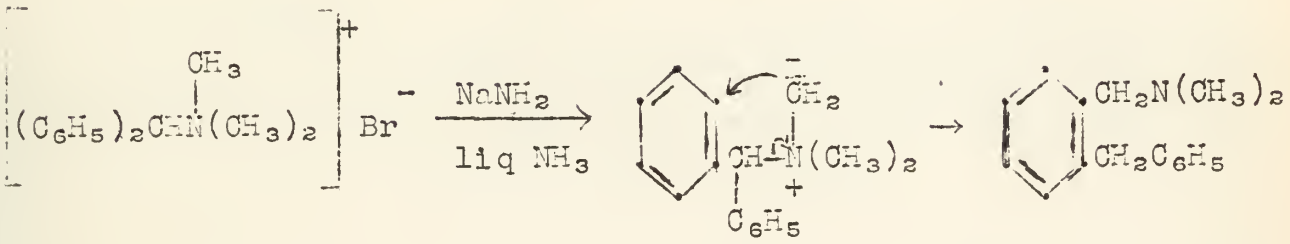
For para substitution, the rates decrease in the order $NO_2 \gg X > CH_3$, $H > OCH_3$ which is qualitatively related to the rate of displacement of Cl by $I^-$ in the corresponding benzyl chlorides ($S_N2$). The kinetics are unimolecular since the reaction is intramolecular. It has also been observed that when C* is asymmetric, no racemization takes place. Molecular models show that the carbanion portion of the molecule must attack C* at the front or side, in relation to A ($S_Ni$), rather than at the rear. A similar example is the reaction of NOCl on apocamphanol-1.

Sommelet Rearrangement:

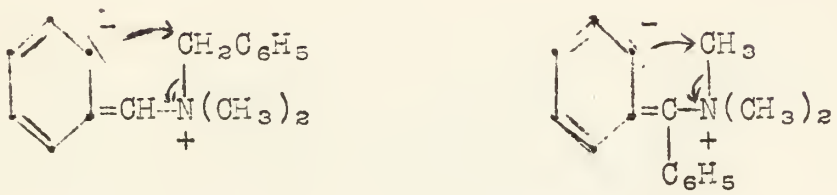
An ylid may rearrange with migration into the ring. This isomerization is designated by Wittig[2] as the Sommelet Rearrangement as the reaction was first observed by him[5] when evaporating benzhydryl trimethylammonium hydroxide in a vacuum dessicator over $P_2O_5$ in sunlight. Kantor and Hauser[6] were able to obtain this rearrangement exclusively when the reaction takes place in the presence of $NaNH_2$ in liquid $NH_3$. Evidently, the rearrangement involves isomerization of ylids VIII and IX to X and XI respectively, since ylids XII and XIII would yield XI and X respectively.



VIII X



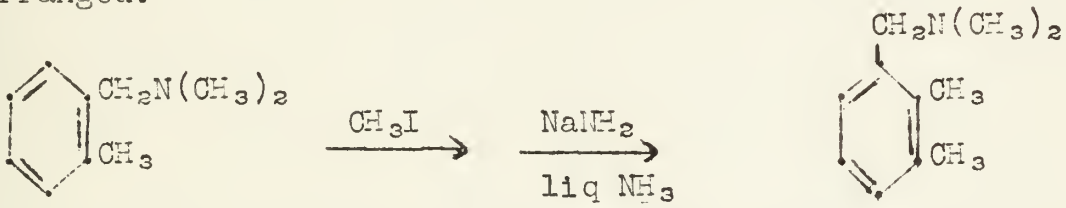
IX XI



XII XIII

We may consider this rearrangement as occurring by an aromatic "nucleophilic" mechanism since the ring serves as an electron accept It appears that the predominant ylids, which undergo the Stevens Rearrangement, require more vigorous conditions than those which undergo the Sommelet Rearrangement.

The amines produced in the Sommelet Rearrangement can be furthe rearranged.



The stepwise conversion of benzyldimethyl amine into 2,3,4,5,6 - pentamethylbenzyldimethyl amine proceeds in successive yields of 97%, 64%, 43%, 47%, and 62%.

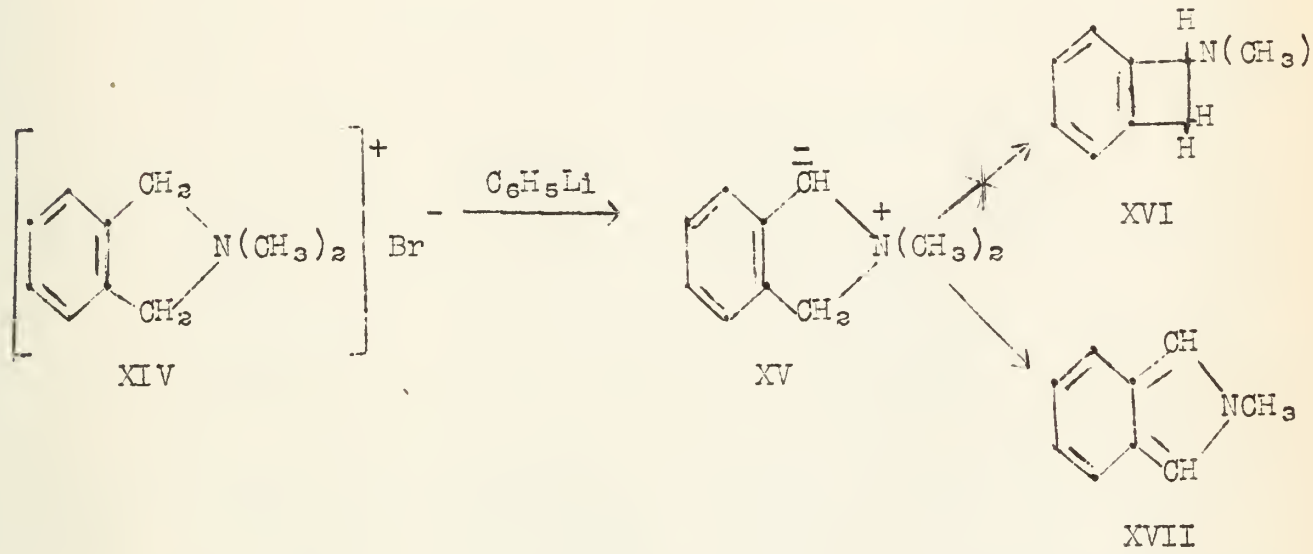
This reaction should prove to be a valuable means of introducing o-methyl groups into a ring, Such compounds may be oxidized to carboxylic acids and reduced to vicinal methyl compounds. Hemimellitene is made in this way in an overall yield of 55% from benzyldimethyl amine, while the older method using "abnormal" Grignard reactions gives only a 26% yield from benzyl chloride.

Alkylation and β-elimination:

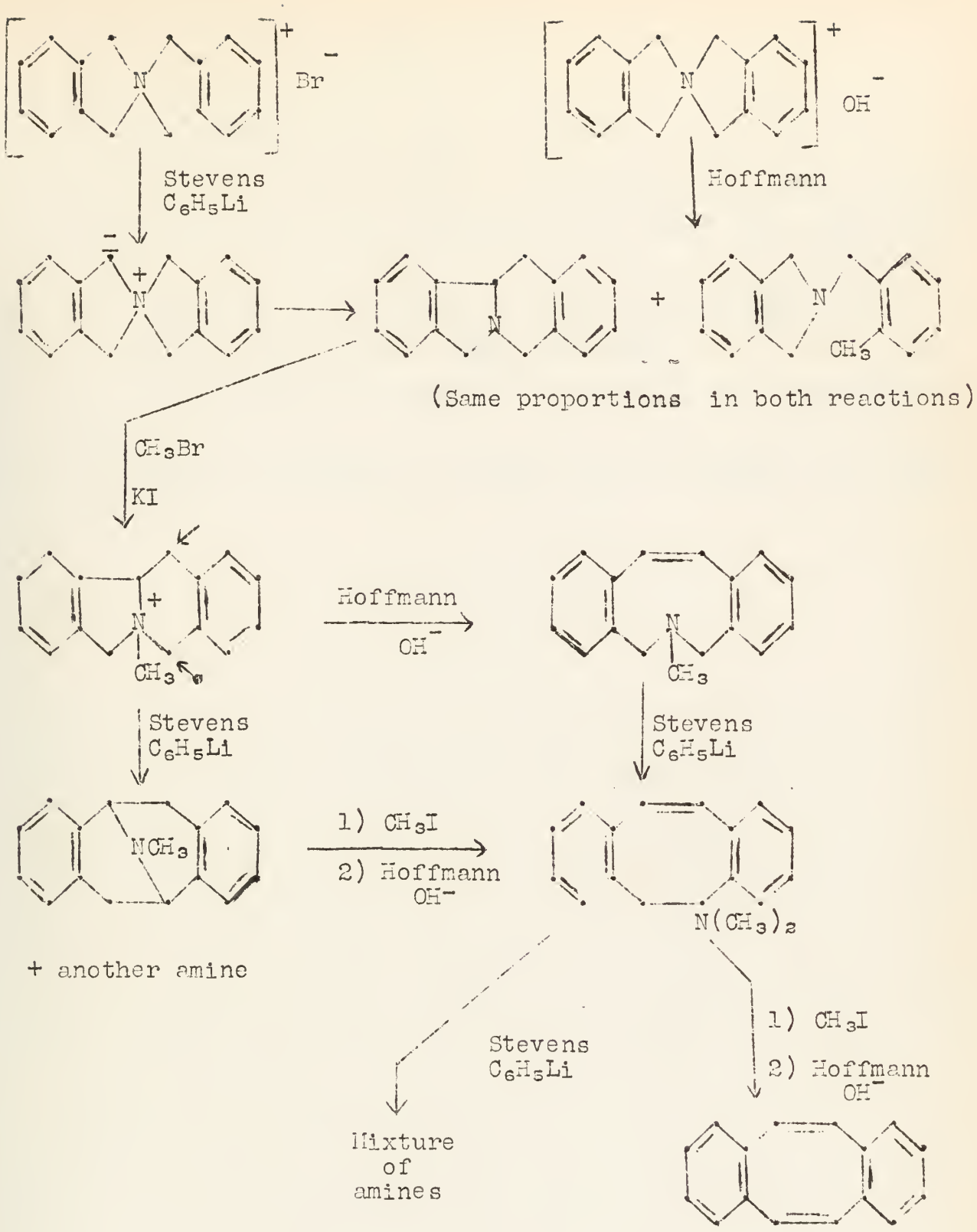
In successive Sommelet Rearrangements, an increase in side reactions is noted. Both neutral and basic compounds are formed and are largely dimers and trimers. The dimerization appears to be an alkylation of an ylid by the quaternary ammonium ion followed by β-elimination or rearrangement. Those quaternary ions having β hydrogens generally undergo β-elimination.

Cyclic Compounds:[1,7]

In a attempt to prepare a new ring system by the Stevens Rearrangement of o-xylylene dimethylammonium bromide XIV, the expected amine XVI was not isolated, but methane was evolved and N-methyl isoindole XVII produced. The ring strain of the amine XVI apparently prevents the rearrangement of the ylid XV.




As a new route to dibenzocyclooctatetraene, other ring systems were subjected to the Stevens Rearrangement and the results compared with the Hoffmann degradation of the same amines. In general, the $C_6H_5^-$, $OC_2H_5^-$, and $OH^-$ ions act as acceptors for protons and the ylid formed stabilizes itself with new compound formation. The difference in behavior of the $C_6H_5^-$ and $OH^-$ ions in the two reaction seems to follow the rule that the $C_6H_5^-$ ion removes protons from a methylene group adjacent to the N, while the $OH^-$ ion removes protons from non-adjacent groups. Satisfactory yields of 1,2,5,6-dibenzocyclooctatetraene have been obtained.


Br
Stevens
$C_6H_5Li$
OH
Hoffmann
$CH_3$
(Same proportions in both reactions)
$CH_3Br$
KI
Hoffmann
$OH^-$
Stevens
$C_6H_5Li$
$NCH_3$
1) $CH_3I$
2) Hoffmann
$OH^-$
$N(CH_3)_2$
+ another amine
Stevens
$C_6H_5Li$
Mixture
of
amines
1) $CH_3I$
2) Hoffmann
$OH^-$

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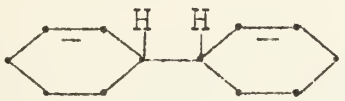
# RADICAL MECHANISMS IN SATURATED AND OLEFINIC SYSTEMS

Reported by Harry R. Beilfuss October 19, 1951

Reaction with Cyclohexene.--At a temperature of 140° in a large excess of olefin, di-tert.-butyl peroxide yields mainly tert. butanol accompanied by traces of acetone (1), and a "polymer" mixture consisting of a dimer, a trimer, a tetramer, and a residue of higher boiling polymers. The dimer proved to be dicyclohex-2-enyl (I). The trimeric fraction is composed of two isomeric tercyclohexenyls (II) and (III). Because of the many structural and stereoisomers of the tetramer, only its tetraolefinic dehydroconstitution was established.



I

II

III

Mechanism of Reaction.--Homolytic scission of the peroxide produces tert.-butoxy radicals which stabilize themselves by abstraction of allylic hydrogen from cyclohexene yielding tert. butanol and cyclohexenyl radicals. The trace of acetone found is to be expected by unimolecular radical decomposition observed in vapor-phase peroxide pyrolysis (2,3,4,5,6). Although it is possible for the cyclohexenyl radicals to stabilize themselves by a substi-

$$(CH_3)_3COOC(CH_3)_3 \rightarrow 2(CH_3)_3CO\cdot \rightarrow 2CH_3COCH_3 + 2CH_3\cdot$$

tution reaction (a), a consideration of activation energies indicates that radical-radical coupling (b) is more plausible. The absence of oxygenated components in the "polymer" mixture rules out the possibility of reactions (c) and (d) taking place. On a purely

a) $C_6H_9\cdot + C_6H_{10} \rightarrow C_6H_9-C_6H_9 + H\cdot$

b) $2C_6H_9\cdot \rightarrow C_6H_9-C_6H_9$ (I)

c) $RO\cdot + -\overset{|}{C}=\overset{|}{C}- \rightarrow RO-\overset{|}{C}-\overset{|}{C}\cdot$

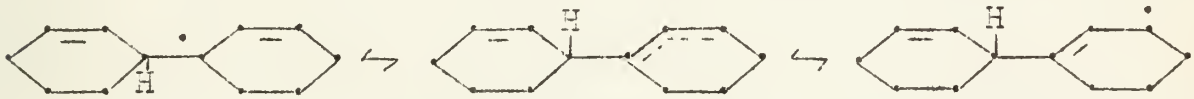
d) $RO\cdot + -CH_2-CH=CH- \rightarrow RO-\overset{|}{C}H-CH=CH- + H\cdot$

statistical basis high yields of the trimer, tetramer, etc., would not be expected because peroxide decomposition is carried out in a large excess of olefin. However, susceptibility to attack decreases rapidly in the order, $3° > 2° > 1°$, and this relationship counterbalances the collision-frequency factor. Evidence for this statement is found in the reaction of dicyclohexenyl with tert.-butoxy radicals in a 2:1 ratio. Sufficient tert.-butoxy radicals

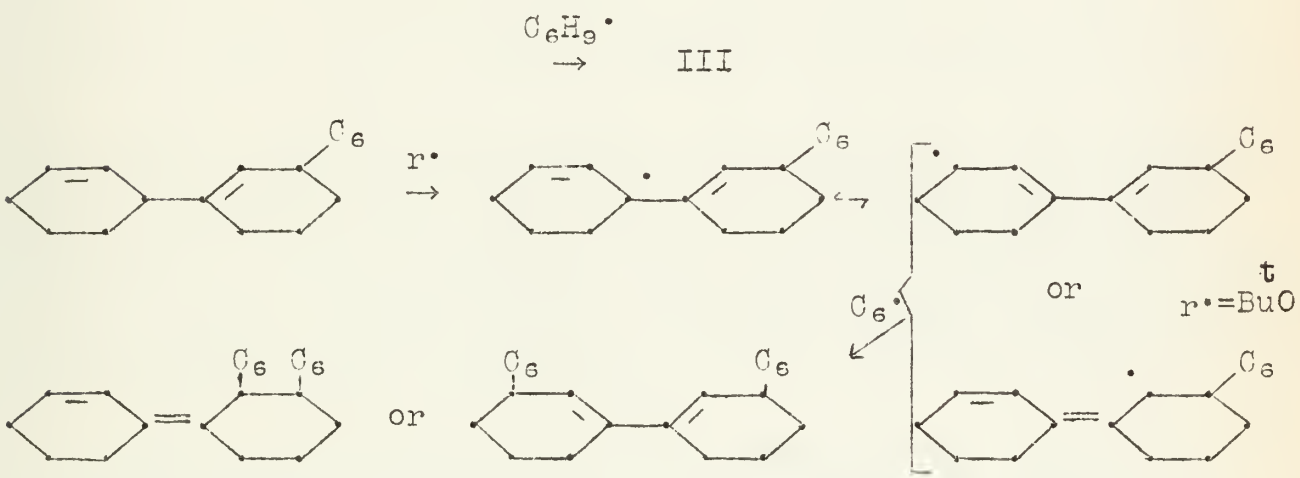
were available to convert all of the $C_{12}$ olefin molecules to the $C_{24}$ dimer, but it was found that one-third of the monomer molecules escaped attack and a corresponding proportion of the tert.-butoxy radicals became available for hydrogen abstraction leading to higher polymer formation. The relatively high yield (33%) of the stereoisomers of II is probably due to the steric hindrance encountered with the relatively large tert.-butoxy and olefin radicals. The presence of III as one of the products may be the direct

IV

result of resonance in the allylic system which, due to steric considerations, is compelled to react via the free radical (VII). Conjugation in the higher dehydropolymers, indicated by ultraviolet analysis, may be accounted for in the following manner. Further



V VI VII



proof for the proposed mechanism is found in an examination of the stoichciometrical data. Correspondence between the observed peroxide expenditure and total peroxide theoretically required for producing the various polymers is excellent.

Reaction with Hept-1-ene.--Two competitive reactions, (a) and (b), take place in the reaction of hept-1-ene, a typical vinylic olefin, with tert.-butoxy radicals. Type (b) is terminated by one or another of the usual methods involving disproportionation, radical coupling, or hydrogen abstraction from external molecules. Resonance in the allylic free radical and the occurrence of exchang

$$2r^{\bullet} + 2\text{-}CH_2\text{-}C{=}C \rightarrow 2rH + \begin{matrix} -CH\text{-}C{=}C \\ | \\ -CH\text{-}C{=}C \end{matrix}$$

Type (a)

$r^{\bullet}$ = $t$-BuO

$$r^{\bullet} + C{=}C\text{-}R \rightarrow r\text{-}C\text{-}C\text{-}R \xrightarrow{n(C{=}CR)} r\text{-}(C\text{-}CR)_{n+1}^{\bullet}$$

Type (b)

reactions between heptene radicals and heptene molecules may account for the non-vinylic unsaturation found in the recovered heptene and in the polymer fraction. This shift of the double bond

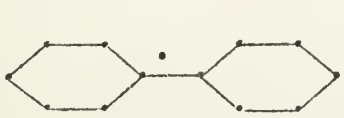
$$R\text{-}\overset{\bullet}{C}H\text{-}CH{=}CH_2 \longleftrightarrow R\text{-}CH{=}CH\text{-}CH_2^{\bullet}$$

$$R\text{-}CH{=}CH\text{-}CH_2^{\bullet} \xrightarrow{R\text{-}CH_2\text{-}CH{=}CH_2} R\text{-}CH{=}CH\text{-}CH_3 + R\overset{\bullet}{C}H\text{-}CH{=}CH_2$$

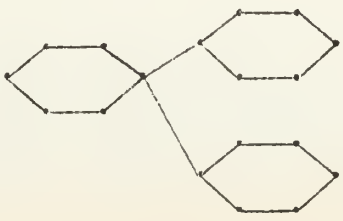
explains why a typical vinylic olefin yields detectable quantities of products expected from reaction (a).

Reaction with Alkyl Benzenes.--Hydrogen abstraction at the alpha position with preferential attack at a tertiary carbon atom accounts for the products isolated from the reaction of toluene, ethylbenzene, and isopropylbenzene with peroxide. In this case the alpha carbon atom in the side chain is activated by the aryl nucleus with the alkyl groups probably exerting a subsidiary activation effect. ($Ar \rightarrow CH_2 \leftarrow R$). The reaction of the alkylbenzenes with di-tert.-butyl peroxide may be summarized as follows: toluene yields dibenzyl and substituted dibenzyls; ethylbenzene gives a mixture of meso- and racemic 2,3-diphenylbutanes and dehydro-trimers, etc.; isopropylbenzene yields only the dehydrodimer, 2,3-dimethyl-2,3-diphenylbutane. From the decomposition of diacetyl peroxide in the presence of ethylbenzene and isopropylbenzene Kharasch (7) also obtained two 2,3-diphenylbutanes and dimethyldiphenylbutane, respectively.

Reaction with Cyclohexane.--This hydrocarbon in the presence of di-tert.-butyl peroxide yields some dicyclohexyl (22.6%) and a much smaller quantity of tercyclohexyl. The major portion of the product (ca. 52%) was a polymeric hydrocarbon (Av. M. Wt. 630) showing some unsaturation including a cyclohexadiene configuration. The products observed may be accounted for by the following scheme.

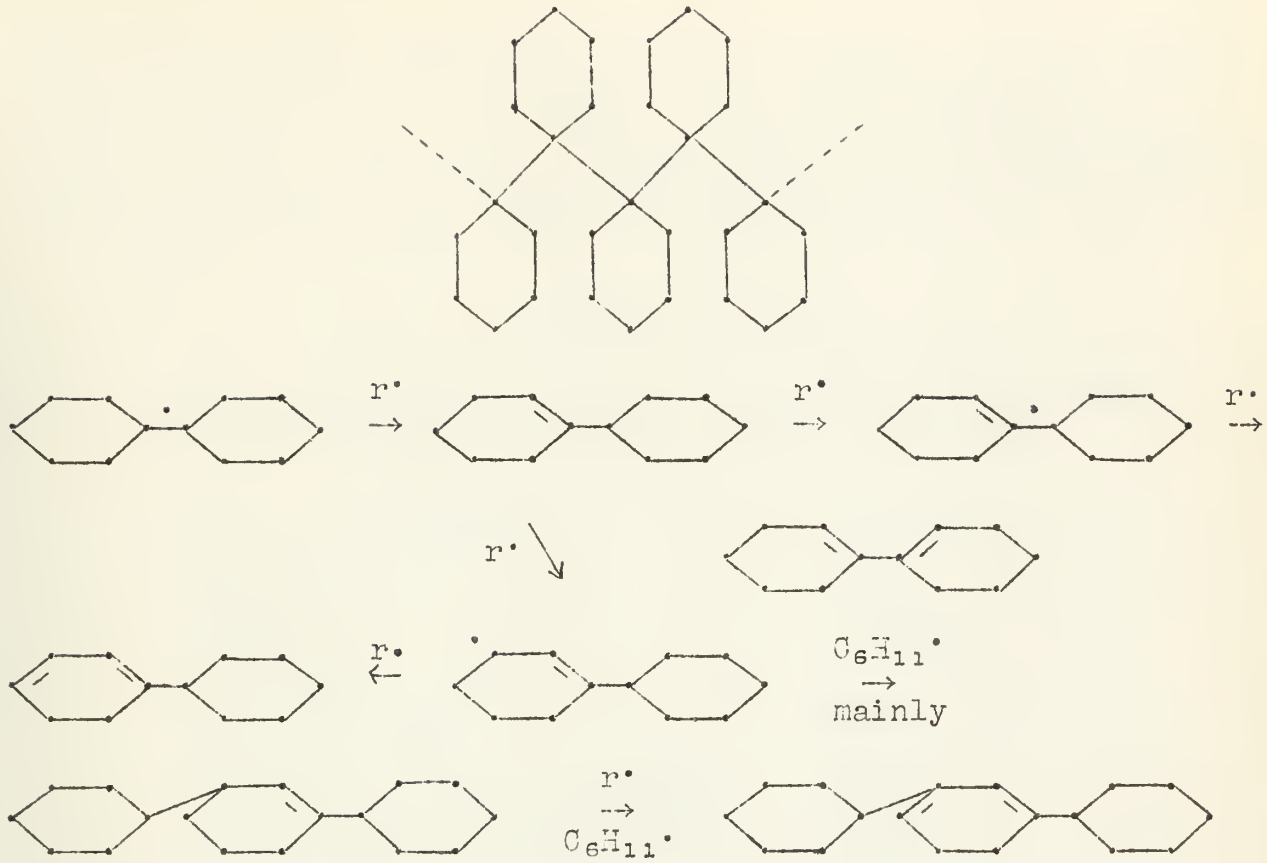


$C_6H_{11}^{\bullet}$ →



$nC_6H_{11}^{\bullet}$ →

$nBu^tO^{\bullet}$




Carbon-Carbon Cross-Linking in Isoprenic Olefins and Rubber.--The induction of radical formation at α-methylenic carbon atoms in non-vinylic olefins by di-tert.-butyl peroxide has been utilized to bring about a carbon-carbon "vulcanization" of the polyisoprenic chains of natural rubber (8). The tensile strengths of the products increase with increasing quantities of peroxide up to a certain critical peroxide concentration. This same phenomenon is observed with rubber-sulfur vulcanisates (9). The negligible incorporation of tert.-butoxy radicals into the rubber is in direct contrast to the results obtained by the use of dibenzoylperoxide (10, 11). Cross-linking also proceeded smoothly when the short isoprenic chain found in 2,6-dimethylocta-2,6-diene was subjected to attack by peroxide. Since the reaction has been shown to proceed essentially via a "dehydropolymerization" mechanism, the loss of 18-20% of the original unsaturation in the product must be due to partial intramolecular cyclization of the monomer radical.

Reaction of Hydroxyl Radicals with Olefins.--In the reaction of tert.-butyl hydroperoxide with a large excess of cyclohexene the tert.-alkoxy group must act as the primary dehydrogenating agent since it reappears as tert.-butanol (95%) (12). However, some of the dehydrogenation of the olefin is due to hydroxyl radicals for

the yield of water is considerably higher than can be accounted for by elimination of water during ketone formation. Dimerization, trimerization, etc., take place in the manner expected of non-vinylic olefins with the mechanism already postulated accounting for the products observed. Correspondingly, most of the hydroxyl radicals appear to have been used in the oxygenation of the olefin. Table I summarizes the results obtained.

TABLE I

Interaction of Cyclohexene (4.0 g.-mols.) with tert.-Butyl-hydroperoxide (0.67 g.-mol.) (140°; 24 hrs.)

| Products | G.-mols. |
|---|---|
| tert.-Butanol | 0.62 |
| Water | 0.19 |
| Acetone | 0.00086 |
| cyclo-Hex-2-enol | 0.18 |
| cycloHex-2-enone | 0.032 |
| Dicyclohexenyl | 0.175 |
| trans-cycloHexane-1,2-diol | 0.011 |
| cycloHexenylcyclohexenol(s) | 0.03 |
| cycloHexenylcyclohexenone(s) | 0.0252 |
| Tercyclohexenyl(s) | 0.011 |
| Residue | 5.1 gms. |

The absence of cyclohexene epoxide in the product suggests that epoxides frequently formed in autoxidation of olefins do not result from simple interaction of hydroxyl radicals with double bonds and may in fact depend for their formation on transient liberation of atomic oxygen from decomposing -OOH groups or -O-O- radicals.

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# BASICITY IN AROMATIC COMPOUNDS

Reported by Sheldon E. Frey October 19, 1951

Introduction.--Aromatic hydrocarbons may be considered as weak bases and several methods have been utilized to show this behavior.

Historical.--Unsaturated hydrocarbons exhibit proton affinity as shown by the fact that they are somewhat soluble in liquid hydrogen fluoride (1). While olefins will polymerize, the aromatic hydrocarbons are recovered unchanged. Agents such as $Hg(CN)_2$, $Hg(N_3)_2$, $AgN_3$, AgF, and TlF increase the solubility of aromatic hydrocarbons in hydrogen fluoride and in turn are more soluble themselves (2).

The complex formation between silver ion and aromatic hydrocarbons could be fully explained on the basis of the formation of $AgAr^+$ and $Ag_2Ar^{++}$. While toluene showed more basicity than benzene in these experiments (3), the xylenes did not show much increase in basic character over toluene. Steric factors were suggested as an explanation for this behavior.

Solutions of iodine in various hydrocarbons were studied (4) by a measurement of dipole moments. The change of dipole moments was related to basic character of the solvents. Electron-donor character gave enhanced dielectric polarization which was attributed to the pi electrons in the aromatic and ethylenic hydrocarbons. A spectrophotometric study (5) of iodine solution in various solvents revealed a band in the ultraviolet which was characteristic of a complex containing one molecule of iodine and one aromatic hydrocarbon molecule. The absorption peaks in the visible region shifted to shorter and shorter wave lengths as the solvent was varied from trifluoromethylbenzene to benzene, toluene, o- and p-xylene, and mesitylene. Using neutral solvents, carbon tetrachloride and n-heptane, it was observed that the iodine-mesitylene complex was more stable than the one between iodine and benzene.

The solubility of hydrogen chloride in aromatic hydrocarbons at low temperatures may be correlated with the variations of the basic properties of the solvent (6). By a determination of Henry's law constant, the following order was obtained: trifluoromethylbenzene, chlorobenzene, benzene, toluene, p-xylene, o-xylene, m-xylene, pseudocumene, hemimellitene, and mesitylene.

Extraction Methods.--It was reported (7) that the individual xylene isomers could be separated by an extraction technique using hydrogen fluoride with added boron trifluoride. The reaction proposed was

$$\text{Xylene} + HF + BF_3 \rightleftharpoons (\text{Xylene}\cdot H)^+ BF_4^-.$$

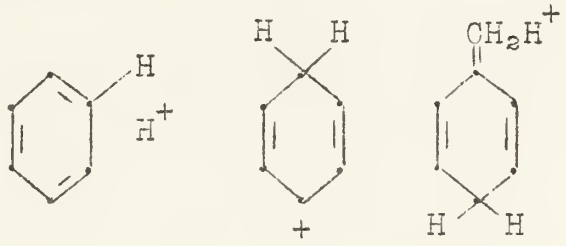
This reaction provided a direct means of measuring basicity and therefore was extended (8) to include all of the methylbenzenes.

In the extraction experiments two methylbenzenes were dissolved in n-heptane in the presence of excess hydrogen fluoride and a limited amount of boron trifluoride. The more basic of the methylbenzenes reacted preferentially and dissolved as a complex in the acid layer. The layers were separated and analyzed.

As a part of this work measurements of the partial pressure of boron trifluoride were taken as it was added stepwise to a fixed amount of aromatic hydrocarbon in the presence of an excess of hydrogen fluoride. The curves obtained for mesitylene and hexamethylbenzene coincided with a line for KF-HF nearly to the point of a 1:1 ratio of hydrocarbon to boron trifluoride. This was considered as ample evidence for a complex of two ions, as $Ar \cdot H^+$ and $BF_4^-$.

Order of Basicity.--The relative basicity of benzene could not be determined by the extraction method but the order of its methyl derivatives were listed by increasing basicity as follows: toluene, p-xylene, o-xylene, m-xylene, pseudocumene, hemimellitene, durene, prehnitene, mesitylene, isodurene, pentamethylbenzene, and hexamethylbenzene. The values show that basicity increases with the number of methyl substituents. m-Xylene being the most basic of the xylenes shows that the 1,3 orientation contributes most to the basic character. Similarly, mesitylene is more basic than the other two trimethylbenzenes as well as being more basic than durene and prehnitene. The fact that hexamethylbenzene is the most basic shows that an unsubstituted position is not required for complex formation.

Structure of the Complex.--The benzene cation formed by the combination of a proton with benzene may be thought of as a resonance hybrid of seven structures (8,9), four no-bond forms (I) and three ortho- and para-quinoid forms (II). As methyl groups are added additional forms may be written. Structure III shows such a form for toluene.



I II III

Basicity and Hyperconjugation.--Hexamethylbenzene was found to be more basic than hexaethylbenzene (8) and this indicates that the substitution of a methyl group by a higher group decreases the basicity of the hydrocarbon. It is thus indicated that hyperconjugation contributes more to the basicity of an aromatic compound than does the inductive effect. This is also shown by data on the 2-alkyl azulenes (10). Extraction experiments with acids on azulenes indicated a decrease in basicity in the order listed:

2-methylazulene, 2-ethylazulene, 2-isopropylazulene, 2-n-propylazulene.

Uses.--Basicity in aromatic hydrocarbons has been suggested as a means of characterization (6) and for the separation of various isomers (7). These uses have also been employed in the study of azulenes (10).

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# THE EFFECT OF VARYING THE CATION IN SOME ORGANIC REACTIONS REQUIRING AN ALKALINE MEDIUM

Reported by Yngve Sundström October 19, 1951

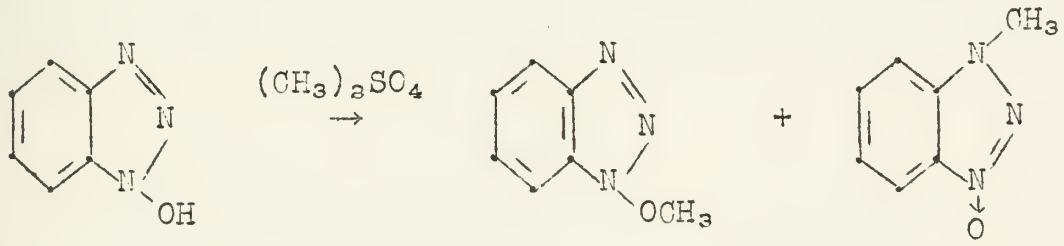
There are instances where change of the cation of an alkaline medium alters the course of organic reactions. Some of these cases are of preparative importance, like the Kolbe-Schmidt synthesis (1).

Recently, Brady and Jakobovits (2) have investigated this cation effect in a few reactions of three types, viz.:

A. Methylation of tautomeric compounds
B. The Reimer-Tiemann Synthesis
C. Hydrolysis of esters.

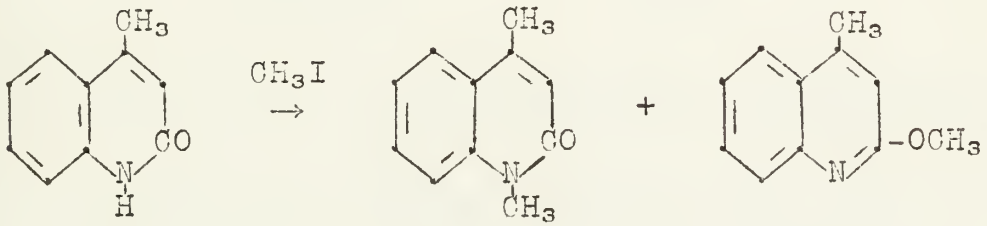
The reactions that are selected for the study have a reasonably well established mechanism and they give fair or good yields of well-defined products.

A. Methylation of Tautomeric Compounds.--Brady and Reynolds (3) found both O- and N-methylation of 1-hydroxybenztriazole (I) with dimethyl sulfate. The ratio between II and III varies with




I II III

the kind of alkali that is used, as is shown in Table I, together with the results of a similar study of the methylation of 2-hydroxylepidine (IV) with methyl iodide and different methoxides in methanol solution.




IV V VI

TABLE I

Methylation of Tautomeric Compounds

| Cation | Ratio N-Me/O-Me: Hydroxybenztriazole | Hydroxylepidine |
|---|---|---|
| Li | 0.89 | |
| Na | 1.03 | 4.5 |
| K | 0.98 | 10.8 |
| Rb | 0.86 | |
| Cs | 0.79 | |
| $NMe_3Et$ | 0.65 | $\infty$ |

While the methylation of hydroxybenztriazole does not give results that are sufficient support for a theory, the methylation of hydroxylepidine is well worth our attention. As is shown in the table, trimethylethylammonium hydroxide gives exclusive N-methylation, and the yield in this case is reported as 82%.

B. The Reimer-Tiemann Synthesis.--The Reimer-Tiemann synthesis was originally presented as independent of the nature of the alkali (4). However, by increasing the concentration of the alkali and determining the resulting aldehydes as 2,4-dinitrophenylhydrazones, Brady and Jakobovits (loc. cit.) were able to find a distinct and reproducible cation effect in the formylation of phenol.

TABLE II

The Reimer-Tiemann Reaction in 15 N Alkali

| Alkali | Ratio ortho/para |
|---|---|
| NaOH | 2.08 |
| KOH | 1.24 |
| CsOH | 0.98 |
| $NMe_3EtOH$ | 0.52 |

The yields are low (10-20%) as usual in this reaction, which detracts from the theoretical importance of the observed effect.

C. Hydrolysis of Esters.--The first ester to be studied by Brady and Jakobovits was diethyl sulfate, which can be hydrolyzed with convenient rate. Alkyl sulfates appear to hydrolyze with alkyl-oxygen-fission (5), differing from carboxylic esters (6), and it is an interesting fact that this difference shows up in the study of cation effects in alkaline hydrolysis. For the study of carboxylic esters, Brady and Jakobovits chose the half-esters of phthalic acid, which are soluble in aqueous alkali.

TABLE III

Hydrolysis of $Et_2SO_4$ in 90% Methanol at 0°C

| Alkali | Normality | Rate Constant $k_2 \cdot 10^5 sec^{-1}$ |
|---|---|---|
| NaOH | 1.0328 | 7.5 |
| KOH | 1.0328 | 9.5 |
| $NMe_3EtOH$ | 1.0534 | 16.9 |

TABLE IV

Rate Constants on Hydrolysis of Phthalates

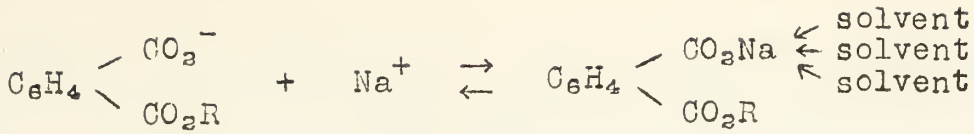
| | Water | | 90% Methanol | |
|---|---|---|---|---|
| Alkali sec. butyl phthalate at 25°C | | | | |
| 1.026-N NaOH | $1.8 \cdot 10^{-4}$ | | 1.047-N NaOH | $1.4 \cdot 10^{-5}$ |
| | | | 0.985-N KOH | $1.1 \cdot 10^{-5}$ |
| 1.026-N $NMe_3EtOH$ | $1.8 \cdot 10^{-4}$ | | 1.077-N $NMe_3EtOH$ | $0.092 \cdot 10^{-5}$ |
| Alkali methyl phthalate at 25°C | | | | |
| 1.005-N NaOH | $4.33 \cdot 10^{-3}$ | | 0.9847-N NaOH | $1.25 \cdot 10^{-4}$ |
| 1.026-N $NMe_3EtOH$ | $3.5 \cdot 10^{-3}$ | | 1.108-N $NMe_3EtOH$ | $0.14 \cdot 10^{-4}$ |

The most interesting thing in Table III and IV is the fact that, compared to sodium hydroxide, trimethylethylammonium hydroxide acts faster on ethyl sulfate and slower on phthalates.

Hypothesis of Explanation.—The facts so far are very interesting. We may think of various explanations. When we compare reactions, in which lithium hydroxide is one of the alkalies, we may have differences in solubility that are great enough to account for a change in the path of the reaction (7,8).

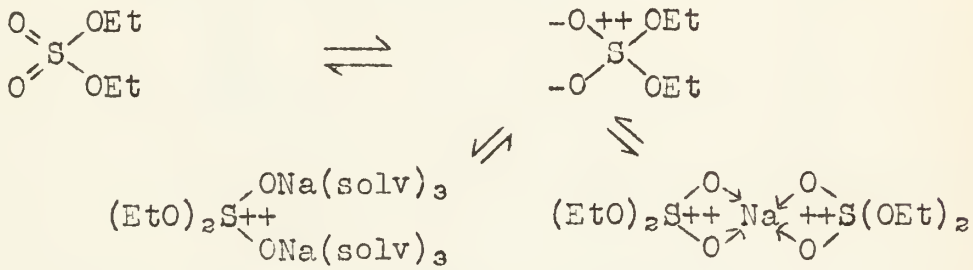
We may also think of solvation, since solvation is one of the known differences between the cations. The solvation explanation does not help, however, when we try to account for the effects in the hydrolysis experiments.

Brady and Jakobovits proceed to give an explanation that will cover the known facts reasonably well. They introduce the idea of "stable covalent bonds" involving the alkali metal. Certainly the tendency to form covalent bonds decreases from sodium to caesium, and when we deal with tertiary ammonium, we do not expect anything but ions. Thus the authors postulate this equilibrium in a solution of the monoester of phthalic acid in concentrated sodium hydroxide:

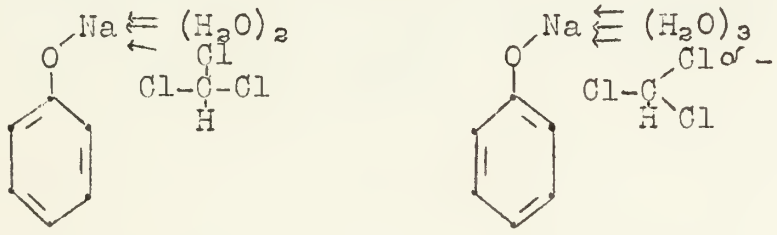


A complex like this should be attacked more readily by hydroxyl than a negatively charged ion.

In a solution of ethyl sulfate, addition of sodium one way or another will result in a positive charge on the sulfur atom:



Here we should expect the $OH^-$ to be attracted in the first place by the positive sulfur. Since we have two charges on the sulfur atom, one hydroxyl is not enough to give acyl-fission, and the engagement of the hydroxyl ion at the sulfur will at the same time undo the accelerating effect of neutralization of the negative charge on the oxygens. Accordingly the hypothesis calls for a more rapid hydrolysis with quaternary ammonium than with sodium as cation. When we run the Reimer-Tiemann reaction in 15 N alkali, the only reacting species would be the phenoxide ion, unless we get intermediary coordination compounds with cations, solvent and chloroform:

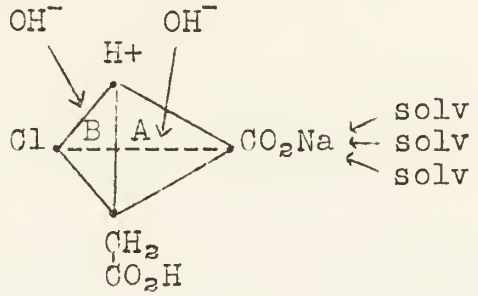


In trimethylethylammonium hydroxide, we find the normal ratio 1:2 for ortho/para-substitution. When 15 N NaOH is used, however, the coordination complex attracts the negative end of the chloroform. The well-known effect of chelate-formation (9) will result in increased ortho-substitution.

We may now guess that Kolbe-Schmidt reactions, analogously, may differ in the amount of coordination complex-formation, when we compare KOH and NaOH (10). Since Kolbe-Schmidt reactions are run under quite different conditions than our reactions here, it may be a little preposterous to give a final theory.

There are other instances of cation effect, where the Brady-Jakobovits theory looks good. One famous example is the original Walden inversion. If coordination compounds are formed at the car-

boxyl group of the chlorosuccinic acid, the steric hindrance may well cause the hydroxyl approach to go through face B rather than face A, and we will get less inversion. Walden found increasing inversion on going from LiOH to RbOH and $NH_4OH$ (11).

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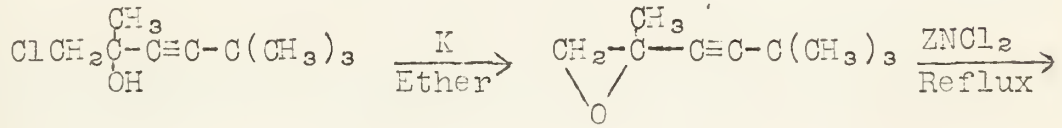
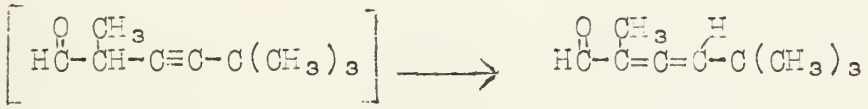
# THE PROPARGYLIC REARRANGEMENT

Reported by James W. Berry October 26, 1951

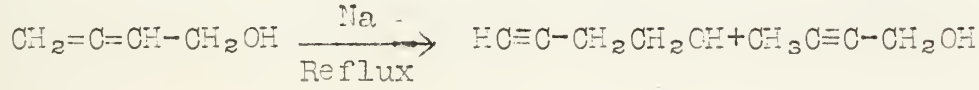
Prototropic and anionotropic systems containing a triple bond possess as one of their tautomeric forms a 1,2-diene of the allene or ketene type.

The formation of an allenic aldehyde from an acetylenic chlorohydrin exemplifies the prototropic system.(1)

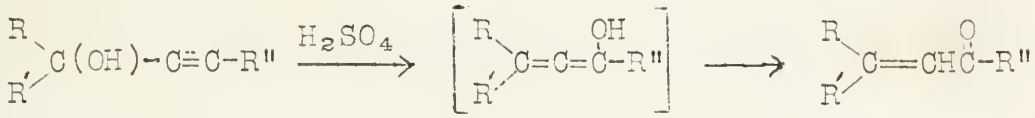




The prototropic allene-acetylene change has been observed in the acetylenic carbinol series.(2)

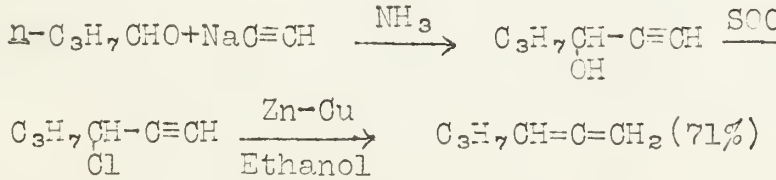


Typical of the anionotropic systems is the Meyer-Schuster Rearrangement, in which a tertiary acetylenic carbinol is converted to an α,β-unsaturated ketone. This probably involves the intermediate formation of an allenic alcohol which ketonizes to form the final product.(3)



The isomerization of acetylenic halides to allenic halides by a halogenating agent or metal is well known,(4) and it has been postulated that allenic halides are intermediates in the formation of rubenes from acetylenic carbinols.(5)

The rearrangement from actylenic to allenic structure has been utilized in the synthesis of 1,2-hexadiene.(6)



A small quantity of isomeric 1-hexyne is also isolated. An organozinc intermediate which yields the allenic product in the presence of ethanol has been proposed.

Using a cyclic reactor for the preparation of Grignard reagents from very active halides, (7) Wotiz has prepared Grignard reagents in practicable yields from primary β-acetylenic bromides. (8) Carbonation of the Grignard reagent affords a mixture of an acetylenic acid, an allenic acid, and an unidentified dimeric acid.

$$R\text{-}C{\equiv}C\text{-}CH_2MgBr \xrightarrow{CO_2} \xrightarrow{\text{Hydrolysis}} R\text{-}C{\equiv}C\text{-}CH_2CO_2H + R\text{-}\underset{CO_2H}{C}{=}C{=}CH_2 + \text{Dimeric Acid}$$

The term "propargylic rearrangement" has been proposed for this type of rearrangement.

Carbonation of the Grignard reagents of secondary and tertiary propargylic bromides has recently been reported.(9) The secondary bromide, 2-bromo-3-octyne(I), gives a mixture of 2,3-octadiene-4-carboxylic acid(II) and 3-octyne-2-carboxylic acid(III); the tertiary bromide, 2-bromo-2-methyl-3-octyne(IV) yields only 2,3-octadiene-2-methyl-4-carboxylic acid(V). The absence of the isomeric acetylenic acid may be due to a steric effect, because the Grignard reagent of the allenic form would be much less hindered than that of the acetylenic form.

$$C_4H_9C{\equiv}C\text{-}\underset{Br}{C}HCH_3 \xrightarrow[\text{Ether}]{Mg} \xrightarrow[2.\text{Hydrolysis}]{1.CO_2} C_4H_9\underset{CO_2H}{C}{=}C{=}CHCH_3 + C_4H_9C{\equiv}C\text{-}\underset{CO_2H}{C}HCH_3$$

(I) (II) (III)

$$C_4H_9C{\equiv}C\text{-}\underset{Br}{\overset{CH_3}{C}}\text{-}CH_3 \xrightarrow[\text{Ether}]{Mg} \xrightarrow[2.\text{Hydrolysis}]{1.CO_2} C_4H_9\underset{CO_2H}{C}{=}C{=}\overset{CH_3}{\underset{CH_3}{C}} \quad (9\%)$$

(IV) (V)

Although the asymmetric synthesis of an optically active allenic hydrocarbon and the resolution of a glycolic acid ester of an allenic acid as the brucine salt have seen reported,(10,11) no <u>direct</u> resolution of an allenic compound has been reported. However, 2,3-octadiene-4-carboxylic acid(II) possesses molecular asymmetry and a direct resolution of its strychnine salt has been accomplished.(9)

Further study of the propargylic rearrangement has involved the dehalogenation of two isomeric propargylic bromides, 1-bromo-2-heptyne(VI) and 3-bromo-1-heptyne(VII), by three different methods: (12)

(A) Hydrolysis of the organomagnesium bromides
(B) Reduction by zinc-copper-ethanol reagent(6)
(C) Reduction by lithium aluminum hydride

In all three methods bromide VI produces a mixture of 2-heptyne(VIII) and 1,2-heptadiene(IX), while bromide VII yields a mixture of 1-heptyne (X) and 1,2-heptadiene(IX).

$$C_4H_9C{\equiv}C\text{-}CH_2Br \longrightarrow C_4H_9C{\equiv}C\text{-}CH_3 + C_4H_9CH{=}C{=}CH_2$$

(VI) (VIII) (IX)

$$C_4H_9\underset{\underset{Br}{|}}{C}HC{\equiv}CH \longrightarrow C_4H_9CH_2\text{-}C{\equiv}CH + C_4H_9CH{=}C{=}CH_2$$

(VII) (X) (IX)

The variation in the ratio of acetylenic and allenic products in all three methods can be explained by assuming a dynamic equilibrium in the starting halide, the "propargylic rearrangement" shown below.

$$R\text{-}C{\equiv}C\text{-}CH_2X \overset{a}{\rightleftharpoons} \left[ R\text{-}C{\equiv}C\text{-}\overset{\oplus}{C}H_2 \leftrightarrow R\text{-}\overset{\oplus}{C}{=}C{=}CH_2 \right] X^{\ominus} \overset{b}{\rightleftharpoons} R\text{-}\underset{\underset{X}{|}}{C}{=}C{=}CH_2$$

(A) (B) (C)

To explain the unusually long carbon-halogen bond length in propargyl halides, form B has been proposed.(13) Such a form might account for an unexplained band in the infrared spectrum of these compounds. (14)

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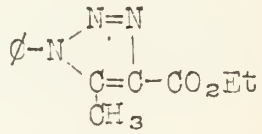
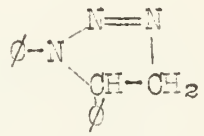
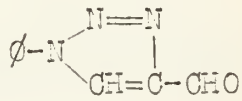
# THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS FROM ARYL AZIDES

Reported by L. Russell Melby October 26, 1951

The early work of Bamberger[1] has shown that aryl azides undergo decomposition in acidic alcoholic media to give complex mixtures of quinones, hydroquinones and various other products, but reactions of this sort, under the conditions described by him, have not been of practical use. Heretofore the most useful reactions of aryl azide have been those involving their addition to compounds capable of keto-enol tautomerism[2] or compounds containing ethylenic[3] or acetylenic linkages[4]. The following equations are illustrative of these reactions.

$\phi N_3$ + $CH_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}OEt$ $\xrightarrow{NaOEt}$ 

$\phi N_3$ + $\phi-CH=CH_2$ $\longrightarrow$ 

$\phi N_3$ + $HC\equiv C-CHO$ $\longrightarrow$ 

The products of such reactions are triazole and triazoline derivatives.

The present seminar deals with the recent work of P. A. S. Smith and co-workders which employs various o-azidobiphenyls in the preparation of derivatives of carbazole and other heterocyclic compounds and exemplifies the reaction of the aryl azido group with aromatic nuclei[5,6]

The preparation of aryl azides may be effected in several different ways;[7]

(A) $(ArN_2)X_3$ + $NH_3$

(B) $(ArN_2)_2PbCl_6$ + $NH_3$

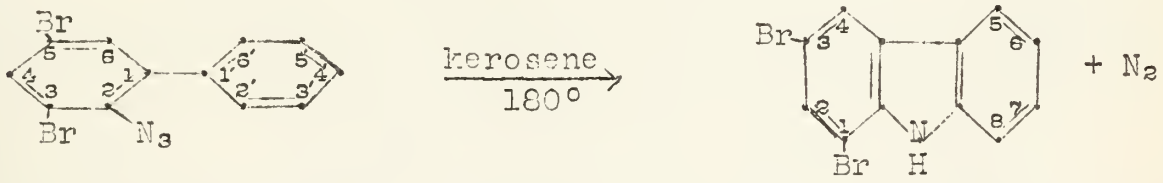
(C) $(ArN_2)SO_4H$ + $H_2NOH$

(D) $(ArN_2)X$ + $HN_3$

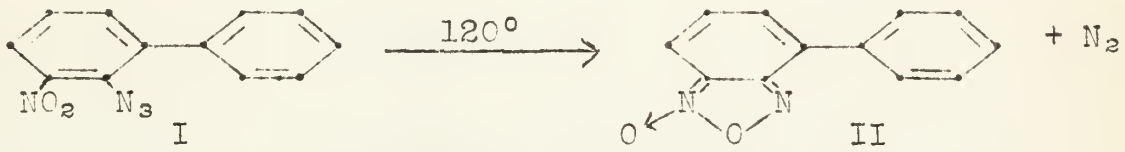
$\longrightarrow$ $ArN_3$ ( X=halogen )

The work under consideration here utilized method (D). This afforded good to excellent yields of the required o-azidobiphenyls through the intermediate o-aminobiphenyls which had been prepared by the reduction of nitrobiphenyls. The latter were obtained either by nitration procedures, Ullmann coupling or Gomberg-Bachmann coupling.

The cyclization reactions were carried out by subjecting dilute solutions ( ca 1% ) of the azide in solvents such as kerosene or tetralin to ultraviolet light or to a temperature of about 180 degrees; the thermal procedure generally proved superior. The following equation illustrates the cyclization:



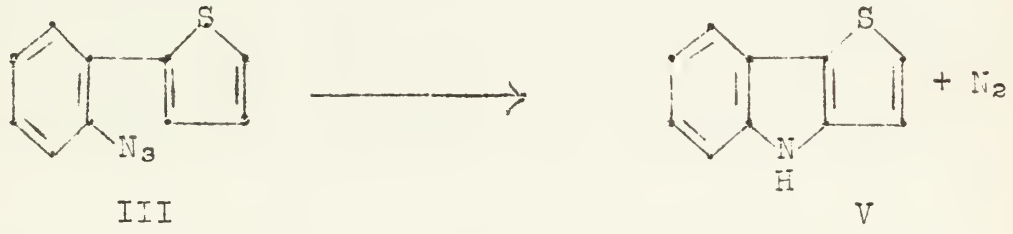

In this manner a total of six carbazoles containing bromo and nitro substituents were prepared, three of which are new.[5] In the case of 3-nitro-1-azidobiphenyl(I), the formation of 4-phenylbenzfuroxan (II) occured to the exclusion of the "normal" ring closure.



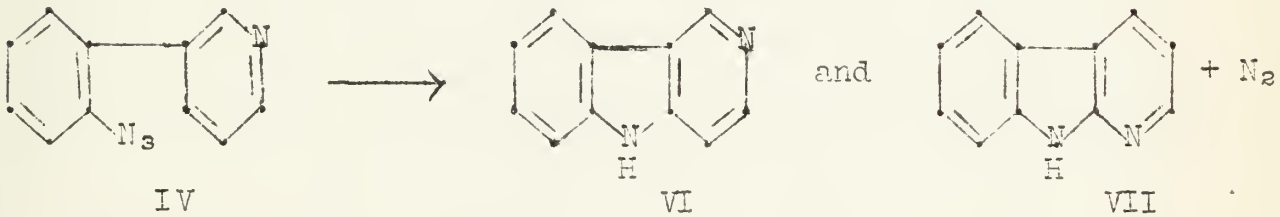

I II

Furoxan formation has been observed in the thermal decomposition of o-nitrophenylazides.[8]

Isosteres of o-azidobiphenyl such as o-(α-thienyl)-phenylazide (III) and o-(β-pyridyl)-phenylazide (IV) when subjected to the thermal treatment gave rise to 4-thieno(3,2-b)indole (V) and α and γ-carbolines (VI, VII) respectively.[6]

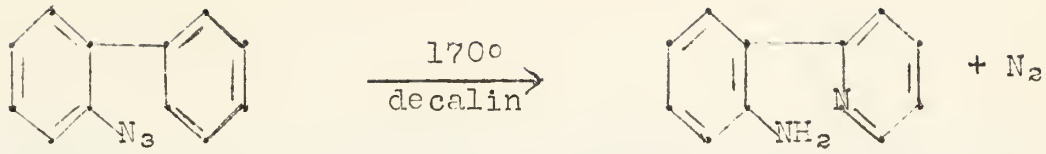



III V

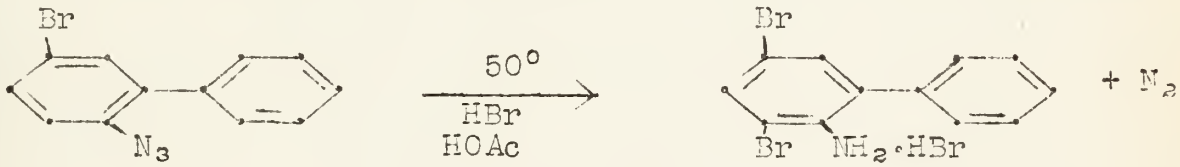



IV VI VII

In cases where cyclization could occur only with great difficulty the azido group was preferentially reduced, apparently through abstraction of hydrogen from the solvent.[6]




Similarly α-naphthyl azide formed α-naphthylamine. Such reduction reactions are reminiscent of the reduction (sometimes with coincident ring halogenation) of aryl azides when the latter are decomposed in an anhydrous solution of hydrogen halide in glacial acetic acid.[9]




Under these conditions no ring closure has been observed.

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# TELOMERIZATION

Reported by Edward D. Weil October 26, 1951

Introduction:

A telomer may be defined as a compound of the type $Y-(A)_n-Z$ produced by treating a compound YZ, called a telogen, under polymerization conditions with more than one molar equivalent of a polymerizable ethylenic compound. A telomer differs from a copolymer in that there is no recurring unit such a $YCH_2CH_2ZCH_2CH_2Y$; the components Y and Z each appear only once in the molecule and always on the terminal carbons of the polymerized ethylenic component. At present, two types of telomerization are known, free radical and ionic. In both types, the products are alway mixtures.

Free Radical Telomerization:

Although most of the telomerization reactions so far investigated fall into this category, only a general review will be given since the subject was discussed in detail in an earlier seminar.[1]

In 1938, Breitenbach[2] and coworkers found that if carbon tetrachloride were used as the solvent for the peroxide-catalyzed polymerization of styrene, the resulting polymers were of low molecular weight and contained approximately four chlorine atoms perpolymer molecule. This is the classical example of free-radical telomerization. The mechanism proposed by Kharasch[3] involves decomposition of the catalyst to produce free radicals which attack the telogen molecules, yielding new free radicals which initiate the familiar chain reaction of vinyl polymerization. Chain growth ends when the free radical terminus of the polymeric chain attacks a telogen molecule.

Many free radical telomerization reactions of industrial value have been described in the recent literature. Some representative examples are the following: (a) Products of the formula $CCl_3-[CH_2CH_2(OAc)]_nCl$ where n=1 to 8 result from the telomerization of carbon tetrachloride with vinyl acetate.[4] (b) Ethylene reacts with hydrochloric acid in the presence of a free radical catalyst to give a mixture of straight chain primary alkyl chlorides having an even number of carbon atoms and ranging from n-butyl to eicosyl chloride; the proportion of longer chains can be increased by raising the ethylene pressure.[5] (c) Products having the general formula $H(CH_2CH_2)_nR$ where n=22 to 54 are formed by polymerizing ethylene in the presence of various oxygen-containing compounds, such as ethyl malonate, ethyl acetoacetate, methyl methoxyacetate, 1,4-dioxane, and 1,3-dioxolane.[6] The equation for the last reaction is as follows:

$$n CH_2=CH_2 + CH_2\begin{cases} O-CH_2 \\ | \\ O-CH_2 \end{cases} \xrightarrow[80°C,800\text{-}1000atm.]{\text{benzoylperoxide}} H(CH_2CH_2)_n CH\begin{cases} O-CH_2 \\ | \\ O-CH_2 \end{cases}$$

This telomer is a soft wax useful as a mold lubricant in rubber vulcanization. (d) The free radical telomerizations most recently studied in industrial laboratories are closely related to the original reaction discovered by Breitenbach, namely, the telomerization of halomethanes with ethylene, using peroxide catalysts.[7,8]

$$n CH_2=CH_2+CH_2ClI \rightarrow I(CH_2CH_2)_nCH_2Cl$$

$$n CH_2=CH_2+CH_2Cl_2 \rightarrow Cl(CH_2CH_2)_nCH_2Cl$$

$$n CH_2=CH_2+CH_3I \rightarrow I(CH_2CH_2)_nCH_3$$

Ionic Telomerization:

In 1932, Wagner-Jauregg[8] synthesized geraniol acetate from isoprene and acetic acid, using sulfuric acid as the catalyst.

$$2CH_2=\overset{CH_3}{\underset{|}{C}}-CH=CH_2+HOAc \xrightarrow{H_2SO_4} CH_3\overset{CH_3}{\underset{|}{C}}=CHCH_2CH_2\overset{CH_3}{\underset{|}{C}}=CHCH_2OAc$$

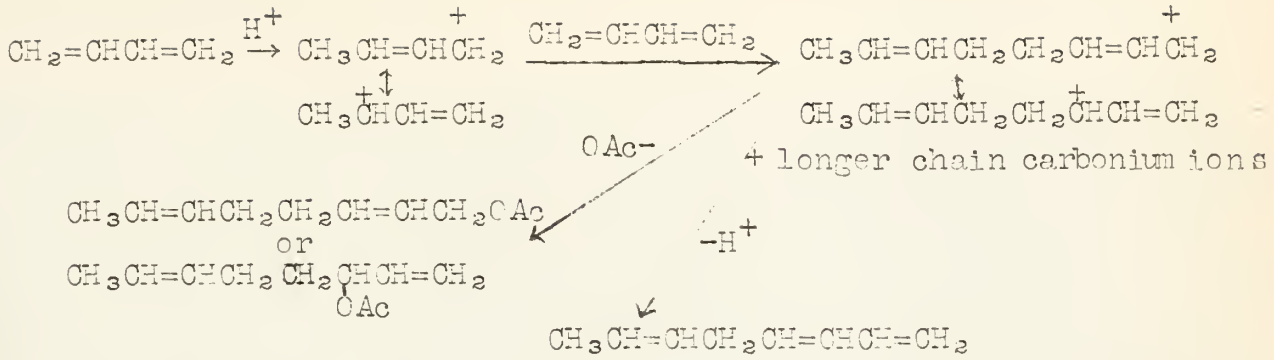
This reaction suggested the possibility of a second form of telomerization--an ionic type. This has recently been confirmed by work carried out at the Du Pont Experimental Station by Jenner and Schreiber.[10] The main reaction developed by these investigators is the following:

$$n CH_2=CH-CH=CH_2+RCOOH \rightarrow H(CH_2CH=CHCH_2)_nCOOR$$

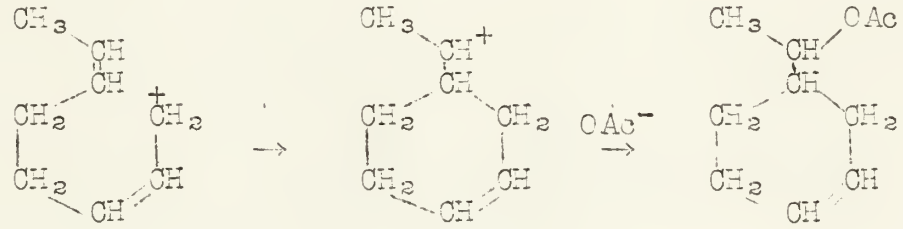
Perchloric acid proved to be the only acid of sufficient strength to catalyze the reaction, although sulfuric acid was strong enough to catalyze the telomerization of isoprene with acetic acid. The telomer used in most of this work was acetic acid although propionic acid was also employed with similar results.

As in all telomerization reactions so far investigated, a mixture of compounds was obtained. The products consisted principally of linear esters of polymeric alcohols, however, isomeric esters in which the acetate group was attached in the 3-position, unsaturated hydrocarbons, and esters of cyclic alcohols were also found in the mixture. Jenner and Schreiber have proposed the following mechanism to explain these results:

The initiation step occurs by the addition of a proton from the perchloric acid or from the conjugate acid of the solvent ($AcOH_2^+$) to a butadiene molecule, producing a carbonium ion. Chain propagation occurs by the attack of a carbonium ion intermediate on another butadiene molecule. The chain may be terminated by addition of an acetate ion, or of acetic acid followed by loss of a proton, to give the telomeric ester. The acetate group may attach at the 1- or 3-position Another type of termination step is the loss of a proton to give an unsaturated hydrocarbon.




Esters of cyclic alcohols result from the cyclization of carbonium ions having double bonds in the 6,7-position, followed by addition of acetate ion.

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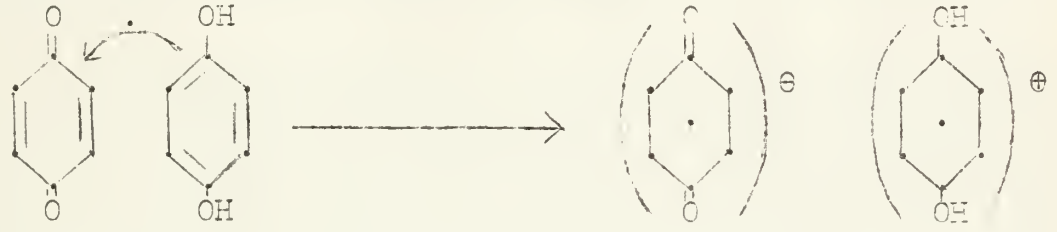
# POLAR RESONANCE CONTRIBUTIONS TO THE TRANSITION STATES OF FREE RADICAL REACTIONS

Reported by Richard C. Fox November 2, 1951

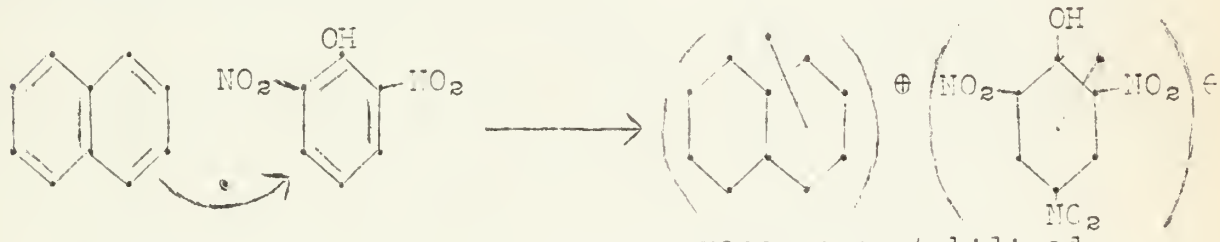
Introduction The effect of change of structure of the reactants on the course of free radical reactions has been explained in the terms of 1) resonance stabilization of the free radicals produced 2) steric affects and 3) polar phenomena. The role of polar affects has only been elucidated in recent years. The mode of explanation has been presented in several theories. The purpose of this seminar is to present at least one of these theories, namely the postulation that the transition states involved may be represented in part by resonance forms which picture the two reactants as ion-radical pairs resulting from a single electron transfer from a donor molecule to an acceptor molecule.

Molecular Compounds: The forerunner of the above mentioned transition state was suggested by Weiss[1 2 3 4 5] in attempting to explain molecular compound formation between quinone and nitro compounds on one hand and certain unsaturated hydrocarbons and their derivatives (eg. amines and phenols) on the other hand. He postulated a complex molecule ionic in character, formed from the electron transfer from the unsaturated compound to the quinone or polynitro compound. For example the system quinhydrone studied by Michaelis[6 7 8 9] (mixture of benzoquinone and hydroquinone) is pictured as:



resonance stabilized

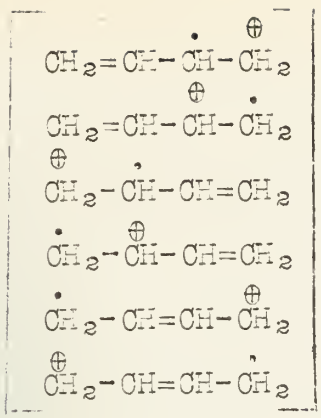
and for naphthalene and picric acid

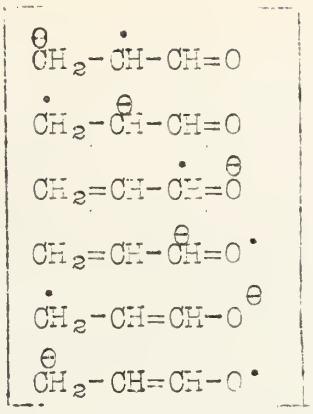


resonance stabilized

Dewar disputed this approach especially on the grounds that these compounds did not exhibit the salt like properties expected of them.[11]

Diels Alder Reaction: The second application of this type of theory was made by Woodward[13 20] in attempting to explain the accumulated evidence in the Duels Alder reaction.[14 15] He postulated an electron transfer from the diene to the dienophile to form an ion-radical pair intermediate. For example in the case of butadiene and acrolein this intermediate would be a resonance hybrid of the following forms:

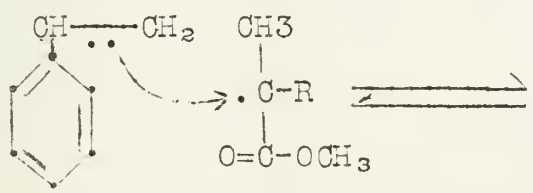


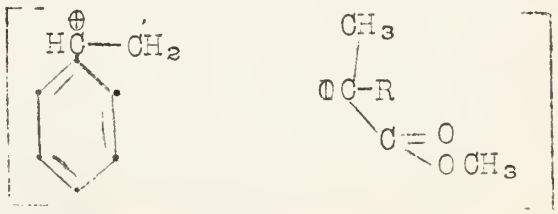


This intermediate would then determine the steric course of the reaction. Preliminary experiments indicated catalysis by donor or acceptor molecules which could not themselves participate in the reaction[16,17,18,19] Woodward and Baer[20] later used this approach to explain why the endo adduct of maleic anhydride and pentamethylene fulvene was formed faster at moderate temperatures while the exo adduct was the stable one at higher temperatures. In evaluating the intermediate ion-radical resonance forms they deduced that the ⊕ charge was distributed mostly in the pentadiene ring, while the ⊖ charged maleic anhydride oriented itself to take advantage of the attraction of charges. These results are paralled in the dimerization of cyclopentadiene.[21]

Their explanation as presented may be open to some question. It has been suggested that this theory gives the wrong isomer prediction in the case of the reaction between 1,3 butadiene -1-carboxylic acid and acrylyl chloride;[22] however, the prediction depends upon the evaluation of the resonance forms for the acrylyl chloride. In dimerization of dienes the theory of Corey's[23] seems to be much easier to handle.

Copolymerization: The third application of this theory was in the realm of copolymerization, to explain the alternating effect. Bartlett and Nozaki[25] first suggested but did not formulate such an application. Walling, Mayo and associates[26,27,28] actually formulated transition states for their studies. In the study of relative reactivities of p and m substituted styrnenes with unsubstituted styrenes they found that the electron donating substituents hindered addition which fitted the inductive polarization idea of Price[29,30] and coworkers. However, in their study of the relative reactivities of substituted styrenes with methyl methacrylate they found that electron donating substituents accelerated addition. This they explained with resonance forms such as:

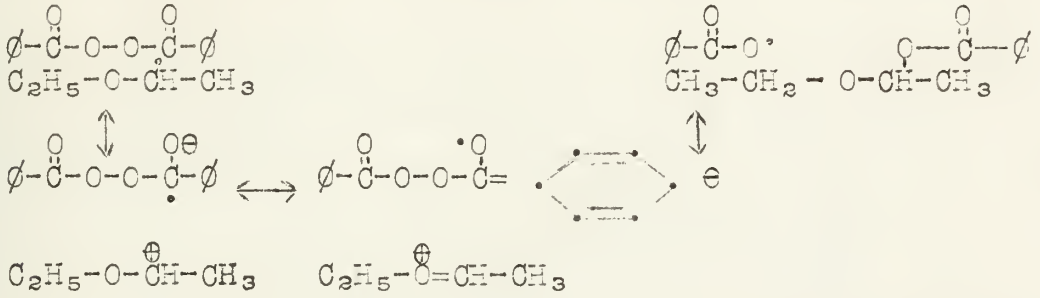




(I) (II)

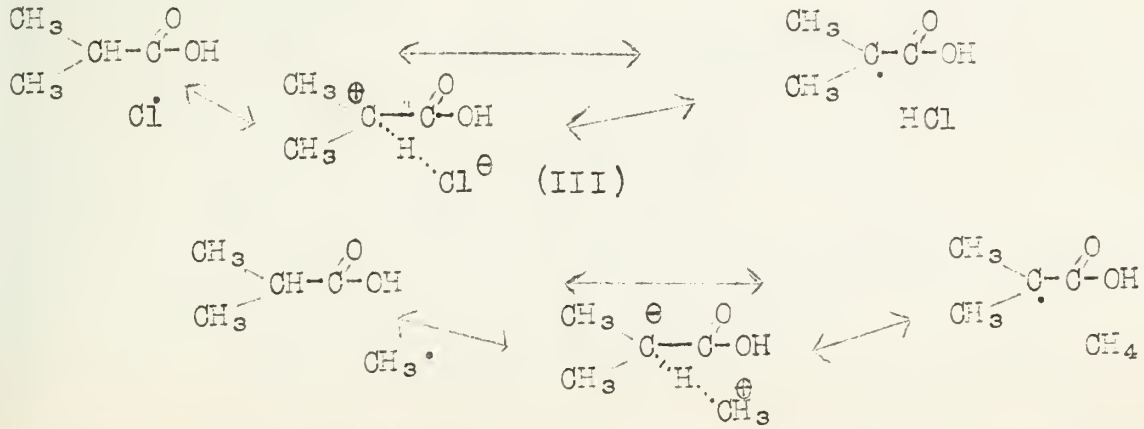
It can easily be seen that form (I) would be stabilized by electron donating substituents in the para position, meanwhile the methyl methacrylate molecule would be stabilized also. These workers repeated their studies with substituted styrenes and maleic anhydride and found the same tendencies except that the relative reactivities were all increased. Maleic anhydride is a stronger alternate monomer than methyl methacrylate and this can be explained since the resonance form for maleic anhydride resembling (II) would have two carbonyl groups to help resonance stabilize the transition state form. Price[31] later attempted to reconcile these facts within the framework of his own induction theory[32] but actually the two ideas are not too different. When Walling re-examined his previous work with better kinetic equations[33] he found that the application of these polar forms still applied

Induced Decomposition of Peroxides: Swain, Stockmayer, and Clarke[34] used this type of treatment to explain why electron rich solvents increased induced decomposition of benzoyl peroxides[34-38] and that benzoyl peroreides with electron withdrawing substituents also increased this tendency. They pictured the transition state as:



This scheme accounts for the experimental evidence gathered by Bartlett and Nozaki[35,36] and by Cass.[37,38]

Aliphatic Free Radical Reactions: This theory has been suggested to explain why isobutyric acid in chloinated by chlorine free radicals in the β position[41] whereas free methyl radicals give coupling in the α position.[42] These reactions were reviewed by Brown and Ash[40] who gave an explanation in terms of classical free-radical stabilization. However, one might write the transition states as:



(IV)

It can be seen that form III is energetically unfavorable while form IV is resonance stabilized, the determining factor being that chlorine being electronegative tends to be an acceptor molecule whereas the methyl group can act as a donor.

Other Applications: This treatment also has been suggested to explain the free radical substitutions of aromatic compounds such such as the coupling of diazohydroxides with substituted benzene compounds.[43] It has been used by Walling and coworkers to relate the relative reactivities of attack by the $\cdot SCH_2CO_2Et$ radical on substituted α methyl styrenes.[44] It was applied also in explaining the relative rates of addition of n- butyl mercapton radicals to various conjugated olefins.[45] It has been used by the same group in explaining the relative rates of peracid catalyzed oxidation of substituted benzaldehydes[46] in the presence of oxygen.

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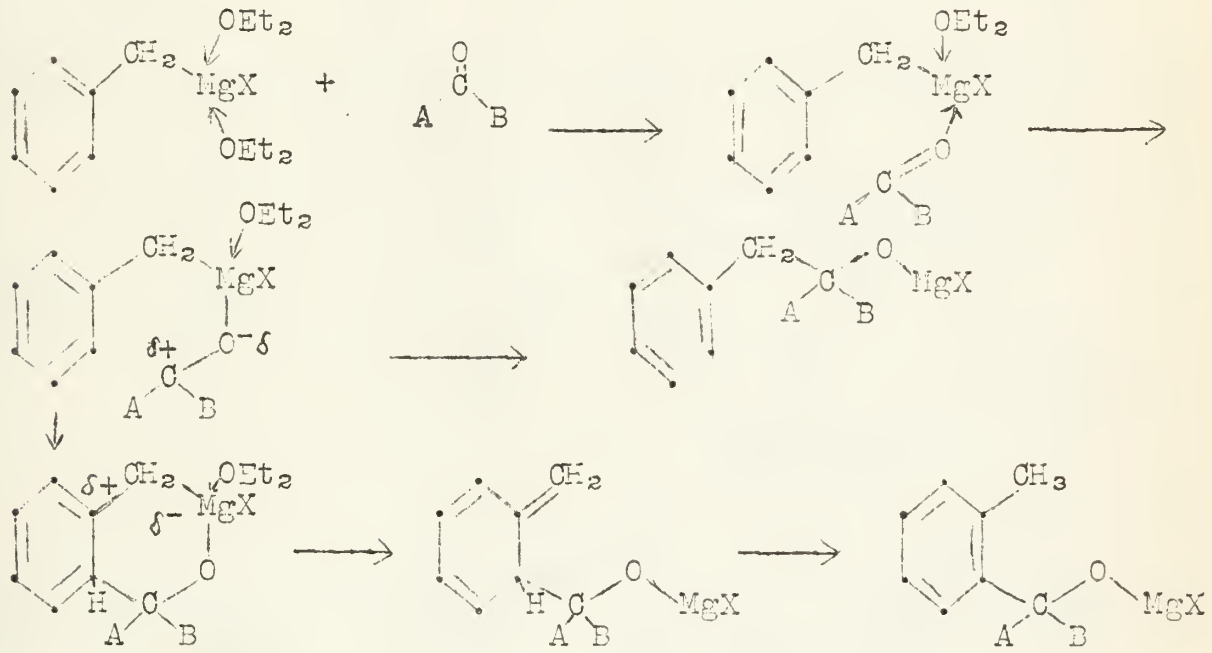
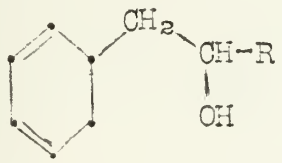
# ABNORMAL REACTIONS OF SOME GRIGNARD REAGENTS

Reported by R. O. Kerr November 2, 1951

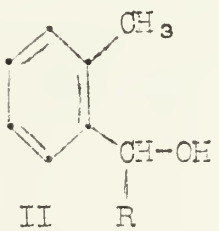
Abnormal reaction of a Grignard reagent was first noted by Tiffeneau and Delange[1] in 1903 when 1-hydroxymethyl-2-methylbenzene was found as the product of benzylmagnesium chloride and formaldehyde.[2] One proposed mechanism nvolved the allyic rearrangement of the Grignard reagent itself before addition to a reactant. Another route proposed by Johson[3] involved a cyclic enol intermediate as follows:



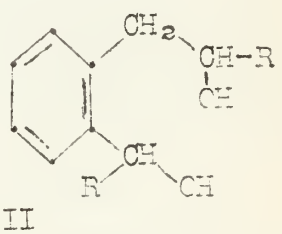
Benzylmagnesium Chloride: Recently Young, Siegel and coworkers have extended and elaborated Johnson's mechanism in order to explain a second type of abnormal product formed when benzylmagnesium chloride is added to an aldehyde.[4,5] A series of aliphatic aldehydes were reacted with the Grignard and three types of products were obtained. The mole % of abnormal product along with the type of product is listed in table I.[6]



I



II



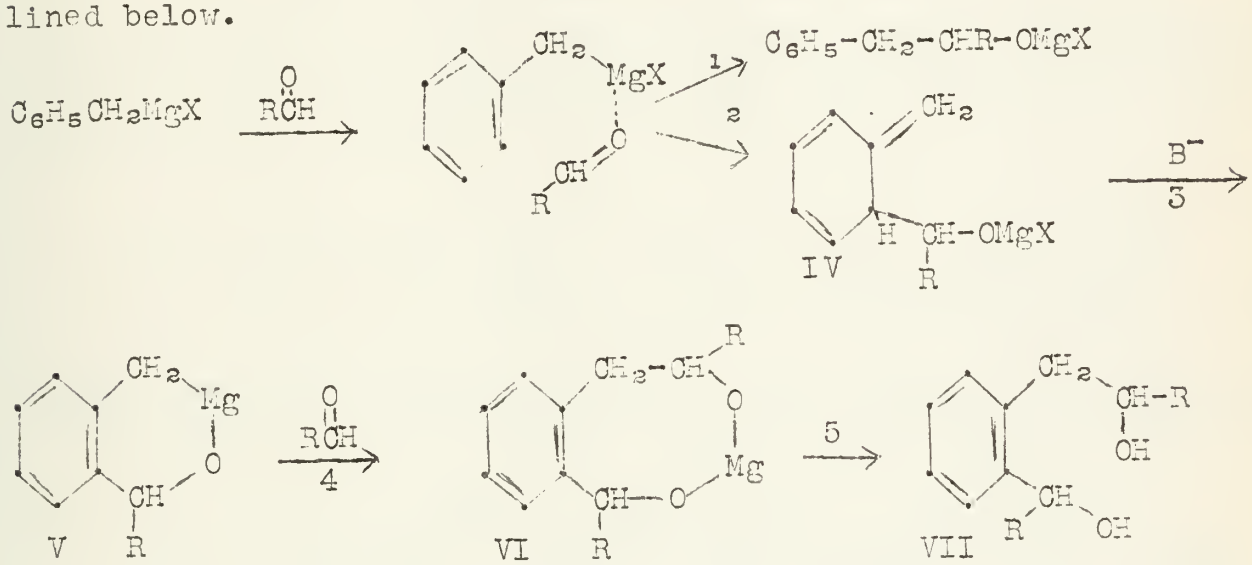
III

Table I

| Aldehyde | Theoretical Yield | Mole % Abnormal Product | Type of Abnormal Product |
|---|---|---|---|
| Formaldehyde | 40% | 100% | II |
| Acetaldehyde | 61% | 47% | III |
| Propionaldehyde | 97% | 64% | III |
| n-Butyraldehyde | 73% | 45% | III |
| i-Butyraldehyde | 88% | 15% | III |
| n-Heptaldehyde | 69% | 20% | III |
| 2-Ethylhexaldehyde | 72% | 8% | III |
| Citronella | | | |

Benzaldehyde produces the normal product and an ether obtained by dehydration of the diol III.[5]

In view of these products the mechanism proposed is outlined below.




Since no o-tolylcarbinols were obtained except with formaldehyde intramolecular transfer of the hydrogen atom involving structure IV is ruled out. Because increasing electrophilic reactants seem to favor abnormal products, e.g., (acyl halides give some abnormal product while esters give only normal ones), the amount of abnormal product should correspond with the electrophilic character of the aldehyde. The aldehydes arranged in this order should be

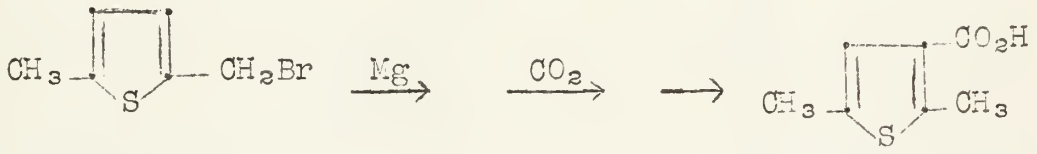
$CH_2O$ i-butyraldehyde propionaldehyde acetaldehyde.

One can assume this order from the hyperconjugation effect of the group attached to the carbonyl. From table I, formaldehyde gave 100% abnormal product, while propionaldehyde is next. A explaination for the decrease of abnormal products in the higher homologs may be that of steric effects.

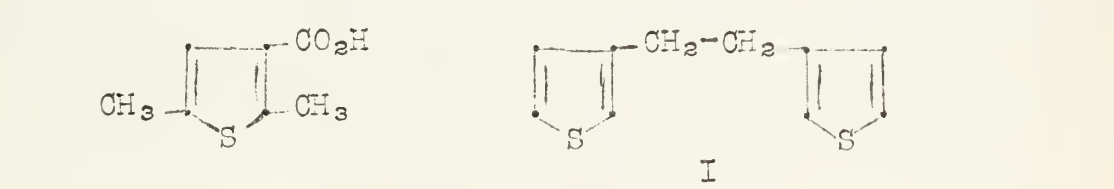
Benzylmagnesium halides react with alkyl-α-haloalkyl ethers, ROCHXR', to give normal ethers along with abnormal ethers. Halm and Simmers[7] investigated the effect of a regular structural variation in a series of these α-haloethers. The abnormal ethers where ring substitution has occurred were not isolated but the reaction mixtures were oxidized and the corresponding acids, benzoic, phthalic or terephthalic acid isolated.

The amount of abnormal product decreases rapidly (12 to 1%) as R' changes from H- to n-$C_3H_7$- and to $CH_3$-. When R increases from $CH_3$- to $C_3H_7$- the percent of abnormal products drops from 12 to 5%. Thus a change in R' greatly influences the path of the reaction, presumably because the methyl group would make the carbon less electrophilic. The increase in the size of R would seemingly make the reactive center more electrophilic but the opposite trend is observed in the amount of abnormal product. This decrease in the amount of abnormal product is observed, however, in the aldehyde series at exactly the same chain length.

Thenylmagnesium Chloride: Although carbon dioxide and benzylmagnesium chloride give normal addition products, carbon dioxide and 2-bromomagnesiummethyl-5-methylthiophene gave only 2,5-dimethyl-3-thiophenecarboxylic acid.[9]

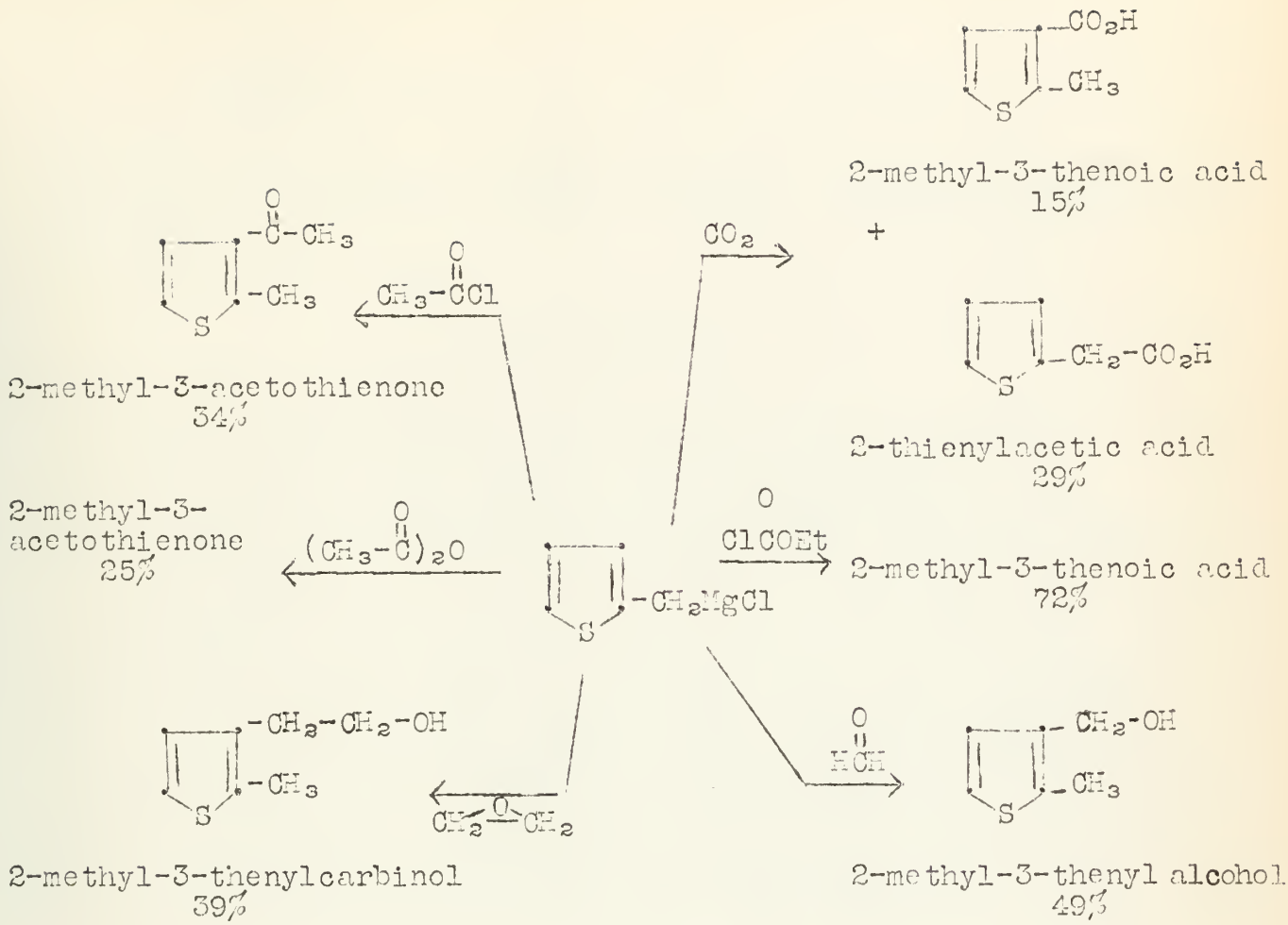


Lecocq and Buu-Hoi accounted for this by an allylic rearrangement of the bromide.



Campaigne and LeSuer[10] treated the Grignard reagent of 3-bromomethylthiophene with $CO_2$ and found that, in addition to the major product bis-2,2'bithenyl(I), some 3-methyl-3-thenoic acid was formed.

2-Thenylmagnesium chloride was prepared in yields up to 95% by using a cyclic reactor. With many reagents abnormal products were obtained in every case.




Because 2-thienylacetic acid was isolated, the Grignard reagent must be 2-thenylmagnesium chloride and not an allylic rearrangement product. In reference to Siegel's work, it would be of interest to see how other aldehydes would behave.

Furfurylmagnesium Chlorides: Although α-furfuryl chloride gives only polymeric products when attempting to prepare the Grignard 3-buryl-methyl chloride when treated with magnesium is converted into the Grignard in 70% yields.[12] Carbonation of the Grignard reagent results in a 33.5% yield of crude acid consisting of 10% 3-furylacetic acid and 90% of 3-methyl-2-furoic acid. Formaldehyde gave 3-methyl-2-furfuryl alcohol.

The conversion of 2-(chloromethyl)-benzofuran in the cyclic reactor to the Grignard appears to be normal, but no acid was formed in treatment with $CO_2$.[13] Instead an unstable, non-isolable product was obtained which behaved like o-allenylphenol.


Thus 2-(chloromethyl)-benzofuran behaves like β-haloethers which are cleaved by active metals to give olefins. (Boord's synthesis of olefins)[14]

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# THE STRUCTURE OF GLIOTOXIN

Reported by Edwin C. Steiner November 2, 1951

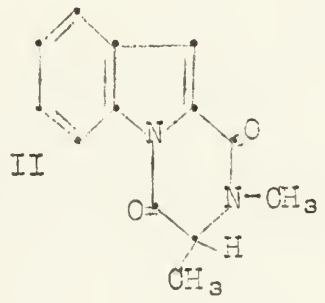
Gliotoxin is a potent crystalline antibiotic produced during the growth of several organisms, namely, Gliocladium Fimbriatum, Aspergillus Fumigatus, and an undefined species of Penicillium. Its potency was compared to that of penicillin, gramicidine, actinomycin, streptothricin and pyocyanace by Waksman.[1] It proved to be the most active bacteriostatic agent of the group. Its fungicidal activity was higher than all but actinomycin, but its bacteriocidal effect was somewhat less than some of the other compounds.

It has a decomposition point of 221.°; a molecular formula of $C_{13}H_{14}N_2O_4S_2$; is a neutral compound, insoluble in water but soluble in pyridine, dioxane and dimethyl formamide and to a lesser extent in the other usual organic solvents.

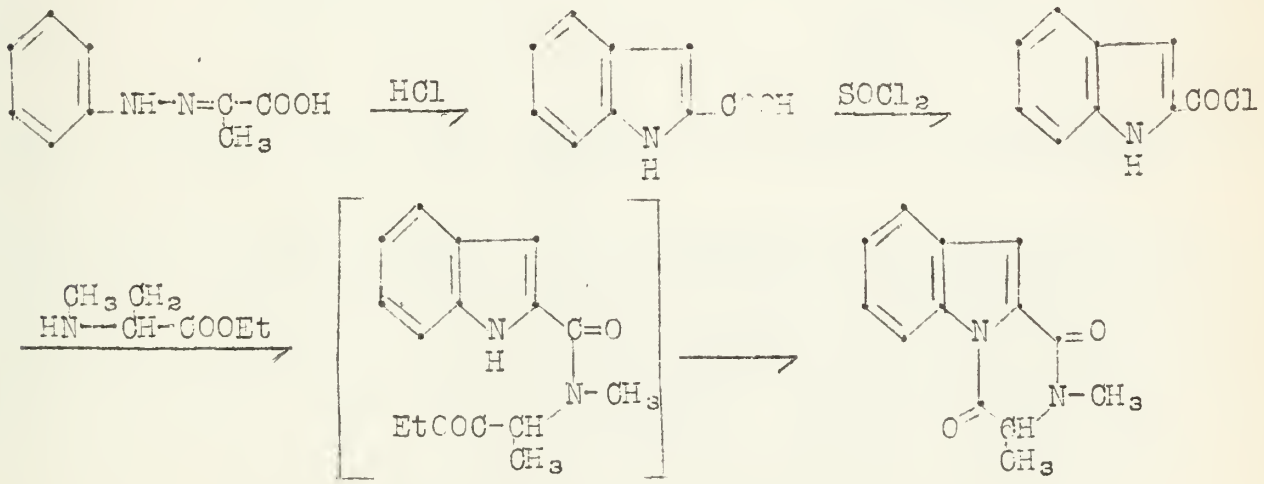
Determination of the structural skeleton of gliotoxin: Gliotoxin on treatment with HI and P in acetic acid yields a crystalline product[4]

Gliotoxin $C_{13}H_{14}N_2O_4S_2$ —(HI+P in HOAc)→ I

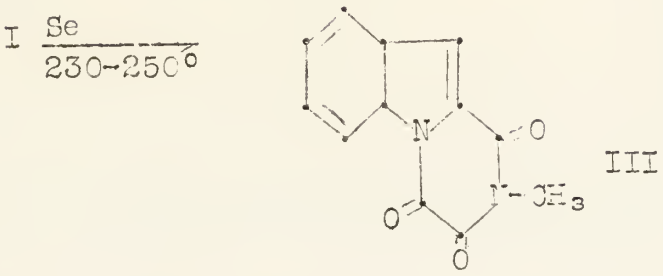
II



The structure of II was determined through successive hydrolyses, which yielded finally indole-2-carboxylic acid and l-methylamino-propionic acid. II was synthesized as follows:[6]

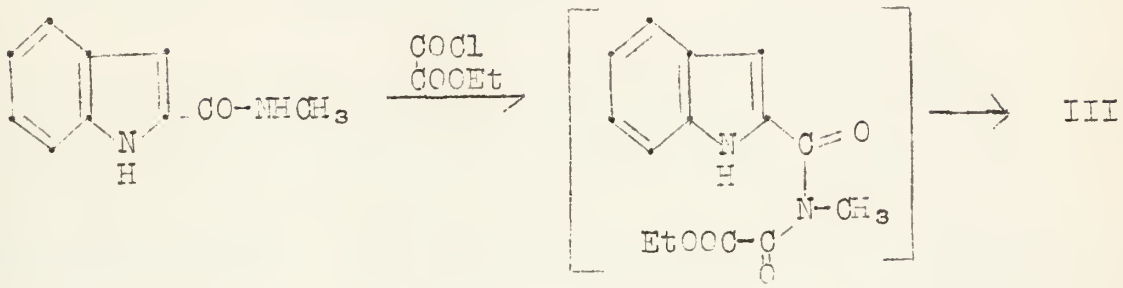


A check for this skeleton was provided by degrading gliotoxin with selenium.[5]

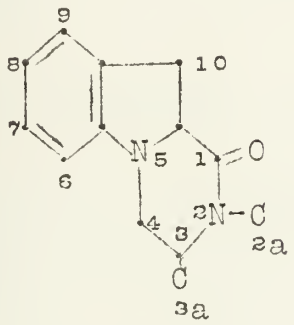


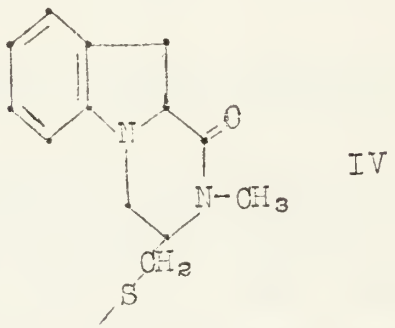

III

The structure of III was again proved by synthesis.[6]




With this evidence, the carbon-nitrogen skeleton of gliotoxin is well-established as being

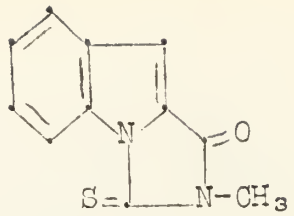



IV

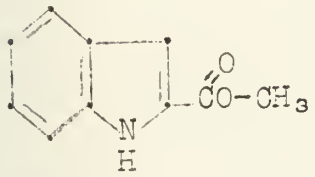
All of the atoms but three oxygens, two sulfurs, and hydrogens are taken care of by this structure.

Placement of the Sulfurs: In the Kuhn-Roth C-methyl determination, gliotoxin yields only 0.12 moles of acetic acid, indicating that there is no free C-methyl grouping. However, after treatment with aluminum amalgam in alcohol, which removes the sulfurs quantitatively as hydrogen sulfide, the compound yields 0.93 moles of acetic acid on oxidation.[7] This evidence indicates that one of the sulfur atoms is attached through a $-C-CH_2-$ linkage. There is only one of these available in the skeleton so that the structure would appear to be IV. Gliotoxin on mild hydrolysis and subsequent neutralization of the reaction mixture[7] yields a thiohydantoin V.

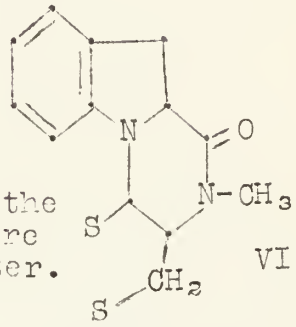
I $\xrightarrow[\text{in MeOH}]{\text{KCH}}$ $\xrightarrow[\text{neutralization}]{H^{\oplus}}$ 

V

The structure of V was proved by synthesis.[10,12]

 + $CH_3NCS$ $\xrightarrow[\text{sealed tube}]{180^\circ}$ V

Since sulfur is attached to the 4-carbon in the derivative, it is assumed to be attached there in gliotoxin. This is shown to be valid later. The structure now appears as VI.



VI

Nature of the Sulfurs: Indications are that the sulfurs exist as a disulfide link.[7]

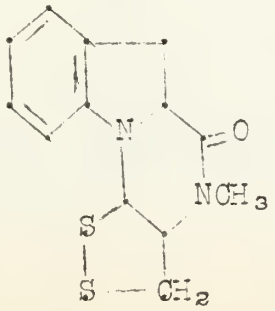
a) I + KOH ⟶ intense yellow which fades to pale yellow may be compared with the known reaction: R-S-S-R + KOH ⟶ RSK + RSOK which is intense yellow and unstable, leading to the fading of color.

b) I + $Na_2PbO_2$ ⟶ PbS in 70-78% yield may be compared with the known reaction: cystine + $Na_2PbO_2$ ⟶ PbS in 75-80% yield.

c) I + $K_2S$ ⟶ $C_{13}H_{16}N_2O_4S_3K_2$, a crystalline salt which is highly unstable, liberates $H_2S$ on acidification, gives precipitates with heavy metals, gives a positive nitroprusside test may be compared with the reaction: R-S-S-R + $K_2S$ ⟶ RSSK + RSK which is a typical disulfide reaction which leads to the same results.

d) A disulfide would neatly explain the thiohydantoin formation as will be shown later.

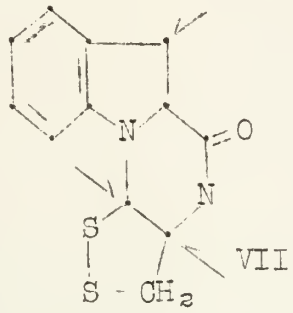
This evidence then leads to the structure VII.



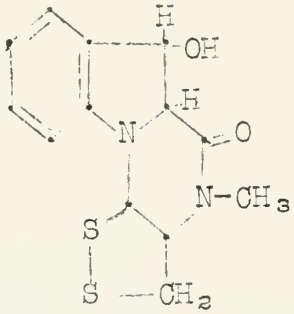
VII

Placement of three Oxygens: In considering where the three remaining oxygens go, several positions may be ruled out. 1) The benzene ring is unsubstituted in all derivatives, hence would be in the original. 2) In all degradation products the 2a-carbon appears as N-$CH_3$, and hence would be ruled out. 3) The 1-carbon must be carbonyl since it comes through all degradations as such and since the adjacent nitrogen would be basic if it weren't in an amide linkage here. 4) The 3a-carbon must be substituted only by sulfur in order to be able to give the observed Kuhn-Roth results after desulfurization by aluminum amalgam.

This leaves positions 3,4 and 10 as possibilities shown in VIII.



VII

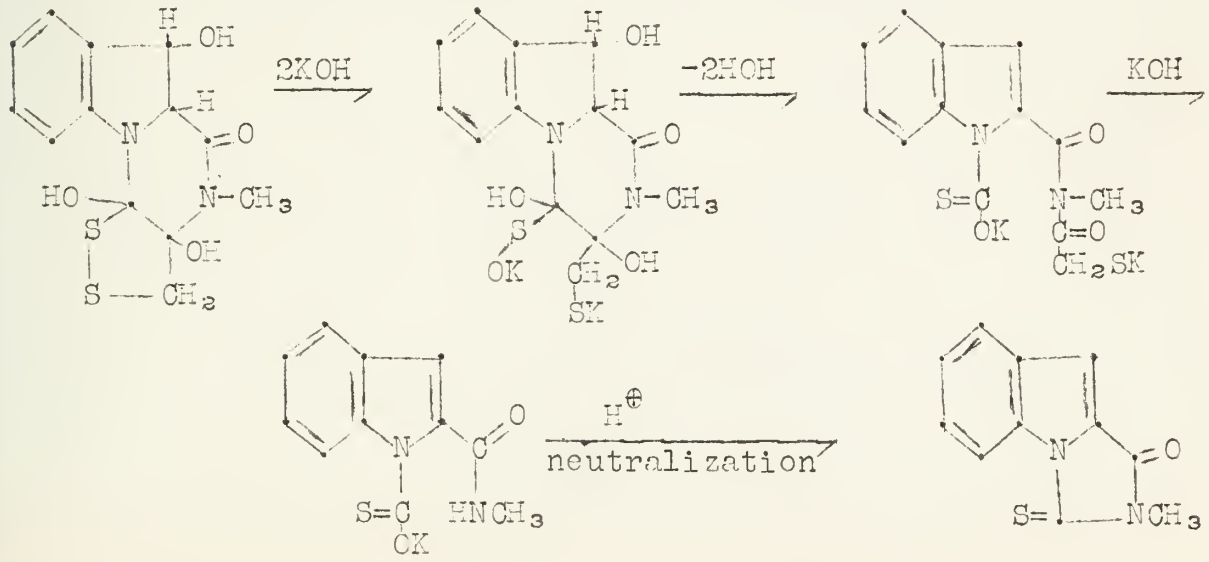


IX

A Zerewittinof determination[3] indicates two and possibly three active hydrogens. Actylation[12] and benzoylation[3] yield diacyl derivatives. The conclusion then is that there are at least two hydroxyl groups and possibly three.

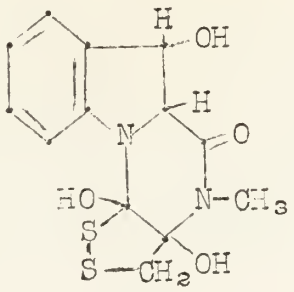
One of these would logically be on the 10-carbon. Either acid or base would dehydrate this to the observed indole nucleus, IX. The compound now has $C_{13}H_{12}N_2O_2S_2$, leaving $O_2H_2$ to be placed. This fragment would have to consist of two -OH groups and they would fall into position 3 and 4.

Now the thiohydantoin formation may be explained[12]:



+ $KSCH_2COOK$

All the reactions and observations are compatible with the rather tentative but preferred structure of gliotoxin (IX):



X

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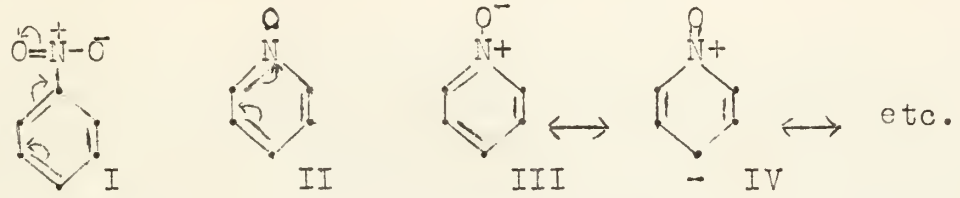
# PYRIDINE-N-OXIDES AS ORGANIC REACTION INTERMEDIATES

Reported by Louis A. Carpino November 9, 1951

ELECTRONIC NATURE The substitution reactions of pyridine resemble those of nitrobenzene since the tertiary nitrogen atom tends to withdraw electrons from the ring. Attack by electrophilic reagents occurs only under extreme conditions, entering groups becoming attached at the 3- and 5- positions. By the simple maneuver of forming the tertiary amine oxide the electronic picture is considerably altered and facile attack at positions 2- and 4- becomes possible, thus indicating the contribution of resonance hybrids such as IV[1].

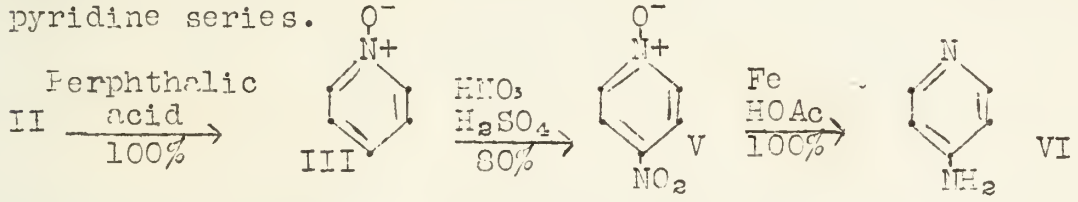



I II III IV

Such resonance forms are also indicated by dipole moment studies[2] since the moment of pyridine-N-oxide (III, PNO) is considerably smaller than that of trimethylamine oxide. This would be expected if the above excited structures of opposite sign contributed toward the overall molecular architecture of PNO.

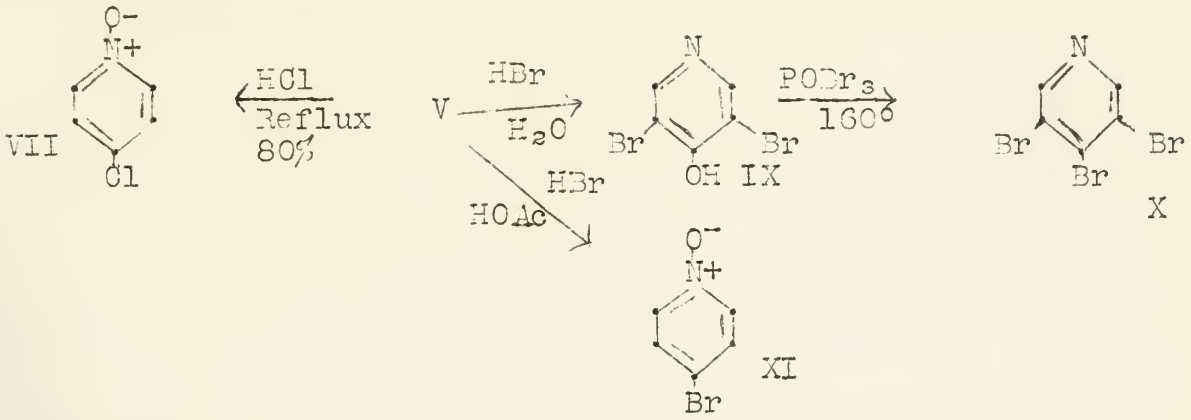
PREPARATION The N-oxides are generally prepared through the use of such oxidants as peracetic, perbenzoic and perphthalic acids. The oxide is formed either to activate substituents already present, e. g., halogens in the 2- and 4- positions or in order to profit by the strong orienting influence of the N-O link.

REACTIONS At temperatures of about 300° pyridine is nitrated to give humble yields (15-20%) of 3-nitropyridine while PNO is easily nitrated, the 4-nitro compound being obtained in nearly the theoretical amount, none of the 2-nitro compound being obtained although it might be expected.[3,4] Due to its ease of preparation in high purity and the interesting reactions which it can be induced to undergo, 4-nitro-PNO (V) is destined to become a choice intermediate in the pyridine series.



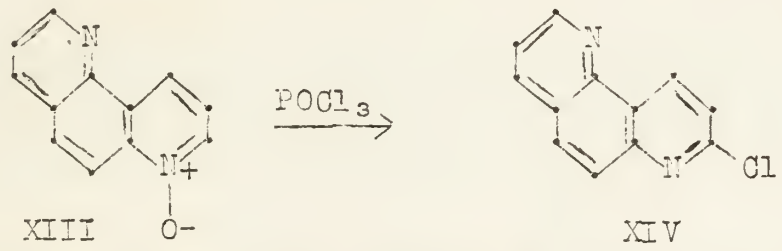

II III V VI

Direct replacement of the labile nitro group leads to a variety of useful products. Refluxing in aqueous HCl provides admirable yields of 4-chloro-PNO (VII). As shown in the following scheme HBr leads to different compounds depending on the conditions.[3] IX was not positively identified but could be converted smoothly into the known tribromo derivative.



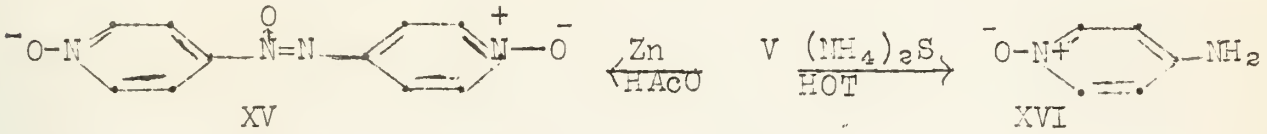

Treatment with aqueous NaOH leads to replacement of the nitro group by hydroxyl[3] but the reaction is complicated by the appearance of by-products. The same conversion has been achieved in fair yield by heating in acetic anhydride in the presence of dimethylaniline.[5] Smoother reactions were observed by using alkali in the presence of alcohols or phenols.[3] This provides a convenient route to 4-alkoxy or phenoxy derivatives.

The action of inorganic oxychlorides on 4-nitro-PNO causes chlorination and reduction at the same time, e. g. sulfuryl chloride provides 2,4-dichloropyridine[1] in modest yields. In cases where a mixture of monochbro compounds is formed there is more extensive attack at the 4-position. Quinoline-N-oxide with $SO_2Cl_2$ gives 62% 4-chloroquinoline and 38% 2-chloroquinoline.[6] The reactions of quinoline-N-oxide and 4-nitroquinoline-N-oxide appear to parallel exactly those of the pyridine series.[7,8,9] This suggests that the reactions could be extended to provide entry into the quite unreactive phenanthrolines which normally cannot be nitrated, sulfonated, brominated or Friedel-Crafted. In an attempted preparation of 4-chloro-m-phenanthroline British workers[10] found surprisingly enough that only the 2-chloro compound (XIV) could be obtained, as shown below.




SELECTIVE REDUCTIONS Aliphatic amine oxides are very readily reduced but in the pyridine series it is fortuitous that the N-oxides are somewhat resistant to reduction. The N-O link will generally survive a sequence of reactions and can be reduced at the desired point to the free base. The customary procedure involves Fe and HOAc as indicated above in the preparation of 4-aminopyridine (VI).

With suitable caution the $-NO_2$ group may be reduced to $-NH_2$ without affecting the N-O link. In addition the usual series of azo-, azoxy- and hydrazo- compounds can be obtained as shown below.[11] It is significant that in the case of the azoxy compound (XV) condensation of two molecules has occurred in an acid medium. This is remarkably different from the case of nitropyridines or nitrobenzenes which requires an alkaline medium for condensation.

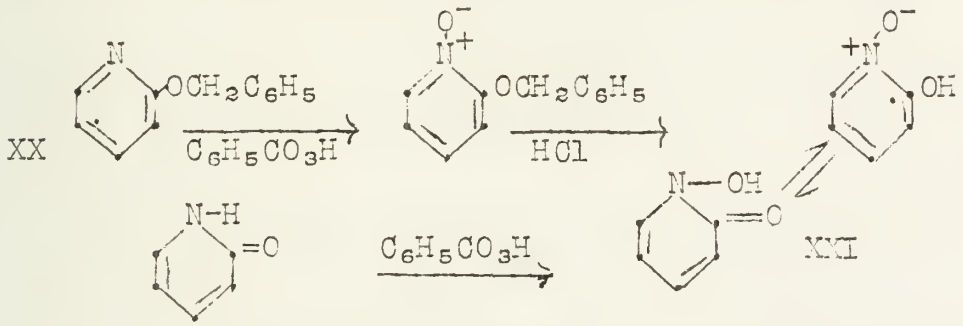


XV XVI

Zn + NaOH ⟶ 4,4'-hydrazopyridine-1,1'-dioxide (XVII)
Cold $(NH_4)_2S$ ⟶ 4,4'-azopyridine-1,1'-dioxide (XVIII)

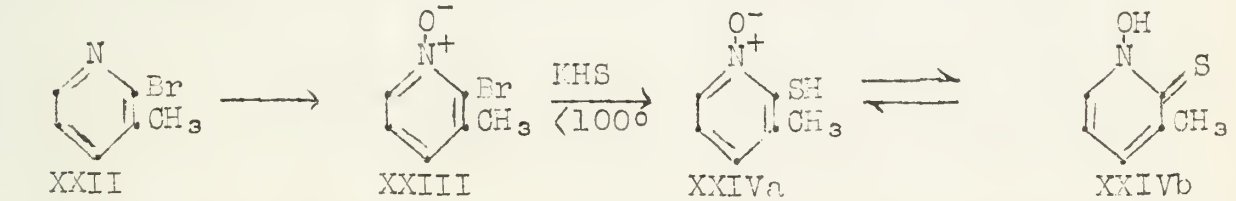
TAUTOMERISM OF HYDROXYPYRIDINE-N-OXIDES Substituted pyridine-N-oxides which contain a hydroxyl group in a 2- or 4- position are tautomeric with the corresponding N-hydroxypyridones which themselves can be thought of as cyclic hydroxamic acids or their vinylogs. Spectral studies[12] show these compounds to exist in the form of the pyridone rather than as the oxide.

N-hydroxy-2-pyridone (XXI) was easily prepared from 2-benzyloxypyridine (XX) and later it was found that 2-pyridone itself could be directly oxidized by perbenzoic acid to the same compound.[16]



XX XXI

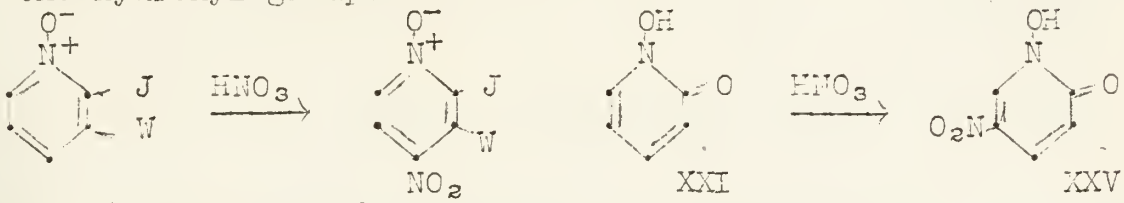
Investigations of the halogenated pyridine-N-oxides have indicated further synthetic uses for these materials. In the preparation of 3-methyl-N-hydroxy-2-pyridinethione[13] (XXIV) it was not possible to proceed by oxidation of a 2-pyridylthioether due to the ease of oxidation of the divalent sulfur.



XXII XXIII XXIVa XXIVb

The above conversion (XXIII ⟶ XXIV) requires only brief heating at steam bath temperatures indicating that 2- and 4- halopyridine-N-oxides are considerably more active than the corresponding pyridine derivatives. Indeed, the transformation of 2-iodopyridine into 2-mercaptopyridine demands extended treatment with KSH at elevated temperatures in sealed tubes.[15]

ORIENTATION IN SUBSTITUTED PYRIDINE-N-OXIDES When the ring contains 2- or 3- bromo, ethoxy, or methyl groups nitration still occurs in the 4- position indicating that the directive influence of the N-O link is even greater than that of the alkoxy group.[1,4,15] On the other hand the nitration of N-hydroxy-2-pyridone (XXI) yields 5-nitro-N-hydroxy-2-pyridone (XXV), in which the entering group is found para to the hydroxyl group.[13]




1) W = $C_2H_5O$-; J = H
2) W = Br ; J = H
3) W = H ; J = $C_2H_5O$
4) W = H ; J = Br
5) W = H ; J = $CH_3$

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# STUDIES ON THE MECHANISM OF THE CANNIZZARRO REACTION

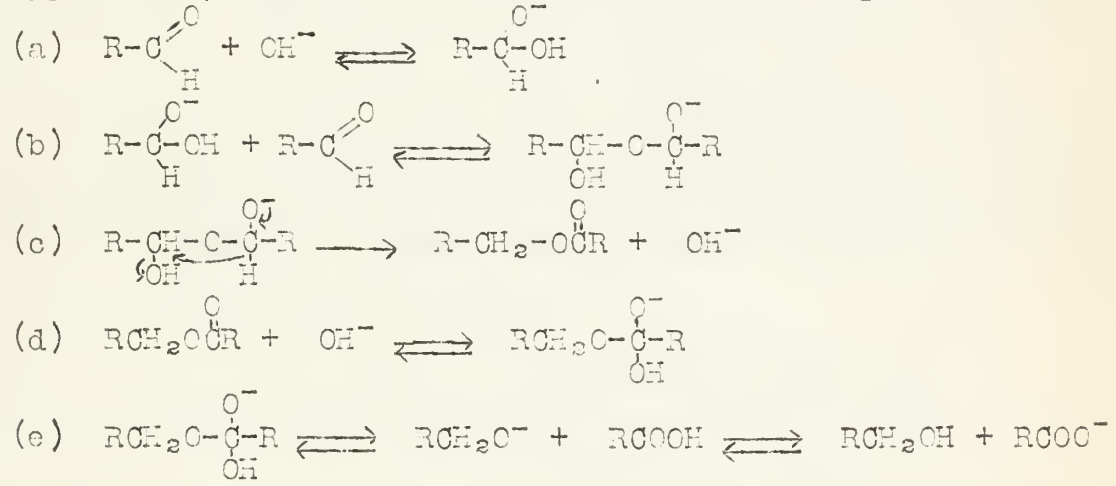
Reported by J. P. Freeman November 9, 1951

The Cannizzarro reaction, the heterogeneous alkaline dismutation of aromatic aldehydes, has been known for several decades, but the mechanism of this reaction has been a matter of some dispute and as yet is still in doubt. Of the various routes proposed for it, those of Geissman[1], and of Hammett[2] as modified by Kharasch and Snyder[3], and Alexander[4] have received the most serious attention.

Into an adequate mechanistic hypothesis the following three salient facts must be integrated:

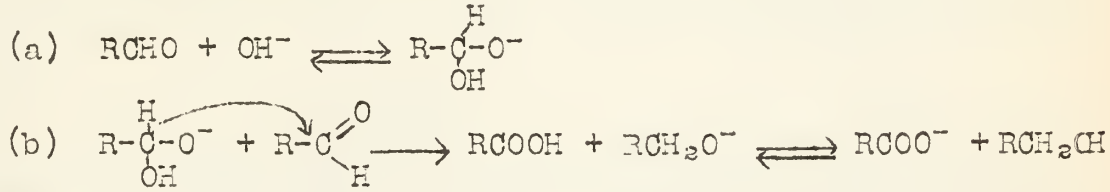
1) Reactions carried out in homogeneous medium are characterized by third order kinetics[4]--- $-d(ArCHO)/dt = k(ArCHO)^2(OH^-)$ [It has been shown that the heterogeneous reaction is a summation of two homogeneous reactions with no complicating occurrence at the liquid interface.[3]]
2) The hydrogen transfer involved in the oxidation-reduction scheme must take place directly between aldehyde molecules without interaction of the solvent. This was shown by carrying out the reaction in heavy water.[5]
3) Benzyl benzoate has been isolated from benzaldehyde reaction mixtures and probably is an intermediate under certain conditions.

Mechanism I--Intramolecular Hydride Ion Shift: On the basis of previous suggestions, Geissmann[1] proposed the following mechanism:

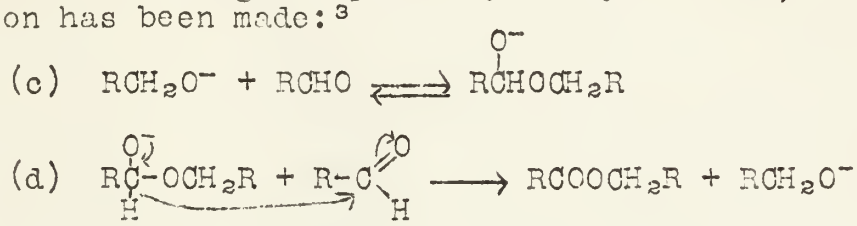


The key step is (c) in which a 1,3 shift of a hydride ion to displace a hydroxyl group is postulated. This transfer is unique in organic chemistry and no precedent is known for it in alkaline solution. Alexander attempted to find some evidence for such a shift in what was thought to be a very favorable case.[6] He subjected a series of β-aminoaldehydes in the form of their quaternary salts to Cannizzarro conditions, but he was unable in any case to find any saturated acid.

Mechanism II--Intermolecular Hydride Ion Shift: Hammett[2] proposed an alternate mechanism involving transfer of a hydride ion directly from one aldehyde molecule to another. He objected to the ester intermediate on the grounds that benzyl benzoate, for instance, is too resistant to hydrolysis. This objection has been shown to be groundless.[4] His mechanism:



This mechanism does not account for the benzyl benzoate formed, but, since it was later shown that the heterogeneous reaction is catalyzed in the organic phase by benzylate ion, the following modification has been made:[3]

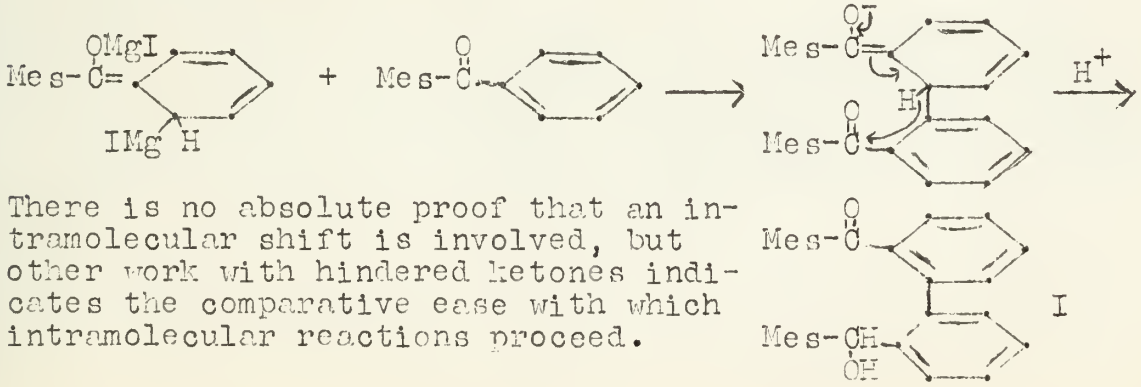


From solubility considerations it should be apparent that this path should be the predominant one in the combined rate expression.

Alexander[4] attempted to distinguish between these two mechanisms in the hydride shift step by studying the kinetics of the reaction in the case of phenylglyoxal. Mechanism I would require second order kinetics, while Mechanism II would be at least third order. The reaction was found to follow second order kinetics.

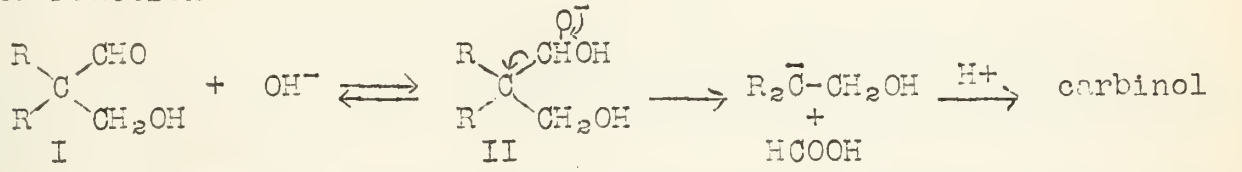
It appears possible then that an intramolecular hydride shift in alkaline solution is possible. Such a shift over a longer carbon chain length has recently been postulated by Fuson and Hornberger.[7] The bimolecular reduction of benzoyl mesitylene with magnesious iodide produced a coupling product which was identified as I.

Its production is pictured as follows:



There is no absolute proof that an intramolecular shift is involved, but other work with hindered ketones indicates the comparative ease with which intramolecular reactions proceed.

Quite recently Burr[8] discovered another course for the reaction. In studying the reaction of formaldehyde with aldehydes containing α-hydrogen atoms, he found that the second step (the crossed Cannizzarro reaction) involves displacement of the aldehyde group as formic acid when the $R_2C-$ group is a strongly basic one. For instance, in the case of 9-formylfluorene, the product obtained was 9-fluorenemethanol. In the case of diphenylacetaldehyde, only the 1,3 glycol was obtained. He proposes the following course for the reaction:




Burr thinks that it is reasonable to expect that (II) is also an intermediate in the ordinary Cannizzarro reaction, and that the course that the reaction takes from there (leading to the carbinol or glycol) depends upon the basicity of the hydrocarbon residue. Thus he postulates that the aldehyde reacts with hydroxyl ion at a faster rate than it can accept a hydride ion from the formaldehyde-hydroxide complex. If this first step is admitted, then the basicity of the aldehyde determines whether it reacts with formaldehyde to form the ester (Mechanism I), or decomposes to formic acid and the carbinol. This explanation would tie up this anomalous reaction with the Cannizzarro reaction. It cannot be related to Mechanism II.

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# EIGHT- AND HIGHER MEMBERED RING COMPOUNDS

Reported by W. E. Smith November 9, 1951

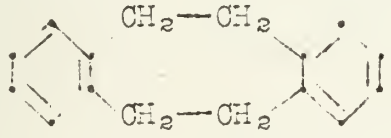
The formation of higher membered ring compounds from an open-chain structure is achieved with difficulty. The possibility of rotation of a group about the bonds joining the atoms of the chain reduces the chance of atoms widely separated along the chain of coming within reacting distance. As the chain length increases, the chance of reaction becomes smaller.

Two methods of overcoming this difficulty are (1) high dilution technique[1] and (2) the acyloin reaction[2] (the restriction in movement of reactive terminal groups by adsorption on the surface of metallic sodium).

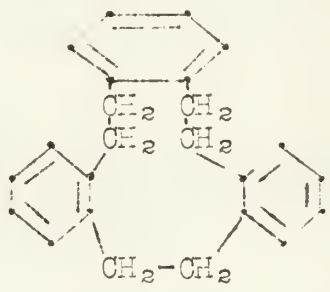
A third method,[3] that might be used, is the restriction of the rotational possibilities by having a number of atoms composing a chain held in the form of a rigid group or groups.

There are several possibilities but the type that will be discussed is the simplest approach in securing the required rigidity, i. e., the ortho, meta and para disubstituted benzene derivatives and 1,7-disubstituted naphthalene derivatives, with x and y representing the same or different functional groups in the positions indicated.

S-Dibenzcyclooctadiene:[7] Probably the simplest of these is the formation of s-dibenzcyclooctadiene (I) in about 6% yield, m. p. 108.5° and a smaller amount of s-tribenzcyclododecatriene (II), m. p. 184.5°, by refluxing o-xylylene dibromide in dry dioxane in the presence of an excess of "powdered" sodium for 15-20 hours.




I

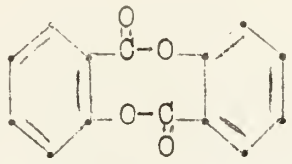



II

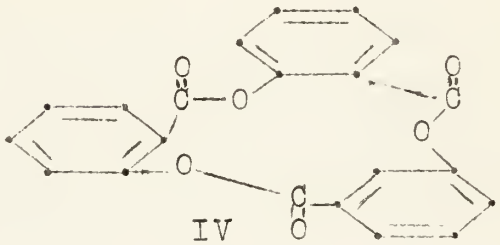
The structure and stereochemistry of the 2 cyclic hydrocarbons is of great interest. Compound (I) is identified by the fact that it has a center of symmetry and the infra-red spectroscopic examination shows no free methyl groups.

S-dibenzcyclooctadiene (I) is probably capable of existing in two forms. In the first form, the molecule is rigid and possesses a plane and center of symmetry. In the second form, the central ring system is mobile and a gentle twisting pressure applied to the right hand benzene ring causes the latter to fold over until it reaches the extreme position above the former left hand ring. The latter has two planes of symmetry, but no center of symmetry. Therefore it follows that the rigid form is the one isolated. A search for the second form has been unsuccessful.

Di- and Tri-Salicylides:[4] O-Acetyl salicylic acid heated under diminished pressure gave off acetic acid leaving a residue probably a polymeric anhydride. The residue was then distilled at 300-350° and two salicylides were isolated by crystallization. One melted at 234° (III) and the other, at 200° (IV).



III

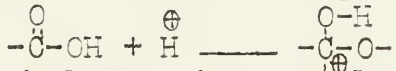


IV

Previous workers using other methods of synthesis had made identical compounds and referred to them as α-and β-disalicylides. However the α-disalicylide had been identified as cis-disalicylide by its dipole moment which was 6.26 D and the β-disalicylide was in truth a trisalicylide. No trans-disalicylide was isolated.

The reactivity of the cis-disalicylide is greater than the tri-form. This is probably owing to two factors:

1. The lactonic groups in the cis-form project in such a manner that reaction initially involving the carbonyl oxygen atoms:

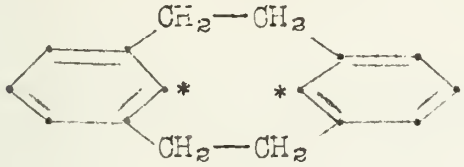


is facilitated while in the trisalicylide steric factors are less favorable

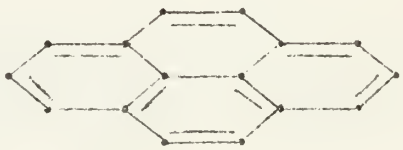
2. In cis-disalicylide the benzene rings and esters groups are inclined at an angle of 90° to one another whereas in the trisalicylide these groups are almost coplanar.

Therefore the possibility of resonance in the cis form is restricted and appears to decrease the stability compared with that of the trisalicylide.

Di-m-xylylene and Tri-p-xylylene:[5] When m-xylylene dibromide is heated in anhydrous ether with powdered sodium and a small quantity of bromobenzene and sodium iodide, it yields a 10-membered ring compound (V) in 12% yield which melts at 132-133°.



V



VI

The formula assigned to compound (V), even though its structure is not attractive stereochemically, proved to be correct. The compound upon treatment with Pd-C in an open tube at 270-310° undergoes cyclodehydrogenation with loss of 6 atoms of hydrogen and bridging of the ring yielding the pyrene (VI).

With $AlCl_3$, 1,2,2a,3,4,5 hexahydropyrene (VII) was formed and characterized as its picrate.

VII

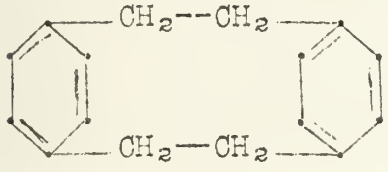
Di-m-xylylene (V), a mobile molecule, may take 3 forms as shown by models:

1. A stepwise trans form in which the benzene rings are in parallel planes.
2. Two identical cis-forms with the benzene rings inclined at an angle of about 60°.
3. A twisted form through which the cis-forms pass during interconversions.

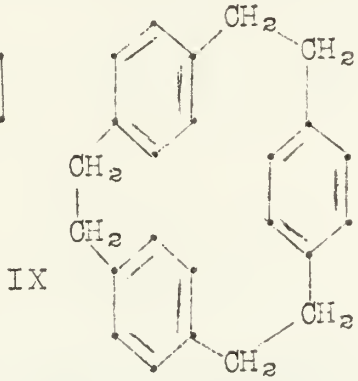
If the molecule (V) possesses the normal bond angles and lengths then the marked C atoms would be separated by a maximum distance of about 1.8 A in trans- and cis-forms. The minimum distance between non-bonded CH groups is normally about 4 A. There is clearly considerable strain in (V) and the most probable form is a somewhat distorted trans-form.

In the action of sodium on either p-xylylene dibromide or dichloride, 1,2 di-p-tolylethane and a mixture of p-di(2-p-tolylethyl) benzene m. p. 140-141° (X) and tri-p-xylylene (IX), m. p. 166-167, difficult to separate, is obtained. None of (VIII) is detected. Compound (IX) and (X) are isolated by fractional distillation and crystallization.

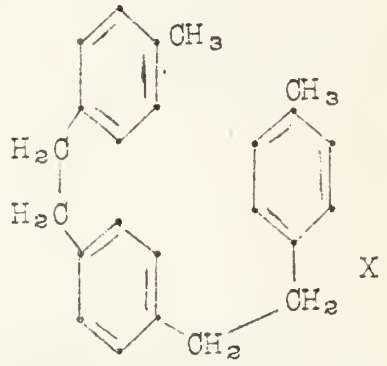
The structures of (IX) and (X)



VIII

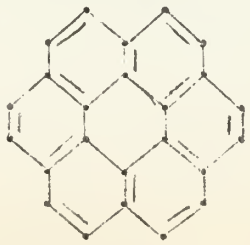


IX



X

which exhibit no properties of unsaturation, are based on analysis and molecular weight determination. Further evidence on support of the structure of (IX) is the dehydrogenation and oxidation with PdO to form coronene (XI) in 1.9% yield. A similar experiment with (X) gives no trace of coronene.



XI

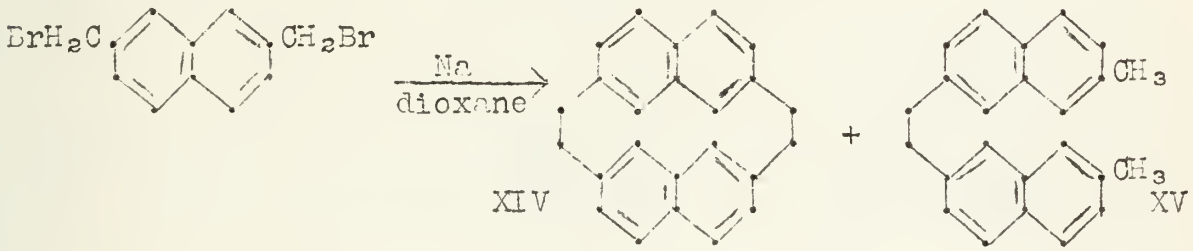
The molecule of tri-p-xylene (IX) should be strainless because the three benzene rings can take up positions inclined to the general plane of the 18-membered ring, thus avoiding interference between non-bonded aromatic CH groups.

Di-(naphthalene 2,7-dimethylene):[6] 2,7-Dimethylnaphthalene in carbon tetrachloride was converted by pure N-bromosuccinimide to dibromomethylnaphthalene (XIII) in the presence of benzoyl peroxide. The compound (XIII) was then treated with sodium in dioxane in the presence of sodium iodide to give di(naphthalene 2,7-dimethylene) (XIV) in 16.3% yield and 1,2 di-(7-methyl-2-naphthyl) ethane (XV) in 4.3% yield.

Compound (XIV) is a 14-membered ring with two rigid groups of seven atoms, in which considerable strain must be present owing to the close proximity of the two pairs of interior CH groups.

The necessary separation of these groups to carbon-carbon distance of something over 3 A is probably achieved by distortion of the normal bond angles in a manner analogous to that of di-m-xylylene.

Direct dehydrogenation of compound (XIV) in an inert atmosphere to produce coronene was unsuccessful. However the action of aluminum chloride on (XIV) in boiling carbon disulfide gave a high yield of 1,2-dihydrocoronene and a small quantity of coronene. When the crude mixture was treated with palladium black at 260°, a 49% yield of pure coronene (XI) was obtained.

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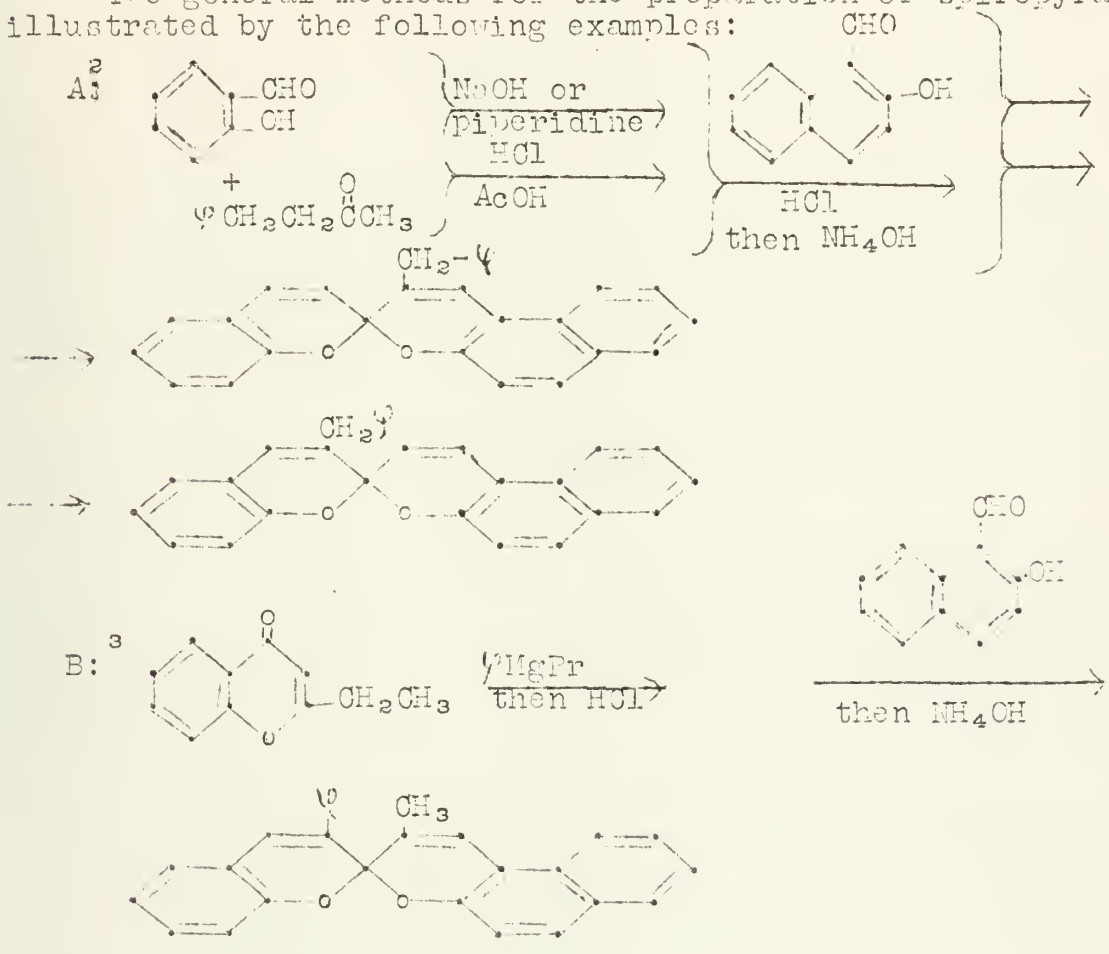
# THERMOCHROMISM OF SPIROPYRANS

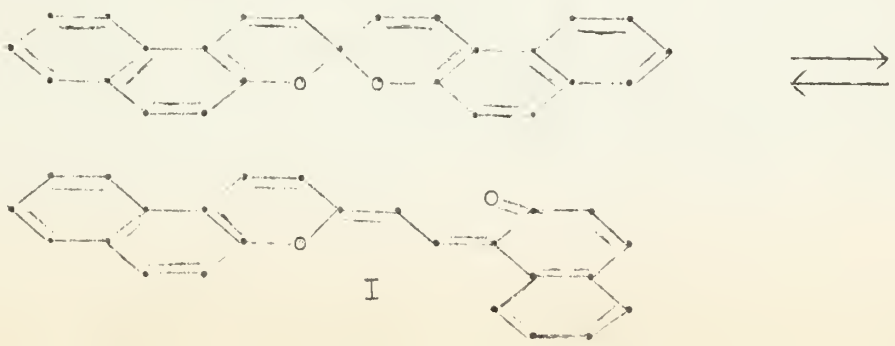
Reported by Eugene A. Kraiman November 16, 1951

Many spiropyrans exhibit thermochromism which is a marked, reversible change in visible light absorption with temperature in solutions of inert solvents. For example, di-β-naphthospiropyran[1] forms a colorless solution in cold xylene which becomes purple at about 100° and deepens as the temperature is raised. This color is stable to air, hydrogen and hydroquinone but is bleached by piperidine.

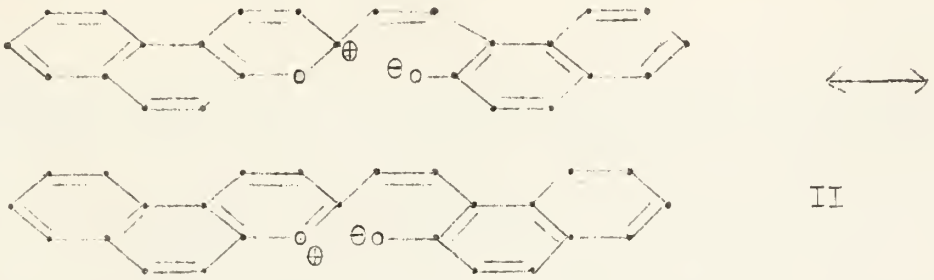
Two general methods for the preparation of spiropyrans are illustrated by the following examples:




Several explanations for this property of spiropyrans were considered. Free radical formation was excluded by reason of normal molecular weights[4,5,6] and stability of the color to oxygen[5] hydrogen[5] and hydroquinone[7] which is supposed to decolorize solutions of all known types of free radicals.[8] Formation of a quinoid type of structure (I) was suggested[6]



However, Dilthey and coworkers[4,5] objected to this hypothesis on the basis of the bleaching effect of piperidine which they ascribed to the formation of a salt with a zwitter-ion (II) formed by the spiropyran.



II

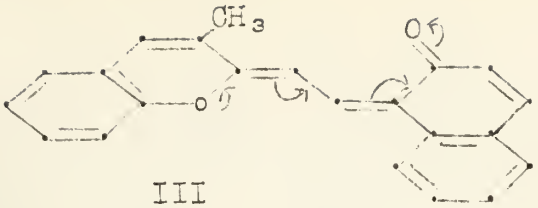
The zwitter-ion hypothesis was supported by the possibility for resonance stabilization[9] and the apparent analogy between base strength and thermochromic tendency.[10] In the case of 3- and 3'-methylbenzo-β-naphthospiropyran[11] this analogy was not valid. In addition, dipole moment measurements[12] did not appear to be in accord with the zwitter-ion structure.

The latest work[13] on this subject explains the thermochromic and basic properties of spiropyrans on the basis of the steric and energy requirements for resonance.

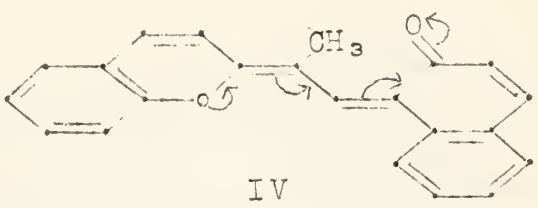
A colored resonance hybrid of the quinoid and zwitter-ion structures is postulated. The reversibility of thermochromism and the mild conditions required to produce it are considered to be indications of a low activation energy. Two general requirments for resonance are used to explain the presence or absence of thermochromism in a spiropyran and the relation to its basicity.

1- The extreme contributing structures must be of about the same energy. For this reason, dibenzospiropyran is not thermochromic as one of the benzeniod systems would be missing in the quinoid structure. However, with benzo-β-naphthospiropyran a naphthaquinoid type of structure is possible, and since this involves a smaller energy change, the compound is thermochromic.

2- All of the atoms participating in the resonance of a conjugated system must be in the same plane. Thus 3,3'-dialkylspiropyrans[7] are not thermochromic since the alkyl groups prevent coplanarity. A 3-methyl group is about 1.5Å from the quinoid oxygen in the planar molecule, but the closest approach is 3.4Å.[14] All four possible planar stereoisomers of the dialkylspiropyrans can be ruled out for steric reasons. This reasoning also explains why 3-methylbenzo-β-naphthospiropyran (resonance hybrid shown as III) is thermochromic and the 3'-methyl isomer (resonance hybrid shown as IV) is not.

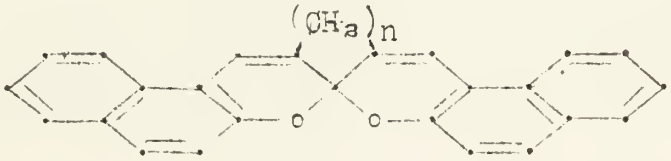


III



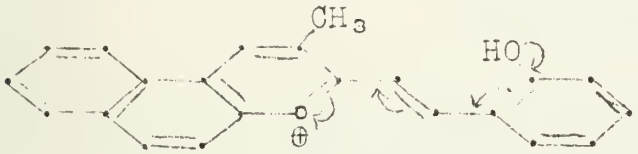
IV

The decreasing tendency for thermochromism in the series (V) where n=2,3,4,[10,15,16] also illustrates the necessity for coplanarity.

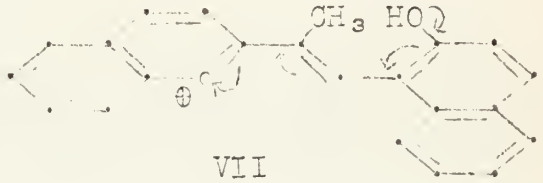


V

The basicity of spiropyrans is affected by the same steric factors since the ion formed with a proton is stabilized by resonance. Hindered spiropyrans[10,17] do not form salts with acids. Basicity and thermochromism are not always directly related because the formation of a salt does not involve a serious disturbance of the resonance of a benzenoid system. This is the reason for the equal basicity of III and IV. The protonated benzoquinoid form (VI) of IV can be planar while the protonated naphthoquinoid form (VII) cannot.



VI

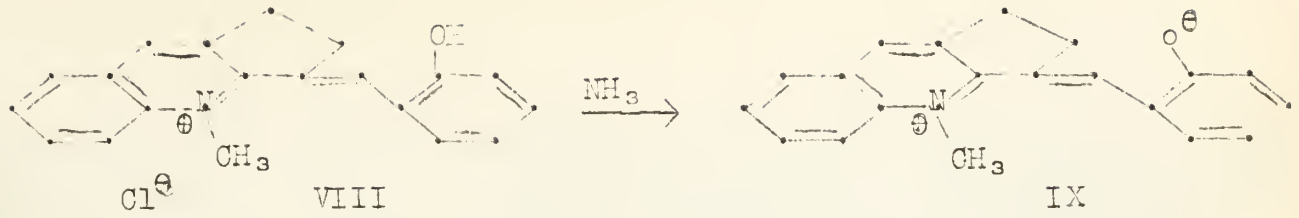


VII

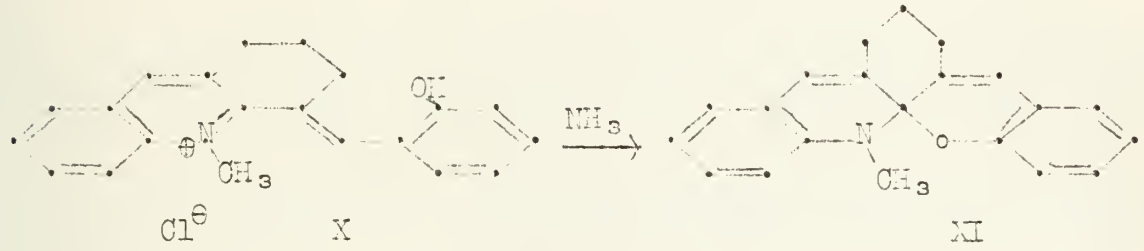
Dibenzospiropyran which is not thermochromic does form a salt.

Quinoline derivatives are used to test the hypothesis with respect to basicity since these compounds contain "centers of undisputed classical basicity". A new type of steric inhibition of resonance is encountered in the preparation of some of these compounds. Quinaldine methochloride reacts readily with salicylaldehyde while 2-ethyl-3-methyl and 2-benzyl-3-phenyl quinoline methochlorides are unreactive. Another example of this steric inhibition of methylene reactivity is cyclopentenoquinoline methochloride which reacts readily with salicyladehyde and 1,2,3,4-tetrahydroacridine methochloride which reacts only with difficulty.[18,19]

The salicylal derivatives of these latter two compounds react very differently toward base. Salicylalcyclopentenoquinoline methochloride (VIII) yields a betaine on treatment with $NH_3$. It is nearly insoluble in benzene, its solution in chloroform is deep green and in alcohol the solution is deep purple. These properties correspond to structure IX.




However, salicylal-1,2,3,4-tetrahydroacridine methochloride (X) yields a red-purple precipitate with $NH_3$ which becomes colorless on standing in contact with the mother liquor or immediately on moistening with an organic solvent. The colorless product is soluble in benzene and its solutions in other solvents are colorless. Here a non-ionic structure (XI) is probable due to the presence of the puckered six membered ring.

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# REACTIONS OF FLUOROCARBON RADICALS

Reported by Richard M. Potts November 16, 1951

The trifluoromethyl radical produced either photometrically or thermally from iodotrifluoromethane is able to bring about the polymerization of ethylene or tetrafluoroethylene. The reactions are of an unusual type yielding addition polymers of the general types $CF_3(CH_2CH_2)_nI$ and $CF_3(CF_2CF_2)_nI$ respectively.[1] The iodotrifluoromethane and ethylene show no reaction in the dark at room temperature. However when irradiated in quartz or Pyrex-glass vessels there is a slow quantitative reaction, the main product being 3-iodo-1,1,1-trifluoropropane, though some 5-iodo-1,1,1-trifluoropentane is also formed.

$$CF_3I + CH_2{=}CH_2 \longrightarrow CF_3(CH_2CH_2)_nI \quad (n = 1,2)$$

Mercury catalyzes this reaction, apparently by combining with the free iodine thereby preventing the recombination of the trifluoromethyl radical with the iodine. Traces of mercury iodide are found in the reaction mixture.

The purely thermal reaction, taking place at temperatures above 200° yields essentially the same products and is also catalyzed by mercury.

The following mechanism is postulated for these reactions.

$$CF_3I + h\nu \rightarrow CF_3\cdot + \cdot I$$
$$CF_3\cdot + CH_2{=}CH_2 \rightarrow CF_3CH_2CH_2\cdot$$
$$CF_3CH_2CH_2\cdot + CF_3I \rightarrow CF_3CH_2CH_2I + CF_3\cdot$$

The unusual chain termination reaction is postulated to account for the fact that the polymers all contain terminal iodine atoms, while only traces of molecular iodine and no compounds of the type $CF_3(CH_2CH_2)_nCF_3$ have been detected in the reaction products. Furthermore, chain termination by disproportionation of two trifluoroproply radicals

$$CF_3CH_2CH_2\cdot + CF_3CH_2CH_2\cdot \rightarrow CF_3CH_2CH_3 + CF_3CH{=}CH_2$$

or by hydrogen abstraction does not occur under optimum conditions.

An ionic mechanism involving the trifluoromethyl anion would explain the reaction products obtained, but a heterolytic bond fission is considered unlikely in these reactions in the vapor phase.

When the irradiation is continued for several days or the temperature is raised above 240° in the above reactions the C-I bond is broken and the fluoroalkane and molecular iodine are formed.[1] The reaction proceeds as follows.

$$CF_3CH_2CH_2I \rightarrow CF_3CH_2CH_2\cdot + \cdot I$$
$$I\cdot + \cdot I \rightarrow I_2$$
$$CF_3CH_2CH_2\cdot + RH \rightarrow CF_3CH_2CH_3 + R\cdot$$

The RH is probably ethylene since no trifluoropropene or -pentene is detected. Again there is no combination of two trifluoropropyl radicals to yield hexafluorohexane.

Tetrafluoroethylene undergoes reaction with iodotrifluoromethane[1] in a manner analagous to that of ethylene. The products are of the type $CF_3(CF_2CF_2)_nI$ where n varies from 2 to 10. This reaction is of interest because although tetrafluoroethylene polymerizes readily to high molecular weight, inert polymers, no method has been found so far for producing short chain polymers.

When the study of the reactions of iodotrifluoromethane and unsaturated compounds was extended to the acetylene series,[2] it was found that an addition polymerization also occurs with acetylene.

$$CF_3I + HC{\equiv}CH \rightarrow CF_3(CH{=}CH)_nI$$

The main product is 3,3,3-trifluoro-1-iodopropene although much smaller amounts of a compound believed to be 5,5,5-trifluoro-1-iodopentadiene-1,3 are produced. The reactions were carried out in sealed tubes at temperatures above 200° or with the aid of ultraviolet light in Pyrex or silica vessels. Increasing the pressure of both reactants increased the rate of reaction without changing the composition of the liquid products. The suggested mechanism is:

$$CF_3I + h\nu \rightarrow CF_3\cdot + \cdot I$$
$$CH_3\cdot + HC{\equiv}CH \rightarrow CF_3CH{=}CH\cdot$$
$$CF_3CH{=}CH\cdot + CF_3I \rightarrow CF_3CH{=}CHI + CF_3\cdot$$

Again the continued irradiation of the reaction mixture led to the breaking of the C-I bond and the formation of 3,3,3-trifluoropropene.

$$CF_3CH{=}CHI + HC{\equiv}CH \rightarrow CF_3CH{=}CH_2 + HC{\equiv}C\cdot + \cdot I$$

The iodotrifluoromethane used in these experiments was originally obtained from the reaction between iodinepentafluoride and carbon-tetraiodide.[3] Another method has since been adopted in which the silver salt of commercially available trifluoroacetic acid is spontaneously decarboxylated and iodinated in one step.[4]

$$CF_3CO_2H \rightarrow CF_3CO_2Ag \xrightarrow{I_2} CF_3I + AgI + CO_2$$

In order to study the effect of the strongly electronegative trifluoromethyl radical on adjacent organic functional groups, trifluoromethylacetylene was synthesized by the dehydroiodination of 3,3,3-trifluoro-1-iodopropene.[5]

$$CF_3CH{=}CHI \xrightarrow{KOH} CF_3C{\equiv}CH$$

Powdered potassium hydroxide proved to be more effective in this reaction than sodamide or alcoholic potassium hydroxide. Since the synthesis of 3,3,3-trifluoro-1-iodopropene involves the somewhat

dangerous handling of acetylene under pressure, this route is not convenient for the preparation of larger quantities of trifluoromethylacetylene. Therefore alternate syntheses have been developed,[6] of which the following is probably best suited for larger-scale preparation.

$$CF_3CH_2CH_2I \xrightarrow{KOH} CF_3CH{=}CH_2 \xrightarrow{Br_2} CF_3CHBrCH_2Br \xrightarrow{KOH} CF_3CBr{=}CH_2 + CF_3C{\equiv}CH$$

$$CF_3CBr{=}CH_2 \xrightarrow{Br_2} CF_3CBr_2CH_2Br \xrightarrow{KOH} CF_3CBr{=}CHBr \xrightarrow[EtOH]{Zn} CF_3C{\equiv}CH$$

Trifluoromethylacetylene is a colorless gas, b.p -48°.[4] The hydrogen atom of this compound is markedly acidic. Treatment with ammoniacal cuprous chloride, ammoniacal silver nitrate, or alkaline potassium mercuric iodide yields the corresponding fluoroacetylides.[5] These acetylides unlike those of acetylene are not of complex formation and do not retain water, groups, or anions which were linked to the metals in the original salts. Trifluoromethylacetylene is regenerated when the acetylides are treated with acid.

From studies on the effect of polyfluoro groups on nearby hydrogen and halogen atoms it has been determined that when the polyfluoro group is separated by one or more carbon atoms from the hydrogen or halogen atom under consideration it has only slight influence. For example the replacement of hydrogen on the $-CH_2X$ group of $CF_3CH_2CH_2X$ by bromine or chlorine can occure, although under more vigorous conditions than for a normal hydrocarbon. Removal of HX from $CF_3CH_2CH_2X$ and $CF_3CH{=}CHX$ is readily achieved.[6] Also $CF_3CH_2CH_2X$ can undergo Grignard formation.[7]

Henne and co-workers observed in a series of chlorination experiments[8,9,10] that a hydrogen attached to a carbon adjacent to a polyfluoro group is substantially protected from attack by atomic reagents. Henne and Whaley[9] found that 1,1,1-trifluoropropane is chlorinated in successive steps in a highly directed manner.

$$CF_3CH_2CH_3 \rightarrow CF_3CH_2CH_2Cl \rightarrow CF_3CH_2CHCl_2 \rightarrow CF_3CH_2CCl_3 \rightarrow CF_3CCl_2CCl_3$$

The chlorination tends to stop at the trichloro-stage and then proceeds directly to the pentachloro-derivative. No tetrachloro-compound was found. In contrast 1,1,1-trichloropropane yields all possible isomers on chlorination with the preponderance of chlorination on the center carbon atom. As would be expected bromine shows less tendency for omega substitution than does chlorine.[11] The acidic nature of the hydrogen atoms on the central carbon in $CF_3CH_2CH_2X$ and $CF_3CH{=}CHX$ is revealed by their ready removal as HX. A halogen atom on a carbon adjacent to the polyfluoro-group is stabilized and its removal as HX is difficult, although removal of halogens from adjacent carbon atoms (e.g., $CF_3CX{=}CHX$) can be effected.[6]

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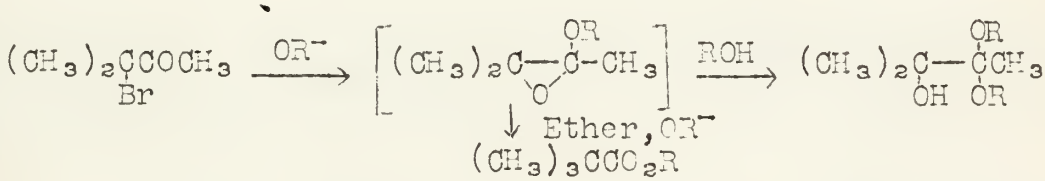
# THE FAVORSKII REACTION

Reported by N. W. Thomas November 16, 1951

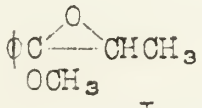
Introduction: In 1894 while carrying out a study on the reactions of α-haloketones, Favorskii[1] observed the rearrangement which now bears his name. At that time Favorskii noted that the hydrolysis of these ketones by strong alkali did not, in general, follow the course of a direct replacement of the halogen atom. Recent work has been reviewed in seminars[2] and by Jacquier[3].

Effect of Solvent: The products of the Favorskii reaction, in general, are esters (acids, amides --) and α-hydroxyacetals. Aston and Greenburg[4] noted that it was possible to obtain the ester only when working with an alkoxide in ether (benzene, toluene). When an alcoholic medium was used, only the hydroxyacetals were obtained.

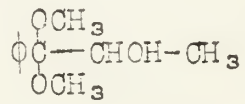
McPhee and Klingsberg[5] did not confirm these results but observed that when working in alcoholic medium, the α-hydroxyacetals were obtained in better yields. Later work[6,7] seemed definitely to establish that the solvent did influence the relative amounts of the products. Nevertheless, the possibility that change of medium alone was the factor influencing the rearrangement to the ester was ruled out by the fact that if any alcohol was present a corresponding amount of hydroxyacetal was obtained in ether medium[4]. These results were interpreted by Aston as indicating the following mechanism (illustrated by a specific example from the paper):



Epoxy intermediates of the type shown had been postulated[8,9] to account for the formation of α-hydroxyacetals from certain α-haloketones in the presence of alcoholic alkoxides. This particular phase of the mechanism has recently received ample verification.[10,11] I was isolated from the reaction of α-chloroethyl phenyl ketone and sodium methylate. Upon treatment with methanol in the presence of methoxide II was also formed, but since it was not possible to affect the transformation of I to the ester, serious doubt was cast on the epoxide as a common intermediate.



I



II

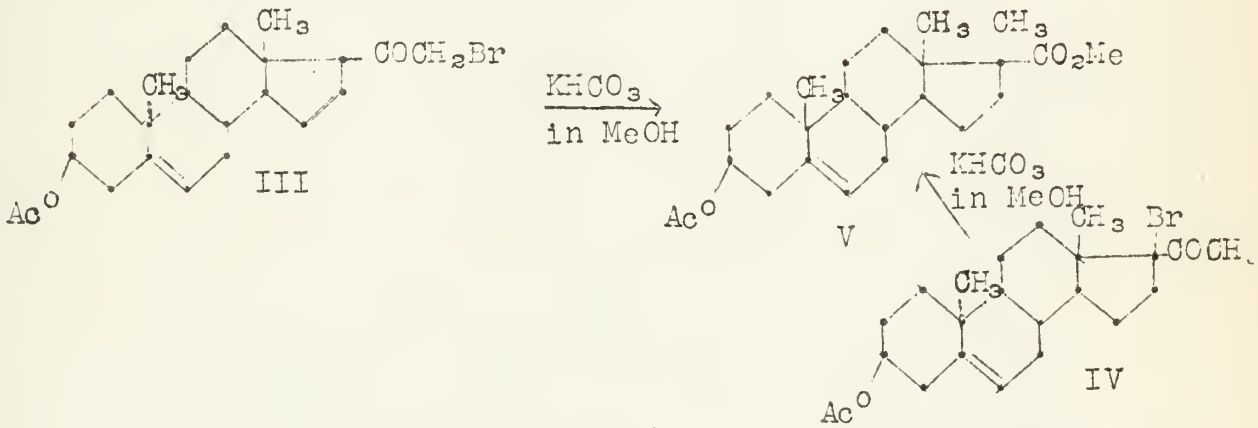
Nature of Base: The bases used in this reaction vary greatly--from calcium hydroxide-sodium carbonate mixtures to the alkoxides and thioalkoxides. From the information available it does not seem possible to predict exactly the course of the reaction. Not only the solvent and base but also the reactant is apparently important.

However, operation in the same solvent upon the same reactant makes it possible to obtain information on the influence of the base. The results of an investigation of this kind[12] carried out with α-chlorocyclohexanone are summarized in the following table.

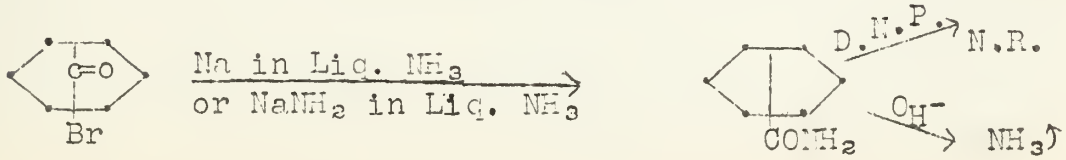
| Basic reagent | Product | Basic Reagent | Product |
|---|---|---|---|
| Sod. ethylate | 1-ethoxy-1,2-epoxy cyclohexane | Sod. cyclohexylate | epoxide |
| " methylate | methyl cyclopentyl carboxylate and 1-methoxy-1,2-epoxy cyclohexane | " phenylate | 2-phenoxy cyclohexanone |
| | | " thioethylate | 2-thioethyl cyclohexanone |
| " n-propylate | increasing amount of ester | " thiophenylate | 2-thiophenyl cyclohexanone |
| " n-butylate | | " thiocyclohexylate | 2-thiocyclohexyl cyclohexanone |
| " i-propylate | | " 2-amino ethylate | ester |
| " t-butylate | | " ethyl lactylate | ester |

In some cases the product isolated is one which can be formed by metathesis. This is not unusual and has been observed in other cases such as the α-halocyclopentanones[7,13,14,15]. Whether these apparently unrearranged products arise by metathesis or not is difficult to ascertain but at least in one case this appears to be true[6].

Illustrations: The Favorskii reaction has been studied in the steroid series[16,17]. The acetate of 21-bromo-pregnenolone, III, and 17-bromo-pregnenolone, IV, give rise to the same product, methyl-3-(β)-acetoxy-17-methyl-etio-cholenate, V.




A reaction recently described by Cope[18] appears to be of this type:



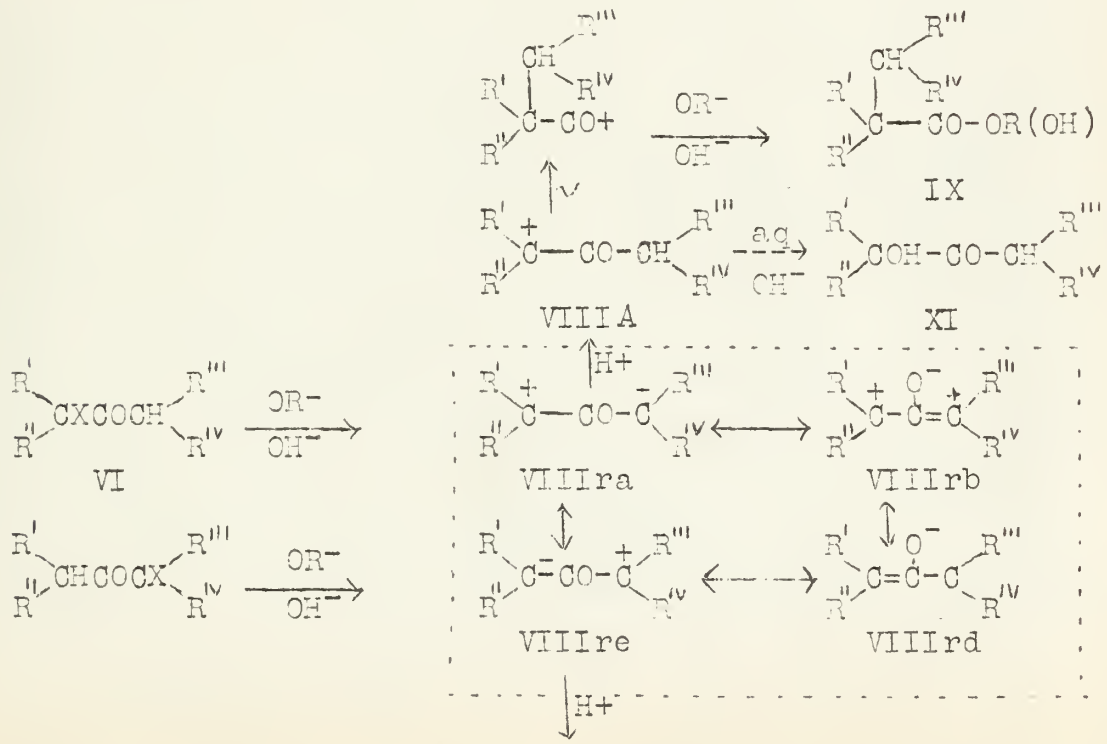
The reaction has been extended to the $\alpha,\alpha'$-dibromoketones[19] and the $\alpha,\beta$-dibromoketones[20] in which the products are found to be $\alpha,\beta$-unsaturated esters and $\beta,\gamma$-unsaturated esters respectively; for example,

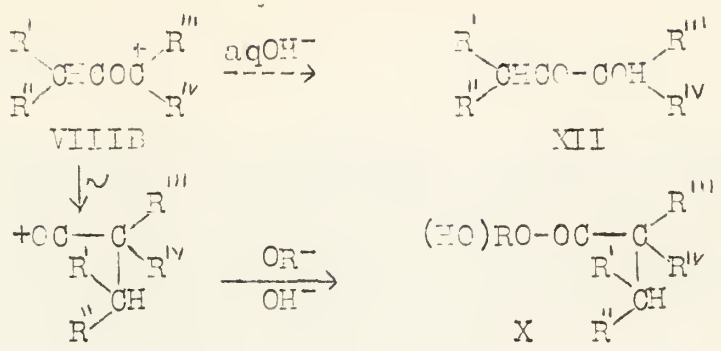
$$H_3C-\underset{\underset{CH_3O}{\overset{\|}{O}}}{\overset{Br}{\overset{|}{C}}}-C-CH_2Br \xrightarrow{OH^-} (CH_3)_2C=CH-CO_2H$$

$$R-CHBr-\underset{CH_3}{CBr}-\underset{O}{\overset{\|}{C}}CH_3 \xrightarrow{NaOCH_3} RCH=\underset{CH_3}{C}CH_2CO_2CH_3$$

Mechanism: Considerable effort has been expended to determine the mechanism of the Faworskii reaction. At least five mechanisms have been proposed[4,5,6,21,22,23,24]. At one time or another these have all been credited but with new developments, some have passed into the background, occasionally to be brought forward again by a new advocate.

The essential features of a recently published mechanism[15] are outlined by the following equations: In this VIII ra and VIII rb are the two resonance forms arising separately by ionization of the keto or enol forms of the portion derived from VI by loss of $X^-$ while VIII rc and VIII rd are the corresponding forms derived from VII. No assumption is made concerning the initial point of attack which may be removal of $X^-$ or by the removal of $H^+$. The intermediate in the rearrangement is stablized by four resonance forms; this may explain the preferance for rearrangement over direct replacement. The ester (acid) obtained will be that at the end of the most favourable path.





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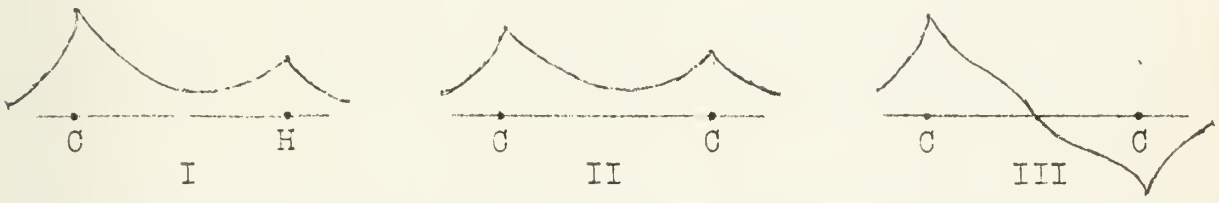
# ACETYLENIC ADIENE

Reported by Robert W. Hill November 30, 1951

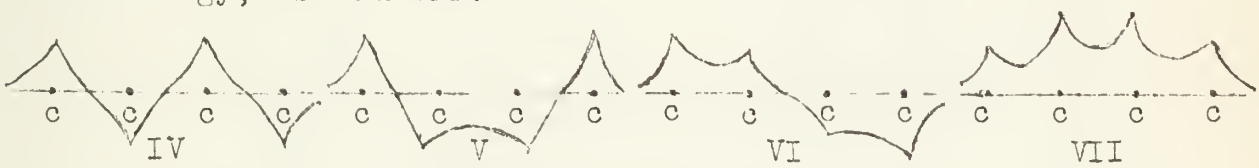
Introduction.[1,2] In quantum mechanics, particles, such as electrons, can be described by a mathematical expression, the wave function or eigenfunction. This function is defined so that the square of its absolute value, when integrated over a certain part of space, is proportional to the probability of finding the electron in that space. Thus the eigenfunction for a free electron is represented by a sine curve, or, mathematically, $\psi = e^{i2\pi x/\lambda}$.

In carbon compounds, each valence electron can be represented with reference to the carbon nucleus. Thus, in methane, or any other saturated carbon atom, functions will be obtained showing the greatest electron density along axes radiating tetrahedrally from the nucleus. A projection of the wave function of any given electron pair (C-H or C-C bond) would give a curve such as I.




In double bonds, one electron pair (the $\sigma$ electrons) is shown by a function similar to that of the saturated bond. The second pair (the $\pi$ electrons) corresponds to another function (III), with which the chemical and stereochemical properties of the double bond can be correlated. (These functions represent only the lowest energy state of the molecules involved. Other functions, representing "excited" states, can be constructed.)

Four possible energy states of the $\pi$ electrons of butadiene, a simple conjugated system, are shown in IV-VII. Here the $\sigma$ electrons will be similar to those in the ethylene structure above. In the unexcited state, the four electrons will fall into the orbits of lowest energy, VI and VII.



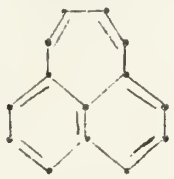

This representation can obviously be extended to other molecules containing chains of 2n molecules connected by alternate double bonds. 2n wave functions can be constructed and the lowest n functions will be filled by the $\pi$ electrons in the unexcited state. Cyclic systems can be included if one recognizes the 2n + 1 atom and the first are identical.

Now the functions IV-VII, each representing a different energy state, were constructed by multiplying the same wave function of the 1th atom by a factor $\sin \pi kl/n$ (where k = 0,1,2,...n) or the similar

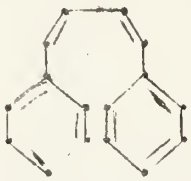
cosine function. Now it can be shown that the energy of a function containing sine terms is equal to the corresponding one containing cosine terms, if k is the same. In other words, the orbits described by the two functions are identical, the two orbits being equivalent to one orbit contining up to four electrons. (Pauli's Principle ordinarily limits the number of electrons in one orbit or energy state to two.)

The lowest wave function (k = 0) can contain two electrons (since the sine term vanishes for k = 0). But the second orbit (k = 1) can contain four electrons; similarly, the third orbit can contain four electrons, etc. A molecule possessing six $\pi$ electrons would have the first two orbits exactly filled in the unexcited state. Such a compound, as benzene, is analogous to a rare gas in that all orbits occupied are completely filled, and thus would be quite stable. Likewise, a compound with ten $\pi$ electrons would have the first three orbits completely filled, and would also be expected to be stable. Naphthalene is such a compound. Thus any compound containing $4n + 2$ $\pi$ electrons would be expected to be stable. Cyclobutadiene, on the other hand possesses, only four electrons, and must leave the second orbit only partially filled. It is analogous to a transition element in the periodic system. It would be expected, then, that it would not be as stable as benzene, even without considering other factors, such as strain.

Application. The above method of describing molecules in terms of wave mechanics, the molecular-orbital method, is distinguished in that it pictures the $\pi$ electrons as moving throughout the entire molecule. Another method, the valence-orbital method can also be used to describe these molecules. In this method, the electrons are pictured as moving only about the nuclei involved in the bond itself, like the representation of the saturated methane bond above. Using this method, molecules of type VIII are described as being very similar to sym-diphenylbutadiene, IX, and it is predicted that the two molecules should have approximately the same resonance energy. Moreover, an empirical formula for resonance energy developed by Wheland[3] predicts a close resemblance between VIII and IX. On the



VIII



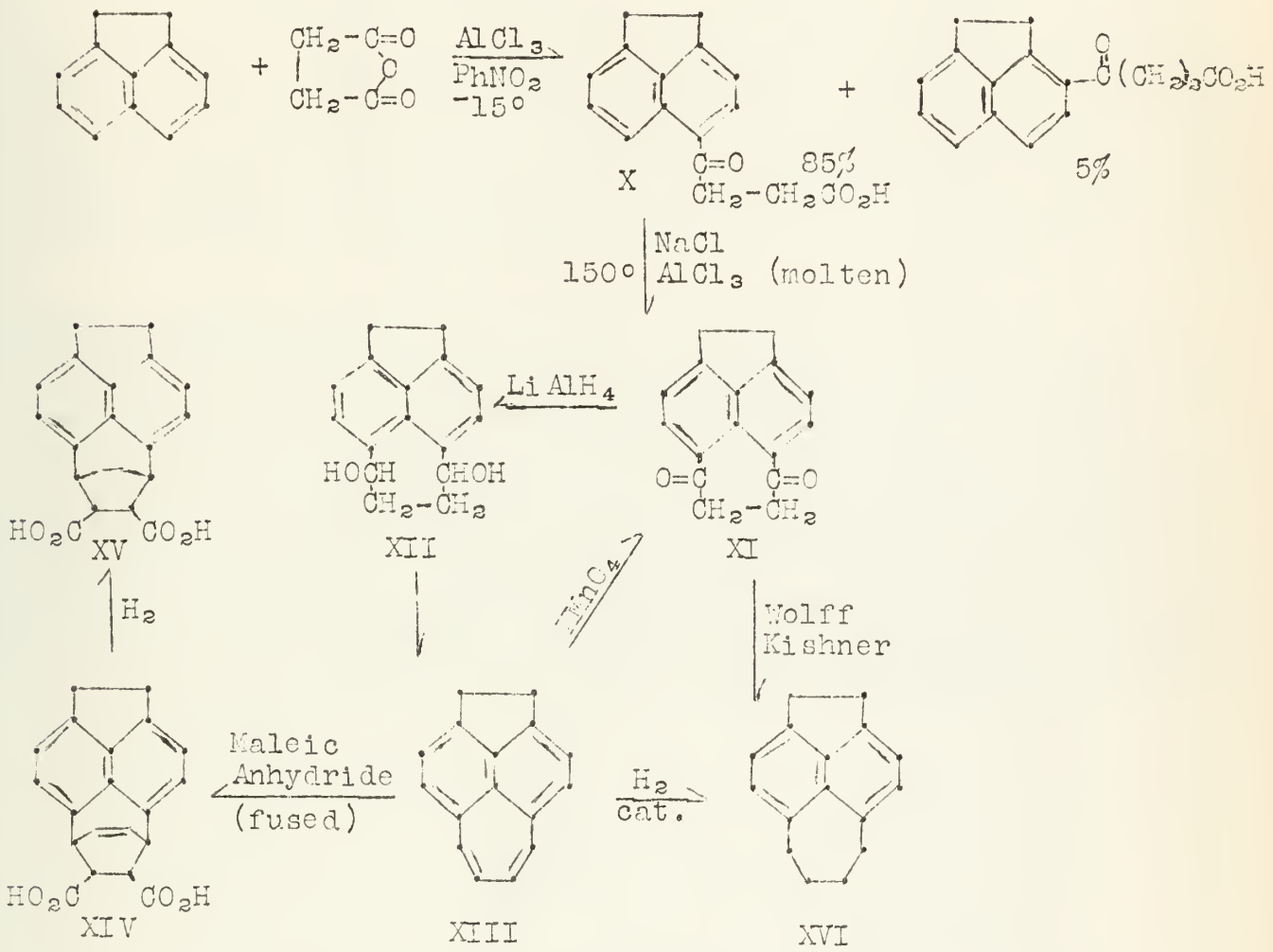
IX

other hand, the ring system VIII possesses the necessary $4n + 2$ $\pi$ electrons to cause considerable stabilization, and thus be much more aromatic in character than IX. A study of the pleiadiene system, VIII, was therefore indicated to determine the relative utility of the different methods.

Acepleiadiene. While pleiadiene itself is quite inaccessable synthetically, acepleiadiene is fairly easily obtained. Acenaphthene can be converted by a Friedel-Crafts reaction with succinic anhydride

to give good yields of 3-(3-acenaphthoyl)propionic acid (X), along with some 3-(1-acenaphthoyl)propionic acid. This keto acid (the methyl ester gives the best yields), if heated at 150° for thirty minutes in a molten mixture of sodium chloride and aluminum chloride cyclizes to give perisuccinoylacenaphthene, or acepleiadanedione (XI).[4] This unusual ring closure also occurs with o-acenaphthoylbenzoic acid (from phthalicanhydride), but fails with many closely related acids, as 4-(3-acenaphthyl)butyric acid.[5,6]

Reaction of the dione (XI) with lithium aluminum hydride gives



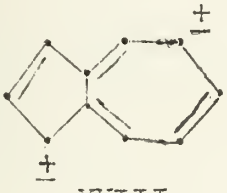

two isomeric glycols, each of which undergo dehydration with anhydrous hydrogen chloride to yield acepleiadiene (XIII), a bright red solid, m.p. 118-120°. This substance, when hydrogenated at room temperature, gives a tetrahydro derivative. Wolff-Kishner reduction of the original diketone (XI) gives the same compound, acepleiadane, (XVI) a white solid, m.p. 138°.[7]

Reactions of Acepleiadiene.[7] Acepleiadiene failed to react with maleic anhydride at 200° in boiling tetralin. However, fusion of the two solids gave an addition product in 27% yield. The diacid produced gave, on hydrogenation, the dihydro derivative, thus supporting the assigned structures (XIII-XV).

Titration of XIII with an ethereal bromine solution showed that four equivalents were taken up, always with the evolution of hydrogen bromide. The isolation of the expected tetrabromide was not successful, but a substance corresponding in composition to dibromoacepleiadiene was obtained. Presumably this compound arose from the dehydrobromination of a 1,2,3,4-tetrabromo intermediate.

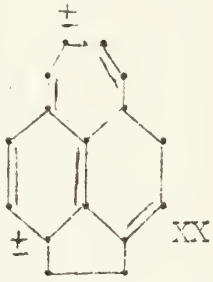
Treatment of XIII with a dilute permanganate solution gave a gummy solid which could not be purified. The fact that it could be converted by sublimation to XI, however, indicated that it was 1,2,3,4-tetrahydroxyacepleiadane. This reaction probably proceeds by the loss of water, first giving the dienol, which then ketonizes, to give XI. Apparently, then, the peri-diene bridge is not sufficiently stabilized by resonance to prevent ketonization from occurring. This is further indicated by the facts that XI readily forms a dioxime, and that it does not decolorize ferric chloride solutions. Nevertheless, it does enolize much more readily than a simple acetophenone derivative. For example, XI is recovered unchanged after treatment with methylmagnesium iodide.

Color in Acepleiadiene. The chemical properties of acepleiadiene indicate a relatively low degree of resonance stabilization of the peri bridge. The presence of absorption bands in the visible spectrum, producing the red color, can be compared with other compounds of relatively low aromaticity, such as azulene and fulvene. The color of these compounds is attributed to the possibility that resonance stabilizes excited states of the molecule more than the ground state.[8] Since excited states can be represented as resonance structures involving separation of charges, this is interpreted as meaning that structures such as XVIII and XIX contribute strongly to the state of the molecules. Thus it can be concluded that structures such as XX do contribute appreciably to the acepleiadiene molecule.



XVIII

XIX



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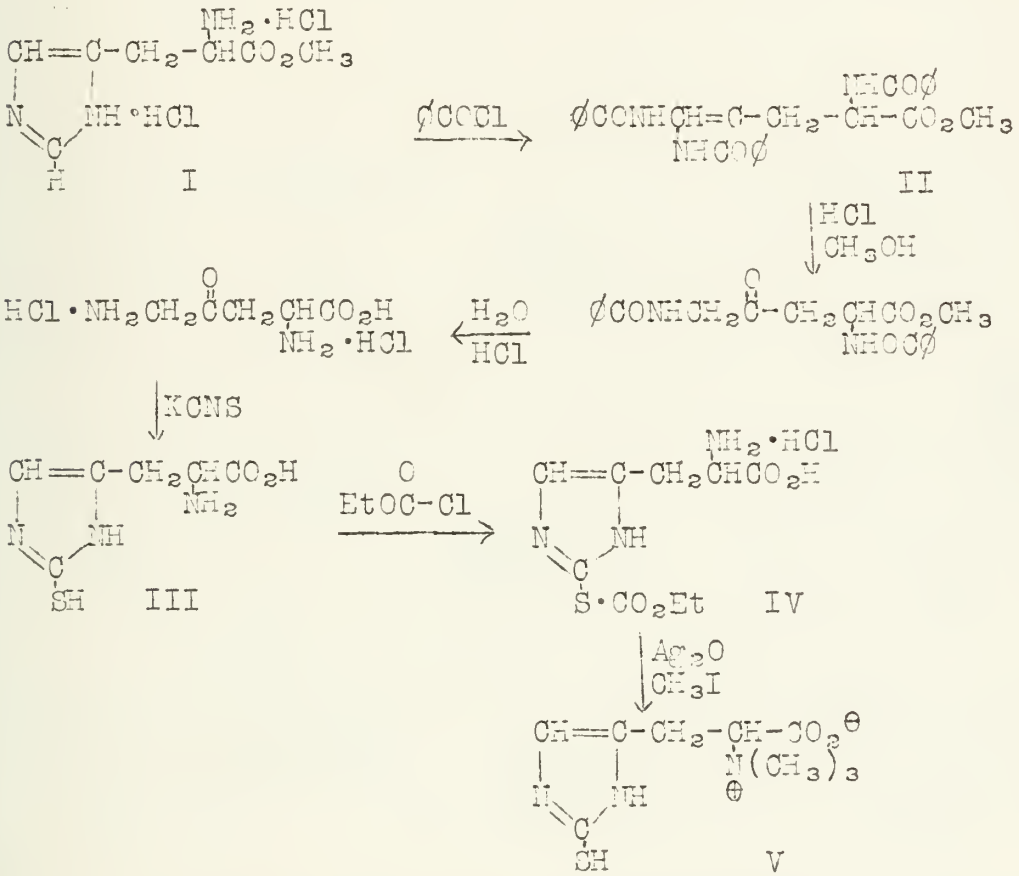
# ERGOTHIONEINES

Reported by John J. Sagura November 30, 1951

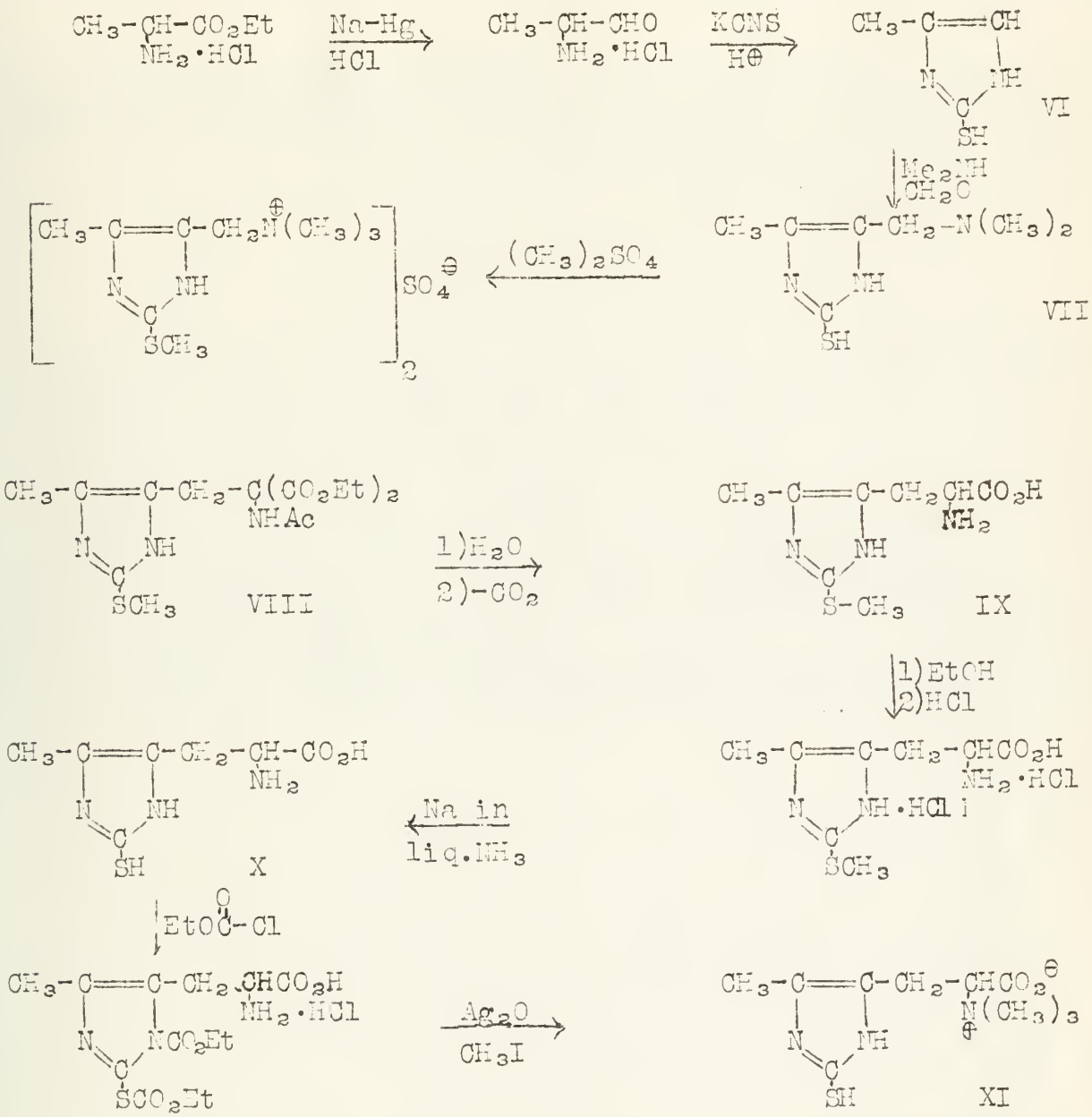
I. The Synthesis of Ergothioneine:[1] Ergothioneine has been isolated from Ergot,[2] and has been shown to make up a large part of the total amount of N-containing reducing substances present in blood.[3,4] It has been assigned the structure (V)[5,6] At one time, Ergothioneine was believed to have a certain amount of pharmacological importance but, with the exception of its detoxicating action toward NaCN, has since been shown to be pharmacologically inactive.

Attempts by previous workers[7,8,9] to synthesize Ergothioneine by methylation of 2-mercaptohistidine (III) were unsuccessful. The two difficulties were (a) histidine betaine is unstable, readily losing trimethylamine to yield urocanic acid and (b) 2-mercaptoglyoxalines readily react with methylating agents to yield methylthioglyoxalines. These difficulties have now been overcome and Ergothioneine has been synthesized in the manner outlined below. The Ergothioneine thus obtained was identical in all respects, except optical activity, with the natural material obtained from Ergot.



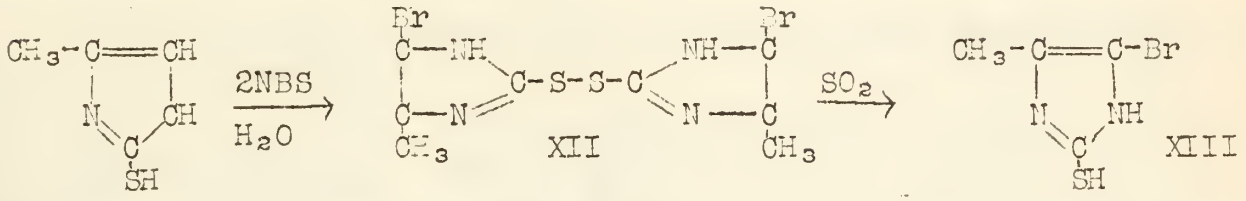

II. The Synthesis of 4-Methylergothioneine:[10] Akabori[11] prepared 2-mercapto-4(5)-methylglyoxaline (VI) from alanine by reduction of its ethyl ester with sodium amalgam to yield the corresponding amino aldehyde followed by a ring closure of the latter with sodium

thiocyanate. The Mannich reaction has been applied to 2-mercapto-4(5)-methylglyoxaline[12] to yield the Mannich base (VII) which was then converted into the quaternary methyl derivative with simultaneous methylation of the thiol group. The malonic ester condensation product (VIII) was hydrolyzed and decarboxylated to yield 4(5)methyl-2-methylthiohistidine (IX). After esterification and subsequent hydrolysis, the pure amino acid hydrochloride was obtained which upon reductive fission in liquid ammonia yielded 2-mercapto-4(5)-methylhistidine (X). Carbethoxylation of this compound followed by methylation and decarboxylation yielded 4-methylergothioneine (XI).



III. Miscellaneous Reactions of 2-Mercapto-4(5)-methylglyoxaline.[13]
A. Reaction with NBS: The action of two equivalents of NBS on an aqueous solution of 2-mercapto-4(5)-methylglyoxaline yielded a compound $C_8H_8N_4S_2Br_2$ in 91% yield which was assigned a disulfide

structure (XII). The NBS in addition to brominating the nucleus had also oxidized the thiol group to the disulfide. Reduction of the disulfide with $SO_2$ proceeded smoothly to give 5(4)-bromo-2-mercapto-4(5)methylglyoxaline (XIII).




D. The Reimer-Tiemann Reaction: The Reimer-Tiemann reaction has been successfully applied to 2-mercapto-4(5)-methylglyoxaline, 5(4)-formyl-2-mercapto-4(5)-methylglyoxaline being isolated as the semicarbazone. The corresponding free aldehyde could not be isolated.

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# THE DECARBOXYLATION REACTION

Reported by John W. Way November 30, 1951

From a general viewpoint the decarboxylation reaction involves the following process:

It will be observed that the $C_\alpha - C_c$ bonding electrons remain with the acyl residue. The conclusion to be drawn, then, is that some way must be found to facilitate this retention of electrons.

The mechanism of decarboxylation seems to fall into two broad categories (1,2). They may be represented as follows:

$SE_1$ $\quad R\text{-}CO_2^- \rightarrow R^- + CO_2$

$SE_2$ $\quad R\text{-}CO_2H + H^+ \rightarrow RH + CO_2 + H^+$

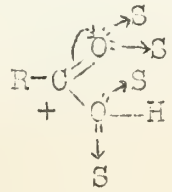
It is considered that the process is one of electrophillic substitution by hydrogen on the acyl residue, and may be either monomolecular or bimolecular.

The $SE_1$ Reaction: Studies of this mechanism have always indicated that the acid is in the form of the anion before decarboxylation, (3,4,5). Briefly one method of determining this is that of Verhoek (5), who studied the decarboxylation of 2,4,6-trinitrobenzoic acid in ethanol-aniline solution. The rate of the reaction was shown to depend on the concentration of the anion as calculated from the equilibrium.

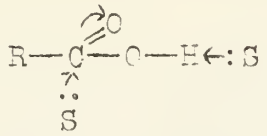
$$RCO_2H + \phi NH_2 \rightleftarrows RCO_2^- + \phi\overset{+}{N}H_3$$

Another type of evidence for the anion form has been obtained for trichloroacetic acid (4), by showing that the free acid, and the copper, barium, sodium, aniline, pyridine, piperidine, and ammonium salts all decarboxylate at the same rate in water solution at 70°C.

The effect of the solvent used may be evaluated in the following manner. A medium of high dielectric constant will favor the dissociation of the acids. This has been verified by Verhoek(4) who found that trichloroacetic acid will not decarboxylate in low dielectric constant media as benzene, toluene, ether. Aside from this function, the solvent may interact with the carboxyl group. If the carboxyl group is highly solvated (the solvent acting as an acid), $C_\alpha$ will become partially positive, thus hindering the reaction.



However, there is also the possibility of the solvent acting as a base and facilitating the reaction in a two-fold manner:



The attack at $C_c$ will aid in the separation of the residue with the bonding electrons. The removal of the proton is also an aid in the decomposition. Verhoek (8) has determined that the rate of decarboxylation of trichloroacetic acid in the presence of an excess of aniline is first order with respect to the acid and second order with respect to the aniline.

Other kinetic studies of the decomposition of trichloroacetic acid (4) have shown that the rate in ethanol solution is faster than that in water solution. Since ethanol is a weaker acid than water it is to be expected that the acid is less highly solvated in this solution than in water. Trivich and Verhoek (7) found that the rate of decarboxylation of 2,4,6-trinitrobenzoic acid in dioxane-water mixtures first increased then decreased with increasing dioxane content. This may be attributed to all three effects of the solvent. Water favors dissociation, but solvates the ion. Increasing dioxane content decreases the solvation, hence increases the rate of reaction, simultaneously it increases somewhat the basic catalysis of the reaction.

The $S_E2$ Reaction: This type of decarboxylation may be characterized by the essential feature that $C_\alpha$ has a high electron density and the reaction is acid catalyzed. The mechanism may be summarized by:

$$R_3\text{-}C\text{-}CO_2H + SH^+ \rightarrow R_3CH + S + CO_2 + H^+$$

However, it is not possible to distinguish this from

$$R_3\text{-}C\text{-}CO_2^- + SH^+ \rightarrow R_3CH + S + CO_2$$

by kinetic methods, (3,9).

Perhaps the most convincing evidence for the $S_E2$ reaction is that presented by Hammick and coworkers (3) who studied the decarboxylation of hydroxybenzoic acids in molten resorcinol at temperatures from 110 to 240°C. The results are summarized in Table I.

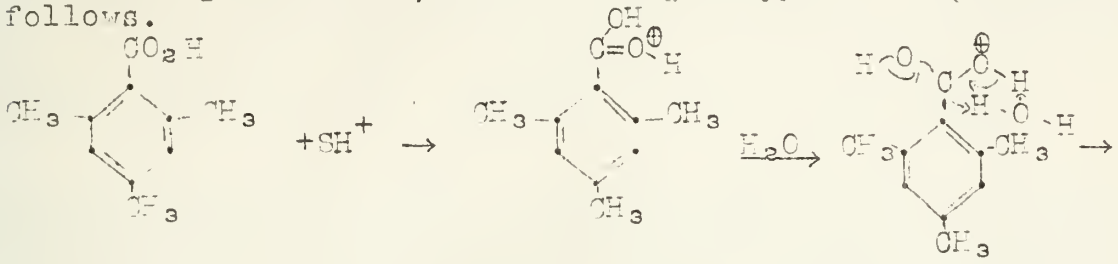
Table I

| Acid | $E_{act.}$ (cal./mole) | $\log_{10} PZ$ |
|---|---|---|
| Benzoic | >39,000* | |
| o-Hydroxybenzoic | 33,600 | 11.5 |
| 2,4-Dihydroxybenzoic | 29,200 | 10.9 |
| 2,4,6-Trihydroxybenzoic | 13,600 | 5.0 |

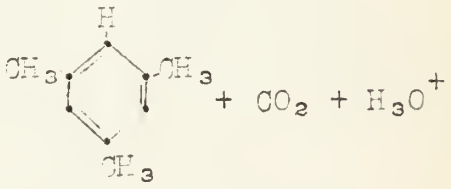
*Estimated from the observation that the acid is undecompared at 250° in resorcinol.

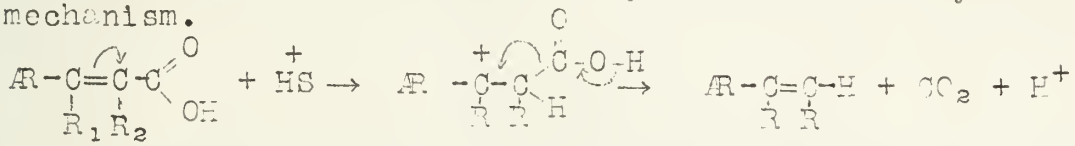
The successive substitution of hydroxyl groups into the ortho and para positions causes a progressive decrease in the activation energy (increases the rate of reaction). From this it may be inferred that the increased electron density on $C_\alpha$ is reducing the repulsion between the attacking group (a solvated **proton**) and the acid molecule. The drop in the PZ factor in going from the 2,4-dihydroxybenzoic acid to the 2,4,6-trihydroxybenzoic acid may be due to the increased steric effect of the second ortho hydroxyl group in inhibiting the approach of the solvated **proton**.

Schubert 9) has studied the decarboxylation of mesitoic acid in 82 to 100% sulfuric acid, and found that the reaction is best explained by the $SE_2$ mechanism. It may be that in this case the steric effect of the ortho methyl groups outweighs the $+I_S$ effect, by forming the carboxyl group out of planarity with the ring, thus diminishing resonance, and allowing a type of ring formation as follows.

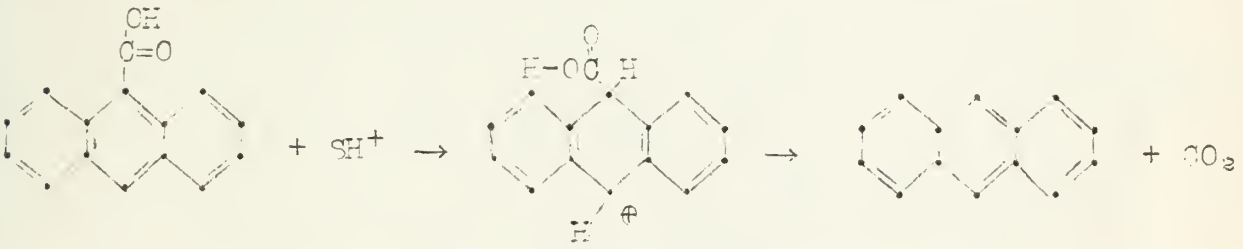


Johnson and Heinz (10) determined that the rate of decarboxylation of cinnamic acids is proportional to the concentration of the hydrobromic acid used as catalyst. They also found that α-and β- substituted acids decarboxylated faster than the unsubstituted acid. For example β-methylannamic acid is faster than α-methylcinnamic acid, which is faster than cinnamic acid. Their results may be summarized by the following mechanism.



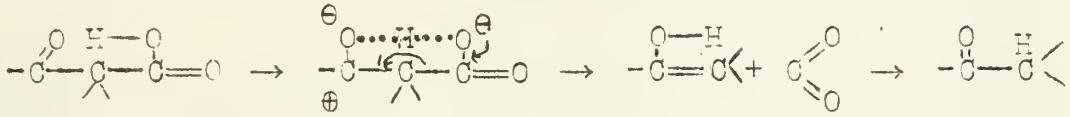


A further example of the mechanism is the work of Schenkel(11) who found that the decarboxylation of anthracene-9-carboxylic acid proceeds by:

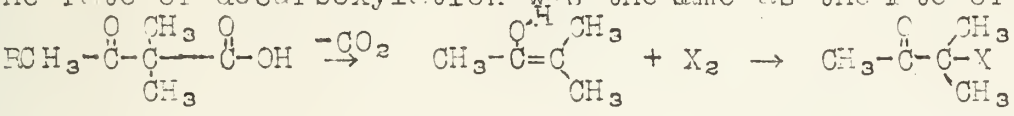


Decarboxylation of β-ketoacids: The mechanisms just presented represent the limiting cases of the decarboxylation process. In many cases the structural features of the compound favor an intermediate process somewhere between the two limits. As an example the β-ketoacids may be mentioned.

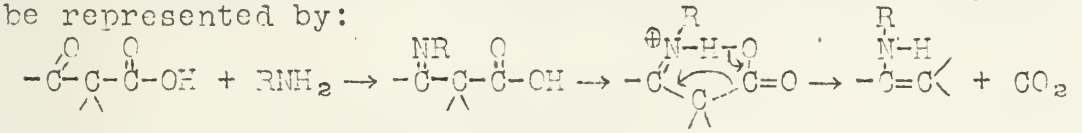
It has been firmly established that the following takes place.



Pederson (12,13) has shown by a study of the acetoacetic and α,α-dimethylacetoacetic acids that the unimolecular decarboxylation must involve the keto form of the free acid to give the enol form of the ketone. By a study of the loss of carbon dioxcide by these two acids in bromine or iodine-water solution, it was found that the rate of decarboxylation was the same as the rate of halogenation.



Further evidence for the decarbonxylation of the free acid is the relative stability of the anions of these acids in solution. The acid catalysis of the reaction (12) is thought to involve the repression of ionization of the acid and also the coordination of a proton with the oxygen at $C_\beta$. The reaction is also catalyzed more so by primary amines than by secondary and tertiary (12). This may be represented by:



Since nitrogen is more basic than oxygen, the formation of the transition state is facilitated.

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# THE LEUCKART REACTION

Reported by Richard S. Colgrove December 7, 1951

Introduction.--The reductive alkylation of ammonia or primary or secondary amines by certain aldehydes and ketones using formic acid or a derivative of formic acid as the reducing agent was discovered by Leuckart[2] in 1885. Wallach[3] proposed a mechanism in 1905. However, the reaction did not come into general use until Ingersoll[4] and coworkers modified it in 1936. Since that time many workers have used and investigated the reaction.[1,5,6,7,8,9,11,12,13,14,15] The subject is excellently covered in "Organic Reactions," Vol. 5, by Moore[16], and also by Herbrandson[17] in Organic Seminar. It is the purpose of this seminar to discuss the mechanisms proposed and in particular that proposed by Pollard and Young[1].

The overall process may be illustrated by the following equations.

$$RR'C{=}O + 2HCOONH_4 \longrightarrow \begin{matrix} R \\ R' \end{matrix}\!\!>\!CHNHCHO + 2H_2O + NH_3 + CO_2$$

$$\begin{matrix} R \\ R' \end{matrix}\!\!>\!CHNHCHO \xrightarrow{H_2O} \begin{matrix} R \\ R' \end{matrix}\!\!>\!CHNH_2 + HCO_2H$$

Factors Affecting the Reaction[1].--Before discussing the various mechanisms let us examine some of the factors affecting the reaction.

1. When water is removed from the reaction, a mixture of formamide and formic acid gives the best yields.

2. When water is removed, ammonium formate gives better yields than formamide, although not as high as formic acid and formamide combined.

3. When water is removed, a mixture of formamide and ammonium formate is as good but no better than ammonium formate alone.

4. At low temperature when water is removed, a mixture of ammonium formate and formamide is best.

5. With any reagent other than formamide yields are improved when water is removed from the reaction mixture.

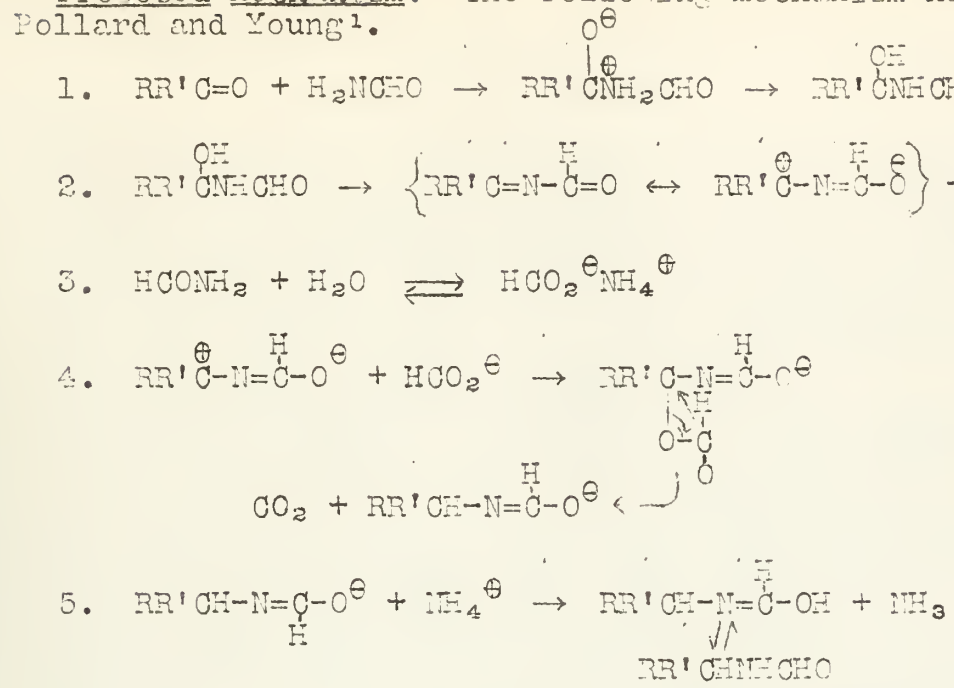
6. The yield is lowered when a dehydrating agent is used along with formamide.

7. Secondary and tertiary amines may be prepared by use of substituted formamides.

8. Acid catalysts increase the yield when formamide is used as the reagent.

9. A reducing agent is required.

Proposed Mechanism.--The following mechanism has been proposed by Pollard and Young[1].



Evidence for Proposed Mechanism[1].--Kinetic studies of the Leuckart reaction using formamide, acetophenone and an excess of formic acid as solvent were carried out and have shown that the reaction is first order in acetophenone and first order in formamide. This agrees favorably with step 1 of the proposed mechanism, which under the conditions of the experiment should be the rate determining step and should be second order.

Ultraviolet absorption data is presented as evidence for the intermediate formimido compound ($RR'C{=}NCHO$). Methylisobutyl ketone was used in the absorption studies, since preliminary determinations indicated that acetophenone was unsatisfactory because the intense absorption maxima would completely obscure the absorption maxima of a compound present in small concentrations. It will be observed that none of the reactants or products contain more than one double bond while the proposed intermediate contains a conjugate system of double bonds. It was found that neither formamide nor 2-methyl-4-formamidopentane show an absorption maximum above 220m$\mu$, while methylisobutyl ketone has a maximum at 280m$\mu$. During the course of the reaction two new maxima appeared, one at 240m$\mu$ and one at 340m$\mu$, and since these new maxima cannot be attributed to starting materials or products it seems reasonable to conclude that an intermediate of the type $RR'C{=}N{-}\underset{H}{C}{=}O$ is indeed formed during the course of the reaction.

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# THE HAMMETT EQUATION

Reported by J. J. Drysdale December 7, 1951

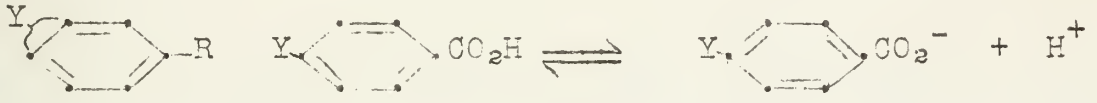
Introduction: In 1937 Hammett[1] correlated the rate and equilibrium constants of 323 reactions which involved m- and p-substituted phenyl compounds with the following equation:

$$\ln \frac{k_Y}{k_H} = \rho \sigma$$

$k_Y$ is the rate constant for the substituted phenyl compound.
$k_H$ is the rate constant for the unsubstituted phenyl compound.
$\rho$ is a constant determined solely by the reaction.
$\sigma$ is a constant determined solely by the substituent and its position.

It is the purpose of this seminar to present briefly the Hammett equation and to illustrate a few of its applications. References 2 and 3 give a brief summary of the development of quantitative relationships between structure and rate through 1936; references 5 and 6 deal with the thermodynamic development of the Hammett equation.

Significance of $\rho$ and $\sigma$: According to Hammett[4], the sigma constant is a measure of the ability of the substituent Y to withdraw or supply electrons at the reaction center R (I). Electron supplying substituents




I II

such as $-NH_2$ have a negative sigma while electron withdrawing substituents such as $-CO_2H$ have a positive sigma.

Rho determines the effect of a change in electron density at R on the reaction rate. In accord with his termolecular reaction theory, Swain[7] has suggested that the sign and magnitude of rho for R = $-C(R_1R_1X)$, X = halide may be determined by four factors 1) the structure of Y, 2) the nucleophilic reagent, 3) the electrophilic reagent, 4) the remainder of the halide. He offers a general expression for the dependence of rho on these factors and cites a number of reactions which qualitatively illustrate his idea. In most cases of course the effect of sigma on rho is small, but it is not surprising that such an effect does exist.

Determination of $\sigma$ and $\rho$: A plot of ln $k_Y$ vs. sigma gives a straight line with slope rho. Since values of rho and sigma are relative, the equilibrium (II) is assigned a rho of 1.000 and the substituent H- a sigma of 0.00. Once reference values have been selected other rho and sigma values may be determined by appropriate calculations from known rate and equilibrium constants.

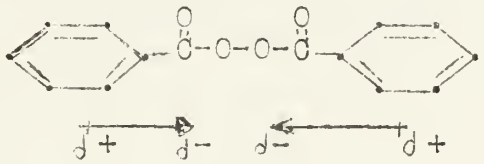
Significance of $\Delta\sigma = \sigma_{para} - \sigma_{meta}$: The electrical effect of ortho and para substituents are transmitted by a combination of resonance and inductive effects; meta substituents act by an inductive mechanism only.[8] Hence it might be assumed that $\Delta\sigma = \sigma_{para} - \sigma_{meta}$ measures the resonance interaction of the substituent with the ring. Price[9] [10] obtained good agreement between $\Delta\sigma$ values and polarization values for substituted benzenes.

Doub and Vandenbelt[11] also found that the shift in the primary ultra-violet absorption band of mono- and p-disubstituted benzenes is related to $\Delta\sigma$ values.

Use of the equation: The Hammett equation has been applied to both ionic and free radical reactions and is a useful means for evaluating the electrical effect of substituents. By 1940 the rates of 332 non-radical reactions had been experimentally determined with a median deviation between calculated and observed rates of $\pm 15\%$. Since the magnitude of the rates varied by as much as a factor of a thousand, the agreement is quite good.[7]

Free radical reactions: Walling[12] observed that the relative reactivities of m- and p-substituted styrenes in copolymerizing with styrene or with methyl methacrylate gave a striking fit with the Hammett equation. The postulated importance of polar resonance contributions to the transition state is in agreement with the polar significance of $\rho$ and $\sigma$.

The first order decomposition of substituted benzoyl peroxides also fits the Hammett equation. Swain and Stockmayer[13] picture the substututed peroxides as two opposing dipoles (III). Electron supplying groups increase the repulsion of the dipoles; electron withdrawing groups diminish the repulsion.



III

Electronic interpretations: For most substituents one $\sigma$ para and one $\sigma$ meta are sufficient for all R groups. In the case of p-nitroaniline, however, the $\sigma$ para for the nitro group is 1.27 as compared to the usual value of 0.78. This is explained by enhanced resonance interaction of the type (IV).

IV

In his study of the trifluoromethyl group, Roberts[14] found $\sigma$ meta = 0.44, $\sigma$ para = 0.50 for p-trifluoromethylbenzoic acid, and

$\sigma$-para = 0.74 for p-aminobenzotrifluoride. These values show that the trifluoromethyl group withdraws electrons from the ring and gives support to hyperconjugation forms such as (V).

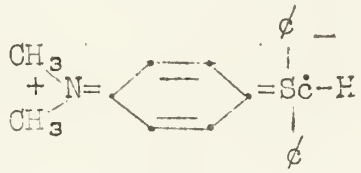
V

The electrical effect of the trimethylammonium group,[15] and the trimethylsilyl group[16] have been determined by similar studies.

Gilman[17] in a slightly different approach measured the rate of hydrolysis of substituted triarylsilanes in wet piperidine. He found $\sigma$-para = 0.411 for the $-N(CH_3)_2$ group. This value is considerably lower than the $\sigma$-para = 0.610 found for the interaction of $-N(CH_3)_2$ with $-CO_2Et$. These measurements suggest the relative unimportance of (VI) and are in agreement with the previous observation that silicon does not form double bonds with carbon.

Limitations of the Hammett Equation: In a few cases in which steric interaction is absent, the Hammett equation applies to o-substituted benzenes. For the most part, however, its use is restricted to m- and p-substituted benzenes; it fails completely with aliphatic compounds. As explained in references 5 and 6, these limitation are commensurate with theory.

Deviations from the Hammett equation are in general predictable and parallel enhanced resonance in the transition state.[18]



VI

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# THE REACTIVITY OF ALPHA HALO SULFONES IN NUCLEOPHILIC DISPLACEMENTS

Reported by Samuel Gelfand December 7, 1951

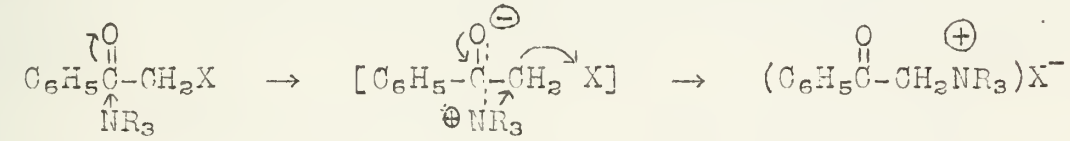
In general most unsaturated, electron attracting groups, such as carbonyl, cyano, carboxy, etc., strongly enhance the reactivity of alpha halogen atoms in nucleophilic displacements. Conant and Kirner[1] found the following relative rates of reactivity in the displacement reaction of potassium iodide with alkyl halides.

TABLE I

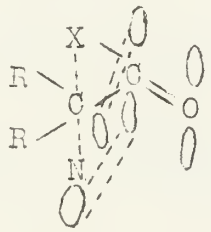
Relative Reactivities Toward Potassium Iodide in Acetone

| | | | |
|---|---|---|---|
| $n\text{-}C_4H_9Cl$ | 1 | $CH_3COOCH_2Cl$ | 270 |
| $n\text{-}C_5H_{11}Cl$ | 1.26 | $CH_3OCH_2Cl$ | 918 |
| iso $C_5H_{11}Cl$ | 0.65 | $N{\equiv}CCH_2Cl$ | 3070 |
| $(CH_3)_3CCl$ | 0.018 | $CH_3COCH_2Cl$ | 35700 |
| $CH_2{=}CHCH_2Cl$ | 79 | $(C_2H_5OCO)_2CHCl$ | 60200 |
| $C_6H_5CH_2Cl$ | 197 | $C_6H_5COCH_2Cl$ | 105000 |

The high rate of activity can be explained in several ways. Baker[2] postulated that the nucleophilic reagent first attacks the carbonyl group to form an addition complex which decomposes with migration of the attacking group from the carbonyl carbon to the alpha carbon resulting in expulsion of the halide ion. This transformation has been formulated in the following way.



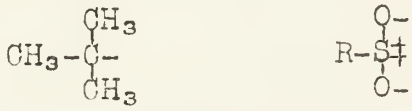
According to Dewar[3] the approach of the nucleophilic reagent to the alpha carbon atom is facilitated by the overlapping of the $\pi$ orbitals of the carbonyl groups with the occupied orbitals (p) of the reagent.



An alternative explanation has been given by Branch and Calvin.[4] The sulfonyl group, in contrast to the other electron attracting groups, exhibits a strong deactivating influence on the reactivity of alpha halogen atoms. Bromomethyl p-tolyl sulfone is unreactive toward tetrahydroquinoline, dimethylamine, potassium

cyanide, and sodium acetate.[5] Bromomethyl phenyl sulfone fails to react with either piperidine or benzyldimethyl aniline.[6] Bordwell and Cooper[7] obtained similar results with chloromethyl phenyl sulfone. It failed to react on heating to reflux with piperidine in benzene for three days and gave only tarry products on treatment with morpholine at 140° and thiourea in cyclohexanol at 160°. No reaction was observed with potassium iodide in acetone in twelve hours at 56° or after ten weeks at 0°. From the latter experiment it was estimated that the rate with potassium iodide was probably much less than one fortieth of the rate with n-butyl chloride.

While the failure of the sulfonyl group to enhance the reactivity of alpha halogens can be rationalized by its inability to function in a manner similar to the other electron attracting functions, its retarding influence remains unexplained. The possibility that it might exert a steric blocking effect was investigated by Bordwell and Cooper. Although the sulfonyl group shows a formal similarity to the neopentyl group, an examination of models shows that it would not be expected to exhibit a very strong steric effect unless the partial negative charge on the oxygen atoms greatly extended their effective radius.



In order to decide between the steric and the electronic nature of the cause of the retarding effect, the sulfonyl group was separated from the halogen by a vinyl group in a test analogous to that applied by Bartlett and Rosen for the neopentyl case.[8] The activity of 1-p-toluenesulfonyl-3-chloro-1-propene (I) was compared to that of 1-cyano-3-chloro-1-propene (II) with potassium iodide in acetone.

I II

TABLE II

Relative Reactivities Toward Potassium Iodide in Acetone

| | | | |
|---|---|---|---|
| $n\text{-}C_4H_9Cl$ | 1 | $CH_2{=}CHCH_2Cl$ | 80 |
| $N{\equiv}CCH_2Cl$ | 3000 | $N{\equiv}CCH{=}CHCH_2Cl$ | 1400 |
| $p\text{-}CH_3C_6H_4SO_2CH_2Cl$ | < 0.02 | $p\text{-}CH_3C_6H_4SO_2CH{-}CHCH_2Cl$ | 1100 |

These results suggest that the sulfonyl group exerts an activating effect on alpha halogen atoms but that this effect is overshadowed by the steric factors, since the sulfonyl group shows an activating effect similar in magnitude to the cyano group when it is separated from the halogen by a vinyl group.

In contrast to the general lack of reactivity described above some compounds with halogen alpha to a sulfonyl group are readily hydrolyzed in alkaline solution.

Johnson and Douglass[9] found that although chloromethanesulfonamide fails to react with aniline or sodium phenolate it is readily hydrolyzed by boiling with 5% sodium hydroxide with both the chloride ion and ammonia being released quantitatively. Chloromethanesulfonanilide reacts similarly.

$$ClCH_2SO_2NHR + 3NaOH = NaCl + NH_2R + CH_2O + Na_2SO_3 + H_2O$$

R=H, $C_6H_5$

By contrast chloromethanesulfonic acid and chloromethanesulfondiethylamide are relatively inert and chloromethanesulfonyl chloride releases only the chloride of the sulfonyl chloride group on hydrolysis. Ramberg and Bäckland[10] described a reaction of alpha halo sulfones with 2 N potassium hydroxide from which olefins are obtained.

$$RCH_2SO_2\underset{X}{C}HR' + 3KOH = RCH{=}CHR' + K_2SO_3 + KX$$

III IV

R=$CH_3$-, R'=$CH_3$-, $C_2H_5$-, X=Br

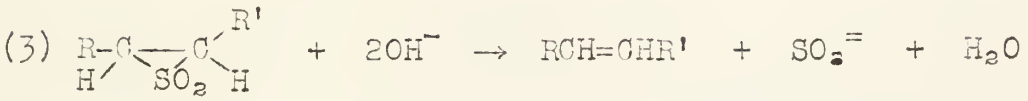
$$CH_3\underset{Cl}{C}HSO_2\underset{Cl}{C}HCH_3 + 3KOH \rightarrow CH_3CH{=}\underset{SO_2OK}{C}CH_3 + 2KCl$$

V VI

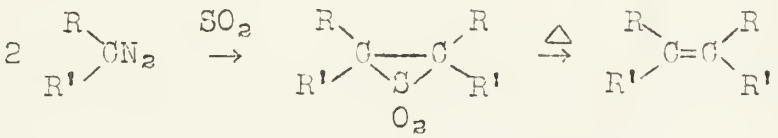
Although the kinetic investigations were carried out with too large an excess of base to allow a decision as to the order of the reaction from a single run, a comparison of the half lives in 1 and 2 N potassium hydroxide indicated that the rate is dependent on a power of the hydroxide ion greater than one and less than two.

Bordwell and Cooper[11] reinvestigated the kinetics of the reaction in the cases of chloromethyl methyl sulfone (III;R=H, R'=$CH_3$, X=Cl) alpha chlorobenzyl methyl sulfone (III;R=H-, R'=$C_6H_5$-, X=Cl) and chloromethyl benzyl sulfone (III;R=H, R'=$C_6H_5CH_2$-, X=Cl) and found them to be second order, first order each in hydroxide and sulfone. The reaction rates agreed with their proposed mechanism and eliminated step (3) as rate determining step.

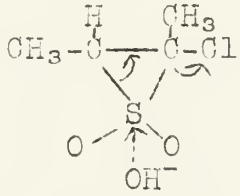
$$(1)\quad R-\underset{H}{C}H-SO_2-\underset{H}{\overset{R'}{C}}-X + OH^- \rightleftarrows R-\overset{-}{C}\begin{matrix}H\\ \diagup\\ \diagdown\\ O_2\end{matrix}S-\overset{R'}{C}-X + H_2O$$



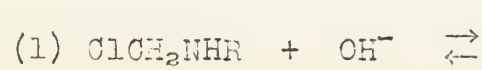
Since the rate constant for this reaction was about one thousandth that for the rate of deuterium exchange for dimethyl sulfone in deuterium oxide at the same temperature and after allowing for the greater rate of ionization of the sulfone in deuterium oxide than in water, step (2) must be the rate determining step.[12,13,14] Several aryl substituted three membered ring sulfones have been reported in the literature.[15,16] They are synthesized as follows.



These compounds are unstable to heat and lose sulfur dioxide to form olefins. Their behavior in alkaline solution has not been investigated. A thermal expulsion of sulfur dioxide in the case of bis(alpha chloroethyl)sulfone (V) would be expected to lead to 2-chloro-2-butene rather than the potassium-2-butene-2-sulfonate (VI) which is actually obtained. The expulsion of the chloride ion rather than the bisulfite ion is in line with the relatively greater ease of cleavage of carbon-chlorine bonds than carbon-sulfur bonds in other displacement processes.



An analogous mechanism is postulated for the hydrolysis of the chloromethanesulfonamides described above. The reaction rate was found to be independent of the hydroxyl ion concentration. This would be expected since the sulfonamides are strong acids and should be almost completely ionized in basic solution.



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# DEHYDROBROMINATION OF BROMOKETOSTEROIDS

Reported by John R. Dyer December 14, 1951

Introduction: The $\Delta^4$-3-keto grouping is common to many steroids in the androgenic, progestational and cortical hormone series. Unless prepared from a steroid with unsaturation in the 4-5 or 5-6 position, these steroids are usually prepared by bromination and subsequent dehydrobromination. Since 3-ketoallosteroids (A:B ring juncture as in trans decalin) on monobromination give the 2-bromo derivative[1], in general only the ketones of the "normal" series (A:B juncture cis) which lead to 4-bromoketones can be employed.[1,2] Until 1947, the resulting bromo-3-ketones were dehydrobrominated in yields of around 60% by refluxing for several hours in pyridine[2,3] or collidine[4].

In 1947, Mattox and Kendall[5] noted that when 3,11-diketo-4-bromocholanic acid was treated with 2,4-dinitrophenylhydrazine in acetic acid a hydrazone was formed which was red. Since 2,4-dinitrophenylhydrazones of saturated ketones are orange to yellow, this chance observation suggested that the hydrazone of an α-β unsaturated ketone had been formed.

Scope of the Reaction: There exists some evidence[3,6] that 3-ketosteroids of the "normal" series on bromination often yield both stereoisomeric 4-bromo compounds. Only one form can eliminate hydrogen bromide in the trans manner with ease. In the case of 2-bromo-3-ketoallosteroids such evidence is not available since trans elimination of hydrogen bromide is possible with either isomer.

The preparation of the hydrazone using 1.1 to 1.2 moles of 2,4-dinitrophenylhydrazine in glacial acetic acid is complete in three to five minutes in excellent yields. The 2-bromo-3-ketoallosteroids yield 85-90% of the dinitrophenylhydrazone of the $\Delta^1$-3-ketone, and 2,2-dibromo-3-ketoallosteroids give 60% of the $\Delta^1$-2-bromo derivative[7]. 4-Bromo-3-ketosteroids of the "normal" series yield 90% of the $\Delta^4$-3-ketosteroid[8]. The $\Delta^{4,6}$-diene hydrazone is obtained in 75% yield from the dibromination product of the 3-ketosteroid. In this case, elimination of two moles of hydrogen bromide with rearrangement is postulated[7].

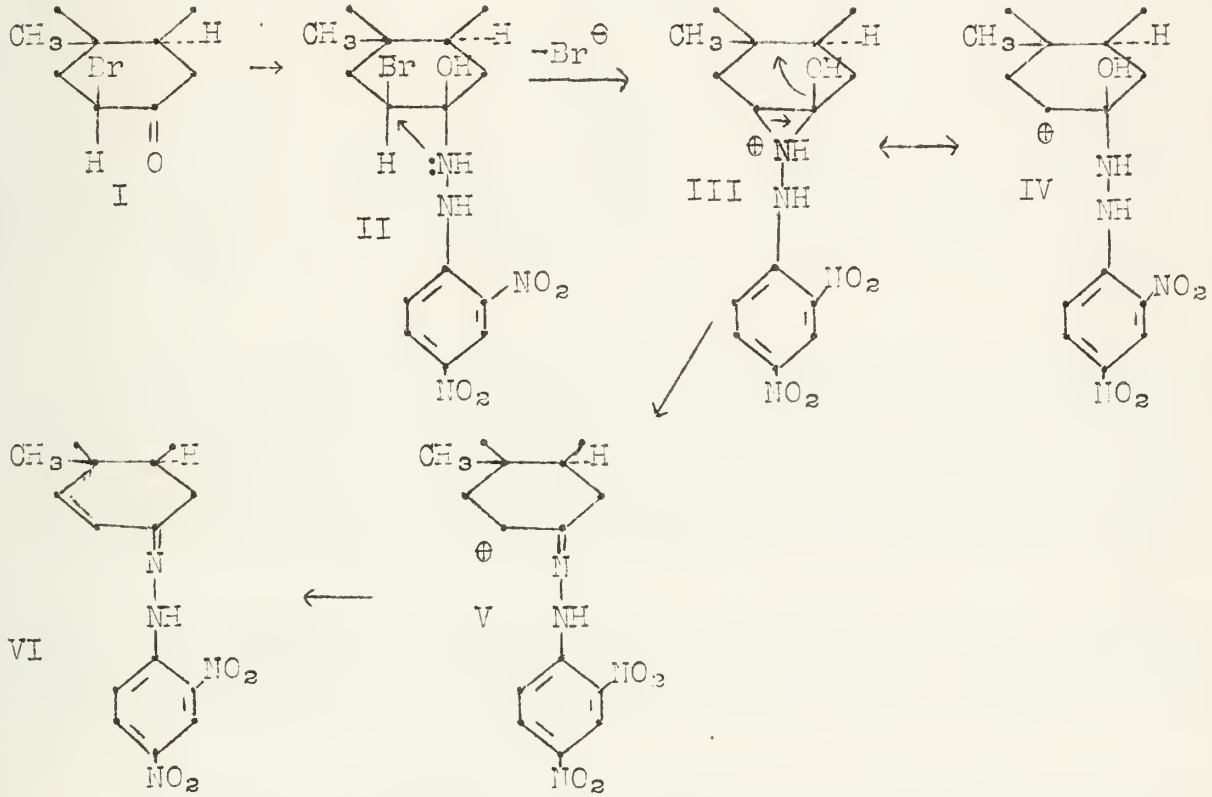
Air will oxidize the hydrogen bromide liberated in the course of the reaction to free bromine, which can then rebrominate the steroid, with the resultant formation of a considerable quantity of the $\Delta^{4,6}$-diene hydrazone. Air may be excluded by operating in an atmosphere of carbon dioxide, or sodium acetate may be added to neutralize the hydrogen bromide liberated. If more than one mole of acetate is used, a considerable quantity of the 4-acetoxy hydrazone may be isolated. Similarly, if methanol is added to the reaction medium, the 4-methoxy derivative is isolated.

4-Acetoxydinitrophenylhydrazones formed with sodium acetate may be converted into the corresponding $\Delta^4$ hydrazone by treatment with hydrogen bromide in acetic acid[9]. Under similar conditions, using

excess sodium acetate, 3,11,20-triketo-2-bromo-17 -hydroxy-21-acetoxypregnane yields both the $\Delta^1$ derivative and some 2-acetoxy dinitrophenylhydrazone which is converted by treatment with hydrogen bromide in acetic acid into the $\Delta^1$ steroidal dinitrophenylhydrazone.

The remarkable fact about the dehydrobromination is that it is complete in a matter of minutes in the presence of one mole of the very weak base dinitrophenylhydrazine, while several hours refluxing is required with a large excess of comparatively strong bases such as collidine or pyridine. Initial attack on the bromine by dinitrophenylhydrazine is unlikely since under the same conditions (1.1-1.2 moles of base in glacial acetic acid) no comparable reaction is observed with benzylamine, aniline, or ethylaniline. By contrast, phenylhydrazine, α-(2,4-diphenyl)-α-methylhydrazine, α,α-diphenylhydrazine, hydrazine, Girard's Reagent T, semicarbazide hydrochloride and hydroxylamine quantitatively or nearly quantitatively remove hydrogen bromide from the bromoketosteroid.[7,8] However, 2,4-dinitrophenylhydrazine forms the most stable and easily isolable derivative.

Mechanism of the Reaction: A mechanism has been proposed by Djerassi[7] which involves the concept of participation of neighboring groups in nucleophilic displacement reactions. Using a 2-bromo-3-ketoallosteroid as an example, it has been depicted as proceeding as follows.

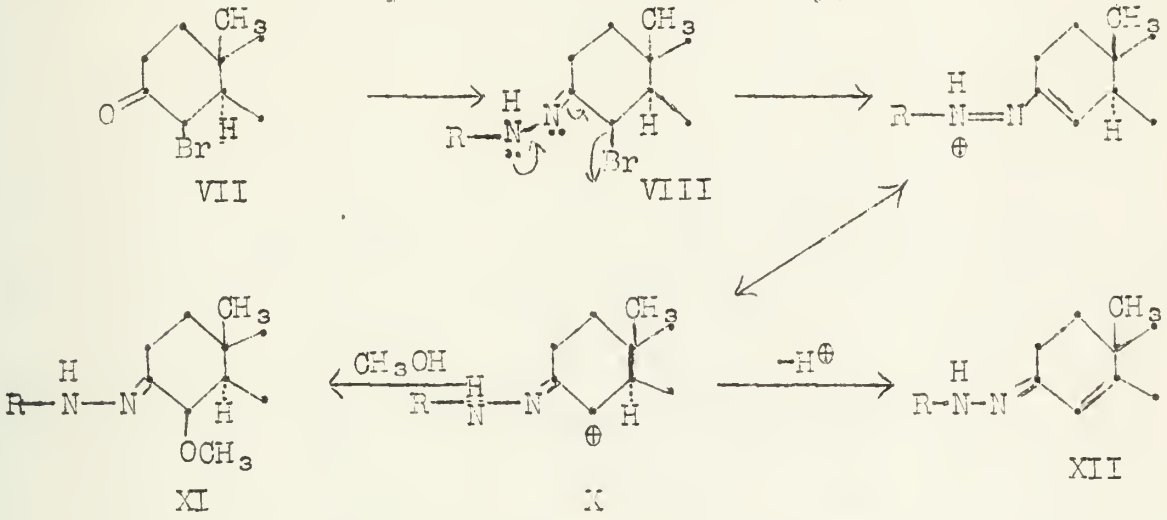



On treatment of I with 2,4-dinitrophenylhydrazine in glacial acetic acid, intermediate II is formed, which is the normal course of the reaction[9]. The loss of bromide from II results in the formation of III, a cyclic imonium intermediate. The carbonium ion IV represents one of the extreme ionic forms contributing to the

resonance hybride. The strain of the positively charged three-membered ring and the tendency toward dehydration constitute a strong driving force in fission of the N-C bond and ultimate expulsion of the proton with the resulting formation of the final product VI.

The probable existence of two diastereoisomeric bromides at both the 2- and 4- positions has been mentioned. Since the formation of the cyclic imonium compound III would require a trans relationship between the bromine atom and the dinitrophenylhydrazine radical as in II in order to allow for rearward attack, it is necessary to postulate that in the case of the 4-bromo compounds of the "normal" series and 2-bromoallosteroids the probable entrance by the dinitrophenylhydrazine molecule as always being directed by steric factors of the steroid molecule in such a manner that a trans relationship (II) is present.

A separate mechanism has been proposed by Mattox and Kendall[10] involving "activation" of the bromine atom by the hydrazine grouping which makes such a postulation unnecessary.




The essential difference in the two proposed mechanisms is that in the latter, the bromine is not lost until after the hydrazone is formed and therefore a hydroxyimino structure is not involved, and with the hydrazone grouping as an intermediate, the atom of nitrogen α to the phenyl group is the principal donor of electrons. This second mechanism can be extended to the formation of $\Delta^{4,6}$-dienes from $\Delta^{4}$-6-bromosteroids.

Applications of the Reaction: The unsaturated ketone 2,4-dinitrophenylhydrazone thus formed can be treated with aqueous pyruvic acid[11] in the presence of hydrogen bromide[8] to generate the unsaturated ketone in 95% yield.

The mono- and dibromination products of the allo series have gained increased importance, since the 2,4-dibromo-3-ketosteroids on dehydrobromination yield the 1,4-dienones which represent the key intermediates in the partial synthesis of the estrogens[12,13]. Dibromination of testosterone acetate, a $\Delta^{4}$-3-ketosteroid, gives a

dibromo derivative which can be dehydrobrominated to give $\Delta^{1,4,6}$-androstatriene-17-ol-3-one. This product can be hydrogenated to estradiol which can then be selectively oxidized to estrone[14].

The reaction is frequently used in the preparation of intermediates in the syntheses of many steroid hormones of the adrenal cortex. For example, 3,11,20-triketo-21-acetoxy-$\Delta^4$-pregnene and 3,11,20-triketo-17-hydroxy-21-acetoxy-$\Delta^4$-pregnene have been prepared in good yields from the corresponding 3-keto-4-bromo derivatives[9]. Also, methyl 3-ketoetio*allo*cholanate[16] may be transformed into the $\Delta^4$ compound[17], and thence the free acid into desoxycorticosterone[18] or progesterone[19]

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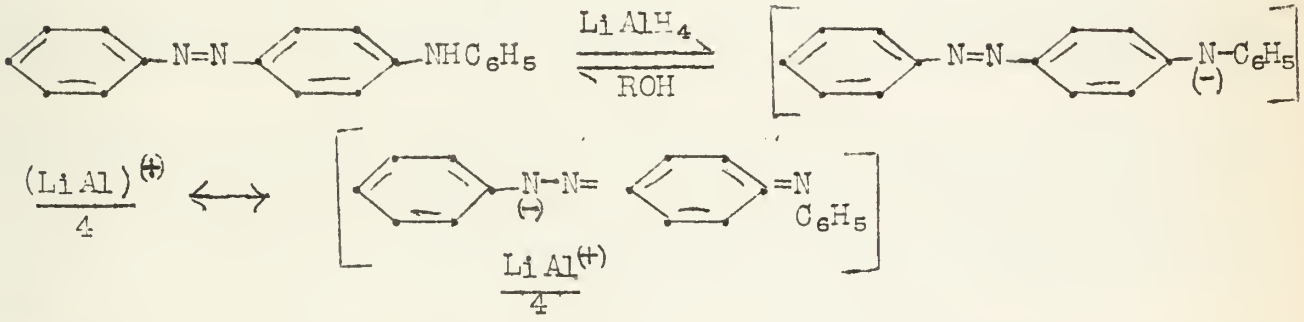
# MIXED METAL HYDRIDES

Reported by John Leak December 14, 1951

Introduction: Metal hydrides may be divided into two classes with respect to reduction of organic compounds. The members of the first class, eg. $LiAlH_4$, $NaBH_4$, $LiBH_4$, will reduce organic compounds. These hydrides have the common property of being soluble in certain solvents and are invariably used in solution. The second class does not successfully cause reduction of organic compounds and the members of this class are insoluble in organic solvents. Apparently, reduction occurs only when the hydride is in solution. This has been explained by Nystrom[7 1] as being due to the fact that when the hydride is in solution reduction can be brought to completion before alkoxide catalized condensations can compete to a great extent. It is possible that NaH and LiH do not function well as reducint agents because reduction can occur only at the hydride surface and the alkoxides formed thereby, if soluble in the medium, initiate non-reductive processes in the liquid phase.

Use in Analysis: Lithium aluminium hydride has been used as an alternate of methyl magnesium iodide in the Zerewitinoff determination of active hydrogen,[1,2,3] for determination of keto-enol equilibria since it freezes the equilibrium instantly by forming a salt of the enol form a nd reducing the keto form, and for determination of water[5] since it is essentially complete in one minute as compared to one to forty eight hours for other methods. A reverse of the procedure for the determination of water is used to standardize the hydride.[6,7,8,9] Indicators[10] as well as potentiometric methods can be used in the determination of very weak acids and other oxygenated compounds including alcohols, phenols, ketones, aldehydes, etc. A suitable compound for an indicator seems to be N-phenyl-p-amino-azobenzene since it changes from yellow to red when excess hydride is present.

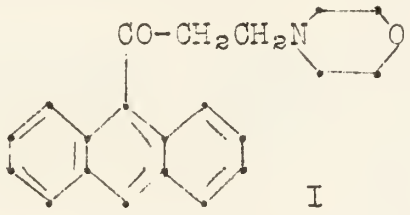



Lithium aluminium hydride has been used in a test for the aromatic nitro group[14 15] and has proved satisfactory with a few exceptions.

Reduction of Aldehydes and Ketones: Lithium borohydride has been used to preferentially reduce ketones in the presence of cyano groups and semicarbazone functions[16] making possible a partial synthesis of Reichstein's Substances E and U as well as the transformation of cortisone to Compound F and 11-dehydrocorticosterone to corticosterone.

Reductions of sugars have been carried out with both $LiAlH_4$[18,19] and $NaBH_4$.[17,20] The latter reagent seems advantagious since solubility of $NaBH_4$ in water makes it ideal for reductions in aqueous solution. Previously, much trouble was encountered in $NaBH_4$ reductions because of the stable boron complexes[21] formed with many reduction products, but use of Amberlite columns, formation of fully acetylated derivatives,[20] or treatment with methanolic HCl eliminate this difficulty. The acetates of the sugars must be used when using $LiAlH_4$ but the acetyl group is removed in the reduction.

Reduction of hindered carbonyls is extremely useful since $LiAlH_4$ is not effected by steric hindrance.[22,23,24,25,26] Platinium oxide reduces the aromatic ring of 9-(3-morpholino-1-oxopropyl)-anthracene (I) but the carbonyl is unaffected while a 90% yield of the alcohol is obtained with $LiAlH_4$.[28] Also the carbonyl of 2-ethyl-2-(2,3-dimethoxyphenyl)-cyclohexanone which will not react with any other carbonyl reagents including Grignard reagents is reduced by $LiAlH_4$.[27]




I

Selective reduction of carbonyls in the presence of halogens has been successful.[30] Reduction of 2,2-dichloro diethyl malonate with $LiAlH_4$ produced 2,2-dichloropropane-1,3-diol[31] and 1,3-dichlorohydrin was produced from 1,3-dichloroacetone.[29] Selective reduction of the carbonyl group in the presence of C-C double bonds has been reported.[32 34 35 36] Reduction of acetyl cyclopropane[33] shows the advantage of $LiAlH_4$ in the presence of strained rings. Recent work with quinones shows the varied products that may be obtained on hydride reduction.[37]

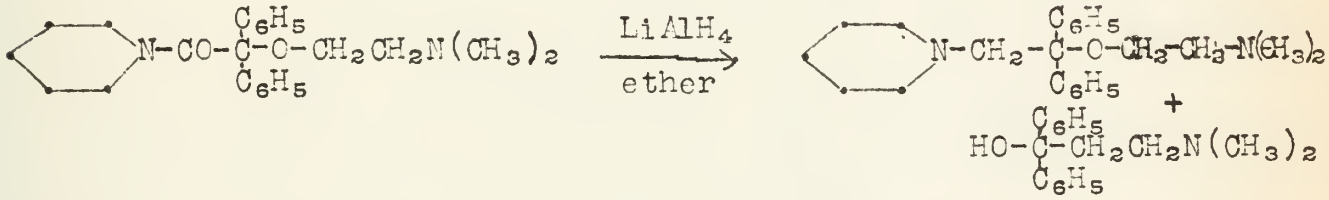
Preferentially, $NaBH_4$ is used ot reduce estrone esters to estradiol esters since $LiAlH_4$ cleaves the ester group.[38] Also in the preparation of adrenalin from adrenalone $NaBH_4$ gives a yield of 98% as compared to 82% for $LiAlH_4$.[39]

Reduction of Ethers: Although enol ethers[40] and acetals[41] are not reduced by hydride, examples of epoxide reductions are numerous.[42 43 44 45 46] Reduction of ortho esters of β-methyl mercaptopropionic acid to the acetal is a surprising new discovery and may be utilized further for the production of aldehydes with $LiAlH_4$.[47] It is reported that ethers are split using $CoCl_2$ as a catlyst.[70]

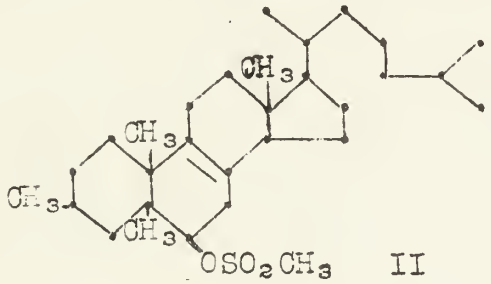
Reduction of C-C Multiple Bonds: Compounds containing double bonds conjugated with a C-O double bond may or may not be reduced.[2 15 22 26 49] Acetylene mono- and dicarboxylic acids can be reduced to allyl alcohol or 2-butene-1,4-diol respectively with no further reduction.[48] Another case of the reduction of an acetylene to an ethylene is the production of the diene from 1-(1-cyclohexene)-3-hydroxy-butyne-1.[50]

Reduction of β-nitro styrenes produces either 2-aryl ethyl amines or 2-aryl acetaldehydes.[51,52] Aromatice hydrocarbons have been reduced.[70] Anthracene is reduced to 9, 10-dihydroanthracene by heating it to 220° with $LiAlH_4$ but phenanthrene is unaffected under similar conditions. Use of a solution of $LiAlH_4$ in carbitol reduces acenaphthylene to acenaphthene almost quantitatively but will not reduce anthracene. Acenaphthylene will not go into a solution of etherial $LiAlH_4$ but 9,9-difluorenylidene is reduced to 9,9-difluorenyl in ether. Pyrene, naphthacene, pentacene and perylene are not reduced by $LiAlH_4$ by any method.[53]

Reduction of Nitriles and Amides: These may be reduced to amines normally[15,54] but there have been cases of production of aldehydes[55,56] by way of imines. Partial reduction occurs with 2,2-diphenyl-3-oxy-4-methyl-morpholine[57] and brucine[60] and sometimes rearrangement accompanies reduction of amides.[57,58]




Reduction of Acids and Acid Derivatives: Most acids, esters, anhydrides, and acid chlorides are reduced normally by $LiAlH_4$ but sometimes abnormalities occur. Heterocyclic carboxylic esters of imidazole, pyrazole, pyrrole, furan, and indole are reduced normally, but pyrazine and oxazole esters undergo decomposition.[59] Sometimes sulfonic esters are reduced to hydrocarbons, but 3-β-methoxy-5-methyl-6-β-mesyloxy-10-nor-8(9)-Cholestene(II) is not affected.[61] The enol acetate of cholestenone gives a variety of products[62] with $LiAlH_4$ but $NaBH_4$ gives good yields of cholesterol[63,64] or the enol acetate of 7-dehydrocholesterol from 7-dehydrocholestenone.[65] Some acetoacetic esters have been reduced to the glycols.[67]




II

Nitro and Nitroso Compounds: Although $LiAlH_4$ reduces nitrobenzene to azobenzene, $LiBH_4$ reduces it to aniline.[68] $LiAlH_4$ reduces aromatic nitroso compounds to azo compounds but unsymetrical dimethyl hydrazine may be prepared by reduction of nitroso dimethyl amine.[69]

Other mixed metal hydrides have not been applied to organic chemistry as yet but uses may soon be made of some of these in the near future.

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# THE BUTENE AND BUTADIENE OXIDES

Reported by Thomas M. Veazey December 14, 1951

I. Structure and Configuration: From theoretical considerations it is apparent that there are two possible structural isomers of butene oxide; namely, butene-1,2-oxide and butene-2,3-oxide. In butene-1,2-oxide carbon atom 2 is asymmetric, making optical enantiomorphs possible. In butene-2,3-oxide carbons 2 and 3 are attached by a double union which prevents rotation and results in cis and trans isomers. There are two possible configurations of the trans form, hence d and l isomers exist. The cis form is internally compensated, therefore a meso form. Butadiene dioxide also exists in racemic and in meso modifications, carbons 2 and 3 being similar asymmetric carbons. No isomerization is possible with isobutene oxide.

II. Formation of the Epoxide Ring:[1] There are two common methods of preparation, either of which serves adequately for the preparation of the butene oxides and for butadiene monoxide: A) Oxidation of the corresponding olefin by a peroxy-acid, and B) Dehydrohalogenation of the corresponding halohydrin by an alkaline reagent. Complications arise in the preparation of butadiene oxide, especially if a particular isomer is desired.

The most obvious method for the preparation of butadiene dioxide appears to be the oxidation of the commercially available butadiene. The reaction proceeds readily to the monoxide, but slowly and with great difficulty to the dioxide. There is also great danger of an explosion of the reaction mixture. One recent paper[2] reports the preparation of the dioxide by treatment of the monoxide with perbenzoic acid at -5° for 14 days, but does not state which isomer was obtained. A mixture of the racemic and meso modifications is to be expected.

Preparation of the dioxide from the 1,4-dihalobutane-2,3-diols,[3,4,5] or from the 2,3-dihalobutane-1,4-diols[5,7] is easily accomplished by treatment in ether or dioxane solution with various alkaline reagents, but these dihalodiols are not too readily obtainable. Addition of hypohalite to butadiene, for example, leads to a mixture of 4 position isomers, two of which lead to products other than the desired dioxide when treated with alkali. Even preparation from the commercially available monoxide by way of the hypohalite addition method gives at best a 15% yield of butadiene dioxide.[6]

The most feasible synthesis of butadiene dioxide is based on the method of Valette[7] and can lead either to the pure meso isomer or to the racemic modification. Acetylene and formaldehyde are reacted in the presence of a copper chloride-calcium carbonate-silver nitrate catalyst to give a 90% yield of dimethylolacetylene, which is then hydrogenated over Raney nickel to produce pure cis-2-butene-1,4-diol. Bromination of the butenediol yields racemic threo-2,3-dibromobutane-1,4-diol which may be dehydrohalogenated with potassium hydroxide to the racemic butadiene dioxide. Proof of structure is afforded by hydrolysis of the dioxide to yield racemic erythritol, m.p. 70°.

The cis-2-butene-1,4-diol can also serve as an intermediate in the preparation of the meso-butadiene dioxide. Treatment with phosphorus tribromide replaces the hydroxyl groups with bromine, and the resultant cis-1,4-dibromobutene, upon oxidation with dilute permanganate yields the racemic erythro-1,4-dibromobutane-2,3-diol. Subsequent dehydrohalogenation yields the meso-butadiene dioxide. Proof of structure is afforded by hydrolysis to meso-erythritol, m.p. 118°.

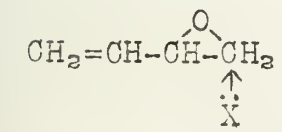
III. Resolution: The unsubstituted epoxy compounds are not readily resolved because of the difficulty of preparing diastereoisomers without destroying the ring structure. However, it is possible to prepare the optically active oxides from optically active precursors. Thus, Winstein and Lucas[8] prepared optically active trans-butene-2,3-oxide from optically active erythro-3-bromo-2-butanol, and could regenerate the optically active bromobutanol by treatment of the active oxide with HBr.

However, if optically active threo-3-bromo-2-butanol was subjected to dehydrohalogenation, the symmetrical cis-butene-2,3-oxide resulted. This, when treated with HBr, gave the racemic threo-3-bromo-2-butanol.

IV. Ring Opening: Opening of the oxide ring in most reactions represents a nucleophilic displacement on carbon,[9] the displaced group being the ring oxygen atom. The reactive species may be the oxide itself, or the conjugate acid of the oxide. The rate of attack by water or by hydrogen chloride is about 400 times as fast upon the conjugate acid as upon the neutral oxide.[10] With phenols, malonic ester, and similar anionic reagents, base catalyzed reactions are usually employed, and in these cases the reaction rate increases with the basicity of the anion.[11]

Since these are bimolecular nucleophilic displacements, it is logical that inversion generally occurs; i.e., the ring opening is trans. Thus cyclohexene oxide on treatment with HBr yields the trans bromohydrin and with water the trans glycol.[12]

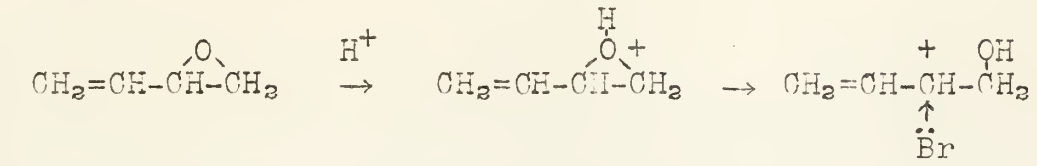
When the oxide is not symmetrically substituted, opening of the ring can give rise to structural isomers. In most instances it is possible to make reliable predictions as to the direction of the opening. For ordinary bimolecular nucleophilic displacements, the rate sequence, primary greater than secondary greater than tertiary, is general and accounts for the major product in the reaction of the neutral epoxide species.



X = Anion from sodium phenoxide, sodiomalonic ester, or similar reagent.

But with the conjugate acid species the direction of the reaction may be completely reversed.[13,14] Thus, whereas butadiene monoxide with sodium hypobromite yields 1-hydroxy-2-bromo-3-butene, with

HBr the product is 1-bromo-2-hydroxy-3-butene. This may be accounted for by a new mechanism involving unimolecular opening of the conjugate acid ring.



Here the rate sequence would be tertiary greater than secondary greater than primary, but the reaction is more likely a concerted displacement since practically none of the isomer to be expected from the other possible resonance hybrid of the carbonium ion is obtained.[13]

In the reaction of either racemic or meso-butadiene dioxide with various reagents in neutral or alkaline medium, Beech reports the following to give exclusively the 1,4-disubstituted butane-2,3-diols:[15] Aniline, methanol, phenol, naphthalene-β-thiol, and piperidene. Oxidation of the two resultant dipiperidinobutanediols (meso and racemic) with periodic acid affords a method of identification of the two isomeric products. Periodic acid is known to oxidize cis-glycols more rapidly than the trans-glycols.[16] For the 1,4-dipiperidinobutane-2,3-diol in acid medium, the mutual repulsion of the positively charged piperidinium ions will bring the two hydroxyls close together in the d or l forms, but will set them apart in the meso form. The racemate would therefore be expected to behave as a cis-glycol (i.e., faster oxidation), and the meso modification to behave as a trans glycol.

Beech found that the dipiperidinobutanediol obtained from the meso-butadiene dioxide required 2590 minutes for complete oxidation whereas the diol obtained from the racemic dioxide was oxidized in 100 minutes.

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# ANIONOTROPY

Reported by D. E. Brasure January 4, 1952

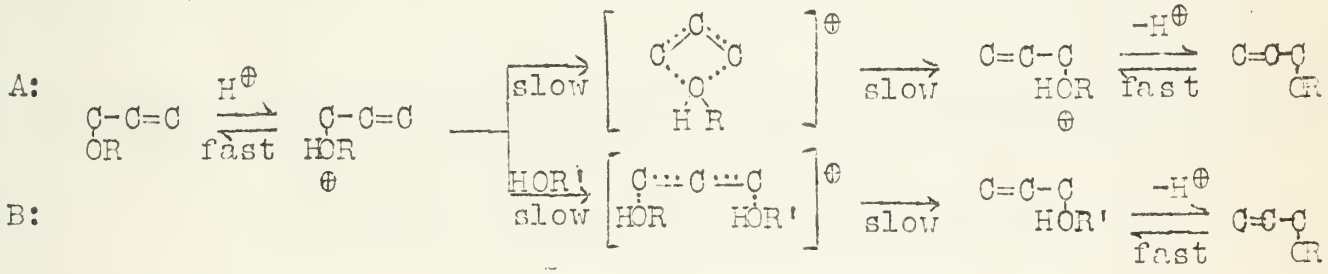
Anionotropy refers to all rearrangements in which the migrating or departing group retains the electron pair by which it was originally linked to the rest of the molecule. According to this definition anionotropy includes the Beckmann and pinacol-pinacolone rearrangements involving two- carbon systems, the allylic rearrangement involving three-carbon systems, and various rearrangements involving five- and higher carbon systems. The three- and five-carbon systems will be considered in this seminar.

## THREE-CARBON SYSTEM

There are, of course, a great many examples of the allylic rearrangement. Braude refers to it as three-carbon oxotropy when the hydroxyl group is the migrating group.[1] A simple example is the heating of 1-methylallyl alcohol (I) with dilute sulfuric acid, the resulting equilibrium containing 70% of (I) and 30% of crotyl alcohol (II).[2]

$$\underset{\text{I}}{\text{Me-CHOH-CH=CH}_2} \rightleftharpoons \underset{\text{II}}{\text{Me-CH=CH-CH}_2\text{OH}}$$

A. Mechanism. The rearrangement follows simple first order kinetics. It has been found that it occurs only in the presence of acid and is catalyzed specifically by the hydrogen ion. The actual rearrangement is preceded by a fast reversible formation of an oxonium ion; migration may then be either intra- or inter- molecular.[3,4] It is believed that the rearrangements of carbinols and esters in dilute solutions in inert solvents proceeds by mechanism A whereas in aqueous solutions it goes by both A and B. A third mechanism involving a carbonium ion intermediate has been disproved by Braude and Coles.[5]



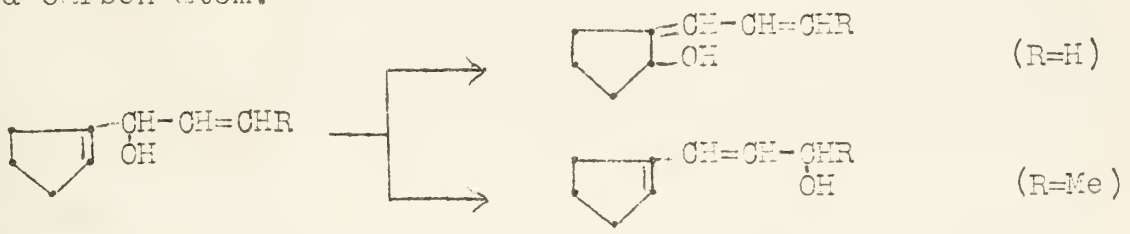
B. Substituted Allyl Alcohols. Whereas the alkylallyl alcohols undergo oxotropic rearrangement slowly and reversibly, arylallyl alcohols rearrange readily, the equilibrium being displaced in favor of the more conjugated isomer. Thus phenylvinylcarbinol (III) is converted quantitatively to cinnamyl alcohol (IV).[6] The introduction of an aryl group in the three position results once again in an equilibrium being established as shown in (V) and (VI).

$$\underset{\text{III}}{\text{Ph-CHOH-CH=CH}_2} \rightarrow \underset{\text{IV}}{\text{Ph-CH=CH-CH}_2\text{OH}}$$

$$\underset{\text{V}}{\text{Ph-CHOH-CH=CH-Ar}} \rightleftharpoons \underset{\text{VI}}{\text{Ph-CH=CH-CHOH-Ar}}$$

These two rearrangements can prove valuable in kinetic studies, the first for determining the electron-donating powers of various substituents on the phenyl group, the second for calculating the resonance energies of various conjugated systems.

As would be expected from the strong electron-attracting properties of the acetylenic group, the alkynylallyl alcohols do not rearrange readily. The alkenylallyl alcohols are more reactive. The hydroxyl group always migrates to the more highly alkyl-substituted carbon atom:[7]




C. Stereochemical Studies. Braude and Coles have recently studied the stereochemistry of the oxotropic rearrangement.[4] Both phenyl-*cis*- and phenyl-*trans*-propenylcarbinol rearrange to methyl-*trans*-styrylcarbinol:[4,8]

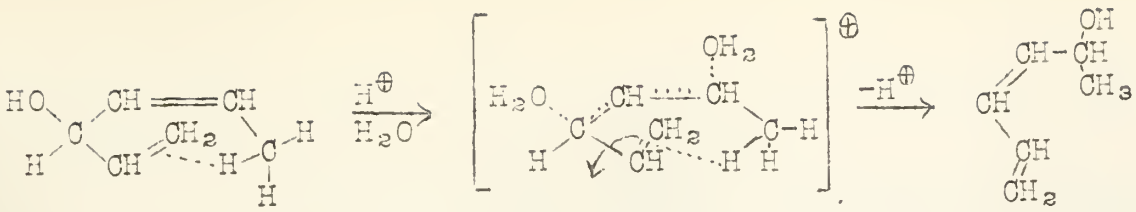
$$Ph\text{-}CHOH\text{-}CH{=}CH\text{-}Me \rightarrow Ph\text{-}CH{=}CH\text{-}CHOH\text{-}Me$$

The explanation for this was found by ultra-violet analysis. The maximum absorption band of methyl-*trans*-styrylcarbinol was displaced from that of styrene; this was traced to additional conjugative effects due to hyperconjugation of the -CHOHMe group.[9] The maximum band of the *cis* compound was almost identical to that of styrene; it was deduced that steric hindrance between the -CHOHMe group and the *ortho*-hydrogen of the phenyl group prevented the coplanarity necessary for conjugation. It is this steric hindrance which must cause the rearrangement to lead exclusively to methyl-*trans*-styrylcarbinol.

The rearrangement of *trans*-propenylvinylcarbinol under mild conditions gave *trans*-butadienylmethylcarbinol, but the *cis* compound, surprisingly, gave *cis*-butadienylmethylcarbinol.

$$\underset{\alpha}{CH_2}{=}\underset{\beta}{CH}\text{-}\underset{\alpha}{CHOH}\text{-}CH{=}CHMe \rightarrow CH_2{=}CH\text{-}CH{=}CH\text{-}CHOH\text{-}Me$$

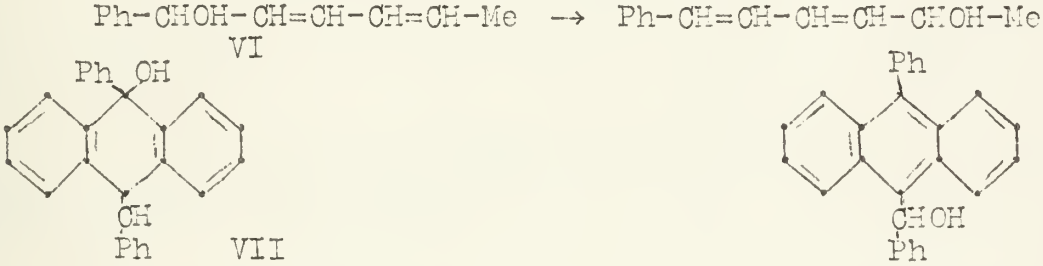
Ultra-violet analysis revealed a situation analogous to that above: hyperconjugation effects present in *trans*-butadienylmethylcarbinol were absent in the *cis* because of steric hindrance. Since there should be free rotation about the $C_\alpha$-$C_\beta$ bond, and since then the *trans* product should be formed preferentially, the formation of the *cis* product was quite unexpected. The anomoly can be accounted for if the rotation of the $C_\alpha$-$C_\beta$ bond in the *cis* compound is not free. Braude and Coles have tentatively proposed that an intramolecular interaction occurs between the $\pi$-electrons of the vinyl group and a hydrogen atom of the methyl group, the hydrogen atom having acquired a partial positive charge through hyperconjugation. This interaction will hold the molecule in the *cis* configuration during the rearrangement.



For this interaction he proposes the term "π-hydrogen bonding." It can be visualized as intermediate between ordinary hydrogen bonding and π-bonding. It is a weak bond, judged to possess a stabilization of no more than 1-2 kcal/mol, as shown by the fact that phenyl-*cis*-propenylcarbinol, where π-hydrogen bonding might also be expected, rearranged to the *trans*- product. The greater steric hindrance in this *cis* compound is believed to be the controlling factor in this rearrangement.

FIVE-CARBON SYSTEM

The same mechanism as was formulated for the triad system is believed to apply to rearrangements involving the pentad system. Two examples are the rearrangements of 1-phenyl-2,4-hexadien-1-ol (VI) involving a linear system[10] and 10-benzylidene-9,10-dihydro-9-phenylanthran-9-ol (VII) involving a cyclic system.[11]



The oxotropic rearrangement in which a nitrogen atom participates has never been observed in open chain systems. However, it is quite probable that the acid-catalyzed rearrangement of phenylhydroxylamine proceeds by successive pentad anionotropic and prototropic changes in the C=C-C=C-N skeleton.[1,12]

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# SYNTHESES OF CYSTINE AND CYSTEINE

Reported by Harold H. Foster January 4, 1951

Introduction: The two closely related amino acids, cystine and cysteine, are readily interconvertible.

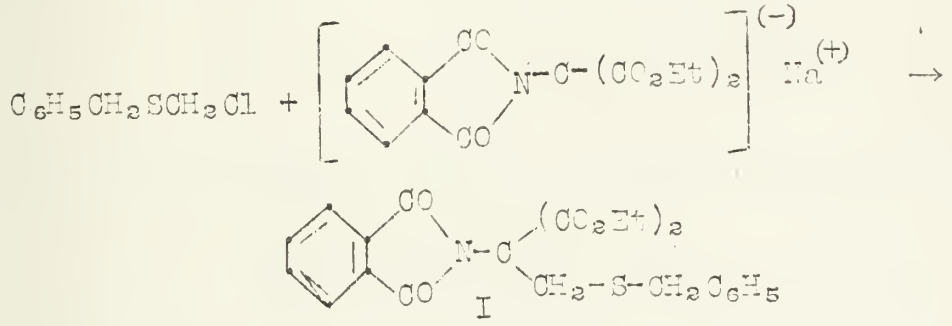
$$2\ HSCH_2CH(NH_2)\text{-}CO_2H \underset{[H]}{\overset{[O]}{\rightleftharpoons}} HO_2C\text{-}\underset{NH_2}{CH}\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\underset{NH_2}{CH}\text{-}CO_2H$$

Thus a synthesis of either compound will also serve as a synthesis for the other.

Syntheses of cystine and cysteine are illustrative of useful methods of introducing sulfhydro groups into compounds. Recent syntheses provide a means of introducing mercaptan groups into positions which are alpha to an amino group.

The earliest successful synthesis of cystine[1] involves treating serine with phosphorus pentachloride. Treatment of the chloro intermediate with $Ba(SH)_2$ gave cysteine which was not isolated. The cysteine was oxidized to cystine by ferric chloride and ammonium hydroxide. Cystine produced in this way is optically inactive even if active serine is used. The overall yield is about 25%.

A second synthesis of cystine[2] involves as the important step the condensation of benzylthiolmethylchloride with phthalimido malonic ester.



The S-benzylthiolmethylphthalimidomalonic ester (I) is hydrolysed and decarboxylated to give S-benzyl-dl cysteine. Treatment of this latter compound with sodium in liquid ammonia followed by air oxidation gives cystine.

Very recently two investigators[3,4] reported a synthesis of cystine involving conjugate addition of thiolacetic acid to α-acetamidoacrylic acid.

$$CH_3COCO_2H + CH_3CONH_2 \rightarrow CH_2{=}C(NHCOCH_3)\text{-}CO_2H \xrightarrow{CH_3COSH} \text{ascaridole}$$

$$CH_3COSCH_2\underset{NHCOCH_3}{CH}\text{-}CO_2H \xrightarrow[I_2]{H^{\oplus}} \text{cystine (70\% yield)}$$

A synthesis for cystine[5] based on hydantoin formation follows.

$$C_6H_5CH_2SCH_2CH(OEt)_2 \xrightarrow[HCl]{5N} C_6H_5CH_2SCH_2CHO \xrightarrow{HCN}$$

$$C_6H_5CH_2SCH_2CH(OH)CN \xrightarrow{(NH_4)_2CO_3} C_6H_5CH_2SCH_2-\underset{\text{II}}{\overset{CO-NH}{\underset{NH-CO}{CH}}}$$

The 5-thiolbenzylmethyl hydantoin (II) was hydrolysed with barium hydroxide to give S-benzyl dl cysteine. Treatment of this compound by sodium in liquid ammonia followed by air oxidation gives cystine.

Two useful methods have been developed for converting serine into cystine.[6] Both methods involve the heterocyclic intermediate, 2-phenyl-4-carboxymethyloxazoline(III).

The replacement reaction:

$$\begin{array}{l} CH_2-CH-CO_2CH_3 \\ | \quad\quad | \\ O \quad N\cdot HCl \\ \quad C \\ \quad C_6H_5 \quad \text{III} \end{array} \longrightarrow Cl-CH_2-\underset{NHCOC_6H_5}{CH}-CO_2CH_3 \xrightarrow[\text{pyridine}]{Mg(SH)_2}$$

$$\left[HS-CH_2-\underset{NHCOC_6H_5}{CH}-CO_2CH_3\right] \xrightarrow{[\,]}$$

58% yield of DL and meso forms of N,N'-dibenzoyl cystine dimethyl ester.

The same product is obtained from either optically active or inactive starting material. Clearly, the formulation of the chlorine displacement must include elimination of the hydrogen at the asymmetric carbon atom. An intermediate which has been proposed to fulfill this requirement is the enol salt--

$$HS-CH_2-\underset{NHCOC_6H_5}{\overset{OMgX}{C}}=C-OCH_3.$$

This possibility was shown to be unlikely when it was found that N-benzoyl-L-cysteine methyl ester did not racemize when dissolved in magnesium methoxide solution.

A more likely intermediate is the cyclic type ester-

$$CH_2=\underset{NHCOC_6H_5}{C}-CO_2CH_3$$

which is an intermediate in the reaction of

$$Br-CH_2-\underset{NHCOC_6H_5}{CH}-CO_2CH_3$$

with pyridine in the presence of hydrogen sulfide. After standing for one hour, 24% of the bromine had become ionic; but no cysteine derivative could be isolated. Formation of cysteine on longer standing indicated addition to the double bond rather than direct displacement. In the presence of magnesium ions the mechanism is speculative. The reaction may involve an imminent replacement as the hydrogen chloride is eliminated or subsequent addition catalyzed by the magnesium ions.

Oxazoline salt rearrangement: This method involves rearrangement of the oxazoline with thiolbenzoic acid. Optical activity is retained.

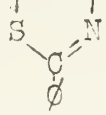
2-phenyl-4 carboxy-L-oxazoline $\xrightarrow[\text{Pyridine}]{C_6H_5COSH}$ Ø-COSCH$_2$CHCOOH (NHCOØ) N,S-dibenzoyl-L-cysteine (isolated) $\xrightarrow[NaOMe]{NaOH}$ $\xrightarrow{[O]}$

HOOC-CH(NHCOØ)-CH$_2$-S-S-CH$_2$-CH(NHCOØ)-CO$_2$H $\xrightarrow[H_2O]{H^\oplus}$ L-cystine-42% yield $[\alpha]_D^{25}$ -212°

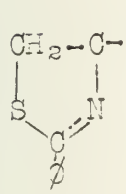
Two novel syntheses for cystine based on a conversion of serine to cystine[7,8] should be especially useful for introducing radioactive carbon into the cysteine system.

$(EtO_2C)_2$-CH-NH$_2$·HCl $\xrightarrow[(C_2H_5)_3N]{Ø\text{-}CS_2CH_2CO_2H,\ PY}$ $(EtO_2C)_2$-CH-NHCSØ $\xrightarrow[PY]{HCHO}$

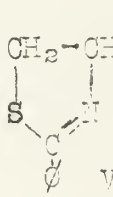
HO-CH$_2$-C(NHCSØ)-$(CO_2Et)_2$ $\xrightarrow[Cold]{SOCl_2}$ IV



V $\xrightarrow[EtOH]{NaOH}$



$\xrightarrow{H^\oplus}$



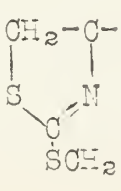
VI $\xrightarrow[H^\oplus]{H_2O}$ $\xrightarrow{[O]}$ Optically inactive cystine

The conversion of ethyl-α-carbethoxy-β-hydroxy-α-thiolbenzamido propionate (IV) to 4,4 dicarbethoxy-2-phenyl-$\Delta^2$-thiazoline (V) probably involved a sulfite ester intermediate. The formation of the thiazoline probably involves an interesting participation by a neighboring thiobenzamido group. Structure VI was shown to be 2phenyl-$\Delta^2$-thiazoline-4-carboxylic acid by two independent syntheses. Condensation of the methyl ester of the hydrochloride of cysteine with ethyl benzimidate followed by alkaline hydrolysis gave VI. Treatment of methyl α-thiobenzamido-β-hydroxy propionate with thionyl chloride gave an intermediate which could be hydrolyzed to VI also.

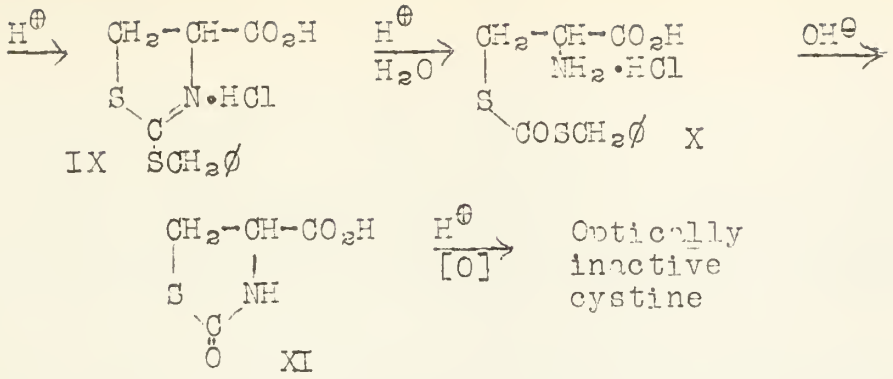
The second synthesis is probably easier and more useful than the first.

CH(NH$_2$·HCl)-$(CO_2Et)_2$ $\xrightarrow[(C_2H_5)_3N]{CS_2,\ PY}$ $\xrightarrow[(C_2H_5)_3N]{ØCH_2Cl,\ PY}$ CH(NHCS$_2$CH$_2$Ø)-$(CO_2Et)_2$ $\xrightarrow[PY]{HCHO}$

CH$_2$OH-C(NHCS$_2$CH$_2$Ø)-$(CO_2Et)_2$ $\xrightarrow[Cold]{SOCl_2}$ VII



VIII $\xrightarrow[EtOH]{NaOH}$



IX



XI

The conversion of the diethyl-α-hydroxymethyl-malonate (VII) to 2benzylthio-4,4 dicarbethoxy-$\Delta^2$-thiazoline (VIII) undoubtedly involves the sulfite ester intermediate. In this instance we may note the possible role of the dithiocarbobenzyloxyamido group as a participating neighbour. The structure of XI, shown to be 2-thiobenzyl-$\Delta^2$-thi zoline-4carboxylic acid was proven by synthesis from serine. Structure X was assigned on the basis of three pieces of evidence:

(1) It contained no free thiol groups.
(2) It appeared to be the hydrochloride of a base, giving ionic chlorine in solution. It gave a positive ninhydrin reaction and yielded a formyl derivative free of chlorine.
(3) Above pH7 it yielded toluene-w-thiol and 2-ketothiazolidine-4-carboxylic acid (XI).

Compound X was unusually stable to acid hydrolysis. Part of this stability may be attributed to the insolubility of the salt in dilute acid.

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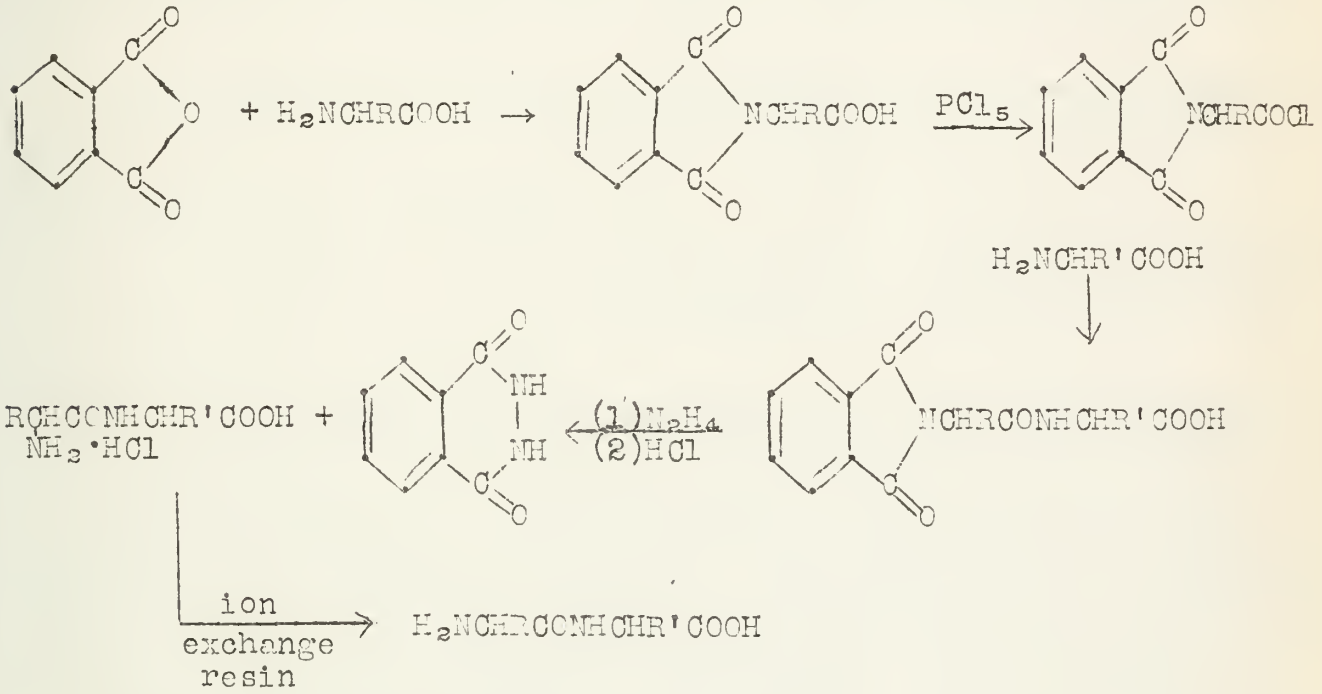
# NEW METHODS OF PEPTIDE SYNTHESIS

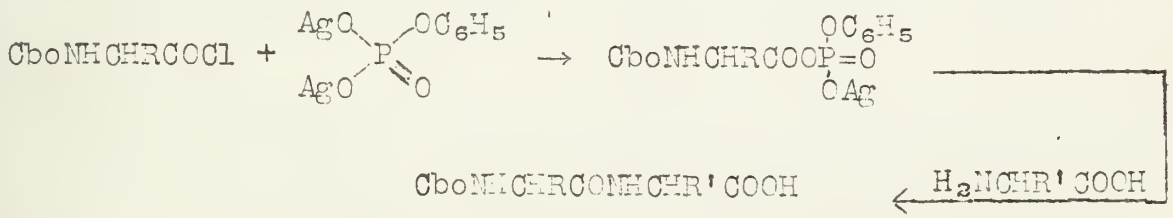
Reported by Byron L. Haines January 4, 1952

Most methods for peptide synthesis depend upon the protection of the amino function of an amino acid while the carboxyl function is converted to the chloride, anhydride, azide, or ester for coupling with a second amino acid or peptide. Emil Fisher intiated the search for a systematic peptide synthesis and was followed by Curtius and Bergmann. These men laid the ground work by investigating, perhaps, the most obvious methods of peptide synthesis.[1]

Until 1949, Bergmann's "carbobenzoxy" method of synthesis was the most satisfactory.[2] At that time, Sheehan and Frank[3] introduced another general synthetic procedure using the phthalyl protecting group and the Ing and Manske procedure for its removal. Since this method is fairly recent, the complete extent of its applicability is not known. The important features are shown in the following series of reactions:




Instead of forming the azide or chloride as the coupling function Chantrenne[4] was able to induce coupling by forming the mixed anhydrides of mono- or diphosphoric esters with carbobenzoxyamino acids. (Cbo = carbobenzoxy.)



By this procedure he prepared glycylglycine, glycyltryptophane, and glycylglycyltryptophane in fair yields.

Wieland and Sehring[5] have shown that mixed anhydrides could be formed by condensing the benzoyl or acetyl chlorides with the silver, sodium, or N-ethylpiperidine salts of the amino acids or of the N-acylated amino acids. In an organic solvent or aqueous solution these mixed anhydrides react smoothly with other amino acids or peptides to give the peptide linkage.

$$\text{CboNHCHRCOOAg} + C_6H_5COCl \rightarrow \text{CboNHCHRCOOCO}C_6H_5 + AgCl$$
$$\text{CboNHCHRCOOCO}C_6H_5 + H_2NCHR'COOH \rightarrow \text{CboNHCHRCONHCHR'COOH} + C_6H_5COOH$$

The isolation of the benzoic anhydride is omitted in most cases as the organic solution needs only to be shaken with alkaline amino acid or peptide solution, and acidified with HCl to get the new peptide. Cbo-glycylglycine, Cbo-d,l-alanyl-d,l-phenylalanine, and N-phthalylglycyl-d,l-alanine are some of the peptides that can be synthesized by this method.

While working on a study of the penicillin ring, Süs[6] found a new synthesis of peptides through the use of $PCl_3$ as a coupling agent.

$$\text{EtOOCCHRNH}_2 \quad Cl_2P \rightarrow \quad \text{EtOOCCHRN}\!=\!PCl \quad \xrightarrow{2\,\text{AcNHCHR'COOH}} \quad \text{2EtOOCCHRNHCOCHR'NHAc}$$
$$\text{EtOOCCHRNH}_2 \quad Cl \qquad \text{EtOOCCHRNH}$$

By this means phenacetylglycyl-d,l-α-alanine, benzoylglycylglycine, N-Cbo-glycylglycine and phenacetyltriglycylglycine were prepared.

The conversion of a Cbo-amino acid or peptide into the Cbo-derivative of a higher peptide without the preparation of carboxylic esters has been achieved by Kenner.[7] A solution of the Cbo-amino acid or peptide in dimethyl formamide is neutralized by a methanolic solution of potassium or phenyltrimethylammonium methoxide and heated to remove the methanol by distillation. After cooling, the resulting solution is allowed to react with a dimethylformamide sulfurtrioxide complex which yields the mixed anhydride. This in turn is condensed with the sodium salt of the second amino acid. The peptide precipitates when the solution is made alkaline.

$$\text{Cbo-NHCHRCOO}^{\ominus} + \text{H-C}(=\overset{\oplus}{\text{O}}\text{-SO}_3^{\ominus})\text{-NMe}_2 \rightarrow \text{CboNHCHRCOOSO}_3^{\ominus} + \text{HCONMe}_2$$

The overall yield is 72%. This method has the advantage that the asymmetric carbon next to the carbonyl group involved in the condensation is exposed to the risk of racemisation for only a very short time, and therefore the method should be applicable to the lengthening of optically active peptide chains.

When working with the mixed anhydrides of carbonic and carboxylic acids, Vaughn[8] found them to be excellent acylating agents for the preparation of amides. In particular, anhydrides of the branched chain alkyl carbonic acids and N-substituted amino acids or peptides react readily at low temperatures with amino acids or peptide esters to give the corresponding peptide or higher peptide in good yield, and with a high degree of purity. The best mixed anhydride was obtained with sec- or iso-butyl-chlorocarbonates.

$$R'''OCOCl + XNHCHRCOOH \rightarrow XNHCHRCOOCOOR''' \xrightarrow{NH_2CHR'COOR''} XNHCHRCONHCHR'COOR'' + R'''OH + CO_2$$

The yields varied from 50-60%. Concurrently, Boissonnas[9] found the same method and reported similar results. His yields ran as high as 71% for the simple dipeptides.

Wieland[10] has developed a newer synthesis which depends upon the reaction of a thioester of an N-acylated amino acid with an amino acid according to the following scheme:

$$CboNHCHRCOSC_6H_5 + H_2NCHR'COOH \rightarrow CboNHCHRCONHR'COOH + R_6H_5SH$$

The thioesters of the amino acids are conveniently prepared by treatment of the acid and N-ethyl piperidine in tetrahydrofuran with ethyl chloro formate, followed by the addition of the thiophenol. With this procedure, analytically pure Cbo-glycylalanine was obtained in a 90% yield.

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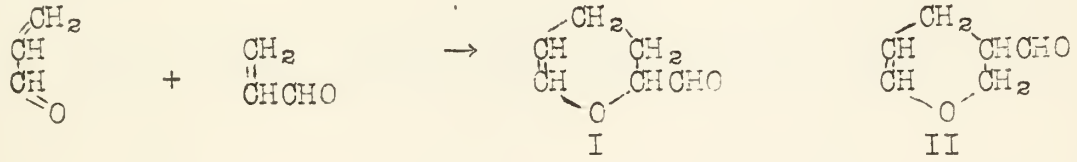
# REACTIONS OF ACROLEIN AND RELATED COMPOUNDS

Reported by Glenn Fuller January 11, 1952

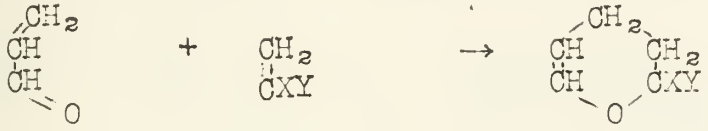
Introduction: In 1941 Alder (1) first determined the structure of the dimer of acrolein and showed that the dimerization of this compound has a formal similarity to the Diels-Alder reaction. This similarity is based on the fact that the conjugated carbonylic compound functions both as a diene (1,4-addition) and as a dienophile (1,2-addition).



I II

At the same time it was determined that I rather than II was the only isomer which could be recovered from the reaction mixture. Other α,β-unsaturated carbonylic compounds which dimerize according to the same scheme are methyl vinyl ketone (2,3) and α-methylene cyclohexanone (4). The latter dimerizes so readily that it is difficult to isolate in monomeric form.

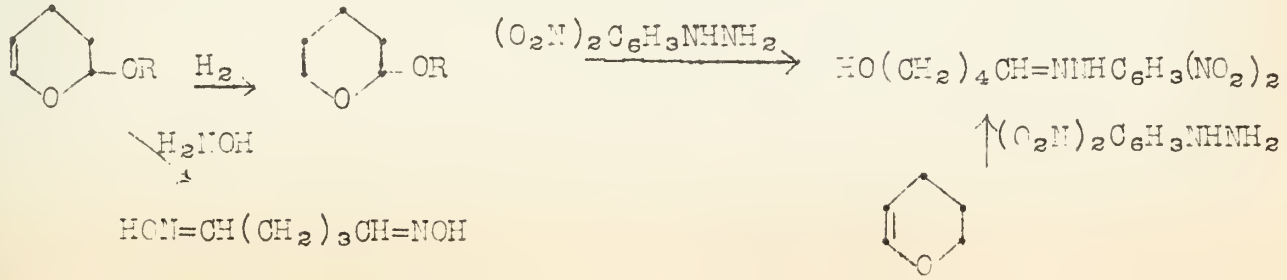
Recent experiments have been carried out to determine if acrolein and other α,β-unsaturated carbonylic compounds will act in a similar manner toward vinyl ethers (5), unsaturated esters (6), and some olefins (7). In all cases the reaction proceeds with the β-carbon atom of the carbonyl compound joined to the least substituted carbon of the dienophile. The groups X and Y in the example below can be either electronegative or electropositive.



Scope of the reaction:

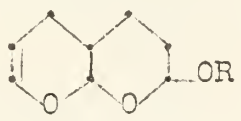
A. Addition of vinyl ethers: For carrying out the addition of α,β-unsaturated aldehydes and ketones to vinyl ethers, the reagents were heated together under autogenous pressure in steel or glass bombs at about 180° without solvent for one to two hours. Longley and Emerson (8) used longer reaction times (12-42 hours) and sometimes lower temperatures. These investigators also added 0.10 - 1.00% hydroquinone to inhibit polymerization.

The products of the addition of acrolein to alkyl vinyl ethers are 2-alkoxy-3,4-dihydro-2H-pyrans (III). The proof of structure of these compounds was carried out as shown.



The α,β-unsaturated carbonylic compounds employed included acrolein, methacrolein, crotonaldehyde, methyl vinyl ketone, cinnamaldehyde, β-furylacrolein, benzalacetone, and benzalacetophenone. The dienophiles used were methyl vinyl ether, ethyl vinyl ether, n-butyl vinyl ether, isobutyl vinyl ether, 2-ethylhexyl vinyl ether, phenyl vinyl ether, phenyl vinyl sulfide, n-butyl cyclohexenyl ether, ethyl isopropenyl ether and divinyl ether.(5,8,9). In the reaction of divinyl ether with acrolein, some product was formed corresponding to the addition of two moles of acrolein to one mole of the ether (IV). Also, in the cases of addition of methyl vinyl ether and isobutyl vinyl ether, products were obtained from reaction of two moles of acrolein with one mole of ether. These products were shown to have a structure corresponding to V rather than VI.

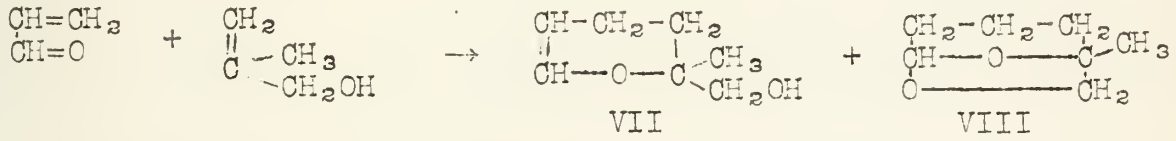
IV



V

VI

V. Reaction of unsaturated esters and methacrylonitrile (6). Reaction of these substances is carried out in an analogous manner to that of the addition of vinyl ethers to α,β-unsaturated carbonylic compounds, i.e. heating the reactants without solvent under autogenous pressure at 180-200°. Again, the β-carbon of the aldehyde was always joined to the unsubstituted carbon of the olefinic bond of the ester or nitrile. When, for example, methyl methacrylate is allowed to react with acrolein, the product is 2-carbomethoxy-2-methyl-3,4-dihydro-2H-pyran. In the case of methallyl alcohol and acrolein, two isomeric products were obtained, illustrated by formulas VII and VIII.



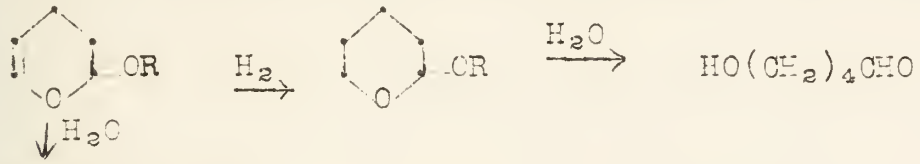
VII VIII

The α,β-unsaturated carbonyl compounds used were acrolein, methacrolein and crotonaldehyde. Both vinyl esters and α,β-unsaturated alkyl esters were employed as dienophiles. These included methyl acrylate, methyl methacrylate, methacrylonitrile, vinyl acetate, methallyl acetate and methallyl alcohol.

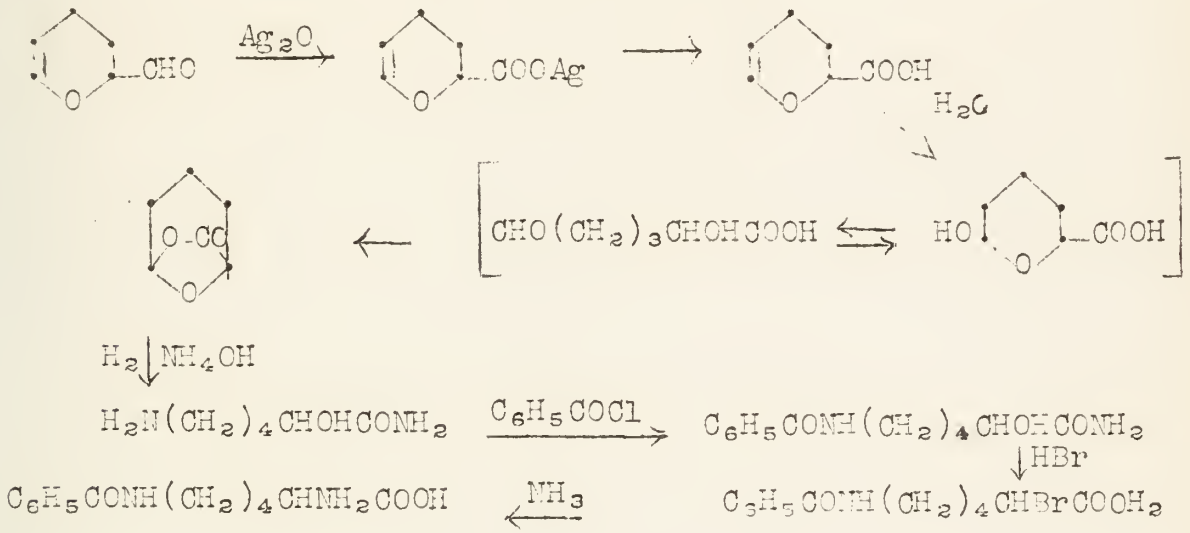
C. Addition of olefins. This addition was carried out in the same manner as with the vinyl ethers, i.e. heating approximately equimolar amounts of the reactants under autogenous pressure to 180-200°. Isobutylene, 1-hexene, diisobutylene, styrene and α-methylstyrene were added to acrolein; also α-methylstyrene was allowed to react with methacrolein, crotonaldehyde, and methyl vinyl ketone. From all these additions, the expected compounds, 3,4-dihydro-2H-pyrans with substitution at the 2-position were recovered. Approximately the same yields were obtained from the reaction of crotonaldehyde and α-methylstyrene, whether the carbonyl compound was inhibited by 1% hydroquinone or activated by 1% benzoyl peroxide.

Mechanism of the reaction. Longley and Emerson (8) have suggested that the reaction proceeds by a polar mechanism similar to that proposed for the conventional diene reaction (10). Smith, Norton and Ballard (7), on the other hand, have postulated a free radical mechanism. The latter mechanism is more consistent with the products obtained, but neither the presence of hydroquinone nor that of benzoyl peroxide seems to affect the rate of reaction or the yield.

Further synthetic applications. A new method of preparing glutaraldehyde and substituted glutaraldehydes has been suggested. This consists in hydrolysis of the 2-alkoxy-3,4-dihydro-2H-pyrans formed from the addition of α,β-unsaturated carbonyl compounds to vinyl ethers. Glutaraldehyde is used in the synthesis of pseudopelletierine (11) and related compounds. From 2-alkoxytetrahydropyrans δ-hydroxyvaleraldehydes may be obtained on hydrolysis.




A new synthesis of lysine has been accomplished by Whetstone and Ballard (12). They start with acrolein dimer and obtain the final product in an overall yield of 12%.

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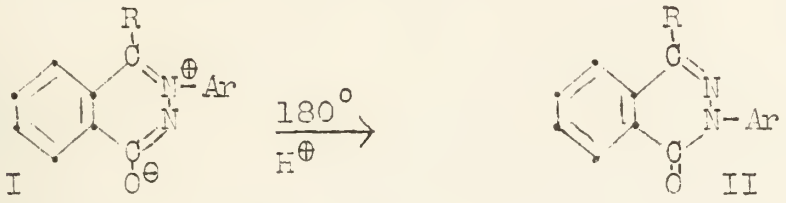
# THE ROWE REARRANGEMENT

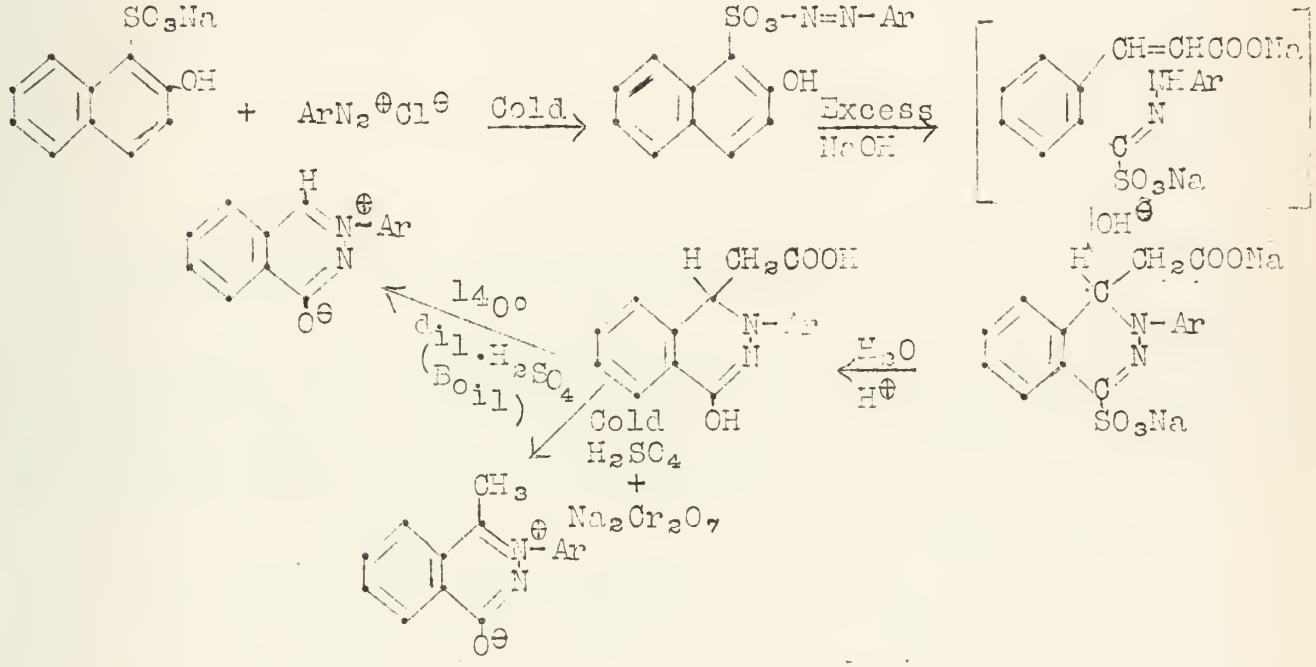
Reported by G. H. McCain January 11, 1952

Introduction: The Rowe rearrangement is a rearrangement of a ψ-phthalazone (I) to a phthalazone (II), under the conditions noted in the equation[1] below.



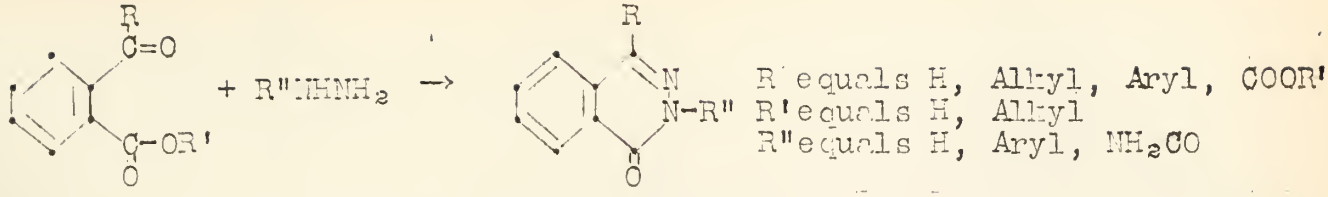
I II

Preparation of Phthalazones and ψ-Phthalazones: The preparation of the ψ-phthalazone was accomplished by Rowe et al.[2,3] in 1926, using the following sequence of reactions, starting with sodium 2-naphthol-1-sulfonate.



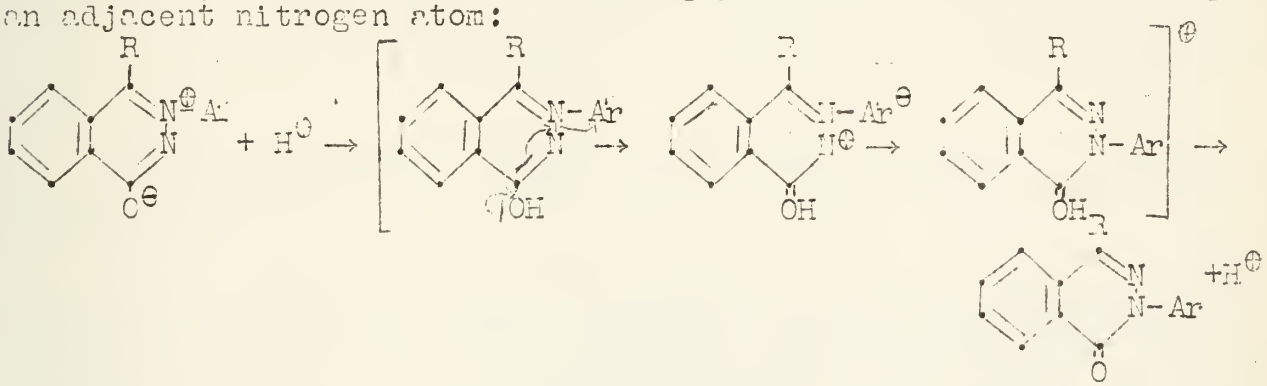
In all cases, Ar must be a nitro compound, although it may be reduced to an amino compound after the heterocyclic ring is closed. Apparently, sodium 2-naphthol-1-sulfonate is the only compound of that type that will undergo this reaction.

Phthalazones are prepared in a number of ways.[3] The most general, particularly for more simple compounds, is by the reaction of an arylhydrazine with an ortho-keto benzoic acid or ester:



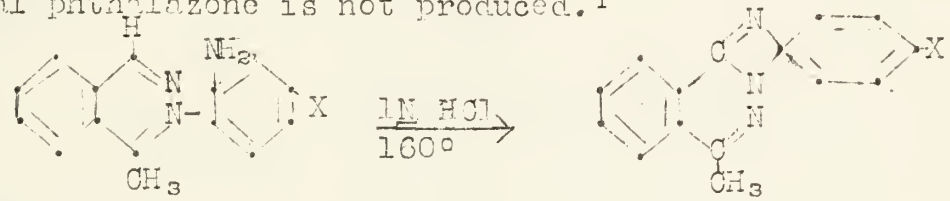

Mechanism of the Rearrangement: The mechanism of the rearrangement has been in doubt since Rowe and his associates first discovered[1] that the Ψ-phthalazone could be converted into phthalazone by heating it in a sealed tube at 175° for several hours with dilute hydrochloric acid. It was proven to be an intramolecular rearrangement by the usual method of using a mixture of reactants, with the R and Ar of I different, and determing that no mixed product was produced.

Rowe and his associates[1] believed that the mechanism involved carbanions, a group with its bonding pair of electrons shifting to an adjacent nitrogen atom:

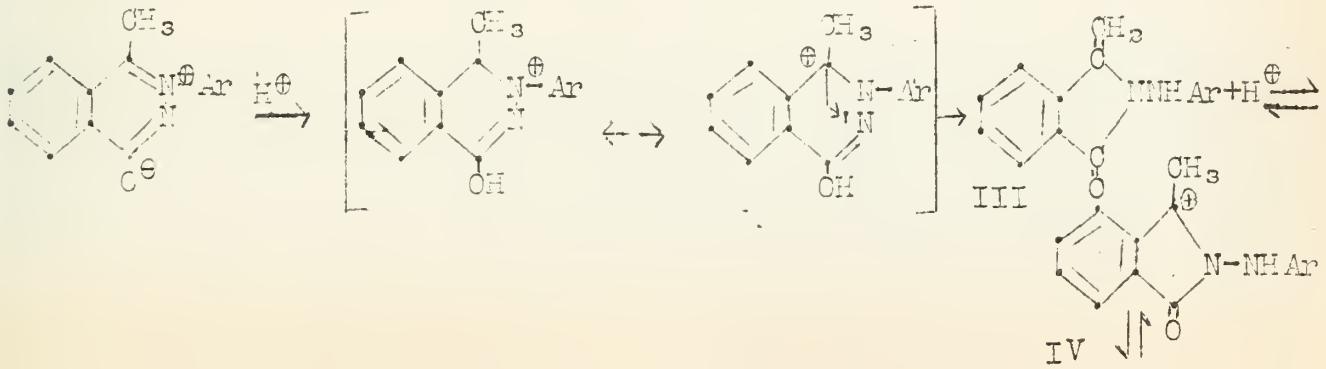


There is no other case known in which an aryl group migrates from one nitrogen to another in a ring.

This mechanism is supported by the fact that if the aryl group has an amino group, which is electron releasing, in the 4 or 3 position in place of the nitro group, no rearrangement occurs. With the amino group in the 2' position a rearrangement does occur, but the normal phthalazone is not produced.[1]



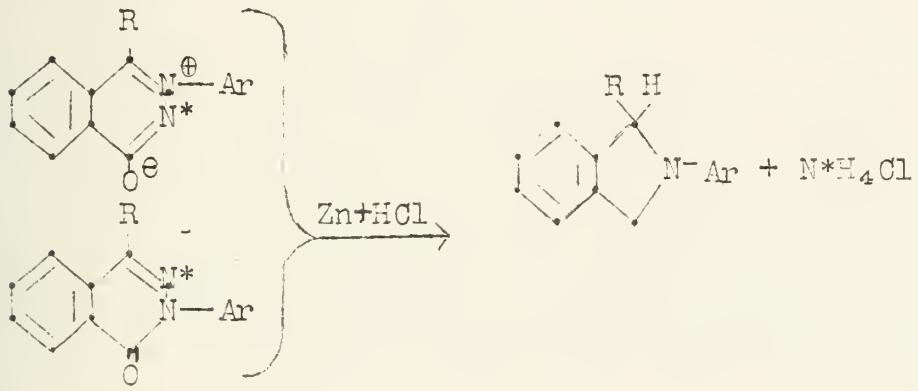

In 1948, Vaughan[3] suggested that the rearrangement involved a contraction to isoindolone type of structure (III):



This mechanism was discarded by Rowe, because if H is substituted for the $CH_3$ group, III obviously could not be formed. However, structure IV obviates this difficulty, by proposing an isoindolone carbonium ion as an intermediate, rather than isoindolone itself. This is supported by the fact that, in certain cases, Rowe isolated compounds with a structure like III[1], by using milder conditions than those required for the rearrangement. This happened only with R as $CH_3$ and with Ar as 2'-nitrophenyl, 2'halo-4'-nitrophenyl or 2',6'-dihalo-4'-nitrophenyl. This intermediate (III) will go on to the phthalazone with further treatment by dilute acid at 180°. Its formation can be explained by the reaction IV → III, under conditions where IV is stable enought to eject a proton without rearranging.

Vaughan suggested[3] that the mechanism could be determined by the use of $N^{15}$ in the ψ-phthalazone. This was done recently in the following way.[4]

Both phthalazone and ψ-phthalazone were prepared, placing $N^{15}$ in the unsubstituted positions. The phthalazones were prepared by the method mentioned above, using 2-acetobenzoic acid and β-$N^{15}$-enriched 4-nitrophenylhydrazine. The ψ-phthalazone was prepared by the method mentioned previously from sodium 2-naphthol-1-sulfonate and 4-nitroaniline, diazotized with $N^{15}$ enriched potassium nitrite. If either the ψ-phthalazone or phthalazone is reduced, an n-substituted isoindolone (V) and ammonium chloride are the chief products.



That the unsubstituted nitrogen is the one released as ammonium chloride was proved by reducing the tagged synthetic phthalazone with zinc and hydrochloric acid and determining that nearly all of the expected $N^{15}$ was found in the ammonium chloride produced. The same thing was found to be true of the $N^{15}$ in the ψ-phthalazone. If Rowe's mechanism is followed, the rearranged phthalazone would give no $N^{15}$ on reduction. However, Vaughan's mechanism would be expected to

produce a phthalazone with the $N^{15}$ still unsubstituted. The latter was found to be true and therefore the second mechanism is to be considered the correct one.

Below is a table of the compounds which have been subjected to this rearrangement.

TABLE I[1]

| Ar | R equals H % Yield | R equals $CH_3$ % Yield |
|---|---|---|
| 4'nitrophenyl[2] | 66 | 82 |
| 4'-nitro-2'-methylphenyl[8] | 30 | 27 |
| 2'-chloro-4'-nitrophenyl[7] | -- | 49 |
| 2'-bromo-4'-nitrophenyl[9] | -- | 27 |
| 2',6'-dichloro-4'-nitrophenyl[6] | 46 | 17 |
| 2',6'-dibromo-4'-nitrophenyl[6] | 30 | -- |
| 3'-nitrophenyl[5] | 14 | 25 |
| 2'-nitro-4'-methylphenyl[2] | 36 | 56 |
| 4'-chloro-2'-nitrophenyl[2] | 38 | 74 |
| 2'-nitrophenyl[1] | -- | 65 |

General Observations: If the nitro group is in the 2' or 4' position the rate of the rearrangement is much more rapid than if it is in the 3' position. Halogens in the 2' position reduce the rate considerably, bromine much more than chlorine. Finally, methyl in the 2' or 4' position reduces the rate.

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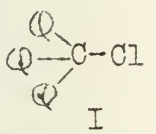
# INTERNAL RETURN

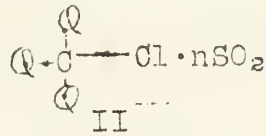
Reported by J. K. Williams January 11, 1952

Recently, evidence has been accumulating which points to a new type of intermediate (not a transition state) in rearrangements of certain alkyl halides and arylsulfonates. There are indications that intermediates of this type occur as a general phenomenon which may be associated with any reaction involving a carbonium ion. These intermediates are undissociated ion pairs and, in the case of rearrangements, they are produced from one isomer and can either collapse into the other isomer or react with some external ion. This process has been given the name "internal return"[1]. In the reactant the rearranging atom or group is covalently bound. In the intermediate the rearranging group has moved farther away from the rest of the molecule and the bond is largely electrostatic. Finally, the product is formed by a return of the moving group to covalent bonding to a different atom than in the starting material.

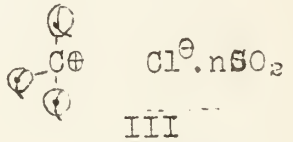
Evidence For Undissociated Ion Pairs. Probably the best evidence for the undissociated ion pair is that reported by Bartlett.[2] While studying the ionization constants of triarylmethyl chlorides, he found that a species was produced from triphenylmethyl chloride (I) in liquid sulfur dioxide solution which had the same molar color intensity as the carbonium ion produced from the same halide in sulfuric acid solution. He found that the conductivity of solutions of I in sulfur dioxide was one half that of solutions of I in sulfuric acid. These facts pointed to the existence of a species (II) which resembled triphenylmethyl carbonium ion (III) closely enough to give the same spectrum, but which was not dissociated into ions and therefore did not lead to conductance.



I
Tetrahedral
colorless



II
planar
yellow
non-conducting

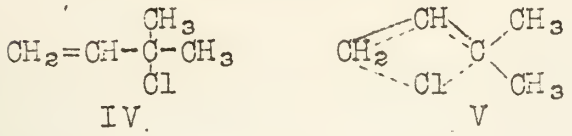


III
planar
yellow
conducting

Evidence For Internal Return.

A. An internal return type mechanism has been postulated for the allylic rearrangements of certain allyl alcohols and esters.[3,4] However Young, Winstein, and Goering[1] have studied the rearrangement of α,α-dimethylallyl chloride (IV) to γ,γ-dimethylallyl chloride (VI) in great detail, making the only successful kinetic study of the rearrangement of an allyl chloride yet reported. The authors were able to determine the rate and kinetic order of rearrangement and the effects of various added ions upon the rate of rearrangement during the acetolysis of IV. It was found that the rate of rearrangement was kinetically first order and that it was independent of initial chloride ion concentration at constant ionic strength.

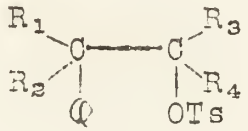
The kinetic data is inconsistent with a carbonium ion intermediate. The overall result of the isomerization is an example of the intramolecular process visualized by Hughes[5] (VII).



IV V VI VII

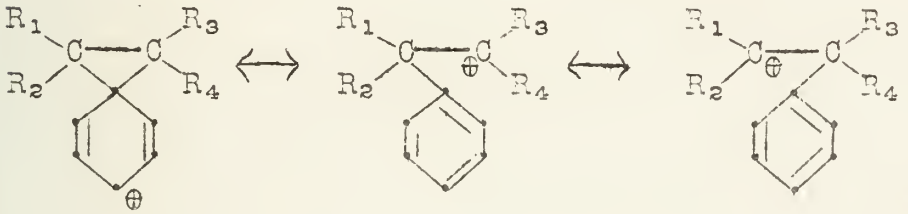
However, there is indication that the rearrangement involves a relatively long lived undissociated ion pair (V) since the tertiary chloride does not give concurrent rearrangement on alcoholysis and the alcoholysis rate is very nearly identical with the acetolysis rate (instead of smaller as is the case with t-butyl chloride.[6])

B. Cram[7,8] has studied the solvolysis and rearrangement of optically active p-toluenesulfonates of alcohols of the type shown below (VIII).



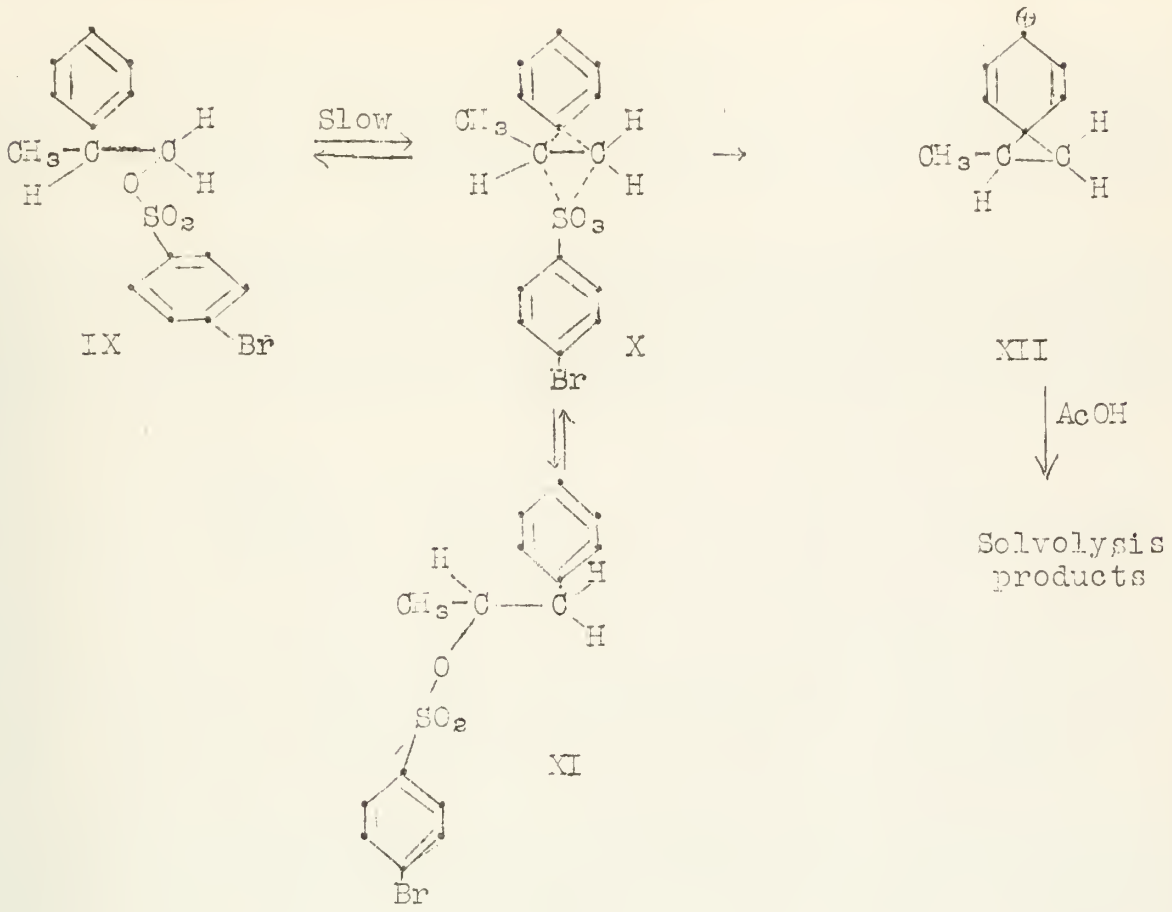
VIII

He originally concluded that the intermediates involved were probably "benzonium" ions which may be represented by the resonance forms:



Winstein[9] has investigated the simultaneous rearrangement and actolysis of 2-phenyl-1-propyl p-bromobenzenesulfonate (IX) using kinetic methods. It was possible to separate the rates of solvolysis of the rearranged (XI) and unrearranged (IX) compounds because the rearranged compound was the sulfonate of a secondary alcohol and thus solvolyzed considerably slower than the unrearranged sulfonate which was primary. Surprisingly, he found that the rate constant for rearrangement was twice that of solvolysis and that this rearrangement was a first order intramolecular process which did not involve external p-bromobenzenesulfonate ion. This anomalous result conflicts with the concept that both rearrangement and solvolysis proceed through a common benzonium ion, since then the amount of rearrangement would be sensitive to p-bromobenzenesulfonate ion and could not be faster than the rate of solvolysis. Again an internal return explains the anomalous behavior as shown below. An undissociated ion pair (X), which is formed before the benzonium ion (XII), can collapse to give rearrangement intramolecularly.

X could also lose sulfonate ion to form a benzonium ion. This ion can then react with solvent to give solvolysis products.

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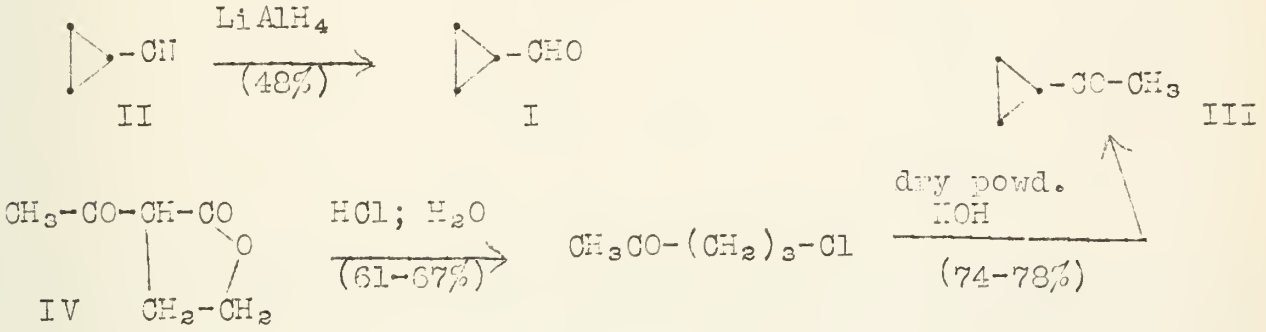
# SOME RECENT DEVELOPMENTS IN THE CHEMISTRY OF CYCLOPROPANE AND CYCLOBUTANE

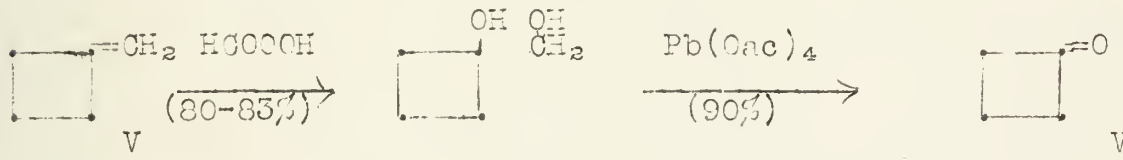
Reported by Herbert O. House January 18, 1952

The presence of an uniquely strained system accompanied by ready accessibility has served to promote an active interest in the chemical and physical properties of three- and four-membered carbocycles. This information is being used to elucidate some of the theoretical aspects of organic chemistry.

A. Synthetic Methods: Cyclopropanecarboxaldehyde (I), whose preparation from tetrahydrofuran was reported in a previous seminar,[1] has been synthesized in a more satisfactory manner by reduction of cyclopropyl cyanide (II)[2]. A superior synthesis of methylcyclopropyl ketone (III) utilizing α-acetobutyrolactone (IV)[2] has recently been reported.




Methylenecyclobutane (V), available from pentaerythritol tetrabromide as reported in a previous seminar,[3] may be transformed to cyclobutanone (VI) in good yield. This ketone may be readily reduced to cyclobutanol with lithium aluminum hydride or to cyclobutane using the modified Wolff-Kishner method.[4]

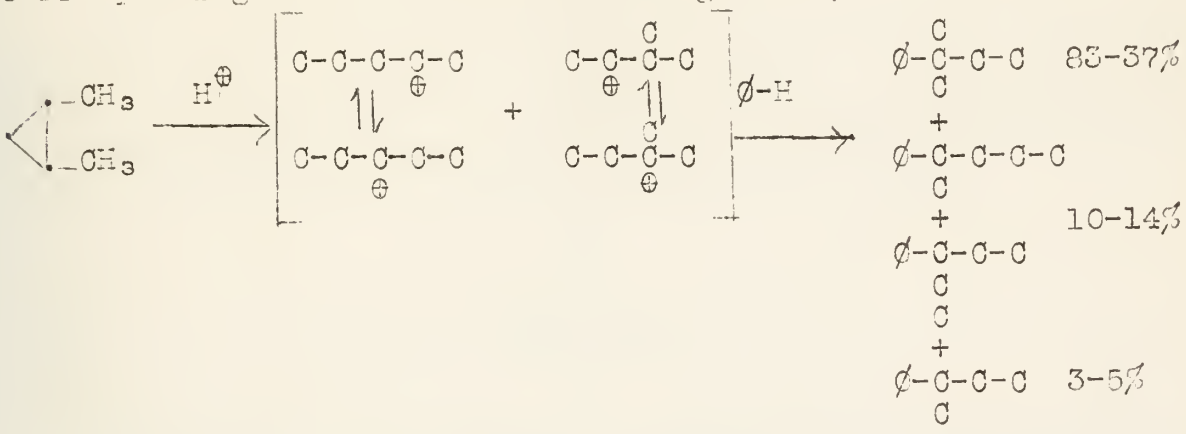



Reductive alkylation of dimethylamine with this ketone gives dimethylcyclobutylamine whose N-oxide or methiodide undergoes thermal decomposition to give cyclobutene. Dehydration of cyclobutanol or thermal decomposition of its xanthate yields only 1,3-butadiene.[4]

The preparation of cyclopropylamine may be readily effected through the rearrangement of the benzenesulfonate of methyl cyclopropyl ketoxime.[5]

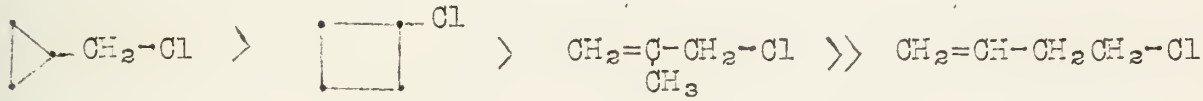
Both cyclopropyl[5] and cyclobutyl[6] bromides are most easily prepared by the action of bromine on the silver salts of the corresponding carboxylic acids at low temperatures. Photochemical chlorination serves to produce cyclopropyl chloride[7] and cyclobutyl chloride.[8]

B. Rearrangements Involving Carbonium-Ion Intermediates: The alkylation of benzene with propane and its alkyl derivatives involves the rearrangement of carbonium-ion intermediates in some cases. While cyclopropane has been found to produce n-propylbenzene at low temperatures using hydrogen fluoride as a catalyst,[9] a higher reaction temperature accompanied by sulfuric acid as catalyst leads to the expected rearrangement with the formation of isopropylbenzene.[10] Use of a mixture of cis- and trans-1,2-dimethylcyclopropanes with hydrogen fluoride at 0-5° as an alkylating agent gives a complex mixture corresponding to the various rearrangement products.[11]



Reactions which proceed via the initial formation of electron-deficient carbon atoms within the cyclopropane or cyclobutane ring seem invariably to lead to rearrangement. The acetolysis of the p-toluenesulfonates of cyclopropanol and cyclobutanol in glacial acetic acid, shown to be strictly unimolecular, leads to the formation of acetates of allyl alcohol and of cyclobutanol(52%), cyclopropylcarbinol (65%), and allylcarbinol (13%).[13]

The extreme ease with which cyclobutyl, cyclopropylcarbinyl, and allylcarbinyl derivatives are interconverted in reactions involving cationic intermediates is attributed to such a rearrangement. Roberts and Mazur suggest that the knowledge of five factors is necessary to enalbe production of the major reaction product: (1) the relative carbonium-ion stabilities, (2) the energy barriers to interconversion of the carbonium ions, (3) the relative reactivities of the carbonium ions toward nucleophilic substances, (4) the reversibility of the various reactions, and (5) the thermodynamic stabilities of the possible products.[8] The order of solvolysis rates for halide derivatives of this series giving a measure of carbonium-ion stabilities was quite unexpected.

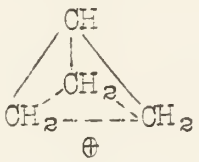


To determine the energy barriers limiting the carbonium-ion interconversions in question the amine derivatives were treated with sodium nitrite in perchloric acid to generate the required cationic intermediates. The results obtained were first interpreted to mean

that, while interconversion of cyclopropylcarbinyl and cyclobutyl carbonium ions has a very low energy barrier, the conversion of either to an allylcarbinyl carbonium ion is attended by a high energy barrier. The energy required for the reverse transformation is intermediate in value.

Action of Lucas reagent on the chlorides served to demonstrate that their order of stability was: allylcarbinyl chloride > cyclobutyl chloride > cyclopropylcarbinyl chloride.

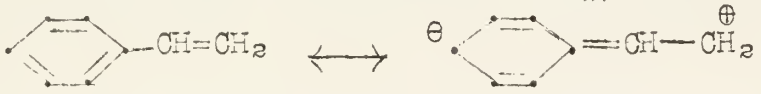
Later work using $C^{14}$-labeled cyclopropylcarbinyl derivatives demonstrated that the three methylene groups become equivalent at some point in the reaction sequence leading to rearrangement products. The authors suggested the existence of a common intermediate in cyclobutyl-cyclopropylcarbinyl interconversions which they formulated as a "non-classical" carbonium-ion structure (VII).

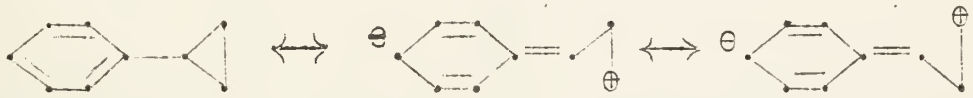


VII

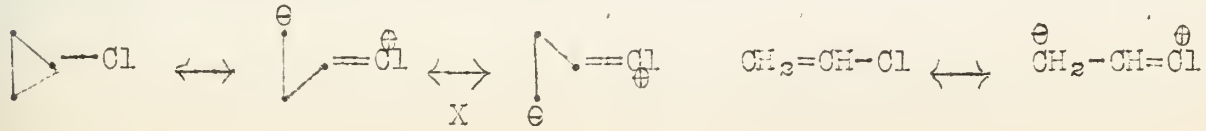
Reactions of this series of compounds which involve free radical or carbanion intermediates seem to proceed without rearrangement in many cases.[8]

C. Influence on Chemical and Physical Properties: The similarity of effect resulting from a vinyl or a cyclopropyl substituent has been noted in a number of instances. Much evidence has been accumulated attesting the similar resonance possibilities available to such compounds; for example styrene (VIII) and phenylcyclopropane (IX).

VIII 

IX 

Existence of these structures is suggested by a similarity in the ultra-violet spectra of the two compounds.[14] Evidence for conjugation involving the cyclopropyl ring was also obtained for methyl cyclopropyl ketone, cyclopropyl cyanide, and vinylcyclopropane[14] as well as 2-cyclopropylpyridine[15] and cyclopropyl chloride.[16] The reduced dipole moment value for the latter compound as compared with isopropyl chloride or cyclopentyl chloride also suggests resonance contributors (X) tending to lower the electron density about the halogen atom corresponding to a similar resonance contributor of the vinyl chloride molecule.[16]

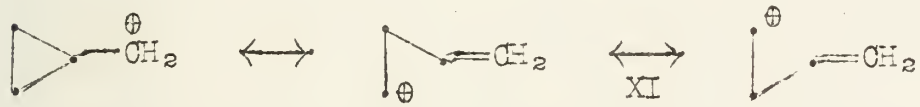


Dipole moment measurements for cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl bromides show that the order of electronegativity of these groups decreases from cyclopropyl to cyclohexyl.[17] The acidities of cycloalkanecarboxylic acids and the basicities of cycloalkylamines vary in a manner which would be predicted by this electrical effect.[17]

2-Phenylbicyclopropyl was prepared to determine whether or not this conjugation effect could be extended through two cyclopropyl groups.[18] The material was found to have a spectrum quite similar to phenylcyclopropane showing that no significant increase in the conjugation of the molecule had occurred.

Chemical properties of such compounds also support the cyclopropyl-vinyl analogy. Cyclopropyl mesityl ketone undergoes ring cleavage to yield γ-substituted butyromesitylenes[19] as would be expected from a conjugate addition. Although neither vinylcyclopropane[20] or 2-phenylbicyclopropyl[18] will serve as a diene in the Diels-Alder reaction, an adduct of this nature is reported in the terpene series.[21] The hydrogenation products of isopropenylcyclopropane and vinylcyclopropane have been shown to differ from those of isopropylcyclopropane in a manner that would be explained by an initial conjugate addition of hydrogen in the first cases.[20]

A further extension of the analogy leads to the expectation that the reactivities of cyclopropyl halides should resemble vinyl halides while cyclopropylcarbinyl halides would be comparable in activity to allyl halides. The order of reactivity of the "allyl-type" bromides was found by kinetic studies of their solvolysis to be: cyclopropylcarbinyl > cyclobutyl > allyl.[3] Stabilizing resonance structures (XI) may be drawn for the cyclopropylcarbinyl carbonium ion although their contribution would not be expected to be as great as the corresponding structure in the allyl series.[3]



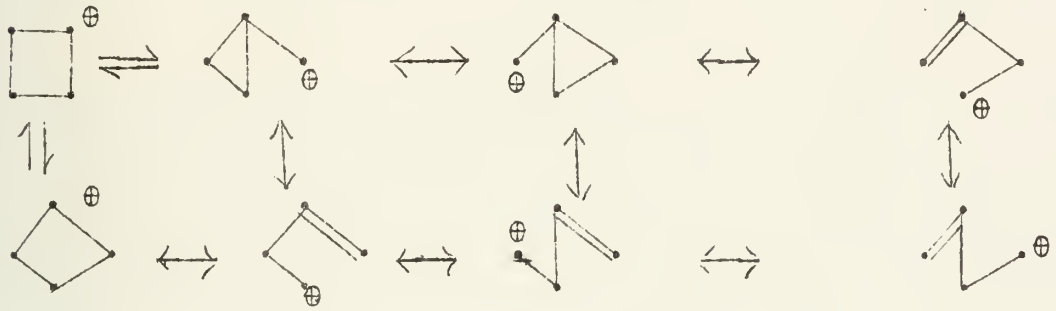
XI

The more highly stabilized "non-classical" carbonium-ion structure would seem to better account for the high degree of reactivity observed.

The order of reactivity in nucleophilic displacement reactions of both the unimolecular and bimolecular type has been found to be: cyclopentyl > cyclobutyl > cyclohexyl >> cyclopropyl.[12] The very low order of reactivity of cyclopropyl derivatives was attributed to (1) decreased ionic character of the C-X bond due to the electronegativity of the cyclopropyl group, (2) delocalization of the unshared electron pairs about the halogen atom which increases the strength of the C-X bond, and (3) increased steric strain in the transition state.

The reactivity of the cyclohexyl p-toluenesulfonate was found to be comparable to that of a typical secondary alkyl compound,

isopropyl p-toluenesulfonate, in a unimolecular displacement reaction.[12] However, the increased reactivities of cyclopentyl and especially cyclobutyl derivatives are quite unexpected on the basis of the previous considerations and are not compatible with the "I-strain" concept of Brown and co-workers which was reviewed in a previous seminar.[22] Roberts and Chambers[12] suggested that the increased reactivity of cyclopentyl compounds might be explained by the lowering of hydrogen-hydrogen interactions which would result in the coplanar transition state. The high order of reactivity of the cyclobutyl derivatives was suggested to be a result of the initial formation of a more stable cyclopropylcarbinyl carbonium ion in rate determing step.[12] It would perhaps be more satisfactory to think of the intermediate as a "non-classical" carbonium-ion structure which could be stabilized by a large number of resonance structures, a few of which are given below.



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14. Rogers, ibid., 69, 2544 (1947).
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# NEWER KETONE SYNTHESES

Reported by K. Chadwick Murdock January 18, 1952

From Organocadmium Compounds: One of the most useful and convenient syntheses of ketones involves the reaction of an acyl halide with an organocadmium compound:[1,2]

$$2\ RCOCl + R'_2Cd \rightarrow 2\ RCOR' + CdCl_2$$

The dialkyl- or diarylcadmium is readily prepared by a metathesis between two moles of the appropriate Grignard reagent and one mole of cadmium chloride and is usually used in the other solution in which it is prepared. Overall yields are generally in the range 65-85%, and the reaction is complete in one to two hours.

Due to its low reactivity, the action of the cadmium reagent is quite specific; the keto group of the product is not attacked in the Grignard manner except in such activated systems as the 1,2-diketones derived from oxalyl chloride. Ester, nitrile or amide groups may also be present. No instance was found of the direct preparation of polyfunctional ketones having functions containing active hydrogen, but it has been stated that diethylcadmium does not react with acetylenes or ordinary amines.[3] The only major limitation to the generality of the method is the fact that it gives only low yields when secondary or tertiary dialkylcadmiums are used in attempts to synthesize branched-chain ketones.

From Acetoacetic Ester:[4] In the G. M. Robinson ketone synthesis the sodium salt of ethyl acetoacetate is first alkylated with an alkyl halide and then acylated with an appropriate acyl chloride. Subsequent acidic and basic hydrolyses without isolation of intermediates effect the removal of both the carbethoxyl and acetyl residues of the original β-ketoester. By this method 4-ketomyristic

$$C_2H_5O_2C\text{-}CH_2Br + \begin{matrix} CO_2C_2H_5 \\ CHNa \\ COCH_3 \end{matrix} \rightarrow \underset{(I)}{C_2H_5O_2C\text{-}CH_2\text{-}\begin{matrix} CO_2C_2H_5 \\ CH \\ COCH_3 \end{matrix}} \xrightarrow[2.\ CH_3(CH_2)_9COCl]{1.\ Na}$$

$$EtO_2C\text{-}CH_2\overset{\overset{CO_2C_2H_5}{|}}{\underset{COCH_3}{C}}CO(CH_2)_9CH_3 \xrightarrow[2.\ OH^{\ominus}]{1.\ H^{\oplus}} C_2H_5OH + CH_3CO_2^{\ominus} + CO_2 + HO_2C\text{-}CH_2CH_2CO(CH_2)_9CH_3$$

(II) (III)

acid (III) is obtained in 72% yield from ethyl acetosuccinate (I). The generality of this method is limited by the tendency of the ketonic cleavage of the disubstituted acetoacetic ester (II) to remove the new acyl group if the latter is either branched in the α-position[5] or if it corresponds to an acid stronger than acetic acid.[4]

From Acylmalonic Esters: The facile double decarboxylation of acylmalonic acids (V) might be expected to give high yields of ketones.

$$\underset{\text{(IV)}}{RCO\text{-}CR'(CO_2R)_2} \rightarrow \underset{\text{(V)}}{RCO\text{-}CR'(CO_2H)_2} \rightarrow RCO\text{-}CH_2R' + 2\ CO_2$$

However, the usual acid- or base-catalized hydrolysis of the acylmalonic ester precursor (IV) also removes the acyl group. Therefore attention has recently been directed toward several non-hydrolytic procedures for cleaving these ester linkages.

A. Acidolysis.[6] Acidolysis of various ethyl acylmalonates with boiling propionic acid containing a catalytic amount of sulfuric acid has been shown to afford methyl ketones in very high yield. However, all attempts to similarly employ alkylated acylmalonic esters proved fruitless.

B. Hydrogenolysis.[7,8] In a ketone synthesis developed by Bowman the salient feature is the hydrogenolysis of a benzyl acylmalonate (VIII).

$$\underset{\text{(VI)}}{R'CNa(CO_2C_2H_5)_2} \xrightarrow{HOCH_2C_6H_5} \underset{\text{(VII)}}{R'CNa(CO_2CH_2C_6H_5)_2} \xrightarrow{RCOCl}$$

$$\underset{\text{(VIII)}}{RCO\text{-}CR'(CO_2CH_2C_6H_5)_2} \xrightarrow[Pd\text{-}SrCO_3]{H_2} \underset{\text{(IX)}}{RCO\text{-}CR'(CO_2H)_2} \xrightarrow{\Delta} \underset{\text{(X)}}{RCOCH_2R'} + 2\ CO_2$$

The method has been demonstrated to be of considerable generality and to be mainly limited only to the absence of readily reducible substituents.

It might be expected that the high boiling points and low crystallizing powers of benzyl malonates might make their isolation difficult. Morever, premature hydrogenolysis could occur during their conversion to the sodio derivatives prior to the acylation step. These problems were neatly solved by forming the sodio benzyl ester *in situ* by transesterification of the corresponding sodio ethyl ester, the sodio enolate catalizing the interchange. The liberated ethanol was azeotropically distilled with benzene in order to force the reaction to completion. Acylation was then conducted in the benzene solution resulting from the transesterification. The crude acylated ester (VIII) was hydrogenated at room temperature over palladized strontium carbonate and the resulting diacid (IX) thermally decarboxylated to give the desired ketone (X). Subsequently[8] it was found that the use of boiling methyl ethyl ketone as the solvent enabled the hydrogenolysis and decarboxylation to occur simultaneously.

By the above procedure the reaction of the readily accessible

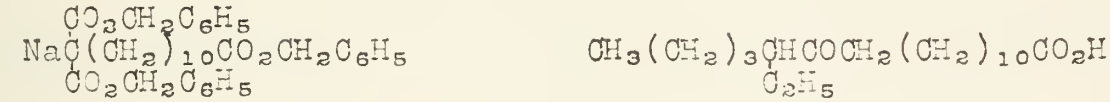
ethyl β-cyanoethylmalonate and decanoyl chloride afforded a 78% yield of 1-cyanopentadecan-4-one (XI) which, on reductive cyclization over Raney nickel at atmospheric pressure, gave a 91% yield of 2-undecylpiperdine (XII).

(XI) (XII)

It was found that in general much lower yields were obtained if the acylation step were effected with an acid anhydride rather than an acid chloride.[8] Therefore, as was found in the organocadmium method[1], a contemplated synthesis involving a cyclic anhydride would better be accomplished with the corresponding ω-carbalkoxyacyl chloride.

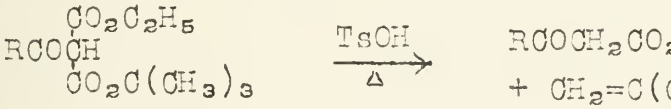
The use of phthalimido-acid chlorides enabled the synthesis of α-aminoketones,[10] though the yields were poor. All attempts to employ aryl malonic esters proved abortive.

As an example of the applicability of the method to the synthesis of α-substituted ketones, the condensation of 2-ethyl hexanoyl choride with benzyl sodioundecan-1,1,11-tricarboxylate (XIII) made possible the attainment of 13-keto-14-ethyloctadecanoic acid (XIV) in 78% yield.[7]



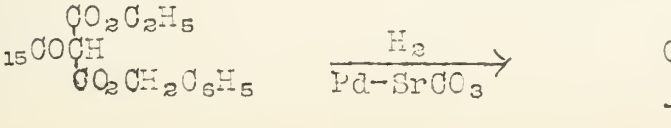
(XIII) (XIV)

Synthesis of β-Ketoesters and β-Ketonitriles: A general synthesis of β-ketoesters depends upon a distinctive mode of cleavage of t-butyl esters.[9]



The yields obtained were in the range 50-70% (where R=ethyl, cyclohexyl, 2-furyl, benzyl and allyl).

A parallel approach involved the hydrogenolysis of a benzyl ethyl acylmalonate.[10]



This procedure worked well in the synthesis of products having no α-substitution, but, in contrast to the t-butyl ester method, gave only poor yields when applied to the synthesis of α-substituted β-ketoesters.

Hydrogenolysis of benzyl acylcyanoacetates yielded β-ketonitriles in good yield. Thus the crude ketonitrile (XV), prepared by condensing pelargonyl chloride with benzyl sodio-n-butylcyanoacetate, gave an overall yield of 63% of 5-cyanotetradecan-4-one (XVI).

$$C_8H_{17}COC(CO_2CH_2C_6H_5)(CN)C_4H_9 \xrightarrow[Pd\text{-}SrCO_3]{H_2} C_8H_{17}COCH(CN)C_4H_9$$

(XV) (XVI)

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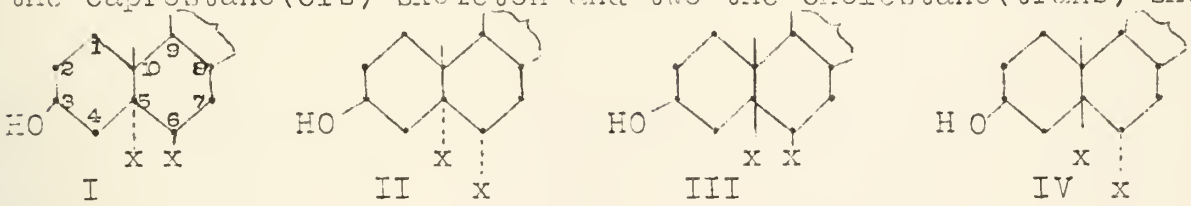
# THE STEREOCHEMISTRY OF CHOLESTEROL DIHALIDES

Reported by John F. Walker January 18, 1952

Introduction.--Addition of chlorine or bromine to cholesterol could theoretically lead to four stereoisomers (I-IV), two possessing the caprostane(cis) skeleton and two the cholestane(trans) skeleton.



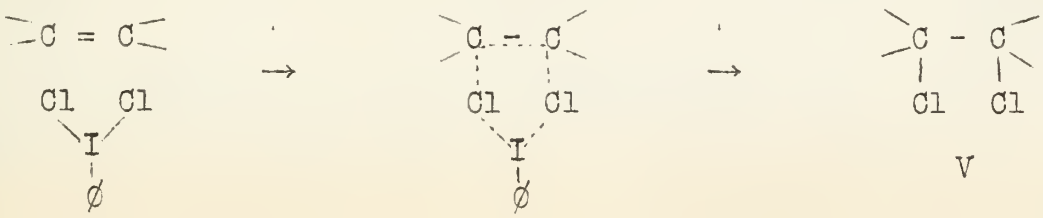

I-3β,5α,6β. } cholestane
II-3β,5α,6α. }

III-3β,5β,6β. } caprostane
IV-3β,5β,6α. }

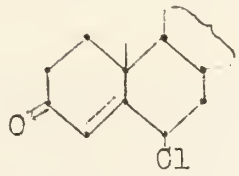
Only one isomer has been isolated by direct bromination or chlorination of the free sterol or its esters. A second dichloro isomer has been isolated by the action (under anhydrous conditions) of iodobenzene dichloride on the benzoate ester of cholesterol(1). Although the configuration of the 5,6 dihydroxycholesterols are known with certainty(2), the stereochemistry of the 5,6 dihalides has only recently been elucidated(1,3). Two recent, simultaneous reports gave conflicting results, but these have now been clarified(4)

Ketone Bromination.--3-keto steroids with a cis fusion of the A/B rings(caprostanones) are brominated in the 4 position while those with a trans fusion of the A/B rings(cholestanones) are brominated in the 2 position(5). Cholesterol dichloride, prepared either by the action of chlorine or iodobenzene dichloride on cholesterol benzoate, after oxidation to the corresponding ketone, can be converted to the 4-bromo ketone by bromination. This was interpreted to indicate that both the dichloro isomers of cholesterol have the caprostane ring structure and thus the 5β chloro configuration(4). This interpretation of the results, however, is mechanistically weak, since the rate controlling step of the bromination of a ketone is the abstraction of a proton from the ketone by a base, and the most acidic, available proton will be removed. The powerful inductive effect of a $C_5$ halogen should lead to substitution in the 4 position regardless of the nature of the A/B ring fusion(6).

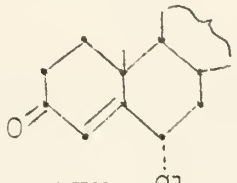
Molecular Rotation Data.--It seems probable that the addition of chlorine or bromine to the olefinic linkage of cholesterol will lead to a trans isomer. This is substantiated by the resistance of this compound to dehydrohalogenation. Iodobenzene dichloride, in the anhydrous condition, should give a cis dichloro compound(V)(1).



The trans isomer could then have the 5α,6β(I) or the 5β,6α(IV) configuration and the cis isomer the 5α,6α(II) or the 5β,6β(III) configuration. Both dichloro isomers can be oxidized to the corresponding ketones which, in the presence of alcoholic sodium acetate, give rise to two stereoisomeric $\Delta^4$-cholestene-3-ones(VI and VII).




VI



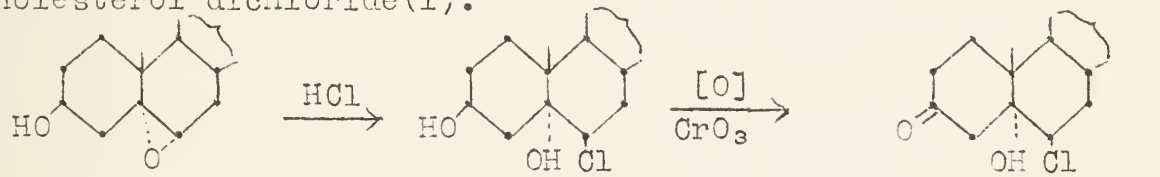

VII

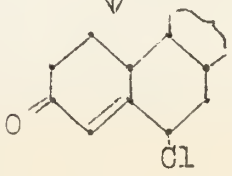
Since destruction of asymmetry at $C_5$ leads to different ketones, the $C_5$ configuration must be the same in both isomers(I).

In the cholestane series 6α hydroxy and acetoxy compounds are more dextrorotary than the corresponding 6β compounds, and the same applies to derivatives of $\Delta^4$-cholestenes(7). The optical activity of halides is often comparable with that of the corresponding alcohol(8), and thus a pair of stereoisomeric halides usually preserve the same sign for differences in molecular rotation as the pair of alcohols of corresponding configuration. The 6-chloro-$\Delta^4$-cholest-3-one from the cis dichloride is much more dextrorotary than the one from the trans dichloride. Therefore the cis dichloride has the 5α,6α configuration(II) and the trans the 5α,6β configuration(I)(1).

| SUBSTANCE | $[M]_D$ | | $\Delta$ |
|---|---|---|---|
| | 6β | 6α | $[M]_D$6α-$[M]_D$6β |
| cholestan-3β-6-diol | +57 | +154 | +97 |
| $\Delta^4$-cholesten-3β-6-diol | +32 | +117 | +85 |
| 6-chloro-$\Delta^4$-cholesten-3-one | +65 | +247 | +182 |

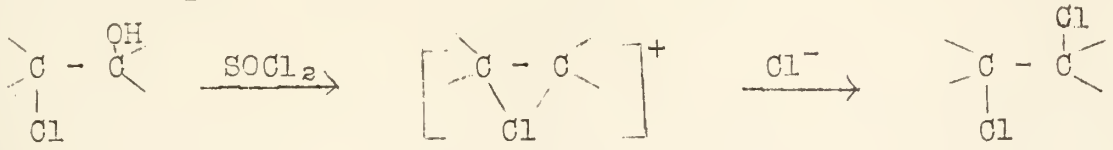
These rotation data were supported by conversion of the known α oxide of cholesterol into 6β-chloro-$\Delta^4$-cholestene-3-one(VIII-IX) which is identical in all respects to that obtained from ordinary cholesterol dichloride(1).



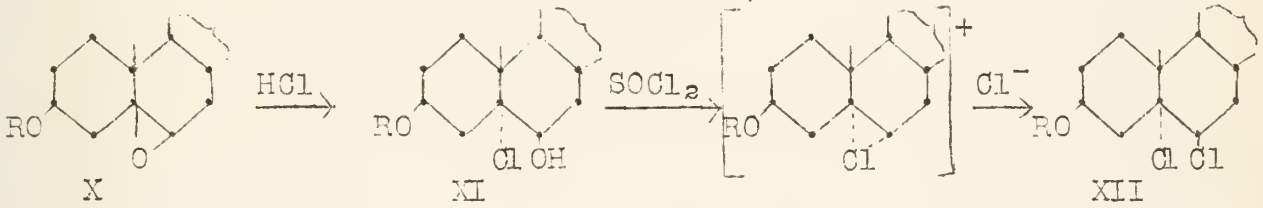

The assumption of the α configuration of the $C_5$ chlorine atom, while not groundless, is perhaps open to some question.

Confirmation of the 5α Configuration.--It has been shown that treatment of a chloro- or bromohydrin with thionyl chloride, hydrogen bromide, etc. produces a dichloro or dibromo compound with complete retention of configuration, i.e. a double inversion takes place through a chloronium or bromonium ion intermediate(9,10).




In the case of an unsymmetrically substituted cyclic chloro- or bromohydrin this could only result in a trans dihalide(4).

Cholesterol benzoate β oxide(X) when treated with HCl gave 5α-chloro-6β-hydroxycholestan-3β-yl benzoate(XI)(11), a compound of known configuration. Treatment of this compound with thionyl chloride gave, via the chloronium ion, a cholesteryl benzoate dichloride(XII) which is identical with that prepared by direct chlorination of cholesterol benzoate(4).




This proves that the configuration of the $C_5$ chlorine is α. Thus, cholesterol dichloride prepared by direct chlorination of cholesterol, or its esters, has the 5α,6β configuration of the chlorine atoms(I). The dichloride prepared by the anhydrous reaction of cholesterol, or its esters, with iodobenzene dichloride must have the 5α,6α configuration of the chlorine atoms(II).

Similar considerations show that direct bromination of cholesterol yields the 5α,6β dibromo compound, although this compound is unstable towards the 5β,6β isomer and mutarotates to it in solution at room temperature(6).

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ORGANIC SEMINAR ABSTRACTS

II SEMESTER 1951-52

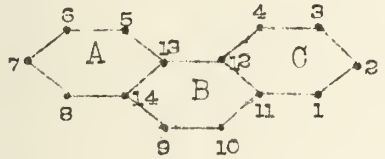
SEMINAR TOPICS

CHEMISTRY 435 II SEMESTER 1951-52

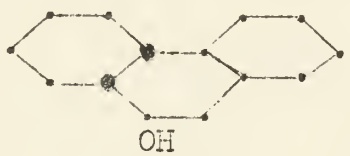
# THE STEREOCHEMISTRY OF CATALYTIC HYDROGENATION

Reported by Paul R. Shafer February 8, 1952

A stereochemical study has been made[1-10] of the products of the catalytic hydrogenation of diphenic acid, ester and anhydride, cis and trans-hexahydrodiphenic acid, 9-phenanthrol, cis- and trans-as-octahydro-9-phenanthrol, cis- and trans-as-9-keto-octahydrophenanthrene, and 9,10-phenanthraquinone over platinum at room temperature and a pressure of three to four atmospheres. Acetic acid was the solvent except for the last three compounds which suffered considerable hydrogenolysis of the C-C bond in this solvent. Ethanol was used for these compounds as well as a few of the others. Where comparison could be made, a slower rate and lower yield were observed with ethanol. The major product in each case, regardless of solvent, resulted from the cis- and syn-addition of hydrogen.



I



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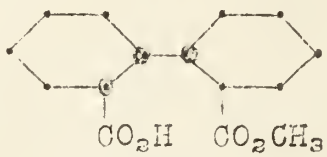


III

Nomenclature: The perhydrophenanthrene nucleus (I) has four asymmetric centers, C-11,12,13,14. The ring fusions A/B and B/C are designated cis or trans according to whether the C-13,14 (C-11, 12) hydrogens are on the same or opposite side of the ring. The configuration of the backbone (C-12,13 bond) is syn when the C-12, 13 hydrogens are on the same and anti when they are on the opposite sides of the molecule. A black dot (always placed on C-13) indicates that the hydrogen is above the plane of the molecule. In naming a perhyrophenanthrene one begins with the bridgehead nearest the substituent (II is cis-anti-cis), while half-esters of perhydrodiphenic acid begin with the ring bearing the ester group (III is trans-syn-cis) and are always drawn in the "pseudo-tricyclic" or coiled state.

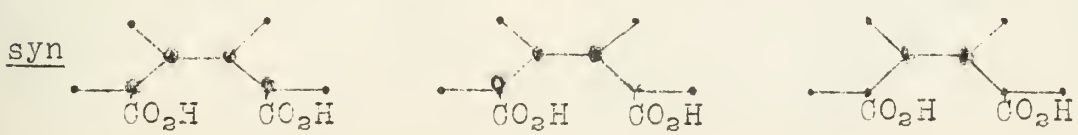
Hydrogenation of Diphenic Acid: There are six theoretically possible perhydrodiphenic acids which comprise two groups of three members each, based on a common syn or anti backbone. The terminal members of the syn-series have a meso or symmetrical configuration while all of the remaining acids are racemic. Perhydrogenation of diphenic acid afforded three of the isomers, cis-syn-cis (I, chart 2.) (about 75% of total perhydroacids), cis-syn-trans (II)(10%), and cis-anti-cis (IV) (15%), together with variable amounts of cis-hexahydrodiphenic acid and recovered diphenic acid. The following interconversions afforded the remaining isomers, distinguished between the groups, and specifically assigned the configuration of each acid. The demonstrated configurations are anticipated for clarity.

(a) Backbone: The cis-syn-cis acid (I) was converted to the trans-syn-trans acid (III) by treating the dimethyl ester with sodium methoxide followed by mild acid hydrolysis. The half-methyl

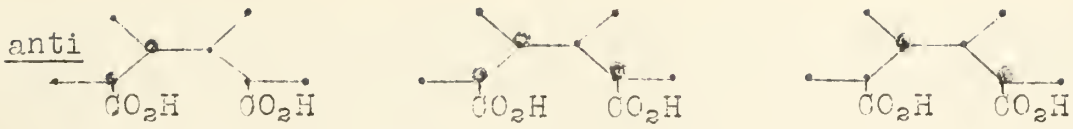
ester of I with sodium methoxide gave the trans-syn-cis half ester of II, which upon esterification and partial saponification gave the other, or cis-syn-trans, half ester of II. The latter with sodium methoxide gave the trans-syn-trans acid (III) after hydrolysis. Acids I, II, and III were stable to dilute acid, aqueous and alcoholic alkali, and alcoholic sodium methoxide, hence the conversions involved only the ester groups on C-11 and/or C-14, II must be intermediate in configuration between I and III, and all have a common backbone configuration. The acid I could not be resolved by the usual means, hence it was converted to the half-ester and resolved. Hydrolysis of one enantiomorph with dilute acid gave the inactive acid (I) while esterification with diazomethane gave the inactive diester of I. It was therefore concluded, according to the principle of Stoermer and Steinbeck[11], that I (and hence III derived from it by a double inversion) was meso, thus identifying the syn-series. The separate enantiomorphs derived from the half-ester of I were inverted with sodium methoxide. Saponification gave the respective active isomers of II and a mixture of these enantiomorphs was identical in all respects with racemic II, thus confirming that I and III were indeed terminal members of the syn-series. An entirely analogous series of conversions established the configurations forthe anti series. In this case, all members could be resolved. Double inversion of one enantiomorph of the dimethyl ester of IV gave optically pure VI (as the diester). This established that the backbone carbons were not involved in any of the inversions, otherwise racemization should have occurred. It was not found possible to interconvert between the series.

(b) Terminal Acids: The hexahydrodiphenic acid obtained (together with other perhydracids) from the partial hydrogenation of diphenic acid gave the know cis-hexahydrophthalic acid when ozonized and hence has a cis-configuration. Thermal isomerization afforded the trans-isomer which was degraded to trans-hexahydrophthalic acid. Hydrogenation of the cis-isomer gave the knownacid I hence, since the hydrogenation proceeds with retention of established configuration, I must be the cis-syn-cis acid because the backbone was shown to be syn (a meso acid) and this symmetry requires both carboxyls to have the same configuration. Hydrogenation of the trans-isomer gave the expected cis-syn-trans acid II.

The oxidation of a 9-ketoperhydrophenanthrene (XIV), stable to heat and alkali and therefore possessing a trans-configuration adjacent to the keto-group, yielded the acid VI. Now, VI was shown to be a terminal member of the anti-series (prepared by a double inversion of IV and a single inversion of a half ester of V), thus it must have a trans-anti-trans configuration. This fixed the configuration of the IV and V acids.

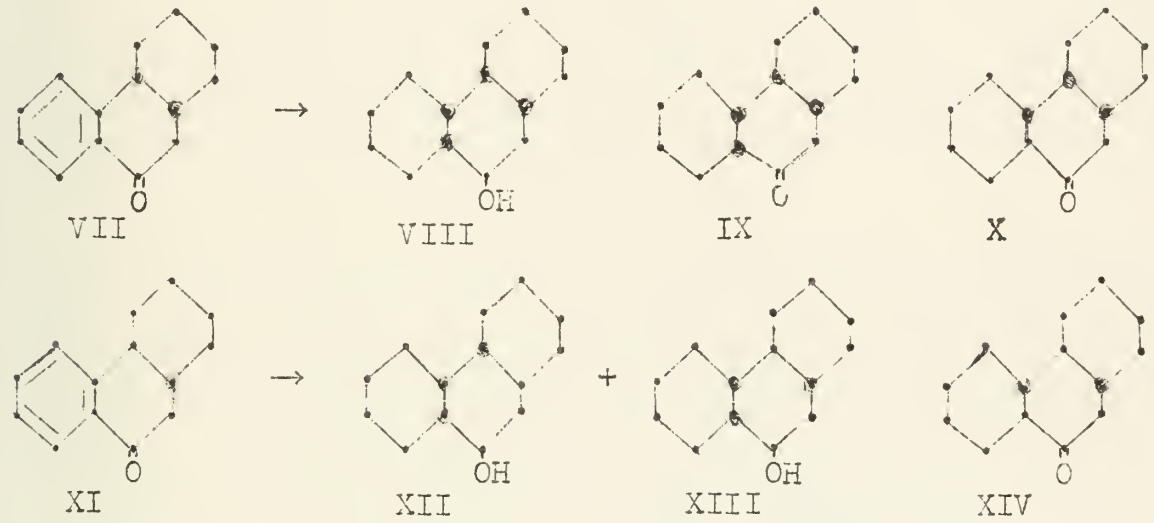



I c-s-c meso II c-s-t rac. III t-s-t meso




IV c-a-c rac. V c-a-t rac. VI t-a-t rac.

Hydrogenation of the Phenanthrene Nucleus: (a) 9-Phenanthrol.- Catalytic hydrogenation over platinum in acetic acid yielded cis-syn-cis-perhydro-9-phenanthrol (VIII) (one epimer, unknown config.) together with a small amount of sym-octahydro-9-phenanthrol and a hydrocarbon fraction. Oxidation of VIII with nitric acid gave only the cis-syn-cis acid (I). Oxidation with chromic acid-acetic acid at room temperature gave the cis-syn-cis ketone (IX) while oxidation at 100° gave the trans-syn-cis ketone (X). Nitric acid oxidation of IX and X gave the cis-syn-cis acid I and cis-syn-trans acid II respectively. Heat or alkali converted IX to X. Catalytic hydrogenation of the ketones produced only one of the two possible epimers in each case. The configuration of the OH-group was not determined.




VII VIII IX X

XI XII XIII XIV

(b) cis- and trans-as-9-Keto-octahydrophenanthrene, (VII,XI).-- Reduction of the cis-ketone in alcohol gave two epimeric cis-as-octahydro-9-phenanthrols and the same epimer of VIII obtained above. Reduction of one of the epimeric octahydro alcohols likewise gave only the cis-syn-cis-perhydro-9-phenanthrol (VIII).

Reduction of the trans-ketone (XI) and of the two epimeric alcohols derived from it by partial hydrogenation gave a mixture of the cis-syn-trans- (XII) (60%) and cis-anti-trans-perhydro-9-phenanthrol (XIII) (40%), a single epimer of each being obtained. Oxidation of the alcohol XII gave the corresponding ketone which could not be inverted to the trans-syn-trans-ketone by heat or alkali. Dehydration of XII followed by ozonization gave acid II which established the configuration. Oxidation of XIII gave the

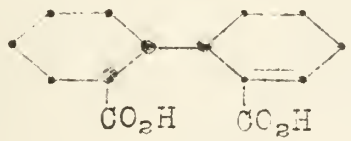
corresponding ketone which could be isomerized to the trans-anti-trans-ketone (XIV), identified by oxidation to acid (VI). This established the configuration of both the alcohol (XIII), the ketone derived from it and the inverted ketone (XIV).

(c) 9,10-Phenanthraquinone: Reduction in alcohol over platinum gave a single epimer (of four possible) of cis-syn-cis-perhydro-9,-10-phenanthrene-diol. Reduction over nickel gave two additional epimers with the cis-syn-cis nucleus (neither identical with the platinum reduction product) together with a small amount of one epimer of the cis-syn-trans-diol. All were identified by oxidation to the respective acids.

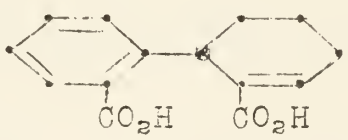
Discussion of Results: In each of the above cases the major product resulted from the cis and syn addition of hydrogen. The regularity of these results together with the previously reported cis-hydrogenation of certain derivatives of benzene, naphthalene, and hydrindene (see ref. 1 for specific examples, proof of config. and original references) suggested that for the specified conditions: (1) when one or more aromatic rings are hydrogenated during a single period of adsorption, the hydrogen atoms add to one side of the molecule, (2) the orientation of the adsorption of the aromatic molecule on the catalyst is affected by hindrance between the catalyst and substrate and, (3) the open chain derivatives of diphenic acid are hydrogenated in the "pseudo-tricyclic" or coiled state (the latter because the same products are obtained from diphenic acid as from diphenic anhydride.

It seems well accepted at present[12] that hydrogenation occurs on the surface of the catalyst, is dependent to a large extent upon the geometry of the surface, and that the catalyst probably functions as a third component of a transition state or activated complex involving the acceptor molecule and the hydrogen (atomic or molecular). Beyond this there is no general agreement as to the detailed mechanism of the process. How in all but one of the above products, the thermodynamically unstable isomer was formed (i.e., all later inversions proceeded exclusively cis → trans) which is a strong argument for cis addition of hydrogen rather than an isomerization reaction of the hydrogenated product on the surface of the catalyst. Further, the formation of predominantely syn products from the cis-octahydrophenanthrenes is consistant with the idea that the perhydro rings will be bent out from the catalyst surface to allow maximum adsorption of the benzenoid ring (e.g. minimum interference of the acceptor molecule with the catalyst surface) which could then give only the syn product. In the case of the trans-octahydrophenanthrene derivatives, however, the acceptor molecule is essentially planar, thus either side can approach the catalyst surface. The products, 60% syn and 40% trans support this view. The question arises, however, why there should be any trans hydrogenation product at all. Linstead suggests that an alternative mechanism may be operating at the surface of the catalyst, based on the assumption that once reduction of the aromatic nucleus has started it goes to completion, at least with respect to

a benzenoid unit. If, however, the partially hydrogenated acceptor is desorbed at an intermediate stage, with a double bond adjacent to one but not both of the ring substituents that define the configuration, then the final configuration will be determined by which side of the molecule approaches the catalyst during succeeding stages of adsorption. In general this would be determined by the geometry of the remainder of the molecule, thus (XV) should give only cis-syn-cis due to the configuration of ring A, while (XVI) may give either cis or trans since it is planar.




XV




XVI

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# THE MECHANISM OF DECOMPOSITION OF NITROSO ACYL ARYL AND NITROSO ACYL ALKYL AMINES

Reported by J. S. Showell February 8, 1952

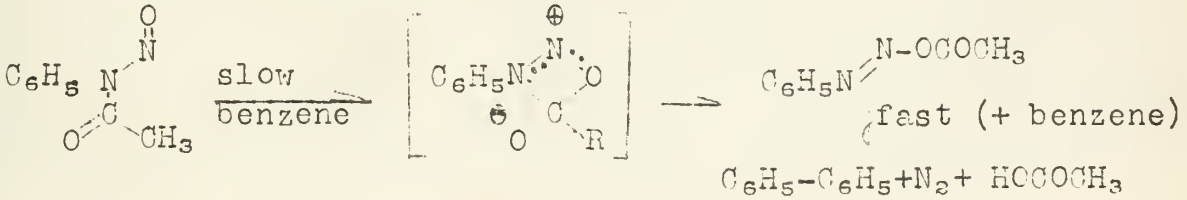
The decomposition of nitrosoacylaryl amines in an organic solvent has long been used as a method for the preparation of unsymmetrically substituted biphenyls. This has been extensively reviewed by Bachmann and Hoffman.[1] The mechanism of the decomposition of nitrosoacylaryl amines, diazonium and diazo compounds has been studied by Waters, Hey and others. The evidence for this work has been summarized by Waters[2] and can be grouped into two classes: 1) orientation and fragmentation and 2) metal effects. On the basis of this, the decomposition of nitrosoacylaryl amines was considered to be a free radical process:

$$\text{Ar-N(NO)COR} \underset{}{\overset{\text{fast}}{\rightleftharpoons}} \text{Ar-N=N-OCOR} \xrightarrow[\text{rate determining}]{\text{slow}} \text{Ar}\cdot + N_2 + \cdot\text{OCOR}$$

$$\text{Ar}\cdot + \text{RH}' \longrightarrow \text{Ar-R}' + \text{H}\cdot$$

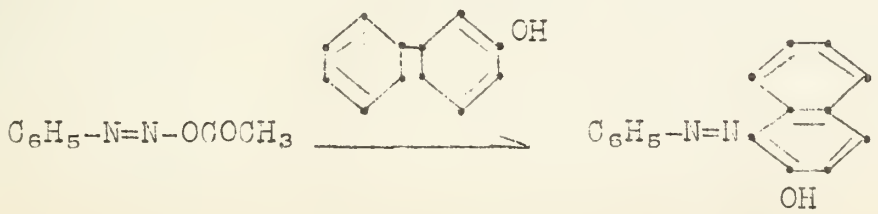
$$\text{RCO}_2\cdot + \text{H}\cdot \longrightarrow \text{RCO}_2\text{H}$$

The reaction mechanism and the experimental evidence supporting it was critically reviewed by R. Huisgen and coworkers[3-10] and in an extensive and elegant series of papers the mechanism was reinterpreted. The earlier workers postulated that the rate determining step was the decomposition of the diazo ester but Huisgen demonstrated that the isomerization was the rate determining step and that it followed strict first order kinetics; further he showed that the rate of isomerization was independent of the solvent and that the decomposition of the resulting diazo ester was an extremely rapid reaction. The unimolecularity and the independence of solvent indicated that the rate controlling process was an intramolecular one and not a reacylation; he postulated the following cyclic mechanism (consider N-nitroso acetyl aniline as a typical example):



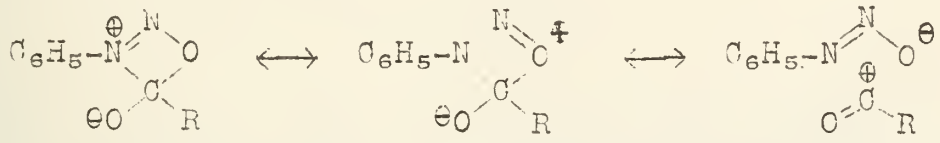

$$C_6H_5\text{-}C_6H_5 + N_2 + HCOOCH_3$$

The rate of the reaction was followed spectrophotometrically using an azo coupling reaction to form the azo dye--this was shown to be extremely rapid and not rate determining (independent of coupling compound)

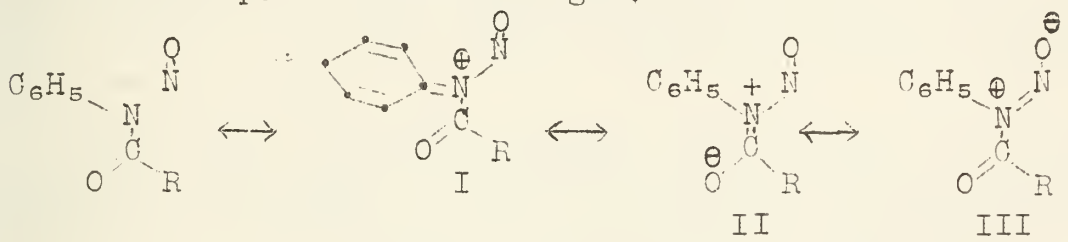


Substituents introduced into the m- and p- positions of the benzene ring only slightly influenced the rate of rearrangement (independent of the electrical nature of the substituent - Cl, Br, $NO_2$, $CH_3$) but when an o-substituent was introduced the rate became 1/6 the "normal" value. This was indicative of a spacial effect. Replacement of the aromatic group by an alkyl group caused a marked drop in the rate constant.

The cyclic transition state, although a strained four membered ring, is made energetically feasible by contribution of the following resonance forms:



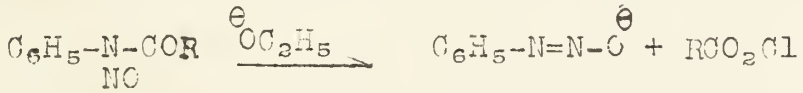
The ground state, from which the transition state is formed, is considered to be planar due to the resonance interaction of the aromatic system ($C_6H_5$), acyl (RCO-) and nitroso (-NO) groups with the electron pair of the nitrogen:



I II III

The existance of a planar ground state is strongly supported by dipole measurements.

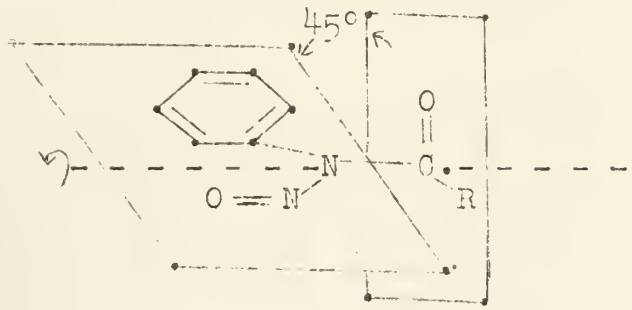
The influence of the acyl group in nitrosophenyl acyl amine upon the rate of rearrangement was determined by systematic variation. It was found that the rate increased in the series $HCO < CH_3CO < CH_3CH_2CO$ n $CH_3CH_2CH_2CO < (CH_3)_2CHCO$ which is just in the reverse order for the rate of the bimolecular alkaline hydrolysis. The inverse order strongly supports the cyclic mechanism. Further studies on the bimolecular base catalyzed cleavage of the nitrosophenyl acyl amines showed that the order of cleavage corresponded to the normal series (bimolecular) observed with esters:



The behavior of the acyl group can be understood if the process of forming the cyclic intermediate is broken into three steps and it is remembered that attack on a carbonyl group is perpendicular to its plane:

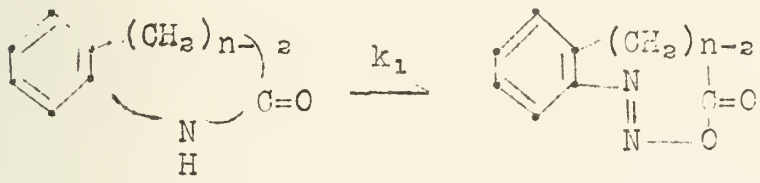
1) Turning of acyl group out of the plane to facilitate basic attack.
2) Rotation of -NO group around N-N single bond so that the oxygen can add to the carbonyl group.

3) Addition of the oxygen atom to the carbonyl group with closing of the ring.

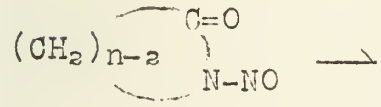


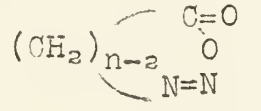

The influence of the R in the acyl group depends on steps #1 and #3. With increasing size of R, resonance form II will contribute less to the ground state so that rotation of the -COR group out of the plane will be energetically easier (smaller double bond character of +C-N bond)--the reversed series of migratory aptitude is thus understandable. Further the greater stability of nitroso alkyl acyl amines can be understood by presence of only two resonance forms (only II, III are present) since the aromatic resonance (I) is no longer present.

The cyclic mechanism requires that the diazo ester which is formed have the trans configuration and from this it follows that the rate of formation of cyclic diazo esters (from nitroso lactams) should be strongly dependent on the size of the ring:




| n | k, x10$^6$ sec$^{-1}$ |
|---|---|
| 5 | 0 |
| 7 | 90.3 |
| 8 | 14,200 |




| n | |
|---|---|
| 5 | 0 |
| 6 | .07 |
| 7 | 154 |
| 8 | 2420 |
| 9 | 5750 |
| 10 | 44.3 |
| 11 | 15.3 |

The work considered conclusively supports the intramolecular migration of the acyl group thru a strained four membered ring. The ultimate fate of unstable trans diazo ester depends upon the nature of the solvent and other molecules present. In this same series of papers, the kinetics and paths of decomposition of the diazo ester were exhaustively treated.

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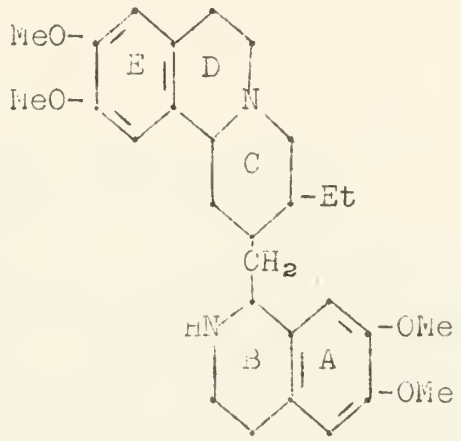
# RECENT STUDIES ON EMETINE

Reported by B. L. vanDuuren February 15, 1952

Emetine, together with closely related bases such as psychotrine, O-methylpsychotrine, iso-emetine and emetamine, occurs in Psychotria ipecacuanha root. It has been used clinically for several centuries in cases of amoebic dysentery and is a powerful emetic. The pure alkaloid (free from related bases) was obtained only towards the end of the nineteenth century.

On the basis of degradation experiments, Späth and Pailer[1,2] suggested two possible structures for emetine. Robinson,[3] on biogenetic grounds, supported one of these structures. This structure, I, was proved to be correct by subsequent work of Pailer and coworkers[4] in Austria and Openshaw and coworkers[5,6] in Great Britain.



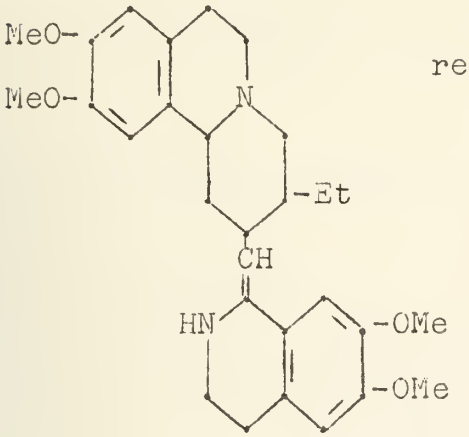

I

Emetine was synthesized recently by a group of Russian workers.[7] Their synthetic emetine gave the reactions characteristic of the natural product and when heated with iodine in ethanol yielded rubremetine iodide, identical with the product from natural emetine.

Although the structure of emetine has been proved beyond doubt the structures of some of its derivatives have not yet been elucidated. These products are discussed in an excellent review on the chemistry of emetine and related bases.[8] Subsequent to the publication of this review article a number of papers have appeared which seem to throw more light on certain aspects of the problem.

Stereochemistry.--Emetine has four dissimilar asymmetric carbon atoms and one can therefore expect 15 other optical isomers. Only one of these is known, viz. iso-emetine.[9,10] The relationship between emetine and iso-emetine was proved as follows: O-methylpsychotrine, II, when converted to the N-benzoyl derivative and oxidized (with either perphthalic acid or ozone)[11] gave N-benzoylcorydaldine, III, the structure of which was recently

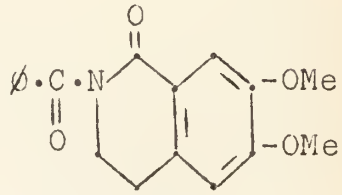
proved by synthesis.[12] This indicated a double bond at the $C_{13}$-$C_1'$ position in O-methylpsychotrine. When O-methylpsychotrine is reduced both emetine and iso-emetine are obtained.[9,11]




II

reduction → emetine and iso-emetine (I)

oxidation of N-benzoyl derivative →




III

From these experiments it followed that emetine and iso-emetine differ in the configuration at $C_1'$.

Hazlett and McEwen[13] recently announced the isolation of two new diastereoisomers of emetine. These compounds were prepared by the procedure used by Battersby and Openshaw[14] for the dehydrogenation of emetine. Dehydrogenation with four moles of mercuric acetate gave tetradehydroemetine. The ultraviolet spectrum of this product suggested that the two new double bonds introduced were in conjugation with each other and with a benzene ring. The substance absorbed two moles of hydrogen during a microhydrogenation. Hazlett and McEwen concluded that since any two double bonds meeting these requirements would remove at least two and possibly three of the asymmetric centers in emetine, it should be possible to isolate other diastereoisomers from the hydrogenation reaction product. Experiments carried out by them proved this to be the case. Besides emetine and iso-emetine, two new diastereoisomers were obtained. Infrared curves indicated as much correspondence as could be expected for diastereoisomers.

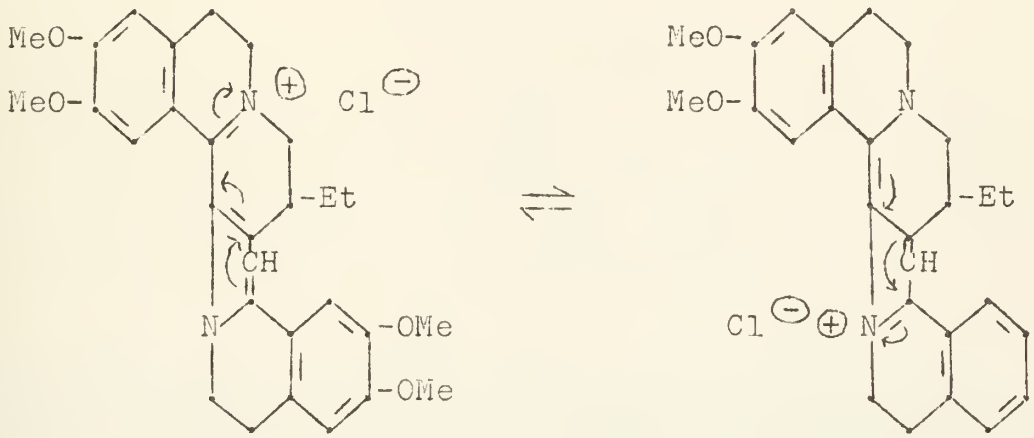
By varying the procedure for working up the dehydrogenation product of emetine, Hazlett and McEwen isolated a second product, isotetradehydroemetine, which on reduction gave emetine as the only product. The ultraviolet curves indicated little difference between the unsaturated systems of the two isomers. The exact nature of these two products remain to be proved.

Rubremetine.--Both tetradehydroemetine and iso-tetradehydroemetine can be dehydrogenated further with mercuric acetate.[6,13,14,15] The product, rubremetine, is usually isolated as the salt. Rubremetinium salts are also obtained by the action of mild oxidizing agents such as ferric chloride, bromine or iodine, on emetine, iso-emetine or O-methylpsychotrine.[16]

In the formation of rubremetinium salts from emetine hydrochloride, eight hydrogen atoms are eliminated, one nitrogen atom becomes quaternary and the other loses its basic character. N-methylemetine does not give rubremetinium salts on oxidation.

When emetine is oxidized with less than the theoretical amount of oxidizing agent, O-methylpsychotrine is obtained[10] so that it is assumed that this compound is an intermediate in the reaction.

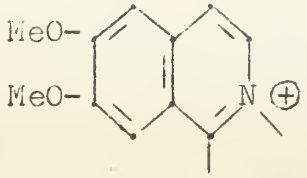
Battersby, Openshaw and Wood[6] suggested structure IV for rubremetinium salts.




IV

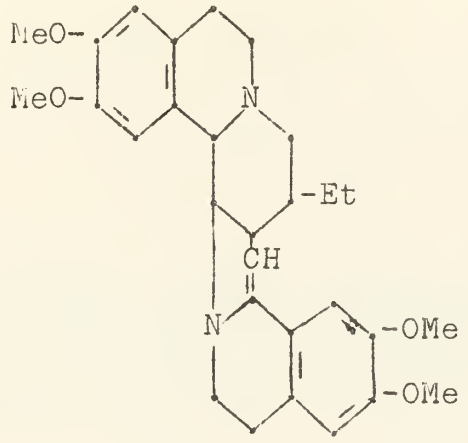
According to these workers rubremetinium salts are resonance hybrids in which the positive charge can oscillate between the two nitrogen atoms. This structure will account for the following: (a) The brilliant orange-red color of the salts; (b) The quaternary nature of one nitrogen atom and the lack of basicity of the other; (c) The non-identity of rubremetinium chloride and the similar dehydrogenation product of emetamine (in which ring B is also aromatic); (d) The reduction of rubremetine yielded a product which gives pyrrole color reactions.

Karrer[17] soon raised objections to this structure on the basis that it "represents an illogical terminal product of a dehydrogenation reaction". He reported that rubremetinium chloride could be reduced with lithium aluminum hydride to a dihydro derivative and that this product catalytically adds hydrogen to give a mixture of two isomeric tetrahydro derivatives, tetrahydrodehydroemetine and iso-tetrahydrodehydroemetine. Karrer accordingly suggested the partial formula, V, for rubremetinium salts.




V

Recent work by Openshaw and coworkers[18] provided further support for structure IV. They found that rubremetinium salts on reduction absorb one mole of hydrogen to give two diastereoisomeric forms of dihydrorubremetine. These products form mono-methiodides only and give pyrrole color reactions. Structure VI was proposed for dihydrorubremetine. One of these products had the same melting point and rotation as one of Karrer's tetrahydrodehydroemetine diastereoisomers.




VI

The validity of structure IV was questioned also by Hazlett and McEwen loc. cit. They reported that when rubremetinium chloride is heated with aqueous-alcoholic alkali an unstable product is obtained. The rubremetinium chloride lost hydrochloric acid during the reaction. The crude dehydrohalorubremetine readily added two moles of hydrogen to give a mixture of two products, probably diastereoisomers. A pure crystalline compound, tetrahydrodehydrohalorubremetine was obtained from the mixture. This substance was racemic and its ultraviolet spectrum was similar to that of Karrer's l-iso-tetrahydrodehydroemetine.

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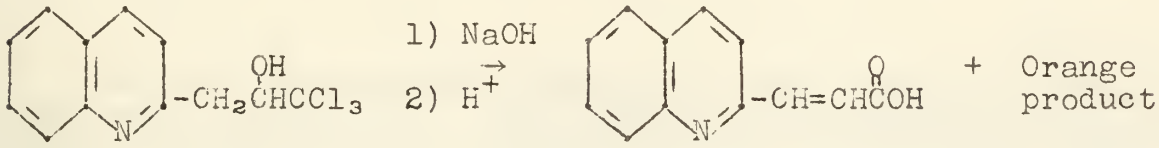
# THE ACTION OF ALKALI ON CHLORAL-QUINALDINE

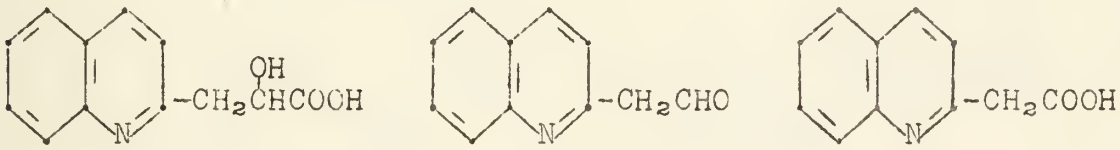
Reported by Irwin J. Pachter February 15, 1952

"Chloral-quinaldine" (I) reacts with alcoholic sodium hydroxide to give two products, 2-quinolineacrylic acid (II) and an orange compound, $C_{12}H_{11}NO_3$ (III).[1]



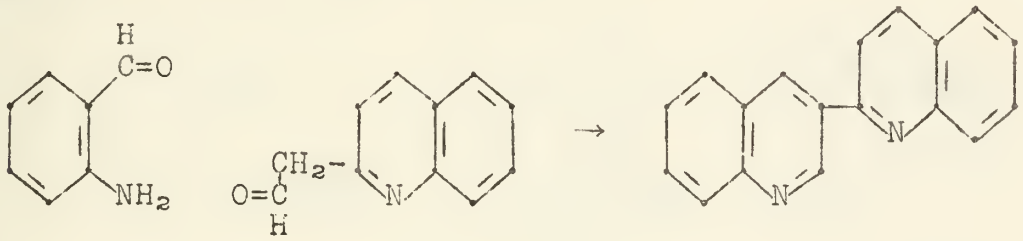

I II III

Einhorn[1] proposed the formula IIIa for the orange compound and reported that oxidation yielded a compound IV, $C_{11}H_9NO$, for which the formula IVa was proposed. Compound IV gave a carbonyl derivative with phenylhydrazine. On vigorous oxidation, IV yielded an acid (V) reported to be Va.[2]

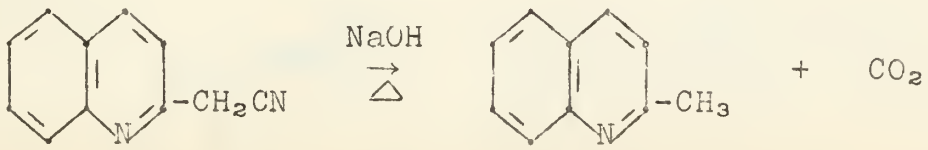



IIIa IVa Va

Treatment of IV with o-aminobenzaldehyde yielded 2,3'-diquinolyl, a compound of known structure. Einhorn and Sherman[2] pictured the reaction as follows.

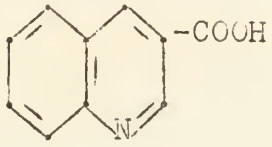



The structure of III thus appeared to be proved (although no theory was advanced to explain the orange color) and the problem received no attention for forty years. Then Borsche and Manteuffel[3] hydrolyzed 2-quinolineacetnitrile (VI) and obtained quinaldine rather than Va.




VI

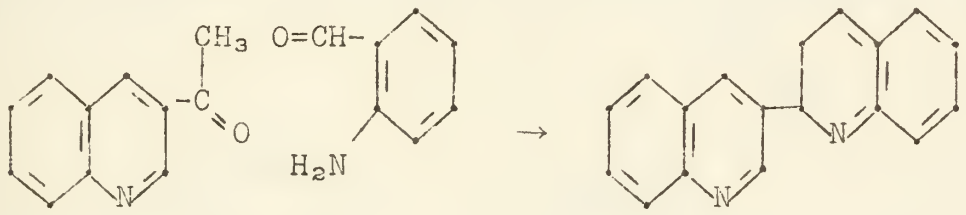
Borsche and Manteuffel repeated the work of Einhorn and Sherman and found that V actually was 3-quinolinecarboxylic acid rather than Va.



V

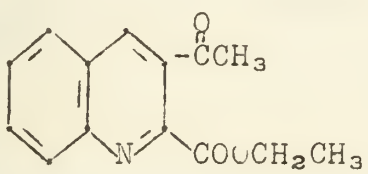
Borsche and Manteuffel proposed a mechanism to explain the conversion of IVa to V. They observed that compound IV gave carbonyl derivatives but no aldehyde tests. They offered reasons to explain why IV was an "unusual" aldehyde.

Woodward and Kornfeld[4] realized that IV was not an aldehyde but was actually a ketone which on vigorous oxidation would give V and which, interestingly, would also yield 2,3'-diquinolyl on treatment with o-aminobenzaldehyde.

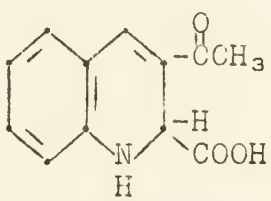


IV

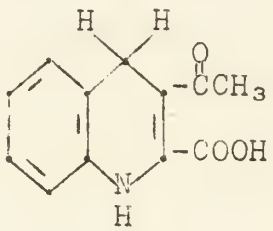
Esterification and oxidation of III yielded the known compound VI. For compound III, two structures, III and IIIb, were possible.



VI

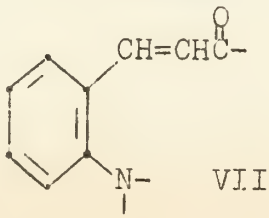


III

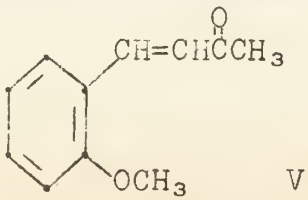


IIIb

It was found that III could be resolved into optically active components, thus eliminating structure IIIb. The orange color of III is due to a grouping of type VII. Compound VIII, for example, is orange.

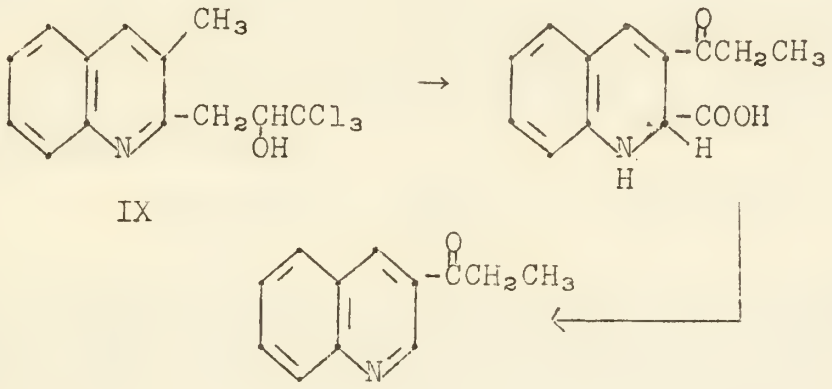


VII



VIII

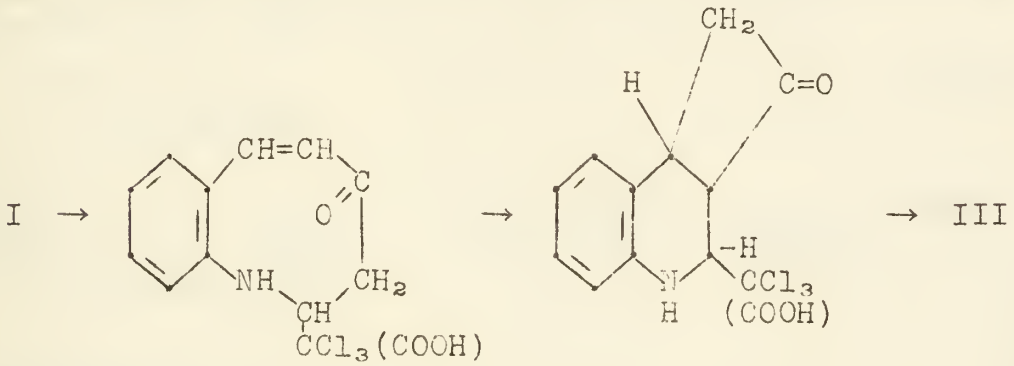
Woodward and Kornfeld proposed a mechanism for the formation of III which was show to be erroneous by Brown, Hammick and Robinson.[5] The latter group found that IX yielded an orange compound upon treatment with alkali which was oxidized to a compound identified as X.



IX

X

The following was offered as a mechanism which is in accord with the facts.



The British workers promised further publications on the subject.

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# NITRILE OXIDES AS SYNTHETIC INTERMEDIATES

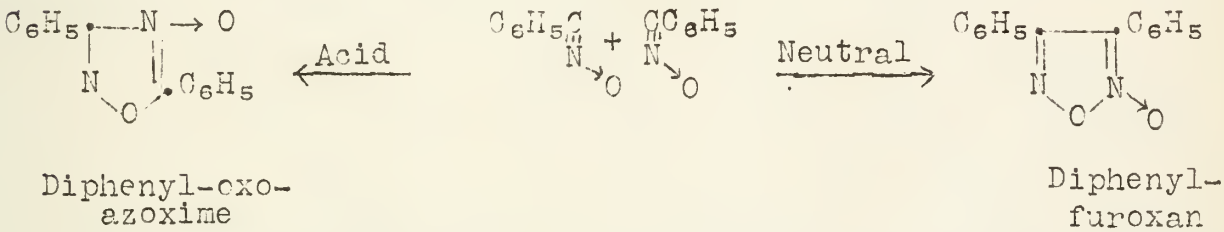
Reported by Louis A. Carpino February 22, 1952

HISTORICAL Only recently, nearly 50 years after their discovery, have the nitrile oxides, RCN → O, become important synthetic intermediates. Their study has been impeded by the impossibility of isolating most of them since they are readily isomerized, polymerized and hydrolyzed. One which is easily isolated is benzonitrile oxide, prepared as shown.[1]

$$C_6H_5\underset{Cl}{C}{=}NOH \xrightarrow{OH^-} C_6H_5C{\equiv}N \rightarrow O$$

For the other members of the group it is necessary to generate the oxide in the reaction mixture by the action of alkali on the appropriate halo-oxime[2] or by decomposition of the corresponding nitrolic acid.[3,4] A special case is the first member of the series, fulminic acid, HONC, which in its tautomeric form, HCN → O, can be considered as the oxide of hydrogen cyanide.[5] In a brief study, Wieland[1] found that the nitrile oxides were reduced quantitatively to nitriles by Zn and HOAc and hydrolyzed by water to carboxylic acids. He also noted the reactions shown below.

$$C_6H_5\underset{NOH}{C}\text{-Me} \xleftarrow{MeMgI} C_6H_5C{\equiv}N \rightarrow O \longrightarrow C_6H_5N{=}C{=}O$$

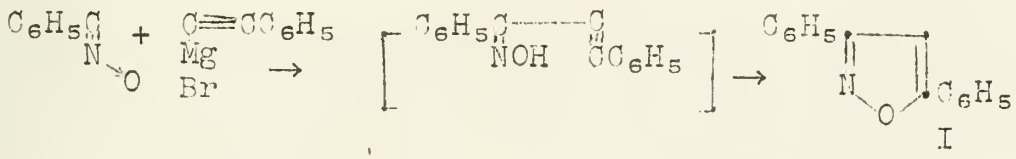


Diphenyl-oxo-azoxime

Diphenyl-furoxan

Under basic conditions the oxide trimerizes in a process which is reminiscent of the change of cyanic to cyanuric acid.

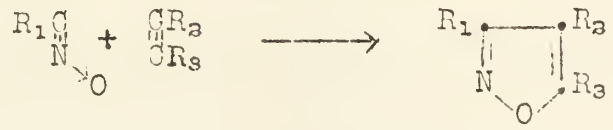
REACTIONS WITH ACETYLENIC GRIGNARD REAGENTS Most of the recently observed transformations of nitrile oxides were discovered in attempts to develop fresh synthetic routes to isoxazoles. Good yields of 3,5-diphenylisoxazole[6] (I) were obtained in the following manner:



I

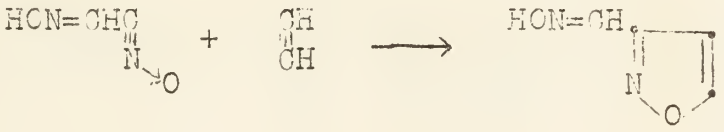
If the chloro-oximes are used the same reaction occurs, one mole of the Grignard reagent being used to convert the oxime to the oxide. For example, isoxazole itself has been prepared from iodoformoxime and HC≡CMgX.

ADDITIONS TO TRIPLE BONDS Generally, acetylenes react with nitrile oxides to give high yields of the corresponding isoxazoles.[3,4,7]

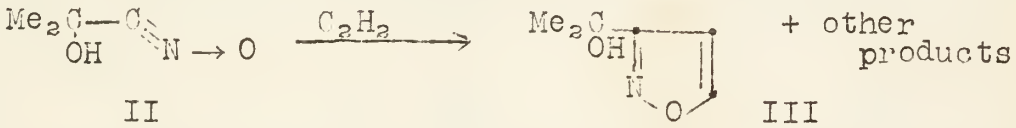


A) $R_1 = Ph$, $R_2 = H$, $R_3 = COOH$
B) $R_1 = Ph$, $R_2 = COOH$, $R_3 = Me$
C) $R_1 = Ph$, $R_2 = COOH$, $R_3 = Ph$

Disubstituted acetylenes (e. g. PhC≡CPh and MeC≡CPh), except where one of the substituents was a carboxyl group, did not react.[8] It can be seen that the nature of the R-groups of the acetylene molecule determines the course of the reaction since two isomers are possible. In all cases a single product is formed, the orientation of which must be determined experimentally. Apparently fulminic acid[8] can react in its dimeric form:

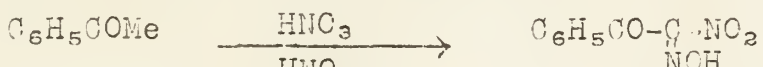


In the presence of acetone,[9] however, acetylene and fulminic acid react to give a 3-isoxazolecarbinol (III). This points to the intermediate formation of an "oxycyanohydrin" (II).

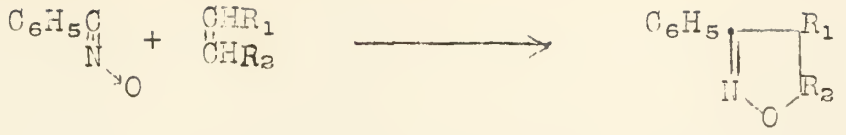


II III

Since methyl ketones could be converted to nitrolic acids by the action of a mixture of nitric and nitrous acid it was thought that acetylene would react with acetophenone in the presence of the acid mixture to give 3-benzoylisoxazole. This was found to be true and the reaction was shown to be general for ketones of the structure RCOMe, where R is alkyl or aryl. After the first step, which is formulated below, the reaction takes the usual course.[4]

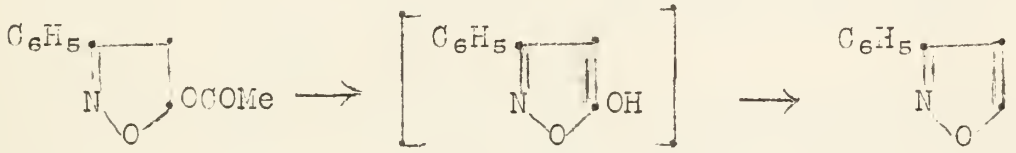


ADDITIONS TO DOUBLE BONDS Like the reactions of aliphatic diazo compounds to give $\Delta^2$-pyrazolines, nitrile oxides yield $\Delta^2$-isoxazolines in the presence of olefins.[10,11,12] This should prove to be quite useful since members of the $\Delta^2$-series have not been extensively studied.

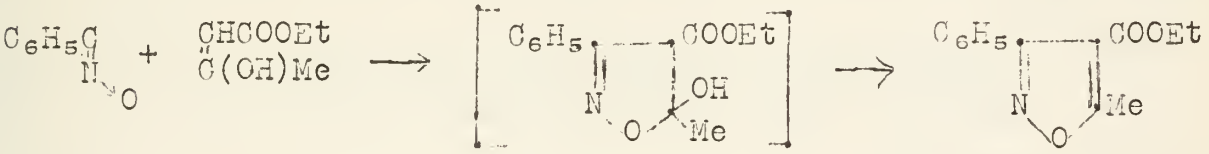


A) $R_1 = H$, $R_2 = CH_2X$, X = Cl, Br, I, or OH
B) $R_1 = H$, $R_2 = CN$
C) $R_1 = H$, $R_2 = Ph$

Particularly interesting is the reaction of vinyl acetate[12] which provides a new general synthesis of isoxazoles since hydrolysis of the isolated acetate is accompanied by the loss of water:

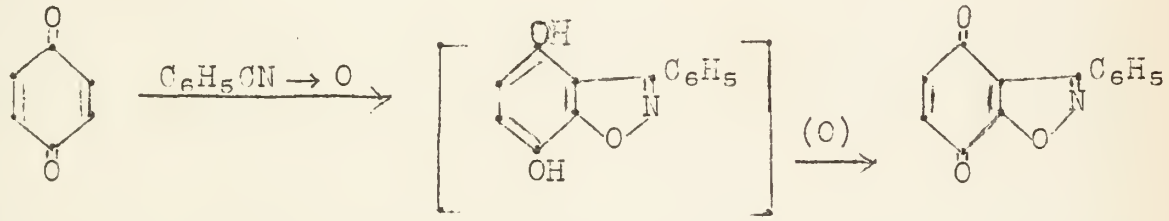


Strictly analogous is the reaction involving a β-keto ester[8] which furnishes still a nother route:

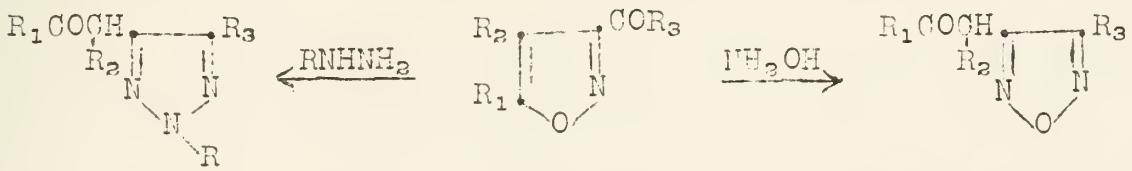


excellent yields

Benzonitrile oxide undergoes smooth reactions with p-benzoquinone and 1,4-napthoquinone giving products analogous to those obtained from the quinones and phenyl azide.[2] The intermediate hydroquinone is oxidized by another molecule of quinone or by molecular oxygen.



Besides being of interest in themselves, properly substituted isoxazoles (containing a 3-acyl substituent) can be readily converted into other heterocyclic compounds. Isoxazoles such as (IV) lead to furazans (V) with hydroxylamine and give triazoles (VI) by the action of primary hydrazines. Such transformations greatly extend the usefulness of nitrile oxides as synthetic intermediates.[3,4]



VI IV V

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# REACTIONS OF ORGANIC COMPOUNDS WITH NITROUS OXIDE

Reported by Harold M. Foster February 22, 1952

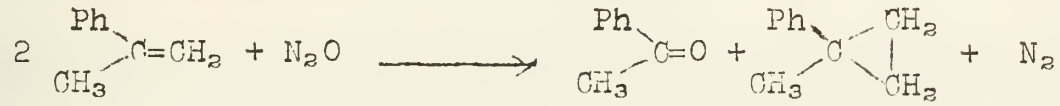
Introduction: Some recent investigations of the reactions of organic compounds with nitrous oxide(1,2,3) have indicated that olefins and acetylenes may be oxidized to ca rbonyl compounds.
The reactions may be placed in four categories:

(I) Oxidation at the double bond to an aldehyde or ketone containing the same number of carbon atoms as the olefin, e.g.,

(II) Oxidative cleavage a t the double bond to give two molecules of carbonyl compounds, e.g.,

$$CH_3CH{=}CHCH_2CH_3 + 2N_2O \longrightarrow CH_3CHO + CH_3CH_2CHO + 2N_2$$

(III) Reaction of two molecules of olefin with one molecule of nitrous oxide to give one molecule of a carbonyl compound and one molecule of a cyclopropane derivative, e.g.,



(IV) Oxidation at the triple bond of an acetylene compound to produce a ketene (dimer), e.g.,

$$RC{\equiv}CH + N_2O \longrightarrow RCH{=}C{=}O + N_2$$

These reactions were carried out at 250-300° and 100-500 atmospheres. Attack was invariably at the double (or triple) bond; in most cases there were no side reactions apart from self-condensation of the carbonyl compounds.

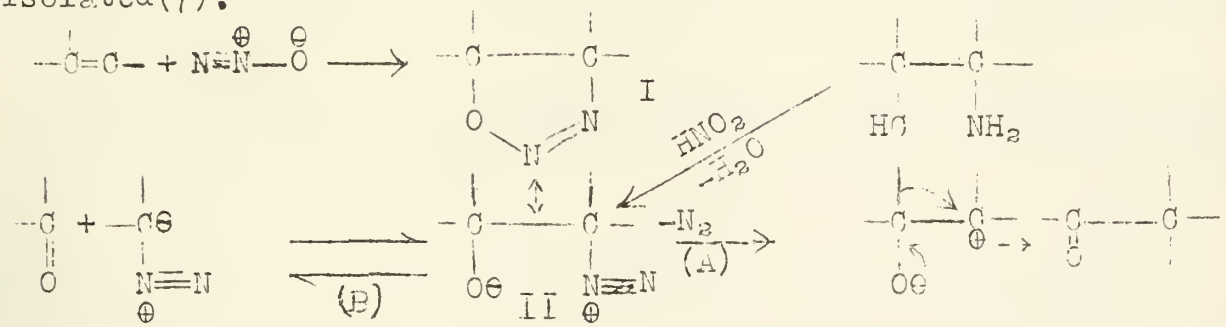
Proposed mechanism for the Reaction: Evidence that the initial step in the reaction between nitrous oxide and the olefin is the addition of the nitrous oxide to the double bond to form a five-membered heterocyclic ring, a 1,2,3-oxadiazoline (I) is quite strong.

That olefin oxides are not intermediates in the reaction was amply demonstrated when cyclohexene oxide was recovered unchanged after treatment with nitrous oxide at 300° and 500 atmospheres for four hours.

Nitrous oxide is closely analogous in structure to diazomethane and phenyl azide (4). Under proper conditions it might be expected that nitrous oxide would add to olefinic double bonds.

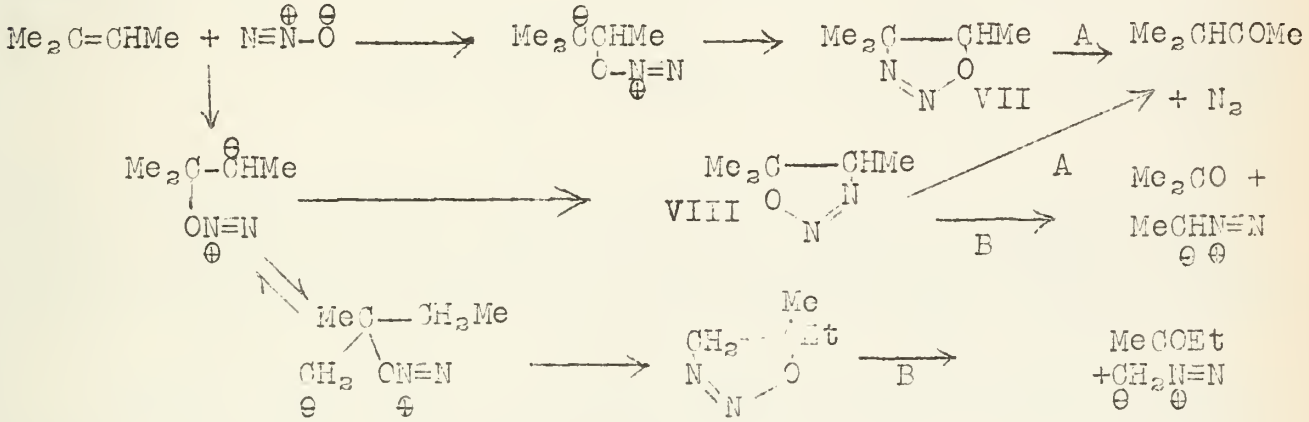
There is strong evidence that the ring system (I), commonly formulated as the diazonium betaine (II), is also formed as an intermediate in the reaction of β-amino alcohols with nitrous acid(5)

and in the reaction of aliphatic diazo compounds with aldehydes and ketones(6). In several instances, the 1,2,3-oxadiazolines were isolated(7).



The 1,2,3-oxidiazolines generally decompose irreversibly, losing nitrogen with the eventual formation of an aldehyde or ketone (A-type decomposition). A second mode of decomposition which has been postulated is the formation of a carbonyl compound and an aliphatic diazo compound(B-type decomposition). The latter reaction is essentially the reversal of a nucleophilic addition to an aldehyde or ketone. The relative importance of these two modes of decomposition will depend largely on the position of the equilibrium in reaction B and on the relative rate of reaction A and of elimination of the diazoparaffin. These factors will depend on the number and the nature of the substituent groups.

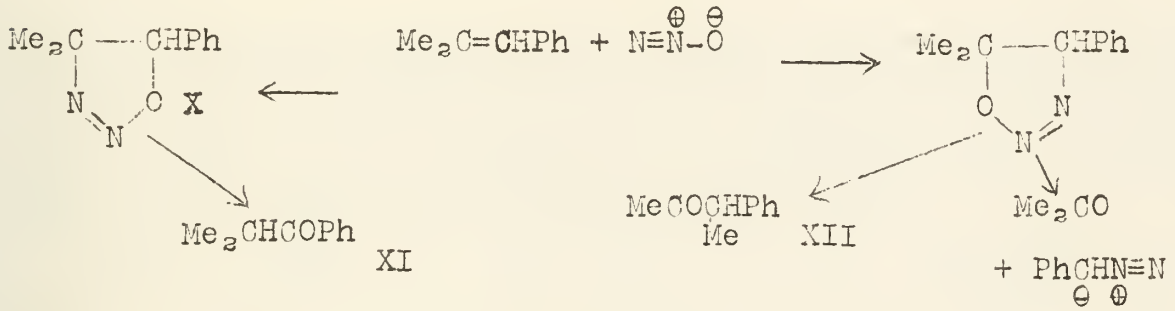
Reactions of Tri- and Tetra-substituted Ethylenes(2): It is evident that olefins of the type CHX=CYZ may react with nitrous oxide to form two isomeric oxadiazolines. In the reaction of a simple case, 2-methyl-2-butene (X=Y=Z), the main product was the expected 3-methyl-2-butanone, the only ketone which can be formed by A-type decomposition of either of the 1,2,3-oxadiazolines, (VII) or (VIII).



Small amounts of acetaldehyde, acetone, 2-butanone, ethylene, 1,1,2-trimethylcyclopropane, and a hydrocarbon, $C_7H_{14}$ (probably the unknown 1,1,2,3-tetramethylcyclopropane) were also formed. Acetone and diazoethane could arise from B-type decomposition of (VIII). The formation of diazoethane is inferred by the appearance of ethylene (from thermal decomposition), acetaldehyde, ($MeCHN_2 + N_2O \longrightarrow MeCHO + N_2$), and 1,1,2,3-tetramethylcyclopropane, ($Me_2C{=}CHMe + MeCHN_2 \longrightarrow MeCHC(Me)_2CHMe + N_2$).

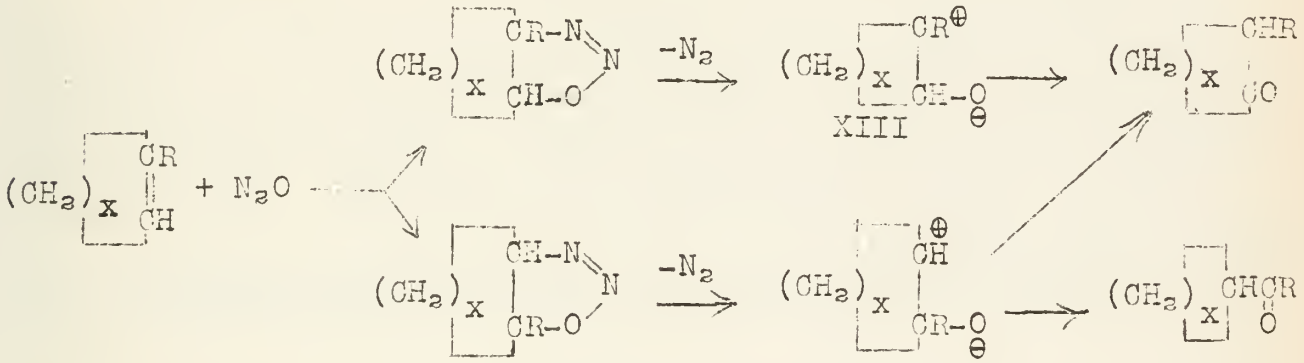
The presence of 2-butanone and 1,1,2-trimethylcyclopropane appears to be explicable by postulating the formation of a small quantity of 5-ethyl-5-methyl-1,2,3-oxadiazoline, (IX), which like all other 5,5-disubstituted 1,2,3-oxadiazolines undergoes only B-type decomposition(1) to give 2-butanone and diazomethane; the diazomethane reacts with the 2-methyl-2-butene to give 1,1,2-trimethylcyclopropane.

The reaction of 2-methyl-1-phenyl-1-propene, (X≠Y=Z), with nitrous oxide resulted in the formation of 3-phenyl-2-butanone (XII) and small amounts of isobutyrophenone (XI), acetone, propanal, and 1,1-dimethyl-2,3-diphenylcyclopropane.



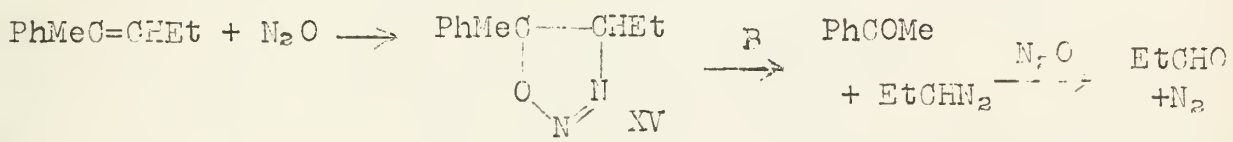
The diazo compound was eliminated by reaction with the olefin.

1-Substituted cycohexenes (X=Y=Z) reacted as shown.



Thus, 1-methylcyclohexene gave approximately equal amounts of 2-methylcyclohexanone and methylcyclopentyl ketone; 1-phenylcyclohexene, 2-phenylcyclohexanone and cyclopentylphenyl ketone. Ring contraction did not occur when 1-methylcyclopentene was treated with nitrous oxide; 2-methylcyclopentanone was the only product.

Nitrous oxide reacted with 2-phenyl-2-pentene (X≠Y≠Z) to give acetophenone, propanal, and a small amount of one or more ketones, $C_{11}H_{14}O$. The main reaction is shown.



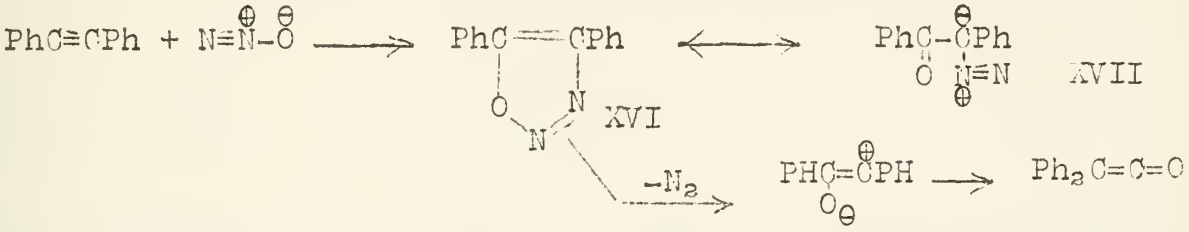
The $C_{11}H_{14}O$ ketone(s) could arise from A-type decomposition of (XV) or of its isomer, 5-ethyl-4-methyl-4-phenyl-1,2,3-oxadiazoline.

Reaction of 2,3-dimethyl-2-butene with nitrous oxide readily gave 3,3-dimethyl-2-butanone; in addition a trace of propanal was found, but no acetone. Tetramethyl-1.2,3-oxadiazoline, therefore,

decomposes almost entirely by the A-type reaction.

Since no formaldehyde was ever found among the products of the reactions, it is evident that substitution in the 5-position of the 1,2,3-oxadiazoline ring is a necessary, although not the sole, requirement for B-type composition. A second alkyl group in the 5-position enhances the probability of B-type decomposition; an alkyl group in the 4-position increases the probabilty of A-type decomposition.

Reactions of Acetylenes(3): By analogy with the interpretation advanced for the reaction of nitrous oxide with olefins, it seems likely that the initial step in the reaction of nitrous oxide with an acetylene is the formation of a 1,2,3-oxadiazole. Diphenylacetylene should yield 4,5-diphenyl-1,2,3-oxadiazole (XVI), a resonance structure of phenylbenzoyldiazomethane (XVII).




Investigations of the decomposition of phenylbenzoyldiazomethane(8) indicated that in boiling benzene diphenylketene was formed; in boiling methanol methyl diphenylacetate was formed. The formation of diphenylketene dimer by reaction of nitrous oxide with diphenylacetylene in inert solvent, and of methyl diphenylacetate in the presence of methanol is consistent with the theory that (XVI) is formed as an intermediate in the reaction.

A similar series of reactions must occur when acetylene itself and monosubstituted acetylenes react with nitrous oxide.

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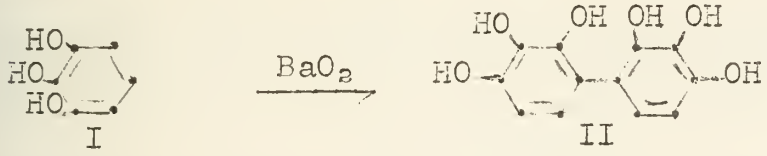
# SOME OXIDATIONS OF PHENOLIC COMPOUNDS

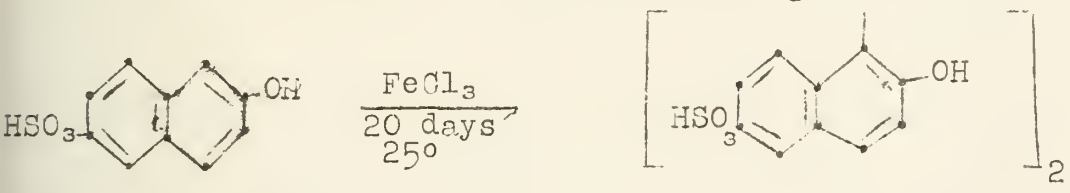
Reported by Edwin C. Steiner February 29, 1952

The oxidation of phenolic compounds is often assumed to be a messy reaction which is only a nuisance. However, under certain conditions the reaction gives well-defined products. These reactions may in general be divided into three groups: 1) those in which simple coupling occurs, 2) those in which further reactions take place after the coupling and 3) those in which simple coupling does not seem to be the first step.

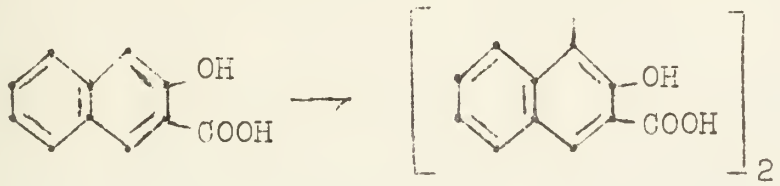
Simple coupling reactions.--These reactions are rather similar and can be explained by a single type of mechanism. Pyrogallol I on treatment with barium peroxide yields hexahydroxybiphenyl II[1].

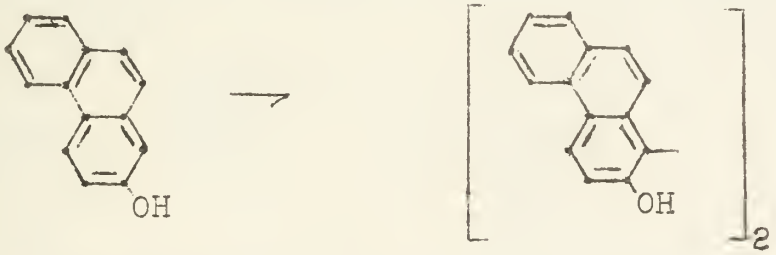


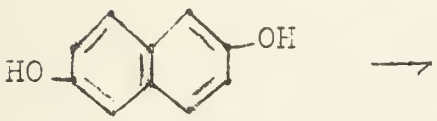

Ferric chloride seems to be a very effective coupling reagent for reactions of this type.[2] Yields of 90% may be obtained under the conditions indicated. It is interesting to note that the reaction




run at elevated temperatures leads to chlorination rather than coupling. Other examples of coupling by ferric chloride may be cited.[2]

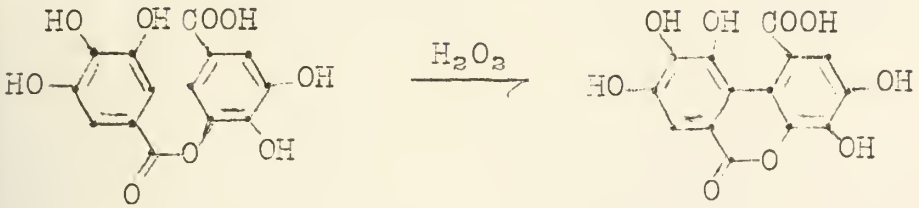


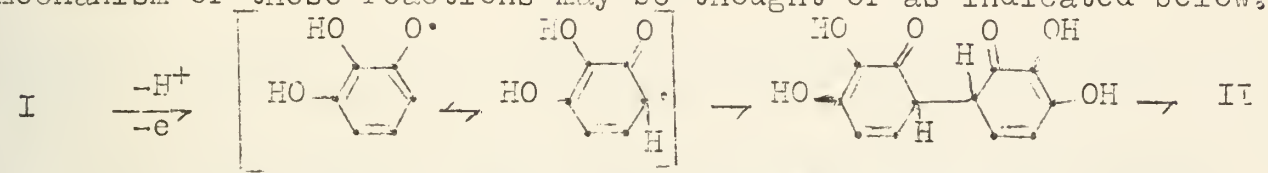




tetramer

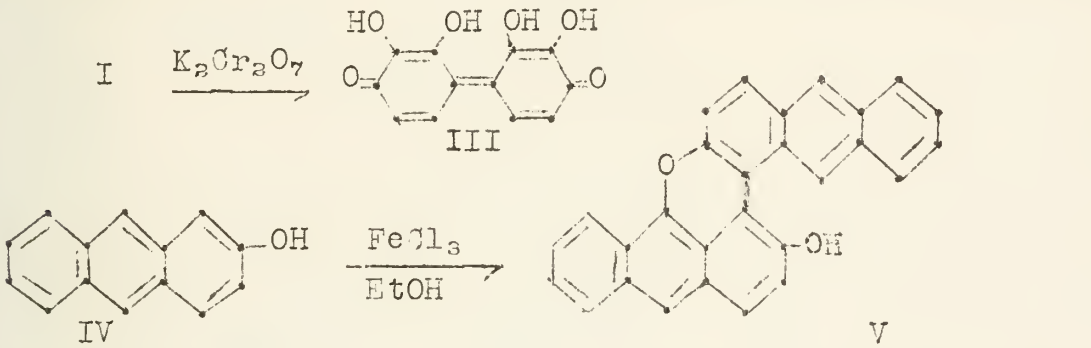
Hydrogen peroxide may also be used in certain instances.[3] The



mechanism of these reactions may be thought of as indicated below.

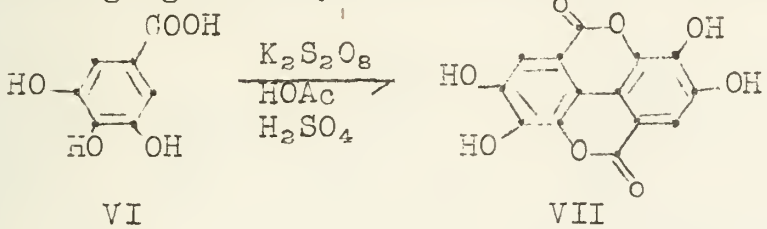


Reactions in which coupling is followed by further changes.— Pyrogallol on treatment with stronger oxidizing agents yields cedriret III[4] which is merely the result of the oxidation of II to its quinone. β-Anthol IV, however, acts somewhat differently when



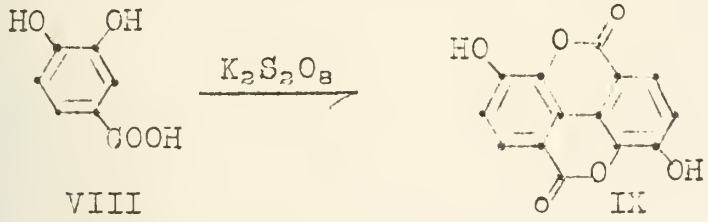
treated with ferric chloride in alcoholic or acetic acid solution.[2] It forms a compound V with an ether linkage.

Lactone formation occurs readily when carboxylic derivatives of phenolic compounds are oxidized. Gallic acid VI yields ellagic acid VII in 38% yield when treated with potassium persulfate in an acetic acid solution containing a little sulfuric acid.[5] Other oxidizing agents may be used for this conversion.



Arsenic acid,[6] iodine in water, or potassium permanganate in sulfuric acid[7] will perform the oxidation. And in the case of the ethyl ester of VI, just boiling in sodium carbonate solution will effect the conversion.[8] The persulfate reagent has been used with

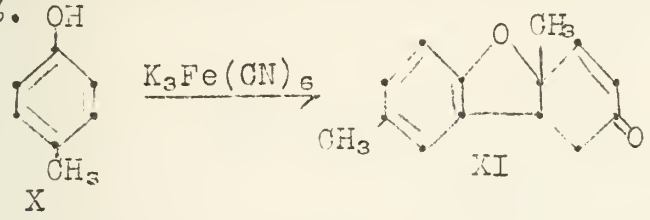
other phenolic compounds with corresponding results.[5] Protocatchuic acid VIII yields catellagic acid IX. p-Hydroxy benzoic acid seemingly is oxidized to VIII and then reacts the same way.




VIII IX

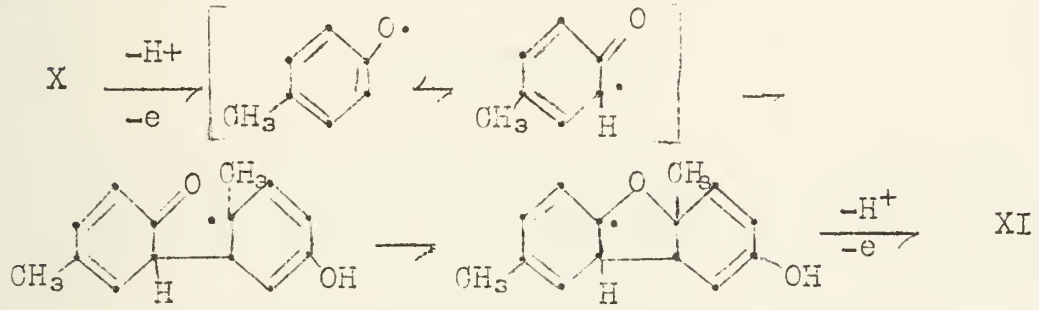
m-Hydroxy benzoic acid is partially oxidized to VIII and then a mixed coupling takes place producing the monohydroxy relative of IX.

An interesting reaction which does not follow the general scheme is the oxidation of p-cresol X by potassium ferricyanide in sodium carbonate solution at 0°.[9,10] The yield of pure XI is about 20%.

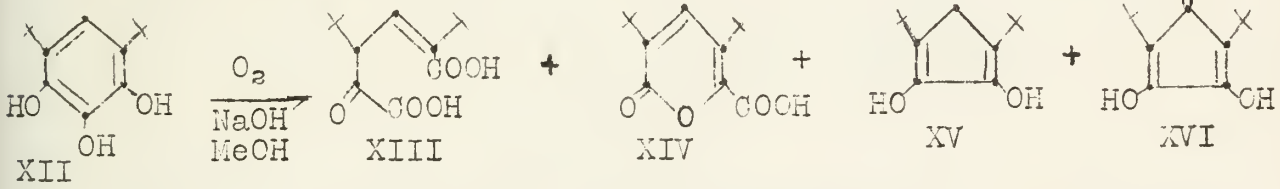



X XI

The reaction might be explained as follows,

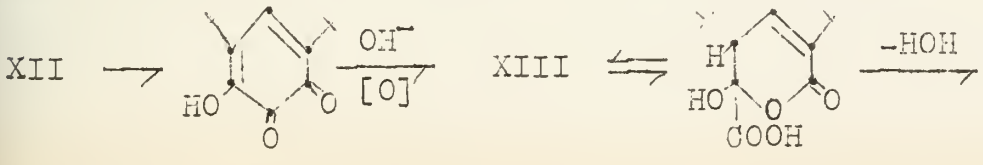



More complicated reactions.--The air-oxidation of di-t-butylpyrogallol XII in alkaline methanolic solution yields some unusual products XIII-XVI.[11]

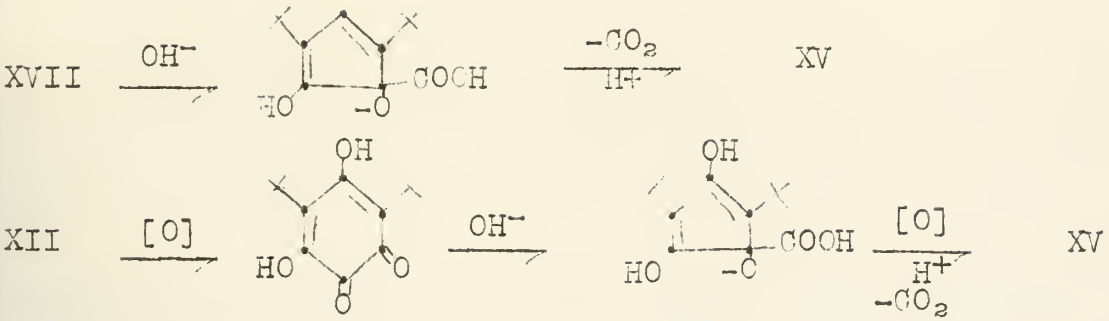



XII XIII XIV XV XVI

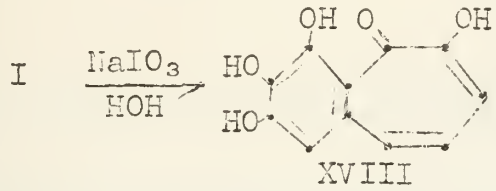
The following mechanism for this reaction has been postulated.[11]




XVII




Perhaps the most unusual example of an oxidation of a phenol is the synthesis of purpurpogallin XVIII. It may be obtained from pyrogallol on oxidation by many reagents, including aqueous sodium iodate,[1,9] aqueous potassium ferricyanide, aqueous sodium nitrite,[13] acidic silver nitrate solution, potassium permanganate in sulfuric acid,[14] quinone, platinum black, gum arabic and even blood.[15,16] The iodate method gives the best yield--92%. The mechanism for the reaction is as yet a rather intriguing puzzle.[17]




XVIII

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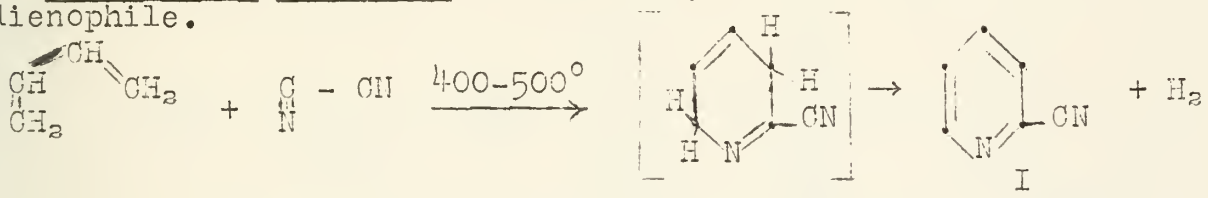
# THE REACTIONS OF CYANOGEN IN ORGANIC CHEMISTRY

Reported by Richard S. Colgrove February 29, 1952

Introduction.--Cyanogen has been available to organic chemists for a long time. It was first prepared by Gay-Lussac in 1815 by thermal decomposition of mercuric cyanide[1]. In 1824 Wöhler prepared oxalic acid from cyanogen by hydrolysis[2]. It is the purpose of this seminar to discuss some of the more interesting reactions of this compound.

Cyanogen is the dinitrile of oxalic acid and most of its reactions can be explained on this basis, since it is both a nitrile and a conjugate diyne. However, in other instances it behaves as a pseudohalogen.

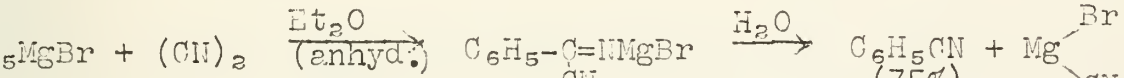
Diels-Alder Reactions.--Towards 1,3-dienes cyanogen behaves as a dienophile.



I

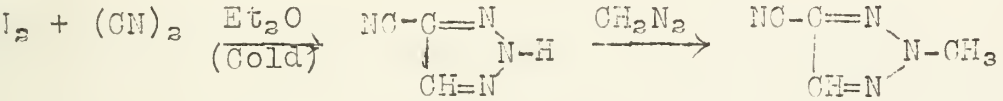
Isoprene, chloroprene, and 2-methylpiperylene behave similarly giving mixtures of the corresponding 2-cyanopyridines[3,4,5].

Grignard Reaction.--Many aliphatic, aromatic, and cycloaliphatic nitriles were prepared by Grignard and coworkers in excellent yields[6].



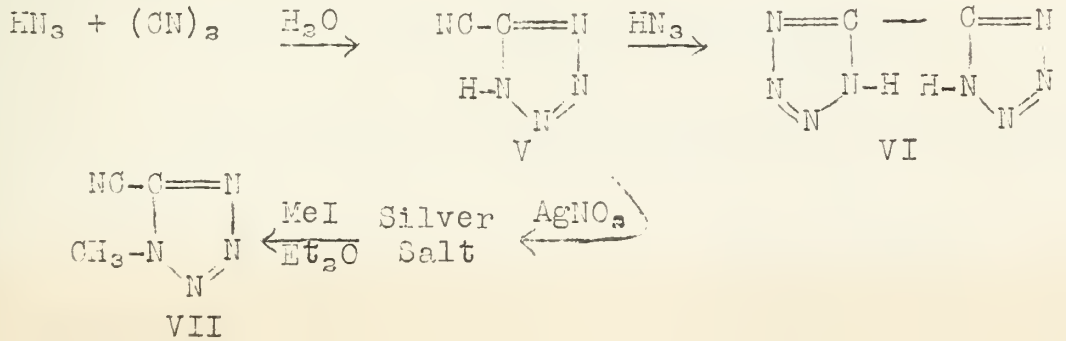
II

Reaction with Diazohydrocarbons.--Cyanogen behaves analogously to acetylene, with respect to the triple bond uniting directly with diazohydrocarbons to form cyanosotriazoles[7].



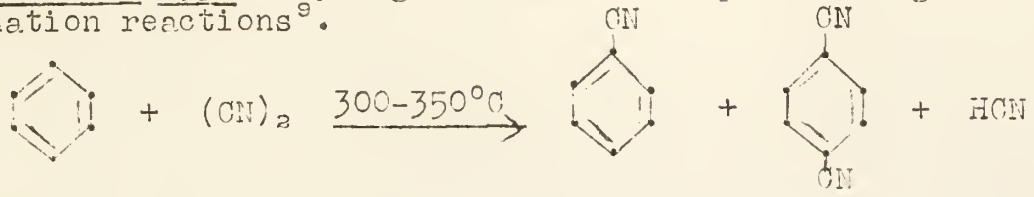
III IV

The reaction with hydrazoic acid is similar but in this case excess hydrazoic acid leads to bis-tetrazole[8].



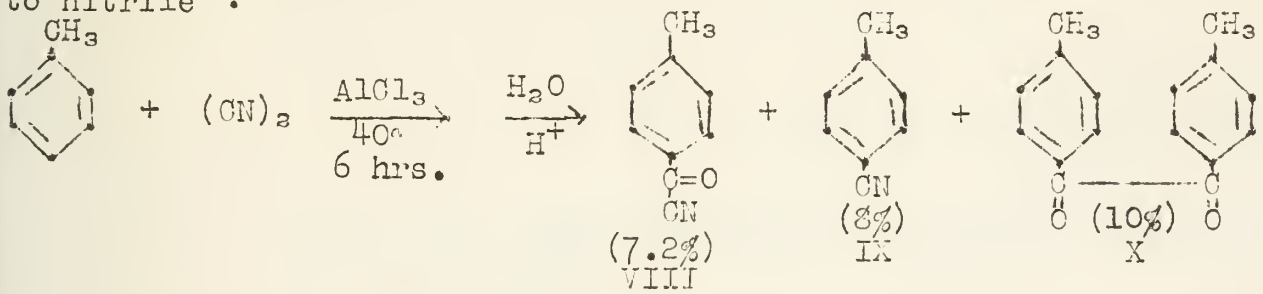
V VI VII

Friedel-Crafts Type.--Cyanogen behaves as a pseudohalogen in certain cyanation reactions[9].

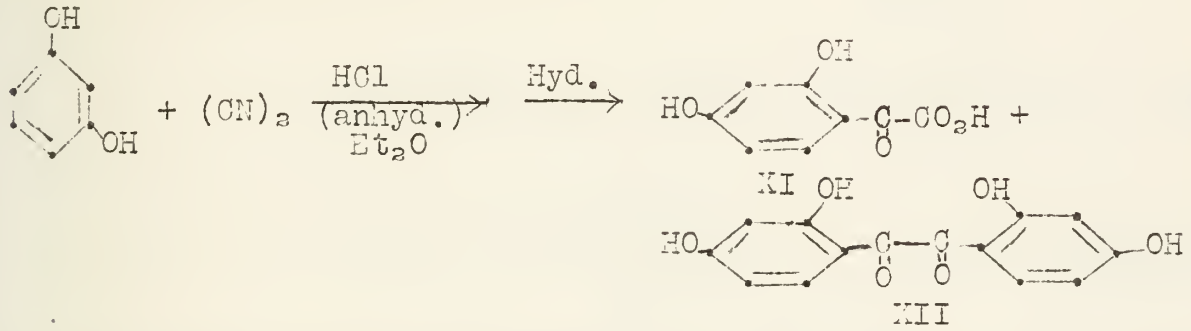


Better yields are obtained if the reaction is carried out in a hot tube using $AlCl_3$ as a catalyst. In this manner benzene, toluene, xylenes, and mesitylene have given the corresponding nitriles in about 12% yield[10].

If cyanogen is allowed to react with aromatic hydrocarbons at moderately low temperatures other products are formed in addition to nitrile[11].



Reaction with Phenols.--With polyhydroxy phenols cyanogen undergoes a Hoesch type reaction[12,13].



If $AlCl_3$ is used as the condensing agent the yields are improved, thus resorcinol gives a 74% yield of 2,2',4,4'-tetrahydroxybenzil[14].

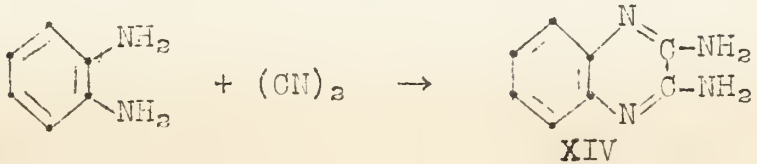
Amine Reactions.--Towards amines, cyanogen behaves as a nitrile and undergoes aminolysis.

A. Primary Aromatic Amines

1. $C_6H_5NH_2 + (CN)_2 \xrightarrow[(Cold)]{EtOH} C_6H_5HN-C(=NH)-C(=NH)-NHC_6H_5$ XIII

p-Toluidine and benzylamine react in the same manner[15]

2.[17]



B. Aliphatic Amines

1. Secondary Amines
Woodburn and coworkers[18] carried out the first reaction between aliphatic amines and cyanogen. A successful reaction depends upon purity of reagents, temperature, and nature of the solvent. When pure amine or an aqueous or alcoholic solution of amine is used, tars result. Solutions of amine in ethyl acetate, benzene, toluene, etc., however, react smoothly and 50-70% yields of N-substituted cyanoformamidines are obtained.

$$R_2NH + (CN)_2 \xrightarrow[0^\circ]{EtOAc} R_2N-\overset{\overset{NH}{\|}}{C}-CN \quad \text{XV} \qquad R=CH_3, C_2H_5, n\text{-}C_3H_7, n\text{-}C_4H_9, n\text{-}C_5H_{11}$$

2. Primary Amines
Both CN groups undergo a reaction with primary amines in yields of 10-35%[19].

$$2RNH_2 + (CN)_2 \xrightarrow{EtOH} RNH-\overset{\overset{NH}{\|}}{C}-\overset{\overset{NH}{\|}}{C}-NHR \quad \text{XVI}$$

$R=CH_3, C_2H_5, n\text{-}C_3H_7$, iso-$C_3H_7$, $n\text{-}C_4H_9$, isc-$C_4H_9$, sec-$C_4H_9$, $n\text{-}C_5H_{11}$

It was found that the oxamidines formed above could undergo (a) substitution and (b) exchange reactions with more amine[20].

a. $$RNH-\overset{\overset{NH}{\|}}{C}-\overset{\overset{NH}{\|}}{C}-NHR + 2RNH_2 \rightarrow RNH-\overset{\overset{NR}{\|}}{C}-\overset{\overset{NR}{\|}}{C}-NHR + 2NH_3$$
(20-80%)
XVII

b. $$RNH-\overset{\overset{NH}{\|}}{C}-\overset{\overset{NH}{\|}}{C}-NHR + 2R'NH_2 \rightarrow R'NH-\overset{\overset{NH}{\|}}{C}-\overset{\overset{NH}{\|}}{C}-NHR' + 2RNH_2$$
XVIII

$$2NH_3 + R'NH-\overset{\overset{NR'}{\|}}{C}-\overset{\overset{NR'}{\|}}{C}-NHR' \quad \text{(17-90\%) XIX} \qquad \xleftarrow{R'NH_2} \text{ where } R' > R \text{ in mol.wt.}$$

C. Primary Heterocyclic Amines
Woodburn and coworkers[21] found that using various methyl substituted 2-aminopyridines they could isolate the intermediate cyanoformamidines as well as the expected oxamidines.

D. Amine Compounds[22]

1. $$2NH_2NH_2 + (CN)_2 \xrightarrow[\text{(cold)}]{H_2O} H_2NNH-\overset{\overset{NH}{\|}}{C}-\overset{\overset{NH}{\|}}{C}-NHNH_2$$
XX

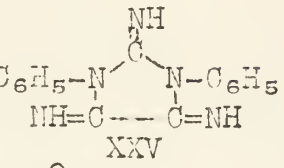
2. $C_6H_5NHNH_2 + (CN)_2 \rightarrow C_6H_5NH-N=C(NH_2)-C-CN$ XXI

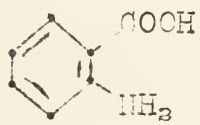
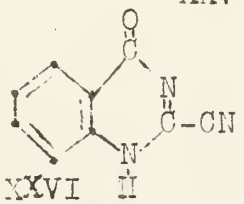
3. $C_6H_5NHOH + (CN)_2 \xrightarrow[(cold)]{Et_2O}$ $C_6H_5-N(OH)-C(NH)-CN$ (75%) XXII

4. $2NH_2OH + (CN)_2 \xrightarrow[(cold)]{H_2O}$ $H_2N-C(N.OH)-C(N.OH)-NH_2$ (40%) XXIII

5. $NH_2CONHNH_2 + (CN)_2 \rightarrow H_2NCONH-N=C(NH_2)-CN$ XXIV

6. $C_6H_5-NH-C(NH)-NH-C_6H_5 + (CN)_2 \rightarrow$ XXV

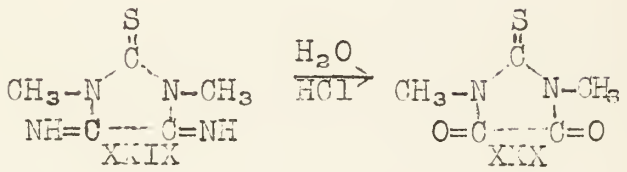


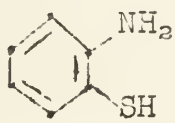
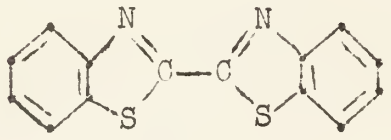
7.  $+ (CN)_2 \xrightarrow{H_2O}$  XXVI

Miscellaneous Reactions[22]--

1.[23] $H_2S + (CN)_2 \rightarrow NH_2-C(S)-CN \xrightarrow{H_2S} NH_2-C(S)-C(S)-NH_2$ XXVII XXVIII

2. $CH_3NH-C(S)-NHCH_3 + (CN)_2 \rightarrow$ XXIX $\xrightarrow[HCl]{H_2O}$ XXX



3. $2$  $+ (CN)_2 \xrightarrow{EtOH}$  $+ 2NH_3$ XXXI

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# THE DISPROPORTIONATION OF ALIPHATIC ALDEHYDES

Reported by J. P. Freeman March 7, 1952

Aromatic aldehydes when heated with strong alkali undergo disproportionation to the corresponding acid and alcohol. All aldehydes which contain no α-hydrogen atom react in this way, usually affording excellent yields of products. This reaction is comparatively unknown with aldehydes having α-hydrogen atoms. The alkaline conditions promote the aldol-type condensation, and this reaction proceeds in preference to dismutation.

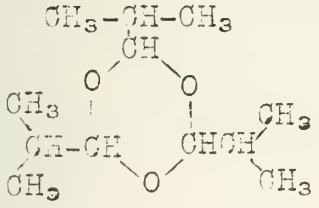
Recently investigations have been made into the alkaline disproportionation of aliphatic aldehydes, and certain conditions have been found in some cases which will favor this reaction in preference to condensation.

A. Saturated Aliphatic Aldehydes

Only scattered accounts of the Cannizzarro reaction with these aldehydes are recorded. One of the first successful attempts involved the disproportionation of isobutyraldehyde "in good yield" when it was heated with barium hydroxide at 150°(1). It has been reported that aldehydes of normal chain length greater than seven produce the corresponding alcohol and acids in yields of 85% or more when heated with potassium benzylate (2).

In a recent investigation it was found that α-monoalkylated saturated aliphatic aldehydes disproportionate quantitatively when heated with sodium hydroxide solution for five hours at 200°(3). A careful study of the conditions for this reaction showed that, below 150°, the aldol condensation predominates. Above that temperature, the aldol reverses to the original aldehyde which then undergoes dismutation. That this was the true reaction path was demonstrated for isobutyraldehyde in the following manner.

In an experiment when the reactants had been mixed rapidly, isobutyrylaldoxan (I) and 2,2,4-trimethylpentane-1,3-diol (II) were isolated. Another study has shown the presence of II and isobutyric acid (4). Also isobutyl alcohol and acids resulting from the oxidation of the aldol products are probably present. There are then



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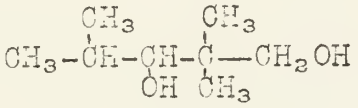
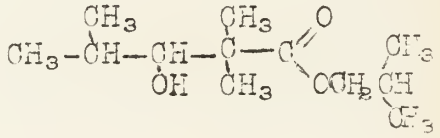


II



III

three possible intermediates in the disproportionation: the isobutyric acid ester of II, I, and 3-hydroxy-2,2,4-trimethylvaleric acid isobutyl ester (III). A mixture of these three were heated at 200° with caustic soda and a 93% yield of isobutyl alcohol and isobutyric acid were produced.

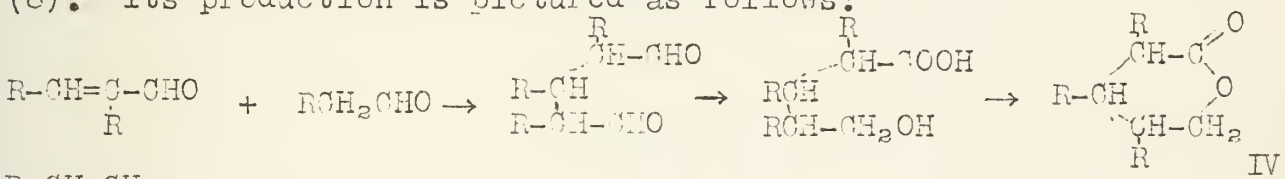
All attempts to produce good yields of disproportionation products with aldehydes with no α-alkyl substitution failed. In all cases aldol resins were isolated as the only products.

B. α,β-Unsaturated Aldehydes

The usual reaction of these unsaturated aldehydes in the presence of base is to reverse the aldol condensation to produce the original aldehyde. Acrolein and crotonaldehyde give only tars and resins (1), while these two and cinnamaldehyde when treated with base in the presence of formaldehyde yield pentaerythritol (5). Many side reactions can occur, such as reduction to the alcohol and/or further condensations (2,7).

The reaction of 2-ethylhexenal was studied in order to find conditions for quantitative disproportionation (6). Only complex mixtures resulted which consisted mainly of the following products: 2-ethylhexanol produced by reduction (7); 2-ethylhexenoic acid which may be produced by nascent hydrogen oxidation; n-butyl alcohol and n-butyric acid resulting from the disproportionation of n-butyraldehyde, which is produced by a retrograde aldol; and a lactone.

The lactone (IV) is produced by an interesting and relatively unknown reaction. It corresponds to one of the so-called carbobenzonic acids whose structures have been determined conclusively (8). Its production is pictured as follows:



R=$CH_3CH_2$-

The Michael addition of an aldehyde to an α,β-unsaturated aldehyde was discovered by Meerwein, who showed it to be a general one for α-mono-substituted aldehydes (9). Isobutyraldehyde and isovaleraldehyde were added to α-methyl-β-ethylacrolein, cinnamaldehyde, α-methylcinnamaldehyde, benzalacetophenone and benzaldesoxybenzoin. In all cases the corresponding δ-lactones were produced in good yield. Desoxybenzoin and phenylacetaldehyde can also be used as the Michael reagent. The 1,5- dicarbonyl compounds can be isolated if desired, or the reaction can be carried to the lactone in one step. The internal Cannizzarro reaction that occurs after addition always seems to produce the hydroxy acid in which the carbonyl group of the original unsaturated aldehyde molecule has been oxidized.

In the present work, the lactone made up the bulk of the product in a yield of about 40%. Although Meerwein's original work was done in absolute ethanol, it was repeated under the Cannizzarro conditions, and a lactone was isolated in a 15% yield.

C. The Tishchencko Reaction

This reaction has been poorly studied in the aliphatic series. In some cases the use of aluminum alkoxides has proved successful,

but more often complex mixtures result. In this study it was found that the use of aluminum isopropoxide produced a small amount of ester, but there was some reduction of the aldehyde to the alcohol, and also condensation of the original aldehyde with the acetone produced. Only when the alcoholate corresponding to the alcohol portion of the expected ester is used is the reaction useful. For instance, 2-ethylhexanal disproportionates to the corresponding ester in 45% yield when aluminum 2-ethylhexylate is used.(10)

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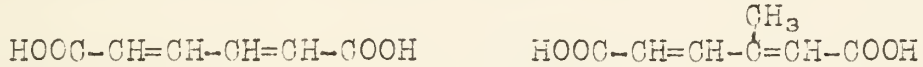
# THE STEREOCHEMISTRY OF THE MUCONIC AND β-METHYLMUCONIC ACIDS

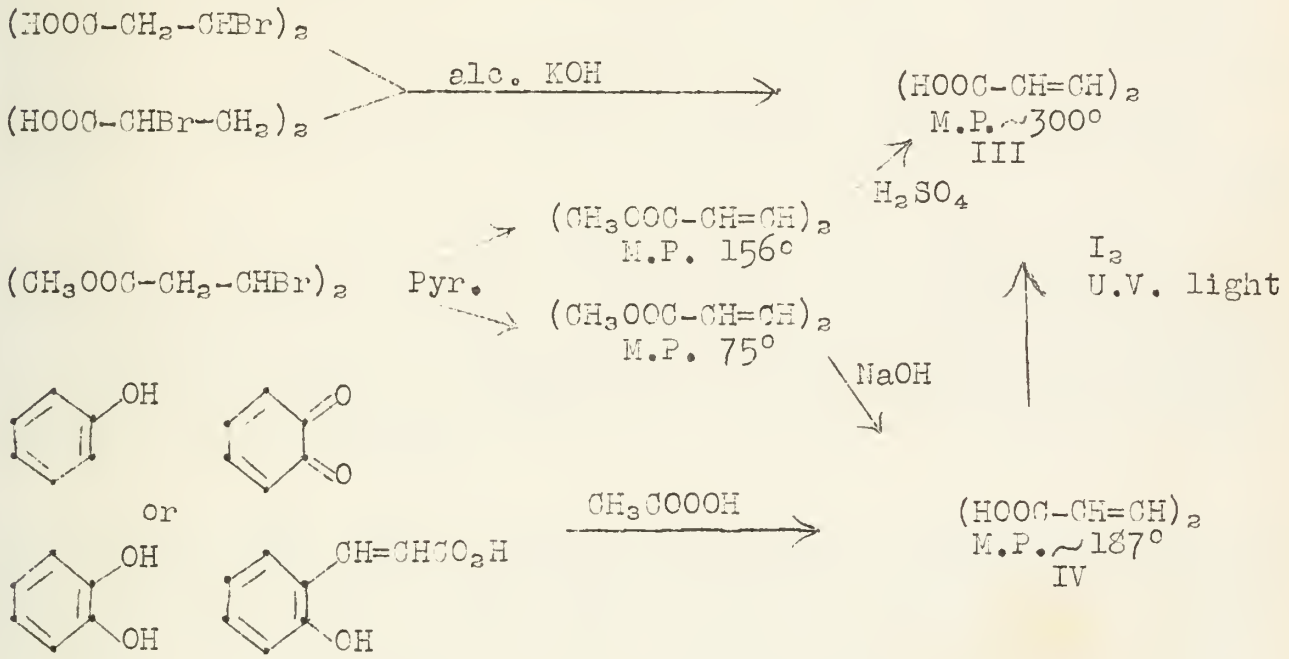
Reported by Samuel Gelfand March 7, 1952

Introduction: Several examples of the isolation of all of the three possible stereochemical forms of a symmetrically substituted 1,3-butadiene system have been reported in the literature. Farmer[1] has described the three forms of ethyl $\alpha,\alpha'$-dibromomuconate and the three stereoisomers of diphenylbutadiene have been prepared and investigated by Straus and Müller[2] and by Pinckard, Wille, and Zechmeister[3]. More recently Linstead has studied the stereoisomeric muconic acids (I)[4,5] and has extended his methods to a study of the isomeric β-methylmuconic acids (II).[6,7] The latter system is of interest because of its connection with cis-trans isomerism in the carotenoids.



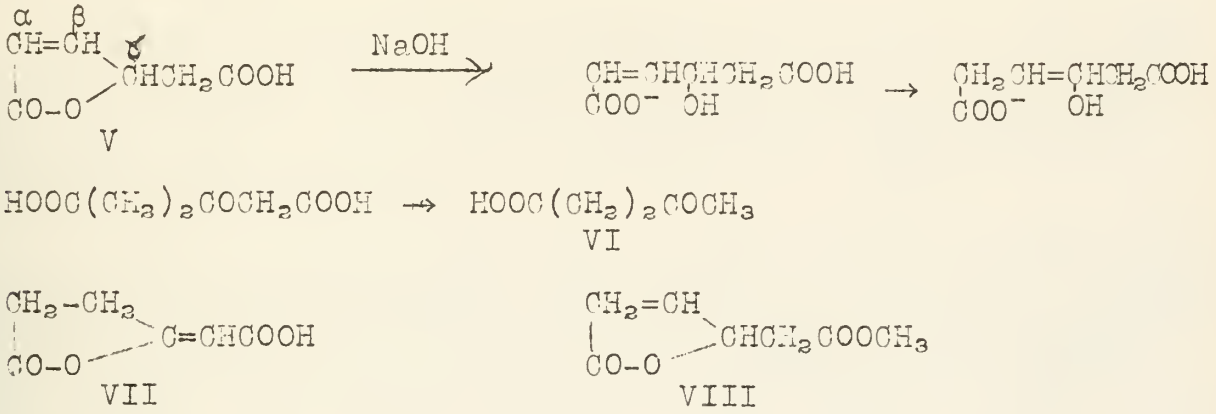
I II

The Muconic Acids: The methods used in the synthesis of the muconic acids lead to two isomeric compounds.[1,8,9,10,11,12,13,14]

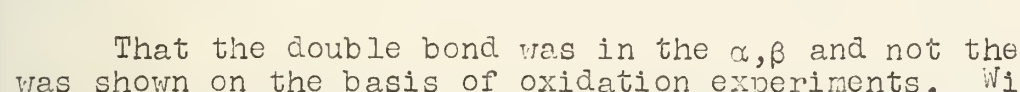



The configuration of the high melting compound (III) was shown to be trans-trans on the basis of its oxidation to dl -tartaric acid with potassium permanganate.[15,16] The low melting isomer (IV) gave meso-tartaric acid on permanganate oxidation and was assigned the cis-cis configuration on the basis of this information and its formation from o-benzoquinone. The trans-trans acid failed to lactonize while the cis-cis form lactonized smoothly in sulfuric acid solution to give γ-carboxymethyl-$\Delta^{\alpha}$-butenolide (V) as the major product. A small amount of an isomeric unsaturated lactone

was obtained which was identified as carboxymethylenebutanolide (VII) by comparison with an authentic sample obtained by lactonising β-ketoadipic acid.[17] The lactone (V) was shown to have a five and not a six membered ring on the basis of its formation of levulinic acid (VI) on hydrolysis with sodium hydroxide. The hydrolysis probably proceeds as follows:



V



VI



VII



VIII

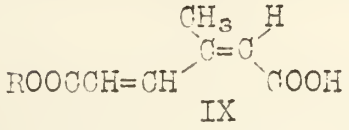
That the double bond was in the α,β and not the β,γ-position was shown on the basis of oxidation experiments. With potassium permanganate in the cold the lactone (V) afforded oxalic acid. Malonic and succinic acids could not be detected. Catalytic hydrogenation, light absorption properties and a comparison of the chemical properties with those of the previously investigated simple α,β- and β,γ-unsaturated lactones confirmed these results.[18,19,20]

The third isomeric cis-trans muconic acid was obtained either by treatment of the lactonic ester (VIII) with sodium methoxide followed by hydrolysis of the ester group or by recrystallisation of the cis-cis muconic acid from boiling water. The latter reaction is remarkable since the cis-cis acid can be recrystallised unchanged from boiling methanol or ethanol and is unaffected by dissolution in alkali and liberation with acid or exposure in ethanol to U.V. light for thirty minutes.

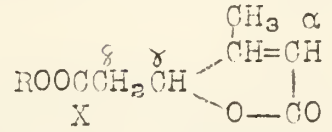
In contrast with the isomeric diphenylbutadienes and the carotenoids which show a shift in the main U.V. absorption band for the different isomers, the isomeric muconic acids all have the same absorption maxima. Likewise they are all strong acids and give closely similar titration curves. Both lines of evidence indicate that the different isomers exist in the trans configuration about the central single bond. In this more elongated form there is the least steric interference to the planar form necessary for resonance and the spacing between the carbonyl groups is roughly the same.

The β-Methylmuconic Acids: Two isomeric β-methylmuconic acids can be obtained by methods analagous to those illustrated above for the muconic acids. By applying the following considerations to the two acids the high melting isomer was identified as the trans-trans and the low melting as the cis-trans.

1. Ease of Lactonization.-In order to lactonize readily a carboxyl group must be disposed cis to the acrylic residue.



IX



X

2. Fission of Unsaturated Lactones.-The product of the ring opening (X) → (IX) would be expected to have initially a cis-trans configuration since the α,β-double bond is initially cis in the lactone and does not take part in the reaction. The α,β-double bond formed in the reaction is considered to be trans by analogy with related ester fissions.

3. Method of Preparation.-Double bonds formed by dehydrohalogenation of α,α'-dibromoadipic acids would be expected to be trans. Muconic acids formed by fission of an aromatic ring under mild conditions would be expected initially to appear in the cis-cis form. Whether the configuration will change depends on the reaction conditions and the inherent stability of the cis-cis isomer.

4. Stability and Interconversion.-The relative stabilities of the various isomerides and the conditions required for their interconversion will be a guide to configuration.

It is probable that the two isomers which have not been isolated (cis-cis and trans-cis) are unstable and will continue to defy isolation.

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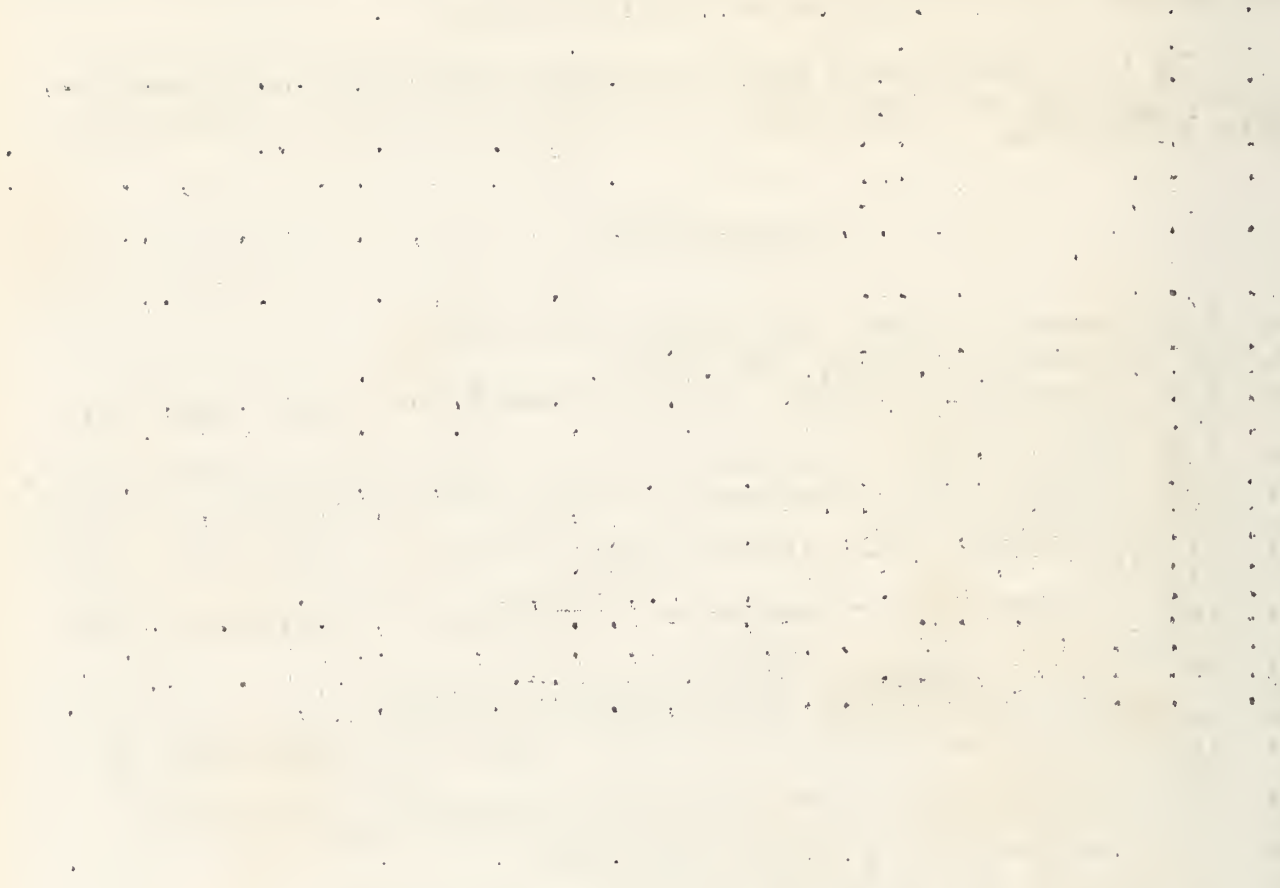
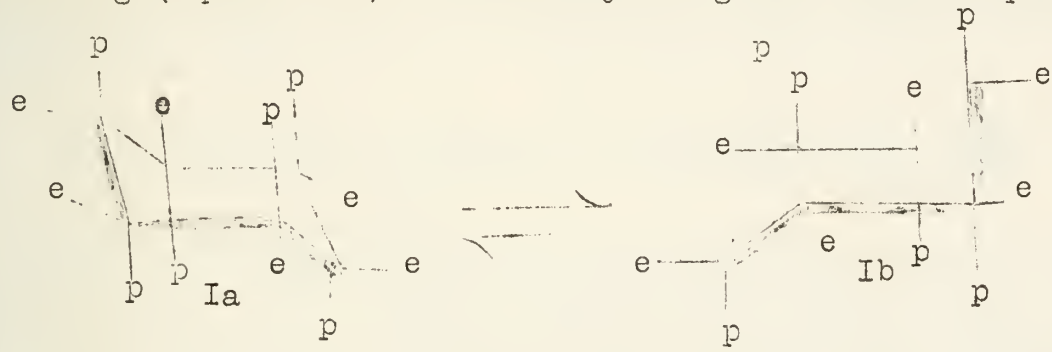


# POLAR AND EQUATORIAL BOND ANALYSIS OF STEROID CONFIGURATIONS

Reported by Richard C. Fox March 14, 1952

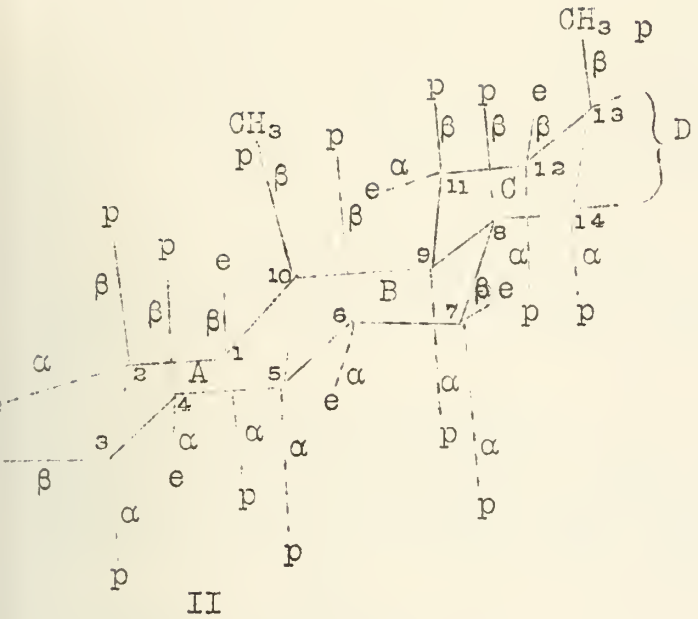
Introduction: Hassel and coworkers,[1,2,3] via electron diffraction measurements in the gas phase, determined that the cyclohexane ring existed predominantly in the more stable chair form, and the bonds other than the C-C bonds could be divided into those parallel to an axis thru the ring, which they called $\epsilon$, and those roughly perpendicular to that axis, which they called $\kappa$. They studied and formulated the preferred conformation of several of the mono-, di-, and tri-, substituted cyclohexanes, as well as rings containing oxygen. The latter studies led to sugar chemistry[4] applications, while the former elucidated reactions of alkaloids,[16] steroids, and terpenes.[8,15,17] Beckett, Pitzer, and Spitzer[5] confirmed these findings and contributed the name polar (p) and equatorial (e) for $\epsilon$ and $\kappa$ respectively. Barton[6,7,8,9] published a series of papers both reviewing the previous work and applying the approach to steroid reactions, heretofore unsystematized.

Generalizations: The chair form is energetically more favorable than the boat, since in the former case consecutive carbon atoms and their substituents exist in the staggered constellation, while in the boat form they do not. This idea coincides with that of Prelog.[10] The bonds of the chair form can be divided into two classes as mentioned above: those roughly lying in the plane of the ring (equatorial) and those jutting out from the plane (polar).

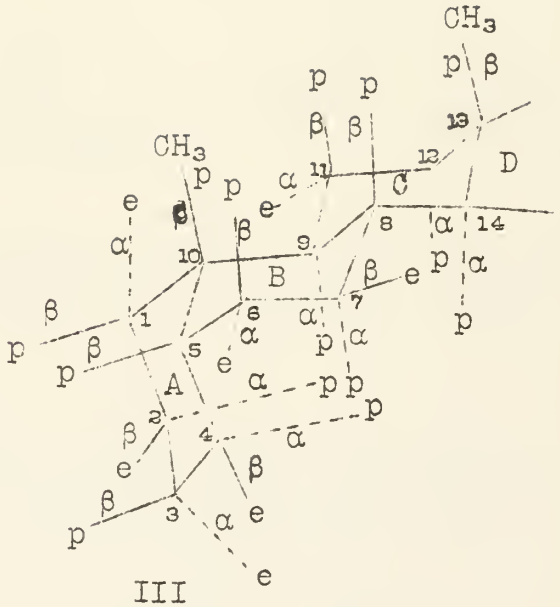



Forms Ia and Ib are interconvertible except in obviously restricted cases. The polar bonds are much closer together than the equatorial and hence possess more Van der Waal's repulsive forces. The isomerization of the various substituted cyclohexane derivatives always proceeds in the manner to give ee or eee bonding rather than polar bonds. This also applies to decalins.[8]

In steroids Barton has pictured the two nuclear series as seen in diagrams II and III with the polar and equatorial bonds designated as well as Fieser's $\alpha$ and $\beta$ nomenclature.



II
trans AB ring juncture
Cholestane series



III
cis AB ring juncture
Coprostane series

1) Reduction of Ketones and Alcohol Equilibrium.
Equilibration of steroidal alcohols, and reductions of ketones would seem to give the more stable alcohols and sterically this implies that the stable alcohols would have equatorial bonds,[8] and this is the case.[11]

eg. Coprostanone-3 red $\rightarrow$ 3αOH, Cholestanone-3 red $\rightarrow$ 3βOH
3βCoprostanol $\xrightarrow{Na}$ 3αOH, 3α Cholestanol $\xrightarrow{Na}$ 3βOH

2) Elimination Reactions.
Ionic elimination reactions requiring concerted 1:2 elimination should proceed more readily when the four centers (2 C atoms and 2 substituents) are in the same plane and trans. This is the case when the eliminated groups are polar as seen both visually and experimentally. eg. in both series the 7αOH(p) and 8βH(p) compounds are more easily dehydrated than the 7βOH[8]; also the 4βOH(p) cholestanol dehydrates easily at R.T. whereas the 4αOH(e) cholestanol yielded no hydrocarbon under the same conditions.[7]

Pyrolytic eliminations probably proceed by some mechanism which requires a cis relationship of the departing groups. eg. the benzoate of 4β-cholestanol yields on pyrolysis the $\Delta^3$-compound, whereas the 4α-benzoate gives a mixture of the $\Delta^3$-and $\Delta^4$-compounds.[8]

3) Esterification and Hydrolysis Reactions (Steric Hindrance)
Since polar substituents are more hindered than equatorial, the polar OH groups in steroids are more difficult to esterify and the esters more difficult to hydrolyze than the equatorial hydroxyls.[8]

eg. 3α-coprostanol easier to esterify than the 3βOH compound.

4) Oxidation Reactions (Steric Hindrance)

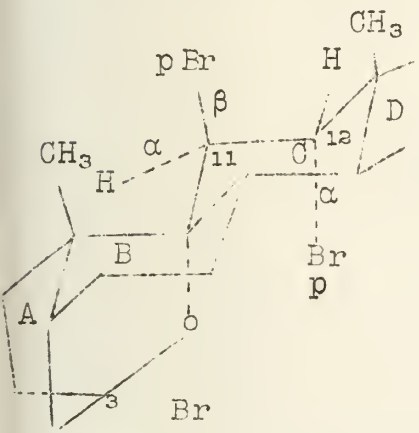
According to the prevalent theory,[12] chromic acid oxidation of alcohols entails the attack on the C-H bond (rather than on the C-OH bond) as the rate determining step. The polar C-H bonds are more hindered (e-OH) therefore, they should be less readily oxidized and this has been found to be true. eg. the 3βH(e) is easier to oxidize than the 3αH cpd in the cholestane series. This idea seems to hold if Br is the oxidizing agent.[8]

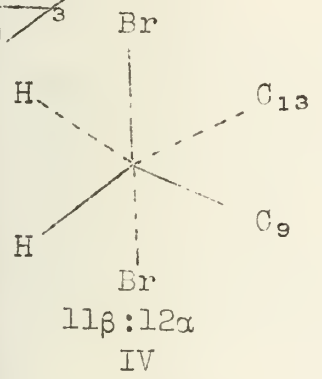
5) The 17-Position in Steroids

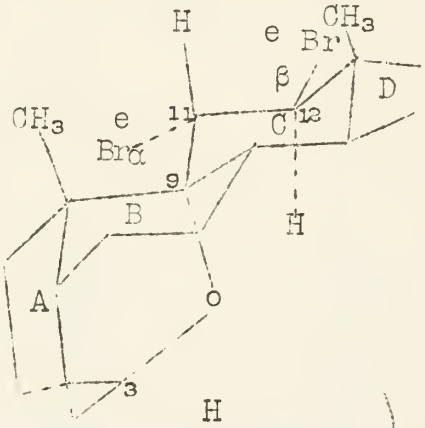
The 17α-bond in steroids has the character of a polar bond with respect to the C ring and the 17β-an equatorial relation. The 17β-substituents seem to show more stability and less hindrance than the 17α.[8]

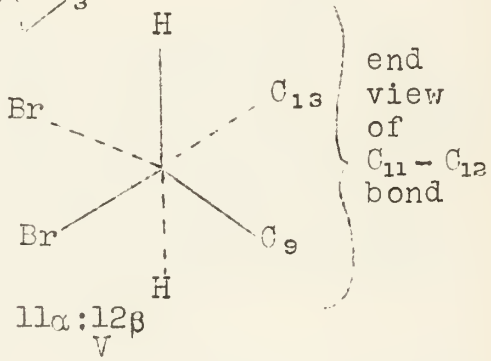
6) Debromination Reaction[9]

Two 3α,9α,-epoxychol -11-enate dibromides exist: the 11β; 12α(IV) and the 11α; 12β(V). The 11β; 12α dibromide was debrominated in a few days with iodide ion. The 11α 12β dibromide was unaffected after 6 months, yet both are trans dibromides.



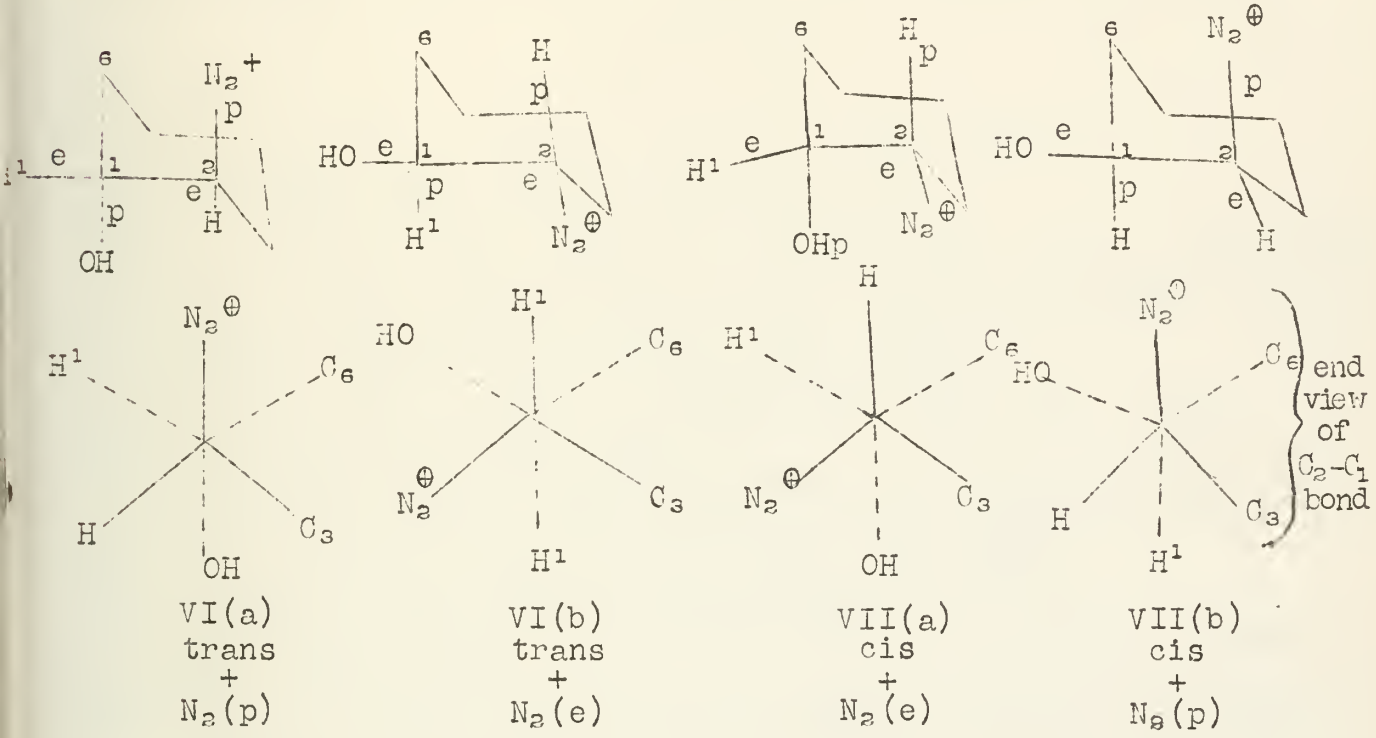

Assuming[9,7,18,19] that optimum condition for reaction is when the two Br atoms lie in the same plane and then go thru an $E_2$ type mechanism, it can be seen from figure IV and V that only the 11β: 12α(2 Br's are p) compound meets these conditions.

Recent Work Other Than Steroids

There have been attempts to ascertain the conformation of the boat form of the 6 ring.[13,14] It occurs unambiguously only where restricted by other rings or connected by a 1,4 bridge, eg. bornyl and isobornyl series. However, any useful results from applying

polar and equatorial analysis are overshadowed by less subtle steric hindrance and cis-trans geometry.

Recently McCasland[20] found that nitrous acid reacted with cis 2 amino cyclohexanol to give both cyclohexanone and cyclopentylmethanal, the trans isomer yielded almost exclusively cyclopentylmethanal. Assuming the intermediate to be a diazonium compound, and optimum conditions for rearrangement occur when the migrating group is trans and coplanar with the diazonium group,[21] he explains the different courses using the polar and equatorial analysis.




From the above diagram one can see that in the trans case when the $N_2^+$ is polar bonded (VIa) neither the carbon 6 nor hydrogen 1 is in a favorable migrating position. When the $N_2^+$ group is in the e position (more stable trans form) ring carbon 6 is favorably situated (VIb) for migration. In the cis isomer, when the $N_2^+$ group is polar the 1 hydrogen is appropriately situated, whereas, with the $N_2^{\oplus}$ equatorial (neither one definitely more stable) the ring carbon 6 is favored. Therefore, one would expect a mixture of cyclohexanone and the contracted ring aldehyde.

However, as suggested by Curtin, Hammett and others, in the case of pinacolic rearrangements it is the configuration of the transition state that determines the course of the reaction, and not that of the initial conformation. In McCasland's case it is fortunate that the transition states one can conceive of, give the same prediction as does the initial conformational analysis; however, one may not always be so fortunate.

Summary: This type of analysis can be applied successfully to many 6 ring compounds where the stable conformation is known (and perhaps in the future to larger rings) in the various fields. In

practice it might be well when dealing with such compounds that can react differently, to apply the accepted mechanism to the reaction and compound and see how the stereo-chemical conformation both of the initial and of the transition states might affect the ease of the reaction and its course remembering the criteria[8 13] for polar bonds are: 1) less stable 2) greater steric hindrance 3) liability to 1:2 ionic elimination, and for equatorial bonds: 1) more stable 2) less hindrance 3) liability to pinacolic rearrangement with ring contraction.

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# CORRELATIONS BETWEEN STRUCTURE AND OPTICAL ROTATORY POWER

Reported by J. K. Williams March 14, 1952

## INTRODUCTION

Correlations have been found between the structures of asymmetric molecules and their effects upon plane polarized light. As a result of certain of these correlations, empirical rules have been formulated. These rules have been used to predict the effect of changes in structure upon the optical properties of compounds. Consequently, these rules have been found to be of value for the determination of the stereochemistry of molecules, particularly of natural products.[1-13] It is the purpose of this seminar to dicuss a few of these rules and some recent work[14] in which they have been applied in an attempt to elucidate the stereochemistry of the asymmetric carbons in the steroid side chain.

van't Hoff's Principle of Optical Superposition.[15] "In a molecule containing several asymmetric centers, each center contributes to the optical rotation independently of the others."

In compounds where the asymmetric centers are separated by at least two methylene groups, van't Hoff's rule seems to hold fairly well. When the asymmetric carbons are closer to each other, the configuration of one will modify the rotation caused by the other.[16]

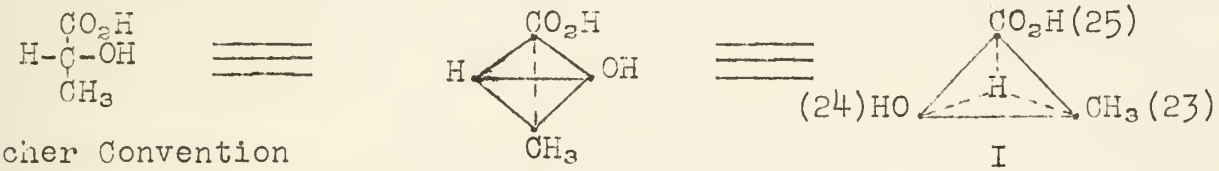
Tschugaeff's Rule.[18,19] "Molecular rotations of the members of a series of optically active compounds of the type $Cr_1r_2r_3R$, in which R represents the radicals of an homologous series, approach a limiting value as R increases in size."

Marker's Rule and Table.[20] Marker was able to correlate the molecular rotations of four series of disubstituted ethanes, $RR_1CHCH_3$ where $R_1$ was n-amyl, n-butyl, propyl, or ethyl and R was any of the 29 various groups listed in Table I below.

Table I

| | | | | | |
|---|---|---|---|---|---|
| 1. | $CH_2CH_2Br$ | 11. | $C_4H_9$ | 21. | $CH_2OH$ |
| 2. | $C_4H_9$-i | 12. | $CH_2CH_2CH_2CH_2OH$ | 22. | $C_3H_7$-i |
| 3. | $CH_2CH_2CH_2Br$ | 13. | $CH_2CH_2CH_2OH$ | 23. | $CH_3$ |
| 4. | $CH_2CH_2CH_2CH_2Br$ | 14. | $C_3H_7$ | 24. | OH |
| 5. | $CH_2CH_2CO_2H$ | 15. | $CH_2CH_2NH_2$ | 25. | $CO_2H$ |
| 6. | $CH_2CH_2CH_2CO_2C_2H_5$ | 16. | $CH_2CO_2C_2H_5$ | 26. | $CO_2C_2H_5$ |
| 7. | $CH_2CH_2CO_2C_2H_5$ | 17. | $CH_2C_6H_5$ | 27. | $C_6H_5$ |
| 8. | $CH_2CH_2CH_2CO_2H$ | 18. | $CH_2CH_2OH$ | 28. | Br |
| 9. | $C_5H_{11}$-i | 19. | $CH_2CO_2H$ | 29. | I |
| 10. | $C_5H_{11}$-n | 20. | $C_2H_5$ | | |

He found that in all four series he could arrange the groups, R, in the same order of increasing molecular rotation of the parent compound (except for numbers 24 through 29, which are in order of decreasing molecular rotation for the parent compounds.) Each group, R, was then assigned an "ordinal number" corresponding to its position in the table. If an asymmetric carbon is written as illustrated with lactic acid below (I), so that one views the face of the tetrahedron opposite to the hydrogen atom, the following rule will be obeyed: If the arrangements of the ordinal numbers in two compounds are both clockwise or both counterclockwise, the compounds have the same configuration for the same sign of rotation.

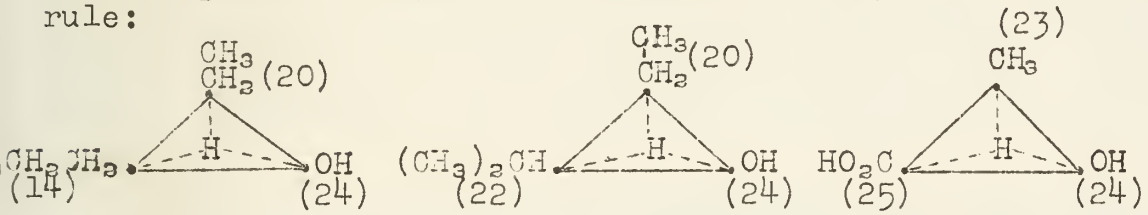



Fischer Convention

D(-) Lactic Acid

I

Marker's rule has been checked with some three hundred compounds of known configuration and no exception has been found. The following three compounds may serve as examples of the use of this rule:




clockwise levorotatory

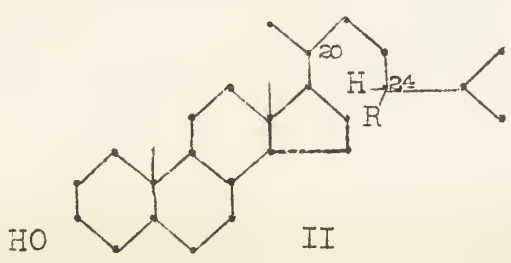
counterclockwise dextrorotatory

clockwise levorotatory

It may be seen that in this list the radicals are arranged in an approximate order of increasing dipole strength and labilities of electrons. To use the term "chromophore" in the sense of Kauzmann, Walter, and Eyring,[17] the radicals are arranged in order of increasing "chromophoric power".

## Stereochemistry of C-20 and C-24 of the Steroid Sidechain

The limitations mentioned above to van't Hoff's Principle are met for substituents at C-24 in the sterol side chain. Replacement of hydrogen at C-24 of cholestanol (II,R=H) by methyl or ethyl creates a new center of asymmetry. Table II shows the rotations of both pairs of isomers. The contribution of C-24 to the molecular rotations is represented by B and the contribution by the nuclear centers of asymmetry and C-20 by A.

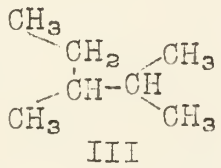



II

Table II

| Sterol | $M_D$ | |
|---|---|---|
| Campestanol (24-a-methylcholestanol; R=$CH_3$) | +125° = A+B | A=+94.5°, B=+30.5° |
| Ergostanol (24-b-methylcholestanol; R=$CH_3$) | + 64° = A-B | |
| Poriferastanol (24-a-ethylcholestanol; R=$C_2H_5$) | + 90° = A+B | A=+95°, B=-5° |
| Stigmastanol (24-b-ethylcholestanol; R=$C_2H_5$) | +100° = A-B | |
| Cholestanol (R=H) | + 93° = A | |

The values of A obtained (+94.5° and +95°) are equal to the molecular rotation of cholestanol within experimental error. The value of B obtained for the two C-24 epimers where R=methyl (+30.5°) is approximately equal to that of methylethylisopropylmethane (III) which has a molecular rotation of +28°.

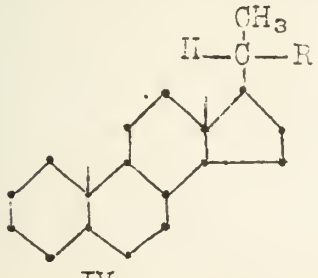


III

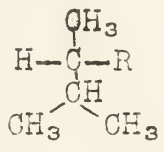
The similarity between the molecular rotation contributed by C-24 to the molecular rotation of (III), in the light of Tschugaeff's Rule, suggests that the saturated sterol molecule up through C-23 closely resembles an ethyl radical attached to C-24. This is further suggested by the fact that when R=ethyl, B becomes quite small (-5°).

From studies of side chain degradations, it has been established that most naturally occurring sterols and bile acids have the same configuration about C-20. It will be noticed that there is a close similarity between the asymmetric centers at C-20 and C-24. They both are surrounded by a hydrogen atom, a methyl group, a secondary carbon atom, and a chain of two methylene groups. It would not seem unreasonable to assume that the rotations associated with both C-20 and C-24 should be of the same order of magnitude (ca.+30°).

Table III summarizes some of the data on which the elucidation of the configuration at C-20 rests. It lists the molecular rotations of some configurationally related steroids, obtained by substituting a C-20 hydrogen in pregnane (IV, R=H) by a side chain. It also lists the molecular rotations of some corresponding trisubstituted methanes (V).



IV



V

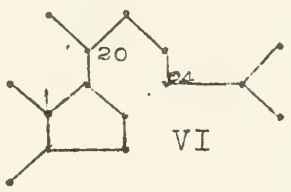
Table III

| R | $M_D$ of IV | $M_D$ of IV-58° | $M_D$ V | Marker's Number |
|---|---|---|---|---|
| H | +58° | 0 | -- | -- |
| $(CH_2)_3CH(CH_3)_2$ | +97° | +39° | (+28°) | (~9) |
| $(CH_2)_2CO_2H$ | +79 | +21° | +17° | 5 |
| $CH_2CO_2H$ | +84 | +26° | +17 | 19 |

The contribution which the C-20 carbon makes to the molecular rotation of the whole molecule is approximated by subtracting the molecular rotation of pregnane (+58°) from the total rotation. The figures in parentheses are for methylethylisopropylmethane. On the basis of Tschugaeff's Rule and Marker's data, the molecular rotation of the isohexyl derivative should also be about +30°.

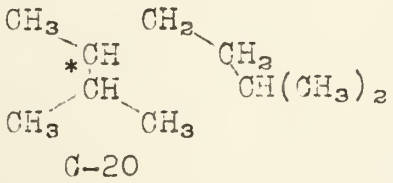
It should be noticed that C-20 is secondary in pregnane but tertiary in all the other cases listed. Since C-20 is not separated by at least two methylene groups from C-17, changing C-20 from secondary to tertiary might be expected to change the contribution of C-17. Thus a change in the contribution of the whole pregnane ring system to some value other than +58° might be expected. Since the molecular rotation of 20-methylpregnane is not available (IV, $R=CH_3$), the mean value of the molecular rotations of methyl norcholanate (+70°) and its C-20 epimer, methyl 20-isonorcholanate (+60°) was used (+65°). The use of the mean value of the molecular rotations of these esters is an improvement over the use of the molecular rotation of pregnane because these esters have a tertiary C-20 carbon. In addition, in the epimeric esters, the contribution by C-20 to the total molecular rotation of the molecule is small (+5°) because the "chromophoric power" of the $CH_2CO_2CH_3$ group is close to that of the isopropyl group and thus the "effective asymmetry" at C-20 is low. By subtracting 65° (rather than 58°) from the isohexyl derivative in table III, +32° is obtained for the contribution of C-20. This figure is in close agreement with the expected value (ca.+30°). Using 65° for the contribution of the ring system in cholanic and norcholanic acids (Table III, $R=(CH_2)_2CO_2H$ and $CH_2CO_2H$ respectively) values of +15° and +19° are obtained. The average of +17° for the contribution of C-20 in these two acids is in very good agreement with the rotations of the corresponding trisubstituted methanes (+17°).

It has been shown that C-20 and C-24 each make contributions of about +30° to the total molecular rotation of steroids which have the side chain shown below (VI).



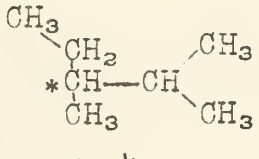

VI

In addition, it has been shown that these two side chain carbons may be considered to be very similar to the two substituted methanes VII and VIII.



C-20

VII

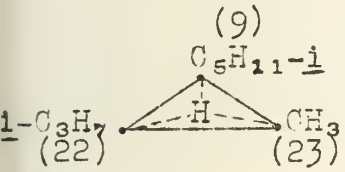


C-24

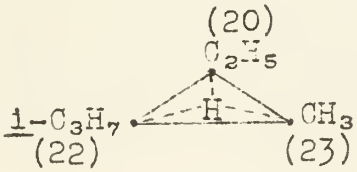
VIII

By making use of Marker's data, we may now relate each of these carbons configurationally to lactic acid and thus to the sugar series. By Marker's Rule, since both carbons have a positive rotation, we must draw them with the ordinal numbers of the various substituents increasing in a counterclockwise direction.

C-20

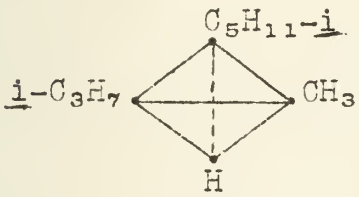


C-24

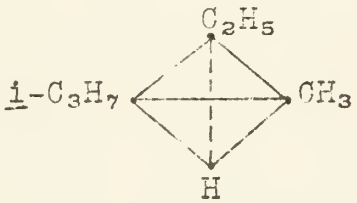


23: $CH_3$
20: $C_2H_5$
22: $C_3H_7$-i
9: $C_5H_{11}$-i

The absolute configuration based on the Fischer convention for sugars will therefore be:

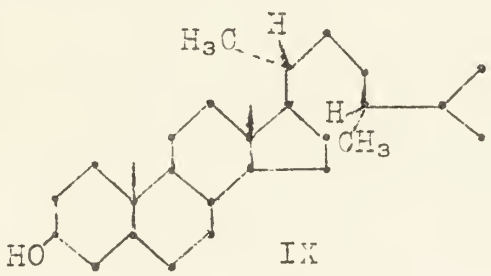


C-20



C-24

And structure IX may be written for campestanol where the hydrogens are above the plane of the paper and the methyl groups are below.



IX

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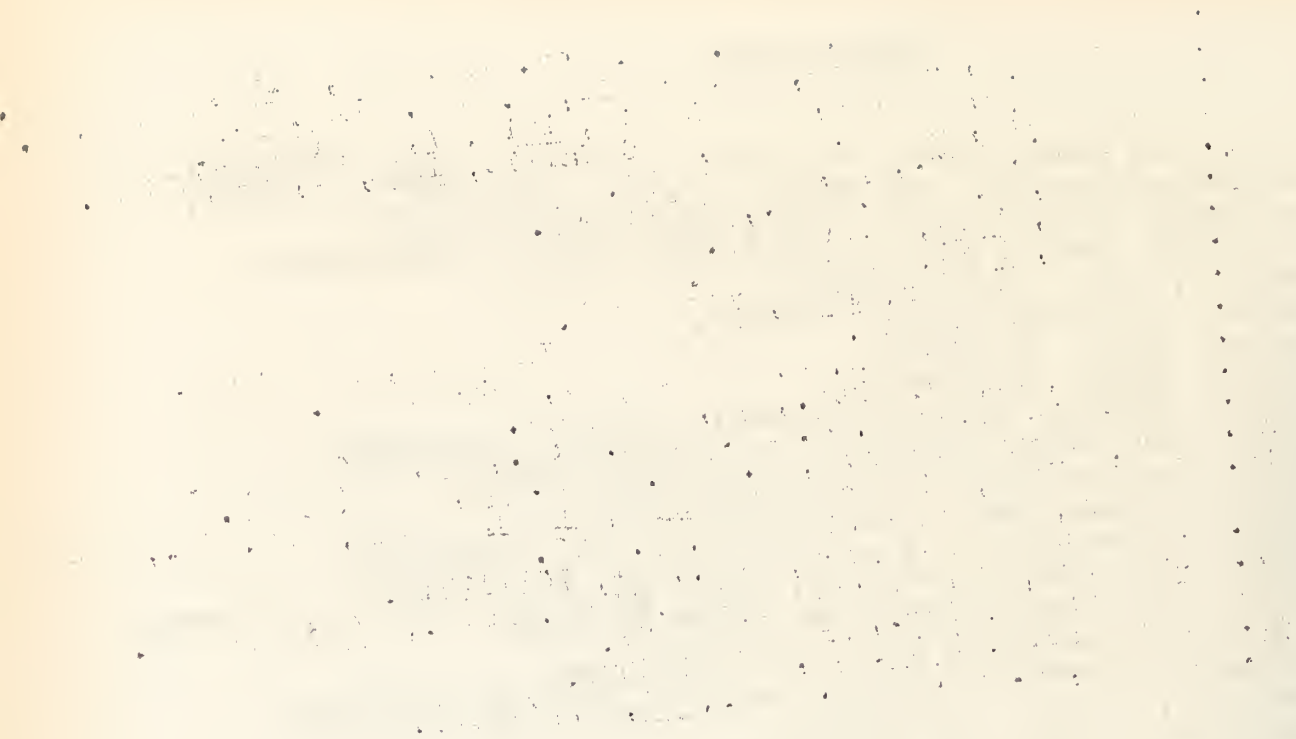
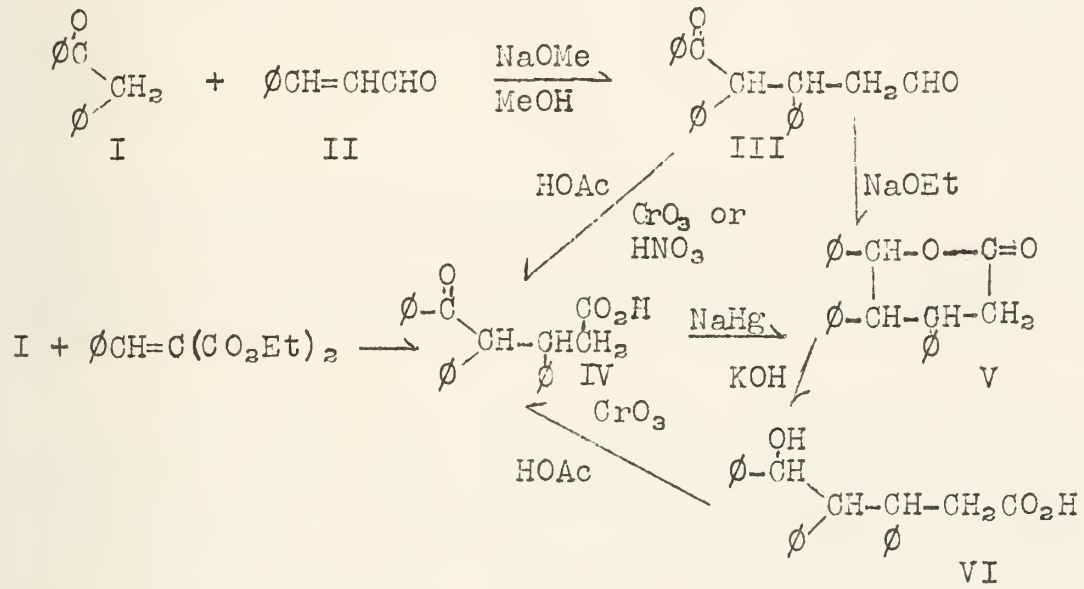


# CONJUGATE ADDITION TO ALDEHYDES

Reported by Robert W. Hill March 21, 1952

It is generally known that α,β-unsaturated aldehydes, like other aldehydes, show a strong tendency to take part in aldol-type condensations with active methylene compounds in the presence of basic catalysts. However, little thought has been given to the possibility of reversing the aldolization reaction, and thus enabling conjugate addition to occur.

Many conjugated aldehydes have been condensed with active methylene compounds, almost always giving typical Knoevenagel reaction products. In a few cases, however, 1,4 addition products have been obtained. Meerwein,[1] in studying the "carbobenzonic acids" discovered by Zagoumenny,[2,3] found that desoxybenzoin, in the presence of small amounts of sodium methoxide, would add 1,4 to cinnamaldehyde, crotonaldehyde, 2-methylpentenal, and acrolein to give the corresponding δ-ketoaldehydes. These compounds with the exception of the product obtained from acrolein, were readily isomerized by sodium methoxide to δ-lactones.[5]

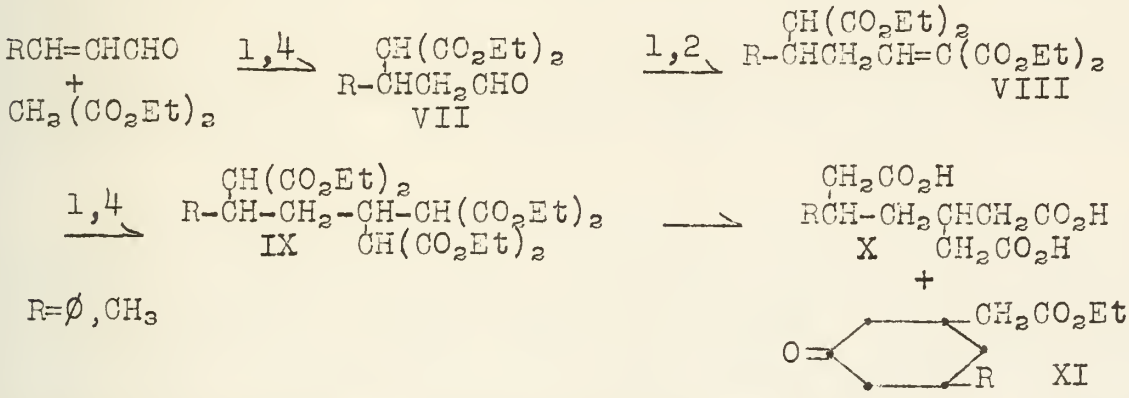



They were identified by oxidation with chromic oxide or nitric acid to the corresponding acids and synthesis of these acids via the condensation of desoxybenzoin and the appropriate malonic ester. Reduction of the ketoacid, IV, with sodium amalgam gave a lactone isomeric with that obtained by disproportionation of the aldehyde. Both of these lactones were hydrolyzed with potassium hydroxide to isomeric acids, VI. Chromic oxide oxidation of either acid produced the same keto-acid, IV.

It was also found that aldehydes would add 1,4 to unsaturated carbonyl compounds, including aldehydes. Phenylacetaldehyde and cinnamaldehyde, with a little sodium methoxide, gave β,γ-diphenyl-δ-valerolactone, the disproportionation product of an intermediate dialdehyde. A similar lactone was obtained from isobutyraldehyde

and 2-methylpentenal or cinnamaldehyde.[6] Since all of these condensations were run in alcoholic solution, the predominance of conjugate addition over aldolization was attributed to hemiacetal formation of the aldehyde.

Crotonaldehyde and ethyl malonate reacted in the presence of a few drops of sodium methoxide, but the reaction products could not be isola ted. When they used molar amounts of catalyst, however, they obtained an addition product containing three molecules of malonate. This reaction was exactly analogous to the reaction observed by Meerwein much earlier with malonate and cinnamaldehyde.[8] This reaction can be considered to be a 1,4 addition followed by 1,2 addition, followed by 1,4 addition to the resulting ester (cf. Ref.4).

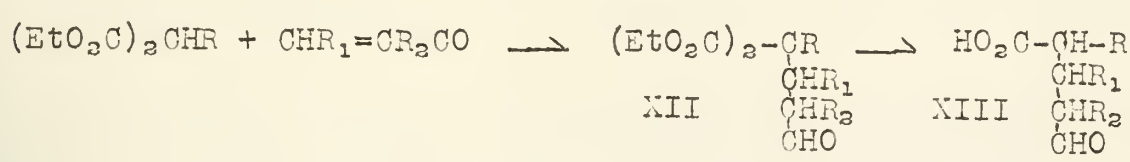


From crotonaldehyde the products obtained were the acid, X, and the cyclohexanone derivative, XI, resulting from a Dieckmann closure of IX. Meerwein isolated the tris-malono derivative, IX, which he could cyclize to XI. He also obtained IX from the reaction of malonate and cinnamalmalonate.

At temperatures over 200° in the presence of alkali, α,β-unsaturated aldehydes are converted to a complex mixture of products.[5,9] 2-Ethylhexenal underwent cleavage of the double bond to produce n-butyraldehyde, in addition to various disproportionation products. The butyraldehyde then condensed 1,4 with unchanged ethylhexenal. The resulting dialdehyde underwent disproportionation, giving a lactone corresponding to V. α,γ-diethyl-β-n-propyl-δ-valerolactone was isolated from the mixture in 35% yield. 2-Methylpentenal and a mixture of 2-methylpentenal and isobutyraldehyde gave similar products under these conditions, but the yields were very low. At the high temperatures, aldolization is largely reversed, allowing conjugate addition to proceed to a greater extent.

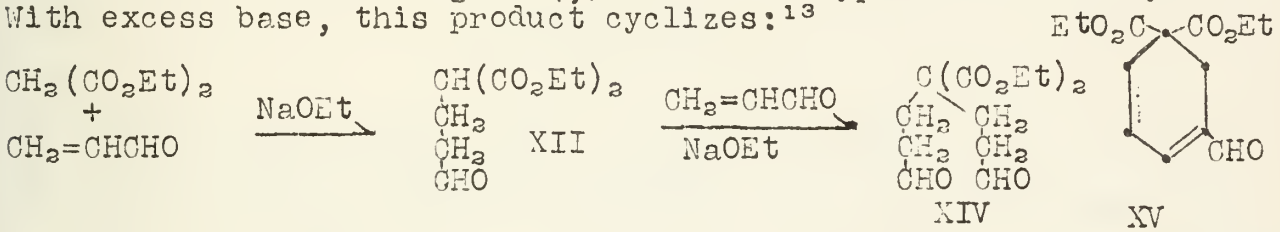
The tendency toward aldolization was overcome by Moe and Warner in another manner. They reasoned that if the active methylene compound had only one active hydrogen atom, dehydration of any aldol formed would be impossible. The equilibrium of the reaction would then be shifted back toward the free aldehyde, thus permitting 1,4 addition to occur. Accordingly, they condensed

several substituted malonate systems with acrolein. Ethyl acetamidomalonate, ethyl phthalimidomalonate, and ethyl acetamidocyanoacetate gave 1,4 addition products in 80-85% yields.[10] The reactions were run at 0° with a small amount of sodium ethoxide in



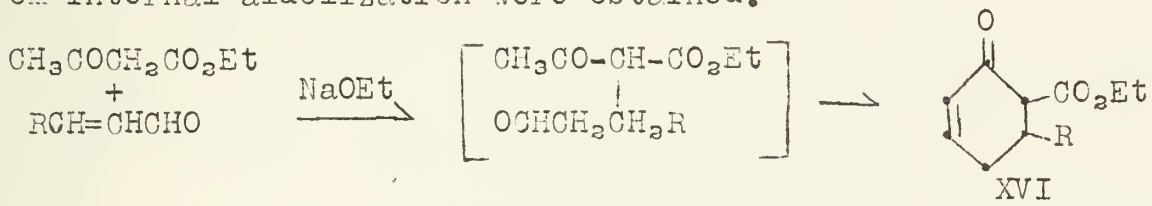
alcohol. The reaction was then extended to substituted acroleins. Crotonaldehyde and methacrolein reacted with acylamidomalonates in equally good yields of 75% to nearly theoretical.[11] Ethyl alkylmalonates (R=ethyl, hexyl, decyl) gave somewhat lower yields.[11,12] In the presence of sodium ethoxide, the product arising from acrolein and ethyl bromomalonate lost hydrogen bromide to give 4,4-dicarbethoxybutenal. When tributylamine was used as the catalyst, however, the normal 1,4 addition product was obtained.[12]

It was found that 1,4 addition was not restricted to malonate systens containing only one α-hydrogen atom. Both ethyl malonate and ethyl cyanoacetate reacted 1,4 with acrolein in 50% yield.[12] It was possible for the resulting aldehydo compounds to add a second mole of aldehyde. Thus, γ,γ-dicarbethoxybutyraldehyde reacted with acrolein to give γ,γ-dicarbethoxypimelic dialdehyde. With excess base, this product cyclizes:[13]



The corresponding cyano compound was obtained from cyanoacetate and acrolein. When methacrolein and malonate were used, the cyclic product formed could not undergo dehydration, and the carbinol was isolated.

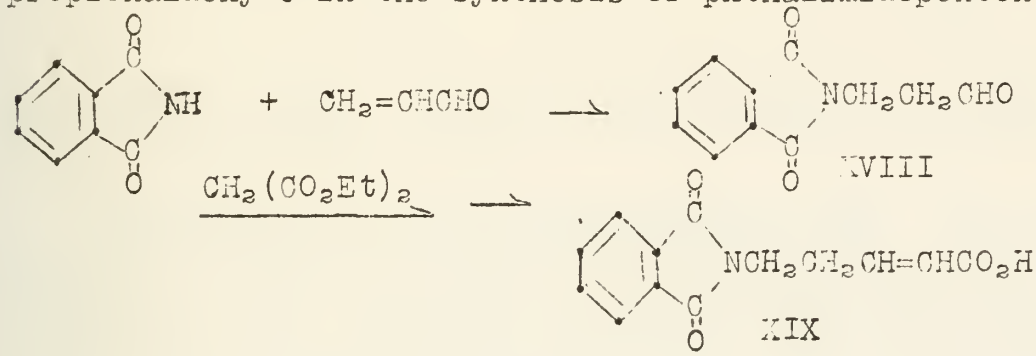
Ethyl acetoacetate has also been condensed in the 1,4 manner. With crotonaldehyde or cinnamaldehyde, cyclohexenones resulting from internal aldolization were obtained.[14]



Conjugate addition to aldehydes has proven to be quite general Very recently, primary and secondary nitroparaffins have been added to acrolein, methacrolein, and crotonaldehyde.[15] 2-Nitropropane was used first, since it possesses only one α-hydrogen atom. 1-Nitropropane was then used with equal success. Conditions were

essentially the same as in the malonate reactions. The yields were only about 30%, however.

Phthalimide and succinimide have also been found to condense smoothly with acrolein, crotonaldehyde, and methacrolein.[16] Yields of the phenylhydrazones ranged from 40 to 80 per cent. A modification of this reaction, using Triton B as the catalyst and pyridine as the solvent, proved superior to the Rosenmund reduction of phthalimidopropionyl chloride as a preparation of phthalimidopropionaldehyde in the synthesis of phthalimidopentenoic acid, XIX.[17]



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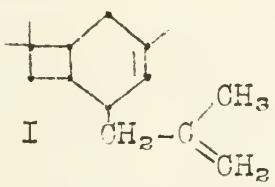
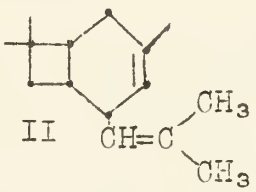
# THE CARYOPHYLLENES

Reported by John F. Walker March 21, 1952

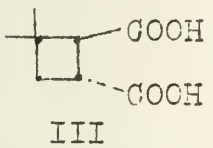
Introduction. The three caryophyllenes(α-β-γ-) are the most widely occurring sesquiterpenes with the exception of cadinene. Little is know about the α-form, and much of the early work was hindered due to lack of homogeneity of the starting materials. Until quite recently structures I and II were the most acceptable for the caryophyllenes as they accounted for all the ozonolysis products (1).




Recent evidence indicates the presence of a 9-membered ring in the caryophyllenes. No other natural product is known to contain such a ring system (2,3,4).

Evidence for the dimethylcyclobutane ring. The presence of a dimethylcyclobutane ring in the caryophyllenes is indicated by the occurence of this ring system in degradation products. Vigorous oxidation of the caryophyllenes gives, among other things, two cyclobutane acids which have been identified and synthesized. These acids are (+) trans-norcaryophyllenic acid, III, and (+) trans-caryophyllenic acid, IV (5,6,7). Ozonolysis of caryophyllenes gives two major products, $C_{11}H_{18}O_3$, a keto acid, and $C_{14}H_{22}O_4$, a diketo acid, both of which contain a methyl ketone group. The $C_{11}H_{18}O_3$ acid was shown to have the structure V since on treatment with sodium hypobromite it was converted to homocaryophyllenic acid, VI, whose structure was proved by synthesis. On oxidation with potassium permanganate, it was converted to caryophyllenic acid, IV. Further, β-caryophyllene nitrosite and γ-caryophyllene on oxidation both yielded definite products, one of which was shown to be V (8,9).



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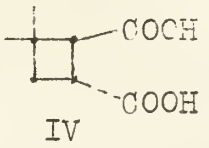
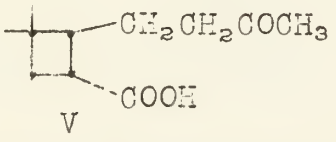
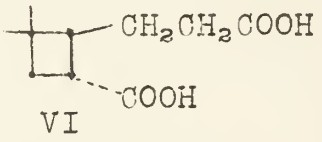


IV



V



VI

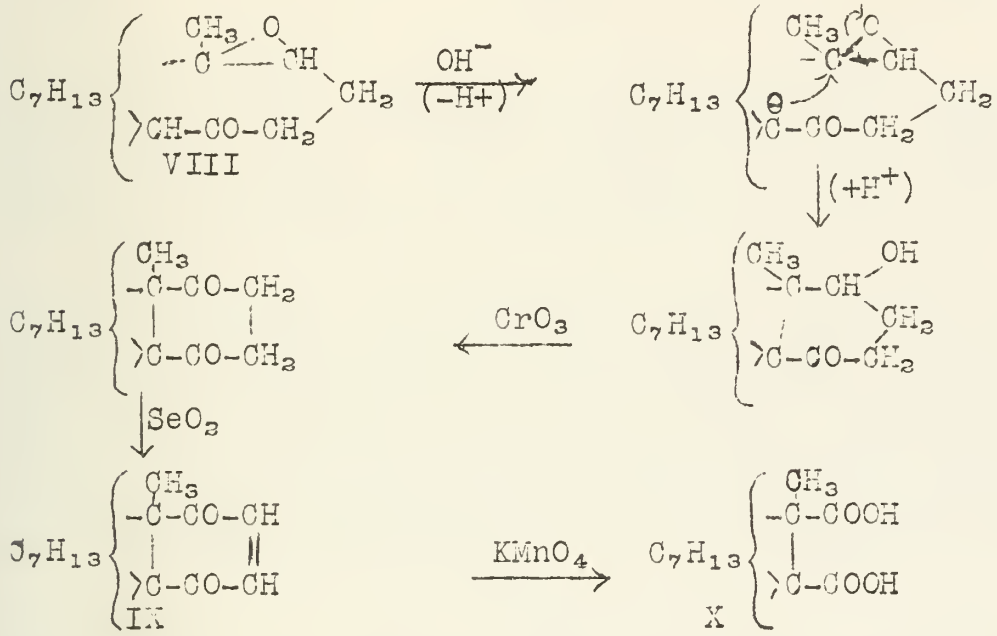
Evidence for the 9-membered ring. Initial indication of a 9-membered ring was provided by a study of the infra-red absorption spectrum of the molecule (2) and its presence has now been substantiated by chemical evidence.

One of the major problems in elucidation of the structure of caryophyllene was the difficulty of obtaining a homogeneous starting material. One way of doing this was by use of the product of autoxidation of caryophyllene, $C_{15}H_{24}O$, which can be obtained pure. This epoxide on treatment with potassium permanganate yielded a carbonyl compound, $C_{14}H_{22}O_3$, VII. It has been know for some time that caryophyllene was a bicyclic compound containing two double

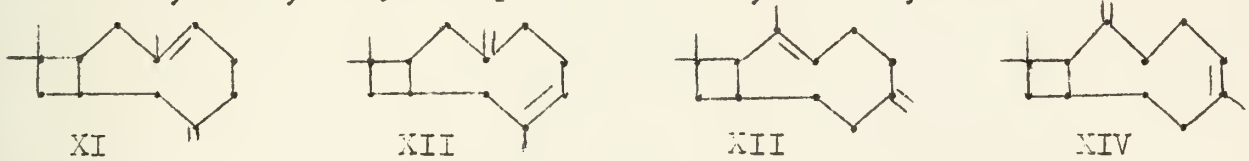
bonds. Obviously, the epoxide formation must have been on the (a)

(a) $-\overset{CH_3}{\overset{|}{C}}=CH-$ (b) $>C=CH_2$

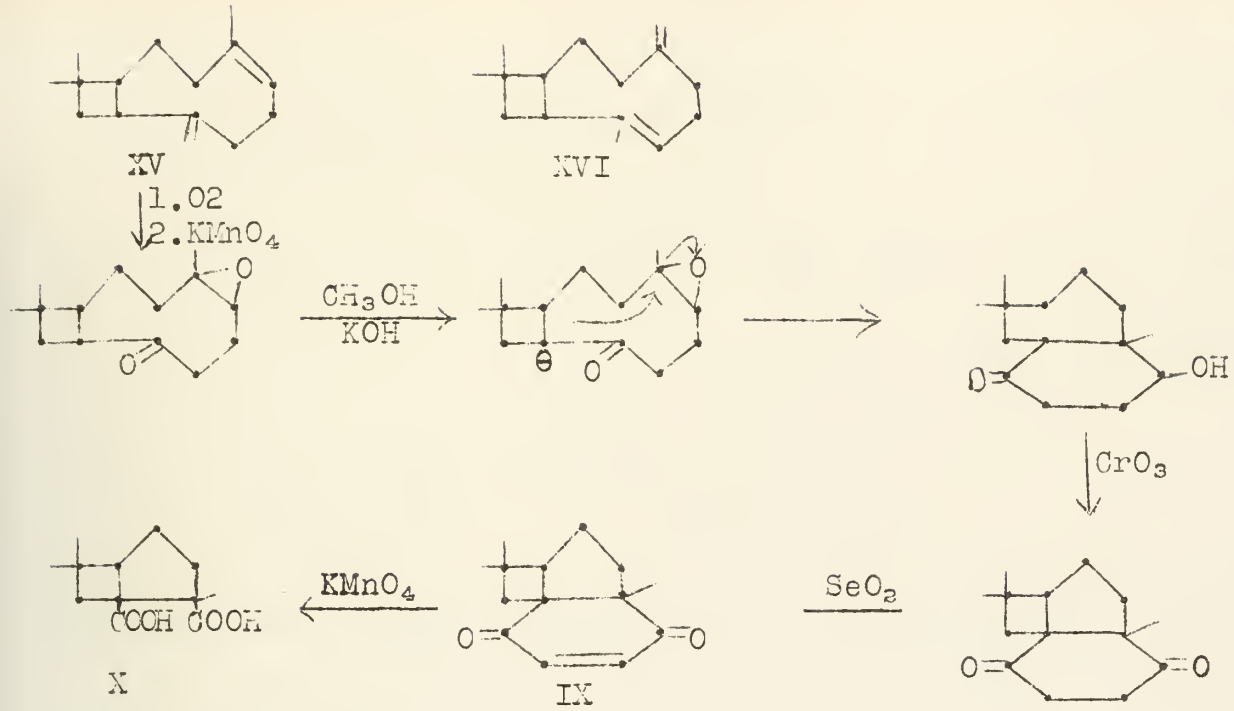
double bond since only the (b) double bond could form a ketone involving only the loss of one carbon atom. This oxido ketone, when refluxed with methanolic potassium hydroxide, isomerized to a substance whose infra-red absorption spectrum showed the presence of one hydroxyl group and one carbonyl group, and indicated that the molecule was saturated, and therefore tricyclic. Oxidation of this isomer afforded a diketone which on further oxidation with selenium dioxide gave an unsaturated diketone, $C_{14}H_{18}O_2$, IX. The absorption spectrum of this compound ($\lambda$max. 221, 367, and 369mu. $\varepsilon$max. 14,700, 100, and 100 respectively) indicated the presence of the chromophore, CO-C=C-CO, in the cisoid configuration. The presence of this group was confirmed by oxidation of the material to a substituted succinic acid, X, which readily formed an anhydride. The course of these reactions can be pictured as follows (4).



Since there is also a dimethylcyclobutane group in the molecule there are, then, only six possibilities, XI-XVI, for the molecule.

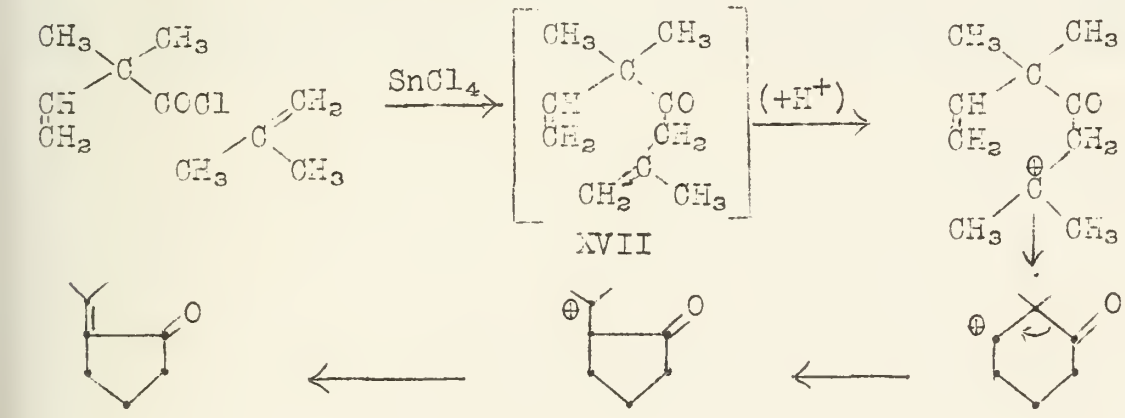


XI XII XII XIV



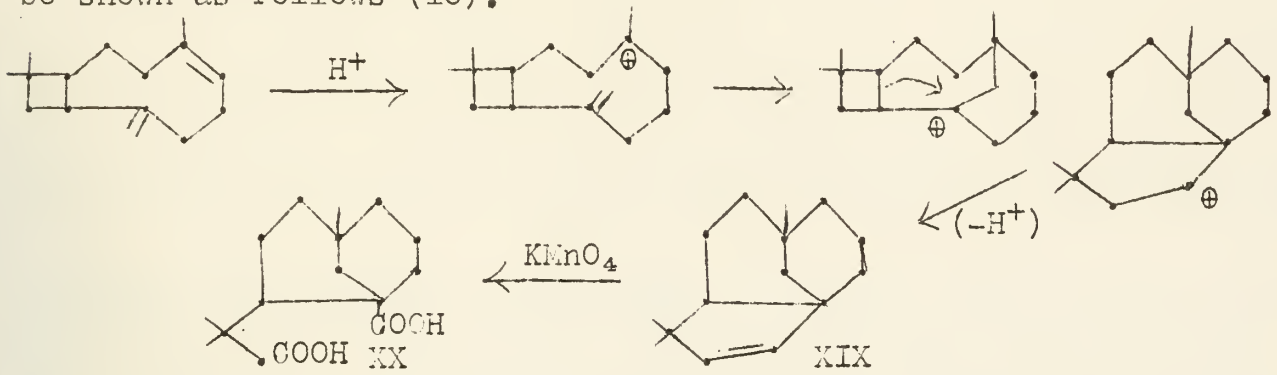

The isolation of homocaryophyllenic acid, VI, and the keto acid, V, from oxidation experiments on caryophyllenes indicates that structures XV and XVI should represent the structures of β- and γ-caryophyllene (8,9). Some confirmation of this postulate is provided by consideration of the mechanism of the acid catalysed isomerization of caryophyllene (10).

Treatment of β-caryophyllene with concentrated sulfuric acid gives a tricyclic sesquiterpene, called clovene, containing one double bond and a dimethylcyclopentene ring. Oxidation converts clovene to an extremely resistant dicarboxylic acid containing all the carbon atoms of the clovene molecule. The mechanism of this isomerization has been related to the cyclization of artamesiaketone, XVII, to cycloartamesiaketone, XVIII, under the influence of an acid catalyst. The mechanism of this reaction is shown in the following sequence (11).




XVIII

Assuming that this mechanism is applicable to the acid catalyzed isomeration ofβ-caryophyllene, the reaction of structure XV to give clovene, XIX, which on oxidation could give clovenic acid, XX, can be shown as follows (10).




Only structure XV seems compatible with the mechanism proposed above for the acid catalysed isomerization of β-caryophyllene to clovene.

The evidence indicates that β- and γ- caryophyllene have structures corresponding to XV and XVI.

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# POISONING OF METALLIC CATALYSTS

Reported by Glenn Fuller March 28, 1952

Introduction: Poisoning of metallic catalysts, especially in hydrogenation and dehydrogenation reactions has long been a cause of trouble to organic chemists, although in a few cases, the poisoning has had a beneficial effect. This poisoning is a result of a preferential adsorption in which abnormally strong types of bonds are formed between a catalyst and certain types of adsorbed species which are usually foreign to the reacting system. True poisons are substances which inhibit reactions even at very low concentrations; thus, coatings of gums or waxes are not to be considered as poisons.

Catalysts susceptible to poisoning: Catalysts which are most often poisoned are the metals of the eighth group of the periodic table with extensions to the metals of group Ib. These metals include Fe, Co, Ni, Cu (Atomic nos. 26, 27, 28, and 29), Ru, Rh, Pd (44, 45, and 46), Os, Ir, and Pt (76, 77, and 78). Silver and gold are also susceptible to poisoning, although these metals are seldom used, due to their low catalytic activity. In general, high susceptibility to poisoning is limited to these metals and their oxide complexes (e.g. nickel chromite). However, in some special cases, metals other than the ones listed above and some non-metallic catalysts may be poisoned (1).

Factors influencing toxicity: In general, the toxic effect of a poison is dependent upon the average length of stay of the poison molecules on the catalyst surface and upon the area or effective coverage by the poison molecules. In order for a substance to be toxic at all, the adsorbed life must be relatively long. Therefore, the low ratio of desorption to adsorption is the factor which causes small amounts of poisons to have such a large toxic effect. The toxicity of many organic compounds (e.g. those which owe their toxic effect to a sulfur or nitrogen atom) is a direct function of the size or chain length of the non-toxic part of the molecule. Thus, the toxic atom may be considered as an anchor or pivot around which the nontoxic remainder of the molecule may revolve, effectively preventing the approach of other molecules (2). For this reason, molecules tied down at two points by two toxic atoms may be less powerful poisons that those containing only one toxic atom per molecule (3).

For obvious reasons, catalysts having a higher specific surface are less sensitive to a given amount of poison than are those catalysts with a low specific surface. At moderate temperatures, an increase in temperature produces little effect, although it should tend to reduce sensitivity by increasing the rate of poison desorption.

The form of catalyst poisoning curves: In many cases the activity of the catalyst varies with poison content as shown in figure I. There is at first a linear variation in which catalytic activity is

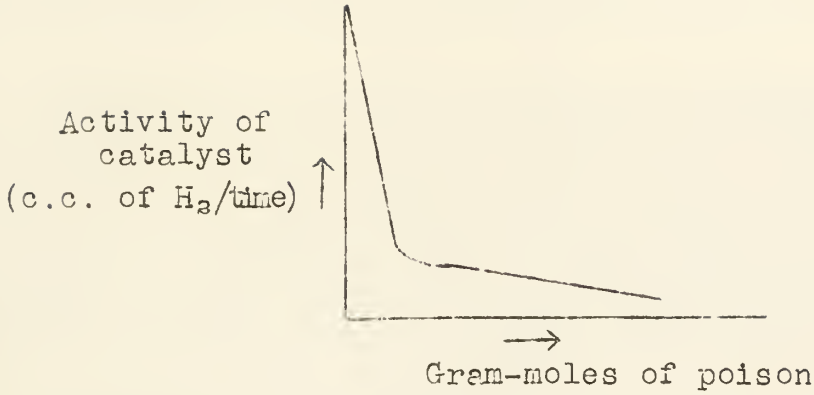


Fig. I

inversely proportional to poison content; then, there is a fairly sharp inflection in the curve. Herington and Rideal (4) have proposed a mathematical derivation for such a relationship. In such cases, the effect of the poison up to the inflection point may be represented by the expression, $k_c = k_o(1-\alpha c)$, in which $k_o$ is the original activity of the catalyst, $k_c$ is its activity at concentration $c$, of the poison, and $\alpha$ is a coefficient representing the specific effect of each unit of poison (1). The values of $\alpha$ for a series of poisons may be used to compare their toxicity toward a given catalyst.

Prinicple types of poisons:

A. Non-Metallic elements of groups Vb and VIb: Compounds of the elements of group Vb (N, P, As, and Sb) and VIb (O, S, Se, and Te) have been shown to be poisonous only if the potentially toxic element still contains unshared external electron pairs or unused valency orbitals. These unshared electrons make possible a chemisorptive bonding to the transition metal catalyst. For example, hydrogen sulfide, phosphine, sulfite ion, organic thiols and organic sulfides are toxic to metallic catalysts, while phosphate ion, sulfate ion, sulfonic acids and sulfones are not (1). Shielded compounds of arsenic and antimony (i.e. arsenates and antimonates) are so easily reducted to arsine and stibine, however, that all ordinary compounds of these two elements are toxic in catalytic hydrogenation reactions. Nitrogen and oxygen are not so strongly toxic as the other elements in this class. However, dry pyridine and dry ammonia both slow down the hydrogenation of cyclohexene over platinum (5). The reduction of pyridine, itself, has been facilitated by addition of an acid promoter which produces shielded pyridinium ions. A recent investigation has shown that molecular oxygen diminishes the catalytic activity of Raney nickel (6).

The bond by means of which these poisons are linked to the metallic catalysts resembles the simple coordinate covalent bond in which the poison is the donor of electrons. The free electrons of the donor element enter the d-band of the adsorbing metal, thus

filling up the deficiencies in the d-band which seem to be responsible for the catalytic activity of the transition metals (1,7).

B. Poisoning by compounds containing halogens: The halogen acids and organic halides have unshielded electrons which might also be expected to cause catalyst poisoning. Adkins has recommended refluxing of hydrogenation mixtures over Raney nickel to remove traces of halogen compounds (8). Pattison and Degering (9) have investigated the poisoning of Raney nickel by HCl and by organic halides. In general, the relative poisoning effect increases in the order Cl<Br<<I. These investigators found little correlation between chain length and toxicity.

C. Poisoning by toxic metals: Platinum and palladium are particularly affected by poisons of this type. The presence of heavy metals such as mercury, lead, bismuth and tin and also of zinc, cadmium, copper or iron inhibits greatly the catalytic activity of palladium and platinum. Maxted (10, 11) has shown that these metals and their ions, which are also toxic have all five orbitals of the d-shell immediately preceding s or p valency orbitals occupied by electron pairs, or at least by a single electron. The toxic metal may donate electrons from the d-shell for coordnate covalent bonds with the catalyst in a manner analogous to that of poisoning by sulfur compounds.

D. Poisoning by molecules containing multiple bonds: These poisons are different from the others in that unsaturated compounds are the substances normally subjected to reduction. The adsorption of unsaturated linkages varies greatly, so that one unsaturated compound may inhibit completely the hydrogenation of another. For example, small amounts of benzene retard the reduction of cyclohexene over nickel or platinum. Carbon monoxide and cyanides are especially strong poisons of this sort. Carbon monoxide, however, can be made non-toxic either by reduction to methane or by oxidation to carbon dioxide.

Detoxication: The elements of groups Vb and VIb may be treated in such a way as to give them a shielded structure. Maxted (12, 13, 14) has converted cysteine into cysteinic acid by using small amounts of perphosphate, pertungstate, permolybdate or pervanadate. Hydrogenation of crotonic acid was then easily accomplished without removal of the cysteinic acid. Maxted (15) has also proposed a method of removal of thiophene from benzene by passing the benzene through a filter column of platinum black. The column, itself, was then revived by passing through hydrogen to convert the thiophene to thiophane and subsequent treatment with per acids to form thiophane sulfone. Most other methods of detoxication involve a prehydrogenation or refluxing with Raney nickel and removal of the spent catalyst before the final hydrogenation. In this connection, it has been found that many spent catalysts of nickel and platinum may be revived by treatment with per acids and subsequent reduction (1).

Beneficial poisoning: A well-known example of beneficial poisoning

is the Rosenmund-Zetsche aldehyde synthesis. Small amounts of poison on a palladium catalyst prevent the complete reduction of the acid chloride to a methyl group. Traces of oxygen have also been found to be necessary for hydrogenation of phthalic anhydride over platinum black (16). Lukes and Wilson (17) have shown that nickel-copper catalysts can be varied in composition in such a way as to give maximum yields of furfuryl alcohol or furan from furfural and that iron-copper catalysts can be used to give good yields of methylfuran from furfuryl alcohol. These authors have proposed that the copper donates s-electrons to fill or partially fill the d-shell of the nickel or iron. This poisoning diminishes the undesirable side reactions, such as ring opening or hydrogenation of the furan nucleus.

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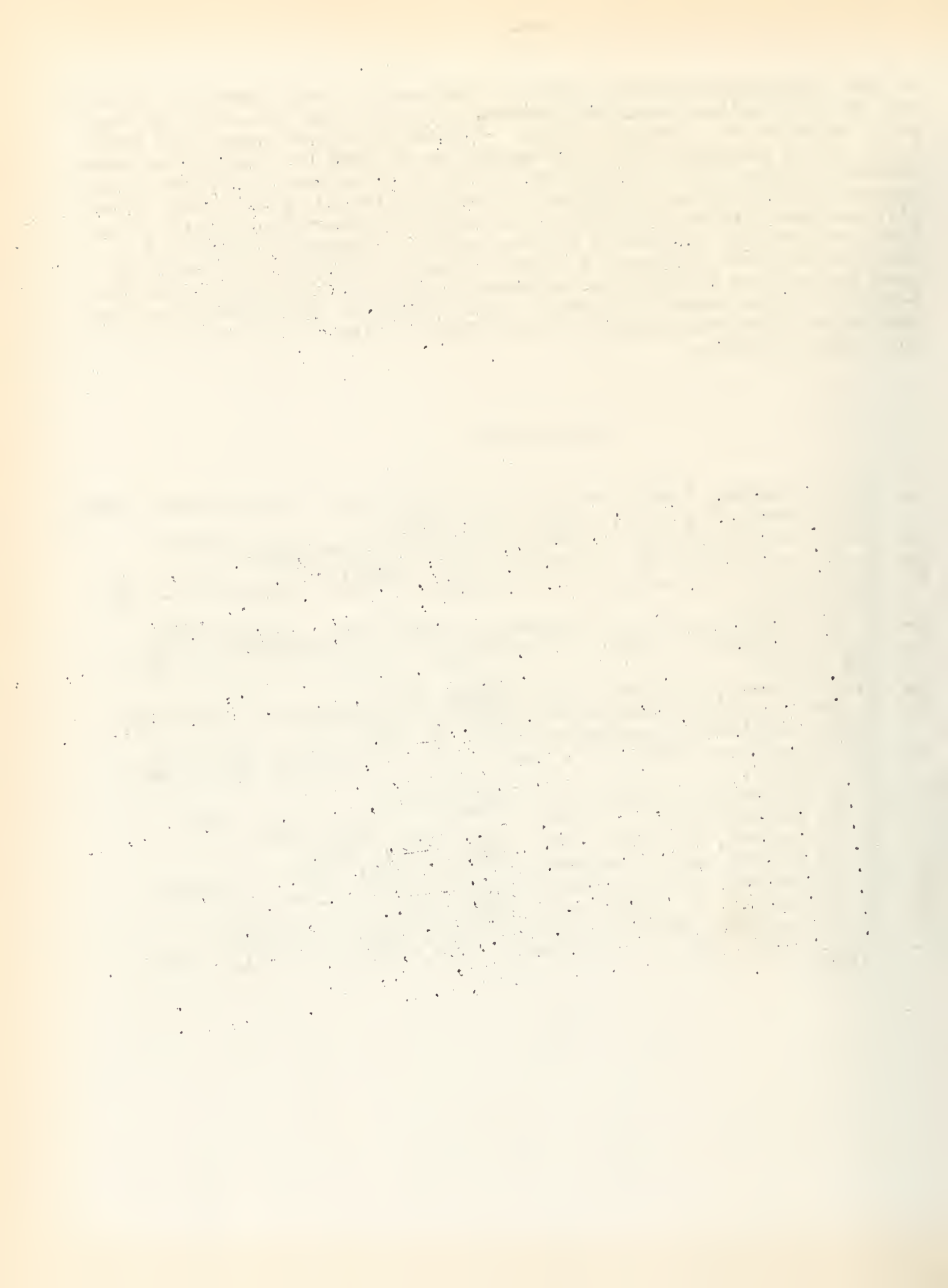
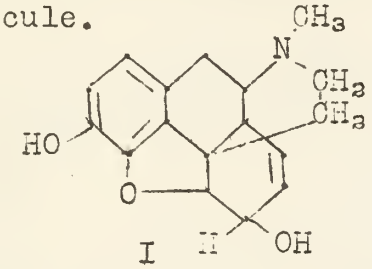


# THE SYNTHESIS OF MORPHINE

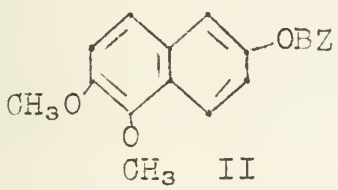
Reported by John W. Way March 28, 1952

The problem of the structure of morphine has attracted much attention in the past seventy years. In spite of the exhaustive investigation of this alkaloid, the entire structure has been certain only since 1950. This structure was originally proposed by Gulland and Robinson (1) in 1923, but has been without direct experimental proof until this year. The least certain point has been the position of attachment of the ethanamine bridge (2,3). Gates and Tschudi recently (4) reported that they had completed a synthesis of morphine and found that structure I is a true representation of the morphine molecule.




I

The synthesis was accomplished in the following manner. 2,6-Dihydroxynapthalene, derived from Schaeffer's acid (5), was the starting material. The monobenzoate was obtained by the use of benzoyl chloride and pyridine. Nitrosation with acetic acid and sodium nitrite gave 1-nitroso-2-hydroxy-6-benzoyloxynapthalene, which was reduced catalytically over palladium on charcoal to the aminonapthol. Ferric chloride oxidized this to the napthoquinone. Sodium hydrosulfite reduction produced the hydroquinone which was then methylated by dimethyl sulfate and potassium carbonate to give II. Aqueous potassium hydroxide saponified II to the napthol, and

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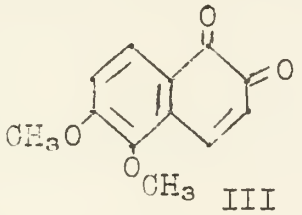


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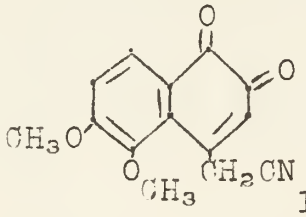
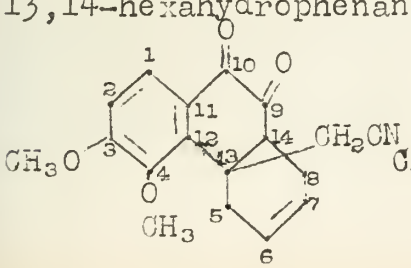



IV

this was then subjected to the series of reactions just given, III resulting. Ethyl cyanoacetate and III were reacted in the presence of triethylamine, a Michael condensation occurring to form the dihydronapthoquinone, which was oxidized with potassium ferriyanide. Claisen's alkali hydrolyzed and decarboxylated the cyanoacetate to give IV. A Diels-Alder reaction of IV and butadiene resulted in the formation of 3,4-dimethoxy-9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene, V, (6).

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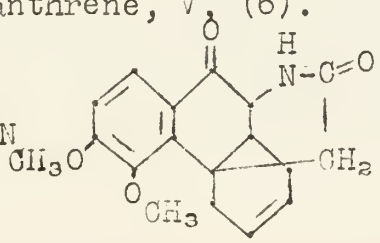


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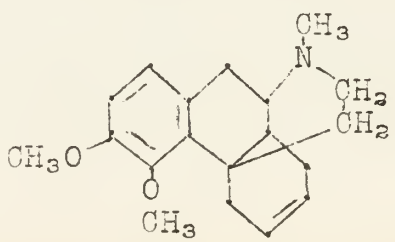
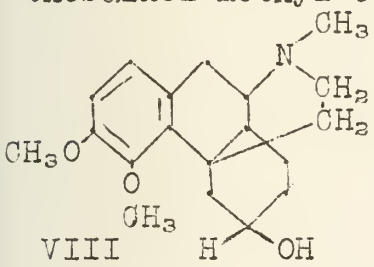



VII

Hydrogenation of V over copper chromium oxide gave the keto-lactam VI. The keto oxygen was removed by a Woelf-Kishner reduction, however, the basic treatment also cleaved the 4-methoxyl group, necessitating remethylation. The amide leakage was then reduced to a secondary amine with ithium aluminum hydride. Formaldehyde and formic acid methylated this substance to give $\Delta^6$-dihydrodesoxycodeine methyl ether, VII. This product can exist in two racemic forms, with reference to the configuration of the two brigde heat atoms, $C_{13}$ and $C_{14}$. Infrared comparison with authentic samples of the epimers showed that the β-form had been obtained. The prefix β refers to a configuration at $C_{14}$ epimeric with that of morphine (4,7), and the ring fusion in this compound is trans.

Resolution of the racemate with L(+)-dibenzoyltartaric acid gave the salt of the d-β-dihydrodesoxycodeine methyl ether. Hydration of the d- base with dilute sulfuric acid gave β-dihydrothebainol methyl ether, VIII.



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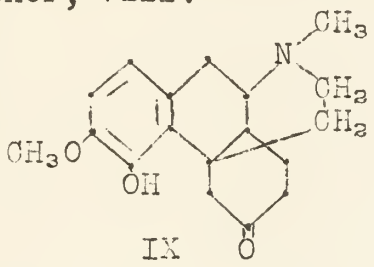

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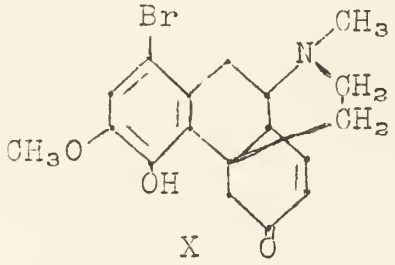
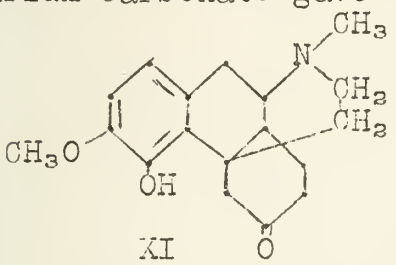
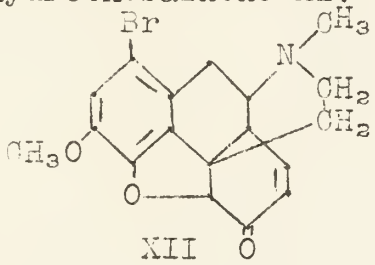


X

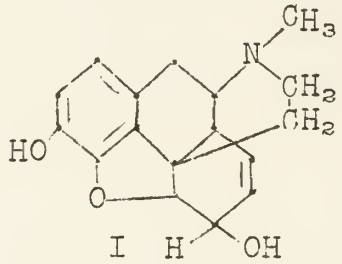
Vigorous treatment with potassium hydroxide in diethylene glycol cleaved the 4-methyl ether to β-dihydrothebainol. Potassium t-butoxide and benzophenone oxidized this to β-dihydrothebainone, I . Treatment with two moles of bromine followed by treatment with 2,4-dinitrophenylhydrazine yielded a dinitrophenylhydrazone which also results from β-thebainone or from thebainone by the action of 2,4-dinitrophenylhydrazine followed by bromination, thus epimerization had also occurred. Acetone and acid cleaved the hydrazone to 1-bromothebainone, X. Catalytic reduction over palladium on barium carbonate gave dihydrothebainone XI.



XI



XII



I

Bromination of XI with three moles of bromine, followed by 2,4-dinitrophenylhydrazine produced 1-bromocodeinone 2,4-dinitrophenylhydrazone, which can be cleared with difficulty to the ketone XII. Lithium aluminum hydride reduces XII directly to codeine. Cleavage of the methyl ether by heating with pyridine hydrochloride (8) produces morphine, I.

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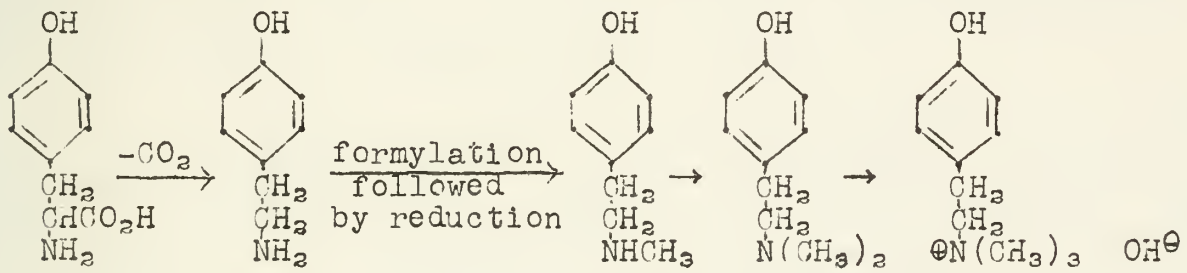
# THE BIOGENESIS OF ALKALOIDS

Reported by J. J. Sagura April 4, 1952

During a study of the route of synthesis of the alkaloid hordenine (N,N-dimethyltyramine) in barley roots it was discovered that certain strains produce N-methyltyramine and not hordenine (1). N-methyltyramine had never been isolated previously from a natural source. The isolation of N-methyltyramine indicates that the plant synthesizes this substance, and hordenine, by the methylation of tyramine through a mechanism similar to that known to exist in certain molds and in animals.

The origin of the N-methyl groups of alkaloids is as yet obscure. It has been postulated that they arise from formaldehyde (2) but there has been no direct experimental evidence for this route. It has also been postulated that the N-methyl groups of alkaloids may arise by a process of transmethylation (3). There is abundant evidence in the recent literature that formate is an extremely important intermediate in the metabolic processes of the higher animals (4,5) and bacteria (6,7). If one is prepared to accept the recent evidence that the folic acid group of vitamins functions as a carrier of formate (8) then it would follow that formate is an important metabolic intermediate in most, if not all, living cells.

Since the recently established synthesis of "labile methyl" in the rat proceeds by way of formate (9) one would expect that the methyl groups of choline and hordenine in the barley plant might arise from the same source. If this proved to be the case one would have reasonable evidence for postulating the following route for the biosynthesis of the alkaloids N-methyltyramine, hordenine and candicene.




tyrosine tyramine N-methyl-tyramine hordenine candicene

Kirkwood and Marion (10) studied the incorporation of labeled formate carbon into the methyl groups of both choline and hordenine by barley roots. Potassium formate labeled with $C^{14}$ was fed to sprouting barley, and choline and hordenine were isolated from the roots. Both of these substances bore the labeled carbon largely, if not entirely, in the methyl groups, as shown by means of degradation experiments.

Location of activity in choline and hordenine

| compounds | activity per millimole base per minute |
|---|---|
| choline chloroplatinate (degraded to) trimethylamine chloroplatinate | $1.47 \times 10^4$ / $1.39 \times 10^4$ |
| hordenine chloroplatinate (degraded to) trimethylamine chloroplatinate | $1.29 \times 10^5$ / $1.36 \times 10^5$ |

These results indicate that the N-methyl groups of these compounds originate from formate ions and that the synthesis of choline in barley proceeds by a route similar to that used in the synthesis of this material by the rat.

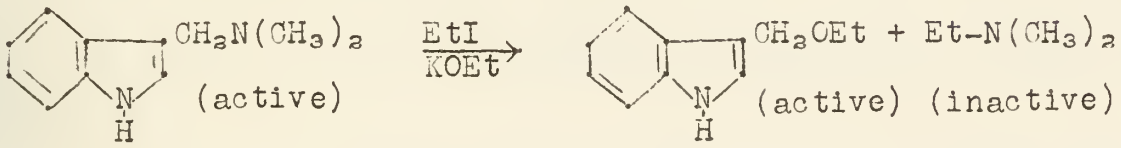
It may be argued that the synthesis of the alkaloid methyls in the above experiment proceeds from carbon dioxide produced from the formate fed rather than by formylation followed by reduction. Experiment showed, however, that when methyl-labeled choline was fed to barley the hordenine isolated had a negligible radioactivity in spite of the fact that the barley could rapidly oxidize these methyls to carbon dioxide. This experiment not only disposes of carbon dioxide as an intermediate but also shows that the N-methyl groups of hordenine do not arise by transmethylation from the choline-methionine system. It seems possible, therefore, that the formylation of amines, followed by reduction, is a general route for the synthesis of N-methyl groups in nature.

In another series of experiments (11) putrescine-1,4-$C^{14}$ was fed to mature Datura stramonium in an investigation of the biosynthesis of l-hyoscyamine. Although $C^{14}$ was metabolized by the plant, no radioactivity was found in the isolated alkaloid. These experiments do not lend support to the postulate of Cromwell(12) that putrescine is an intermediate in the biosynthesis of l-hyoscyamine in D.stramonium. On the other hand, in an investigation of this nature, positive evidence is far more valuable than negative evidence. All consideration of putrescine as a precursor of l-hyoscyamine, therefore, should not be dismissed.

In order to examine the possibility that tryptophan is a precursor of the alkaloid gramine in plants, Bowden and Marion (13) administered tryptophan labeled with $C^{14}$ in the β-position (of the side chain) to barley and degraded the alkaloid formed. The alkaloid isolated from the leaves remained radioactive after repeated purification, indicating that part of the tryptophan molecule had been utilized in the formation of the gramine. The active gramine

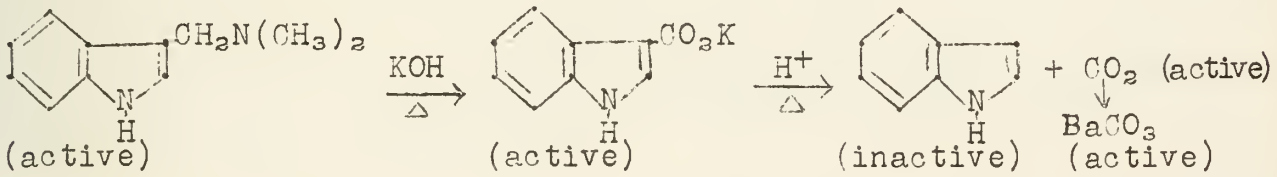
was diluted with inactive gramine and subjected to two series of degradations in order to determine the location of the radioactive atom or atoms in the molecule.

(a) Madinaveitia (14) has shown that gramine will undergo the following reaction:




Degradation of the alkaloid by this means yielded inactive ethyldimethylamine (picrate) and 3-ethoxymethylindole which had a molecular activity equal to that of the starting material, showing that the dimethylamino group in the original alkaloid contained no labeled atoms.

(b) It was found that fusion of gramine with potassium hydroxide gave the potassium salt of indole-3-carboxylic acid. The free acid yielded indole and carbon dioxide on heating and the latter was converted to barium carbonate by absorption in barium hydroxide solution.




In order to test for possible rearrangements which might occur under the rather drastic conditions of fusion with potassium hydroxide, a synthetic sample of gramine with $C^{14}$ in the side chain was submitted to the same treatment. The activities of the products from this material and from the natural alkaloid are given below.

| compound | natural | synthetic |
|---|---|---|
| gramine | $3.06 \times 10^4$ | $2.47 \times 10^4$ |
| indole-3-carboxylic acid | $3.03 \times 10^4$ | $2.48 \times 10^4$ |
| indole picrate | 0 | 0 |
| barium carbonate | $3.04 \times 10^4$ | $2.46 \times 10^4$ |

The activities of the products obtained from the fusion of synthetic gramine with potassium hydroxide show that no rearrangements occur. The results obtained from the degradation of the natural gramine indicate that only one atom in the alkaloid molecule was labeled. The position of this labeled atom in the alkaloid corresponds to

that of the $C^{14}$ in the tryptophan fed to the plants, strongly suggesting that tryptophan is a precursor of gramine in barley.

In order to study the assimilation of tryptophan by the plant and the accumulation of alkaloid in the plant, Bowden and Marion(15) administered the labeled amino acid to the plant and made radioautographs of the leaves harvested at regular intervals. The radioautographs showed that an active area appears at the bottom of the leaf on the first day (after feeding with $C^{14}$ labeled tryptophan acetate) and slowly extends upward on the second or third day. On the fourth day an active area makes its appearance at the top of the leaf and this area of concentration increases on the fifth and sixth days.

It has been shown by ultraviolet absorption studies that the concentration of gramine in a barley leaf increases toward the top of the leaf (16). It seems likely, therefore, that the area of activity in the lower part of the leaf may be due to tryptophan or a gramine precursor, while the area at the top of the leaves might be due to an accumulation of gramine.

The top section of a dried radioactive leaf, harvested six days after administration of tracer, was cut transversely separating the two areas of radioactivity as shown by radioautography. After extraction of the gramine and tryptophan from the two sections it was possible to show that approximately 58% of the activity in the area at the top of the leaf was due to free gramine, while approximately 77% of the activity of the lower part of the leaf was due to free tryptophan thus confirming that the radioactive areas were mainly concentrations of gramine and its probable precursor tryptophan, respectively.

By feeding labeled gramine (as acetate) to the barley, radioautographs were obtained showing active areas only at the bottom of the leaves, indicating that gramine does not tend to travel to the top of the leaf and accumulate there. It would appear then that the active area that appears at the top of the leaf when the plant is fed with labeled tryptophan is the site of formation of the gramine and not just an area of accumulation of the alkaloid.

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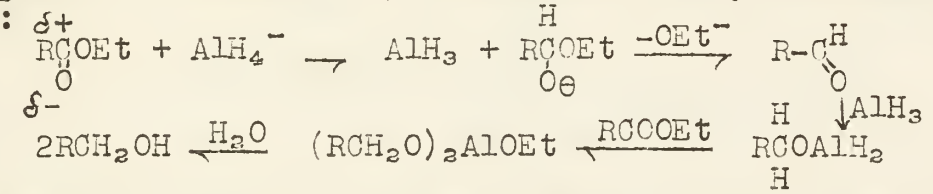
# THE MECHANISM OF LITHIUM ALUMINUM HYDRIDE REDUCTIONS

Reported by D. C. Blomstrom April 4, 1952

Introduction: Shortly after its discovery in 1947 lithium aluminum hydride was successfully used by Nystrom and Brown[1] for the reduction of organic compounds, and it has since been applied to a wide variety of compounds containing oxygen, nitrogen, sulfur, or halogen. The scope and specific applications of the reagent in organic chemistry have been the subject of a chapter in Organic Reactions[2] and of three seminars in this Department.[3,4,5]

General Mechanism: Most of the normal reductions by $LiAlH_4$ involve the displacement of a strongly electronegative atom (oxygen or halogen) and accession of a hydrogen atom to the electron-deficient center, usually a carbon, nitrogen, or sulfur atom. Trevoy and Brown[6] postulate a bimolecular nucleophilic attack by an aluminohydride ion on the center of low electron density. The exact constitution of the attacking ion is not known. Trevoy and Brown reject the concept of free hydride ions ($H^-$) since it would not explain the characteristic differences in reducing action between the aluminum and the borohydrides. The infra-red spectrum of ether solutions of $LiAlH_4$ shows the presence of $AlH_4^-$ ions.[7] All four hydrogens of the hydride are available for reaction. Thus the reducing species is believed to be $AlH_4^-$ initially; as the reaction proceeds the hydrogens are replaced by organic residues. This postulated general mechanism may be illustrated by the reduction of an ester:

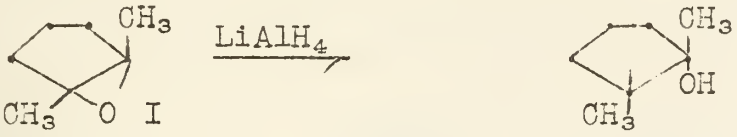


In the reduction of sulfur compounds (e.g., sulfonyl chlorides) the hydride would be pictured as attacking the electron-deficient sulfur atom;[8] reduction of nitro compounds would proceed via reaction at the nitrogen atom.

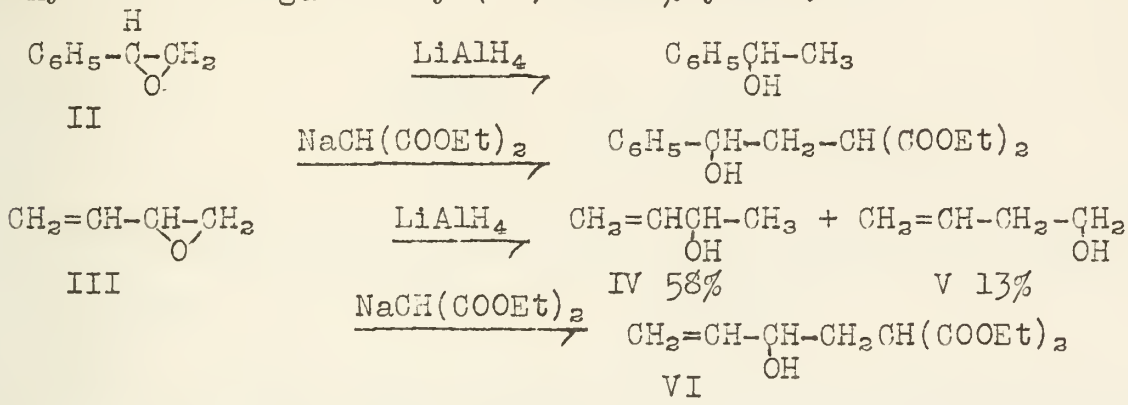
Support for a nucleophilic mechanism is furnished by a consideration of the groups which do not undergo reduction by $LiAlH_4$: alcohols, ethers, ketals, olefins, acetylenes, and sulfones. Compounds in these classes do not usually react with known nucleophilic reagents such as hydroxide, alkoxides, or amines. This general scheme is consistent with the evidence found in the investigations of the reduction of epoxides and halides.

Epoxide Reduction: Trevoy and Brown[6] applied two experimental tests to the theory that reduction of epoxides proceeds through a bimolecular attack on a carbon atom by a complex hydride ion. The first test was a determination of whether inversion of configuration occurs at the reacting carbon. 1,2-Dimethyl-1,2-epoxycyclopentane (I) and 1,2-dimethyl-1,2-epoxycyclohexane were reduced by $LiAlH_4$ to the corresponding dimethylcyclanols and the identity of the products determined by comparison of physical properties with

the compounds of known configuration. Because of difficulties encountered in purifying the products the identifications were not completely unambiguous, but the evidence indicated that in both cases the product was the cyclanol of trans configuration. Since the epoxides were necessarily cis, inversion had occurred at one of the carbons.



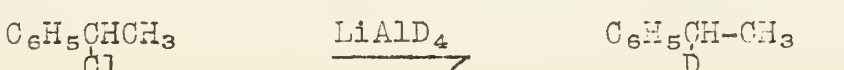
The second test applied was a determination of the direction of ring opening of unsymmetrical epoxides. Reaction of sodium diethyl malonate with epoxides is known to be bimolecular, and the direction of ring opening of several epoxides is known. Styrene oxide (II) and epichlorohydrin were attacked exclusively on the terminal carbon by both reagents. With 3,4-epoxy-1-butene (III) $LiAlH_4$ yielded (IV) and (V) in the amounts shown, while sodium diethyl malonate gave only (VI) in 64% yield.



The results tend to confirm the general theory in the case of epoxides.

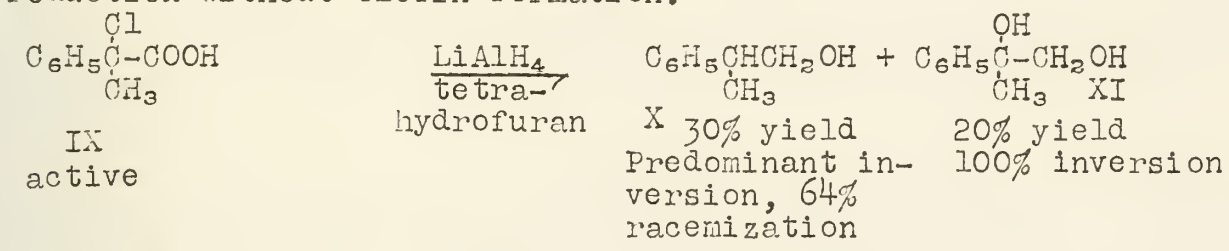
Halide Reduction: Investigations of reduction of alkyl halides to hydrocarbons also offer support to a mechanism based on a bimolecular reaction of a nucleophilic hydride complex with a carbon atom. The halides exhibited the same patterns of reactivity found in alkaline hydrolysis.[6,9] That is, primary halides gave better yields than secondary ones, and tertiary halides gave mostly olefins. Bromides were more reactive than chlorides. Halides of the allyl and benzyl types were easier reduced than the saturated halides. Aryl halides were quite unreactive.

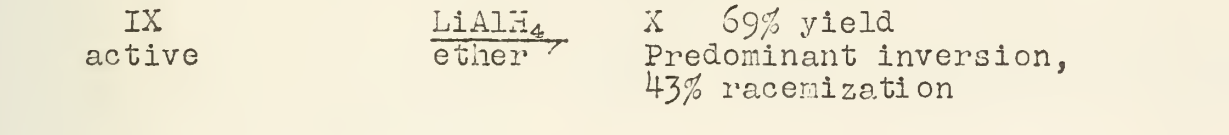
One of the usual criteria for a bimolecular attack at a saturated carbon atom--inversion of configuration--could not be applied to ordinary alkyl halides since inversion would be detectable only in tertiaries, which give olefins with $LiAlH_4$. Reduction of an optically active secondary halide (VII) with $LiAlD_4$ was accomplished however, and a product (VIII) possessing optical activity was isolated.[10]

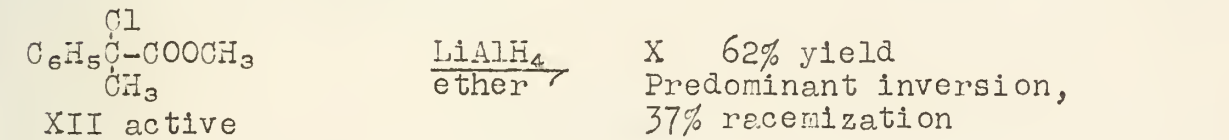


Although the optical purity of the product was not known, the result tends to support the bimolecular nature of the reduction, since monomolecular reactions usually result in racemization.

Eliel and Freeman[11] undertook an investigation of the stereochemistry of the reduction of active 2-chloro-2-phenylpropionic acid, (IX), a tertiary halide which is reactive enough to undergo reduction without olefin formation.

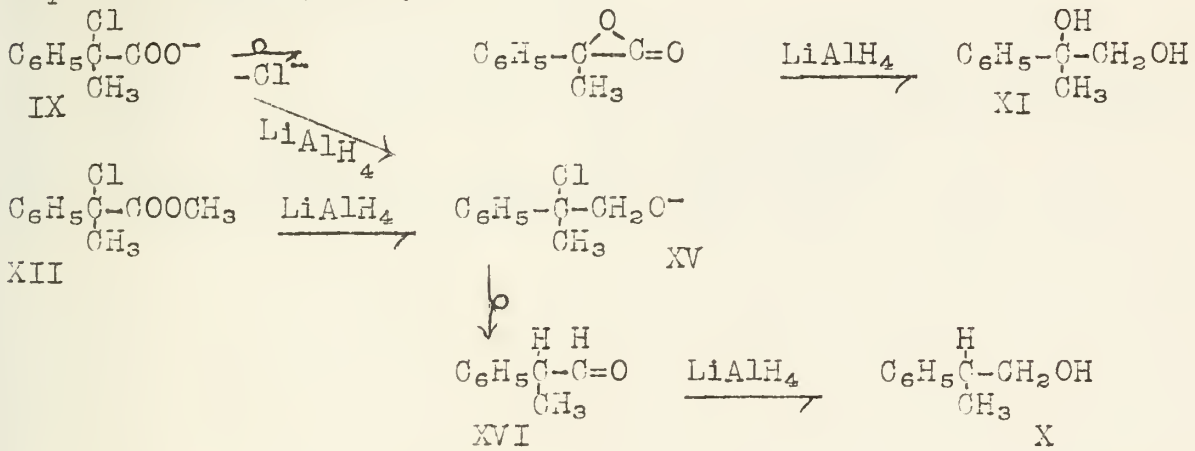



The epoxide (XIII) was excluded as a possible intermediate, since it formed 2-phenyl-2-propanol (XIV) when treated with $LiAlH_4$.


The authors believe the following mechanism best accounts for the experimental results:




The internal displacement of chloride by the carboxylate ion has an analogy in the hydrolysis of α-haloacids.[12] This intermediate would explain the very rapid observed hydrolysis of (IX). Whereas the mechanism of hydrolysis postulates a second inversion by hyd-

roxide ion at the α-carbon, in this case there is apparently an attack by $AlH_4^-$ on the carbonyl carbon, producing the diol. The alternative path for the acid and the only path for the ester is by way of the chlorohydrin anion (XV), in which a hydride shift occurs to give the aldehyde (XVI), which is easily further reduced to the alcohol (X). The configuration at $C_2$ has been largely inverted, but some racemization has occurred. Neither the first nor the third step should cause a change of configuration, since reduction is not occurring at the asymmetric carbon. Therefore the inversion appears to take place in the postulated hydride shift. Lack of complete stereospecificity in this step has not been adequately explained.

Some evidence for the intermediate chlorohydrin was found when only half the calculated quantity of hydride was added. Acid hydrolysis of the reaction mixture produced a very unstable chlorine compound which lost hydrogen chloride easily. On distillation some of the aldehyde (XVI) was obtained. Alkaline decomposition of the mixture led to the epoxide. Both of these compounds could have come from the chlorohydrin.

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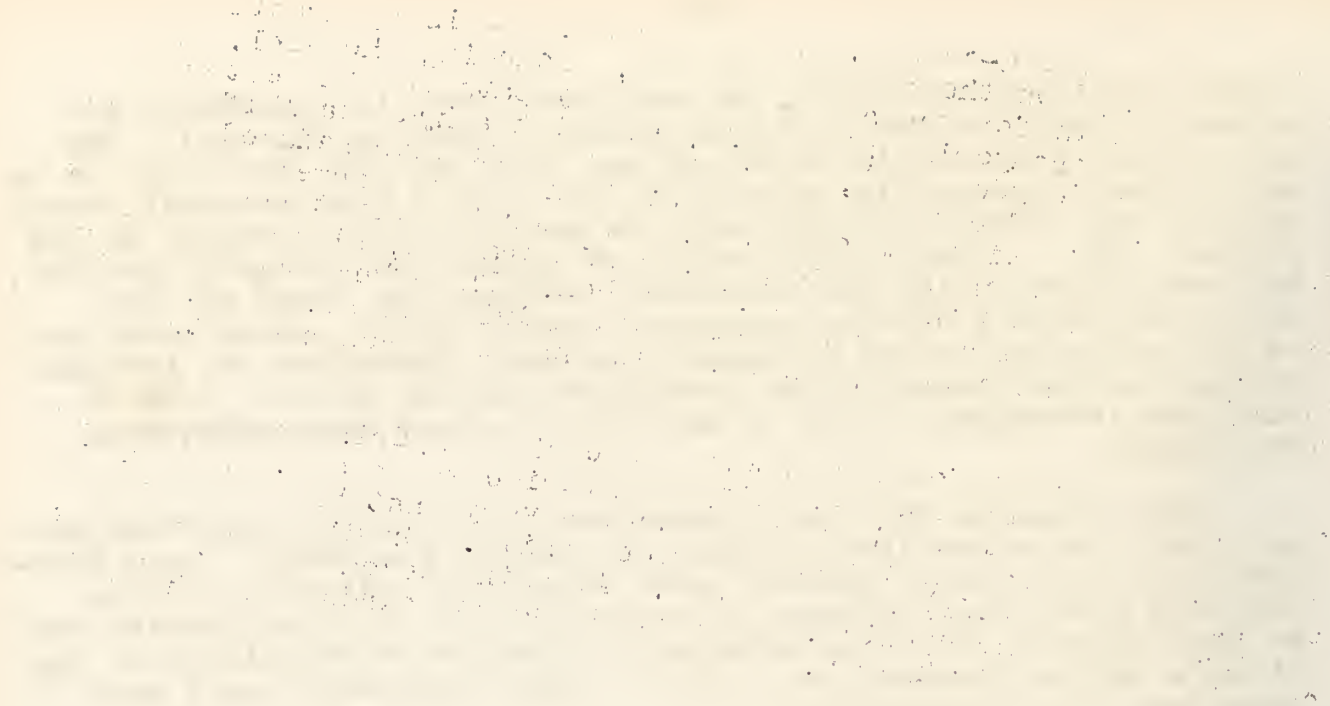
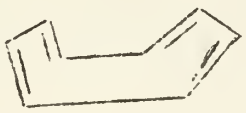


# SOME NEW REACTIONS OF CYCLOOCTATETRAENE

Reported by Barbara J. Hummel April 18, 1952

Ever since the announcement by Willstätter of the synthesis of cyclooctatetraene from pseudopelletierine,[1] a great deal of interest in the properties and reactions of this compound has been displayed. In 1939, Hurd and Drake[2] pointed out the marked similarity in the properties of Willstätter's cyclooctatetraene and those of styrene and they questioned his synthesis of the compound. In 1948, however, Reppe and co-workers[3] published the synthesis of COT from acetylene over nickel cyanide and showed that Willstätter's compound was COT. Excellent summaries of the early work with COT are given in four previous seminars of this department.[4,5,6,7] The present seminar is concerned primarily with the work done during the past year.

The bonds of COT have been shown to be olefinic in nature, both by chemical studies and physical measurements. It is oxidized by standing in air, adds halogens readily and undergoes the Diels-Alder reaction. There are four possible structures, but present information favors either I or II.[8,9]

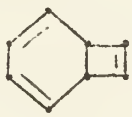


I - "Tub"
all cis

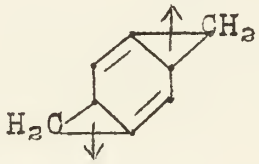
II - "Crown"
all trans

During studies of the derivatives, it was found that reactions fall into three distinct classifications. Reppe attempted to explain this by assuming that COT can react as if present in any one of the three following forms:

III



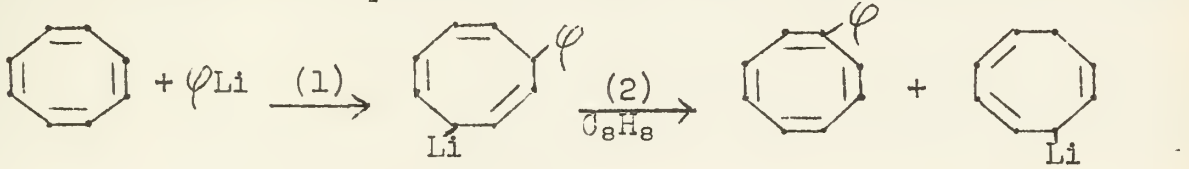
IV




V

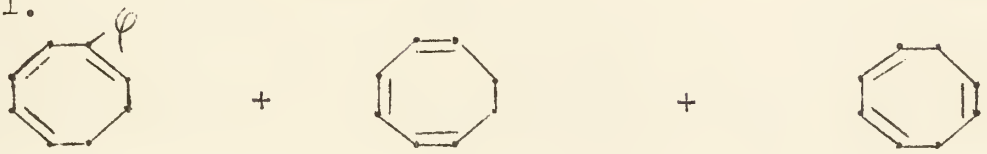
Reactions have been shown bearing out each of these structures.

Reactions: Aryl and alkyl cyclooctatetraenes have been prepared from COT and organometallic compounds.[10,11,12] The reaction of phenyllithium with COT has been found to proceed by addition followed by a process equivalent to the transfer of lithium hydride from the addition compound to another molecule of COT:




(or the 1,2-adduct) VI (or the 1,2-adduct)

Hydrolysis of compounds formed in (1) and (2) would produce VII and VIII.

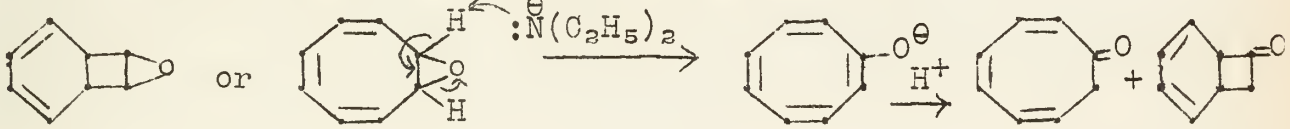


VII (or other isomers) + VIIIa + VIIIb

Other organometallics react in a similar manner, yielding the corresponding aryl or alkyl derivative of cyclooctatetraene and 1,3,5- and 1,3,6-cyclooctatrienes.

Cyclooctatetraenecarboxylic acid has been obtained in low yields by the ozonization of vinylcyclooctetraene at -70°, followed by treatment of the ozonide with silver oxide.[13,14] A much better method, however, consists in the reaction of bromocyclooctatetraene and n-butyllithium at -55°, forming n-butyl bromide and cyclooctatetraenyllithium. Carbonation of the lithium derivative forms COTcarboxylic acid in 58% yield. The structure of the acid has been established by hydrogenation to cyclooctene-1-carboxylic acid and to cyclooctane carboxylic acid. Attempts to resolve COTcarboxylic acid have been unsuccessful.

Cyclooctatetraene oxide (IX) has been prepared by the oxidation of COT with peracetic acid. The reaction of IX with phenyllithium, in an attempt to prepare phenylcyclooctatrienol and dehydration to phenylcyclooctatetraene, formed as one product 8% of a yellow liquid with empirical formula $C_8H_8O$.[15] This compound is formed by a base-catalyzed rearrangement of COT oxide and was obtained in a yield of 39% with mesityllithium as the base and 71% or more with lithium diethylamide. The isomer was proved to be 1,3,5-cyclooctatriene-7-one (X) by the preparation of ketonic derivatives and by hydrogenation to cyclooctanone and cyclooctanol. It would appear that the reaction proceeds thus:

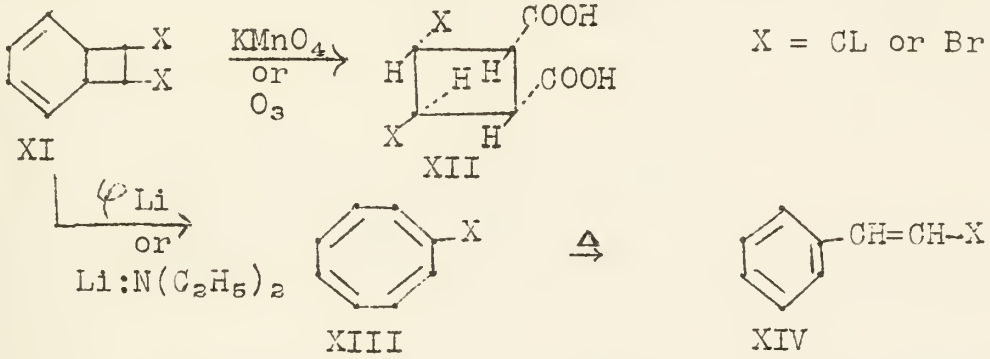


IXa or IX $\xrightarrow{:\overset{\ominus}{N}(C_2H_5)_2}$ $\xrightarrow[H^+]{}$ X + CA. 5%

A choice between structure IX and IXa cannot be made with certainty on the basis of the ultraviolet absorption spectrum of the compound, for the spectra of models with structures related to IX and IXa are too similar. The fact that cyclooctanol is formed by the hydrogenation of COT oxide provides evidence supporting structure IX rather than IXa, for COT dichloride, which has the bridged ring structure analogous to IXa,[17,18] yields bicyclo-[4,2,0]-octane rather than cyclooctane on hydrogenation

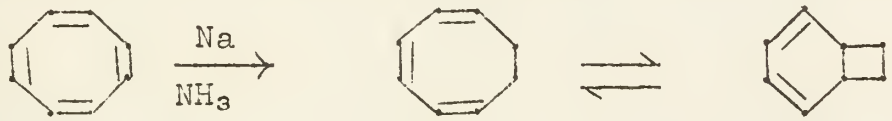
Cope and Burg[18] have prepared cyclooctatetraene dihalides and have shown that they exist in the bridged ring structure by con-

version into 3,4-dihalo-cis-1,2-cyclobutanedicarboxylic acid.(XII) An eight-membered ring structure would be expected to yield dl-α,α'-dihalosuccinic acid. Dehydrohalogenation of the dichloride or dibromide in the presence of base reopens the bridged ring producing chloro- or bromocyclooctatetraene. (XIII)




Bromo- or chloroCOT are isomerized to β-bromo- or β-chloro-styrene (XIV) on heating. (One-half hour at 90-103° for the bromo derivative, and 200-210° for the chloro derivative.)

1,3,5-cyclooctatriene has been prepared by the reduction of COT with sodium in liquid ammonia.[19,20]




III XVa XVb

The triene XVa was characterized by ultraviolet and infrared spectra, hydrogenation to cyclooctane and ozonization followed by oxidation to succinic acid. On heating briefly at 80-100°, XVa formed an equilibrium mixture containing 85% of XVa and 15% of bicyclo-[4,2,0]-octa-2,4-diene, XVb. XVb was characterized by ultraviolet and infrared absorption spectra, hydrogenation to bicyclo-[4,2,0]-octane and oxidation to cis-1,2-cyclobutanedicarboxylic acid. The bridged diene forms an adduct with maleic anhydride at 10°, at which temperature XVa fails to react. However, at 60°, XVa forms the same adduct.

The dynamic isomerism of XVa and b, according to Cope,[20] is a case of "valency tautomerism", in which no atoms or groups shift. The only changes that occur are electronic displacements required to interchange double and single bonds and corresponding changes in interatomic distances and angles.

Other workers[13,14,21] have recently repeated and extended Reppe's original investigations.

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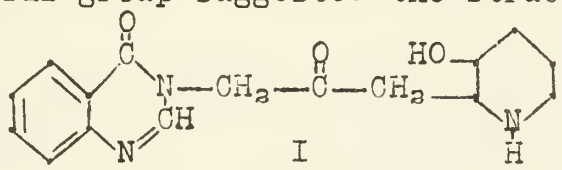
# AN ANTIMALARIAL ALKALOID FROM SAXIFRAGACEAE

Reported by Yngve Sundström April 18, 1952

A classical Chinese antipyretic drug, Ch'an Shan, consisting of the dried roots of the Saxifrage Dichroa febrifuga Lour., has been studied by a number of research groups in recent years as part of the search for antimalarials that started during the second World War (1,2,5,6). The herb contains ca. 0.1% of an alkaloid that has 100 times as great activity against avian malaria as quinine. Koepfli and co-workers suggested the name "febrifugine" for the alkaloid and "isofebrifugine" for an accompanying alkaloid of identical composition and similar antimalarial activity (3).

Koepfli and co-workers studied the chemistry of febrifugine and found that it contains two basic groups, no methoxyl, no N-methyl and no C-methyl. The empirical formula is $C_{16}H_{19}O_3N_3$. Spectroscopic studies, oxidation and hydrolysis all indicates a 3-substituted 4-quinazolone. From these and some further studies, the Koepfli group suggested the structure I for febrifugine:



I

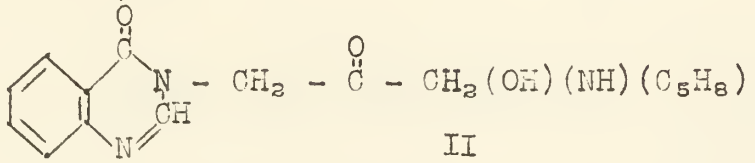
They also suggested that a hemiacetal linkage involving the middle carbonyl and the piperidine-hydroxyl accounts for the two isomeric forms of the alkaloid (3,4).

In the January 1952 issue of Journal of Organic Chemistry there is a sequence of 15 papers dealing with this alkaloid (6-20). Koepfli's formula is established by synthesis, a new source for the alkaloid is found in the garden variety of Hydrangea and a great number of similar substances are reported. The work was done at Lederle, reported by Baker, Querry and various co-workers.

When the work started, the supply of Ch'an Shan in this country was very limited and of dubious identity. The chemical studies were originally undertaken with 13 grams of the pure alkaloid. Later on, the alkaloid isolated from Hydrangea was identified with the Ch'an Shan compound by mixed melting points, spectra, analysis and antimalarial activity. The work as a whole is characterized by the circumstance that maximum use has been made of model compounds (6,7).

Degradation experiments were carried out, giving the same information as the degradation studies by Koepfli and co-workers, and furthermore indicating that there is no ethylenic linkage, no primary amine, but a carbonyl $\alpha$ or $\beta$ to a secondary amine, and a hydroxyl present in the side-chain to the 3-substituted 4-quinazolone.

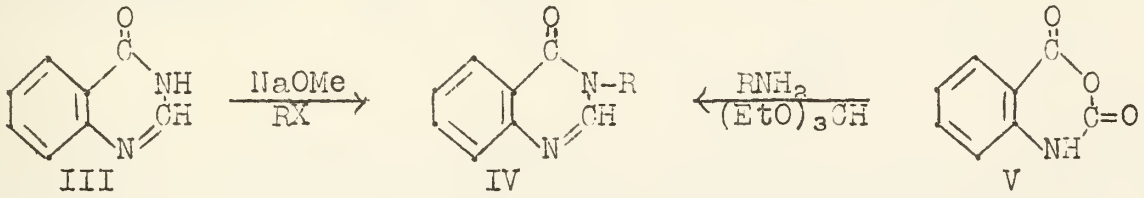
Zn-dust distillation gives 3(β ketopropyl)-4-quinazolone, and as result of all degradative studies, Hutchings and co-workers suggest formula II (7).



II

With this information available, the study was continued with emphasis on the possibilities of some hydroxypiperidyl or hydroxymethylpyrrolidyl group attached to the γ-carbon of the propyl side chain.

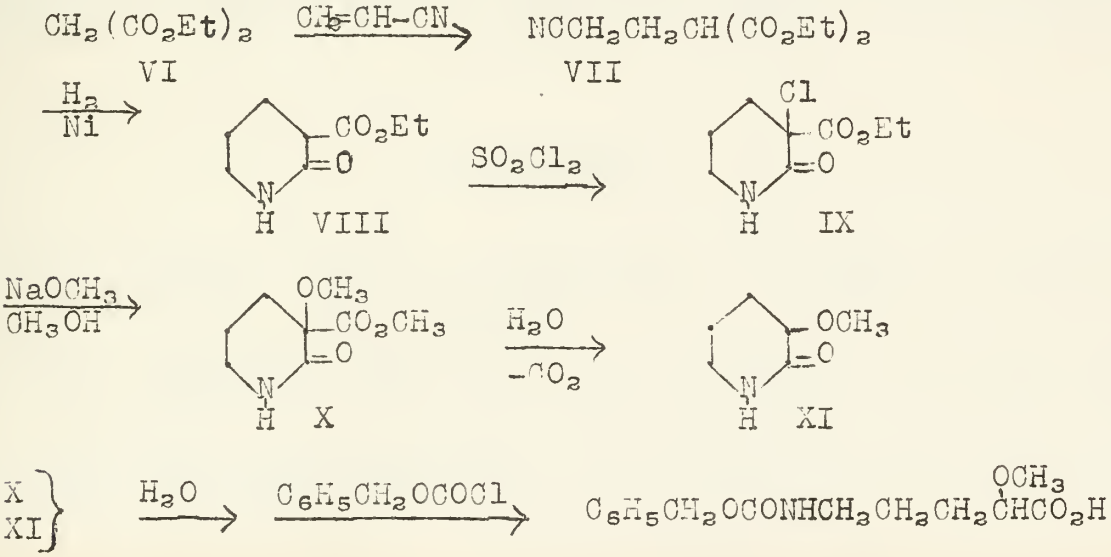
Two main methods were used for preparation of 3-substituted 4-quinazolones:



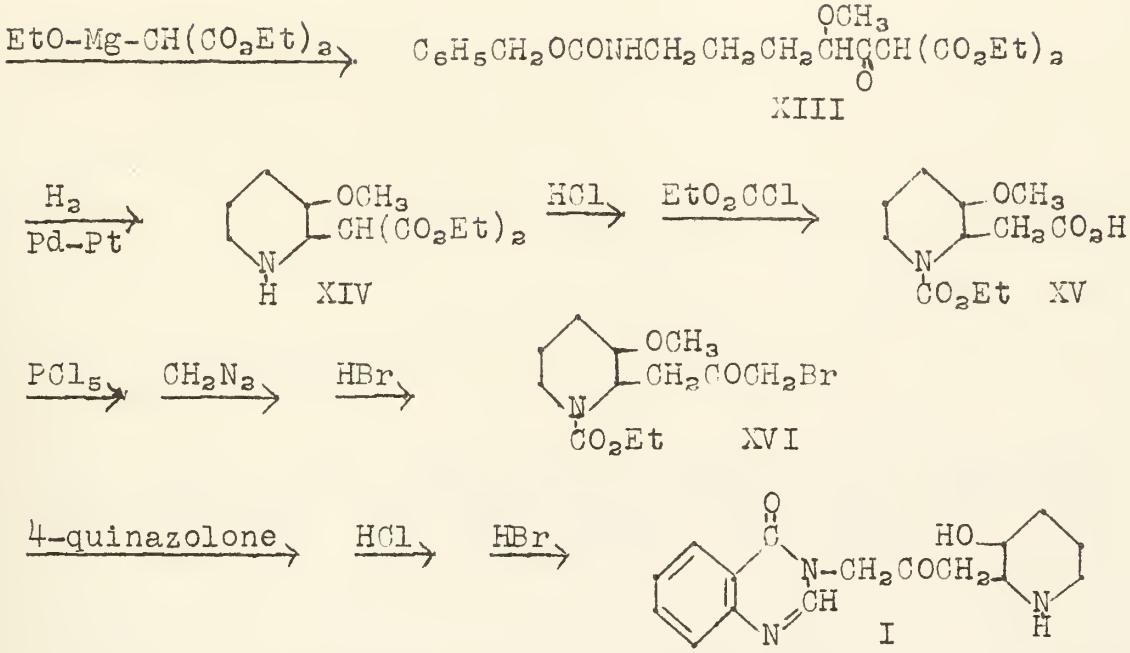
III (8,21) IV V (8,22)

In references 4-20 the preparation of ca 200 model compounds is reported. The approach that proved successful in the end consists in preparation of a suitably substituted straight-chain compound that can be closed to a piperidine system, which then is attached to either 4-quinazolone by the above reaction or to β-ketopropyl quinazolone (prepared from 4-quinazolone and chloroacetone) by a Claisen-type reaction.

A typical example is the synthesis of the dl-alkaloid, 3-(β-keto-γ-(3-hydroxy-2-piperidyl) propyl)-4-quinazolone (16):



XII




In the preparation of the key intermediate XII, the nitrogen is protected by a carbobenzoxy-group and the future hydroxyl methylated. Phthalimido and phenyl groups were employed in some experiments. The final product is one-half as active as the Hydrangea alkaloid towards malaria.

The alkaloid is very active against malaria. However, it has a number of undesirable by-effects, notably emesis. Therefore, a variety of derivatives, substituted in the benzene ring of the 4-quinazolone system, were prepared and tested as antimalarials. Some of them were less toxic than the original alkaloid, but so far, no derivative with pronounced advantages has been found (17-20).

Comparison between the Hydrangea alkaloid and other known antimalarials shows that the Hydrangea alkaloid (febrifugine) is unrelated to quinine and the quininoid drugs.

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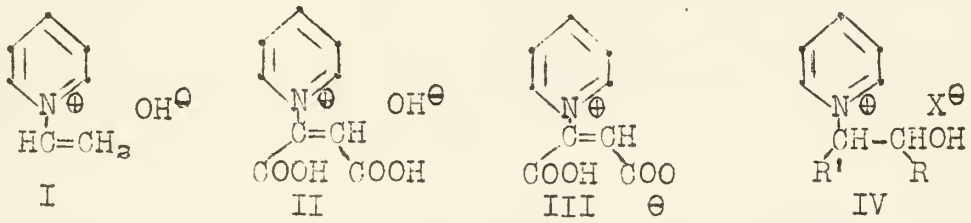
# N-vinylpyridinium Salts

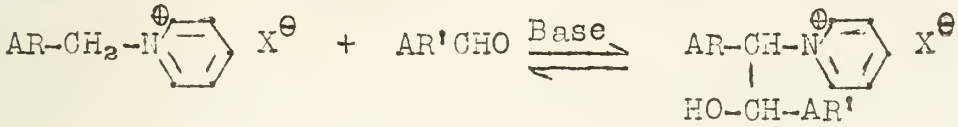
Reported by Robert E. Putnam April 25, 1952

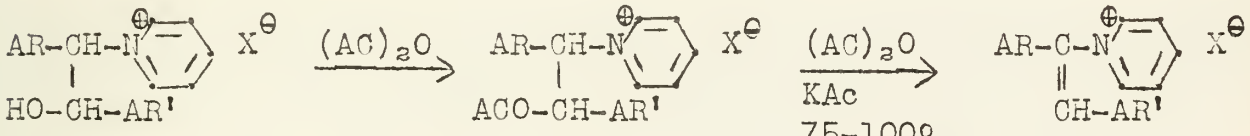
Preparation: N-vinylpyridinium salts of the type RCH=CH-N⊕ X⊖ have been prepared in a number of ways. Treatment of B-bromoethylpyridinium bromide with silver oxide gave the vinylpyridinium hydroxide, I, in low yield(1,2). Pfeiffer and Langenberg (2) obtained the substituted vinylpyridinium hydroxide, II, and its betaine, III, in the same manner. Krŏhnke has prepared several N-vinylpyridinium salts by dehydration of the corresponding ethanolpyridinium salt, IV, under vigorous conditions(3,4). R' can be hydrogen, alkyl or aryl but R must be aryl in order that loss of water take place.



I II III IV

Recently a new and quite general method of preparation was reported in the literature. Salts of type IV had been prepared by condensation of an aromatic aldehyde with a benzylpyridinium salt in the presence of base. The reaction was shown to be reversible and in many cases the equilibrium did not favor the ethanolpyridinium salt(5). Krŏhnke attempted to remove the ethanolpyridinium salt as it was formed by simultaneous acetylation(6,7). The base used was potassium acetate and a temperature of 75 - 100° was maintained. Acetylation took place as expected but only in two cases did the reaction stop here. Under these conditions the product isolated was that formed by loss of acetic acid from the acetylated salt. This proved to be the vinylpyridinium salt, V. The course of the reaction may be represented as





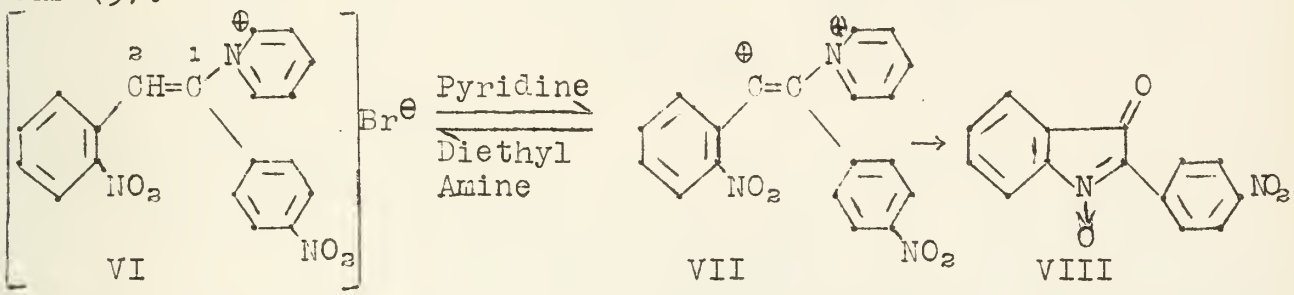
The reaction conditions closely resemble those of the Perkin reaction(6) in everything except temperature. At temperatures above 140° (Perkin temperatures) a sharp decrease in yield was noted and substituted cinnamic acids appeared as by-products. The procedure is quite general. Forty-six substituted vinylpyridinium salts were prepared in yields ranging from 16 to 91%. In most cases the yields amounted to 50 to 80%. The aldehydes used were

substituted and unsubstituted benzaldehydes, cinnamaldehyde and furfural. Benzyl-, substituted benzyl-, cinnamyl- and allyl-pyridinium salts were employed. In only two cases was the reaction unsuccessful; o-nitrobenzylpyridinium bromide did not react with o- or p-nitrobenzaldehyde. This does not seem to be an electrical effect since p-nitrobenzylpyridinium bromide gave excellent yields of product with o- and p-nitrobenzaldehydes. Furthermore 2,4-dinitrobenzylpyridinium bromide condensed with o-nitrobenzaldehyde in 29% yield. This indicates that the effect is probably not steric either. These observations suggest that the two exceptions should be further investigated.

The color of the products varied greatly with the substituents present on the starting aldehyde and pyridinium salts. o- or p-Nitrobenzylpyridinium salts when condensed with aldehydes having auxochromic groups gave deep red to deep yellow products. If the aldehyde was unsubstituted or substituted with Cl or $NO_2$ the product was light yellow or colorless.

Reactions: Kröhnke and his co-workers are at present working on the reactions of these quaternary salts. To date the nitro substituted salts have exhibited the most interesting properties.

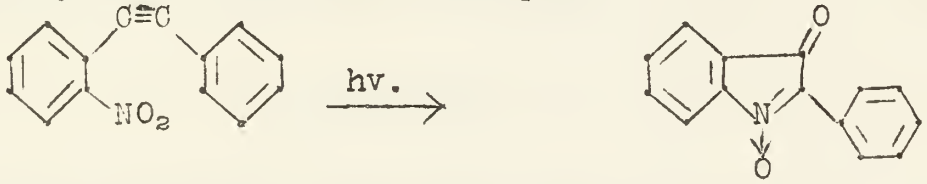
Compounds derived from o-nitrobenzaldehyde and substituted or unsubstituted benzylpyridinium bromides can be converted in excellent yields in one step to 2-substituted isatogens using mild base(9).




VI VII VIII

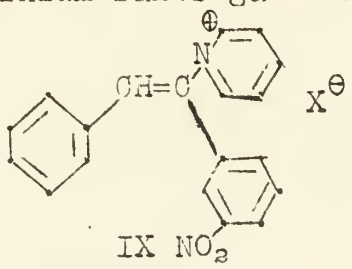
The most useful base is a mixture of pyridine and diethylamine.

This synthesis is reminiscent of that of von Baeyer and others (10,11,12) in which o-nitrotolans are converted to isatogens by the action of light. However in the new synthesis the tolan does not seem to be an intermediate. No substituted tolan could be isolated in any of the reactions attempted and under basic con-

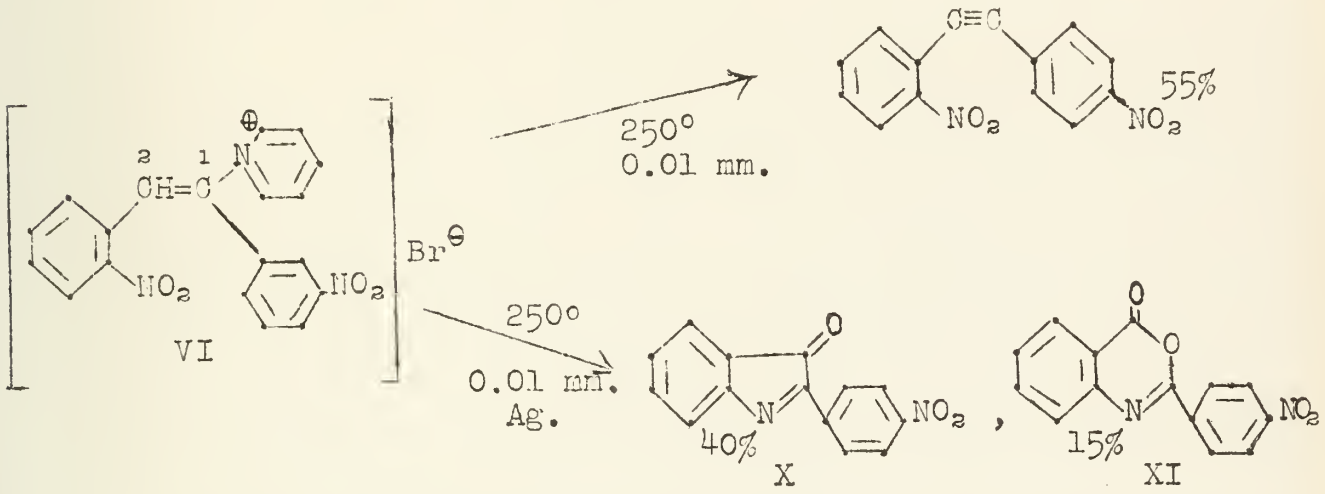



ditions o-nitrotolans were not converted to isatogens. Furthermore IX failed to give any isatogen though it could form the same

tolan as VI. The reaction may proceed through the betaine, VII. These could not be isolated in the case of vinylpyridinium salts but similar isoquinolinium salts gave them readily in stronger base.




However, tolans can be produced from these vinylpyridinium salts by heating in a vacuum. Again the 2-phenyl group must have an o-nitro group. This suggests that the nitro group is necessary for the formation of betaine, VII, or for some other reaction intermediate. The fact that a combination of a p-nitro group on the 2-phenyl with an o-nitro group on the 1-phenyl is not suitable for this transformation indicates once more that the effect is not electrical. If these salts are heated with an excess of silver powder in a vacuum, entirely different products result. From VI the main product is a keto-indolenine, X, and an azlactone, XI, isomeric with the isatogen, VIII.




Recently it has been reported that a 2-substituted isatogen is also produced by the action of $NO_2$ on stilbene(13). This reaction appears to be similar to Von Baeyer's preparation from tolan rather than to Krönhke's synthesis.

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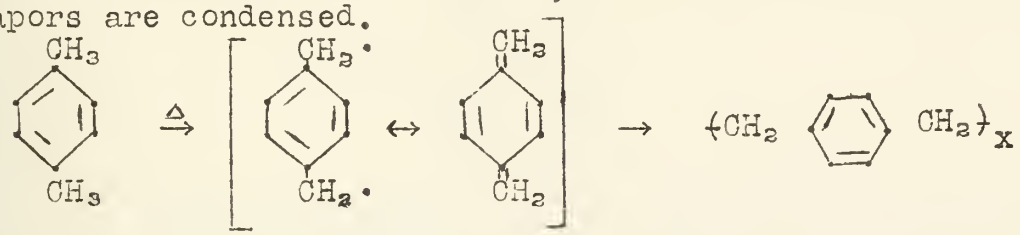
# QUINONE TYPE MONOMERS AND THEIR POLYMERS

Reported by James M. Quinn April 25, 1952

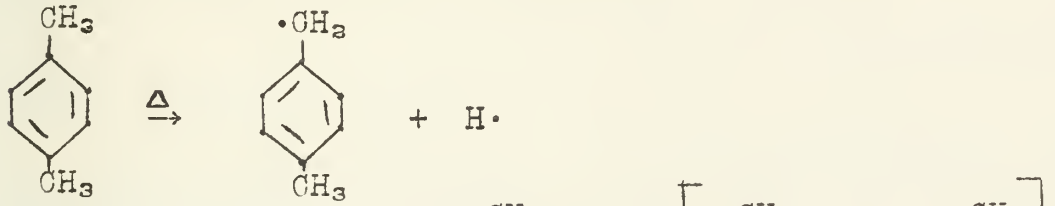
Introduction: Recently there has been reported in the literature, several pyrolyses of p-xylene and similar compounds which lead to the formation of polymers with rather unusual properties. In general a diradical is formed as illustrated below, which may exist in a form similar to a quinone, and this polymerizes when its vapors are condensed.



Two cases of similar polymerizations have been reported. Marvel and co-workers[1] found that hexa-p-tolyl-ethane dissociated into tri-p-tolyl-methyl radicals which disproportionated into tri-p-tolyl-methane and a biradical that polymerized to a glassy residue. When Schlenke and Mayer[2] abstracted HCl from diphenyl-p-tolyl-methyl chloride by treating with pyridine they obtained a diradical which polymerized to a resin.

P-Xylylene: Szwarc[3] found that when p-xylene was pyrolyzed he obtained hydrogen, methane, p-xylene and a poly-p-phenylene-ethylene polymer. The reaction was run by a flow method[4] thru a silica reaction vessel at a temperature of 745-860°C and a pressure of 3.2 to 6.2mm. of Hg with a contact time of 0.4 seconds. The reactions were shown to be homogeneous gas reactions of 1st order and remained so when the time of contact and pressure were varied.

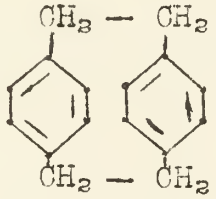
Investigation of the kinetics of this pyrolysis[5,6,7] showed that 1,4-dimethylene-2,4-cyclohexadiene or "p-xylylene"(I) was formed by the following sequence of reactions:



(I)

Evidence for the existence of these diradicals included:

(1) Formation of only diiodo compounds when the diradicals were treated with iodine.
(2) Recently[8] a dimer(II) has been found in the products after pyrolysis and this proves beyond doubt the formation of the corresponding "monomer" in the gas phase.

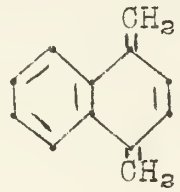
(II) 

(3) Analysis of the polymeric material was the same as that for p-xylylene.

When p-xylylene vapors were cooled to 0°C a transparent film was formed and at -80°C a fibrous white solid formed. This procedure has been modified[9] to give a better product.

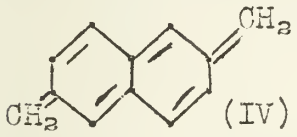
p-Xylylene is an example of a compound which is stable in the gas phase but labile in the condensed phase. Coulson and his colleagues[10] found that the resonance energy of p-xylylene is nearly equal to the resonance energy of the benzene molecule. However, it has been reported[11] as a stable liquid formed from p-benzoquinone and ketene.

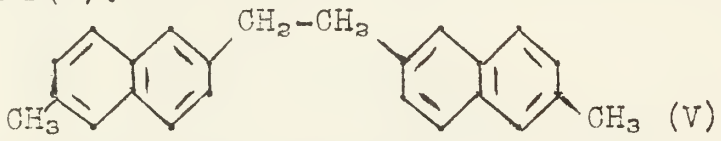
Diradical Formed From 1,4-Dimethylnaphthalene: Pyrolysis of 1,4-dimethylnaphthalene[3,6] produced a diradical(III), which, being less

(III) 

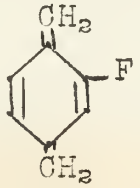
"volatile" than (I) polymerized easily at about 80°C forming a fine, transparent film.

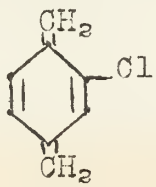
It is interesting that 2,6-dimethylnaphthalene does not produce any polymer, although one might expect the formation of (IV) but instead forms a dimer(V).

 (IV)

 (V)

Diradicals Formed From Substituted p-Xylenes: Pyrolysis of both 2-fluoro-p-xylene and 2-chloro-p-xylene produced the corresponding diradicals:





The latter seems to be slightly less "volatile" than p-xylylene. Both polymers appeared in the form of white films.

Unsuccessful attempts have been made to produce diradicals from 1,2,5-p-xylenol, 1,2,5-p-xylidine and pseudo-cumene.

Diradicals Formed From Some Heterocyclic Compounds: Diradicals were successfully obtained from the following compounds: 2,5-dimethylpyrazine, 2,5-lutadine and 5,8-dimethylquinoline. The diradicals of the 5,8-dimethylquinoline had an extremely low "volatility" and polymerized at 120°C.

Further Attempts to Produce Various Diradicals: All attempts to produce diradicals from 4,4'-dimethylbiphenyl, p-toluidine and p-cresol failed. When o-xylene was pyrolized only 2,2'-dimethyldibenzyl was found and at higher temperatures some anthracene.

When α,β and γ-picolines were pyrolyzed[13] they gave off methane and hydrogen. α and β-picoline yielded a dark violet liquid while γ-picoline yielded a dark violet solid with twice the molecular weight of picoline.

Properties of The Polymers: All of the polymers formed transparent films in thin layers which became white and opaque as the polymers accumulated. X-ray examination showed a crystalline structure. All of the polymers except those with heterocyclic rings present were unaffected by heat until at about 400°C where they melted with decomposition. All of the polymers were insoluble in ordinary solvents and did not swell even with boiling. Neither are they attacked by concentrated $H_2SO_4$ at 150°C with the exception of the N-containing polymers. It was found that the N-containing polymers were soluble in dilute aqueous mineral acids from which they may be precipitated by $NH_3$ or NaOH. It is doubtful if there is any cross linking between polymer chains.

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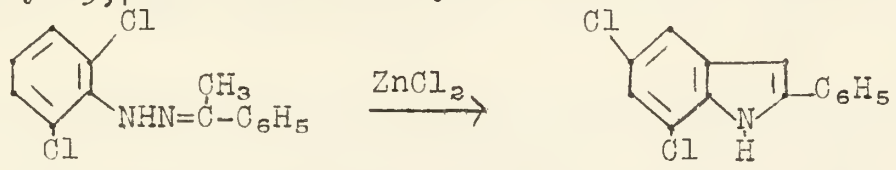
# STUDIES ON HALOGEN MIGRATION IN THE FISHER REACTION

Reported by Paul L. Cook April 25, 1952

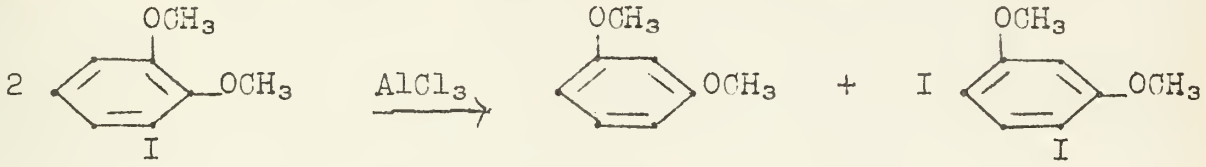
In 1948 Carlin and Fisher[1] observed an unusual halogen migration while carrying out Fisher Indole type reactions. When the 2,6 dichlorophenylhydrazone of acetophenone was heated with zinc chloride the only pure compound recovered from the reaction mixture was 2-phenyl-5,7 dichloroindole.



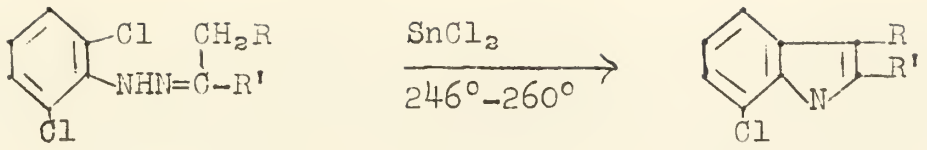

Although the yields were low (7-25%) the remaining parts of the reaction mixture were intractable tars. They observed no such migration when the 2,4, the 2,5 and the 3,5 dichlorophenylhydrazones of acetophenone were converted to phenyldichloroindoles in a similar manner. When they investigated the reaction further with the 2,6 dichlorophenylhydrazones of p-chloroacetophenone, p-phenylacetophenone, acetone and cyclohexanone, they observed that in all cases the 5,7 dichloroindoles were formed. Always the yields were low and at no time did they exceed 33%.

In a recent paper[2] these same authors have announced the results of further investigations as to the nature and mechanism of these reactions.

The Nature of the Migrating Chlorine: A thorough search into the literature provided evidence that the chlorine atom migrates in an electron-deficient or "positive" condition. A number of analogous halogen migration reactions have been observed to occur when aromatic halides having certain structural features are treated with acidic catalysts.[3,4] Meerwein reported the following:




Nicolet and Sampey[5] have shown that halogen atoms so located on aromatic rings as to be susceptible to this type of migration, are substituted by hydrogen when the aromatic halides are treated with stannous chloride but that "non-positive" halogens are not attacked. They went so far as to use $SnCl_2$ as a diagnostic reagent to establish the presence of a "positive" halogen. Carlin et al figured that $SnCl_2$, being an acidic reagent might be used to promote the Fisher reaction and furthermore, if a "positive" halogen were involved, it should capture the "positive" chlorine. They found this to be true. Using 2,6 dichlorophenylhydrazones of various ketones they were able to isolate only the 7-chloroindoles.

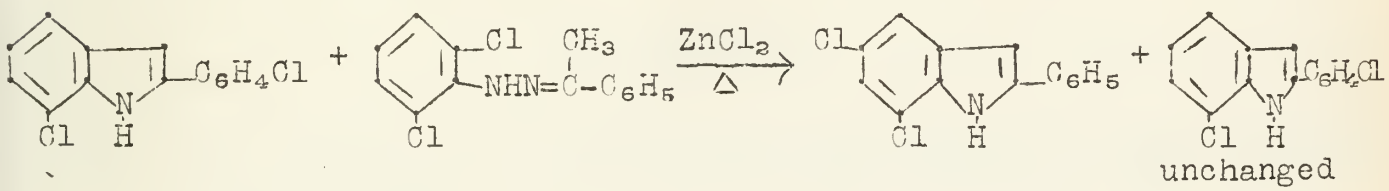


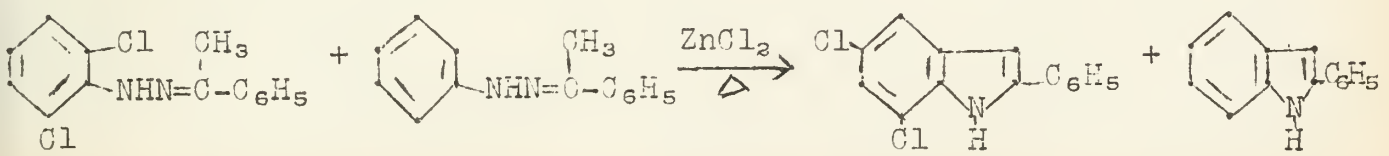
Although mixtures from each reaction were searched carefully for indoles other than 7-chloroindoles, in only one case did they find a by-product, a high molecular weight compound, the structure of which is still being investigated.

The possibility still remained that a 5,7-dichloroindole was first formed, but that then the stannous chloride reductively removed the chlorine atom at the 5-position, leaving the 7-chloroindole. Though this possibility seemed remote, nevertheless it was tested by fusing 2-p-biphenylyl-5,7,-dichloroindole with stannous chloride at 246°. The indole was recovered in 92% yield and there was no evidence of the formation of any other indole.

On the basis of the above evidence the authors suggest that this halogen migration involves a "positive" halogen migration in which the 5,7-dichloroindole is not an intermediate.

Evidence for Intramolecular Rearrangement: At first glance it might appear that since a chlorine atom migrates from a 2,6 dichlorophenylhydrazone molecule to a stannous chloride molecule, the migration was intermolecular. The authors believe, however, that the tin salt is bound to the hydrazone molecule undergoing rearrangement and therefore the abstraction of a chlorine atom by the $SnCl_2$ bound to the same molecule would actually constitute intramolecular chlorine migration. Though they did not actually prove that the rearrangement was intramolecular, they did cite evidence that it was not intermolecular. When they subjected the 2,6-dichlorophenylhydrazone of acetophenone to typical Fisher conditions with zinc chloride as the acid catalyst, using as a solvent p-cresol, a compound shown by Baddeley and Plant[6] to be an excellent bromine acceptor in aluminum chloride induced intermolecular migrations of aromatic bromine, the only significant product was 2-phenyl-5,7-dichloroindole. No chlorinated cresol or 2-phenyl-7-chloroindole could be isolated from the reaction mixture. The following reactions were also tried:

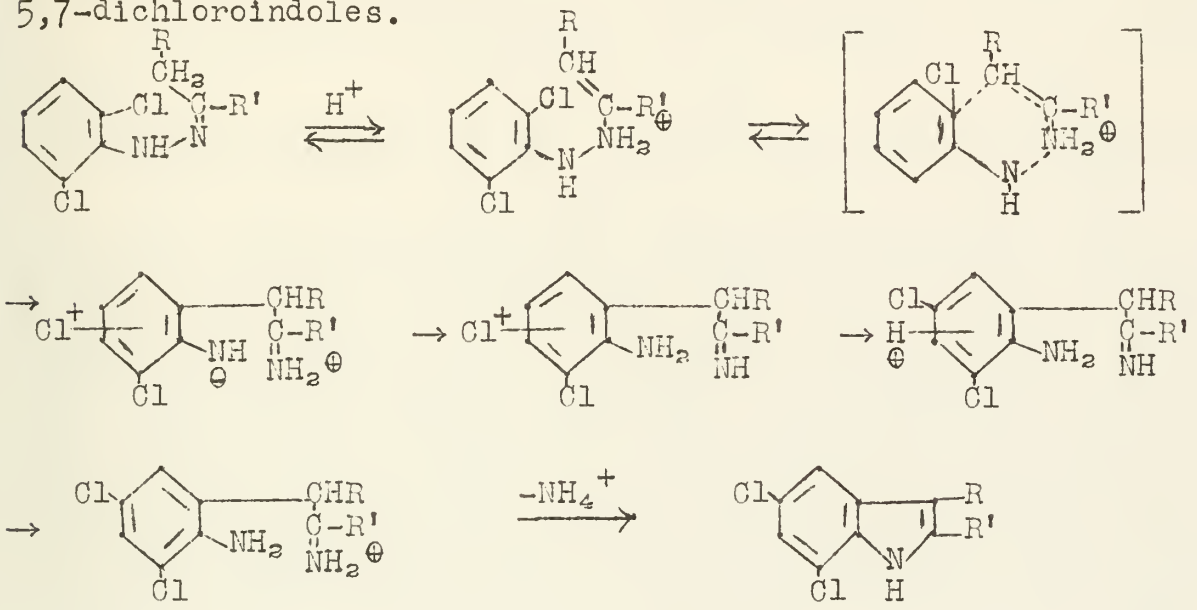


No evidence of intermolecular reaction could be obtained, that is, no 2-phenyl-5-, or 2-phenyl-7-chloroindole could be isolated. It is admitted, however, that these reactions do not constitute proof that the rearrangement is not intermolecular, particularly, since in the latter reaction the formation of 2-phenylindole would likely take place more rapidly than would the formation of 2-phenyl-5,7-dichloroindole. Therefore, very little unchanged acetophenone phenylhydrazone would be left to accept chlorine.

On the basis of this evidence the authors claim that if any intermolecular chlorine migration occurred, it did so only to a very minor extent.

The Proposed Mechanism: Carlin proposes the following mechanism to account for the conversion of 2,6-dichlorophenylhydrazones to 5,7-dichloroindoles.



In this mechanism it is assumed that the "positive" chlorine undergoing migration never leaves the valence atmosphere of the aromatic ring. The above mechanism also accounts for the fact that the migrating chlorine ultimately appears at the 5-position because of the orienting influence of the amino group.

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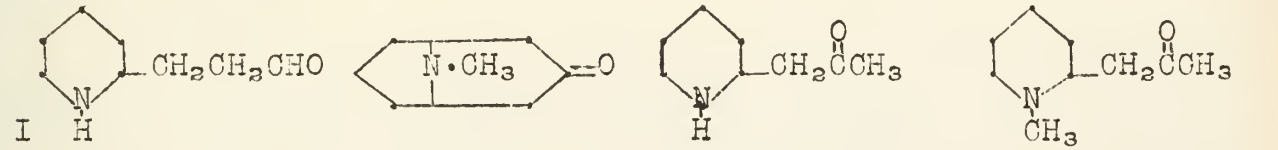
# AN EXAMINATION OF THE STRUCTURE OF PELLETIERINE

Reported by R. Thomas Stiehl May 2, 1952

Tanret[1,2,3] isolated four alkaloids from the root bark of the pomegranate tree (Punica Granatum L.), two of which were reported optically active.

Hess and Eichel[4,5] could isolate none of the alkaloids in optically active forms. They demonstrated, however, that the easily resolved levo form of pelletierine racemized readily just as Tanret[6] reported the natural levo isomer did. The optical activity of the base isolated by Tanret was much greater than that of Hess' base.

After several changes the structures of the four alkaloids were established.

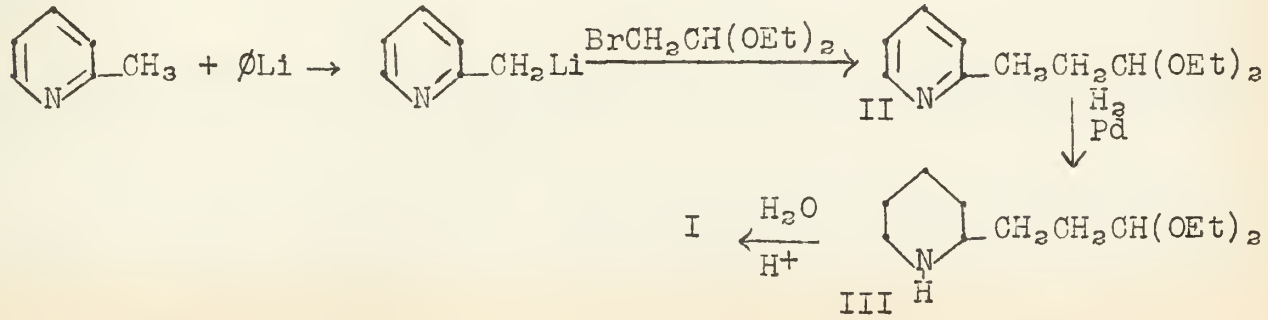


I pelletierine ψ-pelletierine isopelletierine N-methylisopelletierine

Hess and Eichel[7] determined the structure of pelletierine. The empirical formula was $C_8H_{15}NO$. Although pelletierine did not form a nitrosyl derivative with nitrous acid, it did form acetyl and benzoyl derivatives from which the base could be regenerated by heating with sulfuric acid. Pelletierine also formed a hydrochloride, a hydrobromide, and a picrate. Formaldehyde in formic acid produced an N-methyl derivative. Hydroxylamine formed an oxime which could be dehydrated with phosphorus pentachloride to the nitrile which yielded the known ethyl β-(2-piperidyl)propionate. Pelletierine reacted with only one mole of benzaldehyde or one mole of diethyl oxalate. Reduction with sodium in ethanol produced coniine (β-n-propylpiperidine) which was also produced by a Wolff-Kishner reduction. In the isolation of pelletierine from bark, ethyl chloroformate converted it into a urethane from which pelletierine was obtained by heating with hydrochloric acid at 130°.

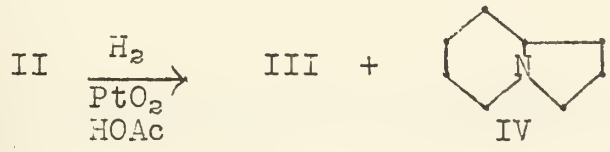
Pelletierine was a colorless, alkaline oil which boiled at 106° at 21 mm. It was soluble in water, ether, and chloroform. Air rapidly converted it into a dark, resinous product.

Wibaut and Beets[8] attempted to synthesize pelletierine according to the following scheme.



Compound III was not obtained pure and readily formed a resin. Although they were unable to isolate pelletierine, they recorded a picrolonate derivative.

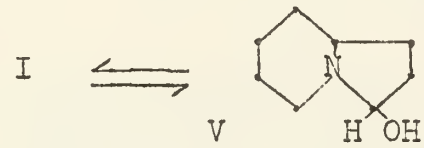
Later Beets and Wibaut[9] attempted hydrogenation of the acetal under different conditions.




Compound III predominated when four or five grams of II was used in each ten ml. of glacial acetic acid. Starting with one gram of II compound IV (δ-conicein or octahydropyrrocoline) was the primary product.

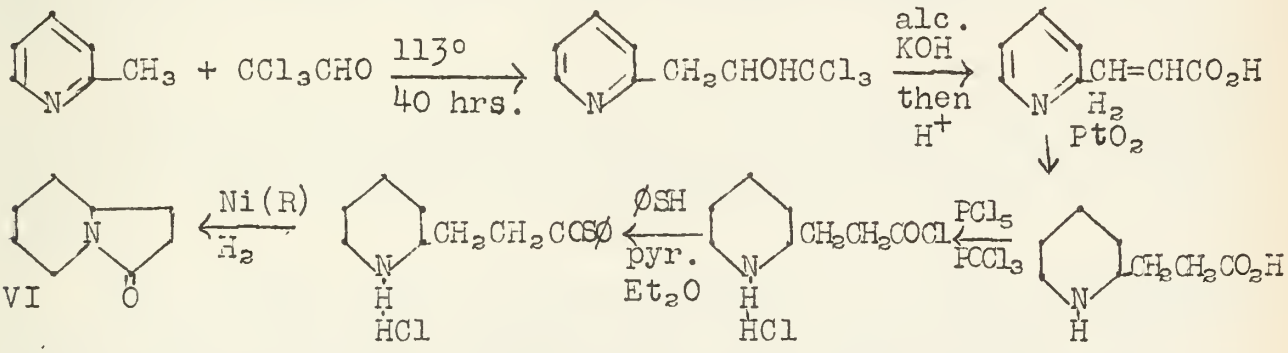
Attempted hydrolysis of the acetal III in hydrochloric acid solution produced an unstable, viscous oil which rapidly formed a resin but which did exhibit reducing properties.

Beets[10] suggested that the aldehyde existed largely as a carbinol amine (V).



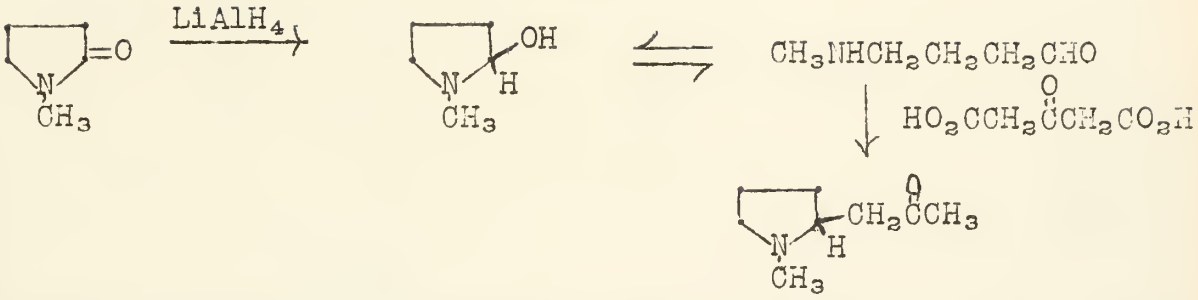

Concurrently but independently Spielman, Swadesh, and Mortenson[11] prepared the same piperidyl acetal and obtained benzoyl, acetyl, and ethyl urethane derivatives of pelletierine that corresponded in properties to those described by Hess. But they, too, were unable to obtain the free aldehyde from any of its derivatives.

King, Hoffman, and McMillan[12] attempted a synthesis in which the aldehyde would be formed under neutral conditions.

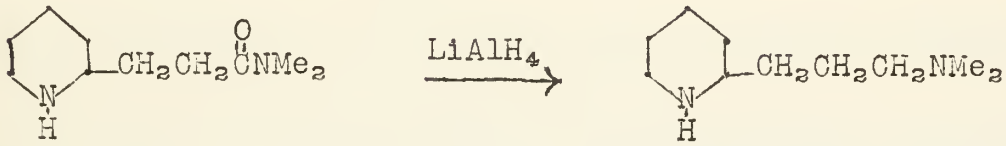



Friedman[13] showed that the low temperature, one-fourth molar quantity lithium aluminum hydride reduction of amides gave excellent yields of some aldehydes.

Galinovsky and Weiser[14] carried out this type of reduction on N-methyl-α-pyrrolidone. They demonstrated the formation of the expected aldehyde through its condensation with acetone dicarboxylic acid, a known reaction[15-18].



King and coworkers[12] obtained only one product in the reduction of the amide.



Next they attempted the reduction of 3-ketooctahydropyrrocoline (VI).

$$\text{VI} \xrightarrow{LiAlH_4} \underset{63\%}{\text{VI}} + \underset{21\%}{\text{higher boiling, resin-forming fraction}}$$

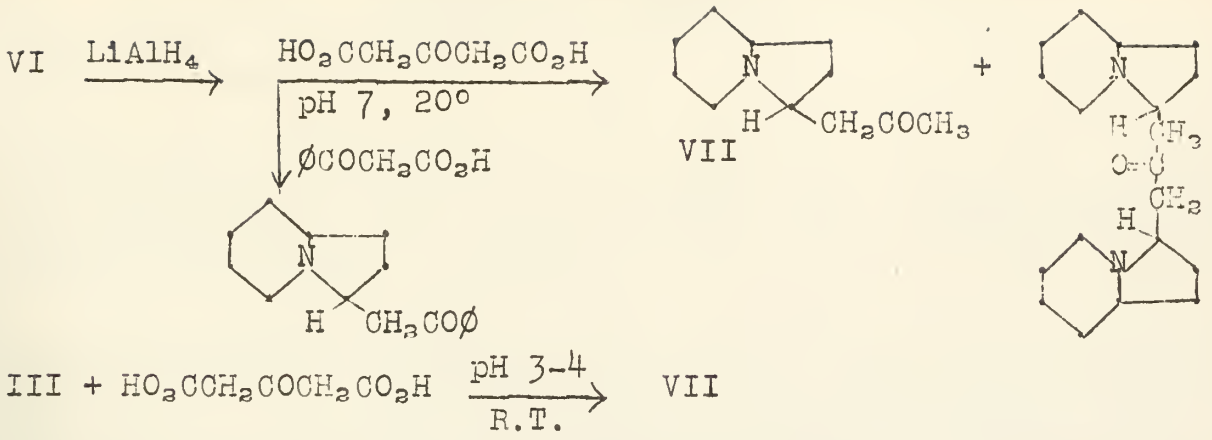
The higher boiling material formed a hydrobromide with a melting point in fair agreement with Hess' corresponding value, and the material had the same empirical formula as pelletierine. Its behavior and high boiling point suggested, however, that the material was a polymeric form of pelletierine.

A short ether reflux of VI with lithium aluminum hydride also produced a higher boiling fraction that gave an equivalent weight of 139 (calculated for pelletierine is 141), an immediate precipitate with Tollen's reagent, and a benzoyl derivative that agreed fairly well in melting point with N-benzoylpelletierine. But again they felt that the high boiling point excluded a monomeric structure.

Since natural antioxidants present in the mixture might have enabled Hess to successfully distill pelletierine, the reduction was repeated employing antioxidants both as a rinse and in the mixture. Only a 16% yield of the higher boiling material was obtained.

The reaction mixture before distillation showed no reducing properties. Therefore, King believed that pelletierine was obtained essentially by pyrolysis (bath temperature 300°, vapor temperature 150-160° at less than 1 mm.) of the polymer formed by an aldol condensation in the reaction mixture.

Galinovsky, Vogl, and Weiser[19] also attempted the same reduction.




The formation of VII in both instances was an indication that the expected aldehyde was being formed.

Since the monomeric aldehyde is so unstable, Galinovsky concluded that it is doubtful that it could be pelletierine since the conditions for isolation alone would polymerize it.

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# NEIGHBORING CARBON AND HYDROGEN IN NUCLEOPHILIC SUBSTITUTION REACTIONS

Reported by J. J. Drysdale May 2, 1952

Introduction: A neighboring group may exert a two-fold influence on a nucleophilic substitution reaction. (1) It may determine the stereochemical course of the reaction, and (2) it may affect the rate of the reaction profoundly.

An evaluation of these effects has been made on a number of systems where the neighboring group is $-O^-$, -Br, $-CO_2^-$, $-O-\overset{O}{\overset{\|}{C}}-CH_3$, etc.[1,2,3,4,5] In a recent series of articles[6-12], Winstein has attempted to treat $-CH_3$, -H, $-(CH_3)_2$ as neighboring groups. This seminar is limited to Winstein's recent work.

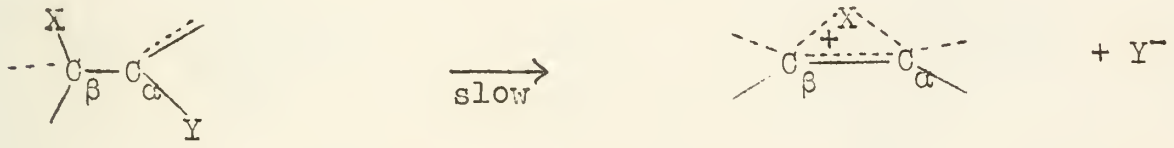
Driving force: $S_N1$ (Winstein's Lim. category) reactions are assumed to proceed through a rate-determining ionization(Fig.1). The activation energy of ionization will be lowered if a new bond

Fig. 1

$$R\text{-}X \xrightarrow[\text{slow}]{} R^+ + X^-$$

is formed at the same time the old bond is broken. Thus a neighboring group may provide a driving force for nucleophilic substitution by participating in the rate determining ionization(Fig. 2.) Two factors which influence this participation are (1) the stereochemical relationship between -X and -Y and (2) the nucleophilic character of -X.

Fig. 2



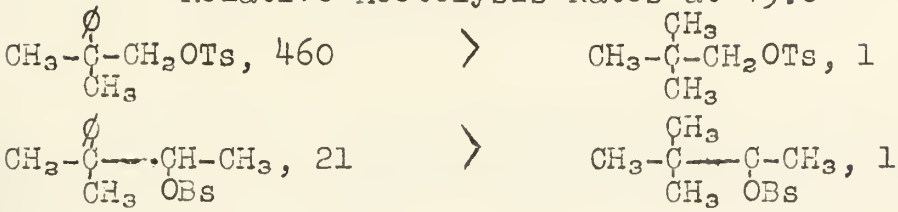

Descriptions of a number of experiments designed to evaluate Carbon and Hydrogen as neighboring groups follow:

1. Winstein[6] measured the solvolysis rates in acetic acid of a series of primary aryl sulfonates ($R_1R_2R_3C-CH_2-OSO_2Ar$ where $R_1R_2R_3$ may be $-\phi$, $-CH_3$, or -H) and a series of secondary arylsulfonates ($R_1R_2R_3C-\underset{\underset{SO_2AR}{|}}{\overset{O}{|}}CH-CH_3$ where $R_1$, $R_2$, $R_3$ may be $-\phi$, $-CH_3$, -H). Products were determined in only one case; the remaining solvolysis products were assigned structures on the basis of known reactions or by analogy to known reactions.

If it is assumed that neighboring group participation is the principal factor affecting the observed trend in rates, the neighboring groups may be associated with driving forces which increase in the order $-CH_3 < -\phi < -(CH_3)_2 < -(\phi)_2$. The relative order was the same for both the primary and the secondary series; the primary series showed considerably larger changes (Fig. 3).

Fig. 3

Relative Acetolysis Rates at 49.6°




The concept of the relief of steric strain in the transition state for hindered systems[13] would predict the same order of rates for each series i.e. $-(\phi)_2\rangle-(\phi)\rangle-CH_3$, but would also predict that the changes in the secondary series should be greater than the changes in the primary series. Since the primary series shows larger changes in rate than the secondary, Winstein concludes that participation and not relief of steric strain is the principal factor affecting the rates.

2. Comparison of the rate sequences[7], A and B, is another means of estimating $-CH_3$ as a participating group. Additional methyl groups enhance the rate in series B where the participation of methyl groups may occur. In series A where the principal participating group is $-CO_2^-$ a decrease in rate is observed in going from ethyl to t-butyl.

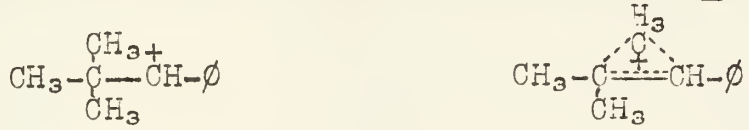
Fig. 4

Relative Solvolysis Rates

| A ($H_2O$, 70°) | | B (HCOOH, 25°) | |
|---|---|---|---|
| $(CH_3)_3CCH(Br)-COO^-$ | 2.1 | $(CH_3)_3-CH(OBs)-CH_3$ | 14.4 |
| $CH_3-CH_2-CH(Br)-COO^-$ | 4.2 | $CH_3-CH_2-CH(OBs)-CH_3$ | 2.5 |
| $CH_3-CH(Br)-COO^-$ | 2.7 | $CH_3-CH(OBs)-CH_3$ | 1 |

The effects observed are small and could easily be accounted for without the concept of the participation of methyl groups.

3. In an attempt to distinguish between structures such as I and II α-phenylneopentyl alcohol was resolved and optically active α-phenylneopentyl chloride and α-phenylneopentyl p-toluenesulfonate prepared.[9]




I II

The chloride and p-toluenesulfonate were solvolized to produce an essentially unrearranged product with a slight predominance of inversion. The results are consistent with I, and a bridged carbonium ion such as II is excluded.

4. The rates of solvolysis of p-methoxybenzylmethylcarbinyl, benzylmethylcarbinyl, and isopropyl esters were determined in a series of solvents.[10] The relative nucleophilic character of the solvents are known to be EtOH>AcOH>HCOOH.[14]

A comparison of the rates (Fig. 5 and Fig. 6) shows (1) that the participating $C_6H_5$- and p-$CH_3O$-$C_6H_4$- are in competition with the solvent for a backside attack on the nucleophilic center; (2) Participation becomes more important as we proceed to less nucleophilic solvents; (3)

p-$CH_3O$-$C_6H_4$- participates to a greater extent than $C_6H_5$-.

Fig. 5

Relative Solvolysis Rates

| | EtOH 50° | AcOH 50° | AcOH 25° | HCOOH 25° |
|---|---|---|---|---|
| p-$CH_3O$-$C_6H_4$-$CH_2$-$\underset{\vert}{C}H$-$CH_3$ | 6 | 20.5 | 32 | 37 |
| $C_6H_5$-$CH_2$-$\underset{\vert}{C}H$-$CH_3$ | 1 | 1 | 1 | 1 |
| $CH_3$-$\underset{\vert}{C}H$-$CH_3$ | 5 | 3.1 | 3.3 | 2 |

Fig. 6

Relative Solvolysis Rates

| | EtOH | AcOH | HCOOH |
|---|---|---|---|
| p-$CH_3O$-$C_6H_4$-$CH_2$-$\underset{\vert}{C}H$-$CH_3$ | 1 | 1.5 | 1500 |
| $C_6H_5$-$CH_2$-$\underset{\vert}{C}H$-$CH_3$ | 2.4 | 1 | 415 |
| $CH_3$-$\underset{\vert}{C}H$-$CH_3$ | 3.8 | 1 | 250 |

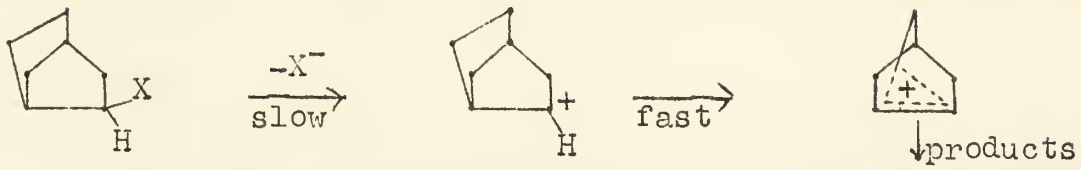
Optically active benzylmethylcarbinyl p-toluenesulfonate was solvolized in EtOH, AcOH, and HCOOH. The stereochemical results (Fig. 7) are consistent with the above interpretation of the kinetic data.

Fig. 7

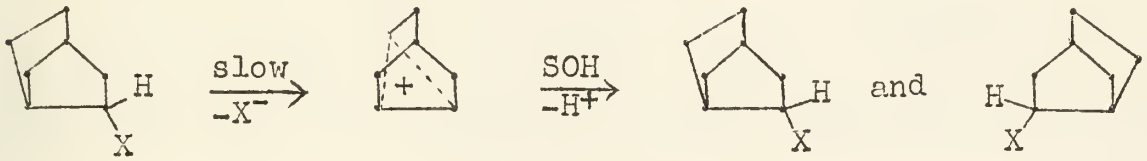
Steric Results of Solvolysis of Benzylmethylcarbinyl p-toluenesulfonate.

| Solvent | Inversion | Retention |
|---|---|---|
| EtOH | 93 | 7 |
| AcOH | 65 | 35 |
| HCOOH | 15 | 85 |

5. Optically active endo-norbornyl p-bromobenzensulfonate is solvolized to the exo-product with nearly complete loss of activity.[11] The rate of racemization equals the rate of solvolysis within the experimental error. These results may be explained by the following mechanism.




6. Optically active exo-norbornyl p-bromobenzenesulfonate is solvolized to the inactive exo-derivative. The rate of solvolysis for the exo-isomer greatly exceeds the rate of solvolysis of the endo-isomer. Winstein believes that the following mechanism best explains these results.

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# DITHIOLS

Reported by Richard F. Heitmiller May 2, 1952

## I. INTRODUCTION

During the past ten years dithiols and their simple oxidation products, linear and cyclic disulfides have received extensive study. The intense interest in these compounds has arisen in widely divergent fields from a combination of some rather unusual properties which are inherent in organic sulfur compounds.

The dissimilarities of organic sulfur compounds to their oxygen analogs which reveal themselves in many differences in chemical and physical properties arise from the marked difference in electronegativity between the two atoms (O=3.5; S=2.5).[1] It is for this reason that the so-called "special" reactions of dithiols are not to be considered anomalous; they are instead to be expected.

## II. PREPARATION

Dithiols may be prepared in three general ways:

A. Nucleophilic Displacement of Dihalides[2,3,4,5]

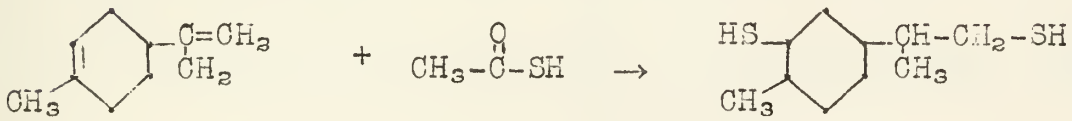
$$-\underset{X}{CH}-(CH_2)_m\underset{X}{CH}- + H_2N-\overset{S}{\overset{\|}{C}}-NH_2 \rightarrow\rightarrow -\underset{SH}{CH}-(CH_2)_m\underset{SH}{CH}-$$

$$\text{"} + KS-\overset{S}{\overset{\|}{C}}-OC_2H_5 \text{"}$$

$$\text{"} + KSCN \text{"}$$

$$\text{"} + KHS \text{"}$$

B. Addition of Thiolacetic Acid to Diolefins[6]



C. Reductive Thiolation of Aldehydes, Ketones, or Nitriles in the Presence of Sulfactive Hydrogenation Catalysts.[7]

$$CH_3-CH=CH-\overset{O}{\overset{\|}{C}}H + S \xrightarrow[\text{cobalt sulfide}\\ \text{2000 psi.}\\ \text{150-200°}]{H_2} CH_3-\underset{SH}{CH}-CH_2-CH_2-SH$$

gem - Dithiols may be prepared in this way also[8]

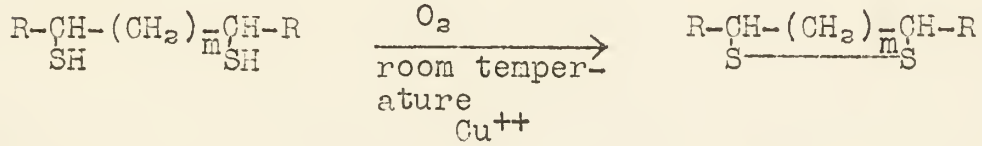
$$R_2C=O + H_2S \xrightarrow[\text{pressure}]{\text{heat}} R_2C(SH)_2$$

## III. CHEMICAL PROPERTIES

A. Oxidation of Dithiols to Cyclic Disulfides.

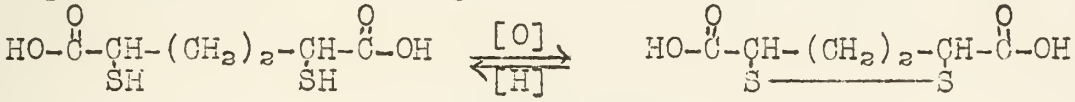
Mild oxidation of dithiols produces cyclic disulfides and

polymeric linear disulfides. The rate of oxidation of dithiols with a heavy metal as a catalyst depends on the pH of the solution, the distance of the -SH groups from each other and on the electron withdrawing power of the residual groups.[9]

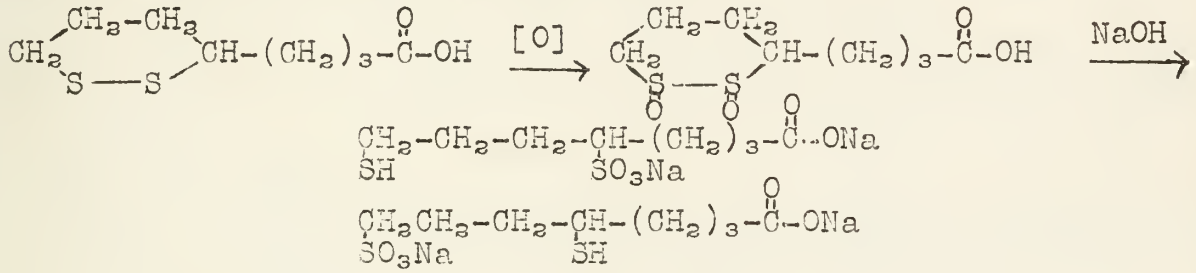



The cyclic disulfide may be formed as the major product if the reaction time is kept to a minimum. These cyclic compounds are reasonably stable at room temperature in the dry state, but are slowly oxidized by air. In solution, a dynamic equilibrium exists between the dithiol and the cyclic disulfide. One thoroughly investigated case is that of α-α'-dithioladipic acid.[3,10]

It has been found that a solution of optically pure l-α-α'-dithioladipic acid partially loses its activity on standing with base. The amount of activity which is lost is a function of the pH of solution, the most basic solution losing the greater amount of optical activity in a given time.




Further oxidation of a cyclic disulfide derived from 5,8-dithioloctanoic acid produces a cyclic compound which is stable to acid, but in the presence of strong base reacts to give a compound which has two acidic hydrogens and one free thiol group.[11] The reaction path is probably as follows:[12]




B. Polymerization Reactions of Dithiols

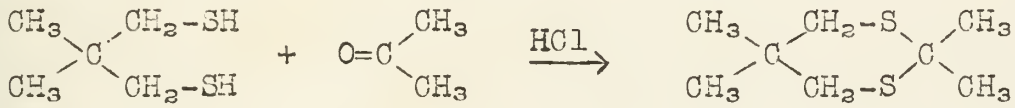
It has been found that dithiols will add to non-conjugated double bonds in a non-Markownikoff manner to yield high molecular weight polyalkylene sulfides. Suitable variations of this procedure will give rubbery products or polymers with fiber forming properties.[13] As has been previously mentioned, mild oxidation of dithiols will give polymeric material. These are linear polymers and have fairly high molecular weights. It is thought at this time that cross-linked polymers can be formed by using stronger oxidizing agents.

C. Reactions with Heavy Metals

Dithiols combine with a number of heavy metals, forming complex compounds, most of which are insoluble. Fe, Pb, Sn, Bi, Cu, Co, Ni, Se, and Sb form colored complexes. Zn, Cd, and Hg give white precipitates. Mg combines forming colorless soluble compounds.[14] Although the reactions are very useful, and quite general, not much work has been done to elucidate the structure of these molecules. Many of the reactions with heavy metals which lead to salt formation also produce desulfurization, with metal sulfide elimination and, presumably, olefin formation.[15]

D. Reaction with Aldehydes and Ketones; the Formation of Cyclic Thioacetals

Dithiols react with aldehydes and ketones to form cyclic thioacetals.[16] The reaction is directly analogous to the formation of cyclic acetals from glycols, and is extremely useful since the cyclic thioacetals are usually solids.



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# NUCLEOPHILIC DISPLACEMENT REACTIONS OF ORTHO- AND PARA-NITROARYL HALIDES

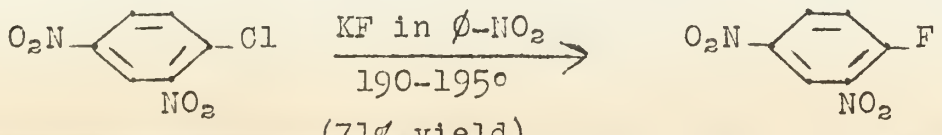
Reported by Herbert O. House May 9, 1952

The labilizing effect exerted by an ortho and/or para nitro group has been useful in many of the synthetic problems of organic chemistry. The halogen atom of nitro- and especially di- and trinitroaryl halides of this type undergoes facile displacement by a variety of nucleophilic reagents including amines, alcohols, and phenols.

Recent Applications of the Reaction: The high order of activity of 2,4-dinitrofluorobenzene has made this reagnet useful in a number of instances. While 2,4-dinitrochlorobenzene will react with the sodium salts of phenols when warmed in ethanol to produce the corresponding diaryl ethers, the corresponding reaction with alcohols is not readily effected even if the sodium alkoxide is used at elevated temperatures. However, alcohols react readily when treated with 2,4-dinitrofluorobenzene in benzene solution in the presence of a small amount of triethylamine as a catalyst.[1] The reaction with primary alcohols is exothermic, but secondary and tertiary alcohols require slight warming. Reaction with all three classes of alcohols as well as unsaturated alcohols proceeds without apparent rearrangement yielding crystalline ethers. Thus the reaction is ideal for the preparation of derivatives for identification purposes. The reagent enjoys certain advantages not found with many of the other materials used to prepare alcohol derivatives. The 2,4-dinitrofluorobenzene is quite stable to atmospheric moisture, the formation of derivatives is not impaired by the presence of small amounts of water, and any 2,4-dinitrophenol produced may be readily removed from the desired derivative.

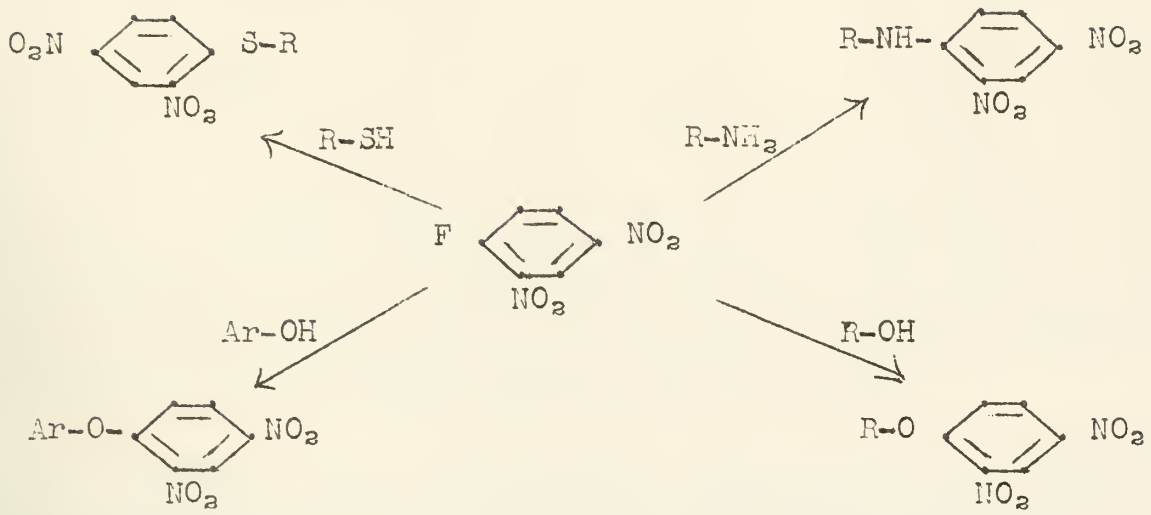
Although 2,4-dinitrochlorobenzene will react with aliphatic primary and secondary amines, extension of the reaction to amino acids requires the use of higher temperatures. Use of the corresponding fluoro compound allows the N-dinitrophenylamino acid to be prepared at room temperature, sodium bicarbonate serving as a catalyst.[2] So mild is the reaction that the free amino groups of proteins may be arylated without hydrolysis of the peptide bonds present. Subsequent acid hydrolysis of the protein permits the terminal amino acid residues of the protein to be identified. Under these conditions the reagent also reacts with phenolic hydroxyl groups and with mercapto groups but not with alcohols. The dinitrophenylamino acids are all yellow-orange solids which may be separated by one of the chromatographic techniquies available and quantitatively determined colorimetrically.

The 2,4-dinitrofluorobenzene, prepared originally by the nitration of p-nitrofluorobenzene obtained from p-nitroaniline,[3] is readily prepared from the corresponding chloro compound utilizing a rather remarkable nucleophilic displacement process.[4]

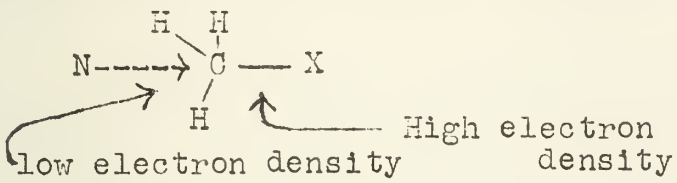



(71% yield)

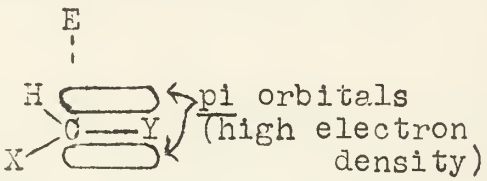
reactions of 2,4-dinitrofluorobenzene




Nucleophilic Reactions of Unsaturated Systems: In general attack by a nucleophilic entity is a property of the saturated carbon atom while unsaturated systems including aromatic molecules are more susceptible to electrophilic attack. The type of bond involved in each system provides an explanation for these facts.[5] The saturated carbon atom (I) is bonded to four other atoms by sigma bonds (the electron density of the bonding pair of electrons is distributed symmetrically about the line joining the centers of the atomic nuclei) while the unsaturated system (II) contains at least one pi bond (the electron density of one pair of bonding electrons involved in the multiple bond is distributed above and below the line joining the centers of the atomic nuclei).




I



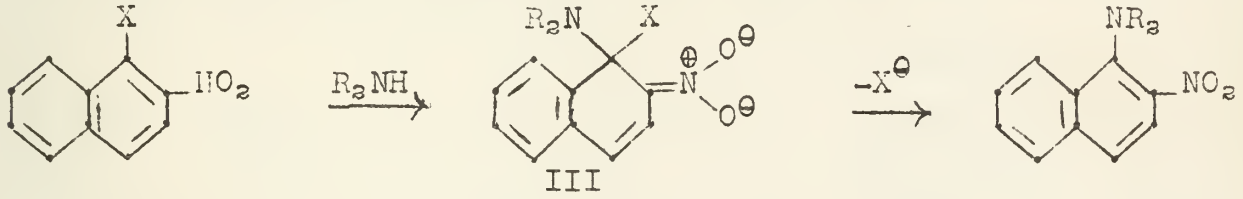

II

While a saturated system could most readily be attacked by an electron-rich nucleophilic reagent (N), the same reagent would be repelled by an unsaturated system which would favor the approach of an electron-poor electrophilic agent (E). However, if atom Y is or is bonded to a powerful electron-withdrawing group the electron density of the pi orbitals is depleted permitting the approach of a nucleophilic reagent with subsequent addition, as in the case of conjugate addition reactions, or displacement occurring.

The order of halogen reactivity in nucleophilic displacement reactions at a saturated carbon atom has been found to be I> Br> Cl> F in accordance with the polarizabilities of the carbon-halogen bonds involved.[6] The order of halogen activity for the nitro- and dinitroaryl halides is the reverse: F> Cl, Br> I.[7]

Mechanism of the Reaction: Kinetic studies of the aminolysis of 2,4-dinitrochlorobenzene with substituted anilines showed the reaction rates to be augmented by an increase in the electron density of the nucleophilic agent.[8] No analogous relationship could be demonstrated between the basicity of a series of aliphatic amines used and their reaction rates. However the bulky members of the series did exhibit a retarding steric effect.[9] Such a steric effect must be of minor importance since with all the mononitroaryl halides measured the ortho isomers proved to be the most active.[10] The activities of a series of 4-substituted-2-nitroaryl chlorides decrease in accordance with the increasing electron-releasing power of the varying substituent.[11] All of these observations, accompanied by the fact that the aminolysis of both 2,4-dinitrochlorobenzene[9] and 2,4-dinitrofluorobenzene[7] are strictly bimolecular, strongly support a bimolecular nucleophilic displacement mechanism.

The displacement process could occur in one of two different ways. Berliner, Quinn, and Edgerton considered the initial step to be the formation of a stable complex (III) whose decomposition is the rate-determining step.[12] These investigators believed the yellow color produced in the reaction mixture was ascribable to the presence of this complex. It was found that 1-halo-2-nitronaphthalenes, in contrast to the monohalonapthalenes, were more reactive than 2-halo-1-nitronaphthalenes. It was suggested that the coplanar structure required for the nitro group in the complex (III) would be sterically more inhibited in the 1- than in the 2-position.



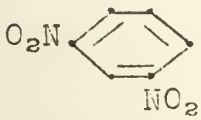

III

Several pieces of evidence oppose such a mechanism. Colored complexes are formed when o-nitrochlorobenzene and 2,4-dinitrochlorobenzene are treated with diphenylamine. The color of the complexes is reduced with an increase in temperature demonstrating the absence of covalent character.[13] Such complexes are not intermediates in the formation of the amines since their decomposition is not unimolecular.[14] Also, the mechanism requires the separation of the halogen as an anion is the rate determining step. Such a process should be inhibited by the presence of an additional electron-withdrawing group in the molecule. However kinetic measurements show the dinitroaryl halides to be more reactive than the mononitro compounds.[7]

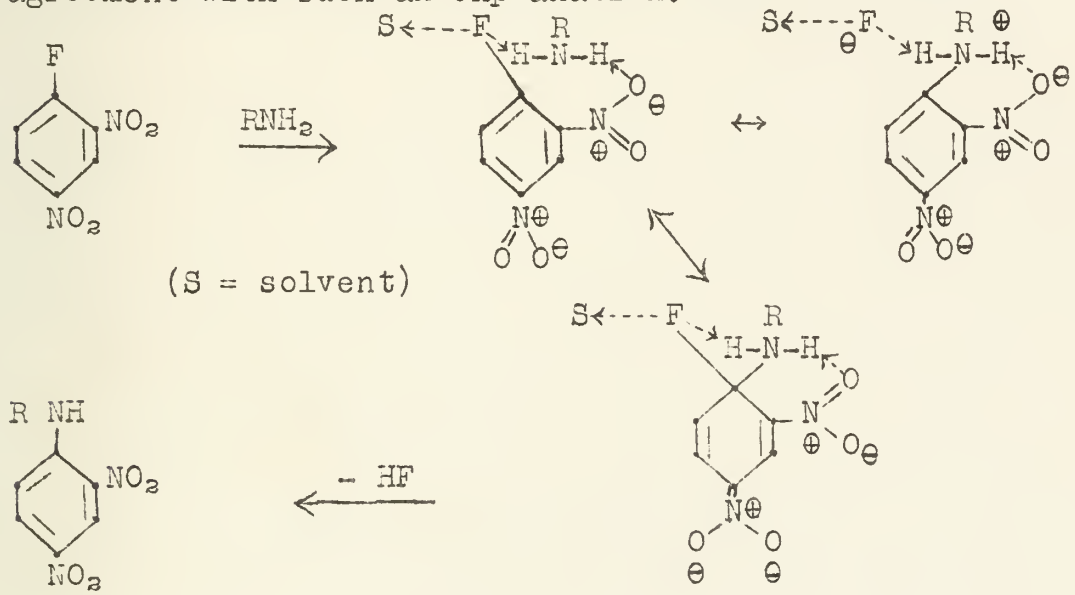
The low energy of activation of the fluoro compound compared with the other dinitroaryl halides is responsible for the high order of reactivity observed (Table I).[7] The variation in the dipole moments of the different halides seems too slight to account for the large differences in activity. Chapman and Parker believe the primary cause for the very low activation energy to be solvation of the departing fluorine anion since solvation of this ion is much greater than that of the other halide ions.[7] Their contention is supported by the increase in rate observed when ethanol-water rather

than ethanol alone is used as a solvent. The catalytic effect of excess amine on the aminolysis rate of 2,4-dinitrochlorobenzene[9] could be of the same nature but to a lesser degree.

Table I

| value of X in  | amine used | | | | | |
|---|---|---|---|---|---|---|
| | aniline | | | m-toluidine | | |
| | $10^4 k_{50}$ | $E_A$(kcal) | log A | $10^4 k_{50}$ | $E_A$(kcal) | log A |
| F | 168 | 6.40 | 2.55 | 282 | 5.55 | 2.88 |
| Cl | 2.69 | 11.2 | 4.0 | 3.91 | 11.6 | 4.4 |
| Br | 4.05 | 11.2 | 4.2 | 5.59 | 11.6 | 4.6 |
| I | 1.31 | - | - | - | - | - |

The stabilizing resonance structures of the transition state suggest a further and, perhaps, an equally important reason for the high reactivity of the fluorine compounds. Formation of hydrogen bonds between the amine and the oxygen and fluorine atoms would facilitate the approach of the attacking entity and increase the stability of the transition state. Since hydrogen bonding is negligible with halogen atoms other than fluorine the increased activity of the fluorine compound is to be expected. Also, the increased activity of the ortho isomers of the mononitroaryl halides is in agreement with such an explanation.

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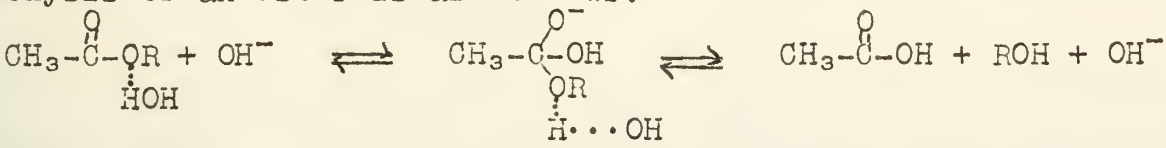
# THE CLEAVAGE OF CARBON SULFUR BONDS

Reported by J. A. MacDonald May 9, 1952

A review of the general field of carbon-sulfur bond cleavage in divalent sulfur compounds is given by Tarbell and Harnish[1]. This seminar deals only with some particular cases of carbon-sulfur bond cleavage which have been investigated recently.

Quantitative studies on the hydrolysis of esters and thiolesters, in both acid and alkali media, have been made by Tarbell and coworkers, and by Schaefgen.

Schaefgen[2] suggests that the mechanism for the alkaline hydrolysis of an ester is as follows:



However he believes that because of the relative weakness of the S···HO bond the hydrolysis of thiolesters proceeds without solvation of the thiolester.

## KINETIC DATA ON HYDROLYSIS IN 62% AQUEOUS ACETONE.[2,3,4]

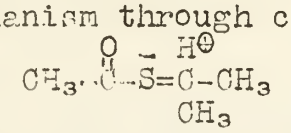
### BASE CATALYZED (SECOND ORDER)

| R | $R-S-\overset{O}{\overset{\|}{C}}-CH_3$ T °C | kx10³ $(m./l.)^{-1}$/sec. | E kcal./mole | $\Delta S^{\ddagger}$ cal./deg./mole | $R-O-\overset{O}{\overset{\|}{C}}-CH_3$ T °C | kx10³ $(m./l.^{-1})$/sec. | E kcal./mole | $\Delta S^{\ddagger}$ cal./deg./mole |
|---|---|---|---|---|---|---|---|---|
| Methyl | 0.0 | 7.77 | 13.1 | -22 | 0.40 | 15.1 | 12.2 | -24 |
| Ethyl | 10.0 | 10.6 | 14.4 | -19 | 0.6 | 6.75 | 12.2 | -27 |
| i Butyl | 10.0 | 4.13 | 18.5 | - 6 | 0.30 | 2.45 | 12.4 | -27 |
| i Propyl | 0.0 | 1.44 | 17.6 | - 9 | 0.30 | 1.05 | 12.2 | -29 |
| t Butyl | 0.0 | 0.431 | 17.0 | -14 | 30.1 | 0.466 | 14.3 | -29 |
| Allyl | 0.00 | 14.9 | 17.9 | - 3 | 0.00 | 9.0 | 9.9 | -33 |
| Benzyl | 0.00 | 10.4 | 16. | -12 | 0.00 | 9.8 | 14.1 | -18 |
| Trityl | 0.00 | 2.2 | 18. | - 5 | - | - | - | - |

### ACID CATALYZED (FIRST ORDER)

| R | $R-S-\overset{O}{\overset{\|}{C}}-CH_3$ T °C | kx10³ $sec.^{-1}$ | E kcal./mole | $\Delta S^{\ddagger}$ cal./deg./mole | $R-O-\overset{O}{\overset{\|}{C}}-CH_3$ T °C | kx10⁵ $sec.^{-1}$ | E kcal./mole | $\Delta S^{\ddagger}$ cal./deg./mole. |
|---|---|---|---|---|---|---|---|---|
| Methyl | 40.0 | 0.803 | 17.1 | -29 | 40.1 | 20 | 15.7 | -27 |
| Ethyl | 40. | 0.581 | 18.0 | -27 | 40.0 | 16.4 | 16.0 | -27 |
| i-Butyl | 40.6 | 0.503 | 20.5 | -19 | 40.0 | 11.9 | 16.1 | -27 |
| i-Propyl | 40.0 | 0.502 | 19.7 | -22 | 40.0 | 7.85 | 16.3 | -27 |
| t-Butyl | 40.6 | 0.460 | 20.7 | -19 | 40.0 | 4.50 | 23.2 | - 6 |
| Allyl | 42.06 | 1.05 | 16.3 | -32 | 42.06 | 11.5 | 17.3 | -24 |
| Benzyl | 40.04 | 0.44 | 19.8 | -21.6 | 40.04 | 8.11 | 17.1 | -24.5 |
| Trityl | 40.04 | 12.7 | 29.7 | +16 | - | - | - | - |

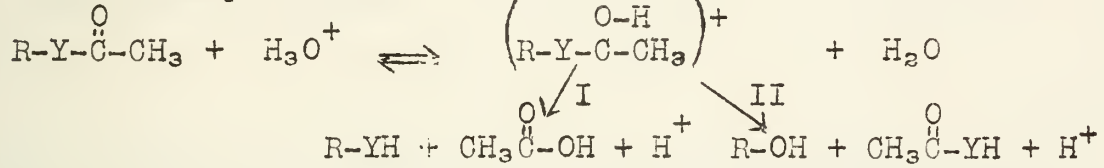
As the series of alkyl esters is ascended, the activation energy for the alkaline hydrolysis of the thiolacetates increases much more than does the activation energy for acetates. This increase in the thiolester series is attributed to the transmission to the carbonyl carbon atom of the electron releasing inductive effect of the alkyl groups. That sulfur is able to transmit this effect while oxygen is not is to be expected in view of the greater polarizability of the sulfur atom. It is also possible that sulfur can increase the electron density at the carbonyl carbon by a hyperconjugative mechanism through contributions from resonance forms such as:[3]



In alkaline hyrolysis the thiolesters have more positive E and $\Delta S^{\ddagger}$ values than the esters. The higher values of E are attributed to the SR group being more effective than OR in increasing the electron density at the carbonyl carbon, and to lack of cooperation from $H_2O$ in lowering the electron density at this point in the case of the thiolesters.[3]

The less positive entropy of activation of esters means that on entering the transition state esters lose more degrees of freedom, with the formation of more rigid, exactly oriented structures, relative to the original compounds, than do thiolesters. This less precise orientation in the thiolesters may be due to less crowding around the sulfur atom as a result of the larger size of sulfur and the lack of hydration of thiolesters in the transition state.[3]

For the acid hydrolysis of esters or thiolesters, two types of fission are possible:



In either case the cleavage step is the rate determining one. Path I involves a weakening of the acyl-Y bond as a result of the attack of water on the conjugate acid of the ester, accompanied by the solvation of RY. Path II involves solvation of the departing $R^+$ group, with the weakening of the alkyl-Y bond.[4]

While most esters follow path I, some, including t-butyl acetate,[3,5] follow path II. t-Butyl thiolacetate, however, follows path I. This difference in the courses of the reactions of the analagous compounds is attributed to the higher electronegativity of oxygen, which would favor the formation of the t-butyl carbonium ion, and hence path II.[3] Not all thiolesters follow path I, however. Trityl thiolacetate was found to follow path II,[6] although allyl and benzyl thiolacetates, in which the carbon-sulfur bond might be expected to be weak, do not.[4]

In kinetic studies, it was shown that in acid solution acetates hydrolyze faster than thiolacetates. $\Delta S^{\ddagger}$ is approximately the same for corresponding esters and thiolesters, indicating similar configurational transformations. It is suggested that E for the thiolesters is higher because the acyl-S bond is less highly polarized than the acyl-O bond. Polarization of the acyl-Y bond of course favors the attack of $H_2O$ on the protonated ester.[2] The greater variation in E in the thiolester series is again attributed to transmission through sulfur of the inductive effect of the alkyl group, and to a hyperconjugative mechanism involving sulfur.[3]

Trityl thiolacetate and t-butyl acetate, which hydrolyze by alkyl-Y cleavage, show much higher values for E, and a much more positive value for $\Delta S^{\ddagger}$ than the other members of their series. This relatively positive value for $\Delta S^{\ddagger}$ suggests that the transition states of these compounds have more degrees of freedom than have the transition states of the other esters. This is in agreement with the idea that the rate determing step is a dissociation.[4]

Tarbell and Harnish[7] have investigated the cleavage of benzyl phenyl sulfide. They found that, in contrast to the facile cleavage of oxygen ethers, benzyl phenyl sulfide was not cleaved by aqueous halogen acids. Glacial acetic acid containing 30% HBr yielded only about 30% of cleavage products. However aluminum bromide in chlorobenzene or benzene gave good yields of thiophenol. Kinetic studies showed the rate to be first order in benzyl phenyl sulfide, and independent of the concentration of aluminum bromide, as long as slightly more than one mole of the latter was present. They suggest the following mechanism:

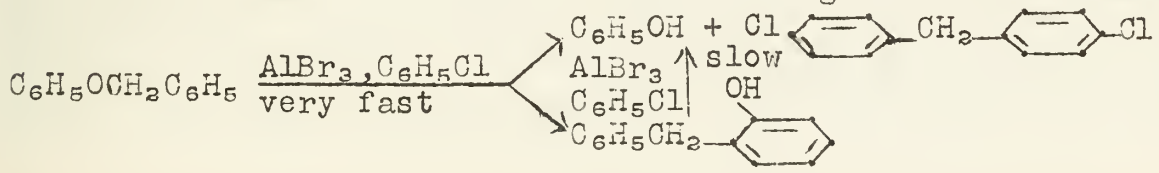
$$C_6H_5SCH_2C_6H_5 + AlBr_3 \rightarrow C_6H_5SCH_2C_6H_5 \rightarrow C_6H_5CH_2Br + C_6H_5S\text{-}AlBr_2$$

$$\downarrow AlBr_3 \qquad\qquad \downarrow H_2O$$

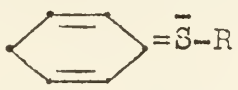
$$C_6H_5SH$$

The cleavage is considered to be the rate determining step. Indirect evidence for the necessity of coordination between benzyl phenyl sulfide and $AlBr_3$ was provided by the fact that the presence of one mole of an oxygenated solvent such as ethyl alcohol, acetic acid or diethyl ether per mole of $AlBr_3$ almost completely prevented cleavage. Determination of the rates of cleavage of some halogenated benzyl phenyl sulfides[8] showed that the presence of electron attracting groups speeded up the cleavage, in accord with the above mechanism.

An investigation of the action of $AlBr_3$ on benzyl phenyl ether in chlorobenzene[9] showed that the following reaction occurred:




The formation of dichlorodiphenylmethanes involves either chlorine transfer or exchange of aryl groups, either reaction being catalyzed by $AlBr_3$. The formation of o-benzylphenol is considered to be intramolecular.

The $AlBr_3$ cleavage of benzyl phenyl sulfide thus follows a different course from the cleavage of benzyl phenyl ether. The results in the two cases emphasize two differences between oxygen and sulfur compounds: (1) Ethers are cleaved at a greater rate by acidic reagents than are sulfides. (2) The hydroxyl or alkoxyl group is more effective in promoting electrophilic substitution on the aromatic nucleus than are the corresponding sulfur containing groups. This is probably due to the fact that the sulfur compounds have an electron withdrawing effect due to contributions from structures such as  in which sulfur has expanded its valence shell[9].

Bonner[10] has investigated the stereochemical path of the reductive desulfuration of (-)-and (+)-2-phenyl-2-phenylmercaptopropionamide by Raney nickel and ethanol, and observed that racemization occurred. That this racemization was a result of mechanism and not of a subsequent reaction was shown by the fact that (-) -2-phenylpropionamide was not racemized by treatment under identical conditions. When the sulfones corresponding to the above sulfides were treated with Raney nickel and ethanol, optically active amides, the rotations of which indicated a racemization of only 10%, were obtained.

Hauptmann and Wladislaw[11] propose that in Raney nickel desulfuration chemisorption involving the unshared electrons of sulfur is the initial step. This weakening of the carbon-sulfur bond permits detachment of a free radical which, in the presence of adsorbed hydrogen, is reduced to the hydrocarbon:

$$R\text{-}S\text{-}R + Ni. \rightarrow R. + NiSR \qquad R. + H(\text{adsorbed}) \rightarrow RH$$

The racemization of the sulfide observed by Bonner is in agreement with this free radical mechanism. But the sulfone desulfuration, with retention of activity, is probably not free radical; nor could Hauptmann's chemisorption occur, since the sulfur here has no unshared electrons. Bonner proposes that in the case of the sulfone, adsorption occurs through the oxygen atoms, and that the adsorbed molecule is then attacked by, or attacks, an adjacent adsorbed hydrogen atom in such a way that the carbon-sulfur bond is broken, and an optically active reduction product is simultaneously formed.

Cronyn[12] has investigated the reduction of substituted bis-(ethanesulfonyl)-methanes. 5,5-Bis-(ethanesulfonyl)-2,8-dimethylnonane(I) proved very resistant to reduction; heating it to 220° with three times its weight of Raney nickel in cyclohexane under 2500 pounds of hydrogen gave a product in which only one sulfone group had been removed. Both sulfone groups were removed only after heating to 250° for 36 hours. In aqueous alkali at 250° over Raney nickel three hydrocarbons, II, III, and IV were obtained.

$R_2C(SO_2C_2H_5)_2$ (I) $\quad R_2CH_2$ (II) $\quad R\text{-}CH{=}CH\text{-}CH_2\text{-}CH(CH_3)\text{-}CH_3$ (III) $\quad R_2C{=}CHCH_3$ (IV)

$R = CH_3\text{-}CH(CH_3)\text{-}CH_2\text{-}CH_2\text{-}$

III presumably arose from the monosulfone by an elimination reaction initiated by base attack on the β carbon. IV was also obtained from the direct action of alkali alone. It is suggested that the formation of IV occurs through a mechanism analagous to that proposed for the reaction of α-halosulfones.[13]

$$R_2C(SO_2C_2H_5)_2 \xrightarrow{OH^-} R_2C(C_2H_5)(SO_2)\text{-}\bar{C}H\text{-}CH_3 \rightarrow R_2C(S(O_2))\text{-}CH\text{-}CH_3 \xrightarrow{OH^-} SO_3^{=} + R_2C{=}CH\text{-}CH_3$$

The acid V desulfurized to 5-phenylpentanoic acid on treatment with Raney nickel alloy in alkaline solution. However VI was desulfurized only by heating to 220° with Raney nickel under hydrogen in dilute sodium hydroxide, and the product was 4-hydroxy-7-methyloctanoic acid lactone.

$C_6H_5\text{-}CH_2\text{-}C(SO_2C_2H_5)_2\text{-}CH_2\text{-}CH_2\text{-}COOH$ (V) $\quad CH_3\text{-}CH(CH_3)\text{-}CH_2\text{-}CH_2\text{-}C(SO_2C_2H_5)_2\text{-}CH_2\text{-}CH_2\text{-}COOH$ (VI)

The ease of reduction of acid V is rationalized on the basis of an elimination reaction initiated by the attack of base on the methylene activated by the phenyl group. The unsaturated sulfone so produced could be desulfurized directly, or by hydrogenation followed by a repetition of the elimination reaction. The reduction of VI is believed to proceed via the hydrogenolysis of one sulfone group, followed by an intramolecular nucleophilic displacement of the remaining sulfone by carboxyl.

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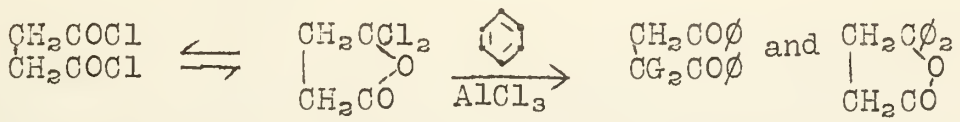
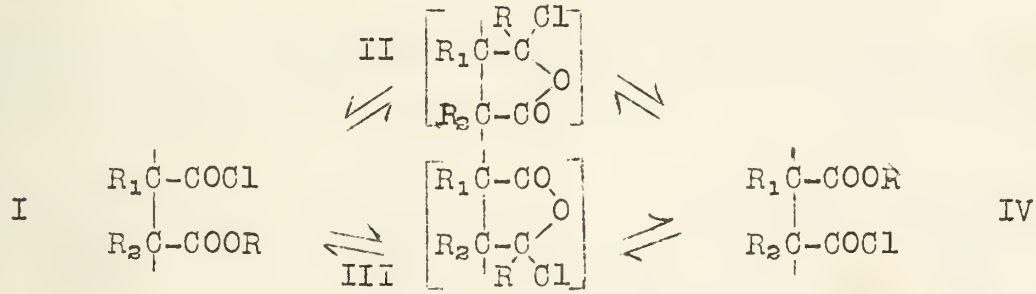
# RING-CHAIN TAUTOMERISM AND REARRANGEMENT IN ACID CHLORIDES

Reported by E. D. Weil May 9, 1952

The existance of ring-chain tautomerism in dihalides of certain dibasic acids has long been recognized. In the case of phthaloyl chloride, both the open-chain and cyclic (pseudo-chloride) forms have been isolated; the dichlorides of various other 1,2- and 1,3-dicarboxylic acids exhibit tautomerism by giving reactions indicative of the presence of both forms.[1]

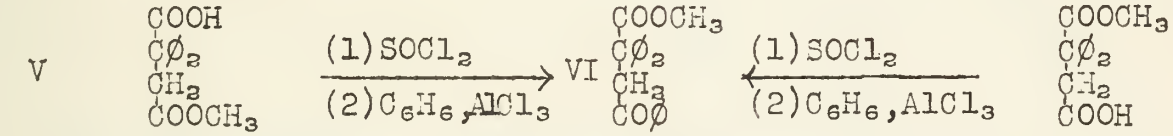


Recent studies have been made on a rearrangement attributable to this sort of tautomerism in the acid chlorides prepared from half-esters of dibasic acids.[2] These compounds have often been employed as synthetic intermediates, consequently a number of syntheses recorded in the literature must now be viewed as equivocal. In general, the acid chloride I may enter into reactions to give derivatives of either I or IV or a mixture of both.



Ring-chain tautomerism of this sort requires the carboxyl groups of the parent acid to be 1,2 or 1,3 in the aliphatic series or 1,2 in the aromatic series.

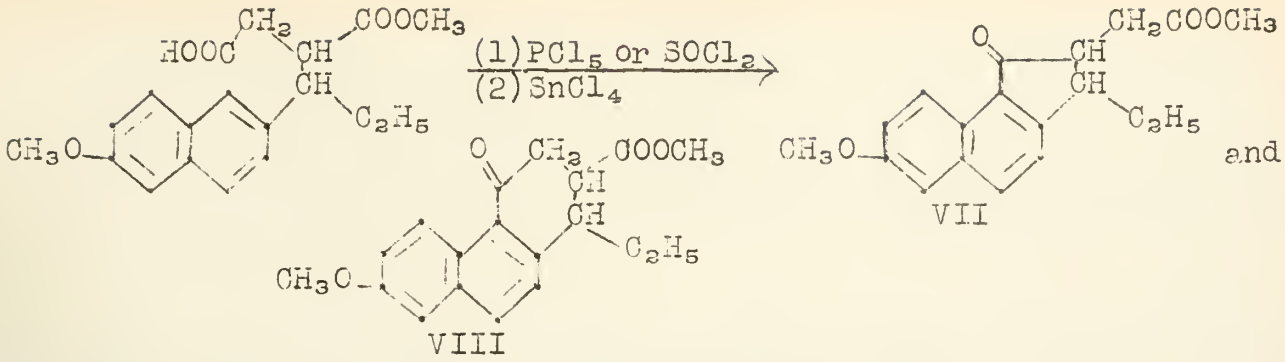
Aliphatic 1,2-dicarboxylic series. An example of the rearrangement is the following,[2,3] from V to VI.



It is postulated that the equilibrium existing between the tautomeric forms of the acid chloride is shifted, during the Friedel-Crafts reaction, to give the product derived from the open-chain chloride least hindered at the α-carbon.

The unrearranged acid chloride corresponding to V may be prepared by the action of pure thionyl chloride in cold absolute ether on the silver salt of V.[3]

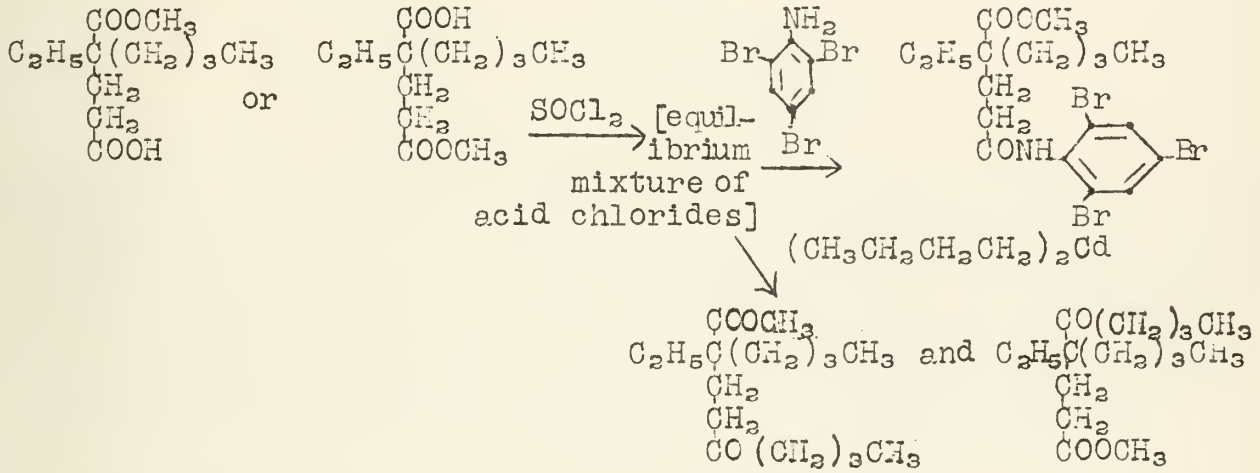
Turner and coworkers performed a ring closure on the acid chloride of a half-ester and obtained rearranged as well as unrearranged products.[4]



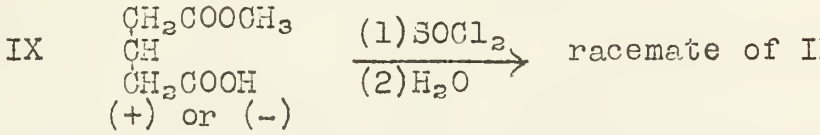

The desired product, VIII, was obtained predominantly, a result predictable on the basis of steric effects. The yield of the rearrangement product, VII, was increased by use of higher reaction temperatures.

Support for the postulated cyclic intermediate in these rearrangements is given by the fact that rearrangement has not been observed in chlorides of the half-esters of trans-alkene 1,2-dicarboxylic acids, where ring formation is prevented.[5]

Aliphatic 1,3-dicarboxylic series. Evidence for the tautomeric equilibrium is provided by Cason's study of the chlorides of α-ethyl-α-butylglutaric acid monoesters.[6] The following reactions were observed.




The rearrangement of acid chlorides can serve as a means of racemization, as found by Ställberg-Stenhagen.[3]

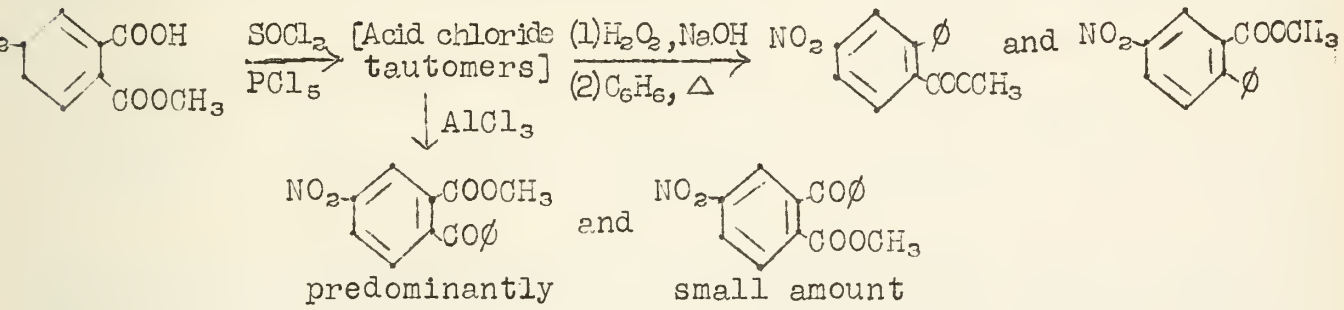



The optically -active acid could be recovered unchanged from the chloride if the latter were prepared using extremely pure thionyl chloride below 30° or by employing oxalyl chloride.

Acid chlorides of aliphatic half-esters have frequently been used in Arndt-Eistert syntheses, particularly in steroid studies. In most of the many examples reported, yields were high and no rearrangement observed; this may be attributed to the widespread use of oxalyl chloride or purified thionyl chloride under mild conditions. When unpurified thionyl chloride or phosphorus pentachloride have been employed, low yields and difficult purifications have often been reported.[2]

Aromatic 1,2-dicarboxylic Acids. The acid chloride rearrangement has led to some confusion in assigning structures to various aroylbenzoic acids prepared by Friedel-Crafts reactions. Doubtful cases have recently been reviewed and reinvestigated by Chase and Hey.[2,8]

Two procedures were used by these workers to detect rearrangement in acid chlorides of the 3- and 4-nitrophthalic half-esters, (1) conversion to peroxides followed by decomposition in benzene to yield nitrobiphenyls, and (2) Friedel-Crafts reactions with benzene. The rearrangement was shown to occur readily in the 4-nitrophthalic series and to a slight extent in the 3-nitrophthalic series.




Mechanism. The absence of rearrangement in acid chlorides of half-esters of substituted isophthalic and terephthalic acids indicates that the reaction is intramolecular, and involves a cyclic intermediate. Chase and Hey consider all rearrangements of this type to procede by way of lactonic intermediates (II,III), these having been originally suggested by Bredt.[9] The lactonic structure is closely analogous to that of pseudo acid chlorides and to the α-hydroxy-α-alkoxyphthalide intermediate recently observed in alcoholysis of substituted phthalic anhydrides.[10]

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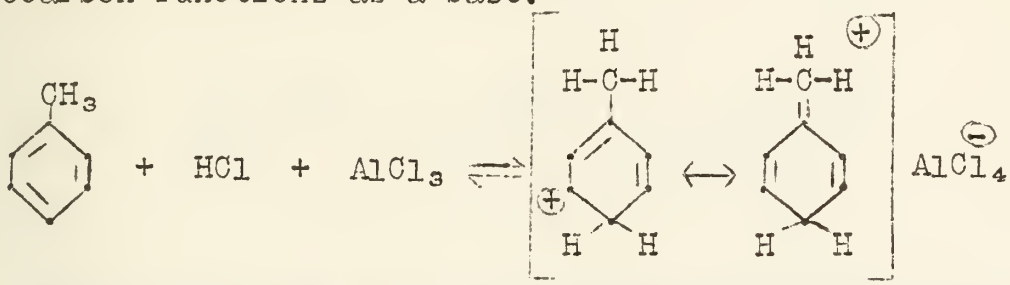
# ISOMERIZATION OF ALKYL ARYL KETONES

Reported by D. E. Brasure May 16, 1952

Although aluminum chloride has been used as a catalyst in organic chemistry for many years, its exact nature has remained a mystery. Early writers referred to the acid $HAlCl_4$ as the active catalytic species, although the available evidence belied its existence. Recently Brown and Pearsall have presented a clearer picture of the catalyst.[1,2] They found that under conditions deemed most favorable for its existence, although salts of the acid did exist, the free acid itself did not. Pure aluminum chloride had no catalytic effect; only when hydrogen chloride was introduced did a reaction with toluene occur. They found that in the presence of toluene at low temperatures (-80°) and high concentrations of hydrogen chloride, aluminum chloride and hydrogen chloride combined in a ratio of 1:1 whereas at higher temperatures and lower concentrations of hydrochloric acid the ratio changed to 2 $AlCl_3$:1 HCl. It is believed that the Friedel-Crafts complexes are organic salts of the hypothetical acids $HAlCl_4$ and $HAl_2Cl_7$ in which the aromatic hydrocarbon functions as a base:

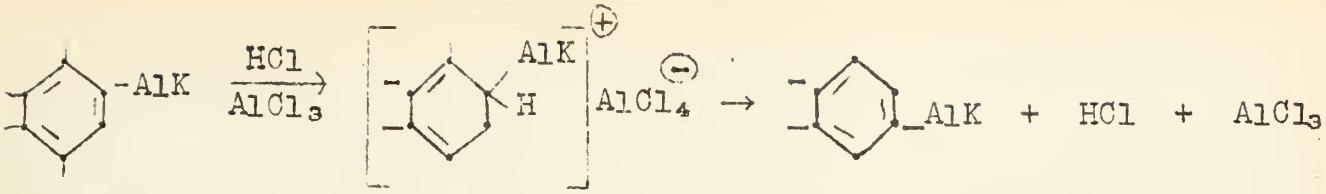


This picture is borne out by the hydrogen exchange which occurs when deuterium chloride is passed into a mixture of benzene and aluminum chloride.[3] Evidence for the basic properties of aromatic hydrocarbons has been presented in a previous seminar.[4]

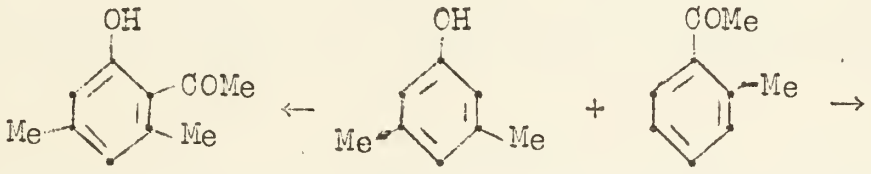
Striking evidence of the $AlCl_3$-HCl catalyst is found in the isomerizations of ortho-substituted alkyl-aryl ketones.[5,6,7] The ketones are stable at 150° in the presence of pure aluminum chloride, but when hydrogen chloride is introduced, the ketones undergo a variety of changes depending upon their structure. The changes can be accounted for by two possible routes. The first is a fission to give an aromatic hydrocarbon and an acyl group which then recombine to give an isomeric ketone. Schubert and Latourette have found that the deacylation of aromatic ketones in concentrated sulfuric acid is a first order decomposition of the conjugate acid of the ketone:

$$B + H^{\oplus} \underset{\text{fast}}{\rightleftharpoons} BH^{\oplus} \xrightarrow{\text{slow}} ArH + RCO^{\oplus}$$

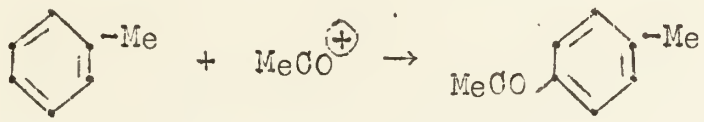
The second route involves a Wagner-Meerwein rearrangement of a carbonium ion and, in view of Brown's work, can be pictured as follows:



An example of the first route, fission and reacylation, is the conversion of 2-methylacetophenone (III) into 4-methylacetophenone (IV). When m-5-xylenol (II) is also present, the yield of 4-methylacetophenone is considerably reduced owing to the formation of 2-hydroxy-4,5-dimethylacetophenone (I). It is reasoned that the formation of an acylating agent which is required to produce the hydroxy-ketone also accounts for the production of 4-methylacetophenone:

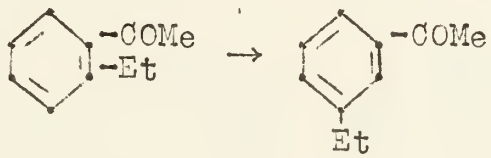


I II III



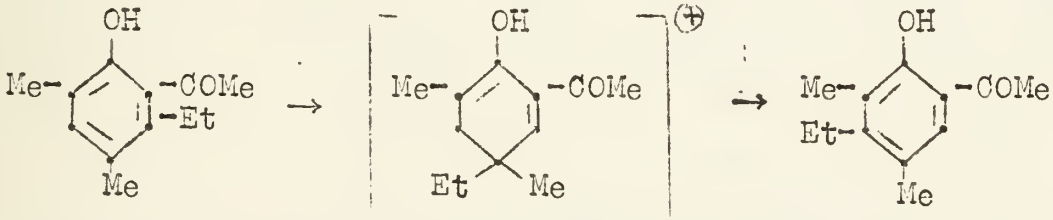
IV

The second route is illustrated by the isomerization of 2-ethylacetophenone (V) to the 3-isomer (VI):



V VI

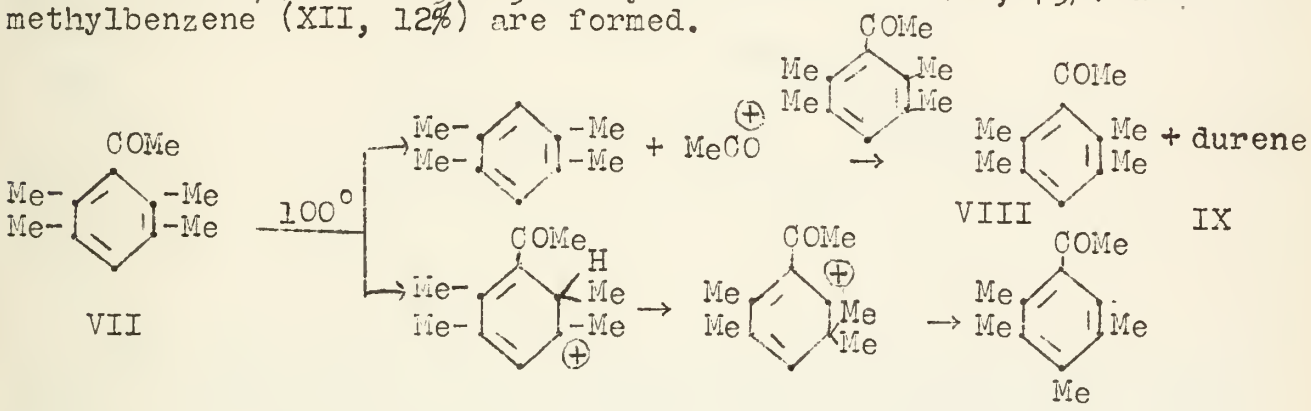
this also being an indication of the greater mobility of the ethyl group compared to the methyl group. An ortho-methyl group may migrate to the adjacent meta position when this is filled; the more mobile group will then migrate to the para position:[9]



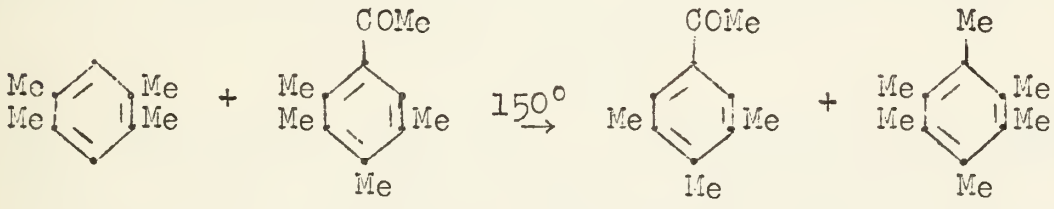
It is noted that the acyl group displaced or the alkyl group which migrates is ortho to a bulky group. It is this steric factor

which is responsible for the isomerizations. In accord with this is the isomerization of 5,8-dimethyl-1-tetralone to the 5,7-isomer, whereas 4,7-dimethyl-1-hydrindone is unchanged under the same conditions. Arnold has demonstrated that steric strain is present in the tetralone whereas a rigid planar structure is present in the hydrindone.[10,11] The inhibition of resonance between the carbonyl group and the aromatic nucleus will increase the susceptibility of the nucleus to electrophilic attack. In addition, since mobility has been conferred only to ortho groups, it is believed that the steric effect between the two groups facilitates a polarization of the nucleus, enhancing the electron availability at one or the other of the two positions. This would also explain the acceleration of the isomerization caused by a para alkyl group. Thus 2-methylacetophenone gives the 4-methyl- isomer, but 2,5-dimethylacetophenone gives chiefly the 3,5-isomer[5]; similarly the deacylation of acetomesitylene occurs 66 times as fast as that of 2,6-dimethylacetophenone.[8]

Further confirmation of the mechanism is the stability of homologues of benzonitrile to $AlCl_3$. The nitrile group is planar and cannot collide with an ortho-alkyl group. On the other hand, homologues of benzenesulfonic acid behave in a manner similar to those of acetophenone, as illustrated by the Jacobsen reaction.[12] A reaction in the acetophenone series which closely parallels the Jacobsen reaction is the conversion of acetyldurene (VII) at 100° into acetylprehnitene (X, 80%) and diacetyldurene (VIII, 10%) and durene (IX 10%). At 150° 5-acetylhemimellitene (XI, 75%) and hexamethylbenzene (XII, 12%) are formed.



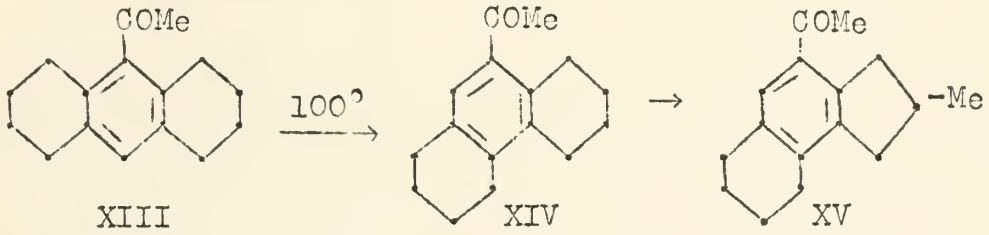
VII VIII IX X



IX X XI XII

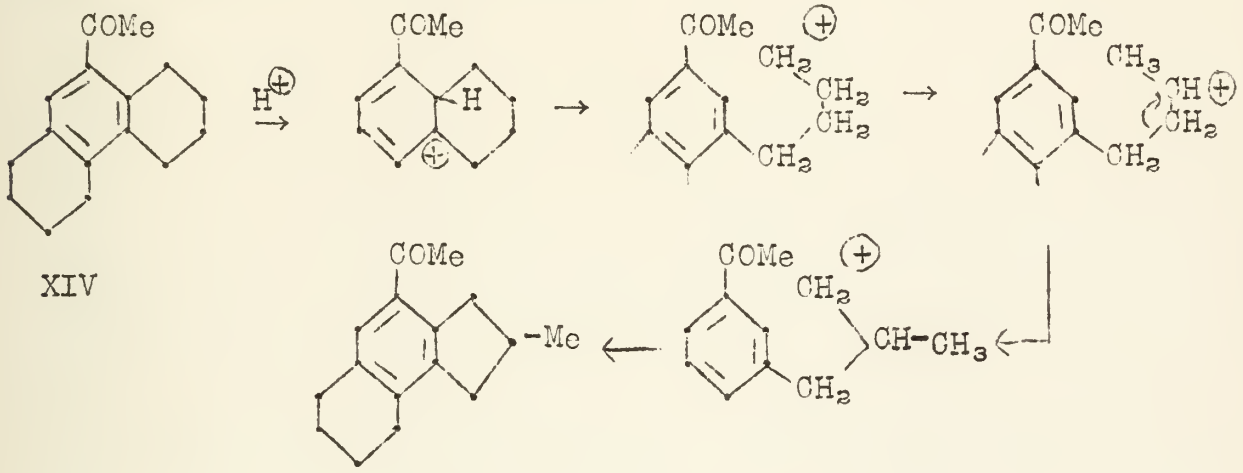
Evidence for the course of the reaction at 150° is found in the stability of acetylprehnitene to aluminum chloride at this temperature in the absence of an aromatic hydrocarbon.

An interesting transformation occurs when 9-acetyl-s-octahydroanthracene is heated with $AlCl_3$ and HCl:[7]




XIII XIV XV

The isomerization (XIII → XIV) is analogous to that of acetyldurene to acetylprehnitene. The subsequent change (XIV → XV) can be explained as follows. Although 2,5-dimethyl and 2,5-diethylacetophenone rearrange to the corresponding 3,5-isomers, 2,5-di-n-propylacetophenone undergoes considerable disproportionation into 3-n-propylacetophenone (35%) and more highly alkylated acetophenones; apparently the 2-n-propyl group can be ejected as the propyl cation. If the cyclohexyl group can also do this, the following sequence is possible:




XIV XV

The steric hindrance between the ortho acyl and alkyl groups which is responsible for the instability of the ketones can also explain the instability of acetyl-s-octahydrophenanthrene. The formation of the five-membered ring will decrease this steric interaction in accord with the work by Arnold.[10,11]

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# THREE-MEMBERED RING CONJUGATION

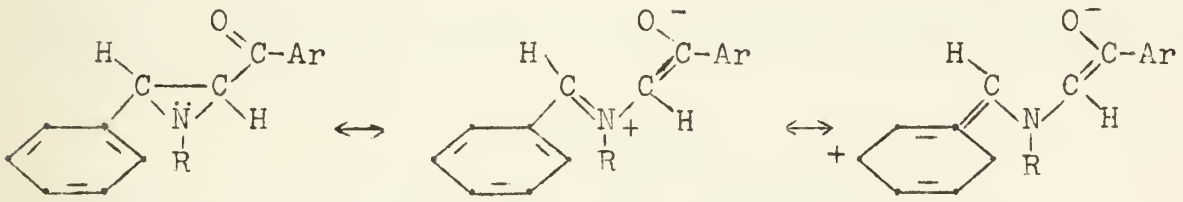
Reported by Eugene A. Kraiman May 16, 1952

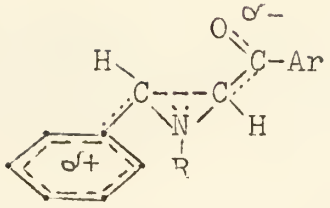
The ultraviolet spectra of compounds in which a cyclopropane ring is attached to an unsaturated group such as phenyl, vinyl or carbonyl resembles that of the corresponding vinyl compounds.[1] For example, the absorption maxima of phenyl cyclopropane are similar to those of styrene (although at shorter wave lengths) rather than propyl benzene. Similar correlations have been obtained for substituted ethylene oxides.[1]

The electronic structure of the cyclopropane ring is still subject to controversy, but at this time the known physical data is best explained by the "bent bond" representation of Coulson and Moffitt.[2] In addition, data for ethylene oxide and ethylene sulfide can be explained in a similar manner.[3]

An electronic structure qualitatively analogous to ethylene oxide has been suggested[4] for the ethylene imine ring in order to account for spectral differences between certain geometric isomers. The ring atoms are considered to be joined by hybrid bonds which have a normal bond angle of 104° which differs from the normal tetrahedral angle of about 109°. However, the actual bond angles are less than the most probable value of 104° in order to conform to the required geometry of a three-membered ring (i.e., bond angles of about 60°). This is the so-called "bent bond" and can be considered analogous to the strain concept of classical theory. This type of bonding results in a greater possibility for overlap with $\pi$-bonds and unshared electron pairs of adjacent atoms. For example, this could be the explanation of the low reactivity of cyclopropyl chloride in solvolysis reactions usually attributed to internal ring strain.[5]

Using this representation, the interaction of the substituents in aryl-aroyl ethylene imines can be considered. The planes of these groups are almost perpendicular to the plane of the ethylene imine ring so that the $\pi$-orbitals (perpendicular to the corresponding $\sigma$ bond) are in a position to overlap the "bent bond" orbitals in the three-membered ring. In the <u>cis</u> compounds of this type steric factors prevent the maximum overlap while in the <u>trans</u> form this is not the case. Resonance structures can be used to illustrate the interaction of the aryl and aroyl groups as follows:

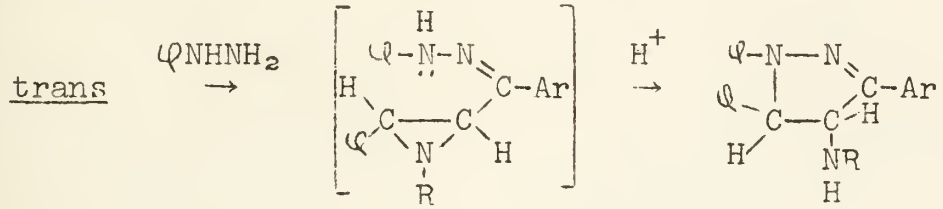


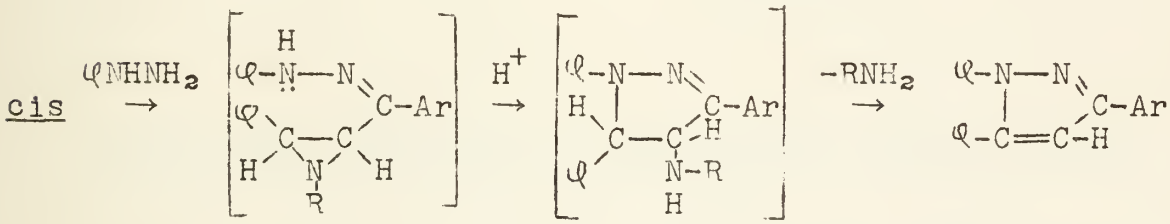


--- stretching hybridization
..... shortening hybridization

The spectra of many pairs of aryl-aroyl ethylene imine isomers were found to possess consistant differences.[6] In the ultraviolet region, the peak between 240 and 260 mμ was at a longer wave length and was more intense for the isomer which was later assigned the trans configuration. The same isomer also had a carbonyl absorption in the infrared region at a longer wave length.

One piece of chemical evidence for this assignment of configuration is the reaction with phenylhydrazine. The trans isomer yields a 4-alkylaminotriaryl pyrazoline while the cis isomer gives a triaryl pyrazole as illustrated below:





The trans elimination of $RNH_2$ from the 4-alkylaminotriaryl pyrazoline in one of the cases is the important step in verifying the assignment of configuration.

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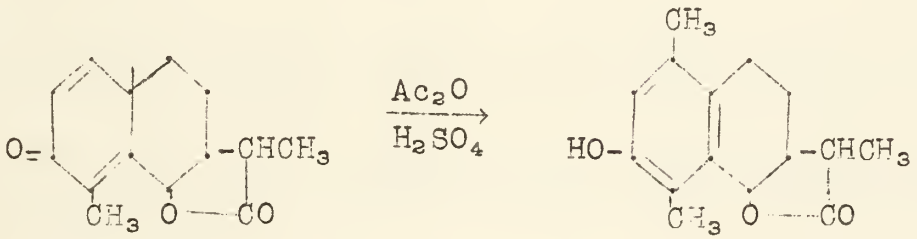
# THE DIENONE-PHENOL REARRANGEMENT

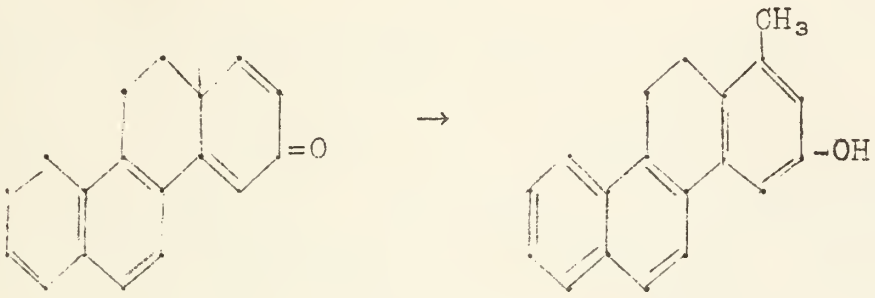
Reported by R. M. Potts May 16, 1952

In 1930 Clemo and co-workers (1) while working with santonin (I) observed the rearrangement of this compound to desmotroposantonin (II). More recently Inhoffen and co-workers (2) observed the dienone-phenol rearrangement in the cholestanone and androstenone series.



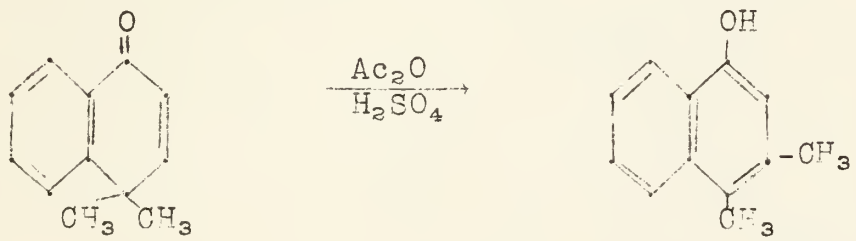

I II

Wilds and Djerassi (3) were the first to synthesize the starting dienone (III) and prove the structure of the rearrangement product by an independent synthesis. 3-Keto-12a-methyl-3,11,12,12a-tetrahydrochrysene (III) rearranged in the presence of acetic anhydride and a few drops of sulfuric acid to 3-hydroxy-1-methyl-11,12-dihydrochrysene (IV)

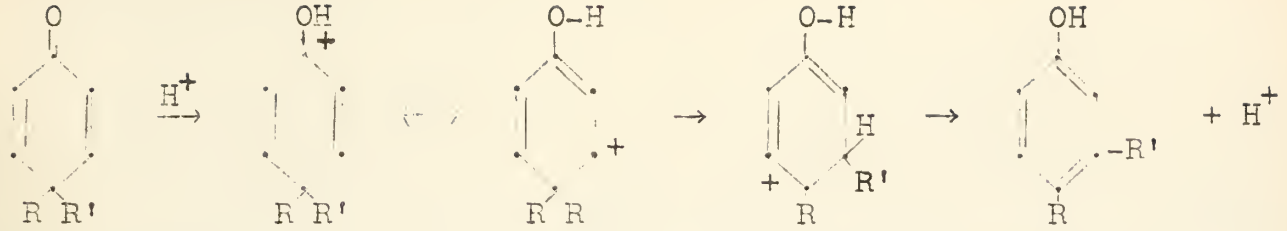



III IV

Arnold and co-workers (4) observed the dienone-phenol rearrangement in the naphthalene series.

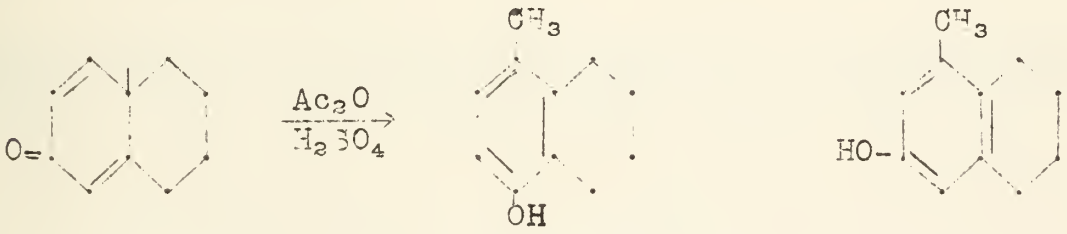



The reaction was regarded as a typical pinacol type rearrangement and the following mechanism was proposed (4, 5).



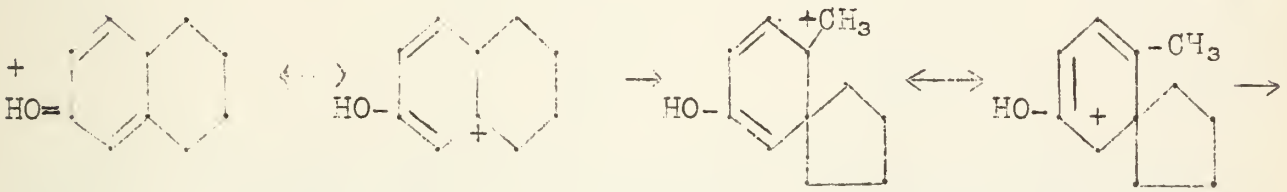
With further analogy to the pinacol rearrangement, the phenyl group was found to migrate preferentially with respect to the methyl group in the dienone-phenol rearrangement also (6).

When Woodward and Singh (7) attempted to rearrange the dienone (V), they did not obtain the expected product (VI), but isolated VII instead in high yield.

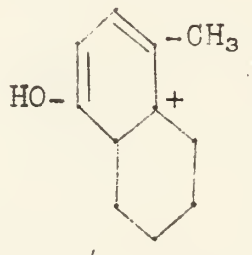


V VII VI

They proposed that the reaction proceeds as follows.



IXa IXb Xa Xb

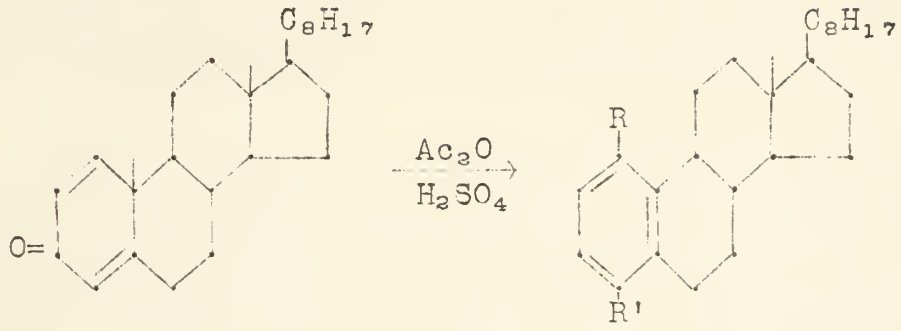


XI

VII + $H^+$

the methyl group retains its position and the ring methylene group migrates. When the saturated ring is unsymmetrically substituted there are two possible abnormal products as in the case with

1,4-cholestadien-3-one (XII) (8).

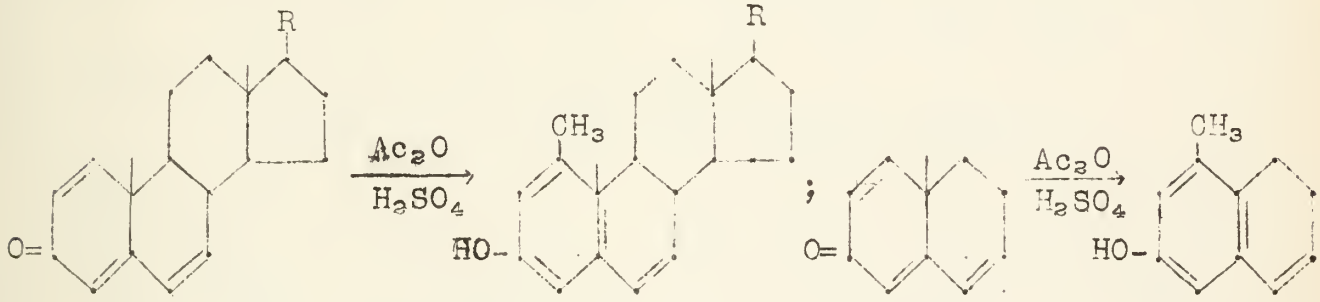



XII

XIII R = $CH_3$; R' = OH

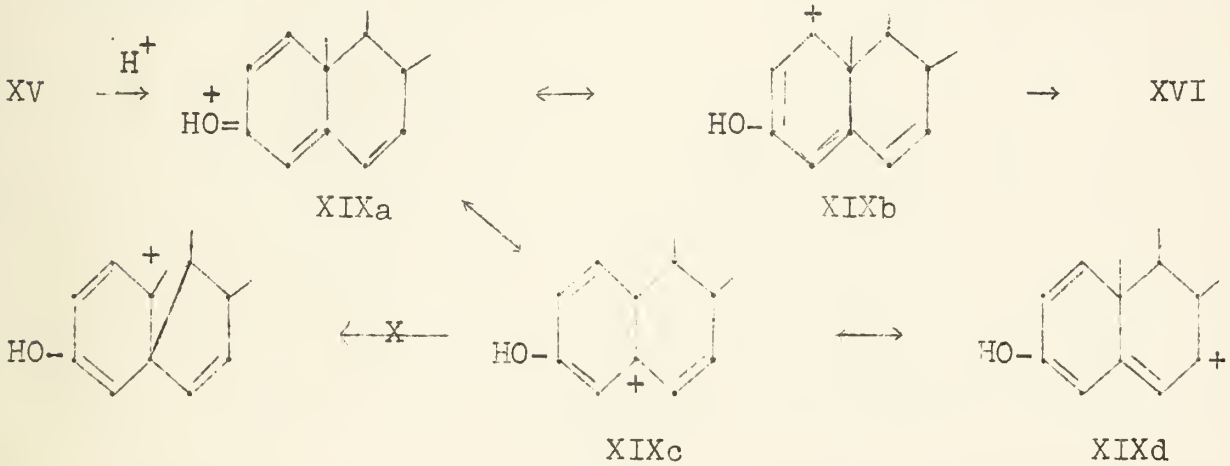
XIV R = OH; R' = $CH_3$

However it was discovered that the presence of an additional conjugated double bond causes the compound to rearrange via methyl migration rather than through spiran formation (9, 10).




XV XVI XVII XVIII

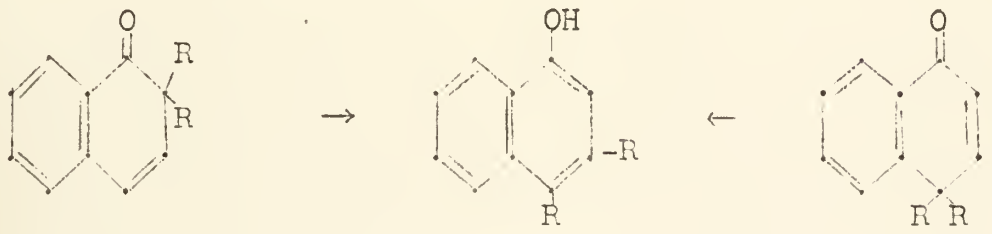
Evidently the reaction proceeds by methyl migration (see XIXb) because the spiran formation (see XIXc) involves the formation of a sterically hindered unsaturated five membered ring (11).




XIXc XIXd

Recently an unusual rearrangement of dienones of the naphthalene series which are disubstituted in the 2 position has been

reported (12). These dienones did not rearrange to the expected 2,3 dialkylphenols but to the 3,4 dialkylphenols. The same products which had been obtained previously from the corresponding dienones disubstituted in the 4 position (4, 13).

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