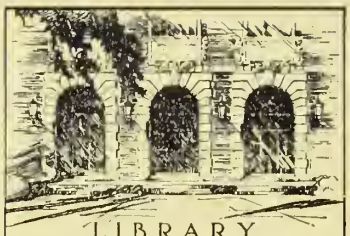
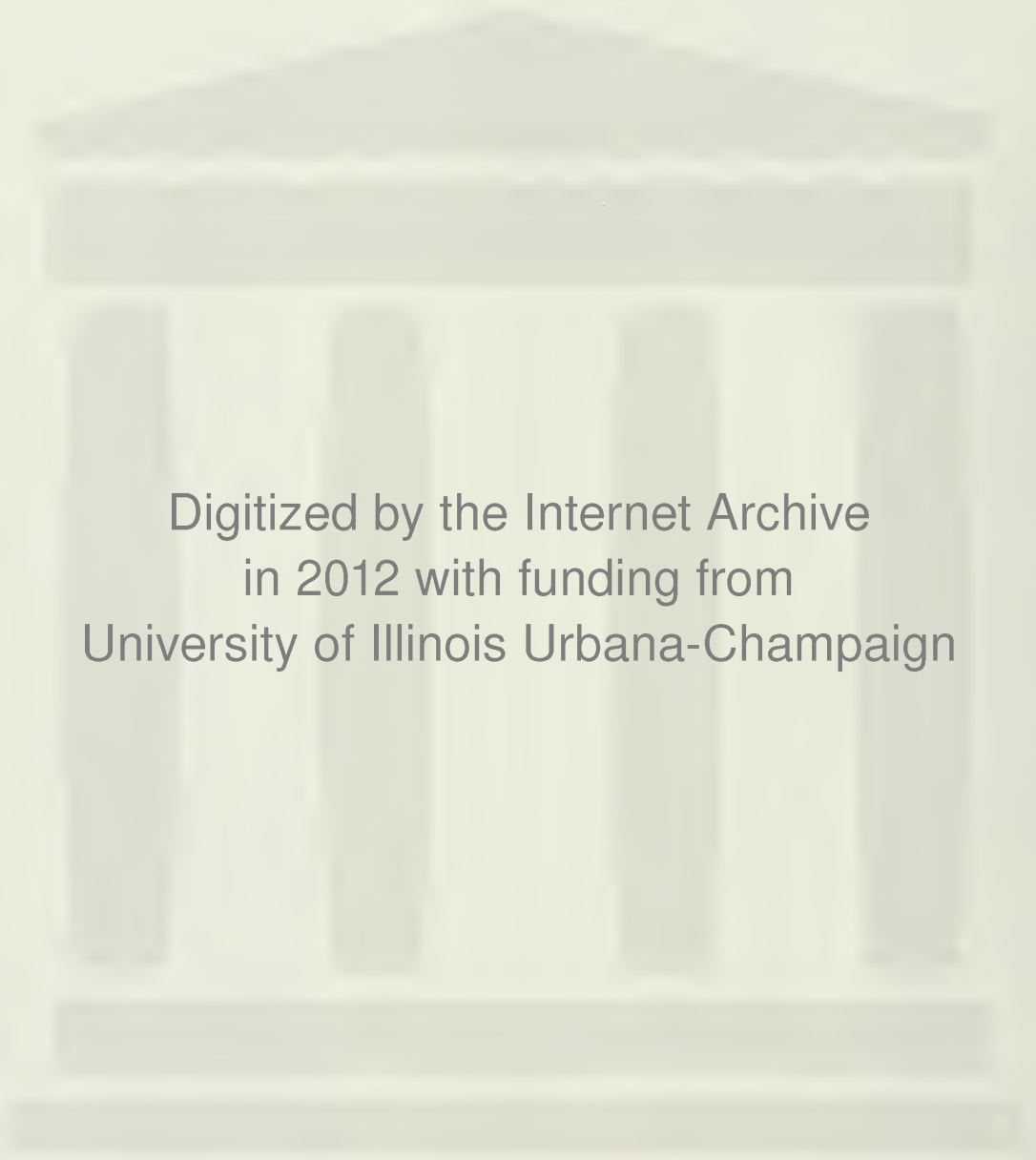




UNIVERSITY OF ILLINOIS

DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING

ORGANIC SEMINARS

SUMMER 1962

SEMINAR TOPICS

Summer Term 1962

THE STEREOCHEMISTRY OF FREE RADICAL ADDITION REACTIONS

Reported by A. C. Button July 2, 1962

I. INTRODUCTION

The general mechanism of a free radical addition reaction to an olefin is as follows:

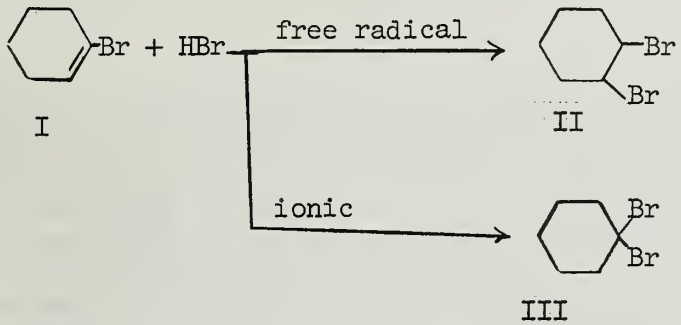
$$R{:}Y \longrightarrow R\cdot + Y\cdot \qquad \text{(Catalyzed by light, heat, or peroxides)}$$

$$R\cdot + \text{>C=C<} \rightleftharpoons R\text{—C—C}\cdot \qquad \text{(Addition step)}$$

$$R{:}Y + R\text{—C—C}\cdot \longrightarrow R\text{—C—C—Y} + R\cdot \qquad \text{(Transfer step)}$$

All such reactions reported before 1950 were found to be non-stereoselective; they produced mixtures of all possible isomers with none of the isomers predominating in the product mixtures.

The direction of radical additions was generally specific; they usually took a course opposite that of ionic additions. For instance, with 1-bromocyclohexene (I), HBr adds ionically to produce 1,1-dibromocyclohexane (III), while under free radical conditions it produces 1,2-dibromocyclohexane (II) (1).



I II III

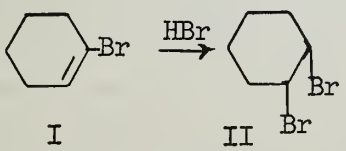
This difference in direction between ionic and free radical addition was general enough so that it could be used as a criterion for determining the mechanism of the reaction. This, up to the last few years, was the only type of limitation on the number of isomers observed in free radical additions to olefins.

Since 1950, however, a substantial number of free radical additions to olefins have been observed which have been completely stereospecific or stereoselective with one isomer predominating in the product mixture. This report deals with such reactions, the conditions required for stereospecificity and the mechanisms postulated.

Three classes of olefinic compounds were investigated with respect to the stereochemistry of their free radical addition reactions. They were (a) cycloalkenes (1-11), (b) acyclic alkenes and alkynes (12-20) and (c) bridged cyclic olefins (21-32). The addenda were hydrogen bromide, bromine, hydrogen sulfide, thiols, thiophenols, thioacids, polyhalomethanes and arylsulfonylchlorides.

II. FREE RADICAL ADDITIONS TO CYCLIC OLEFINS

A stereospecific addition was observed by Goering and coworkers (1) who reacted HBr with 1-bromocyclohexene (I) and 1-methylcyclohexene (IV). The reactions were catalyzed by light or benzoyl peroxide, and were run in pentane solution at ordinary temperatures. They produced only the cis-1,2-disubstituted cyclohexanes (II) and (V) which resulted from trans addition of the Br· and H·.



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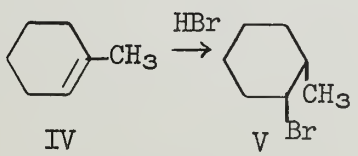
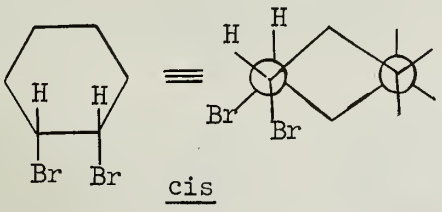


IV V

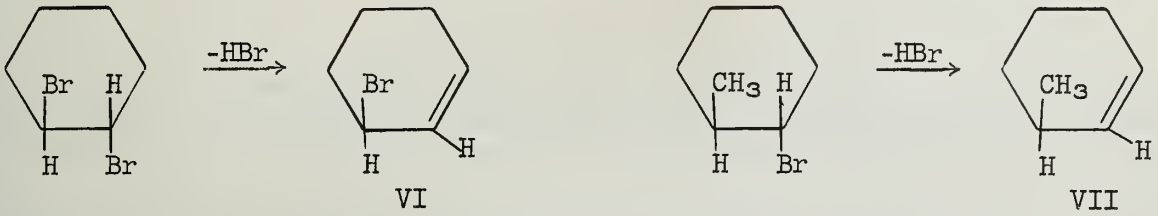
Goering was careful to demonstrate that the addition mechanism was in fact via the free radical and was not ionic, by observing that ionic addition would produce the

1,1-dibromocyclohexane or 1-bromo-1-methylcyclohexane rather than the observed products. Only small amounts of these were found in the reaction mixtures.

Dehydrohalogenation in refluxing ethanolic KOH was employed to establish that the products were the cis isomers. Only the cis isomers would readily undergo the elimination to produce the starting olefins, 1-bromocyclohexene or 1-methylcyclohexene. This type of elimination required that the hydrogen and bromine be trans to each other.

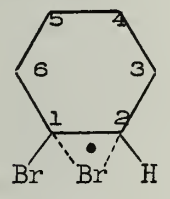


The trans isomer must eliminate a hydrogen from the neighboring carbon in the opposite direction to give 3-bromocyclohexene (VI) or 3-methylcyclohexene (VII).



This was used in subsequent work to establish the isomeric composition of the products

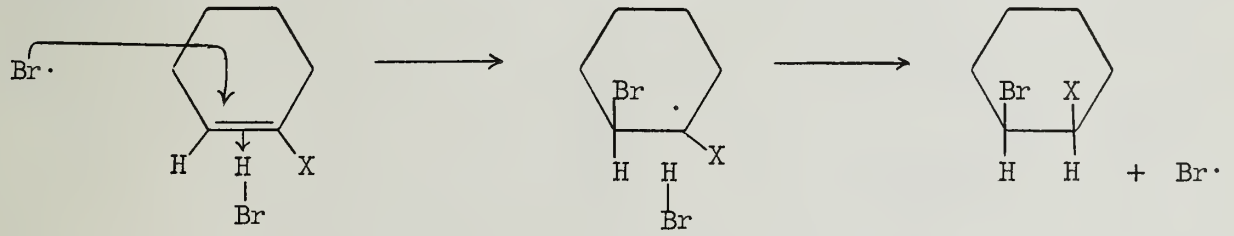
In order to explain why the addition should give entirely the less thermodynamically stable cis isomer, Goering felt that a classical planar free radical was inadequate. He discarded the theory (2, 3) that trans addition was due to sterically less hindered trans approach; by studying molecular models he found that such a classical radical would be about equally susceptible to either cis or trans approach.



VIII

He proposed a cyclic intermediate radical (VIII), in which the bromine is centrally located between C_1 and C_2 and below the plane of the ring as drawn. It would be stabilized by resonance and would force the entering HBr to attack from above the plane of the ring, achieving stereospecific trans addition.

A second mechanism proposed later by Goering and Sims (4) involved the formation of a π-complex between HBr and the olefin such as was proposed by Brown and Brady (5). When a bromine radical attacks such a complex, it would be forced to enter from the side opposite the complexed HBr. The radical thus formed would immediately accomplish the transfer step by collapsing the π-complex, completing a trans addition and freeing another bromine radical.



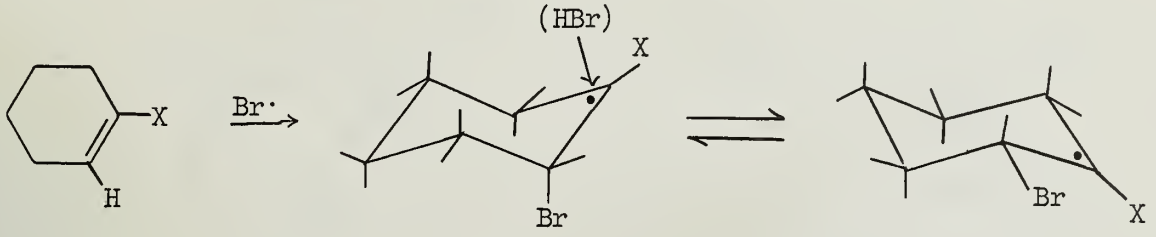
This could occur in two steps as shown or in one simultaneous step. It would explain the stereochemistry of the addition, the fact that a very efficient transfer step was observed with HBr, and the low degree of telomer formation which would be caused by attack of the intermediate radical by a cyclohexene rather than an HBr.

To test this mechanism two reactions were carried out. First, reactions were run in ether-pentane solutions. Ether should preferentially complex with HBr and prevent the π-complex formation. However, under such conditions there was still complete stereospecificity suggesting that the π-complex was not a requirement for stereospecific trans addition.

Second, HCl in large amounts should form the π-complex in preference to a small amount of HBr. However, HCl cannot participate in the transfer step and form a free radical under the reaction conditions. Thus, without the efficient and rapid transfer step, stereospecificity should have been lost. When stereospecificity was achieved in

the reaction with excess HCl in the mixture, doubt was cast on the necessity for such a proposal.

As a third mechanistic possibility the same investigators suggested that in the intermediate free radical, when it is first formed, the bromine is axial (IX) because of the necessity of the Br· attacking from above or below the plane of the alkene substituents. This conformation is not as unstable as might be expected with respect to the flipped conformation in which the bromine would be equatorial (X), because in the latter the two large substituents, Br and X, are eclipsed if the radical is assumed to be planar.



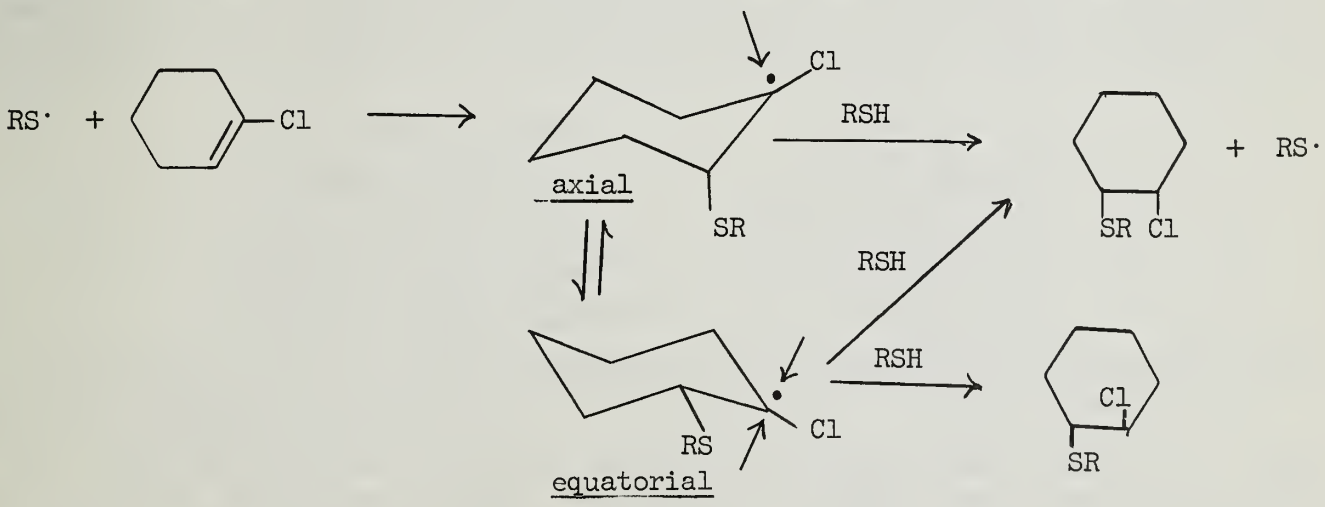
IX X

Thus, while the intermediate remains in the bromine-axial form (IX), attack by HBr is favored trans to the bromine, from above the plane of the ring as it is drawn here. Goering and Sims assumed that the transfer step with HBr is faster than the equilibration (IX⇌X).

Continuing in the cyclic olefin series, Goering and coworkers (6, 7) investigated other free radical additions with H_2S, thiophenol, and thioacetic acid. In ultraviolet light catalyzed reactions with 1-chlorocyclohexene the above addenda produced mixtures of products containing 85%, 94-95% and 66-73% of cis disubstituted cyclohexanes respectively.

The order of stereoselectivity is thiophenol>H_2S>thiolacetic acid and all are less stereoselective than HBr. The H_2S addition was carried out at -80° in the liquid phase. The others were run at room temperature or higher. Product composition was determined primarily by selective solvolysis of the more reactive trans isomers.

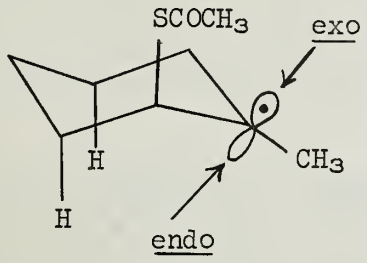
It was noted that the percentage of cis isomer obtained depended on the ratio of the concentration of addendum, RSH, to that of the olefin. More cis product was obtained at higher addendum concentrations. This was explained by the classical axial free radical hypothesis, as in the preceding work (4), the difference here being that the transfer step is slower and a significant amount of the axial free radical can convert to the equatorial conformation before transfer occurs, especially at low RSH concentrations:



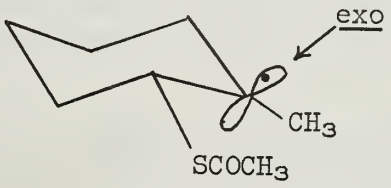
Bordwell and Hewett (8) obtained similar results in the addition of thiolacetic acid to 1-methylcyclohexene (product mixture: 85% cis-2-methylcyclohexylthiolacetate, 15% trans) and 1-methylcyclopentene (70% cis product, 30% trans). Thiophenol also gave predominantly trans addition with 1-methylcyclohexene. Their reaction conditions were similar to those used by Goering et al. (6).

In their explanation of the results they had to reject the possibility of Goering's cyclic intermediate, as it would have yielded 100% trans addition.

Also they said that the axial-planar free radical (XI) would not necessarily result in trans addition because that would require endo attack which is sterically hindered by the β-axial hydrogens. A mixture should result from this form. Trans addition would probably result from exo attack on the equatorial conformer (XII).



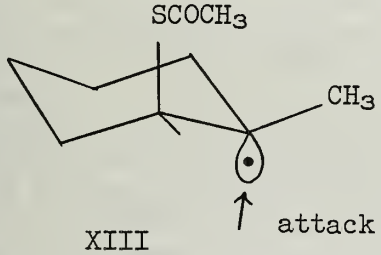
XI



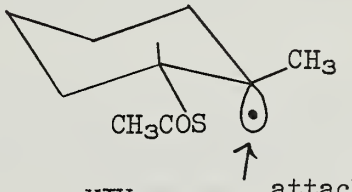
XII

However, the above picture would not account for the difference in stereoselectivity with addendum concentration observed by Goering.

A rather dubious alternative which attempted to explain all the observations was a tetrahedral radical.



XIII attack by CH_3COSH



XIV attack by CH_3COSH

First formed is XIII, which equilibrates with XIV, with the methyl group preferring the equatorial conformation in both cases. Attack on XIII yields the cis isomer, while attack on XIV yields the trans isomer. This could account for the observation that more addendum, which gives faster transfer, yields more predominantly the cis isomer through trans addition.

Finally in the cyclic olefin series, the additions of HBr to 1-bromocyclobutene, 1-bromocyclopentene, 1-bromocycloheptene (9), 1-methylcyclopentene (10) and 1-methylcycloheptene (11) were investigated by Abell and coworkers (9, 11) and by Howe (10). Product compositions determined chiefly by gas chromatography or infrared spectra were as follows:

1,2-dibromocyclobutane	76-82% cis (9)
1,2-dibromocyclopentane	91-95% cis (9)
1,2-dibromocycloheptane	83.5-84.5% cis (9)
1-methyl-2-bromocyclopentane	93.4% cis (10)
1-methyl-2-bromocycloheptane	95% cis (11)

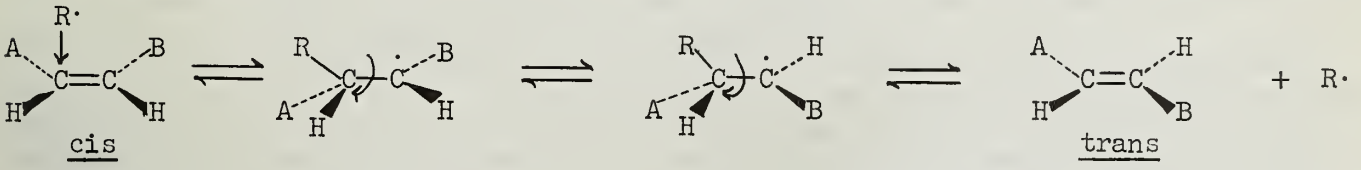
The proposals of the cyclic intermediate and the π-complex were discarded in this case, since complete stereospecificity was not achieved. The planar classical free radical seemed adequate here.

The effect of ring size on product composition was explained as follows (9): The rigid cyclobutane has a true eclipsed interaction in the cis isomer, making it energetically difficult to form; thus a higher propoportion of trans isomer was formed than in the case of cyclopentene adducts where eclipsed interaction can be partially relieved by ring puckering or in the cyclohexane products where the interaction is extensively relieved by ring puckering.

The fact that the additions to cycloheptenes were not completely stereospecific was thought to be due to their increased flexibility and ability to equilibrate between more conformations, some of which would be favorable to cis addition.

III. FREE RADICAL ADDITIONS TO ACYCLIC OLEFINS

The acyclic olefins present a different stereochemical problem from that of the cyclic ones with respect to their free radical additions. First, any intermediate formed is free to rotate about the single bond resulting from collapse of the double bond following radical attack. This complicates the transfer step, depending on how rapidly this rotation occurs in relation to the transfer step. Secondly, results may be complicated by the possibility of isomerization of the alkene through reversal of the addition step.

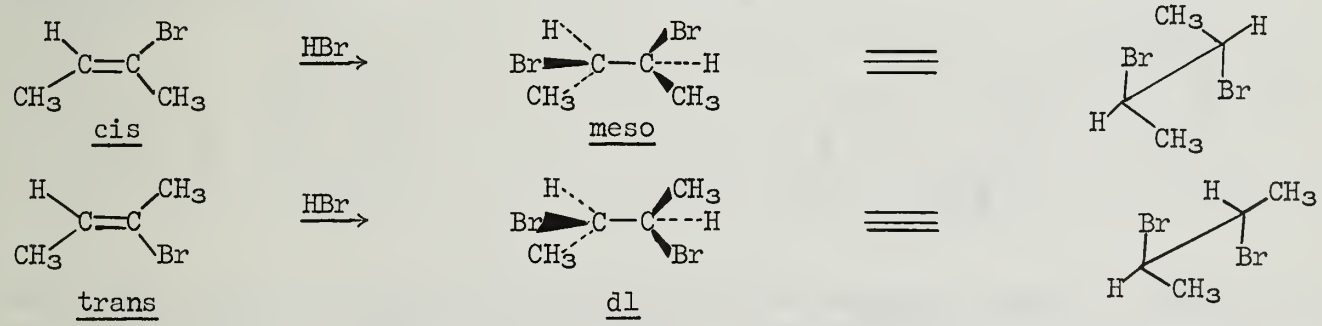


In 1949 Mayo and Wilzbach (12) studied the rate of polymerization of cis and trans dichloroethylenes with vinyl acetate and concluded that the radical intermediates involved were identical from both isomers, since the polymerization rates were identical. This implied a planar or rapidly inverting pyramidal configuration at the radical carbon, with free rotation about the single bond that was formerly the double bond of the olefin.

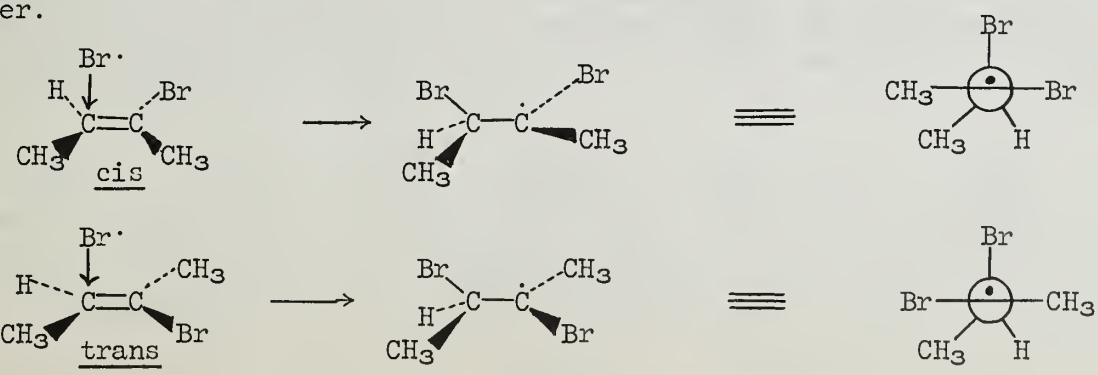
Skell and Woodworth (13) obtained identical mixtures of isomers in the addition of bromotrichloromethane to cis and trans-2-butene in light catalyzed reactions at 0-25° in the liquid phase. They reached the same conclusions as Mayo and Wilzbach regarding the intermediate.

Goering and Larsen (14, 15) were the first to observe a truly stereospecific free radical addition to an acyclic olefin when they obtained 99% trans addition of HBr or DBr to cis or trans-2-bromo-2-butenes. The ultraviolet light catalyzed reactions were carried out at -80° in excess liquid HBr or DBr. The stereoselectivity gradually decreased with higher reaction temperatures until at room temperature the product mixtures from either butene isomer were identical. The stereoselectivity was about the same for HBr and DBr additions under similar conditions.

Trans addition to cis-2-bromo-2-butene resulted in formation of the meso-2,3-dibromobutane, while trans addition to the trans butene yielded the dl-dibromide.



Evidence for a planar methyl free radical was given by Cole (16), and Goering and Larsen assumed that the intermediate was also planar at the free radical carbon atom. Thus, the two radicals, from cis or trans-2-bromo-2-butene are rotational isomers of each other.



Then, they reasoned, the transfer step proceeded faster than the equilibration step at low temperatures to give stereospecific addition. Either of Goering's earlier modifications of the above intermediates, the cyclic intermediate or the π-complex, would explain why transfer occurred before rotation.

Goering and Larsen also predicted that stereospecificity would probably not be achieved with other free radicals in acyclic additions to double bonds, because the transfer step would be slower with other radicals than with HBr, thus allowing equilibration or partial equilibration of the isomeric intermediates before addition of hydrogen.

Skell and Allen (17) achieved results similar to Goering and Larsen's with 2-butene and deuterium bromide, with the advantage that 2-butene was less likely to undergo cis-trans isomerization before addition than the 2-bromo-2-butene used by Goering et al. The deuterated products were diastereoisomers, threo-2-bromo-3-deuterobutane from the cis-2-butene and the erythro isomer from trans-2-butene.

Following Goering's prediction, Neureiter (18) failed to obtain stereospecific addition of thioacetic acid to 2-chloro-2-butene. Skell and Allen (19) also observed nonstereospecific addition of deuteromethylmercaptan to cis and trans-2-butene, but achieved stereospecific trans addition by adding deuterium bromide to the reaction mixture as the transfer agent. The results required that the equilibration

$$Br\cdot + CH_3SD \rightleftharpoons DBr + CH_3S\cdot$$

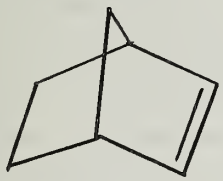
be more rapid than addition of Br· or CH_3S· to the olefin.

Additions of free radicals to alkynes were reviewed recently by Mitchell (20) and were found to be trans and stereospecific by several investigators.

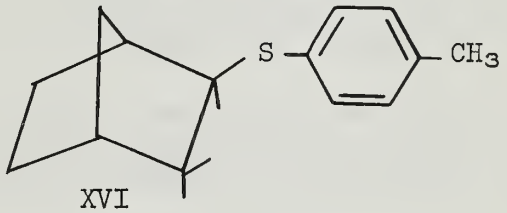
IV. FREE RADICAL ADDITIONS TO BRIDGED CYCLIC OLEFINS

The stereospecificity of additions to norbornylene (XV) and its derivatives is not as clear cut as it is in the acyclic and simple cyclic systems. Yields were often reported to be low, with ionic addition often running in competition with free radical addition. Also, the products were generally mixtures of isomers which were more difficult to interpret theoretically than were the relatively uncontaminated products obtained in the previously discussed work.

An observation, stated as a rule by Alder and Stein (21) is that the first free radical attack occurs from the exo direction. Thus Cristol and Brindell (22) obtained the pure **exo** adduct (XVI) from the reaction of norbornylene with p-thiocresol in the liquid phase at 60-70°.



XV

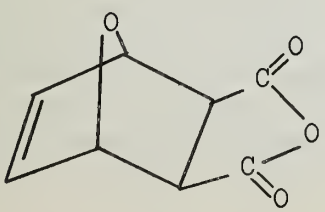


XVI

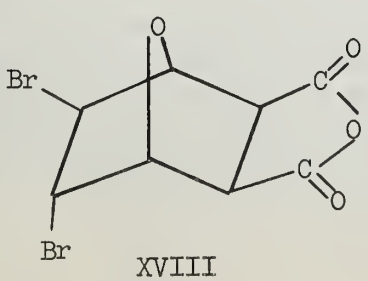
They did not know the direction of addition of the hydrogen, because it was identical to the other hydrogen bonded to the same carbon before addition.

Weinstock (23) observed stereospecific cis addition of ethyl bromoacetate to norbornene, yielding the exo-cis disubstituted norbornane.

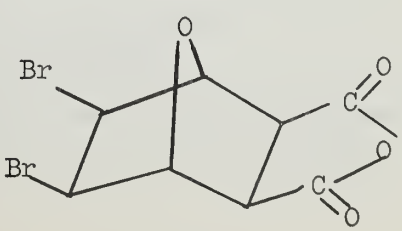
Stereoselectivity was observed by Berson and Swidler (24, 25) when they brominated exo-cis-3,6-endoxo-Δ^4-tetrahydrophthalic anhydride (XVII) in dichloromethane solution in light catalyzed reactions. They obtained yields in which the ratio of the trans adduct (XVIII) to the exo-cis adduct (XIX) was 2:1.



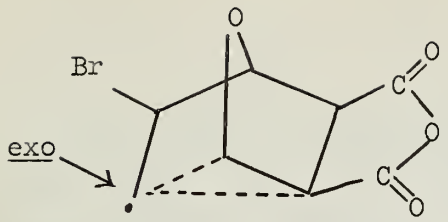
XVII



XVIII



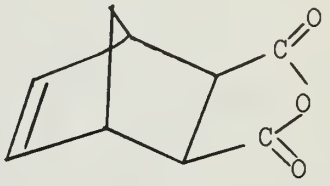
XIX



XX

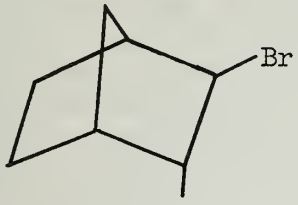
Under ionic conditions, i.e. in ethyl acetate or acetic acid or in the dark, they obtained almost entirely the trans isomer. Free radical conditions favored cis addition, they concluded, to an even greater extent than would be predicted by the relative stabilities of the products. To account for the tendency toward cis addition they proposed a mesomeric free radical intermediate (XX) in which Br_2 would be required to attack from the exo direction in the transfer step.

Berson (26) obtained similar results with exo-cis-3,6-endomethylene-Δ^4-tetrahydrophthalic anhydride (XXI) which, when treated with Br_2 in a nitrogen atmosphere gave a light catalyzed addition at room temperature to yield a mixture of exo-cis and trans dibromides. A mesomeric free radical seemed applicable here also, to explain cis addition in greater quantities than the relative thermodynamic stabilities of the products would suggest. However, the authors said they could offer no other proof or evidence at that time for the existence of such an intermediate.

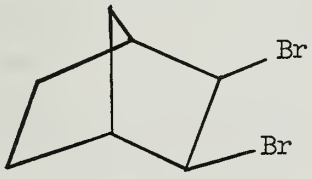


XXI

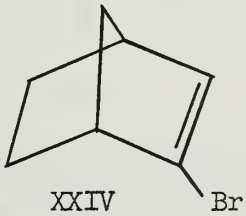
Similarly, LeBel (27, 28) obtained a mixture of trans-2,3-dibromonorbornane (XXII) and exo-cis-2,3-dibromonorbornane (XXIII) in the ratio of between 2:1 and 3:1 from the addition of HBr to 2-bromo-2-norbornene (XXIV). The reactions were carried out at 0° in pentane solution and were catalyzed by ultraviolet light.



XXII



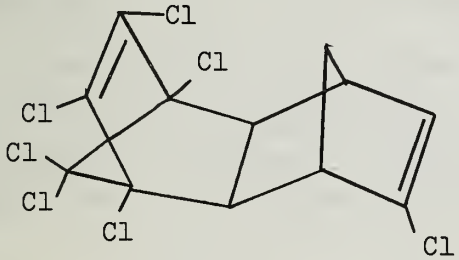
XXIII



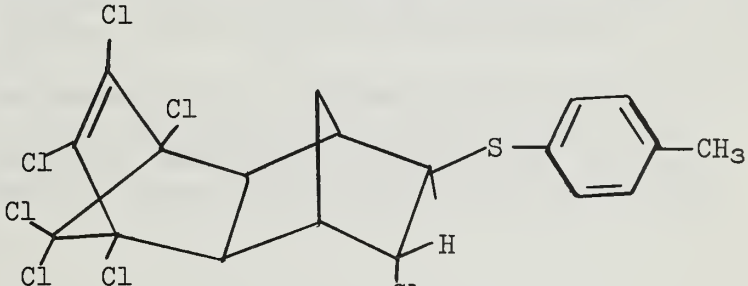
XXIV

LeBel said that the initial attack was exo and that a planar radical resulted which could be attacked either from the exo or endo side. The balance between trans and cis addition reflected, on the one hand, the preference for trans addition of free radicals first noticed by Goering (1), and on the other the steric preference for exo addition, which in this case is the same as cis addition.

A somewhat different case was investigated by Cristol and Arganbright (29) who used the crystalline derivative of norbornene called endo-exo-1,2,3,4,6,10,10-heptachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanonaphthalene, or commonly, 6-chloroaldrin (XXV).



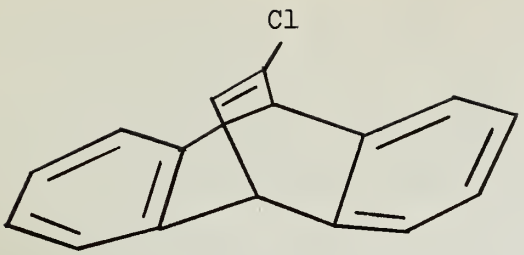
XXV



XXVI

In a hexane solution at 40° p-thiocresol added to XXV in a cis manner by a free radical mechanism to give the trans adduct (XXVI) as the sole product.

Similarly they obtained 67% cis addition and 33% trans addition of p-thiocresol to 11-chloro-9,10-dihydro-9,10-ethenoanthracene (XXVII). The mesomeric radical intermediate was eliminated as a possibility in this study since it should give some rearranged products by virtue of the fact that some free radical character would be present at

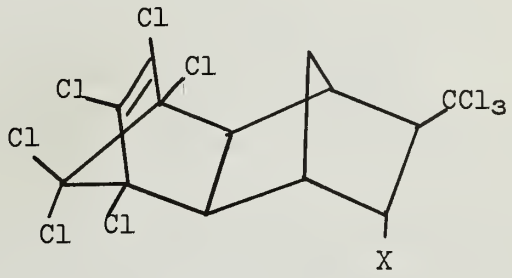


XXVII

three of the carbons of the intermediate. Also, Goering's proposals of the cyclic intermediate (1) and the π-complex (4) were both invalid, since either one would give completely trans addition.

The authors proposed that steric hindrance to endo attack, which always forces the first addition to be exo, in this case also forced the second addition to be exo. The size of the first substituent and the nature of other substituents present would determine whether exo-cis addition or trans, endo addition of the second substituent is favored.

Finally, three cases were investigated in which the addition was predominantly trans. In the first, Kharasch and Friedlander (30) obtained stereospecific trans addition of $BrCCl_3$ to norbornene, evidenced by the fact that no dehydrohalogenation of the adduct occurred in refluxing ethanolic KOH. In the second, Davis (31) added bromotrichloromethane or carbon tetrachloride to aldrin obtaining the trans addition products (XXVIII) exclusively.



XXVIII

In this case, after the initial addition by the $\cdot CCl_3$ radical there is too much steric inhibition from that bulky group to allow exo (cis) attack by a molecule of $BrCCl_3$ or CCl_4, and the latter are forced to attack endo, which is still difficult as evidenced by the long reaction time of 40 hours.

With a somewhat smaller molecule, i.e. chloroform, exo attack is still possible and was achieved in the addition of $HCCl_3$ to 6-chloroaldrin.

The third such investigation involved the addition of p-toluenesulfonylchloride to aldrin or norbornene by Cristol and Reeder (32), who obtained entirely trans addition in both cases via the free radical pathway. The yields were poor, but the trans adducts were the only ones that could be isolated from the reaction mixture. The reactions were catalyzed by benzoyl peroxide, ultraviolet light or di-t-butyl peroxide at elevated temperatures, at 75-90° for norbornene and at 155° for aldrin. Here again the explanation was that steric hindrance from the exo-arylsulfonyl group prevented exo attack by another molecule of p-toluenesulfonyl chloride.

V. SUMMARY

From all the evidence presented above, it appears that the proposed cyclic intermediate radical, the π-complex modification and the tetrahedral radical offered no advantage over the classical planar free radical as the intermediate in radical addition reactions.

In the bridged cyclic systems, the mesomeric free radical intermediate seems to be unlikely, and the observations are best explained by a classical planar free radical, taking into account steric hindrance caused by the bridges and the bulky substituents, resulting in a preference for either an exo (cis) attack or an endo (trans) attack in the transfer step.

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THE CHEMISTRY OF THIOAROMATICS

Reported by Alan N. Scott July 9, 1962

INTRODUCTION

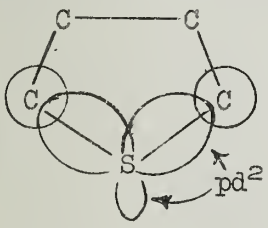
Bivalent sulfur has long been considered an effective carrier of conjugation in cyclic molecules. Victor Meyer, the discoverer of thiophene, after noting many similarities between thiophene and benzene, suggested the formal equivalence of -S- and -CH=CH-. This analogy has proven useful in aromatic systems and has probably inspired much of the work to be reported in this seminar. Nevertheless, some of the new "thioaromatics" seem to lack the stability and other chemical properties generally associated with aromatic compounds. It is true that in the modern view, aromaticity is usually defined as a property of the ground state of molecules, while reactivity depends upon conditions in the transition state as well. Thus, reactivity alone may be an inadequate criterion for aromaticity. Unfortunately, there are insufficient physical data available to estimate the magnitude of ground state aromaticity in the newer heterocycles of sulfur.

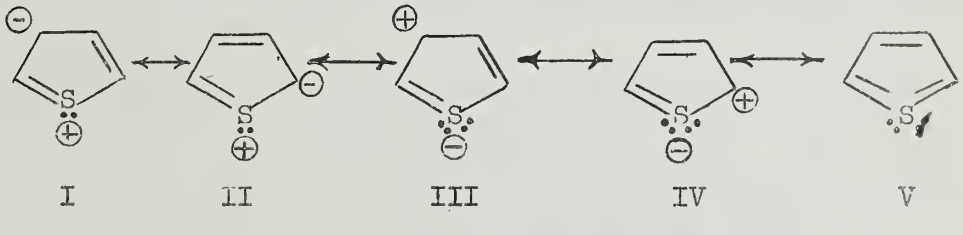
THIOPHENE

Microwave spectra(1) have recently yielded the bond lengths of the planar thiophene molecule: S-C, 1.714Å; C_2-C_3, 1.370Å; and C_3-C_4, 1.423Å. The S-C length indicates considerable double bond character. The C_3-C_4 length is in the aromatic range in contrast to the C_2-C_3 length of 1.47Å in 1,3-butadiene. The observed C-S-C angle of 92° confirms the lack of appreciable sp^2-hybridization in the sulfur atom and can be correlated with the absence of basicity in thiophene, since the attack of a Lewis acid on sulfur would require some sp^2-character.

Thiophene has received the molecular orbital treatment. The sulfur may be considered a "normal" heteroatom, similar to nitrogen and oxygen, which contributes one atomic p_z-orbital and two electrons to a six π-electron system analogous to the cyclopentadienyl anion. In one such approach Kreevoy (2) assigned resonance integrals to each bond according to its length and used a Coulomb integral for sulfur equal to that of carbon on the strength of the comparable Pauling electronegativities of the two elements and the close similarity of the ionization potentials of hydrogen sulfide and ethylene. A rather high delocalization energy of $2.06\beta_o$ was calculated by Kreevoy. Streitwieser(3) has suggested that a larger Coulomb integral should be used because of the +2 core potential of sulfur in thiophene. Estimates of the stabilization energy of thiophene from its heat of combustion are in the range 28-31 kcal/mole.

In an earlier MO treatment, Longuet-Higgins (4) took into account the 3d-orbitals of sulfur. Considerable evidence is now available that under certain conditions, the outer shell of sulfur (5) or phosphorus may expand to form either a 3d π-bond with one adjacent atom, or perhaps several non-interacting 3d π-bonds with several adjacent atoms, but it is debatable whether d-orbitals can participate in the through conjugation of an aromatic ring. According to Longuet-Higgins, the ring conjugation of thiophene is carried by two sulfur $3p3d^2$-hybrid orbitals, which are <u>not</u> mutually orthogonal and are each directed more or less along a S-C valency. A third pd^2-orbital, directed away from the ring, is largely d in character and is unoccupied in the ground state. The Coulomb integral of sulfur is again assumed equal to that of carbon, while the resonance integrals are taken equal to that in benzene, with the exception of the S-C bonds, whose resonance integral is reduced by 20 per cent. Apart from this difference, the

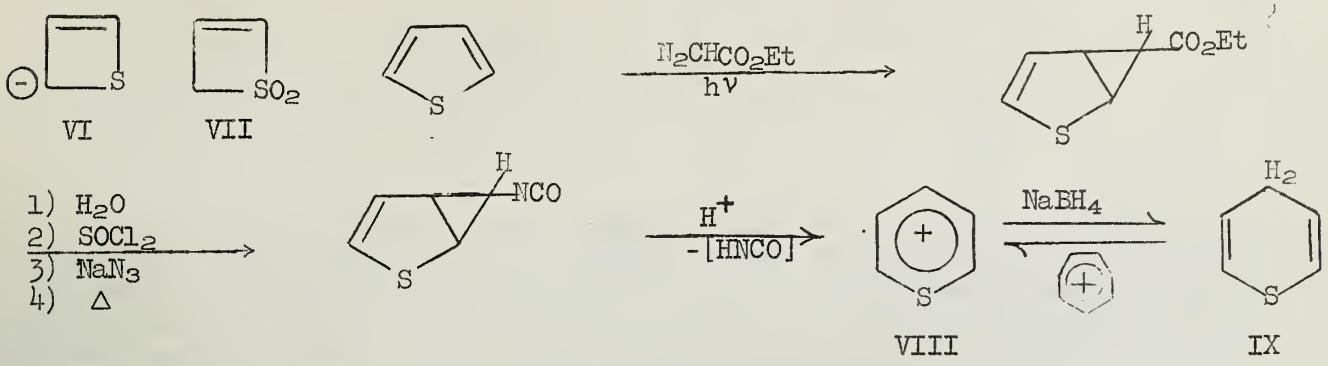




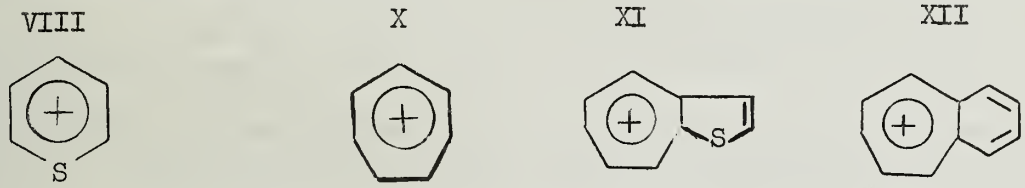
π-system of thiophene is regarded identical to benzene; that is, six electrons in linear combinations of six atomic orbitals. This view was anticipated by Schomaker and Pauling (6), who wrote resonance structures such as I and II (above) showing sulfur as a π-electron donor, but these authors also predicted a small contribution from structures such as III, IV and V with sulfur accepting electrons to form a decet.

OTHER CONJUGATED MONOCYCLES WITH ONE SULFUR ATOM

Unsuccessful attempts have been made to synthesize the cyclopentadienide analog, VI, from thiete sulfone (VII) by reduction (7). Substituted thiapyrylium salts have been



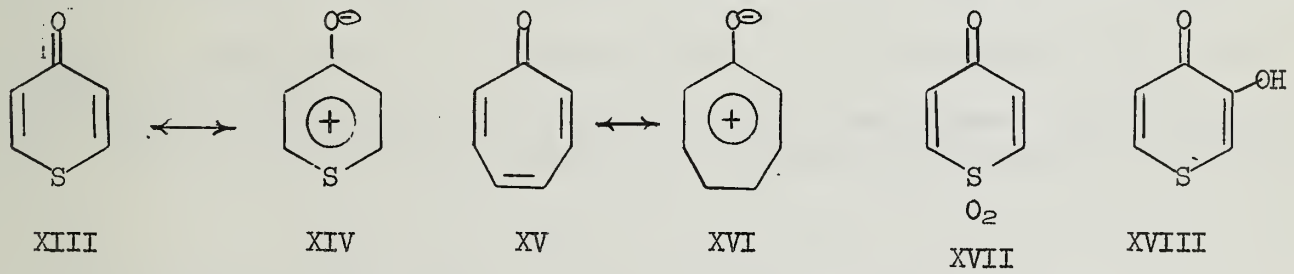
known for some time. Only recently, Pettit (8) reported the preparation of the parent compound (VIII), by the above sequence, analogous to a preparation of tropylium salts from benzene. Compound VII is also available through another route (9). Various salts of VIII form stable aqueous solutions, while some of the corresponding pyrylium salts tend to decompose in water. Compound VIII may be reduced to IX, which reverts almost completely to VIII by hydride transfer when treated with tropylium ion (X).



pK_a: 8.7 4.7 6.1 1.6

The striking stability of VIII is shown by its pK_a (for $R^+ + H_2O \rightleftharpoons ROH + H^+$; see above) relative to that of X(10). The data for XI and XII are included here for comparison and will be mentioned later in connection with fused-ring compounds.

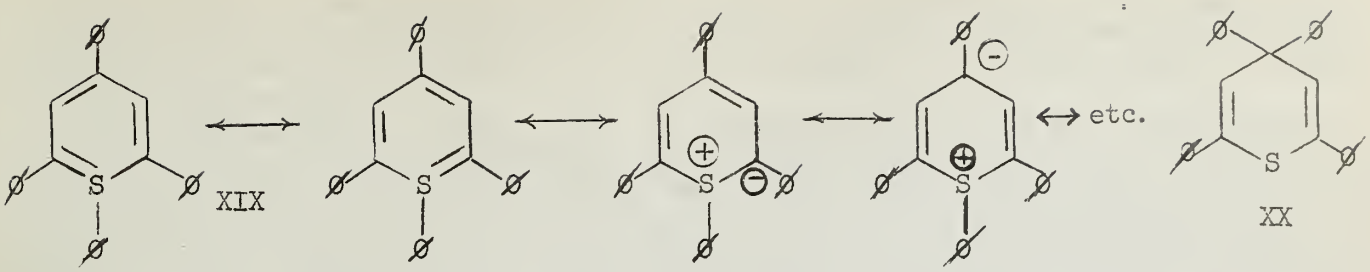
γ-Thiapyrone (XIII) is similar to tropone (XIV). The carbonyl stretching frequencies of these compounds are 1609 and 1635 cm.$^{-1}$, respectively, showing the importance of



resonance forms XIV and XVI (11). In the sulfone XVII the carbonyl frequency is raised to 1657 cm.$^{-1}$, which is in the range expected for a carbonyl flanked by two carbon-carbon double bonds. Further evidence will be given later that the sulfone group cannot take part in cyclic conjugation.

Although tropone may be oxidized to tropolone, the oxidation of XIII usually leads to the sulfone XVII. Compound XVIII was finally prepared through conversion of γ-thiapyrone-4-carboxylic acid to the 3-amine followed by hydrolysis (12). It is reported that XVIII resembles tropolone in most respects. Both compounds are water-soluble, give the ferric chloride test and form non-polar complexes with cupric ion. The IR spectrum of XVIII has a wide O-H band around 3250 cm.$^{-1}$ and a C=O band at 1630 cm.$^{-1}$.

Suld and Price (13) obtained from the reaction of 2,4,6-thiapyrylium perchlorate and phenyl lithium an amorphous, violet solid to which they assigned the structure XIX and the name 1,2,4,6-tetraphenylthiabenzene. Assuming this structure, one might predict the +1 sulfur core to have the outer electronic configuration: $(3s)^2\ (3p)^3$, with the possibility of resonance between the structures shown below, two of which use d-orbitals, while the others are of the ylid-type. A point at issue is whether through conjugation

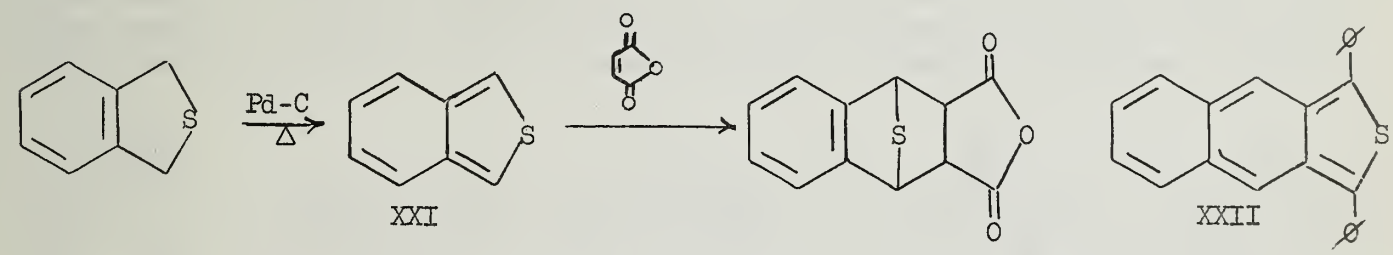


would exist at the sulfur. Price suggests that two orthogonal 3d-orbitals of sulfur may form π-bonds with adjacent p_z-orbitals, and in the process become mutually non-orthogonal. Alternatively, the three σ-bonds at sulfur may become sp^2-hybrids, while the unshared electrons promote to 3d-orbitals, leaving the $3p_z$-orbital open for the π-conjugation. However, the chemistry described for this "thiabenzene" does not reflect aromatic stabilization. Oxygen destroys the compound, reportedly by 2,5-addition. At room temperature in the absence of oxygen, it slowly undergoes a remarkable rearrangement to XX. Alkyl Grignard reagents react with the pyrylium perchlorate in ether to give transiently deep red or purple solutions from which only 2- or 4-alkylthiapyrans can be isolated. The initial formation of thiabenzene is postulated.

FUSED RING SYSTEMS CONTAINING ONE SULFUR ATOM

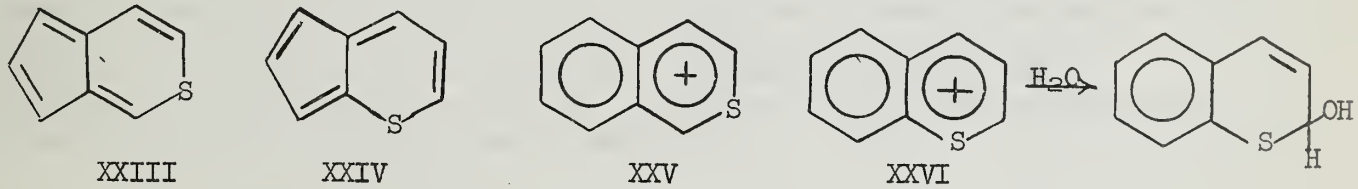
It is well known that electrophilic substitutions in benzothiophene usually occur at the 3-position in analogy with naphthalene. In the transition state of such reactions, the positive charge can be delocalized to sulfur without disrupting the π-system of the benzene ring.

Unsubstituted isobenzothiophene (XXI) is stable for only a few days at -30° under nitrogen (14). The reaction with maleic anhydride demonstrates its o-quinonoid nature.



A similar compound (XXII) is moderately stable. It is less reactive as a diene than its oxygen analog (15).

Two azulene analogs XXIII (16) and XXIV (17) have been prepared by dehydrogenations of more saturated compounds containing the corresponding ring structures. Like azulene,

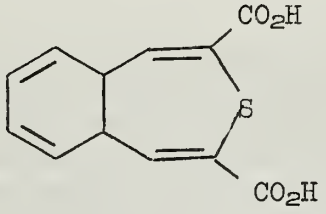


both XXIII and XXIV are very prone to electrophilic substitution at the positions of the 5-ring adjacent to the larger ring. Compound XXIII is quite stable, is soluble in dilute acid and has an electronic spectrum which resembles that of azulene. Compound XXIV is relatively unstable to air.

Salts of both isomeric thianaphtholinium ions, XXV and XXVI, have been made by Lüttringhaus(18). These species are less stable than the thiapyrylium ion and slowly hydrolyze via the hemithioacetals. They have UV maxima at ~ 385 mμ similar to those of quinolinium salts.

Pettit (10) sought to prepare XXVI from benzothiophene using the same reactions shown previously for the preparation of thiapyrylium salts (VIII). Surprisingly, the carbene from ethyl diazoacetate added to the benzene ring and the final product was a thienotropylium ion, XI. Note from the pK_a values shown on a previous page that the tropylium ion is stabilized by a fused thiophene ring, which is electron donating, but destabilized by a fused benzene ring, which withdraws electrons for its own aromatic sextet.

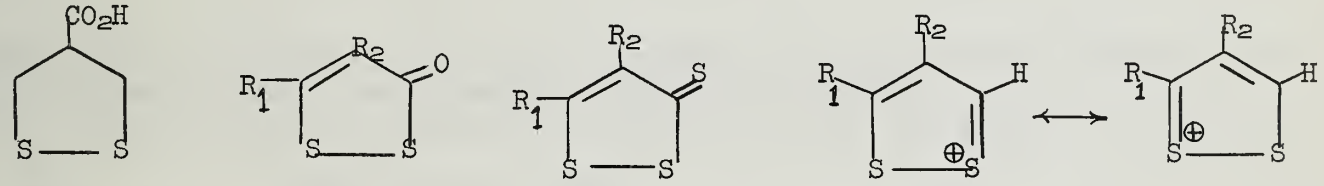
Compound XXVII is unstable and readily loses sulfur to form naphthalene-2,3-dicarboxylic acid. In acids, XXVII polymerizes, while the diesters of XXVII are reportedly stable and can be recovered unchanged from solutions in concentrated acids (19).



XXVII

RINGS CONTAINING SEVERAL SULFUR ATOMS

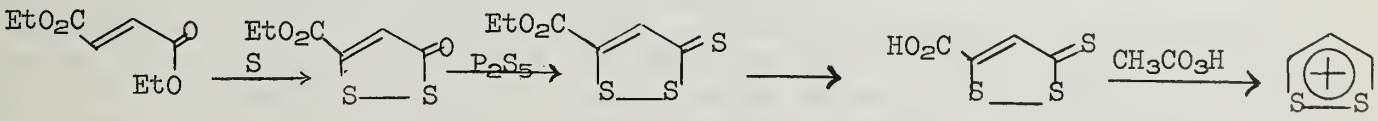
In non-cyclic organic disulfides, the C-S-S angles are 103-107°. The dihedral angle at C-S-S-C is about 90°, with a barrier of rotation around the S-S bond estimated at more than 10 kcal./mole (20). This barrier is thought to arise principally from the mutual repulsion between the unshared pairs of pπ-electrons on adjacent sulfur atoms. In the unstable compound XXVIII, the dihedral angle is reduced to about 27° by the steric demands of the ring. On the other hand, the conjugated "trithione" ring (XXX)



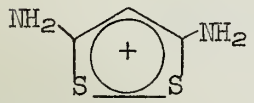
XXVIII XXIX XXX XXXI

is shown by x-ray studies to be approximately planar (21). Trithiones are commonly produced either by heating an α,β-unsaturated ester with sulfur to give XXIX, followed by treatment with phosphorus pentasulfide, or by heating certain olefins with sulfur. To prepare the parent compound (XXX, R_1=R_2=H) propylene is passed into boiling sulfur. Trithions are crystalline, stable to air and acids, but not to strong base. Lüttringhaus and co-workers have studied these compounds in detail (22).

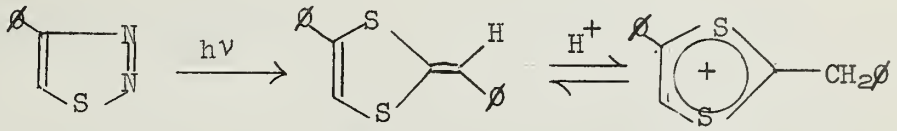
Klingsberg (23) has prepared a new ring system, the 1,2-dithiolium cation (XXXI). The following sequence led to the parent compound:



Both monophenyl derivatives were made, and the symmetry of cation XXXI, where R_1=H and R_2=phenyl, was proven by NMR. When R_1=phenyl, the positive change can be delocalized onto the phenyl ring, but not when R_2=phenyl. This difference between the monophenyl compounds was demonstrated by UV spectra and by orientation in nitration of the benzene rings. Dithiolium salts are stable in the absence of alkalies. Hydroxide ion attacks XXXI at a 3-position giving a hemithioacetal which undergoes further hydrolysis. The iodide of XXXII is formed when dithiomalonamide is treated with iodine (24).



XXXII



XXXIII XXXIV

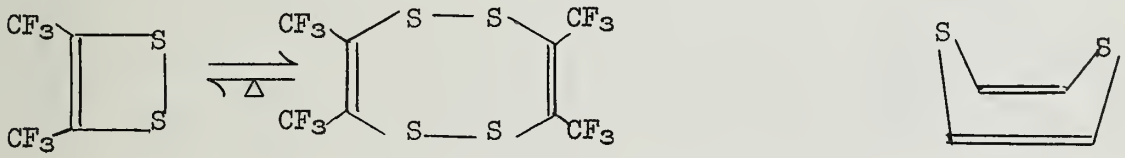
The photolysis of a 1,2,3-thiadiazole gives, among other products, XXXIII, which protonates to form a cation which is quite acidic, but less so than most sulfonium salts. The structure XXXIV has been proposed for the cation. (25)

The treatment of heptane-2,4,6-trione with phosphorus pentasulfide affords a stable substance, $C_7H_8S_3$. The sulfur atoms are linear and the NMR spectrum shows a peak for two protons and another peak in the methyl region for six protons. The resonating structures XXXV fit these data (26). When XXXV is converted to XXXVI, the protons

XXXV XXXVI

at lower field in the NMR are no longer equivalent, showing that the oxygen atom does not participate in the "no-bond" resonance exhibited in XXXV.

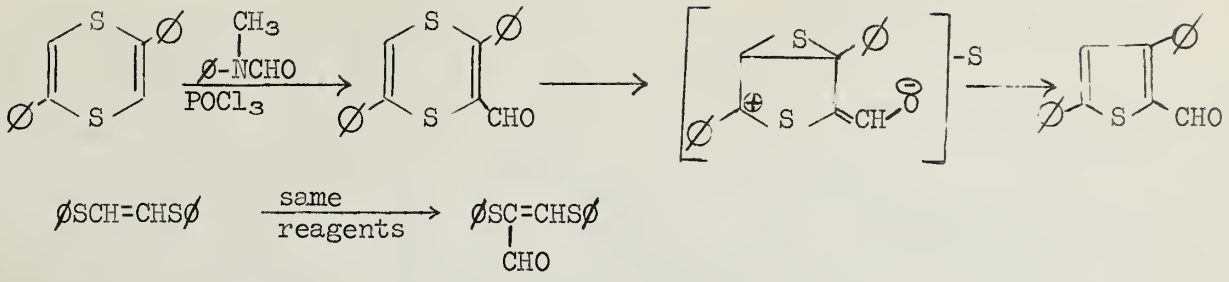
The dithietene XXXVII, prepared from perfluoro-2-butyne and sulfur, is claimed to



XXXVII XXXVIII XXXIX

have "aromatic character" because of its sextet of π-electrons and its thermal stability. However, at room temperature a trace of base causes it to dimerize to XXXVIII which reverts to the monomer at temperatures above 200° (27).

The chemistry of 1,4-dithiadiene (XXXIX) and related compounds has been reviewed by Parham (28). The molecule is in a boat form with a C-S-C angle at 100°. The parent heterocycle is thermally stable. It is not affected by an acidic solution of 2,4-dinitrophenylhydrazine which would hydrolyze aliphatic vinyl sulfides. With strong Lewis acids, XXXIX polymerizes. No electrophilic substitution reactions are known for XXXIX. Benzo-1,4-dithiadiene is even more stable than XXXIX and undergoes electrophilic substitution in the dithiadiene ring under mild conditions. Bromine adds to the 2-3-double bond to give a dibromide which readily loses hydrogen bromide. 2,5-Diphenyl-1,4-dithiadiene forms electrophilic substitution products, but its open chain analogs also show this property to some extent.



ØSCH=CHSØ $\xrightarrow[\text{reagents}]{\text{same}}$ ØSC(CHO)=CHSØ

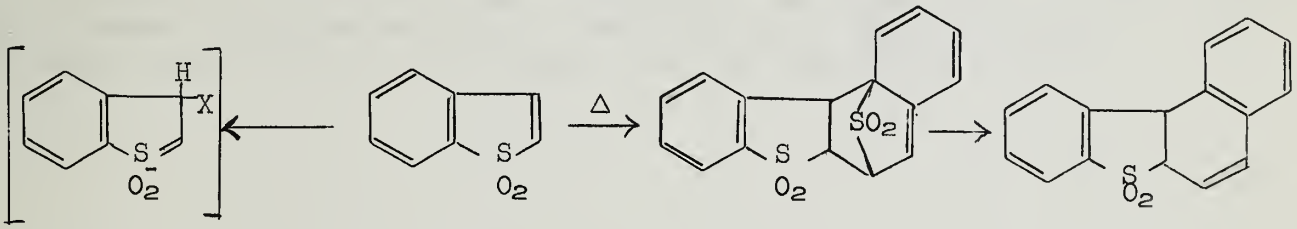
The first reaction above exemplifies the tendency of 2,5-diaryl-1,4-dithiadienes to form 2,4-diarylthiophenes by the loss of a sulfur atom from the polar, resonance-stabilized intermediate. Loss of a sulfur atom also occurs when the diaryl compounds are heated.

Kreevoy performed MO calculations on 1,4-dithiadiene (2) and predicted a large resonance energy of 28 kcal./mole in the boat form.

SULFONES

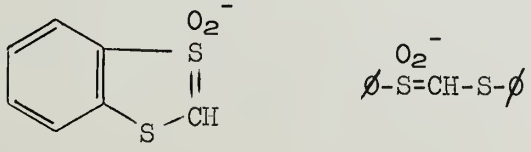
The unstable thiophene-1,1-dioxide is usually prepared through a series of reactions beginning with butadiene and sulfur dioxide. Since the oxidized sulfur atom has no electrons to contribute to an aromatic sextet, the compound may be compared to cyclopentadiene, or perhaps more cogently to the transiently existing cyclopentadienone. All three compounds rapidly form a Diels-Alder dimer (29).

The 1,1-dioxide of benzothiophene (XL) reacts similarly at 200° as shown below. Diel-Alder reactions involving a benzenoid double-bond are not common, but this reaction probably owes its success to the loss of SO_2, which shifts an unfavorable equilibrium (30). The carbonyl analog of XL, indone, polymerizes with extreme ease. The 2-3 bond of XL is olefinic. In the presence of basic catalysts, reagents of the type HX (X=Hal, OH, OR) add to form stable products by the probable intermediate, XLI, which may be stabilized by a sulfur-carbon dπpπ-bond (31).



XLI XL

Breslow and Mohacsi (32) have found that the anion XLII is no less basic than XLIII showing no special stabilization in the sulfur-containing ring of XLII, in which six π-electrons are available.



XLII XLIII

Thus, it appears that a sulfone group cannot sustain aromatic conjugation.

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REACTIONS OF ORGANIC COMPOUNDS WITH SULFUR TETRAFLUORIDE

Reported by D. Kubicek July 11, 1962

INTRODUCTION

Sulfur tetrafluoride has been found to react with both organic (2, 3, 6, 7, 8, 10, 11, 13, 14) and inorganic (4, 9, 12, 14) functional groups. This report will deal only with the reactions of sulfur tetrafluoride with organic functional groups including the carbonyl, thiocarbonyl, carboxyl, hydroxyl, amide, nitrile, isocyanate and boric acid esters.

SYNTHESIS OF SULFUR TETRAFLUORIDE

Several methods are known for the preparation of sulfur tetrafluoride. It has been prepared by the reaction of sulfur with cobalt trifluoride or elemental fluorine (1 and references therein). Schmidt (1) prepared it from iodine pentafluoride and sulfur monobromide. Sulfur tetrafluoride was obtained in 85% yield by Tullock and co-workers (1) by reacting sulfur dichloride with excess sodium fluoride suspended in acetonitrile. Also the reaction of sulfur and boron with fluorine was found to be a method of preparing very pure sulfur tetrafluoride (5).

THE REACTION OF ALDEHYDES WITH SULFUR TETRAFLUORIDE

The general reaction of sulfur tetrafluoride with the replacement of the carbonyl oxygen of the aldehyde can be represented by equation 1 (2, 8, 11, 13, 14). In general, aldehydes having no α-hydrogen atoms gave high yields of the difluoride. Aliphatic aldehydes which possess α-hydrogen atoms were found to be somewhat sensitive to sulfur tetrafluoride and the yields of the difluoride were lower (2). Table I (2) gives data for the reaction of aldehydes with sulfur tetrafluoride.

Table I

Reaction of Aldehydes with Sulfur Tetrafluoride

Starting Material	(moles)	SF_4 (moles)	Temp., °C.	Time, hrs.	Product Structure	Yield
CH_3CHO	0.60	0.75	50	14	CH_3CHF_2	35
$CH_3(CH_2)_5CHO$	0.25	0.37	60	8	$CH_3(CH_2)_5CHF_2$	43
$(HCHO)_x$ (α-polyoxymethylene)	2.33	2.30	150	6	CH_2F_2 FCH_2OCH_2F	49 21
$H(CF_2)_4CHO$	0.25	0.28	100	10	$H(CF_2)_4CHF_2$	55
C_6H_5CHO	0.30	0.60	150	6	$C_6H_5CHF_2$	81
p-$C_6H_4(CHO)_2$	0.15	1.00	150	8	p-$C_6H_4(CHF_2)_2$	88

THE REACTION OF KETONES WITH SULFUR TETRAFLUORIDE

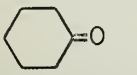
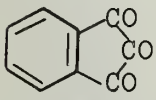
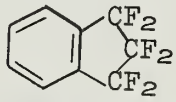
The general reaction of sulfur tetrafluoride with the replacement of the carbonyl oxygen of a ketone by two fluorine atoms can be represented by equation 1 (2, 8, 11, 13, 14). Benzophenone was found to be quite resistant to reaction with sulfur tetrafluoride

$$>C=O + SF_4 \longrightarrow >CF_2 + SOF_2 \qquad 1)$$

even at temperatures considerably higher than those employed for other ketones. This phenomenon was probably due to the steric hindrance of the carbonyl group. However, high yields of diphenyldifluoromethane were obtained from benzophenone and sulfur tetrafluoride using BF_3, AsF_3 or TiF_4 as catalyst (2). With vicinal polyketones, such as benzil and diphenyl-triketone, all of the ketonic oxygen atoms were replaced. Table II (2) gives data for the reaction of ketones with sulfur tetrafluoride.

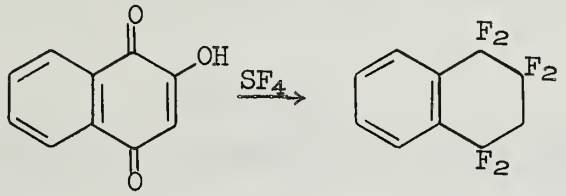
Table II

Reactions of Ketones with Sulfur Tetrafluoride

Starting Material	(moles)	SF_4(moles)	Temp., °C.	Time, hrs.	Product Structure	Yield
CH_3COCH_3	0.60	0.67	110	16	$CH_3CF_2CH_3$	60
	0.40	0.41	39	13		31
$(C_6H_5)_2CO$ (HF cat.)	0.25	0.50	180	6	$(C_6H_5)_2CF_2$	97
$C_6H_5COCF_3$	0.075	0.22	100	8	$C_6H_5CF_2CF_3$	65
$(C_6H_5CO)_2$	0.125	0.50	180	5	$(C_6H_5CF_2)_2$	34
$(C_6H_5CO)_2CO$	0.075	0.50	120	8	$(C_6H_5CF_2)_2CF_2$	50
	0.254	1.55	120	8		25
$(C_2H_5OOCCH_2)_2CO$	0.25	0.50	80	6	$(C_2H_5OOCCH_2)_2CF_2$	29
$MeCO(CH_2)_2COOEt$ (HF cat.)	0.42	0.48	95	10	$MeCF_2(CH_2)_2COOEt$	16
$\phi COCH{=}CHCOOMe$	0.23	0.48	160	10	$\phi CF_2CH{=}CHCOOMe$	25

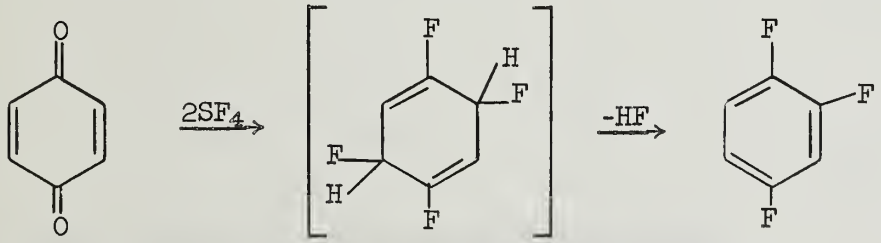
THE REACTION OF QUINONES WITH SULFUR TETRAFLUORIDE

Some quinones, such as anthraquinone and chloranil, react in the same fashion as a ketone to give products in which each oxygen atom is replaced by two fluorine atoms (2, 8). Other quinones are irregular in their behavior. Some hydroxyquinones gave products in which hydrogen fluoride added to an unsaturated bond of the starting material, thus 1,1,2,2,4,4-hexafluoro-1,2,3,4-tetrahydronaphthalene was obtained from 2-hydroxy-1,4-naphthoquinone, equation 2 (2).



2)

Benzoquinone reacts with sulfur tetrafluoride and hydrogen fluoride at 200° to give 1,2,4-trifluorobenzene. This reaction may proceed by 1,4 fluorination of the α,β-unsaturated carbonyl groups followed by the loss of a molecule of hydrogen fluoride, equation 3 (2). Table III gives data for the reaction of quinones with sulfur tetrafluoride (2).



3)

THE REACTION OF HYDROXYLIC COMPOUNDS WITH SULFUR TETRAFLUORIDE

Compounds containing hydroxyl groups react readily with sulfur tetrafluoride to introduce a fluorine atom at the site of the hydroxyl group (2). The yield of the products is roughly correlated to the acidity of the hydroxyl group with the highest yields being for the conversion of carboxylic and sulfonic acids to the acyl and sulfonyl fluorides. Less acidic compounds, such as tropolones, are converted in moderate yield to α-fluorotropone. Still less acidic compounds like alcohols gave the corresponding alkyl fluorides, but the alkyl ether was formed as a major by-product. Tables IV and V (2) give data for the reaction of hydroxylic compounds with sulfur tetrafluoride.

Table III

Reaction of Quinones with Sulfur Tetrafluoride

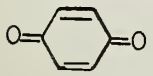
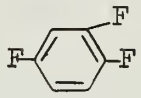
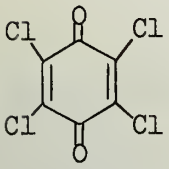
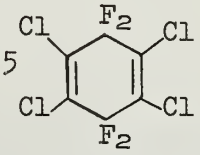
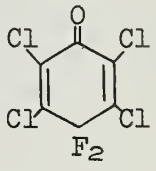
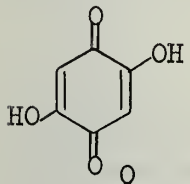
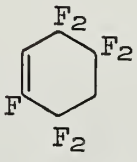
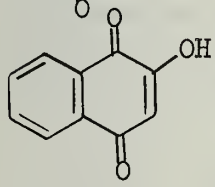
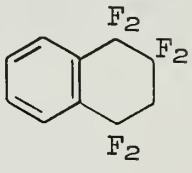
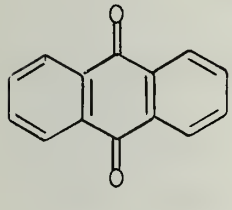
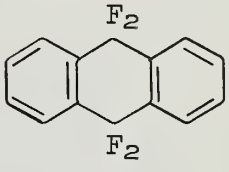
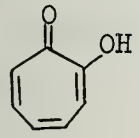
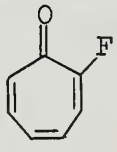
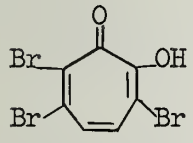
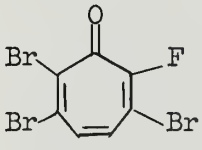
Starting Material	(moles)	SF_4 (moles)	Cat.(moles)	Temp. °C.	Time hrs.	Product Structure	Yield
	0.20	0.35	HF(0.35)	200	4		30
	0.14	0.42	HF(0.15)	270	2.5		75
							2
	0.10	0.55	HF(0.10)	60	8		40
	0.10	0.50	H_2O(0.10)	140	1.5		36
	0.059	0.28	HF(0.05)	255	8		78

Table IV

Reaction of Hydroxylic Compounds with Sulfur Tetrafluoride

Starting Material	(moles)	SF_4(moles)	Temp., °C.	Time, hrs.	Product Structure	Yield
	0.02	0.065	60	10		28
	0.0033	0.02	60	8		57

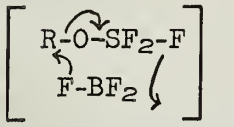
THE REACTION OF BORIC ACID ESTERS WITH SULFUR TETRAFLUORIDE

As has been noted (2), the reaction of alcohols with sulfur tetrafluoride gave as the principal product the dialkyl ether. The reaction of sulfur tetrafluoride with boric acid esters gave the best results so far for the synthesis of alkyl fluorides (10). The formation of alkyl fluorides can occur if the boron in the boric acid ester is an electron pair acceptor and the sulfur tetrafluoride an electron donor, equation 4 (10). The boric acid-tri-n-hexylester was converted to the n-hexyl fluoride by the reaction with sulfur tetrafluoride in 30.8% yield, the tri-n-octylester to the n-octyl fluoride in 43.9% yield, the tri-dodecylester to the dodecyl fluoride in 52% yield and the tri-cyclohexylester to the cyclohexyl fluoride in 58.5% yield.

a) $(RO)_3B + SF_4 \rightarrow [(RO)_3\overset{\ominus}{B}\text{-}\overset{\oplus}{SF_4}] \rightarrow [(RO)_3\overset{\ominus}{B}F]\overset{\oplus}{SF_3} \rightarrow [(RO)_2BF + ROSF_3]$

b) $[(RO)_2BF] + SF_4 \rightarrow [(RO)_2(F)\overset{\ominus}{B}\text{-}\overset{\oplus}{SF_4}] \rightarrow [(RO)_2(F)_2\overset{\ominus}{B}]\overset{\oplus}{SF_3} \rightarrow [ROBF_2 + ROSF_3]$ 4)

c) $[ROBF_2] + SF_4 \rightarrow [(RO)(F)_2\overset{\ominus}{B}\text{-}\overset{\oplus}{SF_4}] \rightarrow [(RO)(F)_3\overset{\ominus}{B}]\overset{\oplus}{SF_3} \rightarrow BF_3 + [ROSF_3]$

d)  $\rightarrow RF + SOF_2 + BF_3$

THE REACTION OF CARBOXYLIC ACIDS WITH SULFUR TETRAFLUORIDE

The general reaction of sulfur tetrafluoride with a carboxylic acid can be represented by equation 5 (2, 8, 13, 14). The formation of the acyl fluoride occurs readily at room temperature or below, while the second step requires elevated temperature. The degree of fluorination with polybasic acids may be controlled by the amount of sulfur

a) $RCOOH + SF_4 \rightarrow RCOF + HF + SOF_2$

b) $RCOF + SF_4 \rightarrow RCF_3 + SOF_2$ 5)

tetrafluoride used. The reaction of sulfur tetrafluoride with a carbonyl compound showed a high degree of specificity in that olefinic and acetylenic bonds are unaffected. Other functional groups including fluoro, chloro, bromo, nitro and methoxy carbonyl usually are unaffected by sulfur tetrafluoride at temperatures up to 160° (2). Table V (2) gives data for the reaction of carboxylic acids with sulfur tetrafluoride.

Table V

Reaction of Carboxylic Acids with Sulfur Tetrafluoride

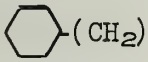
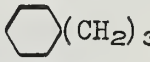
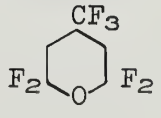
Starting Material	(moles)	SF_4(moles)	Temp., °C.	Time, hrs.	Product Structure	Yield
CH_3CH_2COOH	0.60	1.82	150	8	$CH_3CH_2CF_3$	89
$CH_3(CH_2)_5COOH$	0.20	0.65	130	6	$CH_3(CH_2)_5CF_3$	80
$CH_3(CH_2)_{10}COOH$	0.33	2.00	130	6	$CH_3(CH_2)_{10}CF_3$	88
$CH_3(CH_2)_{16}COOH$	0.35	2.13	130	6	$CH_3(CH_2)_{16}CF_3$	93
$(CH_3)_3CCH_2\underset{CH_3}{\underset{\vert}{C}}HCH_2COOH$	0.19	0.57	120	6	t-$BuCH_2\underset{CH_3}{\underset{\vert}{C}}HCH_2CF_3$	64
	0.20	0.60	120	10		80
$CH_2(COOH)_2$	0.30	0.69	40	16	$CH_2(COF)_2$	70
$CH_2(COOH)_2$	0.40	2.40	150	8	$CH_2(CF_3)_2$	57
$(-CH_2COOH)_2$	0.40	2.40	150	8	$(-CH_2CF_3)_2$	41
$[-(CH_2)_2COOH]_2$	0.67	2.23	130	7	$[-(CH_2)_2CF_3]_2$ $CF_3(CH_2)_4COOH$	19 39
$[-(CH_2)_4COOH]_2$	0.15	0.46	120	6	$CF_3(CH_2)_8CF_3$ $CF_3(CH_2)_8COF$ $FCO(CH_2)_8COF$	27 45 21
$(CH_2COOH)_2CHCOOH$	0.07	0.63	130	10		20
$CH_2BrCHBrCH_2COOH$	0.53	1.85	140	8	$CH_2BrCHBrCH_2CF_3$	54
$HCF_2CF_2COOH(BF_3$ cat.)	0.15	0.48	250	8	$HCF_2CF_2CF_3$	56

Table V, Cont'd.

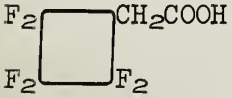
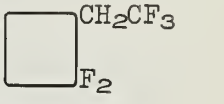
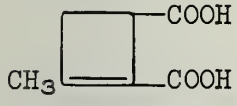
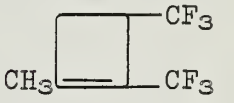
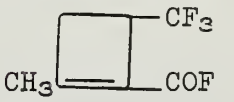
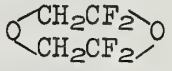
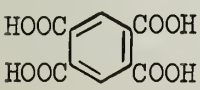
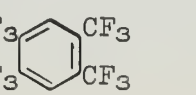
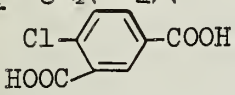
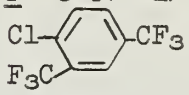
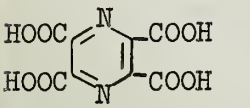
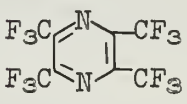
Starting Material	(moles)	SF_4 (moles)	Temp., °C.	Time, hrs.	Product Structure	Yield
	0.28	2.23	150	6		43
	0.08	0.30	160	16		51
CH_2=CHCOOH	0.75	2.00	130	8	CH_2=$CHCF_3$	45
CH_2=C(CH_3)(COOH)	0.75	2.00	130	8	CH_2=C(CH_3)(CF_3)	54
HOOCCH=CHCOOH(trans)	0.55	2.78	130	9	F_3CCH=$CHCF_3$(trans)	95
(=$CHCH_2COOH$)$_2$	0.10	0.55	130	10	(=$CHCH_2CF_3$)$_2$	58
CH_2=C(COOH)(CH_2COOH)	0.62	2.80	160	10	CH_2=C(CF_3)(CH_2CF_3)	26
					CH_2=C(COF)(CH_2CF_3)	41
	0.149	0.89	120	4		31
						30
HC≡CCOOH	2.00	2.10	30-55	3	HC≡CCOF	28
HC≡CCOOH	0.27	0.78	120	3	HC≡CCF_3	60
HOOCC≡CCOOH	0.395	1.67	70	6	FOCC≡COF	51
HOOCC≡CCOOH(TiF_4 cat.)	0.125	0.75	170	8	F_3CC≡CCF_3	80
$HOOCCH_2OCH_2COOH$	0.50	3.00	130	7	$F_3CCH_2OCH_2CF_3$	35
						14
$C_2H_5OOC(CH_2)_4COOH$	0.77	2.00	130	7	$EtOOC(CH_2)_4CF_3$	14
					$HOOC(CH_2)_4CF_3$	13
$HOCH_2COOH$	0.75	3.00	160	5	FCH_2CF_3	48
					FCH_2COF	18
$HOOCCH_2SO_3H$	0.20	0.69	180	6	$CF_3CH_2SO_2F$	41
$HOOC(CH_2)_{10}SO_3H$	0.083	0.41	130	8	$CF_3(CH_2)_{10}SO_2F$	42
$HOOC(CH_2)_6CH(COOH)SO_3H$	0.195	1.61	150	8	$CF_3(CH_2)_6CH(CF_3)SO_2F$	33
C_6H_5COOH	0.25	0.50	120	6	$C_6H_5CF_3$	22
					C_6H_5COF	41
$C_6H_5COCOOH$	0.125	0.51	100	6	$C_6H_5CF_3$	13
					C_6H_5COF	59
o-$C_6H_4(COOH)_2$	0.10	0.55	120	6	o-$C_6H_4(CF_3)_2$	43
					o-$C_6H_4(CF_3)(COF)$	23
p-$C_6H_4(COOH)_2$	0.10	0.60	120	6	p-$C_6H_4(CF_3)_2$	76
					p-$C_6H_4(CF_3)(COF)$	3
	0.07	0.83	150	6		77

Table V, Cont'd.

Starting Material	(moles)	SF_4(moles)	Temp., °C.	Time, hrs.	Product Structure	Yield
p-C_6H_4(COOMe)(COOH)	0.44	1.33	130	7	p-C_6H_4(COOMe)(COF)	63
p-$C_6H_4(NO_2)$(COOH)	0.67	2.12	130	7	p-$C_6H_4(NO_2)(CF_3)$	72
	0.20	1.20	150	8		62
	0.035	0.42	150	6		20

THE REACTION OF ACID ANHYDRIDES, SALTS AND ACYL HALIDES WITH SULFUR TETRAFLUORIDE

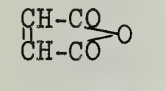
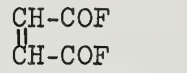
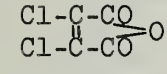
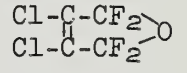
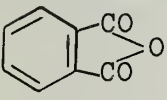
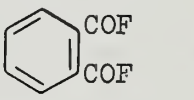
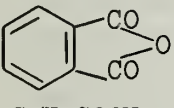
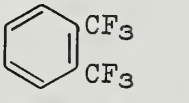
The reaction of sulfur tetrafluoride with carboxylic acid anhydrides, salts and acyl halides gave products analogous to those obtained from acids, however, more vigorous conditions were required. A cyclic anhydride may react without loss of the ring oxygen. The reaction of an acyl chloride is not straight forward, for example, the initial reaction of benzoyl chloride with sulfur tetrafluoride seems to be a halogen exchange. This is followed by chlorination of the ring and replacement of the carbonyl oxygen with two fluorine atoms, equation 6 (2). Table VI (2) gives data for the reaction of acid

$$C_6H_5COCl \xrightarrow{SE_4} C_6H_5COF \xrightarrow{SE_4} m\text{-}C_6H_4(CF_3)(Cl) \qquad 6)$$

anhydrides, salts and acyl halides with sulfur tetrafluoride

Table VI

Reaction of Acid Anhydrides, Salts and Acyl Halides with Sulfur Tetrafluoride

Starting Material	(moles)	SF_4(moles)	Temp., °C.	Time, hrs.	Product Structure	Yield
C_6H_5COF(HF cat.)	0.145	0.30	120	6	$C_6H_5CF_3$	41
C_6H_5COCl	0.20	0.80	150	8	C_6H_5COF	51
C_6H_5COCl(HF cat.)	0.20	0.50	120	6	m-$C_6H_4(CF_3)(Cl)$	25
$(CH_3CO)_2O$	0.30	0.20	300	10	CH_3CF_3	50
	0.30	0.60	150	13		71
	0.20	0.47	300	10		46
	0.20	0.40	180	18		93
	0.40	1.60	350	11		45
C_6H_5COONa	0.25	0.50	120	6	C_6H_5COF	48
$C_6H_5C{\equiv}CCOONa$	0.475	0.52	45	6	$C_6H_5C{\equiv}CCOF$	71

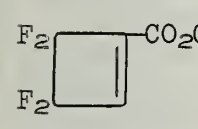
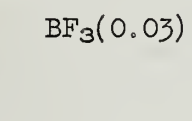
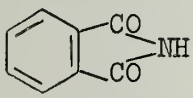
THE REACTION OF ESTERS AND AMIDES WITH SULFUR TETRAFLUORIDE

Vigorous conditions are required for the reaction of carboxylic acid esters with sulfur tetrafluoride, the products again being the trifluoromethyl compounds. α,α-Difluoroethers and acyl fluorides appear to be intermediates in this conversion (2). Although esters react with sulfur tetrafluoride at 130° when catalyzed by boron trifluoride or titanium tetrafluoride, the presence of hydrogen fluoride is without effect at temperatures up to 170° (2, 11). The latter fact has enabled these workers to prepare terminal trifluoro esters from monoesters of dibasic acids.

In contrast to the sluggish behavior of the ester group with sulfur tetrafluoride, the amide group is quite sensitive. In those amides in which there is a nitrogen-hydrogen bond, the carbonyl nitrogen bond breaks to give an acyl fluoride which may then undergo further reaction (2). With amides having no nitrogen-hydrogen bond, the carbonyl-nitrogen bond may or may not be broken. However, the preparation of the difluoroamine could not be repeated consistently (2). When the starting material contained small amounts of contaminates, such as carboxylic acids, which could form hydrogen fluoride by reaction with sulfur tetrafluoride, no difluoroamine was obtained. This would suggest that the cleavage of the carbonyl-nitrogen bond is catalyzed by hydrogen fluoride. Table VII (2) gives data for the reaction of esters and amides with sulfur tetrafluoride.

Table VII

Reaction of Esters and Amides with Sulfur Tetrafluoride

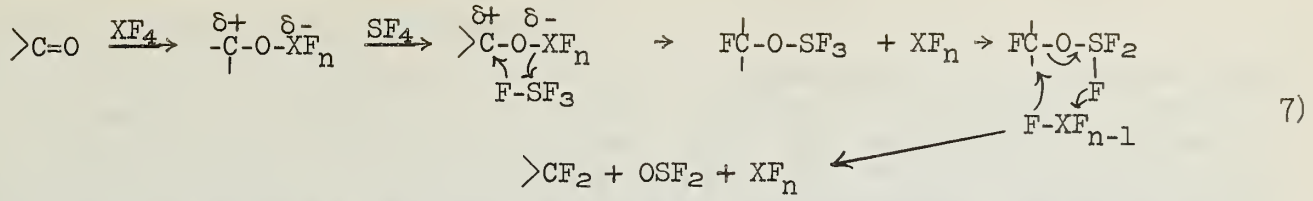
Starting Material	(SF_4) (moles)	Cat.(moles)	Temp. °C.	Time hrs.	Product Structure	Yield
$C_6H_5COOCH_3$	0.30	0.60		300	6	$C_6H_5CF_3$	55
						C_6H_5COF	trace
p-$C_6H_4(COOCH_3)_2$	0.10	0.60	BF_3(0.03)	130	8	p-$C_6H_4(CF_3)_2$	16
						p-$C_6H_4(CF_3)(COF)$	26
						p-$C_6H_4(COF)_2$	14
						CH_3F	high
$HCOOCH_3$	0.10	0.32	HF(0.05)	200	6	CH_3F and CHF_3	high
						HCF_2OCH_3	low
	0.20	0.60	BF_3(0.03)	140	16		10
$C_6H_5CONH_2$	0.20	0.41		150	8	$C_6H_5CF_3$	13
$C_6H_5CONHCH_3$	0.25	0.50	BF_3(0.015)	60	4	C_6H_5COF	48
$C_6H_5CON(CH_3)_2$	0.25	0.50		130	6	$C_6H_5CF_2N(Me)_2$	17
						C_6H_5COF	1.3
	0.20	0.69	BF_3(0.045)	100	10	o-$C_6H_4(COF)(CF_3)$	58

SYNTHESIS OF TETRAHALOMETHANES WITH SULFUR TETRAFLUORIDE

Carbon tetrafluoride has been prepared by several methods by reactions with sulfur tetrafluoride. Carbon dioxide reacts with sulfur tetrafluoride to give carbon tetrafluoride by way of the carbonyl fluoride (2). It was also found that carbon tetrafluoride could be prepared by the reaction of carbon monoxide with sulfur tetrafluoride (2). By this latter method 88% of the fluorine from the sulfur tetrafluoride was found in the final product. Temperatures near 500° were necessary to induce reaction without a catalyst and near 200° with hydrogen fluoride as catalyst. Other reactions used to produce carbon tetrafluoride were the reaction of carbon tetrabromide (7), carbon disulfide(7), and phosgene with sulfur tetrafluoride (2). Mixed tetrahalomethanes were prepared by methathesis reactions of carbon tetrachloride and carbon tetrabromide with sulfur tetrafluoride and by reaction of carbon disulfide with sulfur tetrafluoride with an added source of halogen.

MECHANISM FOR THE REACTION OF SULFUR TETRAFLUORIDE WITH A CARBONYL GROUP

The greater ease of reaction of a carboxylic acid than an anhydride with sulfur tetrafluoride led to the discovery that the reaction was catalyzed by hydrogen fluoride (2). It was found that the yield of diphenyldifluoromethane from benzophenone and sulfur tetrafluoride was increased from 10 to 97% by addition of hydrogen fluoride. Other fluorides such as BF_3, AsF_3, PF_5 and TiF_4, proved to be even better catalysts. A possible route for the replacement of the carbonyl oxygen by two fluorine atoms is given by equation 7 (2, 13).



7)

More vigorous conditions are required when strongly electron-attracting groups are attached to the carbonyl group indicating that the reaction may be initiated by coordination of a Lewis acid to the carbonyl group (2).

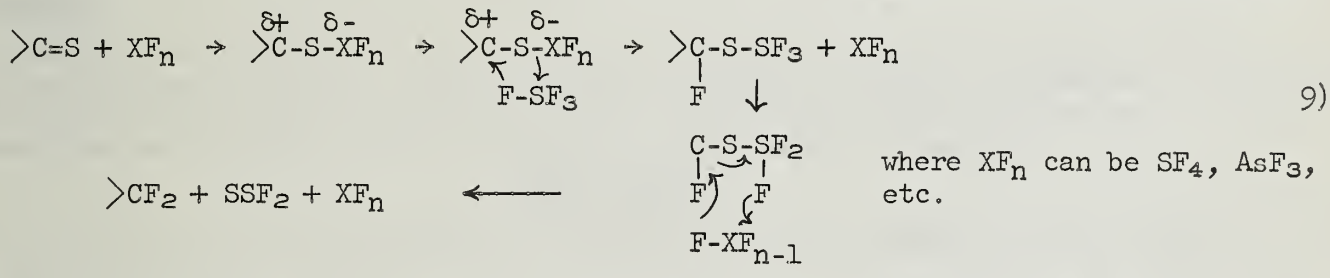
THE REACTION OF THIOCARBONYL COMPOUNDS WITH SULFUR TETRAFLUORIDE

The general reaction of sulfur tetrafluoride with a thiocarbonyl compound can be represented by equation 8 (6). This reaction differs from that of sulfur tetrafluoride

$$2\rangle C{=}S + SF_4 \rightarrow 2\rangle CF_2 + 3S \qquad 8)$$

with carbonyl compounds in that the reduction of the sulfur atoms in the thiocarbonyl by the sulfur tetrafluoride occurs. Ethylene trithiocarbonate reacts with sulfur tetrafluoride at 110° to give 2,2-difluoro-1,3-dithiolane in 82% yield (6). Dithiolane is readily hydrolyzed to ethylene dithiocarbonate, demonstrating that no rearrangement of the ring system occurred during fluorination. The reaction of sulfur tetrafluoride with thiuram sulfides gave a novel series of compounds, the dialkyltrifluoromethylamines. These compounds are highly susceptible to hydrolysis. Both the thione and sulfidic sulfur atoms of the thiuram and the sulfur atom of the sulfur tetrafluoride appeared as free sulfur.

A mechanism can be written for the initial stages of the sulfur tetrafluoride-thiocarbonyl reaction which parallels that proposed for the sulfur tetrafluoride-carbonyl reaction. If the analogy between the two reactions were carried to completion S_2F_2 would result, equation 9 (6). A fluoride of sulfur, S_2F_2, is known, and has been



9)

where XF_n can be SF_4, AsF_3, etc.

found to decompose moderately fast at room temperature to give sulfur tetrafluoride and sulfur, and is not inconsistent with the observed reaction.

SYNTHESIS OF CHLOROFLUOROALKANES FROM CHLOROALKENES

Chloroalkenes react with sulfur tetrafluoride to give products which would have come about from both the addition of fluorine to the double bond and replacement of the chlorine atom by a fluorine atom. Table VIII lists the products formed from the various reactions (7).

Table VIII

Reaction of Chloroalkenes with Sulfur Tetrafluoride

Starting Materials(moles)		Products	Starting Materials(moles)		Products
$Cl_2C{=}CCl_2$	0.12	$ClCF_2CF_2Cl$	C_5Cl_6	0.13	$C_5Cl_5F_3$
SF_4	0.25	C_2F_5Cl	SF_4	0.51	
AsF_3	0.01		BF_3	0.06	
$Cl_2C{=}CHCl$	0.12	$ClCF_2CF_2Cl$	C_6Cl_6	0.10	$C_6F_8Cl_2$
SF_4	0.25	C_2F_5Cl	SF_4	0.31	$C_6F_9Cl_3$

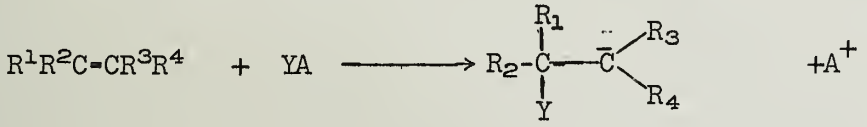
NUCLEOPHILIC ATTACK ON CARBON-CARBON DOUBLE BONDS

Reported by Marvin P. Dixon July 16, 1962

Carbon-carbon double bonds, activated by electron withdrawing substituents, are readily attacked by a variety of nucleophilic reagents. In this seminar the scope and nature of these reactions will be discussed. The products obtained from a nucleophilic attack on carbon-carbon double bonds are varied, depending upon reaction conditions, substituents, and the nucleophile. The resonance and inductive nature of the substituents can greatly effect the reactivity of the double bond. For example, in the exchange reactions of haloalkenes with iodide ion in butanol-water the per cent of iodide ion exchanged for halogen in the compounds were as follows (1):

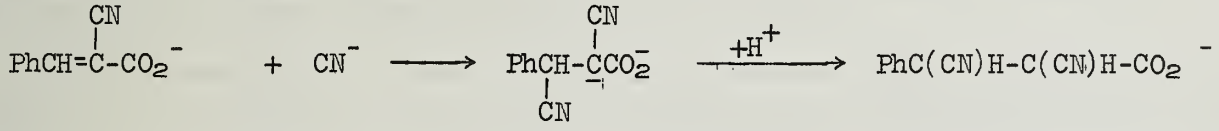
Compound	Time/Hr.	% Exchange
CH_2=CHBr	166	1
cis p-$NO_2C_6H_4$CH=CHBr	2.98	10.5
CF_2=CFCl	24	14.7

The mode of nucleophilic attack on activated carbon-carbon double bonds occurs on the positively polarized β-carbon atom, where the α-carbon is the carbon atom bearing the electron withdrawing substituent. The attack may be written as follows:

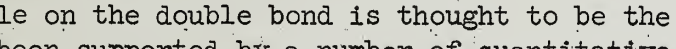


(I)

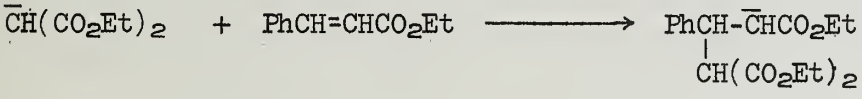
Jones (2) in his kinetic studies of the cyanoethylation of α-cyanocinnamic acid proposed the following mechanism:



Ingold (3) drew an analogy between Jones' mechanism of cyanoethylation and the Michael reactions. In his proposal the first step is the attack of a base on an active methylene compound to form a carbanion which attacks the carbon-carbon double bond. The attack of



the nucleophile on the double bond is thought to be the rate determining step. Ingold's proposal has been supported by a number of quantitative measurements (4-7). A general

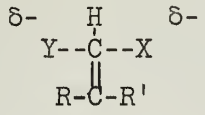


reaction sequence proceeding from the carbanion intermediate (I) may be written for the cyanoethylation and Michael additions as follows:

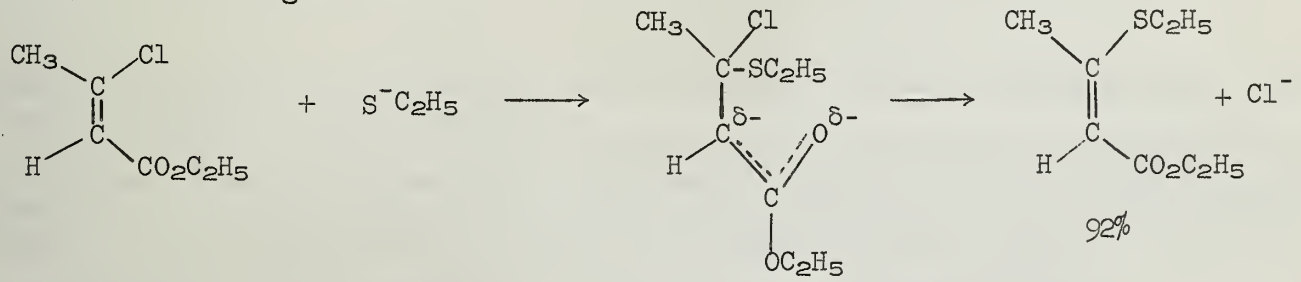
where Y is CN , $CH(CN)_2$, $CNCHO_2Et$, etc. and the substituents R^1, R^2, R^3, and R^4 are such that the carbanion (I) is stabilized, e.g. R^1=Ar, R^2=R^4=H, and R^3 = COAr'. Michael additions and cyanoethylations have been extensively studied (8-12).

A second way in which the carbanion may go to products is the elimination of one of the substituents. This reaction occurs most readily when one of the β-carbon substituents is a halogen. Hughes points out that vinylic halogens are hard to replace in contrast to those found on saturated carbons (13). Gold (14), in 1951, proposed two mechanistic

routes by which the elimination may occur. The first of these involved an analogue of the S_N2 mechanism for a saturated carbon. In the transition state the carbon atom undergoing substitution is thought to have linear sp hybridization. Gold points out that such a reaction path would result in inversion of geometry. His second proposal involved the



formation of a regular tetrahedral structure for the carbanion intermediate, but his proposal was not confirmed due to the lack of suitable examples. Jones and Vernon (15) made a kinetic study on the reaction of cis and trans ethyl-β-chlorocrotonates. They observed second order kinetics; first order in nucleophile and first order in the crotonate. Product analysis showed that the reactions had proceeded with a high degree of retention of configuration.

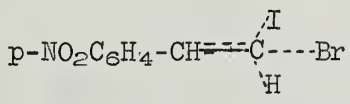


In the reactions involving the ethoxide ion only one product was isolated.

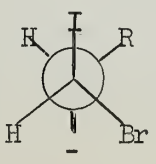
Truce and co-workers (16) have presented kinetic and chemical evidence in favor of an elimination-addition mechanism to account for the stereospecific conversion of cis-dichloroethylene to cis-1,2-bis-(p-tolylmercapto)-ethane.

Truce and Boudakian (17) have also presented evidence of an addition-elimination mechanism in the reactions of 1,1-dichloroethylene with p-tolylmercaptan and with potassium sulfite.

Miller and Yonan (1) studied in detail the displacement of bromide ion by iodide ion in the reactions of cis and trans p-nitro-β-bromostyrene and sodium or potassium iodide in methanol. The reaction proceeded largely in the early stages with retention of configuration, however, at equilibrium all four of the possible geometrical isomers were present. The rates of formation of the trans iodide and bromide from the cis bromide are roughly the same; and the rates of formation of the cis isomers from the trans bromide are similar also. The reaction is first order in substrate and first order in nucleophile. They suggest that the nucleophile attacks the alkene along a line perpendicular to the alkene by interaction with the pi orbital. The activated complex may be represented as:

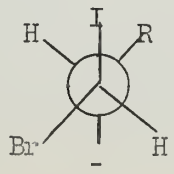


The complex may lose either bromide ion or iodide ion and return to its original configuration. The double bond may be lost also. If it is lost, the activated complex can yield a carbanion intermediate involving a tetrahedral structure similar to that proposed by Gold. The intermediate may be represented as II or its diasterioisomer III.



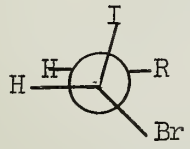
(II)

R= p-nitrophenyl

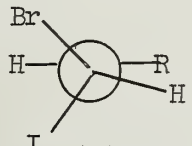


(III)

Carbanion II is one member of a dl pair, and one of a set of three threo rotamers. Carbanion III is one of a set of erythro rotamers. A 3-5 kcal. rotational barrier separates the members of each set. The threo and erythro isomers are separated by a barrier at the carbon adjacent to the reaction site. The inversion barrier at the α-carbon atom has been estimated to be less than 7 kcal. (1). Miller and Yonan assume that the halide departs only when it is trans to the electron pair of any isomer of II. These authors argue that when the rate of inversion is greater than that of internal rotation only the following forms need be considered.



(IV)



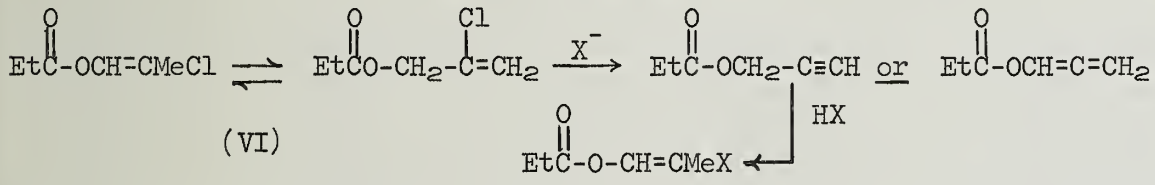
(V)

Exchange with retention of configuration is favored; the isomeric products are a result of internal rotation between IV and V.

If inversion is slower than internal rotation the route from cis to trans should be more difficult since both inversion at the α-carbon atom and internal rotation will be necessary for the isomerization. The best conclusion Miller and Yonan could make as to the nature of the isomerization process was the general reaction scheme.

cis-isomer ⇌ "cis" carbanion ⇌ "trans" carbanion ⇌ trans-isomer.

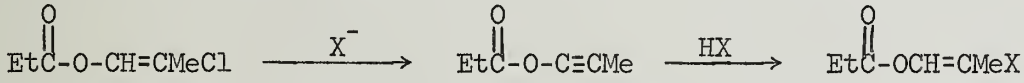
Vernon and co-workers (18) studied the nucleophilic attacks of ethoxide, thioethoxide, phenoxide, and thiophenoxide on the cis and trans isomers of ethyl-β-chlorocrotonate (cis and trans refer to the crotonic acid structure). The reaction exhibited second order kinetics. The following reaction sequence is thought to be unlikely because it involves an unfavorable prototropic rearrangement as the first step.



(VI)

The elimination of hydrogen chloride from the intermediate is unlikely to be rapid, particularly with sulfur containing nucleophiles. This mechanism does not account for the ease of the over all reaction or for the relatively small differences between the rates of reaction with the different nucleophiles.

A second mechanism, which is also consistent with their data, is an elimination-

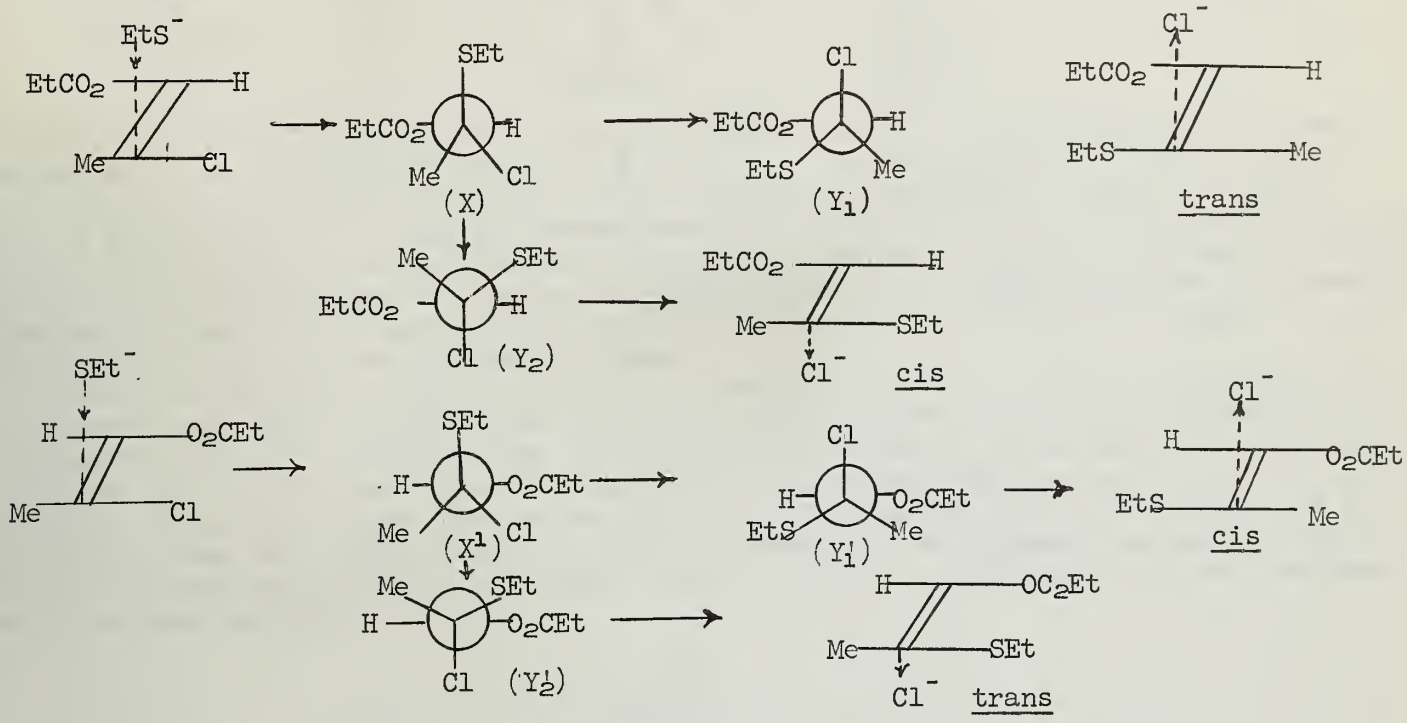


addition mechanism similar to that of Truce and his co-workers which may be eliminated, at least for the thioethoxide and thiphenoxide ions. This mechanism requires the same isomer or mixture of isomers to be formed from both of the chloroesters. The more strongly basic ethoxide ion would be expected to produce a large rate increase over those observed for the sulfur-containing nucleophiles.

Vernon and co-workers confirm the rejection of these two mechanisms, at least for thioethoxide ion, by carrying out the reactions in deuteroethanol. The above mechanisms require that isotopic exchange would compete for one of the hydrogen atoms in the products. No exchange was observed. The above mechanisms were excluded for thiophenoxide by analogy. In the reactions of the ethoxide ion, the elimination of the above mechanistic routes is not possible since there were no deuterium studies made with the ethoxide ion and the fact that only one isomer is isolated from either of the two isomeric crotonates.

The third mechanism they explored is similar to that discussed by Miller and Yonan (1). In their mechanism it is assumed that the approach of the nucleophile is at right angles to the plane of the olefin; that the chloride ion, by the principle of microscopic reversibility, departs along the same or a reciprocal path; and that in the intermediate the groups attached to the distal olefinic carbon remain in the original plane of the molecule.

The reactions of thioethoxide with the chloroesters are



In order for the reactions to proceed the intermediates must pass by rotation into the rotamers Y_1 or Y_2 and Y_1' and Y_2'. In each case, the intermediates pass through conformations in which certain groups are eclipsed.

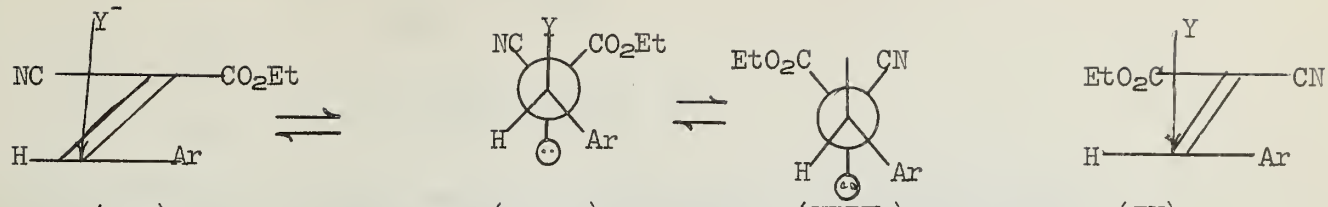
Transformation	Steric Course	Eclipsed Pairs
X---→Y_1	inversion	EtS, $EtCO_2$; Cl, H
X---→Y_2	retention	Me, $EtCO_2$
X'---→Y_1'	inversion	EtS,H; $EtCO_2$, Cl
X'---→Y_2'	retention	Me, H

The authors suggest that the differences in energy barriers of the rotamers must be slight. For the cis-chloroester, which gives 85 per cent of the product with retained configuration, the energy difference is estimated to be about 1 kcal/mole.

If one considers the steric course of the reaction to be determined by the rotational energy barriers in the intermediates X and X', then compounds of the type XCH=CHCl should show a more pronounced tendency to give products with retained configurations than those of the type XCH=CRCl (X is a strongly activating group and R is any other than H.) Examples in support of this argument are found in the literature (18-22).

Gold's S_N2 analogue is excluded on the basis that the products tend to retain their configurations while Gold's proposal requires inversion at the reaction site. Miller and Yonan (1) suggest that the reaction site is highly hindered and that the substituents on the α-carbon are within bonding distances of their respective β-carbon substituents in the transition state. Vernon and co-workers (18) agree with these views.

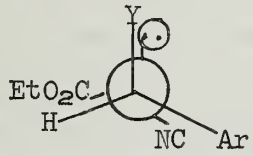
Patai and Rappoport (23) have reported on the nucleophilic catalyzed isomerization of cis-α-cyano-β-o-methoxyphenylacrylate to its trans isomer in 95 per cent ethanol. As in the work of previous authors the nucleophilic attack occurs at the β-carbon atom and results in the following equilibrium. The equilibrium is of a different nature than the one discussed by Miller and Yonan (1). Miller and Yonan studied a system in which a nucleophilic replacement going through a carbanion intermediate may take place on a carbon-carbon double bond with almost complete retention of configuration in which isomerisation was considered to be a much slower process. In the equilibrium presented by Patai and Rappoport the inversion of configuration of the carbanion is considered to be very rapid.



(VII) (VIIIa) (VIIIb) (IX)

Evidence in favor of this proposal is the fact that the rate of isomerization is almost unaffected by acid concentrations up to 2 mole l^{-1}. The fact that the final products of the condensations of ethyl cyanoacetate with aromatic aldehydes are always the trans isomers supports the view that the transformation VIIIa⇌VIIIb is rapid with the equilibrium in favor of VIIIb, the thermodynamically more stable and sterically less hindered carbanion, which on trans elimination of Y gives the trans isomer. The authors felt that the stereochemistry of the product in the condensation or in the isomerisation is probably controlled by the conformation of the elimination stage.

Patai and Rappoport argue that identical results would be obtained by assuming cis elimination for the carbanion VIIIa in its eclipsed conformation VIIIc. Although it is a relatively high-energy conformation, the energy needed for its formation from VIIIa was estimated to be of the same order of magnitude as that required from the inversion of VIIIa to VIIIb. Also, when Y is a neutral molecule (eg. H_2O), after the attack it gains a positive charge, and the electrostatic attraction between the two opposed charges in VIIIa will favor the formation of VIIIc. The experimental results do not render one mechanism more desirable than the other.

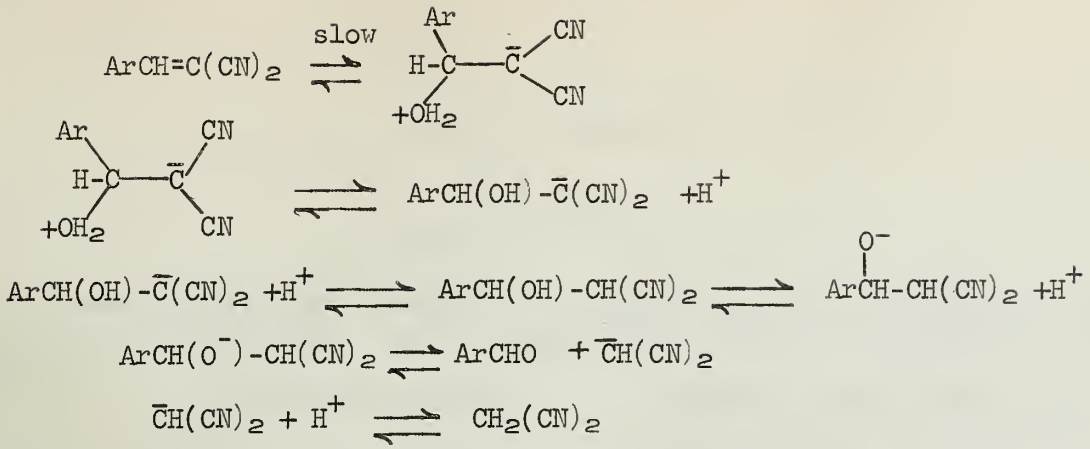


(VIIIc)

For hydroxyl ion concentration greater than 8×10^{-5} mole l^{-1}, hydrolysis of the double bond began to compete appreciably with the isomerisation reaction. The hydrolysis reaction does not occur in the presence of the triethylamine-triethylamine hydrogen chloride buffer, active methylene compounds, or $KC(CN)_3$, although these bases catalyze the isomerization. Therefore, the hydrolysis reaction is specific hydroxyl-ion catalyzed.

The hydrolysis of carbon-carbon double bonds to give the corresponding aldehydes and active methylene compounds has been the subject of several kinetic investigations (23-27). Stewart (25) has studied the base catalyzed cleavage of 3-methoxy-4-hydroxy-β-nitrostyrene in a strongly alkaline solution. He shows that the reaction proceeds with the attack of a hydroxyl ion on the β-carbon atom to give a colorless nitro-alcohol intermediate. Crowell and Francis (27) obtained pseudo-first order reaction kinetics for hydrolysis of 3,4-methylenedioxy-β-nitrostyrene to piperonal and nitromethane over the pH range -0.8 to 6. They suggest that the kinetics are characteristic of two consecutive reactions. The first is reversible and exhibits general base catalysis while the second is pH dependent.

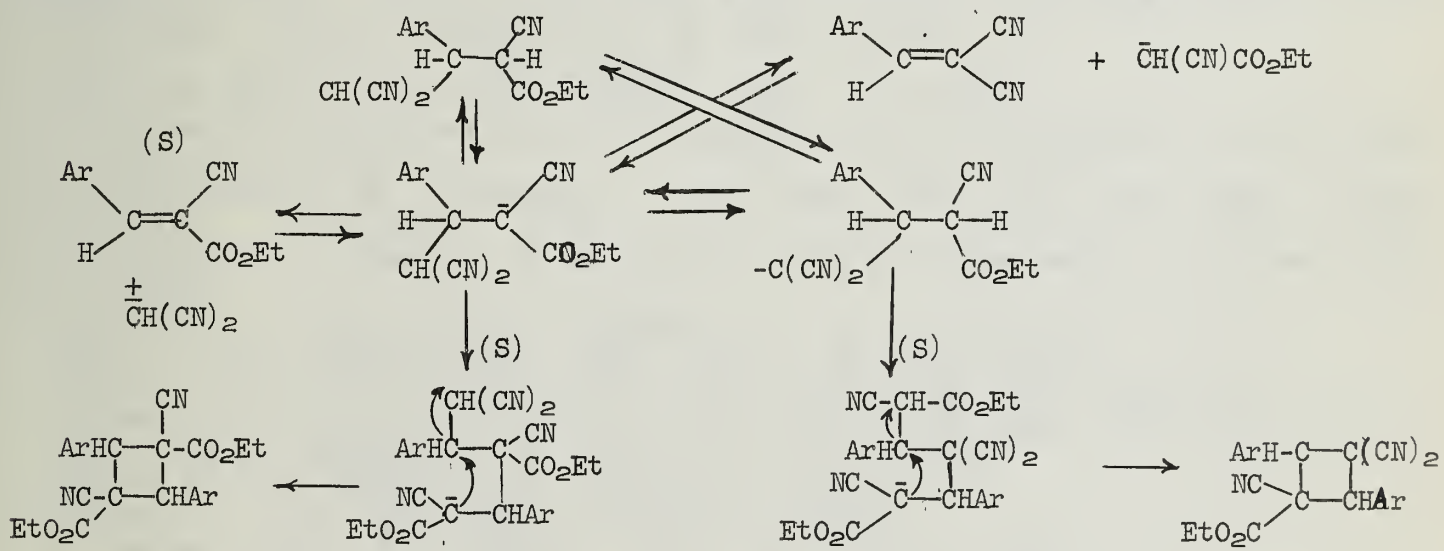
Patai and Rappoport (23) in their kinetic studies of the cleavage of aryl-methylene-malononitriles by water in 95 per cent ethanol to aromatic aldehydes and malononitrile found the reactions to be first order in the substrate concentration. The rates were enhanced by added base and by increasing water content of the medium. Addition of small concentrations of perchloric acid strongly retarded the reaction, and higher concentrations stopped it completely. The relative retardation by identical acid concentrations is smaller with a high concentration of the substrate than with a low one. This shows that the inhibition is due to the substrate itself, or to one of the intermediates of the hydrolysis, and not due to a change in the amount of attacking species in the solution. The following mechanism was postulated.



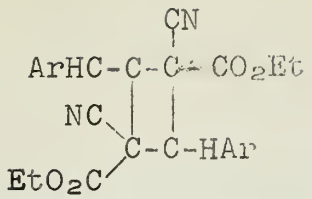
They demonstrated that electron-attracting substituents on the aryl group bound to the β-carbon atom increase the hydrolysis rate while electron-donating substituents decrease it. The sensitivity of the reaction to substituents is large ($\rho > 2$) but decreases if the reaction is rendered faster by raising the temperature, addition of more water or the addition of a catalyst.

From their studies on the base-catalyzed hydrolysis of compounds of the type Ar-CH=CXY, where X and Y were cyano, ethoxycarbonyl, or carbamoyl groups, the effect of α-substituents upon the rate of hydrolysis was determined for the 4-methoxybenzylidene derivative of malononitrile, ethyl cyanoacetate, cyanoacetamide and malonamide. The relative rates at 40° are: $C(CN)_2$, 1; $C(CN)CO_2Et$, 0.1; $C(CN)CONH_2$, 0.025; $C(CO\text{-}NH_2)_2$ 0.00002. The replacement of one cyano-group by a carbamoyl group lowers the rate by a factor of 40, while the second similar replacement lowers it again by a factor of 1250. The qualitative order of reactivity of various active methylene compounds towards aldehydes: $CH_2(CN)_2 > CH_2(CN)CO_2Et > CH_2(CN)CONH_2$ is preserved in the hydrolysis of the corresponding arylmethylene compounds.

Special types of the solvolysis reactions are arylmethylene transfer and cyclodimerization. The former reaction occurs when the arylmethylene group is transferred to the nucleophile (23, 24). Patai and Rappoport have proposed the following mechanism.



The life time of the intermediate (I) determines the nature of the products. Its decomposition resulting in arylmethylene transfer is a unimolecular process; its reaction with another molecule of the starting material is necessarily bimolecular and, moreover, only one special conformation of the carbanion (VI) can result in the desired cyclobutane. Experimentally they could not isolate any of the Michael adduct (III). The cyclobutane derivative was obtained from ethyl trans-α-cyano-β-o-methoxyphenylacrylate only with malononitrile or ethyl cyanoacetate as a by-product. It was identical with a cyclobutane obtained by Baker and Howe (28) by the photo-dimerization of the same compound and was shown by them to have the structure



Cyclodimerization is actually a special case of a broader reaction, that of anionic polymerization. A mechanism for anionic polymerization may be formulated as

$$(I) \quad +n\ R^1R^2C{=}CR^3R^4 \longrightarrow R^1R^2\underset{Y}{C}\text{-}CR^3R^4(CR^1R^2\text{-}CR^3R^4)^-_n$$

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Errata -- page 27, line 13, cis-1,2-bis-(p-tolylmercapto)-ethane should be cis-1,2-bis-(p-tolylmercapto)-ethylene.

Page 28, $EtC(=O)\text{-}O\text{-}CH{=}CMeCl$ should be $EtO\text{-}C(=O)\text{-}CH{=}CMeCl$

Page 29, the group $EtCO_2$- should be EtO_2C- and the group O_2CEt should be $-CO_2Et$.

THE GENETIC CODE

Reported by Richard A. Laursen July 18, 1962

INTRODUCTION

During the past decade the problem of genetic coding, of how genetic information is transmitted in living organisms, has been the subject of much speculation, but it has not been until quite recently that enough experimental data have become available to allow any real insight into the nature of the code.

Simply stated, the problem is: How can a sequence of 4 different nucleotides in a nucleic acid chain determine the sequence of 20 (or possibly more) amino acids in the proteins (enzymes) which determine the characteristics of the cell? Before trying to arrive at an answer, it is necessary to have some idea of the nature of the nucleic acids and of protein biosynthesis.

Nucleic acids

Since the structure and properties of the nucleic acids have been extensively reviewed (1,2), only a brief description of them will be given.

Deoxyribonucleic acid (DNA) is usually found in the nucleus of cells, and is generally supposed to carry genetic information from one cell to succeeding generations. It consists of long chains of the deoxynucleotides adenylic acid (A), cytidylic acid (C), thymidylic acid (T) and guanylic acid (G) joined together by 3' to 5' phosphate ester linkages, and has molecular weights up to 50 or 100 million. Ordinarily the ratio of A to T and of C to G is equal to one (3). From this and x-ray data, Watson and Crick proposed that DNA exists as a double helix in which an A or C in one chain is hydrogen bonded to T or G respectively in the other chain.

Ribonucleic acid (RNA), on the other hand, is usually found in the cytoplasm. It differs from DNA by containing ribose instead of 2'-deoxyribose and the base uracil instead of thymine. [Note: In this seminar the symbols A,T,G,C, and U (uridylic acid) will be used interchangeably for the nucleotides in DNA and RNA.] RNA also exists as long chains, with molecular weights of up to several hundred thousand, but unlike DNA is usually single stranded.

Protein Biosynthesis

The mechanism of protein biosynthesis is as controversial a subject as that of genetic coding. The following discussion is only a summary of some of the current views on the biosynthetic pathway.

DNA contains the information necessary to carry out the metabolic processes of the cell, and passes this information on to successive generations by replication of itself (4). The information is transferred, by a yet unknown process (5), to an RNA which acts as a "messenger" and carries the message to the ribosomes where protein synthesis occurs (6-10). In plant viruses such as tobacco mosaic virus (TMV), DNA is absent and RNA carries the genetic information (11). The concept of messenger RNA was introduced when it was found that infection of E. Coli with T2 bacteriophage led to the formation of an unstable form of RNA which was incorporated into the preexisting cell ribosomes, but which directed the synthesis of phage protein (10,12-16). These experiments suggest that the ribosomes act as "protein factories" and will synthesize any protein if they are supplied with the correct code by the messenger RNA (17).

A second type of RNA, "soluble" or "transfer" RNA (s-RNA), is also involved in protein biosynthesis; its function appears to be that of transferring amino acids to the ribosomes for assembly into polypeptide chains (18-21). There seems to be a different s-RNA for each amino acid (22,23).

Figure 1 shows diagramatically how proteins may be synthesized in living organisms. [Abbreviations: AA, amino acid; ATP, UTP, GTP, CTP, the 5'-triphosphates of adenosine, uridine, guanosine, and cytidine respectively; AMP, adenosine monophosphate; PP_i, inorganic pyrophosphate.]

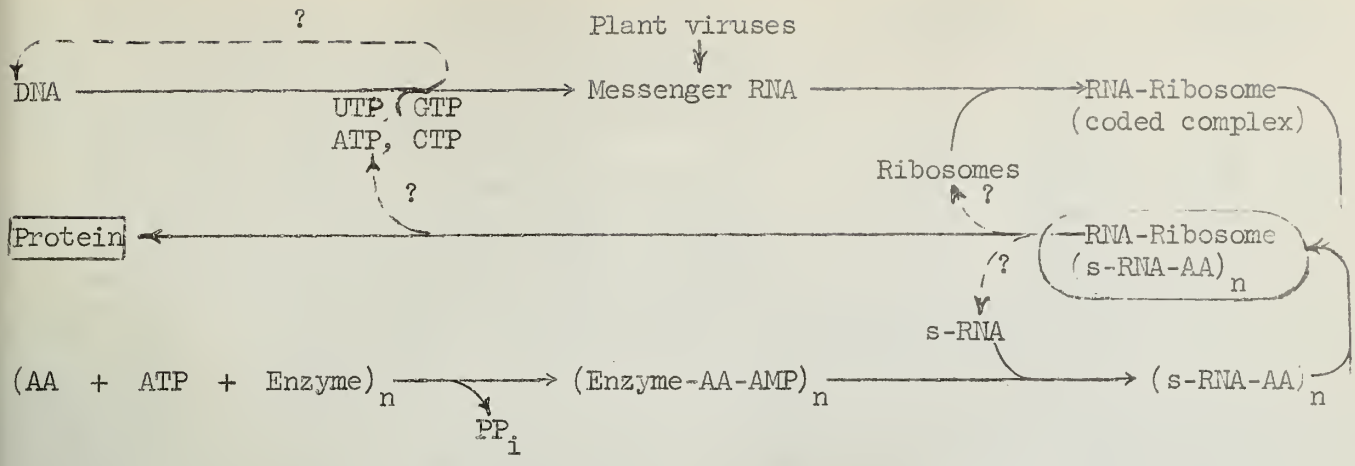

Figure 1.

THE NATURE OF THE CODE

In the subsequent discussion of the code several questions will arise:

1. How many nucleotides are required to code one amino acid?
2. If a sequence of three (a triplet) is needed, as appears to be the case, is the code degenerate, i.e., does more than one triplet code the same amino acid?
3. Are there "nonsense" triplets--sequences which do not code any amino acid?
4. Do sequences overlap one another?
5. Is the code universal, i.e., is it the same for all organisms?

It can be said at the outset that the answers to these questions are not yet known with certainty, but that workers approaching the problem from various points of view--theoretical, statistical, and especially genetic and biochemical--have shed a considerable amount of light on this very intriguing problem.

Theoretical--How can 4 different nucleotides code 20 amino acids? Obviously sequences of nucleotides--sequences of 3 or more-- must be involved, because singlets could code only 4 and doublets only 16 (4^2) amino acids; triplets, however, could code a possible 64 (4^3) amino acids. This was the initial assumption on which many of the first theories were based (25).

The first attempt to devise a triplet code was made by Gamow in 1954 (24). His diamond code, based primarily on the Watson-Crick (double helix) model for DNA, was degenerate and overlapping, i.e., the number of nucleotides in the chain was equal to the number of amino acids in the protein. (Fig.2). Unfortunately, his code, as well as some other overlapping codes (25), did not code for known sequence of amino acids (26).

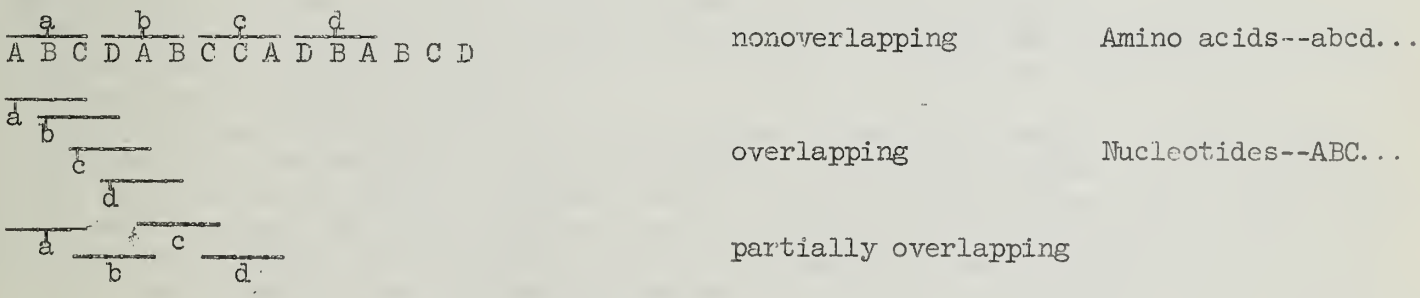

Figure 2

Furthermore, Brenner has shown that, assuming universality, all overlapping triplet codes are impossible (26). Since successive triplets (in the overlapping case) have two nucleotides in common, a given triplet can be succeeded or proceeded by only four different triplets. For the amino acid sequence, j k l, let j be an N-neighbor and l be a C-neighbor Then for every four N-neighbors or C-neighbors, k must have one triplet assigned to it. By taking a large number of known peptide sequences, Brenner was able to construct a table listing the number of different N- and C-neighbors for each amino acid and to calculate how many triplets would be necessary to code each amino acid. For example, methionine has 5 C-neighbors and 7 N-neighbors; therefore two triplets are necessary (Fig. 3). It was

found that a minimum of 70 different triplets would be required; but since 64 is the maximum number of triplets possible, overlapping codes are impossible. This argument does not hold for partially overlapping codes, however.

N-neighbor		C-neighbor	
A	ABC	A	1
B	ABC	B	
C	ABC	C	
D	ABC	D	
A	BBC	A	2
B	BBC	B	
C	BBC		

Figure 3

Crick et.al. (27) also tried to approach the problem from a strictly formal point of view, but the code they devised, like other theoretical codes, has been discredited by more recent experimental evidence. With the accumulation of information on the amino acid composition of proteins, more attention was turned towards statistical approaches.

Statistical--If DNA (or RNA in the case of certain viruses) is the sole factor in determining protein structure, and if the code is universal, one might expect to find correlations between the base composition of DNA (or RNA) and the amino acid composition of proteins. This approach has been taken by several workers, but unfortunately has not resulted in any definitive answers. One of the major assumptions of the statistical method is that there are no nonsense sequences in the nucleic acids. If some of the nucleotides are not used to code amino acids, the amino acid composition will not necessarily be a reflection of the nucleotide composition.

An interesting example of the unsatisfactory nature of the statistical method can be seen in the papers by Yčas (28) and Woese (29,30), who compared the RNA base composition with the protein amino acid composition of 6 viruses. Using the same data (which were admittedly unreliable in the first place), they devised two entirely different codes--Yčas a singlet code (he suggested that some unknown factor was also involved in coding,) and Woese a triplet code.

Sueoka (31) has recently demonstrated correlations between the composition of the DNA and protein of 11 species of bacteria and one species of protozoa. In this study the percentages of individual amino acids of the bulk protein were plotted against the C-G content of the DNA of the bacteria.

The statistical correlations obtained give evidence for the universality of the code, at least among bacteria, and the absense of nonsense sequences; however, more recent work (53) has shown that nonsense sequences can exist. Nonsense sequences had previously been postulated to explain the observation that the DNA base composition of various organisms varies much more widely than does that of the protein(32a); however, this variation can also be explained by degeneracy. (32b).

Genetic Experiments -- Good evidence that the code is non-overlapping has come from the work of Wittmann(33) and of Tsugita and Fraenkel-Conrat (34,35) on amino acid replacements in chemically induced mutants of tobacco mosaic virus (TMV). Their experiments take advantage of the fact that certain chemical agents will alter the virial RNA, thus inducing mutations. For example, cytosine is deaminated with nitrous acid to give uridine.

TMV, the first virus to be recognized as such and the most extensively studied, consists of a coil of RNA surrounded by a protein sheath; the protein and RNA can readily be separated and recombined using suitable methods. The complete amino acid sequence of the TMV protein has been determined (36,33).

Taking advantage of the properties of TMV,Fraenkel-Conrat and Tsugita (34,35) treated isolated RNA with nitrous acid, N-bromo-succinimide or dimethyl sulfate, reconstituted it with TMV protein, and innoculated tobacco plants with the reconstituted virus. When mutant strains were observed, as detected by changes in the symptoms of the infected plant, they were isolated, purified, and the protein portion subjected to amino acid analysis. The amino acid composition of each mutant was compared to that of native TMV. It was found that in certain mutants amino acid exchanges had occurred (Table I). In cases where only one exchange occurred, an overlapping code is precluded, since a change in one nucleotide would cause a replacement of more than one amino acid. Where two or three exchanges occurred, it was shown that the amino acids involved were in non-adjacent parts of the protein. Wittmann (33), using different analytical techniques, obtains similar results.

Smith (37) has compiled a list of amino acid replacements in mutant forms of human hemoglobin (Table 2). The fact that they are all single amino acid replacements is consistant with the idea that the abnormal forms arose by the change of a single nucleotide in a non-overlapping sequence of nucleotides.

Table 1--amino acid composition of TMV mutants.

Amino Acid	Nitrous acid mutants					NBS mutants		DMS mutants	
	TMV	273*	282	171	220	233	187	278	215
asp	18	17	17	17			17		
thr	16		15	15					
ser	16	17	17	17	15		17?		15
glu	16								
pro	8			7		7	7	7	
gly	6								
ala	14		15	15					
cys	1								
val	14								
ileu	9								
leu	12			13		13		13	
tyr	4								
phe	8				9				9
lys	2								
arg	11						10		
try	3								
met	0								
his	0								
Total	158	158	158	158	158	158	158	158	158

*mutant strain number

Abbreviations: NBS, N-bromosuccinimide; DMS, dimethyl sulfate. Blank spaces in the table indicate that the amino acid composition of the mutant is the same as that of TMV.

Table 2--amino acid replacements in human hemoglobin (HbA)

HbA	Mutant
glu	val
glu	lys
glu	gly
glu	glu-NH_2
val	glu
asp	lys
gly	asp
lys	asp
his	try
his	arg
glu	ala
ser	thr
thr	asp-NH_2

The most convincing evidence for the existence of a triplet code has been put forth Crick et.al. (38), using the system developed by Benzer (39-41).

Benzer's work has entailed the mapping of the rII region of the chromosome of the phage T4, the ultimate goal being to determine the sequence of nucleotides in the DNA of this region. The rII region controls the ability of T4 phage to grow on E. Coli strain K. A normal (wild-type) T4 phage will grow on both E. Coli B and K, but certain mutants, which are non-functional in the rII region, show a different (r) plaque morphology when grown on B, and will not grow at all on K. The problem of acquiring mutant phage is made easy by the fact that one mutant out of perhaps a billion particles can be detected by its r morphology (42). By selecting and crossing many pairs of mutants, and noticing which pairs recombine and which do not, Benzer has been able to locate the site of the mutations and to construct a genetic map (39).

It has been suggested that acridines act as mutagens by slipping in between the base pairs in the DNA chain and causing a mistake which leads to the addition or deletion of a base pair or pairs during replication. (43). This suggestion arises from the fact that Lerman has shown that acridine orange will associate with DNA (44). He gives evidence indicating that the acridine orange molecules were intercalated between the base pairs, rather than simply aggregated with the DNA molecules.

Going on the assumption that the mutants were of the addition or deletion type, Crick, et.al. (38) studied a group of acridine induced rII mutants. The mutants were divided into two groups arbitrarily called + and - to stand for addition or deletion mutants, i.e., mutants that would not grow on E. Coli K because they had added or were missing a nucleotide. Therefore, if during coding the sequence of bases (assuming triplets) is read from left to right (Fig. 4), the addition or deletion of a base will result in an incorrect reading to the right of the addition or deletion. If a + and a - mutation are combined in the same gene, it can be seen that the correct reading will be restored. The sequence between the two mutations is incorrect, but if the sites are close enough together, the

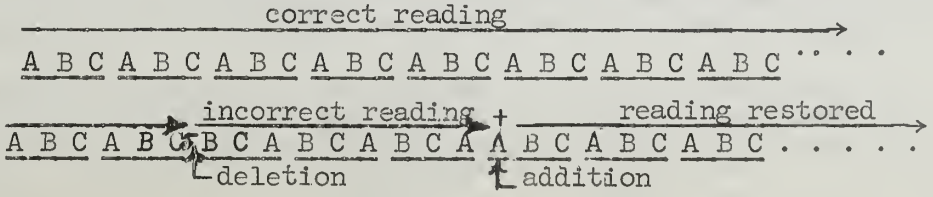

Figure 4

function of the protein produced by this gene may not be altered appreciably. And indeed it was found that when + and - mutants were combined, the revertants were usually "pseudo-wild", that is, they were able to grow on K, but had slightly different plaque morphologies from the wild type.

Evidence for the triplet code came from combining + mutants with + and - with -. If a double mutant of the type ++ or -- was made, it was found that the function of the gene was not restored. But with triple mutants, +++ or ---, function was restored (Fig. 5). This behavior is what would be predicted if the coding ratio were 3, or a multiple of 3.

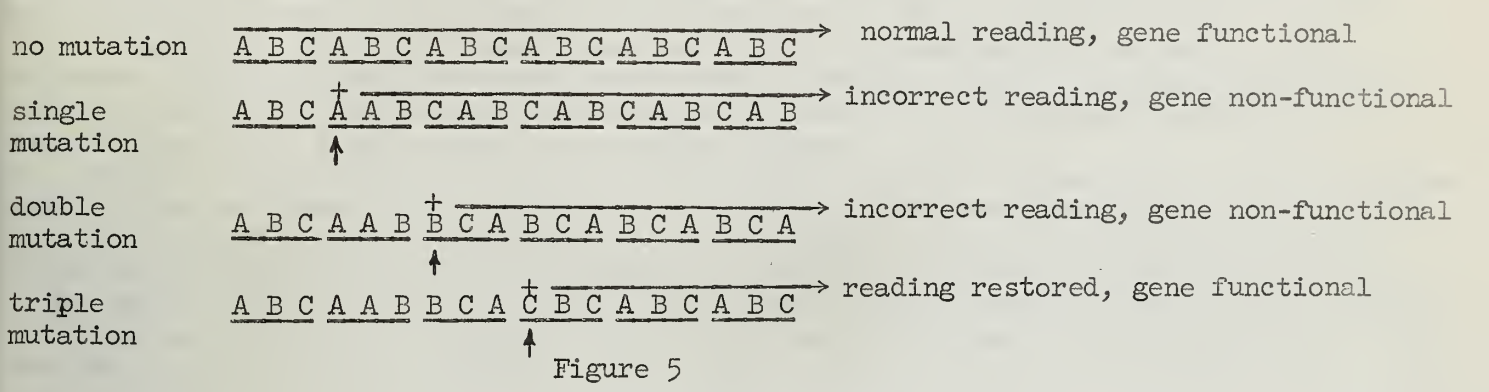

Figure 5

In the same paper, Crick et.al. (38) also give an argument for degeneracy of the code.

Biochemical Experiments -- An important contribution to the solution of the coding problem came with the announcement of Nirenberg and Matthaei (45,46) that they had developed a stable, cell-free enzyme system, dependent upon RNA for the synthesis of protein.

As mentioned earlier, it is believed that in protein synthesis, the base sequence of DNA determines that of RNA which in turn determines the amino acid sequence of protein. One of the difficulties in studying cell-free protein synthesis in E. Coli has been that of getting an enzyme system stable enough that reproducible results can be obtained. Nirenberg and Matthaei found that their preparation was dependent upon ribosomes, an ATP generating system, and a soluble fraction of the cell extracts, containing, presumably, s-RNA and amino acid activating enzymes (45). Furthermore, it was found that the addition of an RNA template, such as TMV or yeast ribosomal RNA, greatly stimulated amino acid incorporation. (9, 46) Even synthetic polynucleotides could stimulate protein synthesis; polyuridylic acid (poly U) stimulated the formation of polyphenylalanine (46). This represents the first known code for an amino acid; assuming a triplet code, the code for phenylalanine is UUU. Homopolymers of C, A, and G did not stimulate incorporation of any amino acid, suggesting that CCC, AAA, and GGG are nonsense triplets.

An immediate consequence of this finding was a series of papers by Ochoa and coworkers (47-51). Using homopolynucleotides and mixed polynucleotides, which can readily be synthesized using polynucleotide phosphorylase (52), they were able to measure the incorporation of different amino acids into protein. The general procedure used is the following: to the cell-free system are added the 20 amino acids, one of which is labelled with ^{14}C. The polynucleotide is added, and, after incubation of the system, the protein precipitated with trichloroacetic acid (TCA) and its radioactivity determined. Since in the mixed polymers the base sequence was not known, a statistical method had to be used. It was soon found that incorporation occurred only with polymers containing U, and that phenylalanine was always incorporated into the protein (47-51, 53). Therefore, by comparing the amount of other amino acids incorporated to the amount of phenylalanine incorporated, it was possible to deduce codes for the other amino acids. For example, assuming a triplet code, the code for phenylalanine is UUU; assuming random mixing in a polymer of UG (5:1), and setting the probability of forming the triplet UUU equal to 1, the probability of obtaining the triplet UUG is 1 X 1/5 or 1/5, while the probability of obtaining UGG is 1 X 1/5 X 1/5 or 1/25. In this system, it was found that cysteine was incorporated 1/5 as well as phenylalanine, glycine 1/24 as well, and tryptophan, 1/20 as well (50). This suggests the codes UUG, UGG, and UGG for cysteine, glycine, and trytophan respectively.

Although elegant in principle, these experiments have not been elegant in practice. Many of the incorporation studies were done using impure polynucleotides, and incorporation ratios often varied considerably from theoretical values; also these experiments assume random mixing in the copolymers--an assumption that remains to be proved. In spite of these defects, the data are consistant with a triplet code, e.g., for a triplet, say UUA, there are three possible sequences; in no case have more than three amino acids

coded for the same triplet. Also no amino acid has been found to require all four nucleotides, as might be the case in a quartet or higher code.

In order to get some idea of the changes that might be occurring when TMV RNA was treated with nitrous acid, Ochoa et.al. (51) treated synthetic polymers with nitrous acid, and noted changes in their coding characteristics. They found that if poly UA (5:1) was treated with nitrous acid, the characteristics of poly UG (5:1) were obtained. This seemed reasonable in view of the similarities in hydrogen bonding properties between hypoxanthine (formed by deamination of adenine) and guanine. Deamination of poly UG, which would give poly UX (X = xanthosine), resulted in complete loss of coding ability, while deamination of poly UC gave a polymer with the characteristics of poly U, as expected. Again, these experiments were somewhat messy; in all cases there was overall loss in activity of the polymer. This may have been due to incomplete deamination or degradation of the polymer chain or to other reasons.

Triplets having been assigned to all the amino acids as a result of the incorporation studies just mentioned (Table 3, Ochoa and Nirenberg), the next step was to try to determine the sequence of the nucleotides within the triplet. Using incorporation data and amino acid replacements from mutant forms of hemoglobin, TMV protein, and other sources (50), Smith (37, 54), Zubay (55), and Jukes (58,59) have proposed triplets whose relative order is known, but whose sequence is not, e.g., once the order for one triplet is determined, the order for the rest is also (Table 3).

Table 3--proposed triplet codes for protein amino acids.

Amino Acid	Nirenberg (53)+	Ochoa (50) +	Smith (54)	Zubay (55)	Jukes (59)
ala	UCG	UCG	CUG	UCG*	CUG
arg	UCG	UCG	UGC	UGC**	GUC
asp-NH_2	---	UAA, UAC	UCA	UCA*	UAA, GUA
asp	---	UAG	UGA	UCA*	GUA
cys	UGG, UUG	UUG	GUU, UGU	?CG***	UGU
glu	UGA	UGA	UAG	UUA*	AUG
glu-NH_2	---	---	UCG	UUA*	UCG
gly	UGG	UGG	UGG	UUG*	GUG
his	---	UCA	UAC	UGU**	AUC
ileu	UUA	UUA	UUA	UAC**	UUA
leu	UUC, UUG	UUC, UUA, UUG	UCU	UCU*	UAU, UUC, GUU
lys	UAA?	UAA	UAA	UGA*	AUA
met	UGA	UGA	GUA	UAU***	UGA
phe	UUU	UUU	UUU	UUU*	UUU
pro	UCC	UCC	CCU	UCC*	UCC, CUC
ser	UUC, UCG	UUC	CUU	UGG*	CUU, UCU
thr	---	UAC, UCC	CUA	UAG*	UCA
try	UGG	UGG	GUG, GGU	UAA**	UGG
tyr	UUA	UUA	UAU	?AU***	AUU
val	UUG	UUG	UUG	UUC**	UUG

+order not implied, incorporation data only
* most probable
** probable
*** uncertain

As can readily be seen, the three codes differ considerably, although those of Jukes and Smith agree fairly well; the differences arise from the different assumptions made by the authors. Smith (54) assumes a universal, non-overlapping triplet code wherein a point mutation involves a single base change, and utilizes the amino acid incorporation data of Ochoa et.al (50) and of Nirenberg et. al. (53). Jukes (59) makes similar assumptions, although they are not specifically stated. Zubay (55) assumes a nondegenerate triplet code--which appears unlikely (32, 38)--and ignores much of the incorporation data.

One of the surprising things about the code developed from incorporation experiments is that all the triplets contain U. If this is the entire code, then it is obvious that all RNA should contain at least 1/3 U. This is not observed to be the case, as Chargaff (56) has pointed out. A calculation of the nucleotide content of TMV RNA using Smith's (54) triplet assignments and the amino acid analyses in Table 3 predicts a U content of 48.3 per cent; only 26 per cent is found experimentally (57). The discrepancy can of

course be explained by assuming either degeneracy or the existence of nonsense triplets.

There is a possible explanation for why U occurs in all triplets (47). In all cases where a copolymer was used, the ratio of U to the other nucleotide(s) was high, usually at least 5:1; therefore the probability of getting sequences of UUU is fairly high (higher than for any other sequences). The method of detection, precipitation with TCA, requires that the protein or polypeptide be acid insoluble. If there were gaps (nonsense sequences) in the polynucleotide chain, then short chain polypeptides might not be precipitable with TCA. But when the concentration of polyphenylalanine, which is a very insoluble protein, is high, it may act as a "handle" for the incorporation of other amino acids into short insoluble polyphenylalanine chains.

The final answers will come when it is possible to synthesize polynucleotides of known sequence to be used in incorporation studies. An alternative method is to determine the sequence of an RNA molecule and its corresponding protein.

CONCLUSIONS

The work of Crick et.al. (38) indicates a triplet code, and the amino acid replacement data of Wittmann (33) and of Tsugita and Fraenkel-Conrat (34,35) seem to preclude an overlapping code. Incorporation studies of Nirenberg and Matthaei (45,46,53) and of Ochoa et.al. (47-51) give specific information as to the nature of the code and also show that nonsense triplets can exist. The code must be either degenerate or contain nonsense triplets, or both, to explain the anomolous U composition predicted from incorporation studies for natural RNA. Sueoka's (31) correlations in bacteria and the fact that TMV RNA can stimulate incorporation of amino acis into protein in the cell-free E. Coli system (9) indicate at least partial universality of the code.

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CHEMISTRY OF ENAMINES

Reported by L. D. Spicer July 23, 1962

INTRODUCTION

Enamines, or vinyl amines, have been shown widespread attention for the synthesis of a variety of compounds in recent years. This seminar will review the recent syntheses and reactions of the simpler enamines, and will exclude haloenamines, aminostyrenes, and heterocyclic enamines in which the nitrogen atom lies in the same ring as the double bond.

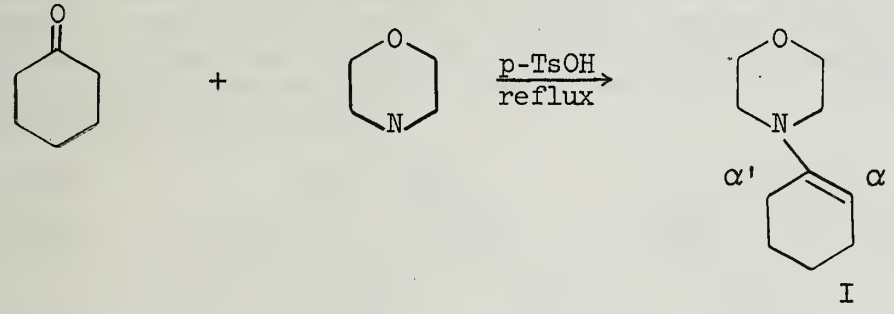
Enamines of simple ketones and aldehydes have been known for some time, but not until 1954 was an intensive search begun in their applications to organic synthesis (1). There have been a number of reviews on enamines (2,3,4,5,6).

PREPARATION

The principal method for enamine synthesis has been reviewed (3,4) and only its major features will be discussed here. This method provides for removal of the water formed in the reaction of a secondary amine and an aldehyde or ketone. An early variation developed by Mannich and Davidson (7) is illustrated below in the preparation of N,N-dimethylisobutenylamine (8).

$$(CH_3)_2CHCHO + (CH_3)_2NH \xrightarrow[\text{xylene}\ 100^\circ]{K_2CO_3} (CH_3)_2C{=}C(H)N(CH_3)_2$$

More recently, the azeotropic removal of the water (9) has become the generally preferred method. In this way, 1-N-morpholinocyclohexene (I) is prepared in good yield (10).



I

The broad utility of the method is indicated in the synthesis of connesine (11,12,13), 2-(aminomethylene)-keto steroids (16) and dienamines (17,18).

Preparation of enamines by dehydrogenation of amines is a less common method. Mercuric acetate (14), benzoyl peroxide, manganese dioxide, and halogenated quinones (15) have all been used.

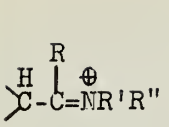
Azulene enamines have been prepared recently by the reaction of azulene with dialkylamides in the presence of phosphorous oxychloride (19).

The synthesis of enamines from barbituric acid derivatives (20), and fulvenecarboxaldehydes (21) has been reported. Spectral measurements and syntheses of a series of enamines have been investigated (22,23,24,25).

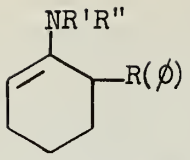
STRUCTURES

Earlier work has shown that in vinyl amines, protonation occurs at the β-carbon to give ternary iminium salts (II). Studies on a variety of enamines have shown characteristic spectra shifts from enamines to iminium salts. The following lead references on this work are recommended (25,26,27).

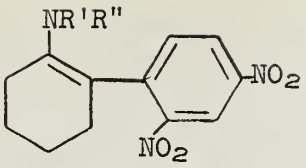
2-Alkyl and 2-phenyl cyclohexene enamines have been shown to be the less substituted isomer (III), (4,28). However, the 2-(2,4-dinitrophenyl)-cyclohexene enamines exist as a mixture of IV and V (29).



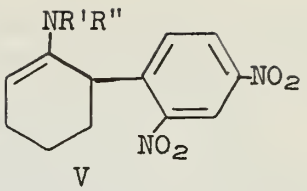
II



III



IV



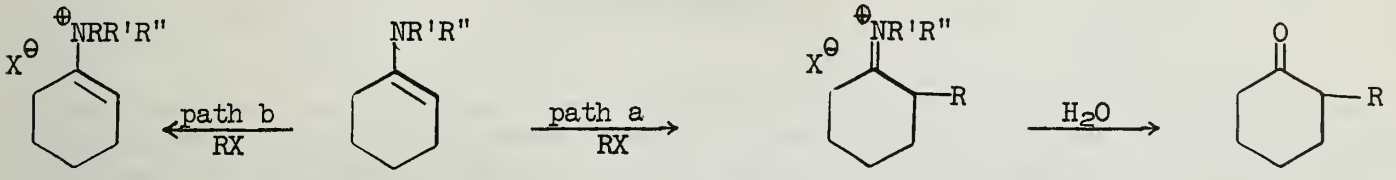
V

R'=R"=alkyl

ALKYLATIONS

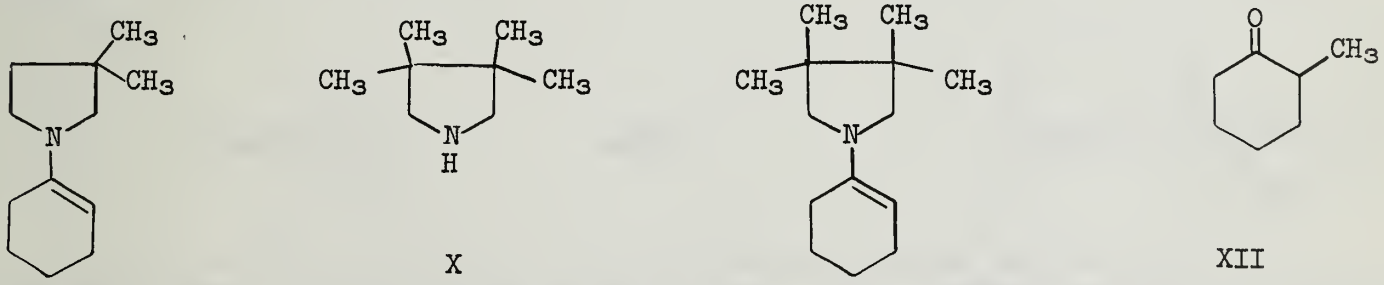
Monoalkylations in good yields, with little dialkylation, is a distinguishing feature in alkylations of enamines derived from cyclic ketones. Alkylations with a great variety of alkyl halides including α-haloalkyl derivatives of ethers, esters, ketones and nitriles; and with α,β-unsaturated aldehydes and nitriles have been reviewed (3,4,6).

The general alkylation reaction of enamines follows two competing routes: a) Path a of C-alkylation to give the ternary iminium salt (VI), which can then be hydrolyzed to VII, and b) Path b which proceeds through N-alkylation to give the N-alkylated amine (VIII). This is illustrated below with a cyclohexene enamine.



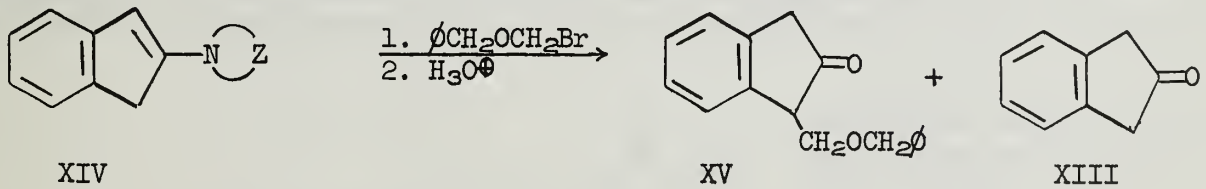
VIII VI VII

The problem of C/N alkylation has been studied by Stork (4) and Blomquist (26). Stork attempted to improve C-alkylation yields by hindering the nitrogen but not the carbon atom. Thus, the 3,3-dimethylpyrrolidine enamine (IX) showed only a slight improvement in the C/N ratio, while the 3,3,4,4-tetramethylpyrrolidine (X) does not form (XI) at an appreciable rate. By otherwise varying the amine from pyrrolidine to heptamethyleneimine and morpholine, yields ranging from 11-47% (based on cyclohexanone consumed) of XII were obtained.



IX X XI XII

In studying the enamines of 2-indanone (XIII), Blomquist alkylated enamines of various amines with bromomethyl benzyl ether (26). (Table I)

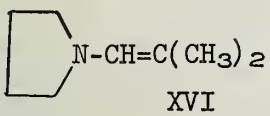


XIV XV XIII

Table I

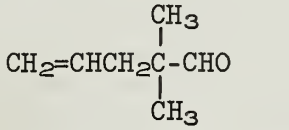
Z(XIV)	% Yield C-alkylation(XV)	N-alkylation(XIII)
$-(CH_2)_4-$	8	14
$-(CH_2)_5-$	22	7
$-(CH_2)_6-$	39	0
$-(CH_2)_2O(CH_2)_2-$	25	0

Alkylation of enamines is not restricted to those derived from cyclic ketones. A series of enamines has been prepared from alkyl aldehydes and alkylated. Elkik obtained only N-alkylation products with the use of alkyl halides on a series of enamines; however, allyl bromide gave C-alkylation products (30). This was confirmed by Opitz who was able to synthesize trisubstituted acetaldehydes from disubstituted aldehydes with allyl halides (31), but obtained only N-alkylation products with alkyl halides (32). Thus, when allyl bromide was allowed to react with XVI, and the mixture hydrolyzed, a 51% yield of the trisubstituted aldehyde (XVII) was obtained. When crotonyl bromide reacts with XVIII, and the mixture is hydrolyzed, the rearranged aldehyde, 2,2,3-trimethyl-4-pentenal (XIX) is obtained. A Claisen type rearrangement has been used to explain the results. Propargyl bromide alkylation partially yields the rearranged allenic aldehyde (33).

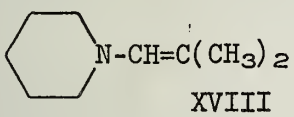


XVI

1. $CH_2=CHCH_2Br$
2. $H_3O^{\oplus}$

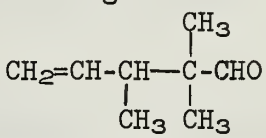


XVII



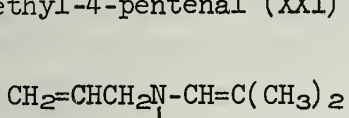
XVIII

1. $CH_3CH=CHCH_2Br$
2. $H_3O^{\oplus}$



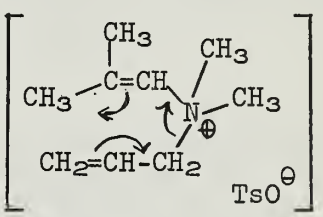
XIX

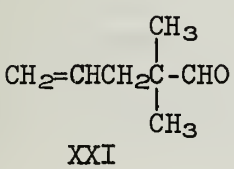
On the other hand, Brannock was able to obtain C-alkylation products from N,N-dimethyl-isobutenylamine only after extended reaction times from alkyl halides. Milder conditions, like those used by Opitz, resulted in N-alkylation. Initial N-alkylation followed by N to C migration was suggested as the probable mechanism in the particular reactions studied. By allowing N-allyl-N-methylisobutenyl amine (XX) to react with methyl tosylate, 2,2-dimethyl-4-pentenal (XXI) was obtained after hydrolysis (8).



XX

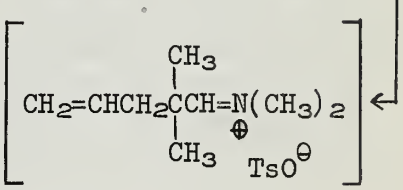
MeOTs



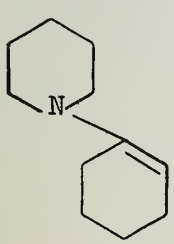


XXI

$H_3O^{\oplus}$

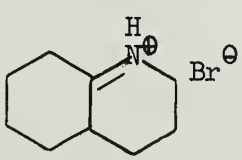


The reaction of dichlorocarbene with cyclohexene enamines has been reported to give 2-dichloromethylcyclohexanone after hydrolysis (34). Enamines can also be alkylated with acrylic esters to give, after several steps, γ-amino dicarboxylic acids (35). Dialkylation of cyclic ketones is feasible when the alkylation is run in the presence of trialkylamines (36). Alkylation of ketones via their enamines has recently proved useful in the synthesis of dehydroabietic acid (37) and 13-propylnorestradiol (38). A bicyclic enamine (XXIII) was synthesized from the reaction of XXII and 1-N-piperidinocyclohexene (39).



\+ $Br(CH_2)_3NH_3^{\oplus}Br^{\ominus}$

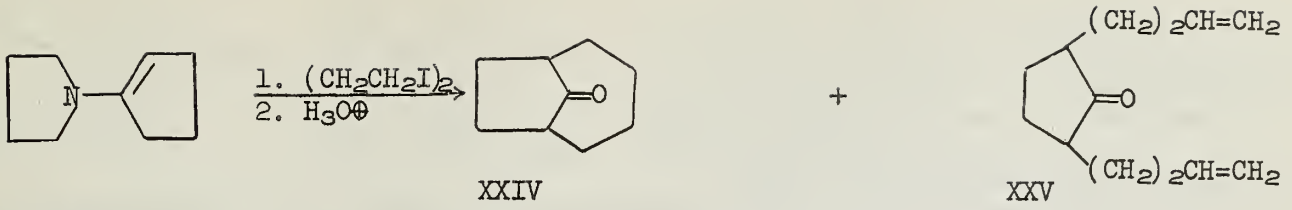
XXII



XXIII

Alkylation of enamines of α,β-unsaturated ketones has been reported to occur exclusively at the α-position of $\Delta^{1(9)}$-2-octalone (40).

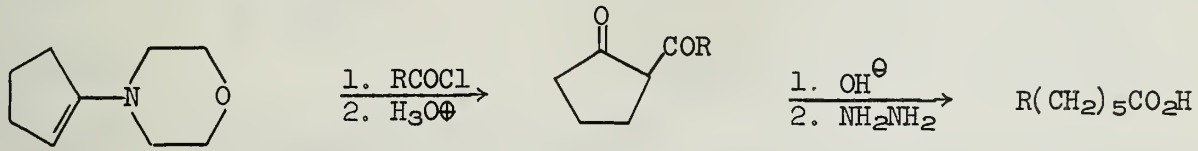
Dihaloalkanes, when allowed to react with enamines of cyclic ketones, yield a variety of products after hydrolysis, including products with one or two alkenyl groups, condensation products, and bi- and tricyclic ketones, depending upon the enamine and dihalide used. When 1-N-pyrrolidinocyclopentene reacted with 1,4-diiodobutane in the presence of ethyldicyclohexylamine, bicyclo[4.2.1]nonan-9-one (XXIV) and 2,5-di(3-butenyl)-cyclopentanone (XXV) were obtained after hydrolysis (41).



XXIV XXV

ACYLATIONS

Acylation of cyclic ketones via enamines has been shown useful for extending chains of monocarboxylic acids by five or six carbons and dicarboxylic acids by five, six, ten, or twelve carbon atoms (42,3,4). Acyl chlorides react with cyclopentanone or cyclohexanone enamines and yield, after hydrolysis of the enamine, the corresponding 2-acylclohexanone or 2-acylcyclopentanone. Ring cleavage with base provides the keto acid, which, after Wolff-Kishner reduction, gives the chain-lengthened monocarboxylic acid.

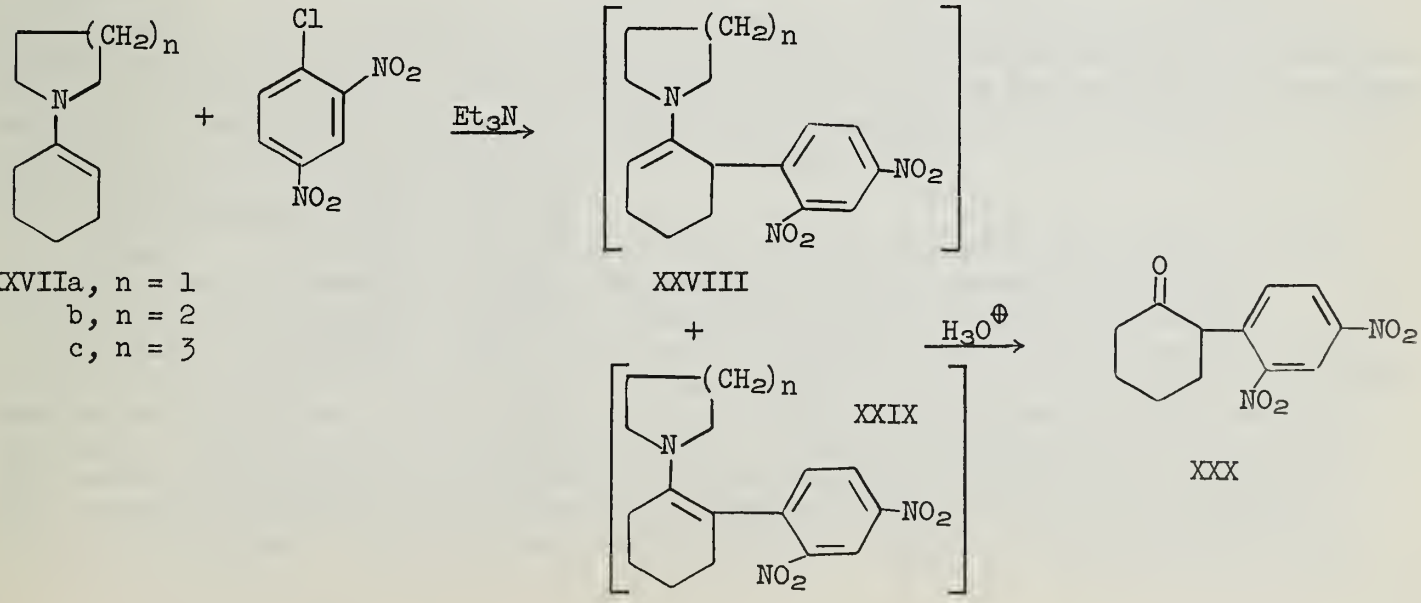


XXVI

Half ester acid chlorides and diacid chlorides of dicarboxylic acids can be used in varying ways to lengthen the chains (43). Thus, 1-N-morpholinocyclopentene (XXVI) reacts with propionyl chloride in the presence of triethylamine to form 2-propionylcyclohexanone after hydrolysis of the reaction mixture. Cleavage with base, followed by reduction, provided octanoic acid in an overall yield of 49% from the enamine (43).

ARYLATIONS

By the reaction of very reactive aryl halides with cyclic ketones, Kuehne succeeded in preparing α-aryl cyclic ketones after the hydrolysis of the reaction mixture (29). Thus, the pyrrolidine enamine of cyclohexanone (XXVIIa) reacted spontaneously with 2,4-dinitrochlorobenzene and triethylamine to give a mixture of two enamines, XXVIII and XXIX. Since these enamines formed highly-colored complexes with the 2,4-dinitrochlorobenzene present in the mixture, they were not isolated, but were characterized by their reactions. Hydrolysis of the enamine reaction mixture gave a 92% yield of 2-(2,4-dinitrophenyl)-cyclohexanone (XXX). Although the hexamethyleneimine enamine (XXVIIc) also gave a 92% yield of XXX, the piperidine enamine (XXVIIb) gave a lower yield, 66%, and no XXX was obtained from the corresponding morpholine enamine.



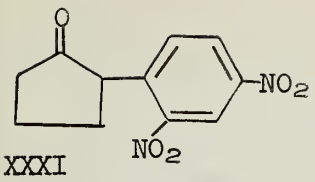
XXVIIa, n = 1
b, n = 2
c, n = 3

XXVIII

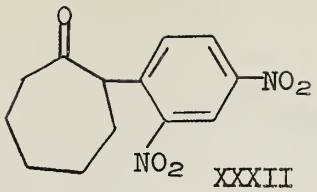
+

XXIX

XXX



XXXI

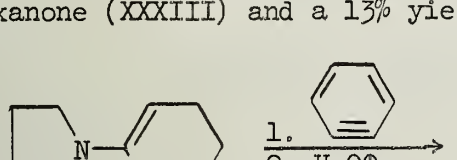


XXXII

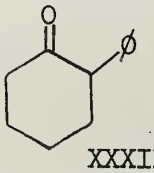
Arylation of XXVIIa to give XXX was also successful with 2,4-dinitrofluorobenzene. Pyrrolidine enamines of cyclopentanone and cycloheptanone with 2,4-dinitrofluorobenzene gave yields of 93% and 5.4% respectively, of XXXI and XXXII.

With less reactive aryl halides such as 4-nitrochlorobenzene and 2-benzoyl-4-nitrochlorobenzene, only N-arylation products were obtained.

Benzyne, formed from o-bromofluorobenzene and magnesium, in the presence of 1-N-pyrrolidinocyclohexene (XXVIIa) gave after hydrolysis, a 17% yield of 2-phenylcyclohexanone (XXXIII) and a 13% yield of the benzocyclobutene (XXXIV) (29).

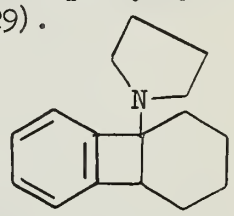


XXVIIa



XXXIII

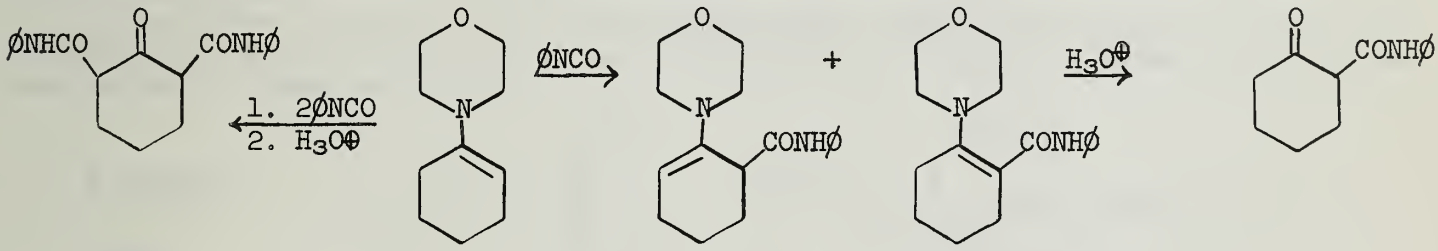
+



XXXIV

REACTIONS WITH ISOCYANATES AND ISOTHIOCYANATES

A useful method for preparing β-keto amides and thionoamides has developed from the reactions of isocyanates and isothiocyanates with enamines. When 1-N-morpholinocyclohexene (I) was heated with phenyl isocyanate and subsequently hydrolyzed, 2-carbanilocyclohexanone (XXXV) was obtained (44,45,46). The question of its structure has been discussed (47). The intermediate enamine was isolated from a mixture with a broad melting point in a 60% yield and was shown to have the structure XXXVI. However, the presence of another isomer (XXXVII) in the mixture was considered possible. When I was allowed to react with two equivalents of phenyl isocyanate, the dicarboxanilide (XXXVIII) was formed in an 87% yield (46).



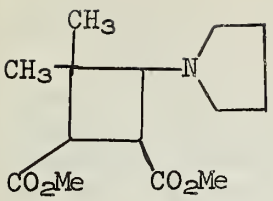
XXXVIII I XXXVI XXXVII XXXV

Similar results were obtained from n-butyl isocyanate (44,46), and numerous other isocyanates and isothiocyanates with both enamines from cyclic ketones and acyclic aldehydes (44). Of further interest, the enamine adducts resulting from the reaction of isocyanates and isothiocyanates and enamines have been shown to be valuable for preparing substituted heterocyclic compounds otherwise difficult to prepare (48).

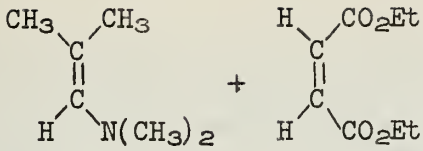
SIMPLE SYNTHESES OF CYCLIC COMPOUNDS

A number of reactions have been described in which cyclobutanes, pyrans, α- and γ-pyrones, and four-membered sulfone compounds are easily formed from enamines.

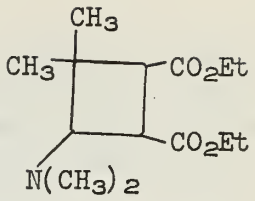
Cycloaddition reactions between isobutenylamines and electrophilic olefins proceed to cyclobutane derivatives (49). The reaction product between methyl maleate and 2-methyl-1-N-pyrrolidino-1-propene had previously been postulated to be XXXIX (50). Later work showed this to be correct, since ethyl maleate and N,N-dimethylisobutenylamine (XL) gave diethyl 4-dimethylamino-3,3-dimethyl-1,2-cyclobutanedicarboxylate (XLI) (51). Cyclobutane compounds are also formed by the cycloaddition of ketenes and enamines. Thus, ketenes or dialkyl ketenes react with enamines having one or no β-hydrogens to form cyclobutanones. Dimethylketene reacts with XL to give the cyclobutanone (XLII).



XXXIX

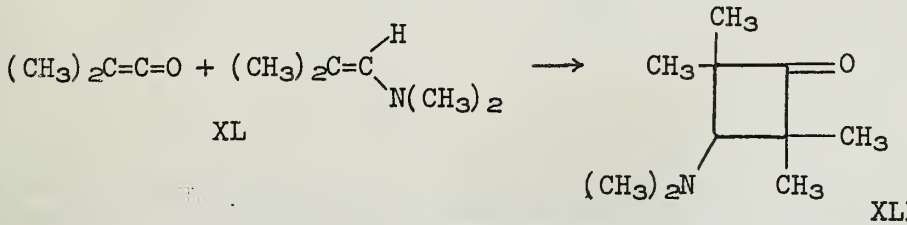


XL

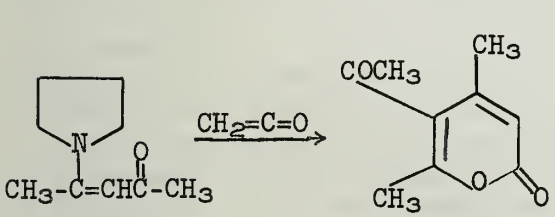


XLI

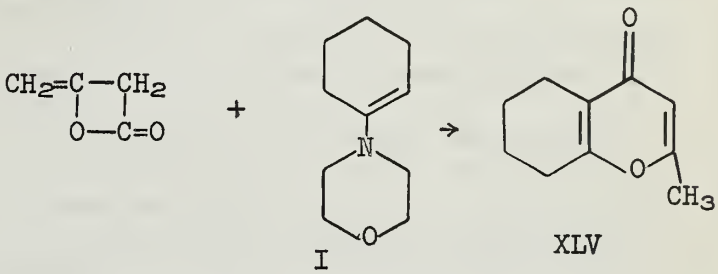
Cyclobutanones which have α-hydrogens are unstable and open irreversibly (52,53). The cyclobutanones may also be obtained from the reaction of acid chlorides and enamines in the presence of triethylamine, supposedly through the ketene generated in situ (54).



XL XLII



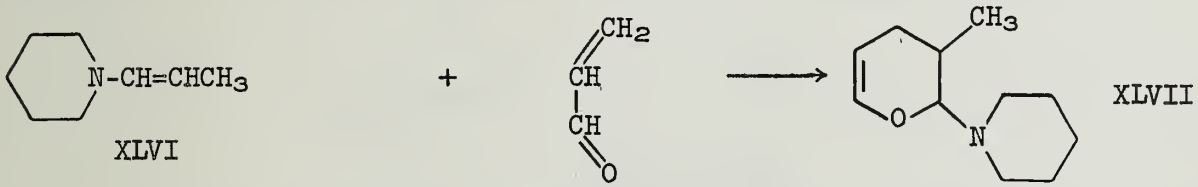
XLIII XLIV



I XLV

The addition of ketenes takes a different course with enamines such as 4-N-pyrrolidino-3-penten-2-one (XLIII), which reacts with an excess of ketene to give the α-pyrone (XLIV) (55).

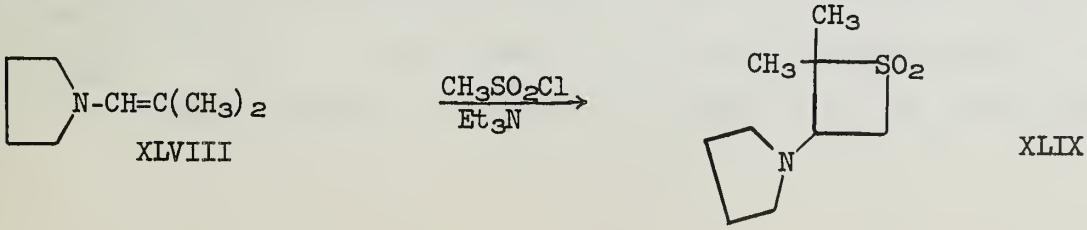
The γ-pyrone, 2-methyl-5,6,7,8-tetrahydrochromone (XLV) was formed by allowing 1-N-morpholinocyclohexene (I) to react with two moles of diketene (56). Other γ-pyrones have been prepared in this way (57).



XLVI XLVII

A Diels-Alder reaction between acrolein and enamines gave variously substituted dihydropyrans. Thus, 1-N-piperidinopropene (XLVI) and acrolein gave an 86% yield of 2-N-piperidino-3-methyl-Δ^5-dihydropyran (XLVII) (58).

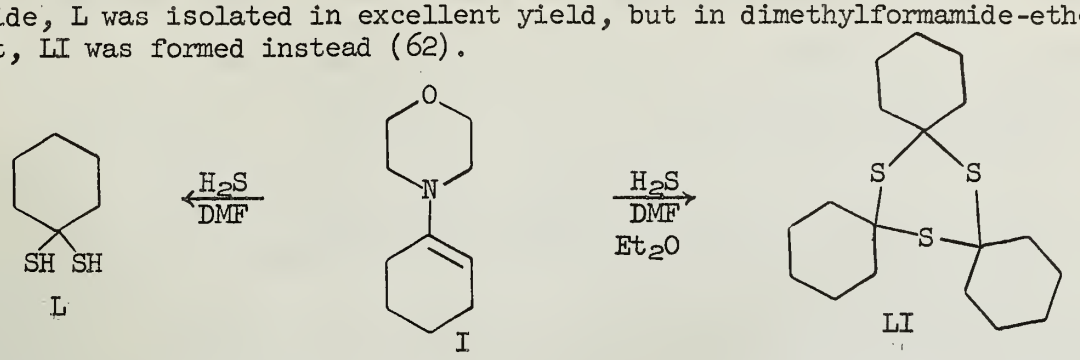
A variety of four-membered cyclic aminosulfones were prepared from various alkyl sulfonyl chlorides and enamines in the presence of triethylamine. It has been suggested that ketene analogues, sulfenes (R_2CSO_2) are formed as a first step from the sulfonyl chloride and triethylamine (59,60). When mesyl chloride was allowed to react with 1-N-pyrrolidinopropene (XLVIII) and triethylamine, a good yield of 2,2-dimethyl-3-N-pyrrolidinotrimethylenesulfone was obtained (XLIX) (60). A variety of sulfones were prepared in a similar manner (59,60).



XLVIII XLIX

MISCELLANEOUS REACTIONS

Enamines of cyclic ketones were thought to react with hydrogen sulfide to form monomeric thiones (61), but it was shown that gem-dithiols or trimeric thiones were formed. When 1-N-morpholinocyclohexene (I) was treated with hydrogen sulfide in dimethylformamide, L was isolated in excellent yield, but in dimethylformamide-ether as the solvent, LI was formed instead (62).

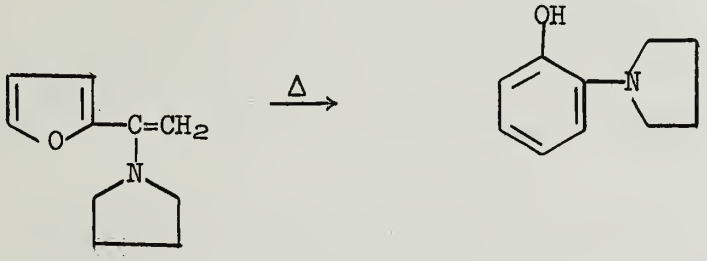


Amines substituted with either a hydroxyl or a single deuterium atom at carbon 2 can be prepared from the reaction of enamines and aluminum dichlorohydride (63). Formic acid reductions of enamines have also been studied (64).

Perchloryl fluoride is a useful reagent for introducing fluorine into the α-position of enamines derived from ketones (3,4,65). Cyanogen chloride forms α-cyano ketones (3), while cyanogen bromide provides α-bromo ketones (66).

Aryl azides react with enamines to give 1-aryl triazoles (67), while the action of hydrazoic acid on dienamines leads to a mixture of azido amines (68). The reaction of carboxylic acids and dienamines has also been examined (69).

A very interesting rearrangement of 2-acylfurans has been reported. The enamine (LII) from 2-acetylfuran and pyrrolidine was converted to 2-(N-pyrrolidino)-phenol by distillation (70).



LII

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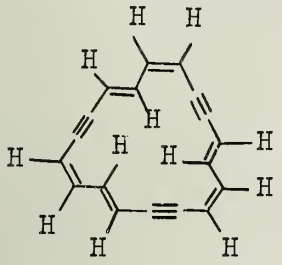
THE CHEMISTRY OF ANNULENES

Reported by Howard E. Dunn July 25, 1962

I. INTRODUCTION

The word "annulene" comes from the Latin word "Annulus" meaning ring. The use of this word to overcome the inconvenience in naming monocyclic fully conjugated polyenes was suggested by Sondheimer and Wolovsky (1). The ring size is indicated by a number in parentheses. The conjugated polyene-polyynes then would become "dehydro-annulenes," e.g. the compound I drawn below is named tridehydro-(18)annulene or more specifically 1,7,13-tridehydro-(18)annulene, rather than the longer more precise name cyclooctadeca-3,5,9,11,15,17-hexaene-1,7,13-triyne. The proposed system, however, has a disadvantage in that it does not specify the stereochemistry of the double bonds. The authors didn't feel that this was too serious of a disadvantage, since the stereochemistry of most of these compounds is not known.



I

Even before the synthesis of monocyclic fully conjugated compounds of this type there was a great deal of general interest as to what would be their chemical properties, stabilities, planarities, and degrees of aromaticity, since they would be homologs of benzene. This interest provoked the writing of a number of theoretical papers discussing these factors. The aromaticity, planarity, synthesis, and chemical properties of annulenes with ring sizes larger than eight will be discussed.

II. GENERAL CHARACTERISTICS ASSOCIATED WITH AROMATICITY

Since 1865 when Kekulé (2) discussed the theory of aromaticity of benzene a number of advances and extensions have been made to his theory. The concept of "aromatic compounds" was very soon extended to naphthalene, anthracene, furan, and pyridine. In more recent years this has led to the prediction of the nature of some unsaturated macrocyclic compounds.

Instead of a compound being classified as aromatic or non-aromatic it seems to be more correct to speak of a "degree of aromaticity" depending on how many properties the compound in question has in common to the only truly aromatic compound, benzene. The characteristics of aromatic compounds may be divided into two groups, the chemical characteristics and the physical characteristics. The chemical characteristics include: (a) the ease of formation of aromatic rings in a variety of reactions; (b) the stability of aromatic rings, in particular to addition reactions at the multiple bonds; (c) the ease of replacement of hydrogen on the ring by electrophilic substitutions, e.g. nitrations, halogenation, sulphonation, etc.; (d) the characteristic properties of substituents on aromatic systems (weakened basicity of amino groups, stability of diazo compounds, acidic properties of aromatic hydroxyls, etc.). Some of the physical properties and structural peculiarities of aromatic compounds are: (a) the character of C-C bonds being intermediate between double and single bonds; (b) the equivalence of all carbons and carbon-carbon bonds in unsubstituted monocyclic carbocyclic systems; (c) the planar or almost planar structure of the ring; (d) characteristic absorption spectroscopy; (e) high polarizability; and (f) anistropy of diamagnetic susceptibility. These properties are characteristic to a lesser or greater degree to all compounds commonly classified as aromatic.

The molecular-orbital approach to the problem of aromaticity, and in particular Hückel's rule ($4n + 2$ rule) has enabled many important predictions to be made. Hückel's rule states that monocyclic conjugated polyolefins having the symmetry of a regular polygon possess a closed electron shell, and consequently aromatic stability, if the number of π-electrons is $4n + 2$ (where n is any interger).

III. PREDICTIONS CONCERNING ANNULENES

On the basis of Hückel's rule it is conceivable that aromatic systems containing more than six π-electrons could be prepared. Aromaticity could be expected in cyclic polyolefins having the general formula C_mH_m where m = 10, 14, 18, 22, 26, 30, etc.

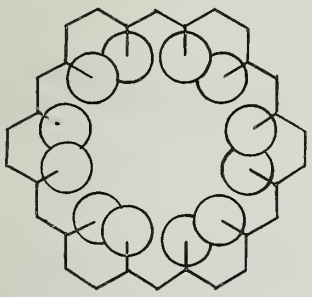
M. E. Vol'pin (3) points out that it is possible to realize unstrained equilateral polygons (molecules) having angles of 120 and 240 degrees. By letting x = the number of 120° angles, y = the number of 240° angles, 2k = the number of internal angles (k is an interger ≥ 3) and conforms to the following relationships: x = k + 3 and y = k - 3. The values of x and y are deduced from the equations (a) the sum of all the angles = 120x + 240y = 180(2k) - 360°; and, (b) total number of angles = 2k = x + y.

Table I

k	$C_{2k}H_{2k}$	x	y
3	C_6H_6	6	0
4	C_8H_8	7	1
5	$C_{10}H_{10}$	8	2
6	$C_{12}H_{12}$	9	3
7	$C_{14}H_{14}$	10	4
8	$C_{16}H_{16}$	11	5
9	$C_{18}H_{18}$	12	6
15	$C_{30}H_{30}$	18	12

Sworski (4) suggested that the quantum mechanical representation of the carbon atom predicts the possible existence of stable, planar, conjugated monocyclic compounds of more than six carbon atoms. He concluded that compounds of their type could be realized by inserting a linear acetylenic (-C≡C-) or a linear cumulene (C=C=) group between two or three positions in the benzene nucleus. He stated that such compounds would be strainless and planar provided the assumption was made that the triple-bonds have conjugative properties. If this is true, each carbon atom will have a perpendicular p-orbital which would allow the formation of a continuous overlapping molecular π-orbital.

The suggestion has been made (5) that cyclic hydrocarbons with $m \geq 8$ might exist in conformations that were unstrained and might, therefore, be coplanar and aromatic. Mislow (6) has pointed out that this assumption is correct in so far as the carbon skeleton itself is concerned, but ignores the hydrogen interference that would be present. He pointed this out by making scale drawings of various conjugated macrocyclic rings using pertinent atomic dimensions (C-C~1.40Å, C-H~1.10Å, Van der Waal's radius of H~1.0Å). He predicted that $C_{30}H_{30}$ may be an open enough structure to be coplanar since interference takes place only between alternate "central" hydrogens within the ring, as shown by the scale drawing II. The estimated delocalization energy of $C_{30}H_{30}$ based on M.O. treatment in which overlap between noncontiguous π-electrons has been neglected is approximately 140 Kcal/mole.



II

Coulson and Golebiewski (7) have pointed out that if all the C-C bond lengths in cyclooctadecanonaene ([18]annulene) are 1.40Å and the angles are all 120°, then the neighboring hydrogen atoms "inside" the molecule would be separated by only 1.72Å. They pointed out that this is exceedingly unlikely, because the shortest H····H distances in aliphatic hydrocarbon crystals are known to be 2.49-2.50Å. Therefore, some molecular deformation would be expected. There seems to be two extreme ways to maintain the van der Waal's radii in this molecule: (a) to change the C-C bond length, and perhaps thus simultaneously change the bond angles, keeping the molecule planar or (b) by buckling some part or parts of the molecule out of the plane. They showed that there is very little probability for (a) because it involves too large a set of changes in bond lengths and bond angles. For example, if the overcrowding were removed by an equal increase in all C-C bond distances, they must be changed from 1.40Å

to 1.74Å, and such an increase would require a large energy. That the relief of steric strain is energetically more favorable for out-of-plan-buckling was shown for [18]-annulene.

Coulson and Golebiewski also pointed out that there was a difficulty connected with the spectrum of [18]annulene in the U.V. range. Davies (8) calculated an N→V transition at 6030Å, but the experimental value is 4080Å. This big difference would still be further increased if steric effects on the spectra were to be introduced. These steric effects would lead to red shifts and thus would increase the calculated wavelength. They therefore suggested that the model which was being used was not correct. For example, if the bonds alternated in length along the carbon chain, then by analogy with linear polyene chains a considerable blue shift relative to the value calculated by Davies should exist.

Davies did molecular orbital calculations on [18]annulene and his results are recorded in Table II.

Table II

Method	Resonance Energy (β) (Kcal/mole)	Energy of N→V transition (β)	Wavelength of N→V transition	Bond Order	Bond Length	Free Valency
Hückel	5.03 103	0.69	6030Å	1.64	1.404Å	0.452
Dewar		0.80	5200Å			
Expt.			4080Å			

Since the energy per π-electron is somewhat less than in benzene, he predicts that [18]annulene should be less stable than benzene. The C-C bond length was obtained from an empirical formula due to H.C. Longuet-Higgins and L. Salem (9).

The transition energies of [18]annulene may also be calculated by the Moffitt (10) theory of cyclic polymers. (See table III for results.) In this theory he assumed all C-C bonds to be equal in length. Gouterman and Wagnière (11) thought that this was a poor assumption and thus modified Moffitt's calculations by letting β_1 = double bond character and β_2 = single bond character. This modification should send the transitions to shorter wavelengths, thus coming closer to the observed transitions. This shift can be seen intuitively from the fact that in the extreme limit the molecule appears as nine ethylenes with $\lambda \cong 1800$Å. After making the assumption that the bond lengths were not equal then Moffitt's method of obtaining the resonance integrals seemed to be no longer justified, so they chose a single value of $\beta = 3.14$eV to fit the average of benzene. By making these assumptions Gouterman and Wagnière calculated λ to be 405 mμ agreeing closely with the average observed for [18]annulene.

Table III

Energy of Transitions Observed (mμ)	Energy of Transitions Predicted (mμ) Moffitt	Ave. Energy of Trans. Predicted (mμ) Gauterman and Wagnière
378	510	
415	580	405
456	730	

By comparison of the β values obtained with the β values of butadiene (12), Gouterman and Wagnière found them to be of the same order of magnitude. This suggested a difference in bond lengths of about 0.1Å which is in agreement with Ooshika's (13) prediction of 0.12Å.

The x-ray work (14) indicates that [18]annulene has C-C bonds of equal length, a center of symmetry, and deviates from coplanarity by no more than 0.1Å. The latter is in direct contradiction to the calculations of Coulson and Golebiewski previously mentioned.

IV. SYNTHESIS OF ANNULENES

The general reaction employed today in the synthesis of annulenes is a modification of a reaction that was discovered almost one hundred years ago by C. Glaser (15), followed by a prototropic rearrangement. Glaser found that terminal acetylenes could be coupled in an ammonical solution, in the presence of cupric chloride, and with the

passage of air through the mixture. Since that time the reaction has become of considerable synthetic importance not only for acetylenic hydrocarbons (16) but also for amines (17), carboxylic acids (18, 19), nitro compounds (20), alcohols (21, 22), and esters (23) giving the coupled products in high yield. The reaction, which takes place under mild conditions, may be brought about by oxidizing the cuprous derivative of the acetylene with air or oxygen (16, 21, 22), cupric chloride (24), hydrogen peroxide (25), potassium ferricyanide (20, 18, 26), or simply by heating (27). Eglinton and Galbraith (28) found that when the coupling of simple monoethynyl compounds is carried out with an excess of cupric acetate in methanolic pyridine, the cuprous derivative does not precipitate and almost quantitative yield of the diynes are obtained.

The mechanism of the reaction has been worked on by Baxendale and Westcott (29, 30). They showed cupric ion to be the oxidizing agent when the solution was buffered to a pH 6 and a stoichiometric amount of cupric ion was employed. The "dimer" was formed in 50% yield, with the remainder of the product being the cuprous acetylide:

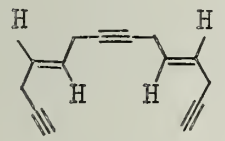
$$4\ RC{\equiv}CH + 2\ Cu^{+2} \rightarrow RC{\equiv}C\text{-}C{\equiv}C\text{-}R + 2\ RC{\equiv}C\ Cu + 4\ H^{+}$$

The acetylide was then slowly oxidized by air or other oxidizing agent. The overall reaction is

$$2\ RC{\equiv}CH + 2\ Cu^{+2} \rightarrow RC{\equiv}C\text{-}C{\equiv}CR + 2\ H^{+} + 2Cu^{+}$$

[10]Annulene was reported formed (31) in the polymerization of acetylene in tetrahydrofuran using a nickel cyanide catalyst. The $C_{10}H_{10}$ fractions originally believed to be stereoisomers of [10]annulene were later shown by Cope and Fenton (32) to be vinylcyclooctatetraene and cis-1-phenyl-1,3-butadiene.

[14]Annulene was prepared by Sondheimer and Gaoni (33) by cyclization of trans-trans-4,10-tetradecadiene-1,7,13-triyne (III) with cupric acetate (15 parts) in pyridine (100 parts) (30) at 50° for one hour and then treated directly with potassium t-butoxide in t-butanol-benzene at 60° for one minute. Chromatography of the product on alumina gave 2% of 1,3,5,7,9,11-cyclotetradecahexen-13-yne (IV) or a stereoisomer. Partial hydrogenation of II in benzene over a "Lindlar" (34) catalyst, followed by chromatography on alumina, yielded 15% of cyclotetradecaheptaene ([14]annulene)(V) or a stereoisomer.



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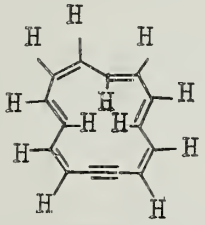

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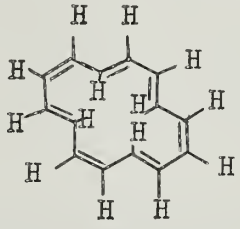
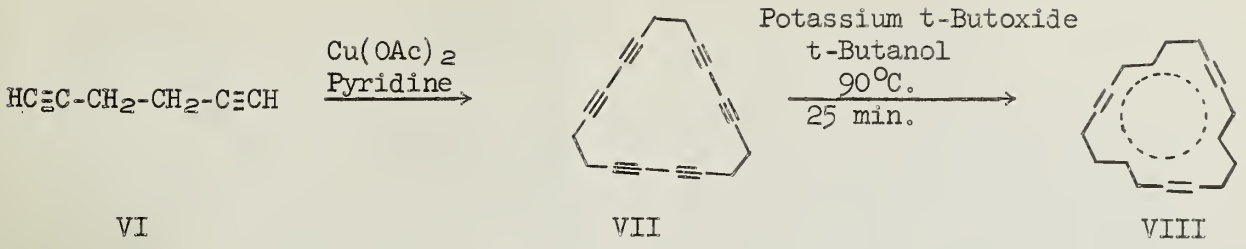


V

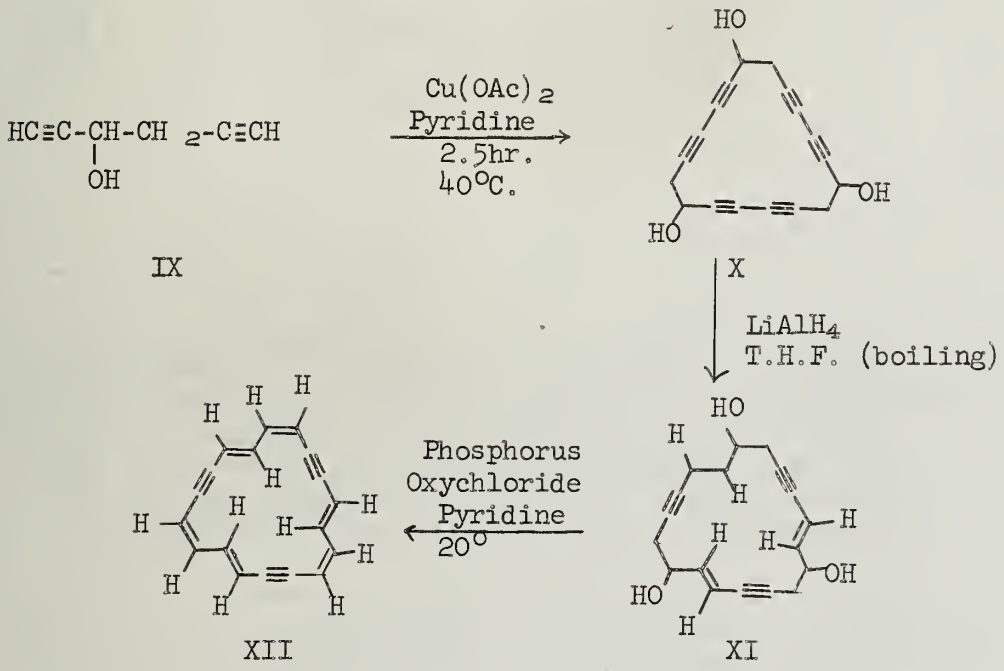
[14]Annulene ($C_{14}H_{14}$) complies to one of the two criteria which has been postulated for aromaticity in such systems, that of complying to Hückel's rule ($4n + 2$), $n=3$. The fact that it is quite unstable seems to provide an experimental demonstration of the importance of planarity for aromaticity in conjugated cyclopolyolefins, especially in view of the much greater stability of cyclooctadecanonaene which also contains ($4n + 2$) π-electrons ($n = 4$), but in addition is planar or nearly planar (35). It should be pointed out here that it is not justified to equate "aromaticity" with stability.

The configuration of [14]annulene is not known, however, there are three possibilities: the periphery of phenanthrene, the periphery of anthracene, or V. Since none of the possibilities can be planar, the observed instability (completely decomposes in light and air in one day) in [14]annulene demonstrates the importance of planarity for aromaticity, irrespective of its actual configuration. It is interesting to note that the dehydro isomers are more stable, which is probably due to relief of steric strain.

[18]Annulene: The precursor (cyclooctadeca-1,7,13-cis-triene-3,9,15-trans-triene-5,11,17-triyne) (VIII) of [18]annulene has been prepared by two routes (36, 37) as outlined.



VI VII VIII

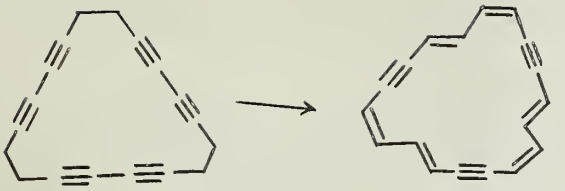


IX XII XI

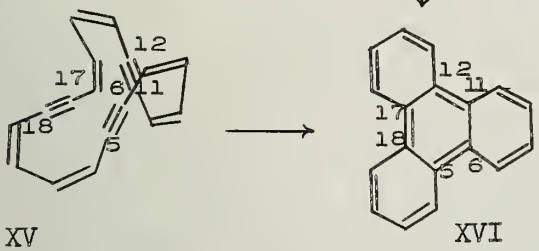
An interesting side reaction takes place in the protropic rearrangement to [18] annulene that leads to the formation of triphenylene (38). Triphenylene (XVI) is probably formed directly from XIII. It is interesting to note that in a model of XIII, C_6 lies close to C_{11}, C_{12} lies close to C_{17}, and C_{18} lies close to C_5. It may be noted that triphenylene has previously been obtained from cyclooctadecane through dehydrogenation over Pd-charcoal at 400° (39).

[18]Annulene has been shown by a 3-dimensional x-ray structure analysis to have the structure XVII (40, 41). This structure indicates that the acetylenic bonds in tridehydro-[18]annulene have undergone hydrogenation to trans-ethylenes, contrary to what is expected to take place (42). It has been noted previously that catalytic partial hydrogenation of acetylenes may give rise to small amounts of the trans-ethylenes in addition to the cis isomers (43), but there has only been one other case reported where the trans double bond is the major product (44).

[18]Annulene is found to have properties more similar to a conjugated polyene than to a typical benzenoid substance. It does not undergo nitration, sulfonation, Friedel-Craft's acetylation, or reaction with benzenediazonium ~~anhydride~~ chloride in boiling benzene (41).



XIII XIV

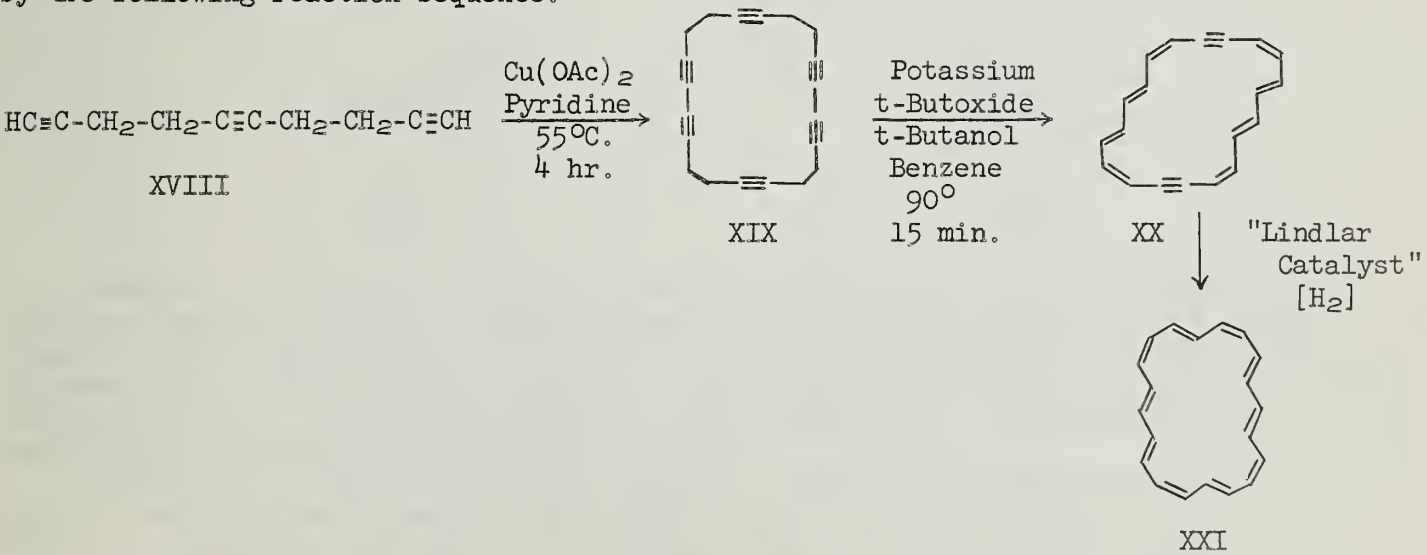


XV XVI

XVII

Large crystals of [18]annulene could be kept fourteen days unprotected in daylight without appreciable change. It complies to the $(4n + 2)$ rule and is within at least 0.1Å of being coplanar. This latter structural property is in disagreement with Coulson and Golebiewski's (7) prediction that it should be far from planar. In the modern sense [18]annulene is aromatic, it can sustain an induced ring current of π-electrons (41), and the carbon-carbon bonds are the same length. The attempt to determine the energy content of [18]annulene by measuring the heat of hydrogenation did not lead to clear results.

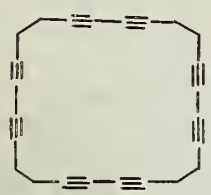
[20]Annulene: Three completely conjugated twenty-membered ring cyclic systems have been prepared (45): 1,3,5,7,11,13,15,17-cycloeicosaoctaene-9,19-diyne (XX), 1,3,5,7,9,11,13,15,17-cycloeicosanonaen-19-yne (or stereoisomer), and 1,3,5,7,9,11,13,15,17,19-cycloeicosadecaene ([20]annulene) (XXI) (or a stereoisomer). The latter was synthesized by the following reaction sequence.



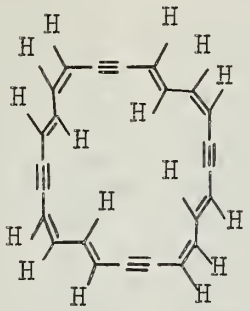
Further structural evidence was provided by the fact that potassium t-butoxide rearrangement of trans-trans-1,11-cycloeicosadiene led to a compound with similar ultraviolet properties.

L 5,7,15,17-tetrayne

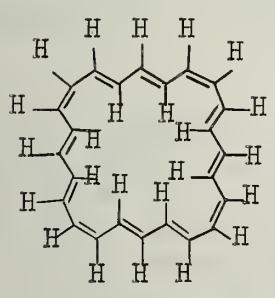
[24]Annulene was the first report of a completely conjugated 24-membered ring cyclic system. Cyclotetracosa-1,3,7,9,13,15,19,21-octayne (XXII) (the cyclic "tetramer" of 1,5-hexadiyne) (37) on treatment with potassium t-butoxide in t-butanol-benzene at 90° for thirty minutes undergoes similar rearrangement to that of the corresponding "trimer" (37). The rearranged product was most likely cyclotetracosa-1,7,13,19-tetra-cis-ene-3,9,15,21-tetra-trans-ene-5,11,17,23-tetrayne (XXIII), which may not be planar due to four cis double bonds. Partial hydrogenation of XXIII in benzene over a "Lindlar" palladium catalyst gave [24]annulene XXIV or XXV in 15% yield. In view of the spectral data Sondheimer and Wolovsky (46) favor XXV for the structure.



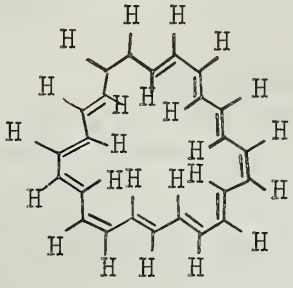
XXII



XXIII



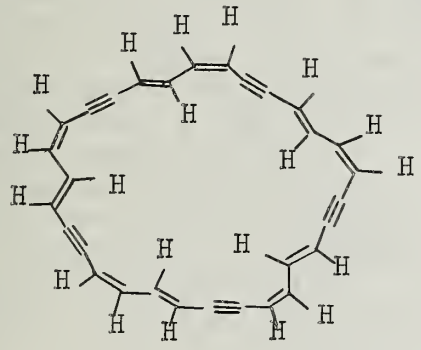
XXIV



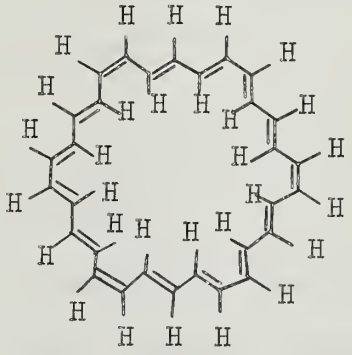
XXV

[24]Annulene does not obey Hückel's rule and therefore would not be expected to exhibit aromatic properties. In view of the possible relationship between aromaticity and stability, its stability was investigated. When [24]annulene was allowed to stand at room temperature for twenty-four hours without protection from daylight, it was found to have 99% decomposed (41); under the same conditions [18]annulene crystals were essentially unchanged.

[30]Annulene (XXVII or an isomer) was synthesized by Sondheimer, Wolovsky, and Amiel (41) by partial hydrogenation of the pentadehydro-[30]annulene (XXVI or isomer).



XXVI



XXVII

Although no satisfactory analysis was obtained, the average result given by two different samples indicated a carbon:hydrogen ratio of 30:30, pointing to a $C_{30}H_{30}$ formula. The infrared spectrum no longer showed the acelylene band at 4.63μ present in the pentadehydro compound (XXVI), and full hydrogenation in dioxane over platinum led to cyclotriacontane. It was on the basis of these facts that a [30]annulene structure was assigned to the partial hydrogenation product.

[30]Annulene should represent an aromatic system if it exists in the configuration XXVII, however, no experimental evidence has thus far been obtained to indicate this point. [30]Annulene complies to the Hückel rule (n=7).

[30]Annulene is very unstable, suffering over 95% destruction on being allowed to stand at room temperature for four hours without protection from daylight. This observed instability was consistant with the fact that an attempted alternate synthesis of [30]annulene, involving potassium t-butoxide rearrangement as the last step, did not lead to clear-cut results.

CONCLUSION

In view of the evidence presented in this seminar the $4n + 2$ rule alone may not be sufficient to explain or predict the existence of aromaticity in a compound containing $4n + 2$ π-electrons. It does account for the fact that [18]annulene is more stable than [20]annulene and [24]annulene. The instability of [14]annulene, which obeys the $4n + 2$ rule, may be attributed to the steric interactions between the "internal" hydrogens forcing the molecule into a non-planar configuration. Such interactions are reduced in the dehydro derivatives and the higher stabilities of these compounds indicated the importance of planarity. The steric interaction of the "internal" hydrogens decreases as the ring size increases yet [30]annulene is very unstable. It is not clear at this moment that the instability of [30]annulene which obeys the $4n + 2$ rule, is due to an abnormal stereochemical configuration. From the investigation of the absorption spectra of annulenes it appears that bond alteration may also be an important factor to the aromaticity of these compounds.

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TOTAL SYNTHESIS OF CONESSINE

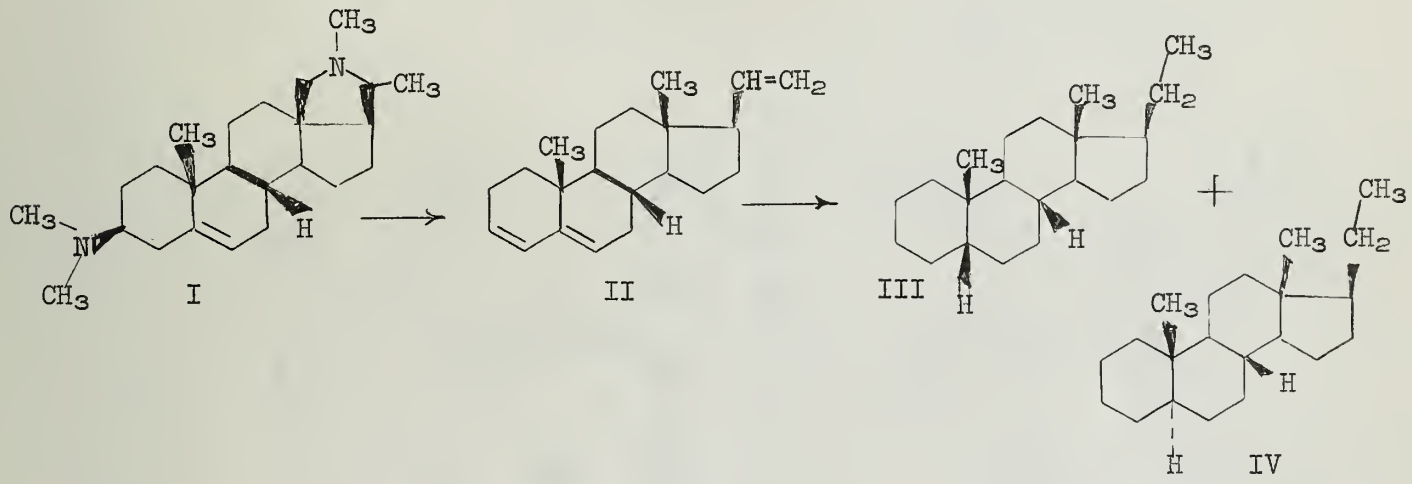
Reported by D. Machiele

July 30, 1962

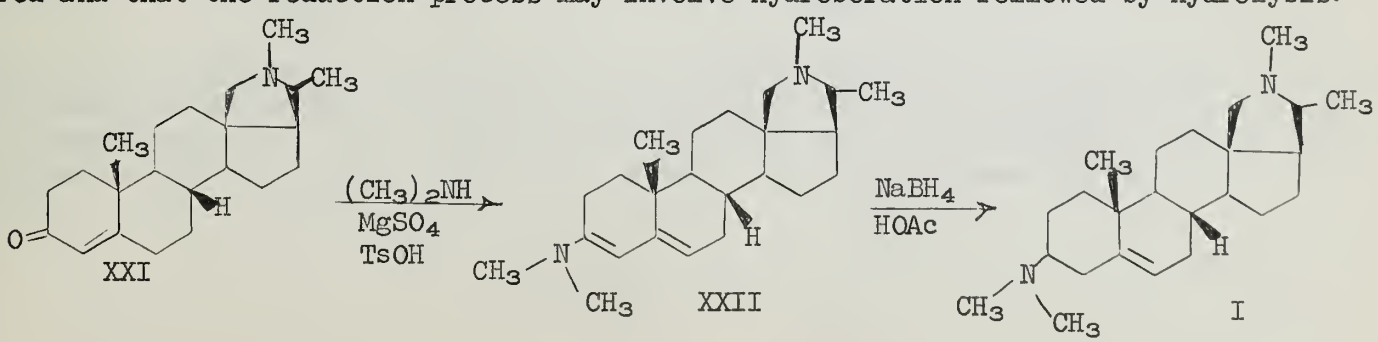
Conessine, the most important representative of the kurchi alkaloids, was isolated as early as 1858 (1,2). The interesting pharmacological properties of conessine have led to the wide investigations of its structure and synthesis. Its structure was determined around 1953 by Haworth, McKenna and co-workers and is reported elsewhere (3). Partial syntheses of conessine have been carried out by Corey and Hertler (4), Jeger and co-workers (5), and more recently by Barton and Morgan (6,7)

Conessine (I), which contains a nitrogen substituted at the 18-methyl group in the steroid nucleus, has been converted into 18-oxygenated steroids (8). It may also be noted that any total synthesis of conessine may result from a variation in the total synthesis of an 18-oxygenated steroid (9) as well as that the synthesis of conessine may be adaptable for the synthesis of other 18-substituted steroids (10).

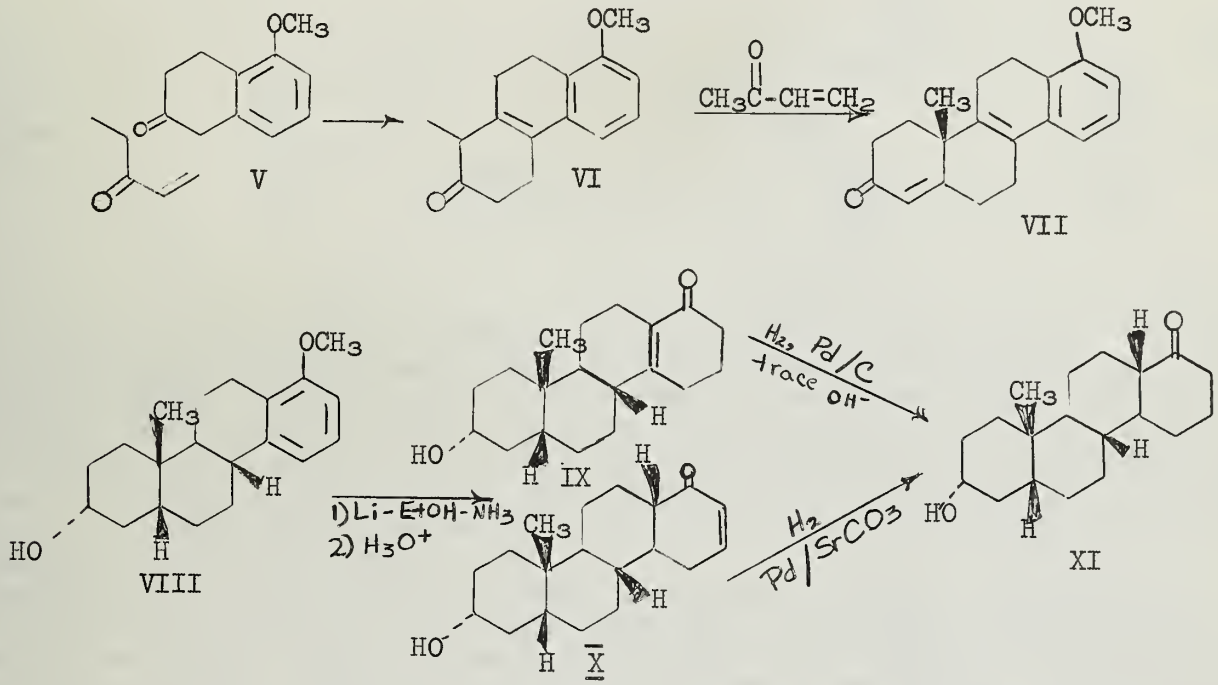
The stereochemistry of conessine (I) was determined by Haworth and co-workers. Hofmann degradation on I followed by an Emde reduction gave pregna-3,5,20-triene (II) which upon catalytic reduction gave pregnane (III) and 5-allopregnane (IV) of known configurations (11). The dimethylamino group was assigned the 3β-configuration on the basis that conessine could be degraded to 3β-dimethylaminopregn-5-ene, a known compound (12).



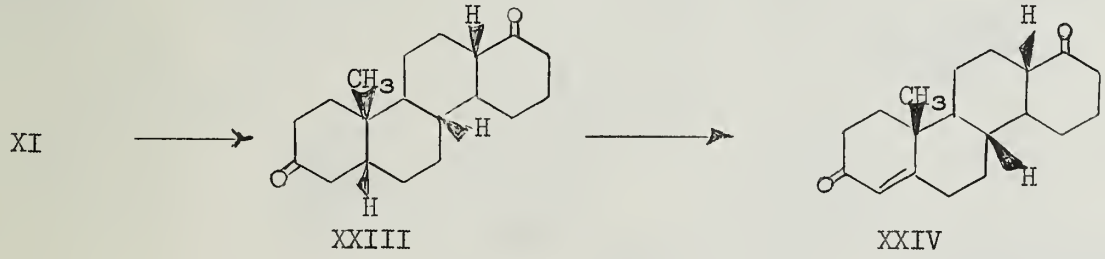
Johnson and Marshall have synthesized dl-conessine (I) by a method which requires the isolation of only ten intermediates (13). The starting point of their synthesis, 1-methoxy-5,6,8,9,10,10a,11,12-octahydrochrysene (VII), was also the intermediate in their synthesis of testosterone (14) and aldosterone (15). The final product was shown by melting point, infrared and mass spectroscopy to be racemic conessine by identity with the natural product. In an attempt to prepare conessine from a 3-oxygenated derivative, it was discovered that Δ^4-3-keto steroids could be converted to 3-enamines with secondary amines (16). Thus, Δ^4-conanene-3-one (XXI) upon reaction with anhydrous dimethylamine, magnesium sulfate and p-toluene-sulfonic acid in a sealed tube (air excluded) gave the corresponding enamine XXII. Enamines of this type are resistant to reduction with lithium aluminum hydride (17), however, reduction was accomplished with sodium borohydride and acetic acid in dioxane (18). The reduction of XXII proceeds smoothly and selectively to give dl-conessine (I). It has been suggested (19) that diborane may be the reducing agent since the acetic acid is required and that the reduction process may involve hydroboration followed by hydrolysis.



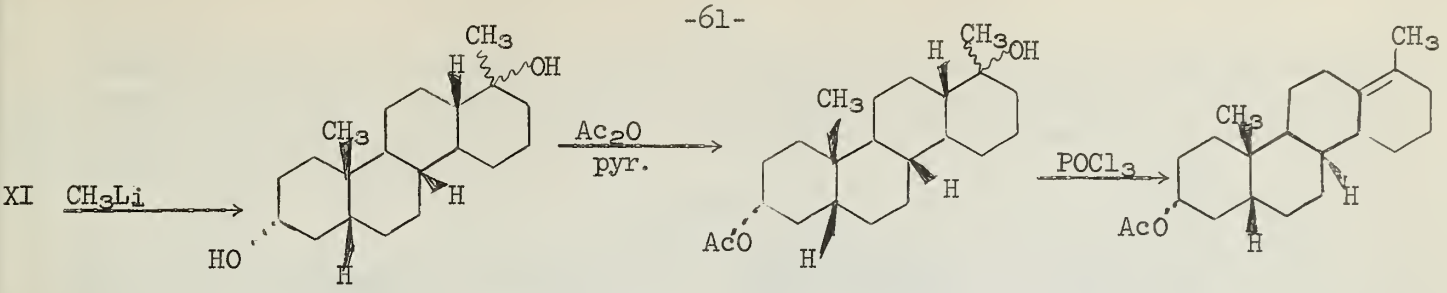
A Michael condensation of 5-methoxy-2-tetralone (V) with 1-dimethylamino-3-pentanone or condensation with ethyl vinyl ketone followed by an aldol condensation gave the tricyclic ketone (VI) which could be condensed similarly with methyl vinyl ketone to give VII (20). In order to obtain the saturated compound XI, a series of reductions were carried out. The 4,5 double bond was reduced catalytically over palladium while lithium aluminum hydride reduction of the carbonyl gave the 3-hydroxy compound. The 8,9-(styrene)-double bond was reduced with potassium and alcohol to give VIII, which still contains an aromatic nucleus. This can be reduced (21) to the enol ethers with lithium-alcohol-liquid ammonia under vigorous conditions. Acid hydrolysis of the enol ethers results in the formation of two α,β-unsaturated ketones, IX and X, which are separated by chromatography. Hydrogenation of the 13,14-dehydro isomer IX over palladium-charcoal produces XI while hydrogenation of the 16,17-dehydro isomer X was accomplished with palladium on strontium carbonate.



The configuration of XI was established (22) by its conversion to a compound (XXIV) derived from an intermediate in the synthesis of testosterone, the configuration of which had been established earlier (14). Oxidation of XI with Sarett reagent gave the diketone XXIII which was selectively brominated at C-4 (23) using one mole equivalent of bromine in dimethylformamide in the presence of p-toluenesulfonic acid and then dehydrohalogenated to give XXIV.

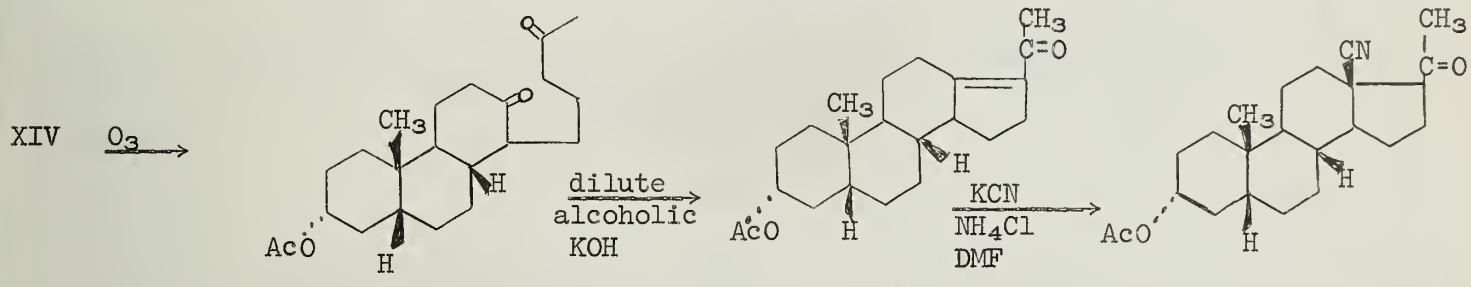


Reaction of 3α-hydroxy-17a-keto-D-homo-18-noretiocholane (XI) with excess methyl lithium gave the dihydroxy XII which was selectively acetylated with acetic anhydride in pyridine at the 3-hydroxyl position. With this group now protected, XIII was dehydrated with phosphorus oxychloride to give a mixture of olefins in which the desired compound XIV was found to predominate.



XII XIII XIV

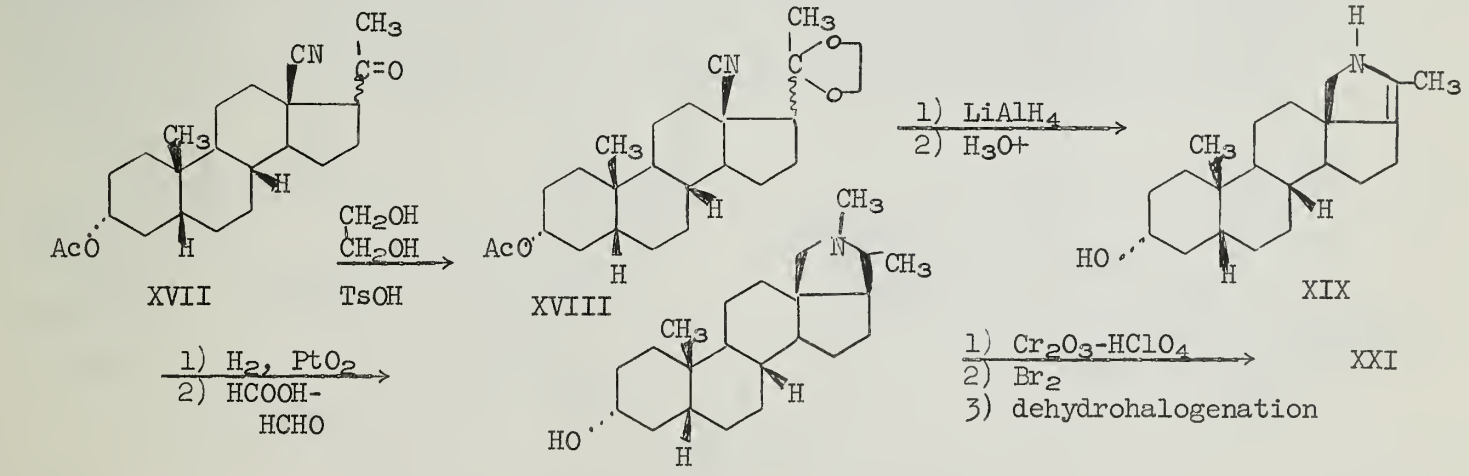
Ozonolysis of XIV produced the diketone XV which underwent a base-catalyzed aldol condensation resulting in cyclization and dehydration to form the five-membered D ring (XVI).



XV XVI XVII

For the formation of ring E, cyanation of XVI gave both the 13α and 13β cyano isomers (XVII). An analogous reaction can be found in the estratriene series (24). The mixture of 13-cyano-3-hydroxy compounds, which were formed in approximately equal amounts, could easily be separated by chromatography. The 13β epimer was desired in order to give the correct stereochemistry and the two epimers were distinguished by their conversion to conessine. It was soon discovered that the 13α epimer, upon heating to 350°, could be converted to the unsaturated compound XVI in excellent yield. In so doing, each step of the synthesis was made stereoselective.

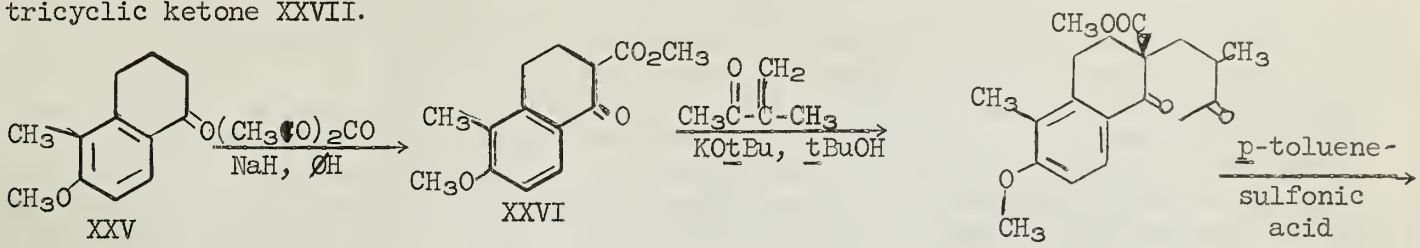
Attempts to convert the 13βcyano ketone XVII directly to XIX were unsuccessful. It was necessary to form the ethylene ketal XVIII first, then reduction of the cyano group with lithium aluminum hydride followed by acid hydrolysis to remove the ketal group and to cause cyclization. Catalytic reduction of XIX over platinum oxide followed by N-methylation using the formic acid-formaldehyde procedure gave XX. Δ^4-Conanene-3-one (XXI) is obtained by oxidation of the corresponding saturated alcohol XX with chromium trioxide and perchloric acid followed by selective bromination in the 4-position and dehydrohalogenation.



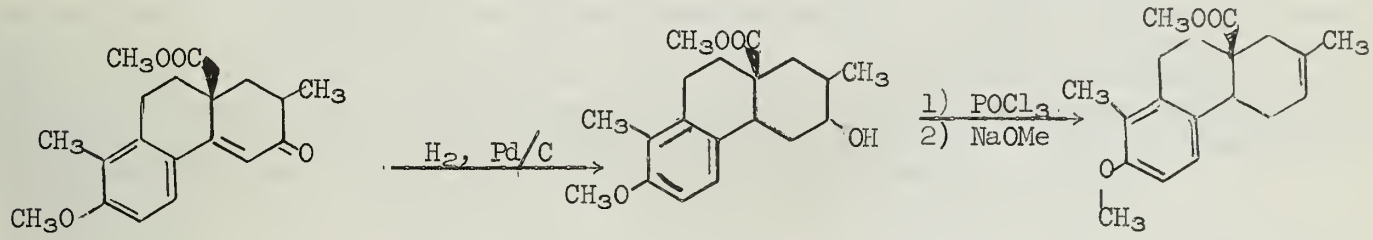
XVII XVIII XIX XX XXI

Almost simultaneously, Stork and co-workers (10) also reported a synthesis of conessine. They were interested in the synthesis of 18-substituted steroids in which the B,C and D rings were constructed first, then addition of the A ring. The synthesis of conessine was demonstrated by this means. It was suggested (10) that XXXI could be used as an intermediate in the synthesis of other 18-substituted steroids.

5-Methyl-6-methoxy-α-tetralone (XXV) was used as the starting point and was reacted with dimethylcarbonate to give the β-keto ester (XXVI). A base-catalyzed condensation with methyl isopropenyl ketone followed by cyclization with p-toluene-sulfonic acid gave the tricyclic ketone XXVII.

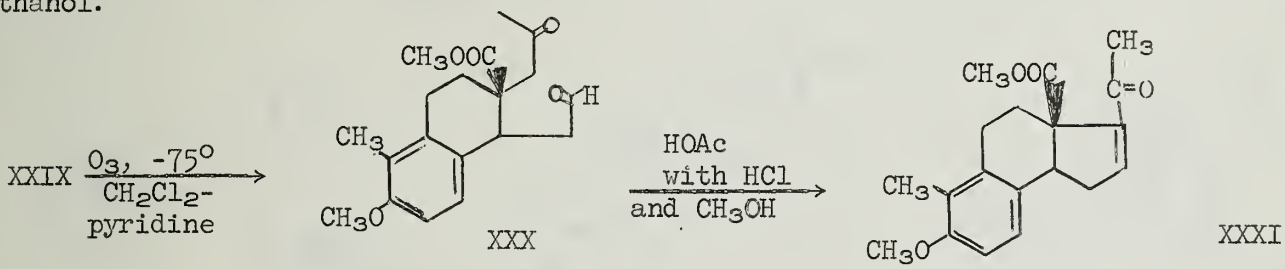


XXV XXVI



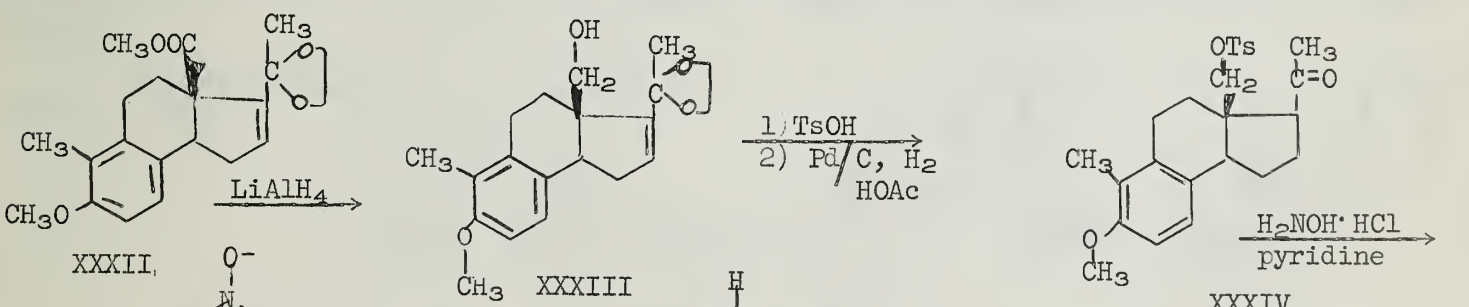
XXVII XXVIII XXIX

In order to obtain the correct olefin for ring contraction with ozone, it was necessary to reduce the α,β-unsaturated ketone to the dihydro alcohol XXVIII, then conversion to the chloro compound with phosphorus oxychloride, and finally, dehydrohalogenation to give the unsaturated ester XXIX. The keto aldehyde XXX produced by the ozonolysis of XXIX was cyclized to the required D ring compound XXXI in acetic acid with hydrogen chloride and methanol.

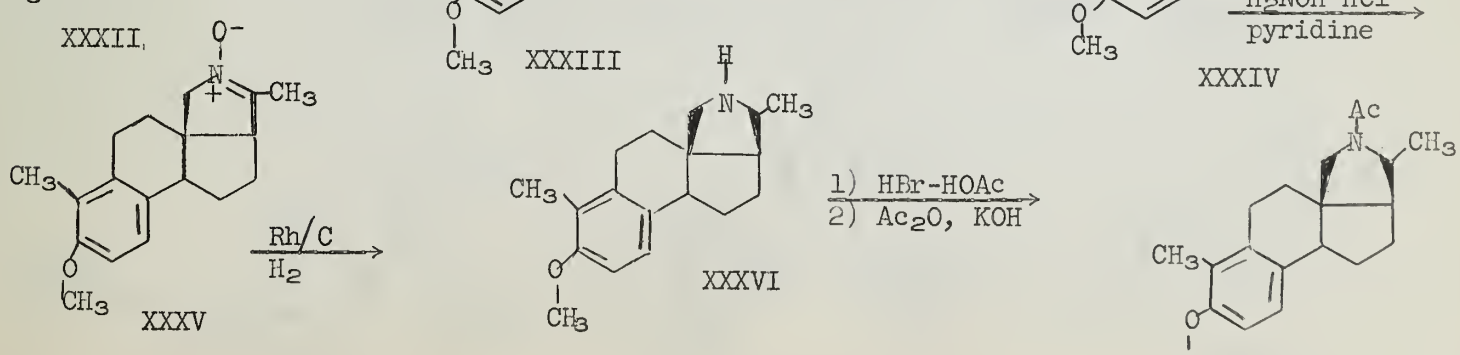


XXX XXXI

Protection of the keto group in XXI as a dioxolane XXXII was necessary before reduction of the carbomethoxy with lithium aluminum hydride could be accomplished. During the formation of the tosylate of the alcohol XXXIII the ketal group was also regenerated. After catalytic reduction of the 16,17 bond, the necessary nitrogen was introduced by reaction of XXXIV with hydroxylamine-hydrochloride which gave the nitrone XXXV.



XXXII XXXIII XXXIV

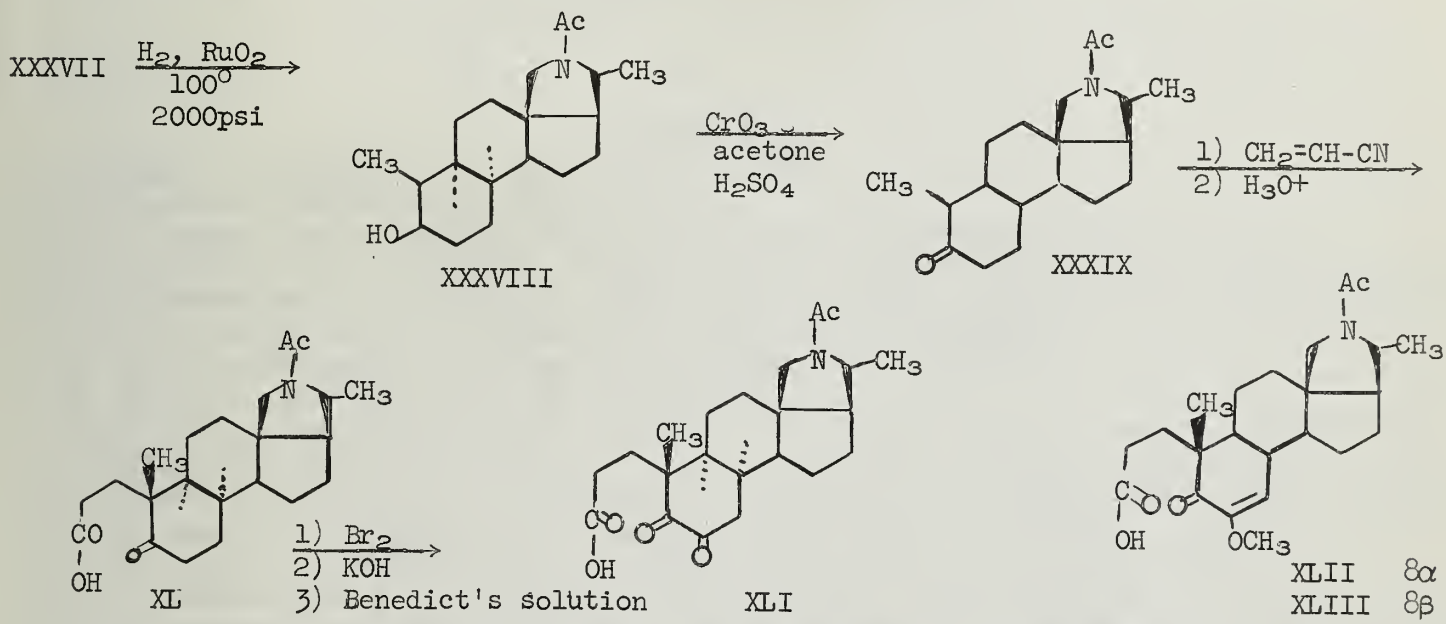


XXXV XXXVI XXXVII

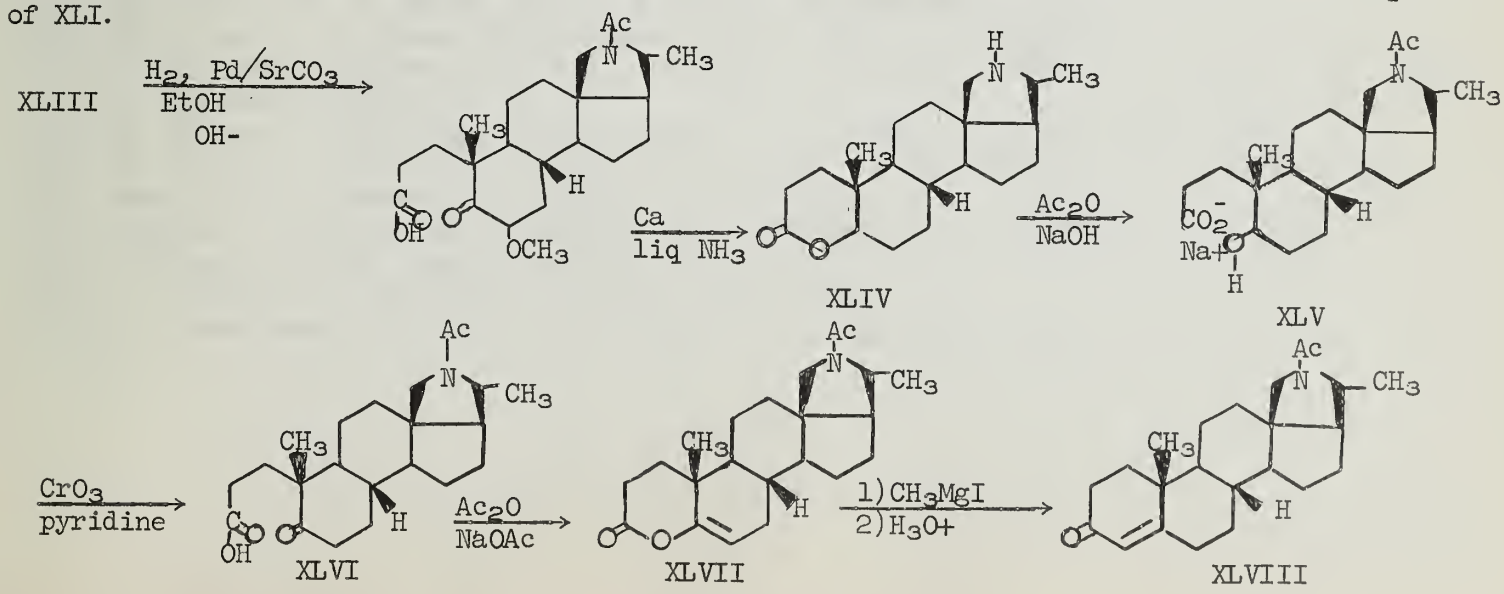
The correct stereochemistry of the pyrrolidine ring was obtained upon reduction of XXXV with rhodium on charcoal. The next step was the acid hydrolysis of the ether followed by N-acetylation to give XXXVII.

For the construction of ring A it was first necessary to hydrogenate ring B to form the saturated compound XXXVIII which was accomplished with ruthenium oxide under pressure. This hydrogenation results in a cis B/C ring juncture, which means that the unnatural or 8α form is obtained. This is used, however, to control the stereochemistry of the C-10 methyl group.

To activate the 10-position the hydroxy group was oxidized to the ketone XXXIX so that reaction with acrylonitrile followed by hydrolysis gave the acid XL. In this tetracyclic system, five of the six assymetric centers already have the stereochemistry which is also that of the final product, but the C-8 hydrogen still has the alpha configuration. Since the propionic acid side chain had the correct stereochemistry, the next step was the transformation of the 8α skeleton to the required 8β epimer. The acid XL was converted to the 5,6-di-ketone XLI by selective bromination at C-6, reaction with aqueous potassium hydroxide to the α-ketol and finally oxidation with Benedict's solution. The α-di-ketone existed as the enol form which could be methylated with methyl sulfate to give XLII. This was then epimerized to the desired 8β epimer (XLIII) after refluxing in aqueous sodium hydroxide.

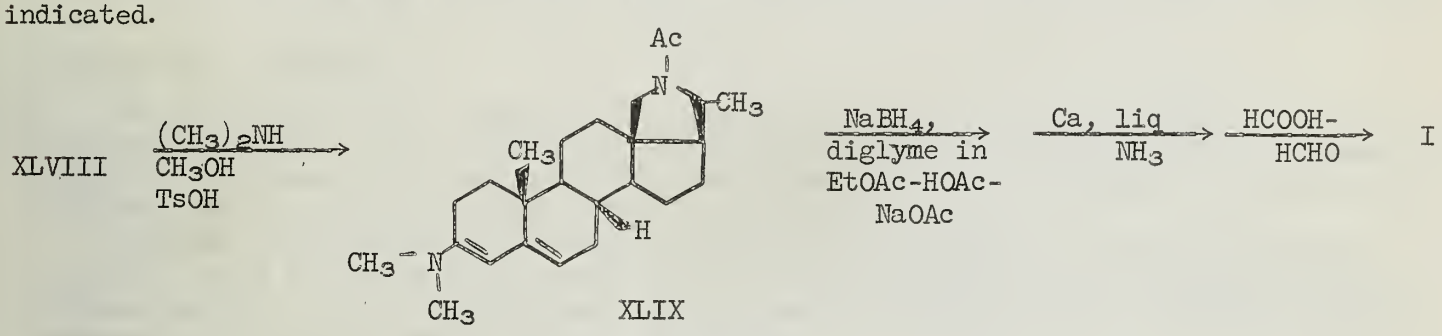


The next step in the total synthesis was the removal of the ether function. The following series of reactions was used: Reduction of XLIII to the saturated ether followed by treatment with calcium in liquid ammonia. This latter reaction results in removal of the ether, deacetylation of the amine and reduction of the carbonyl, producing the lactone XLIV. Reacetylation of XLIV followed by oxidation of XLV gave the ketone XLVI which is the epimer of XLI.



At this point the chief remaining factor was the completion of ring A which requires the insertion of a carbon atom. Treatment of XLVI with acetic anhydride and sodium acetate converted it to the enol lactone XLVII (25). The necessary carbon atom was inserted by reaction with methylmagnesium iodide (26,27) which, upon acidification, proceeded through a series of intermediates to give the enone XLVIII.

Using a procedure adapted from Johnson and Marshall (18) Stork and co-workers converted the enone XLVIII to the enamine XLIX followed by reduction of the 3,4 double bond with sodium borohydride, deacetylation with calcium in ammonia and N-methylation using the formic acid-formaldehyde procedure to give racemic conessine. The fact that the product was identical to the natural product indicates that the stereochemical course is as indicated.



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MASS SPECTROMETRY

Reported by William P. O'Neill August 1, 1962

INTRODUCTION

Mass spectrometric methods are being applied intensively by a few groups of workers in various areas of natural product chemistry. New areas uncovered since the last comprehensive review (1) include work on steroids, triterpenoids, nucleosides, and alkaloids. As demonstrations of the nature of the method, the type of interpretations possible for it, and the scope and limits of its applicability, this seminar will concern some of the recent work in the above fields.

METHODS AND CONVENTIONS

The technique of mass spectrometry has been well reviewed (1-5), and will not be discussed at length here. Most of the work to be discussed was conducted with commercially available instruments with an ion source inlet temperature of 200-250° C., pressure of 10^{-5} mm., and an ionizing voltage of 70 ev except where noted.

Material with extremely low vapor pressure can be vaporized directly in the ion source by using a special vacuum lock (1) or in the extreme, as for nucleosides (6), by sublimation from a hot filament about one centimeter from the beam. This has greatly lowered the volatility requirement of the method.

In the past, 5-20 minutes have been required for scanning a spectrum, but Biemann (6) using a commercially available Time-of-Flight mass spectrometer was able to obtain comparable spectra in 30-60 seconds.

Where applicable the mass spectrometric method allows understandable, multiple degradations of less than one milligram of a complicated organic compound. Experience has shown that the fragmentations and rearrangements can usually be interpreted in terms of reaction pathways similar to those found in common organic reactions.

All figures in this paper represent single positively charged ions resulting initially by loss of one electron from the molecule upon collision with a high energy electron in the electron beam. This positive molecular ion can then undergo fragmentation, principally in the manners indicated by the dotted lines. The mass of the observed ionic fragment is written on the appropriate side of the dotted line.

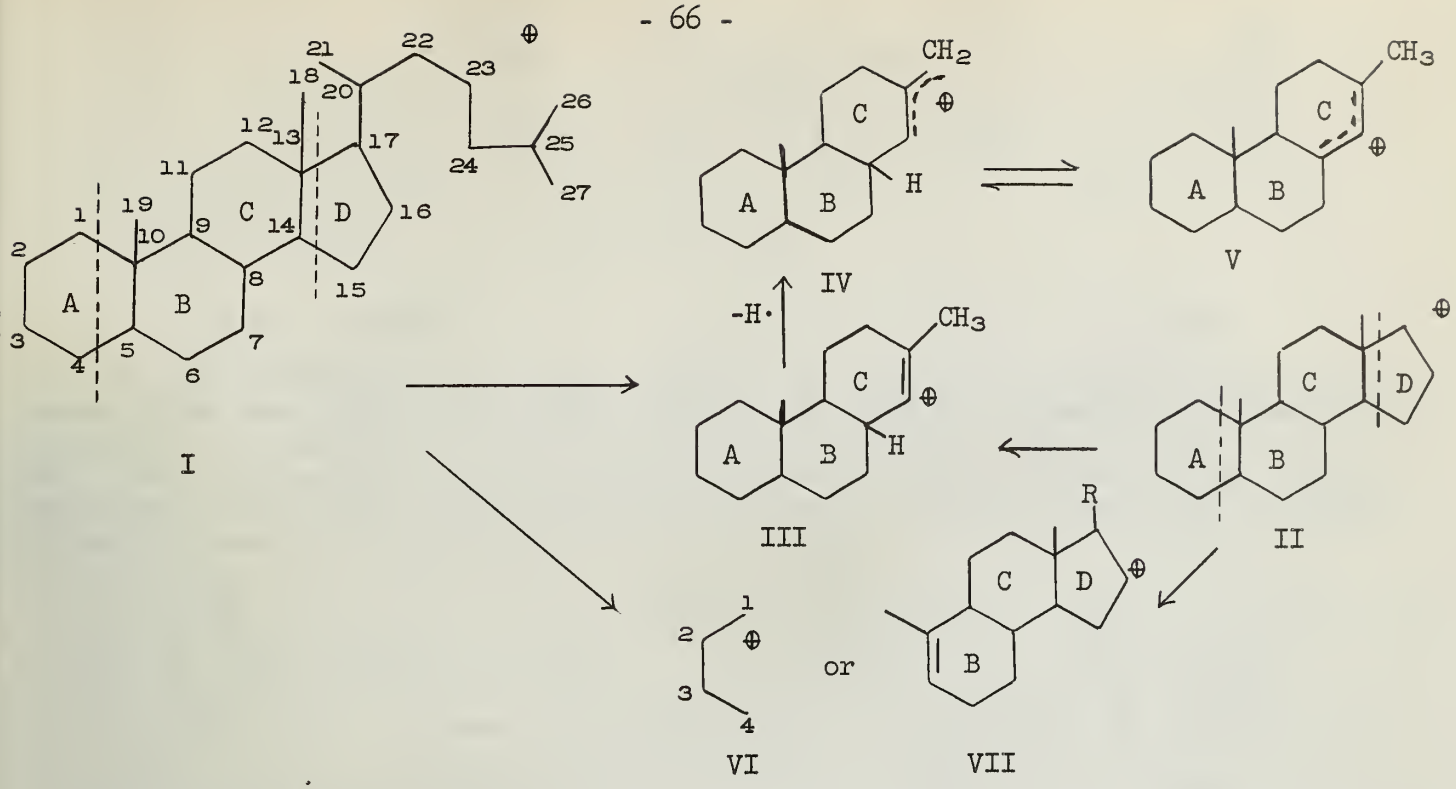
The dotted lines indicate free radical fragmentation in most cases, but are not meant to imply a mechanism or to represent a one-step process. Only the observation of a meta-stable peak, resulting from decomposition of ions after acceleration, allows designation of a fragmentation as a one-step process. The mass value (m/e) of the maximum of the low intensity, broad meta-stable peak is designated m_a, for apparent mass. For the process $m_x \rightarrow m_y$, that is, an ion of mass x going to a neutral fragment and a fragment of mass y, the equation $m_a = m_y^2/m_x$ is found to hold (3).

STEROIDS

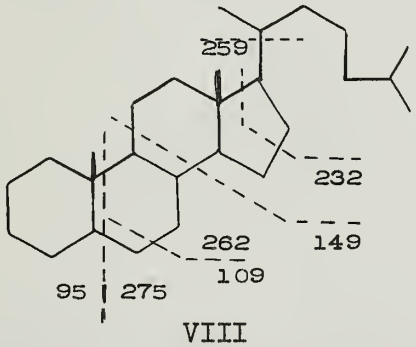
Early work of Reed (7, 8) using 9-15 ev bombardment allowed accurate assignment of molecular weight and determination of the size and nature of the side chains since under these conditions steroid rings are not fragmented. In fact, the ions are probably derived from thermally produced particles as demonstrated by the fact that structures bearing no side chains gave no mass spectra with an ionizing voltage of less than 18 ev (8). Pyrolysis at 350° for 30 minutes, and analysis of the gaseous products of various steroids gave reproducible patterns, but no structural information (9).

Most saturated steroids show a major peak in the mass spectrum at (or near) m/e 217 which can be interpreted as due to loss of the D-ring and the C-17 substituent from the molecular ion, e.g. cholestane (I) and 5α- or 5β-androstane (II) all show this peak, which probably results from loss of a hydrogen atom from intermediate (III) to give the resonance stabilized, prototropic ions (IV) and (V).

A meta-stable peak at m/e 182.5 in the androstane spectrum corresponds to the one-step cleavage 260→217, i.e. II→III (10). Meta-stable peaks corresponding to loss of methyl and/or water from the molecular ion are found in the mass spectra of most steroids (10).



Similarly loss of A-ring carbons leads to strong peaks at m/e 203 (204) for androstane derivatives and m/e 315 (203 + C_8H_{16}) for cholestane derivatives (18), corresponding to type (VII). Also prominent is a peak at m/e 55 (C_4H_7) (VI) for both series. That is, either fragment, in this case, bears the positive charge. Other principal fragmentations of cholestane are shown in (VIII). Also important is the M-15 peak (M = molecular weight) indicating loss of an angular methyl group which is common in both series (9). The indicated fragmentations occur to a greater or lesser extent, along with other fragmentations, in substituted steroids. It is the nature of the effects of substituents on the fragmentation pattern which will be discussed next.

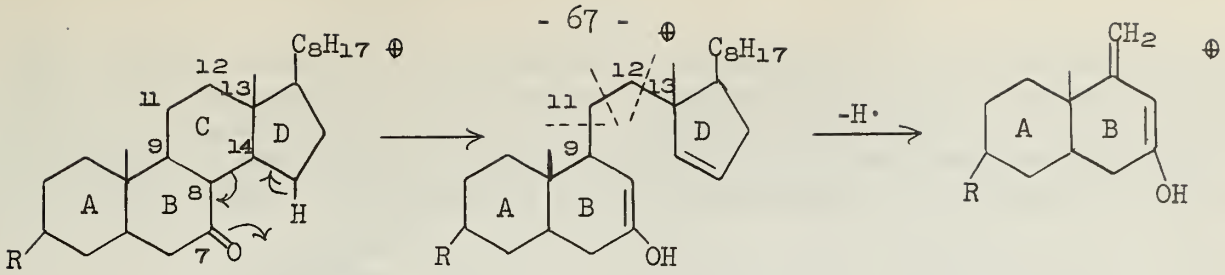


VIII

The most useful work on these effects has so-far been that of Djerassi and co-workers on the mono-keto steroids. As with aliphatic (11), and alicyclic (12) ketones, cleavage is favored both α and β to the carbonyl in keto steroids (10). The principal oxygen-containing, ionic products are thus of the $RCO^{\oplus}$, and the $RCOCH_3^{\oplus}$ type. The latter involves rearrangement of one hydrogen atom from the neutral fragment by a cyclic mechanism.

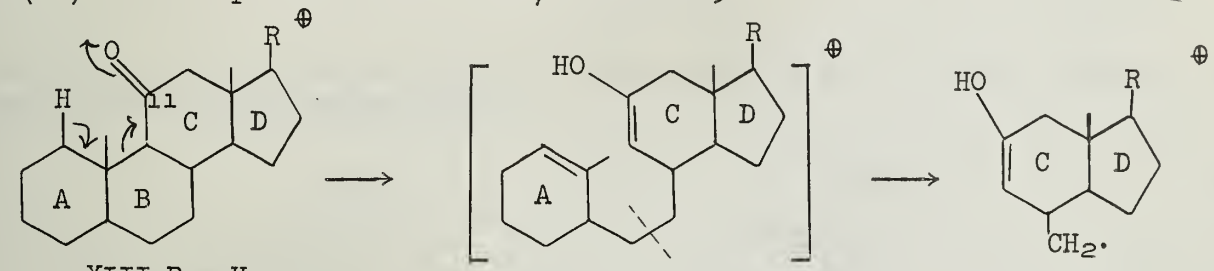
For steroids with the carbonyl in rings B or C several examples have been given. Cholestan-7-one (IX) shows a mass spectrum indicating that the main fragmentation results in cleavage of the most heavily substituted bond 8-14, along with cleavage of the 11-12 (or, to a lesser extent, the 9-11 or 12-13) bond. That the strong peak at m/e 178 includes rings A and B plus probably C-11, (XII) was shown by the shift to m/e 236 for 3β-acetoxycholestan-7-one (X), and the lack of shift when the C-17 substituent is changed (10).

Mechanistically the cleavage of the 8-14 bond most likely proceeds as shown, but the site of hydrogen loss can only be established by current deuterium labeling studies (10). Alternate cleavage of the 9-11, or 12-13 bond in (XI) leads to peaks at m/e 165 and 191.



IX R=H X R=AcO XI XII

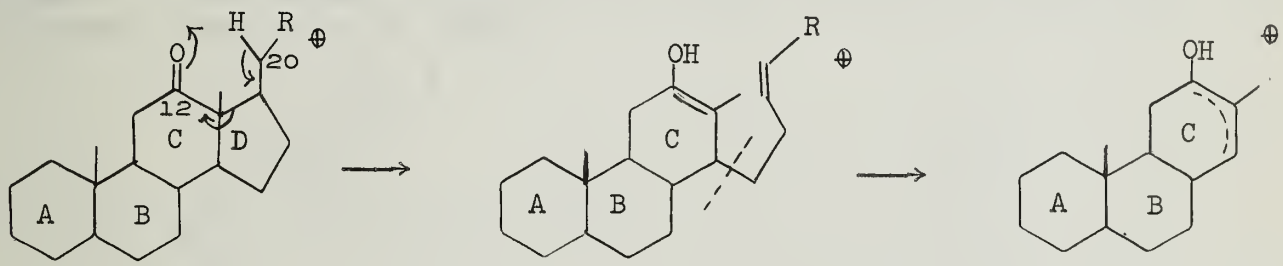
The same rationale can be used to explain the appearance of three characteristic peaks in the mass spectra of 11-keto steroids, e.g. (XIII). Actually the fragmentation (XIII→XIV) is probably a one-step process since a meta-stable peak is observed at m/e 98.5 (10). This mechanism is substantiated by the fact that substitution in ring-A of androstan-11-one (XIII) causes no shift of the base (or largest) peak, but 5α-pregnan-11-one (XV) has its peak shifted from m/e 164 to 192.



XIII R = H
XV R = C_2H_5 XIV

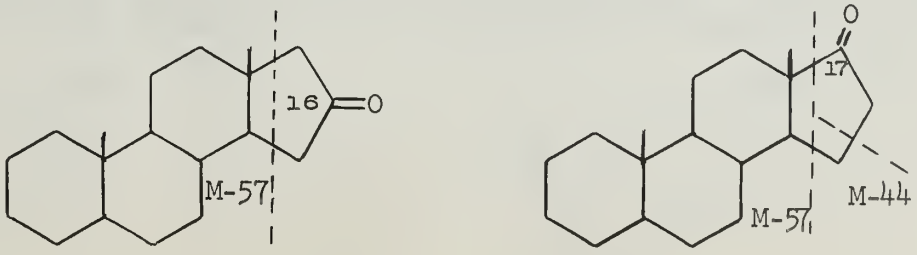
6-Keto steroids show important peaks corresponding to greatly increased ease of loss of carbons 1 to 4 in the A-ring and one additional hydrogen atom (M-55). This was shown by study of compounds substituted in the A-ring, and deuterated at positions 5 and 7 (10).

12-Ketones (XVI) apparently undergo cyclic cleavage only if there is a hydrogen at C-20, i.e. 12-keto-17-substituted steroids show a strong peak at M-C_3H_4R, while other steroids usually show M-C_3H_6R. Deuterated compounds are being studied to elucidate the mechanism of this fragmentation (10).



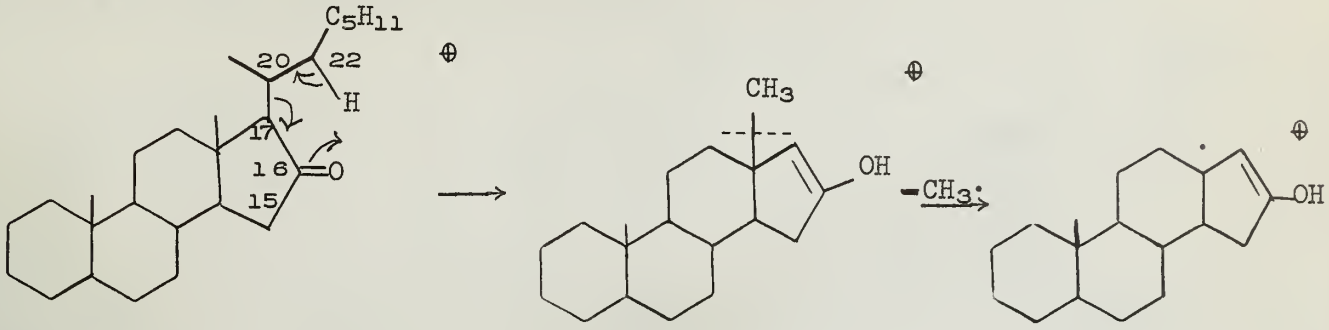
XVI

The mass spectra of steroids with carbonyls in the D- or A-rings do not allow as definite conclusions on the position of the keto group as do the previous examples. Mass spectra of androstan-16-one (XVII) and 17-one (XVIII) are very similar. The principal difference is that the 16-one shows a strong M-57 peak, while the 17-one shows M-44 (not M-43 as in ring-D unsubstituted steroids), and M-56, but only a small peak at M-57.



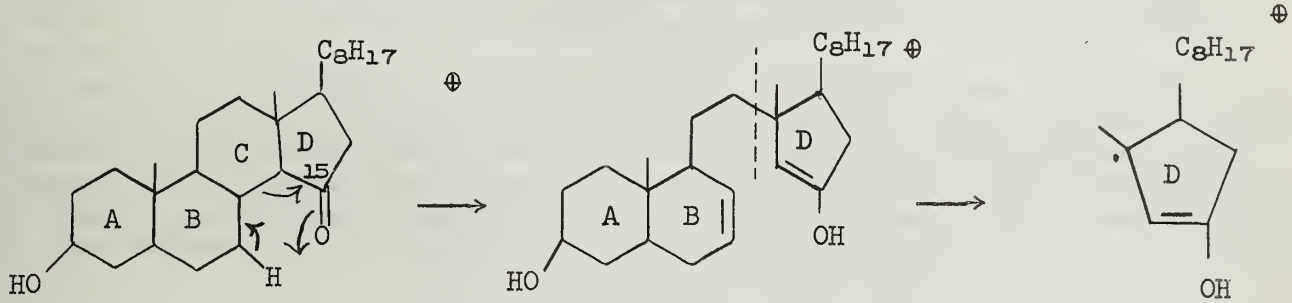
XVII XVIII

This pattern, however, is complicated by the presence of a 3-hydroxyl group (9), or hydrocarbon substitution at C-17. Thus in cholestan-16-one (XIX) cleavage adjacent to the carbonyl is particularly favored (10). That the fragmentation involves the loss of the C-18 methyl rather than C-17 itself was shown by the fact that the 15,15,17-trideutero analog gave a corresponding cation containing all three deuterium atoms (10).



XIX

For 15-ketocholestan-3β-ol (XX) the major peak is due to cyclic cleavage, resulting in the unique m/e 209 fragment (XXI).

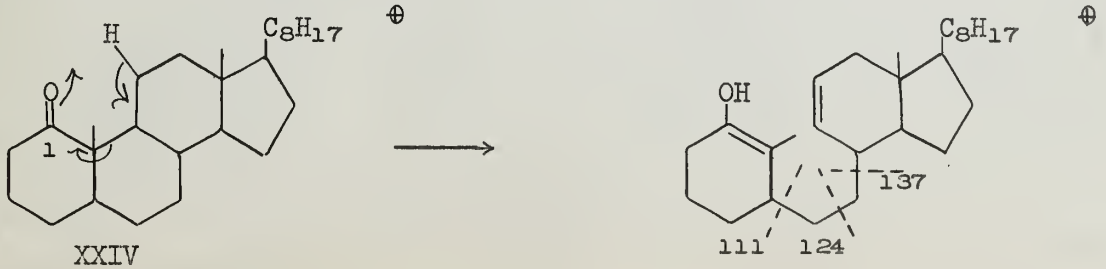


XX XXI

4-Keto steroids show the anticipated mass spectra, giving a single strong peak at m/e 111 by rupture of the 5-6 bond, β to the carbonyl, and the most highly substituted 9-10 bond. In the β isomer, coprostan-4-one (XXII), this peak is much stronger than for the α-isomer, cholestan-4-one (XXIII).

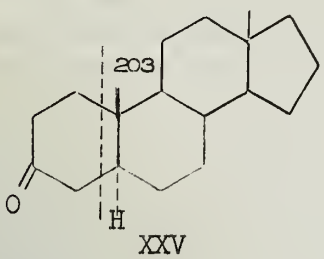
XXII R = ——H
XXIII R = ---H

1-Ketones show cyclic cleavage analogous to 7- and 11-keto steroids with a strong peak at m/e 124, and weaker peaks at 111 and 137 arising as shown (XXIV). Again the indicated cleavage is much favored by β- rather than α-stereochemistry at C-5 (10).

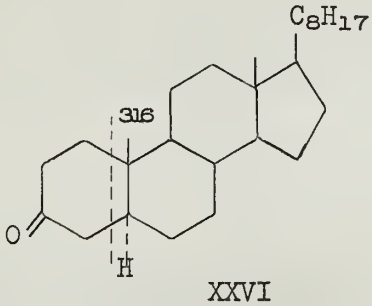


XXIV

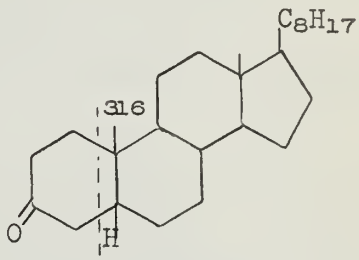
In androstan-3-one (XXV) the principal cleavage involves loss of carbons 1 to 4 and one additional hydrogen, the charge remaining with the tricyclic, non-oxygen-containing system, m/e 203. This fragmentation occurs only where there is no C-17 substituent or the substituent is "such that loss of ring-A is favored for steric reasons." This statement is made because cholestan-3-one (XXVI) shows a very small corresponding peak, while coprostan-3-one (XXVII) shows a fair sized peak.



XXV



XXVI



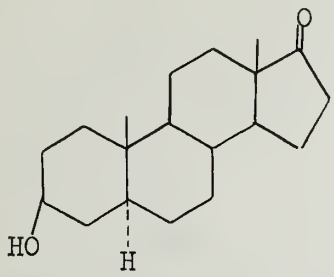
XXVII

Relative Intensity	100	2	30

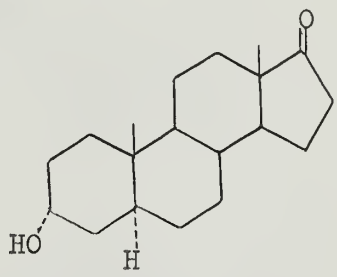
However, one cannot differentiate a 2-ketone from a 3-ketone by mass spectrum, but infrared spectroscopy and optical rotatory dispersion make this readily possible (13). These methods are also more trustworthy than mass spectra for steroids with the keto group in the D-ring (10).

For ring-A or B oxygenated steroids, cleavage of ring-A is invariably favored for the 5β-(rings A/B cis) isomer over the 5α. No such clear cut differences are observed with other keto positions, although certain correlations have been attempted (10).

Biemann (14) has shown that epiandrosterone (XXVIII) with the equatorial hydroxyl gives a greater yield of molecular ions, in terms of total ions formed, than androsterone (XXIX). The differences are even more pronounced for the acetates.



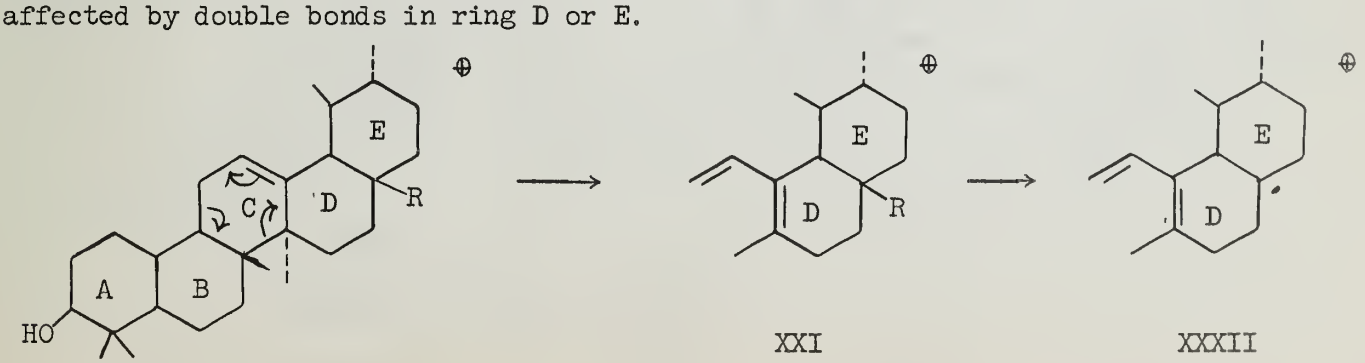
XXVIII



XXIX

UNSATURATED PENTACYCLIC TRITERPENOIDS

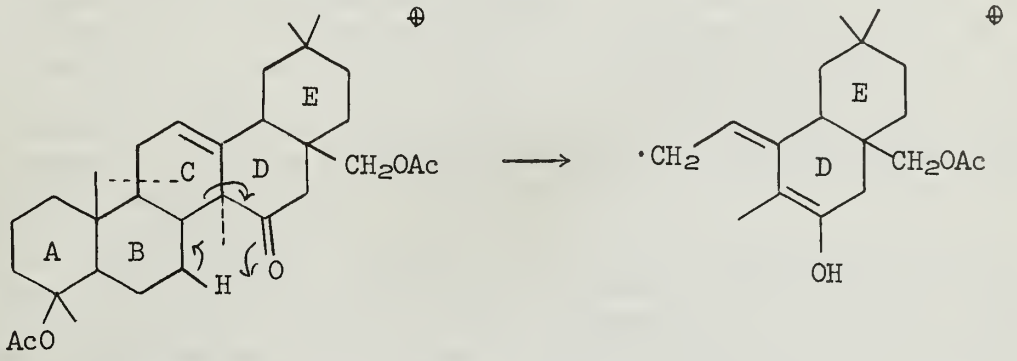
These compounds usually melt at 200-300°, but an all-glass inlet system at 250° was sufficient for their successful mass spectral analysis (15). Below 18 ev an α-amyrin (XXX) gives no mass spectrum since it has no side chain (8), but at 70 ev an informative spectrum is obtained (15). Compounds in the α- or β-amyrin series, which both contain a 12-13 double bond, are observed to undergo the reverse Diels-Alder fragmentation like that pointed out by Biemann (1). This allows assignment from the mass of the ion observed of the nature of the substituents in rings D and E. This fragmentation is not affected by double bonds in ring D or E.



XXX R = CO_2CH_3 XXI XXXII

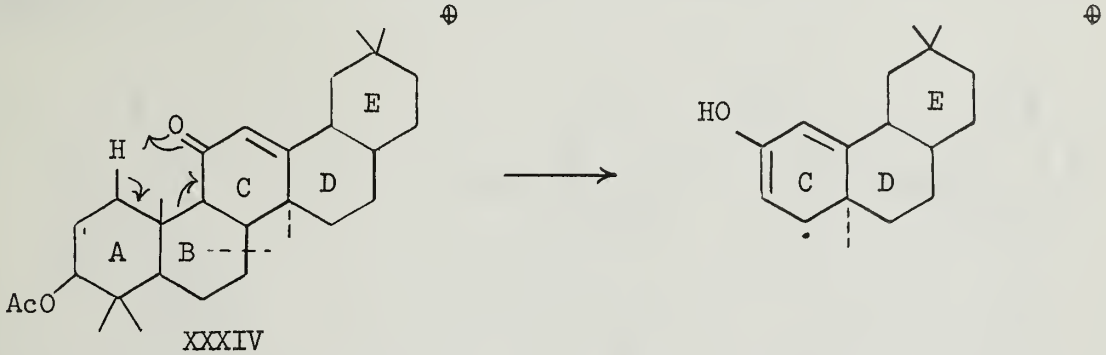
In the example above, methyl ursolate (XXX) has a strong peak at m/e 262 corresponding to (XXXI). A second peak at m/e 203, and a meta-stable peak at 158.5 indicate (XXXI→ XXXII) in one step. The indicated loss of R does not occur as readily if R = CH_3 as R = CO_2CH_3, or CH_2OAc. Unlike the steroidal 3β-acetates, triterpenoid 3β-acetates do not undergo loss of acetic acid, but acetic acid is easily split out if R = CH_2OAc.

15-Keto triterpenes, e.g. 15-oxoerythrodiol diacetate (XXXIII) behave like 15-keto steroids and do not undergo reverse Diels-Alder to give m/e 290, but rather pick up a hydrogen as shown to give a peak at m/e 291.



XXXIII

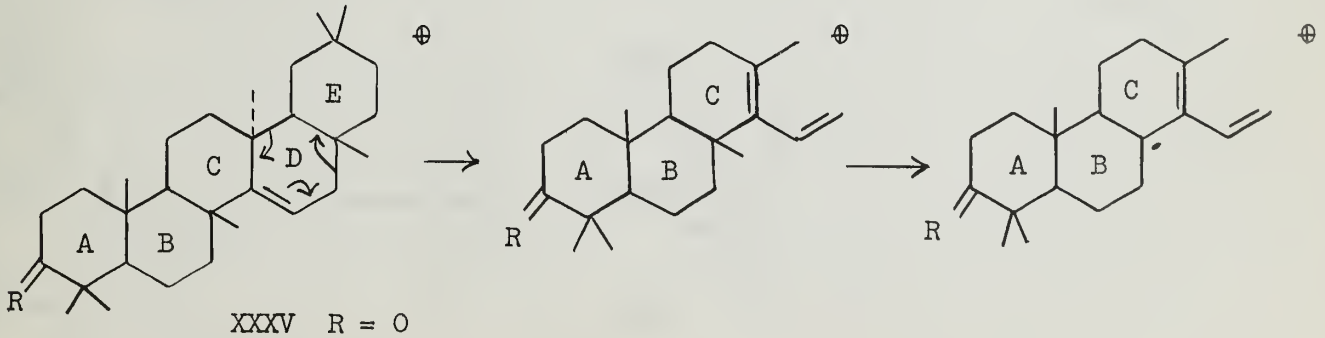
Similarly 11-keto triterpenoids like 18α-11-oxo-β-amyrin acetate (XXXIV) undergo cleavage analogous to that for steroids.



XXXIV

If the carbon-carbon double bond is located at a position other than 12-13, the fragmentation pattern is altered. With the data at hand (15) interpretation of peaks in such spectra does not allow any conclusions as to the position of the double bond in an unknown triterpenoid not of the α- or β-amyrin type, except for the taraxerenes.

In the taraxerene series a retro-Diels-Alder fragmentation is important, e.g. taraxerone (XXXV) shows strong peaks at m/e 300 and 285 resulting from this fragmentation and, in the latter case, from additional loss of a methyl group, most likely by cleavage at the allylically activated C-8 center (15).



XXXV R = O

XXXVI R = OH, H

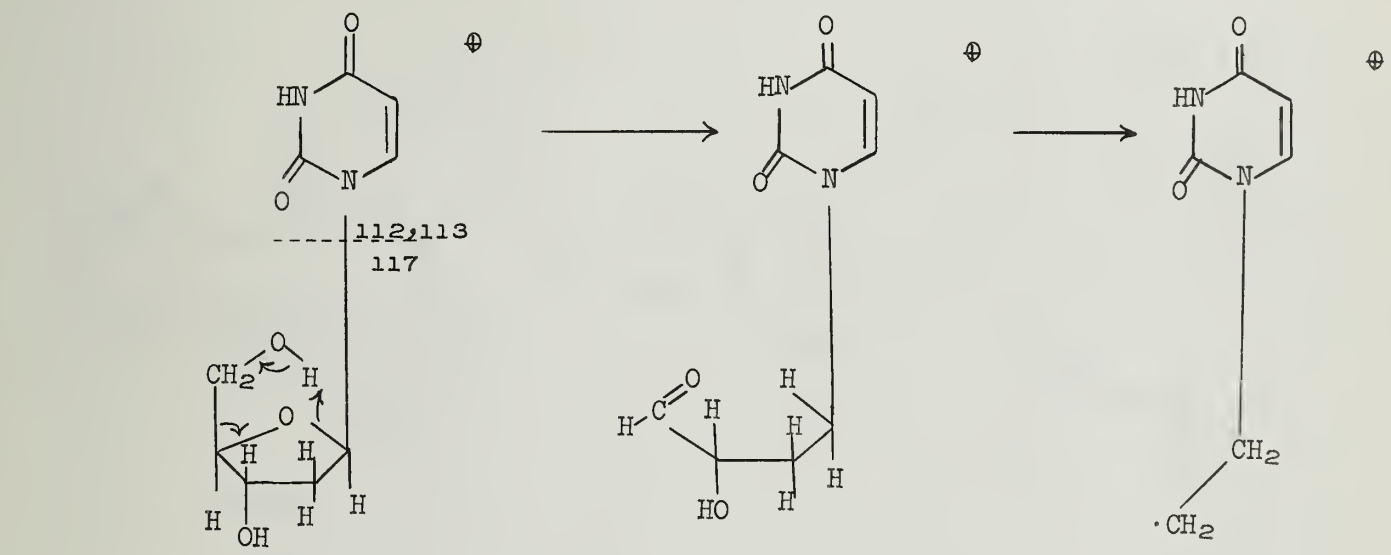
The suggestion that these peaks represent rings A, B and C was confirmed by the observation that peaks of similar intensity appear at 302 and 287 for (XXXVI) (15).

NUCLEOSIDES

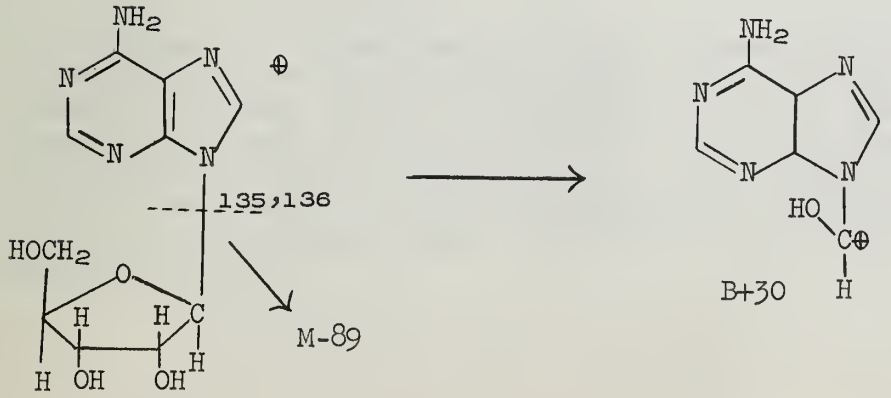
This work is cited principally as a demonstration that useful mass spectra can be obtained from extremely involatile compounds. Biemann (6) has studied the free nucleosides sublimed directly into the ionizing beam rather than by synthesis of more volatile derivatives, as with the amino acids (16) and peptides (17). This saves considerably on both time and material (only 20-50 μg required).

The molecular peaks for all nucleosides examined were very low. The pyrimidine or purine residue gives rise to a prominent peak at the molecular weight of the base (B + 1) or that plus one (B + 2) resulting from the rearrangement of one or two hydrogens, from the hydroxyls, in the fragmentation. The double rearrangement is more facilitated for the ribosides than for the 2'-deoxyribosides, and is more pronounced in pyrimidine derivatives than purines. Thus the relative intensities of the B+1 and B+2 peaks permit differentiation between pentosides and 2'-deoxypentosides, while the mass of these peaks indicates the nature of the base (6).

The mass of the sugar fragment is found at m/e 117 in deoxypentosides and m/e 133 in pentosides. The intensity of this peak is much reduced if the base is a purine rather than a pyrimidine, since a purine, having a higher electron density, competes with the sugar moiety more effectively for the positive charge than can the pyrimidine. The ribose fragment is generally less abundant than the 2'-deoxyribose fragment in a comparable compound. These combine to give deoxyuridine (XXXVII) a base peak m/e 117 corresponding to the sugar moiety, and a negligible sugar fragment peak at m/e 133 for adenosine (XXXVIII).



XXXVII



XXXVIII

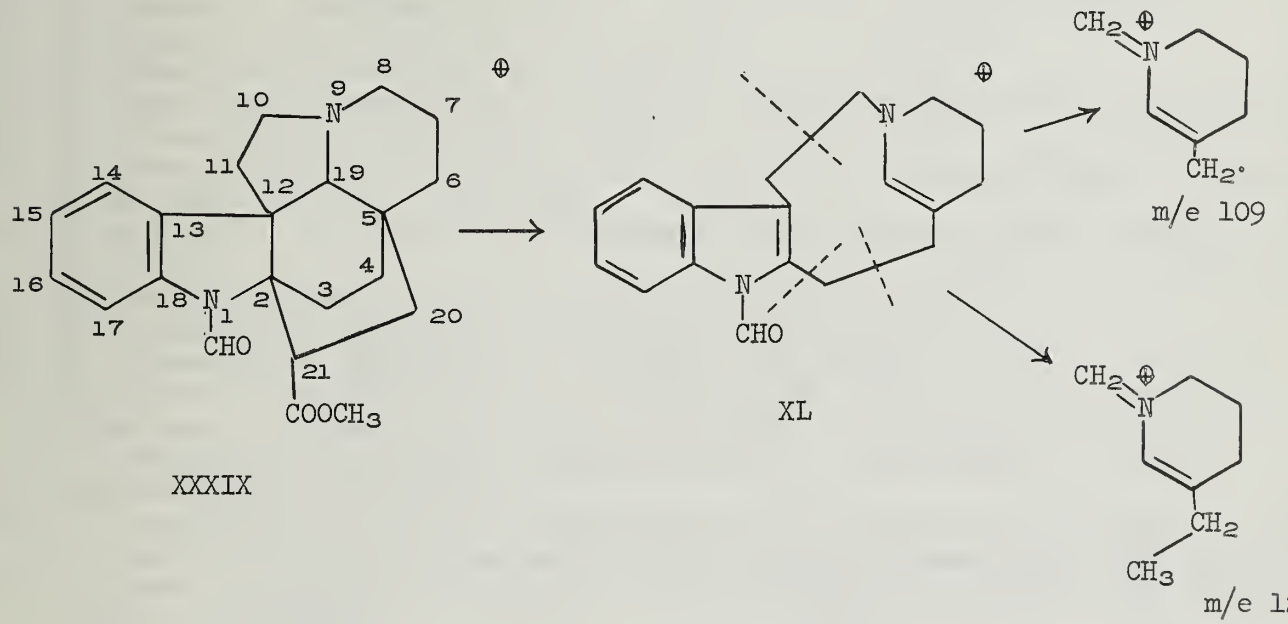
Peaks are also observed at M-18 corresponding to loss of water, and at M-89 and B+30 probably occuring as shown above. The suggestion that the process shown may be the cause of the M-89 peak was substantiated by the failure of a 5'-deoxynucleoside to show this peak (6). The B+30 peak probably results from abstraction of hydrogen from the 2'-hydroxyl since 2'-deoxy compounds do not show this peak.

ALKALOIDS

The recent work by Biemann, Djerassi, and others on the structures of dihydroindole alkaloids (19-21, 25-29) illustrates the use of mass spectrometric principles for the determination of unknown structures in natural products. An example is the work of Djerassi and coworkers on refractine XXXIX (21), which parallels the independent degradative studies by Schmid, Battersby and their coworkers (22, 23) on pleiocarpin and kopsinin.

NMR and chemical tests showed that the compound was an N-formyl-7-methoxydihydroindole with an additional carbomethoxy function. It contained no olefinic double bonds, C-methyl, or hydrogen at C-2. Elemental analysis was compatible with $C_{22}H_{28}N_2O_4$ or $C_{23}H_{28}N_2O_3$, but the mass spectrum M=396) corroborated the latter. Reduction of the carbomethoxy group, followed by tosylation, pyrolysis, and ozonization gave a ketone whose spectra indicated that the carbomethoxy in refractine was attached to a strained 6-member ring.

The mass spectrum showed a strong peak at M-28 which is characteristic of the aspidospermine skeleton (19), and is ascribed to the expulsion of the unsubstituted bridge carbons 3-4 as ethylene, to give in this case XL. The driving force for this is aromatization of the dihydroindole moiety and relief of the strain imposed by the highly fused system.



Molecule ion XL may undergo further fragmentation to give the highly stabilized $CH_2=N\overset{\oplus}{<}$ system and the predicted peaks at 109 involving cleavage at 20-21 and at 124 involving cleavage at 2-21 with hydrogen transfer. The appearance of the 109 and 124 peaks in the spectra of compounds where the carbomethoxy has been modified indicates that this function is not in that area of the molecule, and since it cannot be on C-3 or 4 which are lost in the initial fragmentation it must be at C-11 or 21. Djerassi put it at C-21 on a biogenetic basis (24), and the other work (22, 23) proved that this assignment was correct.

SUMMARY

The applicability of mass spectrometry to the identification of organic compounds is rapidly increasing. These gas phase reactions frequently involve transformations easily understandable in terms of the mechanisms of familiar solution reactions. The method is complimentary with other physical and chemical methods in organic chemistry.

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THE CHEMISTRY OF AZENES

Reported by R. L. Buckson August 6, 1962

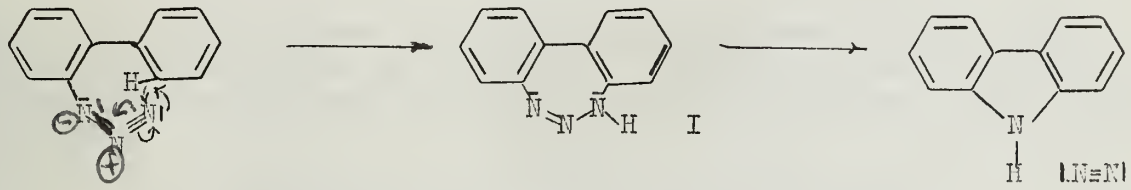
INTRODUCTION

This seminar is concerned with the chemistry and mechanism of the decomposition of organic azides. The early investigations of these reactions have been reviewed (1,2,3) and the results of more recent investigations will be discussed.

POSSIBLE ROUTES OF ORGANIC AZIDE DECOMPOSITION

The decomposition of organic azides may follow several plausible paths which are given below using o-azidobiphenyl as the example:

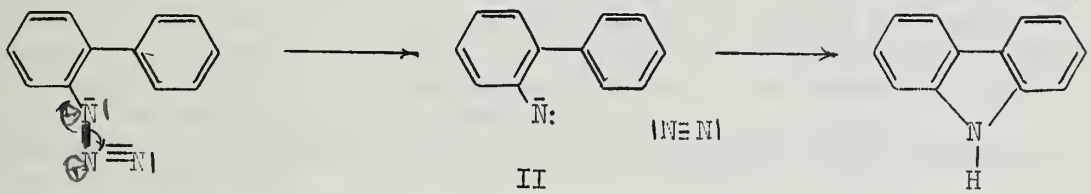
A. Decomposition via a triazoline intermediate I.



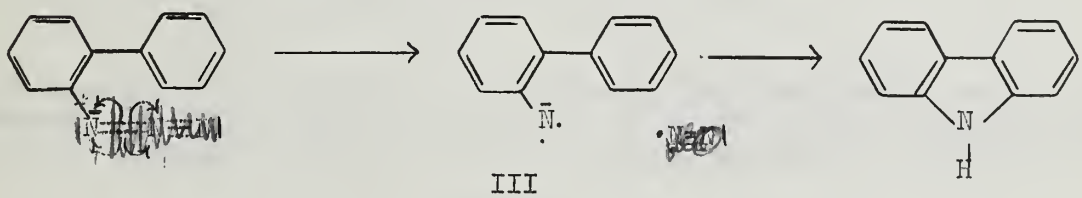
B. Decomposition via a concerted loss of molecular nitrogen.

C Decomposition via an azene intermediate.

1. The formation of a singlet azene II



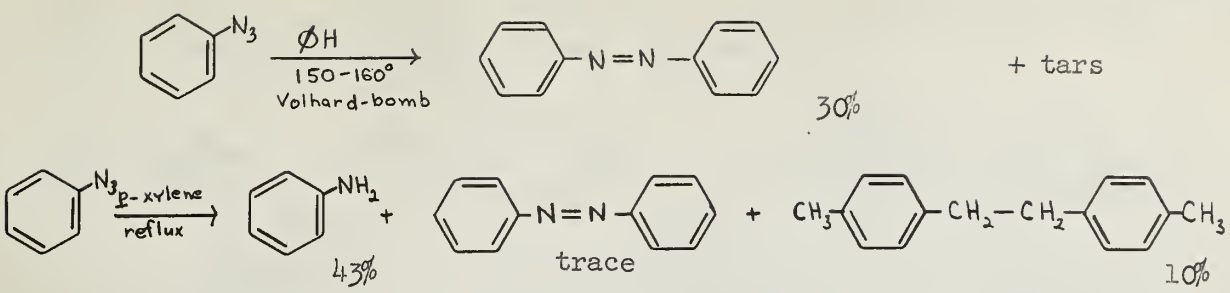
2. The formation of a triplet azene III.



The terms univalent nitrogen, imine radical, imido radical, nitrene and azene have been used to describe a neutral, electron-deficient species. In this seminar the term "azene" will consistently be employed. The terms "singlet azene" and "triplet azene" will describe the species with paired and unpaired electrons, respectively, as illustrated in C-1. and C-2.

THE DECOMPOSTION OF PHENYL AZIDES

In 1924 Bertho reported the decomposition of phenyl azide in benzene and p-xylene (4).



These reactions were explained (4) by an initial loss of nitrogen to form a triplet azene intermediate, which could couple to form azobenzene or abstract hydrogen to form amine. The p,p'-ditolylethane was formed from two radicals produced by hydrogen abstraction.

The rate of decomposition of phenyl azide determined from the pressure increase of evolved nitrogen was reported by Russell (5). The reaction was first order to completion and 0.95 mole of nitrogen was evolved per mole of azide present. Table I summarizes the data obtained.

TABLE I

First order rate constants* for phenyl azide

Phenyl azide, M x 10^2	k x 10^6, $sec.^{-1}$ [a]	k x 10^6, $sec.^{-1}$ [b]
36	6.3	6.5
14.4	6.5	6.6
7.2	6.7	6.6
2.88	7.3	7.0

*Obtained from rate x 10^6, mole /l./sec reported at 130°

[a] In tetralin [b] In nitrobenzene

These data indicate that the rate determining step is not solvent dependent. If the loss of nitrogen were concerted with hydrogen abstraction from the solvent, a solvent dependence would be expected. Russell (5) claimed the rate data demonstrated that the formation of azobenzene is not a bimolecular process. The absence of product analysis, however, limits the validity of this conclusion.

The decomposition of phenyl azide in aniline resulted in the expansion of the benzene ring to form an azepine (6).

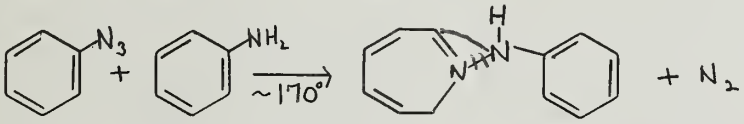


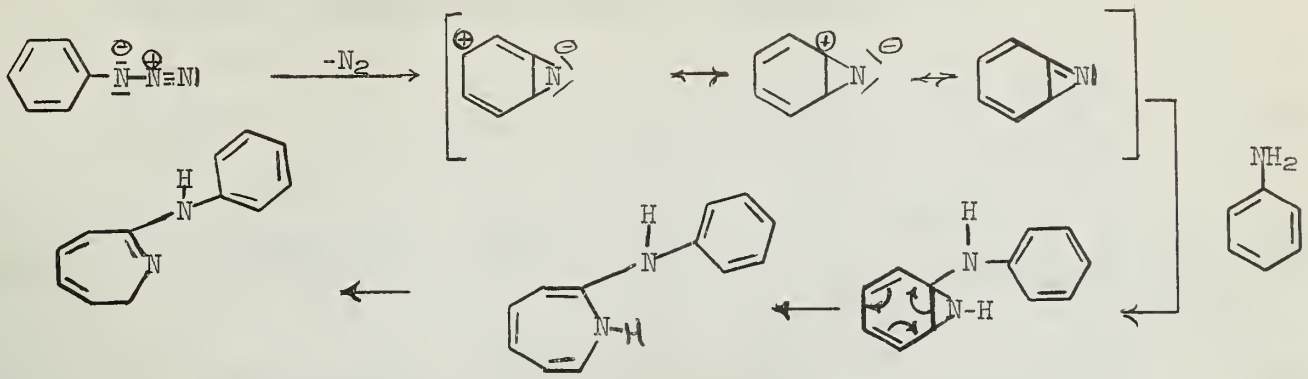
Table II demonstrates the dependence of the yield of anilino azepine on the amount of aniline present. p-Azidotoluene in aniline (1: 42 molar ratio) decomposed under the same conditions to give an 18% yield of the corresponding anilino azepine (6).

TABLE II

Percent yields of anilino azepine

Molar ratio phenyl azide: aniline	% Yields
1: 1.3	7
1: 50	19
1: 80	30
1: 100	41
1: 200	54

The decomposition of phenyl azide (1-C^{14}) under the same conditions demonstrated that the 1-position was ultimately bound to the aniline and Huisgen and Appl proposed the following mechanism to explain these reactions (7):



It is not clear whether the loss of nitrogen is assisted by the o-position of the benzene ring or nitrogen is evolved unassisted to form an azene, which then interacts with the o-position to expand the ring.

The rates of decomposition of three m-substituted phenyl azides have been measured (8). Appl and Huisgen reasoned that if the o-position of the benzene ring was involved in the loss of nitrogen, the rate of evolution of nitrogen would show substituent effects. Table III contains the first order rate constants based on the evolution of nitrogen from the decomposition of m-substituted phenyl azides in aniline (8).

TABLE III

First order rate constants for m-substituted phenyl azides

m-Substituent	k x 10^4, sec^{-1}, 174.1°
-H	8.47
$-CH_3$	8.88
$-OCH_3$	8.84
$-NO_2$	6.80

The initial azide concentration range was 0.7-0.9 M and the reactions were followed to 85% conversion. From this kinetic data the authors concluded that the absence of substituent effects constituted evidence that the nitrogen evolution was not assisted by the o-position of the benzene ring. However, the products of these reactions were evidently not analyzed An estimation of the molar ratio of azide to aniline when compared to Table II suggests the yield of the substituted anilino azepine would be about 45%. It is quite possible that the rates observed are sums of the rates of more than one reaction, in which case the substituent effects might be small.

The decomposition of phenyl azide in the gas phase produced a 72% yield of azobenzene, which might suggest an interaction of aniline prior to or during the loss of nitrogen to initiate azepine formation (9). Finally, an azene intermediate can be interposed into the proposed mechanism without altering it. The kinetic data is unable to exclude any of these possibilities.

Several substituted phenyl azides have been decomposed in the gas phase at 350-360° in a nitrogen stream at 0.1-0.3 mm (9). These reactions with the percent yields of the isolated products are listed in Table IV.

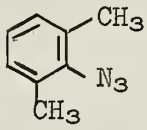
These reactions will be discussed in two groups; Reactions 1-3 and Reactions 4-6.

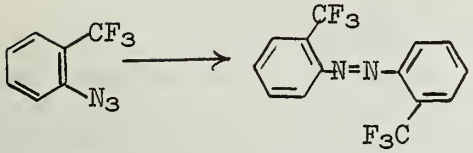
Reaction 1 can be explained by the initial formation of a triplet azene intermediate which abstracts hydrogen from a methyl group forming diradical IV, which then polymerizes.

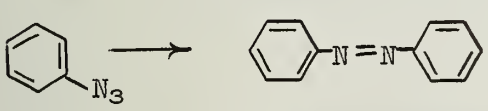
Reactions 2 and 3 are rationalized by the coupling of two triplet azene intermediates (9).

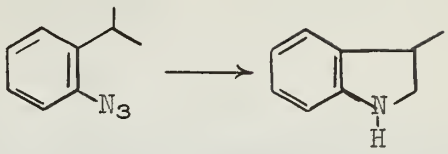
TABLE IV

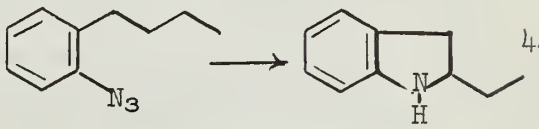
Gas phase decompositions of substituted phenyl azides.

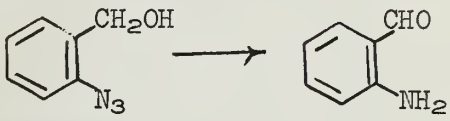
1.  → polymer

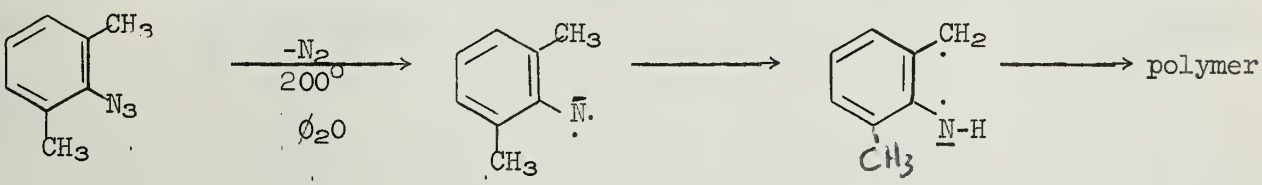
2.  80%

3  72%

4.  55%

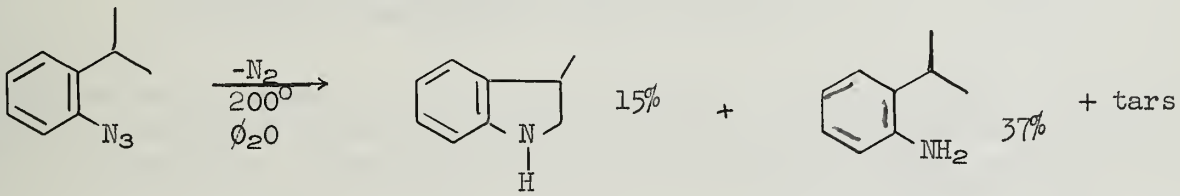
5.  44%

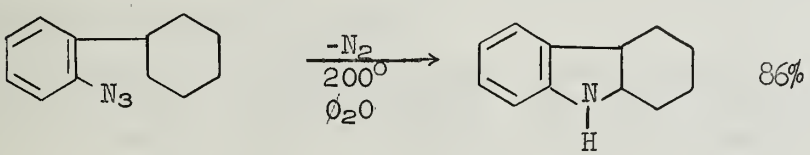
6.  65%



IV

Reactions 4-6 demonstrate the insertion of nitrogen into a C-H bond of a saturated carbon atom (9). Insertion reactions have been reported to occur also in the decomposition of phenyl azides in solution (10). o-Azidocumene and o-azidophenylcyclohexane were decomposed in diphenyl ether to give the following products:

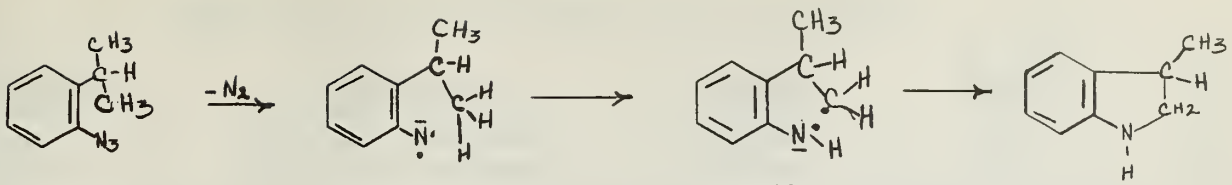




The insertion of nitrogen into the C-H bond can be explained by the initial loss of nitrogen to form an azene intermediate. A singlet azene V could insert in a concerted reaction and form amine by hydride and proton abstraction.

V

A triplet azene could insert by hydrogen abstraction to form the diradical VI which after reversal of electron spin could couple or abstract more hydrogen to form amine. A triazoline intermediate might explain the path to cyclic products.



VI

Very recently kinetic data on the decomposition of various substituted phenyl azides were reported by Smith and Hall (11). Table V summarizes the data obtained from these decompositions in decalin at 141.3°. In all cases drifts from strictly first order kinetics appeared. The drifts were explained by possible interaction of the azido group with unsaturation in the solvent resulting from hydrogen abstraction, while the evolution of excess nitrogen could not be explained (11).

TABLE V

Summarized data for the decomposition of substituted phenyl azides in decalin at 141.3°

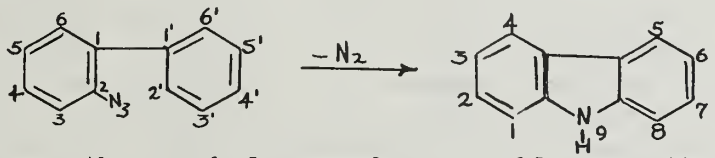
Phenyl azide	Moles nitrogen per mole azide	k x 10^5, sec.$^{-1}$ [a]	phenyl amine % yield
Unsubstituted	1.32	2.8	44
m-Methoxy	1.04	3.3	97
m-Nitro	1.30	2.8	1
m-Methyl	----	1.8	--
p-Methoxy	----	14	--
p-Nitro	1.30[b]	6.5	Small
p-Bromo	----	10	78
2,4-Dichloro	1.10	25	41

[a] Obtained from reported k x 10^3, min.$^{-1}$.
[b] In bis-(2-ethoxyethyl) ether at 163.6°.

Although no accurate estimate of substituent effects can be made from this data, the rate constants for the m-substituted phenyl azides appears to be in agreement with the findings of Appl and Huisgen (8) From the variation in the yield of amine reported it appears that the substituents have a decided effect on the products ultimately formed.

THE DECOMPOSTION BIPHENYL AZIDES

The synthesis of a series of substituted carbazoles in good yields has been reported employing the thermal and photochemical decomposition of the corresponding substituted biphenylyl azides (12,13). The following reaction describes these syntheses:



Carbazoles with methyl-, methoxy-, hydroxy-, bromo-, chloro-, nitro-and benzo- groups on either ring were obtained in 60-100% yields from thermal decomposition (12,13) and 23-77% yields from photodecomposition (12). Obviously the favored path of the thermal decomposition of these biphenylyl azides is cyclization rather than amine formation. The yields of substituted carbazoles presented in Table VI indicates that this cyclization can be selective. Also, the decomposition of biphenylyl azides in which either the 2'- or 6'-position was substituted resulted in carbazole formation at the unsubstituted site (12,13).

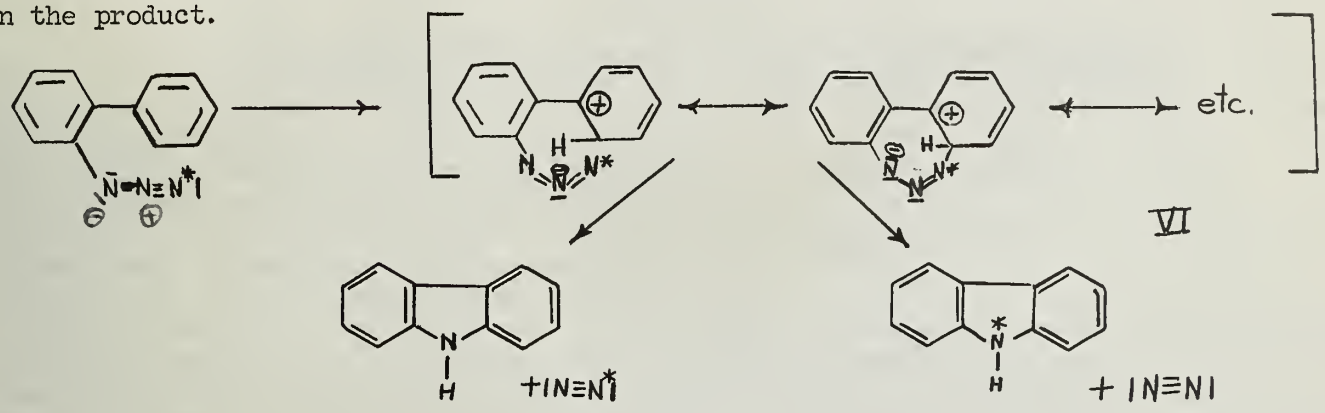
The decomposition of 2-biphenylyl azide-3'-N^{15} prepared from 2-biphenylylhydrazine and 2% N^{15} enriched potassium nitrite resulted in 101 ± 3% of the excess N^{15} occurring in the evolved nitrogen (13). There is little doubt that the nitrogen atom appearing in the carbazole is the carbon-bound nitrogen of the azido group. It apparently is not the

TABLE VI

Decomposition of substituted 2-azido biphenyls

2-Azido biphenyl	Conditions	Carbazole	% yield	Ref.
5'-Chloro	180-200°, Kerosene	3-Chloro	60.5	(13)
5-Bromo	170-190°, Kerosene	3-Bromo	83	(12)
5-Nitro	170-190°, Kerosene	3-Nitro	88	(12)

terminal nitrogen and it is improbable that it is the central nitrogen. Smith et. al. (13) further claim on the basis of this isotope study that a triazoline VI is an unlikely intermediate for this reaction, since at least some of the labeled nitrogen would appear in the product.



First order kinetics have been observed for nitrogen evolution in the thermal decomposition of substituted 2-azidobiphenyls (11). Nitrogen evolution was quantitative and the yields of carbazoles were usually quantitative and never below 75%. Table VII summarizes the first order rate constants for these decompositions in decalin.

TABLE VII

Rate constants for the decomposition of substituted 2-azidobiphenyls

2-azido-biphenyl	k x 10^4, sec. $^{-1}$ [a]		
	148°	155.3°	163.6°
Unsubstituted	1.27	2.42	5.02
5-Methoxy	10.5	17.8	32.4
5-Methyl	2.52	4.55	9.00
5-Bromo	2.69	4.92	9.30
5-Nitro	2.19	4.17	8.75
4-Methoxy	1.39	2.63	5.53
4-Methyl	1.30	2.53	5.27
4-Bromo	1.73	3.74	7.00
4-Nitro	1.07	2.14	4.67

[a] Obtained from reported k x 10^3, min. $^{-1}$.

All p-substituents moderately increase the rate, while the effect of m-substitutents appears to be negligible. Smith and Hall (11) suggest the rate determining step for the decomposition of 2-azidobiphenyls is not unlike that of simple phenyl azides, i.e. this step is not concerned with the various paths taken in the reaction. The rate determining step in this interpretation would be the formation of an azene intermediate.

Table VIII lists the enthalpies and entropies of activation for the decomposition of the 4- and 5-substituted 2- azidobiphenyls under consideration (11). Large differences appear in the enthalpies and entropies of activation for the 2-azidobiphenyls with 5-substituents (para to the azido group), while the differences in these values for 2-azidobiphenyls with 4-substituents (meta to the azido group) are less pronounced. The entropies and enthalpies of activation are approximately linear and give rise to an isokinetic temperature of 250° (11). The order of σ - constants is qualitatively the same as that of $\Delta\sigma(\sigma p-\sigma_m)$.

The electron-donating character of the azido group has been demonstrated and this character is described by VII (14).

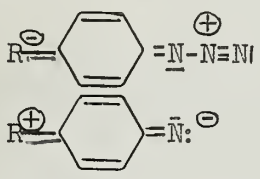
TABLE VIII

Enthalpies and entropies of activation for the decomposition of substituted 2-azidobiphenyls.

2-Azidobiphenyl	$\Delta H^{\ddagger}$, kcal./mole[a]	$\Delta S^{\ddagger}$, cal./deg. mole, 156°[b]
Unsubstituted	31.4 ± 0.5	- 2.5 ± 1.1
5-Methoxy	25.5 ± .2	-12.3 ± 0.4
5-Methyl	29.0 ± .4	- 6.8 ± 1.0
5-Bromo	28.2 ± .8	- 8.6 ± 1.9
5-Nitro	41.6 ± .3	- 1.0 ± 0.7
4-Methoxy	31.7 ± .2	- 2.7 ± .4
4-Methyl	31.8 ± .2	- 1.3 ± .6
4-Bromo	31.8 ± .7	- 0.9 ± 1.5
4-Nitro	33.6 ± 1.1	2.4 ± 2.6

[a] From plot of log k vs. 1/T. [b] From Eyring equation

Smith and Hall (11) suggest the character of the developing azene intermediate (shown in the singlet configuration) is represented by VIII. Under these restrictions a p-substituent which would stabilize the starting material and destabilize the developing azene intermediate, would result in an increase in the enthalpy of activation. This is apparently the case for the 5-nitro group. The opposite effect would be expected from an electron-donating group and this is observed for the 5-methoxy group. If the azene intermediate were in the triplet state, the effects might be less pronounced, but the argument would still apply.

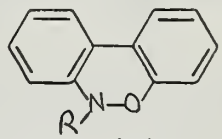


VII

VIII

The thermal decomposition of 2-azido-2'-hydroxybiphenyl, its anion and 2-azido-2',4',6'-trimethoxybiphenyl resulted in the formation of small yields of the corresponding amines and dark tars (10). Although no products other than amines could be identified, the author suggests that compounds such as IX may be formed, but decompose under the reaction conditions. This possibility was not pursued.

The insertion of nitrogen into a C-H bond has been observed in the thermal decomposition of 2-azido-2',4',6'-trimethylbiphenyl (15) and 2-azido-2'-methyl-6'-methoxybiphenyl (10) to form the corresponding substituted phenanthridines. These reactions can be rationalized by an azene intermediate and statements made in connection with the insertion reactions observed for phenyl azides are applicable to these reactions.



IX

THE DECOMPOSITION OF BENZENESULFONYL AZIDES--The decomposition of various substituted benzenesulfonyl azides in aromatic substrates resulting in benzenesulfonamidation (16,17) have been adequately reviewed (3).

More recently competitive experiments were employed to determine the relative rate of benzenesulfonamidation by the decomposition of benzenesulfonyl azide in various aromatic substrates with benzene as the reference solvent(18). Table IX summarizes the results of these experiments.

TABLE IX

Summary of results of benzenesulfonamidation

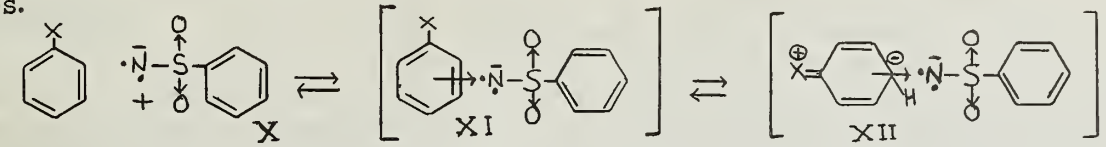
Substrate	Ave. % yield		Substitution Products,[a] mole %				Rate Factors			
	Total	$PhSO_2NH_2$	o-	m-	p-	$PhSO_2$-NHPh		Total	Partial o-	Partial m-	Partial p-
Benzene	30.2	18	--	--	--	100	Benzene	1.00	1.0	1.0	1.0
Toluene	25.8	2	30	0	20	50	Toluene	1.00	1.8	0.03	2.3
Anisole	38.7	3	32	0	17	51	Anisole	0.96	2.0	.06	1.6
Phenol	33.3	15	22	1	21	56	Phenol	.80	1.2	.05	2.3
Chlorobenzene	32.5	4	19	1	21	59	Chloro-benzene	.69	0.95	.04	2.2
Bromobenzene	29.4	15	17	3	21	59	Bromo-benzene	.69	1.0	.10	1.9
Methyl Benzoate	60.0	11	12	17	1	70	Methyl Benzoate	.38	0.49	.62	0.07

[a] From competitive experiments.

The total rate factors were calculated from the average ratios of substituted benzenesulfonanilides to benzenesulfonalide; the partial rate factors were obtained from the total rate factors and the average mole fractions of each isomer obtained in non-competitive experiments (18).

The orientation observed is that expected from an ionic, electrophilic substitution, while the rate factors are similar to those expected from a reaction involving radicals. The effects of substitutions of the substrate on the rate of benzenesulfonamidation are relatively slight. These facts are rationalized (18) by proposing that the first and rate determining step is the loss of nitrogen to give a triplet azene intermediate X which reacts with the first molecule it encounters, thus showing little selectivity.

The orientation observed is then explained by assuming the transition state is very similar to a π-complex of the triplet azene and aromatic substrate XI. The existence of this π-complex must be restricted. It is long-lived enough to allow the strongly electronegative sulfonyl group to shift the electron density resulting in a π-complex intermediate XII with orientation at the position of highest electron density (18). The π-complex must also be short-lived enough to allow substitution of the various aromatic substrates with similar rates.



X XI XII

Benzenesulfonyl azide decomposition has demonstrated a catalytic effect in initiating vinyl polymerization (17); the effect was inhibited by hydroquinone and p-benzoquinone (19). The thermal decomposition of p-toluenesulfonyl azide in the presence of styrene and methyl methacrylate acts as a weak catalyst for polymerization (20). These facts seem to support the proposed triplet azene intermediate.

THE DECOMPOSITION OF SEVERAL OTHER ORGANIC AZIDES -- An azene intermediate has been proposed for the Curtius rearrangement of benzazide (21). The volume change of activation recently evaluated for the rearrangement of benzazide indicates the predominance of bond-breaking in the transition state(22). Table X summarizes the kinetic data which Brower employed to calculate the volume of change of activation from the equation $RT(\delta \ln k/\delta P)_T = -\Delta V^*$ where k is the reaction rate constant, P is pressure and ΔV^* is the change of molar volume resulting from the transformation of one mole of reactant into activated complex(22). From a plot of ln k vs. P the value of the derivative at zero pressure was estimated.

TABLE X

Summary of kinetic data for benzazide rearrangement

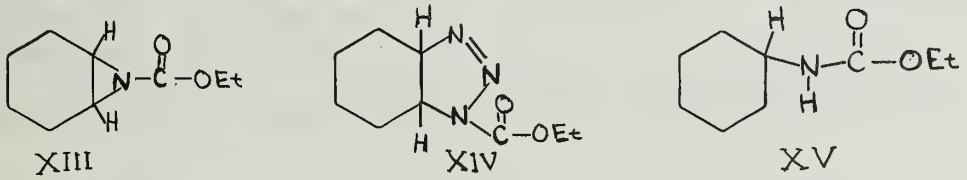
In ligroin, 63.9°							In 50% ethanol-water, 50.3°	
P (atm.)	68	340	610	880	1220	1360	68	1440
k x 10^4 (sec.$^{-1}$)[a]	8.5	8.2	8.0	7.5	6.8	6.8	34.7	32.3

[a] Obtained from k (hr.$^{-1}$) reported.

The volume changes of activation evaluated from the data in Table X are +2 ml. in ethanol-water and +5 ml. in ligroin; the experimental error in these measurements is approximately ± 1 ml. These values may be compared to those arising from the decomposition of aromatic diazonium compounds, $\Delta V^* = +10$ ml. (23), and the values evaluated for reactions in which bond formation occurs in the transition state, $\Delta V^* \geq -10$ ml. (22). Brower suggested that a mechanism involving an azene intermediate is consistent with the observed volume change of activation.

The photodecomposition of ethyl azidoformate in cyclohexene resulted in a 50% yield of 7-carboethoxy-7-azabicyclo (4,1,0) heptane XIII(24). The disappearance of azide and the evolution of nitrogen were found to be simultaneous and nitrogen evolution ceased when irradiation was interrupted. The authors claimed that on the basis of these findings a triazoline intermediate XIV could be excluded... However, since the stability of XIV under the reaction conditions was not established, XIV could still be a short-lived intermediate, especially since the formation of triazolines from azides is not uncommon.(2).

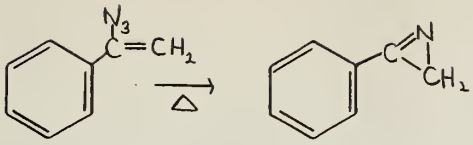
An insertion of nitrogen into a C-H bond was observed when the photodecomposition of ethyl azidoformate in cyclohexane resulted in a 50% yield of N-cyclohexyl-urethane XV (24).

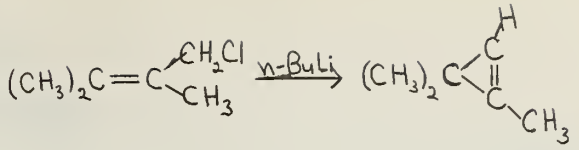


XIII XIV XV

Both decompositions of the ethyl azidoformate can be explained by an azene intermediate, singlet or triplet.

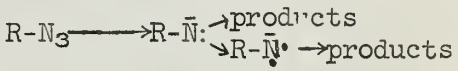
COMPARISON BETWEEN THE CHEMISTRY OF AZENES AND CARBENES--It is of interest to compare the chemistry of azenes and carbenes. Both species have been reported to insert into a C-H bond of a saturated carbon atom (9,10,14,15,24,25). Carbene (25) and azene (24) have both given products resulting from the addition to the carbon-carbon double bond of cyclohexene. Finally, the formation of an azacyclopropene from the decomposition of α-azidostyrene(26) appears to have its counterpart in carbene chemistry, since cyclopropenes are thought to be formed from an alkenyl carbene (27).





CONCLUSION--The behavior of the organic azide decompositions presented in this seminar is as follows: (1) First order kinetics are generally observed. (2) The rate constants appear to be insensitive to substituents. (3) There is little discrimination of the reaction rates among various substrates, i.e., the rate determining step appears to be unconcerned with the products ultimately isolated. (4) A comparison to carbene chemistry can be made.

It appears that the decomposition of organic azides may be explained by the following mechanism. The loss of nitrogen to form a singlet azene intermediate is the first and rate determining step. This singlet azene intermediate could then either react to form products or transform to the lower energy triplet state, which could also react to form products.



These reactions have been applied to synthetic organic chemistry, not only in the preparation of the various substituted carbazoles discussed in this seminar, but also in the preparation of steroids (28) and alkaloids (29).

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AUTOXIDATION

Reported by J. P. Petrovich August 8, 1962

INTRODUCTION

The autoxidation of organic compounds has been investigated extensively (1, 2). It has been known for sometime that most organic compounds undergo oxidation by oxygen from the air yielding a variety of products. Some of the examples which have been studied are aldehydes (3), ketones, olefins (2, 4) and hydrocarbons. The mechanism of these reactions has remained obscure until recently. This seminar is concerned with the mechanism of autoxidation.

Hydrocarbons react with elemental oxygen to give hydroperoxides as the major product along with peroxides, ketones, aldehydes and alcohols as minor products (5, 6). The reaction has the characteristics of a radical chain process (7). It can be initiated by common radical initiators such as ultraviolet light (3), certain dyes activated by light (8), peroxides (1,6), azo compounds (9) and elemental oxygen which is itself a diradical in the ground state. The reaction has a characteristic induction period in the absence of radical initiators (5). It is autocatalytic due to the thermal (10) or radical (11) catalyzed decomposition of the hydroperoxide product. The reaction is inhibited by normal radical scavangers such as mercaptans (9), phenols (12) and the stable free radical α,α-diphenyl-β-picrylhydrazyl (9).

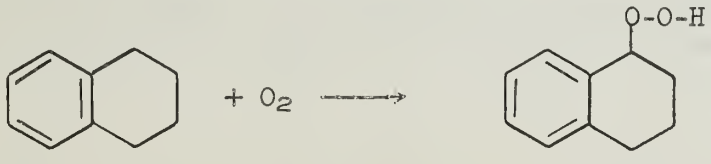
A general reaction scheme for the autoxidation may be written as follows:

Initiation		$P_2 \rightarrow 2P\cdot$
		$RH + P\cdot \rightarrow PH + R\cdot$
Propagation		$R\cdot + O_2 \rightarrow RO_2\cdot$
		$RO_2\cdot + RH \rightarrow RO_2H + R\cdot$
Termination	1)	$2R\cdot \rightarrow RR$
	2)	$R\cdot + RO_2\cdot \rightarrow RO_2R$
	3)	$2RO_2\cdot \rightarrow$ Inactive Products

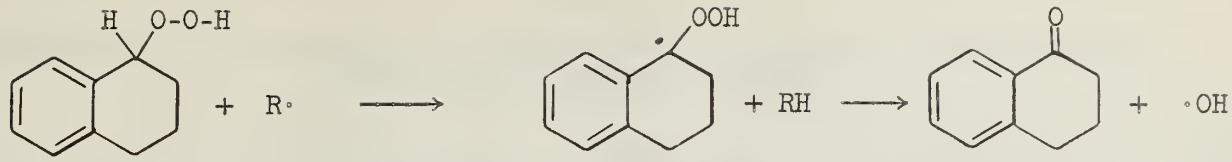
The initiation and propagation steps have been established (13). The peroxy radical intermediate has been trapped using substituted phenols in the autoxidation of tetralin and cumene (14). However, there has been considerable controversy as to the nature of the termination step. The mechanism of this step depends on the type of radical involved, i.e., whether the peroxy radicals involved are primary, secondary or tertiary. One common feature of autoxidation reactions is that in the presence of over 40 mm. of oxygen pressure the termination reaction is independent of oxygen pressure and therefore involves two peroxy radicals (3).

AUTOXIDATION OF TETRALIN

The autoxidation of tetralin was first observed by Medvepov and Podyapolskaya (9). The major product obtained from the reaction was tetralin hydroperoxide.



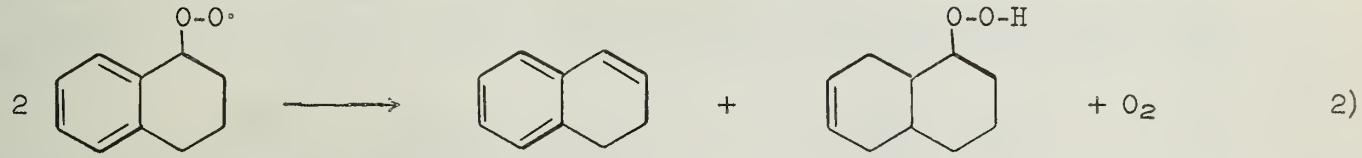
It was observed that the reaction was autocatalytic, which was ascribed to the thermal decomposition of the hydroperoxide yielding hydroxyl radicals by a chain process.



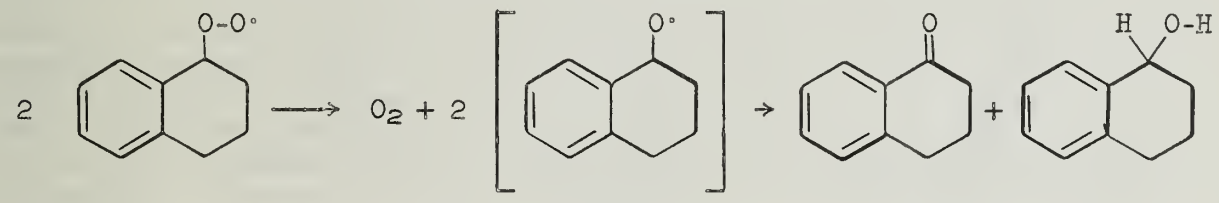
Robertson and Waters (15) investigated the mechanism of the autoxidation using tetralin hydroperoxide as the radical initiator.

$$2R\cdot \longrightarrow RR \qquad 1)$$

Using the combination of two alkyl radicals 1) as the termination step and the steady state approximation, they found their data inconsistant with the expected rate law. Therefore, no conclusion could be drawn as to the nature of the termination step except that 1) was not likely. Bamford and Dewar (7) studied this reaction using a light activated dye as the radical initiator. On the basis of a kinetic study of the rate of oxygen uptake at 25° but without a product study, they postulated that the termination step might be the reaction 2).



However, Tobolsky, Metz and Mesrobian (16) demonstrated by a straightforward mathematical approach that if a) the hydroperoxide is not formed in the termination step, b) the hydroperoxide decomposes by a process which is first order in hydroperoxide and c) an oxygen molecule is liberated in the termination step, then there will be a "steady state" concentration of hydroperoxide and a constant rate of oxygen uptake. This constant rate of oxygen uptake as well as the steady state concentration of hydroperoxide were observed by Woodward and Mesrobian (17), which indicates that the termination step proposed by Dewar is not probable. In place of it, the following step was proposed which involves a disproportionation of two alkoxy radicals.



Robertson has shown that α-tetralone and α-tetralol are the major products of the decomposition of the hydroperoxide. The alcohol to ketone ratio from this decomposition is, however, greater than one, which indicates that the alkoxy radicals formed are also chain carriers.

AUTOXIDATION OF ETHYLBENZENE

Russell (19) has studied the autoxidation of ethylbenzene. The deuterium isotope effect was investigated in the autoxidation of α-deuterocumene and α,α-dideuteroethylbenzene.

Table I

Autoxidation of Cumene and Ethylbenzene at 60° with α,α-Diisobutyronitrile (AIBN) as the Radical Initiator

Reactant	k mole $l.^{-1}$ $sec.^{-1}$ x 10^5	moles of O_2 absorbed	moles of hydroperoxide	kinetic chain length
cumene	2.58	1.86	1.80	19
α-d_1-cumene	1.38	0.90	0.86	10.0
ethylbenzene	0.58	2.00	1.70	4.2
α-d_1-ethylbenzene	0.47	0.915	0.72	2.0

$$ROO\cdot + RH \xrightarrow{k_H} ROOH + R\cdot$$

$$ROO\cdot + RD \xrightarrow{k_D} ROOD + R\cdot$$

In the autoxidation of cumene $k_H/k_D = 5.5$.

Applying the steady state approximation to the following scheme, one obtains equation 3).

$$AIBN \rightarrow (CH_3)_2\dot{C}CN \xrightarrow{O_2} ROO\cdot \qquad (Rate = Ri)$$

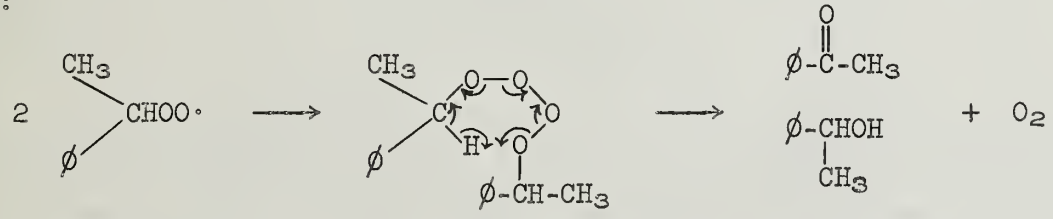
$$ROO\cdot + RH \xrightarrow{k_3} ROOH + R\cdot$$

$$R\cdot + O_2 \xrightarrow{fast} ROO\cdot$$

$$2ROO\cdot \xrightarrow{k_6} \text{NON-RADICAL PRODUCTS} + O_2$$

$$-\frac{d[O_2]}{dt} = \frac{k_3}{(2k_6)^{1/2}}[RH](Ri)^{1/2} + Ri/2 \qquad 3)$$

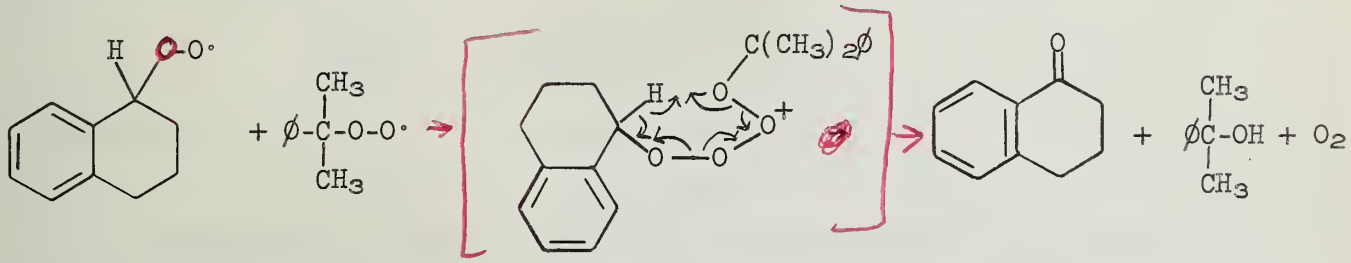
The ratio of $k_3/k_6^{1/2}$ should be 1:0.60 in the autoxidation of α-d_1-ethylbenzene assuming the k_H/k_D ratio for the propagation step in the autoxidation of cumene and no isotope effect in the termination step. The ratio of $k_3/k_6^{1/2}$ was found to be 1:0.79. Assuming no isotope effect in the termination step, the ratio of k_H/k_D in the propagation step would be 1.3 which seems unlikely in view of the k_H/k_D of 5.5 observed for cumene. Therefore, there must be some isotope effect in the termination step. If a k_H/k_D of 5.5 is assumed for α-d_1-ethylbenzene in the propagation step, then the k_H/k_D for the termination step would be 1.9. A termination step consistent with the data is the following:



On the basis of this mechanism for the termination step, 1 molecule of acetophenone should be formed per termination. At a kinetic chain length of 3.4, 0.913 x 10^{-3} mole of oxygen was absorbed. Therefore, 5.8 molecules of hydroperoxide and 1 molecule of acetophenone should be formed per termination. This gives an expected yield of 0.135 mole of acetophenone. Analysis showed 0.13 mole was formed. This termination step could be the route taken by all secondary peroxy radicals. It seems likely that it would be the path for the termination of primary peroxy radicals since they also have the α-hydrogen which this termination mechanism requires.

AUTOXIDATION OF CUMENE

The autoxidation of cumene was first observed by Stepens (20). The reported products at 80° were acetophenone and formic acid. Using milder conditions and a radical initiator, Huck and Lang (6) reported that the yield of cumyl hydroperoxide was nearly quantitative on the basis of the oxygen consumed. This reaction shows the previously mentioned characteristics of a radical chain process (21). The initiation and propagation steps are the same as those of tetralin or ethylbenzene, however, the termination step is necessarily different. This fact was demonstrated by Russell (22). In the competitive autoxidation of tetralin and cumene at 60°, a 500 fold difference in the value of the termination rate constant for cumylperoxy and tetralylperoxy radicals was found. This difference is due to the fact that a secondary peroxy radical can undergo a termination reaction that is not possible for a tertiary peroxy radical. Also, it was found that the termination of a cumylperoxy radical with a tetralylperoxy radical occurs 150 times as fast as the termination between two cumylperoxy radicals. The postulated termination mechanism is the following.



It is also known that primary and secondary alcohols retard the autoxidation of many hydrocarbons (23). A similar termination mechanism could be responsible for this observed fact.

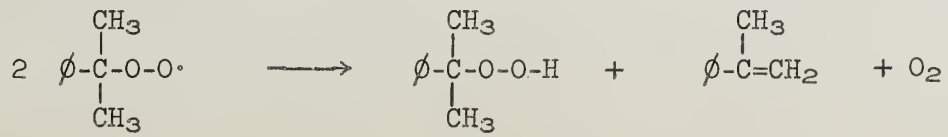
Boozer, Ponder, Trisler and Wightman (14) studied the deuterium isotope effect in the autoxidation of cumene using AIBN as the radical initiator.

Table II

Relative Rates of Autoxidation of Cumene and β-Deuterocumene with and without Inhibitors in Chlorobenzene at 65°.

Deuterium content in atoms D per molecule	Added Inhibitor	k_H/k_D
1.4	None	0.91
3.0	None	0.85
1.4	ρ-nitrophenol	1.05
3.0	ρ-nitrophenol	1.07
1.4	2,4-dichlorophenol	1.19
3.0	2,4-dichlorophenol	1.27

There are two possible isotope effect here. First, a secondary deuterium isotope effect which would be expected to cause a decrease in the rate of autoxidation. Second, if the β C-H bond is broken in the termination step, an increase in the rate of autoxidation should be observed. The two effects are separated by adding an inhibitor which changes the termination step of the reaction. Therefore, the runs with added inhibitor measure the secondary isotope effect alone. From the data summarized in Table II, it can be seen that both effects are operating and that the more important one is the effect in the termination step, which overshadows the secondary isotope effect in the runs without added inhibitor. The proposed termination mechanism was the following.



Blanchard (21) used the following reaction scheme and a product analysis in an attempt to obtain more information concerning the termination step in the autoxidation of cumene.

$$\text{AIBN} \xrightarrow{k_i} 2\ e\text{R}'\cdot + N_2$$

$$\text{R}'\cdot + O_2 \xrightarrow{\text{fast}} \text{R}'\text{OO}\cdot$$

$$\text{R}'\text{OO}\cdot + \text{RH} \xrightarrow{k_p} \text{R}'\text{OOH} + \text{R}\cdot$$

$$\text{R}\cdot + O_2 \xrightarrow{\text{fast}} \text{RO}_2\cdot$$

$$\text{RO}_2\cdot + \text{RO}_2\cdot \xrightarrow{k_t} \text{NON-RADICAL PRODUCTS} + O_2$$

Application of the usual steady state approximation to this scheme yields equation 4).

$$-\frac{d[O_2]}{dt} = \frac{kp[RH](R_i)^{1/2}}{(2k_t)^{1/2}} + R_i/2 \qquad 4)$$

in which R_i, the rate of initiation = $2ek_i[\text{AIBN}]$

Table III

Autoxidation of Cumene at 60° in Chlorobenzene with 0.097M AIBN

Cumene mole $l.^{-1}$	Kinetic Chain Length	Rate mole $l.^{-1}$ $sec.^{-1}$ x 10^5	$\frac{\text{Rate}-R_i/2}{[RH][AIBN]^{1/2}}$ x 10^5	Products[b] Hydro-peroxide	Alkyl peroxide	Aceto-phenone
0.50	2.3	0.25	1.25	60	18.5	11.3
0.85	3.0	0.39	1.22	70	13.3	10.0
1.05	3.6	0.48	1.26	75	12.5	9.4
1.75	5.7	0.76	1.25	85	-	7.1
2.10	6.7	0.88	1.22	87	-	6.0
2.80	8.9	1.18	1.25	90	-	4.4
3.50	10.9	1.44	1.23	91	-	3.5
4.20	12.9	1.70	1.23	92	-	2.7
5.25	15.6	2.06	1.21	94	-	2.2
6.90[a]	20.0	2.68	1.20	96	-	-

[a] pure cumene [b] % of oxygen consumed

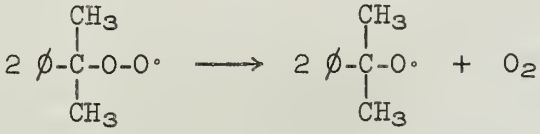
Rearrangement of equation 4) yields

$$\frac{\text{Rate} - R_i/2}{[RH][AIBN]^{1/2}} = \frac{k_p(2ek_i)^{1/2}}{(2k_t)^{1/2}} \qquad 5)$$

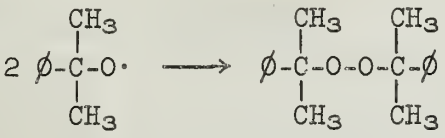
The constancy of column 4 of Table III shows that equation 5) is obeyed rigorously in the autoxidation of cumene in chlorobenzene solutions as well as pure cumene itself. Vapor phase chromatographic anaylsis (VPC) indicated that α,α-dimethylbenzyl methyl ether and α-methylstyrene, one of the products predicted by the mechanism proposed by Boozer, were absent. However, it should be noted here that α-methylstyrene is unstable under the reaction conditions (24). Its oxidation products may be acetophenone and formaldehyde. The VPC analysis also indicated the presence of α,α-dimethylbenzyl alcohol in small yields.

On the basis of the mechanism proposed by Boozer, and at a kinetic chain length of 3, 6 molecules of hydroperoxide (5 from propagation steps and 1 from the termination step) and 1 molecule of acetophenone should be formed. This fact indicates that 85.8% of the oxygen absorbed should appear as hydroperoxide and, in fact, only 70% does appear. Also, only 1 molecule of acetophenone should be formed per termination step. It was found that 1.4 molecules are formed. All of the acetophenone produced cannot be formed by the autoxidation of α-methylstyrene, and in view of the yield of hydroperoxide, it seems unlikely that any is produced by this path.

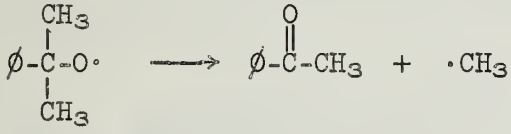
On the basis of the constant number of acetophenone molecules produced per termination regardless of the chain length, it is suggested that the common intermediate is the cumyloxy radical resulting from a non-terminating interaction of two cumylperoxy radicals.



These cumyloxy radicals could then dimerize to give di-α-cumyl peroxide.

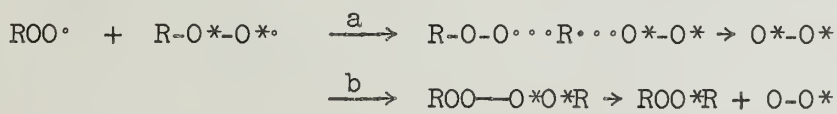


Another possibility is that they can decompose forming acetophenone and a methyl radical.



A third possibility is that the cumyloxy radical could escape the solvent cage, abstract a hydrogen from cumene and continue the chain. However, the latter path can occur only to a small extent since the amount of α,α-dimethylbenzyl alcohol formed is small. It was found that on the average 1.85 molecules of oxygen are present in non-hydroperoxidic products. Under steady state conditions, i.e., the rate of initiation must equal the rate of termination, one molecule of oxygen must be present as cumyl peroxide. Since there is 0.73 molecule of acetophenone and 0.12 molecule of alcohol formed, formation of di-α-cumyl peroxide occurs 54% of the time, formation of acetophenone occurs 39.5% of the time, and 6.5% of the time, the cumyloxy radical escapes the solvent cage and reenters the chain. This type of mechanism has been observed by Dean and Skirrow (25) for the termination of t-butylperoxy radicals in the metal ion catalyzed decomposition of t-butylhydroperoxide. Di-t-butylperoxide is the major product.

Bartlett and Traylor (26) have added support to this mechanism by studying this autoxidation using O^{18}-O^{18} (referred to as O*-O*).



Reaction path a, involving a displacement, would give symmetrically labeled or unlabeled oxygen, where as path b, a head to head interaction, would yield unsymmetrically labeled oxygen. The reaction was followed by analyzing the gas mixture by mass spectroscopy. There was enough unsymmetrically labeled oxygen, O-O*, formed to account for all chain terminating by path b, and also for the extra oxygen evolution which is caused by the formation of cumyloxy radicals and methyl radicals rather than by the chain-terminating peroxide formation.

No correlation has been made between the mechanism proposed by Blanchard and substantiated by Bartlett and the deuterium isotope effect noted by Boozer. The isotope effect noted was small and therefore may only involve a fraction of the termination reaction. However, since no experimental detail has been published by Boozer, no definite conclusion can be drawn from his work at this time.

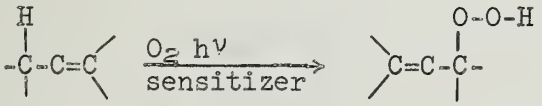
Boardman (27) of the Hercules Powder Company studied the autoxidation of ρ-cymene, ρ-methylisopropylbenzene, arriving at a different conclusion regarding the termination step. According to the results, a molecule of hydroperoxide was formed in the termination step. However, it is a little difficult to see exactly what termination step is being followed. Product analysis showed that 16% of the product mixture was the primary hydroperoxide. In view of Russell's (22) results showing that crossed termination between a secondary peroxy radical and a tertiary peroxy radical occurs 150 times faster, and the termination between two secondary radicals occurs 500 times faster, than the termination of two tertiary peroxy radicals, it would be expected that the major termination step in the autoxidation of ρ-cymene would involve either two primary radicals or a primary and a tertiary peroxy radical rather than the two tertiary peroxy radicals as postulated. Since no attempt was made to distinguish these possibilities, the results seem ambiguous.

STEREOCHEMISTRY OF PHOTOSENSITIZED AUTOXIDATION

As can be seen from the data presented previously, autoxidation can be used to form a variety of hydroperoxides.

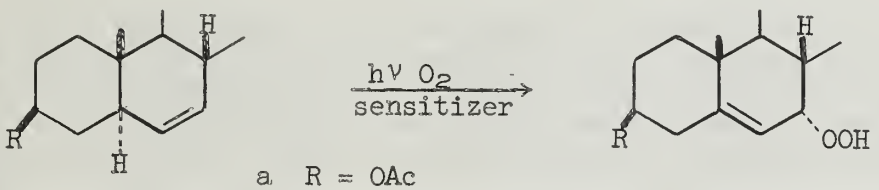
In the case of olefins, under the mild conditions of room temperature, dilute solutions and sensitizing agents, the reaction does not appear to go via a radical chain (28). The mode of oxygen attack is more specific and the hydroperoxide products largely survive further decomposition.

The general scheme is as follows (29):



The role of the "sensitizer" is not very well understood. Two possibilities are, first, the light activated sensitizer directly attacks the olefin followed by the attack on oxygen of the activated olefin or second, the activated sensitizer attacks oxygen which then attacks the olefin. The sensitizer is usually a flourescent dye.

Δ^6-Cholestenes (Ia,b,c) were oxidized by Nickon and Bagli (30). These compounds have an α-orientated allylic hydrogen (at C-5) and a β-orientated one (at C-8). One or both of these must necessarily be involved in this reaction.

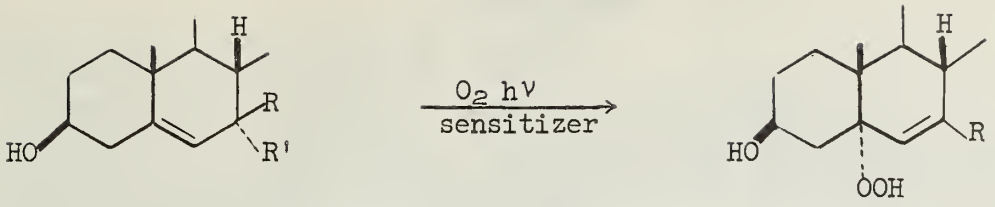


I

a R = OAc
b R = OH
c R = H

In the case of Ia, the only product isolated was the 7-α derivative. No indication of the 7-β derivative was observed. With Ib, less than 1% of the β-derivative was indicated by infrared analysis. With Ic, again no β-derivative was observed.

The autoxidation of cholesterol-7α-d (IIa) gave the hydroperoxide which contained only 8.5% of the original deuterium, while cholesterol-7β-d (IIb) retained 95% of its original deuterium.



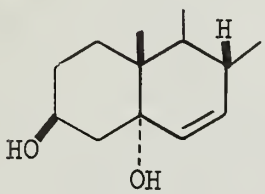
IIa IIb

R = H R = D
R' = D R' = H

These results indicate that the autoxidation is stereospecific, the orientation of the hydroperoxide, with respect to the ring, being the same as that of the reacting hydrogen.

A cyclic mechanism is postulated to explain these results (30).

It was also found that diol III is unchanged by photosensitized oxygenation even on prolonged treatment.



III

The β-side of the ring system (and especially the β-hydrogen at C-8) is shielded by the angular methyl groups, and the inertness of III demonstrates that the reaction can be sterically blocked.

CONCLUSION

In view of the evidence presented, autoxidation occurs by way of a radical process. The termination step involves two peroxy radicals at sufficiently high oxygen pressures. The interaction of these peroxy radicals depends on the nature of the hydrocarbon, for example, cumene which will give rise to a tertiary peroxy radical terminates by a different mechanism from ethyl benzene which will give a secondary peroxy radical as the intermediate.

The photosensitized autoxidation with isolated double bonds appears to be stereospecific and may be used as a synthetic tool. The reaction may be concerted after either the olefin or oxygen is activated.

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