SEMINAR TOPICS

CHEMISTRY 435 I Semester 1959-1960

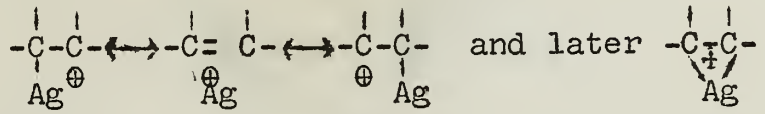
COMPLEXES OF CARBON-CARBON UNSATURATED MOLECULES WITH SILVER ION

Reported by D. V. Young September 24, 1959

HISTORY

That Ag(I) will complex with certain organic molecules containing carbon-carbon unsaturation was first suspected in 1922 when A. E. Hill reported that silver perchlorate exerted a "salting in" effect on benzene in aqueous solution.[1]

It was in 1938 that the first serious study of these silver complexes was reported by Winstein and Lucas.[2] These workers measured the equilibrium constants of many silver-olefin complexes (hereafter referred to as argentation constants.) They also found that Ag(I) neither catalyzed the hydration of olefins nor isomerized them, and they concluded that complexation with Ag(I) was a general property of olefins. The resonance hybrid formulas were assigned to represent



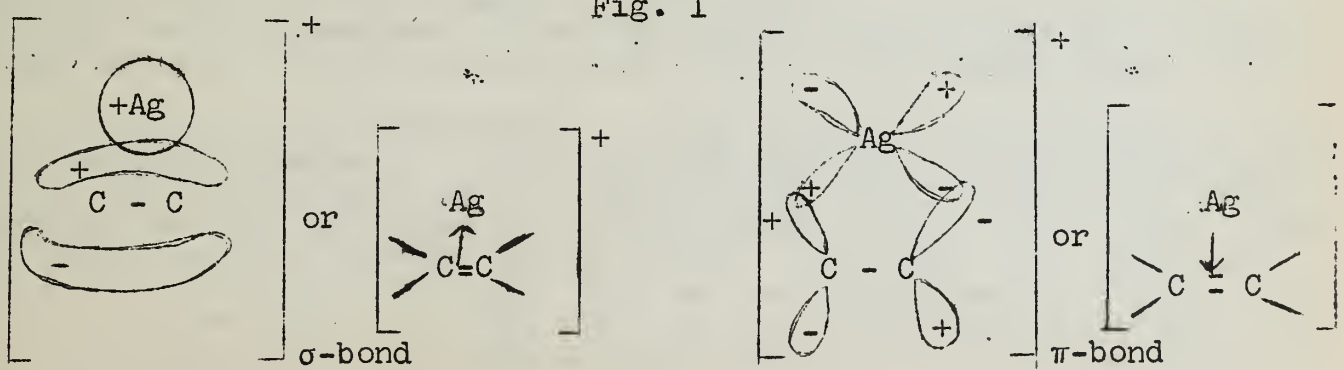
this type of complex.

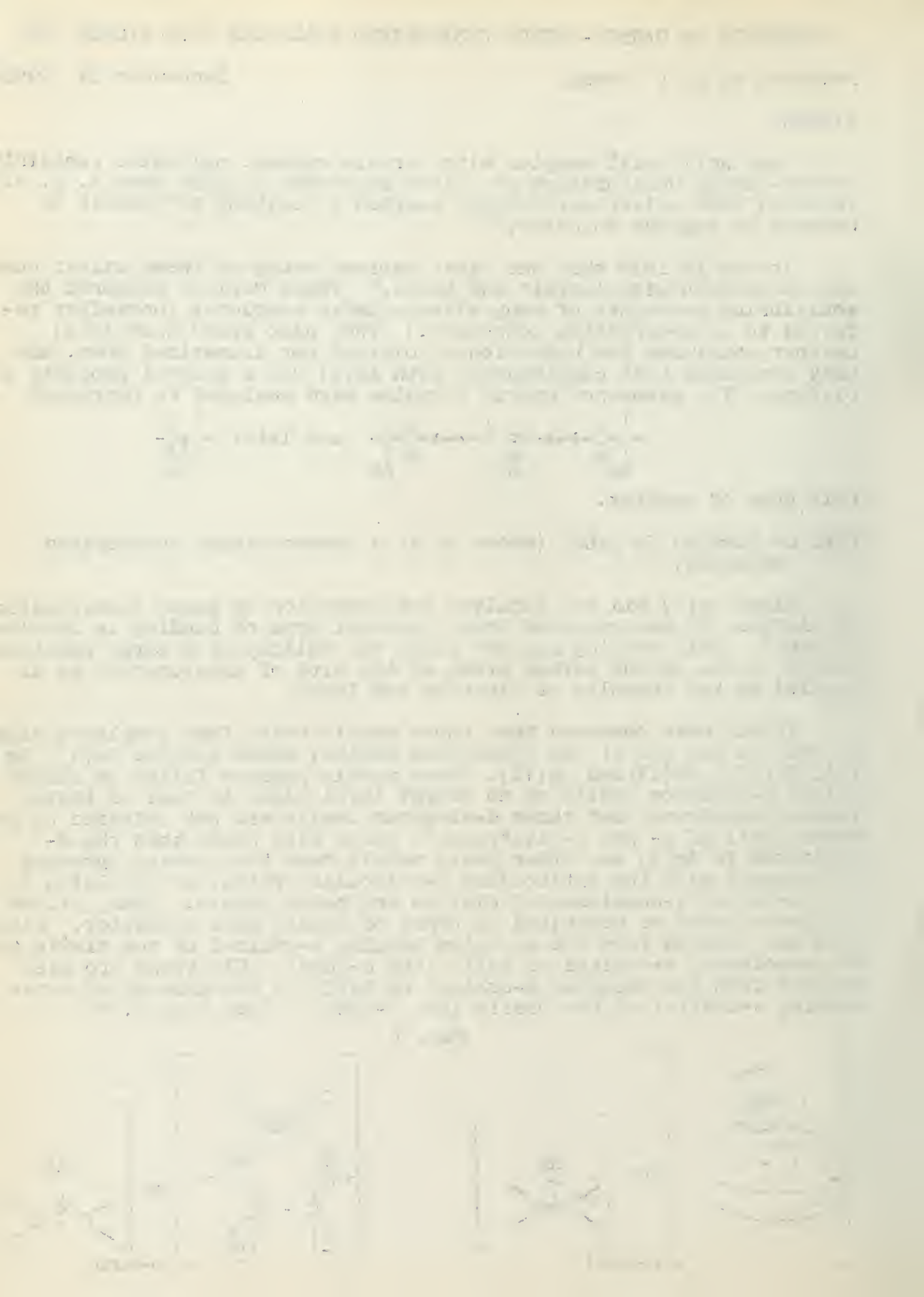
TYPE OF BONDING IN $AgUn^+$ (where Un is a carbon-carbon unsaturated molecule)

Since Ag(I) did not catalyze the hydration or cause isomerization of olefins, it was realized that a special type of bonding is involved in $AgUn^+$. This bonding does not allow the buildup of a large positive charge on one of the carbon atoms at the site of unsaturation, as is implied by the formulas of Winstein and Lucas.

It has been observed that those metals which form complexes with Un come at the end of the transition series; these include Cu(I), Ag (I), Pd(II), Pt(II) and Hg(II). These metals possess filled or almost filled d-electron shells on an energy level close to that of their valency electrons, and these d-electron shells are not shielded by an outer shell of s- and p-electrons.[3] Dewar also noted that the d-electrons in Ag(I) and other heavy metals have the correct symmetry to interact with the antibonding π-molecular orbital of an olefin in the so-called π-complexes of olefins and heavy metals. Thus, silver complexes could be described in terms of double bond character. Electrons are donated from the occupied bonding π-orbital of the olefin to the unoccupied s-orbital of Ag(I) [the σ-bond]. Electrons are also donated from the occupied d-orbital of Ag(I) to the unoccupied antibonding π-orbital of the olefin [the π-bond]. (See Fig. I.)[4]

Fig. I



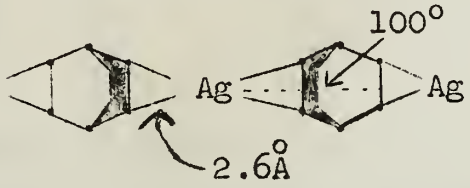


This concept of double bond character explains the suppression of the buildup of a large positive charge on one of the carbon atoms.

THE GEOMETRY OF $AgUn^+$

The geometry of $AgUn^+$ has been elucidated chiefly through an X-ray investigation of the $AgClO_4$·benzene complex.[5] It was found that each silver ion is so bonded to two benzene molecules that the angle made by the silver ion with the middle of the nearest C-C bond and the center of the aromatic ring was 100°; the shortest Ag-C distance was 2.6Å. (See Fig. II.)

Fig. II



The argentation constant of $AgClO_4$·benzene in aqueous solution indicates essentially a 1:1 complex with some evidence that a second Ag(I) is very weakly bonded to the benzene ring.[6,7]

It is interesting to note that this approximate geometry was predicted by Mulliken from theoretical considerations based on symmetries of quantum-mechanical wave functions.[8] Chemical evidence for such geometry (as opposed to Ag(I) being on the six-fold symmetry axis of the aromatic ring as was believed at one time) lies in an examination of the argentation constants of the following aromatic hydrocarbons (Table I).

Table I

Hydrocarbon	K_{Ag} at 25°	No. of locations for Ag(I)
benzene	1.10	6
toluene	1.19	4
o-xylene	1.43	3
mesitylene	0.80	0

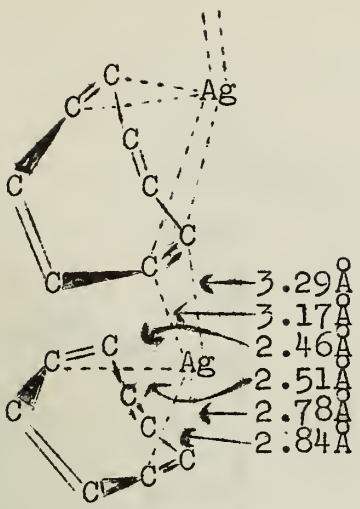
Mulliken suggests that areas of the aromatic nucleus immediately adjacent to the alkylated ring carbons are sterically unfavorable as coordination sites for Ag(I).[8] Thus the observed argentation constants become intelligible as a result of a balance between:

1.) a tendency towards increasing basicity of the aromatic nucleus with increasing number of methyl groups, and

2.) steric hinderance by methyl groups to the attainment of Ag(I) to one of its favored locations next adjoined to a methyl group.

A recent X-ray investigation of the silver-cyclooctatetraene complex has been reported.[10] The Ag(I) COT complex is essentially a 1:1 complex with the nearest Ag-C distance being 2.46Å. Three more longer bonds to the same COT molecule are indicated, and two even longer bonds are formed with an adjacent COT molecule. (See Fig. III.) The COT molecule is in the "tub" form. Because the silver ion is slightly bonded to more than one double bond, it is somewhat displaced from the axis perpendicular to the double bond to which it is most strongly bonded.

Fig. III



THE ENERGY OF THE BONDING IN AgUn+

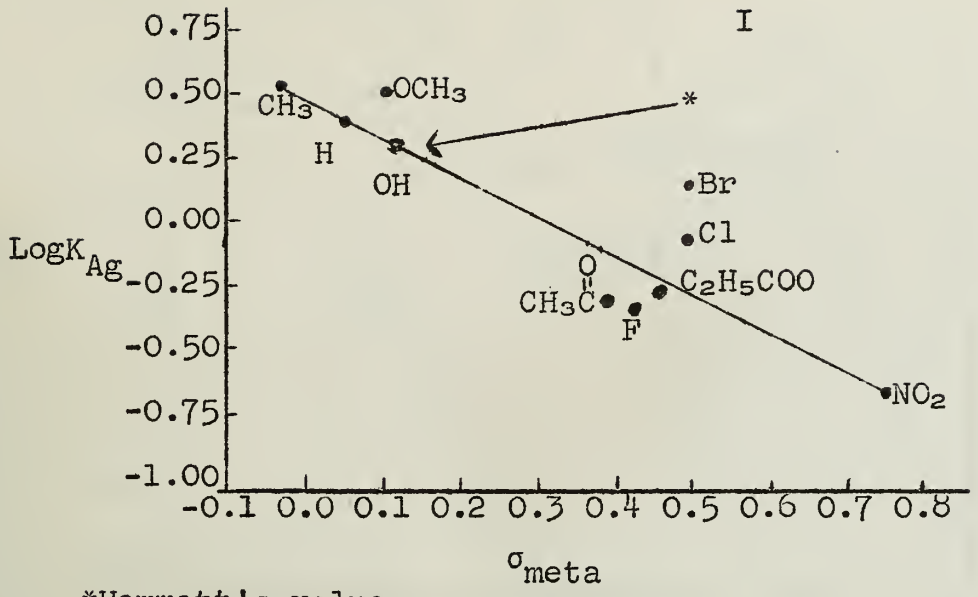
A crude estimation of the energy of the bond in the $AgClO_4$·benze complex has been made from consideration of the crystal lattice energ of $AgClO_4$.[11] The bond energy is something between 25 and 50 kcal./ mole, which is on the same order of magnitude as many ordinary covalent bonds.[12]

SILVER AROMATICS

In general, simple silver aromatics (i.e., those complexes with one aromatic nucleus) form a 1:1 complex. There is evidence, howeve that a second silver ion can coordinate with the aromatic nucleus to a very small extent in aqueous solution. This evidence is based essentially on the fact that there is a slight variation in the argentation constant with a change in Ag(I) concentration. This secon argentation constant has been indirectly calculated and found to be 0.1 to 0.3 in magnitude.[7] This second argentation constant disappea when a solution of equimolal water-methanol is used.[9]

The argentation constants of various monosubstituted benzenes have been determined, and a plot of log K_{Ag} vs. σ_{meta} gives a straigh line correlation.[13] (See Fig. IV.) The significance of this correlation is not completely apparent. A reasonable explanation is base on the assumption that a ring substituent alters the electron densit at the position meta to that substituent more through an inductive effect than a resonance effect. Consequently, the σ_{meta} values for various ring substituents are probably better measures of the inductive effects of these substituents on the π-electrons of the ring tha are the σ_{para} values. It might be concluded that the relative stabilities of these silver complexes are associated primarily with the relative inductive effects of ring substituents. In the case of iod benzene it is postulated that a second silver ion was interacting wi the iodine atom, thus accounting for its great divergence from a straight line.

Fig. IV



*Hammett's value

Evidence that the stability of silver-aromatic complexes depends upon both electronic and steric effects has been set forth by Andrews and his coworkers.[9] Alkyl substituents increase the basicity of the aromatic nucleus, but at the same time they increase the steric congestion above and below the aromatic nucleus. The following plot of log K_{Ag} vs. number of alkyl substituents can be best interpreted as reflecting the opposing electronic and steric effects upon the stability of the complex. (See Fig. V.)

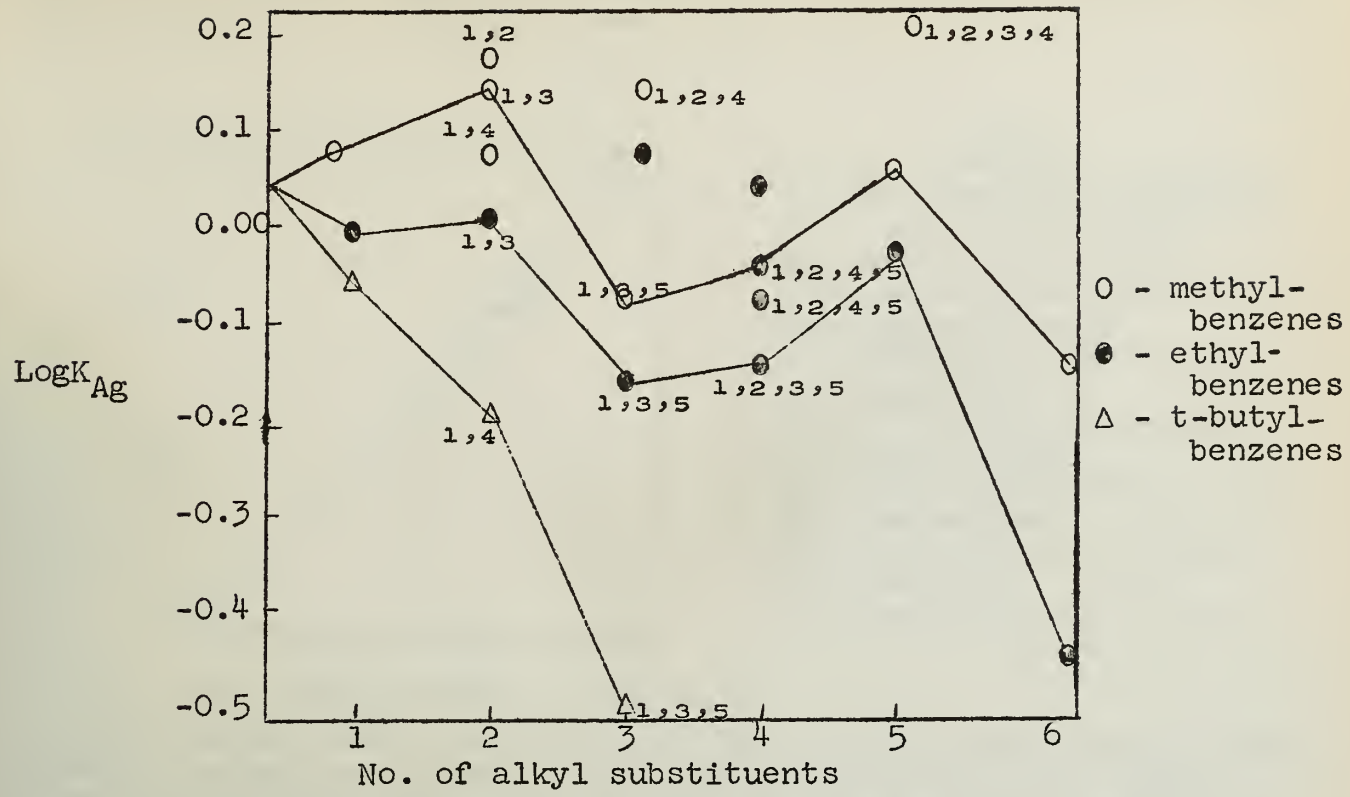
SILVER ALKENES

Extensive work has been done on the determination of the argentation constant for many silver-alkenes.[2,14,15,16,17,18,19] Three types of complexes are most commonly observed in aqueous solution:

1.) 1:1 Ag(I)-alkene
2.) 2:1 Ag(I)-alkene
3.) 1:3 Ag(I)-alkene

The 1:1 complex is by far the most frequently observed and the most stable complex of the three types.[2]

Fig. V.



The argentation constant of the lower alkenes has been more recently determined, and it is of interest to compare the K_{Ag} of the isomeric butenes.[20,21] (Table II).

Table II

	K_{Ag} at 25°
1-butene	119.4
cis-2-butene	62.3
trans-2-butene	24.6
2-methylpropene	71.5

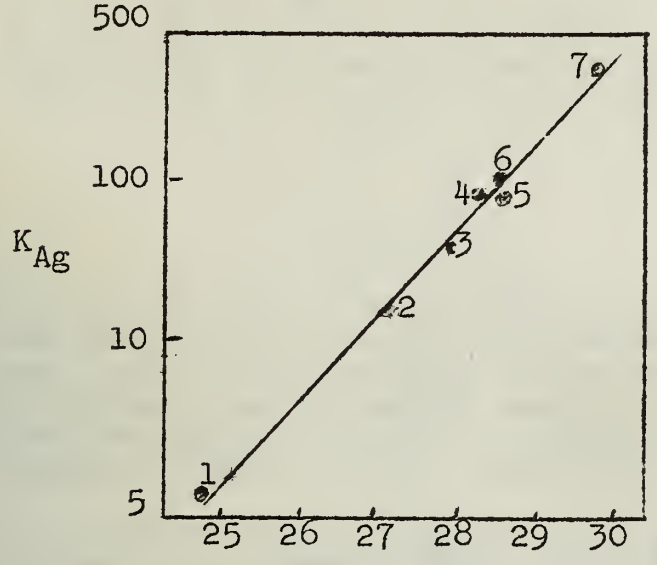
From the data it would seem that steric factors are quite important. 1-Butene, in which there is but one alkyl substituent on the double bond, gives the most stable complex. In the case of cis-2-butene, steric interaction with the methyl groups on one side of the molecule makes the most stable position of Ag(I) slightly displaced from the position directly over the double bond, but still symmetrically located with respect to this bond. Such steric interactions operate in the trans-molecule also;however, only a non-symmetrical shift of the Ag(I), or a displacement of it further from the plane described by the doubly bonded carbons and their methyl groups would result, accompanied by a lower stability of the complex. The stability of 2-methylpropene parallels that of cis-2-butene, and indeed the accessability to the double bond in these compounds must be comparable.

When one considers the argentation constants of ethene (85.3) and propene (87.2), they do not seem to fit into the above explanation, which considers only steric hinderance. Perhaps large differences in electronic environment complicate the comparison of ethene and propene with the isomeric butenes.

The differences in the argentation constants of the alkenes has been discussed from a different perspective by Gardner, Brandon

and Nix.[22] These workers have correlated the log K_{Ag} with the $-\Delta H$ (hydrogenation) of alkenes. (See Fig. VI.)

Fig. VI



alkene
1.) 2,4-dimethyl-2-pentene
2.) 2-methyl-2-butene
3.) trans-2-butene
4.) iso-butene
5.) cis-2-butene
6.) cyclohexene
7.) 1-octene

This relationship suggests that, to a first approximation, the over-all energetics of hydrogenation and argentation are similar. A major factor involved in hydrogenation of alkenes is the relief of strain due to bond oppositions present in cis-isomers, but not in trans-isomers.[23] In argentation, it can be assumed that there is just sufficient twisting of the p-orbitals to relieve partially the bond oppositions in the planar cis-alkenes by permitting a slight rotation about the double bond. The large 5s-orbital of Ag(I) should be capable of accommodating this twisting. Hence, cis-alkenes form more stable complexes than trans-alkenes. This deformation of the π-orbitals of cis-alkene complexes, together with their resultant stability, also shows itself in silver-cyclic alkene complexes.[24,25] The order of relative strain in some cyclic alkenes has been estimated from available thermochemical data.[24] The order of relative strain in bicycloheptene and bicyclooctene has also been qualitatively estimated from the behavior of these olefins in peracid oxidation. (See Table III).[26]

Table III

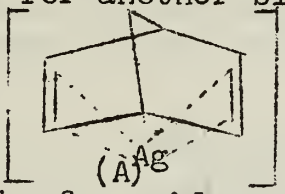
alkene	rel. K_{Ag} 25°	alkene	rel. K_{Ag} 25°
cis-cyclooctene	1.00	bicyclooctene	18.9
cyclohexene	3.65	bicycloheptene	53.2
cycloheptene	4.21		
cyclopentene	23.6		

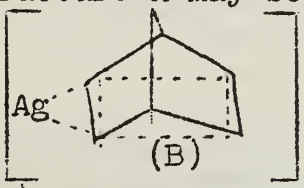
INCREASING STRAIN

These data can be interpreted in terms of ring strain increasing the availability of π-electrons by π-orbital deformation. It is interesting to note that the rates of addition of phenyl azide, of diethylaluminum hydride and of hexachlorocyclopentadiene to a series of cycloalkenes are essentially in the same order as relative strains in the olefins.[24]

The argentation constants of various methylene cycloalkanes have been studied (ring sizes C_4 through C_7) and found to be independent of ring size and about equal in magnitude to their acyclic analog, 2-methylpropene.

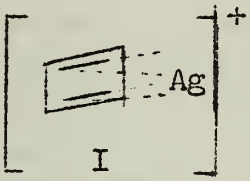
An extraordinary silver complex is that one formed with norbornadiene.[25] Other dienes form both 1:1 and 1:2 complexes with Ag(I). The absence of any 1:2 complex formation may result either from an overlapping of Ag(I) with both π-clouds (structure A), or from homoallylic type resonance with Ag(I) located on one side of the diene in an exo-configuration (structure B). Structure B would make the π-cloud at the 5,6-position relatively positive, and an unattractive bonding site for another silver ion. Structure A may be favored

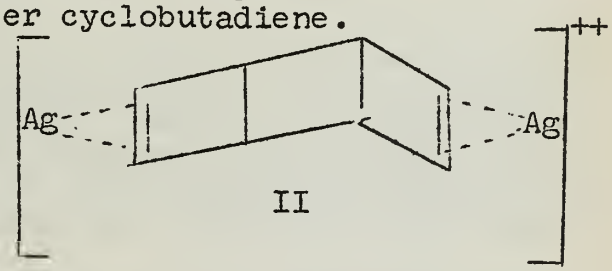




because of the favorable geometry of Ag(I) for overlapping of appropriate orbitals when it is placed under the diene molecule. However, the stereochemistry of the brominated addition products found by Winstein and Shatavsky suggests that bromine approaches the diene from the exo-position.[27] If silver olefin complexes are assumed to resemble halogen-olefin complexes, then structure B is favored.

Another interesting silver olefin complex is the compound having the empirical formula $AgNO_3 \cdot C_4H_4$.[28] When 1,2,3,4-tetrabromocyclobutane was treated with lithium amalgam in ether, a mercury-containing, halogen-free product was obtained. Because of the great instability of this compound it could not be purified for analysis. Treatment of the mercury-containing compound with aqueous silver nitrate resulted in a fairly stable crystalline substance. The analysis corresponds to the empirical formula $AgNO_3 \cdot C_4H_4$. Proposed structures (I and II) include the long-sought-after cyclobutadiene.





SILVER ALKYNES

Silver alkynes have not been so extensively or systematically studied as the silver alkenes or silver aromatics. Silver ions complex with alkynes containing the acid hydrogen, but the results are complicated by the formation of silver acetylides.[29] The value of the argentation constant of 3-hexyne was determined and found to be intermediate between alkenes and aromatics in magnitude. (See Table IV.)

Table IV

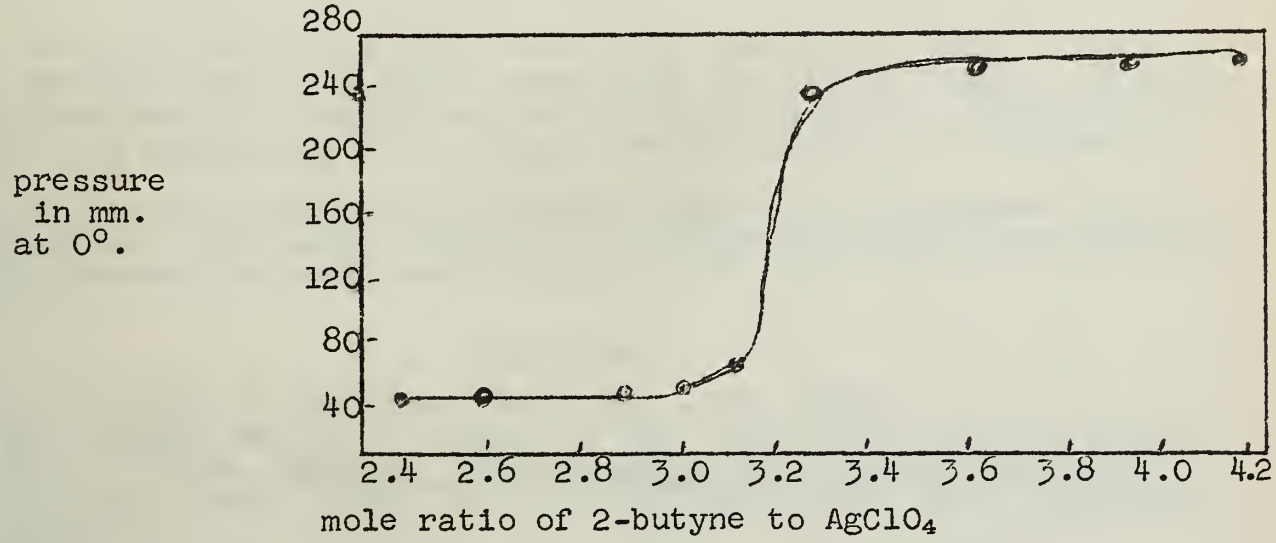
Compound	K_{Ag} 25°
3-hexyne	19.1
cis-2-pentene	112.5
trans-2-pentene	62.2
cyclohexene	79.3
benzene	1.10

It has been suggested that in 3-hexyne the steric effect would be greater than in a cis-alkene and probably comparable to a trans-alkene.[29] This factor, coupled with the general lower reactivity of the triple bond to addition reactions as compared with the olefinic double bond, probably accounts for the relatively low value of the argentation constant.

The compositions of saturated solutions of $AgClO_4$ in 2-pentyne and 3-hexyne at 25° correspond to a molar ratio of alkyne to $AgClO_4$ of 1.4:1. Partial evaporation of the alkyne gives in each case a solid in which this ratio is 3:1.[30]

Vapor pressure data have been obtained on the system $AgClO_4$-2-butyne. Systems containing 2-butyne in excess of the formula $AgClO_4 \cdot 3C_4H_6$ exert a vapor pressure equal to that of 2-butyne (245 mm. at 0°), and those containing between 3 and 2.5 moles of 2-butyne to 1 of $AgClO_4$ have a vapor pressure of 46mm. at 0°. (See Fig. VII.)

Fig. VII

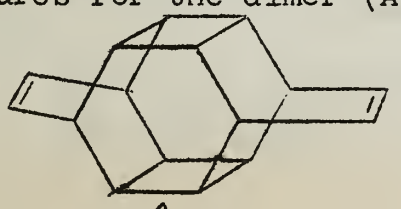


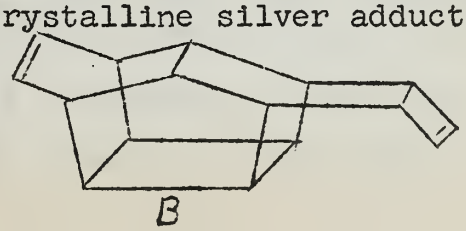
USES OF $AgUn^+$

In an attempt to relate carcinogenic properties of polycyclic aromatic hydrocarbons with their nucleophilicities, an attempt was made to correlate the argentation constant (taken as the criterion for nucleophilicity) of these polycyclic aromatic hydrocarbons with their carcinogenic potencies in mice.[31] The correlation showed that in general some factor other than nucleophilic character must also be involved in carcinogenic potency.

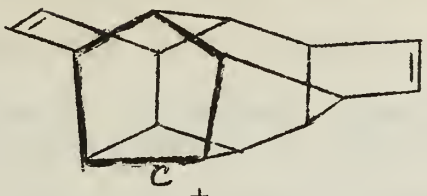
The silver complexes of α- and β- pinene are of use because they allow these two pinenes to be separated from each other and to be obtained optically pure.[32] It was found that when an aqueous solution of $AgClO_4$ was shaken with a mixture of α - and β - pinenes only β-pinene complex precipitated. Under different conditions α -pinene can be made to form a solid silver complex. Argentation also proved to be a convenient and effective way of obtaining optically pure samples of α- or β-pinene from optically impure α- or β-pinene. By this method the rotation of β-pinene is higher than any reported previously in the literature. ($[\alpha]_D^{25}$ - 22.7°).

The silver complex of the dimer of cycloöctatetraene has been employed to determine the structure of this compound.[33] When cyclooctatetraene is refluxed for long periods of time under an atmosphere of N_2, a liquid dimer, $C_{16}H_{16}$, is formed. Reppe proposed two possible structures for the dimer (A and B). The crystalline silver adduct of


A


B

$C_{16}H_{16}$ was subjected to 3-dimensional X-ray analysis, and structure C was found.



Many other uses of $AgUn^+$ have been reported and most of these can be found in reference 34.

PRESENT WORK

Chemical reactions which have been proposed to pass through the high energy transition state resembling the silver complex (bromination, ozonization, peracid oxidation) might permit a correlation with silver ion complexing data. Such work is currently in progress.[22]

An X-ray analysis of the silver complex of cyclohexene is also in progress. This solid complex is interesting in that two molecules of cyclohexene are complexed with Ag(I).[32]

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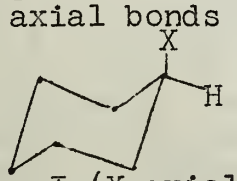
DETERMINATION OF CONFORMATIONAL EQUILIBRIUM CONSTANTS IN CYCLOHEXANE SYSTEMS

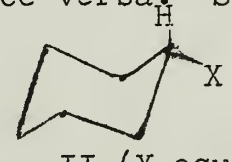
Reported by M. L. Poutsma October 1, 1959

INTRODUCTION

The understanding of the chemistry of cyclohexane compounds was greatly increased by the realization that the cyclohexane ring exist almost exclusively in the chair form at room temperature and that this gives rise to two different types of bonds: the axial and equatorial bonds. It is known that the substituent group on a monosubstituted cyclohexane will assume the equatorial conformation preferentially because of less steric interference there than in the axial position (1). The purpose of this seminar is to describe methods used recently to determine quantitatively the equatorial-axial energy differences for various substituents. We will define the conformational equilibrium constant, K_X, for a substituent X whe placed alone on a cyclohexane ring, as the ratio of the concentratio of the equatorial conformation present to that of the axial conformation present in equilibrium with it. This equilibrium is possible by a "flipping" of the ring through a planar transition state which converts all axial bonds to equatorial and vice versa. So defined,



I (X axial)



II (X equatorial)

$K=II/I$. We can also define a ΔF, the free energy difference between the equatorial and axial conformations, where $\Delta F= -RT \ln K$. Obviously K will be greater than unity and ΔF will be negative.

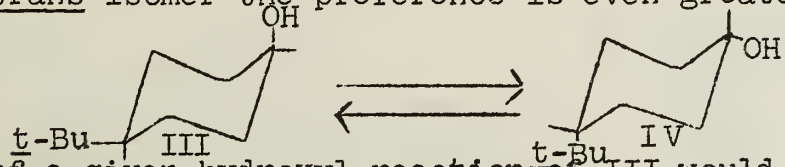
THE KINETIC APPROACH

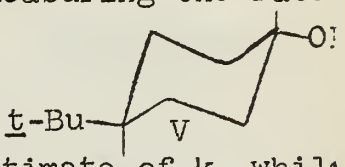
The differences in reactivity of substituents when in axial or equatorial positions have been summarized by Barton (2,3). Winstein (4,5) has proposed equations 1) and 2) to determine K on the basis of these differences in reactivity. The rate constant, k, for a give

1) $k=N_e k_e + N_a k_a$. 2) $K=N_e/N_a$. 3) $K=k_a - k/k - k_e$.

reaction of a substituent on a cyclohexane ring is a composite of k_e and k_a, the rate constants for the same reaction occurring for that substituent entirely in the equatorial or axial conformation, respectively; k_e and k_a must be weighted by the mole fractions of the equatorial and axial conformations present in the reacting species. This relationship is valid only if k, k_e, and k_a are all of the same kinetic order. Eliel (6) has expressed the same relationship in a different, more easily calculated form in equation 3). The constant k, can be determined experimentally. Both Eliel and Winstein have used cis- and trans-4-t-butyl substituted cyclohexyl compounds to obtain estimates of k_a and k_e. Because of its bulk, the t-butyl gro in an equatorial position will be favored over this group in the axial position by an energy factor generally considered to be greate than 5.4 kcal./mole. This causes a 4-t-butyl substituted cyclohexan to be essentially conformationally homogeneous because the ΔF for most other smaller groups is in the range of 0.5 - 2.0 kcal./mole. For example, cis-4-t-butylcyclohexanol (III) would exist almost entirely in the conformation shown with the hydroxyl group axial, while the trans isomer (V) would have the hydroxyl group mainly equatorial. If ΔF_{OH} = -0.8 kcal./mole (vide infra), III would be

preferred over the alternative conformation (IV) by a ΔF factor of -(5.4 - 0.8) or -4.6 kcal./mole; this gives a K value of greater than 1000, or, in other words, cis-4-t-butylcyclohexanol exists with well over 99% of its hydroxyl groups in the axial position. With the trans isomer the preference is even greater. Thus measuring the rate





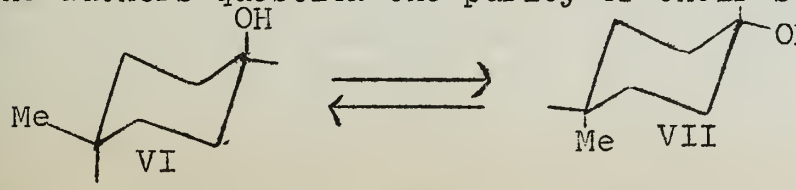
of a given hydroxyl reaction of III would give an estimate of k_a while the same reaction for V would give k_e.

The arguments above assume that a 4(e)-t-butyl group exerts no significant steric or polar effect at the reaction site at position 1. This hypothesis is not only reasonable from an examination of molecular models, but is also supported by various data. For example, cyclohexanol and 4,4-dimethylcyclohexanol, which are conformationally identical because of the symmetrical disubstitution at position 4, are acetylated at the same rate by acetic anhydride in pyridine (6), showing no effect of the alkyl group at position 4.

Data are also available concerning the rates of reaction of one substituent of a disubstituted cyclohexane where both groups are small and of comparable size so that neither conformation of the molecule is favored exclusively, for example, the methylcyclohexanols. In the cases where there is no serious interaction between the two groups (cis-1,4; trans-1,4; trans-1,3; and the diequatorial conformation of cis-1,3), such data can be used to check the consistency of the ΔF values already assigned to the two groups or to determine the value of one of them based on the other. This argument is based on the hypothesis, used throughout this seminar, that the major steric interaction energetically in the cyclohexane system is the 1,3-diaxial interaction.

Calculation of K by equation 3) involves a quotient of difference between numbers, one of which may be quite small (k_e or k_a.) Hence, small experimental errors become seriously magnified in the ΔF values and one should not expect the precision here often associated with the measurement of thermodynamic parameters. Also, the values obtained will be somewhat dependent on the solvent used for the determinations and on the temperature.

Eliel (6) measured the rates of acetylation of various cyclohexanols; the rate constants are cleanly second order and are summarized in Table I. Applying equation 3) to entries 1, 2, and 3 gives $\Delta F_{OH} = -0.5$ kcal./mole for this solvent and temperature (25°). From entry 5 for cis-4-methylcyclohexanol, which can exist in conformations VI and VII, we can derive a value of ΔF_{Me}. The rate data give $F_{VII} - F_{VI} = 1.2$ kcal./mole. This should be the difference between ΔF_{Me} and ΔF_{OH} for in going from VI to VII there is a gain in stability due to the equatorial hydroxyl but a more than compensating loss due to forcing the methyl group necessarily to be axial. Using $\Delta F_{OH} = -0.5$, we find $\Delta F_{Me} = -1.7$ kcal./mole. Entry 4 does not check as well but the authors question the purity of their starting material.



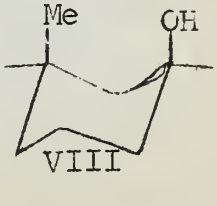


Table I

Data for the reaction of cyclohexanols with acetic anhydride in excess pyridine at 25° C.

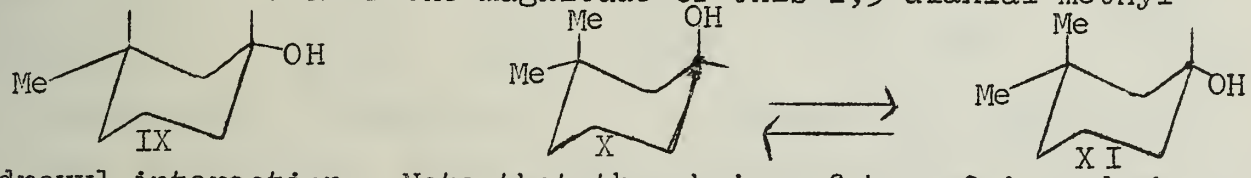
Entry	Alcohol	$k \times 10^5$ (1 mole^{-1}sec^{-1})	K	ΔF (kcal./mole)
1	Cyclohexanol	8.37	2.40	-0.5
2	Trans-4-t-butylcyclohexanol	10.65	∞*	---
3	Cis-4-t-butylcyclohexanol	2.89	0*	---
4	Trans-4-methylcyclohexanol	9.66	6.84	-1.1
5	Cis-4-methylcyclohexanol	3.76	0.13	1.2
6	Cis-3-methylcyclohexanol	10.71	∞	---
7	Trans-3-methylcyclohexanol	3.94	0.16	1.1
8	4,4-Dimethylcyclohexanol	8.43	2.50	-0.6
9	3,3-Dimethylcyclohexanol	9.88	9.08**	-1.3**
			12.8#	-1.5#

*Assumed.

**Assuming $k_a = 2.89 \times 10^{-5}$.

#Assuming $k_a = 0$.

Entry 6 confirms the hypothesis of the serious steric interference of 1,3-diaxial groups. Since entry 6 is essentially equal to entry 2, it is obvious that cis-3-methylcyclohexanol exists in conformation IX primarily rather than conformation VIII. Entry 9 allows a crude calculation of the magnitude of this 1,3-diaxial methyl-



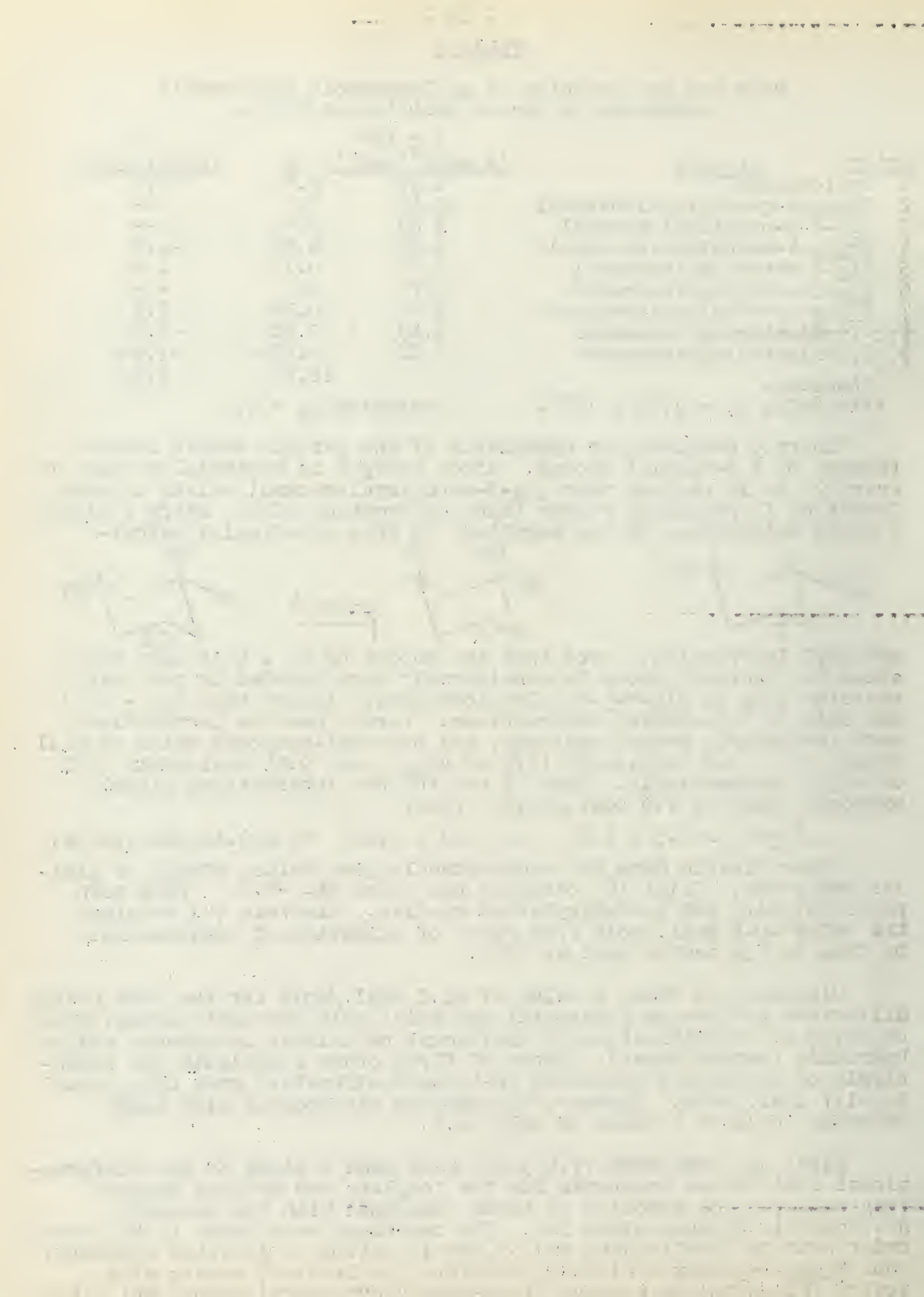
hydroxyl interaction. Note that the choice of $k_a = 0$ is made here since the hydroxyl group is considerably more crowded in the axial position than in cis-4-t-butylcyclohexanol. Assume that $F_{XI} - F_X$ is due only to 1,3-diaxial interactions. Form X has the interactions methyl-hydroxyl, methyl-hydrogen, and hydroxyl-hydrogen which we will equate to x, 0.9 kcal./mole (1/2 of ΔF_{Me}), and 0.25 kcal./mole (1/2 of ΔF_{OH}), respectively. Form XI has the two interactions methyl-hydrogen equal to 1.8 kcal./mole. Thus:

$$F_{XI} - F_X = -1.5 = 1.8 - (x + 0.9 + 0.25) \quad \text{or} \quad x = 2.15 \text{ kcal./mole.}$$

Other kinetic data for cyclohexanols give values of ΔF_{OH} of similar magnitude. Eliel (6) obtained the value $\Delta F = -0.5$ from both propionylation and isobutyrylation studies. Winstein (4) obtained the value -0.8 kcal./mole from rates of oxidation of cyclohexanols by CrO_3 in 75% acetic acid at 40°C.

Winstein (4) found a value of -1.2 kcal./mole for the free energy difference between an equatorial and axial acid phthalate group, based on rates of saponification of cyclohexyl phthalates in aqueous sodium hydroxide (second order). Rates of first order formolysis and ethanolysis of cyclohexyl tosylates (p-toluenesulfonates) gave ΔF_{OTs} equal to -1.7 kcal./mole. However, bimolecular ethanolysis with added ethoxide ion gave a value of only -0.6.

Eliel and coworkers (7,8,9,10) have made a study of the conformational equilibrium constants for the tosylate and bromide groups. They employed the reaction of these compounds with the strongly nucleophilic thiophenolate ion. The reactions were shown to be second order both by kinetic data and by the isolation of inverted products. Thus trans-4-t-butylcyclohexyl tosylate (or bromide) reacts with sodium thiophenolate to give cis-4-t-butylcyclohexyl phenyl thioether. However, some second order elimination also occurs as shown by the



isolation of olefinic products, especially if the tosylate or bromide group occupies the axial position. By a dual titration Eliel has determined both k_S (the second order substitution rate constant) and k_E (the second order elimination rate constant.) The substitution reaction consumes thiophenol and can be followed iodimetrically; both reactions consume total base and can be followed acidimetrically

Substitution: $C_6H_{11}Br + C_6H_5SNa \longrightarrow C_6H_{11}SC_6H_5 + NaBr.$

Elimination: $C_6H_{11}Br + C_6H_5SNa \longrightarrow C_6H_{10} + NaBr + C_6H_5SH.$

since, with methyl orange indicator, sodium thiophenolate is basic and thiophenol is neutral.

Table II

Average values for reaction of cyclohexyl tosylates with sodium thiophenolate in 87% ethanol at 25.1° C.

Substituent	$10^5 k_T$*	$10^5 k_S$	$10^5 k_E$*	K	ΔF(kcal./mole
Hydrogen	18.35	10.09	8.26	3.24', 3.12"	-0.7',-0.7'
Cis-4-t-butyl	70.19	36.12	34.07	0 (assumed)	---
Trans-4-t-butyl	1.95	1.95	0	∞ (assumed)	---
Cis-4-methyl	46.20	18.20	28.00	1.10',0.22"	-0.1',0.9"
Trans-4-methyl	2.58	2.58	0	107.#	-2.8#
Cis-3-methyl	2.41	2.41	0	149.#	-3.0#
Trans-3-methyl	59.30	32.25	26.95	0.12',0.28"	1.2',0.7"
4,4-Dimethyl	19.04	19.04	0	---	---

*1 mole^{-1}sec^{-1} 'Based on k_S "Based on k_E #Based on k_T.

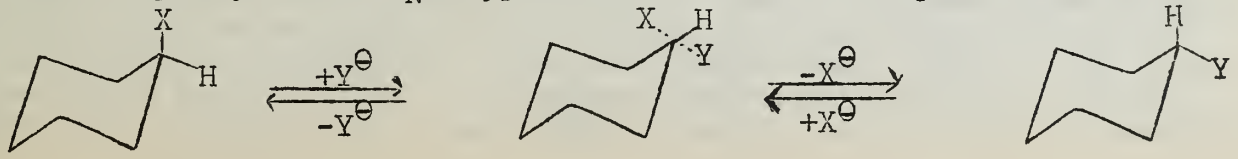
The data in Table II give $\Delta F_{OTs} = -0.7$ kcal./mole in contrast to Winstein's preferred value of -1.7. This is the worst disagreement in the published kinetically-determined energy values. While one would expect the value for the tosylate group to be somewhat higher than that for the hydroxyl group, Winstein's value seems exceptionally high considering that the tosylate group can be rotated to a position where it does not increase the interference of the oxygen atom with the axial hydrogen atoms at positions 3 and 5.

Applying the value $\Delta F_{Me} = -1.8$ kcal./mole to the methyl substituted cyclohexyl tosylates, we calculate:

$\Delta F_{cis\text{-}4\text{-}methyl} = 1.8 - 0.7 = 1.1$ and
$\Delta F_{trans\text{-}4\text{-}methyl} = -1.8 - 0.7 = -2.5.$

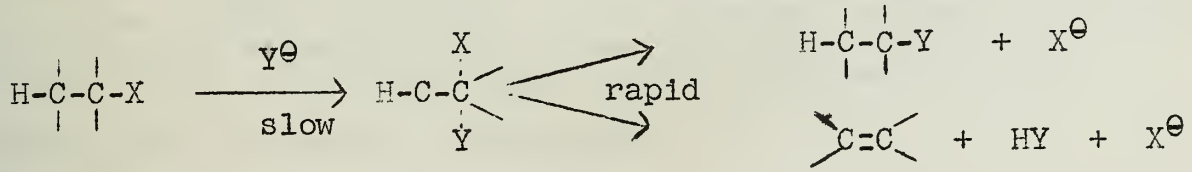
The only serious disagreement between the experimental and calculated energies is the case of $\Delta F_{cis\text{-}4\text{-}Me}$ as calculated from k_S. That this may be due to some undetermined experimental error is supported by the better agreement in the conformationally analogous trans-3-methyl case ($\Delta F_{calc} = 1.1$.) The data also show that the cis-3-methyl compound is more completely in the diequatorial conformation than the trans-4-methyl analog; this is again due to the unfavorable 1,3-diaxial interaction in the diaxial conformation of the former compound.

The data in Table II also indicate that an axial substituent reacts more rapidly in an S_N2-type reaction than an equatorial one.



The transition state for X equatorial differs from that for X axial mainly due to the steric requirements of X and Y. If X and Y are of similar size, the transition state energy level will be about the same regardless of whether X is equatorial or axial in the starting molecule. Thus the axial conformation will react faster since its ground state is higher than the equatorial, leading to a lower activation energy (7).

The reaction of cyclohexyl tosylates and thiophenolate ion seems to be an example of Winstein's "merged mechanism" (8,11). By this hypothesis, the substrate reacts with a nucleophile in a slow rate-determining step to give an intermediate, similar to the transition state for an S_N2 reaction, which then can give either substitution or elimination products in a rapid competition. Thus 4,4-dimethylcyclo-



hexyl tosylate reacts with thiophenolate at an over-all rate essentially equal to that of the unsubstituted tosylate. However, it gives no elimination products while the cyclohexyl compound gives almost one-half cyclohexene. We could explain the lack of elimination in the former case as being due to steric interference toward the nucleophile attacking the axial proton at position 2 caused by the axial methyl group at position 4. However, assuming that this reaction is only a dichotomy of S_N2 and E2 reactions does not explain the <u>increase</u> in substitution rate in the dimethyl case, so that the over-all rate is hardly affected. The merged mechanism does account for this if we assume that the formation of the intermediate is the slow step and that the final product-determining step is rapid compared to it. This view of the mechanism still requires an attacking base for the proton removal in elimination (12).

In Table III are given Eliel's data for the thiophenolate reaction using cyclohexyl bromides as the substrates. The average value for ΔF_{Br} is seen to be -0.7 kcal./mole.

<u>Table III</u>

Average values for reaction of cyclohexyl bromides with sodium thiophenolate in 87% ethanol at 25.1° C.

<u>Substituent</u>	10^5k_T* 10^5k_S* 10^5k_E*	K	<u>ΔF(kcal./mole)</u>
Hydrogen	2.28 1.21 1.07	3.2', 3.56"	-0.7', -0.75"
<u>Cis</u>-4-<u>t</u>-butyl	9.44 4.81 4.63	0 (assumed)	---
<u>Trans</u>-4-<u>t</u>-butyl	0.15 0.08 0.07	∞(assumed)	---
<u>Cis</u>-4-methyl	6.40 3.14 3.26	0.55', 0.43"	0.35', 0.5"

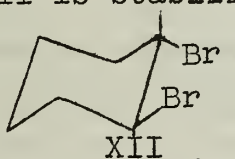
*1 mole^{-1}sec^{-1} 'Based on k_S "Based on k_E.

The data for <u>cis</u>-4-methylcyclohexyl bromide show that ΔF_{Me} is greater than ΔF_{Br}, and the favorable conformation has the methyl group equatorial and the bromine axial. That K differs considerably from unity may be surprising considering that the methyl group and the bromine atom have almost identical Vander Waal radii (1.95 Å for Br and 2.0 Å for Me) (13). In <u>ortho</u>-substituted biphenyls bromine hinders free rotation even more than a methyl group (14). To explain

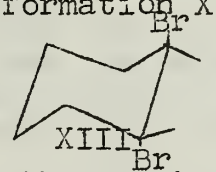
this anomaly Eliel has suggested the importance of the C-X bond length where X is the group being considered. The normal C-Me distance is 1.54 Å and the C-Br distance is 1.91 Å. (15) In a 1,3-diaxial interaction where the interfering groups are parallel, the Br atom would be further removed from the axial H at position 3 and its interference, as compared with the methyl group, would not be as great as expected from a consideration of Vander Waal radii alone. In biphenyls, on the other hand, the interfering groups more or less point toward each other and the longer C-Br bond length accentuates the interference. Secondly, the biphenyl interactions occur at shorter interatomic distances where repulsive forces are predominant. The 2,2' H-Br distance is about 1.61 Å before deformation in a coplanar biphenyl model (16) while the 1,3-diaxial H-Br distance in the cyclohexane system is about 2.67 Å. At the longer distances of the latter case, London attractive forces between hydrogen and bromine begin to play a prominent role since they fall off to a lower exponential power of distance than repulsive forces (17, 18).

METHODS BASED ON PHYSICAL MEASUREMENTS

Corey (19) has calculated a value of ΔF_{Br} based on an electron diffraction study (20) which shows that trans-1,2-dibromocyclohexane in the vapor state exists as about one-half of the diequatorial form XII and one-half of the diaxial form XIII; or, $F_{XIII-XII} = 0$. Conformation XIII is stabilized with respect to conformation XII by a



XII



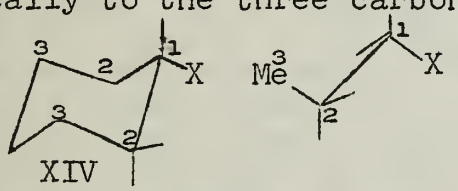
XIII

factor equal to the difference in energy between the gauche and trans forms of 1,2-dibromoethane; it is destabilized by a factor of $2\Delta F_{Br}$. The gauche-trans energy difference for 1,2-dibromoethane has been determined as 1.4 kcal./mole by the variation of IR intensities and dipole moments with temperature (21); thus $\Delta F_{Br} = -0.7$. The same argument can be applied to the data:

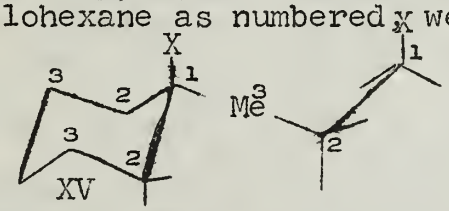
1) Trans-1,2-dichlorocyclohexane in the vapor state exists as a 56/44 mixture of conformations favoring the diequatorial form, corresponding to an energy difference of 0.1 kcal./mole (20).
2) The gauche-trans energy difference for 1,2-dichloroethane is 1.1 kcal./mole (21).

The value of ΔF_{Cl} is then -0.6 kcal./mole.

Another method employs comparisons with n-propyl derivatives. By considering the three carbons of the propyl group to be analogous sterically to the three carbons of cyclohexane as numbered we can



XIV



XV

see that ΔF_X can be approximately equated to twice the gauche-trans energy difference about the 1-2 bond of the corresponding n-propyl derivative, since two trans type C-X interactions are involved in the equatorial form (XIV) and two gauche type interactions in the diaxial form (XV). A summary is given in Table IV.

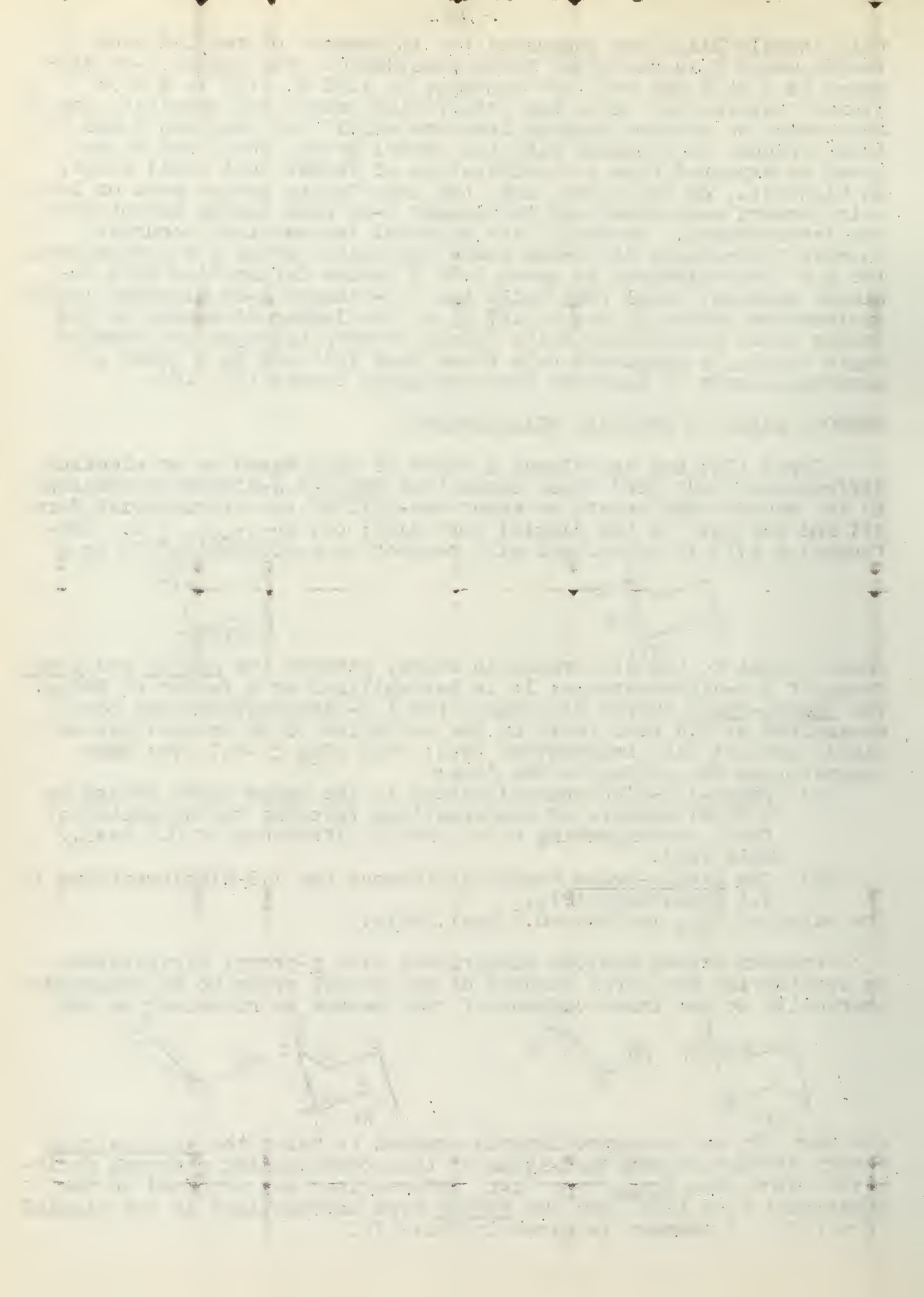


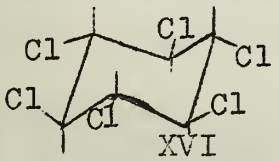
Table IV

Values of ΔF based on n-propyl derivatives

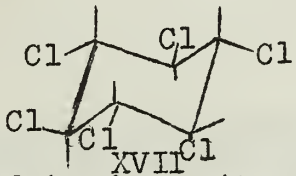
Substituent	Gauche-trans energy difference*	ΔF*	Ref.
Me	0.8 (based on n-butane)	-1.6'	22
Br	0.5 (based on n-propyl bromide)	-1.0	23
Cl	0.3 (based on n-propyl chloride)	-0.6	23
OH	0.8 (based on 1-propanol)	-1.6	24

*kcal./mole 'Revised by Pitzer to -1.8 kcal./mole to give a better fit of calculated and experimental entropies (25).

Schwabe (26) measured the heats of combustion of several of the isomeric hexachlorocyclohexanes and found values of -657.25 kcal./mol for the β-isomer (XVI) and -659.24 for the δ-isomer (XVII). Since the distances (1e:2e) and (1e:2a) are very nearly identical, the energy of XVII should differ from that of XVI by a factor of ΔF_{Cl}; hence, ΔF_{Cl} = -2.0 kcal./mole (assuming $\Delta H \cong \Delta F$). However, the diaxial



XVI



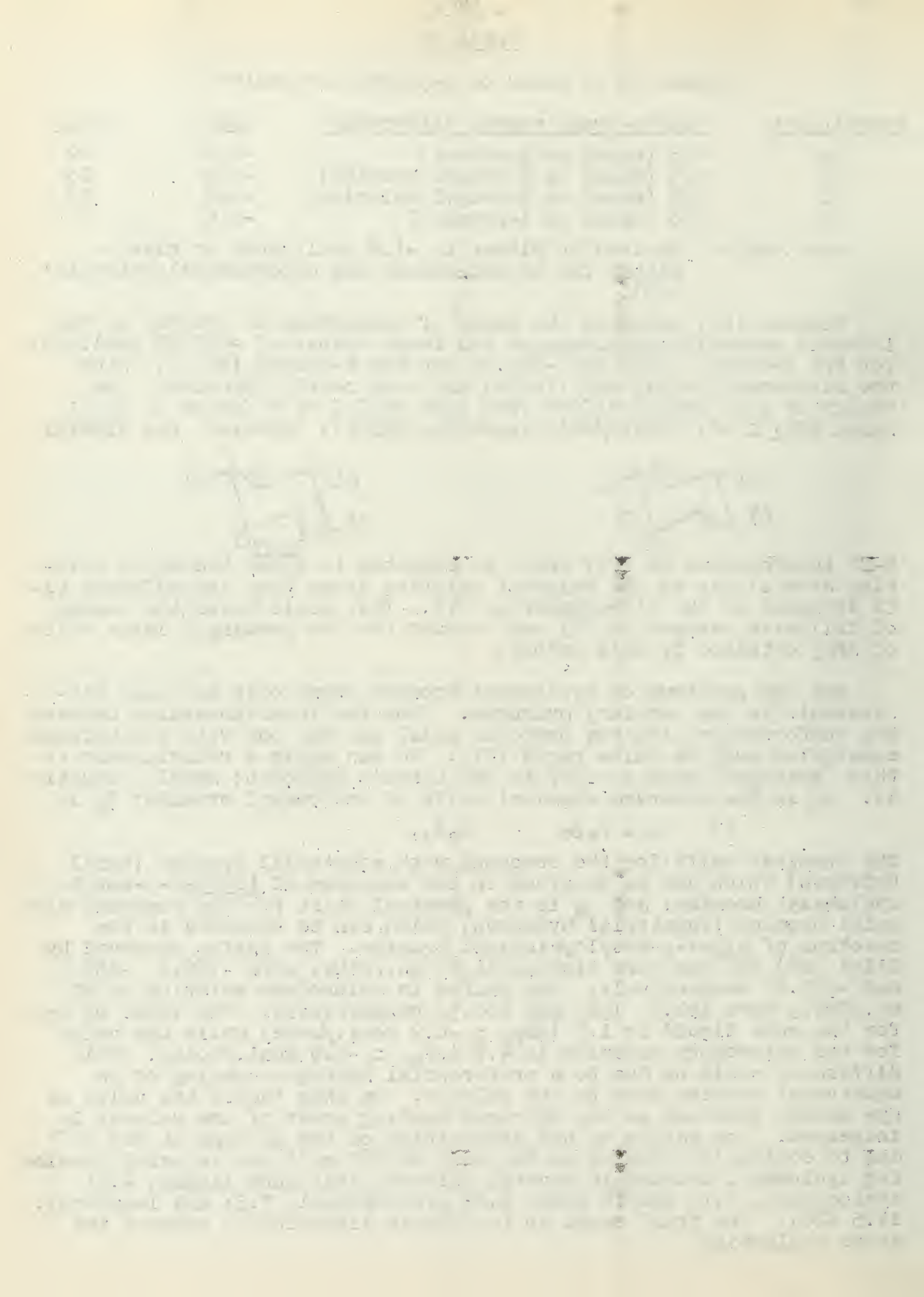
XVII

H-Cl interactions in XVII would be expected to force the axial chlorine atom closer to the adjacent chlorine atoms than the adjacent Cl-Cl distance in the all-equatorial XVI. This would raise the energy of XVII with respect to XVI and account for the seemingly large value of ΔF_{Cl} obtained by this method.

The NMR spectrum of cyclohexyl bromide shows only one peak attributable to the tertiary hydrogen. Thus the interconversion between the conformation with the hydrogen axial and the one with the hydrogen equatorial must be quite rapid (27). We can apply a relationship to this "averaged" peak similar to the kinetic approach; namely, equation 4). δ_H is the observed chemical shift of cyclohexyl bromide; δ_e is

$$4) \quad \delta_H = N_e \delta_e + N_a \delta_a .$$

the chemical shift for the compound with equatorial bromine (axial hydrogen) which can be observed in the spectrum of trans-4-t-butylcyclohexyl bromide; and δ_a is the chemical shift for the compound with axial bromine (equatorial hydrogen) which can be observed in the spectrum of cis-4-t-butylcyclohexyl bromide. The shifts observed by Eliel (28) for the pure liquids at 40 mc./$SiMe_4$ were -166.5, -152.5, and -185.0, respectively. The shifts in chloroform solution at 60 mc./$CHCl_3$ were 191.5, 198, and 160.5, respectively. The value of K_{Br} for the pure liquid is 1.3 (ΔF_{Br} = -0.2 kcal./mole) while the value for the chloroform solution is 4.8 (ΔF_{Br} = -0.9 kcal./mole). This difference could be due to a preferential hydrogen bonding of an equatorial bromine atom to the solvent. On this theory the value of K_{Br} should increase as the hydrogen bonding power of the solvent is increased. The ratios of the intensities of the IR band at 709 cm^{-1} due to equatorial bromine to the band at 685 cm^{-1} due to axial bromine for cyclohexyl bromide in several solvents are: pure liquid, 4.4; cyclohexane, 5.7; acetic acid, 6.6; cyclohexanol, 7.5; and 1-butanol, 11.5 (28). The trend seems in the proper direction to support the above explantion.



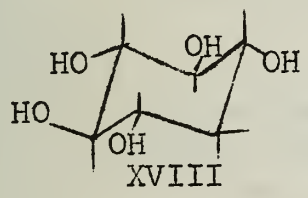
Pickering and Price (29) compared the intensities of the C-OH stretching bands in the IR ascribed to equatorial hydroxyl in cyclohexanol (1069 cm^{-1}) and in trans-4-t-butylcyclohexanol (1062 cm^{-1}). On the basis of the somewhat questionable assumption that the molar extinction coefficients for the two compounds are identical, they calculated that cyclohexanol in a 0.3M solution in CS_2 at 20° C. exists with 62.6-66.2% of its hydroxyl groups in the equatorial position; or, ΔF_{OH} = -0.3 - -0.4 kcal./mole.

DIRECT EQUILIBRATION STUDIES

Eliel and Ro (30) treated the cis- and trans-4-t-butylcyclohexanols with aluminum isopropoxide in a large excess of isopropyl alcohol for 96 hours at 87° C. The equilibrium approached from both directions, determined by IR and VPC, was 79± 2% of the trans-alcohol and 21± 2% of the cis-alcohol. This gives us K_{OH} = 3.76 and ΔF_{OH} = -1.0 kcal./mole. Again this assumes that the t-butyl group will be equatorial. Because of the large excess of isopropyl alcohol, very little of the cyclohexanol was present as the aluminum alkoxide when the equilibration was terminated.

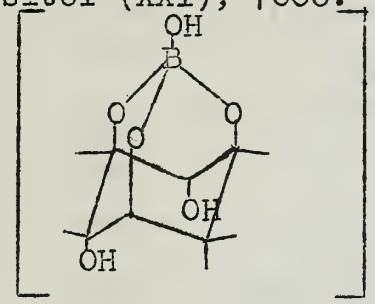
BORATE COMPLEX FORMATION OF CIS-1,3,5 CYCLITOLS

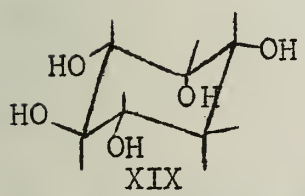
Angyal and McHugh (31) have shown that cis-1,3,5 trihydroxy cyclohexyl compounds form 1:1 complexes with borate ion having a structure requiring a triaxial conformation of the three hydroxyl groups involved. By measuring changes in pH, these workers determined the equilibrium constant (K_B) and free energy change for this reaction with various cyclitols. Values of K_B for cases where the triequatorial conformation of the three hydroxyl groups involved is highly favored are: scylloquercitol (XVIII), 5.0; epiquercitol (XIX), 310.; myoinositol (XX), 25.; and epiinositol (XXI), 7000.



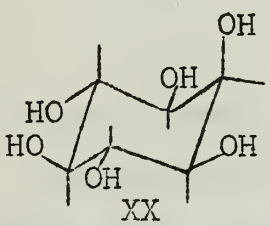
XVIII

+ $borate^{-1}$ ⟶

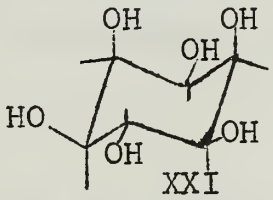




XIX



XX



XXI

Let us define the following terms:

ΔF_B--the free energy of complex formation due to inversion of the ring and esterification with borate ion, but excluding all changes in diaxial interactions and 1,2-dihydroxyl interactions.

$(O_a:O_a)$--the energy of a 1,3-diaxial dihydroxyl interaction.

$(O_a:H_a)$--the energy of a 1,3-diaxial hydroxyl-hydrogen interaction

$(O_1:O_2)$--the energy of a 1,2-dihydroxyl interaction.

To a first approximation, the experimentally determined free energy change during reaction, ΔF_{exp}, is composed of ΔF_B plus the diaxial and adjacent hydroxyl interactions in the complex minus those in the starting cyclitol. Thus for scyllcquercitol (XVIII) above:

$$\Delta F_{exp} = -0.95 = \Delta F_B + (O_a{:}O_a) + 2(O_a{:}H_a) - 4(O_1{:}O_2).$$

Applying this method to the cyclitols studied and treating the data by a least squares method gave a value of $(O_a{:}H_a) = 0.45$ kcal./mole. Since the conformational equilibrium constant for the hydroxyl group is due mainly to two such 1,3-diaxial hydroxyl-hydrogen interactions $\Delta F_{OH} = -0.9$ kcal./mole.

Table V

Summary of ΔF values

Group	Solvent and T	ΔF (kcal./mole)	Method
OH	Pyridine at 25°	-0.5	Kinetic(acetylation).
	75% AcOH at 75°	-0.8	Kinetic(oxidation).
	----	(-1.6)	Comparison to n-propyl cmp
	Water	-0.9	Borate complex formation
	2-Propanol at 87°	-1.0	Equilibrium
	CS_2 at 20°	-0.4	IR analysis
Acid phthalate	Water at 50°	-1.2	Kinetic(hydrolysis)
OTs	HCOOH at 25-50°	(-1.7)	Kinetic(solvolysis).
	Ethanol at 75°	-0.6	Kinetic(bimolecular ethanolysis)
	87% EtOH at 25°	-0.7	Kinetic(thiophenolate)
Br	87% EtOH at 25°	-0.7	Kinetic(thiophenolate)
	----	-0.7	Cmp'n to 1,2-dihalocyclohexanes.
	----	-1.0	Cmp'n to n-propyl cmpd.
	Chloroform	-0.9	NMR
	Pure liquid	-0.2	NMR
Cl	----	-0.6	Cmp'n to 1,2-dihalocyclohexanes
	----	-0.6	Cmp'n to n-propyl cmpd.
	Pure liquid	(-2.0)	Heat of combustion
Me	----	-1.8	Cmp'n to n-propyl cmpd.

( ) --questionable value.

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PSILOCYBINE AND OTHER HALLUCINOGENIC ALKALOIDS

Reported by C. K. Steinhardt October 15, 1959

Man has always been fascinated by materials which when ingested produce a change in mental state. A magnificently illustrated two volume work by the amateur mycologists Valentina and R. Gordon Wasson,[1] as well as a popular article in Life[2] magazine in 1957, aroused the interest of the rest of the world in the custom of certain Mexican Indians of using hallucinogenic mushrooms for religious ceremonies and for invoking prophetic and clairvoyant powers. The Wassons made several expeditions to remote areas of Mexico where the Indians were using these mushrooms, and there they too ate them and experienced colorful visions and euphoria lasting for several hours. On one expedition they were accompanied by an eminent French mycologist, R. Heim, who was able to determine botanically the most important of the mushrooms used for intoxication purposes and to collect samples and spores from them. These hallucinogenic mushrooms belong for the most part to the genus Psilocybe, in which eleven species containing the active agent have been found. In addition it has been found in Stropharia cubensis Earle, which grows in Thailand and Cambodia as well as in Mexico. Heim succeeded in cultivating one of the species, Psilocybe mexicana Heim, in his Paris laboratory. Cooperating with Heim was the Sandoz laboratory in Basel, where the mycelium and sclerotium of the same species were successfully cultivated.[3] The following experimental work on isolation, identification and synthesis was carried out in the Pharmazeutisch-chemisches Laboratorium Sandoz, Basel, and Laboratoire de Cryptogamie du Museum National d'Histoire Naturelle, Paris.

Before any chemical investigation of the cultivated mushrooms was begun, it was necessary to test them to see whether they produced the same psychological changes as the naturally grown Mexican mushrooms. One investigator was given 32 mushrooms grown in Paris and another the same number of mushrooms dried at a slightly elevated temperature (total dry weight: 2.4 g.). In both cases the investigators had colorful visions and exhibited the symptoms observed in the Mexican mushroom ceremonies. Thus the cultivated mushrooms appeared to be psychologically active and the hallucinogen was shown to be stable to drying. Another similar experiment showed that the mycelium and sclerotium, which were more easily cultivated, contained the active agent also.

Since active material could not be distinguished from inactive material by animal tests, the investigators were obliged to follow the initial isolation by tests on humans at each step. It was discovered, however, that an active sample could be clearly distinguished from an inactive sample by a test in which 0.8 g. of dried mushroom was ingested rather than a 2.4 g. sample. In this way material was conserved and the effect on the human volunteers was only mild.

In order to prevent the possibility of destroying a sensitive material during isolation, extractions were carried out in neutral solvent at room temperature. The active material remained in the residue with fat solvents like chloroform, benzene or acetone. On the other hand, it was extracted completely with methanol or aqueous ethanol. The extract (methanol) was evaporated and the resulting residue was extracted with petroleum ether and chloroform to remove impurities. After a further purification with aqueous ethanol, the

residue was about one hundred times as active as the dried mushrooms.

The residue was chromatographed on Whatman #1 paper developed with water-saturated butanol. Four zones were present whose positions were determined by cutting the chromatogram into fine strips perpendicular to the direction of motion of the solvent and extracting each strip with methanol, followed by gravimetric determination of the residue after evaporation of the methanol. One of the spots contained practically all of the activity in the form of a water-soluble halogen-containing powder. The halogen was removed by treatment of the aqueous chromatogram extract with silver carbonate followed by hydrogen sulfide to remove excess silver. When the solution was filtered and concentrated, the active substance separated as fine white needles.

The new substance, which was named psilocybine, gave the violet color characteristic of indole derivatives when treated with the Keller reagent as well as with the Van-Urk reagent. With the aid of these color tests the isolation and purification procedures could be followed and perfected. Thus the chromatogram could be sprayed with the Van-Urk reagent, p-dimethylaminobenzaldehyde in benzene, and then exposed to dry HCl, whereupon a violet spot (R_f 0.1) would appear for psilocybine. With the aid of this reagent another very faintly blue spot was located at R_f 0.5. This second indole compound, present only in trace quantities, was named psilocine. The same procedures were used for the extraction of the active components from the mycelium and sclerotium. Preparative batches were worked up in a similar fashion, except that column chromatography using cellulose powder was substituted for the paper chromatogram. Each fraction was tested for indole derivatives with Keller reagent (ferric chloride, acetic acid and concentrated sulfuric acid). In this way a quantity of psilocybine sufficient for further chemical and psychological studies was obtained. The yield of psilocybine from dried fruiting bodies of Psilocybe mexicana Heim is about 0.2 to 0.4%; from mycelium and sclerotium, about 0.2 to 0.3%.

Recrystallization from water of the material obtained from the chromatogram yielded alkaloid having water of crystallization, m.p. 220-228°; recrystallized from methanol, the alkaloid contained methanol of crystallization, m.p. 185-195°. A 1% solution of psilocybine in 50% aqueous alcohol had a pH of 5.2. An equivalent weight of 284 was found by potentiometric titration of psilocybine in 50% methanol with 0.1 N sodium hydroxide. This equivalent corresponds to its molecular weight. Psilocybine is amphoteric in character since it dissolves in dilute aqueous acid as well as base. Elemental analysis indicates an empirical formula $C_{12}H_{17}N_2O_4P$ (m.w. 284). The compound is optically inactive.

The ultraviolet spectrum shows the characteristic shape of an indole derivative substituted in the 4-position, with maxima at 220, 267, and 290 mμ. In the infrared spectrum, a band at 2350 $cm.^{-1}$ is due to an inner ammonium salt.

Psilocine could be crystallized from the residues of the chromatographic fractions giving a blue Keller's test by extracting the basified residue with ether and taking up the residue from the evaporated ether extracts in acetone. Psilocine crystallized from methanol free from solvent, m.p. 173-176°. The compound sublimed, undecomposed, under high vacuum at 120-140°. Like psilocybine, psilocine

is amphoteric in character, dissolving readily in acidic or basic media. However, in solution, especially basic solutions, it is quite unstable and the solutions turn blue or blue-green on standing. Elemental analysis of psilocine gives an empirical formula $C_{12}H_{16}N_2O$.

The ultraviolet spectrum, with maxima at 222, 260, 267, 283 and 293 mμ, again indicates an indole substituted in the 4-position. The infrared spectrum, with absorption at 2300-2400 cm^{-1}, indicates an ammonium salt like that of psilocybine. Nevertheless both the infrared and the ultraviolet spectra of psilocine are distinguishable from those of psilocybine. The yield of psilocine from the fruiting bodies of Psilocybe mexicana Heim was about 0.05% of the weight of the dried mushroom material. The sclerotium and mycelium contained little or no psilocine.

Hydrolysis of psilocybine in a nitrogen atmosphere in a bomb-tube at 150° gave a quantitative yield of phosphoric acid, which was characterized as magnesium ammonium phosphate, and psilocine. Pyrolysis of psilocybine at 300-320° also yielded psilocine, but the yield was poor. Treatment of psilocybine with diazomethane afforded dimethylpsilocybine, a neutral, water soluble compound which was nearly insoluble in organic reagents. In this compound, psilocybine's alkalititrable group has been esterified, and the second methyl group has been placed on the nitrogen atom which in psilocybine already carries two methyl groups. Dimethylpsilocybine can be pyrolyzed in high vacuum at 280-290° to yield one equivalent of trimethylamine, which can be trapped as the picrate.

From the above considerations and from a knowledge that nearly all of the naturally occurring indole compounds are tryptamine derivatives, the structure X, O-phosphoryl-4-hydroxy-ω-N,N-dimethyltryptamine, was proposed for psilocybine. Correspondingly, for psilocine, 4-hydroxy-ω-N,N-dimethyltryptamine (VIII) and for dimethylpsilocybine, structure XI were proposed. These structures were established by the synthesis outlined in Chart I.

2-Methyl-3-nitrophenol (which can be obtained from 2,6-dinitrotoluene by reduction of one of the nitro groups, diazotization of the resulting amino group and replacement of it with a hydroxy group[4,5,6]) was treated with benzyl chloride and sodium ethoxide to give 2-nitro-6-benzoxytoluene (II)[7]. Treatment of II with diethyl oxalate and potassium ethoxide yields III, which, when reduced with sodium hydrosulfite and decarboxylated, affords 4-benzyloxyindole (V)[7]. Treatment of V with oxalyl chloride followed by dimethylamine formed [4-benzyloxyindolyl-(3)]glyoxalic acid dimethylamide (VI). Reduction of VI with lithium aluminum hydride followed by catalytic hydrogenation on palladium gave 4-hydroxy-ω-N,N-dimethyltryptamine (VIII) which was identical with natural psilocine. The phosphorylation of psilocine to psylocybine was accomplished by causing the sodium salt of psilocine to react with dibenzylphosphoryl chloride. The dibenzyl compound (IX) was reduced catalytically, again using palladium-on-aluminum oxide, to give 4-phosphoryloxy-ω-N,N-dimethyltryptaime (X), which corresponded in all properties to natural psilocybine[3].

Psilocybine's effect on isolated organs is limited to a general suppressing effect. On the organism as a whole it has a vegetative effect and causes such symptoms as mydriasis, tachycardia, rising blood pressure, and contraction of the nictitating membrane, all of which can be interpreted as a consequence of stimulation of the sympathetic nervous system[3,8]. Motor behavior is generally suppressed.

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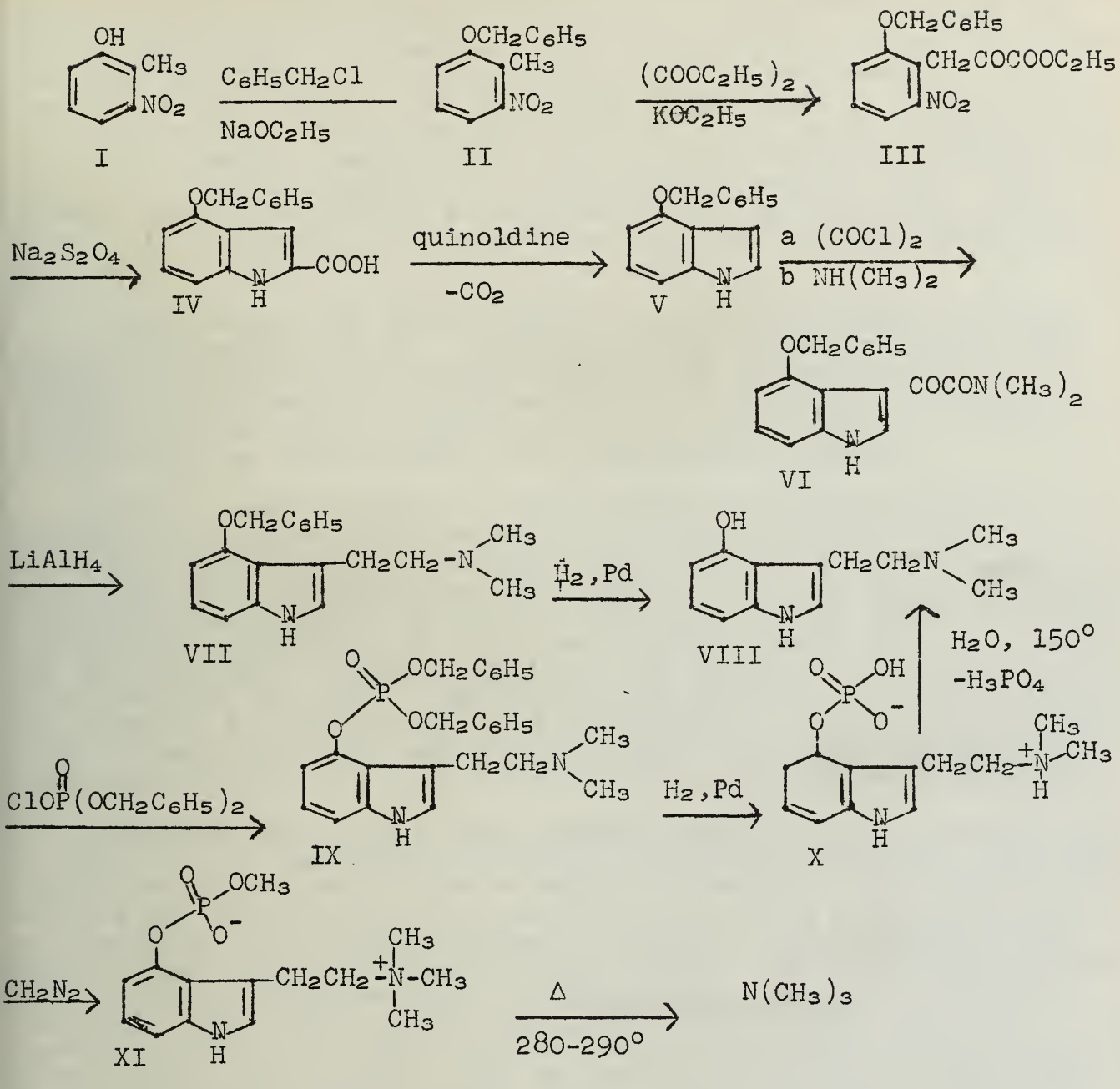
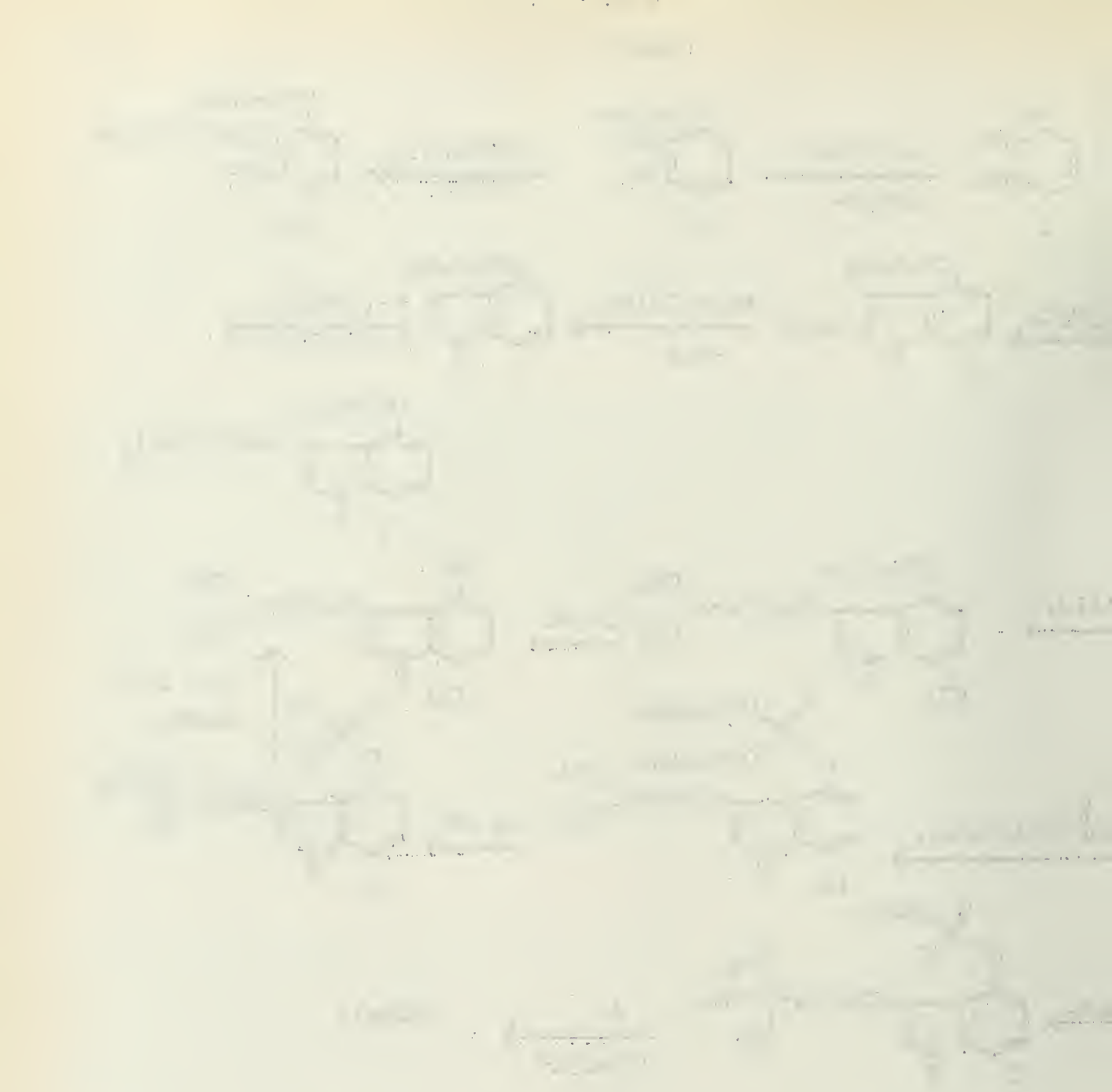
Chart I



The psychological effects of psilocybine are the same as those of the fresh or dried mushrooms. About forty-five to sixty minutes after oral ingestion of 4 to 8 mg. of crystaline psilocybine, a euphoric delirium sets in which lasts for several hours. Although the symptoms vary with the individual, in general this delirium is characterized by a change in one's perception of space, time, and one's self, and often it is accompanied by a feeling of general relaxation. In higher doses, psilocybine provokes vivid color hallucinations and visions in addition to the vegetative disturbances described above. Consciousness is maintained throughout, however, and the subjects are able to report their experiences. In general, even after high doses, no after effects were observed[1,3]. In all tests conducted up to the present time, psilocin has exhibited qualitatively and quantitatively the same effects as psilocybine[3].



There is an increasing amount of evidence that certain indole derivatives, particularly tryptamine derivatives, exert a powerful effect upon the functioning of the nervous system.[9] Serotonin (5-hydroxytryptamine) is a naturally occurring amine which can be isolated from the brain and seems to play a part in the chemistry of the central nervous system. At the present time, there is no proof that serotonin controls normal mental processes, but interference with its action leads to malfunction of the nervous system[10]. Woolley and Shaw[11,12,13] have suggested that the mode of action of these tryptamine derivatives may be as antimetabolates of serotonin. Therefore it is of interest to compare the structure of psilocybine and psilocine to other known psychotropic agents.

A spectacular and widely studied psychotropic drug is lysergic acid diethylamide (LSD-25). This drug, XII, is unique because it produces profound psychological changes when administered in trace amounts. The chemist who synthesized it in 1943 was so overcome by its effects that he was forced to leave the laboratory. As little as 80 to 100 µg. will produce the hallucinogenic effect[14].

LSD is a semi-synthetic product related to a whole group of lysergic acid amides which belong to the ergot alkaloid family. The compounds of this family, together with the newly discovered psilocybe alkaloids, are unique in that they are the only naturally occurring indole alkaloids in which the 4-position of the indole moiety is substituted[3]. The rest of the ergot alkaloid family does not produce the profound psychological effects of LSD however. The psychotropic effect of LSD, in fact, is very sensitive to minor structural changes. For example, 2-bromolysergic acid diethylamide is not hallucinogenic, even in doses 200 times the effective dose for LSD[15], and indeed when given by mouth for two days it will prevent LSD-induced psychosis[16].

Since the discovery of the powerful psychological effects of LSD in 1943, several naturally occurring tryptamine derivatives have been discovered which produce similar effects. Certain Indians of South America and of the Caribbean Islands have for many years used a kind of ceremonial snuff which produced a state of intoxication during which visions and hallucinations were common. The snuff was thought to be prepared from the seeds of Piptadenia peregrina (L.) Benth. Stromberg[17] has described the isolation of bufotenine (XIII), a known tryptamine alkaloid which previously had been found in the secretions of certain toads, from the seeds of this species in 0.94% yield (40% of total alkaloids). This was the first time bufotenine had been isolated from a plant material. Since that time, Fabing and Hawkins[18] have shown that intravenous injection of bufotenine will produce hallucinations in humans. Later, Fish[19] and his coworkers were able to compare authentic snuff from a Piaroa snuff box in the Smithsonian Institute with laboratory-made snuff made accoring to directions of various observers. Three laboratory snuffs were prepared: 1. Snuff was prepared by roasting the seeds at 175° for 40 minutes, followed by mortar grinding. 2. The first procedure was followed, except that calcium carbonate was added before heating. 3. The seeds were fermented and then a sample was dried and ground. A sample of each of the laboratory-prepared snuffs, as well as one of the authentic snuff, was then ground under 0.5 ml. of ethanol and spotted on a paper chromatogram which was developed with a propanol-ammonia system and sprayed with Ehrlich's spray to make the indole alkaloids visible. The authentic snuff showed one intense spot for a major indole constituent and four faint spots for minor constituents.

The laboratory-prepared snuff showed an identical spot of the same intensity for the major component and also two fainter spots corresponding to two of the minor constituents of the authentic snuff. By means of comparison chromatography (the unknown, a sample of authentic bufotenine, and a mixture of the two all being developed in several solvent systems) the major component has been proven to be bufotenine. This confirmed the results of Stromberg and demonstrated that at least a substantial part of the cause of the hallucinations in the authentic snuff is the presence of bufotenine.

The seeds and pods of another species which grows in Florida, Piptadenia macrocarpa, were extracted with a mixture of chloroform, tetrahydrofuran and ammonium hydroxide at 40°. The organic extracts were washed with more ammonium hydroxide and then extracted with aqueous hydrochloric acid. The acid extracts were basified with sodium carbonate and extracted with chloroform. The residue which remained after the dried chloroform extracts were evaporated was spotted on paper chromatograms and developed using four different solvent systems. Ehrlich's spray indicated the presence of five indole alkaloids. Reference compounds were then chromatographed separately and together with the natural alkaloid which had been eluted from the first chromatogram. Four different solvent systems were used. By this procedure, four of the five compounds were identified as bufotenine, N,N-dimethyltryptamine (XIV), bufotenine oxide and N,N-dimethyltryptamine oxide. Further experiments indicated that the N,N dimethyltryptamine oxide was formed during experimental workup, but that the bufotenine oxide was present in the plant materials.

St. Szara[20] has shown that N,N-dimethyltryptamine produces visual hallucinations, euphoria, distortion of spacial perception and body image, and disorders of thought and speech. These symptoms appear three to five minutes after injection of 0.7-1.1 mg./kg. (of body weight) of the drug, and disappear after one hour. Thus at least two hallucinogens are present in the seeds and pods of the genus Piptadenia.

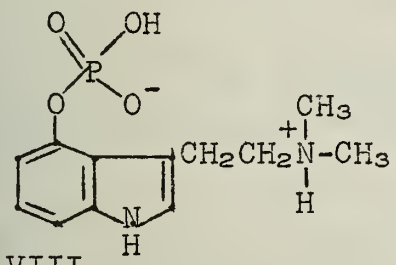
Alkaloids isolated from Banisteria caapi which have been called by such names as telepathine, yageine, and banisterine have been reexamined recently by Hochstein and Paradies[21] using more modern methods, including paper chromatography. Harmine (XV) was isolated in 0.3% hield along with harmaline (3,4-dihydroharmine), and a third compound, 1,2,3,4-tetrahydroharmine. Although harmine has been shown to have a psychotomimetic effect in man[22], a large dose was required and its potency was not thought sufficient to explain the effects experienced by the South American Indians who use a beverage made from Banisteria caapi[23]. Hochstein and Paradies[21] have speculated that dihydro- and tetrahydroharmine may be partially responsible for the symptoms, but clinical tests have not been reported for these compounds. In the hands of these same workers, another South American plant, Prestonia amazonicum, also used by the Indians, yielded N,N-dimethyltryptamine which, as was mentioned previously, is a hallucinogen.

Mescaline (XVI), an alkaloid which can be isolated from the mescal cactus, is an interesting hallucinogen to compare with the indole derivatives discussed so far. Although mescaline is not an indole alkaloid, it produces in man symptoms quite similar to those described for the indole derivatives already discussed. It is not so potent as LSD, since about 10,000 times as much is required to produce

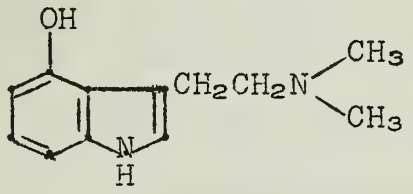
equivalent effects. Because it produces effects like those of the indole alkaloids, some people have tried to see a relation of its chemical structure to that of the other hallucinogens. If the structure is drawn as in structure XVI, mescaline does look more like an indole derivative, but the significance of this has yet to be demonstrated.[24]

There has been much criticism of the theory by which Woolley and Shaw have attempted to correlate the hallucinogenic effects of these indole alkaloids. There are indeed many biological questions for which this theory offers no answers. Nevertheless, it has stimulated considerable research in the field of the chemistry of hallucinogens.

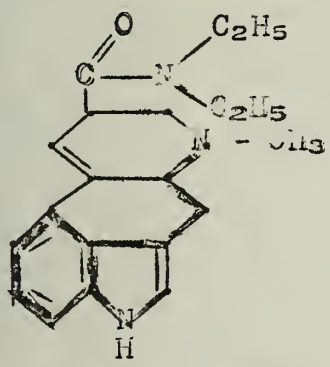
Chart II



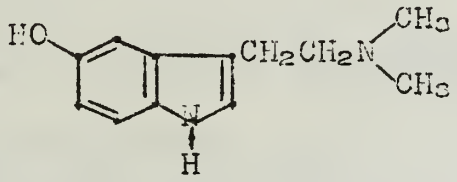
VIII
Psilocybine



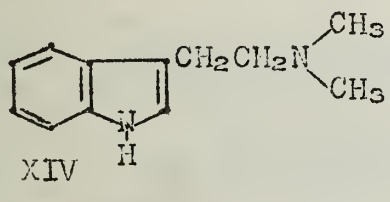
X
Psilocine



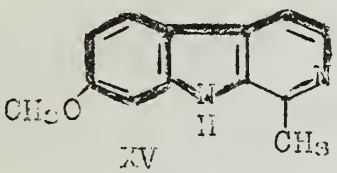
XII
LSD - 25



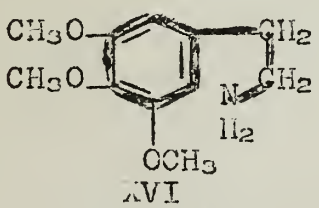
XIII
Bufotenine



XIV
N,N dimethyltryptamine



XV
Harmine



XVI
Mescaline

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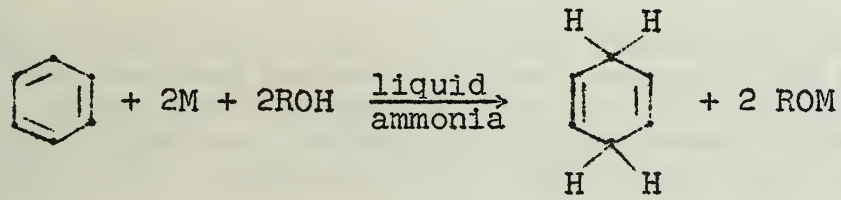
MECHANISM OF THE BIRCH REDUCTION

Reported by G. W. Burton October 22, 1959

The reduction of an aromatic hydrocarbon to the unconjugated dihydro compound in liquid ammonia is usually known as the Birch reduction. In the past few years this reaction has also been carried out in other ammoniacal bases, such as low molecular weight amines. There are two reviews on this reaction, one of which (1) is rather out of date. Birch and Smith have recently reviewed the subject with special emphasis on metal-amine reductions (2). The chemistry of alkali metals in liquid ammonia has also been reviewed in the last year (3). This seminar will deal mainly with a discussion of the proposed mechanism of the Birch reduction.

GENERAL SCOPE OF THE REACTION

The main reaction occurring during the reduction of benzene may be represented by the following equation:

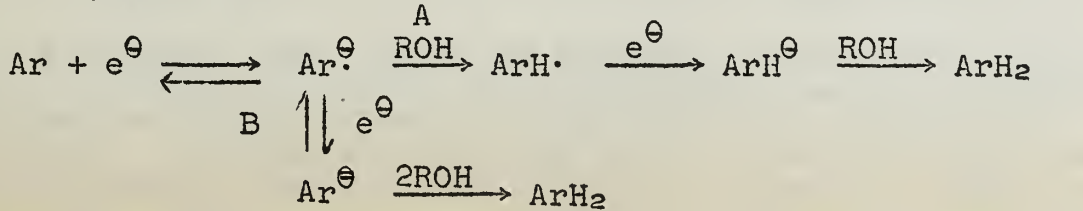


where M is the alkali metal (lithium, sodium, or potassium) and ROH is the proton source, which is usually an alcohol in the case of benzene. When a substituted benzene such as toluene or anisole is reduced, the predominant product is the 2,5-dihydro compound (1). Benzoic acid, on the other hand, forms 1,4-dihydrobenzoic acid (4). In the case of benzenoid compounds, the side products obtained from the reaction are generally cyclohexenes formed from the further reduction of the conjugated diene (1).

PROPOSED MECHANISMS

The oldest theory for the reduction of hydrocarbons is the "nascent" hydrogen theory of Bayer (5), according to which the dissolving metal produces "nascent" hydrogen atoms which are quite reactive and add to organic compounds before combining to form hydrogen molecules. Willstätter and his coworkers (6) rejected this idea because of the results of their study on the reduction of terephthalic acid with sodium amalgam. They were able to prepare a sodium amalgam which did not react appreciably with water, but was able to reduce terephthalic acid which had been dissolved in water. They proposed that the reduction proceeded by the addition of sodium followed by replacement of the sodium by a hydrogen from the solvent.

Birch has proposed a mechanism involving the transfer of electrons from the solvent to the aromatic substance. His mechanism can be represented by the following sequence of reactions (7),



A is proposed as the reaction path for such compounds as benzene and anisole which are thought to form an anion radical and not a dianion in sodium-liquid ammonia solution. The existence of such anion radicals has been shown by the electron paramagnetic resonance work of Weissman and his coworkers (8). Path B has been proposed as the pathway for polynuclear hydrocarbons such as naphthalene and for benzoic acid, since it is thought that they are able to form dianions There is no proof for the formation of a dianion by benzoic acid. Naphthalene is thought to form the dianion, since if sodium is added to a mole of naphthalene in liquid ammonia, at 0.1 moles the solution is green in color, and at 2.0 moles it is orange-red (9). This would indicate that the electron no longer exists in solution, since electrons in solution are blue in color.

A modification of the first step of Birch's mechanism for benzenoid compounds involves the addition of a hydrogen atom instead of an electron (10). There is little experimental evidence which would justify the acceptance of this modification.

KINETICS OF THE REDUCTION OF BENZENE

Krapcho and Bothner-By (11) have determined the kinetic rate law for the reaction between lithium, benzene, and ethanol in liquid ammonia. Vapor phase chromatography was used as the analytical tool. The rates were followed to about seventy five per cent completion. The experimental rate law was found to be

$$\frac{-d(\text{Benzene})}{dt} = k(\text{Benzene})(\text{Li})(\text{EtOH})$$

This rate law is valid for concentrations of benzene in the range 0.02-0.10M. The activation energy between the temperatures -33° and -74° was found to be 2.7 kcal/mole. (The activation energy for the reaction between lithium, benzene, and t-butyl alcohol is 4.4 kcal/mole.) Relative rates also were determined for substituted benzenes (benzene as 1): sodium benzoate$>$200, anisole -3.28, toluene -0.65, and t-butylbenzene -0.05.

EFFECT OF VARIABLES

Krapcho and Bothner-By have also studied the effect of the proton source on the yield. They reduced one mole of benzene with two moles of lithium in liquid ammonia using various kinds of proton sources. The mixture was analyzed by vapor phase chromatography. Their results are given in the following table:

Effect of Proton Source

Kind of Proton Source and Molar Proportion	Major Reduction Product Yield
NH_4Cl, 2	3%
EtOH, 3	94%
H_2O, 5	36%

These data indicate lower yields as stronger proton sources are used. However, in the case of polynuclear hydrocarbons such as naphthalene, good yields are obtained when ammonium chloride is used as the proton source. Ammonium chloride and water, unlike alcohols, react rapidly with alkali metals dissolved in liquid ammonia. Thus it

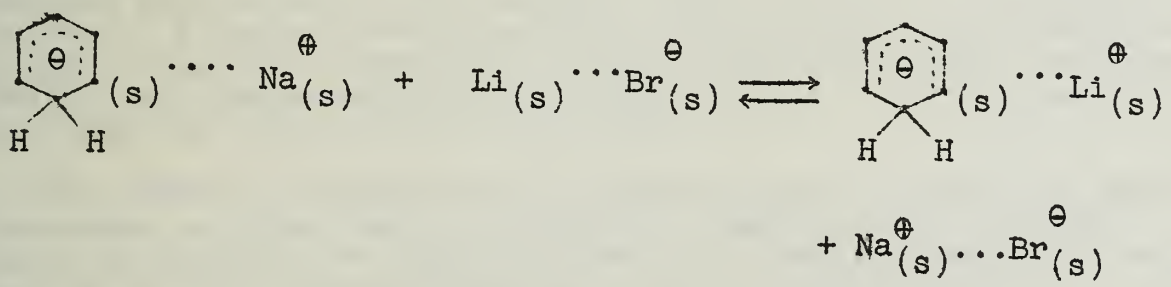
would appear that the reaction between alkali metals and a proton source could compete with the reduction of the aromatic and hence lower its yield.

The effect of the nature of the metal and added salts on the rate of reduction of benzene in liquid ammonia at -34°C., using ethanol as the proton source, has been determined. The initial concentrations of metal, benzene, and ethanol are 0.061M, 0.122M, and 0.122M, respectively. The third order rate constants were determined and are given in the following table:

Effect of Metal and Added Salts

Alkali Metal	Added Salts, moles	k rate $l^2/mole^2$ sec.
Li	...	1.40
Na	...	0.0064
K	...	0.0015
Li	NaCl, 2	0.33
Li	NaCl, 4	0.34
Li	NaBr, 2	0.56
Na	LiBr, 1.9	0.41
Na	NaBr, 2	0.0067

Thus the reaction with lithium is much faster than reactions with sodium or potassium. Lithium bromide accelerated the reaction of sodium by a factor of about sixty; while, sodium bromide or sodium chloride reduced the rate of the lithium reduction by a factor of four. Sodium bromide has little effect on the rate of reduction by sodium metal. These effects of the added salts on the rate are interpreted in terms of the following equilibrium of the ion pairs involved:



The equilibrium would be in favor of the organo-lithium ion pair since the smaller lithium ion would stabilize the anion radical.

Eastham and Larkin (12) have studied the effect of variables on the reduction of potassium 1-naphthoxide to the 1,4-dihydro compound. The rates were measured by following the reaction to the disappearance of the blue color, which was found to be noticeable at a metal concentration below 10^{-3} molar. The following data give some of their results:

Effect of Variables in the Reduction of Potassium 1-Naphthoxide

	Initial Molarity of Reagents			Additives	Reaction time in seconds
	Naphthoxide	Alcohol[a]	Potassium		
1.	0.28	---	0.24	---	2600
2.	---	0.46	0.24	---	1620
3.	0.12	0.46	0.24	---	29
4.	0.12	0.34	0.24	---	27
5.	0.12	0.37	0.24	0.04M H_2O	24
6.	0.12	0.34	0.24	---	19
7.	---	0.34	0.24	---[b]	840
8.	---	0.34	0.24	Ether[b]	622
9.	---	0.34	0.24	Ether[b] and 0.34M KOEt	10600
10.	0.12	0.34	0.24	Ether[b] and 0.34M KOEt	17

Notes: (a) Runs 1-5 were made using t-amyl alcohol.
Runs 6-10 were made using ethyl alcohol.
(b) Ether was 25% by volumn.

In all of the above runs, spectrophotometric analysis showed none of the original aromatic to be present at the end of the reduction. In several of them, the dihydro compound was isolated in about 80% yield.

Comparison of lines 2 and 7 indicates that the nature of the alcohol (primary or tertiary) has an influence on the production of hydrogen in the absence of aromatic compound. The same trend is also found in the reduction of the aromatic compound, the rate being faster with the primary alcohol. (Bothner-By and Krapcho found also that in the reduction of benzene by lithium at -34°, the rate of reduction with ethanol was fourteen times the rate of reduction by t-butanol.) Primary alcohols probably have a larger rate because they are more acidic than tertiary alcohols and because they are more effective in displacing the solvating molecules from around the anion than the bulky tertiary alcohols.

The effect of ether was also investigated (lines 8, 9, and 10) since ether is often used in a reaction because of its better solvent properties for organic material. The data indicate that ether up to 25% concentration has no significant effect.

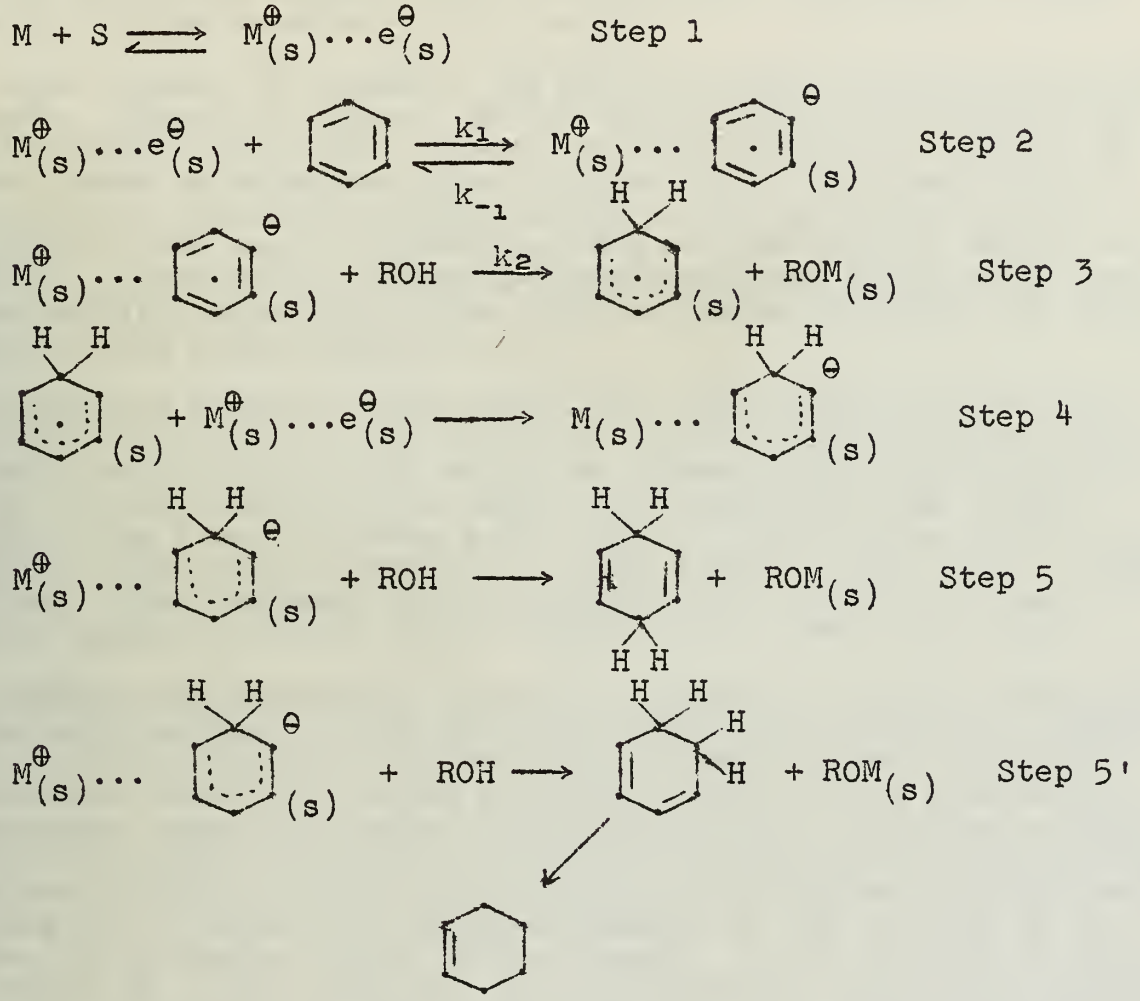
Some interesting observations can be made from the effects of added alkoxide ion. The added alkoxide ion has little effect in the reduction (line 10), but it exhibits a rate decreasing effect in the case of hydrogen liberation (line 9). In fact, it would seem that the hydrogen liberation reaction could almost be eliminated by adding sufficient alkoxide ion.

Eastham and Larkin also have found that oxygen is a good catalyst in this reaction (data not given in this abstract). It promotes both hydrogen liberation and aromatic reduction. The oxygen could not have been consumed in the reaction since the aromatic was reduced. It is thought that the oxygen acts as an electron transfer reagent according to the following equation:

$$K + O_2 \longrightarrow K^{\oplus} + O_2^{\ominus}$$

DETAILED MECHANISM

Krapcho and Bothner-By from their work postulate the following mechanism for the reduction of benzene:

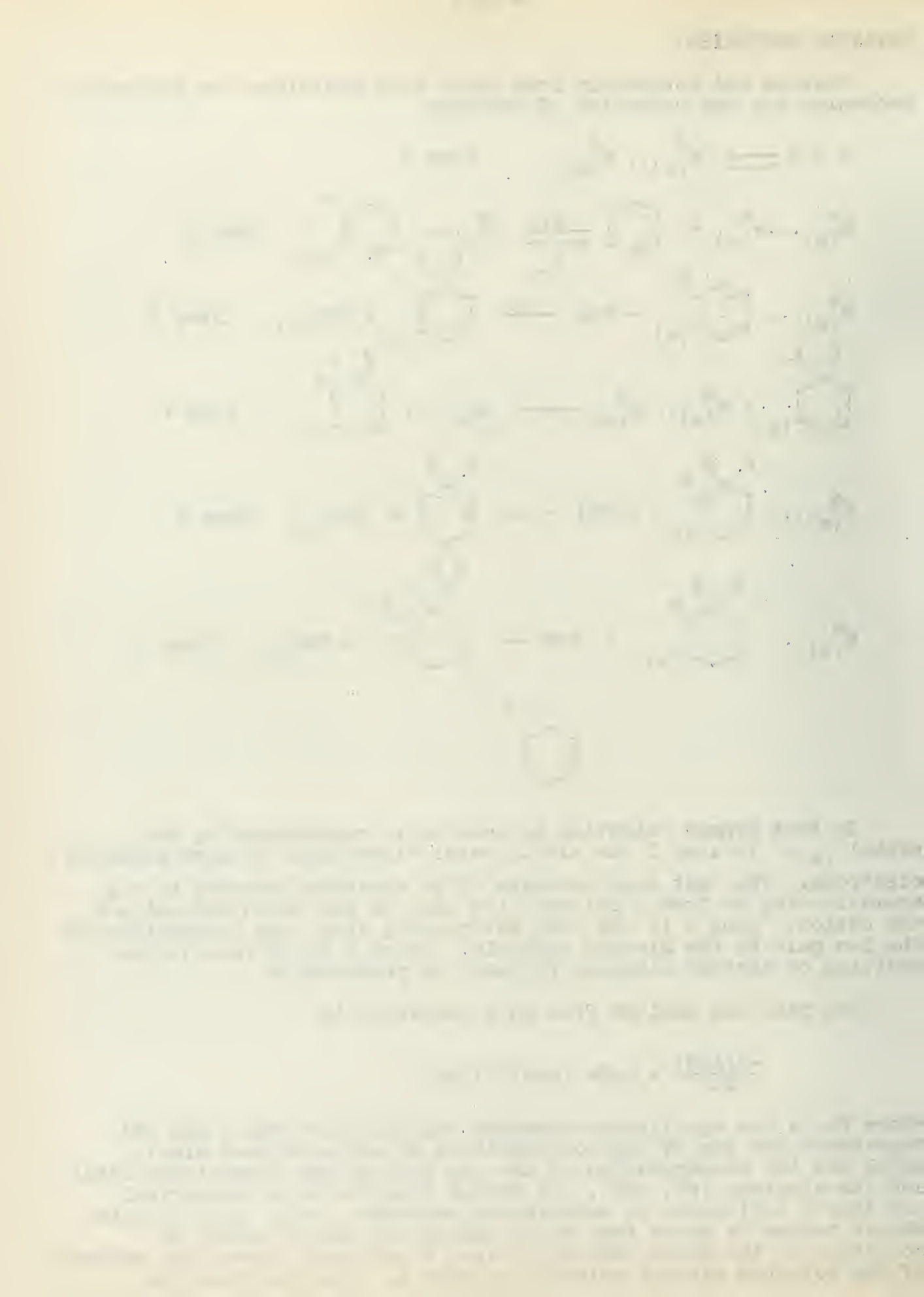


In this scheme solvation by ammonia is represented by the symbol $_{(s)}$. In step 1 the alkali metal dissociates to give solvated electrons. The next step consists of an electron transfer to the aromatic ring to form a solvated ion pair of the anion radical and the cation. Step 3 is the rate determining step, the protonation of the ion pair by the alcohol molecule. Steps 4 and 5 involve the addition of another electron followed by protonation.

The rate law derived from this mechanism is

$$\frac{-d(ArH)}{dt} = k_2 Ke\ (ArH)(M)(ROH)$$

where Ke is the equilibrium constant (k_1/k_{-1}) for step 2 and (M) represents the sum of the concentration of undissociated alkali metal and the concentration of the ion pair of the dissociated metal and its electron ($M^{\oplus}...e^{\ominus}$). Ke should be affected by electrical and steric influences in substituted benzenes. Bulky substituents should reduce Ke since they would lessen the stabilization by solvation of the anion radical in step 2 and would hinder the approach of the solvated alcohol molecule in step 3. Electron donating



groups should also destabilize the radical anion and hence cause a lowering of the rate. When the relative rates of some substituted benzenes were measured, the rate fell from 1 for benzene, to 0.65 for toluene, and to 0.05 for t-butylbenzene. The trend observed here may be due to either steric or electrical effects, or more probably to some combination of the two.

When toluene is reduced, the primary product is the 2,5-dihydro compound. Hence, the attack of the first proton must be at a positio ortho or meta to the alkyl group. In this reaction, there is no product found which arises from protonation in the para position. Electron spin resonance studies indicate that protonation is favorable in the ortho or meta position of the radical anion, since the e.s.r. spectrum in dimethoxyethane indicates about equal density of the unpaired electron at the ortho and meta position, but little or none at the para position (8).

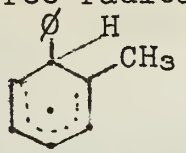
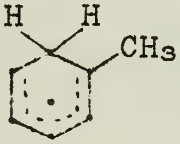
Birch and Nasipuri think that the initial protonation would occu in the meta position. They feel that the accumulation of charge in the ortho and para position would be opposed by the substituent thus making the meta position the position of greatest free charge density. The e.s.r. studies would seem to cast doubts on this explanation since charge density is about equal in the ortho or meta position. Also it seems that the electronic effects of electron donating groups would be to put charge in the ortho position.

Krapcho and Bothner-By also are in favor of initial protonation in the meta position. They give the following reasons for thinking this. The meta position is more open to attack since the alkyl substituents shield the ortho position. The radical produced has the greatest unpaired electrical density at the positions ortho and para to the alkyl group where it could be most efficiently solvated. Subsequent addition of the second proton is hindered by alkyl groups and thus the fraction of reactants passing by way of step 5' to produce cyclohexenes should be increased. In the case of toluene, only about 2% of the products are cyclohexenes, while with t-butylbenzene about 10% of the products formed are assumed to be cyclohexenes (no definite proofs of the structure of these products were made).

It should be pointed out that Krapcho and Bothner-By did not show the stability of the dihydro compounds to the reaction conditions. In fact, Birch has shown (4,13) that 2,5-dihydrotoluene and 2,5-dihydroanisole rearrange upon standing in the reaction medium to the conjugated isomers which are then reduced to the cyclohexenes. Until the rates of isomerization of these compounds are known, little can be said about the significance of the amount of cyclohexenes formed in the reaction.

The solvation of the radical formed in the reaction is of unknown importance. Solvation of radicals is certainly not as important as in cations, yet in electrophilic aromatic substitution, the ortho, para direction of alkyl groups is not disturbed by the inhibition of solvation, since ortho and para products are usually formed in good yields.

The possibility of initial protonation in the ortho position should not be ignored, since from the standpoint of the stability of the resulting radical, ortho protonation would be preferred. In

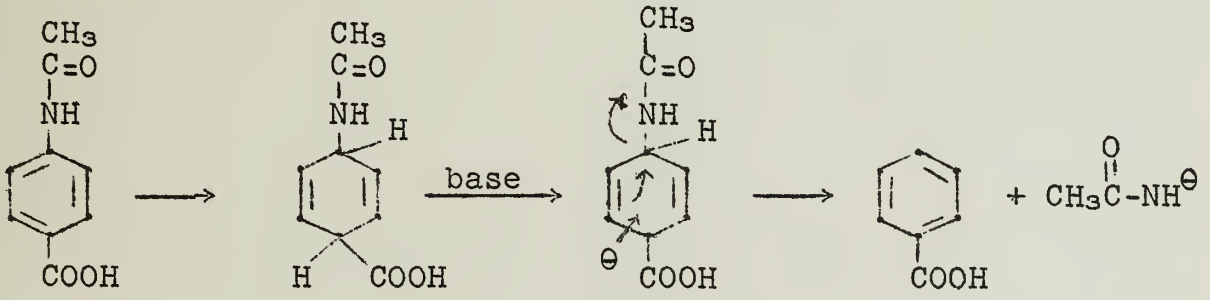
the free radical substitution of toluene by phenyl radical, the isomer distribution of the biphenyls formed is 71% ortho, 17% meta, and 12% para (14). The probable mechanism of free radical substitution involves as an intermediate, the radical  , which is quite similar to the radical,  , which is formed in the Birch reduction if the protonation is ortho.

Birch and Nasipuri have also given some rules for predicting the major products formed when dialkyl or methoxyl-alkyl benzenes are reduced. From the observed products and their supposition of initial meta protonation in the formation of the unconjugated dihydro compound, they conclude that the initial proton will be added meta to the most strongly ortho, para directing group and preferably in a position not occupied by an ortho, para directing group. Thus, meta xylene forms 92% of the 2,5-dihydro compound and only 5% of the 1-4-dihydro compound.

REDUCTION OF AROMATIC ACIDS AND AMIDES

The reduction of aromatic acids and amides has also been investigated recently (15). When aromatic amides derived from ammonia or primary amines are reduced with sodium and ethanol in liquid ammonia, the carbonyl group is reduced before the aromatic ring. If t-butyl alcohol is used in place of ethanol, the 1,4-dihydro compound is formed quite nicely. With the use of the less acidic t-butyl alcohol, the amide can be stabilized by the formation of its conjugate base. Aromatic aldehydes may be prepared by the reduction of aromatic amides formed from secondary amines (16).

One of the interesting aspects of the reduction of aromatic acids occurs in the reduction of acids where there are para substituents which are good leaving groups (methoxyl is excluded). In these cases the substituent can be eliminated. Thus in the reduction of p-acetamidobenzoic acid, acetamide and 1,4-dihydrobenzoic acid are formed. This can be explained on the basis of normal reduction followed by elimination and then a second reduction, i.e.



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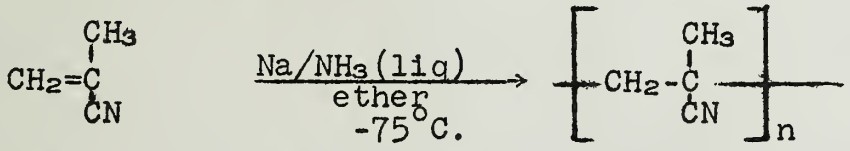
ANIONIC POLYMERIZATION

Reported by David M. Paisley October 29, 1959

The polymerization of vinyl monomers possessing relatively electron-deficient double bonds is readily initiated by reagents capable of generating anions. This seminar will be concerned with recent work in polymer chemistry in which anions clearly play an important role. Certain special types of catalysts generally believed to involve an anionic mechanism will be excluded from consideration; these are coordination catalysis ("Ziegler" catalysis), which has been covered in a recent Organic Seminar (1), and "Alfin" catalysis (2).

EARLY WORK

References to early papers involving examples of anionic polymerization are found in the articles by Higginson and Wooding (3), and Beaman (4). In 1948 Beaman, working in this laboratory, showed that sodium in liquid ammonia is effective in initiating the polymerization which facilitates nucleophilic attacks. The very rapid polymerization of methacrylonitrile can also be effected by Grignard reagents and triphenylmethylsodium, although lower molecular weight polymers are realized. Acrylonitrile and methyl methacrylate also may be polymerized by sodium in liquid ammonia, and styrene yields a



70% conversion (I)

low polymer. Butadiene and isoprene polymerize readily in the presence of metallic sodium at room temperature (5). Alkali metal alkyls have been extensively employed as initiators; for example, in 1930 Marvel and Friedrich (6) observed the rapid addition of ethylene to lithium alkyl and Medvedev (7) in 1944 reported that 2-phenylisopropyllithium catalyzed the polymerization of butadiene in ether solution.

The evidence for a polymerization mechanism involving anionic propagating centers may be summarized as follows:

1. The anionic nature of the effective catalysts. For example, the ionic nature of Grignard reagents and triphenylmethylsodium makes it seem highly unlikely that these reagents would react by homolytic cleavage to yield free radicals, especially in the presence of a highly polar compound such as methacrylonitrile (8).
2. The intense colors which often develop during polymerization (9).
3. The prompt cessation of sodium-catalyzed polymerization upon the introduction of carbon dioxide (10) and the failure of t-butyl-catechol to cause inhibition (11).
4. The conversion of triphenylmethane to triphenylmethylsodium in the zone of polymerization of isoprene under the influence of metallic sodium (10).
5. The structures of the diene polymers obtained which differ from the radical and the cationic polymers (12).
6. The copolymer compositions, which likewise differ from those for both radical and cationic copolymerizations (13).

In a general way, anionic polymerizations in homogeneous media proceed by the following steps. First, the anionic initiator $M^{\delta\oplus}-R^{\delta\ominus}$ adds to the monomer to start a growing polymer chain. The propagating end of the chain is the metal alkyl ($\sim\sim\sim$monomer$^{\delta\ominus}M^{\delta\oplus}$), which determines the structure of the polymer since the entering monomer, as it insinuates itself between the monomer$^{\delta\ominus}$ and the $M^{\delta\oplus}$, is strongly influenced by the electrical and steric forces of the ion pair.

Initiation presumably involves metal alkyls as the primary source of carbanions. These are immediately available from the Grignard reagents, organosodium compounds, or sodium amide used as catalysts; when the alkali metal itself or its solution in liquid ammonia is used, addition to the monomer may precede actual initiation. By analogy to free radical and cationic polymerizations, the propagation step, that is, addition of monomer to the carbanionic center, may occur as shown in Equations II and III.

Initiation: $M^{\delta\oplus}-R^{\delta\ominus} + CH_2=CHY \longrightarrow RCH_2\text{-}\overset{\ominus M^{\oplus}}{CHY}$ (II)

Propagation: $RCH_2\overset{\ominus M^{\oplus}}{CHY} + nCH_2=CHY \longrightarrow RCH_2CHY\left[CH_2CHY\right]_{n-1}CH_2\overset{\ominus M^{\oplus}}{CHY}$ (III)

Higginson and Wooding investigated the kinetics of the polymerization of styrene using potassium amide in liquid ammonia as the catalyst. The rate of polymerization was observed to be proportional to the concentration of the amide ion and to the square of the monomer concentration: $R_p=-dM/dt=k(NH_2^-)(M)^2$. The degree of polymerization, which was independent of the amide ion concentration, increased linearly as the styrene concentration. One nitrogen per polymer molecule was found and the absence of unsaturation in the polymer chains was noted. From these observations the following mechanism was proposed:

$$KNH_2 \rightleftharpoons K^{\oplus} + NH_2^{\ominus}$$

Initiation: $NH_2^{\ominus} + CH_2=CH\emptyset \rightarrow H_2N\text{-}CH_2\overset{\ominus}{\underset{\cdot\cdot}{C}}H\emptyset$ (IV)

Propagation: $H_2N\text{-}CH_2\overset{\ominus}{\underset{\cdot\cdot}{C}}H\emptyset + CH_2=CH\emptyset \rightarrow H_2N\text{-}CH_2CH\emptyset CH_2\overset{\ominus}{\underset{\cdot\cdot}{C}}H\emptyset$ (V)

Termination: $H_2N\left[CH_2CH\emptyset\right]_n CH_2\overset{\ominus}{\underset{\cdot\cdot}{C}}H\emptyset + NH_3 \rightarrow H_2N\left[CH_2CH\emptyset\right]_n CH_2CH\emptyset + NH_2^{\ominus}$ (VI)

Higginson and Wooding also polymerized styrene in liquid ammonia using metallic potassium as the catalyst. The polymers produced were similar to those obtained using potassium amide. In both cases the reaction is second order with respect to styrene, the rate of disappearance of styrene being proportional to $(KNH_2)^{1/2}$ in one case and $(K)^{1/2}$ in the other. The overall rate constants are 2.81 for potassium amide catalysis and 1.75 for potassium catalysis. The inherent viscosities of polystyrene prepared with potassium and potassium amide are similar. The overall similarity indicates that the mechanism of potassium catalysis is the same as that established for potassium amide. In the potassium case it is suggested that amide ion is the actual catalyst, formed in the reduction of styrene by potassium as shown in Equation VII.

$$2\ K + CH_2=CH\emptyset + 2\ NH_3 \longrightarrow 2\ K^{\oplus} + 2\ NH_2^{\ominus} + CH_3CH_2\emptyset \qquad \text{(VII)}$$

LIVING POLYMERS

An interesting situation arises when a polymerization reaction does not involve a termination step. A solution of polymeric molecules then exists in a state of dynamic equilibrium with the ends potentially able to grow further if more monomer is added. Such polymers have been termed "living" polymers and have been prepared by Szwarc (9) and co-workers by anionic polymerizations in tetrahydrofuran.

Termination of polymerization may occur by the transfer of a proton to the carbanionic end of the living polymer or by return of an electron from the carbanionic end to a cation. However, in non-acidic solvents of high solvating power such as tetrahydrofuran neither termination mechanism would be expected to operate. Using styrene as the monomer, the following experiments were performed to test this theory. The polymerization was initiated by the green sodium-naphthalene complex. It has been shown that the mechanism of the initiation involves an electron transfer from the naphthalene anion to the monomer (14). Consequently, ion-radicals are formed which eventually dimerize into species which grow by a carbanionic mechanism until the monomer supply is exhausted (Equation VIII).

$$\text{Ø}CH{=}CH_2 \xrightarrow{e^-} \text{Ø}\overset{\ominus}{C}H\text{-}\dot{C}H_2 \xrightarrow{\text{dimerize}} \text{Ø}\dot{\overset{\ominus}{C}}HCH_2CH_2\overset{\ominus}{C}H\text{Ø} \xrightarrow{n\text{Ø}CH=CH_2} \text{polymer} \qquad \text{(VIII)}$$

The $\sim\sim\sim\overset{\ominus}{C}H\text{Ø}$ ends of the living polymers are red, the color being that of the negative benzyl ions. The green color of the catalyst solution turns red immediately upon being introduced to the styrene solution, and if air and moisture are excluded the red color persists for days without any apparent change of intensity. The observation of color is thus the simplest manifestation of living polymers.

If additional amounts of styrene and of tetrahydrofuran are added to the solution further polymerization ensues. If the ratio of styrene to solvent is chosen to be identical to that in the first batch, then the concentration of polystyrene formed remains unaltered by the polymerization. However, the viscosity of the solution increases greatly. This increase in viscosity, coupled with the fact that both portions of styrene are converted quantitatively into polymer, proves conclusively that the second batch of monomer polymerized on the living ends. A novel method of preparing block copolymers is also suggested: if a second monomer B is added to the still living polymers after the completion of the first polymerization process with monomer A, block copolymers of the type BB...BAA...ABB...B can be prepared.

EFFECT OF INITIATOR

The copolymerization of styrene and methyl methacrylate has been used as a criterion for establishing a polymerization mechanism. The incorporation of styrene and methyl methacrylate into the copolymer depends on the nature of the catalyst as Table I clearly indicates.

TABLE I (15)

Catalyst type	% Styrene	% Methyl Methacrylate
Cationic (as $AlCl_3$)	>99	<1
Free Radical (as $(\text{Ø}CO_2)_2$)	51	49
Anionic (as Na)	<1	>99

However, when Tobolsky (16) and coworkers copolymerized styrene and methyl methacrylate in tetrahydrofuran using metallic lithium as the initiator a copolymer was produced which, unlike a sodium or potassium initiated copolymer, contained an appreciable percentage of styrene. Copolymerization of isoprene and styrene with lithium also gave a copolymer containing styrene (17). In addition, when isoprene and styrene are copolymerized using n-butyllithium as the catalyst the results obtained are identical with those using lithium both in regard to the composition of the copolymer and the stereoisomerism of the isoprene contained in it.

It is therefore very striking to note that when n-butyllithium is used as an initiator for the styrene-methyl methacrylate copolymerization (18), no styrene is detectable in the polymer (quite in contrast to lithium initiation), regardless of the solvent used. If a purely anionic mechanism were operative in the copolymerization of styrene and methyl methacrylate by lithium, then identical results would be expected whether lithium or n-butyllithium were used as the initiator. However, since the two initiators yield such different results with these two monomers, it is interesting to postulate mechanisms which preclude styrene entering a n-butyllithium-initiated copolymerization, yet permit styrene to enter a lithium-initiated copolymerization.

It is believed by Tobolsky and O'Driscoll (18) that the n-butyllithium-initiated copolymerization is a classical anionic polymerization in which the less electronegative methyl methacrylate polymerized preferentially to such an extent that little or no styrene is discernible in the polymer regardless of the solvent used. In the case of the lithium-initiated copolymerization, they believe that lithium may belong to the electron exchange type of catalysts with which Szwarc (15) explains initiation and propagation in the living polymer systems. With such catalysts it is thought that initiation takes place through the exchange of an electron from the catalyst into the unoccupied anti-bonding π-orbital of the vinyl group. This yields a species ($\cdot CH_2\text{-}CXY:^{\delta\ominus}Li^{\delta\oplus}$) which may be considered to be a free radical at one end and an anion at the other. Szwarc states that the radical ends of two such molecules will combine yielding a propagating dianion with associated counterions which will grow anionically in both directions. It is, however, possible that the radical-ion species might propagate at each of the unlike ends, giving in the same molecule a growing anionic end and a growing free radical end. The unusual copolymer properties in the lithium-styrene-methyl methacrylate system may be explained by such a mechanism, bearing in mind that the anionic end would add methyl methacrylate mainly or exclusively, whereas the radical end would add both methyl methacrylate and styrene.

The initial course of the copolymerization in tetrahydrofuran proceeds by an extremely rapid reaction yielding a copolymer containing some 93% methyl methacrylate and 7% styrene (16). The 7% styrene is thought to reflect the relative rates of radical and anionic propagation reactions. The amount of styrene in the copolymer showed a temperature dependence, becoming zero at low temperatures. This is consistent with its introduction into the chain via a free radical propagation reaction of higher activation energy than the propagating anionic step.

A powerful method for establishing this mechanism would be to find an inhibitor which would suppress either the radical or the anionic growth without poisoning the initiator, but no such inhibitors

have been reported.

Methacrylonitrile reacts immediately and quantitatively with lithium in liquid ammonia to give high molecular weight polymers (19). In an attempt to elucidate the mechanism of initiation in this system, Overberger and coworkers have studied the dependence of the number average degree of polymerization on catalyst and monomer concentrations. The kinetic data obtained show that the molecular weight of the polymer is dependent on both methacrylonitrile and lithium concentrations. An increase in the methacrylonitrile concentration or a decrease in the lithium concentration, with the other variable kept constant, increases the molecular weight of the polymer, that is, $\overline{DP}_n \alpha (M)/(C)$. Initiation by amide ion was ruled out by separate experiments in which is was shown that methacrylonitrile is polymerized only very slowly in the presence of lithium amide. Thus Overberger postulates a one-electron transfer from lithium to monomer to produce a propagating danion, with most of the monomer being consumed before termination takes place (Equations IX, X, XI). It is also reasonable to assume coupling of radicals in this system at -75° C. but no experimental evidence is at present available to demonstrate this conclusively.

$$Li + NH_3 \longrightarrow Li^{\oplus}(NH_3) + e^{\ominus}(NH_3) \qquad (IX)$$

$$e^{\ominus} + CH_2{=}\overset{CH_3}{\overset{|}{C}}{-}CN \longrightarrow {}^{\ominus}CH_2{-}\overset{CH_3}{\overset{|}{C}}{-}CN \qquad (X)$$

$$2\,{}^{\ominus}CH_2{-}\overset{CH_3}{\overset{|}{C}}{-}CN \longrightarrow {}^{\ominus}CH_2{-}\underset{CN}{\overset{CH_3}{\overset{|}{C}}}{-}\underset{CN}{\overset{CH_3}{\overset{|}{C}}}{-}CH_2{}^{\ominus} \xrightarrow[\text{nitrile}]{\text{methacrylo-}} \text{polymer} \qquad (XI)$$

EFFECT OF SOLVENT

It is known that the nature of the polymerization medium exerts a strong influence on the propagation step (20). The composition of a copolymer initially formed from an equimolar mixture of monomers, such as styrene and isoprene, should therefore depend upon the solvent in which the polymerization is carried out. Table II shows the effect of solvent media on the styrene content of copolymers with isoprene formed by lithium, n-butyllithium, and sodium initiation.

TABLE II (20)

% Styrene in Isoprene Copolymers at Zero Conversion

Styrene:Isoprene=60:40 by weight(equimolar); M:S=1:2

Solvent	Weight % Styrene Using Li	n-BuLi	Na
Benzene	15±1	18±1	66±3
Undiluted monomers	15±1	17±1	66±3
Triethylamine	59±3	60±3	77±6
Diethyl ether	68±3	68±3	75±6
Tetrahydrofuran	80±6	80±6	80±6

The near identity of composition between copolymers initiated by lithium and n-butyllithium systems in each particular solvent strengthens the argument that the propagating species is the same in both cases. In tetrahydrofuran, diethyl ether, and triethylamine, the high styrene contents can be explained by the basicities of the solvents, which are able to solvate the lithium. In benzene and undiluted monomers the lower styrene content indicates that the propagation step is not the simple addition of a free polymeric anion to the double bond of

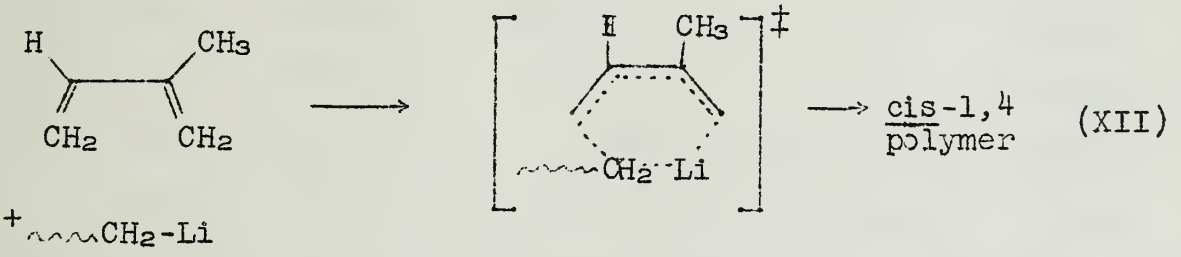
a monomer molecule.

Sodium as a catalyst produces copolymers whose compositions are less dependent upon solvent medium. When the active chain end consists of a carbon-sodium bond the effective charge separation of the ($\sim\sim\sim C^{\delta\ominus}{}_M{}^{\delta\oplus}$) pair will be greater than for a carbon-lithium bond because of its greater inherent ionic character. In benzene and undiluted monomers, ionization of the carbon-sodium bond is not suppressed as much as that of the carbon-lithium bond, and a smaller decrease in styrene content occurs with sodium on changing from ionizing to non-ionizing solvents. In tetrahydrofuran the identical compositions of lithium and sodium copolymers indicate that the lithium polymerization has a propagation step similar to the limiting anionic case of sodium.

STEREOSPECIFIC POLYMERIZATION

Isoprene has been homopolymerized with n-butyllithium initiation (21). If the n-butyllithium is prepared in benzene or n-heptane solutions, the polymer formed has over 90% cis-1,4 structure according to infrared determinations. On the other hand, if the lithium alkyl is prepared in ether and if the polymerization is carried out in ether solution, the polyisoprene has a mixture of 3,4 structure, 1,2 structure, and trans-1,4 structure. Isoprene polymerized in n-heptane by n-butyllithium in ether is a polymer intermediate in structure to those cited above.

A possible explanation (22) of the stereospecificity found in this system lies in the nature of the solvent and its influence on the C-Li bond. In hydrocarbons such as benzene or n-heptane the largely covalent carbon-lithium bond would not be well solvated, repressing ionization even more. This could give rise to a mechanism in which there is a coordination with the 1,4πelectrons of the entering isoprene molecule, holding it in a cis-1,4 configuration and forming a pseudo-cyclic six membered transition state, as shown in Equation XII. In the pres-



(XII)

ence of ether, however, it is reasonable to assume that lithium, because of its strong coordination ability (23), would be similar to a Grignard reagent, that is, there would be ether molecules coordinated to each lithium atom. The solvated propagating end would thus be vulnerable to random addition of the isoprene molecules. In an ether-n-heptane mixture both stereospecific and random addition would occur.

KINETICS AND MECHANISMS

Welch (24) has studied the rate of polymerization of styrene in benzene using n-butyllithium initiation, and has reported that for catalyst concentrations less than 0.02 M the rate of propagation is proportional to the concentration of both catalyst and styrene while for higher catalyst concentrations the rate is proportional to the monomer concentration but independent of the concentration of the catalyst:

$R_p = k_p(M)(BuLi)$, for $(BuLi) < 0.02$ M (XIII)

$R_p = k_p(M)$, for $(BuLi) > 0.02$ M (XIV)

An initial acceleration in the rate of the reaction and the development of a red color which persists as long as reactive impurities are excluded was also observed. The number average degree of polymerization is expressed by the relationship $\overline{DP}_n = (M)/(BuLi)$.

The following mechanism, which involves the successive additions of lithium alkyl to monomer has been proposed, assuming no termination reaction occurs:

$$\text{Initiation:} \quad BuLi + M \xrightarrow{k_i} Bu(M)Li \qquad \text{(XV)}$$

$$\text{Propagation:} \quad Bu(M)_xLi \xrightarrow{k_p} Bu(M)_{x+1}Li \qquad \text{(XVI)}$$

The initial acceleration in the rate of the reaction is attributed to the fact that initiation is slower than propagation. The change in the dependence of the rate on catalyst concentration suggests that above a critical concentration only a part of the lithium alkyl is active in the polymerization. Since it is known that lithium alkyls are associated in solution Welch proposes that associated lithium alkyls are inactive in the polymerization and that 0.02 M represents the critical concentration for association in benzene solution. An association equilibrium, $mRLi \rightleftharpoons (RLi)m$, is therefore considered in the mechanism.

In another kinetic study on the styrene-n-butyllithium-benzene system, O'Driscoll and Tobolsky (25) found that the rate of polymerization is independent of the n-butyllithium concentration for values of (BuLi) above 4.2×10^{-3} M. To explain this observation it was postulated that the n-butyllithium is involved in a termination reaction as well as the initiation reaction. The termination occurs by association between the propagating anion, the lithium counterion, and another molecule of n-butyllithium. The proposed mechanism is as follows:

$$(BuLi)_n \rightleftharpoons BuLi + (BuLi)_{n-1} \qquad \text{(XVII)}$$

$$BuLi + M \xrightarrow{k_1} BuM^{\ominus} + Li^{\oplus} \qquad \text{(XVIII)}$$

$$BuM^{\ominus} + M + Li^{\oplus} \xrightarrow{k_2} \cdots\cdots \xrightarrow{k_2} Bu(M)_x^{\ominus} + Li^{\oplus} \qquad \text{(XIX)}$$

$$Bu(M)_x^{\ominus} + Li^{\oplus} + (BuLi) \xrightarrow{k_3} Bu(M)_xLi \cdot (BuLi) \qquad \text{(XX)}$$

Because of the pronounced effect of solvent media on the stereospecificity of lithium- and n-butyllithium-initiated polymerizations, the kinetics of styrene polymerization were also studied in benzene containing small amounts of tetrahydrofuran. Two tetrahydrofuran molecules are thought to coordinate with each lithium atom in the n-butyllithium. Because the rate of polymerization and the molecular weight were constant for given concentrations of catalyst, monomer, and tetrahydrofuran over a large range of conversion, it is believed that the polymerization is characterized by a slow initiation, a rapid propagation, and a slow termination step. The rate expression suggests that the initiation step is bimolecular with respect to BuLi·2THF and that the termination is brought about by the n-butyllithium which is not coordinated by tetrahydrofuran.

Morton (26) has polymerized styrene in both benzene and tetrahydrofuran using n-butyllithium and ethyllithium as initiators and has determined the molecular weights and molecular weight distributions of the

products. When the initiation reaction proceeds more rapidly than the propagation reaction and no termination occurs, all polymer molecules should be of approximately the same molecular weight since each chain, once initiated, will grow until all the monomer is used up.

The molecular weights agreed with predicted values based on the stoichiometry of one initiator molecule per polymer chain and the absence of a termination process regardless of which solvent was used. The molecular weight distribution was narrow when precautions were taken to prevent chain terminations. This applied especially to the possibility of reaction between the initiator and the tetrahydrofuran since it was shown that the tetrahydrofuran reacts rapidly with the alkyl lithium initiators at room temperature (but not at -80° C.). The initiator was also completely consumed during the polymerization, as was evidenced by the absence of any evolution of ethane gas from the ethyllithium at the end of the reaction. The initiation step appears to be instantaneous at room temperature in both solvents, but has a measurable rate at 0° C. in benzene. Thus the molecular weight distribution can also be affected by the temperature of the polymerization in benzene solution.

The synthesis of several crystallizable forms of polymethyl methacrylate by means of stereospecific polymerizations effected by homogeneous free radical and anionic initiating systems has been reported (27). Crystallization was effected by solvent treatment in borderline solvents such as 4-heptanone. Three polymer types (I, II, III) have been characterized by their different X-ray diffraction patterns and differences in properties (Table III).

TABLE III (27)

Properties of Polymers of Methyl Methacrylate

Type	Glass T., °C.	M.P.	Density, g/ml	Presumed Chain Configuration
I	115	200	1.19	Isotactic
II	45	160	1.22	Syndiotactic
III	60-95	170	1.20-1.22	Isotactic-syndiotactic block copolymer
Conventional	104		1.188	Random

The ability of these polymers to crystallize is ascribed to unusually uniform chain structure resulting from isotactic or syndiotactic arrangement of configurations at the pseudo-asymmetric carbon atoms.

Type I polymethyl methacrylate results from free radical polymerizations conducted at low temperares and from anionic polymerizations in highly solvating media, such as those initiated by 9-fluorenyllithium in 1,2-dimethoxyethane at -60° C. The stereospecificity of these polymerizations is believed to arise from small differences in the free energies of the two transition states, such as the differences which may result from interaction of the groups of the last and penultimate monomer units at each monomer addition step.

Type II polymethyl methacrylate is prepared by anionic polymerizations initiated by organolithium compounds in hydrocarbons. Thus 9-fluorenyllithium at -60° C. in toluene produces quantitative yields of Type II polymers. Under these conditions chain propagation involves

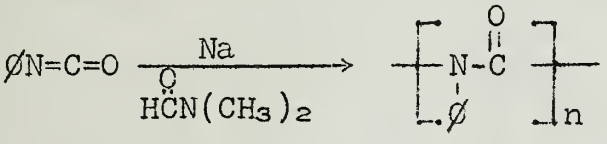
an ion pair rather than free ions; the lithium counterion apparently is involved intimately in the transition state.

Anionic polymerizations at low temperature in media of moderate solvating power for cations produce polymers of Type III. Such polymers are produced by 9-fluorenyllithium at -70° C. in toluene containing small amounts of dioxane. These conditions are intermediate between those leading to Types I and II. Intimate mixtures of Types I and II crystallize to give the same diffraction patterns as those obtained from Type III. However, while the mixtures may be separated by fractionations under special conditions, it has not been possible to obtain an equivalent separation of Type III polymers prepared directly. This evidence suggests that the latter polymers consist of alternating sequences of isotactic and syndiotactic structures. This "block copolymer" character presumably is responsible for the variation in X-ray and physical property data observed with the Type III polymethyl methacrylate. (See also Reference 31.)

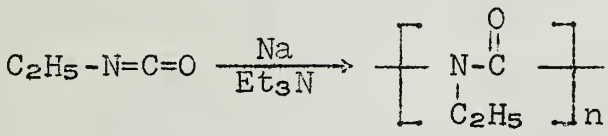
THE HOMOPOLYMERIZATION OF MONOISOCYANATES

There has been little previous work to indicate that addition polymers from monofunctional compounds containing =C=N- groups can be obtained. Shashoua (28), however, has recently polymerized monoisocyanates to linear high molecular weight polymers. These polymers may be regarded as N-substituted "1-nylons."

Ethyl isocyanate and phenyl isocyanate, examples of both aliphatic and aromatic isocyanates, were polymerized (Equations XXI and XXII) at low temperatures (-20° C. to -100° C.) in polar solvents such as N,N-dimethylformamide using metallic sodium as the initiator. Ethyl-1-nylon was obtained in 39% conversion (n=23 to 42) and phenyl-1-nylon in 86% conversion.



XXI



XXII

INDUSTRIAL APPLICATION

The natural rubber, Hevea brasiliensis, is almost all cis-1,4-polyisoprene (29). The most important synthetic rubber, GR-S (Buna S), is a copolymer of styrene and butadiene in which a mixture of 1,2- and cis- and trans-1,4 addition to butadiene has occurred. The physical properties of GR-S, as a result, are not comparable to those of Hevea rubber in many respects.

Recently stereospecific polymerizations of isoprene using lithium metal catalysis have resulted in the so-called "Coral" rubber which possesses over 90% of the cis-1,4 structure and is therefore similar to Hevea in physical properties (30). Coral rubber differs from Hevea rubber in that it has slightly less cis-1,4-structure and slightly more 3,4-structure; it does not absorb oxygen as readily as natural rubber, has higher thermal stability, and is more resistant to cracking in tire treads.

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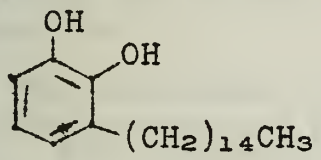
SOME ALLERGENIC COMPONENTS OF THE ANACARDIACEAE

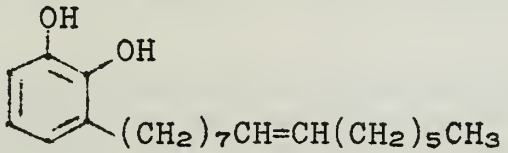
Reported by W. E. Adcock November 5, 1959

Plants of the Anacardiaceae family have long been known to contain vesicant oils to which most humans are quite sensitive. The most dangerous are the members of the Rhus genus of Anacardiaceae, because the poison is found in many parts of the plant, i.e., bark, sap, leaves, flowers, and roots. Among the most prominent of this species are poison ivy and Japanese lac, the oils of which contain phenolic structures carrying long unsaturated side chains.

Around 1900 Majima became interested in the vesicant sap of the Japanese lac tree which was being used as a lacquer for wooden articles manufactured in Japan. He obtained a yellow oil from an alcohol extraction of the sap and noted that this oil gave the typical chemical reactions associated with catechol-type compounds. It reduced an ammoniacal silver solution, gave a white precipitate of the lead salt with lead acetate, and a dark green to black color with ferric chloride (1). The substance was named "urushiol" to indicate that it was a phenolic compound. In the next few years, structural studies on the oil, including ozonolysis and oxidative degradation of the dimethyl ether (2), led Majima to conclude that urushiol was probably a mixture of four compounds which he could not separate by distillation. With the added fact that the toxic oil had an average of two olefinic bonds, he proposed a mixture of four catechols differing in the number of double bonds in a normal fifteen-carbon side chain in position three of the benzene nucleus. Two of the proposed structures were as follows:



I



II

The position of the double bonds in the suggested di- and triolefin structures was later proven to be incorrect.

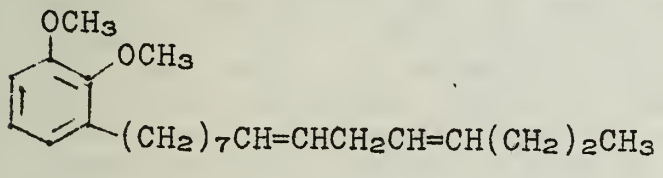
Hill and co-workers in 1934 (3) succeeded in isolating and identifying the toxic principle of poison ivy. They showed that the vesicant oil was similar to urushiol isolated from the sap of the Japanese lac tree. They found that hydrogenation of the poison ivy principle gave a compound identical with that obtained on hydrogenation of urushiol. Other similarities were found on comparison of derivatives (dimethyl ether, diacetate, and dibenzoate) of the hydrogenated side chain compound. This did not exclude the possibility that the positions of the double bonds in the side chain of poison ivy urushiol may differ from their positions in the Japanese lac variety.

Proof that urushiol isolated from poison ivy is a mixture was given by Mason and Schwartz (4) when six bands separated from the toxic oil by chromatographic adsorption using an alumina column. Due to the allergenic properties of the poison ivy oil and its susceptibility to autoxidation, Dawson and Symes (5) found it necessary to work with the relatively more stable and non-toxic

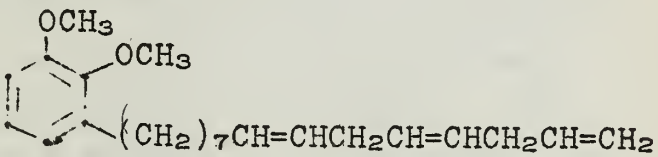
dimethyl ether rather than the free catechol. When the dimethyl ether was chromatographed on a column of activated alumina, fractions of oily liquid were obtained either by fractional elution or extrusion and sectioning of the column (6). The oily liquid showed a parallel increase in double bond value and refractive index with increasing adsorbability. Several of the least strongly adsorbed fractions were combined and treated with 30% performic acid. Of the two crystalline compounds isolated, one was found to be dimethylhydrourushiol, thereby establishing the presence of a saturated component, 3-pentadecylcatechol (I), in the poison ivy principle. The other cyrstalline compound proved to be a monoglycol which on periodic acid oxidation yielded heptaldehyde. This indicates that the monoölefin was 3-(pentadecenyl-8')-veratrole, the dimethylether of II. The glycols corresponding to the higher olefinic components could not be isolated readily in pure form.

The olefinic components of the dimethyl ether were finally separated by repeated chromatography. Fractions of similar refractive indices were combined and rechromatographed, and in this way a monoölefin, n_D^{25} 1.4932, and a diolefin, n_D^{25} 1.5030, were isolated as fractions of constant refractive index. The triolefin was also obtained by combining fractions varying over a range of n_D^{25} 1.5145-1.5175. Each of these olefinic components absorbed the calculated amount of hydrogen on catalytic reduction to give pure hydrourushiol (I). No olefinic fraction took up more hydrogen than the calculated value for a triolefin. The ultraviolet spectrum of the reduction product (I) and the di- and triolefinic components were almost identical in regard to position and magnitude of the absorption maxima and minima. This fact precludes the existence of conjugation in the di- and triolefinic components (6).

The structure of the diolefin was established by ozonolysis. n-Butyraldehyde was isolated and identified as the dimedon derivative. The aldehydic fragment containing the aromatic nucleus was oxidized to the corresponding acid and isolated as the amide. It proved to be identical with a synthetic sample of ω-(2,3-dimethoxyphenyl)-caprylic acid amide. The diolefin is therefore 1,2-dimethoxy-3-(pentadecadienyl-8',11')-benzene (III).



III

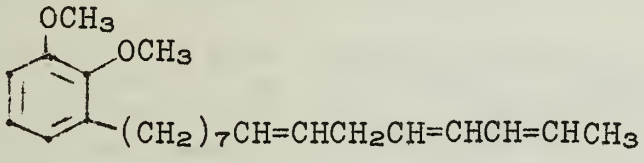


IV

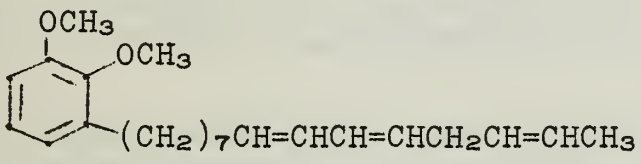
The triolefin on ozonolysis gave formaldehyde in 42% yield, isolated and identified as the dimedon derivative. Oxidation of the aromatic fragment gave the same substituted caprylic acid as obtained from the diolefin. Therefore, there must be a double bond in the 8'- and 14'-positions of the side chain. The position of the third double bond is apparent as it must be between the 8' and 14'-carbons and yet, according to the ultraviolet spectrum, not conjugated with either. Since only the 11'-position meets this requirement, the triolefin must be 1,2-dimethoxy-3-(pentadecatrienyl-8',11',14')-benzene (IV).

Since the diolefin of poison ivy was different from the structure Majima had proposed for the diolefin from Japanese lac, and since Majima had not reported a complete structure for the triolefinic component, Sunthankar and Dawson (7) reinvestigated the olefinic components of lac urushiol. Dimethylurushiol was prepared from the oil, and the saturated, mono- and diolefinic components were isolated by chromatographic separation on alumina. The position of the double bonds in the mono- and diolefin was established by ozonolysis and the same derivatives were isolated as in poison ivy urushiol. Also, from the diolefin (III) malondialdehyde was isolated in 22% yield and characterized as the dimedon derivative.

The triolefin component could not be purified on alumina and appeared to be converted in part into a yellow polymeric product. However, it was found that the triolefin could be separated from the yellow contaminants on a column of Florisil (synthetic magnesia-silica gel). The refractive index of this triolefin was significantly higher than that of the corresponding component of Japanese lac--suggesting a possible difference in the structure of the side chain. From the ozonolysis of the triolefin acetaldehyde, malondialdehyde, and the caprylic aldehyde were isolated. Two structures were proposed for a triolefin that would account for these degradation products--V and VI.



V

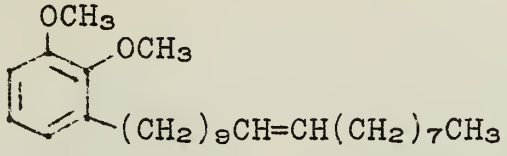


VI

Both of these structures would be expected to give a high intensity band at 227 mμ, as was observed with the pure triolefinic component, due to the conjugation of two of the double bonds in the side chain. To establish the position of the conjugation, the maleic anhydride adduct of the triolefin was prepared. The adduct was ozonized and reduced catalytically, yielding ω-(2,3-dimethoxyphenyl)-capryl aldehyde, the product to be expected from the maleic anhydride adduct of V. All attempts to recover acetaldehyde, the prodct to be expected from the maleic anhydride adduct of VI, were unsuccessful. Therefore, the arrangement of the double bonds in the triolefin may be represented by V.

The role of the double bond in the side chain has received very little attention since pure alkenyl phenols of varying degree of unsaturation have not been available for clinical study. That the role of the double bond is important is suggested by the fact that hydrourushiol is less active than urushiol as judged by the patch test (8). The geometric configuration of the olefinic bonds in the side chain may be of importance if there is a specific reaction between the alkenyl catechol and certain proteins in the skin.

Loev and Dawson (9) have determined the geometrical configuration of the olefinic components of poison ivy urushiol. To accomplish this, they have synthesized 3-(cis-nonadecenyl-10')-veratrole (VII), which is a homolog of dimethylurushenol, and



VII

have compared the infrared spectra and the melting points of the diastereoisomeric glycols. On this basis, they have assigned the cis configuration to the monoölefinic component of poison ivy.

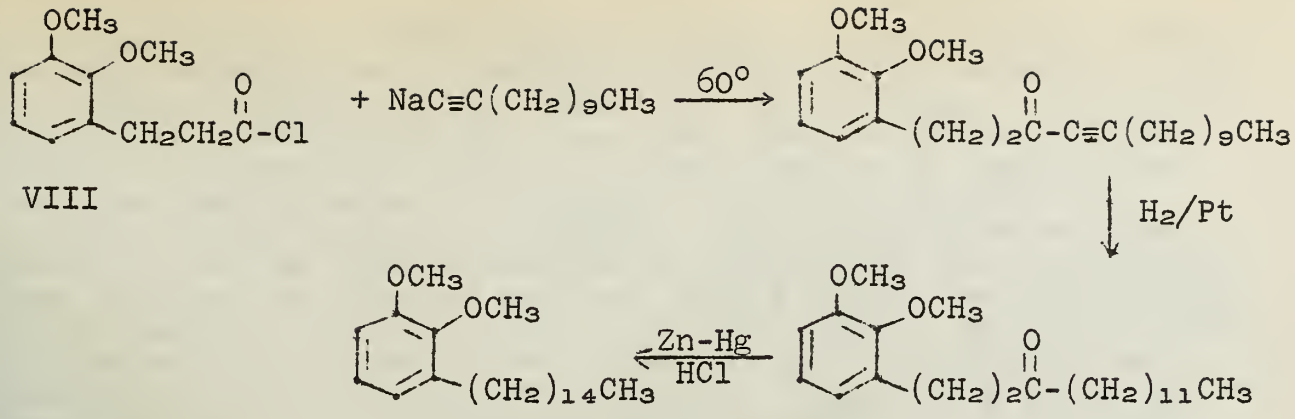
It has been found that trans-olefins absorb at 965 cm^{-1} in the infrared (10). The absence of this absorption band indicates a cis-olefin, if an olefinic linkage is known to be present. Since it was found that the free phenolic hydroxyl group absorbs in the region of 965 cm^{-1}, it was necessary to carry out spectral studies on the ether derivatives rather than the free phenols. The infrared spectra of pure samples of dimethylurushenol (II) and dimethylurushadienol (III) clearly show that each has the cis configuration, on the basis of no absorption at 965 cm^{-1}.

Oxidation of VII with osmium tetroxide, a cis-hydroxylating agent, gave a glycol, m.p. 99.8-100.5°; oxidation of VII with performic acid, a trans-hydroxylating agent, gave the diastereoisomer, m.p. 64.5-65.5°. The hydroxylation results are in agreement with the common observation that trans-hydroxylation of a cis olefin generally gives a lower melting glycol than is obtained by cis-hydroxylation of the same cis olefin (9,11).

Performic acid oxidation of the chromatographically pure poison ivy dimethylurushenol gave a glycol, m.p. 66.8-68.2° (5); hydroxylation by means of osmium tetroxide gave the diastereoisomer, m.p. 94.0-95.0°. Therefore, on the basis of the above observations, the assignment of a cis configuration to the poison ivy dimethylurushenol is supported by chemical evidence.

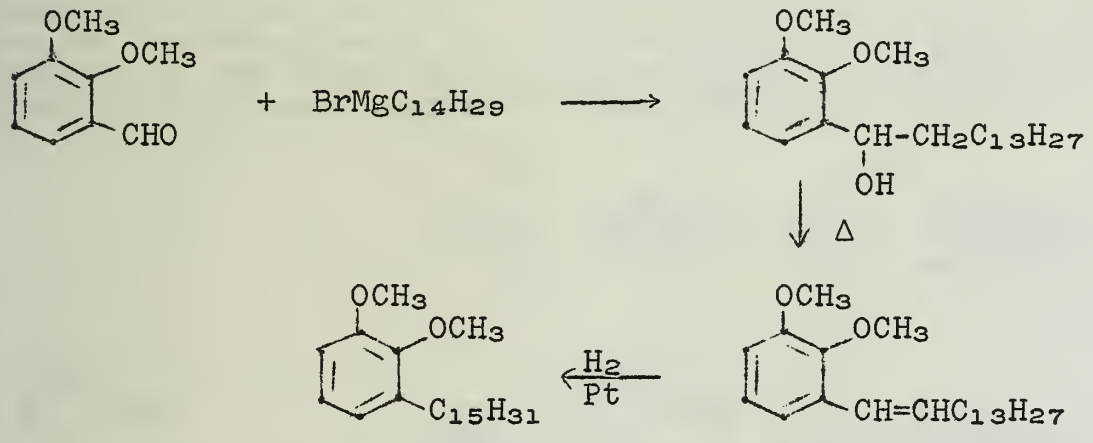
The difficulty in separating the various constituents from the vesicant oils in sufficient quantity for physiological studies spurred the synthesis of these compounds. Also the unavailability of a pure component as a standard allergenic substance has caused much controversy in publications dealing with allergy to poison ivy (12).

The dimethylether of hydrourushiol (I) was the first component synthesized and was used to establish the structure of a compound obtained from a natural source. Majima (13) reported the following synthesis in 1915:



VIII

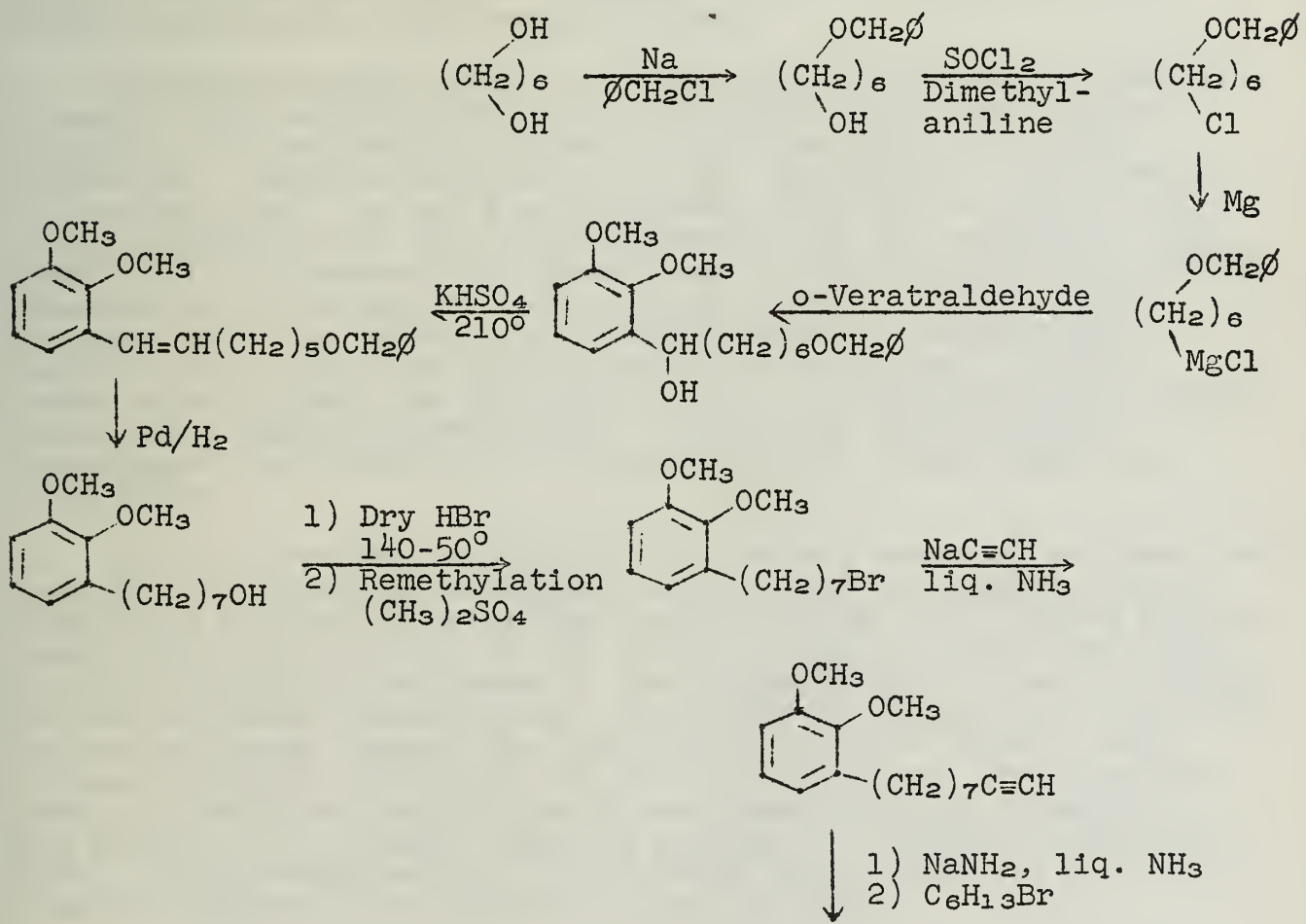
The acid chloride of β-(2,3-dimethoxyphenyl)-propionic acid (VIII) was condensed with the sodium salt of n-decylacetylene. The triple bond in the resulting ketone was reduced in the presence of platinum followed by a Clemmensen reduction of the ketone. Backer and Haack (14) synthesized the above compound by a simpler method, but the yield remained low.

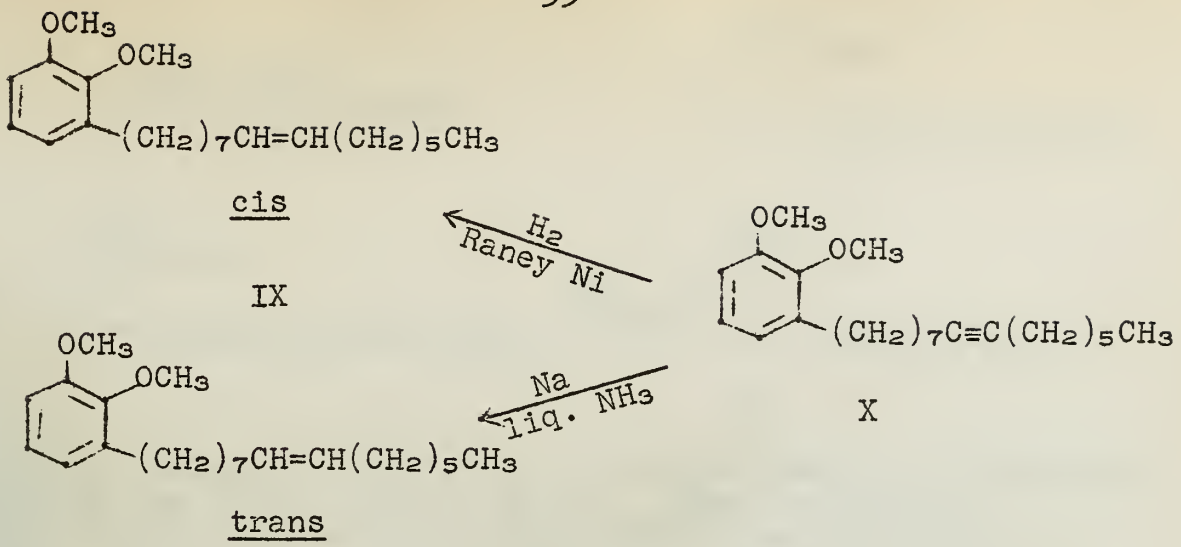


Although the above ether proved useful in structural work, it was found to be clinically inactive (8). Methods were sought to cleave the methyl ether to give the free catechol compound. Early reports of the demethylation of 2,3-dimethoxy-n-pentadecylbenzene with hydrobromic acid (15) and with a mixture of acetic acid, hydroiodic acid, phenol, and red phosphorus (16) were found by Mason (17) to give very low yields. One of the reasons for this was the lability of alkyl substituents in the veratrole molecule under acidic conditions. During the demethylation of 2,3-dimethoxybenzyl halides, catechol itself was formed and isolated in yields up to 18% (18). This has also been encountered by Haworth (19) during the acid demethylation of 3- and 4-substituted catechol ethers. Mason (17) synthesized the methyl ether of hydrourushiol using essentially the Backer-Haack method but with much higher yield. The ethers were cleaved with glacial acetic acid saturated at 0° with hydrogen chloride. The cleavage of of 2,3 dimethoxy-n-pentadecylbenzene (I) was carried out in a sealed tube using the above reagent for 60 hours at 120-130°. Yields obtained were between 65-70%. Dawson (20) cleaved the ether by refluxing with alumnium chloride in chlorobenzene, obtaining comparable yields of 3-n-pentadecylcatechol. It was found that a more easily purified product was obtained in this latter method (21) by reducing the reaction time of alumnium chloride demethylation from 3 hours to 15 minutes.

The reaction of the Grignard reagent directly on the free phenolic aldehyde was investigated by Dawson (21) because it did not involve strongly acidic conditions at any stage. Pauly and Buttlar (22) previously had found that they could obtain a 70% yield of the expected carbinol by the reaction of excess ethyl Grignard reagent on salicylaldehyde. Backer and Haack (23) considered this method of synthesis when they carried out the reaction between tetradecylmagnesium bromide and salicylaldehyde. They obtained the desired carbinol in 31% yield, but dehydration of the carbinol resulted only in polymerization. Dawson and Loev (21) were able to produce the above carbinol in 86% yield and dehydrated it by distillation in vacuo. Using a similar procedure, they prepared 3-(1'-hydroxypentadecyl)-catechol in fairly good yield by the reaction of excess Grignard reagent on 2,3-dihydroxybenzaldehyde. But all attempts to dehydrate the carbinol led only to dark polymeric materials.

The alkenyl catechols isolated from natural sources were found to have greater allergenic properties than hydrourushiol. The ether of an alkenyl catechol was first synthesized by Wasserman and Dawson (24). Using a method that could be applied for the introduction of one or more double bonds in any desired position in the side chain, cis- and trans-3-(pentadecenyl-8')-veratrole (IX) were prepared by the following reactions:





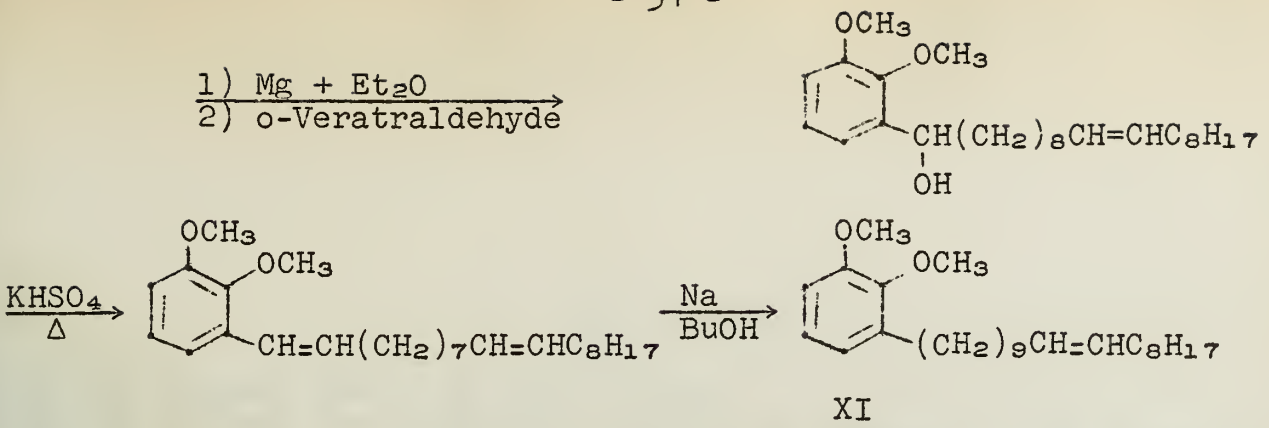
Reduction of the acetylene X with Raney nickel gave the cis isomer and with sodium and liquid ammonia gave the trans isomer. Cleavage of the protecting ethers would be difficult because unsaturated phenols are characterized by extreme susceptibility to polymerization in acidic media. In a search for ways of avoiding strongly acidic alumnium chloride cleavage, Dawson (21) investigated alkaline cleavage of the methyl ethers and the use of other protecting groups, such as the acetate and pyranyl ether. The results of these reactions have not been published.

Diphenylmethylene ethers of 3-n-propylcatechol and 4-t-butylcatechol (25) were prepared in an effort to find a derivative suitable for purposes of synthesis but cleavable under mild conditions. These compounds, which are regarded as cyclic ketals of benzophenone, are split rapidly and completely by dilute alcoholic hydrochloric acid to benzophenone and the catechol. This ether will also undergo hydrogenolysis in the presence of palladium catalyst as do benzyl and cyclic benzal ethers. This latter cleavage would be useless for alkenyl catechols because the double bond in the side-chain would also be reduced. It also seems probable that the hydrochloric acid cleavage mentioned above would cause rapid polymerization. Apparently Mason did not investigate the stability of alkenylcatechols under these same conditions.

Another synthesis of alkenyl veratroles, reported by Dawson and Loev (9), involves the selective reduction of the olefinic bond conjugated with the ring without any effect on the isolated double bond. The configuration of the olefinic double in the side chain was established at the start of the synthesis by the use of alkenyl halides of known configuration. An infrared analysis at each step in the synthesis checked the configuration of the double bond. The experimental procedures are less difficult and less time consuming in this new method than those experienced by Wasserman and Dawson (24) in their previous syntheses of alkenyl veratroles. Thus, 3-(cis-nonadecenyl-10')-veratrole (XI), a homolog of dimethylurushenol, was synthesized as follows:

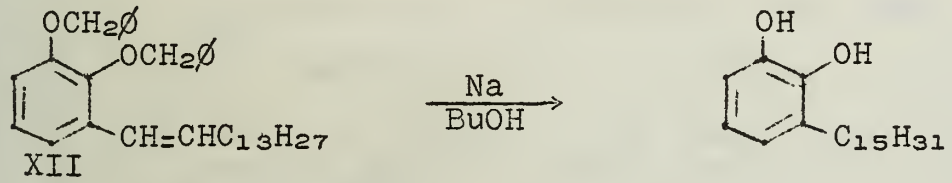
$$C_8H_{17}CH{=}CH(CH_2)_8OH \xrightarrow[-10^\circ]{PBr_3} C_8H_{17}CH{=}CH(CH_2)_8Br$$

cis



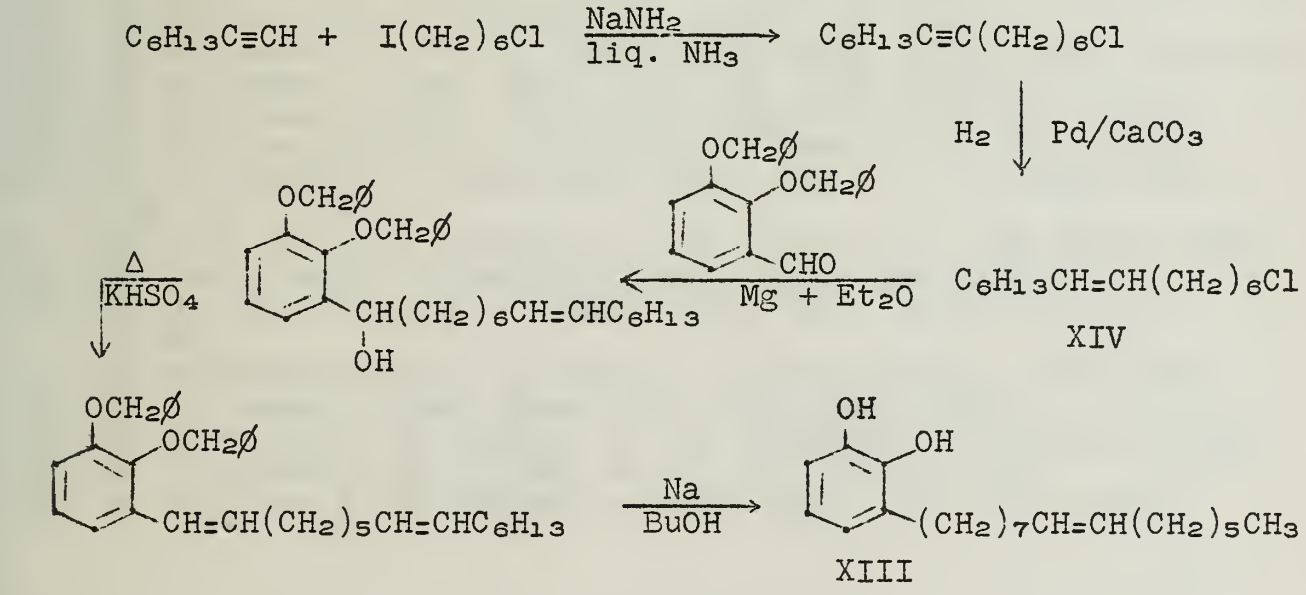
XI

Benzyl ethers of phenols can be cleaved readily by treatment with sodium and butyl alcohol (26,27). Thus, reaction of dibenzyl ether of 2,3-dihydroxybenzaldehyde and tetradecylmagnesium bromide gave, after dehydration, the benzylated alkene (XII) which could be cleaved and reduced simultaneously with the sodium-butyl alcohol treatment to hydrourushiol (I).



XII

Upon further investigation (28), the same technique opened the door to the synthesis of urushenol, the mono-olefinic component. It was found that although the conjugated (styrene-type) double bond was reduced during the sodium-butanol cleavage, an isolated double bond was unaffected.



XIV

XIII

Thus, urushenol (XIII) was prepared in overall yield of 28% from the cis olefinic chloride (XIV). The largest loss in the synthesis was during a final vacuum distillation in the final purification. The synthetic urushenol was found to contain a samll amount of an unsaturated hydrocarbon resulting from the R-R coupling product of the Grignard reaction. It is believed that this method will be adaptable to the synthesis of the higher olefinic components of poison ivy urushiol.

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THE NATURE OF THE CARBONIUM ION INTERMEDIATES IN REACTIONS OF CYCLOBUTYL, CYCLOPROPYLCARBINYL AND ALLYLCARBINYL DERIVATIVES

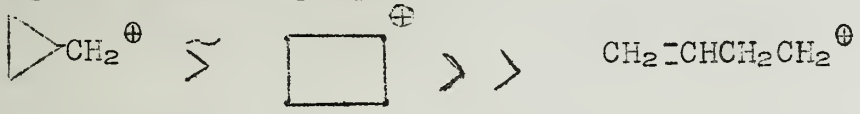
Reported by N. D. Werner November 9, 1959

INTRODUCTION

There is considerable interest in how to best formulate the carbonium ion intermediates in reactions of cyclopropylcarbinyl, cyclobutyl and allylcarbinyl derivatives. This seminar will consider mainly the intermediates from the parent cyclopropylcarbinyl, cyclobutyl and allylcarbinyl derivatives rather than those from compounds such as cyclocholestanyl and nortricyclyl derivatives which contain these systems. The nortricyclyl system and the cyclocholestanyl systems have been discussed in previous seminars (1,2,3).

REACTIONS OF CYCLOPROPYLCARBINYL, CYCLOBUTYL AND ALLYLCARBINYL DERIVATIVES

Roberts and Mazur(4) observed that the rate constant for the solvolysis of cyclopropylcarbinyl chloride in a 50% water-ethanol mixture was twenty-seven times that of cyclobutyl chloride. It was also noted that allylcarbinyl chloride solvolyzed much slower than either of the cyclic derivatives. Similar results were obtained for the solvolysis of the corresponding bromides. The following sequence of carbonium ion stabilities with respect to the starting halides was proposed:

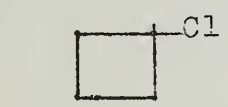


Further evidence that cyclopropylcarbinyl derivatives solvolyze faster than their allylic counterparts was afforded by the work of Bergstrom and Siegel (5) who found that cyclopropylcarbinyl benzenesulfonate solvolyzed ten times faster than allyl benzenesulfonate.

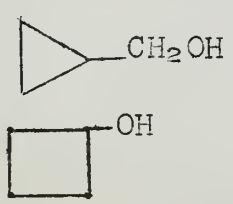
Roberts and Chambers (6) have found that cyclobutyl chloride solvolyzes faster than either cyclopropyl or cyclopentyl chloride.

The large solvolytic reactivities observed for cyclobutyl and cyclopropylcarbinyl derivatives are suggestive of non-classical participation by carbon such as has been well established by the work of Winstein (7) and Roberts (8) on the solvolysis of exo-norbornyl p-bromobenzenesulfonates.

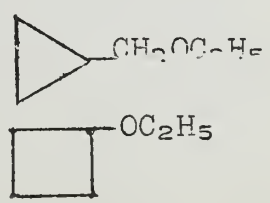
Internal return has been observed in the solvolysis of cyclopropylcarbinyl derivatives. Cyclopropylcarbinyl chloride was solvolyzed (9) in 80% ethanol and the products determined by vapor phase chromatography. The following products were observed in the reaction mixture.



$CH_2=CHCH_2CH_2Cl$

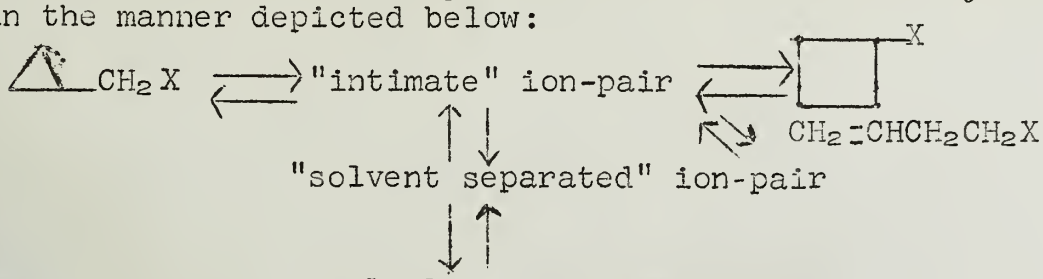


$CH_2=CHCH_2CH_2OH$



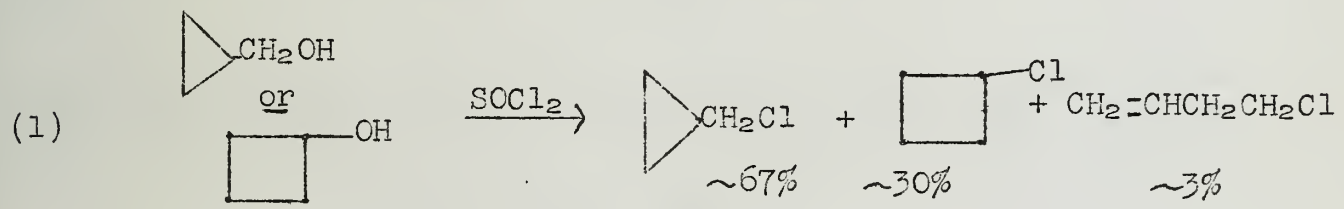
$CH_2=CHCH_2CH_2OC_2H_5$

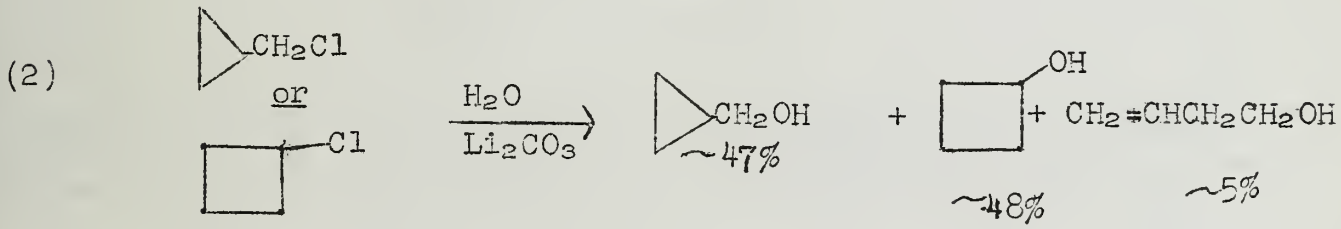
In the solvolysis of cyclobutyl tosylate (6), cyclopropylcarbinyl acetate (65%), cyclobutyl acetate (22%) and allylcarbinyl tosylate (13%) were the observed products. These results may be explained in the manner depicted below:



An extremely noteworthy feature of many reactions of cyclopropylcarbinyl and cyclobutyl derivatives is that similar product mixtures are obtained regardless of whether one starts with the cyclopropylcarbinyl derivative or the cyclobutyl derivative. Demjanow (10,11) observed that deamination of cyclopropylcarbinylamine and cyclobutylamine gave similar mixtures of cyclopropylcarbinol and cyclobutanol. Oxidation of cyclobutanol (12) with chromic acid anhydride and sulfuric acid gave a mixture of cyclobutanone and cyclopropanecarboxaldehyde, the cyclopropanecarboxaldehyde probably arising from oxidation of cyclopropylcarbinol which would be obtained by rearrangement of the cyclobutanol.

Further examples which illustrate this striking interconversion of cyclobutyl and cyclopropylcarbinyl derivatives were discovered by Roberts and Mazur (4). The following reactions have been observed:





The experimental observations which have been mentioned in this section thus suggest that in carbonium-ion type reactions of cyclobutyl and cyclopropylcarbinyl compounds common cationic intermediates are obtained.

The observed product compositions can be simply explained in the following manner: Classical cyclopropylcarbinyl cations and classical cyclobutyl cations are the intermediates and these two cationic species are in rapid equilibrium with each other. Roberts and his co-workers (13) devised a reaction which would be a possible test of this hypothesis. Earlier work of Roberts and Mazur (4) had shown that the reaction of an approximately equal mixture of cyclobutyl chloride (I) and cyclopropylcarbinyl chloride (II) with Lucas reagent gave allylcarbinyl chloride as the final product. It

was also noted that allylcarbinyl chloride did not ionize readily under the reaction conditions, since treatment of allylcarbinyl chloride with Lucas reagent containing ^{38}Cl showed that under conditions where a mixture of cyclopropylcarbinyl chloride and cyclobutyl chloride was 77% isomerized to allylcarbinyl chloride with Lucas reagent containing ^{38}Cl isotopic chloride exchange was complete, while under the same conditions using allylcarbinyl chloride in place of a mixture of (I) and (II) isotopic chloride exchange was only 13% complete. If equilibration of small ring cations is complete before allylcarbinyl chloride is formed then treatment of cyclopropylcarbinol-α-^{14}C with Lucas reagent should afford allylcarbinyl chloride with the ^{14}C distributed equally among the three methylene carbon atoms. A schematic representation of this equilibration is shown in Figure 1.

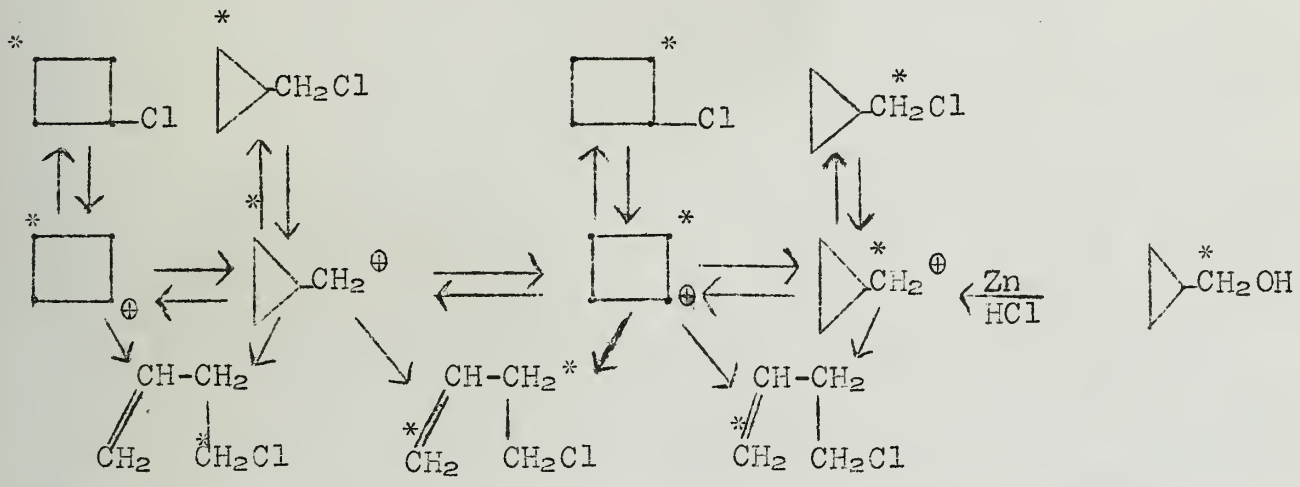


Figure 1

Allylcarbinyl -^{14}C chloride was the only monochloride isolated from treatment of cyclopropylcarbinol-α-^{14}C with Lucas reagent. The following isotopic carbon distribution was observed:

$$Cl\text{-}\underbrace{CH_2\text{-}CH_2}_{65.5\%}\text{-}CH = CH_2 \qquad 0.1\% \qquad 33.4\%$$

The allylcarbinyl -^{14}C chloride was degraded by the two procedures outlined in Figure 2. The experimental carbon isotopic distributions by the two procedures were in good agreement. Thus it appears from the experimental results that the cyclobutyl and

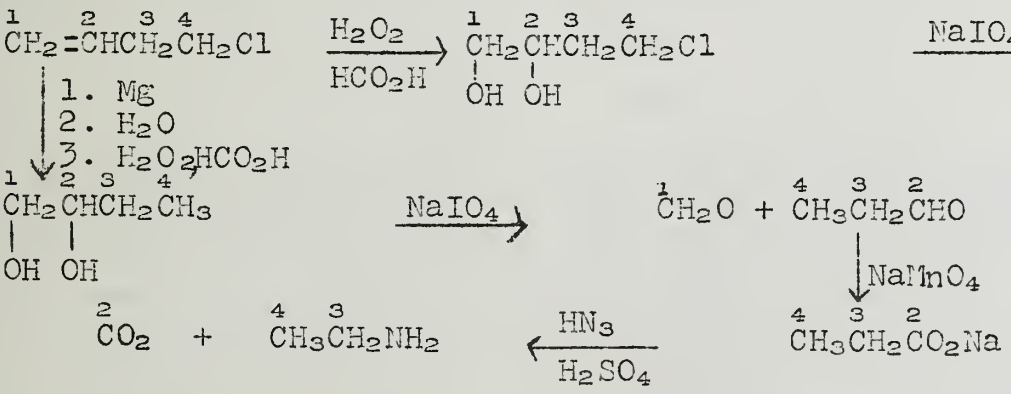


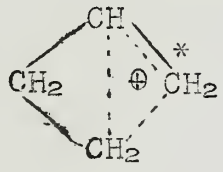
Figure 2

cyclopropylcarbinyl cations are equilibrated before they react to form allylcarbinyl chloride. A direct "push-pull" mechanism is also eliminated since this would lead to a predominance of C_4-labeled allylcarbinyl- ^{14}C chloride.

Although the results of the reaction of cyclopropylcarbinol-α-^{14}C with Lucas reagent can be accommodated by equilibrating classical cyclobutyl and cyclopropylcarbinyl carbonium ions, the large solvolytic reactivities which have been observed for cyclopropylcarbinyl and cyclobutyl derivatives, which have been mentioned previously, are not readily explainable by such intermediates. Relief of strain in the solvolysis transition state by direct formation of the cyclobutyl cation might afford an explanation for the large solvolytic reactivity of cyclopropylcarbinyl derivatives. However this argument does not appear valid in the case of cyclobutyl derivatives unless these derivatives form allylcarbinyl cations directly. Since large amounts of allylcarbinyl derivatives are not observed in irreversible reactions of cyclobutyl compounds and since it is relatively difficult to form the allylcarbinyl cation directly from allylcarbinyl derivatives, the relief of strain may be ruled out as the major driving force for the large solvolytic reactivities observed for cyclobutyl compounds. Although separate explanations could be offered for the great reactivities of the cyclopropylcarbinyl and cyclobutyl derivatives, the experimental data can be explained quite well by assuming a single non-classical cationic intermediate or a rapid equilibrium of several non-classical intermediates. The experimental results are similar to those of the norbornyl system (8) for which enhanced solvolytic reactivity and ^{14}C scrambling seem to be best explained by non-classical cationic intermediates.

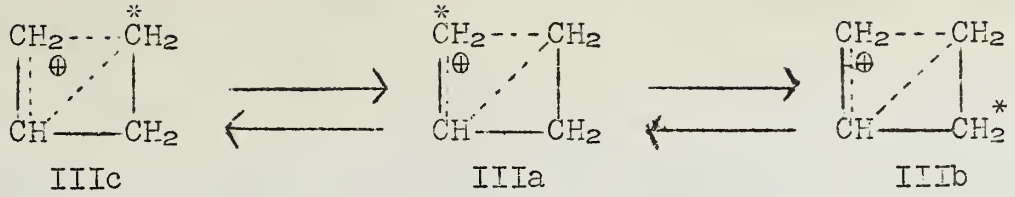
It is now necessary to choose between various non-classical intermediates which may be proposed to see which best fit the experimental data so far presented.

A single pyramidal cation (IIIa), which is unsymmetrical, is not adequate since this would lead to ^{14}C located only in the methylene group of the double bond of the allylcarbinyl- ^{14}C chloride.



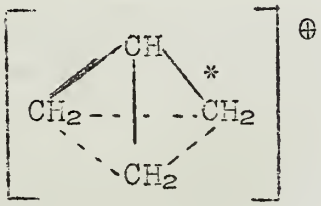
IIIa

However the results of Lucas reagent with cyclopropylcarbinol-α-^{14}C may be explained by a series of pyramidal non-classical cationic intermediates (IIIa-c) which are in rapid equilibrium with each other or a single "tricyclobutonium" cation (IV). It is impossible however to distinguish between these two proposed pathways from the experimental results obtained in the treatment of cyclopropylcarbinol-α-^{14}C with Lucas reagent. An irreversible process in a highly nucleophilic solvent appeared to be the best possibility for distinguishing between the two pathways. One would expect that the degree of equivalence of the methylene groups of the three cation



IIIc IIIa IIIb

or



IV

(IIIa-c) would be less than that achieved by the symmetrical ion (IV) if the cations (IIIa-c) do not equilibrate much faster than they react with the nucleophilic solvent to give the final product. The two formulations are essentially the same if the energy barrier to interconversion of (IIIa-c) is substantially less than five kilocalories.

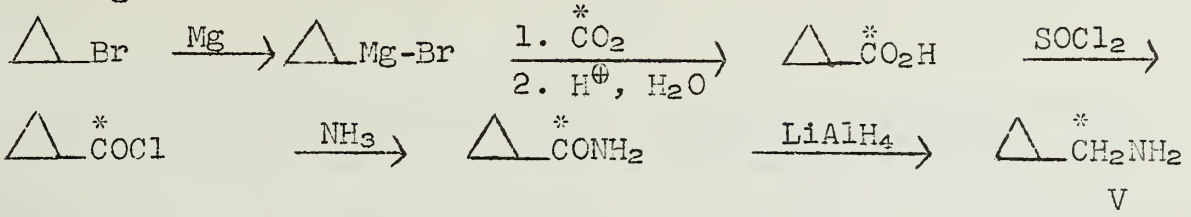
The irreversible reaction chosen by Roberts and his co-workers was deamination with nitrous acid. Although there is some question as to the exact nature of the carbonium ion (14) obtained by loss of nitrogen from an alkyl diazonium ion, the reaction is almost certainly irreversible and is carried out under fairly mild conditions in the presence of water, which is a fairly good nucleophilic agent. Furthermore, product compositions obtained from deamination of both cyclopropylcarbinylamine and cyclobutylamine are quite similar to those obtained for other carbonium ion reactions in this series. The following product compcsitions were observed by Roberts (9) for the deamination of cyclopropylcarbinylamine, cyclobutylamine and allylcarbinylamine:

amine			CH_2=$CHCH_2CH_2OH$	CH_2=$CHCHOHCH_3$	CH_3CH=$CHCH_2OH$
	56%	40%	4%	0%	0%
	51%	45%	4%	0%	0%
CH_2=$CHCH_2CH_2NH_2$	15%	13.5%	42%	22%	7.5%

The presence of crotyl alcohol and α-methylallyl alcohol among the products from the deamination of allylcarbinylamine is quite significant, because it indicates that when the allylcarbinyl cation is actually formed it tends to undergo hydride shifts to resonance stabilized cations, i.e., crotyl and α-methylallyl cations, as well as forming cyclobutyl and cyclopropylcarbinyl products by ring closure. Thus the presence of crotyl and α-methylallyl derivatives among the products from the reactions involving allylcarbinyl derivatives would indicate the presence of the "free" allylcarbinyl cation.

In order to determine the extent of methylene scrambling during the deamination reaction Roberts and co-workers (13) deaminated

cyclopropylcarbinylamine-α-^{14}C (V), which was prepared in the following manner:



V

Deamination of (V) with nitrous acid afforded the distribution of radioactivity in the products shown in Figure 3.

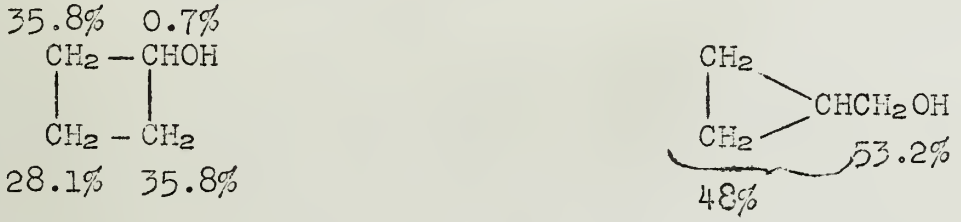


Figure 3

The distribution of ^{14}C in the alcohols obtained by deamination with nitrous acid strongly indicates analogous behavior to that observed in the reaction of cyclopropylcarbinol-α-^{14}C with Lucas reagent. It appears that the single caticnic intermediate (IV) cannot fully account for the observed ^{14}C among the 2,3 and 4 carbon atoms of the cyclobutanol. The ^{14}C distribution in cyclobutanol however is readily accommodated by postulation of the species (IIIa) and partial interconversion of this with (IIIb) and (IIIc). The amount of interconversion is 84% of the theoretical equilibrium value. However, these intermediates cannot explain the excess ^{14}C in the α-position of the cyclopropylcarbinol. The excess ^{14}C can be explained as resulting from a non-rearranging, S_N2-type displacement at the α-carbon of the diazonium ion before (IIIa) is formed. If this hypothesis is correct, one would expect that the yield of cyclopropylcarbinol from the deamination of cyclopropylcarbinylamine would be greater than the amount of cyclopropylcarbinol from the deamination of cyclobutylamine. Experimental evidence which supports this explanation for the excess ^{14}C in the α-position of cyclopropylcarbinol is given by vapor phase chromatography of the products obtained by deamination of the respective amines. Cyclopropylcarbinylamine gave a product composition which contained 56% cyclopropycarbinol and 40% cyclobutanol while that of cyclobutylamine contained only 51% cyclopropylcarbinol and 45% cyclobutanol.

Winstein and Kosower (15) have suggested that symmetrical (VI) and unsymmetrical (VIIa,b) homoallylic cations may afford an alternative explanation for the results obtained by Roberts and coworkers in the deamination of cyclopropylcarbinylamine-α-^{14}C. The main difference between homoallylic cations and bicyclobutonium ions (Figure 4) is that the latter include 1,3 and 1,4 interactions, the former do not. Since the reactions of cyclopropylcarbinyl derivatives yield large amounts of cyclobutyl products, it seems reasonable to expect that some partial bonding between the 1 and 4 carbon atoms (c.f IIIa) is present in the intermediates which lead to cyclobutyl products.

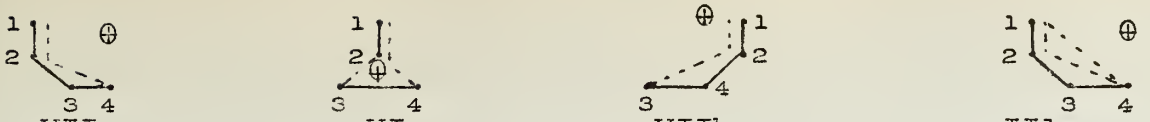
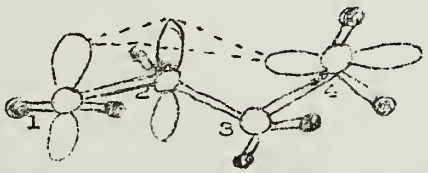


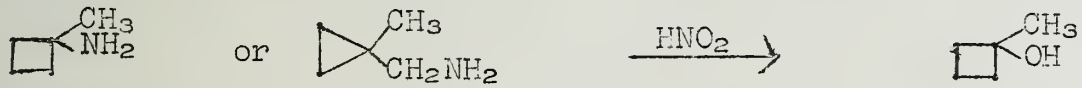
Figure 4

Roberts (13) believes that the most geometrically favored configuration for (IIIa,b,c) is that pictured in Figure 5. It appears that the degree of overlap of the three 2p-orbitals in



O=carbon
●=hydrogen

which the two unsaturation electrons are delocalized is probably quite similar to that visualized for the 7-dehydronorbornyl cation (16,17) which is highly stabilized by electron delocalization. Attack of a nucleophilic agent at positions 1,2 and 4 as shown in Figure 5 would lead to cyclopropylcarbinyl, cyclobutyl or allylcarbinyl products respectively. Since the proportions of the products corresponding to attack on these positions is approximately 13:12:1 one would expect that the charge on the cation must be distributed mainly on the 1 and 2-positions with some on the 4-position. Since such small differences in the energy barriers to interconversion of the intermediates must be controlled by a very delicate balance of steric and electronic factors, it would appear that substitution of even a single methyl group on one of the carbons would produce a large change in the product ratios, because of the resultant change in the charge distribution. Roberts (9) has observed such effects in the deamination of 1-methylcyclopropylcarbinylamine and 1-methylcyclobutylamine. These effects have also



been observed in other methyl substituted cyclobutyl and cyclopropylcarbinyl derivatives which will be discussed in a later section of this seminar.

TERTIARY AND SECONDARY CYCLOPROPYLCARBINYL DERIVATIVES

The similarity which exists between the cholesteryl-cyclocholestanyl, norbornenyl-norticyclyl and allylcarbinyl-cyclopropylcarbinyl systems is shown in Figure 6. All three systems have 1,3 carbon-carbon interactions. However in the cholesteryl-cyclocholestanyl and the norbornenyl-nortricyclyl systems, 1,4 carbon-carbon interactions, which are present in the allylcarbinyl-cyclopropylcarbinyl system, are not possible, because of the geometric

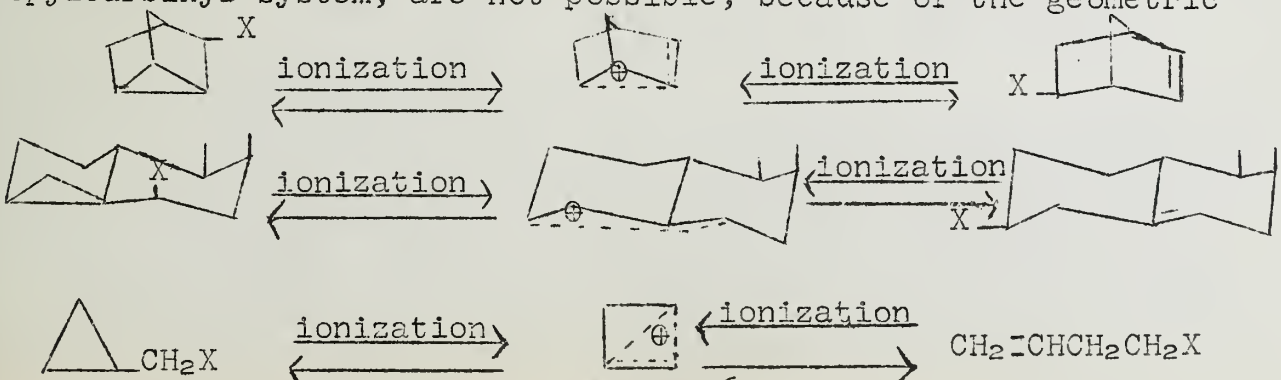


Figure 6

requirements of the ring systems. High reactivity in the solvolysis of cyclocholestanyl derivatives has been observed (15).

The norbornenyl system (1,2) as well as the cholesteryl system (1,3) has been discussed in previous seminars.

Two explanations may be offered for rapid rates of solvolysis of many cyclopropylcarbinyl derivatives. If release of strain is the driving force, one ring might be sufficient to give rate enhancement. However, if delocalization of charge is the driving force, one might expect that for derivatives with two cyclopropyl rings over which the charge would be delocalized that an even larger increase in the rate of solvolysis than that observed for the monocyclopropyl derivative would be observed, such as in the case of the benzyl, benzhydryl and trityl series.

In an experiment designed to determine which alternative prevailed Hart and Sandri (18) studied the solvolysis of the p-nitrobenzoates of dicyclopropylisopropylcarbinol (VIII), di(2-methylcyclopropyl)-isopropylcarbinol (IX), diisopropylcyclopropylcarbinol (X) and dicyclopropylcarbinol (XI) in aqueous and methanolic dioxane.

A rearranged product (XII) was detected only in the solvolysis of (X). As the polarity of the solvent increased the amount of rearrangement decreased. The reaction was always first order regardless of the amount of rearrangement which occurred. It was also demonstrated that isomerization of (X) was not thermal, but required the presence of ionizing solvents.

The relative solvolysis rates of several of the p-nitrobenzoate esters in 80% aqueous dioxane at 60° are listed in Table I. From the series (XIII), (X) and (VIII) it is apparent that the rate increase with the second cyclopropyl group was almost equal to that of the first. Hart and Sandri therefore conclude that the rate enhancement observed for (VIII) compared to (X) is not due to relief of strain in the cyclopropyl ring, but rather to stabilization of the carbonium ion by some mechanism of electron release from each cyclopropyl group as pictured in Figure 7. Hart and Sandri further

Table I $R_1R_2R_3COCO\text{-}\phi\text{-}p\text{-}NO_2$

ester	R_1	$R_2=R_3$	rel. rate
XIII	i-Pr	i-Pr	1
XI	H	cyclo-Pr	60.
X	cyclo-Pr	i-Pr	246
VIII	i-Pr	cyclo-Pr	23,500
IX	i-Pr	2-Me-Cyclo-Pr	124,000

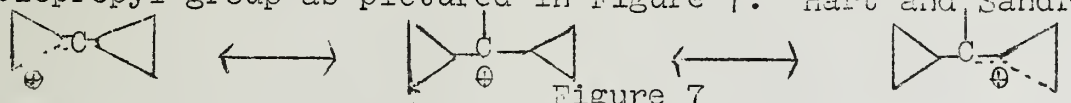


Figure 7

$[(CH_3)_2CH]_2C{=}CH_2CH_2OCO\text{-}\phi\text{-}p\text{-}NO_2$ XII

state that the positive charge is concentrated on the tertiary carbon atom, because rearranged solvolysis products are not obtained. This conclusion by Hart and Sandri implies that non-classical ion formation with cyclopropylcarbinyl derivatives must lead to rearranged products. However it has been well established in the cholesteryl series (19) that non-classical intermediates do not necessarily lead to rearranged products provided that the starting materials have certain predictably favorable structures.

An example of a cyclopropylcarbinyl derivative which should show enhanced reactivity, but would not necessarily lead to rearranged products is the methylcyclopropylcarbinyl system (9). Methylcyclopropylcarbinylamine (XIV) upon treatment with nitrous acid yields methylcyclopropylcarbinol (XVIa) as the sole product. The non-classical intermediates and the expected products which would result from them are shown in Figure 8.

If we assume that the product distribution observed from deamination of the unsubstituted amines gives an indication of the relative amount of positive charge at a given carbon atom then placing a methyl group at a carbon atom which has a large amount of positive charge in the unsubstituted case would greatly increase the stability of the cation (20).

Let us now consider the resonance structures which will contribute to the stability of the intermediates (XVa-c). These structures are shown in Figure 8. In the important resonance structures available for (XV-c) the methyl group is located at a

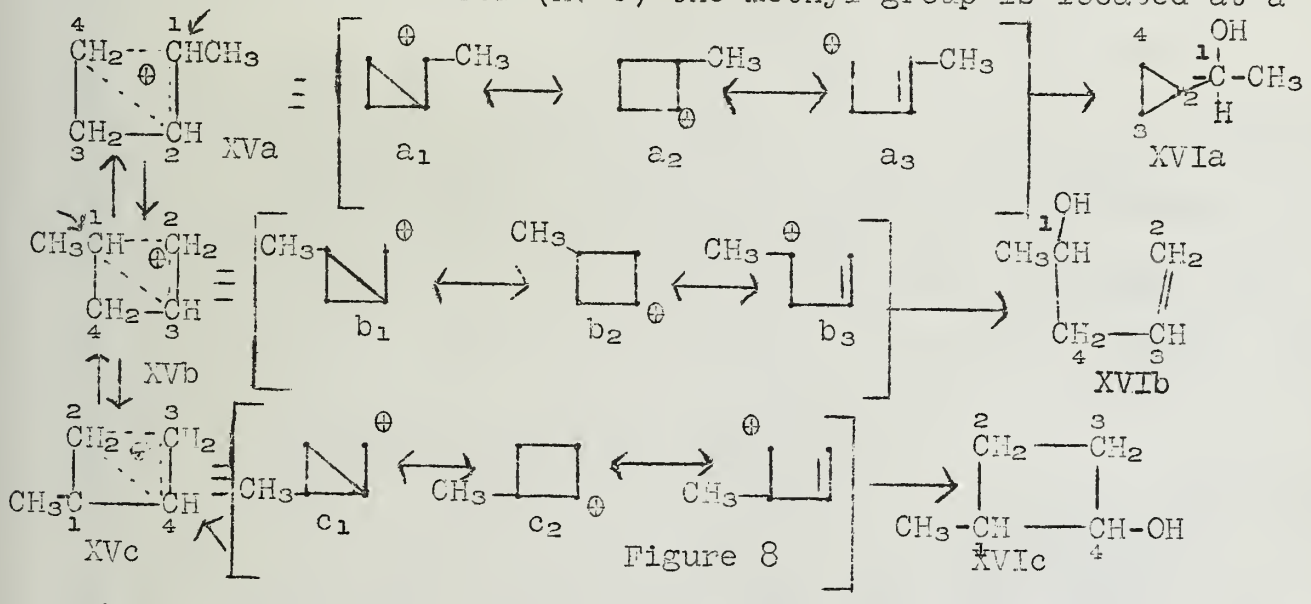


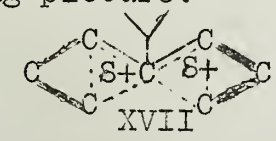
Figure 8

carbon atom where there is none of the positive charge in the unsubstituted case. In the important resonance structures available for (XV-b) structure (b_3) has the methyl group at a carbon where there is some positive charge in the unsubstituted case. One would expect that (XV-b) would yield mainly allylcarbinyl products, because of the heavy contribution of (b_3) to the resonance hybrid. One would also expect that (XV-a) would yield mainly cyclopropylcarbinyl products, because of the heavy contribution of (a_1) to the resonance hybrid. Since in the unsubstituted case at least thirteen times as much cyclopropylcarbinyl as allylcarbinyl products are obtained, one would expect that the methyl group in (a_1) is stabilizing more positive charge than the methyl group in (b_3). Therefore the dominant reaction product should be the cyclopropylcarbinyl derivative. Thus it has been shown from consideration of the possible intermediates that of the three possible products (XVIa-c), (XVI-a) is most likely to be the major product from the deamination of methylcyclopropylcarbinylamine. It can readily be seen from the argument just presented that the presence of non-classical carbonium ions in a secondary, and presumably tertiary, cyclopropylcarbinyl system does not necessarily lead to rearranged products.

Let us now consider the solvolysis of (VIII) again and see

what the non-classical intermediate would look like for this dicyclopropylcarbinyl system. The intermediate might be represented by structure (XVII).

A consideration of the geometric conformation for (XVII) by analogy with that pictured for (IIIa-c) in Figure 5 gives the following picture:



XVII

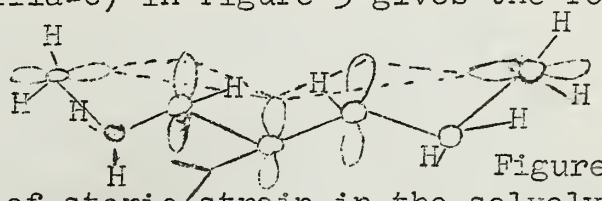


Figure 9

Thus it appears that relief of steric strain in the solvolysis transition state due to non-classical ion formation could play an important part in the rate enhancement observed in the solvolysis of (VIII) since Figure 9 indicates that overlap of the type pictured for (IIIa-c) is also geometrically feasible in the dicyclopropylcarbinyl system.

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STRUCTURES OF PALITANTIN AND FREQUENTIN

Reported by D. L. De Vries November 12, 1959

HISTORY

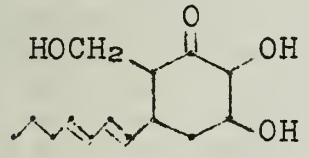
Palitantin ($C_{14}H_{22}O_4$) and frequentin ($C_{14}H_{20}O_4$) are mold metabolites closely related in chemical structure, frequentin containing one more point of unsaturation than palitantin. The isolation of palitantin from Penicillium palitans Westling was described by Birkinshaw and Raistrick in 1936 (1). Strains of Penicillium frequentans and Penicillium cyclopium give good yields of palitantin with certain species also yielding frequentin (2,3). When frequentin was first isolated it was reported only as a dextrorotatory acid. The "acid" properties of frequentin later proved to be due to an enolic carbonyl group. Frequentin has been found to be antifungal and weakly antibacterial. Palitantin has no appreciable antifungal activity.

FORMATION

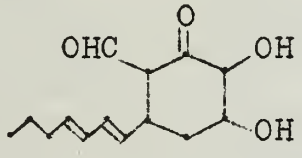
Frequentin and palitantin may be readily formed (4) by growing the mold, Penicillium frequentans, on a 5% glucose medium for about ten days at 25°. Extraction of the medium with chloroform, followed by concentration of the chloroform extracts, causes the colorless crystals of palitantin to be precipitated, followed by frequentin. Frequentin may be conveniently extracted with carbon tetrachloride, which leaves palitantin in the culture filtrate. The primary source of palitantin for study was Penicillium cyclopium, which was freshly isolated from heath soils and grown on a 5% glucose medium. Extraction of the medium with chloroform gave palitantin (2).

STRUCTURE DETERMINATION AND REACTIONS OF PALITANTIN

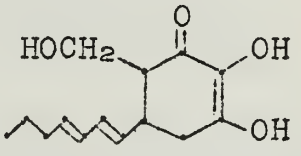
Palitantin is now known to have structure I. The structure of frequentin is less certain but is limited to either structure II or III in the light of recent work. Bowden and co-workers prefer the latter possibility (2).



I



II



III

After Birkinshaw (1) isolated palitantin as a crystalline substance, he made several observations concerning its chemical behavior, but he was unable to elucidate fully its molecular structure and arrived at some conclusions which later proved to be in error. The empirical formula for palitantin was found to be $C_{14}H_{22}O_4$ and it was reported to be inactive. Observance of optical activity in derivatives and breakdown products prompted further investigation under more favorable conditions, and palitantin was found to have a rotation of $[\alpha]_{5461}^{23^\circ}$ + 4.4° (5). Birkinshaw's observations at this point were misleading. He found that palitantin gives a positive Schiff's reaction and the usual aldehyde derivatives (mono-oxime, semicarbazone, and phenyl-

and dinitrophenylhydrazones). Palitantin was readily oxidized by Doeuvre's reagent (alkaline potassium mercuriiodide) to the corresponding palitantic acid ($C_{14}H_{22}O_5$) which would result if an aldehyde group in palitantin were oxidized to a carboxyl group. Doeuvre had shown that formaldehyde will react with potassium mercuriiodide in basic media to give formic acid according to the following equation (6). The experimental results pointed towards an

$$HCHO + HgI_2,2KI + 3NaOH \longrightarrow HCOONa + Hg + 2KI + 2NaI + 2H_2O$$

aldehyde group which did not exist (1).

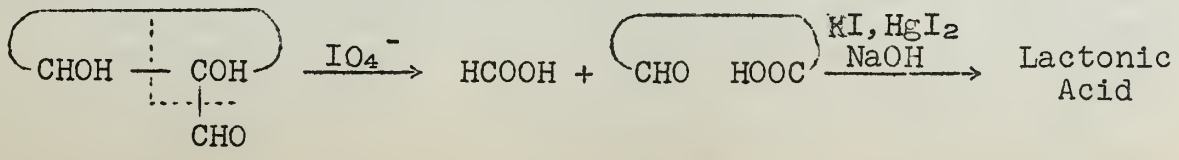
The dibenzoate of palitantin was formed, indicating the presence of two hydroxyl groups in palitantin, yet there was evidence of three active hydrogen atoms (1). This point confused Birkinshaw. He concluded that two of the four oxygen atoms existing in palitantin were included as hydroxyl groups and a third was part of an "aldehyde" group. The function of the fourth oxygen atom was not determined. It was later proven by infrared to be hydroxylic, even though it failed to form a benzoate ester.

Hydrogenation of palitantin with a palladium catalyst gave tetrahydropalitantin ($C_{14}H_{26}O_4$), showing the presence of two double bonds since the resulting compound still gave positive tests characteristic of an aldehyde and was readily oxidized to the corresponding monocarboxylic acid.

Reduction of tetrahydropalitantin with sodium amalgam resulted in the addition of two hydrogen atoms to give rise to a mixture of two isomeric hexahydro-derivatives ($C_{14}H_{28}O_4$), each of which contains four active hydrogens (1). The reduction of an aldehyde group could not account for the formation of two isomeric derivatives. It was not realized that a very reactive carbonyl group, forming part of a ring, was being reduced to give the two possible isomers. Finally, palitantin and tetrahydropalitantin were oxidized by silver oxide to dibasic acids $C_{13}H_{20}O_5$ and $C_{13}H_{24}O_5$ respectively, acids which were isolated as dihydrazides.

Sixteen years elapsed before Birkinshaw (5) made a quantitative study of the periodate oxidation of palitantin, tetrahydropalitantin, and tetrahydropalitantic acid. He found that palitantin and tetrahydropalitantin react with potassium periodate consuming the equivalent of two atoms of oxygen to give formic acid and a new C_{13} molecule containing an acidic group and an aldehyde group. It was this C_{13} molecule which later was used as the starting point in the successful structure determination. Upon oxidation with periodate, one molecule of tetrahydropalitantic acid consumes one atom of oxygen, forming no new acidic groups but two carbonyl groups.

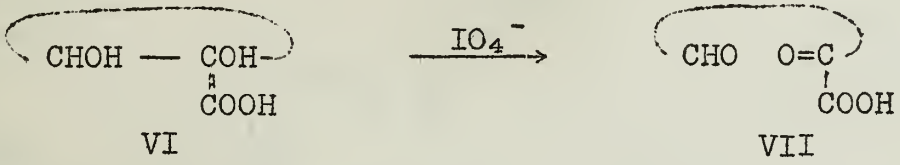
Birkinshaw (5) erroneously concluded from these data that the reactive grouping in palitantin is part of a ring as shown by IV. Treatment with periodate would give V and formic acid, two molecules of periodic acid splitting IV at the dotted lines.



IV V

Oxidation of the periodate oxidation product with alkaline potassium mercuriiodide gave a lactonic acid which was characterized as the dihydrazide of the corresponding hydroxy-dibasic acid ($C_{13}H_{24}O_5$), also obtained by treating tetrahydropalitantin with silver oxide.

In the case of tetrahydropalitantic acid, Birkinshaw concluded that the "aldehyde" group had been oxidized to a carboxyl group and that the periodate oxidation could be represented by VI being converted to VII, which contains an α-keto acid system and therefore resists further oxidation. Tetrahydropalitantic acid can be represented by VI, but it actually resulted from a rearrangement of tetrahydropalitantin and not simply from oxidation of the "aldehyde" group.



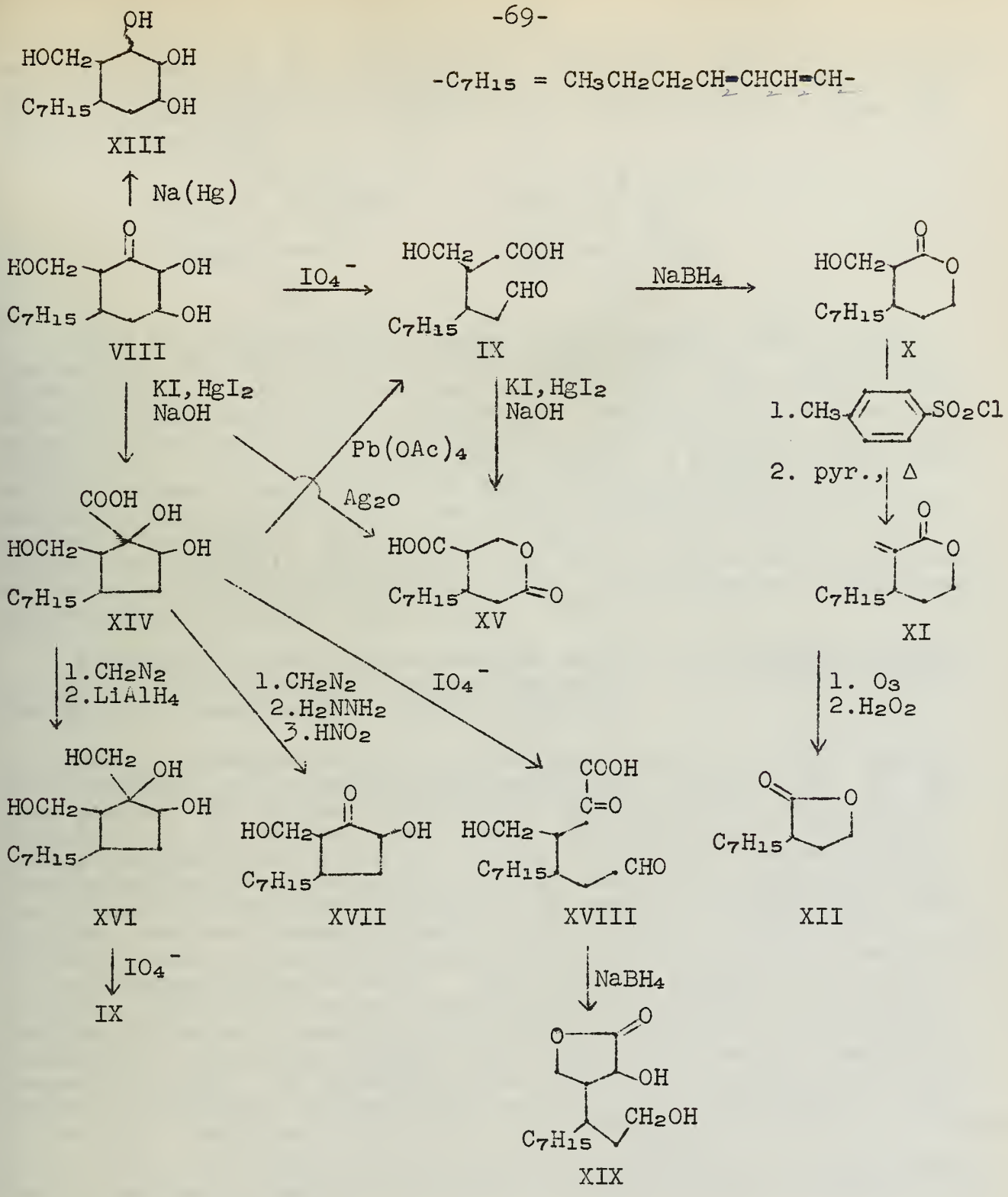
VI VII

Nitric acid oxidation of the C_{13} acid lactone, obtained from tetrahydropalitantin by periodate oxidation followed by alkaline potassium mercuriiodide treatment, gives rise to n-heptylsuccinic acid (loss of 2 carbon atoms), indicating to Birkinshaw that tetrahydropalitantin probably consists of a six-carbon ring with two side chains, one being a -CHO group and the other an n-heptyl chain. The presence of the six-membered carbon ring and the n-heptyl group proved to be correct.

One double bond in palitantin appeared to be situated γ,δ to the terminal methyl group of the C_7 chain to account for the formation of n-butyraldehyde on ozonolysis. Birkinshaw was unable to designate the position of the second double bond or the function of the fourth oxygen atom in palitantin though the C_{13} lactonic acid formation also indicated the presence of a third hydroxyl group.

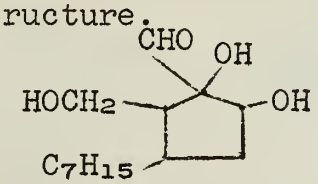
Recently Bowden, Lythgoe, and Marsden (2) became interested in establishing the structure of palitantin. They realized that oxidation of palitantin with alkaline potassium mercuriiodide to give palitantic acid did not necessitate the presence of an aldehyde group as such but could mean the presence of a very reactive carbonyl group. They immediately confirmed that the fourth oxygen atom in palitantin is hydroxylic by the well-defined infrared band at 3500 $cm.^{-1}$ shown by the di-p-bromobenzoate.

The structure determination (2) began by deducing structure IX for the aldehydo-acid ($C_{13}H_{24}O_4$) formed by periodate (or lead tetraacetate) oxidation of tetrahydropalitantin (VIII). No tendency to lactonize was evidenced by IX, whereas the dibasic acid obtained from VIII by treatment with Ag_2O, is completely lactonic, indicating that the lactone ring involves the newly generated carboxyl group and is represented by XV. Sodium borohydride was found to reduce IX to a crystalline δ-lactone (X), $\nu_{max.}$ 1718 $cm.^{-1}$. This lactonization involved the newly generated hydroxyl function and not that which pre-existed in the aldehydo-acid, as evidenced by the fact that lactonization did not take place prior to the reduction of the aldehyde group. The presence of the original hydroxyl was shown by formation of a crystalline tosylate from X. When warmed with pyridine this lost p-toluenesulfonic acid to give an α,β-unsaturated δ-lactone (XI), $\lambda_{max.}$ 212 mμ, $\nu_{max.}$ 1733 $cm.^{-1}$

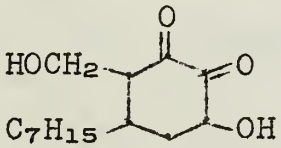


(conjugated lactonic -CO-), 1631 cm.$^{-1}$ (conjugated -C=C-). Ozonolysis gave formaldehyde indicating that the unsaturated lactone contains an α-methylene group. It is interesting to note that the lactone showed no C-H band near 900 cm.$^{-1}$ in the infrared spectrum; instead, it showed bands at 943 and 803 cm.$^{-1}$. Similar behavior was noticed for 2-methylenedodecanoic acid (7). When the ozonide was decomposed (2) with hydrogen peroxide, an optically active γ-lactone (XII), $\nu_{max.}$ 1780 cm.$^{-1}$, was formed. This γ-lactone showed infrared absorption identical with that of synthetic (±)-α-heptyl-γ-butyrolactone, prepared by Rothstein (8). The active lactone was racemized with hot ethanolic sodium ethoxide

and converted into the corresponding hydrazide, which was identical with that prepared from the synthetic (±)-lactone (2). These results indicated that the aldehydo-acid (IX) had been assigned the correct structure.



XX



XXI

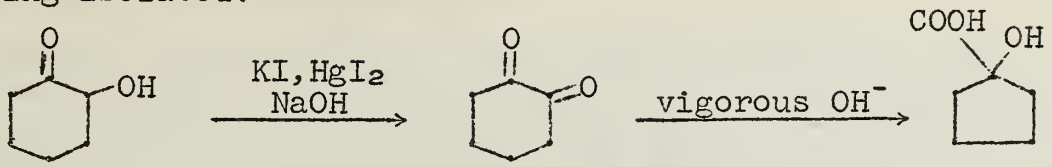
Only two structures for tetrahydropalitantin, VIII and XX, can account for the formation of IX upon oxidation. The aldehyde corresponding to acid XIV is represented by XX. The structure of tetrahydropalitantic acid, obtained by treating tetrahydropalitantin with alkaline potassium mercuriiodide, was shown to be correctly represented by XIV in the following manner. A Curtius degradation, which involves treatment of the methyl ester of the acid with hydrazine and nitrous acid, gave what is believed to be the five-membered ring ketone (XVII), $\nu_{max.}$ 1742 cm.$^{-1}$ (2). Also, the α-keto acid (XVIII), which Birkinshaw (5) had obtained by periodate oxidation of tetrahydropalitantic acid, was reduced by sodium borohydride to a γ-lactone (XII), $\nu_{max.}$ 1780 cm.$^{-1}$ (2).

Lithium aluminum hydride reduced methyl tetrahydropalitantate to the tetrol XVI, which consumed two moles of periodate to give one mole of formaldehyde together with IX.

Since tetrahydropalitantic acid has structure XIV it would seem probable that tetrahydropalitantin has structure XX. It has been proven that tetrahydropalitantin does not have structure XX. Reduction of the carbonyl function of tetrahydropalitantin with sodium amalgam (1,2) gives two tetrols, both with the empirical formula $C_{14}H_{28}O_4$ and referred to as α- and β-tetrahydropalitantol. The β-isomer, more readily obtained by reduction with sodium borohydride, has been characterized as the tetra-p-bromobenzoate. Neither isomer is identical with XVI which is obtained by reduction of tetrahydropalitantic acid. This acid has therefore a carbon skeleton different from tetrahydropalitantin (VIII). The tetrahydropalitantols, formed by reduction of reduction of tetrahydropalitantin with sodium amalgam, are believed to be the diastereoisomers of XIII. In agreement with this, the β-isomer reduced two moles of periodate, giving formic acid but no formaldehyde. The ultraviolet spectrum of palitantin (I) has $\lambda_{max.}$ at 232 mμ (ε 34,000). Palitantol, the tetrol obtained from palitantin by reduction with sodium amalgam or sodium borohydride, shows similar absorption and is therefore dienoid (2).

The ketonic structure (VIII) agrees well with the infrared absorption of tetrahydropalitantin, which shows $\nu_{max.}$ 1706 cm.$^{-1}$ but no aldehydic band near 2800 cm.$^{-1}$. A molecular rearrangement analogous to the benzilic acid change must occur in the formation of tetrahydropalitantic acid. It is possible that the α-diketone (XXI) may be an intermediate, although under similar conditions alkaline potassium mercuriiodide converted adipoin (XXII) only into cyclohexane-1,2-dione (XXIII). More vigorous alkaline treatment is required for rearrangement (9) of XXIII to 1-hydroxycyclopentanecarboxylic acid (XXIV). The palitantic acid rearrangement

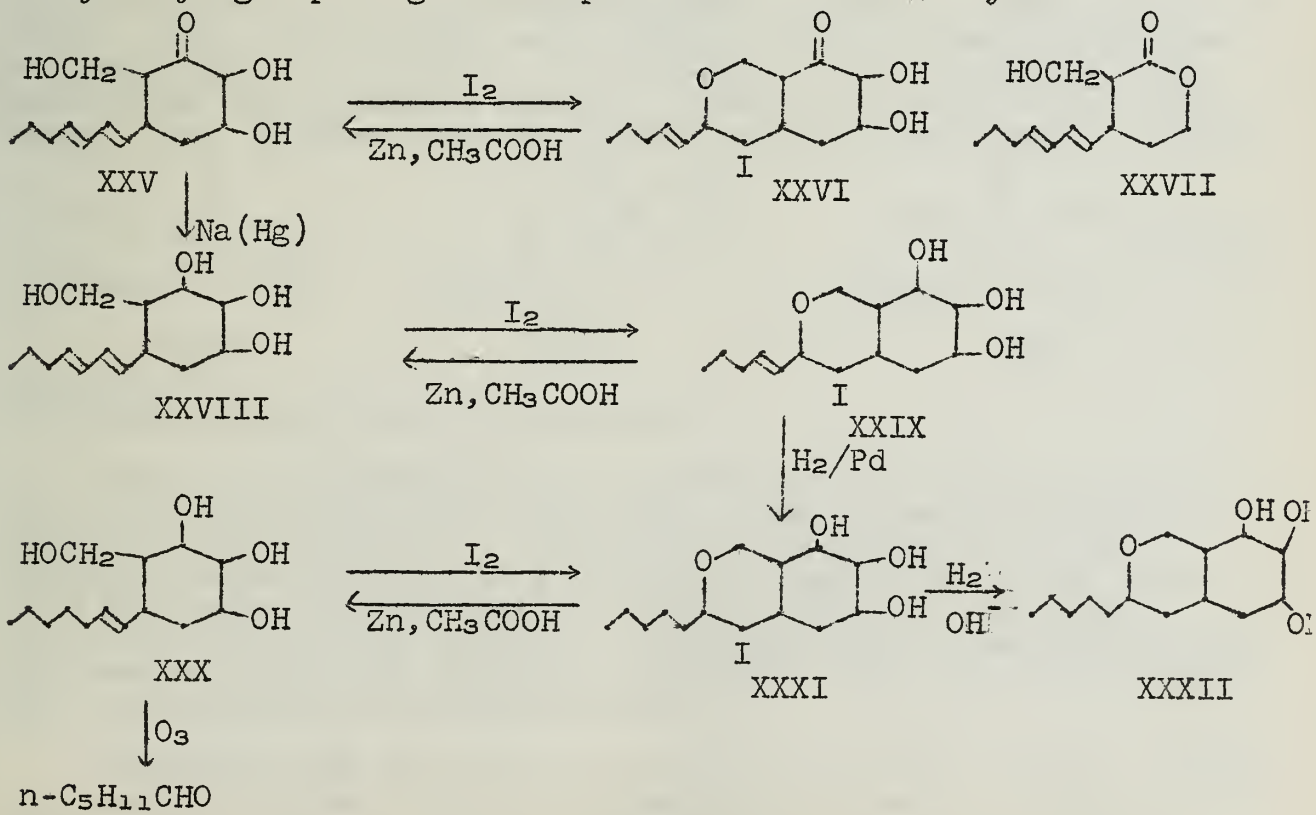
is stereospecific with only one of the two possible diastereo-isomers being isolated.



XXII XXIII XXIV

The system $CH_3CH_2CH_2CH{=}CHCH{=}CH-$ shown to be present in palitantin by the isolation of butyraldehyde on ozonolysis, shows $\nu_{max.}$ 990 (conjugated trans -CH=CH-) and 942 cm.$^{-1}$ (2). A band of the latter frequency is present (10) in the spectra of dienes with one cis and one trans double bond. The $\nu_{max.}$ at 942 cm.$^{-1}$ may be attributed to something else since corresponding saturated compounds of the palitantin series also showed a similar band (2). The combination of one cis and one trans double bond in palitantin is improbable in view of the high intensity of the 232 mμ absorption.

Palitantin and palitantic acid are substituted by iodine (5), giving monoiodo compounds. Bowden, Lythgoe, and Marsden (2) studied this unusual reaction, which they also found took place with palitantol (XXVIII) and with the diunsaturated δ-lactone (XXVII). During the reaction with iodine the dienoid infrared absorption disappeared and a hydroxyl group was masked. For example, the product from XXVII contained no free hydroxyl group. The reaction is therefore a cyclization between one of the double bonds and the hydroxymethyl group to give iodopalitantin with the cyclic structure



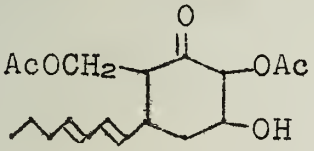
XXVI. In agreement with this, the product was reconverted into palitantin by zinc and acetic acid. Addition of the elements of an alkyl hypoiodite to a double bond is not normally possible.

This example illustrates the favorable effect on reaction velocity often observed when two reacting groups occupy sterically suitable positions within the same molecule.

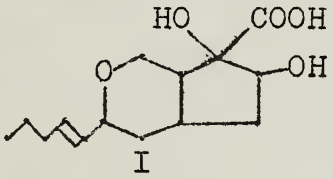
In further confirmation of the proposed structures (2), iodopalitantol (XXIX) was reduced by one mole of hydrogen in the presence of palladium as a catalyst to give the saturated iodoether (XXXI). It was thus shown that the cyclization does not require a diene system. The structure of XXX was shown by ozonolysis which gave hexanal. These reactions provided a means for studying the double bonds in the diene system of palitantin separately. The double bond farthest from the ring in palitantin probably has a trans configuration since XXVI and XXIX showed very strong bands near 960 cm.$^{-1}$ which disappeared on hydrogenation. The monounsaturated tetrol (XXX) was less certain. It showed a band of moderate intensity at 959 cm.$^{-1}$, indicating that the double bond closer to the ring in palitantin is also probably of the trans type.

Acetylation of palitantin (2) readily yielded a diacetate, but no well-defined triacetate. The diacetate was proposed to have structure XXXIII since it failed to form the cyclic iodoether. The resistance of the third hydroxyl group to acylation was attributed to the presence of the keto group in palitantin (I) and tetrahydropalitantin (VIII) since all four hydroxyl groups in tetrahydropalitantol (XIII) are reactive. If the failure to form a triacetate is connected with the presence of the keto-group, it would seem more probable for the secondary hydroxyl group farther from the keto-group in palitantin (I) to be acylated than the hydroxyl function adjacent to the carbonyl group.

Palitantin (I), tetrahydropalitantin (VIII), iodopalitantin (XXVI), and iodopalitantic acid (XXXIV) readily form crystalline isopropylidene derivatives. The formation of the isopropylidene derivatives very probably does not involve the primary hydroxyl group. That obtained from palitantin probably has structure XXXV.

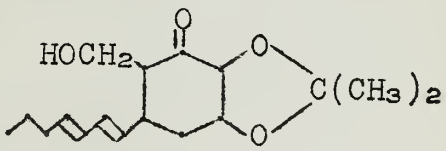


XXXIII



I

XXXIV



XXXV

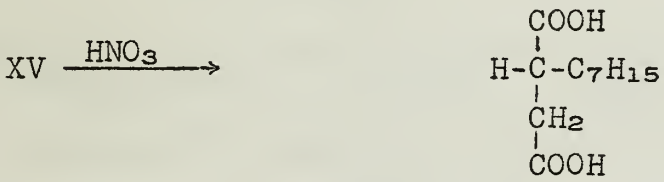
STRUCTURE AND REACTIONS OF FREQUENTIN

Curtis and Duncanson (11) were able to show that the carbon skeletons and positions of the oxygen atoms in palitantin and frequentin are identical. Frequentin was reduced by sodium amalgam in acid solution to a tetrahydro-derivative which proved to be palitantol (XXVIII) and was also obtained by reducing palitantin with sodium amalgam. No depressions of melting points occurred on mixing the reduction products. Their infrared spectra also showed them to be identical (11).

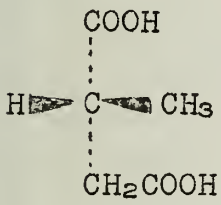
Frequentin has an absorption band at 1732 cm.$^{-1}$ with a slight shoulder at 1720 cm.$^{-1}$ while palitantin has a band at 1718 cm.$^{-1}$. This confirms that there are two carbonyl groups in frequentin and one in palitantin (11). Structures II and III are possible for frequentin (2).

STEREOCHEMISTRY OF PALITANTIN AND PALITANTIC ACID

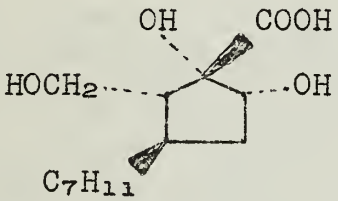
No detailed study of the stereochemistry of palitantin has been attempted. Some observations have been made and conclusions drawn as to the possible geometric configuration of palitantin (2). It is probable that (+)-heptylsuccinic acid (XXXVII), obtained from the lactonic acid (XV) by oxidation, belongs to the same configurational series as D(+)-methylsuccinic acid (XXXVIII) (12, 13). This gives the absolute configuration at the carbon atom attached to the heptadienyl group in palitantin. Iodopalitantin semicarbazone again forms iodopalitantin on treatment with pyruvic acid, so that the two six-membered rings in the iodo-compounds probably have the stable trans fusion, meaning that the hydroxymethyl and the heptadienyl groups are trans-related. The non-primary hydroxyl groups of palitantin (I) and palitantic acid (XIV) are almost certainly cis-related since they react with acetone. Since palitantic acid shows no tendency to form a lactone, its carboxyl and hydroxymethyl groups are probably trans-related. If these assumptions are correct we may write stereostructures XXXIX and XL for palitantic acid and palitantin respectively.



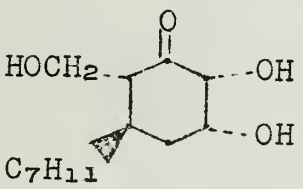
XXXVII



XXXVIII

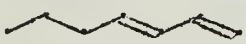


XXXIX



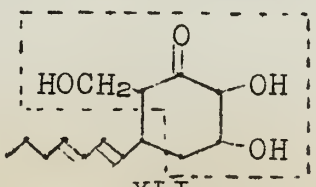
XL

C_7H_{11} =

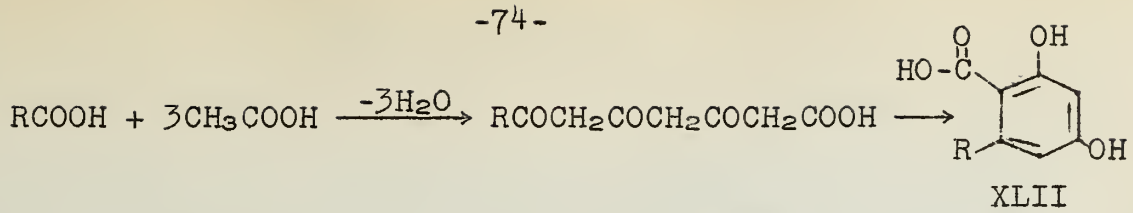


BIOSYNTHESES

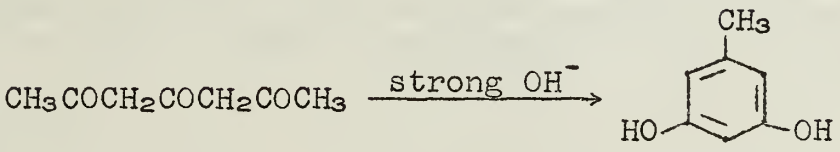
The structures of palitantin (XLI) or frequentin may readily be derived biogenetically from acetate units as are many other mold metabolites (14). For example, many compounds with structure XLII, which is closely related to palitantin and frequentin, are well known in nature and can be imagined to arise from acetate units. This possibility was considered even at the beginning of the nineteenth century when Collie (15) provided laboratory evidence that β-polyketones can be cyclized to phenols. He showed that diacetylacetone cyclizes under strongly alkaline conditions to a phenol (XLIII).



XLI



XLII



XLIII

No investigations have been made with palitantin or frequentin to determine exactly how they might be derived from the glucose medium on which they are grown. The portion of palitantin enclosed with the dotted line (XLI) resembles very closely a glucose molecule.

****

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THE NEF REACTION

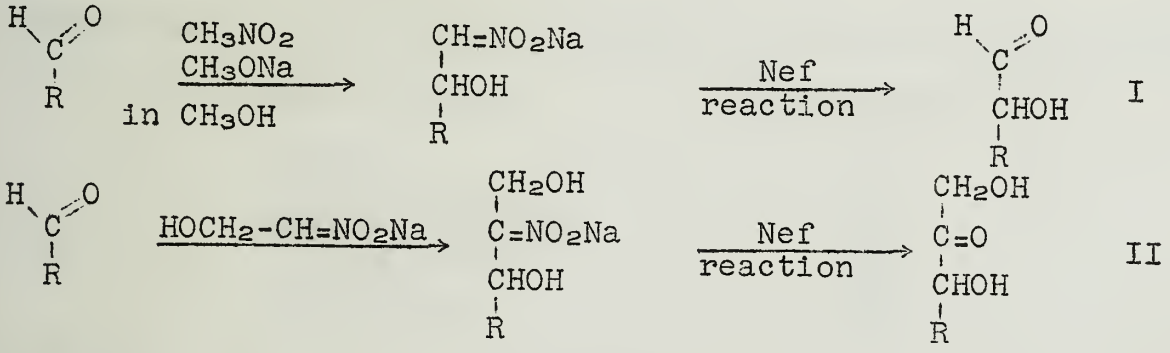
Reported by D. E. Gwynn November 16, 1959

The Nef reaction is defined as the acid hydrolysis of salts of primary and secondary nitroalkanes to aldehydes and ketones. This seminar will deal primarily with the more recent work that has attempted to establish a better understanding of the mechanism of this reaction.

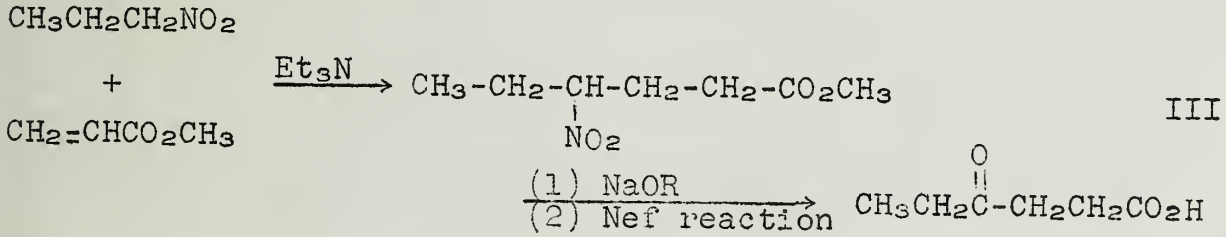
SYNTHETIC APPLICATIONS

The Nef reaction has long been known as a good synthetic tool for preparing carbonyl compounds. Although most of this work has been adequately reviewed by W. E. Noland (1), a thorough discussion of the Nef reaction would not be complete without some mention of its synthetic applications.

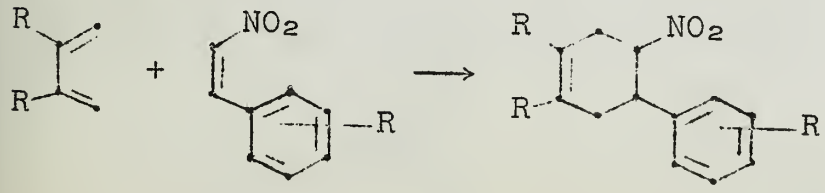
A combination of the aldehyde-nitroparaffin condensation reaction and the Nef reaction constitutes the essential steps of the nitromethane (I) and the 2-nitroethanol (II) synthesis in the sugar series (2). These two reactions are efficient methods for increasing the length of the carbon chain in aldoses by either one or two carbon atoms.

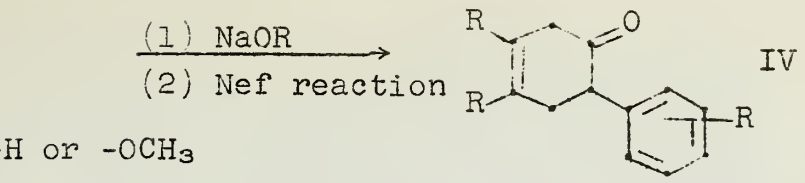


A sequence of the Michael condensation utilizing nitroalkanes followed by the Nef reaction can give rise to a variety of γ-keto acids, as exemplified in equation III (3).



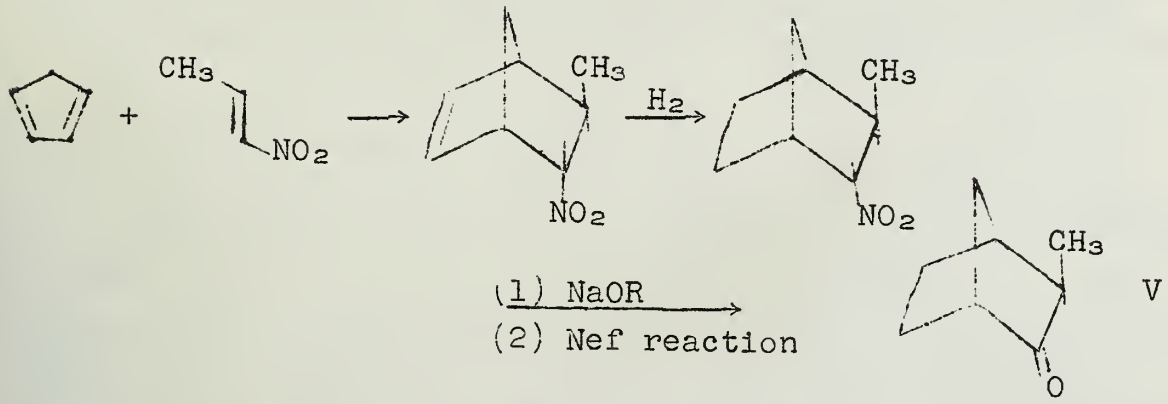
Various cyclohexanones (IV) (4,5,6) and bicyclic ketones (V) (7,8) can conveniently be prepared from the Diels-Alder adducts of primary nitroölefins and 1,3-butadienes followed by the Nef reaction.





IV

R = $-CH_3$, $-H$ or $-OCH_3$



V

The Nef reaction is also quite applicable to the preparation of simple aldehydes and ketones from the corresponding nitroalkanes (9) as the yields listed in Table I will illustrate.

TABLE I

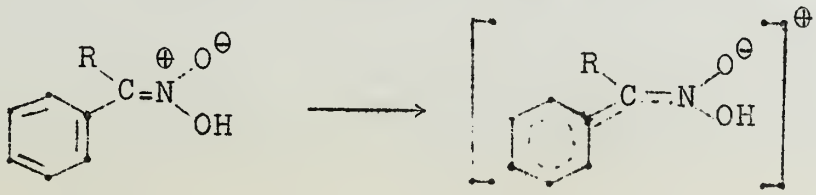
Preparation of Aldehydes and Ketones Utilizing the Nef Reaction

Aldehyde or Ketone	Best Yield %
CH_3CHO	77
CH_3CH_2CHO	80
$CH_3CH_2CH_2CH_2CHO$	85
$(CH_3)_2CH\text{-}CHO$	32
CH_3COCH_3	84
$CH_3CH_2COCH_3$	85

MECHANISM

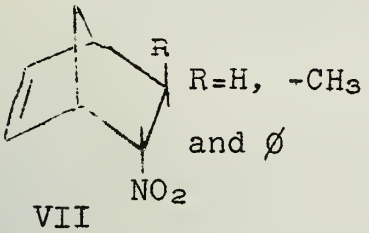
Any mechanism which is proposed for the Nef reaction must take into account a number of facts: (1) aci-nitroalkanes having enhanced resonance stabilization do not normally give the Nef reaction or do so only very slowly. (2) A fleeting blue intermediate having an appreciable lifetime is produced during the normal course of the reaction. (3) The rate-determining transition state for the acid-catalyzed decomposition of aci-nitroalkanes is composed of an aci-nitroalkane molecule, a proton and probably one or more molecules of hydroxylic solvent.

Early workers have reported that nitro compounds such as α-phenylnitroethane (10) and phenylnitromethane (11) fail to give the Nef reaction. In these cases none of the desired ketone was obtained. This fact was attributed to resonance stabilization of the aci-nitro compound by the neighboring phenyl group (VI) (7) which would thus moderate solvent attack at the incipient carbonyl carbon.

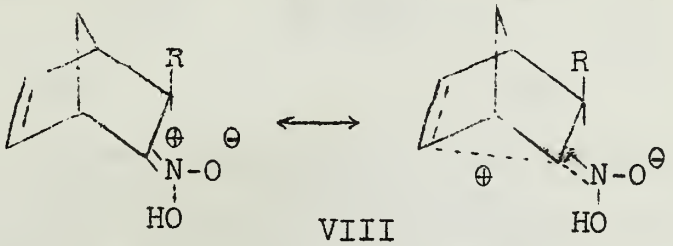


VI

The failure of another system to give the desired ketone under the conditions of the Nef reaction was early noticed but no reasonable explanation was offered until several years later. Derivatives of 5-nitrobicyclo[2.2.1]-2-heptene (VII) were found to give no ketonic material and only unreacted starting material was recovered (5,6,7,8,12). Wildman and Sanders (13) attributed this inertness to the stabilization of the aci-nitroalkane through homoallylic resonance (VIII). Supporting this theory is

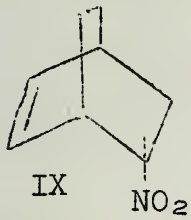


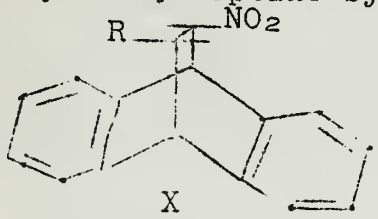
VII



VIII

the observation that 5-nitrobicyclo[2.2.2]-2-octene (IX)(13) undergoes the normal Nef reaction as do 9,10-dihydro-(11-nitroethano)-anthracenes (X) (14). No example of a non-classical type stabilization of a carbonium ion in the bicyclo-[2.2.2]-octanes has been reported (13) while such examples are quite numerous in the bicyclo[2.2.1] heptane system.

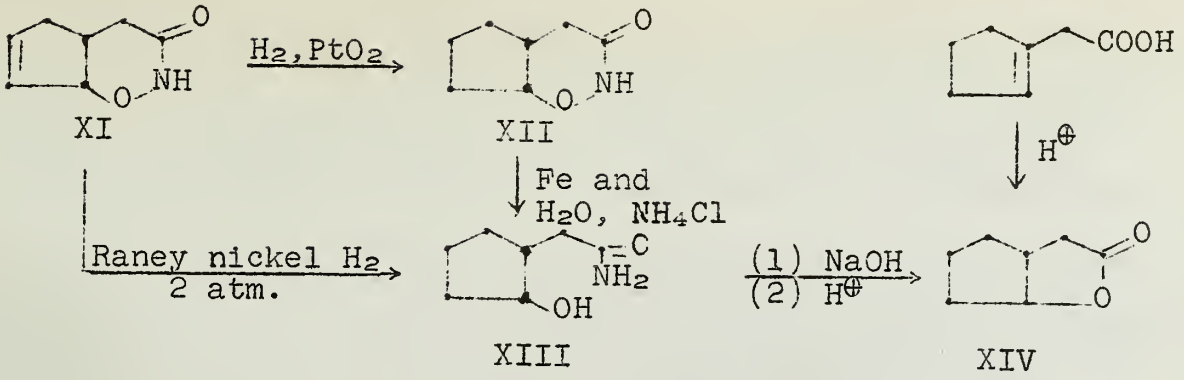




R = -H, -CH3 and -ø

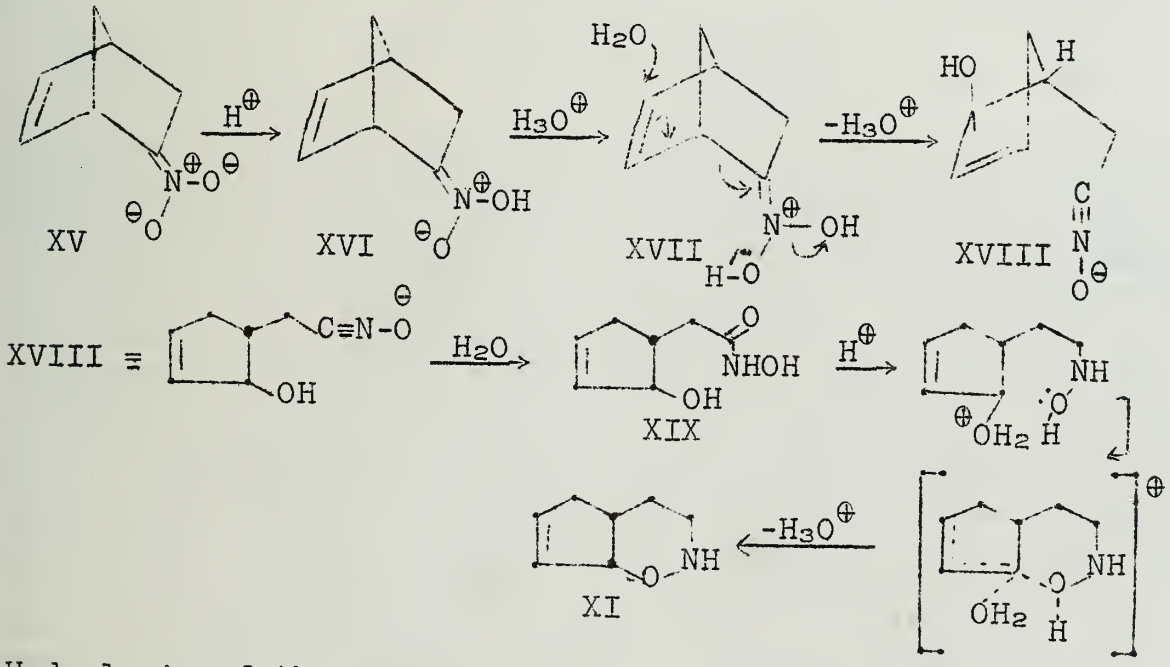
Another explanation for the failure of these systems to give the normal Nef reaction is that the aci-nitro tautomer, under the acidic conditions of the reaction, reverts to starting material, the nitroalkane, much more rapidly than it hydrolyzes to the ketone. Such a possibility has not been investigated.

The resonance stabilization of the aci-nitro tautomer in the bicyclo[2.2.1]heptane system might be expected to lead to rearranged products. Noland and co-workers (15) recently succeeded in isolating a rearranged product from the Nef reaction on the sodium salt of 5-nitronorbornene. The product, however, was not a nortricyclene derivative, as one might have expected from the resonance stabilization and analogies to other examples of bicyclo[2.2.1]heptane reactions, but resulted from a novel fission of the norbornene ring system. A compound, $C_7H_9NO_2$ (XI), isomeric with 5-nitronorbornene was obtained in up to 42% yield along with considerable tarry, brownish material. Hydrogenation of the rearranged product over platinum oxide at 2 atm. produced a dihydro derivative (XII) with the consumption of 1.00 mole of hydrogen. Neither XI nor XII gave a positive color test with ferric chloride; both were weakly acidic; they were resistant to alkaline hydrolysis. Treatment of a chloroform solution of XI with concentrated sulfuric acid gave white crystals of hydroxyl-amine sulfate. These are consistent with a hydroxamic ester structure for the rearranged product and its dihydro derivative. Hydrogenation of XI over Raney nickel catalyst at 2 atm. or reduction of XII with iron powder and aqueous ethanolic ammonium chloride solution yielded a tetrahydro derivative (XIII). Compound XIII evolved a gas on treatment with nitrous acid and liberated ammonia under alkaline saponification conditions



indicating the presence of a primary amide group. The hydroxyl group was detected by the formation of a phenylurethan. Alkaline saponification of XIII followed by acidification, gave the known lactone cis-cyclopentana[b]-tetrahydrofuran-2-one (XIV). The infrared spectrum of this product was identical with that of an authentic sample prepared by lactonization of 1-cyclopenteneacetic acid.

The mechanism proposed to account for the formation of the rearranged product begins with protonation of the 5-nitronorbornene anion (XV) to yield the aci-form XVI. Further protonation yields the cation XVII, which undergoes exo hydrolysis at C_2 with concerted shift of the double bond to C_3-C_4, fission of the C_4-C_5 bond and elimination of water to form the nitrile oxide XVIII.

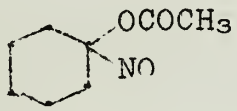


Hydrolysis of the nitrile oxide would yield the hydroxamic acid XIX which upon further treatment with acid would give the observed product as shown.

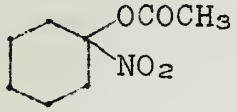
In support of the argument for the nitrile oxide intermediate is the fact that benzonitrile oxide hydrolyzes to benzoic acid and hydroxylamine hydrochloride upon treatment with concentrated hydrochloric acid at room temperature (16). Also it has been shown that intermediate hydroxamic acids can be isolated from the strong acid hydrolysis of primary nitroalkanes (17), a reaction presumed to involve a nitrile oxide intermediate (1)..

The appearance of the transient blue color in the Nef reaction just prior to the evolution of nitrous oxide led early workers (18,19) to postulate an intermediate α-hydroxynitroso compound. The question of this highly colored intermediate has not been answered definitely at this time although the available evidence supports an α-hydroxynitroso intermediate.

Iffland and Criner (20) have found that an unstable blue oil results from treatment of cyclohexanone oxime with lead tetraacetate at 5°. It was suggested that the unstable product has structure XX. Oxidation of this unstable compound yields a stable colorless oil which was assigned structure XXI.



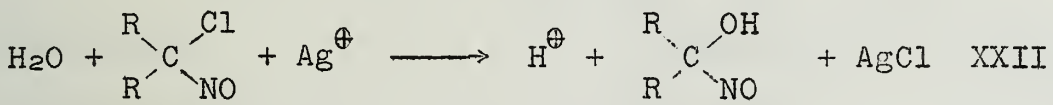
XX



XXI

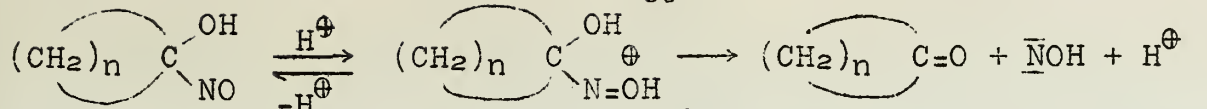
Both XX and XXI upon hydrolysis in dilute sulfuric acid yield cyclohexanone and acetic acid. Acid hydrolysis of XX would give the corresponding ketone presumably proceeding first through an α-hydroxynitroso intermediate.

Hawthorne and Strahm (21) have found that the second order silver ion catalyzed solvolysis of 1-chloronitrosocyclohexane and 1-chloronitrosocyclopentane in 20:30:50 ethanol: water: acetonitrile produces the corresponding ketones in 85-92% yield, nitrous oxide and no hydroxylamine. The reaction obeys the



XXII

the kinetic equation XXII over a range of silver salt concentrations as determined by titration of liberated hydrogen ion. The rate equation in each case was of the form $d[H^{\oplus}]/dt = k[Ag^{\oplus}]$ [chloronitrosocycloalkane] with the second order rate constant, k, equal to 2.0 and 5.0×10^{-2} l./mole min. for 1-chloronitrosocyclohexane and 1-chloronitrosocyclopentane, respectively. It is suggested that these transformations probably proceed via the α-hydroxynitrosocycloalkanes which are in turn produced by the nucleophilic attack of water upon the α-carbon atom. Indicative of this assumption is the fact that the cyclopentane derivative is 2.5 times as reactive as the corresponding cyclohexyl compound. Such a rate difference would be expected if the rate determining process was a Lim type displacement reaction on the carbon atom of the ring. Brown and Ham (22) have found the solvolysis rates of cyclopentyl tosylates to be greater than the rates of the corresponding 6-membered ring derivatives. These rate differences are attributed to the de-eclipsing of bonds in the transition state in the cyclopentyl case as compared to an increase in bond opposition in the transition state for the cyclohexyl derivative. Hydrolysis of the postulated α-hydroxynitrosocycloalkane as in XXIII would thus lead to the observed products. Although nitrous oxide was not isolated, its presence was shown by its characteristic retention time in vapor phase chromatography.

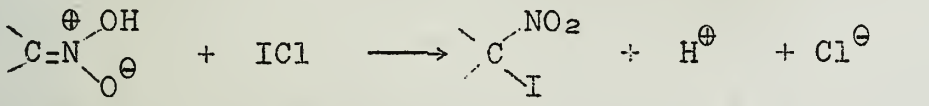


$$2\bar{N}OH \longrightarrow HON{=}NOH \xrightarrow{H^{\oplus}} H_3O^{\oplus} + N_2O \qquad \text{XXIII}$$

Hawthorne (23), in a kinetic study of the acid catalyzed solvolysis of seven sec-aci-nitroalkanes has shown the reaction to follow second order kinetics with an instantaneous rate expression defined by XXIV. The rates were determined at 0° in

$$v = k[H^{\oplus}][\text{aci-nitroalkane}] \qquad \text{XXIV}$$

80% methanol using a spectrophotometric adaptation of the classical halometric determination of aci-nitroalkanes described by equation XXV. Each sec-aci-nitroalkane examined gave acceptable first order plots with the determined first order rate constant



reproducible to 15% and proportional to the hydrogen ion concentration. The second order rate constants obtained are summarized in Table II. Spectrophotometric product analyses for

TABLE II

2nd Order Rate Constants for the Nef Reaction in 80% MeOH at 0.0° C

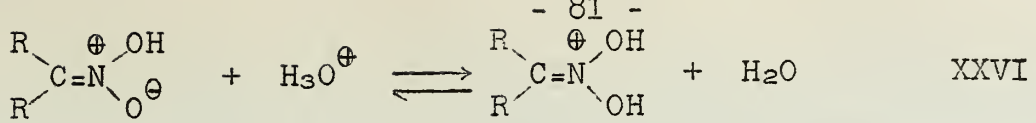
Nitroalkane	2nd Order rate constant l./mole min.	Rel. rate
2-Nitropropane	0.78 ± 0.08	5.57
Nitrocycloheptane	0.14 ± 0.02	1.00
Nitrocyclohexane	8.9 ± 0.50	63.5
Nitrocyclopentane	0.32 ± 0.05	2.28
Nitrocyclobutane*	8.0 ± 0.50	57.1
Dicyclopropylnitromethane	0.18 ± 0.02	1.29
1-Cyclopropylnitroethane	0.27 ± 0.03	1.93

*Questionable rate constant as product other than cyclobutanone was observed.

nitroalkane indicated that, with the possible exception of nitrocyclobutane, no detectable amounts of nitroalkane were regenerated under kinetic conditions. The results in the nitrocyclobutane run indicated that one sixth of the original nitroalkane was regenerated. Product isolation experiments indicated that each of the aci-nitroalkanes studied gave excellent yields of the corresponding ketones (isolated as 2,4-dinitrophenylhydrazones) on hydrolysis under conditions similar to those of the kinetic experiments. In each of these runs, a fleeting blue intermediate was always observed.

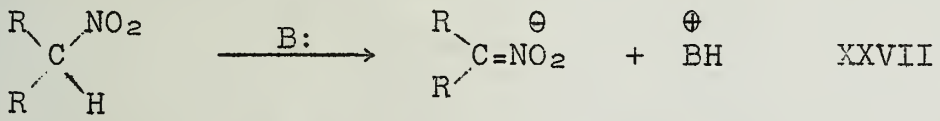
A mechanism consistent with the previously mentioned facts can now be postulated.

The fact that a protonated aci-nitroalkane molecule is involved in the rate-determining transition state suggests that equilibrium XXVI plays an important role in the reaction. The conjugate acid of the aci-nitroalkane molecule produced in this



XXVI

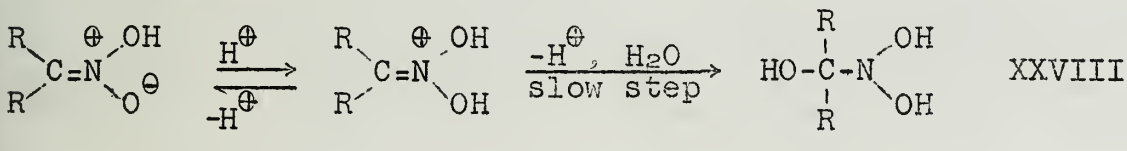
equilibrium would have an electron-deficient carbon atom attached to nitrogen which would be liable to nucleophilic attack by solvent in the rate determining step. This conclusion is further strengthened by the consideration of the relative rates of reaction of the series of nitroalkanes which were studied. The same order of reactivity; cyclohexyl > cyclopentyl ≥ cycloheptyl, was established by Brown, Brewster and Shechter (24,25) after surveying a great deal of reactivity data from reactions which involve the stabilities of cycloalkyl systems having exo-cyclic double bonds. From their conclusions one would expect aci-nitrocyclohexane to be more reactive than aci-nitrocyclopentane and the seven membered ring aci-nitro compound should be much like aci-nitrocyclopentane in reactivity. The high reactivity of aci-nitrocyclobutane can readily be explained as being due to relief of internal strain in the transition state from cleavage of the exo double bond. The validity of this argument, however, becomes questionable when one considers a recent finding by Shechter and co-workers (26) concerned with the neutralization of various nitroalkanes (XXVII). One would expect nitrocyclo-



XXVII

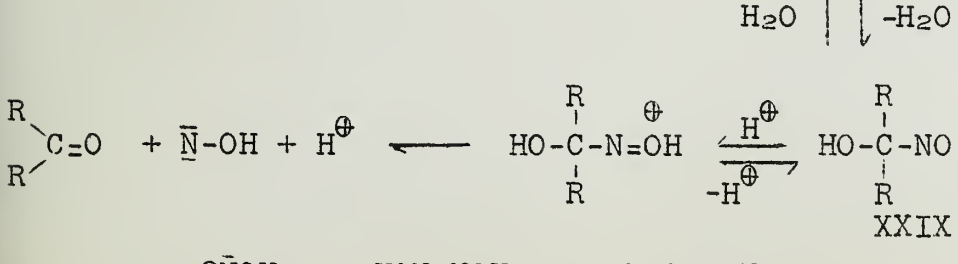
butane to react quite slowly due to the formation of the unfavorable exocyclic double bond; however, this was not the case. The observed rate for nitrocyclobutane was four times as great as that of nitrocyclopentane, a compound which should be quite reactive if Brown's postulate were correct. These results have not been fully explained yet and it is possible that forces other than bond strain may be operative in this case.

That the predicted results are actually observed in the kinetic study leads to the conclusion that the rate-determining step for the Nef reaction consists of nucleophilic attack on carbon which in turn destroys the carbon-nitrogen double bond of the conjugate acid as shown in equation XXVIII. The appearance of the blue color can be satisfactorily explained by postulating an α-hydroxynitroso alkane intermediate (XXIX) which may arise as shown and decompose then to ketone and nitrous oxide.



XXVIII

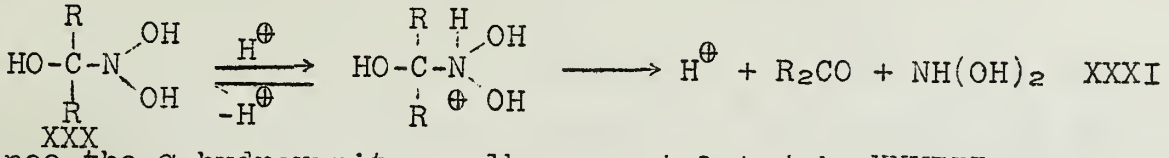
XXX



XXIX

$$2\bar{N}OH \longrightarrow HON{=}NOH \longrightarrow H_2O + N_2O$$

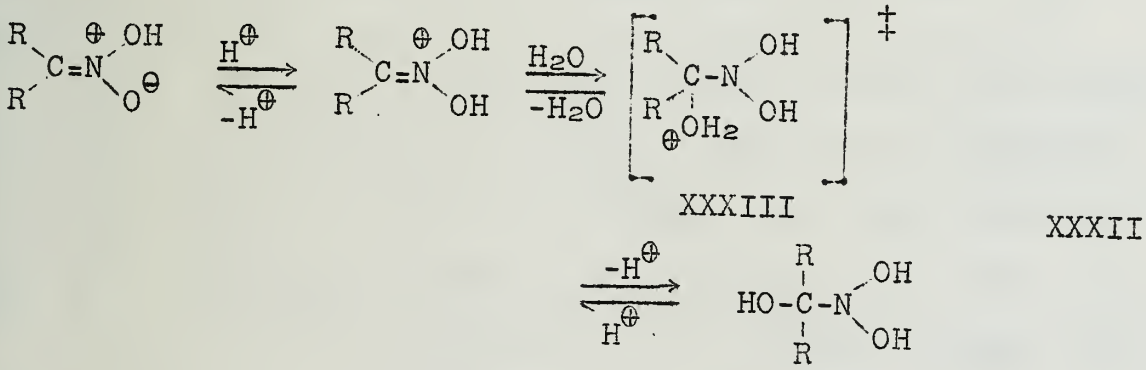
An alternate path for the decomposition of intermediate XXX has been proposed by van Tamelen and Thiede (7) as shown in equation XXXI. However, this possibility fails to account for the formation of the observed blue color.



XXX XXXI

Since the α-hydroxynitrosoalkane postulated in XXVIII may be in mobile hydrolytic equilibrium with XXX, then the modes of decomposition represented by XXXI and by XXVIII are presently indistinguishable.

A better picture of the rate-determining transition state may be obtained from a closer examination of the rate date. The rates observed with cyclopropylnitroethane and dicyclopropylnitromethane appear to be no less than would be expected on the basis of steric hinderance to solvent attack. Since much evidence has shown that the cyclopropyl ring has the ability to stabilize electron deficient species through interaction of its p-orbital system (27), a rate retardation for these compounds might have been expected. Also the corresponding ketones of these compounds were obtained in high yields; this rules out any rearrangement as having occurred. These results imply that the positive charge gained by the aci-nitroalkane in going to its conjugate acid has been lost to the attacking solvent in the succeeding transition state (XXXII). Thus the rate determining transition state for the Nef reaction should resemble XXXIII.



XXXIII XXXII

In the cases where an α-phenyl group is present the energy difference between the stabilized aci-nitro tautomers as compared to a non-stabilized transition state, in which the nucleophilic solvent has gained most of the positive charge, may be enough of an energy barrier to prevent normal product formation.

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CATALYSIS BY ION-EXCHANGE RESINS

Reported by A. J. Bollero November 23, 1959

INTRODUCTION

An ion-exchange resin consists of a network of acidic (sulfonic or carboxylic) or basic (trimethylammonium) groups firmly anchored in a cross-linked polymer with resultant pores in which the compensating cations or anions are present in a fairly mobile condition, resulting in a cation-or anion-exchanger-acid or base when the ions are H^+ and OH^-, respectively. When placed in a solution, solutes and ions are present within the pores in fairly intimate contact. To be of value, the pores must contain the particular catalytically active ion and be large enough to accommodate the reactant solute molecule. This allows some possibility of selectivity according to size in a mixture of reactants. Other advantages which may be cited are (a) by a simple filtration step, catalyst-free products can be obtained; (b) the catalyst can usually be recovered and reused (c) continuous reactions can be obtained by passage of the reactants through beds of ion-exchange resin catalysts; (d) side-reactions can be kept at a minimum; and (e) special corrosion-resistant equipment is not necessary as with some soluble catalysts.

The use of ion-exchange resins as catalysts in the hydrolysis of esters, esterification, sugar inversion and protein hydrolysis has been studied quite extensively and will be used to illustrate the potentialities of these resins as catalysts in organic chemistry.

HYDROLYSIS OF ESTERS

There is reason to suppose that the mechanism of the catalysis of ester hydrolysis is the same for a cation exchange resin, a strong acid of essentially infinite molecular weight, as for a homogeneous acid (1). It involves, therefore, for both a positively charged transition state in which a proton has been transferred to the ester molecule from the oxonium ion of the acid.

A comparison of the catalytic effect of an exchange resin with that of hydrochloric acid shows that the free energy of activation relative to the hydrochloric acid-catalyzed reaction increases almost linearly with the chain length of the ester in the series methyl acetate, ethyl acetate, ethyl n-butyrate, ethyl n-caproate. The following table gives some rate constants obtained for the resin-catalyzed and hydrochloric acid-catalyzed hydrolyses both run in 70% acetone:

Ester	$kx10^5$ HCl	$kx10^5$ resin	k_r/k_{HCl}
Methyl acetate	5.40	2.74	0.502
Ethyl acetate	4.63	1.51	0.326
Ethyl n-butyrate	1.90	0.256	0.134
Ethyl n-caproate	1.52	0.0749	0.049

The ratio k_r/k_{HCl} is defined as the efficiency of the resin compared with acid (1).

The major factor in explaining the above effects is the loss in internal energy of the ester molecule accompanying its fixation on the skeleton of the resin catalyst in the formation of the transition state. This conclusion is consistent with the fact that

the longer chain ester, having more internal entropy, loses more in the formation of the transition state.

For a wide variety of carboxylic esters in aqueous acetone solution the hydrolysis rate was found to be less when the catalyst was an ion- exchange resin than when it was a homogeneously dissolved acid in equivalent amount. There is a significant specificity with respect to both the ester and the resin (2).

The effect of the structure of the reactant was studied by using a number of esters hydrolyzed in the presence of a sample of Rohm and Haas Amberlite IR-110 classified to 45-50 mesh.

Ester	$k \times 10^5$ HCl	$k \times 10^5$ resin	k_{resin}/k_{HCl}
Methyl phenylacetate	2.16	0.213	0.0987
Methyl α-naphthyl-acetate	1.55	0.127	0.0819
Methyl benzoate	0.0614	0.0134	0.218
Methyl cyclopentane-carboxylate	2.4	0.347	0.144

The results show that the structure of the esters has an effect on the efficiency of the hydrolysis by resin catalyst. In particular, esters of cyclic acids like phenylacetic, naphthylacetic, cyclopentanecarboxylic and especially benzoic acid show much higher efficiencies than do straight chain esters of comparable mass (2).

The most obvious way to vary the nature of the resin catalyst is to vary the degree of cross-linking by altering the proportion of divinylbenzene in the styrene-divinylbenzene copolymer whose sulfonation leads to the ion-exchange resin. For two esters-methyl acetate and ethyl hexanoate- the efficiency dropped with increasing degree of cross-linking, but the effect is much greater with the ethyl hexanoate. The result is in accord with the hypothesis that the resin structure imposes restraints upon the transition state which reduce its entropy and hence tend to lower the rate of reaction. The more tightly knit structure of the more highly cross-linked resin imposes more severe restraints than does the looser structure of the less cross-linked resin, and the effect is greater the greater the amount of internal entropy which the ester possesses (2).

Another way in which increased cross-linking affects the efficiency of an ion-exchange resin for hydrolysis of an ester is merely by squeezing out solvent, so that the environment is less like an aqueous solution (3). The solvent content of the resin may also be reduced by partial replacement of the H^+ ions of the cross-linked polystyrene sulfonic acid by other cations and especially by polyvalent cations.

Thus, a very lightly cross-linked resin which in the form of the air-dry acid swells 40-fold on immersion in water shrinks by a factor of 2 when the swollen acid is converted to the fully hydrated magnesium salt and by a factor of 3 when the acid is converted to the salt of the ion $H_3N^+-CH_2-CH_2-NH_3^+$.

The effect on the catalytic properties for the hydrolysis of ethyl acetate and of ethyl hexanoate of replacing part of the H^+ ions by Mg^{++} ions was none, while replacement by the quaternary ion

caused a decrease in the hydrolysis rate for both esters (3).

Replacement of 70% of the H^+ ions in a cross-linked polystyrenesulfonic acid by cetyltrimethylammonium ions has a specifically favorable effect on the effectiveness of the remaining H^+ ions for the hydrolysis of ethyl n-hexanoate; replacement by methyltribenzylammonium ions has a specifically favorable effect on the hydrolysis of methyl phenylacetate (4).

The obvious interpretation of these specific catalytic effects is in terms of the old principle that like dissolves like. In the present case this is to be interpreted in the sense that increasing incorporation into the resin of long-chain aliphatic structures lowers the standard free energy of the transition state for the hydrolysis of an ester containing similar structures relative to the standard free energies of the transition states of esters of different structures, and that the incorporation of additional phenyl groups into the resin has a similar effect on the transition state of an ester containing phenyl groups.

The preparation of the resin affects the efficiency of the resin as a catalyst for ester hydrolysis (5). The conventional method of preparation is by sulfonation of a styrenedivinylbenzene copolymer, while a new process involves copolymerizing an ester of styrenesulfonic acid with divinylbenzene and then partial hydrolysis of the ester to the acid form. These new resins show little swelling and a marked increase in efficiency in the hydrolysis of esters-ethyl acetate, ethyl butyrate, ethyl hexanoate, methyl phenylacetate.

The effect of agitation on the resin-catalyzed hydrolysis of methyl acetate in 70% acetone was studied by subjecting 4 similar samples of heterogeneous reaction mixture to different degrees of agitation. The results showed that more frequent agitation caused the reaction to proceed much faster.

Experiments were performed to elucidate the effect of surface area of the catalyst resin on the rate of ester hydrolysis. For equal weights of samples the resin passing between 80 and 100 mesh sieves had 2.4 times the geometrical area of the 40-45 mesh material. The rate constants obtained with the same liquid mixture of a given ester are summarized in the following table (1):

	10^6k		
Ester	40-45 mesh	80-100 mesh	% difference
Ethyl acetate	14.8	15.4	+4.1
Ethyl n-butyrate	2.27	2.42	+6.3
Ethyl n-caproate	0.74	0.77	+4.4

In water solution a lightly cross-linked ion-exchange resin of the polystyrenesulfonic acid type is a better catalyst for the hydrolysis of aliphatic esters of low molecular weight than is dilute hydrochloric acid (6). This is in agreement with the work of Davies and Thomas (7). The comparison of resin catalysis to homogeneous catalysis by hydrochloric acid showed that the resin was more effective than hydrochloric acid by factors of 1.8 for methyl acetate, 2.3 for ethyl acetate, 10 for n-butyl acetate and 20 for benzyl acetate. A tightly cross-linked resin, however, behaves in water solution in the same way as all such resins do in aqueous acetone solution.

The effects shown by water solutions and mixed solvent solutions may be explained by the following (6):

In the mixed solvents the electrically charged transition state is subjected to restraints arising from solvation, which are stronger than those acting on the ester. In water solution the solvation of the polar groups in the ester itself is so powerful that no further important restraints are imposed on the internal motions of the ester by the solvation of the charged transition state or by the resin network. Consequently the entropy change involved in the conversion of ester to transition state is no longer more negative for esters of greater chain length.

Investigations of some of the structural factors which affect the rate of hydrolysis of an ester in 85% ethanol by a resin of the quaternary ammonium hydroxide type have been made (8). The reaction may be given as follows:

$$-PCH_2NR_1R_2R_3^{\oplus} + OH^{\ominus} + R_4COOC_2H_5 \longrightarrow -PCH_2NR_1R_2R_3^{\oplus} + R_4COO^{\ominus} + C_2H_5OH$$

where $-PCH_2NR_1R_2R_3^{\oplus}$ is a unit of the structure of a bead-form cross-linked polymer obtained by (a) suspension polymerization of styrene together with 0.5% divinylbenzene, (b) chloromethylation of the resulting product to $-PCH_2Cl$ which is a cross-linked polymeric benzyl chloride, (c) ammination of $-PCH_2Cl$ to $-PCH_2NR_1R_2R_3^{\oplus}$, and (d) exchange of the chloride ion with hydroxyl ion.

The following table lists corresponding efficiencies, defined, as in the case of cation-exchange catalysis, as the ratio of the specific rate of reaction of ester with the resin to the specific rate of reaction of ester with strong base in homogeneous solution:

Resin	Ethyl acetate	Ethyl n-hexanoate	Ethyl phenylacetate
$RN(CH_3)_3^+$	0.86	0.36	0.65
$RN(C_2H_5)_3^+$	0.96	0.56	0.98
$RN(C_2H_5)_2(C_6H_{13})^+$	0.93	0.64	1.03
$RN(C_2H_5)(C_6H_{13})_2^+$	0.92	0.70	1.02
$RN(C_6H_{13})_3^+$	0.83	0.68	1.04
$RN(CH_3)_2(CH_2C_6H_5)^+$	0.99	0.61	1.11
$RN(C_2H_5)_2(CH_2C_6H_5)^+$	0.95	0.61	1.04

The relatively low efficiency for hexanoate shown by all resins appears to be another example of the entropy effect (1). Strikingly low efficiencies for all the esters studied are shown by the $RN(CH_3)_3^+$ resin. These are perhaps connected with the fact that this resin does not swell perceptibly in water or 85% ethanol. Hence in some way this resin has become more heavily cross-linked than the others.

The change from the $RN(C_2H_5)_3^+$ to the $RN(CH_3)_3^+$ resin decreases the efficiency for the hydrolysis of ethyl phenylacetate considerably more than it does for that of ethyl acetate. The effect may belong in the category of the specificities observed in the acid-catalyzed hydrolysis of esters by ion-exchange resins. The only other suggestion of this kind of specificity is the relatively high efficiency for the hydrolysis of ethyl phenylacetate shown by the resin $RN(CH_3)_2(CH_2C_6H_5)^+$ (8).

ESTERIFICATION REACTIONS

Esterification reactions are one of the most important groups of industrially significant reactions employing acid catalysts. Saletan and White (9) studied a continuous process for the esterification of ethyl alcohol with acetic acid, using a cation exchange resin as the catalyst (Dowex 50). The average volumetric rate of reaction in a spherical resin-catalyst particle was found to be expressed as the product of the reaction rate in the surface of the resin and an efficiency function, $\emptyset$, which is an analytical function of particle size and the physical constants of the system only. In systems of small particle size or high diffusivity the effective penetration of the reactants into the resin is much greater, and most of the resin volume is utilized in the catalytic reaction, so that the volumetric efficiency of the resin approaches 100%. Thus the analytical formulation of the efficiency function, $\emptyset$, is in accord with the physical realities of the system. The results obtained supports the hope that this concept of a volumetric efficiency function can be applied wherever diffusion within a disperse phase controls reaction rates.

Levesque and Craig (10) studied the esterification of oleic acid in excess butanol and observed that the rate of reaction was dependent on the surface area of resin particles. In this case the large size of the reactants limits the availability of the catalyst sites. As a result of the low diffusivity of the high molecular weight acid, an induction period was observed in the experiments. This was probably the time required for the slow-moving molecules to set up diffusion gradients inside the resin.

The work of Sussman (11) on the synthesis of n-butyl oleate was used to show the effect caused on the esterification by use of different types of cation-exchange resins. Two resins of a phenol-formaldehyde type were compared with a sulfonated coal type exchanger, Zeo-Karb H, which gave satisfactory results. One resin gave similar results, but the ester formed had a darker color perhaps caused by leaching of partially condensed material from the resin by the organic reactants; the second resin gave a slower rate of reaction.

The direct esterification of furfuryl alcohol has been virtually unknown because of the great sensitivity of this alcohol to the strongly acidic catalysts normally used for esterification. Using Zeo-Karb H as the catalyst, Sussman (11) has directly esterified furfuryl alcohol with acetic acid without any evidence of resinification; however, the yields were low (10-21%).

SUGAR INVERSION

Bodamer and Kunin (12) have studied the effectiveness of various cation-exchange resins for the inversion of sucrose. Their work indicated that the rate of sucrose inversion is strongly influenced by ease of diffusion of sucrose into and invert sugar out of the resin particle. The evidence for such a statement is drawn not only from experiments in which the quantity of catalyst or its particle size was varied, but also from reactions employing resins of varying degrees of porosity.

Two types of resin were used- a sulfonated styrene type and a

carboxylic type. The sulfonic type resin promoted considerably more rapid inversion than the carboxylic type resin. The rate constant increased with increasing resin concentration as would be expected, since sucrose inversion is actually a pseudo first order reaction and the value of k will vary with catalyst concentration.

More rapid inversion was caused by smaller size particles as would be expected whether only the surface groups are active or rate of diffusion controlled the rate of reaction. The constants show a striking increase with increasing porosity (degree of cross-linking). This behavior is evidence of the influence of rate of diffusion of the sucrose and invert sugar through the resin structure. These results are in agreement with those of Mariani (13)(14).

When glucose or fructose solutions are allowed to remain in contact with a strong anion-exchange resin— — Amberlite IRA-400— — inversion of both sugars occurs to a considerable degree (13). When cellobiose was allowed to remain in contact with the resin for 70 hours, there was detected, in addition to unreacted cellobiose, a considerable quantity of glucose and fructose. The amount of glucose and fructose increased with time until after 238 hours most of the cellobiose disappeared. Similar results were obtained with maltose.

When turanose was allowed to remain in contact with the resin for 46 hours, the only sugars that could be detected chromatographically were glucose and fructose. No reaction was observed with sucrose and several unidentified spots were obtained with D-arabinose, one of them presumably representing ribulose (15).

The rate of hydrolysis of a soluble starch, with a resin catalyst is exceedingly slow if the solution is first de-ionized by shaking with mixed anion- and cation-exchange resins. However, the use of a trace of free mineral acid in conjugation with the resin gives a rate of hydrolysis greater than the sum of the rates obtained when each is used separately (16). It appears that the inefficiency of the resin as a catalyst for the hydrolysis of starch may be due to the inability of the large molecules to penetrate the resin, but that the presence of a trace of mineral acid degrades the starch to dextrins which may then diffuse into the body of the resin and undergo further hydrolysis by H^+ ions associated with the resin (17).

A further application is in the isolation of a reaction intermediate . When acetone is refluxed through an intimate mixture of mannitol and resin, a high yield of a mixture of mono- and di-isopropylidene mannitols was obtained, the former predominating. The reaction is largely prevented from giving the fully substituted triisopropylidene mannitol by the rapid removal of the soluble, partly substituted derivatives (16).

PROTEIN HYDROLYSIS

Rates of protein hydrolysis by dilute acid depend not only on temperature and acidity, but also on the nature of the anion of the acid used. The method of catalysis is described as providing an increased basicity of the amide and peptide bonds as a result of

a combination of these bonds with the large anion of the catalyst. In the case of a cation-exchange resin, the large nucleophilic anion should be effective in labilizing the protein peptide bond (18).

In the hydrolysis of casein the recovery of amino acids – glutamic, valine, and isoleucine were lower in the case of the resin–Dowex 50– compared with that of the acid catalyzed hydrolysis. These low recoveries are probably due to incomplete hydrolysis or may also have been due to incomplete elution from the resin catalyst (19).

Amberlite IRC–50, a carboxylic type resin, and Dowex – 30, Amberlite IR–105 and Zeo–Rex which are phenolsulfonic acid type resins have also been investigated (18). The phenolsulfonic type resins catalyzed the hydrolysis of casein at a greater rate than Dowex–50, while the carboxylic type resin was found to be less effective. These differences in rate appear to be due to variations in the pH of the hydrolyzates resulting from the number of H^+ ions furnished by the resins of different mesh size and capacity.

The nature of the protein can also affect the hydrolysis rate. For example, the cystine peptide linkage appears to be very resistant to resin–catalyzed hydrolysis, and the resistance of proteins to hydrolysis of this type seems to parallel the cystine content.

The hydrolysis of simple peptides, for example glycylglycine, by Dowex 50 was studied and found to be more efficient than ordinary acid. It would appear that the adsorption of the peptide at the acid group of the resin may be accompanied by the release of a water molecule from the resin, so that the decrease in entropy caused by the activated adsorption is somewhat less than in the ordinary acid hydrolysis (20).

Except for a few industrial examples (22)(23)(24)(25), the use of ion–exchange resins as catalysts still remains an occasional laboratory practice. A deterrent to large–scale use is the present relatively high cost of resins compared to mineral acids or alkalies.

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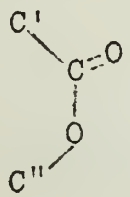
CONFORMATION OF THE ESTER GROUP IN LACTONES

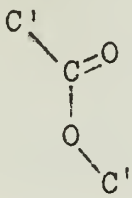
Reported by J. R. Fox November 19, 1959

The rapid hydrolysis of γ-lactones in alkaline solution has been known for a long time (1). This property, which does not hold generally for open-chain esters, has been attributed to a difference between the conformation of the ester group in the lactones and in the esters. This seminar will deal with the work which has led to the establishment of conformation of the ester group in lactones.

For a normal open-chain ester two extreme rotational structures I and II may be drawn and will be referred to as syn and anti respectively. (In order to avoid implying the

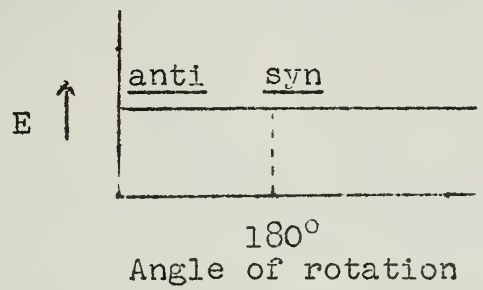


I



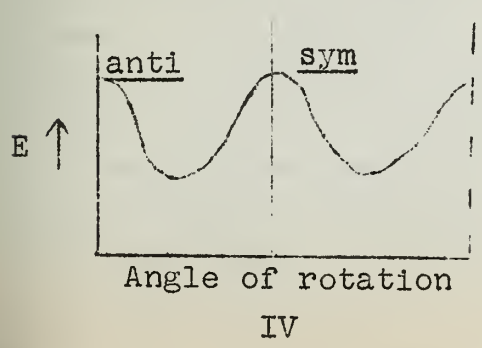
II

existence of a formal double bond the terms "syn" and "anti" are used rather than the terms "cis" and "trans" as found throughout the literature. It should also be pointed out that in the literature use of "cis" and "trans" is not consistent, "cis" and "trans" frequently being applied to the same structure by different authors.) The problem of establishing the conformation of the ester group in open-chain esters is one of determining the relative energies of all the rotational isomers. There are a number of possibilities. 1) The energy of all rotational isomers may be equal as indicated by an energy diagram such as III. 2) Energy minima may exist for rotational

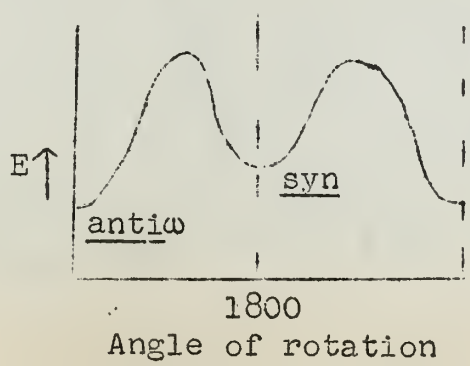


III

isomers intermediate to I and II as indicated by IV. 3) Energy minima may exist at one or both of the extreme configurations I and II (fig. V). 4) Variations of 2) and 3) as to the number and



IV

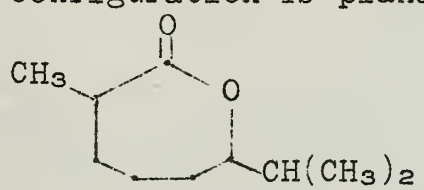


V

relative values of minima should also be included as possibilities.

Early attempts to determine which of the above posssibilities exists in the case of open-chain esters involved the comparison of theoretical values for the dipole moments of structure I and II with observed dipole moments of esters and lactones. Marsden and Sutton (2), for example, predicted dipole moments of 1.53 D for the anti and 3.53 D for the syn configurations of methyl acetate by vector addition of the observed dipole moments for dimethyl ether (1.32 D) and acetone (2.85 D) at angles of 180° for the anti configuration and 70.5° for the syn configuration, these angles being determined by consideration of models of acetone and dimethyl ether. These values are the maximum and minimum values predicted by this method, all other rotational isomers having predicted dipole moments between these two values. Comparison of these values with the observed dipole moments of esters (1.7-1.9 D) and γ-butyrolactone (4.12 D), which for steric reasons must exist in or very near to the planar syn configuration, led to the conclusion that the preferred configuration (lowest energy) of an open-chain ester is nearer the anti than the syn configuration. Possibility (1) is therefore ruled out.

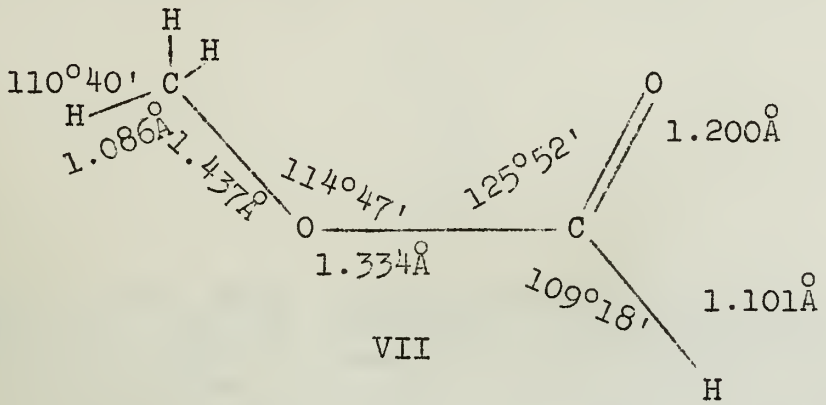
Marsden and Sutton (2) further reasoned that if the preferred configuration of the ester group is intermediate to I and II (but nearer II than I), the dipole moment of a 7-membered lactone should be about 2.7 D. In this case the 7-membered lactone ring is large enough to permit partial rotation from the syn configuration toward the preferred configuration near the anti form. On the other hand, if the ester group in the 7-membered lactone remains planar (as it must be in γ-butyralactone), the dipole moment of the 7-membered lactone should be about the same as the dipole moment of γ-butyrolactone. Marsden and Sutton obtained VI in low yield by the oxidation of ℓ-menthone with potassium persulfate and sulfuric acid. The dipole moment of VI was found to be 4.33 D suggesting that in the above lactones the preferred configuration is planar and syn.



VI

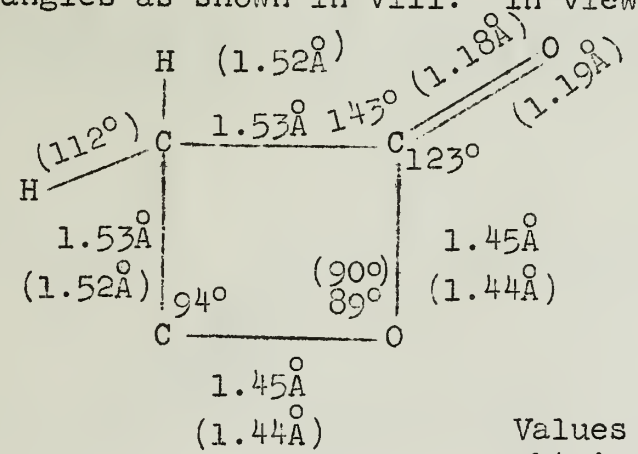
Later and more refined methods of predicting dipole moments involve the vector addition of individual bond moments at angles determined by electron diffraction measurements. Thus Smyth (3), using electron diffraction data of Allen and Sutton (4) on carboxylic acids, and generally accepted bond moments, calculated a value of 1.8 D for open chain esters. This value which is in perfect agreement with present day values (1.7-1.9 D) was based on a model which was equivalent to the rotation of II through 30°. On the basis of electron diffraction measurements, O'Gorman, Shand and Schomaker (5) have determined that the configuration of the ester group in methyl acetate and methyl formate is approximately anti with an average angle of rotation of about 25°.

Recent microwave measurements by Curl (6) have given a very clear picture of the open-chain ester configuration. These measurements indicate that in methyl formate the ester group is in a planar anti configuration with bond lengths and bond angles as shown in VII. In addition, electron diffraction (7)



VII

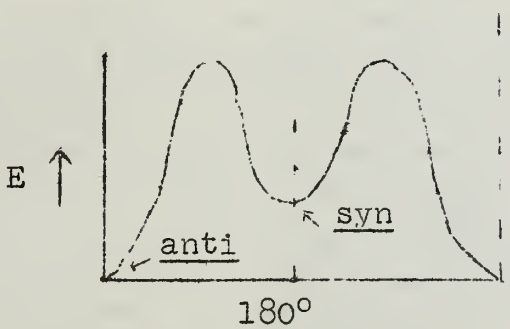
and microwave (8) studies indicate that in β-propiolactone the ester group is in the planar syn configuration with bond distances and angles as shown in VIII. In view of the above



VIII

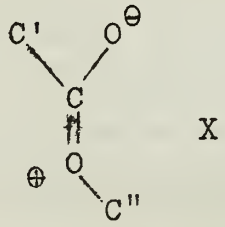
Values in parentheses were obtained from microwave measurements.

findings it is concluded that the rotational energy diagram of the ester group in open-chain esters will show two minima, one corresponding to the planar syn configuration and one corresponding to the planar anti configuration. The anti configuration will have a lower energy than the syn (fig. IX).



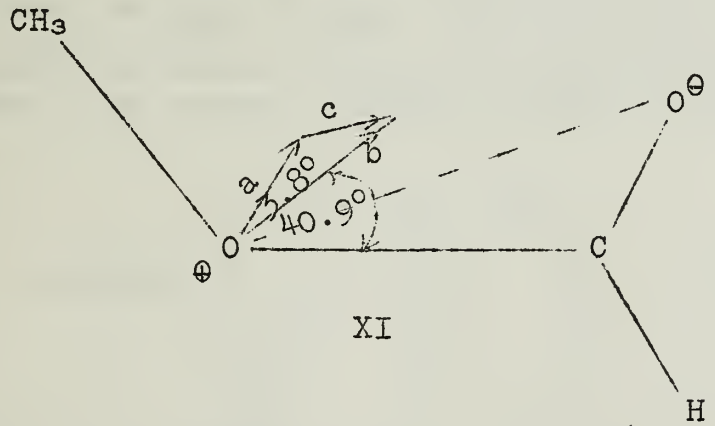
IX

Early attempts to evaluate the energy barrier between the syn and anti configurations also involved an analysis of dipole moment data. The preferred planar configuration of the ester group can be attributed at least in part to contributions of resonance structures such as X. The discrepancy between observed and predicted dipole moments can thus be



X

attributed to the large dipole moment arising from the separation of charges in X and the difference between observed and calculated dipole moments taken as a measure of the extent to which X contributes to the true structure of an open-chain ester. For example, if Smyth's calculations are made on a planar molecule, a predicted dipole moment of 1.43 D at an angle of 44.7° to the C-O bond is obtained. Curl's microwave data (6) gives an observed dipole moment of $1.77 \pm .03$ D at an angle of $39.4 \pm 2^{\circ}$ to the C-O bond. From Curl's data the oxygen-oxygen distance is found to be 2.26Å and the line between the two oxygen atoms makes an angle of 25.5° with the C-O bond (fig. XI). The



XI

a = Smyth's predicted dipole moment 1.43 D
b = Curl's observed moment 1.77 D
c = Contribution due to the oxygen-oxygen dipole

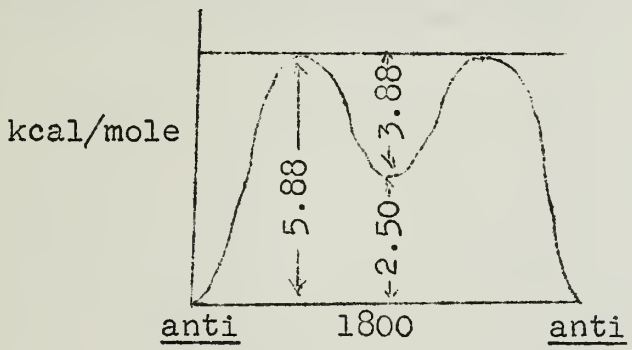
problem is one of determining the value of c (which is parallel to the line between the oxygen atoms) which must be added to Smyth's predicted moment to give the observed resultant dipole moment. Within the limits of error in Curl's data, the three vectors mentioned above determine a unique triangle XI and the value of c is found to be .36 D. The dipole moment due to the charge separation in X is 4.8 e.s.u. x 2.26Å = 11 D. The contribution of X to the structure of an open-chain ester (the double bond character of the C-O bond) is therefore .36/11 = 3.3%. In a similar way Marsden and Sutton (2) and Huisgen (9) have calculated values of 6-8% double bond character based on predicted values for the syn configuration and the observed value of 4.3 D for the 7-membered lactone. Since there is no reason to believe that resonance is more important in the syn

configuration than in the anti configuration, the difference in the values obtained from consideration of the syn and anti configuration is most likely due to the crudeness of the method.

Double bond character has also been estimated from bond lengths. Taking a single bond length as 1.44Å (the length of the H_3C-O bond in VII), 1/3 double bond length as 1.29Å (as determined from calcium carbonate by X-ray diffraction), 1/2 double bond length as 1.27Å (as determined from sodium formate by X-ray diffraction), and full double bond length as 1.21Å (as determined from formaldehyde by microwave measurement), Curl has estimated that the C-O bond length of 1.33Å in methyl formate, VII, represents 20% double bond character.

According to Marsden and Sutton (2) the energy barrier between the syn and anti configurations is 8% (their figure for double bond character) of the energy difference between a C=O and a C-O because rotation of the ester group through 90° would result in complete loss of double bond character. Their estimate for the energy barrier is therefore 7 kcal/mole. Similar reasoning would give an estimate of about 18 kcal/mole based on Curl's 20% double bond character.

A much clearer picture of the energy barrier between the syn and anti configurations is given by work of Tabuchi (10). By measuring the absorption of high frequency sound in ethyl formate, Tabuchi has been able to calculate the rate of conversion between the syn and anti configurations, the activation energy, the equilibrium constant, and the reaction heat involved in the equilibrium between the syn and anti configurations of ethyl formate. The energy diagram in XII is a result of his work.



XII

His figures indicate that at room temperature, 6-7% of ethyl formate is in the syn configuration.

In view of XII it would be predicted that there should be a rapid change from the syn to the anti configuration as the size of the lactone ring is increased, the change occurring only when the lactone ring is of sufficient size so that the energy released in going from the syn to the anti configuration is greater than the energy gained through angle strain as a result of incorporating the anti ester group in the ring. This change in configuration should be indicated by a sharp drop in the dipole moments of the lactones as the ring size is increased.

Until recently a complete series of lactones covering the "transition" region was not available. γ- and δ-lactones are readily obtained by esterification of the corresponding hydroxy acids in the presence of benzene sulfonic acid (11) or by treatment of the corresponding diols with a copper chromite catalyst (12). A number of β-lactones are available by reaction of ketene with aldehydes and ketones (13). ε-caprolactone has been prepared by simply heating the corresponding hydroxy acid (14). In addition, δ- and ε-lactones have been prepared by treatment of cyclopentanone and cyclohexanone with perbenzoic acid (15). Fourteen to eighteen membered lactones have been prepared by treatment of the corresponding ketones with Caro's acid (16). Spangel and Carothers have reported the preparation of the 11-, 12-, 14-, 15-, 16-, and 17-membered ω-lactones by depolymerization of the corresponding polyesters (17). In addition the ten to sixteen membered lactones may be prepared by high dilution cyclization of the ω-bromo acids (9,18). None of the above methods have proved successful for the preparation of the 8- and 9-membered lactones however. In view of the known difficulty in closing medium sized rings Huisgen felt that the peracid oxidation of cyclic ketones seemed the most promising method of obtaining these lactones. Studies of the mechanism of the reaction (19,20,21) indicated that it was acid catalyzed and led to the use of an oxidizing agent composed of a solution of pertrifluoroacetic acid in methylene chloride buffered with disodium phosphate. In this way Huisgen was able to prepare the 8- and 9-membered ω-lactones in 68% and 72% yields by oxidation of cycloheptanone and cyclooctanone (22).

With the preparation of the 8- and 9-membered lactones a complete series of lactones was available and in 1959 Huisgen published the data in Table I (9).

Table I

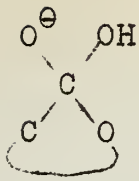
ω-lactone ring size	Dipole Moment (D) in benzene at 25°	Boiling point °C./10-11 mm.	Alkaline hydrolysis rate constant in 60% dioxane at 0°C. 10^4 k_2 (l/mole sec.)
4	3.85[1] (4.18)[2]	51[3]	2770[4]
5	4.09	79-80	1480
6	4.22	97-98	55000
7	4.45	104-106	2550
8	3.70	80-82	3530
9	2.25	72-73	116
10	2.01	86-87	0.22
11	1.88	100	0.55
12	1.86	116	3.3
13	1.86	130	6.0
14	1.86	143	3.0
16	1.86	169	6.5
n-butyl caproate ($C_5H_{11}CO_2C_4H_9$)	1.79	83	8.4

[1]Measured by Miller in benzene at 30°C. (23).
[2]Determined by Kwak, Goldstein and Simmons from microwave data (8).
[3]Reported by Searles, Tamres and Barrow (24).
[4]Measured by Long and Purchase at 0.07°C (25).

These data indicate that 7-membered and smaller lactones (with high dipole moments and rate constants) contain the syn ester configuration while 10-membered and larger lactones, as well as the open-chain esters, contain the anti ester group. The 8- and 9-membered lactones occupy the "transition" position. As expected, the syn lactones, due to their higher polarity, boil 50-60° higher than would be expected from the boiling points of the anti lactones.

The dipole moments for the 12-membered and larger lactones are constant. The reason for the increase in dipole moments with increasing ring size of the syn lactones is not clear. Searles, Tamres and Barrow (24) have observed that hydrogen bonding in the syn lactones increases as the size of the lactone ring increases from 4 to 6 members. They suggest that the reason for this is that in the 4- and to some extent in the 5-membered lactone resonance is "damped" due to unfavorable bond angles with the result that the electron density of the carbonyl oxygen is decreased. Since it is not clear how compression of the normal bond angles would affect the amount of π-orbital overlap in the O=C-O system, Huisgen's "dampening of resonance" explanation (9) for the increase within the syn lactones is questioned.

Huisgen has explained the increased reactivity of the syn lactones in the following way (9). Bender (26) has established that the alkaline hydrolysis of an ester takes place through an intermediate XIII. Huisgen states that the



XIII

formation of this intermediate is rate determining and that in this intermediate the energy difference between syn and anti has disappeared. Since the formation of XIII is endothermic the energies of the syn and anti transition states are nearly equal. The syn configuration therefore reacts faster than the anti because the syn is at a higher energy level in the ground state (see XII).

The increased reactivity of the 6-membered lactone over the 5-membered lactone can be explained in the following way. Based on the observation that in cyclopentane (planar structure) there are 10 bond oppositions whereas in cyclopentanone there are only 6 and that in cyclohexane (chair form) there are no bond oppositions while in cyclohexanone there is a certain amount of bond opposition, Brown et al. have predicted that a reaction which involves the loss of an exocyclic double bond in a 6-membered ring will be favored over the corresponding 5-membered derivative (27,28). The decreased reactivity of the 10- and 11-membered rings is due to the resistance to the formation of a tetrahedral center because of van der Waal's radii interferences (29) in these medium sized rings. At ring size 12 this resistance is no longer present and the 12-membered and larger lactones react at a rate comparable to open-chain esters.

The question which remains is that of assigning a configuration to the 8- and 9-membered lactones. The boiling point of the 8-membered lactone is between the normal values for syn and anti lactones. Assuming the dipole moment for pure syn 8-membered lactone to be the same as for the 7-membered lactone, Huisgen (9) has calculated from the observed moment an equilibrium mixture composed of 25% anti and 75% syn for the 8-membered lactone. A consideration of models indicates that the 9-membered lactone is the smallest, relatively strain free anti lactone possible. If Huisgen's prediction is correct, the 8-membered anti form would be quite strained.

The boiling point for the 9-membered lactone indicates that it is in the anti configuration. However, the dipole moment and rate constant are higher than would be expected for such a configuration. On the basis of these latter two properties Huisgen has calculated that the 9-membered lactone is composed of an equilibrium mixture of 6-10% syn lactone. The other possibility is that the 8- and 9-membered lactones exist in some intermediate configuration but Huisgen prefers the idea of equilibrium mixtures of syn and anti configurations.

By way of comparison it is interesting to note that in similar cyclic systems, transitions from cis to the more preferred trans or syn to the more preferred anti forms take place at the following ring sizes (30): Cycloalkanes--above 10; cycloalk-1-en-1-yl acetates--above 11; 1,2-cycloalkanediones--about 11; lactams--10; N-nitrosolactams--10.

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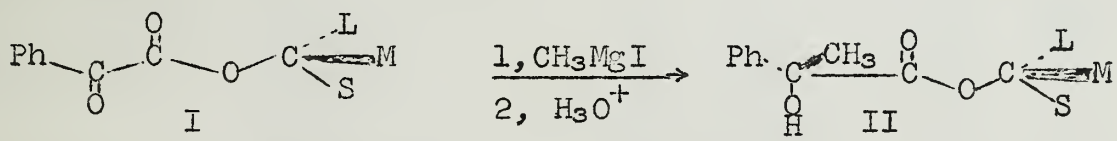
THE MECHANISM OF ASYMMETRIC INDUCTION

Reported by C. D. Mitchell November 30, 1959

The preferential formation of one reflectionally related isomer over another as occurs in nature has long been a goal of synthetic chemistry. While complete stereospecificity has never been obtained, partial asymmetric syntheses have been observed for quite some time. Because of the universal law that asymmetry can not arise from symmetry (1), all such syntheses have had an element of asymmetry somewhere present in the reaction. Six main sources of the asymmetric element have been the following: enzymes (2), optically active solvents (3), optically active reagents for example, Grignard reagents (4,5,6,7,8), presence of one of more asymmetric centers in the substrate molecule (9,10), presence of axial dissymmetry in the substrate molecule, i.e., biphenyl dissymmetry (11,12,13), and circularly polarized light (1). This seminar is largely concerned with asymmetric induction occurring as a result of the presence of an asymmetric center in the substrate molecule. Since asymmetric syntheses have long been the rule in the cyclic steroid and terpene chemistry, the seminar will be restricted to acylic systems.

The development of conformational analysis has greatly facilitated an understanding of asymmetric induction and has led to proposed rules of asymmetric synthesis. While the present seminar will present briefly Prelog's rule (14) and a new, closely analogous, rule, it will concentrate mainly on the postulate of Cram (15).

In 1904 McKenzie (16) initiated a series of experiments on the configurational course of the addition of Grignard reagents to the phenylglyoxylic esters of asymmetric alcohols. Prelog (1953), in a re-interpretation of McKenzie's work, was able to relate the sign of rotation of the atrolactic acid produced on hydrolysis of the ester to the configuration of the original asymmetric alcohol (14). The correlation arises from two factors. 1. The most stable conformation of the ester is (I) wherein the larger groups of the asymmetric carbinol are skew to the ester carbonyl. 2. The Grignard reagent will attack preferentially from the side of the smaller alkyl group (M) yielding the compound (II).

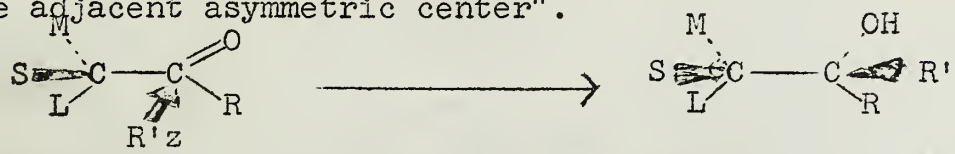


I II

The importance of Prelog's rule is self-evident, for in theory it can be applied in determining the configuration of any alcohol asymmetric at the carbinol carbon. In 1954 Prelog extended his rule, noting that the lithium aluminum hydride reduction of phenylglyoxylic esters of optically active alcohols can be used to determine the configuration of the alcohols. Thus, an ester which forms D-(-)- atrolactic acid with MeMgI will form D-(-)-1-phenyl-1,2-ethanediol on reduction with lithium aluminum hydride (17). In 1956 Prelog published a review of his work on asymmetric induction (18).

In 1952 Cram proposed a rule for the acyclic series (15) which correlates the relative bulk of substituents on an asymmetric carbon atom alpha to a carbonyl with the observed stereospecificity of a reaction in which the carbonyl undergoes transformation to an

asymmetric alcohol. Cram's rule is stated as follows: "In non-catalytic reactions of the type shown below, that diastereomer will predominate which would be formed by the approach of the entering group (R') from the least hindered side of the double bond when the rotational conformation of the C-C bond is such that the double bond is flanked by the two least bulky groups (M and S) attached to the adjacent asymmetric center".



Prior to Cram's proposal of the rule of asymmetric induction a generalization was suggested by Curtin (19) in which S is a hydrogen atom; M is amino, hydroxy, or methoxy; L is phenyl or methyl; R and R' are p-substituted phenyl or alpha-naphthyl. Curtin's work upon twelve reactions of the preceding type provided the first generalization in the acylic series in which the stereochemical course of a reaction could be accurately predicted. Curtin's generalization was easily incorporated into Cram's later rule and gave considerable support to the rule. Numerous reviews are available concerning the early work in this area of both Cram and Curtin (20,21,22,23,24,25).

A major difficulty in using the rule for prediction lies in deciding the order of effective bulk of the groups attached to the asymmetric carbon of the ketone. Table I records those compounds investigated by Cram since the publication of the rule in 1952.

TABLE I

No.	Ketone	Reagent	Ratio t	Ratio e	Rule Predicts	Ref.
1	(+)-3-methyl-3-phenyl-2-pentanone	EtLi	1	2	(+)-e	(26)
2	(-)-3-methyl-3-phenyl-2-pentanone	EtLi	1	2	(-)-e	(26)
3	(+)-4-methyl-4-phenyl-3-hexanone	MeLi	4.5	1	(+)-t	(26)
4	(-)-4-methyl-4-phenyl-3-hexanone	MeLi	4	1	(-)-t	(26)
5	2-phenylbutanal	EtMgBr	1	3	e	(27)
6	4-phenyl-3-hexanone	$LiAlH_4$	3	1	t	(27)
7	D-2-cyclohexyl-propanal	MeMgI in ether	1	1.9	e	(28)
8	"	MeLi in pentane	1	1.5	e	(28)
9	"	MeLi in ether	1	1.2	e	(28)
10	D-3-cyclohexyl-2-butanone	$LiAlH_4$ (normal addition)	1.4	1	t	(28)
11	"	$LiAlH_4$ (inverse addition)	1.4	1	t	(28)
12	"	$NaBH_4$ in MeOH-H_2O	1.7	1	t	(28)
13	"	$Al(O\text{-}i\text{-}prop.)_3$	1	1.9	t	(28)
14	D-threo-3-cyclohexyl-2-butanol	$Al(O\text{-}i\text{-}prop.)_3$ + acetone	3.3	1		(28)
15	D-erythro-3-cyclohexyl-2-butanol	$Al(O\text{-}i\text{-}prop.)_3$ + acetone	1	1		(28)

16	2-phenyl-3-methylbutanal	$(CH_3)_2CHMgBr$	1	1.9	e	(29)
17	"	$(CH_3)_2CHMgBr + MgBr_2$	1	1.3	e	(29)
18	"	$(CH_3)_2CHLi$ in pentane	1	1	e	(29)
19	2,5-dimethyl-4-phenyl-3-hexanone	$LiAlH_4$ (normal addition)	10	1	t	(29)
20	"	$LiAlH_4$ (inverse addition)	10	1	t	(29)
21	3-phenyl-2-butanone	NH_4OOCH (Leuckhart Reac.)	2	1	t	(30)
22	1-cyano-1-phenyl ethane	1, MeMgI 2, $LiAlH_4$ 3. H_3O^+ 4, OH^-	1.9	1	t	(30)

e=erythro; t=threo

In Table I the validity of the rule is supported in every reaction except 13; the formation of the erythro isomer in the aluminum isopropoxide reduction of (D)-3-cyclohexyl-2-butanone. That this reaction is a true violation of the rule was determined by establishing it to be kinetically controlled. This was accomplished by subjecting separately the threo and erythro isomers to the reduction conditions for a period of seven days (14 and 15 in Table I). After this time the reaction had proceeded far enough to indicate that an equilibrium mixture would contain between 23% and 50% of the erythro isomer. Thus, if the reaction were thermodynamically controlled a preponderance of the threo-isomer would have been formed, in contrast to the experimental result. Thus, the rule appears to be unreliable in predicting the steric course of aluminum isopropoxide reductions of ketones (even though it was initially successful in the several cases upon which the rule was originally based) (15). Other steric factors may operate in this reaction that are either absent or not important in the other reductions ($LiAlH_4$, $NaBH_4$, etc.).

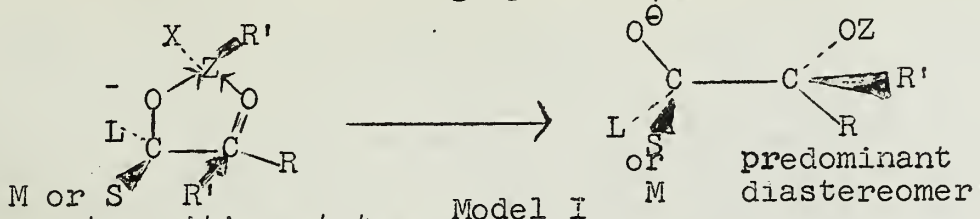
Several other conclusions may be drawn from Table I. Reactions 16, 17, 19, and 20, which are controlled only by steric interactions, indicate that the effective bulk of a phenyl group is greater than that of an isopropyl group. Also, an initial generalization by Cram stating that the Grignard reagent is more stereospecific than the corresponding alkyllithium agent (15) is supported by reactions 7, 8, 16 and 18. It is of interest to further note that the addition of $MgBr_2$ in 17 as compared to 16 results in a lowering of stereospecificity. It has been postulated that the action of magnesium bromide, is in shifting the Grignard equilibrium, toward the less bulky reagent $(CH_3)_2CHMgBr$, which is

$$2(CH_3)_2CHMgBr \rightleftharpoons ((CH_3)_2CH)_2Mg + MgBr_2$$

accordingly less stereospecific. In reaction 21 the rule was tested for the first time in a reaction not involving a metal-containing reagent (the Leuckhart Reaction) and was found to be obeyed.

In his original paper (15) on the rule of asymmetric induction Cram postulated a mechanism for those ketones possessing a group

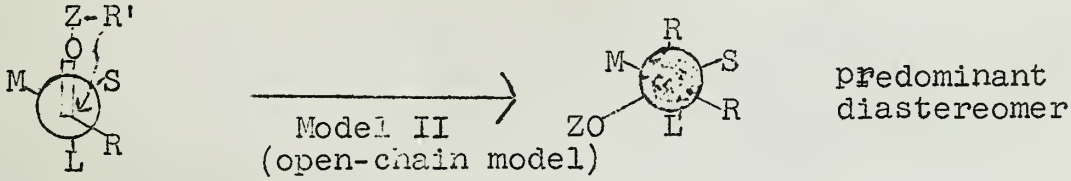
capable of coordinating with the metal of the reducing agent. This involved a relatively rigid, 5-membered ring which fixes the conformation of the reacting species (Model I).



transition state of lowest energy

Model I (rigid model)

This mechanism was noted to predict the same isomer as was predicted by the open chain model (Model II) in those cases where the hydroxy or amino group is the medium (M) sized group.



transition state of lowest energy

Model II (open-chain model)

predominant diastereomer

Cram has recently described a series of reactions (Table II) in which the group capable of coordination is the S group; with ketones of this type the two models predict the predominance of different diastereomers.

TABLE II (9)

Reaction	1	2	3	4	5	6
Ketone	3-hydroxy-3-phenyl-2-butanone	biacetyl	(-)-1,2-diphenyl-2-hydroxy-1-propanone	benzil	(+)-3-methoxy-3-phenyl-2-butanone	(-)-1,2-diphenyl-2-methoxy-1-propanone
Reagent	PhLi	PhLi	MeLi	MeLi	PhLi	MeLi
% Yield	92	63	74	66	78	92
Ratio:						
meso	1	1	11.5	4.6		
(+)&(-)	6.7	8	1	1		
erythro					1	2
threo					9	1
Isomer Isolated:						
Config.	(+)&(-)	(+)&(-)	meso	meso	(-)-threo	(+)-erythro
% Yield	44	54	20	26	---	38
m.p.	122-124	122-124	115-117	116-118	---	94-96
Model I predicts	(+)&(-)	(+)&(-)	meso	meso	(-)-threo	(+)-erythro
Model II predicts	meso	meso	(+)&(-)	(+)&(-)	(+)-erythro	(-)-threo

In Table II the relative order of effective bulk of the groups attached to the asymmetric carbon was estimated by a comparison of their "A-values", by which Winstein (31) has compared the relative tendency of various groups to occupy the less hindered equatorial position on a cyclohexanone ring. The order of decreasing effective size of these groups is $CH_3 > p\text{-}O_3SC_6H_4CH_3 > OCOCH_3 > OH$.

If CH_3 is effectively larger than p-toluenesulfonate, it should also exceed the OH group in effective bulk despite the fact that the OH is undoubtedly involved with metal (either covalently bound or as an ion pair). A comparison of the predictions of Model I and Model II with the data of Table II shows that the model which correctly predicts the configuration of the product is Model I, for those compounds in which either OH or OCH_3 occupies the asymmetric carbon of the starting material. Cram has postulated that the predictions from Model I probably likewise apply to any systems which carry groups (e.g., OH, OR, OAc, NH_2, NHR, $N(R)_2$, NHAc). The data of Table II likewise emphasise that the open chain Model II applies only to systems which contain groups attached to the asymmetric carbon which are incapable of complexing with organometallic reagents.

Cram has attempted to explain the trends in stereospecificity observed in Table II. Stereospecificity can be measured in a general sense by multiplying the factor by which one diastereomer predominates in one synthesis by the factor obtained when the synthesis is carried out by inverting the order of introduction of groups (9). Table III compares a number of systems with this "index of stereospecificity".

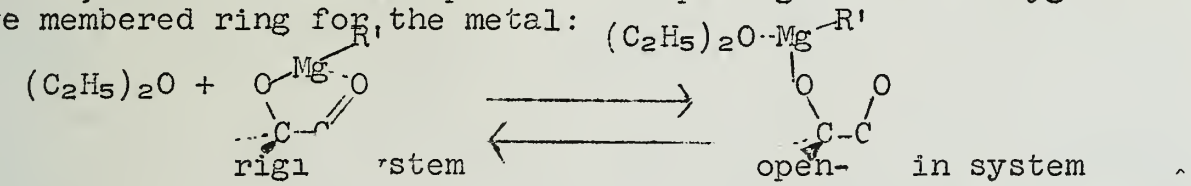
TABLE III (9)

Entry No.	Reaction product	Reagents involved	Model which predicts result	"Index"	Ref.
1	2,3-diphenyl-2,3-butanediol	PhLi or MeLi in pentane	Model I	77	Runs 1 and 3 Table II
2	2,3-diphenyl-3-methoxy-2-butanol	PhLi or MeLi in pentane	Model I	18	Runs 5 and 6 Table II
3	3-phenyl-2-butanol	MeMgI or $LiAlH_4$ in ether	Model II	5	Runs 1 and 2 (14)
4	3-cyclohexyl-2-butanol	MeMgI or $LiAlH_4$ in ether	Model II	2.7	Runs 1 and 4 (28)
5	3-phenyl-2-butanol	PhMgBr or $LiAlH_4$ in ether	Model II	>16	Runs 7 and 8 (14)
6	2,3-diethyl-3-phenyl-2-butanol	EtLi in pentane MeLi in ether	Model II	9	Runs 1 and 3 (26)
7	2-amino-1-phenyl-1-p-tolyl-1-propanol	$CH_3C_6H_4MgBr$ in ether	Both Models	>2500	(9)(32)

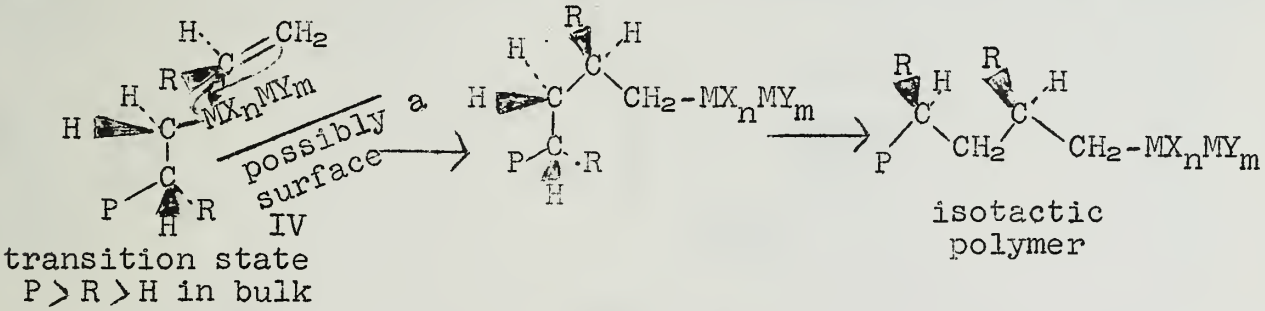
The systems of Table III may be divided into three classes: 1. those in which only the rigid-model (Model I) gives the correct results (entries 1 and 2); 2. those for which only the open-chain model (Model II) gives correct results (entries 3-6); 3. those in which both models predict the same result (entry 7). It was concluded from the data in Table III that the "indexes of stereospecificity" are an order of magnitude higher in the case of class 3 in which both models predict the same result than in the case of

class 1 in which the two models predict different results. Therefore, these data intimate that the molecules in classes 1 and 3 react by two mechanisms which involve stages simulated by both of the two models, i.e., very high stereospecificity is observed when both mechanisms lead to the same steric result (class 3), whereas lower stereospecificity is observed when both mechanisms predict different results, (class 1). In systems in which only the open chain model can apply (class 2), the lowest stereospecificity is observed since conformation adapts itself to mechanism rather than mechanism to conformation.

A difference is stereospecificity was noted between the reaction of (-)-1,2-diphenyl-2-hydroxy-1-propanone with MeMgBr in ether and MeLi in pentane (run 3-Table II); the ratio of meso-2,3-diphenyl-2,3-butanediol to (-)-2,3-diphenyl-2,3-butanediol in the case of MeMgBr is less than 5 and in the case of MeLi is equal to 11.5. Cram suggested that this may be explained if the predominance of the rigid model depends on the ability of the metal to maintain a 5-membered ring. Thus, not only would the character of the metal be important, but the solvent might be even more important. The open chain model might be expected to be more favored in ether than in pentane, since ether is capable of competing with the oxygen of the five membered ring for the metal:

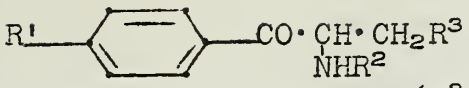


Cram has suggest d that some of the ide eloped in deriving and applying the rule of asymmetric induction may e employed to explain stereospecificity in certain types of polymerization. In the anionic polymerization of mono-substituted ethylenes Cram explains the formation of isotactic polymers by considering that the growing polymer chain is in that conformation which leaves the carbon-metal bond the most exposed to electrophilic attack by the more substituted end of the polarized, olefinic monomer, and that the orientation of the monomer in the transition state (IV) is determined by steric repulsions between substituents on the old and the incipient asymmetric carbon atoms.



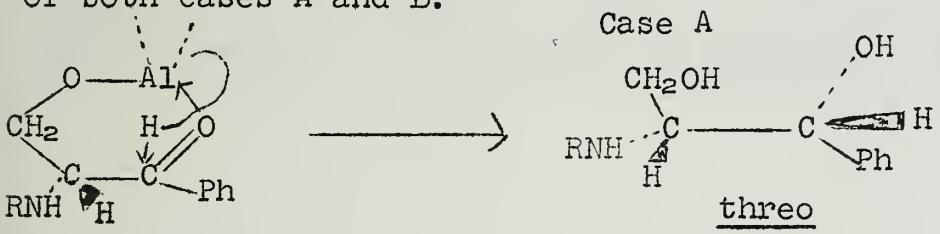
Cram also postulates mechanisms for stereospecific cationic and free radical polymerizations(9).

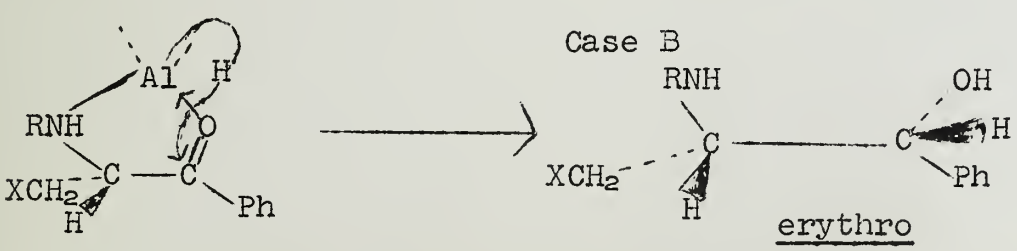
Sorm and co-workers have investigated the reduction of dehydrochloramphenicol (V) and related compounds (33).



Type A (R^3=OH)				Type B (R^3≠OH)			
	R'	R^2	R^3		R'	R	R
V,	NO_2	$-COCHCl_2$	OH	VIII,	NO_2	$-COCHCl_2$	$-O\cdot CO\cdot CH_3$
VI,	NO_2	$-COC_6H_5$	OH	IX,	NO_2	$-COCHCl_2$	$-S-CO\cdot Ph$
VII,	NO_2	$-CO\cdot O\cdot CH_2Ph$	OH	X,	NO_2	$-COCHCl_2$	-O-trityl
				XI,	NO_2	$-COCHCl_2$	-Cl
				XII,	H	$-COCHCl_2$	-H

On the basis of a literature correlation and their own experimental results they concluded that compounds of type A give on Meerwein-Ponndorf reduction exclusively or principally products of the threo-configuration; regardless of the nature of the substituents on the ring (R'), the nature of the acyl grouping (R) and the secondary alcohol moiety of the reducing alcoholate. Compounds of type B, on the other hand, are reduced exclusively or principally to the erythro-diastereomers. The difference in the stereochemical course of reduction would appear to be due to the presence or absence of a free hydroxyl group in the position beta to the carbonyl group reduced. The formation of the threo-products in the case of compounds of type A is entirely consistent with the results predicted by Cram's open chain model (Model II). This same model is also applicable in the reduction of the compounds of type B, IX and X, since clearly $CH_2OTr > NHCOCHCl_2$, and since it is also likely that $CH_2SCOC_6H_5 > NHCOCHCl_2$. The application of Model II is doubtful, however, in reaction VIII, since it appears unlikely that $CH_2OCOCH_3 > NHCOCHCl_2$, and the open chain model clearly fails in alpha-dichloroacetamido-propiophenone (XII), here CH_3 is smaller than $NHCOCHCl_2$, and this leads to the prediction that the threo isomer should predominate, which is clearly inconsistent with the experimental results. Thus, the open-chain model fails to give completely self-consistent results in the reduction of these dehydrochloramphenicol-like compounds. If, however, the dependence of the steric course of the reaction is upon the presence or absence of a free hydroxyl group, then two cyclic mechanisms can be proposed which account for the observed stereospecificity in every instance of both cases A and B.





The preceding work by Sorm is not conclusive, however, for, three reasons, as pointed out by Cram (9): (1) It was not

determined whether the reductions were kinetically or thermodynamically controlled; (2) The amount of the other diastereomer produced was not determined; and (3) The order of addition of substituents to the carbonyl group was not inverted to see if rigid models held for both modes of addition.

A number of papers have dealt recently with types of asymmetric induction somewhat different from the type discussed above with which Cram has been concerned. Walborsky and co-workers have reported asymmetric induction in the addition of diphenyldiazomethane to the menthyl esters of simple olefins ((-)-menthyl acrylate and (-)-menthyl methaacrylate); hydrolysis of the resulting ester yielding a predominance of one enantiomorphic cyclopropane carboxylic acid (34).

C.L. Arcus and D. G. Smyth investigated asymmetric induction in the catalytic hydrogenation (Raney Ni) of 3-ethyl-3-hepten-2-ol; and concluded that the asymmetric center of the olefin controls the conformation in which the molecule is absorbed at the catalyst surface, and that the subsequent cis-addition of hydrogen explains the observed asymmetric synthesis (35).

Balfe, Kenyon, and Waddan reported an asymmetric synthesis resulting from the trans-addition of bromine to (+)-,(-)-, and (±)-trans-1-phenyl-1-penten-3-ol (36).

J. A. Berson and E. Brown proposed a novel type of asymmetric induction in which a center of carbon asymmetry is destroyed concomitant with the generation of a new center of biphenyl asymmetry (12).

Berson and Greenbaum reported asymmetric induction in the biphenyl series of the type explained by Prelog's rule. Specifically, the reaction of MeMgI with the phenylglyoxylates of phenyldihydrothebaine and its derivatives gave atrolactic esters which upon saponification yielded a predominance of one enantiomorphic atrolactic acid over the other, providing a means for determining the absolute configurations of the biphenyls investigated (13).

Finally, a general and direct method for correlating the configuration of a biphenyl with that of a centrally asymmetric compound, and hence, for establishing absolute configuration in the biphenyl series, was reported by Mislow and Newman (11).

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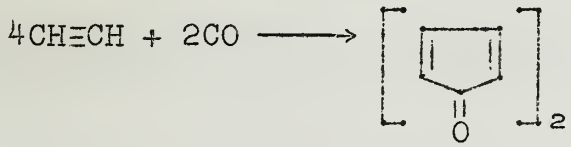
BIFURANDIONES

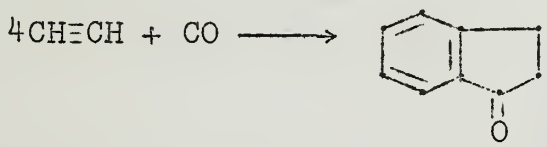
Reported by C. R. McArthur December 3, 1959

There are many reactions resulting from the combination of acetylene and carbon monoxide, generally involving various metallic carbonyls as catalysts. For example, in the presence of a solvent containing a reactive hydrogen atom, the products were mainly acrylic compounds (1). Acrylic esters, for instance, can be prepared either at 12 atm. pressure and 35-40° or at atmospheric pressure by bubbling acetylene into a solution of the carbonyl in the respective alcohol in the presence of an acid. This can be generalized to the preparation of other derivatives of acrylic acid

$$Ni(CO)_3 + 2HCl + 4ROH + 4HC{\equiv}CH \longrightarrow 4CH_2{=}CHCOOR + NiCl_2 + H_2$$

such as amides, acid anhydrides, and thioesters by replacing the alcohol by ammonia or amines, carboxylic acids, and mercaptans, respectively. The combination of acitylene under unspecified conditions has been reported to give dimeric cyclopentadienone or hydrindone (1a). In a recent report by Sauer, Cramer, Engelhardt,





Ford, Holmquist, and Howk (2), two moles of acetylene and four of carbon monoxide have been combined catalytically to give a compound of molecular formula $C_8H_4O_4$. Depending on the conditions, one of two isomers could be formed, characterized by m.p. 237° (I), and m.p. 248° (II).

Compound I was formed readily in 60-70% yield by the reaction of carbon monoxide and acetylene in a mole ratio of CO/C_2H_2 of at least 4/1 in the presence of a cobalt catalyst in an inert solvent at pressures from 100 to 1000 atm., and temperatures between 90 and 120°. The catalyst was dicobalt octacarbonyl, cobalt, or cobalt compounds which apparently are converted into soluble cobalt carbonyl derivatives under the reaction conditions. Good solvents for the reaction producing I were acetonitrile, nitromethane, ethyl acetoacetate, cyclohexane, and acetone. In tetramethylurea, the higher melting isomer II was the sole product formed in 30% yield. Both isomers I and II exhibited low solubility in organic solvents. This facilitated the isolation of the product by filtration of the reaction mixture. The only satisfactory solvent at room temperature for the products was concentrated sulfuric acid. It was observed that the lower melting isomer I, when dissolved in concentrated sulfuric acid, and heated on a steam-bath for four hours was converted to the higher melting isomer II in 80% conversion. In cold concentrated sulfuric acid, the isomerization took several weeks. The reverse isomerization II→I was never observed.

Structure Characterization of I and II.

Hydrogenation of I over platinum in acetic acid at room temperature and 3 atm. pressure gave suberic acid in 87% yield, which establishes the existence of an eight-carbon backbone.

$$C_8H_4O_4 \xrightarrow[H_2,Pt]{} HOOC(CH_2)_6COOH$$

Under controlled hydrogenation conditions over supported palladium catalysts, the isomers took up three moles of hydrogen, suggesting a triene structure. The resulting hydrogenated compound (III) was present in two isomeric forms, one of m.p. 106°, and the other of m.p. 64°, which were seperable by fractional crystallization. The higher melting isomer of III had been reported previously (3) as γ,γ'-bibutyrolactone. Confirmatory evidence for III was obtained from the oxidation with permanganate, which gave succinic acid.

III

The infrared spectral analysis of I and II is summarized in Table I. The intense carbonyl bands at 1770 and 1780 cm.$^{-1}$ for I

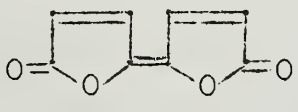
TABLE I

Infrared maxima (cm.$^{-1}$)

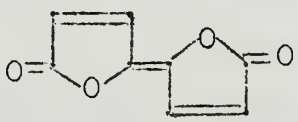
State: KBr wafer.

Isomer I	Isomer II
----	1668 - very intense.
1538 - intense, singlet.	1538 - intense, doublet
1770 - intense.	1780 - intense.
3120.	3120.

and II, respectively are in the expected range for γ-lactones (4). The presence of two lactone groups was indicated by quantitative saponification with aqueous sodium hydroxide solution. On the basis of structure III, obvious structures for the trienedilactones I and II would be those of cis- and trans-$\Delta^{2,2'(5H,5'H)}$-bifuran-5,5'-dione.



cis
I or II

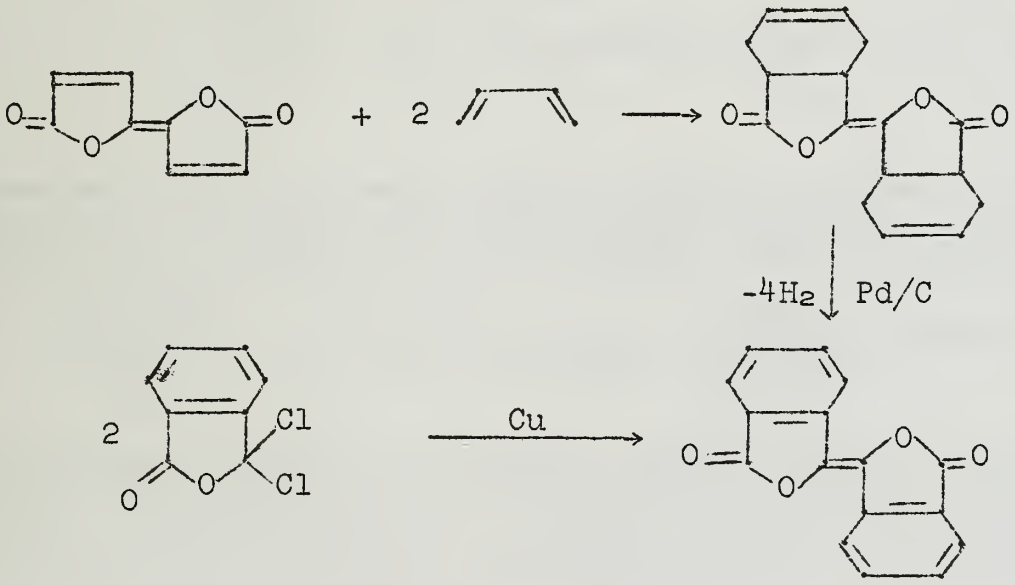


trans
II or I

These formulae are consistent with the infrared spectra, which also can be used to distinguish which isomer is which. The very intense band at 1668 cm.$^{-1}$ in isomer II (m.p. 248°) is attributed to the carbon-carbon bridge double bond. This absorption is conspicuous by its absence in isomer I (m.p. 237°). It can be seen that in the above formulae the trans isomer has a center of symmetry, and that the bridge double bond is astride this center of symmetry. A frequency associated with the stretching of a bond will not appear in the infrared unless the stretching vibration produces a change in the dipole moment. This arises from the selec-

tion rules which affect the intensity of a given absorption and not its position (5). A molecule possessing a center of symmetry, which has C=C or C≡C across this center of symmetry (e.g., ethylene, acetylene, trans-2-butene) will not exhibit the double bond frequency, since no change in dipole moment accompanies such a vibration. Where cis-trans isomerization occurs across such a bond, the trans isomer will not absorb, whereas the cis isomer will. It was concluded, then, that isomer I is trans- and isomer II is cis-bifurandione. The absorption at 1538 cm.$^{-1}$ is attributed to the unsaturations α,β to the carbonyl groups. The doublet is expected in the case of the unsymmetrical cis isomer, while the singlet is expected in the symmetrical trans isomer. The absorption at 3120 cm.$^{-1}$ in each isomer is due to the unsaturated C-H stretching frequency. The nuclear magnetic resonance spectrum of the trans isomer is identical with that of the cis isomer. The spectrum was taken in sulfuric acid or trifluoroacetic acid; it consisted of two peaks, each a doublet, of equal intensity.

The bifurandiones undergo Diels-Alder reactions with various dienes (6). They function only as dienophiles in the cases tried. They react, for example, with butadiene, 2,3-dimethylbutadiene, and α-phellandrene (5-isopropyl-2-methyl-1,3-cyclohexadiene) to give crystalline adducts, while no reaction occurs with maleic anhydride. The Diels-Alder reaction with butadiene was used as final structure proof by converting I into biphthalyl in the following synthesis.

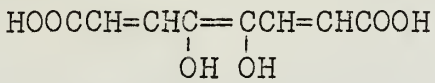


Unsym. phthaloyl chloride — Biphthalyl

The biphthalyl formed was identical with that formed by a known procedure (7) from unsymmetrical phthaloyl chloride and copper powder in pyridine. While the trans isomer exhibited bifunctionality as a dienophile, the cis isomer added only one mole of butadiene, apparently for steric reasons. Trans-bifurandione will also form a mono-adduct if only one mole of diene is present. In the mono-adducts, the carbonyl band in the infrared becomes a doublet which confirms the fact that the double bond adjacent to the carbonyl group rather than the bridge double bond acted as the dienophile. If the central double bond had reacted, the two lactone rings would have remained identical. The di-adducts, being symmetrical, have single carbonyl peaks.

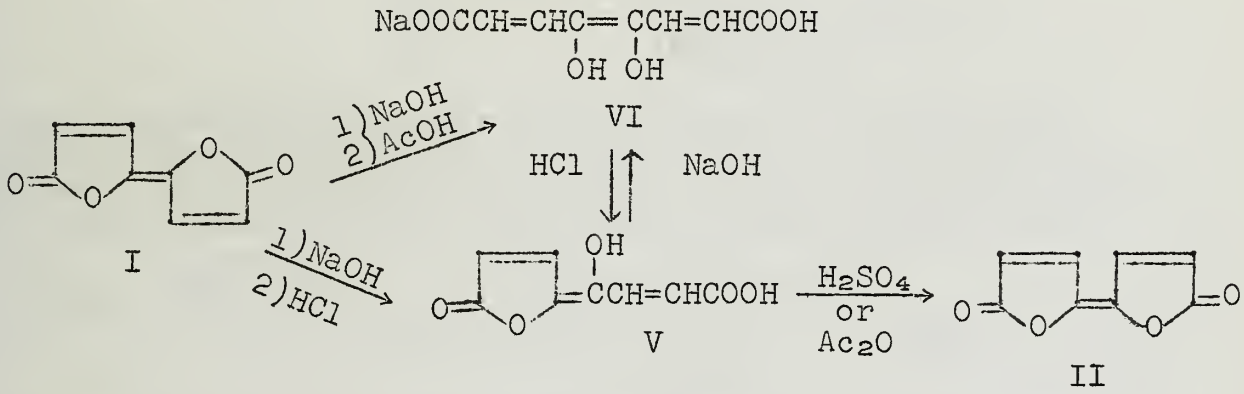
Hydrolysis (6).

The dibasic acid 4,5-dihydroxy-2,4,6-octatriene-1,8-dioic acid (IV) that would result from the hydrolysis of the two lactone rings of bifurandione has not been isolated as such. Bifurandione

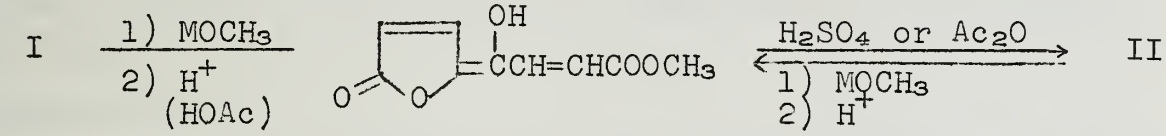


IV

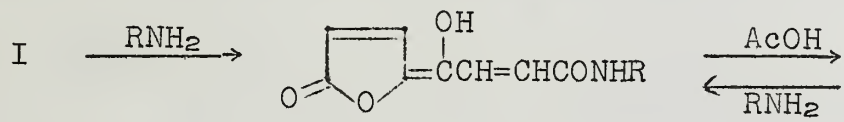
is stable towards acid except for the isomerization of the trans isomer to the cis. It is reactive, however, with organic and inorganic bases. Data available indicate that the both isomers behave in the same manner. The monosodium salt of IV was obtained by careful acidification of an alkaline solution of bifurandione with dilute acetic acid. Complete acidification with hydrochloric acid gave the monolactone V, which is convertible with sulfuric acid or acetic anhydride to cis-bifurandione (II). The monosodium salt and the monolactone are interconvertible.



Treatment with lithium or sodium methoxide followed by acidification gave the methyl ester of V in 92% yield which in turn was converted to cis-bifurandione with strongly acidic reagents.



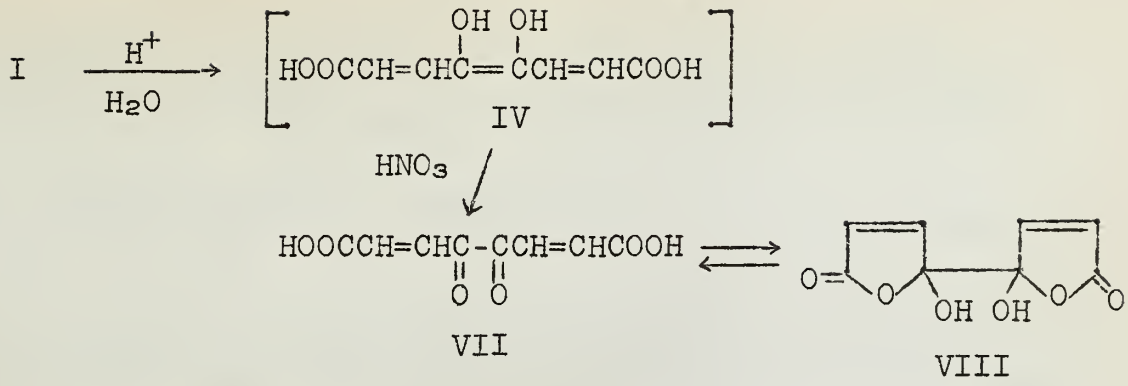
Bifurandione reacted with aqueous ammonia to give the ammonium salt of the monoamide of IV which on acidification yielded the amide of V. A similar reaction occurred with various aliphatic amines as well as p-toluidine, p-aminobenzoic acid, and dodecylaniline.



The authors (6) have not mentioned the stereochemistry of any of these hydrolysis products.

Oxidation.

Oxidation of trans-bifurandione with nitric acid in sulfuric acid gave 2,2'-dihydroxy-2,2'-bifuran-5,5'(2H,2'H)-dione (VIII) in 63% yield. It was formed presumably by hydrolysis to the intermediate (IV), followed by oxidation to VII. The cyclic hemiketal form VIII seems to be favored by the infrared spectrum (table II), however some of the reactions occur as if the compound existed in

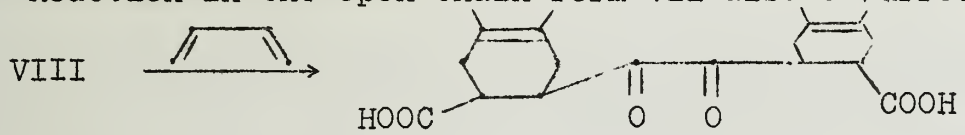


the open-chain form VII.

TABLE II

ν (cm.$^{-1}$)	Function
3390	OH
3130	CH=CH
1770	γ-lactone carbonyl
1625	conjugation

The dihydroxybifurandione VIII reacted as a bifunctional dienophile, apparently in the open-chain form to give 2,2'-dicarboxy-4,4',5,5'-tetramethyl-1,1',2,2',3,3',6,6'-octahydrobenzil (IX). Reaction in the open chain form VII also occurred with

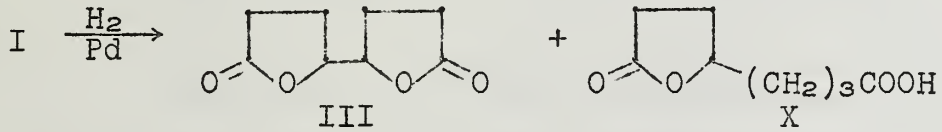


IX

o-phenylenediamine to yield the quinoxaline derivative, benzopyrazine-2,3-diacrylic acid. Catalytic hydrogenation of VIII over platinim gave 4,5-dioxo-1,8-octanedioic acid. This acid was also obtained by the electrolytic reduction of bifurandione (vide infra).

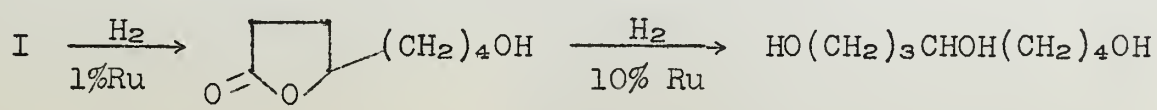
Hydrogenation (8).

In addition to γ,γ'-bibutyrolactone (III), hydrogenation of I in the presence of palladium catalysts or Raney nickel gave γ-(γ'-carboxypropyl)-butyrolactone (X). The conversions with palladium catalysts were essentially quantitative, although the product that predominated depended on the reaction conditions.

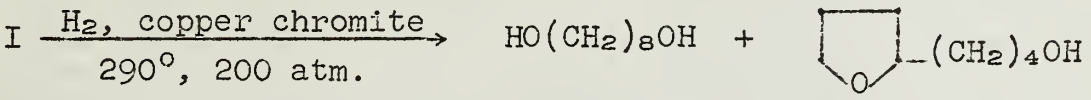


III X

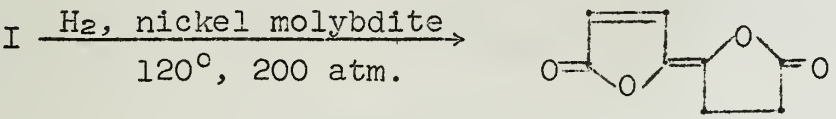
Using ruthenium as catalyst, partial hydrogenolysis of bifurandione occurred to give γ-(δ'-hydroxybutyl)-butyrolactone which could be further hydrogenated using 10% ruthenium catalyst to 1,4,8-octanetriol. Hydrogenation of bifurandione over copper



chromite in dioxane at 190° gave suberic acid (30%). At 290°, 61% of 1,8-octanediol, and a small amount of 2-(4'-hydroxybutyl)-tetrahydrofuran were obtained. No cleavage occurred with nickel molybdite as catalyst. Dihydrobifurandione was obtained in 49%



yield, the same product as was obtained with palladium when the reaction was stopped after the uptake of one mole of hydrogen. The structure of the dihydrobifurandione was assigned on the basis



of the carbonyl band in the infrared, which was split into a doublet because of the two kinds of lactone rings. When the pH of the reaction medium was made less than 2 by the addition of hydrochloric acid, the hydrogenation using palladium on carbon gave γ-ketosuberic acid in 72% yield.

Polarographic Reduction (9).

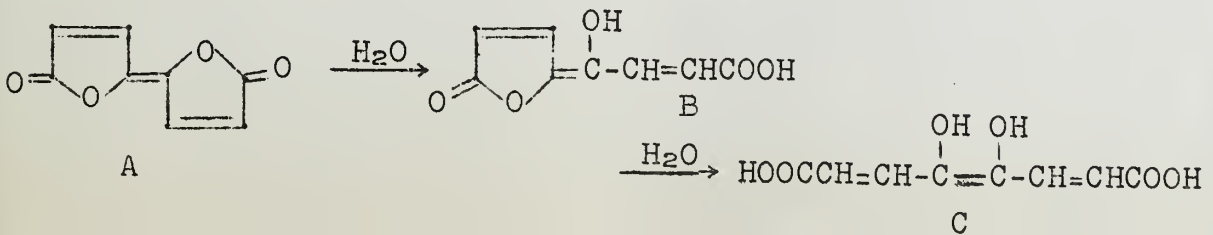
The polarographic behavior at the dropping mercury electrode of both isomers was studied in acetonitrile-water solutions over the pH range of 1 to 12. The isomers behaved identically. A summary of the types of waves formed in the polarograms at various values of the pH is shown in Table III.

TABLE III

(Minimum aged conditions)

pH	Description if polarographic wave
0-4	Single well defined waves.
4-10.9	Second wave is evident at pH 4, but not well defined so as to determine $E_{1/2}$ or i_d until pH 10.3; first wave diminishes.
10.9	First wave less than 1/4 its max. i_d; second wave reaches max. current. Third wave is evident.
12.1	First wave disappeared; second wave nearly vanished; third wave is well defined.

These results are interpreted as indicating three products of hydrolysis which are each reducible at different potentials. This implies stepwise hydrolytic cleavage of the rings. C reduces



at a more negative potential than B, and B reduces at a more negative potential than A.

A time study of hydrolysis was made by running polarographs at constant pH on solutions aged for various lengths of time. A pH of 10.3 was chosen, since all three waves appear at this pH and a time study could be made by watching the appearance or disappearance of all three waves. During the course of the study, the second wave appeared to be made up of two different reductions which have half-wave potentials so close so as to be unresolvable. This may be due to the existence of both cis and trans forms of B.

The disappearance of the first wave (hydrolysis of the first ring) followed first order kinetics. A plot of log (a-x) as a function of time gave a straight line. Concentration is related to the limiting current i_d by the Ilkovic (11) equation. The

$$i_d = 607nD^{1/2}cm^{2/3}t^{1/6}$$, where: n = no. of electrons transfered per molecule at the electrode.

D = diffusion coefficient
c = concentration
m = mercury drop rate (gm./sec.)
t = time for growth of a mercury drop.

following values were found for the first order rate constants for the reaction A→B: $k_{trans} = 1.6 \times 10^2$, $k_{cis} = 1.7 \times 10^2$.

A plot of log i/i_d-i versus the potential E yields a straight line indicating obedience to the Heyrovsky-Ilkovic (11) equation.

$$E_{(d.m.e.)} = E_{1/2} + \frac{0.059}{n}\log(i_d-i)/i \qquad \text{(at 25°)}$$

From a slope of the plot, n can be determined. For the most acid values of the pH, n is close to 2, indicating a two-electron process.

Controlled polarographic studies were also made on concentrated sulfuric acid, but were unsuccessful because of the non-reproducibility of the behavior. This led to the use of 50% sulfuric acid in water, and studies similar to those made in acetonitrile-water solution were made. The isomers obeyed the Ilkovic equation and a plot of log i/i_d-i versus E indicated a two-electron process, in agreement with the controlled electrolytic reduction (vide infra).

Electrolysis; isolation of reduction product.

Because of the solubility of bifurandione in concentrated sulfuric acid, controlled electrolysis was carried out in this medium, using a mercury pool as cathode and a potential of 0.8 volts, in an effort to isolate the product. The product was isolated by pouring the cell contents, after electrolysis, into ice water. A 58% yield of 4,5-dioxo-1,8-octanedioic acid was obtained. The reduction is considered to be a two-electron hydrogenation, or a 1,6-addition to the conjugated double bond system of 4,5-di-

hydroxy-2,4,6-octatriene-1,8-dioic acid (C). From the data available, it cannot be said whether acid hydrolysis occurs before or after the reduction, nor whether the mechanism is the same in the acetonitrile-water system.

$$I + 2e^- + 2H^+ + 2H_2O \longrightarrow HOOCCH_2CH_2\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}CH_2CH_2COOH$$

Ultraviolet absorption as a function of pH.

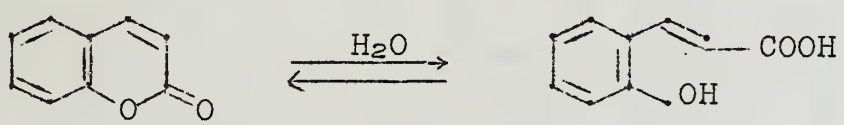
The ultraviolet absorption maximum of trans-bifurandione in acetonitrile-water shifts towards the visible with increasing pH. At pH 10.1, there is a large jump of 340 Å (from 3460 to 3800 Å) corresponding to the hydrolysis of the first ring (i.e. A→B). At pH 11.5 the absorbtivity increases slightly as a maximum amount of B is formed, and then decreases at a pH of 12.6 as B is converted to C. These data are consistent with the polarographic data.

Comparison with coumarin.

It is interesting to compare the polarograms and ultraviolet spectra of coumarin as they vary with pH with those of bifurandione. The data for coumarin (10) indicate that the species exists as the lactone in solution at pH < 6.8, and as coumarinic acid at pH > 11.2, both forms being present in the intermediate pH range.

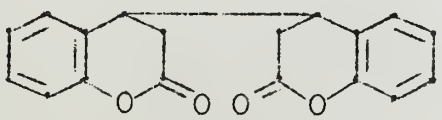
For a given concentration, the polarographic wave height decreased with pH. For any pH where reduction occurred, there was a single wave, the half wave potential of which was independent of pH. The Heyrovsky-Ilkovic equation was obeyed, and the electrolytic reduction of coumarin was found to be one-electron process (n = 1).

A plot of ultraviolet absorption against optical density at various pH values, and plots of optical density at the absorption maxima versus pH indicate a sharp change at pH 9.8. This agrees with pH 9.3 to 10.3 at which the polarographic wave height decreases markedly. Coumarin (D) is stable in acid media and is re-



D E

ducible over the range of potentials (-1.3 to -1.9 volts vs. S.C.E.). Coumarinic acid (E) is not reducible over that range. E is present to a negligible extent below pH 6.8. The product from coumarin was isolated by controlled electrolytic reduction and was found to be racemic- and meso-tetrahydrodi-4-coumarinyl.



The authors (10) concluded that the independence of $E_{1/2}$ on pH meant that at least the potential determining step in the re-

duction is free of proton participation. Therefore the step must consist in the addition of a single electron to the neutral molecule. The following mechanism was proposed.

$$1)\quad R + e^- \longrightarrow R^{\cdot -}$$

$$2)\quad R^{\cdot -} + (H^+) \longrightarrow RH^{\cdot}$$

$$3)\quad 2RH^{\cdot} \longrightarrow R_2H_2$$

Step (1) agrees with the pH invariance of $E_{1/2}$.

Step (3) agrees with the product formed.

Step (2) represents the formation of the necessary intermediate. The proper representation of the proton source cannot be concluded from these data.

****

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ORGANO IRON CARBONYLS

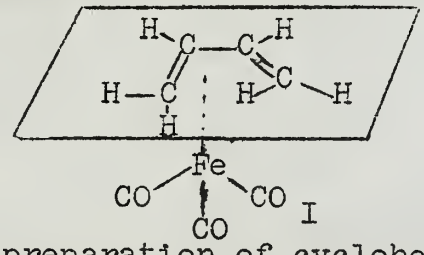
Reported by J. C. Hill December 7, 1959

Complex formation in the reaction of metal carbonyls with certain unsaturated molecules has been the subject of accelerated research in recent years. This seminar will deal with the recent work on organo iron carbonyl complexes 1.) formed from the direct reaction of conjugated olefins with the iron carbonyl and 2.) formed from the reaction of acetylenic compounds with the iron carbonyl.

COMPOUNDS CONTAINING CONJUGATED OLEFINIC BONDS

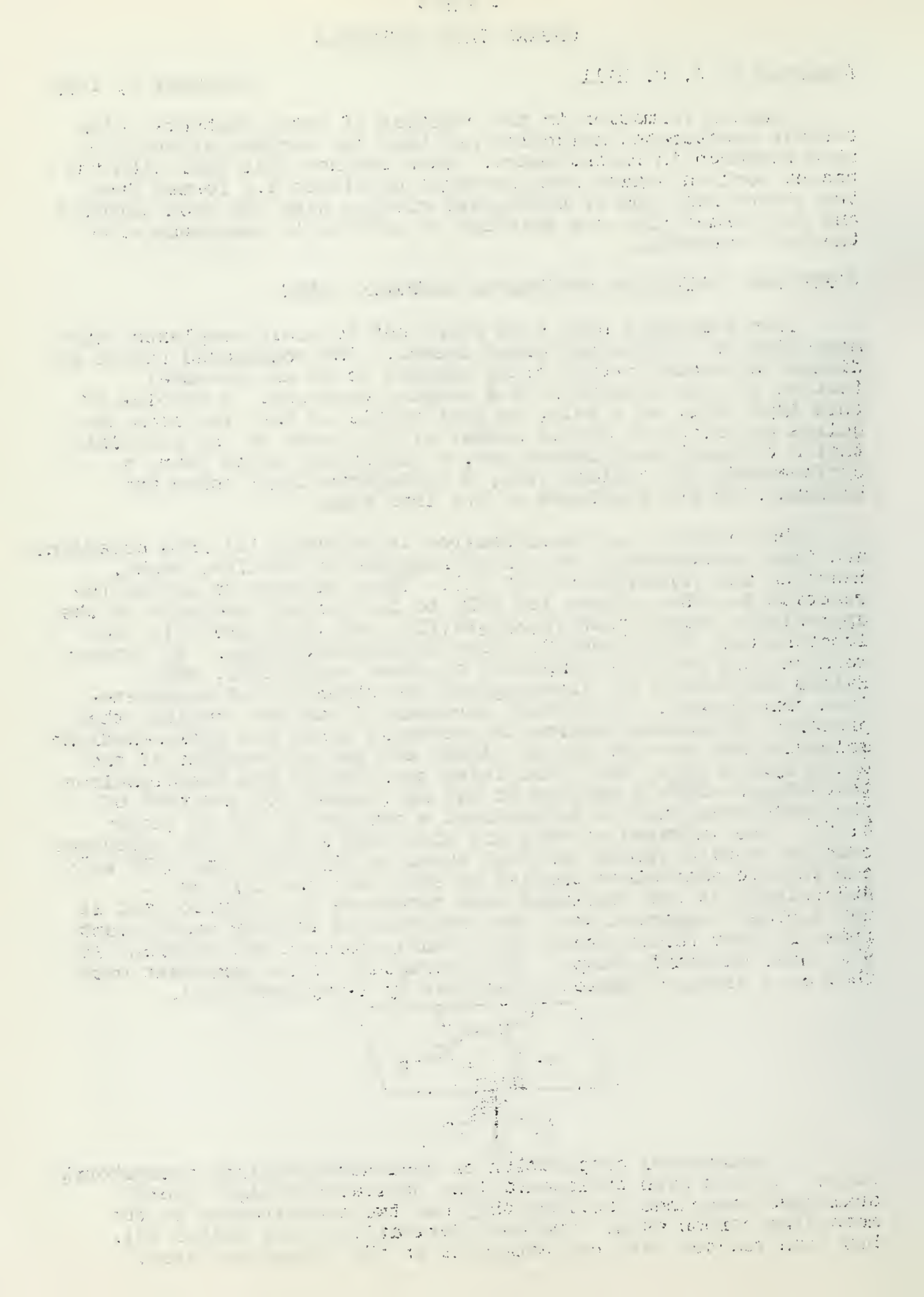
Iron carbonyls have been found not to yield complexes with mono-olefins or non-conjugated dienes. The conjugated nature of dienes and aromatic-type rings appears to be an essential feature for the formation of a complex compound. A complex of this type will, as a rule, be most stable if the iron atom acquires an effective atomic number of 36, based on the postulate that a carbonyl contributes two, a conjugated diene four, a cyclopentadienyl radical five, a cyclopentadienyl anion and benzene ring six electrons to the iron atom.

The formation of butadieneiron tricarbonyl (I) from butadiene and iron pentacarbonyl was first reported by Rheilen, Gruhl, Hessling and Pfrengle in 1930 (1). Their efforts to extend the reaction to other dienes led only to ill-defined products of the approximate composition $(C_5H_8)_2Fe(CO)_3$ and $(C_5H_8)_3Fe(CO)_3$ from isoprene and $(C_6H_{10})_2Fe(CO)_3$ from dimethylbutadiene. No further work on this group of compounds appeared until 1958, when Hallam and Pauson (2) investigated the structure of butadieneiron tricarbonyl. Suspecting structure I for the complex, they prepared cyclohexadieneiron tricarbonyl, since the cyclohexadiene molecule must be very nearly planar and the end carbons of the diene system cis. The ultraviolet spectrum of the butadieneiron tricarbonyl shows a maximum at 211 mμ ($\log\epsilon$=4.36) and that of the cyclohexadieneiron tricarbonyl a maximum at 207 mμ ($\log\epsilon$= 4.36). The infrared spectra are also very similar, the butadiene complex showing strong carbonyl bands at 2051 cm^{-1} and 1978 cm^{-1} and the cyclohexadiene complex at 2066 cm^{-1} and 1978 cm^{-1}. Accordingly it was concluded that structure I is correct and it was further suggested that the iron atom is roughly equidistant from all four carbon atoms and probably forms a tetrahedron with the three carbonyl groups. This structure is in agreement with that of a similar complex determined by X-ray work (13).



I

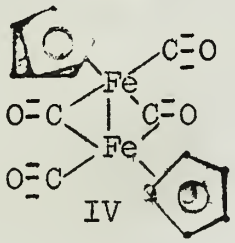
The successful preparation of cyclohexadieneiron tricarbonyl suggested that even cyclopentadiene derivatives might yield analogous compounds provided they had two substituents on the methylene carbon atom. Two such derivatives were tested (3), but both reacted with rearrangement of the carbon skeleton.



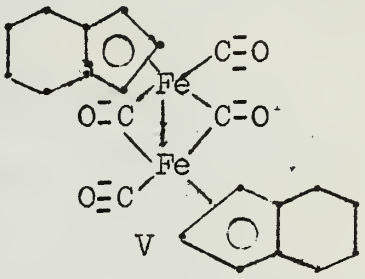
The two compounds studied were spiro-[2,4]hepta-1, 3-diene (II) and spiro-[4,4]nona-1,3-diene (III). When II was heated with iron pentacarbonyl it gave a polymeric gum. A crystalline fraction (1.6%) was identified as the diethyl derivative of dicyclopentadienyldiiron tetracarbonyl (IV) by analysis and infrared spectrum. More clear-cut results were obtained with the spirononadiene (III), which reacted with iron pentacarbonyl to

II

III



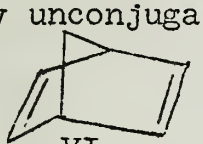
IV



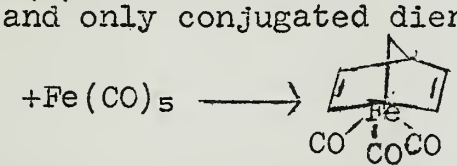
V

give bis-tetrahydroindenyldiiron tetracarbonyl (V) in 39% yield. The structure of V was proved by conversion into the known bis-tetrahydroindenyliron on pyrolysis and also by an independent synthesis from indene. The latter reacted with iron pentacarbonyl yielding diindenyldiiron tetracarbonyl which was hydrogenated to the octahydro derivative (V). Reduction to V proves also that the indene molecules are linked to the metal atoms through the five-membered and not through the benzenoid rings.

Another diene which forms a complex on reaction with iron pentacarbonyl is bicyclo [2.2.1]hepta-2,5-diene (VI). The formation of this compound (4) is of interest because the diene is formally unconjugated and only conjugated dienes have previously



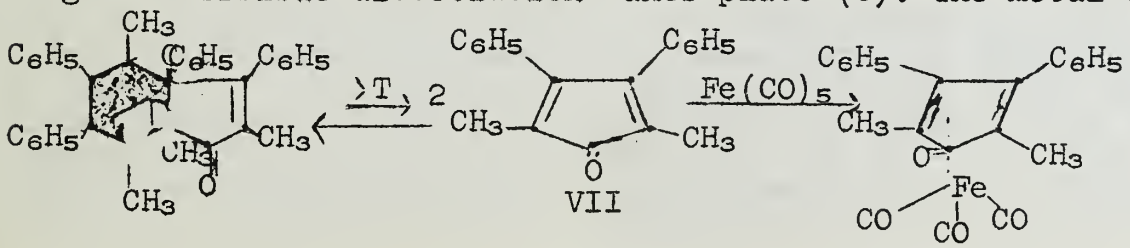
VI



been found to bond to iron. However, due to the shape of the molecule, the bicyclodiene has a suitable spatial arrangement for possible interaction with the metal atomic orbitals.

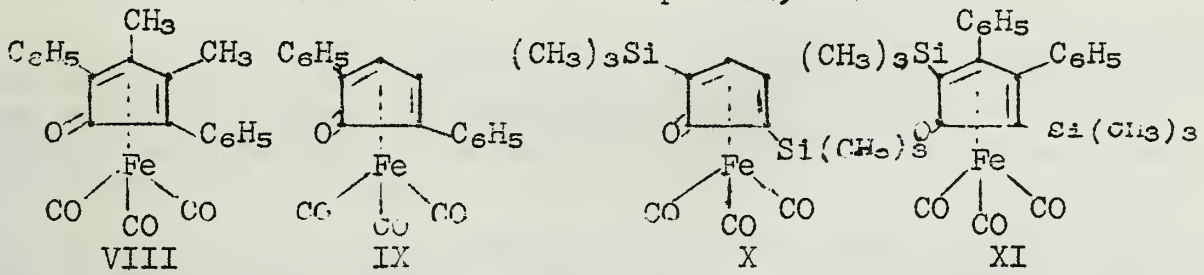
Substituted cyclopentadienones react with iron carbonyls to form stable diamagnetic π - complexes of the general formula (cyclopentadienone)$Fe(CO)_3$ (5). The infrared spectra of these compounds show three bands for the CO ligands between 1988 cm^{-1} and 2070 cm^{-1} and a single band for ketone absorption between 1605 cm^{-1} and 1653 cm^{-1}.

The iron carbonyls react only with the cyclopentadienones which exist as monomers under the reaction conditions. The compound 2,5-dimethyl-3,4-diphenyl-cyclopentadienone (VII) exists as a dimer under normal conditions but in solution and on heating a reversible dissociation takes place (6). The metal carbonyl



VII

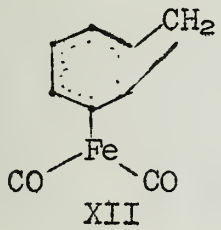
reacts with the monomeric diene, stabilizing it and driving the reaction to the right. Only 2,3,4,5-tetraphenylcyclopentadienone (tetracyclone) and derivatives with substituted phenyls are known to exist as monomers under normal conditions. Four other substituted cyclopentadienone iron tricarbonyl complexes (VIII, IX, X and XI) have been reported. The interesting thing about these complexes is that they were synthesized by reaction of iron carbonyls with substituted acetylenes. The positions of the substituents in X and XI have not been proved, while structures VIII



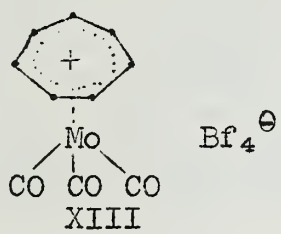
VIII IX X XI

and IX have been established as correct (see below).

In an attempt to prepare an iron carbonyl complex with the tropenium ion $(C_7H_7)^+$, cycloheptatriene was caused to react with iron pentacarbonyl. However, cycloheptatrienyl iron dicarbonyl (XII), $(C_7H_8)Fe(CO)_2$ was the only product isolated. The failure of cycloheptatriene to lose a hydride ion is not too surprising since it has been proposed that in the molecule six carbon atoms other than the methylene lie very nearly in the same plane, and the six electrons form a delocalized system which bypasses the methylene group. The complex may be formulated as XII.



XII

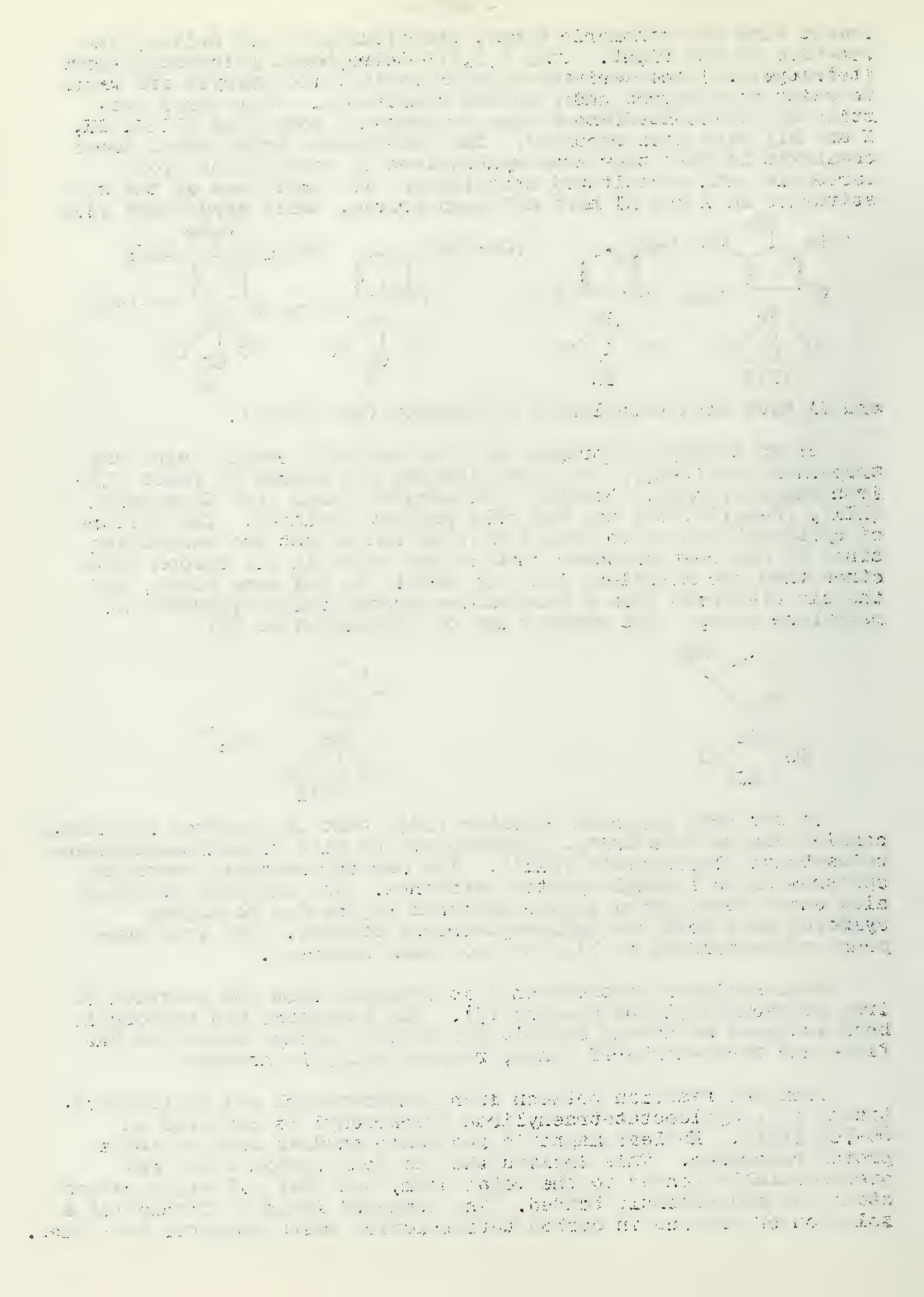


XIII

It has been reported recently (22), that the related molybdenum complex reacts with trityl fluoroborate to give tropeniummolybdenum tricarbonyl fluoroborate (XIII). The nuclear magnetic resonance spectrum shows a single proton resonance. The infrared spectrum also shows fewer peaks in the carbonyl region due to higher symmetry than does the cycloheptatriene complex. The iron compound corresponding to XIII has not been reported.

Azulenediiron pentacarbonyl is obtained from the reaction of iron pentacarbonyl and azulene (7). Its structure has reasonably been assigned as having $Fe(CO)_3$ and $Fe(CO)_2$ groups bonded to the five- and seven-membered rings, respectively, in azulene.

From the reaction between iron pentacarbonyl and cyclooctatetraene (8), cyclooctatetraenyliron tricarbonyl is isolated in 60-70% yield. Nuclear magnetic resonance studies show a single proton resonance. This implies that no four carbon atoms are preferentially bonded to the metal atom, but that all eight carbon atoms are equivalently bonded. The compound fails to decolorize a solution of bromine in carbon tetrachloride which supports this view.



A compound, $C_8H_8Fe_2(CO)_6$, is also isolated in this reaction. It has no carbonyl stretching frequencies in the bridging region of its spectrum and the $Fe(CO)_3$ groups are most likely on either side of a C_8H_8 ring (9). A theoretical treatment of a binuclear transition metal compound having two metal atoms symmetrically separated by a C_nH_n conjugated ring system has been made and indicates such a complex should be stable (10).

ACETYLENIC COMPOUNDS

The success which Reppe had in introducing the metal carbonyls into organic chemistry (11) led him to investigate the action of iron carbonyl hydride on unsaturated organic compounds. Iron carbonyl hydride can be produced by the reaction of aqueous base with iron pentacarbonyl.

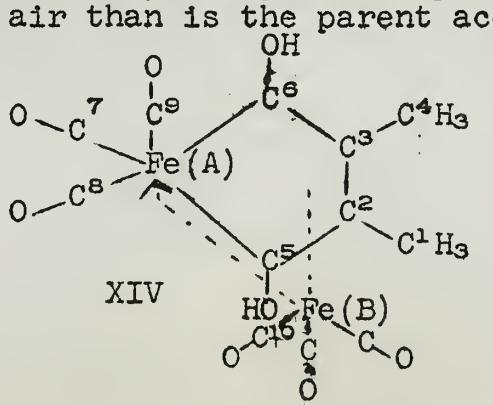
Using iron carbonyl hydride and carbon monoxide Reppe was able to synthesize alcohols from olefins. Using similar conditions he found that hydroquinone and its substituted derivatives were formed from the reaction of acetylene or its derivatives instead of the expected unsaturated alcohols.

Reppe showed the reaction of acetylene as going in this simple way:

$$Fe(CO)_4H_2 + 4C_2H_2 + 2H_2O \longrightarrow 2 \text{ (hydroquinone)} + Fe(OH)_2$$

However, he realized the course of the reaction was not this simple since some well-defined iron carbonyl complexes with acetylene are formed and are probably intermediates. He isolated the complex $FeC_{11}H_7O_5$ and two others, $FeC_8H_4O_4$ and $FeC_7H_4O_3$, which were shown to be formed from the first (12). He did a lot of work with these complexes but was unable to say anything about their structure. The complex $FeC_{11}H_7O_5$ was found to form hydroquinone and $FeC_8H_4O_4$ on treatment with water or dilute acid.

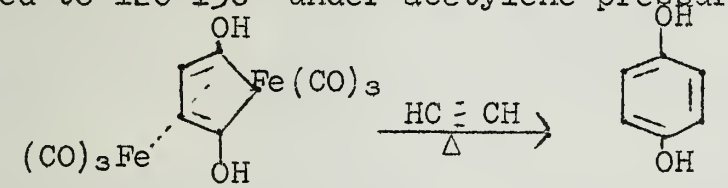
While experimenting with varying reaction conditions, Reppe isolated a new complex $Fe_2C_{10}H_4O_8$ in 45% yield from the reaction of acetylene at 20 atmospheres and 50° with an alkaline solution of iron hydrocarbonyl. Recently (14) it has been shown that the complex can be formed in 70% yield from the reaction of acetylene at atmospheric pressure and room temperature with an alkaline solution of $NaHFe(CO)_4$. The complex was studied by Hock and Mills (13) and was found to have structure XIV on the basis of X-ray analysis. The dimethylacetylene complex was studied since it is more stable to air than is the parent acetylene derivative.



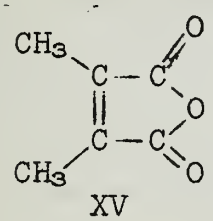
XIV

The two iron atoms are bonded in dissimilar ways. The coordination of Fe(A) is roughly octahedral, five of the six positions being occupied by carbon atoms, two of which (C-5 and C-6) are at a significantly greater distance from the Fe than are the remainder. There are eight carbon atoms (C-1 to C-8) lying in one plane. Perpendicular to this plane and on opposite sides are the remaining CO group bonded to Fe(A) and the $Fe(CO)_3$ group. This second Fe atom is nearly equidistant from atoms C-2,3,5 and 6 and in an arrangement similar to that postulated for butadieneiron tricarbonyl (3). The three CO groups of this π-bonded Fe atom are trigonally arranged around the perpendicular to the plane previously described. A second plane, of approximately mirror symmetry, lies perpendicular to the above plane and contains both Fe atoms and CO groups of C-9 and C-10.

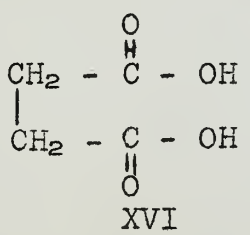
At the present stage of refinement the geometrical arrangement of atoms is correct, but the final bond lengths and angles will be subject to revision. The six Fe-C-O bonds are linear within experimental error and of length found in other carbonyl compounds. The Fe-C bonds to C-5 and C-6 have lengths which may be significantly less than the sum of covalent radii. It appears that the three bond lengths C_5-C_2, C_2-C_3, and C_3-C_6 will be similar, which is to be expected because of conjugation and π-bonding of the Fe atom. The investigators suggest a dative bond between the two Fe atoms since they have a normal separation in XIV for a covalent bond. This would allow each iron atom to acquire an effective atomic number of 36 in the following way: Fe(B) 26+6 (from 3 CO) + 4(πelectrons); Fe(A) 26+6 (from 3 CO) + 2(σ electrons to terminial carbon atoms) + 2(dative bond from Fe(B). The packing of the molecules in the unit cell shows intermolecular hydrogen bonding which is in agreement with the observed infrared spectrum of the solid. The acetylene complex was found to give hydroquinone when heated to 120-150° under acetylene pressure (12).



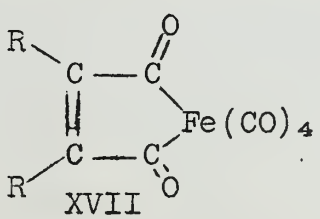
Oxidation of XIV in acidic media with $FeCl_3$ leads to loss of one iron atom and formation of $FeC_{10}H_6O_6$. A series of eight complexes of the form $(RC_2R')Fe(CO)_6$, isolated in the cases where R=R'=H, CH_3-, CH_3CH_2-, or C_6H_5 and R=H and R'=CH_3^-, $CH_3CH_2^-$, $CH_3CH_2CH_2CH_2^-$, or $C_6H_5^-$, has been studied (15). When the dimethylacetylene complex was treated with cold concentrated nitric acid, maleic anhydride (XV) was formed. When the acetylene derivative was first reduced with zinc and acetic acid and then oxidized, the product was succinic acid (XVI). This led to the postulation of XVII for the complex. The acetylene complex under-



XV



XVI



XVII

went a normal Diels-Alder reaction with cyclopentadiene to give the expected adduct (XVIII).

XVIII

Other workers in search of new complexes investigated the reaction of acetylene and substituted acetylenes with iron carbonyls in inert solvents and found that the reaction conditions, the metal carbonyl, and also the acetylene derivative used all played an important role in the nature of the complexes formed (see Table I).

Table I

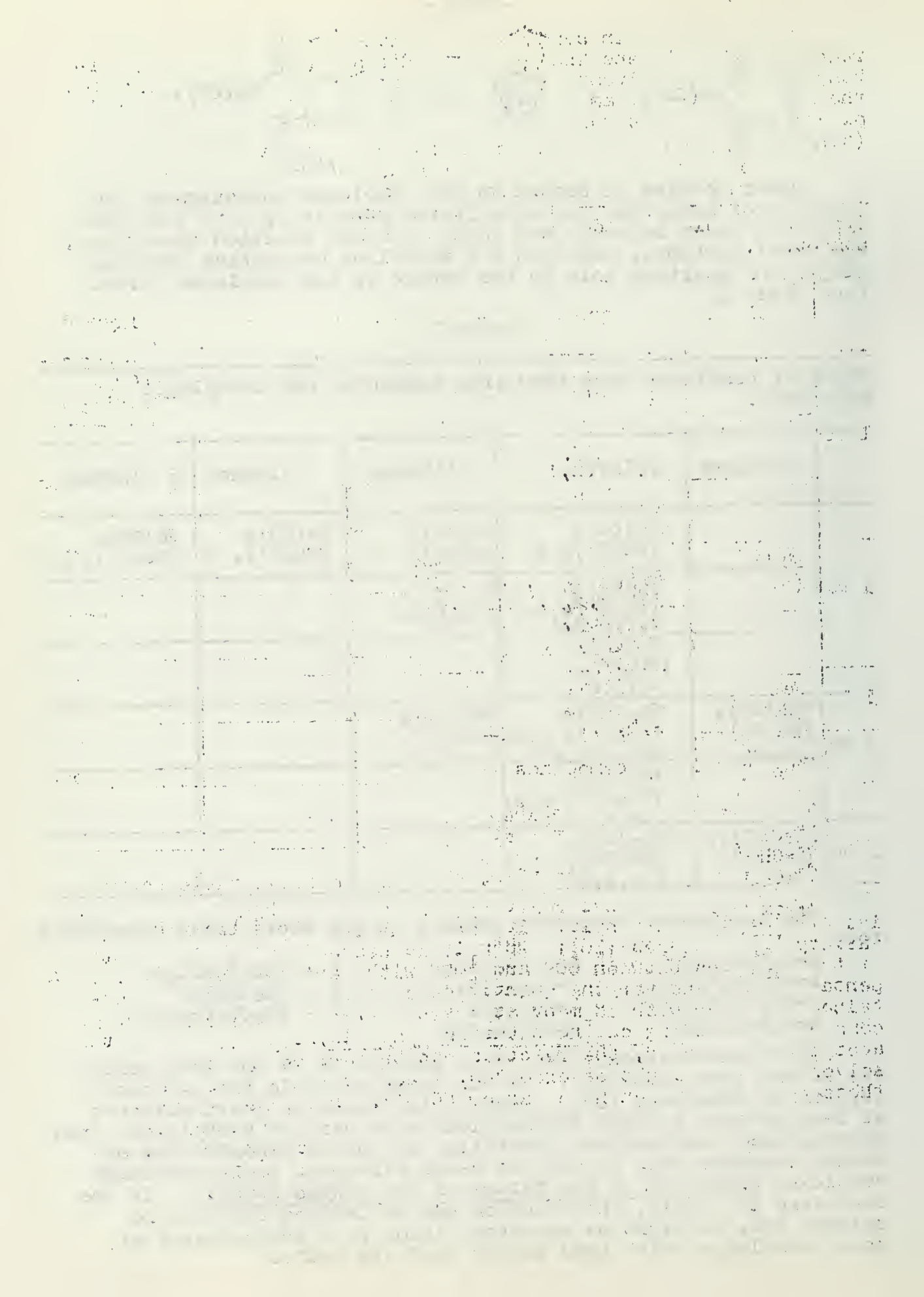
Types of complexes made from iron carbonyls and acetylenic compounds.

	1 Alkyne	2Alkynes	3 Alkynes	4 Alkynes	5 Alkynes
I Fe		$Fe(CO)_3(RC_2R')_2$ a	$Fe(CO)_2(RC_2R')_3$ g	$Fe(CO)_3(RC_2R')_4$ g	$Fe(CO)_4(RC_2R')_5$ g,h
		$Fe(CO)_4(RC_2R')_2$ a,b e,f,g,h,i	$Fe(CO)_4(RC_2R')_3$ g,h		
		$Fe(CO)_5(RC_2R')_2$ d,j,k			
2 Fe	$Fe_2(CO)_6(RC_2R')$ a,b	$Fe_2(CO)_6(RC_2R')_2$ a,b, c,d,e,f,g,h	$Fe_2(CO)_6(RC_2R')_3$ e,g,h		
		$Fe_2(CO)_7(RC_2R')_2$ a,b, d,e,f			
3 Fe	$Fe_3(CO)_{10}(RC_2R')$ e	$Fe_3(CO)_8(RC_2R')_2$ a,b,e,f			

The acetylenic compounds (RC_2R') in the above table correspond to:

a=$C_6H_5C_2C_6H_5$
b=$ClC_6H_4C_2C_6H_4Cl$
c=$CH_3OOCC_2COOCH_3$
d=$C_2H_5C_2C_2H_5$
e=$C_6H_5C_2CH_3$
f=$C_6H_5C_2Si(CH_3)_3$
g=$C_6H_5C_2H$
h=$BrC_6H_4C_2H$
i - $(CH_3)_3SiC_2H$
j - $CH_3C_2CH_3$
k - $HC_2CH_2CH_2CH_3$

Iron dodecacarbonyl $Fe_3(CO)_{12}$ appears to be the most reactive of the iron carbonyls. It was found to yield the greatest variety of complexes (16). When it is heated in inert solvents at temperatures between 60° and 100° with various acetylenes, iron pentacarbonyl and varying quantities of carbon monoxide are obtained together with as many as seven different iron-containing complexes depending on the nature of the alkyne studied. If the acetylene is liquid, the reaction can be carried out with no solvent and, as might be expected, leads to a predominance of those complexes which have larger RC_2R':Fe ratios.



Iron enneacarbonyl, $Fe_2(CO)_9$, can be used in most reactions in place of iron dodecacarbonyl. Some cases have been reported in which this carbonyl favors formation of a specific complex.

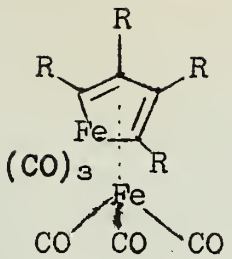
Iron pentacarbonyl, $Fe(CO)_5$, does not react under the above conditions but it does give similar results when it is simultaneously irradiated with ultraviolet light. This method (17) gives better yields and is experimentally the most simple. Because of the fact that upon ultraviolet irradiation of iron pentacarbonyl, $Fe_2(CO)_9$ is formed which, when heated, decomposes into $Fe(CO)_5$ and $Fe_3(CO)_{12}$, it may be concluded that iron dodecacarbonyl is the reacting species.

From table I the following generalizations are possible; apart from certain types which are formed with all substituted acetylenes there are some types which can only be formed from monosubstituted and others only with di-substituted acetylenes. Naturally, as the reaction conditions are made less mild, the more stable compounds tend to form at the expense of the less stable ones.

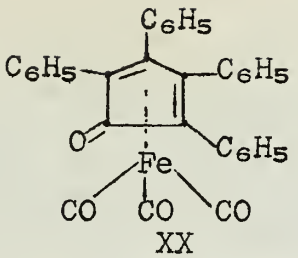
Most of the structure determination has been done on the types of complexes formed in highest yields. No cases have yet been reported where two complexes of the same general $(RC_2R')_xFe_y(CO)_z$ formula definitely have different arrangements of Fe atoms and CO groups with respect to the RC_2R' groups.

The complex which is formed in almost every reaction of an iron carbonyl and an acetylenic compound corresponds to $(RC_2R')_2Fe_2(CO)_6$. Yields range as high as 42% for the diphenyl acetylene derivative (17). The infrared spectra of these complexes do not show a ketone absorption band, but they do have the characteristic bands for metal bound CO ligands. Several structures could be considered for this complex, including a cyclobutadiene ring with $Fe(CO)_3$ groups symmetrically placed on either side of the ring. This structure was quickly ruled out, since the complexes studied showed high dipole moments (16).

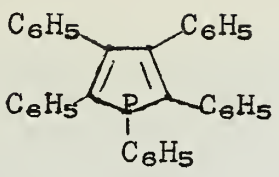
The following observations (16) on the diphenylacetylene derivative favor structure XIX. Oxidation of the complex with bromine in glacial acetic acid gives mainly tetracycloneiron tricarbonyl (XX) and a little tetracyclone. A solution of the complex when exposed to ultraviolet radiation gives tetracyclone and tetraphenylbutadieneiron tricarbonyl. In the presence of sulfur, a solution of the complex on exposure to ultraviolet light yields tetraphenyl thiophene in 49% yield. Heating under carbon monoxide pressure gives $Fe(CO)_5$ and tetracycloneiron tricarbonyl. With lithium aluminum hydride a mixture of 1,2,3,4-tetraphenyl-1-butene and 1,2,3,4-tetraphenylbutane was obtained. These two products were isolated using sodium and liquid ammonia; in addition, 1,2,3,4-tetraphenylbutadieneiron tricarbonyl was isolated. This last complex is formed in good yield when $NaNH_2$ is caused to react with $(C_6H_5C_2C_6H_5)_2Fe_2(CO)_6$. The complex $(C_6H_5C_2C_6H_5)_2Fe_2(CO)_6$ reacts with $C_6H_5PCl_2$ to give pentaphenylphosphole (XXI) in 66% yield (18).



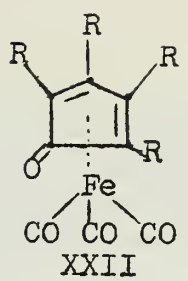
XIX



XX



XXI



XXII

In order to acquire an atomic number of 36 for both iron atoms in XIX a dative bond between the two atoms could be present. This complex is very similar to XIV, isolated with iron hydrocarbonyl.

The complex $(RC_2R')_2Fe(CO)_4$ is also formed in most cases. It shows a ketone absorption band as well as the three characteristic bands for metal bound CO ligands in the infrared spectrum. Structure XXII has been proved to be correct by synthesis from the cyclopentadienones.

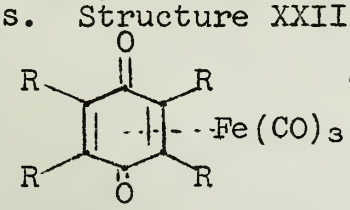
The diphenylacetylene derivative has been isolated in 12% yield from the reaction of diphenylacetylene and iron dodecacarbonyl (16) and in 45% yield from the reaction of diphenylacetylene and iron pentacarbonyl in the presence of ultraviolet radiation (17). Some tetracyclone was present in the reaction mixtures and on pyrolysis of the complex, tetracyclone is isolated in good yield.

From the reaction of phenylacetylene with iron carbonyl, diphenylcyclopentadienoneiron tricarbonyl was isolated and identified from its infrared spectrum (19). Only one complex compound was isolated with this formula and since there is a possibility of three isomers, this result shows that the formation of ring ketones in the complex occurs in a specific way. The structure of the diphenylcyclopentadienone system could not be proved easily by decomposition, since it dimerizes very readily. Schrauzer proposed that the complex was 2,5-diphenylcyclopentadienoneiron tricarbonyl by applying the general mechanism of the carbonylation reaction (11). He proceeded to prove the structure by reducing the complex with hydriodic acid and phosphorous in acetic acid to 2,5-diphenylcyclopentanone. This was identified by oxidation with chromic acid in acetic acid, which gave dibenzoylethane, the latter being identified by comparing melting points and infrared spectra and by taking a mixed melting point with an authentic sample.

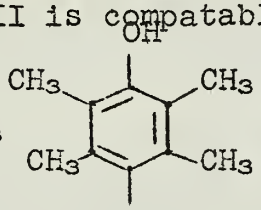
Schrauzer (17) and also Hübel and Bräye (16) isolated the complex $(C_6H_5C_2C_6H_5)_2Fe_2(CO)_7$ in small yields from two very different reactions. Schrauzer was able to isolate the complex by interrupting the reaction soon after the beginning of irradiation. It could not be isolated after a reaction time of two hours. Hübel and Bräye isolated the complex at the end of their reaction. The complex shows a strong band in its infrared spectrum at 1665 cm^{-1} which is probably due to a ketone. Heating the complex in benzene converts it readily into tetracycloneiron carbonyl, iron and iron pentacarbonyl. Oxidation with dilute nitric acid in acetic acid gives small yields of tetraphenyl-p-quinone (17). On reduction with lithium aluminum hydride or sodium in liquid ammonia, the tetraphenyl-p-quinone can also be isolated (16). Under carbon monoxide pressure, the main product is tetracycloneiron tricarbonyl which shows that the ring closes easier than CO

enters the molecule (16).

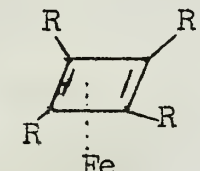
The complex $(RC_2R')_2Fe(CO)_5$ has been prepared in good yields from the reaction of dimethylacetylene, 1-pentyne, or 3-hexyne with iron pentacarbonyl on exposure to sunlight (20). The formation of this complex has been reported only for alkyl substituted acetylenes. Structure XXIII is compatable with the infra-red spectra.



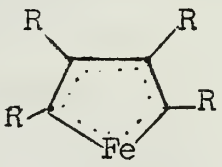
XXIII



XXIV



XXV



XXVI

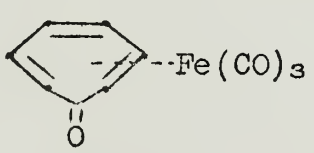
Strong support of XXIII was obtained by treating the dimethylacetylene derivative with hydrochloric acid. Durohydroquinone (XXIV) is obtained quantitatively. Durohydroquinone has been synthesized directly without isolation of an intermediate complex by adding methanolic hydrochloric acid to the mixture of dimethylacetylene and iron pentacarbonyl during irradiation. It is interesting to note that p-benzoquinone fails to react with iron carbonyls to give the acetylenic derivative of XXIII (5).

The complex $(RC_2R')_2Fe(CO)_3$ has been isolated for R=R'=C_6H_5 (16) and R=R'=H (12). Structures XXV and XXVI have been proposed for the complex.

The diphenylacetylene derivative was isolated in low yield form the reaction of diphenylacetylene with iron dodecacarbonyl in an inert solvent at 80°-90°. This is a very stable compound, and it decomposes when caused to react with lithium aluminum hydride to give 1,2,3,4-tetraphenylbutadiene in 92% yield.

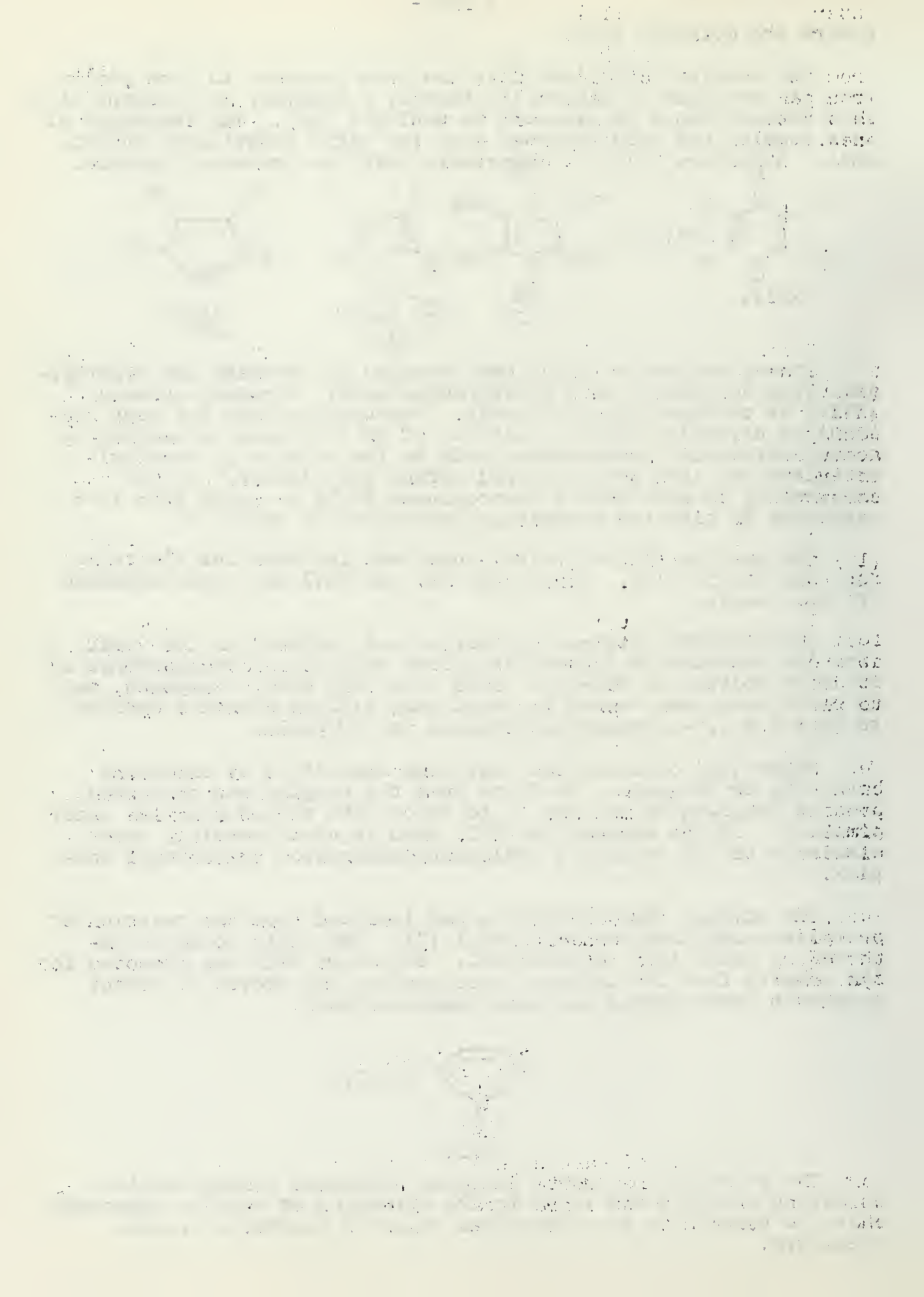
Reppe (12) obtained the acetylene derivative by oxidizing $FeC_{11}H_7O_5$ or $FeC_8H_4O_4$. He found that the complex was converted back to $FeC_8H_4O_4$ by causing it to react with carbon monoxide under pressure. If the complex is XXVI, then it could possibly react similarly to XIX to give a cyclopentadienoneiron tricarbonyl complex.

The complex $(RC_2R')_3Fe(CO)_4$ was isolated from the reaction of acetylene with iron dodecacarbonyl (7). The yield could be improved by using iron ennacarbonyl. Structure XXIV was proposed for the complex from its infrared spectrum and was proved by direct synthesis from tropone and iron dodecacarbonyl.



XXIV

The principle of carbon skeleton synthesis during complex formation offers a new route to the formation of organic compounds which is certain to have practical value in synthetic organic chemistry.



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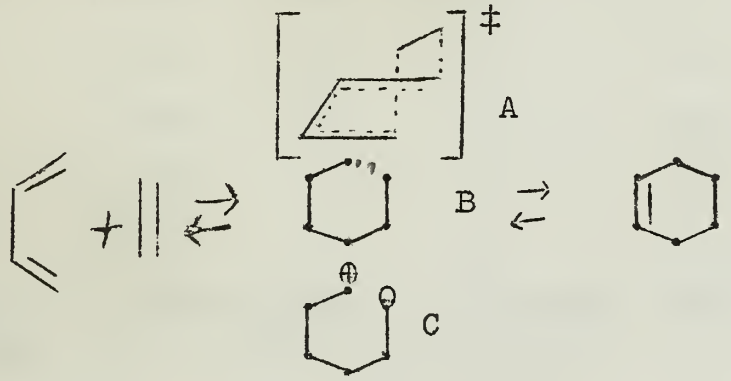
MECHANISM OF THE DIELS-ALDER REACTION

Reported by C. G. Carlson December 10, 1959

The synthetic versatility of the Diels-Alder reaction is demonstrated in several reviews[1-3]. This seminar deals with the mechanism of the reaction specifically involving the formation of carbon carbon bonds in order to reduce the number of parameters to be considered.

Essentially three mechanisms have been proposed.[4]

A. Concerted process, where both bonds form simultaneously in a parallel non-planar transition state.
B. Two step process, involving a biradical intermediate.
C. Two step process, involving an ionic "zwitterion" intermediate.

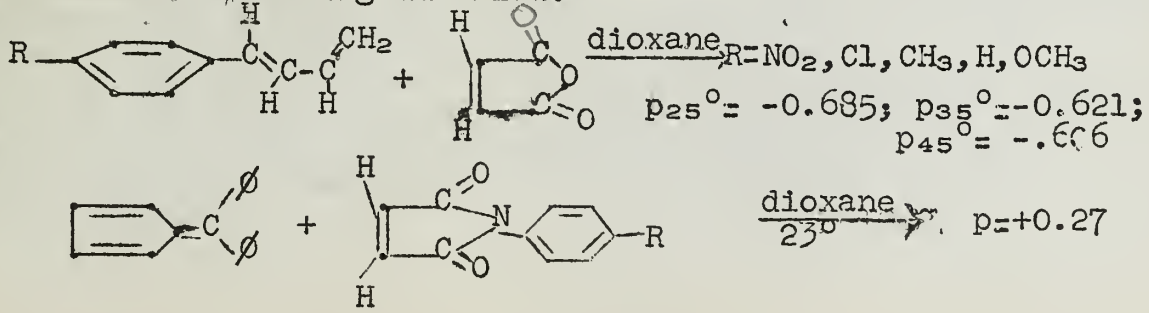


A variation of these processes has also been proposed[5] in which there is an initial electron transfer from diene to dienophile resulting in a dipolar ion pair intermediate which then reacts through one of the paths above.

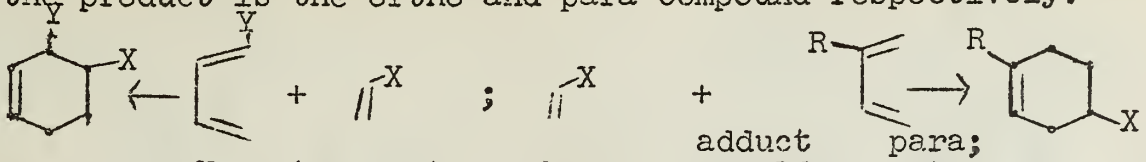
The mechanism involving the zwitterion intermediate is generally considered unlikely since solvent effects on the rate are slight and rates in solution and in the gas phase do not differ.[6]

	Forward reaction		Reverse reaction	
Solvent	$Log_{10}A_2$	E_{a2}	$Log_{10}A_1$	E_{a1}
Benzene	6.1 l/m-s.	16.4 k.cal/mole	$sec.^{-1}$	k.cal/mole
CS_2	5.7	17.7		
Paraffin	7.1	17.4	13.0	34.2
Gas	6.1	16.4	13.1	35

Also, Hammett plots made on both a diene[7] and dienophile[8] do not indicate appreciable charge separation in the transition state relative to the starting material.



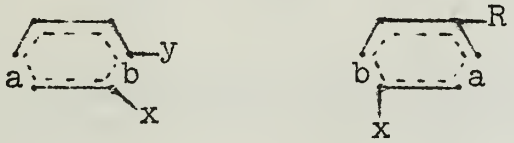
From the reactions of monosubstituted olefins with 1- and 2-substituted -1,3-butadienes, the position isomer predominating in the product is the ortho and para compound respectively.[9]



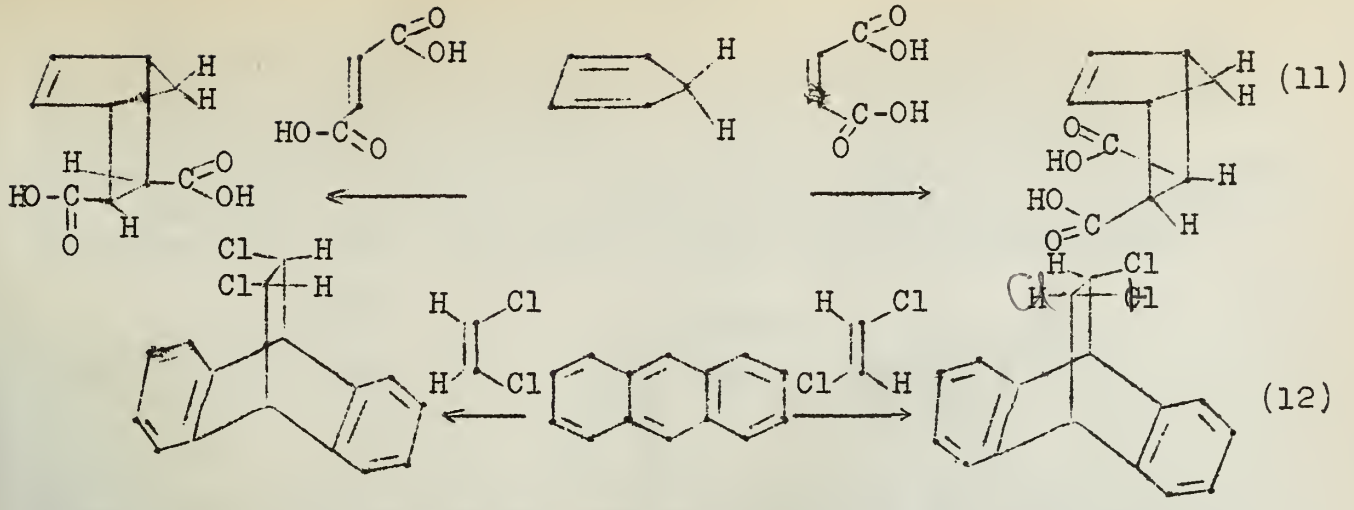
R	X	temperature	hours	adduct yield	para; meta
CH_3	C(=O)-OH	200°	2	80%	1.9:1
∅	C(=O)-OCH_3	150°	5	73	4.5:1
CH_3O	C(=O)-OH	150°	10	72	8:1
Cl	C(=O)-OH	150°	5	83	9.3:1
CH_3	∅	200°	10	31	3.5:1
∅	∅	150°	50	54	only para
CH_3O	∅	150°	10	59	12:1
Cl	∅	150°	12	20	14.3:1

Y	X	adduct yield	ortho-meta	ortho-cis:ortho-trans
∅	C(=O)-OH	61%	39:1	8:1
∅	∅	33	8.1:1	--
C(=O)-OH	C(=O)-OH	86	8.8:1	8.6:1
C(=O)-OH	∅	58	5.7:1	17:1

The position isomer distribution in the product can be explained by both the biradical mechanism and the concerted mechanism by a consideration of the resonance forms of the transition states. In the concerted process, the two new bonds need not be formed to the same degree. The bond order of a would be larger than b.



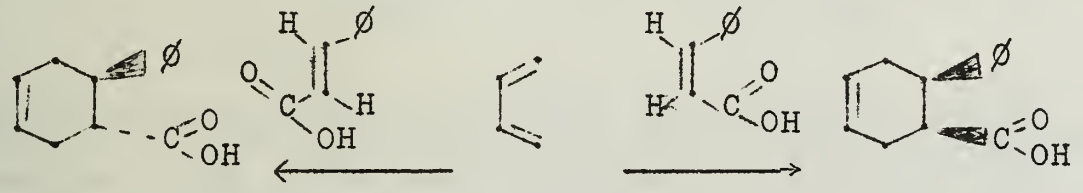
The biradical mechanism seems unlikely from a consideration of the stereochemistry of the products. The adduct stereochemistry can be predicted from three general observations of previous reactions.[10] The diene assumes a cisoid conformation, and addition is cis with respect to both diene and dienophile. The reaction product predominating is the one resulting from the transition state which has the greatest accumulation of unsaturated centers. These generalizations are shown in the following reactions.



(11)

(12)

Retention of configuration of the dienophile would be inconsistent with an open chain biradical, but might be explained if the conformation of the biradical was held until the second bond formed, by 1) a fast cyclization with insufficient time for rotation, and 2) interaction forces between unsaturated centers. However, one would not expect these factors to be large enough to explain the retention of configuration in reactions with open chain dienes.



(13)

From these considerations, the concerted mechanism seems the most favorable. A smooth merging of the concerted process and the biradical mechanism may be disallowed on considerations of the electron spins. The low frequency factor in the forward reaction cannot be explained[14] by a change in spin multiplicity in the transition state resulting in a low transmission coefficient, since the frequency factor of the reverse reaction is normal.

The effect of pressure on a reaction rate can be predicted from the equation

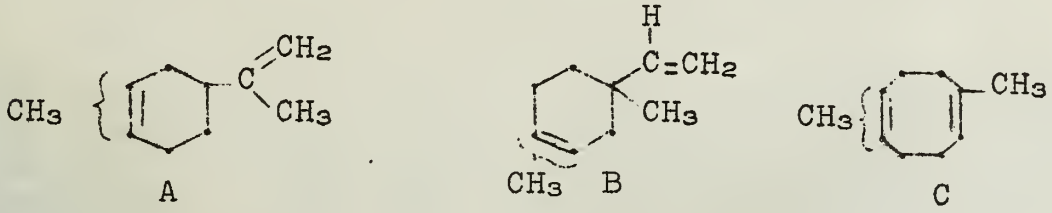
$$\frac{d(\log k)}{dp} = -\Delta V^{\ddagger}/RT \cdot \quad \Delta V^{\ddagger} = V^{\ddagger} - V \text{ starting material}$$ [15]

The dimerization of cyclopentadiene was studied[16] at moderate temperatures, and pressures up to 5000 atmospheres.

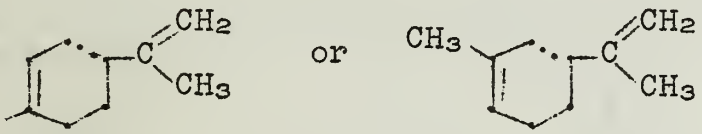
Pressure (atm.)	1	500	1000	2000	2500	3000	3500	4000
Ea(k cal/ mole)	17.0	17.35	17.65	18.25	18.4	18.6	18.8	18.85
$\log_{10}A_2$ (l/m-s)	6.4	6.92	7.37	8.18	8.50	8.81	9.13	9.32

The volume of activation is -20 c.c./mole, compared with an overall volume change of -31.6 c.c./mole.

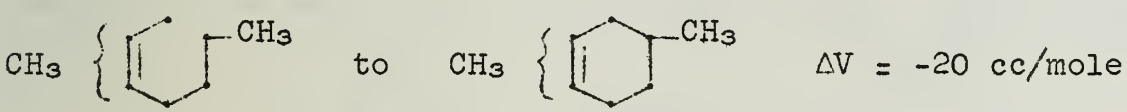
More recently, the dimerization of isoprene was studied[17] at 60° and 75° and pressures up to 7,760 atmospheres, with good second order kinetics throughout. The volume of activation was calculated to be -24.3 and -25.6 c.c./mole and the overall volume change -45.5 and -48.7 c.c./mole at 60° and 75° respectively. From previous work six products were expected, which were separated into three fractions by vapor phase chromatography.

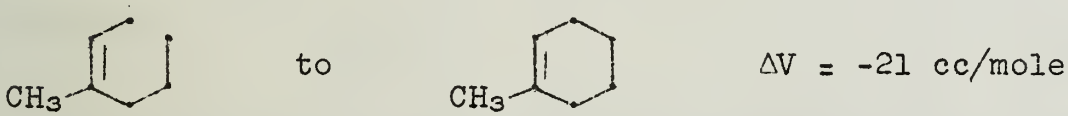


It was felt that the volume change going from the transition state to the product, -21 and -23 c.c./mole, was too large for a concerted transition state, and could be better explained by a biradical intermediate. Since the major products were in fraction A, the biradical leading to them would be



Comparison of some open chain olefins which resemble the biradical, with their cyclic analogues shows a striking similarity between the volume difference going from transition state to product and the differences in the molar volumes between the open chain and cyclic olefins.





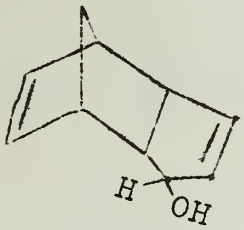
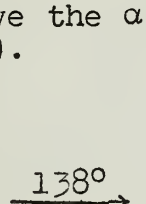
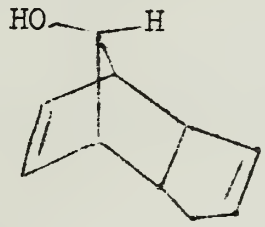
However, the volume of activation is not due only to molecular volumes, but also due to substrate-solvent interaction. Similar work done on the decomposition of di-t-butylperoxide[18] shows that the volume of activation obtained varies with the solvent used. Also, the open chain olefins used for comparison with the biradical are in a random conformation. If the biradical is taken to be in a similar conformation, then the retention of configuration in Diels-Alder reactions would not be observed. The following kinetic results[19] are interesting in this connection.

Addends	Ea kcal/mole
1) butadiene + quinone	14.5 ± 0.06
2) cyclopentadiene + quinone	11.6
3) butadiene + butadiene	23.7
4) cyclopentadiene + cyclopentadiene	16.4

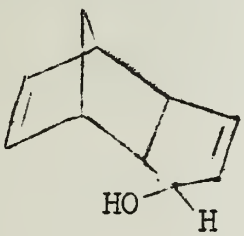
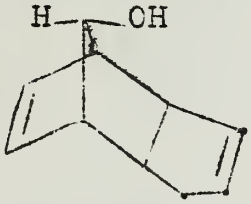
$E_1 - E_2 = 2.9 \pm 1.2$; $E_3 - E_4 = 7.0 \pm 1.1$

The differences in activation energy compare qualitatively with the energy required for the trans diene to rotate to the cis diene (2.3 kcals.). The assumption necessary to make the second case comparable is that both butadiene molecules are cisoid in reaction 3, in order to get maximum accumulation of unsaturated centers.

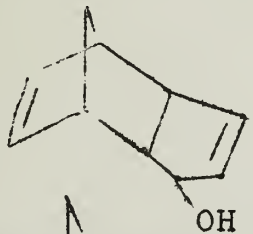
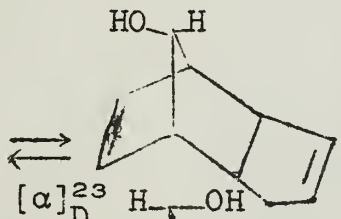
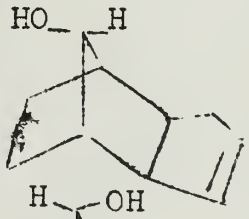
Recently, a set of completely stereospecific isomerizations of α and β-1-hydroxydicyclopentadiene were studied.[20] When α-1-hydroxydicyclopentadiene was heated for 6 hours at 138°, syn-8-hydroxydicyclopentadiene was obtained. Under the same conditions the syn-8-hydroxy compound gave the α-1-hydroxy compound in the same equilibrium mixture (1:1).

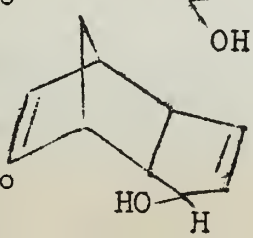
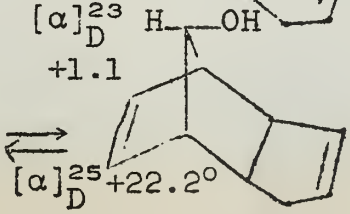
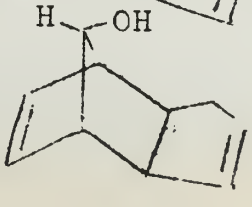
α-1-hydroxy    syn-8-hydroxy

Similarly, the β-1-hydroxy compound yielded the anti-8-hydroxy compound, the equilibrium in this case was far to the right.

β-1-hydroxy    anti-8-hydroxy

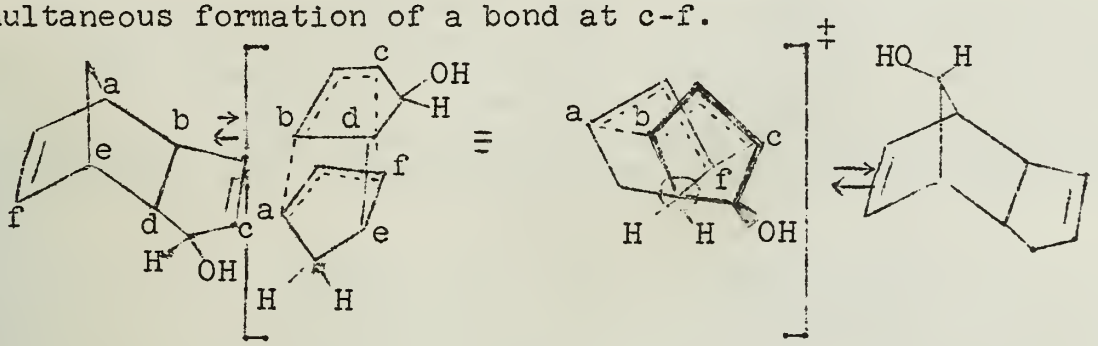
In order to rule out a mechanism in which the hydroxydicyclopentadiene dissociates into cyclopentadiene and hydroxycyclopentadiene followed by selective recombination within a medium cage, the α and β isomers were resolved, and the optical isomers were subjected to the usual conditions. In both cases studied, the isomerizations occurred with optical integrity being maintained.

$[\alpha]_D^{24}$ -87°   $[\alpha]_D^{23}$ +1.1 and not 

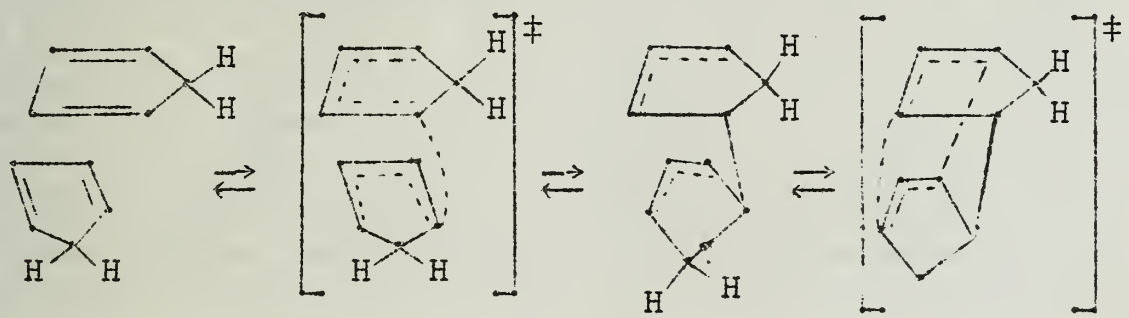
$[\alpha]_D^{25}$ +130°   $[\alpha]_D^{25}$ +22.2° and not 

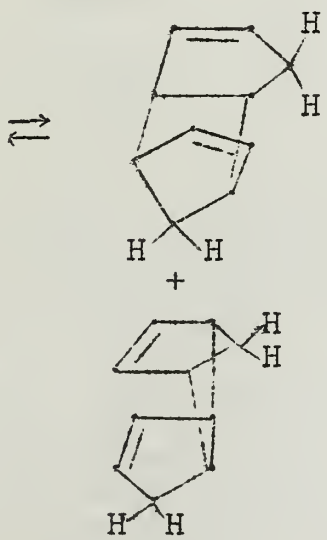
The infrared spectra of the optical isomers were superimposable with those of the racemic mixtures, the absolute configurations are not known, and the product configuration is that expected from the mechanism, and may be the enantiomorphs of the structures indicated.

A concerted process similar to the Cope rearrangement was proposed for these reactions, where bond a-b breaks with the simultaneous formation of a bond at c-f.



Since the isomerization of a dicyclopentadiene skelton had been demonstrated to take place without complete scission of both bonds a-b and d-e it was asserted that the formation of these bonds in the Diels-Alder reaction must take place in two discreet steps, and thus the Diels-Alder reaction is a two stage process. This conclusion led to the proposal of a generalized mechanism demonstrated here by the dimerization of cyclopentadiene.

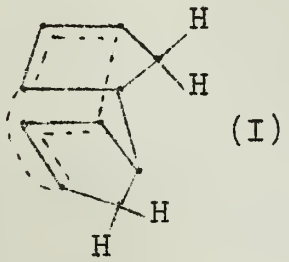




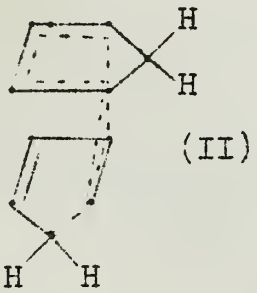
However, the relevance of the adduct isomerization to the Diels-Alder reaction can be questioned.[21] The isomerization was represented as going through a concerted process, therefore the transition state for this process cannot participate in the

reverse Diels-Alder reaction. The only way that the two reactions could be related would be if the isomerization went through a reactive intermediate which could then yield either the adduct or retrogress to the addends. By analogy to related reactions such as the Cope rearrangement, there is no reason to assume a reactive intermediate rather than a concerted process involving one transition state, in the isomerization.

It was later maintained[22] that the isomerization involving the breaking of one bond (a-b) must be related to the reverse Diels-Alder reaction which involves breaking the same bond and one other (a-b and d-e). However, there could be two different competing concerted reactions, the activation energy for the retrogression (II) being greater than that of the isomerization (I).

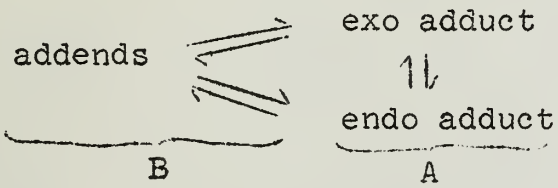


(I)



(II)

Another type of reaction studied is the endo-exo isomerism of Diels-Alder adducts formed from a homocyclic diene and a cis disubstituted olefin. In the case of furan and maleic anhydride, as predicted by the relative overlap of unsaturated centers in the transition states the endo isomer will predominate. However, at a higher reaction temperature or a longer reaction time, the initially minor exo isomer will accumulate at the expense of the endo isomer.[23] Isolated exo isomer can also to a lesser degree yield the endo product. Two routes have been proposed for the isomerizations which can be represented as preferred paths in the following cyclic equilibrium system.



In one case (B)[24] the adducts retrogress to addends which recombine at the higher temperature to give an equilibrium controlled mixture, rather than the original rate controlled mixture. The second path (A)[25] is one where the adducts can isomerize without breaking up into free addends.

It has been demonstrated that the endo adduct from cyclopentadiene and maleic anhydride isomerizes to the exo compound partially by path A.[26] An equimolar mixture of C_{14} labelled endo adduct and unlabelled maleic anhydride were reacted in decalin at 190°. Using a graphical interpolation method (making the assumption that the exo adduct does not exchange, as was shown by a separate experiment) the amount of activity expected in the exo adduct from path A or B alone was calculated.

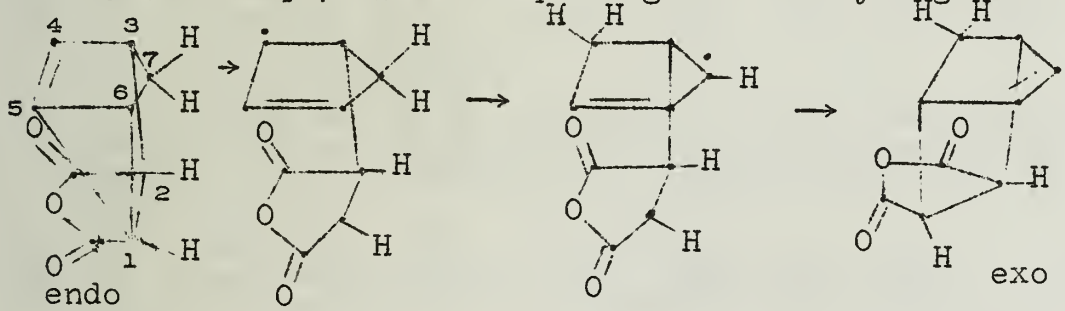
	Reaction time	Counts per minute original endo	αA	αB	αt (observed)
(a)	10 minutes	3017	2340 ± 100	640 ± 40	1600 ± 100
(b)	7	2981	2410 ± 60	540 ± 40	900 ± 70
(c)	7	3003	2480 ± 60	560 ± 40	1100 ± 80

The fraction (A) of exo isomer formed by the internal path is given by the equation

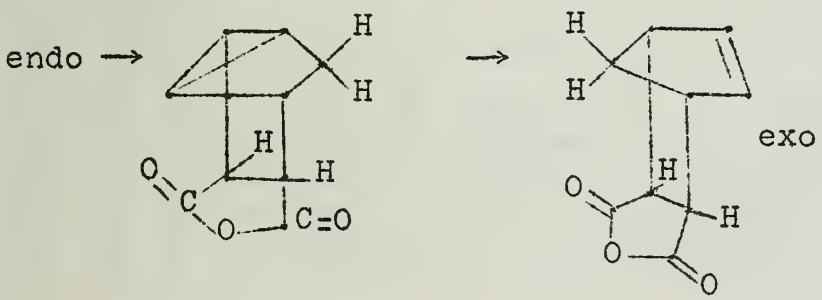
$$A(\alpha A) + (1-A)\alpha B = \alpha t.$$

For runs (a) and (c) A = 0.5 ± 0.07 and 0.3 ± 0.05 respectively.

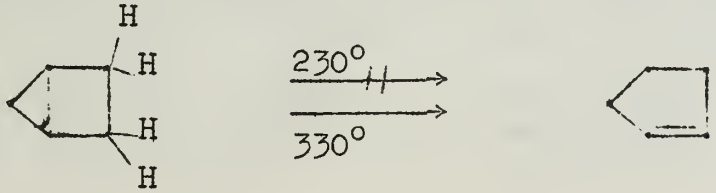
The best description rendered for the internal path is retrogression to addends which undergo a primary recombination. A mechanism proposed previously[25], whereby there is homolytic cleavage of the C_1C_8 bond, a hydrogen shift from C_7 to C_4 and establishment of a bond between C_1 and C_5, was considered unlikely because resonance would flatten the cyclopentenyl ring and make the C_4C_7 distance quite great for hydrogen abstraction.



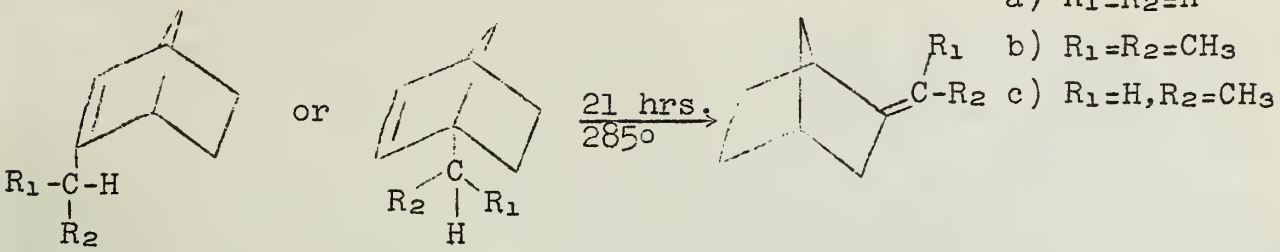
An interesting possibility is that the reaction may go through a bridged intermediate formed in a manner similar to the hydroxydicyclopentadiene isomerism.



This scheme cannot be ruled out since it has the advantage that the analogous unsubstituted bicyclo compound undergoes the same type of reaction,[27] but the high temperature required makes it unlikely.



The latter reaction, however, may be relevant to the following recent observations.[28]



a) $R_1=R_2=H$
b) $R_1=R_2=CH_3$
c) $R_1=H, R_2=CH_3$

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ALKALOIDS OF LUNASIA

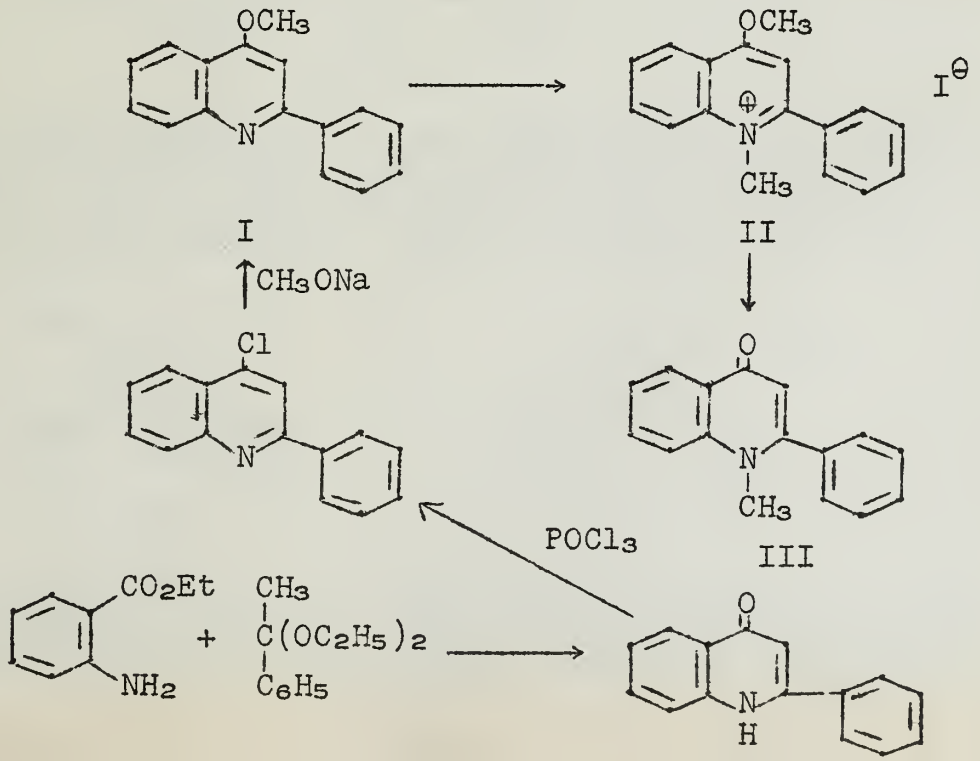
Reported by Miss Y. Chang December 14, 1959

Since the end of the nineteenth century, it has been known that several physiologically active alkaloids were present in the genus Lunasia (Rutaceae family). Several groups of workers had succeeded in isolating some of them, but structural studies have been carried out only in the recent years. For a summary of the earlier work and physiological study, one is referred to an article by Steldt and Chen.[1] For a general review of this group of alkaloids, and related alkaloids of other genera in the Rutaceae family, one is referred to an article by Price.[2] A summary of the latest work was written by Beyerman and Rooda.[3]

Different groups of workers isolated different numbers of alkaloids. According to Beyerman and Rooda[3] six alkaloids were isolated from the bark of Lunasia amara and according to Goodwin, Smith and Horning[4] seven components were isolated from the leaves of Lunasia amara by chromatography on alumina. Up to the present time, the structures of the following alkaloids have been identified.

4-Methoxy-2-phenylquinoline[4]

The first compound eluted from the column, $C_{16}H_{13}NO$, formed colorless, optically inactive needles, m.p. 66-67°. This alkaloid formed a hydrochloride salt which melted at 148-151° with gas evolution; the colorless melt solidified on cooling and thereafter melted at 240-243°. This suggested a thermal demethylation which has been known to yield either 2- or 4-quinolones. A preparative pyrolysis of the alkaloid hydrochloride gave good yield of the high melting product, m.p. 256-258°, which was identical with synthetic 2-phenyl-4-quinolone. When this alkaloid was heated with methyl iodide at 100° in a sealed tube, it gave a compound $C_{17}H_{16}NOI$(II), which under the action of dilute sodium hydroxide gave N-methyl-2-phenyl-4-quinolone (III). Thus, the alkaloid was assigned the structure I, which was proved by synthesis as follows:



7-Methoxy-1-methyl-2-phenylquinolone[5,6]

This alkaloid was isolated from L. quercifolia, a species which occurs in Australia. The identification was carried out in the following way.

Analysis showed the empirical formula, $C_{17}H_{15}NO_2$, with one methoxyl group and one N-methyl group. Demethylation gave a phenol from which the alkaloid could be regenerated. The infrared spectrum showed a band at 1618 cm.$^{-1}$, but the alkaloid was inert toward carbonyl reagents. Lithium aluminum hydride reduction gave a dihydro compound, $C_{17}H_{17}NO_2$, thus ruling out the possibility of an amido grouping which would take up two hydrogen atoms with the loss of one oxygen atom. The infrared spectrum of the dihydro compound showed no O-H stretching and still showed a carbonyl band. Its ultraviolet spectrum (Figure 1) was consistent with a 4-quinolone and different from that characteristic of a 2-quinolone. The latter shows three outstanding characteristic peaks; one of which, 270-285 mμ is either absent or appears as a shoulder in the spectrum of 4-quinolones. The hydrochloride salt of this alkaloid was not demethylated by heating up to 250°, thus showing that the methoxyl group was not located at the 4-position.

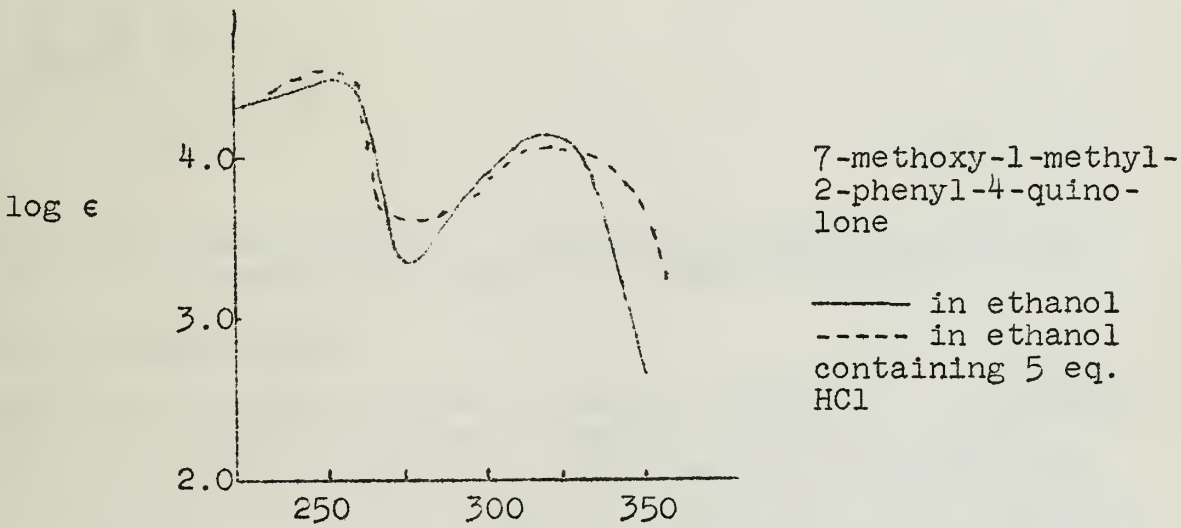
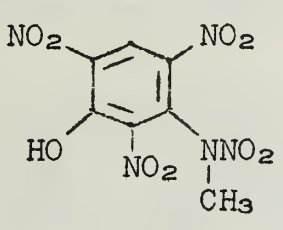
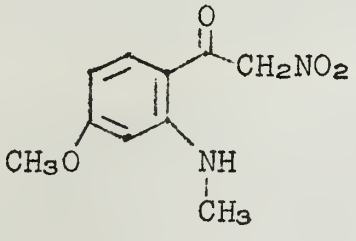


Figure 1

The position of the methoxyl group was established by boiling the alkaloid with 68% nitric acid. 3-Hydroxy-2,4,6-trinitrophenyl methyl nitramine (IV) was isolated in the mixture of benzoic acid and mono- and dinitro compounds. Thus, it was shown that the

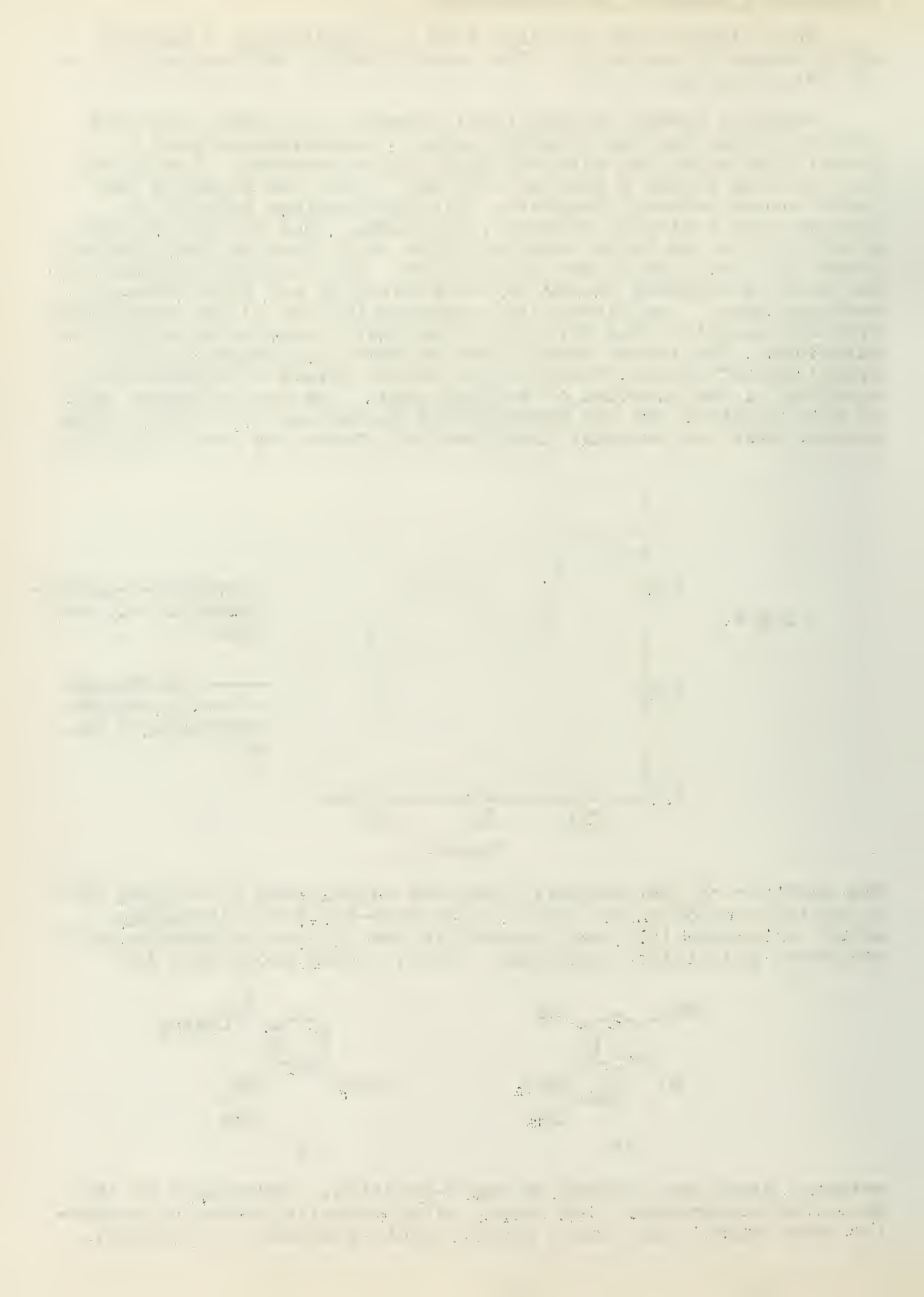


IV

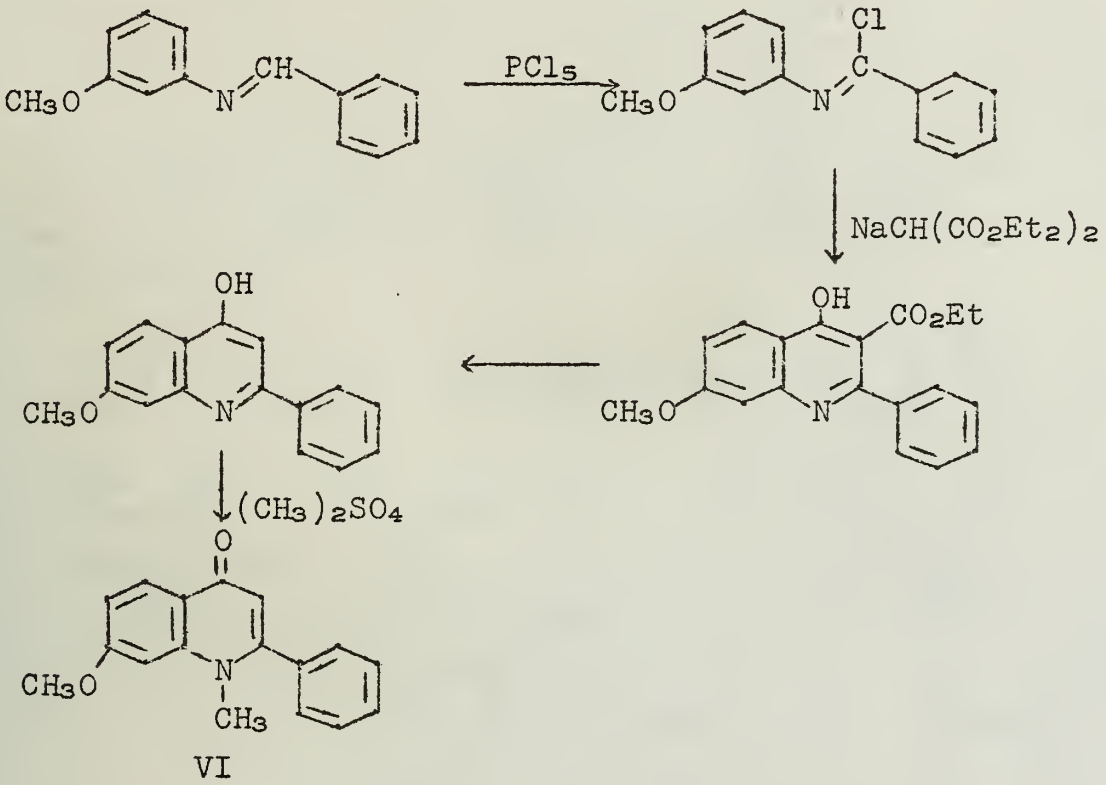


V

methoxyl group was located at the 7-position. Hydrolysis of the mononitro derivative, $C_{17}H_{14}N_2O_4$, with ethanolic potassium hydroxide gave benzoic acid and a yellow acidic substance, $C_{10}H_{12}N_2O_4$,



evidently 4-methoxy-2-methylamino-ω-nitroacetophenone (V). On this basis the 2-position for the phenyl group and structure VI for the alkaloid were established. The above conclusion was fortified by the synthesis:[8]



VI

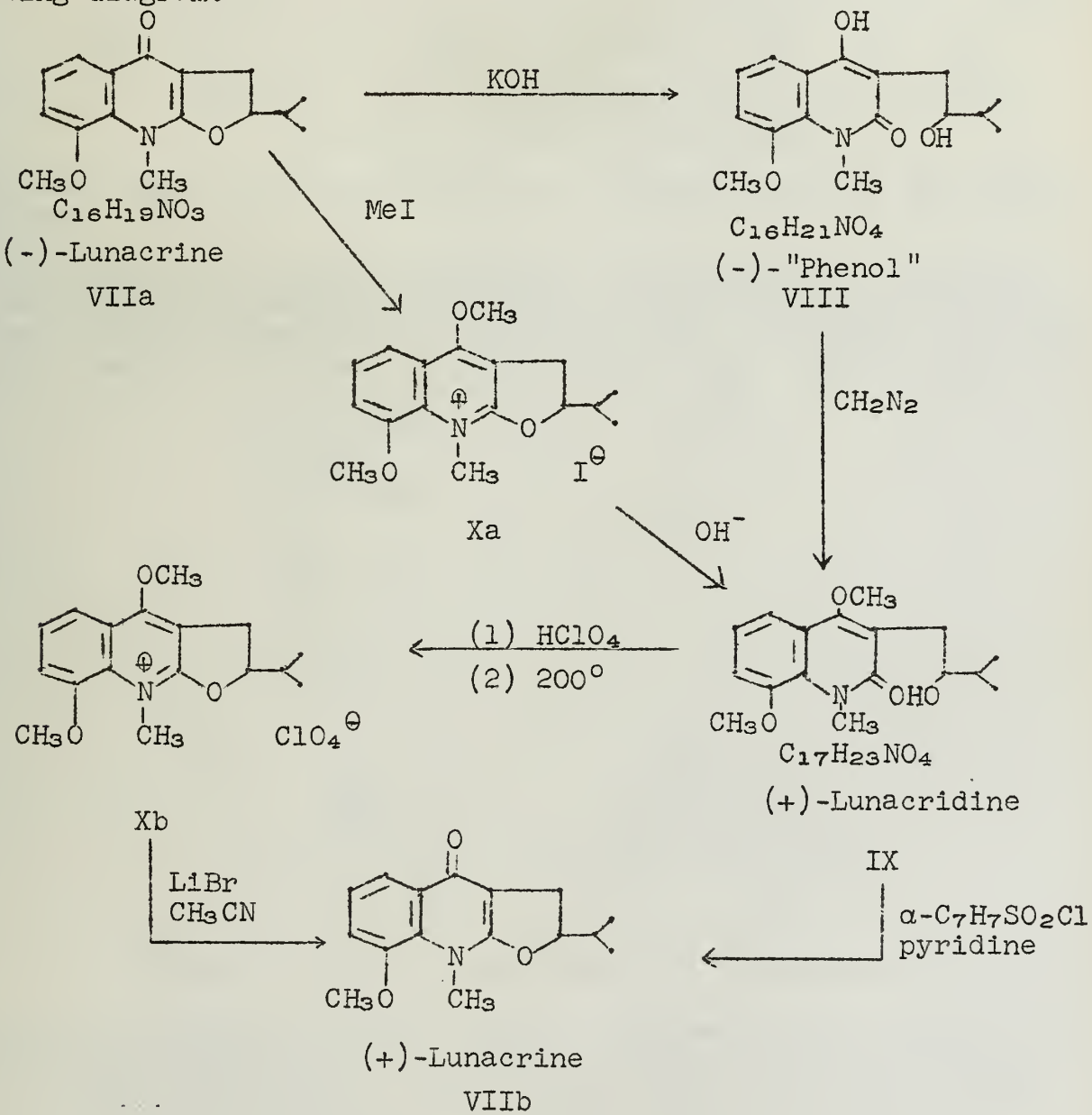
An alkaloid named edulcin,[6] isolated from Casuiminoa edulis Llave et Lex (Rutaceae) was shown to be identical with VI.

Lunacrine and Lunacridine[9]

These two alkaloids are very closely related;[10,11] therefore, they will be discussed together. Lunacrine, $C_{16}H_{19}NO_3$, m.p. 117-119°, $[\alpha]_D$ -50.4°, is the main constituent of the alkaloids isolated from the leaves of L. amara and the barks of L. costulate Miq. It was reported to have one methoxyl group, one N-methyl group and one gem-dimethyl group. It was not reduced catalytically. The ultraviolet spectrum in alcohol was not affected by base, but a marked change occurred on acidification, the long wave length bands (313 and 326 mμ) exhibiting a hypsochromic shift (300 mμ). This recalled the behavior of 1-methyl-2-phenyl-4-quinolone (III) and eliminated the quinoline structure, whose ultraviolet absorption mixima exhibit a bathochromic shift in acid solution.

The natural levorotatory lunacrine was converted by slow reaction with alkali to a levorotatory phenol, $C_{16}H_{21}NO_4$, showing an O-H stretching band at 3310 cm^{-1} and 2-quinolone absorption at 1638 cm^{-1} in infrared spectrum. Methylation of the phenol gave a non-crystallizable oil, $C_{17}H_{23}NO_4$, which formed a crystalline perchlorate. A crystalline free base, $C_{17}H_{23}NO_4$, m.p. 87°, $[\alpha]_D$ +28.1, was obtained from the perchlorate quantitatively, and was found to be identical with lunacridine. Treatment of the dextrorotatory lunacridine with α-toluenesulfonyl chloride in pyridine

gave a crystalline substance, m.p. 118-120°, which was identical with lunacrine in infrared and ultraviolet spectra, but mixed melting point with the natural alkaloid was elevated to 143-145°; the product converted from lunacridine was reported dextrorotatory $[\alpha]_D$ +56°. From the above transformation it is evident that lunacrine has either a furano or a pyrano system fused to the quinolone ring. By analogy with the methoxyfuroquinoline alkaloids, which abound in plants of the Rutaceae family, the oxygen-containing ring was assumed to be five-membered, and hydrofuran rather than furan was suggested in accordance with the empirical formula and the resistance toward hydrogenation. This assignment was confirmed by nuclear magnetic resonance study (see below). The relationship of lunacrine and lunacridine can be summarized in the following diagram.



The position of the methoxyl group and the isopropyl side-chain were established by the nuclear magnetic resonance spectrum.[12] The nuclear magnetic resonance spectrum of lunacrine has seven groups of bands as shown in Figure 2. Based upon the chemical shift, a and b were assigned to the aromatic hydrogens, c and e to the α- and β- hydrogens of the dihydrofuran ring respectively, d to

the N-methyl and O-methyl groups and f and g to the side-chain hydrogens. The total integrated intensities of these groups were

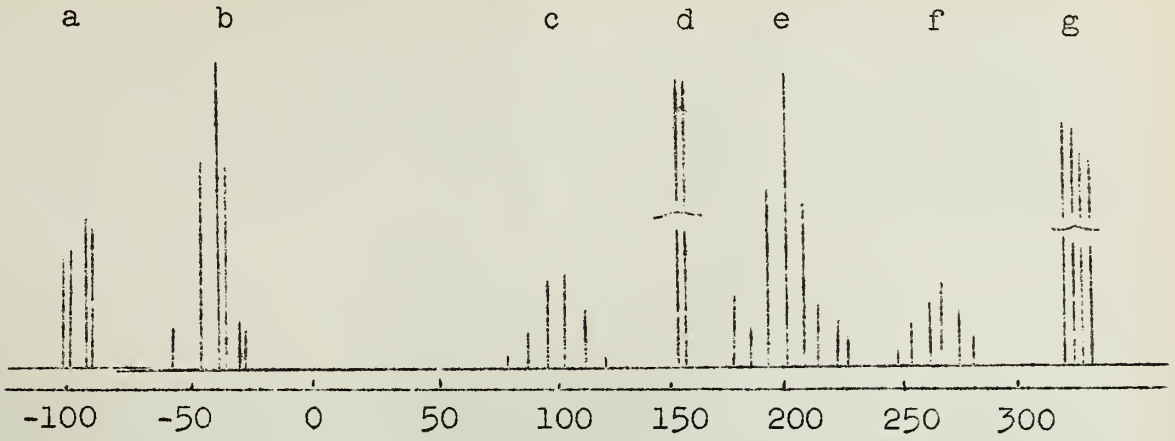
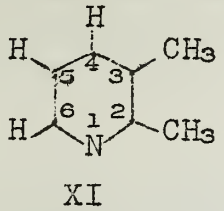


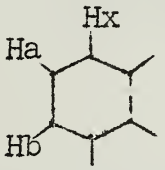
Figure 2. N.M.R. Spectrum of Lunacrine in $CDCl_3$, at 60 mc., Benzene as Referance

found to be a:b:c:d:e:f:g=1:2:1:6:2:1:6, consistent with the above assignment.

From group a, a quartet, andgroup b, a triplet and a quartet, three adjacent hydrogen atoms ABX were assigned based on a study of a very similar compound 2,3-lutidine[13] (XI), which has a nuclear magnetic resonance spectrum as shown in Figure 3. Group a was



XI



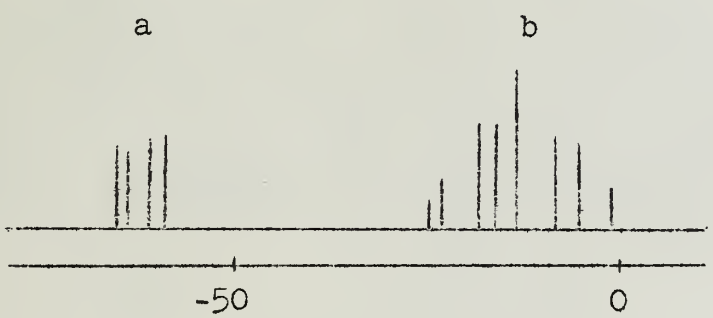
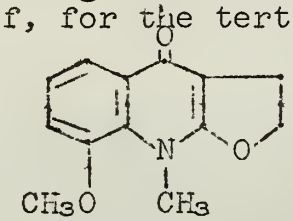


Figure 3. N.M.R. Spectrum of 2,3-Lutidine at 40 mc.

assigned for hydrogen at the 6-position because of the chemical shift and spin-spin coupling. Group b was assigned to hydrogens at the 4- and 5-positions. Since groups a and b in Figure 2 are similar to those of Figure 3, and group a which could be interpreted as first coupled by its α-hydrogen H_A into two lines 9 c.p.s. apart and each again coupled by the β-hydrogen H_B into two doublets with spacing 2 c.p.s.; H_A showed a triplet because $J_{AX}=J_{AB}$, and for the same reason as H_X, H_B showed a quartet. This ruled out the 6- and 7-positions for the methoxyl group. (The 7-position

of VIII

was also ruled out by comparison of the ultraviolet spectrum/with that of 3-ethyl-4-hydroxy-7-methoxy-1-methylcarbostyril[9]). From the chemical shift of group a, -100 c.p.s., a hydrogen atom was assigned to the 5-position to account for the effect of the carbonyl group and methoxyl group at 8-position. The above assignment was confirmed by comparison of the nuclear magnetic resonance spectrum of the dihydro-isofagarine (XII) which showed the same a and b groups. Multiplet c agreed well with one hydrogen atom on the side-chain, and group f, for the tertiary hydrogen of the iso-



XII

propyl side-chain, would be expected to have 14 lines. However, both coupling constants were found to be 7 c.p.s., then an eight line pattern with intensity 1:7:21:35:35:21:7:1 would be expected in theory, although in practice the weak lines would probably be lost in noise. Group g displayed the predicted doublet with a 7 c.p.s. spacing, but in addition each line of the doublet was further split into two lines 3 c.p.s. apart. This could be explained by considering the rotational conformations of the iso-propyl group about the bond joining it to the ring. Due to the lack of symmetry, it was suggested[14] the residence time in the three conformations can differ slightly and that as a result the magnetic environments of the methyl groups would not be identical. A spectrum was obtained at 40 mc. for a check and as expected the doubling of the lines in group g diminished to 2 c.p.s.

Lunine[12]

Lunine was reported to have an empirical formula $C_{16}H_{17}NO_4$, one N-methyl group, and no methoxyl group. In comparison with the empirical formula of lunacrine, $C_{16}H_{19}NO_3$, there are two hydrogen atoms less and one oxygen atom more. Lunine gave positive color tests for the methylenedioxy group. The nuclear magnetic resonance spectrum of lunine as shown in Figure 4 had identical groups c,e,f, and g, with only one peak of d in accordance with the N-methyl group. A new signal at +23 c.p.s. with the proper chemical shift, relative intensity and the lack of fine structure was assigned to methylenedioxy group. In agreement with the 7,8-methylenedioxy grouping, multiples a and b showed only doublets, with spacing at

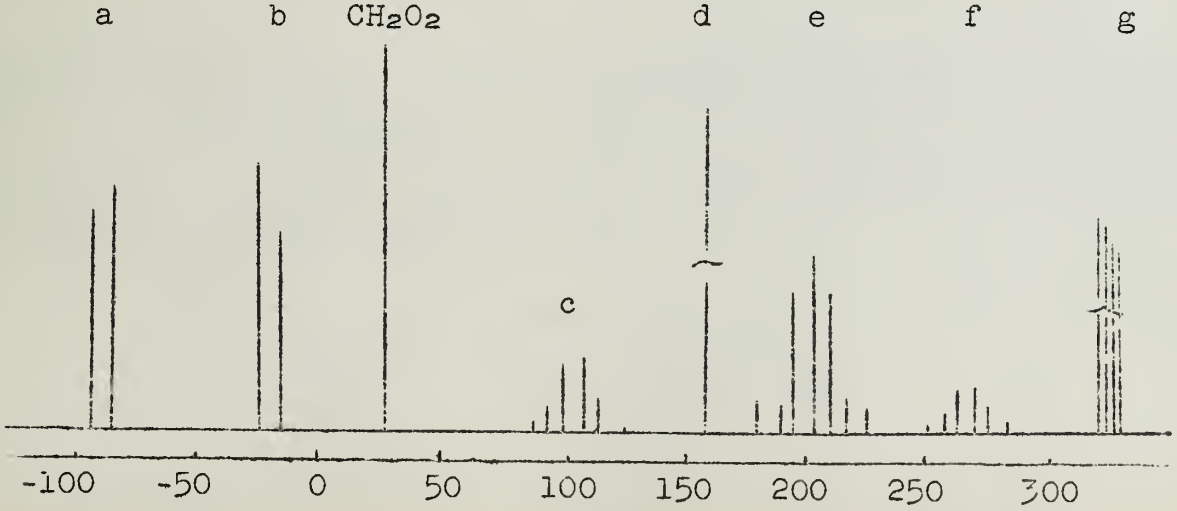
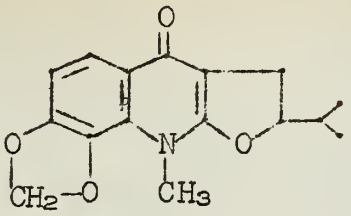


Figure 4. N. M. R. Spectrum of Lunine in $CDCl_3$ (60 mc.)

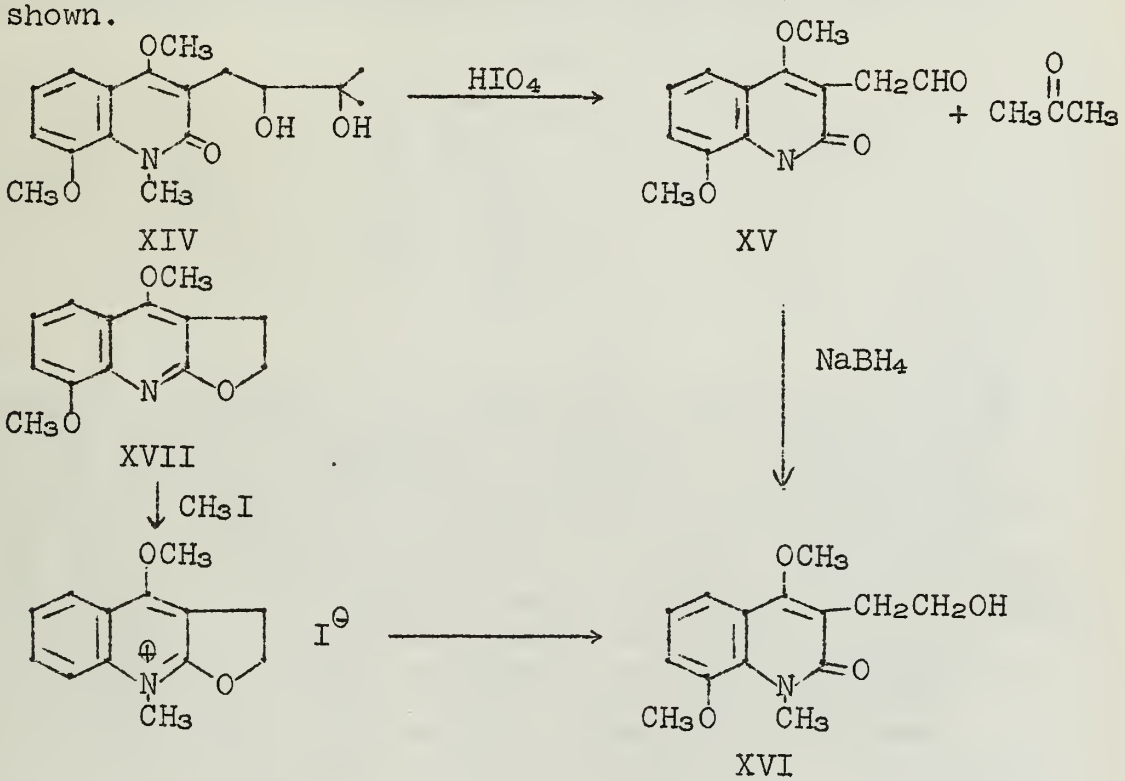
9 c.p.s. From the above evidence, lunine was assigned structure XIII.



XIII

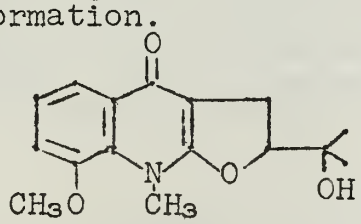
Hydroxylunacridine[15]

Hydroxylunacridine, $C_{17}H_{23}NO_5$, m.p. 100-102°, $[\alpha]_D^{24}$ +31.5°, was reported to have one more oxygen atom than lunacridine, one N-methyl group and two methoxy groups. Its ultraviolet absorption spectrum was identical with that of lunacridine, indicating the 4,8-dimethoxy-1-methyl-3-alkyl-2-quinolone system. The alkaloid was reported to have two active hydrogens. Periodic acid oxidation gave acetone and an aldehyde XV which was reduced to an alcohol XVI. The latter was identified by reduction of dihydro-γ-fagarine (XVII) as shown.



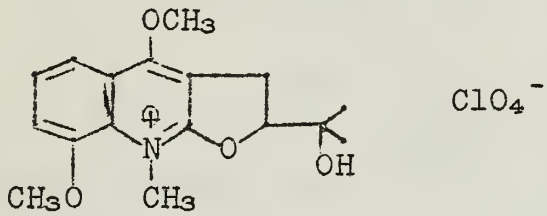
XIV XV XVII XVI

An alkaloid named balfourolone[16], $C_{17}H_{23}NO_5$, m.p. 99-100°, $[\alpha]_D$ -36°, was isolated from Balfourodendron riedilianum, another member of the Rutaceae family. A structure study gave the same result as hydroxylunacridine, but with inversion at the optically active center. Another alkaloid isolated, balfourodine, $C_{16}H_{19}NO_4$, m.p. 188-189°, $[\alpha]_D$ +49° was assigned structure XVIII by analogy of lunacridine-lunacrine transformation.



XVIII

It was suggested that lunacridine was not present in the alkaloid as given by formula IX, but as a quarternary ammonium salt[10] with the cation formulated as X, which underwent ring opening during basification. This was found to be true by the isolation of lunasine picrate,[17] $C_{17}H_{22}NO_3^+C_6H_2N_3O_7^-$, from the aqueous portion after the extraction of bases. It was found identical with the methyl lunacrinium salts from methylation of lunacrine. This was also tested by Rapoport and Holden[16] on balfourolone. They observed that balfourolone was shown to have a distribution coefficient between ether and water which is largely in favor of ether and independent of the pH of the aqueous phase. But during the isolation procedure, no balfourolone was found in the ether extracts when the aqueous phase was extracted with ether at pH 2 and 7, and balfourolone was the only product isolated from the ether extract at pH 10. If the aqueous solution, after being extracted with ether at pH 7, was made 4 M in chloride ion by sodium chloride, extraction with butanol gave a residue which showed an ultraviolet spectrum characteristic of structure X. Addition of perchloric acid gave O^4-methylbalfourodinium perchlorate (XIX), which under mildly basic condition (pH 10) gave balfourolone in good yield.



XIX

Lunamarine[1]

An alkaloid, $C_{18}H_{15}NO_4$, m.p. 230-233°, optically inactive, was isolated by Beyerman and Rooda[3] who named it Lunasia I; it is possibly the same as lunamarine, $C_{18}H_{15}NO_4$, m.p. 245-246°, optically inactive, which was isolated by Steldt and Chen[1], and as "lunacridine," $C_{18}H_{15}NO_4$, m.p. 231°, which was isolated by Dieterle and Beyl.[11] Analysis showed one methoxyl group and one N-methyl group. It gave a positive methylenedioxy test. By means of its resemblance with two other alkaloids in this group, 4-methoxy-2-phenylquinoline and 7-methoxy-1-methyl-2-phenylquinolone, in low hydrogen content, it was tentatively assigned a 1-methyl-2-phenylquinoline (or 1-methyl-2-phenyl-4-quinolone) structure, with an addition of a methoxyl group and a methylenedioxy group.

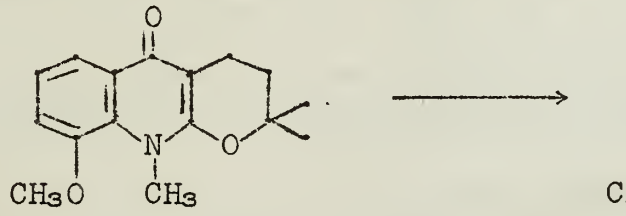
Lunasia III[3]

An alkaloid, with the same empirical formula as lunacridine, $C_{17}H_{23}NO_4$, was isolated. The ultraviolet spectra of the two are very similar, but they not only differ in melting point, 107-109° vs. 79-81°, optical activity, inactive vs. +30°, but also in infrared spectra. The O-H stretching of lunacridine was absent in the spectrum of this alkaloid. Due to the small amount obtained, the detail of the structure is not yet known.

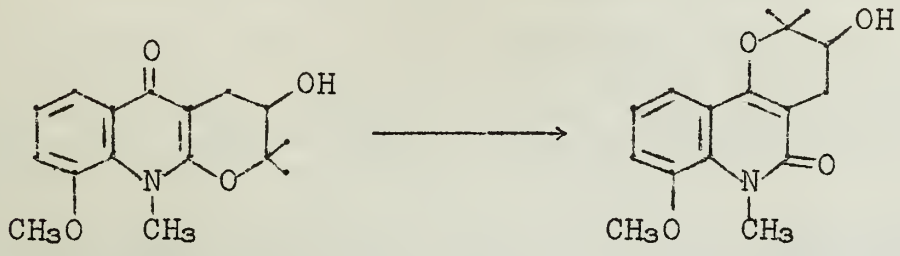
Lunasia II[3]

Lunasia II, $C_{16}H_{19}NO_4$, m.p. 201-203°, $[\alpha]_D$ -14°, has the same empirical formula as balfourodine, and a similar ultraviolet

absorption spectrum, but differs in infrared spectrum and optical activity. While heating with 30% sodium hydroxide, it was converted to an isomer which was less soluble in dilute acid. By comparison of the infrared spectra of the alkaloid and its isomer with that of linear dihydropyranoquinolone (XX) and its angular isomer (XXI), lunasia II and its isomer were assigned structure XXII and XXIII.



XX XXI



XXII XXIII

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STEREOCHEMISTRY OF KETONIZATION-ENOLIZATION REACTIONS

Reported by M. J. Konz December 17, 1959

Investigation of rates on acid and base catalyzed bromination, iodination, deuterium exchange and racemization of simple ketones has revealed that the rates are dependent on ketone and acid or base concentration and independent of bromine concentration (1,2,3). This has led to the proposed mechanism that the enol and enolate are the reacting species in acid (equation 1) and base (equation 2) catalyzed reactions, respectively.

Equation 1: $H\text{-}\overset{|}{C}\text{-}\overset{|}{C}\text{=}O + HB \rightleftharpoons H\text{-}\overset{|}{C}\text{-}\overset{|}{C}\text{=}O^{\oplus}H + B \rightleftharpoons B + H\text{-}\overset{|}{C}\text{-}\overset{|}{C}\text{=}O^{\oplus}H \rightleftharpoons BH + \overset{|}{C}\text{=}\overset{|}{C}\text{-}OH + BH$

Equation 2: $B + \text{-}\overset{|}{C}\text{-}\overset{|}{C}\text{=}O \rightleftharpoons BH^{\oplus} + [\text{-}\overset{|}{C}\text{-}\overset{\ominus}{C}\text{-}\overset{||}{C}\text{-} \leftrightarrow \text{-}\overset{|}{C}\text{=}\overset{|}{C}\text{-}O^{\ominus}] \rightleftharpoons B + \text{-}\overset{|}{C}\text{=}\overset{|}{C}\text{-}OH$

In recent years, Swain (4) and Emmons and Hawthorne (5) have presented evidence for a termolecular mechanism which involves the simultaneous action of base and acid. However most work is based on the older concept since it was the opinion that this second mechanism was not operating exclusively.

In the discussion to follow, bromination and debromination of ketones are considered irreversible. However, the reaction can be made reversible if the bromoketone is treated with a high concentration of acid as hydrobromic or hydriodic (6).

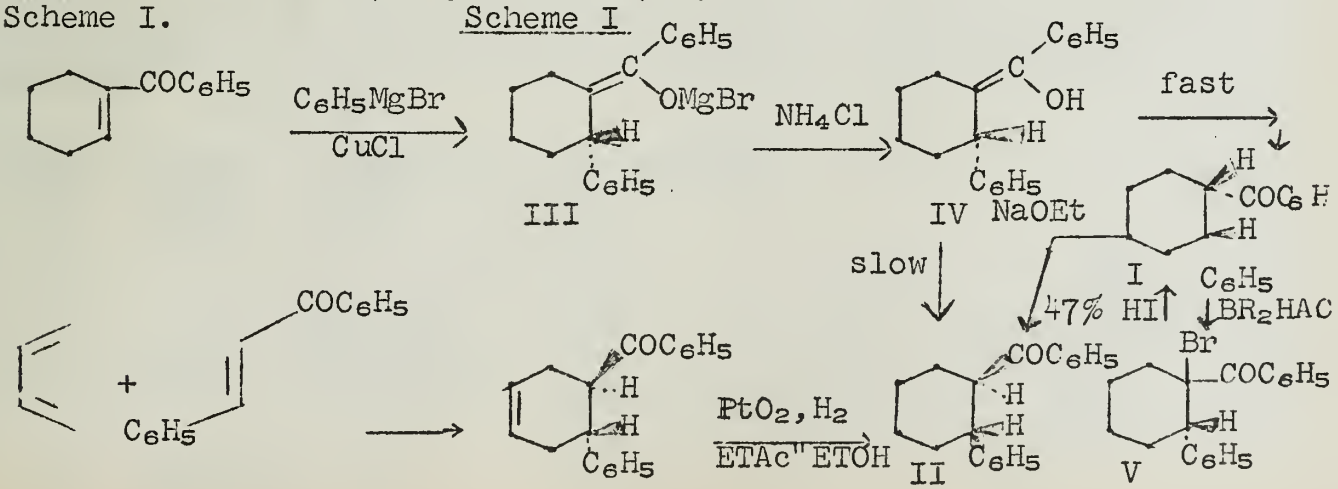
The alicyclic examples to be discussed are divided for convenience into those containing the enolic double bond exocyclic to the ring and those containing an endocyclic enolic double bond.

EXOCYCLIC ENOLS

Zimmerman investigated the ketonization of enols of 1-phenyl-2-benzoylcyclohexane (7), 1-phenyl-2-acetylcyclohexane (8), 2-phenylcyclohexanecarboxylic acid (9,10), and 4-phenylcyclohexanecarboxylic acid (11). The method employed was, 1) to synthesize the cis and trans form of each, 2) generate the enol, and 3) to analyse by infrared spectrum of known mixtures the effect of proton donor size, in relation to steric hindrance, on the percent of isomer formed when the enol ketonized.

The preparation and reactions of bromine with the cis and trans isomers of 1-phenyl-2-benzoylcyclohexane are outlined in Scheme I.

Scheme I



The cis and trans relationship of I and II is shown by the following: 1) preparation of the trans isomer (Alder rule); 2) equilibration of I to II; 3) a difference in melting points and a depression in a mixed melting point determination (cis, 114°; trans, 124°); 4) a difference in the infrared spectrum of the trans isomer above 7 microns.

When the cis and trans ketones were treated with bromine and acetic acid under the same conditions (80°, 10 min.), only a bromoketone from the cis isomer was isolated. As the reaction temperature was raised to 100° in an attempt to brominate the trans ketone, the bromine was consumed by the solvent but II was recovered unbrominated. The bromoketone from the cis isomer was subsequently treated with hydriodic acid in acetone to give an instantaneous liberation of iodine and I as the sole ketonic product.

The indication of the enol IV as an intermediate is apparent (7) from the method of obtaining the cis isomer since it seems likely that prototopic attack on oxygen of III is faster than on carbon. This is substantiated since some trans product (less than 0.1%) was isolated. An enol intermediate can also by justly assumed in the debromination of V by the previous evidence in halogenation experiments of other ketones (1,2,3).

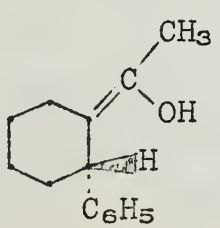
The difference in rates of bromination of the cis and trans ketone may be attributed to a greater free energy content and better transition state between ketone and enol of the cis isomer. However, it may also be due to a higher energy transition state between trans ketone and enol as well as the lower energy ground state for the trans ketone.

Scheme II outlines the preparation of the cis and trans isomer of the second example 2-phenyl-1-acetylcyclohexane as well as the bromination reactions of the isomers. The basis of assignment of configurations was the same as in the previous example (i.e., Alder rule, equilibration, etc.). Table I contains the results of debromination of the bromoketones with various proton sources. In the case of collidine, Zimmerman did not specify which form of collidine (α,β,γ) was used so it was assumed to be the γ form (2,4 6-trimethylpyridine).

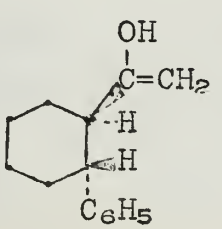
It should be noted the bromine atom in V and IX was assumed to be trans to the phenyl group in analogy to the process of ketonization.

Table I

Run	Solvent	Proton S.	% Cis isomer
1	ether	AcOH	89.4
2,3	CH_3OH	coll.·HCl	92.4, 92.3
4	"	glycine	91.3
5	"	NH_4Cl	93.8
6,7,8	TBH[b,c]	coll.·HCl	91.2, 90.8, 90.5
9	CH_3CN[c]	"	93.6
10	benzene[c]	"	88.6



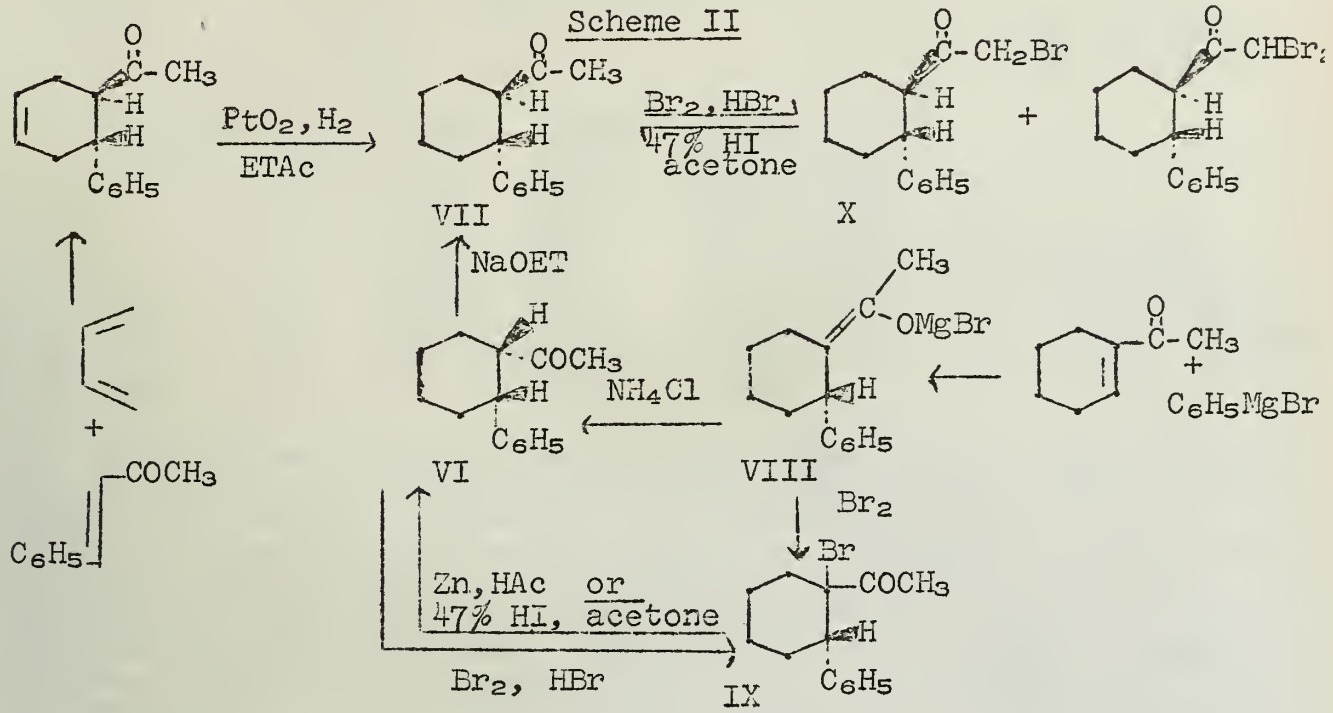
XI



XII

a. collidinium hydrochloride; b. t-butyl alcohol; c. under nitrogen

Scheme II



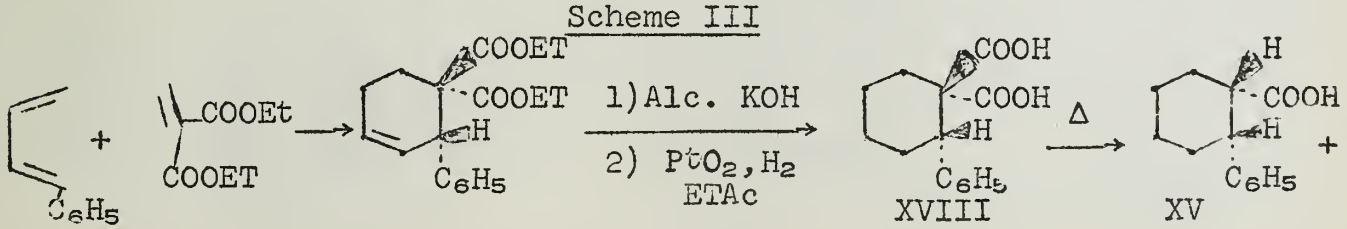
Evidence for an enol intermediate was indicated by formation of the cis and trans isomers by protonation of VIII (80% cis) and debromination of IX (89.4% cis).

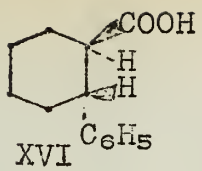
Bromination of VII, however yielded a second bromoketone which upon reduction did not give a mixture of cis and trans (cis stable under reaction conditions). Instead, the debromination gave pure trans ketone. Therefore, the bromoketone was formulated as 1-bromoacetyl - 2-phenylcyclohexane (X).

Thus, there exists a situation similar to that in trans 2-phenyl-1-benzoylcyclohexane, but in II the option of forming a bromoketone similar to X is not present. The abnormal bromination may be explained by the existence of a high energy transition state between the trans ketone and the enol XI, as evidenced by the preferential formation of VI. But a high energy transition state apparently does not prevail between the trans ketone and the enol XII with the resultant formation of X.

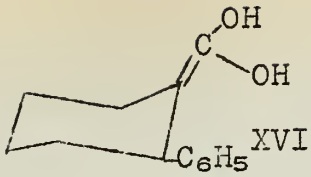
The cis (XV) and trans (XVI) isomers of 2-phenylcyclohexanecarboxylic acid, which had been synthesized previously by Gutsche (12), and the bromine derivatives were prepared as outlined in Scheme III. The results of the investigation in the decarboxylation of the diacid XVIII is contained in Table II.

Scheme III



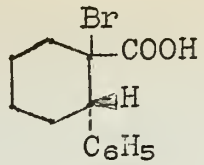


XVI



XVII

XVIII or XV $\xrightarrow{1)\,SOCl_2\ \ 2)\,Br_2\ \ 3)\,H_2O}$



cis and trans

Table II

Run	Reactant	Solv.	Temp.	Time	%Cis	%Cis[b,c]
1	XVIII	coll.[a]	60°C	60 min.	72.5	76.0
2	"	"	90°	30 "	71.4	73.5
3	"	"	130°	20 "	71.3	75.3
4	"	"	165°	20 "	69.7	74.8
5	"	none	195°	8 "	65.5	65.5
6	XV	"	200°	64 hr.	13.7	-
7	"	"	"	102 "	8.5	-
8	XVI	"	"	"	8.9	-

a. collidine
b. corrected for isomerization
c. average of runs 1-4 was 74.9± 1.4%

In the decarboxylation experiments, runs 7 and 8 indicate the enol XVII is the intermediate since the same ratio of cis and trans isomers was obtained. However in the dehalogenation of α-halo acids, previous work indicated α-chloro-α-phenylpropionic acid (13) proceeded with inversion of configuration and ethyl 1-bromo-2-phenylcyclohexanecarboxylate (14) proceeded with retention of configuration. In this case, debromination of the cis-and trans-α-bromo-2-phenylcyclohexanecarboxylic acid (distinguished by the melting points 116° and 153° without assigning a configuration corresponding to the melting point) with zinc-acetic acid and zinc-hydrochloric-acetic acid at 35° for 1 hour gave the same percent cis isomer distribution (85.5 ± 1.7%) from the cis and trans form. Thus the enol XVII is a debromination intermediate.

The decarboxylation experiments (Table II, runs 1-4) indicated a marked absence of temperature dependence. From the product distribution, it was calculated that the transition state for formation of cis isomer was favored over the one leading to trans isomer by 0.81 kcal./mole free energy. If this resulted from a difference in enthalpies of activation for the formation of cis and trans isomers, then a change of 5.5% cis isomer for a 100° temperature change would be expected. However, this is not observed and may be due to masking of an expected small temperature dependence by experimental scatter.

Data from debromination with zinc-acetic acid of the 153° m.p. bromoacid (8 runs, temperature range 20°-115°) provided a plot of log (k_c/k_t) versus 1/T. From the slope, it was found $\Delta\Delta H^{\ddagger}_{c-t}$ was -1.8 kcal./mole. Therefore, if enthalpy alone determined the rate of ketonization, the product should contain 96% cis isomer. Since this is not the case, the lower stereoselectivity is undoubtedly due to a counteracting entropy effect. Table III contains the differential quantities of activation.

TABLE III

$\Delta\Delta F^{\ddagger}_{c-t} = \Delta F^{\ddagger}_{c} - \Delta F^{\ddagger}_{t}$ = -1.0±0.1 kcal./mole

$\Delta\Delta H^{\ddagger}_{c-t} = \Delta S^{\ddagger}_{c} - \Delta H^{\ddagger}_{t}$ = -1.8±0.3 kcal./mole

$\Delta\Delta S^{\ddagger}_{c-t} = \Delta S^{\ddagger}_{c} - \Delta S^{\ddagger}_{t}$ = -2.7±1.0 cal./mole/deg.

For the investigation of the decarboxylation of 4-phenylcyclohexane-1,1-dicarboxylic acid, the diacid (XVIII) and the cis (XIX) (m.p. 129°) and trans (XX) (m.p.202°) forms of 4-phenylcyclohexanecarboxylic acid were synthesized according to Scheme IV. The results of the decarboxylation experiments with various solvents are summarized in Table IV.

SCHEME IV

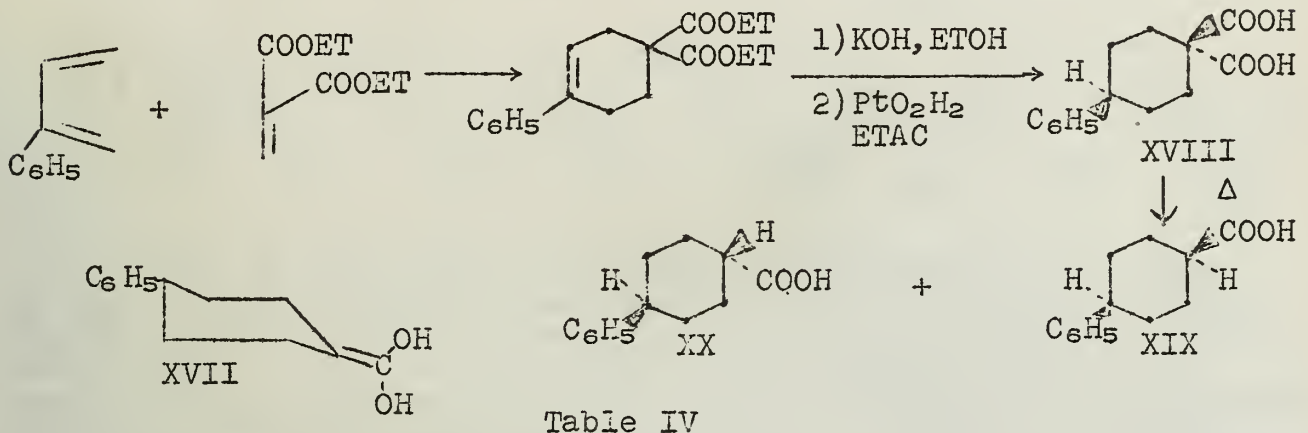


Table IV

Run	Reactant	Solv.	Temp.°C	Time(min.)	%Cis
1-4	XVIII	none	194-225	.3-9	50.5
5	XIX	"	195	1620.0	11.0
6	"	"	194	2.0	96.0
7-8	XVIII	mesit[a]	165-140	27,20	51.57
9	XIX	"	175	60	95.0
10	"	"	175	600	93.0
11	XX	"	175	600	0.0
12-18	XVIII	coll[b]	78-131	3-180	61.0
19	XIX	"	130	12.0	100.0
20	"	"	132	5.0	95.0
	$ClCH_2CO_2H$				

a. mesitylene
b. collidine
c. average

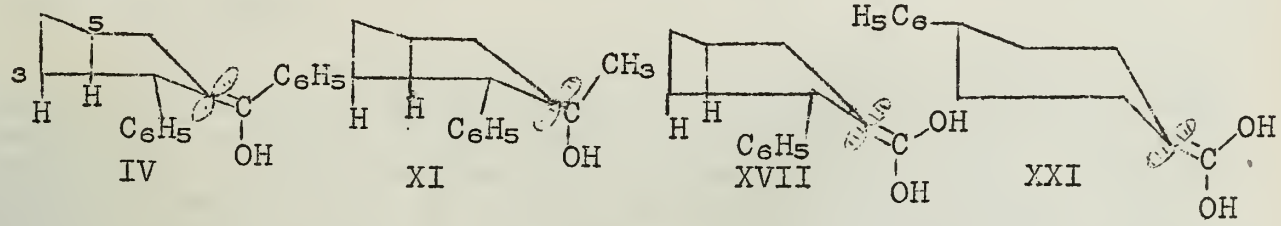
Examination of Table IV shows from the control runs (runs 6,9,10,19,20) that little or no isomerization is taking place. Conversion of cis-4-phenylcyclohexanecarboxylic acid to 89% trans (run 5) confirms the assignments of configuration made previously by Rassow (15) and Fieser (16).

As in previous cases, the indication of an intermediate enol (XXI) is shown by the isolation of cis and trans acid in the decarboxylation experiments.

When collidine is the solvent for decarboxylation, it may be said that a carbanion mechanism is operating to give first an intermediate enolate anion instead of a cyclic mechanism to give the intermediate enol. This would be in analogy to the decarboxylation of the mono-acid anion of malonic acid in presence of N-butylpiperidine (25). However, Corey has shown that malonic acid is essentially undissociated in pyridine (pK 8.85) (26). Since collidine is of nearly the same basicity (pK 7.46), it is doubtful whether a carbanion mechanism would be operating exclusively in preference to a cyclic mechanism.

From the data in the preceding table, the following general conclusions may be made concerning the predominance in formation of cis isomers under non-equilibrating conditions: 1) the

ketonization step is a kinetically rather than a thermodynamically controlled process; 2) the transition state is more sp^2 than sp^3 hybridized; 3) the predominance of cis isomer can be better explained by consideration of a proton and proton donor rather than just a proton in the transition state; 4) protonation is from the less hindered side of the enol; 5) in the transition state, steric interaction is more important than stereoelectronic control in determining the ratio of products.



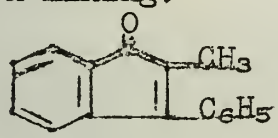
Thus we may explain the relative difference in the ratio of cis to trans isomers by consideration of the transition states IV, XI, XVII, and XXI with respect to proton donor size and steric interaction. In IV, the two phenyl groups equally protect the enolic double bond from both sides (non-selective steric hindrance) thus increasing the effect of the two axial hydrogens at carbon atoms 3 and 5 (selective steric hindrance). The result is that the proton donor is forced into a direct approach from the upper side giving almost entirely cis isomer no matter what the proton donor. However, in XXI, the non-selective steric hindrance is absent and the proton donor can approach as well from either the axial or equatorial side. In the decarboxylation, where the proton donor is likely the small carboxyl group, there was observed a 50:50 mixture of cis and trans isomers. When the decarboxylation was carried out in collidine, cis isomer was obtained to the extent of 61%, thus indicating a preferred equatorial attack. This was probably due to a small selective steric hindrance but some non-selective interaction may be present caused by hydrogen bonding between enolic hydroxyl and collidine. The proton donor with collidine as a solvent may be either the conjugate acid of collidine, its ion-pair equivalent or a hydrogen-bonded collidine-carboxylic acid complex. In the case of XVII, decarboxylation with no solvent and in collidine gave ca. 15% more cis isomer than in XXI. Although models indicate the 2-phenyl group is somewhat out of the enolic plane and does not participate a great deal in non-selective steric hindrance, it nevertheless increases the effect of the axial hydrogens in forcing a more direct approach, thereby increasing the stereoselectivity of ketonization. The enol of XI gives 89% of cis isomer, due to the additional increase in non-selectivity of the methyl group. However, the difference between XI and XVII may be due to a later transition state for XVII (i.e., more sp^3 hybridized since the unshared electrons of the extra hydroxyl group can diminish the importance for electron delocalization so that the carboxyl group forming can occupy the preferred equatorial conformation).

The conclusion that a stereoelectronic factor is of lesser importance may be seen by consideration of the enol of 2-phenyl-1-benzoylcyclohexane. As a proton approaches the sp^2 hybridized carbon atom, there is a change of hybridization to sp^3. The original overlap of the p orbital of the enol must continue, but with decreased energetic importance until there is a benzoyl group formed adjacent to the saturated sp^3 carbon atom. However during

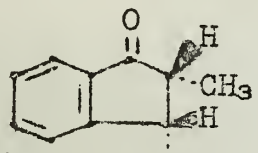
the formation of the benzoyl group, there is an ever increasing conformational requirement caused by the continuation of overlap. Models indicate the interaction between the benzoyl group and axial hydrogens makes this continuation more difficult for the observed formed carbonyl group than for an equatorial one. Therefore, it may be considered that overlap control is not prevalent after a sp^2 hybridized transition state has been left (11).

ENDO CYCLIC ENOLS

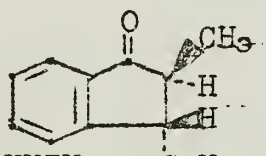
For the investigation of the ketonization reaction of the enol from 2-methyl-3-phenylindanone, Zimmerman (17) prepared the isomers by reduction of 2-methyl-3-phenylindone (XXII) with platinum oxide in ethyl acetate and in ethanol-acetic acid containing sodium hydroxide as well as by lithium and liquid ammonia (18). The cis configuration was assigned XXIII since, 1) it was isomerized to a mixture containing 79% trans isomer (XXIV), 2) possessed similar infrared to the trans isomer except in the 8-15 μregion, and 3) the stereoisomers showed a large melting point depression on mixing.



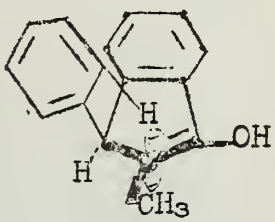
XXII



XXIII



XXIX



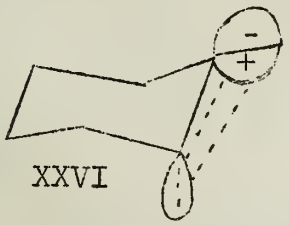
XXV

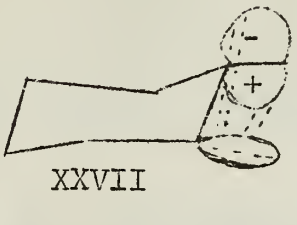
The enolic intermediate was indicated when both cis and trans α-bromoketones, which were prepared, gave a crude reaction product containing 76±3% of cis ketone upon reduction with hydriodic acid in acetone.

As in previous cases, the ketonization is a kinetically controlled process in which the transition state (XXV) resembles the enol in structure. Since the upper side is hindered to attack by the 3-phenyl substituent, the proton approaches from the opposite side, leading to predominant formation of cis product. This transition state would also be of lower energy due to considerablyless steric interaction between the proton donor and hydrogen atom at carbon atom 3 compared to that between the phenyl and proton donor. This preferred attack of the proton donor is supported by the observation that cis ketone brominates instantly at room temperature while the trans isomer requires heating and a catalyst. That is, the same transition state must be available for bromination as for protonation and the difference in rates of bromination is a measure of the ease of enolization.

The examples above concentrate on the effect of steric hindrance in enolization-ketonization reactions. However, there is evidence for an additional controlling factor which is stereoelectonic in nature. Corey (19,20), in consideration of the proposed transition states XXVI and XXVII in Fig. 1, indicated that XXVI would be lower in energy than XXVII due to requirement of maximum bonding in the transition state. Thus, it was expected that a group leaving or entering alpha to the exocyclic carbonyl would prefer axial rather than equatorial orientation. In other words, there would be a maximum of sigma electron delocalization

to an exocyclic π-orbital when in an axial orientation. Inherent in this proposal, is a kinetically controlled product in the ketonization process.

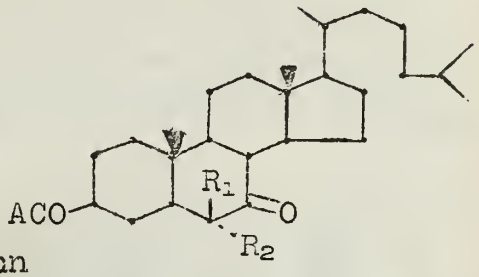




Axial interaction (bonding)

Equatorial interaction (non-bonding)

Fig. 1



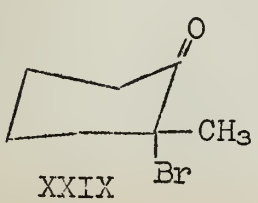
XXVIIIa, $R_1=R_2=H$
XXVIIIb, $R_1=D$, $R_2=H$
XXVIIIc, $R_1=H$, $R_2=D$
XXVIIId, $R_1=Br$, $R_2=H$
XXVIIIe, $R_1=H$, $R_2=Br$
XXVIIIf, $R_1=Br$, $R_2=D$

Corey investigated (19) the enolization and ketonization processes using 3β-acetoxycholestan-7-one (XXVIIIa) as the substate. In enolization experiments, bromination of the substrate labeled with deteurium in the 6β (XXVIIIb) and 6α (XXVIIIc) position gave a kinetic isotope effect of 7.4±0.5 (theoretical max. 7.9 at 10°) and a positional effect (i.e., axial to equatorial loss) of 1.2±0.05. Ketonization studies involving zinc dust and O-deutero-acetic acid reduction of 6β(XXVIIId)- and 6α-bromocholestan-7-one (XXVIIIe), and zinc-acetic acid reduction of 6α-deutero-6-bromo-ketone (XXVIIIf) gave the results in Table V. (The first column is the isomer of 3β-acetoxycholestan-7-one and the third column is the percent product.) The last two entries in the table are in fair agreement with that which would be predicted on the basis of positional effect on protonation of the enol. The predicted composition for debromination with Zn-DBr would be 55% 6β and 45% 6α, and the reverse for Zn-HBr reduction.

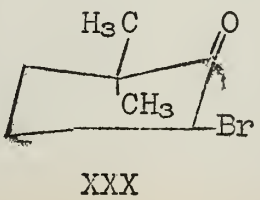
The results of the experiments show, 1) from the isotope effect that the alpha C-H bond is almost completely broken in the transition state, and 2) that the removal or addition of a substituent alpha to the carbonyl function does favor axial orientation. Therefore, protonation and bromination are essentially stereoelectronic controlled. However, in the absence of this factor the equatorial orientation would undoubtedly be favored.

Table V

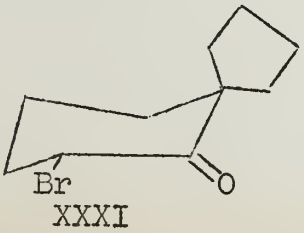
Reactant	Conditions	Deutero isomer 6β	6α
XXVIIId	Zn-DOAc	90	10
XXVIIIe	Zn-DOAc	90	10
XXVIIIf	Zn-HOAc	10	90
XXVIIIf	Zn-HBr	40	60
XXVIIId	Zn-DBr	60	40



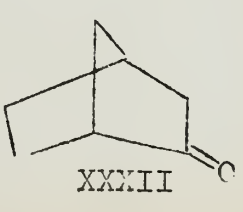
XXIX



XXX



XXXI



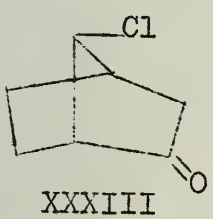
XXXII

Bromination in acetic acid (non-equilibrating conditions) of 2-methylcyclohexanone, 2,2-dimethylcyclohexanone, and spiro (4.5) decane-6-one yielded the corresponding bromine derivatives XXIX, XXX, and XXXI. Since the bromine atom has been shown to have an axial configuration in XXXIX (21) and an equatorial configuration in XXX (21,22) and XXXI (23,22), bromination was probably stereo-electronic controlled in XXIX and sterically controlled in XXX and XXXI.

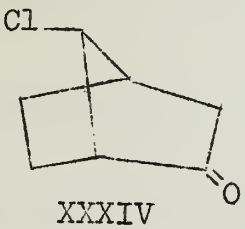
Woods and Roberts (24) determined the base-catalyzed rate of bromination of norcamphor, syn-7-chloronorcamphor (XXXIII), anti-7-chloronorcamphor (XXXIV), exo-3-bromonorcamphor (XXXV), and camphor (XXXVI). The pseudo first order rate constants determined at 35° in 75% acetic acid containing 0.238 M sodium acetate are tabulated in Table VI.

Table VI

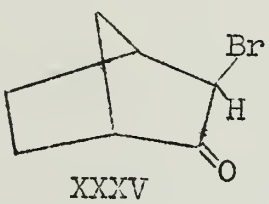
Reactant	Molarity	10^8k/sec.	Rel. to XXXII
XXXII	0.0272	9.8±0.7	1.00
XXXIII	0.0173	3.2±0.5	0.3
XXXIV	0.0174	11.5±0.6	1.2
XXXV	0.0181	2.7±0.4	0.3
XXXVI	0.0217	0.28	0.03



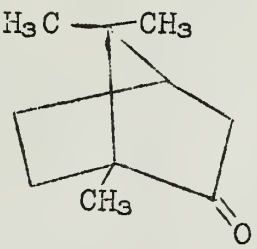
XXXIII



XXXIV



XXXV



It was found that the rate of bromination is in the order XXXIV > XXXII > XXXIII = XXXV > XXXVI. Due to the rates, it may be concluded: 1) Exo α-hydrogens are attacked more readily than endo α-hydrogens. If this were not the case, XXXII, XXXIII, and XXXIV would have approximately the same rate. The relatively small difference between XXXII and XXXIV may be caused by the polar effect of the anti chlorine of XXXIV. 2) The decrease in rates may be generally explained by the steric hindrance of bridge substituents to exo attack by the base.

From the consideration of examples of exocyclic and endocyclic carbonyl compounds, it may be concluded that Zimmerman's and Corey's work concerning enolization-ketonization reactions are complementary.

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RECENT WORK INVOLVING HYDROGEN ISOTOPE EFFECT IN ORGANIC CHEMISTRY

Reported by L. H. Shepherd January 4, 1960

INTRODUCTION

In recent years the hydrogen isotope effect has become an increasingly important tool in the development of the theories of rate processes and reaction mechanisms. This seminar will deal principally with some of the more recent work involving the isotope effect in equilibrium reactions.

THEORETICAL ASPECTS

After the spectroscopic discovery of heavy hydrogen by Urey and coworkers (1), Cremer and Polanyi (2) and Eyring and Sherman (3) predicted that hydrogen- and deuterium-containing compounds should react at different rates. This difference in the reaction rates of compounds in which deuterium (or tritium) has been substituted for hydrogen is known as the hydrogen isotope effect. It is generally found that bonds to deuterium or tritium have a lower reactivity as compared to the corresponding bonds to hydrogen. The major contribution to this observation is the difference in free energy of the bonds which arises from the difference in their zero-point energies in the order E_T, lower than E_D, lower than E_H. Since the deuterium or tritium compound has a lower zero-point energy, it will be more stable than the hydrogen analog. The potential energy curves of hydrogen, deuterium and tritium compounds are essentially the same; if one assumes that the bond undergoing reaction is relatively weak in the transition state compared to the one in the reactant, the isotope effect of the zero-point energy becomes apparent. In general, the difference (ΔE_o) in the dissociation of a bonded hydrogen atom and the corresponding bonded deuterium atom is on the order of 1.2 - 1.5 Kcal/mole. Isotope effects are temperature dependent as shown in the following table (4).

Maximum Value of Deuterium Isotope Effect as a Function of Temperature

Bond	ΔE_o(cal)	T(°C)	k_H/k_D
C-H	~1150	0	8.3
		25	6.9
		100	4.7
		500	2.1
N-H	~1270	0	10.3
		25	8.5
		100	5.5
		500	2.2
O-H	~1400	0	12.6
		25	10.6
		100	6.6
		500	2.5

GENERAL

It has been found experimentally that most acid catalyzed reactions proceed more rapidly in heavy water than in light water, e.g., hydrolysis of esters, nitriles, acetals, etc. These reactions are believed to involve reversible protonation of the reactant molecule followed by the rate-determining step in which the protonated substrate forms products. The letter S represents the substrate.

$$S + H^{\oplus} \rightleftharpoons S^{\oplus}H \xrightarrow{\text{slow}} \text{Pdts}$$

For reactions of this type, where the rate of the reaction is first-order in protonated substrate, the concentration of $S^{\oplus}D$ in D_2O will be larger than the concentration of $S^{\oplus}H$ in H_2O due to equilibrium effects. This can be seen from the following energy diagrams.

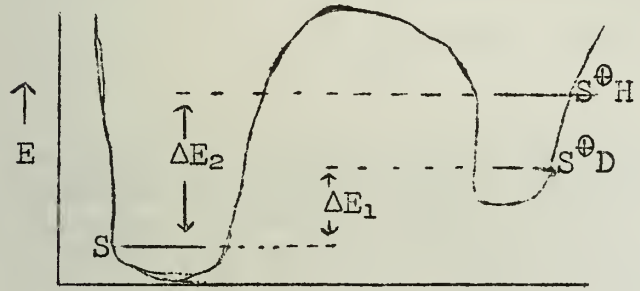


Fig. 1 $S+H^{\oplus}(D^{\oplus}) \rightleftharpoons S^{\oplus}H\ (S^{\oplus}D)$

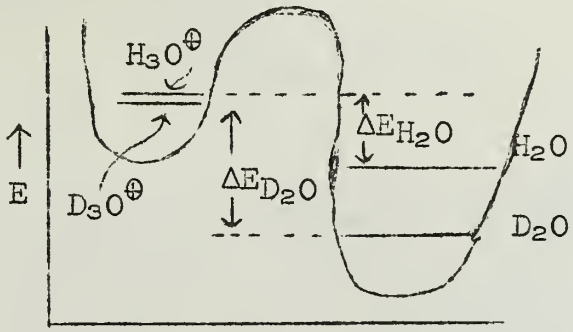


Fig. 2 $H_3O^{\oplus}(D_3O^{\oplus}) \rightleftharpoons H_2O(D_2O)+H^{\oplus}(D^{\oplus})$

From figure 1 it is seen that a larger concentration of $S^{\oplus}D$ compared to the concentration of $S^{\oplus}H$ is expected because of the difference in free energy of the protonated and deuterated substrates, i.e., $\Delta E_D < \Delta E_H$.

Another effect leading to this observation of the higher concentration of $S^{\oplus}D$ in D_2O is represented in Fig. 2 where it is shown that the energy difference between the strong acids $H_3O^{\oplus}$ and $D_3O^{\oplus}$ is relatively small compared to the energy difference between H_2O and D_2O. In the ionization of the strong acids ($H_3O^{\oplus}$ and $D_3O^{\oplus}$) formation of D_2O is slightly more favored than formation of H_2O, i.e., ΔE_{D_2O} is a greater decrease in energy than ΔE_{H_2O}.

As an example of an acid catalyzed reaction which does not proceed more rapidly in D_2O than H_2O, the mutarotation of glucose will be mentioned (5). The mechanism in this case is believed not to involve a reversible protonation equilibrium prior to mutarotation, but instead the proton transfer from the acid to the substrate (glucose) and from the substrate to the base (in this case, water) occurs in the rate-controlling step.

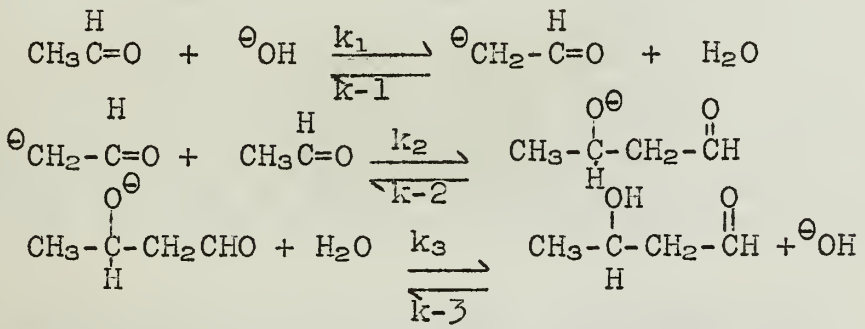
The decreased rate for mutarotation of glucose in heavy water is simply the usual isotope effect in which bonds to the hydrogen or deuterium of the hydronium ion (or $D_3O^{\oplus}$) are broken in the transition state.

Basic catalysis in H_2O and D_2O is somewhat more difficult to interpret as will be seen in this paper. Results have been obtained in which reaction rates show an increase or decrease in changing

solvent from H_2O to D_2O, depending on the base used. The remainder of the paper will be devoted principally to base catalyzed enolizations.

ALDEHYDE CONDENSATIONS

The condensation of acetaldehyde to aldol in basic media is generally assumed (6) to involve an initial abstraction of a methyl hydrogen followed by the slow condensation step to give the aldol anion.



Writing the expression $k_2\,[meCHO] \gg k_1[H_2O]$ is justified for high aldehyde concentrations. Condensation is accompanied by isotopic hydrogen exchange between methyl hydrogens and solvent at low aldehyde (7) concentration due to the initial equilibrium. However at high aldehyde concentrations (10 M) isotopic exchange is not observed (8). Pocker (9) has carried out the condensation in the region where $V_2 \gg V_{-1}$ using deuterium-labeled acetaldehyde in an effort to show that the rate of the aldol condensation equals the rate of proton abstraction from the methyl group. At low aldehyde concentrations the rate of condensation of α,α,α-trideuteroacetaldehyde should be several fold slower than the hydrogen analog. Under such conditions the full difference in zero-point energy between C-H and C-D should be represented in the rate ratio. Pocker confirmed this experimentally as can be seen in the following table. The solvent was water and hydroxide ion was the base.

Compound	Catalytic Coefficient	k_H/k_D
CH_3CHO	0.114 1 $mole^{-1}sec^{-1}$	
CD_3CHO	0.0154 1 $mole^{-1}sec^{-1}$	7.4
CH_3CDO	0.112 1 $mole^{-1}sec^{-1}$	~1

The fact that CD_3CHO is 7.4 times slower in reaction than CH_3CHO under these conditions is compatible with initial hydrogen abstraction, while substitution of deuterium for hydrogen attached to the carbonyl group had negligible effect on the ratio.

KETONE ENOLIZATIONS

Recently Pocker (10) used the kinetic deuterium isotope effect in studying the abstraction of hydrogen ion from acetone by hydroxide and deuteroxide. Acetone reacts with strongly alkaline hypobromite or hypoiodite solution (haloform reaction) according to the following equation:

$$CH_3\overset{O}{\overset{\|}{C}}CH_3 + 3\overset{\ominus}{O}X \longrightarrow CH_3CO_2^{\ominus} + CX_3H + 2\overset{\ominus}{O}H$$

The reaction is zero-order with respect to the halogenating agents and first-order with respect to both acetone and hydroxide ion. The most probable mechanism for the rate determining step is removal of a proton by base.

$$CH_3\overset{O}{\overset{\|}{C}}CH_3 + \overset{\ominus}{O}H \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}CH_2^{\ominus} + H_2O$$

This behavior is analogous to the well established bromination and iodination of acetone in less alkaline solution. Reitz and Kopp (11) determined the primary isotope effect for the reaction using acetate ion as base and obtained $k_H/k_D \sim b$. Pocker (10) has determined the ratio of halogenation of acetone and acetone-d_6 in strongly alkaline solution, thus enabling one to determine the primary isotope effect for proton removal by hydroxide. Rate comparisons were made in terms of the ionization rate coefficient, k ($l\ mole^{-1} min^{-1}$).

Ion Rate Coefficients of Acetone and Deuteroacetone

Catalyst	Solvent	Substrate	k
$^{\ominus}OH$	H_2O	CH_3COCH_3	10.8
$^{\ominus}OD$	D_2O	CH_3COCH_3	15.8
$^{\ominus}OH$	H_2O	CD_3COCD_3	1.44
$^{\ominus}OD$	D_2O	CD_3COCD_3	2.12

From the above table it may be noted that:

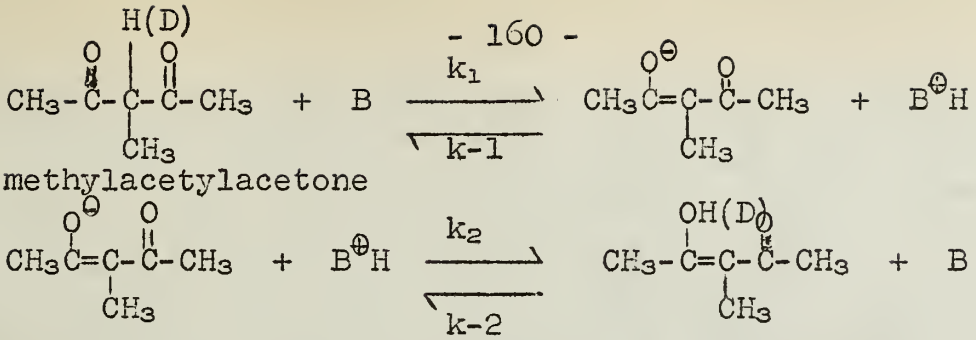
(a) The kinetic isotope effect is 7.5 for both hydroxide and deteroxide catalysis.

(b) In H_2O, hydroxide ion is 4.5×10^6 times more effective than acetate ion ($k^{\ominus}_{OAC} = 2.4 \times 10^{-6}$) in proton abstraction from acetone (12).

(c) Proton removal from acetone is 1.47 times faster by $^{\ominus}OD$ in D_2O than $^{\ominus}OH$ in H_2O.

Other reactions are known to proceed more rapidly in D_2O than H_2O. For example, it is known that chlorohydrins show this effect (13,14) and for 2-chloroethanol and 2-chloropropanol the value of k_H/k_D is 1.54 and 1.58 respectively. Reaction rates for many reactions in mixtures of H_2O and D_2O may be correlated by use of equations derived by Nelson and Butler (15,16) and Gross (17).

Long and Watson (18) have studied the keto-enol transformation of methylacetylacetone in H_2O and in D_2O. The observed isotope effects were attributed to either solvent effects or ordinary isotope effects or a combination of the two. The mechanism for enolization is the same as mentioned previously, namely proton (or deuteron) abstraction by base.



The following table summarizes the results obtained. The symbol KH represents methylacetylacetone whereas KD represents the deuterium substituted ketone.

	Reactant	Solvent	Catalyst	$k_1 \times 10^5$ l.mole^{-1}sec.$^{-1}$
1.	KH	H_2O	H_2O	0.173
2.	KH	D_2O	D_2O	0.126
3.	KD	H_2O	H_2O	0.049
4.	KD	D_2O	D_2O	0.038
5.	KH	H_2O	0.2M NaOAc	725
6.	KH	D_2O	"	580
7.	KD	H_2O	"	125
8.	KD	D_2O	"	124

For simplicity the following symbols will be used for isotope effect calculations. k refers to k_1, superscript H or D refers to solvent H_2O or D_2O respectively, and subscripts refer to the compounds undergoing enolization, KH or KD.

Long and Watson attribute changes in the solvent (ketone and base remaining constant) as giving rise to solvent isotope effects. This may be observed by comparing runs 1 and 2 or 5 and 6.

$$\left(\frac{k^H_{KH}}{k^D_{KH}}\right)_{H_2O\ (Base)} = 1.37 \qquad \left(\frac{k^H_{KH}}{k^D_{KH}}\right)_{\ominus_{OAc}} = 1.25$$

Common isotope effects may be calculated by comparing runs 1 and 3, or 5 and 7.

$$\left(\frac{k^H_{KH}}{k^H_{KD}}\right)_{H_2O} = 3.5 \qquad \left(\frac{k^H_{KH}}{k^H_{KD}}\right)_{\ominus_{OAc}} = 5.8$$

If one changes both the solvent (H_2O to D_2O) and the ketone (KH to KD), both isotope effects and solvent effects are incorporated into the rate ratio. This can be seen by comparing runs 1 and 4, or 5 and 8.

$$\left(\frac{k^H_{KH}}{k^D_{KD}}\right)_{H_2O} = 4.6 \qquad \left(\frac{k^H_{KH}}{k^D_{KD}}\right)_{\ominus_{OAc}} = 6.9$$

It should be noted that these results are in the opposite direction for the enolization of acetone by hydroxide ion and deuteroxide ion (10). Previously, it had been found that enolization proceeded 1.7 times faster upon changing the solvent from H_2O to D_2O in the presence of a strong base. With a weak base (acetate ion) attacking methylacetylacetone, Long and Watson noted that enolization was 1.25 times faster in H_2O than in D_2O. Rietz and Kopp (11) have observed that acetone enolization catalyzed by acetate ion was 15% faster in H_2O than in D_2O and this is attributed to a solvent effect (18). It seems that the strength of the attacking base greatly determines the size of the observed isotope effect.

Enolization of ketones in solutions of weak acids and bases are found to be first-order in ketone. However several terms involving the weak acid and the acid anion are found to replace the usual hydroxide ion terms, i.e., general acid-base catalysis. Dawson and Spivey (19) found that the expression of iodination of acetone in acetate buffers contains a small product term of the form Swain

$$k_p[HOAc][^{\ominus}OAc][ketone].$$

(20) then revived the suggestion originally given by Lowry and Faulkner (21) that reactions catalyzed by acids and bases normally occur by a ternary mechanism, involving simultaneous attack on the substrate by acid and a base. The third-order term was verified by Bell and Jones (22).

For ketone enolization, Swain (23) used the hydrogen isotope effect in an attempt to identify the attacking nucleophile and electrophile in catalysis by acetic acid solution.

$$HA + O{=}\underset{\underset{R}{|}}{C} - \underset{\underset{R}{|}}{\overset{\overset{R}{|}}{C}}{-}H + B \xrightarrow{slow} HOC = \underset{\underset{R}{|}}{R_2} + A^{\ominus} + HB^{\oplus}$$

For catalysis by acetic acid solution, it is possible to have nine combinations of attacking nucleophile (B) and electrophile(HA).

	HA	B		HA	B		HA	B	Kinetically
(1)	H_2O	H_2O	(4)	HOAc	H_2O	(7)	$H_3O^{\oplus}$	H_2O	1 and 9
(2)	H_2O	$^{\ominus}OAc$	(5)	HOAc	$^{\ominus}OAc$	(8)	$H_3O^{\oplus}$	$^{\ominus}OAc$	2 and 6 4 and 8
(3)	H_2O	$^{\ominus}OH$	(6)	HOAc	$^{\ominus}OH$	(9)	$H_3O^{\oplus}$	$^{\ominus}OH$	

The hydrogen isotope effect at the carbon from which the base removes a proton was expected to be useful because its magnitude would be expected to depend on the strength of the base.

In order to determine isotope effects, Swain chose to compare the rate of racemization of an optically active ketone (α-phenylisocaprophenone) with the rate at which the α-tritiated racemic ketone lost tritium to the solvent. The α-phenylisocaprophenone was prepared from leucine by the following method:

$$\underset{\text{L(-) leucine}}{H_2N-\underset{\underset{CH_2CH(CH_3)_2}{|}}{\overset{\overset{CO_2H}{|}}{C}}-H} \xrightarrow[3.\ \text{ØmgBr}\quad 4.\ H_2O,\ NH_4Cl]{1.\ HCl\quad 2.\ C_2H_5OH} \underset{\underset{CH_2CH(CH_3)_2}{|}}{H_2N-\overset{\overset{HOC\text{Ø}_2}{|}}{CH}} \xrightarrow{HNO_2} \underset{\text{D(+) α-phenylisocaprophenone (I)}}{O{=}\overset{\overset{H-\overset{\overset{CH_2CH(CH_3)_2}{|}}{C}-\text{Ø}}{|}}{C}-\text{Ø}}$$

The α-tritiated compound can be made by refluxing I with tritiated water in dioxane and hydrochloric acid. By running the reaction in buffered solutions and determining the total rate the contributions of various catalysts were obtained. The catalytic rate coefficient is found by plotting the total rate vs. catalyst concentration. The following table represents the results obtained in water solution using the indicated catalysts.

Catalyst	$k_H \times 10^6$ l. mole^{-1} sec.$^{-1}$	$k_T \times 10^8$ l. mole^{-1} sec.$^{-1}$	k_H/k_T	HA	B
$H^{\oplus}$	264	27.2	9.7	$H_3O^{\oplus}$	H_2O
HOAc	0.0876	0.00768	11.4	$H_3O^{\oplus}$	$^{\ominus}OAc$
$^{\ominus}OAc$	10.7	1.05	10.2	H_2O	$^{\ominus}OAc$
$^{\ominus}OH$	99200	7680	12.9	H_2O	$^{\ominus}OH$

One would expect the isotope effect to be dependent on the strength of the acid involved provided that the attacking base remains constant, i.e., the larger the isotope effect the stronger the acid involved, because a stronger acid should weaken the bond between carbon and α-hydrogen resulting in relatively more complete bond breaking in the transition state. Likewise, an increase in isotope effect should be noticed for an increase in the strength of the attacking base provided that the attacking electrophile remains constant. This effect is a result of the greater repulsion of the α-hydrogen electron pair due to electrostatic interactions. Making this assumption, the 12.9 (isotope effect for $^{\ominus}OH$) must represent a minimum isotope effect for hydroxide ion attacking as a base since H_2O (the weakest acid) is involved with the hydroxide ion. Catalysis by acetate ion then cannot involve hydroxide ion as base and acetic acid as acid because this would lead to an isotope effect greater than 12.9. Therefore, catalysis by acetate ion must involve water as the acid and acetate ion as the base since the observed value is less than 12.9, i.e., 10.2. Catalysis by hydrogen ion, which involves H_3O as acid and H_2O as base, gives an isotope effect of 9.7. The observed value of 11.4 indicates that hydronium ion is the acid and acetate ion is the base.

Therefore, for the enolization of ketones in aqueous acetic acid the mechanism and the second is a step-wise mechanism involv-

$$CH_3CO_2H + O{=}C{-}CH + H_2O \longrightarrow CH_3CO_2^{\ominus} + HOC{=}C + H_3O^{\oplus} \quad (I)$$

ing fast reversible carbonyl oxygen protonation followed by a

$$H_3O^{\oplus} + O{=}C{-}C{-}H + CH_3CO_2^{\ominus} \longrightarrow H_2O + HOC{=}C + CH_3CO_2H$$

slow hydrogen abstraction from the α-carbon by base.

$$H^{\oplus}(H_3O^{\oplus}) + O{=}C{-}C{-}H \underset{\text{slow}}{\overset{\text{fast}}{\rightleftharpoons}} HO{=}C{-}C{-}H \quad (II)$$

$$HO{=}C{-}C{-}H + CH_3CO_2^{\ominus} \xrightarrow{\text{slow}} HOC{=}C + CH_3CO_2H$$

Swain (24) undertook to show that these two mechanisms could be distinguished by use of the hydrogen isotope effect. If the second mechanism (II), (involving carbonyl protonation) is correct the isotope effect can be estimated from the following equation which can be derived assuming that the slow step is the removal of an α-hydrogen.

$$\text{rate (enolization)} = k(R_2CO) + kH^{\oplus}(H^{\oplus})(R_2CO) + k_{HA}(RCO_2H)(R_2CO)$$

$$\frac{kHA}{kDA} = \frac{kH^{\oplus}}{kD^{\oplus}} \cdot \frac{KHA}{KDA}$$

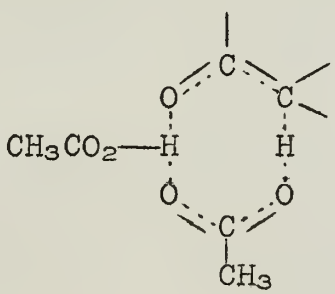
The constant K_{HA} is the ionization constant of acetic acid. The rate constant k_{HA} is for the term involving catalysis by carboxylic acid. The value of $k_{H^{\oplus}}/k_{A^{\oplus}}$ can be approximated for mechanism (II) by noting that the ratio of the isotope effects (4) for many hydrogen ion catalyzed reactions of ketones, esters and sugars in water and 25°, where a prior equilibrium is almost certainly involved, is 0.49 to 0.35.

The ratio of acidities of carboxylic acids, K_{HA}/K_{DA} is 3.3 for acetic acid in water. The product of these two numbers is the expected isotope effect of 1.6 - 1.16 at 25°. The kinetics for determining the isotope effect for α-phenylisocaprophenone were carried out at 100° so it is reasonable to expect that the value of K_{HA}/k_{DA} will be even closer to unity than at 25°.

If the concerted mechanism is correct, there would be a proton transfer from hydronium ion to ketone in the rate-determining step. The observed isotope effect for this reaction should be larger than that for mechanism II by at least a factor of two due to the difference in the zero-point energies of the O-H and O-D bonds.

The measured isotope effect at 100° is very close to unity, i.e., 1.09, which is consistent with mechanism II.

The results on the α-phenylisocaprophenone system are similar to those of Reitz (25) on acetone at 25° where he found an isotope effect (k_H/k_D) of 1.5 for aqueous acetic acid solutions, suggesting that the mechanism applies to the enolization of acetone as well and is consistent with the conclusions of Reitz (15) and Bell (22). It is found that for 0.2M acetic acid and 0.2M acetate ion solutions that the third order term contributes 16% of the total rate. A reversible protonation of the ketone by acetic acid followed by the slow step of proton removal from the carbon by acetate ion predicts only a second-order term, first order in ketone and acetic acid but zero order in acetate ion. Swain has suggested that the reason that acetic acid is effective in catalyzing only the reaction in which acetate ion is the nucleophile, can be accounted for if there is a special cyclic transition state which has the same favorable geometry as the acetic acid dimer.



The hydrogen on the left is bonded to the acetate on the left in the ground state and will become attached to the enol in the product. The hydrogen on the right is attached to the α-carbon of the ketone and will become the hydroxyl hydrogen on the acetate in the product. A cyclic mechanism of this type would explain the observed third-order term.

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RECENT ACETYLENE CHEMISTRY

Reported by P. Kiener January 7, 1959

In recent years, the chemistry of alkynes too become increasingly attractive. New techniques and apparatus have been developed for the safe utilization of acetylenes under pressure on an industrial scale. Numerous natural products with carbon-carbon triple bonds have been discovered.[1] Alkynes with interesting physiological properties have been prepared,[2,3] and some very spectacular syntheses have been achieved with acetylenic compounds. It is thus not surprising that the literature in recent years has recorded many advances in the chemistry of acetylenes. Among these, the coupling reactions of acetylenes reported by Sondheimer and coworkers [4,5,6] are particularly interesting. However, this subject has been reviewed recently and will not be reported in this seminar.[7]

SYNTHESIS OF ACETYLENIC ACETALS, KETALS AND ORTHOESTERS

Previous to the work of Hawk and Sauer[8] no acetylenic ketal, and a single acetylenic orthoformate, namely $C_6H_5C{\equiv}CC(OC_3H_5)_3$ had been reported. Acetylenic acetals in which the triple bond is attached to the acetal have been known for a long time and have found valuable applications as organic intermediates.[9] The synthesis of these classes of compounds can be easily achieved by a one-step catalytic process developed by Hawk and Sauer[8]. The method appears to be a general one and gives very satisfactory yields. Molar equivalents of acetylene and orthoester are heated at atmospheric pressure, removing the alcohol as soon as it forms. The following example illustrates the reaction:

$$C_6H_5C{\equiv}CH + HC(OET)_3 \xrightarrow[ZnCl_2]{\Delta} C_6H_5C{\equiv}C\overset{H}{C}(OET)_2 + ETOH$$

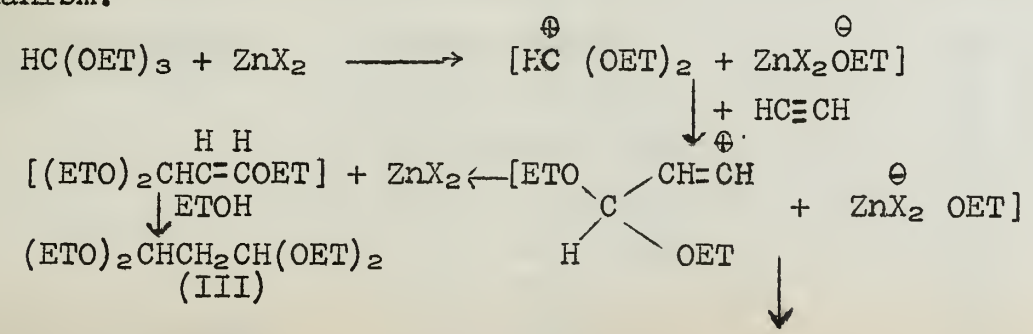
The most effective catalysts are zinc chloride, zinc iodide, zinc nitrate and cadmium iodide.

ACETYLENIC ACETALS

Acetylene reacts under pressure with triethyl orthoformate to give mainly acetylene dicarboxaldehyde bis(diethylacetal) (I; yield 48%) together with a small amount of propialdehyde diethyl acetal (II) and malonaldehyde bis(diethylacetal)(III; yield 28%)

$$HC{\equiv}CH + HC(OET)_3 \xrightarrow[\Delta]{ZnCl_2} (ETO)_2HC\text{-}C{\equiv}C\text{-}CH(OET)_2 \quad (I)$$
$$+ HC{\equiv}C\text{-}CH(OET)_2 \quad (II)$$
$$+ (ETO)_2CHCH_2CH(OET)_2 \quad (III)$$

To explain the reaction, the authors proposed an ionic mechanism.



$$(ETO)_2\text{-}\overset{H}{\overset{|}{C}}\text{-}C\equiv C\text{-}\overset{H}{\overset{|}{C}}(OET)_2 \quad (I) \longleftarrow \left\{ \begin{array}{l} (II)\ (ETO)_2\overset{H}{\overset{|}{C}}\text{-}C\equiv CH + ETOH + ZnX_2 \\ \quad + \overset{\oplus}{H}C(OET)_2 + \overset{\ominus}{Z}nX_2OET \end{array} \right.$$
$$+ ZnX_2 + ETOH$$

ACETYLENIC KETALS

The process, under similar conditions but after substitution of the ortho formic ester by ethyl ortho acetate, gives a ketal.

$$C_6H_5\ C\equiv CH + CH_3\ C(OET)_3 \xrightarrow[ZnCl_2]{\Delta} C_6H_5C\equiv C\ \overset{CH_3}{\overset{|}{C}}\ (OC_2H_5)_2 + C_2H_5OH$$

ACETYLENIC ORTHOESTERS

Similarly the orthoester is obtained as shown below:

$$C_6H_5\ C\equiv CH + C(OET)_4 \xrightarrow[ZnCl_2]{\Delta} C_6H_5\ C\equiv C(OET)_3 + ETOH$$

ALCOHOLS, α-ACETYLENIC δ-ETHYLENIC

Colonge and Falcotet have reported the preparation of alcohols of the following type.[10]

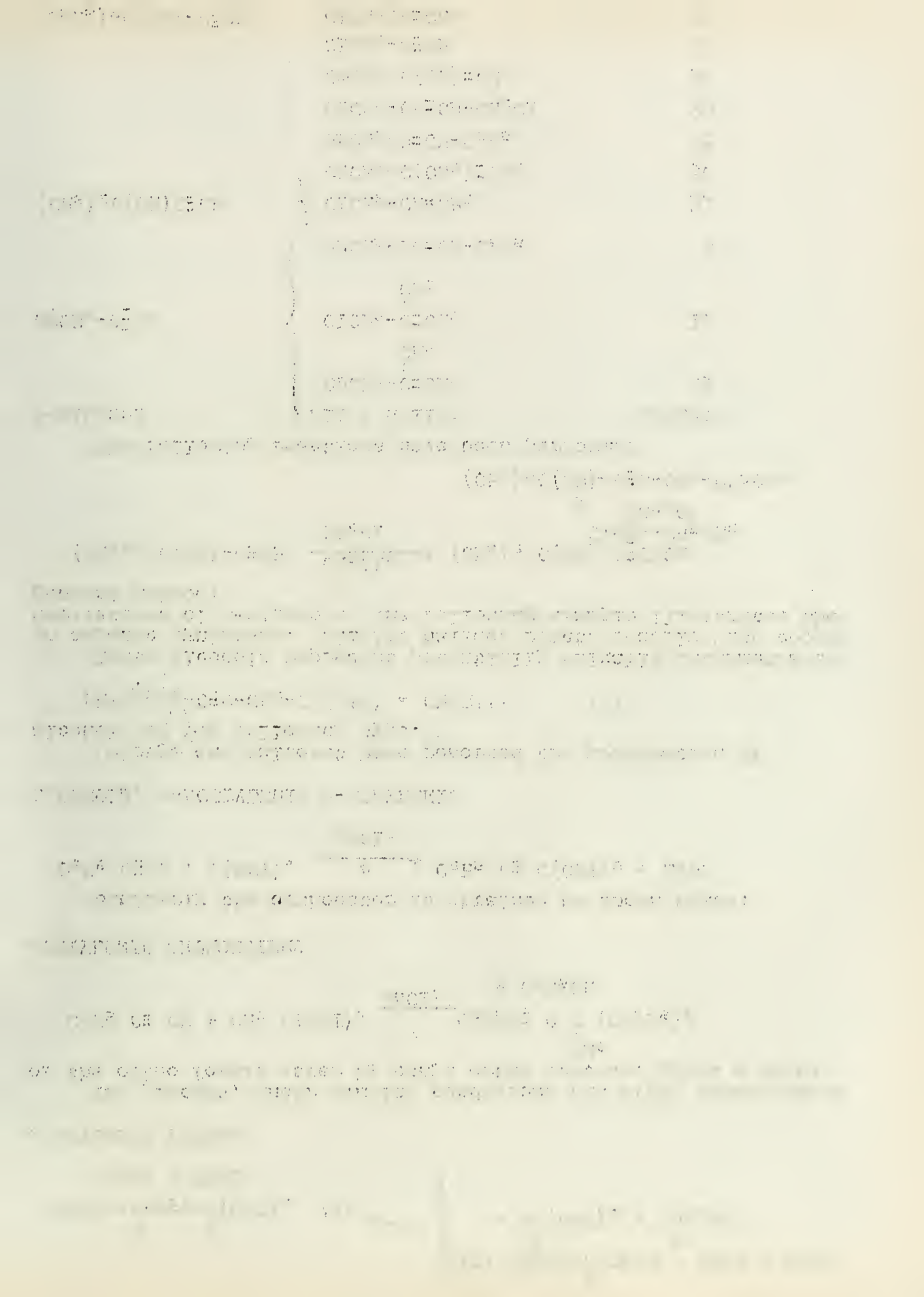
$$RR'C(OH)\text{-}C\equiv C\text{-}CH_2\text{-}C\ (R'') = CH\ R'''$$ (I)

These alcohols represent potentially valuable intermediates in organic synthesis. Allylic halides reacts readily with copper derivatives of α-alkynols The following example illustrates the general method:

$$(CH_3)_2\ C(OH)\text{-}C\equiv CH \xrightarrow[NH_4Cl]{Cu_2Cl_2} (CH_3)_2\ C(OH)\ C\equiv C\text{-}Cu$$
$$\downarrow\ ClCH_2\text{-}CH=CH_2,\ 20\text{-}30^\circ$$
$$(CH_3)_2C(OH)\text{-}C\equiv C\text{-}CH_2\text{-}CH=CH_2$$

The following reactions have been performed

α-alkynol	Allyl halide	Yields %
$HOCH_2\text{-}C\equiv CH$	$BrCH_2\text{-}\overset{CH_3}{\overset{|}{C}}=CH_2$	13
	$ClCH_2\text{-}\overset{CH_3}{\overset{|}{C}}=CH_2$	13
	$BrCH_2\text{-}HC=CH\text{-}C_6H_5$	8
$(CH_3)_2C(OH)C\equiv CH$	$ClCH_2\text{-}CH=CH_2$	53
	$ClCH_2\text{-}C(CH_3)=CH_2$	50
	$BrCH_2CH=CH\text{-}C_6H_5$	45
	$ClCH_2\text{-}CH=CH\text{-}CH_2Cl$	28
	$BrCH_2\text{-}C(Br)=CH_2$	50
	$ClCH_2\text{-}C\equiv CH$	32
$(C_2H_5)_2C(OH)\text{-}C\equiv CH$	$ClCH_2CH=CH_2$	30



PREPARATION OF ALKYL-THIO ALKYNES

The usual method for the obtention of alkyl-thio-alkynes is the following:

1. $RCH_2CHO + R'SH + HCl \rightarrow RCH_2\text{-}CHCl\text{-}SR'$ (I)
2. $RCH_2\text{-}CHCl\text{-}SR' + (CH_3)_2N\text{-}C_6H_5 \rightarrow RCH{=}CHSR'$ (II)
3. $RCH{=}CHSR' + Br_2 \rightarrow RCHBr\text{-}CHBr\text{-}SR'$ (III)
4. $RCHBr\text{-}CHBr\text{-}SR' + (CH_3)_2NC_6H_5 \rightarrow RCBr{=}CHSR'$ (IV)
5. $RCBr{=}CHSR' + KOH \rightarrow RC{\equiv}C\text{-}SR'$ (V)

Steps one and two are accompanied by a number of side reactions and the 1-alkylthioalkenes are obtained in poor yield.

Arens and coworkers have explored systematically numerous methods for the obtention of thioenolethers.[11] They found that acetaldehyde diethylthioacetal when heated with a little phosphoric acid gives a poor yield of vinyl ethyl sulphide, but ethylthioacetals of higher aldehydes could be converted smoothly to thioenol ethers.

$$RCH_2CHO + 2R'SH \xrightarrow{H^+} RCH_2CH(SR')_2 + H_2O$$

$$\uparrow\downarrow H^+$$

$$RCH{=}CHSR' + R'SH$$

II

The alkylthio-alkenes (II) were obtained in very good yield (overall yield 50-60%), and their conversion to alkyl-thio-alkynes (V) was achieved easily following the standard procedure.

The reactivity of the alkyl-thio-alkynes is very interesting since the addition of electrophilic and nucleophilic reagents to the triple bond follows the same orientation.

1. $HC{\equiv}C\text{-}SR' + H_2O \xrightarrow{H^\oplus} H_3C\text{-}COSR' \xrightarrow[H^\oplus]{H_2O} CH_3COOH + R'SH$

2. $HC{\equiv}C\text{-}SR' + RO^- \xrightarrow{ROH} RO\text{-}CH{=}CH\text{-}SR'$

3. $CH_3C{\equiv}C\text{-}SC_2H_5 + H_2O \xrightarrow[HgSO_4]{H^+} CH_3CH_2COSC_2H_5$

4. $CH_3\text{-}C{\equiv}C\text{-}SC_2H_5 + RO^- \xrightarrow{ROH} CH_3\overset{OR}{C}{=}CH\text{-}SC_2H_5$

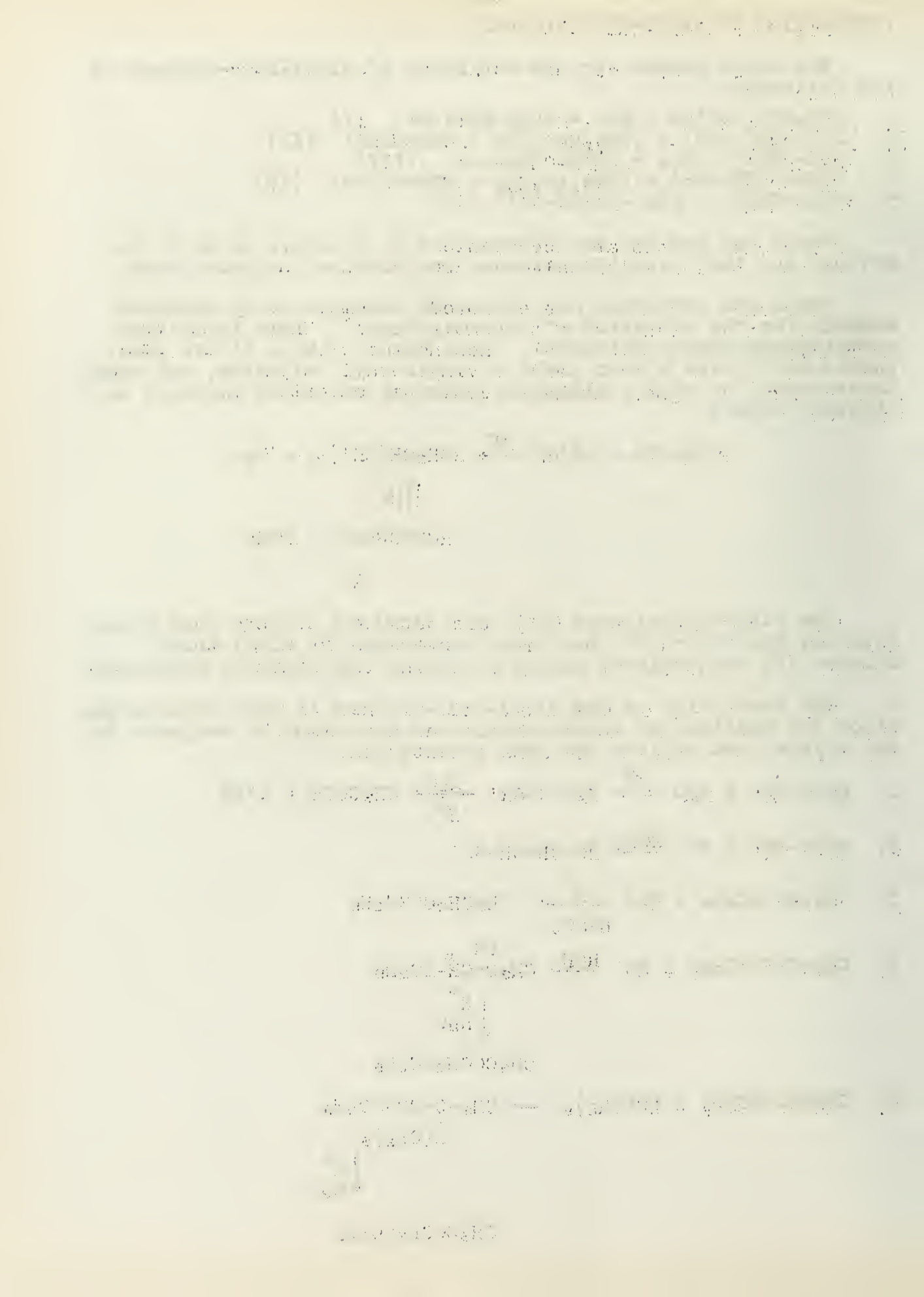
$$\downarrow H^+ \; H_2O$$

$$CH_3COCH_2SC_2H_5$$

5. $CH_3C{\equiv}C\text{-}SC_2H_5 + HN(CH_2)_5 \longrightarrow CH_3\text{-}\overset{N(CH_2)_5}{C}{=}CH\text{-}SC_2H_5$

$$\downarrow H^+ \; H_2O$$

$$CH_3COCH_2SC_2H_5$$



6. $CH_3-C\equiv C-SC_2H_5 + C_2H_5SH \longrightarrow CH_3-\underset{SC_2H_5}{C}=CH-SC_2H_5$

$\downarrow H_2O, H^+$

$CH_3-COCH_2SC_2H_5$

The reactivity of the disubstituted acetylene is much less than for the monosubstituted one.

Synthesis of Conjugated Systems.

In 1905 Straus[12] reported that aerial oxydation of a solution of copper phenyl acetylide in hot acetic acid gave 1,4-diphenyl-butene-yne. Akktor and Weedon have shown that the Straus reaction is a useful general method for the synthesis of vinyl-acetylenes.[13] The reaction yields generally a mixture of cis

$$2\ RC\equiv CCu \xrightarrow[\Delta]{AcOH} RC\equiv C-CH=CHR$$

and trans isomers. No branched chain of the type $CH_2=CR-C\equiv CR$ has been detected.

The following examples illustrate the wide application of the Straus reaction.

1. $2\ C_6H_5-CH=CH-C\equiv CCu \longrightarrow C_6H_5-CH=CH-C\equiv C-CH=CH-CH=CH-C_6H_5$

$\downarrow [H]$ (40%)

1,8,diphenyloctatetraene

2. $2\ CH_3O_2C(CH_2)_8C\equiv CCu \longrightarrow CH_3O_2C(CH_2)_8C=C-C\equiv C-(CH_2)_8CO_2CH_3$

$\downarrow$ hydr.

$HO_2C(CH_2)_8C=C-C\equiv C-(CH_2)_8CO_2H$

trans diacid (75%)

3. $2\ CH_3CO_2CH_2-C\equiv CCu \longrightarrow CH_3CO_2CH_2-CH=CH-C\equiv C-CH_2O_2CCH_3$

4. $2\ CH_3O_2C-C\equiv CCu \longrightarrow [CH_3O_2C-CH=CH-C\equiv C-CO_2CH_3]$

$\downarrow CH_3CO_2H$

$CH_3O_2C-CH=CH-\underset{O_2CCH_3}{C}=CH-CO_2CH_3$

In the last example given above, the vinyl acetylene ester adds spontaneously to yield methyl-β-acetoxymucconate.

Disubstituted Acetylenes

The most widely used process for the obtention of disubstituted acetylenes consists of the reaction of an alkyl halide with a sodium acetylide in liquid ammonia:

$$RX + R'C\equiv CNa \xrightarrow{NH_3\ liq.} RC\equiv CR'$$

This method is limited by the following factors;[14] a) the decreasing solubility of the halide as the chain length of the alkyl portion increases

b) the great tendency of halogen elimination, especially with secondary and tertiary halides.

c) the reaction of ammonia with the halides, particularly when the halogen is very active as in α-halides.

Two recently reported new methods of synthesis of disubstituted acetylenes overcome the above mentioned difficulties.

When α,β-dihydrazones are oxidized at room temperature with silver trifluoroacetate in triethylamine they give disubstituted acetylenes very efficiently.[15]

$$R\text{-}C(=NNH_2)\text{-}C(=NNH_2)\text{-}R' + 4CF_3COOAg + 4\,(C_2H_5)_3N \longrightarrow RC{\equiv}CR' + 4\,CF_3COOH(C_2H_5)_3N + 4\,Ag + 2\,N_2$$

Schlubach and Repenning have reported that acetylenes react smoothly in dioxane with lithium amide to give a pure acetylide.[14]

$$RC{\equiv}CH + LiNH_2 \xrightarrow[\text{dioxane}]{\text{mild temp.}} RC{\equiv}CLi$$

Primary halides react easily in dioxane with the lithium derivative and give an excellent yield of disubstituted alkyne. Branched alkynes which are not obtainable with the sodium ammonia method are synthesized in reasonable yield with the lithium derivative. However, the coupling in this case requires a much more vigorous treatment.

The following examples illustrate the method.

$$C_6H_5\text{-}C{\equiv}CLi + BrCH(CH_3)_2 \xrightarrow[\text{dioxane}]{150^\circ} C_6H_5C{\equiv}C\text{-}CH(CH_3)_2 \quad (65\%)$$

$$CH_3(CH_2)_3C{\equiv}CLi + BrCH(CH_3)_2 \longrightarrow CH_3(CH_2)_3C{\equiv}C\text{-}CH(CH_3)_2 \quad (32\%)$$

With α-haloketone, the reaction occurs exclusively with the carboxyl group. The following equations illustrate this reaction and demonstrate its wide use.

$$C_6H_5C{\equiv}CLi + CO(CH_3)\text{-}CH_2Cl \longrightarrow C_6H_5C{\equiv}C\text{-}C(CH_3)(OLi)\text{-}CH_2Cl$$

$$\downarrow H^+$$

$$C_6H_5C{\equiv}C\text{-}C(CH_3)(OH)\text{-}CH_2Cl \quad \text{(II)}$$

$$\xleftarrow{KOH}$$

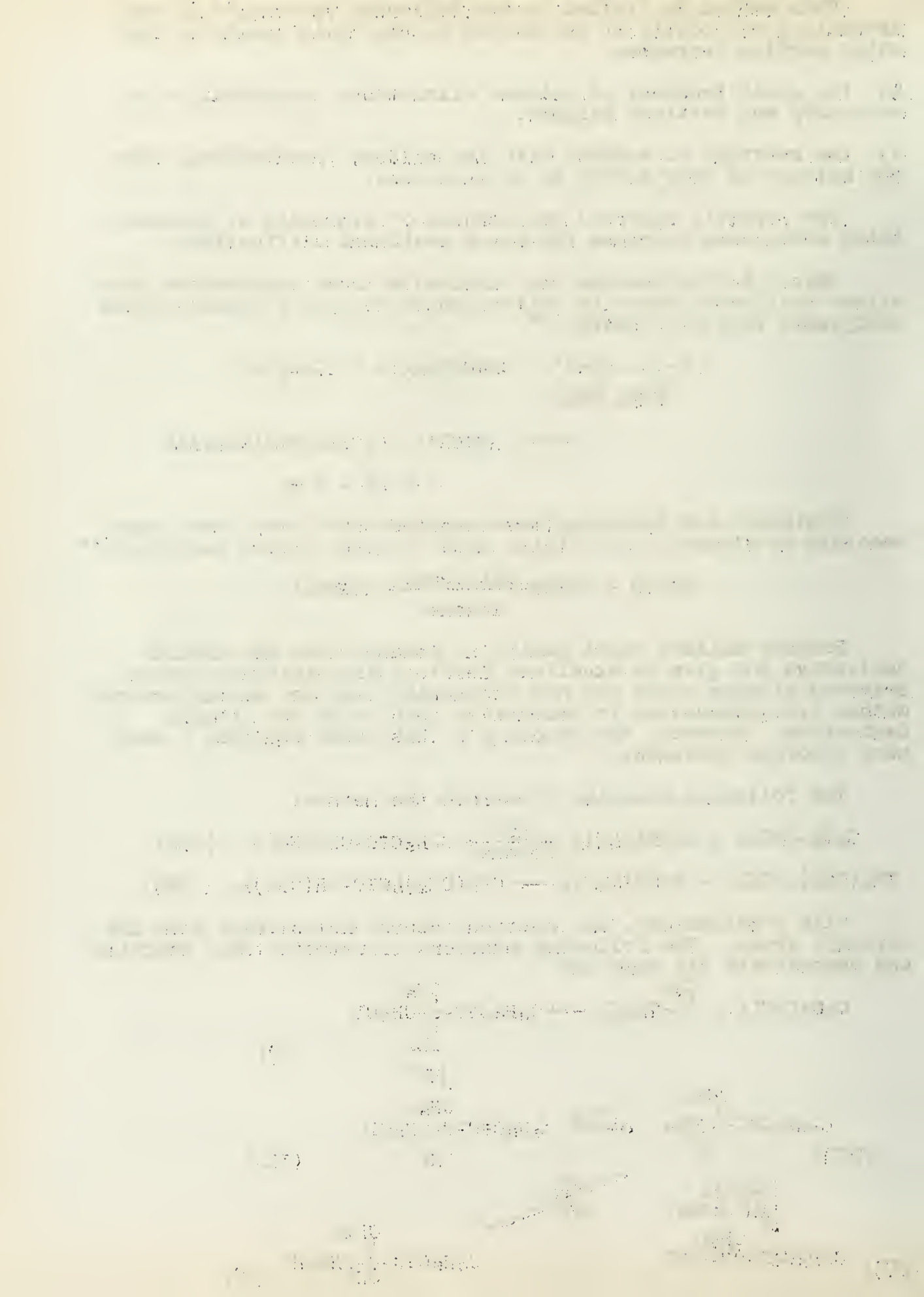
$$C_6H_5C{\equiv}C\text{-}C(CH_3)(O)\text{-}CH_2 \quad \text{(III)}$$

$$\downarrow ZnCl_2 \text{ in ether}$$

$$C_6H_5C{\equiv}C\text{-}CH(CH_3)\text{-}CHO \quad \text{(IV)}$$

$$\xrightarrow[H^+]{H_2O}$$

$$C_6H_5C{\equiv}C\text{-}C(CH_3)(OH)\text{-}CH_2OH \quad \text{(V)}$$



The coupling of lithium phenylacetylide with chloroacetone gives a tertiary alkoxide (I). from which the free alcohol (II) is easily obtained by acidification in a carbon dioxide atmosphere.

In the presence of potassium hydroxide the α-halo alcohol (II) gives an epoxide (III), which in the presence of zinc chloride in ether, rearranges to the aldehyde IV. Acid hydrolysis of the epoxide yields a glycol (V).

Tertiary alkyl halides do not react in dioxane with lithium phenylacetylide even at 150°.

Halo esters give some unexpected reactions as shown below.

1. $C_4H_9\text{-}C{\equiv}CLi + ClCO_2C_2H_5 \xrightarrow[60^\circ]{\text{dioxane}} C_4H_9C{\equiv}CCO_2C_2H_5 + LiCl$

If an excess lithium acetylide is used, a tertiary carbinol is obtained.

$$C_4H_9C{\equiv}CCO_2C_6H_5 + 2\ C_4H_9\text{-}C{\equiv}CLi \longrightarrow (C_4H_9\text{-}C{\equiv}C)_3COLi + C_2H_5OLi$$

2. $C_4H_9C{\equiv}CLi$ or $C_6H_5C{\equiv}CLi + BrCH_2CO_2Et \longrightarrow$ polymers

Lithium butylacetylide or phenylacetylide reacts violently with α-bromo ethylacetate to give polymers.

3. $CH_3CHBrCO_2C_2H_5 + 2LiC{\equiv}CC_4H_9 \longrightarrow CH_3CHBr\text{-}C(OLi)(C{\equiv}CC_4H_9)_2$

$\downarrow H^+$

$CH_3CHBr\text{-}C(OH)(C{\equiv}C_4H_9)_2 \longleftarrow CH_3\text{-}CH(O)\text{-}C(C{\equiv}CC_4H_9)_6$

$\downarrow ZnCl_2$

Oils, but no aldehyde

The epoxide is obtained in reasonable yield (50%). However, on treatment with zinc chloride it gives no aldehydes but a mixture of unidentified oils. The coupling of alkyne halides with lithium acetylide, as illustrated below, gives non-conjugated diynes in variable yields.

$$CH_3(CH_2)_3C{\equiv}C\text{-}CH_2Br + LiC{\equiv}C(CH_2)_2CH_3 \longrightarrow CH_3(CH_2)_3C{\equiv}C\text{-}CH_2\text{-}C{\equiv}C(CH_2)_3CH_3$$

Polyenes

Conjugated polymers are generally obtained by air oxidation of terminal acetylenes in the presence of copper chloride (Glaser Reaction[16]).

$$R(C{\equiv}C)_n\text{-}H + R(C{\equiv}C)_mH \xrightarrow[O_2]{Cu^{\oplus}} R(C{\equiv}C)_{m+n}\text{-}R' + R(C{\equiv}C)_{2n}\text{-}R + R(C{\equiv}C)_{2m}\text{-}R' + \text{cyclic products}$$

As can be seen from the above equations, if two different alkynes are coupled, several side reactions may occur, and the best yield obtained for the product $R(C\equiv C)_{m+n}R'$ is never over 30%.

A method of coupling developed by Chadkievicz and Cadiot have been reported to give excellent yields of dissymmetoic poly alkynes.[17,18]

A polyene is obtained by double decomposition of an acetylene and an alkyne halide in the presence of cuprous ion and an excess of an amine.

$$R(C\equiv C)_nH + Br(C\equiv C)_mR' \xrightarrow[C_2H_5NH_2]{Cu^+} R(C\equiv C)_{n+m}R'$$

A catalytic amount of copper is used. In the presence of air or halo alkyne, the cuprous ions are easily oxidized and the reaction is stopped. The addition of an amine (mono, secondary or tertiary ethylamine generally) prevents the oxidation of the catalyst and thus allows the normal coupling reaction to occur. The chloro alkynes do not undergo the reaction. Only the bromo and iodo derivatives are reactive enough.

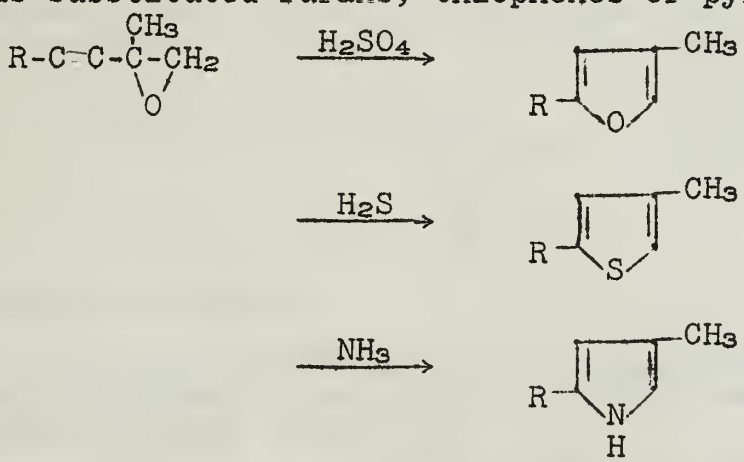
The following polyenes have been prepared:

		Yield
1.	$CH_3CH_2CH_2C\equiv C-C\equiv CCH=CH-CH_2OH$	84%
2.	$CH_3-CH_2CH_2C\equiv C-C\equiv C-CH=CH-CH_2H$	82%
3.	$CH_3-C\equiv C-C\equiv C-C\equiv C-CH=CH-CH_2OH$	95%
4.	$CH_3-C\equiv C-C\equiv C-C\equiv C-CH=CH-CO_2H$	88%
5.	$CH_3-C\equiv C-C\equiv C-C\equiv C-CH_2-CH_2-CH_2OH$	89%
6.	$CH_3-C\equiv C-C\equiv C-C\equiv C-CH_2-CH_2CO_2H$	86%
7.	$C_6H_5-C\equiv C-C\equiv C-CH=CH-CH_2OH$	70%
8.	$C_6H_5-C\equiv C-C\equiv C-CH=CH-CO_2H$	74%
9.	$C_6H_5-C\equiv C-C\equiv C-C\equiv C-CH_3$	91%

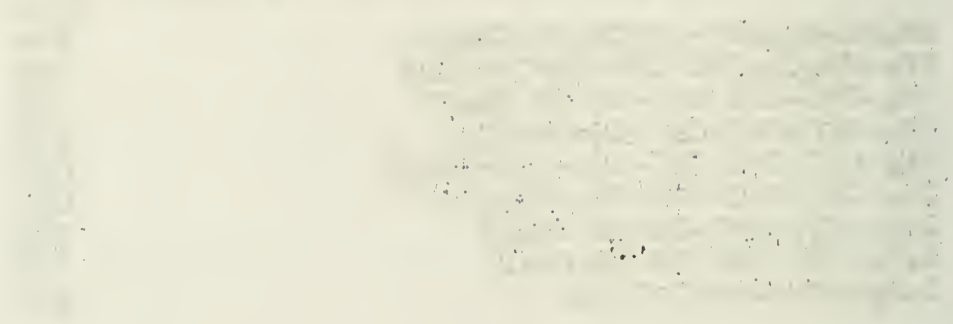
Heterocyclic Compounds.

Alkynes have been increasingly used for the synthesis of heterocyclic rings.

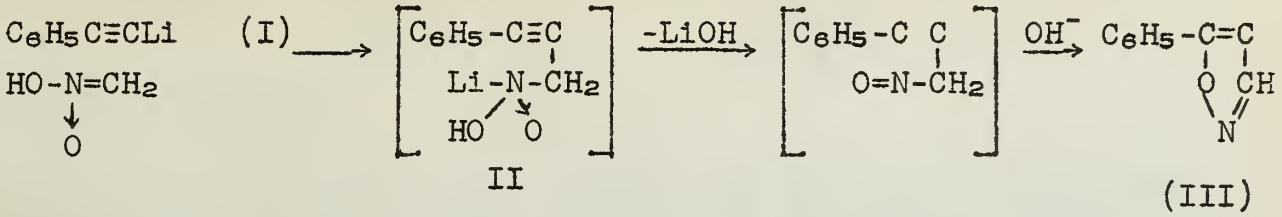
The previously described epoxide, when treated with different reagents yields substituted furans, thiophenes or pyrroles.[14]



Lithium phenylacetylide (I) reacts with the aci-form of nitromethane, to give the addition produce (II) which eliminates lithium hydroxide and when treated with an hydroxide underwent

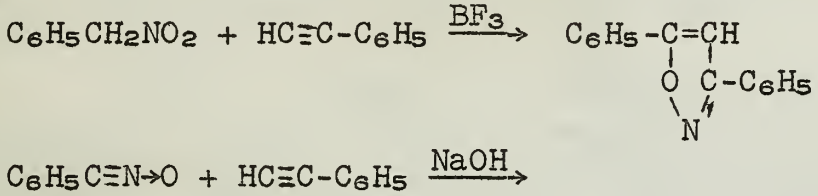


cyclization to the 5-phenylisoxazol (III). Phenylnitromethane in

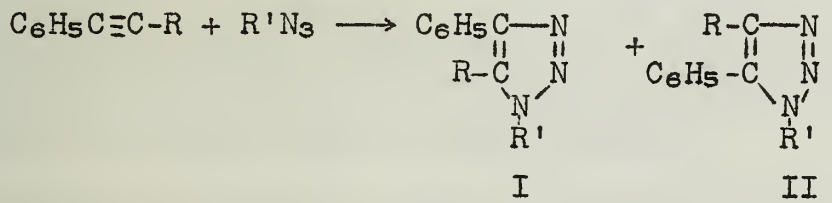


the presence of boron trifluoride reacts with phenylacetylene to give 3,5 diphenylisoxazol.

The same product is obtained when benzonitrile oxide reacts with phenylacetylene in the presence of sodium hydroxide.



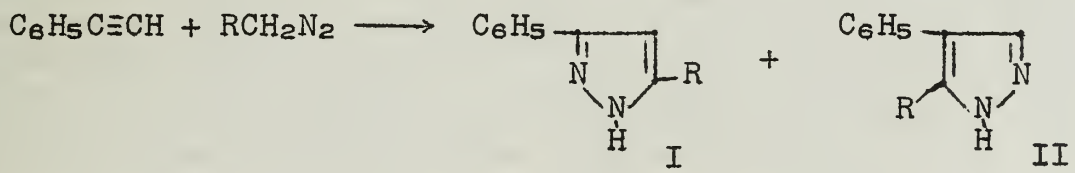
Acetylenes react with azides and form a mixture of heterocyclic isomers.[19]



With 2 different azides and acetylenes the results are as indicated below.

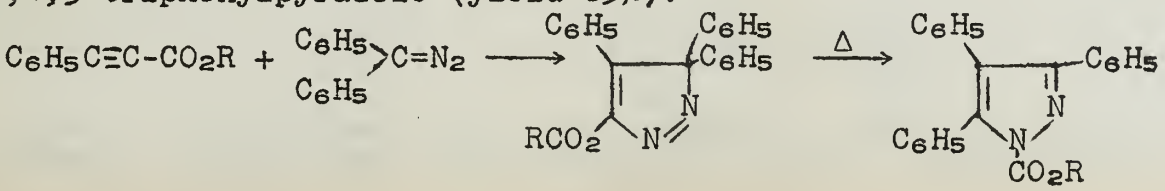
	$C_6H_5CH_2N_3$		$C_6H_5N_3$	
	I	II	I	II
$C_6H_5C{\equiv}CCO_2H$	yields 2.5%	12%	traces	14%
$C_6H_5C{\equiv}CH$	" 39. %	55%	43%	52%

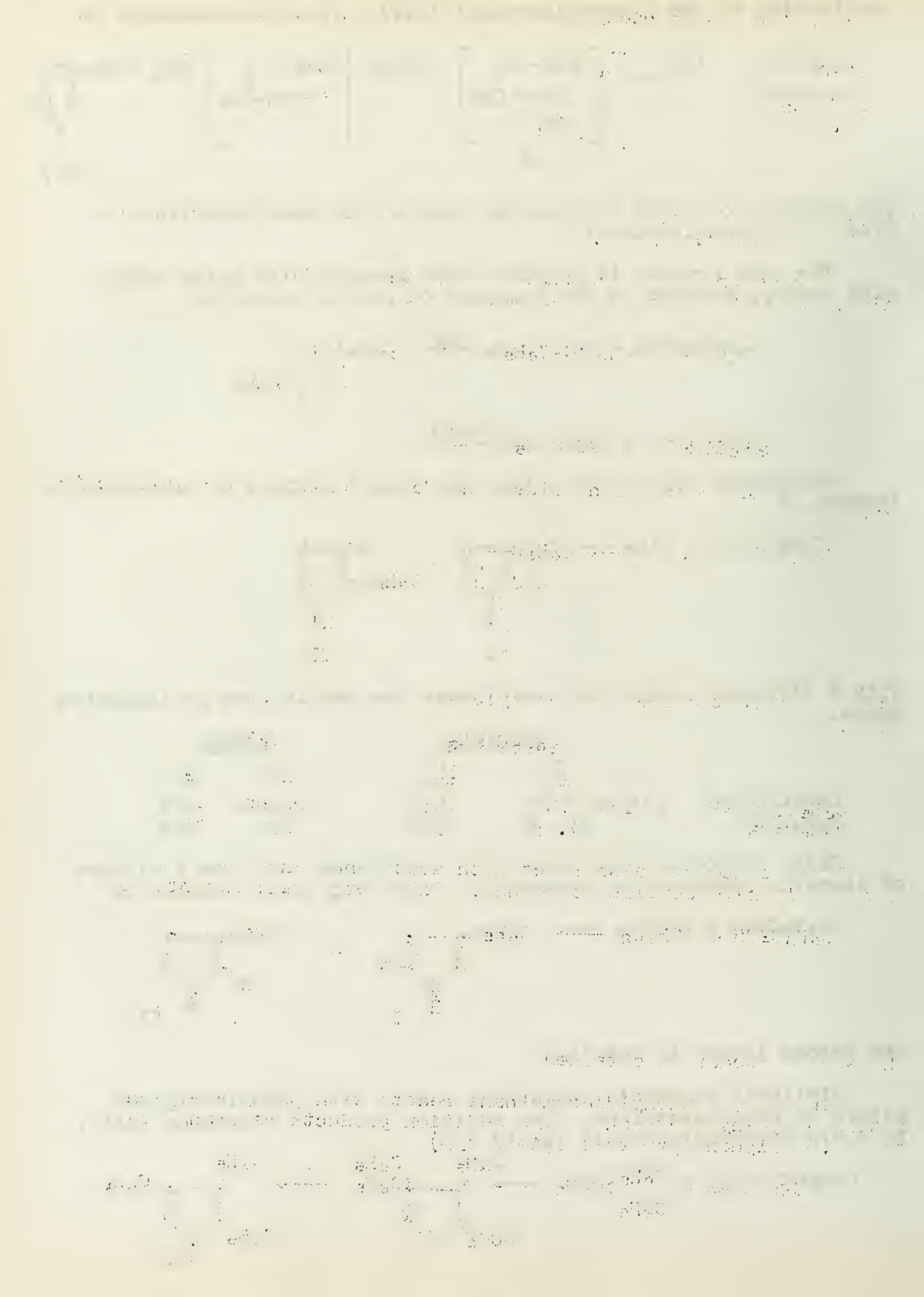
Diazo compounds also react with acetylenes and form a mixture of isomeric heterocyclic compounds. Only very small amounts of

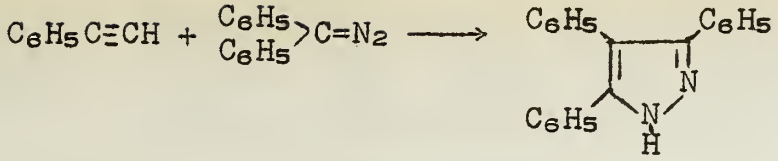


the second isomer is obtained.

Similarly diphenyldiazomethane reacts with phenylacetylene esters or phenylacetylene. The addition products rearrange easily to 3,4,5-triphenylpyrazole (yield 83%).







Practical Techniques.

Some very attractive new practical synthetic procedures have been reported in recent years. Among them the direct obtention of Grignard derivatives and stereospecific reduction methods of triple bonds are of particular interest.

Grignard Derivatives of Acetylenes.

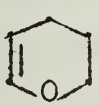
The bromo magnesium derivatives of acetylenes are obtained by interaction of ethyl magnesium bromide and compounds possessing a terminal ethynyl group.[20]

$$RC\equiv CH + C_2H_5MgBr \longrightarrow RC\equiv CMgBr + C_2H_6$$

Some examples of direct attack of magnesium by iodo alkynes in ether have been reported, but the bromides or chlorides derivatives do not react. This weak reactivity appear very similar to the one of vinyl and arylhalides, from which, however, the magnesium halides have been obtained directly by using solvents of higher boiling points. It is thus not too surprising that the Grignard derivatives of acetylene can be obtained directly by action of the haloalkyne on metallic magnesium. All the halides react well with the exception of phenylchloroacetylene ($C_6H_5C\equiv CCl$), which reacts well with magnesium but after hydrolysis gives very little phenylacetylene and much nondistillable residue.

Alkynols can also be used. In this case the preparation of the Grignard derivatives requires several steps:

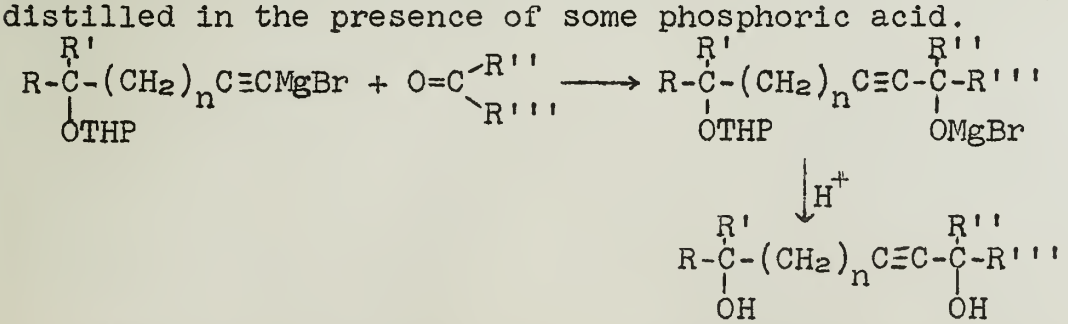
1. $RR'C(OH)C\equiv CH + KOBr \longrightarrow RR'C(OH)C\equiv CBr$

2. $RR'C(OH)C\equiv CBr +$  $\xrightarrow{H^+}$ $RR'C(O\text{-}THP)C\equiv CBr$ (THP)

(DHP)

3. $RR'C(OTHP)\text{-}C\equiv CBr + Mg \longrightarrow RR'C(C\text{-}THP)\text{-}C\equiv CMgBr$

After condensation of the Grignard derivative the tetrahydropyrane portion (THP) is easily removed by slight heating under reduced pressure in the presence of phosphoric acid. This method is excellent for the synthesis of unsymmetrical glycols. The Grignard derivative is condensed with a ketone or an aldehyde then distilled in the presence of some phosphoric acid.



However, the method fails if a tertiary α-acetylenic function is present. In this case the main product is not a glycol but a

complex mixture of dehydration product. Very good yields of magnesium halide derivatives have been obtained, even with tertiary alcohols. In this case, however, the reaction is very slow.

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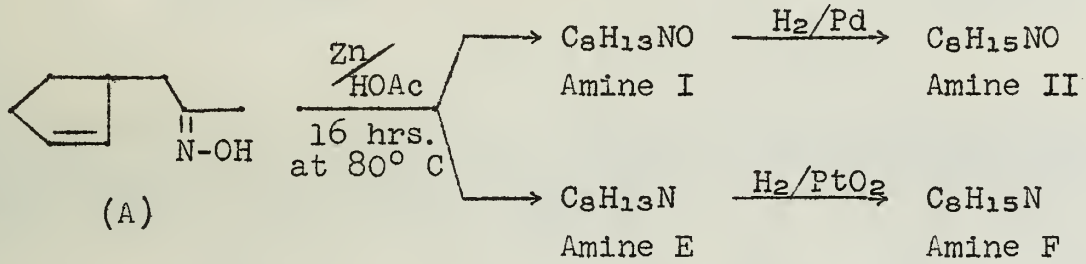
CHEMISTRY OF SOME AZABICYCLO COMPOUNDS FORMED BY A NOVEL OXIME REACTION

Reported by H. B. Renfroe January 11, 1960

INTRODUCTION

This seminar is concerned with the unexpected course of a novel oxime reaction and the structure determination and chemistry of its products. It was discovered that treatment of Δ^2-cyclopentenylacetoneoxime (A) with zinc dust and acetic acid did not lead to the expected product, 1-(Δ^2-cyclopentenyl)-2-aminopropane. Instead, a strongly basic compound--$C_8H_{13}NO$ (Amine I)--arose in 30% yield, along with a second base--$C_8H_{13}N$ (Amine E)--in 4% yield.[1]

Scheme I



Since Amine E and Amine I were found to be related structurally (Scheme V), Amine E was investigated first.

Amines E and F

In the infrared spectrum of Amine E are bands at 3445 cm.$^{-1}$ and 1650 cm.$^{-1}$. There is one C-methyl group and no active hydrogen present.[2] The base reacted quickly with bromine and potassium permanganate, and gave a yellow color with tetranitromethane Oxidation with potassium permanganate produced acetic, succinic, and glutaric acids. The action of nitrous acid on the base gave, with loss of nitrogen, Δ'-cyclopentenylacetone quantitatively.

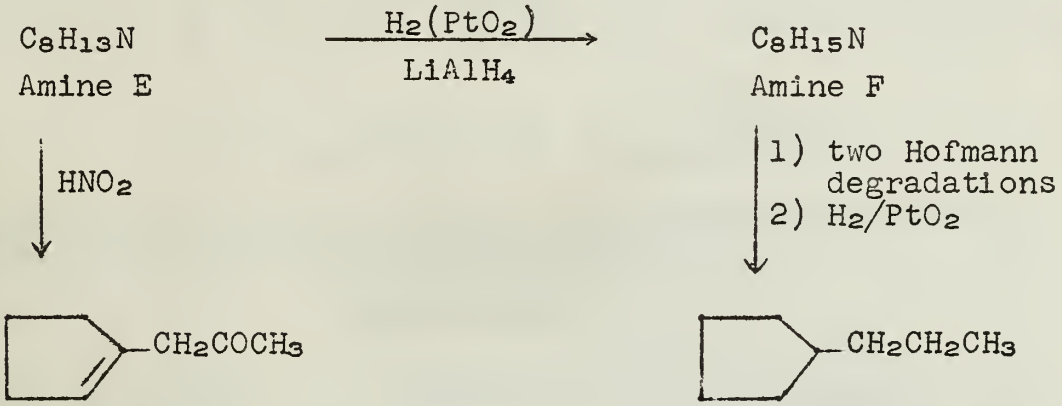
The infrared band at 1650 cm.$^{-1}$ in conjunction with the nitrous acid reaction, led at first to the assignment of a primary amino group. Later, however, this was shown to be incorrect.[3,4] The strong band at 1650 cm.$^{-1}$ disappeared on hydrogenation leaving bands in the infrared spectrum of Amine F at the same position, but of much lower intensity. The band in Amine F shifts from 1650 cm.$^{-1}$ to 1675 cm.$^{-1}$ on formation of the perchlorate, which suggested the presence of a $-\overset{|}{C}=\overset{|}{C}-\overset{|}{N}-$ group[5,6] and its transformation to $-\overset{|}{C}H-\overset{|}{C}=\overset{|}{N}-$.[7]

The reduction of Amine E with lithium aluminum hydride or hydrogen/platinum gave rise to Amine F with consumption of one mole of hydrogen. Amine F formed an alkali-insoluble tosylate and gave the characteristic blue color of secondary amines with sodium nitroprusside and acetaldehyde.[8]

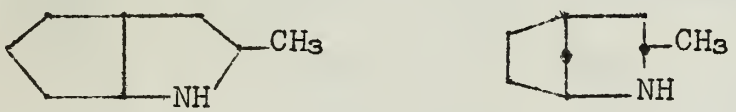
From methylated Amine F, proceeding through two successive Hofmann degradations, a doubly unsaturated hydrocarbon arose

which, on catalytic hydrogenation, consumed two moles of hydrogen to give n-propylcyclopentane (Scheme II), identified by comparison of infrared spectra and physical constants with those of an authentic sample.[9]

Scheme II

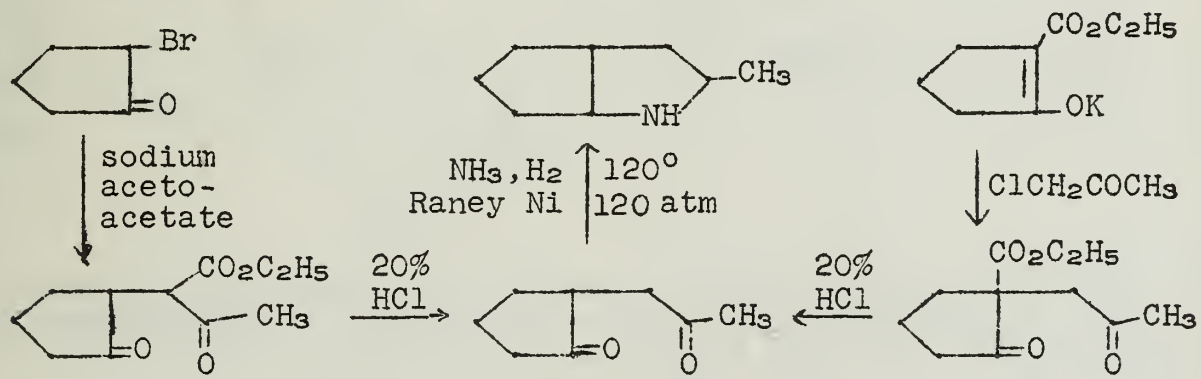


If one assumes on the basis of the results of deamination of Amine E with nitrous acid that the linkage of the nitrogen atom is to the middle of the n-propyl side chain, then one of the following formulas must fit for Amine F:

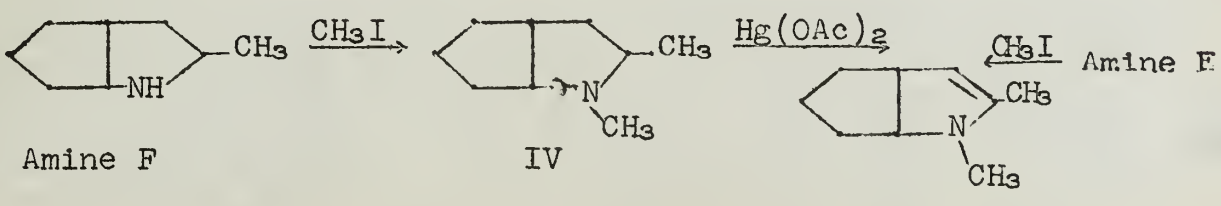


I II

Amine F was synthesized unequivocally by the following method, and was shown to possess structure (I) (3-methyl-2-azabicyclo-[3,3,0]-octane).[10] The ring fusion is cis.



The structure of Amine E could be deduced from the following transformations:[11,12]

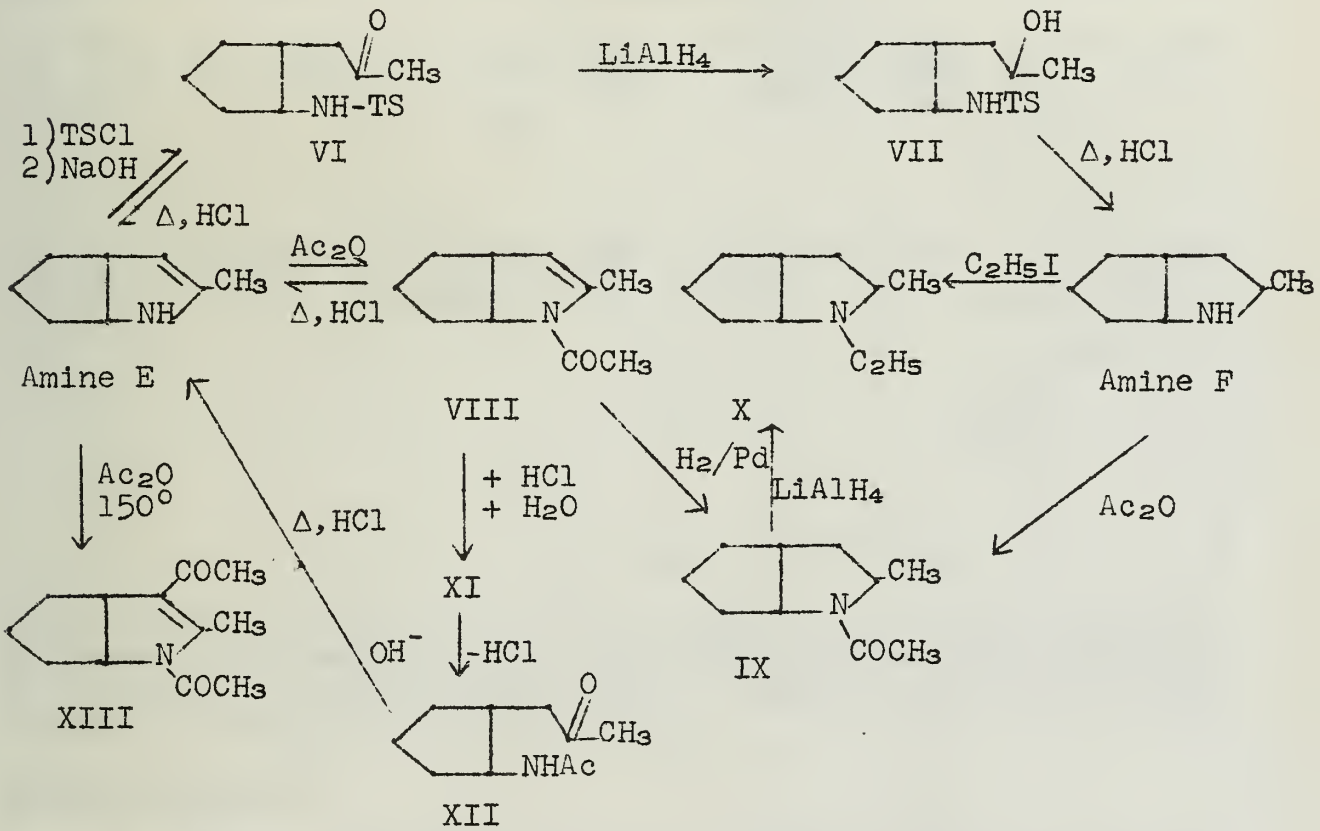


Amine F IV V

Compound (V) possesses an infrared band at 1640 cm.$^{-1}$ characteristic of enamine double bonds (1675 cm.$^{-1}$ for the perchlorate and picrate). The ultraviolet absorption maximum is displaced from 211 mμ (ε=4280) to 236 mμ[13] (ε=13,250) and the basicity from pK_a= 10.1 to pK_a=11.9[14] in the change from compound (IV) to (V), corresponding to the usual differences between the hydrogenated products and the corresponding enamines. Amine E could therefore be represented by the following enamine-imine tautomeric relationship:

The relations of Amine E, Amine F, and their acetylated and tosylated derivatives are shown in Scheme III.

Scheme III



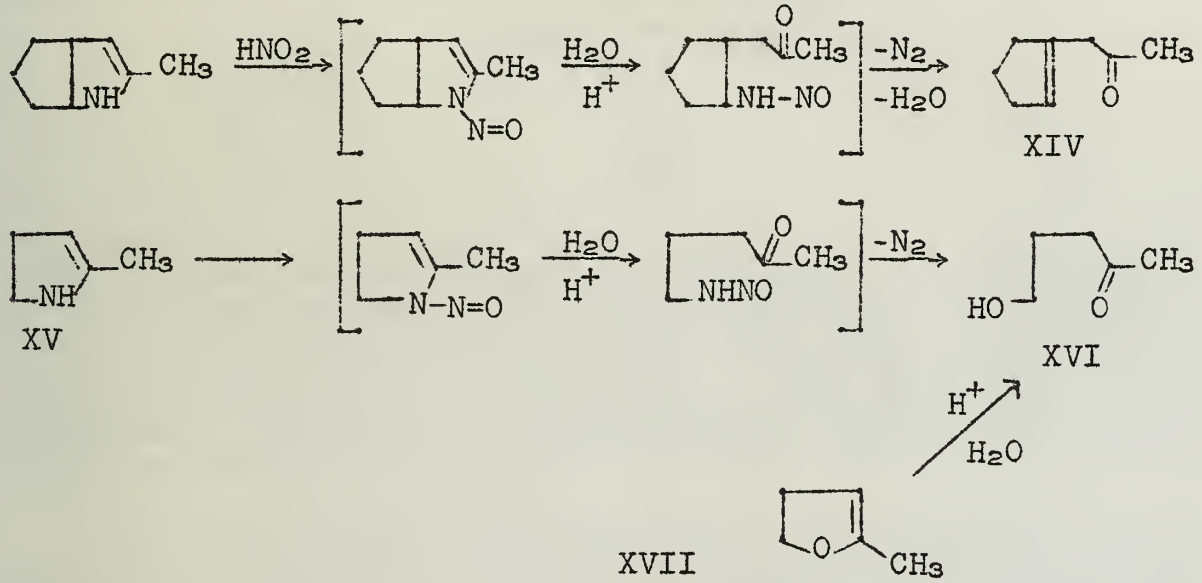
Compound (VI) gave an iodoform reaction at room temperature and a semicarbazone; it possesses a band in the infrared at 1712 cm.$^{-1}$, and an active hydrogen, (in agreement with the -$NHSO_2$-group). The opening of the ring in Amine E by tosyl chloride and base is analogous to the reaction of 2-methyl-Δ^2-pyrroline with benzoyl chloride and potassium hydroxide.[15]

Monoacetyl-Amine E (VIII) was obtained by action of acetic anhydride on Amine E; it gave a brown color with tetranitromethane, reacted with potassium permanganate, and by titration with monoperphthalic acid[16] showed one double bond. The ultraviolet absorption spectrum had a maximum at 245 mμ (ε=11,380), compatible with an enamine structure,[17] as is the infrared spectrum, which possesses strong bands at 1670 cm.$^{-1}$ (amide) and 1645 cm.$^{-1}$ (C=C). The relation of VIII to Amine F is shown in the above scheme.

The action of concentrated hydrochloric acid on VIII at room temperature gave a compound (XI) whose structure was not determined, but which possessed a mole of HCl and a mole of water more than (VIII) and gave rise to compound (XII) on addition of base. Compound (XII), m.p. 77 to 78°, was formulated as shown on the basis of its ultraviolet and infrared spectra, positive iodoform reaction, and its reaction with hydrochloric acid to form Amine E.

The diacetyl compound XIII contains an acetyl group bound to carbon, probably in the position β to the nitrogen atom. XIII gave a positive iodoform reaction, possesses an ultraviolet maximum at 308 mμ (ϵ=16,300) and gave a deep red dinitrophenylhydrazone.

In order to illustrate the reaction of a secondary amine with nitrous acid, such as Amine E's giving rise to a Δ'-cyclopentenylacetone (XIV), 2-methyl-Δ^2-pyrroline (XV) was investigated, and found to react in the same manner.

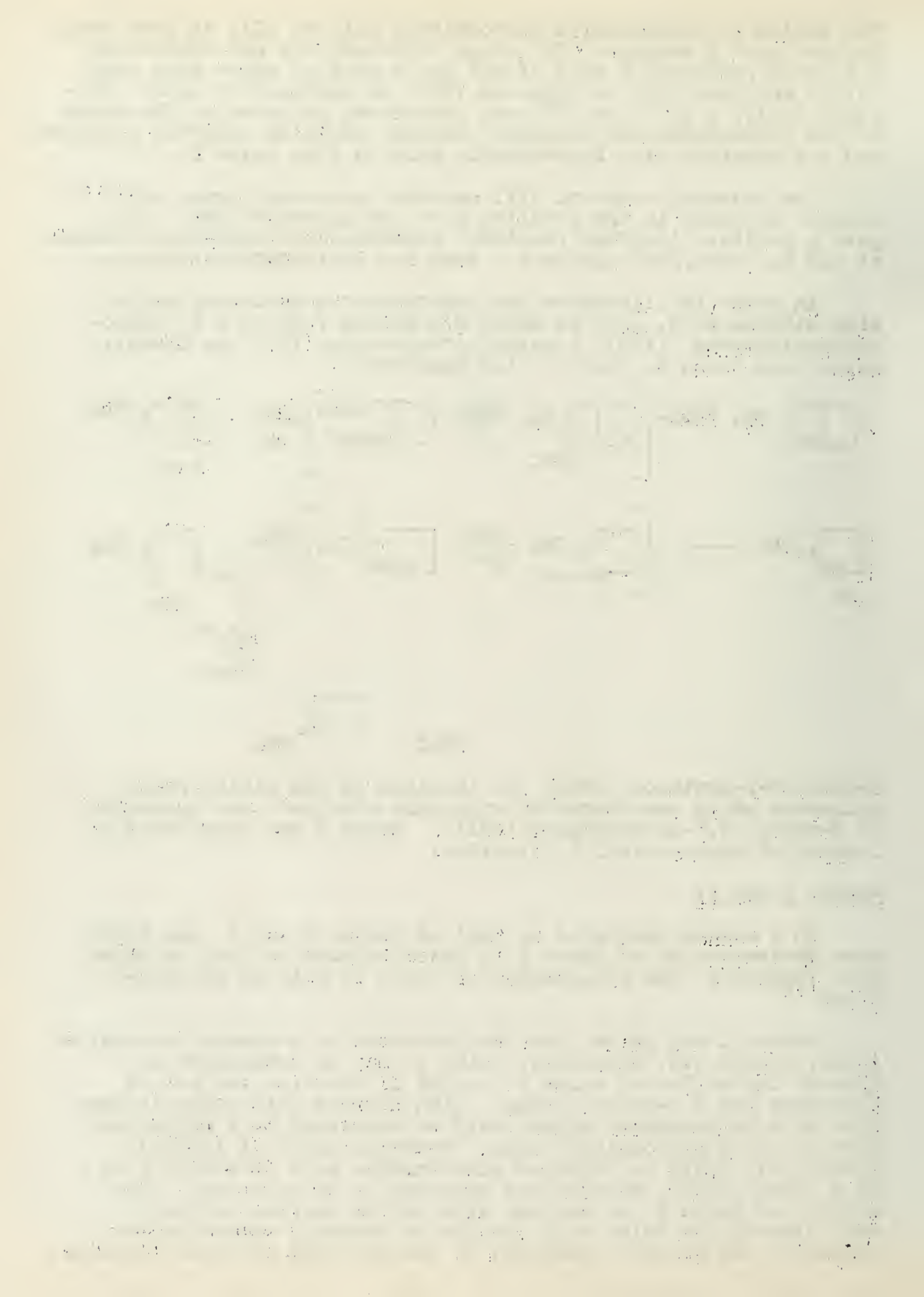


5-hydroxy-2-pentanone (XVI) was isolated as its dinitrophenylhydrazone which was identical with that obtained from hydrolysis of 2-methyl-4,5-dihydrofuran (XVII). Amine E was formulated as 3-methyl-2-azabicyclo[3,3,0]-octene.

Amines I and II

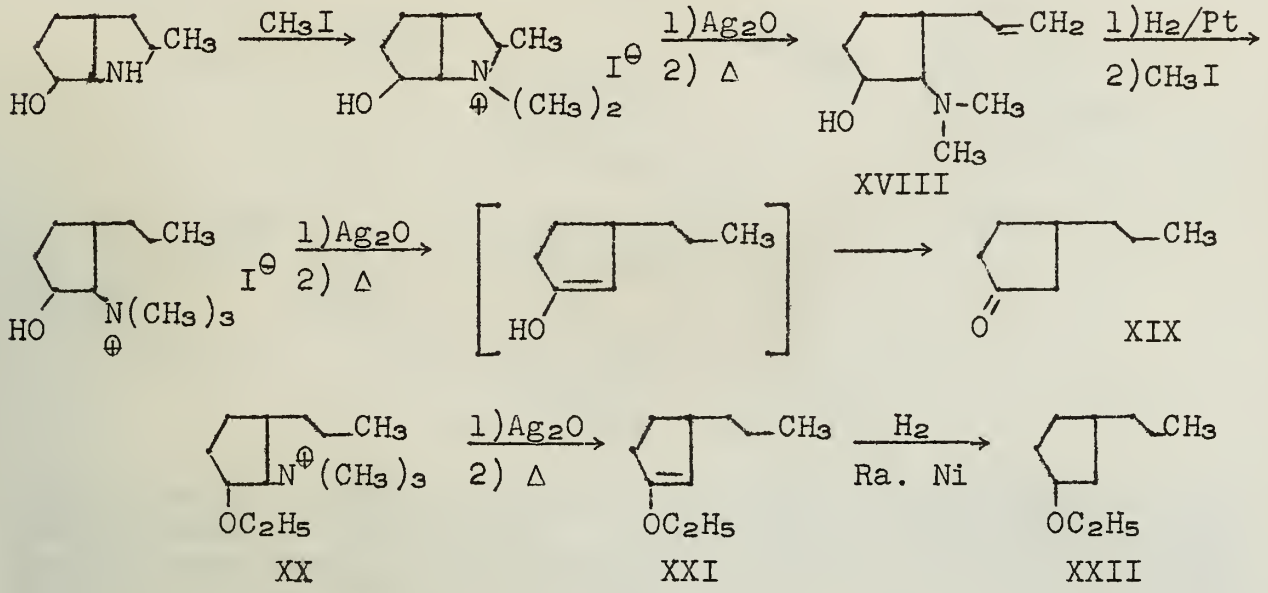
In a manner analogous to that of Amines E and F, the structure determination of Amine I is based in part on that of Amine II. Therefore, the elucidation of Amine II will be described first.[18]

Amine II and Amine F can be converted to a common derivative (XXXI, Scheme VI); therefore, Amine II may be considered as a hydroxy derivative of Amine F. Amine II contains two active hydrogens and a C-methyl group. With nitrous acid Amine II gave rise to a nitrosoamine which could be converted to a hydrazine with zinc and hydrochloric acid. N-acetyl-Amine II (XXVIII, Scheme VI), could be oxidized with chromic acid in acetic acid to a ketone (XXX), showing the hydroxyl to be secondary. The ability of Amine II to complex with cupric sulfate, giving a dark blue-violet color very similar to N-methyl ethanolamines, suggested the relative position of the nitrogen atom and hydroxyl



group. Conclusive evidence for the position of the hydroxyl group was established by means of the two-stage Hofmann degradation shown in Scheme IV.

Scheme IV



The presence of the terminal methylene in XVIII was shown by isolation of formaldehyde dinitrophenylhydrazone after oxidation with sodium metaperiodate-potassium permanganate, and terminal olefin bands in the infrared spectrum. The formation of (XVIII) showed that the nitrogen atom is bound to the carbon atom holding the methyl group. That the nitrogen was directly bound to the cyclopentane ring was shown by the product (XIX) of the second Hofmann degradation (Scheme IV).

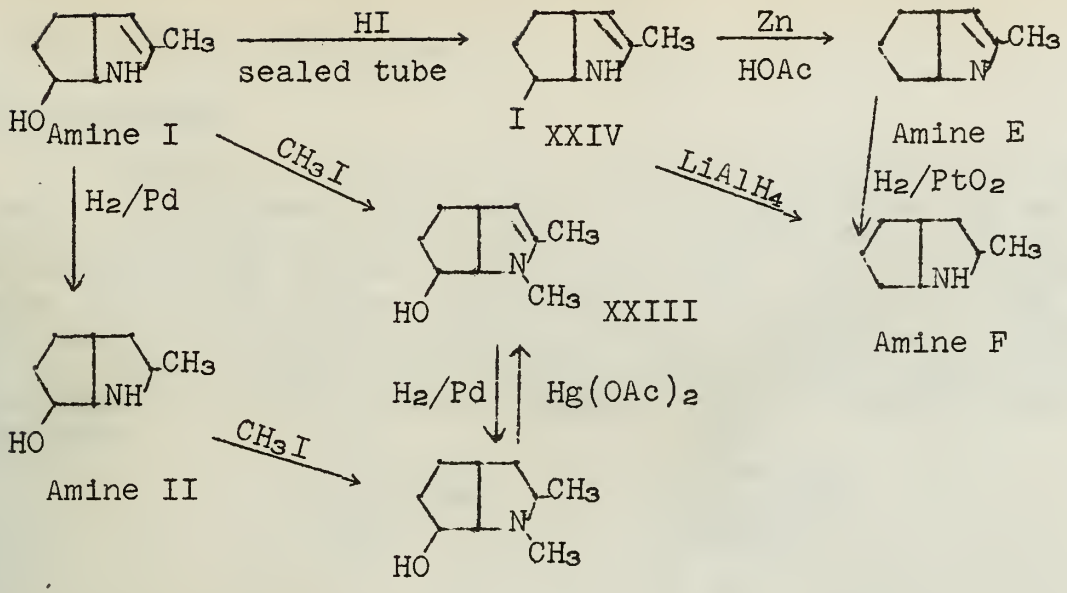
The second Hofmann degradation gave rise to n-propyl cyclopentanone-3 (XIX), identified by its 2,4-dinitrophenylhydrazone, semicarbazone, and by comparison of properties with an authentic sample. Hofmann degradation of (XX) yielded (XXI), substantiating the enol intermediate. (XXI) and XXII) were identified by comparison of infrared spectra and melting points with authentic samples.

Amine II could therefore be formulated as 3-methyl-8-hydroxy-2-azabicyclo[3,3,0]-octane.

With the assumption that Amines E and F have the same relationship to each other as Amines I and II, the following structures should correspond to Amine I:

Amine I is a strong base of great stability, which can be distilled undecomposed over zinc dust. The compound is optically active and contains one C-methyl group and one active hydrogen. The relationship of Amine I to Amines II, E, and F is shown in Scheme V.

Scheme V



The hydroxyl function of Amine I was shown by the formation of a phenylurethane from (XXIII). Under vigorous conditions the hydroxyl group could be replaced using hydriodic acid in a sealed tube, producing (XXIV), which gave rise to Amine E or F on reduction.

The reaction of Amine I with nitrous acid is similar to that of Amine E. A compound was isolated which had carbonyl bands in the infrared spectrum at 1750 cm.$^{-1}$ and 1720 cm.$^{-1}$, gave a positive iodoform reaction, and formed a bis-2,4-dinitrophenylhydrazone. The compound is not identical with acetonyl-cyclopentanone-2, and from the formula shown for Amine I should be acetonyl cyclopentanone-3, but unfortunately this was not established.

Treatment of Amine I at 100° with acetic anhydride yielded a diacetyl derivative (XXV) (Scheme VI) from which Amine I could be regenerated by dilute acid hydrolysis. The unsaturation in (XXV) was detected by permanganate and tetranitromethane tests, and by consumption of one mole of bromine. (XXV) has a band in its ultraviolet absorption spectrum at 244 mμ (ϵ=9960) compatible with an N-acetylated enamine, while infrared bands at 1735 cm.$^{-1}$ and 1250 cm.$^{-1}$ suggested the presence of an ester group. An infrared band at 1677 cm.$^{-1}$ was attributed to amide carbonyl and at 1650 cm.$^{-1}$ to an olefinic group.

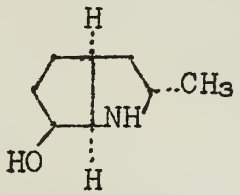
Catalytic hydrogenation in methanol of the diacetyl compound (XXV) produced the diacetyl derivative of Amine II (XXVI), which on reduction with lithium aluminum hydride gave the N-ethyl derivative (XXVII) of Amine II, formed also by hydride reduction of N-acetyl-Amine II (XXVIII). Hydrogenation of compound (XXV) in acetic acid produced a compound containing a C-acetyl group in addition to O- and N-acetyl groups, for it possesses a typical ketone absorption in its ultraviolet spectrum at 276 mμ (ϵ=15), and forms a semicarbazone. Structure XXIX was assumed for this compound.

In Scheme VI are shown the acetylated and tosylated derivatives of Amines I, II, and F. Amine I is known as 3-methyl-8-hydroxy-

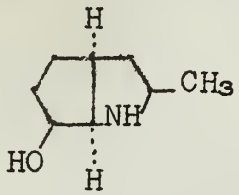
2-azabicyclo[3,3,0]-octene.

Stereochemistry

In addition to Amine II, an Amine IIa originated in small amount on hydrogenation of Amine I. N-acetyl-Amine IIa on chromic acid oxidation yielded a ketone which was different from the corresponding ketone of Amine II (XXX). It is possible that Amines II and IIa differ only in steric arrangement of the methyl group since the infrared spectra are not dissimilar. Amine IIa did not form a complex with cupric sulfate while Amine II did. From these facts the authors suggested the following stereochemistry:



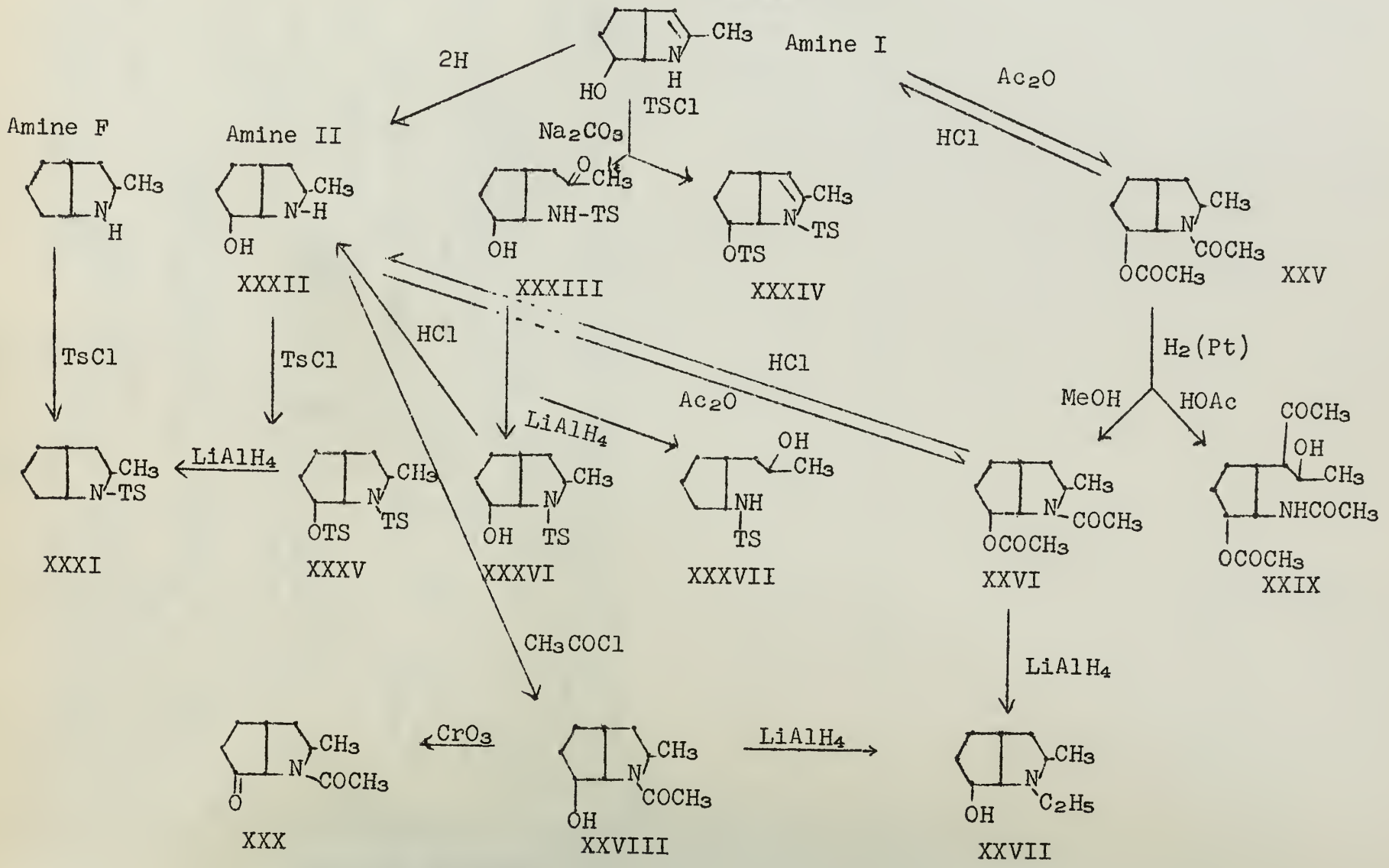
Amine II

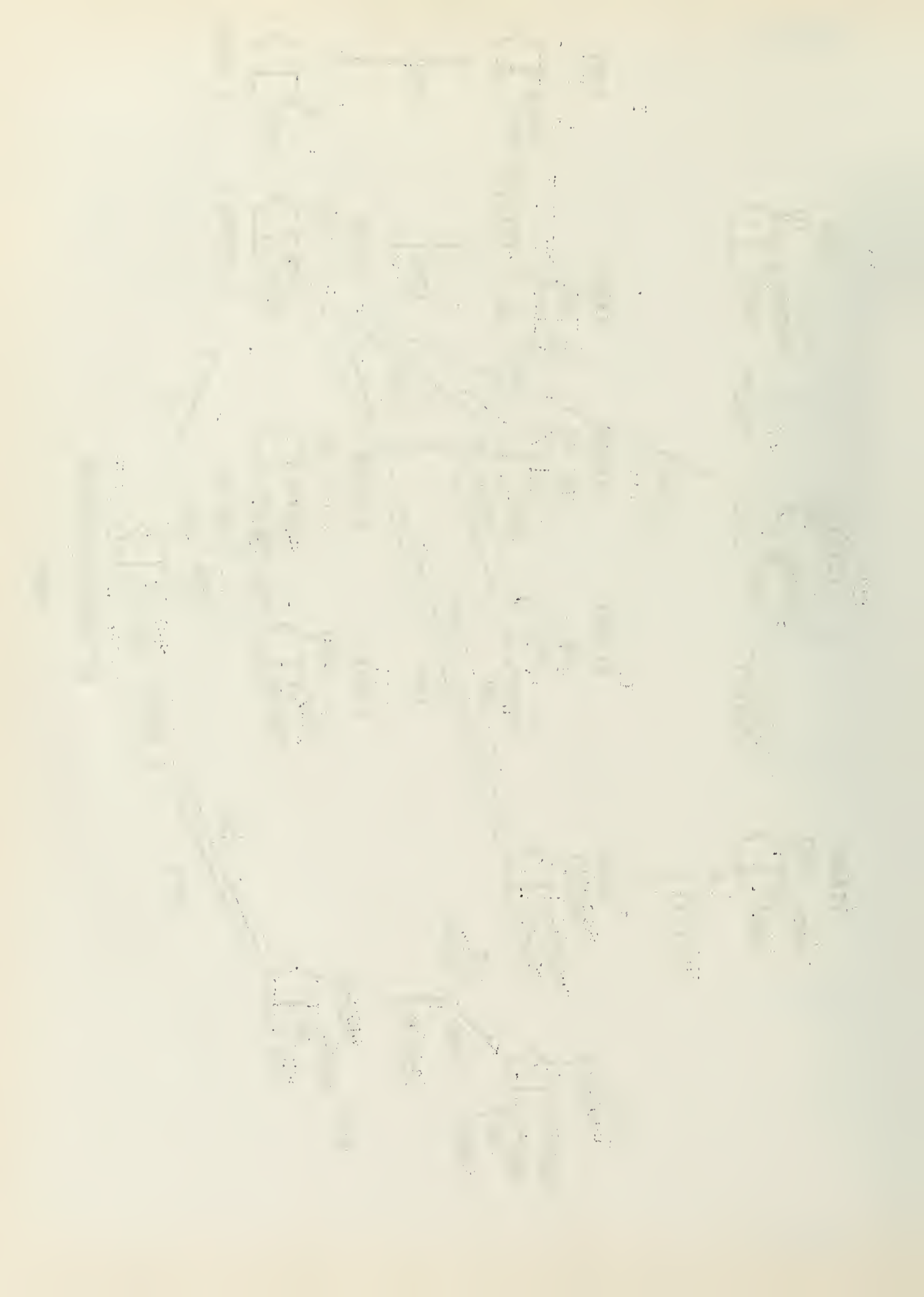


Amine IIa

In Amine IIa steric interaction from the endo methyl group would appear to prevent chelate formation. Also, if the hydroxyl were exo rather than endo chelate and hydrogen bond formation would not appear possible.[19] That the hydroxyl is exo in Amine IIa can not be ruled out; however, it would seem unlikely that the stereochemistry at the carbinol carbon should be different in Amines II and IIa, since they both arise from Amine I by hydrogenation.

Reaction Scheme VI





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THE EFFECT OF METAL SALTS UPON FREE RADICAL REACTIONS

Reported by Robert E. Pearson January 14, 1960

While metal salt catalysis of free radical reactions and the production of free radicals by inorganic redox systems may or may not be identical phenomena, they long have been of interest from both the practical and theoretical standpoints. Industrial use has been made of the ability of ferrous ions to decompose hydrogen peroxide and initiate radical chain polymerizations. The investigations and conclusions concerning this and similar decompositions and the catalyzed oxidations of hydrocarbons have been many and varied (1,2). Recently metal salts have been found to influence the products of radical reactions, opening new synthetic possibilities and yielding insights into the operative mechanism (3-6). It is these latest reactions with which this seminar is most concerned.

NEW AND MODIFIED REACTIONS

In Table I are indicated a number of cases whereby a slightly activated proton is replaced by an alkyl or aralkyl peroxy group, a phthalimido group, or an ester group. Although some of these reactions do proceed to a slight extent in the absence of metal salts, catalytic amounts of copper, cobalt, or manganese salts give good to excellent yields of the various products, with fewer by-products. Kharasch and Fono (5,6) suggest some mechanisms whereby the metal salts not only initiate a free radical reaction but participate in the reaction by stabilizing the intermediate radical or radical complex. The best evidence for this stabilization is found in some reactions whose course is greatly modified by the presence of certain metal salts.

A chain mechanism for the decompositions of hydroperoxides has been suggested, with metal salts acting as both oxidants and reductants.

(a) $ROOH + M^{+} \longrightarrow RO\cdot + M^{++} + (OH)^{-}$

(b) $ROOH + M^{++} \longrightarrow ROO\cdot + M^{+} + H^{+}$

$RO\cdot + M^{+} \longrightarrow RO^{-} + M^{++}$

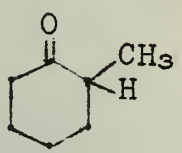
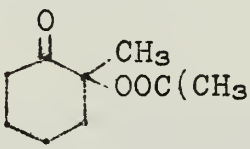
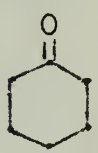
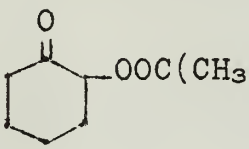
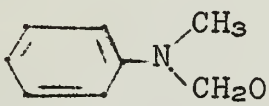
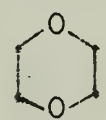
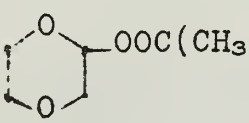
$RO\cdot + ROOH \longrightarrow$ induced decomp. of peroxide (ketone, alcohol, RO·)

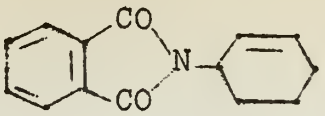
Direct evidence for the existence of RO· radicals has been obtained (7) by decomposing hydroperoxides with equimolar amounts of ferrous salts in the presence of butadiene. The RO· radicals add to the olefin and the resultant radical dimerizes.

$RO\cdot + H_2C{=}CHCH{=}CH_2 \longrightarrow (ROC_4H_6)\cdot$

$2(ROC_4H_6)\cdot \longrightarrow (ROCH_2CH{=}CHCH_2{-})_2$

TABLE I (4,5)

Substrate	Peroxide	Catalyst	Product	Yield
Cyclohexene	$(CH_3)_3COOH$	Co^{++}(naphthenate)	t-bu. peroxy-cyclohexene-2	60%
$C_6H_{13}CH=CH_2$	"	"	1-t-bu. peroxyoctene-2 3-t-bu. peroxyoctene-1	85%
Cyclohexene	$C_6H_5(CH_3)_2COOH$	Cu_2Cl_2	α-cumylperoxy-cyclohexene	quant.
$C_5H_{11}CH_2CH=CH_2$	$(CH_3)_3COOH$	Cu_2Cl_2, Co^{++} (2-ethyl hexoate)	$C_5H_{11}CH=CHCH_2OOC(CH_3)_3$, $C_5H_{11}CHCH=CH_2$ $\vert$ $OOC(CH_3)_3$	
$C_6H_5(CH_3)_2CH$	"	Cu_2Cl_2, $CuCl_2$, Cu_2Br_2, $CuBr_2$, Cu^+, Cu^{++}(benzoate) Co 2-ethylhexoate Manganous Bromide	$C_6H_5(CH_3)_2COOC(CH_3)_3$, $C_6H_5(CH_3)_2COH$	
	"	Cu_2Cl_2		75%
	"	Cu_2Cl_2		20%
	"	"		90%
p-$CH_3C_6H_4CH_3$	"	"	p-$CH_3C_6H_4CH_2OOC(CH_3)_3$	85%
	"	"		50%
$CH_2=CHCH=CH_2$	"	Co^{++}(naphthenate)	1,4-di (t-bu peroxy) butene-2 2,3-di (t-bu peroxy) butene-1	
Cyclohexene C_6H_5COOH	"	Cu_2Cl_2	2-cyclohexen-1-yl benzoate	>90%
$C_6H_5(CH_3)_2CH$, C_6H_5COOH	"	"	$C_6H_5(CH_3)_2COCOC_6H_5$	<20%
$C_6H_{13}CH=CH_2$, C_6H_5COOH	"	"	$C_5H_{11}CHCH=CH_2$ $\vert$ $OCOC_6H_5$	50%

 $(CH_3)_3COOH$ Cu_2Cl_2  14%

$C_6H_5(CH_3)_2CH$, $((CH_3)_3CO)_2$ " $C_6H_5(CH_3)_2COCOC_6H_5$ --
C_6H_5COOH

Similarly, $RO_2\cdot$ radicals were produced in butadiene from t-butyl hydroperoxide with a catalytic amount of cobaltous naphthenate (8). The radical formed by the addition of $RO_2\cdot$ to the butadiene gives a dialkyl peroxybutane.

$$ROO\cdot + H_2C{=}CHCH{=}CH_2 \longrightarrow (ROOC_4H_6)\cdot \longrightarrow ROOC_4H_6OOR$$

Oxygen evolution probably comes from one of the following reactions:

$$2\ ROO\cdot \longrightarrow 2\ RO\cdot + O_2$$

$$2\ ROO\cdot \longrightarrow \text{non-radical products} + O_2$$

$$ROO\cdot + R'OOH \longrightarrow ROH + O_2 + R'O\cdot$$

Russell (9) has verified the second reaction, and the first is likely in the cases involving tertiary alkyl peroxy radicals.

It has been shown (5,10) that a carbon free radical apparently reacts simultaneously with a hydroperoxide and an oxidizing agent in the decomposition of acetyl peroxide in cumene and t-butyl hydroperoxide, a radical complex being formed.

$$(CH_3CO_2)_2 \longrightarrow 2\ CH_3\cdot + 2\ CO_2$$

$$CH_3\cdot + C_6H_5(CH_3)_2CH \longrightarrow CH_4 + C_6H_5(CH_3)_2C\cdot$$

$$C_6H_5(CH_3)_2C\cdot + ROOH \longrightarrow ROOH\cdot C(CH_3)_2C_6H_5 \text{ (radical complex)}$$

$$(\text{complex}) + Ox \longrightarrow ROOC(CH_3)_2C_6H_5 + (Ox + e)$$

The oxidizing agent may be the peroxide. The radical complex is identical to the one formed from a peroxy radical and a hydrocarbon. Kharasch and Fono visualize it as a resonance hybrid of a hydrogen bonded species and a charge-transfer complex. Unpalatable as this explanation may be, the alternative requires the presence of $ROO\cdot$ radicals that pick up cumyl radicals as soon as they are formed. These would be produced by

$$CH_3\cdot + ROOH \longrightarrow CH_4 + ROO\cdot$$

From these considerations, the authors suggested the following mechanism for the metal-catalyzed formation of peroxides from hydroperoxides and molecules containing activated hydrogen:

$$ROOH + M^{+} \longrightarrow RO\cdot + M^{++} + (OH)^{-}$$

$$RO\cdot + R'H \longrightarrow ROH + R'\cdot$$

$$R'\cdot + ROOH \longrightarrow R'\cdot HOOR$$

$$ROOH + M^{++} \longrightarrow ROO\cdot + M^{+} + H^{+}$$

$$ROO\cdot + R'H \longrightarrow R'\cdot HOOR$$

$$R'\cdot HOOR + Ox \longrightarrow R'OOR + (Ox + e) + H^{+}$$

The oxidant may be either the metal ion or the hydroperoxide.

Another possibility is that an organocupric compound is formed which attacks at the position of the activated hydrogen and then collapses, giving the unsymmetrical peroxide and free copper. By detecting 1- and 3-substituted products from the reaction of t-butyl hydroperoxide with octene-1, an alternate mechanism whereby the initial step is an addition of a peroxy radical to a double bond is rejected. Postulation of a radical complex may be avoided by considering that the intermediate carbon radical is oxidized to a carbonium ion which then reacts with a hydroperoxide to yield a peroxide. However, in acetic acid, an acetate should form with the carbonium ion intermediate, but experimentally, the unsymmetrical peroxide is still isolated in 92% yield. This would be expected only if the hydroperoxide is a better nucleophile than acetic acid.

Additional work by the same authors (6) has shown some cases where the course of a homolytic reaction is modified by the presence of trace amounts of copper salts. They have tried to envisage a mechanism explaining all observations: that copper salts act in some reactions as inhibitors, in others as deactivators, and in other cases as promoters of induced decomposition of peroxides. Solvent effects have also been noted in these reactions. These requirements are considered to be filled by the postulation of a loosely bound compound of the free radical and the cuprous cation, altering the reactivity of the radical.

One mole percent cuprous chloride serves to completely inhibit the bromination of chloroform by N-bromosuccinimide. The bromination of octene-1 in the same fashion is only retarded by the presence of copper salts. It is proposed that the trichloromethyl radical formed by abstraction of a proton by a succinimidyl radical reacts with a cuprous cation to give an unstable organocupric compound as a reaction intermediate. Two of these "trapped" or complexed radicals combine in a chain ending step.

$$\cdot CCl_3 + Cu^{+} \rightleftharpoons Cu^{+}CCl_3$$

$$2\ Cu^{+}CCl_3 \longrightarrow 2\ Cu^{+} + Cl_3C\text{-}CCl_3$$

A like explanation is used to account for the fact that when the pyrolysis of dicumene is carried out in the presence of copper salts, the cumyl radicals do not disproportionate. They are trapped on the copper salt and recombine.

A trapped free radical may cause an induced decomposition of a peroxide. When benzoyl peroxide is decomposed in octene-2, the major products are the 1:1 (1 benzoyl or phenyl:1 octene) adduct with 60% unsaturation and some benzoic acid. The addition of one mole percent cuprous chloride gives a 93%

unsaturated monoadduct and an equivalent amount of benzoic acid. Locations of the substituent and the double bonds were not examined. In the case of octene-1, the presence of cuprous salts effects the following changes from the uncatalyzed reaction: the high molecular weight products are greatly decreased, the 1:1 and 1:2 adducts contain a higher degree of unsaturation, much more benzoic acid is formed, and less carbon dioxide is evolved. Using an aromatic solvent in the catalyzed reaction, still further changes are found. The main product is 1-phenyloctene-1 (45%) with various benzoyloxyoctenes (23%), chief among which is 1-benzoyloxy octene-2. No 1-phenyloctene-2, the hydrocarbon found in the catalyzed reaction in excess octene, was formed. These results may be explained by the following considerations: the initial reaction is the addition of a benzoyloxy (or phenyl) radical to the double bond.

$$(C_6H_5CO_2)_2 \longrightarrow 2\ C_6H_5CO_2\cdot$$

$$C_6H_5CO_2\cdot + C_8H_{16} \longrightarrow C_6H_5CO_2C_8H_{16}\cdot$$

In the absence of a metal salt, this radical adds to another olefin and/or disproportionates. In the presence of the copper salt, the radical is reversibly trapped and can attack a peroxide molecule.

$$C_6H_5CO_2C_8H_{16}\cdot Cu^+ + (C_6H_5CO_2)_2 \longrightarrow C_6H_5CO_2C_8H_{15} + C_6H_5COOH + C_6H_5CO_2\cdot + Cu^+$$

It can be expected that in these reactions where altering their reactivity by trapping the radicals changes the course of the reactions, a solvent effect will be exhibited. Though not explained by the authors, if the trapped 1-phenyloctenyl radical is given additional stabilization in the aromatic solvent, the conjugated and more stable product would be the one expected, and is found in the experimental results. This work has not indicated, however, that no rearrangement of the initial products occurs.

An alternate mechanism, the oxidation of the radicals by cupric ion, is found by a competitive reaction to be of secondary significance. The relative amounts of cuprous or cupric salts added are of little importance, since both species are always present.

The following reactions, presumed to go by similar mechanism, also illustrate the induced decomposition of peroxides in the presence of copper salts:

(1) $((CH_3)_3CO)_2 \longrightarrow 2\ (CH_3)_3CO\cdot$

$$(CH_3)_3CO\cdot + C_6H_5CHO \longrightarrow (CH_3)_3COH + C_6H_5CO\cdot$$

$$C_6H_5CO\cdot + CuCl \longrightarrow C_6H_5COCuCl$$

$$C_6H_5COCuCl + ((CH_3)_3CO)_2 \longrightarrow C_6H_5CO_2C(CH_3)_3 + (CH_3)_3CO\cdot + CuCl$$

This is the first observed induced decomposition of t-butyl peroxide by this type of mechanism. The benzoyl radical is trapped, and instead of adding to another benzaldehyde carbonyl group, attacks the peroxide. In the absence of cuprous salts, the product is benzopinacol dibenzoate.

$$C_6H_5CO\cdot + C_6H_5CHO \longrightarrow C_6H_5C(H)-OCOC_6H_5 \xrightarrow{2X} \begin{matrix} C_6H_5CH-OCOC_6H_5 \\ | \\ C_6H_5CH-OCOC_6H_5 \end{matrix}$$

(2) $(C_6H_5CO_2)_2 + C_6H_5CHO + CuCl \longrightarrow (C_6H_5CO)_2O$

Benzopinacol dibenzoate is found with the anhydride in the uncatalyzed reaction.

(3) $(C_6H_5CO_2) + CH_3(CH_2)_3CHO + CCl_4 \xrightarrow{CuCl} C_6H_5COOH +$ mixture of anhydrides

The copper salts prevent particpation of trichloromethyl radicals in a chain reaction (see above) and the reaction between the trapped valeroyl radical and the peroxide takes place.

The metal salt catalyzed decomposition of benzoyl peroxide in cumene yields the same amount of isopropylbiphenyls as the uncatalyzed, but almost no dicumene is formed; instead α-cumyl benzoate is formed in an amount equal to the dicumene found in the absence of cuprous chloride. Two mechanisms probably operate in the decomposition of the peroxide in cumene: abstraction of the active proton to form cumyl radicals, and phenylation of cumene. The latter is unaffected by copper salts while in the former, the cumyl radicals are trapped and instead of dimerizing, attack the peroxide. This may be a simultaneous reaction, with the formation of a stabilized complex of cumene and a benzoyloxy radical which loses a proton to the peroxide. Alternately, the attacking agent may be a cupric benzoate compound. Since the phenyl radical does not appear to have been trapped, it follows that cuprous salts have the greatest effect on the reactions involving relatively unreactive radicals.

In these reactions it has not been important whether a free radical or radical complex was trapped by the copper salt, since another molecule of substrate or solvent could have served as the complexing agent. In the introduction of alkyl or aralkyl peroxy groups, radical complexes were postulated as intermediates. Another reaction can now be described in terms of a trapped free radical complex as an intermediate. Cuprous chloride causes the induced decomposition of t-butyl peroxide in cumene without affecting the formation of dicumene. The uncatalyzed reaction is first order; with catalyst it is much faster.

$$((CH_3)_3CO)_2 \longrightarrow 2\ (CH_3)_3CO\cdot$$

$$(CH_3)_3CO\cdot + C_6H_5(CH_3)_2CH \longrightarrow C_6H_5(CH_3)_2C\cdot + (CH_3)_3COH$$

$$C_6H_5(CH_3)_2C\cdot + C_6H_5(CH_2)_2CH + CuCl \longrightarrow C_6H_5(CH_3)_2CH\cdot C(CH_3)_2-C_6H_5CuCl$$

$$(\text{complex}) + ((CH_3)_3CO)_2 \rightarrow (C_6H_5(CH_3)_2C)_2 + CH_3)_3COH + (CH_3)_3CO\cdot + CuCl$$

When this reaction is run in the presence of benzoic acid, the product is α-cumyl benzoate, with no dicumene formed. Perhaps, in preference to the above, a complex is formed of benzoic acid and cumyl radical and is stabilized by cuprous chloride. Without catalysis dicumene and α-cumyl benzoate are formed in about equal amounts.

The last five reactions of Table I describe replacement of an active hydrogen by a benzoyloxy or phthalimido group. Although no mechanism is proposed by the authors, radical complexes stabilized by cuprous chloride may be intermediates.

$$R\cdot + C_6H_5COOH + CuCl \longrightarrow R\overset{H}{\cdot}OCOC_6H_5CuCl$$

$$(complex) + ((CH_3)_3CO)_2 \longrightarrow ROCOC_6H_5 + (CH_3)_3COH + (CH_3)_3CO\cdot + CuCl$$

As suggested above, a cupric benzoate group may be the species attacking the radical.

In another series of reactions, Kharasch, Sosnovsky, and Yang (3,11) have replaced active hydrogens with an ester group by decomposing t-butyl peresters in the presence of copper or cobalt salts. The remarkable result is that olefins form allylic esters without rearrangement. These results are tabulated in Table II. In the absence of the metal salt catalysts, high molecular weight products are obtained. If these reactions are carried out in an aliphatic acid as solvent, the ester of that acid is formed. In the absence of catalyst, it has been shown that ester exchange occurs. The authors formulate a mechanism involving a concerted displacement of the allylic hydrogen of olefins by the benzoyloxy radical, so the allylic radical is never free.

$$C_6H_5COOOC(CH_3)_3 + Cu^+ \longrightarrow C_6H_5CO_2Cu^+ + \cdot OC(CH_3)_3$$

$$(CH_3)_3CO\cdot + RCH_2CH{=}CH_2 + C_6H_5CO_2Cu^+ \longrightarrow RCH(OCOC_6H_5)CH{=}CH_2 + (CH_3)_3COH + Cu^+$$

Use of the allylic isomers to prove the reaction is not kinetically controlled would have insured the validity of this work. The following sequences might also be worthy of consideration:

$$C_6H_5COOOC(CH_3)_3 \longrightarrow C_6H_5CO_2\cdot + \cdot OC(CH_3)_3$$

$$C_6H_5CO_2\cdot + RH + Cu^+ \longrightarrow C_6H_5CO_2\overset{H}{\cdot}RCu^+$$

$$(complex) + C_6H_5COOOC(CH_3)_3 \longrightarrow C_6H_5CO_2\cdot + HOC(CH_3)_3 + C_6H_5CO_2R$$

or $C_6H_5CO_2\cdot + Cu^+ \longrightarrow C_6H_5CO_2Cu^+$

$$C_6H_5CO_2Cu^+ + RCH_2CH{=}CH_2 \longrightarrow C_6H_5CO_2CuCH(R)CH{=}CH_2 + H^+$$

$$C_6H_5CO_2CuCH(R)CH{=}CH_2 \longrightarrow C_6H_5CO_2CH(R)CH{=}CH_2 + Cu$$

To investigate this last possibility, we have heated cupric acetate, $cu(OAc)_2\cdot H_2O$, in cyclohexene for 5 hours. The results have not yet been completely assessed, but it appears that some cyclohexenyl acetate may have been formed. No rate studies have been made on this reaction.

TABLE II (11)

Substrate	Peroxide	Catalyst	Product	Yield
$C_3H_7CH_2CH=CH_2$ $C_5H_{11}CH_2CH=CH_2$ $C_6H_5CH_2CH=CH_2$	$(CH_3)_3COOCOC_6H_5$	Cu_2Br_2	$RCHCH=CH_2$ $\vert$ $OCOC_6H_5$	40% 35% 55%
Cyclohexene	"	"	2-cyclohexen-1-yl benzoate	50-77%
2-octene	"	"	Structures uncertain	53%
2,4,4-trimethyl pent-1-ene	"	"		37%
4-vinyl cyclohexene	"	"		61%
α-pinene	"	"		33%
cumene	"	"	$C_6H_5(CH_3)_2COCOC_6H_5$	--
2-phenyl butane	"	"	$C_6H_5(CH_3)(C_2H_5)COCOC_6H_5$	--

DECOMPOSITIONS OF HYDROPEROXIDES

Studies on metal salt catalyzed decomposition of hydroperoxides have seldom been directed toward an elucidation of the mechanism. Those few of mechanistic implication have been largely qualitative investigations in conjunction with autoxidation studies. The information at hand indicates an initial decomposition of the hydroperoxide into RO· and/or RO_2· fragments as in equations (a) and (b). Existence of both these radical species has been shwon by Kharasch (7,8) by trapping them with butadiene. Product studies have not indicated that the products (usually ketones and alcohols) are stable under the reaction conditions, so they offer no valid information. Color changes indicative of a change in the valence state of metal ions have been noticed upon the addition of a hydroperoxide (12). Oxygen is usually evolved, except in the case of ferrous salts. With ferrous ion, an equimolar amount or greater is often necessary to decompose the hydroperoxide, and it is possible that the concentration of the metal affects the mechanism. Of the group two metal stearates, only magnesium stearate has been found to cause the decomposition of tetralyl hydroperoxide to proceed by a free radical chain (14). It is doubtful that this follows the course described above for the metals of variable valence. The inhibited decomposition shows almost the same rate with and without catalysis, indicating that the rate of chain starting is not affected.

The order of the reaction catalyzed by variable-valence metal salts is not even unequivocal. It is apparently first order in hydroperoxide, but by different groups has been found to be first and second order in catalyst (22,15). Contradictory results have also been obtained concerning the effect of alkali on the decomposition (16,17). Nor is there much evidence for evaluation of some of the propagation and termination steps that have been proposed (12,14).

$$ROOH + M^{+} \longrightarrow RO^{-} + \cdot OH + M^{++}$$

$$ROOH + \cdot OH \longrightarrow ROO\cdot + H_2O$$

$$ROOH + \cdot OR' \longrightarrow ROO\cdot + HOR'$$

$$\rangle CHOOH + \cdot OH \longrightarrow \rangle \dot{C}OOH + \rangle C{=}O + H_2O + \cdot OH$$

$$RO\cdot \text{ (or } \cdot OH) + ROOH \longrightarrow \text{ketone} + H_2O + RO\cdot \text{ (or } \cdot OH)$$

$$2\ ROO\cdot \longrightarrow 2\ RO\cdot + O_2$$
$$2\ ROO\cdot \longrightarrow \text{ketone} + \text{alcohol} + O_2$$

The termination mechanisms for the tertiary hydroperoxides likely differ from those for the primary and secondary species.

AUTOXIDATIONS

Metal salt catalyzed autoxidations of hydrocarbons have been subjected to considerable scrutiny, but the results are often complex and contradictory, owing in part to the experimental difficulties involved in work of this nature. Several conclusions concerning these catalyzed reactions seem well founded; however, the entire reaction sequence is still uncertain.

(1) The presence of small amounts of metal salts increases the velocity of autoxidation of many hydrocarbons, and cause these to occur at lower temperatures than the uncatalyzed reactions.

(2) Direct initiation involving the pure hydrocarbon, the metal ion, and oxygen is very slow, if it occurs at all.

(3) The autoxidation, after a short induction period, exhibits a steady rate of reaction during which radical chains are initiated by the decomposition of the hydroperoxide formed during the reaction. This is caused by the metal ions in the manner described above.

The complexity of the effects of the metal ions in these reactions has prompted one author (2) to comment on the likelihood that the mechanism varies from one system to another and even with concentration of constituents in one given system. Evidence that the metal ion is the catalytically active species comes from the observation that otherwise active metal ions have no effect on the reaction when chelated (2). While there is evidence (23,24) that the only important initiation step is the decomposition of the hydroperoxide, other workers claim the activation of oxygen by the metal, with subsequent abstraction of a proton from the substrate (18-21). Both views take support from kinetic evidence which doesn't seem capable of reconciliation. The catalytic activity of hydroperoxides on the autoxidations has been established (25). To further confuse the picture, Lippincott and Lloyd (26) feel it is necessary to treat these reactions with non-steady state kinetics. They found exponential variation of the inhibition time with both inhibitor and catalyst concentrations. Blanchard (13,24,27) has found the inhibition time to be independent of catalyst concentration below 0.004 molar and directly dependent upon inhibitor concentration.

The propagation steps undoubtedly involve

$$R\cdot + O_2 \longrightarrow RO_2\cdot \xrightarrow{RH} ROOH + R\cdot$$

At first, most of the oxygen absorbed is found in the hydroperoxide, but this parallelism falls off during the course of the oxidation. An oxidation of the metal ions has been found to coincide with the first substantial uptake of oxygen (23). This is probably an oxidation-reduction reaction with the hydroperoxide.

(a) $M^{+} + ROOH \longrightarrow M^{++} + RO\cdot + (OH)^{-}$

Robertson and Waters (25), however, maintain that the ·OH radical is the active species. In the case of ferrous ion, Williams (28, 29) and his coworkers have shown reaction (a) to be of greater importance than (b).

$$(b)\quad M^{++} + ROOH \longrightarrow M^{+} + ROO\cdot + H^{+}$$

In hydrocarbon oxidations, (b) has been found to be the slow step, with (a) being a rapid reoxidation of the metal.

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