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ORGANIC SEMINAR ABSTRACTS

1963-1964

SEMESTER II

Department of Chemistry and Chemical Engineering

University of Illinois



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SEMINAR TOPICS

II Semester 1963-1964

Recent Progress in the Deamination of Aliphatic Amines	
R. Feiertag	1
The Origin of Potential Barriers to Internal Rotation	
W. A. Bennett	10
The Effect of High Pressure on Reaction Rates	
Linda R. Brammer	19
Mechanism of Heterogeneous Catalytic Hydrogenation	
L. Walker	28
The Structure and Synthesis of the Onocerins	
Kermit Carraway	37
Recent Mechanistic Studies of Base-Catalyzed Olefin Migration Reactions	
D. Druliner	46
The Question of the Carbonium Ion From Solvolyses of 2-Norbornyl Derivatives	
Thomas P. Doherty	55
Displacement Reactions on Silicon. Recent Developments	
F. M. Vigo	63
Intramolecular Attack at C-19 of Steroids by a Neighboring Oxygen Function	
Elizabeth McLeister	71
The Karplus Rules and Conformational Analysis	
J. Miesel	80
The Pummerer Reaction	
Bruce M. Monroe	89
Recent Chemistry of Unsaturated Azlactones	
Allan C. Buchholz	97
Solvent Isotope Effects on Acid Dissociation Constants and Acid Catalyzed Reactions	
Raymond Feldt	106
Cyclizations of Propynyl Carbamates and Propynylureas	
Barry E. Galbraith	115
Chemistry of Sulphenes	
Robert Y. Ning	124
Replacement of Oxygen with Sulfur Using Phosphorus Pentasulfide	
Ronald Hackler	130
Carbonyl-Containing Three-Membered Rings as Reaction Intermediates	
D. W. Lamson	139

RECENT PROGRESS IN THE DEAMINATION OF ALIPHATIC AMINES

Reported by R. Feiertag

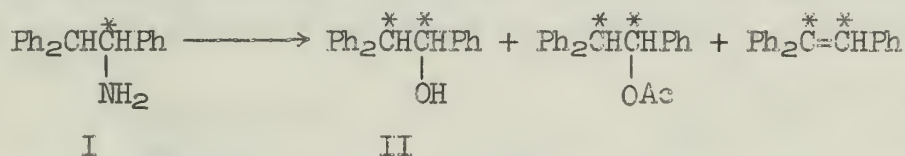
February 10, 1964

Introduction.--The deamination of aliphatic amines has been an area of intense chemical interest for some time. In recent years more information about the reaction has been obtained from a number of aliphatic systems. It is the purpose of this abstract to report the results of several investigations into the nature of the intermediates involved in deamination.

A general review of deamination has appeared (1), as well as more specific reviews on deaminations involving ring expansion (Demjanov reaction)(2), bicyclic systems (3), the cyclopropylcarbonyl system (4,5,6,7), and substituted ethylamines (8).

Deamination of Substituted Ethyl and Propyl Amines.--Collins and coworkers have studied the deaminations of a number of substituted ethyl and propyl amines and amino alcohols. These studies have been carried out using amines labeled with carbon-14, optically active amines, and optically active carbon-14 labeled amines. In every case extensive rearrangement took place. Collins' earlier work, which has been reviewed (8), indicated that these rearrangements did not take place through bridged phenonium ions. Instead, a mechanism in which open carbonium ions whose formation was controlled by the ground state conformations of the molecules was used to explain the observed results. A kinetic treatment of the data gave support to this mechanism (9).

A number of additional experiments were designed to test the hypothesis that only open carbonium ions are involved in these deaminations. The results support the earlier conclusions. Deaminations of (+) and (-)-1,2,2-triphenylethyl-1-C¹⁴-amine (I) were carried out in water to which a small amount of acetic acid had been added at temperatures ranging from -2° to 36.6° (10). The major product was 1,2,2-triphenylethanol (II); the remainder (about 10%) was composed of 1,2,2-triphenylethyl acetate and 1,1,2-triphenylethylene. In every case there was net retention of con-



figuration with some racemization, and rearrangement of the C¹⁴ label. The carbinols were resolved into samples of completely retained configuration and into racemic mixtures. Each sample was then oxidized to benzophenone which was assayed for radioactivity. This gave the activity at C.2 and therefore the percent rearrangement of C¹⁴. From the percent C¹⁴ rearrangement in the optically active carbinol of retained configuration and that in the racemic mixture, the percent C¹⁴ rearrangement in the carbinol of inverted configuration may be calculated. The results are given in Table 1.

Table 1

Starting Material	% Overall Retention	% C ¹⁴ Rearrangement in Product Carbinol II		
		Retained Configuration	Racemic	Inverted Configuration
(+)-I	64	26.5	28.1	29.7
(-)-I	70	20.6	24.5	28.4

Reaction exclusively through bridged phenonium ions (Figure 1) should lead to product with retained configuration in which 33% of the label is found at C.2, and product with inverted configuration in which all the label is found at C.2. But in both cases more rearrangement of the label took place in the product with inverted

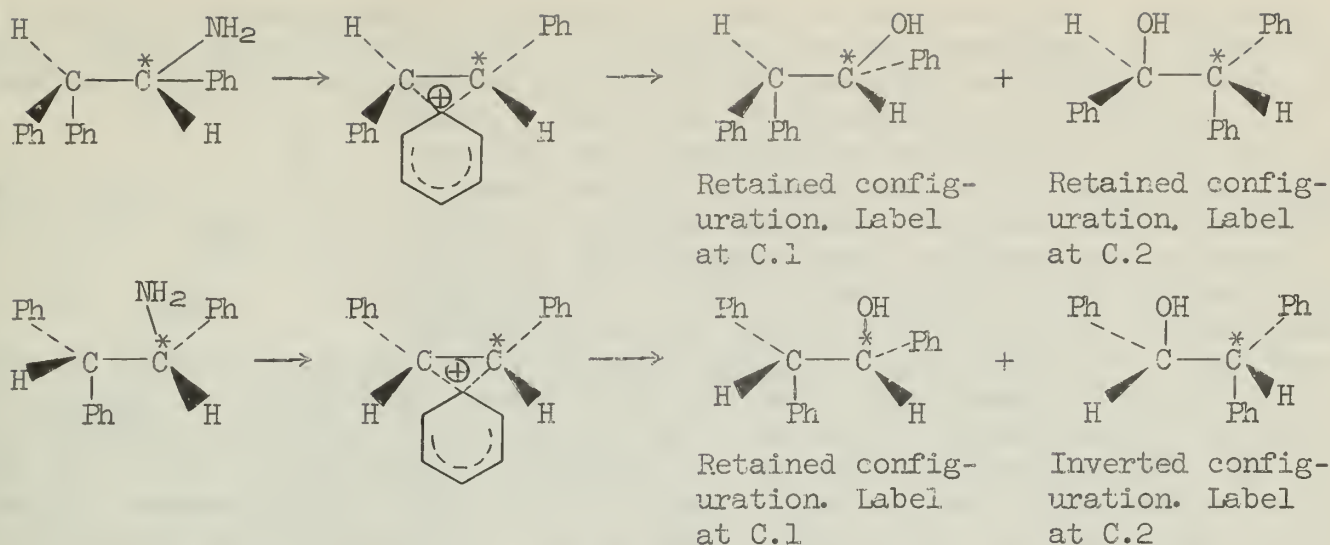
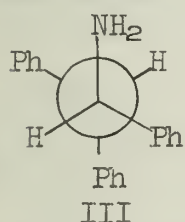


Figure 1

configuration than in that with retained configuration. On this basis bridged ions were ruled out.



If it is assumed that the amine exists primarily in its most stable conformation (III), the above results may be explained on the basis of classical open carbonium ions. The reaction mechanism shown in Figure 2 was proposed. In this mechanism, none of the intermediate ions are subject to rearward attack, the ionic site being protected by the phenyl group on the adjacent carbon atom. A kinetic treatment of the above mechanism (11) led to a series of equations which were solved for the mole fractions of the products. The observed and calculated mole fractions were in good agreement, indicating the compatibility of this mechanism with the experimental results.

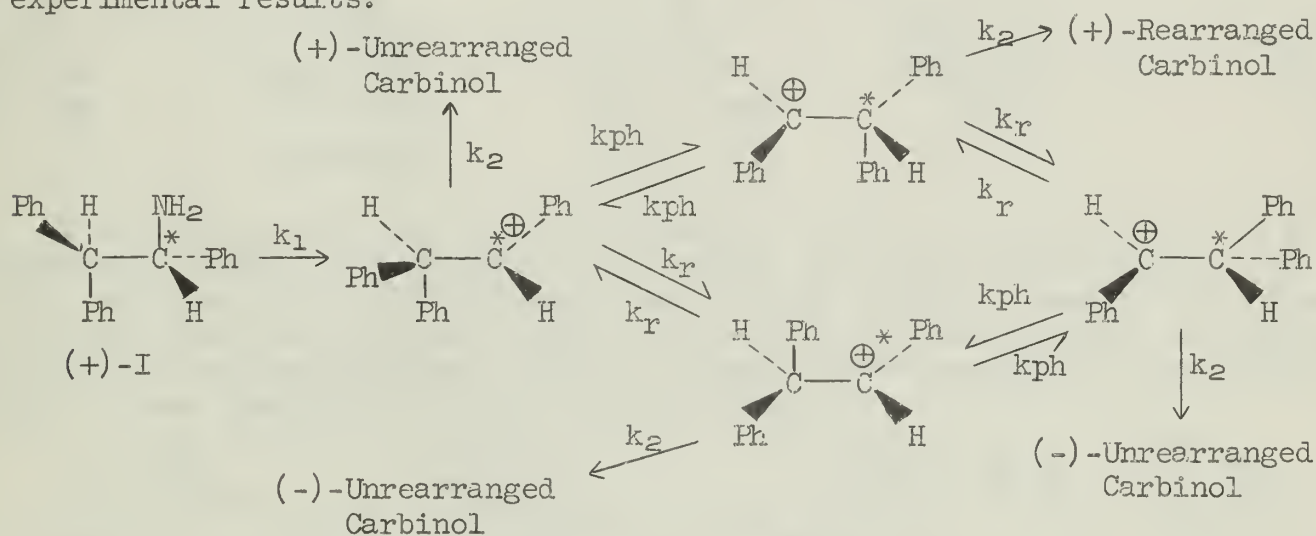
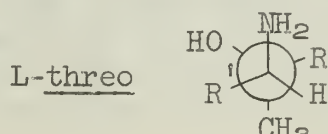
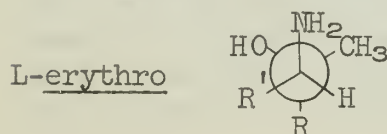


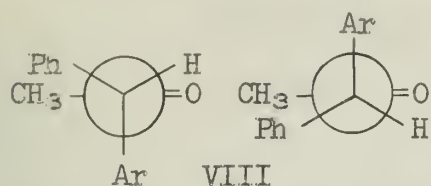
Figure 2

Additional experiments were carried out in order to further test the validity of the above conclusions. Optically active erythro-1-amino-1,2-diphenyl-2-propanol-1-phenyl- C^{14} (IV)(12), erythro- and threo-1-amino-1-phenyl-2-p-tolyl-2-propanol-2- C^{14} (V)(13), erythro- and threo-1-amino-1-phenyl-2-p-methoxyphenyl-2-propanol (VI), and erythro- and threo-1-amino-1-phenyl-2-o-tolylpropanol (VII)(14) were prepared



- IV. R = Ph, R' = Ph*
- V. R = p-CH₃Ph, R' = Ph
- VI. R = p-CH₃OPh, R' = Ph
- VII. R = o-CH₃Ph, R' = Ph

and subjected to semipinacolic deamination. The products were the corresponding ketones (VIII) in yields of 70-98%. If bridged ions are important, it would be expected that the electron donating ability of the *p*-methoxy and *p*-methyl groups would



cause a larger amount of bridging for ions from V and VI than for the corresponding ion from IV. This would cause a greater amount of inversion in the case of the erythro isomers. If open classical carbonium ions arising from the most stable ground state conformer are important, erythro-IV, -V, and -VI should all give the same amount of inversion, and threo-V and -VI should give a greater

amount of retention than the corresponding erythro isomers (Figure 3). Moreover, both erythro- and threo-VII, having different steric requirements, should give products in ratios different from those of the other three. Experimentally it was found that in the deaminations of erythro-IV, -V, and -VI there was 73%, 74%, and 77% inversion, respectively. Deamination of threo-V and -VI led to products with 57% and 59% retention, respectively. In contrast, erythro-VII gave 96% inversion and threo-VII, 45% retention. These results were explained by the mechanisms shown in Figure 3 in which open carbonium ions arising from the most stable ground-state conformers of the molecules are the intermediates. In the case of VII the bulky *o*-tolyl group makes rotation about the carbon-carbon bond difficult in the intermediate ions, leading to greater amounts of inversion in the erythro case. Deamination of threo-VII leads to anomalous results when discussed in terms of this mechanism.

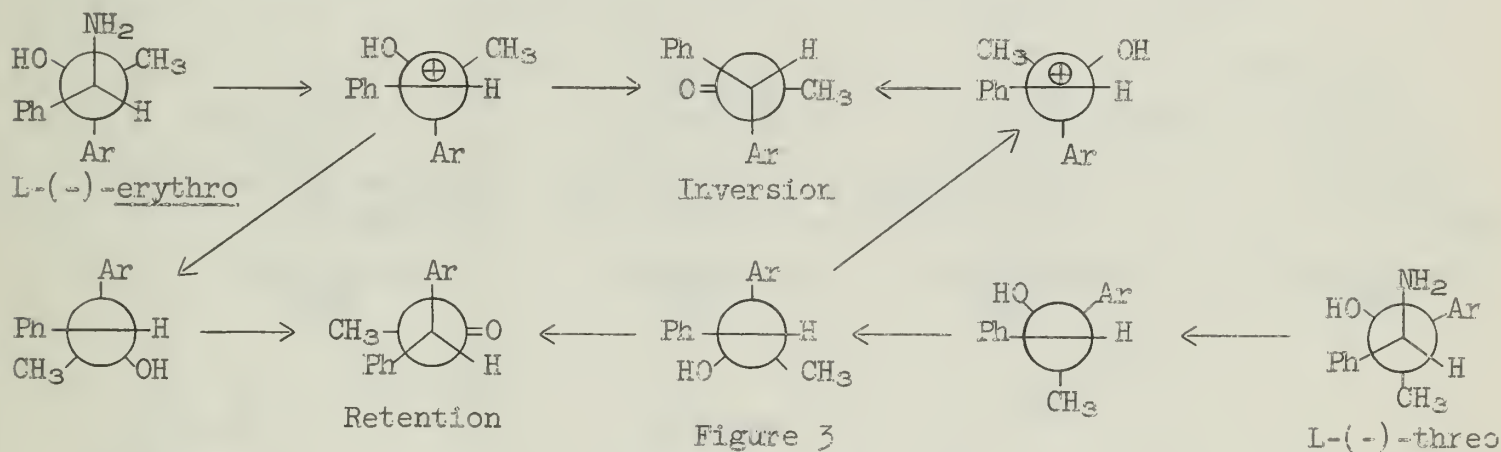


Figure 3

Of special interest was the deamination of IV (12). L-(+)-IV gave the ketone IX (Figure 4) which was converted to its oxime. This was reduced to give (+)-Xa and (-)-Xb, which are both optical isomers and isotope position isomers. The amine (+)-Xa was then subjected to deamination, yielding the alcohols erythro- and threo-XI. The products were degraded and counted to determine the position of the isotope labeling. These transformations are shown in Figure 5.

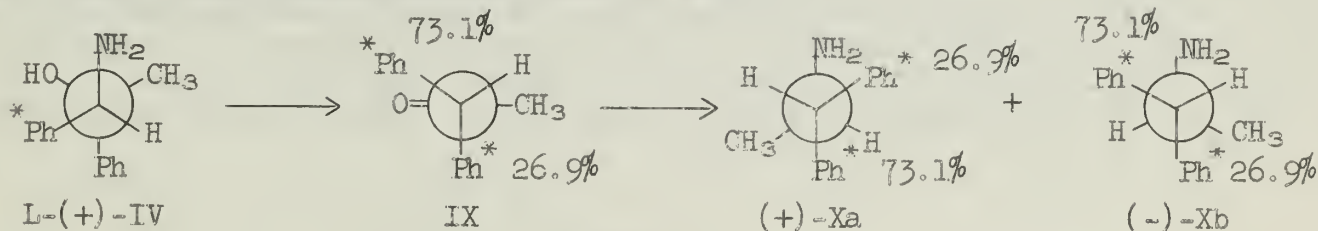


Figure 4

The results of this double deamination were interpreted (in the case of (+)-Xa) as follows (Figure 6): It is assumed that the conformation shown for (+)-Xa in Figure 5 is the only important ground state conformation. There are conceivably four possible products, formed via discrete intermediates. D-threo-XIa and L-erythro-XIa, both formed from ion XIIb, should have the same isotopic distribution. This distribution should be different from that of L-threo-XIb and D-erythro-XIb which potentially

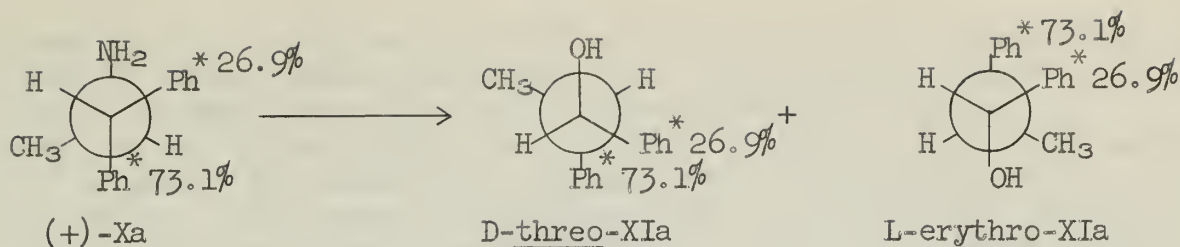
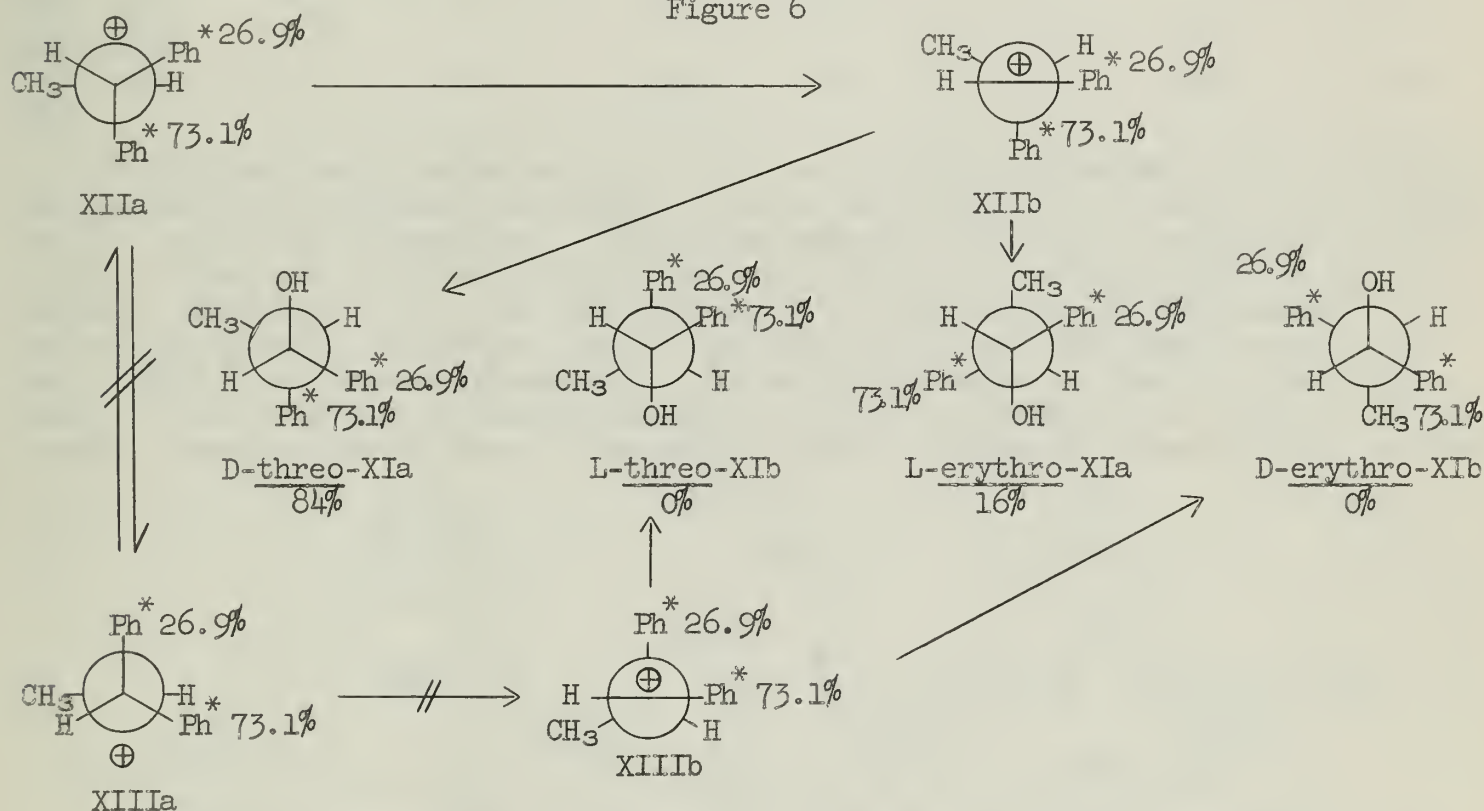


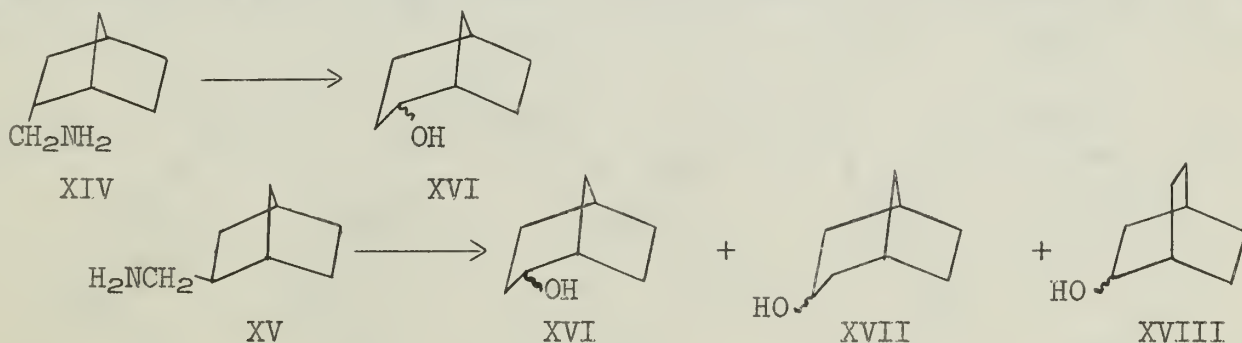
Figure 5

might arise from ion XIIIb. The complete absence of L-threo-XIb and D-erythro-XIb in the products from (+)-Xa demonstrates that ions XIIIa and XIIIb are not formed. All reaction, therefore, proceeds through ions XIIa and XIIb, and no scrambling of the label takes place in this reaction. This requires that the observed isotopic ratios of the products arise from the deamination of L-(+)-IV. Similar results were found in the case of D-(-)-IV. Furthermore, these results are in accord with those discussed earlier for V and VI.

Figure 6



Deamination of Bicyclic Amines.--Alder and coworkers (15,16) synthesized and studied the deaminations of endo- and exo-2-norbornylcarbinylamines (XIV and XV). They identified 2-bicyclo[3.2.1]octanol (XVI) as the only product from the deamination of XIV, and XVI (53-63%), 3-bicyclo[3.2.1]octanol (XVII) (27%), and 2-bicyclo[2.2.2]octanol (XVIII) (10-20%) as the products from the deamination of XV. The car-



binols were separated by oxidizing the reaction mixture to the corresponding ketones, converting these to their benzal derivatives, and separating the derivatives. Thus it was not learned in what proportion the isomers of XVI were obtained.

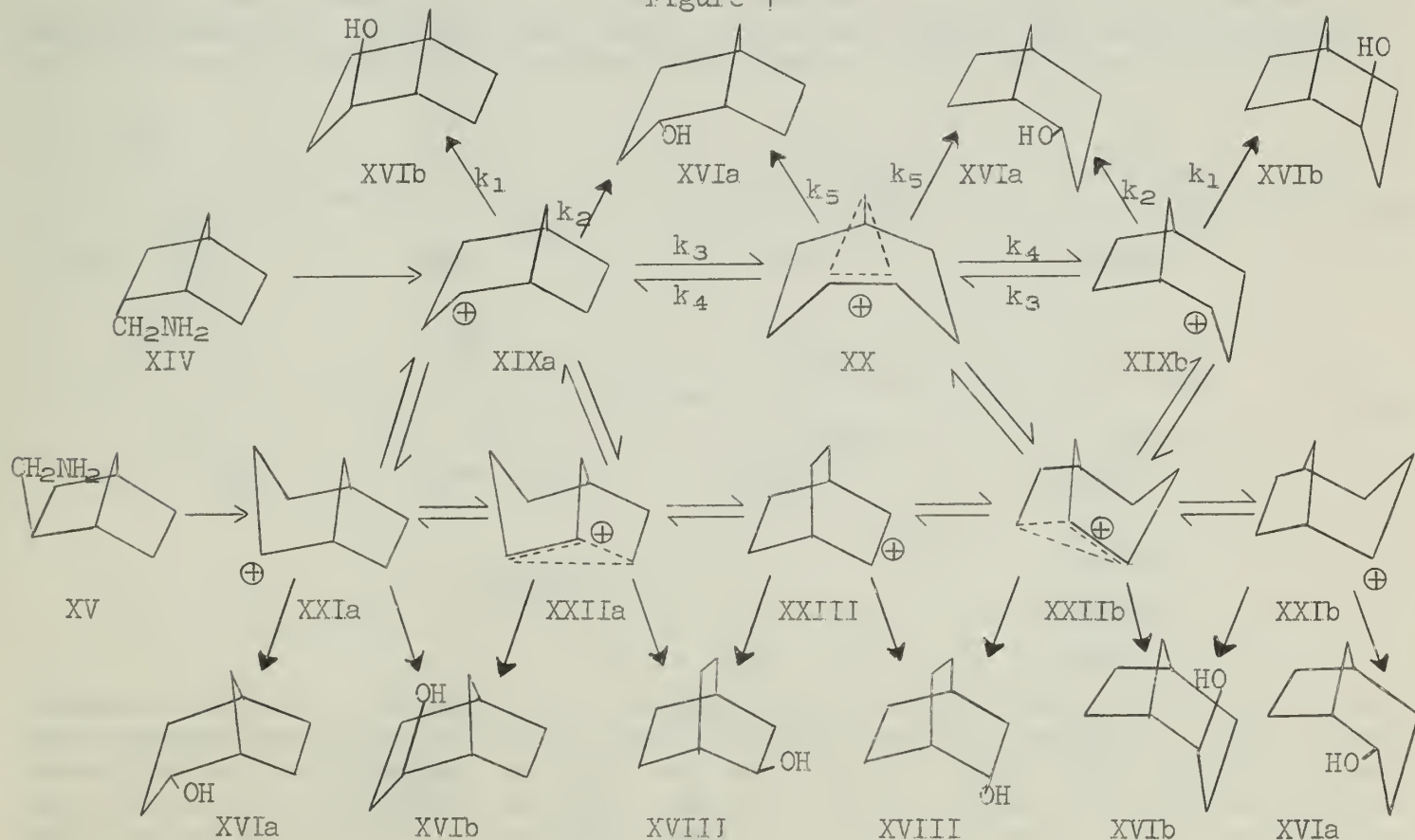
Berson and coworkers have studied the deamination of XIV (3,17,18,19) and XV (3,18,20,21) in detail. Both amines were prepared by an unambiguous method (22,23) and partially resolved. The optically active amines were deaminated, and the products were separated by vapor-phase chromatography. The results are summarized in Table 2. In the case where deamination was carried out in glacial acetic acid, the product acetates were converted to carbinols with lithium aluminum hydride.

Table 2

Reactants	XVIa		XVIb		XVIII		XVII
	Yield	% Opt. Purity	Yield	% Opt. Purity	Yield	% Opt. Purity	
XIV + HONO H ₂ O + HOAc	83	7-13	9	50	7	----	0
XV + HONO H ₂ O + HOAc	3	----	37	----	41	----	19
XV + HONO HOAc	5	----	35-40	94	35-40	55±7	17-20

The difference in products in the two cases renders it probable that XIV and XV are reacting via different mechanisms. Any mechanism which is proposed must account for the following observations: (1) In the endo case (XIV) both endo-2-bicyclo[3.2.1]octanol (XVIa) and exo-2-bicyclo[3.2.1]octanol (XVIb) are extensively, but not completely, racemized. (2) XVIa and XVIb are not racemized to the same extent. (3) In the exo case (XV in glacial acetic acid) XVIb is formed with little racemization while XVIII is racemized extensively. The mechanism shown in Figure 7, where the course of the reaction is highly dependent upon the conformation of the starting material, accounts for all these observations with a minimum of intermediates. In the

Figure 7



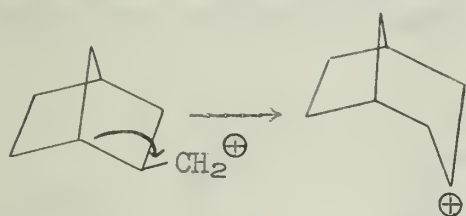
endo case (XIV) the optically active intermediates XIXa and XIXb allow some racemization of XVIb, while the non-classical ion XX allows more complete racemization of XVIa. This may be shown analytically. If the optical purity of a species *i* is defined as $\text{opt. purity} = \frac{D_i - L_i}{D_i + L_i}$ where D and L are arbitrary designations of

configuration, the ratio of the optical purity of XVIa to that of XVIb may be obtained by a steady state treatment of the equations in Figure 7, and is given by equation (1). When $k_5 = 0$, i.e., when XX is not a product-forming intermediate, the ratio of optical purities is unity. When k_5 is greater than zero, the ratio is less than unity,
$$\frac{\text{opt. purity of XVIa}}{\text{opt. purity of XVIb}} = \frac{D_{\text{XVIa}} - L_{\text{XVIa}}}{D_{\text{XVIa}} + L_{\text{XVIa}}} \bigg/ \frac{D_{\text{XVIb}} - L_{\text{XVIb}}}{D_{\text{XVIb}} + L_{\text{XVIb}}} = \frac{k_4(k_4+k_5)}{k_2(k_4+k_5) + k_3k_5} \quad (1)$$

in accord with experiment. In the exo case (XV), ion XXIIa is converted to ion XXIII, but conversion of XXIII to XXIIa or XXIIb is very slow. This accounts for the greater racemization of XVIII and the nearly complete retention in XVIb.

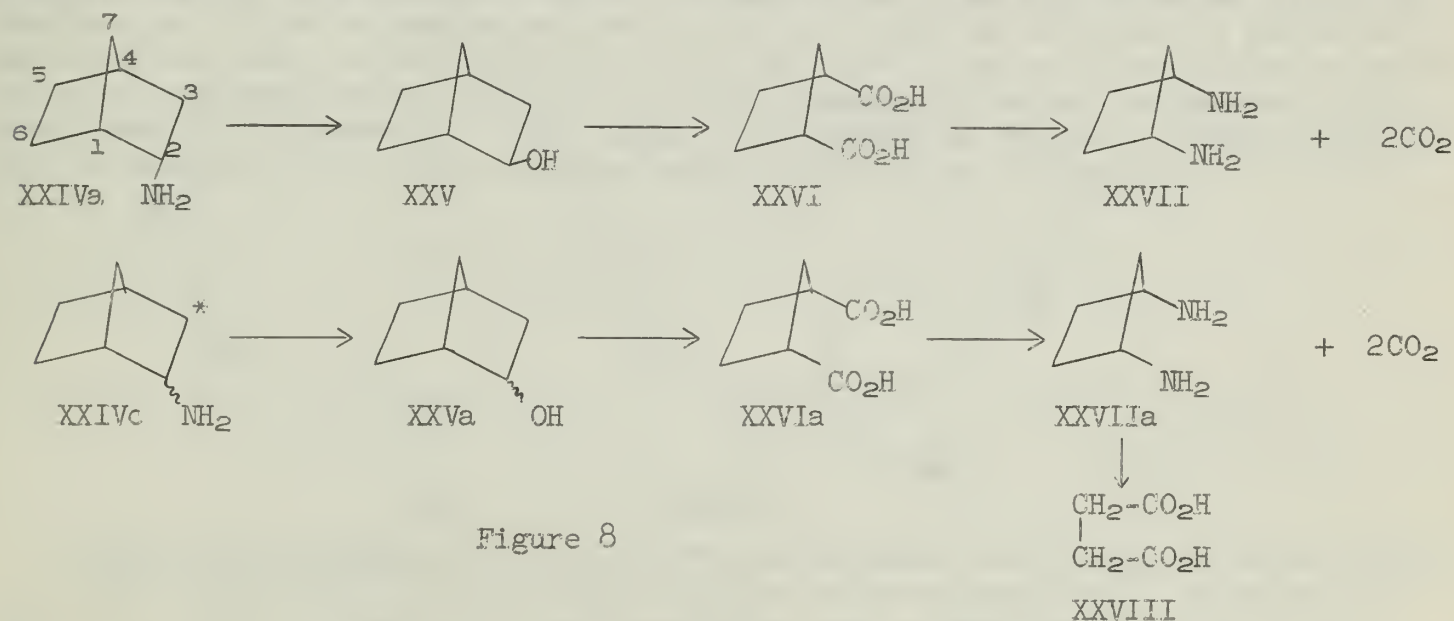
The small amount of XVIII formed in the deamination of XVIa arises from cross-over via XIXa \rightarrow XXIIa or XIXa \rightarrow XXIIb. As much as 6% of XVIb may also arise in this manner. Crossover in the opposite direction, i.e., XXIIa \rightarrow XIXa or XXIIb \rightarrow XIXa is not very important, since less than 5% of XVIa is formed in the deamination of XV.

The meso product XVII is not formed from the deamination of XIV presumably because although migration of C.1 (secondary) is more favorable electronically than migration of C.3 (primary), it leads to a sterically unfavorable cation in which the six-membered ring is in the boat conformation. In the exo case (XV), C.1 migration



is both electronically and sterically favorable, leading to the ion in which the six-membered ring is in the chair form. However, other effects must also affect the migration, for if no other effects were present, XVII should be the predominant product from the deamination of XV.

Roberts and coworkers (24) studied the deamination of endo-norbornylamine-3-C¹⁴ (XXIVa) (Figure 8). exo-Norborneol (XXV), the major product, was degraded via XXVI and XXVII and the degradation products were counted. XXVI gave the activity of the

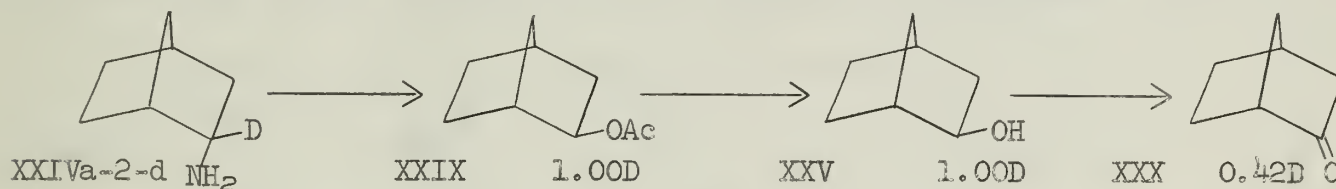


product norborneol, and XXVII, the activity in C.1 and C.4 through C.7. The percent rearrangement was calculated as (activity of XXVII/activity of XXVI) X 100. It was found that 44% rearrangement of label had taken place. In a closely related experiment, a mixture of (30%/70%) of endo- and exo-norbornylamine-3-C¹⁴ (XXIVc) was deaminated and the product degraded via XXVIa, XXVIIa, and XXVIIIa. The percentage of

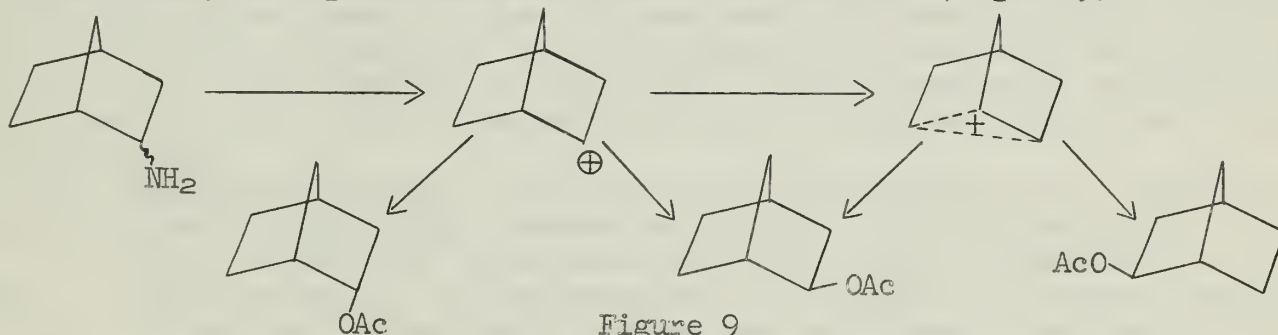
label at C.7 was calculated as follows: % activity at C.7 = $\frac{\text{activity of XXVIIa}}{\text{activity of XXVIII}} \times 100$. It was found that 46.2% of the label was at C.7, i.e., of XXIVc

within experimental error, all of the label which migrated was at C.7. Berson and Ben-Efraim (25) reported that the deamination of optically active (+)-XXIVa in glacial acetic acid proceeded with 23-24% retention of configuration although the product was the exo-carbinol (XXV). It was later found that 5% of the product was the optically active endo-carbinol (3b). However, exo and endo carbinol of the same configuration give the same sign and nearly the same magnitude of optical rotation. Thus, there was 18-19% retention in the exo isomer and 5% retention in the endo isomer. The earlier results (in which exo carbinol was thought to be the only product) were explained by a mechanism in which an S_N2 displacement of solvent on the leaving group leads to retention of configuration, while formation of a non-classical carbonium ion leads to racemization.

Corey and co-workers (26) deaminated optically active exo-norbornylamine (XXIVb) in glacial acetic acid, obtaining as the major product exo-norbornyl acetate (XXIX) contaminated by a small amount (about 4% of the total yield) of the endo isomer. Any retention of configuration in this case could not come from S_N2 displacement since backside attack is sterically hindered. Moreover, the amount of retention observed (15%) could not be due to the small amount of endo product. Deamination of endo-norbornylamine-2-d (XXIVa-2-d) and conversion of the product acetates (95% exo and 5% endo) to norcamphor (XXX) demonstrated that rearrangement of 42% of the deuterium had taken place (26). If rearrangement of deuterium is accompanied by racemization, this corresponds to 16% retention of configuration. The n.m.r. spectra of norcamphor and the deuterated norcamphor showed two peaks at τ 7.43 p.p.m. and τ 7.62 p.p.m. which were assigned to the bridgehead hydrogen atoms. Their relative

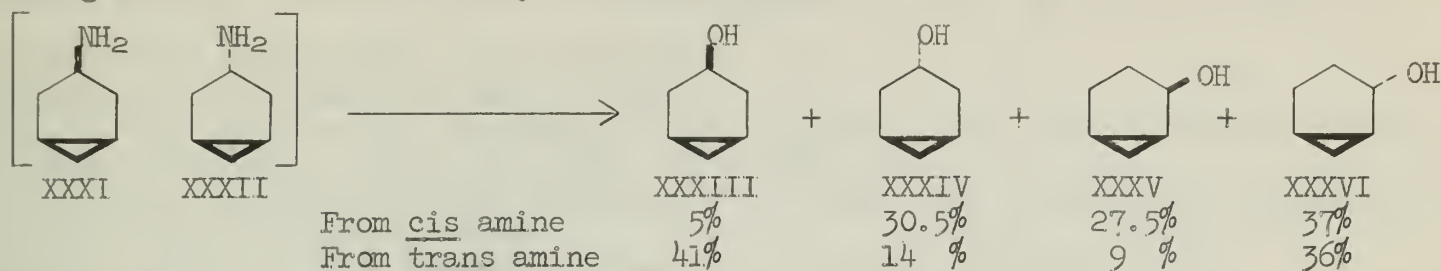


areas were 1:1 in norcamphor and 1:0.6 in the deuterated product, suggesting that the deuterium in the rearranged molecule is found at C.1. Corey interpreted these observations in terms of a mechanism which, although similar to that proposed by Berson, involved only classical carbonium ions. However, there is no reason to prefer this mechanism over that of Berson, particularly in light of Berson's recent investigations into the norbornylcarbinyl system where equilibrating classical and non-classical ions appear to be operating. Only slight modification of Berson's original proposal (25) is necessary to explain the more recent observations (Figure 9).



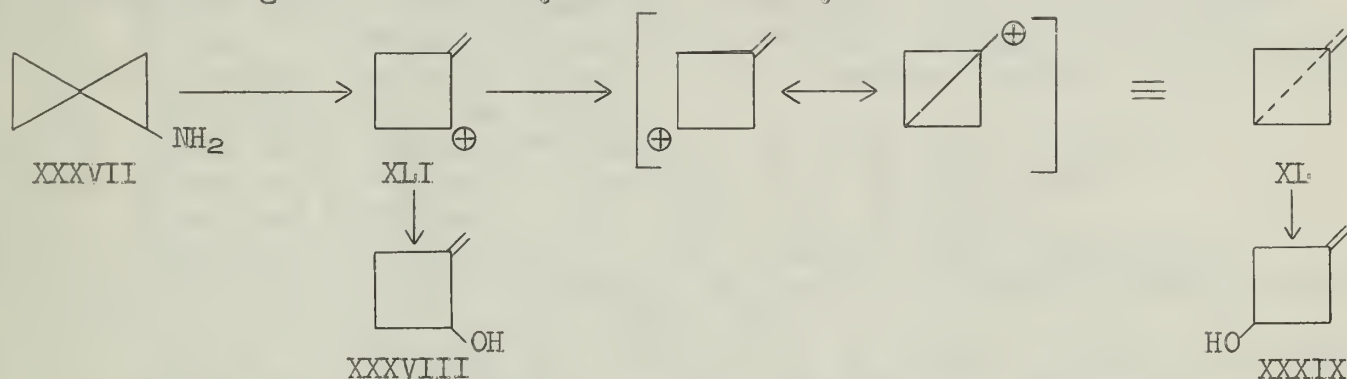
Homoaromatic Systems.--In 1959 Winstein introduced the concept of homoaromaticity (27,28). His early work in this field has been reviewed (29). Acetolysis of cis-3-bicyclo[3.1.0]hexyl toluenesulfonate-3-d gave a quantitative yield of cis acetate in which the deuterium was distributed equally over C.1, C.3, and C.5. Acetolysis of the trans isomer gave (in 67% yield) only cis acetate in which no deuterium rearrangement was observed. The results in the case of the cis isomer were interpreted in terms of the trishomocyclopropenyl cation, reaction in the case of the trans isomer being considered as a nucleophilic displacement by solvent. Deamination of the corresponding deuterated amines XXXI and XXXII led to two different

mixtures of cis- and trans-3-ols (XXXIII and XXXIV) and isomeric cis- and trans-2-ols (XXXV and XXXVI). The cis-3-ol and trans-3-ol from deamination of the cis-3-amine and the cis-3-ol from deamination of the trans-3-amine were oxidized to the corresponding ketones which were analyzed for deuterium content. It was found that no



rearrangement had taken place in the trans-3-ol from the cis-3-amine and in the cis-3-ol from the trans-3-amine. Only one-third of the deuterium in the cis-3-ol from the cis amine, or less than 2% of the total, had rearranged. Although these results show the trishomocyclopropenyl cation to be unimportant in the deamination of these amines, there does not appear to be any simple explanation for the observed product ratios.

Evidence for participation of homoallylic intermediates is found in the deaminations of spiropentylamine and a series of androstanones. Deamination of spiropentylamine (XXXVII) gives the rearranged products XXXVIII and XXXIX in 6.7% and 32% yields, respectively (31). Formation of a greater amount of XXXIX than of XXXVIII is cited as evidence for greater stability of the homoallylic cation XL over ion XLI.



Tadinier and Cole (32) studied the deamination of 6 α - and 6 β -amino-3 α ,5 α -cycloandrostan-17-ones (XLII and XLIII), and 3 α - and 3 β -aminoandrost-5-en-17-ones (XLIV and XLV). It was found that XLII, XLIII, and XLV all gave as the major product 6 β -hydroxy-3 α ,5 α -cycloandrostan-17-one. In contrast, XLIV gave a mixture of products believed to be the nitrite esters of 4-hydroxyandrost-5-en-17-one and 5-hydroxyandrost-4-en-17-one. The geometry of XLII, XLIII, and XLV favors the formation of a common homoallylic ion, while deamination of XLIV is believed to proceed through a normal allylic ion.

Other Deamination Studies.--Deamination of neopentylamine and *t*-pentylamine (33) yields a mixture of substituted products and olefins. *n*-Propylamine (34), 3-methyl-2-butylamine, and isopentylamine (35,36) yield, in addition to the expected products, cyclopropane and 1,2-dimethylcyclopropane, respectively. In the case of the substituted amines the product distribution differs from that from solvolysis of the corresponding halides (33,35,36). This difference has been interpreted as resulting from the presence of an "unusual" carbonium ion intermediate in deamination (34,36); while the formation of the cyclopropanes has been explained by the presence of an ion such as XLVI (33,35).

Deamination of 2-cyclopropylethylamine-1- C^{14} was carried out by Cartier and Bunce (37). They interpreted their observations using a mechanism which involves open ions whose formation is controlled by the most stable ground-state conformation of the molecule.

Deamination of trans-2-aminocycloheptanol yields only cyclohexylmethanal, while deamination of cis-2-aminocycloheptanol yields 80% cycloheptanone and 20% cyclohexylmethanal (38). These differences in product have been ascribed to conformational effects.

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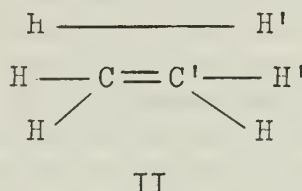
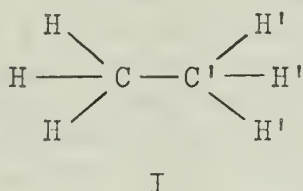
THE ORIGIN OF POTENTIAL BARRIERS TO INTERNAL ROTATION

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Introduction - The phenomena of hindered internal rotation and its importance in numerous organic molecules is well-known (1) (2). An understanding of the origin of such barriers would be desirable from the standpoint of being able to predict the occurrence of such potential barriers and their quantitative effect on, for example, reaction rates and polymer structure. The purpose of this seminar is to review and relate the various theories which have been proposed for the origin of such barriers to internal rotation. The experimental methods employed in determining the magnitude of potential barriers to internal rotation are microwave, infrared, Raman and nuclear magnetic resonance spectroscopy, thermodynamic, dipole moment, and electron-diffraction measurements, and ultrasonic absorption. The application of these methods to the study of potential barriers to internal rotation has been reviewed by Wilson (3).

Early Considerations - The σ -bond between the two carbon atoms in ethane is assumed to involve an electron distribution which is cylindrically symmetrical about the carbon-carbon bond axis. As a result it would not be expected to exert any restrictions upon the rotation of the methyl groups about this bond axis, such as occurs when a π -bond is also present as in the case of ethylene. It therefore might be assumed that free rotation of the methyl groups occurs in ethane. This assumption was investigated on quantum mechanical grounds by Eyring in 1932 (4). He applied valence bond procedures to the perfect-paired structure of ethane, I, (the term perfect-paired referring to the pairing of the spins of the electrons in the bonding orbitals, and may be contrasted with a nonperfect-paired structure, II). Eyring concluded that the



true potential barrier was in the range 0.18-0.36 kcal./mole, with the minimum energy corresponding to the staggered conformation. The barrier was attributed to nonbonded hydrogen-hydrogen repulsions. Penny pointed out that these are the only type of repulsions that would be expected if only the perfect-paired structure of ethane is considered in such valence bond calculations (5). In 1935 Teller and Topley made a calculation of the equilibrium constant for the hydrogenation of ethylene based upon experimental data. They found a discrepancy which would disappear if the barrier hindering internal rotation in ethane were actually 3.00 kcal./mole (6). Pitzer and Kemp reported in 1936 that the experimental third law entropy and the calculated statistical mechanical entropy for ethane agree if a barrier to rotation of 3.150 kcal./mole is assumed (7)(8). The currently accepted values for the barrier in ethane are 2.875 ± 0.125 kcal./mole based on thermodynamic measurements (9) and 3.030 ± 0.300 kcal./mole based on spectroscopic data (10). Spectroscopic data indicate that the staggered form is the stable conformation for ethane (11)(12).

Gorin, Walter, and Eyring in 1939 calculated an upper limit of 5.2 kcal./mole for the barrier in ethane, with the staggered conformation more stable, by considering the Coulomb repulsions due to the hydrogen protons (13). This value represents the calculated difference in the nuclear-nuclear repulsion potential between the two conformations. A valence bond calculation by Gorin, et. al., which considered the perfect-paired structure, I, and nine nonperfect-paired structures, e.g., II, predicted that the eclipsed conformation would be more stable than the staggered by 0.7-1.9 kcal. mole⁻¹. Rather crude and approximate values for exchange integrals were available for this calculation. It has been suggested that better values for these integrals might have led to the correct prediction of the stable staggered conformation (14).

In valence bond calculations on ethane there are three types of exchange integrals (electron exchange interactions) which are dependent upon the dihedral angle, ϕ , i.e., the relative angle of internal rotation, and which can contribute to the barrier.

These are the carbon-hydrogen integrals for electron exchange between a carbon orbital and a hydrogen orbital which are not chemically bonded to each other, designated for the purposes of this discussion as I_{CH} ; hydrogen-hydrogen exchange integrals for exchange between hydrogens chemically bonded to different carbons, designated I_{HH} ; and integrals for exchange between the orbitals of the carbon atoms which are bonded to these hydrogens, designated I_{CC} , (14).

The effect of the inclusion into valence bond calculations of the $3d$ and $4f$ orbitals on carbon was also considered by Gorin, et. al. (13). Consideration of the effect of $3d$ character on the sp^3 hybridized carbon orbitals led to the prediction of a 0.60 kcal./mole barrier with the eclipsed conformation the more stable. Although the effect of $3d$ character on the I_{CC} interaction led to a contribution favoring the staggered conformation of ethane, the contribution of the I_{CH} interaction favored the eclipsed conformation and was of larger magnitude. Eucken and Schäffer had proposed that the barrier in ethane results from a lack of cylindrical symmetry in the electron distribution about the C-C bond axis (15). They suggested that the C-C bonding orbitals were perturbed by an inductive effect from the C-H bonds which led to a lack of cylindrical symmetry. Their calculations predicted the eclipsed conformation of ethane to be more stable by about 3.00 kcal./mole. Gorin, et.al., pointed out that such a perturbation may be considered from a mathematical standpoint as being due to the inclusion of some carbon $4f$ character, i.e., a deviation from cylindrical symmetry about the C-C bond axis due to $4f$ character in the bonding carbon orbitals. When this effect was taken into account a calculated barrier of negligible height resulted (13).

Classical Mechanical Considerations - The failure of approximate quantum mechanical calculations to lead to definitive results in understanding and calculating barriers to internal rotation in ethane led to a series of classical approaches to understanding and predicting barriers. Aston, Isserow, Szasz, and Kennedy suggested on empirical grounds that barriers were due to repulsions between nonbonded hydrogen atoms and were proportional to $1/R^5$, where R is the distance between hydrogens (16). Lassettre and Dean noted that since the energy of interaction of two quadrupoles varies inversely as the 5th power of the distance that the barrier arises not from hydrogen atom repulsions, but from electrostatic interactions of the charges of one bond with the charges of another bond (17)(18). The expansion of the electrostatic potential in inverse powers of distance from the interaction of two neutral charge distributions has been reviewed by Margenau (19). The characteristic features are that the dipole-dipole interaction potential is proportional to $1/R^3$, the dipole-quadrupole interaction produces a potential proportional to $1/R^4$, and the quadrupole-quadrupole potential is proportional to $1/R^5$. Higher order terms include octupole interactions, etc. A dipole may be considered as a neutral charge distribution composed of two point charges of opposite signs at a certain distance apart. A quadrupole may be pictured as an arrangement of four charges on the corners of a parallelogram, with the signs of the charges alternating as one goes around the parallelogram. Eight point charges on the corners of a parallelepiped, alternating in sign as one goes around any face of it, constitute an octupole (19). As early as 1928 Williams had suggested that the variation of molecular dipole moment with temperature in molecules of the type CH_2XCH_2Y (X, Y = halogen) could be explained qualitatively by the presence of a barrier to internal rotation which was due to the angularly dependent bond dipole interactions of the C-X and C-Y bonds (20). Extensions of this dipole interaction theory have been reviewed by Smith (21). Lassettre and Dean calculated dipole and quadrupole bond moments for the C-H bond and then calculated the electrostatic interaction potential for ethane. Their calculations predicted the staggered conformation to be more stable than the eclipsed by about 1.5-1.8 kcal./mole. The quadrupole-quadrupole term was by far the most significant if higher order multipoles were assumed to have small values and contribute negligibly to potential energy differences. Oosterhoff calculated bond dipole, quadrupole, and octupole moments for the C-H bond and suggested that the octupole moment contributes more to the barrier in ethane than the quadrupole moment of the C-H bond (22). Au-Chin Tang has suggested that only bond octupole moments contribute to the barrier in ethane (23). Because of the lack of experimental data on bond multipole moments the electrostatic theory resolves itself to assuming a value of, for example, a bond dipole moment and then calculating the

value of the bond quadrupole moment necessary to account for the barrier in a given molecule. For this reason alone the electrostatic theory does not serve as a very useful basis for understanding the origin of potential barriers to internal rotation.

Luft has considered the effect of London dispersion forces (due to induced dipoles and proportional to $1/R^6$) in ethane and based on this effect alone found the eclipsed conformation to be more stable by 0.37 kcal./mole (24). Mason and Kreevoy considered van der Waals repulsions between nonbonded atoms as an explanation for the barrier in certain molecules (25). Values for hydrogen-hydrogen repulsions were based upon experimental data for hydrogen atom repulsions, while data for fluorine-fluorine and chlorine-chlorine nonbonded interactions was based upon experimental data for neon-neon and argon-argon repulsions respectively. Table I contains a comparison of calculated and experimental values for the potential barrier in three molecules where their theory should give its best showing. In all molecules considered by Mason and Kreevoy the calculated value of the barrier was less than the experimental value.

TABLE I

	$\Delta E(\text{calc.})$	$\Delta E(\text{exp.})$	
CH_3CH_3	1.77 kcal./mole	2.88 kcal./mole	(9)
CF_3CF_3	2.14 " "	3.92 " "	(26)
CCl_3CCl_3	9.19 " "	10.8 " "	(27)

These forces do however appear to be a major contributing factor in the case of hexachloroethane.

Wilson has reviewed the experimental data on the barrier height for a number of molecules (28). He concluded that the potential barrier to internal rotation in the case where one group in an ethane-like molecule carries only hydrogens is due to some inherent property of the axial bond (e.g., a lack of cylindrical symmetry) rather than to direct forces between the attached substituent atoms. Wilson drew this conclusion after ruling out van der Waals and electrostatic interactions as satisfactory explanations for barriers. He points out for example that van der Waals forces predict only a 0.53 kcal./mole barrier for methyl silane (25), while the experimental value is 1.70 kcal./mole (29). Also the maximum electrostatic barrier for methyl silane which would arise from bare protons is only 2.8 kcal./mole, and since the C-H and Si-H bonds are not nearly this ionic, this is not an adequate explanation (28). It would appear however that all of these classical forces make some contribution to potential barriers to internal rotation, and that there is no one classical factor which is responsible. Wilson has also pointed out that classical approaches which are based upon electrostatic interaction potentials, steric repulsion forces or dispersion forces do not introduce any new forces which could not be included in a proper quantum-mechanical analysis of the barrier problem (30).

Recent Quantum Mechanical Considerations - Pauling has suggested that the introduction of about 2% \underline{d} and 2% \underline{f} character in the sp^3 hybridized orbitals on carbon would account for the barrier in ethane, due to the interaction of adjacent hybrid bond orbitals (31). This amounts to an interaction of the I_{CC} type due to \underline{f} character (the specific effect of \underline{d} orbitals was not considered by Pauling). Harris and Harris have pointed out that if the effect of \underline{f} character on the I_{CH} interactions were considered that the eclipsed conformation might have been predicted to be more stable than the staggered since the \underline{f} orbitals would be expected to overlap more strongly than \underline{d} orbitals which Gorin, et. al., found to favor the eclipsed conformation (32). Pauling also states that substituted ethanes would be expected to have essentially the same barrier as ethane provided the substituent groups are not large enough to cause steric effects (see Table II for experimental values). These calculations by Pauling were very approximate in nature and merely pointed out that it might be worthwhile to consider such higher orbital effects in more detailed calculations.

TABLE II

	$\Delta E(\text{exp.})$ (kcal./mole)	$J_{\text{HH}'}(\text{vic.})$ (cycles/sec.)
$\text{CH}_3\text{CH}_2\text{Br}$	3.567 (33)	7.25 (39)
$\text{CH}_3\text{CH}_2\text{Cl}$	3.560 (33)	7.07 (39)
$\text{CH}_3\text{CH}_2\text{CH}_3$	3.30 (34)	7.26 (40)
$\text{CH}_3\text{CH}_2\text{F}$	3.250 (33)	7.00 (41)
$\text{CH}_3\text{CH}_2\text{I}$	3.220 (35)	7.16 (39)
CH_2CHF_2	3.18 (36)	4.48 (41)
$\text{CH}_3\text{CH}_2\text{CN}$	3.05 (37)	7.24 (39)
$\text{CH}_3\text{C}\equiv\text{CCH}_2\text{Cl}$	<0.1 (38)	2.5 (42)

The virial theorem states that in a system composed of electrons and nuclei between which the only forces are electrostatic the average kinetic energy is equal to the negative of one-half the average potential energy (43). From a consideration of the virial theorem Clinton has suggested that the barrier to internal rotation is given exactly by (44):

$$\Delta E = \frac{1}{2} \Delta V = - \Delta T$$

$$\text{since } \Delta E = \Delta V + \Delta T \text{ and } \Delta T = - \frac{1}{2} \Delta V$$

Here ΔE is the difference in total energy between the staggered and eclipsed conformations, ΔV is the average electrostatic potential energy, and ΔT is the average kinetic energy. The quantity ΔV can be separated into its various components:

$$\Delta V = \Delta V_{ee} + \Delta V_{ne} + \Delta V_{nn}$$

where the subscripts refer to electron-electron, electron-nuclear, and nuclear-nuclear interactions respectively. Clinton observed the relationship shown in Table III between the experimental value for ΔE for several molecules and the calculated value

TABLE III

	$\frac{1}{2} \Delta V_{nn}$ (kcal./mole)	$\Delta E(\text{exp.})$ (kcal./mole)
CH_3CH_3	2.6	2.9
CH_3NH_2	2.1	2.0
CH_3OH	0.9	1.1
$\text{CH}_3\text{C}\equiv\text{CCH}_3$	0.0	0.0

of $\frac{1}{2} \Delta V_{nn}$, and suggested that to a good approximation, for the cases considered at least, that the value of the barrier is given by one-half the change in internuclear repulsion energy between the staggered and eclipsed conformations, and that $\Delta V_{ee} = - \Delta V_{en}$. These results implied that the C-H bond acts as if it were a unit point charge located at the hydrogen. A consideration of the barrier height in substituted ethanes of the type $\text{CH}_3\text{CH}_2\text{X}$ also suggested to Clinton that the C-X bond appears as if it were a unit point charge located at the X atom (44) (see Table II).

Karplus and Parr arrived at a model for the barrier which is similar to that of Clinton, but derived differently (45). They started with Equation (1) and a model for

$$E = T + V_{nn} + V_{ne} + V_{ee} \quad (1)$$

ethane-like molecules which is essentially a delocalized cylindrically symmetric electron cloud as an initial approximation, i.e., a smeared-out electron cloud which gives the staggered and eclipsed conformations the same electron distribution and only the proton positions differ in the two conformations. To this approximation the only difference between the staggered and eclipsed conformations is V_{nn} , and thus:

$$\Delta E = \Delta V_{nn}$$

Table IV gives the value of ΔV_{nn} , $0.603 \Delta V_{nn}$, and ΔE (exp.) for a number of ethane-like molecules. While predicting a smaller barrier for methyl silane than for ethane,

TABLE IV

	ΔV_{nn} (kcal./mole)	$0.603 \Delta V_{nn}$ (kcal./mole)	ΔE (exp.) (kcal./mole)
CH_3CH_3	4.770	2.875	2.875 ± 0.125 (9)
CH_3SiH_3	2.800	1.688	1.700 ± 0.100 (29)
CH_3GeH_3	2.600	1.567	1.239 ± 0.025 (46)
CH_3SnH_3	2.097	1.265	0.650 ± 0.030 (47)
CH_3NH_2	2.870	1.730	1.977 (48)
CH_3PH_2	3.289	1.982	1.942 ± 0.014 (49)
CH_3OH	1.770	1.067	1.067 (50)
CH_3SH	2.210	1.332	1.269 ± 0.003 (51)
$\text{CH}_3\text{C}\equiv\text{CCH}_3$	0.051	0.031	0.000 (52)

the calculated value for methanethiol is larger than that for methanol. The calculated values are thus in good qualitative agreement with the observed values of barrier heights. Karplus and Parr have pointed out that the most important geometric parameter in the calculations is the C-X-H angle, which for example is smaller in methanethiol than in methanol, $96^\circ 30'$ versus $108^\circ 24'$ respectively (51)(50). This model violates the virial theorem because it implies that there is a change in potential energy without a change in kinetic energy in going from the staggered to the eclipsed conformation. Karplus and Parr suggested that the model could be adjusted by introducing an over-all scale factor into the cylindrical wave function which expands it in the eclipsed configuration. There is then an appropriate decrease in the kinetic energy, $\Delta T = -\Delta V_{nn} = -(\Delta V_{ee} + \Delta V_{ne})$, but the change in potential energy is $\Delta V = 2 \Delta V_{nn}$, leaving ΔE the same. The total energy for the barrier can be written as

$$\Delta E = \Delta E_{nn} + \Delta E_{ne} + \Delta E_{ee}$$

and on the basis of the model, $\Delta E_{nn} = \Delta V_{nn}$ and $(\Delta E_{ne} + \Delta E_{ee}) = 0$; although $\Delta E_{ne} + \Delta E_{ee} \cong -2/5 \Delta E_{nn}$ fits the experimental data better. Karplus and Parr pointed out that it is important to compare ΔE_{ne} and ΔE_{ee} individually with ΔE_{nn} . If ΔE_{nn} is much larger in absolute value than either of these two terms then the proton-proton repulsion model can serve as a basis for understanding the barrier. If the reverse situation holds true the simple model is not satisfactory without modification (45).

The solution of the Schrödinger equation for ethane would as a natural consequence give the value of the barrier to internal rotation. A detailed attempt in this direction has been reported by Pitzer and Lipscomb (53). These workers carried out an approximate solution using Hartree-Fock self-consistent-field wavefunctions constructed from a limited basis set of Slater atomic orbitals -- and a digital computer to evaluate the some 1200 integrals for each of the two conformations. Sixteen basis functions were used which included the 1s functions of each hydrogen and carbon, and the 2s and 2p functions on each carbon. The Hamiltonian was taken over all eighteen

electrons and ^{eight}~~nine~~ nuclei of ethane. The staggered conformation was calculated to be more stable than the eclipsed conformation by 3.3 kcal./mole. The calculated value of the total energy of the staggered form of ethane of -78.99115 atomic units (1 atomic unit = 627.71 kcal./mole (54)) should be compared with the experimental value of -79.843 atomic units. The discrepancy in the value of the total energy is assumed to be due to the approximations in the form of the wave functions rather than the numerical accuracy of the calculations. In obtaining the energies of the staggered and eclipsed conformations these approximations in the form of the wave functions and the geometry, except for internal rotation, are not changed, so that the authors felt that the errors in the total energy, about 500 kcal./mole, will largely cancel out making the value of 3.3 kcal./mole for the barrier a significant number. The results of this molecular orbital calculation do not describe localized "valence bond" type interactions and therefore little in the way of physical significance can be drawn from the results. Although a barrier of 3.3 kcal./mole is calculated using the limited basis set of atomic orbitals mentioned, it can not be concluded that the effect of the d and f orbitals on carbon is unimportant since their effect was not considered (for example, their inclusion in this calculation might have led to a larger or a smaller calculated barrier). Table V gives the energy differences between the eclipsed and staggered conformations of ethane as calculated by Lipscomb and Pitzer (53) (converted from

TABLE V

Energy term (eclipsed - staggered)	Unscaled (kcal./mole)	Scaled (kcal./mole)
ΔV_{nn}	4.702	0.408
ΔV_{ee}	16.678	9.957
ΔV_{ne}	-30.746	-3.609
ΔV	-9.365	6.760
ΔT	12.642	-3.367
ΔE	3.277	3.383

atomic units). It will be noted that although the value of ΔE in the column headed "Unscaled" predicts that the staggered conformation is more stable than the eclipsed, the individual values of ΔT and ΔV violate the virial theorem. Scale factors were applied to the wave functions in both conformations. A scale factor is introduced to give an improved wave function which will satisfy the virial theorem and also lead to a better total energy (55). In the calculations of Pitzer and Lipscomb the scale factors (1.006427 for the eclipsed and 1.006591 for the staggered conformation) were divided into the bond distances and multiplied into orbital exponents. Pitzer and Lipscomb suggested that the values observed for the kinetic and potential energy terms rule out the simple proton-proton repulsion model of Karplus and Parr since the values of ΔV_{en} and ΔV_{ee} are much larger than the value of ΔV_{nn} . Although the value of ΔE may be significant, the values of ΔV_{ee} and ΔV_{en} with the unscaled wave function are not significant since the virial theorem is violated (ΔV_{nn} is calculated classically and based on experimental internuclear distances). The result of scaling the wave functions is to decrease the internuclear distances (more in the staggered conformation than in the eclipsed) such as to increase the electronic kinetic energy and decrease the potential energy in each conformation to comply with the virial theorem. The effect of this scaling is also to make ΔV_{nn} very small. However the internuclear distances used to calculate the scaled ΔV_{nn} are not necessarily the equilibrium distances. Clinton has pointed out that at the equilibrium internuclear distance the electronic kinetic energy of a system increases with decreasing internuclear distance (56). Therefore no conclusions about the validity of the Karplus and Parr model would be expected from the calculations of Pitzer and Lipscomb.

Eyring, Stewart, and Smith suggested that electrons seek lowered kinetic energy by avoiding orbital bending (57). In the delocalized electron path H-C-C-H in ethane there would be less bending in the path when the hydrogen atoms are trans to each other

than when they are cis. Eyring, et al., pointed out that in the staggered conformation of ethane there are three such trans paths, which are absent in the eclipsed conformation, and that this effect alone may account for the barrier to internal rotation.

Harris and Harris carried out valence bond calculations for ethane by representing the molecule as a six electron, six orbital system, H-C-C'-H', which includes most of the types of exchange interactions found in ethane (32). Five singlet valence bond states are possible for this structure and result from the pairing of the six electrons in various ways, giving rise to one perfect-paired structure and four nonperfect-paired structures. The six spatial orbitals used were the 1s orbitals on hydrogen and the sp³ hybrid orbitals on carbon. This calculation considered only the effect of the variation of dihedral angle on I_{CC'} type exchange integrals, neglecting the effect on I_{CH'} and I_{HH'} integrals. Their calculations gave a value for the barrier of 7.5 kcal./mole with the staggered conformation being the more stable of the two. Although Harris and Harris considered this numerical value only approximate, they concluded that the barrier could be attributed to the effect of spin coupling upon the exchanges between electrons on different carbon atoms in the C-H bonding orbitals, i.e., deviations from perfect pairing. They suggested that since I_{CC'} type interactions account for the barrier that the substitution of other groups for hydrogen would be expected to cause only second order changes in the magnitude of the barrier height (see Table II).

Karplus has also discussed deviations from perfect-pairing, which have the desired property of being somewhat insensitive to substituents, as a possible factor in barriers (see Table II for a comparison of ΔE and J_{HH'}) (58). Karplus had used the H-C-C'-H' model for ethane to develop a relationship for the variation of the nuclear spin-spin coupling constant with dihedral angle for vicinal protons (59). A nonzero coupling constant implies that significant deviations from perfect pairing occur in a molecule, the magnitude of the deviation being directly related to the numerical value of the coupling constant. A consideration of the energies associated with Karplus' calculation of the coupling constant in the ethane fragment led to a barrier height of 0.05 kcal./mole due to deviations from perfect-pairing. As in the calculation by Harris and Harris, only the angularly dependent I_{CC'} exchange integrals were considered. The nonperfect-paired valence bond structure which makes the most important contribution to the barrier in this calculation and to the coupling constant has a wave function which may be associated with structure III (the two hybrid orbitals on each carbon are bonded to each other in the sense that their spins are paired), and designated ϕ_2 . The magnitude of the coefficient c₂ in the linear combination of valence bond structures is a measure of the contribution of ϕ_2 to the total wave



III

$$\psi_0 = c_1\phi_1 + c_2\phi_2 + c_3\phi_3 + c_4\phi_4 + c_5\phi_5$$

function for the H-C-C'-H' fragment. Karplus has pointed out that both c₂ and ΔE_2 (contribution of structure III to the barrier) depend on the variation of I_{CC'} with dihedral angle (58). Now J_{HH'} is largely determined by c₂ and since the predicted values of J_{HH'} are in good agreement with the observed value from the NMR spectrum of ethane-type compounds it was assumed by Karplus that his choice of values for I_{CC'} exchange integrals was reasonable, and therefore it could probably be assumed that the barrier was not due to deviations from perfect-pairing. Karplus pointed out that the energies calculated by Harris and Harris led to a prediction that the vicinal coupling constant for the protons would be almost insensitive to variation of dihedral angle.

It should be pointed out that although neglect of the angularly dependent I_{HH'} and I_{CH'} exchange integrals may be justified in calculating values of J_{HH'}, it is not necessarily valid in calculating energies.

Hecht, Grant, and Eyring also considered the effect of deviations from perfect pairing on the barrier to rotation in ethane (60). They derived the following expression for the barrier in ethane:

$$\Delta E = \left(\frac{1}{280}\right)^{\frac{1}{2}} \left[3J_{HH'}^{\frac{1}{2}} I_{HH'} \Big|_{180^\circ} + 6J_{HH'}^{\frac{1}{2}} I_{HH'} \Big|_{60^\circ} - 3J_{HH'}^{\frac{1}{2}} I_{HH'} \Big|_{0^\circ} - 6J_{HH'}^{\frac{1}{2}} I_{HH'} \Big|_{120^\circ} \right]$$

They reported a calculated barrier height of 2.3 kcal./mole for ethane, but unfortu-

nately did not give the values of $I_{HH'}$, which they used so that a comparison cannot be made using more recent experimental values for $J_{HH'}$. Barriers for substituted ethanes determined from such a formula would be dependent on a number of factors which influence $J_{HH'}$. Karplus has recently discussed the effect of ionic substitution perturbations, bond angle and bond length dependence on $J_{HH'}$, (61). These factors would also be expected to influence the height of the barrier to internal rotation in substituted ethanes.

Eyring, Grant and Hecht have extended the general valence bond approach of Harris and Harris, and Karplus to a ten-electron model for ethane, $CH_3-C'-H'$ (14). Carbon orbitals were taken as sp^3 hybridized orbitals with $1s$ orbitals used for hydrogen. This model yields 42 singlet valence bond structures. The mathematical solution of the 1764 matrix elements was simplified through use of digital computer techniques. The lone hydrogen rotating in the ten-electron model represents all of the types of interactions which will contribute to the barrier. The effect of the two remaining hydrogens will be the same as the lone one considered. The effect on the barrier of the three angularly dependent exchange integrals $I_{HH'}$, $I_{CH'}$ and $I_{CC'}$ were considered, allowing none, one, two, or all of them vary with dihedral angle. Table VI shows some of the results obtained. The effect of each integral appears to be essentially inde-

TABLE IV

$I_{HH'}$	$I_{CH'}$	$I_{CC'}$	E (kcal./mole)
1. Constant	Constant	Constant	0.00
2. Variable	Constant	Constant	2.88
3. Constant	Variable	Constant	11.94
4. Constant	Constant	Variable	-1.17
5. Variable	Variable	Variable	13.53

pendent of the other two and their effects additive. Of the three types of angularly dependent exchange integrals used, Eyring, et.al., considered the $I_{HH'}$ values the most reliable as they were based on experimental Morse curve data. The values of the other two integrals were considered less reliable, particularly $I_{CH'}$. They suggested that better values for $I_{CC'}$ and $I_{CH'}$ might lead to a cancellation of these two contributions to the barrier. If so, the hydrogen-hydrogen exchange interaction may be the best valence bond explanation of the barrier since the value calculated from this integral alone gives a value of 2.88 kcal./mole.

Conclusions - Both valence bond and molecular orbital considerations of the ethane molecule have been at least partially successful in calculating a barrier to the internal rotation of one methyl group relative to the other, but have added less than hoped to a physical understanding of the origin of such barriers. A detailed consideration of the effect on the barrier of the inclusion into calculations of higher orbitals on carbons, i.e., d and f orbitals, should be made. The possibility exists in the valence bond case that the inclusion of higher orbitals may favor the eclipsed conformation such that the effects of the $I_{CH'}$ and $I_{CC'}$ exchange integrals cancel each other leaving $I_{HH'}$ as the significant factor. Any satisfactory explanation for the ethane case will have to be extended to other ethane-like molecules to ascertain general applicability. Hopefully in the near future the molecular orbital approach will be able to answer the questions raised by Karplus and Parr concerning the merits of the simple proton-proton repulsion model. From a classical standpoint van der Waals repulsion forces, electrostatic and dispersion forces are all contributing factors to barriers although the magnitude of their importance is uncertain, as is the quality of their physical significance when they are mixed together into an explanation for a barrier.

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THE EFFECT OF HIGH PRESSURE ON REACTION RATES

Reported By Linda R. Brammer

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Introduction: Interpretation of reaction rates by the transition state theory implies the concept of an activation volume (1,2). For a reaction $aA + bB \rightleftharpoons X^* \rightarrow$

Products in solution, $k = \frac{RT}{Nh} K^* \frac{\gamma_A \gamma_B}{\gamma_{X^*}} = \frac{RT}{Nh} K^* K_\gamma$ where k is the rate constant, K^* the

thermodynamic equilibrium constant at infinite dilution for the conversion of reactants to transition state, X^* , and the γ 's are activity coefficients. The pressure

dependence of the rate constant is $\left(\frac{\delta \ln k}{\delta P}\right)_T = \left(\frac{\delta \ln K^*}{\delta P}\right)_T + \left(\frac{\delta \ln K_\gamma}{\delta P}\right)_T$. Substituting

$\ln K^* = -\Delta F^*/RT$ and $(\delta F/\delta P)_T = V$, this becomes $\left(\frac{\delta \ln k}{\delta P}\right)_T = \frac{-\Delta V^*}{RT} + \left(\frac{\delta \ln K_\gamma}{\delta P}\right)_T$ where

ΔV^* represents the difference in partial molar volume ($V_t - \Sigma V_r$) between the transition state and the reactants, and ΔF^* represents the corresponding change in standard partial molar free energies (3). Benson and Berson have shown that the contribution of ionic activity coefficient effects, $(\delta \ln K_\gamma/\delta P)_T$, to the pressure dependence of reaction rates is negligible in aqueous solutions for all but the least pressure-sensitive reaction rates. In solvents of lower dielectric constant than water such effects may become important and can be calculated by appropriate equations (3).

Interpretation of experimentally determined values of ΔV^* can be made in terms of reaction mechanisms (1,2). For reactions involving ions or ionic transition states ΔV^* can be considered as a composite of short range changes in molecular dimensions, packing and geometry, and long range solute-solvent effects (3,4). The latter, which reflect the degree of solvation of the transition state with respect to reactants and products, are known as electrostrictive effects, and become overwhelmingly large in non-aqueous systems (3). Brower (4) has attempted to separate solvation effects from short range effects by varying the solvent polarity and noting the effect on ΔV^* . His results are consistent with the effects expected for the various charge types investigated. This type of analysis may prove valuable in determining the extent of polarization in the transition state.

For molecular or radical reactions, in which there are no incipient charges in the transition state, contributions of solvent effects to ΔV^* are negligible. In these cases ΔV^* is not constant with pressure (3). It has been the practice to estimate ΔV^* at "zero" external hydrostatic pressure (1 atm.) from the slope of the $\ln k$ vs. P plot extrapolated to 1 atmosphere (1). Benson and Berson (3) object to this treatment on the grounds that much of the data is being ignored and that from the curvature of the $\ln k$ vs. P plot the compressibility of the transition state may be obtained.

Compressibility of Transition States: Brower (5), in a study of the reaction of piperidine with a series of bromoquinolines and bromonaphthalenes, observed that ΔV^* varied with pressure. He related the curvature of the $\ln k$ vs. P plot to relative transition state compressibilities by the equation $(\delta \Delta V^*/\delta P)_T = \Sigma V - B^*V^*$, where ΣV is the sum of the reactant molar volumes, B and B^* are compressibilities of reactant and transition state, and V^* is the molar volume of the transition state. For the highly reactive 2-bromoquinoline, $(\delta \Delta V^*/\delta P)_T \approx 0$ and $B/B^* = V^*/\Sigma V$. The right hand term is approximately unity and $B \approx B^*$, which agrees with the Hammond principle for an exothermic reaction. For the relatively unreactive 8-bromoquinoline the average value of $(\delta \Delta V^*/\delta P)_T \approx 10^{-5}$ l/atm. for the pressure range 0 to 1000 atm. Setting $B = 6 \times 10^{-5}$ /atm. gives $B^* = 2 \times 10^{-5}$ /atm. This low compressibility implies a tightly knit system with considerable electrostriction of solvent.

For non-ionic systems Benson and Berson (3) suggest that when the reactants obey the Tait equation (eq. 1), the activated complex can be assumed to obey it also,

$$K = \frac{V_o - V_P}{V_o} = C \log (1+P/B) \quad (1)$$

since transition state theory ascribes molecular properties to the activated complex. In equation 1, V_o and V_P are volumes of liquid at atmospheric pressure and at P atmospheres respectively, K is the compressibility of the

liquid, and C and B are positive constants. Combining the Tait equations for ground and transition states with the equation for ΔV^* gives equation 2,

$$-RT(\delta \ln k / \delta P)_T = (V_t^o - V_g^o) - \frac{CV_t^o}{2.3} \ln(1 + P/B_t) + \frac{CV_g^o}{2.3} \ln(1 + P/B_g) \quad (2)$$

where subscripts g and t refer to ground and transition states. Integration of equation 2 gives equation 3,

$$\frac{\log(k^P/k^o)}{P} = \frac{-\Delta V_o^*}{2.3RT} - \frac{CV_g^o}{2.3RT} \psi \quad (3)$$

where $\tau(x) = (1/x + 1) \log(1+x) - 0.4343$; $x = P/B$; $\psi = \tau(x_g) - \frac{V_t^o}{V_g^o} \tau(x_t)$. The in-

tercept of a plot of $\frac{\log(k^P/k^o)}{P}$ vs. ψ should be $\frac{-\Delta V_o^*}{2.3RT}$. To plot ψ , however, it is necessary to know V_t^o and B_t , neither of which is directly measurable. Benson and Berson (3) simplify the problem by the approximation, $\tau(x) \approx \sigma x^n + Q$. In the range of x equals 2 to 25, which includes pressures from about 1000 to 16,000 kg./cm², the values $\sigma = 0.200$, $Q = 0.008$, and $n = 0.523$ give a linear plot which does not deviate from the true value of τ by more than 4%. Using these values, equation 3 re-

duces to $\frac{\log(k^P/k^o)}{P} \approx \frac{-\Delta V_o^*}{2.3RT} (1-0.008C) - \frac{0.200 CV_g^o}{2.3RT} \left[\frac{1}{B_g^{0.523}} - \left(1 + \frac{V_o^*}{V_g^o}\right) \frac{1}{B_t^{0.523}} \right] P^{0.523}$.

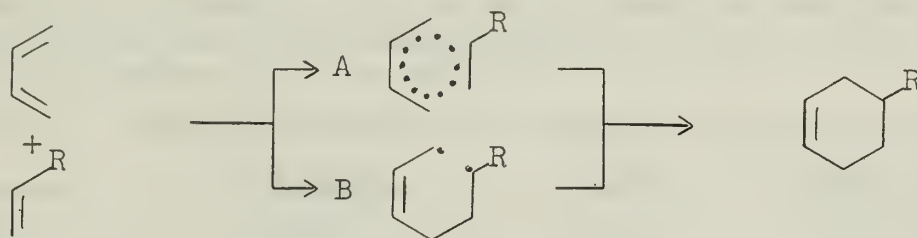
From the intercept, I , of a $\frac{\log(k^P/k^o)}{P}$ vs. $P^{0.523}$ plot, $-\Delta V_o^* = \frac{2.3 RTI}{1-0.008C}$.

Walling and Tanner (6) point out that three different types of volume change behavior may be observed to occur in going from reactants to products: 1) the transition state is a volume minimum, as observed for radical displacements, 2) the transition state is a volume maximum, as observed in the racemization of 1-6-nitro-2,2'-carboxybiphenyl (7), and 3) there is a monotonous change in volume along the reaction coordinate, as observed in the Diels-Alder reaction. Walling and Tanner conceded the plausibility of Benson and Berson's treatment of transition state compressibility for the first two cases, but contend that pressure will actually shift the transition state along the reaction coordinate in the third case and there will be an apparent abnormal compressibility associated with the activated complex which cannot be accommodated by treatment of the transition state as a normal molecule. Benson and Berson (8) calculate a numerical estimate of this pressure effect using a model with extremely compressible bonds (force constant of 7×10^3 dynes/cm.) and find the shift in ΔV^* to be 0.6 cc/mole, which is well within the limit of experimental error of measurement of ΔV^* (± 1 cc/mole). They conclude that pressure deformation of the transition state will be small and comparable to that of the ground state. They also point out that intermolecularly hydrogen bonded liquids such as water and alcohols, whose weak hydrogen bonds can be compared to the weak bonds breaking or forming in the transition state, show no abnormal compressibility in the pressure range under discussion and their behavior can be accommodated by the Tait equation.

Molecular Reactions: Benson and Berson (3) made plots of $\log(k^P/k^o)$ vs. $P^{0.523}$

for Ewald's data on the decomposition of azobisisobutyronitrile in toluene in the presence of I_2 (14) and for Walling and Peisach's data on isoprene dimerization at

60° and 75° (9). In the first case the plot was linear up to 5000 atm. after which it became concave downward. The deviation at high pressures may be due to the "cage effect" discussed later. The value obtained for ΔV^* was +12.4 cc/mole as compared to +9.4 cc/mole previously reported (14). Linear plots were obtained in the isoprene dimerization above 4000 kg/cm², but at lower pressures they fall away from linearity badly and there is a great deal of scattering, probably attributable to the uncertainty in low pressure measurement. The values obtained from the data at 75° were $\Delta V^* = -38.4$ cc/mole and $B_t = 530$ kg/cm², and from that at 60°, $\Delta V^* = -36.5$ cc/mole and $B_t = 525$ kg/cm². The values for B_t are reasonable for a C₁₀ hydrocarbon and too high for a C₅ hydrocarbon. Walling and Peisach (9) had previously reported ΔV^* 's of -25.6 and -24.3 cc/mole, respectively. They had considered these low values ($\Delta V_{\text{overall rx.}} = -45.5$ (60°), -48.7 cc/mole (75°)) inconsistent with a cyclic transition state (A), ΔV^* estimated as -35 cc/mole, and good evidence for an open-chained diradical (B), ΔV^* estimated from the difference in molecular volumes of cyclic and non-cyclic hydrocarbons as -21 to -23 cc/mole. Benson and Berson's values for ΔV^* are consistent with A.



Walling and Schugar (10) found that in a similar dimerization of 2,3-dimethylbutadiene and butyl acrylate the $\ln k$ vs. P plot was linear below 3000 kg/cm², and ΔV^* obtained from the slope at 1 atm. had a value of -22.6 cc/mole, in agreement with their earlier work on isoprene. It should be pointed out that no measurements were made for pressures above 3000 kg/cm². It may be that Benson and Berson's treatment could be applied above this pressure and a more negative ΔV^* obtained. The failure of these data to be accommodated at low pressures by Benson and Berson's treatment should not be ignored, however, since it may imply that the transition state does not obey the Tait equation over the whole pressure range.

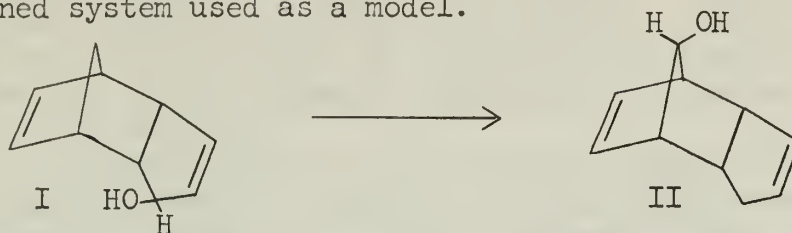
Brower (11) in a study of the Curtius rearrangement of benzazide in ethanol-water and ligroin at high pressures obtained values for ΔV^* of +2 cc/mole and +5 cc/mole, respectively. The small difference in ΔV^* for the two solvents indicates the transition state is not highly polarized. The small positive values agree with a transition state in which bond-breaking is occurring. If bond formation were involved significantly, the ΔV^* would probably have been negative. Other evidence requires nearly simultaneous bond-breaking and migration. This requirement can be satisfied with no bond formation in the transition state.

Brower (11) reports ΔV^* of -14 to -18 cc/mole for the Claisen rearrangement of p-cresyl allyl ether, m-methoxyphenyl allyl ether, and vinyl allyl ether in benzene, cyclohexane, ethanol-water, and neat, consistent with the formation of a cyclic transition state. ΔV^* showed very little variation with solvent. Walling and Naiman (12) also found ΔV^* of -14 to -18 cc/mole (as calculated by Benson and Berson's method) for the Claisen rearrangement of allyl phenyl ether in a variety of solvent systems.

Walling and Naiman (12) found $\Delta V^* \simeq -14$ cc/mole for the Cope rearrangement of ethyl (1-ethylpropenyl)-allylcynoacetate in a variety of solvents, in good agreement with the proposed cyclic transition state which is expected to have ΔV^* approximately equal to the volume difference between the starting material and a cyclic compound which approximates the transition state.

Walling and Schugar (10) interpret the value of ΔV^* (6 cc/mole) obtained for the Woodward-Katz rearrangement of β -1-hydroxydicyclopentadiene (I) to anti-8-hydroxydi-

cyclopentadiene (II) as evidence that the reaction is a partial retro-Diels-Alder reaction (ΔV^* expected to be positive) instead of a Cope rearrangement (ΔV^* for open-chained systems are negative (12)). Benson and Berson (8) feel that this conclusion is unjustified in view of the rigidity of the cyclic system in comparison with the open-chained system used as a model.



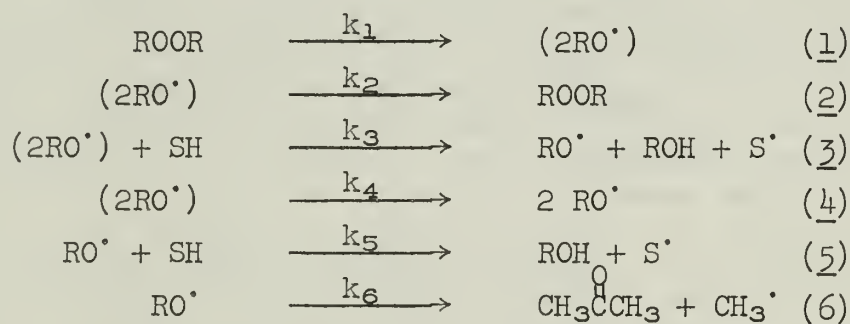
Radical Reactions: Homolytic dissociation processes are expected to be retarded by pressure and exhibit positive values of ΔV^* . Measurements of the effect of pressure on the rate of decomposition of di-tert-butylperoxide (13), azobisisobutyronitrile (14), and benzoylperoxide (15) were made in a variety of solvents and small positive values for ΔV^* were obtained (Table I) and were found to vary with solvent. Walling and Metzger (13), seeing no reason to postulate any contribution from a direct bimolecular displacement reaction in these solvents, interpreted this solvent effect in terms of a "cage effect".

Table I. Volume of Activation for Homolytic Dissociations.

Compound	Solvent	T(°C)	$\Delta V^*(\text{cc/mole})$	Ref.
di- <u>t</u> -butylperoxide	toluene	120	5.4 ± 0.6	13
di- <u>t</u> -butylperoxide	cyclohexene	120	6.7 ± 0.3	13
di- <u>t</u> -butylperoxide	benzene	120	12.6 ± 1.3	13
di- <u>t</u> -butylperoxide	CCl ₄	120	13.3 ± 3	13
azobisisobutyronitrile	toluene	62.5	3.8^{a}	14
azobisisobutyronitrile	toluene	62.5	9.36^{b}	14
benzoylperoxide	acetophenone	80	4.8	16
benzoylperoxide	CCl ₄	60	9.65	15
benzoylperoxide	CCl ₄	70	8.56	15

a) photometric analysis; b) I₂ scavenger technique.

Taking the decomposition of di-t-butylperoxide as an example, if (2RO[•]) represents a pair of radicals still confined within the same solvent cage and SH represents the solvent, a reasonable reaction mechanism is (13):

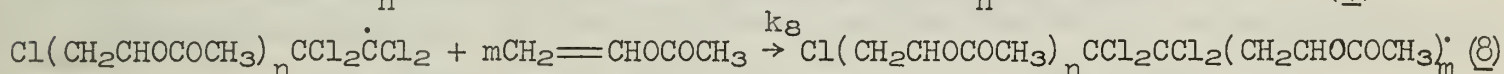
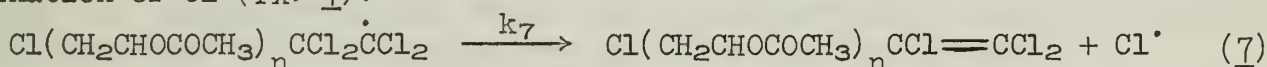


For this mechanism $k_{\text{obs}} = k_1(k_3 + k_4)/(k_2 + k_3 + k_4)$. Under pressure the recombination of "caged" radicals (k_2) and attack of "caged" radicals on solvent (k_3) should increase, while dissociation (k_1) and diffusion out of the cage (k_4) should decrease. This suggests that in toluene and cyclohexene, solvents readily attacked by t-butoxide radicals, $k_3 > k_2$, $k_{\text{obs}} = k_1$, and the measured ΔV^* is essentially that of the initial dissociation. In benzene and carbon tetrachloride k_3 is negligible, and under pressure $k_4 < k_2$, $k_{\text{obs}} = k_1 k_4/(k_2 + k_4)$, and ΔV^* observed is a composite quantity.

Since the ratio $k_4/(k_2+k_4)$ decreases with increasing pressure, the larger values for ΔV^* obtained in benzene and CCl_4 are accounted for.

A similar explanation accounts for the differences in Ewald's values of ΔV^* for the dissociation of azobisisobutyronitrile as measured photometrically ($k_{\text{obs}} = k_1'$) and by the I_2 scavenger technique ($k_{\text{obs}} = k_1'k_4'/(k_2'+k_4')$). Benzoylperoxide qualitatively follows the same trend in CCl_4 and acetophenone. These results suggest that high pressures decrease the efficiency of radical chain initiators which dissociate homolytically unless they yield fragments sufficiently reactive to attack the substrate while within a solvent cage.

Ewald, Hamann and Stutchbury (17) found that the effect of high pressure on the benzoylperoxide catalyzed reaction of cis-1,2-dichloroethylene was to decrease the rate of isomerization and increase the rate of polymerization. This is to be expected since isomerization involves bond-breaking and polymerization, bond formation. The observation by Zhulin, Gonikberg and Zagorbinina (18) that the average number of tetrachloroethane units per molecule in telomers of vinyl acetate and tetrachloroethylene increases with pressure can be accounted for by a similar acceleration of radical addition to the double bond (rx. 8) and retardation of the unimolecular elimination of Cl^{\bullet} (rx. 7).



In general, interpretation of pressure effects on radical chain reactions is complicated, as the rates are composites of several simultaneous reactions. For example, in the polymerization of styrene, $\text{dln } R_p/\text{dP} = \Delta V_{\text{Overall}}^*/RT = -(\Delta V_p^* - \Delta V_i^*/2 - \Delta V_t^*/2)/RT$, where ΔV_p^* , ΔV_i^* and ΔV_t^* refer to activation volume changes for chain propagation, initiation and termination, respectively. Walling and Pellon (19) have been able to separate these pressure effects by comparing the data obtained on the emulsion polymerization of styrene with that obtained for the benzoylperoxide initiated (20) and thermally initiated polymerizations (21). Emulsion polymerization occurs in three stages, the initial period covering the first few per cent of reaction in which the reaction rate rises to a constant, a prolonged period extending to 50-60% conversion in which the reaction rate is zero order, and a final stage in which the rate decreases as the monomer is exhausted. In the second stage all of the polymerization occurs within small particles of polymer containing dissolved monomer. These are small enough to support only one radical chain. Any new radical which diffuses into such a particle will immediately combine in a chain termination step. The rate in this stage is dependent only upon chain propagation and ΔV_{obs}^* is ΔV_p^* . Using this value, $\Delta V_p^* = -11.5$ cc/mole, the value $\Delta V_i^* = 4.8$ cc/mole obtained from the decomposition of benzoylperoxide in acetophenone (16), and $\Delta V_{\text{Overall}}^* = -11.1$ cc/mole, obtained by Merrett and Norrish (20) for the benzoylperoxide initiated polymerization of styrene, they calculated $\Delta V_t^* > 4.0$ cc/mole. Chain termination involves bond formation and a negative ΔV_t^* was expected. The positive value can be accounted for if it is assumed that chain termination is diffusion controlled at high pressures. From these values for ΔV_p^* and ΔV_t^* , and $\Delta V_{\text{Overall}}^*(\text{thermal}) = -17.5$ cc/mole from the thermal polymerization data of Kobeko (21), $\Delta V_i^*(\text{thermal}) = -8$ cc/mole can be calculated. Since thermal initiation is undoubtedly polymolecular, the negative value is plausible and indicates that thermal initiation becomes increasingly important at high pressures.

From experimental determination of the effect of pressure on the transfer constant of styrene in CCl_4 , Walling and Pellon (19) conclude that the radical displacement reaction between styrene radical and CCl_4 is accelerated by pressure to approximately the same extent as addition of styrene radical to the double bond and that $\Delta V_{\text{tr}}^* \simeq -11$ cc/mole.

Kilroe and Weale (22) in a study of the polymerization of α -methylstyrene under pressure found the ceiling temperature (the temperature at which the rate of deprop-

agation exceeds the rate of propagation) increased with increasing pressure. It is expected that the equilibrium between monomer and polymer would shift with pressure, since propagation is accelerated by pressure and depropagation, which involves bond breaking, should be retarded ($\Delta V_{\text{est.}}^* = 4 \text{ cc/mole}$).

The effect of high pressure on radical chain processes can be summarized (23): 1) Radical formation by unimolecular decomposition of initiators is slightly repressed by pressure, but polymolecular processes, e.g. thermal initiation, are accelerated. 2) Both radical addition to unsaturated molecules and radical displacements are strongly accelerated by pressure. 3) Bimolecular radical destroying reactions may be retarded by pressure as they become diffusion controlled. 4) Degradative chain transfer becomes increasingly unimportant as the relatively stable radicals produced become able to start new chains. For example, Walling and Pellon (23) observed in the benzoylperoxide initiated polymerization of allyl acetate that the ratio of monomer to polymer decreased somewhat at low initial polymer concentrations, but the molecular weight of the polymer remained constant. This they attributed to restarting of chains by the relatively unreactive $\text{CH}_2=\text{CHCHOAc}$. High pressure should increase the efficiency of chain reactions which depend on competition between chain-carrying and chain-termination steps, but should have little effect when the yield depends on competition between radical addition and displacement.

Menshutkin Reaction: In the Menshutkin reaction two neutral molecules react to form two ions.

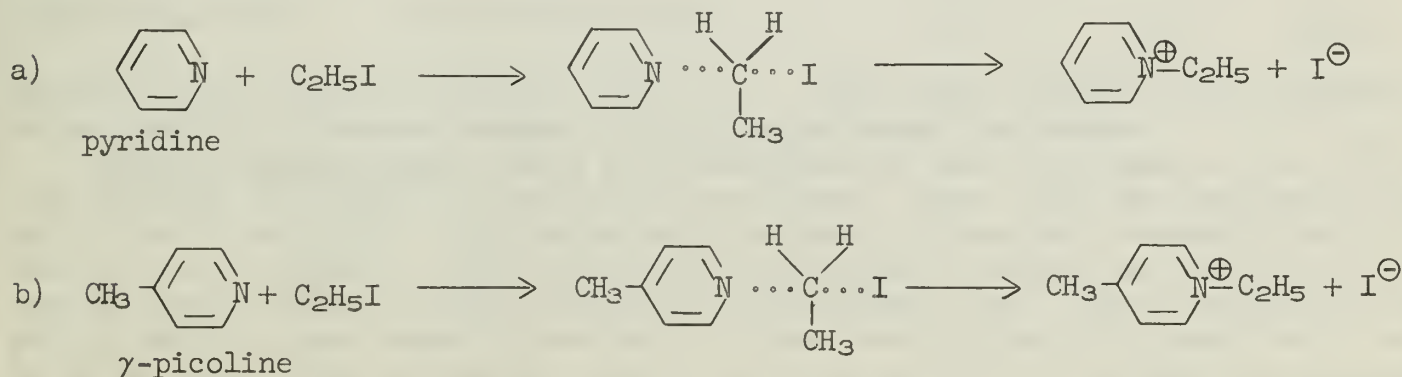


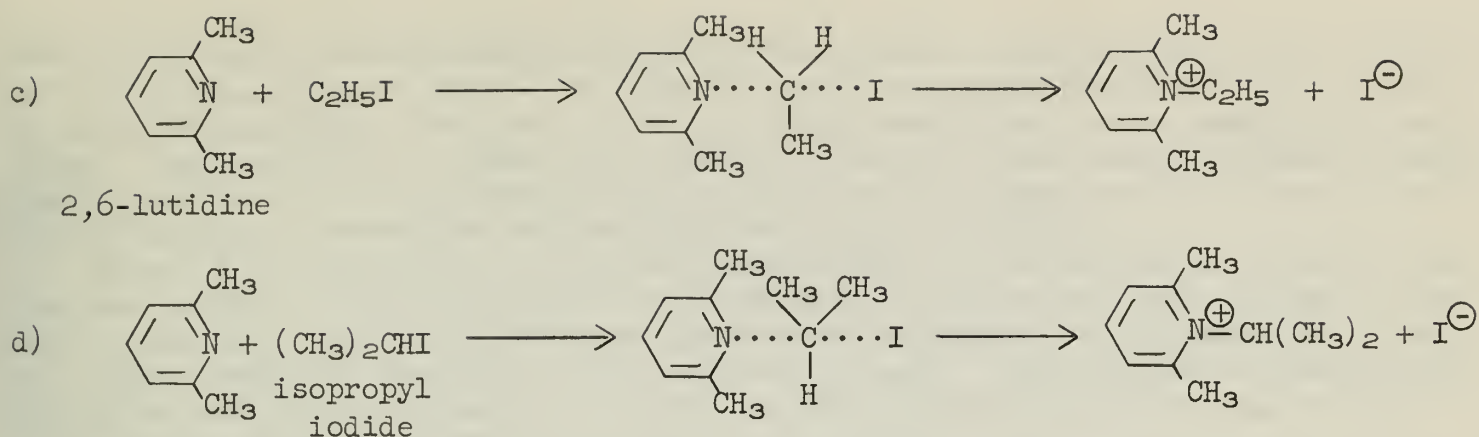
The large negative volumes of activation obtained for these reactions are attributed to electrostriction of solvent in the transition state. The exact nature of the transition state has been a subject of some controversy. As Stewart and Weale (24) and Gonikberg and Zhulin (25) have pointed out, $-\Delta V^*$ is usually considerably less than $-\Delta V_s$, the overall decrease in volume for the reaction in the same solvent. This is not in accord with the idea that the transition state closely resembles the solvated product ions. In a study of a reverse Menshutkin reaction, the decomposition of methyldiethylanilinium iodide in nitrobenzene, Stewart and Weale (24) obtained a value for $\Delta V_{\text{reverse}}^*$ of $+45 \text{ cc/mole}$ at 65° . Thus the transition state is considerably less solvated than the product ions.

From calculations for the reaction between pyridine and ethyl iodide based on the dependence of ΔV^* on molar volumes of a variety of solvents, Gonikberg and El'yanov (26,27) conclude that the solvation envelope of the transition state contains no more than two solvent molecules.

Gonikberg and Kitaigorodskii (28) calculated that acceleration by pressure should increase with increased steric hindrance in the Menshutkin reaction because of increased compression in the transition state. Gonikberg and El'yanov (29) confirmed this prediction in the series of reactions in Figure 1.

Figure 1. Steric Hindrance in the Menshutkin Reaction in Nitrobenzene.





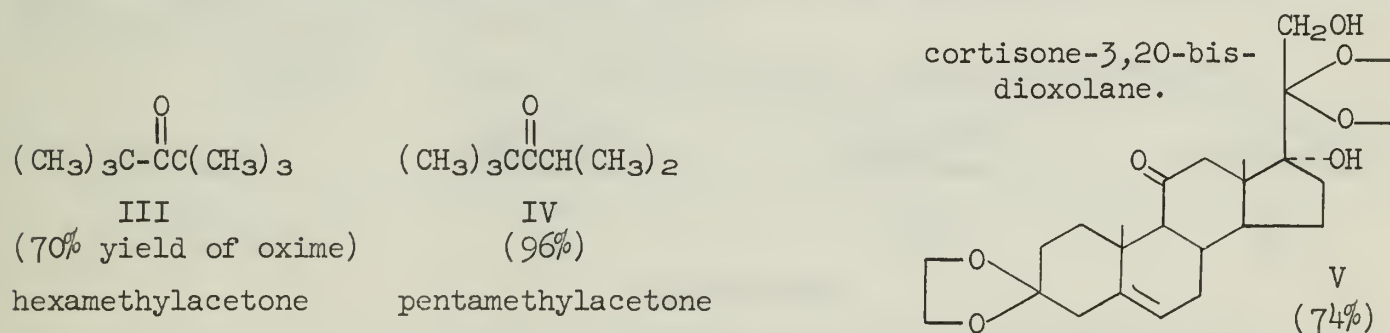
As indicated in Table II, ΔV^* becomes more negative with increased steric hindrance.

Table II. Effect of Steric Hindrance on ΔV^* .

Rx	ΔV^* (cc/mole)	$(\Delta V^* - \Delta V_a^*)_{\text{exp}}$	$(\Delta V^* - \Delta V_a^*)_{\text{calc}}$
a	-23.8	0	0
b	-24.3	-0.5	0
c	-27.2	-3.4	-5.7
d	-30.5	-6.7	-11.5

Acid Catalyzed Reactions: Whalley (30) has suggested that ΔV^* values could be useful as a means of distinguishing between unimolecular and bimolecular mechanisms for reactions catalyzed specifically by hydrogen ion. ΔV^* for a unimolecular decomposition is expected to be close to zero and usually positive, while for a bimolecular mechanism the effect of bond formation should overwhelm effects due to bond breaking and charge dispersion and ΔV^* is expected to be negative by several cc/mole. Whalley and coworkers have applied this criterion to a number of acid catalyzed reactions and have compared their conclusions with those made on the basis of the Zucker-Hammett hypothesis (31,32). In several cases the two methods give conflicting results.

Jones, Tristram and Benning (33) were able to prepare oximes in good yields from the sterically hindered ketones III, IV and V at 140,000 p.s.i. From rate data they



obtained $\Delta V^* = -11.5$ cc/mole (error ~25%) for V. This highly negative value suggests that oxime formation proceeds through a highly polar transition state.

Aromatic Substitution: Very few investigations have been made of the effect of high pressure on aromatic substitution reactions. Brower (34) has determined that the values of volumes of activation for a series of diazonium decompositions lie between 9 and 11 cc/mole. This positive ΔV^* is strong evidence that nucleophilic attack by water is not involved in the rate determining step. The size of ΔV^* is compatible with a unimolecular dissociation if the leaving group is large, as it would be if it were tightly solvated. Brower found no correlation between reactivity and ΔV^* in this series. However, in the reaction of piperidine with the series 1-bromonaphthalene

($\Delta V^* = -53$ cc/mole), 2-bromonaphthalene ($\Delta V^* = -63$ cc/mole), 6-bromoquinoline ($\Delta V^* = -64$ cc/mole), 8-bromoquinoline ($\Delta V^* = -41$ cc/mole) and 2-bromoquinoline ($\Delta V^* = -36$ cc/mole), he observed (5,35) that acceleration with pressure was highest where reactivity was lowest. Rationalizing by Hammond's principle, the less endothermic activated complex should involve less contraction along the reaction coordinate and less electrostriction of solvent, because of weaker polarization in the complex.

Brower (36) calculated the percent polarization of the activated complex in the reaction between 2-chloroquinoline and piperidine by taking the ratio of the difference in the ΔV^* 's for two solvents of contrasting polarity to the difference in overall volume change of reaction in the same two solvents. The solvents selected were piperidine and piperidine-water. A value of 70% polarization was calculated, but large errors were introduced due to poor miscibility.

Coillet and Hamann (37) have studied the effect of pressure on the rate of mononitration of benzene, toluene, chlorobenzene, and *p*-dichlorobenzene by an excess of nitric acid in inert solvents. The large $-\Delta V^*$'s they obtained are consistent with partial formation of a covalent bond between the attacking nitronium ion and the benzene ring.

LeNoble (37) interprets the effect of high pressure (Table III) on the alkylation of phenoxide ion by allyl chloride in terms of the hydrogen-bonding efficiency of the solvents.

Table III. Product Distribution in the Alkylation of Sodium Phenoxide with Allyl Chloride as a Function of Pressure at 30°.

Solvent	P (atm.)	allylphenyl ether (%)	<i>o</i> -allylphenol (%)	<i>p</i> -allylphenol (%)
water	1	62	17.5	20.5
water	7000	42	17.5	40.5
1,2-dimethoxyethane	1	100	0	0
1,2-dimethoxyethane	5500	100	0	0
methanol	1	100	0.4	<0.1
methanol	5500	92	5.1	2.9

Gonikberg *et al.* (38) found that at 4000 kg/cm² the relative amounts of *ortho*, *meta* and *para*-products differed from those at atmospheric pressure in the radical phenylation of *t*-butylbenzene (Table IV).

Table IV. Product Distribution as a Function of Pressure.

Pressure	2- <i>t</i> -butylbiphenyl (%)	3- <i>t</i> -butylbiphenyl (%)	4- <i>t</i> -butylbiphenyl (%)
1 atm.	19	52	29
4000 kg/cm ²	28	46.5	25.5

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MECHANISM OF HETEROGENEOUS CATALYTIC HYDROGENATION

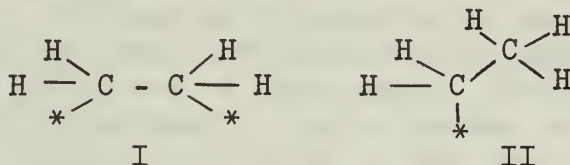
Presented by L. Walker

March 12, 1964

Introduction: This seminar will be concerned with the recent work on the mechanism of heterogeneous catalytic hydrogenation. Some aspects of the earlier evidence have been reviewed (1,2,3).

Methods used to study the mechanism of hydrogenation include, product analysis, rate studies, and deuterium exchange reactions. The various proposed mechanisms with evidence supporting each have been summarized (30).

In 1934, Horiuti and Polanyi (4) proposed a mechanism for the hydrogenation of ethene on nickel. They proposed that an ethene-nickel adsorbed species I (the * denotes a catalyst site) interacts with an adsorbed hydrogen to give a half hydrogenated state II. The half hydrogenated form could then react with another adsorbed hydrogen to give the product.



Deuterations: Burwell and co-workers (5,6) have recently investigated the gas phase deuterations of 2-butyne, 1-butyne, and 1,2-butadiene. The results lend considerable support to the original "classical" picture. The reaction products and deuterium incorporation are summarized in Tables I, II, and III. The products were separated by vapor phase chromatography and the deuterium content was determined by mass spectrometry.

Table I

Product Analysis from the Deuteration of 2-Butyne on 0.03% Pd/Al₂O₃ in a Flow System*

Temperature	% Completion of the Reaction	Cis-2-Butene	% Hydrocarbons Trans-2-Butene	1-Butene	Butane
14°	78	99.0	0.9	0.0	0.1
27°	47	97.8	0.85	0.42	1.06
58°	86	95.9	1.4	0.8	1.9

Isotopic Distribution of Cis-2-Butene

Temperature	d ₀	d ₁	d ₂	d ₃	d _{av}
14°	0.5	1.8	97.5	0.2	1.97
27°	0.2	5.8	93.7	0.3	1.94
58°	1.0	5.4	91.4	2.2	1.95

* Similar distribution of products resulted from the hydrogenation of 2-Butyne (29) but hydrogen was incorporated about twice as fast as deuterium (5).

Table II

Products and Isotope Distribution from the Deuteration of 1-Butyne over Pd/Al₂O₃ at 35°. D=0.09 to 0.73 ** in a Flow System

Products	%	Isotope Distribution				
1-Butene	99.1		d ₀	d ₁	d ₂	d _{av}
Cis-2-Butene	0.2	1-Butene	1.8	14.1	72.2	0.40
Trans-2-Butene	0.2	1-Butyne	98.4	1.6	0.0	
Butane	0.5					

** D (H) is the ratio of deuterium (hydrogen) reacting / atom hydrocarbon

Products at 8° $D=0.38$

	η	Compound	Temp.	d_0	d_1	d_2	d_3	d_{av}
Cis-2-Butene	53							
Trans-2-Butene	7	Cis-2	8°	2.2	9.7	85.2	2.4	1.89
1-Butene	40	"	40°	2.0	12.5	81.8	2.8	1.88
Butane	0.1	1-Butene	8°	1.1	9.0	85.4	3.0	1.95
		"	40°	1.0	11.3	80.6	4.9	1.96

$$\begin{array}{c}
 \text{CH}_3-\text{C}\equiv\text{C}-\text{CH}_3 \\
 \text{A}
 \end{array}
 \xrightarrow{1}
 \begin{array}{c}
 \text{CH}_3 \quad \text{CH}_3 \\
 \diagdown \quad \diagup \\
 \text{C}=\text{C} \\
 \diagup \quad \diagdown \\
 * \quad * \\
 \text{I}
 \end{array}
 \xrightarrow[\text{(D)}]{\text{H}-*}
 \begin{array}{c}
 \text{CH}_3 \\
 | \\
 \text{CH}_3-\text{C}=\text{C}-\text{H} \text{ (D)} \\
 | \\
 * \\
 \text{III}
 \end{array}
 \xrightarrow{3}
 \begin{array}{c}
 \text{CH}_3 \quad \text{CH}_3 \\
 \diagdown \quad \diagup \\
 \text{C}=\text{C} \\
 \diagup \quad \diagdown \\
 \text{H} \quad \text{H} \text{ (D)} \\
 \text{(D)} \quad \text{B}
 \end{array}$$

$$\begin{array}{c}
 \text{H}_2\text{C}=\text{C}=\text{C} \begin{array}{l} \diagup \text{CH}_3 \\ \diagdown \text{H} \end{array} \\
 \text{E}
 \end{array}
 \xrightarrow[5']{5}
 \begin{array}{c}
 \text{CH}_3 \\
 | \\
 \text{CH}_2-\text{CH}=\text{C}-\text{H} \text{ (D)} \\
 | \quad | \\
 * \quad * \\
 \text{II}
 \end{array}$$

$$\begin{array}{c}
 \text{CH}_2=\text{C}-\text{CH}-\text{CH}_3 \\
 | \quad | \\
 * \quad * \\
 \text{II}'
 \end{array}
 \xrightarrow[7']{7}
 \begin{array}{c}
 \text{(D)} \\
 | \\
 \text{H}_2\text{C}=\text{C}-\text{C} \begin{array}{l} \diagup \text{H} \\ \diagdown \text{CH}_3 \end{array} \\
 | \quad | \\
 * \quad \text{H} \text{ (D)} \\
 \text{III}'
 \end{array}$$

$$\begin{array}{c}
 \text{CH}_2=\text{C}-\text{CH}-\text{CH}_3 \\
 | \quad | \\
 * \quad * \\
 \text{II T}
 \end{array}
 \xrightarrow{12}
 \begin{array}{c}
 \text{H} \\
 | \\
 \text{H}_2\text{C}=\text{C}-\text{C}-\text{CH}_3 \\
 | \quad | \\
 \text{(D)} \quad \text{H} \text{ (D)} \\
 \text{C}
 \end{array}$$

$$\begin{array}{c}
 \text{H} \\
 | \\
 \text{CH}_2-\text{CH}=\text{C}-\text{CH}_3 \\
 | \quad | \\
 * \quad * \\
 \text{II T}
 \end{array}
 \xrightarrow{8}
 \begin{array}{c}
 \text{(D)} \\
 | \\
 \text{H}-\text{C}=\text{C}-\text{CH}_2\text{CH}_3 \\
 | \quad | \\
 * \quad * \\
 \text{I}'
 \end{array}
 \xrightarrow{10}
 \begin{array}{c}
 \text{HC}\equiv\text{C}-\text{CH}_2\text{CH}_3 \\
 \longleftrightarrow
 \end{array}$$

Fig. 1

species then picks up another deuterium the trideuterated butene is produced. The results in Table I indicate that as the reaction temperature rises, step 4' (the loss of a proton) is favored more since more d_1 and d_3 are found in the products. Since recovered starting material was deuterium free, the reverse of steps 1 and/or 2 is slow.

If II is a true intermediate formed in the conversion of A to B, then cis-2-butene would be expected from any other reaction that can form II. Adsorbed state II should be formed by the adsorption of 1,2-butadiene. As can be seen from Table III, cis-2-butene is indeed the major product from this substrate. In the adsorption of E to give II, the molecule can be adsorbed with the methyl group either up or down. If it is up, the intermediate will be II; if it is down, the intermediate will be IIT. Intermediate IIT will give the trans olefin. The approach of a methyl group to the surface would be less favored and therefore the low yield of the trans isomer is predicted. The other major product, 1-butene, is formed from a 2,3-diadsorbed species II'. Some reversal in steps 4 and 7 will explain the isotope distribution in the products. Again, at a higher temperature, there is more exchange of deuterium. The breakage of the C-H (C-D) bond required for steps 4' and 7' would be favored by the higher temperature. The products as determined by n.m.r. were 1,2-dideutero-cis-2-butene and 2,3-dideutero-1-butene.

The products and isotopic distribution resulting from the reaction of 1-butyne with deuterium are given in Table II. The product is more than 99% 1-butene. However, it will be noted that there is nearly 2% of exchanged deutero-1-butyne formed during the reaction. The 1-butene contains 12% of d_3 and 14% d_1 . The normal disubstituted butene may result from the direct conversion of F to I'. The extensive exchange probably occurs via IV. The hydrogen lost by one molecule is gained by another giving equal amounts of d_1 and d_3 compounds.

The mechanism of reaction is the same in the liquid phase. Table IV shows that the same results are obtained for the liquid phase hydrogenation of 3-hexyne (5) as for the gas phase hydrogenation of 2-butyne. "Nickel boride" catalyst (27) gave even more stereospecific results. Hydrogenation in ethanol gave 98-99% of the cis olefin.

Table IV

Liquid Phase Deuteration of 3-Hexyne at 0° over 13.8% Pd/Al₂O₃

Hydrocarbons	% at D=0.35	Isotope Distribution of <u>Cis</u> -3-Hexene					
<u>Cis</u> -3-Hexene	92.5	d_0	d_1	d_2	d_3	d_4	d_{av}
<u>Trans</u> -3-Hexene	3.5	1.0	10.6	87.3	0.8	0.4	1.89
<u>Trans</u> -2-Hexene	1.2						
<u>Cis</u> -2-Hexene	0.9						
1-Hexene	0.0						
Hexane	2.0						

In the hydrogenation of alkenes, some rearrangement is frequently observed. When deuterium is used in place of hydrogen, the deuterium incorporation indicates that a simple addition is not the only important process. In Table V is presented data on the deuteration of 1-hexene (7). The mechanistic scheme presented in Fig. 2 which corresponds closely to Fig 1, will conveniently explain this data. Steps 1, 2, and

Table V

Hydrocarbons present during the Liquid Phase Deuteration of 1-Hexene on PtO₂ at 25° and 1 atm.

Hexane (% Reaction)	1-Hexene	<u>Trans</u> -2-Hexene	<u>Cis</u> -2-Hexene
12.5	86.9	0.3	0.2
44.4	57.3	0.7	0.6
60.1	37.8	1.1	0.9
86.5	10.7	1.8	1.0
97	0.4	1.6	0.9
100	0.0	0.0	0.0

Deuterium Distribution

% Reaction		10.2	25.6	68.3	93.7	100
Hexenes	d ₀	97	91.9	79	70	
	d ₁	3.0	8.1	21	30	
Hexane	d ₀	15.0	13.5	16.1	9.7	9.8
	d ₁	35.5	35.2	35.1	33.9	31.5
	d ₂	29.5	31.1	29.5	33.8	32.8
	d ₃	10.7	10.7	12.1	13.9	14.6
	d ₄	4.6	5.5	4.3	5.7	6.6
	d _{av}	1.71	1.76	1.65	1.83	1.96

3 give the normal d₂ hexane. The reversal of 2,4, and 6 can lead to the rearranged products. Since the bonds in III are free to rotate, the formation of V is not hindered and a larger amount of the more stable trans-2-hexene is thus isolated. As can be seen from the compound analysis, the two isomers build up until all the 1-hexene has reacted. This isomerization is even more noticeable in the hydrogenation of 1-

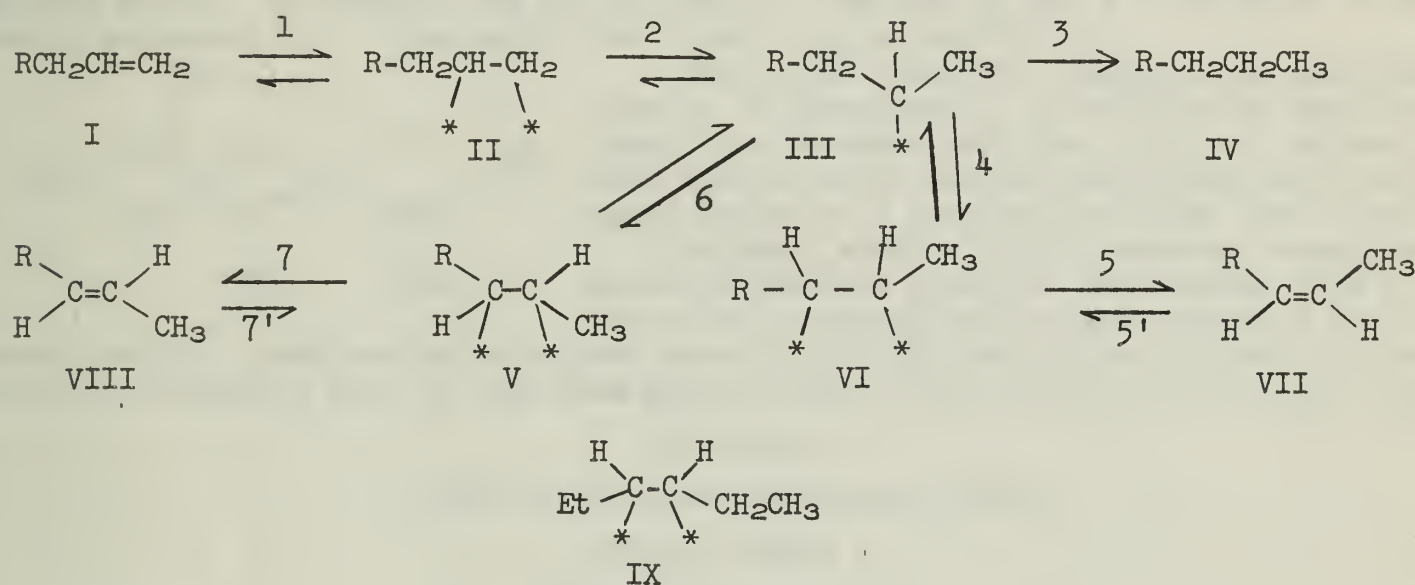


Fig 2

penene over Raney nickel in ethanol. When half of the starting alkene had been hydrogenated, half of the unreacted alkene mixture consisted of the two 2-isomers (11). The hydrogenation of I is therefore faster than either VII or VIII. By using a copper chromium oxide catalyst (8) some of the 3-isomers were detectable. The intermediate adsorbed species such as IX would lead to these products.

Other workers (9) have obtained similar results from the 1-butene system. In addition it was found that the rate of double bond migration was half order in both hydrogen and 1-butene at 0°. An isotope effect favors hydrogen over deuterium by a factor of four at 60° (30). For hydrogenation at 198°, first order kinetics were observed for both hydrogen and 1-butene. At lower temperatures, the hydrogenation is normally only first order in hydrogen and zero order in the alkene.

Deuteration of ethene on nickel films gave a deuterium distribution almost identical to that for 1-hexene in Table V.

Nature of the Adsorbed Species - The adsorbed alkyne species I shown in Fig 1 could retain its linearity or the methyl groups could be bent back away from the surface. To help resolve this question, rates of hydrogenation (12) of a series of alkynes and alkenes were determined. Table VI shows that the rate of reaction depends on the initial concentration of the alkyne and the amount of catalyst present. This dependence indicates that the diffusion of hydrogen is not the limiting process in the reaction. The product from step i was largely the cis-olefin. As can be seen from the table, the rate of hydrogenation of the alkynes is not affected by the size of the R. Since step ii shows a definite retardation in rate with increasing size of

Table VI

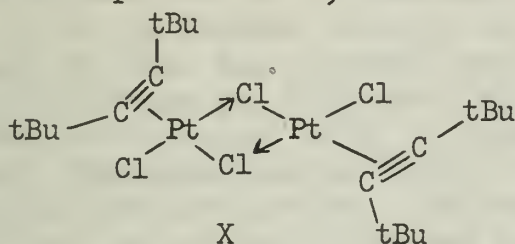
R	$R-C\equiv C-R \xrightarrow{i} RCH=CHR$		$RCH=CHR \xrightarrow{ii} RCH_2CH_2R$	
	Concentration $\times 10^{-2}$ M.	Initial Rate* i ii	Concentration $\times 10^{-2}$ M.	Initial Rate i ii
CH ₂ OH	4.3	0.42 0.48	17.2	0.34 0.67
CHCH ₃ OH	3.7	.40 .28	14.1	.64 .43
C(CH ₃) ₂ OH	3.1	.45 .12	13.6	.62 .22

* rate as ml. H₂ per minute per mg. of Pd/C catalyst.

Effect of amount of Catalyst for 0.03 M. R=C(CH₃)₂OH in 30 ml. alcohol

Mg. Catalyst	4.0	8.4	14.9	21.0	37.8
i rate*	0.4	0.4	0.35	0.35	0.4
ii rate	0.1	0.1	0.1	0.1	0.1

the R group, it may be assumed that the olefin retains its planarity as it approaches the surface of the catalyst. Unfortunately all the R groups studied possessed a hydroxyl group. This could lead to the possible conclusion that a hydroxyl to surface bond is important in i, thus making the linear form a possibility.



Chatt (13) prepared a ditert-butyl acetylene complex of structure X. On the basis of an infrared study, he concluded that the tert-butyl groups were bent back from the line of the triple bond. The tert butyl groups in X are similar to the R's in Table VI

Infrared studies (14) of adsorbed ethene have given interesting results. Two samples of η aluminum oxide differing only in particle size gave different results. Sample A had a surface area of 295 m²/g while B had 190 m²/g. Ethene adsorbed on sample A gave the spectrum given in Table VII A, while that from B is given

Table VII

Infrared Spectrum of Adsorbed Ethene

Catalyst Sample A		
Assignment	Range for Saturated Hydrocarbons (28)	Adsorbed Ethene
Vibration asymmetric C-H in CH ₃	2962 \pm 10 cm. ⁻¹	2970 cm. ⁻¹
" " C-H in CH ₂	2926 \pm 10	2932
" symmetric C-H in CH ₃	2872 \pm 10	2880
Bends asymmetric CH ₃	1450 \pm 20	1465
" " C-H in CH ₃	1375 \pm 5	1383
Catalyst Sample B		
CH ₂ asymmetric vibration	2926 \pm 10	2928
" symmetric vibration	2853 \pm 10	2855
" deformation	1465 \pm 20	1468

in Table VII B. The spectrum from A suggests the presence of a CH₃(CH₂)_n- group. Since there was no band near 720 cm.⁻¹, n must be less than four. The absorbance ratio of the 2970 to 2932 cm.⁻¹ bands is 1.33. This may be compared to adsorbed ethyl bromide, n-butane, and n-pentane at 1.35, 1.36, and 1.26 respectively. These data indicate the presence of an adsorbed ethyl group. The spectrum of B shows only methylene groups. When sample B with adsorbed ethene was heated, a spectrum similar to that of A was produced. When A was heated in hydrogen at high temperatures for extended periods of time, methane, ethane and propane were produced. These data support the formation of a di-



adsorbed species which can then pick up a hydrogen atom to give a monoadsorbed species and finally the hydrocarbon.

When a similar study was carried out on silica gel, no adsorbed ethene spectrum was produced.

Other work on the hydrogenation of ethene (15) indicates that the aluminum oxide may adsorb the ethene and then transfer it to the catalyst surface. Data given in Table VIII demonstrate that when aluminum oxide is present the rate of hydrogenation of ethene on the Pt/SiO₂ is greatly accelerated. Since the ethene is not adsorbed on the silica gel, it appears that the ethene is adsorbed by the aluminum oxide and then is transferred to the catalyst surface or interacts with a hydrogen on the catalyst surface.

Table VIII

Hydrogenation of Ethene on Pt in a Flow System

Catalyst	Dilutant	1:9	% Conversion to Ethane	
			100°	153°
Pt/SiO ₂	SiO ₂		0.10	2.1
Pt/SiO ₂	Al ₂ O ₃	ground together	2.1	39
Pt/SiO ₂	Al ₂ O ₃	simple mixture	0.5	14

A finely divided catalyst has a very large surface area. However, only a small number of sites are available for reaction. This was easily demonstrated by an experiment by Thomson and Wishlade (16) using ethene-C¹⁴. The radioactive ethene was adsorbed onto a nickel film. A mixture of normal ethene and hydrogen was then introduced. Hydrogenation proceeded normally but only 11% of the radioactive ethene was removed from the surface. The removal of the radioactive ethene occurred quickly. When pure ethene was introduced to the chamber containing the adsorbed radioactive ethene, there was only a 2% exchange, this again occurring within two minutes after the ethene was added. These data show that only a small fraction of adsorption sites are active in hydrogenation. When a small amount of a foreign substance is present, it may be adsorbed on the few active sites thus "poisoning" the catalyst. The effectiveness of the poison depends on the structure and amount present. Horner and co-workers (17) determined the poisoning effect of some 170 compounds on the hydrogenation of cyclohexene and other compounds. For small amounts of poison compound, the poisoning is proportional to the concentration of the poison compound. At higher concentrations of poison, the poisoning levels off. The leveling value reflects the ability of the compound being hydrogenated to compete with the poison for the surface sites.

The entire poison effect, however, may not rest with site competition alone. The data (12) in Table IX show that poisons or competitors do not have a uniform effect on the rates of reaction. Certain trends are apparent, eg. for the halogens I⁻ > Br⁻ > Cl⁻. It will be noted however that competitors 1 and 2 have the same effect on A and C but 2 depresses the rate of B much more. Also comparison of 5 and 11 shows an even more notable change. If a straight surface competition effect were the only important factor, a given competitor would be expected to have the same trend for all three substrates.

Table IX

Relative Rates of Hydrogenation on Pd/C in Alcohol in the Presence of Competitors

Competitor	Compounds 0.05 M., Competitor 0.01 M.*		
	A Butyne diol	B Butene diol	C Mesityl oxide
1. Diphenylamine	1.0	0.8	0.36
2. 2-aminoethanol	1.1	.4	.33
3. Pyridine	1.2	.36	.36
4. Ethylenediamine	0.9	.25	.35
5. 8-hydroxyquinoline	1.06	.23	.03
6. Triphenylphosphite	0.2	.03	nil
7. Triphenylphosphine	.1	.04	nil
8. Calcium Chloride	.95	.97	1.0
9. Lithium Bromide	.7	.8	0.6

10. Sodium iodide	.12	.04	.02
11. Potassium acetate	.75	.48	.8
12. Potassium hydroxide	.15	.13	.65

* This quantity represents a value in the leveled off region.

In the original classical mechanism (4), it was suggested that the olefin reacted with an adsorbed hydrogen. At that time no attempt was made to establish whether the hydrogen was adsorbed or if the chemisorbed olefin reacted with gaseous hydrogen. An early infrared study (18) carried out on the products resulting from the hydrogenation of ethene using both a 1:1 mixture of hydrogen and deuterium and an equilibrium mixture revealed that the products from both reactions were the same but different from an equimolar mixture of ethane and 1,2-dideuteroethane. This result together with the fact that hydrogen and deuterium as well as ortho and para hydrogen were not equilibrated on the catalyst in the presence of ethene led Twigg to the conclusion that gaseous hydrogen reacts with adsorbed ethene to give a half hydrogenated form plus an adsorbed hydrogen as shown in equation 2. He stated that the dissociation of hydrogen to give two adsorbed hydrogen atoms is of no significance since the free surface is too small. If this is true, it would be expected that little exchange, eg. to form monodeutero ethane,



would occur since the adsorbed hydrogen formed in step 9 of equation 2 would be close at hand to react with the adsorbed ethyl group to give ethane. The experimental results do not support equation 2 since there is a large quantity of the monodeuterated ethane formed. The results are more easily explained by the adsorption of free hydrogen atoms onto the surface.

Selwitz (19) further claimed support for the Twigg concept on the basis of a fuel cell experiment. In a cell with 3% platinum on carbon electrodes and 20% potassium hydroxide electrolyte, a potential of 1.0 volt ("open circuit") was produced when hydrogen was passed over one electrode and air was passed over the other. When a mixture of hydrogen and ethene (containing 29% hydrogen) was passed over the hydrogen electrode, the "open circuit" potential was 0.19 volt and the product was ethane. Since little current is required for the potential measurement, the rate of reaction of hydrogen with water could be slow with respect to hydrogenation and still maintain the same potential as produced in the absence of ethene. Since the potential dropped greatly in the presence of the ethene, it was concluded that the hydrogen did not get adsorbed but reacted in the gaseous form. When ethene was replaced with isobutene (the hydrogen concentration was not reported) the potential increased to 0.57 volt, thus indicating that considerably more hydrogen was adsorbed. Although the author claimed that the hydrogen was not adsorbed in the presence of ethene, it should be noted that the concentration of hydrogen was 29% when the potential dropped to 0.19 volt. The potential is really about 65% of that expected for hydrogen at a partial pressure of 0.29 atmosphere. This work seems to support rather than deny the adsorbed hydrogen concept.

In the studies on 2-butyne (5), it was found that a statistical distribution of products resulted when a mixture of deuterium and hydrogen was used for the hydrogenation.



Furthermore, it was found that the equilibrium equation 3 was retarded in the presence of the alkyne. In the absence of 2-butyne, the hydrogen and deuterium were equilibrated 40 times faster. These observations strongly support the classical idea since the retarding effect on equilibrium 3 caused by 2-butyne results from surface competition. A statistical distribution of deuterium and hydrogen in the butenes is hard to explain by other non adsorbed species.

Pliskin and Eischens (32) have observed chemisorbed hydrogen and deuterium on alumina supported platinum. Adsorbed hydrogen absorbs at 2110 and 2058 cm^{-1} while deuterium absorbs at 1515 and 1479 cm^{-1} . The first listed band for each represents a weakly adsorbed species. The band could be diminished by heating or evacuating the sample. The second band was not affected by evacuation or heating. An equilibrium

mixture of hydrogen and deuterium gave only bands characteristic of pure deuterium and hydrogen. Therefore the adsorbed species are the free atoms. The bands for hydrogen correspond closely to those observed (33) for platinum hydrogen bonds in a complex.

Since catalytic hydrogenations are frequently carried out at high pressures, it is of some importance to understand what effect the pressure may have on the reaction. The hydrogenation of a series of disubstituted benzenes (20) revealed a rather marked pressure trend. The data listed in table X show that the amount of cis compound in-

Table X
% Cis Dialkyl Cyclohexanes from Hydrogenation of
Disubstituted Benzenes at 25° on PtO₂

Pressure in atm.	o-xylene	m-xylene	p-xylene	p- <u>tert</u> butyltoluene
0.25		77	70	
1.0	92	77	73	61
4	88		74	63
75		82	80	68
300	93	85	82	71

creases with pressure. This can be visualized as in Fig 3. Steps 1, 2, and 3, an extension of the classical mechanism, lead to the cis compound. A free olefin of form XIII would allow one R group to come into the plane of the ring. On readsorption, the trans form can be formed. In forming the trans compound, an adsorbed species such as

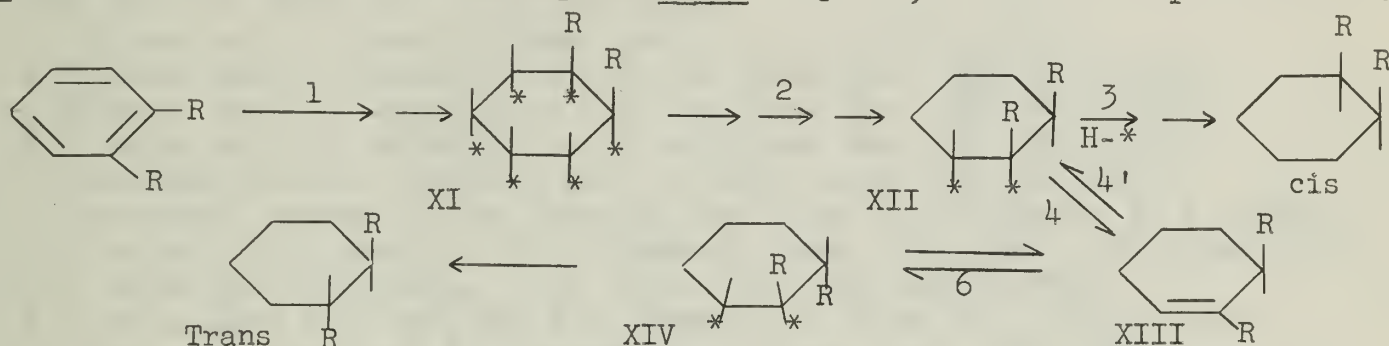
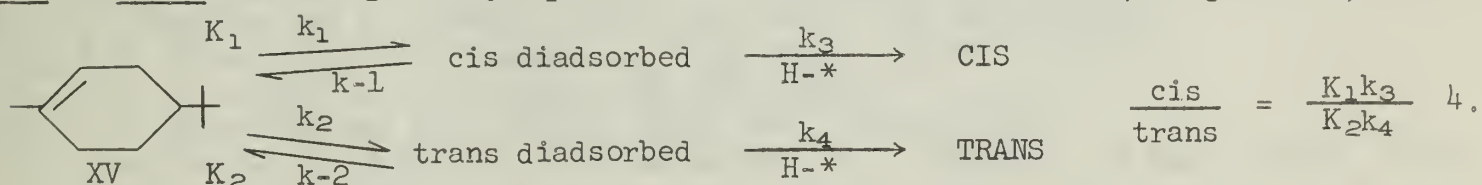


Fig 3

XIV would be required. For the 1,2-derivative, the R on the side of the catalyst would make this intermediate less favorable. As the R moves to the 3 and 4 positions the interaction with the surface would be less and therefore more trans compound is formed. At higher pressures more hydrogen will be adsorbed and thus step 3 will be favored over 4 giving more cis.

When compound XV has hydrogenated (21), a similar pressure effect was noted. Compound XV may be adsorbed to give either cis or trans diadsorbed species. The ratio of cis to trans will be given by equation 4. At normal conditions (low pressure) the value



of the ratio is about 0.5. The reaction of the adsorbed species with hydrogen is slow so the ratio is determined by K_1k_3 and K_2k_4 . At higher pressure, k_3 and k_4 become large so the cis/trans ratio depends on the ratio of k_1 to k_2 . At high pressure the ratio approaches one, indicating that XV can be adsorbed from either side with equal probability.

On the basis of Fig 3, it would be expected that step 4 would be favored by an increase in temperature. This prediction has been realized (23). The quantity of trans isomer increased with temperature.

Deuterium exchange experiments carried out by Kemball (22) support the existence of an adsorbed species resembling XI.

Catalyst - Factors such as quantity and concentration of catalyst may have rather significant effects on the results of a hydrogenation. As was indicated for the hydrogenation of some of the alkynes, an increase in the amount of catalyst increased the

rate of reaction proportionally. This means that the rate is dependent on the amount of surface area available for reaction. As the amount of catalyst and therefore surface area of the catalyst increases, a limit is reached where the diffusion of hydrogen to the surface becomes the rate limiting process (31). For the hydrogenation of 2 ml. 1-hexene in 9 ml. of ethanol at 1.9 atm. of hydrogen over platinum oxide, it was found that the rate increased linearly with catalyst up to about 50 mg. and then leveled off.

The nature of the catalyst surface has been determined by such methods as x-ray studies and magnetic susceptibility determinations. Magnetic studies are particularly useful for the study of the inner transition metals. The magnetic method (34) gives evidence on the oxidation state in the metal, the bonding between ions and the environment of the ions. Studies (35) indicate that platinum is deposited on alumina in a micro crystalline state. Nickel reduced on silica was found to exist at 50 Å units.

Conclusion - The mechanism of reaction may be summarized. The hydrocarbon and hydrogen are adsorbed on to the surface. The adsorbed hydrogen atoms and hydrocarbon react to give a monoadsorbed species which can; (a) pick up another hydrogen atom and leave the surface as an alkane (alkene), (b) react to give the same or different di-adsorbed species and eventually give exchanged products.

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THE STRUCTURE AND SYNTHESIS OF THE ONOCERINS

Reported by Kermit Carraway

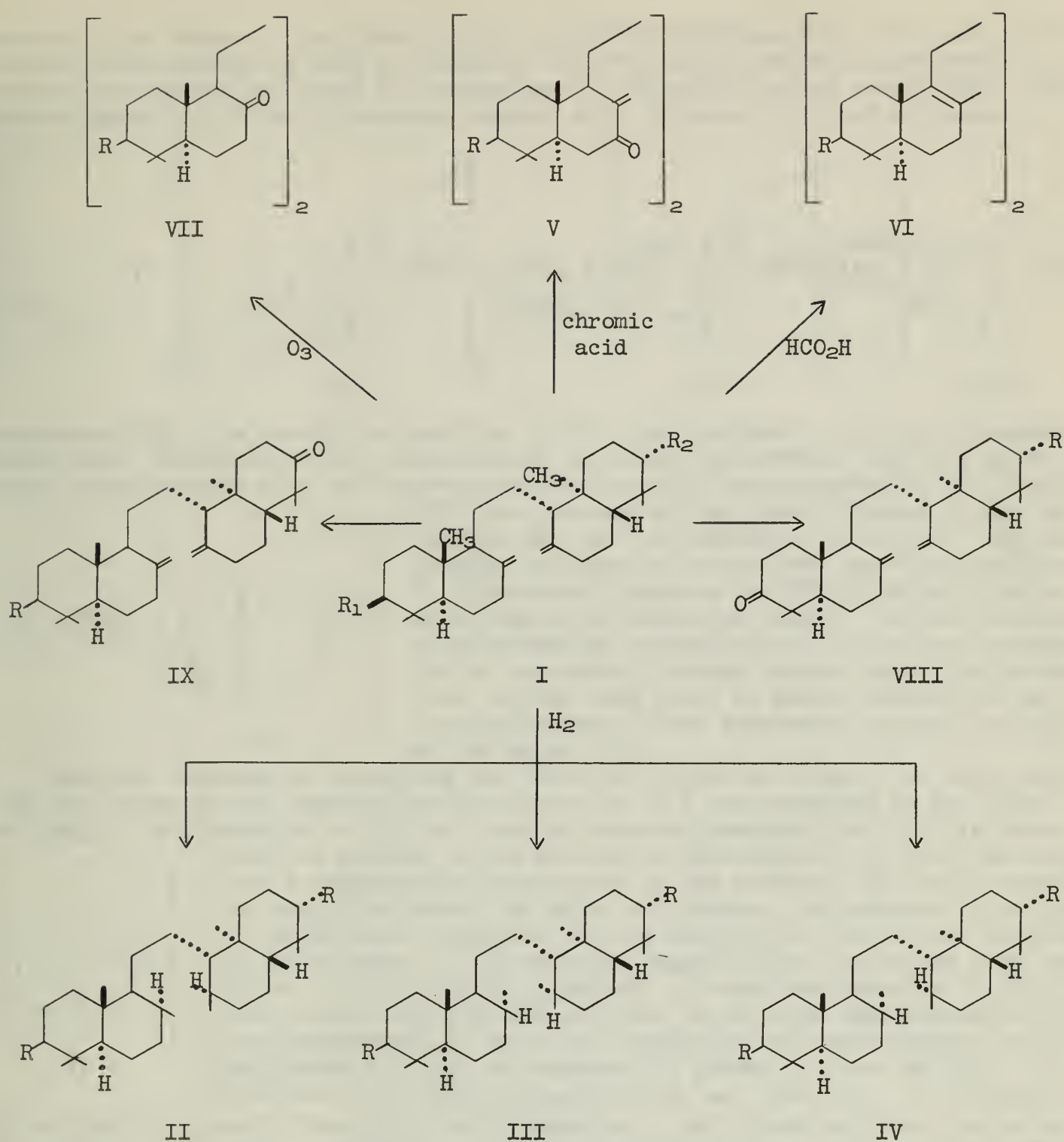
March 16, 1964

Introduction: α -Onocerin I ($R_1=R_2=OH$) is a naturally-occurring triterpene, first isolated by Hlasiwetz (1) in 1855 from the roots of Ononis spinosa L. Considerable interest has been centered upon this compound because of its unique position in the squalene biogenetic scheme for triterpenes (2,3,4). In contrast to other triterpenes, whose biosynthesis may be explained in terms of an acid-catalyzed unidirectional cyclization, the cyclization of squalene to form α -onocerin would have to involve two separate processes proceeding from either end of the squalene molecule. The fact that α -onocerin is a tetracyclic unsaturated triterpene suggests that it might act as a precursor in the biosynthesis of pentacyclic triterpenes, but no evidence has been found in support of this point (4). In view of possible complications which might arise in the nomenclature of the onocerins, Barton and Overton (5) have suggested that they be named as derivatives of the saturated tetracyclic hydrocarbon onocerane, II, III, or IV ($R=H$). Using this system α -onocerin would become α -onoceradienediol. This convention will be followed in the remainder of this abstract. A brief outline of some of the synthetic work in the onocerin series has been reported in the general review of di- and triterpene synthesis by Rogers and Barltrop (6).

Few significant investigations into the structure of α -onoceradienediol I ($R_1=R_2=OH$) were made before 1930. At this time the presence of two olefinic bonds was indicated by the formation of a tetrabromide and two hydroxyl groups by diacetate formation and the facile oxidation to a diketone (7). The failure of I to precipitate with digitonin suggested that it did not have the steroid structure. The first systematic investigation of this compound was made by Schulze (8), who proposed the molecular formula $C_{30}H_{48}O_2+2H$ on the basis of analytical data. The presence of two double bonds was confirmed by perbenzoic acid titration, and the absence of any UV absorption above 250 m μ was established. It was also found that selenium dehydrogenation yielded 1,2,5,6-tetramethylnaphthalene. Zimmerman (9) found that the oxidation of α -onoceradienediol diacetate I ($R_1=R_2=OAc$) gave a di- α,β -unsaturated ketone V ($R=OAc$), the UV spectrum of which was consistent with this functionality. The diene-diol I ($R_1=R_2=OH$), when treated with 90% formic acid, underwent a rearrangement to a new compound VI ($R=OH$), designated β -onoceradienediol by Barton's nomenclature, which also showed two double bonds by perbenzoic acid titration (10).

The true molecular formula of α -onoceradienediol was established as $C_{30}H_{50}O_2$ by Barton and Overton (5) in an investigation which led to complete elucidation of the compound's structure. Hydrogenation of the diene-diol I led to a mixture of three compounds II, III, and IV ($R=OH$), which were separated by alumina chromatography and crystallized as their various alcohol derivatives. Oxidation to the corresponding ketones and subsequent Wolff-Kishner reduction led to three different saturated onoceranes II, III, and IV ($R=H$), whose analytical data proved them to be tetracyclic. Ozonolysis of the diacetate I ($R_1=R_2=OAc$) provided formaldehyde plus a bisnordioxo-onoceradienediol diacetate VII ($R=OAc$) (5,9), which indicated the presence of two exocyclic methylene groups. IR bands at 3100, 1643, and 890 cm^{-1} in the diene-diacetate I provided further evidence for the presence of these two groups. The diacetate also showed IR bands at 1735 and 1240 cm^{-1} , the latter of a strength indicative of two acetate residues. The presence of bands at 1390 and 1365 cm^{-1} in α -onoceradiene suggested the presence of two gem-dimethyl groupings.

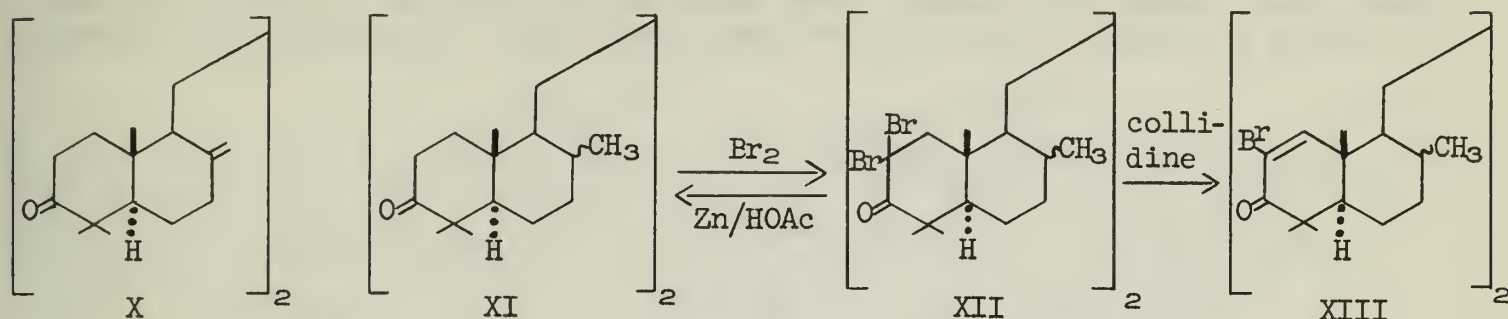
The multiplicity of functionality observed in the IR suggests the repetition of some grouping in the compound. In view of the previous information Barton and Overton (5) proposed the structure I ($R_1=R_2=OH$) for α -onoceradienediol on the basis of its relationship to the triterpene biogenetic scheme. The most striking feature of the structure is the presence of the two-fold axis of symmetry. This point was proven by the following scheme. The diacetate I ($R_1=R_2=OAc$) was partially hydrolyzed



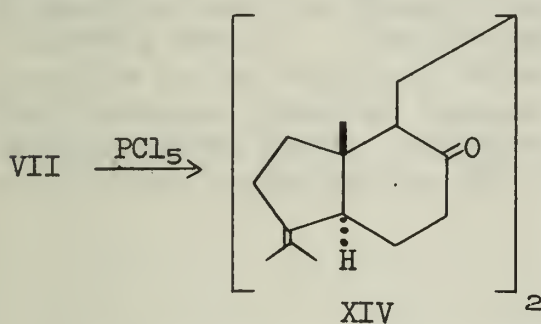
to a monoacetate I ($R_1=OH$, $R_2=OAc$), which could be benzoylated to the acetate-benzoate I ($R_1=OCOC_6H_5$, $R_2=OAc$) or oxidized to the acetate-ketone VIII ($R=OAc$). The acetate-benzoate, after hydrolysis to the hydroxy-benzoate I ($R_1=OCOC_6H_5$, $R_2=OH$), could be oxidized to the benzoate-ketone IX ($R=OCOC_6H_5$). Hydrolysis of either of these acylated hydroxy-ketones led to the same compound (either VIII or IX, $R=OH$), proving the identity of the two hydroxyl groups and the unique symmetry of the triterpene. This symmetry also explains the formation of three different compounds on hydrogenation of I, since two of the four possible conformational isomers would be identical.

Further investigations were needed to clarify the structure of the four rings. Oxidation of α -onoceradienediol I ($R_1=R_2=OH$) gave the corresponding dione X, which showed an IR band at 1708 cm^{-1} of a strength of two ketone groups and typical of six-

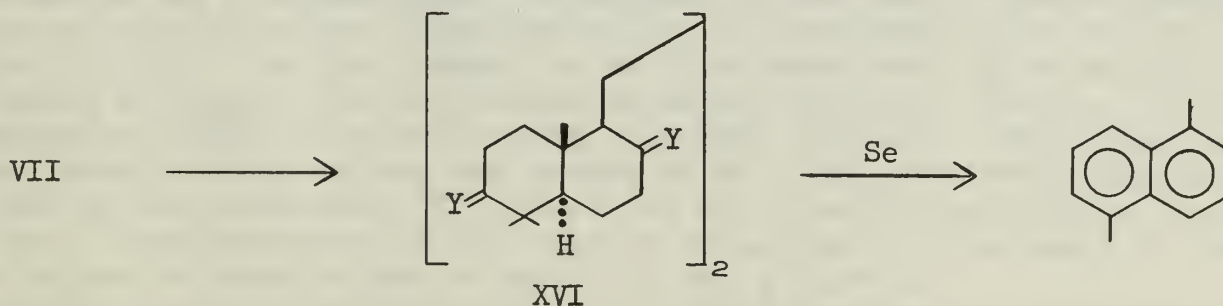
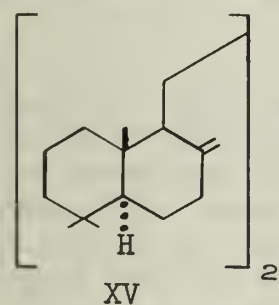
membered ring ketones. The dione X gave a positive Zimmerman test (11), and one of its saturated analogs XI gave a tetrabromo derivative XII, which was resistant to further bromination and could be reduced back to XI with zinc and acetic acid. Dehydrohalogenation of the tetrabromo compound with collidine afforded a bismono-



bromoenone XIII, the absorption spectrum of which was indicative of two chromophores of the type $-\text{CO}-\text{CBr}=\text{CH}-$ (12). Treatment of the dihydroxy-diketone VII with phosphorus pentachloride gave the expected dehydration with rearrangement to the diketone XIV, the presence of two isopropylidene groups being demonstrated by the ozonolysis to acetone. The preceding evidence indicates that the α -onoceradiene-diol structure contains two $-\text{C}(\text{Me})_2-\text{CH}(\text{OH})-\text{CH}_2\text{CH}_2-$ groupings in six-membered rings. The rearrangement with phosphorus pentachloride is also good evidence for an equatorial hydroxyl group, since the contraction of the ring would be geometrically favored in the dehydration of the equatorial alcohol, but not of the axial (13).



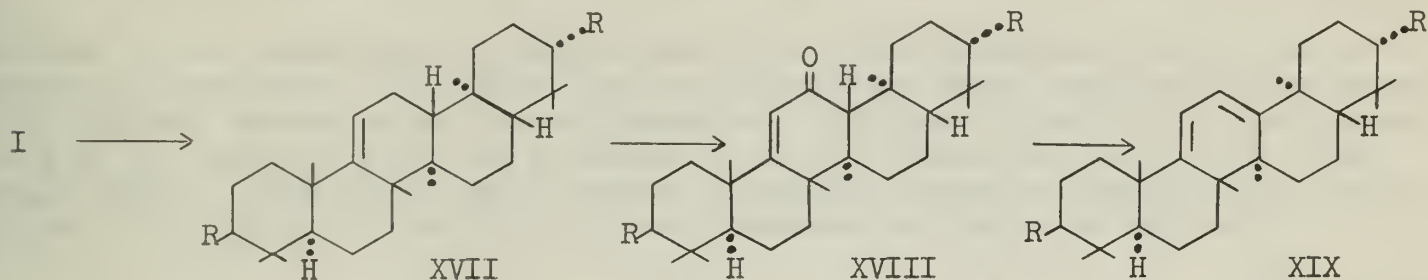
From the information concerning the first two identical rings it is most likely that the ketone groups obtained by the ozonolysis of I are contained in the other two rings. IR absorption at 1710 cm^{-1} and a positive Zimmerman test (11) indicate they are present in six-membered rings adjacent to methylene groups. From a quantitative bromination on the diketone VII, which showed the uptake of about five moles of bromine, the presence of at least six replaceable hydrogens must be inferred because of the symmetry of the molecule. This evidence suggests that the second ring contains a $-\text{CH}_2-\text{C}(=\text{CH}_2)\text{CH}-$ grouping. Further confirmation of the proposed carbon skeleton was obtained by selenium dehydrogenation of α -onoceradiene XV, in which the possibility of rearrangement of the gem-dimethyl groups is minimized by removal of the hydroxyl. In this case 1,2,5-trimethylnaphthalene was obtained. The position of the exocyclic double bond of α -onoceradienediol I was determined from its ozonolysis product VII ($\text{R}=\text{OH}$). Oxidation to the tetraketone XVI ($\text{Y}=\text{O}$) and subsequent Wolff-Kishner reduction gave a saturated hydrocarbon XVI ($\text{Y}=\text{H}_2$), which was dehydrogenated



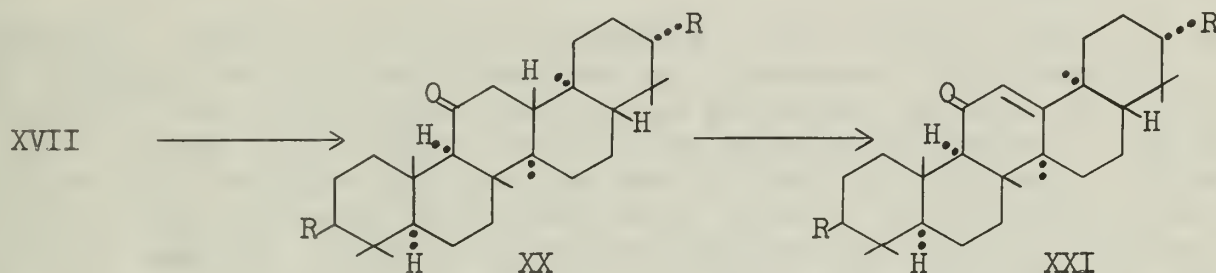
to 1,5-dimethylnaphthalene. The establishment of the exocyclic double bond also places the bridge between the rings at C-9. At this point the carbon skeleton has

been elucidated with the exception of the two angular methyl groups, whose positions had only been inferred on the basis of biogenetic argument.

Further information about the skeletal structure was obtained from the product of the acid-catalyzed isomerization with an acetic-sulfuric acid mixture. The product, designated γ -onocerenediol diacetate XVII (R=OAc), could be converted to the diene XIX (R=OAc) by oxidation to the enone XVIII (R=OAc) with chromic acid, LiAlH_4 reduction, and dehydration. The diene showed an ultraviolet absorption maximum at



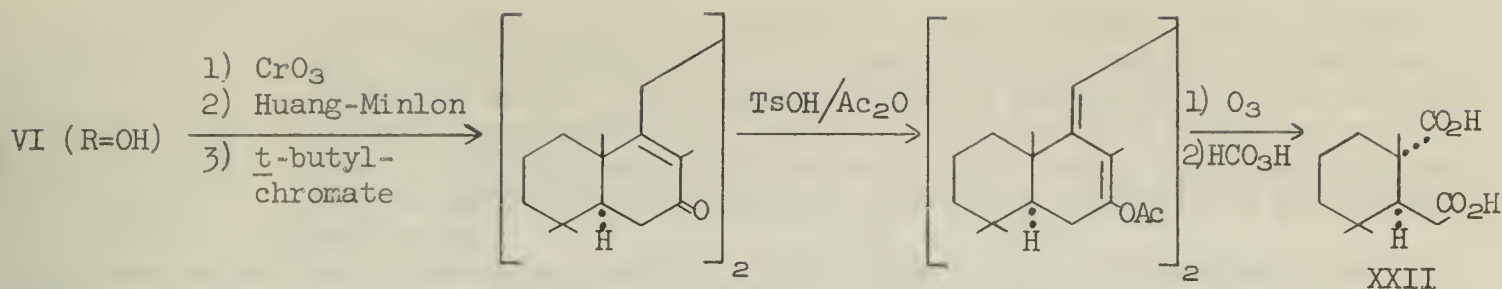
281 m μ ($\epsilon = 10,600$), which is identical in position with that of the ring-C homoannular dienes in the α - and β -amyrin series. The presence of a single olefinic bond in γ -onocerene and the symmetry properties of the pentacyclic series were proven in the following manner. γ -Onocerenediol diacetate XVII (R=OAc) was oxidized with hydrogen peroxide to the saturated ketone XX (R=OAc), which was resistant as expected to Wolff-Kishner reduction because of the steric hindrance imposed by the two axial angular methyl groups. Monobromination and subsequent dehydrobromination furnished an α,β -unsaturated ketone XXI (R=OAc), which was identical with that obtained pre-



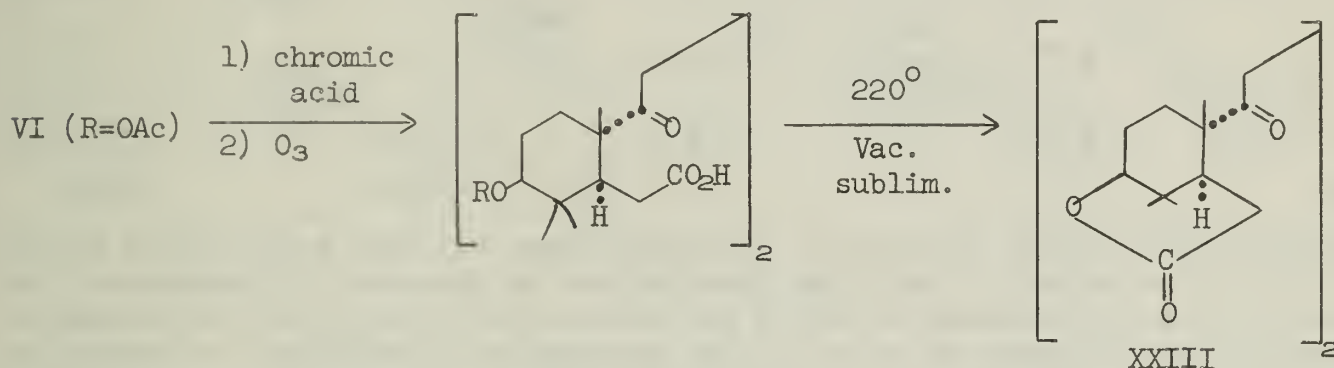
viously. This sequence proves that the symmetry of α -onoceradienediol is maintained in the γ -series, provides further support for the proposed structures, and explains the formation of a single isomer from the isomerization. The β -series, being diolefinic (10), must result from an isomerization of the two double bonds of α -onoceradienediol to the endocyclic positions. The tetrasubstituted positions for the double bonds (see VI) were assigned by Cocker and Halsall (14) on the basis of molecular rotation changes during the isomerization from α to β and during the hydrogenation of the β -isomer.

The hydroxyl group of the α -onoceradienediol was assumed by Barton and Overton (5) to be in the more stable equatorial position, since reduction of the diene-dione X with sodium and 1-propanol gave I ($\text{R}_1=\text{R}_2=\text{OH}$) in good yield. The molecular rotation changes on acetylation were consistent with a 3β -configuration for the hydroxyl, but not for a 3α (15). For the hydroxyl to be β and equatorial, it is necessary that the ring fusion be trans. This supposition is supported by the molecular rotation data as compared to other triterpenes and by biogenetic arguments. The bridge between the two identical ring systems was assumed to be in the more stable equatorial position because the bisnordione VII (R=OAc) was not isomerized on vigorous treatment with base. Stereochemistry of the γ -series was assigned on the basis of comparison of the molecular rotation data to that of α - and β -amyryns.

A more conclusive investigation of the stereochemistry of α -onoceradienediol was reported by Schaffner and coworkers (16). The degradation of β -onoceradienediol according to the scheme below gave a diacid XXII which was identical with that

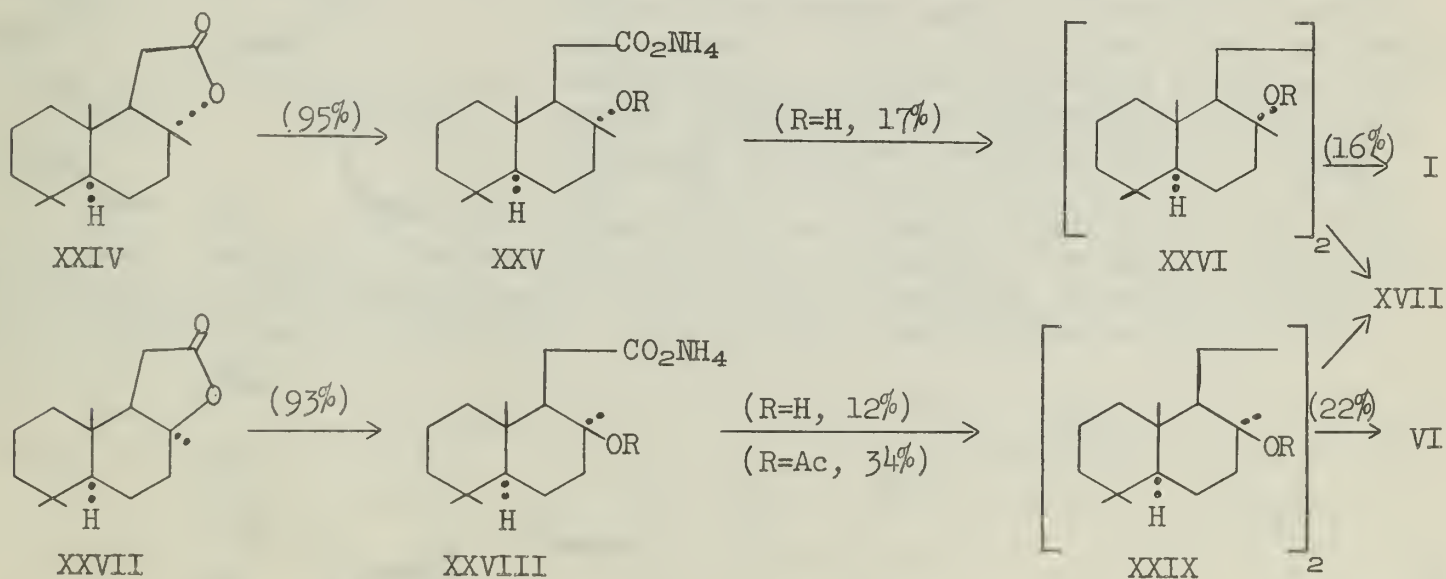


obtained by the degradation of abietic acid, the stereochemistry of which had been previously determined (17). This identity indicates a trans ring junction as shown and a "normal" terpene absolute configuration. Additional proof of the stereochemistry of the hydroxyl group was presented by the following reactions to yield the lactone XXIII. Formation of this lactone indicates a trans configuration of the hydrogen at C-5 and the hydroxyl at C-3 and therefore an equatorial hydroxyl.

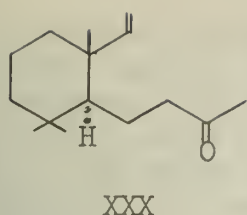


Synthesis: Because of the unique symmetry of the onocerin series the synthesis of these compounds can be broken down into two operations: (1) construction of a ring system with the correct functional groups and stereochemistry, and (2) coupling of the two identical ring systems to afford the symmetrical product. Although the basic sequence of reactions is always the same as that outlined above, further modifications are often necessary after coupling in order to achieve the desired products.

The first approach to this synthetic problem was that of Corey and Sauers (4,18), who used the stereoisomeric lactones XXIV and XXVII derived from the diterpene sclareol. Electrolytic oxidative coupling of the ammonium salts XXV and XXVIII of the corresponding hydroxy acids led to an unsaturated ketone and a low yield of the

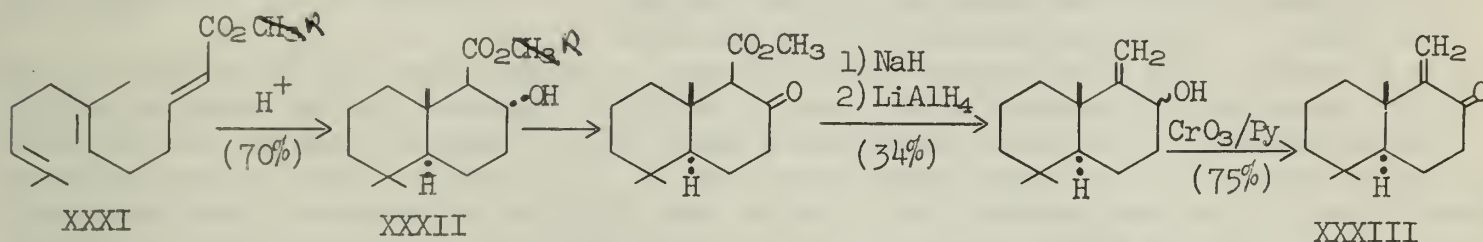


coupling products XXVI and XXIX. Further investigations showed that the unsaturated ketone in each case was the ring-opened product XXX. In view of this result the yields of the coupled products were substantially improved by converting XXV and



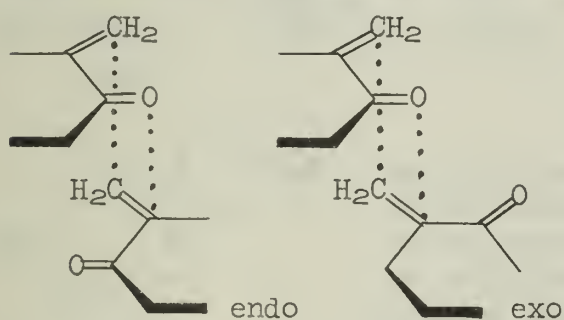
XXVIII ($R=H$) to their respective acetates before electrolyzing. Diols XXVI and XXIX could be converted to α - and β -onoceradiene, I ($R_1=R_2=H$) and VI ($R=H$) respectively, by dehydration, or to the pentacyclic γ -onocerene XVII ($R=H$) by treatment with perchloric acid. Thus the first example of the use of the electrolytic coupling with such a complex reactant offered the first synthesis of an onocerin derivative.

A second method of coupling involved a Diels-Alder type of dimerization of the compound XXXIII. It had been found previously (19) that the acid-catalyzed cyclization of 7,11-dimethyl-2(*trans*),6(*trans*),10(~~*trans*~~)-dodecatrienoic acid XXXI stereospecifically gave the hydroxy acid XXXII. This conversion is of considerable interest because it gives the *trans*-fused ring system, which is the same as that of naturally-occurring terpenes, plus the stereospecific placement of the hydroxyl group. The authors explained this stereospecificity on the basis of a *trans*-coplanar addition

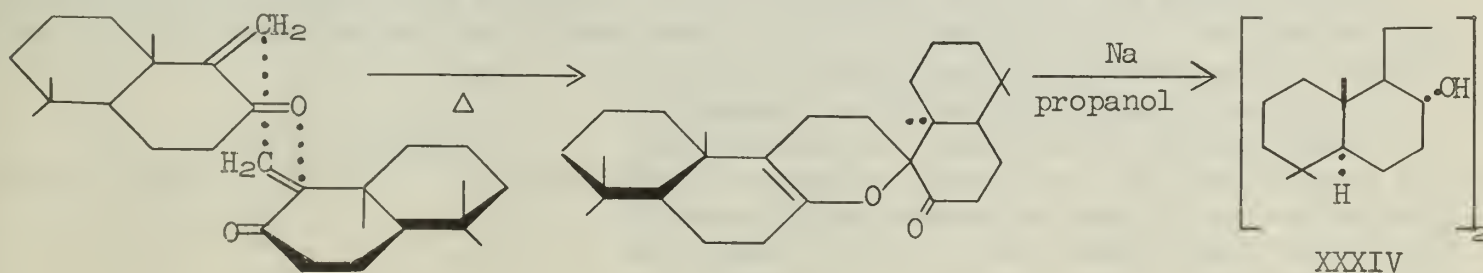


during ring closure with the reacting triene in the more stable chair conformation. The stereospecific placement of the hydroxyl group can be explained by direct *trans*-coplanar addition following cyclization or by the intermediacy of a non-classical carbonium ion, which would be attacked only to give the required stereochemistry. It might also be noted that the entire cyclization process could be explained on the basis of a series of non-classical ions.

The hydroxy-acid XXXII could be easily converted to the methylene ketone XXXIII as shown above. This ketone gave a mixture of two dimers (48% and 20%, respectively) when heated in xylene (20). On the basis of earlier work (21) a Diels-Alder addition may be postulated. Alder's Rule (maximum accumulation of π -bonding) indicates an *endo* orientation as most favorable for the dimerization. There are four possible *endo* configurations, depending upon the positions of the angular methyl groups during the reaction. The more energetically preferred configuration would have both methyls *trans* to the opposite ring system and would lead to a racemic bisnor-onoceradiol after reduction with sodium and propanol. It also can be shown that the least-favored *endo-cis-cis* configuration would lead to a racemic product, but the *endo-trans-cis* and *endo-cis-trans* configurations would lead to the *meso* form. That the reaction did lead chiefly to the racemic diol was shown by resolution of the major product (after reduction) into the corresponding enantiomers. It was also found that the minor dimerization product could be converted to the major product by heating, but this reaction was not reversible. This evidence lends further support to the

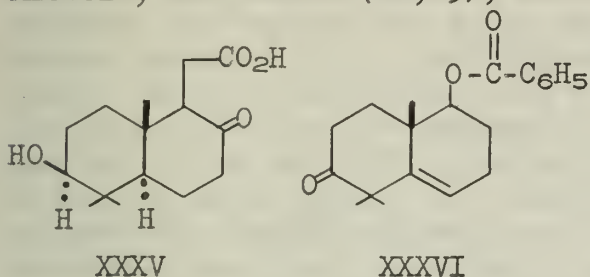


product (after reduction) into the corresponding enantiomers. It was also found that the minor dimerization product could be converted to the major product by heating, but this reaction was not reversible. This evidence lends further support to the



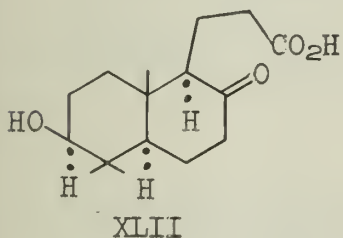
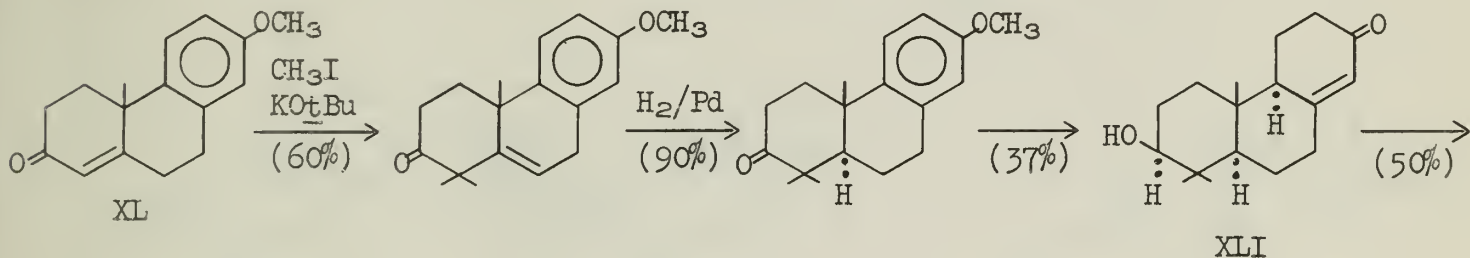
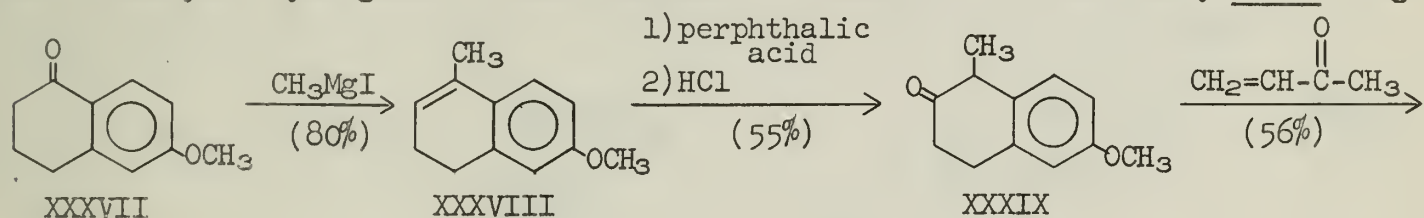
illustrated pathway as the favored one in the dimerization. The resolved (+)-diol XXXIV could be oxidized to the corresponding (-)-ketone, which was converted by treatment with methylmagnesium iodide to the (+)-onoceranediol I ($R_1=R_2=H$), identical in all respects to that synthesized by Corey (4).

The first total synthesis of (+)- α -onoceradienediol was accomplished by Stork, Miesels, and Davies (22,23), who electrolytically coupled the acid XXXV in a fashion



similar to that used by Corey. This intermediate has been independently synthesized by three separate routes, two of which involved the intermediate XXXVI (25,26,27,28) and the other which will be described in more detail (22,23). This synthesis began with 6-methoxy- α -tetralone XXXVII, which could be converted into 3,4-dihydro-1-methyl-6-methoxynaphthalene XXXVIII simply by the addition of methylmagnesium iodide. Oxidation

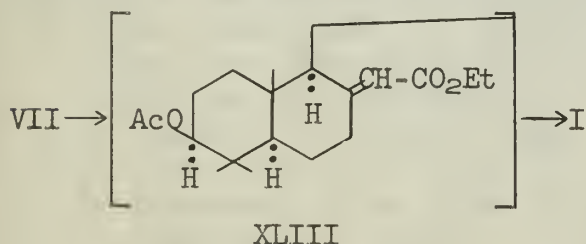
with perphthalic acid and subsequent treatment with hydrochloric acid offered a very facile sequence to the β -tetralone XXXIX. Direct methylation of 6-methoxy-2-tetralone was not feasible because of the rapid dialkylation reaction. Although an enamine procedure could be used (29), it offered no advantage over the described method. Base-catalyzed condensation of XXXIX with methyl vinyl ketone gave the α,β -unsaturated ketone XL, which could be dimethylated with excess methyl iodide and potassium butoxide. Catalytic hydrogenation was then used to establish the necessary trans ring



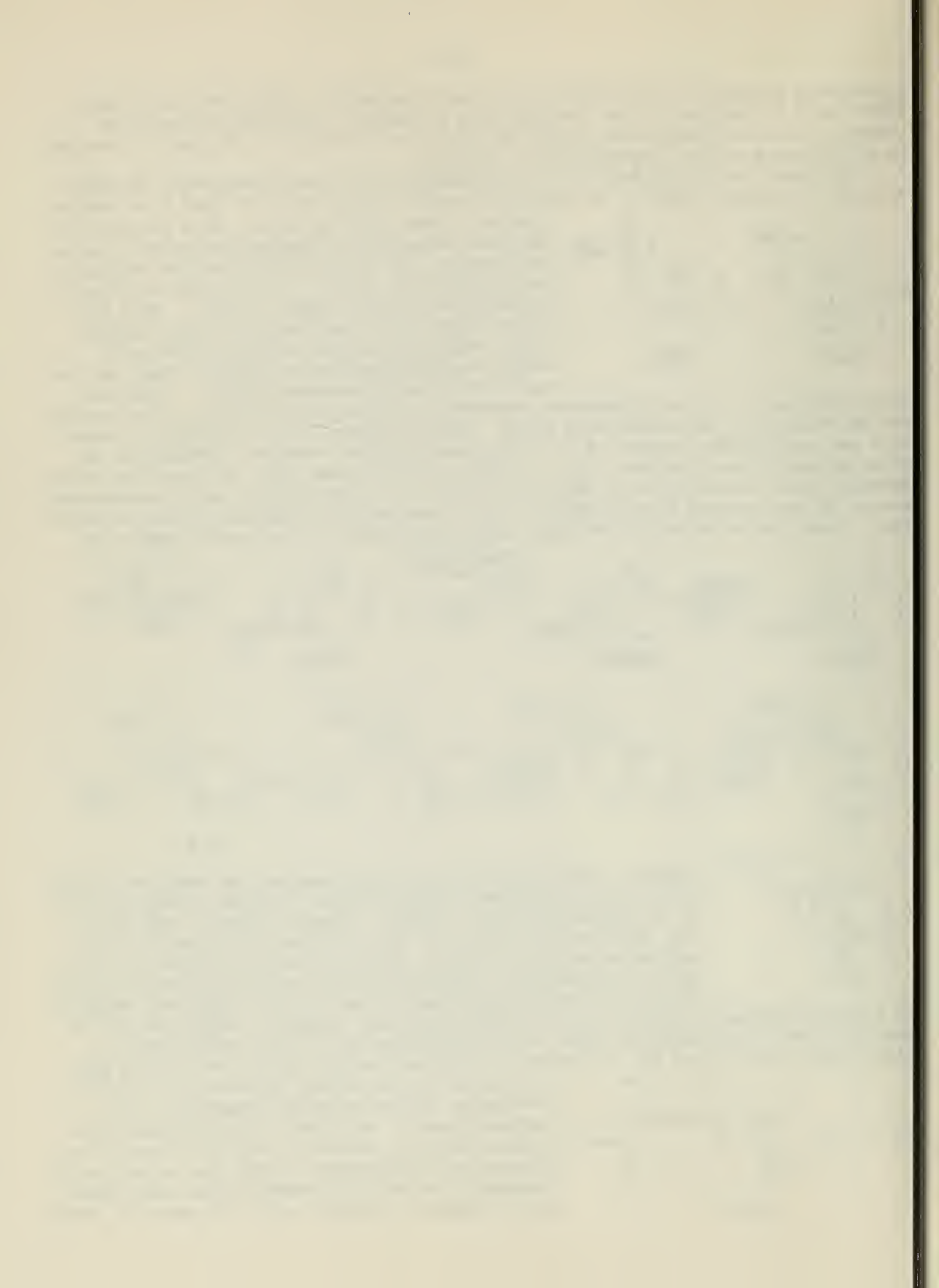
fusion. This stereoselective hydrogenation was expected because of the steric hindrance offered by the two axial methyl groups to the approach of the catalyst, a factor which is enhanced by the rigidity conferred upon the system by the Δ^5 -double bond and the aromatic ring (24). Birch reduction followed by treatment with methanolic hydrochloric acid gave the tricyclic enone XLI, which could be ozonized to the keto acid XLII and degraded

by a Barbier-Wieland procedure to the desired coupling reactant. Resolution of the acid XXXV was accomplished by means of the strychnine salt of the half-phthalate.

Electrolytic coupling of the (-)-keto-acid XXXV and acetylation of the product gave (+)-bisnor-onoceranediol diacetate VII ($R=OAc$).

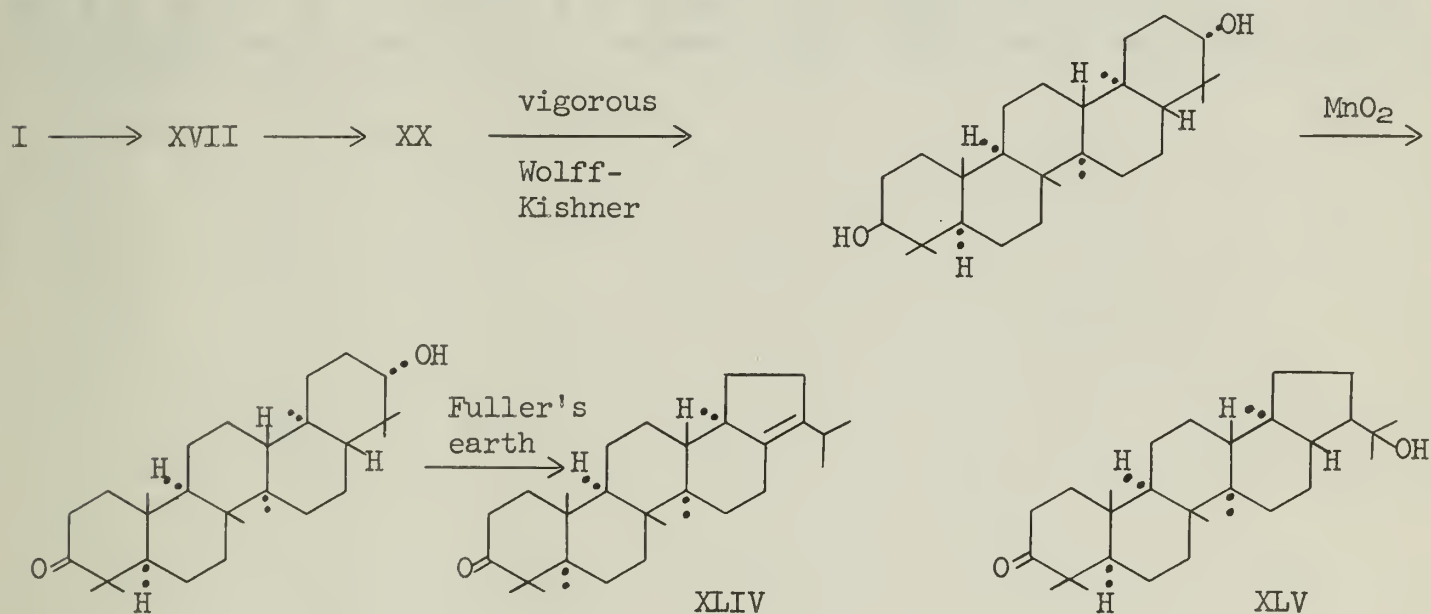


Naturally-occurring (+)- α -onoceradienediol could not be accomplished by a Wittig reaction; therefore, VII was treated with ethoxyacetylenemagnesium bromide and subsequently rearranged to the di- α,β -unsaturated ester XLIII with methanolic sulfuric acid. In order to obtain



the desired exocyclic methylene it was necessary to decarboxylate the unsaturated acid. One possible mechanism for this type of decarboxylation requires the intermediacy of the β,γ -isomer of the unsaturated acid. Since isomerization of the double bond in the $\alpha \rightarrow \beta$ -onoceradienediol conversion leads to the tetrasubstituted isomer, the intervention of this mechanism would lead to the destruction of stereochemistry at C-9. For stereochemistry to be maintained, a stereospecific introduction of the carboxyl proton into the axial position would have to occur. The formation of a single isomer I ($R_1=R_2=OAc$) indicates that stereospecific decarboxylation did occur. Stork, Miesels, and Davies (23) have suggested that stereospecific introduction of the proton in the β,γ -unsaturated isomer would be expected because of the continuous overlap of the developing sp^3 orbital on C-9 with the p-orbitals on the incipient methylene group during the reaction. The occurrence of this mechanism has not been rigorously established, however. This sequence completed the synthesis of the naturally-occurring tetracyclic terpene, the first of its type to be synthesized.

The total synthesis of the onocerin series is of interest from another standpoint, since the conversion of the tetracyclic triterpenes to their pentacyclic analogs can be easily accomplished. Hopenone-I XLIV, a dehydration product of the naturally-occurring pentacyclic triterpene hydroxyhopenone XLV, has been obtained by a simple five-step procedure from α -onoceradienediol (30), as outlined below. Therefore, the total synthesis of the onocerin series also represents the first total synthesis of this pentacyclic series.



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RECENT MECHANISTIC STUDIES OF BASE-CATALYZED OLEFIN MIGRATION REACTIONS

Reported by D. Druliner

March 19, 1964

Introduction - The subject of this abstract will be pure hydrocarbon olefins which undergo migration of double bonds in homogeneous basic media. Several recent reviews have appeared which deal with carbanion formation in systems where alkoxide (1), (2), (3), lithium in ethylenediamine (4), and potassium amide in ammonia (5) serve as base. The use of alkyl metal reagents as a source of carbanions has also been reviewed (6).

Migrations of Acyclic Olefins - Schriesheim and co-workers have made extensive thermodynamic and kinetic studies of olefin isomerizations employing a series of substituted propenes, butenes, and pentenes as well as several alkylidenecycloalkanes. All reactions were carried out in dimethylsulfoxide, DMSO, as solvent with potassium *t*-butoxide as catalyst. Unless otherwise stated, the concentrations of olefin and base were at approximately 0.70 M each throughout the series of their experiments. The isomerization of 2-methyl-1-pentene was carried out at 40°, 55°, and 75° with the concentration of olefin and base at 0.73 and 0.70 molar respectively. No noticeable deviation from linearity in plots of log (mole % remaining) vs. time was observed up to 70% reaction at these temperatures, an indication that the reaction is first order in olefin (7). The order of *t*-butoxide for this isomerization was determined at 55° by carrying out a series of isomerizations at constant 2-methyl-1-pentene concentration with *t*-butoxide concentration ranging from 0.05 to 1.0 molar. A plot of log *k* (isomerization) vs. log (*t*-butoxide molarity) revealed that the isomerization reaction is 1.92 order in *t*-butoxide from 0.05 to about 0.20 molar and approaches zero order from 0.25 to 1.0 molar (7). Cram and co-workers, while studying the base-catalyzed racemization of (+)-2-methyl-3-phenylpropionitrile in 97% DMSO-3% methanol, found that the dependence of rate on sodium methoxide is first order below 0.06 molal and 1.94 in order over the range 0.06 to 0.2-0.3 molal (8). Both Cram and Schriesheim postulate that at low base concentration, below 0.06 molar, the alkoxide base is completely ionized and as base concentration increases, ion pairing occurs. Schriesheim proposes that the approach to zero order in *t*-butoxide ion at greater than 0.25 molarity is due to agglomeration giving rise to an effectively constant concentration of catalytic species. According to this analysis the ion pair of potassium *t*-butoxide has been suggested by Cram to be a better catalyst than the dissociated *t*-butoxide ion. An alternative explanation which involves methylsulfinyl carbanion or the dianion derived from DMSO seems unlikely in the light of isotopic experiments carried out by Schriesheim which indicate that loss of deuterium from labeled olefin occurs only one-sixteenth as fast as isomerization (9). If protonation of the dianion occurred preferentially on O rather than C, then the exchange results would be reasonable.

Schriesheim and co-workers studied the effects of adding *t*-butyl alcohol to the DMSO-*t*-butoxide system and found that the pseudo first-order rate constant for isomerization of 2-methyl-1-pentene at 25° decreased by 77% when the *t*-butyl alcohol/*t*-BuOK mole ratio changed from 0.0 to 0.90, olefin and *t*-BuOK concentration remaining constant as *t*-butyl alcohol was successively increased (7). The effect of decreased alkoxide basicity in solutions containing increasing amounts of added alcohol has been studied by Steiner who proposes that added alcohol decreases the alkoxide basicity by forming hydrogen-bonded species (10).

The enhanced basicity of alkoxide bases in DMSO has been discussed in a previous University of Illinois Organic Seminar (11), and has been postulated by Cram as being due to the ability of DMSO to better solvate cations than anions and also as being due to the lack of hydrogen-bonding ability of DMSO (12).

Schriesheim and co-workers investigated the effect of varying the structure of terminal olefins and found that correlation of average relative rates of isomerization with Taft σ^* values led to deviations from linearity as the bulkiness of the substituent increased, indicating that steric as well as inductive effects are important (13). In order to facilitate a comparison of isomerization rate as a function of substituent in these studies, four classes of olefin were designated as indicated in Table I. The average rates used for the Taft σ^* correlations were obtained by the relation

Table I

Relative Rates at 55°


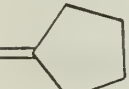
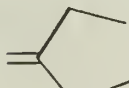



	I	II	III	IV
R	$\text{CH}_2=\text{CHCH}_2\text{R}$ k rel.	$\text{CH}_2=\text{CCH}_3\text{CH}_2\text{R}$ k rel.	$\text{CH}_2=\text{CHCHRCH}_3$ k rel.	$\text{CH}_2=\text{CRCH}_2\text{CH}_3$ k rel.
H	4.1	6.5
Me	1	1	1	1
Et	0.57	0.50	0.54	0.58
Pr	0.55	0.43
i-Pr	0.17	0.12	0.15	...
t-Bu	0.0074	0.0085
Vinyl	2.0×10^6
Phenyl	9.4×10^5

$\log \frac{k_{aI}}{k_{oI}} = \log \frac{k_{aII}}{k_{oII}} = \log \frac{k_{aIII}}{k_{oIII}} \log \frac{k_{aIV}}{k_{oIV}} = \left(\log \frac{k_a}{k_o} \right)_{\text{av.}}$, where k_{aI} , k_{aII} , etc., are the pseudo first order rate constants for substituent a in olefin series I, II, etc., k_{oI} , k_{oII} , etc., are the rate constants for methyl compounds in series I, II, etc., and $k_{oI} = 8.4 \times 10^{-4}$, $k_{oII} = 2.6 \times 10^{-4}$, $k_{oIII} = 2.0 \times 10^{-4}$, $k_{oIV} = 2.6 \times 10^{-4}$ sec.⁻¹.

In an attempt to gain information concerning conformation effects in olefin isomerizations, Schriesheim and co-workers studied the exo \rightarrow endo isomerization reactions of the series of methylenecycloalkanes, where n varies from 1 to 5. The corresponding series of cycloalkanones were brominated using NaOH as catalyst and a comparison of the relative rate of exo \rightarrow endo isomerization with the relative rate of α -bromination as a function of ring size was determined as shown in Table II (14). A plot of log (isomerization

Table II

Relative Rates of Selected Alkylidene
Isomerizations and Alkanone Brominations

Compound	Rel. Rate (isom.) 55°	Rel. Rate (brom.) 0°
	1070	15.5
	454	9.9
	35	4.0
	1.0	1.0
	5.8	1.7
	17	3.4

rate) vs. log (α -bromination rate) yielded a good straight line. From this result Schriesheim concludes that the linear free-energy relationship between α -bromination and isomerization strongly suggests similar transition states and rate-determining steps for the two reactions. It is possible, however, that the two reactions could

have similar transition states and not have the same rate-determining step.

Corey (11), (15) has noted that the energy of the transition state for enolization of a ketone will be at a minimum when there is maximum opportunity for bond formation between the $sp^3 \rightarrow p$ orbital made available by the leaving hydrogen and the p orbital of the carbonyl carbon. This generalization would predict the rate of bromination of cyclic ketones to decrease in the order $C_4 > C_5 > C_6$. This prediction is born out in Table II. The greater rate of reaction for the C_7 and C_8 compounds as compared to the C_6 is reported by Schriesheim (14) to be due to a greater ease of reaching coplanarity with the carbonyl double bond, in that models of the C_7 and C_8 compounds are less rigid than the C_6 compound. Since the alkylidenecycloalkanes and cyclic alkanones possess similar structures, the same stereoelectronic factors should apply to help to explain the differences in isomerization rate as depicted in Table II. Schriesheim and co-workers obtained activation data by carrying out isomerizations of the methylenecycloalkanes at three different temperatures over a 30° range as depicted in Table III (14). The

Table III

Rate Constants and Activation Parameters for
Alkylidenecycloalkane Isomerizations at 55°


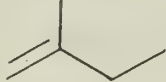
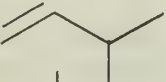
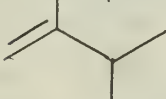
Ring Size	4	5	6	7	8
Rate Const. $\times 10^6 \text{ sec.}^{-1}$	9171	3898	8.6	50.1	146
ΔH^\ddagger , kcal/mole	13.3	17.3	27.1	19.7	16.8
ΔS^\ddagger , e.u.	-27.3	-17.0	0.7	-18.0	-25.4

lower values of ΔH^\ddagger for the C_4 and C_5 compounds and the C_7 and C_8 compounds as compared to the C_6 compound is in accord with the previously discussed concept of stereoelectronic control. The rate-retarding effect of the six-membered ring possibly results from the introduction of non-bonded interactions and angle strain in going to the transition state. These stereoelectronic considerations are not sufficient to account for differences in ΔH^\ddagger values in that a consideration of differences in ground state energies of the different substrates was not made by Schriesheim. The large negative ΔS^\ddagger values for the C_7 and C_8 compounds is attributed by Schriesheim to the loss in flexibility in going to the transition state. That solvent effects may be important is indicated by large negative values of ΔS^\ddagger for the C_4 and C_5 compounds.

In order to compare the relative importance of inductive and steric effects of substituents, comparisons of isomerization rates were made employing data shown in Table IV. If one assumes that the effects of the methyl groups are additive, then the

Table IV

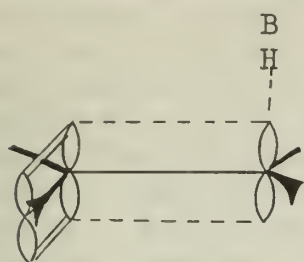
Isomerization of α - and β -Methyl Substituted Butenes at 55°

Olefin	$k \text{ rel.}$	$k \text{ Calc.}$
	1.0	
	0.31	
	0.24	
	0.0071	0.074 (0.31 \times 0.24)

rate of isomerization of 2,3-dimethyl-1-butene would be calculated as 0.074. However, the experimental value is only about one-tenth of this value. This indicates that some effects of methyl substitution are not additive, a characteristic of steric interaction.

It is proposed by Schriesheim (13) that the decrease in reactivity is due to a

marked reluctance of the di-substituted butene to assume the coplanar conformation necessary to maximize the $p \rightarrow \pi$ bond overlap in the idealized transition state:



This idealized transition state accounts for the fact that replacing a vinyl hydrogen by methyl in 1-butene decreases the rate by a factor of 3.2 whereas replacing an allylic hydrogen by methyl decreases the rate by a slightly larger factor, 4.2. These factors reflect the order of carbanion stabilities being primary > secondary > tertiary. Support for this order of carbanion stability has been presented by Applequist and O'Brien in equilibrium studies involving alkyl lithium reagents (16).

While investigating structural effects, Schriesheim and co-workers discovered that isomerization of terminal olefins initially proceeds with kinetic control to give preferential cis-2-olefin (17). This effect is seen in the results tabulated in Table V.

Table V

Comparison of cis/trans Ratios

Olefin	(cis/trans) _{t→0}	(cis/trans) _{equil.}	(cis/trans) _{t→0} / (cis/trans) _{equil.}
Allyl-Me	47.4	0.25	190
Allyl-Et	10.8	0.23	47
Allyl- <u>i</u> -Pr	3.2	0.23	14
Allyl- <u>t</u> -Bu	0.25	0.001	250

These results indicate that the preference of cis- over trans-olefin formation decreases as the bulkiness of the group increases. The fact that (cis/trans)_{t→0} is as large as it is in the case of the t-butyl substituted compound would seem to indicate that steric factors alone are not sufficient to correlate rates with structure.

In order to gain information concerning the amount of intramolecular character to the reaction of terminal olefin isomerizing to a 2-olefin, Schriesheim and co-workers studied the rate of isomerization of 1-pentene and perdeuterio-1-pentene as a function of temperature using approximately equimolar concentrations of t-BuOK and olefin in DMSO (9). Both reaction mixtures for the hydrogen and deuterium compounds contained equimolar quantities of 2-methyl-1-pentene as an internal standard. No deviation from linearity in pseudo first-order rate plots for the disappearance of terminal olefin was noted up to 75% conversion. When 75% of the perdeuterio-1-pentene had isomerized, less than 6% of a deuterium had exchanged from the total perdeuterio-pentenes. The per cent exchange was calculated by the relation: $(C_5D_9H / C_5D_9H + C_5D_{10}) \times 100$. The rate constant at 55° for isomerization of perdeuterio-1-pentene is $2.19 \times 10^{-4} \text{ sec.}^{-1}$, while the rate constant for the exchange reaction measured in duplicate runs is $1.37 \times 10^{-5} \text{ sec.}^{-1}$. Consequently the isomerization is taking place at least 16 times faster than exchange. The pertinent rate constants and values of enthalpies and entropies of activation obtained in the isomerization reactions of the hydrogen and deuterium compounds are summarized in Table VI.

Table VI

Rates of Isomerization of 1-Pentene and Perdeuterio-1-Pentene at 55°

Olefin	Rate const. $\times 10^4 \text{ sec.}^{-1}$	k_H/k_D	ΔH^\ddagger , kcal/mole	ΔS^\ddagger , e.u.
1-pentene	9.54 ± 0.10	4.4	16.3 ± 0.3	-22.9 ± 1.0
2-methyl-1-pentene	1.22 ± 0.08			
perdeuterio-1-pentene	2.19 ± 0.09		17.5 ± 0.4	-22.2 ± 1.2
2-methyl-1-pentene	1.28 ± 0.06			

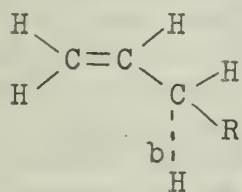
Olefin conc. 0.36M, t-BuOK conc. 0.4M in DMSO

Further relevant data were obtained by Schriesheim and co-workers by carrying out exchange and crossover experiments (9). In separate experiments premixed solutions of perdeuterio-1-pentene and 2-methyl-1-pentene were isomerized at 55°. In a sample taken at 3 half-lives of the pentene isomerization it was found that when 18% of the deuterium had been exchanged, less than 0.4% deuterium had been incorporated in the 2-methyl-1-

pentene or 2-methyl-2-pentene. The isomerization and exchange of a premixed solution of perdeuterio-1-pentene and 2-methyl-1-pentene were also studied in the presence of added *t*-butyl alcohol (9). The concentrations of olefin, base, and alcohol were 0.36, 0.40, and 0.43 molar respectively. At the end of 31.5 hours, which corresponds to more than 7 half-lives for this system or greater than 99.5% complete reaction at 55°, the reaction mixture was quenched and it was found that 35% of the deuterium had been exchanged from the total pentene fraction containing 1-pentene and *cis*- and *trans*-2-pentene. Again, less than 0.4% deuterium had been incorporated into the 2-methyl-pentenes. Schriesheim concluded from the experimental observation of less than 0.4% deuterium crossover between olefins that the isomerization reaction does not involve olefin-olefin interaction. In another experiment Schriesheim and co-workers isomerized a 50-50 weight mixture of 1-pentene and 1-hexene for 312 hours at 55°. The 1-pentene olefin contained 0.01mC/mM of tritium and at the conclusion of the experiment it was shown that the solvent, DMSO, contained essentially all of the exchanged tritium (18).

Schriesheim calculated a theoretical maximum primary isotope effect value of 5.2 for k_H/k_D by employing experimental values of the C-H and C-D allylic stretching frequencies for 1-pentene and perdeuterio-1-pentene respectively, using an unspecified equation (19). As shown in Table VI the experimental value of k_H/k_D is 4.4, which contains contributions from both primary and secondary effects. Schriesheim further states that contributions from the secondary effects should be small and should be in such a direction as to diminish the k_H/k_D value. A possible reason for assuming a diminished k_H/k_D would be a primary isotope effect resulting from the zero-point energies of the stretching vibration involving the proton being transferred not being the same value in the transition state due to the force constant between C and H or D and the force constant between O and H or D not being equal (20).

Even though this effect would lead to a diminished k_H/k_D , several possible secondary isotope effects might lead to an increased k_H/k_D . The differences in ground state bending and stretching frequencies between the hydrogen and deuterium olefins as compared to the transition states would lead to greater energy of activation for the perdeuterated olefin which in turn would lead to an increased k_H/k_D . The inductive effect of the deuterium atoms would also lead to a greater stability of the ground state deuterated olefin and if the transition state or intermediate has any degree of carbanion character then the differences in the inductive effects of the hydrogen and deuterium olefins would lead to destabilization of the deuterium olefin, again giving rise to an increased k_H/k_D . Schriesheim states that since the direction of the secondary isotope effects for this type of process would be such as to diminish the value of k_H/k_D , and since the difference in enthalpies of activation (1.2 ± 0.5 kcal/mole) and similarity of entropies of activation (a difference of 0.7 ± 1.5 e.u.) substantiates that rate differences are due to differences in ground state zero-point energy, the observed rate ratio may be taken as lower limit primary isotope effect and that bond b is largely

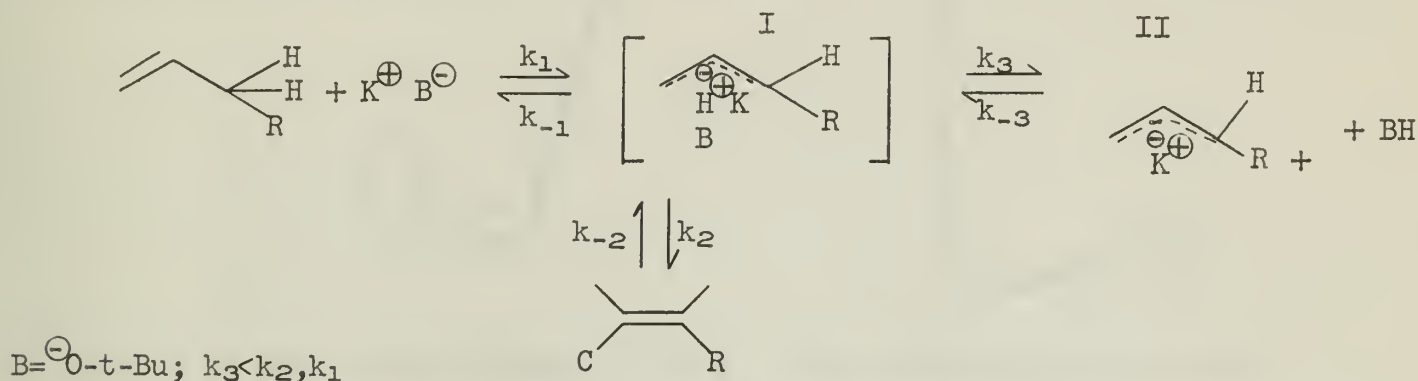


broken in the transition state (9). Schriesheim further concludes that, since the linear free-energy relationship between base-catalyzed ketone bromination and olefin isomerization strongly suggests similar transition states for the two reactions, the occurrence of the primary isotope effect found in this work clearly shows that carbon to hydrogen cleavage is rate-determining (9). In this connection Bell states that several conditions must be fulfilled before an observed kinetic

hydrogen isotope effect can be interpreted quantitatively in terms of a simple molecular model (21). First, the reaction must involve a single rate-determining step, without a pre-equilibrium step; second, the values of k_H and k_D must be compared in the same solvent; and third, isotopic substitution in either reaction partner must be confined to the proton which is transferred during the reaction. In the work by Schriesheim the second condition was fulfilled and an attempt was made to show that in this case the secondary isotope effect would affect the measured k_H/k_D ratio in such a way as to justify disregarding the third requirement. The first conclusion, which has to do with whether or not a pre-equilibrium is involved, must be discussed in connection with the overall mechanism which Schriesheim proposes. Since most of the isomerization reaction, at least 94%, does not involve exchange, this may be interpreted as either an intra-

molecular proton transfer or a process in which the anion and deuterated *t*-butyl alcohol separate and later react. The latter possibility was shown to be non-operative in that during the crossover experiments employing perdeuterio-1-pentene, 2-methyl-1-pentene, and added *t*-butyl alcohol, the amount of olefin-olefin exchange, 0.4%, was the same as that amount during the crossover experiments when added *t*-butyl alcohol was not present.

To account for the observed primary isotope effect, the slow rate of exchange, the large negative ΔS^\ddagger , and the intramolecular nature of the reaction, Schriesheim proposes the following overall mechanism (9). He states that the complex I is formed in the



rate-determining step. This statement rests almost entirely upon the large observed kinetic isotope effect. This conclusion does not appear to be the only one since these results do not permit one to distinguish between a reaction which does not involve an intermediate or a reaction which involves an intermediate either before or after the transition state.

Cram and co-workers have reported that at least 54% of the isomerization of 0.38 molar optically active 3-phenyl-1-butene catalyzed by 0.409 molar *t*-BuOK in *t*-butyl alcohol-OD at 75° for 257 minutes proceeds by intramolecular proton transfer (22). No deuterated starting material was recovered, which indicates that in this case, a pre-equilibrium is not involved. In this work no kinetic isotope effect was calculated and presence of the phenyl group may offer extra driving force for rearrangement which was not present in the pentene isomerizations investigated by Schriesheim.

In the case of isomerization of the 1-pentene, the existence of a pre-equilibrium would mean that there would be a dependence upon the equilibrium constant in the observed k_H/k_D . In the event of a pre-equilibrium, it is possible that the observed kinetic isotope effect could result from differences in stabilities of the perdeuterio-1-pentene and 1-pentene intermediates which would cause $K_{eq.} (C_5H_9)$ to be greater than $K_{eq.} (C_5D_9)$.

Although the scheme proposed by Schriesheim may or may not be of general applicability when olefins with bulky groups are considered, the conclusions that the reaction does proceed with a very large degree of intramolecular character and that olefin-olefin exchange is not operative are important findings.

Migrations Involving Cyclic Dienes - The isomerizations of hexahydronaphthalenes and dihydrobenzenes have been investigated by Bates, Carnighan and Staples. In order to determine the difference in ΔF between 1,4-dihydrobenzene I and 1,2-dihydrobenzene II, the equilibrium mixture of I and II was obtained, starting from either I or II at 95° using *t*-amyloxide in *t*-amyl alcohol. The equilibrium mixture was found to contain 31.1% of I and 68.9% of II (23). This means that II is more stable than I by 0.07 kcal/mole. In order to determine the maximum or maxima on an energy profile for the conversion of I to II, Bates and co-workers partially isomerized I and II in separate experiments using *t*-amyloxide in *t*-amyl alcohol-OD at 95° for 45 minutes (one half-life) (24). There was reported less than 0.3% of di- and polydeuterated I or II. In the isomerization starting from I, the yields of monodeuterated I and II were 5.10 and 1.28% respectively, indicating that if deuteration of III in Fig. 1 is the reaction which gives these species, that III deuterates 8 times faster at a as at b. And starting from II, the yields of monodeuterated I and II were 1.49 and 0.37% respectively, again indicating a factor of 8 for the rate difference. Thus it was concluded

that a common intermediate was involved.

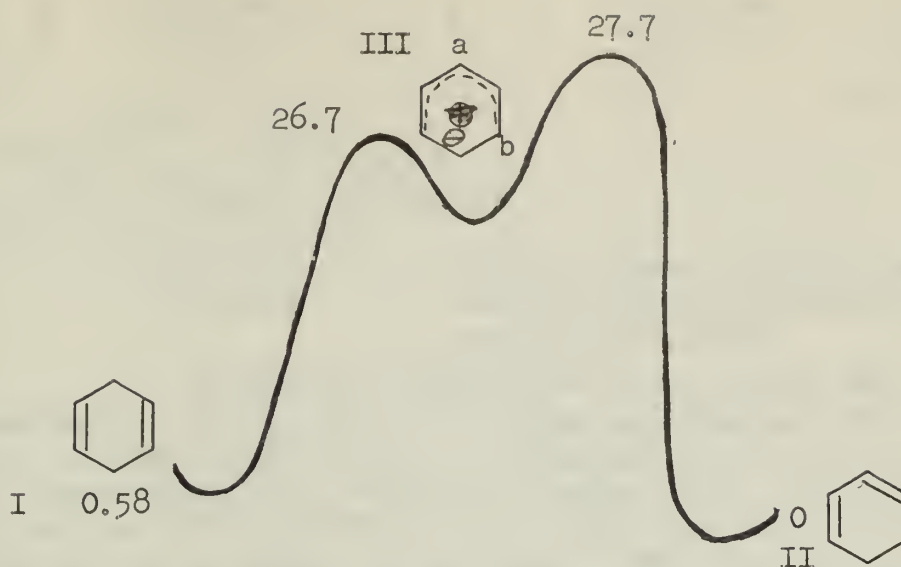
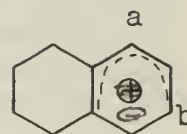


Fig. 1 ΔF , kcal/mole from II. No statistical corrections.

It is interesting to note that when the same experiments were carried out in the hexahydronaphthalene series, it was found that deuteration occurred at least 2.5 times faster at a than at b in the resonance stabilized carbanion IV. It should be noted that in both the dihydrobenzene series and hexahydronaphthalene series that a considerable amount of undeuterated product was formed. This is indicative of an intramolecular proton transfer similar to that reported by Schriesheim (9). Since a rate constant of $2.19 \times 10^{-4} \text{ sec}^{-1}$ was calculated for the conversion of II to I, it was possible for Bates to assign numerical values to four of the five extremes as shown in Fig. 1. The relative rate of protonation of III at a and at b is highly dependent upon reaction conditions as Doering reports that the rate of protonation at a was 300 times as fast as at b for conditions specified only as base-catalyzed equilibration of the dihydrobenzenes (25).



In order to show that of the various types of resonance stabilized pentadienyl carbanions shown in Fig. 2, the U-shaped carbanion IV (to the extent that the transition state for H abstraction resembles the carbanion being formed) is the most stable, Bates carried out equilibrium and kinetic experiments using the hexahydronaphthalenes. Four hexahydronaphthalenes were detected in the equilibrium mixture prepared from either $\Delta^{1,8}$ -hexahydronaphthalene IX or $\Delta^{2,9}$ -hexahydronaphthalene XI with *t*-amyloxide in *t*-amyl alcohol at 184° for 24 hours. When statistical factors are considered, the percentage composition values reported in Table VII permit the calculation of relative stabilities and it is found that the other hexahydronaphthalenes are less stable than VIII by 1.31 (IX), 1.85 (X), 1.93 (XI), and at least 3.6 kcal/mole (other isomers) assuming that as much as 1% of another isomer would have been detected (23). By taking into account the relative stabilities of the dienes shown in Table VII, Bates calculated that the transition state for the reaction via IV($\text{XI} \rightleftharpoons \text{X}$) is more stable than that for the reaction via V($\text{X} \rightleftharpoons \text{VIII}$) by 2.3 kcal/mole and that the transition state for the reaction via IV($\text{XI} \rightleftharpoons \text{X}$) is more stable than that for reactions via VII($\text{XI} \rightleftharpoons \text{IX}$ and $\text{X} \rightleftharpoons \text{IX}$) by at least 3.4 kcal/mole (26).

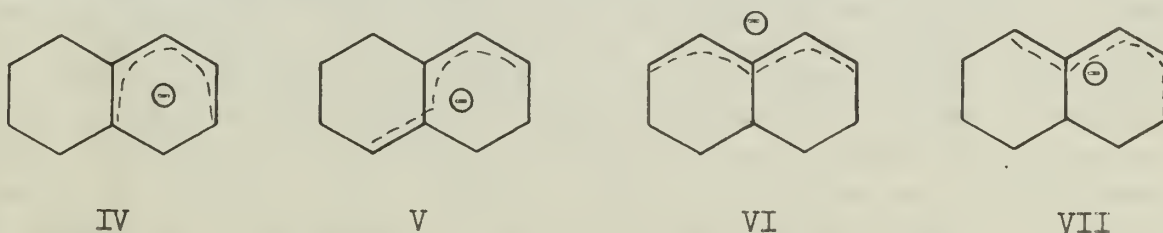
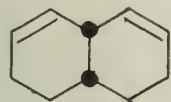
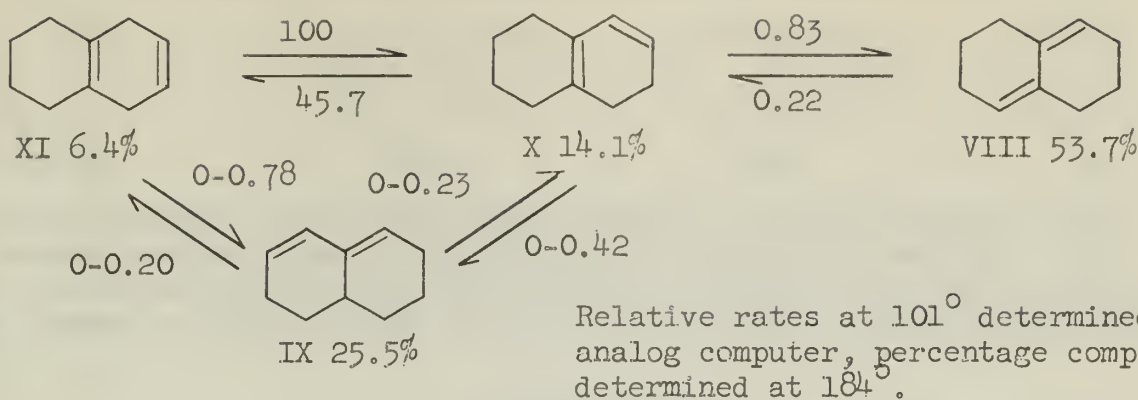


Fig. 2 Resonance Stabilized Pentadienyl Carbanions.

Table VII



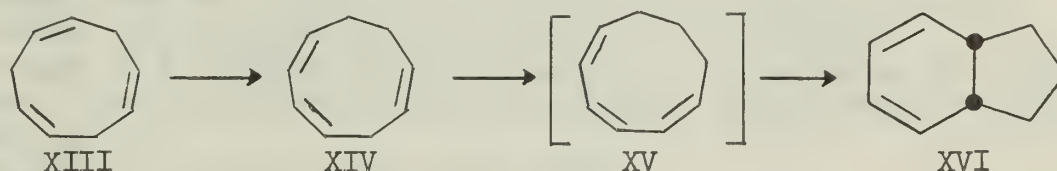
XII

In another experiment it was shown that the rate of isomerization of cis - $\Delta^{1,7}$ -hexahydronaphthalene XII, to IX via VI is greater than that for isomerization of XI to X by a factor of 3.6. Again employing a statistical correction, the transition state for the reaction via IV (XI \rightleftharpoons X) is more stable than that for the reaction via VI (XII \rightleftharpoons IX) by at least 2.6 kcal/mole. Thus Bates concludes that U-

shaped carbanions are more stable than other planar types with similar substitution by about 2-5 kcal/mole (26). Bates suggested that this phenomenon may be due to ease of solvation of U-shaped carbanions by metal cations similar to that effect proposed by Bauld to explain the predominance of cis- over trans-2-pentene obtained in the Na-NH₃ reduction of 1,3-pentadiene at -33° (27), (11). In this connection, Birch and co-workers have obtained qualitative evidence that alkyl groups destabilize pentadienyl carbanions and they attribute this more to steric hindrance to solvation than to the inductive effect of the alkyl group (28).

Migrations Involving Cyclic Trienes - Winstein and Watthey (29) have made isomerization studies on 1.2 molar cis-cis-cis-1,4,7-cyclononatriene XIII using 0.7 molar t-BuOK in DMSO and have proposed that the sequence of reactions as shown in Fig. 3 takes place.

Fig. 3



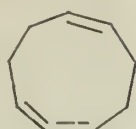
That XIV is an intermediate preceding the formation of XVI is shown by examination of Table VIII.

Table VIII

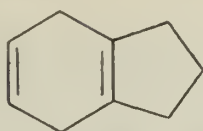
Percentage Composition of VPC Fractions					
Time, minutes	Temp. C	XIII	XIV	XVI	A
5	25	45	52	3	
7	25	12	77	10	1
5	50		51	46	3
25	50		8	86	6
60	75		5	42	53

Winstein proposes that the most likely route between XIV and XVI involves 1,3,5-cyclononatriene as an intermediate and points out that the failure to detect XV during the isomerization is reasonable since only v.p.c. was used to follow the reaction and the isomerization of XV to XVI could be expected to be rapid and complete in light of Cope's findings that the equilibrium between 85% 1,3,5-cyclooctatriene and 15% bicyclo[4.2.0]octa-2,4-diene is rapidly established by simply heating at 85° (30). Fraction A, indicated in Table VIII, was not analyzed by Winstein but Gardner and co-workers (private communication to S. Winstein, ref. 29) have identified XVI as an intermediate in the DMSO-t-BuOK catalyzed isomerization of 1,2,6-cyclononatriene XVII, to 4,7-dihydroindane XVIII, which is in turn converted to either bicyclo[4.3.0]nona-4,6 or 1,8-diene XIX, or XX (31). If this latter isomerization does take place by way of XIV as is suggested

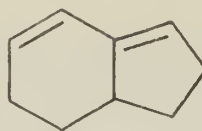
by Winstein (29), then very likely fraction A contains XVIII and XIX or XX.



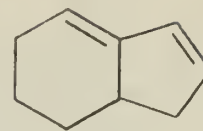
XVII



XVIII



XIX



XX

Product distribution ratios have been obtained from equilibration studies carried out in the octahydronaphthalene series using benzyl sodium as catalyst (32). Preliminary results have been reported for equilibration studies in the methylcyclohexene series using *t*-BuOK in DMSO (33) and in the *n*-octene series using lithium in ethylenediamine (34).

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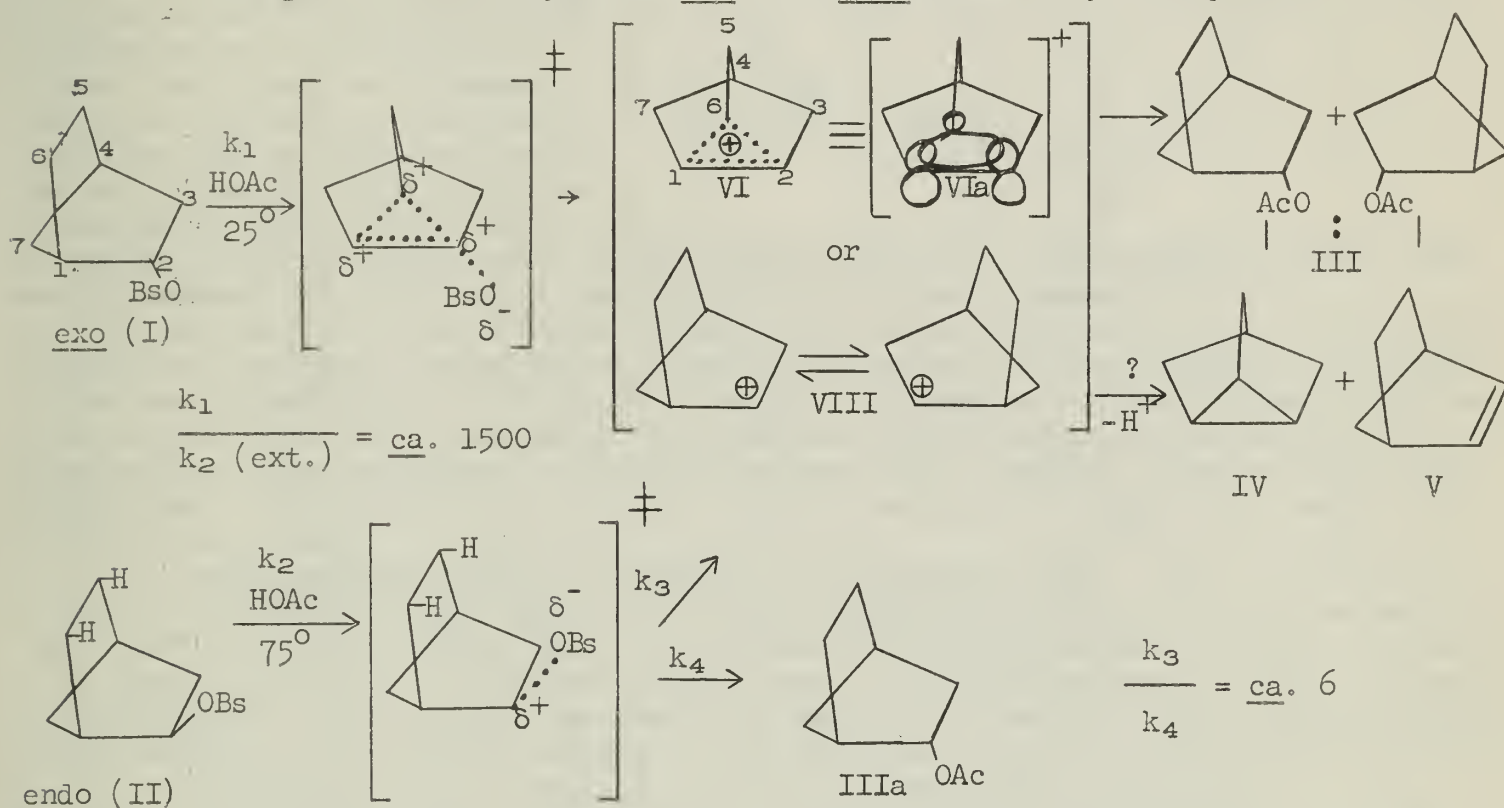
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THE QUESTION OF THE CARBONIUM ION FROM SOLVOLYSES OF 2-NORBORNYL DERIVATIVES

Reported by Thomas P. Doherty

April 6, 1964

Introduction: Winstein and coworkers (1) have produced strong evidence for the participation of a saturated hydrocarbon group in a nucleophilic displacement reaction on carbon. It was shown (Figure 1) that optically active exo-norbornyl brosylate (I), upon acetolysis at 25°, yields 95.6% of racemic exo-acetate (III) and 4.4% of a hydrocarbon product. Its endo-epimer (II), upon acetolysis at 75°, yields 88% of an acetate product composed of 92-93% of racemic exo-acetate (III) and 7-8% of unrearranged exo-acetate (IIIa). The endo-acetolysis also produces 12% of a hydrocarbon product. In both the exo- and endo-cases, the acetate product is > 99.7% exo; and the hydrocarbon product is a mixture of nortricyclene (IV) and norbornene (V) (1b). Accompanying polarimetric kinetic studies showed the relative ionization rates (extrapolated to 25°) of the exo- and endo-brosylates to be ca. 1500 : 1 respectively.

Figure 1: Acetolysis of exo- and endo-2-Norbornyl Brosylate

Numerous workers have found similar results for this and other carbonium-ion-forming solvolyses in several norbornyl systems. The entirety has produced an upsurge in the evaluation of these seemingly anomalous data and in the search for the nature of the intermediate in these reactions. Several recent books (2), reviews (3), symposia (4), and seminars (5) have dealt with aspects of this topic. The purpose of this abstract is to discuss the relative merits of the various mechanistic explanations used in the evaluation of these data. In addition, recent work will be presented; and it will be determined whether or not this work has led to a greater understanding of the true nature of the mechanistic pathway for carbonium-ion-forming solvolyses in 2-norbornyl systems.

Analysis of Interpretations: Interpretations of these data will be discussed in two categories: "bridged" ions and equilibrating "open" ions. The decision to use this terminology instead of the more common "classical" and "nonclassical" terminology is a result of the more descriptive nature of the words "bridged" and "open". In like manner, the method of drawing the norbornyl structure was chosen because of the ease with which the symmetry of the intermediate and the racemic nature of the products can be visualized.

"Bridged" ("nonclassical", "mesomeric", "syntactic", or "complex") carbonium ions. Winstein and coworkers (1) interpret their results by describing the intermediate as a symmetrical "bridged" carbonium ion (VI). This is to be distinguished from

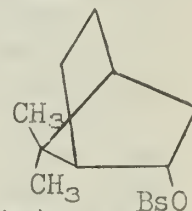
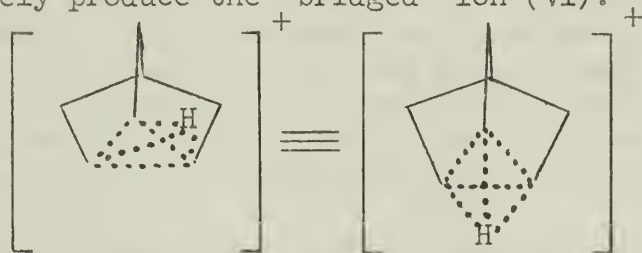
a "bridged" transition state. Carbon number six (C_6) of VI is assumed (2a) to be partially bonded by a single electron pair to both C_1 and C_2 ; in addition, a partial double-bond character is imputed to the C_1 - C_2 bond. Streitwieser (2g) depicts an orbital picture (VIa) of the "bridged" ion where the electron deficient bond contains two electrons in a three center molecular orbital derived by overlap of a C_3 sp^3 orbital with p orbitals at C_1 and C_2 . Walden inversion attack at either C_1 or C_2 , the symmetrically equivalent positions of the "bridged" ion, results in racemic exo-product. In the acetolysis of the exo-epimer (I), it is assumed (1) that "anchimeric assistance" ("synaptic acceleration", "electronic delocalization", or "mesomerism") is provided by neighboring group participation of the 1,6-bonding pair in the transition state. This "anchimeric assistance" results in a lower energy of the transition state relative to that of the endo-epimer (II). The endo-epimer, whose rate cannot be enhanced by 1,6-bonding pair assistance, is thought (1) to form initially the "open" transition state (VII). This transition state can either give optically active exo-product (IIIa) or ultimately produce the "bridged" ion (VI). Symmetrical hydrogen-bridged structures (e.g.

intermediates or as transition states, have also been proposed (1a,6) on the basis of isotopic labeling studies which have detected 3,2 and 6,2 hydride shifts.

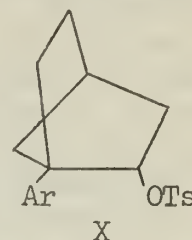
It should be noted that these structures may account for some of the racemic products. These phenomena have been amply reviewed (2a, 3a, 5a, 5b) and will not be further discussed.

It must be remembered (2c) that any stabilization a system receives from delocalization of a positive charge may be offset by a decrease in the energy of solvation of the carbon skeleton. In addition, changes in energy and entropy caused by distortions of the carbon skeleton may also offset any stabilization by delocalization. Furthermore, it is not always necessary to assume that "bridged" ions are of a lower energy than "open" ions; the transition states leading to "bridged" ions might just be of a lower energy.

Equilibrating "open" ("classical" or "simple") ions. Let us consider the case if the common intermediate in the exo- and endo-2-norbornyl brosylate solvolyses is an "open" ion (VIII). The lack of detectable endo-product may be ascribed to a steric inhibition to approach of an acetic acid molecule caused by the C_5 and C_6 endo-hydrogens. Although this proposal can explain the data of the 2-norbornyl brosylate solvolyses, it cannot explain the similar product data obtained (2a,8a) in the exo-7,7-dimethyl-2-norbornyl brosylate (IX) solvolysis where indeed the exo-side is more sterically crowded (2a). Evidence (2a) for this greater steric hindrance in the exo-epimer (IX) comes from its lower thermodynamic stability, slower rate of formation and saponification of the esters, and less amount of intermolecular association in benzene. Furthermore, reductions of the 2-ketone with $LiAlH_4$ or sodium/alcohol produce predominant amounts of endo-addition products (2a). The exo(I)-endo(II) IX rate difference has been attributed (4e), not to an unusual rate enhancement of the exo-epimer's rate, but to a rate depression of the endo-epimer's rate. This rate depression has been assigned to a steric-hindrance-to-ionization of the brosylate caused by the C_5 and C_6 endo-hydrogens. That is, the transition state is thought to be more sterically hindered than the ground state. It should be noted that this argument appears to be unprecedented and is in direct contrast to a relief-of-steric-compression argument where the ground state is thought to be more sterically hindered than the transition state. If the steric-hindrance-to-ionization argument were used to predict the exo/endo ratio of the 7,7-dimethyl compound (IX), a rate ratio less than one would be expected. However, the exo-epimer of IX has a rate (8) of acetolysis ca. 2000 times that of endo-2-norbornyl brosylate (II). A steric-hindrance-to-ionization argument cannot explain this result, but a combination of an "anchimeric assistance" argument and a relief-of-steric-compression argument can explain the result.

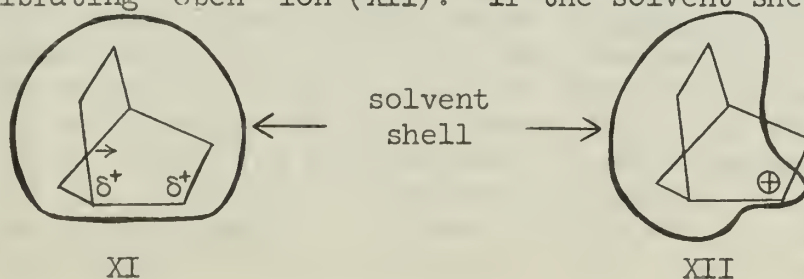


In view of the preceding discussion and in lieu of a simpler explanation, the presence of "anchimeric assistance" in the transition state in these solvolyses will be accepted as the best available interpretation of the rate enhancement observed. Evidence in favor of this argument is found in a Hammett treatment (2f) of the kinetic results obtained from the acetolysis reaction at 25° of p-substituted-1-aryl-exo-2-norbornyl tosylates (X). These reactions possess relative rate factors of 0.3 (p-NO₂) to 7.7 (p-CH₃O) times faster than that for exo-2-norbornyl tosylate. Compound X gives a $\rho = -1.36$ using σ values (2a,9). The Hammett correlation is less satisfactory with σ^+ values. This suggests that there is a relatively small but definite part of the positive charge on C₁ in the transition state. These results can be easily explained by involving the concept of "anchimeric assistance". The difficulty in defending the steric-inhibition-to-approach-of-HOAc argument demands an alternate proposal (4e) for explaining the > 99.7% exo-products. This proposal requires the use of a second "open" ion intermediate that is in equilibration with its mirror image brother (VII). These two "open" ion intermediates are separated by a transition state that resembles the "bridged" ion (VI). The equilibration is said (4e) to be sufficiently rapid so as to prevent an accumulation of solvent near the endo-position. This concept has been dubbed the "windshield wiper" effect.



Comparisons and Contrasts: The obvious opposition between the "bridged" ion and the rapidly equilibrating "open" ion proposals provides the necessity of comparing their relative pros and cons. The credibility of two proposals rests in their simplicity and in their consistency with known phenomena. Considering the postulated "bridged" ion intermediate, it is assumed that the structure represents an energy minimum. Analogous electron deficient bonding is found in the dimer of trimethylaluminum (7a) and the polymer of dimethylberyllium (7b) which possess methyl bridges and in the boron hydrides (7c) which possess hydrogen bridges. Other analogies are the numerous "bridged" transition state postulations(2) which are difficult to explain in other ways. The best analogy available is the strong evidence (supra) for the "bridged" norbornyl geometry in the transition state. If a transition state can be stabilized by electronic delocalization, therefore, why cannot an intermediate be stabilized in the same way? In this connection, some molecular orbital calculations have been performed (2i,7d) on this system; but no conclusions can be made at this time.

Let us now consider the alternate proposal of rapidly equilibrating "open" ions. In this proposal, one of the set of "open" ions will be formed initially. First it must be assumed that these "open" ions arise from a "bridged" transition state. It must then be assumed that these ions will first equilibrate through a transition state that resembles the "bridged" ion before collapse to products; otherwise, some optical activity would be retained. Furthermore, it must be assumed that the ΔF^\ddagger between the transition state to endo-product and the intermediate cation is at least 3.4 kcal. greater than the ΔF^\ddagger for the exo- case. (This calculation was made using the relation (10), $\Delta\Delta F^\ddagger = -RT \ln 99.7/0.3$, with the consideration that > 99.7% exo-epimer was formed.) If these ions were not equilibrating, it would be difficult to find a factor to which this difference could be attributed. If the 7,7-dimethyl case (IX) is equated with the 2-norbornyl case, steric factors will not explain the lack of detectable endo-product (supra). Rapid equilibration could be used as an explanation but only if it is assumed that the solvent shell around an "open" ion that is rapidly equilibrating (XI) with its mirror image brother is different than that around a nonequilibrating "open" ion (XII). If the solvent shells were the same,



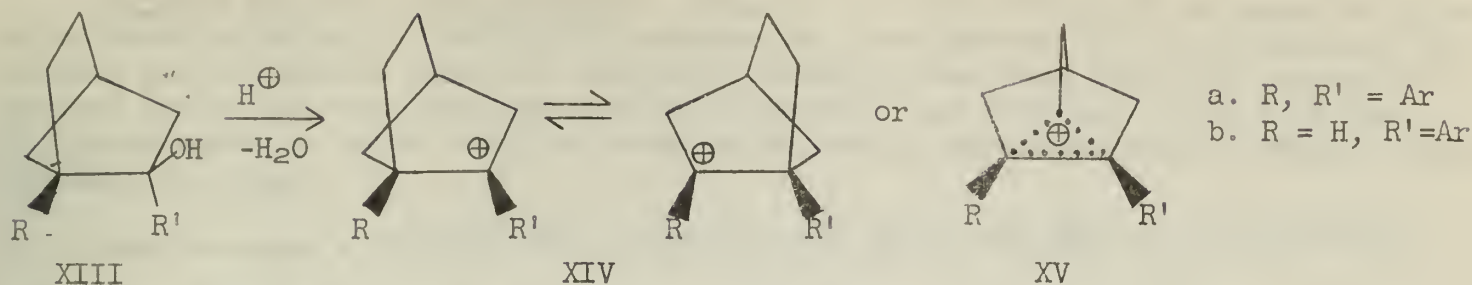
endo-products would be predicted. But in order to receive $< 0.3\%$ endo-product, it must be assumed that the ΔF^\ddagger between the transition states leading to exo- and endo-product from XI is larger than the same ΔF^\ddagger from XII. That this effect could be caused by a difference in the solvent shell is shown by the use of the following argument. The laws of classical kinetics state (10) that the rate of collapse to product is equal to a rate constant times the macroscopic concentrations of the intermediate cation and the solvent and nearly independent of whether or not these species are in slow, medium, or rapid equilibration with other species. In the two systems, XI and XII, the concentration of solvent is the same. Similarly, the concentration of cation is nearly the same in each system. From transition state theory, the rapid equilibration would lower the concentration of the "open" ions by an amount approximately equal to the concentration of the "bridged" transition state between the two ions. For example, a lowering of only ca. 1% would result from equilibration if the barrier were of $\Delta F^\ddagger = 2.9$ kcal. Hence, it must be assumed that the difference in rate is due to a difference in the rate constant. That is, the "windshield wiper" effect may be said to lower the rate constant for collapse to endo-product. Calculation of the relative magnitudes of the two rate constants would involve an estimate of solvent-solvent and solvent-"open" ion interactions on both the exo- and endo-sides of the molecule.

A summary of the assumptions inherent in both the "bridged" ion and the rapidly equilibrating "open" ion proposals is now in order. The "bridged" ion proposal involves the following assumptions: (a) a "bridged" intermediate can be stabilized in the same manner as a "bridged" transition state; (b) for the exo-case, a "bridged" transition state can produce a "bridged" ion; and for the endo-case, an "open" transition state can ultimately produce a "bridged" ion; (c) the "bridged" ion is symmetrical; and (d) attack on the "bridged" ion occurs only from the exo-side of the molecule. Assumption (a) appears to be unprecedented with regards to the stabilization of a positive charge by a saturated carbon atom. The rapidly equilibrating "open" ion proposal involves the following assumptions: (a) the "open" ions represent energy minima; (b) for the exo-case, a "bridged" transition state can produce an "open" ion intermediate; and for the endo-case, an "open" transition state can produce an "open" ion; (c) complete equilibration can take place before collapse to products; and (d) the "windshield wiper" effect can lower the rate constant for collapse to endo-product. Assumption (d) appears to be unprecedented. Since there exists a major deviation from precedent in each proposal, it is difficult to dispose of one in favor of the other unless a divergence is made to philosophical grounds. Occam's Rule states that the "simplest" interpretation of the experimental facts is assumed to be the correct interpretation. That is, the pathway which a reaction will follow is composed of the least number of intermediate steps, provided that all of the mechanistic schemes available have the same degree of precedent. In the light of the previous discussion, the rapidly equilibrating "open" ion proposal is at least as unprecedented as the "bridged" ion proposal, if not more so.

Occam's Rule is best applied if we consider the effect of lowering the barrier to interconversion of the two "open" ions. As the height of the energy barrier to interconversion is lowered, the concentration of the "bridged" positively-charged transition state increases; and, consequently, the concentration of the "open" ions decreases. At the limit (i.e. $\Delta F^\ddagger = 0$), there will be a complete spectrum of unsymmetrical positively-charged "bridged" geometries with the two "open" ions at the extremes and the symmetrical positively-charged "bridged" geometry at the center. It is at these low barrier heights that the two equilibrating "open" ions appear as one "bridged" ion to the "eyes" of the solvent. As a result, at low barrier heights, it becomes difficult to speak of a differentiation between "bridged" ions and rapidly equilibrating "open" ions. Using Occam's Razor to shave off the two superfluous "open" cation intermediates, it is concluded that the resulting "bridged" cation intermediate is the simplest explanation of the observed results in the secondary 2-norbornyl brosylate solvolyses. It must be noted that this conclusion does not rule out the possibility of "open" ion intermediates in other norbornyl systems, such as, in the reactions of the 1,2-diaryl-2-norbornyl derivatives (XIII)(infra).

Direct Methods of Measurement: Schleyer, Kleinfelter, and Richey (11) have performed several measurements of the properties of the intermediate cation (XIV or XV)

formed from some diaryl and monoaryl norbornyl alcohols (XIII, e.g. Ar = $p\text{-CH}_3\phi$,



$p\text{-CH}_3\text{O-}\phi$, ϕ). They used UV spectral investigations, thermodynamic stability measurements, kinetics of aromatic substitution, and NMR studies. The UV spectra of the monoaryl and diaryl cations in concentrated H_2SO_4 were essentially the same. The monoanisyl and dianisyl cations were half-formed in 41% and 51% aqueous H_2SO_4 solutions respectively, indicating a greater stability for the monoanisyl cation. This can be explained by a negative inductive effect produced in the dianisyl cation from the added anisyl group. Electrophilic substitution reactions, such as bromination and sulfonation, proceed much faster in the diaryl ion than in the monoaryl ion. The authors explain the preceding experimental facts by proposing the "open" ion structures (XIV). But, their interpretation of the results of these first three methods requires the use of the assumption that, in the "bridged" ion, a positive charge in the diaryl cation can be delocalized onto both rings because of extended conjugation. The fact that they did not receive any effects of this extended conjugation was interpreted in favor of the nonexistence of "bridged" ions in these systems. This assumption requires that the aryl rings can overcome their energy barrier to rigid geometry in order to obtain the correct geometry to conjugate with the positive charge. Further, it requires that the steric repulsion between the two aryl rings in the "bridged" structure cannot "force" the aryl rings out of conjugation with the positive charge. This steric interaction resembles that in the cis-diarylcyclopentanes (12), the cis-diarylcyclopropanes (12), and the cis-stilbenes (13). The NMR spectrum of the dianisylnorbornyl alcohol, XIII ($R, R' = p\text{-CH}_3\text{O-}\phi$), in trifluoroacetic acid at room temperature can be explained by postulating either XIV or XV, indicating equivalence of the anisyl rings. This is shown by the two AB doublets ($\tau = 2.28$, ortho to the norbornyl ring; $\tau = 2.83$, meta to the norbornyl ring) of the anisyl ring protons and by the methoxyl singlet. Upon cooling the solution to -70° , the ortho- and meta-proton peaks lost detail and finally collapsed into a single broad peak indicating non-equivalence of the anisyl rings. The authors state that this is "dramatic evidence in favor of rapidly equilibrating asymmetrical ion structures." However, the difference in the spectrum at the two temperatures could also be due to a slower rotation of the anisyl rings at the lower temperature than at room temperature. At room temperature, fast rotation would equilibrate all the ortho-protons and, similarly, all the meta-protons. As the temperature is lowered, the rotation of the rings could become hindered causing nonequivalence of the ortho-protons and, similarly, of the meta-protons. This nonequivalence could arise from a difference in the diamagnetic anisotropy effect of the anisyl ring currents operating on the eight ring protons. These phenomena could very easily result in a single broad peak. Alternate explanations involve an equilibrium between the "bridged" ion (XV) and the "open" ions (XIV) and an equilibrium between the "bridged" ion (XV) and the alcohol (XIII). Upon cooling, a shift in the position of the equilibrium in favor of the "bridged" ion whose anisyl rings are probably closer together could result in a single broad peak. Upon inspection of molecular models, it is seen that as a result of an equilibrium shift to "bridged" ion, the ortho-protons are more affected by the ring current than the meta-protons. This would result in a greater shift to higher field by the ortho-protons than the meta-protons resulting in collapse to a broad singlet. A temperature effect similar to this has been observed in cis-1,2-dianisylcyclopentane (12). On the basis of the numerous reservations in the four methods, a conclusion as to whether these diaryl cations possess the rapidly equilibrating "open" structures or the "bridged" ion structure is not possible at this time.

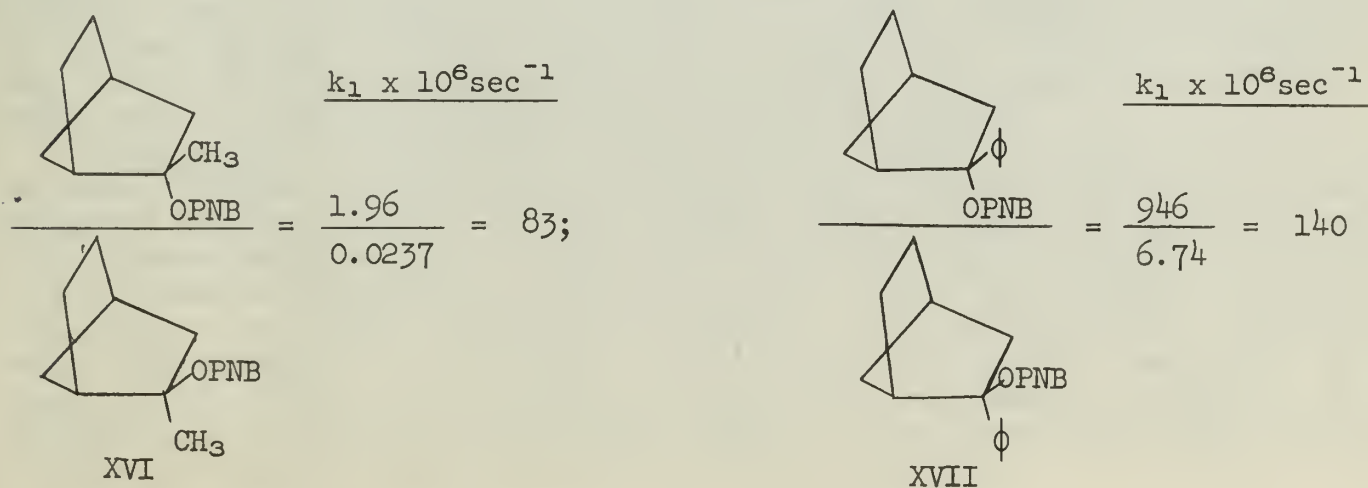
Indirect Methods of Measurement: Schleyer (14) has formulated an equation from which rates relative to cyclohexyl tosylate for acetolysis at 25° "of relatively uncrowded arenesulfonate esters of secondary alcohols free from classical resonance or serious inductive contributions" can be estimated. The rates are found from the following equation which considers bond angle strain, torsional strain, and non-bonded interaction strain:

$$\text{relative rate} = (10^{0.125(1715 - \nu_{\text{CO}})}) (\prod 10^{1.32(1 + \cos 3\phi_i)}) (10^{0.735(\text{GS-TS})})$$

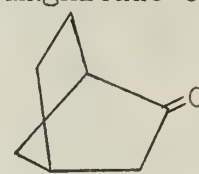
where ν_{CO} is the frequency of the ketone (in cm^{-1}) corresponding to the carbonium ion, ϕ is the dihedral angle between the tosyl group and the nearest group on the adjacent carbons, and GS-TS is the difference in non-bonded interaction strain (in kcal) between the ground and transition states. Hyperconjugative and steric hindrance to solvation effects did not appear to be important (14). Using this equation, it was found that the endo-norbornyl epimer (II)'s calculated rate and the rates of some twenty other model compounds are almost in exact agreement with their observed rates (average deviation = $10^{\pm 0.25}$); whereas, the exo-epimer (I)'s rate is calculated to be $10^{3.3}$ times slower than what is observed. The discrepancy is thought (14) to be an estimate of the magnitude of "anchimeric assistance" in the transition state. However, when using this equation to predict rates, there is no assurance that all the appropriate factors are taken into account or even that the considered factors are in the correct magnitudes. Nonetheless, a qualitative understanding may be obtained. It must be remembered, however, that rate studies such as these can at most only describe the transition state leading to the carbonium ion intermediate. The possibility that "bridged" transition states can produce "open" carbonium ion intermediates must first be ruled out in each individual case before any conclusion concerning the nature of the intermediate can be reached.

It should be noted that Schleyer's equation can at most be used only for some secondary tosylates. A tertiary 2-norbornyl cation would possess at least another factor--the stabilization of the ion by the third group. In fact, this factor and some experimental evidence has led Winstein (15) and Bunton (2c) to suggest that maybe some tertiary norbornyl ions (e.g. XIVa) are stabilized so strongly by the tertiary group that participation of the 1,6-bonding pair is not required and an "open" ion intermediate exists. In other words, the amount of stabilization provided by the "bridged" ion may not be great enough to overcome the energy barrier to its formation. Using the assumption that tertiary norbornyl derivatives undergo ionization to essentially "open" cations, Brown, Chloupek, and Rei (17), in a series of three communications, have attempted to substantiate this conclusion and have attempted to assign, by analogy, an "open" nature to the secondary 2-norbornyl cation. They have shown (Figure 2) that solvolyses in 60% dioxane at 50° of 2-methyl-(XVI) and 2-phenyl-(XVII)-2-norbornyl p-nitrobenzoates give exo/endo rate ratios of 83 and 140 respec-

Figure 2: Solvolyses in 60% Dioxane at 50°

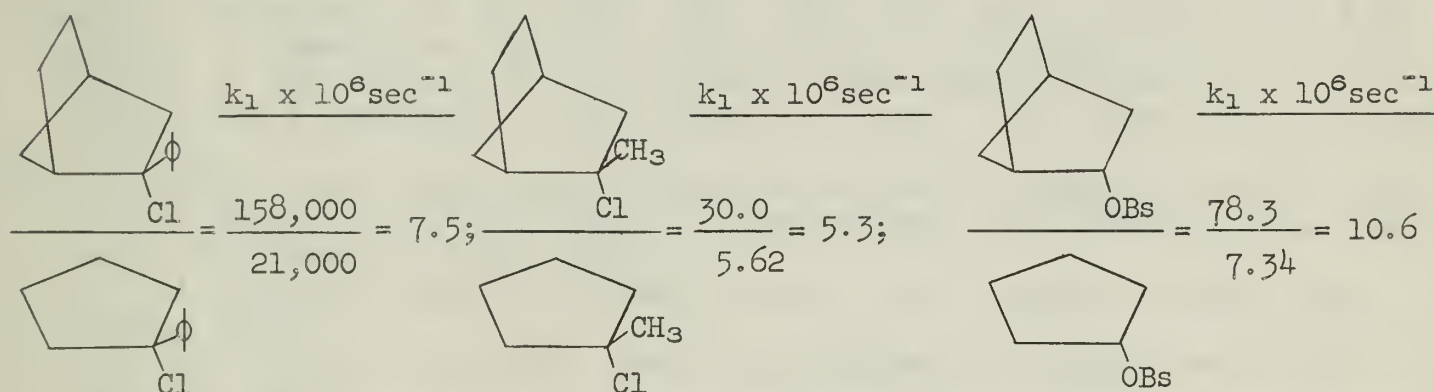


tively. Assuming that these solvolyses produce essentially "open" ions, they state that the obtained rate ratios are of the "same order of magnitude" (17) as the rate ratios for acetolysis of secondary norbornyl sulfonate esters for which "bridged" ions are postulated (1) as intermediates. Therefore, they reason that the existence of "a high exo-endo ratio in a norbornyl derivative does not provide a unique basis for concluding that this system undergoes ionization to a non-classical ["bridged"] cation." However, relief of steric compression, as they admit (17), may contribute a factor of about five (or more?) to the elevation of the rate ratio in the 2-phenyl- and 2-methyl-exo-2-norbornyl chlorides. Furthermore, the change in the leaving group may substantially effect the difference between the ground and the transition state energies. If these factors are considered and if there is still a similarity, it might also be valid to state that both the secondary and the tertiary solvolyses do not proceed through essentially "open" transition states but, in fact, proceed through essentially "bridged" transition states. Comparisons were also made (16,17) of the reactivities of norbornyl derivatives with those of corresponding cyclopentyl derivatives. The choice of cyclopentyl derivatives instead of cyclohexyl derivatives depended upon a comparison of nonbonded repulsions and the observed magnitude of the carbonyl group stretching vibration (in cm^{-1}): cyclopentanone, 1750; cyclohexanone, 1717; and norcamphor (XVIII), 1751. On the other hand, the ΔH^\ddagger and ΔS^\ddagger values for several norbornyl systems more closely resemble their cyclohexyl analogs (1). However, it would seem that the best available model for the exo-solvolysis rate would be the corresponding endo-solvolysis rate. The rate ratios for ethanolysis at 25° of 2-phenyl- and 2-methyl-exo-2-norbornyl chlorides and 2-norbornyl brosylate (a different leaving group) are shown in Figure 3 compared with their respective cyclopentyl analogs. Brown and coworkers (17) propose that the fact that the behavior of the secondary solvolysis is similar



XVIII

Figure 3: Ethanolysis at 25°



to that exhibited by the tertiary solvolysis "argues strongly for the position that there is no major factor influencing the solvolysis of the secondary norbornyl derivative that is not present in the highly stabilized tertiary norbornyl cations." However, before a statement such as this can be made, the effect of the difference in the leaving group, ion-pair phenomena, a comparison of the steric effects of H, CH_3 , and ϕ , and a product study must be considered. The lack of consideration of these factors could very easily account for the similarity.

Conclusion: No compelling evidence has been advanced during the past few years in favor of either "bridged" ions or rapidly equilibrating "open" ions in saturated norbornyl systems; however, spectroscopy may eventually give us "positive" methods for differentiating between "bridged" and "open" structures. Quantitative approaches, such as those of Schleyer (11) may also become of great significance. Concerning the solvolyses of secondary 2-norbornyl derivatives, the considerations in this abstract would tend to support the validity of the proposed "anchimeric assistance" in the transition state and of the proposed "bridged" ion intermediate. However, it must be admitted that no absolute experimental method of distinguishing between the "bridged" ion and the rapidly equilibrating "open" ions is available.

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DISPLACEMENT REACTIONS ON SILICON. RECENT DEVELOPMENTS.

Reported by F. M. Vigo

April 9, 1964

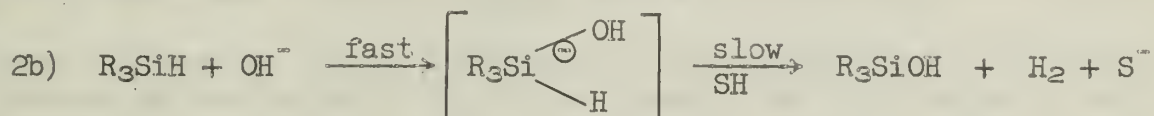
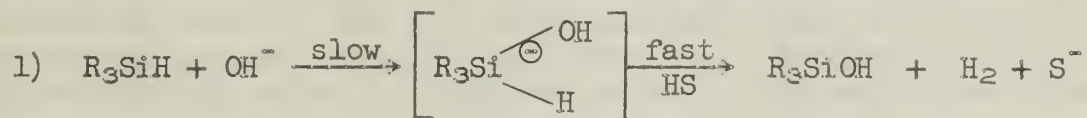
Introduction: Organosilicon chemistry has become of great interest in recent years. However the mechanisms of displacement reactions, long established in the case of carbon, are still being elucidated for silicon. A previous seminar (1) and a text-book (2) cover the material up to 1960, so that this seminar will place special emphasis on later developments.

Solvolysis of Silicon Hydrides: Silanes are easily hydrolyzed to silanols or, through solvolysis by other solvents, to siloxanes. As noted by Gilman (3) this makes the silicon-hydrogen bond more similar in chemical behavior to the carbon-halogen bond than to the carbon-hydrogen bond.

Base catalyzed hydrolysis has been one of the most investigated reactions:



Early kinetic studies showed that two main mechanisms were possible (4):



Mechanism 1 involves the rate determining attack of hydroxide on the silane to form a pentacovalent silicon intermediate which reacts quickly with the solvent to give the products. Mechanism 2 involves two similar variations a) simultaneous attack by hydroxide ion and a solvent molecule to yield the products and b) a rapid equilibrium of hydroxide ion with the silane to form a pentacovalent silicon intermediate which reacts slowly with the solvent to give the products. The mechanisms shown here are simplified because they do not show any equilibrium between base and substrate, as exists in the case of ethanol-water.

Price (5) supported mechanism 2a, since he found that the second order rate constants obtained at constant water concentration increased linearly with water concentration, thus indicating possible substrate participation in the transition state:



These results, however, can be questioned because Price had disregarded the effect of changing water concentration on the hydroxide concentration.

Kaplan and Wilzback (4) found the isotope effect for the hydrolysis of triphenylsilane in pyridine to be rather small ($k_{\text{SiH}}/k_{\text{SiD}} = 1.152$). The results could be interpreted in terms of mechanism 1 by assuming a weakening of the Si-H bond in the intermediate, or in terms of mechanism 2, by assuming the hydride-hydrogen bonding to be strong. However the authors favored mechanism 2 on the added evidence of the hydrolysis of tripropylsilane with 0.53 M KOH, which gave a rate of hydrolysis 1.44 times greater in ethanol-water than for EtOD-D₂O at the same concentration.

In 1961 Steward and Pierce (6) investigated the base catalyzed hydrolysis of various silanes in ethanol-water and correlated the second order constants with Taft's σ^* values. No correlation could be obtained for eight ω -phenylalkylsilanes, probably owing to steric effects caused by the ring. The 16 remaining silanes gave a good straight line correlation, yielding $\rho^* = 4.27$ (correlation factor = 0.998). Evidence for a slightly concave upward curve was not so well supported by statistical data and can be disregarded. Mechanism 1, with a negatively charged silicon intermediate formed at the rate determining step would be expected to have the highest ρ^* value, since mechanism 2 would involve a transition state in which a solvent molecule would reduce the negative charge on silicon by partially accepting the departing hydride ion. How-

ever both mechanisms would involve a positive ρ^* value and, since no relative standards are available we cannot choose between mechanisms 1 and 2.

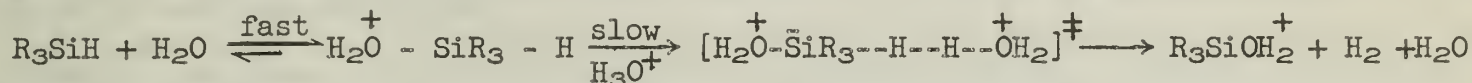
In 1952 Gilman (7) had achieved rather poor correlation in his attempt to correlate the second order rates for the hydrolysis in base of various substituted arylsilanes with Hammett's σ values. His correlation was worst for the para-substituted compounds. He obtained a ρ value of 3.1.

Schott and Gutshick (8,9) correlated the second order rates for the hydrolysis of p-substituted triarylsilanes and dimethylarylsilanes with KOH in ethanol-water with σ_{Si} values, devised by them for silicon:

$$\sigma_{Si} = \sigma \text{ inductive} + 0.75 \sigma \text{ resonance}$$

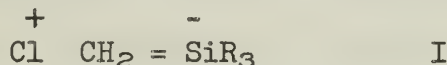
They obtained a good correlation yielding $\rho = 1.96$ for the triarylsilanes and $\rho = 2.1$ for the dimethylarylsilanes. Since the compounds examined were only nine, excessive importance should not be given to σ_{Si} , admittedly an empirically obtained value, but it is nevertheless remarkable that it can correlate the reaction of two different groups of compounds such as the triarylsilanes and the dimethylarylsilanes.

In an investigation of the acid catalyzed hydrolysis of silanes Baines and Eaborn (10) proposed a mechanism involving rapid reversible nucleophilic attack by water, followed by electrophilic attack by a hydronium ion in the rate determining step:



The reaction was carried out in 95% ethanol on di-n-propyl and cyclohexylsilane and, at acid concentrations below 0.5 M, it was found to be first order in silane and first order in acid. The first order dependence in acid, plus the isotope effect study in which the reaction of cyclohexylsilane was found to be 2.25 times faster in 20:80 water:dioxane than in 20:80 deuterium oxide-dioxane, pointed to the proton transfer occurring in the rate determining step. The reaction was found to be slightly retarded by electron release to the silicon atom, as in halogen and methyl-substituted aryl silanes.

Steward and Pierce (11) determined the first rate constants for hydrolysis with 1.54 N acid in 95% ethanol, and again correlated the results with Taft's σ^* values for the various constituents. A fair correlation was obtained for thirteen alkyl, ω -cyano-alkyl and fluoroalkylsilanes, yielding $\rho^* = 0.77$ (correlation factor = 0.96). Correlation of the rates of 4 diorganosilanes and 2 monoorganosilanes yielded two straight lines parallel to that for triorganosilanes. Chloromethyldimethylsilane appeared below the line, the authors explaining the lack of correlation by proposing that direct interaction between the filled orbitals of the chlorine atom with the vacant d-orbitals of the silicon atom could take place so that a resonance form such as I would have to be taken into consideration: -



This is analogous to the proposal made by Brook (12) in the case of O-C-Si interaction in the case of 1-silyl ketones. Steward and Pierce mentioned a mechanism involving fast reversible electrophilic attack by hydroxonium ion followed by nucleophilic attack of solvent in the rate determining step, i.e., the reverse of that proposed by Baines and Eaborn (11). Both mechanisms are consistent with the data given so far.

Solvolysis of Haloorganosilanes: - Haloorganosilanes are also solvolyzed to give silanols or siloxanes, and hydrochloric acid.

In an early investigation Swain, Esteve and Jones (13) postulated the existence of an intermediate in the hydrolysis of triphenylsilyl fluoride in 50% acetone-water. Pseudo first order rates were obtained for the reaction, ~~together with evidence of strong catalytic action by base (hydroxide 10^6 faster than water)~~. Neutral salts and increasing medium polarity accelerated the reaction, while p-methyl substitution retarded it. However, as Hughes pointed out (14), this evidence does not rule out a modified S_N2 mechanism in which bond making is predominant, as in the case of mechanism 2a as mentioned previously in the basic hydrolysis of silanes.

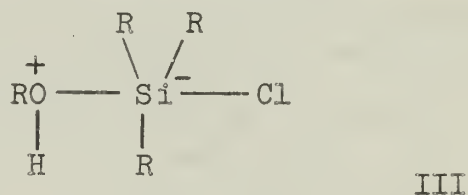
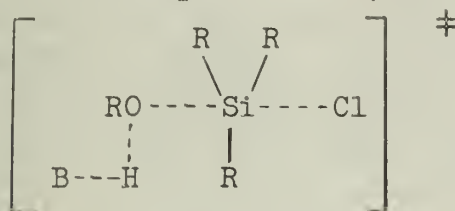
Allen and co-workers (15,16) found the rate of hydrolysis of tri-isopropylsilyl

chloride in 2-propanol to be first order in silane and first order in methanol or water. The rate was greatly accelerated if the reaction was carried out in ethanol or methanol, but was no longer second order. Of greater interest are their results and conclusions from the hydrolysis of triphenylsilyl chloride in dioxane. A pseudo first order rate constant was obtained for each water concentration used (0.25 to 0.50 M). The rate was accelerated by addition of salts such as tetraethylammonium perchlorate, but a greater acceleration was observed when tetraethylammonium chloride (9×10^{-5} M) was added. Addition of a greater quantity of hydrochloric acid (0.001 M) caused only a doubling of the rate. Since the reaction showed autocatalysis only the initial readings were used in a zero point extrapolations to obtain the rates. In a more detailed study of the salt effect at different concentrations of water (0.25 to 0.5 M) and salt (0.27×10^{-4} to 1×10^{-4} M) in dioxane solvent, the authors found that the increment in rate due to catalysis followed the equation:

$$\text{Rate} = k_1(\text{H}_2\text{O}) [\text{R}_3\text{SiCl}] + k_3 [\text{R}_3\text{SiCl}] [\text{H}_2\text{O}] [\text{Cl}^-] \quad (1)$$

where $k_1(\text{H}_2\text{O})$ = first order rate coeff. at a given water concentration and $[\text{Cl}^-]$ is postulated to be equal to the salt concentration. The uncatalyzed part of eq. 1 varies from 0.5 to 15% of the catalyzed part, the importance of the uncatalyzed part decreasing with water concentration.

On the basis of these results Allen and Modena (16) strongly advocated a $\text{S}_{\text{N}}2$ type mechanism catalyzed by chloride ion with a transition state II. However there is no definite evidence to exclude the formation of a pentacovalent silicon intermediate, either in a equilibrium (mech. 2b) or in the rate determining step (mech. 1)



Petersen and Ross (17) attacked the problem in a different fashion by investigating the solvolysis of triphenylsilyl chloride with 2-propanol. The solvent used was CCl_4 , a substrate far less active than dioxane. A pseudo first order plot for this reaction showed an apparent induction effect, ascribed to autocatalysis, due to either associated or undissociated HCl . The reaction was supposed to be initiated by a small amount of HCl , shown to be present as an impurity in the starting solution of the halo-silane. In view of this no zero time extrapolations were made by the authors. The later part of the plot showed a slowing down of the reaction, presumably due to the reverse reaction. The data obtained fitted best the rate equation: -

$$dP/dT = k_1 \text{CAP where } C = [2\text{-PrOH}], A = [\text{C}_6\text{H}_5\text{SiCl}] \text{ and } P = [\text{HCl}] \quad (2)$$

Conductance measurements indicated that hydrochloric acid was only slightly dissociated in CCl_4 , so that the authors maintained that catalysis by individual H^+ or Cl^- would involve the use of \sqrt{P} in eq. 2, a substitution that did not give a good correlation. However they disregarded the possibility of the following dissociation taking place: $2\text{HCl} \rightleftharpoons \text{H}^+ + \text{HCl}_2$. Since three species were found to be involved in the rate equation the authors postulated an intermediate III including two of the species to be formed first, rather than a three body reaction to occur. Further, the rate data for the hydrolysis with added benzyltriethylammonium chloride yielded no correlation with eq. 1, but was found to follow:

$$dP/dT = k_1 \text{CAP} + k_2 \text{CAS}/P \text{ where } S = \text{salt concentration } (1.03 \times 10^{-3} \text{ to } 2.38 \times 10^{-3} \text{ M}) \quad (3)$$

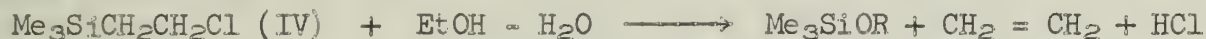
The first and second terms of the right side of the equation were of approximately equal significance at the concentrations used. Although the authors try to explain the catalytic action of the quaternary ammonium salt in terms of interaction of the salt with 2-propanol, the possibility of catalysis by chloride ion cannot be ruled out.

Hydrolysis of Cyclosilanes: Sommer and co-workers (18) in their studies of the hydrolysis of cyclosilanes found that rearward attack by base was not necessary in certain base catalyzed hydrolysis, since 1-silabicyclo[2,2,1]heptane and 1-silabicyclo[2,2,2]octane gave rates of reaction a thousand and ten times faster, respectively, than triethylsilane. These results were rationalized in terms of a pentacovalent silicon intermediate.

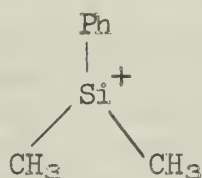
In an interesting investigation Smith and Clark (19) obtained a product in 0.1% yield from the high pressure reaction of silicon tetrachloride and trimethylsilyl chloride in presence of aluminum chloride at temperature in excess of 500°. The compound gave a simple IR with no bands attributable to $\text{Me}_3\text{Si}-$ or $\text{ClCH}_2\text{Si}-$, only bands characteristic of SiCH_2Si being present in the 2 to 12 μ region. NMR gave a single peak at $\delta = -0.265$ ppm as referred to tetramethylsilane, and X-ray studies showed a molecular weight of 355. On the basis of this evidence the authors identified the product as 1,3,5,7-tetrachloro-1,3,5,7-tetrasiladamantane. This compound is unusual because it resists hydrolysis. This behavior can be rationalized because rearward attack cannot occur and, since the adamantane structure has hardly any strain, there is no driving force towards the formation of a pentacovalent silicon intermediate.

Evidence for the Occurrence of Siliconium Ions: A puzzling facet of organosilicon displacement reactions is the dearth of siliconium ion intermediates, especially in view of silicon's lesser electronegativity with respect to carbon.

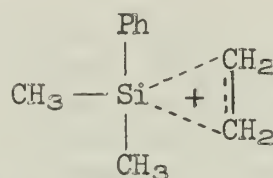
In 1961 Sommer and Baugham (20) investigated the hydrolysis-elimination of β -chloroethyltrimethylsilane (IV):



The reaction was found to follow a first order rate law in excellent agreement, as measured by ethylene evolution, for ethanol-water concentrations ranging from 80:20 to 50:50. Addition of 0.54 M KOH caused a slight decrease in rate (0.95 relative to neutral). Even addition of 4 M KOH resulted in a rate of 1.54 as compared to neutral, the rate being still first order. Salts effects of KCl, KBr or KNO_3 were found to be small. A correlation of the rates of hydrolysis of β -chloroethylphenyldimethylsilicon and β -chloroethyldimethyl(m- CF_3 phenyl) silicon with σ values for the substituents on phenyl gave $\rho = -2.15$. From these results Sommer concluded that positive charge was present on silicon in the intermediate. However the mechanism is not limited to the formation, or near formation, of a trivalent siliconium ion (V), as Sommer proposed, but there is also the possibility of forming a pentacovalent siliconium ion such as VI.



V



VI

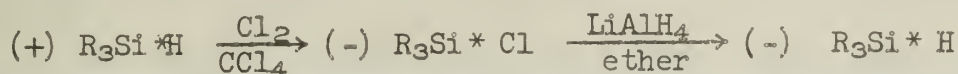
In view of this, Sommer's opinion that the accessibility of trialkyl carbonium and siliconium ions is similar, but that silicon can follow a more favorable path through an expanded octet intermediate, is not adequately supported by the facts. Indeed the presence of a siliconium ion intermediate similar to carbonium ions is as yet not proven.

In conductivity and cryoscopic measurements on various silanols in 100% H_2SO_4 Flowers, Gillespie and Robinson (21) found no evidence for the formation of siliconium ions.

An attempt made by Corey and West (22) to generate a siliconium ion was unsuccessful. Thus when triphenylsilane was added to a solution of triphenylcarbonium bromoborate in dichloroethane the products were triphenylmethane, boron tribromide and triphenylbromosilane.

The Stereochemistry of Displacement Reactions: Although organosilicon compounds showing weak optical activity had been made by Kipping (22), and an optically active compound without a reactive functional group was made by Eaborn and Pitt in 1958 (23), it was not until late in the same year when Sommer (24) made compounds containing the α -naphthylphenylmethylsilyl group plus a reactive functional group that the stereo-

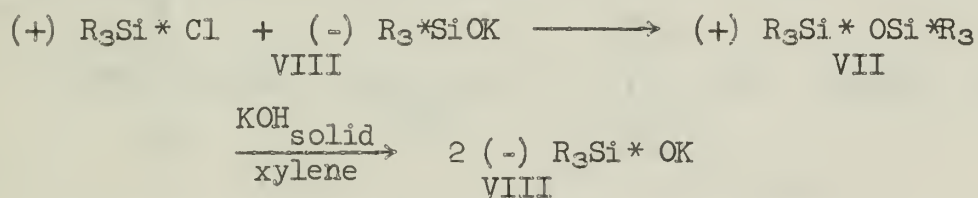
chemistry of displacement reactions could be investigated. Henceforth the α -naphthyl-phenylmethylsilyl group will be represented as R_3Si^* . In 1962 Sommer reviewed (24) his previous communications (25) on the stereochemistry of silicon, so that the material contained there will be dealt with here only briefly. Soon after the synthesis of the optically active compounds the first Walden cycle for silicon was discovered:



$$[\alpha]_D = +33^\circ \text{ (a)} \quad [\alpha]_D = -6.8^\circ \text{ (b)} \quad [\alpha]_D = -33^\circ$$

By X-ray application of the Fregda method based on differences in phase behavior (26) Sommer found $(-)\ R_3Si^*H$, $(+)\ R_3Si^*Cl$, and $(-)\ R_3Si^*F$ to have the same configuration. Thus reaction (a) proceeds with retention and reaction (b) with inversion. Optical rotary dispersion studies provided evidence that $(-)\ R_3Si^*F$, $(-)\ R_3Si^*H$, $(-)\ R_3Si^*OMe$, $(-)\ R_3Si^*OH$, $(-)\ R_3Si^*OAc$, and $(+)\ R_3Si^*Cl$ had the same configuration. Correlation of $(-)\ R_3Si^*OH$, $(-)\ R_3Si^*OMe$, $(-)\ R_3Si^*OAc$, and $(+)\ R_3Si^*OK$ was also obtained through reactions not involving the asymmetric central silicon atom. These correlations, together with the products of various reactions of $(-)\ R_3Si^*Cl$, such as reduction and solvolysis in solvents such as ether, pentane, and xylene, indicated that displacement reactions of this chlorosilane have common stereochemistry and proceed predominately with inversion of configuration. Reactions of the methoxy silane with lithium aluminum hydride showed predominant retention. It should be emphasized that stereo-specific results were obtained in media of low polarity. Thus racemisation of the Si-O bond occurs for the hydrolysis in acetone or methanol with acid or base present.

In a very interesting and useful reaction Sommer found that cleavage of $(+)\ R_3Si^*OSi^*R_3$ (VII) by solid KOH in xylene gave optically active potassium silanoate (VIII), which was found to retain its optical purity for long periods of time in xylene solution and in simultaneous contact with KOH. This rigorously proved retention to be the stereochemical path for the cleavage.



The optically active disiloxane VII was prepared from VIII and $(+)\ R_3Si^*Cl$, while the potassium silanoate (VIII) was prepared by the reaction of $(+)\ R_3Si^*OH$ with KOH. Nucleophilic displacements on R_3Si^*OCOR could follow two different paths, one with cleavage of the Si-O bond with inversion, and the other with cleavage of the O-COR bond, which would result in retention, since the asymmetric center would not be involved. Reactions of compounds with $R = -Me$, $-Ph$ or CH_2Cl with solid KOH in xylene, methanol in pentane, of lithium aluminum hydride in ether gave predominant inversion, showing that the Si-O bond is involved.

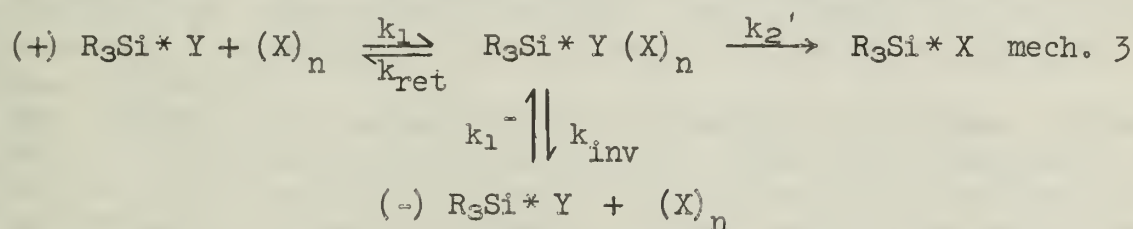
It is interesting to note the relationship between the stereospecific course of the reaction and the leaving group involved. If the leaving group is poor, such as H , $-OMe$ or $-OSi^*R$, where the conjugate acids of the leaving group have $pK > 10$, retention results. If the leaving group is good, such as $-Cl$ and $-OCOR$, with conjugate acids with $pK < 10$, inversion results. Displacement of poor leaving groups as in the case of R_3Si^*OMe , R_3Si^*H , and $R_3Si^*OSi^*R$ does not occur normally in carbon chemistry, so that Sommer postulated a mechanism for silicon not possible for carbon, namely that the reactions of these compounds proceed through a pentacovalent or hexacovalent silicon intermediate. If the entering and leaving groups formed an angle of 180° with the silicon atom in the trigonal bipyramid (IX) or a square pyramid (X) silicon intermediate inversion would result, while if the entering and leaving groups form an angle of 90° retention would result.

The results from having the entering or leaving groups at an angle of 120° in X, or for an hexacovalent intermediate cannot be determined a priori.

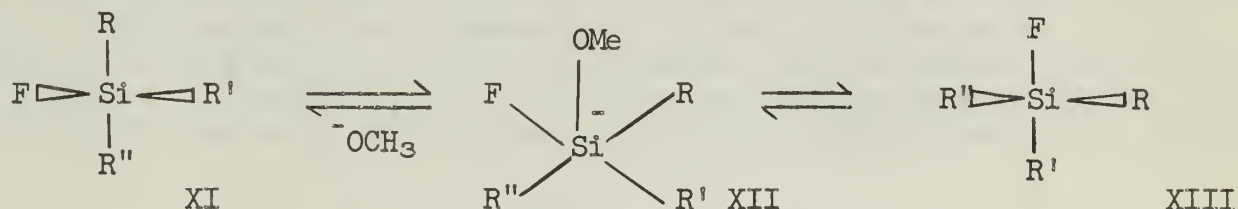


In the case of R_3Si^*Cl and R_3Si^*OCOR' Sommer postulated an S_N2 mechanism because of the prevailing inversion and the high capacity of the leaving groups to take up negative charge.

In a recent communication (27) Sommer and Rodewald investigated the racemization of R_3Si^*F by methanol in pentane and t-butyl alcohol. In all the racemizations carried out the product was pure racemic fluorosilane. Considering the high energy of the Si-F bond (ca. 130 kcal.) and the high electronegativity of fluorine the authors postulated mechanism 3 with $k_{inv} \sim k_{ret} \gg k_2$ to apply in this case:



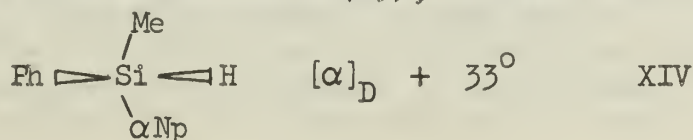
The racemization could not be due to fluoride-fluoride exchange since addition of hydrogen fluoride (7.5×10^{-4} M) retarded the rate of racemization by a factor of almost a thousand. The formation of ionic intermediates was likewise considered unlikely because of the high bond energy of the Si-F bond, the low dielectric constant of the solvents used, and because of the lack of stabilization upon addition of HF through the formation of the HF_2^- anion. Addition of optically active methoxy silane had no effect on the reaction. The authors proposed the following reaction path:



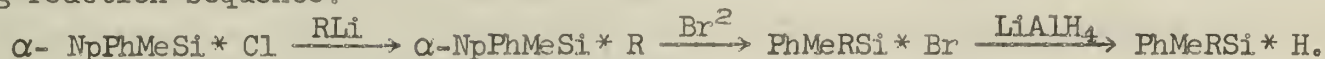
Addition of methoxide ion (from $\text{MeOH}_2^+ - \text{MeO}^-$) to the central silicon atom would give a pentacovalent silicon intermediate in the form of a square pyramid. As the methoxide group left either XI or XIII would result depending whether F and R', or R and R'' would move up to restore the tetrahedral structure. Retardation by HF could be explained by its acid action on methoxide to limit its availability. However the explanation given for the formation of the methoxide is somewhat questionable, due to the low polarity of the solvents involved in the reaction.

In investigating coupling reactions of R_3Si^*OMe , R_3Si^*Cl and R_3Si^*F with Grignard and organolithium compounds Sommer, Rodewald, and Parker (28) postulated inversion to be predominant in the case of the methoxy and chlorosilane. In the case of the fluorosilane, however, retention was postulated to occur predominately with three alkyl lithium reagents in ether and pentane, while inversion occurred predominately in the reaction with 9-fluorenyl lithium in benzene. The assignments in stereochemistry were made by preparing the same adducts from different starting materials of known stereochemistry and noting their rotations. Essentially, though, the assignment rests on postulated retention in the reaction of R_3Si^*H with $n-BuLi$.

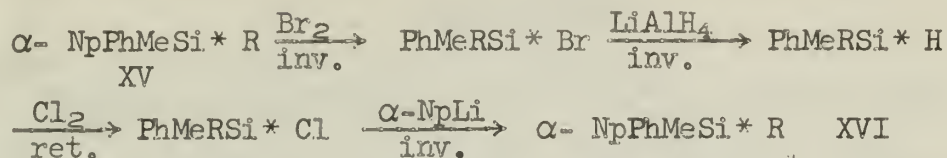
The absolute configuration for (+) $\text{R}_3\text{Si}^*\text{Cl}$, XIV, was first proposed by Brook and co-workers from chemical considerations (29), and was later confirmed by X-ray analysis (30).



Sommer and co-workers (31) have recently proposed a method of synthesizing other optically active compounds from α -naphthylphenylmethylsilyl compounds through the following reaction sequence:



This reaction was shown to be highly stereospecific by the cycle:

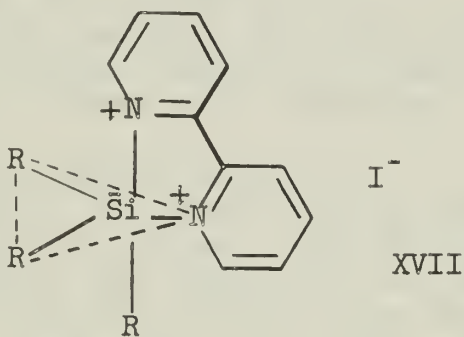


For R = neopentyl XV had $[\alpha]_D = 23.2^\circ$, while XVI had $[\alpha]_D = -18.6^\circ$.

Conclusions: The data obtained so far discount a S_N1 mechanism for the displacement reactions of organosilicon compounds. The evidence for it as forwarded by Sommer (20) is really inconclusive since the reaction on which he bases his evidence also involves elimination.

The evidence for a pentacovalent intermediate is stronger. Kinetic data such as the rates of hydrolysis of cyclosilanes lend support to intermediate formation, as well as the stereospecificity of reactions occurring with retention, as in the displacement of hydrogen by halogen in silanes. Other kinetic data exclude as S_N1 mechanism, but cannot distinguish between S_N2 and expanded octet mechanisms.

Further evidence for a pentacovalent intermediate is provided by the recent announcement by Corey and West (32) of the preparation of a chelate stabilized 'siliconium ion' from the interaction of triphenylsilyliodide and 2,2'-bipyridine. The compound was isolated as a pale yellow solid. Ultraviolet absorption gave maxima at 245 and 305 m μ , characteristic of the bipyridyl moiety where the nitrogen atoms are cis to each other. The IR contained no bands attributable to OH and NH, and comparative studies showed that it was free from the two most probable hydrolysis products, 2-(2'-pyridyl)pyridinium iodide and hexaphenyldisiloxane. On the basis of this, a structure (XVII) was proposed for the ion in solution. At the time of publication it was not known whether the solid existed as XVII or as a hexacoordinate species $\text{Ph}_3\text{Si}(\text{bipy})\text{I}$. However the naming of XVII by the authors as a 'siliconium ion' is misleading,



since the central silicon atom really has negative formal charge. In this respect it is then similar to the proposed pentacovalent intermediates, which also have negatively charged silicon.

While no evidence excluding the occurrence of a hexacovalent silicon intermediate has been produced, its formation seems unlikely in view of the stereospecificity of some reactions and the steric problems involved.

The evidence for an S_N2 mechanism, somewhat modified, is also good, but no unequivocal distinction from a mechanism going through a pentacovalent intermediate can be made, so that the evidence is somewhat circumstantial.

The investigations carried out so far can hardly be considered to give us rules for the behavior of organosilicon compounds in displacement reactions. The problem is that the kinetic investigations have been carried out under so many different condi-

tions, especially with regards to experimental technique and handling of results, and that stereochemical investigations have given us information only regarding compounds containing the α -naphthylphenylmethyl group.

Only further work will provide rules as efficient for displacement reactions on silicon as the ones available now for carbon.

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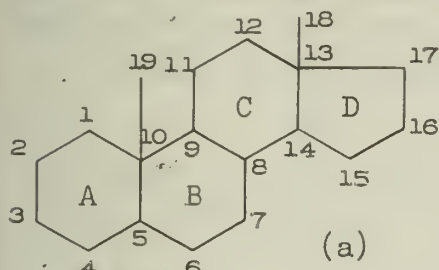
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INTRAMOLECULAR ATTACK AT C-19 OF STEROIDS BY A NEIGHBORING OXYGEN FUNCTION

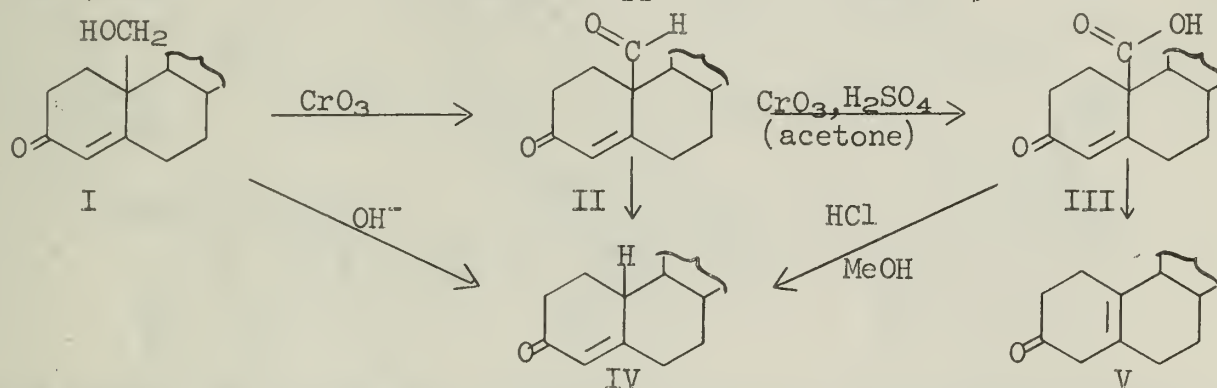
Reported by Elizabeth McLeister

April 13, 1964

Introduction: Recently a great deal of work has been devoted to the preparation of steroids in which the 19-carbon, present in most naturally-occurring steroids (a), contains an oxygen function. Much of the interest in such compounds is based upon their ability to be converted to 19-norsteroids, in which C-19 (the angular methyl group at C-10) is absent. These compounds, which are of interest particularly for their properties as oral contraceptives (1), can be prepared from 19-hydroxy steroids (I) in low yields by base-catalyzed elimination of formaldehyde (2,3). Yields are greatly improved if the 19-hydroxy compound is first oxidized to the aldehyde (II), then treated with base. The corresponding carboxylic acid (III) gives excellent yields of the 19-nor compound, giving (IV) upon treatment with methanolic HCl, or (V) upon heating with pyridine (4).

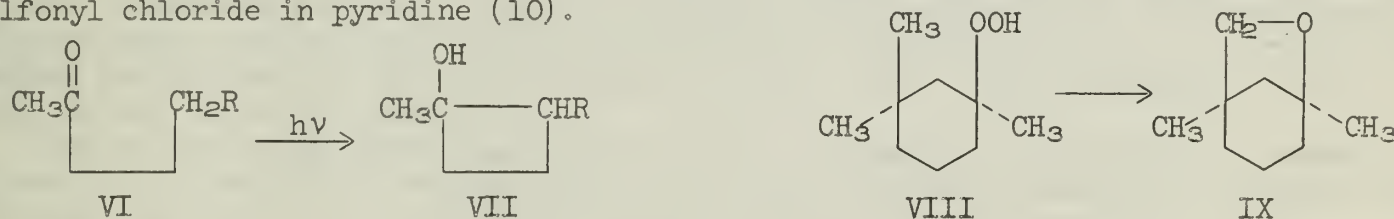


Because of the quaternary nature of the C-10 position, however, standard synthetic methods involving attack at saturated carbon atoms activated by neighboring carbonyl functions or double bonds are not applicable at the C-19 position. Aside from



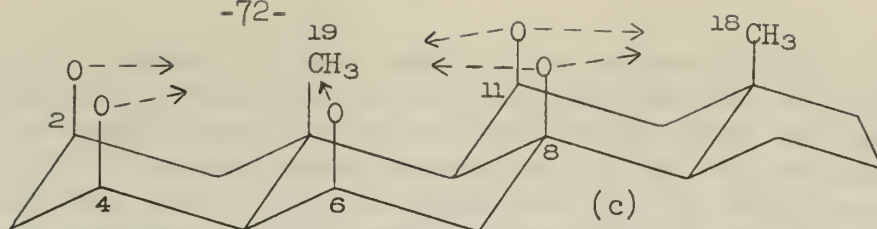
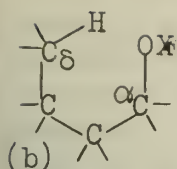
total synthesis (5), most 19-norsteroids have thus been prepared by Birch reduction of steroids with aromatic A rings (6), or by treatment as above of the few 19-hydroxy steroids which occur naturally (7) or which can be obtained by biological methods (3,8).

Recently, however, methods have been developed which permit selective intramolecular attack at a non-activated carbon atom by a neighboring oxygen function. Early reports of this type of reaction describe the formation of cyclobutanol derivatives (VII) by the photolysis of aliphatic ketones (VI) (9), and the formation of the bicyclic ether (IX) from the hydroperoxide VIII upon treatment with p-nitrobenzenesulfonyl chloride in pyridine (10).



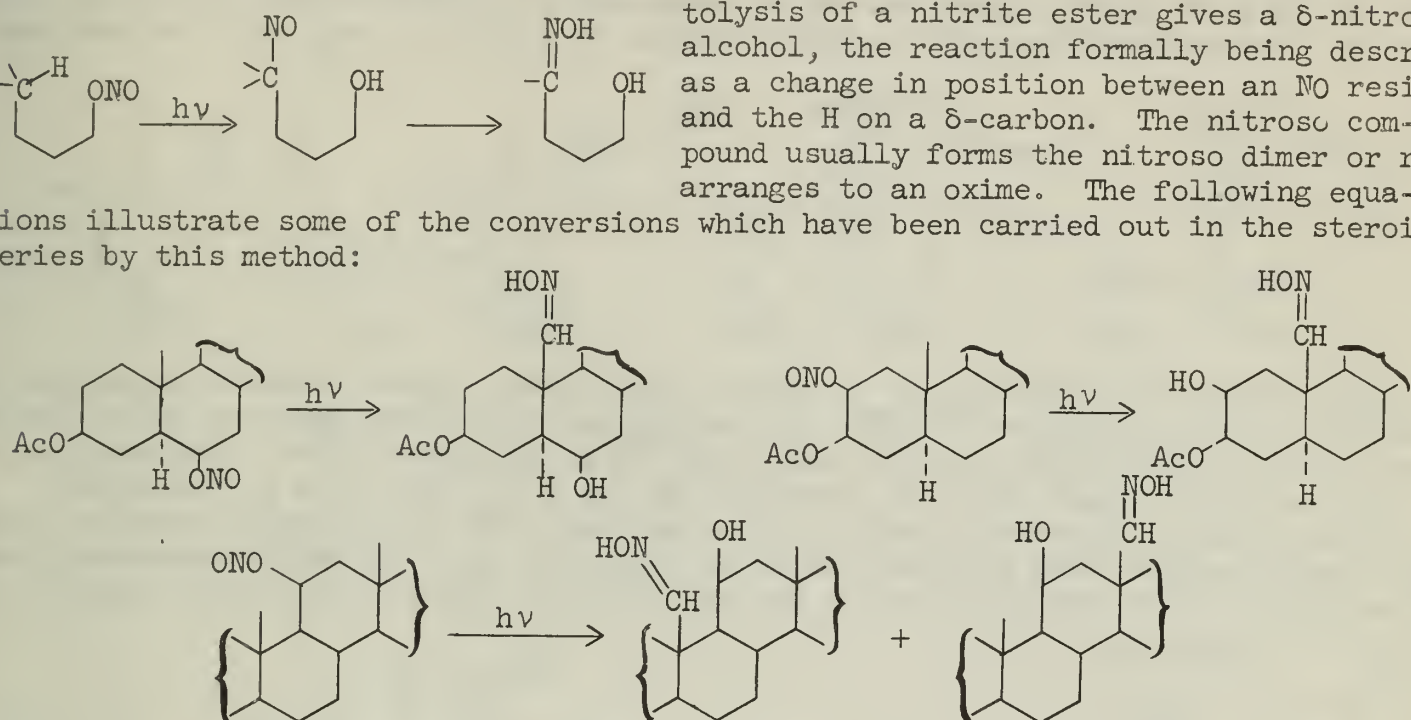
Methods which have been used to effect attack at C-19 of steroids, and which will be discussed in this abstract, include the photolysis of nitrite esters and of hypochlorites, lead tetraacetate oxidation of steroid alcohols, photolysis of "hypoiodites" (a modification of the $\text{Pb}(\text{OAc})_4$ reaction), and the photolysis of 11-keto steroids. The application of similar reactions to the synthesis of steroids containing oxygen functions at C-18 has already been reviewed (11).

Each of the above-mentioned methods, except the photolysis of ketones, involves selective attack at a carbon atom δ to the oxygen function, suitably situated so as to permit a quasi six-membered cyclic intermediate (b). (Throughout this abstract, the carbon atom bearing the oxygen will be designated as the α -carbon.) From consideration of the steric relationships in the steroid framework (c), it is evident that such intramolecular attack might occur from oxygen functions at the 2β -, 4β -, 6β -, 8β -, and 11β - positions of 5α -steroids, the 8β - and 11β - positions being



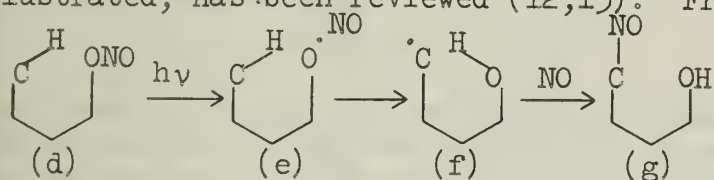
expected to attack both C-19 and C-18, and from 6 β -, 8 β -, and 11 β - of the 5 β - series. Such reactions have been reported for all but the 8 β - oxygenated steroids.

Nitrite Ester Photolysis: In the conversion known as the Barton reaction, photolysis of a nitrite ester gives a δ -nitroso alcohol, the reaction formally being described as a change in position between an NO residue and the H on a δ -carbon. The nitroso compound usually forms the nitroso dimer or rearranges to an oxime. The following equations illustrate some of the conversions which have been carried out in the steroid series by this method:



The C-19 oximes thus formed can easily be converted to the 19-norsteroids.

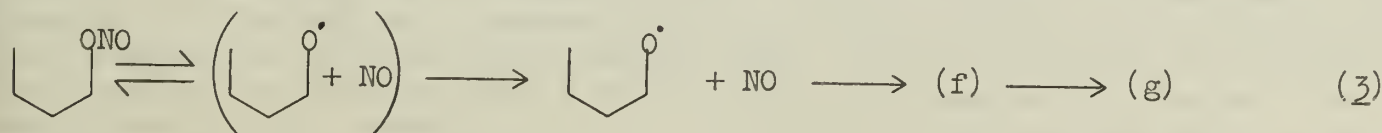
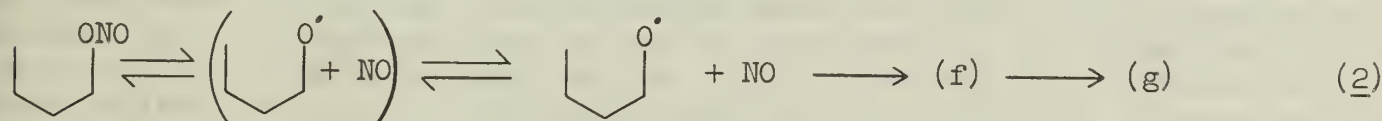
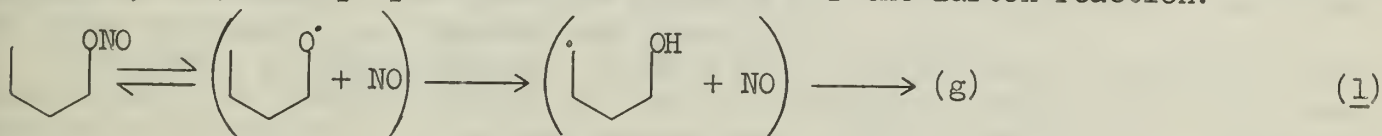
Most of the earlier work on the Barton reaction, including the reactions just illustrated, has been reviewed (12,13). From observations based upon these and other



transformations, the following general mechanism has been proposed: The O-NO bond of the nitrite ester (d) is cleaved photochemically to give NO and an alkoxy radical (e) which then, undergoing one of the common reactions of alkoxy radicals (14), ab-

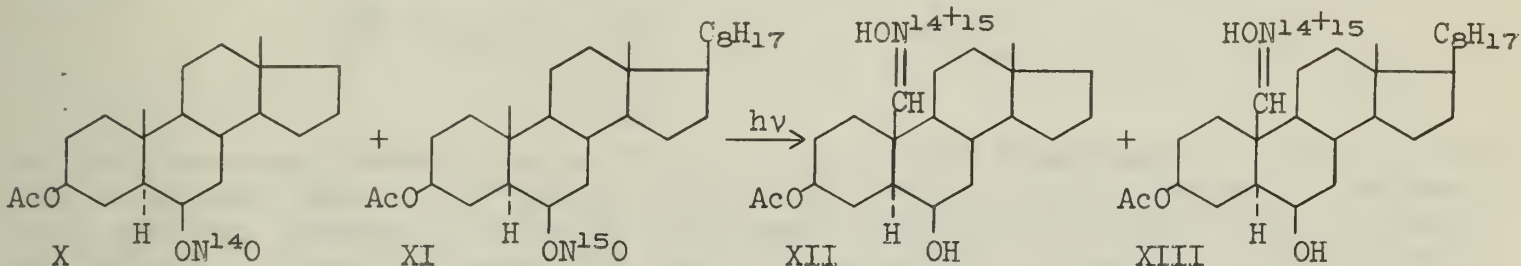
stracts a hydrogen from the δ -carbon to give an alkyl radical (f), which subsequently reunites with an NO molecule to give the observed δ -nitroso alcohol (g). It has been assumed on the basis of the low quantum yield ($\Phi = 0.25$) that the reaction does not occur by way of a chain process.

Akhtar and Pechet have suggested that the low quantum yield might be caused by a reversible decomposition-recombination of the type $d \rightleftharpoons e$; in accord with such an hypothesis, they have proposed three mechanisms for the Barton reaction:



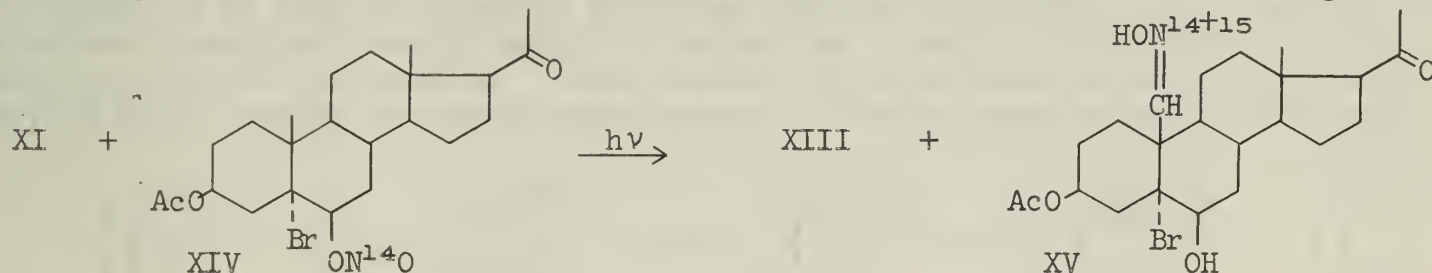
In the first scheme, the NO and alkoxy radical remain in a solvent "cage" during the reversible $d \rightleftharpoons e$ step and until the combination of alkyl radical and NO to give the product; thus, the NO residue would remain in the molecule from which it originated. In the second pathway, the $d \rightleftharpoons e$ recombination could occur after the two species were completely separated. An extreme case of (2) is mechanism (3), in which recombination from the free alkoxy radical is negligible so that reversible recombination occurs only between the nitrite ester and a radical cage, which subsequently separates while going to the product.

Photolysis of a 1:1 mixture of two 6β -nitrite esters, one in the androstane series with N^{14} in its -ONO residue (X), the other in the cholestane series with N^{15} in its -ONO residue (XI), gave a mixture of oximino alcohols XII and XIII obtained from the



corresponding nitroso dimers. Mass spectrometry of the keto-nitriles formed by CrO_3 oxidation of the oximino alcohols showed that the N^{15}/N^{14} ratios for the two products were comparable. Such scrambling of N^{15} indicates that the sequence (1) does not occur.

Photolysis of a mixture of XI and XIV for half the usual reaction time showed that, although scrambling of N^{15} occurred in the over-all reaction as indicated by mass spectrometric study of the keto-nitrile of the isolated pure oximino alcohol XIII, no exchange of N^{15} had occurred in the recovered starting nitrite XI. Although such



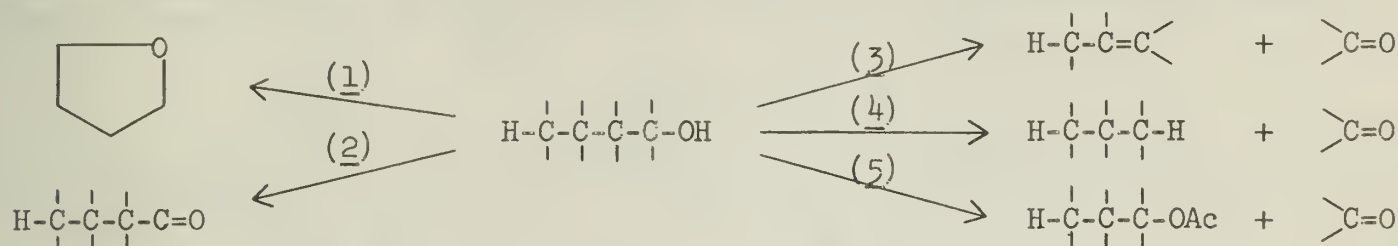
data are in accord with mechanism (3) rather than (2), there is no evidence that the unreacted nitrite XI ever dissociated at all; a low quantum yield need not be caused by recombination of NO with alkoxy radical but could be explained in other ways.

Upon photolysis of N^{15} -nitrite XI with an eight-fold excess of N^{14} -*t*-butyl nitrite, however, the formation of XIII is inhibited and 60% of XI can be recovered, having an N^{15}/N^{14} ratio of 1.0/3.45. Under such "forcing" conditions, in which photolysis of *t*-butyl nitrite is believed to give rise to an excess of NO, recombination $e \rightarrow d$ apparently becomes important (equation 2); however, photolysis of XI with NO itself would have been more indicative, eliminating the possibility of any unknown reaction with *t*-butyl nitrite. In fact, since no controls were reported for any of these tracer studies to determine if the products exchange N^{15} under the reaction conditions, all of these conclusions are somewhat ambiguous (15).

Photolysis of Hypochlorites: Studies with tertiary alkyl hypochlorites have shown that, upon thermal, photolytic, or free-radical initiation, the O-Cl bond is cleaved homolytically to an alkoxy radical and a chlorine atom (16). The alkoxy radical thus formed can undergo three competing chain reactions: (1) fragmentation or β -scission to give a carbonyl compound and an alkyl radical, (2) intramolecular H abstraction, resulting in an alkyl radical, or (3) intermolecular H abstraction from either solvent or a second hypochlorite molecule. The first two of these reactions generally predominate. When intramolecular H abstraction occurs, resulting in the formation of chloroalcohols, removal of the H on the δ -carbon is the preferred reaction; abstraction of H from the ϵ -carbon occurs less than one-tenth as frequently, as determined by the relative amounts of 1,4- and 1,5-chloroalcohols obtained from long-chain hypochlorites. Ease of such intramolecular H abstraction decreases in the order

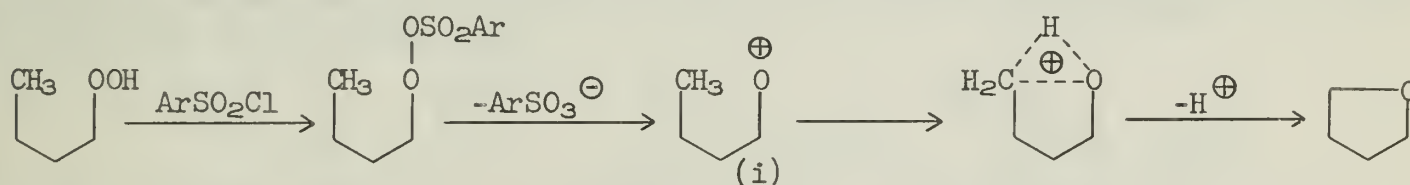
reactions of steroidal alcohols with $\text{Pb}(\text{OAc})_4$ describes the various cyclic products which have been reported (22). The analogous oxidation of long-chain aliphatic alcohols has been reported to give tetrahydrofuran derivatives in yields as great as 50%, with minor amounts of six-membered cyclic ethers also being formed (23,24).

The ketone corresponding to the starting alcohol is a major side-product of $\text{Pb}(\text{OAc})_4$ oxidation, the yield of ketone increasing with the inability of the alcohol to form cyclic derivatives for steric reasons. As cyclic ether formation becomes less favored, ketone formation is often accompanied by fragmentation reactions of types (3), (4), and (5), which can be of preparative significance in some systems (25).

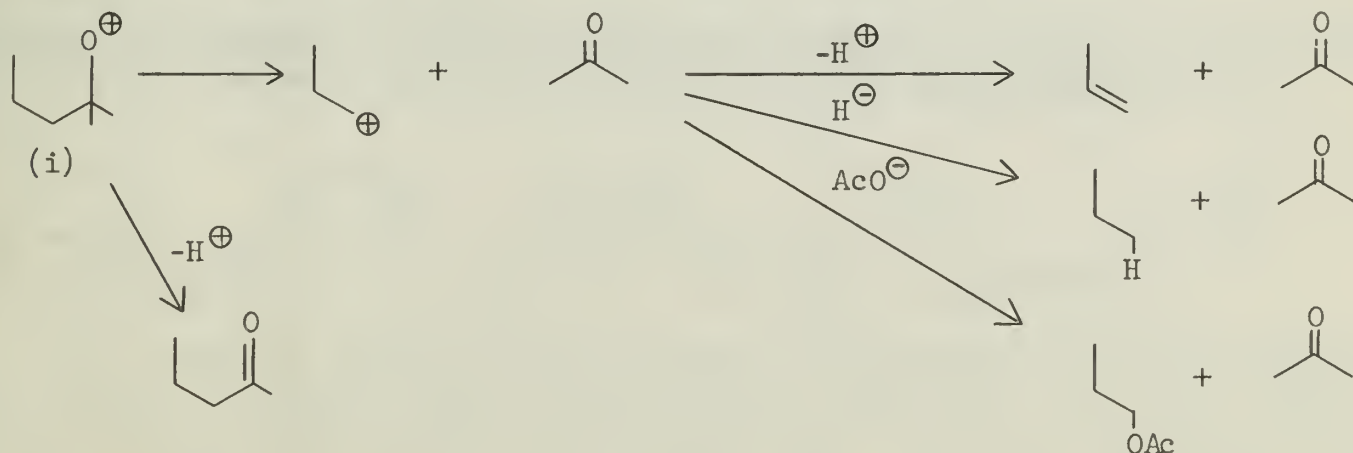


Both free-radical and ionic processes are believed to be important in $\text{Pb}(\text{OAc})_4$ oxidations, the mechanism varying with reaction conditions and with the nature of the substrate. $\text{Pb}(\text{OAc})_4$ is reduced to $\text{Pb}(\text{OAc})_2$ and two acetate residues, the nature of the latter also varying with the reaction. It has been proposed that the initial reaction of $\text{Pb}(\text{OAc})_4$ with an alcohol is the formation of a lead alkoxylate (h), which can decompose either heterolytically to a "cationic oxygen" intermediate (i) or homolytically to an alkoxy radical (j) (26). The formation of all five types of products originating from $\text{Pb}(\text{OAc})_4$ oxidation of monohydroxy alcohols can be rationalized by both ionic and radical processes:

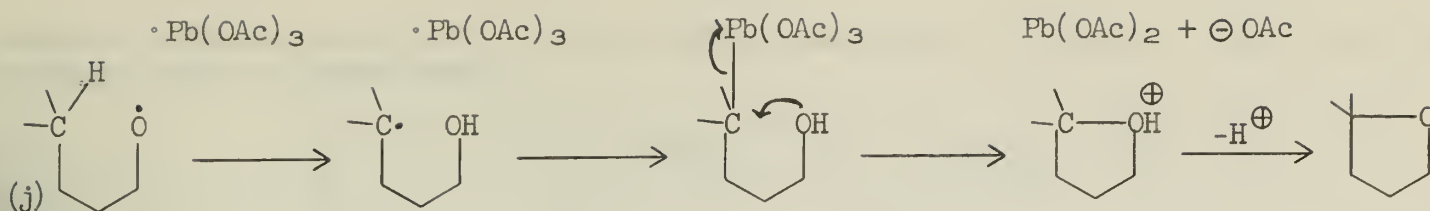
Corey, has proposed that a "cationic oxygen" intermediate participates in the formation of the bicyclic ether IX from the hydroperoxide VIII, with the assumption that an arylsulfonate intermediate would decompose heterolytically (10):



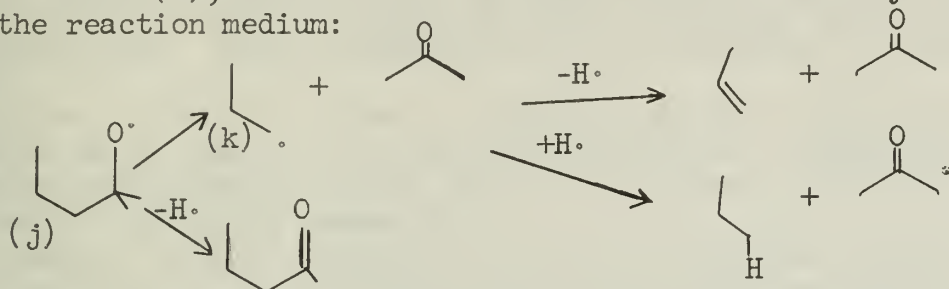
A cationic oxygen intermediate (i) formed from decomposition of a lead alkoxylate might form the cyclic ether in an analogous manner. Such an intermediate (i) could also give the other products as follows:



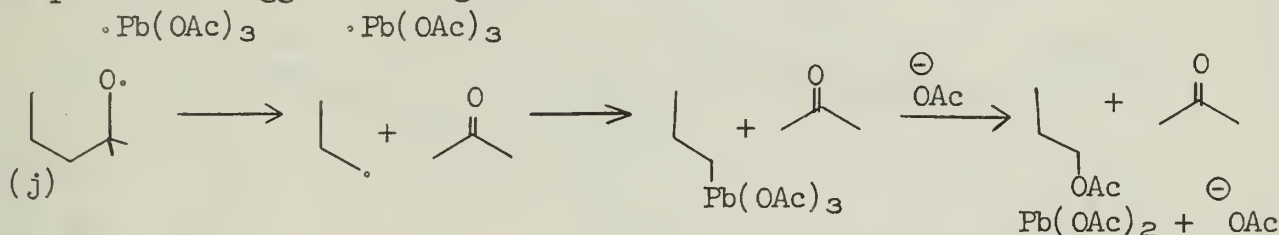
Cyclic ether formation is difficult to explain by a free-radical mechanism; a possible rationalization might be as follows:



Loss of a hydrogen atom from (j) could explain ketone formation. Fragmentation products (3) and (4) could originate by cleavage of (j) to a carbonyl compound and an alkyl radical (k); the latter could then either lose a hydrogen atom or abstract one from the reaction medium:

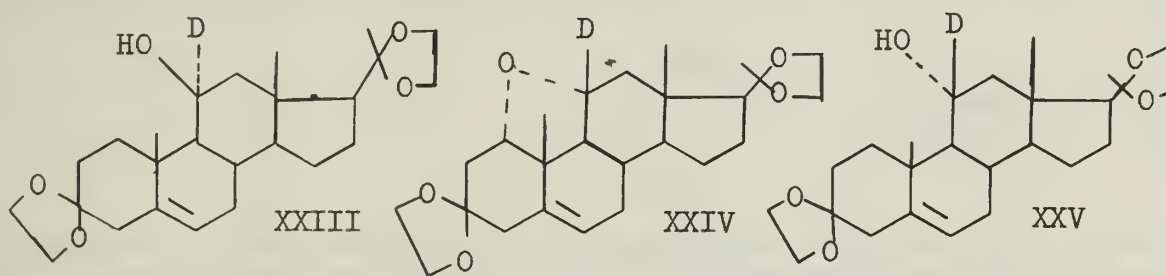


The probability of (k)'s reacting with an acetoxy radical to form the fragmentation product (5) is unlikely, since $\text{CH}_3\text{COO}^\bullet$ would be expected to decompose to CO_2 and $^\bullet\text{CH}_3$. A plausible suggestion might be as follows:

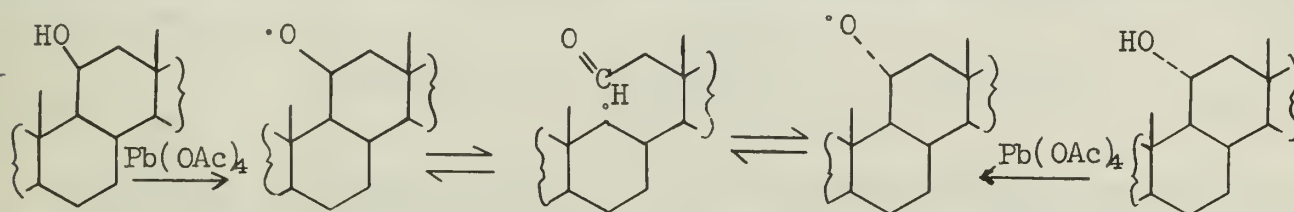


There is no evidence, however, by which one can distinguish whether radical or ionic processes are involved.

Epimerization of the reaction center has been observed in several steroid alcohol oxidations (27-29). One example of this is the formation of the $1\alpha,11\alpha$ -oxido compound XXIV from $\text{Pb}(\text{OAc})_4$ oxidation of either 11β -alcohol XXIII or 11α -alcohol XXV. When the deuterated derivatives were oxidized, the $1\alpha,11\alpha$ ether exhibited complete retention of D at C-11 in both cases (27).

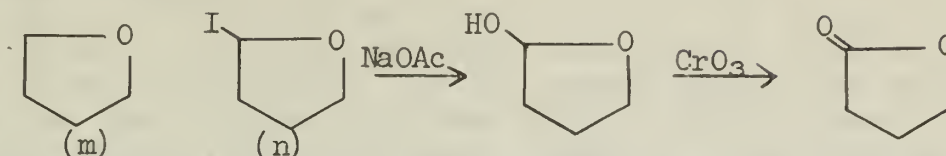


Wettstein has proposed a cleavage-recombination mechanism to account for such observations; such a process could also take place via ionic intermediates: (28)



In an attempt to study the species formed upon decomposition of the postulated lead alkoxyate, Wettstein and co-workers tried to use iodine as a radical "trapping" agent. Various steroid alcohols were combined with $\text{Pb}(\text{OAc})_4$ and I_2 in cyclohexane or CCl_4 , refluxed, and irradiated with visible light. Following oxidation of the crude reaction mixture, two types of products were isolated: (1) five-membered cyclic ethers (m) of the type obtained with $\text{Pb}(\text{OAc})_4$ alone, and (2) γ -lactones, pre-

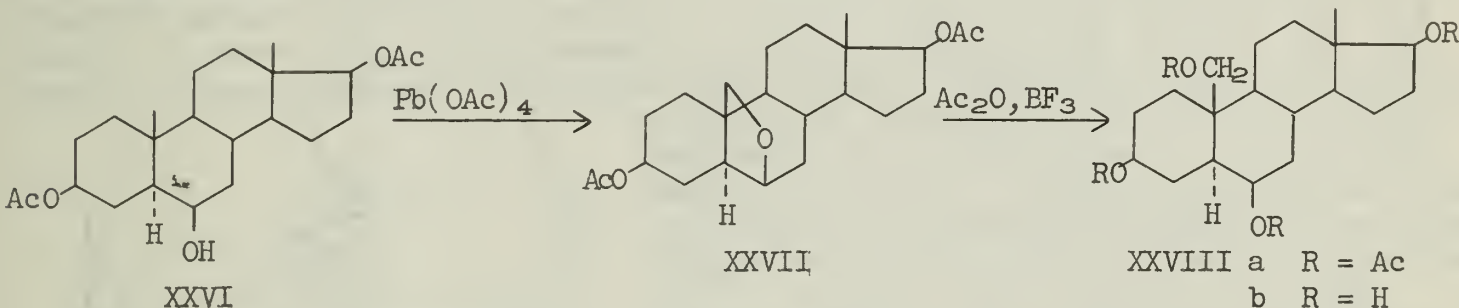
sumably formed by oxidation of iodine-containing ethers of type (n), which could also be hydrolyzed to hemiacetals:



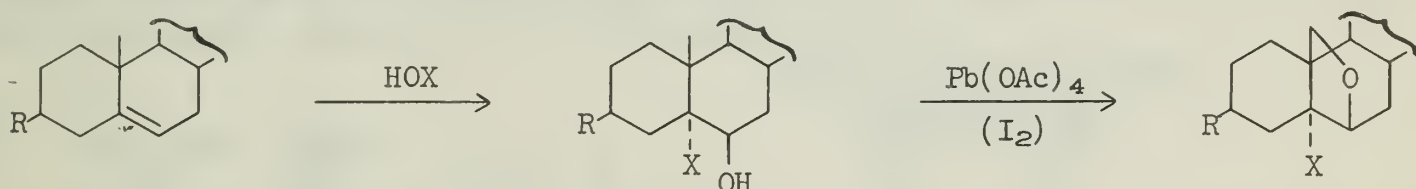
To account for such products, Wettstein has proposed that the -OH group reacts with $\text{Pb}(\text{OAc})_4$ and I_2 to give a hypoiodite which is then cleaved photolytically, leading to the products (m) and (n); there is little evidence, however, for the existence of such an intermediate. These transformations are discussed in several recent reviews (22, 30, 31).

Attack at C-19 by $\text{Pb}(\text{OAc})_4$ oxidation and the "hypoiodite" reaction has been reported to occur from 2 β - (32-34), 4 β - (28, 34), 6 β - (29, 35-42), and 11 β - (28, 43) hydroxy steroids. These methods provide an effective route to the 19-oxygenated steroids and thus to the 19-nor compounds.

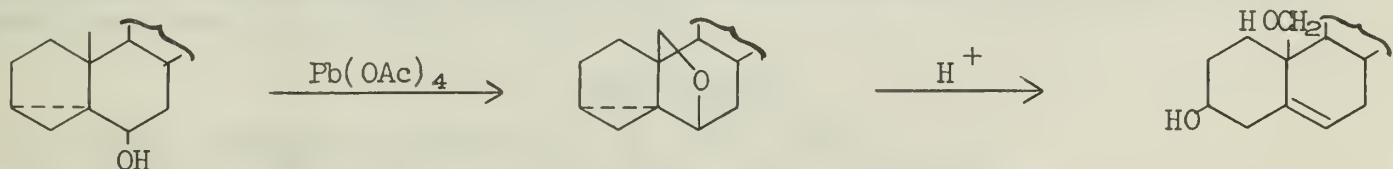
Treatment of the 6 β -hydroxy-5 α -steroid XXVI with $\text{Pb}(\text{OAc})_4$ to form the 6 β ,19-ether XXVII, followed by ring opening with acetic anhydride containing BF_3 -etherate, gives the tetraacetate XXVIIIa, which can be hydrolyzed to the corresponding tetrahydroxy compound XXVIIIb (35, 36).



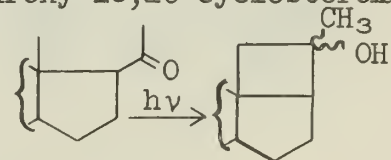
Addition of HOCl or HOBr to Δ^5 -steroids gives the corresponding 5 α -halo-6 β -hydroxy compounds, which form the 5 α -halo-6 β ,19-oxido compounds upon treatment with $\text{Pb}(\text{OAc})_4$ or $\text{Pb}(\text{OAc})_4$ and I_2 . The 5 α -halo-6 β ,19-ethers, however, are stable to basic and acidic hydrolysis and can be opened directly (without prior oxidation to the γ -lactone) only by reductive cleavage methods, using Zn and HOAc or Li and liquid NH_3 , to give 19-hydroxy- Δ^4 - or Δ^5 -steroids (38-41).



One route to the preparation of 19-oxygenated steroids which leaves intact the 3 α -OH- Δ^5 function involves the use of 6 β -OH-3 α ,5 α -cyclosteroids, or the i-steroids; these compounds are known to rearrange to 3 α -OH- Δ^5 -compounds upon acid hydrolysis. The following transformations have been reported using these compounds (44-47):



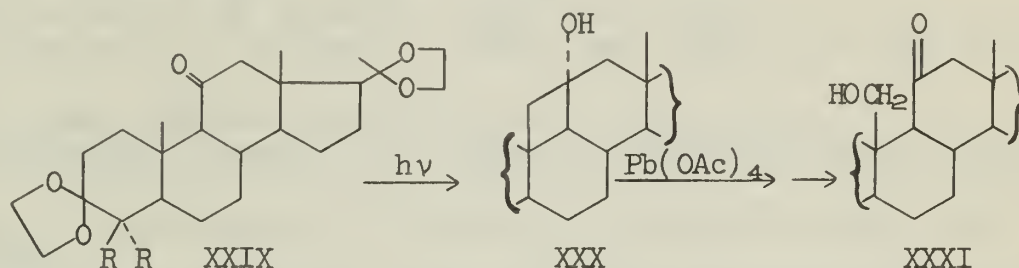
Photolysis of 11-Keto Steroids: Jeger and co-workers have reported that the photolysis of 20-keto steroids leads to the formation of 20-hydroxy-18,20-cyclosteroids (48). Such a reaction is analogous to the formation of cyclobutanol derivatives from aliphatic methyl ketones, mentioned previously in this abstract (9). Similar results have been obtained in studies carried out on 11-keto steroids by Jeger and his group:



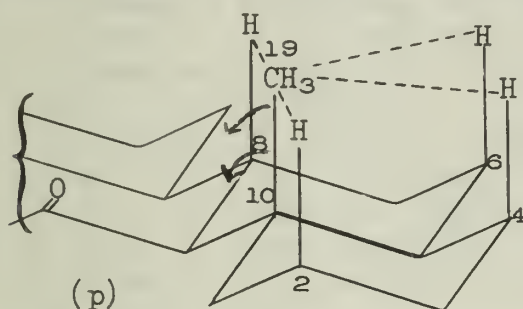
Upon UV irradiation in ethanolic solution, the 11-keto-5 α steroid XXIXa gave an alcohol isomeric with the original ketone. Chemical evidence and NMR indicated that

the new compound, isolated in 38% yield, was a tertiary alcohol; NMR further showed that there was only one angular methyl group, indicating that attack had occurred at C-18 or C-19. To determine which methyl group was involved, the photolysis product was treated with $\text{Pb}(\text{OAc})_4$ in benzene, giving a fragmentation product subsequently identified as the keto-alcohol XXXIa. (It was assumed that the actual product of the $\text{Pb}(\text{OAc})_4$ reaction was the 19-acetate and that XXXIa originated upon hydrolysis during work-up.) From the structure of the cleavage product, from subsequent chemical transformations, and by a study of steric relationships possible at C-11 and C-19, the structure XXXa was assigned to the photolysis product. The reaction sequence XXIX \rightarrow XXX \rightarrow XXXI illustrates another method for preparing C-19 oxygenated steroids (49).

- a) 5α , R = H
- b) Δ^5 , R = H
- c) 5β , R = H
- d) 5α , R = CH_3
- e) Δ^5 , R = CH_3



Under similar reaction conditions, photolysis of the Δ^5 compound XXIXb gave a 24% yield of product identified as XXXb; the 5β analog XXIXc formed XXXc in only 1.5% yield. To account for the dependence of yields of photoproduct upon the A/B ring junction, Jeger proposed a transition state in which C-19, C-10, C-9, and C-11 approach



planarity by deformation of the A and B rings, (assumed to be in chair form). It was further suggested that such a deformation might be aided by relief of 1,3-diaxial interactions between the angular methyl group and the axial (β) hydrogens at C-8, C-6, C-4, and C-2 in the 5α -series, Fig. (p), at C-8, C-4, and C-2 in the Δ^5 -series, and at only C-8 and C-6 in 5β -steroids (50).

If such relief of steric interactions is responsible for the variation of yields with conformation at C-5, the presence of bulky substituents in positions 1,3-diaxial to C-19 would be expected to increase the yield of photoproduct. UV irradiation of the 4,4-dimethyl compounds XXIXd and XXIXe under conditions identical with those used with the unsubstituted compounds gave the following results:

Reactant	Product		Percent yield of product	
			Photolysis time	
			12 hr	24 hr
XXIXb	XXXb	Δ^5 , R = H	25	30
XXIXe	XXXe	Δ^5 , R = CH_3	41	51
XXIXa	XXXa	5α , R = H	27	40
XXIXd	XXXd	5α , R = CH_3	48	65

These results are not inconsistent with the hypothesis that CH_3 -19 approaches a planar four-centered transition state (51).

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Reported by J. Miesel

April 16, 1964

Introduction: In recent years nuclear magnetic resonance spectroscopy, nmr, has become a tool of extraordinary importance for the organic chemist. Although the chemical shift of a proton from a reference peak and its correlation to structural features has had the widest utility in organic chemistry, the study of spin-spin splitting patterns and their coupling constants is becoming more important. Several books deal with the subject of nmr in general (1,2,3). Recently attempts have been made to relate theoretically and empirically the magnitude of the coupling constant, J , to structural features. Two reviews on some aspects of this problem are available (4,5). For the purposes of simplicity only short-range proton coupling constants will be discussed here.

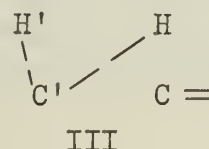
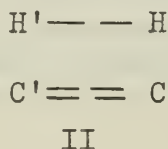
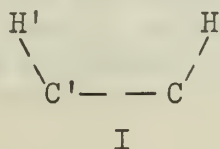
Theoretical Background: Spin-spin splitting is used to describe the fine structure of the principal groups of proton resonance lines. It is attributed to increments in the total magnetic field produced at the absorbing nucleus by the magnetic moments of the neighboring nuclei. The effective magnetic field at the absorbing nucleus will therefore have different values depending on the magnetic quantum numbers, $+1/2$ or $-1/2$, of an adjacent proton. The absorbing proton will then show resonance at two values of external applied field. The magnitude of this splitting, J , usually in cycles per second (cps), is the coupling constant.

In recent years, several attempts have been made to use the methods of quantum mechanics to describe this phenomenon theoretically and predict the coupling constants for various types of molecules. In 1953, Ramsey (6) derived a general expression for $J_{NN'}$ (N and N' are the interacting nuclei) and used it to predict the coupling constant for the HD molecule. By using a second order energy perturbation calculation, he determined the term which contributed almost all the energy change due to nuclear spins described the magnetic interaction of the nuclei with electron spins which then interact. This is described as the "contact integral". The energy of interaction, $E_{NN'}$, could be calculated from this expression if a constant, the difference in energy between the ground state and the first excited state of the system (ΔE), and the ground-state wavefunction of the system, ψ_0 , are known; all other terms in the expression were known from studies of the nuclei. Since $E_{NN'} = h J_{NN'} I_N I_{N'}$, the coupling constant between the two nuclei can be calculated. I_N is the spin of nucleus N in units of \hbar . Using these expressions, Ramsey obtained a value of $J=40$ cps for the HD molecule; the observed coupling constant is 43.5 cps.

Following this success two groups employed the Ramsey expression to calculate coupling constants between protons not directly bonded to each other. The problem in these calculations lies in the determination of a proper ground-state wavefunction in many-electron systems.

McConnell (7) first attempted such a calculation using molecular-orbital theory to determine the wavefunctions. Using this type of wavefunction in the Ramsey expression, he obtained a value of $J=200 \eta^2$ cps. The term η can be calculated from the constants used in forming the MO wavefunction and can be described as formally similar to a proton-proton bond order. In H_2 with $\eta=1$, $J=200$ cps versus an observed value of about 280 cps. But in methane a similar calculation gives $J_{HH'}=3.0$ cps although the observed value is 12.4 cps. However the author noted that the MO form of calculation does not allow for configurational interactions which might be quantitatively important.

The most important contributions to this field have been made by Karplus and his coworkers in their studies using valence bond theory (8,9,10). Valence bond theory seemed particularly useful in this type of calculation since it pictures bonds being formed by the pairing of electrons, offering a mechanism for electron spin interactions between protons not directly bonded. Using an $HCC'H'$ fragment, there is one perfect paired structure I with valence bonds between "chemically bonded" pairs of atoms and various non-perfect paired structures such as II and III. The ground-state wave-



function ψ_0 necessary to solve the Ramsey formulation is given by the equation $\psi_0 = \sum_i c_i \psi_i$ where ψ_i are the wavefunctions for the nonionic valence bond structure like I, II, and III and c_i are constants. To simplify the calculation Karplus (9) assumed that in considering H-H coupling constants only the perfect paired structure I and the non-perfect paired structures with an H-H' valence bond make significant contributions. Since coupling is mediated by electron spin interaction, the contribution of such structures as II is necessary for coupling between H and H'. He also assumed that "structures" with more "broken chemical bonds" than II would not contribute significantly to ψ_0 . Karplus and Anderson then used such a treatment with the Ramsey expression in the case of methane (8). Using sp^3 hybridized carbon electrons and hydrogen 1s electrons, they obtained a value for J of $113/\Delta E_{cps}$ where ΔE is the average singlet-triplet excitation energy for the system. From calculations on CH_2 Karplus assigned a value of 9.0 ev to this quantity. The theoretical coupling constant of 12.5 cps agrees well with the observed value of 12.4 ± 0.6 cps.

Karplus extended this work to the HCCH fragment (9). The integrals describing bonding between hydrogen and carbon orbitals were expressed as functions of the HCC angle; all other integrals were expressed as functions of the dihedral angle ϕ (Fig. 1). Solving the ground-state wavefunction for values of dihedral angle between 0° and 180° and using a value for ΔE of 9.0 ev, Karplus found values for J_{HH} which were approximately fitted by a $\cos^2\phi$ curve. The approximate solution for this curve is the common expression of the Karplus rule for coupling constants of vicinal protons:

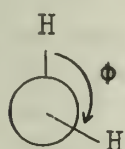


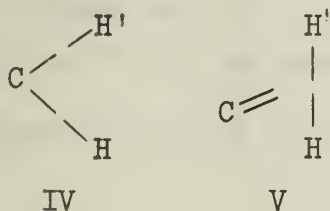
Fig. 1

$$J_{HH} = 8.5 \cos^2\phi - 0.28 \text{ cps} \quad 0^\circ \leq \phi \leq 90^\circ$$

$$J_{HH} = 9.5 \cos^2\phi - 0.28 \text{ cps} \quad 90^\circ \leq \phi \leq 180^\circ$$

It must be remembered that these expressions are only convenient approximations of the theoretical curve and do not arise from the theoretical calculation itself. To determine this relationship the following approximations were made: Ramsey's approximation that only the contact integral contributes significantly to the coupling constant calculation; the electron density at the hydrogen nuclei can be obtained from free 1s electron functions; the carbon orbitals are sp^3 hybridized and the carbon-carbon bond length is 1.54 \AA ; the structures used to calculate ψ_0 can be limited to those selected; and ΔE is equal to 9.0 ev. Calculations for ethylene showed $J = 6.1$ cps at $\phi = 0^\circ$ and $J = 11.9$ cps at 180° giving changes of more than 2 cps in changing the carbon hybridization and bond length. Gutowsky and Porte (11) later showed that increasing the HCC bond angle reduced the theoretical coupling.

Gutowsky, Karplus and Grant (10) used the same method of calculation in the $XYCH_2$ system to calculate geminal coupling constants. The valence bond structures considered



here were IV and V with $\psi_0 = \psi_{IV} + c \psi_V$. Calculating J versus the HCH angle, θ , they obtained values of J from 32.3 cps at $\theta = 100^\circ$ to 0 cps at $\theta = 125^\circ$ and negative values at higher angles. The authors pointed out that interpretation of small coupling constants, those near the sign change, would be unreliable since the calculation depends on small differences between large numbers. The same approximations which were made in the previous calculation

were also used here. However errors in these approximations might be more significant due to the large change in coupling constant for a small change in θ .

Several authors have since offered comments on the validity of the Ramsey-Karplus method. In 1960, McLachlan (12) noted that the mathematics used in obtaining the second order perturbation energy corrections involves a procedure which could lead to false conclusions, even predicting the wrong sign for the perturbation. He particularly noted that the Karplus calculations fall in this category. In 1961, Alexander (13) recalculated in detail spin-spin interactions using valence bond theory. He justified the mathematics of the Ramsey calculation and showed that only perturbations of the type considered by Karplus and his coworkers are important in the cases which

they discussed. Karplus has recently commented critically on the approximations in the calculation of vicinal coupling constants (14). He pointed out that vicinal coupling constants are not expected to depend only on the dihedral angle between the protons. Introduction of substituents of varying electronegativity on the HCCH fragment is expected to have an effect on the coupling constant by causing changes in the hybridization of the carbon atoms as well as by a "direct" inductive effect on the polarity of the C-H bonds which would affect the electron distribution about the hydrogen nuclei. He reemphasized the point that the HCC angle is also a variable in the calculation and pointed out that for constant bond angles and hybridization, carbon-carbon bond length will affect vicinal coupling constants. Ranft has also discussed theoretically the "direct" inductive effects of substituents. He proposed that such effects could be predicted by calculating the ground-state wavefunctions including "ionic" valence bond structures. The contribution of these ionic terms to ψ_0 is limited by a coefficient I_c . This coefficient is related to the difference in electronegativity between hydrogen and the substituent. Inclusion of such terms may lower the theoretical coupling constant up to 2 cps for very electronegative substituents. This is viewed qualitatively as a more electronegative substituent pulling the electron cloud closer to carbon; since there is then a lower electron density around the hydrogen nucleus, the interaction of electron spins and therefore the coupling constant will be lower.

Additional calculations have been performed to calculate the effect of π electrons on coupling constants. Karplus (15) calculated a π electron contribution of 1.5 cps to the coupling constant in ethylenic systems. Barfield and Grant have shown that substituents with π electrons will raise geminal coupling constants (16).

Empirical Observations: The validity of these theoretical calculations were checked with empirical observations. In his paper on vicinal coupling constants, Karplus offered some evidence to support his theoretical values. Lemieux, *et al.* (17) had published data on acylated pyranoses with $J_{aa}=5-8$ cps ($\phi = 180^\circ$), $J_{ae}=2-3$ cps ($\phi = 60^\circ$), and $J_{ee}=3-4$ cps ($\phi = 60^\circ$). Bothner-By and Glick reported coupling constants of 6-7.4 cps for substituted ethanes compared to a predicted value of 4.2 cps (18). However these are flexible systems where the observed coupling constants are time-averaged values from several conformations. Since the populations of the various conformational states may not be equal, the predicted coupling constants, calculated on the basis of free rotation, would not be quantitatively accurate. Since then a number of workers have reported coupling constants with their corresponding dihedral angles. A number of these are in relatively rigid systems where the dihedral angles are known or can be measured with some degree of accuracy (Table I). From these data a general agreement with the qualitative shape of the theoretical curve can be noted but the quantitative calculations of the theory are only approximately satisfied.

TABLE I

Compound	ϕ	J_{obs}	J_{calc}
Substituted cyclopropanes (19,20,21,22)	0° (cis)	7.4-9.3	8.2
	$144, 60^\circ$ (trans)	4.1-6.5	5.9
Camphane-2,3-diols (23)	0°	7.7, 8.9	8.2
	44°	4.4, 4.4	4.1
	79°	0, 0	0
	120°	2.2, 2.3	2.2
Substituted hexachloro-bicyclo(2,2,1)heptenes (24)	0°	7.6-9.3	8.2
	120°	2.5-4.6	2.2
	60° (ae)	3.4-4.2	1.7
1-substituted-2-arylcyclohexanes (25)	180° (aa)	10.2-12.4	9.2
	60° (ae)	6.3	1.7
2-bromocholestane-3-one (26)	180° (aa)	13.1	9.2
(2,2)-metacyclophane (27)	$59 \pm 1^\circ$	3.2-3.4	1.7

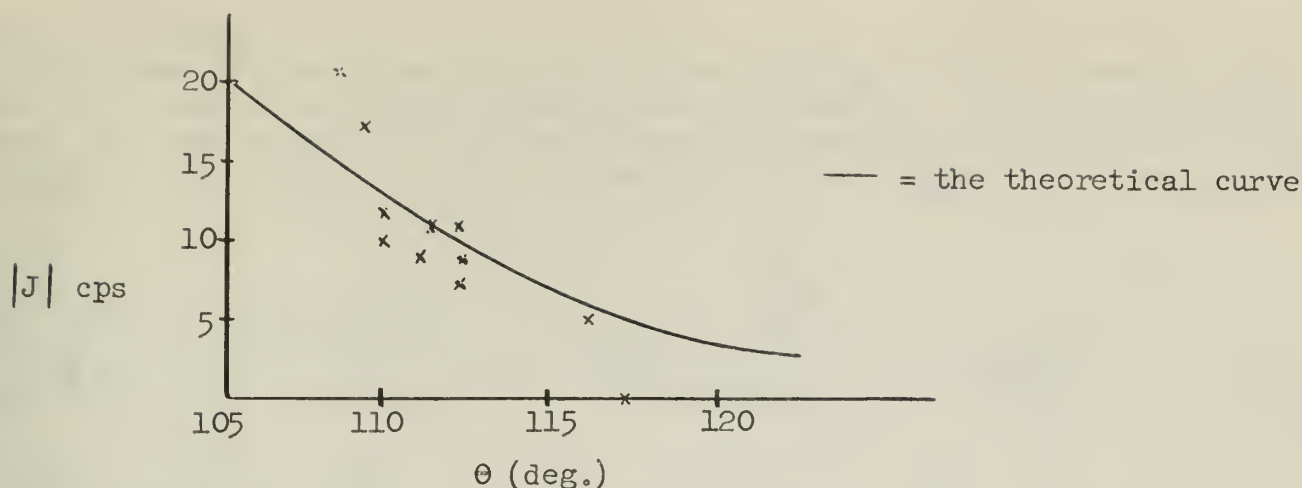
This lack of agreement between theory and observation may be explained in part by deviations from sp^3 carbon hybridization in rigid systems, but several authors have

proposed that the magnitude of vicinal coupling constants is also dependent on the electronegativity of substituents on the HCCH fragment. This was first suggested by Glick and Bothner-By (18) in 1956 to explain variations in coupling constants in a series of $\text{CH}_3\text{CH}_2\text{X}$ and CH_3CHX compounds. They proposed the empirical relations: $J_{\text{CH}_3\text{CH}_2} = 8.4 - 0.4E$ cps, $J_{\text{CH}_3\text{CH}} = 8.0 - 0.55E$ cps where E is the Huggin's electronegativity of the substituting atom. This effect has also been noted by other workers in compounds of the type $\text{X}(\text{CH}_2\text{CH}_3)_n$ (28,29,30). Williamson (24) noted a steady decrease in coupling constant as the substituent became more electronegative in his study of substituted hexachloro-bicyclo(2,2,1)heptenes. The coupling constants of ethylene sulfide ($J_{\text{cis}} = 7.1$ cps, $J_{\text{trans}} = 5.6$ cps) and ethylene oxide ($J_{\text{cis}} = 4.4$ cps, $J_{\text{trans}} = 3.1$ cps) are distinctly different although microwave studies indicate the HCH and HCC bond angles and the carbon-carbon bond length are almost identical (31,32). Cyclopropanes fit in the same trend as seen from Table I. Variation of coupling constant with electronegativity has also been noted in members of the cyclopropane series (21) and the cyclohexane series (25) but in these cases no clear correlations to coupling constant were reported. Williamson and coworkers (33) have since noted that 1,1-dichloro-2-substituted cyclopropanes and substituted ethoxides show an algebraic decrease in vicinal coupling constant with increasing substituent electronegativity. These reports indicate that substituent electronegativity does affect vicinal coupling constants. Although some empirical correlations have been derived to describe this in some systems, no general correlation, either empirical or theoretical, has been proposed to describe this phenomenon.

The Karplus theory predicts $J_{\text{trans}} = 13.4$ cps and $J_{\text{cis}} = 7.6$ cps for ethylenic coupling constants; in ethylene the corresponding values are 19.0 cps and 11.7 cps. The variation of vicinal coupling constants in ethylenic compounds with HCC bond angle previously proposed (11) is in agreement with findings of several groups using cyclic compounds of various ring sizes (34,35,36). Banwell and Sheppard (37) found that ethylenic coupling constants in substituted olefins vary sharply with the electronegativity of the substituent and proposed an empirical correlation to describe this.

In the original communication, Gutowsky, Karplus and Grant cited values of geminal coupling constants for a number of compounds with known HCH angles (10). These coupling constants fitted the theoretically calculated curve quite well with the exception of methylene chloride which was 3.1 cps low. However several experimenters have since reported cases where analysis of the nmr spectra gave a better fit for the observed data assuming J_{gem} opposite in sign to J_{vic} . This was noted for diethyl sulfite (38), dioxalanes (39) (2,2)-metacyclophane (27) substituted cyclopropanes (21), and others. But this type of analysis gives only relative signs. Since both types of coupling constants are predicted to be positive, one of the original proposals must be incorrect. It was suggested that the geminal coupling constants had the wrong sign since the approximations in their derivation were less certain. Anet (40) reported that J_{CH} and J_{gem} have opposite signs in CH_2DOH . Carbon-13-hydrogen coupling constants are also predicted to be positive by the same type of valence bond calculation used previously (41, 42). Since these calculations involved only two-electron functions to construct the ground-state wavefunction, they were believed to be more probably correct in sign. The question of absolute sign in coupling constant has been partially resolved by Buckingham and McLauchlan (43). A strong electric field induces a partial alignment of the electric dipoles of a system which produces nuclear magnetic dipole-dipole interactions. This can either increase or decrease the magnitude of splitting in an nmr peak depending on the sign of J and the geometry of the system. It was found that a strong electric field parallel to the main magnetic field of the spectrophotometer caused a decrease of 2.4 cps in the coupling of ortho protons of p-nitrotoluene. This implies that J_{ortho} is positive, which agrees with the assignment of a positive sign to J_{CH} . Therefore the geminal coupling constant should be assigned a negative sign in cases where it differs from the vicinal coupling constant.

Berstein and Sheppard (44), using data from a large number of CH_2XY compounds, concluded that the problem is not merely the wrong theoretical sign. They determined that even empirically there was no useful correlation of geminal coupling constant with angle (Fig. 2). They attributed this to superimposed substituent effects. It

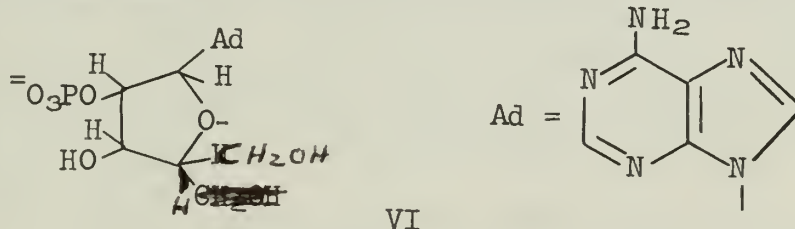


was also noted that epoxides have geminal coupling constants around + 5.7 cps while ethylene sulfide with the same HCH angle has a value around 0 cps. This difference was attributed to the electronegativity difference between oxygen and sulfur. Cyclopropanes with an HCH angle about 2.2° lower have J_{gem} from -4.3 to -8.4 cps. This could either be attributed to an electronegativity or a structural effect. Variations in J_{gem} in vinyl compounds have been attributed either to an angle dependence (37) or to a substituent effect (43).

Applications: Although the Karplus rules for vicinal coupling constants can be used to determine gross structural features, cis from trans hydrogens etc., its main application has been as a new tool for conformational analysis of compounds in solution. Due to the uncertainties in the validity of the theoretical proposals, no use of geminal coupling constants in structural determinations has been reported.

The most intensively studied field using coupling constants is that of conformations of sugars, sugar derivatives, and other natural products. This interest stems from the fact that sugar derivatives, especially the nucleic acid derivatives, as well as the sugars themselves are extremely important intermediates in biochemical pathways. Some information of the configuration of these compounds in crystalline form is known from X-ray analysis, but a knowledge of the conformation of such compounds in solution is important in examining the stereochemical factors of their chemical interactions with biological agents such as enzymes. Differing conformations of the sugars in solution could possibly explain the specificity of an enzyme for a single nucleic acid as due to a very exacting stereochemical requirement. This concept is in keeping with current biochemical thought.

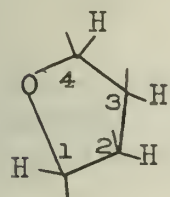
A typical example of this type of work is that of Jardetzky (45) in her study of the ribose ring conformation in 2'-adenine monophosphate, VI, in D_2O solution. The nmr spectrum was simple enough to allow assignment of the peaks to specific protons



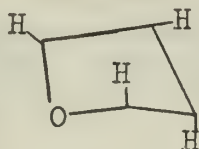
by a study of the splitting and analogy to earlier work on similar compounds. The coupling constants were determined by measurement of the multiplets of the spectrum. However in all these conformational studies, there may be considerable quantitative deviation from the theoretical values due to substituent effects. The theoretical approximations may also introduce errors. Jardetzky attempted to minimize such errors by determining the 1,2 coupling constant in 3',5'-cyclic adenine monophosphate. The ribose ring of this compound is known to have a fixed conformation due to the cyclic phosphate group. From models a dihedral angle of 105° was measured giving a predicted coupling constant, J_{12} , of 0.36 cps; experimentally the coupling was observed to be less than one cps. This offers some justification for applying the method in this

series of compounds.

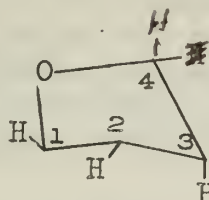
The ribose ring of VI can be pictured as existing in any of several ring structures or in some time-averaged equilibrium conformation. From a study of molecular models, the most probable of the individual structures were planar VIa, C_2' endo VIb, C_3' endo VIc, C_2' endo - C_3' exo VIId, and C_2' exo - C_3' endo VIE. The coupling protons



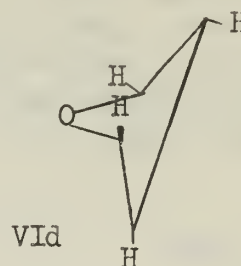
VIa



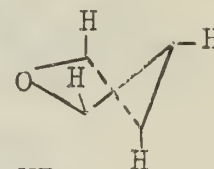
VIb



VIc



VIId



VIE

are drawn in. Using molecular models, dihedral angles were measured and coupling constants calculated in each case for the maximally puckered conformation (Table 2).

TABLE II

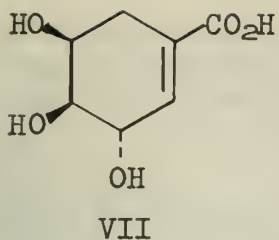
Conformation	ϕ_{12}	J_{12}	ϕ_{23}	J_{23}	ϕ_{34}	J_{34}
VIa	120°	2.1	0°	8.2	120°	2.1
VIb	165°	8.6	45°	4.0	105°	0.36
VIc	105°	0.36	45°	4.0	165°	8.6
VIId	165°	8.6	60°	1.8	75°	0.32
VIE	75°	0.32	60°	1.8	165°	8.6

The observed coupling constants were $J_{12} = 6.0$ cps, $J_{23} = 5.2$ cps, and $J_{34} = 3.4$ cps. This suggests that the C_2' endo conformation VIb is the closest approximation to the actual structure of the ribose ring. The differences in the magnitude of the coupling constants were postulated to be due to slight variations from the ideal conformation pictured, less than maximum puckering of the C_2' atom and some C_4' puckering. It should be noted that the angles obtained by this method can not be considered accurate to one degree of angle in any case. This conformation is favored for steric reasons since the bulky phosphate and adenine groups are equatorially and quasi-equatorially oriented.

Jardetzky also noted that since the ring is flexible, the actual conformation might be a time-averaged form rather than a single conformation. Anet (46) has shown that the coupling constants of both conformations of 3,3,4,4,5,5-hexadeuterocyclohexyl acetate could be determined in the nmr spectrum at -110° . However Lemieux (47) and Abraham and his coworkers (48) have both asserted that considerable conformational purity of 5-member sugar rings in solution was indicated by their spectra and the magnitude of the coupling constants. This idea is supported by similar data in 5-member rings containing nitrogen, the proline series (49). In the case of 2'-adenine monophosphate the coupling constants can be satisfied by postulating either a single conformation or a time-averaged form. A study of the temperature dependence of the spectrum might solve this problem.

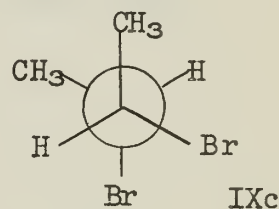
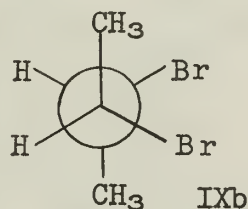
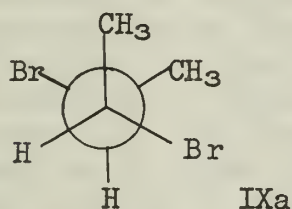
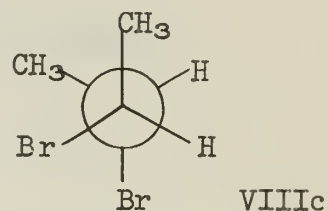
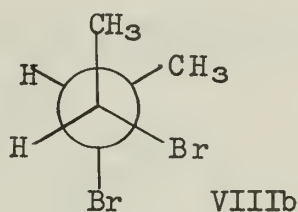
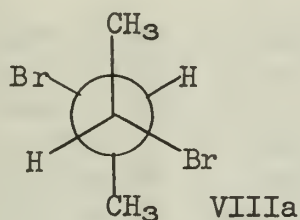
Other studies of a similar nature on the conformations of sugars have been reported by Jardetzky (50,51), Lemieux (52), and other groups (53,54,55,56). In some of these other studies the constants first proposed by Karplus were altered to give more accurate results for dihedral angles with very high or low coupling constants. It was also noted that purine and pyrimidine nucleosides seem to have different conformations for the ribose ring (53).

Coupling constants have been used in other cases to determine conformations in rings other than sugar rings. Hall (57) has used the method to show that shikimic acid VII in solution more closely adopts a conformation approximating a half-chair form than a boat form; in terms of a time-average conformation the half-chair species makes the major contribution. Similar studies have been reported in other simple ring



systems (58,59). The nmr technique has also been used by several groups to study the conformation of one ring in the multi-ring systems of steroids and other similar systems (60,61,62). The main problem in such studies is the complexity of the spectrum which prevents assignment of proton peaks and determination of coupling constants for all protons in the molecule.

The concept of time-averaged conformations has been used in one recent application of the Karplus rules. Several studies have used vicinal coupling constants to estimate rotamer populations in straight chain compounds (63,64,65). The technique can be shown as it was applied in the study of 2,3-dibromobutane (63,64). The rotational conformers of the meso form, VIIIA, VIIIB, VIIIC,



and VIIIC and the dl (IXA, IXB, IXC) may be drawn and the coupling constant, J_{23} , for each conformation calculated from the dihedral angle. The conformations VIIIA and IXC will have high J 's ($\phi = 180^\circ$) while the others having gauche hydrogens will give lower coupling constants. Anet (59) proposed that if interconversion in the meso compound is rapid, as expected for rotation, the observed coupling constant J_{23} will be given by the formula:

$$J_{23} = 1/100 [XJ_{23}(\text{VIIIA}) - (100-X)J_{23}(\text{VIIIB})]$$

where X is the percentage of conformation VIIIA. A coupling constant of 7.85 cps was observed for pure meso-2,3-dibromobutane. Using $J_{\text{trans}}=10-12$ cps and $J_{\text{gauche}}=1-3$ cps, this corresponds to $66 \pm 10\%$ of conformation VIIIA in the sample. The rest of the sample is an equal mixture of the other two conformations. A solution of the meso isomer in CS_2 or CCl_4 showed an upward shift of the coupling constant of approximately 1 cps (63,64). This was considered consistent with the effect of changing the solvent from 2,3-dibromobutane to a nonpolar solvent on the relative energies of the nonpolar, VIIIA, and polar, VIIIB and VIIIC, forms of the meso isomer. This rotamer population is consistent with the expected steric repulsion and electric dipole repulsion between gauche bromine atoms; it is also in agreement with electron diffraction studies. The pure dl isomer had an observed coupling constant of 3.15 cps. This low value indicated that conformation IXA or IXB must be a major contributor. Anet calculated that the pure dl isomer will contain $14 \pm 10\%$ IXC; the rest is expected to be mainly IXA because of the more unfavorable steric interactions in IXB. As expected the dl isomer showed a change in coupling constant of only 0.08 cps when placed in CS_2 solution.

Summary: The evidence indicates that the Karplus valence bond calculation offers a valid theoretical basis for calculating the variation of vicinal proton coupling constants with variation in the dihedral angle between them. It must be remembered however that the dihedral angle is not the only factor to be considered. If this method is to be used in conformational analysis, the possible effects of substituents on the observed coupling constants should be considered. This method should not be considered as valid to $\pm 1^\circ$ in most systems. It is possible that such accuracy might be obtained when better approximations in the theory, especially regarding substituent effects, can be made. The original theory concerning the variation of geminal coupling

constants with HCH angles must be considered incorrect at this time. Any meaningful study using this proposal should include a critical appraisal of the original approximations in the theoretical calculation as they relate to the system under study.

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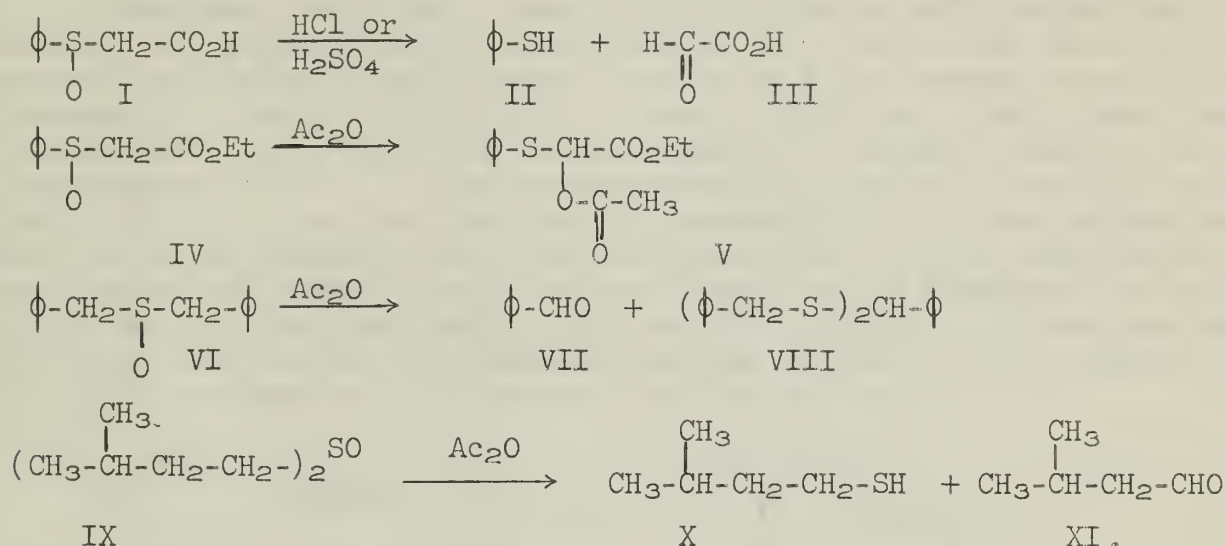
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THE PUMMERER REACTION

Reported by Bruce M. Monroe

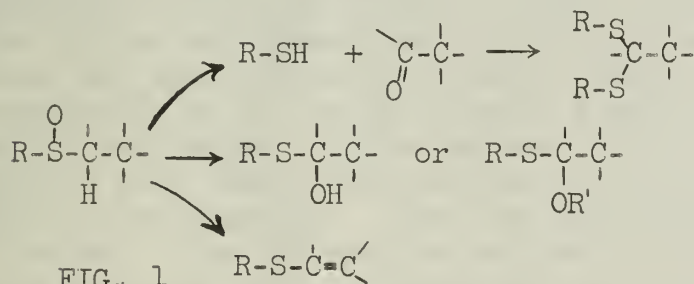
April 23, 1964

Introduction.--In 1909 Pummerer (1) reported that the reaction of phenylsulfinylacetic acid (I) with boiling, dilute, aqueous mineral acid gave thiophenol (II) and glyoxylic acid (III). The next year he (2) reported that heating ethyl phenylsulfinylacetate (IV) with acetic anhydride gave ethyl acetoxymethylphenylthioglycollate (V). In 1909 Smythe (3) observed a similar reaction. He found that dibenzyl sulfoxide (VI) was cleaved to benzaldehyde (VII) and its dibenzyl mercaptal (VIII) by the action of acetic anhydride. A further example of this reaction is due to Hilditch (4) who observed that di-isoamylsulfoxide (IX) produced isoamylmercaptan (X) and isovaleraldehyde (XI) when treated with acetic anhydride.



Formally the products of these reactions can be viewed as arising from reduction of the sulfoxide and oxidation of the α -carbon by a sulfur to carbon oxygen transfer. It has been suggested that this reaction be called the Pummerer reaction (5). It is formally analogous to the Polonovski reaction (6-8), a reaction of amine oxides with anhydrides in which the nitrogen is reduced and a carbon atom oxidized.

Scope and Synthetic Application of the Reaction 1. Nature of the Products.--A variety of products, dependent upon the nature of the sulfoxide and the experimental conditions used, may be obtained. In a formal sense, however, the sulfoxide has been reduced and the α -carbon atom oxidized in each case (Fig. 1).

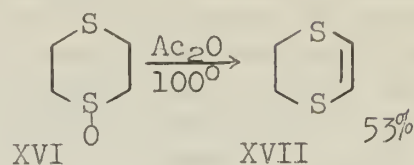
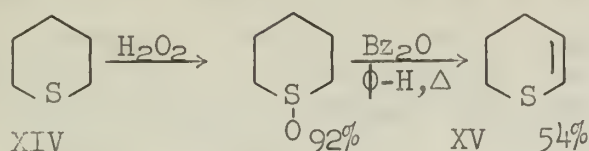
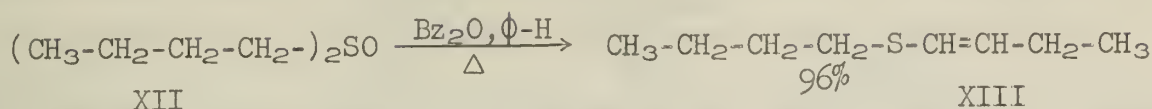


Reactions of this type may be divided into two classes, those that are brought about by anhydrides and those that are catalyzed by acid. Because of the difference in products and probable differences in mechanism these two types will be considered separately.

2. Reaction of Sulfoxides with Anhydrides.

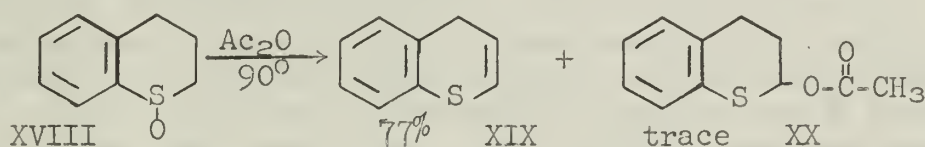
--The scope of the reaction of sulfoxides with anhydrides has been studied (9). An α -hydrogen is necessary for the reaction to take place. Diphenyl sulfoxide is recovered unchanged from refluxing acetic anhydride. Symmetrical sulfoxides with one or more α -hydrogen atoms react with acetic or benzoic anhydride to give α -acyloxy sulfides, olefins, or cleaved products. Dimethyl, diethyl, diisopropyl, and tetramethylene sulfoxides give α -acyloxy sulfides in 56-96% yield at room temperature for three days in chloroform or for six hours in refluxing benzene, but di-n-butylsulfoxide (XII) gives an olefin, n-butyl-[n-buten-(1)-yl(1)] sulfide (XIII). Oxidation of a sulfide to a sulfoxide followed by reaction with an anhydride has proved useful in the synthesis of α,β unsaturated sulfides from saturated sulfides (10,11,12). Δ^2 -Dihydrothiopyran (XV) has been prepared from tetrahydrothiopyran (XIV) in this manner (12). 1,4-Dithiane 1-oxide (XVI) is also converted to the olefin, 1,4-dithiane (VII), by the action of acetic anhydride (11). It is not

known whether the olefin is the initial product of the reaction or whether it arises

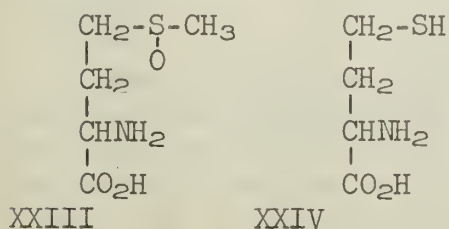
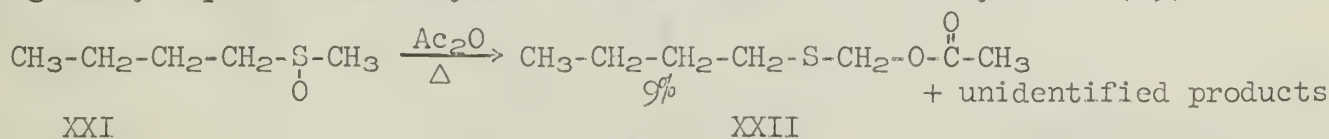


from further reaction of an initially formed α -acyloxy derivative. Dibenzylsulfoxide is cleaved to benzaldehyde and benzyl mercaptan by refluxing acetic anhydride (9). Succinic, maleic, and phthalic anhydrides were found to be unreactive with sulfoxides.

Unsymmetrical sulfoxides with hydrogen atoms on only one α -carbon atom also give α -acyloxy compounds or olefin in high yield. Phenyl methyl and phenyl benzyl sulfoxides are unreactive with benzoic or acetic anhydride in boiling benzene but yield α -acyloxy compounds at 120° (9). Higher temperatures are probably required because these sulfoxides are aryl, not because they are unsymmetrical. Acetic anhydride converts thiochrom-S-oxide (XVIII) to 4H-1-benzothiopyran (XIX), an α, β unsaturated sulfide (10). A small amount of material whose infrared spectrum and elemental analysis are consistent with the α -acetoxy derivative (XX) was also isolated. It has been suggested that the olefin (XIX) arises from further reaction of the α -acetoxy compound (XX), but there is little evidence to indicate that this is the case.

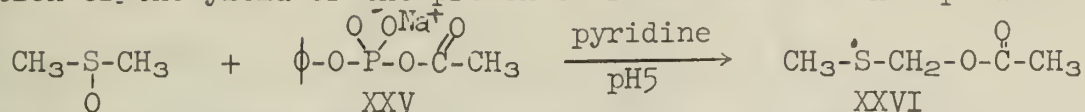


Only two examples of the reaction of unsymmetrical sulfoxides containing hydrogen atoms on both α positions have been reported (13). When methyl n-butyl sulfoxide (XXI) was treated with refluxing acetic anhydride a 9% yield of α -acetoxy methyl n-butyl sulfide (XXII) was obtained along with several unidentified products and a large amount of residual oil. The unidentified products had infrared bands characteristic of sulfonate or sulfinic groups but none characteristic of a double bond. It was suggested that rearrangement takes place exclusively to the methyl group, but the low yield of rearranged product (XXII) makes this a questionable conclusion. Methionine sulfoxide (XXIII) was also treated with refluxing acetic anhydride. When the mixture was hydrolyzed with dilute hydrochloric acid, condensed with formaldehyde, and then subjected to paper chromatographic analysis, the predominant spot was reported to be due to the product formed by the condensation of homocysteine (XXIV) with formaldehyde, indicating that homocysteine had been formed in the reaction. Several other spots were observed indicating that homocysteine was not the only product of the reaction. There was no indication of the per cent conversion to homocysteine. Since methionine sulfoxide (XXIII) occurs in living systems (14), it has been suggested that the Pummerer reaction may serve as a model reaction for the biologically important demethylation of methionine to homocysteine (15).

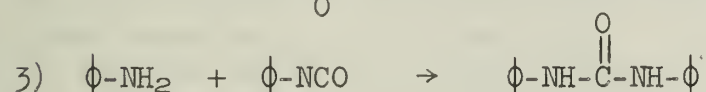
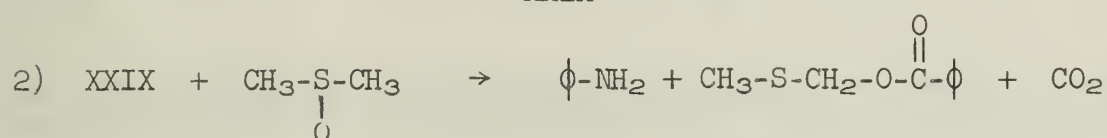
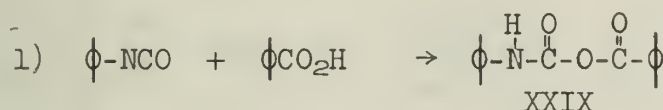
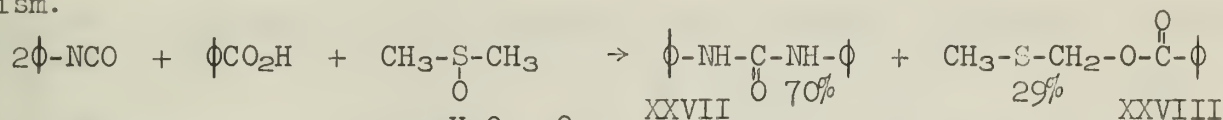


The reaction of sulfoxides with unsymmetrical carboxylic acid anhydrides has not been reported. However, the reaction of dimethyl sulfoxide with acetylphenylphosphate (XXV), a mixed inorganic-organic anhydride, has been carried out (13). A few drops of pyridine were necessary for the reaction to take place. The presence of α -acetoxyethyl methyl sulfide (XXVI) was shown by vapor phase analysis, but there was no indi-

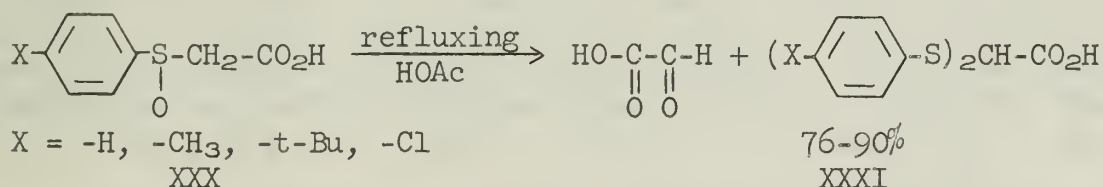
cation of the yield or the presence or absence of other products.



The reaction of dimethyl sulfoxide with a mixed carboxylic-carbamic anhydride has been proposed as an intermediate step in the reaction of benzoic acid and phenylisocyanate in dimethyl sulfoxide to produce sym-diphenyl urea (XXVII) and an α -benzyl sulfide (XXVIII) (16). It was proposed that phenyl isocyanate and benzoic acid react to form a mixed carboxylic-carbamic anhydride (XXIX) (Step 1) which then reacts with dimethyl sulfoxide (Steps 2 and 3). However, there is no evidence to support this mechanism.

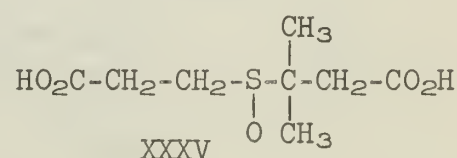
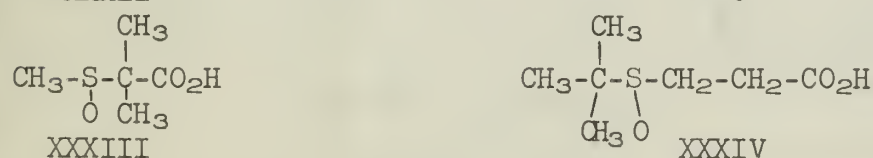
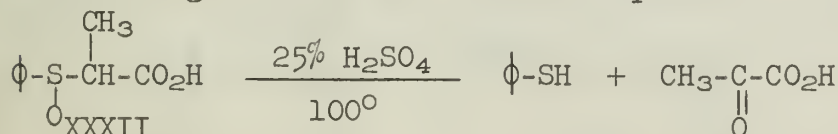


3. Reaction of Sulfoxides With Acids.--Phenylsulfinylacetic acid (I) has been found to undergo the Pummerer reaction in a wide variety of acidic conditions (1,2,17, 18). In refluxing acetic acid a series of para-substituted phenylsulfinylacetic acids (XXX) gave glyoxalic acid and bis-(aryl mercapto)-acetic acids (XXXI) (17). It was indicated that a para methyl group promoted the reaction and a para nitro group retarded it, but no rate data were given. Warm 6N H_2SO_4 was also found to be effective. Phenylsulfinylacetic acid is reported to undergo reaction standing in water at room



temperature for long periods of time (6 days to 3 months), in refluxing benzene, or in refluxing methyl ethyl ketone (18). It is suggested that the acid catalyzes its own rearrangement under these conditions.

α -Phenylsulfinyl propionic acid (XXXII) gives only traces of thiophenol when boiled with 1% H_2SO_4 , but it is readily cleaved to thiophenol and pyruvic acid by 25% H_2SO_4 at 100° (2). α -Methylsulfinyl isobutyric acid (XXXIII), β -(t-butylsulfinyl)-propionic acid (XXXIV), and β -(β -carboxyethylsulfinyl)-isovaleric acid (XXXV) are stable in glacial acetic acid and aqueous acid at room temperature (19,20).



β -Keto sulfoxides (XXXVI) can be easily rearranged to methyl hemimercaptals of α -ketoaldehydes (XXXVII) by aqueous hydrochloric acid at room temperature (21-23). This reaction may prove useful in the synthesis of substituted glyoxals. β -Keto sulfoxides are readily prepared by the base catalyzed condensation of esters with dimethyl sulfoxide (23) or by base catalyzed condensation of aldehydes with dimethyl sulfoxide

followed by oxidation of the resulting β -hydroxy sulfoxide with manganese dioxide

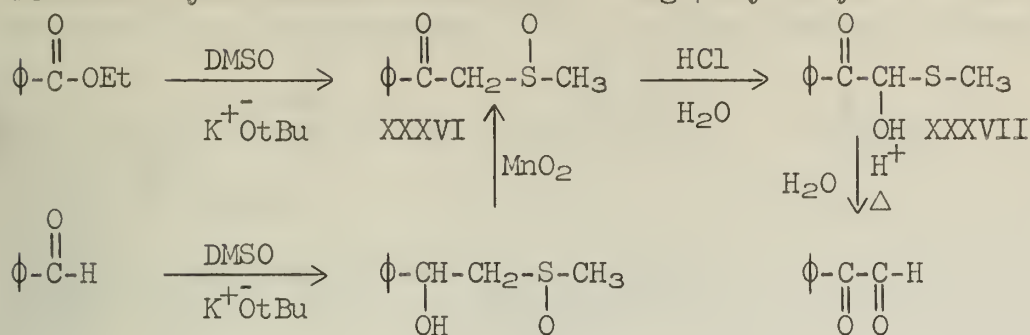
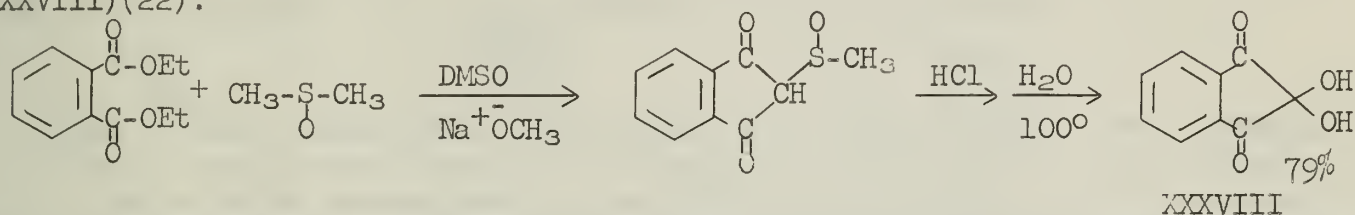
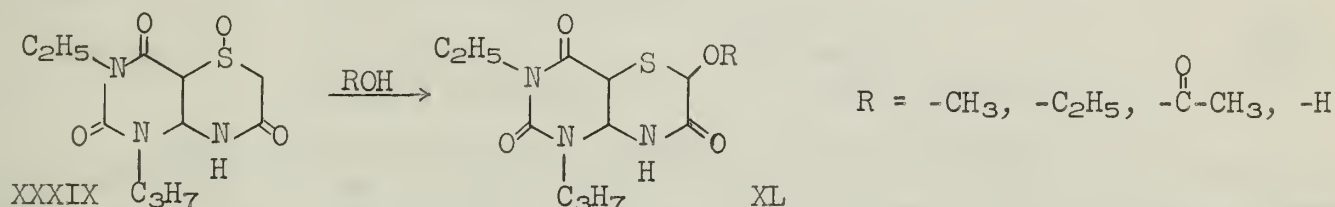


FIG. 3

(Fig. 3)(24). A sequence of this type has given a simple synthesis of ninhydrin (XXXVIII)(22).



4. Other Examples of Sulfoxide Rearrangement.--1-Propyl-3-ethyl-1H-pyrimido [5,4-b][1,4] thiazine-2,4,7-(3H,6H,8H)-trione 5-oxide (XXXIX) rearranges under very mild conditions in non-acidic media (25). The α -methoxy, α -ethoxy, α -acetoxy, and α -hydroxy derivatives (XL) are formed when it is recrystallized from methanol, ethanol, acetic acid, or water respectively.



Paraformaldehyde, bis-methylthiomethane, dimethyl disulfide, dimethyl sulfide, and water are obtained from the decomposition of refluxing dimethyl sulfoxide (26). These products can be rationalized by an initial cleavage of dimethyl sulfoxide into formaldehyde and methyl mercaptan (Fig. 4) followed by further reactions.

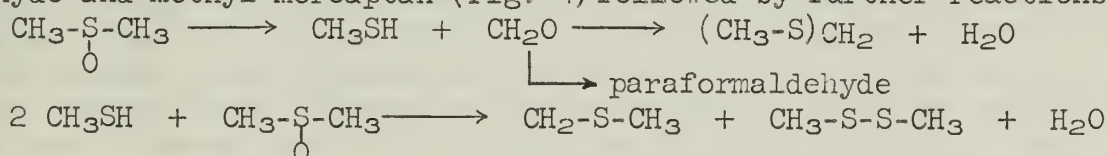


FIG. 4

Mechanism of the Reaction 1. With Anhydrides.--Several mechanistic proposals have been made for the reaction of sulfoxides with anhydrides (9,11,27,28). These are summarized in Fig. 5. Acylation of the sulfoxide on oxygen (29) would lead to

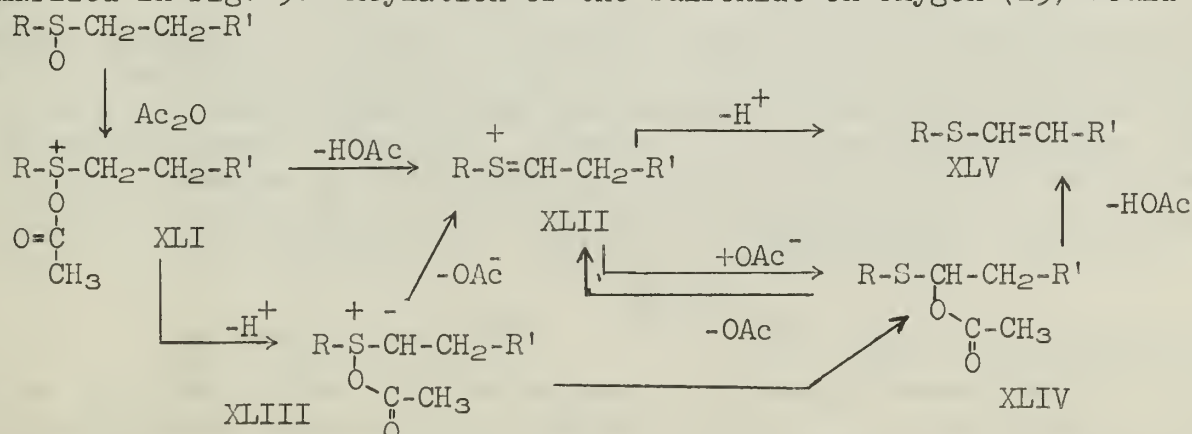


FIG. 5

XLI which can lose acetic acid in one or two steps to form XLII, an intermediate that can lose a proton to form olefin (XLV) or give the α -acetoxy compound (XLIV) by attack of acetate ion. Olefin can alternatively be formed by loss of acetic acid from the α -acetoxy compound, possibly by loss of acetate to form XLII. Alternatively, XLI could lose a proton to form XLIII, an intermediate which can give the α -acetoxy product

(XLIV) by three possible pathways (Fig. 6): intermolecular attack by acetate ion (1), intramolecular rearrangement (2), or a cage radical process (3).

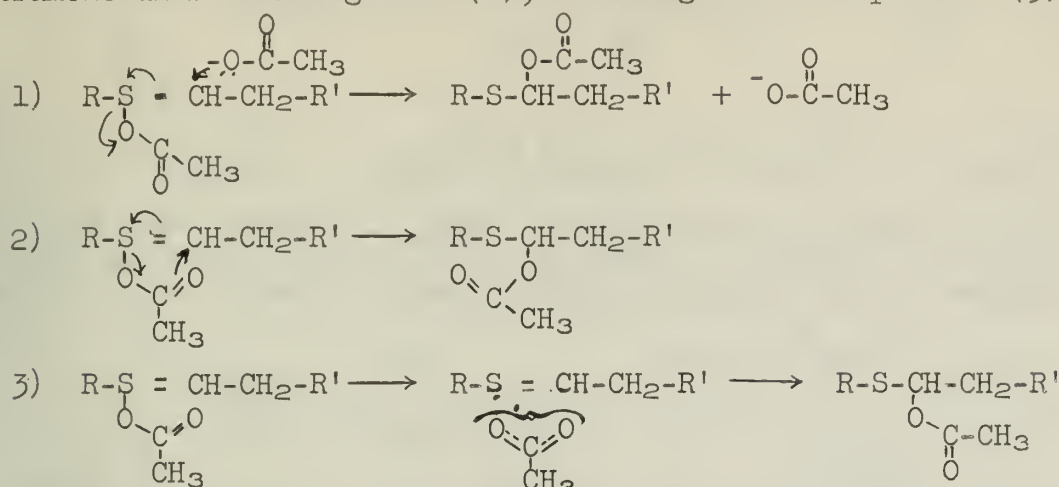


FIG. 6

There is some experimental evidence, but it is inconclusive. When dimethyl sulfoxide reacts with excess uniformly O^{18} labeled acetic anhydride (30) in refluxing ether, a value which corresponds to statistical distribution of O^{18} throughout the system is obtained in the product (Fig. 7)(28). Refluxing ether was used because it was found that the acetoxy group of the product did not exchange with acetic acid under the conditions.

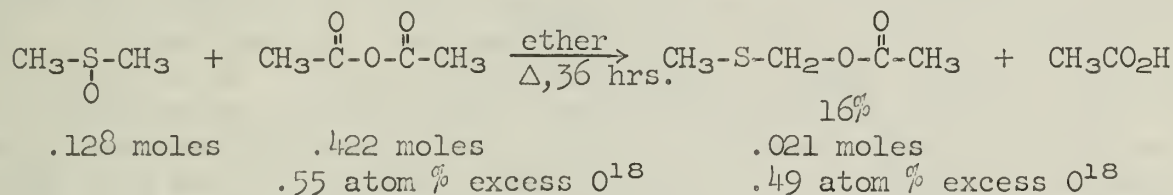
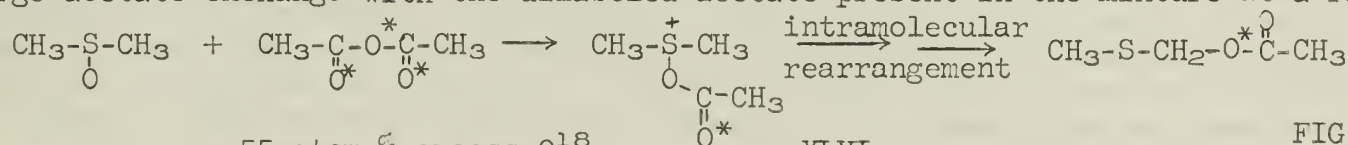


FIG. 7

Statistical distribution requires .50 atom % excess O^{18}

The authors suggest that the observation supports an intermolecular attack by acetate (Fig. 6- No. 1) since the acetate oxygens are scrambled by this process. However, several assumptions, not discussed by the authors, are necessary for a statistical distribution of O^{18} to be obtained by this mechanism. All of the oxygen atoms present must be available to the oxygen pool. Therefore, the acetic acid produced by the reaction must exchange with the excess acetic anhydride present. Further all the sulfoxide oxygen atoms must be available. This requires that the reaction go to completion or that there be exchange between the sulfoxide oxygen and acetic anhydride or acetic acid oxygen atoms. It was not stated whether or not the reaction had gone to completion but it seems unlikely since only a 16% yield of product was obtained. Unreacted starting material was not recovered and analyzed for O^{18} so it is not known if the sulfoxide oxygen exchanged under these conditions. Furthermore, if exchange does take place, statistical distribution of O^{18} would be observed regardless of mechanism.

Another possibility is that it is merely fortuitous that the observed value corresponds to a statistical distribution of O^{18} . Acylation of the sulfoxide followed by loss of a proton and intramolecular rearrangement predicts a value of .28 atom % excess O^{18} for the product (Fig. 8). However, if the acylated sulfoxide (XLVI) can undergo acetate exchange with the dilabeled acetate present in the mixture at a rate



.55 atom % excess O^{18}

XLVI .55/2 = .28 atom % excess O^{18}

FIG. 8

competitive with proton loss and rearrangement, dilabeled acetate will be incorporated into the product thus increasing the observed atom % O^{18} in the product. Monolabeled acetate produced by the process could exchange with labeled acetic anhydride generating more dilabeled acetate (Fig. 9). In view of the difficulties involved with the interpretation of this experiment, it is doubtful that any conclusion should be made from it.

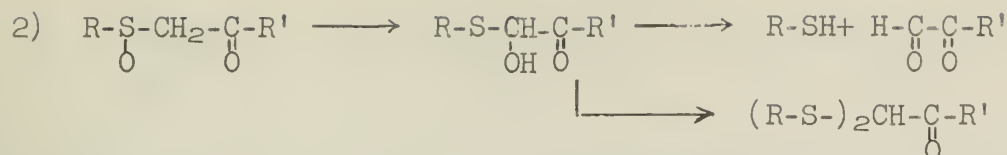


FIG. 11

If an aldehyde or ketone is the first product of the reaction, it should be possible to trap it and prevent the formation of the α -hydroxy sulfide and bis-mercaptal. The rearrangement of phenylsulfinylacetic acid (I) in 2:1 acetic acid-water containing a few drops of sulfuric acid was carried out in the presence and absence of hydrazine sulfate (18). When equimolar amounts of phenylsulfinylacetic acid and thiophenol, added to form the bis-mercaptal, were allowed to react in the presence of a 10% molar excess of hydrazine sulfate, a 32% yield of bis-(phenylmercapto)acetic acid (LV) was obtained. A 40% yield was obtained in the absence of hydrazine sulfate. This experiment was repeated using equimolar amounts of thiophenol and glyoxalic acid in place of phenylsulfinylacetic acid. A 14.5% yield of bis-(phenylmercapto)acetic acid was obtained in the absence of hydrazine sulfate, but none was obtained in the presence of hydrazine sulfate (Fig. 12). Although it is not possible to rule out completely

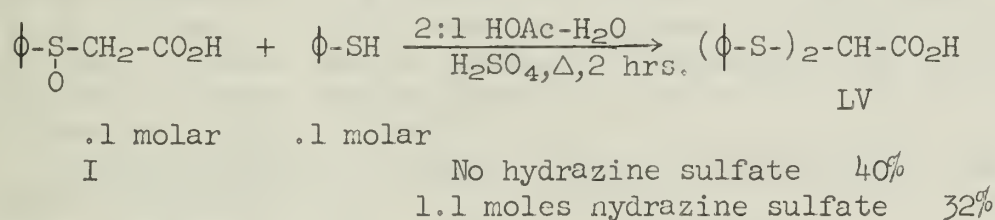
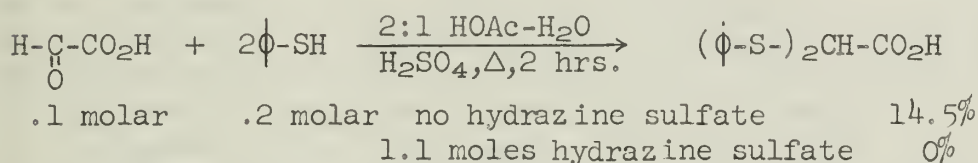
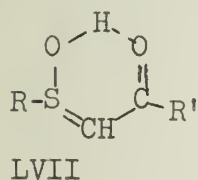


FIG. 12

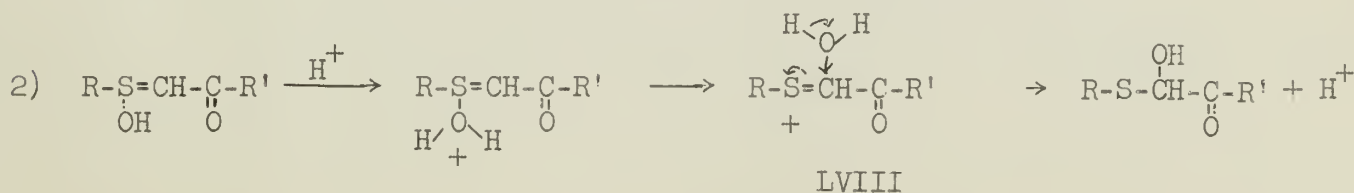
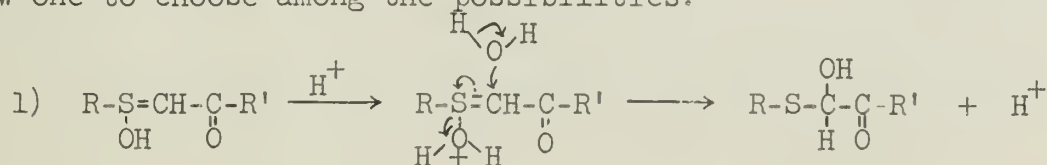


an initial cleavage to mercaptan and glyoxalic acid on the basis of this experiment, it does indicate that this is not the principal reaction pathway under these conditions.

Several variations of the second pathway have been suggested (23). Protonation of the sulfoxide on oxygen followed by loss of a proton from the α -carbon atom could lead to resonance stabilized intermediate LVI which might exist as hydrogen bonded form LVII. This intermediate could give the observed products by several possible



pathways (Fig. 13). Protonation followed by nucleophilic attack of the solvent would give the observed product (#1). Protonation of the sulfoxide oxygen followed by loss of water would give an ion (LVIII) which could react with the solvent (#2). The conversion could involve a true intramolecular (#3) rearrangement. This would indicate a transition of the type LIX. However, there is no experimental work which would choose among the possibilities.



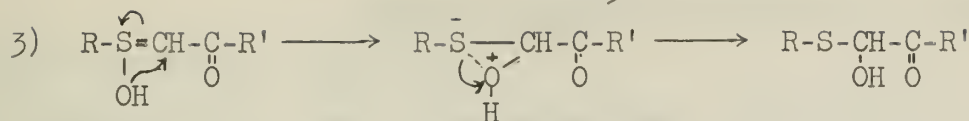


FIG. 13

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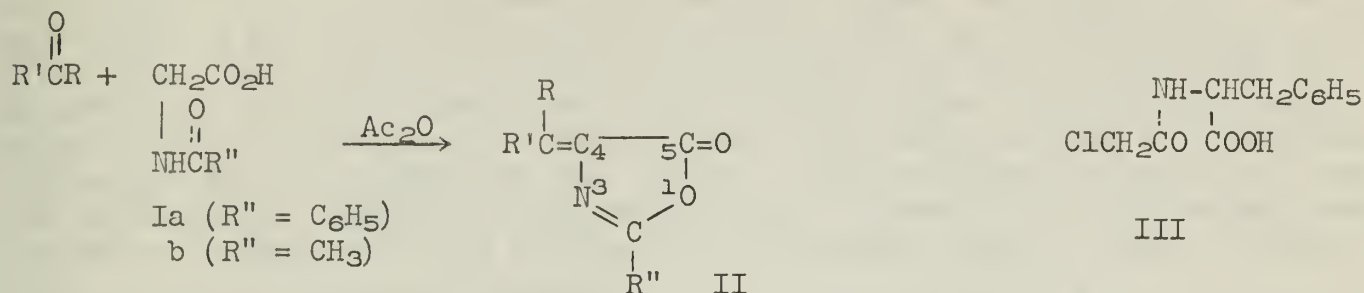
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RECENT CHEMISTRY OF UNSATURATED AZLACTONES

Reported by Allan C. Buchholz

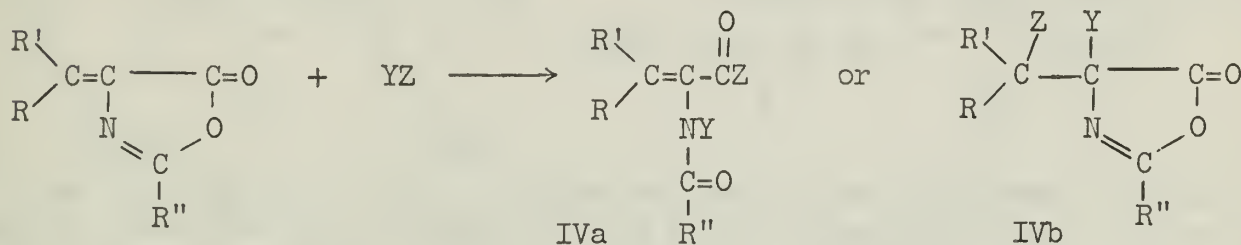
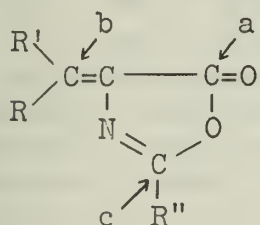
April 27, 1964

Introduction - Unsaturated azlactones, possessing the cyclic structure II and the numbering system indicated, are also known as 4-alkylidene or 4-alkylidene-5(4)-oxazolones. They are usually prepared by the reaction of an aldehyde or ketone with hippuric acid (Ia) or aceturic acid (Ib) in the presence of acetic anhydride (1,2,3,4).



Fused sodium acetate is often added but is not always necessary (4). The unsaturated azlactones can also be prepared by dehydration of β -hydroxy- α -acylamino acids with acetic anhydride or by the action of acetic anhydride on α -(α' -haloacyl)-amino acids (III). As the preparative aspect of azlactones has been thoroughly reviewed (1,2,3,4), this abstract will discuss reactions of the unsaturated azlactones.

Chemical Properties - The 4-alkylidene-5(4)-oxazolones possess several electrophilic centers as shown. Because of the α,β -unsaturated carbonyl system, the carbonyl carbon reactivity (a) is diminished from that of an azlactone containing saturated groups at C-4, although this C-5 reactivity usually predominates over reaction at the electrophilic center of the exocyclic double bond (b). There is also an electrophilic center in the carbon of the imino group (c) although reactions at this center are rare (4). Thus many of the reactions of nucleophiles with unsaturated azlactones can be classified as electrophilic attack leading to cleavage and where

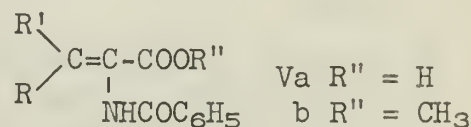


where $\text{ZY} = \text{H}_2\text{O}, \text{H}_2\text{S}, \text{NH}_3, \text{RNH}_2, \text{R}_2\text{NH}, \text{OH}^{\ominus}, \text{SH}^{\ominus}, \text{H}_2\text{NOH} \cdot \text{HOAc}$

(IVa) is either isolated or reacts further under the reaction conditions. Attack at the exocyclic double bond usually leads to retention of the ring, thus giving (IVb). Reactions with other nucleophiles are too strongly dependent on conditions and reactants to make any generalizations. These latter reactions along with those above will be discussed in the following sections.

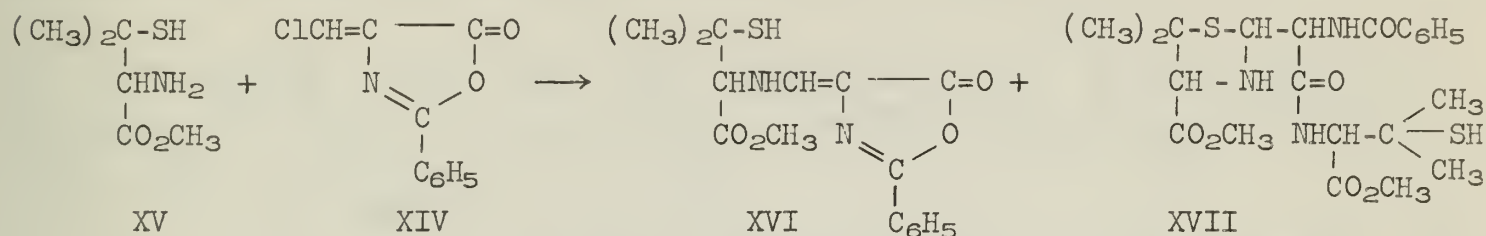
Reactions of electrophiles with unsaturated azlactones also are not amenable to generalizations. These are discussed separately below.

Reactions of Azlactones with Nucleophiles - Hydrolysis of unsaturated azlactones cleaves the azlactone ring between C-5 and the oxygen to give α -acylamino β -substituted acrylic acids (V) (5); further treatment with mineral acid removed the acylamino group to give an α -keto acid. This occurs when R or R' is an alkyl, aryl (6), amino, arylamino (7), or halo group (8). Treatment with alcohol containing traces of base gives the corresponding acrylic acid ester (Vb) (6,7).

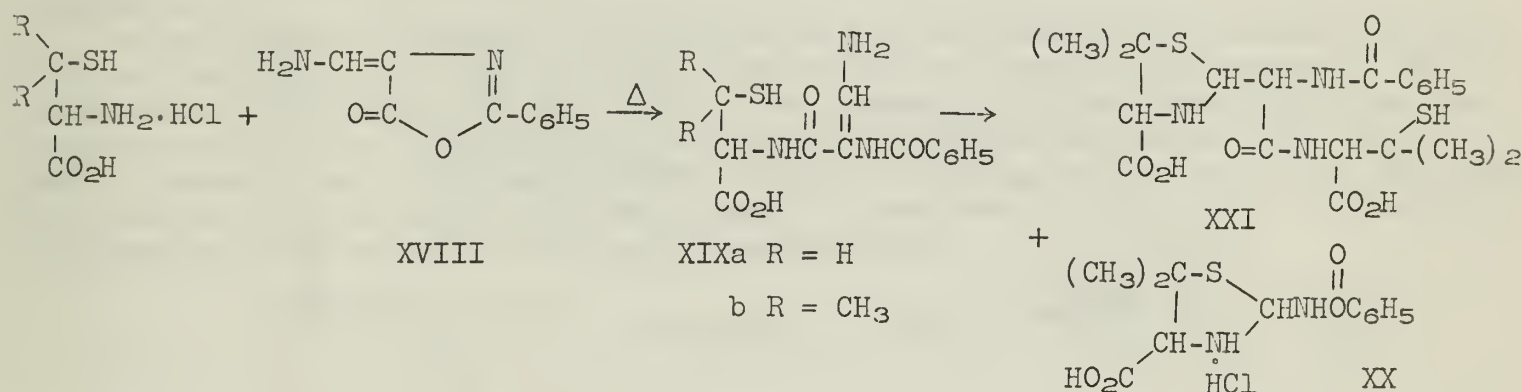


The results with H_2S gave an acrylic thiol acid (Va, OH replaced by SH, $\text{R}=\text{R}'=\text{CH}_3$) only if the 2 substituent in the azlactone was phenyl and only when a secondary amine

The addition of penicillamines to oxazolones yields results which are often different from those of regular amine additions. For example, the reaction of 2-phenyl-4-chloromethylene-5(4)-oxazolone (XIV) in ether adds one mole of penicillamine methyl ester (XV) to give an oxazolone product (XVI) in which the chloro group has been replaced. Use of chloroform as solvent permits the addition of two moles of penicillamine. The resulting product (XVII) corresponds to nucleophilic attack of the mercapto

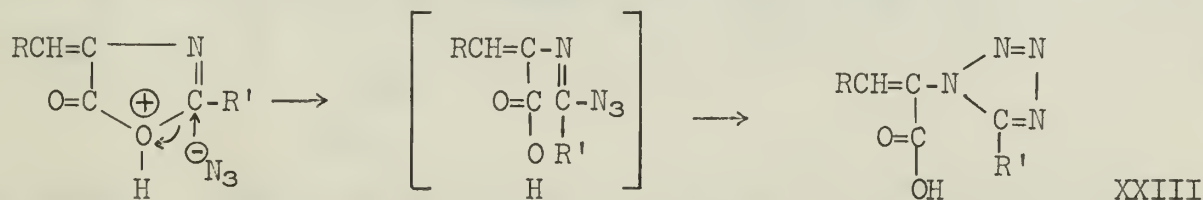


group on the exocyclic double bond of the penicillaminomethylene oxazolone (XVI) as well as nucleophilic attack by the second mole of penicillamine at the oxazolone carbonyl carbon (7). Heating 2-phenyl-4-aminomethylene-5(4)-oxazolone (XVIII) with *d,l*-cysteine or *d,l*-penicillamine hydrochlorides caused nucleophilic addition at C-5 to take place to give *N*-(α -benzoylamino- β -aminoacryl)-cysteine (XIXa) or its penicillamine analog (XIXb). In the case of penicillamine only, further reaction occurred by ring closure to give the hydrochloride (XX) or by addition of another mole of penicillamine to give XXI (14):



When the nitrogen of the penicillamine is deactivated by acylation, the nucleophilic center of the penicillamine at the sulfur reacts with unsaturated azlactones. Thus reaction of 2-phenyl-4-ethoxymethylene-5(4)-oxazolone with *N*-benzoylpenicillamine gives *S*-(2-phenyl-5-oxazolonomethylene-4)-*N*-benzoyl penicillamine (XXII) (15).

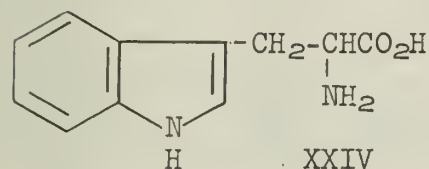
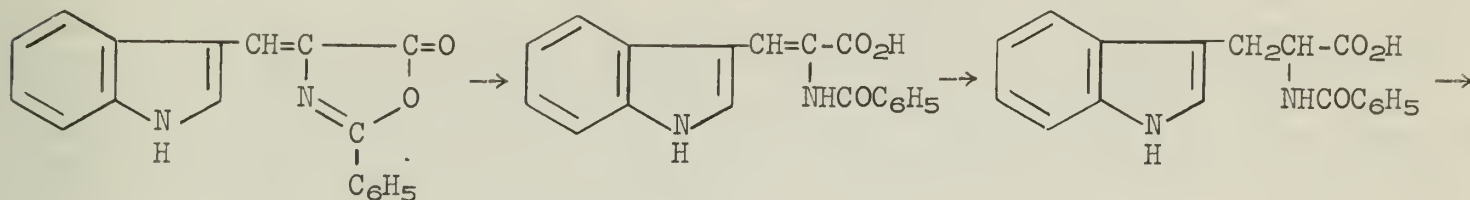
Behringer, in a study of the reactions of azlactones with hydrazoic acid (formed from the sodium salt and sulfuric acid), found that the 2-methyl oxazolones were cleaved much more easily than their 2-aryl counterparts. Nucleophilic attack of the hydrazoic acid is postulated to occur at C-2 leading to the unstable imidazide which immediately cyclizes to a tetrazole carboxylic acid (XXIII) (16). A wide variety of substituted 4-benzylidene oxazolones underwent this reaction. The



α -[5-methyl-tetrazolyl (1)]-cinnamic acid formed from 2-methyl-4-benzylidene-5(4)-oxazolone was decomposed to benzaldehyde (isolated as its 2,4-DNP), oxalic acid, and 5-methyltetrazole (identified by mixed melting point, IR and its copper salt).

4-Aralkylidene oxazolones were found by Behringer (17) to be readily prepared from 4-chloromethylene oxazolone by reaction of aryl hydrocarbons in the presence of

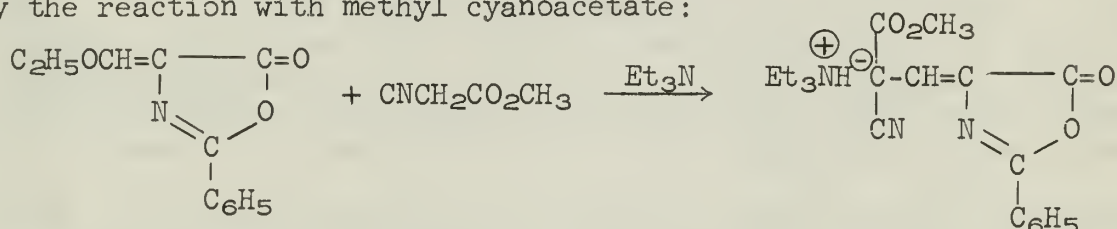
AlCl_3 . Some aryl hydrocarbons only reacted when they were in the form of their Grignard reagents. Besides various substituted benzenes, pyrene, trichloroethylene, 3-carbethoxy-2,4-dimethylpyrrole and its 3,5-dicarbethoxy analog also reacted in the presence of aluminum chloride. Less reactive species, such as indoles, only displace the chloro group when they are in the form of their Grignard reagents. Reactive species, such as pyrroles, react without catalyst. Yields in this reaction varied



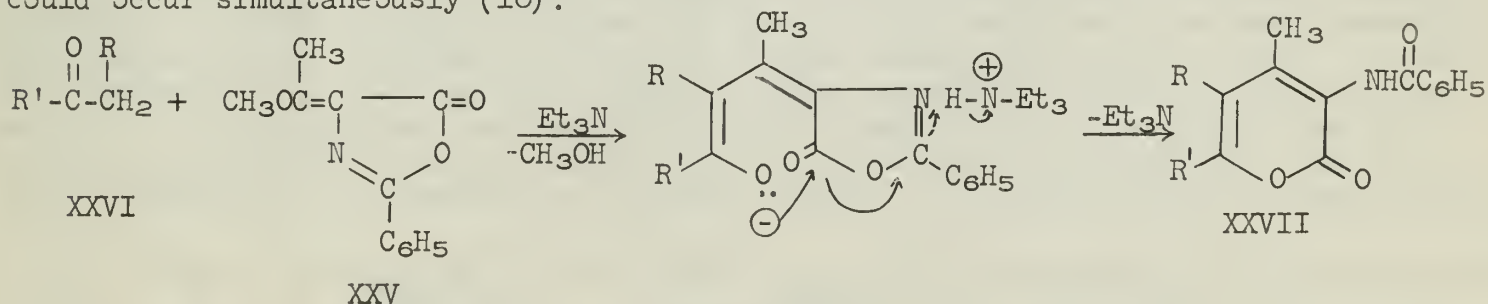
from 60 to 98%, depending on reactants: indoles gave yields of 60-93%, benzenes 93-98%, pyrroles 87-98%. Several of the unsaturated azlactones obtained in this manner were used to prepare unusual amino acids. The sequence for d,l-tryptophane (17) is given above. Thus hydrolysis of the unsaturated azlactone by base, occurring in the usual manner at C-5, hydrogenation to an

α -acyltryptophane, followed by deacylation gave d,l-tryptophane (XXIV) in 75% yield. The d,l-5- and d,l-7-methoxytryptophanes and a pyrrolalanine were also prepared in this manner.

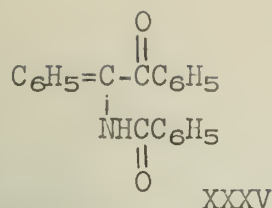
An analogous nucleophilic substitution on the exocyclic double bond of the azlactone occurs when active methylene compounds react with 2-phenyl-4-ethoxymethylene or 4-(α -methoxyethylidene)-5(4)-oxazolone in the presence of triethylamine at room temperature to give the correspondingly substituted methylene oxazolone (18). Thus methyl cyanoacetate, $\text{CNCH}_2\text{CO}_2\text{CH}_3$; malononitrile, $(\text{CN})_2\text{CH}_2$; or cyanoacetamide, $\text{CNCH}_2\text{CONH}_2$ all condense to give the triethylamine salt of oxazolones in good yields. This can be illustrated by the reaction with methyl cyanoacetate:



If the active methylene compounds contained an adjacent nucleophilic carbonyl group, α -pyrones were formed. These required less than molar amounts of the amine. Two mechanisms were postulated. In the first, carbon-carbon condensation may occur, followed by opening of the oxazolone ring and recyclization to form the stable α -pyrone system. Alternatively, the oxazolone ring cleavage and the pyrone ring closure could occur simultaneously (18):

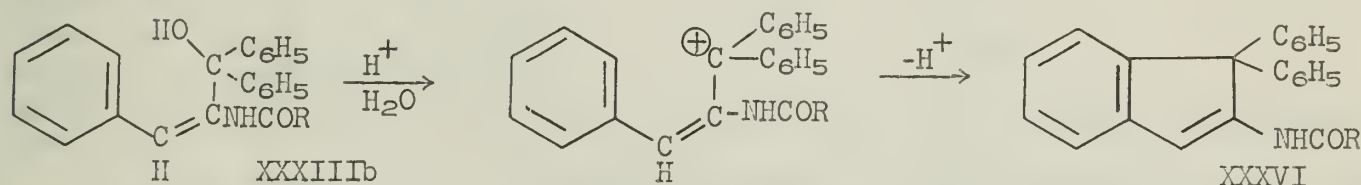


For example, 2-phenyl-4-(α -methoxy)-ethylidene-5(4)-oxazolone(XXV) reacted with ethyl acetoacetate (XXVI, $\text{R}=\text{CO}_2\text{C}_2\text{H}_5$, $\text{R}'=\text{CH}_3$) to give 3-benzoylamino-4,6-dimethyl-5-carbethoxy-2-pyrone (XXVII, $\text{R}=\text{CO}_2\text{C}_2\text{H}_5$, $\text{R}'=\text{CH}_3$). This structure was confirmed by an independent synthesis. Triacetic acid lactone (XXVIII) gave 3-benzoylamino-7-methyl-2,5-dioxo-2(H), 5(H)-pyrano[4,3b]pyran (XXIX), a compound with two fused α -pyrone rings (18):



inverse addition gave mostly starting material and a small amount of α -benzamido-benzalacetophenone (XXXV), whose structure was tentatively proposed on the basis of its UV and IR spectra.

The reaction of azlactones with a threefold excess of Grignard reagent was found to be independent of temperature and solvent but strongly dependent on dilution. At high dilution, the predominant product was the alcohol XXXIIa. This alcohol was formed in preference to the oxazoline XXXIV by a factor of 8:1 (26). At lower dilutions, the oxazoline was overwhelmingly predominant (25). However, neither group (25,26) investigating reaction conditions could reproduce oxazoline formation by heating the 1,1-diphenyl-2-benzamido-cinnamyl alcohol (XXXIIa) with HOAc-HCl, a reaction reported earlier (24). This reaction gave an indene (XXXVI) in high yield (94%) when performed at room temperature or with slight heating (26). The indene was postulated to be formed by a carbonium ion from the unsaturated alcohol XXXIIb.

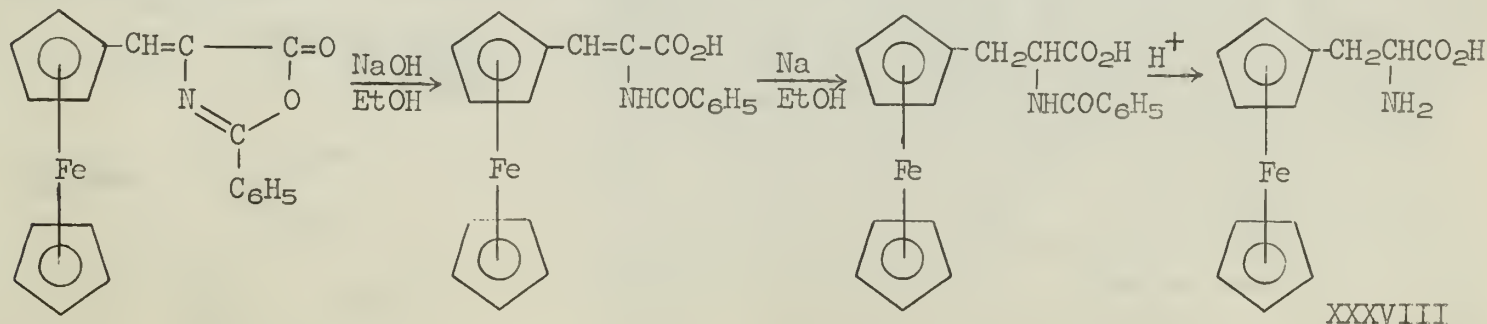


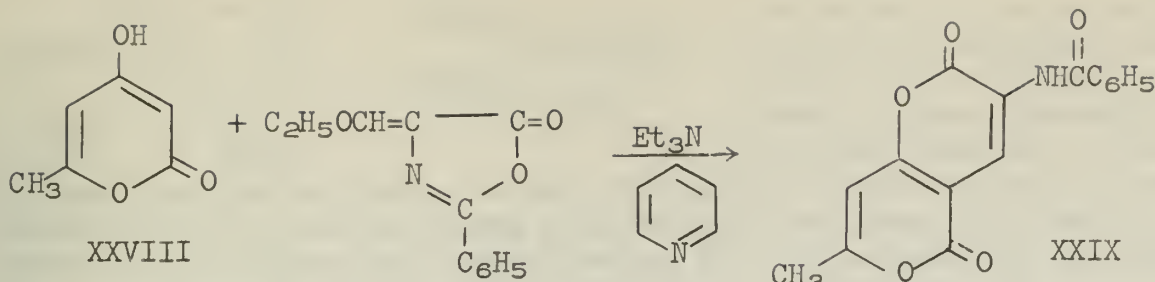
The indene structure was supported by oxidation ($\text{H}_2\text{SO}_4\text{-HgSO}_4$) to phthalic acid and by IR data. Other aryl Grignards, for example p-methoxy phenyl, reacted with 2-phenyl oxazolones to give mixtures of oxazolines similar to XXXIV and alcohols similar to XXXIIb, formed by cleavage (27). Alkyl or aralkyl Grignard reagents in *large* excess at high dilutions gave the saturated azlactones similar to XXXVII (27,28) whereas at *small* excesses they gave the ring cleaved alcohols XXXIII (27).

The 2-methyl-4-aralkylidene-5(4)-oxazolones, systems which were found to be less stable than their 2-phenyl counterparts (4), gave predominantly the alcohols (XXXIIa) derived from reaction at C-5 and ring cleavage (23,25,26), although only aromatic Grignards have been investigated with this system. These alcohols could be closed to the oxazolines by an acetic anhydride-sodium acetate mixture (25,26).

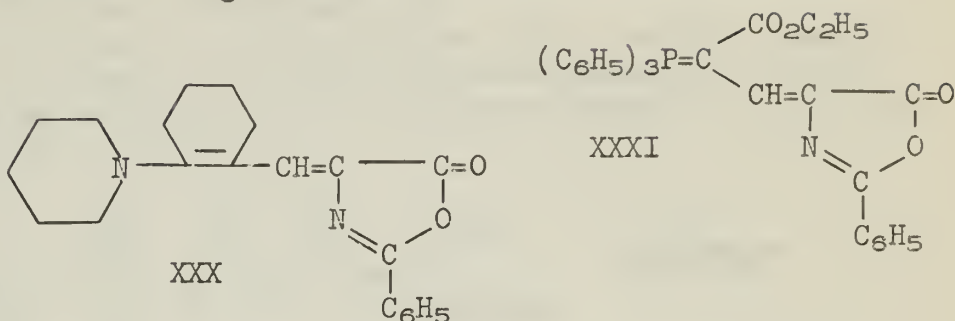
Attack on the exocyclic double bond of 2-phenyl-4-benzylidene-5(4)-oxazolone by phenylmagnesium bromide could be accomplished by carrying out the reaction in the presence of cuprous chloride under conditions of high dilution and with a ratio of cuprous chloride to Grignard of 2:3 (28). Some alcohol (XXXIIa) and oxazoline (XXXIV) were obtained. This reaction could also be accomplished in the presence of cobaltous chloride.

Azlactones have been extensively employed in the preparation of amino acids and peptides (1,2,3,4). Indeed this has been one of their main uses. The usual procedure is cleavage of the oxazolone ring at C-5 by some nucleophile, usually base, followed by hydrogenation of the resulting acylated amino acrylic acid and deacylation to an alanine. Recent applications involve the use of azlactones in preparing labeled amino acids (29,30,31) or unusually substituted alanines (6,19,32,33,34). An interesting example is the preparation of small amounts of ferrocenylalanine (XXXVIII) (32).

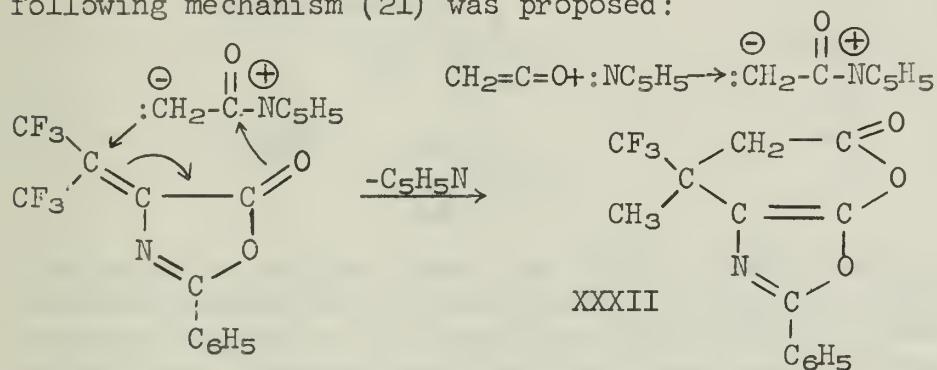




Enamines as well as triphenyl alkylidene phosphoranes react spontaneously with ethoxymethylene oxazolones to give the corresponding 4-alkylidene oxazolones (XXX) and (XXXI) respectively. An earlier report noted that trivalent triphenyl phosphorous reacted in a nucleophilic manner by adding across the exocyclic double bond of the 4-benzylidene azlactone (19).

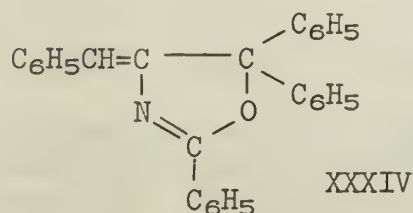
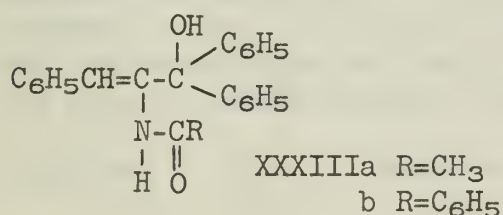


A recent study of the very reactive 2-phenyl-4-hexafluoroisopropylidene-5(4)-oxazolone showed that it reacts with nucleophiles to give the product corresponding to attack at the carbonyl carbon and then fission of the oxazolone ring (20). It reacted readily with water, aniline and thiophenol, three nucleophiles with which its non-fluorinated isopropylidene analog reacts only sluggishly. Ketene formed from the pyrolysis of diketene was added 1,4 across this very reactive oxazolone in the presence of pyridine to give XXXII. As this would only occur in the presence of pyridine, the following mechanism (21) was proposed:

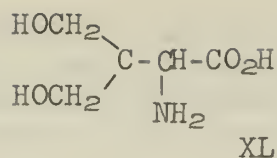
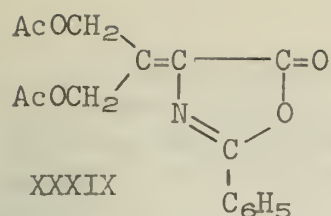


This adduct can be converted back to starting materials with zinc chloride in the presence of aluminum chloride. It is converted to a diacid with water; methanol gives the diester. The adduct formation requires a very reactive azlactone; again the non-fluorinated analog would not react.

The position of nucleophilic attack of Grignard reagents upon the oxazolones is a complicated function of starting material, excess of Grignard, concentration, and other conditions. Pourrat (22) and later Gomper (23) found that a threefold excess of phenylmagnesium bromide attacked the C-5 carbonyl-carbon of 2-methyl-4-benzylidene-5(4)-oxazolone causing oxazolone ring cleavage between C-5 and the oxygen in the one position to give the alcohol (XXXIIIa).



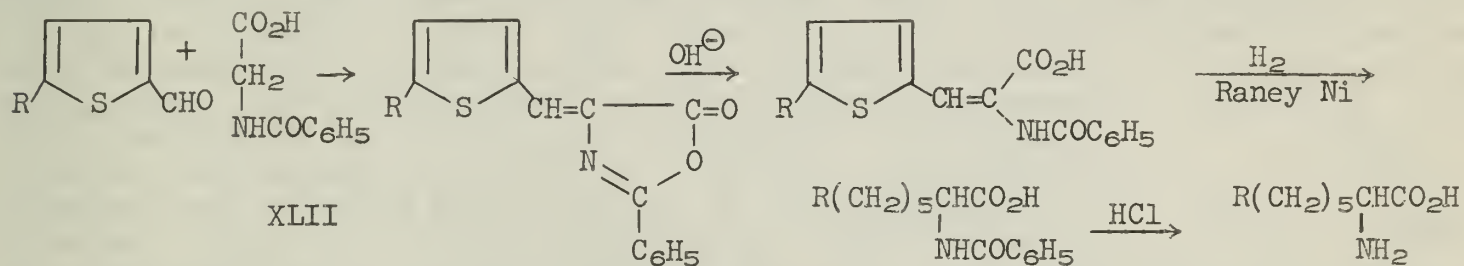
The 2-phenyl-4-benzylidene-5(4)-oxazolone, an oxazolone more stable to ring cleavage, gave the oxazoline XXXIV. Mustafa (24) disputed the results with the 2-phenyl oxazolone, claiming that 1,1-diphenyl-2-benzamidocinnamyl alcohol (XXXIIIb) was the only product and that the action of an HCl-HOAc solution and heat would cause ring closure in this alcohol to form XXXIV. In an attempt to clarify this problem, a reinvestigation of the reaction conditions was made (25). Equimolar amounts of the 2-phenyl azlactone and phenylmagnesium bromide using



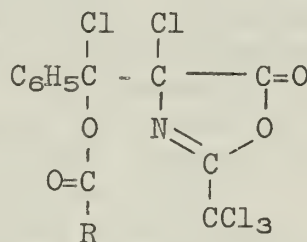
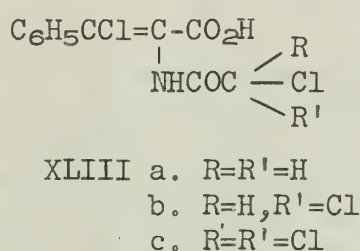
Acetoxymethylene azlactones XXXIX gave after several steps d,l- γ,γ' -dihydroxy valine (XL) (34). By the Friedel-Crafts reaction of 2-phenyl-4-benzylidene-5(4)-oxazolone with substituted benzenes, followed by cleavage at

C-5 and reaction as above, several unusual β,β -diphenylalanines have been prepared (33). Reaction of the same oxazolone with Grignard reagents, followed by cleavage was declared to be an easy and general method for the preparation of substituted alanines. The substituents were alkyl or substituted aryl groups (19).

Condensation of substituted thiophene 2-carboxaldehydes (XLI, R=ethyl, isobutyl, carbethoxy, propyl, acetamido) with hippuric acid gave thenylidene azlactones (XLII) which were cleaved, then hydrogenated and desulfurized with Raney nickel to give higher aliphatic α -amino acids in good yields (35,36):



Reaction of Azlactones with Electrophiles - Chlorination of 2-methyl-4-benzylidene-5(4)-oxazolone in acetic anhydride at 80° with chlorine gas gave the 2-dichloromethyl derivative (37). With acetic acid as solvent and at 80° (38) the benzylidene hydrogen and only one hydrogen of the methyl group were substituted although the oxazolone ring was cleaved at C-5 to give α -(chloroacetamino)- β -chlorocinnamic acid (XLIIIa). Irra-



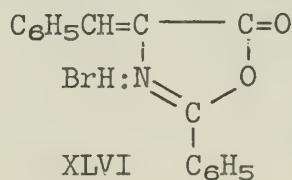
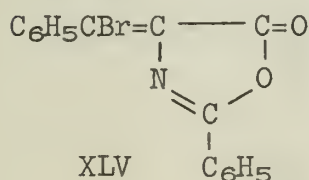
XLIV

diation with sunlight under the latter conditions gave the α -di- and trichloroacetamino- β -chlorocinnamic acids (XLIIItb and c) as well as 2-trichloromethyl-4-chloro-4(α -chloro, α -acetoxy-benzyl)-5(4)-oxazolone (XLIV, R=CH₃) in 60% yield. A similar adduct (XLIV, R=C₂H₅) was obtained when propionic acid was used instead of acetic acid.

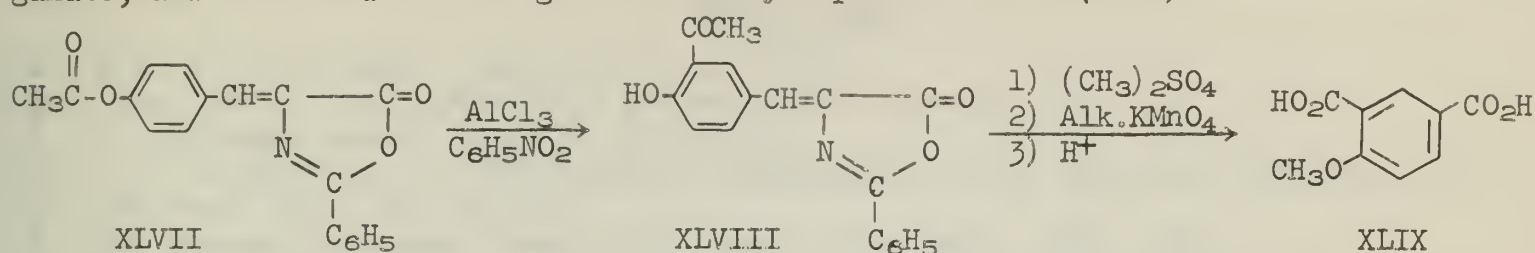
2-Methyl-4-benzylidene-5(4)-oxazolone can be brominated to the 2-dibromomethyl derivative in acetic anhydride-acetic acid, carbon tetrachloride, or acetic anhydride alone (37). The hydrogen of the benzylidene group is replaced only if the ring is cleaved to give the bromo derivative of XLIIItb (cleavage at C-5 occurs only in acetic acid). After bromination, the oxazolone can be re-formed by the dehydrating action of the HBr formed in the reaction on this α -acylamino- β -bromo-cinnamic acid. Hydrogen bromide was also shown to cause formation of unsaturated azlactones from α -acylamino cinnamic acids. Bromination of 2-tolyl-4-(α -bromobenzylidene)-5(4)-oxazolone gives the 2-p-monobromomethylphenyl analog in acetic anhydride with irradiation by sunlight; the 2-p-dibromomethylphenyl analog obtains in carbon tetrachloride.

It was found that 2-phenyl-4-benzylidene-5(4)-oxazolone in the presence of calcium carbonate halogenated to give the 4- α -halo-benzylidene azlactone more slowly than the ethylidene derivative gave the α -haloethylidene product. This was postulated to be a manifestation of the resonance stability of

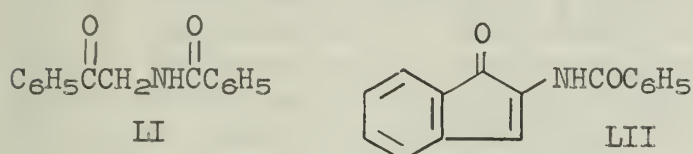
the benzylidene group (39). When the calcium carbonate was omitted, both the 4- α -bromo-benzylidene azlactone (XLV) and a hydrobromide at the nitrogen of the oxazolone ring (XLVI) resulted. The former could be obtained with substituted benzylidenes or with chlorine, but no hydrohalides could be found.



A Fries rearrangement was carried out on 2-phenyl-4-p-acetoxybenzylidene-5(4)-oxazolone (XLVII) to give the 4-(m-acetyl-p-hydroxybenzylidene) analog (XLVIII) (40). This was methylated with dimethyl sulfate, oxidatively cleaved with alkaline permanganate, and then acidified to give 4-methoxyisophthalic acid (XLIX):

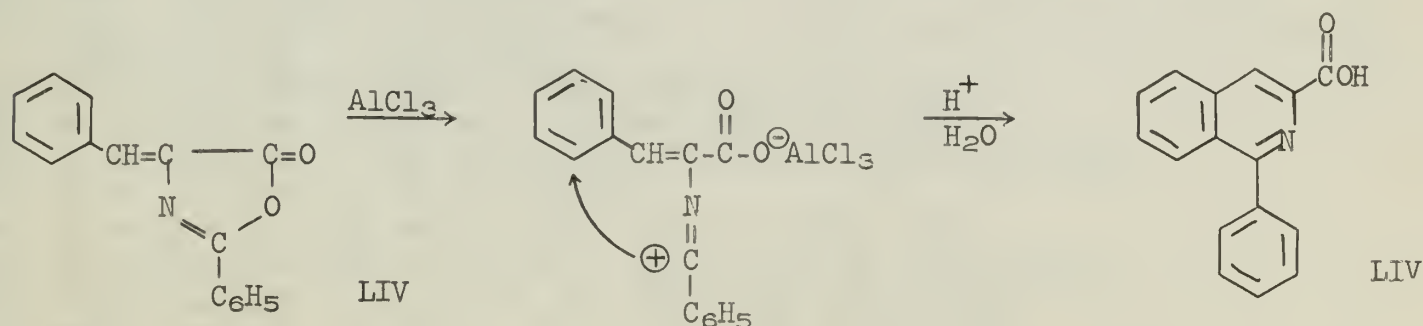


A rigorous study of the conditions of the Friedel-Crafts reaction of 2-phenyl-4-benzylidene-5(4)-oxazolone with benzene has been made to determine the effect of conditions on the products formed (41). Thus attack occurs on the exocyclic double bond when specially dried benzene is used in the presence of anhydrous AlCl_3 under a nitrogen atmosphere to give 2-phenyl-4-benzhydryl-5(4)-oxazolone (L) in 70-75% yield (12,33,42,43). If traces of moisture were present in the benzene or if aged aluminum chloride was used, cleavage at C-5 and loss of the 4-substituent occurred to give ω -benzamidoacetophenone (LI) (structure proven by independent synthesis and degradation) and small amounts of 2-benzamidoindenone (LII), formed by intramolecular acylation (seen from independent synthesis and IR spectrum) (44). It was postulated that in the formation of the acetophenone LI, aralkylidene cleavage occurs after ring opening in the final step (an acid hydrolysis) (41). This conclusion was supported when 2-benzamidobenzalacetophenone was converted to the ω -benzamidoacetophenone (LI) in the presence of benzene and AlCl_3 only when traces of moisture were present. However the formation of 2-phenyl-5-oxazolone (LIII) by a retrograde aldol reaction, followed by reaction with benzene cannot be ruled out (41).



The substituents on the phenyl ring of the aralkylidene group are also important in the Friedel-Crafts reaction of unsaturated azlactones; electron withdrawing substituents enhance the formation of the 2-phenyl-4-benzhydryl-5(4)-oxazolone (L) whereas electron donors cause increases in the yields of the acetophenones at the expense of the saturated azlactones. Meta-substitution in the azlactone's aralkylidene group gave the acetophenone as the sole product while ortho or para-substitution gave both acetophenone and azlactone. Unsaturated azlactones derived from heterocyclic aldehydes failed to react.

When the Friedel-Crafts reaction was conducted at temperatures higher than room temperature, small amounts of 1-phenylisoquinoline-3-carboxylic acids (XIV) were found in addition to the acetophenone and indenone. An intramolecular alkylation was postulated for their formation (41).



The structure of LIV was seen by decarboxylation to the known 1-phenylisoquinoline hydrochloride and comparison of this with an authentic sample.

Summary - This seminar abstract has discussed the reactions of nucleophiles and

electrophiles with the unsaturated azlactone ring system. It was found that most reactions led to reaction at C-5 and azlactone ring cleavage. Examples were given of the use of unsaturated azlactones as intermediates for the preparation of amino acids.

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SOLVENT ISOTOPE EFFECTS ON ACID DISSOCIATION
CONSTANTS AND ACID CATALYZED REACTIONS

Reported by Raymond Feldt

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Introduction.--The solvent isotope effect, the difference in dissociation constants and rate constants determined in H_2O and D_2O , has been the subject of much interest in recent years. Solvent isotope effects may be of use in mechanistic studies. The early work in the field has been reviewed by Wiberg (1), Purlee (2), and Bell (3). Due to the large amount of work done in the field, this seminar will be limited to solvent isotope effects on acid dissociation constants and acid catalyzed reactions.

Solvent Isotope Effects on Acid Dissociation Constants.--The determination of pK_a values for a variety of carboxylic acids, phenols, alcohols and other weak acids has shown that acids are less dissociated in D_2O than in H_2O . This difference, ΔpK_a , tends to increase as the pK_a in H_2O increases (4,5,6). Some representative values are given in Table I.

Table I

Dissociation Constants of Some Acids in H_2O and in D_2O at $25^\circ C$.

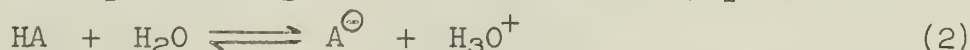
Acid	pK_a in H_2O	pK_a in D_2O	K_H/K_D
Formic	3.75	4.21	2.89
Benzoic	4.21	4.71	3.13
Acetic	4.74	5.26	3.33
2,4-dinitrophenol	4.02	4.53	3.28
2,2,2-trifluoroethanol	12.37	13.02	4.50
Water	14.00	14.81	6.5

In determining pK_a values, spectrophotometric, conductimetric and potentiometric experimental procedures have been used. In the potentiometric method, a standard glass electrode, usually with a calomel reference electrode, is used as for pH measurements in H_2O . By comparing the apparent pH of HCl solutions of equal molarity in H_2O and in D_2O , the following relationship was found, (eq.1) (7),

$$pD = \text{pH meter reading} + 0.40 \quad (1)$$

where pH meter reading is the reading obtained in D_2O solution using an electrode system standardized in H_2O solution. The relation was also shown to hold for weak acids such as formic and acetic acids by comparing K_H/K_n ratios, K_H is the equilibrium constant in H_2O and K_n is the equilibrium constant in D_2O - H_2O mixtures of atom fraction n of D in the solvent, obtained by the potentiometric method to those obtained by the conductimetric method which is believed to be quite reliable (8). Since the spectrophotometric method has given some results which are quite different than those obtained by the above methods (9), Long and co-workers (10) have recently studied the problem again. Using a glass electrode standardized in H_2O solution, they determined K_H/K_n ratios using acetic acid solutions in H_2O - D_2O mixtures with atom fraction of deuterium n . The results obtained at 25° are within $\pm 2\%$ of the values obtained conductimetrically. The ionic product of pure H_2O and D_2O - H_2O mixtures was also determined by taking measurements on 0.01 molar solutions of barium hydroxide at 25° . These experiments led to pK_w of 14.00 for pure H_2O and pK_w of 14.81 for pure D_2O . These values agree with conductimetric results, therefore the potentiometric method appears to be reliable.

The physical origin of the solvent isotope effects on acid dissociation constants is of interest in itself and as a first step toward understanding the effects on reaction rates. Bell (3) proposed that the effect could be explained, at least qualitatively, on the basis of zero point energies. In the reaction (eq. 2)



the process of dissociation involves a decrease in zero point energy. This means that the zero point energy lost on breaking the H-A bond and weakening the O-H bonds in the water molecule is not completely compensated for by the formation of an O-H bond in H_3O^+ . Since a D-A bond has a lower zero point energy than an H-A bond, the decrease will be smaller for deuterated systems. Therefore, there should be a smaller tendency to dissociate in D_2O systems.

Bunton and Shiner (11,12) have elaborated this approach to stress the importance of hydrogen bonding of both the acids and the bases present with the solvent in determining the solvent isotope effects and the dependence of hydrogen bond strength and therefore zero point energies on acidity and basicity.

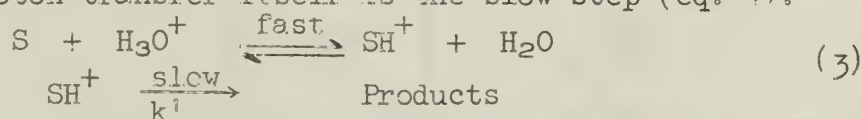
These workers focused attention on the fact that the conjugate base of an acid and a solvated proton will be hydrogen bonded to the solvent differently than the undissociated acid. When the solvent is changed to D₂O from H₂O, these differences will be altered, thus giving solvent isotope effects

A method for quantitative predictions of K_H/K_D for oxygen acids was set up. This method is based on the difference in the sum total of the vibrational frequencies for hydrogen bonded hydrogens in the undissociated acid and in the dissociated ions. An empirical formula was defined which relates the vibrational frequency of the hydrogen bonded atom to the pKa of the acid donating it, analogous to such a relationship giving the frequency of the hydrogen atoms donated from water to some acceptor in terms of the pKb of the acceptor. Then by inserting pKa values to obtain vibrational frequencies, and by making arbitrary assumptions as to the number of hydrogen bonds to a molecule, K_H/K_D can be predicted. For acetic acid, the predicted K_H/K_D is 3.1 at 25° which compares well with the observed value of 3.3. The predicted value of K_H/K_D for the dissociation of water is 4.6 at 25° compared to the observed value of 6.5.

In the above work, a solvated proton was represented as H₃O⁺. Whether this is the correct formulation or whether a higher or lower state of solvation is actually present is of interest in the relationships to be discussed later.

Gold and Lowe (13) have determined the ionic product of H₂O-D₂O mixtures at 25° using a glass electrode system. The observed difference in pKw in H₂O-D₂O mixtures and pure H₂O was plotted against n, the atom fraction of D in the solvent. When the observed curve was compared to curves predicted from derived equations, an equation based on H₃O⁺ as the model for a solvated hydrogen ion fit the data better than one based on an unsolvated hydrogen ion. This was taken by the authors as evidence that H₃O⁺ is the correct formula. Similar results were obtained by Long and co-workers (10), however they indicate that an equation based on H₉O₄⁺ as the model for a solvated hydrogen ion fits the data just as well.

Equations to Predict K_H/K_D and k_H/k_D in D₂O-H₂O mixtures.--Solvent isotope effects on reaction rates of acid catalyzed reactions may be of use in distinguishing between mechanisms. In particular, the effects may be useful in distinguishing a reaction in which a proton is donated to a substrate in a rapid equilibrium step followed by a rate determining decomposition of the protonated substrate (eq. 3) from a reaction in which the proton transfer itself is the slow step (eq. 4).



Several equations for determining the ratio of rates in H₂O and H₂O-D₂O mixtures of various composition have been derived to aid in mechanistic studies.

Gross-Butler Equation:--This equation was derived specifically for reactions involving a proton transfer preliminary to the rate determining step (2,14). Expressions for the rate of the reaction in H₂O, D₂O and mixtures of the two can be derived for a first order reaction based on equation 3. Then these can be combined to give equation 5 for a given acid concentration. This equation is based on the assumption that the ratio of rate constants (k'_D/k'_H) for the reaction of the conjugate acid of the substrate in D₂O and H₂O, respectively, is independent of the mixed solvent composition.

$$\frac{k_D}{k_H} = \frac{\left(\frac{a_{H^+}}{a_{H^+}}\right)_n \left(f_{*}\right)_H}{\left(\frac{a_{H^+}}{a_{H^+}}\right)_H \left(f_{*}\right)_n} + \frac{k_D}{k_H} \frac{\left(\frac{a_{D^+}}{a_{D^+}}\right)_n \left(f_{*}\right)_H}{\left(\frac{a_{H^+}}{a_{H^+}}\right)_H \left(f_{*}\right)_n} \quad (5)$$

$\left(\frac{a_{H^+}}{a_{H^+}}\right)$ = activity of the proton in H₂O

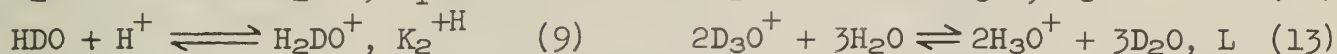
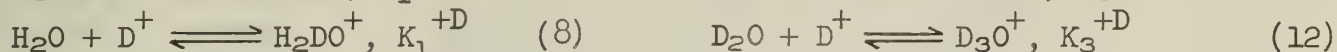
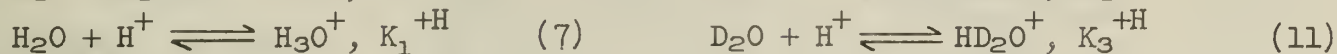
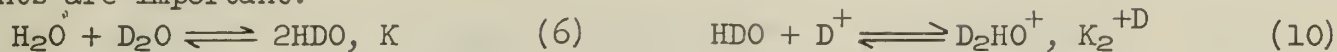
$\left(\frac{a_{D^+}}{a_{D^+}}\right)$ = activity of the deuteron in D₂O

n = atom fraction of deuterium in the solvent = $\frac{(D)}{(D+H)}$

f_{*} = activity coefficient of the reaction transition state

k_H, k_D, k'_D = observed rate constants in H₂O, D₂O-H₂O mixture and in D₂O, respectively

In a mixed D₂O-H₂O solvent, the following equilibria and their equilibrium constants are important.



The activities of the proton (a_{H^+}) and deuteron (a_{D^+}) are obtained by setting $K_1^{+\text{H}}$ (eq. 7) and $K_3^{+\text{D}}$ (eq. 12) equal to unity. The activities of the other lyonium ions, L_3O^+ where $L = \text{H}$ or D in any combination, can be expressed in terms of the equilibrium constants above. In an acidified mixed solvent, the total lyonium ion activity ($a_{\text{L}_3\text{O}^+}$) is the sum of the activities of the individual lyonium ions. By appropriate substitutions, the proton and deuteron activities are given by eq. 14,

$$\frac{a_{\text{H}^+}}{Q^1(n)} = \frac{(a_{\text{L}_3\text{O}^+})(a_{\text{H}_2\text{O}})^{1/2}}{Q^1(n)} \quad \text{and} \quad \frac{a_{\text{D}^+}}{Q^1(n)} = \frac{(a_{\text{L}_3\text{O}^+})(a_{\text{D}_2\text{O}})^{1/2}}{Q^1(n)(L)^{1/2}} \quad (14)$$

where $a_{\text{L}_3\text{O}^+}$ is the total activity of all lyonium ions present in the solution and $Q^1(n)$ is a shorter notation for equation 15.

$$Q^1(n) = \left[(a_{\text{H}_2\text{O}})^{3/2} + (a_{\text{H}_2\text{O}})^{1/2} (a_{\text{HDO}})k_2^{+\text{H}} + (a_{\text{H}_2\text{O}})^{1/2} (a_{\text{D}_2\text{O}})k_3^{+\text{H}} + \frac{(a_{\text{D}_2\text{O}})^{3/2}}{L^{1/2}} \right] \quad (15)$$

By assuming that the activity coefficients of the various lyonium ions are equivalent at a given acid concentration and that the ratio of the lyonium ion activity coefficient to the transition state activity coefficient is independent of solvent composition and with proper rearranging, equation 5 becomes equation 16.

$$\frac{k_n}{k_H} = \frac{1}{Q^1(n)} \left[(a_{\text{H}_2\text{O}})^{1/2} + \frac{k_D (a_{\text{D}_2\text{O}})^{1/2}}{k_H L^{1/2}} \right] \quad (16)$$

Since the equilibrium constant, K (eq. 6), has been found to be 3.96 (2,15), which is very near the statistical value of 4, the activities of H₂O and D₂O can be given in terms of n , the atom fraction of D in the solvent (eq. 17).

$$\frac{a_{\text{H}_2\text{O}}}{a_{\text{D}_2\text{O}}} = \frac{(1-n)^2}{n^2} \quad (17) \quad \text{By substitutions, eq. 16 may then be written as eq. 18.}$$

$$\frac{k_n}{k_H} = \frac{1}{Q^1(n)} \left[1-n + \frac{nk_D}{k_H L^{1/2}} \right] \quad (18)$$


Gold (22) has shown that by application of the rule of the geometric mean (23) the parameters $K_2^{+\text{H}}$ and $K_3^{+\text{H}}$ in $Q^1(n)$, $K_2^{+\text{H}} = 3/2L^{-1/6}$ (eq. 15) are related by equation 19, $K_3^{+\text{H}} = L^{-1/3}$ (19)

When these values are substituted into eq. 15 and activities are expressed in terms of n , $Q^1(n)$ becomes $(1-n+nL^{-1/6})^3$. This factor substituted into equation 18 transforms the Gross-Butler equation into the following form (eq. 20).

$$\frac{k_n}{k_H} = \frac{[1-n + nL^{-1/2}(k_D/k_H)]}{(1-n+nL^{-1/6})^3} \quad (20)$$

Solvent Structure Model.--Robertson and co-workers (16,17,18) have carried out a thorough study of the rate of hydrolysis of alkyl halides in neutral solution by a conductimetric method. The majority of the observed k_D/k_H ratios were between 0.70 and 0.90. Table II contains a sample of representative data. The observed solvent isotope effects were attributed to structure differences between H₂O and D₂O and changes in the structure as a reaction proceeds. From measurements of physical properties such as fluidity, dielectric relaxation, and ion mobility, they conclude that D₂O has a greater degree of structure than H₂O. Therefore the relative change in structure of the solvent on hydrolysis of RX will be different giving rise to the

Table II

Alkyl Halide	Temp.	$k_{D_2O} \times 10^5 \text{sec}^{-1}$	$k_{H_2O} \times 10^5 \text{sec}^{-1}$	k_D/k_H
Methyl chloride	89.96	4.38	5.64	0.78
Methyl Bromide	89.95	54.8	67.0	0.81
t-Butyl chloride	4.00	95.0	136.7	0.70
 -CHCl ₂	29.98	198	297	0.66

observed k_D/k_H ratio. The greater the change in structure as the reaction goes from the initial state to the transition state, the larger the solvent isotope effect. According to these authors, most of the effect is due to differences in initial state structure rather than differences at the transition state.

While Robertson did not propose a specific model for the solvent structure and derive equations for predictions from it, Swain and co-workers (19) have used a detailed model first proposed by Bernal and Fowler (20) on the basis of spectral and x-ray data. This model has each water molecule tetrahedrally hydrogen bonded to four other water molecules. The stronger these bonds are, the greater the degree of structure and the higher the librational frequency. The librational frequencies are those resulting from motion of the hydrogens in the water molecule perpendicular to the O-H line. The motion is similar to two pendulums moving in phase (21). The frequency of the librational motion is designated by ω_r in cm^{-1} . The librational temperature, Θ , (eq. 21) and the difference in librational temperatures between H_2O and D_2O , $\Delta\Theta$, (eq. 22) are given in terms of ω_r .

h = Planck's constant

k = Boltzman constant

c = speed of light

$\omega_r^1 = \omega_r/1.3815$

$$\Theta = \frac{h c \omega_r}{k} = 1.439 \omega_r \quad (21)$$

$$\Delta\Theta = \frac{h c \Delta\omega_r}{k} = \frac{h c (\omega_r - \omega_r^1)}{k} \quad (22)$$

The value for ω_r^1 , the librational frequency for D_2O , is arrived at on the basis of theoretical calculations. ω_r is determined from infrared spectra and is usually between 600 cm^{-1} and 700 cm^{-1} . In the above definitions, the internal vibrational frequencies of a water molecule have been ignored since they do not change with a structure change in the water. The degree of structure in D_2O is greater than that in H_2O under similar conditions due to its smaller librational thermal energy. The potential energy of interaction with other water molecules or solutes is the same for H_2O and D_2O , however the amplitudes of the librational oscillations are smaller leading to lower librational energy.

A decrease in structure caused, for example, by the addition of solutes also decreases ω_r , Θ , and $\Delta\Theta$. The quantity $\Delta\Theta$ therefore is a measure of the structure difference. By evaluating $\Delta\Theta$ for the initial and final states, the thermodynamic differences and therefore isotope effects may be calculated. It is the change in the structure difference of the two waters which results in the solvent isotope effects.

Since the thermodynamic properties of water can be calculated on the basis of this model and agree well with values from other sources, the authors assume that the model is reasonable and that the assumptions made are correct to a good approximation.

On this basis, the direction and magnitude of kinetic solvent isotope effects, not due to the transfer of a proton in the rate determining step, are determined by the difference in $\Delta\Theta$ between the transition state and the reactants. A reaction which destroys the structure of the water in the formation of the transition state, by the creation of charge, will proceed more rapidly in H_2O . A reaction which returns structure to the solvent, by neutralization or distribution of charge, will have a higher rate in D_2O .

To derive a definite equation, it is necessary to make an assumption equivalent to the assumption that the ratio of the activity coefficient of H_3O^+ to that of any of its isotopic isomers is unity and is independent of solvent composition. It is necessary to apply the rule of the geometric mean to determine the equilibrium concentrations of H_2DO^+ and HD_2O^+ . This is equivalent to assuming that each OH bond is independent of the others in the ion, in the sense that the OH bond, for example, in

HD_2O^+ is considered to have the same frequency as an OH bond in H_3O^+ . The symmetry numbers of the ions must also be taken into account. This gives equation 23 for the dissociation constants of acids.

$$\text{L}=\text{H or D} \quad \frac{K_{\text{H}}}{K_{\text{n}}} = \frac{[\text{H}_3\text{O}^+][\text{L}_2\text{O}]}{[\text{L}_3\text{O}^+][\text{H}_2\text{O}]} + \frac{K_{\text{H}}[\text{D}_3\text{O}^+][\text{L}_2\text{O}]}{K_{\text{D}}[\text{L}_3\text{O}^+][\text{D}_2\text{O}]} \quad (23)$$

The concentration ratios $[\text{H}_2\text{O}]/[\text{L}_2\text{O}]$, $[\text{D}_2\text{O}]/[\text{L}_2\text{O}]$, $[\text{H}_3\text{O}^+]/[\text{L}_3\text{O}^+]$ and $[\text{D}_3\text{O}^+]/[\text{L}_3\text{O}^+]$ can be calculated by using the assumptions above.

The treatment can be extended to rate constant ratios for acid catalyzed reactions run in mixed solvents. For a reaction where a proton is transferred to the substrate in a prior equilibrium, equation 24 gives $k_{\text{n}}/k_{\text{H}}$.

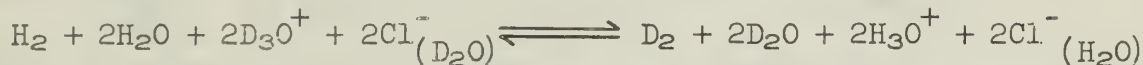
$$\frac{k_{\text{n}}}{k_{\text{H}}} = \frac{[\text{H}_3\text{O}^+]_{\text{H}} [\text{H}_2\text{O}]_{\text{H}} (\gamma_{\text{H}_3\text{O}^+})_{\text{H}} (\gamma_{\text{H}_2\text{O}})_{\text{H}} (\gamma_{\text{S}})_{\text{H}} (\gamma_{\text{SH}^+}^*)_{\text{H}}}{[\text{H}_3\text{O}^+]_{\text{H}} [\text{H}_2\text{O}]_{\text{n}} (\gamma_{\text{H}_3\text{O}^+})_{\text{H}} (\gamma_{\text{H}_2\text{O}})_{\text{n}} (\gamma_{\text{S}})_{\text{H}} (\gamma_{\text{SH}^+}^*)_{\text{n}}} + \frac{k_{\text{D}} [\text{D}_3\text{O}^+]_{\text{n}} [\text{D}_2\text{O}]_{\text{D}} (\gamma_{\text{D}_3\text{O}^+})_{\text{n}} (\gamma_{\text{D}_2\text{O}})_{\text{D}} (\gamma_{\text{S}})_{\text{n}} (\gamma_{\text{SD}^+}^*)_{\text{D}}}{k_{\text{H}} [\text{D}_3\text{O}^+]_{\text{D}} [\text{D}_2\text{O}]_{\text{n}} (\gamma_{\text{D}_3\text{O}^+})_{\text{D}} (\gamma_{\text{D}_2\text{O}})_{\text{n}} (\gamma_{\text{S}})_{\text{D}} (\gamma_{\text{SD}^+}^*)_{\text{n}}} \quad (24)$$

Since H_2O , D_2O and HDO form ideal solutions, $(\gamma_{\text{H}_2\text{O}})_{\text{n}} = (\gamma_{\text{H}_2\text{O}})_{\text{H}}$ and $(\gamma_{\text{D}_2\text{O}})_{\text{n}} = (\gamma_{\text{D}_2\text{O}})_{\text{D}}$ and the following ratios of activity coefficients can be set equal to one; $(\gamma_{\text{H}_2\text{O}})_{\text{H}}/(\gamma_{\text{H}_2\text{O}})_{\text{n}}$ and $(\gamma_{\text{D}_2\text{O}})_{\text{D}}/(\gamma_{\text{D}_2\text{O}})_{\text{n}}$. Since H_3O^+ and D_3O^+ do not change the structure of water, as shown by no change in the librational frequency of acidic water solutions, $(\gamma_{\text{H}_3\text{O}^+})_{\text{H}} = (\gamma_{\text{H}_3\text{O}^+})_{\text{n}}$ and $(\gamma_{\text{D}_3\text{O}^+})_{\text{n}} = (\gamma_{\text{D}_3\text{O}^+})_{\text{D}}$. Therefore the activity coefficient ratios $(\gamma_{\text{H}_3\text{O}^+})_{\text{n}}/(\gamma_{\text{H}_3\text{O}^+})_{\text{H}}$ and $(\gamma_{\text{D}_3\text{O}^+})_{\text{n}}/(\gamma_{\text{D}_3\text{O}^+})_{\text{D}}$ are equal to one. The assumptions that $(\gamma_{\text{SH}^+}^*)_{\text{n}}/(\gamma_{\text{SH}^+}^*)_{\text{H}} = (\gamma_{\text{S}})_{\text{n}}/(\gamma_{\text{S}})_{\text{H}}$ and $(\gamma_{\text{SD}^+}^*)_{\text{n}}/(\gamma_{\text{SD}^+}^*)_{\text{D}} = (\gamma_{\text{S}})_{\text{n}}/(\gamma_{\text{S}})_{\text{D}}$ are equivalent to assuming that solvation of the transition state changes in the same way with n as solvation of the ground state.

When concentrations in equation 24 are expressed in terms of n , the atom fraction of D in the solvent, equation 25 is derived.

$$\text{Equation 25 is equivalent to the Gross-Butler equation (eq. 20).} \quad \frac{k_{\text{n}}}{k_{\text{H}}} = \frac{1-n+nL^{-1/2} (k_{\text{D}}/k_{\text{H}})}{(1-n + nL^{-1/2})^3} \quad (25)$$

The evaluation of L has led to several results. Purlee (2) calculated L from the free energy change of the reaction



and found that $L=11$. Swain and co-workers (19) have found $L=8.2$ from a similar calculation but using a different experimental method.

Recently a direct method for measuring L has been reported by Gold (26) and Kresge and Allred (27). When a strong mineral acid is added to water, the water proton signal in the n.m.r. spectrum is shifted down field, the amount of shift being dependent on the number of protons in the acid species. Thus the shift can be related to the amount of D_2O and H_2O in a mixed solvent and then to the equilibrium constant L . Using equivalent experimental methods and calculations, m , the observed quantity, was found to be 0.67 ± 0.02 by Kresge and Allred and $m=0.68$ and 0.69 ± 0.02 by Gold. These correspond to $L=11$ and $L=9.3$ since $L=m^{-6}$.

Purlee calculated the value Q_{n}^{H} using equation 15 with $L=11$ and activities given in terms of n . The equilibrium constants K_2^{H} and K_3^{H} in equation 15 were treated as parameters and adjusted to give a best fit of Q_{n}^{H} to points calculated from thermodynamic distribution constants for picric acid between H_2O and H_2O - D_2O mixtures. The best values found are: $K_2^{\text{H}} = 1.02$ and $K_3^{\text{H}} = 1.37$.

Linear equation.---The derivations above are all based on the assumptions that a solvated hydrogen ion is best represented by H_3O^+ . This led to a cubic form in the denominator of equations 20 and 25. If the hydrogen ion is assumed to be unsolvated or that the molecules in the solvation sphere have no influence on the behavior of the hydrogen ion, the denominator becomes linear in that it is no longer raised to the

third power (28). Thus equations 20 and 25 become equation 26.

$$\frac{k_n}{k_H} = \frac{1-n + nL^{-1/2}(k_D/k_H)}{(1-n + nL^{-1/2})} \quad (26)$$

Medium Effect.--If it is assumed that changes in K_H/K_n and k_n/k_H are due to medium effects, the following equation results. $\frac{K_H}{K_n} = \left(\frac{k_H}{k_D}\right)^n$ (27)

Rate Determining Proton Transfer.--Gold (22) has derived an equation for the rate constant of an acid catalyzed reaction in D_2O-H_2O mixtures in which the proton transfer is the rate determining step. If the catalyzing agent is a strong acid present in concentration C , the rate is given by equation 28. $\text{rate} = k_n[S]C$ (28)
The rate constant, k_n , is the sum of terms for each lyonium ion present in the solution (eq. 29)

$$k_n C = k_{H_3O^+}^H [H_3O^+] + (k_{H_2DO^+}^H + k_{H_2DO^+}^D) [H_2DO^+] + (k_{HD_2O^+}^H + k_{HD_2O^+}^D) [HD_2O^+] + k_{D_3O^+}^D [D_3O^+] \quad (29)$$

The k 's indicate rate constants for transfer of H^+ or D^+ , indicated by superscript, to the substrate from the ion given as the subscript. The quantities in brackets are concentrations which can be related to L (eq. 13) and n , the atom fraction of D in the solvent. It is assumed that the rate constants for H^+ or D^+ transfer from the lyonium ions present to S , the substrate, are related to the acidity constants by an expression of the general form of the Brönsted catalysis law (eq. 30). $k = pG\left(\frac{K}{P}\right)^\alpha$ (30)

This treatment gives the following rate constant expressions:

$$\begin{aligned} k_{H_2DO^+}^H &= 2/3 m^{-\alpha} k_{H_3O^+}^H & k_{HD_2O^+}^D &= 2/3 m^\alpha k_{D_3O^+}^D \\ k_{HD_2O^+}^H &= 1/3 m^{-2\alpha} k_{H_3O^+}^H & k_{H_2DO^+}^D &= 1/3 m^{2\alpha} k_{D_3O^+}^D \end{aligned} \quad m = L^{-1/6}$$

Substitution of the above relationships and the relationships for concentration in terms of L into equation 28, gives equation 31.

$$k_n = \frac{k_H}{Q^1(n)} (1-n) \left\{ (1-n)^2 + 2(1-n)nm^{(1-\alpha)} + n^2m^{2(1-\alpha)} \right\} + \frac{k_D}{Q^1(n)} nm \left\{ (nm)^2 + 2(1-n)nm^{(1+\alpha)} + (1-n)^2m^{2\alpha} \right\} \quad (31)$$

Evaluation of Applicability.--Gold has shown (22) that the Gross-Butler equation (eq. 20) is quite insensitive to changes in the value of L . When the expected rate ratios, k_n/k_H , were calculated for $L = 1.88, 5.619, 11.06$ and 21.43 ; $k_D/k_H = 1, 2, 3$; and n from 0 to 1, it was found that for $k_D/k_H = 2$, the predicted curves for the three largest L values are within $\pm 1\%$ of each other. The difference is slightly larger for $k_D/k_H = 3$, but a reliable best fit can not be made. For $k_D/k_H = 1$, it appears that one value of L should give a best fit. However, data for reactions of this type are too limited to make a choice.

This author has also calculated predicted K_H/K_n curves by equation 20 and the linear equation (eq. 26) with $L = 11$ and for various K_H/K_D ratios. The curves by each equation for K_H/K_D greater than about 1.5 are likely to be within experimental error of each other, (Fig. 1). The same will hold for rate ratios. Thus the use of these equations to aid in assigning the correct representation to the solvated hydrogen ion is limited.

Long (28) has derived equation 26, the linear equation, but has replaced $L^{-1/2}$ by ϵ . According to this author, if unspecified solvation is assumed, there will be no link between ϵ and $L^{-1/2}$. Therefore, ϵ is treated as a parameter and adjusted to give a best fit to the data. It was found that $\epsilon = 0.45$ fit best. This equation was then used to show that the linear equation gives better predictions than the Gross-Butler equation (eq. 20). However, in most cases it is difficult to make a reliable choice (Fig. 2,3,4).

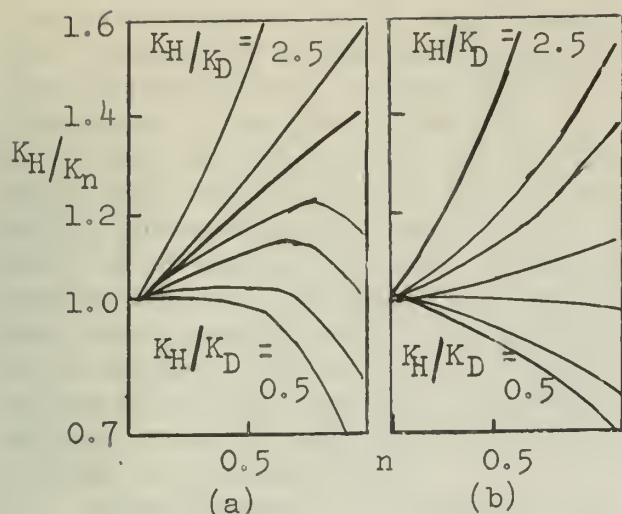


Fig. 1: Comparison of K_H/K_n predictions by the Gross-Butler equation, (a), and the linear equation, (b), for various K_H/K_D ratios.

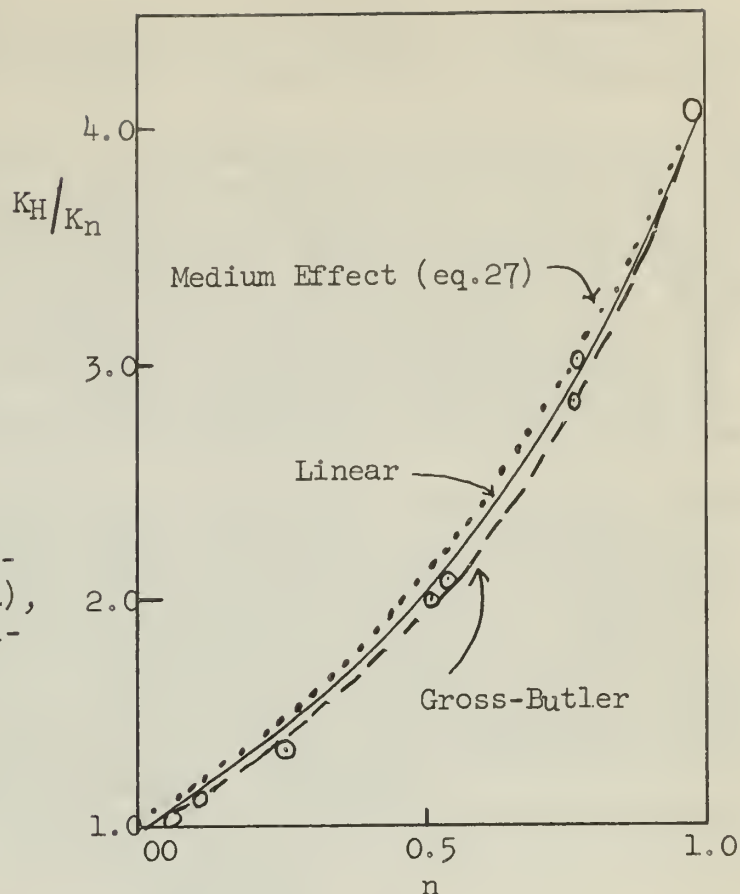


Fig. 2: Comparison of equations to data for ionization of hydroquinone.

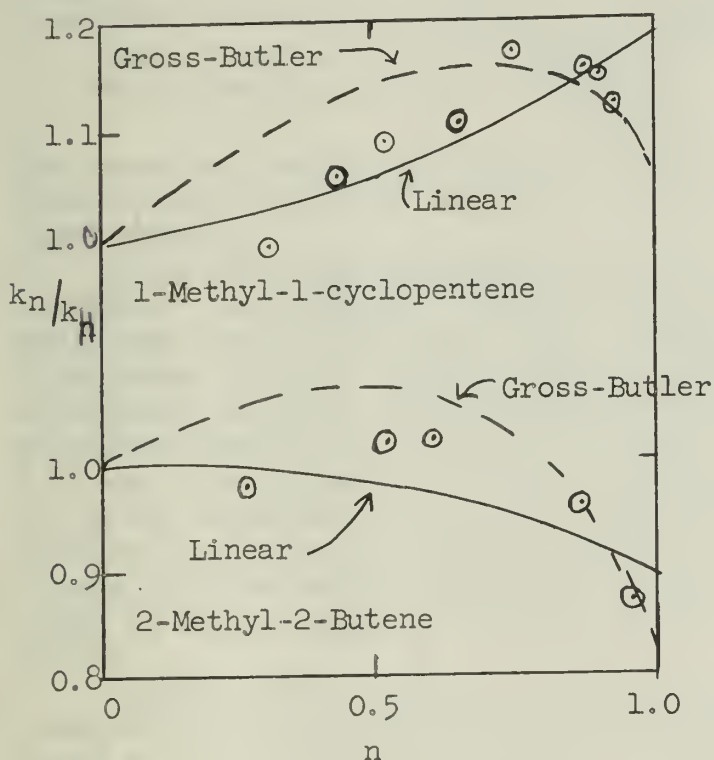


Fig. 3: Comparison of predictions to data for hydration of olefins.

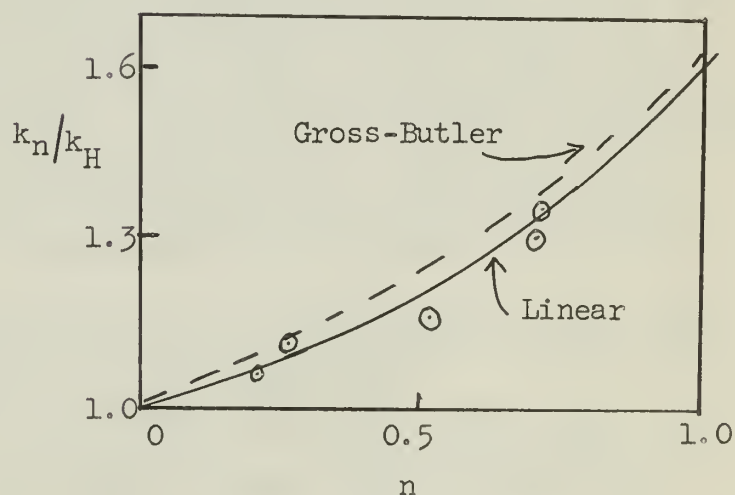


Fig. 4: Predictions for hydrolysis of Methyl Acetate compared to data.

Since the above curves were calculated from equations derived for a prior equilibrium mechanism, the fit to the data are assumed to indicate such a mechanism. If a rate determining proton transfer to the substrate is involved, it is generally assumed that plots of k_n/k_H versus n will be linear. This implies that mechanistic studies of acid catalyzed reactions should be run in D_2O - H_2O mixtures rather than pure H_2O and D_2O only.

However, it is questionable whether a rate determining proton transfer to a substrate should give a linear plot. In mixtures of D_2O and H_2O , the following lyonium

ions are present; H_3O^+ , H_2DO^+ , HD_2O^+ , D_3O^+ , in order of increasing acid strength. The proportion of the more acidic ions will increase as n increases. However, it is not necessary that the total acidity will increase linearly with n and therefore the rates would not vary linearly.

This effect on rate ratio plots is shown by calculations using equation 30. When this was done for $\alpha=0, 0.3, 0.5, 0.7$, and 1 ; $L = 11$; and $k_D/k_H = 2$, which is near the value for most reactions studied, it was found that all the predicted points are within $\pm 2\%$ of those predicted by the Gross-Butler equation. Thus it is experimentally impossible to distinguish between the two mechanism, at least when $k_D/k_H = 2$. Whether the method would work for higher and lower k_D/k_H ratios has not been studied but it is indicated that if $\alpha = 1$, there are no cases where the two can be separated since equation 30 then becomes equivalent to 20. It thus is apparent that the ability of solvent isotope effects to distinguish between mechanisms in acid catalyzed reactions is not well established.

Applications.--In addition to the applications shown above, rate studies in D_2O - H_2O mixtures have been carried out on several other reactions. These include the bromination of acetone, hydrolysis of diethyl acetal of acetaldehyde, the decomposition of diazoacetic ester and the acid catalyzed inversion of sucrose. It has been shown (2,28) that the k_n/k_H ratios determined experimentally can be fit reasonably well with the Gross-Butler equation. This is interpreted to indicate a prior equilibrium mechanism for these reactions. It should be noted that these reactions have k_D/k_H ratios of 2.0 to 2.9. Thus in view of the discussion of the rate determining proton transfer given earlier, additional information would be desirable.

More recently, Kreevoy (29-31) and co-workers have studied the deoxymercuration of the following compounds:

$$\begin{array}{ccc} \text{CH}_3-\text{CH}-\text{CH}_2 & \text{and} & \text{CH}_3-\text{CH}-\text{CH}_2 \\ | & & | \\ \text{OH} & \text{HgI} & \text{OCH}_3 \text{ HgI} \end{array}$$

The reactions have k_D/k_H ratios of 2.16 and 2.80 respectively. Their conclusion for mixed solvents are the same as for the reactions above and are subject to the same reservations.

The acid catalyzed mutarotation of glucose has been the subject of several discussions. The k_D/k_H vs. n plots are nearly linear. Purlee (2) interpretes this to mean that the reaction has a rate determining proton transfer. However, since several independent studies indicate that a prior equilibrium actually is present, Gold (28) interprets this as evidence that the Gross-Butler equation is not reliable for mechanism assignments. Recently Wiberg (41) has shown that the small k_D/k_H ratio, 0.73, can be rationalized in the following manner. Since D_3O^+ is a stronger acid than H_3O^+ the prior equilibrium in D_2O will lie toward the conjugate acid of the substrate. However, the rate determining step is the removal of a proton. This proton can exchange with the solvent before it is removed, thus giving a rate reduction in D_2O which is large enough to overcome the rate enhancement from increased concentration of SH^+ .

Several other studies, of which references 32-40 are representative, have been carried out in pure D_2O and H_2O but at present have not been studied in H_2O - D_2O mixtures to gain the maximum amount of information on the mechanisms.

Summary.--It has been shown that acids dissociate less in D_2O than in H_2O . Reaction rates also differ for reactions run in H_2O and D_2O . Several equations have been derived to predict k_n/k_H and K_H/K_n . The basis of these equations and their application to mechanistic studies have been discussed.

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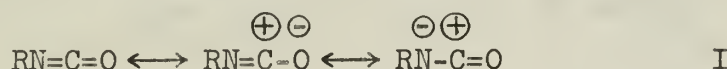
CYCLIZATIONS OF PROPYNYL CARBAMATES AND PROPYNYLUREAS

Presented by Barry E. Galbraith

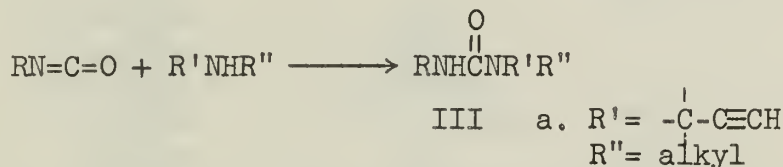
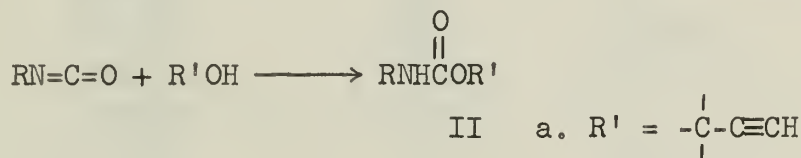
May 4, 1964

Introduction: Organic isocyanates (I) have been studied for more than a century. The chemistry of these compounds has been the subject of a number of literature surveys (1-6). Of recent interest have been reactions of isocyanates with acetylenic alcohols and amines to give O-propynyl carbamates (IIa) and propynylureas (IIIa), respectively, which can undergo intramolecular cyclization. This abstract is a discussion of the formation and cyclization of such carbamates and ureas.

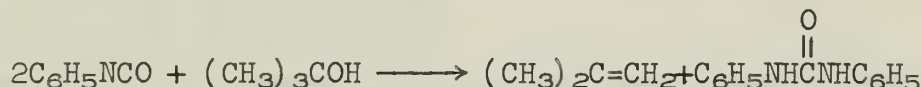
The carbonyl carbon atom of an isocyanate (I) is readily attacked by nucleophilic species. The reactions with alcohols to give carbamates (II) and with primary and



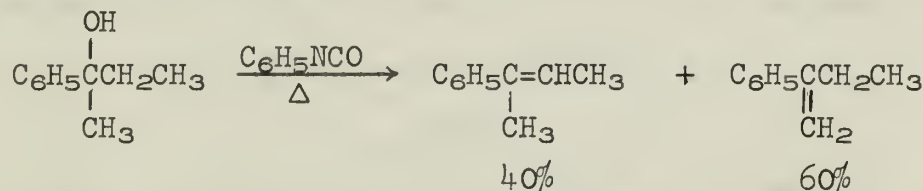
secondary amines to give substituted ureas (III) may be visualized as additions to the carbon-nitrogen double bond of the isocyanate.



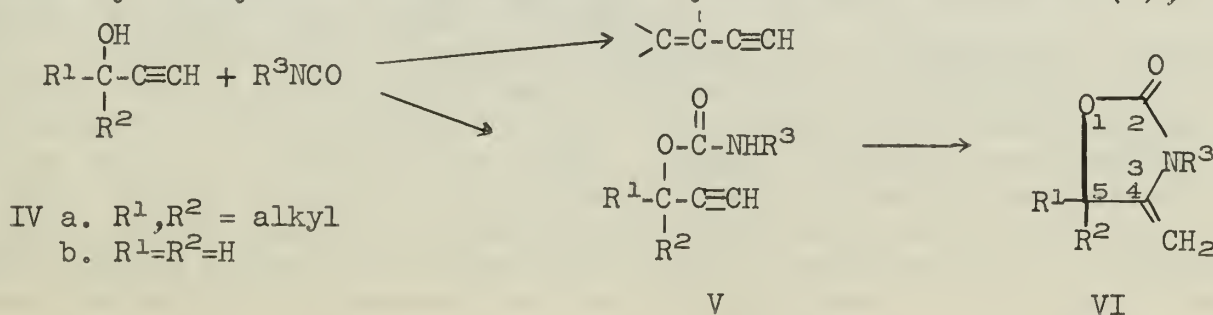
Simple primary and secondary alcohols react readily with isocyanates giving nearly quantitative yields of the carbamates. The latter compounds, especially those derived from certain readily available aromatic isocyanates, are satisfactory solid derivatives for the identification of the alcohols (3). In general, however, tertiary alcohols require more vigorous conditions for carbamate formation. As a result, dehydration of the alcohol usually occurs (5). A synthesis of α -substituted styrenes and other olefins by heating tertiary alcohols with aryl isocyanates is based upon



this dehydration (7,8,9). The elimination tends to follow the Hofmann rule.



Carbamates of t-ethynyl alcohols: Tertiary alcohols with an ethynyl group at the 1-position undergo carbamate formation more readily than do other tertiary alcohols. A marked reduction in steric hindrance in these compounds has been attributed to the linear ethynyl substituent (10). Although prolonged heating of t-ethynyl alcohols (IVa) with aryl isocyanates does result in dehydration of the alcohol (8), under less



strenuous conditions either carbamates (V) or their cyclic isomers, 4-methylene-2-oxazolidinones (VI), can be isolated, depending on the reaction conditions. Some of the carbamates and corresponding oxazolidinones which have been reported are listed in Table I.

TABLE I
Carbamates (V) and 4-Methylene-2-oxazolidinones (VI)

$$\begin{array}{c}
 \text{O} \\
 \parallel \\
 \text{O}-\text{C}-\text{NHR}^3 \\
 | \\
 \text{R}^1-\text{C}-\text{C}\equiv\text{CH} \\
 | \\
 \text{R}^2
 \end{array}
 \quad \text{V}$$

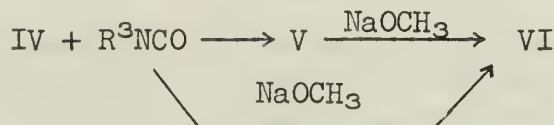
$$\begin{array}{c}
 \text{O} \\
 \parallel \\
 \text{O} \quad 2 \\
 | \quad | \\
 1 \quad 3 \text{NR}^3 \\
 | \quad | \\
 \text{R}^1 \quad 4 \\
 | \quad | \\
 \text{R}^2 \quad \text{CH}_2
 \end{array}
 \quad \text{VI}$$

		reference	
V, VI	R ¹ , R ²	R ³	V
a	CH ₃ , CH ₃	C ₂ H ₅	11
b	CH ₃ , CH ₃	C ₆ H ₅	12, 16, 21
c	CH ₃ , CH ₃	3-ClC ₆ H ₄	21
d	CH ₃ , CH ₃	4-ClC ₆ H ₄	-
e	CH ₃ , C ₂ H ₅	H	12
f	CH ₃ , C ₂ H ₅	C ₂ H ₅	11
g	CH ₃ , C ₂ H ₅	C ₆ H ₅	-
h	CH ₃ , C ₂ H ₅	4-ClC ₆ H ₄	-
j	CH ₃ , C ₂ H ₅	3, 4-Cl ₂ C ₆ H ₃	13, 21
k	(CH ₂) ₅	H	12
m	(CH ₂) ₅	C ₆ H ₅	12, 21
n	(CH ₂) ₅	3-ClC ₆ H ₄	13, 21
o	(CH ₂) ₅	3, 4-Cl ₂ C ₆ H ₃	21
p	H, H	H	21
q	H, H	C ₂ H ₅	21
r	H, H	C ₆ H ₅	12, 13, 21, 22
s	H, H	3, 4-Cl ₂ C ₆ H ₃	13
			VI
			12
			12, 16, 21
			21
			16
			-
			12
			12
			10 ^a , 12, 16
			13, 21
			-
			12, 13, 21, 22
			10 ^b , 13, 21
			13, 21
			21
			21
			21
			12, 13, 21
			13

^a reported to be the oxazinone VIIh

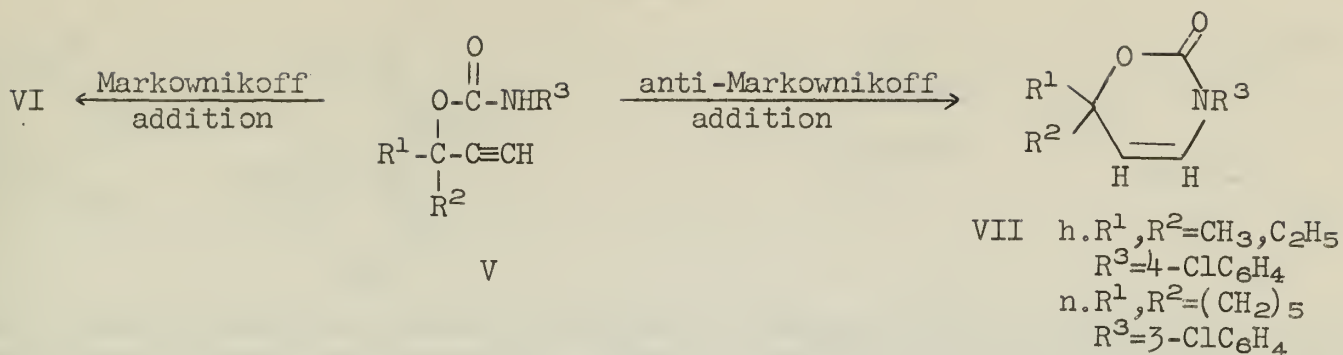
^b reported to be the oxazinone VIIn

Shachat and Bagnell (12) obtained 4-methylene-2-oxazolidinones (VI) from the reaction of 1-ethynyl alcohols (IV) with isocyanates in the presence of a catalytic amount of sodium methoxide. In the absence of base, the carbamates (V) were isolated.

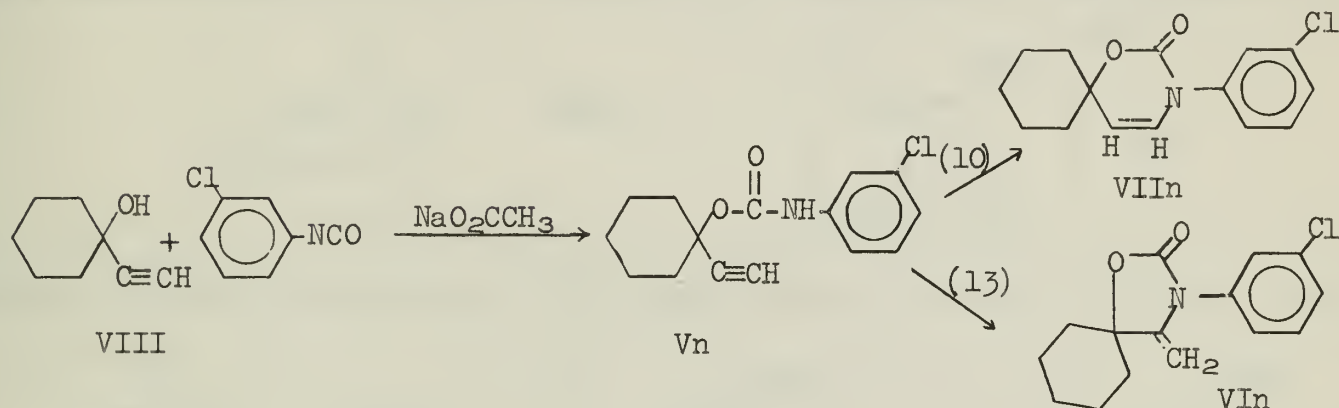


These could be readily cyclized by treatment with sodium methoxide. That cyclization occurred was indicated by infrared (IR) spectral data. Thus the IR spectra of the products obtained in the presence of base showed characteristic absorption bands at 1775-1760 (C=O) and 1658-1635 cm⁻¹ (>C=CH₂). The regions 3600-3100 and 2200-2000 cm⁻¹ contained no significant absorption. In contrast, the spectra of several carbamates synthesized for comparison exhibited bands at 3460-3400 (N-H), 3330-3300 (≡C-H), 2140-2100 (C≡C), 1740 (C=O), and 1585 cm⁻¹ (-CONH-).

The cyclization of the O-propynyl carbamates (V) to 4-methylene-2-oxazolidinones (VI) appears to be a particularly facile intramolecular nucleophilic addition to an acetylenic bond. If the N-H addition occurred in the anti-Markownikoff direction, the product would be a 1,3-oxazin-2-one (VII). Shapiro, Bandurco, and Freedman (10) assigned this type of structure to the product obtained from the reaction of 1-ethynylcyclohexanol (VIII) with 3-chlorophenyl isocyanate in the presence of sodium acetate. The only evidence presented by these authors which would favor the six-membered ring over the alternative five-membered one was the appearance in the IR spectrum of two



bands at about 1410 and 705 cm^{-1} , attributed to cis-hydrogens on an olefinic double bond. The same reaction was carried out by Stoffel and Speziale (13), who isolated only a compound identified as 3-(3-chlorophenyl)-4-methylene-1-oxa-3-azaspiro[4.5]-

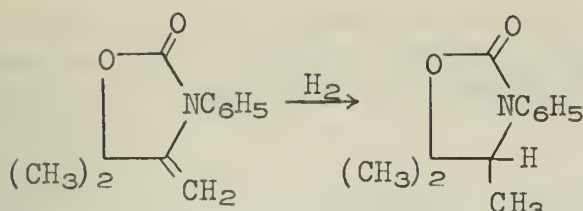


decan-2-one (VIIn). This compound was also obtained by using pyridine instead of sodium acetate or, more simply, by heating the isocyanate and alcohol or the pre-formed carbanilate (Vn). The authors presented spectral data in support of the 2-oxazolidinone structure (VIIn). Thus it was found that the carbonyl absorption in the IR spectra of five-membered heterocyclic compounds derived from ureas (X) and those derived from carbanilates (XII) is shifted to higher frequency than that of the corresponding six-membered compounds (IX, XI) (14). IR spectra of the cyclic products

	Z	y	$\nu_{\text{C=O}} (\text{cm}^{-1})$
IX	NH	3	1653
X	NH	2	1712
XI	O	3	1695
XII	O	2	1754

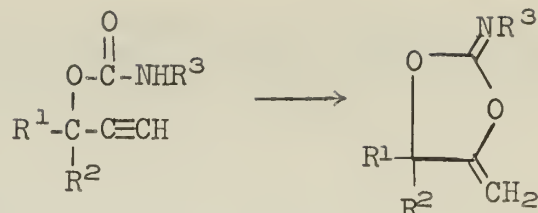
prepared by Stoffel and Speziale (13) showed the characteristic absorption band for the carbonyl group at 1754-1739 cm^{-1} indicative of the five-membered ring. This method of distinguishing between five- and six-membered cyclic carbonyl compounds by the shift in IR carbonyl absorption has previously been described for ketones by Bellamy (15). The IR spectra of VI also showed absorption at 1681-1653 cm^{-1} ($\text{C}=\text{CH}_2$). The bands at 3390 (N-H) and 3333 cm^{-1} ($\text{C}\equiv\text{C}-\text{H}$) associated with the carbamates (V) were absent.

Nuclear magnetic resonance (NMR) spectra of the compounds confirm unequivocally that the 4-methylene-2-oxazolidinone structure (VI) is correct. Easton, Cassady, and Dillard (16) reported that the NMR spectrum of VIId showed a series of four peaks centered at τ , 5.93 with a coupling constant of about 3 cycles per second (cps), indicative of nonequivalent hydrogens on a doubly bonded carbon atom. Similarly, in the spectrum of VIj, a symmetrical 1:2:2:1 "quartet" at τ , 5.85 was assigned to the 4-methylene hydrogens (13). The coupling constant of 3.5 cps is compatible with hydrogens of the exocyclic methylene group but lower than the predicted value of 10-15 cps for olefinic cis-hydrogens. Further confirmation was obtained (16) by hydrogenation of VIb to XIII, the NMR spectrum of which contained a doublet at τ , 8.87 (4- CH_3) and a quartet at τ , 5.91 (4-H).



VIb

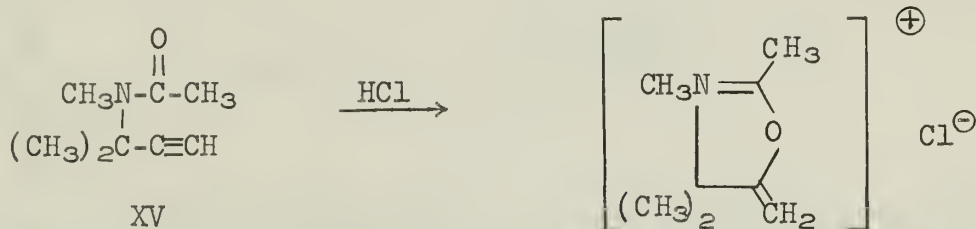
XIII



V

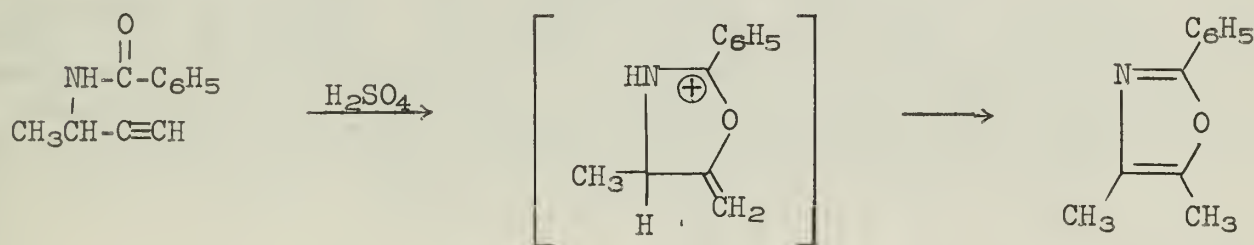
XIV

The evidence summarized above conclusively eliminates the 1,3-oxazin-2-one structure (VII) from further consideration. Another possible cyclization product would be an iminocarbonate (XIV), which could be formed if oxygen ring closure occurred. This type of cyclization has been reported to occur when N-acyl-*t*-ethynylamines (XV) are treated with mineral acid (17,18). Oxazole (XVI) formation was observed in a similar



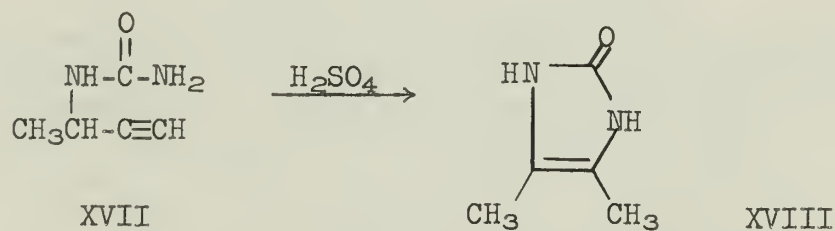
XV

reaction carried out by Yura (19). If oxygen ring closure did occur in the cycliza-



XVI

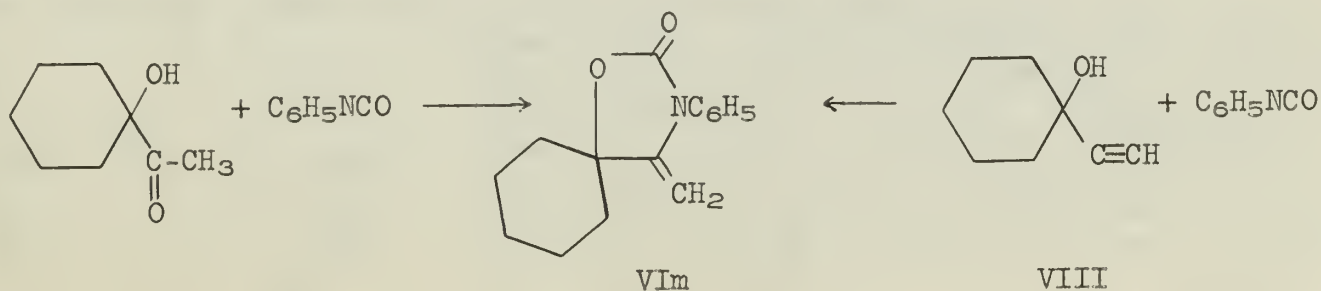
tion of the O-propynyl carbamates (V), the iminocarbonate (XIV) should be readily detectable by IR spectroscopy. Iwai (20) has noted that although O-ring closure has been observed with N-propynyl amides, as shown above, the propynylurea XVII gives only an imidazolinone (XVIII) when treated with sulfuric acid.



XVII

XVIII

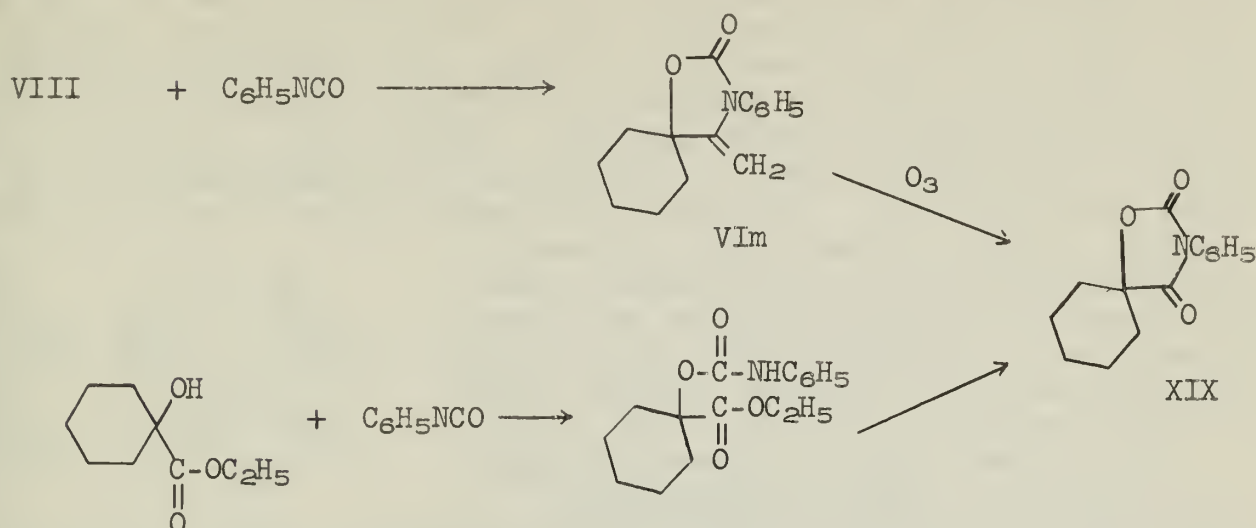
Chemical evidence in support of the 4-methylene-2-oxazolidinone assignment for the cyclic products from O-propynyl carbamates (V) has also been obtained. Cameron (21) and Easton, *et al.* (16) used 2-hydroxy ketones to prepare compounds identical with those isolated from the reactions of *t*-ethynyl alcohols (IVa) with isocyanates. For example, refluxing a solution of 1-ethynylcyclohexanol and phenyl isocyanate in pyridine gave 4-methylene-3-phenyl-1-oxa-3-azaspiro[4,5]decan-2-one (VIIm), which was



VIIm

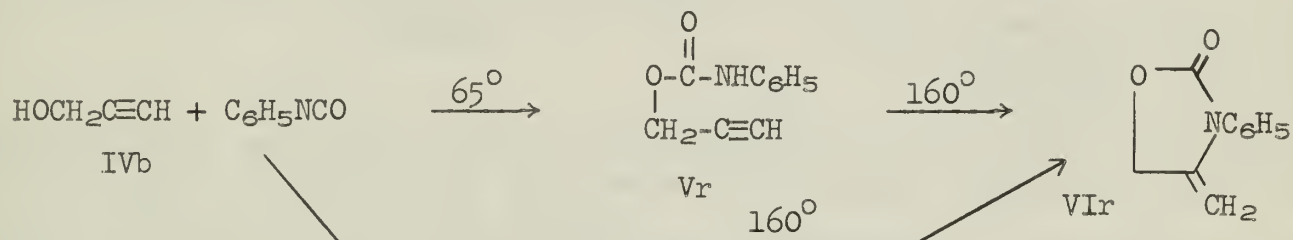
VIII

identical with the product of the reaction of 1-acetylcyclohexanol with phenyl isocyanate (21). Sisido, Hukuoka, Tuda, and Nozaki (22) treated the same compound (VIIm) with ozone and found the product (XIX) to be identical with that prepared from ethyl



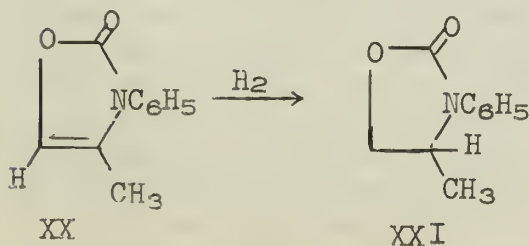
1-hydroxycyclohexyl carboxylate and phenyl isocyanate. It has been definitely established, then, that O-propynyl carbamates (V) can be cyclized to 4-methylene-2-oxazolidinones (VI) under a variety of experimental conditions.

Propargyl carbanilate: The carbamates (V) discussed above contained alkyl groups at carbon 1 of the propynyl substituent (R^1, R^2). Propargyl carbanilate (Vr) will now be considered. Stoffel and Speziale (13) found that heating propargyl alcohol (IVb) with phenyl isocyanate to 65° gave the carbanilate (Vr). Heating the same reactants or Vr to 160° gave 4-methylene-3-phenyl-2-oxazolidinone (VIr), similar to the reactions considered above. Compound VIr could also be obtained directly from IVb and



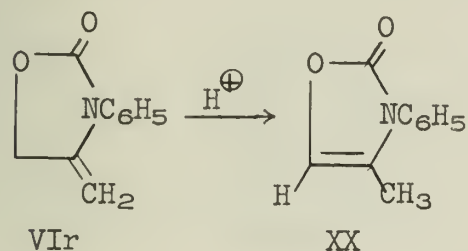
phenyl isocyanate using pyridine (13,21), sodium acetate (13), potassium hydroxide (13,22), or sodium methoxide (12). The NMR spectrum of VIr showed a band at τ , 2.77 (aromatic) and two multiplets at τ , 5.08 and 5.92, with intensity ratios of 5:2:2, respectively (12). Stoffel and Speziale (13) assigned the latter two multiplets, appearing at τ , 5.05 and 5.85 in their data for VIr, to the endocyclic and exocyclic methylene hydrogens, respectively. The absorption at τ , 5.05 was reported to be a triplet and that at τ , 5.85 a "quartet", with a coupling constant between the two methylene groups of 2.5 cps. It is difficult to explain this observed pattern. In order for the former absorption to be a triplet, the coupling between the endocyclic methylene hydrogens and each of the exocyclic hydrogens must be equal. Moreover, if the "quartet" at τ , 5.85 is due to geminal coupling of the 4-methylene hydrogens, apparently no splitting of these peaks due to coupling with the 5-hydrogens is observed.

The endocyclic isomer of VIr, 4-methyl-3-phenyl-4-oxazolin-2-one (XX), has also been reported. Shachat and Bagnell (12) obtained XX as a minor product in the preparation of VIr with sodium methoxide as a catalyst. Sisido, *et al.* (22) found that treatment of propargyl carbanilate (Vr) with methanolic potassium hydroxide gave XX in all but one case (in which VIr contaminated with XX was obtained). The NMR spectrum of XX showed a doublet at τ , 8.25, a quartet at τ , 3.33, and a multiplet



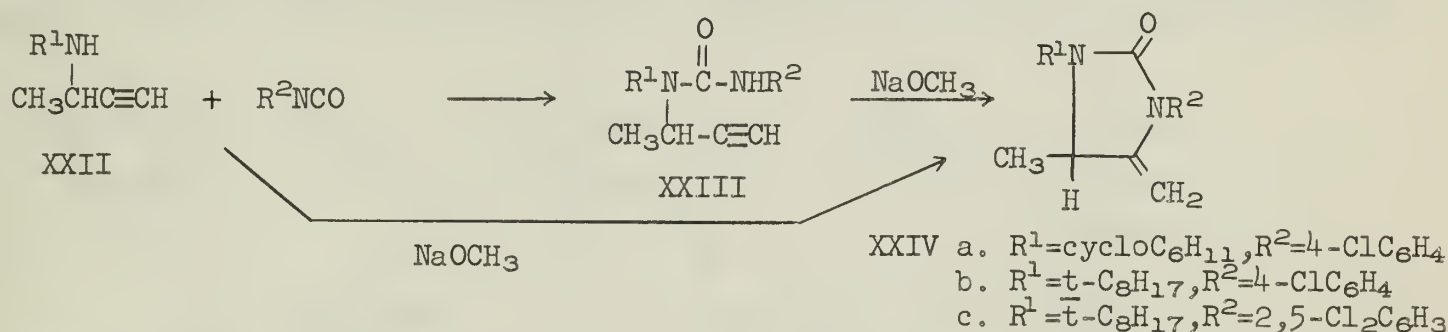
at τ , 2.77, with intensity ratios of 3:1:5, respectively (12). Similar data were given by Sisido, *et al.* (22), who reported a doublet at τ , 8.1 and a quartet at τ , 3.4 in an intensity ratio of 3:1 with a coupling constant of 2.0 cps. Compound XX was hydrogenated to XXI, the NMR spectrum of which was consistent with the assigned structure.

A possible explanation for the conflicting results summarized above has been proposed by Stoffel and Dixon (23). These authors have found that heating propargyl alcohol with phenyl isocyanate to 185° in the presence of strong acid gives only the carbanilate (Vr) and no cyclic product. Addition of excess base results in cyclization of Vr to VIr, in agreement with the majority of previous observations. Treatment of VIr with strong acid, however, gives the isomeric XX. In no case could XX be obtained



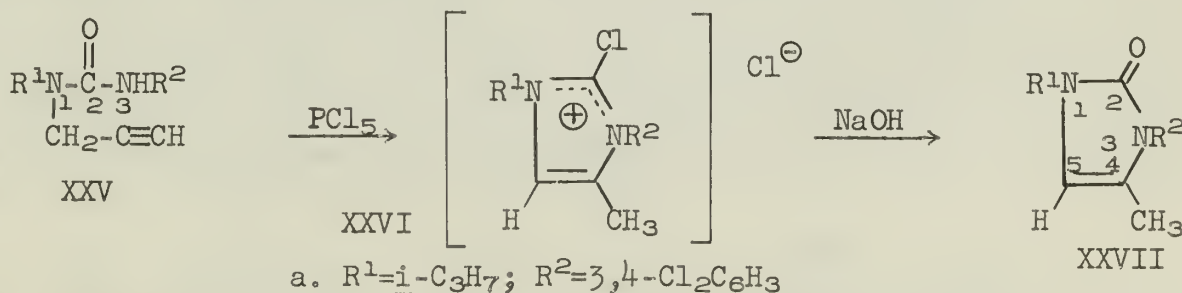
without the prior formation of VIr. It has been noted in this report (23) that the use of acid to neutralize the reaction mixture in the work-up of XX may account for its formation in the cases cited above (12,22). If such is the case, an acid-catalyzed allylic shift of the carbon-carbon double bond of VIr apparently results in the formation of XX.

Propynylureas: Shachat and Bagnell (12) extended the base-catalyzed cyclization of O-propynyl carbamates to that of propynylureas. Similar to the reaction with ethynyl alcohols, propynylamines (XXII) reacted with isocyanates in the absence of base to give ureas (XXIII) which cyclized to 4-methylene-2-imidazolidinones (XXIV) on treatment with sodium methoxide.



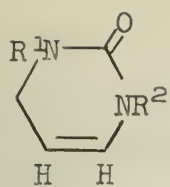
The imidazolidinone was formed directly when the reaction was carried out in the presence of the base. The structural assignments for the ureas (XXIII) and their cyclization products (XXIV) were based on IR data.

Stoffel and Speziale (14) have reported the intramolecular cyclization of propynylureas (XXV) with phosphorus pentachloride. An intermediate imidazolium chloride (XXVI) can be isolated and converted to a 4-methyl-4-imidazolin-2-one (XXVII) by treatment with sodium hydroxide. The action of phosphorus pentachloride on 3-(3,4-dichlorophenyl)-1-isopropyl-1-(2-propynyl)urea (XXVa) gave a crystalline imidazolium chloride

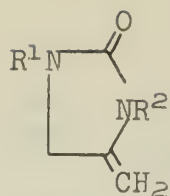


(XXVIIa). This compound, the first reported cyclic carbamido chloride, was shown to contain one readily hydrolyzable chloride ion. Its IR spectrum showed bands for carbon-carbon and carbon-nitrogen double bonds but lacked the acetylenic band present in the spectrum of XXVa. Upon treatment of XXVIIa with sodium hydroxide, the product gave two equivalents of chloride ion with simultaneous precipitation of XXVIIa. The IR spectrum of the latter compound showed carbonyl and olefinic absorption but lacked the band for the carbon-nitrogen double bond which was characteristic of XXVIIa.

The NMR spectrum of XXVIIa permitted an unambiguous structural assignment and



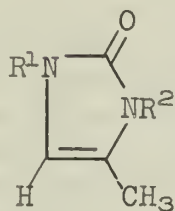
XXVIII



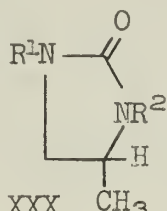
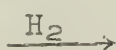
XXIX

a. $R^1 = \text{isopropyl}$; $R^2 = 3,4\text{-Cl}_2\text{C}_6\text{H}_3$

excluded two alternative structures (XXVIII, XXIX) for the cyclization product. Thus in addition to the absorptions assigned to the aromatic and isopropyl hydrogens, a doublet at τ , 8.06 (4-CH₃) and a quartet at τ , 4.00 (5-H) were observed. Hydrogenation of XXVIIa to XXX and synthesis of the latter compound from 1-(2-chloropropyl)-3-(3,4-dichlorophenyl)-1-isopropylurea (XXXI) confirmed that XXVIIa had the assigned structure.

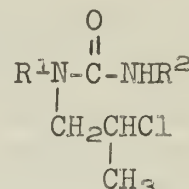
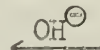


XXVIIa



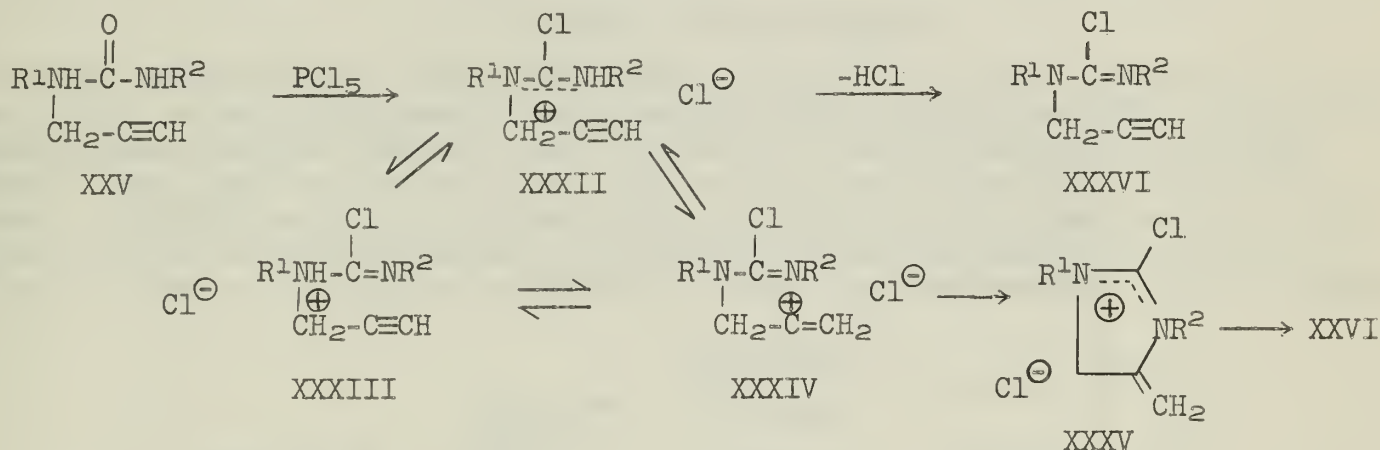
XXX

$R^1 = \text{isopropyl}$; $R^2 = 3,4\text{-Cl}_2\text{C}_6\text{H}_3$



XXXI

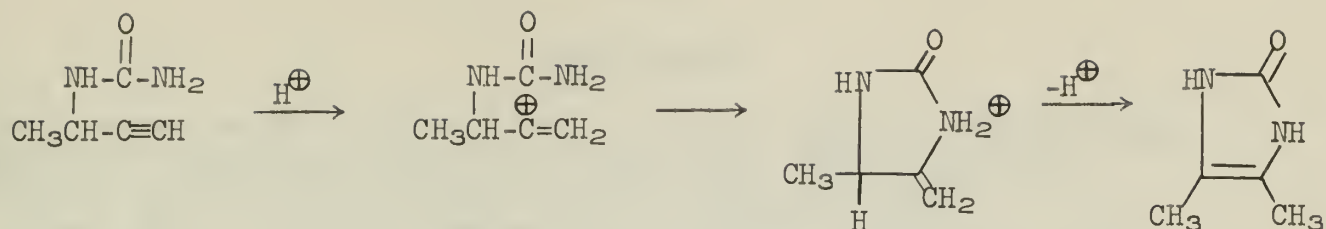
A mechanism for the cyclization of the ureas (XXV) to 4-methyl-4-imidazolin-2-ones (XXVII) via imidazolium chlorides (XXVI) has been postulated by Stoffel and Speziale (14). The reaction is visualized as proceeding through an intermediate carbamido chloride (XXXII) which is resonance-stabilized. Since the reaction mixture is highly acidic, a series of equilibria is proposed in which protonation can occur



at N-1 (XXXII), N-3 (XXXIII), or at the terminal carbon of the propynyl group (XXXIV). The latter protonation could result in ring closure to XXXV, followed by an allylic shift of the exocyclic double bond to give the imidazolium salt (XXVI). The transformation XXXII \rightarrow XXXVI was excluded by the authors because XXXVI was not isolated and because only a trace of hydrogen chloride was evolved at the beginning of the reaction. However, XXXVI could presumably participate in an acid-base equilibrium with any or all of the species XXXII, XXXIII, and XXXIV. The possibility that XXV is converted directly to XXVII via an allenic intermediate (XXXVII) was proven to be untenable by the observation that XXVIIa gave only intractable tars when treated with phosphorus pentachloride under the reaction conditions (22).

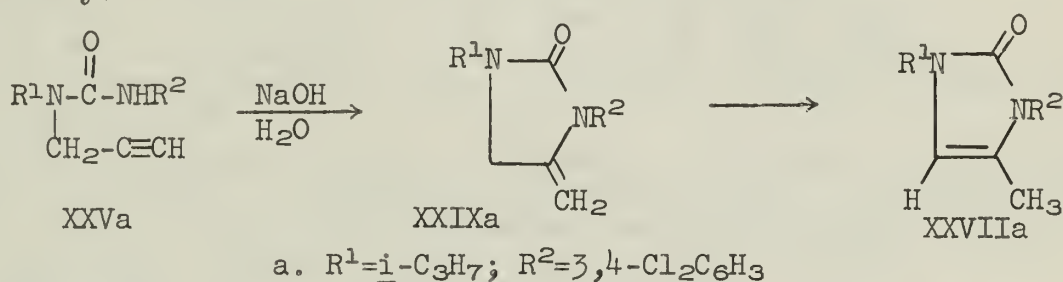


The cyclization of XXVa to XXVIIa could also be effected with sulfuric acid, p-toluenesulfonic acid, or hydrogen chloride, followed in each case by treatment with sodium hydroxide (24). It was proposed that the acid-catalyzed cyclization of XXVa follows a route similar to that postulated (above) for the phosphorus pentachloride

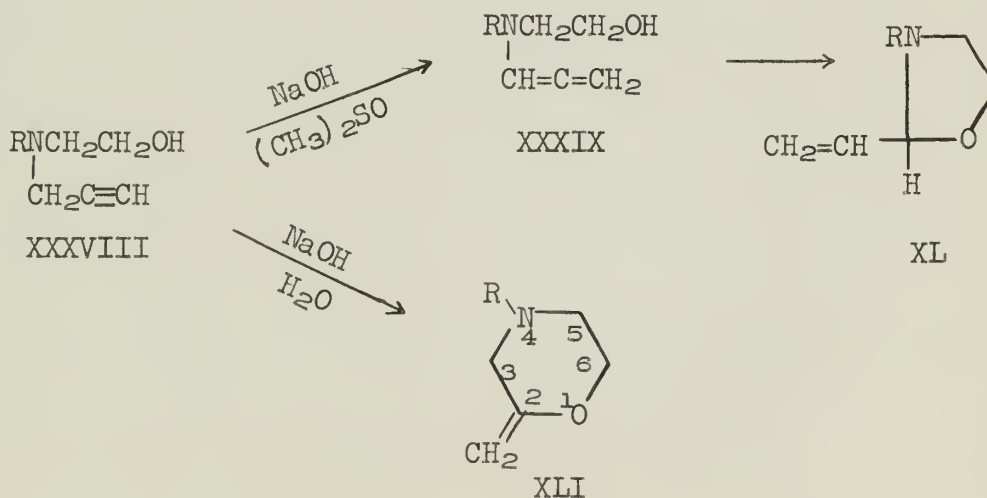


reaction. A similar mechanism has been given by Iwai for the cyclization of alkynylureas and related compounds with strong acids (20).

Treatment of XXVa with aqueous sodium hydroxide gave the imidazolidinone (XXVIIa) directly. Stoffel and Speziale have suggested that this base-catalyzed cyclization may involve the allene intermediate XXXVII, formed by isomerization of the propynyl group prior to ring closure. No supporting evidence has so far been presented. An alternative would be N-H addition directly to the triple bond of XXVa to give the exocyclic 4-methylene product (XXIXa), followed by an allylic shift of the olefinic double bond to give XXVIIa, analogous to the cyclization of propargyl carbanilate (Vr) discussed previously.



Allenic intermediates (XXXIX) have been postulated by Bottini, Mullikin, and Morris (25) to explain the formation of 3-alkyl-2-vinyloxazolidines (XL) when N-alkyl-N-propargylethanolamines (XXXVIII) were treated with sodium hydroxide in dimethyl sulfoxide. The same reaction in water gave 4-alkyl-2-methylenemorpholines (XLI). Treatment of XXXVIII with sodium deuterioxide in deuterium oxide gave deuterated XLI in which only the exocyclic methylene hydrogens had been replaced by deuterium, indicating that direct cyclization of XXXVIII, rather than intermediate allene formation,



takes place. In the latter case, deuterium incorporation at the 3-position of XLI would be expected. On the basis of these results, intramolecular addition to the triple bond of XXVa and subsequent rearrangement to XXVIIa seem more probable than does the possibility of isomerization to XXXVII prior to ring closure.

Summary: The isolation of heterocyclic compounds from the reactions of organic isocyanates with ethynyl alcohols and ethynylamines has led to the elucidation of the structures of the cyclic compounds. The cyclization of O-propynyl carbamates gives 4-methylene-2-oxazolidinones (VI) and 4-methyl-4-oxazolin-2-ones (XX); ring closure of the analogous propynylureas gives 4-methylene-2-imidazolidinones (XXIV) and 4-methyl-4-imidazolin-2-ones (XXVII).

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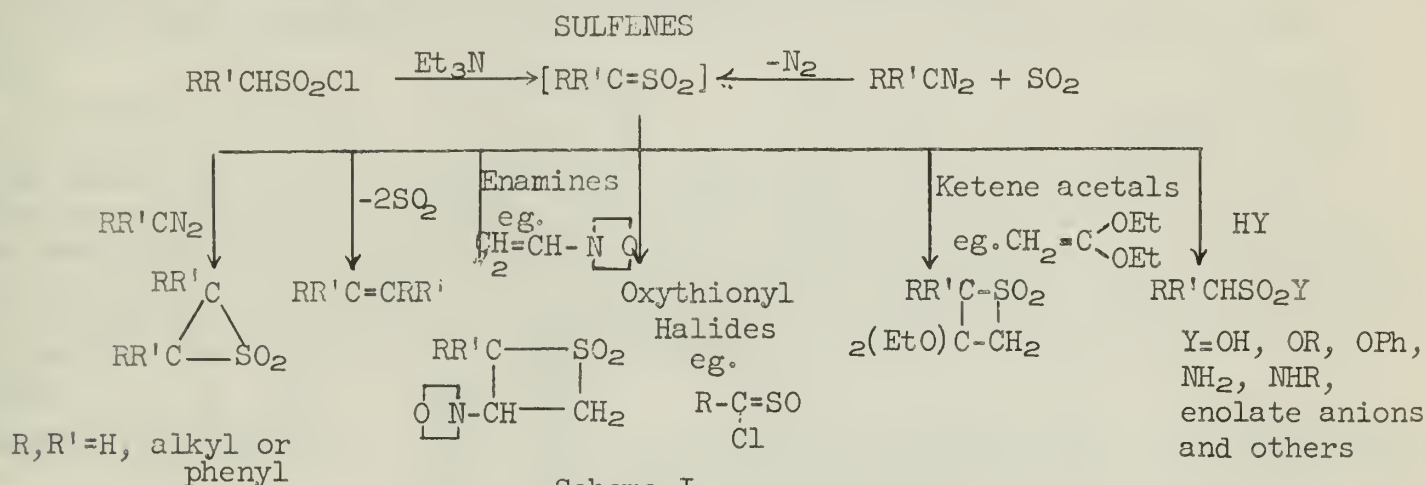
CHEMISTRY OF SULFENES

Reported by Robert Y. Ning

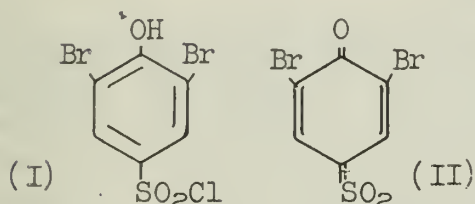
May 7, 1964

Introduction.--Sulfenes $RR'C=SO_2$ are postulated reaction intermediates which have appeared in the literature sporadically since 1911. Although never yet decisively isolated, sulfenes as a concept have satisfactorily explained the course of numerous reactions, mainly involving alkyl sulfonyl chlorides $RR'CHSO_2Cl$, which can readily be dehydrohalogenated by a base. The generation, structure and reactions of sulfenes are similar in many respects to ketenes, and it was upon this analogy that the name was first coined (3). Interest in sulfenes began to flourish in 1962. All indications point to a rapid development of this topic in the next few years.

Reactions in which Sulfenes are Postulated Intermediates:

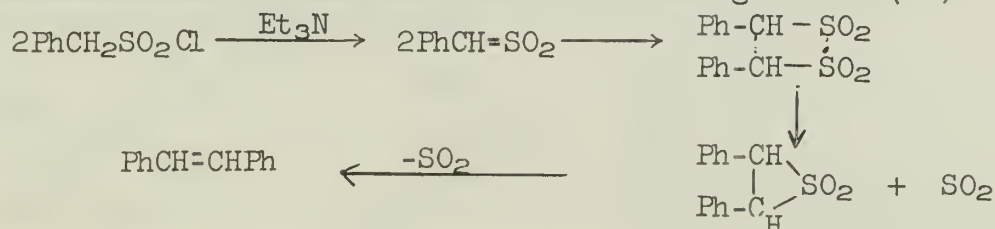


Scheme I



Zinke and Brune reported in 1908 (1) that treatment of I with sodium acetate in acetone gave a yellow color, formulated as II, which rapidly faded with deposition of polymer.

This concept of dehydrohalogenation of sulfonyl halides with a base to form sulfenes analogous to the formation of ketenes from acyl halides became commonly accepted and applied (3). Wedekind and Schenk obtained trans-stilbene in unspecified yields by treating benzylsulfonyl chloride with triethylamine in aprotic solvent. The following mechanism was proposed to explain this reaction: (a) abstraction of hydrogen chloride from sulfonyl chloride forming sulfene (b) in the absence of moieties which might add to it, phenylsulfene decomposes to phenylcarbene and sulfur dioxide (c) coupling of two phenylcarbene molecules to form stilbene. Later evidences, however, cast doubt on the intermediacy of phenylcarbene in this instance. Ethylene sulfones had been isolated from systems which generate sulfenes (4,14,17), and these sulfones readily eliminate sulfur dioxide to give ethylenes upon heating. Hence it seems very likely that the formation of trans-stilbene resulted from dimerization of sulfene followed by a stepwise elimination of sulfur dioxide as formulated in the following scheme (14).

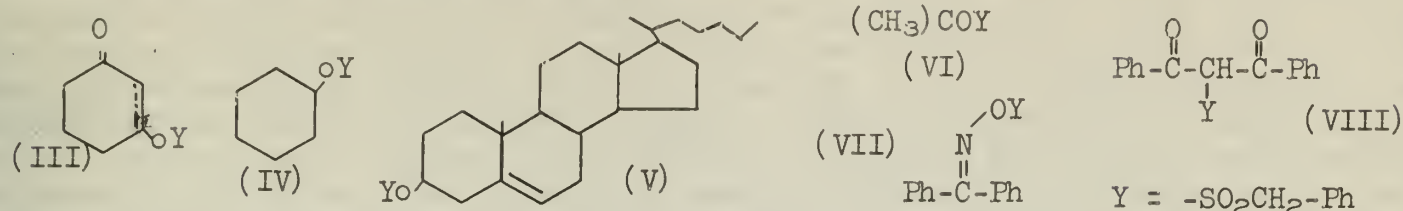


Failure of an attempt to trap carbene with acenaphthalene in this system pointed to the absence of a carbene intermediate (28).

Dehydrohalogenation is more difficult in the case of benzylsulfonyl fluoride. A stronger base like butyl lithium was required to yield trans-stilbene (33).

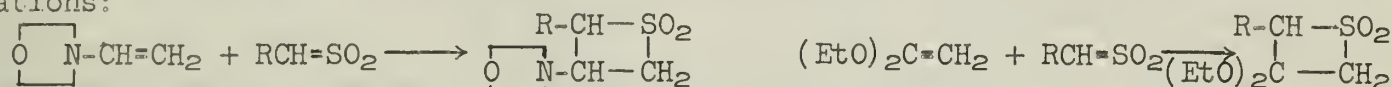
Alkyl sulfonyl chloride with triethyl or trimethylamine in ether or benzene constitutes a powerful sulfonylating agent for primary and secondary amines (3,15), and a wide variety of hydroxyl groups (33) as evident from the sulfonates III through VII

which were readily prepared from the corresponding hydroxides. Sulfonate VIII can readily be made from benzoylacetophenone.

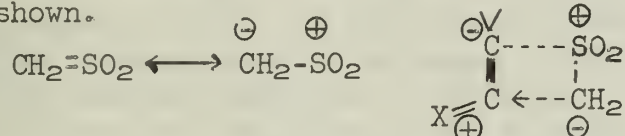


All these sulfonates can be obtained in one minute at room temperature with benzylsulfonfyl chloride and triethylamine. The course of reaction in all cases seems to involve the addition of the substrates to the sulfene intermediate.

Sulfenes can be trapped to form four-membered rings in high yields with enamines (22,23,29,32) and keteneacetals (20,28), as shown in the following representative equations:

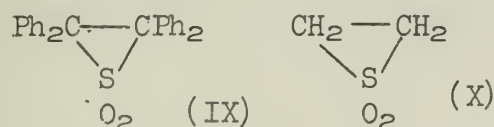


The formation of these rings, however, are severely limited to enamines and keteneacetals. Attempts to extend this to olefins and a wide variety of conjugated double bonds have failed (28,32). For four-ring formation to occur, it appears that a highly-polarizable double bond is required, the polarization being induced by strongly electron donating substituents. This high polarity required of olefins coupled with ylid structure for sulfenes (17) suggests polar interactions in the transition state as shown.



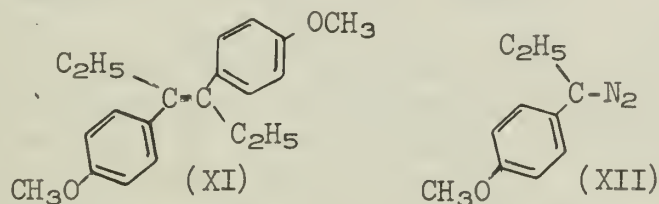
Another general method of generating sulfenes is via the reaction of diazoalkanes with sulfur dioxide (4,12,14,15,17,29). If gaseous sulfur dioxide is passed through

solutions containing diazoalkanes, sulfenes are formed immediately with evolution of nitrogen. The fate of the sulfene will depend on the type of reactive moieties in its immediate environment. In the presence of compounds with active hydrogens, sulfonation will occur in the usual manner, or it may be trapped with enamines or keteneacetals to form four-ring sulfones (29), though with lower efficiency compared to generating sulfenes from sulfonyl chlorides due to competing side reactions. In the absence of other reactive species, a second mole of diazoalkane may add to the sulfene followed by elimination of nitrogen to give symmetrical three-membered ring sulfones. Sulfones IX and X were prepared from diphenyldiazomethane and diazomethane respectively with sulfur dioxide (4,14). To confirm the understanding of the process as the addition



tion of the elements of carbene to sulfene, diazomethane was shown to add to sulfenes generated from sulfonyl chlorides to yield unsymmetrical three-ring sulfones (29). Sulfones IX and X decompose readily upon heating to give the corresponding olefins and sulfur dioxide.

This reaction sequence was employed gainfully in the preparation of physiologically active stilbestrols-trans-symmetrical dialkyldiarylethylene compounds. For instance, XI was made from XII and sulfur dioxide in one step (12).

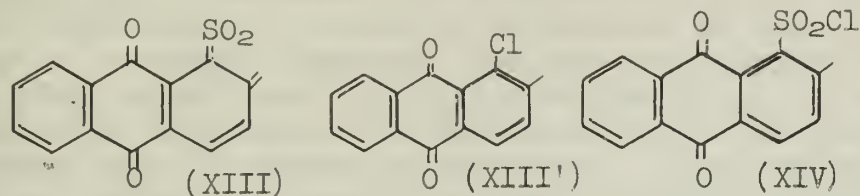


In the absence of excess diazoalkanes and in the presence selenium dioxide, sulfur dioxide or air, competing amounts of ketones may be formed from oxidation of sulfenes (4,14). For instance, benzophenone was obtained in

90% yield from the reaction of diphenyldiazomethane with liquid sulfur dioxide (4). The sulfene initially formed reacts with another mole of sulfur dioxide to give benzophenone, sulfur trioxide and colloidal sulfur.

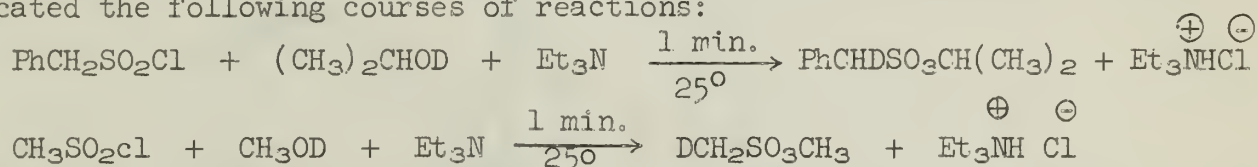
The Existence of Sulfenes.--The only record of the preparation of a stable crystalline sulfene is that of substance XIII by Locher and Fierz (10), who reported that

it was formed in poor yield on heating the acid chloride XIV in chlorobenzene. Though not entirely without chemical analogy (18), the unlikely nature of this transformation prompted a later reinvestigation (26) which refuted this claim. King tried to repeat the results of Locher without success. After heating XIV in chlorobenzene, only XIII' and the corresponding sulfonic acid were obtained. The scanty data reported on the properties of "sulfene" XIII were considered to be consistent with an anhydrous form of the sulfonic acid. To see if the sulfonic acid might be formed by rapid addition of water to a sulfene, King treated the reaction mixture with deuterium oxide immediately after refluxing, but could detect no $\text{CH}_2\text{-D}$ in the infrared (1375 cm^{-1}) and thus concluded that a sulfene was not formed even as an intermediate in this reaction.



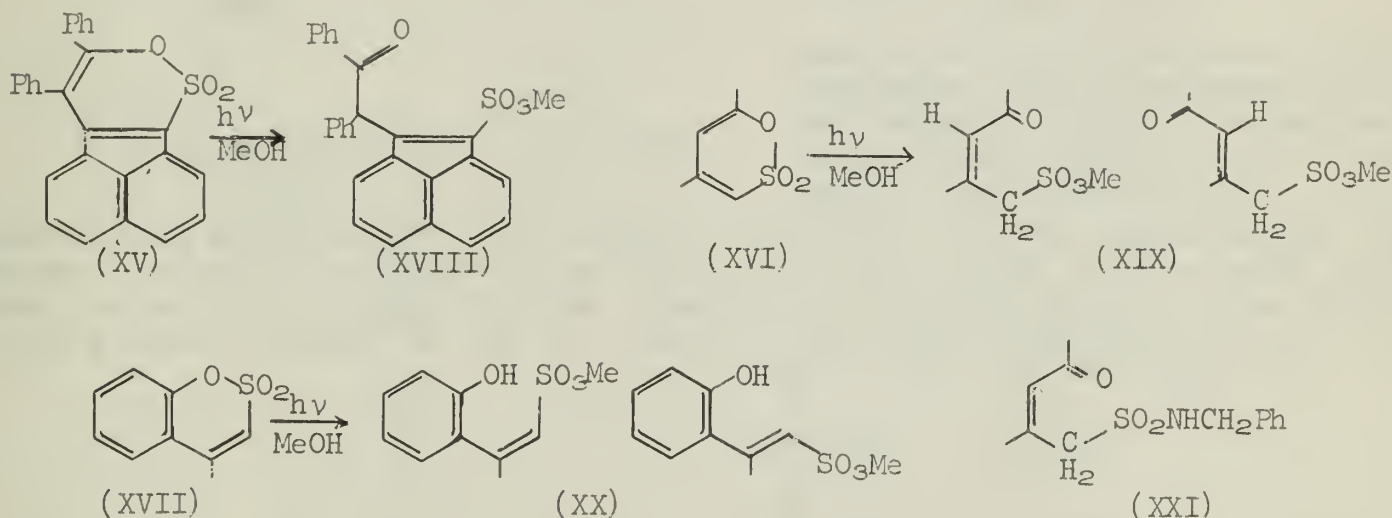
Despite numerous failures in attempts at isolating sulfenes, the actual existence of sulfenes as reactive intermediates remains very probable. Two independent

crucial experiments using mass spectrometry appeared simultaneously only very recently (30,31), rendering considerable support to the credibility of sulfenes. These experiments indicated the following courses of reactions:



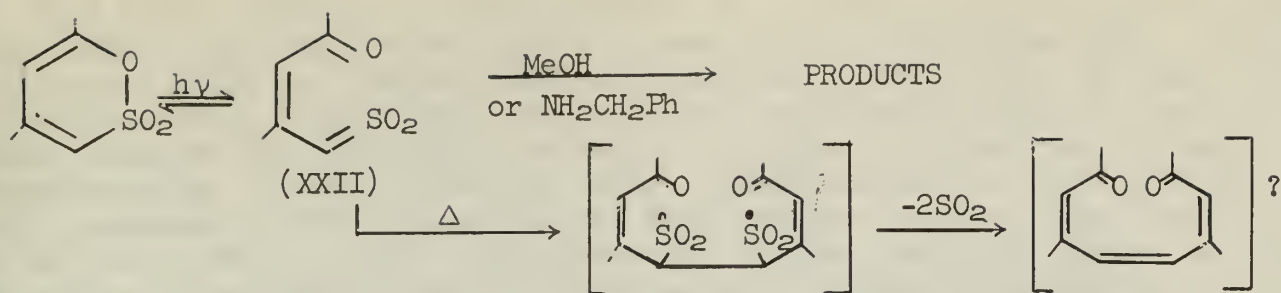
The absences of di- or trideuterated esters in both cases exclude possibility of deuterium incorporation by exchange of deuterium from the alcohols with the alpha protons of the sulfonyl chlorides. This led to the conclusion that sulfenes are first formed with subsequent addition of the elements of the alcohols.

Sulfenes as Photochemical Intermediates.--King and co-workers (26) irradiated the unsaturated sultones XV, XVI, XVII with ultraviolet light in methanol and obtained the corresponding sulfonic acid esters XVIII, XIX, XX.

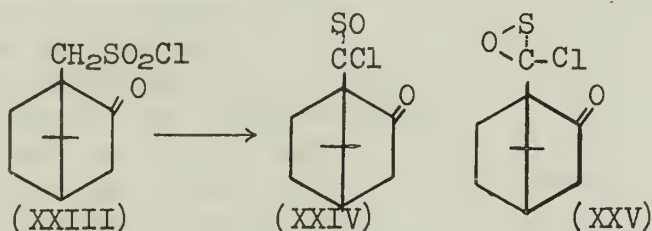


Irradiation of the sultone XVI in ether containing two equivalents of benzylamine gave the corresponding sulfonamide XXI. Appropriate controls showed that all these transformations were photochemically induced. It appeared to these workers that such photolyses proceed by rearrangement to form sulfene intermediates as in the case of sultone XVI through the sulfene XXII. Products are formed from addition of methanol or benzylamine to sulfene intermediates.

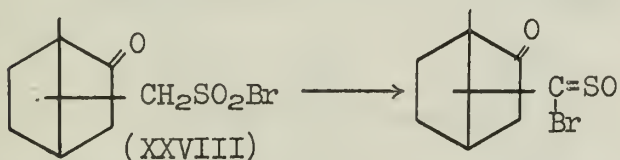
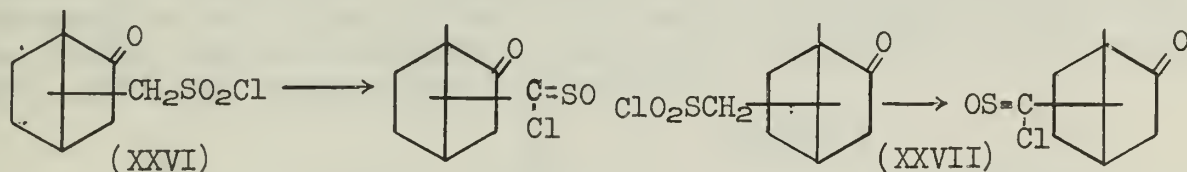
Competitive thermal dissociation of the sulfene was also demonstrated by irradiation of XVI in hot dry diglyme solutions, in which treatment up to 25% sulfur dioxide was evolved, reminiscent of the elimination of sulfur dioxide from sulfenes to form olefins. Sulfur dioxide evolved was determined by sweeping with nitrogen into a trap containing standardized iodine solutions which were titrated with thiosulfate. The presumed product resulting from the evolution of sulfur dioxide from sulfene XXII was not isolated.



Oxythiones.--Oxythiones ($\text{RR}'\text{C}=\text{SO}$) apparently are reactive species, and have thus far not been isolated. Oxythiono derivatives of type ($\text{RC}=\text{SO}$) where X can be chlorine or bromine are stable compounds, and have been prepared and studied as an outgrowth of the study of sulfenes. In 1923, Wedekind *et al.* (7) extended their earlier work on benzylsulfonyl chloride to camphor-10-sulfonyl chloride (XXIII) which with triethylamine or pyridine gave "camphorchlorosulfoxide". These authors showed that the chlorine, sulfur and one of the oxygen atoms were attached directly or indirectly to carbon-10, and suggested structure XXIV though structures such as XXV were not excluded.

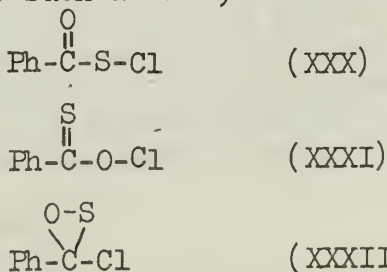
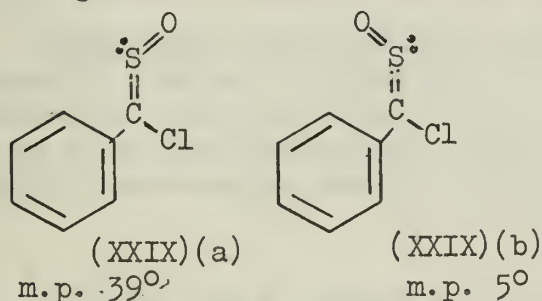


Shortly afterward, the analogous reactions were carried out on XXVI (6), XXVII (8) and XXVIII (11) to give the corresponding oxythionyl halides, but subsequently except for



mention in the abstracts and terpene literature, the rearrangement of primary sulfonyl halides with tertiary amines in the absence of other reagents has not been further studied. In 1963

however, King and Durst (24) reinvestigated Wedekind's work with benzylsulfonyl chloride and reported the isolation of oxythiobenzoyl chloride XXIX under suitable conditions, in addition to *trans*-stilbene. Purification of XXIX (27) lead to the separation of two geometric isomers (a) and (b). Spectroscopic data disfavoured alternate structures such as XXX, XXXI and XXXII.

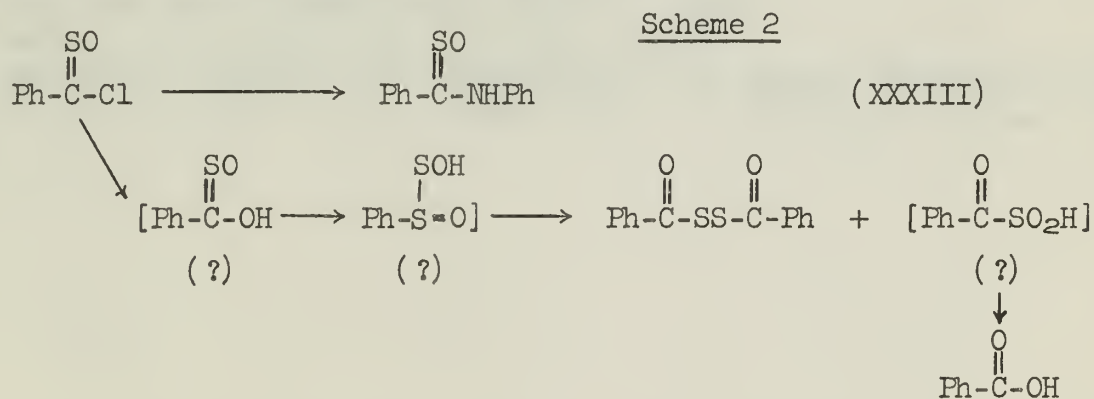


Structure XXX would require a carbonyl band in the infrared which was not observed. Structure XXXI, in analogy to allyl thionbenzoates (34), would be expected to show a weak absorption in the region of $420\text{ m}\mu$; however, the maxima for both XXIX (a) and (b) occur at $325\text{ m}\mu$, with negligible extinction coefficient at $420\text{ m}\mu$. Structure XXXII was disfavoured by C^{13} n.m.r. The C^{13} n.m.r. spectra for XXIX (a) and (b) were reported to be almost identical, each with a singlet (one carbon) at 12 p.p.m. chemical shift from CS_2 , and a multiplet (six carbons) at 66 p.p.m. The multiplets at 66 p.p.m. are normal for phenyl ring carbons, while the chemical shift of 12 p.p.m. for the singlet coincides in magnitude to carbonyl carbons of esters, ketones and alde-

hydes. This is in contrast to chemical shifts of the order of 100 p.p.m. or more for saturated carbons including those bonded to one or more heteroatoms (35). On this basis structure XXXII was disqualified. Furthermore, if one isomer were XXX, XXXI or XXXII, then the other isomer would have to have a completely different structure from the first, since neither XXX, XXXI nor XXXII is capable of geometrical isomerism or diastereoisomerism. However, since the molar refractivities and the ultraviolet and C^{13} n.m.r. spectra of XXIX (a) and (b) are very similar, and the three strongest bands in the infrared spectrum of (a) (excluding those due to the phenyl group) at 1145, 1025 and 920 cm^{-1} respectively have counterparts of comparable intensities in the spectrum of (b) at 1120, 1005 and 910 cm^{-1} , the given structures were assigned. This elucidation of structures of oxythiobenzoyl chlorides confirmed to a large degree the structures of oxythionyl halides as a class of compounds. There has yet been no report of separation of similar isomers of other oxythionyl halides.

Isomers XXIX (a) and (b) represent the first instance of geometrical isomerism about a carbon-sulfur double bond. Geometrical isomerism about carbon-carbon, carbon-nitrogen and nitrogen-nitrogen double bonds has been known for many years, while isomers XXIX (a) and (b) apparently represent the first case of geometrical isomerism about a double bond to an element outside the first period of the periodic table. The geometrical structures of (a) and (b) were assigned solely on the basis of dipole moments, for which a difference of 1.43 Debyes was found. It was assumed that the S-O and C-Cl bonds are polarized so that the oxygen and chlorine atoms are each partially negatively charged; thus the dipole moment of (a) should be greater than that of (b). The isomer (b) was found to isomerize to (a) upon heating. The half-life of (b) is about 0.75 hours in refluxing toluene and about 8 hours in refluxing carbon tetrachloride. King and associates are now actively involved in the elucidation of mechanism in the formation of oxythiobenzoyl chlorides.

Chemically, oxythionyl chlorides behave more like acid chlorides than sulfenes. Oxythiobenzoyl chloride for instance (24) reacted with aniline to give thiobenzanilide S-oxide XXXIII, and upon hydrolysis with dilute hydrochloric acid yielded dibenzoyl disulfide, XXXI, and benzoic acid (see scheme 2).



Conclusion.--Explorations with sulfenes have thus far proven to be fertile as synthetic routes. Mechanistic understanding of most of the processes involved are admittedly in a rudimentary state of development. Synthetic potentials have thus far by no means been exhausted. It is certain that further results on this topic will be rapidly forthcoming, and contributive to the chemistry of sulfur compounds.

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REPLACEMENT OF OXYGEN WITH SULFUR USING PHOSPHORUS PENTASULFIDE

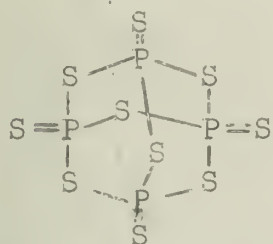
Reported by Ron Hackler

May 18, 1964

Introduction --Phosphorus pentasulfide has been known for many years as a useful reagent for the direct replacement of oxygen with sulfur in a great variety of organic compounds. Never has the scope of this reaction been delineated. This abstract intends to consider the replacement of oxygen with sulfur using phosphorus pentasulfide by considering the nature of the reagent itself, and some related reactions which help one to understand its action.

Consideration of this reaction is complicated by the fact that much of the work done in this area was done before the modern concepts of organic chemistry were developed and the primary concern was getting out a product, often with little concern for yields, other products, or mechanisms.

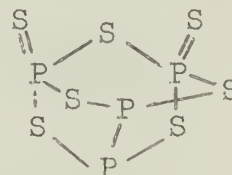
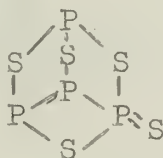
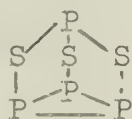
Preliminary Consideration of Phosphorus Pentasulfide (1,2) --Phosphorus pentasulfide is a yellow solid, m.p. $286-290^{\circ}$, b.p. $513-515^{\circ}$. Although commonly written P_2S_5 , its molecular formula is actually P_4S_{10} . X-ray diffraction (3) shows that its structure is the same as that of P_4O_{10} , suggesting that P_4O_{10} may be a useful model in considering the mode of action of P_4S_{10} . Its structure consists of phosphorus atoms in a tetrahedral arrangement with six sulfur atoms linked between phosphorus atoms along the edges of the tetrahedron, and four sulfur atoms coordinately bound as depicted below:



The P-S bond length to the shared sulfur atoms is $2.09 \pm 0.03 \text{ \AA}$, and to the isolated sulfur atoms is $1.96 \pm 0.03 \text{ \AA}$, indicating that the latter has considerable pi bonding.

The melting point diagram for the P-S system shows only the compounds P_4S_3 , P_4S_5 , P_4S_7 , and P_4S_{10} , although there is some evidence for a phase between P_4S_5 and P_4S_7 . The other phosphorus sulfides also have structures based on a tetrahedral arrangement of phosphorus atoms as shown. The past chemistry of the phosphorus sulfides has been filled with confusion and in the past work was unwittingly done with mixtures of the legitimate compounds. There are reactions in the literature (4) which purport to involve the replacement of oxygen with sulfur using P_2S_3 , but it is felt that the work done in the past with " P_2S_3 " was probably done with a mixture consisting of mainly P_4S_7 .

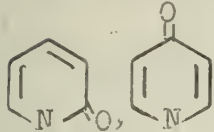
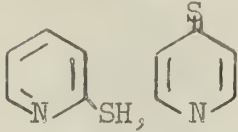
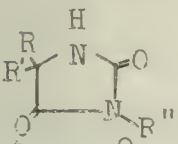
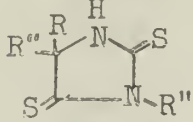
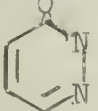
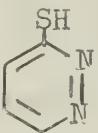
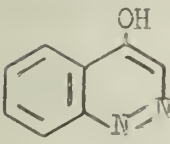
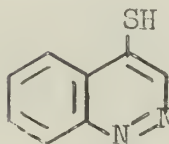
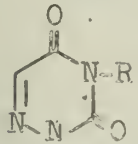
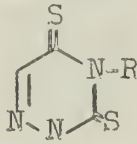
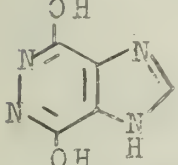
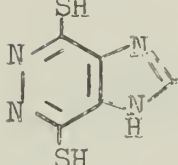
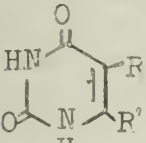
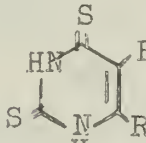
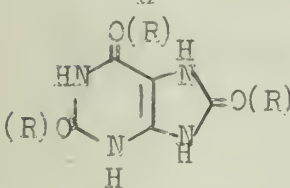
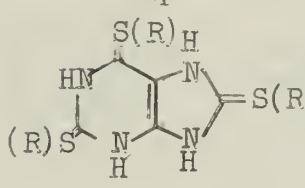
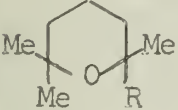
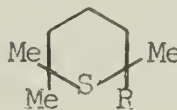
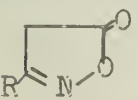
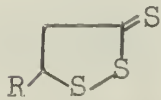
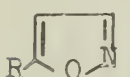
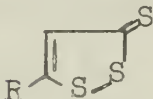
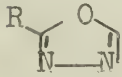
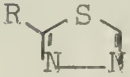
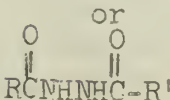
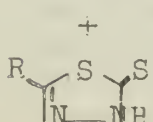
Preparation of P_4S_{10} is usually done by the direct reaction of the elements at elevated temperatures.

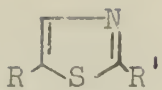
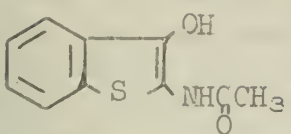
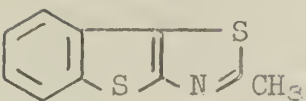

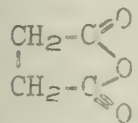


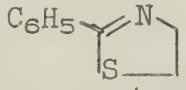

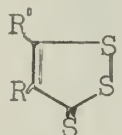


Experimental Method --This reaction is carried out either by fusion of the P_4S_{10} with the organic compound or by heating the two reactants together in an inert solvent such as benzene, xylene, or tetralin. Often the solvent is chosen on the basis of its boiling point, the higher boiling solvents being used for the less reactive compounds. Pyridine has been shown to be superior as a solvent in some reactions (5), and some compounds which cannot be thiated in tetralin or pyridine are easily thiated in triethylamine or 3-picoline (6). The latter compounds, however, give somewhat lower yields with 2,6-lutidine as a solvent. In addition to basicity and boiling point, solvating power for the reactants is an important consideration in choosing a solvent.

Occasionally sulfur is used with P_4S_{10} (7).

Scope of the Reaction --The following table shows the types of compounds which have been thiated with phosphorus pentasulfide, the main products, yields, and references. Discussion of many of the reactions follows the table. Yields are approximate and references were selected to be representative rather than comprehensive.

Reactant	Product	Yield	Reference
ROH RCHO, RCOR' RCONH ₂	$(RO)_2PSSH \longrightarrow RSH$ $(RCHS)_x (RC SR')_x$ RCSNH ₂	70% \longrightarrow 20-35% 70% 5-90%	8-13 14-17 18-20
		70-90%	5, 21-23
		40-50%	24
		20%	25
		80-90%	26
		45-95%	27
		80%	28
		55-100%	29-30
		55-95%	31-32
		25%	33
		?	34
		?	34
		40%	35
		20%	

$\text{RCCH}_2\text{NHCR}'$		50-70%	36
		65-70%	37
$\text{R}-\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{R}'$		50-80%	38
		?	39
$\text{CH}_2\text{CH}(\text{OH})\text{CH}(\text{OH})\text{CH}_2\text{OH}$		78%	40
$\text{C}_6\text{H}_5\text{C}(=\text{O})\text{NHCH}_2\text{CH}_2\text{OH}$		15%	41
$\text{ROOC}-\text{C}(=\text{O})-\text{CH}(\text{COOR})-\text{CH}(\text{OR})_2$	$(\text{C}_6\text{H}_5\text{CONHCH}_2\text{CH}_2\text{S})_2$	37%	
		?	42
$\text{R}'-\text{C}(=\text{O})-\text{CH}(\text{R})-\text{C}(=\text{O})-\text{OR}''$ or $\text{R}'-\text{C}(=\text{O})-\text{CH}(\text{R})-\text{CH}_3$		2-35%	43-44

Discussion - In order to understand the action of P_4S_{10} upon alcohols and phenols it is useful to compare the reaction of phosphorus pentoxide with alcohols.

The formation of the phosphate esters is postulated (45)

$$\text{P}_4\text{O}_{10} + 6\text{ROH} \longrightarrow 2 (\text{RO})_2\text{POH} + 2 \text{RO}-\text{P}(\text{OH})_2 \quad (45)$$

to arise from attack of the alcohol upon the anhydride

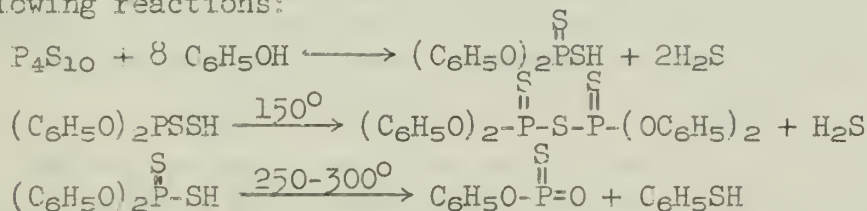
$$\text{P}_4\text{S}_{10} + 8\text{ROH} \longrightarrow 4 (\text{RO})_2\text{PSH} + 2 \text{H}_2\text{S} \quad (10,11)$$

linkages of P_4O_{10} until products with but one phosphorus atom are produced.

A similar mechanism could exist for P_4S_{10} , with the difference arising from the fact that acids of the type $\text{ROPS}(\text{SH})_2$ are more reactive than their oxygen analogs (45).



The dialkyl dithiophosphoric acids are important commercially because of their use in extreme pressure lubricants, oil additives, and flotation agents. If the dialkyl dithiophosphate is isolated and heated, or the reaction run at a higher temperature, the corresponding mercaptan is obtained (8,11,12). Cambi (12) reports the following reactions:



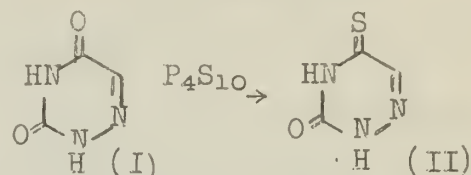
On the other hand, with tertiary alcohols such as t-butyl or t-amyl, 5-6 hours reaction at 85° gives the olefin in 65% yield plus a small amount of the mercaptan, while the same

reaction at 45° gives the dialkyl dithiophosphate in good yield (8).

Cholesterol reacts with P_4S_{10} in boiling carbon disulfide to yield thiocholesterol (13).

Excluding the compounds in which heterocyclic oxygen is replaced, it can be seen from the table that with the other compounds it is carbonyl oxygen or potential carbonyl oxygen that is replaced with sulfur. Many of the compounds are cyclic amides. It seems likely that a different mechanism may exist for the replacement of carbonyl

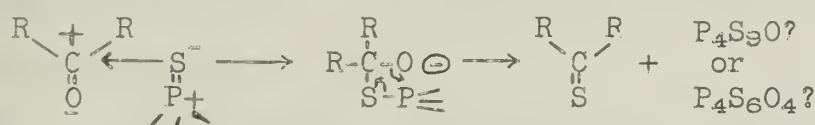
oxygen than that for the reaction with alcohols. Indeed there is evidence that only the four coordinately linked sulfurs are effective in the replacement of carbonyl oxygen, the other sulfurs being ineffective or at least less effective. It has been shown that the monothiation of either uracil or 6-azauracil (I) proceeds in highest yield when a ratio of compound to P_4S_{10} of four to one is employed (46). When a smaller ratio is used the reaction is incomplete, and when a larger ratio is used an increased yield of dithiated product is observed. The reactions were all run in boiling pyridine for 3 hours, but the product was not treated for a longer time to see if the other sulfurs were used to any extent. These workers report that if anhydrous pyridine (b.p. 115°) was used, a tarry residue was produced and it was difficult to isolate the product. If low boiling pyridine (b.p. 113°), thought to contain an appreciable amount of water, was used, almost theoretical yield could be obtained. The data for 6-azauracil is shown:



6-azauracil		g.	P_4S_{10}		moles total S	Yield of 5-SH Derivative (II)
g	moles		moles P=S	moles PSP		
2.5	0.022	0.9	0.008	0.012	0.020	28.6%
"	"	1.4	0.013	0.020	0.033	35.7
"	"	2.2	0.020	0.030	0.050	71.4
"	"	2.3	0.021	0.031	0.052	75.0
"	"	2.4	0.022	0.033	0.054	100.0
"	"	2.5	0.023	0.034	0.057	78.6
"	"	2.6	0.024	0.035	0.059	64.3
"	"	7.5	0.068	0.101	0.171	7.1

This data invites correlation with the composition of the complexes reported by Kindler (19) which gave analyses consistent with $(amide)_2P_2S_5$ or $(amide)_4P_4S_{10}$. These complexes decomposed upon heating to give the thioamides.

To account for these observations one can postulate that the coordinately bound sulfurs represent sites of greater nucleophilic activity capable of nucleophilic attack on the carbonyl. One can then postulate a mechanism similar to that of the Wittig reaction (47). It would be interesting to see if oxygen replacement with sulfur could be achieved using tri-



phenyl phosphine sulfide. It would also be interesting to observe the reactivities of the

other phosphorus sulfides to see if the coordinately bound sulfurs of these compounds are more reactive than the divalent ones.

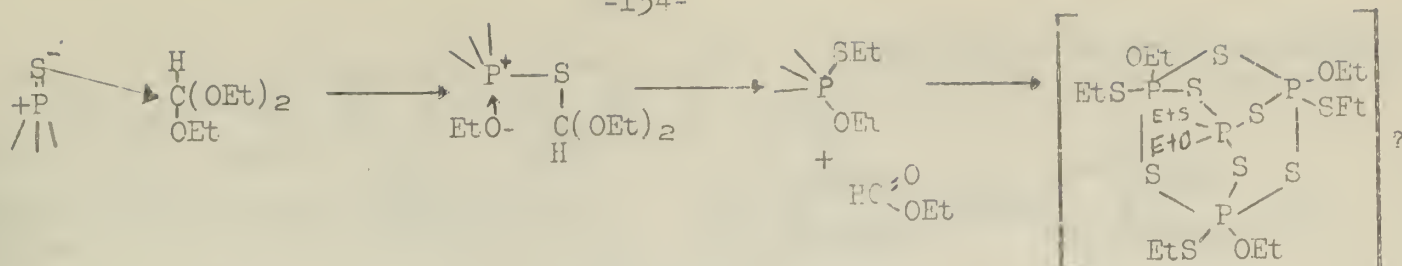
A systematic study of substituent effects upon yields has not been reported but there are indications that it may be quite large and the electrophilic character of the carbonyl may be quite important. The 3- and 4-nitrobenzanilides or the N(3-nitrophenyl)- and N-(4-nitrophenyl)-benzamides yield the corresponding thioamides in 70-90% yield upon treatment for a short time with P_4S_{10} in boiling xylene, while the corresponding 3- and 4-amino analogs can be obtained in only about 5% yields even when a fused, powdered mixture of P_4S_{10} and K_2S is used (20). This is of course further evidence for a mechanism involving nucleophilic attack on the carbonyl.

An interesting related reaction is that of P_4S_{10} with ortho esters (48):

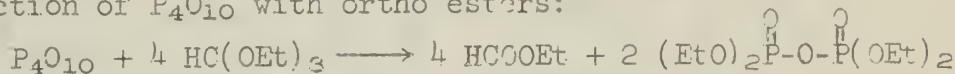


No chemical evidence was obtained to justify the assignment of a definite structure to the triethyl dithiophosphate, but its boiling point ($115-115.5^\circ/10\text{mm.}$) indicates that it may be O,O,S-triethyl dithiophosphate, with reported (11) boiling point $128^\circ/20\text{mm.}$, as compared to $148^\circ/20\text{mm.}$ for O,S,S-triethyl dithiophosphate (11).

It is easily seen that four ortho ester molecules take one route, and two another route, again suggesting interaction with the four coordinately bound sulfurs. One can postulate something like the following:

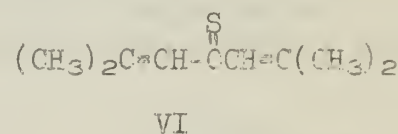
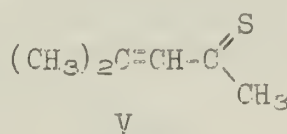
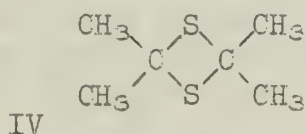
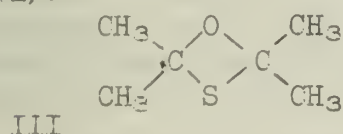


Support for this type of mechanism is given by the reaction of P_4O_{10} with ortho esters:



Reaction of P_4S_{10} with simple aldehydes and ketones yields the corresponding thials and thiones in the dimeric, trimeric, or other polymeric forms (14-17). This reaction is subject to various side reactions (15,17). When Spring

(15) treated acetone with P_4S_{10} he obtained methyl mercaptan, isopropyl mercaptan, oxythioacetone (III), dithioacetone (IV), and perhaps mesityl sulfide (V) and thiophorone (VI).



Bottcher and Bauer (17) treated several aromatic aldehydes and ketones with P_4S_{10} under various conditions. A summary of their results, with products and yields, is shown:

	CS_2 , reflux 46°, 5-12 hrs.	Xylene, reflux 140°, 2 hrs.	No Solvent, 160-170°, 2 1/2-4 hrs.
Benzaldehyde	Trithio-benzaldehyde	20% Trithiobenzaldehyde, 15% Stilbene	5% Stilbene
Anisaldehyde	65% Trithio-anisaldehyde	15% 4,4'-dimethoxystilbene	4,4'-dimethoxystilbene
Acetophenone	Trithio-acetophenone	20% 2,5-diphenyl thiophene	15% 2,4-diphenyl thiophene
p-methoxyacetophenone	---	---	30% 2,5-(4,4'-dimethoxyphenyl) thiophene
p-methoxypropiophenone	---	---	20% 3,4-dimethyl-2,5-(4,4'-dimethoxyphenyl) thiophene

Bottcher and Bauer postulate thiophene formation to arise from the condensation of two thione molecules.

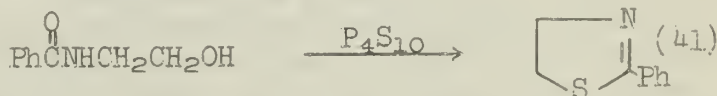
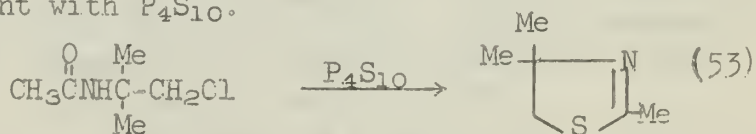
The thiation of amides with P_4S_{10} was first reported in 1878 (18). Kindler (19) found increased yields using an intimate mixture of P_4S_{10} and K_2S ; however, a decrease of up to 50% has been observed with the mixture as opposed to P_4S_{10} alone (49).

When 4,4'-dinitrooxanilide was treated with P_4S_{10} for 7 hours in boiling xylene, the elemental analysis indicated that reduction of the nitro groups to the amines had occurred in addition to thiation (50).

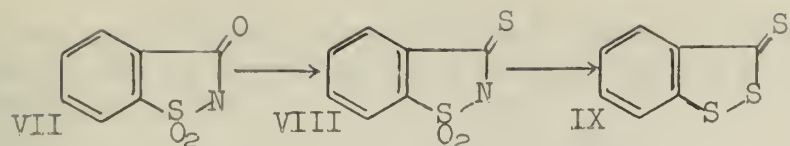
N-substituted amides with functional groups in the N substituent beta to the nitrogen may undergo cyclization upon treatment with P_4S_{10} .

The latter reaction gave a cystamine derivative ($\text{PhCONHCH}_2\text{CH}_2\text{S-}$)₂ in addition to the illustrated 2-phenyl-2-thiazoline.

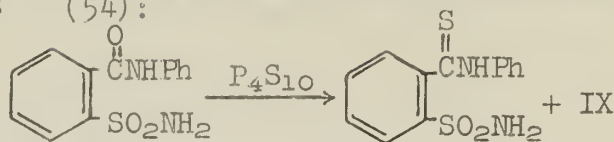
This disulfide was believed to have arisen from the oxidation of N-(2-mercaptoethyl) benzamide, formed by the replacement of a hydroxyl group by a mercapto group.



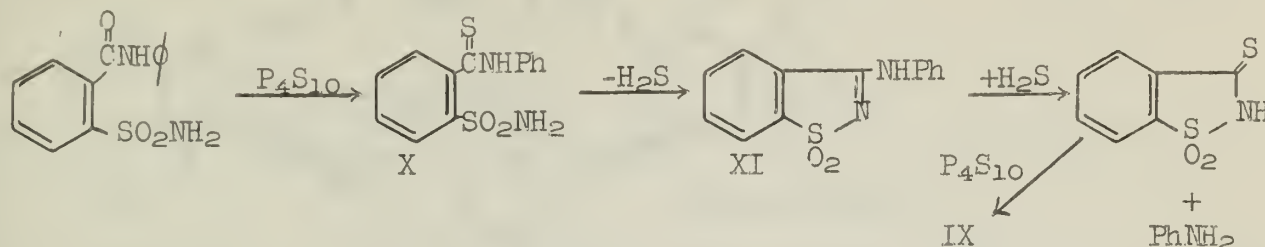
Saccharin (VII) can be converted to thionsaccharin (VIII) in 90% yield when treated with P_4S_{10} , while further treatment of the thionsaccharin gives 1,2-benzodithiole-3-thione (IX) (51-52).



Formation of IX has been reported from a different starting material (54):

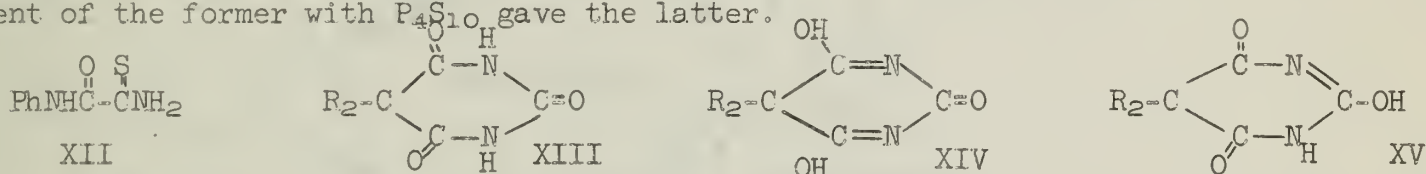


A proposed route for this reactions is as follows:



Support for this route consists of the fact that heating X gives H₂S, IX, and XI, and treating X with P₄S₁₀ gives IX.

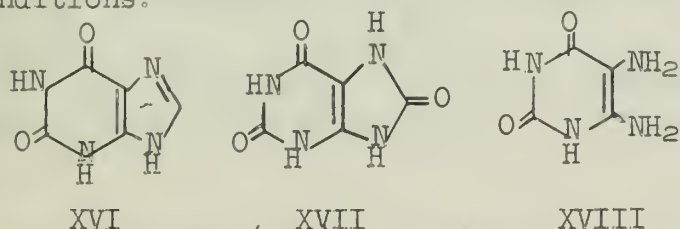
Treatment of diamides with P₄S₁₀ results in both mono- and dithioamides being formed. A mixture of 2,4-diacetamidotoluene and P₄S₁₀ in a 2/1 molar ratio gave a mixture of mono- and dithiated products in a 7/2 molar ratio (55). Similarly, N-phenyloxamide gave both oxanilothioamide (XII) and N-phenyl-dithiomoxamide (56). Treatment of the former with P₄S₁₀ gave the latter.



Carrington (7) found that the urea type carbonyl of barbituric acids (XIII) is more reactive than the other carbonyls. After sixteen hours reflux in toluene he obtained the mono- and dithiated compounds, and after sixteen hours reflux in xylene the di- and trithiated compounds. The monothiated compound was thiated at the urea type position. On the basis of a mechanism involving nucleophilic attack one might expect just the opposite, but other factors such as steric factors or degree of enolization may be playing a role here. An enolized form such as XIV and XV may be predominate in solution and may account for the differences in reactivity.

Beaman (57) observed that 2,6-dihydroxypurine (XVI) is thiated selectively at the six position. Isolation and further treatment showed no conversion to the dithiated compound, although 2-mercapto-6-hydroxypurine could be easily converted to the dithiated compound, indicating that the 2-position is resistant to thiation and not just that thiation at one position makes thiation at a second position more difficult. One might expect this result on the basis of the 6-position being more electrophilic than the urea type 2-position because of electron donation from the nitrogens to the latter.

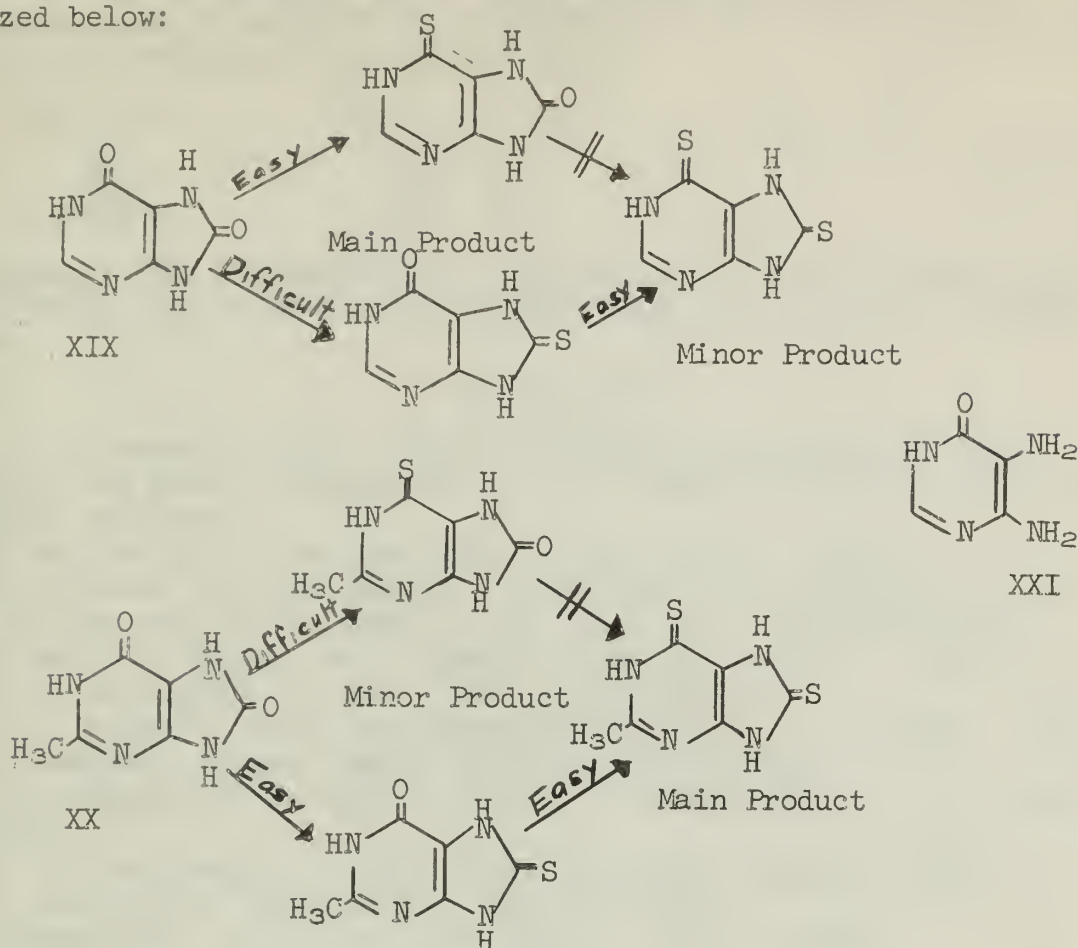
Uric acid (XVII) (2,6,8-trihydroxypurine) gives as the main thiation product 2,8-dihydroxy-6-mercaptapurine plus a small amount of the 6,8-dithiated product after 11 hours reflux in pyridine (58). The 6-mercapto compound will not react further with P₄S₁₀, but the 8-mercapto compound easily gives the dithiated product under the same conditions.



4,5-diaminouracil (XVIII) is thiated only at the 6-position after 2.5 hours reflux in pyridine (59). Again, 2-mercapto-6-hydroxy-4,5-diamino-pyrimidine easily gives the dithiated product.

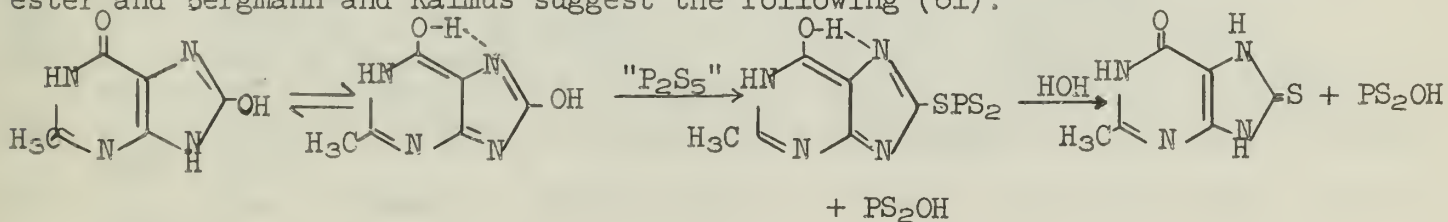
Bergmann and Kalmus report that 6,8-dihydroxypurine (XIX) is thiated selectively at the 6-position in 75% yield after 6 hours in boiling pyridine (60), while 2-methyl-6,8-dihydroxypurine (XX) gives the 6,8-dithio derivative in 52% yield under the same conditions, with the 6-thio derivative as a minor product (61). The 6-thio derivative is unchanged under the reaction conditions. Reinvestigation (61,62) of the 6,8-dihydroxypurine thiation revealed that some dimercapto derivative was present as a minor product, apparently arising from the 8-mercapto compound, since the 6-mercapto compound would not yield any dithiated product under these conditions. Thus the relative reactivities of the 6 and 8 carbonyls of 6,8-dihydroxypurine are reversed from the same carbonyls of 2-methyl-6,8 dihydroxy-

purine, and thiation at position 8 seems to proceed only if oxygen is present at position 6, and is prevented by a mercapto group at position 6. These observations are summarized below:



Bergmann and Kalmus (62) suggest that direct deactivation of the 6-carbonyl could be a result of transmission of the inductive effect of the methyl group through the conjugated chain $\text{Me}-\text{C}=\text{N}-\text{C}=\text{C}-\text{C}=\text{O}$ in the pyrimidine part of the molecule, thus reducing the electrophilic character at position six. Support of this is seen in a model compound, 4,5-diamino-6-hydroxypyrimidine (XXI). Treatment of this compound with P_4S_{10} for 2 hours gives a 50% yield of 4,5-diamino-6-mercaptopyrimidine, while the corresponding 2-methyl compound does not react after six hours of the same treatment. That this is not just a steric effect is seen by the observations that both 6,8-dihydroxy-2-phenylpurine and 4,5-diamino-6-hydroxy-2-phenylpurine are thiated easily in the 6-position (63).

Bergmann and Kalmus also suggest that formation of a hydrogen bridge between the 6-oxo group and the 7-imino group will enhance enolization at position 8, and will be strengthened by the inductive effect of the 2-methyl group, thus explaining the reactivity of the 8-carbonyl. This assumes the intermediate formation of a thiophosphate ester and Bergmann and Kalmus suggest the following (61):

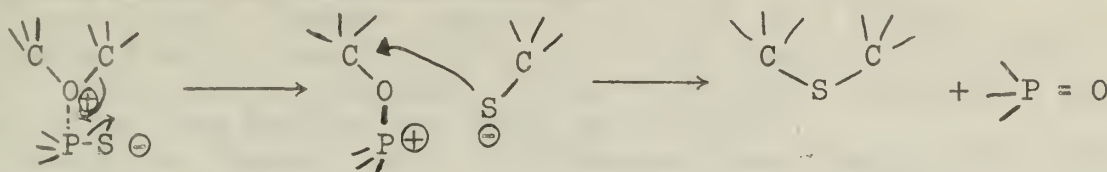


A mercapto group in position six would not participate so extensively in hydrogen bonding. Support for this type of hydrogen bonding is offered from the fact that the NH infrared band of 1,6-dihydro-1-methyl-6-oxopurine lies at a slightly lower frequency than that of purine itself (64). Intermediates in the above scheme have not been isolated or identified and it is not known whether the enol or keto form reacts.

Interest in the thiated nucleic acid bases has been great in recent years because they have shown considerable biological activity, apparently through interference

with polynucleotide biosynthesis (65). Nucleosides of these bases have been thiated using O-benzoyl blocking groups to protect the sugar (30,32).

Replacement of oxygen from a heterocyclic ring would presumably go by a ring opening mechanism something like the following:



Summary. --The replacement of oxygen with sulfur using P_4S_{10} has been very useful synthetically, but is still little understood and in need of the application of modern methods.

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CARBONYL-CONTAINING THREE-MEMBERED RINGS AS REACTION INTERMEDIATES

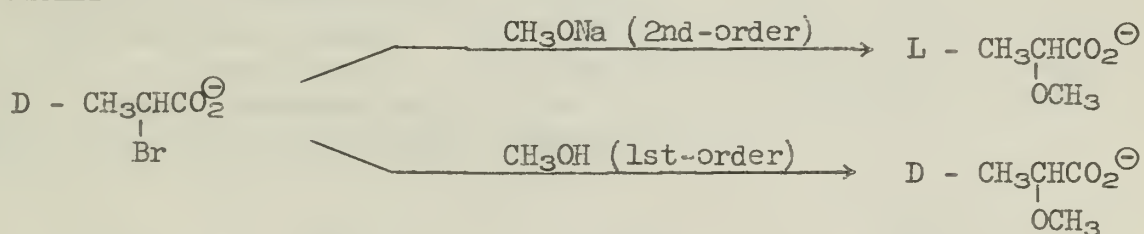
Reported by D.W. Lamson

May 21, 1964

It is the intent of this seminar to present evidence concerning the existence of α -lactones, cyclopropanones and α -lactams as possible transient reaction intermediates. This abstract is not meant to represent an exhaustive review but rather as a description of the more pertinent evidence in the three cases.

I. α -Lactones - Although no α -lactones have ever been isolated, there is ample stereochemical evidence for their existence as reaction intermediates. This evidence has been summarized in textbooks of physical-organic chemistry (1,2) and in reviews (3,4). The material presented here is supplied as a basis for comparison of α -lactones with the other two ring systems.

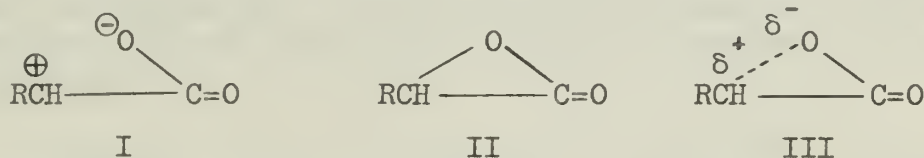
Cowdrey, Hughes and Ingold (5) reported that the reaction of 2-bromopropionate ion with methoxide ion followed second-order kinetics and yielded 2-methoxypropionate ion with inversion of configuration. The methanolysis of the bromopropionate in weakly basic solution followed first-order kinetics and yielded 2-methoxypropionate ion with retention of configuration.



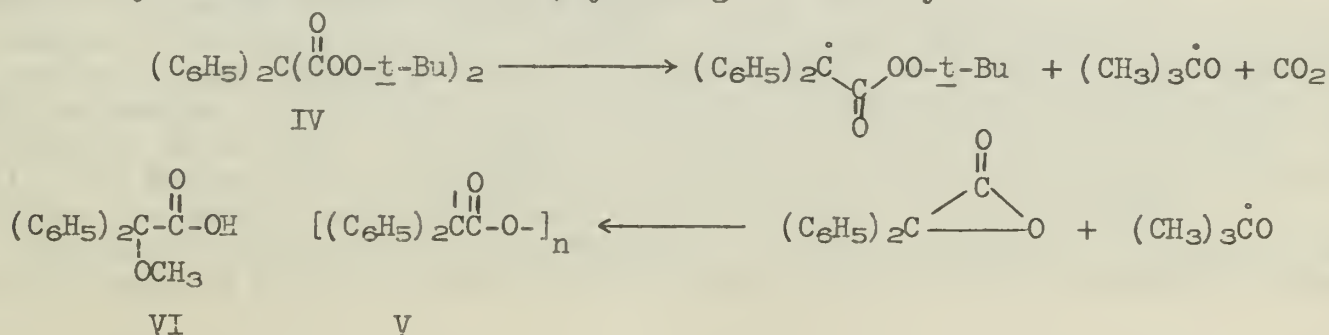
Similarly, the reaction of 2-tosyloxypropionic acid with aqueous silver oxide, yielded lactic acid with retention of configuration (6) and the deamination of an α -amino acid gave the α -hydroxy acid with the same configuration (7).

Grunwald and Winstein found that the rate of methanolysis of the 2-bromopropionate ion was about twenty times greater than that for isopropyl bromide (8). These reactivities were reversed for hydrolysis in water where the bromopropionate ion reacted only 2.4 times faster. The insensitivity to solvent effect and the only slightly positive salt effect along with the high relative rate in methanol are good evidence that the rate determining step of the solvolysis of the 2-bromopropionate ion involves direct intramolecular displacement by the carboxylate group. If the reaction involved prior ionization followed by ring-closure, a greater solvent effect would be expected.

The intermediate has been variously considered to be a zwitterion (I) (5), an α -lactone (II) (9), and an α -lactone with much ionic character (III) (8,10).

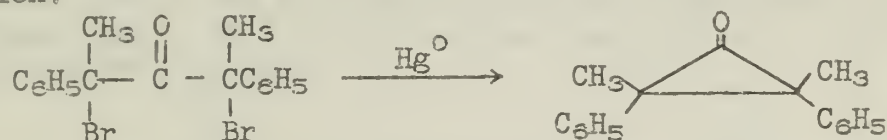


The most recent invocation of an α -lactone intermediate is that by Bartlett and Gortler (11) for the decomposition of certain peresters. Di-*t*-butylperoxy diphenylmalonate (IV) yielded the benzylic acid polyester V when decomposed in cumene solvent. When methanol was present a 54% yield of the methoxy-acid VI resulted. When methanol reacted directly with the polyester under essentially the same conditions, reaction occurred only to the extent of 10-20% yielding the methoxy-acid.

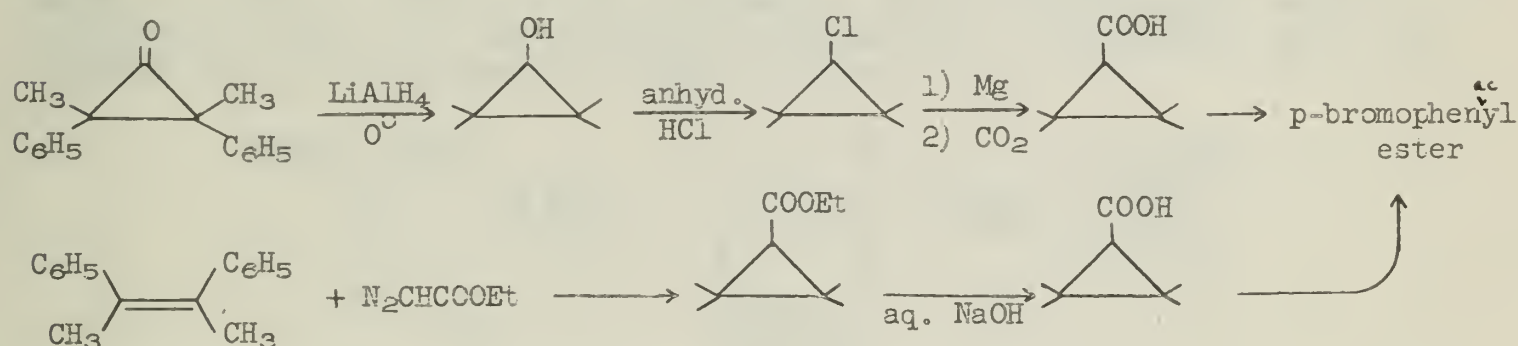


II. Cyclopropanones - Most of the reported carbonyl derivatives of cyclopropanones, such as ketals, have been prepared directly in such ways that there were probably no cyclopropanone intermediates. The few cases where this possibility occurs will be mentioned. Of the proposed preparations of cyclopropanones only two appear not to have been seriously questioned in the literature. LaForge and Acree (12) claimed to have prepared 2-methyl-3-phenylcyclopropanone. No structural proof was furnished for their compound, which had an unsatisfactory analysis and was unaccompanied by spectral data. The assignment was based on their initial belief that the compound was a butenone, though it was not one of the known butenones. The possibility of an aldehyde group being present in the compound was not discussed.

Cogdell (13) claims to have prepared 2,3-dimethyl-2,3-diphenylcyclopropanone by the following reaction:

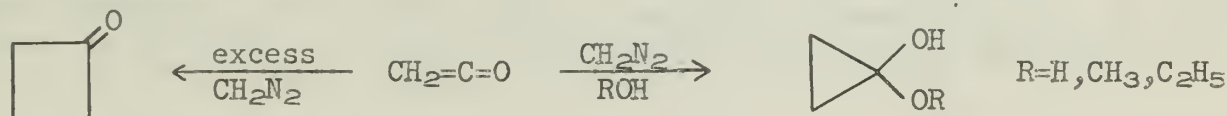


The product was purified by molecular distillation and gave a satisfactory analysis but slightly high molecular weight. The following structural proof offered for the material involved its conversion into 2,3-dimethyl-2,3-diphenylcyclopropane carboxylic acid and ester. These compounds were synthesized independently for comparison. The thesis abstract contained no spectral information.



All reported analyses were satisfactory. The final identification was by a series of mixed melting points of the p-bromophenacyl esters obtained by the two routes. Perhaps it is significant that this cyclopropanone synthesis has not yet been reported in a journal.

The reaction of diazomethane with ketene to yield cyclobutanone was investigated by Lipp, Buchkremer and Seeles (14). By including an alcohol or water in the reaction mixture, compounds were isolated which gave satisfactory analyses for hemiketals or the hydrate of cyclopropanone.



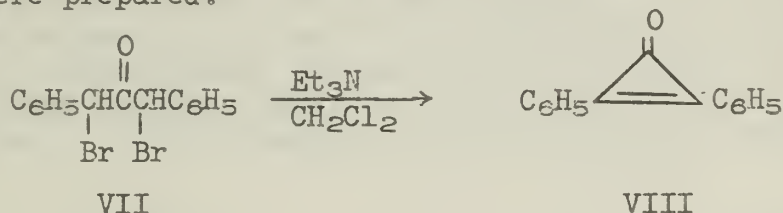
The hydrate or hemiketals yielded propionic acid or esters when treated with aqueous base. (This result directly parallels the known rearrangement of cyclopropanols to propionaldehydes (15)). For these reasons, cyclopropanone was proposed as an intermediate in the preparation of cyclobutanone.

Semenow, Cox, and Roberts (16) further investigated the reaction of diazomethane with ketene through the use of carbon-14 diazomethane. By isolation and degradation of the radioactive cyclobutanone, the following percentages of C¹⁴ incorporation into each position were found: C-1, 0.00%; C-2, 37.06%; C-3, 25.76% and C-4, 37.06%. This result is in agreement with the calculated values of 0, 37.50, 25.00 and 37.50 for a postulated cyclopropanone intermediate in the formation of cyclobutanone.

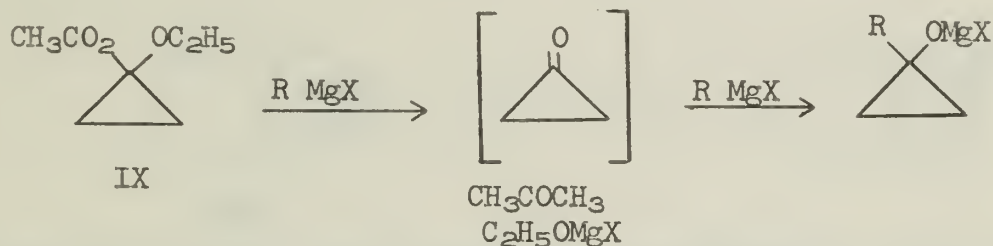
Kistiakowsky and Sauer (17) investigated the flask photolysis of ketene and presented an argument for the formation and decomposition of a cyclopropanone intermediate.

DeMore, Pritchard and Davidson (18) conducted a series of low temperature photolysis experiments. In one such experiment, diazomethane was photolyzed in the presence of ketene in a matrix of solid nitrogen at 20 K. An infrared spectrum revealed an absorption at 1825 cm^{-1} among others. The matrix was allowed to warm to 77 K and the volatile materials removed. The infrared spectrum of the remaining material at room temperature showed a broad absorption at 2950 cm^{-1} and a strong absorption at 1815 cm^{-1} . When diazomethane was added to the material, the latter band disappeared and new absorptions appeared at 1775 and 1760 cm^{-1} . These were postulated as being due to cyclobutanone and possibly cyclopentanone.

The dehydrohalogenation of 2,3-dibromo-2,3-diphenylpropanone-3 (VII) to yield 2,3-diphenylcyclopropanone (VIII) was reported by Breslow, Posner and Krebs (19) as what they termed "the interception of a cyclopropanone intermediate". In the same manner, other cyclopropanones were prepared.

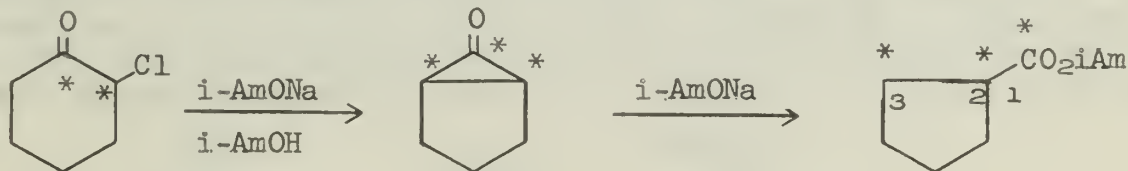


Wasserman and Clagett (20) prepared 1-acetyloxy-1-ethoxycyclopropane (IX). This reacted with lithium aluminum hydride to produce cyclopropanol and with Grignard reagents to produce 1-substituted cyclopropanols. Since a displacement reaction on the cyclopropane ring has not been previously demonstrated, it is possible that cyclopropanone may be an intermediate in this reaction.

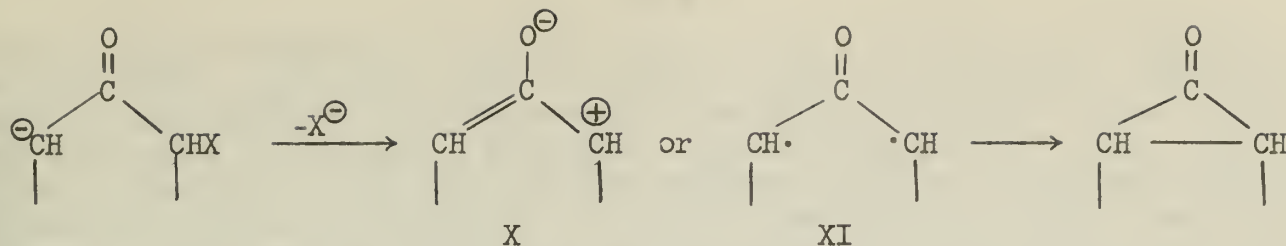


The Favorskii rearrangement is the skeletal rearrangement of α -haloketones in the presence of certain nucleophilic bases to give carboxylic acid salts, esters or amides. This reaction has been recently reviewed (21), but since it is sometimes considered to involve a cyclopropanone-like intermediate, it is pertinent to discuss mechanistic investigations on this reaction as well as late attempts to describe the intermediate involved.

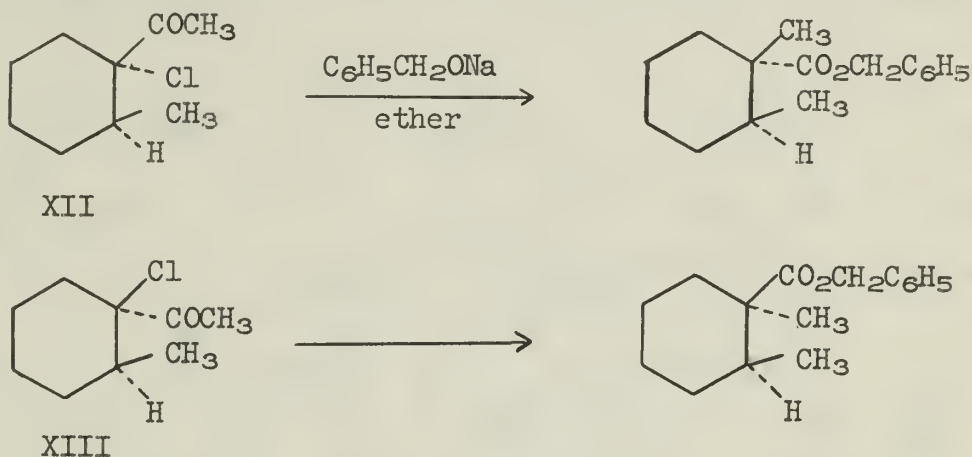
In 1950, Loftfield (22) offered evidence for a cyclopropanone intermediate which successfully explained the products of many Favorskii rearrangements. The reaction of 2-chlorocyclohexanone-1,2- C^{14} with sodium isoamylate in isoamyl alcohol yielded isoamyl cyclopentane carboxylate. A series of degradation steps showed that 52% of the radioactivity was in C-1 and 24% in each C-2 and C-3.



The Loftfield mechanism implies that cyclopropanone formation is synchronous with an internal $\text{S}_{\text{N}}2$ -type displacement on the halogen-bearing carbon atom with consequent inversion at that center. This view has been questioned on quantum mechanical grounds by Burr and Dewar (23) who furthered the suggestion by Aston and Newkirk (24) that loss of halide ion from the enolate anion preceded cyclopropanone formation and involved a generation of a species variously represented as a mesomeric zwitterion (X) or as a form such as XI. Subsequent collapse of this species to the more stable cyclopropanone would lead to the product.

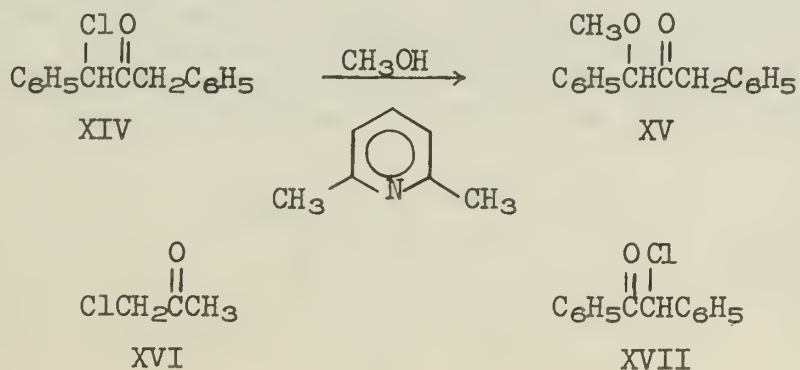


The synchronous and non synchronous mechanisms are not kinetically distinguishable if enolate formation is rate determining, but they clearly differ in stereochemical implications. The synchronous process would necessitate steric inversion at the halogen-bearing carbon atom, while the intermediacy of a discrete species X or XI of high resonance energy would predict racemization of the α -carbon atom. The pathways would appear to be differentiated by the rearrangement of a suitable optically active haloketone. This appeared to be performed when Stork and Borowitz (25) rearranged the two epimeric chloroketones XII and XIII and received the products shown. The authors pointed out that although their work supported the direct formation of a cyclopropanone intermediate, other mechanisms could be operative under other conditions.

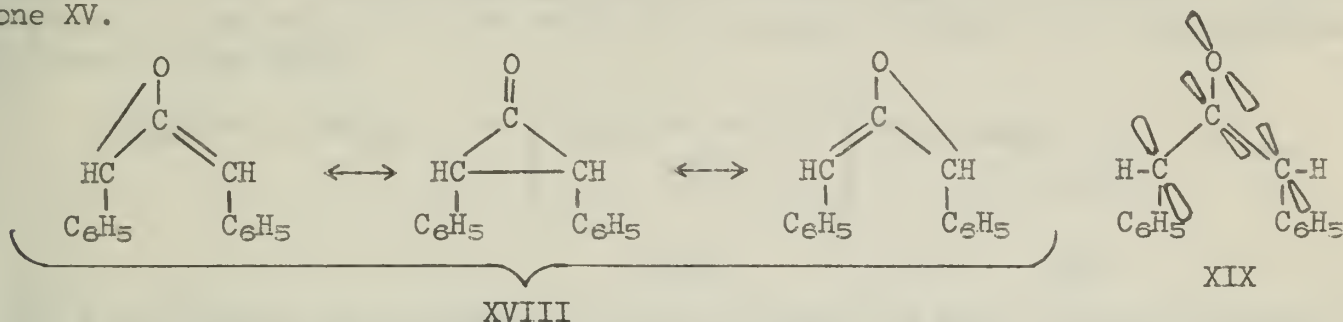


House and Gilmore (26) reinvestigated the rearrangement of the chloroketone XII and found that the rearrangement was essentially stereospecific in the nonpolar solvent 1,2-dimethoxyethane, but became non-stereospecific in the polar solvent methanol. The same results were observed in the reactions of certain 2,3-epoxycyclohexanones which appear to behave similarly to α -haloketones. Thus the authors concluded that the course of the Favorskii rearrangement is dependent on the polarity of the reaction medium. In a study of 9-chloro-trans-1-decalone with methoxide ion (27), a reaction run to partial completion in methanol- d_1 demonstrated that the formation of the enolate anion is either rate determining or at least comparable in rate with the subsequent loss of chloride ion.

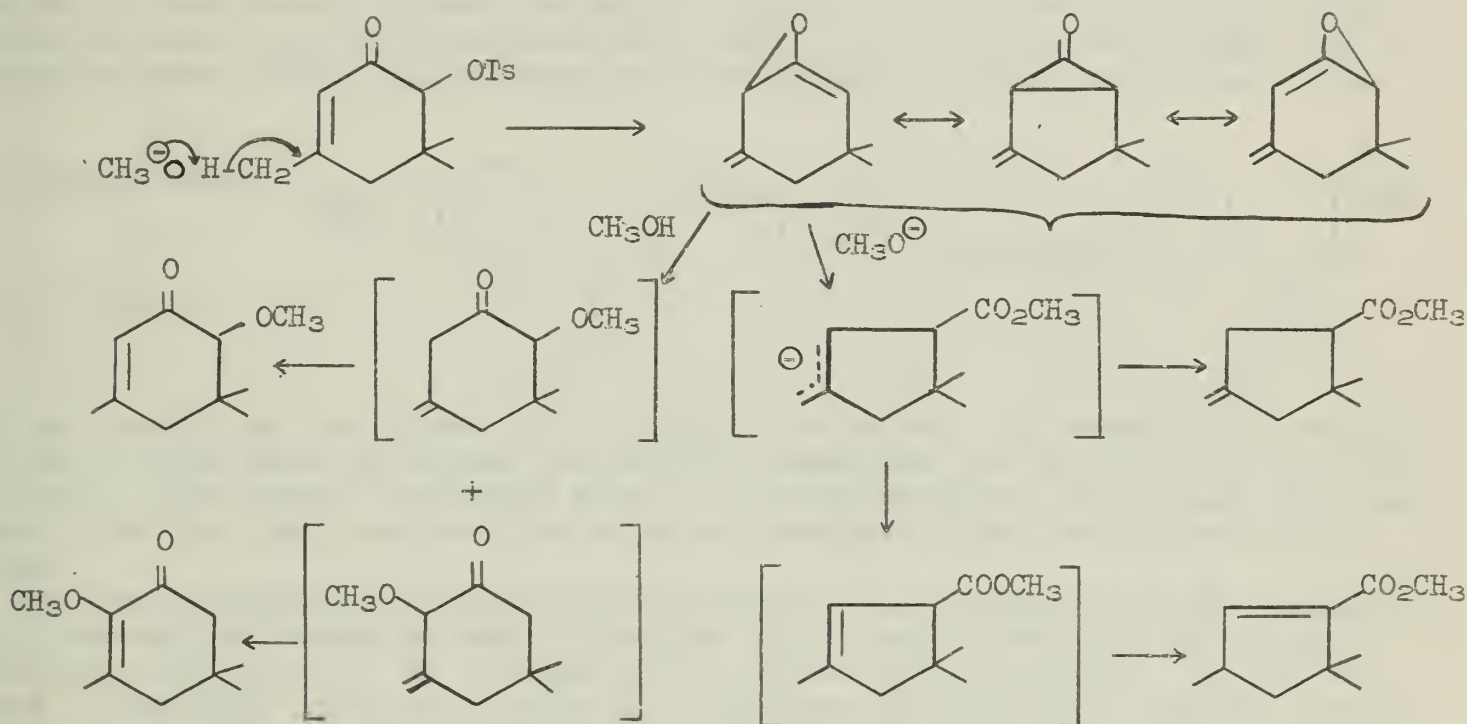
Fort (28) found that the reaction of α -chlorodibenzyl ketone (XIV) with 2,6-lutidine in methanol yielded α -methoxydibenzyl ketone (XV). The reaction was first order in chloroketone and in lutidine and was almost independent of lutidinium ion. Chloroacetone (XVI) and desyl chloride (XVII) were found to be unreactive under the same conditions. These experimental results were interpreted in terms of the loss of



chloride ion from a negatively charged enolate ion with formation of the delocalized intermediate XVIII. Since Fort wishes to imply a planar intermediate, perhaps structure XIX is more satisfactory. This intermediate was proposed because of the formation of the α -methoxyketone XV instead of Favorskii rearrangement product in the absence of strong base. The author concluded that the apparent function of the aryl groups was to stabilize the forming intermediate. A further observation was made that α,α' -dibromodibenzyl ketone reacted with iodide ion in methanol to also produce the α -methoxyketone XV.

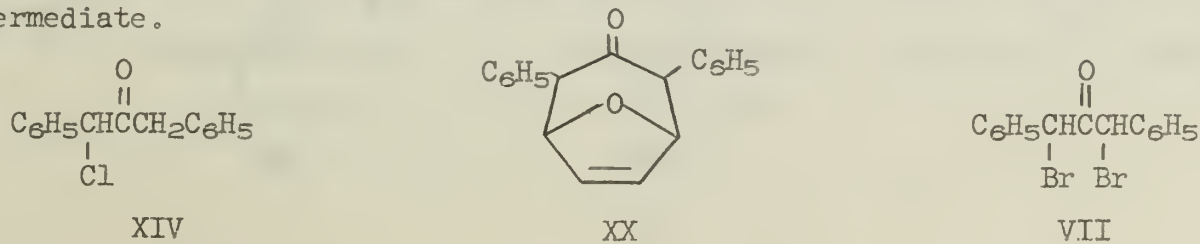


Fort (29) observed that the reaction of 6-tosyloxyisophorone with excess sodium methoxide led to the formation of the four products depicted and rationalized by the scheme below.



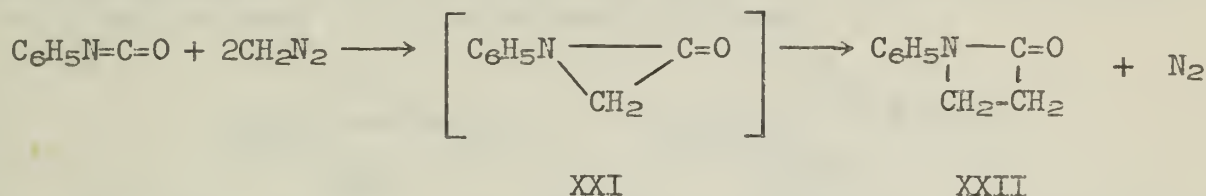
The author admits that the products may be rationalized by other mechanisms, but he finds the postulate of a common intermediate desirable, especially from the finding that the lower the base concentration or the slower its addition, the less rearrangement products are found (with the overall yield remaining about the same). The possibility that a "classical" cyclopropanone may react to yield the products described was given minimum consideration.

Other work by Fort (30) and by Cookson and Nye (31) reported the capture of the reactive intermediate. Fort treated the chloroketone XIV with lutidine in the presence of furan and received an adduct considered to be structure XX on the basis of analysis, IR and NMR spectra. This trapping was interpreted as being evidence for a delocalized intermediate.

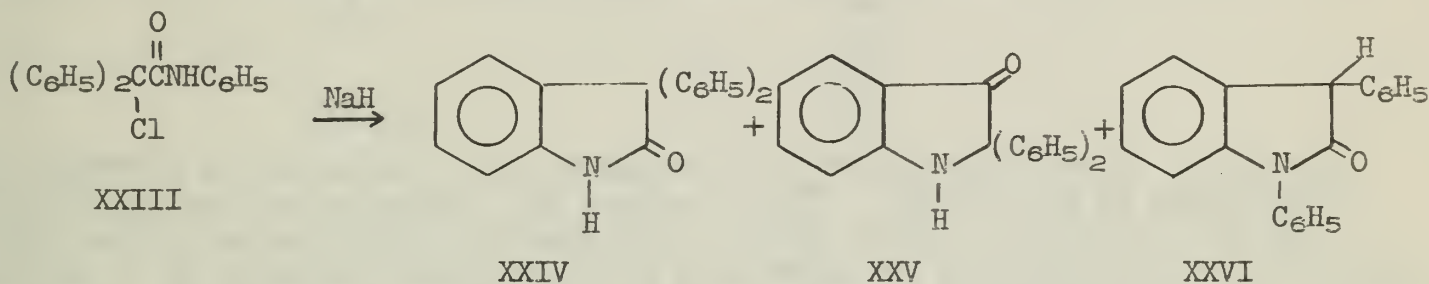


Cookson and Nye treated the dibromoketone VI with iodide ion in the presence of various dienes and of tetracyanoethylene. The latter yielded a five-membered ring adduct and the former yielded compounds similar to that of Fort, including XX. These authors felt that no conclusions could be reached as to the nature of the reactive intermediate. Here again, we have no assurance that the observed reactions would not be typical of a "classical" cyclopropanone.

III. α -Lactams - In 1949 Sheehan and Izzo (32) proposed 1-phenylaziridinone (XXI) as a possible intermediate in the reaction of phenyl isocyanate with diazomethane to yield the β -lactam XXII.

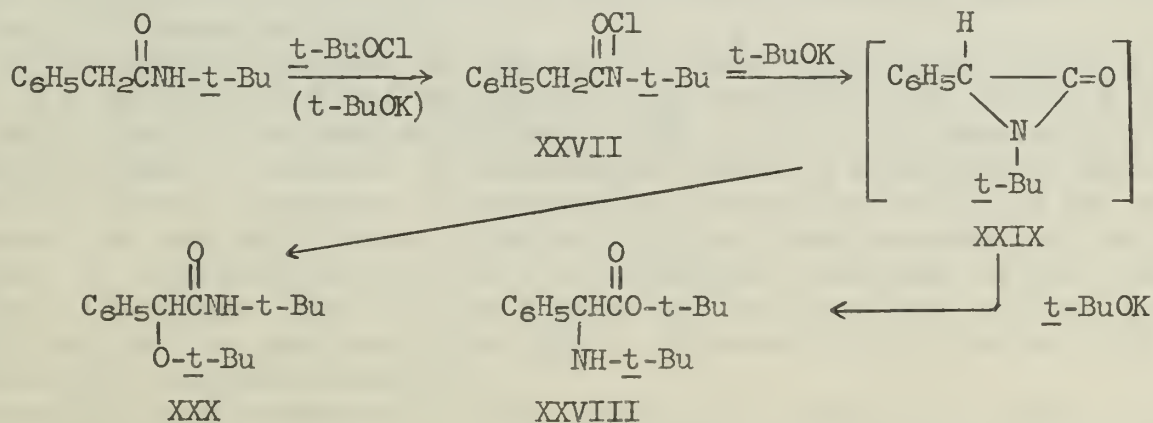


The work of Sarel and co-workers (33,34) claiming to have produced α -lactams was disputed by Sheehan and Frankenfeld (35). The former workers isolated compounds which showed carbonyl absorptions in the 1700 cm^{-1} region and were of considerably greater stability than would be expected for α -lactams. The latter workers reinvestigated the reaction of α -chloro- α , α -diphenylacetanilide (XXIII) with sodium hydride in benzene solvent and found only 3,3-diphenyloxindole (XXIV), 2,2-diphenyloxindole (XXV) and 1,3-diphenyloxindole (XXVI). All of these products possess carbonyl absorption in the

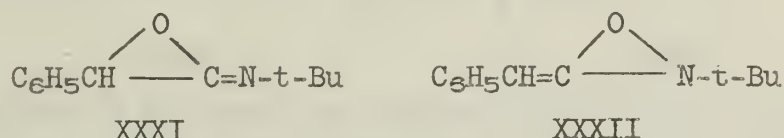


1700 cm^{-1} region and are isomers of the supposed α -lactam. The authors were not able to isolate an α -lactam by varying the reaction conditions nor to detect one spectroscopically. The authors considered that the observed products were primary reaction products and that they were not able to be rationalized without an α -lactam intermediate.

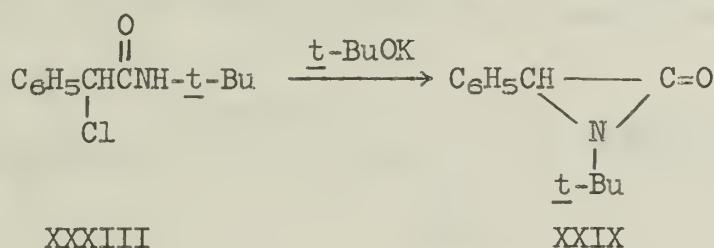
The work of Baumgarten and co-workers (36,37,38) has substantiated the existence of an intermediate resembling an α -lactam and these workers have done much toward elucidating the nature of the intermediate (referred to as α -lactam). In what was termed a "Favorskii-like" transformation of N-*t*-butyl-N-chloroamides (XXVII) into N-*t*-butylamino acid derivatives (XXVIII), an absorption at 1847 cm^{-1} appeared and disappeared in the course of the reaction. The authors stated that "one reasonable explanation" for the observation would be the aziridinone intermediate XXIX.



By adjustment of the reaction conditions the intermediate compound was isolated in 31% yield. Data for the compound were as follows: m.p. 29-31°C; analysis and molecular weight satisfactory; IR in chloroform, 1849 cm.⁻¹ (nothing 1600-1800 or 3100-3500 cm.⁻¹); NMR in carbon tetrachloride, nine methyl protons at 8.67 p.p.m. (τ), five aromatic protons at 2.63 and a single ring proton at 6.22. The purified material was described as "stable but reactive." Its reaction at room temperature with *t*-butyl alcohol, *t*-butyl amine, phenylhydrazine and aqueous or ethanolic hydrogen chloride gave only products similar to XXX. Reaction with potassium *t*-butoxide gave only XXVIII. The authors concluded that the data were most easily rationalized in terms of the aziridinone XXIX, but stated that alternate structures XXXI and XXXII or a highly delocalized intermediate could not be ruled out with the available data.



Further work by Baumgarten revealed that the α-haloamide XXXIII, similar to that originally proposed by Sarel and co-workers and reinvestigated by Sheehan and Frankenfeld, could be made to react and give α-lactam XXIX identical to the structure isolated previously.



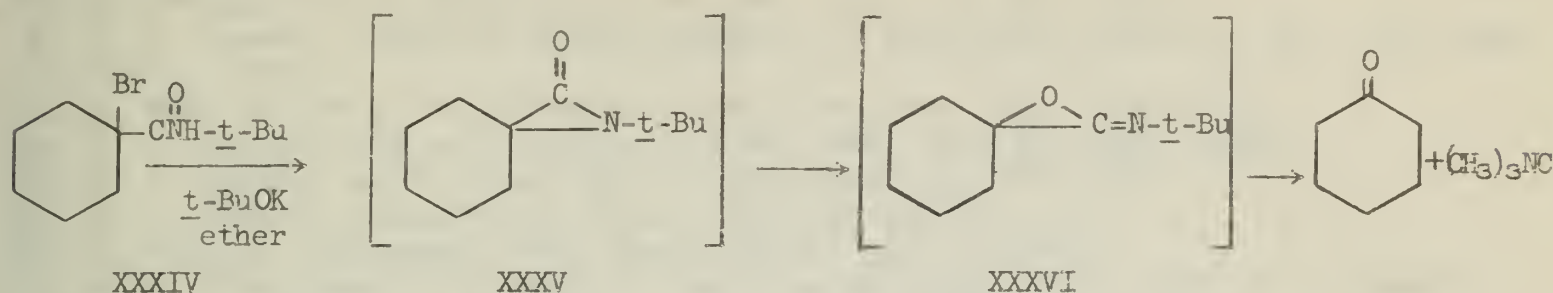
This synthesis was extended to the preparation of optically active α-lactam from optically active α-chloroamide. The product ($[\alpha]_D^{28} = -32.4^\circ$) was of undetermined optical purity and uncertain configuration, but the authors considered that the existence of an optically active α-lactam eliminated the possibility of a delocalized structure. (This may not seem clear since the nature of any proposed delocalized structure is rather vague. Apparently Baumgarten is inferring that the delocalized structure which he envisions cannot retain optical activity due to sp² configuration at the α-carbon.) The results do appear to eliminate structure XXXII as a possibility in itself.

With a view toward distinguishing the valence tautomers XXIX and XXXI, the intermediate was prepared with slightly less than 50% oxygen-18. The amide starting material showed a doublet at 1668 and 1645 cm.⁻¹ in methylene chloride. The α-lactam intermediate showed a doublet at 1848 and 1827 cm.⁻¹ in methylene chloride. The authors considered that this evidence tended to indicate the aziridinone structure XXIX. (Obviously this was interpreted in terms of a carbonyl function and is in fact consistent with similar results involving an amide function (38). However since structures like the imino-α-lactone XXXI are presently unknown, there is no assurance that it may not behave similarly.)

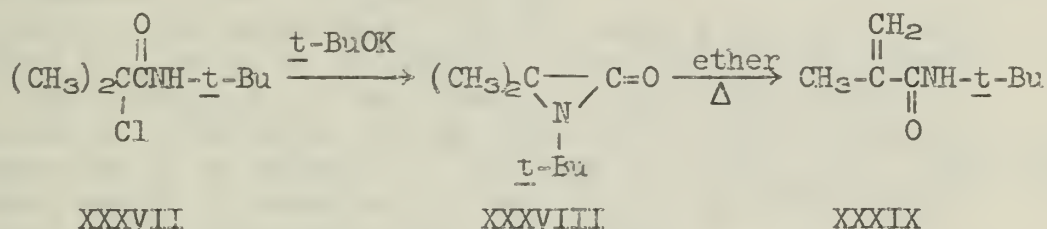
The C¹³-H coupling constant for the α-C-H of the isolated intermediate must be accounted for by any structural assignment. The observed value of 168 ± 0.5 is consistent with those for related aziridines (~168). (It is not necessarily inconsistent with structure XXXI.) Although the individual pieces of experimental data can be explained by various structures, Baumgarten and co-workers feel that the entire picture lends support to the aziridinone structure XXIX, but they mention that the possible intermediacy of a delocalized structure in subsequent reactions of the α-lactam is not eliminated. (It appears however that a firm case has been made neither for the aziridinone XXIX nor for the imino-α-lactone XXXI. It seems likely that an X-ray study will be necessary for conclusive results.)

Concurrently with Baumgarten's work, Sheehan and Lengyel (40) have investigated the effects of varying the substituents in precursors to α-lactam intermediates. The reaction of 1-bromo-1-N-*t*-butylcarboxamidocyclohexane (XXXIV) with potassium *t*-butoxide

in ether furnished cyclohexanone and *t*-butyl isocyanide as major products with a smaller quantity of 1-cyclohexene-1-*N*-*t*-butylcarboxamide. Because of the detection of an absorption at 1835 cm^{-1} during the reaction, the authors postulate α -lactam XXXV as intermediate. The imino- α -lactone XXXVI was postulated as subsequent intermediate in order to account for the products.



When α -chloro- α -methyl-*N*-*t*-butylpropionamide (XXXVII) was treated with potassium *t*-butoxide a compound was isolated and identified as 1-*t*-butyl-3,3-dimethylaziridinone (XXXVIII) which possessed the following properties: m.p. 22-24 $^{\circ}\text{C}$; analysis and molecular weight satisfactory; IR in carbon tetrachloride, 1837 cm^{-1} (nothing 3100-3500 cm^{-1}); NMR in carbon tetrachloride, singlet at 8.67 p.p.m. (τ) for the *N*-*t*-butyl protons and a singlet at 8.55 for the methyl protons. When the compound was refluxed in ether, *N*-*t*-butylmethacrylamide (XXXIX) resulted along with smaller amounts of acetone and *t*-butyl isocyanide.



Treatment of the α -lactam with nonionic reagents such as water, *t*-butyl alcohol, benzyl amine, α -toluenethiol and ethyl glycinate produced compounds of type XXX, while ions such as *t*-butoxide produce type XXVIII. These results directly parallel those of Baumgarten.

Substitution of the *N*-*n*-propyl group for the *N*-*t*-butyl group in the starting amide apparently resulted in an intermediate of less selectivity, since compounds of type XXVIII and type XXX resulted from the same reaction. Replacement of one of the two α -methyl groups by hydrogen (while keeping the *N*-*t*-butyl group) in the starting amide resulted in product of type XXVIII only. This product is not the one expected from generalization of the previous examples. The intermediate in this latter case was detected by its absorption at 1840 cm^{-1} .

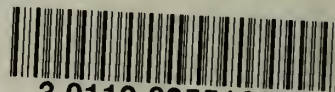
IV. Summary - At this point there remains a great deal of uncertainty as to the nature of the intermediate in each of the three areas discussed. Therefore it is premature to make direct analogies among them, but it remains an interesting possibility for the future. Certainly the information gathered in each of the three areas will be useful in the others, not necessarily as generalizations but in particular as criteria for testing similarities and differences. Hopefully the isolation of an alleged α -lactam will be a stimulus toward further attempts at the isolation of a cyclopropanone. The study of a "classical" cyclopropanone would do much toward elucidating the possible structures for the Favorskii intermediate as well as forming a relation with the α -lactam structure.

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